# Synthesis of Benzocyclooctene Derivatives via Thermal Ring Expansion of Dienylbenzocyclobutenes

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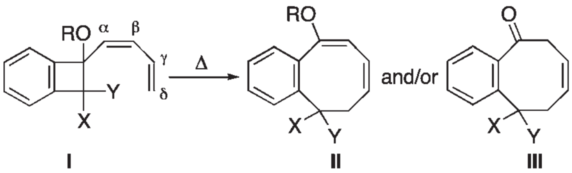
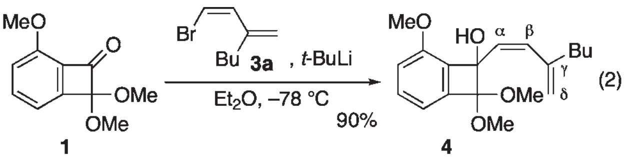
Dienylbenzocyclobutenes, readily available by the cycloaddition of benzyne and ketene silyl actetal followed by addition of dienyllithium, underwent thermal four-carbon ring expansion to give benzocyclooctenone derivatives in high yields. In some cases, acid treatment of the thermal product gave tricyclic ketones via transannular bond formation.

The synthetic challenge posed by eight-membered rings has attracted considerable interest in the synthesis of this structure motif imbedded in natural products such as taxol and ophioborin.[1] The major difficulty stems from the strain inherent in such a medium ring by the transannular interactions.[2] Herein, we report a facile access to the eight-membered ring fused to an aromatic ring by way of the [4 + 4] process[3] summarized in eq 1, *i.e.*, the thermal rearrangement of the dienylbenzocyclobutene **I** to give the eight-membered ring **II**, which is transformed spontaneously ($R = H$) or by acid hydrolysis ($R = SiMe_3$) to the benzocyclooctenone **III** in high yield.[5]

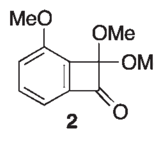


(1)

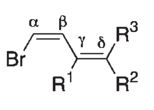
Eq 2 exemplifies the synthesis of the starting material **4** by the reaction of the dienyllithium [generated from **3a**[6] and *t*-BuLi (2 equiv)] and benzocyclobutenone **1**. The latter, in turn, was regiospecifically prepared by the [2 + 2] cycloaddition of benzyne and ketene silyl acetal.[7] Related compounds having different substitution patterns at the $\gamma$ and $\delta$ positions were similarly prepared by using the dienylbromides **3b**–**3d** as the precursor to the respective dienyllithium. In one case, the isomeric benzocyclobutenone **2**[8] was also used (*vide infra*, see Table 1, entry 1).



(2)

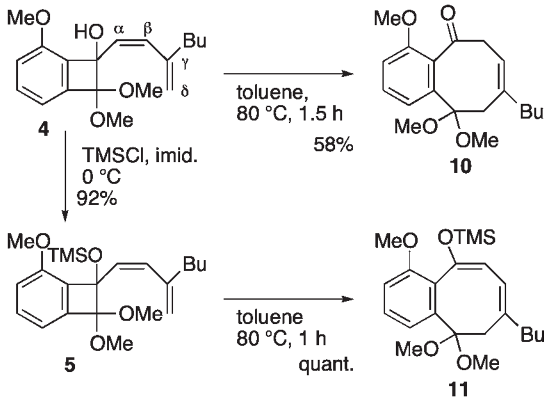


**2**



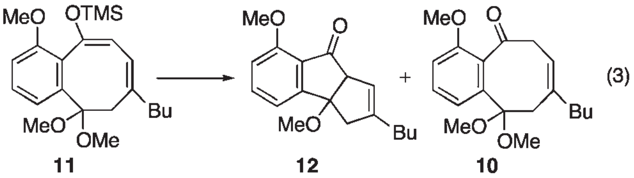
**3b**: $R^1 = H$, $R^2 = Bu$, $R^3 = H$
**3c**: $R^1 = Me$, $R^2 = Me$, $R^3 = H$
**3d**: $R^1 = H$, $R^2 = Me$, $R^3 = Me$

Preliminary experiments showed that the skeletal change of the alcohol **4** was effected by simple heating in toluene (80 °C, 1.5 h), thereby giving the cyclooctenone **10** in 58% yield.[9] The product was solely composed of the unconjugated enone, implying that the tautomerization of the initially formed dienol occurred in a deconjugative manner. The transformation of **4** to **10** was further facilitated by the conversion of **4** to the corresponding silyl ether **5** (TMSCl, imidazole/DMF, 92%), which underwent the ring expansion by heating in toluene at 80 °C for 1 h. Evaporation of the solvent gave quantitative yield of the silyl ether **11** that was essentially pure by NMR analysis (Scheme 1).



**Scheme 1.**

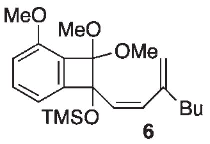
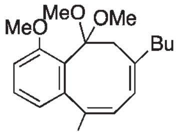
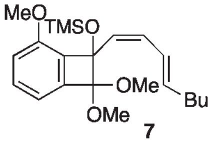
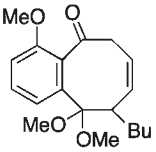
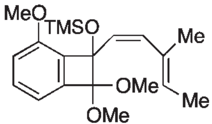
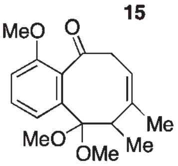
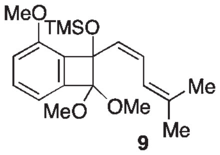
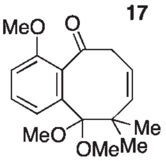
Hydrolytic conversion of **11** into **10** requires special notes due to the competing transannular cyclization (see, eq 3). Treatment of **11** with 0.1 M $H_2SO_4$ gave the expected enone **10** along with the tricyclic compound **12**, which was not too unexpected if one considers the close proximity of the dimethyl acetal moiety and the $\pi$-face of the silyl ether.[3b,4] This transannular cyclization became the sole event observed by employing PPTS in MeOH at 60 °C. However, it was found that KF in $CH_3CN$ effected clean hydrolysis of **11** to give the enone **10** in 91% yield (eq 3).



(3)

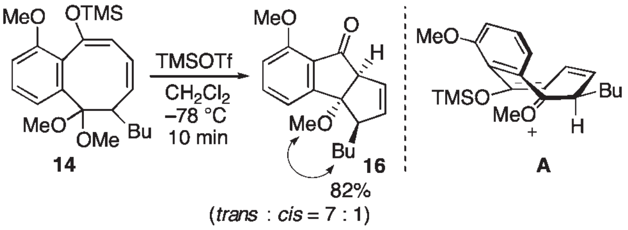
| | 12 | 10 |
|---|---|---|
| 0.1 M $H_2SO_4$<br>THF, 0 °C | 46% | 54% |
| PPTS, MeOH<br>60 °C | 83% | — |
| sat. aq KF<br>$n$-$Bu_4NCl$<br>$CH_3CN$, 0 °C | — | 91% |

**Table 1.**

| Entry | Substrate | Conditions$^a$ | Product$^b$ | Yield/% |
|---|---|---|---|---|
| 1 |  **6** | A (1 h) |  **13** | quant. |
| 2 |  **7** | A (2.5 h);<br>B (10 min) |  **15** | 82 |
| 3 |  **8** | A (5 h);<br>B (10 min) |  **17** | 82 |
| 4 |  **9** | A (17 h);<br>B (10 min) |  **18** | 71 |

$^a$A: 80 °C, toluene; B: 0.1 M $H_2SO_4$,THF, 0 °C. $^b$All new compounds were fully characterized by spectroscopic means and combustion analysis.

Application of the protocol to other substrates is summarized in Table 1. The silyl ether **6**, isomeric to **5**, rearranged to give the dienol silyl ether **13** in quantitative yield (entry 1), which was also hydrolyzed to the corresponding ketone in 90% yield by the KF procedure (*vide supra*). The thermal reaction was also applied to the silyl ethers **7** and **8**, having a $\delta$-butyl group or $\gamma,\delta$-dimethyl groups, to achieve ring expansion, albeit at a diminished rate. Treatment of the respective products with acid (0.1 M $H_2SO_4$/THF, 0 °C) cleanly gave the enones **15** and **17** without accompaniment by the transannular reaction,[10] presumably due to the increased steric bulk around the acetal moiety. If required, however, the transannular bond formation could be cleanly achieved by employing TMSOTf as exemplified the reaction of **14**, the initial product from the thermal reaction of **7**, to give the ketone **16** in 82% yield (see below). The NOE experiment showed that the main product had a *trans* relation with respect to the methoxy and the butyl groups, which could be rationalized by the reactive conformer **A** with the butyl group in a *pseudo*-equatorial disposition.



**14** **16** **A**

82%
(*trans* : *cis* = 7 : 1)

Finally, the *gem*-dimethyl substrate **9** also underwent slow ring expansion to give 71% yield of the enone **18**, which is particularly notable in view of the high steric hindrance at the reacting centers (entry 4).

In summary, the present [4 + 4] approach to the benzocyclooctenone derivatives starting from cyclobutenes and dienes should find utility in natural product synthesis, and further studies are currently underway in our laboratories.

Dedicated to Professor Teruaki Mukaiyama on occasion of his 75th birthday.

**References and Notes**

1 For syntheses of taxol and ophioborin, see: a) T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem. Eur. J*, **5**, 121 (1999). b) R. A. Holton, H.-B. Kim, C. Somoza, F. Liang, R. J. Biediger, P. D. Boatman, M. Shindo, C. C. Smith, S. Kim, H. Nadizadeh, Y. Suzuki, C. Tao, P. Vu, S. Tang, P. Zhang, K. K. Murthi, L. N. Gentile, and J. H. Liu, *J. Am. Chem. Soc.*, **116**, 1599 (1994). c) K. C. Nicolaou, H. Ueno, J.-J. Liu, P. G. Nantermet, Z. Yang, J. Renaud, K. Paulvannan, and R. Chadha, *J. Am. Chem. Soc.*, **117**, 653 (1995). d) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn, and M. J. Di Grandi, *J. Am. Chem. Soc.*, **118**, 2843 (1996). e) P. A. Wender, N. F. Badham, S. P. Conway, P. E. Floreancig, T. E. Glass, J. B. Houze, N. E. Krauss, D. Lee, D. G. Marquess, P. L. McGrane, W. Meng, M. G. Natchus, A. J. Shuker, J. C. Sutton, and R. E. Taylor, *J. Am. Chem. Soc.*, **119**, 2757 (1997). f) K. Morihira, R. Hara, S. Kawahara, T. Nishimori, N. Nakamura, H. Kusama, and I. Kuwajima, *J. Am. Chem. Soc.*, **120**, 12980 (1998). g) M. Rowley, M. Tsukamoto, and Y. Kishi, *J. Am. Chem. Soc.*, **111**, 2735 (1989), and references cited therein.

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3 For relateded [4 + 2 + 2] approaches to the cyclooctene and the benzocyclooctene syntheses, see: a) L. A. Paquette and J. Tae, *Tetrahedron Lett.*, **38**, 3151 (1997). b) M. Brands, R. Goddard, H. G. Wey, and H. Butenschön, *Angew. Chem., Int. Ed. Engl.*, **32**, 267 (1993).

4 L. A. Paquette and T. M. Morwick, *J. Am. Chem. Soc.*, **119**, 1230 (1997).

5 For selected examples for the related ring expansion of benzocyclobutene derivatives, see: a) L. A. Spangler and J. S. Swenton, *J. Org. Chem.*, **49**, 1800 (1984); J. S. Swenton, D. K. Anderson, D. K. Jackson, and L. Narasimhan, *J. Org. Chem.*, **46**, 4825 (1981). b) L. S. Liebeskind, S. Iyer, and C. F. Jewell, Jr., *J. Org. Chem.*, **51**, 3065 (1986). c) D. N. Hickman, K. J. Hodgetts, P. S. Mackman, T. W. Wallace, and J. M. Wardleworth, *Tetrahedron*, **52**, 2235 (1996); D. N. Hickman, T. W. Wallace, and J. M. Wardleworth, *Tetrahedron Lett.*, **32**, 819 (1991). d) M. P. Winters, M. Stranberg, and H. W. Moore, *J. Org. Chem.*, **59**, 7572 (1994).

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7 T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto, and K. Suzuki, *Synlett*, **1995**, 177. T. Hosoya, T. Hasegawa, Y. Kuriyama, and K. Suzuki, *Tetrahedron Lett.*, **36**, 3377 (1995). T. Hosoya, T. Hamura, Y. Kuriyama, M. Miyamoto, T. Matsumoto, and K. Suzuki, *Synlett*, **2000**, 520.

8 Unpublished. Preparation of **2** will be reported elsewhere.

9 The attempts at an anion-accelerated version were unfruitful (cf. T. Matsumoto, T. Hamura, M. Miyamoto, and K. Suzuki, *Tetrahedron Lett.*, **39**, 4853 (1998).)

10 Because of the lability toward hydrolysis, purification of the silyl ether **14** with PTLC gave **14** (63%) and hydrolyzed ketone **15** (12%).