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# Stereochemical Anomaly in the Thermal Conversion of 7,8-Dioxy-7-alkenylbenzocyclobutenes to Dihydronaphthalenes

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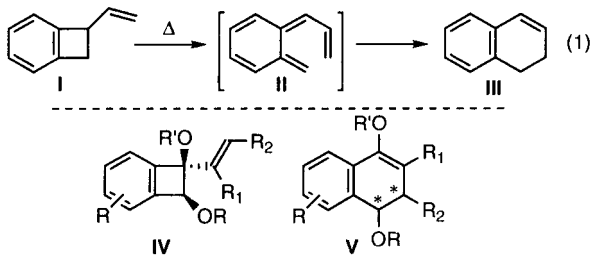
## ABSTRACT




**The stereochemistry of the thermal conversion of alkenylbenzocyclobutenol into dihydronaphthalene was studied. Experiments on the substrates IV, in which two oxy functions are cis, often resulted in the formation of *abnormal* products in view of the orbital consideration.**

Thermal conversion of alkenylbenzocyclobutene **I** to dihydronaphthalene **III** is an intriguing tandem electrocyclic reaction with potential synthetic utility (eq 1).[1,2] Reported herein is the observation of an unexpected stereochemical outcome in this two-step process (**IV**→**V**) in that product **V** was composed exclusively or mainly of the stereostructure opposite to that expected from orbital consideration. The anomaly comes most probably from a characteristic feature shared by the compounds **IV** employed in the present study, namely *cis*-dioxy groups on the four-membered ring.

A wide variety of starting compounds **IV** were prepared by taking advantage of the ready availability of the benzocyclobutenones **1a**−**c** via the regioselective [2 + 2] cycloaddition of α-alkoxybenzynes and ketene silyl acetals,[3] to which stereodefined alkenyl groups were installed, and the product was methylated in situ (Scheme 1).

The addition of styryllithium to **1a** or **1b** was completely stereoselective, giving **2a** or **2b** as a single product and establishing the cis relationship of two oxy functionalities.[4] Alcohol **2c** and acetate **2d** were prepared as shown in Scheme 1.

Thermolysis of **2a**−**d** showed a reactivity dependence on the R group (Scheme 2). The alcohol **2c** was a poor substrate for the reaction, and prolonged reaction in refluxing toluene gave a complex mixture of products. In sharp contrast, the corresponding silyl ether **2a** underwent smooth rearrangement to give the dihydronaphthalene **3a**,[5] and no naphthalene

(1) For selected examples, see: (a) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. (b) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800. (c) Liebeskind, L. S.; Iyer, S.; Jewell, C. F., Jr. *J. Org. Chem.* **1986**, *51*, 3065. (d) Hickman, D. N.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron Lett.* **1991**, *32*, 819. (e) Hickman, D. N.; Hodgetts, K. J.; Mackman, P. S.; Wallace, T. W.; Wardleworth, J. M. *Tetrahedron* **1996**, *52*, 2235. (f) Winters, M. P.; Stranberg, M.; Moore, H. W. *J. Org. Chem.* **1994**, *59*, 7572. (g) Matsumoto, T.; Hamura, T.; Miyamoto, M.; Suzuki, K. *Tetrahedron Lett.* **1998**, *39*, 4853. (h) Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, *4*, 229.

(2) Diels−Alder reaction of quinodimethane and ethylene is a relevant approach to such bicyclic structures. For a recent example of the *intermolecular* version of the reaction, see: Allen, J. G.; Hentemann, M. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 571.

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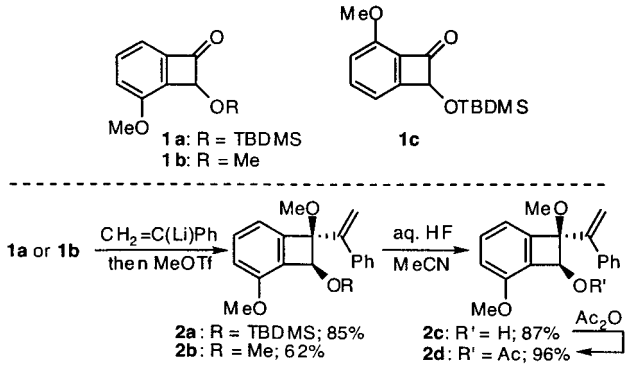
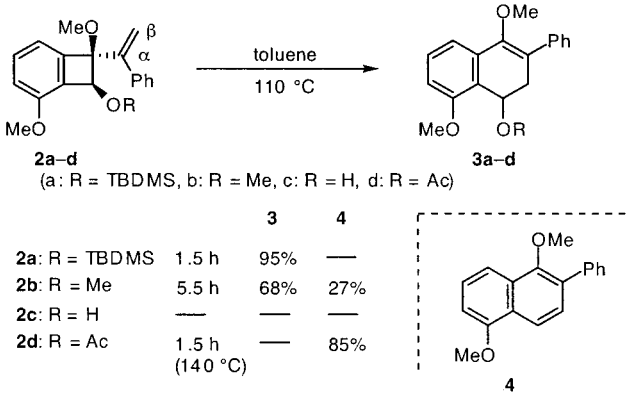
**Scheme 1**



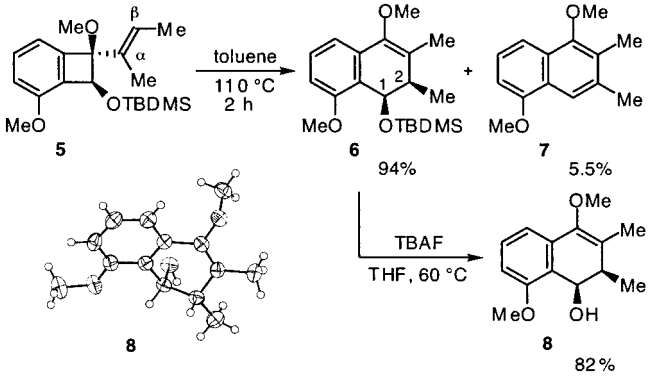

**4** was observed.[6] The reactivity of the ether **2b** or the ester **2d** was by far inferior, requiring a longer reaction time for **2b** or a higher reaction temperature, i.e., xylene reflux for **2d**. In either case, the naphthalene **4** was obtained as the side or the sole product.

**Scheme 2**




To examine the stereochemistry of the reaction, compound **5** possessing an α,*β*-dimethylvinyl group with (*E*)-configuration was prepared. It turned out that the reaction proceeded

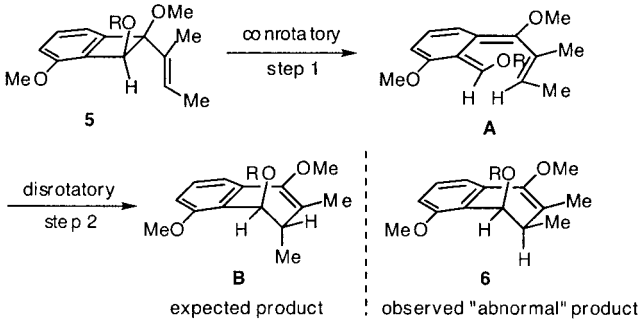
**Scheme 3.** Thermal Ring Enlargment-1: *Abnormal*




stereoselectively, giving the cis ether **6** ($J_{1,2}$ = 3.3 Hz) as a single isomer, which was unambiguously verified by X-ray analysis of the derived alcohol **8**.

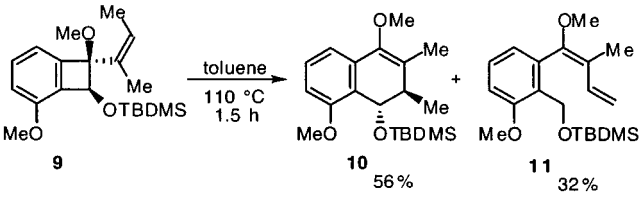
*Remarkably, this stereochemical outcome was opposite to the one expected from orbital consideration.* The expected scenario is the *conrotatory* opening of **5** to the quinodimethane **A**[7] and its 6*π*-electrocyclization in a *disrotatory* fashion to give the trans silyl ether **B**, whose stereochemistry would be opposite to that of the observed "abnormal" product **6** (Scheme 4).

**Scheme 4.** Stereochemical Course Expected from Orbital Symmetry




Reaction of **9**, containing a (*Z*)-olefin (cf. **5**), also provided the abnormal ring expansion product **10** (= **B**) as a single isomer (Scheme 5). In this case, the observed product was

**Scheme 5.** Thermal Ring Enlargement-2: *Abnormal*




the trans dihydronaphthalene **10** ($J_{1,2}$ = 1.7 Hz) rather than the cis product as expected by orbital considerations. The lower yield of **10** was due to the competing formation of the diene **11** (single isomer; the geometry was undefined) that could be rationalized by the 1,7-hydrogen shift in the quinodimethane intermediate (vide infra).

Likewise, substrates **12** and **13**, positional isomers of **5** and **9** with respect to the location of the methoxy group on the aromatic ring,[8] were also converted to the abnormal

(3) (a) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177. (b) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *36*, 3377. (c) Hosoya, T.; Hamura, T.; Kuriyama, Y.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Synlett* **2000**, 520.

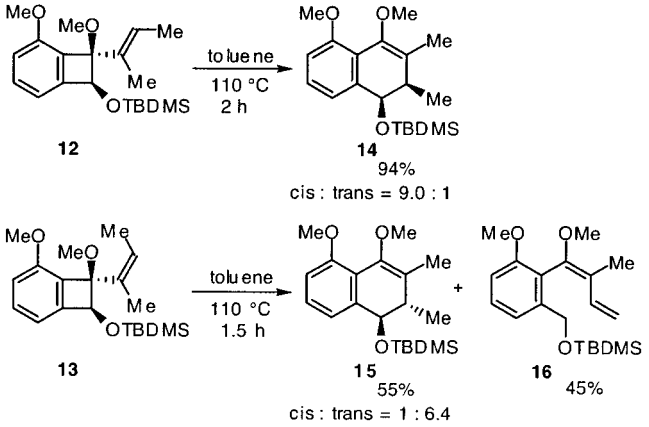
(4) The stereochemistry was determined by NOE studies.

(5) All new compounds were fully characterized by spectroscopic means and combustion analysis. See Supporting Information.

(6) The result was different from the cases for the corresponding reactions under basic conditions; see ref 1g.

(7) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199.

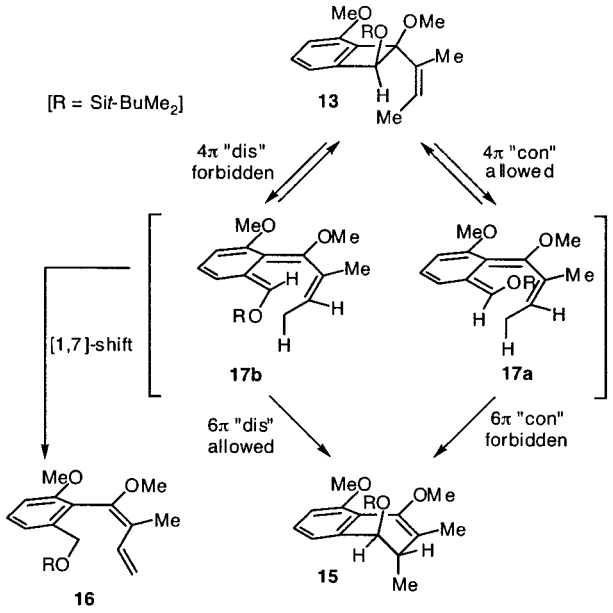
**Scheme 6.** Thermal Ring Enlargement-3: *Abnormal*




products **14**[9] and **15** (Scheme 6). In these cases, however, the stereoselectivity was not as complete as with substrates **5** and **9** (cf. Schemes 3 and 5).

The two possible explanations for the conversion of **13**→**15** using orbital symmetry considerations both require the involvement of a forbidden electrocyclization (Scheme 7). Although this is perhaps not unreasonable given the

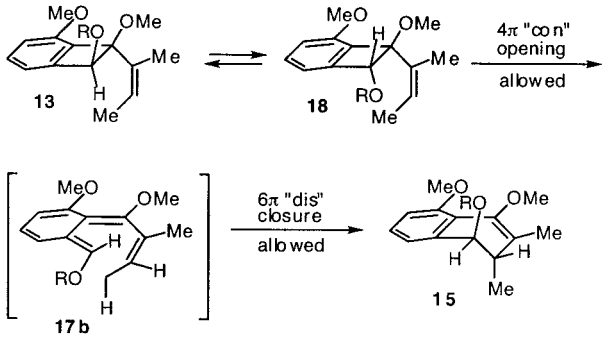
**Scheme 7.** Two Possible Stereochemical Explanations Involving Forbidden Electrocyclization




increasing number of forbidden processes reported in the literature, particularly when the systems are perturbed by the electron-donating/withdrawing substituent(s),[10] we sought an alternative explanation.

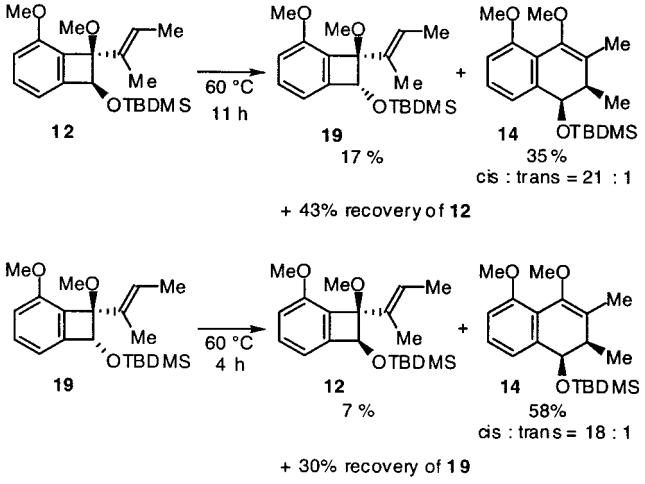
It is the prior stereomutation of the starting material **13** into the *trans*-dioxy compound **18**. Such an isomerization was recently documented for the related *cis*-benzocyclobutenediols and was ascribed to the intermediacy of a diradical species.[10d,e] Given this case, we need to only consider two *allowed* electrocyclic reactions of the isomerized product **18** in order to explain the abnormal product **15**. Importantly, in view of the torquoselectivity,[11] the reactivity of **18** is safely assumed to be higher in the conrotatory opening in comparison that of the corresponding *cis*-dioxy isomer **13** (Scheme 8).

**Scheme 8.** Another Possible Stereochemical Explanation




Upon gently heating the *cis*-dioxy isomer **12** (60 °C, 11 h), we indeed observed the cis/trans isomerization (Scheme 9). The *trans*-dioxy isomer **19** was isolated along with

**Scheme 9.** Stereochemical Mutation of Dioxybenzocyclobutenes




recovered **12** and the ring-enlarged product **14**. The isomerization was also observed even upon starting from the *trans*-dioxy substrate **19**,[12] giving the *cis*-dioxy isomer **12** together with recovered **19** and the product **14**.

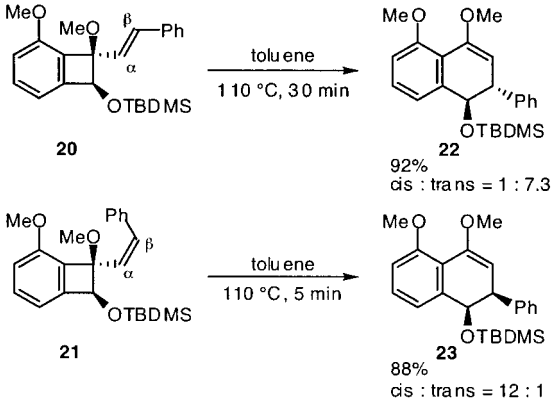
(8) Prepared from **1c**; see Supporting Information.

(9) The stereochemistry was determined by X-ray analysis of the corresponding alcohol (TBAF, THF, rt).

(10) (a) Berson, J. A. *Acc. Chem. Res.* **1972**, *5*, 406. (b) Carpenter, B. K. *Tetrahedron* **1978**, 1877. (c) Spellmeyer, D. C.; Houk, K. N.; Rondan, N. G.; Miller, R. D.; Franz, L.; Fickes, G. N. *J. Am. Chem. Soc.* **1989**, *111*, 5356. (d) Roth, W. R.; Rekowski, V.; Börner, S.; Quast, M. *Liebigs Ann.* **1996**, 409. (e) Paul, T.; Boese, R.; Steller, I.; Bandmann, H.; Gescheidt, G.; Korth, H.-K.; Sustmann, R. *Eur. J. Org. Chem.* **1999**, 551.

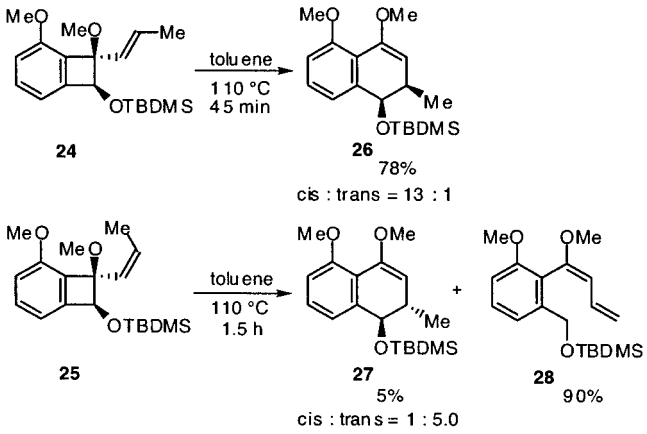
Although both of these possibilities seemed to explain the abnormal stereochemistry, an additional puzzling feature appeared. Some of the reactions followed the *normal* stereochemical course, depending on the substituent of the vinyl group. For example, the (*E*)-*β*-styryl ether **20** gave the trans product **22** and the (*Z*)-styryl ether **21** gave the cis product **23**[13] as a major isomer, as expected by orbital consideration (Scheme 10).

**Scheme 10.** Thermal Ring Enlargtement-4: *Normal*




In contrast, the (*E*)-propenyl substrate **24** gave largely the abnormal cis product **26**[13] (Scheme 11). Thus, an impressive

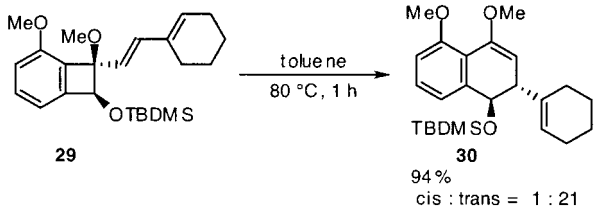
**Scheme 11.** Thermal Ring Enlargement-5: *Abnormal*




changeover of the stereochemistry occurs depending on the *β*-substituent on the vinyl group. The (*Z*)-propenyl substrate **25** underwent predominantly the 1,7-hydrogen shift, giving **28** in 90% yield along with a small amount of the rearranged product **27**, which again was mainly abnormal.

It was also noted that the reactivity was dependent on the *β*-substituent of the vinyl group. Styryl substrates **20** and **21** reacted much faster than the corresponding propenyl compounds **24** and **25**. With the notion that the differences in stereochemistry and reactivity may stem from the presence or absence of an additional $\pi$ system on the vinyl group, substrate **29** possessing a *β*-cyclohexenyl group was subjected to the rearrangement. Indeed, upon being heated at 80 °C, substrate **29** underwent smooth rearrangement to give trans ether **30** as the major product.[14] Thus, the stereochemical relationship was the same as the *β*-styryl case and followed the expected pathway (Scheme 12).

**Scheme 12.** Thermal Ring Enlargement-6: *Normal*




The observation in Schemes 10−12 suggested an interesting notion that a styryl or dienyl group, *not a simple alkenyl group*, might have a strong preference for the inward rotation that even overcomes the energetics associated with placing the alkoxy group inside.[15]

In summary, we have described unusual stereochemical courses of the thermal ring expansion of various alkenylbenzocyclobutenol derivatives into dihydronaphthalenes. Further studies are currently underway in our laboratories.

**Supporting Information Available:** General procedures and spectral data for compounds **2**−**30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125. (c) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157. (d) Nakamura, K.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 686.

(12) The silyl ether **19** was prepared by Mitsunobu reaction of the "cis" alcohol obtained from **12** and subsequent silylation.

(13) The stereochemistry was determined by X-ray analysis of the corresponding siloxy ketone (0.12 M $H_2SO_4$, THF, rt).

(14) The stereochemistry was determined by X-ray analysis of the corresponding hydroxy ketone (0.12 M $H_2SO_4$, THF, rt, and then TBAF, THF).

(15) Experimental and computational studies on this hypothesis are in progress. We thank one of the referees for a helpful suggestion.