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

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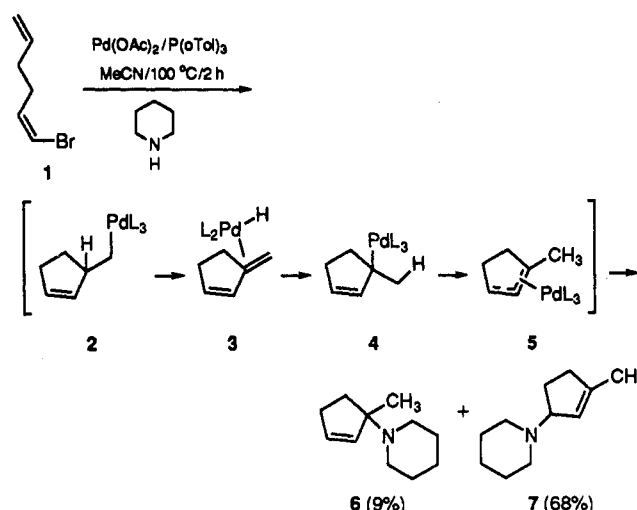
Intramolecular palladium-mediated three-component cyclizations of substrates containing vinyl halide, olefin, and sulfonamide moieties to generate a diverse group of nitrogen heterocycles have been developed. The methodology has been applied to construction of both fused and bridged bicyclic systems. 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 reaction² in both its inter-³ and intramolecular⁴ 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



* 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.; Narayanan, 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.; Ortari, 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'Connor, 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'Connor, 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.

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}

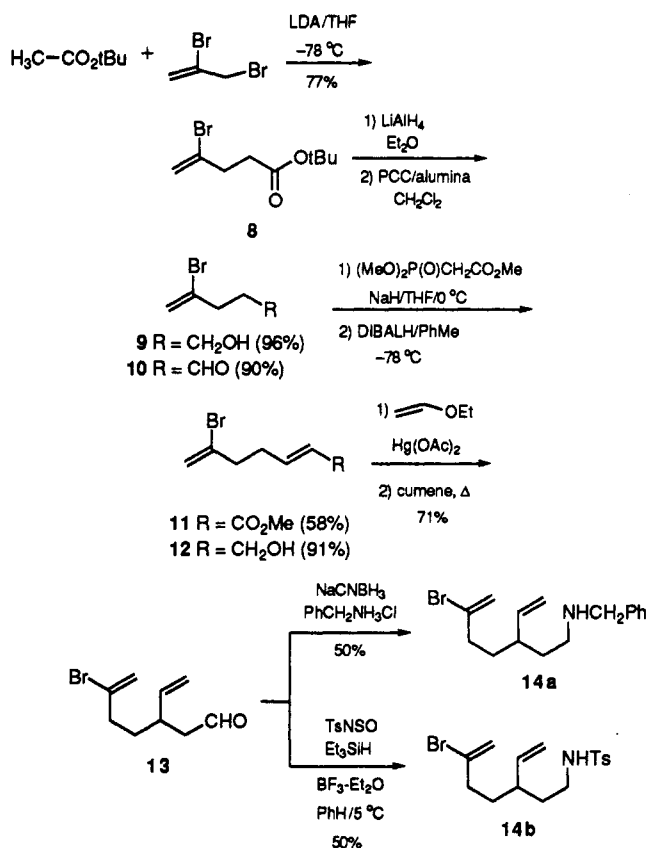
It appears from inspection of the many examples of this type of reaction reported by Heck that formation of the π -allylpalladium intermediate is regiospecific.⁵ The implication is that the readdition of PdH occurs selectively to the π -complexed double bond of diene 3 before Pd

(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: Akermarck, B.; Akermarck, 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. π -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 Asym.* 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.

Scheme II



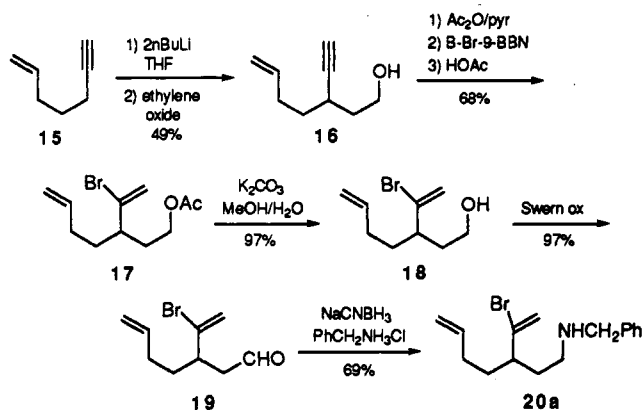
migration.⁸ Interestingly, this point had apparently never been explicitly addressed.

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 regioselectivity 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

Scheme III



for reduction of 11 also caused conjugate reduction of the α,β double bond.

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 method¹² recently developed in these labs in which aldehyde 13 was treated with *N*-sulfinyl-*p*-toluenesulfonamide¹³ 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 15¹⁵ 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 17 was then deprotected using potassium carbonate in aqueous methanol to afford alcohol 18. Swern oxidation¹⁷ of 18 provided aldehyde 19 in high yield. This aldehyde was then reductively aminated¹¹ with benzylamine hydrochloride and NaBH_3CN to afford diene benzylamine 20a (69% yield).

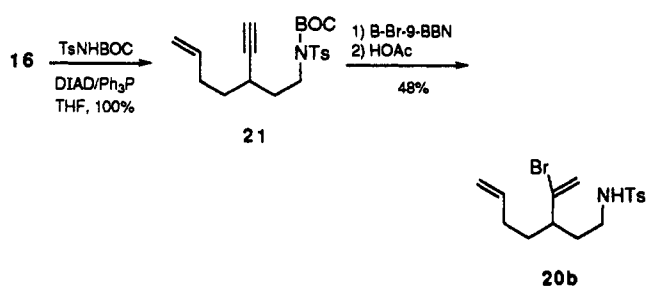
The corresponding sulfonamide 20b was synthesized as shown in Scheme IV. Application of Mitsunobu chemistry developed in these laboratories¹⁸ to alcohol 16 afforded *N*-BOC-sulfonamide 21. Conversion of the alkyne to the vinyl bromide¹⁶ and BOC cleavage yielded substrate 26b (48% from 16).

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

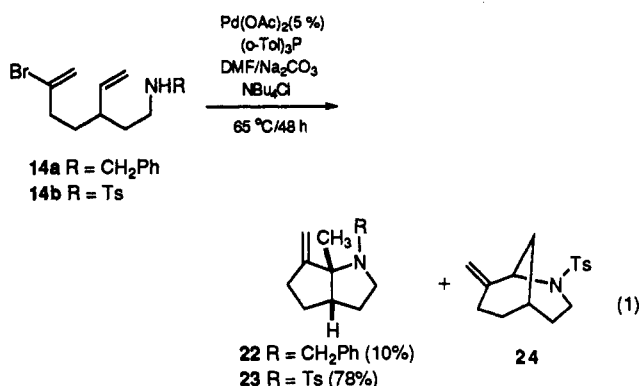
(9) For a preliminary account of portions of this work, see: (a) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* 1992, 57, 2528. (b) Harris, G. D., Jr. Ph.D. Thesis, The Pennsylvania State University, 1993.

(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

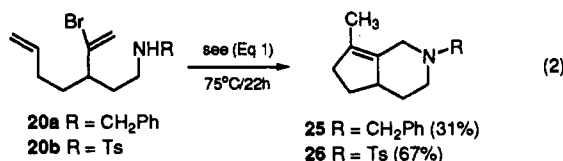


wide variety of Heck conditions, only a 10% yield of the desired bicyclic product **22** could be isolated at best (eq 1).



Diene sulfonamide **14b** was next subjected to reaction conditions described by Jeffery¹⁹ and modified by Larock²⁰ 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 Na₂CO₃, and 2 equiv of Bu₄NCl 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, NEt₃, 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 Et₃N 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 NEt₃ 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 regioselective. 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 chloride²⁴ 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

(21) Compounds **25** and **26** possess the ring skeleton of the skytanthine alkaloids: Snieckus, 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 Heck²⁵ 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.

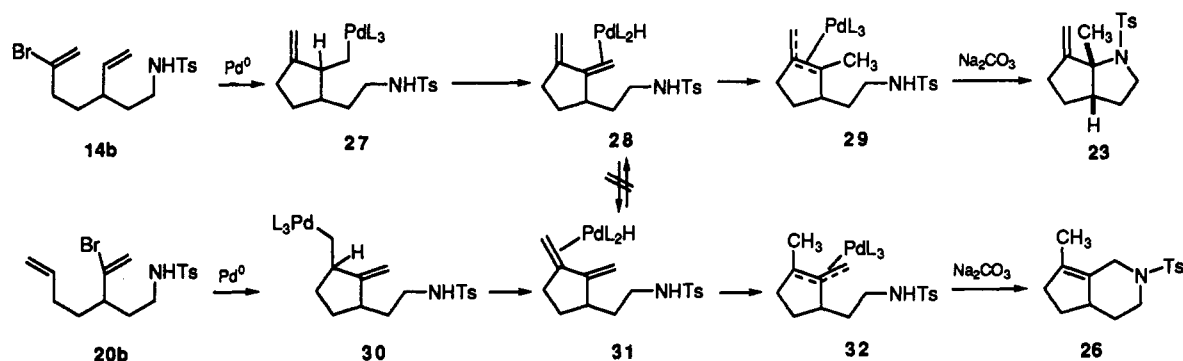
(23) Bender, D. D.; Stakem, F. G.; Heck, R. F. *J. Org. Chem.* 1982, 47, 1278.

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

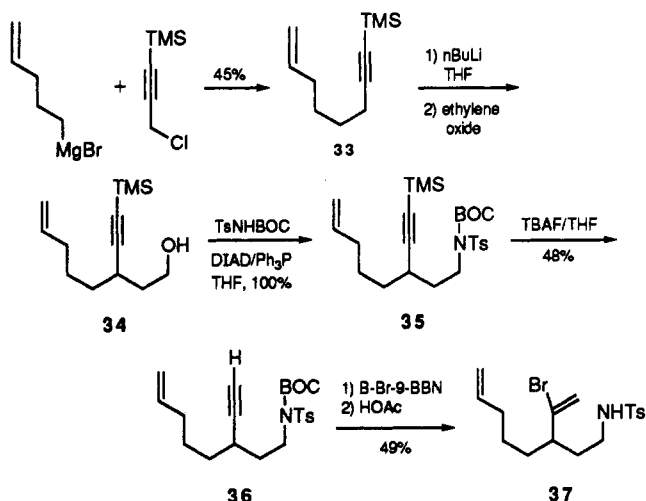
(19) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* 1984, 1287. (b) Jeffery, T. *Tetrahedron Lett.* 1985, 26, 2667. (c) Jeffery, T. *Synthesis* 1987, 70.

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

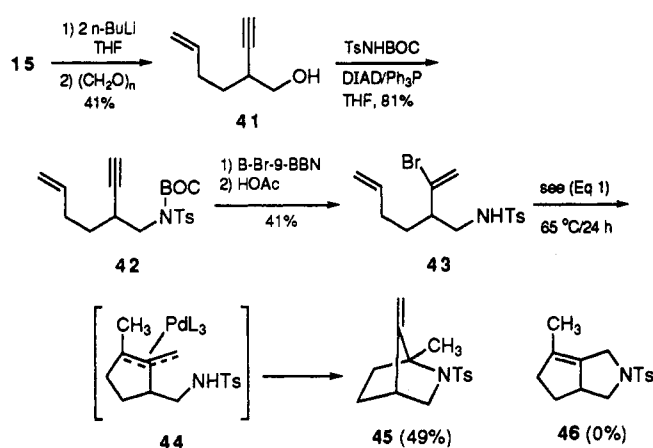
Scheme V



Scheme VI

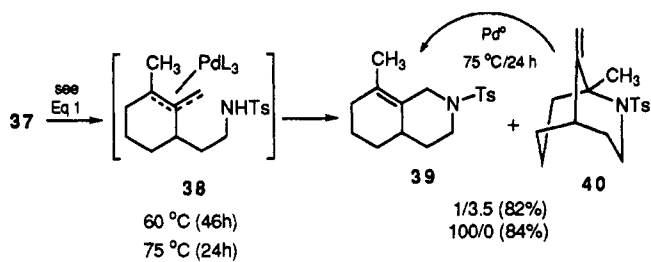


Scheme VII



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



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 hydroboration²⁶ were unsuccessful.

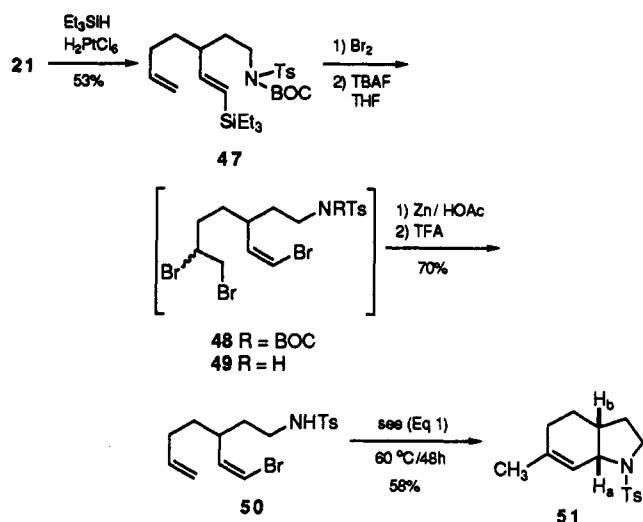
However, enyne **21** could be hydrosilylated exclusively at the triple bond in the presence of triethylsilane and a catalytic amount of chloroplatinic acid²⁷ to give *E*-vinylsilane **47** in 53% yield. This vinylsilane was then

(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.

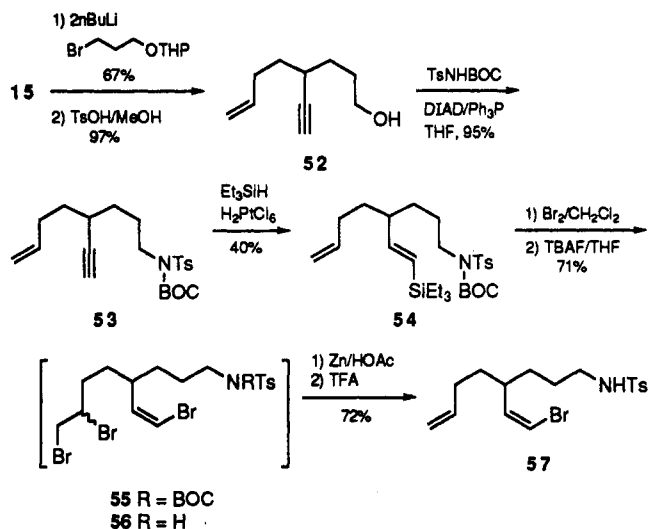
(26) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* 1973, 95, 6456.

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

Scheme VIII



Scheme IX

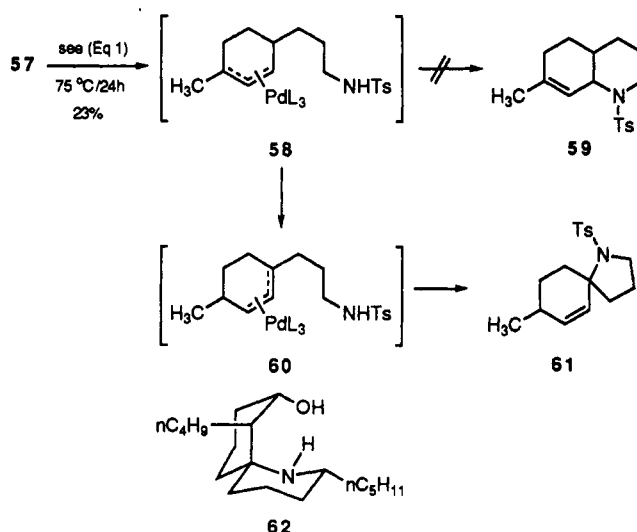


brominated at both double bonds at -78°C and debromosilylated by treatment with tetrabutylammonium fluoride to provide diastereomeric *Z*-vinyl bromides 48 and 49 in yields of 23 and 42%, respectively. Treatment of the combined mixture with zinc powder in 5:1 ether/glacial acetic acid,²⁸ followed by 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 bis-cyclization 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

Scheme X



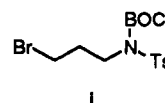
conversion of alcohol 52 to the *N*-BOC-sulfonamide 53 was accomplished in high yield via the Mitsunobu procedure.^{18,29} *E*-Vinylsilane 54, produced in 40% yield by treating *N*-BOC-sulfonamide alkyne 53 with triethylsilane and a catalytic amount of chloroplatinic acid, was then brominated and debromosilylated 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, subjecting 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 rearrangement³¹ of ester 67 and desilylation provided *E*-alkene acid 68, which was reduced to alcohol 69 (84% overall yield). A Mitsunobu reaction¹⁸ of 69 afforded

(29) An alternative attempt to synthesize 53 by alkylation of the dianion of 15 with **1** failed.

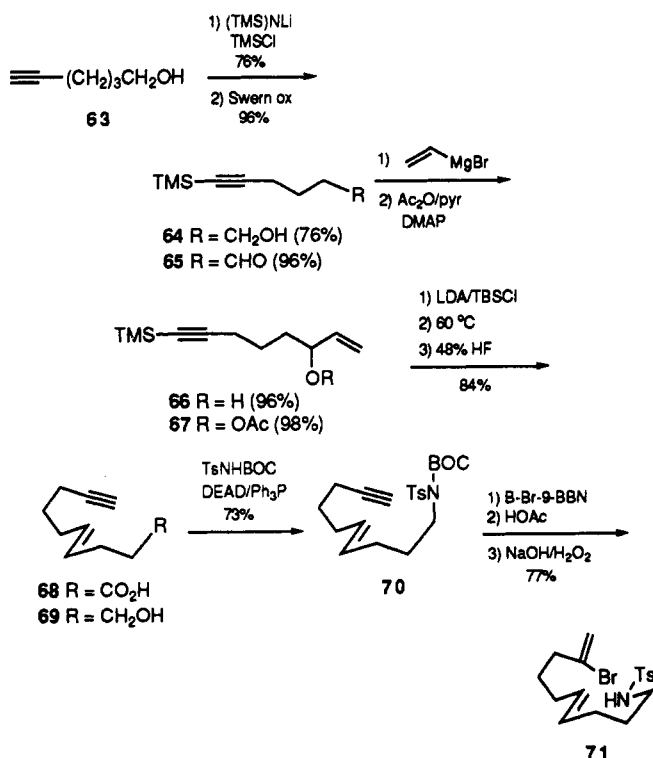


(30) For other Pd-mediated routes to the histrionicotoxin spirocyclic system, see: Tanner, D.; Sellen, M.; Backvall, J. E. *J. Org. Chem.* 1989, 54, 3374. Godieski, S. A.; Heacock, D. J.; Meinhart, J. D.; van Wallendael, S. *J. Org. Chem.* 1983, 48, 2101. For a review of syntheses of histrionicotoxins,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

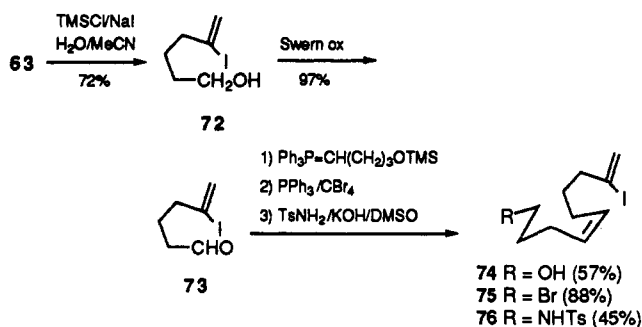
(31) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* 1972, 94, 5897.

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

Scheme XI



Scheme XII

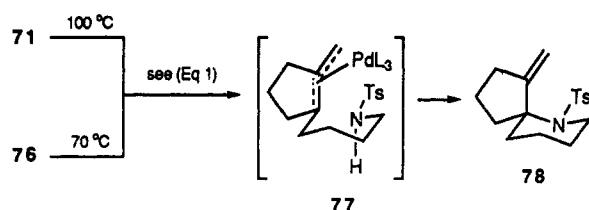


N-BOC sulfonamide 70, and conversion of the alkyne functionality to the vinyl bromide¹⁶ (cf. Schemes II, VI) gave cyclization precursor 71.

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.

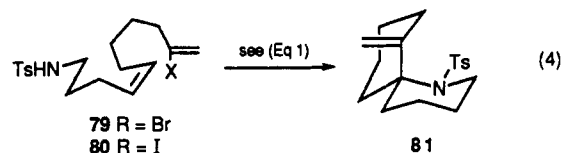
A number of cyclization experiments were conducted with *E*-alkene vinyl bromide 71 using variations of the standard cyclization conditions. Using 10 mol % of Pd(OAc)₂ at 100 °C for 48 h, 71 could be converted to [6,5]-spirocycle 78 in 52% yield (85% based upon recovered starting material) (Scheme XIII). 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%

Scheme XIII



corrected for recovered starting material). The problem here seemed to be competing elimination of HI from 76 to give the corresponding acetylene derivative.

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



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 N₂ 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 N₂. 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, H₂O (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 Na₂SO₄. 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, CDCl₃) 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 LiAlH₄ (2.175 g, 57.31 mmol) in anhydrous Et₂O (44 mL) was added a solution of *tert*-butyl 4-bromo-4-pentenoate (8, 12.24 g, 52.11 mmol) in Et₂O (16 mL) dropwise, maintaining a steady rate of reflux. After stirring the mixture under N₂ for 2 h, the excess LiAlH₄ was carefully destroyed with H₂O (2.4 mL), followed by 15% NaOH (2.4 mL) and H₂O (7.2 mL). The white precipitate was filtered and washed with Et₂O. The filtrate was dried over Na₂SO₄, 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, CDCl₃) δ 5.60 (d, 1H,

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(33) Schmidt, U.; Lieberknecht, A.; Griesser, H.; Utz, R.; Beuttler, T.; Bartkowiak, F. *Synthesis* 1986, 361.

$J = 1.2$ Hz), 5.39 (d, 1 H, $J = 1.2$ 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-pental (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-pental (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 \times 150 mL). The extract was washed with brine (100 mL) and dried over Na_2SO_4 . The crude product was purified by flash chromatography 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 ($\text{M}^+ + 1$), 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 \times 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 $\text{Hg}(\text{OAc})_2$ (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 $\text{Hg}(\text{OAc})_2$ 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 ($\text{M}^+ + 1$), 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 ($\text{M}^+ + 1$), 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 \times 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} ; ^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*-toluenesulfonamide¹³ (0.150 g, 0.691 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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 \times 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 intens) 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 $\text{C}_{16}\text{H}_{22}\text{NO}_2\text{SBr}$ 371.0555, found 371.0534.

Heck Cyclization of Sulfonamide 14b. To a mixture of $\text{Pd}(\text{OAc})_2$ (0.0011 g, 0.0047 mmol), $\text{P}(\text{o-tol})_3$ (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 \times 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

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(s, 3 H), 1.11 (m, 1 H); ^{13}C NMR (90 MHz, CDCl_3) δ 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 $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}$ 291.1293, found 291.1318.

HPLC purification also yielded 24 as a colorless oil: ^1H 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 $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}$ 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 \times 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} ; ^1H 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 $\text{C}_9\text{H}_{14}\text{O}$ 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 \times 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: ^1H NMR (360 MHz, CDCl_3) δ 5.72 (m, 1 H), 4.95 (m, 2 H), 4.18 (m, 2 H), 2.45 (m, 1 H), 2.16 (m, 2 H), 2.05 (d, 1 H, $J = 2.8$ Hz), 1.97 (s, 3 H), 1.71 (m, 2 H), 1.5 (m, 2 H).

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).¹⁸ 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 \times 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: ^1H NMR (200 MHz, CDCl_3) δ 5.73 (m, 1 H), 5.59 (d, 1 H, $J = 1.4$ Hz), 5.45 (d, 1 H, $J = 1.4$ 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 \times 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: ^1H NMR (200 MHz, CDCl_3) δ 5.73 (m, 1 H), 5.61 (d, 1 H, $J = 1.4$ 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

$^\circ\text{C}$ 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 \times 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: ^1H 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 \times 20 mL). The aqueous acidic layer was basified with saturated Na_2CO_3 and was extracted with Et_2O (5 \times 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} ; ^1H 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 PPh₃ (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 diisopropylazodicarboxylate (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} ; ^1H 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 $\text{C}_{21}\text{H}_{29}\text{NO}_4\text{S}(\text{C}_4\text{H}_9)$ 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), $\text{Pd}(\text{OAc})_2$ (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: ^1H 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% H₂O₂ (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 Na₂SO₄. 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₂₂BrNO₂S 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 Na₂CO₃ (0.070 g, 0.658 mmol), Bu₄NCl (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, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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 C₁₆H₂₁NO₂S 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 Et₂O (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 Et₂O (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 Et₂O (16 mL) was added dropwise, again maintaining a steady rate of reflux. The mixture was stirred overnight, diluted carefully with H₂O (34 mL), and extracted with Et₂O (2 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na₂SO₄. 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, CDCl₃) 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); ¹³C NMR (50 MHz, CDCl₃) 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 NaHCO₃ (25 mL), and extracted with Et₂O (3 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over Na₂SO₄, 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, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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), 189 (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 NH₄Cl (50 mL), the mixture was extracted with Et₂O (3 × 50 mL). The combined ether layers were washed with brine (50 mL) and dried over Na₂SO₄. 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, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₄BrNO₂S 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 Na₂CO₃ (0.0370 g, 0.350 mmol), Bu₄NCl (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, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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, 17.4; 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 C₁₇H₂₃NO₂S 305.1449, found 305.1442.

Flash chromatography also afforded pure 40 as a colorless oil: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (90 MHz, CDCl₃) 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 C₁₇H₂₃NO₂S 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: ^1H 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} ; ^1H 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 $\text{C}_{20}\text{H}_{27}\text{NO}_4\text{S}$ 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} ; ^1H 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 $\text{C}_{15}\text{H}_{20}\text{BrNO}_2\text{S}$ 357.0399, found 357.0426.

Heck Cyclization of Sulfonamide 43. Sulfonamide 43 was cyclized in the same manner as sulfonamide 14b using $\text{Pd}(\text{OAc})_2$ (0.0011 g, 0.0049 mmol), $\text{P}(\text{o-tol})_3$ (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: ^1H 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 $\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}$ 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} ; ^1H 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 $\text{C}_{27}\text{H}_{46}\text{NO}_4\text{SSi}$ 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: ^1H 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: ^1H 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 mmol) 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} ; ^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), 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 $\text{C}_{16}\text{H}_{22}\text{BrNO}_2\text{S}$ 371.0555, found 371.0538.

Heck Cyclization of Sulfonamide 50. Cyclization was conducted in the same manner as for sulfonamide 14b using $\text{Pd}(\text{OAc})_2$ (0.0005 g, 0.0022 mmol), $\text{P}(\text{o-tol})_3$ (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} ; ^1H 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 $C_{18}H_{21}NO_2S$ 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: 1H 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 $-78^\circ C$ 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 $-30^\circ C$, the above THP ether of 3-bromo-1-propanol was added dropwise. The solution was stirred at $-30^\circ C$ for 1 h, $-20^\circ C$ for 1 h, then at $-10^\circ C$ for 18 h. The solution was diluted with saturated $NaHCO_3$ (25 mL) and extracted with ether (3 \times 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: 1H 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 \times 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} ; 1H 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; CI 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} ; 1H 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: 1H 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: 1H 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} ; 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), 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), $P(o\text{-tol})_3$ (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 $75^\circ C$ 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: 1H 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 $C_{17}H_{22}NO_2S$ 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 $-78^\circ C$ 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 $-78^\circ C$ 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} ; 1H 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 $-78^\circ C$ under Ar was added dropwise 1.4 mL (19.6 mmol) of DMSO at a rate which kept the stirred solution below $-60^\circ C$. 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; 1H 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 $-78^\circ C$ 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} ; 1H 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); CI 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 $\text{C}_{18}\text{H}_{26}\text{SO}_2\text{NBr}$ 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 $\text{C}_{17}\text{H}_{25}\text{SO}_2\text{N}$ 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 ($\text{M}^+ + 1$), 263, 221, 207, 181, 153, 185; exact mass calcd for $\text{C}_{10}\text{H}_{16}\text{OI}$ 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 ($\text{M}^+ + 1$), 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 ($\text{M}^+ + 1$), 306, 224, 135; exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{SO}_2\text{NI}$ 433.0574, found 433.0560.

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 ($\text{M}^+ + 1$), 255, 164, 91; exact mass calcd for $\text{C}_{18}\text{H}_{26}\text{SO}_2\text{N}$ 319.1606, found 319.1599.

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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.

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