JOC Article

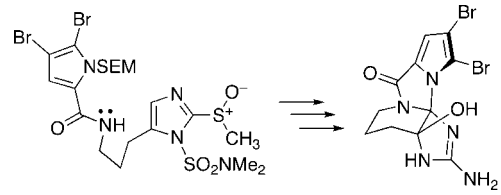
Extending Pummerer Reaction Chemistry: (±)-Dibromoagelaspongin Synthesis and Related Studies

Ken S. Feldman* and Matthew D. Fodor

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

ksf@chem.psu.edu

Received February 10, 2009



The sponge-derived alkaloid dibromoagelaspongin was prepared from a dihydrooroidin derivative by exploiting the Pummerer reaction twice in succession. Oxidative cyclization of the substrate's pyrrole-2-carboxamide function into the imidazole moiety was achieved in a regiospecific manner to establish both C−N bonds to C(6) of the target.

Introduction

The sponge-derived pyrrole-imidazole alkaloids represent yet another example of Nature's capacity for generating astonishing structural diversity from a simple precursor.[1] The roster of cyclization/oxidation products formally derived from either of the naturally occurring progenitors oroidin (**1**)[2] or dihydrooroidin (**2**)[3] is continually increasing as bioprospecting efforts expand in kind. Monomeric, dimeric, and tetrameric cyclized derivatives of **1**/**2** have been discovered to date,[1,4] and there is no reason to suspect that this family has been exhausted. The monomeric cyclization/oxidation products of **1**/**2** that feature connections between the imidazole and pyrrole cores represent one large subclass of these species, as illustrated in Figure 1. Isomerization/cyclization from **1** or oxidative cyclization from **2** leads almost exclusively to attachment of N(14) to C(10) of the 2-aminoimidazole ring (cf. **3** and **4**) with concomitant bonding of the nucleophilic pyrrole to the nascent electrophilic C(6) of a putative imidazoline intermediate (phakellin numbering). Theme and variation are manifest through reaction of either the pyrrole's C(3) position (cf. **4**, the isophakellin skeleton) or the nitrogen (cf. **3**, the phakellin skeleton), and by the incorporation of heteroatoms at C(11) and/or C(12) of the precursor oroidin skeleton. One sponge isolate, dibromoagelaspongin (**6**),[5] stands alone among these monomeric oroidin/dihydrooroidin derivatives in that the initial connection between N(14) and the 2-aminoimidazole ring is forged to C(6) instead of C(10). In addition, the three heteroatoms (nitrogens) attached to C(6) and the two heteroatoms attached to C(10) require that cyclization of oroidin must be accompanied by a formal oxidation as well, a second point of distinction between **6** and the more numerous

(1) (a) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, *23*, 7–243. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753–1783. (c) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551–1565. (d) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931–948. (e) Pettit, G. R.; McNulty, J.; Herald, D. L.; Doubek, D. L.; Chapuis, J.-C.; Schmidt, J. M.; Tackett, L. P.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 180–183. (f) Gautschi, J. T.; Whitman, S.; Holman, T. R.; Crews, P. *J. Nat. Prod.* **2004**, *67*, 1256–1261.

(2) From *Agelas oroides*: (a) Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *J. Chem. Soc., Chem. Commun.* **1971**, *112*, 9–1130. From *Axinella verrucosa* and *Acanthella aurantiaca*: (b) Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767–768. From *Pseudaxinyssa cantharella*: (c) De Nanteuil, G.; Ahond, A.; Guilhem, J.; Poupat, C.; Tran Huu Dau, E.; Potier, P.; Pusset, M.; Pusset, J.; Laboute, P. *Tetrahedron* **1985**, *41*, 6019–6033. From *Agelas mauritiana*: (d) Tsukamoto, S.; Kato, H.; Hirota, H.; Fusetani, N. *J. Nat. Prod.* **1996**, *59*, 501–503. From *Acanthella carteri*: (e) Mancini, I.; Guela, G.; Amade, P.; Roussakis, C.; Francesco, P. *Tetrahedron Lett.* **1997**, *38*, 6271–6274. From *Agelas clathrodes*, *Agelas conifera*, *Agelas dispar*, and *Agelas longissima*: (f) Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Vallefuoco, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2283–2288. From *Stylissa carteri*: (g) Eder, C.; Proksch, P.; Wray, V.; Steube, K.; Bringmann, G.; Van Soest, R. W. M.; Sudarsono; Ferdinandus, E.; Pattisina, L. A.; Wiryowidagdo, S.; Moka, W. *J. Nat. Prod.* **1999**, *62*, 184–187. From *Agelas wiedenmeyeri*: (h) Assmann, M.; Lichte, E.; Van Soest, R. W. M.; Köck, M. *Org. Lett.* **1999**, *1*, 455–457. From *Agelas sventres*: (i) Assmann, M.; Zea, S.; Köck, M. *J. Nat. Prod.* **2001**, *64*, 1593–1595. From *Stylissa massa*: (j) Tasdemir, D.; Mallon, R.; Greenstein, M.; Feldberg, L. R.; Kim, S. C.; Collins, K.; Wojciechowicz, D.; Mangalindan, G. C.; Concepcion, G. P.; Harper, M. K.; Ireland, C. M. *J. Med. Chem.* **2002**, *45*, 529–532. From *Axinella damicornis*: (k) Hammami, S.; Ben Jannet, H.; Ciavatta, M. L.; Mollo, E.; Cimino, G.; Mighri, Z. *J. Soc. Algerienne Chim.* **2006**, *16*, 79–89. From *Stylissa caribica*: (l) Mohammed, R.; Peng, J.; Kelly, M.; Hamann, M. T. *J. Nat. Prod.* **2006**, *69*, 1739–1744.

(3) From *Agelas nemoecinata*: Pedpradab, S. Ph.D. thesis, Heinrich-Heine Universität, Düsseldorf, 2005.

(4) Grube, A.; Köck, M. *Org. Lett.* **2006**, *8*, 4675–4678.

(5) (a) Fedoreyev, S. A.; Ilyin, S. G.; Utkina, N. K.; Maximov, O. B.; Reshetnyak, M. V.; Antipin, M. Y.; Struchkov, Y. T. *Tetrahedron* **1989**, *45*, 3487–3492. (b) Piña, I. C.; White, K. N.; Cabrera, G.; Rivero, E.; Crews, P. *J. Nat. Prod.* **2007**, *70*, 613–617.

10.1021/jo900283g CCC: $40.75
Published on Web 03/30/2009

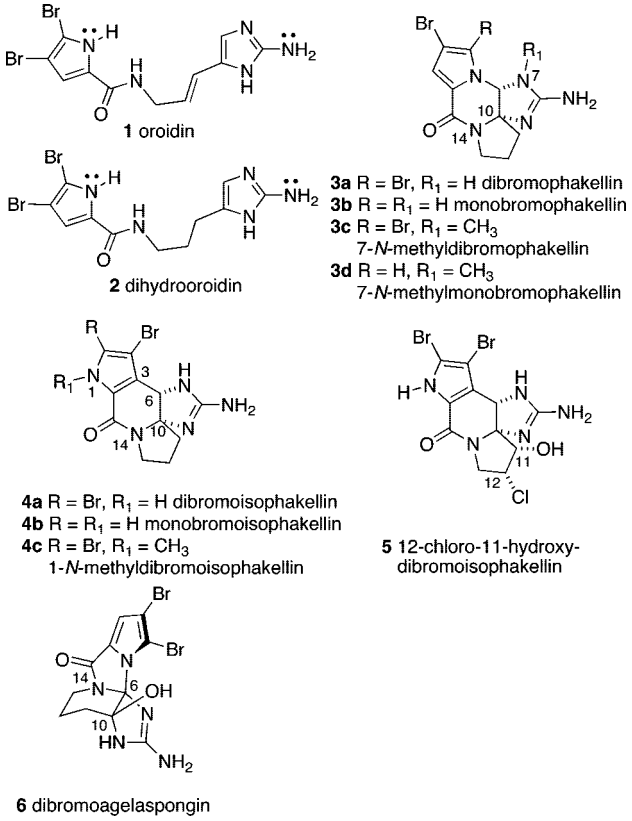


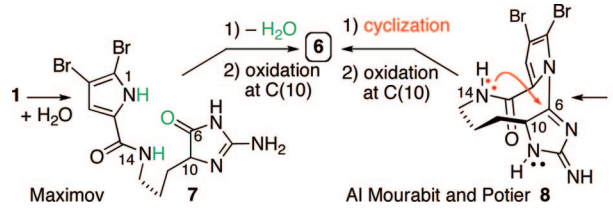
FIGURE 1. Members of the tetracyclic family of monomeric oroidin/dihydrooroidin derivatives.

phakellin/isophakellin species **3** and **4**, respectively. In fact, the triaminomethane unit within **6** has been described only rarely in the natural products arena.[6] Dibromoagelaspongin was coisolated with a methyl ether derivative (OCH_3 instead of OH), although that species is likely just an artifact of the methanol-mediated isolation procedure. Nevertheless, this observation points to the facility of nucleophile exchange at C(10), which in turn may inform synthesis planning for accessing the target **6**. The hydrogenolysis product of **6** displays no optical activity and is described as a racemate, although no optical activity measurements were reported for dibromoagelaspongin itself. This observation suggests, but does not demand, that **6** is racemic in the sponge as well.

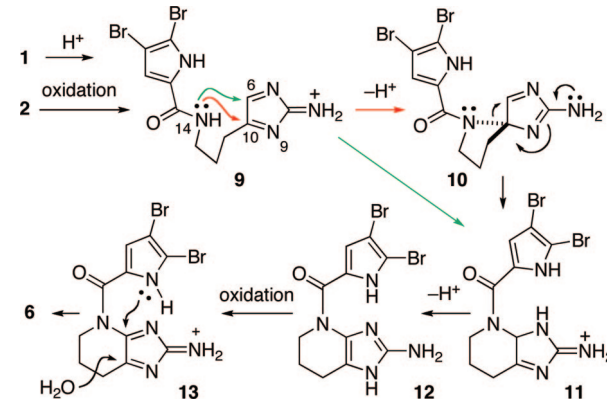
Many members of the tetracyclic oroidin-derived family of sponge metabolites exhibit promising biological activity against a range of diseases.[1b] For example, whereas dibromophakellin (**3a**) generated only modest cytotoxicity data (ED_{50}s of 15−20 μg/mL against several human cancer cell lines), **3a**'s naturally occurring formal hydrolysis product dibromophakellstatin (urea instead of guanidine, not shown) displayed potent activity (ED_{50}s < 1 μg/mL against these same cell lines).[1e] The N(7) methylated version **3c** inhibits 12-human lipoxygenase (10 μM), an enzyme implicated in cell proliferation.[1f] No biological activity studies for dibromoagelaspongin (**8**) have been reported to date.

Biosynthesis postulates for this structurally unique member **6** of the oroidin family have followed two distinct lines of thought, Scheme 1. The authors who first isolated and characterized **6** postulate that initial hydration/tautomerization of oroidin proceeds to afford an imidazolinone intermediate **7**, which

SCHEME 1. Speculation on the Subject of Dibromoagelaspongin Biosynthesis



SCHEME 2. Alternative Biosynthesis Proposal for Dibromoagelaspongin, Featuring Successive Formation of Two Electrophilic Triazafulvene Units from 2-Aminoimidazole

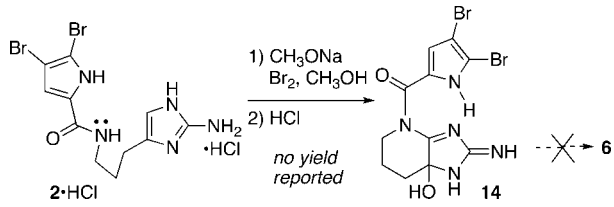


suffers formal dehydration via initial N(14)/C(6) condensation followed by N(1)/C(6) closure to complete the tetracyclic skeleton.[5a] Oxidation at C(10) by undescribed means then completes the biosynthesis. Maximov et al.'s proposal also leaves open the possibility that dibromophakellin itself serves as a precursor to **6** via a series of oxidations and rearrangements.[5a] An alternative biosynthesis rationale is offered by Potier and Al Mourabit,[1a] who consolidate their dibromoagelaspongin and dibromophakellin thinking by citing a common nine-membered ring intermediate **8** for both targets. This species is presumed to originate through nucleophilic addition of the pyrrole's N(1) to a transiently electrophilic C(6) derived from the 2-amino-4-alkenyl-imidazole portion of oroidin. Subsequent transannular cyclization of N(14) into (an sp^2 version of) C(10) would deliver the phakellin structure, whereas similar cyclization of N(14) into C(6) as shown provides the agelaspongin skeleton. Once again, a subsequent oxidation at C(10) by undescribed means would formulate the complete natural product **6**.

Neither of these biosynthesis proposals provides much guidance for developing a rational chemical synthesis plan for dibromoagelaspongin, given the mysterious C(10) oxidation that is required in each case. However, an alternative biosynthesis scheme, which utilizes two successive oxidative cyclizations from dihydrooroidin (or an isomerization/cyclization followed by an oxidative cyclization from oroidin), can be envisioned, Scheme 2. In this hypothesis, the triazafulvene electrophile illustrated in both **9** and **13** plays a prominent role in facilitating bond formation to assemble the core tetracycle. The formation of the distinctive N(14)/C(6) bond might occur directly as per **9** → **11**, or indirectly via either N or C migration (N shown for simplicity) within the intermediate phakellin-like spirocycle **10**. Both of these conceptualizations raise the specter of competition with simple formation of the phakellin structure by addition of the pyrrole's N(1) to the C(6) electrophile in **10**. Thus, an

(6) Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Org. Lett.* **2005**, *7*, 941–943.

SCHEME 3. Horne and Olofson's Approach to Dibromoagelaspongin

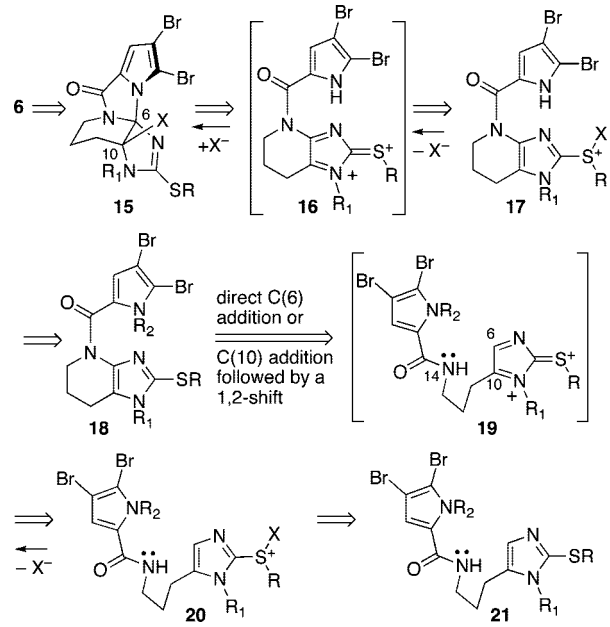


interesting aspect of this hypothesis is the basis for selective agelaspongin construction rather than phakellin formation; a priori it is not possible to invoke any explanation more thoughtful than enzymatic intervention. As the chemistry transpired (vide infra), a decisive role for protecting group(s) on N(1) and N(9) in steering intermediates like **9**/**10** toward the agelaspongin skeleton was revealed.

Horne and Olofson first considered this alternative biosynthesis proposal for dibromoagelaspongin and it guided their preliminary synthesis efforts in this area, Scheme 3.[7] Treatment of dihydrooroidin•HCl with base and the oxidant Br_2 furnished a product following acidification that they tentatively identified as the tricyclic species **14**. Unfortunately, they were not able to advance this species to the agelaspongin skeleton via subsequent transformations. Dibromoagelaspongin synthesis based on the biosynthetic blueprint of Scheme 2 is not necessarily contraindicated by the unpromising results of Scheme 3, provided that alternative approaches to the second cyclization step (e.g., **14** → **6**) are available. Thus, the formulation of an alternative bicyclic core to that contained in **14**, which features different and more reactive electrophilic functionality, might be sufficient to sustain a synthesis plan based upon the overall oxidative cyclization strategy.

A comprehensive synthesis program for the oroidin-based alkaloids based upon the premise that a Pummerer oxidation sequence might serve as a useful surrogate for 2-aminoimidazole → triazafulvene oxidation has been initiated.[8] Application of this chemistry to the dibromoagelaspongin problem is illustrated in retrosynthetic format, Scheme 4.[9] The hypothetical biosynthesis described in Scheme 2 serves as the guiding theme for this presumably biomimetic approach to the target. In this chemistry, the sulfur moiety in **21** serves as the initial locus of oxidation, thereby minimizing selectivity problems with alternative oxidation sites within this electron rich substrate. Then, through either a vinylogous or an additive Pummerer reaction mechanism, the sulfur's oxidation charge is translocated to either C(6) or C(10) of the imidazole nucleus (cf. **19**), where nucleophilic addition by the pendant N(14) nitrogen ensues. In the context of dibromoagelaspongin synthesis, both the R_1 substituent on N(9) and protection of the pyrrole's nitrogen provide the key to steering the transformation toward one or the other regiochemical outcome (C(6) vs C(10) attachment, vide infra). The desired bicycle **18**, reminiscent of the related species **14** reported by Horne and Olofson, is now poised for a

SCHEME 4. Biomimetic Retrosynthetic Analysis for Dibromoagelaspongin (6) Based upon the Biosynthetic Proposal Illustrated in Scheme 2



second Pummerer-mediated oxidative cyclization sequence to close the fourth ring and deliver the intact agelaspongin tetracycle of **15**. In this plan, selective generation of the reactive diazacyclopentadienethionium ion of **16** from the 2-thioimidazole unit in **18** sets up the final C−N closure, and hopefully unreactive intermediates like the iminoguanidine of **14** can be avoided. Finally, removal of the R_1 protecting group, replacement of the product's SR unit with NH_2 and OH-for-X exchange (recall the facility of dibromoagelaspongin methyl ether formation upon exposure of **6** to methanol during isolation) within **15** will complete the installation of the functionalized 2-aminoimidazoline moiety of the target dibromoagelaspongin.

Results and Discussion

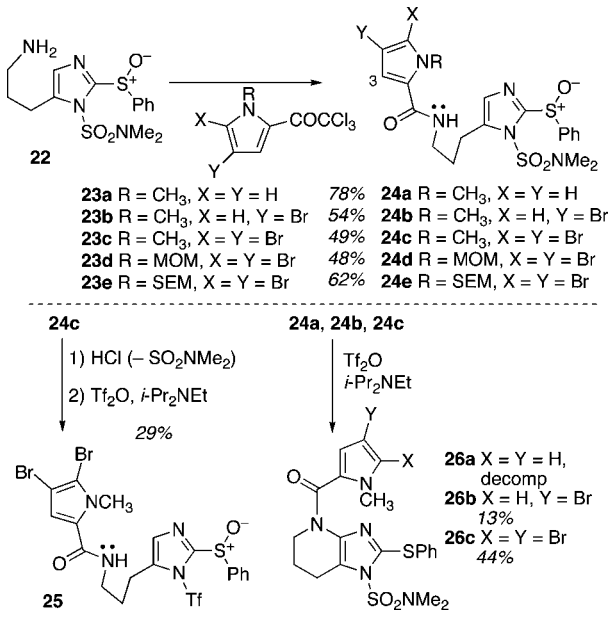
The entire dibromoagelaspongin synthesis project evolved from a serendipitous observation that emerged from attempts at securing the isophakellin skeleton from a dihydrooroidin precursor. Specifically, the hypothesis that simply protecting the pyrrole's nitrogen would steer cyclization to C(3) and the isophakellin structure was tested, Scheme 5. Initially, a series of N(1) protected dihydrooroidin analogues **24a**−**24e** were prepared by previously described methodology.[8g] Treatment of the exemplary species **24c** with aqueous HCl discharged the dimethylaminosulfonyl (DMAS) protecting group to afford the unprotected imidazole-2-sulfinate. Exposure of this sulfoxide to standard Pummerer initiation conditions (Tf_2O, *i*-Pr_2NEt) did not afford any cyclized material; rather, simple triflation of the free NH of the imidazole moiety led to the only characterized product, **25**. In an attempted workaround, reaction of the sulfide corresponding to the desulfamoylation product of **24c** with PhI(CN)OTf[8c] led to consumption of starting material without formation of any characterizable products. Since the free NH of this substrate appeared to be problematic, recourse was made to the simple expedient of leaving the DMAS group in place during the Pummerer chemistry. This plan was not without its concerns as well, as a lack of a proton to lose from the imidazole nitrogen implies that the electrophilic Pummerer intermediate

(7) Olofson, A. S. Ph.D. thesis, Columbia University, 1998.

(8) (a) Feldman, K. S.; Vidulova, D. B. *Org. Lett.* **2004**, *6*, 1869–1871. (b) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2004**, *6*, 2849–2852. (c) Feldman, K. S.; Vidulova, D. B. *Tetrahedron Lett.* **2004**, *45*, 5035–5037. (d) Feldman, K. S.; Vidulova, D. B.; Karatjas, A. G. *J. Org. Chem.* **2005**, *70*, 6429–6440. (e) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929–931. (f) Feldman, K. S.; Karatjas, A. G. *Org. Lett.* **2006**, *8*, 4137–4140. (g) Feldman, K. S.; Skoumbourdis, A. P.; Fodor, M. D. *J. Org. Chem.* **2007**, *72*, 8076–8086.

(9) Feldman, K. S.; Fodor, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 14964–14965.

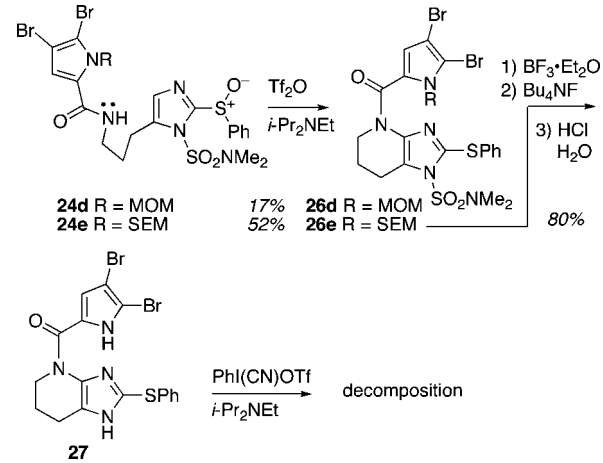
SCHEME 5. Approach to the Isophakellin Skeleton Leads Unexpectedly to the Bicyclic Core of the Agelaspongin Skeleton



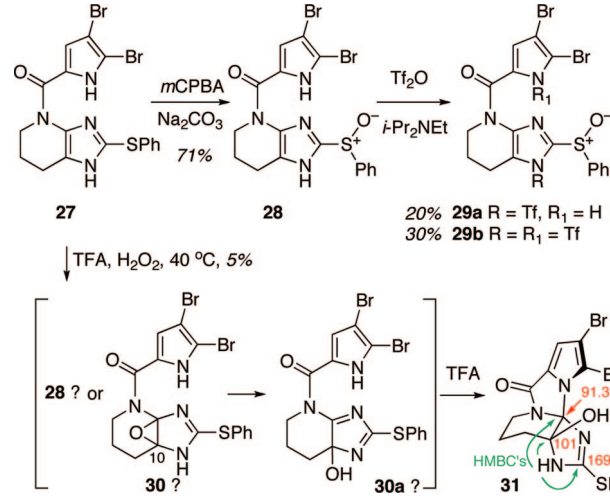
(cf. **19**, Scheme 4) might be doubly charged. Nevertheless, some precedent for this type of doubly cationic intermediate is known,[10] and so Pummerer-based oxidative cyclizations with **24a**−**24c** were explored. These dihydrooroidin derivatives in particular were selected with the expectation that the bromination pattern on the pyrrole ring might influence the nucleophilicity at C(3) in an exploitable manner. Oxidative cyclization did proceed smoothly but in modest yield for the cases where at least one pyrrole bromide was present, **24b** and **24c**. Remarkably, the cyclization proceeded with N(14) → C(6) bond formation rather than the expected N(14) → C(10) closure required for the isophakellin objective. Unfortunately, the pyrrole's C(3) position did not engage any intermediate electrophile in productive cyclization, thus thwarting any further progress toward the isophakellin series. Attempted PhI(CN)OTf-mediated oxidative cyclization of the sulfide corresponding to **24c** led to recovered starting material. Nevertheless, the end of the isophakellin project marked the beginning of the dibromoagelaspongin work, since the cyclization product **26c** maps nicely onto that particular oroidin-derived skeleton.

Continuation of this chemistry within the context of dibromoagelaspongin synthesis requires an unprotected pyrrole nitrogen, and the prospects for identifying reaction conditions for the deprotection of the N(1) methyl substituent within **26c** without compromising the structural integrity of the remainder of the molecule were not good. Therefore, the more readily deprotected MOM and SEM ethers **24d** and **24e**, respectively, were prepared and examined in a Pummerer-mediated oxidative cyclization, Scheme 6. The SEM-protected species **24d** was the clear winner among the substrates examined, as it provided the desired bicyclic product **26e** in the highest yield. The SEM protecting group could be removed in a two-step procedure followed by DMAS cleavage with mild acid to furnish the fully

SCHEME 6. Formation of the Fully Deprotected Bicycle of Dibromoagelaspongin



SCHEME 7. Second Serendipitous Reaction: Formation of the Dibromoagelaspongin Tetracycle



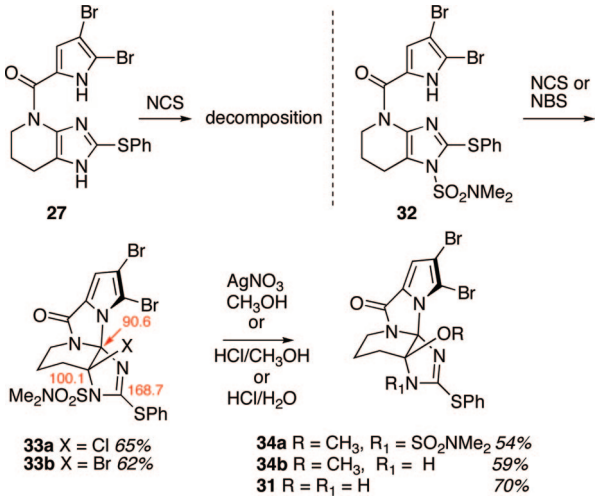
deprotected imidazole-2-sulfide **27** ready for subsequent oxidative cyclization chemistry. Preliminary scouting experiments with Stang's reagent (PhI(CN)OTf) and either **27** or an analogue with the SO_2NMe_2 group in place were not fruitful, leaving sulfide-to-sulfoxide oxidation followed by Pummerer chemistry as the most promising alternative.

Oxidation of the sulfide **27** to the sulfoxide **28** was achieved with *m*CPBA; inclusion of Na_2CO_3 was critical for obtaining the product in good yield (Scheme 7). Unfortunately, treatment of this sulfoxide with the standard Pummerer initiator Tf_2O/*i*-Pr_2NEt led to no more than nitrogen triflation to form **29a/29b**, a result reminiscent of the earlier Pummerer failure with the dihydrooroidin derivative **24c** (Scheme 5, **24c** → **25**). Attempts to prepare the N-SO_2NMe_2 protected variant of **28** by either direct sulfamoylation of **28** or by oxidation of a sulfide substrate **32** bearing the intact N-SO_2NMe_2 group, failed. However, the synthesis plan took an unexpected turn when alternative oxidation conditions with **27** were examined as part of a general survey of reagents. Thus, exposure of sulfide **27** to TFA and H_2O_2 (→ CF_3CO_3H)[11] at elevated temperature led to the formation of trace amounts of a tetracyclic species **31** that only

(10) (a) Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312–2317. (b) Yokoyama, A.; Ohwada, T.; Shudo, K. *J. Org. Chem.* **1999**, *64*, 611–617. (c) Saitoh, T.; Ichikawa, T.; Horiguchi, Y.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **2001**, *49*, 979–984. (d) Saitoh, T.; Shikiya, K.; Horiguchi, Y.; Sano, T. *Chem. Pharm. Bull.* **2003**, *51*, 667–672.

(11) Venier, C. G.; Squires, T. G.; Chen, Y. Y.; Smith, B. F. *J. Org. Chem.* **1982**, *47*, 3773–3774.

SCHEME 8. Formation of the Dibromoagelaspongin Tetracycle by Oxidative Cyclization



differed from the target dibromoagelaspongin by a (nontrivial) SPh → NH_2 exchange. The structure of **31** was secured by analysis of the ^{13}C NMR spectrum and HMQC/HMBC correlations (see structure **31** for key data), and by comparison of the spectral data to those reported for dibromoagelaspongin methyl ether.[5b] Efforts to improve the yield of **31** went unrewarded, and the small amount of material in hand precluded extensive efforts to effect NH_2 installation. Nevertheless, the acquisition of **31** prompted a new direction in the attempts to force closure of the final ring of dibromoagelaspongin. The mechanistic course of this transformation remains a matter of speculation, but plausible intermediates might include the epoxide **30** and its derived imino alcohol **30a**[12] or the sulfoxide **28**. Attempts to promote Pummerer reaction with concomitant N(1)/C(6) closure by treating **28** directly with various acids did not lead to any cyclization products.

The use of halonium ion sources to promote oxidative additions to imidazole derivatives within the oroidin series dates back to Büchi's seminal work on the dihydrooroidin → dibromophakellin transformation,[13a] and more recent efforts by Horne have illustrated how broad the scope of these transforms are.[7,13b] This background, along with the formation of **31** from **27**, suggested that prospecting among "X^+" sources might be profitable, Scheme 8. The initial entry point utilized *N*-chlorosuccinimide (NCS) with the free NH substrate **27** and led to rapid consumption of substrate without concomitant formation of any isolable/characterizable products. Recalling the lessons learned in the dihydrooroidin series **24c**−**24e**, retention of the DMAS imidazole protecting group appeared to be a logical modification of the system. In fact, this simple and expedient alternative was quickly rewarded with a high-yielding oxidative cyclization to afford the halogen-substituted tetracycles **33a** and **33b** from **32**, itself already in hand from the earlier studies. The structural assignment of **33a** was suggested by the position of characteristic ^{13}C NMR signals relative to those of **31** and dibromoagelaspongin (see structure **33a** for key data), and was secured by single crystal X-ray analysis (see Supporting Information).[14] The structure of the bromo analogue **33b** followed from comparison of its spectral data to those of **33a**. A discussion of the possible mechanism(s) of this transformation is deferred until later in this account. The anticipated lability of the halides in **33a/33b** (cf. formation of dibromoagelaspongin methyl ether by treatment of dibromoagelaspongin with methanol)[5] was realized by the ease with which **33a** and **33b** were converted to either the methyl ether **34** or the free alcohol **31**.

All that remained to complete the synthesis of dibromoagelaspongin was the aforementioned SPh → NH_2 transformation, and now sufficient material was available to systematically explore several options. In fact, this functional group interchange completed the conversion of a thiophenyl derivative of dibromophakellin into dibromophakellin itself, as reported earlier.[8g] Toward this end, conversion of the thioamidine of **31** into a urea moiety using CAN or $HgCl_2$ was explored. Unfortunately, the success realized in the phakellin series with these conditions was not matched in the dibromoagelaspongin case, as starting material was recovered in both cases, even under forcing conditions. Several direct displacements of the thiophenyl unit in **31** with NH_3, $EtCO_2NH_4$, or NaN_3 were attempted, but these efforts either returned sulfide or complete decomposition resulted. Indirect methods relying on initial sulfur oxidation prior to substitution held promise,[15] but conditions/reagents to effect this transformation with **31** or **34b** (SPh → SOPh or SO_2Ph) could not be identified. Again, starting material or decomposition resulted from treatment of **34b** with *m*CPBA, H_2O_2, *t*-BuOOH, DMDO, Oxone, or $NaIO_4$. At this point, it became apparent that both **31** and **34b** suffered from a insurmountable blend of global sensitivity coupled with thioamidine refractivity compared to the phakellin series, and the target molecule dibromoagelaspongin could not be reached via this chemistry.

The precedented procedures for effecting thioamidine → guanidine conversion were pursued with S-methyl variants rather than the S-phenyl unit of **31/34** (Scheme 9).[15] Thus, a workaround was implemented whereby the chemistry described in Schemes 6 and 8 with the SPh-bearing imidazole substrate was duplicated with an SCH_3 analogue. This plan was not without its risks, primarily in the initial Pummerer reaction where now the relatively acidic methyl protons of the $-S^+(X)-CH_3$ unit might deprotonate in competition with the desired N-lone pair participation within the imidazole ring. Nevertheless, this avenue was pursued commencing with the known imidazole derivative **35**[16] and utilizing chemistry developed in the SPh series. Fortunately, the Pummerer oxidative cyclization of **38** proceeded cleanly and without any evidence for untoward reaction at the $S-CH_3$ group, so the concerns expressed above appeared to be unfounded. The yield of isolated bicycle **39** was rather modest, but that deficiency is largely due to the compound's instability to chromatographic purification. The crude ^1H NMR spectrum of **39** suggests that the chemical yield is more in the 85% range, and carrying on

(12) (a) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965–992. (b) Sivappa, R.; Koswatta, P.; Lovely, C. J. *Tetrahedron Lett.* **2007**, *48*, 5771–5775. (c) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775.

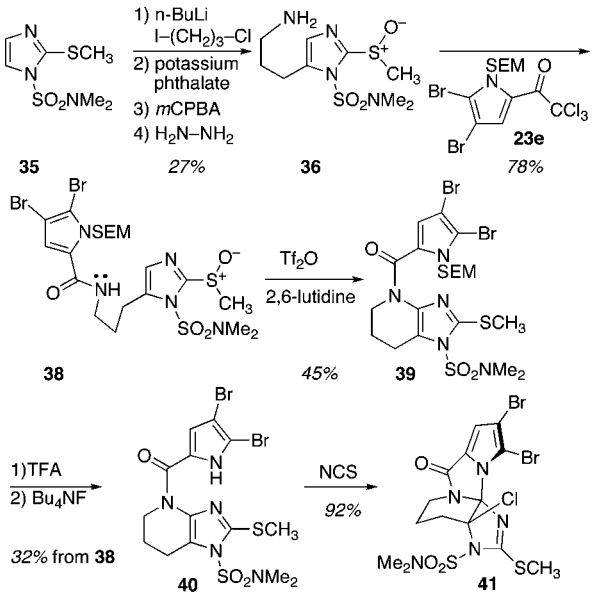
(13) (a) Büchi, G.; Foley, L. H. *J. Am. Chem. Soc.* **1982**, *104*, 1776–1777. (b) Olofson, A.; Yakushijin, K.; Horne, D. A. *J. Org. Chem.* **1998**, *63*, 1248–1253.

(14) Cambridge Crystallographic Data Centre deposition number: CCDC 714079. The data can be obtained free from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

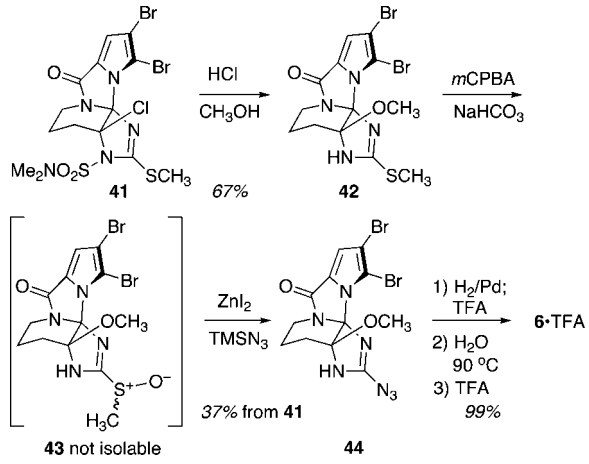
(15) (a) Meketa, M. L.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1443–1446. (b) Chauviere, G.; Bouteille, B.; Enanga, B.; de Albuquerque, C.; Croft, S. L.; Dumas, M.; Perie, J. *J. Med. Chem.* **2003**, *46*, 427–440. (c) Bierer, D. E.; O'Connell, J. F.; Parquette, F. R.; Thompson, C. M.; Rapoport, H. *J. Org. Chem.* **1992**, *57*, 1390. (d) Ronne, E.; Grivas, S.; Olsson, K. *Acta Chem. Scand.* **1994**, *48*, 823–830.

(16) Lee, J. J.; Haung, L.; Zaw, K.; Bauer, L. *J. Heterocyclic Chem.* **1998**, *35*, 81–89.

SCHEME 9. Preparation of an SCH_3 Analogue of the Dibromoagelaspongin Tetracycle



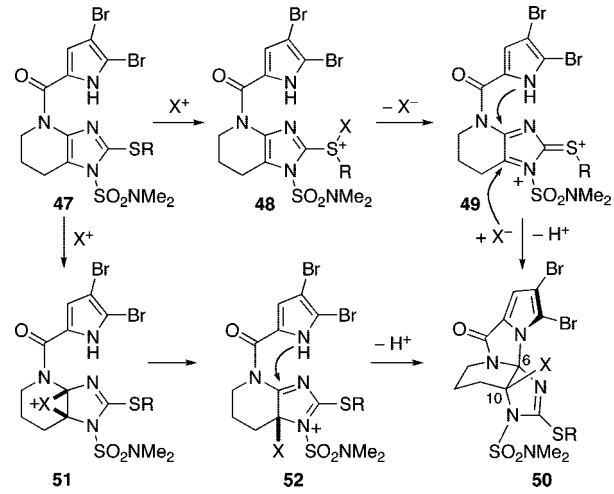
SCHEME 10. Completion of the Dibromoagelaspongin Synthesis



this material crude through the SEM deprotection steps led to an overall yield for the three-step sequence (**38** → **40**) of 32%. The second oxidative cyclization was mediated equally efficiently by NCS (92%) or by NBS (62%, Br replaces Cl in **41**). Thus, through this 9-step sequence, the frontier of the work was reached with the hopefully more tractable SCH_3 group now incorporated in the tetracycle **41**.

The completion of the dibromoagelaspongin synthesis is detailed in Scheme 10. Treatment of tetracycle **41** with acidic methanol furnished the methyl ether **42** with concomitant loss of the DMAS protecting group. Contrary to the SPh series, substitution of water for methanol in this transformation did not lead to a stable and isolable C(10) alcohol analogue of **42**. The basis for the difference in alcohol stability between the PhS- and CH_3S-containing species at present is unknown. Access to **42** sets the stage for the final test of the SCH_3 hypothesis—will this methyl analogue be susceptible to further sulfur oxidation to furnish a demonstrably more labile sulfinyl moiety? It was gratifying to observe that simple treatment of **42** with base and *m*CPBA did deliver an unstable sulfoxide **43** in good yield. Spectral data displayed by the crude material supported the

SCHEME 11. Mechanistic Dichotomy for the Halonium Ion Induced Oxidative Cyclization of 32 and 40 into Tetracycles 33 and 41, Respectively

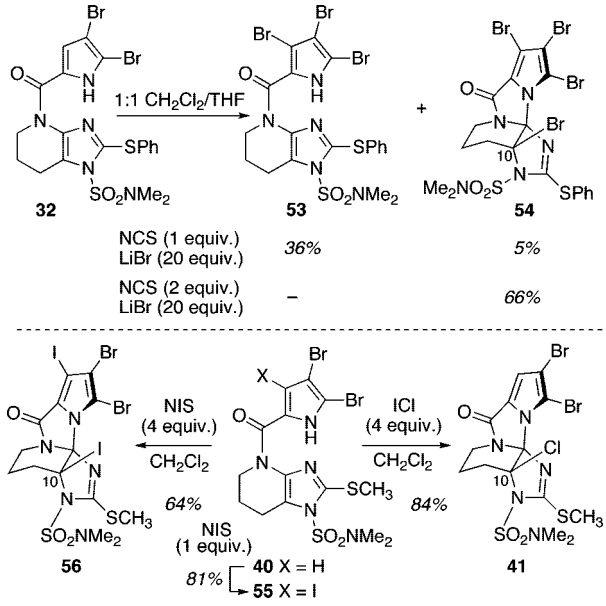


structural assignment; in particular a 0.6 ppm downfield shift for the methyl group was observed, and the ^1H NMR splitting patterns become much more complex due to the introduction of a new stereogenic center at sulfur. Finally, the mass spectrum of this unpurified species indicated that one oxygen atom had been incorporated in the starting material. The lability of **43** presaged successful replacement of the sulfur unit, and a procedure adapted from work of Kita[17] proved serviceable in this transformation. Treatment of the crude sulfoxide with ZnI_2 and $TMSN_3$ led cleanly to the corresponding azide **44**. Attempts to use ammonia directly in this displacement did not provide any isolable guanidine-containing product. Cleavage of the azide moiety without competitive scission of the C−Br bonds was required next. Although there are, in principle, procedures involving R_3P-type reagents that are documented to achieve this goal, it turned out that chemistry no more complicated than hydrogenolysis with Pd/H_2 sufficed to deliver the free amine without loss of Br. Finally, exposure of the TFA salt of the crude hydrogenation product to hot water quantitatively effected the OH-for-OCH_3 exchange to deliver the desired target (±)-dibromoagelaspongin as its TFA salt. The spectral data of the synthetic material matched in every way those data reported for the natural isolate.

One final unresolved issue in this work remains—the mechanism of the halonium ion-mediated oxidative cyclization of **32** and **40**. In principle, two distinct and unrelated mechanisms seem reasonable to consider, Scheme 11. The transform could proceed through an orthodox Pummerer reaction where the halonium ion serves as the initiator (**47** → **48** → **49**), or it could proceed via direct imidazole halogenation followed by pyrrole nitrogen trapping by the nascent C(6) electrophile (**47** → **51** → **52**). One approach to distinguishing between these two pathways lies in the manner by which the halogen becomes attached to C(10). In the Pummerer sequence, the halogen arrives as X^- in a second step following discharge from the activated sulfonium ion intermediate **48**. In the imidazole attack mechanism, the halogen presents as X^+ in the first step of the mechanism. Thus, employing a different exogenous halide (Y^-) in the presence of electrophilic halide X^+ may, in principle provide the means

(17) Kita, Y.; Shibata, N.; Yoshida, N.; Tohjo, T. *Tetrahedron Lett.* **1991**, *32*, 2375–2378.

SCHEME 12. Mechanistic Probes of the Halonium Ion Induced Oxidative Cyclization of 32/40



to differentiate between the two mechanistic pathways. The Pummerer pathway would yield product with halogen Y incorporated at C(10), whereas the imidazole attack pathway should only have X attached to C(10), provided that halogen exchange pathways are not operational.

With these thoughts as background, exposure of **32** to NCS (1 equiv) and LiBr (20 equiv) in a 1:1 mixture of CH_2Cl_2 and THF led to the first surprise of this mechanistic inquiry; fairly clean bromination of the pyrrole's free position, **32** → **53**, Scheme 12. A small amount of the tetrabromo cyclized material **54** was isolated as well. Increasing the amount of NCS to 2 equiv led exclusively to this tetrabrominated cyclized material. Whereas the formation of the C(10) brominated product **54** instead of the C(10) chloro alternative is consistent with the prediction of the Pummerer mechanism and not the imidazole attack alternative, the indisputable presence of some type of electrophilic bromine species (NBS?, Br_2?, BrCl?) as revealed by the bromination of the pyrrole ring clearly calls that conclusion into question.

Apparently, some sort of disproportionation (i.e., $X^+ + Y^- \rightarrow X^- + Y^+$) has compromised the results. Further insight into this process was gained by the control experiments described next. Mixing freshly recrystallized NBS with LiCl in d_8-THF/CD_2Cl_2 led to the second surprise of this series of experiments; ^{13}C NMR monitoring of the mixture indicated that signals corresponding to succinimide (δ 179.2 in this particular solvent mixture) were present but neither NBS (δ 174.2) nor NCS (δ 171.8) were evident. In addition, the reaction solution immediately turned orange, suggesting that Br_2 or perhaps BrCl had been formed. The complementary combination, NCS and LiBr was explored next. In this instance, mixing freshly recrystallized NCS with LiBr in d_8-THF/CD_2Cl_2 again led to instantaneous orange color formation. Furthermore, the ^{13}C NMR spectrum of this mixture did not display signals for NCS, NBS or succinimide. Thus, these results were taken to indicate that the mixtures NCS/LiBr or NBS/LiCl were not suitable for probing the questions raised in Scheme 11.

An alternative approach that would not be victimized by halide exchange was required. The commercially available reagent ICl held promise in this regard, as this species is well documented to react as an iodonium (I^+) and not a chloronium source.[18] Initial experiments with NIS (4 equiv) demonstrated that "I^+" is sufficient to promote the oxidative cyclization of the imidazole-2-methylsulfide **40** to provide the diiodotetracycle **56** in good yield, Scheme 12. Once again, initial electrophile attack at the pyrrole unit trumped all other reactivity options; reaction of **40** with 1 equiv of NIS led only to the pyrrole iodination product **55**. In the definitive experiment of this series, treatment of imidazole-2-methylsulfide **40** with ICl (4 equiv) afforded single isolable tetracyclic product **41**, identical in all respects to the product of **40** + NCS (Scheme 9), in excellent yield. This species unequivocally bore a chloride at C(10), and no pyrrole iodination took place. A control experiment (**56** + Bu_4NCl) confirmed that **41** did not arise from initial C(10) iodination followed by a subsequent halide exchange. This result (Cl at C(10) of **41**) can only be accommodated by the Pummerer mechanism of Scheme 11; the alternative direct imidazole attack mechanism would have placed an iodide at C(10).

The first total chemical synthesis of (±)-dibromoagelaspongin (**6**) has been accomplished via application of two successive Pummerer reactions on a dihydrooroidin-based substrate. The key recognition is that protection of the pyrrole nitrogen *and* the imidazole nitrogen is sufficient to steer the initial Pummerer-mediated oxidative cyclization to C(10) bond formation rather than the precedented C(6) bond formation of the phakellin series of oroidin derivatives. Argument-by-analogy from unambiguous results in a model system support the hypothesis that the second oxidative cyclization also proceeds through a Pummerer-type process that features an underutilized halonium ion initiation to trigger the multistep sequence and furnish the second N → C(6) bond that characterizes this unique target structure. Overall, this chemistry expands the repertoire of oroidin derivatives accessible by synthesis.

Experimental Section

General Procedure 1: Coupling of Trichloroacetyl Pyrrole Derivatives with Aminoimidazole Substrates. A stirring solution of aminoimidazole in either acetonitrile or DMF (0.1 M) was treated with Na_2CO_3 (1 equiv) followed by addition of the corresponding acyl pyrrole (1 equiv). The resulting solution was held at room temperature for 16 h. In cases where a solid precipitated, it was collected and rinsed with water (20 mL) and then with ether (50 mL) to yield an analytically pure product. In all other cases where no precipitate formed, the reaction mixture was concentrated in vacuo to yield a dark-yellow oil. Purification of this oil by flash column chromatography using the indicated eluent provided the pure carboxamide.

General Procedure 2: Triflic Anhydride-Mediated Pummerer Cyclizations. A stirring solution of amidosulfoxide in CH_2Cl_2 (0.05 M) was treated with *i*-Pr_2NEt (2 equiv) and then cooled to −78 °C. After 5 min, Tf_2O (1.1 equiv) was slowly added dropwise to the reaction mixture. After 10 min, the reaction mixture was rapidly warmed to room temperature and poured into ice-cold water. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2×), dried over Na_2SO_4, and concentrated to give a red oil. Purification of this oil by flash column chromatography using the indicated eluent provided the pure cyclization product.

Methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)-propyl]-amide (24a). Fol-

(18) (a) Bell, A. S.; Campbell, S. F.; Morris, D. S.; Roberts, D. A.; Stefaniak, M. H. *J. Med. Chem.* **1989**, *32*, 1552–1558. (b) Marsh, S. J.; Kartha, K. P. R.; Field, R. A. *Synlett* **2003**, *9*, 1376–1378.

lowing General Procedure 1, aminosulfoxide **22** (1.89 g, 5.30 mmol) in 25 mL of DMF was treated with acyl pyrrole **23a** (1.20 g, 5.30 mmol). Purification of the residue by flash column chromatography (gradient, 1%→20% acetone/EtOAc) gave carboxamide **24a** (1.85 g, 78%) as a tan solid. mp 70−72 °C; IR (thin film) 3347, 1637 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86−7.81 (m, 2H), 7.49−7.46 (m, 3H), 7.00 (s, 1H), 6.69 (t, J = 2.0 Hz, 1H), 6.53 (dd, J = 4.0, 1.7 Hz, 1H), 6.11 (t, J = 4.9 Hz, 1H), 6.05 (dt, J = 3.9, 2.6 Hz, 1H), 3.90 (s, 3H), 3.51−3.34 (m, 2H), 2.93 (s, 6H), 2.88−2.68 (m, 2H), 1.92 (quint, J = 6.9 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 162.1, 151.0, 143.0, 136.0, 131.7, 129.13, 129.11, 127.9, 126.2, 125.4, 111.4, 107.2, 38.4, 38.0, 36.6, 28.6, 23.0; LRMS (ESI) m/z (relative intensity) 464.1 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{20}H_{26}N_5O_4S_2]^+$, 464.1426, found 464.1440.

4-Bromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)-propyl]-amide (24b). Following General Procedure 1, aminosulfoxide **22** (0.450 g, 1.26 mmol) in 5 mL of DMF was treated with Na_2CO_3 (0.147 g, 1.39 mmol) followed by acyl pyrrole **23b** (0.424 g, 1.39 mmol). Purification of the residue by flash column chromatography (gradient, 1→20% acetone/EtOAc) gave carboxamide **24b** (0.372 g, 54%) as a white solid. mp 72−74 °C; IR (thin film) 3334, 1645 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82−7.79 (m, 2H), 7.46−7.44 (m, 3H), 6.97 (s, 1H), 6.64 (d, J = 1.8 Hz, 1H), 6.56 (d, J = 1.8 Hz, 1H), 6.47 (t, J = 5.8 Hz, 1H), 3.83 (s, 3H), 3.41−3.34 (m, 2H), 2.89 (s, 6H), 2.84−2.66 (m, 2H), 1.88 (quint, J = 7.0 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 161.0, 150.8, 142.9, 136.0, 131.7, 129.1, 129.0, 127.0, 126.2, 126.1, 113.4, 94.2, 38.4, 38.0, 36.7, 28.2, 22.9; LRMS (ESI) m/z (relative intensity) 542.1 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{20}H_{25}N_5O_4S_2Br]^+$, 542.0531, found 542.0560.

4,5-Dibromo-1-methyl-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)-propyl]-amide (24c). Following General Procedure 1, aminosulfoxide **22** (0.450 g, 1.26 mmol) in 5 mL of DMF was treated with Na_2CO_3 (0.147 g, 1.39 mmol) followed by acyl pyrrole **24c** (0.534 g, 1.39 mmol). Purification of the residue by flash column chromatography (gradient, 1→20% acetone/EtOAc) gave carboxamide **24c** (0.381 g, 49%) as a white solid. mp 61−62 °C; IR (thin film) 3337, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84−7.79 (m, 2H), 7.52−7.43 (m, 3H), 6.98 (s, 1H), 6.66 (s, 1H), 6.34 (t, J = 5.4 Hz, 1H), 3.91 (s, 3H), 3.49−3.34 (m, 2H), 2.93 (s, 6H), 2.89−2.67 (m, 2H), 1.90 (quint, J = 7.0 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 160.6, 150.9, 142.9, 136.0, 131.8, 129.2, 129.1, 127.4, 126.2, 113.6, 111.6, 97.8, 38.6, 38.1, 35.6, 28.4, 23.0; LRMS (ESI) m/z (relative intensity) 620.0 (90% M + H^+); HRMS (ESI) m/z calcd for $[C_{20}H_{24}N_5O_4S_2Br_2]^+$, 619.9636, found 619.9656.

4,5-Dibromo-1-methoxymethyl-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)-propyl]-amide (24d). Following General Procedure 1, aminosulfoxide **22** (0.450 g, 1.26 mmol) in 5 mL of DMF was treated with Na_2CO_3 (0.147 g, 1.39 mmol) followed by acyl pyrrole **23d** (0.626 g, 1.51 mmol). Purification of the residue by flash column chromatography (gradient, 60→100% EtOAc/hexanes) gave carboxamide **24d** (0.391 g, 48%) as a yellow solid. mp 62−64 °C; IR (thin film) 3327, 1651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.74−7.71 (m, 2H), 7.39−7.37 (m, 3H), 6.88 (s, 1H), 6.82 (t, J = 7.2 Hz, 1H), 6.72 (s, 1H), 5.63 (s, 2H), 3.32 (q, J = 7.2 Hz, 2H), 3.25 (s, 3H), 2.81 (s, 6H), 2.75−2.68 (m, 2H), 1.81 (quint, J = 7.2 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 160.1, 150.9, 142.9, 135.9, 131.8, 129.2, 129.1, 128.5, 126.3, 115.8, 111.0, 100.0, 76.8, 56.2, 38.8, 38.0, 28.3, 23.0; LRMS (ESI) m/z (relative intensity) 672.0 (100% M + Na^+); HRMS (ESI) m/z calcd for $[C_{21}H_{26}N_5O_5S_2Br_2]^+$, 649.9742, found 649.9749.

4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(2-Benzenesulfinyl-3-dimethylsulfamoyl-3H-imidazol-4-yl)-propyl]-amide (24e). Following General Procedure 1, aminosulfoxide **22** (3.60 g, 10.1 mmol) in 50 mL of acetonitrile was treated with Na_2CO_3 (1.20 g, 11.3 mmol) and acyl pyrrole **23e** (5.60 g, 11.2 mmol). Purification of the residue by flash column chromatography (EtOAc) gave carboxamide **24e** (4.62 g, 62%) as a yellow solid. mp 42−43 °C; IR (thin film) 3225, 1651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.84−7.81 (m, 2H), 7.48−7.46 (m, 3H), 6.98 (s, 1H), 6.87 (t, J = 5.4 Hz, 1H), 6.78 (s, 1H), 5.71 (s, 2H), 3.59 (t, J = 7.9 Hz, 2H), 3.42 (t, J = 6.5 Hz, 2H), 2.92 (s, 6H), 2.87−2.67 (m, 2H), 1.90 (quint, J = 7.2 Hz, 2H), 0.88 (t, J = 8.2 Hz, 2H), −0.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.9, 142.9, 135.9, 131.7, 129.1, 129.0, 128.7, 126.2, 116.0, 110.7, 99.8, 75.0, 66.2, 38.8, 28.2, 23.0, 17.8, −1.5; LRMS (ESI) m/z (relative intensity) 736.1 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{25}H_{36}N_5O_5SiS_2Br_2]^+$, 736.094, found 736.0262.

4,5-Dibromo-1-methyl-*N*-(3-(2-(phenylsulfinyl)-1-(trifluoromethylsulfonyl)-1H-imidazol-5-yl)propyl)-1H-pyrrole-2-carboxamide (25). To a stirring solution of protected amide **24c** (70 mg, 0.11 mmol) in 1 mL of THF was added aqueous HCl (1.5 M, 0.50 mL) and the reaction mixture was heated at reflux for 15 min. The reaction solution was cooled to room temperature and poured into ice-cold $NaHCO_3$ (5 mL). The resulting aqueous solution was extracted with EtOAc (2 × 20 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. This oil was immediately taken up in 5 mL of CH_2Cl_2, cooled to −78 °C, and sequentially treated with i-Pr_2NEt (0.040 mL, 0.24 mmol) and Tf_2O (0.020 mL, 0.13 mmol). After 10 min, the black solution was poured into 10 mL of ice-cold H_2O. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (70% Et_2O/hexanes) gave triflate **25** (21 mg, 29% over 2 steps) as a colorless oil. IR (thin film) 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88−7.85 (m, 2H), 7.56−7.50 (m, 3H), 7.17 (s, 1H), 6.62 (s, 1H), 6.21 (t, J = 5.8 Hz, 1H), 3.94 (s, 3H), 3.65 (q, J = 6.7 Hz, 2H), 2.68 (t, J = 7.4 Hz, 2H), 1.93 (quint, J = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 152.3, 145.8, 141.8, 132.7, 129.6, 127.4, 126.3, 118.4, 113.5, 111.6, 97.9, 38.2, 35.7, 28.1, 25.0; LRMS (ESI) m/z (relative intensity) 644.9 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{19}H_{18}N_4O_4Br_2S_2F_3]^+$, 644.9088, found 644.9075. R-SO_2CF_3 was not observed in the ^{13}C spectrum due to insufficient material.

4-(4-Bromo-1-methyl-1H-pyrrole-2-carbonyl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (26b). Following General Procedure 2, amidosulfoxide **24b** (0.039 g, 0.072 mmol) in 1.4 mL of CH_2Cl_2 was treated with i-Pr_2NEt (24 μL, 0.14 mmol) and Tf_2O (66 μL, 0.39 mmol). Purification of the residue by flash column chromatography (2% MeOH/CH_2Cl_2) gave cyclization product **26b** (5 mg, 13%) as a white gum. IR (thin film) 1637 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34−7.29 (m, 5H), 6.57 (d, J = 1.8 Hz, 1H), 6.16 (d, J = 1.8 Hz, 1H), 3.77 (dd, J = 7.2, 5.4 Hz, 2H), 3.62 (s, 3H), 3.02 (s, 6H), 2.90 (t, J = 6.8 Hz, 2H), 2.07 (quint, J = 6.5 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 160.0, 140.3, 138.5, 132.8, 129.9, 129.0, 128.3, 127.6, 125.7, 117.2, 116.1, 94.1, 43.6, 38.5, 35.7, 23.2, 22.7; LRMS (ESI) m/z (relative intensity) 524.0 100% (M + H^+); HRMS (ESI) m/z calcd for $[C_{20}H_{23}N_5O_3S_2Br]^+$, 524.0426, found 524.0442.

4-(4,5-Dibromo-1-methyl-1H-pyrrole-2-carbonyl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (26c). Following General Procedure 2, amidosulfoxide **24c** (0.040 g, 0.064 mmol) in 1.3 mL of CH_2Cl_2 was treated with i-Pr_2NEt (21 μL, 0.13 mmol) and Tf_2O (59 μL, 0.35 mmol). Purification of the residue by flash column chromatography (gradient, 0→5% MeOH/CH_2Cl_2) gave cyclization product **26c** (17 mg, 44%) as a white gum. IR (thin film) 1615 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5H), 6.21 (s, 1H), 3.78 (dd, J = 5.4, 3.5 Hz, 2H), 3.59 (s, 3H), 3.03 (s, 6H), 2.89 (t, J = 6.6 Hz, 2H), 2.08 (quint, J = 6.7 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 159.2, 141.4, 138.2, 133.7, 129.6, 129.09, 129.05, 129.0, 128.9, 116.6, 116.1, 97.5, 43.3, 38.5, 35.1, 23.2, 22.6; LRMS (ESI) m/z (relative intensity) 602.0 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{20}H_{22}N_5O_3S_2Br_2]^+$, 601.9531, found 601.9524.

4-(4,5-Dibromo-1-methoxymethyl-1H-pyrrole-2-carbonyl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (26d). Following General Procedure 2, amidosulfoxide **24d** (0.097 g, 0.15 mmol) in 1.4 mL of CH_2Cl_2 was treated with *i*-Pr_2NEt (49 μL, 0.30 mmol) and Tf_2O (137 μL, 0.810 mmol). Purification of the residue by flash column chromatography (1:1 EtOAc/hexanes) gave cyclization product **26d** (16 mg, 17%) as a white gum. IR (thin film) 1615 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33−7.30 (m, 2H), 7.29−7.26 (m, 3H), 6.25 (s, 1H), 5.49 (s, 2H), 3.77 (dd, J = 7.2, 3.6 Hz, 2H), 3.08 (s, 6H), 2.90 (t, J = 7.2 Hz, 2H), 2.70 (s, 3H), 2.08 (quint, J = 7.2 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 158.8, 142.3, 138.0, 134.4, 129.2, 129.14, 129.07, 128.3, 117.3, 116.4, 109.5, 99.3, 76.9, 55.6, 43.1, 38.5, 23.1, 22.5; LRMS (ESI) *m/z* (relative intensity) 632.0 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{21}H_{24}N_5O_4S_2Br_2]^+$, 631.9636, found 631.9597.

4-[4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrole-2-carbonyl]-2-phenylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (26e). Following General Procedure 2, amidosulfoxide **24e** (0.990 g, 1.34 mmol) in 100 mL of CH_2Cl_2 was treated with *i*-Pr_2NEt (465 μL, 2.81 mmol) and Tf_2O (453 μL, 2.67 mmol). Purification of the residue by flash column chromatography (3:2 Et_2O/hexanes) gave cyclization product **26e** (0.505 g, 52%) as a yellow solid. mp 86−88 °C; IR (thin film) 1615 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34−7.27 (m, 5H), 6.23 (s, 1H), 5.53 (s, 2H), 3.78 (dd, J = 5.4, 3.2 Hz, 2H), 3.18 (t, J = 8.3 Hz, 2H), 3.05 (s, 6H), 2.91 (t, J = 6.8 H, 2H), 2.08 (quint, J = 6.1 Hz, 2H), 0.68 (t, J = 8.3 Hz, 2H), −0.15 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.5, 142.8, 139.5, 135.1, 130.6, 130.5, 130.1, 129.8, 118.7, 118.0, 111.1, 100.7, 75.9, 66.7, 44.8, 40.0, 24.6, 24.1, 18.7, 0.00; LRMS (ESI) *m/z* (relative intensity) 718.0 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{25}H_{34}N_5O_4SiS_2Br_2]^+$, 718.0188, found 718.0145.

4-(4,5-Dibromo-1H-pyrrole-2-carbonyl)-2-phenylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (32). A stirring solution of SEM-protected bicyclopyrrole **26e** (1.94 g, 2.70 mmol) in 30 mL of CH_2Cl_2 was cooled to 0 °C and BF_3Et_2O (3.39 mL, 27.0 mmol) was added dropwise to the reaction mixture. After an additional 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature and held there for 3 h before being poured into 50 mL of ice-cold H_2O. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic fractions were dried over Na_2SO_4 and then concentrated to give a yellow oil. This oil was immediately taken up into 5 mL of THF and sequentially treated with ethylenediamine (362 μL, 5.40 mmol) followed by TBAF (1.0 M in THF, 27 mL, 27 mmol), and then the solution was heated at reflux for 30 min. The reaction mixture was allowed to cool to room temperature and then was poured into an ice-cold saturated NH_4Cl solution. The resulting mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated to give a red oil. Purification of this oil by flash column chromatography (Et_2O) gave deprotection product **32** (994 mg, 63% over 2 steps) as a yellow solid. When the crude pyrrole deprotection product **32** was carried on through the next step (removal of the DMAS group), the overall yield of the three-step sequence was 80%. mp 160−162 °C; IR (thin film) 3164, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 7.52−7.50 (m, 2H), 7.40−7.33 (m, 3H), 6.76 (app d, J = 2.8 Hz, 1H), 3.89 (dd, J = 7.5, 5.6 Hz, 2H), 3.07 (s, 6H), 2.90 (t, J = 6.6 Hz, 2H), 2.04 (quint, J = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 158.2, 138.1, 137.6, 132.0, 130.2, 129.0, 128.3, 127.5, 118.1, 116.3, 104.7, 97.8, 43.8, 38.1, 22.8, 22.2; LRMS (ESI) *m/z* (relative intensity) 587.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{20}N_5O_3S_2Br_2]^+$, 587.9374, found 587.9399.

(4,5-Dibromo-1H-pyrrol-2-yl)-(2-phenylsulfanyl-1,5,6,7-tetrahydro-imidazo[4,5-b]pyridin-4-yl)-methanone (27). Following SEM deprotection of bicycle **26e** (1.00 g, 1.39 mmol), the crude DMAS protected bicycle **32** (714 mg) was taken up in 50 mL of THF and aqueous HCl (1.5 M, 27 mL) was added to the reaction solution. After 16 h at room temperature, the reaction mixture was carefully poured into 50 mL of ice-cold $NaHCO_3$. The resulting mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic fractions were dried with Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (Et_2O) gave the deprotection product **27** (537 mg, 80% over the 3 step sequence) as a yellow solid. mp 122−124 °C; IR (thin film) 1592 cm^{-1}; ^1H NMR (300 MHz, d_4-MeOH) δ 7.33−7.21 (m, 5H), 6.65 (br s, 1H), 3.77 (br s, 2H), 2.71 (t, J = 6.5 Hz, 2H), 2.06 (quint, J = 6.3 Hz, 2H); ^{13}C (75 MHz, d_6-DMSO) δ 157.8, 137.8, 135.6, 129.6, 129.5, 127.7, 127.5, 126.6, 118.8, 116.6, 104.3, 97.8, 44.4, 22.9 19.4; LRMS (ESI) *m/z* (relative intensity) 480.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{15}N_4OSBr_2]^+$, 480.9333, found 480.9348.

(2-Benzenesulfinyl-1,5,6,7-tetrahydro-imidazo[4,5-b]pyridin-4-yl)-(4,5-dibromo-1H-pyrrol-2-yl)-methanone (28). A stirring solution of bicycle **27** (200 mg, 0.416 mmol) in 20 mL of CH_2Cl_2 at room temperature was sequentially treated with Na_2CO_3 (93 mg, 0.87 mmol) and then *m*CPBA (103 mg, 0.416 mmol). After 30 min, the reaction mixture was poured into ice-cold $NaHCO_3$ (20 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (gradient, 80→100% EtOAc/hexanes) gave sulfoxide **28** (147 mg, 71%) as a tan solid. mp 110−112 °C; IR (thin film) 3112, 1581 cm^{-1}; ^1H NMR (400 MHz, d_4-MeOH) δ 7.71−7.69 (m, 2H), 7.56−7.51 (m, 3H), 6.56 (s, 1H), 4.00 (m, 1H), 3.81 (m, 1H), 2.67 (t, J = 6.7 Hz, 2H), 1.99 (quint, J = 7.2 Hz, 2H); ^{13}C (90 MHz, d_6-DMSO) δ 158.7, 142.7, 141.8, 135.3, 132.4, 130.4, 127.0, 125.1, 121.7, 117.2, 106.2, 98.8, 46.1, 22.8, 20.2; LRMS (ESI) *m/z* (relative intensity) 496.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{15}N_4O_2SBr_2]^+$, 496.9282, found 496.9325.

(2-Benzenesulfinyl-1-trifluoromethanesulfonyl-1,5,6,7-tetrahydro-imidazo[4,5-b]pyridin-4-yl)-(4,5-dibromo-1H-pyrrol-2-yl)-methanone (29a) and (2-Benzenesulfinyl-1-trifluoromethanesulfonyl-1,5,6,7-tetrahydro-imidazo[4,5-b]pyridin-4-yl)-(4,5-dibromo-1-trifluoromethanesulfonyl-1H-pyrrol-2-yl)-methanone (29b). Following General Procedure 2, bicycle **28** (0.020 g, 0.040 mmol) in 8 mL of CH_2Cl_2 was treated with *i*-Pr_2NEt (14 μL, 0.084 mmol) and Tf_2O (13 μL, 0.042 mmol). Purification of the residue by flash column chromatography (gradient, 30→60% Et_2O/hexanes) gave monotriflation product **29a** (5 mg, 20%) as a white tacky solid and bistriflation product **29b** (9 mg, 30%) as a colorless oil. Spectral data for **29a**: IR (thin film) 3172, 1607 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 12.8 (br s, 1H), 7.71−7.55 (m, 5H), 6.55 (d, J = 2.7 Hz, 1H), 3.98−3.90 (br m, 1H), 3.62−3.57 (br m, 1H), 2.81 (br m, 2H), 2.11−1.93 (br m, 2H); ^{13}C (75 MHz, d_6-DMSO) δ 158.4, 149.1, 141.1, 139.5, 132.4, 129.4, 126.8, 126.4, 120.1, 117.0, 106.0, 98.3, 44.4, 22.0, 20.6; LRMS (ESI) *m/z* (relative intensity) 628.7 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{18}H_{14}N_4O_4F_3S_2Br_2]^+$, 628.8775, found 628.8779. R-SO_2CF_3 was not observed in ^{13}C spectrum due to insufficient material. Spectral data for **29b**: IR (thin film) 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.55 (m, 5H), 6.66 (br s, 1H), 4.03 (br m, 1H), 3.74 (br m, 1H), 2.90 (s, 2H), 2.20−2.03 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 151.5, 139.0, 133.3, 132.5, 129.6, 125.7, 121.05, 121.03, 118.2, 116.76, 116.72, 42.4, 21.1, 20.9; LRMS (ESI) *m/z* (relative intensity) 760.8 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{13}N_4O_6S_3Br_2F_6]^+$, 760.8268, found 760.8254. R-SO_2CF_3 was not observed in ^{13}C spectrum due to insufficient material.

1H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridin-8-one, 2-(phenylthio)-10,11-dibromo-3a,4,5,6-tetrahydro-3a-hydroxy- 31. Method A. A stirring solution of bicycle 27 (97 mg, 0.20 mmol) in 5 mL of CH_2Cl_2 was treated with trifluoroperoxy-

acetic acid (4 M, 50 μL, 0.20 mmol) and the reaction solution was warmed to 40 °C and held at this temperature for 16 h. The reaction mixture was then allowed to cool to room temperature and poured into saturated aqueous $NaHCO_3$ (5 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic fractions were combined, dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography gave hydroxytetracycle 31 (6 mg, 5%) and recovered starting material 27 (41 mg).

Method B. To a stirring solution of bromotetracycle **33b** (100 mg, 0.150 mmol) in 10 mL of THF was added 10 mL of a 1.5 M HCl solution. The reaction mixture was heated to 65 °C for 16 h after which time it was cooled to room temperature and then poured into 10 mL of ice-cold NH_4OH. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (Et_2O then EtOAc) gave hydroxytetracycle **31** (52 mg, 70%) as a white oil. IR (thin film) 3216, 1693 cm^{-1}; ^1H NMR (300 MHz, d_4-MeOH) δ 7.69−7.66 (m, 2H), 7.51−7.42 (m, 3H), 6.65 (s, 1H), 3.93 (m, 1H), 3.16 (m, 1H), 2.05−1.93 (m, 2H), 1.73−1.60 (m, 2H); ^{13}C NMR (125 MHz, d_6-DMSO) δ 169.8, 156.9, 134.8, 129.5, 129.3, 126.9, 126.5, 107.0, 102.6, 102.8, 100.9, 91.4, 35.9, 33.3, 17.2; LRMS (ESI) *m/z* (relative intensity) 496.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{15}N_4O_2SBr_2]^+$, 496.9282, found 496.9284.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridine-3-sulfonamide, 10,11-dibromo-3a-chloro-3a,4,5,6-tetrahydro-*N*,*N*-dimethyl-2-(phenylthio)-8-oxo- (33a). A stirring solution of bicycle **32** (25 mg, 0.042 mmol) in 1 mL of CH_2Cl_2 was treated with NCS (11 mg, 0.084 mmol). After 5 min, the reaction mixture was diluted with CH_2Cl_2 to a volume of 20 mL and poured into 10 mL of ice-cold H_2O. The organic layer was sequentially washed with H_2O (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), 1 M H_3PO_4 (1 × 10 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (3:2 Et_2O/hexanes) gave tetracycle **33a** (17 mg, 65%) as a white solid. A small portion of this solid was dissolved in acetone and allowed to evaporate slowly over 72 h, which resulted in the growth of an X-ray quality crystal. mp 146−148 °C; IR (thin film) 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59−7.57 (m, 2H), 7.46−7.38 (m, 3H), 6.66 (s, 1H), 4.08 (dt, *J* = 13.2, 8.7 Hz, 1H), 3.16 (s, 6H), 3.11−2.96 (m, 2H), 2.16 (ddd, *J* = 12.3, 8.0, 3.2 Hz, 1H), 1.90 (m, 1H), 1.72 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 168.7, 157.1, 135.4, 130.6, 129.5, 127.2, 125.9, 109.4, 105.2, 102.7, 100.1, 90.6, 38.2, 37.1, 35.6, 17.7; LRMS (ESI) *m/z* (relative intensity) 621.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{19}N_5O_3S_2ClBr_2]^+$, 621.8985, found 621.9014.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridine-3-sulfonamide, 3a,10,11-tribromo-3a,4,5,6-tetrahydro-*N*,*N*-dimethyl-2-(phenylthio)-8-oxo- (33b). A stirring solution of bicycle **32** (10 mg, 0.017 mmol) in 1 mL of CH_2Cl_2 was treated with NBS (6.0 mg, 0.034 mmol). After 5 min, the reaction mixture was diluted with CH_2Cl_2 to a volume of 20 mL and poured into 10 mL of ice-cold H_2O. The organic layer was sequentially washed with H_2O (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), 1 M H_3PO_4 (1 × 10 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (14:5:1 Et_2O/hexanes/CH_2Cl_2) gave tetracycle **33b** (6.6 mg, 62%) as a white solid which was unavoidably contaminated by a small amount of tetrabromo compound **54**. Spectral Data for **33b**: mp 143−144 °C; IR (thin film) 1716 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.60−7.56 (m, 2H), 7.45−7.36 (m, 3H), 6.67 (s, 1H), 4.11 (dt, *J* = 13.0 7.9 Hz, 1H), 3.17 (s, 6H), 3.10 (m, 1H), 3.01 (m, 1H), 2.46 (ddd, *J* = 14.4, 11.6, 3.2 Hz, 1H), 1.82 (m, 1H), 1.70 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 168.7, 157.2, 135.5, 130.6, 129.6, 127.1, 125.9, 109.3, 105.2, 102.4, 100.2, 83.6, 39.6, 38.2, 36.2, 18.6; LRMS (ESI) *m/z* (relative intensity) 665.8 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{19}N_5O_3S_2Br_3]^+$, 665.8479, found 665.8492.

Tetracyclic Methyl Ether (34a). A stirring solution of chlorotetracycle **33a** (3.0 mg, 0.0048 mmol) in 750 μL of MeOH was treated with $AgNO_3$ (15 mg, 0.088 mmol) and the reaction mixture was held at room temperature for 16 h after which time it was heated to 45 °C for an additional 1 h. The resulting blue solution was allowed to cool to room temperature and then concentrated. The residue was dissolved in 5 mL of $CHCl_3$ and poured into H_2O (5 mL). The resulting solution was partitioned between $CHCl_3$ and H_2O, and the organic layer was washed with H_2O (1 × 5 mL), dried over Na_2SO_4, and then concentrated to give a colorless oil. Purification of this oil by flash column chromatography (hexanes then Et_2O) gave methyl ether **34a** (1.6 mg, 54%) as a white semisolid. IR (thin film) 1712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H), 7.42−7.34 (m, 3H), 6.66 (s, 1H), 4.08 (dt, *J* = 13.1, 9.2 Hz, 1H), 3.10 (s, 6H), 3.01 (m, 1H), 2.99 (s, 3H), 2.76 (m, 1H), 2.06 (m, 1H), 1.87−1.75 (m, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 167.9, 157.2, 135.4, 130.3, 129.4, 127.3, 126.6, 109.2, 104.8, 103.1, 100.3, 98.8, 52.3, 38.4, 34.3, 25.1, 16.6; LRMS (ESI) *m/z* (relative intensity) 617.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{20}H_{22}N_5O_4S_2Br_2]^+$, 617.9480, found 617.9460.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridin-8-one, 2-(Phenylthio)-10,11-dibromo-3a,4,5,6-tetrahydro-3a-methoxy-TFA Salt (34b). To a stirring solution of chlorotetracycle **33a** (0.150 g, 0.240 mmol) in 4.8 mL of MeOH was added HCl (conc, 240 μL), and the reaction solution was held at room temperature for 16 h after which time it was concentrated to ∼1 mL and then diluted with 30 mL of CH_2Cl_2. This organic solution was washed with $NaHCO_3$ (1 × 20 mL), dried over Na_2SO_4, and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (gradient, 80→100% Et_2O/hexanes) gave methyl ether **34b** (86 mg, 59%) as a white solid after conversion to its TFA salt. [Note: Fractions from column chromatography containing the desired product were combined and TFA (100 μL) was added before concentrating in vacuo.] IR (thin film) 1694 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.79−7.76 (m, 2H), 7.64−7.54 (m, 3H), 6.72 (s, 1H), 3.98 (dt, *J* = 13.0, 8.6 Hz, 1H), 3.56 (s, 3H), 3.25 (m, 1H), 2.37 (m, 1H), 2.14 (m, 1H), 1.83−1.65 (m, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 174.7, 158.8, 137.1, 133.4, 131.9, 127.9, 123.0, 110.5, 106.4, 105.7, 97.1, 95.3, 52.3, 37.6, 29.4, 17.3; LRMS (ESI) *m/z* (relative intensity) 510.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{18}H_{17}N_4O_2SBr_2]^+$, 510.9439, found 510.9445.

5-(3-Amino-propyl)-2-methanesulfinyl-imidazole-1-sulfonic Acid Dimethylamide (36). A stirring solution of sulfide **35**[15] (20.8 g, 94.0 mmol) in 500 mL of THF was cooled to −78 °C and *n*-BuLi (45.0 mL, 113 mmol) was added dropwise to the reaction solution over 15 min. After an additional 45 min, the resulting brown solution was treated with 1-chloro-3-iodopropane (11.9 mL, 113 mmol), and the reaction mixture was allowed to slowly warm to room temperature over 16 h after which time 200 mL of saturated NH_4Cl and 100 mL of H_2O were added sequentially. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (1 × 150 mL), dried over Na_2SO_4, and concentrated to give a dark-yellow oil. Purification of this oil by flash column chromatography (gradient, 33%→40% EtOAc/hexanes) gave the chloropropyl imidazole product (25.6 g, 91%) as a pale-yellow oil. IR (thin film) 2930 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.81 (s, 6H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.43 (s, 3H), 1.96 (quint, *J* = 6.5 Hz, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 146.9, 133.0, 127.4, 43.7, 37.9, 30.6, 23.1, 14.8; LRMS (ESI) *m/z* (relative intensity) 298.1 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_9H_{17}N_3O_2S_2]^+$, 298.0451, found 298.0465.

To a stirring solution of this chloride (25.0 g, 83.9 mmol) in 420 mL of DMF was added potassium phthalate (18.6 g, 101 mmol). The resulting suspension was heated to 80 °C and held at this temperature for 16 h after which time the reaction mixture was cooled to room temperature and filtered to remove any remaining

solids. The filtrate was collected and partitioned between CH_2Cl_2 (500 mL) and H_2O (100 mL). The aqueous layer was extracted with CH_2Cl_2 (1 × 500 mL) and the combined organic fractions were sequentially washed with H_2O (2 × 500 mL) and brine (saturated, 500 mL), dried over Na_2SO_4 and concentrated to give a brown oil. Purification of this oil by flash column chromatography (gradient, 30→90% EtOAc/hexanes) gave the phthalimide product (18.6 g, 54%) as a white solid. mp 108−109 °C; IR (thin film) 1711 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.86−7.83 (m, 2H), 7.73−7.70 (m, 2H), 6.78 (app t, J = 1.1 Hz, 1H), 3.78 (t, J = 6.8 Hz, 2H), 2.93 (s, 6H), 2.76 (app dt, J = 8.3, 1.1 Hz, 2H), 2.57 (s, 3H), 2.06−1.98 (quint, J = 7.6 Hz, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 168.4, 147.4, 134.0, 133.9, 132.1, 127.5, 123.2, 38.2, 37.4, 27.4, 23.8, 15.3; LRMS (ESI) *m/z* (relative intensity) 409.2 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{21}N_4O_4S_2]^+$, 409.1004, found 409.1011.

A stirring solution of this phthalimidosulfide (0.630 g, 1.54 mmol) in 30 mL of CH_2Cl_2 was cooled to 0 °C and treated with *m*CPBA (75% purity, 0.390 g, 1.70 mmol). After 15 min, the reaction solution was warmed to room temperature and held at this temperature for an additional 1 h after which time the reaction mixture was poured into aqueous $NaHCO_3$ (30 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (1 × 30 mL). The organic fractions were combined, dried with Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (80% EtOAc/hexanes then 25% acetone/EtOAc) gave the phthalimidosulfoxide product (0.646 g, 99%) as a tacky white gum; IR (thin film) 1714 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.81−7.77 (m, 2H), 7.71−7.68 (m, 2H), 7.01 (s, 1H), 3.76 (t, J = 6.8 Hz, 2H), 2.98 (s, 3H), 2.95 (s, 6H), 2.89 (m, 1H), 2.72 (m, 1H), 2.09−1.99 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.2, 150.7, 135.7, 134.0, 131.8, 128.5, 123.1, 40.9, 38.0, 37.1, 27.0, 23.1; LRMS (ESI) *m/z* (relative intensity) 425.1 (100% M+H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{21}N_4O_5S_2]^+$: 425.0953, found 425.0951.

To a stirring solution of this phthalimide (11.0 g, 25.9 mmol) in 500 mL of EtOH was added anhydrous hydrazine (16.3 mL, 518 mmol). The reaction solution was heated at reflux for 30 min after which time a white precipitate had formed. The reaction mixture was then cooled to room temperature and partitioned between H_2O (300 mL) and $CHCl_3$ (400 mL). The aqueous layer was extracted with $CHCl_3$ (1 × 100 mL) and the combined organic fractions were washed with brine (1 × 150 mL), dried over Na_2SO_4 and concentrated to give amine **36** (4.20 g, 55%) as a colorless oil which required no further purification. IR (thin film) 3342 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.91 (s, 1H), 2.93 (s, 3H), 2.91 (s, 6H), 2.86−2.61 (m, 4H), 1.79−1.70 (m, 2H), 1.33 (br s, 2H); ^{13}C (90 MHz, $CDCl_3$) δ 150.2, 136.7, 128.2, 41.1, 40.7, 37.9, 31.4, 22.8; LRMS (ESI) *m/z* (relative intensity) 295.1 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_9H_{19}N_4O_3S_2]^+$, 295.0899, found 295.0917.

4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrole-2-carboxylic Acid [3-(3-dimethylsulfamoyl-2-methanesulfinyl-3H-imidazol-4-yl)-propyl]-amide (38). A solution of SEM protected pyrrole **23e** (0.306 g, 0.612 mmol) in 5 mL of DMF was added to a neat mixture of amine **36** (0.150 g, 0.510 mmol) and Na_2CO_3 (0.60 g, 0.56 mmol) via cannula. After 15 min, the reaction solution was concentrated to give a brown oil. Purification of this oil by flash column chromatography (EtOAc then 25% acetone/EtOAc) gave amidosulfoxide **38** (0.269 g, 78%) as a white gum. IR (thin film): 1651 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.80 (t, J = 5.4 Hz, 1H), 6.79 (s, 1H), 5.73 (s, 2H), 3.61 (t, J = 7.9 Hz, 2H), 3.46 (ddd, J = 12.6, 6.8, 2.9 Hz, 2H), 3.03 (s, 3H), 2.99 (s, 6H), 2.91 (m, 1H), 2.76 (m, 1H), 1.96 (quint, J = 7.2 Hz, 2H), 0.89 (t, J = 8.2 Hz, 2H), −0.03 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.1, 150.5, 136.3, 128.8, 128.7, 116.0, 110.8, 99.9, 75.1, 66.3, 40.8, 38.9, 38.2, 28.5, 23.2, 17.8, −1.46; LRMS (ESI) *m/z* (relative intensity) 674.0 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{20}H_{34}N_5O_5S_2Br_2Si]^+$, 674.0137, found 674.0142.

4-[4,5-Dibromo-1-(2-trimethylsilanyl-ethoxymethyl)-1H-pyrrole-2-carbonyl]-2-methylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (39). To a stirring solution of amidosulfoxide **38** (0.200 g, 0.296 mmol) in 5.9 mL of CH_2Cl_2 was added 2,6-lutidine (72 μL, 0.62 mmol) and the reaction mixture was cooled to −78 °C. After 5 min, Tf_2O (55 μL, 0.33 mmol) was added and the reaction solution turned from colorless to light yellow. After 5 additional min, the reaction mixture was diluted with CH_2Cl_2 to a total volume of 15 mL and then poured into ice-cold H_2O (5 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (1 × 10 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give a yellow foam. Purification of this foam by flash column chromatography (1:1:1 Et_2O/hexanes/CH_2Cl_2) gave bicycle **39** (88 mg, 45%) as a tacky white gum. IR (thin film): 1616 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.40 (s, 1H), 5.55 (s, 2H), 3.85−3.82 (m, 2H), 3.53 (t, J = 8.3 Hz, 2H), 2.95 (s, 6H), 2.84 (t, J = 7.2 Hz, 2H), 2.27 (s, 3H), 2.05 (quint, J = 6.1 Hz, 2H), 0.84 (t, J = 8.3 Hz, 2H), −0.09 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 159.4, 143.8, 137.6, 129.1, 116.7, 115.8, 108.5, 99.0, 75.2, 65.9, 43.8, 38.3, 22.8, 22.2, 17.6, 15.0, −1.52; LRMS (ESI) *m/z* (relative intensity) 656.1 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{20}H_{32}N_5O_4S_2Br_2Si]^+$, 656.0005, found 656.0032.

4-(4,5-Dibromo-1H-pyrrole-2-carbonyl)-2-methylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (40). Following the Pummerer-mediated cyclization of amidosulfoxide **38** (3.20 g, 4.73 mmol) the crude material **39** (3.71 g) was immediately taken up in 100 mL of CH_2Cl_2 and TFA (20 mL) was added to the reaction mixture. After 24 h, the reaction solution was diluted with CH_2Cl_2 to a volume of 250 mL and poured into 100 mL of an ice-cold dilute $NaHCO_3$ solution. Caution: This acid−base reaction is very exothermic and care should be taken during the entire workup process.

The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL), dried with Na_2SO_4, and concentrated to give a red foam. This foam was immediately taken up in 20 mL of THF, and ethylenediamine as a formaldehyde trap[19] (1.58 mL, 23.7 mmol) was added to the reaction mixture followed by the addition of TBAF (1.0 M, 46 mL, 46 mmol). The reaction mixture was heated to reflux and held at that temperature for 20 min after which it was cooled to room temperature and poured into 50 mL of a dilute ice-cold NH_4Cl solution. The resulting solution was partitioned between EtOAc (50 mL) and H_2O, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give dark-brown foam. Purification of this foam by flash column chromatography (1:1 Et_2O/CH_2Cl_2) gave the deprotection product **40** (811 mg, 32% over 3 steps) as a white solid. mp. 184−186 °C; IR (thin film): 3166, 1599 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 12.6 (br s, 1H), 6.87 (s, 1H), 3.97−3.94 (m, 2H), 3.01 (s, 6H), 2.84 (t, J = 6.5 Hz, 2H), 2.68 (s, 3H), 2.04 (quint, J = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 144.1, 136.8, 126.7, 120.1, 118.1, 104.5, 99.9, 44.1, 38.4, 22.7, 22.5, 15.7; LRMS (ESI) *m/z* (relative intensity) 525.9 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{14}H_{18}N_5O_3S_2Br_2]^+$, 525.9218, found 525.9233.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridine-3-sulfonamide, 10,11-Dibromo-3a-chloro-3a,4,5,6-tetrahydro-N,N-dimethyl-2-(methylthio)-8-oxo- (41). *Method A:* To a stirring solution of fused bicycle **40** (0.460 g, 0.872 mmol) in 18 mL of CH_2Cl_2 was added *N*-chlorosuccinimide (NCS) (128 mg, 0.959 mmol). After 1 min, the reaction mixture was poured into 20 mL of H_2O. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give chlorotetracycle **41** (452 mg, 92%) as a cream colored solid. A small amount of this material was purified by flash column chromatography (Florasil, 60% Et_2O/hexanes) for charac-

(19) Rawal, V. H.; Cava, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2110–2112.

terization purposes. *Method B*: To a stirring solution of fused bicycle **40** (12.1 mg, 0.0229 mmol) in 850 μL of CH_2Cl_2 was added ICl (0.0916 mmol, 146 μL of a freshly prepared 0.628 M solution in CH_2Cl_2). The reaction solution immediately turned from colorless to dark red. After 1 min, the reaction mixture was diluted with CH_2Cl_2 to a volume of 20 mL and poured into 15 mL of $NaHCO_3$ (sat.). The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give a black oil. Purification of this oil by flash column chromatography (hexanes then Et_2O) gave chlorotetracycle **41** (10.9 mg, 84%) as a light yellow solid whose spectral data were identical with that of the product from Method A. mp. 177−178 °C; IR (thin film): 1714 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.72 (s, 1H), 4.15 (dt, J = 13.0, 9.0 Hz, 1H), 3.16−3.01 (m, 2H), 3.07 (s, 6H), 2.50 (s, 3H), 2.16 (ddd, J = 15.0, 12.0, 3.2 Hz, 1H), 1.89 (m, 1H), 1.69 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.6, 157.2, 127.0, 109.5, 105.3, 102.8, 100.0, 90.5, 38.1, 37.0, 35.8, 17.7, 15.7; LRMS (ESI) *m/z* (relative intensity) 559.9 (35%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{14}H_{17}N_5O_3S_2Br_2Cl]^+$, 559.8828, found 559.8854.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridin-8-one, 2-(Methylthio)-10,11-dibromo-3a,4,5,6-tetrahydro-3a-methoxy- (42). To a stirring solution of chlorotetracycle **41** (0.130 g, 0.231 mmol) in MeOH/THF (2.5:1, 7 mL total) was added HCl (conc, 100 μL) and reaction solution was heated to reflux. After 3 h, the reaction solution was cooled to room temperature and concentrated. The residue was dissolved in 50 mL of CH_2Cl_2 and washed with $NaHCO_3$ (1 × 20 mL). The organic fraction was dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (Et_2O) gave methyl ether **42** (70 mg, 67%) as a white solid. mp 203−204 °C; IR (thin film) 3218, 1684 cm^{-1}; ^1H NMR (300 MHz, d_8-THF+ DCl) δ 6.71 (s, 1H), 3.93 (m, 1H), 3.44 (s, 3H), 3.36 (m, 1H), 2.86 (s, 3H), 2.64 (m, 1H), 2.09 (m, 1H), 1.72−1.61 (m, 2H); ^{13}C NMR (75 MHz, d_8-THF) δ 175.6, 157.9, 127.6, 109.9, 105.5, 105.2, 96.3, 93.5, 52.8, 37.5, 29.0, 16.8, 14.7; LRMS (ESI) *m/z* (relative intensity) 449.0 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{13}H_{15}N_4O_2Br_2S]^+$, 448.9282, found 448.9250.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridin-8-one, 2-Azido-10,11-dibromo-3a,4,5,6-tetrahydro-3a-methoxy- (44). A stirring solution of sulfide **42** (400 mg, 0.889 mmol) in 20 mL of CH_2Cl_2 was treated with *m*CPBA (219 mg, 0.889 mmol). After 30 min, the reaction mixture was poured into 20 mL of a saturated $NaHCO_3$ solution. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give a yellow oil (330 mg) that was used without further purification. A portion of the crude sulfoxide (200 mg) was immediately up in 20 mL of MeCN and treated with ZnI_2 (10 mg). After 2 min, $TMSN_3$ (306 μL, 2.33 mmol) was added to the reaction solution followed by the addition of H_2O (50 μL). After 5 min, the resulting yellow solution was diluted with EtOAc to a total volume of 40 mL and poured into 20 mL of a saturated $NaHCO_3$ solution. The resulting solution was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (1 × 20 mL). The organic fractions were combined, dried with Na_2SO_4, and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (gradient, 70% Et_2O/hexanes to 100% Et_2O) gave azidotetracycle **44** (89 mg, 37% over 2 steps) as a tacky white solid. IR (thin film): 2146, 1713 cm^{-1}; ^1H NMR (360 MHz, d_4-MeOH) δ 6.77 (s, 1H), 4.04 (m, 1H), 3.35 (s, 3H), 2.31 (m, 1H), 2.10 (m, 1H), 1.84−1.78 (m, 2H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 160.3, 155.8, 126.1, 109.2, 104.8, 104.6, 100.0, 93.3, 53.0, 36.3, 28.4, 16.2; LRMS (ESI) *m/z* (relative intensity) 444.1 (30%, M + H^+); HRMS (ESI) *m/z* for $[C_{12}H_{12}N_7O_2Br_2]^+$, 443.9419, found 443.9448. One proton signal at ~3.30 ppm is not reported due to overlap with solvent.

Dibromoagelaspongin•TFA Salt (6•CF_3CO_2H). To a stirring solution of azidotetracycle **44** (89 mg, 0.20 mmol) in MeOH:THF (8:2, 10 mL total volume) was added 10% Pd/C (9 mg) and the reaction solution was placed under an atmosphere of H_2 (balloon). After 16 h, the reaction mixture was filtered through a thin pad of Celite that was then washed with an additional 10 mL of MeOH. TFA (100 μL) was added to the filtrate which, upon concentration, gave dibromoagelaspongin methyl ether (103 mg, 100%) as its TFA salt. A portion of this material (28 mg, 0.054 mmol) in 3 mL of H_2O was heated in a sealed tube at 90 °C and held at this temperature for 16 h. The reaction solution was then cooled to room temperature and concentrated to give a colorless oil. This oil was redissolved in 10 mL of MeOH and 50 μL of TFA was added. The solution was concentrated to give dibromoagelaspongin (**6**) (26 mg, 99%) as its TFA salt. IR (thin film): 3183, 1682 cm^{-1}; ^1H NMR (300 MHz, d_4-MeOH) δ 6.78 (s, 1H), 4.05 (m, 1H), 3.25 (m, 1H), 2.15 (m, 1H), 2.04 (m, 1H), 1.81−1.66 (m, 2H); ^{13}C NMR (90 MHz, d_4-MeOH) δ 159.1, 158.7, 128.1, 110.5, 106.3, 105.4, 93.4, 91.2, 37.3, 34.5, 18.0; LRMS (ESI) *m/z* (relative intensity) 404.2 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{11}H_{12}N_5O_2Br_2]^+$, 403.9358, found 403.9354.

2-Phenylsulfanyl-4-(3,4,5-tribromo-1H-pyrrole-2-carbonyl)-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (53). A stirring solution of bicycle **32** (15 mg, 0.025 mmol) in a 1:1 mixture of CH_2Cl_2:THF (1 mL total volume) was treated with LiBr (43 mg, 0.50 mmol) and then with NCS (3.3 mg, 0.025 mmol). After 5 min, the reaction mixture was diluted with CH_2Cl_2 to a volume of 20 mL and poured into 10 mL of ice-cold H_2O. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the organic layer was sequentially washed with H_2O (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), 1 M H_3PO_4 (1 × 10 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (3:2 Et_2O/hexanes) gave tribromobicycle **53** (6 mg, 36%) as a yellow oil along with bromotetracycle **54** (1 mg, 5%). Spectral data for **53**: IR (thin film) 1600 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.2 (br s, 1H), 7.30 (s, 5H), 3.89 (dd, J = 5.4, 4.0 Hz, 2H), 3.04 (s, 6H), 2.90 (t, J = 6.5 Hz, 2H), 2.04 (quint, J = 6.1 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 157.9, 141.4, 137.6, 133.4, 129.2, 129.0, 128.9, 126.8, 117.5, 103.9, 103.3, 102.7, 43.6, 38.7, 23.1, 22.7; LRMS (ESI) *m/z* (relative intensity) 665.9 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{19}N_5O_3S_2Br_3]^+$, 665.8479, found 665.8476.

3H, 8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridine-3-sulfonamide, 3a,10,11,12-tetrabromo-3a,4,5,6-tetrahydro-*N*,*N*-dimethyl-2-(phenylthio)-8-oxo- (54). A stirring solution of bicycle **32** (10 mg, 0.017 mmol) in a 1:1 mixture of CH_2Cl_2:THF (1 mL total volume) was treated with LiBr (30 mg, 0.34 mmol) and then with NCS (4.5 mg, 0.034 mmol). After 5 min, the black reaction mixture was diluted with CH_2Cl_2 to a volume of 20 mL and poured into 10 mL of ice-cold H_2O. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the organic layer was sequentially washed with H_2O (1 × 10 mL), saturated aqueous $NaHCO_3$ (1 × 10 mL), 1 M H_3PO_4 (1 × 10 mL), dried over Na_2SO_4 and concentrated to give a black oil. Purification of this oil by flash column chromatography (14:5:1 Et_2O/hexanes/CH_2Cl_2) gave tetrabromotetracycle **54** (8.4 mg, 66%) as a yellow oil. IR (thin film) 1716 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.45−7.38 (m, 3H), 4.12 (dt, J = 13.3, 7.9 Hz, 1H), 3.17 (s, 6H), 3.10 (ddd, J = 14.5, 6.5, 2.5 Hz, 1H), 3.00 (m, 1H), 2.44 (ddd, J = 14.4, 7.9, 3.2 Hz, 1H), 1.89−1.78 (m, 1H), 1.74−1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 156.0, 135.5, 130.7, 129.6, 125.8, 124.9, 108.7, 102.8, 100.5, 97.6, 83.2, 39.5, 38.2, 36.2, 18.5; LRMS (ESI) *m/z* (relative intensity) 743.8 (100% M + H^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{18}N_5O_3S_2Br_4]^+$, 743.7585, found 743.7524.

4-(4,5-Dibromo-3-iodo-1H-pyrrole-2-carbonyl)-2-methylsulfanyl-4,5,6,7-tetrahydro-imidazo[4,5-b]pyridine-1-sulfonic Acid Dimethylamide (55). To a stirring solution of bicycle **40** (9.0 mg, 0.017 mmol) in 1 mL of CH_2Cl_2 was added NIS (3.8 mg, 0.017 mmol). After 5 min, the reaction mixture was diluted with CH_2Cl_2

to a volume of 20 mL and the yellow solution was poured into saturated $NaHCO_3$ (10 mL). The reaction solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Purification of this oil by flash column chromatography (80% Et_2O/hexanes) gave iodopyrrole **55** (9.0 mg, 81%) as a white solid. mp 142−144 °C; IR (thin film) 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.1 (br s, 1H), 3.90 (br m, 2H), 3.00 (s, 6H), 2.87 (t, J = 6.4 Hz, 2H), 2.52 (s, 3H), 2.14−2.08 (br m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 144.1, 136.9, 128.7, 117.9, 109.1, 103.1, 75.9, 43.9, 38.6, 22.62, 22.60, 15.7; LRMS (ESI) m/z (relative intensity) 651.9 (100% M + H^+); HRMS (ESI) m/z calcd for $[C_{14}H_{17}N_5O_3S_2Br_2I]^+$, 651.8184, found 651.8187.

3H,8H-Imidazo[4,5-b]pyrrolo[1′,2′:3,4]imidazo[1,2-a]pyridine-3-sulfonamide, 10,11-Dibromo-3a,4,5,6-tetrahydro-3a,9-diiodo-*N*,*N*-dimethyl-2-(methylthio)-8-oxo- (56). To a stirring solution of fused bicycle 40 (59 mg, 0.11 mmol) in 6 mL of CH_2Cl_2 was added NIS (99 mg, 0.44 mmol). The reaction solution instantly changed from colorless to red. After 1 min, the reaction mixture was poured into 20 mL of $NaHCO_3$ (sat.). The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (1 × 25 mL). The organic fractions were combined and dried with Na_2SO_4. This dried solution was poured through a thin pad of silica and additional CH_2Cl_2 (100 mL) was used to rinse the silica until no colored impurities continued to elute. The filtrate was discarded. Next, the silica was rinsed with Et_2O (50 mL), and the filtrate was concentrated to give a yellow oil. This oil was redissolved in CH_2Cl_2 (20 mL) and sequentially washed with H_3PO_4 (1 M, 1 × 20 mL) followed by $NaHCO_3$ (sat., 20 mL), dried with Na_2SO_4, and concentrated to give diodotetracycle 56 (52 mg, 64%) as a yellow oil which required no further purification. IR (thin film): 1638 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (quint, J = 6.5 Hz, 1H), 3.07 (m, 1H), 3.10 (s, 6H), 2.85 (dt, J = 6.2, 4.4 Hz, 2H), 2.51 (s, 3H), 1.69−1.50 (m, 2H, overlaps with H_2O peak); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 156.7, 128.3, 113.5, 101.8, 101.1, 65.2, 63.0, 44.1, 38.1, 37.3, 19.9, 16.0; LRMS (ESI) m/z (relative intensity) 777.8 (35%, M + H^+); HRMS (ESI) m/z calcd for $[C_{14}H_{16}N_5O_3S_2Br_2I_2]^+$, 777.7151, found 777.7192.

Acknowledgment. We thank the National Science Foundation for support of this work through CHE 0808983 and for support of the Huck Institutes of the Life Sciences X-ray crystallography facility through CHE 0131112.

Supporting Information Available: General Experimental procedures; copies of ^1H and ^{13}C NMR spectra for **24a−e, 25, 26b−e, 27−29a/b, 31−33a/b, 34a/b, 36**, **42** and **53−55**; X-ray crystallographic data for **33a**. Note that copies of ^1H and ^{13}C NMR spectra for **38−41**, **44**, **56** and **6** were submitted as Supporting Information along with the publication listed in ref 9. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900283G