Asymmetric Synthesis

Acetylenic Allenophanes: An Asymmetric Synthesis of a Bis(alleno)-bis(butadiynyl)-*meta*-cyclophane**

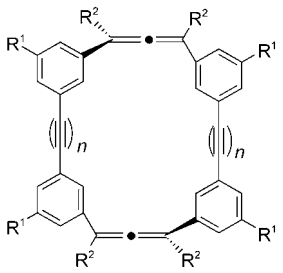
*Matthew D. Clay and Alex G. Fallis**

We have an ongoing interest in the design and synthesis of novel cyclophanes, many of which contain a twisted conformation that imparts helical chirality[1] to the assembled molecule.[2] This helical chirality is a consequence of the number, type, and combination of unsaturated linkages present in these molecules. The synthesis and design of cyclophanes[3] and cage compounds with high carbon content in novel shapes and supramolecular geometries[4] continues to be a topic of current interest.

Allenes are a unique family of organic molecules because of their diverse chemistry, axial chirality, and synthetic versatility,[5] and so investigations into allene-containing natural products and their total syntheses continue to increase.[6] Furthermore, medical applications for these compounds include employing them as inactivators of monoamine oxidase.[7]

In contrast, cyclophanes that have only allene bridges (termed allenophanes)[8] have received little attention and the only reported example was prepared as a mixture of diastereomers.[8] A related family of cyclophanes comprises structures that contain both allene and acetylene bridges. These acetylenic allenophanes should also possess interesting properties. Herein, we report the first asymmetric synthesis of an acetylenic allenophane that contains two allene bridges. This compound appears to be the first cyclophane of this general class.

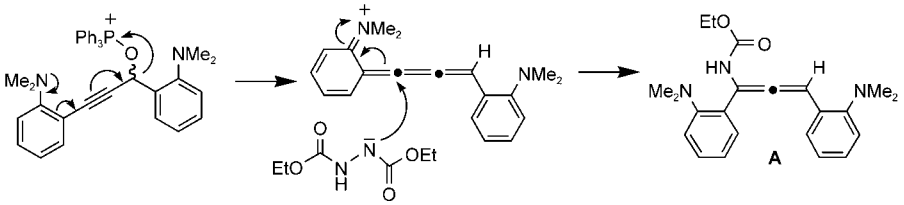
The general structure of an acetylenic allenophane is depicted in Scheme 1. The R^1 substituents aid solubility: the absence of similar groups in the previously prepared allenophane[8] limited its solubility and prevented a full investigation into its properties. The R^2 substituents may be hydrogen atoms or alkyl groups, depending on the method selected to synthesize the allene moiety. The number of acetylene bridges may also be varied.



Scheme 1. An acetylenic allenophane.

We devised a strategy to an acetylenic allenophane related to **16** based on the dimerization of desilylated **15** (see Scheme 4). We[9a] and others[9b] observed previously that the separation of the alkyne termini dictates whether the intra- or intermolecular product dominates. Molecular modeling studies have strongly suggested that the intermolecular product is favored when the termini separation is greater than 7 Å.[9c] In the case of **15**, the calculated alkyne separation of 8.87 Å[10] indicated that the intramolecular product **16** should be preferred.

We initially examined the allene preparation used by Myers and Zheng for the synthesis of an allenophane in which R^2 groups are hydrogen atoms (Scheme 1).[11] This asymmetric method had the advantage that the allene precursor, a secondary propargyl alcohol, was readily available through the addition of an acetylide to an aldehyde.[12] Initially, *ortho*-amino substituents at the aryl ring were chosen to aid solubility, but this idea had to be abandoned because electron donation from the lone pair of electrons on the nitrogen atom in the *ortho*-amino substituent leads to the formation of cumulene-type intermediates during allene formation (Scheme 2), and so *tert*-butyl groups were selected instead.



Scheme 2. Proposed mechanism for the formation of allene **A** because of *ortho*-amino aryl substituents.

Unfortunately, the procedure of Myers and Zheng afforded a disappointing yield of 18%.

An attractive alternative for the generation of asymmetric allenes employs an S_N2' addition of an organocuprate to a propargyl acetate.[13] This method allows fully substituted allenes to be synthesized, but requires the asymmetric synthesis of a tertiary propargyl alcohol. Reported methods for the preparation of this species are limited to examples that utilize the asymmetric addition of a zinc acetylide to a ketone[14] or the asymmetric addition of an alkyl zinc to a ketone.[15] Unfortunately, the asymmetric addition of dimethylzinc to the ketone precusor of **13** failed (see Scheme 4).

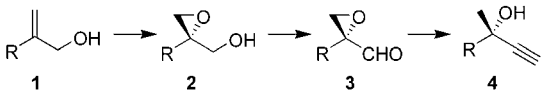
[*] M. D. Clay, Prof. Dr. A. G. Fallis
Department of Chemistry
University of Ottawa
10 Marie Curie, Ottawa, Ontario, K1N 6N5 (Canada)
Fax: (+1) 613-562-5170
E-mail: afallis@science.uottawa.ca

[**] We are grateful to the National Sciences and Engineering Research Council of Canada (NSERC) for financial support of this research. We thank H. Foucault and L. Barriault (University of Ottawa) for assistance with the molecular modeling studies. M.D.C. also thanks the NSERC, OGS, and University of Ottawa for graduate scholarships.

 DOI: 10.1002/anie.200500484

Similarly, the combination of the zinc acetylide to the appropriate acetophenone to generate **13** directly was also unsuccessful. This failure was likely due to the steric encumbrance of the *tert*-butyl solubilizing groups as well as the inherent poor electrophilicity of the ketones employed. Consequently, a new strategy was developed to construct these tertiary propargyl alcohols.

We designed a method in which the requisite stereogenic centers could be installed by using a Sharpless asymmetric epoxidation (Scheme 3). Oxidation of epoxy alcohol **2** should

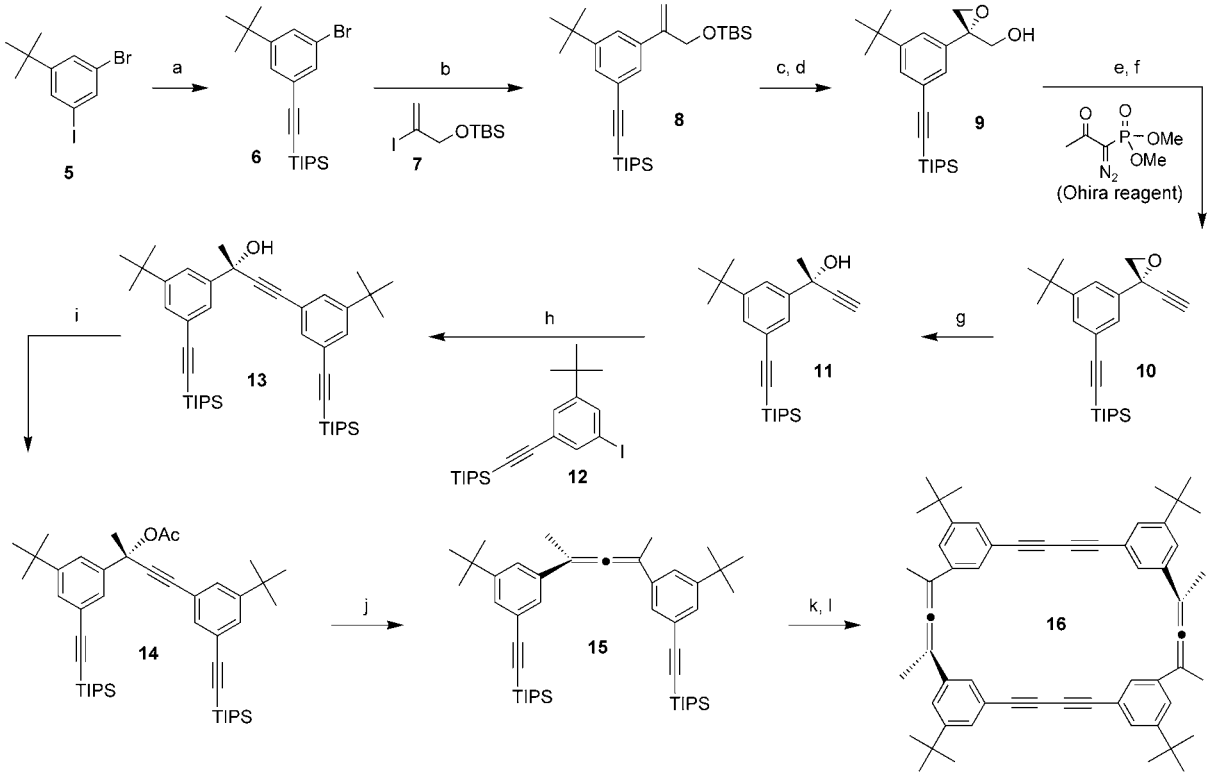


Scheme 3. An asymmetric synthetic route to tertiary propargyl alcohols.

afford the desired aldehyde **3**, which upon exposure to the reagent developed by Ohira[16] would give an epoxy alkyne that could undergo ring opening with a suitable hydride reagent to yield the desired tertiary propargyl alcohol **4**. The synthetic pathway that was developed is given in Scheme 4.

A Sonogashira coupling between 1-bromo-3-iodo-5-*tert*-butylbenzene (**5**)[17] and (triisopropylsilyl)acetylene smoothly generated aryl bromide **6** in 99% yield. A lithium–halogen exchange followed by quenching of the resulting anion with zinc bromide generated an organozinc intermediate, which was coupled with vinyl iodide **7**[18] to generate the *tert*-butyldimethylsilyl (TBS) ether **8**, also in 99% yield. Selective cleavage of the TBS group followed by Sharpless asymmetric epoxidation of the allylic alcohol provided the allylic epoxy alcohol **9** in 93% yield (88% *ee*).[19] Initially, the ring opening of **9** was examined with various aluminum hydride reagents. In each case, the epoxide was cleaved readily, however, despite a literature precedent[20] the resulting diol was partially racemized. This occurred presumably through a Payne rearrangement[21] of the epoxy alcohol. Therefore, the ring opening of the epoxide was postponed until a later stage in the synthesis.

Oxidation of **9** with the Dess–Martin periodinane gave an aldehyde in 89% yield, which was subsequently converted into a terminal alkyne with the Ohira reagent (93%). The epoxide in **10** was opened cleanly on exposure to L-selectride to provide tertiary propargyl alcohol **11**, and no lowering of enantiomeric excess was detected (HPLC analysis). This sequence for the conversion of an epoxide into a tertiary



Scheme 4. Synthesis of acetylenic allenophane **16**. Reagents and conditions: a) (triisopropylsilyl)acetylene, $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, THF, RT, 16 h (99%); b) 1. **6**, *t*BuLi, THF, −78°C, 5 min; 2. $ZnBr_2$, THF, −78→0°C, 30 min; 3. **7**, $[Pd(PPh_3)_4]$, THF, RT, 16 h, (99%); c) 10% HCl, THF, RT, 4 h (79%); d) $[Ti(O\mathit{i}Pr)_4]$, L-DIPT, *t*BuOOH, 4-Å molecular sieves, CH_2Cl_2, −50→20°C, 16 h (93%, 88% *ee*); e) Dess–Martin periodinane, CH_2Cl_2, RT, 30 min (89%); f) Ohira reagent, K_2CO_3, MeOH, 0°C→RT, 90 min (93%); g) L-selectride, THF, 0°C, 10 min (88%); h) **12**, $[PdCl_2(PPh_3)_2]$, CuI, Et_3N, THF, RT, 16 h (51%); i) Ac_2O, DMAP, pyridine, CH_2Cl_2, RT, 24 h (85%); j) CH_3MgBr, LiBr, CuI, THF, 0°C, 2 h (74%); k) TBAF, THF, 0°C, 10 min (98%); l) addition of **15** to a solution of $Cu(OAc)_2$ in pyridine/diethyl ether (3:1) over 6 h, RT, total time: 8 h (40%). L-DIPT = diisopropyl L-tartrate, L-selectride = lithium tri-*sec*-butylborohydride, DMAP = 4-dimethylaminopyridine, TBAF = tetrabutylammonium fluoride, TIPS = triisopropylsilyl, Ac = acetyl.

propargyl alcohol was easily completed within one day in an overall yield of 73%. A Sonogashira reaction between **11** and aryl iodide **12** (prepared through a lithium–halogen exchange of **6** followed by quenching with iodine) generated the propargyl alcohol **13** in 51% yield. A modification of the standard Sonogashira coupling conditions failed to increase the yield.[22]

Acetylization of **13** with acetic anhydride gave acetate **14** in 85% yield. As anticipated, (*S*)-allene **15** was formed through the addition of **14** to the organocuprate generated from a mixture of CH_3MgBr, LiBr, and CuI (74% yield). Removal of the triisopropylsilyl groups with TBAF generated the terminal bisalkyne **15** in 98% yield with 83% *ee*. This indicated that there was minimal racemization during generation of the allene. The slow addition of (*S*)-**15** to a solution of $Cu(OAc)_2$ in pyridine and diethyl ether afforded the desired (*S*,*S*)-acetylenic allenophane **16** in 40% yield. The desilylation–dimerization sequence could also be conducted in a one-pot procedure, but the isolation of **16** was more difficult because of the presence of several highly fluorescent impurities. Unfortunately, crystals of **16** suitable for X-ray crystallographic studies could not be obtained; however, molecular modeling studies revealed the unique conformation of this cyclophane:[23] Figure 1a illustrates the chirality of **16**, whereas Figure 1b reveals its helical nature.

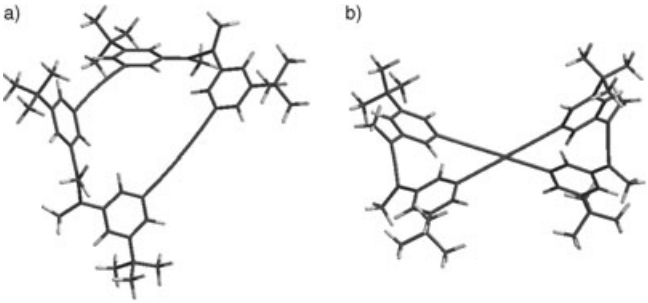


Figure 1. Molecular models of **16**: a) stereochemical configuration and b) helical arrangement.

The UV/Vis absorption and circular dichroism (CD) spectra of **16** in a solution of chloroform were recorded and are illustrated in Figures 2 and 3, respectively. There are very few reported examples of UV/Vis and CD spectra of cyclic

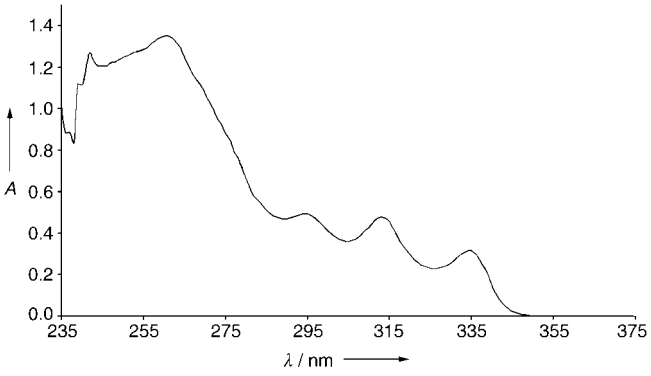


Figure 2. UV/Vis absorption spectrum of **16**.

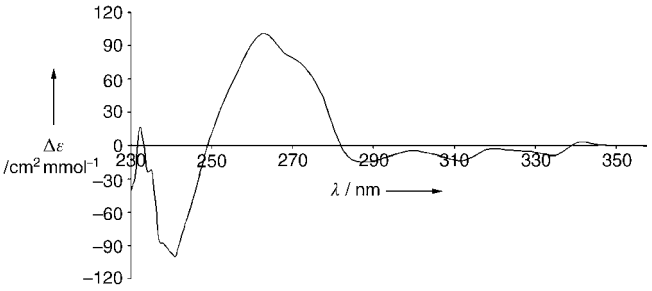


Figure 3. CD spectrum of **16**.

allenes with which to compare the spectra of our acetylenic allenophane.[24] Nevertheless, the typical "fingerprint" pattern for acetylenes with bands at 295, 313, and 335 nm is apparent in the UV/Vis spectrum. Major signals at 263 and 270 (sh) nm were observed in the CD spectrum that may have arisen from the through-space interactions of the phenyl rings.

In conclusion, a novel single-enantiomer acetylenic allenophane **16** has been synthesized by a series of palladium- and copper-mediated coupling reactions. A new protocol was developed that allowed the stereochemistry of the allene to be controlled by the use of a Sharpless asymmetric epoxidation and a tertiary α-hydroxyethyne intermediate. We are currently investigating the scope and synthetic utility of this reaction sequence for other targets.

Received: February 8, 2005
Published online: May 20, 2005

Keywords: alkynes · allenes · asymmetric epoxidation · cyclophanes · diynes

[1] For some examples of helical chirality in cyclophanes, see: a) R. Boese, A. J. Matzger, K. P. C. Vollhardt, *J. Am. Chem. Soc.* **1997**, *119*, 2052; b) M. M. Haley, M. L. Bell, S. C. Brand, D. B. Kimball, J. J. Pak, W. B. Wan, *Tetrahedron Lett.* **1997**, *38*, 7483; c) M. J. Marsella, I. T. Kim, F. Tham, *J. Am. Chem. Soc.* **2000**, *122*, 974.

[2] a) M. A. Romero, A. G. Fallis, *Tetrahedron Lett.* **1994**, *35*, 4711; b) S. K. Collins, G. P. A. Yap, A. G. Fallis, *Angew. Chem.* ***2000***, *112*, 393; *Angew. Chem. Int. Ed.* **2000**, *39*, 385; c) S. K. Collins, G. P. A. Yap, A. G. Fallis, *Org. Lett.* **2000**, *2*, 3185; d) S. K. Collins, G. P. A. Yap, A. G. Fallis, *Org. Lett.* **2002**, *4*, 11; e) M. A. Heuft, A. G. Fallis, *Angew. Chem.* **2002**, *114*, 4720; *Angew. Chem. Int. Ed.* **2002**, *41*, 4520; f) M. A. Heuft, S. K. Collins, A. G. Fallis, *Org. Lett.* **2003**, *5*, 1911.

[3] a) F. Diederich, *Cyclophanes*, Royal Society of Chemistry, Cambridge, UK, **1991**; b) F. Vögtle, *Cyclophane Chemistry*, Wiley, New York, **1993**; c) Y. Tobe, *Top. Curr. Chem.* **1994**, *172*, 1; d) J. Schulz, F. Vögtle, *Top. Curr. Chem.* **1994**, *172*, 41; e) G. J. Bodwell, *Angew. Chem.* **1996**, *108*, 2221; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2085; f) A. de Meijere, B. König, *Synlett* **1997**, 1221.

[4] a) *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), Wiley-VCH, Weinheim, **1995**; b) B. König, *Top. Curr. Chem.* **1998**, *196*, 92; c) T. Tsuji in *Adv. Strained Interesting Org. Mol.*, *Vol. 7* (Ed.: B. Halton), JAI, Greenwich, CT, **1999**, pp. 103; d) G. J. Bodwell, T. Satou, *Angew. Chem.* **2002**, *114*, 4175; *Angew. Chem. Int. Ed.* **2002**, *41*, 4003; e) C. Grave, A. D. Schlüter, *Eur. J. Org. Chem.* **2002**, 3075.

[5] a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; b) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 3067; c) *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**.

[6] A. Hoffmann-Roder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196.

[7] R. A. Smith, R. L. White, A. Krantz, *J. Med. Chem.* **1988**, *31*, 1558.

[8] S. Thorand, F. Vögtle, N. Krause, *Angew. Chem.* ***1999***, *111*, 3899; *Angew. Chem. Int. Ed.* **1999**, *38*, 3721.

[9] a) S. K. Collins, PhD Thesis, University of Ottawa, **2001**; b) M. A. Heuft, PhD Thesis, University of Ottawa, **2003**; c) Y. Tobe, J. Kishi, I. Ohki, M. Sonoda, *J. Org. Chem.* **2003**, *68*, 3330; d) A. G. Fallis, *Synlett* **2004**, 2249.

[10] Semiempirical AM1 calculations were performed by using the Cerius^2–Dmol^3 Molecular Modeling Suite from Molecular Simulations Inc. of San Diego, CA (1999) and by using the methods in: M. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4499.

[11] A. G. Myers, B. Zheng, *J. Am. Chem. Soc.* **1996**, *118*, 4492.

[12] For a review, see: L. Pu, *Tetrahedron* **2003**, *59*, 9873.

[13] T. L. Macdonald, D. R. Reagan, *J. Org. Chem.* **1980**, *45*, 4740.

[14] a) G. Lu, X. Li, X. Jia, W. L. Chan, A. S. C. Chan, *Angew. Chem.* **2003**, *115*, 5211; *Angew. Chem. Int. Ed.* **2003**, *42*, 5057; b) P. G. Cozzi, *Angew. Chem.* **2003**, *115*, 3001; *Angew. Chem. Int. Ed.* **2003**, *42*, 2895.

[15] a) D. J. Ramón, M. Yus, *Angew. Chem.* **2004**, *116*, 286; *Angew. Chem. Int. Ed.* **2004**, *43*, 284; b) S.-J. Jeon, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 9544.

[16] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521; c) G. J. Roth, B. Liepold, S. Müller, H. J. Bestmann, *Synthesis* **2004**, 59.

[17] S. Höger, A.-D. Meckenstock, H. Pellen, *J. Org. Chem.* **1997**, *62*, 4556.

[18] Synthesized by protection of the corresponding alcohol with TBS, see: S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis* **1988**, 366.

[19] The enantiomeric excess was determined using a chiralcel OD-H column, eluent: hexane/*i*PrOH (99:1), 0.8 mL min^{-1}, t_R(major): 12.00 min, t_R(minor): 12.75 min; absolute configuration was inferred from a literature precedent, see: K. A. Jørgensen, R. A. Wheeler, R. Hoffmann, *J. Am. Chem. Soc.* **1987**, *109*, 3240.

[20] a) W. Adam, M. Braun, A. Griesbeck, V. Lucchini, E. Staab, B. Will, *J. Am. Chem. Soc.* **1989**, *111*, 203; b) V. Capriati, S. Florio, R. Luisi, A. Salomone, *Org. Lett.* **2002**, *4*, 2445.

[21] G. B. Payne, *J. Org. Chem.* **1962**, *27*, 3819.

[22] a) A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841; b) W. P. Gallagher, R. E. Maleczka, Jr., *J. Org. Chem.* **2003**, *68*, 6775.

[23] Semiempirical AM1 calculations were performed by using a PC Spartan Pro (v. 1.03) program from Wavefunction, Inc. of Irvine, CA (2000).

[24] For CD spectra of cyclic allenes, see: C. Zelder, N. Krause, *Eur. J. Org. Chem.* **2004**, 3968.