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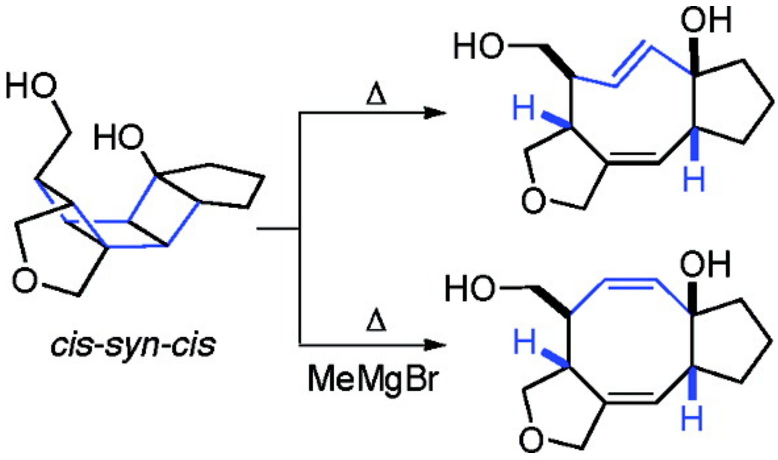

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# Intramolecular [2 + 2] Photocycloaddition/Thermal Fragmentation: Formally "Allowed" and "Forbidden" Pathways toward 5−8−5 Ring Systems

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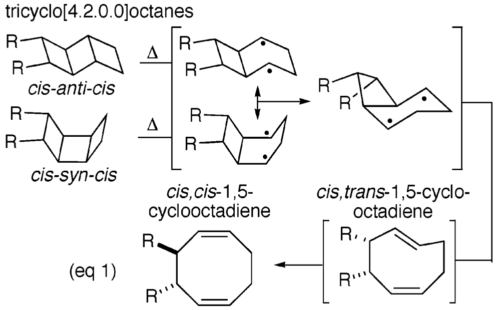
***Abstract:*** The thermal fragmentation of highly functionalized, linear polycyclobutanes with a *cis*,*syn*,*cis*-relative stereochemistry is shown to offer a rapid entry into the dicyclopenta[*a*,*d*]cyclooctenyl (5−8−5) ring system. The thermolysis of polyfused cyclobutanes with a *cis*,*syn*,*cis*- or a *cis*,*anti*,*cis*-relationship proceeds in a formally "symmetry-allowed" manner through the intermediacy of a *cis*,*trans*-cyclooctadiene. When a bridging tether used to establish the *cis*,*syn*,*cis*-stereochemistry in the intramolecular [2 + 2] photocyclization is present in the thermolysis step, however, the result of a formally "symmetry-forbidden" fragmentation is observed yielding *cis*,*cis*-cyclooctadiene-containing 5−8−5 products. In general, the stereochemical observations noted in these fragmentations offer new opportunities for accessing a variety of stereochemical relationships in these 5−8−5 ring systems.

## Introduction

Martin and others have shown that *cis*,*cis*-1,5-cyclooctadiene is generated upon thermal fragmentation of *cis*,*syn*,*cis*- and *cis*,*anti*,*cis*-tricyclo[4.2.0.0$^{2,5}$]octanes (eq 1).[11] Independent of whether this is a concerted, symmetry-allowed [$\sigma 2_a + \sigma 2_s$] fragmentation[2] or a stepwise, biradical process as shown, it is likely that the reaction proceeds through the intermediacy of a *cis*,*trans*-1,5-cyclooctadiene.[3] The resulting strained cyclooctadiene can then isomerize through several Cope rearrangements to the observed *cis*,*cis*-1,5-cyclooctadiene.[4] Due to the stereospecificity of Cope rearrangements, the configuration of one of the allylic substituents on the *cis*,*trans*-cyclooctadiene becomes inverted in the resulting *cis*,*cis*-1,5-cyclooctadiene product.



(eq 1)

Along these lines, we have applied this fragmentation in the rapid preparation of dicyclopenta[*a*,*d*]cyclooctenyl (5−8−5) ring systems,[5] a framework related to several diterpene natural products. As illustrated in Scheme 1, we have shown that the thermolysis of substituted *cis*,*anti*,*cis*-polyfused cyclobutanes,

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(1) (a) Martin, H.-D.; Eisenmann, E. Thermolysis of *syn*- and *anti*-Tricyclo-[4.2.0.0$^{2,5}$]octane. *Tetrahedron Lett.* **1975**, 661−664 and references therein. For related fragmentations, see: (b) Cobb, R. L.; Mahan, J. E.; Fahey, D. R. Dimers of Cyclobutene-1,2-dicarbonitrile and 1,3-Butadiene-2,3-dicarbonitrile: Preparation and Chemistry. *J. Org. Chem.* **1977**, *42*, 2601−2610. (c) Walsh, R.; Martin, H.-D.; Kunze, M.; Oftring, A.; Beckhaus, H.-D. Small Rings. Part 32. The Gas-Phase Kinetics, Mechanism, and Energy Hypersurface for the Thermolyses of *syn*- and *anti*-Tricyclo[4.2.0.0$^{2,5}$]-octane. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1076−1083. (d) Martin, H.-D.; Hekman, M.; Rist, G.; Sauter, H.; Bellus, D. *cis,trans*-1,5-Cyclooctadienes. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 406−407. (e) Martin, H.-D.; Eisenmann, E.; Kunze, M.; Bonacic-Koutecky, V. Die $C_8H_{12}$-Energiehyperfläche Thermolyse van *syn* und *anti*-Tricyclo[4.2.0.02, 5]octan. Experimentelle und Theoretische Untersuchungen. *Chem. Ber.* **1980**, *113*, 1153. (f) Dave, P. R.; Duddu, R.; Li, J.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* **1998**, *39*, 5481. (g) Bakkern, F. J. A. D.; Schröer, F.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 9531−9534.

(2) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie Academic Press: Weinheim, Germany, 1970.

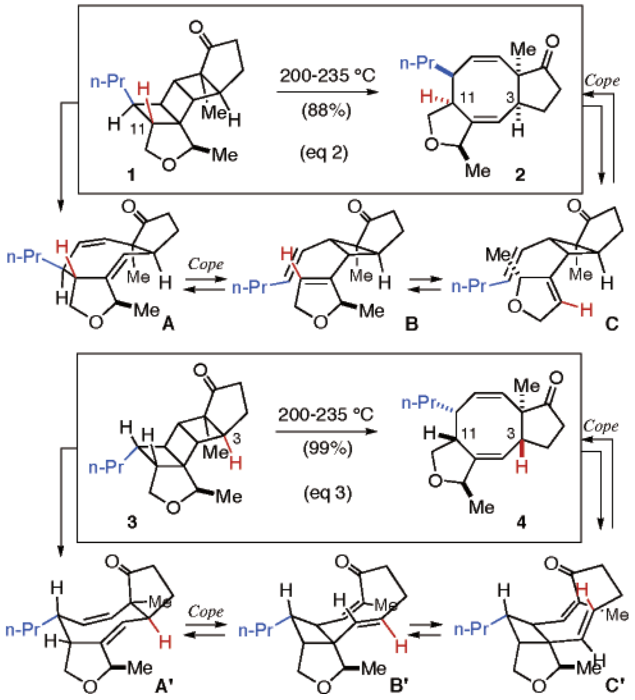
(3) Conformation restrictions limit stereomutation and fragmentation pathways of these systems relative to the thermolyses of free cyclobutane. For lead references into fragmentations of cyclobutanes, see: (a) Schaumann, E.; Ketcham, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 225. (b) Lewis, D. K.; Glenar, D. A.; Kalra, B. L.; Baldwin, J. W.; Cianciosi, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 7225−7227. (c) Chickos, J. S.; Annamalai, A.; Keiderling, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 4398−4402. (d) Doubleday, C., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 11968−11983. (e) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **2001**, *123*, 4069−4072. For studies of related systems, see: (f) Khuong, K. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 14867−14883.

(4) (a) Berson, J. A.; Dervan, P. B. *J. Am. Chem. Soc.* **1972**, *94*, 7597−7598. (b) Berson, J. A.; Dervan, P. B.; Jenkins, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 7598−7599.

(5) (a) Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534−4535. (b) Lo, P. C.-K.; Snapper, M. L. *Org. Lett.* **2001**, *3*, 2819−2821. For examples of related cycloaddition/fragmentations, see: (c) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365−367. (d) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003−2020. (e) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453−1473. (f) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135−141. (g) Wender, P. A.; Eck, S. L. *Tetrahedron Lett.* **1982**, *23*, 1871−1874. (h) Lange, G. L.; Organ, M. G. *J. Org. Chem.* **1996**, *61*, 5358−5361. (i) Lange, G. L.; Lee, M. *J. Org. Chem.* **1987**, *52*, 325−331. (j) Kammermeier, S.; Herges, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 417−419. (k) Prinzbach, H.; Weber, K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2239−2257. (l) Mehta, G.; Reddy, A. V.; Srikrishna, A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 291−297. (m) White, J. D.; Kim, J.; Drapela N. E. *J. Am. Chem. Soc.* **2000**, *122*, 8665.

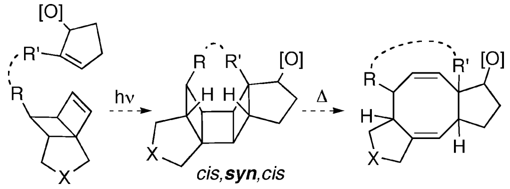
**10.1021/ja044542i CCC: $30.25**

***Scheme 1.*** Fragmentations to 5−8−5 Ring Systems



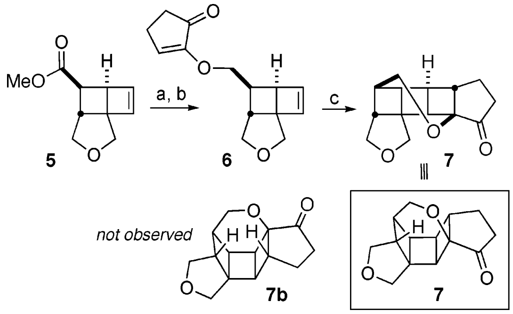
such as **1** and **3**, yield the 5−8−5 ring systems **2** and **4**, respectively. Of particular importance, a unique stereochemical outcome is observed in these thermolyses, an outcome depending primarily on the relative stereochemistry of the fused thermal precursors. Substrate **1** rearranges to cyclooctadiene **2** with inversion of C-11 (eq 2 in Scheme 1), whereas substrate **3** yields cyclooctadiene **4** with inversion at C-3 (eq 3 in Scheme 1). The stereochemical differences in the products are the result of the stereospecific Cope rearrangements on the conformationally biased *cis*,*trans*-cyclooctadiene intermediates **A** and **A′**. The formation of either 5−8−5 product is consistent with both a stepwise, biradical mechanism and a symmetry-allowed [$\sigma 2_a + \sigma 2_s$] fragmentation.

In the interest of expanding our understanding of these thermal fragmentations, as well as to access stereochemically different 5−8−5 ring systems, we sought to prepare and explore the fragmentation of substituted *cis*,*syn*,*cis*-tricyclo[4.2.0.0]-octanes, such as illustrated in eq 4. Of particular interest, especially considering potential natural product targets, is the relative stereochemistry of the cyclooctadiene products arising from these fragmentations. To overcome the known stereochemical preference in the [2 + 2] photocycloaddition for generating the *cis*,*anti*,*cis*-polyfused product, we developed a new intramolecular route for accessing the desired *cis*,*syn*,*cis*-thermolysis precursors. Reported herein are our findings on the intramolecular photocycloaddition of cyclopentenones tethered to functionalized cyclobutenes and the subsequent thermal fragmentation of the resulting *cis*,*syn*,*cis*-polyfused photoadducts.



(eq 4)

***Scheme 2.*** Synthesis of the *syn*,*cis*,*syn*-Thermolysis Precursor **7**[a]



[a] (a) LAH, $Et_2O$, 0 °C (98%); (b) 1,2-cyclopentadione, Amberlyst 15, $CH_2Cl_2$, reflux (87%); (c) hν (Pyrex), acetone, −78 °C (74%).

## Results and Discussion

We envisioned using cyclobutene **5**, available through an intramolecular cycloaddition of a functionalized cyclobutadiene,[6] as a convenient starting point for our studies (Scheme 2). The reduced ester could serve as a handle to link a cyclopentenone chromophore for the intramolecular [2 + 2] photocycloaddition. Toward this goal, reduction of the methyl ester to the corresponding alcohol using LAH and an acid-catalyzed coupling to 1,2-cyclopentadione produced the desired photoprecursor **6**. Irradiation of enone **6** through a Pyrex filter in acetone at −78 °C furnished the *cis*,*syn*,*cis*-polyfused cyclobutane system **7** in 74% yield. An X-ray crystallographic analysis of the product revealed the relative head-to-tail stereochemistry in this cycloaddition. As has been observed previously, the capto-dative stabilization of the α-oxygen in the photoexcited state of the cyclopentenone[7] overrides the usual “rule of five” regiochemical preference observed typically in this type of photocycloaddition (i.e., **6** → **7b**).[8]

In a related sequence, methyl ester **5** could also be converted in one step to Weinreb amide **8**.[9] Addition of cyclopentenyl anions could then furnish an exocyclic α,*β*-unsaturated ketone that should produce the head-to-head *cis*,*syn*,*cis*-products in the photocycloaddition step. As illustrated in Scheme 3, the reaction of cyclopentenyllithium[10] with the Weinreb amide **8** provides ketone **9** in 96% yield. Other lithiated cyclopentenes can also be prepared via a Shapiro reaction.[11] For example, 2,2-dimethylcyclopentanone[12] can be transformed to the 2,4,6-triisopropyltosylhydrazone upon treatment with the corresponding hydrazide. Treatment of this hydrazone with *n*-BuLi followed by addition of Weinreb amide **8** furnished compound **11** in 82% yield. Irradiation of either enone **9** or **11** in $CH_2Cl_2$ at low temperature through a Pyrex filter provided the desired *cis*,*syn*,*cis*-polycyclic systems **10** or **12** in 70 and 50%[13] yields,

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(6) (a) Deak, H. L.; Stokes, S. S.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 5152−5153. For the preparation of related cycloadducts, see: (b) Limanto, J.; Tallarico, J. A.; Porter, J. R.; Khuong, S. K.; Houk, K. N.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 14748−14758. (c) Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *J. Am. Chem. Soc.* **1996**, *118*, 9196−9197.

(7) Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917−932.

(8) (a) Takahashi, M.; Uchino, T.; Ohno, K.; Tamura, Y.; Ikeda, M. *J. Org. Chem.* **1983**, *48*, 4241−4247. (b) Pirrung, M.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824−5831.

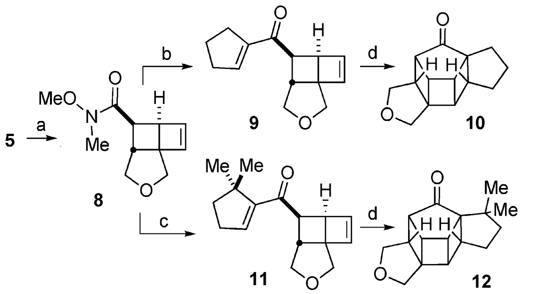
(9) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. *Tetrahedron Lett.* **1995**, *36*, 5461−5464.

(10) Prepared from 1-chlorocyclopentene and $Li^+$ in $Et_2O$ at room temperature under Ar atmosphere for 2 days.

(11) For a review, see: Shapiro, R. H. *Org. React.* **1976**, *23*, 405−423.

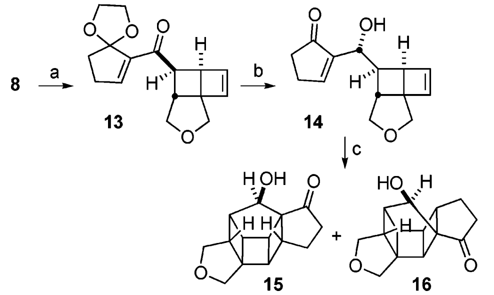
(12) Purchased from Aldrich Chemical Co.

***Scheme 3.*** Thermolysis Precursors **10** and **12**[a]



[a] (a) *i*-PrMgCl, *N*,*O*-dimethylhydroxylamine hydrochloride, THF, −20 °C (99%); (b) cyclopentenyllithium, THF, −78 to 0 °C (96%); (c) 2,2-dimethylcyclopentylhydrazone, *n*-BuLi, THF, −78 to 0 °C; **8**, THF, −78 to 0 °C (82%); (d) h$\nu$ (Pyrex), $CH_2Cl_2$, −78 °C (70%, **10**; 50%,[13] **12**).

***Scheme 4.*** Synthesis of Photoadducts **15** and **16**[a]



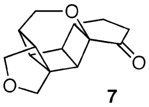
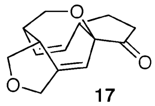
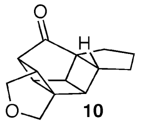
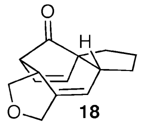
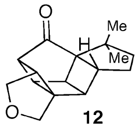
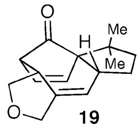
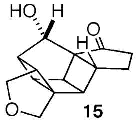
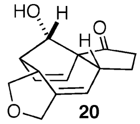
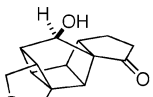
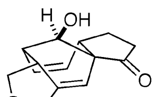
[a] (a) 6-Bromo-1,4-dioxaspiro[4.4]non-6-ene, *n*-BuLi, THF, −78 °C; **5**, THF, −78 to 0 °C (94%); (b) NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, 0 °C; 1 N HCl (100%); (c) h$\nu$ (Pyrex), $CH_2Cl_2$ (57% **15**/**16** (1:10)) or acetone/H$_2$O (72% **15**/**16** (7:1)).

respectively. An X-ray crystal structure confirmed the head-to-head cycloaddition stereochemistry in photoadduct **10**.

To introduce additional functionality in the five-membered ring, the vinyllithium reagent derived from a protected cyclopentenone made by Smith et al.[14] was used (Scheme 4). The acetal-protected cyclopentenyl bromide undergoes a lithium−halogen exchange upon exposure to *n*-BuLi at −78 °C. Exposure of the cyclopentenyl anion to Weinreb amide **8** yields compound **13** in 94% yield. Irradiation of **13** under a variety of reaction conditions did not, however, lead to any desired photoadducts. In comparison, reduction of the *exo*-$\alpha,\beta$-unsaturated ketone, followed by a mild acidic workup, produced compound **14** in quantitative yield. Irradiation of enone **14** generates two photoadducts in a ratio that is dependent on the solvent employed. Photocycloaddition in a protic media, such as acetone/water, leads to compounds **15**/**16** in a 7:1 ratio.[15] In an aprotic solvent, such as $CH_2Cl_2$, however, **15**/**16** are produced in a 1:10 ratio. Our rationale for the regiochemical dependence of this photocycloaddition on solvent is based on the presence of an intramolecular hydrogen bond between the ketone and the $\beta$-hydroxyl group in aprotic solvents that restrict the accessible conformations, allowing the head-to-tail product **16** to prevail. Disruption of this hydrogen bond in protic solvents, however, relaxes the conformational preference of the molecule and favors formation of the head-to-head product **15**.

With access to several highly substituted *cis*,*syn*,*cis*-polycyclobutane systems, we were well poised to examine their thermal fragmentations. In general, compounds were heated in a heavy-walled sealed tube in degassed benzene with BHT (2 equiv) to a temperature at which the starting material began to convert.

***Table 1.*** Symmetry-Forbidden Thermal Fragmentations of Bridged *cis*,*syn*,*cis*-Systems

| entry | substrate | temp. (°C) | product | yield (%) |
|---|---|---|---|---|
| (1) |  **7** | 200 |  **17** | >99[a] |
| (2) |  **10** | 260 |  **18** | >99[a] |
| (3) |  **12** | 250 |  **19** | >99 |
| (4) |  **15** | 215 |  **20** | 86[a] |
| (5) |  **16** | 200 |  **21** | 85[a] |

[a] X-ray crystal structure available in the Supporting Information. Thermolysis: benzene, BHT (2 equiv), heat.

Each substrate in Table 1 undergoes the thermal fragmentation to provide cleanly the ring-expanded cyclooctadiene products.

The relative stereochemistry of the fragmented products is particularly noteworthy. Whereas our previous thermal fragmentations of the *cis*,*anti*,*cis*-systems proceeded along a formal symmetry-allowed[16] pathway resulting in an inversion of stereochemistry in the observed products (i.e., Scheme 1), the *cis*,*syn*,*cis*-substrates illustrated in Table 1 fragmented without additional stereochemical consequences.[17] Each substrate reacted through a mechanism that is consistent with a "symmetry-forbidden" [$\sigma 2_s + \sigma 2_s$] fragmentation.

A possible explanation for the difference in fragmentations between the two ring systems is that the bridging tether present in the *cis*,*syn*,*cis*-ring system precludes the formation of the expected *cis,trans*-cyclooctadiene intermediate by not allowing the initially generated cyclohexyl diradical to rearrange through a chair transition state.[3d] For example, eq 5 illustrates a stepwise fragmentation of the *cis*,*anti*,*cis*-precursor **1**. Presumably, the initially formed boat cyclohexyl diradical can relax into a chair conformation, which leads to *cis*,*trans*-cyclooctadiene intermediate **A**. In contrast, eq 6 shows the generation of cyclooctadiene **18** from the *cis*,*syn*,*cis*-ring system **10**. Note that the substituents and bridging carbonyl in **10** preclude the initially generated cyclohexyl diradical(s) from adopting a chair conformation.

To separate the stereochemical influence of the bridging tether from the *cis*,*syn*,*cis*-ring fusion stereochemistry in the thermoly-

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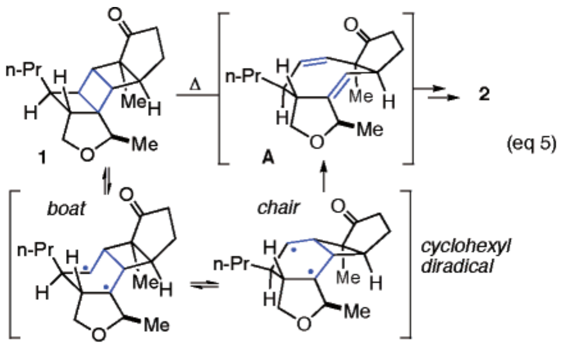
(13) With 50% yield based on 50% conversion.

(14) Smith, A. B., III.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855−1869.

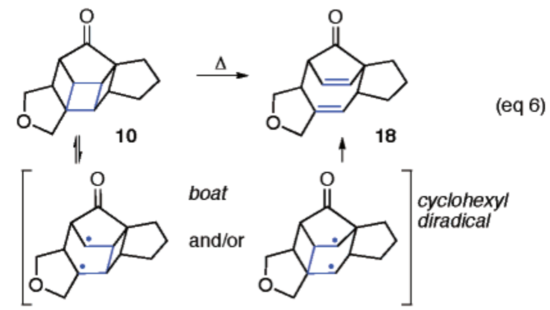
(15) Determined by $^1$H NMR on the crude reaction mixture.

(16) While the fragmentations are likely to proceed through biradical intermediates, the terms symmetry-allowed and symmetry-forbidden are used to describe the stereochemical changes occurring between the fused cyclobutane starting materials and the corresponding cyclooctadiene products.

(17) For related observations, see: Doering, W. v. E.; DeLuca, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 10608−10614.



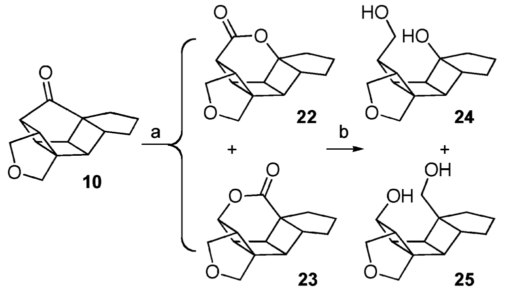
(eq 5)



(eq 6)

sis, we chose to examine the fragmentation in the absence of the bridging group. Baeyer–Villiger oxidation[18] of ketone **10** using *m*-CPBA gave an inseparable mixture of the regiochemical lactones **22** and **23** in a 9:1 ratio (Scheme 5). Reduction of the lactones with LAH provided the two diols **24** and **25**, respectively, which now could be readily separated in overall 98% yield for the two steps. The minor regioisomer provided a solid that could be analyzed by X-ray crystallography; this indicated that the removal of the tether does not change the *cis*,*syn*,*cis*-relationship of the polyfused cyclobutane rings.

***Scheme 5.*** Synthesis of Diols **24** and **25**[a]

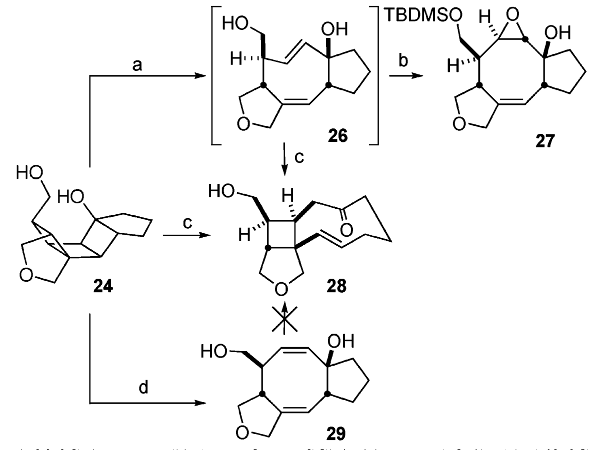


[a] (a) *m*-CPBA, *p*-TsOH, benzene (99%, **22/23** (9:1)); (b) LAH, $Et_2O$, 0 °C (99%, **24/25** (9:1)).

As illustrated in Scheme 6, heating diol **24** to 90 °C in benzene revealed, by $^1H$ NMR, a new diol **26** with three olefinic protons. A major difference from previous 5–8–5 thermolyses products, however, was the large, 18 Hz vicinal coupling between a pair of olefinic protons that was observed in this structure, an indication that the 5–8–5 system possessed a *trans*-olefin in its cyclooctadienoid framework. This is not unprecedented since studies by Martin and Eisenmann revealed that *cis*,*trans*-cyclooctadiene is formed, along with *cis*,*cis*-cyclooctadiene, in the thermolysis of *syn*- and *anti*-tricyclo-[4.2.0.0$^{2,5}$]-octane.[1a]

Upon exposure to air, the *trans*-olefinic protons of compound **26** apparently shift upfield. Treatment of this new compound with 3,5-dinitrobenzoyl chloride generated a crystalline material that confirmed our suspicion (Figure 1); the thermolysis product possessed a strained *trans*-olefin that epoxidizes readily in air. In an optimized procedure, the thermolysis is run at 90 °C in benzene for 3 h and is subsequently exposed to $O_2$ (1 atm), followed by TBS protection of the primary alcohol to give epoxide **27** in 78% yield (Scheme 6). Of particular importance, this result shows that unlike the examples described in Table 1 and eqs 2 and 3, thermolysis of a polyfused ring system with the *cis*,*syn*,*cis*-relative stereochemistry and no bridging tether rearranges in a formally symmetry-allowed fashion, but stops at the *cis*,*trans*-cyclooctadiene intermediate.

***Scheme 6.*** Tether Influence on Thermolysis[a]



[a] (a) At 90 °C, benzene; (b) 1 atm $O_2$, TBSCl, imid., $Et_3N$ (78%); (c) 160 °C, benzene, or 90 °C, DBU, benzene (98%); (d) MeMgBr, (2.2 equiv) benzene, 110 °C (89%, based on 90% conv.).

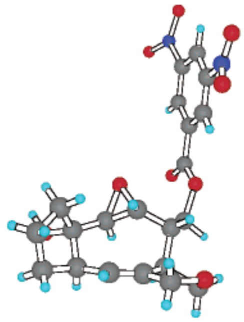


***Figure 1.*** X-ray crystal structure of thermolysis product **26** reacted with air and 3,5-dinitrobenzoyl chloride.

A minor product isolated in the thermolysis of diol **24**, which contained only two olefinic protons and a carbonyl stretch by IR, is ketone **28**. It is expected that this compound arose through a [3,3]-sigmatropic rearrangement of compound **26**, much like that which is occurring in eq 3 of Scheme 1. Whereas the cyclononadiene is only a predicted intermediate in the previous thermolyses, the oxygen substituent in this case facilitates the oxy-Cope and stabilizes the nine-membered ketone-containing product **28**. The thermolysis of the diol **24** could be optimized to give exclusively the cyclononenone **28** by heating substrate **24** to 160 °C or by warming to 90 °C in the presence of DBU. To determine whether *cis*,*trans*-cyclooctadiene **26** is indeed an intermediate in the formation of the nine-membered ring compound **28**, the starting diol **24** was first heated to 90 °C in benzene for 3 h to provide **26**, and was then subjected to DBU

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[18] For a review, see: Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1999**, 737.

and heated to 90 °C for an additional 3 h. The nine-membered ring ketone **28** was isolated in 98% after purification on silica.

These results indicate that the bridge used to prepare the photoadducts in Table 1 is responsible for the symmetry-forbidden fragmentation pathway observed in these thermolyses. Remarkably, similar control over the stereochemical course of the thermolysis is possible by even the introduction of a temporary bridging element. Treatment of diol **24** with MeMgBr (2.2 equiv) in benzene by heating it to 110 °C for 6 h yielded *cis*,*cis*-cyclooctadiene **29** in 80% with a 10% recovery of starting material (Scheme 6). Presumably, the bridging magnesium chelate established between the two alkoxide groups is sufficient to steer the fragmentation toward the symmetry-forbidden pathway. The structural and stereochemical identity of compound **29** was confirmed by correlating this product with thermal adduct **18**, a structure established unambiguously through X-ray crystallography. Interestingly, our inability to effect a thermal oxy-Cope rearrangement on compound **29** provides additional support that its formation is through a unique and separate pathway from the *trans*-isomer **26**.

## Summary

The above observations highlight the substantial influence a bridging substituent can have in the thermal fragmentation of polyfused cyclobutanes with the *cis*,*syn*,*cis*-relative stereochemistry. In the absence of the bridge, the reaction proceeds in a formal symmetry-allowed manner through a *cis*,*trans*-cyclooctadiene product, whereas when a conformationally restrictive tether is present, a symmetry-forbidden process is followed to yield a *cis*,*cis*-cyclooctadiene-containing 5−8−5 product.

Overall, these highly strained, polyfused cyclobutane systems provide a unique and rapid entry into the 5−8−5 ring system, a framework found in several diterpenoid natural products. Given the variety of relative stereochemical relationships in the ring fusions of the possible natural product targets, it is particularly important to have a flexible and predictable method for generating these materials in a concise and stereocontrolled manner. Knowledge on how to manipulate the relative stereochemistry in these thermal fragmentations provides a unique opportunity for accessing a wider range of suitable targets.

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**Supporting Information Available:** Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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