JOC Article

Tandem Conjugate Additions and 3-Aza-Cope Rearrangements of Tertiary Allyl Amines and Cyclic α-Vinylamines with Acetylenic Sulfones. Applications to Simple and Iterative Ring Expansions Leading to Medium and Large-Ring Nitrogen Heterocycles

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Tertiary acyclic allyl amines and tertiary cyclic α-vinyl amines undergo conjugate additions to acetylenic sulfones to produce zwitterion intermediates, followed by 3-aza-Cope rearrangements. In the case of cyclic α-vinyl amines, the process results in ring-expansion, providing a novel route to 9- to 17-membered cyclic amines. The Hammett plot for the reaction of **8b** with **2a**−**2f** shows $\rho = +1.19$, which is consistent with formation of the proposed zwitterion in the rate-determining step, where electron-withdrawing substituents on the arylsulfonyl moiety stabilize the negative charge and enhance the rate of the reaction. Alternative pathways were observed in methanol in the case of **11**, where a methoxy substituent promotes a dissociative mechanism of the corresponding zwitterion via a stabilized allyl cation, whereas the zwitterion derived from amine **12** undergoes ring-opening by direct attack of methanol upon the strained aziridinium moiety instead of by rearrangement. An iterative process was developed, where the product of one ring-expansion is converted into a new cyclic α-vinyl amine, followed by a repetition of the conjugate addition and [3,3] rearrangement. This protocol was illustrated by its application to the synthesis of motuporamine A and B.

Introduction

Aza variations[1] of the Cope rearrangement provide the opportunity to transpose a nitrogen functionality during the usual allyl migration associated with this classical [3,3] sigmatropic reaction. Thus, a variety of 2-aza-Cope rearrangements of 3-alkenylimines or, more commonly of 3-alkenyliminium species, have been reported.[2] Similarly, the 3-aza-Cope rearrangements[3] of allyl vinyl amines (Scheme 1) have been investigated and are sometimes referred to as aza-Claisen or amino-Claisen reactions.[4] The 3-aza-Cope rearrangement typically requires high temperatures that curtail its synthetic utility. This can be mitigated by employing cationic quaternary amines as starting materials, or through the use of tertiary amines in the presence of Bronsted or Lewis acid catalysts,[5] which permit the use of milder conditions.

Medium- and large-ring nitrogen heterocycles occur widespread in nature and often display interesting biological proper-

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(1) For reviews see: (a) Nubbemeyer, U. *Top. Curr. Chem.* **2005**, *244*, 149–213. (b) Enders, D.; Knopp, M.; Schiffers, R *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. (c) Blechert, S. *Synthesis* **1989**, 71–82. (d) Przheval'skii, N. M.; Grandberg, I. I. *Russ. Chem. Rev.* **1987**, *56*, 477–491. (e) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205–246.

(2) For recent examples of 2-aza-Cope rearrangements, see: (a) Merino, P.; Tejero, T.; Mannucci, V. *Tetrahedron Lett.* **2007**, *48*, 3385–3388. (b) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039. (c) Sugiura, M.; Mori, C.; Hirano, K.; Kobayashi, S. *Can. J. Chem.* **2005**, *83*, 937–942. (d) Earley, W. G.; Jacobsen, J. E.; Madin, A.; Meier, G. P.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18046–18053. (e) Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913–916. (f) Brüggermann, M.; McDonald, A. I.; Overman, L. E.; Rosen, M. D.; Schwink, L.; Scott, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15284–15285. (g) Brummond, K. M.; Hong, S. *J. Org. Chem.* **2005**, *70*, 907–916. (h) Kvaerno, L.; Norrby, P.-O.; Tanner, D. *Org. Biomol. Chem.* **2003**, *1*, 1041–1048. (i) Cooke, A.; Bennett, J.; McDaid, E. *Tetrahedron Lett.* **2002**, *43*, 903–905. (j) Müller, P.; Bernardinelli, G.; Nury, P. *Tetrahedron: Asymmetry* **2002**, *13*, 551–558. (k) Müller, P.; Toujas, J.-L.; Bernardinelli, G. *Helv. Chim. Acta* **2000**, *83*, 1525–1534. (l) Obrecht, D.; Zumbrunn, C.; Müller, K. *J. Org. Chem.* **1999**, *64*, 6891–6895. (m) Rutjes, F. P. J. T.; Veerman, J. J. N.; Meester, W. J. N.; Hiemstra, H.; Schoemaker, H. E. *Eur. J. Org. Chem.* **1999**, 1127–1135. (n) Dorizon, P.; Su, G.; Ludvig, G.; Nikitina, L.; Paugam, R.; Ollivier, J.; Salaün, J. *J. Org. Chem.* **1999**, *64*, 4712–4724. (o) Strachan, J.-P.; Sharp, J. T.; Crawshaw, M. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 443–451.

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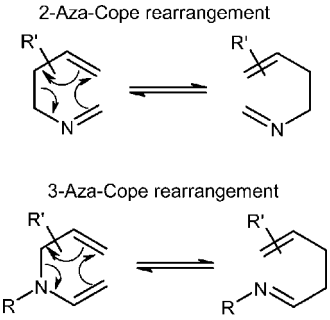
SCHEME 1



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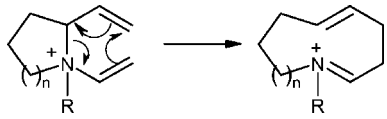
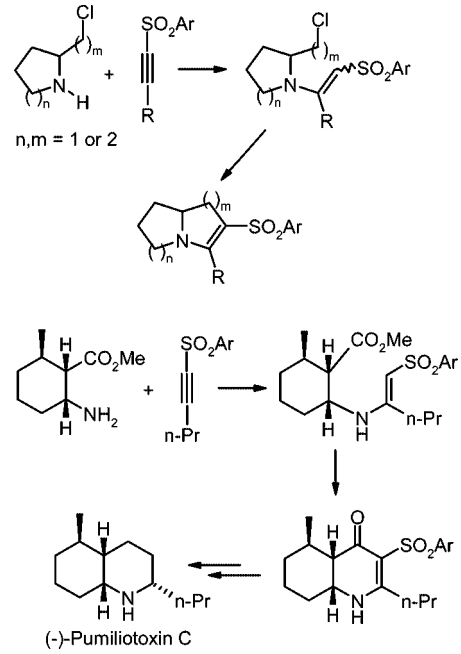


ties. New methods for their synthesis are therefore in demand. The preparation of these compounds by direct ring-closure methods such as intramolecular alkylation or acylation reactions is often challenging because of combinations of destabilizing Pitzer, transannular, and large-angle strain in the products, as well as an unfavorable loss of entropy.[6] Ring-closing metathesis affords a popular and effective alternative strategy, providing that the corresponding bis(alkene) precursor is readily available.[7] A third approach is based on the expansion of an existing ring.[8] In principle, a cyclic tertiary amine containing *N*- and α-vinyl substituents should undergo a 3-aza-Cope rearrangement to afford a ring-expanded product, particularly when the amine is quaternary (Scheme 2). In related processes, [3,3] sigmatropic rearrangements leading to ring-expanded products were observed in the case of the addition products of a vinylazetine to a cyclopropenone[3c] and in amide enolates derived from cyclic α-vinylamines.[3f,l,n]

During the past few years, we have investigated a series of cyclization protocols based on the conjugate additions of primary or secondary amines to acetylenic sulfones,[9] followed by intramolecular alkylations or acylations. This has provided access to a variety of nitrogen heterocycles, such as piperidines, pyrrolizidines, indolizidines, quinolizidines decahydroquinolines, and quinolones.[10] The products, after further transformation, include (−)-pumiliotoxin C,[10a] other dendrobatid alkaloids,[10b] myrtine,[10c] (−)-lasubine II,[10c] two quinolone alkaloids from the medicinal plant *Ruta chalepensis*,[10d] and (−)-julifloridine.[10e] Examples are shown in Scheme 3.

SCHEME 3



As a continuation of our studies of cyclization reactions of acetylenic sulfones, we investigated the conjugate additions of acyclic tertiary allyl amines and cyclic tertiary α-vinylamines **1** and **5**, respectively, to acetylenic sulfones **2**. The resulting zwitterion intermediates **3** and **6** were expected to undergo spontaneous 3-aza-Cope rearrangements to afford the corresponding rearranged and ring-expanded products **4** and **7,** respectively (Scheme 4).[11,12] The dipolar nature of **3** and **6** led us to anticipate that their [3,3] sigmatropic rearrangements would be exceptionally facile. We now report the results of this investigation, along with mechanistic studies and a novel iterative ring expansion based on the sequential application of the ring-expansion protocol shown in Scheme 4.

(3) For recent examples of 3-aza-Cope rearrangements, see: (a) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138–4139. (b) Craig, D.; King, N. P.; Mountford, D. M. *Chem. Commun.* **2007**, 1077–1079. (c) Hemming, K.; O'Gorman, P. A.; Page, M. I. *Tetrahedron Lett.* **2006**, *47*, 425–428. (d) Fiedler, D.; van Halbeek, H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 10240–10252. (e) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751. (f) Zheng, J.-F.; Jin, L-R.; Huang, P.-Q. *Org. Lett.* **2004**, *6*, 1139–1142. (g) Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Savory, E. D.; Smith, A. D. *Chem. Commun.* **2003**, 2134–2135. (h) For a related example of a 1-aza-Cope rearrangement (formally the reverse of a 3-aza-Cope process), see: Kang, J.; Kim, T. H.; Yew, K. H.; Lee, W. K. *Tetrahedron Asymmetry* **2003**, *14*, 415–418. (i) Winter, R. F.; Rauhut, G. *Chem.—Eur. J.* **2002**, *8*, 641–649. (j) Gomes, M. J. S.; Sharma, L.; Prabhakar, S.; Lobo, A. M.; Glória, P. M. C. *Chem. Commun.* **2002**, 746–747. (k) Cardoso, A. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2000**, *41*, 3611–3613. (l) Lindström, U. M.; Somfai, P. *Chem.—Eur. J.* **2001**, *7*, 94–98. (m) McComsey, D. F.; Maryanoff, B. E. *J. Org. Chem.* **2000**, *65*, 4938–4943. (n) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545–3547.

(4) For a discussion of the use of the terms "3-aza-Cope" and "3-aza-Claisen", see note 1 in Walters, M. A. *J. Org. Chem.* **1996**, *61*, 978–983.

(5) For example, ab initio calculations by Walters (ref 4) revealed that the activation energy for the [3,3] sigmatropic rearrangement of allyl vinyl amine is 34.6 kcal/mol, whereas that for its protonated counterpart is only 21.4 kcal/mol. For early examples of the beneficial effects of quaternization or Lewis acid catalysis, see references cited therein.

(6) Smith, M. B.; March, J. *March's Advanced Organic Chemistry —Reactions, Mechanisms and Structure* 5th ed.; Wiley: New York, 2001; pp 184−186 and 280−281.

(7) For a review of the synthesis of nitrogen and oxygen heterocycles by ring-closing metathesis, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.

(8) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, Germany, 1991.

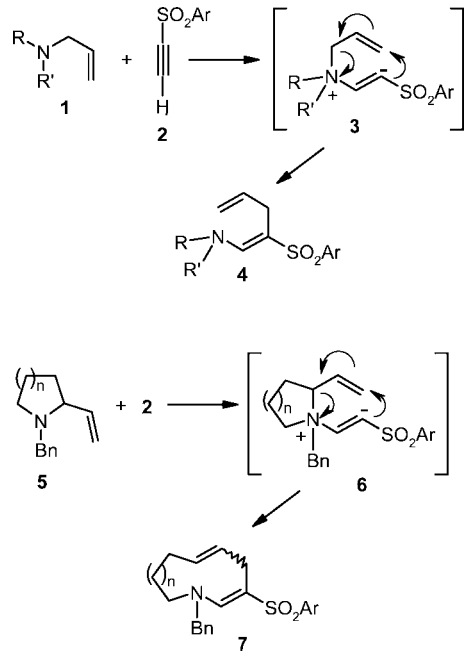
(9) For a review of acetylenic and allenic sulfones, see: Back, T. G. *Tetrahedron* **2001**, *57*, 5263–5301.

(10) (a) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566–6571. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543–4552. (c) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967–972. (d) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223–2233. (e) Zhai, H.; Parvez, M.; Back, T. G. *J. Org. Chem.* **2007**, *72*, 3853–3852.

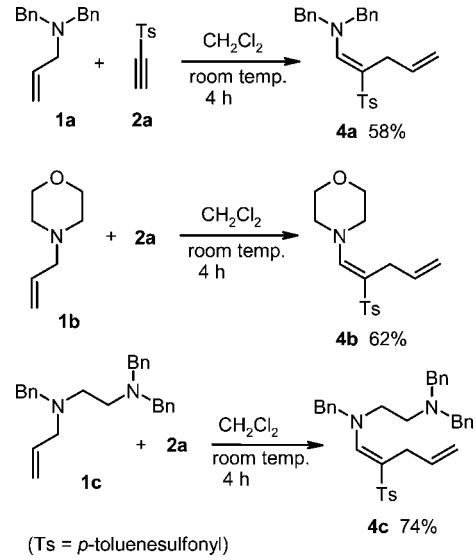
(11) Preliminary communication: Weston, M. H.; Nakajima, K.; Parvez, M.; Back, T. G. *Chem. Commun.* **2006**, 3903–3905.

(12) For earlier studies of aza-Cope reactions that proceed via dipolar intermediates produced from tertiary allyl amines and DMAD or propiolate esters, see: (a) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579–588. (b) Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682–7692. (c) Schwan, A. L.; Warkentin, J. *Can. J. Chem.* **1988**, *66*, 1686–1694. (d) Kandeel, K. A.; Vernon, J. M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2023–2026. (e) Hassner, A.; D'Costa, R.; McPhail, A. T.; Butler, W. *Tetrahedron Lett.* **1981**, *22*, 3691–3694. (f) Hassner, A.; Chau, W.; D'Costa, R. *Isr. J. Chem.* **1982**, *22*, 76–81.

SCHEME 4



SCHEME 5



Results and Discussion

We first investigated several examples of tandem conjugate additions and 3-aza-Cope rearrangements of allyl amines **1**. The latter were prepared by *N*-allylation of the corresponding secondary amines by a standard procedure.[13] The results are displayed in Scheme 5, which shows that the rearranged products **4a**−**4c** were obtained in moderate yield under mild conditions from amines **1a**−**1c**, respectively.

The results of similar reactions with cyclic α-vinyl amines **5a**−**5d**, **8a**−**8c**, and **9**−**12** with **2a** are presented in Table 1. Compounds **5a**,[14] **5b**,[14] **8a**,[15] **10**,[16] and **12**[17] were obtained by literature methods, whereas the preparation of **11** is described in the Experimental Section. The preparation of **5c**, **5d**, **8b**, **8c**, and **9** was described in the Supporting Information of our preliminary communication.[11] Acetylenic sulfones **2a**−**2f**[18,19] (vide infra) were obtained by known methods.

In general, the reactions proceeded smoothly and rapidly at temperatures ranging between −78 °C and refluxing dichloromethane or THF to afford good to excellent yields of the products. Among a variety of solvents investigated, dichloromethane proved particularly effective (compare entries 1−8), whereas methanol, a protic solvent, delivered comparable yields of **7a** and **7b** (entries 2 and 8), but resulted in the formation of anomalous products **15** and **16** (entries 17 and 18) from the methoxyvinyl-substituted piperidine **11** and the vinylaziridine **12** (vide infra). The polar aprotic solvent DMF delivered the lowest yield of **7b** (entry 7) because of competing polymerization. A mixture of ether and dichloromethane was used in entry 16 because pure dichloromethane resulted in a very rapid reaction accompanied by extensive decomposition. The products include rings ranging from 9- to 17-membered (**7a** and **7d**, respectively) and can accommodate an additional heteroatom (**13**), or fusion to another ring (**14**). Substituents on the vinyl group were also tolerated (**12a**−**12c**). The diene moiety in **8c** resulted in the usual [3,3] instead of a possible [3,5] sigmatropic rearrangement, although the product **12c** was obtained in relatively low yield. The use of *N*-methyl instead of *N*-benzylamines proved unsuccessful because of rapid and extensive polymerization of the starting materials. Similarly, attempts to employ 2-substituted 1-(arylsulfonyl)acetylenes failed because of sluggish rates attributed to increased steric hindrance and competing side reactions.

The azonine derivative **7a** was formed as the pure 5*Z*-isomer, presumably because of the expected constraints imposed by the 9-membered ring. This was confirmed by its olefinic coupling constant $J_{cis} = 11.3$ Hz. Products **7b**, **7c**, and **13**, all containing larger rings, were obtained solely or predominantly as the *E*-isomers, as evidenced by the coupling constants J_{trans} of 15.7 and 15.9 Hz for **7c** and **13**, respectively. An X-ray structure of the major isomer of **7b**[11] confirmed its 5*E* geometry, as well as its expected 2*E* configuration. The presence of overlapping olefinic ^{1}H NMR signals and the unavailability of suitable crystals for X-ray structure determinations precluded unequivocal *E*/*Z* assignments for the isolated alkene moieties of the remaining ring-expanded compounds in Table 1, although we assume that they are predominantly *E*, except in the case of **14**.

Cope and similar [3,3] sigmatropic rearrangements typically proceed in a concerted manner via the interaction of the two respective π-systems of a 1,5-hexadiene, resulting in the formation of a new σ-bond between the terminal positions, with concomitant allyl migration. In the present case, three distinct possibilities must be considered upon completion of the initial conjugate addition of the amine to the acetylenic sulfone. First, in anhydrous aprotic solvents such as dichloromethane or THF, the rearrangement must proceed directly via the interaction of the sulfone-stabilized vinyl anion with the alkene π-system in the corresponding zwitterionic intermediate such as **3** or **6** in

(13) Allyldibenzylamine (**1a**) was prepared from allyl bromide and dibenzylamine by the method of Alcaide, B.; Almendros, P.; Alonso, J.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781–3784. *N*-Allylmorpholine (**1b**) and *N*-allylamine **1c** were prepared similarly.

(14) Compounds **5a** and **5b** were previously investigated in aza-Cope rearrangements of chromium carbene complexes: Deur, C. J.; Miller, M. W.; Hegedus, L. S *J. Org. Chem.* **1996**, *61*, 2871–2876.

(15) Nazabadioko, S.; Pérez, R. J.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1597–1604.

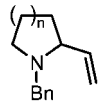
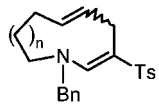
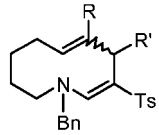
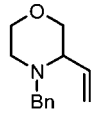
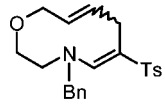
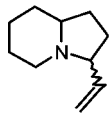
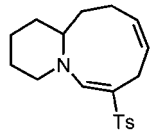
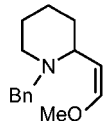
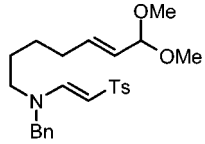
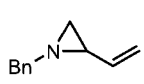
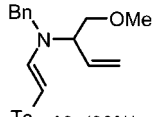
(16) Agami, C.; Couty, F.; Evano, G *Org. Lett.* **2000**, *2*, 2085–2088.

(17) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837.

(18) Chen, Z.; Trudell, M. L. *Synth. Commun.* **1994**, *24*, 3149–3155.

(19) Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1971**, *1*, 145–149.

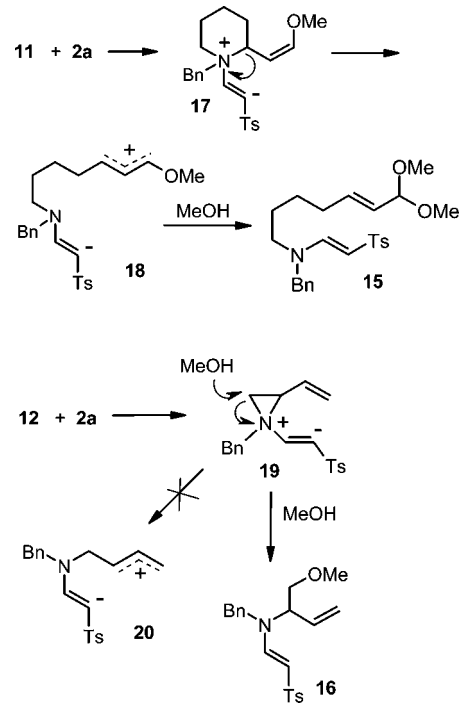
TABLE 1. Reactions of Cyclic A-Vinyl Amines with 2a

Entry	Amine	Product (yield)	Solvent,[a] temp.,[b] time
			
1	**5a** (n = 1)	**7a** (87%)	DCM, 0°C, 0.5 h
2		(91%)	MeOH, 0°C, 4 h
3	**5b** (n = 2)	**7b** (91%)	DCM, 0°C, 0.5 h
4		(75%)	Ether, RT, 48 h
5		(72%)	$CHCl_3$, RT, 12 h
6		(63%)	MeCN, 0°C, 2 h
7		(27%)	DMF, 0°C, 0.5 h
8		(87%)	MeOH, 0°C, 2 h
9	**5c** (n = 3)	**7c** (89%)	DCM, 0°C, 0.5 h
10	**5d** (n = 9)	**7d** (63%)	DCM, RT, 30 h
			
11	**8a** R = H; R' = Me	**12a** (89%)	DCM, RT, 12 h
12	**8b** R = Me; R' = H	**12b** (86%)	DCM, reflux, 8 h
13	**8c** R = H, R' = vinyl	**12c** (58%)	DCM, RT, 12 h
			
14	**9**	**13** (87%)	DCM, RT, 12 h
15		(84%)	THF, reflux, 14h
			
16	**10**	**14** (61%)	DCM-ether (3:5), RT, -78°C, 3 h
			
17	**11**	**15** (64%)	MeOH, -78°C, 3 h then RT 3 h
			
18	**12**	**16** (89%)	MeOH, RT, 12 h

[a] DCM = Dichloromethane. [b] RT = Room temperature.

Scheme 4. Alternatively, in the presence of a proton source such as methanol (e.g., entry 2 in Table 1), protonation of the vinyl anion would produce a neutral vinyl sulfone moiety that is tethered to an allyl group via a quaternary nitrogen atom, resulting in a more conventional cationic 3-aza-Cope rearrangement. This outcome is contingent upon protonation occurring more rapidly than the sigmatropic rearrangement of the initial zwitterion. The formation of products **15** and **16** in entries 17 and 18, respectively, illustrates a third possibility, wherein C−N

SCHEME 6



bond cleavage[20] a of the zwitterions **17** and **19** occurs in lieu of sigmatropic rearrangement, and is either preceded or followed (as shown in Scheme 6) by proton transfer from the solvent. In the case of **17**, C−N cleavage likely produces the methoxy-stabilized allyl cation **18**, although an S_N2' reaction with methanol cannot be unequivocally ruled out. On the other hand, ring-opening of **19** appears to proceed via S_N2 attack by methanol at the methylene group of the strained aziridinium cation, either before or after proton transfer to the vinyl sulfone moiety. This results in the formation of methyl ether **16**, rather than of products from the quenching of allyl cation **20** by methanol (Scheme 6).[20] Because the other examples that were also performed in methanol in Table 1 (entries 2 and 8) afforded the normal products of sigmatropic rearrangement, we attribute the anomalous result in entry 17 to the electron-donating methoxy substituent in amine **11**, which promotes C−N cleavage and stabilizes the resulting allyl cation **18** (Scheme 6). Similarly, in entry 18, the release of aziridine ring strain promotes a more rapid direct ring-opening by the nucleophilic solvent, relative to the rate of the usual [3,3] sigmatropic rearrangement (Scheme 6). When the reactions of **11** and **12** with **2a** were repeated in dichloromethane, only complex mixtures of unidentified products were obtained.

Attempts to detect the postulated zwitterion intermediates by NMR in several of the reactions summarized in Table 1 proved fruitless, suggesting that the initial conjugate addition is rate-determining, followed by the rapid sigmatropic rearrangement of the zwitterion (or possibly of its conjugate acid in the presence of a proton source). To confirm this assumption, as well as the existence of the postulated zwitterion, we performed the following experiments. The relatively slow reactions of **8b** with acetylenic sulfones **2a**−**2f** enabled us to measure their rates

(20) (a) For related examples of dissociative mechanisms involving C−N bond cleavage, see refs 12a and 12c. (b) For examples where vinylaziridines underwent aza-Cope rearrangements upon addition to other unsaturated electrophiles, in contrast to the ring-opening of **12**, see refs 3l, 12e and 12f.

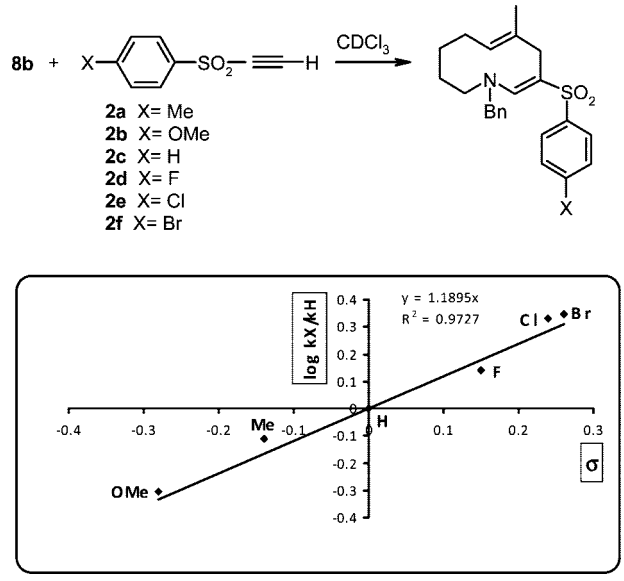
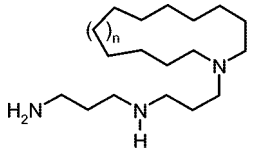


FIGURE 1. Hammett plot for the reaction of **8b** with **2a**−**2f**.

conveniently by monitoring the formation of the corresponding products via NMR spectroscopy, using *tert*-butyldimethylsilyl phenyl ether as an internal standard. The resulting kinetic data (see the Supporting Information) were consistent with a bimolecular reaction and resulted in the Hammett plot shown in Figure 1. The reaction constant $\rho = +1.19$ indicates that the transition state in the rate-determining step is significantly stabilized by electron-withdrawing substituents on the arylsulfonyl moiety. These observations are consistent with a rate-determining conjugate addition to afford the proposed zwitterion intermediate, followed by a rapid [3,3] sigmatropic rearrangement.

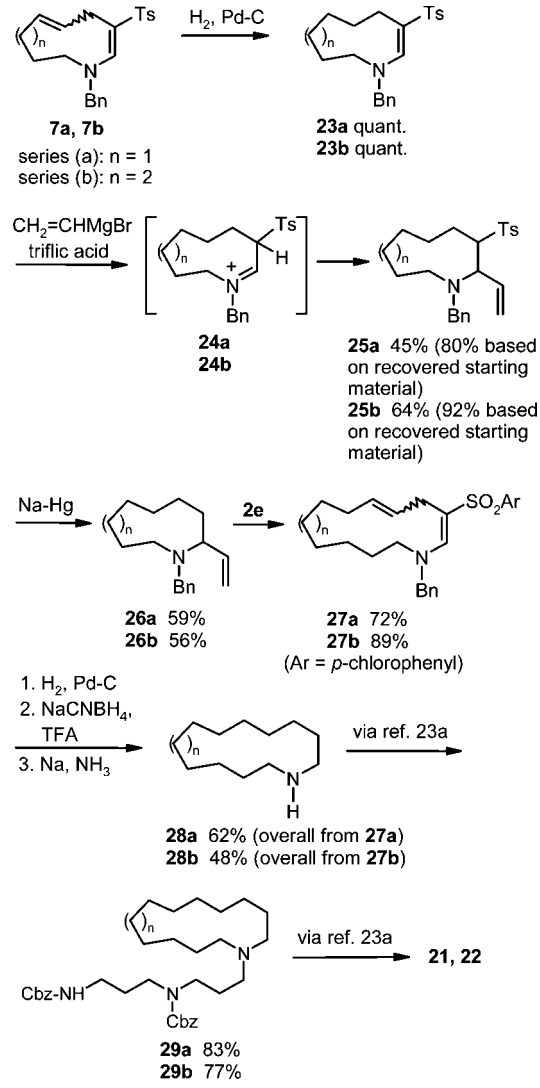
It also seemed plausible that the ring-expansion reaction that leads to medium- and large-ring nitrogen heterocycles **7** in Scheme 4 could be employed in an iterative manner if the enamine sulfone functions of the products could in turn be converted into new α-vinyl amines, thereby setting the stage for a second ring expansion. We now illustrate the iterative protocol through its application to the synthesis of the alkaloids motuporamine A and B (**21** and **22**, respectively). The latter products were isolated in 1998 from the sponge *Xestospongia exigua* by Andersen and co-workers[21] and were shown to display strong anti-invasive and antiangiogenic activity.[22] Several earlier syntheses of motuporamines A and B have been reported.[22a,23]



motuporamine A (n = 1) (**21**)
motuporamine B (n = 2) (**22**)

In the first stage of the iterative protocol, the 3-aza-Cope ring expansions of amines **5a** and **5b** to **7a** and **7b**, respectively, were performed as shown in entries 1 and 3 in Table 1. The products were then transformed into the corresponding α-vinyl amines **26a** and **26b**, respectively, followed by a second ring expansion, as shown in Scheme 7. Thus, introduction of the

SCHEME 7



vinyl group into the iminium intermediates **24a** and **24b** was achieved with vinylmagnesium bromide. This was accompanied by competing β-deprotonation, thereby regenerating the starting material, which could be easily recovered and recycled. Reductive desulfonylation[24] of **25a** and **25b** then afforded the desired α-vinyl amines **26a** and **26b**. The second ring-expansion of the latter products proceeded more efficiently with (*p*-chlorobenzenesulfonyl)ethyne (**2e**) than with **2a** to afford the 13- and 14-membered products **27a** and **27b**. Reduction of the latter, as before, provided the parent amines **28a** and **28b**, which were then converted into the bis(Cbz)-protected motuporamine A

(21) Williams, D. E.; Lassota, P.; Andersen, R. J. *J. Org. Chem.* **1998**, *63*, 4838–4841.

(22) For lead references on the bioactivity of the motuporamines, see: (a) Williams, D. E.; Craig, K. S.; Patrick, B.; McHardy, L. M.; van Soest, R.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2002**, *67*, 245–258. (b) Roskelley, C. D.; Williams, D. E.; McHardy, L. M.; Leong, K. G.; Troussard, A.; Karsan, A.; Andersen, R. J.; Dedhar, S.; Roberge, M. *Cancer Res.* **2001**, *61*, 6788–6794. (c) McHardy, L. M.; Sinotte, R.; Troussard, A.; Sheldon, C.; Church, J.; Williams, D. E.; Andersen, R. J.; Dedhar, S.; Roberge, M.; Roskelley, C. D. *Cancer Res.* **2004**, *64*, 1468–1474. (d) To, K. C. W.; Loh, K. T.; Roskelley, C. D.; Andersen, R. J.; O'Connor, T. P. *Neuroscience* **2006**, *139*, 1263–1274. (e) Kaur, N.; Delcros, J.-G.; Martin, B.; Phanstiel, O. *J. Med. Chem.* **2005**, *48*, 3832–3839.

(23) (a) Baldwin, J. E.; Vollmer, H. R.; Lee, V. *Tetrahedron Lett.* **1999**, *40*, 5401–5404. (b) Goldring, W. P. D.; Weiler, L. *Org. Lett.* **1999**, *1*, 1471–1473.

(24) Trost, B. M.; Arndt, H. C.; Strege, P. E; Verhoeven, T. R *Tetrahedron Lett.* **1976**, *17*, 3477–3478.

(**29a**) and B (**29b**), respectively, by the method of Baldwin, followed by hydrogenolysis.[23a,25]

Summary and Conclusions

We have found that the reactions of tertiary acyclic allyl amines or tertiary cyclic α-vinyl amines with acetylenic sulfones result in initial conjugate additions, followed by 3-aza-Cope rearrangements. In the case of cyclic α-vinyl amines, these rearrangements result in the ring-expansion of the starting materials by four carbon atoms, providing a novel, efficient route to cyclic amines ranging from 9- to 17-members.

Kinetic studies were consistent with a bimolecular process, and a Hammett plot obtained with amine **8b** and a series of acetylenic sulfones **2a**-**2f** containing variously *p*-substituted arylsulfonyl groups produced a reaction constant $\rho = +1.19$. Thus, the reaction is facilitated by electron-withdrawing substituents on the arylsulfonyl moiety, which stabilize a negative charge in its proximity. These observations are consistent with a rate-determining conjugate addition step, leading to the formation of the zwitterion intermediate, followed by its rapid [3,3] sigmatropic rearrangement to afford the ring-expanded products. The anomalous formation of **15** and **16** from amines **11** and **12**, respectively, in methanol demonstrates that a dissociative mechanism leading to a stabilized allyl cation is possible when an electron-donating methoxy group is present at the terminus of the exocyclic vinyl group of the starting amine, or when direct attack by methanol on a strained aziridinium intermediate occurs more rapidly than sigmatropic rearrangement.

Finally, the ring-expansion protocol can be employed iteratively by conversion of the enamine sulfone moiety of the initial ring-expanded product to a new α-vinyl substituent, followed by a second 3-aza-Cope rearrangement and ring-expansion in the usual manner. The iterative protocol was demonstrated in the synthesis of the marine natural products motuporamine A and B.

Experimental Section

NMR spectra were taken in $CDCl_3$ unless otherwise noted. Flash chromatography was performed on silica gel (230−400 mesh).

(*p*-Fluorobenzenesulfonyl)ethyne (2d). *p*-Flourobenzenesulfonyl chloride (2.00 g, 10.3 mmol) was dissolved in dichloromethane (15 mL) and $AlCl_3$ (1.37 g, 10.3 mmol) was added. This mixture was stirred for 30 min, cooled to 0 °C, and a solution of bis(trimethylsilyl)acetylene (1.75 g, 10.3 mmol) in dichloromethane (15 mL) was added. This was warmed to room temperature over 30 min and stirred for a further 24 h. The reaction was quenched with 10% HCl solution, extracted with dichloromethane, dried, and concentrated. The crude product was dissolved in THF (10 mL) and a $K_2CO_3/KHCO_3$ (7.0×10^{-3} M, 20 mL) buffer solution was added. The mixture was stirred for 30 min, extracted with ethyl acetate, dried, concentrated, and purified by flash chromatography (10% ethyl acetate−hexanes) to afford 1.27 g (67%) of **2d** as a pale yellow solid: mp 57−58 °C (from ether); IR (film) 2070, 1591, 1335, 1170 cm^{-1}; ^1H NMR (200 MHz) δ 8.03−7.96 (m, 2 H), 7.29−7.21 (m, 2 H), 3.65 (s, 1 H); ^{13}C NMR (50 MHz) δ 166.2 (d, $J_{CF} = 258.1$ Hz), 136.6 (d, $J_{CF} = 1.5$ Hz), 130.6 (d, $J_{CF} = 10.3$ Hz), 116.9 (d, $J_{CF} = 23.1$ Hz), 82.5, 79.8; mass spectrum, *m*/*z* (%) 184 (M^+, 75), 143 (100), 120 (50); HRMS calcd for $C_8H_5FO_2S$, 183.9994; found, 183.9990.

The previously reported acetylenic sulfones **2a**, **2b**, **2c**, **2e**, and **2f** were prepared similarly, by literature procedures.[18,19]

Typical Procedure for the aza-Cope Rearrangement of Acyclic α-Vinyl Amines: *N*,*N*-Dibenzyl-[2-(*p*-toluenesulfonyl)penta-1,4-dienyl]amine (4a). A solution of acetylenic sulfone **2a** (57 mg, 0.32 mmol) in dichloromethane (2 mL) was added slowly to a solution of allyldibenzylamine (**1a**) (74 mg, 0.31 mmol) in dichloromethane (1.0 mL). The mixture was stirred at room temperature for 4 h, concentrated in vacuo, and purified via flash chromatography (10% ethyl acetate−hexanes) to afford 76 mg (58%) of **4a** as a yellow oil: IR (film) 1622, 1294, 1135 cm^{-1}; ^1H NMR (400 MHz) δ 7.92 (s, 1 H), 7.72 (d, $J = 8.3$ Hz, 2 H), 7.42−7.21 (m, 8 H), 7.16 (d, $J = 6.8$ Hz, 4 H), 5.68 (ddt, $J = 17.1$, 10.2, 5.1 Hz, 1 H), 4.90 (dd, $J = 10.3$, 1.6 Hz, 1 H), 4.86 (dd, $J = 17.2$, 1.6 Hz, 1 H), 4.39 (s, 4 H), 2.98−2.92 (m, 2 H) 2.42 (s, 3 H); ^{13}C NMR (100 MHz) δ 147.6, 142.3, 139.9, 136.9, 136.7, 129.3, 128.9, 127.7, 127.3, 126.9, 115.5, 102.0, 55.5, 28.9, 21.4; mass spectrum, *m*/*z* (%) 417 (M^+, 2), 326 (9), 262 (61), 170 (45), 91 (100); HRMS calcd for $C_{26}H_{27}NO_2S$, 417.1763; found, 417.1766.

Products **4b** and **4c** were prepared similarly.

***N*-[2-(*p*-Toluenesulfonyl)penta-1,4-dienyl]morpholine (4b).** Compound **4b** was obtained in 46% yield as a yellow oil: IR (film) 1624, 1279, 1137 cm^{-1}; ^1H NMR (400 MHz) δ 7.70 (d, $J = 8.2$ Hz, 2 H), 7.40 (s, 1 H), 7.25 (d, $J = 8.4$ Hz, 2 H), 5.66 (ddt, $J = 17.1$, 10.1, 5.1 Hz, 1 H), 4.96 (dd, $J = 10.2$, 1.7 Hz, 1 H), 4.88 (dd, $J = 17.2$, 1.7 Hz, 1 H), 3.09−3.05 (m, 2 H) 2.40 (s, 3 H); ^{13}C NMR (100 MHz) δ 146.0, 142.3, 139.4, 135.3, 129.2, 127.2, 115.7, 101.9, 66.5, 50.1, 29.1, 21.3; mass spectrum, *m*/*z* (%) 307 (M^+, 7), 152 (100), 120 (55), 91 (25); HRMS calcd for $C_{16}H_{21}NO_3S$, 307.1242; found, 307.1234.

***N*,*N*,*N*′-Tribenzyl-*N*′-[(1E)-2-(*p*-toluenesulfonyl)penta-1,4-dienyl]ethane-1,2-diamine (4c).** Compound **4c** was obtained in 74% yield as a yellow oil: IR (film) 1616, 1273, 1127 cm^{-1}; ^1H NMR (300 MHz) δ 7.68 (d, $J = 8.2$ Hz, 2 H), 7.66 (s, 1 H), 7.35−7.25 (m, 15 H), 7.01 (d, $J = 6.7$ Hz, 2 H), 5.75−5.55 (m, 1 H), 4.91−4.79 (m, 2 H), 4.26 (s, 2 H), 3.57 (s, 4 H), 3.23 (t, $J = 6.6$ Hz, 2 H), 2.87−2.79 (m, 2 H), 2.59 (t, $J = 6.6$ Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (50 MHz) δ 147.4, 142.1, 140.1, 138.9, 137.3, 136.7, 129.2, 128.8, 128.7, 128.3, 127.5, 127.3, 127.1, 126.6, 115.4, 101.0, 59.1, 55.2, 51.8, 50.9, 28.8, 21.4; mass spectrum (CI), *m*/*z* (%) 551 (M+1, 100), 224 (30), 210 (20); HRMS calcd for $C_{35}H_{38}N_2O_2S$, 550.2654; found, 550.2628.

Typical Ring-Exapansion Procedure: (2*E*,5*Z*)-*N*-Benzyl-3-(*p*-toluenesulfonyl)azacyclonona-2,5-diene (7a, Table 1, entry 1). A solution of acetylenic sulfone **2a** (84 mg, 0.47 mmol) in dichloromethane (3 mL) was added to a solution of *N*-benzyl-2-vinylpyrrolidine (**5a**)[14] (87 mg, 0.47 mmol) in dichloromethane (15 mL) over 10 min at 0 °C. After 30 min at 0 °C, the mixture was concentrated and purified by flash chromatography (10% ethyl acetate−hexanes) to afford 149 mg (87%) of **7a** as a yellow oil: IR (film) 1616, 1283, 1135 cm^{-1}; ^1H NMR (300 MHz) δ 7.95 (d, $J = 8.2$ Hz, 2 H), 7.84 (s, 1 H), 7.26−7.05 (m, 3 H), 7.02−6.88 (m, 2 H), 6.91 (d, $J = 8.2$ Hz, 2 H), 5.43 (dt, $J = 11.3$, 8.2 Hz, 1 H), 5.13 (dt, $J = 11.3$, 6.7, Hz, 1 H), 3.72 (s, 2 H), 3.26 (d, $J = 6.7$ Hz, 2 H), 2.81 (t, $J = 4.9$ Hz, 2 H), 1.97 (s, 3 H), 1. 92−1.80 (m, 2 H), 1.15−1.02 (m, 2 H); ^{13}C NMR (75 MHz) δ 149.4, 142.5, 139.9, 137.6, 130.0, 129.5, 128.9, 128.0, 127.6, 127.4, 124.6, 103.2, 60.5, 48.9, 29.4, 25.4, 24.2, 21.6; mass spectrum, *m*/*z* (%) 367 (M^+, 2), 212 (27), 91 (100); HRMS calcd for $C_{22}H_{25}NO_2S$, 367.1606; found, 367.1590.

The other products in Table 1 were produced in a similar manner under the conditions given in the Table and their characterization, except for **14**−**16** (see below), was described in the Supporting Information of our preliminary communication.[11]

(25) The removal of the Cbz groups from **29a** and **29b** was effected by hydrogenolysis, as reported by Baldwin et al.,[23a] to afford the crude motuporamines A and B (**21** and **22**, respectively). Attempts to purify the triamines **21** and **22** as the free bases was ineffective, and the products were more easily isolated as the protected derivatives **29a** and **29b**. Alternatively, isolation and purification of **21** and **22** as the corresponding bis-*N*-acetyl derivatives has also been reported.[21,23]

(2*E*,5*Z*)-1-Aza-3-(*p*-toluenesulfonyl)-[7.4.0]bicyclotrideca-2,5-diene (14). Acetylenic sulfone **2a** (69 mg, 0.38 mmol) in dichloromethane (3 mL) was added slowly to a solution of vinyl indolizidine **10**[17] (58 mg, 0.38 mmol) in ether (5 mL) at −78 °C. The solution was allowed to warm to room temperature after 3 h and was concentrated and purified via chromatography (25% ethyl acetate−hexanes) to give 77 mg (61%) of **14** as a yellow oil. The product decomposed rapidly when concentrated and so spectra are reported on a crude sample. IR (film) 1730, 1604, 1278 cm^{-1}; ^1H NMR (200 MHz) δ 7.69 (d, J = 8.4 Hz, 2 H), 7.47 (s, 1 H), 7.23 (d, J = 8.4 Hz, 2 H), 5.66−5.47 (m, 1 H), 5.24−5.10 (m, 1 H), 4.32−4.15 (m, 1 H), 3.55−2.90 (m, 3 H), 2.50−2.30 (m, 2 H), 2.39 (s, 3 H), 2.00−1.07 (m, 9 H); ^{13}C NMR (50 MHz) δ 148.9, 142.0, 139.9, 129.2, 128.8, 127.0, 126.0, 98.7, 52.5, 50.1, 31.9, 30.7, 26.6, 26.3, 22.3, 21.4, 18.9; mass spectrum, *m*/*z* (%) 331 (M^+, 15), 176 (100), 91 (20); HRMS calcd for $C_{19}H_{25}NO_2S$, 331.1606; found, 331.1598.

***N*-Benzyl-2-(2-methoxyvinyl)piperidine (11) and (*E*)-1-[*N*-Benzyl-*N*-(5*E*-7,7-dimethoxyhept-5-enyl)amino]-2-(*p*-toluenesulfonyl)ethene (15).** To a solution of (methoxymethyl)triphenylphosphonium chloride (2.21 g, 6.46 mmol) in THF (15 mL) was added *n*BuLi (2.27 mL, 5.68 mmol) at −78 °C. The solution was warmed to 0 °C and stirred for 1 h at 0 °C. The red mixture was cooled to –78 °C and *N*-benzylpiperdine-2-carbaldehyde[15] (1.05 g, 5.17 mmol) in THF (15 mL) was added. The mixture was allowed to warm to room temperature over 3 h and was furthered stirred for 6 h. The reaction was quenched with saturated $NaHCO_3$ solution, extracted with ether, dried, and concentrated under a vacuum. Because the triphenyphosphine oxide could not be separated from **11**, the crude product was used without purification in the subsequent step: ^1H NMR (200 MHz) δ 7.48−7.07 (m, 5 H), 5.99 (d, J = 6.5 Hz, 1 H), 4.55 (dd, J = 6.5, 6.3 Hz, 1 H), 4.11 (d, J = 13.5 Hz, 1 H), 3.62 (s, 3 H), 3.20 (m, 1 H) 3.16 (d, J = 13.5 Hz, 1 H), 2.81 (m, 2 H), 1.9−1.3 (m, 6 H); mass spectrum, *m*/*z* (%) 231 (M^+, 68), 200 (100), 91 (76); HRMS calcd for $C_{15}H_{21}NO$, 231.1623; found, 231.1622.

Amine **11** (0.35 mmol) was dissolved in methanol (5 mL) and cooled to −78 °C. After addition of acetylenic sulfone **2a** (63 mg, 0.35 mmol), the solution was kept at −78 °C for 3 h and was then stirred at room temperature for an additional 3 h. The solution was concentrated and purified via flash chromatography (25% ethyl acetate−hexanes) to afford 100 mg (64%) of **15** as a yellow oil: IR (film) 1608, 1134 cm^{-1}; ^1H NMR (200 MHz) δ 7.71 (d, J = 6.8 Hz, 2 H), 7.48 (d, J = 12.8 Hz, 1 H), 7.38- 7.10 (m, 7 H), 5.71 (dt, J = 15.9, 6.8 Hz, 1 H), 5.42 (dd, J = 15.9, 5.2 Hz, 1 H), 4.98 (d, J = 12.8 Hz, 1 H), 4.72 (d, J = 5.1 Hz, 1 H), 4.30 (s, 2 H), 3.30 (s, 6 H), 3.25−2.85 (m, 2 H), 2.40 (s, 3 H), 2.10−1.98 (m, 2 H), 1.68−1.15 (m, 4 H); ^{13}C NMR (50 MHz) δ 149.9, 142.1, 134.3, 129.3, 128.8, 128.7, 127.9, 127.2, 127.1, 126.1, 103.0, 93.5, 59.3, 52.7, 48.7, 31.5, 28.0, 25.9, 21.4; mass spectrum, *m*/*z* (%) 411 (M^+ − MeOH, <1), 256 (100), 91 (90); HRMS calcd for $C_{24}H_{29}NO_3S$ (M^+ − MeOH), 411.1868; found, 411.1886.

1-{*N*-Benzyl-*N*-[2-(1-methoxybut-3-enyl)]amino}-2-(*p*-toluenesulfonyl)ethene (16). Acetylenic sulfone **2a** (48 mg, 0.26 mmol) was added to a solution of vinylaziridine **12**[17] (42 mg, 0.26 mmol) in methanol (5 mL) at 0 °C, the solution was warmed to room temperature and stirring was continued for 12 h. The mixture was concentrated and purified via flash chromatography (25% ethyl acetate−hexanes), affording 85 mg (89%) of **16** as a light yellow oil: IR (film) 1609, 1274, 1135 cm^{-1}; ^1H NMR (200 MHz) δ 7.71 (d, J = 7.8 Hz, 2 H), 7.51 (d, J = 12.8 Hz, 1 H), 7.38−7.12 (m, 7 H), 5.73−5.47 (m, 1 H), 5.33−5.20 (m, 2 H), 5.00 (d, J = 12.8 Hz, 1 H), 4.40 (m, 2 H), 3.85−3.60 (m, 1 H), 3.35−2.95 (m, 2 H), 3.22 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (50 MHz) δ 150.7, 142.2, 142.0, 135.1, 129.3, 128.7, 127.7, 127.2, 126.1, 119.4, 94.0, 80.4, 60.3, 56.4, 21.4; mass spectrum, *m*/*z* (%) 371 (M^+, 5), 300 (20), 216 (30), 91 (100); HRMS calcd for $C_{21}H_{25}NO_3S$, 371.1555; found, 371.1531.

(*E*)-*N*-Benzyl-3-(*p*-toluenesulfonyl)azacyclonon-2-ene (23a). Palladium on charcoal (10%, 106 mg) was added to a solution of azonine **7a** (2.04 g, 5.55 mmol) in methanol (40 mL). The suspension was stirred under hydrogen (1 atm) overnight, filtered through Celite, concentrated and purified by flash chromatography (10% ethyl acetate−hexanes) to afford 2.04 g (100%) of **23a** as a clear oil: IR (film) 1617, 1278, 1126 cm^{-1}; ^1H NMR (200 MHz) δ 7.70 (d, J = 8.0 Hz, 2 H), 7.68 (s, 1 H), 7.42−7.20 (m, 7 H), 4.37 (s, 2 H), 3.35 (m, 2 H), 2.46 (m, 2 H), 2.41 (s, 3 H), 1.67−1.33 (m, 8 H); ^{13}C NMR (50 MHz) δ 147.4, 142.1, 140.3, 137.1, 129.2, 128.8, 127.9, 127.4, 127.2, 103.2, 60.4, 45.5, 30.3, 29.0, 26.9, 24.0, 23.9, 21.4; mass spectrum, *m*/*z* (%) 369 (M^+, 35), 214 (55) 172 (100). HRMS calcd for $C_{22}H_{27}NO_2S$, 369.1763; found, 369.1771.

(*E*)-*N*-Benzyl-3-(*p*-toluenesulfonyl)azacyclodec-2-ene (23b). The same procedure as for the preparation of **23a** was followed, using **7b** and affording 100% of **23b**: IR (film) 1626, 1126 cm^{-1}; ^1H NMR (200 MHz) δ 7.70 (d, J = 8.0 Hz, 2 H), 7.55 (s, 1 H), 7.45−7.20 (m, 7 H), 4.37 (s, 2 H), 3.33 (t, J = 6.9 Hz, 2 H), 2.46−2.38 (m, 2 H), 2.41 (s, 3 H), 1.75−1.38 (m, 10 H); ^{13}C NMR (50 MHz) δ 146.3, 142.1, 140.3, 137.2, 129.2, 128.7, 127.8, 127.6, 127.1, 105.9, 60.5, 44.4, 28.0, 26.3, 25.3, 23.2, 22.1, 21.5 21.4; mass spectrum, *m*/*z* (%) 383 (M^+, 76), 186 (55), 91 (100); HRMS calcd for $C_{23}H_{29}NO_2S$, 383.1919; found, 383.1897.

***N*-Benzyl-3-(*p*-toluenesulfonyl)-2-vinylazacyclononane (25a).** Triflic acid (0.56 mL, 6.3 mmol) was added slowly to a solution of azonine **23a** (1.15 g, 3.11 mmol) in dichloromethane (25 mL) at −10 °C. The solution was stirred for 30 min at −10 °C, followed by the slow addition of vinylmagnesium bromide in ether solution (12.8 mL, 12.8 mmol). The mixture was warmed to room temperature over 2 h, quenched with saturated $NaHCO_3$ solution, filtered, extracted with dichloromethane, dried, concentrated, and purified via flash chromatography (10% ethyl acetate−hexanes) to give 503 mg (44%) of recovered **23a** and 558 mg (45%; 80% based on recovered starting material) of **25a** (single diastereomer) as a yellow oil: IR (film) 1287, 1130 cm^{-1}; ^1H NMR (200 MHz) δ 7.63 (d, J = 8.0 Hz, 2 H), 7.35−7.14 (m, 7 H), 5.63 (dt, J = 16.9, 7.9 Hz, 1 H), 5.32 (dd, J = 10.3, 1.8 Hz, 1 H), 5.03 (dd, J = 16.9, 1.9 Hz, 1 H), 3.61 (d, J = 13.0 Hz, 1 H), 3.40 (d, J = 13.0 Hz, 1 H), 3.24−3.12 (m, 1 H), 3.00−2.73 (m, 2 H) 2.42 (s, 3 H), 2.36−2.18 (m, 1 H), 2.10−0.97 (m, 10 H); ^{13}C NMR (50 MHz) δ 144.0, 138.8, 135.9, 132.5, 129.5, 129.2, 128.9, 128.2, 126.9, 118.8, 65.5, 61.8, 56.1, 44.5, 26.9, 26.3, 22.1, 21.5, 19.8, 19.7; mass spectrum, *m*/*z* (%) 397 (M^+, 3), 242 (100), 91 (55); HRMS calcd for $C_{24}H_{31}NO_2S$, 397.2076; found, 397.2092.

***N*-Benzyl-3-(*p*-toluenesulfonyl)-2-vinylazacyclodecane (25b).** The same procedure as for the preparation of **25a** was followed, using **23b** and affording 30% of recovered **23b** and 64% (92% based on recovered starting material) of **25b** (3:1 mixture of two diastereomers) as a yellow oil: IR (film) 1282, 1139 cm^{-1}; ^1H NMR (200 MHz) major diastereomer δ 7.60 (d, J = 8.2 Hz, 2 H), 7.37−7.16 (m, 7 H), 5.52 (dt, J = 16.9, 9.5 Hz, 1 H), 5.31 (dd, J = 10.3, 2.0 Hz, 1 H), 4.98 (dd, J = 17.1, 1.9 Hz, 1 H), 3.72 (d, J = 13.3 Hz, 1 H), 3.23 (d, J = 13.3 Hz, 1 H); minor diastereomer δ 7.76 (d, J = 8.0 Hz), 5.11 (dd, J = 17.0, 2.1 Hz); ^{13}C NMR (50 MHz) major diastereomer δ 144.0, 138.7, 132.8, 129.4, 129.3, 129.2, 129.0, 128.2, 126.8, 119.2, 66.9, 60.3, 54.3, 47.8, 27.1, 27.0, 24.9, 24.1, 22.6, 21.5, 21.5; mass spectrum, *m*/*z* (%) 411 (M^+, 3), 256 (90), 91 (100); HRMS calcd for $C_{25}H_{33}NO_2S$, 411.2232; found, 411.2244.

***N*-Benzyl-2-vinylazacyclononane (26a).** To a solution of sulfonylazonane **25a** (202 mg, 0.508 mmol) in saturated K_2HPO_4 in methanol (15 mL) was added 10% Na/Hg (1.50 g). The mixture was stirred at room temperature for 4 h, filtered through Celite, concentrated, and purified via flash chromatography (hexanes to 5% ethyl acetate−hexanes) to afford 73 mg (59%) of **25a** as a yellow oil: IR (film) 1143, 1070, 983, 904 cm^{-1}; ^1H NMR (200 MHz) δ 7.44−7.15 (m, 5 H), 5.74 (m, 1 H), 5.15 (dd, J = 10.4, 2.1 Hz, 1 H), 4.95 (dd, J = 17.2, 2.1 Hz, 1 H), 3.70 (d, J = 13.2 Hz, 1 H), 3.52 (d, J = 13.2, 1 H), 3.10−2.78 (m, 2 H), 2.30−2.15 (m, 1 H), 1.90−1.10 (m, 12 H); ^{13}C NMR (50 MHz) δ 140.7, 137.2,

129.3, 128.0, 126.5, 115.8, 61.8, 57.6, 44.3, 28.6, 27.5, 27.2, 21.0, 20.3, 19.5; mass spectrum, *m/z* (%) 243 (M^+, 15), 186 (64), 152 (65), 91 (100); HRMS calcd for $C_{17}H_{25}N$, 243.1987; found, 243.1983.

***N*-Benzyl-2-vinylazacyclodecane (26b).** The same procedure as for the preparation of **26a** was followed, using **25b** and affording 56% of **26b** as a yellow oil: IR (film) 1139, 1113, 1076, 1027, 996, 914 cm^{-1}; ^1H NMR (200 MHz) δ 7.44−7.15 (m, 5 H), 5.72 (ddd, J = 17.1, 9.5, 7.7 Hz, 1 H), 5.15 (dd, J = 10.4, 2.2 Hz, 1 H), 4.95 (dd, J = 17.1, 2.2 Hz, 1 H), 3.81 (d, J = 13.3 Hz, 1 H), 3.22 (d, J = 13.3 Hz, 1 H), 2.90 (td, J = 12.8, 4.1 Hz, 1 H), 2.37−2.26 (m, 2 H), 2.00−1.15 (m, 14 H); ^{13}C NMR (50 MHz) δ 140.5, 137.0, 129.2, 128.0, 126.4, 116.0, 60.5, 54.9, 47.0, 30.1, 26.6, 26.5, 26.0, 24.9, 23.7, 22.8; mass spectrum, *m/z* (%) 257 (M^+, 3), 166 (100), 91 (83); HRMS calcd for $C_{18}H_{27}N$, 257.2144; found, 257.2139.

***N*-Benzyl-3-(*p*-chlorobenzenesulfonyl)azacyclotrideca-2,5-diene (27a).** Acetylenic sulfone **2e** (100 mg, 0.50 mmol) was added to a solution of azacyclononane **26a** (80 mg, 0.33 mmol) in dichloromethane (5 mL) and stirred at room temperature for 24 h. The mixture was concentrated and purified via flash chromatography (10% ethyl acetate−hexanes), affording 105 mg (72%) of **27a** (ca. 2.5:1 mixture of geometric isomers) as a yellow oil, which was used directly in the next step.

N-Benzyl-3-(4-chlorobenzenesulfonyl)azacyclotetradeca-2,5-diene (27b). The same procedure as for the preparation of **27a** was followed, using **26b** and affording 89% of **27b** (ca. 1.5:1 mixture of geometric isomers) as a yellow oil, which was used directly in the next step.

Azacyclotridecane (28a). Palladium on charcoal (10%, 18 mg) was added to a solution of azacyclotridecadiene **27a** (105 mg, 0.236 mmol) in methanol (10 mL). The suspension was stirred under hydrogen (1 atm.) overnight, filtered through Celite, concentrated, and purified by flash chromatography (10% ethyl acetate−hexanes) to afford 105 mg (100%) of (*E*)-*N*-benzyl-3-(*p*-chlorobenzenesulfonyl)azacyclotridec-2-ene as a clear oil: IR (film) 1617, 1283, 1139, 1087 cm^{-1}; ^1H NMR (200 MHz) δ 7.67 (d, J = 8.7 Hz, 2 H), 7.51 (s, 1 H), 7.39 (d, J = 8.9 Hz, 2 H), 7.36−7.12 (m, 5 H), 4.44 (s, 2 H), 3.24 (t, J = 6.9 Hz, 2 H), 2.28 (t, J = 7.2 Hz, 2 H), 1.70−1.00 (m, 16 H); ^{13}C NMR (50 MHz) δ 147.3, 141.9, 138.1, 137.4, 129.1, 129.0, 128.7, 128.0, 127.3, 105.5, 57.4, 52.1, 28.0, 27.4, 26.2, 26.1, 25.5, 25.3, 25.2, 24.4; mass spectrum, *m/z* (%) 445 (M^+, 15), 270 (100) 172 (25), 91 (43); HRMS calcd for $C_{25}H_{32}ClNO_2S$, 445.1842; found, 445.1857.

Trifluoroacetic acid (0.38 mL, 5.1 mmol) was added to a suspension of the above product (220 mg, 0.493 mmol) and $NaCNBH_3$ (308 mg, 4.90 mmol) in dichloromethane (15 mL). The mixture was stirred for 30 min at room temperature, refluxed for 30 min, cooled to room temperature, quenched with 10% KOH solution, extracted with dichloromethane, dried, and concentrated in vacuo. The crude amine was purified via flash chromatography (10% ethyl acetate−hexanes) to afford 165 mg (75%) of *N*-benzyl-3-(*p*-chlorobenzenesulfonyl)azacyclotridecane as a clear oil: IR (film) 1317, 1139 cm^{-1}; ^1H NMR (200 MHz) δ 7.71 (d, J = 8.5 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H), 7.28−7.03 (m, 5 H), 3.55 (d, J = 13.0 Hz, 1 H), 3.26 (d, J = 13.3 Hz, 1 H) 2.76 (dd, J = 13.1, 2.3 Hz, 1 H), 2.60−2.22 (m, 4 H), 1.80−1.00 (m, 18 H); ^{13}C NMR (50 MHz) δ 140.1, 138.4, 136.8, 130.0, 129.3, 129.2, 128.1, 127.1, 63.0, 58.6, 55.4, 54.7, 27.0, 26.2, 26.1, 25.5, 25.4, 24.8, 24.1, 23.7, 23.2; mass spectrum, *m/z* (%) 447 (M^+, 5), 356 (55) 272 (95), 91 (100); HRMS calcd for $C_{25}H_{34}ClNO_2S$, 447.1999; found, 447.1979.

To a solution of the above product (87 mg, 0.19 mmol) in dry THF (5 mL) at −78 °C was added liquid ammonia (5 mL), followed by the addition of sodium (275 mg, 11.9 mmol). This mixture was stirred for 30 min at −78 °C, ethanol was added (0.05 mL), and the solution was stirred at −78 °C for a further 2 h. It was allowed to warm to −30 °C and NH_4Cl was added carefully. A saturated $NaHCO_3$ solution was added, the mixture was warmed to room temperature, extracted with ethyl acetate, dried, concentrated, and purified using flash chromatography (hexanes to 5% ethyl acetate−hexanes), affording 30 mg (85%) of **28a** as a clear oil: ^1H NMR (200 MHz) δ 2.65 (t, J = 5.2 Hz, 4 H), 1.7−1.2 (m, 20 H); ^{13}C NMR (50 MHz) δ 47.9, 27.9, 26.5, 26.0, 25.4, 24.6; lit.[22a] ^1H NMR (400 MHz, MeOH-d_4) δ 2.64 (t, J = 5.9 Hz, 4 H), 1.55 (m, 4 H), 1.39 (m, 16 H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 48.0, 28.1, 27.3, 27.0, 26.5, 25.4.

Azacyclotetradecane (28b). Compound **27b** was hydrogenated as in the preparation of **28a**, affording 100% of (*E*)-*N*-benzyl-3-(*p*-chlorobenzenesulfonyl)-azacyclotetradec-2-ene as a clear oil: IR (film) 1626, 1130 cm^{-1}; ^1H NMR (200 MHz) δ 7.67 (d, J = 8.7 Hz, 2 H), 7.52 (s, 1 H), 7.39 (d, J = 8.7 Hz, 2 H), 7.40−7.13 (m, 5 H), 4.42 (s, 2 H), 3.23 (t, J = 6.4 Hz, 2 H), 2.21 (t, J = 6.7 Hz, 2 H), 1.80−1.15 (m, 18 H); ^{13}C NMR (50 MHz) δ 147.3, 142.0, 137.8, 137.1, 128.8, 128.7, 128.4, 127.8, 127.0, 104.1, 55.4, 53.4, 27.8, 27.2, 25.8, 25.7, 25.4, 25.1, 25.0, 24.3, 24.0, 23.5; mass spectrum, *m/z* (%) 459 (M^+, 5), 284 (98), 186 (40), 91 (100); HRMS calcd for $C_{26}H_{34}ClNO_2S$, 459.1999; found, 459.2019.

The above compound was reduced with sodium cyanoborohydride and TFA by the same procedure as in the preparation of **28a**, affording 74% of *N*-benzyl-3-(*p*-chloro-benzenesulfonyl)azacyclotetradecane, isolated as clear oil: IR (film) 1583, 1304, 1148 cm^{-1}; ^1H NMR (200 MHz) δ 7.72 (d, J = 8.7 Hz, 2 H), 7.51 (d, J = 8.9 Hz, 2 H), 7.30−7.05 (m, 5 H), 3.58 (d, J = 13.3 Hz, 1 H), 3.24 (d, J = 13.7 Hz, 1 H), 3.04 (m, 1 H), 2.80−2.40 (m, 3 H), 2.35−2.15 (m, 1 H), 2.05−1.10 (m, 20 H); ^{13}C NMR (50 MHz) δ 140.1, 130.0, 129.3, 129.0, 128.1, 127.0, 62.7, 58.2, 54.1, 53.0, 26.6, 26.2, 26.0, 25.8, 25.5, 25.2, 24.7, 24.6, 24.1, 23.7; mass spectrum, *m/z* (%) 461 (M^+, 2), 370 (25) 286 (50), 91 (100). HRMS calcd for $C_{26}H_{36}ClNO_2S$, 461.2155; found 461.2134.

The reduction of the above compound with sodium and liquid ammonia was carried out by the same procedure as in the preparation of **28a**, affording **28b** in 65% yield: ^1H NMR (200 MHz) δ 2.68 (t, J = 5.7 Hz, 4 H), 1.70−1.15 (m, 22 H); ^{13}C NMR (50 MHz) δ 45.9, 26.9, 25.9, 25.1, 24.3, 23.8, 23.2.

Motuporamine A (21). Azacyclotridecane (**28a**) was converted into **29a** by the procedure of Baldwin et al.[23a] in 83% yield; ^1H NMR (200 MHz) δ 7.35 (m, 10 H), 5.12 (s, 2 H), 5.09 (s, 2 H), 3.35−3.16 (m, 6 H), 2.88−2.45 (m, 6 H), 2.12−1.99 (m, 2 H), 1.77−1.26 (m, 22 H); ^{13}C NMR (50 MHz) δ 156.3, 136.3, 128.5, 128.4, 128.1, 128.0, 67.3, 66.5, 59.0, 57.3, 44.8, 44.0, 37.8, 26.6, 25.6, 25.4, 25.1, 22.8, 19.9. Hydrogenolysis of bis(carbobenzyloxy)motuporamine A (**29a**) afforded crude **21**.[25]

Motuporamine B (22). Azacyclotetradecane (**28b**) was converted into **29b** by the procedure of Baldwin et al.[23a] in 77% yield; ^1H NMR (200 MHz) δ 7.33 (m, 10 H), 5.12 (s, 2 H), 5.08 (s, 2 H), 3.34−3.16 (m, 6 H), 2.91−2.41 (m, 6 H), 2.14−1.96 (m, 2 H), 1.80−1.14 (m, 24 H); ^{13}C NMR (50 MHz) δ 156.4, 136.4, 128.5, 128.4, 128.1, 128.0, 67.3, 66.5, 59.3, 57.0, 44.9, 43.9, 38.0, 29.6, 26.3, 26.1, 25.7, 23.6, 23.4, 19.2. Hydrogenolysis of bis(carbobenzyloxy)motuporamine B (**29b**) afforded crude **22**.[25]

Kinetic Determinations. NMR tubes were charged with **8b** (20 mg, 0.093 mmol) and the respective acetylenic sulfones **2a**−**2f** (0.093 mmol) in a solution of *tert*-butyldimethylsilyl phenyl ether (0.050 M, internal standard) in $CDCl_3$ (1.00 mL). The reactions were maintained at 21 °C and monitored by measuring the disappearance of the diastereotopic benzylic methylene signal in **8b** and the appearance of the methylene singlets in the corresponding aza-Cope products. For plots of the results, see the Supporting Information.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of new compounds, and kinetic plots for the reactions of **8b** with **2a**−**2f** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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