The Asymmetric Synthesis of (-)-Quinocarcin via a 1,3-Dipolar Cycloadditive Strategy

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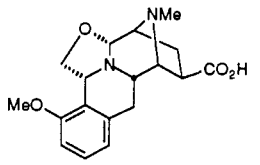
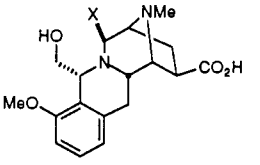
Abstract: Details of the asymmetric synthesis and complete structure elucidation of (-)-quinocarcin (**1**), an antitumor antibiotic that inhibits DNA (and in some systems RNA) synthesis, are reported. Key steps in the synthesis include the use of an auxiliary-controlled 1,3-dipolar cycloaddition reaction (**24** + **25** → **26**) as well as an unprecedented intramolecular imide olefination (**30** → **31**) to assemble the 3,8-diazabicyclo[3.2.1]octane (CD ring) and isoquinoline (B ring) subunits of **1** in a stereo- and regiocontrolled manner. A comparison of the optical rotations of synthetic and natural quinocarcin confirms that the absolute configuration of this antibiotic is as depicted. Conclusive evidence for the (2a*R*) stereochemistry in **1** is provided by a NOESY experiment on quinocarcin citrate.

Introduction

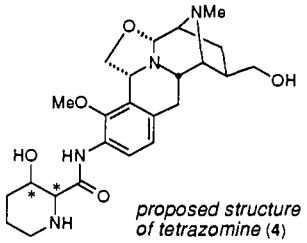
Quinocarcin (**1**)[1] is an antitumor antibiotic isolated from *Streptomyces melanovinaceus* representative of a group of isoquinoline alkaloids that incorporate the 3,8-diazabicyclo[3.2.1]-octane substructure. The antitumor activity of this compound



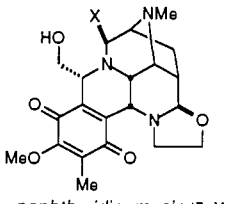
quinocarcin (1)



quinocarcinol (2, X = H)
DX-52-1 (3, X = CN)



proposed structure of tetrazomine (4)



naphthyridinomycin (5, X = OH)
cyanocycline A (6, X = CN)

apparently derives from its ability to inhibit DNA and/or RNA synthesis.[2] This seems to occur at the template level via the irreversible and selective binding of these drugs to dG-dC base pairs, although an oxidative degradation path has also been proposed for **1**.[3] The citrate salt of quinocarcin exhibits good activity against a variety of tumor systems. Quinocarcin itself is rather labile but can be converted to the more stable aminonitrile derivative DX-52-1 (**3**) by treatment with CN^- and **1** regenerated with $AgNO_3$ or strong acid.[4] A structurally related antibiotic named tetrazomine (**4**) was recently isolated from an actinomycete strain, and it also shows good antitumor activity.[5] The structural similarities between these compounds and the more complex naphthyridinomycin family of antitumor antibiotics (cf. **5**) are obvious.

The relative stereochemistry of quinocarcin had been deduced from X-ray crystallographic analysis of quinocarcinol (**2**), an inactive homologue which lacks the hemiaminal functionality. At the outset of work, the absolute configuration of **1** had not been determined, but computational studies[6] suggested that the enantiomer shown may be preferred for binding to duplex DNA via nucleophilic attack of the 2-amino group of guanine onto an iminium species derived from the hemiaminal. This would also have been consistent with biogenetic[7] and synthetic[8] work on naphthyridinomycin (**5**) and cyanocycline A (**6**). Although total syntheses of racemic quinocarcin (**1**) and quinocarcinol (**2**) have been reported,[9] recent efforts have focused on enantiospecific approaches to these DNA-reactive molecules.[10] We now present the details of our studies, culminating in the asymmetric synthesis and complete structure elucidation of (-)-quinocarcin (**1**).[11]

Our approach to these substances is based upon a unified strategy wherein appropriately functionalized 3,8-diazabicyclo-[3.2.1]octanes **III** and **IV** would be assembled in one step via stereocontrolled 1,3-dipolar cycloaddition of azomethine ylides such as **II** and monosubstituted olefinic dipolarophiles.[12] Topological and diastereofacial control can be accomplished either

® Abstract published in *Advance ACS Abstracts,* October 1, 1993.

(1) (a) Takahashi, K.; Tomita, F. *J. Antibiot.* **1983**, 468. (b) Hirayama, N.; Shirahata, K. *J. Chem. Soc., Perkin Trans.* **2 1983**, 1705.

(2) (a) Tomita, F.; Takahashi, K.; Tamaoki, T. *J. Antibiot.* **1984**, *37*, 1268. (b) Fujimoto, K.; Oka, T.; Morimoto, M. *Cancer Res.* **1987**, *47*, 1516. (c) Kanamaru, R.; Konishi, Y.; Ishioka, C.; Kakuta, H.; Sato, T.; Ishikawa, A.; Asamura, M.; Wakui, A. *Cancer Chemother. Pharmacol.* **1988**, *22*, 197.

(3) Williams, R. M.; Glinka, T.; Flanagan, M. E.; Gallegos, R.; Coffman, H.; Pei, D. *J. Am. Chem. Soc.* **1992**, *114*, 733.

(4) (a) Saito, H.; Hirata, T. *Tetrahedron Lett.* **1987**, *28*, 4065. (b) Saito, H.; Kobayashi, S.; Uosaki, Y.; Sato, A.; Fujimoto, K.; Miyoshi, K.; Morimoto, A.; Hirata, T. *Chem. Pharm. Bull.* **1990**, *38*, 1278.

(5) (a) Suzuki, K.; Sato, T.; Morioka, M.; Nagai, K.; Abe, K.; Yamaguchi, H.; Saito, T.; Ohmi, Y.; Susaki, K. *J. Antibiot.* **1991**, *44*, 479. (b) Sato, T.; Hirayama, F.; Saito, T.; Kaniwa, H. *J. Antibiot.* **1991**, *44*, 1367.

(6) Hill, G. C.; Wunz, T. P.; Remers, W. A. *J. Comput.-Aided Mol. Des.* **1988**, *2*, 6029. In this paper, the configuration at C-6a was erroneously inverted in the (2a*R*,11c*R*) diastereomer, possibly accounting for the rather high energy difference between this structure and that found for (2a*R*,11c*S*)-quinocarcin.

(7) Zmijewski, M. J., Jr.; Paliniswamy, V. A.; Gould, S. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1261.

(8) (a) Illig, C. R. The Total Synthesis of (±)-Cyanocycline A and (+)-Cyanocycline A. Ph.D. Dissertation, Harvard University, Cambridge, MA, 1987. (b) Fukuyama, T.; Li, L. Total Synthesis of (+)-Naphthyridinomycin (ORGN 272). 21st ACS Central Regional Meeting (May 31-June 2, 1989), Cleveland, OH. Fukuyama, T. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; Vol 2, p 189.

(9) (a) (±)-**3**: Danishefsky, S. J.; Harrison, P. J.; Webb, R. R.; O'Neil, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421. (b) (±)-**1**: Fukuyama, T.; Nunes, J. J. *Ibid.* **1988**, *110*, 5196.

(10) (a) Saito, S.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* **1988**, *29*, 6301. (b) Sato, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Terashima, S. *Ibid.* **1989**, *30*, 7423. (c) Lessen, T. A.; Demko, D. M.; Weinreb, S. M. *Ibid.* **1990**, *31*, 2105.

(11) Preliminary communication: Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1992**, *114*, 2767.

(12) For a related approach to quinocarcin, see: (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Ibid.* **1990**, *31*, 1012.

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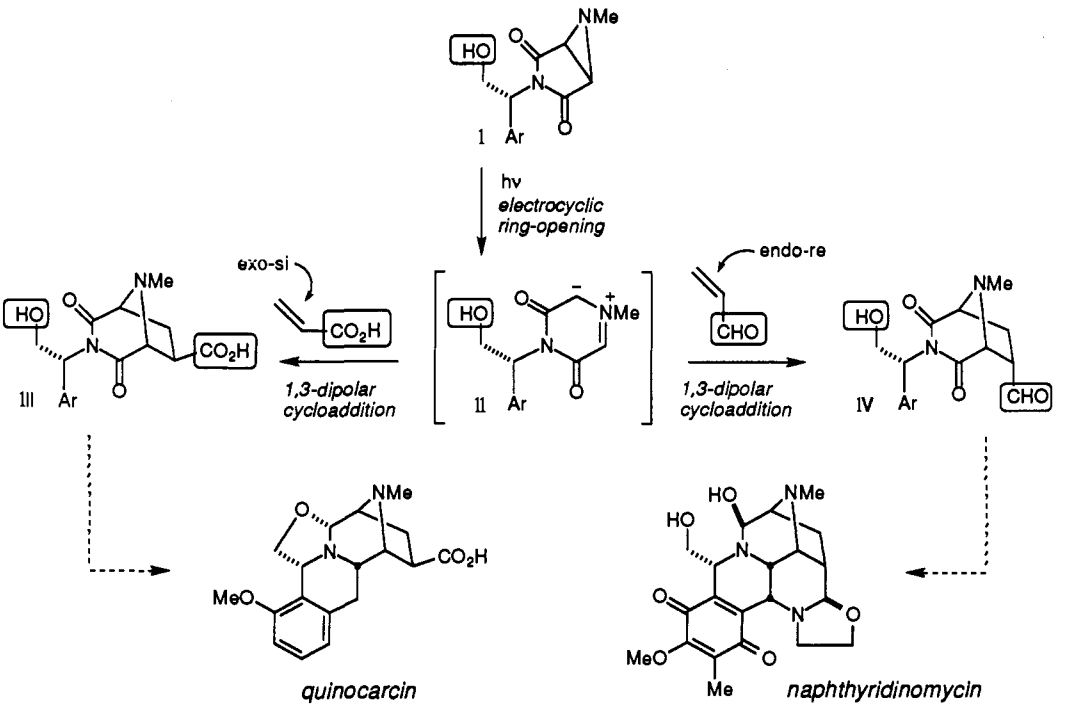
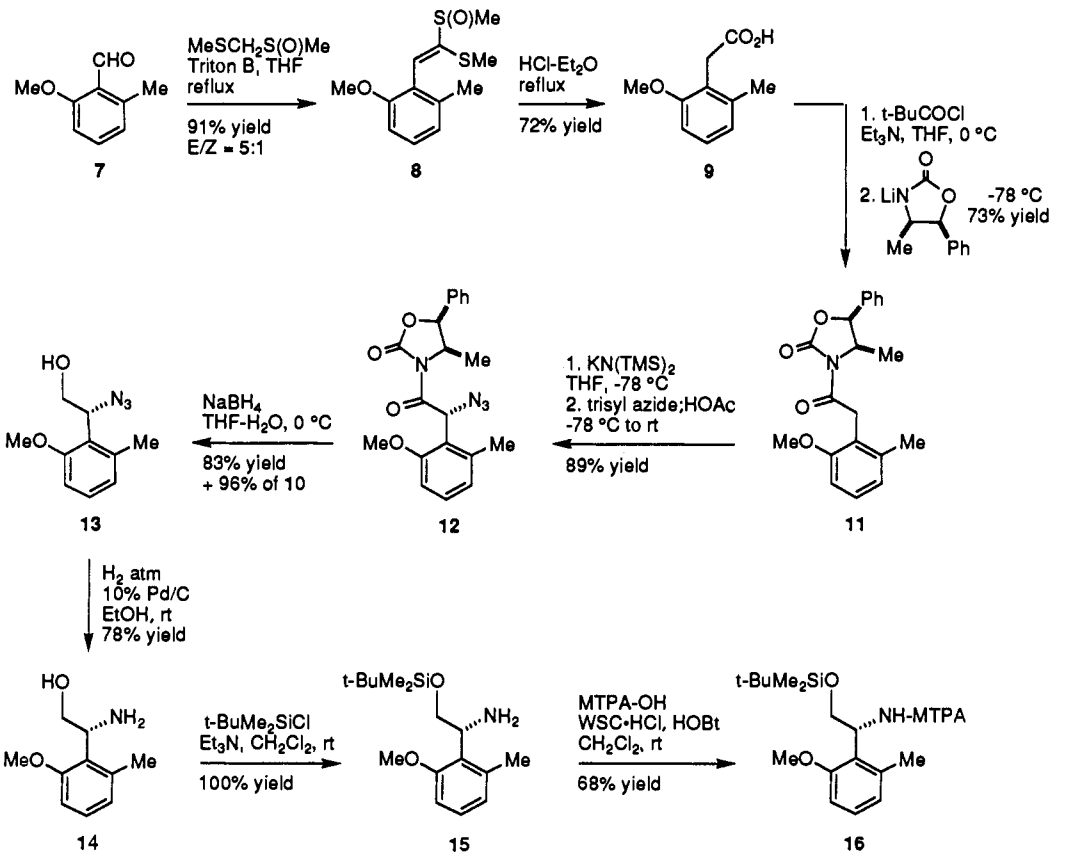
Scheme I



Scheme II



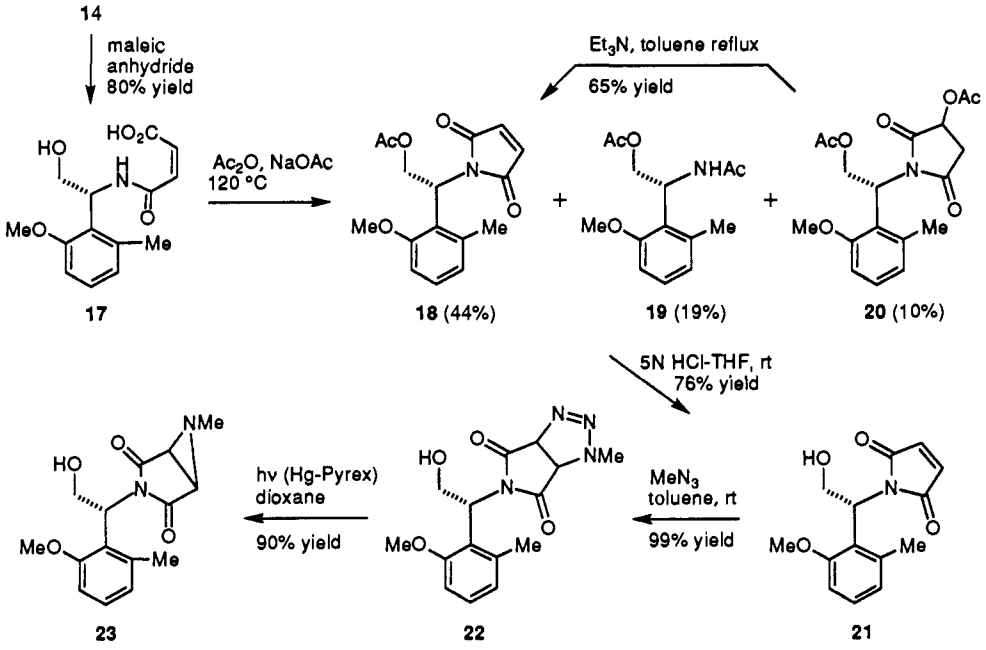
by incorporating a chiral auxiliary onto the dipolarophile to provide **III** as required for quinocarcin[13] or by rendering the cycloaddition intramolecular to provide **IV** as required for naphthyridinomycin.[14] The "exo-si" cycloadduct **III** would possess four of the six stereogenic centers present in **1** and also provide a suitable template for introduction of the remaining functionality and chirality as well. Generation of the cyclic azomethine ylide **II** was to be accomplished by means of a photochemically initiated electrocyclic ring opening of a precursor aziridine **I**.[15,16]

(13) Garner, P.; Ho, W. B.; Grandhee, S. K.; Youngs, W. J.; Kennedy, V. O. *J. Org. Chem.* **1991**, *56*, 5893.

(14) Garner, P.; Sunitha, K.; Ho, W. B.; Youngs, W. J.; Kennedy, V. O.; Djebli, A. *J. Org. Chem.* **1989**, *54*, 2041.

(15) (a) Huisgen, R.; Mäder, H. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 604. (b) Oida, S.; Ohki, E. *Chem. Pharm. Bull.* **1968**, *16*, 764.

Scheme III



Results and Discussion

The first order of business involved enantioselective synthesis of the substituted phenylglycinol derivative **14**, which was to serve as a precursor to a suitably functionalized aziridine corresponding to **I**. The sequence began with the base-catalyzed condensation of 2-methoxy-6-methylbenzaldehyde (**7**)[17] with methyl methylsulfinylmethyl sulfide to give a 91% yield of the α-methylthiovinylsulfoxide **8**, which was then hydrolyzed with concentrated HCl to 2-methoxy-6-methylphenylacetic acid (**9**) in 72% yield.[18] By following Evans' asymmetric azidation protocol,[19] carboxylic acid **9** was converted to its mixed pivalic anhydride and treated with the lithiated oxazolidine **10** derived from (1*S*,2*R*)-norephedrine to give the chiral carboximide **11** in 73% yield. The potassium enolate of **11** was then treated with trisyl azide at −78 °C and the intermediate sulfonyl triazene quenched with glacial acetic acid to give the α-azido carboximide **12** in 88% yield after chromatography. Sodium borohydride reduction of **12** afforded the azido alcohol **13** in 83% yield along with a 96% yield of recovered auxiliary **10**. Palladium-catalyzed hydrogenation of **13** produced the required phenylglycinol **14** in 78% yield.

The absolute stereochemistry shown for the α-azido carboximide **12** is that expected for azide transfer to the least-hindered face of a chelated potassium enolate. Even though **12** appeared to be homogeneous by ^{1}H NMR, suggesting a very high diastereoselectivity for the asymmetric azidation, a Mosher analysis[20] was carried out to confirm the enantiomeric purity of **14**. First, the alcohol moiety was protected as its *tert*-butyldimethylsilyl ether and then the resulting amine **15** was condensed with (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA-OH) to give the Mosher amide **16** in 68% yield after chromatography. Care was taken not to effect fortuitous resolution of the Mosher amide diastereomers. Compound **16** was shown to be >99% pure by comparison of its ^{1}H NMR spectrum with that of a diastereomeric mixture deliberately prepared from racemic **14** and (+)-MTPA-OH.

Preparation of the substituted aziridine **23** followed our previously elaborated route (see ref 13). Reaction of phenylglycinol **14** with maleic anhydride gave the maleamic acid **17** in 80% yield. Of the methods which we explored for maleimide formation, the Ac_2O-mediated dehydration proved superior, producing the O-acetylated maleimide **18** in 44% isolated yield. Byproducts **19** and **20** were also isolated from this reaction in 19 and 10% yields; the former could be saponified back to **14** in 70% yield, while AcOH could be eliminated from the latter to give **18** in 65% yield. Acidic hydrolysis (maleimides are not stable to basic conditions) of the extraneous *O*-acetyl group afforded the imide alcohol **21** in 76% yield. Maleimide **21** underwent a very clean reaction with methyl azide to give an essentially quantitative yield of the triazoline **22**. Photochemical extrusion of nitrogen was accomplished by irradiation with a high-pressure Hg lamp through Pyrex, producing the desired aziridine **23** in 90% yield.[21]

For the cycloaddition, irradiation of a dioxane solution of aziridine **23** at 2537 Å in a quartz vessel provided a steady-state concentration of azomethine ylide **24**. A total of 1.2 equiv of Oppolzer's chiral acryloyl sultam **25**[22] was added in 0.2 equiv portions to this photolyzed mixture. A very clean 1,3-dipolar cycloaddition occurred giving the exo-si adduct **26** in 61% isolated yield (based on 14% recovered **23**) after flash chromatography. The absence of any other detectable stereoisomers in the crude reaction mixture (^{1}H NMR) was indicative of the high level of stereocontrol generally associated with additions to **25**.[23] It was necessary to limit the concentration of dipolarophile **25** during this photolysis since it absorbed about three times as much light as the aziridine substrate **23**. At this point, the absolute configuration of the 6-exo-substituted 3,8-diazabicyclo[3.2.1]-octyl system of **26** relative to the arylglycinol stereocenter was based solely on analogy with our model studies. This assignment was eventually confirmed upon completion of our synthesis of (−)-**1**. Methoxymethylation of the free hydroxyl group of **26**

(16) For a related approach to the 3,8-diazabicyclo[3.2.1]octane portion of quinocarcin based on 1,3-dipolar cycloaddition to achiral 2-oxidopyrazinium species, see: Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187. Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Ibid.* **1990**, *31*, 4781.

(17) Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723.

(18) Ogura, K.; Ito, Y.; Tuchihashi, G. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2013.

(19) Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

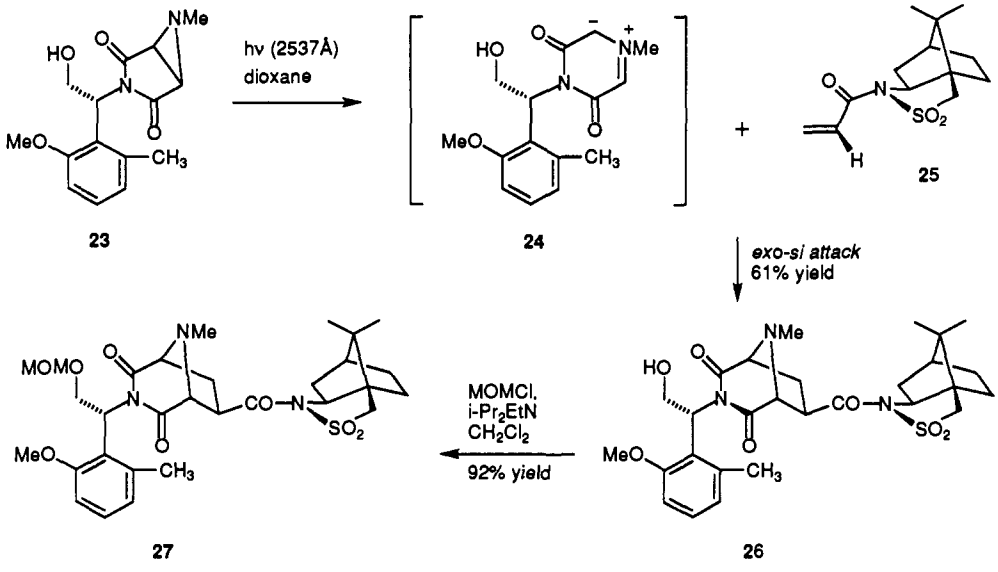
(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(21) Scheiner, P. *J. Org. Chem.* **1965**, *30*, 7.

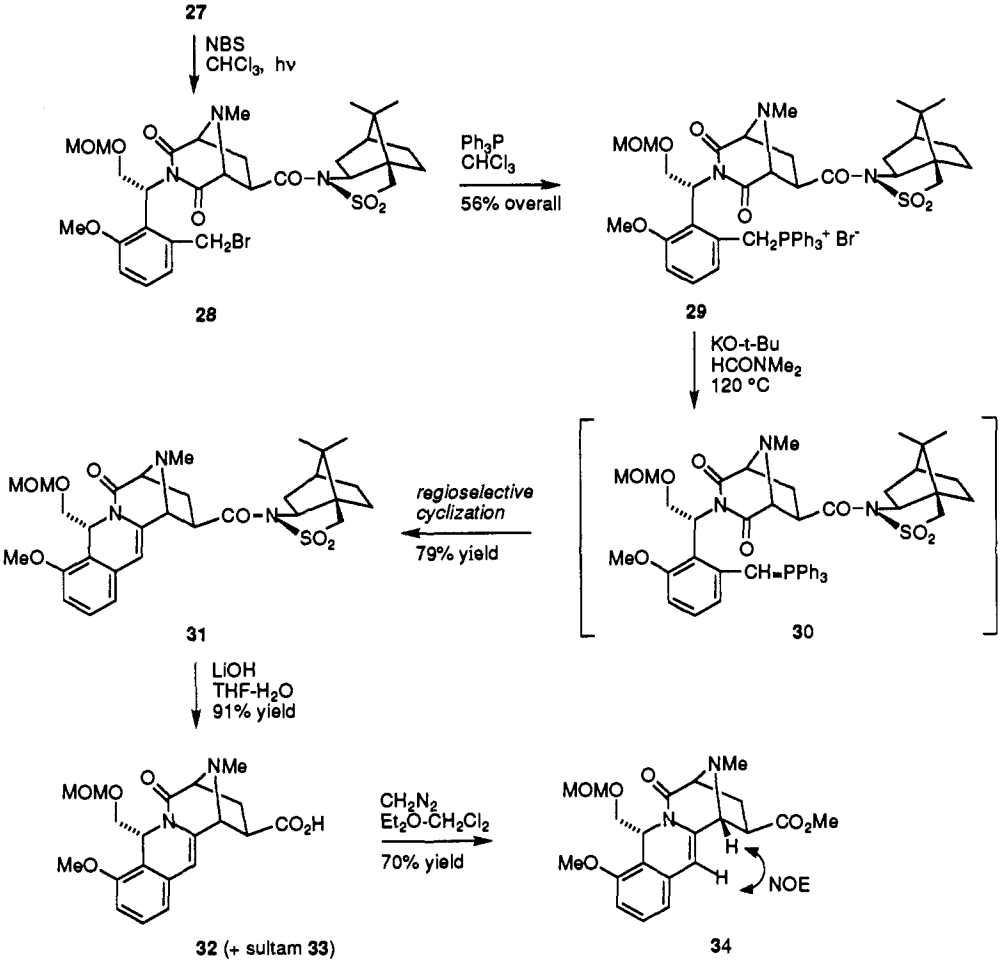
(22) Vandewalle, M.; Van der Eycken, J.; Oppolzer, W.; Vullioud, C. *Tetrahedron* **1986**, *42*, 4035. For an improved synthesis of compound **25**, see: Thom, C.; Kocienski, P. *Synthesis* **1992**, 582.

(23) Cf. Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. We thank Professor Curran for providing us a copy of this review article prior its publication.

Scheme IV



Scheme V

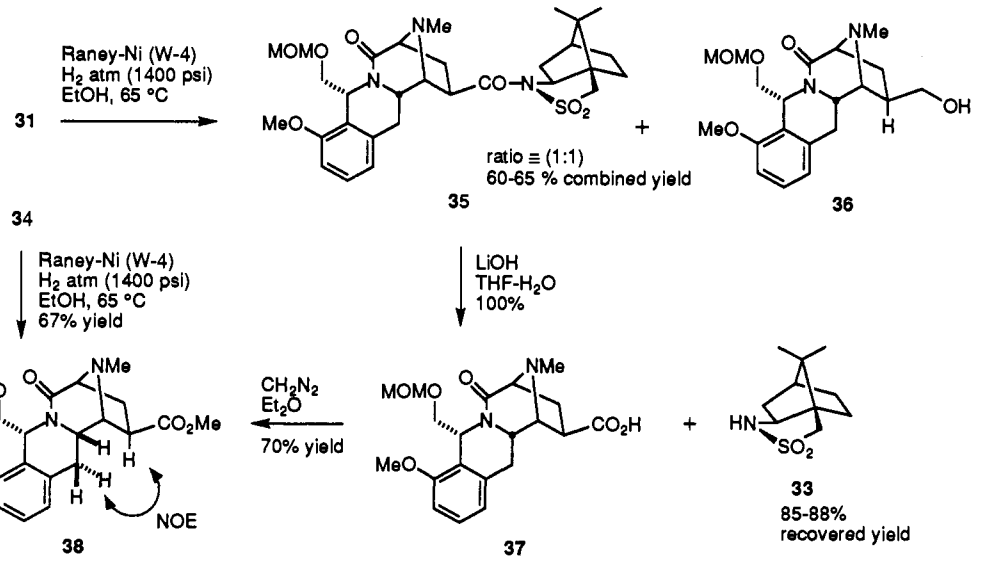


using the standard procedure ((MOM)Cl + Hünig's base) afforded the MOM ether **27** in 92% yield after flash chromatography.

It was felt that formation of the B ring of quinocarcin might be accomplished by transforming the aromatic methyl group (corresponding to C-7 in **1**) into a nucleophilic species that would then react selectively with the *pro-R* imide carbonyl (*vide infra*). An attractive option was based on the work of Flitsch, who had shown that 2-succinimidyl benzylphosphonium ylides underwent smooth intramolecular "Wittig olefination" to give the mitosane ring system.[24] First, chemoselective benzylic bromination was achieved by irradiating a dilute (0.01 M) solution of **27** + NBS (1.2 equiv) in dry $CHCl_3$ at 2537 Å *through Pyrex* to give the benzylic bromide **28** in 60% yield along with some recovered **27**. This radical chain reaction might actually be proceeding through the intermediacy of bromotrichloromethane which is formed *in*

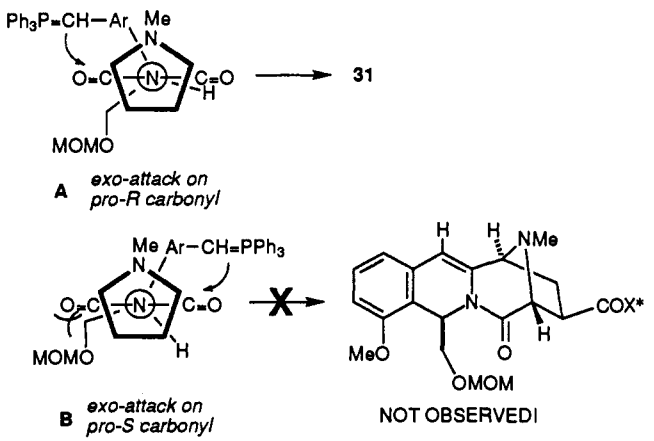
(24) Flitsch, W.; Langer, W. *Liebigs, Ann. Chem.* **1988**, 391. Flitsch, W.; Russkamp, P.; Langer, W. *Ibid.* **1985**, 1413.

Scheme VI



situ. The use of a quartz rather than Pyrex vessel resulted in a poor yield of **28**, an expected consequence of the demonstrated lability of **27** under these photochemical conditions. However, no reaction was observed when 3000-Å lamps were used—a puzzling result since pyrex cuts off light below 2750 Å. Electrophilic aromatic bromination was the dominant reaction path when higher concentrations (0.10 m) of **27** were employed. The reaction of crude **28** with triphenylphosphine resulted in theformation of the crystalline phosphonium salt **29** in 56% yield (from **27**).

Treatment of **29** with KO-*t*-Bu in DMF produced an orange solution of ylide **30** which, upon heating to 120 °C, cyclized to give a *single* regioisomer **31** in 79% yield. In spite of the extensive work by Flitsch on related Wittig olefinations, this appears to be the first reported dihydroisoquinoline synthesis using this methodology. Interestingly, model studies with simpler substrates seem to suggest that the electron-donating methoxy substituent is crucial for the success of this reaction.[25] The regiochemical assignment of structure of **31** was readily confirmed by a series of NOE difference experiments on ester **34**, obtained in 64% yield from **31** after saponification and esterification with diazomethane, indicating the proximity of H-7 to H-6 but not H-3 (quinocarcin numbering).[26] This result can be rationalized by a transition-state conformation that has the ylide approaching the *pro-R* imide carbonyl from the exo face to avoid placing the CH_2O(MOM) group in the imide plane (see A vs B below).[27] It is also possible that the exo-carbonyl substituent exerts a stereoelectronic effect on the *pro-R* carbonyl, rendering it more electrophilic (larger LUMO coefficient).[28]

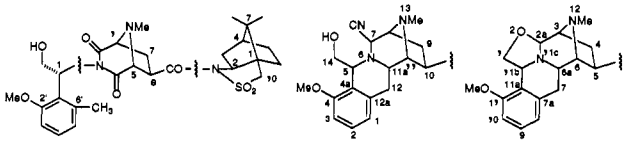


Hydrogenation of **31** over Raney Nickel occurred at high pressures to afford nearly equal amounts of **35** and the overreduced byproduct **36** in 64% combined yield. Since these reactions were conducted in a sealed "bomb" (see the Experimental Section), it was not possible to conveniently follow the course of the reduction by TLC. Thus, the ratio of **35** to **36** varied from run to run with the activity of the Raney nickel, hydrogen pressure, and temperature. In any case, the combined yield of **35** + **36** was always on the order of 60–65%. Saponification of **35** produced the carboxylic acid **37** in quantitative yield along with 85–88% of the sultam auxiliary **33**, which could in principle be recycled. Reaction of **37** with etheral diazomethane produced the corresponding methyl ester **38** in 70% yield. NOE experiments on this compound confirmed the proximity of H-5 and H-7 and thus the stereochemical course of the hydrogenation. While the formation of **36** was not desirable in the context of our quinocarcin synthesis (although we do note that Fukuyama successfully oxidized a related alcohol to its carboxylic acid), the similarity between structure **36** and that of tetrazomine (**4**) is noteworthy. Alternatively, the previously described ester **34** underwent clean hydrogenation to give **38** in 67% yield without any overreduction.

The final sequence commenced with partial reduction of the lactam moiety in **37**. This transformation was of some concern to us in light of Danishefsky's inability to effect partial reduction of the (racemic) primary alcohol corresponding to **37** (see ref 9a). Hirata, on the other hand, did manage to effect the partial reduction of a quinocarcin model system that corresponded to **37** minus the aromatic methoxy and CH_2O(MOM) substitutents using $LiAlH_4$ (see ref 4a). Unfortunately, compound **37** remained

(25) Ho, W. B. The Asymmetric Synthesis of (–)-Quinocarcin. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 1992.

(26) The following numbering schemes are used to describe post-cycloaddition structures. Prior to B-ring formation, nomenclature is based on the parent 3,8-diazabicyclo[3.2.1]octane system i, whereas the 8,11-iminoazepine[1,2-*b*]isoquinoline system ii and 3,6-imino-1*H*-2-oxa-11c-azanaphth[1,2,3-*cd*]azulene skeleton iii are employed once the scarbon skeleton of quinocarcin is intact.

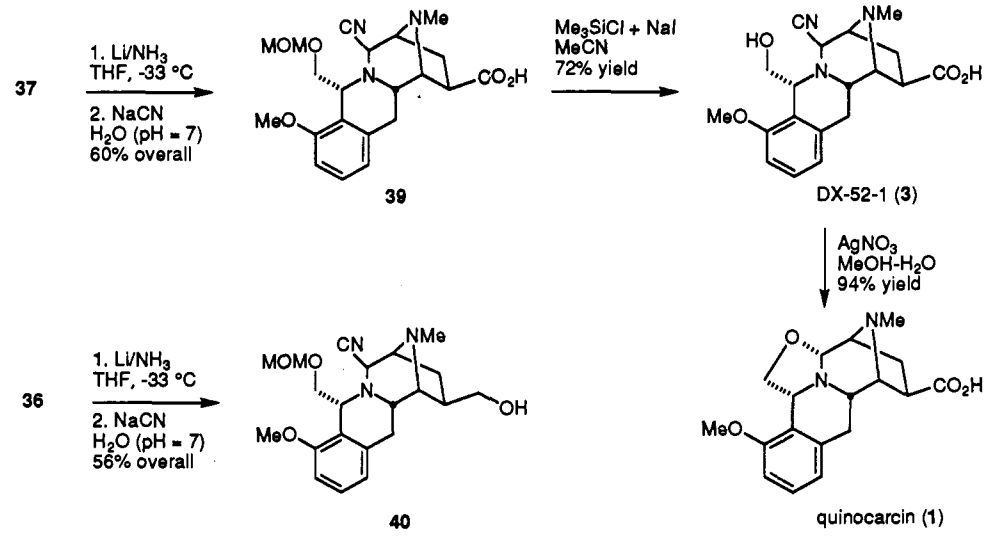


I II III

(27) For a similar argument governing a highly stereoselective intramolecular cycloaddition, see: ref 14.

(28) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192. Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurty, H. G. *Ibid.* **1982**, *60*, 1199.

Scheme VII



intact even after exposure to $LiAlH_4$ at elevated temperatures, apparently the result of steric shielding about the lactam carbonyl. We then turned to the dissolving metal reduction conditions that Evans had used to effect a similar partial lactam reduction in his cyanocycline A synthesis. Exposure of **37** to an excess of Li–NH_3 presumably resulted in formation of the desired hemiaminal, which was not isolated but treated directly with NaCN at neutral pH to give the stable aminonitrile derivative **39** in 60% overall yield. The same sequence was used to convert compound **36** to the aminonitrile **40** in 56% yield. Racemic versions of both **39** and **40** were intermediates in Fukuyama's synthesis of (±)-quinocarcin.

Deprotection of **39** with (TMS)Cl + NaI–MeCN[29] afforded DX-52-1 (**3**). The ^1H NMR spectrum of this material in 10% CD_3OD–$CDCl_3$ was identical to Fukuyama's, but the corresponding spectrum in D_2O did not match that reported by Hirata. However, the spectrum of an authentic sample of DX-52-1 in D_2O did match that of our synthetic material. These observations illustrate the sensitivity of the NMR spectra of ionizable amino acids to differences in pH and concentration. The optical rotation of our synthetic DX-52-1 was almost identical to that measured for the authentic sample: $[\alpha]_D$ = 35 vs 36° (*c* 0.51, MeOH). Treatment of synthetic **3** with $AgNO_3$ produced (-)-quinocarcin (**1**) in 94% yield. Since **1** is unstable to silica gel,[30] its purification was problematic. It was eventually found that the silver salts could be cleanly removed from the reaction mixture by addition of a basic ion-exchange resin followed by simple filtration. Final purification of **1** was then achieved by reverse-phase HPLC on a C18 column. The ^1H and ^{13}C NMR data obtained for synthetic **1** matched that reported in the literature as well as those of an authentic sample. Furthermore, comparison of the optical rotation of synthetic **1** ($[\alpha]_D$ −30° (*c* 0.2, H_2O)) with that of natural quinocarcin (lit. $[\alpha]_D$ −32° (*c* 0.50, H_2O) confirmed that the absolute configuration of our synthetic material is the same as that of the natural product.

Since the original structure of quinocarcin (actually ent-**1**) was based on crystallographic analysis of quinocarcinol (**2**), the stereochemistry at C-2a could not be assigned unambiguously. The reported relative configuration at C-2a was based on an observed vicinal coupling constant of 3.2 Hz between H-2a and

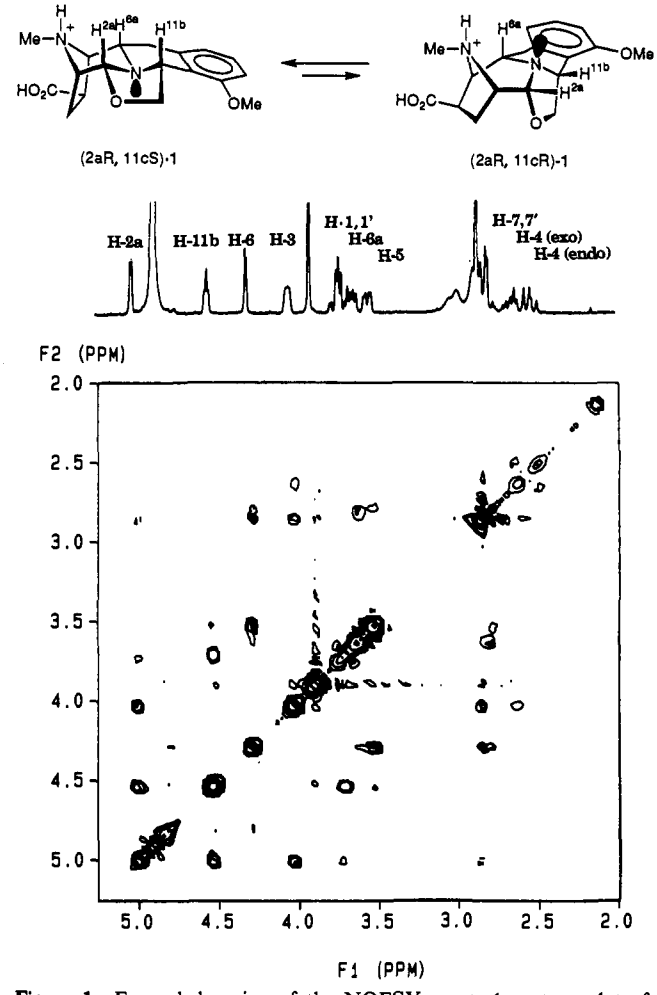


Figure 1. Expanded region of the NOESY spectral contour plot of quinocarcin citrate.

H-3, but this information alone does not rule out alternative structures which might also have the required dihedral angles for this *J* value. If one considers that N-11c is also a chiral center, then four diastereomeric modifications are possible for the quinocarcin molecule. Molecular modeling of each of these quinocarcin diastereomers (as their zwitterions) led to four low-energy conformers corresponding to the (2a*R*,11c*S*), (2a*R*,11c*R*), (2a*S*,11c*S*), and (2a*S*,11c*R*) configurations. Our modeling

(29) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(30) Fukuyama attempted to purify his synthetic quinocarcin by normal-phase PTLC on silica gel, eluting with (1:1) $CHCl_3$–MeOH, but found that the resulting ^1H NMR spectrum was quite different from that reported in the literature. However, when natural quinocarcin was submitted to these same PTLC conditions, the same spectrum was obtained and identity concluded. (T. Fukuyama, personal communication.)

results[31] agreed qualitatively with those of Remers and coworkers (ref 6) in that the lowest energy structure corresponded to (2a*R*,11c*S*)-configured quinocarcin, but with an energy difference of ~3 kcal/mol between (2a*R*,11c*S*)-**1** and (2a*R*,11c*R*)-**1**.

Positive diagnostic evidence for the (2a*R*) configuration came from a NOESY experiment on quinocarcin citrate. The resulting 2D spectrum (Figure 1) showed an off-diagonal crosspeak connecting H-2a and H-11b, indicating their spacial proximity ($r \sim 2.6$-3.0 Å according to models). The distance between H-2a and H11b increases to ~3.7 Å in structures having the (2a*S*) configuration, where they are 1,3-trans to each other. A strong NOE between H-2a and endo H-4 ($r \sim 2.1$–2.2 Å from models) might have been expected for this compound but was not observed. The NOESY spectrum also showed a weak interaction between H-6a and H-11b, but no crosspeak was observed between H-2a and H-6a. The experimental data are consistent with either the (2a*R*,11c*S*) or (2a*R*,11c*R*) configuration for quinocarcin (**1**), or some average thereof. Unfortunately, our NOESY experiment did not permit unambiguous assignment of the configuration at N-11c. These structural aspects of quinocarcin are of biomechanistic interest since iminium formation (required for DNA alkylation) requires the N-11c lone pair to be anti to O-2 whereas redox self-disproportionation (leading to oxidative DNA cleavage) is stereoelectronically favored when the N-11c lone pair is anti to H-2a (see ref 3).

Experimental Section

Silica gel TLC plates were visualized with UV illumination followed by charring with either 5% anisaldehyde in (95:5:1) EtOH–AcOH–H_2SO_4 (char A), 0.3% ninhydrin in (97:3) *n*-BuOH–AcOH (char B), or 2% vanillin in (98:2) EtOH–H_2SO_4 (char C). Melting points are uncorrected. The ^1H NMR signal assignments were based on selective homonuclear decoupling experiments, while the ^{13}C assignments were based on APT (attached proton test) experiments and proton-coupling data. High-resolution mass spectral (HRMS) data are reported in units of *m/e* for M^+ or the highest mass fragment derived from M^+. All reactions were performed under an inert (N_2 or Ar), moisture-free atmosphere except when working in aqueous media. Solvents were purified beyond reagent grade as follows: 1,4-dioxane, THF, and toluene were distilled from sodium + benzophenone; CH_2Cl_2 and DMF were distilled from CaH_2 and stored over 4-Å molecular sieves; $CHCl_3$ was washed with H_2O, dried over K_2CO_3, and distilled from P_2O_5. Photolyses were performed either with a Canrad-Hanovia 450-W medium-pressure Hg lamp or with low-pressure Hg lamps (2537 Å) in a Rayonet Photochemical Reactor RPR-100.

1-(Methylsulfinyl)-1-(methylthio)-2-(2-methoxy-6-methylphenyl)-ethylene (8). To a solution of **7** (22.4 g, 0.149 mol) in THF (50 mL) was added methyl methylsulfinylmethyl sulfide (20.6 mL, 0.197 mol) followed by Triton B (15 mL, 40% w/w, 33 mmol). The mixture was refluxed for 24 h when the TLC showed the reaction to be complete. After the reaction mixture was cooled to room temperature, it was acidified with 1 N HCl to pH = 1 and the THF evaporated. The mixture was partitioned between H_2O (50 mL) and CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 52.2 g of crude product. Flash chromatography over silica gel, eluting with (6:1) hexanes–EtOAc, gave **8** (34.6 g, 91%, *E*/*Z* = 5:1) as a yellow liquid. For analytical purposes, pure samples of *E*-**8** and *Z*-**8** were obtained by PTLC.

For *E*-**8**: R_f 0.47 in (1:1) EtOAc–hexanes; IR ($CHCl_3$) 3010, 1600, 1580, 1470, 1440, 1265, 1085, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.59 (s, 1H, C=CH), 7.21 (t, *J* = 7.9 Hz, 1 H, Ar), 6.83 (d, *J* = 7.6 Hz, 1 H, Ar), 6.74 (d, *J* = 8.5 Hz, 1 H, Ar), 3.76 (s, 3 H, OCH_3), 2.80 (s, 3 H, $SOCH_3$), 2.10 (s, 3 H, SCH_3), 1.53 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 156.7 (Ar), 144.7 (Ar or *C*(SMe)SOMe), 137.4 (Ar or *C*(SMe)SOMe), 133.3 (Ar or *C*HAr), 129.0 (Ar or *C*HAr), 122.9 (Ar), 122.3 (Ar), 107.9 (Ar), 55.4 (OMe), 40.8 (SOMe), 19.9 (Ar*C*H_3 or SMe), 17.4 (Ar*C*H_3 or SMe); HRMS calcd for $C_{12}H_{16}OS_2$ ($M^+ - O$) 240.0643, found 240.0646.

For *Z*-**8**: R_f 0.25 in (1:1) EtOAc–hexanes; mp 122–124 °C; IR ($CHCl_3$) 3010, 1600, 1580, 1470, 1440, 1265, 1085, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.24 (t, *J* = 8.0 Hz, 1 H), 6.86 (d, *J* = 7.6 Hz, 1 H), 6.76 (d, *J* = 7.91 Hz, 1 H), 6.75 (s, 1 H, C=CH), 3.80 (s, 3 H, OCH_3), 2.66 (s, 3 H), 2.60 (s, 3 H), 2.30 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.3 (Ar), 146.7 (Ar or *C*(SMe)SOMe), 136.8 (Ar or *C*(SMe)SOMe), 129.7 (Ar or *C*HAr), 128.6 (Ar or *C*HAr), 122.1 (Ar), 121.8 (Ar), 107.4 (Ar), 54.6 (OMe), 38.2 (SOMe), 19.5 (Ar*C*H_3 or SMe), 17.6 (Ar*C*H_3 or SMe); HRMS calcd for $C_{12}H_{16}OS_2$ ($M^+ - O$) 240.0643, found 240.0622.

(2-Methoxy-6-methylphenyl)acetic Acid (9). HCl (230 mL) was added dropwise to a solution of **8** (34.4 g, 0.140 mol) in Et_2O (320 mL). The resulting reddish mixture was refluxed for 72 h when the TLC showed the reaction to be complete. After cooling, the mixture was basified to pH = 11 with 10 N NaOH and washed with CH_2Cl_2 (3 × 200 mL). The aqueous layer was acidified to pH = 1 with N HCl whereupon a pale yellow oil (≈30 g) separated out. This oil was dissolved in EtOAc and a crop of crystalline **9** (9.7 g) was collected. Incompletely hydrolyzed material (≈11 g) was obtained from the organic wash, and this was refluxed in 10 N NaOH (10 mL) overnight. After cooling, the reaction mixture was washed with Et_2O (3 × 50 mL), acidified to pH = 1, and extracted with EtOAc (3 × 50 mL) to afford a yellow solid (2.2 g). This solid was combined with mother liquor of the first crop and crystallized from EtOAc to give a second crop of **9** (7.8 g, total = 17.5 g or 72% yield): R_f 0.52 in (1:1) EtOAc–hexanes; mp 154–156 °C; IR ($CHCl_3$) 3510, 3010, 2950, 1715, 1590, 1480, 1270, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.15 (t, *J* = 8.0 Hz, 1 H, ArH), 6.80 (d, *J* = 7.4 Hz, 1 H, ArH), 6.74 (d, *J* = 8.4 Hz, 1 H), 3.80 (s, 3 H, OCH_3), 3.72 (s, 2 H, CH_2CO_2H), 2.28 (s, 3 H, $PhCH_3$); ^{13}C NMR ($CDCl_3$) δ 177.5 (CO_2H), 156.9, 137.7, 127.7, 122.0, 120.4, 107.5 (Ar), 55.0 ($PhOCH_3$), 31.1 (CH_2CO_2H), 19.1 ($PhCH_3$); HRMS calcd for $C_{10}H_{12}O_3$ (M^+) 180.0786, found 180.0794.

(4*S*,5*R*)-3-(2-(2-Methoxy-6-methylphenyl)acetyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (11). To a solution containing **9** (30.0 g, 0.167 mol) dissolved in THF (1.2 L) was added fresh distilled pivaloyl chloride (21.5 mL, 0.174 mol) at −78 °C followed by Et_3N (24.4 mL, 0.175 mol). The mixture was stirred at −78 °C for 15 min, at 0 °C for 45 min, then recooled to −78 °C. In a separate flask, 2.5 M *n*-BuLi (76.4 mL, 0.191 mol) was added to a solution of **10** (32.5 g, 0.183 mol) in THF (600 mL) at −78 °C and stirred for 15 min, then transferred to the flask containing pivalic anhydride via cannula. The mixture was stirred for 15 min at −78 °C and 9 h at room temperature when TLC analysis showed the reaction to be complete. The reaction was quenched with 2 M $KHSO_4$ (350 mL) and, after evaporation of most of the THF, was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with brine (250 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude product. Crystallization from (3:1) EtOAc–hexanes afforded the product **11** (41.6 g, 73% yield) as a white solid: R_f 0.43 in (4:1) hexanes–EtOAc; mp 149–151 °C; $[\alpha]_D$ −14.1° (*c* 1.95, $CHCl_3$); IR ($CHCl_3$) 3010, 1785, 1715, 1590, 1480, 1360, 1270, 1245, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.49–7.26 (m, 5 H), 7.17 (t, *J* = 7.9 Hz, 1 H, ArH), 6.83 (d, *J* = 7.3 Hz, 1 H, ArH), 6.76 (d, *J* = 8.1 Hz, 1 H, ArH), 5.73 (d, *J* = 7.6 Hz, 1 H, PhCH), 4.80 (dq, *J* = 7.6, 6.6 Hz, 1 H, MeCH), 4.39 (d, *J* = 18.2 Hz, 1 H, $^1/_2PhCH_2N$), 4.27 (d, *J* = 18.2 Hz, 1 H, $^1/_2PhCH_2N$), 3.79 (s, 3 H, $PhOCH_3$), 2.26 (s, 3 H, $PhCH_3$), 0.92 (d, *J* = 6.6 Hz, 3 H, CH_3CHN); ^{13}C NMR ($CDCl_3$) δ 170.8 (CH_2CON), 157.6 (Ph), 153.6 (NCO_2), 138.2, 133.4, 128.7, 127.8, 125.6, 122.6, 121.5, 108.07 (Ar/Ph), 79.0 (PhCHN), 55.6, 54.9 ($NCHCH_3$), 33.5 ($PhCH_2CON$), 19.8 (CH_3Ph), 14.5 (CH_3CHN); HRMS calcd for $C_{20}H_{21}NO$ (M^+) 339.1471, found 339.1485.

(4*S*,5*R*,2′*R*)-3-(2-Azido-2-(2-methoxy-6-methylphenyl)acetyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (12). A solution of $KN(SiMe_3)_2$ (117 mL of a 0.5 M in toluene, 0.0587 mol) was added to a solution of **5** (20.0 g, 0.059 mol) in dry THF (800 mL) at −78 °C via cannula over 5 min, and stirring continued for 15 min. To this cold enolate solution was added a −78 °C solution of trisyl azide (22.7 g, 0.073 mol) in THF (200 mL) over 3 min via cannula. After 2 min at −78 °C, glacial acetic acid (10.1 mL, 0.177 mol) was injected in one portion followed by immediate heating to room temperature. After 18 h of stirring, the bulk of the THF was removed and the residue dissolved in EtOAc (750 mL), washed with saturated $NaHCO_3$ (250 mL) followed by brine (250 mL), and dried over $MgSO_4$. After filtration and concentration, the resulting yellow gum (≈25 g) was purified by flash chromatography over SiO_2, eluting

(31) Molecular modeling was performed on the zwitterionic structures using the Biograf 3.1 software package. Conformational sampling was done by subjecting each diastereomer to 20 ps of quenched dynamics at 1000 K with 300 steps of minimization every 0.1 ps. For each diastereomer, the lowest energy structure was extracted, atomic charges were calculated using the program's "Q equilibrate" option, and its energy was minimized to an rms force of 0.100 or less using the Dreiding II force field. Structure, E_t (ϵ_0 = 1), E_t (ϵ_0 = 4): (2a*R*,11c*S*)-**1**, 95.1, 85.5 kcal/mol; (2a*R*,11c*R*)-**1**, 98.6, 88.1 kcal/mol; (2a*S*,11c*R*)-**1**, 100.4, 85.5 kcal/mol; (2a*S*,11c*S*)-**1**, 99.1, 85.9 kcal/mol.

with (20:3) hexanes–EtOAc to afford the desired product **12** (19.7 g, 88% yield) as a white solid: R_f 0.43 in (4:1) hexanes–EtOAc; mp 104–106 °C; $[\alpha]_D$ –280.7° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 3020, 2405, 2120, 1790, 1730, 1540, 1470, 1360, 1200, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44–7.19 (m, 6 H), 6.91 (d, *J* = 7.6 Hz, 1 H, ArH), 6.80 (d, *J* = 8.2 Hz, 1 H, ArH), 5.71 (s, H, CHN_3), 5.49 (d, *J* = 7.6 Hz, 1 H, PhCHO), 4.66 (dq, *J* = 7.6, 6.6 Hz, 1 H, MeCHN), 3.81 (s, 3 H, $PhOCH_3$), 2.49 (s, 3 H, $PhCH_3$), 1.02 (d, *J* = 6.6 Hz, 3 H, CH_3CHN); ^{13}C NMR ($CDCl_3$) δ 169.6 (N_3CHCO), 156.6 (Ph), 152.2 (NCO_2), 140.6, 132.7, 129.9, 128.7, 128.6, 125.5, 124.1, 121.8, 109.7 (Ar/Ph), 79.7 (PhCHO), 61.0 (CHN_3), 56.5 ($PhOCH_3$), 56.1 (NCHMe), 19.6 ($PhCH_3$), 14.3 ($NCHCH_3$); HRMS calcd for $C_{20}H_{20}N_2O_4$ ($M^+ - N_2$) 352.1423, found 352.1427.

(2*R*)-2-Azido-2-(2-methoxy-6-methylphenyl)ethanol (13). To a solution of **12** (17.3 g, 0.0455 mol) in (2:1) THF–H_2O (800 mL) was added $NaBH_4$ (7.0 g, 0.185 mol) at 0 °C. After the mixture was stirred at 5 °C for 42 h, TLC analysis showed the reaction to be complete. The reaction was quenched with 1.6 M NaH_2PO_4 solution (63 mL), and the bulk of the THF was removed. The resulting gum was partitioned between EtOAc (4 × 300 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to give the crude product which was purified by flash chromatography over silica gel, eluting with (4:1) hexanes-EtOAc to afford **13** as a yellow gum (7.9 g, 83% yield) along with 7.7 g (96%) of recovered auxiliary **10**. For **13**: R_f 0.62 in (4:1) hexanes–EtOAc; $[\alpha]_D$ –154.5° (*c* 1.75, $CHCl_3$); IR ($CHCl_3$) 3600, 3010, 2850, 2020, 1590, 1475, 1260, 1190, 1135 cm^{-1}; ^1H NMR ($CDCl_3$ + one drop of D_2O, 200 MHz) δ 7.19 (t, *J* = 8.0 Hz, 1 H), 6.82 (d, *J* = 7.4 Hz, 1 H), 6.79 (d, *J* = 8.2 Hz, 1 H), 5.22 (dd, *J* = 9.2, 4.6 Hz, 1 H, CHN_3), 4.13 (dd, *J* = 11.5, 9.1 Hz, 1 H, $^1/_2CH_2OH$), 3.83 (s, 3 H, $PhOCH_3$), 3.75 (dd, *J* = 11.5, 4.6 Hz, 1 H, $^1/_2CH_2OH$), 2.42 (s, 3 H, $PhCH_3$); ^{13}C NMR ($CDCl_3$) δ 158.7, 139.3, 130.0, 124.5, 122.5, 109.7 (Ar), 64.3 (CH_2OH), 62.8 (CHN_3), 56.3 ($PhOCH_3$), 21.1 ($PhCH_3$); HRMS calcd for $C_{10}H_{13}N_3O_2$ (M^+) 207.1008, found 207.1005.

(2*R*)-2-Amino-2-(2-methoxy-6-methylphenyl)ethyl Alcohol (14). To a solution of azido alcohol **13** (164 mg, 0.790 mmol) in absolute EtOH (4 mL) was added 10% Pd/C (13 mg). The mixture stirred under H_2 at room temperature for 24 h when TLC analysis showed the reaction to be complete. The catalyst was filtered off through a Celite pad and the solvent removed to give the crude product which was purified by flash chromatography over silica gel, eluting with (100:20:1) $CHCl_3$–MeOH–NH_4OH, to afford the amino alcohol **14** (113 mg, 78% yield) as a white solid: R_f 0.08–0.28 in (100:20:1) $CHCl_3$–MeOH–NH_4OH; mp 132–134 °C; $[\alpha]_D$ –40.5° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$) 3620, 3420, 3010, 2980, 1600, 1585, 1475, 1280, 1265, 1250, 1080, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.12 (t, *J* = 7.9, 1 H, ArH), 6.80–6.75 (m, 2 H, ArH), 4.15 (dd, *J* = 9.9, 5.3 Hz, 1 H), 3.83 (s, 3 H, $PhOCH_3$), 3.78 (t, *J* = 9.9, 1 H), 3.55 (dd, *J* = 10.0, 5.3 Hz, 1 H), 2.35 (s, 3 H, $PhCH_3$), 2.41–2.18 (bs, 2 H, NH_2); ^{13}C NMR ($CDCl_3$) δ 158.4, 137.0, 128.5, 127.7, 123.3, 109.2 (Ar), 64.1 (CH_2OH), 55.1 ($PhOCH_3$), 53.5 ($PhCHNH_2$), 20.3 ($PhCH_3$); HRMS calcd for $C_9H_{12}NO$ ($M^+ - CH_2OH$) 150.0919, found 150.0919.

Mosher Amide Analysis of Enantiomeric Purity. To a solution of **14** (99 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) was added *t*-$BuMe_2SiCl$ (116 mg, 10.8 mmol) followed by Et_3N (220 mL, 2.92 mmol). This mixture was stirred at room temperature for 23 h when TLC analysis showed the reaction to be complete. The solvent was removed and the residue purified by flash chromatography over silica gel, eluting with (10:1) $CHCl_3$–MeOH, to afford **15** (159 mg, 100% yield) as a pale yellow oil: R_f 0.55 in (100:20:1) $CHCl_3$–MeOH–NH_4OH; $[\alpha]_D$ –8.26° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 3690, 3015, 2400, 1740, 1525, 1480, 1425, 1220 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.09 (t, *J* = 7.9 Hz, 1 H, ArH), 6.75 (d, *J* = 7.8 Hz, 1 H, ArH), 6.71 (d, *J* = 7.46 Hz, 1 H, ArH), 4.26 (dd, *J* = 8.2, 6.3 Hz, 1 H, $CHNH_2$), 3.94–3.69 (m, 2 H, CH_2OSi), 3.79 (s, 3 H, $PhOCH_3$), 3.46 (bs, 2 H, NH_2), 2.34 (s, 3 H, $PhCH_3$), 0.82 (s, 9 H, $(CH_3)_3CSi$), –0.02 (s, 3 H, CH_3Si), –0.07 (s, 3 H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 159, 138.8, 128.6, 126.7, 124.1, 109.7 (Ar), 66.2 (CH_2OSi), 55.8 ($PhOCH_3$), 54.2 ($CHNH_2$), 26.5 ($(CH_3)_3CSi$), 21.2 (CH_3Ar), 18.9 (Me_3CSi), –4.8 (CH_3Si); HRMS calcd for $C_{16}H_{26}O_2Si$ ($M^+ - NH_3$) 278.1702, found 278.1822. To a vial containing 1-hydroxybenzotriazole monohydrate (16 mg, 0.11 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (18 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) was added (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (14.3 mg, 0.061 mmol) and **15** (15 mg, 0.051 mmol) in CH_2Cl_2 (180 mL). The reaction mixture was stirred at room temperature for 13 h when TLC analysis showed the reaction to be complete. After concentration, the crude product was purified by PTLC on silica gel to give **16** (18 mg, 68% yield) as a colorless oil. A wide band was cut to prevent accidental separation of the diastereomeric Mosher amide (R_f 0.69). For compound **16**: R_f 0.73 in (5:1) hexanes–EtOAc; $[\alpha]_D$ –29.9° (c, 1.20, $CHCl_3$); IR (CHCl) 3010, 2970, 2940, 1700, 1520, 1475, 1275, 1260, 1190, 1170, 1130, 1110, 910, 840 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.66 (bd, *J* = 9.3 Hz, 1 H), 7.41–7.24 (m, 5 H, ArH), 7.11 (t, *J* = 8.0 Hz, 1 H, ArH), 6.79 (d, *J* = 7.6 Hz, 1 H, ArH), 6.63 (d, *J* = 8.2 Hz, 1 H, ArH), 5.54 (dt, *J* = 9.3, 7.5 Hz, 1 H, PhC*H*NH), 3.94 (dd, *J* = 10.0, 7.9 Hz, 1 H, $^1/_2CH_2OSi$), 3.79 (dd, *J* = 10.0, 7.0 Hz, 1 H, $^1/_2CH_2OSi$), 3.53 (s, 6 H, $PhOCH_3$ and CH_3OCCF_3), 2.47 (s, 3 H, $PhCH_3$), 0.81 (s, 9 H, $(CH_3)_3CSi$), –0.03 (s, 3 H, CH_3Si), –0.09 (s, 3 H, CH_3Si); HRMS calcd for $C_{26}H_{37}NO_4SiF_3$ (MH^+) 512.2443, found 512.2511.

[*R*(*Z*)]-4-[[2-Hydroxy 1-(2-methoxy-6-methylphenyl)ethyl]amino]-4-oxo-2-butenoic Acid (17). A solution of maleic anhydride (1.5 equiv) in dry Et_2O (ca. 0.5 M) was added dropwise to an ice-cold solution of amine **14** (1 equiv) in Et_2O (ca. 0.002 M). After the addition was complete (1.5 h), the resulting suspension was stirred at ambient temperature for 20 h. The white solid was collected and washed twice with Et_2O to give the crude product which was partitioned between saturated $NaHCO_3$ solution and Et_2O. The aqueous phase was acidified to pH 1–2 with 5 N HCl in an ice bath, then extracted with (1:1) EtOAc–THF. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated to give the maleamic acid **17** as a white solid in 80% yield: mp 160.5–162.0 °C (from MeOH); R_f 0.8 in (4:1:1) BuOH–H_2O–AcOH (char C); $[\alpha]_D$ –150.6° (*c* 1.6, MeOH); ^1H NMR (200 MHz, DMSO-d_6) δ 9.34 (br d, *J* = 8.3 Hz, 1 H, NH), 7.11 (t, *J* = 7.8 Hz, 1 H, Ar), 6.80 (d, *J* = 8.1 Hz, 1 H, Ar), 6.48 (d, *J* = 7.4 Hz, 1 H, Ar), 6.60 (d, *J* = 12.7 Hz, 1 H, C*H*CO_2H), 6.25 (d, *J* = 12.7 Hz, 1 H, C*H*CONH), 5.23 (m, 1 H, ArCH), 4.92 (t, *J* = 5.8 Hz, 1 H, CH_2OH), 3.84 (m, 1 H, $^1/_2CH_2OH$), 3.76 (s, 3 H, OMe), 3.59 (m, 1 H, $^1/_2CH_2OH$), 2.38 (s, 3 H, Me); ^{13}C NMR (50 MHz, DMSO-d_6) δ 165.5, 165.0 (CO), 158.0, 137.5 (Ar), 133.6, 131.45 (CH=CH), 128.2, 125.0, 122.8, 109.7 (Ar), 61.5 (CH_2-OH), 55.5 (OMe), 51.8 (ArCH), 19.8 (ArMe); HRMS calcd for $C_{13}H_{14}NO_4$ ($M^+ - CH_2OH$) 248.0923, found 248.0922.

(*R*)-1-[2-(Acetyloxy)-1-(2-methoxy-6-methylphenyl)ethyl]-1*H*-pyrrole-2,5-dione (18). A mixture of maleamic acid **17** (1 equiv) and anhydrous NaOAc (0.8 equiv) was heated to 120 °C in an oil bath. Acetic anhydride (8 mL/mmol of **17**) was added, and the resulting mixture was stirred at this temperature for 20 h, at which time the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and 0.5 N HCl, and the aqueous layer was extracted two more times with EtOAc. The combined organic layers were washed successively with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated to give a crude gummy product. This material was purified by flash chromatography over silica gel, eluting with EtOAc-hexanes, to furnish the desired maleimide **18** in 44% isolated yield along with small amounts of the acetamide **19** (19%) and conjugate addition product **20** (10%).

For **18**: R_f 0.36 in (2:1) hexanes-EtOAc (char A); $[\alpha]_D$ 151.2° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 1740, 1705, 1580 cm^{-1}; ^1H NMR (400 MHz, $CHCl_3$) δ 7.13 (t, *J* = 7.9 Hz, 1 H, Ar), 6.76 (d, *J* = 7.5 Hz, 1 H, Ar), 6.70 (d, *J* = 8.3 Hz, 1 H, Ar), 6.57 (s, 2 H, CH=CH), 5.48 (dd, *J* = 9.7, 5.2 Hz, 1 H, ArCH), 5.25 (dd, *J* = 11.7, 9.7 Hz, 1 H, $^1/_2CH_2OAc$), 4.55 (dd, *J* = 11.7, 5.1 Hz, 1 H, $^1/_2CH_2OAc$), 3.72 (s, 3 H, OMe), 2.45 (s, 3 H, ArMe), 2.01 (s, 3 H, OAc); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 170.5 (CO), 158.2, 138.9 (Ar), 133.9 (CH=CH), 129.1, 123.2, 122.3, 109.1 (Ar), 62.4 (CH_2OAc), 55.2 (OMe), 51.3 (ArCH), 20.9, 20.1 (ArMe, OAc); HRMS calcd for $C_{16}H_{17}NO_5$ (M^+) 303.1107, found 303.1107.

For **19**: R_f 0.33 in EtOAc (char A); $[\alpha]_D$ –117.1° (*c* 1.24, $CHCl_3$); IR ($CHCl_3$) 3440, 1730, 1660 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.9 Hz, 1 H, ArH), 6.78 (br t, *J* = 8.3 Hz, 2 H, ArH), 5.72 (m, 1 H, ArCH), 4.37 (dd, *J* = 10.8, 8.7 Hz, 1 H, $^1/_2CH_2OAc$), 4.21 (dd, *J* = 10.8, 6.1 Hz, 1 H, $^1/_2CH_2OAc$), 3.87 (s, 3 H, OMe), 2.44 (s, 3 H, ArMe), 1.99 (s, 3 H, Me), 1.94 (s, 3 H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 169.4 (CO), 158.0, 138.3, 128.6, 124.1, 123.6, 109.0 (Ar), 64.8 (CH_2OAc), 55.4 (OMe), 47.2 (ArCHN), 23.5, 20.8, 20.2 (3 Me).

For **20**: 2 diastereomers; R_f 0.17 in (2:1) hexanes–EtOAc (char A); ^1H (200 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, ArH), 6.73 (br t, 2 H, ArH), 5.50 (dd, *J* = 9.6, 5.3 Hz, 1 H, ArCH), 5.41–5.24 (m, 2 H, C*H*OAc, $^1/_2CH_2OAc$), 4.51 (m, 1 H, $^1/_2CH_2OAc$), 3.74 (s, 3 H, OMe), 3.05 (dd, *J* = 18.3, 8.8 Hz, 0.5 H, $^1/_4CH_2C{=}O$), 3.04 (dd, *J* = 18.3, 8.8 Hz, 0.5 H, $^1/_4CH_2C{=}O$), 2.59 (m, 1 H, $^1/_2CH_2C{=}O$), 2.43 (s, 1.5 H, $^1/_2ArCH_3$), 2.42 (s, 1.5 H, $^1/_2ArCH_3$), 2.13 (s, 1.5 H, $^1/_2OAc$), 2.12 (s, 1.5 H, $^1/_2OAc$), 2.01 (s, 3 H, OAc); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 172.7, 170.7, 169.9 (CO), 158.2, 139.3, 123.3, 121.5, 109.1 (Ar), 67.3, 67.0 (*C*HOAc), 62.3, 62.1 (CH_2OAc), 55.2 (OMe), 52.7 (ArCH),

35.6, 35.5 (CH_2C=O), 20.9, 20.6, 20.1 (2OAc, ArMe); HRMS calcd for $C_{16}H_{17}O_5N$ (M^+ – HOAc) 303.1107, found 303.1106.

20 → 18: A solution of **20** (4.28 g, 0.0118 mmol) and triethylamine (11.4 g, 0.113 mol) in dry toluene (80 mL) was heated to 120 °C for 2 days. The volatiles were removed, and the residue was purified by flash chromatography over silica gel, eluting with (2:1) hexanes–EtOAc, to afford 2.30 g (65% yield) of the imide **18**.

19 → 14: A solution of **19** (97.0 mg, 0.435 mmol) and (1:1) 3 N NaOH–MeOH (10 mL) was stirred at 85 °C for 18 h. The reaction mixture was diluted with H_2O (10 mL) and then extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to give 55 mg (70% yield) of the amino alcohol **14**.

(*R*)-1-[2-Hydroxy-1-(2-methoxy-6-methylphenyl)ethyl]-1*H*-pyrrole-2,5-dione (21). A mixture of **18** (1.26 g, 4.15 mmol) in (2:1) 5 N HCl–THF (60 mL) was stirred at ambient temperature for 36 h when TLC analysis showed the reaction to be complete. The mixture was neutralized to pH 7 by the careful addition of 5 N NaOH at 0 °C and then extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to a crude product which was purified by flash chromatography over silica gel, eluting with (3:2) EtOAc-hexanes, to afford 817 mg (76% yield) of **21** as a pale yellow solid: R_f 0.29 in (1:1) EtOAc–hexanes (char A); mp 100.5–101.5 °C (EtOAc–hexanes); $[\alpha]_D$ 237.4° (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3620–3340, 1705, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.0 Hz, 1 H, ArH), 6.76 (d, *J* = 7.6 Hz, 1 H, ArH), 6.68 (d, *J* = 8.3 Hz, 1 H, ArH), 6.59 (s, 2 H, CH=CH), 5.33 (dd, *J* = 9.9, 4.7 Hz, 1 H, ArCH), 4.64 (ddd, *J* = 12.6, 9.9, 6.9 Hz, 1 H, $^1/_2CH_2OH$), 3.79 (ddd, *J* = 12.6, 8.4, 4.7 Hz, 1 H, $^1/_2CH_2OH$), 3.68 (s, 3 H, OMe), 3.05 (dd, *J* = 8.4, 6.9 Hz, 1 H, OH), 2.45 (s, 3 H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (CO), 158.2, 138.9 (Ar), 134.0 (CH=CH), 128.8, 123.3, 122.7, 109.2 (Ar), 60.7 (CH_2-OH), 55.6, 55.3 (ArCH, OMe), 20.0 (ArMe); HRMS calcd for $C_{14}H_{15}$-NO_4 (M^+) 261.1001, found 261.1000.

5-[2-Hydroxy-1-(2-methoxy-6-methylphenyl)ethyl]-3a,6a-dihydro-1-methylpyrrolo[3,4-*d*]-1,2,3-triazole-4,6(1*H*,5*H*)-dione (22). To a flask containing maleimide **21** was added a 14% solution of methyl azide in toluene (2.7 mL/mmol of **21**). The resulting clear solution was stirred at room temperature for 24 h when TLC analysis showed the reaction to be complete. Excess methyl azide and solvent were removed on a rotary evaporator, giving the crude product which was purified by flash chromatography over silica gel, eluting with (1:1) hexanes–EtOAc, to provide triazolines **22** in 99% yield: R_f 0.13 in (1:1) EtOAc–hexanes (char A); IR ($CHCl_3$) 3600–3450, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.11 (t, *J* = 8.0 Hz, 1H, Ar), 6.75 (d, *J* = 7.6 Hz, 1 H, Ar), 6.64 (d, *J* = 8.5 Hz, 1 H, Ar), 5.40 (d, *J* = 10.8 Hz, 1 H, CHN=NN), 5.25 (dd, *J* = 10.2, 4.7 Hz, 1 H, ArCH), 4.63 (ddd, *J* = 12.6, 10.2, 6.8 Hz, 1 H, $^1/_2CH_2OH$), 4.09 (d, *J* = 10.8 Hz, 1 H, CHNN=N), 3.69 (m, 1 H, $^1/_2CH_2OH$), 3.61 (s, 3 H, OMe), 3.32 (s, 3 H, NCH_3), 3.09 (d, *J* = 7.4, 6.8 Hz, 1 H, OH, exchangable with D_2O), 2.42 (s, 3 H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0 (C=O), 157.5, 138.4, 129.0, 123.2, 121.1, 108.9 (Ar), 81.3 (CHN=NN), 61.1 (CH_2OAc), 58.8, 57.7 (CHNN=N, OMe), 55.2 (ArCH), 35.5 (NCH_3), 19.8 (ArMe); HRMS calcd for $C_{15}H_{18}N_4O_4$ (M^+) 318.1328, found 318.1332.

(*R*)-3-[2-Hydroxy-1-(2-methoxy-6-methylphenyl)ethyl]-6-methyl-3,6-diazabicyclo[3.1.0]hexane-2,4-dione (23). A 0.2 M solution of triazoline **22** in spectrophotometric grade 1,4-dioxane in a pyrex immersion flask was purged with N_2 for 10 min, then irradiated using a high-pressure Hg lamp for 5 h. TLC analysis indicated the clean conversion of triazoline to aziridine. The solvent was removed on a rotary evaporator, and the resulting oil was purified by flash chromatography over silica gel, eluting with (10:1) $CHCl_3$–MeOH, to furnish the desired aziridine **23** in 90% yield: R_f 0.44 in (10:1) $CHCl_3$–MeOH (char A); $[\alpha]_D$ 139.2° (*c* 1.86, $CHCl_3$); IR ($CHCl_3$) 3610–3400 (br), 1705, 1580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$–D_2O) δ 7.10 (t, *J* = 7.9 Hz, 1 H, Ar), 6.71 (br t, 2 H, Ar), 5.19 (dd, *J* = 9.5, 4.7 Hz, 1 H, ArCH), 4.52 (dd, *J* = 12.3, 9.5 Hz, 1 H, $^1/_2CH_2OH$), 3.72 (s, 3 H, OMe), 3.67 (m, hidden under OMe, 1 H, $^1/_2CH_2OH$), 2.72 (s, 2 H, CHNMeCH), 2.38 (s, 6 H, ArMe, NMe); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.4, 172.5 (C=O), 157.9, 138.4, 128.7, 123.1, 122.1, 109.2 (Ar), 60.7 (CH_2OAc), 56.0, 55.2 (ArCH, OMe), 45.1 (NMe), 41.6, 41.4 (CHNCH), 19.8 (ArMe); HRMS calcd for $C_{15}H_{18}O_4N_2$ (M^+) 290.1267, found 290.1274.

[3a*R*-[1[1*S,3(*R**),5*R**,6*R**],3aα,6α,7aβ]]-1-[[3-[2-Hydroxy-1-(2-methoxy-6-methylphenyl)ethyl]-8-methyl-2,4-dioxo-3,8-diazabicyclo[3.2.1]oct-6-yl]carbonyl]hexahydro-8,8-dimethyl-2,2-dioxo-3*H*-3a,6-methano-2,1-benzisothiazole (26)**. To a quartz tube (diameter 2.5 cm) containing aziridine **23** (2.15 g, 7.34 mmol) in 1,4-dioxane (74 mL, 0.1 M) was added 0.2 equiv of solid acrylimide **25**. The resulting solution was purged with N_2 for 3 min and photolyzed at 2537 Å with efficient stirring for 1 h, then checked by TLC. This procedure was repeated until a total of 1.2 equiv of **25** had been introduced. The solvent was evaporated, and the crude product was purified by flash chromatography over silica gel, eluting with (2:1) EtOAC-hexanes, to afford 2.23 g (54% yield) of **26** and 0.27 g (14%) of unreacted **23**.

For **26**: R_f 0.30 in (2:1) EtOAc–hexanes (char A); $[\alpha]_D$ 36.3° (*c* 0.9, $CHCl_3$); IR (neat) 3600–3200 (br), 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J* = 8.0 Hz, 1 H, Ar), 6.75 (d, *J* = 7.5 Hz, 1 H, Ar), 6.72 (d, *J* = 8.3 Hz, 1 H, Ar), 5.58 (dd, *J* = 8.6, 4.7 Hz, 1 H, ArCH), 4.41 (br t, 1 H, $^1/_2CH_2OH$), 3.91 (s, 1 H, H-5), 3.81 (m, 3 H, H-1, SO_2NCH, $^1/_2CH_2OH$), 3.77 (s, 3 H, OMe), 3.51 (dd, *J* = 9.3, 5.6 Hz, 1 H, H-6), 3.45 (d, *J* = 13.9 Hz, 1 H, $^1/_2CH_2SO_2$), 3.39 (d, *J* = 13.9 Hz, 1 H, $^1/_2CH_2SO_2$), 3.37 (br s, 1 H, OH exchangable with D_2O), 2.62 (m, 1 H, $^1/_2$H-7), 2.55 (s, 3 H, ArMe), 2.40 (s, 3 H, NMe), 2.36 (dd, *J* = 13.6, 9.3 Hz, 1 H, $^1/_2$H-7), 2.06-1.23 (m, 7 H), 1.09 (s, 3 H, $^1/_2C$-$(CH_3)_2$), 0.92 (s, 3 H, $^1/_2C(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 171.7, 170.5 (C=O), 157.8, 138.5, 128.5, 123.4, 123.3, 109.2 (Ar), 69.6 (C-5), 67.1, 65.5 (C-1, C-2′), 62.0 (CH_2OH), 56.8 (OMe), 55.3 (ArCHN), 52.8 (C-10′), 48.5 (C-1′), 47.8 (C-3′), 45.1 (C-6), 44.4 (C-4′), 38.3 (C-6′), 35.7 (NMe), 33.7 (C-5′), 32.0 (C-7), 26.4 (C-7′), 20.9, 19.8 (C-8′, C-9′, ArMe); HRMS calcd for $C_{28}H_{37}O_7N_3S$ (M^+) 559.2352, found 559. 2322.

[3a*R*-[1[1*S,3(*R**),5*R**,6*R**],3aα,6α,7aβ]]-1-[[3-[2-(Methoxymethoxy)-1-(2-methoxy-6-methylphenyl)ethyl]-8-methyl-2,4-dioxo-3,8-diazabicyclo[3.2.1]oct-6-yl]carbonyl]hexahydro-8,8-dimethyl-2,2-dioxo-3*H*-3a,6-methano-2,1-benzisothiazole (27)**. To an ice-cold solution of **26** (1.07 g, 1.91 mmol) and diisopropylethylamine (2.22 g, 17.2 mmol) in dry CH_2Cl_2 (22 mL) was added, dropwise, methoxymethyl chloride (1.08 g, 13.4 mmol). The resulting solution was stirred at room temperature for 15 h when TLC analysis showed the reaction to be complete. At this point, Et_2O (60 mL) was added and the mixture acidified to pH 2–3 with 1 N HCl in an ice bath (two clear layers formed). The organic layer was separated off, and the aqueous layer was extracted with Et_2O (20 mL). The combined organic layers were washed successively with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography over silica gel, eluting with (3:2) EtOAc–hexanes, to afford 1.06 g (92% yield) of **27** as an oil: R_f 0.54 in (2:1) EtOAc–hexanes (char A); $[\alpha]_D$ –9.5° (*c* 2.6, $CHCl_3$); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (t. *J* = 8.0 Hz, 1 H, Ar), 6.71 (br t, 2 H, Ar), 5.90 (dd, *J* = 10.0, 5.4 Hz, 1 H, PhCH), 4.60 (s, 2 H, OCH_2O), 4.55 (t, *J* = 10 Hz, 1 H, $^1/_2CH_2O$(MOM)), 4.04 (dd, *J* = 10.0, 5.4 Hz, 1 H, $^1/_2CH_2O$(MOM)), 3.89, (s, 1 H, H-5), 3.83 (dd, *J* = 7.3, 5.1 Hz, 1H, SO_2NCH), 3.76 (br, s, 4 H, H-1, ArOMe), 3.58 (dd, *J* = 9.2, 5,5 Hz, 1 H, H-6), 3.46 (d, *J* = 13.9 Hz, 1 H, $^1/_2CH_2SO_2$), 3.40 (d, *J* = 13.9 Hz, 1 H, $^1/_2CH_2SO_2$), 3.28 (s, 3 H, CH_2OCH_3), 2.62 (m, 1 H, H-7a), 2.53 (s, 3 H, ArMe), 2.43 (s, 3 H, NCH_3), 2.23 (dd, *J* = 13.4, 9.2 Hz, 1 H, H-7b), 2.07–1.25 (m, 7 H), 1.12 (s, 3 H, $^1/_2C(CH_3)_2$), 0.94 (s, 3 H, $^1/_2C(CH_3)_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7, 170.7, 170.5 (C=O), 158.0, 139.5, 128.5, 123.6, 123.4, 109.0 (Ar), 96.3 (OCH_2O), 69.7 (C-5), 67.6 (CH_2O(MOM)), 66.6, 65.5 (C-1, C-2′), 55.4, 55.3 (OMe), 52.9 (C-10′), 52.3 (ArCHN), 48.5 (C-1′), 47.9 (C-3′), 45.2 (C-6), 44.4 (C-4′), 38.3 (C-6′), 35.5 (NMe), 32.7 (C-5′), 32.0 (C-7), 26.4 (C-7′), 20.9, 19.8 (C-8′, C-9′, PhMe); HRMS calcd for $C_{30}H_{41}O_8N_3S$ (M^+) 603.2614, found 603.2502.

[3a*R*-[1[1*S,3(*R**),5*R**,6*R**],3aα,6α,7aβ]]-1-[[3-[2-(Methoxymethoxy)-1-(2-methoxy-6-(bromomethyl)phenyl)ethyl]-8-methyl-2,4-dioxo-3,8-diazabicyclo[3.2.1]oct-6-yl]carbonyl]hexahydro-8,8-dimethyl-2,2-dioxo-3*H*-3a,6-methano-2,1-benzisothiazole (28)**. A solution of **27** and NBS (1.2 equiv) in dry $CHCl_3$ (0.01 M in **27**) was added to a Pyrex tube (diameter 1.5 or 2.5 cm) and purged with N_2 for 1 min. The resulting clear solution was photolyzed at 2537 Å with efficient stirring for 2 h, and the reaction was monitored by ^1H NMR and stopped at the onset of aromatic bromination. The solvent was evaporated, and the residue was purified by flash chromatography over silica gel, eluting with EtOAc–hexanes. Owing to their similar chromatographic mobilities, **28** and unreacted **27** were collected together (generally in a ratio of 3:1) and used for the next reaction without further purification. However, an analytically pure sample of **28** could be obtained by PTLC on silica gel: $[\alpha]_D$ 35.3° (*c* 0.3, $CHCl_3$); R_f 0.51 in (2:1) EtOAc–hexanes (char A); IR ($CHCl_3$) 1735 (weak), 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1 H, Ar), 6.96 (d, *J* = 7.6 Hz, 1 H, Ar), 6.81 (d, *J* = 8.2 Hz, 1 H, Ar), 5.91 (dd, *J* = 10.3, 4.2 Hz, 1 H, ArCH), 4.96 (d, *J* = 10.7 Hz, 1 H, $^1/_2CH_2Br$), 4.76 (t, *J* = 10.2 Hz, 1 H, $^1/_2CH_2O$(MOM)),

4.68 (d, J = 6.7 Hz, 1 H, $^1/_2OCH_2O$), 4.64 (d, J = 6.7 Hz, 1 H, $^1/_2OCH_2O$), 4.59 (d, J = 10.7 Hz, 1 H, $^1/_2CH_2Br$), 4.06 (dd, J = 10.3, 4.2 Hz, 1 H, $^1/_2CH_2O(MOM)$), 3.88 (s, 1 H, H-5), 3.81 (dd, J = 7.5, 5.1 Hz, 1 H, SO_2NCH), 3.78 (s, 3 H, ArOMe), 3.76 (d, J = 7.2 Hz, 1 H, H-1), 3.58 (dd, J = 9.4, 5.6 Hz, 1 H, H-6), 3.46 (d, J = 13.7 Hz, 1 H, $^1/_2SO_2CH_2$), 3.39 (d, J = 13.7 Hz, 1 H, $^1/_2SO_2CH_2$), 3.33 (s, 3 H, CH_2OCH_3), 2.63 (ddd, J = 13.1, 7.2, 5.6 Hz, 1 H, H-7a), 2.52 (s, 3 H, NMe), 2.26 (dd, J = 13.4, 9.5 Hz, 1 H, H-7b), 2.1–1.2 (m, 7 H), 1.11 (s, 3 H, $^1/_2C(CH_3)_2$), 0.93 (s, 3 H, $^1/_2C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 171.0 (CO), 138.8, 129.4, 123.9, 123.7, 111.8 (Ar), 96.4 (OCH_2O), 69.9 (C-5), 66.8 ($CH_2O(MOM)$), 66.7, 65.6 (C-1, C-2′), 55.5, 55.4 (OMe), 53.0 (ArCHN), 52.9 (C-10′), 48.7 (C-1′), 47.9 (C-3′), 45.2 (C-6), 44.5 (C-4′), 38.4 (C-6′), 35.6 (NMe), 32.8 (C-5′), 32.2 (CH_2-Br), 32.0 (C-7), 26.5 (C-7′), 20.9, 19.9 (C-8′, C-9′); HRMS calcd for $C_{29}H_{37}N_3O_8SBr^{79}$ (M^+ – OMe) 650.1536, found 650.1547, calcd for $C_{29}H_{37}N_3O_8SBr^{81}$ (M^+ – OMe) 652.1516, found 652.1289.

Phosphonium Salt 29. A solution of a (3:1) mixture of **28** and **27** (548 mg, 0.621 mmol) and triphenylphosphine (316 mg, 1.20 mmol) in dry $CHCl_3$ (3 mL) was stirred at room temperature for 22 h when TLC analysis showed the reaction to be complete. The solution was concentrated to one-half volume and the product precipitated by the addition of Et_2O (5 mL). The white solid was collected to afford 467 mg (48% yield in two steps from **27**) of pure phosphonium salt **28**. The filtrate was concentrated and the residue chromatographed over silica gel, eluting with (2:1) EtOAc–hexanes to recover 87 mg (11% yield) of **27**. An analytical sample of **28** was obtained by flash chromatography over silica gel, eluting with (1:1) acetone–$CHCl_3$: mp > 200 °C (dec); R_f 0.32 in (1:1) acetone–$CHCl_3$ (char B); $[\alpha]_D$ –27.6° (c 0.7, $CHCl_3$); IR ($CHCl_3$) 1735 (weak), 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.51 (m, 15 H, 3 Ph), 7.03 (t, J = 8.0 Hz, 1 H, Ar), 6.85 (d, J = 8.0 Hz, 1 H, Ar), 6.64 (d, J = 7.2 Hz, 1 H, Ar), 5.25 (t, J = 15.1 Hz, ABX, 1 H, $^1/_2CH_2P$), 5.03 (dd, J = 9.8, 3.4 Hz, 1 H, ArCHN), 4.54 (t, J = 15.0 Hz, ABX, 1 H, $^1/_2CH_2P$), 4.31 (d, J = 16.6 Hz, 1 H, $^1/_2OCH_2O$), 4.23 (t, J = 10.7 Hz, 1 H, $^1/_2CH_2O(MOM)$), 4.19 (d, J = 16.6 Hz, 1 H, $^1/_2OCH_2O$), 3.85 (s, 1 H, H-5), 3.82 (m, 1 H, SO_2NCH), 3.80 (s, 3 H, ArOMe), 3.76 (d, J = 7.0 Hz, 1 H, H-1), 3.54 (d, J = 13.7 Hz, 1 H, $^1/_2SO_2CH_2$), 3.53 (m, 1 H, H-6), 3.46 (d, J = 13.7 Hz, 1 H, $^1/_2SO_2CH_2$), 3.14 (s, 3 H, CH_2OCH_3), 3.10 (dd, J = 10.8, 3.6 Hz, 1 H, $^1/_2CH_2O$-(MOM)), 2.61 (m, 1 H, H-7a), 2.49 (s, 3 H, NMe), 2.1–1.3 (m, 8 H), 1.10 (s, 3 H, $C(CH_3)_2$), 0.95 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 171.0, 170.1 (CO), 160.9, 135.3, 134.2, 134.1, 130.4, 130.2, 130.0, 127.6, 127.5, 124.8, 124.7, 124.4, 124.3, 117.6, 116.5, 113.0 (Ph/Ar), 96.2 (OCH_2O), 69.6 (C-5), 68.2 ($CH_2O(MOM)$), 66.3, 65.6 (C-1, C-2′), 56.1, 55.4 (OMe), 53.0 (C-10′), 51.1 (ArCHN), 48.6 (C-1′), 47.8 (C-3′), 45.4 (C-6), 44.4 (C-4′), 38.3 (C-6′), 35.9 (NMe), 32.7 (C-5′), 31.5 (C-7), 27.6 (CH_2P), 26.3 (C-7′), 20.9, 19.9 (C-8′, C-9′); FABMS $(M - Br)^+$ 864.

[5*R*-(5α,8β,10β(3a*R6*S**,7a*S**),11β)]-1-[[5,7,8,9,10,11-Hexahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-7-oxo-8,11-iminoazepino[1,2*b*]isoquinoline-10-yl]carbonyl]hexahydro-8,8-dimethyl-2,2-dioxo-3*H*-3a,6-methano-2,1-benzisothiazole (31).** A solution of **29** (1.16 g, 1.23 mmol) in dry DMF (15 mL) was added to a suspension of potassium *tert*-butyloxide (152 mg, 1.35 mmol) in DMF (10 mL). The resulting orange mixture was stirred at 120 °C for 10 h when TLC analysis showed the reaction to be complete. The mixture was cooled to room temperature, quenched with pH 7 buffer (10 mL), and partitioned between H_2O (50 mL) and Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a residue which was purified by flash chromatography over silica gel, eluting with (2:1) EtOAc–hexanes, to afford 568 mg (79% yield) of **31**: R_f 0.46 in (4:1) EtOAc–hexanes (char A); $[\alpha]_D$ 84.3° (c 1.7, CH_2Cl_2); IR ($CHCl_3$) 1680, 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14 (t, J = 8.0 Hz, 1 H, Ar), 6.67 (br t, J = 8.0 Hz, 2 H, Ar), 6.21 (dd, J = 6.6, 4.5 Hz, 1 H, H-5), 5.69 (s, 1 H, H-12), 4.61 (d, J = 6.5, 1 H, $^1/_2OCH_2O$), 4.50 (d, J = 6.5, 1 H, $^1/_2OCH_2O$), 3.87 (m, 2 H, H-11, H-2′), 3.80 (s, 3 H, $ArOCH_3$), 3.70 (m, 2 H, H-8, H-10), 3.58–3.38 (m, 4 H, H-14, H-10′), 3.22 (s, 3 H, CH_2OCH_3), 2.90 (m, 1 H, H-9), 2.43 (s, 3 H, NCH_3), 2.33 (d, J = 13.2, 9.1 Hz, 1 H, H-9), 2.14-1.23 (m, 7 H), 1.20 (s, 3 H, $C(CH_3)_2$), 0.98 (s, 3 H, $C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 169.1 (CO), 155.1 (Ar), 133.7, 131.6 (Ar, C-11a), 128.7, 117.6, 117.5, (Ar), 109.1 (C-12), 107.0 (Ph), 96.3 (OCH_2O), 67.7 (C-2′), 67.3 (C-14), 66.8 65.7 (C-11, C-8), 55.4 (ArOMe), 55.2 (CH_2OCH_3), 53.1 (C-10′), 48.4 (C-1′), 47.9 (C-5), 47.8 (C-3′), 46.1 (C-10), 44.6 (C-4′), 38.5 (C-6′), 35.7 (NMe), 33.6 (C-9), 32.8 (C-5′), 26.4 (C-7′), 21.0, 19.9 (C-8′, C-9′); HRMS calcd for $C_{30}H_{39}N_3O_7S$ (M^+) 585.2508, found 585.2491.

[5*R*-(5α,8β,10β,11β)]-5,7,8,9,10,11-Hexahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylic Acid, Methyl Ester (34). A suspension of **31** (60.5 mg, 0.103 mmol) and $LiOH\cdot H_2O$ (64.4 mg, 1.53 mmol) in (2:1) THF–H_2O (4.6 mL) was stirred at room temperature for 2 h. The resulting solution was diluted with H_2O (10 mL) and then extracted with (3:2) hexanes–EtOAc (2 × 10 mL) to remove the sultam auxiliary **33**, which was recovered in 85% yield. The aqueous layer was acidified to pH 6–7 by careful addition of 0.1 N HCl and was extracted with of (3:2) EtOAc–THF (4 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give 40 mg (91% yield) of the carboxylic acid **32**. This product was used directly, for the next reaction, but an analytical sample was obtained by PTLC on silica gel: R_f 0.15 in (10:1) $CHCl_3$–MeOH (char A); $[\alpha]_D$ 109.6° (c 0.3, $CHCl_3$); IR ($CHCl_3$) 1740 (weak), 1680, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J = 7.9 Hz, 1 H, Ar), 6.73 (d, J = 8.2 Hz, 1 H, Ar), 6.65 (d, J = 7.7 Hz, 1 H, Ar), 6.19 (dd, J = 6.7, 4.5 Hz, 1 H, H-5), 5.74 (s, 1 H, H-12), 4.60 (d, J = 6.5 Hz, 1 H, $^1/_2OCH_2O$), 4.41 (d, J = 6.5 Hz, 1 H, $^1/_2OCH_2O$) 4.06 (s, 1 H, H-11), 3.82 (s, 3 H, ArOMe), 3.77 (d, J = 7.0 Hz, 1 H, H-8), 3.56 (m, 2 H, H-14), 3.28 (dd, J = 9.6, 5.1 Hz, 1 H, H-10), 3.19 (s, 3 H, CH_2OCH_3), 2.68 (m, 1 H, H-9), 2.52 (s, 3 H, NMe), 2.50 (m, hidden under NMe, 1 H, H-9); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 169.9 (CO, very weak), 155.2 (Ar), 133.1, 131.2 (Ar, C-11a), 129.0, 117.8, 117.2 (Ar), 109.6 (C-12), 107.2 (Ar), 96.7 (OCH_2O), 67.1 (C-14), 66.1, 65.7 (C-8, C-11), 55.5, 55.3 (OMe), 47.6 (C-5), 46.4 (C-10), 35.1 (NMe), 34.4 (C-9); HRMS calcd for $C_{20}H_{24}N_2O_6$ (M^+) 388.1634, found 388.1634. To an ice-cold solution of **32** (56 mg, 0.15 mmol) in dry CH_2Cl_2 (5 mL) was added ca. 0.6 M ethereal CH_2N_2[76] in 1-mL aliquots every 10 min (2 mL total). After removal of the excess CH_2N_2, the reaction mixture was partitioned between saturated $NaHCO_3$ solution (10 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was flashed chromatographed over silica gel, eluting with (5:2) EtOAc–hexanes, to afford 40 mg (70% yield) of **34**: R_f 0.26 in (2:1) EtOAc–hexanes (char A); $[\alpha]_D$ 92.2° (c 1.37, $CHCl_3$); IR ($CHCl_3$) 1735, 1680, 1640 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (dd, J = 8.0 Hz, 1 H, Ar), 6.70 (d, J = 8.3 Hz, 1 H, Ar), 6.64 (d, J = 7.6 Hz, 1 H, Ar), 6.19 (dd, J = 6.2, 4.9 Hz, 1 H, H-5), 5.67 (s, 1 H, H-12), 4.61 (d, J = 6.5 Hz, 1 H, $^1/_2OCH_2O$), 4.42 (d, J = 6.5 Hz, 1 H, $^1/_2OCH_2O$), 4.00 (s, 1 H, H-11), 3.81 (s, 3 H, $ArOCH_3$), 3.74 (s, 3 H, CO_2Me), 3.66 (d, J = 6.2 Hz, 1 H, H-8), 3.55 (m, 2 H, H-14), 3.27 (dd, J = 10.0, 6.2 Hz, 1 H, H-10), 3.19 (s, 3 H, CH_2OCH_3), 2.58 (m, 1 H, H-9), 2.44 (s, 3 H, NCH_3), 2.38 (m, hidden under NMe, 1 H, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (Ar), 131.9, 131.0 (Ar, C-11a), 129.2, 118.0, 117.2 (Ar), 110.6 (C-12), 110.0 (Ar), 96.0 (OCH_2O), 67.0 (C-14), 66.8, 65.2 (C-11, C-8), 55.5, 55.3, 52.9, (OMe), 46.8 (C-5), 46.5 (C-10), 35.2 (NMe), 33.9 (C-9); HRMS calcd for $C_{21}H_{26}N_2O_6$ (M^+) 402.1791, found 402.1794.

[5*R*-(5α,8β,10β(3a*R,6*S**,7a*S**),11β,11aβ)]-Hexahydro-8,8-dimethyl-1-[[5,7,8,9,10,11,11a,12-octahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-yl]carbonyl]-2,2-dioxo-3*H*-3a,6-methano-2,1-benzisothiazole (35) and [5*R*-(5α,8β,10β,11β,11aβ)]-8,9,10,11,11a,12-Hexahydro-10-(hydroxymethyl)-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-8,11-iminoazepino[1,2-*b*]isoquinoline-7(5*H*)-one (36).** To a solution of **31** (266 mg, 0.459 mmol) in absolute ethanol (40 mL) was added 2.4 mL of a Raney-Ni (W-2)[77] suspension (ca. 1.44 g). The resulting mixture was submitted to high-pressure hydrogenation (1400 psi) in a Parr bomb with efficient stirring at 65 °C for 20 h. At this point, the reaction was depressurized, the catalyst filtered off, and the filtrate concentrated. The crude residue was chromatographed over silica gel, eluting successively with (4:1) EtOAc–hexanes followed by (8:1) EtOAc–MeOH, to afford 79.1 mg of **35** (30% yield) and 58.9 mg of **36** (35% yield).

For **35**: R_f 0.32 in (4:1) EtOAc–hexanes (char A); $[\alpha]_D$ –33° (c 1.24, $CHCl_3$); IR ($CHCl_3$) 1690, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, J = 7.9 Hz, 1 H, Ar), 6.72 (t, J = 7.5 Hz, 2 H, Ar), 5.58 (br d, J = 2.7 Hz, 1 H, H-5), 4.44 (s, 2 H, OCH_2O), 4.19 (dd, J = 9.7, 3.3 Hz, 1 H, $^1/_2$H-14), 3.99 (dd, J = 8.8, 6.3 Hz, 1 H, H-10), 3.90 (t, J = 6.3 Hz, 1 H, H-2′), 3.82 (m, 1 H, $^1/_2$H-12), 3.79 (s, 3 H, ArOMe), 3.57 (d, J = 6.0 Hz, 1 H, H-8), 3.52–3.32 (m, 5 H, H-10′, $^1/_2$H-14, H-11a, H-11), 2.96 (s, 3 H, CH_2OCH_3), 2.57 (s, 3 H, NMe), 2.50 (dd, J = 12.7, 6.4 Hz, 1 H, H-9), 2.41 (m, 2 H, H-9, $^1/_2$H-12), 2.1–1.3 (m, 7 H), 1.19 (s, 3 H, $^1/_2C(CH_3)_2$), 0.98 (s, 3 H, $^1/_2C(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 171.0 (CO), 155.6, 138.6, 127.6, 123.0, 119.6, 108.5 (Ar), 96.2 (OCH_2O), 67.9 (C-2′), 67.5 (C-14), 67.0, 65.8 (C-11, C-8), 55.3, 54.5 (OMe), 53.3 (C-10′), 49.3 (C-5), 48.3 (C-1′), 47.8 (C-3′), 44.8, 42.6 (C-4′, C-11a), 38.7 (C-6′), 36.9, 36.8 (NMe, C-9), 33.0 (C-

5′), 31.8 (C-12), 26.4 (C-7′), 21.1, 19.9 (C-8′, C-9′); HRMS calcd for $C_{30}H_{41}N_3O_7S$ (M^+) 587.2665, found 587.2654.

For **36**: R_f 0.29 in (10:1) EtOAc–MeOH (char A); $[\alpha]_D$ −108.3° (*c* 1.25, $CHCl_3$); IR ($CHCl_3$) 3500–3100 (weak), 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, *J* = 8.0 Hz, 1 H, Ar), 6.74 (d, *J* = 8.3 Hz, 1 H, Ar), 6.70 (d, *J* = 7.6 Hz, 1 H, Ar), 5.60 (br s, 1 H, H-5), 4.37 (d, *J* = 16.0 Hz, 1 H, $^1/_2OCH_2O$), 4.26 (d, *J* = 16.0 Hz, 1 H, $^1/_2OCH_2O$), 4.17 (dd, *J* = 10.0, 2.7 Hz, 1 H, $^1/_2$H-14), 3.82 (m, hidden under ArOMe, 1 H, H-11), 3.79 (s, 3 H, ArOMe), 3.70 (dd, *J* = 10.0, 4.2 Hz, 1 H, $^1/_2$H-14), 3.56 (m, 2 H, $^1/_2$H-12, $^1/_2CH_2OH$), 3.43 (d, *J* = 6.5 Hz, 1 H, H-8), 3.16–3.06 (m, 2 H, $^1/_2CH_2OH$, H-11a); 2.92 (s, 3 H, CH_2OCH_3), 2.68 (br m, 1 H, OH), 2.64 (m, 1 H, H-9), 2.52 (s, 3 H, NMe), 2.40 (d, *J* = 13.7 Hz, 1 H, $^1/_2$H-12), 2.11 (dd, *J* = 12.6, 9.3 Hz, 1 H, H-9), 1.96 (m, 1 H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (CO), 155.8, 138.8, 127.9, 122.7, 119.5, 108.7 (Ar), 96.3 (OCH_2O), 68.0 (C-14), 66.3 (CH_2OH, C-11), 64.9 (C-8), 55.4 (ArOMe), 54.7 (CH_2OCH_3), 51.7 (C-5), 49.4 (C-11a), 38.2 (C-10), 35.0 (NMe), 34.9 (C-9), 31.9 (C-12); FABMS ($M + 1)^+$ 377.

[5*R*-(5α,8β,10β,11β,11aβ)]-(−)-5,7,8,9,10,11,11a,12-Octahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-7-oxo-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylic Acid (37). The reaction was carried out with **35** by following the procedure described for **31** → **34** to afford **37** in 100% yield and recover (+)-sultam **33** in 88% yield. The analytical sample was obtained by PTLC on silica gel: R_f 0.28 in (8:1) $CHCl_3$–MeOH (char A); mp 181–185 °C; $[\alpha]_D$ −110.9° (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 1730, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1 H, Ar), 6.78 (d, *J* = 8.2 Hz, 1 H, Ar), 6.74 (d, *J* = 7.7 Hz, 1 H, Ar), 5.6 (br s, 1 H, H-5), 4.39 (d, *J* = 16.3 Hz, 1 H, $^1/_2OCH_2O$), 4.27 (d, *J* = 16.3 Hz, 1 H, $^1/_2OCH_2O$), 4.20 (dd, *J* = 10.0, 3.0 Hz, 1 H, $^1/_2$H-14), 3.86 (br d, *J* = 12.2 Hz, 1 H, $^1/_2$H-12), 3.81 (s, 3 H, ArOMe), 3.77 (br s, 1 H, H-11), 3.67 (d, *J* = 6.2 Hz, 1 H, H-8), 3.52 (d, *J* = 10.0, 1.9 Hz, 1 H, $^1/_2$H-14), 3.36 (dd, *J* = 10.0, 5.5 Hz, 1 H, H-10), 3.18 (m, 1 H, H-11a), 2.93 (s, 3 H, CH_2OCH_3), 2.67–2.56 (m, 2 H, H-9, $^1/_2$H-12), 2.63 (s, 3 H, NMe), 2.36 (dd, *J* = 13.2, 10.0 Hz, 1 H, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (CO), 156.0 137.8, 128.1, 122.0, 119.6, 108.8 (Ar), 96.2 (OCH_2O), 67.8 (C-14), 65.9, 65.5 (C-8, C-11), 55.4, 54.8 (OMe), 52.5 (C-5), 49.6 (C-11a), 41.7 (C-10), 35.2 (NMe), 34.5 (C-9), 31.8 (C-12); HRMS calcd for $C_{20}H_{26}N_2O_6$ (M^+) 390.1791, found 390.1788.

[5*R*-(5α,8β,10β,11β,11aβ)]-5,7,8,9,10,11,11a,12-Octahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-7-oxo-8,11-iminoazepino-[1,2-*b*]isoquinoline-10-carboxylic Acid, Methyl Ester (38). From **37**: The reaction of **37** with 0.6 M CH_2N_2–Et_2O was carried out by the procedure described for **31** → **34** to afford **38** in 43% yield. From **34**: The high-pressure hydrogenation reaction from **34** was carried out by following the procedure described for **31** → **35** to afford **38** in 67% yield (based on 19% recovered **34**): R_f 0.29 in (2:1) EtOAc–hexanes (char A); $[\alpha]_D$ − 127.7° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) 1705, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 7.9 Hz, 1 H, Ar), 6.77 (t, *J* = 8.7 Hz, 2 H, Ar), 5.60 (br d, *J* = 2.4 Hz, 1 H, H-5), 4.42 (d, *J* = 6.3 Hz, 1 H, $^1/_2OCH_2O$), 4.29 (d, *J* = 6.3 Hz, 1 H, $^1/_2OCH_2O$), 4.20 (dd, *J* = 10.0, 2.9 Hz, 1 H, $^1/_2$H-14), 3.87 (dd, *J* = 10.0, 2.4 Hz, 1 H, $^1/_2$H-12), 3.82 (s, 3 H, ArOMe), 3.77 (s, 3 H, CO_2Me), 3.65 (br d, *J* = 1.4 Hz, 1 H, H-11), 3.58–3.54 (m, 2 H, H-8, $^1/_2$H-14), 3.36 (dd, *J* = 9.7, 6.7 Hz, 1 H, H-10), 3.15 (t, *J* = 13.3 Hz, 1 H, H-11a), 2.96 (s, 3 H, CH_2OCH_3), 2.63 (m, 1 H, H-9), 2.54 (dd, *J* = 14.3, 2.4, Hz, 1 H, $^1/_2$H-12), 2.50 (s, 3 H, NMe), 2.30 (dd, *J* = 13.1, 9.6 Hz, 1 H, H-9); ^{13}C NMR (75 MHz $CDCl_3$) δ 174.9, 171.0 (CO), 155.7, 138.2, 127.9, 122.7, 119.5, 108.7 (Ar), 96.3 (OCH_2O), 68.0 (C-14), 67.1, 66.4 (C-11, C-8), 55.3 (ArOMe), 54.7, 54.3 (OMe), 52.4 (C-5), 49.4 (C-11a), 41.3 (C-10), 37.0 (NMe), 34.4 (C-9), 32.1 (C-12); HRMS calcd for $C_{21}H_{28}HN_2O_6$ (M^+) 404.1947, found 404.1963.

General Procedure for Lactam Partial Reduction and Cyanation. A 10-fold volume of liquid ammonia (distilled from Na) at −78 °C was condensed into a solution of lactam (**37** or **36**) in THF (1 mL/0.024 mmol of substrate). To this clear solution was added 100 equiv of lithium metal (cleaned and weighed under xylene). The resulting deep blue mixture was refluxed at −25 °C for 15 min when ethanol was slowly injected until the deep blue color faded. After stirring for additional 5 min, 3.5 equiv of solid ammonium chloride was introduced and then the ammonia evaporated under a flow of nitrogen at room temperature. Saturated aqueous sodium bicarbonate (two times the THF volume) was added just prior to the final evaporation (white precipitates formed). The mixture was acidified to pH 6–7 with 1 N HCl at 0 °C, and the resulting solution was treated with 0.1 M NaCN (1.8 equiv) and stirred room temperature for 15 h. If necessary, the reaction mixture was acidified to pH 6–7 again. The product was extracted out with (1:1) THF–EtOAc. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a residue which was purified by flash chromatography over silica gel, eluting with EtOAc + AcOH (1 drop/10 mL), to afford the pure aminonitrile (**39** or **40**).

[5*R*-(5α,7β,8β,10β,11β,11aβ)]-7-Cyano-5,7,8,9,10,11,11a,12-octahydro-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylic Acid (39): 63% yield; R_f 0.39 in EtOAc + AcOH (1 drop/10 mL) (char A); ^1H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 8.0 Hz, 1 H, Ar), 6.70 (t, *J* = 8.6 Hz, 2 H, Ar), 4.61 (d, *J* = 6.7 Hz, 1 H, $^1/_2OCH_2O$), 4.54 (d, *J* = 6.7 Hz, 1 H, $^1/_2OCH_2O$), 4.35 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-5), 4.22 (d, *J* = 2.8 Hz, 1 H, H-7), 3.80 (s, 3 H, ArOMe), 3.74 (dd, *J* = 9.3, 2.3 Hz, 1 H, $^1/_2$H-14), 3.49 (s, 1 H, H-11), 3.47–3.43 (m, 1 H, H-8), 3.30 (s, 3 H, CH_2OCH_3), 3.32–3.28 (m, 1 H, $^1/_2$H-14), 3.23 (dd, *J* = 9.6, 5.5 Hz, 1 H, H-10), 3.06 (br d, *J* = 10.4 Hz, 1 H, H-11a), 2.64–2.53 (m, 3 H, H-9, H-12), 2.38 (s, 3 H, NMe), 2.07 (dd, *J* = 13.0, 9.6 Hz, 1 H, H-9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2 (C=O), 155.8, 136.2, 127.9, 121.6, 120.3, (Ar), 118.4 (CN), 108.5 (Ar), 96.7 (OCH_2O), 74.1 (C-14), 70.6 (C-11), 64.5 (C-8), 58.7, 57.4 (C-7, C-11a), 55.8, 55.4 (2 OMe), 55.3 (C-5), 42.7 (C-10), 41.5 (NMe), 32.8 (C-9), 28.8 (C-12); HRMS calcd for $C_{20}H_{24}N_3O_4$ (M^+ − OCH_3) 370.1767, found 370.1792.

[5*R*-(5α,7β,8β,10β,11β,11aβ)]-5,7,8,9,10,11,11a,12-Octahydro-10-(hydroxymethyl)-4-methoxy-5-[(methoxymethoxy)methyl]-13-methyl-8,11-iminoazepino[1,2-*b*]isoquinoline-7-carbonitrile (40): 56% yield; R_f 0.38 (10:1) EtOAc–MeOH (char A); IR ($CHCl_3$) 1590, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.9 Hz, 1 H, Ar), 6.69 (m, 2 H, Ar), 4.61 (d, *J* = 6.3 Hz, 1 H, $^1/_2OCH_2O$), 4.54 (d, *J* = 6.3 Hz, 1 H, $^1/_2OCH_2O$), 4.36 (dd, *J* = 8.1, 2.1 Hz, 1 H, H-5), 4.19 (d, *J* = 2.5 Hz, 1 H, H-7), 3.80 (s, 3 H, ArOMe), 3.78–3.71 (m, 2 H, $^1/_2$H-14, H-11), 3.60 (m, 2 H, CH_2OH), 3.48 (br d, *J* = 4.2 Hz, 1 H, H-8), 3.32–3.34 (m, 1 H, $^1/_2$H-14), 3.30 (s, 3 H, CH_2OCH_3), 3.15 (br d, *J* = 14.2 Hz, 1 H, H-11a), 2.98 (s, 1 H, OH), 2.65 (s, 3 H, NMe), 2.68–2.54 (m, 2 H, $^1/_2$H-12, H-9), 2.43 (dd, *J* = 14.8, 2.4 Hz, 1 H, $^1/_2$H-12), 1.98–2.06 (m, 1 H, H-9), 1.92–1.86 (m, 1 H, H-10); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 136.6, 127.9, 121.6, 120.1 (Ar), 119.0 (CN), 108.5 (Ph), 96.7 (OCH_2O), 74.3 (C-14), 67.6 (C-11), 66.8 (CH_2OH), 62.8 (C-8), 56.3, 55.9, 55.4, 55.2, (2OMe, C-7, C-5), 53.3 (C-11a), 40.0 (C-10), 38.4 (NMe), 32.7 (C-9), 31.2 (C-12); HRMS (FAB) calcd for $C_{21}H_{30}N_3O_4$ ($M + 1)^+$ 388.2236, found 388.2177.

[5*R*-(5α,7β,8β,10β,11β,11aβ)]-7-Cyano-5,7,8,9,10,11,11a,12-octahydro-5-(hydroxymethyl)-4-methoxy-13-methyl-8,11-iminoazepino[1,2-*b*]-isoquinoline-10-carboxylic Acid, DX-52-1 (3). To a solution of **39** (20 mg, 0.05 mmol) and NaI (78 mg, 0.52 mmol) in dry MeCN (4 mL) was added, dropwise, (TMS)Cl (43 mg, 0.40 mmol) at room temperature. The resulting brown mixture was stirred for 2 h, and then treated with excess $Na_2S_2O_3$ to remove iodine. The solid was filtered off through Celite and the pale yellow filtrate concentrated to give a crude product which was purified by flash chromatography over silica gel, eluting with (8:1) $CHCl_3$–MeOH to afford 12.8 Mg (72% yield) of **3**: R_f 0.20 in (8:1) $CHCl_3$–MeOH (char A); $[\alpha]_D$ 35° (*c* 0.51, MeOH); ^1H NMR (300 MHz, D_2O) δ 7.32 (t, *J* = 7.9 Hz, 1 H, Ar), 6.98 (d, *J* = 8.0 Hz, 1 H, Ar), 6.91 (d, *J* = 7.6 Hz, 1 H, Ar), 4.72 (d, *J* = 2.5 Hz, 1 H, H-7), 4.37 (br d, *J* = 6.4 Hz, 1 H, H-8), 4.30 (dd, *J* = 5.0, 2.9 Hz, 1 H, H-5), 4.25 (s, 1 H, H-11), 3.86 (s, 3 H, OMe), 3.78 (dd, *J* = 11.5, 2.9 Hz, 1 H, $^1/_2$H-14), 3.67 (dd, *J* = 11.5, 5.1 Hz, 1 H, $^1/_2$H-14), 3.48 (dd, *J* = 10.5, 5.5 Hz, 1 H, H-10), 3.20 (dd, *J* = 9.1, 4.5 Hz, 1 H, H-11a), 2.85–2.71 (m, 3 H, H-9, H-12), 2.82 (s, 3 H, NMe), 2.47 (dd, *J* = 14.4, 10.5 Hz, 1 H, H-9); ^{13}C NMR (75 MHz, D_2O) δ 179.3 (C=O), 155.7, 135.9, 128.7, 121.0, 120.5 (Ar), 116.2 (CN), 109.7 (Ar), 71.2 (C-14), 65.4, 64.7 (C-8, C-11), 57.1, 56.5, 56.4 (C-7, C-11a, OMe), 55.6 (C-5), 42.1 (C-10), 40.2 (NMe), 31.2 (C-9), 28.6 (C-12); HRMS (FAB) calcd for $C_{19}H_{24}N_3O_4$ ($M + 1)^+$ 358.1767, found 358.1777.

[2a*R*-(2aα,3α,5α,6α,6aα,11bα)]-2a,3,4,5,6,6a,7,11b-Octahydro-11-methoxy-12-methyl-3,6-imino-1*H*-oxa-11c-azanaphth[1,2,3-*cd*]azulene-5-carboxylic Acid, (−)-Quinocarcin (1). A suspension of **3** (12.2 mg, 0.034 mmol) and $AgNO_3$ (23.3 mg, 0.137 mmol) in of (4:1) MeOH–H_2O (5 mL) was stirred at room temperature for 4 h. A large excess of basic ion-exchange resin (Amberlite IRA-401, Cl^- form) was added to remove Ag(I). After stirring at room temperature for 30 min, the solid was filtered through Celite and the filtrate was concentrated to afford pure quinocarcin (10.6 mg, 94% yield). The analytical sample was obtained by reverse-phase HPLC (C18 column, MeOH–H_2O linear gradient from 50–70% MeOH between 1.5 and 2.5 min, flow rate = 1.0 mL/min): t_R 4.3 min; $[\alpha]_D$ −30° (*c* 0.2, H_2O)]lit.[1a] $[\alpha]_D$ −32° (*c* 0.50, H_2O)]; ^1H NMR (300 MHz, D_2O)δ 7.27 (t, *J* = 8.0 Hz, 1 H, Ar), 6.94

(d, J = 8.1 Hz, 1 H, Ar), 6.86 (d, J = 7.7 Hz, 1 H, Ar), 4.95 (d, J = 3.1 Hz, 1 H, H-2a), 4.49 (t, J = 3.9 Hz, 1 H, H-11b), 4.20 (s, 1 H, H-6), 3.96 (m, 1 H, H-3), 3.86 (s, 3 H, OMe), 3.72–3.60 (m, 2 H, H-1), 3.47 (dd, J = 9.9, 4.9 Hz, 2 H, H-5, H-6a), 2.79 (s, 3 H, NMe), 275 (m, 2H, H-7), 2.60–2.52 (m, 1 H, H-4), 2.43 (dd, J = 14.0, 10.6 Hz, 1 H, H-4); ^{13}C NMR (75 MHz, D_2O) δ 181.1 (CO), 156.8, 137.7, 129.3, 123.6, 121.5, 110.5 (Ar), 82.3 (C-2a) 72.3, 70.1, (C-3, C-6), 65.9 (C-1), 56.5 (OMe), 54.7 (C-11b), 54.2 (C-6a), 42.0 (C-5), 40.6 (NMe), 32.4 (C-4), 27.9 (C-7); HRMS calcd for $C_{17}H_{20}N_2O_3$ ($M^+ - CH_2O$) 300.1474, found 300.1464.

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Supplementary Material Available: Proton NMR spectra for all compounds and plots of the complete NOESY experiment for quinocarcin citrate (35 pages). Ordering information is given on any current masthead page.