Synthesis of Petrosins C and D

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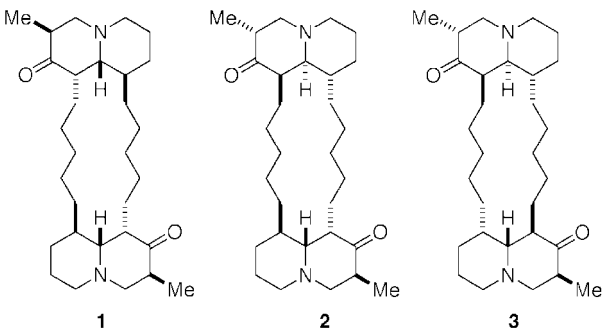
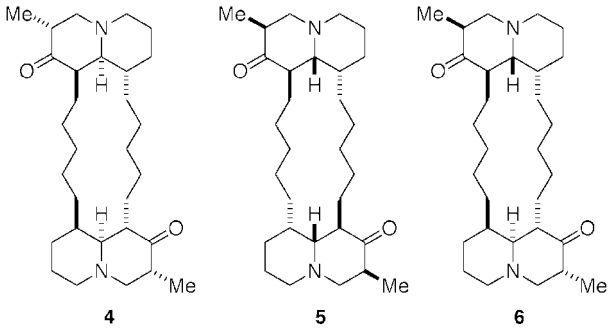
Petrosins C and D (**5** and **6**), diastereomers of the known natural products petrosin (**1**), petrosin A (**2**), and petrosin B (**3**), have been prepared. The synthetic route involved initial creation of a 16-membered bis-pyridine intermediate, exemplified by compounds **7**, **28**, and **52**. Several different methods for formation of the macrocycle were evaluated, and the most efficient (Schemes 7−9) involved use of *Z* double bonds in the six-carbon chains linking the two pyridine rings. This approach permitted the two pyridine subunits (**37** and **39**) to be joined by alkylation of a lithiated α-methylpyridine with an allylic chloride (e.g., **37** + **39** → **40** and **49** → **45**). Bisannulation of compounds **7** and **28** was complicated by a surprising lack of acidity of the α-pyridyl methylene groups. Eventually, this problem was solved by stepwise introduction of two allyl groups, using the more acidic sulfone for introduction of the first (e.g., **52** → **53**) and direct allylation to introduce the second (e.g., **54** → **55** + **56**). The bisannulation was completed by hydroboration and conversion of the primary alcohols into methanesulfonate derivatives, which cyclized to afford bis-pyridinium derivatives. Reduction of these intermediate salts with sodium borohydride provided crystalline bis-enol ethers (**60** and **63**) and the relative configuration was established by single-crystal X-ray analysis of **63**. After hydrolysis of the enol ethers to the corresponding ketones, the syntheses of **5** and **6** were completed by enolate methylation. As expected, compounds **5** and **6** do not form imine derivatives when treated with primary amines, presumably because of $A^{1,3}$ strain.

In the previous paper in this issue, we reported the total synthesis of the marine alkaloid petrosin (**1**).[1] This synthesis also provided synthetic samples of the natural products petrosin A (**2**) and petrosin B (**3**), as well as the previously unknown diastereomer petrosin B′ (**4**). In this paper, we report the synthesis of two other diastereomers that have not yet been found in nature, petrosin C (**5**) and petrosin D (**6**).

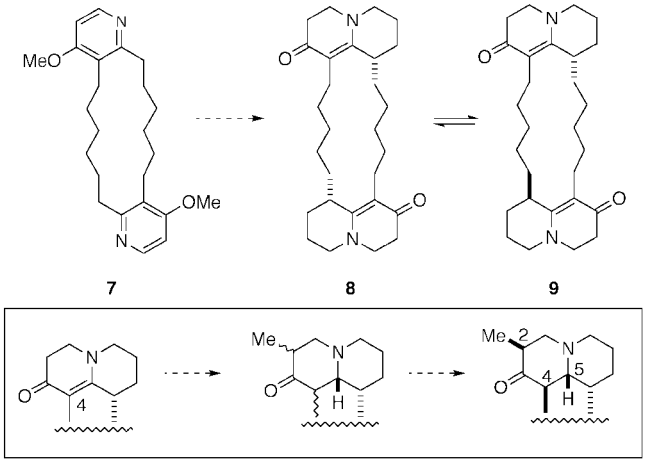


1 **2** **3**



4 **5** **6**

Scheme 1



7 **8** **9**

Our plan for the synthesis of compounds **5** and **6** is summarized in Scheme 1. We thought that if we could prepare the symmetrical, achiral macrocyclic bis-pyridine **7**, we might be able to convert it to bis-enones **8** and **9**. These two diastereomers might then be individually converted into petrosins C and D by reduction of the two double bonds and introduction of the two methyl groups by enolate alkylation. This plan also appeared to offer hope of stereocontrol. First, it might be possible to control the stereoselectivity of the annulations leading from **7** to **8** and **9**. Alternatively, it might be possible to equilibrate these diastereomers under basic conditions. Indeed, molecular mechanics global minimization studies suggested a significant difference in energy of the two isomers; Monte Carlo conformational searches using Marcomodel and the MM2 force field found low-energy conformations of **8** and **9** with energies of −15.2 and −8.2 kJ/mol, respectively. Furthermore, reduction the two double bonds in each case should be controlled by the

(1) Scott, R. W.; Epperson, J. E.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, xxxx.

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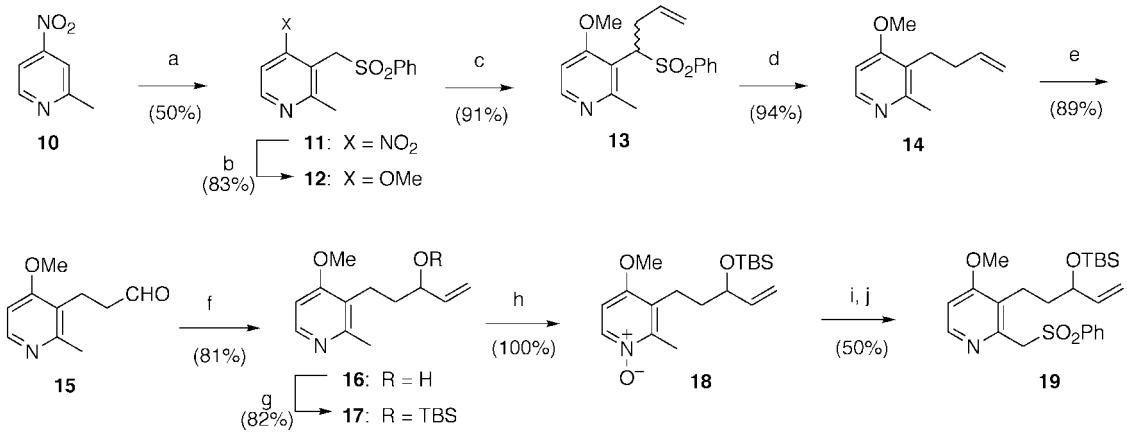
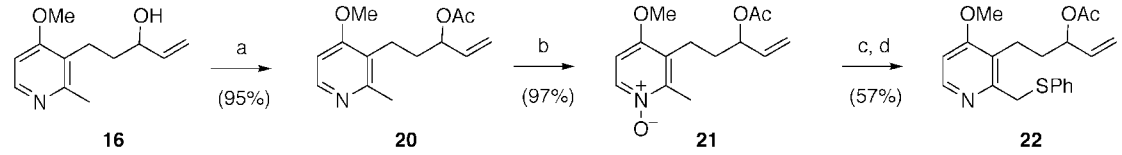
Scheme 2[a]



[a] Key: (a) $PhSO_2CH_2Cl$, NaOH, DMSO; (b) NaOMe, MeOH, rt; (c) (i) *n*-BuLi, THF; (ii) $CH_2{=}CHCH_2Br$; (d) 6% Na/Hg, Na_2HPO_4, MeOH; (e) OsO_4, $NaIO_4$, THF, H_2O; (f) $CH_2{=}CHMgBr$, THF; (g) TBSCl, Et_3N, DMAP, CH_2Cl_2; (h) *m*-CPBA, CH_2Cl_2; (i) *p*-TsCl, Et_3N, CH_2Cl_2; (j) $NaSO_2Ph$, DMF.

Scheme 3[a]



[a] Key: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (b) *m*-CPBA, CH_2Cl_2; (c) *p*-TsCl, Et_3N, CH_2Cl_2; (d) NaSPh, DMF.

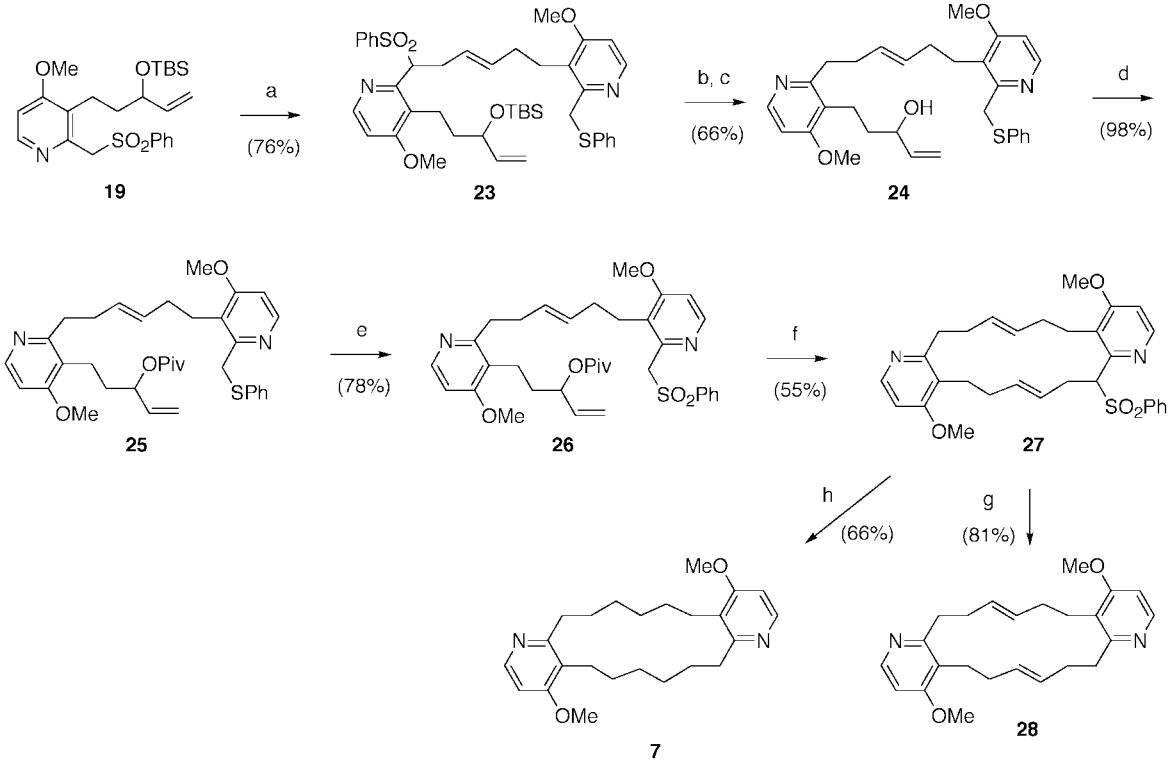
adjacent C-6 stereocenter, with addition of hydrogen to C-5 coming from the face trans to the methylene substituent at C-5. With the relative configurations of C-5 and C-6 established in this manner, simple keto−enol equilibration would provide the correct relative configurations at C-2 and C-4.

As shown in Scheme 2, the synthesis of bis-pyridine **7** began with application of Makosza's "vicarious nucleophilic substitution" to the known[2] 2-methyl-4-nitropyridine (**10**). Treatment of phenyl chloromethyl sulfone with NaOH in DMSO, followed by addition of **10**, affords the substitution product. Makosza reports that this reaction provides the 3-substituted product **11** in 60% yield.[3] We found that the reaction gives a 4.5:1 mixture of regioisomeric sulfones in 94% total yield. A single recrystallization from isopropyl alcohol gives the desired isomer **11** in 50% yield on a 50-g scale. Treatment of **11** with sodium methoxide in methanol affords methyl ether **12** in 83% yield. Deprotonation of **12** with *n*-butyllithium and addition of the resulting anion to excess allyl bromide gives the alkylation product **13** in good yield. Although compound **13** exists as a 2:1 mixture of rotamers on the NMR time scale, reductive desulfonylation provides a spectroscopically homogeneous product, **14**. Cleavage of the double bond occurs smoothly when **14** is treated with sodium periodate and catalytic osmium tetraoxide. This cleavage can also be accomplished by ozonolysis in excellent yield on a small scale (27 mg, 85%) but in only modest yield on a large scale (4.5 g, 64%). Aldehyde **15** reacts with vinylmagnesium bromide to provide allylic alcohol **16**, which is protected as the corresponding *tert*-butyldimethylsilyl ether **17**. To functionalize the methyl group, we employed a method originally introduced by Ash and Pews, wherein a picoline *N*-oxide is treated with a halogenating agent.[4] To this end, the *N*-oxide **18** was prepared in quantitative yield and treated with *p*-toluenesulfonyl chloride, followed by sodium benzenesulfenate to obtain sulfone **19** in modest yield. Preparation of a coupling partner to use with **19** is shown in Scheme 3. Allylic alcohol **16** is acetylated to give **20**, which is subjected to a similar procedure to functionalize the methyl group, except that the chloromethyl intermediate is treated with sodium thiophenoxide to obtain sulfide **22**.

To join sulfone **19** and allyl acetate **22**, we employed Trost's Pd(0) method, whereby the sulfone anion attacks a π-allylpalladium (Scheme 4).[5] Treatment of **19** with a slight excess of sodium hexamethyldisilazane in THF gives the anion, which is added slowly to a THF solution of allylic acetate **22** and 4 mol % of $Pd(dba)_2{\cdot}CHCl_3$. The coupled product, **23**, is obtained in this manner in good yield. Reductive desulfonylation followed by desilylation provides allylic alcohol **24**. This is acylated by treatment with pivalic anhydride to obtain the allylic ester **25**, which is oxidized by tetrabutylammonium peroxymonosulfate (TBA-Oxone)[6] to sulfone **26**. This material is appropriately constituted for application of a second Trost alkylation to close the 16-membered central ring. Cyclization is accomplished by a similar protocol as was used for joining the two fragments, except that the anion formed by treatment of the sulfone with NaHMDS is added to a refluxing solution of the palladium catalyst with a syringe in order to achieve conditions of high dilution. Scheme **4** shows that the cyclization does work and gives the *E*,*E* diene **27** in 55% yield. Reductive desulfonylation provides the symmetrical compound **28**,

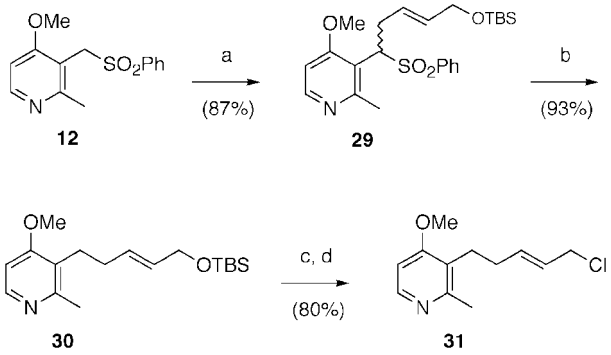
(2) Wiley: R. H.; Hartman, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 494.
(3) Makosza, M.; Chylinska, B.; Mudryk, B. *Liebigs Ann. Chem.* **1984**, 8.
(4) Ash, M. L.; Pews, R. G. *J. Heterocycl. Chem.* **1981**, *18*, 939.
(5) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.
(6) Trost, B. M.; Breslau, R. *J. Org. Chem.* **1988**, *53*, 532.

Scheme 4[a]



[a] Key: (a) (i) NaHDMS, THF; (ii) **22**, 3.7 mol % $Pd_2(dba)_2$·$CHCl_3$, dppe, reflux; (b) Na/Hg, Na_2HPO_4, MeOH; (c) TBAF, THF; (d) (*t*-$BuCO)_2O$, Et_3N, DMAP, CH_2Cl_2; (e) TBA-Oxone, CH_2Cl_2; (f) (i) NaHDMS; (ii) 12 mol % $Pd_2(dba)_3$·$CHCl_3$, dppe, THF, reflux; (g) AlHg, THF, H_2O; (h) H_2, Raney Ni, MeOH.

Scheme 5[a]



[a] Key: (a) (i) *n*-BuLi, THF; (ii) (*E*)-$ClCH_2CH{=}CHCH_2OTBS$; (b) 5% Na/Hg, MeOH; (c) 1 N HCl, THF; (d) MsCl, lutidine, LiCl, DMF.

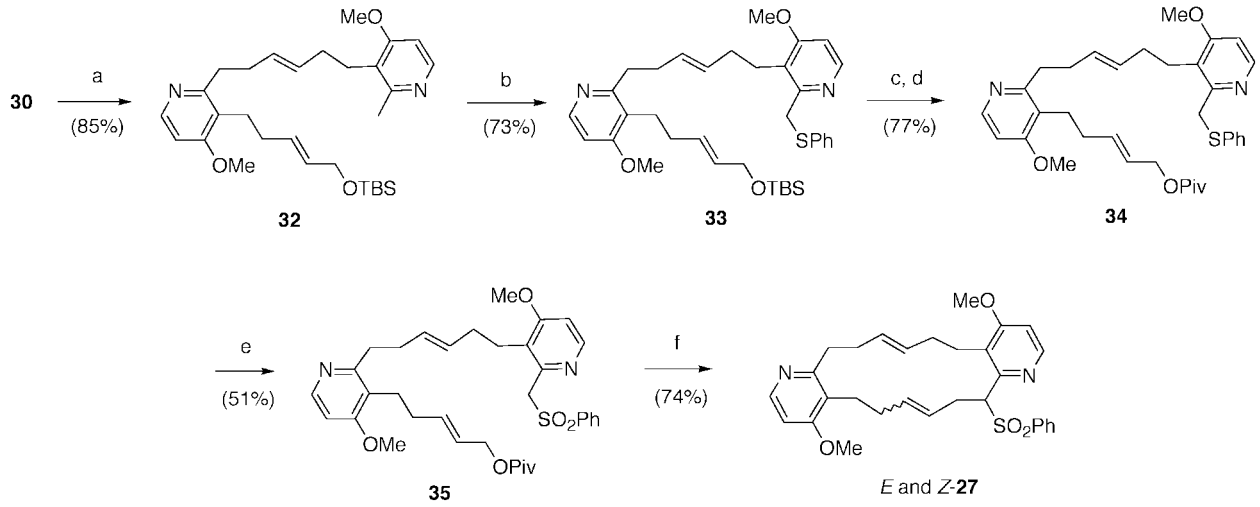
and hydrogenation of **27** provides the bis-pyridine **7**. Later work (vide infra) revealed that the cyclization reaction had actually produced **27** and its *E*,*Z* isomer in a 2:1 ratio, in a total yield of about 80%, and that we had missed the minor isomer in the chromatographic separations.

Although successful in delivering the desired macrocyclic bis-pyridine, the foregoing route proved to be difficult to scale-up, and we decided to develop a somewhat more convergent version. In addition, we thought we might be able to replace at least one and possibly both of the palladium-mediated alkylations by more low-tech methods. As shown in Scheme 5, alkylation of sulfone **12** with the *tert*-butyldimethylsilyl ether of (*E*)-4-chlorobut-2-en-1-ol provides sulfone **29** in high yield. Once again, compound **29** shows NMR evidence of restricted rotation about the indicated C−C bond. Reductive desulfonylation of **29** cleanly affords the expected trisubstituted pyridine **30**. Removal of the silyl protecting group under acidic conditions gives an allylic alcohol that is treated with methanesulfonyl chloride and lithium chloride in 2,6-lutidine to provide allylic chloride **31** about 80% yield for the two steps. This material is prone to polymerization, and it is necessary to use it immediately in the following step.

Compound **30** is metalated with *n*-butyllithium and the resulting anion treated with freshly prepared chloride **31** to obtain **32** in excellent yield (Scheme 6). The pyridine methyl group is functionalized by regioselective metalation with *n*-butyllithium and treatment of the derived lithiated intermediate with diphenyl disulfide; thioether **33** is obtained in 73% yield. Removal of the silyl protecting group and acylation of the resulting allylic alcohol with pivaloyl chloride provides **34**, which is oxidized by TBA-Oxone to obtain sulfone **35** in moderate yield. To close the macrocycle, we again used the Trost Pd(0) methodology. To this end, sulfone **35** is treated sequentially with sodium hexamethyldisilazane and 4 mol % of $Pd(dba)_2$·$CHCl_3$. In this manner, the macrocycle **27** is obtained in 74% yield as a 2.5:1 mixture of *E*,*E* and *E*,*Z* isomers. This stereochemical outcome is consistent with the intermediacy of rapidly equilibrating *E* and *Z* π-allylpalladium intermediates, which undergo ring closure at different rates to afford the observed isomeric mixture.[7] Normally the *E* π-allylpalladium species is

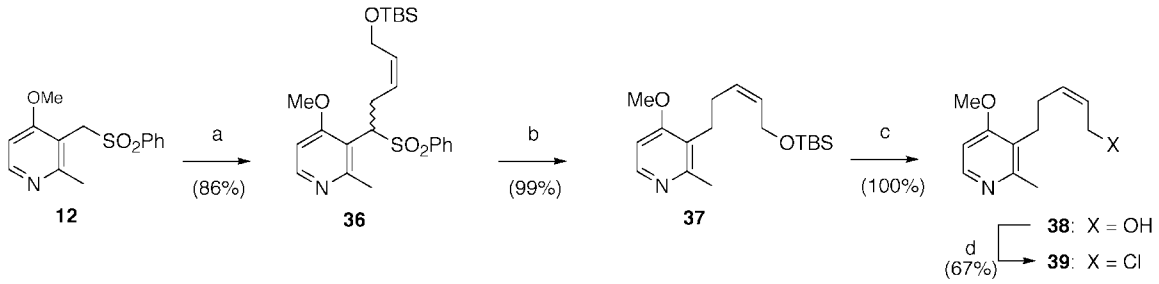
(7) (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 3.3, pp 585−562.

Scheme 6[a]



[a] Key: (a) *n*-BuLi, **31**; (b) (i) *n*-BuLi; (ii) PhSSPh; (c) TBAF; (d) Me_3CCOCl; (e) $Bu_4N^+HSO_5^-$; (f) (i) NaHDMS; (ii) 6 mol % $Pd_2(dba)_3 \cdot CHCl_3$, dppe, THF, reflux.

Scheme 7[a]



[a] Key: (a) (i) *n*-BuLi, THF; (ii) (*Z*)-$ClCH_2CH{=}CHCH_2OTBS$; (b) 5% Na/Hg, MeOH; (c) 1 N HCl, THF; (d) MsCl, lutidine, LiCl, DMF.

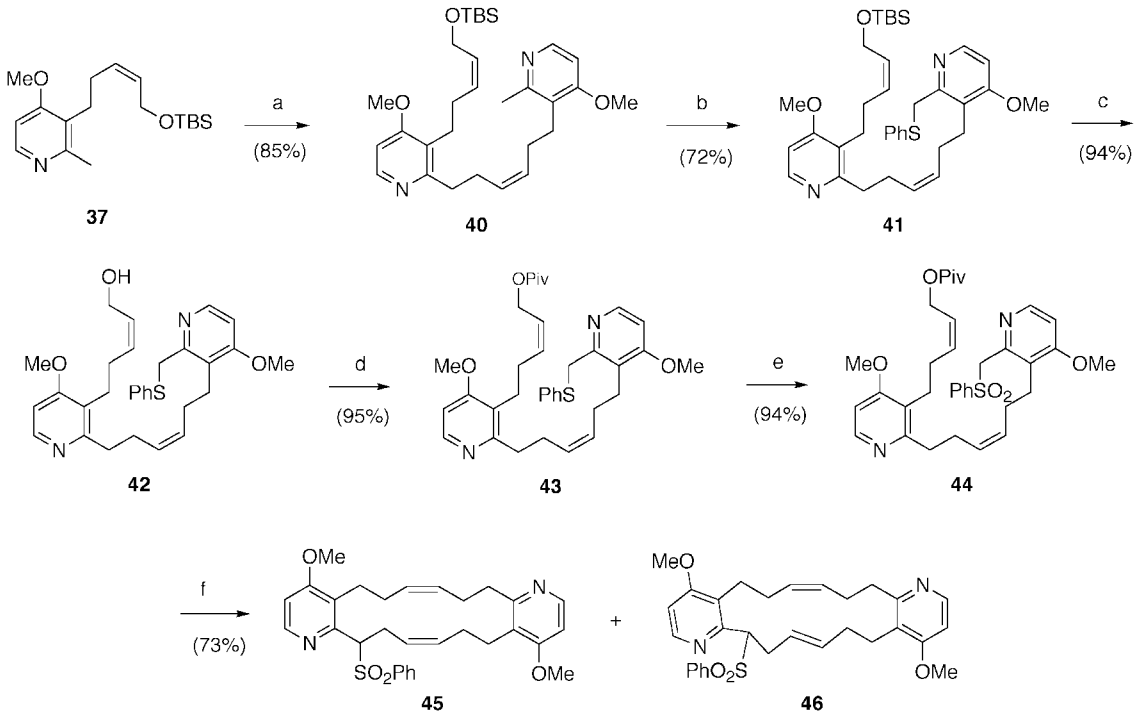
strongly favored in such equilibria. The observation of so much of the *E*,*Z* diene in this cyclization may indicate that the *Z* isomer cyclizes significantly faster than the *E* isomer.

Although this route did provide the desired marcocyclic sulfone in better overall yield, and did eliminate one of the Pd-mediated alkylations, (*E*)-$ClCH_2CH{=}CHCH_2$-OTBS is difficult to prepare on a large scale. Furthermore, the production of a mixture of double-bond isomers in the cyclization reaction limited some of our options, particularly the possibility of leaving these double bonds in place until after the double-annulation process suggested in Scheme 1. We thought that both these problems might be alleviated by using *Z* double bonds in the linking chains, which necessitated the preparation of (*Z*)-$ClCH_2CH{=}CHCH_2OTBS$. This was conveniently prepared in about 70% overall yield on a 25−30 g scale using literature procedures.[8] As shown in Scheme 7, the *Z* allylic chloride was employed in the same manner as previously used for the *E* isomer to alkylate lithiated sulfone **36**. Once again, the alkylation product (**36**) was obtained in excellent yield and as a mixture of rotamers on the NMR time scale. Desulfonylation of this mixture provides a homogeneous substance, **37**, which is converted by way of alcohol **38** into the *Z* allylic chloride **39**.

Like its *E* isomer, chloride **39** is prone to polymerization if stored for any length of time, so it was freshly prepared and immediately used for alkylation. Following the previously developed route, the *Z* allylic TBS ether **37** was lithiated and the resulting anion treated with chloride **39**. This procedure delivers the coupled product **40** in high yield (Scheme 8). Some problems were encountered in thiolating the methyl group of **40** when the reaction was carried out as in the preparation of the *E*,*E* isomer **32** (see Scheme 6). When the alkylation was carried out on the lithiated methylpyridine, the yield of desired product was variable and the product was usually contaminated with significant amounts of the bissulfinylated product. This problem was completely eliminated if the initial lithiated methylpyridine was transmetalated to the magnesium derivative by addition of $MgBr_2$−etherate before addition of the diphenyl disulfide. In this manner, thioether **41** may be prepared on a multigram scale in more than 70% yield. Removal of the silyl protecting group provides allylic alcohol **42**, which is converted into the corresponding pivalate **43** in standard fashion. Oxidation of the sulfide to the corresponding sulfone **44** proceeds in very high yield using ammonium molybdate and hydrogen peroxide. The sodium salt of the *Z*,*Z* substrate **44** was cyclized by treatment with 2.5 mol % of $Pd(dba)_2 \cdot CHCl_3$. As with the *E*,*Z* isomer, cyclization occurred in good yield, and once again, a mixture of double-bond isomers was produced. In this case, the ratio of *E*,*Z* isomer **46** and *Z*,*Z* isomer **45** was variable, ranging from 2:1 to 5:1 (always favoring the *E*,*Z* isomer). The isomer ratio tended to be dependent on the

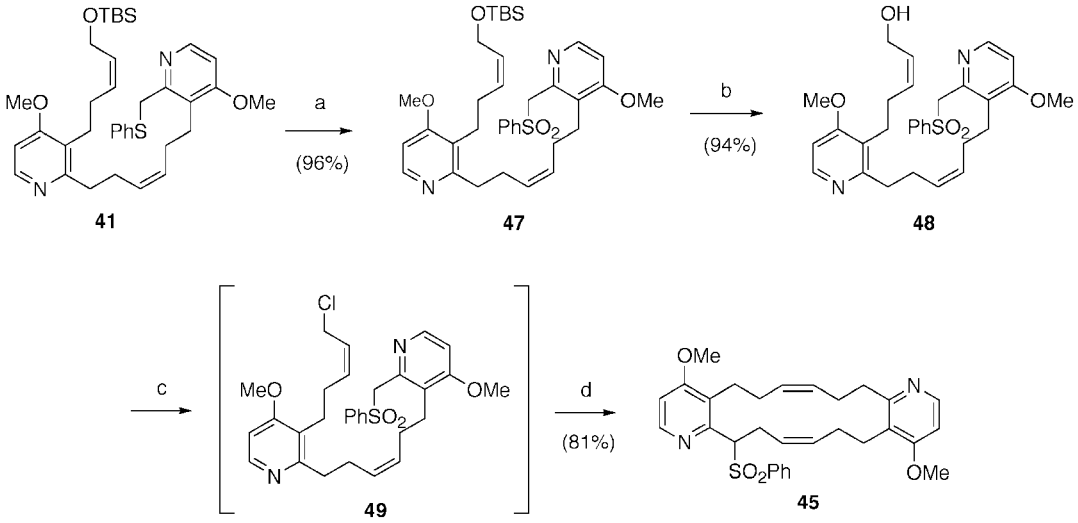
(8) (a) McDougal, P. G.; Rico, J. G.; Oh, Y.-I., Condon, B. *J. Org. Chem.* **1986**, *51*, 3388. (b) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

Scheme 8[a]



[a] Key: (a) (i) *n*-BuLi, THF; (ii) **39**; (b) (i) *n*-BuLi, THF; (ii) $MgBr_2 \cdot Et_2O$; (iii) PhSSPh; (c) 1 N HCl, THF; (d) Piv-Cl, Et_3N, DMAP, CH_2Cl_2; (e) $(NH_4)_6Mo_7O_{24}$, H_2O_2; (f) (i) NaHDMS; (ii) 6 mol % $Pd_2(dba)_3 \cdot CHCl_3$, dppe, THF, reflux.

Scheme 9[a]



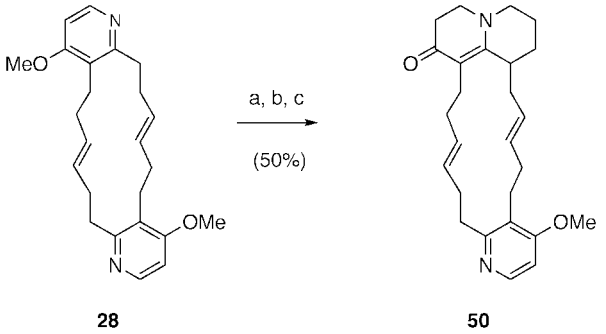
[a] Key: (a) $(NH_4)_6Mo_7O_{24}$, H_2O_2; (b) 1 N HCl, THF; (c) MsCl, LiCl, 2,6-lutidine, DMF; (d) NaHMDS, THF.

scale at which the reaction was carried out. It is possible that in this case the rate of isomerization of the *Z* and *E* π-allylpalladium is comparable with the rate of cyclization. Because the allyl pivalate is *Z*, the first-formed π-allylpalladium presumably has the *Z* configuration, and this isomer is expected to equilibrate to the more stable *E* isomer. However, if the cyclization is more rapid in this case than it is with the isomer used previously (see Scheme 4), some cyclization may occur before equilibration of the π-allylpalladium intermediates has been fully established.

Because the macrocyclization seemed somewhat more facile in the *Z*,*Z* series, it seemed possible that we might be able to forego the Pd-catalyzed methodology altogether. To this end, as shown in Scheme 9, sulfide **41** was oxidized to sulfone **47**, which was deprotected to obtain *Z* allylic alcohol **48**. Treatment of this material with methanesulfonyl chloride and lithium chloride in a mixture of 2,6-lutidine and dimethylformamide afforded the unstable allylic chloride **49**. Cyclization was accomplished by the method suggested by Keinan and coworkers,[9] whereby a solution of **49** is added by syringe pump to a refluxing solution of sodium hexamethyldisilazane in tetrahydrofuran. This procedure provided the *Z*,*Z* macrocyclic sulfone **45** in greater than 80% overall yield for the two-step sequence. This discovery greatly

(9) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3333.

Scheme 10[a]



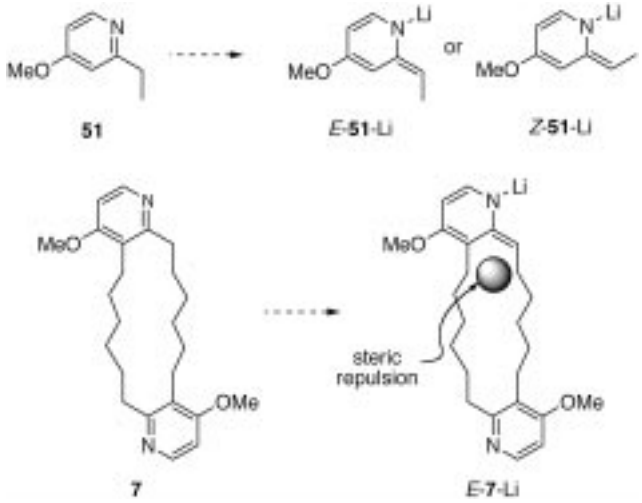
[a] Key: (a) (i) 2.7 equiv of *n*-BuLi, THF, (ii) $BrCH_2CH_2CH_2Cl$; (b) NaI, acetone, reflux; (c) L-Selectride, THF.

facilitated the scale-up of this synthesis, especially in that the direct cyclization of chloride **49** actually worked better as the scale was increased, in contrast to the Pd(0)-mediated cyclization, which tended to give lower yields on scale-up.

With a good synthesis to the 16-membered ring bispyridine worked out, we were able to turn our attention to the proposed bisannulation set forth in Scheme 1. Unsaturated sulfone **27** was easily converted into **7** by desulfonylation with aluminum amalgam, followed by catalytic hydrogenation over Raney nickel, as shown in Scheme 4. However, our initial attempts to generate the bis-quinolizidone framework met with no success. We had hoped to exploit the well-known acidity of the position α to the pyridine ring to generate a dianion from **7**. However, treatment of **7** with 2 or more equiv of various strong bases, followed by 1,3-dibromopropane, gave no evidence of a diakylated product. In an early experiment, we treated **28** with excess *n*-butlyllithium in THF and then added 1-bromo-3-chloropropane to the resulting anion. After treatment of the resulting salt with sodium iodide in refluxing acetone (to exchange the primary chloride for iodide), we obtained a polar product that was taken up in THF and treated with L-Selectride. This treatment provided quinolizidone **50** in 50% yield (Scheme 10). The formation of a mono-annulated product in this process suggests that **28** only undergoes monolithiation, even though an excess of *n*-butyllithium was used.

To test the proposed dianion formation, we treated **7** with *n*-butyllithium, *sec*-butyllithium, or *tert*-butyllithium in various solvents (THF, THF−HMPA, THF−TMEDA) and quenched with excess methyl iodide to measure the extent of deprotonation. Although evidence for monolithiation was obtained, exhaustive studies failed to provide a synthetically useful method to generate the dianion. We believe failure to generate the dianion can be attributed to the reduced kinetic acidity of the macrocycle **7**, combined with its very low solubility in appropriate solvents (**7** is only marginally soluble in THF, 1,4-dioxane, THF−HMPA, or toluene and is virtually insoluble in ether or hexane). Qualitative evidence for the reduced kinetic acidity of **7** was provided by deuterium-exchange experiments in D_3COD/D_3CONa at elevated temperatures. Very little or no deuterium incorporation was seen, even after extended periods. In contrast, 2-ethyl-4-methoxypyridine (**51**) showed substantial deuterium incorporation under the same conditions. This reduced acidity may be due to the cyclic nature of **7**. As

Scheme 11



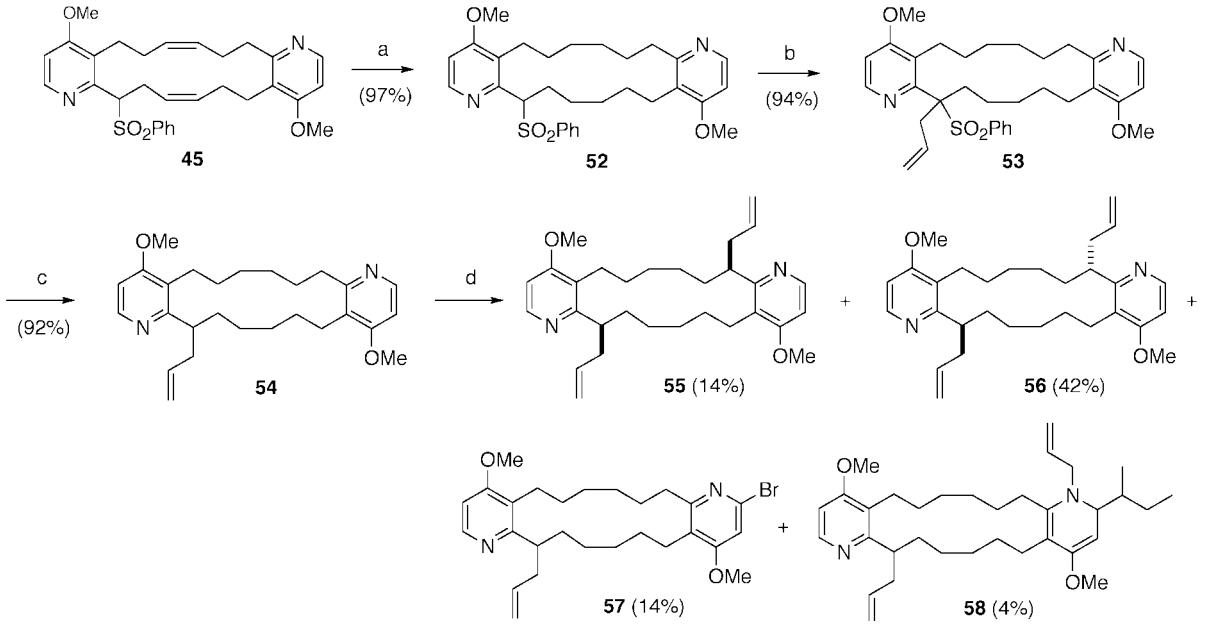
shown in Scheme 11, deprotonation of 2-ethyl-4-methoxypyridine can give two isomeric lithiated derivatives, (*E*)- and (*Z*)-**51**−Li. Because the acidic methylene groups of **7** are in a ring, it is likely that only one lithiated derivative, (*E*)-**7**−Li, can be formed. This derivative is subject to severe $A^{1,3}$ strain, as indicated in Scheme 11. The situation would be greatly exacerbated in the formation of the dilithiated derivative because of the necessity of creating a dianion, both of which would suffer from $A^{1,3}$ strain.

Fortunately, the presence of the sulfone on the macrocycle provides a handle that we hoped to be able to use to introduce the side chains in a stepwise fashion. The desired sulfone **52** was prepared by diimide reduction of the macrocyclic diene **45** as hydrogenation over Raney Ni proved to be unreliable, slow, and relatively low yielding. The seemingly trivial alkylation of the sulfone **52** was not straightforward due to its low nucleophilicity. Only highly reactive electrophiles such as allyl bromide (required HMPA) and methyl iodide would react with the lithiated sulfone at a useful rate. Although allylation of **52** in THF−HMPA (2:1) with allyl bromide provided the desired product **53** in a respectable 60−70% yield, separation of unreacted starting sulfone from HMPA was tedious and time consuming. This technical problem was solved in a most unusual way—by using 2,6-lutidine as a cosolvent. This solvent displayed a number of virtues: (i) it is readily removed under high vacuum, (ii) it enhances the reactivity of the sulfone anion sufficiently to react with allyl iodide rapidly at room temperature, (iii) the solubility of sulfone **52** in THF−2,6-lutidine is significantly greater than in THF−HMPA, and (iv) the acidity of the 2,6-lutidine (pK_a around 34.5 in THF)[10] allows an excess of *n*-BuLi to be used to deprotonate the sulfone, the excess removing a proton from the 2,6-lutidine, ensuring complete deprotonation of sulfone and providing a "buffering" effect. Under the conditions shown in Scheme 12, the desired allylated product **53** was obtained in over 90% yield. Reductive desulfonylation proceeded cleanly to provide **54**.

To introduce the second three-carbon unit, compound **54** was deprotonated with *s*-BuLi and TMEDA and the

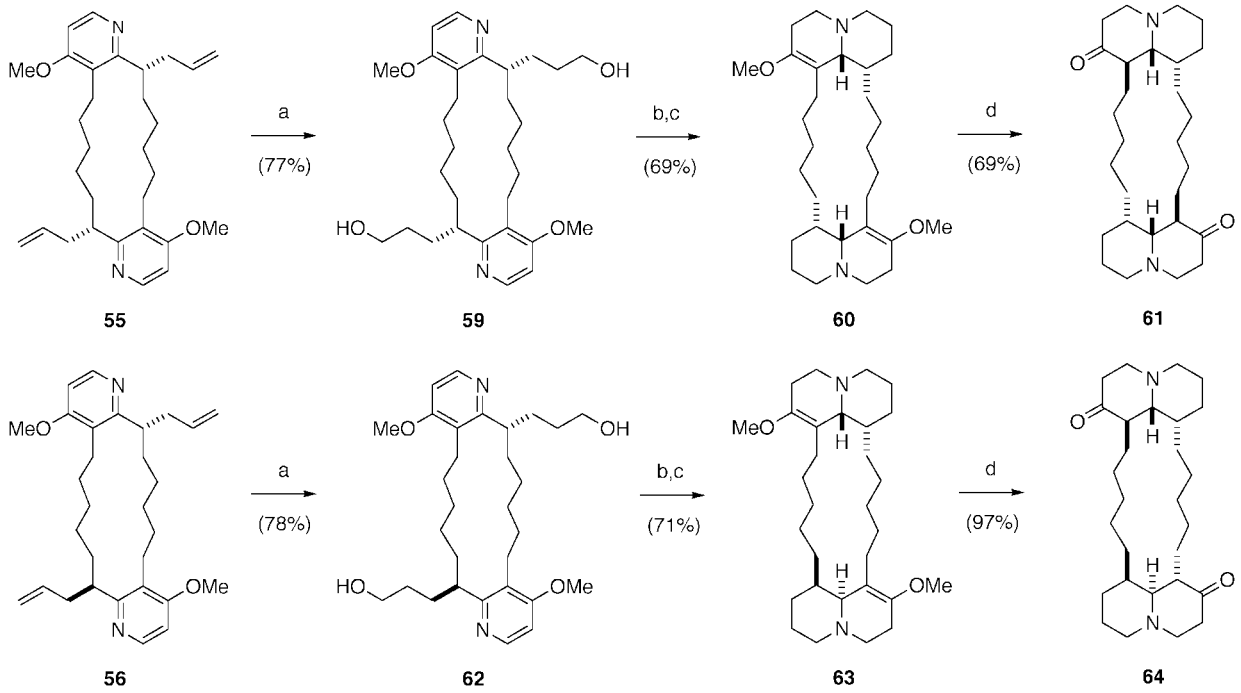
(10) Fraser, R. R.; Breese, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620.

Scheme 12[a]



[a] Key: (a) *p*-TsNHNH$_2$, NaOAc, THF, H$_2$O; (b) (i) 3 equiv of *n*-BuLi, 2,6-lutidine, THF; (ii) CH$_2$=CHCH$_2$I; (c) Na/Hg, THF, MeOH; (d) (i) *s*-BuLi, TMEDA, ether, (ii) CH$_2$=CHCH$_2$Br.

Scheme 13[a]



[a] Key: (a) (i) 9-BBN, THF, (ii) H$_2$O$_2$; (b) MsCl, Et$_3$N, CH$_2$Cl$_2$; (c) NaBH$_4$, EtOH; (d) aqueous HCl.

resulting anion treated with allyl bromide. The diallylated macrocycles **55** and **56** were conveniently separated by radial chromatography on silica, along with two byproducts (**57** and **58**) and recovered starting material. The presence of byproduct **57** implies that the pyridine ring was metalated, again illustrating the rather harsh conditions required to deprotonate at the desired position. Fortunately, bromopyridine **57** was easily recycled by halogen−metal exchange followed by protonation.

The two diastereomers **55** and **56** were taken through the final steps of the synthesis separately (Scheme 13). To close the quinolizidone rings, we needed to functionalize the allyl side chains. We thought that a sequence of hydroboration and activation of the resulting alcohol would provide the desired dipyridinium salt. However, hydroboration of diene **56** with BH$_3$·DMS led to an unexpectedly complex mixture of products that contained mixtures of secondary alcohols in addition to the desired primary alcohols. Isolation of the desired diol **62** from the reaction mixture proved to be very difficult and required derivatization of the mixture with acetic anhydride followed by several chromatographic separations.

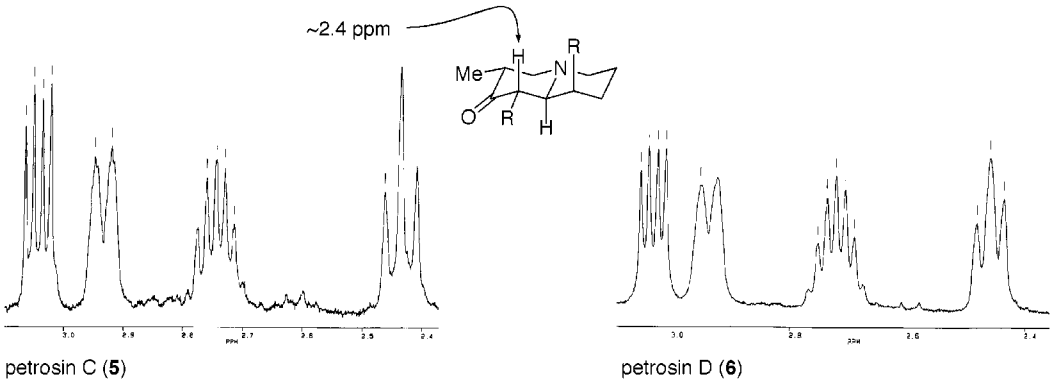


Figure 1. Portions of the ^{1}H NMR spectra of petrosin C (**5**) and petrosin D (**6**).

However, hydroboration with 9-BBN provided a much cleaner reaction, yielding desired diol **62** in almost 80% yield. However, significant amounts of what were thought to be secondary alcohols were still present. Again, purification of the diol **62** by chromatography proved to be very difficult. Fortunately, it was possible to crystallize most of the desired diol **62** from the reaction mixture. The rather unusual regioselectivities and reactivities observed during the hydroboration of diene **56** are probably due to the presence of the pyridine nitrogen in the proximity of the olefin. Similar hydroboration of the minor diallylated product **55** provided diol **59**.

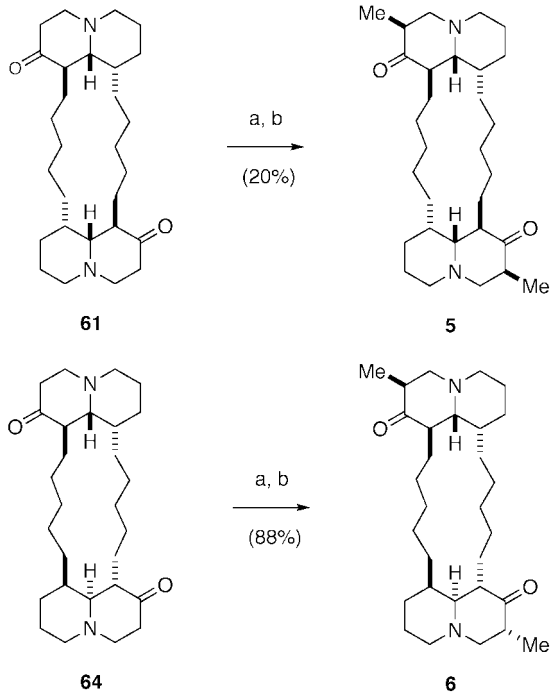
Activation of the diols **59** or **62** with methanesulfonyl chloride resulted in smooth cyclization to stable dipyridinium salts. We were not able to reduce these pyridinium salts with L-Selectride in THF as we had in several previous models. This is almost certainly due to the insolubility of the dication, rather than a reactivity problem as both the bicyclic model compound and the monoannulated macrocycle **50** (Scheme 10) were prepared in this way. In contrast, reduction with $NaBH_4$ in ethanol provided the dienol ethers **60** and **63**, which were difficult to purify by chromatography. Gratifyingly, like all of the macrocycles encountered in this work, these reduction products can be purified by recrystallization and obtained in about 70% yield. The structure of diether **60** was elucidated by single-crystal X-ray analysis. Hydrolysis of the dienol ethers **60** and **63** cleanly provided diketones **61** and **64**.

Clean dimethylation of diketone **64** proved to be quite troublesome, especially on a small scale. When **64** was treated with an excess of LDA, the dienolate precipitated from solution, and introduction of methyl iodide followed by very carefully monitoring of the reaction did allow reasonable yields of the axially dimethylated product to be obtained, along with starting material and some polymethylated material. However, the insolubility of the dienolate resulted in the reaction being very difficult to control with an excess of base present. On a larger scale (~20 mg), when only 2 equiv of LDA was used, the dimethylated product was obtained in good yield, and equilibration with K_2CO_3 in methanol afforded the target, petrosin D (**6**) (Scheme 14). Petrosin C (**5**) was obtained in the same way, but the final dimethylation was never achieved in good yield due to problems associated with performing the dienolate chemistry on a small scale.

The NMR spectra of petrosins C and D are in good accord with their symmetrical structures. Because of their symmetry, both isomers show only 15 signals in their ^{13}C NMR spectra. The ^{1}H NMR are also simpler than those of the unsymmetrical isomers, petrosins B and B′. The most diagnostic region in the ^{1}H NMR spectra is the 2.4−3.2 ppm region. As shown in Figure 1, both isomers display a characteristic broad triplet structure at approximately 2.4 ppm. This resonance arises from the axial proton at C-4, adjacent to the carbonyl group. The two large coupling constants that are responsible for the triplet appearance of this multiplet result from a diaxial coupling to the bridgehead proton and one of the protons in the linking five-carbon chain. The spectral regions in Figure 1 should be compared with the corresponding regions in the spectra of petrosin, petrosin A, petrosin B, and petrosin B′.[11]

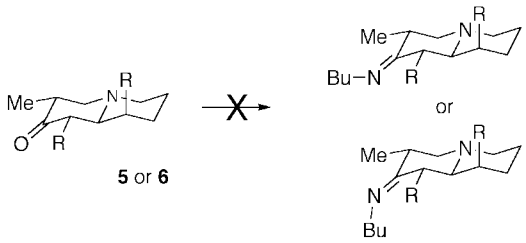
As expected, neither petrosin C nor petrosin D forms an imine when treated with butylamine under conditions that served to form imines from the mixture of petrosin isomers reported in the previous paper in this issue.[1] This is understandable in terms of A[1,3] strain, as shown by the following structures:

Scheme 14[a]

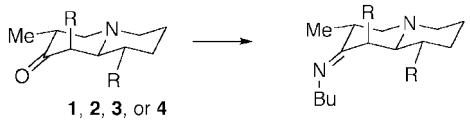


[a] Key: (a) LDA, THF, MeI; (b) K_2CO_3, MeOH, H_2O.

(11) See Figure 3 in ref 1.



The mixture of diastereomers resulting from the double Mannich cyclization[1] consisted principally of petrosin, petrosin A, petrosin B, and petrosin B′. Each of these isomers has at least one quinolizidone that can form an imine without A[1,3] strain:



Thus, the following equilibrations are possible via the intermediate imines: petrosin with petrosin A and petrosin B with petrosin B′. Since petrosin A is achiral (meso), this could account for the fact that natural petrosin is racemic. Since both petrosin B and petrosin B′ are chiral, equilibrating them would not give rise to a racemic natural product. It follows that, if petrosins C and D are eventually found in natural sources, they will probably be enantiomerically pure.

Experimental Section

General Methods. All moisture- or air-sensitive reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware. All reagents and solvents were used as obtained from commercial suppliers except for the following: THF and diethyl ether were freshly distilled from sodium−benzophenone ketyl. Benzene, methylene chloride, diisopropylamine, and triethylamine were freshly distilled from CaH_2 prior to use. 2,6-Lutidine was distilled from CaH_2 and stored over KOH pellets. DMF and HMPA were distilled from CaH_2 and stored over 4 Å molecular sieves. Mesyl chloride was distilled. Allyl bromide, allyl iodide, and methyl iodide were passed through a plug of basic alumina immediately prior to use. Organolithium reagents and NaHMDS were regularly titrated against 2,6-di-*tert*-butyl-4-methylphenol using fluorene to determine the end point.

Purification on silica refers to "flash chromatography", which was adapted from the procedure described by Still et al.[12] Column dimensions are given as height × width (cm). Either Merck silica gel (230−400 mesh) or Fischer basic alumina, activity 1,60-325 mesh, was used as the stationary phase. Solvents were of HPLC quality and were used as supplied. Thin-layer chromatography (TLC) analysis was used to monitor the progress of all reactions. Merck silica gel 60 F_{254} coated glass plates were used, visualizing with long-wave ultraviolet illumination, iodine vapor, or ceric ammonium molybdate stain.

Melting points are uncorrected in open-ended capillaries except when a sealed tube is specified, "sealed tube" refers to a capillary tube sealed under vacuum. IR spectra were recorded on Mattson Gemini or Nicolet Magna 550 FTIR spectrometers from thin films or from solutions in the solvent specified. ^{1}H NMR spectra were recorded using Bruker AM-instruments at 400 or 500 MHz in $CDCl_3$, and chemical shifts are reported in ppm relative to internal $CHCl_3$ (7.27 ppm). ^{1}H NMR data are described in the following order: chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q(quartet), m (multiplet), br (broadened)], integration, and coupling constant-(s) (Hz). ^{13}C NMR spectra were recorded at 100 MHz with proton decoupling using a Bruker AM-400. Distortionless enhancement by polarization transfer (DEPT) was routinely conducted to assist with signal assignments. Mass spectra were recorded at U. C. Berkeley using fast atom bombardment, or at Pfizer Central Research, Sandwich, Kent, U.K., using atmospheric pressure chemical ionization.

2-Methyl-4-nitropyridine (10). A 100-mL flask equipped with an addition funnel was charged with a solution of 2-methyl-4-nitropyridine *N*-oxide[13] (2.50 g, 16.0 mmol) in reagent-grade $CHCl_3$ (53 mL) and was cooled to 0 °C. Phosphorus trichloride (7.0 mL, 80 mmol) was added dropwise to the *N*-oxide solution from the addition funnel. The addition was complete in 20 min, the ice bath was removed, and the milky yellow solution was allowed to stir at room temperature for 40 h. The mixture was poured onto ice and basified with 10% NaOH solution. Extraction with $CHCl_3$ (3 × 40 mL), drying (Na_2SO_4), and evaporation of the solvent provided a crude material that was contaminated with $POCl_3$. This impurity was removed by washing an ether solution of the crude produce with 10% HCl. The aqueous layer was collected and carefully basified with 10% NaOH. Extraction with CH_2Cl_2, drying, and evaporation of the solvent provided a yellow oil. Purification by flash chromatography on silica gel (2:98 methanol/$CHCl_3$) afforded 1.9 g (84%) of 2-methyl-4-nitropyridine (**10**) as a colorless solid. Mp: 43−44 °C (lit.[2] mp 43−44 °C). ^{1}H NMR (400 MHz): δ 2.73 (s, 3), 7.83 (dd, 1, J = 1.9, 5.3), 7.88 (d, 1, J = 1.8), 8.79 (d, 1, J = 5.4). ^{13}C NMR (100 MHz): δ 24.43, 113.14, 115.39, 151.15, 153.94, 161.69.

2-Methyl-4-nitro-3-(phenylsulfonylmethyl)pyridine (11). To a stirring suspension of NaOH (2.12 g of Aldrich 20−40 mesh beads, 53.0 mmol) in reagent-grade DMSO (17 mL) cooled to 15 °C (cold water bath) was added a solution of chloromethyl phenyl sulfone (2.54 g, 13.3 mmol) and nitropyridine **10** (1.86 g, 13.3 mmol) in DMSO (22 mL) dropwise with a Teflon cannula, while the temperature was maintained below 20 °C. The intensely colored mixture (usually a cobalt blue) was stirred vigorously for 30 min at 15−20 °C and was then poured into a stirring solution of 1% HCl (200 mL, 66.0 mmol). Chloroform (50 mL) was added to solubilize the organic material. The aqueous layer was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic extracts were washed repeatedly with water to remove any DMSO. Drying (Na_2SO_4) of the organics and evaporation of the solvent provided 3.65 g (94%) of **10**. Mp: 139−140 °C (lit.[3] mp 141−142 °C).[3] ^{1}H NMR (400 MHz): δ 2.66 (s, 3), 5.00 (s, 2), 7.53−7.79 (m, 6), 8.73 (d, 1, J = 5.3). ^{13}C NMR (100 MHz): δ 23.2, 53.5, 114.6, 115.7, 128.0, 129.4, 134.4, 150.8, 155.9, 162.3.

4-Methoxy-2-methyl-3-[(phenylsulfonyl)methyl]pyridine (12). Sodium methoxide was prepared by adding small pieces of Na (2.2 g, 96 mmol) to precooled (0 °C) reagent-grade methanol (70 mL). Nitropyridine **11** (18.8 g, 64.0 mmol) was dissolved in methanol (60 mL) and added dropwise to the NaOMe solution. The resulting deep red solution was stirred at room temperature overnight and was then neutralized with aqueous NH_4Cl. The reaction mixture was partitioned between $CHCl_3$ and aqueous NH_4Cl, and the aqueous layer was extracted with $CHCl_3$ (3 × 70 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The remaining residue was chromatographed on silica gel (1:99 methanol/$CHCl_3$) to afford 14.8 g (83%) of methoxypyridine **12**. ^{1}H NMR (400 MHz): δ 2.53 (s, 3), 3.28 (s, 3), 4.48 (s, 2), 6.40 (d, 1, J = 5.7), 7.39−7.63 (m, 5), 8.25 (d, 1, J = 5.7). ^{13}C NMR (125 MHz): δ 15.24, 53.45, 55.71, 105.21, 114.96, 128.50, 128.77, 133.87, 138.10, 139.97, 150.55, 155.15. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 60.65; H, 5.41; N, 5.05. Found: C, 60.41; H, 5.34; N, 5.09.

4-Methoxy-2-methyl-3-[1-(phenylsulfonyl)-3-butenyl]-pyridine (13). A solution of pyridine **12** (1.30 g, 4.67 mmol) in freshly distilled THF (15 mL) cooled to −78 °C was treated

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(13) 2-Methyl-4-nitropyridine *N*-oxide was obtained from the Aldrich Chemical Co., catalog no. 45,485-0.

with *n*-butyllithium (3.09 mL of a 1.66 M solution in hexanes, 5.14 mmol). The resulting yellow solution was stirred for 1 h at −78 °C, warmed to 0 °C for 45 min, and then recooled to −78 °C. The yellow anionic solution was then added with a cannula to cooled (0 °C) neat allyl bromide (4.04 mL, 46.0 mmol). Once the addition was complete, the reaction was stirred for 1.25 h and quenched with a saturated NH_4Cl solution. The neutralized mixture was transferred to a separatory funnel, extracted with ether (3 × 25 mL), and washed with a saturated NaCl solution. The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The residue was chromatographed on silica gel (1.5:98.5 methanol/$CHCl_3$) to afford 1.35 g (91%) of **13** as a 67:33 mixture of rotamers (as observed by ^{1}H NMR). ^{1}H NMR (500 MHz): major rotamer δ 2.40 (s, 3), 3.17−3.22 (m, 2), 3.38 (s, 3), 4.56 (dd, 1, J = 5.3, 5.7), 4.84 (d, 1, J = 10.0), 4.95 (d, 1, J = 17.0), 5.13−5.36 (m, 1), 6.50 (d, 1, J = 5.7), 7.30−7.62 (m, 5), 8.23 (d, 1, J = 5.7); minor rotamer δ 2.78 (s, 3), 2.80−2.99 (m, 2), 3.33 (s, 3), 4.90 (d, 1, J = 10.4), 5.03 (d, 1, J = 17.0), 5.15 (dd, 1, J = 4.3, 6.0), 5.39−5.56 (m, 1), 6.29 (d, 1, J = 5.7), 7.30−7.62 (m, 5), 8.19(d, 1, J = 5.7). ^{13}C NMR (125 MHz): mixture of rotamers δ 23.45, 24.58, 29.79, 31.44, 54.76, 55.23, 60.52, 67.42, 103.32, 103.35, 104.94, 104.96, 114.42, 115.09, 117.80, 128.19, 128.62, 128.66, 128.93, 133.06, 133.24, 133.45, 138.32, 138.78, 150.29, 150.40, 159.82, 160.56, 164.05, 164.68. Anal. Calcd for $C_{17}H_{18}NO_3S$: C, 64.33; H, 6.03; N, 4.40. Found: C, 64.14; H, 5.99; N, 4.70.

4-Methoxy-2-methyl-3-(3-butenyl)pyridine (14). Mercury (16.92 g) was placed in a 100-mL flask equipped with a magnetic stirring bar, and small pieces of Na (1.08 g, 47.0 mmol) that had been rinsed in hexanes were added one at a time. The initial reaction was exothermic, creating flame and smoke within the flask. As the amalgam was formed, however, it was more sluggish in its reaction with the added Na, and a heat gun was used to cause the last pieces of Na to react. The freshly prepared 6% amalgam was cooled under N_2, and Na_2HPO_4 (8.91 g, 63.0 mmol) was added in a single portion. Sulfone **13** (5.00 g, 15.7 mmol) in methanol (52 mL) was then added dropwise with a cannula at room temperature. The resulting cloudy yellow solution was stirred for 2.5 h and was then partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed with a rotary evaporator, and the remaining residue was chromatographed on silica gel (1:99 methanol/$CHCl_3$) to afford 2.60 g (94%) of **14** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 2.19−2.24 (m, 2), 2.50 (s, 3), 2.69 (t, 2, J = 7.7), 3.83 (s, 3), 4.96 (d, 1, J = 10.9), 5.03 (d, 1, J = 17.1), 5.83−5.90 (m, 1), 6.63 (d, 1, J = 5.7), 8.23 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 22.05, 25.19, 32.80, 55.24, 104.06, 114.73, 123.68, 138.17, 147.80, 157.80, 160.18. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 73.94; H, 8.49; N, 7.91.

4-Methoxy-2-methyl-3-(3-oxopropyl)pyridine (15). A solution of compound **14** (1.23 g, 6.90 mmol) in 75:25 water/THF (35 mL) was cooled to 0 °C, and OsO_4 (1.75 mL of a 0.039 M solution in THF, 0.690 mmol) was added, followed immediately by $NaIO_4$ (3.69 g, 17.2 mmol). A cloudy suspension formed and was stirred for 7 h, with warming to room temperature. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The crude residue (1.09 g, 89%) was carried on without purification. ^{1}H NMR (400 MHz): δ 2.51 (s, 3), 2.61 (t, 2, J = 8.1), 2.94 (t, 2, J = 8.1), 3.83 (s, 3), 6.64 (d, 1, J = 5.7), 8.27 (d, 1, J = 5.7), 9.81 (t, 1, J = 1.5). ^{13}C NMR (100 MHz): δ 18.47, 21.89, 42.54, 55.19, 104.04, 122.02, 148.26, 156.97, 163.37, 201.56.

3-(3-Hydroxy-4-pentenyl)-4-methoxy-2-methylpyridine (16). A solution of aldehyde **15** (2.81 g, 15.6 mmol) in freshly distilled THF (150 mL), cooled to −50 °C, was treated with vinylmagnesium bromide (15.6 mL of a 1.5 M solution in THF, 23.5 mmol). The resulting mixture was allowed to warm to room temperature as it stirred for 4.5 h. The reaction was quenched with a saturated NH_4Cl solution (60 mL) and extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The residue was chromatographed on silica gel (8:92 methanol/$CHCl_3$) to afford 3.37 g (81%) of **16** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.70 (q, 2, J = 6.7), 2.52 (s, 3), 2.65 (br s, 1), 2.68−2.73 (m, 2), 3.87 (s, 3), 4.09 (q, 1, J = 6.1), 5.10 (d, 1, J = 9.2), 5.24 (d, 1, J = 15.8), 5.86−5.94 (m, 1), 6.62 (d, 1, J = 5.8), 8.22 (d, 1, J = 5.8). ^{13}C NMR (100 MHz): δ 21.42, 21.87, 35.72, 55.34, 72.31, 104.01, 114.58, 123.63, 140.84, 147.82, 157.31, 163.47. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.45; H, 8.35; N, 6.48.

3-[3-(*tert*-Butyldimethylsiloxy)-4-pentenyl]-4-methoxy-2-methylpyridine (17). To allylic alcohol **16** (2.60 g, 12.0 mmol) diluted in freshly distilled CH_2Cl_2 (40 mL) was added distilled triethylamine (3.02 mL, 21.6 mmol), *tert*-butyldimethylsilyl chloride (2.83 g, 18.8 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was stirred for 48 h at room temperature and was partitioned between CH_2Cl_2 and aqueous NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was removed with a rotary evaporator, and the remaining oil was purified by flash chromatography (40:60 hexanes/ethyl acetate), affording 3.17 g (82%) of allylic silyl ether **17** as a colorless oil. ^{1}H NMR (400 MHz): δ 0.06 (s, 3), 0.09 (s, 3), 0.93 (s, 9), 1.56−1.66 (m, 2), 2.48 (s, 3), 2.58−2.68 (m, 2), 3.82 (s, 3), 4.21 (m, 1), 5.09 (d, 1, J = 10.4), 5.20 (d, 1, J = 17.2), 5.86 (dddd, 1, J = 17.1, 10.4, 5.7), 6.62 (d, 1, J = 5.7), 8.22 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −4.90, −4.38, 18.24, 21.33, 21.96, 25.83, 36.58, 55.14, 73.54, 103.94, 113.84, 124.17, 141.16, 147.77, 157.16, 163.41. Anal. Calcd for $C_{18}H_{31}NO_2Si$: C, 67.23; H, 9.71; N, 4.36. Found: C, 66.88; H, 9.86; N, 4.54.

3-[3-(*tert*-Butyldimethylsiloxy)-4-pentenyl]-4-methoxy-2-methylpyridine *N*-Oxide (18). To a solution of pyridine **17** (143 mg, 0.450 mmol) in freshly distilled CH_2Cl_2 (1.5 mL) cooled to −78 °C was added *m*-CPBA (184 mg of 50 wt % reagent, 0.530 mmol) in a single portion. The reaction was monitored by TLC and was judged to be complete after stirring for 2 h at −78 °C. The reaction was neutralized at −78 °C with aqueous $NaHCO_3$. After being warmed to room temperature, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. Flash chromatography (15:85 methanol/ethyl acetate) of the crude material provided 151 mg (100%) of pyridine *N*-oxide **18**. ^{1}H NMR (400 MHz): δ −0.04 (s, 3), −0.01 (s, 3), 0.83 (s, 9), 1.46−1.52 (m, 2), 2.42 (s, 3), 2.56−2.62 (m, 2), 3.76 (s, 3), 4.11 (dd, 1, J = 5.4, 11), 4.99 (d, 1, J = 10.4), 5.13 (d, 1, J = 17.1), 5.70−5.78 (m, 1), 6.55 (d, 1, J = 5.7), 8.04 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.12, −4.61, 13.75, 18.01, 21.65, 25.56, 36.27, 55.64, 72.92, 104.82, 114.10, 127.37, 137.15, 140.54, 148.53, 155.33. Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.05; H, 9.26; N, 4.15. Found: C, 64.03; H, 9.10; N, 4.10.

3-[3-(*tert*-Butyldimethylsiloxy)-4-pentenyl]-4-methoxy-2-(phenylsulfonyl)methylpyridine *N*-Oxide (19). To a solution of pyridine *N*-oxide **18** (5.10 g, 15.0 mmol) in freshly distilled CH_2Cl_2 (50 mL) was added *p*-toluenesulfonyl chloride (4.38 g, 23.0 mmol). The resulting solution was cooled to −50 °C, and triethylamine (3.17 mL, 23.0 mmol) was added dropwise over 75 min using a syringe pump. Over the course of the addition, the reaction mixture became orange and cloudy. The mixture was allowed to stir overnight, warming to room temperature, and was then partitioned between aqueous NH_4Cl and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed with a rotary evaporator leaving a bright red oil, which was passed through a plug of SiO_2 (2.5:97.5 methanol/$CHCl_3$). After evaporation of the volatiles, the collected red oil was diluted in reagent-grade DMF (30 mL). Sodium benzenesulfinate (2.46 g, 15.0 mmol) was added in a single portion, and the resulting bright orange mixture was stirred at room temperature for 18 h and

was then partitioned between water and ether. The aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4). The volatiles were removed with a rotary evaporator, and the remaining DMF was removed under high vaccuum (30 min). The remaining oil was chromatographed on silica gel (65:35 ethyl acetate/hexane) to provide 3.49 g (50% from pyridine *N*-oxide **18**) of sulfone **19** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 0.02 (s, 3), 0.05 (s, 3), 0.89 (s, 9), 1.51−1.65 (m, 2), 2.57−2.74 (m, 2), 3.78 (s, 3), 4.15−4.19 (m, 1), 4.55 (s, 2), 5.03 (d, 1, J = 10.4), 5.17 (d, 1, J = 17.1), 5.74−5.82 (m, 1), 6.62 (d, 1, J = 5.6), 7.41 (t, 2, J = 7.9), 7.55 (t, 1, J = 7.5), 7.67 (d, 2, J = 7.4), 8.11 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ −4.99, −4.64, 18.07, 21.03, 25.73, 36.67, 55.30, 61.45, 73.10, 105.58, 113.97, 128.01, 128.30, 128.69, 133.43, 138.97, 140.78, 147.27, 148.23, 164.01. Anal. Calcd for $C_{24}H_{35}NO_4SSi$: C, 62.43; H, 7.64; N, 3.03. Found: C, 62.57; H, 7.57; N, 2.78.

3-(3-Acetoxy-4-pentenyl)-4-methoxy-2-[(phenylsulfonyl)-methyl]pyridine (22) (Scheme 3). A solution of allylic alcohol **16** (8.79 g, 42.2 mmol) in freshly distilled CH_2Cl_2 (140 mL) was treated with freshly distilled triethylamine (19.6 mL, 140 mmol), acetic anhydride (9.20 mL, 97.0 mmol), and a catalytic amount of 4-(dimethylamino)pyridine. The resulting mixture was stirred at room temperature for 6.5 h and was then partitioned between aqueous NH_4Cl and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL), and the combined organic extracts were dried (Na_2SO_4). Removal of the solvent with a rotary evaporator provided a crude orange oil that was chromatographed on silica gel (5:95 methanol/$CHCl_3$), providing 9.94 g (95%) of allylic acetate **20** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.71−1.77 (m, 2), 2.02 (s, 3), 2.43 (s, 3), 3.77 (s, 3), 5.14 (d, 1, J = 11.6), 5.20−5.24 (m, 2), 5.72−5.78 (m, 1), 6.57 (d, 1, J = 5.7), 8.17 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 21.03, 21.15, 21.78, 32.73, 55.15, 74.35, 103.90, 116.65, 123.10, 136.05, 147.95, 156.99, 163.35, 170.14.

To a solution of allylic acetate **20** (890 mg, 3.60 mmol) in freshly distilled CH_2Cl_2 (12 mL) was added *m*-CPBA (1.87 g of 50 wt % reagent, 5.42 mmol) in a single portion. The resulting white solution was stirred at room temperature for 3 h and was then partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 until TLC analysis showed no product to be present in the aqueous extracts. The combined organic extracts were dried (Na_2SO_4), and the solvent was removed with a rotary evaporator. The remaining residue was chromatographed on silica gel (2:98 methanol/$CHCl_3$) to afford 917 mg (97%) of pyridine *N*-oxide **21** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.70−1.81 (m, 2), 2.09 (s, 3), 2.52 (s, 3), 2.66−2.70 (m, 2), 3.85 (s, 3), 5.22 (d, 1, J = 10.6), 5.26−5.30 (m, 2), 5.76−5.81 (m, 1), 6.64 (d, 1, J = 7.3), 8.17 (d, 1, J = 7.3). ^{13}C NMR (100 MHz): δ 13.77, 20.90, 21.72, 32.53, 55.70, 73.78, 104.91, 116.92, 126.23, 135.54, 137.42, 148.46, 155.20, 169.90.

To a solution of pyridine *N*-oxide **21** (7.25 g, 27.0 mmol) in freshly distilled CH_2Cl_2 (90 mL) was added *p*-toluenesulfonyl chloride (7.72 g, 41.0 mmol). The resulting solution was cooled to −50 °C, and triethylamine (5.74 mL, 41.0 mmol) was added dropwise over 60 min with a syringe pump. Over the course of the addition, the reaction mixture became orange and cloudy. The mixture was allowed to stir for 5 h, warmed to room temperature, and partitioned between aqueous NH_4Cl and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed with a rotary evaporator, leaving a bright red oil that was (without further purification) diluted in reagent-grade DMF (54 mL). Sodium thiophenoxide (4.65 g, 35.1 mmol) was added in a single portion, and the resulting bright orange mixture was stirred at room temperature for 12 h and was then partitioned between water and ether. The aqueous layer was extracted with ether (3 × 60 mL), and the combined organic extracts were dried (Na_2SO_4). The volatiles were removed with a rotary evaporator, and the residual DMF was removed under high vaccuum (30 min). The remaining oil was chromatographed on silica gel (55:45 ethyl acetate/hexane) to provide 5.43 g (57% from pyridine *N*-oxide **21**) of sulfide **22** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.80−1.86 (m, 2), 2.01 (s, 3), 2.67 (m, 2,), 3.83 (s, 3), 4.26 (s, 2), 5.16 (d, 1, J = 10.5), 5.23−5.27 (m, 2), 5.74−5.78 (m, 1), 6.65 (d, 1, J = 5.6), 7.16−7.41 (m, 5), 8.29 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 21.01, 21.09, 33.34, 38.85, 55.36, 74.34, 104.93, 116.73, 124.24, 126.33, 128.73, 129.06, 136.00, 136.38, 148.52, 155.45, 163.90, 170.16. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.19; H, 6.48; N, 3.92. Found: C, 67.11; H, 6.62; N, 4.00.

Sulfone 23. Before carrying out this reaction, both allylic acetate **22** and sulfone **19** were separately azeotroped with benzene and placed under high vacuum to ensure dryness. Sulfone **19** (1.78 g, 3.80 mmol) was dissolved in freshly distilled THF (3 mL) and cooled to −78 °C. In a separate pear-shaped flask was dissolved NaHMDS (892 mg of an 84 wt % reagent, 4.09 mmol) in THF (3 mL). The resulting yellow solution was added dropwise with a Teflon cannula to the cooled sulfone solution. An additional portion of THF (500 μL) was passed through the cannula as a rinse. The resulting yellow/orange anionic solution was stirred under argon at −78 °C for 70 min and was then warmed to 0 °C. While the sulfone was warming to 0 °C, in a separate flask were dissolved $Pd_2(dba)_3{\cdot}CHCl_3$ (136 mg, 3.7 mol %) and 1,2-bis(diphenylphosphino)ethane (157 mg, 11.1 mol %) in THF (1 mL). The resulting dark purple mixture was stirred at room temperature for 10 min to give the active catalyst as a homogeneous yellow/orange solution. Allylic acetate **22** (1.25 g, 3.55 mmol) was dissolved in THF (3 mL) and was added dropwise with a Teflon cannula to the active catalyst solution. The resulting red/orange mixture was immediately added with a cannula to the anionic solution at 0 °C. An additional portion of THF (500 μL) was passed through the cannula as a rinse. The ice bath was removed and replaced with a heating mantle. Under a steady stream of argon, a reflux condenser was attached, and the mixture was heated at reflux for 4 h. After cooling, the mixture was partitioned between ethyl acetate and saturated NH_4Cl. The aqueous layer was extracted with ethyl acetate (2 × 10 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent provided an impure red oil that was purified by flash chromatography on silica gel (40:60 hexanes/ethyl acetate) to afford 2.03 g (76%) of **23** as a mixture of diastereomers. ^{1}H NMR (d_8-toluene, 100 °C, 400 MHz): δ 0.09 (s, 1.5), 0.11 (s, 1.5), 0.13 (s, 1.5), 0.17 (s, 1.5), 0.99 (s, 4.5), 1.01 (s, 4.5), 1.70−1.89 (m, 2), 1.91−1.95 (m, 2), 2.59 (dt, 2, J = 2.2, 5.6), 2.83−2.88 (m, 1.5), 3.09−3.31 (m, 1.5), 3.20−3.30 (m, 2), 3.27 (s, 3), 3.31 (s, 3), 4.15 (s, 2), 4.25 (t, 1, J = 5.7), 4.77 (dt, 1, J = 4.1, 5.9), 5.04 (dt, 1, J = 1.5, 10.9), 5.17−5.28 (m, 1), 5.44−5.50 (m, 1), 5.86−5.95 (m, 1), 6.14 (d, 1, J = 5.6), 6.18 (d, 1, J = 5.4), 6.90−7.12 (m, 6), 7.35 (d, 2, J = 7.1), 7.66 (dt, 2, J = 1.56, 7.0), 8.00 (d, 0.5, J = 5.5), 8.02 (d, 0.5, J = 5.5), 8.09 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ −3.89, −3.72, −3.60, 19.04, 21.72, 21.91, 26.58, 26.75, 26.79, 26.85, 31.15, 31.21, 33.12, 33.66, 34.94, 38.44, 38.52, 40.11, 55.35, 55.43, 55.51, 70.08, 74.79, 105.59, 105.68, 106.09, 108.18, 114.49, 114.64, 126.71, 127.25, 127.31, 130.71, 130.99, 131.20, 133.20, 133.98, 137.22, 138.54, 140.43, 140.55, 142.45, 142.70, 148.57, 148.96, 153.59, 157.66, 164.73, 164.82. Anal. Calcd for $C_{42}H_{54}N_2O_5S_2Si$: C, 66.44; H, 7.17; N, 3.69. Found: C, 66.04; H, 7.15; N, 3.54.

Allylic Alcohol 24. Sodium amalgam was prepared in a 100-mL flask equipped with a magnetic stirring bar from 726 mg of mercury and 44 mg (1.9 mmol) of Na (44 mg, 1.9 mmol) as described previously in the preparation of compound **14**. The freshly prepared 6% amalgam was cooled under N_2, and Na_2HPO_4 (323 mg, 2.27 mmol) was added in a single portion. Sulfone **23** (287 mg, 0.380 mmol) in methanol (2.0 mL) was then added dropwise with a cannula at room temperature. The resulting cloudy yellow solution was stirred for 2 h and was then partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed with a rotary evaporator, and the remaining residue was chromatographed on silica gel (70:30 ethyl acetate/hexanes), affording 174 mg (66%) of the *tert*-butyldimethylsilyl ether of alcohol **24** as a pale yellow oil. This compound is a mixture of diastereomers, and many of the NMR resonances

were doubled. Anal. Calcd for $C_{36}H_{50}N_2O_3SSi$: C, 69.86; H, 8.14; N, 4.52. Found: C, 69.86; H, 8.07; N, 4.79.

A cooled (0 °C) solution of the foregoing silyl ether (1.05 g, 1.50 mmol) in freshly distilled THF (2.0 mL) was treated with tetra-*n*-butylammonium fluoride (7.5 mL of a 1 M solution in THF, 7.5 mmol). The resulting mixture was allowed to stir for 5.5 h, warming to room temperature, and was then partitioned between aqueous NH_4Cl and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was removed with a rotary evaporator, and the remaining oil was chromatographed on silica gel (5:95 methanol/ethyl acetate). Allylic alcohol **24** (756 mg, 100%) was obtained as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.67 (m, 2), 2.17 (m, 2), 2.34 (m, 2), 2.64−2.75 (m, 6), 3.19 (br s, 1), 3.79 (s, 3), 3.80 (s, 3), 4.09 (t, 1, J = 5.8), 4.26 (s, 2), 5.08 (d, 1, J = 10.4), 5.24 (d, 1, J = 17.2), 5.39−5,49 (m, 2), 5.85−5.93 (m, 1), 6.58 (d, 1, J = 5.7), 6.61 (d, 1, J = 5.7), 7.13−7.39 (m, 5), 8.30 (m, 2). ^{13}C NMR (100 MHz): δ 21.10, 25.51, 31.97, 32.48, 34.63, 36.52, 38.79, 55.23, 55.29, 72.18, 103.77, 104.92, 114.28, 123.45, 124.69, 126.24, 128.70, 129.60, 129.92, 130.38, 136.40, 141.02, 148.02, 148.17, 155.50, 160.13, 163.54, 163.96. Anal. Calcd for $C_{30}H_{36}N_2O_5S$: C, 71.39; H, 7.19; N, 5.55. Found: C, 71.72; H, 6.95; N, 5.52.

Allylic Pivalate 25. To a solution of allylic alcohol **24** (1.22 g, 2.41 mmol) in freshly distilled CH_2Cl_2 (3.0 mL) was added distilled triethylamine (1.70 mL, 12.1 mmol), trimethyl acetic anhydride (2.44 mL, 12.1 mmol), and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine. The resulting solution was stirred at room temperature for 50 h and was then partitioned between CH_2Cl_2 and saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (3 × 12 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent provided a yellow oil that was purified by flash chromatography on silica gel (2:98 methanol/ethyl acetate) to afford 1.39 g (98%) of **25** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.22 (s, 9), 1.75−1.79 (m, 2), 2.16−2.20 (m, 2), 2.33−2.38 (m, 2), 2.64 (dt, 4, J = 5.8, 8.0), 2.88 (t, 2, J = 8.3), 3.80 (s, 3), 3.82 (s, 3), 4.25 (s, 2), 5.15 (d, 1, J = 10.6), 5.22−5.31 (m, 2), 5.48 (dd, 2, J = 1.6, 5.2), 5.76−5.84 (m, 1), 6.59 (d, 1, J = 5.7), 6.64 (d, 1, J = 5.7), 7.13−7.40 (m, 5), 8.27 (d, 1, J = 5.6), 8.28 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 20.97, 25.72, 27.22, 27.47, 32.24, 32.73, 33.80, 34.79, 38.90, 55.31, 55.39, 73.87, 103.93, 105.01, 116.20, 123.12, 124.83, 126.34, 128.81, 130.02, 130.06, 130.10, 136.39, 136.62, 148.27, 148.37, 155.57, 160.06, 163.73, 164.04, 177.63. Anal. Calcd for $C_{35}H_{44}N_2O_4S$: C, 71.39; H, 7.53; N, 4.75. Found: C, 71.11; H, 7.67; N, 4.72.

Sulfone 26. A solution of sulfide **25** (1.09 g, 1.85 mmol) in freshly distilled CH_2Cl_2 (9.2 mL) was treated with a single portion of tetra-*n*-butylammonium peroxymonosulfate (5.23 g of a 38 wt % solid, 5.55 mmol). The resulting viscous mixture was stirred at room temperature for 24 h and was then partitioned between CH_2Cl_2 and 1 N NaOH. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent provided a yellow oil that was purified by flash chromatography on silica gel (2.5:97.5 methanol/ethyl acetate) to provide 903 mg (78%) of sulfone **26** as a pale yellow oil. ^{1}H NMR (400 MHz): δ 1.21 (s, 9), 1.75 (m, 2), 2.10 (m, 2), 2.33 (m, 2), 2.62 (m, 2), 2.69−2.75 (m, 4), 3.79 (s, 3), 3.81 (s, 3), 4.55 (s, 2), 5.13 (d, 1, J = 10.6), 5.21−5.29 (m, 2), 5.43 (m, 2), 5.75−5.84 (m, 1), 6.59 (d, 1, J = 5.6), 6.64 (d, 1, J = 5.6), 7.43 (t, 2, J = 7.8), 7.56 (t, 1, J = 7.2), 7.67 (t, 2, J = 7.4), 8.10 (d, 2, J = 5.5), 8.25 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 20.81, 25.56, 27.08, 31.73, 32.50, 33.64, 34.66, 38.77, 55.18, 55.36, 61.72, 73.73, 103.82, 105.67, 116.06, 122.92, 127.46, 128.37, 128.76, 129.51, 130.31, 133.49, 136.24, 138.94, 147.52, 148.21, 148.31, 159.86, 163.52, 164.08, 177.51.

Macrocyclic Sulfone 27. Before carrying out this reaction, sulfone **26** was azeotroped with benzene and placed under high vacuum to ensure dryness. Sulfone **26** (38.8 mg, 0.630 mmol) was dissolved in freshly distilled THF (630 μL), cooled to −78 °C under argon, and treated with NaHMDS (72 μL of a 1 M solution in THF, 0.66 mmol). A bright yellow solution resulted and was stirred at −78 °C for approximately 30 min and was then warmed to room temperature. While the anion was warming to room temperature, in a separate 15-mL two-necked flask equipped with a coldfinger condenser were dissolved $Pd_2(dba)_3$•$CHCl_3$ (7.8 mg, 24 mol % of Pd(0)) and 1,2-bis(diphenylphosphino)ethane (7.5 mg, 30 mol %) in THF (550 μL) to give a deep red homogeneous solution. After being stirred for 5−10 min, the catalyst solution was diluted with THF (3.40 mL) to give a 0.0038 M solution of Pd(0) catalyst. At rt, the bright yellow anion (if the anion is orange, it should be quenched with water and repurified) was diluted with THF (2.4 mL) to give a 0.02 M solution, which was taken into a 5-mL gastight syringe. Several drops of the anion were added to the red catalyst solution before it was immersed in a hot (70 °C) oil bath. Within 5 min, the catalyst solution turned orange, and the dropwise addition of the anion to the refluxing catalyst solution was initiated. The addition was complete after 2 h, and the reaction mixture was stirred at reflux until TLC analysis of the mixture indicated that no further conversion was occurring (usually 5 additional h). After being cooled to room temperature, the reaction mixture was partitioned between ethyl acetate and aqueous $NaHCO_3$, the aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvent provided an oil that was purified by flash chromatography on silica gel (3:97 methanol/ethyl acetate; TLC solvent was 3:97 methanol/$CHCl_3$) to afford 17.8 mg (56%) of macrocyclic sulfone **27** as a coarse yellow solid. ^{1}H NMR (400 MHz): δ 2.10−2.25 (m, 5), 2.37−2.77 (m, 7), 2.94−2.97 (m, 1), 3.06−3.10 (m, 1), 3.78 (s, 3), 3.83 (s, 3), 4.75 (dd, 1, J = 4.8, 9.6), 5.12−5.17 (m, 1), 5.32−5.45 (m, 2), 5.54−5.61 (m, 1), 6.54 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.5), 7.37 (t, 2, J = 7.6), 7.45 (d, 2, J = 7.2), 7.54 (t, 1, J = 7.4), 8.18 (d, 1, J = 5.7), 8.20 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ 25.45, 25.49, 30.62, 31.81, 32.25, 32.37, 35.45, 55.16, 55.31, 67.62, 103.89, 105.51, 123.52, 125.56, 127.85, 128.36, 128.39, 129.41, 131.16, 133.33, 133.48, 137.03, 147.99, 150.40, 160.36, 163.65, 164.31.

Bis-pyridine 28. Small strips of aluminum foil (99 mg, 3.7 mmol) were dipped into an aqueous 2% $HgCl_2$ solution for 15 s. The strips were rinsed thoroughly with 95% ethanol followed by ether and added to a cooled (0 °C), stirring solution of sulfone **27** (191 mg, 0.370 mmol) in 10:1 THF/water (21 mL). The mixture was stirred at 0 °C for 1.5 h and filtered through a pad of Celite, and the solvent was removed. Purification of the residue by flash chromatography on silica gel (3.5:96.5 methanol/ethyl acetate) provided 113 mg (81%) of symmetrical macrocycle **28** as a white solid. ^{1}H NMR (400 MHz): δ 2.27−2.35 (m, 4), 2.41−2.57 (m, 4), 2.67−2.73 (m, 4), 2.80−2.87 (m, 4), 3.83 (s, 6), 5.34−5.45 (m, 2), 5.55−5.63 (m, 2), 6.62 (d, 2, J = 5.6), 8.29 (d, 2, J = 5.6). ^{13}C NMR (100 MHz): δ 25.94, 31.08, 31.86, 34.40, 55.13, 103.82, 123.15, 129.62, 131.02, 147.91, 159.98, 163.70.

Bis-pyridine 7. Raney nickel (20 mg of a 50% slurry in water, 20 wt %) was washed several times with ether and placed under N_2. A solution of macrocyclic sulfone **28** (52 mg, 0.10 mmol) in reagent-grade methanol (300 μL) was added to the catalyst with a cannula. The flask was alternately evacuated (aspirator) and purged with H_2 three times, and the mixture was stirred under a positive pressure of H_2. After 20 h, the reaction mixture was partitioned between CH_2Cl_2 and a 0.05 M solution of NaOH. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts were dried (Na_2SO_4). Removal of the solvent and purification of the remaining residue by flash chromatography on silica gel (3:97 methanol/$CHCl_3$) afforded 34 mg (65%) of **7** as a white solid. ^{1}H NMR (400 MHz): δ 1.51−1.55 (m, 12), 1.72−1.76 (m, 4), 2.60−2.62 (m, 4), 2.72−2.76 (m, 4), 3.83 (s, 6), 6.59 (d, 2, J = 5.6), 8.27 (d, 2, J = 5.6). ^{13}C NMR (100 MHz): δ 25.25, 28.45, 28.48, 28.66, 29.39, 34.49, 55.20, 103.65, 124.01, 148.05, 160.89, 163.88.

(*E*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-4-methoxy-2-methylpyridine (30). To a solution of the sulfone **12** (305 mg, 1.1 mmol) in dry THF (5 mL) was added *n*-BuLi (460 μL, 1.1 mmol) at −78 °C. The solution was allowed to warm to −50 °C over 0.5 h, before addition to the allylic chloride (265 mg, 1.2 mmol) in THF (500 μL) at room

temperature. The solution was stirred for 40 min and then quenched with saturated NH_4Cl (aq). Ether was added, and the layers were separated, re-extracting the aqueous solution twice with ether. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a brown oil that was purified on SiO_2 (7 × 3.5 cm) eluting with CH_2Cl_2/MeOH (100:0 then 99:1) to provide compound **29** (444 mg, 0.96 mmol, 87%). NMR spectra were complicated by the presence of two rotational isomers.

To a freshly prepared Na/Hg amalgam (50 g of 5 wt %) and NaH_2PO_4 (14.4 g, 120 mmol) in MeOH (10 mL) was added a solution of the sulfone **29** (4.43 g, 9.6 mmol) in MeOH (50 mL) with ice cooling. When the addition was complete, the bath was removed and the mixture stirred at room temperature for 6 h. The bulk of the solvent was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2 and then decanted from the mercury metal. The layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil (2.6 g). The material was purified on SiO_2 (9 × 4 cm), eluting with EtOAc/hexanes (1:1) to provide the title compound **30** (2.87 g, 8.9 mmol, 93%) as a colorless oil. ^{1}H NMR (400 MHz): δ 0.07 (s, 6), 0.91 (s, 9), 2.17−2.25 (m, 2), 2.50 (s, 3), 2.67−2.72 (m, 2), 3.82 (s, 3), 4.12 (dd, 2, J = 1.3, 5.2), 5.57 (ddt, 1, J = 10.0, 3.9, 6.6), 5.67−5.77 (m, 1), 6.63 (d, 1, J = 5.7), 8.23 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.1, 18.4, 22.2, 25.5, 26.0, 31.3, 55.2, 63.9, 104.0, 123.7, 129.7, 130.4, 148.0, 157.2, 163.5. Anal. Calcd for $C_{18}H_{31}NO_2Si$: C, 67.2; H, 9.7; N, 4.4. Found: C, 67.0; H, 10.0; N, 4.2.

(*E*)-3-(5-Chloropent-3-en-1-yl)-4-methoxy-2-methylpyridine (31). To a solution of the silyl ether **30** (132 mg, 0.41 mmol) in THF (2 mL) was added 1 N HCl (2 mL) at room temperature. After 0.25 h, aqueous Na_2CO_3 was added to adjust the pH to about 10. CH_2Cl_2 was added, and the layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a colorless oil. Purification by chromatography on SiO_2 (1 × 2.5 cm) eluting with EtOAc/MeOH (19:1) afforded the allylic alcohol (85 mg, 0.41 mmol, 100%) as a colorless oil that solidified after prolonged standing in the refrigerator. ^{1}H NMR (400 MHz): δ 2.19 (dd, 2, J = 6.9, 14.9), 2.48 (s, 3), 2.63−6.70 (m, 2), 2.80−2.93 (br, 1), 3.81 (s, 3), 4.09 (dd, 2, J = 5.5, 1.0), 5.65 (dt, 1, J = 15.3, 5.5), 5.75 (dt, 1, J = 15.3, 6.4), 6.62 (d, 1, J = 5.7), 8.20 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 22.1, 25.5, 31.4, 55.4, 63.4, 104.2, 123.8, 130.0, 131.9, 147.9, 157.2, 163.7.

To an ice-cooled solution of the foregoing allylic alcohol (90 mg, 0.43 mmol), LiCl (42.5 mg, 1.0 mmol), and 2,6-lutidine (120 μL, 1.0 mmol) in dry DMF (2 mL) was added MsCl (63 μL, 0.8 mmol). After 5 min, the cooling bath was removed and the solution stirred at room temperature for 16.5 h. The mixture was partitioned between aqueous Na_2CO_3 and ether, and the organic layer was separated. The aqueous solution was re-extracted twice with ether. The organic extracts were combined, washed with three portions of water to remove any residual DMF, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil. The material was purified on SiO_2 (2.5 × 2.5 cm) eluting with EtOAc/hexanes (1:1) to provide the title compound **31** as a colorless oil (92 mg, 0.41 mmol, 95%). Due to the instability of the allylic chloride, it was used without delay in the next reaction.

(*E*,*E*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-2-[6-(4-methoxy-2-methylpyridin-3-yl)hex-3-en-1-yl]-4-methoxypyridine (32). To a solution of the methylpyridine **30** (120 mg, 0.37 mmol) in THF (2 mL) was added *n*-BuLi (160 μL of 2.45 M, 0.39 mmol) dropwise at −78 °C. The resulting solution was allowed to warm to −50 °C in the bath over 40 min and then treated with a solution of the allylic chloride **31** (60 mg, 0.27 mmol) in THF (1 mL). After 5 min at −50 °C, the bath was removed and the solution allowed to stir at room temperature for 10 min. Water was added, and the resulting mixture was extracted with three portions of CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a brown oil that was purified on SiO_2 (3 × 2.5 cm) eluting with EtOAc/hexanes/MeOH (1:1:0, 1:0:0, 47:0:3) to afford the title compound **32** as a pale yellow oil (116 mg, 0.23 mmol, 85% based on **30**). ^{1}H NMR (400 MHz): δ 0.07 (s, 6), 0.90 (s, 9), 2.10−2.25 (m, 4), 2.35−2.41 (m, 2), 2.49 (s, 3), 2.60−2.73 (m, 4), 2.75−2.82 (m, 2), 3.80 (s, 3), 3.81 (s, 3), 4.12 (dd, 2, J = 1.2, 5.2), 5.45−5.60 (m, 3), 5.66−5.77 (m, 1), 6.61 (d, 2, J = 5.7), 8.21 (d, 1, J = 5.7), 8.29 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.0, 18.6, 22.3, 25.2, 26.0, 26.2, 31.8, 32.1, 32.9, 35.1, 55.4, 55.4, 64.1, 104.0, 104.2, 123.6, 124.0, 129.8, 130.2, 130.3, 130.6, 148.0, 148.3, 157.4, 160.4, 163.7, 163.9.

(*E*,*E*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-[(phenylsulfanyl)methyl]pyridin-3-yl]-hex-3-en-1-yl]-4-methoxypyridine (33). To a solution of the compound **32** (40 mg, 0.078 mmol) in THF (1 mL) was added *n*-BuLi (33 μL of 2.45 M, 0.081 mmol) dropwise at −78 °C. The resulting orange solution was allowed to warm to −50 °C over 20 min. The solution was recooled to −78 °C, and PhSSPh (87 mg, 0.4 mmol) in THF (500 μL) was added in one portion. The cooling bath was removed, and stirring was continued at room temperature for 30 min. The pale yellow solution was diluted with ether and washed with water. The aqueous solution was extracted with an additional two portions of ether. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil that was purified on SiO_2 (6 × 1.5 cm) eluting with EtOAc/hexanes (7:3 then 8:2) to provide the title compound **33** (35 mg, 0.057 mmol, 73%) as a colorless oil. ^{1}H NMR (400 MHz): δ 0.07 (s, 6), 0.90 (s, 9), 2.15−2.25 (m, 4), 2.35−2.43 (m, 2), 2.61−2.73 (m, 4), 2.75−2.83 (m, 2), 3.83 (s, 3), 3.84 (s, 3), 4.12 (dd, 2, J = 1.2, 5.2), 4.27 (s, 2), 5.50 (quintet, 2, J = 2.7), 5.53−5.60 (m, 1), 5.67−5.75 (m, 1), 6.63 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.7), 7.18 (tt, 1, J = 1.2, 7.3), 7.23−7.28 (m, 2), 7.39−7.43 (m, 2), 8.30 (d, 2, J = 5.7). ^{13}C NMR (100 MHz): δ −5.2, 18.4, 24.9, 25.6, 25.9, 31.7, 32.1, 32.7, 33.8, 38.8, 55.4, 55.7, 63.7, 104.3, 105.0, 124.4, 125.0, 126.5, 129.0, 129.8, 130.1, 130.2, 130.6, 136.7, 146.7, 148.5, 155.6, 159.2, 164.2, 165.0.

(*E*,*E*)-3-[5-(Pivaloyloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-(phenylsulfanyl)methylpyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (34). To an ice-cooled solution of the TBS ether **33** (32 mg, 0.052 mmol) in THF (500 μL) was added a solution of TBAF (70 μL of 1.0 M in THF, 0.07 mmol). The solution was stirred at room temperature for 20 h and then partitioned between H_2O and CH_2Cl_2, and the layers were separated. The aqueous solution was extracted with two additional portions of CH_2Cl_2, and the organic layers were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil that was purified on alumina (4 × 1.5 cm) eluting with EtOAc/methanol (1:0 then 98:2) to provide the alcohol (26 mg, 0.042 mmol, 80%) as a colorless oil. ^{1}H NMR (400 MHz): δ 2.17−2.26 (m, 5), 2.32−2.38 (m, 2), 2.69 (apparent q, 4, J = 7.5), 2.73−2.79 (m, 2), 3.84 (s, 3), 3.86 (s, 3), 4.11 (d, 2, J = 5.0), 4.29 (s, 2), 5.46−5.49 (m, 2), 5.66 (dt, 1, J = 15.4, 5.5), 5.76 (dt, 1, J = 15.4, 6.1), 6.63 (d, 1, J = 5.7), 6.68 (d, 1, J = 5.7), 7.19 (tt, 1, J = 1.2, 7.3), 7.23−7.30 (m, 2), 7.38−7.43 (m, 2), 8.29 (d,1, J = 5.7), 8.30 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 25.2, 25.8, 32.0, 32.2, 33.0, 35.0, 39.1, 55.5, 55.6, 63.7, 104.1, 105.2, 123.6, 124.9, 126.6, 129.0, 129.9, 130.0, 130.3, 130.6, 131.9, 136.7, 148.2, 148.5, 155.8, 160.2, 164.0, 164.3.

To a solution of the foregoing allylic alcohol (600 mg, 1.19 mmol) and Et_3N (280 μL, 2.0 mmol) in CH_2Cl_2 (6 mL) was added pivaloyl chloride (180 μL, 1.46 mmol), followed by DMAP (15 mg, 0.12 mmol). The solution was stirred at room temperature for 1.5 h and then diluted in CH_2Cl_2 and washed with Na_2CO_3 (aq). The aqueous solution was extracted with two additional portions of CH_2Cl_2, the organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a yellow oil. Purification on SiO_2 (4.5 × 2.5 cm) eluting with EtOAc/hexanes (9:1 then 1:0) provided the title compound **34** as a viscous oil (677 mg, 1.15 mmol, 97%). IR (film): 1726 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.17 (s, 9), 2.15−2.25 (m, 4), 2.32−2.39 (m, 2), 2.67 (apparent

q, 4, J = 7.5), 2.74−2.79 (m, 2), 3.79 (s, 3), 3.81 (s, 3), 4.25 (s, 2), 4.48 (dd, 2, J = 1.0, 6.1), 5.45−5.57 (m, 3), 5.76 (dt, 1, J = 6.7, 15.4), 6.59 (d, 1, J = 5.7), 6.63 (d, 1, J = 5.7), 7.14 (tt, 1, J = 2.2, 7.2), 7.20−7.26 (m, 2), 7.36−7.41 (m, 2), 8.27 (d, 1, J = 5.7), 8.27 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 24.9, 25.7, 27.2, 32.1, 32.3, 32.7, 34.9, 38.7, 39.0, 55.3, 55.4, 64.9, 104.0, 105.0, 123.1, 124.7, 124.8, 126.3, 128.8, 130.0, 130.0, 130.2, 134.6, 136.7, 148.3, 148.4, 155.6, 160.2, 163.8, 164.1, 178.3.

(*E*,*E*)-3-[5-(Pivaloyloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-(phenylsulfonyl)methylpyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (35). A solution of the thioether **34** (677 mg, 1.15 mmol) and TBA-Oxone (2.8 g) in CH_2Cl_2 was stirred at room temperature for 24 h. The mixture was diluted in EtOAc and washed with Na_2CO_3 (aq), re-extracting the aqueous solution with two portions of EtOAc. The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a yellow oil. Purification on SiO_2 (4 × 2 cm) eluting with CH_2Cl_2/methanol (99:1 then 19:1) provided the title compound **34** as a viscous oil (362 mg, 0.58 mmol, 51%). IR (film): 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.18 (s, 9), 2.09−2.17 (m, 2), 2.23 (q, 2, J = 7.3), 2.33−2.40 (m, 2), 2.65−2.80 (m, 6), 3.83 (s, 3), 3.84 (s, 3), 4.49 (dd, 2, J = 0.9, 6.2), 4.58 (s, 2), 5.44−5.48 (m, 2), 5.55 (dt, 1, J = 15.4, 6.2), 5.79 (dt, 1, J = 15.4, 6.7), 6.63 (d, 1, J = 5.7), 6.67 (d, 1, J = 5.7), 7.46 (t, 2, J = 7.5),7.60 (tt, 1, J = 1.2, 7.5), 7.71 (dd, 2, J = 1.2, 7.5), 8.13 (d, 1, J = 5.7), 8.29 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 24.9, 25.8, 27.3, 31.9, 32.1, 32.7, 34.9, 38.8, 55.3, 55.6, 61.9, 65.0, 104.0, 105.9, 123.2, 124.7, 127.7, 128.6, 129.0, 129.6, 130.7, 133.7, 134.7, 139.2, 147.7, 148.3, 148.5, 160.1, 163.8, 164.3, 178.4.

(4*E*,16*E*)-19-(Benzenesulfonyl)-12,24-dimethoxy-9,21 diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),4,8(13),9,11,16,-20,22-octaene ((*E*)-27) and (4*E*,16*Z*)-19-(Benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}-]tetracosa-1(24),4,8(13),9,11,16,20,22-octaene ((*Z*)-27). To a solution of the *E*,*E*-sulfone **35** (297 mg, 0.479 mmol) in THF (40 mL) at −78 °C was added NaHMDS (560 μL of a 0.94 M solution in THF, 0.527 mmol). The solution was allowed to warm to room temperature. In a separate flask equipped with a reflux condenser, a solution of $Pd(dba)_3$·$CHCl_3$ (18.7 mg, 0.018 mmol) and dppe (18.2 mg, 0.0458 mmol) in THF (18 mL) was warmed to gentle reflux, whereupon the solution changed from a deep red to a pale orange color. The yellow solution of the sulfone anion was added to the refluxing catalyst solution over 2.5 h using a syringe pump. The resulting dark orange mixture was then allowed to cool to room temperature, the bulk of the THF was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and water. The layers were separated, and the aqueous solution was re-extracted twice with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a viscous yellow oil. Purification on SiO_2 (7 × 2.5 cm) eluting with EtOAc provided a 2.5:1 mixture of the title compounds (*E*)-**27** and (*Z*)-**27** as a white solid (184 mg, 0.355 mmol, 74%). Data for (*E*)-**27**. ^{1}H NMR (400 MHz): δ 2.10−2.25 (m, 5), 2.37−2.77 (m, 7), 2.94−2.97 (m, 1), 3.06−3.10 (m, 1), 3.78 (s, 3), 3.83 (s, 3), 4.75 (dd, 1, J = 4.8, 9.6), 5.12−5.17 (m, 1), 5.32−5.45 (m, 2), 5.54−5.61 (m, 1), 6.54 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.5), 7.37 (t, 2, J = 7.6), 7.45 (d, 2, J = 7.2), 7.54 (t, 1, J = 7.4), 8.18 (d, 1, J = 5.7), 8.20 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ 25.4, 25.5, 30.6, 31.8, 32.2, 32.4, 35.5, 55.2, 55.3, 67.6, 103.9, 105.5, 123.5, 125.6, 127.8, 128.4, 128.4, 129.4, 131.2, 133.3, 133.5, 137.0, 148.0, 150.4, 160.4, 163.7, 164.3.

(*Z*)-3-[1-(Benzenesulfonyl)-5-(*tert*-butyldimethylsiloxy-)pent-3-en-1-yl]-4-methoxy-2-methylpyridine (36). To a solution of sulfone **12** (23.2 g, 84 mmol) in THF (280 mL) at −45 °C was added *n*-BuLi (35 mL of a 2.5 M solution in hexane, 88.2 mmol) dropwise. After the addition was complete, the bath was removed and the mixture allowed to warm to 15 °C. (*Z*)-$ClCH_2CH{=}CHCH_2OTBS$[8] (22 g, 100 mmol) was added dropwise, and a slight exotherm was observed. The reaction temperature was allowed to reach 29 °C. The brown solution was stirred at room temperature for 50 min and then poured into a saturated solution of NH_4Cl (aq). The layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a brown oil (45 g). The material was divided into two portions and purified on SiO_2 (9 × 6.5 cm) eluting with EtOAc/hexanes (4:6, 1:1, 1:0) to provide the title compound **36** (33.2 g, 72 mmol, 86%). ^{1}H NMR reported for a mixture of rotational isomers (400 MHz): δ 0.01 and 0.03 (s, 6), 0.86 and 0.84 (s, 9), 2.39 and 2.80 (s, 3), 2.99−3.32 (m, 2), 3.36 and 3.47 (s, 3), 3.97−4.05 and 4.12−4.21 (m, 2), 4.52 and 5.13 (dd, 1, J = 5.1, 11.1 and 6.2, 10.6), 5.02−5.17 and 5.40−5.54 (m, 2), 6.32 and 6.55 (d, 1, J = 5.7), 7.32−7.68 (m, 5), 8.23 and 8.26 (d, 1, J = 5.7). ^{13}C NMR reported for a mixture of rotational isomers: δ −5.12, −5.08, −5.07, 18.4, 23.6, 24.4, 24.6, 25.6, 26.0, 55.1, 55.5, 59.2, 59.4, 61.0, 67.6, 103.6, 105.2, 114.7, 124.9, 125.2, 128.4, 128.8, 128.9, 129.0, 132.9, 133.0, 133.5, 133.7, 139 2, 150.5, 150.6, 160.1, 160.8, 164.4, 165.0. Anal. Calcd for $C_{24}H_{35}NO_4SiS$: C, 62.4; H, 7.6; N, 3.0. Found: C, 62.3; H, 7.8; N, 3.2.

(*Z*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-4-methoxy-2-methylpyridine (37). To a solution of sulfone **36** (4.0 g, 8.7 mmol) in MeOH (30 mL) was added NaH_2PO_4 (2.1 g, 15 mmol). Na/Hg amalgam (5%, a total of 12 g) was added portionwise over 1 h. A small amount of water was added to quench the excess amalgam, the bulk of the methanol was removed under reduced pressure, and the residue was partitioned between water and CH_2Cl_2 and then decanted from the mercury metal. The layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil (2.9 g). The material was purified on SiO_2 (6 × 4.5 cm) eluting with EtOAc/hexanes (3:7) to provide the title compound **37** (2.76 g, 8.6 mmol, 99%). ^{1}H NMR (400 MHz): δ 0.0 (s, 6), 0.84 (s, 9), 2.17 (m, 2), 2.45 (s, 3), 2.61 (dd, 2, J = 6.2, 8.1), 3.78 (s, 3), 4.07 (d, 2, J = 4.6), 5.40−5.52 (m, 2), 6.58 (d, 1, J = 5.7), 8.19 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.1, 18.4, 22.2, 25.7, 26.0, 26.7, 55.2, 59.2, 104.1, 123.5, 129.6, 130.5, 148.0, 157.3, 163.6. Anal. Calcd for $C_{18}H_{31}NO_2Si$: C, 67.2; H, 9.7; N, 4.4. Found: C, 67.1; H, 9.9; N, 4.6.

(*Z*)-3-(5-Hydroxypent-3-en-1-yl)-4-methoxy-2-methylpyridine (38). To a solution of silyl ether **37** (11 g, 34.3 mmol) in THF (75 mL) was added 1 N HCl (75 mL) at room temperature. After 1 h, solid K_2CO_3 was added to adjust the pH to about 10. The layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a very pale yellow solid (7.1 g, 34.3 mmol, 100%). Crude **38** was routinely used without purification in the next reaction. A sample of analytical purity was prepared by chromatography on SiO_2 eluting with EtOAc/MeOH (1:0 then 19:1) followed by recrystallization (colorless needles from EtOAc/petroleum ether. Mp: 75−77 °C. IR ($CHCl_3$): 3610 m, 3026 m, 2968 s, 1582 s, 1478 s, 1289 s cm^{-1}. ^{1}H NMR (400 MHz): δ 2.17 (s, 1), 2.25−2.33 (m, 2), 2.53 (s, 3), 2.70 (dd, 2, J = 7.5, 8.0), 3.88 (s, 3), 4.09 (d, 2, J = 5.1), 5.58−5.68 (m, 2), 6.78 (d, 1, J = 5.7), 8.26 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 22.0, 25.7, 26.6, 55.4, 57.9, 104.2, 123.6, 130.1, 130.9, 147.8, 157.1, 163.8. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.2; H, 8.0; N, 7.0.

(*Z*)-3-(5-Chloropent-3-en-1-yl)-4-methoxy-2-methylpyridine (39). To a mixture of allylic alcohol **38** (3.8 g, 18.4 mmol), 2,6-lutidine (3.1 mL, 27 mmol), and LiCl (1.1 g, 27 mmol) in dry DMF (54 mL) was added methanesulfonyl chloride (2.1 mL, 27 mmol) dropwise with ice-cooling. When the addition was complete, the bath was removed and the mixture was stirred at room temperature for 4 h. The mixture was partitioned between aqueous Na_2CO_3 and ether, and the organic layer was separated. The aqueous solution was re-extracted twice with ether. The organic extracts were combined, washed with three portions of water to remove any residual DMF, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil. The material was purified on SiO_2 (8 × 4 cm) eluting with EtOAc/hexanes (4:6 then 1:1) to provide the title compound **39** as a colorless

oil (2.8 g, 12.4 mmol, 67%). Due to the instability of allylic chloride **39**, it was used without delay in the next reaction.

(*Z*,*Z*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-2-[6-(4-methoxy-2-methyl-pyridin-3-yl)hex-3-en-1-yl]-4-methoxypyridine (40). To a solution of methylpyridine **37** (4.8 g, 14.9 mmol) in THF (37 mL) was added *n*-BuLi (6.3 mL of 2.5 M, 15.6 mmol) dropwise at −78 °C. The resulting solution was allowed to warm to −50 °C in the bath over 40 min and then treated with a solution of allylic chloride **39** (2.8 g, 12.4 mmol) in THF (10 mL). After 5 min at −50 °C, the bath was removed and the solution allowed to stir at room temperature for 30 min. Water was added, and the resulting mixture was extracted with three portions of CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil (7.0 g) that was purified on SiO_2 (12 × 4 cm) eluting with EtOAc/hexanes (1:1 then 1:0) to afford the title compound **40** as a colorless oil (5.4 g, 10.6 mmol, 85% based on **39**). ^{1}H NMR (400 MHz): δ 0.05 (s, 6), 0.88 (s, 9), 2.17−2.25 (m, 4), 2.38−2.47 (m, 2), 2.48 (s, 3), 2.62 (dd, 2, J = 6.1, 8.2), 2.67 (dd, 2, J = 7.7, 9.9), 2.76 (dd, 2, J = 7.6, 9.7), 3.80 (s, 3), 3.83 (s, 3), 4.12 (d, 2, J = 4.7), 5.40−5.55 (m, 4), 6.61 (d, 1, J = 5.7), 6.63 (d, 1, J = 5.7), 8.21 (d, 1, J = 5.7), 8.30 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.1, 18.4, 22.2, 25.3, 25.8, 26.0, 26.4, 27.3, 27.4, 34.8, 55.2, 55.3, 59.2, 103.9, 104.0, 123.2, 123.8, 129.5, 129.6, 130.5, 147.9, 148.3, 157.3, 160.2, 163.6, 163.7. Anal. Calcd for $C_{30}H_{46}N_2O_3Si$: C, 70.5; H, 9.1; N, 5.5. Found: C, 70.2; H, 9.2; N, 5.7.

(*Z*,*Z*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-2-[6-[[4-methoxy-2-(phenylsulfanyl)methyl]pyridin-3-yl]-hex-3-en-1-yl]-4-methoxypyridine (41). To a solution of methyl pyridine **40** (4.1 g, 8.0 mmol) in THF (40 mL) was added *n*-BuLi (5.7 mL of 1.56 M, 8.84 mmol) dropwise at −78 °C. The solution was allowed to warm to −20 °C over 40 min then recooled to −50 °C. A solution of $MgBr_2{\cdot}OEt_2$ (10 mmol in ether 10 mL) was added and the mixture stirred at between −40 and −50 °C for 30 min. The solution was recooled to −78 °C, and PhSSPh (2.6 g, 12 mmol) in THF (10 mL) was added over 10 s. The cooling bath was removed, and stirring was continued at room temperature for 30 min. A saturated aqueous solution of NH_4Cl (aq) was added, and the layers were separated, washing with 1 M NaOH (aq). The aqueous solution was extracted with an additional portion of ether, again washing with 1 M NaOH (aq). The organic extracts were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil (6.4 g) that was purified on SiO_2 (12 × 4 cm) eluting with EtOAc/hexanes (7:3, 9:1, 0:1) to provide the title compound **41** as a colorless oil (3.6 g, 5.8 mmol, 72%) then EtOAc/MeOH (19:1) to recover starting material **40** (660 mg, 1.3 mmol, 16%). ^{1}H NMR (400 MHz): δ 0.02 (s, 6), 0.86 (s, 9), 2.15−2.29 (m, 4), 2.37−2.45 (m, 2), 2.64 (pair of overlapping dd, 4, J = 8.0, 8.0), 2.74 (dd, 2, J = 7.5, 8.3), 3.79 (s, 3), 3.81 (s, 3), 4.10 (d, 2, J = 5.1), 4.27 (s, 2), 5.37−5.55 (m, 4), 6.58 (d, 1, J = 5.7), 6.62 (d, 1, J = 5.7), 7.10−7.41 (m, 5), 8.26 (d, 1, J = 5.7), 8.27 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ −5.1, 18.4, 25.3, 25.8, 26.0, 27.0, 27.3, 27.4, 34.7, 39.0, 55.3, 55.4, 59.2, 104.0, 105.0, 123.3, 124.8, 126.3, 128.8, 129.4, 129.5, 129.8, 129.9, 130.5, 136.7, 148.2, 148.4, 155.6, 160.1, 163.8, 164.1.

(*Z*,*Z*)-3-(5-Hydroxypent-3-en-1-yl)-2-[6-[4-methoxy-2-[(phenylsulfanyl)methyl]pyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (42). A mixture of silyl ether **41** (1.68 g, 2.72 mmol) in THF (5 mL) and 1 N HCl (5 mL) was stirred at room temperature for 17 h. The pH of the reaction mixture was carefully adjusted to about 10 with solid K_2CO_3. Extraction with three portions of CH_2Cl_2 followed by drying (Na_2SO_4) and removal of solvent under reduced pressure afforded a yellow oil that was purified on alumina (6 × 2.5 cm) eluting with EtOAc/MeOH (1:0, 99:1, 98:2) to provide the title compound **42** (1.3 g, 2.56 mmol, 94%). ^{1}H NMR (400 MHz): δ 2.18−2.40 (m, 7), 2.63 (dd, 2, J = 7.7, 8.1), 2.67 (dd, 4, J = 7.4, 9.3), 3.84 (s, 3), 3.85 (s, 3), 4.07 (d, 2, J = 5.9), 4.29 (s, 2), 5.40−5.65 (m, 4), 6.63 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.7), 7.15−7.28 (m, 3),7.36−7.40 (m, 2), 8.28 (d, 1, J = 5.7), 8.29 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 25.3, 25.6, 26.9, 27.2, 27.2, 34.5, 38.8, 55.3, 55.4, 57.9, 104.0, 105.1, 123.3, 124.8, 126.3, 128.8, 129.2, 129.8, 129.9, 130.1, 130.7, 136.5, 148.1, 148.3, 155.5, 160.0, 163.8, 164.2. Anal. Calcd for $C_{30}H_{36}N_2O_3S$: C, 71.4; H, 7.2; N, 5.5. Found: C, 71.5; H, 7.3; N, 5.5.

(*Z*,*Z*)-3-[5-(Pivaloyloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-[(phenylsulfanyl)methyl]pyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (43). To a solution of allylic alcohol **42** (610 mg, 1.21 mmol) and Et_3N (280 μL, 2.0 mmol) in CH_2Cl_2 (6 mL) was added pivaloyl chloride (220 μL, 1.8 mmol) followed by DMAP (7 mg, 0.06 mmol). The solution was stirred at room temperature for 2 h, diluted in CH_2Cl_2, and then washed with water, re-extracting the aqueous layer twice with CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a yellow oil. Purification on SiO_2 (4.5 × 2.5 cm) eluting with EtOAc/hexanes (9:1) provided the title compound **43** as a viscous oil (678 mg, 1.15 mmol, 95%). ^{1}H NMR (400 MHz): δ 1.18 (s, 9), 2.23−2.33 (m, 4), 2.38−2.47 (m, 2), 2.67 (dd, 4, J = 6.2, 8.1), 2.77 (dd, 2, J = 6.0, 8.2), 3.83 (s, 3), 3.86 (s, 3), 4.29 (s, 2), 4.52 (d, 2, J = 5.8), 5.40−5.57 (m, 3), 5.61−5.70 (m, 1), 6.63 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.7), 7.15−7.28 (m, 3), 7.36−7.41 (m, 2), 8.29 (d, 1, J = 5.7), 8.30 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 25.3, 25.8, 27.0, 27.2, 27.3, 34.8, 38.7, 39.0, 55.3, 55.4, 60.1, 104.0, 105.1, 123.0, 124.6, 124.8, 126.3, 128.8, 129.4, 129.9, 129.9, 133.6, 136.7, 148.4, 148.5, 155.6, 160.1, 163.8, 164.1, 178.4. Anal. Calcd for $C_{35}H_{44}N_2O_4S$: C, 71.4; H, 7.5; N, 4.8. Found: C, 71.1; H, 7.5; N, 4.8.

(*Z*,*Z*)-3-[5-(Pivaloyloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-[(phenylsulfonyl)methyl]pyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (44). To an ice-cooled solution of thioether **43** (1.38 g, 2.35 mmol) in ethanol (26 mL) was added a solution of ammonium molybdate (880 mg, 0.71 mmol) in H_2O_2 (1.75 mL of a 30% aqueous solution) dropwise. The yellow mixture was stirred for 12 min and then partitioned between K_2CO_3 (aq) and CH_2Cl_2, extracting three times with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a viscous yellow oil. Purification on SiO_2 (4.5 × 2.5 cm) eluting with EtOAc/MeOH (99:1 then 98:2) provided the title compound **44** as a viscous pale yellow oil (1.37 g, 2.21 mmol, 94%). ^{1}H (400 MHz): δ 1.18 (s, 9), 2.23 (q, 2, J = 7.9), 2.28 (q, 2, J = 7.9), 2.37 (q, 2, J = 7.9), 2.67 (dd, 2, J = 6.1, 8.1), 2.70−2.77 (m, 4), 3.84 (s, 3), 3.86 (s, 3), 4.52 (dd, 2, J = 1.2, 5.8), 4.61 (s, 2), 5.37−5.57 (m, 3), 5.64−5.72 (m, 1), 6.63 (d, 1, J = 5.7), 6.66 (d, 1, J = 5.7), 7.43−7.50 (m, 2),7.60 (tt, 1, J = 1.3, 7.5), 7.70−7.74 (m, 2), 8.13 (d, 1, J = 5.7), 8.30 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): δ 25.2, 25.6, 26.5, 27.1, 27.2, 34.5, 38.6, 55.3, 55.5, 60.0, 61.9, 103.9, 105.8, 122.9, 124.5, 127.5, 128.4, 128.8, 130.0, 133.6, 139.1, 147.6, 148.3, 148.4, 159.9, 163.6, 164.2, 178.2. Anal. Calcd for $C_{35}H_{44}N_2O_6S$: C, 67.7; H, 7.1; N, 4.5. Found: C, 67.7; H, 7.3; N, 4.6.

(4*Z*,16*Z*)-19-(Benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),4,8(13),9,11,16,-20,22-octaene (45) and (4*Z*,16*E*)-19-(Benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),4,8(13),9,11,16,20,22-octaene (46). To a solution of *Z*,*Z*-sulfone **44** (641 mg, 1.03 mmol) in THF (25 mL) at −78 °C was added NaHMDS (580 μL of a 1.97 M solution in THF, 1.14 mmol). The solution was allowed to warm to room temperature. In a separate flask equipped with a reflux condenser, a solution of $Pd(dba)_3{\cdot}CHCl_3$ (26.8 mg, 0.0258 mmol) and dppe (26.1 mg, 0.0655 mmol) in THF (26 mL) was warmed to gentle reflux, whereupon the solution changed from a deep red to a pale orange color. The yellow solution of the sulfone anion was added to the refluxing catalyst solution over 1.5 h using a syringe pump. The resulting dark orange mixture was then allowed to cool to room temperature, the bulk of the THF was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 and water. The layers were separated, and the aqueous solution was re-extracted twice with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a viscous yellow oil. Purification on SiO_2 (7 × 2.5 cm) eluting with EtOAc provided the title compounds **45** and **46** as a white solid (387 mg, 0.75 mmol, 73%). The two isomers were inseparable by chromatography

on silica. A pure sample of **46** was obtained by HPLC: Chirapak AD 25 cm × 2 cm column with a flow rate of 12 mL/min monitoring with UV detection at 220 nm. Hexane:IPA containing 1% diethylamine (85:15). ^{1}H NMR (400 MHz): δ 2.0−2.35 (m, 6), 2.35−2.74 (m, 5), 2.88 (ddd, 1, J = 7.0, 9.7, 13.9), 2.96 (ddd, 1, J = 2.2, 9.7, 11.9), 3.24 (dt, 1, J = 5.6, 12.0) 3.81 (s, 3), 3.83 (s, 3), 4.55 (dd, 1, J = 2.4, 11.2), 5.15 (ddd, 1, J = 6.5, 7.6, 14.7), 5.44 (dt, 1, J = 10.7, 6.1), 5.51−5.63 (m, 2), 6.60 (d, 1, J = 5.9), 6.69 (d, 1, J = 5.6), 7.42 (t, 2, J = 8.2), 7.58 (m, 3), 8.24 (d, 1, J = 5.6), 8.31 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 24.1, 25.6, 28.1, 28.2, 31.7, 31.9, 36.4, 55.1, 55.4, 68.0, 104.1, 105.6, 123.3, 125.2, 128.4, 128.6, 129.3, 129.7, 133.5, 133.6, 137.4, 148.2, 148.3, 150.3, 160.0, 163.6, 163.9. Anal. Calcd for $C_{30}H_{34}N_2O_4S$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.3; H, 6.7; N, 5.4. APCI-MS m/z (rel intensity): 519 (MH^+, 100). See direct cyclization for data (later) for **45**.

(*Z*,*Z*)-3-[5-(*tert*-Butyldimethylsiloxy)pent-3-en-1-yl]-2-[6-[4-methoxy-2-[(phenylsulfonyl)methyl]pyridin-3-yl]-hex-3-en-1-yl]-4-methoxypyridine (47). To an ice-cooled solution of thioether **41** (1.57 g, 2.54 mmol) in ethanol (26 mL) was added a solution of ammonium molybdate (880 mg, 0.71 mmol) in H_2O_2 (1.75 mL of a 30% aqueous solution) dropwise. The yellow mixture was stirred for 17 min and then partitioned between (aq) and CH_2Cl_2, extracting three times with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a viscous yellow oil. Purification on SiO_2 (4 × 2.5 cm) eluting with EtOAc/MeOH (99:1 then 98:2) provided the title compound **47** as a colorless oil (1.58 g, 2.43 mmol, 96%). ^{1}H (400 MHz): δ 0.02 (s, 6), 0.9 (s, 9), 2.21 (quintet, 4, J = 7.5), 2.37 (q, 2, J = 8.0), 2.65 (dd, 2, J = 7.7, 8.1), 2.69−2.77 (m, 4), 3.83 (s, 6), 4.12 (d, 2, J = 4.8), 4.61 (s, 2), 5.36−5.56 (m, 4), 6.62 (d, 1, J = 5.7), 6.69 (d, 1, J = 5.7), 7.47 (broad t, 2, J = 7.8), 7.61 (tt, 1, J = 1.4, 7.5), 7.73 (d, 2, J = 7.5), 8.16 (d, 1, J = 5.7), 8.29 (d, 1, J = 5.7). ^{13}C NMR (100 MHz): −5.1, 18.4, 25.3, 25.7, 26.0, 26.6, 27.2, 27.4, 34.6, 55.3, 55.5, 59.2, 62.0, 104.0, 105.9, 123.2, 127.6, 128.5, 128.9, 129.0, 129.5, 130.1, 130.5, 133.6, 139.1, 147.7, 148.3, 148.5, 160.0, 163.7, 164.3. Anal. Calcd for $C_{36}H_{50}N_2O_5SSi$: C, 66.4; H, 7.7; N, 4.3. Found: C, 66.3; H, 7.8; N, 4.3. APCI-MS m/z (rel intensity): 651 (MH^+, 100).

(*Z*,*Z*)-3-(5-Hydroxypent-3-en-1-yl)-2-[6-[4-methoxy-2-[(phenylsulfonyl)methyl]pyridin-3-yl]hex-3-en-1-yl]-4-methoxypyridine (48). A mixture of silyl ether **47** (800 mg, 1.29 mmol) in THF (3 mL) and 1 N HCl (3 mL) was stirred at room temperature for 8 h. The pH of the reaction mixture was carefully adjusted to about 10 with solid K_2CO_3. Extraction with three portions of CH_2Cl_2 followed by drying (Na_2SO_4) and removal of solvent under reduced pressure afforded a yellow oil which that purified on alumina (6 × 2.5 cm) eluting with EtOAc/MeOH (99:1, 98:2) to provide the title compound **48** (610 mg, 1.21 mmol, 94%). ^{1}H NMR (400 MHz): δ 2.13−2.43 (m, 7), 2.61 (q, 4, J = 8.6), 2.77 (t, 2, J = 7.5), 3.83 (s, 6), 4.04 (d, 2, J = 5.6), 4.62 (s, 2), 5.36−5.47 (m, 2), 5.50−5.64 (m, 2), 6.61 (d, 1, J = 5.7), 6.67 (d, 1, J = 5.6), 7.47 (t, 2, J = 7.7), 7.59 (t, 1, J = 7.4), 7.70 (d, 2, J = 8.0), 8.10 (d, 1, J = 5.7), 8.26 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 25.3, 25.5, 26.5, 27.1, 27.2, 34.4, 55.3, 55.5, 58.0, 61.8, 103.9, 105.8, 123.1, 127.6, 128.5, 128.7, 128.8, 129.6, 130.1, 131.2, 133.6, 138.9, 147.6, 148.2, 148.3, 159.9, 163.6, 164.4. APCI-MS m/z (rel intensity): 537 (MH^+, 100).

(4*Z*,16*Z*)-19-(Benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),4,8(13),9,11,16,-20,22-octaene (45). To a mixture of allylic alcohol **48** (1.2 g, 2.24 mmol) 2,6-lutidine (290 μL, 2.5 mmol), and LiCl (190 mg, 4.5 mmol) in dry DMF (10 mL) was added MsCl (200 μL, 2.5 mmol) dropwise with ice-cooling. When the addition was complete, the bath was removed and the mixture was stirred at room temperature for 2 h. The mixture was partitioned between aqueous Na_2CO_3 and ether, and the organic layer was separated. The aqueous solution was re-extracted twice with ether. The organic extracts were combined, washed with three portions of water to remove any residual DMF, and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a yellow oil. The material was purified on alumina (6 × 4 cm) eluting with EtOAc/methanol (1:0 then 99:1) to provide the title compound **49**, which was contaminated with a small amount of 2,6-lutidine, as a colorless oil (1.3 g, greater than 100% mass recovery). Due to the instability of the allylic chloride, it was used without delay in the next reaction.

A solution of crude sulfone **49** (1.3 g) in THF (30 mL) was added to a refluxing solution of NaHMDS (4 mL of 1.97 M in THF) in THF (125 mL) over 2.5 h. The excess base was quenched with H_2O (1 mL), and the bulk of the THF was removed under reduced pressure. The residue was partitioned between CH_2Cl_2 and water. The layers were separated, and the aqueous solution was re-extracted twice with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a viscous yellow oil. Purification on SiO_2 (6 × 3.5 cm) eluting with EtOAc provided the title compounds **45** as a white solid (940 mg, 1.81 mmol, 81% over two steps). Mp: 186−187 °C (white microcrystalline solid from EtOAc). ^{1}H NMR (400 MHz): δ 1.95−2.61 (m, 10), 2.70−2.86 (m, 2), 2.91 (ddd, 1, J = 3.4, 9.0, 11.8), 3.22 (dt, 1, J = 7.4, 11.8), 3.81 (s, 3), 3.83 (s, 3), 4.49 (dd, 1, J = 3.4, 11.3), 5.09−5.28 (m, 2), 5.39−5.57 (m, 2), 6.66 (d, 1, J = 5.7), 6.70 (d, 1, J = 5.6), 7.36 (t, 2, J = 7.6),7.50 (tt, 1, J = 1.1, 7.6), 7.61 (dd, 2, J = 1.2, 7.6), 8.30 (d, 1, J = 5.7), 8.32 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): d 24.7, 25.8, 26.1, 26.2, 27.7, 28.1, 36.1, 55.2, 55.4, 67.0, 104.1, 105.7, 122.9, 124.5, 128.2, 128.5, 128.7, 129.1, 129.7, 132.8, 133.5, 137.5, 148.3, 148.3, 150.1, 159.9, 163.8, 164.0. Anal. Calcd for $C_{30}H_{34}N_2O_4S$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.6; H, 6.6; N, 5.4.

Pyridine 50. A solution of symmetrical macrocycle **28** (28 mg, 0.07 mmol) in freshly distilled THF (740 μL) was cooled to −78 °C and treated with *n*-butyllithium (90 μL of a 2.21 M solution in THF, 0.20 mmol). A cloudy orange solution resulted and was stirred for 1 h, warming to room temperature. At rt, the solution appeared homogeneous and darker in color. Neat 1-bromo-3-chloropropane (34 μL, 0.35 mmol) was added with a syringe, causing the solution to fade in color. After being stirred at room temperature for 1 h, the volatiles were removed with a rotary evaporator, and the excess 1-bromo-3-chloropropane was removed under a static high vacuum (15 min). The remaining residue was dissolved in reagent-grade acetone (5 mL), and NaI (63 mg, 0.42 mmol) was added. A reflux condenser was attached to the flask, and the mixture was heated at reflux for 1.5 h to produce a crude pyridinium salt. The solvent was removed with a rotary evaporator, and the remaining salts were dissolved in distilled THF (740 μL). After the mixture was cooled to −78 °C, L-Selectride (246 μL of a 1 M solution in THF, 0.250 mmol) was added. The mixture stirred, warming to room temperature over 2.5 h, and methanol (5 μL) was added cautiously to quench any unreacted L-Selectride. The quenched reaction mixture was diluted with water (740 μL), and $NaBO_3 \cdot 4H_2O$ (113 mg, 0.740 mmol) was added in small portions over 2 h. An ice bath was used periodically to maintain a reaction temperature of 25 °C. After all of the organoborane had been oxidized, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent with a rotary evaporator and purification of the residue by flash chromatography on silica gel (4:96 methanol/$CHCl_3$) afforded 15 mg (50%) of monoannulated pyridine **50**. ^{1}H NMR (400 MHz): δ 1.43−1.48 (m, 2), 1.71−1.77 (m, 4), 1.92−1.99 (m, 4), 2.04−2.16 (m, 3), 2.34−2.86 (m, 8), 3.08 (dt, 1, J = 5.3, 11.6), 3.21−3.24 (m, 2), 3.30 (ddd, 1, J = 6.5, 12.8, 19.5), 3.85 (s, 3), 5.47−5.49 (m, 2), 5.51−5.58 (m, 2), 6.64 (d, 1, J = 5.6), 8.34 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 18.08, 22.07, 22.21, 25.26, 25.67, 30.00, 31.51, 33.66, 34.10, 35.33, 36.51, 50.73, 51.30, 55.13, 103.74, 109.68, 123.29, 127.77, 130.03, 131.89, 131.99, 147.98, 159.43, 163.88, 164.32, 190.91.

19-(Benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,22-hexaene (52). A mixture of *Z*,*Z*-diene **45** (790 mg, 1.53 mmol), tosylhydrazine (1.7 g, 9.1 mmol), and NaOAc (750 mg, 9.1 mmol) in THF (9 mL) and water (9 mL) was heated at reflux for 14.5

h. K_2CO_3 (aq) was added, and the mixture was extracted with three portions of CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a white solid. Purification on SiO_2 (4 × 2.5 cm) eluting with CH_2Cl_2/MeOH (1:0, 99:1 then 97.5:2.5) provided the title compound **52** as a white solid (780 mg, 1.49 mmol, 97%). Mp: 205−205.5 °C (white microcrystalline solid from CH_2Cl_2/ether). ^{1}H NMR (500 MHz): δ 1.1−1.8 (m, 14), 2.25−2.35 (m, 1), 2.41 (dt, 1, J = 3.8, 12.8), 2.5−2.7 (m, 5), 2.76 (dt, 1, J = 5.4, 14.2), 3.80 (s, 3), 3.86 (s, 3), 4.80 (dd, 1, J = 3.1, 10.9), 6.57 (d, 1, J = 5.7), 6.71 (d, 1, J = 5.5), 7.40 (t, 2, J = 7.7),7.53 (d, 2, J = 7.7), 7.57 (t, 1, J = 7.5), 8.21 (d, 1, J = 5.7), 8.27 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ 24.0, 25.6, 27.6, 28.2, 28.8, 29.5, 29.6, 29.9, 34.5, 55.2, 55.4, 67.9, 103.8, 105.7, 123.8, 128.4, 128.5, 129.3, 133.5, 137.4, 148.0, 148.2, 150.6, 160.9, 163.7, 164.1. Anal. Calcd for $C_{30}H_{38}N_2O_4S$: C, 68.9; H, 7.3; N, 5.4. Found: C, 69.0; H, 7.3; N, 5.6.

19-Allyl-19-(benzenesulfonyl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,22-hexaene (53). To a solution of sulfone **52** (620 mg, 1.19 mmol) in THF (6 mL) and 2,6-lutidine (3 mL) was added *n*-BuLi (1.6 mL of a 2.2 M solution in hexane, 3.5 mmol) dropwise at −78 °C. The orange slurry was stirred at −78 °C for 20 min. Allyl iodide (500 μL, 5.47 mmol) was added, and the bath was removed. After 30 min at room temperature, brine was added and the mixture extracted with three portions of CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a yellow solid. Purification on SiO_2 (6 × 2.5 cm) eluting with CH_2Cl_2/MeOH (99:1 then 98:2) provided the title compound **53** as a white solid (630 mg, 1.12 mmol, 94%). Mp: 193−194 °C (prisms from EtOAc). ^{1}H NMR (500 MHz): δ 1.2−1.9 (m, 13), 2.22−2.35 (m, 2), 2.4−2.6 (m, 2), 2.73−2.9 (m, 2), 2.9−3.05 (m, 2), 3.1 (t, 1, J = 11.6), 3.3−3.4 (m, 1), 3.62 (broad d, 1, J = 11.5), 3.79 (s, 3), 3.80 (s, 3), 4.97 (broad d, 1, J = 10.2), 5.17 (broad d, 1, J = 17.1), 5.50 (m, 1), 6.51 (d, 1, J = 5.4), 6.56 (d, 1, J = 5.7),7.17−7.25 (m, 4), 7.38 (tt, 1, J = 1.5, 7.2), 7.77 (d, 1, J = 5.4), 8.26 (d, 1, J = 5.6). ^{13}C NMR (100 MHz): δ 23.8, 25.9, 27.5, 27.8, 28.4, 28.7, 30.0, 31.1, 31.6, 32.5, 37.0, 55.3, 55.7, 78.2, 103.6, 105.2, 118.1, 124.4, 128.0, 129.5, 131.2, 132.8, 134.6, 137.1, 146.1, 148.1, 152.6, 160.9, 163.7, 165.5. Anal. Calcd for $C_{33}H_{42}N_2O_4S$: C, 70.4; H, 7.5; N, 5.0. Found: C, 70.5; H, 7.6; N, 4.9.

19-Allyl-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]-tetracosa-1(24),8(13),9,11,20,22-hexaene (54). To a solution of sulfone **53** (207 mg, 0.37 mmol) in MeOH (3 mL) and THF (3 mL) was added 5% Na/Hg amalgam (2 g) portionwise. The mixture was stirred at room temperature for 12 h and then decanted from the mercury metal, washing several times with CH_2Cl_2. The solvent was removed under reduced pressure to afford a white solid. Purification on SiO_2 (2.5 × 2.5 cm) eluting with EtOAc provided the title compound **54** as a white solid (142 mg, 0.34 mmol, 92%). Mp: 122−123 °C (white prisms from ether/hexanes). ^{1}H NMR (400 MHz): δ 1.2−1.8 (m, 15), 1.88−1.99 (m, 1), 2.34 (t, 2, J = 7.0), 2.42−2.70 (m, 5), 2.79 (dt, 1, J = 6.1, 13.5), 3.16 (quintet, 1, J = 7.5), 3.77 (s, 3), 3.81 (s, 3), 4.78−4.92 (m, 2), 5.57 (ddt, 1, J = 10.1, 17.1, 7.1), 6.51 (d, 1, J = 5.7), 6.56 (d, 1, J = 5.5), 8.21 (d, 1, J = 5.7), 8.35 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ 24.4, 25.2, 27.4, 27.9, 28.8, 28.9, 29.1, 29.1, 29.4, 34.2, 34.3, 40.3, 41.4, 55.0, 55.0, 103.3, 103.6, 115.4, 123.9, 124.4, 137.0, 147.8, 148.1, 160.9, 162.8, 163.6, 163.6. Anal. Calcd for $C_{27}H_{38}N_2O_2$: C, 76.7; H, 9.1; N, 6.6. Found: C, 76.7; H, 9.2; N, 6.9.

(7*R,19*R**)-7,19-Diallyl-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,22-hexaene (55) and *meso*-7,19-Diallyl-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,22-hexaene (56).** To a solution of the macrocycle **54** (314 mg, 0.744 mmol) in ether (6 mL) containing TMEDA (120 μL, 0.8 mmol) was added *s*-BuLi (580 μL of a 1.29 M solution in *c*-hexane, 0.744 mmol) dropwise at −78 °C. The resulting bright-orange solution was stirred at −78 °C for 25 min. Allyl bromide (140 μL, 1.6 mmol) was added in one portion. The color discharged rapidly, leaving a pale yellow solution. The cooling bath was removed and the solution stirred at room temperature for 20 min. Brine was added, and the mixture was extracted with three portions of CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a yellow oil. The starting macrocycle **54** (56 mg, 0.13 mmol, 18%) was recovered by chromatography on SiO_2 (3.5 × 2.5 cm) eluting with EtOAc/hexanes (1:3, 1:1, 1:0). The mixture of products was separated by radial chromatography on SiO_2 eluting with EtOAc/hexanes (1:1) to provide the following compounds (in order of elution):

Compound 58 (14 mg, 0.027 mmol, 4%) as a mixture of diastereoisomers. R_f: 0.71 (EtOAc).

19-Allyl-10-bromo-12,24-dimethoxy-9,21-diazatricyclo-[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,22-hexaene (57) (52 mg, 0.104 mmol, 14%). R_f: 0.63. ^{1}H NMR (400 MHz): δ 1.2−1.7 (m, 16), 1.9−2.0 (m, 1), 2.36 (t, 2, J = 7.0), 2.40−2.70 (m, 4), 2.80 (dt, 1, J = 6.1, 13.5), 3.17 (quintet, 1, J = 7.6), 3.80 (s, 3), 3.84 (s, 3), 4.83 (dd, 1, J = 1.1, 10.1), 4.90 (dd, 1, J = 1.1, 17.1), 5.57 (ddt, 1, J = 10.1, 17.1, 7.1), 6.60 (d, 1, J = 5.5), 6.74 (s, 1), 8.38 (d, 1, J = 5.5). ^{13}C NMR (100 MHz): δ 24.6, 25.5, 27.7, 28.1, 29.1, 29.1, 29.2, 29.3, 29.5, 34.3, 34.5, 40.6, 41.7, 55.3, 55.8, 103.6, 107.8, 115.7, 124.0, 124.7, 137.3, 139.3, 148.4, 161.9, 163.0, 163.9, 165.1. FAB-MS *m*/*z* (rel intensity): 503 (M^+, 80), 501 (M^+, 80).

Compound 56 (143 mg, 0.310 mmol, 42%). Mp: 84−86 °C (white powder from hexanes). ^{1}H NMR (400 MHz): δ 1.2−1.9 (m, 16), 2.2−2.3 (m, 2), 2.33−2.43 (m, 2), 2.55 (ddd, 2, J = 8.0, 8.0, 13.4), 2.65 (ddd, 2, J = 5.1, 8.5, 13.5), 2.97−3.05 (m, 2), 3.82 (s, 6), 4.7−4.78 (m, 4), 5.40−5.53 (m, 2), 6.59 (d, 2, J = 5.6), 8.33 (d, 2, J = 5.6). ^{13}C NMR (100 MHz): δ 24.2, 27.3, 28.1, 29.1, 34.5, 38.6, 41.1, 55.3, 103.5, 115.5, 124.3, 137.6, 148.3, 163.6, 163.8. Anal. Calcd for $C_{30}H_{42}N_2O_2$: C, 77.9; H, 9.1; N, 6.0. Found: C, 78.0; H, 9.2; N, 6.0.

Compound 55 (50 mg, 0.108 mmol, 15%). Mp: 99−102 °C (white powder from hexanes). ^{1}H NMR (400 MHz): δ 1.15−1.63 (m, 12), 1.63−1.75 (m, 2), 1.75−1.87 (m, 2), 2.38 (dd, 2, J = 7.1, 13.5), 2.44 (dd, 2, J = 7.1, 13.5), 2.49−2.58 (m, 2), 2.67−2.77 (m, 2), 3.20 (quintet, 2, J = 7.5), 3.82 (s, 6), 4.83 (dd, 2, J = 2.2, 10.1), 4.93 (dd, 2, J = 2.2, 17.1), 5.57 (ddt, 2, J = 10.1, 17.1, 6.8), 6.58 (d, 2, J = 5.6), 8.33 (d, 2, J = 5.6). ^{13}C NMR (100 MHz): δ 25.6, 27.2, 28.8, 29.8, 34.1, 39.3, 39.7, 55.3, 103.5, 115.6, 125.0, 137.5, 148.3, 163.0, 163.7.

***meso*-7,19-Bis(3-Hydroxyprop-1-yl)-12,24-dimethoxy-9,-21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),9,11,20,-22-hexaene (62).** To an ice-cooled solution of the diallyl macrocycle **56** (170 mg, 0.368 mmol) in THF (7 mL) was added 9-BBN dimer (180 mg, 0.74 mmol). After 10 min, the bath was removed and the solution was stirred at room temperature for 19 h. NaOH (aq) (5 mL of 3 N) and H_2O_2 (5 mL of 30% solution in water) were added with ice-cooling. The bath was removed after 5 min and the mixture left for 2 h at room temperature. The mixture was brought to reflux and then stirred at room temperature for a further 2 h before being extracted with three portions of CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford a white solid that was recrystallized three times from EtOAc to give the title compound **62** as a white solid (110 mg, 0.221 mmol, 60%). Further diol **62** (30 mg, 0.065, 18%) of lower purity was obtained from purification of the residue on alumina (3 × 2.5 cm) eluting with EtOAc/MeOH (1:0, 99:1, 98:2, 96:4, 95:5). ^{1}H NMR (400 MHz): δ 1.09−1.21 (m, 2), 1.23−1.80 (m, 22), 2.22−2.42 (br, 2), 2.55 (ddd, 2, J = 7.9, 7.9, 13.4), 2.68 (ddd, 2, J = 5.1, 8.6, 13.4), 2.94 (broad septet, 2, J = 7.5), 3.35−3.45 (m, 4), 3.83 (s, 6), 6.58 (d, 2, J = 5.6), 8.29 (d, 2, J = 5.6). ^{13}C NMR (100 MHz): δ 24.3, 27.1, 28.2, 29.0, 29.6, 30.8, 35.2, 40.4, 55.3, 62.9, 103.6, 124.5, 148.3, 163.9, 164.0.

(7*R,19*R**)-7,19-Bis-(3-hydroxyprop-1-yl)-12,24-dimethoxy-9,21-diazatricyclo[18.4.0.0^{18,13}]tetracosa-1(24),8(13),-9,11,20,22-hexaene (59).** The same procedure used to prepare diol **62** provided the racemic chiral diol **59** (85 mg, 0.171 mmol, 77%) as a white solid. ^{1}H NMR (400 MHz): δ 1.15−1.28 (m, 4), 1.30−1.81 (m, 20), 2.50−2.60 (m, 2), 2.60−2.75 (m, 4), 3.12 (quintet, 2, J = 7.1), 3.43−3.55 (m, 4), 3.80 (s, 6), 6.57 (d, 2, J = 5.6), 8.28 (d, 2, J = 5.6). ^{13}C NMR (100 MHz):

25.6, 27.2, 28.8, 29.7, 30.5, 30.9, 34.9, 39.5, 55.3, 63.0, 103.5, 125.2, 148.3, 163.4, 163.8. Anal. Calcd for $C_{30}H_{46}N_2O_4$: C, 72.3; H, 9.3; N, 5.6. Found: C, 72.0; H, 9.6; N, 5.3.

***meso*-Dienol Ether (63).** To a mixture of the diol **62** (110 mg, 0.221 mmol) and Et_3N (280 μL, 2 mmol) in CH_2Cl_2 (4 mL) at −78 °C was added methanesulfonyl chloride (60 μL, 0.8 mmol). The cooling bath was removed and the mixture stirred at room temperature for 8 h. The solvent was removed under reduced pressure to leave a yellow solid that was dissolved in EtOH (8 mL). $NaBH_4$ (250 mg, 6.6 mmol) was added portionwise and the resulting mixture stirred at room temperature for 13 h. Brine was added and the mixture extracted with three portions of CH_2Cl_2. The organic extracts were combined and dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a yellow solid that was purified on alumina (6 × 2.5 cm) eluting with CH_2Cl_2/MeOH (1:0, 99.7:0.3, 99.5:0.5, 99:1) followed by crystallization from MeOH to provide **63** as a white solid (73 mg, 0.157 mmol, 71%). Mp: 170−172 °C. ^{1}H NMR (400 MHz): δ 1.22−1.55 (m, 20), 1.70−2.20 (m, 14), 2.28 (dt, 2, J = 3.9, 11.1), 2.44−2.58 (m, 4), 2.76 (dd, 2, J = 5.6, 10.7), 2.85 (broad d, 2, J = 10.7), 3.48 (s, 6). ^{13}C NMR (100 MHz): δ 21.0, 24.9, 25.4, 25.8, 26.2, 27.9, 29.7, 33.9, 53.0, 55.7, 57.5, 68.1, 117.7, 148.3. Anal. Calcd for $C_{30}H_{50}N_2O_2$: C, 76.5; H, 10.7; N, 6.0. Found: C, 76.5; H, 10.8; N, 5.7.

Chiral Dienol Ether (60). The same procedure used to prepare dienol ether **63** provided the racemic chiral dienol ether **60** (40 mg, 0.085 mmol, 69%) as colorless prisms. Mp: 130−131 °C. ^{1}H NMR (500 MHz): δ 0.7−1.07 (m, 2), 1.20−1.55 (m, 20), 1.60−1.75 (m, 4), 1.75−1.97 (m, 4), 2.08−2.22 (m, 4), 2.25 (dt, 2, J = 3.7, 11.1), 2.45−2.56 (m, 4), 2.76 (ddd, 2, J = 1.0, 5.6, 10.7), 2.81−2.88 (m, 2), 3.47 (s, 6). ^{13}C NMR (100 MHz): δ 21.1, 24.7, 25.7, 27.0, 27.3, 28.4, 28.9, 30.1, 35.8, 53.0, 55.8, 57.4, 69.0, 117.8, 148.7.

Didemethylpetrosin D (64). To an ice-cooled solution of the dienol ether **63** (73 mg, 0.157 mmol) in THF (10 mL) was added HCl (aq) (10 mL of a 5 M solution) dropwise. After 20 min, the cooling bath was removed and stirring continued at room temperature for 4 h. The reaction solution was cautiously added to an excess of solid K_2CO_3, and the mixture was partitioned between water and CH_2Cl_2. The layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a buff solid that was purified on alumina (8 × 1.5 cm) eluting with CH_2Cl_2/MeOH (1:0, 99.8:0.2, 9.7:0.3) to afford the title compound **64** as a white solid (67 mg, 0.152 mmol, 97%). Mp: 171−172 °C (colorless plates from EtOAc/MeOH). IR: 1711 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.15−1.65 (m, 22), 1.69−1.88 (m, 8), 1.93−2.02 (m, 4), 2.20−2.33 (m, 4), 2.44 (t, 2, J = 8.6), 2.67 (dt, 2, J = 5.4, 13.1), 2.95 (broad d, 2, J = 11.7), 3.05−3.12 (m, 2). ^{13}C NMR (100 MHz): δ 20.1, 23.8, 24.3, 25.7, 26.6, 26.9, 29.4, 33.7, 42.0, 50.7, 57.3, 57.4, 71.3, 211.2.

Didemethylpetrosin C (61). The same procedure used to prepare **64** provided the racemic chiral diketone **61** (27 mg, 0.061 mmol, 69%). ^{1}H NMR (400 MHz): δ 1.17−2.03 (m, 34), 2.20−2.33 (m, 4), 2.42 (t, 2, J = 10.2), 2.69 (dt, 2, J = 6.3, 13.7), 2.95 (broad d, 2, J = 11.0), 3.07−3.14 (m, 2). ^{13}C NMR (100 MHz): δ 20.1, 22.8, 23.3, 25.5, 26.7, 26.7, 28.2, 34.3, 42.4, 51.3, 57.1, 57.8, 71.3, 211.4.

Petrosin D (6). To a solution of the diketone **64** (15 mg, 0.034 mmol) in THF (1 mL) was added a freshly prepared solution of LDA (240 μL of 0.37 M in THF/hexane, 0.088 mmol) at −78 °C. After 5 min, the reaction solution was transferred to an ice bath, and stirring was continued for 5 min during which time a colorless precipitate formed. The mixture was re-cooled to −78 °C, and MeI (8 μL, 0.130 mmol) was added. After 10 min, the mixture was placed in an ice bath, as the reaction proceeded the solid material dissolved. After 15 min, the reaction was quenched by addition of a small amount of water (ca. 100 μL). The solvent was removed under reduced pressure, and the residue was taken up in MeOH (2 mL). $K_2CO_3 \cdot 1.5H_2O$ (0.2 mmol) was added and the mixture stirred at room temperature for 14 h. The mixture was partitioned between brine and CH_2Cl_2, and the layers were separated, re-extracting the aqueous solution twice with CH_2Cl_2. The organic solutions were combined and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a buff solid that was purified on alumina (6 × 1.5 cm) eluting with CH_2Cl_2/MeOH (1:0, 99.75:0.25) to afford the petrosin D (**5**) as a white solid (14 mg, 0.030 mmol, 88%). Mp: (sealed tube): 159−161 °C (colorless needles from MeOH). IR: 1711 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.97 (d, 6, J = 6.5), 1.15−2.00 (m, 36), 2.44 (t, 2, J = 9.2), 2.53 (septet, 2, J = 6.2), 2.95 (broad d, 2, J = 11.4), 3.04 (dd, 2, J = 5.5, 10.4). ^{13}C NMR (100 MHz): δ 11.6, 20.1, 24.0, 24.2, 25.9, 26.7, 26.9, 29.5, 33.8, 44.4, 50.6, 57.0, 65.3, 71.9, 212.4.

Petrosin C (5). Petrosin C was prepared in the same way as petrosin D (**6**). However, significant overmethylation occurred in this case. Partial purification was carried out on alumina (6 × 1.5 cm) eluting with CH_2Cl_2/MeOH (1:0, 99.75:0.25) to afford the impure petrosin C as an oil. A pure sample was obtained by radial chromatography on silica eluting with EtOAc/MeOH (99.5:0.5) to provide petrosin C (**5**) as a white solid. Mp: (sealed tube): 152−154 °C (colorless needles from MeOH). ^{1}H NMR (400 MHz): δ 0.96 (d, 6, J = 6.5), 1.16−2.00 (m, 36), 2.44 (t, 2, J = 10.5), 2.53 (broad septet, 2, J = 6.1), 2.93 (broad d, 2, J = 10.1), 3.04 (dd, 2, J = 6.4, 11.4). ^{13}C NMR (100 MHz): δ 11.6, 20.1, 22.6, 23.2, 25.4, 26.6, 28.3, 34.4, 44.8, 51.2, 56.9, 65.8, 71.8, 77.4, 212.7.

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Supporting Information Available: Single-crystal X-ray data for compound **60**, ^{1}H NMR and ^{13}C NMR spectra of compounds **5**−**7**, **27**, **28**, **31**−**35**, **41**, **55**, **57**, **60**−**62**, and **64** (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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