Total Synthesis of the *Cephalotaxus* Alkaloids *dl*-Cephalotaxine, *dl*-11-Hydroxycephalotaxine, and *dl*-Drupacine[1]

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Abstract: This paper reports the chemical details of our total synthesis of *dl*-cephalotaxine (**1**) and the completion of the first total synthesis of *dl*-11-hydroxycephalotaxine (**3**) and *dl*-drupacine (**4**). Key steps in the synthesis of *dl*-cephalotaxine include: (1) conjugate addition/alkylation of aryllithium **23C** to vinyl sulfone **21** to afford adduct **24C**, bearing the entire carbon assemblage; (2) self-immoliative elimination of homoallyl sulfone **24C** to exocyclic diene **25** via treatment with *t*-BuLi; (3) establishment of the tetracyclic array by an intramolecular Diels–Alder reaction of an acylnitroso moiety to the exocyclic diene of **16**. This latter reaction features the first example of a regiochemical outcome which violates the implicit rule of syn-tether specificity in an intramolecular [4 + 2] cycloaddition. The first total syntheses of *dl*-11-hydroxycephalotaxine (**3**) and *dl*-drupacine (**4**) features a reductive 1,2-carbonyl transposition strategy on lactam **28ac** involving: (a) sulfenylation of the enolate derived from **28ac** with *S*-phenyl benzenethiosulfonate, (b) oxidation of the enolate derived from **33β** with molecular oxygen; and (c) reduction with BH_3/THF to give the requisite 11-β-hydroxy amine **36β** as the major product (56% overall). The equilibrating methylation conditions utilized to convert **38** to **40** also resulted in the formation of macrocyclic amine **41**. This result has substantial negative implications with regard to the use of diketone intermediates related to **3** and **38** for synthesis of enantiomerically pure materials in the cephalotaxine area.

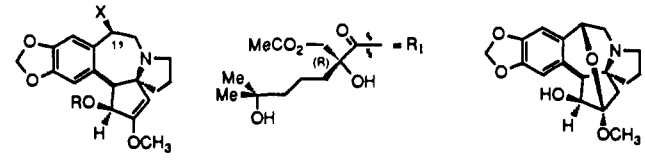
Introduction

The *Cephalotaxus* alkaloid cephalotaxine **1** is the parent structure of a group of C-3 α-hydroxysuccinate esters designated the harringtonines (cf. homoharringtonine, HHT **2**) which have recently been favorably evaluated in Phase II clinical trials as antileukemia agents.[2] HHT **2**[3] and several analogues[4] were found to be quite active in several tumor models of the NCI screen. While the conversion of 11-hydroxycephalotaxine (**3**) to drupacine (**4**) is known,[5] a total synthesis of **3** (or **4**) has not been previously achieved even though several attempts to effect oxidative functionalization at C-11 of cephalotaxine **1** have been reported.[6] This paper reports the details of our total synthesis of *dl*-cephalotaxine (**1**)[7,8] as well as the first total synthesis of *dl*-11-hydroxycephalotaxine (**3**) and *dl*-drupacine (**4**) (Scheme I).

Our interest in this family of targets arose from the possibility of utilizing triply convergent vinyl sulfone methodology for the introduction of the requisite carbon assemblage.[9] Our synthetic plan incorporates the method of refunctionalization of the D ring (**5** → **1**) developed by Weinreb and Auerbach in their synthesis of cephalotaxine.[8a,c] Prior to this study, several unsuccessful approaches for synthesis of the cephalotaxine nucleus had been investigated as part of our vinyl sulfone program. These strategies included:[10] (1) a 5-exo intramolecular Michael approach to the C ring (**8** → **7**); (2) a 7-exo intramolecular Michael approach to tbe B ring (**11** → **10**); (3) a palladium-catalyzed intermolecular addition of an amine to an exocyclic diene to form ring C (**9** → **7**); and (4) an intramolecular oxidative addition of a nitrene to an exocyclic diene to form the B/C ring (**11** → **7**) (Scheme II).[11] While these approaches uniformly failed at establishing the spiro B/C pyrrolidine moiety, the aforementioned studies provided important lessons with respect to efficient construction of the arylated cyclopentane nucleus.

The above failed cyclizations suggested that introduction of the spirocyclic B/C tertiary amino moiety might better be accomplished under the kinetic conditions of an intramolecular acylnitroso [4 + 2] cycloaddition (**16** → **15**) (Scheme III).[12] Standard mechanistic thinking dictated that the nitroso moiety in **16** would approach the exocyclic diene from the face of the aryl tether, to give the requisite cis-fused seven-membered ring **15**. Synthesis of the substrate (**16**) for the acylnitroso [4 + 2] cycloaddition was projected to employ previously developed vinyl sulfone technology.[10,11] The acylnitroso [4 + 2] cycloaddition required C-10 at

Scheme I



1 (X=R=H) Cephalotaxine
2 (X=H, R=R_1) Homoharringtonine
3 (X=OH, R=H) 11-Hydroxycephalotaxine
4 Drupacine

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(1) (a) Synthesis via Vinyl Sulfones 38. This work was presented in part at the Regional ACS Meeting at Morgantown, West Virginia, June 1988. (b) Burkholder, T. P. Ph.D. Thesis, Purdue University, 1988.

(2) (a) Ohnuma, T.; Holland, J. F. *J. Clin. Oncol.* **1985**, *3*, 604. (b) Warrell, R. P.; Coonley, C. J.; Gee, T. S. *J. Clin. Oncol.* **1985**, *3*, 617. (c) Ajani, J. A.; Dimery, I.; Chawla, S. P.; Pinnamaneni, K.; Benjamin, R. S.; Legha, S. S.; Krakoff, I. H. *Cancer Treat. Rep.* **1986**, *70*, 375. (d) O'Dwyer, P. J.; King, S. A.; Hoth, D. F.; Suffness, M.; Leyland-Jones, B. *J. Clin. Oncol.* **1986**, *4*, 1563. (e) Stewart, J. A.; Cassileth, P. A.; Bennett, J. M.; O'Connell, M. J. *Am. J. Clin. Oncol.* **1988**, *11*, 627. (f) Han, J. *J. Ethnopharmacol.* **1988**, *24*, 1. (g) Kantarjian, H. M.; Keating, M. J.; Walters, R. S.; Koller, C. A.; McCredie, K. B.; Freireich, E. J. *Cancer* **1989**, *63*, 813. (h) Feldman, E. J.; Arlin, Z. A.; Ahmed, T.; Mittelman, A.; Ascensao, J. L.; Puccio, C. A.; Coombe, N.; Baskind, P. *Acta Haematol.* **1989**, *82*, 117. (i) Welborn, J. L.; Lewis, J. P.; Meyers, F. J. *Leukemia* **1988**, *2*, 711.

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(6) Hudlicky, T.; Kwart, L. D.; Reed, J. W. In *Alkaloids: Chemical and Biological Perspectives*; Pellectier, S. W., Ed.; John Wiley and Sons, Inc.: New York, 1987; Vol. 5, pp 639–690 (see page 647 and references cited therein).

(7) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341 (For additional total syntheses of **1**, see ref 8).

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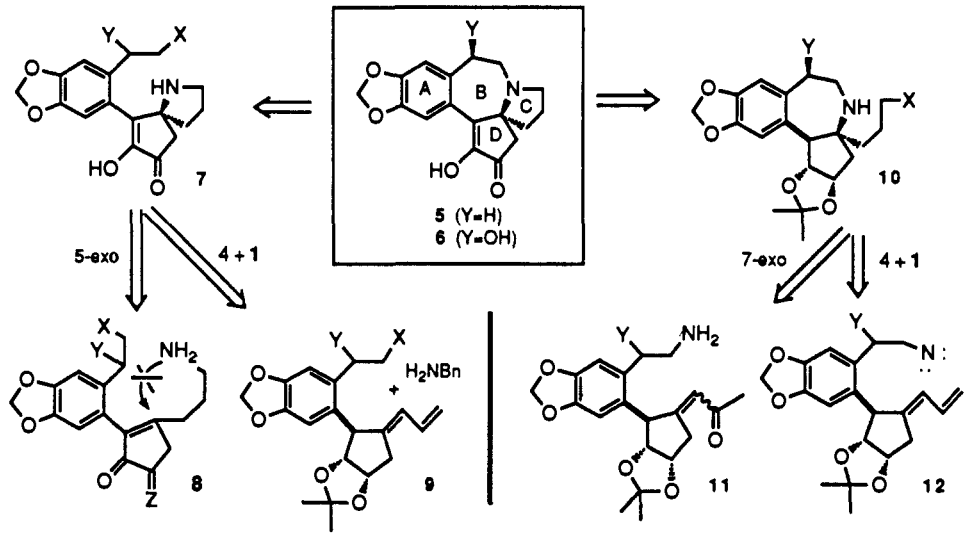
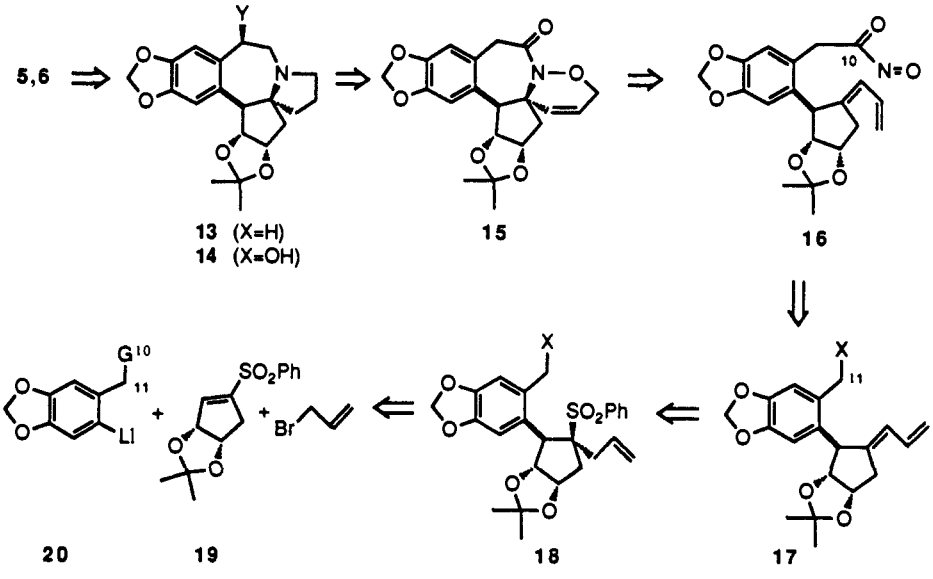
Scheme II



Scheme III



the carboxylic acid oxidation state. Previously, it was found that with C-10 at the alcohol oxidation state (**17** or **18**, X = CH_2OPG) the vinyl sulfone conjugate addition/α-sulfonyl anion functionalization reaction worked very well to introduce the requisite carbon assemblage.[10,11] While the C-10 alcohol (**17** or **18**, X = CH_2OH) could be oxidized to the corresponding aldehyde (**17** or **18**, X = CHO); extensive efforts to convert the fragile aldehyde to the corresponding carboxylic acid (**17** or **18**, X = CO_2H) were uniformly unsuccessful.[11] On the basis of this limitation, it was deemed necessary to prepare a substrate which carried a masked C-10 carboxylic acid.

Results

Three C-10-protected aryl anions (**23A–C**) were investigated in the triplyconvergent, conjugate addition/α-sulfonyl anion alkylation reaction with vinyl sulfone **21**.[13] Although ketene thioacetal **23A** and ketene acetal **23B** underwent the reaction sequence, the experimental protocols involved were exceptionally demanding because of the hydrolytic lability of the protected ketene moieties (The chemistry of these two series is described in the supplementary material section).

The preferred route starts with orthoester **22C** which was prepared from piperonyl alcohol in five steps in 41% yield.[14] Treatment of **22C** with 2 equiv of *tert*-butyllithium at −78 °C provided aryl anion intermediate **23C**, which was allowed to react with vinyl sulfone **21** at −78 °C for 2 h (Scheme IV). The α-sulfonyl anion was further functionalized by cannula addition to a −78 °C solution of allyl bromide in THF/HMPA to afford "three-piece" adduct **24C** in 76–84% yield. The triply convergent reaction sequence with vinyl sulfone **21** and a variety of aryl anions had been previously shown to produce a single diastereomer with the stereochemistry as indicated.[10,11] Self-immolative elimination[15]

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(9) For a review of this strategy, see: Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903.

(10) (a) Conrad, P. C. Ph.D. Thesis, Purdue University, 1980. (b) Kwiatkowski, P. L. Ph.D. Thesis, Purdue University, 1985. (c) Conrad, P. C.; Kwiatkowski, P. L.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 586.

(11) Radisson, X. Ph.D. Thesis, Purdue University, 1987.

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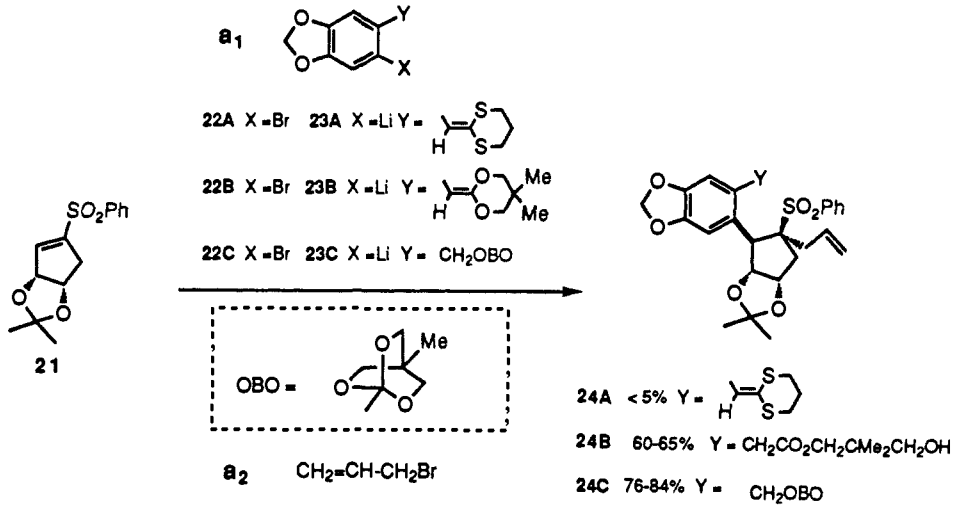
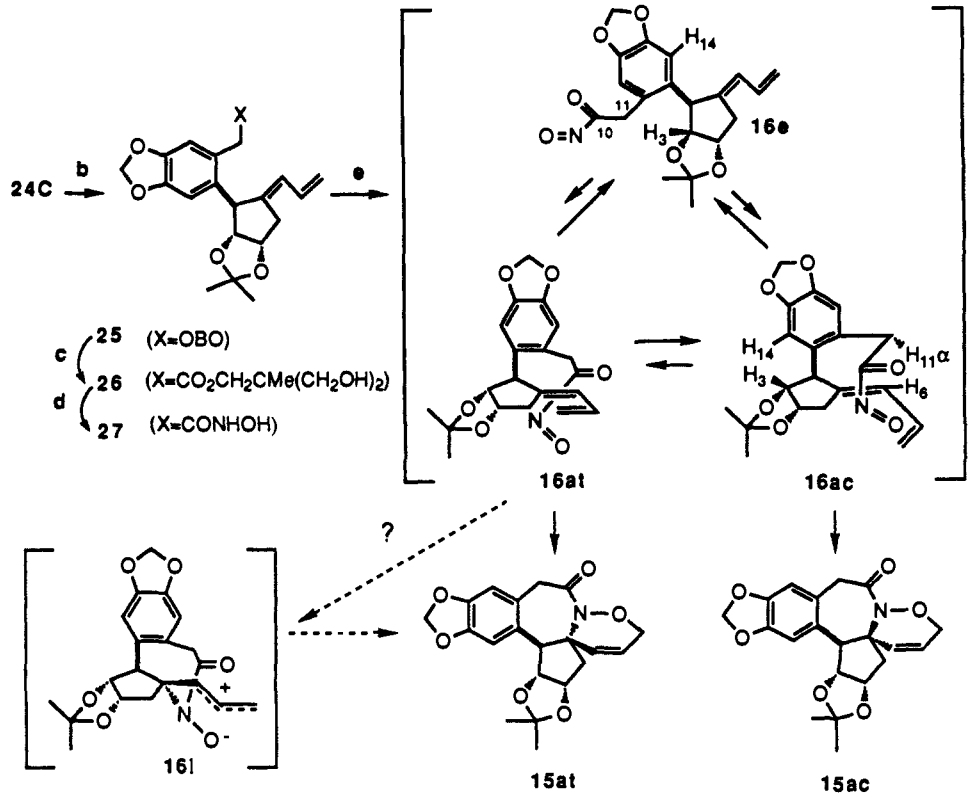
(13) Radisson, X.; Nantz, M. H.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 55.

(14) For synthesis and spectra of **22c** see supplementary material.

Scheme IV



Scheme V[a]



[a] (b) *t*-BuLi, THF, −78 °C → room temperature, (c) *p*-TsOH (0.2 equiv), THF, H_2O, 0 °C; (d) NH_2OH, MeOH, 0 °C; (e) *n*-Bu_4NIO_4, CH_2Cl_2, −78 °C → room temperature.

allowed the sulfone to be used in an active manner to efficiently introduce the requisite exocyclic diene. Treatment of homoallyl sulfone **24C** with *t*-BuLi at −78 °C produces a 17:1 mixture of exocyclic dienes **25** in 70–81% yield after purification (0.9–3 mmol scale).[16] Trioxabicyclo[2.2.2]octane (OBO) ester **25** was reacted with 0.2 equiv of *p*-TsOH in THF/H_2O at 0 °C for 1 h to afford ester **26** in 99% yield. Subsequent reaction with NH_2OH in methanolic KOH at 0 °C for 3 to 5 h followed by solvent evaporation and treatment of the residue with 1.25 N acetic acid in ethyl acetate at 0 °C for 1 h afforded hydroxamic acid **27**.[17]

Crude **27** was dissolved in dichloromethane (0.006 M) and treated with tetra-*n*-butyl ammonium periodate[18] at −78 °C to generate acylnitroso intermediate **16**. The solution was allowed to slowly warm to room temperature over 7 h. The fate of intermediate **16** was especially informative. While the [4 + 2] process required the exocyclic diene to adopt an unfavorable s-cis conformation, the intramolecular nature of the trapping process was able to overcome this limitation. The reaction was quenched at room temperature with sodium bisulfate and the residue purified by plug filtration on silica gel to afford an inseparable mixture of two isomeric components (66–74% yield from ester **26**). These isomers were tentatively assigned to be tetracyclic lactams **15ac** and **15at** (Scheme V). The formation of **15at** was *formally* the result of an intramolecular Diels–Alder reaction which required the

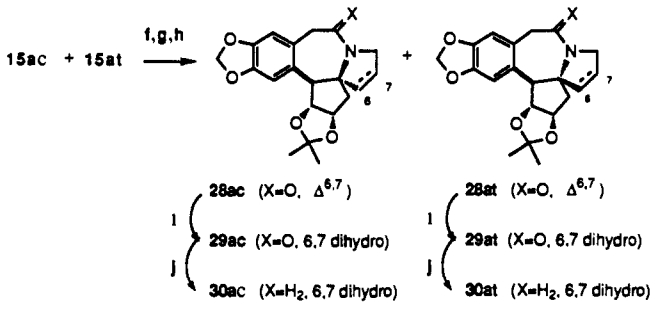
(15) Kwiatkowski, P. L.; Radisson, X.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 39.

(16) For stereochemical assignment of diene **25** see supplementary material.

(17) Hauser, C. R.; Renfrow, W. B. Jr., *Organic Syntheses*; Wiley: New York. 1943; Collect. Vol. II, p 67.

(18) Santaniello, E.; Manzocchi, A.; Farachi, C. *Synthesis* **1980**, 563.

Scheme VI[a]

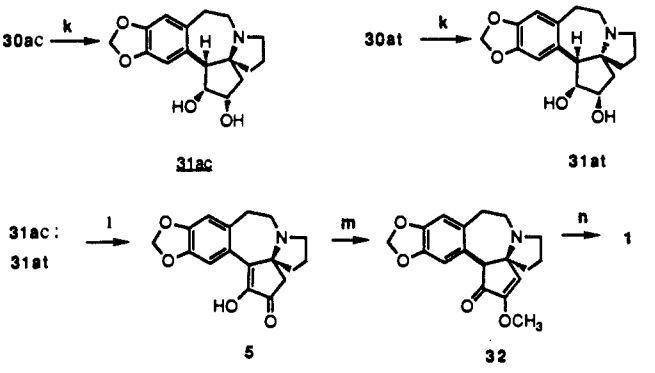


[a] (f) 6% Na(Hg), EtOH, room temperature; (g) MsCl, Et_3N, CH_2Cl_2, 0 °C; (h) NaH, THF, room temperature; (i) H_2, 10% Pd/C, EtOH; (j) BH_3/THF, THF, reflux; MeOH, reflux.

acylnitroso moiety to *approach the diene moiety from the opposite face of the tethering arene group*. The observation of product **15at**, derived from the unprecedented antifacial delivery, is presumably due to destabilization of the transition state **16ac**. The most stable conformation of **16** undoubtedly has the diene in the s-trans conformation and the aryl side chain (C_{10}—C_{11}—N=O) extended away from the five-membered ring (**16e**). In order for the acylnitroso [4 + 2] cycloaddition to occur, the diene moiety, must be in the s-cis conformation at the same instant that the acylnitroso moiety is positioned above the diene. This conformational equilibrium is retarded by an interaction between H_{14} and H_3 and between $H_{11\alpha}$ and H_6, and **16ac** appears to have more steric destabilization than **16e**. In the extended conformation (**16e**), the acylnitroso moiety can approach the diene moiety from the α-face. There does not appear to be good orbital overlap for a [4 + 2] cycloaddition to occur in this conformation (**16at**) (Drieding models); however, a stepwise ionic mechanism could account for the minor product. The seven-membered ring could be formed in a nonconcerted fashion, affording an ionic intermediate **16i**, which would subsequently collapse to yield **15at**.[19] Although several examples of unusual regiochemical arrangements have been observed in the macrocyclic version of the intramolecular Diels–Alder reaction,[20] and other examples of simultaneous formation of fused 7/6 ring systems are known,[21] this observation was unprecedented in the intramolecular Diels–Alder literature.[22] This finding would seem to necessitate critical evaluation of the implicit assumption of "syn-tether specificity" in all intramolecular reactions where a ring size of seven or greater is being formed.

When the mixture of lactams **15ac**/**15at** was subjected to reductive cleavage using 6% Na(Hg) in ethanol in the presence of Na_2HPO_4,[23] the two diastereomeric allylic alcohols could be separated (1.9–2.1:1.0 ratio in 55–87% yield); however, it was more expedient to simply carry the mixture through the three steps of NO bond cleavage, mesylation, and intramolecular nitrogen alkylation of the resultant lactam mesylate. This procedure affords

Scheme VII[a]



[a] (k) 1 N HCl/THF (1:1), room temperature; (l) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C; (m) dimethoxypropane, dioxane, *p*-TsOH, reflux; (n) $NaBH_4$, MeOH, −78 °C → room temperature.

46% of **28ac** and 23% of **28at** which were conveniently separated with use of preparative HPLC (Scheme VI).[24]

Hydrogenation of **28ac** with 10% palladium on activated carbon in ethanol at 50 psi for 1 h afforded lactam **29ac** in 91% yield. Reduction of the lactam with 7 equiv of borane/tetrahydrofuran complex in THF at reflux for 10 min followed by hydrolysis of the amine/borane complex in methanol at reflux for 30 min yielded tetracyclic amine **30ac** (89%).[25] In a similar manner, hydrogenation of **28at** afforded lactam **29at** in 99% yield and reduction followed by hydrolysis yielded tetracyclic amine **30at** (87%). At this stage it was possible to verify by X-ray crystallography[26] that **30at** (and by implication, **15at**, **28at**, and **29at**) bore the assigned anti-trans stereochemistry.

To complete the synthesis of *dl*-cephalotaxine (**1**) refunctionalization of the D ring of tetracyclic amines **30ac** and **30at** was required. It was thought that oxidation of the racemic diastereomeric 1,2-diols (**31ac** and **31at**) would afford racemic demethylcephalotaxinone (**5**) on the basis of Weinreb's finding that enolization of the corresponding α-dione gave exclusively demethylcephalotaxinone (**5**). It is interesting to note that if racemic **15at** were the only product from the intramolecular acylnitroso [4 + 2] cycloaddition, its structure could easily have been misassigned as **15ac** on the basis of the intramolecular Diels–Alder precedence. The misassignment might have gone undetected because both racemic **15ac** and racemic **15at** have subsequently been converted to demethylcephalotaxinone (**5**), whereas homochiral **15ac** or homochiral **15at** would have been converted to *antipodes* of demethylcephalotaxinone (**5**). The mixture obtained in the intramolecular acylnitroso [4 + 2] cycloaddition led to rigorous structural assignments for both products.

Culmination of the synthesis involved individual deprotection of the acetonide moieties of **30ac** and **30at** with 1 N HCl in THF at room temperature for 3 h (Scheme VII). The cis-fused amine diol **31ac** was obtained in 92% yield and the trans-fused amine diol **31at** was obtained in 99% yield. Separate Swern oxidations[27] of these diols in dichloromethane at −78 °C with DMSO/TFAA for 1 h followed by treatment with triethylamine afforded demethylcephalotaxine (**5**) (75–89%). The proton NMR of this material compared favorably with that previously described for **5**.[8] Demethylcephalotaxine (**5**) was converted to cephalotaxinone

(19) An alternative structure for the minor product from the acylnitroso [4 + 2] cycloaddition (iii) was considered. but rejected see supplemental material.

(20) (a) Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, 2537. (b) Bailey, S. J.; Thomas, E. J.; Turner, W. B. *J. Chem. Soc., Chem. Commun.* **1978**, 474. (c) Harkin, S. A.; Thomas, E. J. *Tetrahedron Lett.* **1983**, *24*, 535. (d) Stork, G.; Nakamura, E. *J. Am. Chem. Soc.* **1983**, *105*, 5510. (e) Bailey, S. J.; Thomas, E. J.; Vather, S. M.; Wallis, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 851. (f) Tapolczay, D. J.; Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1985**, 143. (g) Craven, A.; Tapolczay, D. J.; Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1985**, 145. (h) Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877.

(21) (a) Wenkert, E.; Naemura, K. *Synth. Commun.* **1973**, *3*, 45. (b) Oppolzer, W.; Snowden, R. L. *Helv. Chim. Acta* **1981**, *64*, 2592. (c) Kametani, T.; Honda, T.; Shiratori, Y.; Matsumato, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1386. (d) Tuchinda, P.; Prapansiri, V.; Naengchomnong, W.; Reutrakul, V. *Chem. Lett.* **1984**, 1427.

(22) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (c) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.

(23) Keck, G. E.; Fleming, S.; Nickell, D.; Weider, P. *Synth. Commun.* **1979**, *9*, 281.

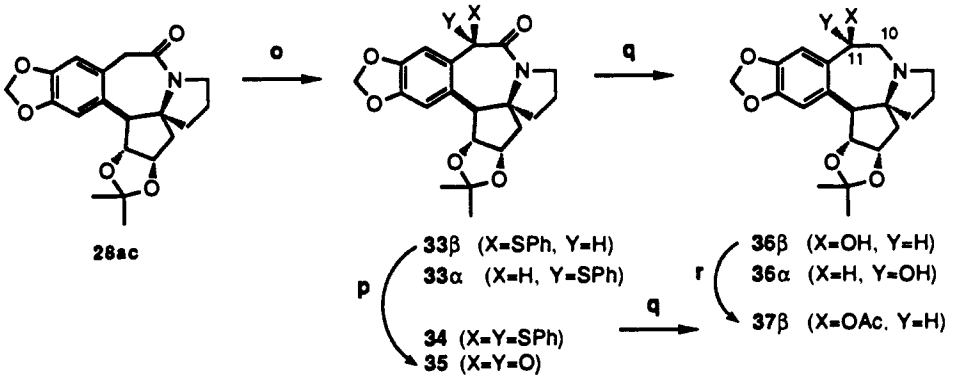
(24) Two-dimensional NOE NMR analysis of **28ac** and **28at** was consistent with the assigned structures on the basis of the previous stereochemical assignment of the precursor allylic alcohols. The 2-D NOE NMR analysis is summarized in the supplemental material.

(25) Brown, H. C.; Choi, Y. M.; Narasimhan, S. J. *J. Org. Chem.* **1982**, *47*, 3153.

(26) We wish to thank Dr. P. Fanwick of the Purdue Chemistry department X-ray crystallography center for these results. The MICROVAX computer and diffractometer were provided by NSF grant no. CHE-8615556. ORTEP and stereoscopic drawings of **30at** are shown in the supplemental material.

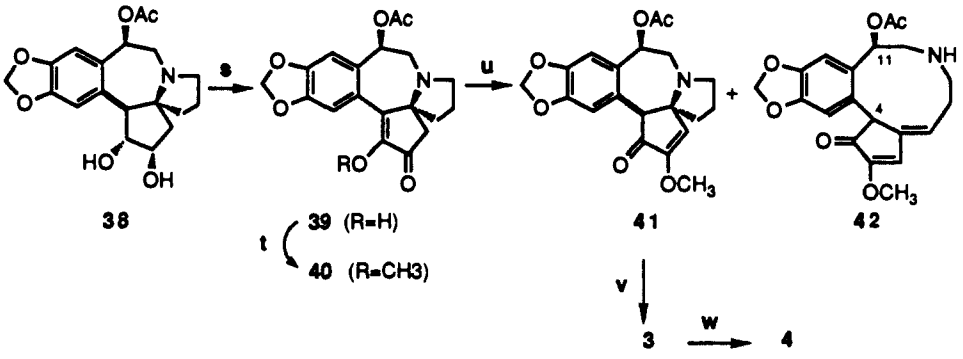
(27) For references on the 1,2-diol to α-diketone oxidations, see: (a) Govindan, S. V.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 2593. (b) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851. (c) Regen, S. L.; Whitesides, G. M. *J. Org. Chem.* **1972**, *37*, 1832.

Scheme VIII[a]



[a] (o) 2 equiv of LDA, THF, −78 °C → 0 °C; inverse-addition $PhSSO_2Ph$, THF/HMPA, −78 °C; (p) LiHMDS, toluene/THF, −78 °C → 0 °C; O_2, room temperature; (q) BH_3/THF, THF, −78 °C → room temperature; MeOH, reflux; (r) Ac_2O, pyridine, CH_2Cl_2, DMAP.

Scheme IX[a]



[a] (s) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C; (t) CH_2N_2, Et_2O (u) DMP, dioxane, *p*-TsOH, reflux, 6 h; (v) $NaBH_4$, MeOH, room temperature; (w) 1 N HCl/THF.

(**32**) by a Merck[28] modification of the original Weinreb procedure[8a,c] with 2,2-dimethoxypropane and *p*-TsOH at reflux in dioxane for 11 h (70–84%). Reduction of cephalotaxinone (**32**) with sodium borohydride in methanol afforded *dl*-cephalotaxine (**1**) (99%). Direct comparison of the spectra and TLC of this material with those of the natural product showed them to be identical.[29]

The synthesis of *dl*-11-hydroxycephalotaxine (**3**) and *dl*-drupacine (**4**) begins with tetracyclic lactam **28ac**[30] which was treated with LDA in THF at 0 °C to afford the corresponding enolate which was further functionalized by cannula addition to a −78 °C solution of *S*-phenyl benzenethiosulfonate (TPTS)[31] in THF/HMPA to afford monosulfenylated lactam **33β** in 85% yield.[32] In an attempt to effect a second sulfenylation of C-11, lactam **33β** was treated with lithium hexamethyldisilazane (LHMDS) in toluene at room temperature for 30 min, followed by inverse addition to a solution TPTS in toluene/HMPA. This reaction yielded three products after chromatography: isomeric monosulfide **33α** (33%), dithioacetal **34** (41%), and α-keto lactam **35** (20%). In a separate experiment, **33β** was treated with excess potassium hydride in THF at room temperature for 3 h followed by quenching with aqueous ammonium chloride to afford a 7:1 mixture of **33α**/**33β** in 83% along with a 15% yield of **35**. These results indicate that enolates derived from tetracyclic lactams **28ac** and **33** undergo selective delivery of the electrophile from the β-face.

Although dithioacetal **34** can be hydrolyzed to α-keto lactam **35** in 95% yield with use of boron trifluoride and mercuric oxide in aqueous THF,[33] the difficulty at cleanly effecting the bissulfenylation detracted from this option. On the basis of the hypothesis that the low yields of **35** obtained in the sulfenylation studies resulted from adventitious oxygen in the reaction medium, lactam **33β** was treated with LHMDS in toluene at room temperature for 30 min, followed by introduction of excess molecular oxygen through a syringe needle to provide α-keto lactam **35** in 81% yield (Scheme VIII). While the mechanistic details of this oxidation have yet to be investigated,[34] it seems possible that the reaction involves an internal redox reaction of an α-hydroperoxy sulfide intermediate to generate **35** and the anion of sulfenic acid, since the known disproportionation product, *S*-phenyl benzenethiosulfonate, was also isolated (23%) in this reaction.

Reduction of α-keto lactam with BH_3/THF[25] at −78 °C in THF for 12 h followed by slow warming to room temperature and subsequent liberation of the amine/borane intermediate with methanol at reflux for 5 h afforded 81% of **36β** and 17% of **36α**.[35] Sodium borohydride reduction of the keto lactam **35** followed by borane reduction of the hydroxy lactam afforded >10:1 (**36α**/**36β**) mixture favoring the undesired α-hydroxyamine **36α**. L-Selectride reduction of the keto lactam **35** followed by borane reduction of the hydroxy lactam afforded 1.8:1 (**36α**/**36β**). The selectivity observed for the reduction of keto lactam **35** can be rationalized by examining the conformation of the seven-membered ring (Drieding models). Axial delivery of hydride to the β-face with

(28) The Merck modification of the original Weinreb procedure allowed for the conversion of **5** to **32** in 99% yield. We thank Professor Weinreb for this information and for a copy of the optimized Merck procedure.

(29) We wish to thank R. G. Powell of the USDA, Peoria, IL, for authentic samples of **1**, **3**, and **4**.

(30) A variety of experimental conditions were examined for the oxidative functionalization of **24ac** at C-11. See ref 2b for further details.

(31) Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405.

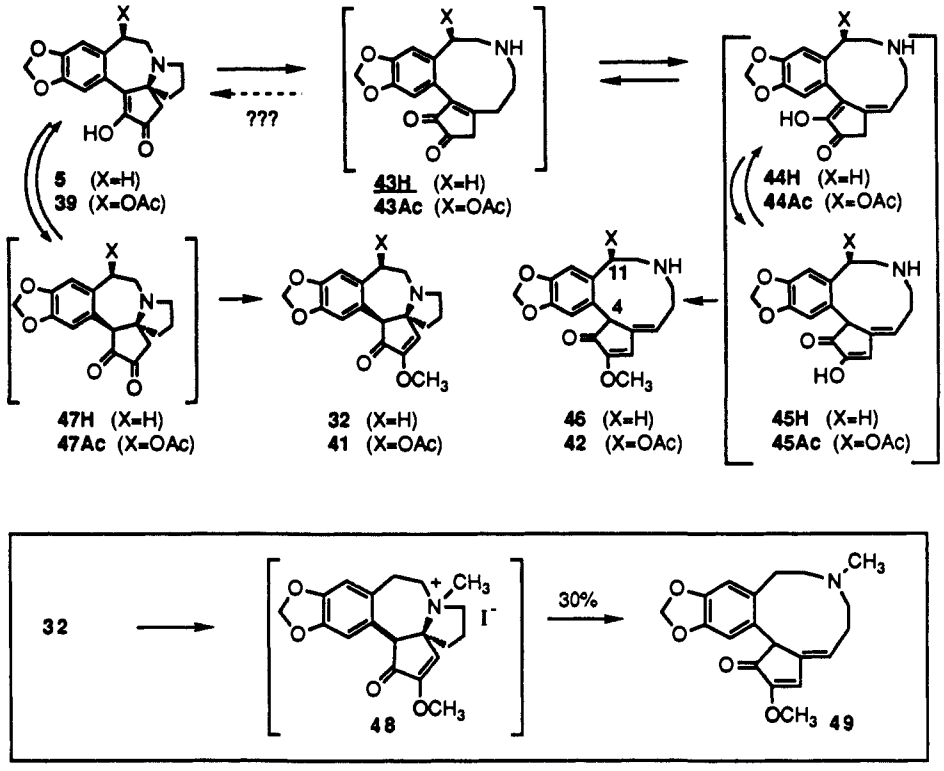
(32) The kinetic monosulfenylated lactam was assigned as **33β** on the basis of 2D-NOE studies of **33β** and **33α** and on the observed downfield shift of H_{17} in **33α** (7.57 ppm) relative to 6.56 ppm in **33β** due to the deshielding from the SPh moiety. Additional chemical and spectral evidence in support of the structures assigned for **33β** and **33α** may be found in the supplemental material.

(33) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366.

(34) See the supplemental material for a scheme showing one possible mechanism for the reaction of the enolate of **33β** with oxygen to generate **35**.

(35) Additional chemical and spectral evidence in support of **36β** and **36α** may be found in the supplemental material.

Scheme X



$NaBH_4$ and L-Selectride with the seven-membered ring in the chair conformation appears to be favored. With borane/tetrahydrofuran complex, the reduction of the α-keto lactam may have occurred in an intramolecular fashion, where the borane first complexed with the lactam and then the hydride was delivered to the C-11 carbonyl. Inspection of Dreiding models suggested that the vector approach angle for intramolecular hydride delivery was better from the α-face with the seven-membered ring in the pseudo-boat conformation. The stereochemical assignments for **36β** and **36α** were made on the basis of the coupling between H_{11} and H_{10}, H_{10}' in the proton NMR. These tentative assignments were verified by conversion of **36β** to 11-hydroxycephalotaxine (**3**) (vide infra). The C-11 hydroxyl of **36β** was protected as the acetate to give **37β** in 96% yield.

Hydrolysis of the acetonide moiety of **37β** with 1 N HCl/THF at room temperature for 6 h smoothly provided diol **38** (90%). Swern oxidation[27] of **38** afforded 11-acetoxydemethylcephalotaxinone (**39**) in 88% yield (Scheme IX). Treatment of **39** with diazomethane exclusively gave methyl enol ether **40** (96%). This observation was consistent with Weinreb's observation that methylation of demethylcephalotaxinone with diazomethane yields unnatural isocephalotaxinone.[8a,c] Treatment of **39** under equilibrating conditions (2,2-dimethoxypropane, *p*-TsOH, dioxane reflux, 6 h)[8a,c] afforded 11-acetoxycephalotaxinone (**41**) (43%), isomeric dienone **42** (17%, as a single diastereomer of unknown relative stereochemistry at $C_{4,11}$), and recovered **39** (26%) (Scheme X). Longer reaction times resulted in the formation of additional products at the expense of **41**.

Culmination of the synthesis was accomplished by borohydride reduction of 11-acetoxycephalotaxinone (**41**) to provide *dl*-11-hydroxycephalotaxine (**3**) in 88% yield. The acid-catalyzed conditions of Powell[4a] were utilized to convert **3** to drupacine (**4**) (83%). Direct comparison of the spectra and TLC of **3** and **4** with those of the natural products showed them to be identical.[29]

The isolation of macrocyclic secondary amine **42** has substantial negative implications with regard to the use of diketone intermediates related to **5** and **39** for synthesis of enantiomerically pure materials in the cephalotaxine area. While racemic intermediate **5** has been converted to cephalotaxinone **32** in high yield,[8a,c,6] the same reaction has yet to be tested on optically active material. In the course of their biosynthetic studies, Schwab and Perry have observed that treatment of cephalotaxinone **32** with methyl iodide yields the *N*-methyl dienyl ketone **49**, presumably via retro-Michael reaction of methiodide intermediate **48**.[36] Related rearrangements in the 11-deoxycephalotaxine series have been observed by Powell[37] and Dolby.[38]

Experimental Section

(3aα,4α,5*S,6aα)-(±)-4-Methyl-1-[[6-[tetrahydro-2,2-dimethyl-5-(phenylsulfonyl)-5-(2-propenyl)-4*H*-cyclopenta-1,3-dioxol-4-yl]-1,3-benzodioxol-5-yl]methyl]-2,6,7-trioxabicyclo[2.2.2]octane (24C).** Orthoester **22C** (4.25 g, 12.39 mol, 1.2 equiv) was dissolved in THF (35 mL) at −78 °C under argon, and the solution was treated dropwise with *tert*-butyllithium (13.5 mL, 26.19 mmol, 2.0 equiv based on ortho ester, 1.94 M) over 25 min. The resulting slurry was allowed to stir at −78 °C for 1 h. Vinyl sulfone **21** (3.20 g, 11.51 mmol) in THF (30 mL) was added dropwise at −78 °C, and the resulting yellow solution was allowed to stir 2 h. The α-sulfonyl anion was further functionalized by addition through a cooled cannula to a solution of allyl bromide (4.00 mL, 46.2 mmol, 4.0 equiv) in THF (20 mL)/HMPA (5 mL) at −78 °C. The solution was allowed to stir at −78 °C for 1 h and then an additional 1 h at room temperature. The solution was cooled to −60 °C and treated with water (200 mL) and diluted with ether. The aqueous phase was extracted three times with ether, and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), filtered, and concentrated in vacuo to a foam. Plug filtration (neutralized SiO_2 (1% TEA in hexanes) with 35% ethyl acetate in hexanes or neutral alumina oxide (50–200 mesh) and gradient elution with 30–50% ethyl acetate in hexane followed by dissolving in benzene and evaporating (repeat three times) and drying under high vacuum afforded 5.14 g (77%) of **24C**: oil, TLC R_f = 0.51, deactivated SiO_2, 50% ethyl acetate in hexanes; ^1H NMR (C_6D_6) δ 7.51 (d, 2 H, *o*-SO_2Ph), 7.18 (s, 1 H, aromatic), 6.89 (t, 1 H, *p*-SO_2Ph), 6.81 (t, 2 H, *m*-SO_2Ph), 6.68–6.56 (cm, 1 H, H7), 6.44 (s, 1 H, aromatic), 5.43 (d, 1 H, $J_{7,8c}$ = 10 Hz, H8 cis), 5.36 (d, 1 H, $J_{7,8t}$ = 17 Hz, H8 trans), 5.30 (d, 1 H, J_{gem} = 25 Hz, methylenedioxy), 4.91 (app d, 1 H, $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 7 Hz, H3), 4.86 (b d, 1 H, $J_{3,4}$ = 7 Hz, H4), 4.52 (app t, 1 H, $J_{2,3}$ = 7 Hz. $J_{1\beta,2}$ = 7 Hz, H2). 4.10 (A part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 3.53 (s, 6 H, orthoester three methylenes), 3.33 (B part of AB q overlapping, 1 H, $J_{11,11'}$ = 15 Hz, H11), 3.36–3.28 (m overlap-

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

(37) Powell, R. G.; Weisleder, D.; Smith, C. R., Jr.; Wolff, I. A. *Tetrahedron Lett.* **1969**, 4081.

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

ping, 1 H, H8), 2.85 (ABX, 1 H, $J_{1\beta,2}$ = 7 Hz, $J_{1\alpha,1\beta}$ = 15 Hz, H1β), 2.66–2.59 (m, 1 H, H8′), 2.02 (d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α), 1.48 (s, 3 H, acetonide methyl), 1.14 (s, 3 H, acetonide methyl), –0.073 (s, 3 H, orthoester methyl); ^{13}C NMR (C_6D_6) δ 146.71 (e, C15), 146.60 (e, C16), 139.33 (e, ipso-SO_2Ph), 134.28 (o, *p*-SO_2Ph), 132.65 (o, C7), 131.78 (e, C12), 129.80 (o, *o*-SO_2Ph), 128.57 (e, C13), 128.53 (o, *m*-SO_2Ph), 128.37 (o, *m*-SO_2Ph), 120.10 (e, C8), 112.77 (o, C14), 110.260 (e, acetonide quat), 110.20 (o, C17), 109.20 (e, C10), 100.85 (e, C18), 90.67 (o, C3), 80.02 (o, C2), 78.09 (e, C5), 72.44 (e, orthoester three methylenes), 51.33 (o, C4), 41.66 (e, C6), 40.95 (e, C11), 39.91 (e, C1), 30.06 (e, orthoester quat), 25.97 (o, acetonide methyl), 23.43 (o, acetonide methyl), 13.88 (o, orthoester methyl); IR (CH_2Cl_2) cm^{-1} (μm) 3050 (3.28), 1210 (8.26), 800–710 (12.50–14.09); MS *m/e* (rel intensity) 584 (M^+, 80), 443 (26), 385 (64), 367 (50); CIMS *m/e* (rel intensity) 585 (M + H, 100), 443 (23); Exact mass (EI) calcd for $C_{31}H_{36}O_9S$ (M^+) 584.2080, found 584.2061.

(3aα,4α,5*E*,6aα)-(±)-4-Methyl-1-[[6-[tetrahydro-2,2-dimethyl-5-(2-propenylidene)-4*H*-cyclopenta-1,3-dioxol-4-yl]-1,3-benzodioxol-5-yl]-methyl]-2,6,7-trioxabicyclo[2.2.2]octane (25). Sulfone **24C** (500 mg, 0.856 mmol) in THF (9 mL) was cooled to –78 °C under argon and treated dropwise with *tert*-butyllithium (0.53 mL, 1.03 mmol, 1.20 equiv, 1.94 M) to give a red solution. The addition of *tert*-butyllithium was titrated by TLC. The *tert*-butyllithium was added dropwise (one drop/5–10 s), and the reaction was sampled at –78 °C with a 1.0-μL capillary. The aliquot was allowed to warm in the capillary. *tert*-Butyllithium addition was continued until TLC visualization showed the absence of sulfone **24C**. The reaction was allowed to warm to room temperature over 7 h. During this time the solution became yellow. The solution was treated with water and diluted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried (Na_2SO_4), and filtered, and the solvents were removed in vacuo to afford a foam. Purification by plug filtration (50 g neutral aluminum oxide, 35% ethyl acetate in hexanes) yielded 305 mg (81%) of **25**: oil, TLC R_f = 0.79, neutralized SiO_2 plates, 50% ethyl acetate in hexanes; ^{1}H NMR (C_6D_6) δ 7.12 (s, 1 H, aromatic), 6.51 (s, 1 H, aromatic), 6.47–6.40 (cm, 1 H, H7), 6.07 (d of d, 1 H, $J_{6,7}$ = 11 Hz, J = 2 Hz, H6), 5.25 (AB q, 2 H, J_{gem} = 33 Hz, methylenedioxy), 5.00–4.92 (m overlapping, 2 H, H8 and H8′), 4.72 (b s, 1 H, H4), 4.39–4.35 (m overlapping, 2 H, H2 and H3), 3.68 (A part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 3.43 (s, 6 H, orthoester three methylenes), 3.18 (B part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11′), 2.80 (d, 1 H, $J_{1\alpha,1\beta}$ = 18 Hz, H1α), 2.52 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 18 Hz, $J_{1\beta,2}$ = 2 Hz, H1β), 1.52 (s, 3 H, acetonide methyl), 1.19 (s, 3 H, acetonide methyl), –0.14 (s, 3 H, orthoester methyl); ^{13}C NMR (C_6D_6) δ 147.84 (e, C5), 147.23 (e, C15), 146.06 (e, C16), 136.38 (e, C12), 134.60 (o, C6), 128.53 (e, C13), 126.23 (o, C7), 115.35 (e, C8), 112.74 (o, C14), 111.14 (e, acetonide quat), 100.77 (e, C18), 109.03 (e, C10), 107.90 (o, C17), 89.09 (o, C3), 79.81 (o, C2), 72.44 (e, orthoester three methylenes), 54.16 (o, C4), 39.96 (e, C11), 36.11 (e, C1), 30.01 (e, orthoester C-quat), 28.02 (o, acetonide methyl), 25.61 (o, acetonide methyl), 13.85 (o, orthoester methyl); IR (CCl_4) cm^{-1} (μm) 2925 (3.42), 1485 (6.73), 1110 (9.00), 1090 (9.17); MS *m/e* (rel intensity) 442 (M^+, 51), 384 (10), 225 (18); CIMS *m/e* (rel intensity) 443 (M + H, 100), 385 (51); Exact mass (EI) calcd for $C_{25}H_{30}O_7$ (M^+) 442.1992, found 442.1990.

(3aα,4α,5*E*,6aα)-(±)-5-[[[3-Hydroxy-2-(hydroxymethyl)-2-methylpropyloxy]carbonyl]methyl]-6-[tetrahydro-2,2-dimethyl-5-(2-propenylidene)-4*H*-cyclopenta-1,3-dioxol-4-yl]-1,3-benzodioxole (26). Orthoester **25** (238 mg, 0.538 mmol) was dissolved in THF (5.0 mL)/water (0.1 mL) at 0 °C and treated with *p*-TsOH (5 mg). The reaction was allowed to stir at 0 °C for 1 h. The reaction was diluted with dichloromethane and quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane (three times). The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford **26**, 245 mg (99%): oil, TLC R_f = 0.23, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR ($CDCl_3$) δ 6.72 (s, 1 H, aromatic), 6.48 (s, 1 H, aromatic), 6.46–6.38 (m, 1 H, H7), 5.94 (d, 2 H, J_{gem} = 1.4 Hz, methylenedioxy), 5.59 (d, 1 H, $J_{6,7}$ = 11 Hz, H6), 5.06 (s, 1 H, H8 cis), 5.04 (d, 1 H, $J_{7,8t}$ = 5.6 Hz, H8 trans). 4.78 (app t, 1 H, $J_{2,3}$ = 5.8 Hz, $J_{1\beta,2}$ = 3 Hz, H2), 4.50 (app t, 1 H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 4.2 Hz, H3), 4.24 (A part of AB q, 1 H, $J_{11,11'}$ = 11 Hz, H11), 4.09 (B part of AB q, 1 H, $J_{11,11'}$ = 11 Hz, H11′), 3.94 (d, 1 H, $J_{3,4}$ = 4.2 Hz, H4), 3.74 (AB q, 2 H, J = 16 Hz, CO_2CH_2), 3.51–3.31 (m, 4 H, $(CH_2OH)_2$), 2.94 (ABX, 1 H, $J_{1\beta,2}$ = 3 Hz, $J_{1\alpha,1\beta}$ = 18 Hz, H1β), 2.84 (d, 1 H, $J_{1\alpha,1\beta}$ = 18 Hz, H1α), 1.54 (s, 3 H, acetonide methyl), 1.32 (s, 3 H, acetonide methyl), 0.75 (s, 3 H, ester methyl); ^{13}C NMR ($CDCl_3$) δ 172.08 (e, C10), 147.29 (e, C15), 146.29 (e, C16), 145.21 (e, C5), 133.86 (e, C12), 126.16 (o, C7), 126.15 (e, C13), 116.82 (e, C8), 111.93 (e, acetonide quat), 110.57 (o, C14), 108.02 (o, C17), 101.16 (e, C18), 88.11 (o, C3), 79.30 (o, C3), 67.71 (e, CO_2CH_2), 67.31 (e, CH_2OH), 66.79 (e, CH_2OH), 53.78 (o, C4), 40.57 (e, ester C quat), 39.10 (e, C11), 35.03 (e, C1), 27.68 (o, acetonide methyl), 25.30 (o, acetonide methyl), 16.82 (o, ester methyl); IR ($CHCl_3$) cm^{-1} (μm) 3469 (2.88), 2937 (3.40), 1727 (5.79), 1505 (6.64), 1487 (6.72), 1002 (9.98); MS *m/e* (rel intensity) 460 (M^+, 1), 442 (4), 402 (38), 282 (100); CIMS *m/e* (rel intensity) 461 (M + H, 1), 443 (2), 403 (30), 385 (100); Exact mass (EI) calcd for $C_{25}H_{32}O_8$ (M^+) 460.2097, found 460.2083.

(3aα,4α,5*E*,6aα)-(±)-5-[[(Hydroxyamino)carbonyl]methyl]-6-[tetrahydro-2,2-dimethyl-5-(2-propenylidene)-4*H*-1,3-cyclopenta-1,3-dioxol-4-yl]-1,3-benzodioxole (27). Ester **26** (2.91 g, 6.33 mmol) in methanol (60 mL) at 0 °C was treated with NH_2OH in methanolic KOH (50 mL, 89 mmol, 1.78 M). After 5.5 h the solvents were removed in vacuo. The residue was dissolved in ethyl acetate (145 mL) at 0 °C and treated with 1.25 N HOAc (200 mL). The aqueous phase was extracted with ethyl acetate (three times). The organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and filtered, and the solvents were removed in vacuo. The residue was dissolved in benzene and evaporated (repeated twice) to afford **27** (2.36 g, 100%) as a tan foam: TLC R_f = 0.30, (**26** R_f = 0.13 on the same plate) 7:3:1 (toluene/ethyl acetate/acetic acid), unidentified impurities had R_f = 0.55, **27** stained red with a solution of $FeCl_3$/ethanol/HCl and **27** stained black with PAA: ^{1}H NMR ($CDCl_3$) δ 6.85 (s, 1 H, aromatic), 6.67–6.53 (overlapping cm, 1 H, H7), 6.48 (overlapping s, 1 H, aromatic), 5.90 (d, 2 H, J_{gem} = 5 Hz, methylenedioxy), 5.68 (d of d, 1 H, $J_{6,7}$ = 10.7 Hz, $J_{6,8}$ = 1.8 Hz, H6), 5.09 (s, 1 H, H8 cis), 5.03 (d, 1 H, $J_{7,8t}$ = 2.2 Hz, H8 trans), 4.77 (app q, 1 H, J = 9.5 Hz, H2), 4.41 (app t, 1 H, J = 5.4 Hz, H3), 3.93 (d, 1 H, $J_{3,4}$ = 1.4 Hz, H4), 3.50 (ABq, 2 H, $J_{11,11'}$ = 4.8 Hz, H11 and H11′), 2.99–2.90 (m, 2 H, H1α and H1β), 1.55 (s, 3 H, acetonide methyl), 1.33 (s, 3 H, acetonide methyl); ^{1}H NMR (C_6D_6) δ 7.08 (s, 1 H, aromatic), 6.35–6.22 (cm, 1 H, H7), 5.72 (d, 1 H, $J_{6,7}$ = 10 Hz, H6), 5.29 (d, 2 H, J_{gem} = 12 Hz, methylenedioxy), 4.95 (s, 1 H, H8 cis), 4.90 (d, 1 H, $J_{7,8t}$ = 5.8 Hz, H8 trans), 4.18 (app t, 1 H, $J_{2,3}$ = 5.3 Hz, $J_{1\beta,2}$ = 2.5 Hz, H2), 3.96 (app t, 1 H, J = 5.1 Hz, H3), 3.87 (b s, 1 H, H4), 3.24 (AB q, 2 H, $J_{11,11'}$ = 7 Hz, H11 and H11′), 2.70 (d, 1 H, $J_{1\alpha,1\beta}$ = 18 Hz, H1α), 2.35 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 18 Hz, $J_{1\beta,2}$ = 2.5 Hz, H1β), 1.47 (s, 3 H, acetonide methyl), 1.14 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 169.07 (e, C10), 147.32 (e, C15), 146.46 (e, C16), 144.56 (e, C5), 133.35 (e, C12), 133.08 (o, C6), 126.61 (o, C7), 126.00 (e, C13), 117.01 (e, C8), 112.16 (e, acetonide quat), 110.11 (o, C14), 107.94 (o, C17), 101.16 (e, C18), 88.23 (o, C3), 79.37 (o, C2), 53.96 (o, C4), 36.93 (e, C11), 34.87 (e, C1), 27.44 (o, acetonide methyl), 25.18 (o, acetonide methyl); MS *m/e* (rel intensity) 355 (1), 340 (3), 297 (7), 205 (99); CIMS *m/e* (rel intensity) 374 (M + H, 100).

(3aα,4a*S (and 4a*R**), 16bβ,16cα)-(±)-3a,11,16b,16c-Tetrahydro-2,2-dimethyl-7*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopent[1,2-*a*]-[1,2]oxazino[3,2-*b*][3]benzazepin-10(4*H*)-one (15ac and 15at).** Hydroxamic acid **27E** (2.36 g, 6.33 mmol) in dichloromethane (875 mL) at –78 °C under argon was treated dropwise with tetra-*n*-butylammonium periodate (3.00 g, 6.92 mmol, 1.09 equiv) in dichloromethane (125 mL). The solution was allowed to warm to room temperature over 6 h. The reaction was quenched with a solution of aqueous sodium bisulfite. The organic phase was washed with saturated aqueous $NaHCO_3$, water, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (250 g) with 35–50% ethyl acetate in hexanes to afford **15ac**/**15at** 1.67 g (71%) as a foam: TLC R_f = 0.53, 7:3:1 (toluene/ethyl acetate/acetic acid), R_f = 0.29 50% ethyl acetate in hexane, stained brown with PAA and stained green with PMA; HPLC partially resolved peaks with t_R = 11.17 min and 12.06 min in a ratio of 1.64:1.00 with 18% ethyl acetate in hexanes (flow rate = 1.00 mL/min); proton NMR ratio for aromatic peaks was 1.56:1.00; however, following reductive N–O bond cleavage, mesylate formation, intramolecular nitrogen alkylation of the resulting lactam mesylate, and separation by preparatory HPLC a 2.10:1.00 ratio of **28ac**/**28at** was obtained (vide infra): ^{1}H NMR ($CDCl_3$) δ 6.98 (s, aromatic), 6.76 (s, aromatic), 6.71 (s, aromatic), 5.96 (AB q, methylenedioxy), 5.77 (d, J = 8.3 Hz, H6), 5.58–5.53 (m, H7), 5.17 (app t, J = 7.6 Hz, H3), 4.89 (app q, J = 6 Hz, H2), 4.80–4.72 (m, H8), 4.18–4.08 (m, H8), 4.04 (A part AB q, J = 15 Hz, H11), 3.74 (d, J = 8 Hz, H4), 3.43 (B part of AB q, J = 15 Hz, H11′), 2.90 (ABX, $J_{1,2}$ = 7 Hz, $J_{1\alpha,1\beta}$ = 13.5 Hz), 2.62 (ABX, $J_{1,2}$ = 5.3 Hz, $J_{1\alpha,1\beta}$ = 13.5 Hz), 1.59 (s, acetonide methyl), 1.56 (s, acetonide methyl), 1.42 (s, acetonide methyl), 1.35 (s, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 165.44 (e, s), 147.34 (e, s), 147.09 (e, s), 146.70 (e, s), 128.07 (o, d), 127.50 (e, s), 127.39 (e, s), 126.81 (e, s), 125.04 (o, d), 113.91 (e, s), 110.45 (o, d), 110.06 (o, d), 105.79 (o, d), 101.27 (e, t), 101.9 (e, t), 83.29 (o, d), 79.06 (o, d), 78.19 (o, d), 75.20 (o, d), 71.64 (e, s), 67.27 (e, t), 66.99 (e, t), 51.83 (o, d), 45.73 (e, t), 44.41 (e, s), 41.91 (e, t), 41.38 (e, t), 27.51 (o, q), 24.96 (o, q); MS *m/e* (rel intensity) 371 (M^+, 42), 266 (19), 190 (53); CIMS *m/e* (rel intensity) 372 (M + H, 100).

(3aα,4a*S (and 4a*R**), 15bβ,15cα)-(±)-3a,10,15b,15c-Tetrahydro-2,2-dimethyl-7*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]-

[3]pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (28ac and 28at). Acylnitro [4 + 2] cycloaddition product mixture **15ac** and **15at** (797.8 mg, 2.15 mmol) in absolute ethanol (40 mL) was treated with powdered anhydrous Na_2HPO_4 (1.53 g, 10.75 mmol, 5 equiv) at room temperature under argon. Sodium amalgum (6% Na(Hg)) (8.0 g, 10 wt %, freshly ground under N_2 in a mortar and pestle) was added to the above slurry. After 2 h the slurry was cooled to 0 °C and treated with saturated aqueous NH_4Cl (5 mL). The solution was allowed to stir 0.5 h. The solution was diluted with ether and water. The aqueous phase was extracted with ether (three times). The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), and filtered, and solvents were removed in vacuo. The allylic alcohols were separated by flash chromatography with fine SiO_2 (100 g). The column was packed with 7:3 (toluene/ethyl acetate) and eluted with 7:3:1 (toluene/ethyl acetate/acetic acid) to afford secondary amide allyl alcohols i-OH (392 mg, 49%) and ii-OH (181 mg, 23%), in addition to, 39 mg (5%) of a mixture of i-OH and ii-OH.

i-OH: oil, TLC R_f = 0.36, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR ($CDCl_3$) δ 7.73 (b s, exch, 1 H, N-H), 6.96 (s, 1 H, aromatic), 6.54 (s, 1 H, aromatic), 5.92 (d, 2 H, J_{gem} = 16 Hz, methylenedioxy), 5.78 (d, 1 H, $J_{6,7}$ = 12 Hz, H6), 5.73–5.68 (m, 1 H, H7), 4.84 (app q, 1 H, $J_{1\beta,2}$ = 7 Hz, $J_{1\alpha,2}$ = 6 Hz, $J_{2,3}$ = 6 Hz, H2), 4.50 (app t, 1 H, $J_{2,3}$ = 6 Hz, $J_{3,4}$ = 7 Hz, H3), 4.32 (app t, 2 H, J = 8 Hz, H8 and H8′), 4.26 (A part AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 3.25 (overlapping d, 1 H, $J_{3,4}$ = 7 Hz, H4), 3.24 (overlapping B part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11′), 2.58 (A part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, $J_{1\beta,2}$ = 7 Hz, H1β), 2.06 (B part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, $J_{1\alpha,2}$ = 6 Hz, H1α), 1.59 (s, 3 H, acetonide methyl) 1.29 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 175.29 (e, C10), 146.80 (e, C15), 146.75 (e, C16), 132.71 (o, C6), 132.64 (o, C7), 129.16 (e, C12), 122.00 (e, C13), 113.66 (e, acetonide quat), 110.57 (o, C14), 110.20 (o, C17), 101.10 (e, C18), 86.59 (o, C3), 77.54 (o, C2), 64.82 (e, C5, not suppressed in APT (attached proton test), D_1 = 4 ms), 59.19 (o, C4), 58.77 (e, C8, suppressed in APT, D_1 = 4 ms), 45.45 (e, C11), 42.68 (e, C1), 27.53 (o, acetonide methyl), 24.93 (o, acetonide methyl); IR ($CHCl_3$) cm^{-1} (μm) 3394 (2.95), 1664 (6.01); MS *m/e* (rel intensity) 373 (M^+, 3); CIMS *m/e* (rel intensity) 374 (M + H, 100); Exact mass (EI) calcd for $C_{20}H_{23}NO_6$ (M^+) 373.1525, found 373.1519.

ii-OH: oil, TLC R_f = 0.28, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR ($CDCl_3$) δ 7.44 (b s, exch, 1 H, N-H), 6.95 (s, 1 H, aromatic), 6.66 (s, 1 H, aromatic), 5.93 (d, 2 H, J_{gem} = 10 Hz, methylenedioxy), 5.54–5.49 (m, 1 H, H7), 5.19 (d, 1 H, $J_{6,7}$ = 12 Hz, H6) 4.90 (app t, 1 H, $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 8 Hz, H3), 4.71 (app q, 2 H, $J_{2,3}$ = 8 Hz, $J_{1\beta,2}$ = 7 Hz, $J_{1\alpha,2}$ = 6 Hz, H2), 4.07 (overlapping A part of ABX, 1 H, $J_{8,8'}$ = 14 Hz, $J_{7,8}$ = 6 Hz, H8), 4.02 (overlapping A part of AB q, 1 H, $J_{11,11'}$ = 17 Hz, H11), 3.78 (B part of ABX, 1 H, $J_{8,8'}$ = 14 Hz, $J_{7,8'}$ = 5 Hz, H8′), 3.69 (d, 1 h, $J_{3,4}$ = 8 Hz, H4), 3.57 (B part of AB q, 1 H, $J_{11,11'}$ = 17 Hz, H11′), 2.78 (A part of ABX, 1 H, $J_{1\beta,2}$ = 7 Hz, $J_{1\alpha,1\beta}$ = 13 Hz, H1β), 2.21 (B part of ABX, 1 H, $J_{1\alpha,2}$ = 6 Hz, $J_{1\alpha,1\beta}$ = 13 Hz, H1α), 1.55 (s, 3 H, acetonide methyl), 1.38 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 170.33 (b s, C10), 147.04 (s, C15), 146.57 (s, C16), 133.65 (d, C7), 130.14 (d, C6), 128.67 (s, C12), 126.32 (s, C13), 113.93 (s, acetonide quat), 110.45 (d, C14), 106.87 (d, C17), 101.13 (t, C18), 80.48 (d, C3), 76.21 (d, C2), 65.43 (s, C5) 57.99 (t, C8), 55.01 (d, C4), 46.83 (t, C11), 42.98 (t, C1), 27.42 (q, acetonide methyl), 27.42 (q, acetonide methyl), 24.87 (q acetonide methyl); IR ($CHCl_3$) cm^{-1} (μm) 3372 (2.97), 1643 (6.09); MS *m/e* (rel intensity) 373 (M^+, 15); CIMS *m/e* (rel intensity) 374 (M + H, 100); Exact mass (EI) calcd for $C_{20}H_{23}NO_6$ (M^+) 373.1525, found 373.1505.

Allyl alcohols i-OH and ii-OH (1.118 mg, 3.00 mmol) in dichloromethane (53 mL) under argon at 0 °C were treated with triethylamine (2.5 mL, 17.9 mmol, 6 equiv) and then with methanesulfonyl chloride (0.60 mL, 7.75 mmol, 2.6 equiv). The solution was allowed to stir at 0 °C for 1.5 h. The reaction was quenched with 0.1 N HCl (10 mL). The organic phase was washed with ice cold 0.1 N HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and water (20 mL), dried (Na_2SO_4), and filtered, and the solvents were removed in vacuo. The residue was dissolved in THF (50 mL) at room temperature under argon and treated with NaH (1.7 g). After the mixture was stirred for 8 h, an additional portion of NaH (1.0 g) was added. After 15 h total reaction time the slurry was filtered under nitrogen. The solids were rinsed with THF (10 mL) and ether (2 × 25 mL). The filtrate was washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic phase was dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was purified on a preparatory 500 A HPLC with 60% ethyl acetate in hexanes to afford **28at** 250 mg (23%, retention time of 15 min) and **28ac** 480 mg (45%, retention time of 41 min).

28at: oil, TLC R_f = 0.38, 50% ethyl acetate in hexanes, R_f = 0.53, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR δ 6.88 (s, 1 H, H14), 6.73 (s, 1 H, H17), 5.88 (s, 2 H, methylenedioxy), 5.84 (d, 1 H, $J_{6,7}$ = 6 Hz, H7), 5.73 (d, 1 H, $J_{6,7}$ = 6 Hz, H6), 5.03 (app t, 1 H, $J_{2,3}$ = 8 Hz, $J_{3,4}$ = 8 Hz, H3), 4.68 (app q, 1 H, $J_{1\beta,2}$ = 7 Hz, $J_{1\alpha,2}$ = 7 Hz, $J_{2,3}$ = 7 Hz, H2), 4.61 (A part of AB q, 1 H, $J_{8,8'}$ = 16 Hz, H8), 4.11 (A part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11′), 3.78 (d, 1 H, $J_{3,4}$ = 8 Hz, H4), 3.68 (B part of AB q, 1 H, $J_{8,8'}$ = 16 Hz, H8′), 3.39 (B part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 2.33 (A part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 12 Hz, $J_{1\beta,2}$ = 7 Hz, H1β), 2.22 (B part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 12 Hz, $J_{1\alpha,2}$ = 7 Hz, H1α), 1.53 (s, 3 H, endo acetonide methyl), 1.39 (s, 3 H, exo acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 168.93 (e, C10), 147.17 (e, C15), 146.71 (e, C16), 131.98 (o, C6), 129.30 (o, C7), 128.55 (e, C12), 127.00 (e, C13), 113.75 (e, acetonide quat), 109.95 (o, C14), 105.10 (o, C17), 101.02 (e, C18), 77.47 (o, C3), 75.98 (e, C5), 75.08 (o, C2), 52.30 (e, C8), 51.68 (o, C4), 45.90 (e, C11), 42.57 (e, C1), 27.30 (o, acetonide methyl), 24.73 (o, acetonide methyl); IR ($CHCl_3$) cm^{-1} (μm) 1633 (6.12), 1612 (6.20); MS *m/e* (rel intensity) 355 (M^+, 15); CIMS *m/e* (rel intensity) 356 (M + H, 100); Exact mass (EI) calcd for $C_{20}H_{21}NO_5$ (M^+) 355.1420, found 355.1406.

28ac: oil, TLC R_f = 0.23, 50% ethyl acetate in hexanes, R_f = 0.50, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR δ 6.78 (s, 1 H, H14), 6.65 (s, 1 H, H17), 6.02 (d, 1 H, $J_{6,7}$ = 6 Hz, H7), 5.90 (d, 2 H, J_{gem} = 2 Hz, methylenedioxy), 5.70 (d, 1 H, $J_{6,7}$ = 6 Hz, H6), 4.67 (app t, 1 H, $J_{2,3}$ = 5 Hz, $J_{1\beta,2}$ = 5 Hz, H2), 4.47 (app t, 1 H, $J_{2,3}$ = 5 Hz, $J_{3,4}$ = 5 Hz, H3), 4.15 and 4.03 (AB q, 2 H, $J_{8,8'}$ = 17 Hz, H8 and H8′), 3.55 (A part of AB q, 1 H, $J_{11,11'}$ = 14 Hz, H11′). 3.25 (overlapping B part of AB q, $J_{11,11'}$ = 14 Hz, H11), 3.24 (overlapping d, 1 H, $J_{3,4}$ = 5 Hz, H4), 2.67 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 16 Hz, $J_{1\beta,2}$ = 5 Hz, H1β), 2.53 (d, 1 H, $J_{1\alpha,1\beta}$ = 16 Hz, H1α), 1.63 (s, 3 H, endo acetonide methyl), 1.33 (s, 3 H, exo acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 169.63 (e, C10), 147.10 (e, C15), 147.01 (e, C16), 138.29 (o, C6), 131.14 (e, C12), 126.17 (e, C13), 121.13 (o, C7), 111.46 (o, C14), 111.16 (e, acetonide quat), 110.24 (o, C17), 101.14 (e, C18), 90.14 (o, C3), 78.71 (o, C2), 75.15 (e, C5), 60.63 (o, C4), 53.65 (e, C8), 45.94 (e, C11). 42.11 (e, C1), 27.92 (o, acetonide methyl), 25.44 (o, acetonide methyl); IR ($CHCl_3$) cm^{-1} (μm) 1646 (6.08), 1625 (6.15); MS *m/e* (rel intensity) 355 (M^+, 40), 241 (54); CIMS *m/e* (rel intensity) 356 (M + H, 100); Exact mass (EI) calcd for $C_{20}H_{21}NO_5$ (M^+) 355.1420, found 355.1409.

(3aα,4a*S,15bβ,15cα)-(±)-3a,6,7,10,15b,15c-Hexahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo-[2,1-*b*][3]benzazepin-9(4*H*)-one (29ac).** $\Delta^{6,7}$ Lactam **28ac** (720 mg, 2.03 mmol) was dissolved in absolute ethanol (150 mL) and treated with H_2 (50 psi) over 10% palladium on activated carbon (Aldrich) 50 mg on a Parr hydrogenator for 2 h. The solution was filtered through a Celite pad and the pad was rinsed with ethyl acetate (4 × 10 mL). The solvents were removed in vacuo to afford **29ac** 713 mg (98%). An analytical sample was prepared by recrystallization from absolute ethanol: mp = 188–189 °C; TLC R_f = 0.30, 7:3:1 (toluene/ethyl acetate/acetic acid), **28ac** and **29ac** had very similar R_f's, therefore, it was necessary to double spot them in order to determine when the reaction was complete: ^{1}H NMR δ 6.79 (s, 1 H, aromatic), 6.66 (s, 1 H, aromatic), 5.91 (s, 2 H, methylenedioxy), 4.68 (app t, 1 H, $J_{2,3}$ = 5 Hz, $J_{1\beta,2}$ = 5 Hz, H2), 4.50 (app t, 1 H, $J_{2,3}$ = 5 Hz, $J_{3,4}$ = 5.8 Hz, H3), 3.66 (app b t), 1 H, J = 10 Hz, H8), 3.42 (A part of AB q, 1 H, $J_{11,11'}$ = 14 Hz, H11), 3.26 (d, 1 H, $J_{3,4}$ = 5.8 Hz, H4), 3.22 (overlapping B part of AB q, $J_{11,11'}$ = 14 Hz, H11′). 3.18 (overlapping m, 1 H, H8′), 2.44 (overlapping d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α), 2.40 (overlapping m, 1 H, H6), 2.30 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, $J_{1\beta,2}$ = 5 Hz, H1β), 2.00 (app q, 1 H, H6′), 1.81 (app b t, 2 H, J = 7 Hz, H7 and H7′), 1.60 (s, 3 H, acetonide methyl). 1.32 (s, 3 H, acetonide methyl); ^{13}C NMR δ 169.57 (e, C10), 146.93 (e, C15), 146.86 (e, C16), 130.39 (e, C12), 126.87 (e, C13), 111.34 (e, acetonide quat), 111.28 (o, C14), 110.12 (o, C17), 101.03 (e, C18), 88.87 (o, C3), 78.86 (o, C2), 70.68 (e, C5), 61.25 (o, C4), 46.77 (e, C11), 45.19 (e, C8), 44.24 (e, C7), 41.81 (e, C1), 28.05 (o, acetonide methyl), 25.51 (o, acetonide methyl), 20.82 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 2991 (3.34), 1630 (6.14), 1504 (6.65); 1485 (6.73); MS *m/e* (rel intensity) 357 (M^+, 100), 281 (27), 243 (61), 214 (51). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.33; H, 6.71; N, 3.92.

(3aα,4a*R,15bβ,15cα)-(±)-3a,6,7,10,15b,15c-Hexahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo-[2,1-*b*][3]benzazepin-9(4*H*)-one (29at).** $\Delta^{6,7}$ Lactam **28at** (240 mg, 0.676 mmol) was dissolved in absolute ethanol (30 mL) and treated with H_2 (50 psi) over 10% palladium on activated carbon (Aldrich) (50 mg) on a Parr hydrogenator for 1 h. The solution was filtered through a Celite pad, and the pad was rinsed with ethyl acetate (4 × 10 mL). The solvents were removed in vacuo to afford **29at** 239 mg (99%): oil, TLC R_f = 0.43, 7:3:1 (toluene/ethyl acetate/acetic acid); ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 1 H, aromatic), 6.75 (s, 1 H, aromatic), 5.93 (d, 2 H, J_{gem} = 3.8 Hz, methylenedioxy), 4.89 (app t, 1 H, $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 9 Hz, H3), 4.71 (app q, 1 H, $J_{2,3}$ = 7 Hz, $J_{1\beta,2}$ = 7 Hz, H2), 4.12 (A part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 4.04–3.97 (cm, 1 H, H8), 3.80 (d, 1 H, $J_{3,4}$ = 9 Hz, H4), 3.42 (B part of AB q, 1 H, $J_{11,11'}$ = 15 Hz, H11), 3.08–3.04

(cm, 1 H, H8′), 2.47 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 13 Hz, $J_{1\beta,2}$ = 7 Hz, H1β), 1.96–1.98 (cm, 1 H, H7), 1.77–1.71 (overlapping cm, 2 H, H7′ and H1α), 1.54 (s, 3 H, acetonide methyl), 1.40 (s, 3 H, acetonide methyl), 1.29 (app t, 1 H, J = 11 Hz, H6), 1.17 (app t, 1 H, J = 11 Hz, H6′); ^{13}C NMR ($CDCl_3$) δ 166.63 (e, C10), 146.82 (e, C15), 146.39 (e, C16), 128.29 (e, C12), 126.92 (e, C13), 113.28 (e, acetonide quat), 109.79 (o, C14), 105.88 (o, C17), 100.82 (e, C18), 77.83 (o, C3), 75.33 (o, C2), 70.28 (e, C5), 51.61 (o, C4), 43.39 (e, C11), 42.18 (e, C8), 41.33 (o, C1), 30.44 (e, C7), 27.31 (o, acetonide methyl), 24.74 (o, acetonide methyl), 18.70 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 2995 (3.34), 1620 (6.17), 1505 (6.64), 1488 (6.72); MS m/e (rel intensity) 357 (M^+, 100), 281 (45), 243 (59); CIMS m/e (rel intensity) 358 (M + H, 100).

(3aα,4a*S,15bβ,15cα)-(±)-3a,4,6,7,9,10,15b,15c-Octahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo-[2,1-*b*][3]-benzazepine (30ac).** Lactam **29ac** (480 mg, 1.345 mmol) was dissolved in THF (16 mL) and heated to reflux under argon. A solution of borane/tetrahydrofuran complex (Aldrich) (9.6 mL, 9.6 mmol, 1 M, 7.1 equiv) was added dropwise. After 0.5 h the solution was allowed to cool to room temperature, and the solvents were removed in vacuo. The residue was dissolved in methanol (35.0 mL) and heated to reflux under argon for 0.5 h. The solvents were removed in vacuo, and the residue was purified by plug filtration on neutral aluminum oxide (50 g) with 50% ethyl acetate in hexanes to afford **30ac** 389 mg (84%) as a white solid: mp = 149–151 °C dec; TLC R_f = 0.33, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.75 (s, 2 H, two aromatic), 5.86 (s, 2 H, methylenedioxy), 4.75 (app t, 1 H, H2), 4.63 (app t, 1 H, H3), 3.30 (d, 1 H, H4), 3.10–2.80 (m, 2 H), 2.60–2.35 (m, 4 H), 2.30–2.12 (m, 2 H), 1.80–1.60 (m, 4 H), 1.58 (s, 3 H, acetonide methyl), 1.33 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 146.33 (e, C15), 146.03 (e, C16), 132.81 (e, C12), 130.03 (e, C13), 111.12 (o, C14), 110.71 (e, acetonide quat), 109.85 (o, C17), 100.70 (e, C18), 87.74 (o, C3), 80.22 (o, C2), 69.36 (e, C5), 62.92 (o, C4), 53.41 (e, C10), 48.34 (e, C8), 43.11 (e, C1), 32.01 (e, C11), 31.63 (e, C7), 28.02 (o, acetonide methyl), 25.51 (o, acetonide methyl), 19.78 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 2937 (3.40), 1504 (6.65), 1487 (6.72); MS m/e (rel intensity) 343 (M^+, 16), 328 (10), 258 (11), 229 (30), 164 (29), 122 (100); CIMS m/e (rel intensity) 344 (M + H, 60), 286 (100); Exact mass (EI) calcd for $C_{20}H_{25}NO_4$ 343.1784, found 343.1786.

(3aα,4a*R,15bβ,15cα)-(±)-3a,4,6,7,9,10,15b,15c-Octahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo-[2,1-*b*][3]benzazepine (30at).** Lactam **29at** (136 mg, 0.38 mmol) was dissolved in THF (5 mL) and heated to reflux under argon. A solution of borane/tetrahydrofuran complex (Aldrich) (3.0 mL, 3.0 mmol, 1 M, 7.9 equiv) was added dropwise. After 0.5 h the solution was allowed to cool to room temperature, and the solvents were removed in vacuo. The residue was dissolved in methanol (10.0 mL) and heated to reflux under argon for 1 h. The solvents were removed in vacuo, and the residue was purified by plug filtration on neutral aluminum oxide (15 g) with 50% ethyl acetate in hexanes to afford **30at** 112.9 mg (87%): oil, TLC R_f = 0.51, 50% ethyl acetate in hexanes on neutral aluminum oxide plates, (also **29at**, R_f = 0.27 and amine/borane complex R_f = 0.82 under the same TLC conditions); ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 1 H, aromatic), 6.57 (s, 1 H, aromatic), 5.89 (d, 2 H, J_{gem} = 11.7 Hz, methylenedioxy), 4.81 (app t, 1 H, $J_{2,3}$ = 7 Hz, $J_{3,4}$ = 9 Hz, H3), 4.60 (app q, 1 H, $J_{2,3}$ = 7 Hz, $J_{1\beta,2}$ = 7.2 Hz, $J_{1\alpha,2}$ = 4.3 Hz, H2), 3.65 (d, 1 H, $J_{3,4}$ = 9 Hz, H4), 3.21–3.09 (m, 2 H), 2.99–2.80 (m, 2 H), 2.70–2.57 (m, 2 H), 2.21 (A part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 13 Hz, $J_{1\beta,2}$ = 7.2 Hz, H1β), 1.90 (B part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 13 Hz, $J_{1\alpha,2}$ = 4.3 Hz, H1α), 1.77–1.64 (m, 2 H), 1.51 (s, 3 H, acetonide methyl), 1.37 (s, 3 H, acetonide methyl), 1.32–1.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 145.83 (e, C15), 145.71 (e, C16), 133.95 (e, C12), 129.58 (e, C13), 112.41 (e, acetonide quat), 109.74 (o, C14), 107.16 (o, C17), 100.66 (e, C18), 80.53 (o, C3), 75.48 (o, C2), 72.55 (e, C5), 52.68 (o, C4), 52.21 (e, C10), 47.75 (e, C8), 44.82 (e, C1), 34.13 (e, C11), 29.53 (e, C7), 27.67 (o, acetonide methyl), 25.12 (o, acetonide methyl), 21.66 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 2940 (3.40), 1505 (6.64), 1488 (6.72); MS m/e (rel intensity) 343 (M^+, 73), 328 (46), 258 (56), 229 (100); CIMS m/e (rel intensity) 344 (M + H, 100); Exact mass (EI) calcd for $C_{20}H_{25}NO_4$ 343.1784; found 343.1784.

(1aα,2α,3a*S,14bα)-(±)-1,2,3,5,6,8,9,14b-Octahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine-1,2-diol (31ac).** Acetonide **30ac** (100 mg, 0.292 mmol) was dissolved in THF (15.0 mL) at room temperature and treated with 1 N HCl (15.0 mL). The solution was allowed to stir for 3 h and then neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane (4 × 50 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo to afford **31ac** 87.5 mg (99%): mp = 192–194 °C dec; TLC R_f = 0.08, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.68 (s, 1 H, aromatic), 6.64 (s, 1 H, aromatic), 5.91 (s, 2 H, methylenedioxy), 4.32 (d of d, 1 H, $J_{3,4}$ = 10 Hz, $J_{2,3}$ = 6 Hz, H3), 4.22 (app t, 1 H, J = 6 Hz, H2), 3.05 (d, 1 H, $J_{3,4}$ = 10 Hz, H4), 3.04–2.85 (m, 4 H), 2.58–2.50 (m, 2 H), 2.40–2.28 (m, 2 H), 2.40–2.30 (m, 2 H), 2.00–1.95 (m, 1 H), 1.83–1.74 (m, 1 H), 1.72–1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 146.46 (e, C15), 146.07 (e, C16), 131.97 (e, C12), 130.60 (e, C13), 111.85 (o, C14), 110.82 (e, C18), 110.64 (o, C17), 78.07 (o, C3), 72.28 (o, C2), 66.39 (e, C5), 59.93 (o, C4), 53.62 (e, C10), 47.59 (e, C8), 43.65 (e, C1), 31.39 (e, C11), 30.91 (e, C7), 19.30 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 3560 (2.81), 3400 (2.94), 2931 (3.41), 1504 (6.65), 1487 (6.72); MS m/e (rel intensity) 303 (M^+, 78), 286 (22), 258 (44), 229 (100); Exact mass (EI) calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1470, found 303.1464.

(1aα,2α,3*R,14bα)-(±)-1,2,3,5,6,8,9,14b-Octahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine-1,2-diol (31at).** Amine **30at** (100 mg, 0.292 mmol) was dissolved in THF (15.0 mL) at room temperature and treated with 1 N HCl (15 mL). The solution was allowed to stir for 12 h and then neutralized with saturated aqueous $NaHCO_3$ (15 mL). The THF was removed in vacuo, and the aqueous slurry was extracted with dichloromethane (3 × 80 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo to afford **31at** 88 mg (99%): oil, TLC R_f = 0.08, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1 H, aromatic), 6.59 (s, 1 H, aromatic), 5.91 (d, 2 H, J_{gem} = 7 Hz, methylenedioxy), 4.25–4.20 (m, 2 H, H2 and H3), 3.87 (d, 1 H, $J_{3,4}$ = 7.7 Hz, H4), 3.02–2.95 (m, 2 H), 2.66–2.57 (m, 2 H), 2.36 (app t, 1 H, J = 11.5 Hz), 2.18 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 14.8 Hz, $J_{1\beta,2}$ = 6.5 Hz, H1β), 1.95 (d, 1 H, $J_{1\alpha,1\beta}$ = 14.8 Hz, H1α), 1.84–1.78 (m, 1 H), 1.71–1.66 (m, 1 H), 1.20 (app t, 2 H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 146.29 (e, C15), 145.89 (e, C16), 134.61 (e, C12), 130.09 (e, C13), 109.41 (o, C14), 107.55 (o, C17), 100.87 (e, C18), 73.77 (o, C3), 68.83 (o, C2), 69.18 (e, C5), 52.57 (o, C4), 50.84 (e, C8), 49.32 (e, C10), 46.95 (e, C1), 33.58 (e, C11), 29.00 (e, C7), 20.10 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 3583 (2.79), 3300 (3.03), 2928 (3.42), 1504 (6.65), 1488 (6.72); MS m/e (rel intensity) 303 (M^+, 58), 286 (7), 258 (26), 229 (88); CIMS m/e (rel intensity) 304 (M + H, 100), 286 (4); Exact mass (EI) calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471, found 303.1461.

(±)-5,6,8,9-Tetrahydro-1-hydroxy-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-2(3*H*)-one (5). DMSO (0.2 mL, 2.818 mmol, 8.5 equiv) was dissolved in dichloromethane (10.0 mL) at −78 °C under argon and treated with trifluoroacetic anhydride (0.2 mL, 1.416 mmol, 4.25 equiv). The solution was allowed to stir 10 min at −78 °C and then treated dropwise with diol **31ac** (101 mg, 0.333 mmol) in dichloromethane (13.0 mL). The solution was allowed to stir for 1 h at −78 °C and then treated with triethylamine 0.51 mL (3.659 mmol, 11 equiv). The solution was allowed to warm to 0 °C and stir for 0.5 h. The reaction was quenched with water (2 mL) and diluted with dichloromethane. The aqueous phase was extracted with dichloromethane (3 × 40 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue was triturated with dichloromethane/ether. The slurry was filtered, rinsed with ether, and dried under vacuum to afford **5** (89.6 mg, 90%): mp = 166–170 °C; TLC R_f = 0.42, 10% methanol in dichloromethane, direct comparison of this material (prepared from **31ac** *or* **31at**) by TLC with an authentic sample showed them to be identical; ^{1}H NMR ($CDCl_3$) δ 6.91 (s, 1 H, aromatic), 6.68 (s, 1 H, aromatic), 5.96 (d, 2 H, J_{gem} = 8 Hz, methylenedioxy), 3.36–3.31 (m, 2 H), 3.02–2.92 (m, 4 H), 2.63–2.54 (m, 2 H, H1α and H1β), 1.91–1.73 (m, 3 H), 1.71–1.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 200.80 (e, C2), 148.19 (e, C3 and C15), 148.04 (e, C16), 145.73 (e, C4), 132.42 (e, C12), 124.06 (e, C13), 109.82 (o, C14 and C17), 101.24 (e, C18), 70.65 (e, C5), 53.40 (e, C10), 50.75 (e, C1), 49.58 (e, C8), 38.73 (e, C7), 32.57 (e, C11), 24.12 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 3485 (2.87), 3300 (3.03), 3000 (3.33), 1710 (5.85), 1505 (6.64), 1487 (6.72); MS m/e (rel intensity) 299 (M^+, 100), 256 (64), 228 (39); Exact mass (EI) calcd for $C_{17}H_{17}NO_4$ (M^+) 299.1158, found 299.1162.

(±)-Cephalotaxinone (32). Demethylcephalotaxinone (**5**) (20.0 mg, 0.06689 mmol) was dissolved in dioxane (6.0 mL) and treated with 2,2-dimethoxypropane (Aldrich) (6.0 mL) and *p*-toluenesulfonic acid monohydrate (50.0 mg, 0.2629 mmol, 3.9 equiv) under argon. The solution was heated to reflux for 22.5 h. The reaction was allowed to cool to room temperature, and the solvents were removed in vacuo to afford after flash chromatography on fine SiO_2 (4.4 g) with ethyl acetate **32** (17.7 mg, 84%): oil, TLC R_f = 0.54, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.71 (s, 1 H, aromatic), 6.66 (s, 1 H, aromatic), 6.41 (s, 1 H, H1), 3.81 (s, 3 H, OCH_3), 3.55 (s, 1 H, H4), 3.15–3.08 (b app q, 1H), 2.94 (app q, 1 H, J = 13 Hz), 2.70 (app q, 1 H, J = 13 Hz), 2.57–2.50 (m, 1 H), 2.48–2.41 (m, 2 H), 2.11 (app q, 1 H, J = 15 Hz), 2.00–1.93 (m, 1 H), 1.92–1.83 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 200.34 (e, C3), 157.40 (e, C2), 146.02 (e, C15), 145.23 (e, C16), 130.92 (e, C12), 129.82 (e, C13), 125.74 (e, C1), 112.18 (o, C14), 109.65 (o, C17), 100.62 (e, C18), 64.62 (e, C5), 59.49 (o, C4), 57.00 (o, OCH_3), 54.88 (e, C10), 51.98 (e, C8), 46.66 (e, C11), 30.48 (e, C7), 19.65 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 1724 (5.80), 1627 (6.15), 1504 (6.65), 1487 (6.72);

MS *m/e* (rel intensity) 313 (M^+, 44), 298 (7); CIMS *m/e* (rel intensity) 314 (M + H, 100); Exact mass (EI) calcd for $C_{18}H_{19}NO_4$ 313.1314, found 313.1318.

(±)-Cephalotaxine (1). Cephalotaxinone (**32**) (30 mg, 0.0958 mmol) was dissolved in methanol (3.0 mL). The solution was cooled to −78 °C under argon and treated with $NaBH_4$ (50 mg, 1.32 mmol, 41 equiv). The solution was allowed to warm to room temperature. After 80 min at room temperature the reaction was treated with water, and the solvents were removed in vacuo. The aqueous slurry was extracted with dichloromethane (3 × 50 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue was dissolved in hot hexanes, filtered, and allowed to crystallize to afford **1** (29.2 mg, 97%): TLC R_f = 0.17, 10% methanol in dichloromethane, R_f = 0.18, 35% ethyl acetate in hexanes on neutral aluminum oxide, direct comparison of the spectra and TLC of this material with those of the natural product showed them to be identical. ^1H NMR ($CDCl_3$) δ 6.69 (s, 1 H, aromatic), 6.65 (s, 1 H, aromatic), 5.92 (s, 2 H, methylenedioxy), 4.92 (s, 1 H, H1), 4.78 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H3), 3.72 (s, 3 H, OCH_3), 3.68 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H4), 3.40–3.30 (m, 1 H), 3.12–3.05 (m, 1 H), 2.98–2.89 (m, 1 H), 2.63–2.55 (m, 2 H), 2.40–2.30 (m, 1 H), 2.08–1.96 (m, 1 H), 1.92–1.83 (b m, 1 H), 1.80–1.70 (b m, 1 H), 1.70–1.60 (b m, 1 H); ^1H NMR (C_6D_6) δ 6.57 (s, 1 H, aromatic), 6.46 (s, 1 H, aromatic), 5.34 (d, 2 H, J_{gem} = 23 Hz), 4.61 (s, 1 H, H1), 4.21 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H3), 3.59–3.52 (m, 1 H, H10), 3.33 (d, 1 H, $J_{3,4}$ = 9.2 Hz, H4), 3.23 (s, 3 H, OCH_3), 2.89–2.85 (m, 1 H, H8), 2.80–2.73 (m, 1 H, H11), 2.64–2.61 (m, 1 H, H11′), 2.60–2.45 (m, 1 H, H8′), 2.17–2.12 (m, 1 H, H10′), 1.89–1.83 (m, 1 H, H7), 1.71–1.65 (m, 1 H, H7′), 1.57–1.49 (m, 2 H, H6 and H6′); ^{13}C NMR (C_6D_6) δ 161.57 (e, C2), 146.90 (e, C15), 146.16 (e, C16), 135.25 (e, C12), 129.81 (e, C13), 112.90 (o, C14), 110.46 (o, C17), 100.67 (e, C18), 97.84 (o, C1), 73.48 (o, C3), 70.52 (e, C5), 59.01 (o, C4), 56.54 (o, OCH_3), 53.84 (e, C8), 48.31 (e, C11), 44.00 (e, C10), 32.29 (e, C7), 21.16 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 3676 (2.72), 3583 (2.79), 1654 (6.05), 1504 (6.65), 1487 (6.72); MS *m/e* (rel intensity) 315 (M^+, 100), 300 (57), 298 (64), 284 (75); CIMS *m/e* (rel intensity) 316 (M + H, 47), 298 (100); Exact mass (EI) calcd for $C_{18}H_{21}NO_4$ (M^+) 315.1471, found 315.1479.

(3aα,4a*S*,10β,15bβ,15cα)-(±)-10-Phenylthio-3a,6,7,10,15b,15c-hexahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (33β).** To a solution of LDA (0.988 mmol, 2.0 equiv) in THF (3.0 mL) at −78 °C under argon was added dropwise lactam **28ac** (170 mg, 0.47 mmol) in THF (4.0 mL). The solution was allowed to warm to 0 °C and stir at that temperature for 0.5 h. The reaction was cooled to −78 °C and treated with *S*-phenyl benzenethiosulfonate (475 mg, 1.9 mmol, 4 equiv) in THF (3.0 mL)/HMPA (0.18 mL). The solution was allowed to stir at −78 °C for 0.5 h and then at 0 °C for an additional 0.5 h. The reaction was quenched with saturated aqueous NH_4Cl and diluted with ether. The aqueous phase was extracted with ether (2 × 50 mL). The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on coarse SiO_2 (25 g) with 20% ethyl acetate in hexanes to afford **33β** 190 mg (86%) and **34** 31 mg (11%). (When the enolate was quenched in an inverse manner **34** was not formed.) The TLC and spectral data for **34** were identical with those described below in another procedure.

33β: mp 256–258 °C; TLC R_f = 0.57, 50% ethyl acetate in hexanes, R_f = 0.55, 7:3:1 (toluene/ethyl acetate/acetic acid): ^1H NMR δ 7.50–7.30 (m, 5 H, SPh), 6.76 (s, 1 H, H14), 6.56 (S, 1 H, H17), 5.94 (s, 2 H, J_{gem} = 5 Hz, methylenedioxy), 5.10 (app t, 1 H, $J_{2,3}$ = 5.2 Hz, $J_{3,4}$ = 5.7 Hz, H3), 4.98 (s, 1 H, H11), 4.83 (app t, 1 H, $J_{2,3}$ = 5.2 Hz, $J_{1\beta,2}$ = 5.1 Hz, H2), 3.69–3.56 (m, 1 H, H8), 3.55–3.49 (overlapping m, 1 H, H8′), 3.54 (overlapping d, 1 H, $J_{3,4}$ = 5.7 Hz, H4), 2.90 (ABX, 1 H, $J_{1\beta,2}$ = 5.1 Hz, $J_{1\alpha,1\beta}$ = 15 Hz, H1β), 2.55–2.48 (overlapping m, 1 H, H6), 2.53 (d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α), 2.18–2.00 (app q, 1 H, *J* = 10.2 Hz, H6′), 1.90–1.82 (m, 2 H, H7 and H7′), 1.66 (s, 3 H, acetonide methyl), 1.39 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 167.54 (e, C10), 148.08 (e, C15), 146.74 (e, C16), 134.18 (e, ipso-SPh), 131.79 (e, C12), 131.45 (o, *o*-SPh), 129.18 (o, *m*-SPh), 127.84 (o, *p*-SPh), 126.06 (e, C13), 112.08 (o, C14), 111.57 (o, C17), 110.40 (e, acetonide quat), 101.36 (e, C18), 90.45 (o, C3), 79.39 (o, C2), 70.58 (e, C5), 62.82 (o, C4), 58.92 (o, C11), 48.51 (e, C8), 46.80 (e, C7), 45.56 (e, C1), 28.11 (o, acetonide methyl), 25.55 (o, acetonide methyl), 19.81 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 1612 (6.20), 1505 (6.64), 1488 (6.72); MS *m/e* (rel intensity) 465 (M^+ 4), 450 (2), 356 (25), 328 (15), 298 (100); CIMS *m/e* (rel intensity) 466 (M + H, 100); Exact mass (EI) calcd for $C_{26}H_{27}NO_5S$ (M^+) 465.1610, found 465.1614.

(3aα,4a*S*,15bβ,15cα)-(±)-10-Bis(phenylthio)-3a,6,7,15b,15c-pentahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-a]pyrrolo[2,1-b][3]benzazepin-9(4*H*)-one (34), (3aα,4a*S***,10α,15bβ,15cα)-(±)-10-Phenylthio-3a,6,7,10,15b,15c-hexahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (33), and (3aα,4a*S***,15bβ,15cα)-(±)-10-Oxo-3a,6,7,15b,15c-pentahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (35).** To a solution of LHMDS (0.077 mmol, 2 equiv) in toluene (1.0 mL) at −78 °C under argon was added dropwise monosulfenylated lactam **33β** (18 mg, 0.0287 mmol) in toluene (1.0 mL). The solution was allowed to warm to 0 °C and stir at that temperature for 1 h. The reaction was allowed to warm to room temperature and stir at that temperature for an additional 0.5 h. The enolate solution was treated with *S*-phenyl benzenethiosulfonate[31] (50 mg, 0.2 mmol, 5 equiv) in toluene (1.0 mL)/HMPA (1.0 mL). The reaction was stirred for 1 h and then quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (2 × 50 mL). The organic phase was washed with saturated aqueous NaCl, then dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on coarse SiO_2 (4 g) with a gradient of 20% ⇒ 50% ethyl acetate in hexanes to afford **34** (9 mg, 41%), **33β** (6 mg, 33%), and **35** (3 mg, 20%). The TLC and spectral data for **33β** and **35** were identical with those described below in other procedures.

34: oil, TLC R_f = 0.70, 50% ethyl acetate in hexanes, R_f = 0.20, 20% ethyl acetate in hexanes: ^1H NMR ($CDCl_3$) δ 8.09 (s, 1 H, H17), 7.22–6.91 (m, 10 H, $(SPh)_2$), 6.80 (s, 1 H, H14), 5.98 (d, 2 H, J_{gem} = 3.2 Hz, methylenedioxy), 5.22 (app t, 1 H, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 5.3 Hz, H3), 4.68 (app t, 1 H, $J_{2,3}$ = 5.4 Hz, $J_{1\beta,2}$ = 5.7 Hz, H2), 3.71 (overlapping d, 1 H, $J_{3,4}$ = 5.3 Hz, H4), 3.72–3.60 (m, 2 H, H8 and H8′), 2.92 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, $J_{1\beta,2}$ = 5.7 Hz, H1β), 2.48 (app d, 1 H, *J* = 11.7 Hz, H6), 2.32 (d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α), 2.03 (app q, 1 H, *J* = 6.9 Hz, H7), 1.88–1.80 (m, 2 H, H6′ and H7′), 1.60 (s, 3 H, acetonide methyl), 1.30 (s, 3 H, acetonide methyl); MS *m/e* (rel intensity) 465 (<1), 450 (<1), 356 (2), 298 (6), 218 (70), 109 (100); CIMS *m/e* (rel intensity) 466 (87), 422 (21), 406 (100); DCI *m/e* (rel intensity) 574 (M + H, 100).

(3aα,4a*S*,10α,15bβ,15caα)-(±)-10-Phenylthio-3a,6,7,10,15b,15c-hexahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (33).** Monosulfenylated lactam **33β** (96 mg, 0.206 mmol) was slurried in THF (10.0 mL) under argon at room temperature and treated with potassium hydride (ca. 25 mg). The solution was allowed to stir at room temperature for 3 h and then cooled to −78 °C and quench with THF/saturated aqueous NH_4Cl. The aqueous phase was extracted with ether (2 × 50 mL). The organic phase was washed with saturated aqueous NaCl, then dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on coarse SiO_2 (100 g) with a gradient of 20% ⇒ 35% ethyl acetate in hexanes to afford **33** (as a 7:1 ratio of **33α**/**33β**) (80 mg, 83%) and **35** (12 mg, 15%). The TLC and spectral data for **35** were identical with those described below in another procedure.

33α: oil, TLC R_f = 0.51, 7:3:1 (toluene/ethyl acetate/acetic acid); ^1H NMR δ 7.57 (s, 1 H, H17), 7.27–7.15 (m, 5 H, SPh), 6.66 (s, 1 H, H14), 5.92 (s, 2 H, methylenedioxy), 4.80 (s, 1 H, H11), 4.63 (app t, 1 H, $J_{2,3}$ = 4.9 Hz, $J_{1\beta,2}$ = 5 Hz, H2), 4.40 (app t, 1 H, $J_{2,3}$ = 4.9 Hz, $J_{3,4}$ = 6 Hz, H3), 3.69–2.65 (m, 1 H, H8), 3.30 (d, 1 H, $J_{3,4}$ = 6 Hz, H4), 3.16–3.13 (m, 1 H, H8′), 2.50 (overlapping d, 1 H, $J_{1\alpha,\beta}$ = 15.9 Hz, H1α), 2.50–2.42 (overlapping m, 1 H, H6), 2.30 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 15.9 Hz, $J_{1\beta,2}$ = 5 Hz, H1β), 2.05–1.90 (m, 1 H, H6′), 1.88–1.75 (m, 2 H, H7 and H7′), 1.60 (s, 3 H, acetonide methyl), 1.30 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 167.15 (e, C10), 147.74 (e, C15), 147.24 (e, C16), 135.41 (e, ipso-SPh), 129.78 (e, C12), 129.55 (o, *o*-SPh), 129.04 (o, *m*-SPh), 128.15 (e, C13), 126.43 (o, *p*-SPh), 111.58 (o, C14), 111.44 (e, acetonide quat), 107.72 (o, C17), 101.26 (e, C18), 88.60 (o, C3), 78.87 (o, C2), 71.00 (e, C5), 62.04 (o, C4), 55.41 (o, C11), 47.27 (e, C8), 45.45 (e, C7), 44.59 (e, C1), 28.12 (o, acetonide methyl), 25.51 (o, acetonide methyl), 21.12 (e, C6).

(3aα,4a*S*,15bβ,15cα)-(±)-10-Oxo-3a,6,7,15b,15c-pentahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]-pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (35).** Red mercury(II) oxide[33] (Aldrich 10 mg, 0.046 mmol, 5 equiv) and boron/trifluoride etherate (0.01 mL, 0.081 mmol, 9.3 equiv) were stirred at room temperature in THF (0.9 mL)/water (0.1 mL). Bissulfenylated lactam **34** (5 mg, 0.0087 mmol) was dissolved in THF (0.9 mL)/water (0.1 mL) and added dropwise to the above solution. The solution turned purple for 5 s and then yellow-orange. The reaction was allowed to stir for 5 min and then it was triturated with ether. The slurry was filtered, and the solids were rinsed with ether. The aqueous phase was extracted with ether (2 × 20 mL). The organic phase was washed with 10% NaOH and saturated aqueous NaCl, then dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (4 g) with a gradient of 20% ⇒ 50% ethyl acetate in hexanes to afford **35** (3 mg, 95%). The TLC and spectral data were identical with

those described below in another procedure.

(3aα,4a*S*,15bβ,15cα)-(±)-10-Oxo-3a,6,7,15b,15c-pentahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]-pyrrolo[2,1-*b*][3]benzazepin-9(4*H*)-one (35).** Monosulfenylated lactam **33β** (315 mg, 0.677 mmol) was slurried in THF (20.0 mL) at −78 °C under argon and treated dropwise with a solution of LHMDS (1.22 mmol, 1.8 equiv) in toluene (8.0 mL). The solution was allowed to warm to room temperature and stir at that temperature for 1 h. The solution became homogeneous and yellow-golden during this time. The enolate solution was sparged with dry molecular oxygen for 0.5 h. The reaction was diluted with ether and quenched with water. The aqueous phase was extracted with ether (2 × 50 mL). The organic phase was washed with water (2 × 50 mL) and saturated aqueous NaCl, then dried ($MgSO_4$), and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (60 g) with a gradient of 20% ⇒ 50% ethylacetate in hexanes to afford **35** (203 mg, 81%): oil, TLC R_f = 0.36, 7:3:1 (toluene/ethyl acetate/acetic acid); ^1H NMR δ 7.03 (s, 1 H, aromatic), 6.81 (s, 1 H, aromatic), 6.04 (d, 2 H, methylenedioxy), 4.52 (app t, 1 H, $J_{2,3}$ = 6.6 Hz, $J_{1\beta,2}$ = 6.2 Hz, H2), 4.42 (d, 1 H, $J_{2,3}$ = 6.6 Hz, H3), 3.72–3.59 (overlapping m, 2 H, H8 and H8′), 3.59 (overlapping s. 1 H, H4), 2.57–2.35 (overlapping m, 1 H. H6 and H6′), 2.35 (overlapping ABX, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, $J_{1\beta,2}$ = 6.2 Hz, H1β), 2.22 (d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α), 1.95–1.88 (m, 2 H, H7 and H7′), 1.55 (s, 3 H, acetonide methyl), 1.22 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 193.23 (e, C11), 164.96 (e, C10), 152.77 (e, C15), 147.35 (e. C16), 136.21 (e, C12), 128.58 (e, C13), 110.30 (o, C14), 109.67 (e, acetonide quat). 108.58 (e, C17), 102.18 (e, C18), 90.20 (o, C3), 76.85 (o, C2), 68.18 (e, C5), 60.77 (o, C4), 47.15 (e, C1), 45.61 (e, C8), 43.46 (e, C7), 25.36 (o, acetonide methyl), 23.29 (o, acetonide methyl), 22.16 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 3014 (3.32), 1682 (5.95), 1643 (6.09). 1506 (6.64), 1485 (6.73); MS *m/e* (rel intensity) 371 (M^+, 7), 356 (6), 343 (11). 271 (30), 229 (100); ClMS *m/e* (rel intensity) 372 (M + H, 100); Exact mass (El) calcd for $C_{20}H_{21}NO_6$ (M^+) 371.1369, found 371.1368.

(3aα,4a*S*,10β,15bβ,15cα)-(±)-10-Hydroxy-3a,4,6,7,9,10,15b,15c-octahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepine (36β) and (3aα,4a*S***,10α,15bβ,15cα)-(±)-10-Hydroxy-3a,4,6,7,9,10,15b,15c-octahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepine (36α).** α-Keto lactam **35** (165 mg, 0.445 mmol) in THF (12.0 mL) at −78 °C under argon was treated dropwise with borane/tetrahydrofuran complex (Aldrich) (2.2 mL, 2.2 mmol, 1 M, 4.9 equiv). The solution was allowed to stir at −78 °C 12 h and then allowed to warm slowly to room temperature over an additional 15 h. The solvents were removed in vacuo, and the residue was dissolved in methanol (10.0 mL) and heated to reflux for 0.5 h. The solvents were removed in vacuo, and the residue was purified by plug filtration on course SiO_2 (20 g) with a gradient of dichloromethane ⇒ 10% methanol in dichloromethane to afford **36β** (130 mg, 81%) and **36α** (27 mg, 17%).

36β: oil, TLC R_f = 0.21, 10% methanol in dichloromethane; ^1H NMR (C_6D_6) δ 6.74 (s, 1 H, aromatic), 6.71 (s, 1 H, aromatic), 5.35 (s. 2 H, methylenedioxy), 4.96 (app t, 1 H, $J_{2,3}$ = 5.7 Hz, $J_{3,4}$ = 4.9 Hz, H3), 4.67 (app d of t, $J_{2,3}$ = 5.7 Hz, $J_{1\beta,2}$ = 6.4 Hz, H2), 4.38 (app t, 1 H. $J_{10,11}$ = 6.7 Hz, $J_{10',11}$ = 4.8 Hz, H11), 3.39–3.24 (overlapping m, 1 H), 3.30 (overlapping d, 1 H, $J_{3,4}$ = 4.9 Hz, H4), 2.91 (A part of ABX, 1 H, $J_{10,11}$ = 6.7 Hz, $J_{10,10'}$ = 14 Hz, H10), 2.68 (B part of ABX, 1 H, $J_{10',11}$ = 4.8 Hz, $J_{10,10'}$ = 14 Hz, H10′), 2.62–2.44 (m, 3 H), 2.27 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, $J_{1\beta,2}$ = 6.4 Hz, H1β), 2.11–2.03 (m, 1 H), 1.80 (d, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, H1α), 1.57 (s, 3 H, acetonide methyl). 1.53–1.27 (m, 2 H), 1.24 (s, 3 H, acetonide methyl); ^1H NMR ($CDCl_3$) δ 6.81 (s, 1 H, aromatic), 6.63 (s, 1 H, aromatic), 5.90 (d, 2 H, J_{gem} = 12 H), 4.88 (app t, 1 H, $J_{2,3}$ = 5.7 Hz, $J_{3,4}$ = 4.2 Hz, H3), 4.78 (app q, 2 H, H2 and H11), 3.20 (overlapping d, 1 H, $J_{3,4}$ = 4.2 Hz, H4), 3.20–3.15 (overlapping A part of ABX, 1 H, $J_{10,11}$ = 6.8 Hz, $J_{10,10'}$ = 13.6 Hz, H10), 2.82–2.78 (m, 1 H), 2.71 (overlapping B part of ABX, 1 H, $J_{10',11}$ = 4.8 Hz, $J_{10,10'}$ = 13.6 Hz, H10′), 2.75–2.50 (overlapping b m, 2 H), 2.30 (overlapping A part of ABX, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, $J_{1\beta,2}$ = 6.2 Hz. H1β), 2.30–2.15 (overlapping m, 1 H), 1.90–1.70 (overlapping m, 3 H), 1.78 (overlapping B part of ABX, $J_{1\alpha,1\beta}$ = 14 Hz, $J_{1\alpha,2}$ = 1 Hz, H1α), 1.56 (s, 3 H, acetonide methyl), 1.31 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 146.84 (e, C15), 146.27 (e, C16), 133.22 (e, C12), 131.46 (e, C13), 110.33 (e, acetonide quat), 110.21 (o, C14), 108.69 (o. C17), 100.99 (e, C18), 87.23 (o, C3), 79.71 (o, C2), 73.15 (e, C5), 71.61 (o, C11), 59.93 (o, C4), 54.93 (e, C8), 52.97 (e, C10), 38.53 (e, C1), 38.23 (e, C7), 27.04 (o, acetonide methyl). 24.62 (o, acetonide methyl), 20.98 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 3601 (2.78), 3406 (2.94), 2989 (3.35), 1505 (6.64), 1488 (6.72); MS *m/e* (rel intensity) 359 (M^+, 100). 344 (44), 300 (7), 284 (19), 274 (48), 245 (62), 228 (65); ClMS *m/e* (rel intensity) 360 (M + H, 77). 342 (74). 302 (100), 284 (80); Exact mass (El) calcd for $C_{20}H_{25}NO_5$ (M^+) 359.1733, found 359.1734.

36α: oil, TLC R_f = 0.52, 10% methanol in dichloromethane; ^1H NMR ($CDCl_3$) δ 7.09 (s, 1 H, H17), 6.64 (s, 1 H, H14), 5.91 (d, 2 H, J_{gem} = 7.8 Hz, methylenedioxy), 4.70 (app t, 1 H, $J_{1\beta,2}$ = 5.6 Hz, $J_{2,3}$ = 5.3 Hz, H2), 4.61 (ABX, 1 H, $J_{10,11}$ = 6.5 Hz, $J_{10',11}$ = 11 Hz, H11), 4.50 (app t, 1 H, $J_{2,3}$ = 5.3 Hz, $J_{3,4}$ = 5.4 Hz, H3), 3.20 (d, 1 H, $J_{3,4}$ = 5.4 Hz, H4), 3.04–2.98 (m, 1 H), 2.79 (ABX, 1 H, $J_{10,11}$ = 6.5 Hz, $J_{10,10'}$ = 11 Hz, H10), 2.68 (app t, 1 H, $J_{10',11}$ = 11 Hz, $J_{10,10'}$ = 11 Hz, H10′), 2.40 (app q, 1 H, J = 6.5 Hz), 2.60 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, $J_{1\beta,2}$ = 5.6 Hz, H1β), 2.25–2.19 (m, 1 H), 1.82 (overlapping d, 1 H, $J_{1\alpha,1\beta}$ = 15 Hz, H1α). 1.84–1.76 (m, 1 H), 1.72–1.68 (m, 2 H), 1.58 (s, 3 H, acetonide methyl), 1.31 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 146.85 (e, C15), 146.31 (e, C16), 133.39 (e, C12), 129.69 (e, C13), 111.33 (o, C14), 110.97 (e, acetonide quat), 104.67 (o, C17), 100.92 (e, C18). 87.53 (o, C3), 80.22 (o, C2), 69.60 (e, C5), 67.54 (o, C11), 62.87 (o, C4), 55.97 (e, C8), 53.37 (e, C10), 43.53 (e, C1), 31.29 (e, C7), 28.07 (o. acetonide methyl), 25.56 (o, acetonide methyl), 19.74 (e, C6); IR ($CHCl_3$) cm^{-1} (μm) 3601 (2.78), 3450 (2.90), 2936 (3.41), 1503 (6.65), 1485 (6.73); MS *m/e* (rel intensity) 359 (M^+, 52), 344 (23), 300 (5), 284 (18), 274 (35); CIMS *m/e* (rel intensity) 360 (M + H, 100), 342 (27), 302 (86), 284 (23); Exact mass (EI) calcd for $C_{20}H_{25}NO_5$ (M^+) 359.1733, found 359.1730.

(3aα,4S*,10β,15bβ,15cα)-(±)-10-Acetoxy-3a,4,6,7,9,10,15b,15c-octahydro-2,2-dimethyl-5*H*-[1,3]dioxolo[4,5-*h*]-1,3-dioxolo[4,5]cyclopenta[1,2-*a*]pyrrolo[2,1-*b*][3]benzazepine (37β). Alcohol **36β** (130 mg, 0.362 mmol) was dissolved in dichloromethane (13.0 mL), under argon, and treated with pyridine (0.33 mL, 4.08 mmol, 11 equiv), acetic anhydride (0.33 mL, 3.5 mmol, 10 equiv) and DMAP (ca. 5 mg). The solution was allowed to stir at room temperature for 3 h. The solvents were removed in vacuo, and the residue was purified by plug filtration on course SiO_2 (40 g) with a gradient of 50% ethyl acetate in hexanes ⇒ 10% methanol in dichloromethane to afford **37β** (139 mg, 96%): oil, TLC R_f = 0.54, 10% methanol in dichloromethane; ^1H NMR (C_6D_6) δ 6.91 (s, 1 H, aromatic), 6.73 (s, 1 H, aromatic), 6.05 (d of d, 1 H, $J_{10,11}$ = 7.7 Hz, $J_{10',11}$ = 4.8 Hz, H11), 5.25 (d, 2 H, J_{gem} = 12 Hz, methylenedioxy), 4.92 (app t, 1 H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 5.4 Hz, H3), 4.64 (b app t, $J_{2,3}$ = 5.8 Hz, $J_{1\alpha,2}$ = 1.9 Hz, $J_{1\beta,2}$ = 6.4 Hz, H2), 3.35 (d, 1 H, $J_{3,4}$ = 5.4 Hz, H4), 3.13 (A part of ABX, 1 H, $J_{10,11}$ = 7.7 Hz, $J_{10,10'}$ = 14.5 Hz, H10), 2.64 (overlapping B part of ABX, 1 H, $J_{10',11}$ = 4.8 Hz, $J_{10,10'}$ = 14.5 Hz, H10′), 2.70–2.58 (overlapping m, 1 H), 2.43–2.35 (app q, 1 H, J = 7.6 Hz). 2.17 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 14.4 Hz, $J_{1\beta,2}$ = 6.4 Hz, H1β), 2.10–1.97 (m, 1 H), 1.85 (overlapping ABX, $J_{1\alpha1\beta}$ = 14.4 Hz, $J_{1\alpha,2}$ = 1.9 Hz, H1α), 1.85–1.70 (overlapping app q, 1 H, J = 10.6 Hz), 1.58 (s, 3 H, acetonide methyl), 1.51 (s, 3 H, acetate methyl), 1.50–1.38 (m, 2 H), 1.26 (s, 3 H, acetonide methyl); ^1H NMR ($CDCl_3$) δ 6.83 (s, 1 H, aromatic), 6.65 (s, 1 H, aromatic), 5.99 (d of d, 1 H, H11), 5.92 (d, 2 H, J_{gem} = 12.8 Hz, methylenedioxy), 4.84–4.78 (m, 2 H, H2 and H3), 3.38 (ABX. 1 H, $J_{10,11}$ = 7.7 Hz, $J_{10,10'}$ = 14.4 Hz, H10), 3.28 (d, 1 H, $J_{3,4}$ = 4.5 Hz, H4), 2.90–2.85 (m, 1 H), 2.78–2.75 (m, 1 H), 2.64–2.61 (m, 1 H), 2.27–2.20 (m, 2 H), 2.07 (s, 3 H, acetate methyl), 1.87–1.70 (m, 2 H), 1.58 (s, 3 H, acetonide methyl), 1.32 (s, 3 H, acetonide methyl); ^{13}C NMR ($CDCl_3$) δ 169.61 (e, acetate C=O), 147.65 (e. C15), 146.49 (e, C16), 132.38 (e, C12), 128.09 (e, C13), 110.83 (o, C14), 110.67 (e, acetonide quat), 110.31 (o, C17), 101.19 (e, C18), 87.32 (o, C3), 79.67 (o, C2 and C11), 73.52 (o, C4), 72.98 (e, C5), 52.62 (e, C8 and C10), 51.77 (e, C1), 37.35 (e, C7), 27.29 (o, acetonide methyl), 24.82 (o, acetonide methyl), 21.36 (o, acetate methyl), 20.90 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 2937 (3.40), 1735 (5.76), 1506 (6.64), 1489 (6.72); MS *m/e* (rel intensity) 401 (M^+, 35), 386 (23), 341 (37); CIMS *m/e* (rel intensity) 402 (M + H, 19), 342 (100); Exact mass (EI) calcd for $C_{22}H_{27}NO_4$ (M^+) 401.1838, found 401.1834.

(1aα,2α,3a*S*,9β,14bα)-(±)-9-Acetoxy-1,2,3,5,6,8,9,14b-octahydro-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepine-1,2-diol (38).** Amine **37β** (139 mg, 0.347 mmol) was dissolved in THF (10 mL) at room temperature and treated with 1 N HCl (10.0 mL). The solution was allowed to stir for 6.5 h and then was neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane (3 × 40 mL) and ethyl acetate (1 × 40 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (15 g) with a gradient of dichloromethane ⇒ 10% methanol in dichloromethane to afford **38** (112 mg, 90%) and **37β** (8 mg, 6%): oil. TLC R_f = 0.42, 10% methanol in dichloromethane; ^1H NMR ($CDCl_3$) δ 6.86 (s, 1 H, aromatic), 6.69 (s, 1 H, aromatic). 6.00 (d of d, 1 H, $J_{10,11}$ = 8.8 Hz, $J_{10',11}$ = 3.0 Hz, H11), 5.93 (d, 2 H, J_{gem} = 2.14 Hz. methylenedioxy). 5.20 (d of d, 1 H, $J_{2,3}$ = 4 Hz. $J_{3,4}$ = 10 Hz, H3). 4.23 (app t, 1 H, $J_{2,3}$ = 4 Hz. $J_{1\beta,2}$ = 4 Hz, H2), 3.60 (A part of ABX, 1 H, $J_{10,10'}$ = 15.1 Hz, $J_{10,11}$ = 8.8 Hz, H10), 3.17 (d. 1 H, $J_{3,4}$ = 10 Hz, H4), 2.91 (app q, 1 H, J = 8.4 Hz), 2.74 (B part of ABX, $J_{10,10'}$ = 15.1 Hz, $J_{10',11}$ = 3 Hz, H10′), 2.52 (overlapping app q, 1 H. J = 7.4 Hz), 2.60–2.15 (overlapping b s,

OH), 2.30–2.10 (overlapping m, 1 H), 2.13 (ABX, 1 H, $J_{1\alpha,1\beta}$ = 14.4 Hz, $J_{1\beta,2}$ = 4 Hz, H1β), 2.00 (s, 3 H, acetate methyl), 1.97–1.60 (overlapping m, 3 H), 1.70 (overlapping d, $J_{1\alpha,1\beta}$ = 14.4 Hz, H1α); ^{13}C NMR ($CDCl_3$) δ 169.80 (e, acetate C=O), 147.72 (e, C15), 146.47 (e, C16), 133.64 (e, C12), 128.09 (e, C13), 113.32 (o, C14), 113.14 (o, C17), 101.26 (e, C18), 80.08 (o, C3), 75.90 (o, C2), 71.89 (o, C11), 67.87 (e, C5), 60.03 (o, C4), 52.49 (e, C8), 50.79 (e, C10), 42.95 (e, C1), 34.15 (e, C7), 21.46 (o, acetate methyl), 20.08 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 3607 (2.77), 3560 (2.81), 3440 (2.91), 2898 (3.45), 1730 (5.78), 1507 (6.64), 1489 (6.72); MS *m/e* (rel intensity) 361 (M^+, 6), 301 (4), 288 (100), 214 (29); ClMS *m/e* (rel intensity) 362 (M + H, 75), 302 (100); Exact mass (EI) calcd for $C_{19}H_{23}NO_6$ (M^+) 361.1525, found 361.1523.

(3a*S,9β)-(±)-9-Acetoxy-5,6,8,9-tetrahydro-1-hydroxy-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]pyrrolo[2,1-*b*][3]benzazepin-2(3*H*)-one (39).** DMSO (0.24 mL, 3.38 mmol, 13.6 equiv) was dissolved in dichloromethane (10 mL) at −78 °C under argon, and the solution was treated with trifluoroacetic anhydride (0.14 mL, 0.991 mmol, 4 equiv). The solution was allowed to stir 10 minutes at −78 °C and then was treated dropwise with a solution of diol **38** 90 mg (0.249 mmol) in dichloromethane (4.0 mL). The solution was allowed to stir for 1.5 h at −78 °C and then treated with triethylamine (0.57 mL, 4.09 mmol, 16 equiv). The solution was allowed to warm to 0 °C and stir for 0.5 h. The reaction was quenched with water and diluted with ether. The organic phase was extracted with water (2 × 10 mL). The ether phase was discarded. The aqueous phase was extracted with dichloromethane (3 × 40 mL). The dichloromethane phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (20 g) with ether to afford **39** (79 mg, 89%): oil, TLC. R_f = 0.25, 50% ether in dichloromethane, R_f = 0.40, 5% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.93 (s, 1 H, aromatic), 6.86 (s, 1 H, aromatic), 6.35 (d of d, 1 H, $J_{10,11}$ = 6 Hz, $J_{10',11}$ = 10 Hz, H11), 6.00 (d, 2 H, J_{gem} = 5.8 Hz, methylenedioxy), 3.28 (A part of ABX, 1 H, $J_{10,11}$ = 6 Hz, $J_{10,10'}$ = 15 Hz, H10), 3.13 (overlapping B part of ABX, 1 H, $J_{10',11}$ = 10 Hz, $J_{10,10'}$ = 15 Hz, H10′), 3.10–3.01 (overlapping m, 1 H), 2.91–2.84 (m, 1 H), 2.58 (AB q, 2 H, $J_{1\alpha,1\beta}$ = 18.5 Hz, H1α and H1β), 2.04 (s, 3 H, acetate methyl), 1.90–1.70 (m 4 H); ^{13}C NMR ($CDCl_3$) δ 201.39 (e, C2), 170.38 (e, acetate C=O), 148.36 (e, C3), 147.73 (e, C15). 147.65 (e, C16), 143.94 (e, C4), 130.29 (e, C12), 124.76 (e, C13), 110.82 (o, C14), 109.53 (o, C17), 101.66 (e, C18), 71.69 (o, C11), 69.17 (e, C5), 50.56 (e, C10), 50.01 (e, C8), 47.00 (e, C1), 39.64 (e, C7), 24.46 (e, C6), 21.20 (o, acetate methyl); IR (CH_2Cl_2) cm^{-1} (μm) 3467 (2.88), 3400 (2.94), 1729 (5.78), 1705 (5.87), 1505 (6.64), 1488 (6.72); MS *m/e* (rel intensity) 357 (M^+, 11), 314 (4), 297 (100); CIMS *m/e* (rel intensity) 358 (M + H, 56), 298 (100); Exact mass (EI) calcd for $C_{19}H_{19}NO_6$ (M^+) 357.1212, found 357.1209.

(3a*S,9β)-(±)-9-Acetoxy-5,6,8,9-tetrahydro-1-methoxy-4*H*-cyclopenta[*a*][1,3]dioxolo[4,5-*h*]-pyrrolo[2,1-*b*][3]benzazepin-2(3*H*)-one (40).** α-Dione **39** (10 mg, 0.028 mmol) was dissolved in ether (1.0 mL) and treated with an etheral solution of diazomethane[39] (which had been prepared from methylnitrosourea)[40] until a yellow color persisted. The solution was allowed to stir for 4 h. The solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (3 g) with 50% ether in dichloromethane to afford **40** (10 mg, 96%): oil, TLC R_f = 0.60, 5% methanol in dichloromethane: ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 1 H, aromatic), 6.77 (s, 1 H, aromatic), 6.29 (d of d, 1 H, $J_{10,11}$ = 6.6 Hz, $J_{10',11}$ = 10 Hz, H11), 6.01 (d, 2 H, J_{gem} = 3.2 Hz, methylenedioxy), 3.91 (s, 3 H, OCH_3), 3.35 (A part of ABX, 1 H, $J_{10,10'}$ = 15 Hz, $J_{10,11}$ = 6.6 Hz, H10), 3.13 (B part of ABX, 1 H, $J_{10,10'}$ = 15 Hz, $J_{10',11}$ = 10 Hz, H10′), 3.03 (app t, 1 H, J = 7.4 Hz), 2.83–2.75 (m, 1 H), 2.53 (AB q, 2 H, $J_{1\alpha,1\beta}$ = 18.1 Hz, H1α and H1β), 2.04 (s, 3 H, acetate methyl), 1.87–1.50 (m. 4 H).

(3a*S,9β)-(±)-9-Acetoxycephalotaxin-1-one (41).** α-Dione **39** (29 mg, 0.08 mmol) was dissolved in ether (7.0 mL) and treated with 2,2-dimethoxypropane (Aldrich) (7.0 mL) and *p*-toluenesulfonic acid monohydrate (60 mg, 0.315 mmol, 3.9 equiv) under argon. The solution was heated to reflux for 6 h. The reaction was allowed to cool to room temperature, and the solvents were removed in vacuo. The residue was dissolved in ether and water. The ether was extracted with water (3 × 10 mL). The ether phase was discarded. The aqueous phase was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 40 mL). The dichloromethane phase was dried ($MgSO_4$) and filtered, and the solvents were removed in vacuo. The residue was purified by flash chromatography on fine SiO_2 (5 g) with (column 1) 50% ether in dichloromethane; (column 2) ether; (column 3) ether; (column 4) 50% ether in dichloromethane to afford **41** (13 mg, 43%), **42** (5 mg, 17%), and **39** (7.5 mg, 26%). The TLC and spectral data for **39** were identical with those described previously in another procedure.

41: oil, TLC R_f = 0.45, 50% ether in dichloromethane, R_f = 0.60, 5% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.81 (s, 1 H, aromatic), 6.77 (s, 1 H, aromatic), 6.21 (s, 1 H, H1), 5.95 (d, 2 H, J_{gem} = 13.3 Hz, methylenedioxy), 5.74 (d, 1 H, $J_{10,11}$ = 8 Hz, H11), 3.82 (s, 3 H, OCH_3), 3.56 (s, 1 H, H4), 3.30 (ABX, 1 H, $J_{10,11}$ = 8 Hz, $J_{10,10'}$ = 14.7 Hz, H10), 3.07–3.02 (m, 1 H, H8), 2.82–2.75 (overlapping m, 1 H, H8′), 2.77 (overlapping d, 1 H, $J_{10,10'}$ = 14.7 Hz, H10′), 2.16–2.09 (m, 1 H, H6), 2.05–1.94 (m, 1 H, H6′), 1.90 (overlapping s, 3 H, acetate methyl), 1.94–1.85 (overlapping m, 2 H, H7 and H7′); ^{13}C NMR ($CDCl_3$) δ 199.01 (e, C3), 170.11 (e, acetate C=O), 158.92 (e, C2), 148.01 (e, C15), 146.97 (e, C16), 128.72 (e, C12), 127.71 (e, C13), 121.75 (o, C1), 114.21 (o, C14), 112.03 (o, C17), 101.48 (e, C18), 74.96 (o, C11), 66.03 (e, C5), 60.22 (o, C4), 57.14 (o, OCH_3), 52.59 (e, C8), 52.15 (e, C10), 39.50 (e, C7), 20.67 (o, acetate methyl), 20.05 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 2967 (3.37), 1727 (5.79), 1631 (6.13), 1507 (6.64), 1490 (6.71); MS *m/e* (rel intensity) 371 (M^+, 2), 328 (6), 311 (100), 296 (47), 268 (17), 252 (11), 240 (11), 227 (13), 208 (15), 166 (69); CI MS *m/e* (rel intensity) 372 (M + H, 2), 312 (100); Exact mass (EI) calcd for $C_{20}H_{21}NO_6$ (M^+) 371.1369, found 371.1368.

42: oil, TLC R_f = 0.57, 50% ether in dichloromethane, R_f = 0.75, 5% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.94 (s, 1 H, H1), 6.70 (s, 1 H, aromatic), 6.38 (s, 1 H, aromatic), 5.95 (d, 2 H, J_{gem} = 5.8 Hz, methylenedioxy), 5.55 (d of d, 1 H, $J_{10,11}$ = 7.2 Hz, $J_{10',11}$ = 10.3 Hz, H11), 4.50 (app t, 1 H, J = 4.4 Hz, H6), 4.38 (s, 1 H, H4), 3.84 (s, 3 H, OCH_3), 3.55 (s, 1 H, NH), 3.06–3.02 (m, 1 H), 2.95 (ABX, 1 H, $J_{10,10'}$ = 10.9 Hz, $J_{10,11}$ = 7.2 Hz, H10), 2.73 (app q, 1 H, J = 8 Hz), 2.63 (app t. 1 H, J = 10.4 Hz, H10′), 2.12 (s, 3 H, acetate methyl), 2.10–2.00 (m, 1 H), 1.92–1.84 (m, 1 H); MS *m/e* (rel intensity) 371 (M^+, 6), 328 (6), 311 (100), 296 (32); CIMS *m/e* (rel intensity) 372 (M + H, 36), 312 (100).

(±)-11-Hydroxycephalotaxine (3). Enone **41** (21 mg, 0.0566 mmol) was dissolved in methanol (5.0 mL)/dichloromethane (1.0 mL) at 0 °C and treated with $NaBH_4$ (55 mg, 1.45 mmol, 25 equiv). The reaction was allowed to warm to room temperature and stirred for 1 h. A second portion of $NaBH_4$ (55 mg, 1.45 mmol, 25 equiv) was added, and reaction was stirred for an additional hour. A third portion of $NaBH_4$ (55 mg, 1.45 mmol, 25 equiv) was added, and the reaction was stirred for 1 h. The reaction was quenched (after 3 h total reaction time) with saturated aqueous NaCl. The aqueous phase was extracted with dichloromethane (3 × 40 mL). The organic phase was dried ($MgSO_4$) and, filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (5 g) with a gradient of dichloromethane ⇒ 10% methanol in dichloromethane to afford **3** 16.5 mg (88%). Direct comparison of the spectra and TLC of this material with those of the natural product showed them to be identical:[29] TLC R_f = 0.14, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.89 (s, 1 H, aromatic), 6.63 (s, 1 H, aromatic), 5.93 (d, 2 H, J_{gem} = 7.8 Hz, methylenedioxy), 4.81 (app t, 1 H, $J_{10,11}$ = 8.5 Hz, $J_{10',11}$ = 7.1 Hz, H11), 4.67 (s, 1 H, H1), 4.50 (d, 1 H, $J_{3,4}$ = 8.2 Hz, H3), 3.73 (s, 3 H, OCH_3), 3.52 (d, 1 H, $J_{3,4}$ = 8.2 Hz, H4), 3.34 (A part of ABX, 1 H, $J_{10,10'}$ = 14.8 Hz, $J_{10,11}$ = 8.5 Hz, H10), 3.09 (B part of ABX, 1 H, $J_{10,10'}$ = 14.8 Hz, $J_{10',11}$ = 7.1 Hz, H10′), 2.70–2.30 (b s, 2 H, $(OH)_2$), 2.91–2.80 (m, 2 H, H8 and H8′), 1.96–1.89 (m, 2 H, H6 and H6′), 1.75–1.68 (m, 2 H, H7 and H7′), ^{13}C NMR ($CDCl_3$) δ 161.18 (e, C2), 147.17 (e, C15), 147.09 (e, C16), 135.61 (e, C12), 126.82 (e, C13), 112.96 (o, C14), 112.76 (e, C17), 101.16 (e, C18), 99.88 (o, C1), 74.41 (o, C11), 74.24 (o, C3), 73.30 (e, C5), 58.03 (o, C4), 57.12 (o, OCH_3), 51.02 (e, C8), 50.57 (e, C10), 39.68 (e, C7), 21.58 (e, C6); IR (CH_2Cl_2) cm^{-1} (μm) 3583 (2.79), 3389 (2.95), 1651 (6.06), 1506 (6.64), 1489 (6.72); MS *m/e* (rel intensity) 331 (M^+, 33), 314 (27), 295 (20), 270 (35); CIMS *m/e* (rel intensity) 332 (M + H, 25), 314 (100); Exact mass (EI) calcd for $C_{18}H_{21}NO_5$ (M^+) 331.1420, found 331.1417.

(±)-Drupacine (4). 11-Hydroxycephalotaxine (**3**) (6 mg, 0.018 mmol) was dissolved in THF (1.0 mL) at room temperature and treated with 1 N HCl (1.0 mL). The reaction was allowed to stir for 5 h and then was neutralized with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with dichloromethane (4 × 30 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed in vacuo. The residue was purified by plug filtration on course SiO_2 (5 g) with a gradient of dichloromethane ⇒ 10% methanol in dichloromethane to afford **4** (5 mg, 83%) and **3** (1 mg, 16%). Direct comparison of the spectra and TLC of this material (**4**) with those of the natural product showed them to be identical:[29] oil, TLC R_f = 0.58, 10% methanol in dichloromethane; ^{1}H NMR ($CDCl_3$) δ 6.65 (s, 1 H, aromatic), 6.64 (s, 1 H, aromatic), 5.94 (d, 2 H, J_{gem} = 4.9 Hz, methylenedioxy), 4.87 (d, 1 H, $J_{10,11}$ = 4.5 Hz, H11), 4.03 (app t, 1 H, $J_{3,4}$ = 9.0 Hz, $J_{3,OH}$ = 9.0 Hz, H3), 3.48 (overlapping s, 3 H, OCH_3), 3.45 (overlapping d, 1 H, $J_{3,4}$ = 9.0 Hz, H4), 3.15–3.00 (overlapping m, 1 H). 3.12 (overlapping ABX,

(39) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 165.
(40) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 461.

1 H, $J_{10,10'}$ = 13.1 Hz, $J_{10,11}$ = 4.8 Hz, H10), 2.98 (d, 1 H, $J_{10,10'}$ = 13.1 Hz, H10'), 2.65 (d, 1 H, $J_{1\alpha,1\beta}$ = 14 Hz, H1β), 2.41 (app q, 1 H, J = 8.6 Hz), 2.24–2.14 (m, 1 H), 2.07–1.98 (m, 1 H), 1.83–1.58 (m. 2 H), 1.47 (d, 1 H. $J_{1\alpha,1\beta}$ = 14 Hz, H1α), 1.43–1.35 (m. 1 H): IR (CH_2Cl_2) cm^{-1} (μm) 3553 (2.81), 3450 (2.90), 2934 (3.41), 1504 (6.65), 1487 (6.72); MS *m/e* (rel intensity) 331 (M^+, 33), 314 (6), 300 (7), 272 (4), 243 (5), 228 (18), 214 (12), 190 (45); CIMS *m/e* (rel intensity) 332 (M + H, 100), 314 (62); Exact mass (EI) calcd for $C_{18}H_{21}NO_5$ (M^+), 331.1420; found 331.1420.

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Supplementary Material Available: Experimental procedures, spectra, and spectral interpretations (49 pages). Ordering information is given on any current masthead page.