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Ring Expansion of Cyclopropylbenzocyclobutenes En Route to Benzocycloheptenes

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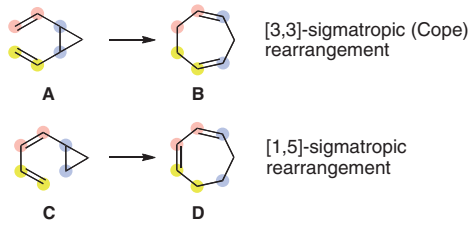
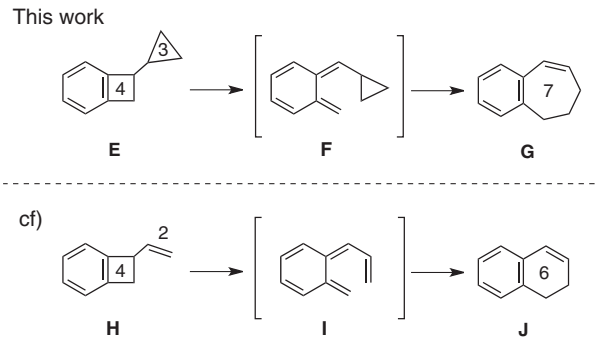
Ring expansion of benzocyclobutenes bearing a cyclopropane ring to benzocycloheptenes is described, which allows facile construction of highly functionalized seven-membered ring compounds.

Cope rearrangement of *vic*-divinylcyclopropane (**A** → **B**) is a typical "cyclopropane trick," providing an access to seven-membered ring frameworks (Scheme 1).[1] We became interested in applying such a trick to *isomeric* substrates, dienylcyclopropanes (**C** → **D**), which has been unprecedented, to our knowledge, due presumably to the relative stability of the starting conjugated system in **C**. In a formal sense, this process could be regarded as an "full-carbon" [1,5]-sigmatropic rearrangement, which is also rare.[2]



Scheme 1. Sigmatropic approaches to seven-membered rings.

We centered our particular attention to the *benzo*surrogates **F** with a hope that the diene moiety in **F** is an *o*-quinodimethane,[3] being reactive enough to take part in the projected reaction (Scheme 2). Further support for this idea came from our experiences in the "nor-methylene" surrogate **I** that is involved in the conversion of *vinyl*benzocyclobutene **H** into dihydronaphthalene **J**.[4,5]



Scheme 2. An analogy.

Given the case, an effective approach would become available en route to functionalized benzocycloheptenes,[6] which are embedded as a structural motif in some biologically active natural products (Figure 1).[7]

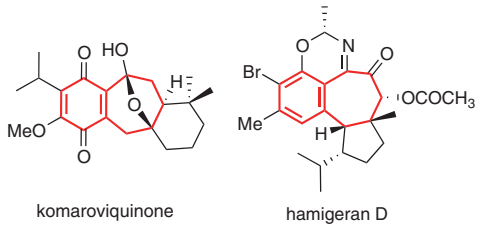
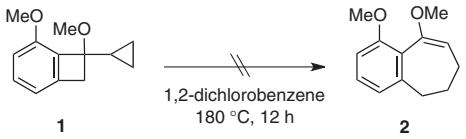


Figure 1. Natural products with benzocycloheptene skeleton.

Herein, we report an affirmative answer to this scenario, opening a route to highly substituted benzocycloheptenes.

As the initial experiment, model substrate **1** was subjected to thermal conditions (1,2-dichlorobenzene, 180 °C), which however, gave only a mixture of unidentified products, suggesting that the reaction pattern is not so straightforward (eq 1).



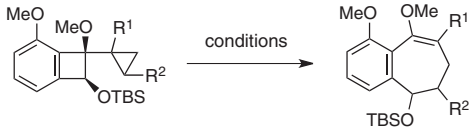
(1)

However, several clues for the viable substrates became available from further trials using model substrates **3a**–**3d**. (Table 1). Substrate **3a** with a siloxy substituent on the cyclobutene ring gave a trace amount of benzocycloheptene **4a** under thermal conditions (1,2-dichlorobenzene, 180 °C, 12 h, Entry 1). Substituents on the cyclopropane ring proved important as well, since substrate **3b** possessing a trimethylsilyl group led to smooth formation of **4b** in 41% yield (mesitylene, 160 °C, 12 h, Entry 2). Introduction of a formyl group (R^2 = CHO) posed a dramatic effect on the reactivity: aldehyde **3c** underwent the reaction at lower temperature (*p*-xylene, 140 °C, 2 h), giving smoothly two stereoisomeric benzocycloheptenes **4c** in 74% combined yield (Entry 3). Again the presence/absence of the TMS group on the cyclopropane ring[8] made a difference: the non-silyl substrate **3d** only gave an intractable mixture of unidentified products (Entry 4). In all, a TMS- and a CHO-groups cooperate to realize the reaction.

The planar structure of the product **4c** was assigned by ^{1}H–^{1}H COSY and HMBC analyses, which indicated the regioselectivity in cleavage of the three-membered ring. Production of **4c** as the sole product, but not its regioisomer **4c′**, clearly shows that the bond cleavage occurred at bond A within the cyclopropane ring, but not at bond B (Figure 2).[9]

Furthermore, the product **4c** was a mixture of *cis*/*trans*-isomers (*cis*:*trans* = 1:1.2). Assignment of the stereochemistry relied on X-ray crystallographic analysis on single crystals of *trans*-**4c** (recrystallization from hexane and CH_2Cl_2)[10] (Figure 3).

Table 1. Substituent effect on cyclopropane ring



3a–d **4a–d**

Entry	Substrate	R^1	R^2	Product	Yield/%
1	**3a**	H	H	**4a**	5
2	**3b**	$SiMe_3$	H	**4b**	41
3	**3c**[a]	$SiMe_3$	CHO	**4c**[b]	74 (80)[c]
4	**3d**	H	CHO	**4d**	—[d]

[a]Single diastereomer. [b]Diastereomers ratio (d.r.) = 1.2:1. [c]Two diastereomers of **3c** were independently subjected to the reaction. [d]Mixture of unidentified products.

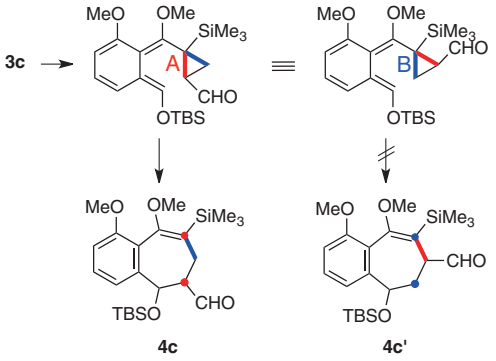


Figure 2. Two possible modes of bond cleavage.

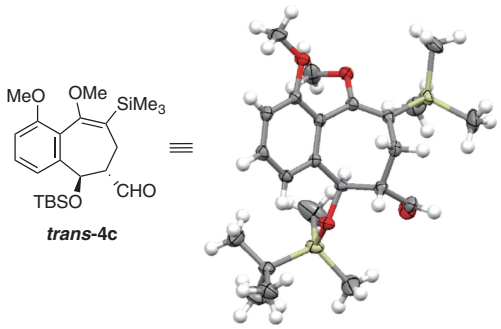
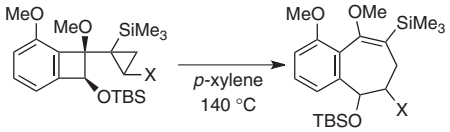


Figure 3. Structure assignment on *trans*-**4c**.

Upon application of the thermal conditions to other related substrates, we noted that the structural requirements for viable substrates were fairly strict.

First, the necessity of an electron-withdrawing group (e.g., CHO in **3c**) could be ascribed to the ease of bond cleavage of the cyclopropane ring.[11] Indeed, substrate **3e** with an ester function underwent smooth reaction to give **4e** in excellent yield (Entry 1, Table 2). Interestingly, a phenyl group in **3f** had a similar effect, allowing the conversion to benzocycloheptene **4f** in high yield (Entry 2). Substrate **3g** having an ethynyl group also reacted smoothly to give product **4g**, albeit a longer reaction time was needed (Entry 3). Vinyl derivative **3h** gave the corresponding product **4h** in 70% yield in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical inhibitor (Entry 4). On the other hand, the reaction of silyl ether **3i** lacking such an electron-withdrawing group was sluggish, giving only 24% yield of the product **4i** even after 4 h (Entry 5).

Table 2. Substrate scope

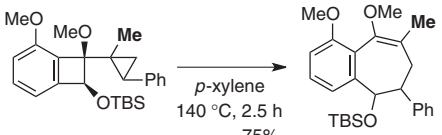


3e–i **4e–i**

Entry	Substrate	X	Time/h	Product[a]	Yield/%
1	**3e**[b]	CO_2Me	0.5	**4e**[c]	97 (88)[d]
2	**3f**[e]	Ph	0.5	**4f**[b]	87
3	**3g**[b]	C≡CH	5	**4g**[c]	72
4[f]	**3h**[g]	$CH{=}CH_2$	1.5	**4h**[e]	70
5	**3i**[b]	CH_2OTBS	4[h]	**4i**[b]	24

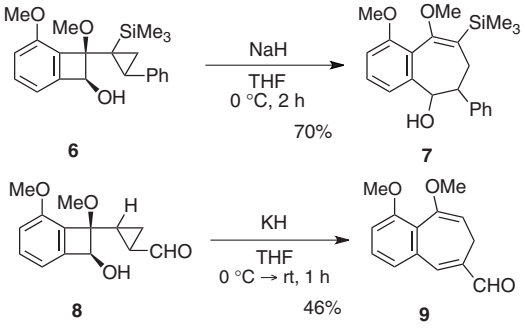
[a]For the relative stereochemistry, see Supporting Information.[14] [b]Single diastereomer. [c]d.r. = 1.3:1. [d]Two diastereomers of **3e** were independently subjected to the reaction. [e]d.r. = 3.5:1. [f]BHT was used as an additive. [g]d.r. = 4.9:1. [h]Mesitylene, 160 °C.

Second, the effect of the Me_3Si-group on the cyclopropane ring is notable, which could be interpreted by steric factors (Thorpe–Ingold effect)[12] to place the cyclopropane in the vicinity to the quinonedimethide moiety.[13] Given the case, this group could be replaced by any other substituents larger than a hydrogen. Indeed, substrate **3j**, in which a Me_3Si-group was replaced by a methyl group, also underwent the reaction to give 75% yield of product **4j**,[14] albeit requiring a longer reaction time (eq 2).



3j **4j** (2)

In order to expand the scope, we sought milder conditions for this ring enlargement, finding that the alkoxide-induced conditions dramatically accelerated the reaction.[15,16] Upon treatment with NaH in THF, alcohol **6** underwent smooth ring expansion at lower reaction temperature (0 °C), giving **7**[14] in 70% yield (eq 3). In the same way, alcohol **8** with non-silyl cyclopropane was treated with KH at 0 °C. Upon warming up to ambient temperature, the seven-membered ring product **9** was produced in 46% yield, resulting from the desired ring enlargement followed by dehydration (eq 4).

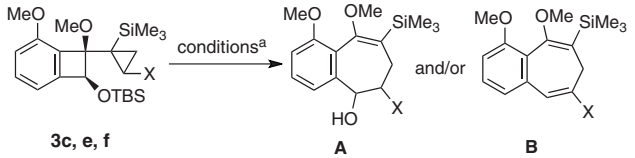


6 **7** (3)

8 **9** (4)

Furthermore, starting with silyl ethers, we found that the reaction was possible under desilylating conditions (Table 3). Upon treatment of **3c** with tetra(*n*-butyl)ammonium fluoride (TBAF) in THF (0 °C → 25 °C), the desilylation induced the ring enlargement, giving seven-membered enal **10** (Entry 1). It should be noted that no alcohol product **A** was obtained, giving instead the dehydrated product **B**. With gentle heating (45 °C), the protocol was also applicable to ester **3e**, giving alcohol **11** in 64% yield. In this case, the dehydrated product **12** was coproduced in 17% yield (Entry 2). Likewise, phenyl derivative **3f** gave the corresponding product **7** in high yield (Entry 3). Notably, no dehydrated product **B** was obtained in this case. Thus, this TBAF-promoted protocol is effective for the ring enlargement stage. However, it is also noted that the fairly basic conditions effect the primary product to undergo further dehydration, depending on the nature of the substituent X.

Table 3. TBAF-promoted ring expansion



3c, e, f **A** **B**

Entry	Substrate	X	Temp./°C	Product (Yield/%)	
				A[b]	**B**
1	**3c**[c]	CHO	0 → 25	—	**10**[d] (72)
2	**3e**[c]	CO_2Me	45	**11**[e] (64)	**12** (17)
3	**3f**[f]	Ph	45	**7**[c] (73)	—

[a]TBAF (1.5 equiv), THF, 0.5–8 h. [b]For the relative stereochemistry, see the Supporting Information.[14] [c]Single diastereomer. [d]Desilylated product of **3c** was obtained in 22% yield. [e]d.r. = 1.1:1. [f]d.r. = 4.9:1.

In conclusion, ring expansion of benzocyclobutenes bearing a cyclopropane ring is described, allowing facile construction of highly functionalized seven-membered ring compounds. Further work on the exploitation of the process in natural product synthesis is in progress in our laboratory.

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9 The stereochemical course of the reaction is not defined, while the *trans*-isomer was recovered after the reaction in Table 1, Entry 1. For stereochemical insight for a related reaction, see Ref. 4b.

10 Crystallographic data reported in this manuscript have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-842518. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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