evaporating. The **3c/4c** ratio was instead determined by HPLC with use of a 25-cm Hypersil 10 silica column (HPLC technology) with hexane–ethyl acetate (99:1 v/v) as the eluent at a flow rate of 2 mL/min. All reactions were carried out in triplicate. The **3/4** ratios reported in Table II were reproducible to ±1%, whereas the **2**/(**3** + **4**) ratios were reproducible to ±10% of the quoted figures. All product ratios were independent of the percent conversion. The reactions performed at the lowest concentrations were slow and were analyzed only at incomplete conversion. However, reactions stopped at several different conversions gave similar **3/4** and **2**/(**3** + **4**) ratios. For each olefin **1**, reactions were also carried out in the presence of *trans*-1,2-dichloroethylene at a concentration equal to that of **1**. No isomerization to *cis*-1,2-dichloroethylene was ever observed by HPLC analysis.

The stability of dibromides **3** and **4** in the presence of the halogen was checked by exposing all dibromides to Br_2 under conditions identical with those employed in the bromination reactions, followed by HPLC analysis (for **3b**,**4b** and **3c**,**4c**) or NMR analysis (for **3a**,**4a** and **3d**,**4d**).

Kinetic Measurements. 1,2-Dichloroethane Br_2 solutions, prepared shortly before use, were protected from the daylight and adjusted to twice the desired initial concentrations in the kinetic runs. Aliquots of these solutions, prethermostated at 25 ± 0.05 °C, were mixed with equal volumes of prethermostated solutions of olefins **1** and **2** of suitable concentrations. The reactions of **1a** and **2a** were carried out with the stopped-flow apparatus, those of **1b** and **2b**, **1c** and **2c**, and **1d** and **2d** with the conventional spectrophotometer. The following olefin and Br_2 concentrations (molar), pathlength (centimeters), and monitored wavelengths (nanometers) were used. **1a**: 1 and 2×10^{-1}, 2 and 4×10^{-3}, 2, 410 and 480. **2a**: 1×10^{-3}, 1×10^{-3}, 2, 410. **1b**: 5×10^{-3}, 5×10^{-3}, 1, 410. **2b**: 3×10^{-3}, 3×10^{-3}, 1, 410. **1c**: 4×10^{-2}, 4×10^{-3}, 1, 410. **2c**: 5×10^{-2}, 5×10^{-2}, 0.1, 410. **1d**: 5×10^{-2}, 5×10^{-2}, 0.1 and 0.2, 410 and 480. **2d**: 1×10^{-1}, 1×10^{-1}, 0.1 and 0.2, 410 and 500. The absorbance/time data were fitted to the appropriate third-order or pseudo-second-order rate equation. All reactions were carried out at least in triplicate. The k_3 values are reported in Table I.

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Registry No. 1a, 1657-45-0; **1b**, 645-49-8; **1c**, 124562-04-5; **1d**, 42134-70-3; **2a**, 1860-17-9; **2b**, 103-30-0; **2c**, 1149-56-0; **2d**, 42134-74-7; (±)-**3a**, 135733-73-2; **3c**, 135733-74-3; (±)-**3d**, 135733-72-1; (±)-**4a**, 135733-75-4; (±)-**4c**, 135733-76-5; (±)-**4d**, 135733-77-6; Br_2, 7726-95-6.

The Total Synthesis of Cystodytins

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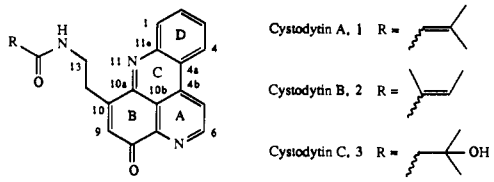
Contribution from the Department of Chemistry, Rice University, P.O. Box 1892, Houston, Texas 77251. *Received March 4, 1991*

Abstract: The first chemical preparation of the cystodytins has been accomplished. A modified Knoevenagel–Stobbe pyridine formation and a photochemical nitrene insertion into a C–H bond constitute the key phases of this efficient total synthesis.

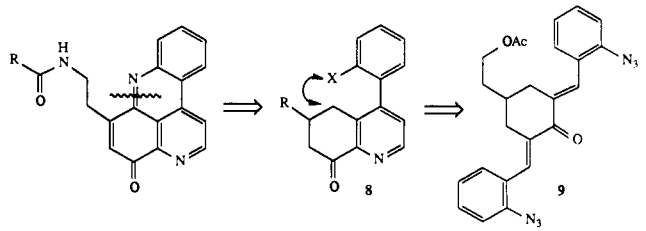
Introduction

The cystodytins are antineoplastic alkaloids isolated from the Okinawan tunicate, *Cystodytes dellechiajei* (Della Valle).[2] An inseparable 3.5:1 mixture of cystodytins A, **1**, and B, **2**, exhibited strong cytotoxicity (ID50 toward L1210 murine leukemia: 240 ng/mL = 6.7×10^{-7} M) and Ca^{2+} releasing activity from sarcoplasmic reticulum equal to 36 times that of caffeine. A third substance, cystodytin C, **3**, was obtained in pure form, but it was found to be almost devoid of biological activity.[2] The biological



effects induced by **1** and **2**[3] and their novel ring system render them particularly appealing both as targets for total synthesis and as candidates for pharmacological evaluation. Interest in cystodytins is reinforced by the recent discovery that many quinones, particularly heterocyclic ones, inhibit reverse transcriptase;[4] questions concerning the possible antiretroviral activity of **1**–**3** therefore emerge. Bioassay and analogue work would require

Scheme I



significant quantities of cystodytins, but given the scarcity of the compounds in their natural sources, totally synthetic materials are clearly needed.

Cystodytins share architectural similarities with other recently discovered marine natural products incorporating highly condensed polycyclic heteroaromatic skeleta, some of which attain a considerable degree of complexity.[5] It is remarkable that, in contemplating possible routes to such structures, a number of deficiencies of contemporary methodology become evident. In particular, lengthy sequences and low-yielding steps may be anticipated to adversely affect plans based on existing reactions. The difficulties associated with the construction of the framework of

(1) Recipient of the Robert A. Welch Predoctoral Fellowship.
(2) Kobayashi, J.; Cheng, J.-F.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Org. Chem.* **1988**, *53*, 1800.
(3) Nakamura, Y.; Kobayashi, J.; Gilmore, J.; Mascal, M.; Rinehart, K. L., Jr.; Nakamura, H.; Ohizumi, Y. *J. Biol. Chem.* **1986**, *261*, 4139.
(4) Inouye, Y.; Take, Y.; Oogose, K.; Kubo, A.; Nakamura, S. *J. Antibiot.* **1987**, *40*, 105.
(5) For examples, see: (a) Schmitz, F. J.; DeGuzman, F. S.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1991**, *56*, 804. (b) DeGutzman, F. S.; Schmitz, F. J. *Tetrahedron Lett.* **1989**, *30*, 1069. (c) Rudi, A.; Benayahu, Y.; Goldberg, I.; Kashman, Y. *Tetrahedron Lett.* **1988**, *29*, 6655. (d) Cooray, N. M.; Scheuer, P. J.; Parkanyi, L.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4619. (e) Cimino, G.; De Rosa, S.; De Stefano, S.; Sodano, G. *Pure Appl. Chem.* **1986**, *58*, 375. (f) Schmitz, F. J.; Agarwal, S. K.; Gunasekera, S. P.; Schmidt, P. G.; Shoolery, J. N. *J. Am. Chem. Soc.* **1983**, *105*, 4835 and references cited therein.

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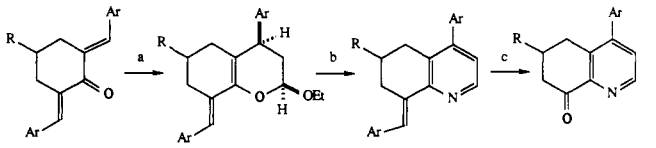
Scheme II

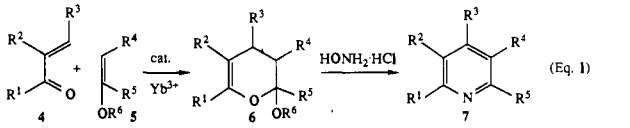


10 R = H; Ar = Ph 11 R = H; Ar = Ph 12 R = H; Ar = Ph 13 R = H; Ar = Ph

9 R = $(CH_2)_2OAc$, Ar = 2-N_3-C_6H_4 20 R = $(CH_2)_2OAc$, Ar = 2-N_3-C_6H_4 21 R = $(CH_2)_2OAc$, Ar = 2-N_3-C_6H_4 22 R = $(CH_2)_2OAc$, Ar = 2-N_3-C_6H_4

[a] CH_2=CHOEt, $(CH_2Cl)_2$, cat. Yb(fod)$_3$, reflux, 100% for **11**, 99% for **20**. [b] $HONH_2$·HCl, MeCN, reflux, 86% for **12**, 56% for **21**. [c] O_3, MeOH, −78 °C, then Me_2S, −78 to 25 °C, 75% for **13**, 77% for **22**.

cystodytins may be simplified to a considerable degree by an approach based on our method for the synthesis of highly substituted pyridines (eq 1).[6] We recently described technology for the preparation of substances that incorporate the complete ring system of **1**–**3**.[7] Herein, we present a full account of the first total synthesis of the cystodytins.



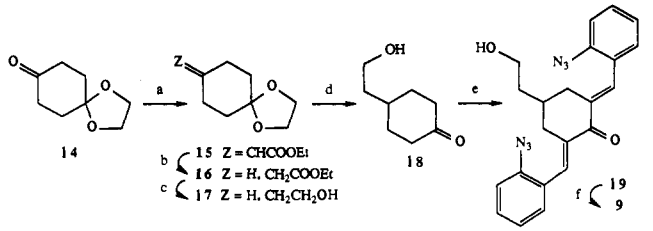
(Eq. 1)

Discussion

The retrosynthetic diagram of Scheme I illustrates how the implementation of a synthetic strategy based on the logic of eq 1 is subordinate to the availability of a protocol for the installation of ring C of the target molecule. The precise manner in which such a goal could be achieved constituted an issue that was ultimately resolved by experimentation. In general terms, it was envisioned that substituent X in **8** should be amenable to conversion into a reactive nitrogen functionality suitable for establishing the desired connectivity. An azido group appeared to offer the best compromise between reactivity, ease of handling, and synthetic efficiency. This led to the identification of **9** as the starting material. Only one of the two benzylidene groups in this nicely symmetrical molecule could possibly react under the conditions of eq 1. Ozonolytic cleavage of the remaining olefin would subsequently introduce a requisite carbonyl at C-8.

The full scope of the new pyridine synthesis was largely unexplored at the onset of this investigation. Therefore, it seemed prudent to model construction of a molecular framework similar to the one found in the cystodytins by using a simpler, readily available system. Dibenzylidenecyclohexanone, **10**, was chosen as a substrate for model work. Aromatic enones of this type deviate in behavior from their aliphatic congeners[8] in that they combine readily with vinyl ethers under catalysis[9] by Yb(III).[6] Heterocycloaddition[10] of **10** with ethyl vinyl ether furnished **11** (Scheme II), obtained as an 18:1 mixture of two stereoisomers. Separation of these was not attempted, but the NMR spectrum of the major component exhibited a resonance attributable to the anomeric proton as a doublet of doublets at 4.93 ppm, J_1 = 8.7, J_2 = 1.9 Hz, suggesting that the ethoxy substituent occupies an equatorial position within the pyran ring. The benzylic proton appeared as a broad triplet (fine structure evident) at 3.41 ppm with an apparent coupling constant J = 8.3 Hz. Scrutiny of the resonances of the equatorial (2.68 ppm) and axial (1.91 ppm) hydrogens located on the neighboring methylene group indicated that the actual coupling constants must be J_1 = 7.4 and J_2 = 10.1 Hz, respectively. These observations imply that the phenyl substituent must also occupy an equatorial position in what is clearly a rather distorted pyran ring. The stereochemistry of the major diastereomer of **11** may therefore be assigned as cis, suggesting that the cycloaddition reaction prefers an endo topological course. Cycloadducts of the type **11** are recognized as latent forms of 1,5-dicarbonyl compounds, and as such they undergo clean conversion into pyridines upon exposure to hydroxylamine hydrochloride in refluxing acetonitrile. Compound **11** was no exception, affording pyridine **12** smoothly and in good yield. Subsequent ozonolysis of the benzylidene group provided **13** in 65% overall yield from **10**. It is noteworthy that in the foregoing sequence a vinyl ether is utilized as the synthetic equivalent of the enolate of acetaldehyde. Clearly, any "classical" synthetic scheme involving such a reactive intermediate in an expressed form would be fraught with severe difficulties.

Scheme III



[a] $(MeO)_2P(O)CH_2COOEt$, NaH, DME, 95%. [b] H_2, Pd(C), 100%. [c] LAH, Et_2O, 90%. [d] Aqueous HCl, THF, 99%. [e] *o*-$C_6H_4(N_3)CHO$, aqueous EtOH, NaOH, 88%. [f] Ac_2O, pyridine, 99%.

The actual cystodytin dienone **9**, mp 98.5–100 °C, was easily obtained by condensation of ketone **18** with 2-azidobenzaldehyde[11] in aqueous medium,[12] followed by acetylation (Scheme III). Compound **9** combined readily with ethyl vinyl ether under catalysis by Yb(III), producing dihydropyran **20** as a 1:1 mixture of two diastereomers (Scheme II). It was not possible to fully characterize the diastereomers of **20**, but on the basis of results obtained from model compound **11**, it may be inferred that these resulted from an endo-selective cycloaddition process that, however, does not discriminate between the two diastereotopic faces of enone **9**. In any event, facile conversion into pyridine **21** occurred upon refluxing an acetonitrile solution of **20** and hydroxylamine hydrochloride (68% overall yield). It is noteworthy that **21**, and indeed all subsequent tricyclic cystodytin intermediates, was obtained as a 1:1 mixture of diastereomeric atropisomers. Ozonolysis of the surviving 2-azidobenzylidene group afforded the key intermediate for cystodytin synthesis, ketone **22**, in 76% chromatographed yield (the first purification in the entire scheme). With **22** in hand, an investigation directed towards completion of the crucial C ring was launched.

Formation of Ring C

A number of key transformations could conceivably produce an advanced tetracyclic structure from the versatile intermediate **22**, but an intramolecular aza-Wittig reaction from *p*-quinone **23**, a cycloaddition between a Δ^5 olefin (quinoline numbering) and the azide in a structure such as **25**, or a direct insertion of a nitrene, arising through deazoniation of the azide, into the neighboring C–H bond (cf. **27** → **28**) seemed to offer particularly good opportunities for success. Such general strategies may be described as nucleophilic (eq 2), pericyclic (eq 3), and electrophilic (eq 4) modes of cyclization.

Exploration of the nucleophilic mode of ring-C formation required quinone **23**, which was envisioned as arising through oxidation of phenol **31**. Ketone **22** was thus aromatized by a two-step sequence that involved conversion into an enol acetate derivative

(6) Ciufolini, M. A.; Byrne, N. E. *J. Chem. Soc., Chem. Commun.* **1988**, 1230.

(7) Ciufolini, M. A.; Byrne, N. E. *Tetrahedron Lett.* **1989**, *30*, 5559.

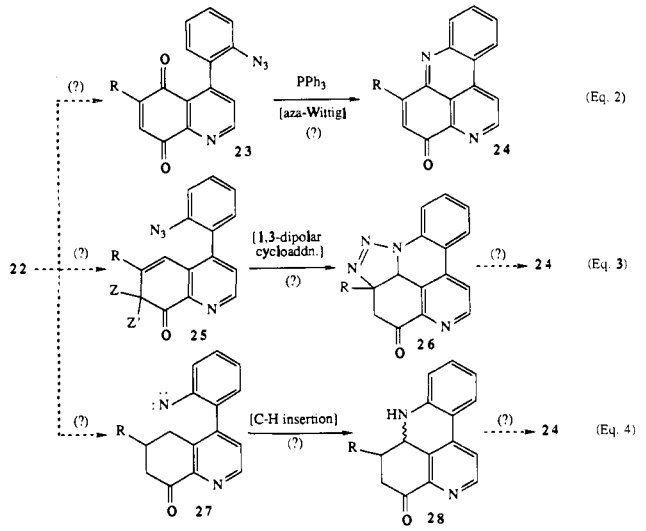
(8) (a) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1984**, *25*, 721. (b) For an interesting exception, see: Chapleur, Y.; Euvrard, M.-N. *J. Chem. Soc., Chem. Commun.* **1987**, 884.

(9) Uncatalyzed reactions of this type are known, but they require heating at 200 °C for 12 h in a high-pressure autoclave (ca. 75% yield): Longley, R. I.; Emerson, W. S.; Blardinelli, A. J. In *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, 311. See especially note 6 therein. Clearly, catalysis by lanthanide complexes renders this chemistry considerably more practical.

(10) The term "cycloaddition" is used herein solely to describe the outcome of the transformation. No mechanistic inferences should be drawn from such usage.

(11) Ardakani, M. A.; Smalley, R. K.; Smith, R. H. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2501.

(12) Cf. Conard, C. R.; Dolliver, M. A. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, 167.

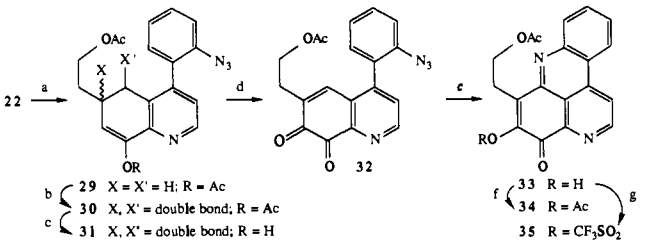


followed by treatment with DDQ. Selective hydrolytic cleavage of the phenolic acetate, a potentially difficult step, occurred remarkably smoothly upon treatment of **30** with aqueous $NaHCO_3$ solution. By contrast, oxidation of **31** to a quinone proved to be quite troublesome. 8-Hydroxyquinolines bearing substituents at position 4 are generally difficult to convert to *p*-quinones,[13] and perhaps as a result of this, a variety of oxidants either produced complex mixtures from **31** (DDQ/acetone/water; CAN/MeCN/water) or did not react at all (O_2/salcomine/DMF) (Scheme IV). Eventually, it was found that Fremy's salt oxidized phenol **31** cleanly to *o*-quinone **32**, mp 174–177 °C, uncontaminated by the desired para isomer. Fremy's salt appears to be uniquely suited for the conversion of heterocyclic phenols to the corresponding quinones, and indeed, the effectiveness of this reagent in cases where other reactants failed to achieve the desired oxidation has been appreciated in other contexts.[14] Conversely, the regioselectivity observed in this oxidation, while not without precedent,[15] dealt a fatal blow to the nucleophilic approach.

The structure of **32** was unequivocally determined by its gated-decoupled ^{13}C NMR spectrum. The ^{13}C resonances of the carbonyl carbons in this molecule appear at 179.4 and 178.5 ppm under broad-band decoupling conditions. In the gated-decoupled mode, the 178.5 ppm resonance remained as a sharp singlet, but the 179.4 ppm signal became a doublet of triplets (J_1 = 11 Hz; $J_2 = J_3$ = 3.8 Hz). The ortho, but not the para, quinoid structure is consistent with the observed spectrum. The splitting pattern may only be explained on the basis of ^3J coupling of the C-7 carbon (quinoline numbering) to the protons on the neighboring side-chain methylene (J = 3.8 Hz) and to the olefinic hydrogen at C-5 (J = 11 Hz). The C-8 carbon experiences only ^4J interactions with those protons ($J \approx 0$ Hz); therefore it appears as a singlet. The para isomer would still show one of the carbonyls as a doublet of triplets, but the other signal would be spiit into a doublet because of ^2J coupling between the C-8 carbon and the C-7 proton.

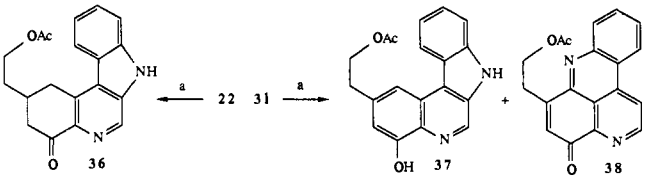
The unfavorable regioselectivity of the Fremy oxidation nevertheless provided a perfectly viable substrate for an investigation of the pericyclic approach. It was pleasing indeed to observe that quinone **32** was converted directly into bright orange quinonimine **33**, mp 204 °C dec, upon refluxing in toluene solution. The precise mechanism of quinonimine formation is not clear, but it is likely that an initial 1,3-dipolar cycloaddition between the azide and the quinone olefin[16] might have formed a triazoline (cf. **26**).

Scheme IV



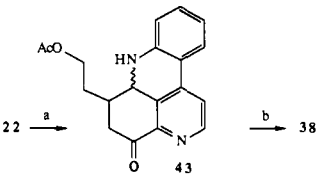
[a] CH_2=C(OAc)CH_3, TfOH, reflux. [b] DDQ, toluene, heat. [c] Aqueous $NaHCO_3$, MeOH, 40% *a–c*. [d] $(KO_3S)_2NO$, phosphate buffer, MeOH, 56%. [e] Toluene, reflux, 80%. [f] Ac_2O, pyridine, 99%. [g] Tf_2O, CH_2Cl_2, Hünig base, 90%.

Scheme V



[a] 1,2-Dichlorobenzene, reflux, 80% for **36**, 86% for **37** (plus a trace of **38**).

Scheme VI



[a] *hν*, Pyrex, PhCl, 110 °C. [b] DDQ, 25 °C, 31% *a–b*.

Subsequent deazoniation and rearrangement would lead to the observed product.[17] Unusual quinone–azide reactions of this type should be useful for the preparation of a variety of complex heterocycles.

Quinonimine **33** possesses the complete ring system of the cystodytins, but relative to the natural products, it incorporates an extra OH group. This functionality was found to be amenable to derivatization to furnish compounds of potential interest in connection with SAR studies. Acetate **34** and triflate **35** are obtained particularly easily. In principle, compound **35** is amenable to Ortar deoxygenation,[18] a reaction that would establish the full cystodytin ring system. Unlike simpler quinoline phenols, triflate **35** proved to be entirely resistant to the Ortar reaction. The molecule was rapidly reduced to a hydroquinone, which, more slowly, would suffer cleavage of the trifluoromethanesulfonyl group. In all cases, workup returned enol **33** in excellent yield. The monotony of this series of frustrating results was finally broken by a key observation made during parallel investigations of the electrophilic chemistry of eq 4, which, in the end, provided a remarkably direct route to the target natural products from ketone **22**.

The (formal) insertion of a nitrene or a nitrenoid into a C–H bond represents a very unusual mode of reactivity. Reports of successful reactions of the desired type are scant.[19] Moreover, controversy exists concerning the mechanistic implications of such processes, particularly with regard to the spin state of the nitrene. Experimentally, the simplest route to an intermediate with nitrenoid reactivity is the thermal activation of an azide.[20] Initial

(13) Oxidation to *p*-quinones appears to be disfavored on steric grounds: (a) Zimmer, H.; Lankin, D. C. *Chem. Rev.* **1971**, *71*, 229. (b) Naruta, Y.; Maruyama, K. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, U. K., 1988; Chapter 8.

(14) Cf. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(15) Deya, P. M.; Dopico, M.; Raso, A. G.; Morey, J.; Saa, J. M. *Tetrahedron* **1987**, *43*, 3523.

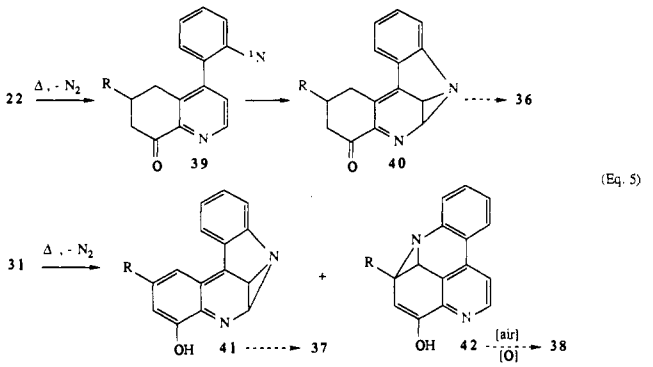
(16) For example, see: Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, Chapter 12.

(17) Reactions of this type are well precedented. For example, see: (a) Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett.* **1990**, *31*, 7531. (b) Bennett, R. B., III; Choi, J. R.; Montgomery, W. D.; Cha, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 2580.

(18) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(19) Cf. McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *Tetrahedron Lett.* **1976**, *17*, 925.

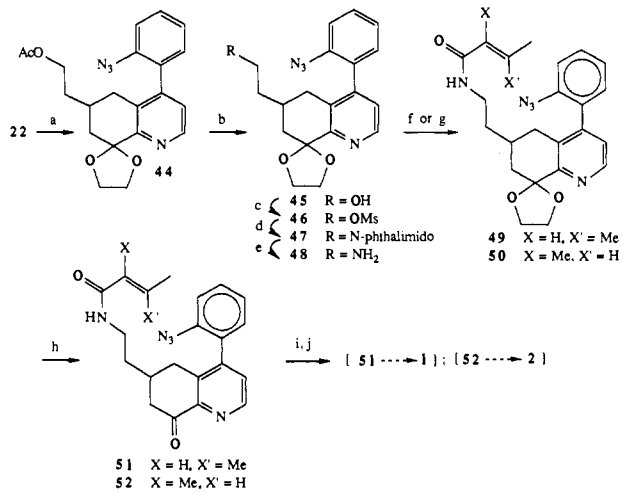
skirmishes with the electrophilic mode of cyclization involved, therefore, thermolysis of **22**. This rather heat-stable material was quantitatively recovered after prolonged refluxing in toluene solution; however, a rapid, clean conversion into carboline **36**, mp 260–265 °C dec, occurred in 80% yield upon refluxing in 1,2-dichlorobenzene. Unfortunately, none of the desired cystodytin-like compound was formed. Likewise, pyrolysis of **31** produced carboline **37** as by far the major product, even though a proton NMR spectrum of a chromatographic fraction obtained during the purification of **37** exhibited signals not inconsistent with structure **38** (Scheme V). Preferential formation of carbolines in the foregoing reactions may be rationalized on the basis of thermolytic formation of a singlet nitrene (eq 5). Cycloaddition



of the latter to a π system and rearrangement of an intermediate aziridine would lead to the observed products.[21] In accord with experimental results, this mechanistic picture predicts that while **22** should form essentially none of the desired tetracyclic system, its congener **31** might produce some, via intermediate **42**. On the other hand, the kinetic preference for 5- vs 6-membered-ring formation would still favor the carboline.

An excellent investigation of nitrene reactivity was reported in 1967 by Meth-Cohn.[22] Results described in that paper suggested that if a *triplet* nitrene were to result from deazoniation of the azide, a cystodytin-like end product might result via hydrogen-atom abstraction by the nitrene from the adjacent "benzylic" methylene, followed by radical pair recombination. This possibility was initially researched using acetate **22**. Triplet-sensitized photolysis of **22** under Meth-Cohn conditions (10% acetophenone in chlorobenzene, 107 °C,[23] Sylvania 250-W sunlamp)[24] *indeed promoted conversion into a mixture of diastereomeric lumiproducts* **43** (Scheme VI). The mixture of tetracycles **43** may be isolated by column chromatography as a sensitive, intensely purple, thick oil. This material becomes slowly air-oxidized to **38**, especially in the presence of silica gel; however, other products are also formed. A much cleaner oxidation may be achieved by treatment of **43** with DDQ immediately after chromatography, but it was found that a substantially more convenient protocol involved titration of the crude photolysis mixture with DDQ at room temperature. The lumiproduct was instantly converted into bright yellow quinonimine **38**, mp 157–160 °C dec, obtained in 31% yield after chromatography. The new procedure bypasses isolation of the sensitive **43** and eliminates the need for one additional chromatographic purification to the

Scheme VII



[a] $(CH_2OH)_2$, $(EtO)_3CH$, cat. CSA, reflux, 90%. [b] K_2CO_3, MeOH, 99%. [c] MsCl, Et_3N, CH_2Cl_2, 100% crude. [d] Potassium phthalimide, DMF, 50 °C, 90%. [e] Hydrazine hydrate, MeOH, 60 °C, 90%. [f] β,β-Dimethylacryloyl chloride, Et_3N, CH_2Cl_2, 70%. [g] Tigloyl chloride, Et_3N, CH_2Cl_2, 77%. [h] 4 N aqueous HCl, THF, 50 °C, 95% for **51**, 94% for **52**. [i] *hν*, Pyrex, PhCl, 110 °C. [j] DDQ, 25 °C, 31% for **1**, 32% for **2**.

advantage of overall efficiency. It was further discovered that photolysis may be carried out even more easily by irradiating a plain chlorobenzene solution of **22** maintained at 110 °C in a Pyrex flask. The pyridyl ketone chromophore present in **22** evidently possesses photochemical properties conducive to intramolecular sensitization; moreover, omission of acetophenone facilitated isolation of the desired product to a considerable extent. Titration of the crude mixture of primary photoproducts with DDQ again furnished **38**, in yields identical with those obtained via the externally sensitized reaction. Since the UV absorptions of the unsaturated amide subunits of compounds such as **51** and **52** do not overlap with the photochemically reactive n–π^* transition of the pyridyl ketone, it was anticipated that photolysis of those substrates would produce cystodytins (Scheme VII).

Ketone **22** was thus advanced to amides **51** and **52** in a conventional fashion. The latter compounds were again obtained as 1:1 mixtures of diastereomeric atropisomers. It was truly delightful to observe that irradiation of **51** in chlorobenzene and workup of the crude reaction mixture with DDQ *provided fully synthetic cystodytin A as yellow crystals*, mp 182–184 °C (lit. mp 181–183 °C),[2] in 30% yield after chromatography. In an analogous fashion, cystodytin B was obtained as yellow crystals, mp 180–182 °C (uncorr; lit. mp 181–183 °C),[2] in 31% chromatographed yield from tiglamide **52**. It is known that (biologically inactive) cystodytin C may be obtained by treatment of **1** with aqueous HCl.[2] The synthesis of cystodytin A amounts, therefore, to a formal synthesis of **3**.

Conclusions

This synthesis of **1** or **2** proceeds in an overall 8% yield from **9** over 11 steps (78% average yield/step). The minor discrepancies between the melting points of synthetic and natural cystodytins are entirely understandable: literature melting points actually refer to an inseparable 3.5:1 mixture of **1** and **2**. Not without some reluctance, such a mixture was prepared from synthetic cystodytins, and its melting point was measured as 180–183 °C (uncorr). It should also be pointed out that, although it was not possible to secure authentic samples of the cystodytins, the spectral data of synthetic materials are in complete agreement with the literature.[2] The availability of **33**, which is a 9-hydroxy congener of **1–3** and now of the natural products themselves, should provide much incentive for further pharmacological evaluation of these substances, since cystodytins are scarce and difficult to obtain from their natural sources. Of course, materials similar to **33**, but possessing side chains such as those found in **1–3**, could be de-

(20) All attempts directed toward generating a nitrenoid by treatment of the azide with $Rh_2(OAc)_4$, under various conditions and by analogy with the chemistry of diazo compounds, met with failure.

(21) For a discussion, see: Smith, P. A. S. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, FL, 1984; Chapter 3. An alternative mechanistic interpretation is offered in ref 22.

(22) Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2194.

(23) Heating is apparently necessary in order to favor hydrogen abstraction by the presumed triplet nitrene: Lindley, J. M.; McRobbie, I. M.; Meth-Cohn, O.; Suschitzsky, H. *Tetrahedron Lett.* **1976**, *17*, 4513. See also ref 22.

(24) In accordance with Meth-Cohn's directions (ref 22), this reaction was carried out by irradiating the solution in a Pyrex apparatus maintained at 107 °C by bathing in vapors evolving from refluxing 1-butanol. Fortunately, a much simpler setup (see the Experimental Section) was later found to be equally effective.

rivatized to furnish cystodytin analogues, which would be otherwise difficult—or even impossible—to prepare from the natural products, since the latter do not lend themselves readily to chemical modification.

From a chemical standpoint, this synthesis demonstrates the usefulness of our pyridine-forming reaction and the value of thermal and photochemical transformations of azides in the construction of complex polycyclic heteroaromatic frameworks. Principles set forth herein will undoubtedly facilitate the preparation of many other members of the family of natural products to which the cystodytins belong. On a final note, it should be recognized that whereas additional research might establish a viable procedure for the deoxygenation of **33**, and thus an alternative route to the natural products, a synthesis of cystodytins via **33** would be at least seven steps longer than the one described herein and probably eleven, including protection/deprotection of two sensitive intermediates. The moderate yields registered in the photochemical reaction are entirely acceptable when viewed in this broader context.

Experimental Section

General Protocols. Melting points were measured on a Fischer-Johns hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz for ^1H and 62.5 MHz for ^{13}C). Unless otherwise indicated, all NMR measurements were carried out at room temperature in $CDCl_3$ solutions. Chemical shifts are reported as parts per million on the δ scale, relative to the resonance of the $CDCl_3$ solvent (7.26 ppm in the ^1H, 77.0 ppm for the central line of the triplet in the ^{13}C modes, respectively). Splitting patterns are described as "s" (singlet); "d", "dd", "ddd", etc (doublet, doublet of doublets, doublet of doublets of doublets, etc); "t" (triplet); "q" (quartet); "m" (multiplet); and further characterized as "app" (apparent), "br" (broad), or "c" (complex), as appropriate. Infrared spectra were obtained from films deposited on NaCl plates by evaporation of an organic solution and were recorded with a Perkin-Elmer 1600 FTIR spectrophotometer. Band positions are reported as reciprocal centimeters (cm^{-1}). Low-resolution mass spectra were obtained on a Finnigan 6000 quadrupole instrument in the direct probe insertion/EI (70 eV) mode. High-resolution mass spectra were obtained on a CEC 21-110 instrument in the EI (70 eV) mode. In either case, signals are reported as *m/e*. Analytical thin-layer chromatography (TLC) was carried out on commercial Merck silica gel 60 plates, 0.25-mm thickness, with fluorescent indicator. Spots were visualized with UV light and fixed by staining with one or more of the following reagents: molybdic acid,[25] anisaldehyde, iodine, and Dragendorf.[26] Preparative TLC was carried out on Merck silica gel 60 plates, 1-mm thickness, with fluorescent indicator. Merck 230–400-mesh silica gel was used for column chromatography. The following solvents were purchased from Mallinckrodt and purified as specified: anhydrous diethyl ether, chloroform, hexanes (used as received), ethyl acetate (distilled at atmospheric pressure), methanol (dried over 4-Å molecular sieves), and benzene, dichloromethane (first passed through alumina, then distilled from CaH_2). Commercial 200-proof ethanol was used as received. Other organic chemicals were obtained from Aldrich and treated as follows: *N,N*-diisopropylethylamine, 1,2-dimethoxyethane (DME), pyridine, toluene, and triethylamine were distilled from CaH_2 at atmospheric pressure; chlorobenzene, 1,2-dichlorobenzene, 1,2-dichloroethane (DCE), and ethyl vinyl ether (EVE) were distilled at atmospheric pressure; methanesulfonyl chloride was vacuum (water aspirator) distilled. All other reagents were used as received. Photolyses and pyrolyses were carried out in solutions that had been thoroughly degassed by bubbling Ar through them for at least 20 minutes and that were kept under Ar atmosphere (balloon) throughout the duration of the experiment. Irradiations were performed with a Sylvania 250-W sunlamp. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

2,6-Dibenzylidenecyclohexanone (10). A solution of 2 g (20.4 mmol) of cyclohexanone and 4.33 g (40.8 mmol) of benzaldehyde in 20 mL of EtOH plus enough water to make the solution slightly cloudy was treated with 5 mL of 20% aqueous NaOH. The solution became warm, and a yellow precipitate formed while stirring for 30 min at room temperature. The solid was filtered, washed well with water, redissolved in CH_2Cl_2, and the new solution passed through a short plug of silica gel. Evaporation yielded 5.09 g (91%) of **10** as a yellow solid, mp 101–102 °C, after one recrystallization from hexanes: R_f (10% EtOAc/hexanes) 0.40; ^1H NMR 7.89 (br s, 2 H), 7.31–7.61 (m, 10 H), 3.55 (app dt, 4 H, $J_1 = J_2 = 6.0$ Hz, $J_3 = 1.9$ Hz), 2.17 (quintet, 2 H, $J = 6.0$ Hz); ^{13}C NMR 190.1, 136.8, 136.0, 135.8, 130.2, 138.5, 128.2, 28.3, 22.8; IR 3054, 2933, 2863, 1667, 1607, 1580, 1574, 1445, 1273, 1164, 1144, 772, 695; MS 274 (M^+, 100), 273, 246, 245, 217, 186, 141, 129, 128, 115; HRMS expected 274.1358, obsd 274.1362.

8-Benzylidene-2-ethoxy-4-phenyl-3,4,5,6,7,8-hexahydro-2*H*-benzopyran (11). A solution of 4.75 g (17.3 mmol) of **10** and 933 mg (0.86 mmol) of $Yb(fod)_3$ in 50 mL of DCE and 20 mL of EVE was refluxed for 2 days (Ar atmosphere). The solvents were evaporated, the residue was dissolved in CH_2Cl_2, and the resulting solution was washed with water. The organic phase was dried (Na_2SO_4) and the solvent was evaporated to give 5.95 g (100% crude yield) of **11** as a fluorescent green oil: R_f (10% EtOAc/hexanes) 0.53; ^1H NMR (major isomer) 7.25–7.01 (m, 10 H), 6.90 (s, 1 H), 4.93 (dd, 1 H, $J_1 = 8.7$, $J_2 = 1.9$ Hz), 3.98 (app dq, 1 H, $J_1 = 9.52$, $J_2 = J_3 = J_4 = 7.1$ Hz), 3.57 (app dq, 1 H, $J_1 = 9.52$, $J_2 = J_3 = J_4 = 7.1$ Hz), 3.41 (br t, 1 H, app $J = 8.3$ Hz, actual $J_1 = 10.1$, $J_2 = 7.4$ Hz), 2.68 (app dt, 1 H, $J_1 = 15.1$, $J_2 = 4.6$ Hz), 2.22 (ddd, 1 H, $J_1 = 13.3$, $J_2 = 7.4$, $J_3 = 1.9$ Hz), 1.91 (ddd, 1 H, $J_1 = 13.3$, $J_2 = 10.1$, $J_3 = 8.7$ Hz), 1.80–1.35 (m, 4 H), 1.17 (t, 3 H, $J = 7.1$ Hz); ^{13}C NMR 144.4, 143.5, 137.9, 132.4, 129.2, 128.3, 128.1, 127.9, 126.3, 126.0, 121.2, 114.5, 99.0, 64.2, 43.9, 38.5, 27.6, 27.2, 22.8, 15.2; IR 3024, 2930, 1630, 1601, 1492, 1443, 1373, 1140, 1071, 972, 704; MS 346 (M^+), 300, 273, 258, 212, 186 (100), 185, 161, 115; HRMS expected 346.1933, obsd 346.1928.

8-Benzylidene-4-phenyl-5,6,7,8-tetrahydroquinoline (12). A mixture of 3.09 g (8.94 mmol) of **11** and 1.55 g (22.46 mmol) of hydroxylamine hydrochloride in 36 mL of CH_3CN was gently refluxed overnight. The solvents were evaporated and the residue was taken up in CH_2Cl_2. The resulting solution was washed with 10% aqueous Na_2CO_3, and then it was passed through a short plug of silica gel. The solvent was evaporated to yield 2.27 g (86%) of **12** as a tan solid: mp 128–130 °C; R_f (80% EtOAc/hexanes) 0.73; ^1H NMR 8.52 (d, 1 H, $J = 4.8$ Hz), 8.04 (s, 1 H), 7.49–7.22 (c m, 10 H), 7.04 (d, 1 H, $J = 4.8$ Hz), 2.92 (dt, 2 H, $J_1 = J_2 = 6.1$ Hz, $J_3 = 1.8$ Hz), 2.73 (t, 2 H, $J = 6.1$ Hz), 1.74 (quintet, $J = 6.1$ Hz); ^{13}C NMR 153.3, 149.7, 146.7, 139.2, 138.0, 135.8, 130.4, 129.7, 128.6, 128.3, 128.0, 127.8, 127.5, 126.7, 122.8, 28.0, 22.9; IR 3050, 2940, 2896, 1575, 1550, 1500, 1460, 1450, 1400, 900, 840, 775, 705; MS 297 (M^+), 296, 280, 209, 208, 115, 84; HRMS expected 297.1517, obsd 297.1516.

4-Phenyl-5,6,7,8-tetrahydroquinolin-8-one (13). Ozone was bubbled for 30 min through a cold (−78 °C) solution of 225 mg (0.76 mmol) of **12** in a mixture of 50 mL of MeOH and 7 mL of CH_2Cl_2. The solution was purged with Ar, and then 2 mL of Me_2S was added. The solution was allowed to warm to room temperature over 2 h, the solvents were removed, and the residue was chromatographed with 80% EtOAc/hexanes to afford 127 mg (75%) of **13** as cream-colored stars: mp 131–132 °C; R_f (80% EtOAc/hexanes) 0.17; ^1H NMR 8.62 (d, 1 H, $J = 4.7$ Hz), 7.43–7.22 (c m, 6 H), 2.84 (t, 2 H, $J = 6.1$ Hz), 2.70 (t, 2 H, $J = 6.0$ Hz), 1.98 (quintet, 2 H, $J = 6.0$ Hz); ^{13}C NMR 196.5, 150.3, 148.2, 138.1, 137.3, 128.3, 128.2, 127.0, 39.2, 27.2, 22.4; IR 3059, 2947, 2862, 1702, 1576, 1337, 1230, 1144, 905, 772, 706; MS 223 (M^+), 222, 194, 168, 167 (100), 166, 140, 139; HRMS expected 223.0997, obsd 223.1006.

8-(Carbethoxymethylene)-1,4-dioxaspiro[4.5]decane (15). Dimethyl carbethoxymethylphosphonate (32.3 g, 0.192 mol, 1.5 equiv) was added via syringe to a cold (0 °C) solution of 21.5 g of KOtBu (0.192 mol, 1.5 equiv) in 350 mL of DME (Ar atmosphere) with good overhead stirring, whereupon a thick white suspension formed. The suspension was warmed to room temperature, and a solution of 20 g (0.128 mol) of **14** in 60 mL of DME was rapidly added with good stirring. The suspension became homogeneous, and then a precipitate formed. The reaction was over instantly (TLC). The DME was evaporated, the residue was dissolved in 200 mL of water and extracted twice with ether, and the combined extracts were dried (Na_2SO_4). Evaporation yielded 27.55 g (95%) of **15** as a clear, colorless liquid of good enough quality to be used for the next step without further purification: R_f (30% EtOAc/hexanes) 0.55; ^1H NMR 5.59 (br s, 1 H), 4.06 (q, 2 H, $J = 7.1$ Hz), 3.9 (s, 4 H), 2.93 (t, 2 H, $J = 6.5$ Hz), 2.3 (t, 2 H, $J = 6.4$ Hz), 1.69 (q, 4 H, $J = 6.4$ Hz), 1.2 (t, 3 H, $J = 7.1$ Hz); ^{13}C NMR 166.4, 160.1, 114.2, 107.8, 64.3, 59.5, 35.6, 34.8, 34.5, 25.9, 14.2; IR 2950, 2880, 1720, 1657, 1450, 1383, 1201, 1175, 1140, 1091, 1043, 950, 910, 870, 700; MS 226 (M^+), 197, 171, 170, 153 (100), 135, 107; HRMS expected 226.1205, obsd 226.1204.

8-(Carbethoxymethyl)-1,4-dioxaspiro[4.5]decane (16). A stainless steel Parr bomb equipped with a stirring bar was charged with a solution of 19.0 g (84.1 mmol) of **15** in 150 mL of absolute EtOH and 4.45 g (4.2 mmol) of 10% Pd/C catalyst and pressurized with H_2 to 2100 psi. The mixture was stirred for 20 min at room temperature, at which time the reaction was finished (TLC). The solution was vacuum-filtered through

(25) Solution of 24 g of $(NH_4)_6Mo_7O_{24}$ and 0.5 g of $Ce(SO_4)_2$ in 500 mL of 10% aqueous H_2SO_4.

(26) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley: New York, 1972; pp 378–379.

Celite, which was further washed with EtOAc. Evaporation yielded 19.1 g (100%) of **16** as a clear, colorless liquid of good enough quality to be used for the next step without further purification: R_f (30% EtOAc/hexanes) 0.50; ^{1}H NMR 4.12 (q, 2 H, J = 7.1 Hz), 3.93 (s, 4 H), 2.21 (br d, 2 H, J = 6.8 Hz), 1.75 (br m, 5 H), 1.56 (br t, 2 H, J = 12.3 Hz), 1.31 (br t, 2 H, J = 12.3 Hz), 1.24 (t, 3 H, J = 7.1 Hz); ^{13}C NMR 173.9, 109.3, 64.6, 60.6, 41.2, 34.5, 33.6, 30.1, 14.4; IR 2940, 2860, 1715, 1441, 1380, 1260, 1140, 1100, 1020, 953; MS 228 (M^+), 183, 141, 140, 99 (100); HRMS expected 228.1361, obsd 228.1364.

8-(2-Hydroxyethyl)-1,4-dioxaspiro[4.5]decane (17). A solution of 21.3 g (93.5 mmol) of **16** in 50 mL of ether was added slowly via syringe to a cold (−20 °C) solution of 5.2 g of LAH (0.137 mmol) in 350 mL of anhydrous diethyl ether (Ar atmosphere). The reaction completed immediately (TLC). The reaction was worked up by sequential addition of 5.2 mL of water (**CAUTION**: strongly exothermic reaction and vigorous evolution of H_2), 5.2 mL of 20% aqueous NaOH solution, and 15.6 mL of water. Stirring was continued for 30 min, during which time a white precipitate formed. The solution was filtered over Celite, and the solids were washed well with EtOAc. Evaporation gave 17.2 g (90%) of **17** as a clear, colorless liquid of good enough quality to be used for the next step without further purification: R_f (40% EtOAc/hexanes) 0.20; ^{1}H NMR 3.90 (s, 4 H), 3.63 (t, 2 H, J = 6.6 Hz), 2.01 (s, 1 H), 1.70 (m, 4 H), 1.46 (m, 5 H), 1.24 (m, 2 H); ^{13}C NMR 108.9, 64.1, 60.6, 38.97, 34.4, 32.7, 30.1; IR 3400, 2929, 2865, 1447, 1375, 1107, 1088, 1005, 940; MS 186 (M^+), 157, 141, 99 (100), 86; HRMS expected 186.1256, obsd 186.1253.

4-(2-Hydroxyethyl)cyclohexanone (18). A solution of 17.2 g (92.5 mmol) of ketal **17** in a mixture of 50 mL of THF, 75 mL of water, and 50 mL of aqueous 4 N HCl was stirred overnight. The THF was evaporated and the aqueous residue was extracted with 50-mL portions of CH_2Cl_2 until TLC showed no evidence of product remaining in the aqueous phase. The combined extracts were dried (Na_2SO_4) and evaporated to give 13.02 g (99%) of **18** as a colorless liquid of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.33; ^{1}H NMR 3.75 (t, 2 H, J = 6.5 Hz), 2.38 (m, 4 H), 2.15–1.85 (m, 3 H), 1.60 (q, 2 H, J = 6.5 Hz), 1.48 (m, 2 H); ^{13}C NMR 214.2, 61.2, 41.3, 38.5, 33.0; IR 3409, 2931, 2860, 1709, 1448, 1421, 1334, 1168, 1055; MS 142 (M^+), 99 (100), 98, 86; HRMS expected 142.0994, obsd 142.0995.

2,6-Bis(2-azidobenzylidene)-4-(2-hydroxyethyl)cyclohexanone (19). A solution of 12.45 g (87.7 mmol) of **18** and 25.78 g (175 mmol) of azidobenzaldehyde in 80 mL of ethanol and enough water (~30 mL) to make the solution slightly cloudy was treated with 15 mL of 20% aqueous NaOH. The solution became warm and opaque. A voluminous yellow precipitate formed during 30 min of stirring at room temperature. The precipitate was filtered, washed well with water, redissolved in 50 mL of CH_2Cl_2, and the new solution was passed through a short plug of silica gel. Evaporation gave 31.0 g (88%) of **19** as yellow crystals of good enough quality to be used for the next step without further purification. A recrystallized (hexane) sample had a melting point of 129–131 °C: R_f (40% EtOAc/hexanes) 0.28; ^{1}H NMR 7.84 (br s, 2 H), 7.42–7.12 (c m, 8 H), 3.58 (t, 2 H, J = 6.5 Hz), 2.94 (dd, 2 H, J_1 = 15.5 Hz, J_2 = 3.5 Hz), 2.46 (ddd, 2 H, J_1 = 15.6 Hz, J_2 = 10.5 Hz, J_3 = 2.4 Hz), 1.93 (c m, 1 H), 1.58 (q, 2 H, J = 6.5 Hz); ^{13}C NMR 189.4, 139.6, 136.1, 132.9, 130.4, 129.8, 127.4, 124.2, 118.5, 60.3, 38.0, 34.2, 30.8; IR 3421,3061, 2927, 2125, 1668, 1606, 1570, 1481, 1446, 1292, 1145, 754; MS 373 (M^+ − N_2), 359, 196, 168, 156, 143 (100), 130, 129, 119; HRMS expected 400.1647, obsd 400.1638. Anal. Calcd for $C_{22}H_{20}N_6O_2$: C, 65.99; H, 5.03. Found: C, 66.27; H, 5.28.

4-(2-Acetoxyethyl)-2,6-bis(2-azidobenzylidene)cyclohexanone (9). Acetic anhydride (23.6 g, 0.231 mol) was added to a solution of 30.9 g (77.2 mmol) of **19** in 80 mL of pyridine, and the mixture was stirred overnight at room temperature (Ar atmosphere). Aqueous H_2SO_4 (350 mL of a 10% solution) was added and the solution was extracted three times with CH_2Cl_2. The combined extracts were sequentially washed with saturated aqueous $NaHCO_3$, 5% aqueous $CuSO_4$, and water, and then passed through a short plug of silica gel. Evaporation yielded 33.8 g (99%) of **9** as a yellow-orange solid of good enough quality to be used for the next step without further purification. A recrystallized sample (hexane) had a melting point of 98.5–100 °C: R_f (40% EtOAc/hexanes) 0.72; ^{1}H NMR 7.78 (br s, 2 H), 7.35–7.05 (c m, 8 H), 3.93 (t, 2 H, J = 6.4 Hz), 2.87 (dd, 2 H, J_1 = 15.5, J_2 = 3.4 Hz), 2.40 (ddd, 2 H, J_1 = 15.7, J_2 = 10.5, J_3 = 2.3 Hz), 1.85–1.65 (c m, 1 H), 1.84 (s, 3 H), 1.58 (q, 2 H, J = 6.6 Hz); ^{13}C NMR 188.9, 170.8, 139.5, 133.0, 130.3, 129.9, 127.3, 124.2, 118.4, 62.2, 34.1, 34.0, 31.5, 20.7; IR 2931, 2124, 1735, 1676, 1594, 1482, 1447, 1288, 1238, 1043, 752; MS 400 (M^+ − 2 N_2), 372, 312, 297, 269, 180, 168, 130 (100), 129; HRMS, 442.1753, obsd 442.1760.

6-(2-Acetoxyethyl)-8-(2-azidobenzylidene)-4-(2-azidophenyl)-2-ethoxy-3,4,5,6,7,8-hexahydro-2*H*-benzopyran (20). A solution of 4.32 g (9.77 mmol) of **19** and 517 mg (5 mol %) of Yb(fod)$_3$ in 20 mL of DCE and 20 mL of EVE was refluxed gently for 24 h (Ar atmosphere). The solvents were evaporated, and the residue was dissolved in 30 mL of CH_2Cl_2 and washed once with water. The organic layer was dried (Na_2SO_4) and evaporated to give 5.0 g (99%) of **20** as a thick brown oil, a 1:1 mixture of two isomers. This crude material was used directly for the pyridine-forming reaction; R_f (20% EtOAc/hexanes) 0.48. The molecule contains 30 protons, but the ^{1}H NMR spectrum is reported as a total of 60 protons because of the 1:1 mixture of two isomers: 7.32–7.03 (c m, 16 H), 6.97 (br s, 1 H), 6.95 (br s, 1 H), 5.13 (dd, 1 H, J_1 = 5.2, J_2 = 2.4 Hz), 5.09 (dd, 1 H, J_1 = 8.4, J_2 = 1.9 Hz), 4.16–3.90 (c m, 7 H), 3.79–3.59 (c m, 3 H), 2.76 (br s, 1 H), 2.70 (br s, 1 H), 2.35–2.25 (c m, 3 H), 2.22–1.47 (c m, 13 H), 2.01 (s, 3 H), 2.00 (s, 3 H), 1.29 (t, 3 H, J = 7.0 Hz), 1.20 (t, 3 H, J = 7.0 Hz); ^{13}C NMR 170.6, 144.8, 144.3, 138.2, 137.9, 134.5, 134.1, 133.0, 132.4, 130.6, 130.0, 129.6, 129.5, 127.9, 127.8, 127.6, 124.9, 124.5, 124.2, 118.3, 117.9, 117.6, 117.2, 113.2, 112.3, 99.1, 98.1, 64.5, 64.0, 62.7, 62.5, 36.8, 35.1, 34.5, 34.1, 33.6, 33.3, 31.6, 31.1, 21.0, 15.3; IR 3050, 2931, 2123, 1738, 1635, 1580, 1484, 1448, 1286, 1240, 1141, 1046, 910, 753, 733; MS 487 [(M + 1)$^+$ − N_2], 413, 399, 269, 256, 168, 158, 130 (100); HRMS expected 514.2328, obsd 514.2327.

6-(2-Acetoxyethyl)-8-(2-azidobenzylidene)-4-(2-azidophenyl)-5,6,7,8-tetrahydroquinoline (21). A mixture of 5.0 g (9.77 mmol) of crude cycloadduct **20**, 2.5 g (36 mmol) of hydroxylamine hydrochloride, and 42 mL of CH_3CN was refluxed overnight, during which time the color of the solution changed from a deep orange to a dark brown. The solvents were evaporated, the residue was dissolved in CH_2Cl_2, the solution was washed with saturated aqueous $NaHCO_3$, and the organic layer was passed through a short plug of silica gel. Evaporation gave 2.51 g (56%) of **21** as a thick oil, a 1:1 mixture of atropisomers. This material was of good enough quality to be used for the next step without further purification: R_f (50% EtOAc/hexanes) 0.29; ^{1}H NMR 8.47 (d, 1 H, J = 4.8 Hz), 7.95 (br s, 1 H), 7.39 (dt, 1 H, app J_1 = J_2 = 7.42, J_3 = 0.5 Hz), 7.30–7.05 (c m, 7 H), 6.90 (d, 0.5 H, J = 4.8 Hz) and 6.88 (d, 0.5 H, J = 4.8 Hz), 3.92 (t, 2 H, J = 6.6 Hz), 2.89 (dt, 1 H, J_1 = 14.9, J_2 = J_3 = 1.5 Hz), 2.64–2.14 (c m, 4 H), 1.82 (s) and 1.81 (s) (3 H total), 1.55 (m, 2 H); ^{13}C NMR 171.0, 152.1, 146.9, 146.7, 139.0, 137.5, 136.0, 130.5, 130.3, 130.0, 129.6, 128.3, 125.0, 124.8, 124.2, 123.8, 123.6, 118.4, 118.3, 118.3, 62.4, 34.2, 34.0, 33.8, 33.6, 33.3, 33.1, 31.0, 30.9, 20.8; IR 3056, 2926, 2124, 1738, 1600, 1575, 1493, 1443, 1291, 1240, 1046, 910, 754, 732; MS 438 [(M + 1)$^+$ − N_2], 410, 409, 219, 205, 130, 43 (100); HRMS expected 465.1913, obsd 465.1913.

6-(2-Acetoxyethyl)-4-(2-azidophenyl)-5,6,7,8-tetrahydroquinolin-8-one (22). Ozone was bubbled for 1.25 h through a cold (−78 °C) solution of 8.4 g (18.06 mmol) of **21** in 150 mL of dry methanol. The solution was then purged with Ar, 5 mL of dimethyl sulfide was added, and the solution was warmed to room temperature over a period of 1.5 h. The solvent was evaporated, the residue was dissolved in a small volume of CH_2Cl_2 and applied to a column of silica gel, and azidobenzaldehyde was eluted with CH_2Cl_2. Further elution with EtOAc afforded 4.87 g (77%) of **22** as a thick oil, a 1:1 mixture of atropisomers: R_f (100% EtOAc) 0.55; ^{1}H NMR 8.67 (d, 1 H, J = 4.7 Hz), 7.46 (br t, 1 H, J = 7.29 Hz), 7.26–7.08 (c m, 4 H), 4.01 (t, 2 H, J = 6.3 Hz), 2.94–2.15 (c m, 5 H), 1.89 (s) and 1.88 (s) (3 H total), 1.74–1.62 (m, 2 H); ^{13}C NMR 195.8, 170.8, 148.5, 148.3, 147.8, 147.6, 138.5, 138.2, 137.8, 137.3, 130.2, 130.2, 129.1, 128.9, 128.2, 127.9, 125.1, 125.0, 118.6, 118.3, 61.7, 45.2, 34.0, 33.9, 32.8, 32.6, 31.7, 20.7; IR 3056, 2955, 2126, 1733, 1700, 1601, 1579, 1493, 1441, 1366, 1293, 1238, 1036, 758, 730; MS 350 (M^+), 322, 270, 262, 235, 207, 206, 180, 179, 43 (100); HRMS expected 350.1379, obsd 350.1380. Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18. Found: C, 64.85; H, 5.24.

6-(2-Acetoxyethyl)-4-(2-azidophenyl)-8-hydroxyquinoline (31). Trifluoromethanesulfonic acid (12 drops) was added to a solution of 4.12 g (11.77 mmol) of ketone **22** in 50 mL of isopropenyl acetate. The flask was fitted with a Vigreaux column and the solution was refluxed to distill off the acetone that was produced. After 12 h the solvents were evaporated to give 4.12 g (89% crude yield) of **29** as a black oil. Without further purification, this crude material was dissolved in 80 mL of toluene and treated with 2.67 g (10.5 mmol) of DDQ. The solution immediately turned cherry red. After refluxing for 30 min, the color changed to brown and the reaction was finished. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and applied to a dry column of silica gel. Elution with 50% EtOAc/hexanes afforded 2.93 g (71% crude yield) of **30** as a light brown oil, which was immediately dissolved in 70 mL of MeOH and treated with 50 mL of saturated aqueous $NaHCO_3$. After the solution was stirred overnight, the MeOH was evaporated and the aqueous solution was neutralized to pH 7 by addition of saturated aqueous NH_4Cl solution. The product was extracted with EtOAc, and the extracts were passed through a short plug of silica gel. The solvent was evaporated to yield 1.61 g (40% overall yield from **22**) of **31** as a

cream-colored foam: R_f (70% EtOAc/hexanes) 0.38 (streaky); ^{1}H NMR 8.78 (d, 1 H, J = 4.4 Hz), 7.56 (m, 1 H), 7.25–7.37 (c m, 4 H), 7.09 (d, 1 H, J = 1.7 Hz), 6.83 (d, 1 H, J = 1.7 Hz), 4.28 (t, 2 H, J = 6.9 Hz), 2.98 (t, 2 H, J = 6.9 Hz), 2.02 (s, 3 H); IR 2122, 1744, 1501, 1235; MS 348 (M^+), 260 (100), 259, 247, 233, 218, 205, 43; HRMS expected 348.122, obsd 348.1224.

6-(2-Acetoxyethyl)-4-(2-azidophenyl)-7,8-dihydroquinoline-7,8-dione (32). A solution of 5.12 g (19.1 mmol) of potassium nitrosodisulfonate (Fremy's salt) in 275 mL of 0.5 M KH_2PO_4 buffer was added to a well-stirred solution of 1.10 g (2.86 mmol) of **31** in 260 mL of MeOH and the resulting mixture was stirred at room temperature for 3.5 h. The solvents were evaporated, and the residue was diluted with 300 mL of water and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO) and the solvent was evaporated to yield 579 mg (56%) of **32** as an orange-yellow solid: mp 174–177 °C; R_f (70% EtOAc/hexanes) 0.42; ^1H NMR 8.79 (d, 1 H, J = 5.7 Hz), 7.59 (br t, 1 H, J = 7.5 Hz), 7.40–7.21 (br m, 3 H), 7.03 (s, 1 H), 4.18 (q, 2 H, J = 7.2 Hz), 2.73 (t, 2 H, J = 7.2 Hz), 1.92 (s, 3 H); ^{13}C NMR 179.4, 178.5, 170.6, 150.4, 146.7, 146.2, 138.0, 137.8, 137.4, 131.2, 130.8, 130.6, 130.0, 126.8, 125.4, 118.8, 62.2, 29.0, 21.4, 20.7; IR 2921, 2843, 2134, 1735, 1584, 1238, 1045, 758; MS 364 (M^+ + 2), 293, 276, 275 (100), 263, 221, 205, 180, 179, 43; HRMS expected 362.1015, obsd 362.1013.

Hydroxyquinonimine 33. A degassed solution of 578 mg (1.60 mmol) of **32** in 250 mL of toluene was refluxed for 10 h. Upon cooling, a fine orange precipitate formed. The solvent was evaporated to give 426 mg (80%) of **33** as an orange solid: mp 204 °C dec; R_f (80% EtOAc/hexanes) 0.12; ^{1}H NMR 9.23 (d, 1 H, J = 5.5 Hz), 8.59 (d, 1 H, J = 5.5 Hz), 8.52 (br d, 1 H, J = 7.2 Hz), 8.24 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 0.9 Hz), 7.88 (dt, 1 H, J_1 = J_2 = 7.8 Hz, J_3 = 1.4 Hz), 4.53 (t, 2 H, J = 6.6 Hz), 3.50 (t, 2 H, J = 6.6 Hz), 2.00 (s, 3 H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) 178.8, 170.4, 151.7, 150.4, 149.1, 145.4, 144.9, 136.3, 130.9, 130.4, 127.9, 123.1, 122.4, 120.2, 119.7, 62.2, 23.0, 20.4; IR 3265, 2923, 2852, 1733, 1646, 1380, 1229, 1111, 775, 733; MS 336 (M^+ + 2), 334 (M^+), 292, 276, 275 (100), 274, 264, 233, 218, 205; HRMS expected 334.0953, obsd 334.0955.

Acetate Derivative 34. A solution of 21.0 mg (0.063 mmol) of **33** and 19.3 mg (0.189 mmol) of acetic anhydride in 1.5 mL of pyridine was stirred for 3 h at room temperature (Ar atmosphere). The volatiles were removed under high vacuum to yield 23 mg (99%) of **34** as a bright yellow solid: mp 150–154 °C; R_f (100% EtOAc) 0.24; ^{1}H NMR 9.26 (d, 1 H, J = 5.5 Hz), 8.57 (m, 2 H), 8.28 (br d, 1 H, J = 8.0 Hz), 7.92 (br t, 1 H, J = 8.0 Hz), 7.83 (br t, 1 H, J = 7.3 Hz), 4.52 (t, 2 H, J = 6.5 Hz), 3.46 (t, 2 H, J = 6.5 Hz), 2.48 (s, 3 H), 2.02 (s, 3 H); ^{13}C NMR 176.4, 171.1, 166.2, 150.1, 149.0, 148.6, 146.1, 145.5, 138.6, 137.0, 131.8, 129.8, 122.6, 121.4, 119.6, 117.2, 63.0, 42.9, 25.0, 21.0, 20.5; IR 2925, 2853, 1777, 1738, 1666, 1377, 1237, 1184, 1104, 1044, 766; MS 378 (M^+ + 2), 336, 334, 292, 275 (100), 274, 264, 233, 218, 42; HRMS expected 376.1059, obsd 376.1066.

Triflate Derivative 35. To a cold (0 °C) solution of 62.2 mg (0.186 mmol) of **33** and 33.7 mg (0.26 mmol) of *N,N*-diisopropylethylamine in 8 mL of CH_2Cl_2 was added 63.0 mg (0.22 mmol) of triflic anhydride (Ar atmosphere). After 10 min, the solution was warmed to room temperature, the solvent was evaporated, and the green-brown residue was chromatographed (70% EtOAc/hexanes) to give 78 mg (90%) of **35** as a bright yellow solid: mp 145–155 °C dec; R_f (100% EtOAc) 0.74; ^{1}H NMR 9.33 (d, 1 H, J = 5.5 Hz), 8.67 (d, 1 H, J = 5.5 Hz), 8.64 (dd, 1 H, J_1 = 10.1 Hz, J_2 = 1.3 Hz), 8.34 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 8.02–7.87 (m, 2 H), 4.62 (t, 2 H, J = 6.1 Hz), 3.63 (t, 2 H, J = 6.1 Hz), 2.02 (s, 3 H); ^{13}C NMR 175.2, 170.8, 150.4, 148.1, 147.3, 145.2, 141.6, 137.1, 132.0, 130.6, 128.5, 122.8, 121.5, 120.1, 118.7 (q, J_{CF} = 260.4 Hz), 117.9, 62.5, 25.5, 20.5; IR 1745, 1670, 1422, 1219, 1137, 1094, 1036, 973; MS 424 ($M^+ - CH_2{=}C{=}O$), 334, 291 (100), 275, 264, 263, 233, 218; HRMS expected 466.0446, obsd 466.0446.

Carboline 36. A degassed solution of 40.6 mg (0.116 mmol) of **22** in 15 mL of *o*-dichlorobenzene was refluxed for 1.5 h. The cooled reaction mixture was applied to a short column of silica gel, and the solvent was removed by eluting with hexane. Subsequent elution with 50% MeOH/$CHCl_3$ afforded 30.0 mg (80%) of the very polar carboline **36**: mp 260–265 °C dec; R_f (5% MeOH/$CHCl_3$) 0.10 (streaky); ^{1}H NMR 12.10 (br s, 1 H (NH)), 9.18 (s, 1 H), 8.17 (d, 1 H, J = 8.2 Hz), 7.94 (d, 1 H, J = 8.2 Hz), 7.61 (t, 1 H, J = 7.1 Hz), 7.32 (t, 1 H, J = 7.1 Hz), 4.30 (m, 2 H), 3.47 (br d, 1 H, J = 14 Hz), 2.97 (br d, 1 H, J = 14 Hz), 2.79–2.40 (m, 3 H), 2.10 (s, 3 H), 1.90 (m, 2 H); IR 3192, 2935, 1742, 1682, 1562, 1346, 1264, 1035, 740; MS 322 (M^+), 235 (100), 206, 180, 179; HRMS expected 322.1317, obsd 322.1313.

Carboline 37. A degassed solution of 26.2 mg (0.075 mmol) of **31** in 4 mL of *o*-dichlorobenzene was refluxed for 30 min. The cooled reaction mixture was applied to a short plug of silica gel and the reaction solvent was eluted with hexane. Elution with 10% MeOH/$CHCl_3$ provided 21.7 mg (86%) of **38**: R_f (50% EtOAc/hexanes) 0.09; ^{1}H NMR 10.47 (br s, 1 H, (NH)), 8.88 (s, 1 H), 8.35 (d, 1 H, J = 8.1 Hz), 7.80 (s, 1 H), 7.49 (d, 1 H, J = 8.1 Hz), 7.37 (t, 1 H, J = 7.2 Hz), 7.19 (t, 1 H, J = 7.2 Hz), 6.82 (s, 1 H), 4.27 (t, 2 H, J = 7.0 Hz), 3.02 (t, 2 H, J = 7.0 Hz), 1.86 (s, 3 H); ^{13}C NMR 170.1, 152.7, 141.1, 139.2, 138.1, 134.9, 133.4, 131.1, 128.6, 126.5, 124.5, 122.7, 120.2, 113.1, 111.9, 107.7, 64.2, 36.5, 21.7; IR 3336, 2939, 2841, 1738, 1501, 1398, 1241, 1057, 1033, 741; MS 310 (M^+), 277, 260 (100), 219; HRMS expected 320.1161, obsd 320.1156.

Quinonimine 38. A degassed chlorobenzene (15 mL) solution of 70 mg (0.2 mmol) of **22** in an ordinary Pyrex flask was warmed to 110 °C in a sand bath. The solution was irradiated until the starting material had been completely converted (TLC) to a major purple spot, R_f 0.10 (5% MeOH/$CHCl_3$). Irradiation was stopped and the solution was cooled to room temperature. DDQ was added to the crude reaction mixture in portions until the purple spot was completely converted (TLC) into a new product, R_f (5% MeOH/$CHCl_3$) 0.43. The solvent was evaporated and the residue was chromatographed by preparative TLC (5% MeOH/$CHCl_3$) to afford 19.0 mg (31%) of **38** as bright yellow crystals: mp 157–159 °C; ^{1}H NMR 9.24 (d, 1 H, J = 5.5 Hz), 8.59 (dd, 1 H, J_1 = 6.6 Hz, J_2 = 1.2 Hz), 8.58 (d, 1 H, J = 5.5 Hz), 8.29 (dd, 1 H, J_1 = 8.2 Hz, J_2 = 1.2 Hz), 7.93 (dt, 1 H, J_1 = J_2 = 7.2 Hz, J_3 = 1.5 Hz), 7.83 (dt, 1 H, J_1 = J_2 = 7.4 Hz, J_3 = 1.4 Hz), 6.97 (s, 1 H), 4.57 (t, 2 H, J = 6.3 Hz), 3.44 (t, 2 H, J = 6.3 Hz), 2.02 (s, 3 H); IR 1737, 1660, 1588, 1324, 1234, 1040, 861, 771; MS 276 ($M^+ - CH_2{=}C{=}O$), 259, 247, 217 (100), 216, 164, 115; HRMS expected 318.1004, obsd 318.1000.

6-(2-Acetoxyethyl)-4-(2-azidophenyl)-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (44). A mixture of 450 mg (1.29 mmol) of **22**, ethylene glycol (10 mL), triethyl orthoformate (1 mL), and 50 mg of camphorsulfonic acid was heated at 60 °C for 3 days (Ar atmosphere). The solution was diluted with 50 mL of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined extracts were washed once with water, dried (Na_2SO_4), and evaporated to give 456 mg (90%) of **44** as a tan solid, mp 102–103 °C, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.57; ^{1}H NMR 8.53 (d, 1 H, J = 4.8 Hz), 7.44 (m, 1 H), 7.28–7.03 (c m, 3 H), 6.98 (d, J = 4.8 Hz) and 6.97 (d, J = 4.8 Hz) (1 H total), 4.67–4.55 (c m, 1 H), 4.43–4.32 (c m, 1 H), 4.27–4.17 (c m, 1 H), 4.12–4.02 (c m, 3 H); ^{13}C NMR 171.0, 156.2, 155.8, 147.4, 147.3, 146.5, 146.2, 137.7, 137.3, 130.8, 130.6, 130.4, 130.2, 130.1, 129.7, 125.0, 124.8, 124.5, 124.3, 118.6, 118.3, 106.3, 106.2, 66.9, 66.8, 65.3, 65.2, 62.2, 62.1, 41.1, 34.7, 33.3, 32.7, 29.5, 20.9; IR 2956, 2894, 2125, 1737, 1577, 1495, 1442, 1292, 1239, 1083, 1051, 950, 758, 734; MS 395 (M^+ + 1), 394 (M^+), 351 (100), 323, 263, 235, 179, 125; HRMS expected 394.1641, obsd 394.1643.

4-(2-Azidophenyl)-6-(2-hydroxyethyl)-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (45). A mixture of 450 mg (1.14 mmol) of **44** and 50 mg of solid K_2CO_3 in 4 mL of dry methanol was stirred for 1.5 h at room temperature. The solvent was evaporated, and the residue was taken up with 10 mL of water and extracted twice with methylene chloride. Evaporation of the combined extracts gave 397 mg (99%) of **45** as a thick oil, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.23; ^{1}H NMR 8.53 (d, 1 H, J = 4.8 Hz), 7.45 (m, 1 H), 7.29–7.05 (c m, 3 H), 6.99 (d, J = 4.8 Hz) and 6.98 (d, J = 4.8 Hz) (1 H total), 4.68–4.57 (c m, 1 H), 4.44–4.32 (c m, 1 H), 4.28–4.04 (c m, 2 H), 3.70–3.62 (c m, 2 H), 2.60–1.80 (c m, 5 H), 1.75–1.55 (c m, 2 H); ^{13}C NMR 156.1, 155.8, 147.2, 147.1, 146.5, 146.1, 137.7, 137.2, 131.0, 130.7, 130.6, 130.3, 130.1, 129.6, 124.9, 124.7, 124.5, 124.2, 118.5, 118.3, 106.4, 66.9, 65.2, 60.2, 60.1, 41.0, 38.8, 38.7, 33.7, 32.9, 29.0, 28.9; IR 3386, 3055, 2927, 2124, 1577, 1495, 1443, 1291, 1182, 1084, 950, 736; MS 353 (M^+ + 1), 352 (M^+), 324, 309 (100), 281, 235, 207, 179; HRMS expected 352.1535, obsd 352.1537.

4-(2-Azidophenyl)-6-[2-[(methylsulfonyl)oxy]ethyl]-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (46). A cold (0 °C) solution of 1.34 g (3.80 mmol) of **45** and 500 mg (4.96 mmol) of triethylamine in 15 mL of CH_2Cl_2 was treated with 524 mg (4.58 mmol) of methanesulfonyl chloride (Ar atmosphere). The reaction completed immediately (TLC). The reaction mixture was added to 100 mL of $^1/_2$ saturated brine and extracted twice with CH_2Cl_2. The combined extracts were washed once with brine, once with water, dried (Na_2SO_4), and evaporated to give 1.63 g (100%) of **46** as a thick tan oil, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.54; ^{1}H NMR 8.56 (d, 1 H, J = 4.8 Hz), 7.47 (m, 1 H), 7.30–7.05 (c m, 3 H), 7.01 (d, J = 4.8 Hz) and 7.00 (d, J = 4.8 Hz) (1 H total), 4.68–4.58 (c m, 1 H), 4.44–4.33 (c m, 1 H), 4.29–4.18 (c m, 3 H), 4.15–4.05 (c m, 1 H), 2.95 (s) and 2.93 (s) (3 H total), 2.66–1.77 (c m, 7 H); ^{13}C NMR 156.0, 155.7, 147.5, 147.4, 146.5, 146.3, 137.7, 137.3, 130.4, 130.2, 130.0, 129.7, 125.0, 124.8, 124.5, 124.3, 118.6, 118.3, 106.1, 67.3, 67.1, 66.9, 66.8, 65.3, 40.7, 37.3, 34.8, 33.1,

32.5, 29.0, 28.9; IR 3404, 3056, 2939, 2896, 2126, 1577, 1495, 1443, 1352, 1292, 1175, 1051, 951, 735; MS 431 ($M^+ + 1$), 430 (M^+), 387, 263 (100), 125; HRMS expected 430.1131, obsd 430.1314.

Phthalimido Derivative 47. A solution of 1.64 g (3.8 mmol) of **46** and 809 mg (4.37 mmol) of potassium phthalimide in 10 mL of DMF was heated at 50 °C for 18 h (Ar atmosphere). The reaction mixture was diluted with 75 mL of 10% aqueous Na_2CO_3 and extracted with EtOAc. The combined extracts were washed once with 10% Na_2CO_3, twice with water, and once with brine, dried over Na_2SO_4, and evaporated to give 1.65 g (90%) of **47** as a cream yellow solid, mp 180–181 °C, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (80% EtOAc/hexanes) 0.52; ^{1}H NMR 8.55 (d, 1 H, J = 4.8 Hz), 7.81 (c m, 2 H), 7.70 (c m, 2 H), 7.46 (br t, 1 H, J = 7.6 Hz), 7.05–7.32 (c m, 3 H), 6.99 (br d, 1 H, J = 4.8 Hz), 4.55–4.65 (c m, 1 H), 4.20–4.40 (c m, 2 H), 4.11 (br q, 1 H, J = 6.0 Hz), 3.71 (br t, 2 H, J = 6.8 Hz), 1.68–2.75 (c m, 7 H); ^{13}C NMR 168.2, 155.9, 155.7, 147.4, 147.3, 146.5, 146.4, 137.6, 137.4, 133.8, 132.0, 130.9, 130.6, 130.4, 130.2, 130.1, 129.6, 124.9, 124.7, 124.4, 124.3, 123.1, 118.5, 118.3, 106.3, 106.2, 66.9, 66.8, 65.2, 65.2, 40.7, 40.5, 35.4, 34.3, 32.9, 32.5, 29.6, 29.4; IR 2943, 2360, 2124, 1709, 1575, 1495, 1397, 1291, 1176, 1082, 720; MS 453 (M^+), 439, 438, 411, 410 (100), 235, 207, 179, 160, 125; HRMS expected 481.1750, obsd 481.1748.

4-(2-Azidophenyl)-6-(2-aminoethyl)-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (48). A solution of 1.60 g (3.33 mmol) of **47** and 400 mg (8 mmol) of hydrazine hydrate in 13 mL of MeOH was warmed to 45 °Cf for 3 h. The cooled solution was evaporated and the residue was dissolved in 20 mL of $CHCl_3$, and then the new solution was washed once with 10% aqueous NaOH, dried (Na_2SO_4), and evaporated to yield 1.05 g (90%) of **51** as a thick tan oil, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) base line; ^{1}H NMR 8.51 (d, 1 H, J = 4.8 Hz), 7.43 (br t, app J = 7.4 Hz) and 7.42 (br t, app J = 7.4 Hz) (1 H total), 7.22–7.15 (m, 2 H), 7.06 (br t, app J = 7.5 Hz) and 7.05 (br t, app J = 7.5 Hz) (1 H total), 6.96 (d, J = 4.8 Hz) and 6.95 (d, J = 4.8 Hz) (1 H total), 4.64–4.55 (m, 1 H), 4.40–4.30 (m, 1 H), 4.24–4.15 (m, 1 H), 4.11–4.02 (m, 1 H), 2.73–2.60 (m, 2 H), 2.53–2.20 (m, 1 H), 2.15–2.01 (m, 2 H), 2.00–1.70 (m, 1 H), 1.65–1.35 (m, 3 H); ^{13}C NMR 156.3, 155.9, 147.2, 147.1, 146.4, 146.0, 137.7, 137.1, 131.1, 130.7, 130.6, 130.3, 130.1, 129.6, 124.9, 124.7, 124.4, 124.2, 118.5, 118.3, 106.4, 66.8, 65.2, 41.1, 40.0, 39.3, 33.6, 32.9, 29.8, 29.7; IR 3365, 3055, 2923, 2124, 1601, 1577, 1494, 1442, 1291, 1183, 1083, 1050, 950, 757, 731; MS 351 (M^+), 308, 290 (100), 264, 263, 262, 235, 207, 179; HRMS expected 351.1695, obsd 351.1690.

4-(2-Azidophenyl)-6-(2-(3-methylbut-2-enoylamino)ethyl)-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (49). A solution of 570 mg (5.7 mmol) of 3,3-dimethylacryloyl chloride in 1.5 mL of THF was added to a cold (0 °C) solution of 584 mg (1.66 mmol) of **48** and 748 mg (7.41 mmol) of triethylamine in 10 mL of THF (Ar atmosphere). The reaction mixture was warmed to room temperature, the solvent was evaporated, and the residue was dissolved in $CHCl_3$. This solution was washed once with 10% aqueous Na_2CO_3, once with water, once with brine, dried (Na_2SO_4), and evaporated to give 503 mg (70%) of **49** as a tan oil, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.29; ^{1}H NMR 8.48 (d, 1 H, J = 4.8 Hz), 7.39 (br t, 1 H, J = 7 Hz), 7.23–6.96 (c m, 3 H), 6.92 (d, J = 4.8 Hz) and 6.93 (d, J = 4.8 Hz) (1 H total), 5.41 (br s, 1 H), 5.29 (br s, 1 H (NH)), 4.60–3.98 (c m, 4 H), 3.22 (br m, 2 H), 2.50–2.00 (c m, 4 H), 2.05 (s, 3 H), 1.89–1.71 (br m, 1 H), 1.74 (s, 3 H), 1.49 (br m, 2 H); ^{13}C NMR 166.9, 150.8, 147.4, 147.3, 130.9, 130.5, 130.2, 130.1, 129.7, 124.8, 124.6, 124.3, 123.3, 118.6, 118.3, 106.4, 66.9, 65.2, 40.9, 36.7, 36.6, 35.8, 35.7, 33.4, 32.8, 30.0, 27.1, 19.7; IR 3303, 3055, 2936, 2124, 1669, 1636, 1540, 1442, 1291, 1181, 1083, 1050, 757, 731; MS 390 (M^+ – 43), 279, 262, 235, 217, 179, 125, 83 (100); HRMS expected 433.2114, obsd 433.2118.

4-(2-Azidophenyl)-6-[2-((*E*)-2-methylbut-2-enoylamino)ethyl]-5,6,7,8-tetrahydroquinolin-8-one, Ethylene Ketal (50). A procedure identical with the one above furnished 553 mg (77%) of **50** as a tan oil from 584 mg (1.66 mmol) of **48** and 570 mg (5.7 mmol) of tigloyl chloride, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (70% EtOAc/hexanes) 0.30; ^{1}H NMR 8.55 (d, 1 H, J = 4.8 Hz), 7.46 (m, 1 H), 7.29–7.02 (c m, 3 H), 7.00 (d, J = 4.8 Hz) and 6.99 (d, J = 4.8 Hz) (1 H total), 6.38 (br q, 1 H, J = 6.9 Hz), 5.70 (br s, 1 H (NH)), 4.68–4.05 (c m, 4 H), 3.32 (br m, 2 H), 2.51–2.00 (c m, 4 H), 2.05 (d, 3 H, J = 0.9 Hz), 1.87–1.68 (br m, 1 H), 1.74 (d, 3 H, J = 6.9 Hz), 1.52 (br m, 2 H); ^{13}C NMR 169.3, 156.2, 155.8, 147.4, 147.3, 146.5, 146.2, 137.7, 137.2, 131.7, 130.8, 130.5, 130.4, 130.2, 130.1, 129.7, 128.3, 128.2, 125.0, 124.8, 124.5, 124.3, 118.6, 118.3, 106.4, 66.9, 65.2, 40.8, 37.2, 37.1, 35.6, 35.5, 33.4, 32.8, 30.0, 13.8, 12.3; IR 3341, 3060, 2922, 2124, 1662, 1617, 1533, 1442, 1291, 1182, 1083, 1050, 912, 756, 732; MS 433 (M^+), 404, 390, 279, 262, 235, 217, 179, 83 (100); HRMS expected 433.2114, obsd 433.2118.

4-(2-Azidophenyl)-6-[2-[(3-methylbut-2-enoyl)amino]ethyl]-5,6,7,8-tetrahydroquinolin-8-one (51). A solution of 500 mg (1.15 mmol) of **49** in 5 mL of THF and 1 mL of 2 N aqueous HCl was heated to 60 °C for 24 h. The reaction mixture was neutralized with 10% aqueous $NaHCO_3$ and extracted twice with $CHCl_3$. The combined extracts were dried (Na_2SO_4) and evaporated to give 426 mg (95%) of **51** as pale yellow crystals, mp 154–156 °C, a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (100% EtOAc) 0.32; ^{1}H NMR 8.72 (d, 1 H, J = 4.65 Hz), 7.52 (br t, 1 H, app J = 7.7 Hz), 7.34–7.21 (m, 3 H), 7.17 (br t, 1 H, app J = 7.7 Hz), 5.80–5.60 (m, 1 H), 5.50 (br s, 1 H), 3.38–3.20 (m, 2 H), 3.01–2.18 (c m, 5 H), 2.12 (br s, 3 H), 1.80 (br s, 3 H), 1.79–1.50 (m, 2 H); ^{13}C NMR 196.4, 196.3, 167.0, 150.7, 148.2, 148.1, 147.7, 147.4, 138.5, 138.0, 137.7, 137.2, 130.2, 129.0, 128.7, 128.2, 127.9, 125.1, 124.9, 118.6, 118.3, 118.2, 45.0, 36.3, 35.2, 34.9, 33.0, 32.7, 32.0, 27.0, 19.5; IR 3311, 3060, 2933, 2126, 1701, 1668, 1635, 1540, 1442, 1293, 757, 731; MS 390 (M^+ + 1), 389 (M^+), 360, 280, 261, 247, 235 (100); HRMS expected 389.1851, obsd 389.1849. Anal. Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95. Found: C, 68.25; H, 6.27.

4-(2-Azidophenyl)-6-[2-((*E*)-2-methylbut-2-enoylamino)ethyl]-5,6,7,8-tetrahydroquinolin-8-one (52). A procedure identical with the one above furnished 449 mg (94%) of **52** as pale yellow crystals (mp 154–155 °C) from 540 mg (1.25 mmol) of **50**; a 1:1 mixture of atropisomers of good enough quality to be used for the next step without further purification: R_f (100% EtOAc) 0.33; ^{1}H NMR 8.72 (d, 1 H, J = 4.6 Hz), 7.52 (br t, 1 H, app J = 8.0 Hz), 7.34–7.21 (m, 3 H), 7.18 (br t, 1 H, app J = 8.0 Hz), 6.39 (br q, 1 H, J = 6.9 Hz), 6.02 (br m, 1 H), 3.38–3.20 (m, 2 H), 3.01–2.20 (c m, 5 H), 1.80–1.56 (c m, 2 H), 1.79 (br s, 3 H), 1.71 (br d, 3 H, J = 6.9 Hz); ^{13}C NMR 196.2, 169.3, 148.4, 148.3, 148.0, 147.7, 147.4, 138.4, 137.9, 137.7, 137.3, 131.4, 130.6, 130.2, 129.1, 128.8, 128.2, 127.9, 125.2, 125.0, 118.6, 118.3, 45.2, 45.1, 36.9, 35.3, 35.0, 32.9, 32.7, 32.1, 13.8, 12.2; IR 3340, 3055, 2928, 2126, 1700, 1663, 1617, 1533, 1493, 1441, 1293, 758, 733; MS 390 (M^+ + 1), 389 (M^+), 361, 360, 261, 249, 235 (100); HRMS expected 389.1851, obsd 389.1848. Anal. Calcd for $C_{22}H_{23}N_5O_2$: C, 67.85; H, 5.95. Found: C, 67.72; H, 6.22.

Cystodytin A (1). A degassed chlorobenzene (15 mL) solution of 50 mg (0.128 mmol) of **51** in a common Pyrex flask was heated to 110 °C. Irradiation at that temperature was continued for 10 h, after which time two major products were evident by TLC: some cystodytin A plus an intensely purple spot corresponding to the primary photoadduct. Irradiation was discontinued, and small portions of DDQ were added to the cooled solution until all of the purple material was converted to cystodytin A. The solvent was evaporated and the residue was chromatographed by preparative TLC (5% MeOH/$CHCl_3$) to give 14.2 mg (31%) of cystodytin A as bright yellow crystals. A sample recrystallized from $CHCl_3$ had a melting point of 182–184 °C: R_f (5% MeOH/$CHCl_3$) purple spot 0.06, cystodytin A 0.26; ^{1}H NMR 9.12 (d, 1 H, J = 5.5 Hz), 8.53 (dd, 1 H, app J_1 = 8.0, J_2 = 1.2 Hz), 8.43 (d, 1 H, J = 5.5 Hz), 8.31 (dd, 1 H, app J_1 = 8.0, J_2 = 1.0 Hz), 7.95 (dt, 1 H, app $J_1 = J_2$ = 7.2, J_3 = 1.2 Hz), 7.86 (dt, 1 H, app $J_1 = J_2$ = 7.2, J_3 = 1.2 Hz), 6.91 (s, 1 H), 6.11 (br m, 1 H), 5.57 (br s, 1 H), 3.82 (dt, 2 H, $J_1 = J_2$ = 6.6, J_3 = 5.7 Hz), 3.30 (t, 2 H, J = 6.1 Hz), 2.12 (d, 3 H, J = 0.9 Hz), 1.80 (d, 3 H, J = 0.9 Hz); ^{1}H NMR (2:1 $CD_3OD/CDCl_3$) (Note: Chemical shifts proved to be extremely sensitive to the precise ratio of CD_3OD to $CDCl_3$.) 9.07 (d, 1 H, J = 5.5 Hz), 8.58 (m, 2 H), 8.29 (dd, 1 H, app J_1 = 8.0, J_2 = 1.0 Hz), 7.96 (dt, 1 H, app $J_1 = J_2$ = 7.0, J_3 = 1.2 Hz), 7.86 (dt, 1 H, app $J_1 = J_2$ = 7.0, J_3 = 1.2 Hz), 6.88 (s, 1 H), 5.66 (br s, 1 H), 3.75 (t, 2 H, J = 6.6 Hz), 3.30 (t, 2 H, J = 6.6 Hz), 2.07 (d, 3 H, J = 1.1 Hz), 1.82 (d, 3 H, J = 1.1 Hz); ^{13}C NMR (2:1 $CD_3OD/CDCl_3$) 183.3, 167.9, 152.6, 150.6, 149.7, 148.9, 145.8, 145.0, 137.0, 131.8, 131.5, 131.5, 131.4, 129.7, 122.8, 121.3, 119.6, 117.9, 117.6, 117.6, 38.3, 31.1, 26.4, 19.1; IR (KBr) 3437, 3060, 2919, 1658, 1616, 1587, 1465, 1384, 1185, 862, 773; MS 359 (M^+ + 2), 357 (M^+), 329, 328, 274, 273, 260, 248, 247 (100), 218, 83; HRMS expected 357.1477, obsd 357.1482.

Cystodytin B (2). A procedure identical with the one above afforded 14.8 mg (32%) of cystodytin B as bright yellow crystals from 50.5 mg (0.130 mmol) of ketone **52**. A sample recrystallized from $CHCl_3$ had a melting point of 180–182 °C: R_f (5% MeOH/$CHCl_3$) purple spot 0.06, cystodytin B 0.27; ^{1}H NMR 9.20 (d, 1 H, J = 5.5 Hz), 8.57 (dd, 1 H, app J_1 = 7.4, J_2 = 1.2 Hz), 8.52 (d, 1 H, J = 5.5 Hz), 8.29 (dd, 1 H, app J_1 = 8.1, J_2 = 1.2 Hz), 7.94 (dt, 1 H, app $J_1 = J_2$ = 8.1, J_3 = 1.4 Hz), 7.83 (dt, 1 H, app $J_1 = J_2$ = 7.4, J_3 = 1.4 Hz), 6.91 (s, 1 H), 6.35 (br s, 1 H), 6.31 (dq, 1 H, J_1 = 6.9, $J_2 = J_3 = J_4$ = 1.4 Hz), 3.81 (dt, 2 H, $J_1 = J_2$ = 6.5, J_3 = 5.8 Hz), 3.32 (t, 2 H, J = 6.5), 1.74 (br t, 3 H, app J = 1.1 Hz), 1.65 (br dd, J_1 = 6.9, J_2 = 1.1 Hz); ^{1}H NMR (2:1 $CD_3OD/CDCl_3$) (Note: Chemical shifts proved to be extremely sensitive

to the precise ratio of CD_3OD to $CDCl_3$.) 9.16 (d, 1 H, J = 5.5), 8.68 (d, 1 H, J = 5.5), 8.66 (dd, 1 H, J_1 = 8.2, J_2 = 1.0 Hz), 8.31 (dd, 1 H, J_1 = 7.0, J_2 = 1.0 Hz), 7.97 (dt, 1 H, app $J_1 = J_2$ = 7.0, J_3 = 1.0 Hz), 7.88 (dt, 1 H, app $J_1 = J_2$ = 7.0 Hz, J_3 = 1.0 Hz), 6.92 (s, 1 H), 6.33 (dq, 1 H, J_1 = 7.0 Hz, $J_2 = J_3 = J_4$ = 1.4 Hz), 3.78 (t, 2 H, J = 6.7 Hz), 3.35 (t, 2 H, J = 6.7 Hz), 1.75 (t, 3 H, J = 1.2 Hz), 1.69 (dd, 1 H, J_1 = 7.0, J_2 = 1.0 Hz); ^{13}C NMR (2:1 $CD_3OD/CDCl_3$) 183.4, 170.5, 152.7, 149.9, 149.1, 146.0, 145.0, 127.2, 131.9, 131.5, 131.4, 131.1, 130.8, 129.7, 122.8, 121.4, 119.7, 117.7, 39.2, 30.8, 13.2, 11.6; IR (KBr) 3467, 3060, 2931, 1654, 1612, 1588, 1540, 1465, 1384, 1185, 862, 774; MS 359 (M^+ + 2), 357 (M^+), 272, 260, 247 (100), 218; HRMS expected 357.1477, obsd 357.1482.

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Diastereoselective Synthesis of Phycocyanobilin–Cysteine Adducts

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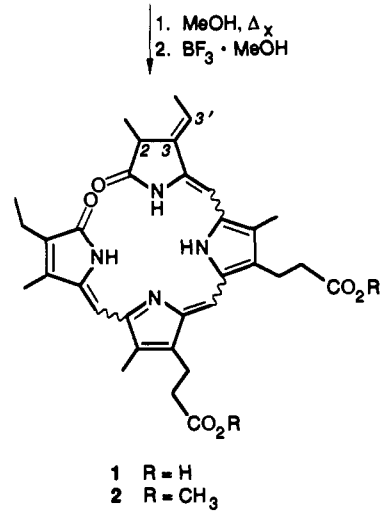
Abstract: Methodology is presented for the synthesis of two diastereomers of a cysteine-linked phycocyanobilin derivative. The crucial reaction is a diastereoselective 1,6-Michael addition of cysteine methyl ester to an appropriate dihydropyrromethenone educt. The diastereomers so generated were then elaborated to two phycocyanobilin trimethyl esters. Definitive assignments of relative stereochemistry, double bond geometry, and solution conformation are accomplished by application of ROESY NMR experiments, while absolute stereochemical assignments are based on degradation to compounds of known chirality.

Introduction

Plant bile pigments, due to their extremely important photosynthetic and regulatory functions in numerous species, have been of considerable interest for well over 100 years. Such attention may also be, in part, a result of the pigments' brilliant and intense colors. The blue protein C-phycocyanin (C-PC), an antenna pigment isolated from the blue-green alga *Synechococcus* sp. 6301, was found to contain three distinct tetrapyrrole-based chromophores that are attached by thioether linkages to the protein, with a total molecular weight of approximately 36 700 Da.[1] Figure 1 depicts the structure that has been determined for the three identical phycocyanobilin (PCB) groups. NMR data from smaller peptide fragments determined the site of protein attachment to be C-3',[2] and when combined with data from appropriate synthetic model compounds,[3] showed a *trans*-dihydro relative stereochemistry at C-2 and C-3. However, the remaining stereochemical features of the molecule, namely the absolute stereochemistry assignments at C-2, C-3, and C-3', as well as the exocyclic double-bond geometries, were undetermined by this methodology. A recent X-ray crystal structure study on C-PC derived from *Mastigocladus laminosus* at 2.1-Å resolution convincingly assigned the absolute stereochemistry as 2*R*,3*R*,3'*R* for two of the chromophores, designated α-1 and β-1 PCB. The remaining PCB unit, β-2, was likewise assigned as 2*R*,3*R*,3'*R*; however, assignment of the C-3' stereocenter appears to be less convincing.[4,5] The X-ray diffraction data also showed *Z* double-bond geometries and an anti/syn/anti conformational relationship for the single bonds separating the four rings.

Scheme I. Cleavage of Phycocyanobilin from Phycocyanin



1 R = H
2 R = CH_3

Because of its chemical instability, as well as the presence of numerous stereochemical elements and complex functionalities, no total synthesis of a peptide-bound phycocyanobilin has been reported. Earlier studies concentrated primarily on the synthesis of natural product degradation products. Treatment with boiling methanol was found to cleave the tetrapyrrole–protein bond in an apparent elimination reaction, producing diacid **1** (Scheme I).[5-7]

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(5) C-PC consists of two peptide chains, α and β. The use of α-1, β-1, and β-2 PCB refers to the three sites of chromophore attachment. In *Synechococcus* sp. 6301 C-PC, these designations correspond to the α chain's cysteine-84 residue and the β chain's cysteine-82 and cysteine-155 residues, respectively. See: Glazer, A. N. *Biochim. Biophys. Acta* **1984**, *768*, 29.
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