Organic LETTERS

Letter

pubs.acs.org/OrgLett

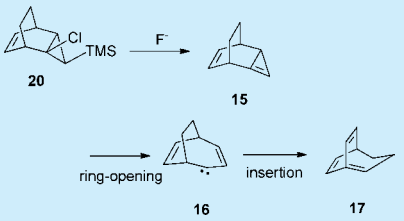
Synthesis of an Anti-Bredt Compound, Bicyclo[3.2.2]nona-1,6,8-triene, via the Isomerization of Tricyclo[3.2.2.0^{2,4}]nona-2,6-diene

Gon-Ann Lee* and Hung-Chun Lin

Department of Chemistry, Fu Jen Catholic University, Xinzhuang, New Taipei 24205, Taiwan, R.O.C.

Supporting Information

ABSTRACT: A highly strained 1,3-fused tricyclic cyclopropene, tricyclo[3.2.2.0^{2,4}]-nona-2,6-diene (**15**), was designed for use in the synthesis of a new highly strained anti-Bredt compound, bicyclo[3.2.2]nona-1,6,8-triene (**17**). Tricyclic cyclopropene **15** was subjected to a ring-opening reaction followed by insertion of the resulting carbene to produce an anti-Bredt compound **17**. The tricyclic cyclopropene **15** was prepared by the fluoride-induced elimination of 2-chloro-3-trimethylsilyltricyclo[3.2.2.0^{2,4}]non-6-ene (**20**), via the reaction of 1-chloro-3-trimethylsilylcyclopropene with 1,3-cyclohexadiene. Both the tricyclic cyclopropene **15** and the anti-Bredt compound **17** were trapped by diphenylisobenzofuran (DPIBF).



The synthesis and chemistry of strained olefins has attracted the interest of chemists for years. A publication of a study of bicyclic systems containing camphene and pinene by J. Bredt in 1924 attracted the attention of chemists focusing on bridgehead alkenes.[1] The Bredt rule implies that a double bond cannot be placed at the bridgehead of a bicyclic system, unless the rings are sufficiently large. Prelog et al. established the limitations of Bredt's rule, and Fawcett introduced the *S* number to bicyclic systems (Figure 1).[2] It is generally believed

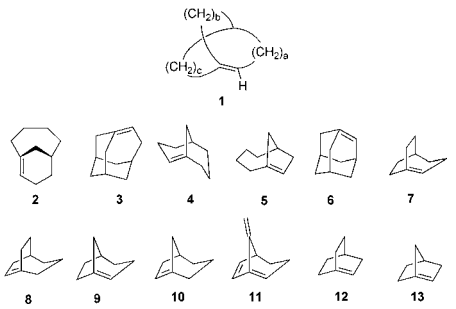


Figure 1. Structures of some *anti*-Bredt compounds.

that the bridgehead alkenes with $S \leq 8$ would be too unstable to permit their isolation; however, bicycle[4.3.1]decan-1-enes **2**, with $S = 8$ and a *trans*-cyclononene skeleton, were prepared via a Wittig reaction by Dauben,[3a] and an intramolecular Diels–Alder reaction (IMDA) developed by Shea was also found to be an efficient method.[2b,3b] Homoadamantene (**3**), also containing a *trans*-cycloheptene skeleton, could be generated by carbene insertion.[3c,d] The smaller analogue, bicyclo[3.3.1]non-1-ene (**4**) with $S = 7$, was first prepared via elimination reactions and was independently isolated by Wiseman[4a] and Marshall.[4b] Bicyclo-[3.3.1]non-1-ene and derivatives thereof could be obtained or trapped as intermediates from IMDA,[3b] Wittig reaction-s,[2a,3a,4c−e] and elimination reactions.[4f,g] Bicyclo[4.2.1]non-1-enes **5** were reported to be generated via pyrolysis,[4h] Wittig reactions,[4c,d] or decarboxylation.[4i] Both compounds **4** and **5** contain a stable *trans*-cyclooctene skeleton. The well-known polycyclic derivative, adamantene (**6**) containing a trans-cyclohexene, could be generated and gave dimers via elimination[4j,k] and carbene insertion.[4l] Bicyclo[3.2.2]non-1-ene (**7**) and bicyclo[3.2.2]non-1(7)-ene (**8**), which contain a *trans*-cycloheptene structure, were synthesized and trapped by diphenylisobenzofuran (DPIBF) via pyrolysis by Wiseman.[4m] More strained bridgehead alkenes with $S = 6$ and the *trans*-cycloheptene, bicyclo[3.2.1]octenes **9** and **10**, could also be synthesized via Wittig reactions[3a,5a,b] or pyrolysis.[5c] In a previous study, we reported on the isomerization of a 1,2-fused tricyclic cyclopropene to give the bicyclo[3.2.1]oct-1-ene **11**.[5d] Bicyclo[2.2.2]oct-1-ene (**12**) could be obtained from 1,2-elimination[5e] and carbene insertion.[5f] Keese reported on the synthesis of the bicyclo[2.2.1]hept-1-ene (**13**), with $S = 5$, which was trapped via 1,2-elimination.[6]

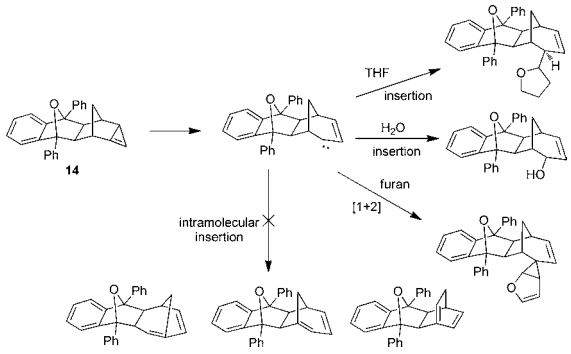
The insertion of highly reactive alkyl carbenes would be a feasible method for the synthesis of highly strained bridgehead olefins.[3c,d,4l,5f] In our previous publication, the 1,3-fused tricyclic cyclopropene, tricyclo[3.2.1.0^{2,4}]oct-1-ene **14**, was subjected to a ring-opening reaction to give a vinylcarbene, which could then be inserted into the α C−H bond of THF or the O−H bond of water, or undergo [1 + 2] cycloaddition with a furan. However, intramolecular carbene insertion to form highly strained *anti*-Bredt compounds was not feasible (Scheme 1).[7] We report herein on the design of the higher analog, tricyclo[3.2.2.0^{2,4}]nona-2,6-diene (**15**), for use as a precursor in the synthesis of the anti-Bredt compound **17**.

In principle, there are three pathways by which the vinyl carbene **16**, formed from a ring-opening reaction of **15**, can undergo carbene insertion to yield the two anti-Bredt compounds **17** and **18**. Theorical calculations were carried

Received: August 13, 2014
Published: September 29, 2014

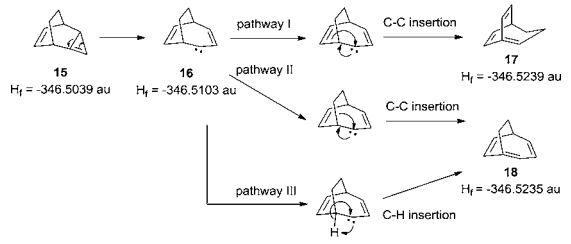
dx.doi.org/10.1021/ol5024085 | *Org. Lett.* 2014, 16, 5275–5277

Scheme 1. Reactions of Tricyclic Cyclopropene 14



out for the tricyclic cyclopropene **15**, carbene **16**, and the anti-Bredt compounds **17** and **18** using HF/6-31++G(d,p), and the heats of formation of these four compounds were determined to be −346.5039 au, −346.5103 au, −346.5239 au, and −346.5235 au (Scheme 2). The results indicate that the anti-

Scheme 2. Theoretical Calculations of Anti-Bredt Compounds



Bredt compound **17** would be the thermodynamic product of this isomerization. According to the theoretical calculation model of vinylcarbene **16**, the empty p-orbital was located at the axial position, the C5−C6 and C5−C9 bonds were at the pseudoaxial position, and the C5−H bond was in an equatorial position. The C5−C6 (sp^3−sp^2) bond is shorter and closer to the carbene carbon than the C5−C9 (sp^3−sp^3) bond. Thus, the vinyl carbene would be expected to be easily inserted into the C5−C6 σ bond to give the *anti*-Bredt compound **17**, which contains three noncoplanar and alternating π bonds. For that reason, the formation of compound **17** should be the kinetically preferred product of this carbene insertion (Figure 2).

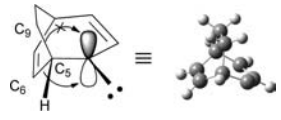
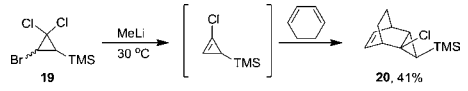


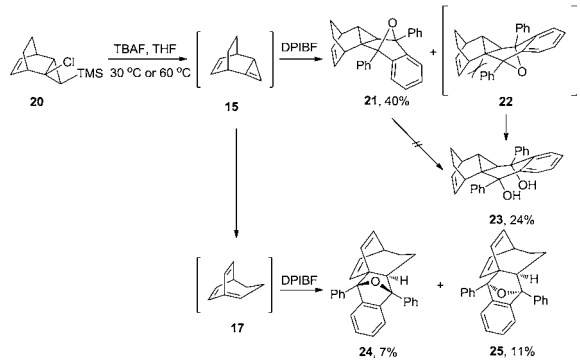
Figure 2. Theoretical calculation model of the structures of vinylcarbene **16**.

In order to generate the 1,3-fused tricyclic cyclopropene **15**, the essential precursor **20** was synthesized by treating 1-bromo-2,2-dichloro-3-trimethylsilylcyclopropane with methyllithium in 1,3-cyclohexadiene in order to induce an elimination and [4 + 2] cycloaddition (Scheme 3). Compound **15** was synthesized and trapped by DPIBF, and the adduct was purified by column chromatography. Four products, **21** and **23**−**25**, were isolated in 40%, 24%, 7%, and 11% yields, and their structures were determined by single crystal X-ray analysis (Scheme 4).

Scheme 3. Synthesis of 2-Chloro-3-trimethylsilyltricyclo[3.2.2.0^{2,4}]oct-6-ene (19)



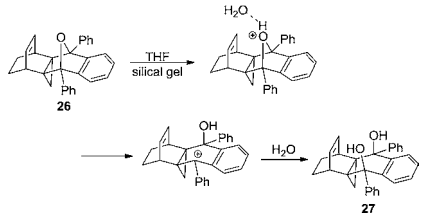
Scheme 4. Trapping of Tricyclo[3.2.2.0^{2,4}]nona-2,6-diene (15) and the Anti-Bredt Compound 17



Compound **21** was formed directly from compound **15** and DPIBF. The stereochemistry of this compound indicated that the Diels−Alder reaction of 1-chloro-3-trimethylsilylcyclopropene with 1,3-cyclohexadiene was via an *endo* (from the view of the cyclopropene) transition state and that of cyclopropene **15** with DPIBF was via an *exo* (from the view of the cyclopropene)-*exo* (from the view of bicyclic system) transition state.

The hydrolysis of the polycyclic cyclopropane-fused furanoid **26** to the diol **27** is well-known (Scheme 5).[8] According to the

Scheme 5. Hydrolysis of the Cyclopropane-Fused Furanoid Compound to a Diol



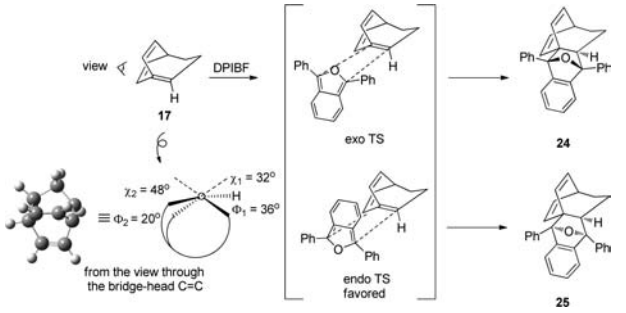
X-ray analysis results, compound **23** contains an *endo*-fused cyclopropyl ring. Because of this, it would be generated from the hydrolysis of compound **21** or **22**. In order to determine the origin of compound **23**, compound **21** was subjected to the same reaction conditions; however, no diol was produced by hydrolysis in the acidic conditions. Obviously, diol **23** was generated from the hydrolysis of the *endo-exo* adduct **22**, which was generated directly from the Diels−Alder reaction of the 1,3-fused tricyclic cyclopropene **15** with DPIBF. The *endo-exo* adduct **22** would be more crowded than the *exo-exo* adduct and, as a result, would easily be hydrolyzed during the workup to give diol **23**.

Compounds **24** and **25** were identified by single crystal X-ray analysis, showing that the two adducts were generated directly from the [4 + 2] cycloaddition of the anti-Bredt compound **17** with DPIBF, via *endo* and *exo* transition states in a ratio of 2:3. Based on the theoretical calculation model of the anti-Bredt compound **17**, the twisting angles were $\Phi_1 = 36°$, $\Phi_2 = 20°$; the

dx.doi.org/10.1021/ol5024085 | *Org. Lett.* 2014, 16, 5275−5277

pyramidalization angles were χ_1 = 32°, χ_2 = 48°; and the dihedral angles were C3C2C1C7 = 111°, H2C2C1C9 = 168°. The model shows that the proton of the bridged-head double bond protruded from the bridged ring, so that the DPIBF approaching via the *exo*-TS would encounter more steric hindrance at the fused benzene ring than that of the *endo*-TS of the oxygen. Therefore, the Diels–Alder cycloaddition proceeded in favor of the *endo*-adduct **24** compared to the *exo*-adduct **25** (Scheme 6).

Scheme 6. Trapping of the Anti-Bredt Compound 16



In summary, we successfully utilized the chemical properties of highly strained 1,3-fused tricyclic cyclopropenes and theoretical calculations to design a new 1,3-fused tricyclic cyclopropene, tricyclo[3.2.2.0^{2,4}]nona-2,6-diene (**15**), which was used in the synthesis of the *anti*-Bredt compound, bicyclo[3.2.2]nona-1,6,8-triene (**17**). The 1,3-fused tricyclic cyclopropene **15** was generated from fluoride-induced elimination and trapped with DPIBF to give compounds **21** and **23**. The *anti*-Bredt compound **17** was obtained from tricyclic cyclopropene **15** by way of a ring-opening reaction, followed by carbene insertion. Compound **17** was trapped by DPIBF and gave two stereoisomers, **24** and **25**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data and X-ray data for all new compounds, and the computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: 016850@mail.fju.edu.tw.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the Ministry of Science and Technology, Taiwan, R.O.C. under Grant No. NSC102-2113-M-030-007-MY2 for financial support and the National Center for Highperformance Computing for computer time, and also the facilities are gratefully acknowledged. We thank Professor M. Shieh and Mr. T.-S. Kuo at the National Taiwan Normal University for the X-ray structure determination.

■ REFERENCES

(1) Bredt, J.; Thouet, H.; Schmitz, J. *Justus Liebigs Ann. Chem.* **1924**, *437*, 1.

(2) (a) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067. (b) Shea, K. J. *Tetrahedron* **1980**, *36*, 1683. (c) Szeimies, G. In *Reactive Intermediates*, Vol. 3; Abranovitch, R. A., Ed.; Plenum: New York, 1983; pp 299–366. (d) Keese, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 528. (e) Fawcett, F. S. *Chem. Rev.* **1950**, *47*, 219. (f) Prelog, V. *J. Chem. Soc.* **1950**, 420. (g) Prelog, V.; Barman, P.; Zimmermann, M. *Helv. Chim. Acta* **1949**, *32*, 1284.

(3) (a) Dauben, W. G.; Ipaktschi, J. *J. Am. Chem. Soc.* **1973**, *95*, 5088. (b) Bear, B. R.; Sparks, S. M.; Shea, K. J. *Angew. Chem., Int. Ed.* **2010**, *40*, 820. (c) Adams, B. L.; Kovacic, P. *J. Am. Chem. Soc.* **1973**, *95*, 8206. (d) Farcasiu, M.; Farcasiu, D.; Conlin, R. T.; Jones, M., Jr.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 8207.

(4) (a) Marshall, J. A.; Faubl, H. *J. Am. Chem. Soc.* **1967**, *89*, 5965. (b) Wiseman, J. R. *J. Am. Chem. Soc.* **1967**, *89*, 5966. (c) Becker, K. B. *Helv. Chim. Acta* **1977**, *60*, 68. (d) Becker, K. B.; Chappuis, J. L. *Helv. Chim. Acta* **1979**, *62*, 34. (e) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Chem. Soc., Chem. Commun.* **1979**, 82. (f) House, H. O.; Kleschick, W. A.; Zaiko, E. J. *J. Org. Chem.* **1987**, *43*, 3653. (g) Bloch, R.; Boivin, F.; Bortolussi, M. *J. Chem. Soc., Chem. Commun.* **1976**, 371. (h) Tobe, Y.; Fukuda, Y.; Kakiuchi, K.; Odaira, Y. *J. Org. Chem.* **1984**, *49*, 2012. (i) Carruthers, W.; Qureshi, M. I. *J. Chem. Soc. (C)* **1970**, 2230. (j) Lenoir, D. *Tetrahedron Lett.* **1972**, *13*, 4049. (k) Grant, D.; McKervey, M. A.; Rooney, J. J.; Samman, N. G.; Step, G. *J. Chem. Soc., Chem. Commun.* **1972**, 1186. (l) Martella, D. J.; Jones, M., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 2896. (m) Chong, J. A.; Wiseman, J. R. *J. Am. Chem. Soc.* **1969**, *91*, 7775.

(5) (a) House, H. O.; Haack, J. L.; McDaniel, W. C.; Van Derveer, D. *J. Org. Chem.* **1983**, *48*, 1643. (b) Bestmann, H. J.; Schade, G. *Tetrahedron Lett.* **1982**, *23*, 3543. (c) Chong, J. A.; Wiseman, J. R. *J. Am. Chem. Soc.* **1972**, *94*, 8627. (d) Lee, G.-A.; Lin, Y.-H.; Huang, A.-N.; Li, Y.-C.; Jann, Y.-C.; Chen, C.-S. *J. Am. Chem. Soc.* **1999**, *121*, 5328. (e) Grootveld, H. H.; Blomberg, C.; Bickelhaupt, F. *J. Chem. Soc., Chem. Commun.* **1973**, 542. (f) Wolf, A. D.; Jones, M., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 8209.

(6) (a) Keese, R.; Krebs, E.-P. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 262. (b) Keese, R.; Krebs, E.-P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 518.

(7) Lee, G.-A.; Chan, L.-E.; Tsai, R.-T.; Chen, K.-C. *Eur. J. Org. Chem.* **2012**, 2824.

(8) Lee, G.-A.; Cherng, C.-H.; Huang, A. N.; Lin, Y.-H. *Tetrahedron* **2003**, *59*, 1539.