Two Interrelated Strategies for Cephalotaxine Synthesis

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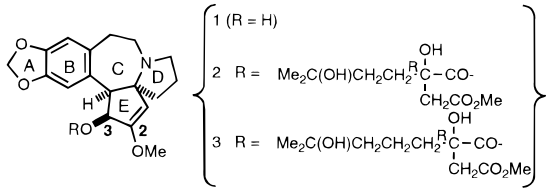
Studies of two interrelated strategies for the synthesis of members of the cephalotaxus alkaloid family have culminated in a concise route for the preparation of the parent member cephalotaxine (**1**). As part of efforts exploring the use of an SET-promoted photocyclization reaction of aryl-substituted silylallyliminium salts to generate the spirocyclic DE unit of the target, we noted that attempts to generate the pentacyclic amino ketone **23** by deacylation of the enol ester **20** led to production of a mixture of **23** and the macrocyclic amino enone **24**. A rapid equilibrium was shown to exist between **23** and **24**, favoring the latter ring-opened form. This contrasts with the behavior of desmethylcephalotaxinone (**22**), a key late intermediate in several earlier cephalotaxine syntheses, which is known to exist in a ring-closed form. These observations led to the design of a second generation strategy which relies on transannular cyclization of the macrocyclic amino enedione **28**. In practice, the sequence following this design transforms the known iodopiperonylethanol derivative **4** to **22** in 13 steps and a 12% overall yield and, thus, corresponds to an efficient formal synthesis of cepahalotaxine.

Introduction

Interest in members of the cephalotaxus alkaloid family that are structurally related to cephalotaxine (**1**) has remained high since their isolation and characterization in the 1960s.[1−4] Reasons for this reside in the anticancer properties reported[5−9] for several substances in this family and in the unique features of the pentacyclic structure common to members of this series. As expected, the cephalotaxus alkaloids have served as the focal point for a number of synthetic efforts aimed at developing and demonstrating the preparative power of methods to construct the core skeleton[10] of cephalotaxine (**1**), the parent member of this series,[11−17] and to introduce the complex C-3 ester side chains found in its biologically interesting relatives, including harringtonine (**2**) and homoharringtonine (**3**).[18]

The general approaches utilized for cephalotaxine synthesis can be classified into three groups distinguished by the strategies used to construct its unique pentacyclic core. The key element of routes developed by Weinreb[11] and Hanaoka[12] is the preparation of an appropriate pyrrolobenzohydroazepine intermediate (**I** in



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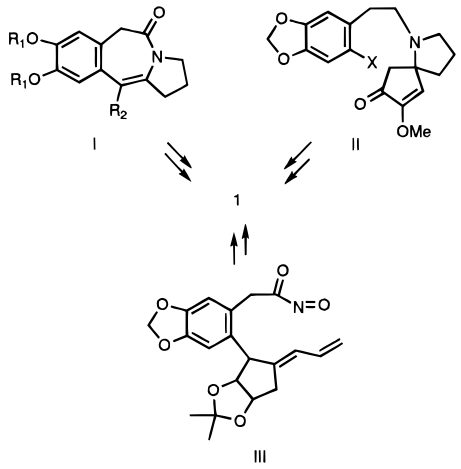
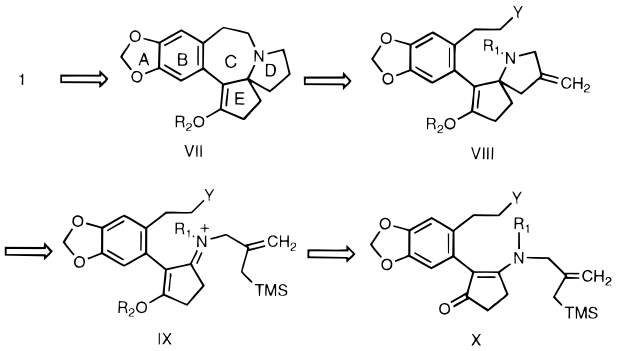
Scheme 1

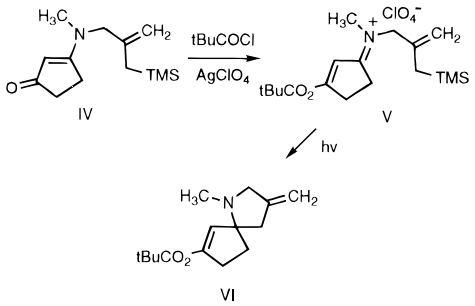


Scheme 2



Scheme 1) and its elaboration by E-ring-forming methodologies. The designs used by Semmelhack,[13] Kuehne,[14] Ikeda,[15] and Mori[16] recognize that the cephalotaxine ring system can be constructed by first generating an appropriate arylethyl spirocyclic amine (*e.g.*, **II**) and then inducing hydroazepine C-ring formation by either N-alkylation or C-arylation methodologies. Finally, a plan based upon sequential formation of the hydroazepine and pyrrolidine rings starting with an arylcyclopentene derivative (**III**) serves as the foundation for Fuchs'[17] successful cephalotaxine synthesis.

We have had a long-standing interest in the development of preparatively applicable, single-electron-transfer (SET) induced excited state reactions. A number of early explorations in this area uncovered novel carbon−carbon bond-forming photoreactions of systems comprised of allyl- and benzylsilane donors and conjugated iminium salt acceptors.[19] The results arising from this exploratory work stimulated several synthetic investigations which relied on these processes as key N-heterocycle ring building steps for the preparation of members of the protoberberine and erythrina alkaloid families.[20] At that time, we also discovered that tethered allylsilane−iminium salts related to **V** could be readily prepared from β-enamino ketone precursors **IV** and that these substances undergo SET-promoted photocylization to produce spirocyclic amine products (*e.g.*, **VI**).[21]



Further investigations demonstrated that a dual mechanistic sequence (*i.e.*, diradical and diradical cation coupling) was responsible for carbon−carbon bond formation in this process[22] and that the scope of the photocyclization reaction was narrow when α-aryl-substituted iminium salts were used.[21b,23] In spite of these issues, the high efficiency of the spirocyclic amine forming sequence exemplified by the transformations **IV** → **V** → **VI** suggested that it might serve as the basis for a new strategy for cephalotaxus alkaloid synthesis. As depicted in Scheme 2, a cephalotaxine synthetic route based on this design relies on photocyclization of a silylallyliminium salt (**IX**) which itself derives from a β-enaminone precursor **X**. The specific choice of a non-hydroazepine-ring-containing salt such as **IX** is guided by our earlier observation which showed that excited state SET occurs efficiently only in those α-aryl-substituted iminium salts which exist in nonplanar arylcyclopentene ring conformations.[23,24] Cephalotaxine would then come from **VIII** in this scheme by a sequence involving excision of the exocyclic methylene unit, hydroazepine C-ring formation to produce the pentacyclic intermediate **VII**, and finally, E-ring functionality adjustment.

It will become clear when the results of our efforts in this area are described below that this strategy has several positive features when viewed in the context of a method to construct the basic pentacyclic framework of the cephalotaxus alkaloids. However, mechanistically interesting observations made during the course of this work have given rise to a much more concise plan for cephalotaxine synthesis. The details of our studies (1) probing the photochemical approach described above, (2) uncovering an interesting ring-opening reaction of 2-demethoxycephalotaxinone, and (3) successfully executing a concise transannular cyclization strategy for cephalotaxine synthesis are discussed in detail below.[25]

Results and Discussion

Photochemical Approach for Cephalotaxine Ring Construction. The strategy delineated in Scheme 2 for cephalotaxine (**1**) synthesis relies on a key SET-promoted photocyclization reaction of an appropriately substituted silylallyliminium salt of general structure **VI**. Exploratory photochemical studies[21,23] leading up to the current effort suggested that the iminium perchlorate **13** contains

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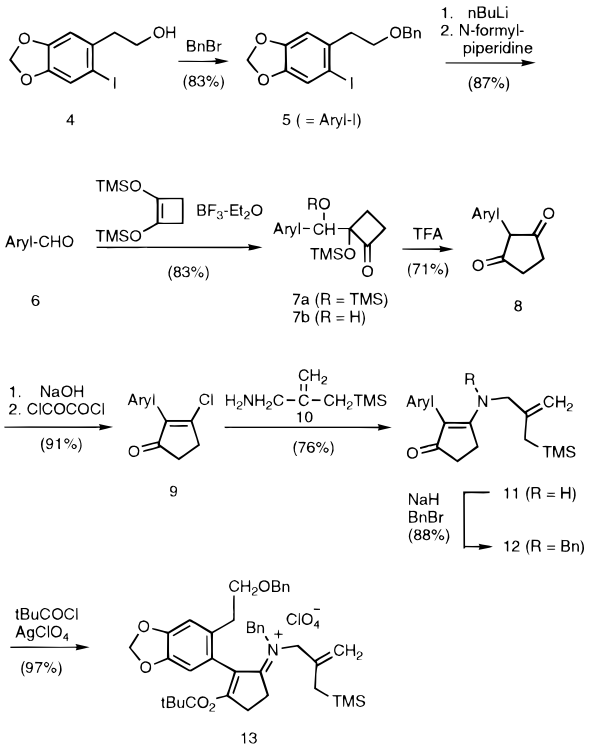
(24) This is due to the low excited state reduction potential of aryl-conjugated iminium salts which results in inefficient SET from the allylsilane donor grouping (see refs 19 and 21b).

(25) Preliminary accounts of a portion of these studies have appeared in the following: Kavash, R. W.; Mariano, P. S. *Tetrahedron Lett.* **1989**, *30*, 4185. Lin, X. D.; Kavash, R. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1994**, *116*, 9791.

Scheme 3



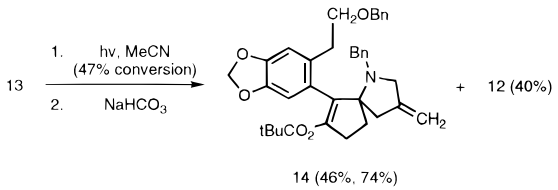
the proper structure and functionality necessary for both efficient photochemical reactivity and ensuing installation of the hydroazepine C-ring and functionalized E-ring of the target.

Investigations testing the viability of the photochemical route to **1** began with preparation of the β-enaminone **12** which we judged to be an ideal precursor of **13**. The sequence starts with the known[13] (iodopiperonyl)ethanol **4** (Scheme 3) which is prepared by using a minor modification (see Experimental Section) of the method reported by Semmelhack.[13] The alcohol function in **4** is protected as the benzyl ether **5** by use of the procedure suggested by Johnstone and Rose.[26] Three protocols were initially probed in order to uncover an efficient method to transform **5** into the 2-arylcyclopentane-1,3-dione **8**. These include (1) a copper-assisted nucleophilic aromatic substitution reaction of **5** with the sodium salt of 1,3-cyclopentadione,[27] (2) a Dieckmann cyclization strategy, and (3) an aldol−pinacol rearrangement procedure developed by Kuwajima and his co-workers.[28] The latter sequence proved to be the most practical. It is initiated by conversion of arene **5** into aryl aldehyde **6** by use of a kinetic[29] halogen−metal interchange formylation[30] process. Aldol addition of 1,2-bis(trimethylsiloxy)cyclobutene to aldehyde **6**, catalyzed by BF_3 etherate at −78 °C, gives cyclobutanone products **7** comprised of diastereomeric mixtures of both the α-siloxy (**7a**) and α-hydroxy (**7b**) derivatives. Since all of these cyclobutanone-containing substances are substrates for the ensuing pinacol rearrangement process, the crude mixture of **7** is directly subjected to treatment with trifluoroacetic acid at 0 °C. In accord with the reports by Kuwajima,[28] this two-step sequence efficiently affords arylcyclopentanedione **8** (71%).

Placement of the silylmethallylamine unit into the β-enaminone **11** employs a vinylogous amide forming reaction of the β-chloro enone **9** (derived from **8**) with (silylmethallyl)amine **10** (derived from the known[31] mesylate analog). The final step for preparation of the tertiary β-enamino ketone **12** involves N-benzylation of the sodium salt of **11**. Implementing the methodology developed earlier in our laboratory,[21,23] O-pivaloylation of enaminone **12** is promoted by reaction with pivaloyl chloride and silver perchlorate to afford the (silylallyl)-iminium perchlorate **13** in near quantitative yield.

^1H and ^{13}C NMR spectroscopic analysis showed that the iminium salt **13** is produced as an *ca.* 1:1 mixture of *E*- and *Z*-C=N isomers. Moreover, the spectrum of each of these isomers contains sharp resonances which demonstrate the existence of each species in a slowly interconverting (NMR time scale) nonplanar conformation. Characteristic in this regard are the AB quartets seen for the dioxolene A-ring methylene protons (5.78, 5.87 ppm, J = 1.2 Hz; 5.90, 5.95 ppm, J = 1.1 Hz), the *N*-benzyl methylene protons (4.20, 5.00 ppm, J = 15.5 Hz; 4.74, 5.15 ppm, J = 15.7 Hz), the *N*-allyl methylene protons (3.82, 4.12 ppm, J = 17.3 Hz; 3.87, 4.24 ppm, J = 17.9 Hz), and the *O*-benzyl protons (4.29, 4.38 ppm, J = 12.3 Hz; 4.39, 4.43 ppm, J = 12.2 Hz). The diastereotopic relationships revealed in this analysis are a consequence of atropisomerism associated with the biphenyl-like asymmetry in the nonplanar *E*- and *Z*-isomers of **13**. Moreover, the UV spectrum of **13** displays a maximum at 284 nm ($\epsilon = 2.6 \times 10^4$, MeCN) which is close to those of nonarylated iminium salt analogs.[21,23]

As demonstrated in our earlier efforts, this conformational characteristic of aryl-substituted silylallyliminium salts often parallels their efficient photocyclization chemistry.[24] Accordingly, irradiation of an acetonitrile solution of iminium perchlorate **13** by using Corex glass-filtered light (λ > 280 nm) to bring about 47% conversion of **13** (by UV analysis) followed by aqueous $NaHCO_3$ workup and alumina chromatography affords the spirocyclic amine **14** (46%) and the tertiary enaminone **12** (40%). The latter substance originates by base-induced depivaloylation of the unreacted iminium salt **13**. It is imperative to conduct this photoprocess to *ca.* 50% conversion of **13** since irradiation for extended periods, while engendering higher conversion of **13**, leads to lower yields of spirocyclic amine **14**. This is a result of secondary (as yet unidentified) photoreaction of protonated **14** formed in the photolysate. In any event, photolysis of **13** does lead to efficient (74% based on one recycle **12** → **13**) construction of the spirocyclic DE portion of the cephalotaxine skeleton.



To briefly assess the mechanistic pathway(s) operating in the photocyclization reaction, tetradeuterioiminium salt **13D$_4$** was prepared and subjected to direct irradia-

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(28) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 961. Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759.
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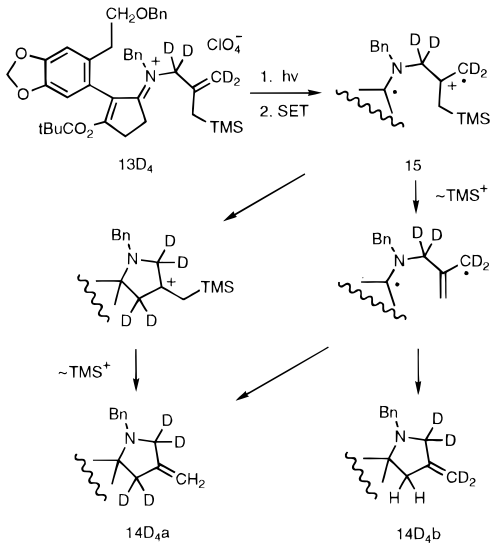
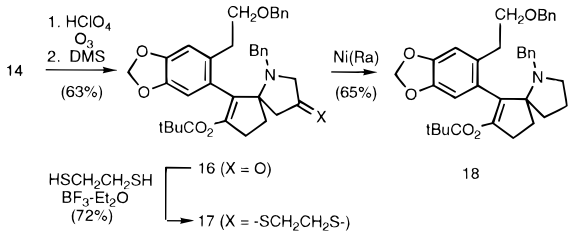
Scheme 4



Scheme 5

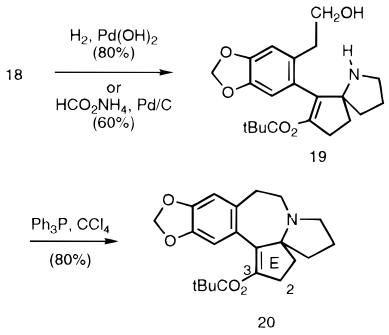


tion. ^{1}H NMR analysis of the spirocyclic amine product arising in this process showed that it was comprised of a 9:1 mixture of the isotopomers **14D$_4$a** and **14D$_4$b**. This result suggests that spirocyclic amine **14** arises in the photochemistry of **13** by two mechanistic routes, both involving SET-promoted formation of the cation diradical intermediate **15** (Scheme 4) but distinguished by whether **15** undergoes cyclization and desilylation (giving **14D$_4$a**) or desilylation and cyclization (giving 1:1 **14D$_4$a**/**14D$_4$b**). The dominance (*ca.* 8:1) of cation diradical cyclization in this mechanism as compared to that operating for non-aryl analogs[22] (*ca.* 1:1) is not easily rationalized.

With the route to aryl-substituted spirocyclic amine **14** now established, our attention next focused on the three remaining issues associated with the photochemical strategy for cephalotaxine synthesis. Specifically, methods were needed to (1) excise the exocyclic methylidene group in the pyrrolidine D-ring, (2) install the hydroazepine C-ring, and (3) adjust E-ring functionality.

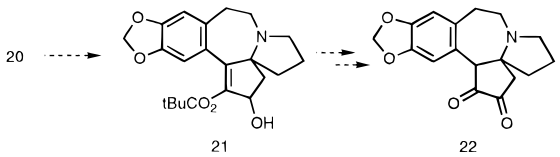
The SET-photochemical methodology produces the pyrrolidine ring of the spirocyclic amine unit with an appended exocyclic methylene moiety. While this functionality could be visualized as an entry into D-ring-substituted analogs of the cephalotaxus alkaloids, it must be removed in routes targeted at the parent members of this family. Methods for this purpose must be compatible with the oxidative lability of the amine function and potential instability of the γ-amino enol ester group in **14**. Exploratory efforts surveying a number of potential protocols led to the development of an appropriate oxidative cleavage−reduction sequence (Scheme 5). Accordingly, ozonolytic cleavage of the N-protonated salt of **14** cleanly produces ketone **16** in 63% yield. Thioketal **17** formation[32] followed by hydrogenolysis to afford **18** then completes the sequence.

Scheme 6



As a result of our initial planning, the spirocyclic amine intermediate **18** contains alcohol and amine blocking groups which can be removed simultaneously to liberate proper functionality for executing intramolecular N-alkylation required for hydroazepine ring formation (Scheme 6). As anticipated, hydrogenolysis of **18** by use of catalytic HOAc, hydrogen (3 atm), and 20% Pd(OH)$_2$/C in ethanol[33] affords amino alcohol **19** in an 80% yield. Unfortunately, this process is rather capricious with its success rate being about 66%. As a result, a more consistent yet lower yielding procedure to produce **19** was developed. This involves the treatment of **18** with 10% Pd/C and ammonium formate in refluxing methanol[34] and consistently yields **19** but only in a 60% yield. A modification of a method developed by Meyers,[35] employing typical alcohol to chloride transforming conditions (Ph$_3$P/CCl$_4$), is used to convert amino alcohol **19** into **20**, a substance which possesses all of the carbons in the pentacyclic framework of cephalotaxine.

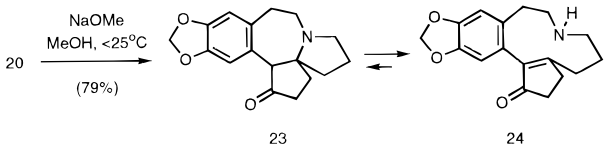
In order to use pentacyclic enol ester **20** as a viable intermediate in a cephalotaxine synthesis sequence, conditions to introduce ketone functionality at C-2 of the E-ring must be uncovered. At the outset, we did not anticipate that this task would be problematic and two approaches for this purpose were explored. The first involves allylic oxidation of **20** to produce alcohol **21** followed by oxidation and liberation of the C-3 ketone by enol ester cleavage. This sequence would generate 2-desmethylcephalotaxanone (**22**), an intermediate in Weinreb's[11] and a number of later syntheses of cephalotaxine. However, attempts to carry out selenium dioxide[36] and related allylic oxidations of **20** met with failure.



Another strategy to transform **20** into the Weinreb intermediate **22** involves liberation of the C-3 ketone by enol ester cleavage to form the C-3 ketone **23** followed by regioselective α-oxidation to produce **22**. However, under all of the conditions explored nucleophilic deacylation of the enol ester function in **20** failed to produce **23** as a homogeneous entity. Specifically, treatment of **20** with sodium methoxide in MeOH at ≤25 °C provides

(32) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303.
(33) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663.
(34) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.
(35) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108.
(36) Rabjohn, N. *Organic Reactions*; Dauben W. G., Ed.; Wiley: New York, 1976; Vol. 24, Chapter 4.

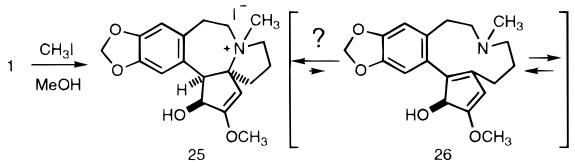
an inseparable 10:1 mixture of the macrocyclic amino enone **24** and the desired C-3 ketone **23**. The ratio of these products was not altered by the reaction temperature or by chromatography, suggesting that **24** and **23** exist as a rapidly interconverting equilibrium mixture (see supporting evidence below).



Both the ^{1}H and ^{13}C NMR spectra clearly reveal the presence of **23** and **24** in this product mixture. For example, two pairs of aromatic proton singlets at 6.57 and 6.62 ppm (for **23**) and 6.36 and 6.70 ppm (for **24**) and two dioxolene methylene proton AB quartets at 5.88 and 5.89 ppm (for **23**) and 5.90 and 5.93 ppm (for **24**) are observed in the ^{1}H NMR spectrum. Moreover, a singlet is observed at 3.40 ppm which integrates for one proton relative to the minor aromatic singlets. This resonance corresponds to the C-4 tertiary hydrogen in **23**. Evidence for the enone moiety in **24** comes from the ^{13}C NMR spectrum of the mixture which contains quaternary carbon resonances at 208 (C=O), 175 (β C=C), and 144 ppm (α C=C).

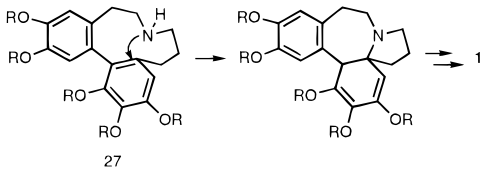
Reevaluation of Strategy. It is clear from the observations described above that synthetic strategies targeted at the cephalotaxus alkaloids which employ pentacyclic amino ketone **23** as a key intermediate need not concentrate on novel methodology for construction of the DE-ring spirocyclic amine component. The rapid and reversible ring-opening process interconverting **23** and the macrocyclic amino enone **24** serves as a deterrent for embarking on lengthly sequences to prepare **23**, independent of whether or not they incorporate novel design features or reaction processes.

The ring-opening reaction described above is not unique to amino ketone **23**. Related processes which lead to unraveling of the spirocyclic ring system have been noted in earlier investigations focusing on elucidation of the structure and stereochemistry of cephalotaxine,[4a] its biosynthetic origin,[37] and synthesis.[10e,17c] An example of this is seen in preparation of the methiodide **25** by N-methylation of natural optically active cephalotaxine for X-ray crystallographic purposes. Abraham and his co-workers[4a] noted that **25** was produced as a racemic mixture, most likely a result of reversible ring opening *via* the macrocycle **26**.

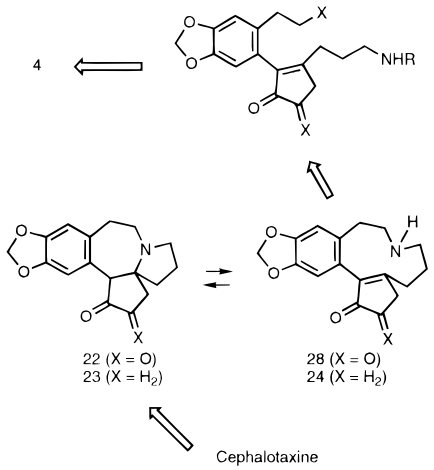


Closely related to the ring-opening reactions of the cephalotaxine skeleton and highly pertinent to our reevaluation of a synthetic strategy is the proposed biosynthesis of **1** and related cephalotaxus alkaloids. Precursor incorporation experiments led Parry and his collaborators[39] to propose that the pentacyclic nucleus of these alkaloids is constructed by transannular cyclization of an intermediate of general structure **27** followed by E-ring contraction (Scheme 7).[40]

Scheme 7



Scheme 8



Observations made in our attempt to execute the photochemical route to cephalotaxine, when put in the perspective of the biosynthetic proposal by Parry,[24] led to the design of a much simpler and more concise plan to approach this target. Both in our original sequence as well as in those used in several earlier cephalotaxine syntheses, spirocyclic amine DE-ring construction garnered much attention. As we have seen, in sequences which rely on pentacyclic amino ketone **23** as a late intermediate the benefits of early spirocyclic amine generation would be lost. We hypothesized that the same ring-opening phenomenon is also associated with desmethylcephalotaxinone (**22**) (see Scheme 8), a late intermediate in several earlier cephalotaxine approaches. Specifically, we believed that **22** exists in rapid reversible equilibrium with the macrocyclic enedione **28** and that this equilibrium heavily favors **22** owing to an unfavorable α-diketone dipole interaction which can not be compensated for by formation of what would be an unstable diosphenol.

Owing to the fact that **22** is used as a penultimate intermediate in cephalotaxine syntheses and our evaluation that its potential precursor **28** might be easily prepared by a short uncomplicated route, we believed that a cephalotaxine synthesis strategy based on a biomimetic transannular cyclization process could lead to an efficient route to the target. The redesigned strategy, outlined in Scheme 8, again begins with the (iodopiperonyl)ethanol derivative **4** and proceeds through a C-ring unclosed enone as an intermediate in the formation of **28**.

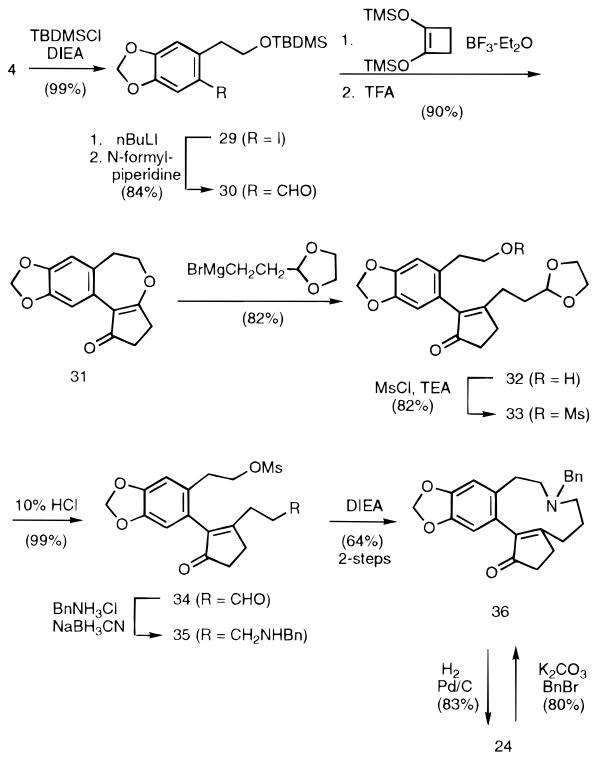
(37) Schwab, J. M.; Parry, R. J.; Foxman, B. M. *J. Chem. Soc., Chem. Commun.* **1975**, 906.

(38) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691.

(39) (a) Parry, R. J.; Chang, M. N. T.; Schwab, J. M.; Foxman, B. M. *J. Am. Chem. Soc.* **1980**, *102*, 1099. (b) Schwab, J. M.; Chang, M. N. T.; Parry, R. J. *J. Am. Chem. Soc.* **1977**, *99*, 2368. (c) Parry, R. J.; Schwab, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 2555.

(40) (a) Kupchan and his co-workers (ref 40b) have successfully modeled the proposed biogenetic cyclization process. (b) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 4464.

Scheme 9



Transannular Cyclization Approach. Inspection of the refined cephalotaxine synthetic strategy gives rise to several interesting questions which were addressed during the course of our work. Of course, the key issue concerns transannular cyclization of enedione **28** to form **22**. Another problem involves the introduction of the α-carbonyl functionality into an enone related to **24**. The development of a concise synthesis of the macrocyclic amino enone **24** was an issue that needed to be addressed first. We felt that **24** could derive from an appropriately substituted aminopropyl enone (*e.g.*, **27**) which itself would arise from the tetracyclic enol ether **31** (Scheme 9).

To test these proposals, (iodopiperonyl)ethanol **4**[13] was converted into its TBDMS ether **29** before being subjected to carboxaldehyde-forming conditions (→ **30**). Application of the Kuwajima[28] cyclopentandione-forming protocol led to direct production of the internal enol ether **31** as a consequence of TBDMS deprotection and cyclic enol ether formation under the TFA-promoted pinacol rearrangement conditions. The three-carbon unit in intermediate **32** was then introduced by use of Stork's[41] enone synthesis methodology and the Grignard of acetal-blocked β-bromopropanal.[42] Mesylation to generate **33** followed by aldehyde liberation and reductive amination provided the aminopropyl derivative **35**. As anticipated, macrocyclization of **35** occurred smoothly under N-alkylation conditions (1×10^{-3} M substrate) to generate the amino enone **36**. The independent preparation of **36** by N-benzylation of **24**, produced in the photochemical route described above, confirms the structural characterization of **24**.

Tangential Issues. To test the proposal that formation of **23** and **24** from **20** (see above) is due to rapid and reversible equilibration of the former substances, **36** was debenzylated (83%) under typical hydrogenolytic conditions. Importantly, this process generated a mixture of **23** and **24** in the same 1:10 ratio obtained in the deacylation reaction of enol ester **20**. It is interesting to note in this regard that NMR analysis of the (β-aminopropyl)cyclopentenone **35** shows that this substance does not exist to a detectable extent in its ring closed, spirocyclic amine form. This observation is consistent with that made by Fuchs and his co-workers[17a] in model studies probing an unsuccessful cephalotaxine synthetic plan.

In a related vein, ^{1}H NMR analysis of several intermediates in the sequence portrayed in Scheme 9 demonstrate that they are chiral on the NMR time scale. Specifically the substances **32**−**35**, which all contain a 2-aryl-3-alkylcyclopentenone moiety, have spectra in which key methylene protons (*e.g.*, dioxolene ring) appear as AB quartets as a consequence of their diastereotopic relationship. The origin of the chirality of **32**−**35** is the existence of a preferred biphenyl-like nonplanar conformation in each and a slow interconversion of the conformers/enantiomers. Even the macrocyclic *N*-benzyl amino enone **36** possesses this unique stereochemical feature as characterized by the appearance of AB quartets in the NMR for its methylenedioxy (5.99 and 5.90 ppm, $J = 1.4$ Hz) and benzylic (3.68 and 3.60 ppm, $J = 14.2$ Hz) protons.

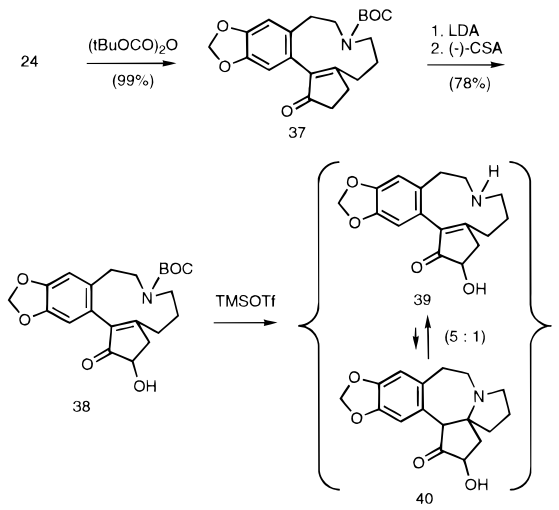
A final comment concerns a comparison of the two sequences described above for preparation of the **23** + **24** mixture from (iodopiperonyl)ethanol **4**. The route based on the photospirocyclization strategy requires 17 steps and proceeds in an overall 4% yield. In contrast, the macrocyclic amino enone design gives rise to a route from **4** to **23** + **24** which transverses 9 steps in a 30% overall yield.

Cephalotaxine Synthesis by Amino Enedione Cyclization. As depicted in Scheme 8 and discussed above, our revised plan for cephalotaxine synthesis is based on the proposal that the macrocyclic amino enedione **28** would undergo rapid and nearly irreversible transannular cyclization to generate desmethylcephalotaxinone (**22**), an intermediate in a number of previous routes to this target. Execution of this strategy requires methodology for introduction of oxygen functionality at C-2 (cephalotaxine numbering) of the cyclopentenone group. While several methods and intermediates (*e.g.*, **31**−**36**) exist for this purpose, we choose to construct the enedione grouping as late in the sequence as possible by use of a Davis-type[43] oxidation protocol (Scheme 10). Accordingly, the amino-enone **24** (+**23**) was first transformed to its BOC derivative **37** which in turn was α-hydroxylated by sequential treatment[44] with LDA and ((−)-camphorsulfonyl)oxaziridine ((−)-CSO).[43] This furnished **38** as a mixture of diastereomers (see below) in a 78% yield.

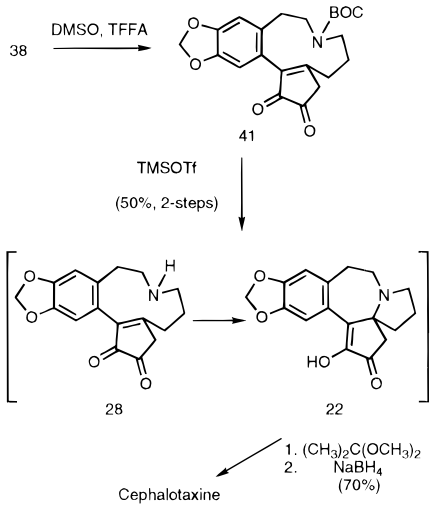
As an aside, **38** was N-deprotected by treatment with TMSOTf to produce an inseparable mixture of ring-opened and -closed α-hydroxy ketones **39** and **40** in a 5:1 ratio. Thus, introduction of an electronegative α-substituent shifts the equilibrium (as compared to **23** + **24**) slightly in the direction of the ring-closed form.

(41) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.
(42) Buchi, G.; Wuest, H. *J. Org. Chem.* **1969**, *34*, 1122. Loozen, H. J. *J. Org. Chem.* **1975**, *40*, 520. Stowell, J. C. *J. Org. Chem.* **1976**, *41*, 560.
(43) (a) Davis, F. A.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1991**, *56*, 1143. (b) Davis, F. A.; Sheppard, A. C.; Chen. B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. (c) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(44) Holton, R. A.; *et al. J. Am. Chem. Soc.* **1994**, *116*, 1597.

Scheme 10



Scheme 11



By use of the modified Swern/Moffat oxidation conditions employed by Fuchs,[17c] the *N*-BOC α-hydroxy ketones **38** were converted to the enedione **41** (Scheme 11). Characterization of **41** was made difficult by its chromatographic instability and its nondescript NMR spectroscopic patterns. The latter is likely due to both slow carbamate rotation and the possible existence of **41** in exocyclic enolic forms. In any event, the structural assignment of **41** is assured by the following chemical transformations. TMSOTf-induced BOC deprotection of **41** occurred cleanly to directly afford desmethylcephalotaxinone (**22**).[45] Thus, the initial proposal that the amino enedione **28** would undergo rapid and reversible Michael cyclization is substantiated. The preparation of **22**, the Weinreb cephalotaxine precursor, by a 13-step sequence in a 12% overall yield from the (iodoaryl)ethanol **4** represents a formal total synthesis of the natural product. Indeed, **22** in our hands is converted by use of the modified[17c] Weinreb[11] two-step procedure (see Scheme 11) to cephalotaxine in a 70% yield. The synthetic material had spectroscopic and chromatographic properties which are identical to the authentic natural product (Sigma).

Summary and Afterthoughts. The strategic foundation of the successful and concise cephalotaxine synthetic sequence described above arose from mechanistic thoughts about equilibration of potential spirocyclic amino ketone intermediates. As we suggested, the existence of desmethylcephalotaxinone (**22**) in its ring-closed, pentacyclic form is a consequence of the thermodynamics. In this regard, it is not yet known whether **22** can undergo ring opening to produce the amino enedione **28**. Fuchs[17c] has suggested that this equilibration process could have an adverse impact on attempts to use **22** as an advanced intermediate in a nonracemic cephalotaxine synthesis. However, the more recent work of Mori and his co-workers[16] has demonstrated that enantiomerically pure **22** can be prepared and transformed under proper conditions to cephalotaxinone as part of a synthesis of (+)-cephalotaxine.

Observations made during the course of our work in this area are relevant to this stereochemical issue. As pointed out repeatedly in the above discussion, macrocyclic amino enones related to **24**, **36**, and **37** may be chiral substances as a consequence of slow rotation about the bond connecting the aryl and cyclopentenone moieties and a sterically driven preference for nonplanar conformations. We believe that the energy barriers for conformer interconversion in these substances are reasonably high (see below). Thus, nonracemic macrocyclic amino enones or enediones, formed directly or by reversible ring opening of pentacyclic precursors, may maintain their enantiomeric integrity under mild preparative conditions (*e.g.*, modestly low temperatures).

Initial, albeit highly qualitative and approximate, information about this issue was gained from molecular mechanics (Macromodel, MM2) calculations on the energy-minimized amino enedione **28**. The calculated, globally minimized structure **28a**, depicted in Figure 1, possesses a nonplanar aryl enedione grouping (57 °C, C-3, C-4, C-13, C-14 dihedral angle). The calculated twist angle is surprisingly close (78.2 °C) to that determined by X-ray analysis of a closely related amino enone (replace C-2 ketone in **28** by *gem*-dimethoxy) arising during Parry's[39c] cephalotaxine chemical degradation studies. In comparison, the minimized (0 °C dihedral angle as only constraint) planar structure **28b** was found to be *ca.* 10 kcal/mol higher in energy than **28a**. One of the factors contributing to making **28b**, a model for the conformer/enantiomer interconversion transition state, more energetic is the exceedingly close distance (2.17 Å) between the C_3-carbonyl oxygen and H_{14}-aromatic hydrogen.

Further insight into this issue is gained from the results of a variable temperature ^{1}H NMR study of the *N*-benzylamino enone **36** in which an attempt was made to measure the energy barrier for conformer interconversion *via* coalescence of the resonances for diastereotopically related methylene protons. Although unique changes in chemical shifts and peak shapes were noted when the temperature was varied in the experimentally accessible range of 25−136 °C, coalescence was not reached in any case. Thus, **36** remains chiral on the NMR time scale up to temperatures of 136 °C but the exact energy of activation for the racemization process cannot be evaluated by this NMR technique.

A final observation indicating the high conformational/enantiomeric integrity of the macrocyclic amino eneones, has come from our exploration of the α′-hydroxylation reaction of the *N*-benzyl analog **36**. Oxidation of the α′-enolate of **36** with the Davis (−)-CSO at −78 °C leads to efficient (96%) production of the α′-hydroxy enone **42**. ^{1}H NMR analysis of the crude product mixture, obtained by

(45) Spectroscopic data recorded for this substance matched those reported earlier by Fuchs and his co-workers (ref 17c). We thank Professor Fuchs for kindly providing with copies of NMR spectra.

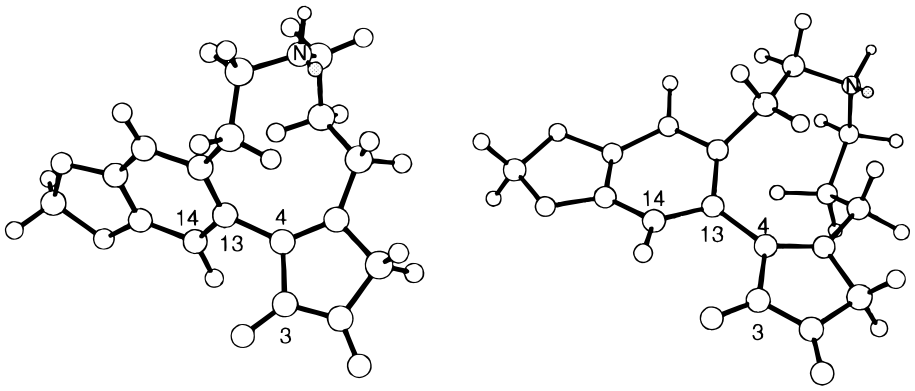
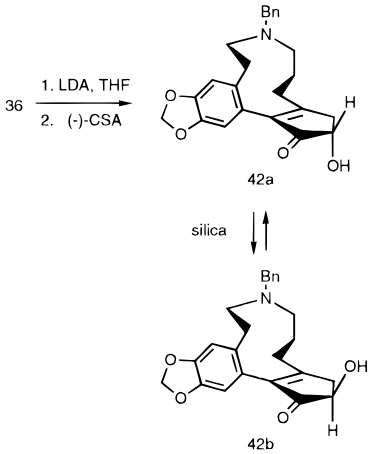


Figure 1. Chem-3D plots of the Macromodel (MM2) calculated structures of enedione **28a** (completely minimized by the multiconformer analysis routine) and its constrained, planar (0 °C $O_3-C_3-C_4-C_{14}$ dihedral angle) analog **28b**.

aqueous base workup, showed that α′-hydroxylation had produced a single diastereomer to which we assign the stereochemistry represented by **42a** on the basis of steric arguments alone. Representative ^{1}H NMR data for **42a** includes resonances for H_2 at 4.41 ppm (dd, J = 6.8, 3.4 Hz) and for the benzylic methylenes at 3.67 and 3.02 ppm (AB quartet, J = 14.2 Hz). Interestingly, attempts to purify this substance by silica gel or Florisil chromatography caused extensive isomerization and resulted in column fractions containing varying ratios (28:1 early and 2:1 late) of the respective epimeric α′-hydroxy enones **42a** and **42b**. The close spectroscopic characteristics of **42b** (H_2, 4.38 ppm, dd, J = 6.8, 3.1 Hz and $PhCH_2$-, 3.68 and 3.03 ppm, ABq, J = 14.2 Hz) and **42a** (see above) coupled with the ability to derive mixtures enriched in **42a** by treatment of those in which **42b** predominates under chromatographic conditions strongly indicates that these substances are epimers by virtue of the C-2 and biphenyl-like centers of chirality. Moreover, the epimerization process occurring upon chromatography is likely a result of acid-catalyzed α′-enolization.



These results all point to the chirality of macrocyclic amino enones and enediones related to **24** and **28** and to the possible implementation of the transannular cyclization strategy described above in a nonracemic cephalotaxine synthesis.

Experimental Section

General. All reactions were carried out under a nitrogen atmosphere. Unless otherwise noted, all reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained by distillation from the indicated drying agents: ether (Na, benzophenone ketyl), tetrahydrofuran (Na, benzophenone ketyl), methylene chloride (P_2O_5), acetonitrile (CaH_2), DMF (BaO). Drying of organic solutions following workup of reaction mixtures was done using anhydrous sodium sulfate unless indicated otherwise. Column chromatography was performed with silica gel 60 (230−400 mesh), Florisil (100−200 mesh), or Alcoa Type F-20 Alumina (neutral, 80−120 mesh). Preparative TLC was conducted using 20 × 20 cm plates coated with Type-60, GF-254 silica gel. All new compounds were obtained as oils and judged to >95% pure by ^{1}H NMR and ^{13}C NMR analysis unless otherwise specified.

^{1}H NMR spectra were recorded at 500 MHz, 400 MHz, and 200 MHz and ^{13}C NMR spectra were recorded at 126 MHz, 101 MHz, and 50 MHz. Infrared (IR) bands are reported in units of cm^{-1}.

2-(2-Iodo-4,5-(methylenedioxy)phenyl)ethanol (4). This known[13b] compound was prepared by a slight modification of the silver trifluoroacetate mediated iodination procedure of Janssen and Wilson.[46] To a vigorously stirred mixture of 6.35 g (28.7 mmol) of AgO_2CCF_3 and 4.15 g (25.0 mmol) of 2-(4,5-(methylenedioxy)phenyl)ethanol[13b] in 10 mL of $CHCl_3$ was added 7.30 g (28.7 mmol) of iodine in 375 mL of $CHCl_3$. After stirring at 25 °C for 1.5 h, the reaction mixture was filtered and the yellow precipitate was washed extensively with $CHCl_3$. The filtrate was washed with 10% aqueous $Na_2S_2O_3$, dried, and concentrated *in vacuo*, giving a residue which was crystallized from methanol−water to afford 6.10 g (83%) of aryl iodide **4**, mp 68.5−69.5 °C (lit.[13b] mp 68−69.5 °C): ^{1}H NMR 1.46 (broad s, 1 H), 2.91 (t, J = 6.7 Hz, 2 H), 3.78 (t, J = 6.7 Hz, 2 H), 5.93 (s, 2 H), 6.76 (s, 1 H), 7.21 (s, 1 H); ^{13}C NMR 43.5, 62.4, 88.0, 101.6, 110.1, 118.7, 134.3, 147.1, 148.4; IR ($CHCl_3$) 3600; MS, *m*/*z* (relative intensity) 292 (M, 100), 261 (100), 165 (40), 135 (35); HRMS, *m*/*z* 291.9601 ($C_9H_9O_3I$ requires 291.9597).

2-(2-Iodo-4,5-(methylenedioxy)phenyl)ethyl Benzyl Ether (5). To 14.8 g (0.229 mol) of powdered 86.8% KOH in 100 mL of DMSO was added a solution of 16.73 g (0.0573 mol) of iodo alcohol **4** in 25 mL of DMSO. The addition of 13.7 mL (0.115 mol) of benzyl bromide in one portion immediately followed, and the mixture was stirred for 4 h at 25 °C, poured into cold water, and extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried, and concentrated *in vacuo* to give a residue which was subjected to Florisil column chromatography (95:5 hexanes/ethyl acetate). The solid obtained was recrystallized from hexanes−ethyl acetate to afford 18.11 g (83%) of benzyl ether **5**, mp 49−50 °C: ^{1}H NMR 2.98 (t, J = 7.1 Hz, 2 H), 3.63 (t, J = 7.1 Hz, 2 H), 4.54 (s, 2 H), 5.92 (s, 2 H), 6.80 (s, 1 H), 7.22 (s, 1 H), 7.30−7.35 (m, 5 H); ^{13}C NMR 40.8, 69.6, 72.9, 88.0, 101.4, 110.0, 118., 127.5, 127.5, 128.3, 134.8, 138.3, 147.0, 148.4; IR ($CHCl_3$)

(46) Jannsen, D. E.; Wilson, C. V. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, p 576.

2880, 2860, 1040, 935, 860; MS, *m/z* (relative inensity) 382 (M, 15), 306 (6), 261 (100), 256 (15), 179 (8), 135 (60), 105 (23), 91 (94); HRMS, *m/z* 382.0086 ($C_{16}H_{15}IO_3$ requires 382.0066). Anal. Calcd for $C_{16}H_{15}IO_3$: C, 50.28; H, 3.96. Found: C, 50.40; H, 3.96.

2-(2-Formyl-4,5-(methylenedioxy)phenyl)ethyl. Benzyl Ether (6). A solution of 18.11 g (47.4 mmol) of aryl iodide **5** in 355 mL of anhydrous THF was cooled to −78 °C, and 42.0 mL of 1.38 M *n*-BuLi in hexane (Aldrich) was added dropwise. Following addition, the mixture was stirred for 1 h at −78 °C. Anhydrous *N*-formylpiperidine (distilled from BaO; 12.0 mL, 108 mmol) was added dropwise and stirring was continued at −78 °C for 8 h. The cold reaction was poured into an ice water slurry and extracted with $CHCl_3$. The extracts were combined, washed with water and saturated aqueous NH_4Cl, dried, and concentrated *in vacuo* to yield a residue which was subjected to Florisil column chromatography (90:10 hexanes/ethyl acetate) affording 11.72 g (87%) of aldehyde **6**: ^{1}H NMR 3.24 (t, J = 6.7 Hz, 2 H), 3.65 (t, J = 6.7 Hz, 2 H), 4.48 (s, 2 H), 6.01 (s, 2 H), 6.74 (s, 1 H), 7.22−7.40 (m, 5 H), 7.30 (s, 1 H), 10.12 (s, 1 H); ^{13}C NMR 32.4, 70.8, 72.9, 101.8, 108.7, 110.9, 127.4, 127.5, 128.9, 138.1, 139.1, 146.9, 152.1, 189.5; IR ($CHCl_3$) 2720, 1675, 1620, 1605; MS, *m/z* (relative intensity) 284 (M, 14), 193 (28), 178 (59), 163 (100), 148 (12), 135 (19), 105 (8), 91 (83); HRMS, *m/z* 284.1048 ($C_{17}H_{16}O_4$ requires 284.1048).

2-[2′-(2-(Benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-1,3-cyclopentanedione (8). To a solution of 2.38 g (8.36 mmol) of aldehyde **6** in 35 mL of anhydrous CH_2Cl_2 cooled to −78 °C was added 1.03 mL (8.36 mmol) of $BF_3{\cdot}OEt_2$. After 30 min a solution of 2.44 g (10.0 mmol) of 95% 1,2-bis-((trimethylsilyl)oxy)cyclobutene (Aldrich) in 17.5 mL of anhydrous CH_2Cl_2 was added dropwise. The reaction mixture was stirred at −78 °C for 10.5 h, poured into 5% aqueous $NaHCO_3$, and extracted with ether. The ethereal extracts were dried and concentrated *in vacuo* to yield 4.05 g of crude product which was shown by ^{1}H NMR to be a mixture of diastereomeric siloxycyclobutanones **7a** and diastereomeric hydroxycyclobutanones **7b**: ^{1}H NMR −0.08 to −0.02 (s, 18 H and 9 H), 1.7−2.0 (m, 1 H), 2.42−2.85 (m, 4 H), 3.04−3.37 (m, 1 H), 3.52−3.62 (m, 2 H), 4.43−4.51 (s, 2 H), 5.01−5.14 (s, 1 H), 5.86−5.93 (ABq, 2 H), 6.60−6.65 (s, 1 H), 6.89−7.06 (s, 1 H), 7.28−7.36 (br s, 5 H); ^{13}C NMR −0.2 to 1.2, 23.0−26.4, 32.4−32.9, 40.8−42.0, 70.3−73.4, 70.8, 72.9, 96.1-96.4, 100.7−101.0, 107.6−109.6, 127.6−128.3, 130.2−132.1, 138.3, 145.7−146.7, 210.2−213.3; IR ($CHCl_3$) 3520, 3020, 1785, 1505; MS for **7a** (from analysis of the mixture), *m/z* (relative intensity 442 (M, 0.68), 357 (34), 251 (8), 249 (12), 239 (12), 177 (9), 163 (9), 147 (7), 91 (100), 73 (93); HRMS of **7a**, *m/z* 442.1800 ($C_{24}H_{30}SiO_6$ requires 442.1812).

The mixture of **7a** and **7b** (4.05 g) in 25 mL of trifluoroacetic acid at 0 °C was placed in a sonicator for 45 min, poured into 125 mL of 0 °C methanol, and concentrated *in vacuo*. The solution was brought to pH 2 with concd HCl at 0 °C and extracted with CH_2Cl_2. The organic extracts were combined, dried, and concentrated *in vacuo* to yield 2.08 (71% from aldehyde) of 2-aryl-1,3-cyclopentanedione **8** which was crystallized from hexanes−ethyl acetate to give pure **8**, mp 98−99 °C: ^{1}H NMR (d_4-MeOD) 2.56 (s, 4 H), 2.66 (t, J = 7.3 Hz, 2 H), 3.50 (t, J = 7.3 Hz, 2 H), 4.43 (s, 2 H), 5.89 (s, 2 H), 6.48 (s, 1 H), 6.78 (s, 1 H), 7.28−7.30 (m, 5 H); ^{13}C NMR (d_4-MeOD) 31.6, 34.8, 72.0, 73.8, 102.3, 110.6, 111.7, 119.5, 124.6, 128.6, 128.8, 129.3, 133.3 (C-2′), 139.7, 147.4, 148.8, 198.2; IR ($CHCl_3$) 3600−2400, 1682, 1614, 1504; MS, *m/z* (relative intensity) 352 (M, 4), 310 (10), 244 (100), 231 (19), 229 (27), 188 (24), 105 (24), 91 (70), 84 (100); HRMS, *m/z* 352.1302 ($C_{21}H_{20}O_5$ requires 352.1310). Anal. Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.40; H, 5.72.

3-Chloro-2-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-2-cyclopenten-1-one (9). To a solution of 1.46 g (4.16 mmol) of 2-aryl 1,3-dione **8** in 25 mL of distilled water was added 43 mL of 0.108 M NaOH (*ca.* 4.16 mmol) dropwise. The mixture was stirred for 2 h at 25 °C and then concentrated by vacuum distillation to afford 1.57 g (100%) of the sodium salt of **8** as a solid: ^{1}H NMR (D_2O) 2.30 (s, 4 H), 2.59 (t, J = 7.6 Hz, 2 H), 3.42 (t, J = 7.6 Hz, 2 H), 4.39 (s, 2 H), 5.85 (s, 2 H), 6.46 (s, 1 H), 6.66 (s, 1 H), 7.14−7.26 (m, 5 H); ^{13}C NMR (d_6-DMSO) 33.0, 33.6, 70.9, 71.6, 100.1, 108.8, 111.6, 112.1, 127.4, 127.5, 128.4, 130.6, 131.1, 139.0, 144.3, 144.5, 198.0; IR (KBr) 1630, 1540.

To a solution of 1.56 g (4.16 mmol) of the sodium salt in 90 mL of anhydrous benzene at 10 °C was added dropwise a solution of 0.580 mL (6.65 mmol) of oxalyl chloride in 50 mL of anhydrous benzene. The resulting mixture was stirred at 50−55 °C for 24 h, cooled to 10 °C, poured into cold 5% aqueous $NaHCO_3$, and extracted with benzene. The benzene extracts were washed with brine, dried, and concentrated *in vacuo* to yield 1.41 g (91%) of chloro enone **9** as an oil: ^{1}H NMR 2.61−2.68 (m, 4 H), 2.88−2.93 (m, 2 H), 3.50 (t, J = 7.5 Hz, 2 H), 4.44 (s, 2 H), 5.91, 5.94 (ABq, J = 1.3 Hz, 2 H), 6.48 (s, 1 H), 6.80 (s, 1 H), 7.28−7.35 (m, 5 H); ^{13}C NMR 33.1, 33.7, 35.4, 70.8, 72.9, 101.2, 109.5, 109.9, 122.2, 127.5, 127.6, 128.3, 131.7, 138.3, 142.1, 146.2, 148.2, 166.2, 203.0; IR ($CHCl_3$) 1710, 1630, 1610, 1500; MS, *m/z* (relative intensity) 372, 370 (M + 2, 6; P, 16), 264, 262 (24, 72), 251, 249 (24, 66), 236, 234 (14, 41), 227 (61), 209, 207 (33, 100), 199 (10), 185 (84), 172 (23); HRMS, *m/z* 370.0967 ($C_{21}H_{19}ClO_4$ requires 370.0972).

3-[2-[(Trimethylsilyl)methyl]-2-propenyl]amino]-2-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-2-cyclopenten-1-one (11). A solution of 0.77 g (5.3 mmol) of [2-((trimethylsilyl)methyl)-2-propenyl]amine (**10**), 1.41 g (3.8 mmol) of chloro enone **9**, and 1.58 g (11 mmol) of K_2CO_3 in 120 mL of 95:5 (v/v) CH_3CN/H_2O was stirred at 75−80 °C for 67 h. The reaction was cooled to 0 °C, poured into cold saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to Florisil column chromatogrpahy (50:50 hexanes/ethyl acetate) yielding 1.38 g (76%) of enaminone **11**: UV max (CH_3CN) 276 nm (ϵ 23 600); ^{1}H NMR 0.00 (s, 9 H), 1.41 (s, 2H), 2.46−2.59 (AA′BB′, 4 H), 2.65−2.85 (m, 2 H), 3.49 (br d, J = 3.0 Hz, 2 H), 3.58 (t, J = 7.0 Hz, 2 H), 4.42 (s, 2 H), 4.62, 4.64 (s and s, 2 H), 5.41 (br t, J = 3.0 Hz, 1 H,), 5.87, 5.92 (ABq, J = 1.2 Hz, 2 H), 6.54 (s, 1 H), 6.80 (s, 1 H), 7.23−7.29 (m, 5 H); ^{13}C NMR −1.4, 24.1, 24.3, 33.2, 33.4, 49.4, 70.9, 72.9, 100.9, 107.7, 109.7, 110.6, 113.9, 124.4, 127.5, 127.6, 128.3, 132.4, 138.3, 143.6, 146.4, 147.4, 173.5, 200.6; IR ($CHCl_3$) 1660 (w), 1640 (w), 1585 (s); MS, *m/z* (relative intensity) 477 (M, 1) 462 (2), 386 (9), 369 (24), 354 (3), 242 (100), 228 (18), 185 (3), 91 (12), 73 (13); HRMS, *m/z* 477.2342 ($C_{28}H_{35}SiNO_4$ requires 477.2335).

3-[*N*-Benzyl-*N*-[2-[(trimethylsilyl)methyl]-2-propenyl]-amino]-2-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)-phenyl]-2-cyclopenten-1-one (12). A solution of 538 mg (1.13 mmol) of N-H enaminone 11 in 50 mL of anhydrous THF was added to 68 mg (1.7 mmol) of 60% NaH, and the resulting mixture was heated at reflux for 60 min. The mixture was cooled in an ice bath, and a solution of 0.670 mL (5.63 mmol) of benzyl bromide (distilled from CaH_2) in 25 mL of anhydrous THF was added dropwise. The mixture was stirred at 25 °C for 48 h, cooled to 0 °C, poured into ice water, and extracted with ether. The ethereal layers were combined, dried, and concentrated in vacuo to yield a residue which was subjected to Florisil column chromatography (60:40 hexanes/ethyl acetate) to give 564 mg (88%) of *N*-benzylated enaminone 12: UV max (CH_3CN) 282 nm (ϵ 25 500); ^{1}H NMR −0.04 (br s, 9 H), 1.41 (br s, 2 H), 2.48−2.80 (br m, 6 H), 3.46−3.64 (br m, 4 H), 4.29 (br s, 2 H), 4.43 (s, 2 H), 4.74 (br s, 2 H), 5.81, 5.82 (br s and br s, 2 H), 6.37 (br s, 1 H), 6.69 (br s, 1 H), 6.89 (br s, 2 H), 7.23−7.34 (m, 8 H); ^{13}C NMR −1.5, 24.1, 27.5, 32.8, 33.9, 53.4, 55.6, 70.8, 72.8, 100.7, 107.3, 109.3, 111.3, 113.6, 126.4, 127.3, 127.4, 127.5, 127.5, 128.2, 128.7, 132.2, 136.7, 138.6, 141.3, 145.6, 147.1, 171.3, 202.5; IR ($CHCl_3$) 3000, 1655, 1560, 1500; MS, m/z (relative intensity) 567 (M, 1), 552 (0.5), 494 (1), 476 (4), 459 (5), 386 (2), 360 (9), 332 (6), 257 (3) 242 (4), 228 (10), 185 (6), 91 (100), 73 (58); HRMS, m/z 567.2804 ($C_{35}H_{41}SiNO_4$ requires 567.2805).

***N*-Benzyl-*N*-[3-(pivaloyloxy)-2-[2′-(2-(benzyloxyl)ethyl)-4′,5′-(methylenedioxy)phenyl]cyclopent-2-enylidene]-*N*-[2-[(trimethylsilyl)methyl]-2-propenyl]ammonium Perchlorate (13).** A solution of 647 mg (1.14 mmol) of enaminone **12** in 30 mL of anhydrous CH_3CN was cooled to 0 °C, and 9.00 mL of a freshly prepared 1.27×10^{-1} M solution of anhydrous $AgClO_4$ (1.14 mmol) in anhydrous CH_3CN was added in one

portion. To this mixture at 0 °C was added dropwise a solution of 0.155 mL (1.26 mmol) of pivaloyl chloride in 50 mL of anhydrous CH_3CN. The mixture was stirred at 0 °C for 2 h, warmed to 25 °C for 45 min, and filtered through Celite. The filtrate was concentrated *in vacuo* giving a residue which was carefully washed with petroleum ether/ether (3:1) to afford 837 mg (97%) of a foam comprised of a 1:1 *E*,*Z* mixture of iminium salt **13**: UV max (CH_3CN) 284 nm (ϵ 26 000); ^{1}H NMR −0.25, −0.07 (S, 9 H), 0.81 and 0.84 (ABq, J = 5.5 Hz), 1.41 and 1.48 (ABq, J = 12.5 Hz, 2 H), 1.02 (s, 9 H), 2.54−2.74 (m, 2 H), 3.27−3.86 (m, 6 H), 3.82 and 4.12 (ABq, J = 17.3 Hz, 1H), 3.87 and 4.24 (ABq, J = 17.9 Hz, 1H) 4.20 and 5.00 (ABq, J = 15.5 Hz, 1H), 4.74 and 5.15 (ABq, J = 15.7 Hz, 1H), 4.29 and 4.38 (ABq, J = 12.3 Hz, 1H), 4.39 and 4.43 (ABq, J = 12.2 Hz, 1H), 4.61 and 4.85, 4.81 and 4.88 (s, 2 H), 5.78 and 5.87 (ABq, J = 1.2 Hz, 1H), 5.90 and 5.95 (ABq, J = 1.1 Hz, 1H), 6.63 and 6.75, 6.69 and 6.81 (s, 2 H), 7.00 (d, J = 6.4 Hz), 7.10−7.39 (m, 9 H); ^{13}C NMR −1.8, −1.6, 24.3, 24.4, 26.2, 30.3, 31.7, 32.1, 33.3, 39.7, 56.2, 57.3, 58.7, 59.5, 69.7, 69.7, 72.7, 73.0, 101.3, 108.0, 110.8, 108.9, 109.2, 109.7, 109.9, 121.2, 122.4, 122.5, 127.1, 127.3, 127.5, 127.6, 127.7, 128.2, 128.3, 128.5, 129.0, 129.1, 129.5, 131.4, 131.7, 131.9, 132.4, 137.8, 137.9, 138.0, 138.3, 146.1, 146.4, 148.8, 148.9, 172.3, 172.4, 187.4, 187.4, 187.9; IR ($CHCl_3$) 1785, 1565, 1500; MS, *m*/*z* (relative intensity) 651 (M − $HClO_4$, 0.03), 568 (28), 496 (63), 476 (12), 459 (40), 404 (39), 387 (100), 368 (23), 332 (32), 296 (58), 254 (33), 242 (28), 227 (26), 214 (22), 185 (10); HRMS, *m*/*z* 651.3374 ($C_{40}H_{49}SiNO_5$ requires 651.3380).

Irradiation of Iminium Perchlorate 13. Formation of 1-Aza-1-benzyl-6-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-3-methylidene-7-(pivaloyloxy)spiro[4.4]non-6-ene (14). A nitrogen-purged 3.4×10^{-3} M solution of iminium salt **13** in CH_3CN (837 mg, 1.11 mmol in 336 mL) was irradiated with Corex-filtered light for 12 h at which time the absorbance at 284 nm was 47% of the initial value. Saturated aqueous $NaHCO_3$ (4 mL) was added, and the resulting mixture was concentrated *in vacuo* to give a residue which was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried and concentrated *in vacuo* to yield a residue which was subjected to F-20 alumina column chromatography giving 297 mg (46%) of spirocyclic amine **14** (elution with 90:10 hexanes/ethyl acetate) and 251 mg (40%) of enaminone **12** (elution with ethyl acetate). **14**: UV max (CH_3CN) 291 (ϵ 5100); ^{1}H NMR 1.00 (s, 9 H), 1.65 (d of apparent t, J = 13.7, 9.7, 8.3 Hz, 1 H), 2.08 (d, J = 15.3 Hz, 1 H), 2.32−2.46 (m, 3 H), 2.71−2.79 (m, 2 H, H-8), 2.80−2.91 (m, 2 H), 3.25 (d, J = 13.7 Hz, 1 H), 3.46 (d, J = 14.3 Hz, 1 H), 3.54 (dt, J = 9.2, 6.2 Hz), 3.61 (dt, J = 9.2, 6.1 Hz, 1 H), 4.51 (d, J = 13.7 Hz, 1 H), 4.54 (ABq, J = 12.1 Hz, 2 H), 4.71, 4.73 (s, 2 H), 5.88, 5.89 (ABq, J = 1.4 Hz, 2 H), 6.75 (s, 1 H), 6.77 (s, H), 7.17−7.41 (m, 10 H); ^{13}C NMR (CD_3CN) 27.1, 27.2, 31.0, 34.4, 39.5, 45.1, 52.5, 55.7, 71.6, 73.3, 77.6, 102.2, 105.7, 110.0, 110.9, 126.4, 127.4, 127.7, 128.5, 128.6, 129.0, 129.4, 133.0 (C-2′), 140.1, 141.0, 146.3, 147.4, 148.0, 152.3, 176.7; IR ($CHCl_3$) 1740, 1685 (w), 1500; MS, *m*/*z* (relative intensity) 579 (M, 4), 494 (7), 488 (5), 386 (4), 372 (2), 238 (3), 198 (4), 184 (29), 149 (3), 129 (4), 115 (3), 106 (4), 91 (100), 85 (5), 57 (67); HRMS, *m*/*z* 579.3009 ($C_{37}H_{41}NO_5$ requires 579.2985).

1-Aza-1-benzyl-6-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-7-(pivaloyloxy)spiro[4.4]non-6-en-3-one (16). To a solution of 297 mg (0.512 mmol) of spirocyclic amine **14** in 90 mL of methanol at −78 °C was added 0.050 mL of 70% aqueous $HClO_4$ (0.58 mmol). After the solution was stirred for 30 min, 32 mL of a −78 °C O_3-saturated CH_2Cl_2 solution (1.2 mmol of O_3) was added. The mixture was maintained at −78 °C for 30 min, quenched sequentially with 2 mL of dimethyl sulfide and 2 mL of saturated aqueous $NaHCO_3$, warmed to 25 °C, poured into cold water, and extracted with $CHCl_3$. The organic extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to Florisil column chromatography (90:10 hexanes/ethyl acetate) to afford 187 mg (63%) of ketone **16**: ^{1}H NMR 0.99 (s, 9 H), 1.74 (d of apparent t, J = 13.8, 9.7, 8.4 Hz, 1 H), 2.09 (d, J = 17.4 Hz, 1 H), 2.43 (d, J = 17.4 Hz, 1 H), 2.43−2.51 (m, 2 H), 2.67−2.74 (m, 1 H), 2.72 (d, J = 17.8 Hz, 1 H), 2.79−2.87 (m, 2 H), 3.23 (d J = 17.8 Hz, 1 H), 3.36 (d, J = 13.5 Hz, 1 H), 3.51 (dt, J = 9.0, 6.4 Hz, 1 H), 3.60 (dt, J = 9.0, 5.9 Hz, 1 H), 4.50, 4.53 (ABq, J = 12.7 Hz, 2 H), 4.66 (d, J = 13.5 Hz, 1 H), 5.87, 5.89 (ABq, J = 1.4 Hz, 2 H), 6.78 (s, 1 H), 6.82 (s, 1 H), 7.20−7.34 (m, 10 H); ^{13}C NMR 26.5, 26.7, 30.2, 33.3, 38.6, 49.9, 51.6, 57.7, 70.7, 72.9, 74.7, 100.9, 108.9, 110.2, 124.1, 125.3, 126.9, 127.5, 127.6, 128.1, 128.3, 128.4, 131.5, 138.2, 138.3, 145.6, 147.2, 151.7, 175.6, 212.6; IR ($CHCl_3$) 2950, 2925,2860, 1745,1680 (w); MS, *m*/*z* (relative intensity) 581 (M, 24), 496 (6), 406 (6), 242 (7), 200 (6), 186 (6), 120 (43), 91 (100), 57 (73);HRMS, *m*/*z* 581.2780 ($C_{36}H_{39}NO_2$ requires 581.2777).

1-Aza-1-benzyl-6-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-7-(pivaloyloxy)spiro[4.4]non-6-en-3-one Dithioketal (17). To a solution of 119 mg (0.204 mmol) of ketone **16** in 1.85 mL (22.0 mmol) of 1,2-ethanedithiol at −15 to −20 °C was added dropwise 0.215 mL (1.75 mmol) of $BF_3{\cdot}OEt_2$. The resulting mixture was stirred at −15 to −20 °C for 8.5 h, poured into cold saturated aqueous $NaHCO_3$, and extracted with ether. The ethereal extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to Florisil column chromatography (90:10 hexanes/ethyl acetate) to afford 97 mg (72%) of thioketal **17**: ^{1}H NMR 0.97 (s, 9 H), 1.80 (ddd, J = 13.6, 9.5, 8.3 Hz, 1 H), 2.23 (d, J = 13.9 Hz, 1 H), 2.32−2.39 (m, 1 H), 2.46 (d, J = 13.9 Hz, 1 H), 2.48−2.57 (m, 1 H), 2.69−2.76 (m, 2 H), 2.79−2.89 (m, 2 H), 2.83 (d, J = 10.2 Hz, 1 H), 2.98−3.03 (m, 1 H), 3.14−3.20 (m, 2 H), 3.30 (d, J = 10.2 Hz, 1 H), 3.34 (d, J = 13.9 Hz, 1 H), 3.52 (dt, J = 9.2, 6.1 Hz, 1 H), 3.61 (dt, J = 9.2, 5.9 Hz, 1 H), 4.47 (d, J = 13.9 Hz, 1 H), 4.51, 4.55 (ABq, J = 12.1 Hz, 2 H), 5.86, 5.92 (ABq, J = 1.5 Hz, 2 H), 6.74 (s, 1 H), 6.83 (s, 1 H), 7.18−7.44 (m, 10 H); ^{13}C NMR (CD_3CN) 27.1, 29.0, 31.1, 34.4, 39.5, 40.7, 40.9, 50.9, 55.7, 65.7, 68.4, 71.5, 73.3, 77.6, 102.2, 109.9, 111.2, 126.3, 127.2, 127.7, 128.5, 129.0, 129.4, 133.1, 140.1, 140.8, 146.3, 148.0, 152.5, 176.7; IR ($CHCl_3$) 1735; MS, *m*/*z* (relative intensity) 657 (M, 100), 572 (44), 566 (31), 556 (24), 550 (11), 538 (36), 537 (35), 453 (21), 345 (22), 262 (70), 223 (33), 185 (23), 120 (40); HRMS, *m*/*z* 657.2605 ($C_{38}H_{43}NO_5S_2$ requires 657.2583).

1-Aza-1-benzyl-6-[2′-(2-(benzyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-7-(pivaloyloxy)spiro[4.4.]non-6-ene (18). Raney nickel (Aldrich) (5.6 g of a 50% slurry in pH 10 water) was sequentially repetitively washed with 50 mL portions of water and THF, suspended in 50 mL of THF, and added as a slurry to 188 mg (0.286 mmol) of thioketal **17**. The mixture was stirred for 2.5 h at 25 °C and filtered through Celite. The filtrate was concentrated *in vacuo* to yield a residue which was subjected to F-20 alumina column chromatography (hexanes to 95:5 hexanes/ethyl acetate) to afford 105 mg (65%) of spirocyclic amine **18**. Crystallization from hexanes−ethyl acetate gave pure **18**, mp 114−115 °C: UV max (CH_3CN) 290 nm (ϵ 4000); ^{1}H NMR 0.97 (s, 9 H), 1.45−1.74 (m, 5 H), 2.23 (dt, J = 9.1, 6.9 Hz), 2.32−2.36 (m, 1 H), 2.36 (dd, J = 16.5, 8.5 Hz, 1 H), 2.73 (p, J = 8.3 Hz, 1 H), 2.76−2.91 (m, 3 H), 3.25 (d, J = 13.6 Hz), 3.55 (dt, J = 9.2, 6.2 Hz, 1 H), 3.26 (dt, J = 9.2, 6.2 Hz, 1 H), 4.44 (d, J = 13.6 Hz), 4.52, 4.55 (ABq, J = 12.1 Hz, 2 H), 5.86, 5.90 (ABq, J = 1.5 Hz, 2 H), 6.75 (s, 1 H), 6.77 (s, 1 H), 7.16−7.40 (m, 10 H); ^{13}C NMR 20.9, 26.8, 27.1, 30.1, 33.4, 36.9, 38.7, 49.6, 52.1, 71.1, 72.9, 76.2, 100.7, 108.7, 110.5, 125.8, 126.4, 127.1, 127.5, 127.6, 128.2, 128.3 128.4, 131.2, 138.5, 140.4, 145.3, 146.8, 150.3, 175.8; IR ($CHCl_3$) 1735, 1680; MS, *m*/*z* (relative intensity) 567 (M, 15), 482 (36), 476 (30), 466 (52), 432 (8), 374 (21), 186 (23), 173 (52), 149 (40), 120 (100); HRMS, *m*/*z* 567.3006 ($C_{36}H_{41}NO_5$ requires 567.2985). Anal. Calcd for $C_{36}H_{41}NO_5$: C, 76.16; H, 7.28; N, 2.47. Found: C, 75.80; H, 7.26; N, 2.41.

1-Aza-6-[2′-(2-hydroxyethyl)-4′,5′-(methylenedioxy)phenyl]-7-(pivaloyloxy)spiro[4.4]non-6-ene (19). To a solution of 79 mg (0.14 mmol) of **18** in 14 mL of anhydrous methanol were added 80 mg of 10% Pd/C and 4.8 mL of a freshly prepared 0.25 M solution of anhydrous ammonium formate (1.2 mmol) in anhydrous methanol. The resulting mixture was stirred at reflux for 25 min, cooled to 0 °C, and filtered through Celite. The collected solids were washed with ethyl acetate, and the resulting filtrate was extracted with cold saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the organic layers were combined, dried, and concentrated *in vacuo* to give **19** which was not purified further: ^{1}H

NMR 0.97 (s, 9 H), 1.66−1.80 (m, 3 H), 1.86−1.92 (m, 1 H), 2.02 (ddd, J = 13.0, 8.5, 4.8 Hz, 1 H), 2.13 (ddd, J = 13.0, 8.6, 5.5 Hz, 1 H), 2.47−2.55 (m, 2 H, H-8), 2.64−2.72 (m, 2 H,), 2.88−2.97 (m, 2 H), 3.68 (ddd, J = 12.2, 10.5, 3.3 Hz, 1 H), 3.93 (ddd, J = 10.5, 4.9, 2.5 Hz, 1 H), 5.85, 5.90 (ABq, J = 1.4 Hz, 2 H), 6.43 (s, 1 H), 6.78 (s, 1 H); ^{13}C NMR 24.5, 26.8 ($C(CH_3)_3$), 28.8, 35.2, 35.7, 38.4, 38.8, 44.8, 62.7, 73.1, 100.8, 108.1, 109.8, 125.6, 130.1, 133.0, 145.5, 147.5, 148.8, 176.0; IR (CS_2) 3350; MS, m/z (relative intensity) 387 (M, 1), 286 (31), 124 (21), 96 (47), 57 (100); HRMS, m/z 387.2052 ($C_{22}H_{29}NO_5$ requires 387.2046).

2,3,5,6,8,9-Hexahydro-1-(pivaloyloxy)-4*H*-cyclopenta-[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine (20). To a solution of 56 mg (0.21 mmol) of triphenylphospine in 1.0 mL of anhydrous CH_3CN were added sequentially 0.028 mL (0.29 mmol) of carbon tetrachloride and 0.041 mL (0.29 mmol) of triethylamine. After the solution was stirred for 15 min, amino alcohol **19** was added and the resulting mixture was stirred for 28 h at 25 °C, poured into cold saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to F-20 alumina column chromatography (90: 10 hexanes/ethyl acetate) to afford 22 mg (43% from **18**) of **20**: UVmax (CH_3CN) 254 nm (ϵ 7100), 296 nm (ϵ 4100); ^{1}H NMR 1.15 (s, 9 H), 1.60 (t, J = 11.0 Hz, 1 H), 1.65−1.84 (m, 3 H), 1.91 (ddd, J = 12.5, 7.9, 2.3 Hz, 1 H), 2.03 (br dt, J = 12.2, 9.1 Hz, 1 H), 2.44 (ddd, J = 15.5, 9.1, 2.1 Hz, 1 H), 2.56 (p, J = 8.0 Hz, 1 H), 2.77−2.86 (m, 2 H,), 2.90−2.97 (m, 2 H), 3.15 (7 line m, 1 H), 3.51 (7 line m, 1 H), 5.86, 5.87 (ABq, J = 1.5 Hz, 2 H), 6.52 (s, 1 H), 6.57 (s, 1 H); ^{13}C NMR (CD_3CN) 23.9, 27.3, 29.9, 33.0, 36.4, 36.5, 39.5, 44.8, 50.2, 76.8, 102.2, 110.6, 125.8, 132.3, 133.1, 146.4, 147.3, 148.0, 176.9; IR ($CHCl_3$) 1735, 1500; MS, m/z (relative intensity) 369 (M, 62), 354 (5), 312 (10), 284 (100), 268 (18), 256 (25), 242 (16), 228 (10), 57 (49); HRMS, m/z 369.1937 ($C_{22}H_{27}NO_4$ requires 369.1940).

Macrocyclic Amino Enone 24 and Pentacyclic Amino Ketone 23. To a solution of 23 mg (0.062 mmol) of enol ester **20 i**n 5 mL of anhydrous methanol at 0 °C was added 4.0 mL of a 2.3×10^{-2} M solution of sodium methoxide (0.093 mmol) in anhydrous methanol. The reaction mixture was stirred at 25 °C for 16 h, cooled to 0 °C, poured into cold water, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to F-20 alumina column chromatography (50:50 hexanes/ethyl acetate) to afford 14 mg (79%) of an inseparable 10:1 mixture of amino enone **24** and spirocyclic amino ketone **23**: UVmax (CH_3CN) 292 (ϵ 4200); ^{1}H NMR 1.60−1.80 (m, 2 H), 2.09−2.22 (m, 2 H), 2.34 (dt, J = 13.6, 2.8 Hz, 1 H), 2.49 (ddd, J = 13.8, 10.8, 5.4 Hz, 1 H), 2.54−2.58 (m, 3 H), 2.68−2.89 (m, 5 H), 3.39 (s, 1), 5.88 and 5.89 (ABq, J = 1.4 Hz, 2 H), 5.90 and 5.93 (ABq, J = 1.5 Hz, 2H), 6.36 and 6.70 (s, 2 H), 6.57 and 6.62 (s, 2H); ^{13}C NMR (**23**) 208.2, 176.0, 148.0, 146.2, 144.3, 133.3, 126.4, 109.1, 109.0, 101.1, 49.2, 42.4, 34.6, 30.6, 28.5, 27.0, 24.9; ^{13}C NMR (**24**) 218.4, 147.1, 147.0, 131.1, 128.3, 112.1, 109.9, 101.0, 66.1 (C3a), 63.5, 52.4, 47.4, 41.4, 37.5, 32.5, 24.5, 19.8; IR ($CHCl_3$) 1740, 1705, 1650, 1500; MS, m/z (relative intensity) 285 (M, 8), 229 (10), 137 (20), 129 (31), 91 (26), 70 (37), 57 (100); HRMS, m/z 285.1347 ($C_{17}H_{19}NO_3$ requires 285.1365).

2-(2-Iodo-4,5-(methylenedioxy)phenyl)ethyl *tert*-Butyldimethylsilyl Ether (29). A solution of *tert*-butyldimethyl-silyl chloride (9.45 g, 62.3 mmol) and *N*,*N*-diisopropylethylamine (13.6 mL, 78.1 mmol) in 60 mL of anhydrous DMF was added to a solution of iodo alcohol **4** (15.5 g, 51.9 mmol) in 135 mL of anhydrous DMF. After the solution was stirred at 25 °C for 2 h, 11 mL of water was added and the mixture was stirred for 10 min. Ether and saturated aqueous $NaHCO_3$ were added, and the mixture was stirred for 15 min. The ether layer was separated, dried, and concentrated *in vacuo* to yield silyl ether **29** (21.5 g, 100%): ^{1}H NMR 7.18 (s, 1H), 6.74 (s, 1H), 5.91 (s, 2H,), 3.71 (t, J = 6.9, 2H,), 2.84 (t, J = 6.9, 2H,), 0.86 (s, 9H), −0.01 (s, 6H); ^{13}C NMR 148.3, 147.0, 135.2, 118.5, 110.5, 101.4, 87.9, 62.8, 43.8, 25.9, 18.3, −5.3, IR 2850, 1500, 1470, 1405; MS m/z (relative intensity) 406 (M, 10), 349 (100), 261 (25), 223 (100), 222 (100), 208 (60), 207 (100), 89 (60), 73 (80); HRMS m/z 406.0457 ($C_{15}H_{23}O_3ISi$ requires 406.0461).

2-(2-Formyl-4,5-(methylenedioxy)phenyl)ethyl *tert*-Butyldimethylsilyl Ether (30). A solution of aryl iodide **29** (21.3 g, 52.4 mmol) in 250 mL of anhydrous THF was cooled to −78 °C, and *n*-BuLi (47.0 mL, 1.35 M) was added dropwise. The mixture was stirred for 1 h at −78 °C. A solution of anhydrous DMF (9.0 mL, 0.116 mol) in 20 mL of anhydrous THF was added dropwise, and stirring was continued at −78 °C for 10 h. The mixture was poured into an ice water slurry and extracted with chloroform. The extracts were combined, washed with water and saturated aqueous NH_4Cl, dried, and concentrated *in vacuo* to yield a residue which was subjected to column chromatography (Florisil, hexane−EtOAc, 95/5) yielded 13.6 g (84% yield) of aldehyde **30** as crystals which were recrystallized from hexane−EtOAc, mp 53−54 °C: ^{1}H NMR 10.12 (s, 1H), 7.30 (s, 1H), 6.70 (s, 1H, 5.99 (s, 2H), 3.78 (t, J = 6.5 Hz, 2H), 3.12 (t, J = 6.5 Hz), 0.80 (s, 9H), −0.09 (s, 6H); ^{13}C NMR 192.8, 154.3, 148.9,141.4 130.7, 112.0, 109.0, 102.5, 63.9, 33.9, 24.4, 16.5, −7.9; IR 2930, 2860, 1680, 1480, 1260; MS m/z (relative intensity) 308 (M, 2), 293 (64), 253 (100), 252 (100), 251 (100), 221 (100), 209 (100), 193 (100); HRMS m/z 308.1458 ($C_{16}H_{24}O_4Si$ requires 308.1444). Anal. Calcd for $C_{16}H_{24}O_4Si$: C, 62.30; H, 7.84. Found: C, 62.29; H, 7.88.

Tetracyclic Enol Ether 31. To a solution of aldehyde **30** (2.48 g, 8.04 mmol) in 32 mL of anhydrous CH_2Cl_2 at −78 °C was added dropwise boron trifluoride etherate (1.04 mL 8.44 mmol), and the mixture was stirred for 20 min, followed by addition of 1,2-bis(trimethylsilyoxycyclobutene (Aldrich) (2.48 mL, 9.65 mmol) in 16 mL of CH_2Cl_2. The mixture was stirred at −78 °C for 10 h, poured into 5% aqueous $NaHCO_3$, and extracted with ether. The organic extracts were dried and concentrated *in vacuo* giving 4.28 g of residue oil which was treated with 80.0 mL of trifluoroacetic acid at 25 °C for 21 h. The resulting dark brown solution was concentrated under reduced pressure giving a brown solid which was crystallized from THF to afford 1.76 g (90%, 2 steps) of **31**, mp 145−146 °C: ^{1}H NMR 7.84 (s, 1H), 6.53 (s, 1H), 5.91 (s, 2H), 4.47 (dd, J = 5.0, 3.3 Hz, 2H), 2.97 (dd, J = 5.0, 3.3 Hz, 2H), 2.53−2.62 (AA′BB′m, 4H); ^{13}C NMR 204.3, 182.0, 142.6, 142.1, 133.6, 123.8, 114.9, 108.7, 108.5, 101.0, 73.5, 37.0, 33.9, 27.2; IR 2902, 2355, 2337, 1678, 1594, 1504, 1481; MS m/z (relative intensity) 244 (M, 100), 229 (47), 188 (8), 173 (8), 160 (15); HRMS m/z 244.0721 ($C_{14}H_{12}O_4$ requires 244.0736). Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.94; H, 5.09.

3-[2-(1,3-Dioxolanyl)ethyl]-2-[2′-(2-hydroxyethyl)-4′,5′-(methylenedioxy)phenyl]- 2-cyclopenten-1-one (32). To a solution of tetracyclic enol ether **31** (4.12 g, 16.9 mmol) in 400 mL of THF was added (2-(1,3-dioxolanyl)ethyl)magnesium bromide (76.0 mL, 0.894 M, 67.9 mmol). The mixture was stirred at 25 °C for 24 h, dilluted with aqueous NH_4Cl, and extracted with ether. The organic extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to column chromatography (Florisil, hexane−EtOAc, 50/50) to give 4.76 g (82%) of **32**: ^{1}H NMR 6.78 (s, 1H), 6.39 (s, 1H), 5.95 and 5.90 (ABq, J = 1.4 Hz, 2H), 4.78 (t, J = 4.5 Hz, 1H,), 3.92−3.78 (A_2B_2m, 4H), 3.69 (t, J = 6.5 Hz, 1H), 2.69 (m, 2H), 2.56−2.44 (m, 6H), 1.84 (m, 2H); ^{13}C NMR 208.8, 176.7, 147.9 and 146.3, 141.8, 131.2, 124.8, 109.8 and 109.4, 103.5, 101.1, 65.0, 63.0, 36.0, 34.6, 30.9, 29.3, 26.1; IR 3424, 2884, 1693, 1634, 1508, 1475; MS m/z (relative intensity) 346 (M, 8), 328 (52), 255 (12), 227 (88), 185 (100); HRMS m/z 346.1388 ($C_{19}H_{22}O_6$ requires 346.1416).

3-[2-(1,3-Dioxolanyl)ethyl]-2-[2′-(2-mesyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-2-cyclopenten-1-one (33). To a solution of alcohol **32** (5.31 g, 15.3 mmol) in 150 mL of CH_2Cl_2 were added sequentially triethylamine (2.60 mL, 18.7 mmol) and methanesulfonyl chloride (1.43 mL, 18.4 mmol). The mixture was stirred at 25 °C for 9.5 h, diluted with water, and extracted with ether. The organic extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to column chromatography (Florisil, hexane−EtOAc, 50/50) to give 6.51 g (100%) of **33**: ^{1}H NMR 6.73 (s, 1H), 6.40 (s, 1H), 5.93 and 5.89 (ABq, J = 1.4 Hz, 2H), 4.77 (t, J = 7.4 Hz, 2H), 3.89−3.77 (A_2B_2 m, 4H,), 2.86 (s, 3H), 2.75−2.67 (m, 4H), 2.54−2.39 (m, 4H), 1.88−1.78 (m, 2H); ^{13}C NMR 208.3, 176.9, 147.7, 146.7, 141.1, 128.4, 125.3, 110.0, 109.8, 103.3, 101.2, 70.0, 64.9,

37.0, 34.6, 33.2, 30.8, 29.2, 26.0; IR 2923, 1694, 1636, 1505, 1486; MS *m/z* (relative intensity) 424 (M, 2), 328 (63), 255 (42), 242 (44), 227 (70), 185 (100); HRMS *m/z* 424.1227 ($C_{20}H_{24}O_8S$ requires 424.1192).

2-[2′-(2-(mesyloxy)Ethyl)-4′,5′-(methylenedioxy)phenyl]-3-(2-formylethyl)-2-cyclopenten-1-one (34). To a solution of 1,3-dioxolane **33** (2.60 g, 6.13 mmol) in 250 mL of acetone at 0 °C was added 125 mL of 10% aqueous HCl. The mixture was stirred at 25 °C for 44 h, poured into ice water, and extracted with ether and CH_2Cl_2. The extracts were dried and concentrated in vacuo to yield a residue which was subjected to column chromatography (Florisil, ether−EtOAc, 50/50) to yield 2.15 g (92%) of aldehyde **34**: ^{1}H NMR 9.73 (s, 1H), 6.75 (s, 1H), 6.44 (s, 1H), 5.96 and 5.93 (ABq, J = 1.4 Hz, 2H), 4.19 (m, 2H), 2.89 (s, 3H), 2.77−2.55 (m, 10H); ^{13}C NMR 208.1, 199.9, 175.0, 148.0, 146.9, 141.8, 128.5, 125.0, 110.0, 101.4, 70.0, 40.7, 37.2, 34.6, 33.4, 29.4, 24.1; IR 2923, 1716, 1694, 1636, 1505, 1486; MS *m/z* (relative intensity) 380 (M, 4), 284 (100), 255 (25), 227 (62), 199 (40), 185 (93); HRMS *m/z* 380.0915 ($C_{18}H_{20}O_7S$ requires 380.0930).

3-[3-(*N*-Benzylamino)propyl]-2-[2′-(2-(mesyloxy)ethyl)-4′,5′-(methylenedioxy)phenyl]-2-cyclopenten-1-one (35). A mixture of aldehyde **34** (0.775 g, 2.04 mmol) and benzylamine hydrochloride (1.17 g, 8.15 mmol) in 45 mL of THF and 20 mL of absolute alcohol was stirred at 25 °C for 1 h. To this mixture were added NaOAc (0.669 g, 8.15 mmol) and sodium cyanoborohydride (0.256 g, 4.08 mmol). The reaction mixture was stirred at 25 °C for 13 h, poured into ice water, and extracxted with ether and CH_2Cl_2. The extracts were dried and concentracted *in vacuo* giving 0.955 g (100%) of amine **35** which was not purified prior to use in further reactions. The spectroscopic data were obtained with material purified by Florisil chromatography (10% MeOH in $CHCl_3$): ^{1}H NMR 7.33−7.18 (m, 5H), 6.74 (s, 1H), 6.41 (s, 1H), 5.92 and 5.91 (ABq, J = 1.3 Hz, 2H), 4.16 (t, J = 7.4 Hz, 2H), 3.71 (s, 2H), 2.87 (s, 3H), 2.75−2.33 (m, 10H),1.69 (p, J = 7.3 Hz, 2H); ^{13} C NMR 208.4, 177.4, 147.8, 146.8, 141.2, 140.0, 128.4, 128.4, 128.1, 127.1, 125.4, 110.1, 109.9, 101.3, 70.0, 53.6, 48.7, 37.1, 34.7, 33.4, 29.6, 29.3 (C4), 27.4; IR 3479, 2920, 2855, 1694, 1625, 1455; MS *m/z* (relative intensity) 471 (M, 3), 375 (69), 318 (16), 284 (19), 256 (32), 228 (24), 199 (19), 185 (30), 111 (100); HRMS *m/z* 471.1698 ($C_{25}H_{29}NO_6S$ requires 471.1716).

Macrocyclic Amino Enone 36 by Cyclization of Amino Alcohol 35. To a solution of amine **35** (0.955 g, 2.04 mmol) in 700 mL of MeCN (2.91×10^{-3} M) was added diisopropylethylamine (1.50 mL, 8.16 mmol). The reaction mixture was stirred at 65 °C for 77 h, cooled to 25 °C, poured into ice water, and extracted with ether and CH_2Cl_2. The organic extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to column chromatography (Alumina, hexane−EtOAc, 60/40) to give 0.491 g (64% from **34**) of the macrocyclic amino enone **36**: ^{1}H NMR 7.12 (m, 3H), 6.74 (d, J = 7.2, 2H), 6.40 (s, 1H, 6.28 (s, 1H), 5.99 and 5.90 (ABq, J = 1.4 Hz, 2H), 3.68 and 3.60 (ABq, J = 14.2 Hz, 2H), 3.11 (t brd, J = 12.8, 4.0 Hz, 1H), 2.77 (ddd, J = 17.2, 6.5, 2.5 Hz, 1H), 2.58−2.19 (m, 8H), 2.09 (d brt, J = 12.1 Hz, 1H), 1.82 (m, 1H), 1.62 (m, 2H); ^{13}C NMR 208.7, 177.1, 147.3, 145.5, 144.4, 139.4, 134.1, 128.3, 127.8, 126.5, 125.9, 109.5, 108.6, 100.8, 58.5, 54.7, 48.9, 34.7, 30.9, 28.3, 28.0, 23.5; IR 2923, 1699, 1636, 1558, 1540, 1483, 1457; MS *m/z* (relative intensity) 375 (M, 100), 284 (35), 256 (13), 227 (12), 199 (8), 185 (15); HRMS *m/z* 375.1846 ($C_{24}H_{25}NO_3$ requires 375.1834).

***N*-Benzyl Macrocyclic Amino Enone 36 by N-Benzylation of 24.** To a solution of pentacyclic enol ester **20** (12 mg, 0.033 mmol) in 2 mL of MeOH was added sodium methoxide (3 mg, 0.056 mmol) in 2 mL of MeOH. The reaction mixture was stirred at 25 °C for 17 h, poured into cold water, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated *in vacuo* giving 9 mg of a residue which was shown to contain a 10:1 mixture of enone **24** and spirocyclic ketone **23** by ^{1}H NMR. This mixture was dissolved in 3 mL of anhydrous MeCN, and K_2CO_3 (9 mg, 0.065 mmol) and benzyl bromide (0.010 mL, 0.084 mmol) were added. The mixture was stirred at 45 °C for 5 h, poured into cold water, and extracted with ether. The organic extracts were dried and concentrated in vacuo to yield a residue which was subjected to TLC (silica gel, $CHCl_3$−MeOH, 95/5) to give 9 mg of *N*-benzyl **36** (76% yield, two steps).

Macrocyclic Amino Enone 24 from 36. A mixture of 10% Pd/C (0.80 g), and *N*-benzylaminoenone **36** (1.00 g, 2.67 mmol) in 135 mL of isopropyl alcohol was stirred under H_2 for 3 days, filtered through a Celite. The filtrate was concentrated in vacuo to yield a residue which was subjected to column chromatography (alumina, ethyl acetate and 5% MeOH in $CHCl_3$) affording 0.145 g of recovered **36** (86% conversion) and 0.543 g (83% yield based upon recovered starting material) of an inseparable 10:1 mixture of enone **24** and spirocyclic ketone **23**.

Macrocyclic *N*-*tert*-Butoxycarbonyl Amino Enone 37. To amine **24** (0.339 g, 1.19 mmol) in 9.0 mL of anhydrous CH_2Cl_2 at 0 °C was added di-*tert*-butyl dicarbonate (0.310 g, 1.42 mmol) in 6.0 mL of CH_2Cl_2 dropwise. The mixture was warmed to 25 °C and stirred for 12 h, poured into ice water, and extracted with CH_2Cl_2. The extracts were dried and concentrated in vacuo to yield a residue which was subjected to column chromatography (Florisil, ether) to yield 0.353 g (100% yield) of **37**: ^{1}H NMR 6.73 (s, 1H), 6.35 (s, 1H), 5.90 and 5.88 (ABq, J = 1.33 Hz, 2H), 3.41 (br s, 1H), 3.29 (br s, 1H), 2.99 (br t, 2H), 2.85−2.77 (m, 1H), 2.54−2.39 (m, 6H), 2.20−2.11 (m, 2H), 1.63 (br t), 1.31 (s, 9H); ^{13}C NMR 207.9, 177.8, 156.1, 147.6, 146.1, 142.4, 132.7, 125.9, 109.8, 108.6, 100.9, 79.4, 51.4, 47.5, 34.7, 32.0, 29.7, 28.9, 28.2, 24.0; IR 2921, 1687, 1486; MS *m/z* (relative intensity) 385 (M, 12), 329 (27), 285 (16), 242 (9), 228 (10), 57 (100); HRMS *m/z* 385.1887 ($C_{22}H_{27}NO_5$ requires 385.1889).

Macrocyclic *N*-*tert*-Butoxycarbonyl α′-Hydroxy Amino-Enone 38. To 6.0 mL (0.36 M, 2.16 mmol) of lithium diisopropylamide in THF at −78 °C was added enone **37** (0.353 g, 0.917 mmol) in 5.0 mL of anhydrous THF. The mixture was stirred at −78 °C for 1 h, followed by addition of ((−)-camphorsulfonyl)oxaziridine (1.05 g, 4.58 mmol) in 5.0 mL of THF dropwise. The mixture was stirred at −43 °C for 1.5 h, dilluted with aqueous NH_4Cl, warmed to 25 °C, and extracted with CH_2Cl_2. The extracts were dried and concentrated *in vacuo* to yield a residue which was subjected to column chromatography (silica gel, ether) to yield 0.050 g of recovered **37** (86% conversion) and 0.247 g (78% yield based upon recovered starting material) of **38** as a pair of diastereomers (*ca.* 1:1): ^{1}H NMR 6.79, 6.75 (s, 1H), 6.40, 6.36 (s, 1H), 5.92 (m, 2H), 4.37 (m, 1H), 3.72 (br s, 1H), 3.40 (m, 1H), 3.19−2.09 (m, 9H), 1.65 (br t), 1.30, 1.22 (s, 9H); ^{13}C NMR 207.2, 175.4, 156.2, 147.7, 146.1, 139.5, 139.4, 132.6, 125.9, 109.9, 109.8, 108.7, 108.3, 101.1, 79.5, 72.2, 71.5, 51.6, 50.7, 47.9, 46.5, 38.4, 37.9, 32.2, 31.4, 29.6, 28.9, 28.3, 23.9; IR 3391, 2911, 1682, 1486; MS *m/z* (relative intensity) 401 (M, 58), 345 (47), 328 (44), 301 (50), 283 (100), 229 (38); HRMS *m/z* 401.1840 ($C_{22}H_{27}O_6N$ requires 401.1838).

Macrocyclic α′-Hydroxy Amino Enone 39 and Spirocyclic α′-Hydroxy Amino Ketone 40. To a solution of enone **38** (34 mg, 0.085 mmol) in 1.5 mL of anhydrous CH_2Cl_2 at 0 °C was added trimethylsilyl trifluoromethanesulfonate (0.049 mL, 0.245 mmol). After stirring at 0 °C for 1 h, the mixture was warmed to 10 °C and stirred for 1 h, poured into water, and extracted with CH_2Cl_2. The extracts were dried and concentrated in vacuo to give a residue characterized as a 5:1 inseparable mixture of macrocyclic enone **39** and spirocyclic ketone **40** (24 mg, 92%), both existing as a pair of diastereomers: ^{1}H NMR **39**, 6.70 (s, 1H), 6.69 (s, 1H), 6.37 (s, 1H), 6.34 (s, 1H), 5.93−5.89 (m, 2H), 4.38−4.32 (m, 1H), 3.08 (dd, J = 17.9, 6.8 Hz, 1H), 2.95−1.67 (m, 1H); **40**, 6.66 (s, 1H), 6.54 (s, 1H), 5.93−5.89 (m, 2H), 4.52 (dd, J = 10.3, 2.3 Hz, 1H), 4.50 (dd, J = 10.3, 2.1 Hz, 1H), 3.62 (s, 1H), 3.61 (s, 1H), 2.95−1.67 (m, 12H); ^{13}C NMR **39**, 207.0, 174.1, 148.2, 148.1, 146.25, 146.19, 141.2, 131.1, 125.4, 109.2, 109.1, 109.0, 108.6, 101.13, 71.8, 71.6, 49.1, 49.0, 47.8, 42.7, 32.1, 31.9, 26.7, 27.3, 24.7, 24.6; **40**, 215.8, 147.3, 133.6, 133.0, 126.7, 125.7, 111.9, 109.8, 101.1, 73.0, 62.0, 60.1, 52.5, 42.6, 42.2, 37.4, 37.2, 30.7, 30.6, 19.8; IR 3391, 2923, 1703, 1695, 1634, 1505, 1406, 1381, 1225; MS *m/z* (relative intensity) 301 (M, 24), 284 (9), 256 (15), 229 (60), 209 (23), 165 (21), 147 (48), 135 (100); HRMS *m/z* 301.1320 ($C_{17}H_{19}O_4N$ requires 301.1314).

Macrocyclic *N*-*tert*-Butoxycarbonyl Amino Endione 41. A solution of DMSO (0.058 mL, 1.10 mmol) and trifluoroacetic anhydride (0.078 mL, 0.551 mmol) in 2 mL of anhydrous CH_2Cl_2 was stirred at −78 °C for 10 min, followed by the addition of *N*-BOC α′-hydroxy enone **38** (52 mg, 0.130 mmol) in 4 mL of anhydrous CH_2Cl_2. After the solution was stirred at −78 °C for 1 h, triethylamine (0.10 mL, 0.739 mmol) was added. The mixture was stirred at 0 °C for 0.5 h, dilluted with water, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated *in vacuo* to give 66 mg of a residue whose ^{1}H NMR spectrum shows the absence of starting material resonances (*e.g.*, 4.37 ppm for H2). Due to the unstable nature of **41**, the crude product was used without further purification: MS *m*/*z* (relative intensity) 399 (M, 8), 359 (30), 299 (100), 283 (87), 229 (77); HRMS *m*/*z* 399.1668 ($C_{22}H_{25}O_6N$ requires 399.1682).

Desmethylcephalotaxinone (22). To a solution of **41** (0.130 mmol) in 2 mL of CH_2Cl_2 at 0 °C was added trimethylsilyl trifluoromethanesulfonate (0.075 mL, 0.39 mmol). The mixture was stirred at 0 °C for 30 min, poured into water, and washed with CH_2Cl_2. The aqueous phase was adjusted to pH 10 with 5% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic extracts were dried and concentrated *in vacuo* to give desmethylcephalotaxinone (**22**) (25 mg, 50% yield from **38**). The spectroscopic data of this compound were identical with those reported by Fuchs:[17c] ^{1}H NMR 6.91 (s, 1H), 6.63 (s, 1H), 5.94 and 5.92 (ABq, *J* = 1.1 Hz, 2H), 5.02 (br s, 1H), 3.41 (m, 1H), 3.21−3.10 (m, 2H), 3.02−2.91 (m, 3H), 2.65 and 2.49 (ABq, *J* = 18.5 Hz, 2H), 1.92−1.85 (m, 3H), 1.67 (m, 1H); ^{13}C NMR 200.4, 149.6, 148.0, 145.9, 132.0, 124.3, 109.9, 109.7, 101.3, 71.3, 50.0, 49.8, 46.0, 38.0, 32.1, 23.6; IR 2923, 1699, 1575, 1486; MS *m*/*z* (relative intensity) 299 (M, 82), 256 (100), 228 (44); HRMS *m*/*z* 299.1135 ($C_{17}H_{17}O_4N$ requires 299.1158).

N-Benzyl Macrocyclic α′-Hydroxy Amino-Enone 42. To 5.2 mL of lithium diisopropylamide in a THF solution (0.35 M, 1.8 mmol) at −78 °C was added dropwise enone **36** (0.343 g, 0.915 mmol) in 6 mL of anhydrous THF. The resulting solution was stirred at −78 °C for 1 h, followed by introduction of HMPA (0.64 mL, 3.7 mmol) and ((−)-camphorsulfonyl)-oxaziridine (0.42 g, 1.8 mmol) in 3.0 mL of THF. The mixture was stirred at −78 °C for 5 h, quenched by addition of saturated aqueous NH_4Cl, and extracted with $CHCl_3$. The extracts were dried and concentrated in vacuo to yield a residue which was subjected to column chromatography (Florisil, hexane−EtOAc, 60/40) to yield 0.090 g of recovered **36** (74% conversion) and 0.255 g (96% yield based upon recovered starting material) of α′-hydroxy enone **42a**. ^{1}H NMR of the crude product showed that it contained only diastereomer **42a** while upon purification by silica gel column chromatography a pair of diastereomers **42a** and **42b** are produced in ratios which vary from fraction to fraction in a range of 28:1 to 2:1: ^{1}H NMR 7.11 (m, 3H), 6.72 (d, *J* = 7.3 Hz, 2H), 6.43 (s, 1H, **42b**), 6.40 (s, 1H, **42a**), 6.29 (s, 1H, **42a**), 6.27 (s, 1H, **42b**), 6.00 (m, 1H), 5.91 (m, 1H), 4.41 (dd, *J* = 6.8, 3.0 Hz, **42a**), 4.38 (dd, *J* = 6.8, 3.1 Hz, **42b**), 3.69 and 3.03 (ABq, *J* = 14.2 Hz, 2H, **42b**), 3.67 and 3.02 (ABq, *J* = 14.2 Hz, 2H, **42a**), 3.21−3.07 (m, 2H), 2.92 (dd, *J* = 17.8, 6.8 Hz, 1H), 2.66 (dd, *J* = 17.8, 3.0 Hz, 1H), 2.50−1.59 (m, 8H); ^{13}C NMR **42a** 207.7, 175.0, 147.5, 145.6, 141.5, 139.4, 134.5, 128.3, 127.8, 126.5, 124.9, 109.6, 108.3, 100.9, 72.0, 58.5, 54.7, 48.8, 37.2, 30.8, 28.2, 23.4, **42b** 175.1, 139.3, 133.9, 126.6, 109.4, 108.7, 58.4, 54.6, 49.1, 36.9, 31.0, 27.6, 23.1; IR 3400, 1710; MS *m*/*z* (relative intensity) 391 (M, 29), 373 (1), 300 (10), 272 (5), 242 (4), 215 (8), 186 (19), 146 (22), 91 (100); HRMS *m*/*z* 391.1773 ($C_{24}H_{25}NO_4$ requires 391.1784).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds characterized in this work (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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