Synthesis of Bicyclic Nitrogen Compounds via Tandem Intramolecular Heck Cyclization and Subsequent Trapping of Intermediate π-Allylpalladium Complexes

G. Davis Harris, Jr., R. Jason Herr, and Steven M. Weinreb*

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

Received May 4, 1993•

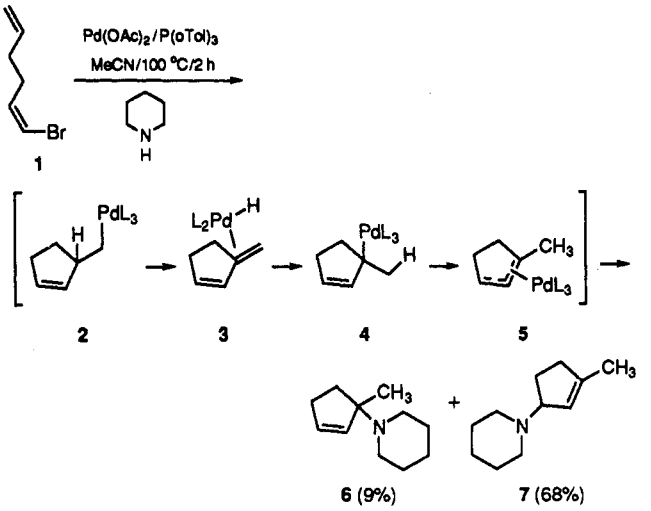
Intramolecular palladium-mediated three-component cyclizations of substrates containing vinyl halide, olefin, and sulfonamide moieties to generate a diverse group of nitrogen heterocycles have been developed. The methodology has been applied to construction of both fused and bridged bicyclic systems. The strategy can also be used for spirocyclizations. This chemistry involves regiospecific generation of π-allylpalladium complexes via Heck reactions of vinyl halides and simple olefins, followed by nucleophilic addition of sulfonamide anions to these intermediates.

Introduction

Since its initial disclosure over 20 years ago,[1] the Heck reaction[2] in both its inter-[3] and intramolecular[4] versions has assumed an important position as a carbon–carbon bond-forming method. In general, the palladium catalyzed coupling of an aryl halide with an olefin is an excellent way to prepare a 1,3-diene. However, if a vinyl halide is used, a problem which often arises is formation of a stable π-allylpalladium species. The consequence of this is that the palladium is irreversibly removed from the reaction, thereby terminating the catalytic cycle. If, however, one conducts the reaction in the presence of a secondary amine, an allylic amine is formed with regeneration of the metal catalyst.[5]

An example of this process is shown in Scheme I, where cyclization of 1 in the presence of piperidine affords a mixture of aminocyclopentenes 6 and 7. The mechanism

Scheme I



for this transformation is believed to involve initial closure of palladated 1 to 2, which undergoes β-hydride elimination to produce diene η^2-complex 3. Readdition of PdH to 3 would lead to σ-allylpalladium intermediate 4, which can rearrange to π-allylpalladium species 5. Attack of piperidine at the two termini of 5 would produce the observed allylic amine products 6 and 7.[6,7]

It appears from inspection of the many examples of this type of reaction reported by Heck that formation of the π-allylpalladium intermediate is regiospecific.[5] The implication is that the readdition of PdH occurs selectively to the π-complexed double bond of diene 3 before Pd

• Abstract published in *Advance ACS Abstracts*, August 15, 1993.

(1) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(2) For reviews, see (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345. (c) Heck, R. F. Catalytic Applications of Palladium in Organic Synthesis. In *The Place of Transition Metals in Organic Synthesis*; Slocum, D. W., Ed.; The New York Academy of Sciences: New York, 1977; Vol. 95, p 201. (d) Heck, R. F. Vinyl Substitutions with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 833. (e) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

(3) For recent examples, see inter alia: (a) Larock, R. C.; Berrios-Pena, N.; Narayanen, K. *J. Org. Chem.* **1990**, *55*, 3447. (b) Larock, R. C.; Leung, W.-Y. *J. Org. Chem.* **1990**, *55*, 6244. (c) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (d) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 6845. (e) Cabri, W.; Candiana, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558. (f) Amorese, A.; Arcadi, A.; Bernocchi, E.; Cacchi, S.; Cerrini, S.; Fedeli, W.; Ortar, G. *Tetrahedron* **1989**, *45*, 813.

(4) For some recent examples of intramolecular Heck reactions, see: (a) Abelman, M. A.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Zhang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5588. (c) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003 and refs cited therein. (d) Negishi, E.; Zhang, Y.; O'Conner, B. *Tetrahedron Lett.* **1988**, *29*, 2915. (e) Larock, R. C.; Song, H.; Baker, B. E.; Gong, W. H. *Tetrahedron Lett.* **1988**, *29*, 2919. (f) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694. (g) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 4525. (h) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328. (i) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953. (j) Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028. (k) Meyer, F. E.; de Meijere, A. *Synlett* **1991**, 777.

(5) (a) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792. (b) Shi, L.; Narula, C. K.; Mak, K. T.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894. (c) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (d) Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 3898. (e) Kim, J. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067. (f) Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1980**, *45*, 3584.

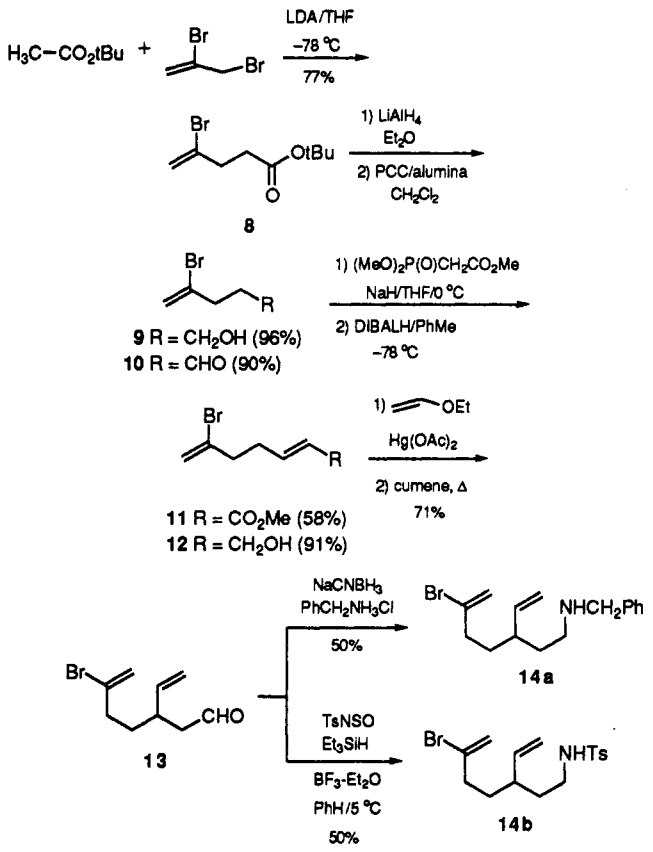
(6) For nucleophilic displacements with carboxamides and sulfonamides onto π-allylpalladium complexes, see inter alia: (a) Backvall, J. E.; Andersson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683. (b) Bystrom, S. E.; Aslanian, R.; Backvall, J. E. *Tetrahedron Lett.* **1985**, *26*, 1749. For mechanistic studies of amination of π-allyl palladium complexes, see: Akermark, B.; Akermark, G.; Hegedus, L. S.; Zetterberg, K. *J. Am. Chem. Soc.* **1981**, *103*, 3037.

(7) For reviews of π-allylpalladium chemistry, see: (a) Hegedus, L. S. Nucleophilic Attack on Transition Metal Organometallic Compounds. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: New York, 1985; Vol. 2, p 401. (b) Tsuji, J. η^3-Allylpalladium Complexes. *Ibid.* Vol. 3, p 163. (c) Pearson, A. J. Transition Metal-Stabilized Carbocations in Organic Synthesis. *Ibid.* Vol. 4, p 889. (d) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Assym.* **1992**, *3*, 1089. (e) Godleski, S. A. Nucleophiles with Allyl-Metal Complexes. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 585.

(8) For an apparent isomerization of an η^2-diene/palladium complex, see: Kim, J. I.; Patel, B. A.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1067.

0022-3263/93/1958-5452$04.00/0

Scheme II



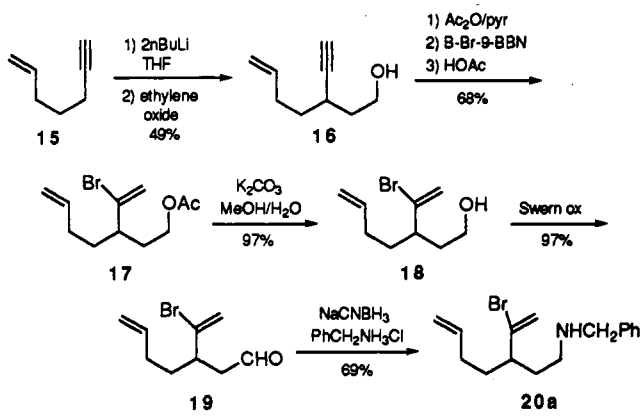
migration.[8] Interestingly, this point had apparently never been explicitly addressed.

We recently became interested in the possibility of utilizing this variation of the Heck reaction in construction of nitrogen heterocycles. In particular, we considered effecting a three-component condensation whereby the vinyl halide, alkene, and nitrogen nucleophile would be incorporated into a cyclization substrate.[9] In order to pursue this strategy, we decided it was necessary to first probe the key issue of regiospecificity of π-allylpalladium complex formation via Heck chemistry and therefore prepared two sets of isomeric cyclization substrates **14** (Scheme II) and **20** (Schemes III, IV).

Results and Discussion

Cyclization substrates **14a/b** were synthesized by the straightforward eight-step route outlined in Scheme II. *tert*-Butyl acetate was converted to its lithium enolate using LDA and smoothly alkylated with 2,3-dibromopropene to give *tert*-butyl 4-bromo-4-pentenoate **8** in 77% yield. Reduction of the ester with lithium aluminum hydride afforded 4-bromo-4-penten-1-ol (**9**) in 96% yield. Oxidation of **9** with a slurry of pyridinium chlorochromate and neutral alumina in methylene chloride produced 4-bromo-4-pentenal (**10**). The ester **11**, made in 58% yield using the Horner–Emmons reaction, was reduced with diisobutylaluminum hydride in toluene at −78 °C to afford allylic alcohol **12** in high yield. Attempted use of $LiAlH_4$ for reduction of **11** also caused conjugate reduction of the α,β double bond.

Scheme III



A vinyl ether was synthesized (82%) by treatment of allylic alcohol **12** with ethyl vinyl ether in the presence of mercury(II) acetate,[10] and subsequent thermal Claisen rearrangement in refluxing cumene produced aldehyde **13** in 87% yield. Bromovinyl benzylamine **14a** was then formed via standard reductive amination using benzylamine hydrochloride and $NaBH_3CN$ in methanol in the presence of 4-Å molecular sieves.[11] Diene sulfonamide **14b** was synthesized in one step by a novel reductive sulfonamidation method[12] recently developed in these labs in which aldehyde **13** was treated with *N*-sulfinyl-*p*-toluenesulfonamide[13] in the presence of boron trifluoride etherate, followed by addition of triethylsilane.

Isomeric cyclization precursor **20a** was prepared by an efficient six-operation route starting from 1-hepten-6-yne (**15**)[14] (Scheme III). The dianion of **15**[15] could be alkylated with ethylene oxide to afford alcohol **16** (49%). Alcohol **16** was then acylated with acetic anhydride in the presence of pyridine and DMAP. The product acetate was treated with B-Br-9-BBN at 0 °C, followed by addition of glacial acetic acid, to produce vinyl bromide **17** in 71% yield.[16] Vinyl bromide acetate **17** was then deprotected using potassium carbonate in aqueous methanol to afford alcohol **18**. Swern oxidation[17] of **18** provided aldehyde **19** in high yield. This aldehyde was then reductively aminated[11] with benzylamine hydrochloride and $NaBH_3CN$ to afford diene benzylamine **20a** (69% yield).

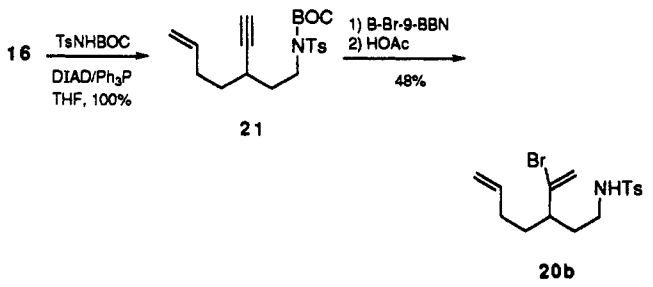
The corresponding sulfonamide **20b** was synthesized as shown in Scheme IV. Application of Mitsunobu chemistry developed in these laboratories[18] to alcohol **16** afforded *N*-BOC-sulfonamide **21**. Conversion of the alkyne to the vinyl bromide[16] and BOC cleavage yielded substrate **26b** (48% from **16**).

Initial cyclization experiments were conducted with *N*-benzylamine substrate **14a**. Unfortunately, under a

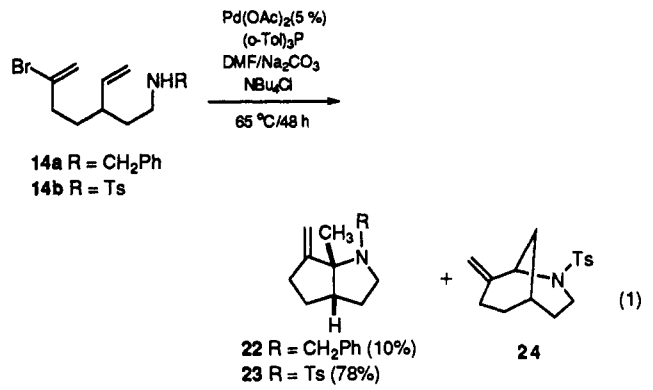
(9) For a preliminary account of portions of this work, see: (a) Harris, G. D., Jr.; Herr, R. J., Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528. (b) Harris, G. D., Jr. Ph.D. Thesis, The Pennsylvania State University, 1993.

(10) Dauben, W. G.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212.
(11) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(12) Alexander, M. D.; Anderson, R. E.; Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 2563.
(13) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.
(14) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436.
(15) Bhanu, S.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1218.
(16) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.
(17) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
(18) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

Scheme IV

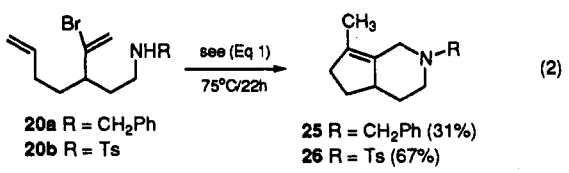


wide variety of Heck conditions, only a 10% yield of the desired bicyclic product **22** could be isolated at best (eq 1).



Diene sulfonamide **14b** was next subjected to reaction conditions described by Jeffery[19] and modified by Larock[20] in which sodium carbonate is used as a base and tetrabutylammonium chloride is employed as a phase transfer catalyst in DMF. We were pleased to find that treatment of **14b** with 5 mol % $Pd(OAc)_2$, 10 mol % P(o-tol)$_3$, 3.5 equiv of Na_2CO_3, and 2 equiv of Bu_4NCl in a 0.1 M DMF solution at 65 °C for 48 h afforded a 4:1 mixture of two isomeric bicyclic allylic sulfonamides **23** and **24** in a combined yield of 78% (eq 1). Other bases such as NaH, NEt_3, and LDA gave the cyclization products in very low yields.

As in the cyclization of **14a**, diene amine **20a** was subjected to varying amounts of palladium catalyst and base at reaction temperatures from 50–100 °C. The highest yield of cyclized product was achieved using 10% $Pd(OAc)_2$, 20% P(o-tol)$_3$, and 10 equiv of Et_3N in a 0.4 M solution of MeCN at 100 °C. Exposure of **20a** to these conditions for 28 h in a sealed tube provided bicyclic allylic amine **25**, but in a disappointing 31% yield (eq 2).



Diene sulfonamide **20b**, on the other hand, was found to cyclize to **26** in 67% yield using the optimum conditions developed for **14b** (cf. eq 1).[21] Once again, bases such as KOtBu, NaH, NaOH, BuLi, and NEt_3 gave consistently lower yields of **26**.[9b]

The results of these experiments strongly support the hypothesis that π-allylpalladium complex formation by the Heck reaction is indeed regiospecific. Mechanistically, we believe substrate **14b** cyclizes via a 5-exo process to **27** which β-hydride eliminates, yielding η^2-complex **28** (Scheme V). Regiospecific readdition of PdH to the π-bond to which the metal is complexed and rearrangement affords π-allylpalladium intermediate **29**. Nucleophilic attack by the deprotonated sulfonamide nucleophile then gives bicyclic compound **23**. The minor isomer **24** is derived from an initial 6-endo ring closure, followed by a similar rearrangement process to a π-allylpalladium species.[22]

Similarly, isomeric substrate **20b** first closes to **30** and then β-hydride eliminates to η^2-complex **31**. Rearrangement of **31** affords π-allylpalladium complex **32**, which undergoes nucleophilic attack to give bicyclic sulfonamide **26**. The fact that **14b** yields only bicyclic pyrrolidine **23**, and **20b** only isomer **26**, indicates that fluxional isomerization of the η^2-complexes **28** and **31** is slower than readdition of PdH to the double bond.[8]

It should be noted that we know nothing about the stereochemistry of the π-allylpalladium intermediates **29** and **32**. It is known, however, that nucleophilic attack onto a π-allylpalladium complex can occur both syn[6,7] and anti[6,7,23] to palladium, and thus either diastereomer may lead to the observed products. Thus, in the case of **23**, it is not clear if the initial alkene insertion to form **27**, or the closure of the sulfonamide onto the π-allylpalladium complex **29** governs the stereochemistry of the final product.

Having established the feasibility of regioselective formation and intramolecular nucleophilic attack on π-allylpalladium complexes resulting from 5-exo-trig cyclizations of vinyl bromide olefins, we investigated the possibility of performing a similar tandem cyclization via initial 6-exo-ring closure. In order to explore this issue, substrate **37**, a one-carbon homologue of precursor **20b**, was synthesized by the five-step procedure outlined in Scheme VI. The Grignard reagent from 5-bromo-1-pentene was coupled with (trimethylsilyl)propargyl chloride[24] to afford 8-(trimethylsilyl)-1-octen-7-yne (**33**). The propargyl carbanion of **33**, formed by deprotonation with *n*-BuLi, was alkylated with ethylene oxide at −5 °C to give alcohol **34** in 28% yield, along with a 30% recovery of starting material. The alkylation with ethylene oxide was also attempted on the dianion of 1-octen-7-yne, but inexplicably was totally unsuccessful. Alcohol **34** was coupled with *N*-BOC-*p*-toluenesulfonamide giving **35** in quantitative yield.[18] Desilylation of *N*-BOC-sulfonamide **35** to **36** was accomplished with tetrabutylammonium fluoride, and diene sulfonamide **37** was produced by the treatment of **36** with B-Br-9-BBN.[16] As in the synthesis

(19) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (c) Jeffery, T. *Synthesis* **1987**, 70.

(20) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.

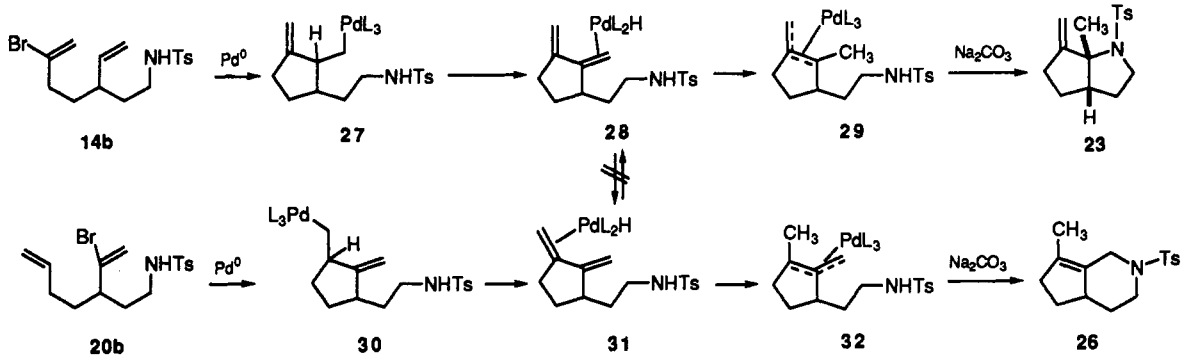
(21) Compounds **25** and **26** possess the ring skeleton of the skytanthine alkaloids: Śnieckus, V. Mono- and Sesqui-terpenoid Alkaloids. In *International Review of Science*; Wiesner, K., Ed.; Organic Chemistry Series 2; Butterworths: London, 1976; Vol. 9, p 208.

(22) It is known from the work of Heck[2,5] that 5-exo closure is preferred over 6-endo. This is the only example of a 6-endo cyclization we have observed to date. For another example of such a Heck cyclization, see: Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697.

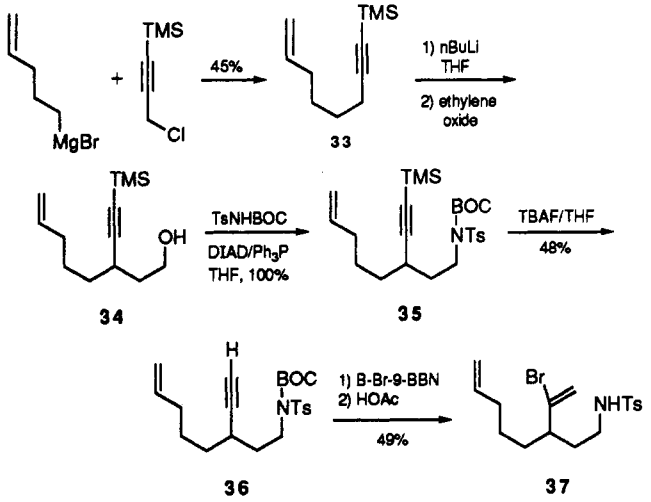
(23) Bender, D. D.; Stakem, F. G.; Heck, R. F. *J. Org. Chem.* **1982**, *47*, 1278.

(24) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; p 121.

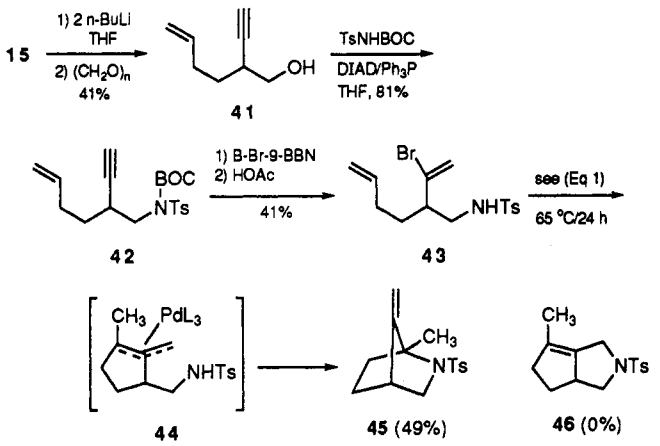
Scheme V



Scheme VI

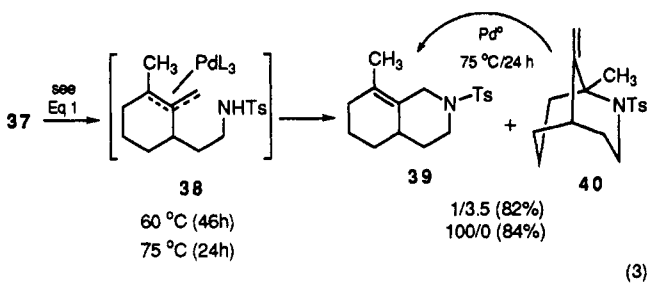


Scheme VII



of diene sulfonamide **20b** (Scheme IV), enough HBr is apparently generated in the bromination step to cleave the BOC group.

Exposure of diene **37** to the Heck conditions of (eq 1) at 60 °C led to an initial 6-exo-cyclization to produce the π-allylpalladium intermediate **38** (eq 3) which cyclized to afford a 1/3.5 mixture of fused bicycle **39** and bridged



(3)

product **40**. Although amine nucleophiles generally add to the least substituted carbon of a π-allylpalladium system,[7] Backvall has found[6b] that addition of a sulfonamide anion preferentially afforded the more substituted product. Thus, formation of **40** as the major product seems reasonable. Interestingly, when the cyclization was conducted at 75 °C, *only* fused isomer **39** was produced. Exposure of a pure sample of bridged compound **40** to the Heck reaction conditions caused isomerization to fused product **39** (8:1 mixture of **39**/**40** after 56 h at 75 °C). Therefore, it seems that kinetically formed bridged isomer **40** reverts to π-complex **38** which cyclizes to the thermodynamic product **39**. To our knowledge, this is the first example of π-allylpalladium complex formation from an allylic sulfonamide.[7,25]

Another system which we investigated was sulfonamide **43**, which was prepared by an efficient four step route (Scheme VII). The dianion of 1-hepten-6-yne (**15**) was alkylated with paraformaldehyde at the propargyl position at −25 °C to give alcohol **41**. This alcohol was coupled with *N*-BOC-*p*-toluenesulfonamide to afford sulfonamide **42**,[18] and bromination with B-Br-9-BBN also conveniently caused BOC cleavage to give the requisite diene sulfonamide substrate **43**. Vinyl bromide olefin **43** cyclized at 65 °C using the conditions in (eq 1) to yield only the bridged product **45** in 49% unoptimized yield (based on a 20% recovery of starting material), presumably via π-allylpalladium complex **44**. None of the strained [5,5]-fused isomer **46** could be detected. Running the reaction at a higher temperature to induce rearrangement of **45** to **46** only led to a reduced isolated yield of **45**.

We decided to next examine the possibility of utilizing a terminal (Z)-alkenyl bromide in the intramolecular three component Heck process and looked at converting alkyne sulfonamide **21** to substrate **50** (Scheme VIII). Attempts to selectively functionalize the alkyne group of **21** via hydroboration[26] were unsuccessful.

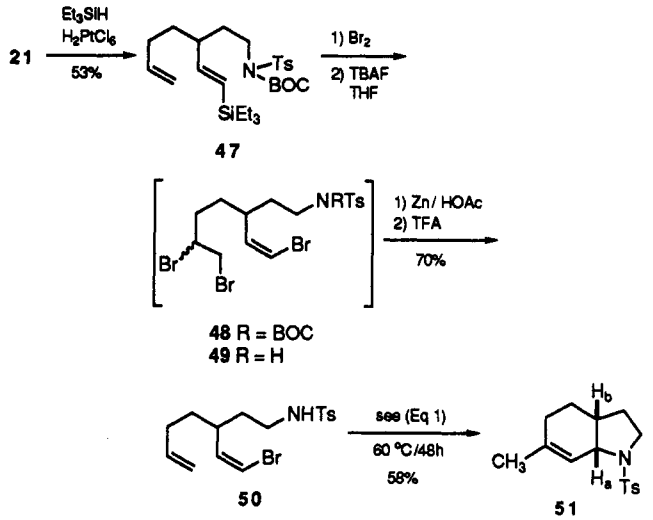
However, enyne **21** could be hydrosilylated exclusively at the triple bond in the presence of triethylsilane and a catalytic amount of chloroplatinic acid[27] to give *E*-vinylsilane **47** in 53% yield. This vinylsilane was then

(25) For another example of π-allylpalladium complex formation via an allylic sulfonamide, see: McIntosh, M.C.; Weinreb, S. M. *J. Org. Chem.*, in press.

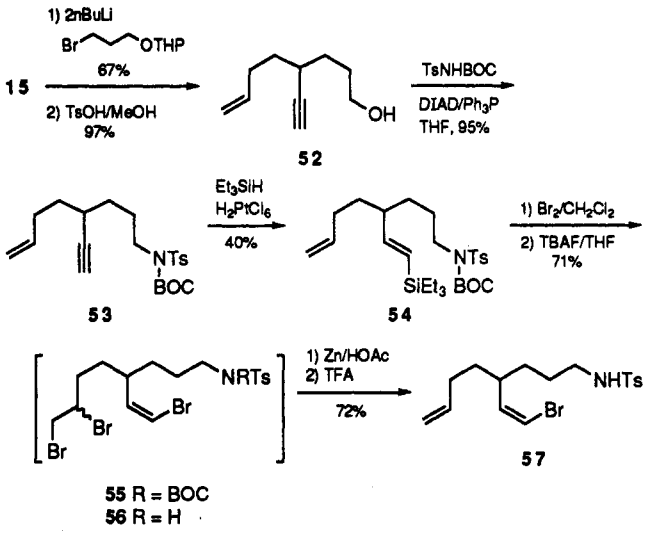
(26) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456.

(27) Colvin, E. W. *Silicon Reagents in Organic Synthesis*; Harcourt, Brace, Jovanovich: New York, 1988; p 50.

Scheme VIII



Scheme IX



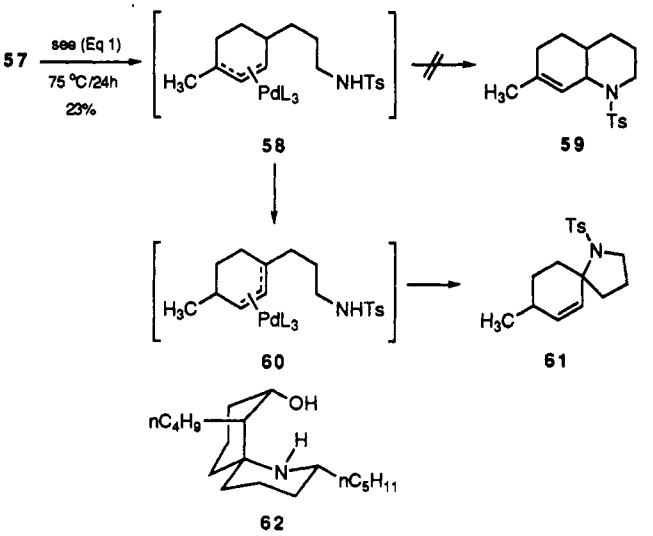
brominated at both double bonds at −78 °C and debromosilylated by treatment with tetrabutylammonium fluoride to provide diastereomeric *Z*-vinyl bromides **48** and **49** in yields of 23 and 42%, respectively. Treatment of the combined mixture with zinc powder in 5:1 ether/glacial acetic acid,[28] followed by addition of trifluoroacetic acid, afforded the desired Heck precursor **50** in 70% yield.

Substrate **50** was then subjected to the standard Heck reaction conditions at 60 °C for 48 h, effecting closure to the expected bicycle **51** in 58% yield. The stereochemistry of **51** was established as shown by an NOE experiment (irradiation of H_a gave an 11% enhancement of H_b).

In light of the successful Heck cyclization of terminal *Z*-vinyl bromide **50** to yield hexahydroindole derivative **51**, we next tried to perform the palladium-catalyzed biscyclization of *Z*-vinyl bromide **57** to produce the corresponding octahydroquinoline derivative. Therefore, substrate **57**, a homologue of precursor **50** with an extra carbon in the nucleophile-containing tether, was synthesized by the route in Scheme IX. The dianion of alkyne **15** was alkylated with the THP ether of 3-bromo-1-propanol. As expected, this alkylation occurred exclusively at the propargyl position to give **52** after THP hydrolysis. The

(28) Martin, J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 516.

Scheme X



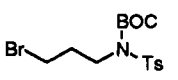
conversion of alcohol **52** to the *N*-BOC-sulfonamide **53** was accomplished in high yield via the Mitsunobu procedure.[18,29] *E*-Vinylsilane **54**, produced in 40% yield by treating *N*-BOC-sulfonamide alkyne **53** with triethylsilane and a catalytic amount of chloroplatinic acid, was then brominated and debromosilylated with tetrabutylammonium fluoride to provide *Z*-vinyl bromides **55** and **56** in a combined yield of 71%. Treatment of this crude mixture with zinc in acetic acid, followed by trifluoroacetic acid, afforded the Heck precursor **57** in 72% yield.

To our surprise, subjection of the *Z*-vinyl bromide **57** to the standard reaction conditions (cf. eq 1) gave only spirocyclic system **61** as a single diastereomer of unknown configuration in 23% yield. We believe **61** is formed via an initial π-allylpalladium complex **58** (Scheme X). However, for some reason, **58** does not cyclize to octahydroquinoline **59**, but rather undergoes a series of β-hydride eliminations/readditions to isomeric π-allylpalladium species **60**. Closure of **60** provides the observed product **61**.

We have also looked at the feasibility of developing a simple new approach to the spirocyclic system of the histrionicotoxins, exemplified by perhydrohistrionicotoxin (**62**).[30] In order to conduct initial exploratory experiments, two closely related Heck cyclization substrates **71** (Scheme XI) and **76** (Scheme XII) were prepared.

Synthesis of the *E*-olefin vinyl bromide **71** began with 5-hexynol (**63**), which was C-silylated to **64** and oxidized to aldehyde **65** (Scheme XI).[17] Addition of vinylmagnesium bromide to **65** gave alcohol **66** and acetylation provided acetate **67** in high overall yield. Ireland Claisen rearrangement[31] of ester **67** and desilylation provided *E*-alkene acid **68**, which was reduced to alcohol **69** (84% overall yield). A Mitsunobu reaction[18] of **69** afforded

(29) An alternative attempt to synthesize **53** by alkylation of the dianion of **15** with **i** failed.

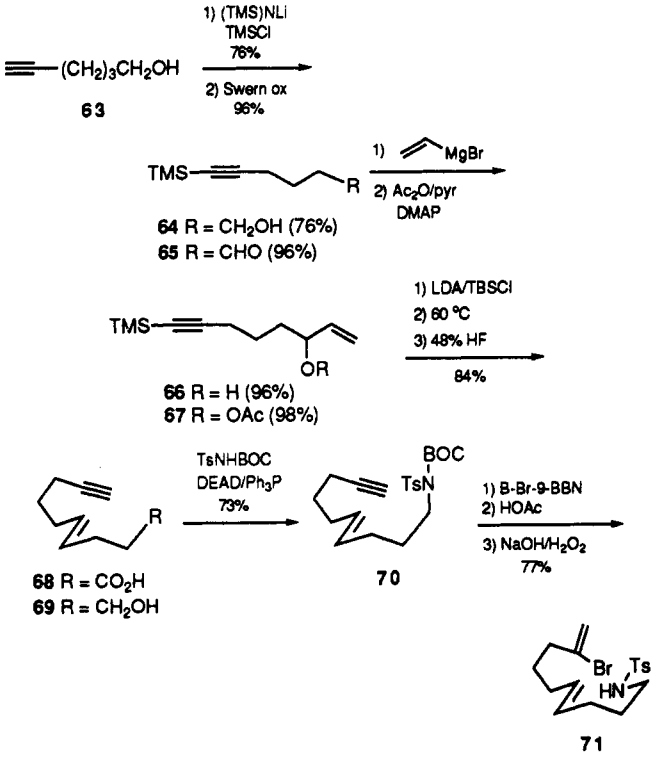


i

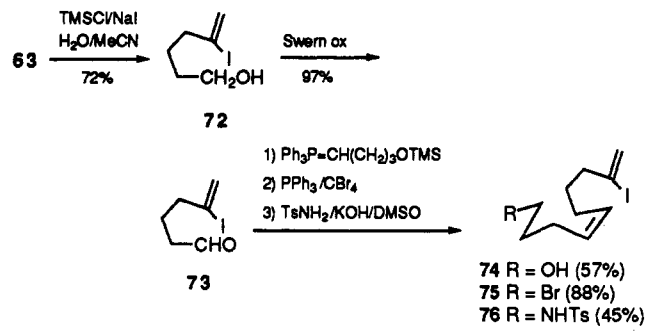
(30) For other Pd-mediated routes to the histrionicotoxin spirocyclic system, see: Tanner, D.; Sellen, M.; Backvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374. Godleski, S. A.; Heacock, D. J.; Meinhart, J. D.; van Wallendael, S. *J. Org. Chem.* **1983**, *48*, 2101. For a review of syntheses of histrionicotoxins, see: Kotera, M. *Bull Soc. Chim. Fr.* **1989**, 370.

(31) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.

Scheme XI



Scheme XII

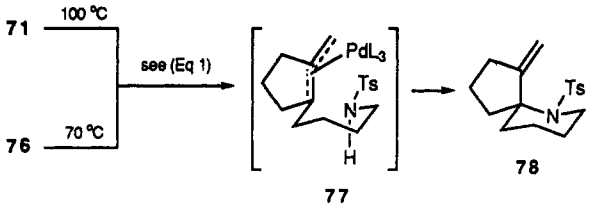


N-BOC sulfonamide **70**, and conversion of the alkyne functionality to the vinyl bromide[16] (cf. Schemes II,VI) gave cyclization precursor **71**.

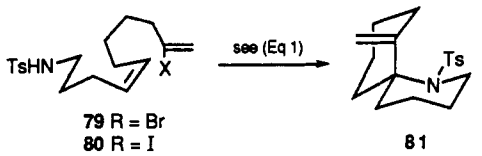
Preparation of *Z*-olefin vinyl iodide substrate **76** also began with 5-hexynol (**63**) (Scheme XII), which was first transformed to vinyl iodide **72** (72%)[32] and then oxidized to aldehyde **73**,[17] and Wittig reaction provided *Z*-alkene alcohol **74**.[33] The alcohol functionality of **74** was converted via bromide **75** to sulfonamide **76**.

A number of cyclization experiments were conducted with *E*-alkene vinyl bromide **71** using variations of the standard cyclization conditions. Using 10 mol % of $Pd(OAc)_2$ at 100 °C for 48 h, **71** could be converted to [6,5]-spirocycle **78** in 52% yield (85% based upon recovered starting material) (Scheme XIII). We believe **71** undergoes an initial 5-exo closure, leading to π-allylpalladium intermediate **77** which cyclizes to spirocyclic sulfonamide **78**. *Z*-olefin vinyl iodide **76** reacted faster than the bromide, but proved to be a somewhat inferior substrate for the cyclization.[5c,d] Optimum conditions (10 mol % Pd $(OAc)_2$, 70 °C, 48 h) gave spirocycle **78** in 39% yield (67% corrected for recovered starting material). The problem here seemed to be competing elimination of HI from **76** to give the corresponding acetylene derivative.

Scheme XIII



In order to test whether one can also construct a [6,6]-spirocycle using this methodology, two additional substrates **79** and **80** were synthesized using chemistry analogous to that in Scheme XII (for details, see supplementary material). We were pleased to find that cyclization of bromide **79** under the standard conditions of (eq 1) (100 °C, 24 h) gave the expected spirocycle **81** in 67% yield (eq 4). As in the [6,5]-case, iodide **80** gave a slightly



(4)

lower yield of **81** (51%, 80 °C, 12 h). Thus, we can rapidly construct the skeleton of the histrionicotoxins (**62**) from a simple acyclic precursor using this three component tandem cyclization strategy.

We are currently investigating applications of the methodology outlined here to various alkaloid targets. Moreover, extensions of the methodology to tandem synthesis of carbobicycles is presently underway.

Experimental Section

Synthesis of *tert*-Butyl 4-Bromo-4-pentenoate (8). A solution of diisopropylamine (2.456 g, 24.27 mmol) in anhydrous THF (20 mL) was cooled to 0 °C and 1.40 M *n*-BuLi (15.8 mL, 22.14 mmol) was added dropwise by syringe. The solution was stirred under N_2 at 0 °C for 1 h. In a separate flask equipped with an addition funnel, a solution of *tert*-butyl acetate (2.473 g, 21.29 mmol) in THF (20 mL) was cooled to −78 °C under N_2. The LDA solution was transferred by cannula into the addition funnel and added dropwise to the reaction mixture. After stirring the solution for 1 h at −78 °C, 2,3-dibromopropene (4.255 g, 21.29 mmol) was added dropwise. The solution was stirred at −78 °C for 2 h and was warmed to rt. After removing the solvent under reduced pressure, H_2O (100 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The extract was washed with brine (50 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was distilled [45.5–47.5 °C (0.09 Torr)] to provide *tert*-butyl 4-bromo-4-pentenoate (**8**, 3.849 g, 77%) as a colorless oil: IR (film) 3010, 1730, 1630, 1150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.59 (d, 1H, J = 1.2 Hz), 5.38 (d, 1H, J = 1.2 Hz), 2.67 (t, 2H, J = 7.5 Hz), 2.43 (t, 2H, J = 7.5 Hz), 1.40 (s, 9H).

Reduction of *tert*-Butyl 4-Bromo-4-pentenoate (8). To a mixture of $LiAlH_4$ (2.175 g, 57.31 mmol) in anhydrous Et_2O (44 mL) was added a solution of *tert*-butyl 4-bromo-4-pentenoate (**8**, 12.24 g, 52.11 mmol) in Et_2O (16 mL) dropwise, maintaining a steady rate of reflux. After stirring the mixture under N_2 for 2 h, the excess $LiAlH_4$ was carefully destroyed with H_2O (2.4 mL), followed by 15% NaOH (2.4 mL) and H_2O (7.2 mL). The white precipitate was filtered and washed with Et_2O. The filtrate was dried over Na_2SO_4, followed by removal of the solvent under reduced pressure to yield 4-bromo-4-penten-1-ol (**9**, 8.234 g, 96%) as a light yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 5.60 (d, 1 H,

(32) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675.
(33) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Beuttler, T.; Bartkowiak, F. *Synthesis* **1986**, 361.

J = 1.2 Hz), 5.39 (d, 1H, J = 1.2 Hz), 3.61 (t, 2 H, J = 6.3 Hz), 2.49 (t, 2 H, J = 6.3 Hz), 1.77 (m, 2H), 1.22 (br s, 1 H).

Oxidation of 4-Bromo-4-penten-1-ol (9). A slurry of pyridinium chlorochromate (5.104 g, 23.68 mmol) and neutral alumina (23.02 g) in anhydrous CH_2Cl_2 (21 mL) was stirred under N_2 for 10 min. To this slurry was added dropwise a solution of 4-bromo-4-penten-1-ol (**9**, 2.935 g, 17.80 mmol) in CH_2Cl_2 (7 mL) over 15 min. After stirring the reaction mixture under N_2 for 12 h, hexanes (35 mL) were added to the dark brown slurry which was filtered through a plug of Florisil and washed thoroughly with Et_2O. Removal of solvent under reduced pressure afforded 4-bromo-4-pentenal (**10**, 2.6 g, 90%) as a yellow oil of sufficient purity for use in the next step: IR (film) 2840, 2710, 1720, 1622 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.81 (s, 1 H), 5.61 (d, 1 H, J = 1.2 Hz), 5.42 (d, 1 H, J = 1.2 Hz), 2.70 (m, 4 H).

Synthesis of Ester 11. An 80% NaH dispersion in mineral oil (1.794 g, 59.8 mmol) was washed with hexane, and anhydrous THF (180 mL) was added. After cooling the suspension to 0 °C, trimethyl phosphonoacetate (10.89 g, 59.8 mmol) was added dropwise, forming a white viscous slurry. After 35 min, the slurry was allowed to warm to rt and after another 25 min was cooled to 0 °C. A solution of 4-bromo-4-pentenal (**10**, 9.748 g, 59.8 mmol) in THF (30 mL) was added dropwise over 1 h. The reaction mixture was warmed to 25 °C and was stirred under N_2 overnight. After removal of the THF under reduced pressure, saturated NH_4Cl (200 mL) was added. The mixture was extracted with EtOAc (4 x 150 mL). The extract was washed with brine (100 mL) and dried over Na_2SO_4. The crude product was purified by flash chromatograph using 10% ethyl acetate in hexanes to yield the ester **11** (7.569 g, 58%) as a pale yellow oil: IR (film) 3010, 1730, 1663, 1637 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.90 (dt, 1 H, J = 15.8, 6.7 Hz), 5.86 (dt, 1 H, J = 15.8, 1.4 Hz), 5.58 (d, 1 H, J = 1.4 Hz), 5.42 (d, 1 H, J = 1.4 Hz), 3.69 (s, 3 H), 2.51 (m, 4 H); CI MS m/z 221, 219 (M^+ + 1), 187, 139, 107, 79.

Reduction of Ester 11 to Alcohol 12. To a solution of ester **11** (7.569 g, 34.6 mmol) in anhydrous toluene (95 mL) cooled to −78 °C was added dropwise 1 M DIBAL-H in hexane (76.1 mL, 76.1 mmol) over 20 min using a syringe pump. The solution was stirred at −78 °C under N_2 for 2 h and a saturated aqueous solution of Rochelle's salt (158 mL) was added with vigorous stirring. The mixture was warmed to 25 °C and was stirred until two distinct layers appeared (30 min). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with brine (150 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded allyl alcohol **12** (6.0 g, 91%) as a yellow oil: IR (film) 3300, 3010, 1670, 1632 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.70 (m, 2 H), 5.58 (d, 1 H, J = 1.3 Hz), 5.42 (d, 1 H, J = 1.3 Hz), 4.10 (d, 2 H, J = 3.4 Hz), 2.52 (t, 2 H, J = 7.5 Hz), 2.35 (m, 2 H), 1.45 (br s, 1 H); CI MS m/z 191, 189, 175, 173, 93.[34]

Claisen Rearrangement of Allyl Alcohol 12. A solution of allyl alcohol **12** (0.895 g, 4.69 mmol) and $Hg(OAc)_2$ (0.260 g, 0.760 mmol) in ethyl vinyl ether (59 mL) was heated at reflux under N_2 for 10 h, adding an additional 0.195 g (0.574 mmol) of $Hg(OAc)_2$ every 2 h, and then heating at reflux was continued overnight. To the cooled solution was added glacial acetic acid, and the mixture was stirred under N_2 for 3 h. The solution was diluted with hexanes (48 mL), washed with 5% aqueous KOH, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by chromatography on Florisil (2% EtOAc/hexane) to yield the vinyl ether (0.839 g, 82%) as a colorless oil: IR (film) 3100, 3030, 3010, 1625, 1606 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.42 (dd, 1 H, J = 14.3, 6.7 Hz), 5.68 (m, 2 H), 5.55 (dt, 1 H, J = 1.5, 1.2 Hz), 5.39 (d, 1 H, J = 1.5 Hz), 4.19 (dd, 1 H, J = 10.8, 2.0 Hz), 3.99 (dd, 1 H, J = 6.7, 2.0 Hz), 2.49 (td, 2 H, J = 6.8, 1.2 Hz), 2.33 (m, 2H); CI MS m/z 217, 215 (M^+ + 1), 175, 173, 93, 91.

A solution of the above vinyl ether (2.613 g, 12.05 mmol) in cumene (260 mL) was heated at reflux for 17 h under N_2. Removal of the cumene under high vacuum yielded aldehyde **13** (2.268 g, 87%) as a yellow oil of sufficient purity for use in the next step: IR (film) 3058, 2707, 1718, 1621 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.65 (s, 1 H), 7.14 (m, 1 H), 5.56 (m, 1 H), 5.50 (d, 1 H, J = 1.4 Hz), 5.34 (d, 1 H, J = 1.4 Hz), 5.02 (m, 1 H), 2.5–2.10 (m, 5 H), 1.62 (m, 2 H); CI MS m/z 219, 217 (M^+ + 1), 201, 199, 175, 173, 137, 119, 109, 107, 95, 93, 91, 67.

Reductive Amination of Aldehyde 13. To a solution of benzylamine hydrochloride (0.922 g, 6.42 mmol) in methanol (2 mL) and a small amount of 4-Å molecular sieves was added aldehyde **13** (0.231 g, 1.07 mmol), followed immediately by $NaBH_3CN$ (0.047 g, 0.75 mmol). The reaction mixture was stirred under N_2 at 25 °C for 8 h, and solvent was removed under reduced pressure. To the residue was added 20 mL of 20% aqueous KOH. The mixture was saturated with solid NaCl and extracted with Et_2O (3 × 10 mL). The extract was dried over Na_2SO_4. Removal of the solvent under reduced pressure and purification of the crude product by chromatography on basic alumina eluting with CH_2Cl_2 followed by MeOH afforded 0.165 g (50%) of bromovinyl benzylamine **14a** as a yellow oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 5.57 (d, 1 H, J = 1.2 Hz), 5.55 (m, 1 H), 5.40 (d, 1 H, J = 1.2 Hz), 5.04 (dd, 1 H, J = 10.3, 1.8 Hz), 4.99 (dd, 1 H, J = 17.3, 1.8 Hz), 3.78 (s, 2 H), 2.65 (m, 2 H), 2.51–2.31 (m, 2 H), 2.09 (m, 1 H), 1.76–1.40 (m, 4 H), 1.32 (br s, 1 H).

Heck Cyclization of Diene Benzylamine 14a. A solution of amine **14a** (0.057 g, 0.185 mmol), triethylamine (0.019 g, 0.185 mmol), tri-*o*-tolylphosphine (0.011 g, 0.037 mmol), and palladium acetate (0.004 g, 0.019 mmol) in anhydrous acetonitrile (2 mL) was heated under N_2 at 75 °C for 6 h. Removal of the solvent under reduced pressure and purification of the crude product by chromatography on basic alumina eluting with CH_2Cl_2, 1% MeOH/CH_2Cl_2, 2% MeOH/CH_2Cl_2, 4% MeOH/CH_2Cl_2, and finally 8% MeOH/CH_2Cl_2 afforded 0.0042 g (10%) of bicyclic amine **22** as a colorless oil: IR (film) 3070, 3025, 1655, 1603, 1492, $cm^{-1}cm^{-1}$; ^1H NMR (360 MHz, $CDCl_3$) δ 7.27 (m, 5 H), 4.97 (s, 1 H), 4.79 (s, 1 H), 3.52 (s, 2 H), 2.63–2.25 (m, 3 H), 2.14–1.94 (m, 1 H), 1.87–1.70 (m, 1 H), 1.60–1.31 (m, 4 H), 1.22 (s, 3 H); MS m/z (rel intens) 227 (25), 212 (38), 186 (38), 173 (15), 172 (11), 91 (100), 65 (15), 41 (11), 39 (10), 28 (28).

Synthesis of Sulfonamide 14b. To a solution of *N*-sulfinyl-*p*-toluenesulfonamide[13] (0.150 g, 0.691 mmol) and BF_3·Et_2O (0.050 g, 0.353 mmol) in anhydrous benzene (4 mL) cooled to 5 °C under N_2 was added aldehyde **13** (0.055 g, 0.252 mmol) over 0.5 h using a syringe pump. Immediately following addition of the aldehyde, Et_3SiH (0.029 g, 0.252 mmol) was rapidly added to the reaction mixture. After stirring the solution at 5 °C for 1 h, saturated $NaHCO_3$ (3 mL) was added. The benzene was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 5 mL). The extract was washed with brine (5 mL) and dried over Na_2SO_4. The crude product was purified by flash chromatography (20% ethyl acetate/hexanes) to afford sulfonamide **14b** (0.047 g, 50%) as a colorless oil: IR (film) 3262, 3059, 3022, 1621, 1320, 1155 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.72 (d, 2 H, J = 8.3 Hz), 7.28 (d, 2 H, J = 8.3 Hz), 5.48 (d, 1 H, J = 1.1 Hz), 5.39 (m, 1 H), 5.34 (d, 1 H, J = 1.6 Hz), 4.98 (dd, 1 H, J = 10.3, 1.8 Hz), 4.90 (dd, 1 H, J = 17.3, 1.8 Hz), 4.71 (t, 1 H, J = 6.4 Hz), 2.90 (m, 2 H), 2.40 (s, 3 H), 2.30 (m, 2 H), 1.98 (m, 1 H), 1.53 (m, 2 H), 1.38 (m, 2 H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 140.6, 136.8, 134.1, 129.5, 126.9, 116.5, 116.4, 41.0, 40.2, 38.7, 34.3, 32.7, 21.4; MS m/z (rel inten) 371 (0.7), 292 (22), 218 (16), 216 (17), 184 (42), 155 (82), 92 (12), 91 (100), 65 (20), 53 (10), 41 (15), 39 (13), 30 (36); exact mass calcd for $C_{16}H_{22}NO_2SBr$ 371.0555, found 371.0534.

Heck Cyclization of Sulfonamide 14b. To a mixture of $Pd(OAc)_2$ (0.0011 g, 0.0047 mmol), P(*o*-tol)$_3$ (0.0029 g, 0.0094 mmol), anhydrous Na_2CO_3 (0.0349 g, 0.329 mmol), and Bu_4NCl (0.0522 g, 0.188 mmol) was added a solution of diene sulfonamide **14b** (0.0350 g, 0.094 mmol) in DMF (0.94 mL). The mixture was degassed using the freeze-thaw method and heated at 65 °C under vacuum in a sealed tube for 40 h. The mixture was then filtered through a plug of flash silica gel with 30% ethyl acetate/hexanes. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 0.0213 g (78%) of a 4:1 mixture of **23** and **24**. Purification of the mixture by HPLC (5% ethyl acetate/hexanes) using a Beckman Ultrasphere Si 5m, 10.0 mm × 25 cm column afforded pure **23** as a colorless oil: ^1H NMR (360 MHz, $CDCl_3$) δ 7.66 (d, 2 H, J = 8.3 Hz), 7.23 (d, 2 H, J = 8.3 Hz), 5.35 (s, 1 H), 5.03 (s, 1 H), 3.68 (m, 1 H), 3.25 (m, 1 H), 2.38 (s, 3 H), 2.30 (m, 1 H), 2.10–2.01 (m, 2 H), 1.73 (m, 1 H), 1.61 (m, 2 H), 1.58

(34) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937.

(s, 3 H), 1.11 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) d 151.9, 142.3, 137.8, 129.0, 127.2, 111.4, 73.8, 52.6, 48.4, 32.1, 28.9, 27.7, 24.5, 21.3; MS *m/z* (rel inten) 291 (23), 277 (12), 276 (68), 250 (50), 155 (49), 136 (36), 91 (100); exact mass calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1318.

HPLC purification also yielded **24** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2 H, J = 8.3 Hz), 7.25 (d, 2 H, J = 8.3 Hz), 4.87 (s, 1 H), 4.70 (s, 1 H), 4.54 (dd, 1 H, J = 3.3, 3.3 Hz), 3.62 (m, 1 H), 3.23 (m, 1 H), 2.41 (s, 3 H), 2.12 (m, 2 H), 2.01 (m, 2 H), 1.93 (m, 1 H), 1.74–1.65 (m, 4 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.2, 142.9, 136.1, 129.2, 127.9, 111.8, 55.1, 42.0, 34.9, 31.1, 30.3, 29.7, 24.6, 21.5; MS *m/z* (rel inten) 291 (51), 236 (72), 155 (45), 136 (76), 94 (42), 93 (32), 91 (100), 67 (30), 41 (34), 32 (64), 31 (92), 29 (45), 28 (41); exact mass calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1303.

Alkylation of 1-Hepten-6-yne (15) with Ethylene Oxide. After cooling a solution of 1-hepten-6-yne (**15**, 1.6 g, 16.99 mmol) in anhydrous THF (22 mL) to –78 °C under Ar, 1.5 M *n*-BuLi in hexanes (23.8 mL, 35.68 mmol) was added dropwise. The solution was slowly warmed to rt over 3 h and was stirred for an additional 1 h. After the mixture was cooled to –40 °C, ethylene oxide (1.497 g, 33.98 mmol) was added. The solution was stirred at –30 °C for 15 h, and diluted carefully with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was purified by flash chromatography (20% ethyl acetate/hexanes) to afford the alcohol **16** (1.152 g, 49%) as a yellow liquid: IR (film) 3350, 3310, 3080, 2115, 1643, 1060 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 5.02 (dd, 1 H, J = 11.2, 1.6 Hz), 4.95 (dd, 1 H, J = 7.2, 1.6 Hz), 3.79 (dd, 2 H, J = 5.6, 3.6 Hz), 2.53 (m, 1 H), 2.32–2.10 (m, 2 H), 2.08 (d, 1 H, J = 1.6 Hz), 1.90 (br s, 1 H), 1.68 (m, 2 H), 1.55 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 114.9, 86.7, 70.1, 60.4, 37.3, 34.0, 31.1, 27.5; MS *m/z* (rel inten) 138 (0.94), 123 (10), 110 (22), 107 (32), 105 (40), 95 (32), 92 (34), 91 (77), 79 (100), 77 (53), 66 (33), 55 (71), 53 (59), 41 (67), 39 (81), 31 (46), 29 (37), 28 (49); exact mass calcd for $C_9H_{14}O$ 138.1045, found 138.1043.

Preparation of Vinyl Bromide Acetate 17. To a solution of alcohol **16** (0.894 g, 6.478 mmol), pyridine (0.615 g, 7.774 mmol, and Ac_2O (0.800 g, 7.774 mmol) in anhydrous CH_2Cl_2 (13 mL) was added 4-(dimethylamino)pyridine (0.040 g, 0.324 mmol). The mixture was stirred under N_2 for 1.5 h at 25 °C, diluted with 1 N HCl (25 mL) and extracted with hexanes (3 x 40 mL). The extract was washed with brine (25 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure afforded the alkyne acetate (1.123 g, 96%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.72 (m, 1 H), 4.95 (m, 2 H), 4.18 (m, 2H), 2.45 (m, 1H), 2.16 (m, 2H), 2.05 (d, 1H, J=2.8 Hz), 1.97 (s, 3H), 1.71 (m, 2H), 1.5 (m, 2H).

To a solution of 1 M B-Br-9-BBN in CH_2Cl_2 (7.625 mL, 7.625 mmol) in anhydrous CH_2Cl_2 (26 mL) cooled to 0 °C was added dropwise the above alkyne acetate (0.915 g, 5.083 mmol).[16] After stirring the solution under N_2 at 0 °C for 3 h, glacial AcOH (3.41 mL) was added. The solution was stirred for an additional 1 h at 0 °C and warmed to 25 °C. Water (40 mL) was added and the mixture was extracted with hexanes (3 × 40 mL). The extract was washed with H_2O (40 mL) and brine (40 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash chromatography (5% ethyl acetate/hexanes) to provide vinyl bromide **17** (0.938 g, 71%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 5.59 (d, 1 H, J = 1.4 Hz), 5.45 (d, 1H, J = 1.4 Hz), 4.96 (m, 2 H), 4.03 (m, 2 H), 2.30 (m, 1 H), 2.02 (s, 3 H), 2.02 (m, 2 H), 1.82–1.30 (m, 4 H).

Synthesis of Alcohol 18. A solution of acetate **17** (0.623 g, 2.389 mmol), K_2CO_3 (0.826 g, 5.973 mmol), MeOH (60 mL), and H_2O (30 mL) was stirred at 25 °C for 3 h. Brine (40 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The extract was washed with brine (50 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure yielded alcohol **18** (0.509 g, 97%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 5.61 (d, 1H, J = 1.4 Hz), 5.43 (d, 1 H, J = 1.4 Hz), 4.93 (m, 2 H), 3.62 (m, 2 H), 2.41 (m, 1 H), 2.02 (m, 2 H), 1.75–1.30 (m, 4 H).

Oxidation of Alcohol 18. A solution of oxalyl chloride (0.568 g, 4.475 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to –78 °C under N_2, and a solution of DMSO (0.769 g, 9.844 mmol) in CH_2Cl_2 (2 mL) was added dropwise, keeping the temperature below –65 °C.[17] After stirring the mixture for 10 min., a solution of alcohol **18** (0.653 g, 2.983 mmol) in CH_2Cl_2 (3 mL) was added dropwise, again keeping the temperature below –65 °C. After stirring the mixture for 20 min, triethylamine (2.059 g, 20.35 mmol) was added dropwise. The reaction mixture was then warmed to 25 °C, and H_2O (25 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the organic extract was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was filtered through a short plug of flash silica gel to afford aldehyde **19** (0.627 g, 97%) as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.70 (s, 1 H), 5.75 (m, 1 H), 5.72 (d, 1 H, 1.4 Hz), 5.50 (d, 1 H, J = 1.4 Hz), 5.03 (d, 1 H, J = 10.0 Hz), 4.97 (d, 1 H, J = 8.5 Hz), 2.87 (m, 1 H), 2.68 (dd, 1 H, J = 16.5, 8.0 Hz), 2.41 (dd, 1 H, J = 16.5, 5.5 Hz), 2.02 (m, 2 H), 1.70–1.32 (m, 2 H).

Reductive Amination of Aldehyde 19. To a stirred mixture of aldehyde **18** (0.400 g, 1.844 mmol) and benzylamine hydrochloride (1.589 g, 11.064 mmol) in anhydrous MeOH (7.4 mL) containing a small amount of 4-Å molecular sieves at 25 °C was added $NaBH_3CN$ (0.081 g, 1.291 mmol).[11] After stirring the mixture under N_2 overnight, the methanol was removed under reduced pressure and concentrated HCl (20 mL) was added. The aqueous acidic layer was extracted with Et_2O (4 × 20 mL). The aqueous acidic layer was basified with saturated Na_2CO_3 and was extracted with Et_2O (5 × 20 mL). The organic extract was dried over Na_2SO_4. Removal of the solvent under aspirator pressure and removal of excess benzylamine under high vacuum gave the amine **20a** (0.394 g, 69%) as a yellow oil of sufficient purity for use in the next step: IR (film) 3290, 3070, 3020, 1635, 1618 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.78 (m, 1 H), 5.60 (d, 1 H, J = 1.3 Hz), 5.43 (d, 1 H, J = 1.3 Hz), 5.01 (d, 1 H, J = 14.2 Hz), 4.95 (d, 1 H, J = 9.0 Hz), 3.80 (m, 2 H), 2.61 (m, 2 H), 2.31 (m, 1 H), 2.08 (m, 1 H), 1.94 (m, 1 H), 1.75–1.23 (m, 4 H).

Synthesis of *N*-BOC-sulfonamide 21. To a solution of PPh_3 (2.851 g, 10.87 mmol), *N*-BOC-*p*-toluenesulfonamide (1.473 g, 5.434 mmol), and alcohol **16** (0.500 g, 3.623 mmol) in anhydrous THF (14.5 mL) was added dropwise diisopropylazo dicarboxylate (1.832 g, 9.058 mmol).[18] The resulting orange slurry was stirred at 25 °C overnight. The solvent was removed under reduced pressure. The remaining slurry was purified by flash chromatography (10% ethyl acetate/hexanes) to yield *N*-BOC-sulfonamide **21** (1.417 g, 100%) as a viscous yellow oil: IR (film) 3258, 3041, 2085, 1710, 1628, 1347, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.4 Hz), 5.78 (m, 1 H), 5.03 (d, 1 H, J = 17.9 Hz), 4.96 (d, 1 H, J = 11.0 Hz), 4.11–3.78 (m, 2 H), 2.42 (m, 1 H), 2.41 (s, 3 H), 2.21 (m, 2 H), 2.10 (d, 1 H, J = 2.4 Hz), 1.89 (m, 2 H), 1.57 (m, 2 H), 1.32 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 150.8, 144.1, 137.8, 137.3, 129.2, 127.8, 115.2, 85.9, 84.2, 70.3, 45.5, 34.9, 33.9, 31.2, 28.7, 27.9, 21.6; CI MS *m/z* 392, 336, 300, 292, 258, 184, 182, 180, 164, 157, 155, 139, 136, 121, 91; exact mass calcd for $C_{21}H_{29}NO_4S(-C_4H_8)$ 335.1191, found 335.1198.

Heck Cyclization of Diene Amine 20a. A solution of amine **20a** (0.0620 g, 0.20 mmol), tri-*o*-tolylphosphine (0.0122 g, 0.04 mmol), $Pd(OAc)_2$ (0.0045 g, 0.02 mmol), and triethylamine (0.203 g, 2.00 mmol) in acetonitrile (0.5 mL) was degassed by the freeze-thaw method and heated at 100 °C in a sealed tube under vacuum for 28 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc) to afford bicyclic amine **25** (0.0143 g, 31%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 3.64 (d, 1 H, J = 11.2 Hz), 3.58 (d, 1 H, J = 11.2 Hz), 3.50 (d, 1 H, J = 10.5 Hz), 2.88 (d, 1 H, J = 10.5 Hz), 2.44 (m, 1 H), 2.26 (m, 1 H), 2.05 (m, 2 H), 1.83 (m, 1 H), 1.56 (s, 3 H), 1.38–1.18 (m, 4 H); MS *m/z* (rel inten) 224 (64), 226 (39), 213 (10), 212 (62), 92 (10), 91 (100), 65 (13), 28 (19).

Preparation of Sulfonamide 20b. To a solution of *N*-BOC-sulfonamide **21** (0.500 g, 1.278 mmol) in anhydrous CH_2Cl_2 (6.4 mL) cooled to 0 °C under Ar was added dropwise 1 M B-Br-9-BBN in CH_2Cl_2 (4.219 mL, 4.219 mmol). After stirring the solution under Ar at 0 °C for 3 h, glacial AcOH (3.20 mL) was added.[16] The solution was stirred for an additional 1 h at 0 °C and warmed to 25 °C and stirred overnight. To the solution were

then added 3 N NaOH (34 mL) and 30% H_2O_2 (4.7 mL). After 0.5 h the mixture was extracted with 20% ethyl acetate/hexanes (3 × 20 mL). The extract was washed with brine (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash chromatography (20% ethyl acetate/hexanes) to provide sulfonamide **20b** (0.228 g, 48%) as a pale yellow oil: IR (film) 3265, 3053, 3020, 1632, 1617, 1322, 1158 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, 2 H, J = 8.0 Hz), 7.28 (d, 2 H, J = 8.0 Hz), 5.70 (m, 1 H), 5.58 (d, 1 H, J = 1.5 Hz), 5.41 (d, 1 H, J = 1.5 Hz), 4.95 (d, 1 H, J = 13.7 Hz), 4.92 (d, 1 H, J = 9.9 Hz), 4.82 (t, 1 H, J = 6.4 Hz), 2.88 (m, 2 H), 2.40 (s, 3 H), 2.24 (m, 1 H), 1.98 (m, 1 H), 1.85 (m, 1 H), 1.56 (m, 1 H), 1.47 (m, 2 H), 1.25 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.8, 137.6, 136.8, 129.7, 127.0, 119.1, 115.1, 45.7, 40.7, 33.1, 32.3, 30.8, 21.5; MS m/z (rel inten) 371 (0.5), 292 (57), 218 (16), 216 (16), 184 (33), 155 (79), 152 (30), 136 (26), 91 (100), 83 (17); exact mass calcd for $C_{16}H_{22}BrNO_2S$ 371.0555, found 371.0557.

Heck Cyclization of Sulfonamide 20b. Sulfonamide **20b** was cyclized in the same manner as sulfonamide **14b** using $Pd(OAc)_2$ (0.0021 g, 0.0094 mmol), P(*o*-tol)$_3$ (0.0057 g, 0.0188 mmol), anhydrous Na_2CO_3 (0.070 g, 0.658 mmol), Bu_4NCl (0.104 g, 0.376 mmol), sulfonamide **20b** (0.0700 g, 0.188 mmol), and DMF (1.88 mL). The mixture was heated at 75 °C for 22 h. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield the bicyclic sulfonamide **26** (0.037 g, 68%) as a colorless oil: ^1H NMR (360 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 8.2 Hz), 7.29 (d, 2 H, J = 8.2 Hz), 4.44 (dd, 1 H, J = 13.2, 1.2 Hz), 3.81 (d, 1 H, J = 12.0 Hz), 2.76 (dd, 1 H, J = 12.8, 1.2 Hz), 2.39 (s, 3 H), 2.30 (m, 1 H), 2.27 (dd, 1 H, J = 12.8, 2.3 Hz), 2.19 (m, 2 H), 1.99 (m, 1 H), 1.83 (m, 1 H), 1.62 (s, 3 H), 1.25 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.3, 133.5, 133.3, 129.5, 128.9, 127.7, 46.2, 45.4, 44.2, 37.3, 33.4, 28.9, 21.5, 13.6; MS m/z (rel inten) 291 (82), 276 (38), 155 (22), 136 (87), 135 (68), 134 (30), 109 (100), 91 (86), 67 (71), 41 (29), 28 (77); exact mass calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1314.

Synthesis of 8-(Trimethylsilyl)-1-octen-7-yne (33). A mixture of magnesium turnings (2.153 g, 88.56 g atom) and a few crystals of iodine in anhydrous Et_2O (43 mL) was heated at reflux under Ar until the yellow color disappeared (30 min). To the mixture was added dropwise a solution of 5-bromo-1-pentene in Et_2O (21 mL), maintaining a steady rate of reflux. After stirring the mixture under Ar for 1 h, a solution of (trimethylsilyl)propargyl chloride (11.80 g, 80.51 mmol) in Et_2O (16 mL) was added dropwise, again maintaining a steady rate of reflux. The mixture was stirred overnight, diluted carefully with H_2O (34 mL), and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. After removal of ether by distillation and removal of excess (trimethylsilyl)propargyl chloride by distillation under aspirator pressure, the product **33** (6.481 g, 45%, bp 39–43 °C/0.65 Torr) was distilled as a colorless liquid: IR (film) 3052, 2157 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.79 (m, 1 H), 5.00 (d, 1 H, J = 15.5 Hz), 4.93 (d, 1 H, J = 9.3 Hz), 2.26–1.88 (m, 4 H), 1.51 (m, 4 H), 0.13 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 114.6, 107.4, 84.3, 33.2, 28.0, 19.7, 0.14.

Alkylation of 8-(Trimethylsilyl)-1-octen-7-yne (33) with Ethylene Oxide. After cooling a solution of **33** (2.500 g, 13.86 mmol) in anhydrous THF (18 mL) to 0 °C under Ar, 2.5 M *n*-BuLi in hexanes (6.10 mL, 15.25 mmol) was added dropwise. The solution was stirred under Ar at 0 °C for 2.5 h and cooled to −5 °C, and ethylene oxide (1.221 g, 27.72 mmol) was added to the reaction mixture. The solution was stirred at −5 °C for 37 h, diluted carefully with saturated $NaHCO_3$ (25 mL), and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The crude residue was purified by flash chromatography (15% ethyl acetate/hexanes) to afford the alcohol **34** (0.873 g, 28%) as a yellow liquid: IR (film) 3300, 3055, 2142, 1627 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 4.97 (m, 2 H), 3.79 (dd, 2 H, J = 7.2, 5.6 Hz), 2.51 (m, 1 H), 2.07 (m, 3 H), 1.76–1.41 (m, 6 H), 0.13 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.6, 114.5, 110.0, 86.4, 61.2, 37.5, 34.4, 33.4, 29.5, 26.3, 0.10; MS m/z (rel inten) 224 (0.47), 180 (6.8), 119 (9.3), 106 (13), 91 (9.8), 79 (6.5), 75 (78), 73 (100), 59 (10), 45 (10), 41 (7.9).

Synthesis of *N*-BOC-sulfonamide 35. Using the procedure for the synthesis of **21**, *N*-BOC-sulfonamide **35** (1.731 g) was produced from alcohol **34** (0.813 g, 3.624 mmol) in 100% yield as a colorless oil: IR (film) 3048, 2145, 1711, 1628, 1350, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, 2 H, J = 8.4 Hz), 7.29 (d, 2 H, J = 8.4 Hz), 5.80 (m, 1 H), 4.98 (m, 2 H), 4.02 (m, 1 H), 3.84 (m, 1 H), 2.43 (s, 3 H), 2.41 (m, 1 H), 2.07 (m, 2 H), 1.87 (m, 2 H), 1.54 (m, 4 H), 1.35 (s, 9 H), 0.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 144.0, 138.6, 137.4, 129.2, 127.8, 114.5, 108.9, 86.2, 84.0, 45.6, 34.9, 34.1, 33.4, 30.3, 27.9, 26.3, 21.6, 0.16; CI MS 478 (M^+ + 1), 462, 450, 422, 406, 378, 362, 306, 266, 222, 206, 168, 150, 133, 91, 73.

Desilylation of *N*-BOC-sulfonamide 35. A solution of 1 M tetrabutylammonium fluoride in THF (2.39 mL, 2.39 mmol) was added to a stirred solution of **35** (0.951 g, 1.99 mmol) in THF (17.5 mL) under Ar. After dilution with saturated NH_4Cl (50 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combined ether layers were washed with brine (50 mL) and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield acetylene **36** (0.386 g, 48%) as a viscous oil: IR (film) 3260, 3046, 2087, 1711, 1628, 1351, 1152 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.78 (d, 2 H, J = 8.4 Hz), 7.30 (d, 2 H, J = 8.4 Hz), 5.81 (m, 1 H), 5.02 (d, 1 H, J = 17.2 Hz), 4.96 (d, 1 H, J = 10.2 Hz), 4.05 (m, 1 H), 3.88 (m, 1 H), 2.43 (s, 3 H), 2.40 (m, 1 H), 2.10 (d, 1 H, J = 2.4 Hz), 2.07 (m, 2 H), 1.91 (m, 2 H), 1.70–1.46 (m, 4 H), 1.34 (s, 9 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 150.9, 144.0, 138.4, 137.4, 129.2, 127.8, 114.6, 86.2, 84.1, 70.1, 45.5, 35.0, 34.2, 33.4, 29.2, 27.9, 26.3, 21.6.

Preparation of Sulfonamide 37. Using the procedure for the synthesis of **20b**, sulfonamide **37** (0.179 g) was prepared from *N*-BOC-sulfonamide **36** (0.386 g, 0.953 mmol) in 49% yield as a colorless oil: IR (film) 3270, 3119, 3054, 1632, 1618, 1310, 1139 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2 H, J = 8.3 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 5.75 (m, 1 H), 5.60 (d, 1 H, J = 1.5 Hz), 5.42 (d, 1 H, J = 1.5 Hz), 4.98 (d, 1 H, J = 16.8 Hz), 4.94 (d, 1 H, J = 9.5 Hz), 4.54 (t, 1 H, J = 6.2 Hz), 2.91 (m, 2 H), 2.43 (s, 3 H), 2.23 (m, 1 H), 2.00 (m, 2 H), 1.65–1.16 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 138.7, 138.1, 136.9, 129.7, 127.1, 118.7, 114.7, 46.5, 40.8, 33.4, 33.2, 32.7, 26.1, 21.5; MS m/z (rel inten) 387 (1.6), 385 (1.7), 306 (48), 232 (25), 230 (26), 184 (28), 166 (38), 155 (69), 150 (16), 96 (18), 91 (100), 65 (15), 41 (17), 30 (19); exact mass calcd for $C_{17}H_{24}BrNO_2S$ 385.0712, found 385.0723.

Heck Cyclization of Sulfonamide 37. Sulfonamide **37** was cyclized in the same manner as sulfonamide **14b** using $Pd(OAc)_2$ (0.0011 g, 0.0050 mmol), P(*o*-tol)$_3$ (0.0030 g, 0.0100 mmol), anhydrous Na_2CO_3 (0.0370 g, 0.350 mmol), Bu_4NCl (0.0560 g, 0.200 mmol), sulfonamide **37** (0.0390 g, 0.100 mmol), and DMF (1.0 mL). The mixture was heated at 60 °C for 46 h. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield 0.0274 g (82%) of a 3.5:1 mixture of bridged bicyclic sulfonamide **40** to fused bicyclic sulfonamide **39**. Further purification by flash chromatography yielded pure **39** as a colorless oil: IR (film) 3072, 3014, 1643, 1331, 1322, 1158 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1 H, J = 8.3 Hz), 7.25 (d, 1 H, J = 8.3 Hz), 4.77 (s, 1 H), 4.76 (s, 1 H), 3.55 (m, 1 H), 2.69 (m, 3 H), 2.40 (s, 3 H), 2.12 (m, 1 H), 1.89 (m, 1 H), 1.82–1.48 (m, 5 H), 1.15 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 142.3, 140.1, 129.4, 126.8, 107.4, 64.1, 42.7, 41.5, 37.2, 34.7, 29.8, 22.8, 21.4, 17.2; MS m/z (rela inten) 305 (30), 150 (12), 109 (100), 91 (61), 81 (18), 79 (14), 67 (49), 65 (21), 55 (17), 53 (12), 42 (13), 41 (29); exact mass calcd for $C_{17}H_{23}NO_2S$ 305.1449, found 305.1442.

Flash chromatography also afforded pure **40** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, 2 H, J = 8.2 Hz), 7.31 (d, 2 H, J = 8.2 Hz), 4.61 (dd, 1 H, J = 12.8, 2.0 Hz), 3.78 (m, 1 H), 2.57 (m, 1 H), 2.43 (s, 3 H), 2.37 (m, 1 H), 2.06–1.77 (m, 3 H), 1.69 (s, 3 H), 1.76–1.57 (m, 3 H), 1.34 (m, 2 H), 1.12 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.2, 133.6, 129.5, 129.4, 127.8, 125.4, 47.4, 46.6, 35.8, 33.0, 32.2, 30.4, 29.6, 21.5, 21.4, 19.0; MS m/z (rel inten) 305 (86), 290 (100), 150 (36), 149 (31), 91 (78), 81 (29), 42 (30), 41 (33); exact mass calcd for $C_{17}H_{23}NO_2S$ 305.1449, found 305.1425.

Heating sulfonamide **37** at 75 °C for 24 h under exactly the same conditions produced exclusively **39** (84%).

Alkylation of 1-Hepten-6-yne (15) with Formaldehyde. After cooling a solution of 1-hepten-6-yne (15, 2.0 g, 21.3 mmol) in anhydrous THF (26 mL) to 0 °C, 1.6 M *n*-BuLi in hexanes (29.3 mL, 46.81 mmol) was added dropwise. After stirring the mixture

under Ar for 1.5 h, the solution was cooled to −78 °C. Paraformaldehyde (1.596 g, 53.2 mmol) was added in one portion, and the mixture was warmed to −25 °C and stirred overnight. The mixture was diluted carefully with saturated $NaHCO_3$ (25 mL) and was extracted with Et_2O (4 × 25 mL). The extract was washed with brine (25 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude residue was purified by flash chromatography (20% ethyl acetate/hexanes) to give the alcohol **41** (1.075 g, 41%) as a yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.73 (m, 1 H), 4.97 (d, 1 H, J = 17.5 Hz), 4.90 (d, 1 H, J = 10.6 Hz), 3.51 (d, 2 H, J = 6.3 Hz), 2.57 (br s, 1 H), 2.48 (m, 1 H), 2.11 (m, 2 H), 2.05 (d, 1 H, J = 2.5 Hz), 1.48 (m, 2 H).

Synthesis of *N*-BOC-sulfonamide 42. Using the procedure for the synthesis of **21**, *N*-BOC-sulfonamide **42** (1.226 g) was produced from alcohol **41** (0.500 g, 4.03 mmol) in 81% yield as a colorless oil: IR (film) 3260, 3052, 2091, 1711, 1629, 1350, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, 2 H, J = 8.4 Hz), 7.28 (d, 2 H, J = 8.4 Hz), 5.79 (m, 1 H), 5.03 (d, 1 H, J = 18.9 Hz), 4.96 (d, 1 H, J = 10.2 Hz), 4.01 (dd, 1 H, J = 14.3, 8.2 Hz), 3.82 (dd, 1 H, J = 14.3, 7.3 Hz), 2.95 (m, 1 H), 2.37 (s, 3 H), 2.31–2.09 (m, 2 H), 2.06 (d, 1 H, J = 2.4 Hz), 1.56 (m, 2 H), 1.26 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.9, 144.1, 137.6, 137.3, 129.2, 128.0, 115.3, 84.4, 84.1, 71.6, 49.7, 31.9, 31.0, 27.8, 21.6; MS *m/z* (rel inten) 321 (3.6), 280 (4.0), 184 (93), 166 (18), 155 (71), 122 (12), 106 (22), 91 (100); exact mass calcd for $C_{20}H_{27}NO_4S$ 377.1661, found 377.1665.

Preparation of Sulfonamide 43. Using the procedure for the synthesis of **20b**, sulfonamide **43** (0.282 g) was prepared from *N*-BOC-sulfonamide **42** (0.726 g, 1.935 mmol) in 41% yield as a colorless oil: IR (film) 3257, 3048, 3010, 1632, 1612, 1322, 1157 cm^{-1}; ^{1}H NMR (200 MHz,$CDCl_3$) δ 7.73 (d, 2 H, J = 8.4 Hz), 7.28 (d, 2 H, J = 8.4 Hz), 5.65 (m, 1 H), 5.58 (d, 1 H, J = 1.6 Hz), 5.49 (d, 1 H, J = 1.6 Hz), 4.91 (d, 1 H, J = 17.5 Hz), 4.90 (d, 1 H, J = 10.3 Hz), 4.83 (m, 1 H), 3.02–2.72 (m, 2 H), 2.36 (s, 3 H), 2.28 (m, 1 H), 2.05–1.72 (m, 2 H), 1.32 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 137.3, 137.0, 135.1, 129.7, 127.1, 121.0, 115.5, 48.9, 45.4, 30.5, 29.5, 21.5; MS *m/z* (rel inten) 359 (0.43), 357 (0.45), 184 (95), 155 (91), 95 (16), 91 (100), 65 (24), 41 (19), 30 (18), 28 (34); exact mass calcd for $C_{15}H_{20}BrNO_2S$ 357.0399, found 357.0426.

Heck Cyclization of Sulfonamide 43. Sulfonamide **43** was cyclized in the same manner as sulfonamide **14b** using $Pd(OAc)_2$ (0.0011 g, 0.0049 mmol), P(*o*-tol)$_3$ (0.0030 g, 0.0098 mmol), anhydrous Na_2CO_3 (0.0360 g, 0.343 mmol), Bu_4NCl (0.0540 g, 0.196 mmol), sulfonamide **43** (0.0390 g, 0.1090 mmol), and DMF (0.98 mL). The mixture was heated at 65 °C for 24 h. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to yield starting material **43** (0.0078 g, 20%) and bicyclic sulfonamide **45** (0.0120 g, 40%) as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.72 (d, 2 H, J = 8.3 Hz), 7.27 (d, 2 H, J = 8.3 Hz), 4.68 (s, 1 H), 4.66 (s, 1 H), 3.44 (d, 1 H, J = 8.2 Hz), 3.37 (m, 1 H), 2.67 (dd, 1 H, J = 4.0, 4.0 Hz), 2.41 (s, 3 H), 2.04 (m, 1 H), 1.74 (m, 1 H), 1.58 (s, 3 H), 1.50 (m, 1 H), 1.41 (m, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.0, 142.8, 139.1, 129.4, 127.0, 96.8, 66.6, 56.6, 40.1, 35.7, 28.1, 21.5, 15.3; MS *m/z* (rel inten) 277 (46), 122 (51), 95 (22), 94 (100), 91 (40), 81 (37), 79 (14), 53 (26), 42 (24); exact mass calcd for $C_{15}H_{19}NO_2S$ 277.1136, found 277.1131.

Synthesis of *E*-Vinylsilane 47. To a solution of alkyne **21** (1.000 g, 2.55 mmol) and triethylsilane (0.327 g, 2.809 mmol) in Et_2O (2.55 mL) cooled to 0 °C under Ar was added 0.1 M H_2PtCl_6 in 2-propanol (0.255 mL, 0.025 mmol) dropwise via syringe. After stirring at 0 °C for 6 h, the solution was warmed to rt and stirred overnight. Ether and triethylsilane were removed *in vacuo*, and the same amounts of ether, triethylsilane, and 0.1 M H_2PtCl_6 in 2-propanol as above were added to the residue at 0°C. After again stirring the mixture at 0 °C for 6 h, the solution was warmed to rt and stirred overnight. Ether and triethylsilane were removed under reduced pressure, and the residue was purified by flash chromatography (5% ethyl acetate/hexanes) to afford vinylsilane **47** (0.686 g, 53%) as a colorless oil: IR (film) 3058, 1717, 1632, 1606, 1358, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2 H, J = 8.4 Hz), 7.28 (d, 2 H, J = 8.4 Hz), 5.78 (m, 1 H), 5.77 (dd, 1 H, J = 18.7, 8.0 Hz), 5.56 (d, 1 H, J = 18.7 Hz), 4.96 (m, 2 H), 3.72 (m, 2 H), 2.40 (s, 3 H), 2.05 (m, 3 H), 1.78 (m, 2 H), 1.40 (m, 2 H), 1.31 (s, 9 H), 0.92 (t, 9 H, J = 8.0 Hz), 0.55 (q, 6 H, J = 7.8 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 150.9, 150.8, 143.9, 138.7, 137.5, 129.1, 127.7, 127.3, 114.5, 83.8, 45.9, 44.8, 34.8, 33.9, 31.2, 27.8, 21.5, 7.4, 3.5; MS *m/z* (rel inten) 507 (1.3), 478 (26), 422 (21), 378 (20), 268 (53), 257 (25), 124 (22), 115 (23), 92 (20), 91 (61), 87 (34), 59 (34), 57 (100), 41 (35), 29 (21), 28 (45); exact mass calcd for $C_{27}H_{45}NO_4SSi$ 507.2839, found 507.2865.

Bromination of Vinylsilane 47. Bromine (0.092 g, 0.574 mmol) in CH_2Cl_2 (0.191 mL) was added dropwise as rapidly as the color disappeared to a stirred solution of vinylsilane **47** (0.142 g, 0.280 mmol) in CH_2Cl_2 (0.560 mL) at −78 °C under Ar. The solution was warmed to rt, stirred for 0.5 h, diluted with 10% sodium sulfite (10 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was dissolved in THF (2.46 mL). To this solution was added 1 M tetrabutylammonium fluoride in THF (0.336 mL, 0.336 mmol) via syringe. After stirring at rt overnight, the solution was diluted with saturated NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The combined ether layers were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure left a viscous residue which was purified by flash chromatography (10% ethyl acetate/hexanes) to yield *N*-BOC-sulfonamide **48** (0.075 g, 42%) as a colorless mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, 2 H, J = 8.4 Hz), 7.30 (d, 2 H, J = 8.4 Hz), 6.33 (m, 1 H), 5.94 (m, 1 H), 4.17 (m, 1 H), 3.82 (m, 3 H), 3.62 (m, 1 H), 2.75 (m, 1 H), 2.44 (s, 3 H), 2.18 (m, 1 H), 1.97 (m, 1 H), 1.88–1.60 (m, 4 H), 1.33 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) (major isomer) δ 150.8, 144.1, 137.4, 137.3, 129.2, 127.7, 109.5, 84.3, 52.7, 45.3, 37.6, 35.9, 34.9, 33.5, 31.6, 27.9, 21.6; (minor isomer) δ 150.8, 144.1, 137.4, 137.3, 129.2, 127.7, 109.6, 84.3, 52.6, 45.3, 37.2, 36.0, 35.2, 33.4, 31.6, 27.9, 21.6. Further elution with 20% ethyl acetate/hexanes afforded the deprotected secondary sulfonamide **49** (0.034 g, 23%) as a colorless mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2 H, J = 8.3 Hz), 7.32 (d, 2 H, J = 8.3 Hz), 6.26 (m, 1 H), 5.76 (m, 1 H), 4.62 (t, 1 H, J = 6.4 Hz), 4.11 (m, 1 H), 3.82 (m, 1 H), 3.58 (m, 1 H), 3.03 (m, 1 H), 2.88 (m, 1 H), 2.65 (m, 1 H), 2.45 (s, 3 H), 2.09 (m, 1 H), 1.70–1.30 (m, 5 H).

Synthesis of Sulfonamide 50. To a stirred mixture of N-BOC-sulfonamide **48** (0.075 g, 0.119 mmol), secondary sulfonamide **49** (0.034 g, 0.064 mmol), and Zn dust (0.225 g, 3.440 mol) in Et_2O (1.72 mL) under Ar was added glacial acetic acid (0.34 mL) dropwise via syringe. After stirring the mixture overnight, the precipitates were filtered off and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (0.86 mL), and trifluoroacetic acid (0.059 g, 0.516 mmol) was added dropwise. After stirring overnight, the solution was diluted with saturated $NaHCO_3$ (10 mL) and extracted with 20% ethyl acetate/hexanes (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Purification of the residue by flash chromatography (20% ethyl acetate/hexanes) yielded sulfonamide **50** (0.045 g, 70%) as a colorless oil: IR (film) 3262, 3058, 3008, 1631, 1612, 1322, 1158 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2 H, J = 8.3 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 6.21 (d, 1 H, J = 7.0 Hz), 5.75 (m, 1 H), 5.73 (dd, 1 H, J = 9.7, 7.0 Hz), 4.97 (m, 2 H), 4.56 (t, 1 H, J = 6.3 Hz), 3.02 (m, 1 H), 2.85 (m, 1 H), 2.62 (m, 1 H), 2.43 (s, 3 H), 1.97 (m, 2 H), 1.66 (m, 1 H), 1.38 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.0, 137.9, 137.1, 129.7, 127.1, 115.0, 109.1, 41.2, 37.0, 34.5, 34.0, 31.1, 21.5; MS *m/z* (rel inten) 373 (0.45), 371 (0.40), 292, (16), 184 (25), 155 (48), 92 (13), 91 (100), 82 (14), 65 (29), 55 (11), 53 (14), 41 (22), 39 (19), 30 (40); exact mass calcd for $C_{16}H_{22}BrNO_2S$ 371.0555, found 371.0538.

Heck Cyclization of Sulfonamide 50. Cyclization was conducted in the same manner as for sulfonamide **14b** using $Pd(OAc)_2$ (0.0005 g, 0.0022 mmol), P(*o*-tol)$_3$ (0.0014 g, 0.0045 mmol), anhydrous Na_2CO_3 (0.0167 g, 0.1580 mmol), Bu_4NCl (0.0250 g, 0.0900 mmol), sulfonamide **50** (0.0167 g, 0.0450 mmol), and DMF (0.45 mL). The mixture was heated at 60 °C for 48 h. Purification of the residue by flash chromatography (10% ethyl acetate/hexanes) yielded bicyclic sulfonamide **51** (0.0076 g, 58%) as a colorless oil: IR (film) 3020, 1665, 1340, 1160, cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.73 (d, 2 H, J = 8.4 Hz), 7.30 (d, 2 H, J = 8.4 Hz), 5.59 (d, 1 H, J = 1.3 Hz), 3.97 (m, 1 H), 3.46 (m, 1 H), 3.15 (m, 1 H), 2.42 (s, 3 H), 1.92 (m, 2 H), 1.76–1.53 (m, 5 H), 1.68 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 136.0, 135.0, 129.6,

127.5, 121.9, 58.3, 47.3, 36.0, 27.7, 25.9, 23.7, 23.3, 21.5; MS m/z (rel inten) 291 (11), 276 (38), 136 (29), 91 (100), 65 (37), 55 (33), 41 (49), 39 (31); exact mass calcd for $C_{16}H_{21}NO_2S$ 291.1293, found 291.1284.

Alkylation of 1-Hepten-6-yne (15) with the THP Ether of 3-Bromo-1-propanol. To a stirred mixture of a catalytic amount of Amberlite IR 120 resin and dihydropyran (3.026 g, 35.97 mmol) in CH_2Cl_2 under Ar was added 3-bromo-1-propanol dropwise. The resin was filtered off after 1.5 h. Removal of solvent under reduced pressure and purification by flash chromatography (10% ethyl acetate/hexanes) afforded the THP ether of 3-bromo-1-propanol (1.372 g, 85%) as a colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.54 (t, 1 H, J = 3.9 Hz), 3.78 (m, 2 H), 3.43 (m, 4 H), 2.06 (m, 2 H), 1.85–1.35 (m, 6 H).

A solution of alkyne **15** (2.000 g, 21.24 mmol) in THF (28 mL) was cooled to −78 °C under Ar, and 2.25 M *n*-BuLi in hexanes (19.8 mL, 44.60 mmol) was added dropwise. The solution was warmed to rt over 2 h and stirred for an additional 2 h. After cooling the solution to −30 °C, the above THP ether of 3-bromo-1-propanol was added dropwise. The solution was stirred at −30 °C for 1 h, −20 °C for 1 h, then at −10 °C for 18 h. The solution was diluted with saturated $NaHCO_3$ (25 mL) and extracted with ether (3 × 25 mL). The combined ether layers were washed with brine (25 mL) and dried over Na_2SO_4. Purification of the residue by flash chromatography (5% ethyl acetate/hexanes) provided the THP ether (3.347 g, 67%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1 H), 5.00 (d, 1 H, J = 17.2 Hz), 4.93 (d, 1 H, J = 10.2 Hz), 4.54 (t, 1 H, J = 3.9 Hz), 3.75 (m, 2 H), 3.40 (m, 2 H), 2.37 (m, 1 H), 2.19 (m, 2 H), 2.03 (d, 1 H, J = 2.4 Hz), 1.87–1.42 (m, 12 H).

A solution of the above THP ether (3.347 g, 14.16 mmol) and a catalytic amount of *p*-toluenesulfonic acid in methanol (14 mL) was stirred overnight. Upon addition of saturated $NaHCO_3$ (50 mL), the mixture was extracted with Et_2O (3 × 50 mL). The combined ether layers were washed with brine (50 mL) and dried over Na_2SO_4. Removal of the ether under reduced pressure left alcohol **52** (2.084 g, 97%) as a colorless liquid: IR (film) 3320, 3278, 3058, 2094, 1630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.76 (m, 1 H), 5.00 (d, 1 H, J = 17.1 Hz), 4.93 (d, 1 H, J = 10.1 Hz), 3.61 (t, 2 H, J = 6.4 Hz), 2.38–2.07 (m, 3 H), 2.05 (d, 1 H, J = 2.4 Hz), 1.82–1.37 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 114.9, 87.2, 69.7, 62.3, 34.1, 31.2, 31.0, 30.6, 30.2; Cl MS 153 (M^+ + 1), 135, 109, 107, 105, 97, 95, 93, 91, 85, 83, 81, 79, 71; exact mass calcd for $C_{10}H_{16}O$ 152.1201, found 152.1191.

Synthesis of *N*-BOC-sulfonamide 53. Using the procedure for the synthesis of **21**, *N*-BOC-sulfonamide **53** (2.531 g) was produced from alcohol **52** (1.000 g, 6.569 mmol) in 95% yield as a colorless oil: IR (film) 3262, 3050, 2094, 1713, 1631, 1350, 1155 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, 1 H, J = 8.4 Hz), 7.28 (d, 1 H, J = 8.4 Hz), 5.78 (m, 1 H), 5.00 (d, 1 H, J = 17.3 Hz), 4.91 (d, 1 H, J = 10.4 Hz), 3.80 (t, 2 H, J = 7.4 Hz), 2.38 (s, 3 H), 2.18 (m, 2 H), 2.04 (d, 1 H, J = 2.5 Hz), 2.01–1.65 (m, 2 H), 1.49 (m, 4 H), 1.28 (s, 9 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.9, 144.0, 138.0, 137.5, 129.2, 127.8, 115.0, 87.0, 84.0, 69.9, 46.8, 34.1, 31.8, 31.3, 30.6, 27.8, 21.5, 21.3; CI MS m/z 406 (M^+ + 1), 350, 306, 258, 184, 178, 155, 150, 135.

Synthesis of *E*-Vinylsilane 54. Using the procedure for the synthesis of **47**, vinylsilane **54** (0.287 g) was produced from *N*-BOC-sulfonamide **53** (0.552 g, 1.360 mmol) in 40% yield as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, 2 H, J = 8.4 Hz), 7.27 (d, 2 H, J = 8.4 Hz), 5.78 (m, 1 H), 5.70 (dd, 1 H, J = 18.7, 8.0 Hz), 5.52 (d, 1 H, J = 18.7 Hz), 4.94 (m, 2 H), 3.78 (m, 2 H), 2.41 (s, 3 H), 2.00 (m, 3 H), 1.69 (m, 2 H), 1.32 (m, 4 H), 1.30 (s, 9 H), 0.91 (t, 9 H, J = 7.6 Hz), 0.54 (q, 6 H, J = 7.8 Hz).

Bromination of Vinylsilane 54. Using the procedure for the bromination of **47**, sulfonamides **55** and **56** (0.254 g) were produced from vinylsilane **54** (0.287 g, 0.550 mmol) in 71% combined yield as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, 2 H, J = 8.4 Hz), 7.30 (d, 2 H, J = 8.4 Hz), 6.34 (m, 1 H), 5.95 (m, 1 H), 4.18 (m, 1 H), 3.81 (m, 3 H), 3.63 (m, 1 H), 2.74 (m, 1 H), 2.44 (s, 3 H), 2.17 (m, 1 H), 1.96 (m, 1 H), 1.90–1.58 (m, 6 H), 1.32 (s, 9 H).

Synthesis of Sulfonamide 57. Using the procedure for the synthesis of sulfonamide **50**, **57** (0.109 g) was produced from a crude mixture of sulfonamides **55** and **56** (0.254 g) in 72% yield as a colorless oil: IR (film) 3252, 3048, 3026, 1626, 1609, 1317, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, 2 H, J = 8.3 Hz), 7.31 (d, 2 H, J = 8.3 Hz), 6.18 (d, 1 H, J = 7.0 Hz), 5.77 (m, 1 H), 5.71 (dd, 1 H, J = 9.7, 7.0 Hz), 4.98 (d, 1 H, J = 17.0 Hz), 4.94 (d, 1 H, J = 11.3 Hz), 4.45 (t, 1 H, J = 6.2 Hz), 2.94 (m, 2 H), 2.55 (m, 1 H), 2.43 (s, 3 H), 1.99 (m, 2 H), 1.44 (m, 4 H), 1.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.5, 138.3, 136.9, 129.7, 127.1, 114.7, 108.5, 43.2, 38.9, 34.0, 31.4, 31.2, 27.1, 21.5; MS m/z (rel inten) 387 (0.60), 385 (0.63), 184 (18), 155 (55), 150 (28), 135 (19), 92 (15), 91 (100), 65 (20), 41 (17), 30 (44), 28 (22); exact mass calcd for $C_{17}H_{24}BrNO_2S$ 385.0712, found 385.0726.

Heck Cyclization of Sulfonamide 57. The cyclization was run as for sulfonamide **14b** using $Pd(OAc)_2$ (0.0011 g, 0.0050 mmol), P(*o*-tol)$_3$ (0.0030 g, 0.0100 mmol), anhydrous Na_2CO_3 (0.0371 g, 0.350 mmol), Bu_4NCl (0.0556 g, 0.200 mmol), sulfonamide **57** (0.0386 g, 0.100 mmol), and DMF (1.00 mL). The mixture was heated at 75 °C for 24 h. Purification of the residue by flash chromatography (10% ethyl acetate/hexanes) yielded spirocyclic sulfonamide **61** (0.0071 g, 23%) as a colorless oil: ^{1}H NMR (300 MHZ, $CDCl_3$) δ 7.73 (d, 2 H, J = 8.4 Hz), 7.26 (d, 2 H, J = 8.4 Hz), 5.66 (ddd, 1 H, J = 10.1, 4.6, 1.1 Hz), 5.32 (dt, 1 H, J = 10.1, 1.1 Hz), 3.57 (m, 1 H), 3.30 (m, 1 H), 2.55 (td, 1 H, J = 12.8, 3.5 Hz), 2.41 (s, 3 H), 2.18 (m, 1 H), 1.97–1.48 (m, 7 H), 1.14 (d, 3 H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 138.8, 133.7, 130.5, 129.2, 127.4, 67.1, 49.1, 40.6, 30.8, 28.4, 28.1, 22.7, 21.5, 19.6; MS m/z (rel inten) 305 (29), 277 (34), 264 (15), 263 (88), 150 (40), 123 (19), 122 (100), 108 (18), 91 (72), 79 (16), 65 (17), 41 (25); exact mass calcd for $C_{17}H_{23}NO_2S$ 305.1449, found 305.1448.

Silylation of 5-Hexynol (63). To a solution of 22.0 mL (104 mmol) of hexamethyldisilazane in 150 mL of dry THF under argon at −78 °C was added dropwise 100 mmol of *n*-butyllithium (2.5 M solution in hexanes). After the solution was stirred for 15 min, 5.0 mL (45.3 mmol) of 5-hexyn-1-ol (**63**) was added. The mixture was kept at −78 °C for 2 h before 14.4 mL (114 mmol) of chlorotrimethylsilane was added, and the solution was warmed to rt overnight. 5% HCl solution was added until the mixture became acidic to pH paper. After stirring for 1 h, the mixture was extracted three times with 150-mL portions of ether. The combined organic extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$ and concentrated in vacuo. The resulting silylacetylene **64** (colorless oil) was suitable for use without further purification (5.9 g, 76%): IR (film) 3200–3400, 2980, 2160, 860 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 1H), 1.60 (m, 4H), 1.62 (s, 1H), 2.22 (t, 2H, J = 6.3 Hz), 3.63 (t, 2H, J = 6.3 Hz); CI MS m/z 171 (M^+ + 1), 155, 137.

Oxidation of Acetylene Alcohol 64. To a solution of 1.0 mL (11.5 mmol) of oxalyl chloride in 50 mL of dry CH_2Cl_2 at −78 °C under Ar was added dropwise 1.4 mL (19.6 mmol) of DMSO at a rate which kept the stirred solution below −60 °C. After the solution was stirred for 15 min, 1.31 g (7.7 mmol) of silylated acetylene alcohol **64** was added. The mixture was stirred for 20 min, and 5.4 mL (38.7 mmol) of triethylamine was added. The mixture was warmed to rt and the mixture was extracted with three 100 mL portions of CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude mixture was filtered through a column of Florisil, eluting with ether. The filtrate was concentrated *in vacuo* to produce aldehyde **65** as a yellow oil which was suitable for use without further purification (1.24 g, 96%): IR (film) 2940, 2700, 2160, 1710, 1240, 835; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (s, 9H), 1.83 (p, 2H, J = 7.0 Hz), 2.29 (t, 2H, J = 7.0 Hz), 2.57 (dt, 2H, J = 1.3, 7.0 Hz), 9.80 (t, 1H, J = 1.3 Hz); CI MS m/z 169 (M^+ + 1), 153, 129.

Vinyl Grignard Addition to Aldehyde 2. To a solution of 1.24 g (7.4 mmol) of aldehyde **65** in 50 mL of dry THF at −78 °C under Ar was added dropwise 8.1 mmol of vinylmagnesium bromide (1.0 M solution in THF). The mixture was stirred for 20 min, was warmed to rt and stirred for an additional 20 min. The mixture was diluted with 5% HCl solution until acidic to pH paper and was stirred for another 15 min. The mixture was extracted three times with 50 mL portions of ether. The combined organic extracts were washed with saturated $NaHCO_3$ solution, water, and brine, dried over $MgSO_4$, and concentrated *in vacuo* to produce allylic alcohol **66**, a yellow oil suitable for use in the next step without further purification (1.39 g, 96%): IR (film) 3400–3200, 2900, 1430, 990, 920 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$)

δ 0.05 (s, 9H), 1.63 (m, 2H, J = 5.2 Hz), 1.95 (t, 1H, J = 2.7 Hz), 2.22 (m, 2H, J = 5.2 Hz), 4.12 (m, 2H, J = 5.2 Hz), 5.01 (dd, 1H, J = 1.2, 10.4 Hz), 5.22 (dd, 1H, J = 1.2, 17.2 Hz), 5.85 (m, 1H); CI MS m/z 197 (M^+ + 1), 181, 179, 149.

Acetylation of Alcohol 66. To a solution of 0.620 g (3.2 mmol) of allylic alcohol **66** and a catalytic amount of DMAP in 20 mL of dry CH_2Cl_2 under argon was added dropwise 0.31 mL (3.8 mmol) of pyridine, followed by the dropwise addition of 0.33 mL (3.5 mmol) of acetic anhydride. The solution was stirred for 2 h and then diluted with 100 mL of water. The mixture was extracted three times with 30 mL of CH_2Cl_2. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Removal of solvent *in vacuo* produced a yellow oil suitable for use without further purification (0.737 g, 97%): IR (film) 2940, 2160, 1760, 1360, 1270, 1010, 830, 750 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.14 (s, 9H), 1.56 (m, 2H, J = 6.8 Hz), 1.71 (m, 2H, J = 6.8 Hz), 2.05 (m, 1H, J = 7.9 Hz), 2.06 (s, 3H), 2.24 (t, 2H, J = 7.0 Hz), 5.17 (d, 1H, J = 10.5 Hz), 5.24 (d, 1H, J = 17.2 Hz), 5.77 (m, 1H); CI MS *m/z* 239 (M^+ + 1), 179, 163.

Claisen Rearrangement of Acetate 67. To a solution of 4.90 mL (35.0 mmol) of diisopropylamine in 100 mL of dry THF at −78 °C under Ar was added dropwise 32.0 mmol of *n*-butyllithium (1.6 M solution in hexanes). After the solution was stirred for 15 min, a solution of 6.34 g (26.6 mmol) of allylic acetate **67** and 5.20 mL (34.5 mmol) of chloro-*tert*-butyldimethylsilane in 30 mL of dry THF was added dropwise. The mixture was stirred for 5 min at −78 °C, slowly heated to 60 °C, and stirred for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in 100 mL of acetonitrile. To this solution was added 1.0 mL (58.5 mmol) of 48% aqueous HF and the mixture was stirred for 2 h. The mixture was extracted three times with 50 mL portions of ether and the combined organic extracts were dried over $MgSO_4$. The solvent was removed in vacuo and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:4), to produce acid **68** as a colorless oil (3.72 g, 84%). IR (film) 2700–3200, 3270, 2900, 2150, 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.53 (m, 2H), 1.90 (t, 1H, J = 3.0 Hz), 2.10 (m, 4H), 2.35 (m, 2H), 5.43 (m, 2H); CI MS m/z 167 (M^+ + 1), 149, 121, 107.

Reduction of Carboxylic Acid 68 to Alcohol 69. To a solution of 0.34 g (0.90 mmol) of $LiAlH_4$ in 50 mL of dry THF at 0 °C under argon was added dropwise 0.15 g (0.90 mmol) of carboxylic acid **68** in 10 mL of dry THF. The mixture was kept at 0 °C for 1 h before quenching the excess reducing agent by dropwise sequential additions of 1 mL of ethyl acetate, 1 mL of 15% NaOH solution, 1 mL of water, and 4 mL of saturated NH_4Cl solutions. The organic layer was washed with brine dried over $MgSO_4$ and concentrated *in vacuo* to produce alcohol **69** as a colorless oil suitable for use without further purification (0.13 g, 95%): IR (film) 3400–3200, 2900, 2080, 1420, 1240, 1030, 960 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (m, 4H), 1.90 (t, 1H), 2.17 (m, 6H), 3.65 (t, 2H, J = 6.6 Hz), 5.42 (m, 2H); Cl MS m/z 153 (M^+ + 1), 151 (M^+ − 1), 135.

Preparation of Sulfonamide 70. To a solution of 0.42 g (1.5 mmol) of *N*-BOC-*p*-toluenesulfonamide and 0.32 g (1.2 mmol) of triphenylphosphine in 25 mL of dry THF at 0 °C under Ar was added 0.155 g (1.0 mmol) of alcohol **69**, followed by dropwise addition of 0.24 mL (1.2 mmol) of diisopropyl azodicarboxylate. The mixture was then warmed to rt and stirred for 3 h. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to produce **70** as a yellow oil (0.300 g, 73%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.56 (m, 2H), 1.80 (m, 2H), 1.95 (s, 1H), 2.13 (m, 6H), 2.43 (s, 3H), 3.75 (t, 2H, J = 8.0 Hz), 7.35 (d, 2H, J = 8.0 Hz), 7.78 (d, 2H, J = 8.0 Hz), CI MS *m/z* 306 (M^+ + 1), 224, 184, 135.

Formation of Vinyl Bromide 71 from Acetylene Sulfonamide 70. To a solution of 18.4 mmol of B-Br-9-BBN (1.0 M solution in CH_2Cl_2) in 100 mL of dry CH_2Cl_2 at 0 °C under Ar was added dropwise a solution of 2.26 g (5.6 mmol) of sulfonamide **70** in 25 mL of dry CH_2Cl_2.[16] After the solution was stirred at 0 °C for 3 h, 3.2 mL (56 mmol) of glacial acetic acid was added. The mixture was kept at 0 °C for 1 h before the addition of excess 3 M NaOH and 30% H_2O_2 solutions and the mixture was stirred at rt overnight. The mixture was extracted three times with 50 mL portions of hexanes and the combined organic extracts were washed with water and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to produce **71** as a yellow oil (1.66 g, 77%): ^1H NMR (200 MHz, $CDCl_3$) δ 1.55 (m, 4H), 1.95 (q, 4H, J = 7.3 Hz), 2.37 (t, 2H, J = 7.3 Hz), 2.40 (s, 3H), 2.95 (m, 2H), 4.40 (s, 1H), 5.30 (m, 2H), 5.35 (s, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 21.1, 27.1, 28.8, 29.0, 30.7, 40.3, 42.2, 116.6, 127.2, 129.6, 129.8, 130.7, 134.6, 137.2, 143.5; CI MS *m/z* 385 (M^+ + 1), 306, 224, 135; exact mass calcd for $C_{18}H_{26}SO_2NBr$ 399.0868, found 399.0900.

Heck Cyclization of Sulfonamide 71. As described for **14b**, cyclization was conducted with 0.0050 g (0.022 mmol) of palladium acetate, 0.0136 g (0.044 mmol) of tri-*o*-tolylphosphine, 0.0830 g (0.77 mmol) of sodium carbonate, 0.1243 g (0.44 mmol) of tetrabutylammonium chloride, and 0.0864 g (0.22 mmol) of sulfonamide **71** in 2.2 mL of dry DMF. The mixture was heated at 100 °C for 48 h and filtered through a plug of silica gel with ethyl acetate/hexanes (3:7), and the filtrate was concentrated *in vacuo*. The product was isolated by preparative TLC, eluting with ethyl acetate/hexanes (1:9), to produce **78** as a yellow oil (0.0355 g, 52% yield, 85% corrected for 0.0334 g of recovered starting material): ^1H NMR (360 MHz, $CDCl_3$) δ 1.52 (m, 5H), 1.67 (m, 2H), 1.84 (M, 1H), 2.05 (m, 1H), 2.25 (m, 2H), 2.40 (s, 3H), 2.67 (m, 1H), 3.11 (t, 1H, J = 9.2 Hz), 3.78 (d, 1H, J = 11.8 Hz), 4.68 (s, 1H), 4.91 (s, 1H), 7.35 (d, 2H, J = 8.0 Hz), 7.73 (d, 2H, J = 8.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 156.0, 142.4, 140.2, 129.0, 127.1, 107.8, 68.5, 45.5, 38.8, 35.8, 33.2, 25.5, 22.7, 21.5, 21.2; CI MS *m/z* 306 (M^+ + 1), 150, 135; exact mass calcd for $C_{17}H_{23}SO_2N$ 305.1449, found 305.1470.

Preparation of Vinyl Iodide 72. To a solution of 0.51 g (3.4 mmol) of NaI in 10 mL of dry acetonitrile under Ar was added dropwise 0.39 mL (3.1 mmol) of chlorotrimethylsilane. After the solution was stirred for 5 min, 0.028 mL (1.6 mmol) of distilled water was added, followed by the dropwise addition of 0.15 g (1.5 mmol) of 5-hexyn-1-ol (**63**). The solution was stirred for 2 h, the mixture was quenched with 50 mL of water ,and extracted three times with 50-mL portions of ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to produce iodide **72** as a yellow oil (0.25 g, 72%): IR (film) 3400–3200, 2920, 1610, 1420 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.59 (m, 4H), 2.41 (m, 2H), 3.66 (m, 2H), 5.70 (s, 1H), 6.03 (s, 1H); CI MS *m/z* 227 (M^+ + 1), 209, 181, 99, 81.

Oxidation of Vinyl Iodide Alcohol 72. To a solution of 0.41 mL (4.7 mmol) of oxalyl chloride in 20 mL of dry CH_2Cl_2 at −78 °C under Ar was added dropwise 0.58 mL (8.1 mmol) of DMSO at a rate which kept the stirred solution below −60 °C. After the solution was stirred for 15 min., 0.70 g (3.1 mmol) of vinyl iodide alcohol **72** was added. The mixture was stirred for 20 min, and 2.2 mL (15.6 mmol) of triethyl amine was added. The mixture was warmed to rt and was extracted with three 50 mL portions of CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude mixture was filtered through Florisil, eluting with ether. The filtrate was concentrated *in vacuo* to produce aldehyde **73** as a yellow oil which was suitable for use without further purification (0.67 g, 97%): IR (film) 2910, 1660, 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 2H), 2.46 (m, 4H), 5.73 (s, 1H), 6.05 (s, 1H), 9.78 (s, 1H); CI MS *m/z* 225 (M^+ + 1), 207, 97.

Wittig Reaction of Aldehyde 73. To a solution of 11.75 g (28.3 mmol) of triphenyl-(4-hydroxybutyl)phosphonium bromide **33** in 40 mL of dry CH_2Cl_2 under Ar was added 13.5 mL (64.0 mmol) of hexamethyldisilazane and the solution was heated at reflux for 3 h. The solvent was removed in vacuo and the mixture was rediluted with 50 mL of dry THF and cooled to 0 °C under Ar. To the solution was added 28.3 mmol of lithium hexamethyldisilazide. After stirring the mixture for 15 min, 5.76 g (25.7 mmol) of aldehyde **73** was added and stirring was continued for an additional 30 min before warming to rt. The solution was diluted with 5% HCl solution and extracted three times with 100-mL portions of ethyl acetate. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes

(1:9), to produce **74** as a yellow oil (4.01 g, 57%): IR (film) 3400–3200, 2900, 1610, 1415, 1040, 870 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.60 (m, 4H), 2.07 (m, 4H), 2.10 (m, 1H), 2.37 (t, 2H, J = 7.5 Hz), 3.61 (t, 2H, J = 7.5 Hz), 5.38 (m, 2H, J = 6.0), 5.67 (d, 1H, J = 1.4 Hz), 6.00 (d, 1H, J = 1.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.5, 25.5, 28.9, 32.4, 44.6, 62.3, 112.2, 125.4, 129.4, 129.7; CI MS m/z 281 (M^+ + 1), 263, 221, 207, 181, 153, 185; exact mass calcd for $C_{10}H_{16}OI$ 279.0246, found 279.0248.

Preparation of Bromide 75. To a solution of 4.10 g (14.6 mmol) of alcohol **74** and 11.52 g (43.9 mmol) of triphenylphosphine in 100 mL of dry DMF under Ar was added 14.56 g (43.9 mmol) of CBr_4.[35] After the mixture was stirred for 12 h, 100 mL of water was added and the mixture was extracted three times with 150-mL portions of hexanes. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (5:95), to produce bromide **75** as a yellow oil (4.42 g, 88%): IR (film) 2950, 1605, 1410, 1225, 870, 640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.59 (m, 2H), 1.95 (m, 4H), 2.20 (m, 2H), 2.39 (t, 2H), 3.41 (t, 2H), 5.40 (m, 2H), 5.70 (s, 1H), 6.02 (s, 1H); CI MS 343 (M^+ + 1), 341, 259, 257, 217, 215.

Preparation of Sulfonamide 76. A solution of 0.32 g (5.7 mmol) of NaOH and 1.95 g (11.4 mmol) of *p*-toluenesulfonamide in 10 mL of dry DMSO was heated at 50 °C for 30 min, after which 1.78 g (5.2 mmol) of bromide **75** was added and the mixture was stirred for an additional 1 h. The cooled mixture was poured into 100 mL of ice-water and extracted three times with 100 mL portions of CH_2Cl_2. The combined organic extracts were washed twice with 15% NaOH solution, once with water and brine, and dried over $MgSO_4$. The solvent was removed *in vacuo* and the product was isolated by flash chromatography on silica gel, eluting with ethyl acetate/hexanes (1:9), to produce sulfonamide **76** as a yellow oil (1.00 g, 45%): IR (film) 3300–3200, 2720, 1590, 1420, 1310, 1150, 1080, 890, 810, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (m, 4H), 1.96 (m, 4H), 2.33 (t, 2H, J = 7.9 Hz), 2.41 (s, 3H), 2.90 (m, 2H), 5.09 (s, 1H), 5.28 (m, 2H), 5.66 (s, 1H), 5.99 (s, 1H), 7.29 (d, 2H, J = 8.3 Hz), 7.75 (d, 2H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 24.2, 25.4, 28.8, 29.3, 42.7, 44.5, 112.3, 125.4, 126.9, 128.8, 129.6, 129.8, 143.2; CI MS m/z 434 (M^+ + 1), 306, 224, 135; exact mass calcd for $C_{17}H_{24}SO_2NI$ 433.0574, found 433.0560.

(35) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1972**, *37*, 2289.

Heck Cyclization of Sulfonamide 76. As described for **14b**, cyclization was conducted with 0.0022 g (0.010 mmol) of palladium acetate, 0.0061 g (0.020 mmol) of tri-*o*-tolylphosphine, 0.0372 g (0.35 mmol) of sodium carbonate, 0.0557 g (0.20 mmol) of tetrabutylammonium chloride and 0.0434 g (0.10 mmol) of sulfonamide **76** in 1.0 mL of dry DMF. The mixture was heated at 70 °C for 48 h and filtered through a plug of silica gel with ethyl acetate/hexanes (3:7), and the filtrate was concentrated *in vacuo*. The product was isolated by preparative TLC, eluting with ethyl acetate/hexanes (1:9), to produce **78** as a yellow oil (0.0120 g, 39% yield, 67% corrected for 0.0180 g of recovered starting material).

Heck Cyclization of Sulfonamide 79. As described for **14b**, cyclization was done with 0.00090 g (0.0040 mmol) of palladium acetate, 0.0024 g (0.0080 mmol) of tri-*o*-tolylphosphine, 0.030 g (0.28 mmol) of sodium carbonate, 0.044 g (0.16 mmol) of tetrabutylammonium chloride, and 0.0320 g (0.080 mmol) of sulfonamide **79** in 1.0 mL of dry DMF. The solution was heated at 100 °C for 24 h and filtered through a plug of silica gel with ethyl acetate/hexanes (3:7), and the filtrate was concentrated *in vacuo*. The product was isolated by preparative TLC, eluting with ethyl acetate/hexanes (1:9), to produce **81** as a yellow oil (0.0170 g, 67%): ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (m, 4H), 1.65 (m, 6H), 2.10 (m, 1H), 2.28 (m, 2H), 2.40 (s, 3H), 2.63 (m, 1H), 3.47 (m, 1H), 3.85 (m, 1H), 5.03 (s, 1H), 5.07 (s, 1H), 7.25 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.0 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ 19.1, 21.4, 22.4, 24.8, 28.0, 33.2, 33.7, 37.8, 44.2, 67.1, 110.7, 126.8, 129.8, 141.4, 142.3, 149.0; CI MS m/z 320 (M^+ + 1), 255, 164, 91; exact mass calcd for $C_{18}H_{25}SO_2N$ 319.1606, found 319.1599.

Acknowledgment. We are grateful to the National Science Foundation for financial support on grant CHE-9202848. We also wish to thank Dr. Alan Freyer and Dr. Alan Benesi for their assistance in product characterization by 2D-NMR methods.

Supplementary Material Available: NMR spectra for new compounds and experimental details for synthesis of cyclization substrates **79** and **80** and cyclization of **80** to **81** (75 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.