JOC*Article*

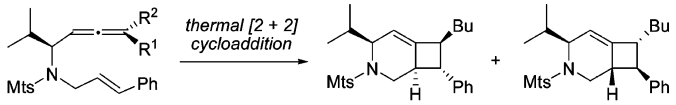
A Highly Regio- and Stereoselective Formation of Bicyclo[4.2.0]oct-5-ene Derivatives through Thermal Intramolecular [2 + 2] Cycloaddition of Allenes

Hiroaki Ohno,*[,‡] Tsuyoshi Mizutani,[†] Yoichi Kadoh,[†] Akimasa Aso,[†] Kumiko Miyamura,[†] Nobutaka Fujii,[‡] and Tetsuaki Tanaka*[,†]

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565-0871, Japan, and Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan

hohno@pharm.kyoto-u.ac.jp; t-tanaka@phs.osaka-u.ac.jp

Received January 9, 2007



Thermal [2 + 2] cycloaddition of allenes with an additional multiple bond is described. By simply heating the allenenes or allenynes having a three-atom tether in an appropriate solvent such as dioxane or DMF, the distal double bond of the allenic moiety regioselectively participates in the cycloaddition to form bicyclo[4.2.0]oct-5-ene derivatives in good to excellent yields. In all the reactions of allenenes, the olefin geometry was completely transferred to the cycloadducts. While the reaction of terminal allenes afforded bicyclic cyclobutane derivatives as a single isomer, the cycloaddition of some internal allenes with axial chirality yielded a diastereomeric mixture of cycloadducts. These results are in good accordance with the stepwise mechanism through a biradical intermediate with a coplanar allyl radical.

Introduction

The design and discovery of reactions with high atom economy that proceed, ideally, in the absence of any reagents or catalysts, without forming any waste are critical to extending the practical reach of organic synthesis.[1] Particularly, atom-economical reactions involving formation of two or more carbon−carbon bonds with a great increase in complexity of the molecule are attractive to achieve this goal. Thermal cycloaddition between carbon−carbon multiple bonds is one powerful approach to construct various cyclic molecules with extremely high atom economy.

During the past decades, allene chemistry has been revealed as an established member of the weaponry utilized in modern synthetic chemistry. On account of the current interest in the reactions of allenes with an additional multiple bond including transition metal-catalyzed carbocyclizations,[2,3] considerable research efforts have been focused on the development of cycloaddition of allenes. Intermolecular [2 + 2] cycloaddition reaction of allenes is well documented and constitutes an efficient method for accessing strained cyclobutane rings with one extra carbon−carbon double bond for further elaboration.[4,5] Meanwhile, the intramolecular [2 + 2] version of this cycloaddition is an extremely attractive approach to bicyclic derivatives

* Author to whom correspondence should be addressed. Tel: 81-6-6879-8210. Fax: 81-6-6879-8214.
[†] Osaka University.
[‡] Kyoto University.

(1) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705. See also, (b) Trost, B. M. *Science* **1991**, *254*, 1471−1477.

(2) (a) Shin, S.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416−8417. (b) Oh, C. H.; Jung, S. H.; Rhim, C. Y. *Tetrahedron Lett.* **2001**, *42*, 8669−8671. (c) Franzén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2002**, *124*, 11246−11247. (d) Franzén, J.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056−6057. (e) Oh, C. H.; Jung, S. H.; Park, D. I.; Choi, J. H. *Tetrahedron Lett.* **2004**, *45*, 2499−2502.

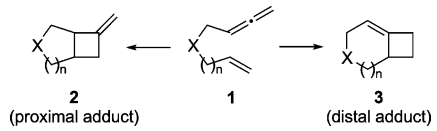
(3) (a) Ohno, H.; Takeoka, Y.; Miyamura, K.; Kadoh, Y.; Tanaka, T. *Org. Lett.* **2003**, *5*, 4763−4766. (b) Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 4541−4544.

(4) For excellent reviews, see: (a) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805−2827. (b) Murakami, M.; Matsuda, T. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K. Eds.; Wiley−VCH: Weinheim, 2004; Vol. 2, pp 727−815.

(5) For some recent examples, see: (a) Gu, Y.; Hama, T.; Hammond, G. B. *Chem. Commun.* **2000**, 395−396. (b) Akiyama, T.; Daidouji, K.; Fuchibe, K. *Org. Lett.* **2003**, *5*, 3691−3693. (c) Horino, Y.; Kimura, M.; Tanaka, S.; Okajima, T.; Tamaru, Y. *Chem. Eur. J.* **2003**, *9*, 2419−2439. (d) Hue, B. T. B.; Dijkink, J.; Kuiper, S.; van Schaik, S.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2006**, 127−137.

10.1021/jo0700528 CCC: $37.00
Published on Web 05/10/2007

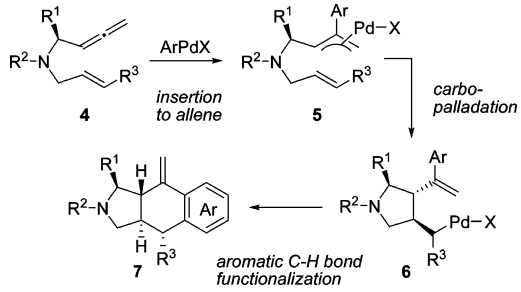
SCHEME 1. Intramolecular [2 + 2] Cycloaddition of Allenenes



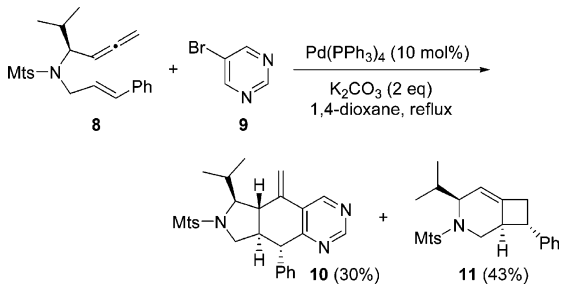
fused with a strained cyclobutane ring (Scheme 1).[6] However, intramolecular cycloaddition, including the reaction of bisallenes,[7,8] always encounters regioselectivity problems: formation of proximal and distal adducts.[9] In 1965, Skattebøl and Solomon observed unselective formation of a distal adduct of the type **3** as well as a proximal adduct in the vapor-phase thermal cycloaddition of octa-1,2,7-triene at 410 °C.[10] Recently, highly regioselective preparations of distal adducts under thermal conditions were reported; however, these reactions were limited to a special class of allenes as substrates, such as allene carboxylates,[11] allenyl sulfones,[12] difluoroallenes,[13] β-lactam-[14] or aryl-tethered allenes,[15] or diyne-diallenes.[16]

As a part of our ongoing program aimed at development of novel useful methodologies for construction of nitrogen-containing heterocycles from allenic compounds,[3,17,18] we recently reported a palladium-catalyzed tandem cyclization of

SCHEME 2. Palladium(0)-Catalyzed Tandem Cyclization of Allenenes



SCHEME 3. Formation of Distal Adduct 11[a]



[a] Abbreviation: Mts = 2,4,6-trimethylphenylsulfonyl.

allenenes **4** in the presence of an aryl halide and potassium carbonate to yield tricyclic products **7**, through insertion of arylpalladium halide to allene, carbopalladation onto the double bond, and aromatic C−H functionalization (Scheme 2).[19] In the course of this study, we observed regioselective formation of distal adducts **11** in the reaction mixture of the palladium-catalyzed cyclization of allenene **8** with 5-bromopyrimidine **9** possessing relatively low reactivity (Scheme 3). On the basis of this result, we found that this cycloaddition proceeds by simply heating the allenenes in an appropriate solvent in the absence of any catalyst.[20] Quite recently, microwave-assisted[21] or palladium-catalyzed [2 + 2] cycloaddition of allenynes[22] providing distal adducts regioselectively have appeared; however, our cycloaddition is the sole example of exclusive conversion of unactivated simple allenes to distal adducts under thermal conditions. In this contribution, we present full details

(6) For recent examples, see: (a) Shepard, M. S.; Carreira, E. M.; *J. Am. Chem. Soc*. **1997**, *119*, 2597−2605. (b) Tsuno, T.; Sugiyama, K. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 519−531.

(7) (a) Murakami, M.; Ashida, S.; Matsuda,T. *J. Am. Chem. Soc*. **2004**, *126*, 10838−10839. (b) Jiang, X.; Cheng, X.; Ma, S. *Angew. Chem., Int. Ed*. **2006**, *45*, 8009−8013. For transition metal-catalyzed [2 + 2] cycloaddition, see: (c) Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc*. **2000**, *122*, 11529−11530.

(8) An interesting [2 + 2] cycloaddition of *in situ*-generated bis(phosphinylallene)s furnishing naphtho[*b*]cyclobutenes has recently appeared, see: Kitagaki, S.; Okumura, Y.; Mukai, C. *Tetrahedron Lett*. **2006**, *47*, 1849−1852.

(9) The compounds having the bicyclo[4.2.0]octane skeleton constitute an important class of molecules in synthetic and natural product chemistry. For example, see: (a) Piers, E.; Lu, Y.-F. *J. Org. Chem*. **1989**, *54*, 2267−2268. (b) Suginome, H.; Takeda, T.; Itoh, M.; Nakayama, Y.; Kobayashi, K. *J. Chem. Soc. Perkin Trans. 1* **1995**, 49−61. (c) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519−6522. (d) Naik, J. T.; Mantle, P. G.; Sheppard, R. N.; Waight, E. S. *J. Chem. Soc. Perkin Trans. 1* **1995**, 1121−1125. (e) Carotenuto, A.; Conte, M. R.; Fattorusso, E.; Lanzotti, V.; Magno, S. *Tetrahedron* **1995**, *51*, 10751−10758. (f) Kurata, K.; Taniguchi, K.; Agatsuma, Y.; Suzuki, M. *Phytochemistry* **1998**, *47*, 363−369. (g) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559−1563.

(10) Skattebøl, L.; Solomon, S. *J. Am. Chem. Soc*. **1965**, *87*, 4506−4511.

(11) (a) Yoshida, M.; Hiromatsu, M.; Kanematsu, K. *J. Chem. Soc. Chem. Commun*. **1986**, 1168−1170. (b) Yoshida, M.; Hiromatsu, M.; Kanematsu, K. *Heterocycles* **1986**, *24*, 881−884. (c) Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudziñski, J. M.; Õsawa, E.; Kanematsu, K. *J. Am. Chem. Soc*. **1988**, *110*, 1232−1238. (d) Gillmann, T.; Hülsen, T.; Massa, W.; Wocadlo, S. *Synlett* **1995**, 1257−1259. For a related reaction of cumulenes, see: (e) Garcia, J. G.; Ramos, B.; Pratt, L. M.; Rodríguez, A. *Tetrahedron Lett.* **1995**, *36*, 7391−7394.

(12) (a) Kanematsu, K.; Sugimoto, N.; Kawaoka, M.; Yeo, S.; Shiro, M. *Tetrahedron Lett.* **1991**, *32*, 1351−1354. (b) Padwa, A.; Filipkowski, M. A.; Meske, M.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc*. **1993**, *115*, 3776−3777. (c) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc*. **1995**, *117*, 7071−7080. (d) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem*. **2003**, *68*, 6238−6250. See also, (e) Inagaki, F.; Mukai, C. *Org. Lett*. **2006**, *8*, 1217−1220.

(13) Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc*. **2002**, *124*, 6534−6535.

(14) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett*. **2003**, *5*, 3795−3798. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C.; Torres, M. R. *Chem. Eur. J*. **2006**, *12*, 1539−1546.

(15) Ikemoto, C.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1998**, *39*, 5053−5056.

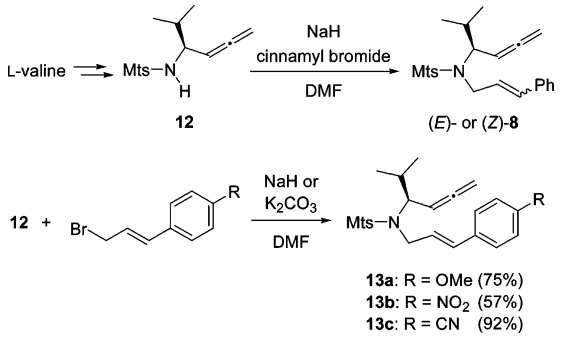
(16) Recently, in their study of molybdenum-mediated allenic Pauson−Khand reaction, Cook and co-workers observed the formation of distal adducts in 30−40% yield, by heating of conformationally restricted diyne-allenes in toluene at 100 °C in the absence of any catalyst. As far as we are aware, this is the first example of thermal [2 + 2] cycloaddition between unactivated allenes and alkynes, see: (a) Cao, H.; Flippen-Anderson, J.; Cook, J. M. *J. Am. Chem. Soc*. **2003**, *125*, 3230−3231. (b) Cao, H.; Van Ornum, S. G.; Deschamps, J.; Flippen-Anderson, J.; Laib, F.; Cook, J. M. *J. Am. Chem. Soc*. **2005**, *127*, 933−943.

(17) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem*. **1999**, *64*, 2992−2993. (b) Ohno, H.; Anzai, M.; Toda, A.; Ohishi, S.; Fujii, N.; Tanaka, T.; Takemoto, Y.; Ibuka, T. *J. Org. Chem.* **2001**, *66*, 4904−4914. (c) Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749−1753. (d) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc*. **2004**, *126*, 8744−8754. (e) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513−1517. (f) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, *8*, 947−950.

(18) For recent reviews, see: (a) Ohno, H. *Yakugaku Zasshi* **2001**, *121*, 733−741. (b) Ohno, H. *Chem. Pharm. Bull*. **2005**, *53*, 1211−1226. (c) Ohno, H. *Yakugaku Zasshi* **2005**, *125*, 899−925.

(19) (a) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647−2650. (b) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J*. **2005**, *11*, 3728−3741.

SCHEME 4. Preparation of Allenenes 8 and 13a−c



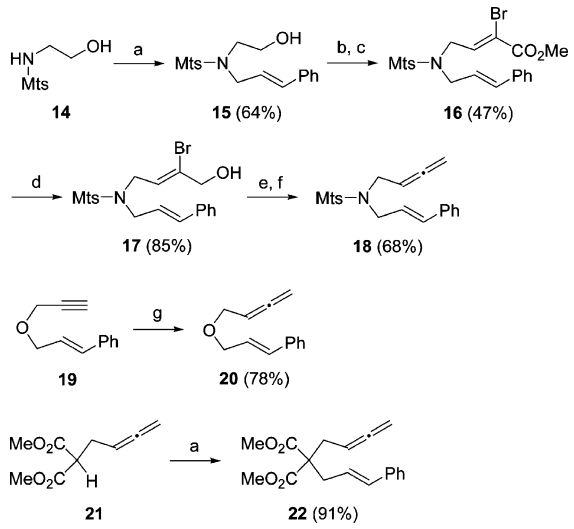
of our investigation into the thermal intramolecular [2 + 2] cycloaddition of allenenes and allenynes. The stereochemical outcome of axially chiral allenenes as well as mechanistic considerations of this transformation are also described.

Results and Discussion

Preparation of Allenenes. Known allenene **8** was synthesized according to our reported procedure through cinnamylation of protected amino allene **12**,[19b] which, in turn, was readily obtained through diethylzinc-mediated allene synthesis catalyzed by palladium(0) (Scheme 4).[23] Other L-valine-derivatives **13a−c** having a substituted phenyl group were similarly prepared by the reaction of **12** with a substituted (*E*)-cinnamyl bromide under basic conditions. The trimethylphenylsulfonyl (Mts) group was used as a nitrogen protecting group because it can withstand a wide range of chemical manipulations and yet be removed by the use of Yajima's protocol.[24] In addition, many Mts amides forming good crystals can be easily handled.

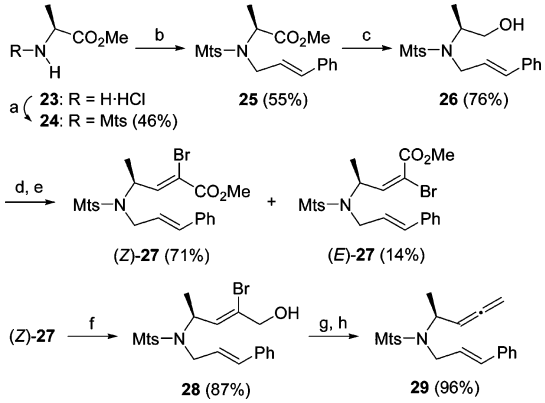
α-Unsubstituted allene **18** was prepared as shown in Scheme 5. Alkylation of protected 2-aminoethanol **14**, oxidation with SO_3·pyridine, and Wittig olefination with brominated ylide[25] afforded α-bromo-α,β-unsaturated ester **16**. Reduction of **16** with DIBAL-H and mesylation of the resulting alcohol **17** followed by treatment with diethylzinc in the presence of palladium(0)[23] furnished the desired allenene **18** in good yield. Allenene **20** tethered by an oxygen atom was prepared by copper(I)-mediated one-carbon elongation of terminal alkyne **19** with paraformaldehyde in the presence of *i*-Pr_2NH (Crabbé conditions).[26] Treatment of known allene **21**[27] with NaH and (*E*)-cinnamyl bromide gave dimethyl malonate-derived allenene **22** in 91% yield.

SCHEME 5. Preparation of Allenenes 18, 20, and 22[a]



[a] Reagents: (a) NaH, (*E*)-cinnamyl bromide, DMF; (b) SO_3·py, Et_3N, DMSO; (c) $Ph_3P{=}C(Br)CO_2Me$, $CHCl_3$; (d) DIBAL-H, CH_2Cl_2; (e) MsCl, Et_3N, THF; (f) cat. $Pd(PPh_3)_4$, Et_2Zn, THF; (g) $(HCHO)_n$, CuBr, *i*-Pr_2NH, dioxane.

SCHEME 6. Preparation of Allenene 29[a]



[a] Reagents: (a) MtsCl, Et_3N, DMF; (b) (*E*)-cinnamyl bromide, NaH, DMF; (c) $LiAlH_4$, THF; (d) SO_3·py, Et_3N, DMSO; (e) $Ph_3P{=}C(Br)CO_2Me$, $CHCl_3$; (f) DIBAL-H, CH_2Cl_2; (g) MsCl, Et_3N, THF; (h) cat. $Pd(PPh_3)_4$, Et_2Zn, THF.

For preparation of alanine-derived substrate **29**, N-cinnamylated methyl alaninate derivative **25** was employed (Scheme 6):[28] by a sequence of reactions including Wittig olefination and reductive allene formation, the ester **25** was converted to allenene **29**.

We encountered difficulty in preparation of α,α-dimethylated allene derivative **34**: thus, the desired brominated enoate **31** was not obtained by Wittig olefination of aldehyde derived from N-protected 2-amino-2-metylpropan-1-ol **30** with brominated phosphorus ylide, presumably due to steric hindrance of the neighboring quaternary carbon center (Scheme 7). However, the reaction with *in situ*-generated brominated phosphonate, $(EtO)_2P(O)CH(Br)CO_2Et$, afforded **31** in synthetically acceptable yield (49%). The usual transformation through reduction, allene formation, and alkylation yielded **34** having a quaternary carbon center.

(20) A portion of this study on the reaction of terminal allenes was already reported in a preliminary communication: Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113−5115.

(21) (a) Brummond, K. M.; Chen, D. *Org. Lett*. **2005**, *7*, 3473−3475. (b) Oh, C. H.; Gupta, A. K.; Park, D. I.; Kim, N. *Chem. Commun*. **2005**, 5670−5672.

(22) Oh, C. H.; Park, D. I.; Jung, S. H.; Reddy, V. R.; Gupta, A. K.; Kim, Y. M. *Synlett* **2005**, 2092−2094.

(23) (a) Ohno, H.; Toda, A.; Oishi, S.; Tanaka, T.; Takemoto, Y.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **2000**, *41*, 5131−5134. (b) Ohno, H.; Miyamura, K.; Tanaka, T.; Oishi, S.; Toda, A.; Takemoto, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem*. **2002**, *67*, 1359−1367.

(24) Fujii, N.; Otaka, A.; Ikemura, O.; Akaji, K.; Funakoshi, S.; Hayashi, Y.; Kuroda, Y.; Yajima, H. *J. Chem. Soc., Chem. Commun.* **1987**, 274−275.

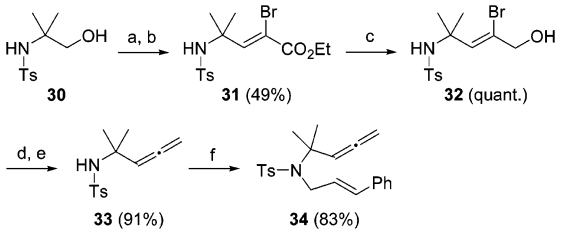
(25) (a) Denney, D. B.; Ross, S. T. *J. Org. Chem*. **1962**, *27*, 998−1000. For a recent synthesis of stabilized halo-ylides, see: (b) Kayser, M. M.; Zhu, J.; Hooper, D. L. *Can. J. Chem*. **1997**, *75*, 1315−1321.

(26) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747−751.

(27) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem*. **2002**, *67*, 2837−2847.

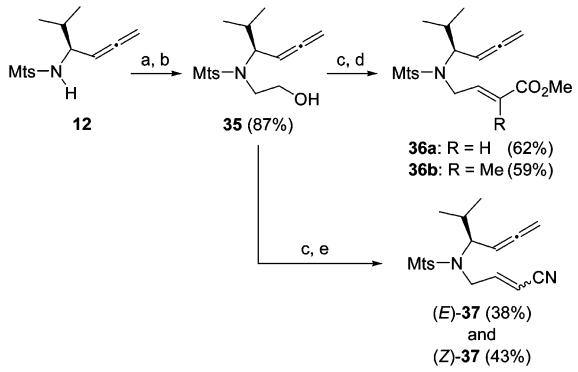
(28) For a reason that is unclear, preparation of **23**-derived aldehyde having an NH group by oxidation of the corresponding alcohol was not reproductive.

SCHEME 7. Preparation of Allenene 34[a]



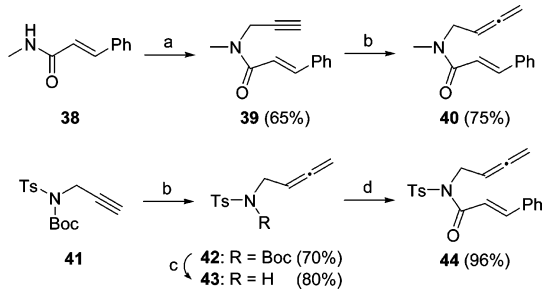
[a] Reagents: (a) SO_3·py, Et_3N, DMSO; (b) $(EtO)_2P(O)CH_2CO_2Et$, NaH, Br_2, THF; (c) DIBAL-H, CH_2Cl_2; (d) MsCl, Et_3N, THF; (e) cat. $Pd(PPh_3)_4$, Et_2Zn, THF; (f) NaH, (*E*)-cinnamyl bromide, DMF.

SCHEME 8. Preparation of Allenenes 36 and 37[a]



[a] Reagents: (a) $BrCH_2CH_2OTHP$, K_2CO_3, DMF; (b) 4 N HCl, MeOH; (c) SO_3·py, Et_3N, DMSO; (d) $Ph_3P{=}C(R)CO_2Me$, THF; (e) $Ph_3P{=}CHCN$, THF.

SCHEME 9. Preparation of Allenene 40 and 44[a]



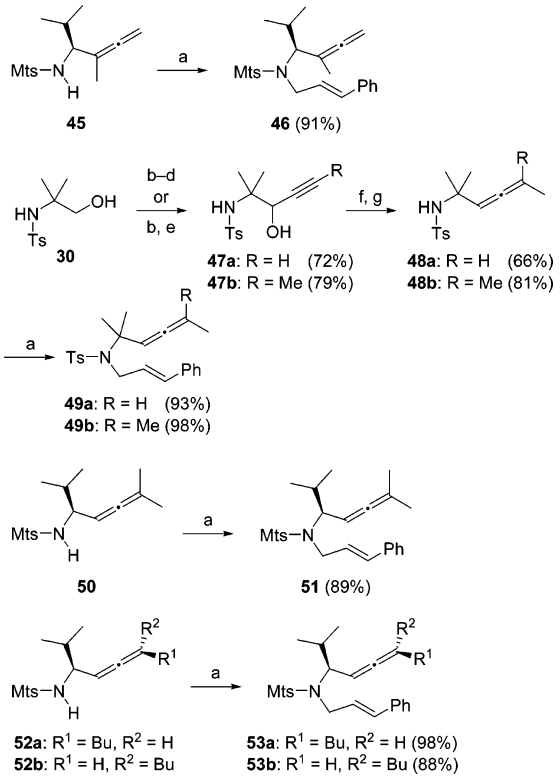
[a] Reagents: (a) 3-bromopropyne, NaH, DMF; (b) $(HCHO)_n$, CuBr, *i*-Pr_2NH, dioxane; (c) TFA, CH_2Cl_2; (d) (*E*)-cinnamoyl chloride, NaH, DMF.

Next, various allenenes bearing substituents on the double bond other than the phenyl group were synthesized. Alkylation of the protected amino allene **12** with $BrCH_2CH_2OTHP$ and treatment with HCl gave allenol **35** in 87% yield (Scheme 8). Oxidation with SO_3·pyridine and subsequent Wittig reaction gave (*E*)-enoate **36a** and α-methylated derivative **36b**. In contrast, unselective formation of (*E*)- and (*Z*)-nitriles **37** was observed in the reaction with cyanated phosphonium ylide.

Cinnamide-derived allenes **40** and **44** were readily synthesized as shown in Scheme 9. Propargylation of *N*-methyl cinnamide **38**[29] followed by Crabbé reaction of the resulting amide **39** yielded **40**. Similarly, a sequence of reactions through Crabbé reaction of **41**,[30] removal of the Boc group with TFA, and acylation with cinnamoyl chloride afforded **44** in good yield.

(29) Lewis, F. D.; Reddy, G. D.; Schneider, S.; Gahr, M. *J. Am. Chem. Soc.* **1991**, *113*, 3498−3506.

SCHEME 10. Preparation of Allenenes 46, 49, 51, and 53[a]



[a] Reagents: (a) NaH, (*E*)-cinnamyl bromide, DMF; (b) SO_3·py, Et_3N, DMSO; (c) trimethylsilylacetylene, *n*-BuLi, THF; (d) MeONa, MeOH; (e) prop-1-ynylmagnesium bromide, THF; (f) MsCl, Et_3N, THF; (g) MeMgBr, CuBr, THF.

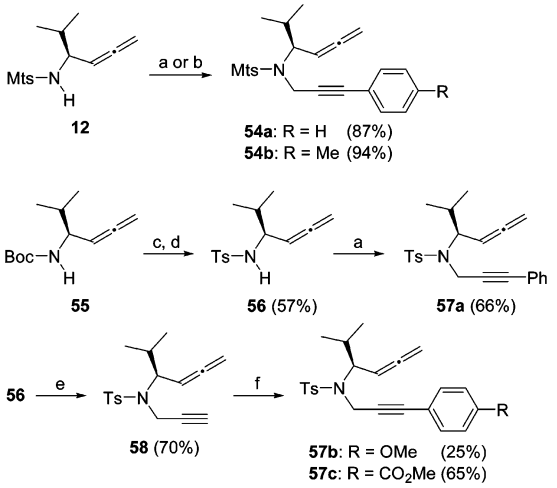
Finally, we synthesized allenenes having various substituent(s) on the allenic moiety as shown in Scheme 10. Cinnamylation of known protected amino allene **45**[17b] gave **46** having a methyl group on the proximal allenic carbon. Alkynylation of **30**-derived aldehyde, mesylation of the resulting propargylic alcohols **47a** and **47b**, and methylcopper-mediated S_N2' substitution gave internal allenes **48a** and **48b**, which were readily transformed to the corresponding allenenes **49a** and **49b**. Similarly, known protected amino allene **50**[31] was converted to **51**. In order to examine the stereochemical course of the [2 + 2] cycloaddition of allenes with axial chirality, diastereomerically pure allenenes, (*S*,a*S*)-**53a** and (*S*,a*R*)-**53b**, were prepared from known allenes **52a** and **52b**, respectively, which were stereospecifically obtained by organocopper-mediated ring-opening reaction of chiral ethynylaziridines.[31]

Preparation of Allenynes. Next, we prepared various allenynes as shown in Scheme 11. Alkylation of **12** with NaH and 3-phenylpropargyl halide gave allenynes **54a** and **54b** in good yields (87−94%). Similarly, *N*-tosyl derivative **57a** was prepared starting from known *N*-Boc amino allene **55**.[3b] Synthesis of allenynes **57b** and **57c** with a substituent on the phenyl group by direct alkylation of **56** was inefficient, because of the relatively low stability of 3-phenylpropargyl bromides having a substituent on the phenyl group.[32] However, stepwise

(30) (a) Oppolzer, W.; Stammen, B. *Tetrahedron* **1997**, *53*, 3577−3586. (b) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K. *J. Org. Chem.* **2006**, *71*, 91−96.

(31) (a) Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1999**, *40*, 349−352. (b) Ohno, H.; Toda, A.; Fujii, N.; Takemoto, Y.; Tanaka, T.; Ibuka, T. *Tetrahedron* **2000**, *56*, 2811−2820.

SCHEME 11. Preparation of Allenynes 54 and 57[a]



[a] Reagents: (a) 3-phenylpropargyl bromide, NaH, DMF; (b) 3-(4-methylphenyl)propargyl iodide, NaH, DMF; (c) TFA, CH_2Cl_2; (d) TsCl, Et_3N, CH_2Cl_2; (e) propargyl bromide, NaH, DMF; (f) 4-RPhI, $PdCl_2(PPh_3)_2$, CuI, i-Pr_2NH, THF.

reaction including propargylation of **56** and Sonogashira cross-coupling of **58** with 1-iodo-4-methoxybenzene or methyl 4-iodobenzoate afforded **57b** and **57c**, respectively.

L-Phenylalanine- and isoleucine-derived allenynes **60a** and **60b**, and α-unsubstituted allene derivative **66**, were similarly obtained as shown in Scheme 12. In a similar manner to the preparation of alanine-derived allenene **29** (Scheme 6), allenyne **60c** was synthesized through *N*-(3-phenylpropargyl)alaninate derivative **61**. α-Unsubstituted allenene **66** was prepared by condensation of known protected amino allene **65**[23] with 3-phenylpropargyl alcohol.

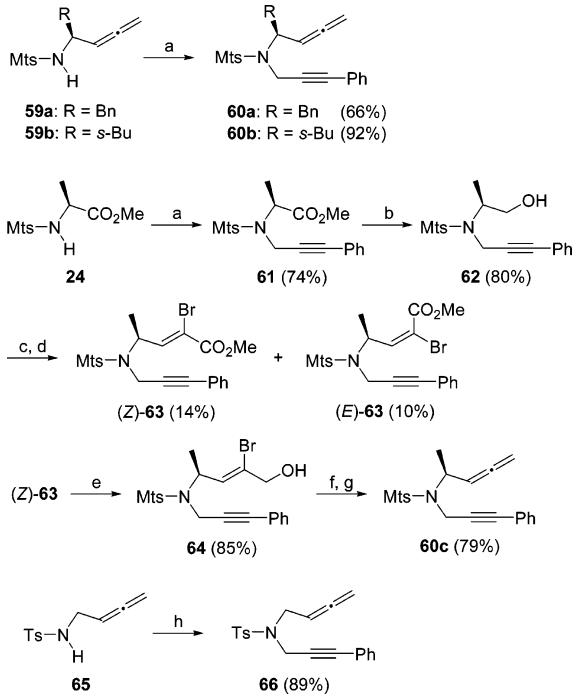
[2 + 2] Cycloaddition of Allenenes. On the basis of the result shown in Scheme 3 in which the [2 + 2] cycloadduct **11** was obtained in 43% yield under the palladium-catalyzed cyclization conditions using aryl halide and potassium carbonate, we began our investigations by screening a variety of conditions to find the optimal procedure for the cycloaddition to occur. The results in Table 1 showed that addition of aryl halide, palladium catalyst, or potassium carbonate is not essential for this transformation: these reagents, especially the palladium catalyst, did decrease the yield of **11a** rather than promote the cycloaddition (entries 1−3). Thermal cycloaddition in dioxane in the absence of any reagent or catalyst proceeded quite well to give the desired bicyclic cyclobutane **11a** in 89% yield (entry 4). It should be noted that addition of galvinoxyl to the reaction of (*E*)-**8** did not affect the cycloaddition.[33] This is the first example of exclusive conversion of unactivated simple allenes to distal adducts under thermal conditions without using microwave irradiation.[21,34]

Next, the thermal [2 + 2] cycloaddition of allenene **8** under various reaction conditions was examined (Table 2). As well as dioxane (entry 1), solvents with high boiling points such as xylenes (entry 2), DMF (entries 4 and 5), NMP (entry 6), and

(32) Mitsunobu condensation with the corresponding alcohols required higher reaction temperature, which makes control of the selective alkylation (without causing [2 + 2] cycloaddition) difficult.

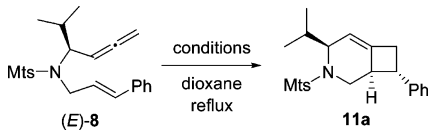
(33) However, these result does not conflict with the biradical mechanism depicted in Schemes 14 and 15, because intramolecular coupling or biradicals such as **94** and **101** to the corresponding cyclobutanes would be extremely fast.

SCHEME 12. Preparation of Allenynes 60 and 66[a]



[a] Reagents: (a) 3-phenylpropargyl bromide, NaH, DMF; (b) $LiAlH_4$, THF; (c) SO_3·py, Et_3N, DMSO; (d) $Ph_3P{=}C(Br)CO_2Me$, $CHCl_3$; (e) DIBAL-H, CH_2Cl_2; (f) MsCl, Et_3N, THF; (g) cat. $Pd(PPh_3)_4$, Et_2Zn, THF; (h) 3-phenylpropargyl alcohol, PPh_3, DIAD, THF.

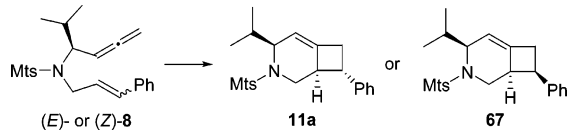
TABLE 1. Effect of Additive and a Palladium Catalyst[a]



entry	PhI	$Pd(PPh_3)_4$	K_2CO_3	time (h)[b]	yield (%)
1	2 equiv	10 mol %	2 equiv	7.5	8
2	none	10 mol %	2 equiv	18	19
3	none	none	2 equiv	60	87
4	none	none	none	65	89

[a] Addition of galvinoxyl did not affect the cycloaddition. [b] The required time for complete consumption of all the starting material on TLC.

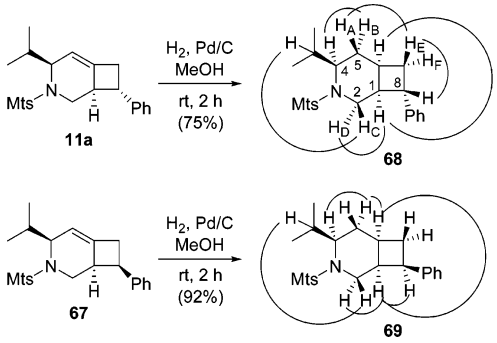
TABLE 2. Effect of Solvent and Reaction Temperature



entry	substrate	solvent	temp	time (h)	product	yield (%)
1	(*E*)	dioxane	reflux	65	**11a**	89
2	(*E*)	xylenes	reflux	3	**11a**	81
3	(*E*)	xylenes	110 °C	40	**11a**	32
4	(*E*)	DMF	150 °C	3	**11a**	96
5	(*E*)	DMF	110 °C	65	**11a**	86
6	(*E*)	NMP	150 °C	2	**11a**	84
7	(*E*)	DMI	150 °C	2	**11a**	79
8	(*Z*)	dioxane	reflux	65	**67**	63

DMI (entry 7) can be similarly used for this transformation. Among them, dioxane and DMF were the solvents of choice leading to 3-azabicyclo[4.2.0]oct-5-ene derivative **11a** in 89%

SCHEME 13. Synthesis and NOE Analysis of Saturated Derivatives 68 and 69

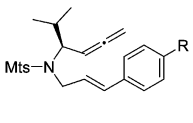
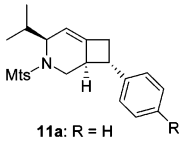
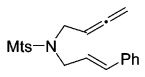
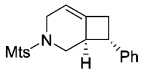
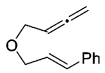
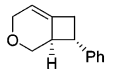
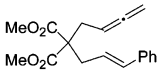
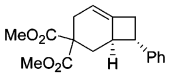
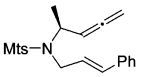
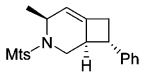
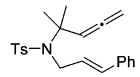
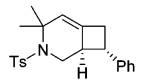


and 96% yields, respectively, as the sole isolable isomer (entries 1 and 4). As we expected, the reaction of (*Z*)-**8** exclusively furnished cycloadduct **67** with the opposite configuration to **11a** at the 8-position. These stereochemical outcomes with complete selectivity are in good accordance with the observation using allenyl sulfones.[12b−d]

The structure and configuration of the cycloadducts **11a** and **67** were confirmed by COSY and NOESY analyses of the corresponding saturated derivatives **68** and **69**. Results of the NOE experiment are summarized in Scheme 13.[35] We observed NOE between 4-H and the methylene proton at C-5 in **68**, which was assigned as H_B. NOE between H_A and another methylene proton allowed assignment of H_E. Finally, NOE between H_E and 8-H revealed that the phenyl group at C-8 directs the opposite side to the isopropyl group at C-4. On the other hand, NOE was observed between the methyne proton of the isopropyl group and one of the methylene protons at C-2, which was assigned as H_C. We confirmed the configuration at the 1-position by NOE between H_D and 1-H. Similarly, NOE experiment of **69** was consistent with the relative configuration shown in Scheme 13. Furthermore, the structure determination of **68** and **69** was unequivocally made by HMQC analysis.

Next, we investigated the thermal [2 + 2] cycloaddition of allenes having a cinnamyl group (Table 3). Although we already confirmed that the reaction in dioxane under reflux was rather slow (Table 2), we first performed the cycloaddition of allenenes **8** and **13a**−**c** in dioxane for a careful examination of the substituent effect on the aryl group. While the reaction of **13a** having a methoxy group was slow (60 h) to give **11b** in 44% yield, this cycloaddition was strongly promoted by the presence of an electron-withdrawing group such as a nitro or cyano group to afford **11c** (entry 3) and **11d** (entry 4) in 10−20 h. As can be expected, the reaction of **8** and **13a**−**c** in DMF at 150 °C completed in 1−3 h to afford the desired products **11a**−**d** in good yields (71−96%, entries 5−8). More important than the effect of the electron-donating and -withdrawing aryl group is the α-substituent of the allene: the reaction of α-unsubstituted allene derivative **18** required prolonged reaction time (19 h) even at the refluxed temperature in DMF (entry 9). Similarly,

TABLE 3. [2 + 2] Cycloaddition of Various Allenenes

entry	substrate	conditions	time (h)	product	yield (%)
					
1	**8**: R = H	dioxane, reflux	65	**11a**: R = H	89
2	**13a**: R = OMe		60	**11b**: R = OMe	44
3	**13b**: R = NO_2		10	**11c**: R = NO_2	87
4	**13c**: R = CN		20	**11d**: R = CN	92
5	**8**: R = H	DMF, 150 °C	3	**11a**: R = H	96
6	**13a**: R = OMe		3	**11b**: R = OMe	71
7	**13b**: R = NO_2		1	**11c**: R = NO_2	93
8	**13c**: R = CN		2	**11d**: R = CN	86
9	 **18**	DMF, reflux	19	 (±)-**70**	68
10	 **20**	DMF, reflux	30	 (±)-**71**	40
11	 **22**	DMF, reflux	30	 (±)-**72**	69
12	 **29**	DMF, 150 °C	15	 **73** (*ca.* 5:2)	67
13		DMF, reflux	6		84
14	 **34**	DMF, 150 °C	1	 (±)-**74**	91

allenenes **20** and **22** tethered by an oxygen or a carbon atom, respectively, required 30 h to complete the reaction giving 3-oxabicyclo[4.2.0]oct-5-ene derivative **71** and its carbocycle analogue **72** both in a stereospecific manner (entries 10 and 11). It should be clearly noted that alanine-derived allenene **29** having an α-methyl group cyclized into **73** as a diastereomixture (*ca.* 5:2; entries 12 and 13). As expected, α,α-disubstituted derivative **34** showed extremely high reactivity to give **74** bearing a quaternary carbon center in 91% yield within 1 h (entry 14).

Next, intramolecular [2 + 2] cycloaddition of allenes with various types of double bond was examined. The results are summarized in Table 4. The reaction of allenene **75** with a geminal dimethyl group on the olefinic carbon atom was a good substrate for this transformation, although the reaction was relatively slow (entry 1). In contrast, N-allylated amino allene derivative **77** was completely inert under the cycloaddition conditions, leading to recovery of unchanged starting material (entry 2). These results are comparable to Padwa's observation,[12c] in which a tertiary radical intermediate promotes the [2 + 2] cycloaddition of sulfonyl allenes (45 min) better than the cyclization via a primary radical intermediate (22 h). In this case, a sulfonyl group on the allenic carbon did stabilize the allyl radical intermediate for cycloaddition to occur.

Allene **36a** having an α,*β*-unsaturated ester group showed sufficient reactivity to give the cycloadduct **79** in 73−76% yield (entries 3 and 4). Similarly, the reaction of α-methylated enoate

(34) Formation of the same framework (3-azabicyclo[4.2.0]oct-5-ene) via intermolecular [2 + 2] cycloaddition of in situ-generated cyclic amino allenes with styrene was reported: Christl, M.; Braun, M.; Wolz, E.; Wagner, W. *Chem. Ber*. **1994**, *127*, 1137−1142.

(35) In order to determine the relative configuration between C-4 and C-1 (or C-4 and C-8), transformation of **11a** and **67** to the corresponding saturated analogues **68** and **69** was desirable. We could unambiguously confirm the relative configuration of **68** and **69** by NOEs including that of the introduced hydrogens at C-5 and C-6. For more details, see the Supporting Information

TABLE 4. [2 + 2] Cycloaddition of Allenes with Various Double Bonds

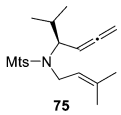
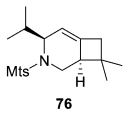
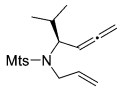
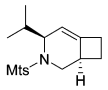
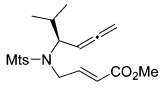
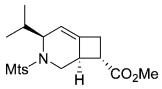
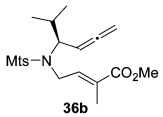
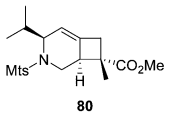
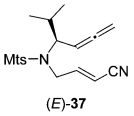
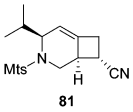
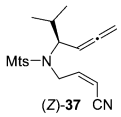
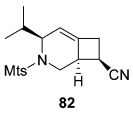
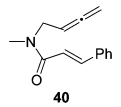
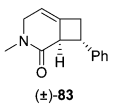
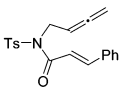
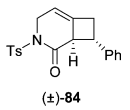
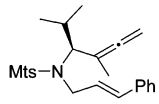
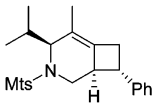
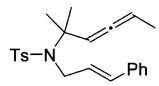
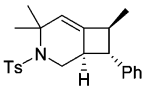
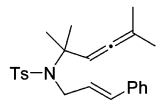
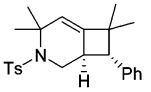
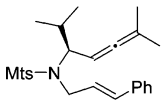
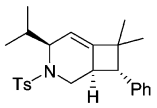
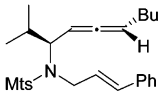
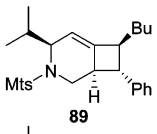
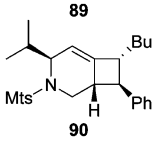
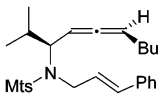
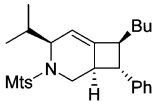
entry	substrate	conditions	time (h)	product	yield (%)
1	 **75**	DMF, reflux	24	 **76**	82
2	 **77**	DMF, 150 °C	15	 **78**	0
3	 **36a**	dioxane, reflux	65	 **79**	76
4		DMF, 150 °C	2		73
5	 **36b**	dioxane, reflux	20	 **80**	93
6		DMF, 150 °C	1		87
7	 (*E*)-**37**	DMF, 150 °C	3	 **81**	78
8	 (*Z*)-**37**	DMF, 150 °C	2	 **82**	75
9	 **40**	DMF, reflux	18	 (±)-**83**	43
10	 **44**	DMF, reflux	15	 (±)-**84**	31

TABLE 5. [2 + 2] Cycloaddition of Allenenes Having Substituent(s) on the Allenic Carbon[a]

entry	substrate	time (h)	product	yield (%)
1	 **46**	2	 **85**	90
2	 **49a**	1	 (±)-**86**	94
3	 **49b**	5	 (±)-**87**	63
4	 **51**	36	 **88** 3:1 mixture of diastereomers	46
5	 (*S*,a*S*)-**53a**	15	 **89**	65
			 **90**	23
6	 (*S*,a*R*)-**53b**	3	 **89**	88

[a] All reactions were carried out at 150 °C in DMF.

derivative **36b** gave bicyclic ester **80** with a chiral quaternary carbon (entries 5 and 6). As well as the reaction of the allenes (*E*)- and (*Z*)-**8** having a cinnamyl group on the nitrogen atom (Table 2), the cycloaddition of (*E*)- and (*Z*)-α,*β*-unsaturated nitriles (*E*)-**37** and (*Z*)-**37** proceeded stereospecifically to afford isomeric bicyclic nitriles, **81** and **82** (entries 7 and 8). Compared to allenenes **36** and **37** having an electron-withdrawing group on the terminal olefinic carbon, cinnamide-derived allenes **40** and **44** gave relatively low yields of the cycloadducts **83** and **84** after prolonged reaction times (entries 9 and 10). Although the exact reason is unclear, this marked difference of reactivities can be attributed to the electronic character of the olefinic moiety, in addition to the effect of an α-substituent. Since the phenyl-stabilized radical generated on the olefinic moiety (*vide infra*) would have a similar reactivity to other related substrates having a cinnamyl group (Table 3), the cinnamide derivatives **40** and **44** would have low reactivity on the first cyclization. This hypothesis is partially supported by the fact that radical reaction of cinnamide derivatives generally proceeds at the *β*-position to give the radical intermediates stabilized by the carbonyl group.[36] Additionally, we could not rule out the first cyclization at the *β*-position of the cinnamide forming an eight-membered ring biradical intermediate, followed by the second cyclization.[12c,14b]

Finally, [2 + 2] cycloaddition of allenenes bearing substituent(s) on the allenic moiety was investigated (Table 5). Monosubstitution at the proximal allenic carbon (entry 1) and distal carbon (entry 2) has proven to be tolerated and the expected products **85** and **86** were obtained in high yields (90−94%). On the other hand, decreased reactivity toward the cycloaddition was observed with allenenes **49b** and **51** bearing a geminal dimethyl group at the terminal position, leading to cycloadducts **87** (63%) and **88** (46%; 3:1 mixture of diastereomers) in longer reaction time at 150 °C (entries 3 and 4). Quite interestingly, the reaction of internal (*S*,a*S*)-allene **53a** showed lower reactivity to produce bicyclic cyclobutane **89** as the major product in 65% yield (entry 5), in which the chirality of the allenic moiety is not preserved. In this case, the corresponding

(36) (a) Rück, K.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 694−696. (b) Sibi, M. P.; Jasperse, C. P.; Ji, J. *J. Am. Chem. Soc.* **1995**, *117*, 10779−10780. (c) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227−4235. (d) Hein, J. E.; Zimmerman, J.; Sibi, M. P.; Hultin, P. G. *Org. Lett.* **2005**, *7*, 2755−2758.

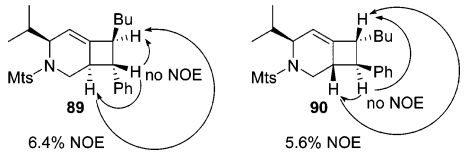
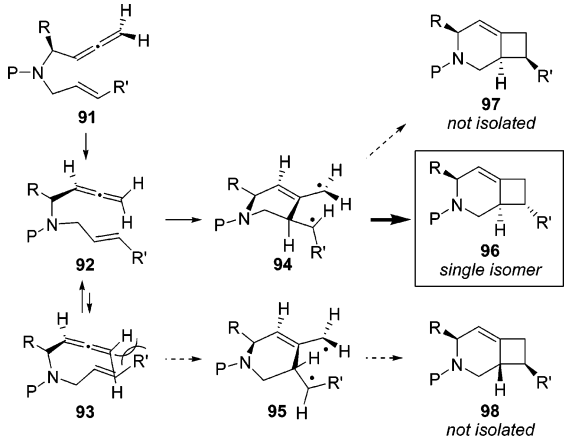


FIGURE 1. Determination of relative configuration of the adducts **89** and **90** by NOE analyses.

SCHEME 14. Stereoselective Formation of 96 as the Single Isomer

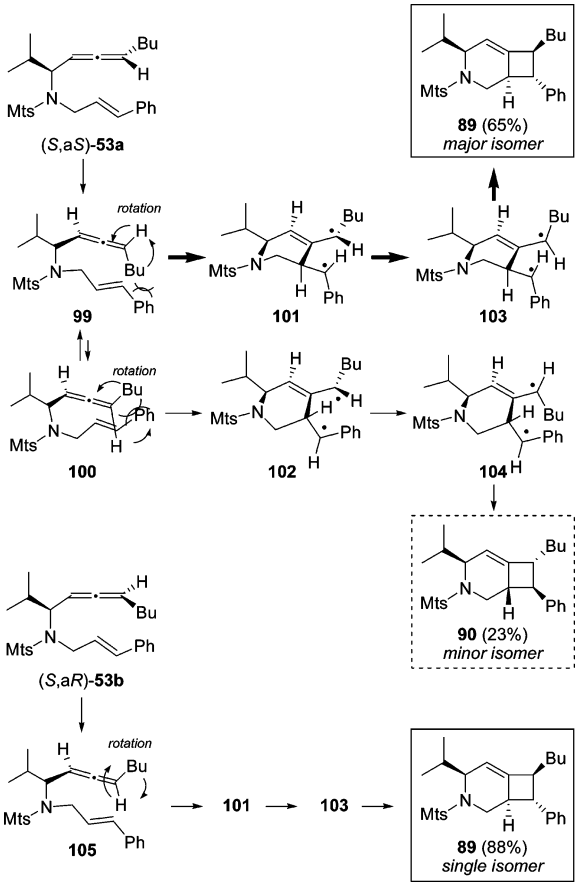


diastereomer **90** was also isolated in 23% yield. In sharp contrast, the reaction of the (*S*,a*R*)-isomer **53b** completed in 3 h to give **89** having the same configuration as the starting allenes. Thus, cycloadduct **89** was obtained as the favored product in both cases. These stereochemical outcomes strongly support the formation of biradical intermediates having a coplanar allyl radical moiety (*vide infra*). Assignment of the relative configuration of these adducts was readily made by NOE analysis shown in Figure 1.

Mechanism and Stereoselectivity of the Cycloaddition. Although the [2 + 2] thermal reactions of allenes are usually assumed to proceed via two steps including the participation of a biradical intermediate,[37,10,12,14b] a $\pi_{2a} + \pi_{2s}$ concerted process via antarafacial−suprafacial orbital interaction cannot be ruled out.[38] While the concerted process would result in a stereospecific cyclization, a stepwise reaction can also give cycloaddition products stereoselectively preserving the olefin geometry when the second cyclization process is more rapid than the bond rotation.[12b−d] Because the known cycloaddition reaction of allenenes proceeds in a stereospecific manner in many cases, it has not been unequivocally established from the aspect of product distribution of the cycloaddition whether the reactions are concerted or stepwise.[12] In contrast, our present study, including a novel finding on the stereospecificity of the alkene geometry and stereomutation of the allenic axial chirality, strongly supports the biradical mechanism.

First, stereoselective formation of the cycloadducts **96** from terminal allenes **91** is shown in Scheme 14. Among the two conformations **92** and **93** of the first cyclization, the latter would

SCHEME 15. Stereoselectivity on the Reaction of Internal Allenes 53



be destabilized by unfavorable steric interaction between methylene protons of the terminal allenic carbon and the R′ group at the olefin terminal. Accordingly, the first cyclization preferentially occurred through **92** to give a biradical intermediate **94**. Since the geometry of the olefin is completely preserved to yield the cycloadduct **96** without formation of **97** in all cases examined, the second cyclization would involve a rapid ring-closure before the bond rotation can occur. The fact that diastereomer **98** derived from relatively unstable conformer **93** was not detected from terminal allenes suggests that the energy difference between the two conformers **92** and **93** is significant in the case of terminal allenes.

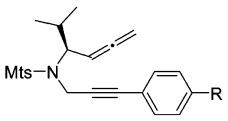
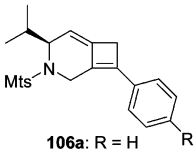
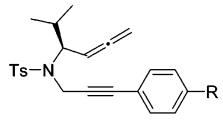
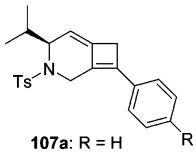
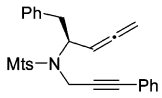
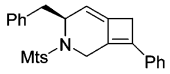
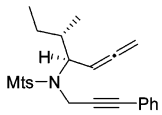
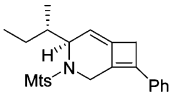
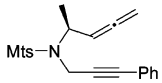
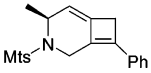
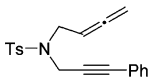
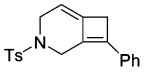
Stereoselectivity of the cycloaddition of internal allenes **53a** including partial stereomutation (Table 5, entry 5) can be rationalized as follows (Scheme 15): the first cyclization of the more abundant conformer **99** would give biradical intermediate **101**, in which the allyl radical moiety will have a coplanar structure by rotation of the terminal allenic bond.[39] At this stage, the butyl group directs the same side as the vinyl proton, avoiding the steric crowding, and information of the allenic axial chirality will be completely lost. The second cyclization would proceed through the conformation **103** to minimize the unfavorable steric interaction between the butyl and phenyl groups, giving rise to cyclobutane **89** as the major

(37) (a) Dolbier, W. R., Jr. *Acc. Chem. Res*. **1991**, *24*, 63−69. (b) Dai, S.-H.; Dolbier, W. R., Jr. *J. Am. Chem. Soc*. **1972**, *94*, 3946−3952. (c) Froese, R. D.; Lange, G. L.; Goddard, J. D. *J. Org. Chem*. **1996**, *61*, 952−961. (d) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165−166. (e) Yang, Y.; Petersen, J. L.; Wang, K. K. *J. Org. Chem*. **2003**, *68*, 8545−8549.

(38) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970.

(39) (a) Roth, W. R.; Ruf, G.; Ford, P. W. *Chem. Ber*. **1974**, *107*, 48−52. (b) Dolbier, W. R., Jr.; Wicks, G. E. *J. Am. Chem. Soc*. **1985**, *107*, 3626−3631. For a review, see: (c) Hartung, J.; Kopf, T. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley−VCH: Weinheim, 2004; Vol. 2, pp 701−726.

TABLE 6. [2 + 2] Cycloaddition of Allenynes[a]

entry	substrate	time (h)	product	yield (%)
1	 **54a**: R = H	2	 **106a**: R = H	92
2	**54b**: R = Me	4	**106b**: R = Me	94
3	 **57a**: R = H	3	 **107a**: R = H	70
4	**57b**: R = OMe	2	**107b**: R = OMe	61
5	**57c**: R = CO_2Me	2	**107c**: R = CO_2Me	67
6	 **60a**	8	 **108a**	91
7	 **60b**	3	 **108b**	93
8	 **60c**	54	 **108c**	75
9	 **66**	117	 **109**	94

[a] All reactions were carried out in dioxane under reflux.

product. In contrast to the terminal allenes **91**, the presence of a butyl group of (*S*,a*S*)-internal allene **53a** would partially destabilize the favorable conformer **99** of the first cyclization. Accordingly, both the prolonged reaction time required for the reaction of **53a** (15 h) and formation of the minor cycloadduct **90** through a relatively unfavorable conformer **100** are understandable. The lower reactivity of allenene **51** having a dimethyl group on the terminal allenic carbon as well as formation of cycloadduct **88** as a diastereomixture from this allenene (Table 5, entry 4) can be explained by the same reason. On the other hand, the (*S*,a*R*)-substrate **53b** exclusively gave cycloadduct **89** as the single isomer within 3 h (Table 5, entry 6). This result can be attributed to the predominance of the conformer **105** (Scheme 15) on the first cyclization, in which the butyl group directs the opposite side of the reacting alkene and would not destabilize this conformer.

[2 + 2] Cycloaddition of Allenynes. Finally, the thermal cycloaddition of allenynes was investigated (Table 6). In contrast to the cycloaddition of allenenes **8** which required 65 h in refluxed dioxane (Table 3, entry 1), the reaction of allenyne **54a** completed within 2 h under the identical reaction conditions to give cyclobutene derivative **106a** in 92% yield (entry 1). Similarly, cycloaddition of **54b** bearing a methyl substituent on the benzene ring afforded the corresponding cyclobutene derivative **106b** (entry 2). Next, the effect of electron-donating and -withdrawing substituents on the aryl group was investigated using N-tosylated analogues **57a**−**c** (entries 3−5). In all cases, the desired cycloadducts **107a**−**c** were obtained in 61−70% yield in 2−3 h. These results show that the effect of aryl substituents on the reactivity is not dramatic. Likewise as in the reaction of allenenes, the α-substituent of the allene has proven to be significantly important (entries 6−9): the reaction of allenynes **60a** and **60c** bearing a smaller substituent (benzyl and methyl group, respectively) at the α-position required longer reaction time (8 and 54 h, respectively). It should be clearly noted that the cycloaddition of α-unsubstituted allene derivative **66** required several days for completion of the reaction.

The relatively high reactivity of allenynes over allenenes is consistent with the observation of Pasto et al. on intermolecular [2 + 2] cycloaddition of allenes with a multiple bond.[40] They claimed that the difference of the reactivity comes from the relative changes in the heats of formation on going from the reactants to the intermediate biradicals and on to the products, because heat of formation of acetylene is considerably higher compared to that of ethene.

Conclusion

In conclusion, we have developed thermal [2 + 2] cycloaddition of allenenes or allenynes leading to bicyclo[4.2.0]octane derivatives in good to excellent yields. Interestingly, the reaction of terminal allenes afforded bicyclic cyclobutane derivatives in a highly stereoselective manner, while the cycloaddition of some internal allenes yielded a diastereomeric mixture of cycloadducts. Furthermore, the olefin geometry was completely transferred to the cycloadducts in all cases. These stereochemical outcomes can be rationalized by considering the formation of biradical intermediates with the allyl radical moiety having a coplanar structure. This study first demonstrated that the distal double bond of unactivated simple allenes can regioselectively undergo intramolecular [2 + 2] cycloaddition with an appropriately substituted multiple bond. This simple and environmentally benign process would extend the potential application of fused bicyclic cyclobutane derivatives in synthetic and medicinal chemistry.

Experimental Section

***N*-(2-Hydroxyethyl)-2,4,6-trimethyl-*N*-[(*E*)-3-phenylprop-2-enyl]phenylsulfonamide (15)**. To a mixture of **14** (3.00 g, 12.3 mmol) and K_2CO_3 (3.41 g, 24.7 mmol) in DMF (15 mL) was added (*E*)-cinnamyl bromide (2.92 g, 14.8 mmol), and the mixture was stirred at room temperature for 15 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (20:1 to 1:1) to give **15** (2.82 g, 64%): colorless oil; IR (KBr) cm^{-1} 3521 (OH), 1313 (SO_2N), 1149 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (br, 1H, OH), 2.29 (s, 3H, CMe), 2.64 (s, 6H, 2 × CMe), 3.40 (t, J = 5.6 Hz, 2H, 1-CH_2), 3.72 (dt, J = 5.6, 5.0 Hz, 2H, 2-CH_2), 4.00 (d, J = 6.9 Hz, 2H, 1′-CH_2), 6.00 (dt, J = 16.2, 6.9 Hz, 1H, 2′-H), 6.46 (d, J = 16.2 Hz, 1H, 3′-H), 6.96 (s, 2H, Ar), 7.23−7.30 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.9 (2C), 48.0, 49.3, 60.2, 123.8, 126.4 (2C), 128.0, 128.5 (2C), 132.1 (2C), 132.6, 134.3, 136.0, 140.2 (2C), 142.8; MS (FAB) *m*/*z* (%) 360 (MH^+, 30), 117 (100); HRMS (FAB) calcd for $C_{20}H_{26}NO_3S$ (MH^+) 360.1633; found 360.1628.

(40) Pasto, D. J.; Kong, W. *J. Org. Chem.* **1989**, *54*, 3215−3216.

General Procedure for Oxidation and Wittig Olefination of Alcohols: Synthesis of *N*-[(*Z*)-3-Bromo-3-methoxycarbonylprop-2-enyl]-2,4,6-trimethyl-*N*-[(*E*)-3-phenylprop-2-enyl]phenylsulfonamide (16). To a solution of **15** (2.30 g, 6.40 mmol) and Et_3N (4.46 mL, 32.0 mmol) in DMSO (12 mL) was added SO_3·Py (2.04 g, 12.8 mmol), and the mixture was stirred at room temperature for 1 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with 1 N HCl, water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give aldehyde as a yellow oil. To a solution of the aldehyde in $CHCl_3$ (50 mL) was added $Ph_3P{=}C(Br)CO_2Me$ (3.16 g, 7.65 mmol), and the mixture was stirred at room temperature for 15 h. After evaporation of solvent, the residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (20:1 to 5:1) to give **16** (1.47 g, 47%): pale yellow oil; IR (KBr) cm^{-1} 1732 (CO_2Me), 1321 (SO_2N), 1263 (CO_2Me), 1153 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H, CMe), 2.64 (s, 6H, 2 × CMe), 3.77 (s, 3H, OMe), 3.92 (d, J = 6.2 Hz, 2H, 1′-CH_2), 4.08 (d, J = 6.2 Hz, 2H, 1-CH_2), 6.00 (dt, J = 16.2, 6.2 Hz, 1H, 2′-H), 6.47 (d, J = 16.2 Hz, 1H, 3′-H), 6.97 (s, 2H, Ar), 7.23−7.33 (m, 6H, 2-H and Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.8 (2C), 47.1, 49.4, 53.4, 117.4, 123.0, 126.5 (2C), 128.0, 128.5 (2C), 132.1 (2C), 132.2, 135.2, 136.0, 140.3 (2C), 141.3, 143.0, 162.0; MS (FAB) *m*/*z* (%) 494 (MH^+, ^{81}Br, 15), 492 (MH^+, ^{79}Br, 19), 117 (100); HRMS (FAB) calcd for $C_{23}H_{27}BrNO_4S$ (MH^+, ^{79}Br) 492.0844; found 492.0816.

General Procedure for Reduction of α,β-Unsaturated Esters with DIBAL-H: Synthesis of *N*-[(*Z*)-3-Bromo-4-hydroxybut-2-enyl]-2,4,6-trimethyl-*N*-[(*E*)-3-phenylprop-2-enyl]phenylsulfonamide (17). To a solution of **16** (1.25 g, 2.54 mmol) in CH_2Cl_2 (15 mL) was added 0.94 M DIBAL-H in *n*-hexane (9.5 mL, 8.93 mmol) under dry ice−acetone cooling, and the mixture was stirred at 0 °C for 1 h. HCl (4 N) was added, and the aqueous solution was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (10:1 to 3:1). The crude product was recrystalized with *n*-hexane−Et_2O (1:1) to give **17** (997 mg, 85%): colorless crystals; mp 86−88 °C (*n*-hexane−Et_2O); IR (KBr) cm^{-1} 3504 (OH), 1313 (SO_2N), 1151 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CMe), 2.41 (br, 1H, OH), 2.62 (s, 6H, 2 × CMe), 3.89 (d, J = 6.9 Hz, 2H, 1′-CH_2), 3.99 (d, J = 6.2 Hz, 2H, 1-CH_2), 4.18 (s, 2H, 4-CH_2), 5.98 (dt, J = 16.2, 6.9 Hz, 1H, 2′-H), 6.13 (t, J = 6.2 Hz, 1H, 2-H), 6.48 (d, J = 16.2 Hz, 1H, 3′-H), 6.95 (s, 2H, Ar), 7.22−7.31 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.8 (2C), 46.3, 48.7, 67.7, 123.4, 124.6, 126.5 (2C), 127.9, 128.5 (2C), 129.5, 132.0 (2C), 132.6, 134.7, 136.2, 140.3 (2C), 142.8. Anal. Calcd for $C_{22}H_{26}BrNO_3S$: C, 56.90; H, 5.64; N, 3.02. Found: C, 56.90; H, 5.59; N, 2.97.

General Procedure for Reductive Allenylation of Brominated Allylic Alcohols: Synthesis of *N*-(Buta-2,3-dienyl)-2,4,6-trimethyl-*N*-[(*E*)-3-phenylprop-2-enyl]phenylsulfonamide (18). To a solution of **17** (500 mg, 1.08 mmol) and Et_3N (0.30 mL, 2.15 mmol) in THF (10 mL) was added MsCl (185 mg, 1.61 mmol) under dry ice−acetone cooling and the mixture was stirred at 0 °C for 1 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with 1 N HCl, water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. To a solution of the mesylate and $Pd(PPh_3)_4$ (37.3 mg, 0.032 mmol) in THF (10 mL) was added 1 M Et_2Zn in *n*-hexane (2.16 mL, 2.16 mmol) and the mixture was stirred at room temperature for 1 h. After adding saturated NH_4Cl, the mixture was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (50:1 to 10:1) to give **18** (270 mg, 68%): pale yellow oil; IR (KBr) cm^{-1} 1954 (C═C═C), 1317 (SO_2N), 1153 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H, CMe), 2.63 (s, 6H, 2 × CMe), 3.83 (dt, J = 7.4, 2.4 Hz, 2H, 1-CH_2), 3.97 (d, J = 6.6 Hz, 2H, 1′-CH_2), 4.73 (dt, J = 6.6, 2.4 Hz, 2H, 4-CH_2), 5.05 (tt, J = 7.4, 6.6 Hz, 1H, 2-H), 6.00 (dt, J = 15.9, 6.6 Hz, 1H, 2′-H), 6.45 (d, J = 15.9 Hz, 1H, 3′-H), 6.94 (s, 2H, Ar), 7.22−7.31 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9, 22.8 (2C), 44.4, 47.7, 76.0, 85.7, 123.6, 126.4 (2C), 127.8, 128.5 (2C), 131.9 (2C), 133.0, 134.4, 136.2, 140.2 (2C), 142.5, 209.7; MS (FAB) *m*/*z* (%) 368 (MH^+, 24), 117 (100); HRMS (FAB) calcd for $C_{22}H_{26}NO_2S$ (MH^+) 368.1684; found 368.1681.

General Procedure for Allene Formation by Crabbé Reaction: Synthesis of 4-[(*E*)-3-Phenylprop-2-enyloxy]buta-1,2-diene (20). To a mixture of paraformaldehyde (102 mg, 3.40 mmol) and CuBr (97.5 mg, 0.679 mmol) in dioxane (5 mL) were added **19** (234 mg, 1.36 mmol) and *i*-Pr_2NH (275 mg, 2.72 mmol), and the mixture was heated under reflux for 8 h. The mixture was cooled to room temperature and diluted with EtOAc. The insolubles were filtered off, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (20:1 to 10:1) to give **20** (198 mg, 78%): colorless oil; IR (KBr) cm^{-1} 1955 (C═C═C), 1080 (COC); ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (dt, J = 7.1, 2.4 Hz, 2H, 1-CH_2), 4.17 (d, J = 6.1 Hz, 2H, 1′-CH_2), 4.80 (dt, J = 6.6, 2.4 Hz, 2H, 4-CH_2), 5.28 (tt, J = 7.1, 6.6 Hz, 1H, 2-H), 6.29 (dt, J = 16.1, 6.1 Hz, 1H, 2′-H), 6.61 (d, J = 16.1 Hz, 1H, 3′-H), 7.20−7.41 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.8, 70.4, 75.7, 87.7, 125.8, 126.4 (2C), 127.6, 128.5 (2C), 132.6, 136.6, 209.3; MS (FAB) *m*/*z* (%) 193 (MLi^+, 38), 160 (100); HRMS (FAB) calcd for $C_{13}H_{14}LiO$ (MLi^+) 193.1205; found 193.1207.

General Procedure for Cinnamylation: Synthesis of Dimethyl 2-Buta-2,3-dienyl-2-[(*E*)-3-phenylprop-2-enyl]malonate (22). To a suspension of 60% NaH (23.5 mg, 0.586 mmol) in DMF (2 mL) was added **21** (72.0 mg, 0.391 mmol) under ice−water cooling, and the mixture was stirred at 0 °C for 0.5 h. (*E*)-Cinnamyl bromide (84.7 mg, 0.430 mmol) was added under ice−water cooling, and the mixture was stirred at 0 °C for 2 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (20:1 to 10:1) to give **22** (107 mg, 91%): colorless oil; IR (KBr) cm^{-1} 1955 (C═C═C), 1736 (CO_2Me), 1275 (CO_2Me); ^1H NMR (300 MHz, $CDCl_3$) δ 2.66 (dt, J = 8.1, 2.4 Hz, 2H, 1-CH_2), 2.84 (d, J = 7.6 Hz, 2H, 1′-CH_2), 3.73 (s, 6H, 2 × OMe), 4.69 (dt, J = 6.6, 2.4 Hz, 2H, 4-CH_2), 4.99 (tt, J = 8.1, 6.6 Hz, 1H, 2-H), 6.03 (dt, J = 15.6, 7.6 Hz, 1H, 2′-H), 6.44 (d, J = 15.6 Hz, 1H, 3′-H), 7.18−7.34 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 32.1, 36.2, 52.4 (2C), 58.1, 74.7, 84.1, 123.7, 126.2 (2C), 127.4, 128.5 (2C), 134.2, 137.0, 171.0 (2C), 210.1; MS (FAB) *m*/*z* (%) 301 (MH^+, 41), 117 (100); HRMS (FAB) calcd for $C_{18}H_{21}O_4$ (MH^+) 301.1440; found 301.1450.

General Procedure for Preparation of Ethanol Amine Derivatives: Synthesis of *N*-(2-Hydroxyethyl)-*N*-[(1*S*)-1-isopropylbuta-2,3-dienyl]-2,4,6-trimethylphenylsulfonamide (35). To a mixture of **12** (500 mg, 1.70 mmol) and K_2CO_3 (824 mg, 5.96 mmol) in DMF (5 mL) was added $BrCH_2CH_2OTHP$ (891 mg, 4.26 mmol) and the mixture was stirred at 80 °C for 20 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. To the residue in MeOH (5 mL) was added 4 N HCl (0.5 mL), and the mixture was stirred at room temperature for 1 h. The solution was diluted with water and extracted with EtOAc. The organic layer was separated, washed with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (50:1 to 1:1) to give **35** (500 mg, 87%): colorless oil; $[\alpha]^{26}_D$ −84.7 (*c* 1.035, $CHCl_3$); IR (KBr) cm^{-1} 3527 (OH), 1955 (C═C═C), 1321 (SO_2N), 1151 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.8 Hz, 3H, CMe), 0.88 (d, J = 6.3 Hz, 3H, CMe), 1.80−1.88 (m, 1H, C*H*Me_2), 2.30 (s, 3H, CMe), 2.39 (br, 1H, OH), 2.63 (s, 6H, 2 × CMe), 3.38 (t, J = 6.6 Hz,

2H, 1′-CH_2), 3.61 (ddt, J = 8.1, 8.1, 2.0 Hz, 1H, 1-H), 3.64−3.82 (m, 2H, 2′-CH_2), 4.68 (dd, J = 6.8, 2.0 Hz, 2H, 4-CH_2), 5.16 (dt, J = 8.1, 6.8 Hz, 1H, 2-H), 6.95 (s, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.0, 20.7, 20.9, 23.4 (2C), 30.7, 46.0, 61.9, 63.2, 76.2, 88.3, 132.1 (2C), 133.0, 140.1 (2C), 142.5, 209.1; MS (FAB) *m*/*z* (%) 338 (MH^+, 14), 244 (100); HRMS (FAB) calcd for $C_{18}H_{28}NO_3S$ (MH^+) 338.1790; found 338.1793.

General Procedure for Oxidation and Alkynylation of Alcohols: Synthesis of *N*-(2-Hydroxy-1,1-dimethylbut-3-ynyl)-4-methylphenylsulfonamide (47a). To a stirred mixture of **30** (2.50 g, 10.3 mmol) and Et_3N (7.16 mL, 51.4 mmol) in DMSO (20 mL) was added SO_3·Py (3.27 g, 20.5 mmol) under water cooling, and the mixture was stirred at room temperature for 1 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with 1 N HCl, water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give aldehyde as a yellow oil. To a solution of trimethylsilylacetylene (1.83 mL, 13.0 mmol) in THF (15 mL) was added 1.5 M *n*-BuLi in *n*-hexane (16.0 mL, 24.0 mmol) under dry ice−acetone cooling, and the mixture was stirred at −78 °C for 0.5 h. The aldehyde (2.41 g, 9.99 mmol) in THF (5 mL) was added, and the mixture was stirred at −78 °C for 1 h. The mixture was partitioned between EtOAc and saturated NH_4Cl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. To the residue in MeOH (30 mL) was added MeONa (54.0 mg, 0.999 mmol), and the mixture was stirred at room temperature for 15 h. After evaporation of solvent, the residue was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (20:1 to 1:1). The crude product was recrystalized with *n*-hexane−EtOAc (2:1) to give **47a** (2.03 g, 72%): colorless crystals; mp 127−128 °C (*n*-hexane−EtOAc); IR (KBr) cm^{-1} 3487 (OH), 3296 (C≡CH), 3271 (SO_2NH), 2117 (C≡CH), 1319 (SO_2N), 1157 (SO_2N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H, CMe), 1.26 (s, 3H, CMe), 2.43 (s, 3H, CMe), 2.51 (d, J = 2.2 Hz, 1H, 4-CH), 2.77 (br, 1H, OH), 4.28 (m, 1H, 2-H), 5.07 (br, 1H, NH), 7.30 (d, J = 8.2 Hz, 2H, Ar), 7.80 (d, J = 8.2 Hz, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5, 22.6, 23.5, 59.7, 69.4, 75.3, 81.4, 127.1 (2C), 129.6 (2C), 139.6, 143.4. Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.24. Found: C, 58.22; H, 6.33; N, 5.22.

General Procedure for Allenylation of Propargyl Alcohols: Synthesis of *N*-(1,1-Dimethylpenta-2,3-dienyl)-4-methylphenylsulfonamide (48a). To a solution of **47a** (887 mg, 3.32 mmol), Et_3N (671 mg, 6.64 mmol) in THF (10 mL) was added MsCl (570 mg, 4.98 mmol) under ice−water cooling, and the mixture was stirred at 0 °C for 1 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to give the corresponding mesylate as a yellow oil. To a solution of 1 M MeMgBr in THF (15 mL, 15 mmol) in THF (10 mL) was added CuBr (1.89 g, 13.2 mmol) under dry ice−acetone cooling, and the mixture was stirred at −20 °C for 0.5 h. The mesylate in THF (5 mL) was added under dry ice−acetone cooling, and the mixture was stirred at −78 °C for 0.5 h and at 0 °C for 0.5 h. The mixture was partitioned between EtOAc and saturated NH_4Cl. The organic layer was separated, washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (50:1 to 5:1) to give **48a** (581 mg, 66%): colorless oil; IR (KBr) cm^{-1} 3271 (SO_2NH), 1963 (C=C=C), 1321 (SO_2N), 1144 (SO_2N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 6H, 2 × CMe), 1.64 (dd, J = 7.0, 3.1 Hz, 3H, 5-CH_3), 2.42 (s, 3H, CMe), 4.69 (br, 1H, NH), 5.09 (dq, J = 6.4, 3.1 Hz, 1H, 2-H), 5.23 (dq, J = 7.0, 6.4 Hz, 1H, 4-H), 7.27 (d, J = 8.2 Hz, 2H, Ar), 7.76 (d, J = 8.2 Hz, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0, 21.4, 28.6, 28.8, 55.5, 89.6, 98.6, 127.1 (2C), 129.3 (2C), 140.2, 142.7, 202.0; MS (FAB) *m*/*z* (%) 266 (MH^+, 39), 95 (100); HRMS (FAB) calcd for $C_{14}H_{20}NO_2S$ (MH^+) 266.1215 found 266.1221.

General Procedure for Sonogashira Cross-Coupling: Synthesis of *N*-[(1*S*)-1-Isopropylbuta-2,3-dienyl]-*N*-[3-(4-methoxyphenyl)prop-2-ynyl]-4-methylphenylsulfonamide (57b). To a suspension of 4-iodoanisole (425 mg, 1.82 mmol), $Pd(PPh_3)_2Cl_2$ (12.7 mg, 0.0185 mmol), CuI (1.40 mg, 0.00726 mmol), and *i*-Pr_2-NH (0.0509 mL, 0.363 mmol) in THF (2 mL) was added **58** (110 mg, 0.363 mmol) in THF (1 mL) under ice−water cooling, and the mixture was stirred at 0 °C for 6 h. $Pd(PPh_3)_2Cl_2$ (12.7 mg, 0.0185 mmol) and CuI (3.5 mg, 0.0185 mmol) were added, and the mixture was stirred at room temperature for 1 h. The insolubles were filtered off and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (15:1) to give **57b** (36.5 mg, 25%): yellow oil; $[\alpha]^{26}_D$ −11.5 (*c* 0.560, $CHCl_3$); IR (KBr) cm^{-1} 2251 (C≡C), 1955 (C=C=C), 1329 (SO_2N), 1147 (SO_2N), 1200 (ArOMe); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H, CMe), 1.05 (d, J = 6.6 Hz, 3H, CMe), 1.96−2.05 (m, 1H, C*H*Me_2), 2.36 (s, 3H, CMe), 3.80 (s, 3H, OMe), 4.07 (dddd, J = 8.3, 6.8, 1.7, 1.7 Hz, 1H, 1-H), 4.16 (d, J = 18.6 Hz, 1H, 1′-C*H*H), 4.31 (d, J = 18.6 Hz, 1H, 1′-CH*H*), 4.56 (ddd, J = 11.0, 6.6, 1.7 Hz, 1H, 4-C*H*H), 4.67 (ddd, J = 11.0, 6.6, 1.7 Hz, 1H, 4-CH*H*), 5.07 (ddd, J = 6.8, 6.6, 6.6 Hz, 1H, 2-H), 6.80 (d, J = 6.6 Hz, 2H, Ar), 7.15 (d, J = 6.6 Hz, 2H, Ar), 7.20 (d, J = 6.6 Hz, 2H, Ar), 7.80 (d, J = 6.6 Hz, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.1, 20.4, 21.5, 30.8, 33.8, 55.3, 64.1, 76.1, 83.5, 84.2, 88.2, 113.8 (2C), 114.8, 127.8 (2C), 129.2 (2C), 132.8 (2C), 137.9, 143.0, 159.5, 209.0; MS (FAB) *m*/*z* (%) 410 (MH^+, 23), 73 (100); HRMS (FAB) calcd for $C_{24}H_{28}NO_3S$ (MH^+) 410.1790; found 410.1803.

General Procedure for Mitsunobu Condensation: Synthesis of *N*-(Buta-2,3-dienyl)-4-methyl-*N*-(3-phenylprop-2-ynyl)phenylsulfonamide (66). To a solution of **65** (130 mg, 0.582 mmol), $HOCH_2C$≡CPh (0.22 mL, 1.75 mmol), PPh_3 (458 mg, 1.75 mmol) in THF (3 mL) was added DIAD (0.34 mL, 1.75 mmol) under ice−water cooling, and the mixture was stirred at 0 °C for 7 h. After evaporation of solvent, the residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (10:1) to give **66** (176 mg, 89%): colorless crystals; mp 64−65 °C (*n*-hexane−Et_2O); IR (KBr) cm^{-1} 2243 (C≡C), 1955 (C=C=C), 1348 (SO_2N), 1163 (SO_2N); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H, CMe), 3.93 (dt, J = 6.7, 2.4 Hz, 2H, 1-CH_2), 4.37 (s, 2H, 1′-CH_2), 4.80 (dt, J = 7.3, 2.4 Hz, 2H, 4-CH_2), 5.11 (tt, J = 7.3, 6.7 Hz, 1H, 2-H), 7.09 (d, J = 8.5 Hz, 2H, Ar), 7.22−7.29 (m, 5H, Ar), 7.77 (d, J = 8.5 Hz, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4, 36.8, 45.9, 76.4, 81.6, 85.6 (2C), 122.2, 127.7 (2C), 128.1 (2C), 128.3, 129.5 (2C), 131.5 (2C), 136.0, 143.5, 209.9. Anal. Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.01; H, 5.73; N, 4.14.

General Procedure for [2 + 2] Cycloaddition of Allenenes: Synthesis of (1*R*,4*S*,8*S*)-3-Aza-4-isopropyl-8-phenyl-3-(2,4,6-trimethylphenylsulfonyl)bicyclo[4.2.0]oct-5-ene (11a). A solution of (*E*)-**8** (30.0 mg, 0.073 mmol) in DMF (1 mL) was stirred at 150 °C for 3 h. The mixture was partitioned between EtOAc and water. The organic layer was separated, washed with water and brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (50:1 to 20:1) to give **11a** (28.7 mg, 96%): colorless oil; $[\alpha]^{26}_D$ +110 (*c* 1.025, $CHCl_3$); IR (KBr) cm^{-1} 1319 (SO_2N), 1146 (SO_2N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H, CMe), 0.89 (d, J = 6.9 Hz, 3H, CMe), 1.74−1.82 (m, 1H, C*H*Me_2), 2.28 (s, 3H, CMe), 2.60 (s, 6H, 2 × CMe), 2.82 (dd, J = 13.1, 10.8 Hz, 1H, 2-C*H*H), 2.96−3.11 (m, 4H, 1-H, 7-CH_2 and 8-H), 3.96−4.04 (m, 2H, 2-CH*H* and 4-H), 5.49 (d, J = 1.9 Hz, 1H, 5-H), 6.93 (s, 2H, Ar), 7.12 (d, J = 6.9 Hz, 2H, Ar), 7.17−7.31 (m, 3H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 19.8, 20.9, 22.8 (2C), 34.0, 39.8, 43.9, 44.7, 46.9, 58.8, 111.9, 126.4 (3C), 128.4 (2C), 131.9 (2C), 134.0, 138.3, 140.0 (2C), 142.2, 143.0; MS (FAB) *m*/*z* (%) 410 (MH^+, 56), 366 (100); HRMS (FAB) calcd for $C_{25}H_{32}NO_2S$ (MH^+) 410.2154; found 410.2156.

(1*R*,4*S*,8*R*)-3-Aza-4-isopropyl-8-phenyl-3-(2,4,6-trimethylphenylsulfonyl)bicyclo[4.2.0]oct-5-ene (67). A solution of (*Z*)-**8**

(50.0 mg, 0.122 mmol) in dioxane (2 mL) was heated under reflux for 65 h. After evaporation of solvent, the residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (30:1) to give **67** (31.5 mg, 63%): colorless oil; $[\alpha]^{24}_D$ +42.9 (*c* 1.00, $CHCl_3$); IR (KBr) cm^{-1} 1317 (SO_2N), 1146 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (d, J = 7.1 Hz, 3H, CMe), 0.76 (d, J = 6.8 Hz, 3H, CMe), 1.57−1.64 (m, 1H, C*H*Me_2), 2.10 (dd, J = 13.2, 10.3 Hz, 1H, 2-C*H*H), 2.29 (s, 3H, CMe), 2.54 (s, 6H, 2 × CMe), 2.89 (d, J = 14.4 Hz, 1H, 7-C*H*H), 3.23−3.40 (m, 3H, 1-H, 7-CH*H* and 8-H), 3.72 (ddd, J = 13.2, 9.3, 2.7 Hz, 1H, 2-CH*H*), 3.90 (m, 1H, 4-H), 5.54 (d, J = 1.7 Hz, 1H, 5-H), 6.91 (s, 2H, Ar), 7.17−7.31 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8, 19.7, 20.9, 22.8 (2C), 33.9, 36.2, 40.1, 40.4, 43.1, 58.6, 112.8, 126.6, 127.3 (2C), 128.3 (2C), 131.8 (2C), 134.0, 139.6, 140.0 (2C), 140.7, 142.1; MS (FAB) *m*/*z* (%) 410 (MH^+, 54), 366 (100); HRMS (FAB) calcd for $C_{25}H_{32}NO_2S$ (MH^+) 410.2154; found 410.2162.

General Procedure Hydrogenation of Cycloadducts: Synthesis of (1*S*,4*R*,6*R*,8*S*)-3-Aza-4-isopropyl-8-phenyl-3-(2,4,6-trimethylphenylsulfonyl)bicyclo[4.2.0]octane (68). A mixture of **11a** (119 mg, 0.291 mmol) and 10% Pd/C (12 mg) in MeOH (3 mL) was stirred under 1 atm H_2 at room temperature for 2 h. The catalyst was filtered off, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with *n*-hexane−EtOAc (50:1 to 20:1) to give **68** (90.0 mg, 75%): colorless oil; $[\alpha]^{25}_D$ +82.2 (*c* 1.105, $CHCl_3$); IR (KBr) cm^{-1} 1317 (SO_2N), 1149 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, J = 7.1 Hz, 3H, CMe), 0.86 (d, J = 6.8 Hz, 3H, CMe), 1.60−1.69 (m, 2H, C*H*Me_2 and 5-C*H*H), 1.90 (ddd, J = 13.4, 5.6, 5.6 Hz, 1H, 5-CH*H*), 2.07−2.14 (m, 1H, 7-C*H*H), 2.28 (s, 3H, CMe), 2.31−2.39 (m, 2H, 6-H and 7-CH*H*), 2.62 (s, 6H, 2 × CMe), 2.88−3.00 (m, 1H, 1-H), 3.00 (dd, J = 13.4, 10.5 Hz, 1H, 2-C*H*H), 3.28−3.38 (m, 1H, 8-H), 3.67 (ddd, J = 5.9, 5.6, 5.4 Hz, 1H, 4-H), 3.95 (dd, J = 13.4, 7.1 Hz, 1H, 2-CH*H*), 6.91 (s, 2H, Ar), 7.13−7.20 (m, 3H, Ar), 7.22−7.30 (m, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.0, 19.1, 20.9, 22.9 (2C), 24.3, 26.2, 31.8, 32.6, 39.5, 43.5, 45.6, 58.0, 125.9, 126.3 (2C), 128.3 (2C), 131.8 (2C), 133.9, 139.9 (2C), 142.1, 144.6; MS (FAB) *m*/*z* (%) 412 (MH^+, 70), 368 (100); HRMS (FAB) calcd for $C_{25}H_{34}NO_2S$ (MH^+) 412.2310; found 412.2300.

(1*R*,4*S*,7*S*,8*S*)-3-Aza-7-butyl-4-isopropyl-8-phenyl-3-(2,4,6-trimethylphenylsulfonyl)bicyclo[4.2.0]oct-5-ene (89) and Its (1*S*,4*S*,7*R*,8*R*)-Isomer (90). By a procedure identical with that described for the synthesis of **11a**, **53a** (50.0 mg, 0.107 mmol) was converted into **89** (32.5 mg, 65%) and **90** (11.5 mg, 23%).

Compound **89**: colorless oil; $[\alpha]^{25}_D$ +61.3 (*c* 1.04, $CHCl_3$); IR (KBr) cm^{-1} 1321 (SO_2N), 1151 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (d, J = 6.8 Hz, 3H, CMe), 0.83 (t, J = 6.8 Hz, 3H, $(CH_2)_3CH_3$), 0.89 (d, J = 6.8 Hz, 3H, CMe), 1.23−1.29 (m, 4H, $(CH_2)_2CH_3$), 1.54−1.60 (m, 1H, (C*H*H)C_3H_7), 1.68−1.75 (m, 1H, (CH*H*)C_3H_7), 1.75−1.84 (m, 1H, C*H*Me_2), 2.29 (s, 3H, CMe), 2.55 (dd, J = 8.1, 8.1 Hz, 1H, 8-H), 2.59 (s, 6H, 2 × CMe), 2.77 (dd, J = 12.7, 10.0 Hz, 1H, 2-C*H*H), 2.82−2.88 (m, 1H, 1-H), 3.15−3.27 (m, 1H, 7-H), 3.93 (dd, J = 12.7, 5.9 Hz, 1H, 2-CH*H*), 3.99−4.03 (m, 1H, 4-H), 5.48 (d, J = 2.2 Hz, 1H, 5-H), 6.92 (s, 2H, Ar), 7.09−7.22 (m, 3H, Ar), 7.25−7.31 (m, 2H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 18.8, 19.8, 20.9, 22.8 (3C), 29.8, 32.9, 34.1, 44.5, 44.8, 50.7, 53.9, 58.5, 110.1, 126.4, 126.8 (2C), 128.4 (2C), 131.9 (2C), 133.9, 140.0 (2C), 142.1, 142.7, 144.3; MS (FAB) *m*/*z* (%) 466 (MH^+, 74), 422 (100); HRMS (FAB) calcd $C_{29}H_{40}NO_2S$ (MH^+) 466.2780; found 466.2794.

Compound **90**: colorless oil; $[\alpha]^{22}_D$ +3.78 (*c* 0.570, $CHCl_3$); IR (KBr) cm^{-1} 1321 (SO_2N), 1151 (SO_2N); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, J = 6.8 Hz, 3H, CMe), 0.85 (d, J = 6.8 Hz, 3H, CMe), 0.86 (t, J = 6.8 Hz, 3H, $(CH_2)_3CH_3$), 1.10−1.28 (m, 4H, $(CH_2)_2CH_3$), 1.40−1.51 (m, 1H, (C*H*H)C_3H_7), 1.60−1.70 (m, 1H, (CH*H*)C_3H_7), 1.86−1.94 (m, 1H, C*H*Me_2), 2.24 (dd, J = 8.5, 8.3 Hz, 1H, 8-H), 2.31 (s, 3H, CMe), 2.63 (s, 6H, 2 × CMe), 2.78−2.84 (m, 1H, 1-H), 3.04−3.10 (m, 1H, 7-H), 3.33 (dd, J = 13.4, 3.2 Hz, 1H, 2-C*H*H), 3.43 (dd, J = 13.4, 7.3 Hz, 1H, 2-CH*H*), 3.89 (dd, J = 8.3, 6.6 Hz, 1H, 4-H), 5.89 (dt, J = 6.6, 2.4 Hz, 1H, 5-H), 6.95 (s, 2H, Ar), 7.08 (d, J = 6.8 Hz, 2H, Ar), 7.19−7.31 (m, 3H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 18.8, 20.2, 20.9, 22.7, 23.2 (2C), 29.8, 32.4, 32.5, 42.4, 46.0, 50.4, 52.8, 58.9, 115.7, 126.5, 126.8 (2C), 128.4 (2C), 131.9 (2C), 134.1, 139.8 (2C), 142.0, 142.4, 143.3; MS (FAB) *m*/*z* (%) 466 (MH^+, 67), 422 (100); HRMS (FAB) calcd for $C_{29}H_{40}NO_2S$ (MH^+) 466.2780; found 466.2787.

General Procedure for [2 + 2] Cycloaddition of Allenynes: Synthesis of (4*S*)-3-Aza-4-isopropyl-8-phenyl-3-(2,4,6-trimethylphenylsulfonyl)bicyclo[4.2.0]octa-1(8),5-diene (106a). By a procedure identical with that described for the synthesis of **67**, **54a** (50.5 mg, 0.124 mmol) was converted into **106a** (46.6 mg, 92%): yellow oil; $[\alpha]^{25}_D$ −74.3 (*c* 0.655, $CHCl_3$); IR (KBr) cm^{-1} 1323 (SO_2N), 1159 (SO_2N); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (d, J = 6.7 Hz, 3H, CMe), 0.95 (d, J = 6.7 Hz, 3H, CMe), 1.98−2.05 (m, 1H, C*H*Me_2), 2.25 (s, 3H, CMe), 2.59 (s, 6H, 2 × CMe), 3.25 (dd, J = 13.4, 3.7 Hz, 1H, 7-C*H*H), 3.29 (ddd, J = 13.4, 3.7, 3.7 Hz, 1H, 7-CH*H*), 3.98 (dd, J = 7.9, 4.9 Hz, 1H, 4-H), 4.14 (ddd, J = 17.7, 3.7, 3.7 Hz, 1H, 2-C*H*H), 4.66 (d, J = 17.7 Hz, 1H, 2-CH*H*), 5.44 (d, J = 4.9 Hz, 1H, 5-H), 6.88 (s, 2H, Ar), 7.18−7.35 (m, 5H, Ar); ^{13}C NMR (75.5 MHz, CDCl3) δ 19.1, 20.4, 20.9, 23.1 (2C), 34.5, 35.9, 39.8, 59.6, 109.0, 126.2 (2C), 127.8, 128.6 (2C), 131.9 (2C), 133.4, 134.2 (2C), 136.2, 138.7, 139.9 (2C), 142.0; MS (FAB) *m*/*z* (%) 408 (MH^+, 12), 119 (100); HRMS (FAB) calcd for $C_{25}H_{30}NO_2S$ (MH^+) 408.1997; found 408.1972.

Acknowledgment. We thank Dr. S. Aoki, Graduate School of Pharmaceutical Sciences, Osaka University, for NMR analyses. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Mitsubishi Chemical Corporation Fund, which are gratefully acknowledged.

Supporting Information Available: Synthetic procedure, characterization, and ^1H NMR for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

JO0700528