Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 6677–6679

Impressive changeover of reaction course in ring expansion of styrylbenzocyclobutenol under alkoxide-forming conditions

Isao Takemura, Takashi Matsumoto and Keisuke Suzuki*

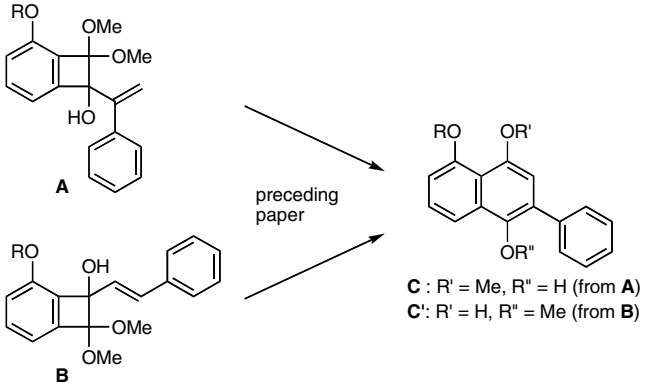
Department of Chemistry, Tokyo Institute of Technology, and SORST, Japan Science and Technology Agency (JST), 2-12-1 Ookayama, Meguro-ku, Tokyo 152-8551, Japan

Received 27 April 2006; revised 12 June 2006; accepted 15 June 2006
Available online 28 July 2006

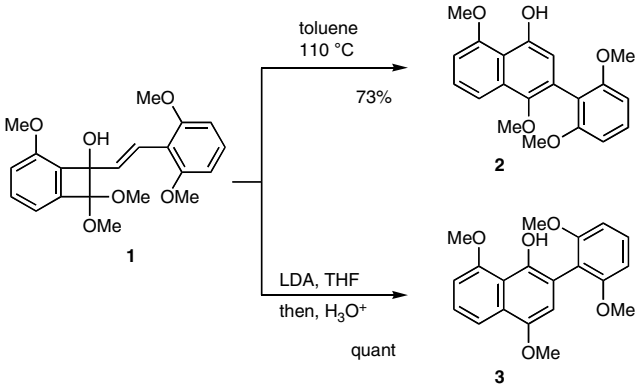
Abstract—Impressive changeover of the reaction course was observed in the rearrangement of styrylbenzocyclobutenol derivative **1**. While the thermal reaction gave naphthalene **2**, the base-promoted reaction gave the isomeric product **3** in high yield.

In relevance to the synthesis of polycyclic aromatic natural products, we have described in the preceding letter an approach for constructing phenylnaphthalene structures via the ring enlargement of styrylbenzocyclobutenols under *thermal* conditions (Scheme 1).[1] Two isomeric starting materials **A** and **B**, differing in the connectivity of the styryl unit (α or β) and the benzocyclobutene unit, could be converted to closely related structures **C** and **C′**, which share the same skeleton, but with complementary protection pattern.

In contrast to the *convergency* of this process, described herein is its *divergency*, which was unexpectedly found in continuing studies (Scheme 2; **1**→**3**). Thus, simple heating of benzocyclobutenol **1** in refluxing toluene gave the



Scheme 1.



Scheme 2.

expected phenylnaphthalene **2**.[2] The same reaction was attempted under the base-promoted conditions, hoping to gain rate acceleration effect, if any. Indeed, upon conversion of **1** to the corresponding lithium alkoxide (LDA, THF, −78 °C), the starting material **1** was smoothly consumed during the warmup to 0 °C in 2 h. Unexpectedly, however, the product isolated in quantitative yield was isomer **3**, after careful quenching with 2 M aqueous hydrochloric acid. The structure of **3** was assigned by extensive NOE study (Fig. 1).[3] Note the difference in the locations of the aryl groups in **2** and **3**. Herein, we feature the origin of this unexpected result, involving an intriguing skeletal rearrangement.

For gaining insight into the reaction mechanism, labeling experiments were carried out. Upon subjection of the ^{13}C-labeled substrate **1*** to the reaction conditions

* Corresponding author. Tel.: +81 5734 2228; fax: +81 3 5734 2788; e-mail: ksuzuki@chem.titech.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.06.079

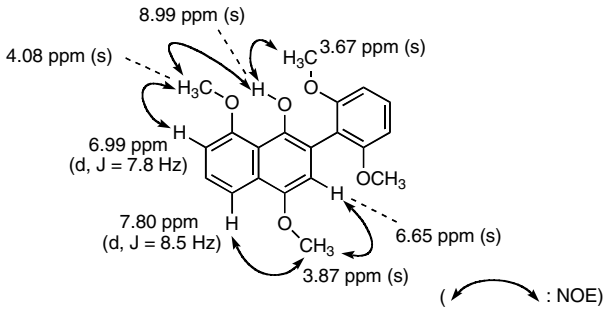
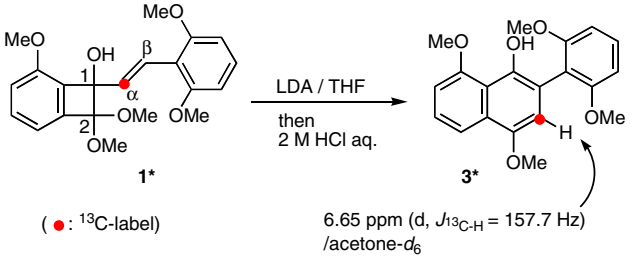


Figure 1. NOE study of compound **3**.

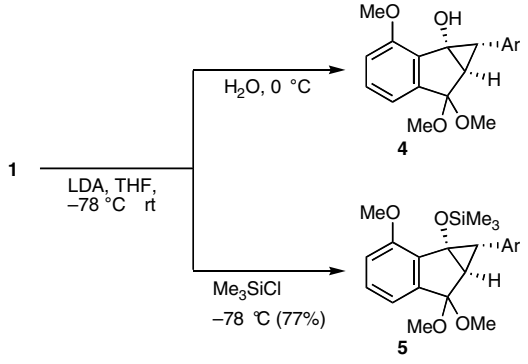
as stated above, the final location of the labeled carbon in **3*** was as shown in Scheme 3, clearly indicating that the fission of the C(1)–C(α) bond was involved.[2]

TLC-Monitoring suggested the presence of an intermediate in this puzzling reaction. Upon careful quenching with water, the unstable intermediate was identified as cyclopropanol **4** (Scheme 4). Since **4** was unstable toward chromatographic purification (SiO_2), we attempted to trap it as a stable derivative. After some experimentation, quenching of the reaction with Me_3SiCl, rather than aqueous HCl, enabled us to obtain silyl ether **5**, which gave nice single crystals for X-ray analysis (Fig. 2).[4] Thus, the intermediate was proven to be tricyclic compound **4**, in which the 2,6-dimethoxyphenyl group is disposed to the *exo* direction.

Based on these data, a possible mechanism could be drawn (Scheme 5). Assuming an ionic mechanism, the first step would be the alkoxide-induced 1,2-shift of the acetal carbon, that is C(2), to generate transient benzyl anion **II**, which counterattacks the carbonyl group to give cyclopropanolate **III**.[5]



Scheme 3.



Scheme 4.

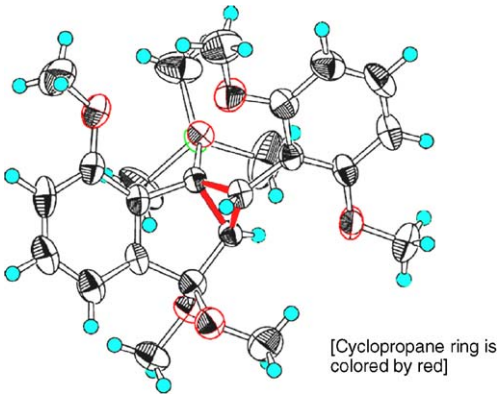
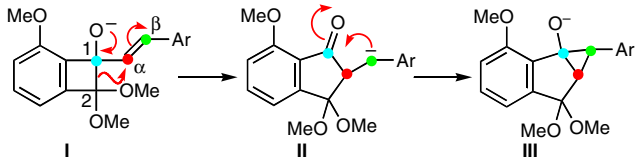


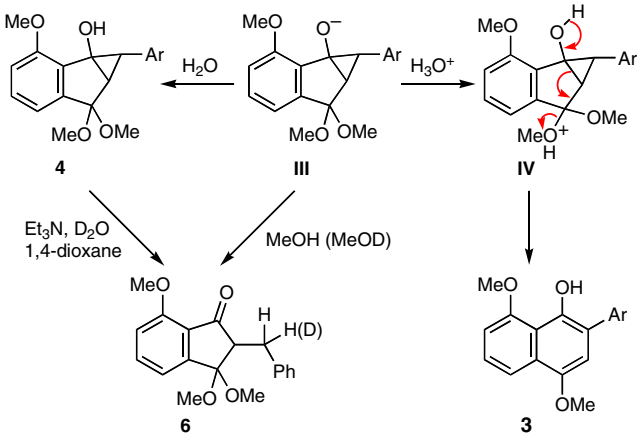
Figure 2. ORTEP drawing of the X-ray structure of **5**.[4]

Subsequent fate of tricyclic intermediate **III** depends on the method of quenching (Scheme 6). In the case of the acid quenching, phenol **3** was the product, which could be explained by the acid activation of the dimethyl acetal to induce the cleavage of cyclopropanol as in **IV**. By contrast, quenching with water gave acid-sensitive cyclopropanol **4**, which manifests another key aspect in the present skeletal rearrangement to **3**. Furthermore, it is interesting to note that quenching with MeOH (0 °C) gave indanone **6** in quantitative yield. Use of MeOD furnished deuterated **6** as indicated. The diverse modes of the cyclopropane cleavage are related to the well-known tautomeric behavior of cyclopropanols under basic conditions.[6] Conversion of **4** was also promoted by treatment with Et_3N in D_2O, giving indanone **6** deuterated at the benzylic position.

Finally, we examined the generality of this reaction. Table 1 shows the comparison of the reactions under thermal/basic conditions for the related substrates **1b–d** with different aromatic moieties (Ar). We found the thermal

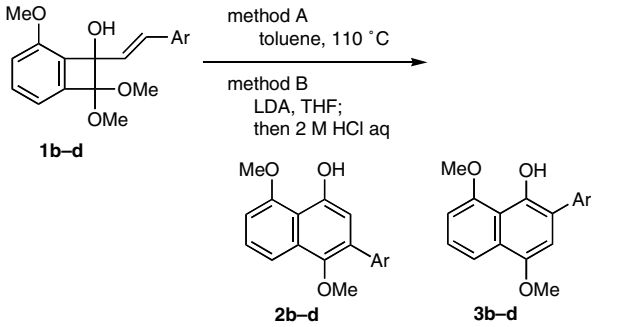


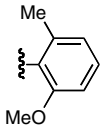
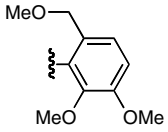
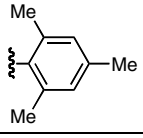
Scheme 5.



Scheme 6.

Table 1.



Run	Ar	Method	Yield (%)	2:3
1		A	96	**2b** only
		B	90	2:98
2		A[a]	88	**2c** only
		B	46	7:93
3		A	79	**2d** only
		B	79	38:63

[a] See Ref. 7.

reactions (method A) invariably afforded the expected products **2b–d**, while the base-promoted conditions led to mixtures of products **3b–d** accompanied by variable amounts of 'thermal products' **2b–d**.

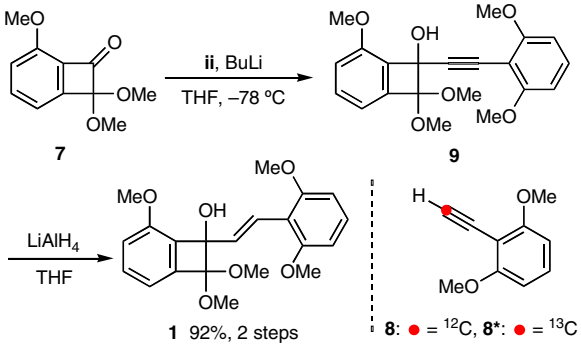
In conclusion, we have described an impressive change-over of reaction course in the rearrangement of styryl-benzocyclobutenol derivative **1**, which is not only interesting from mechanistic standpoints, but also have implication related to the synthesis of polyaromatic natural products.

Acknowledgments

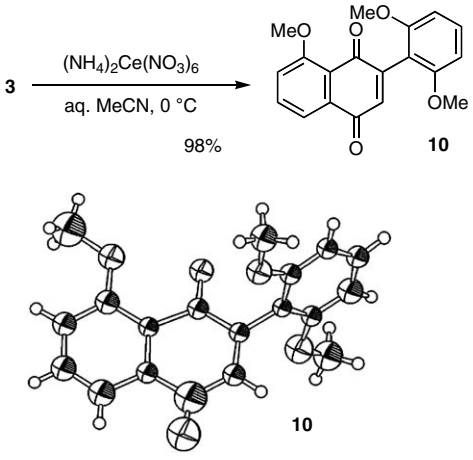
Thanks are due to Professors Daisuke Uemura (Nagoya) and Tohru Fukuyama (Tokyo) for helpful suggestions. We thank Mr. M. Bando, Otsuka Pharmaceutical Co., for X-ray analysis. Partial financial support by 21st Century COE Program is gratefully acknowledged.

References and notes

1. Takemura, I.; Imura, K.; Matsumoto, T.; Suzuki, K., see preceding paper. *Tetrahedron Lett.* **2006**, *47*, doi:10.1016/j.tetlet.2006.06.078.
2. Compound **1** was prepared by reaction of ketone **7** and the anion from alkyne **8** followed by hydroalumination. ^{13}C-Labeled substrate **1*** was prepared by using the labeled alkyne **8***.

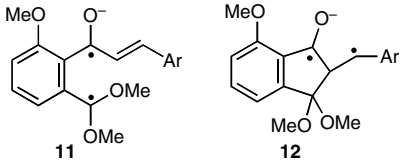


3. Conversion to the corresponding quinone derivative **10** was the additional structure proof.



ORTEP drawing of quinone **10**.[4]

4. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 243852 (for compound **5**) and 244793 (for compound **10**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
5. Since considerable data have been accumulated for the role of homolytic processes in the related system, the corresponding radical-based mechanism also could be possible, including homolysis of the four-membered ring to form a diradical **11** followed by recombination via **12**.



Roth, W. R.; Rekowski, V.; Börner, S.; Quast, M. *Liebigs Ann. Chem.* **1996**, 409–430; Paul, T.; Boese, R.; Steller, I.; Bandmann, H.; Gescheidt, G.; Korth, H.-G.; Sustmann, R. *Eur. J. Org. Chem.* **1999**, 551–563.
6. Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605–624.
7. Compound **13** was also obtained in 10% yield as a side product.