

Synthesis of 3,4-Bis(benzylidene)cyclobutenes

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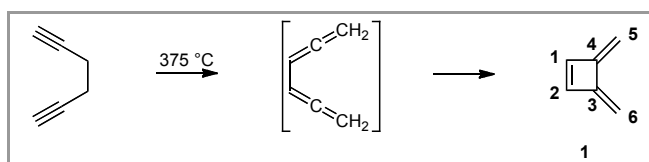
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Abstract: The syntheses of several derivatives of 3,4-bis(benzylidene)cyclobutene are reported. Previously unknown 1,2-dibromo-3,4-bis(benzylidene)cyclobutene was obtained through *in situ* generation of 1,6-diphenyl-3,4-dibromo-1,2,4,5-tetraene followed by electrocyclic ring closure. Ensuing reduction and metal-catalyzed cross-coupling provided additional derivatives. The effects of ring strain on the geometry and electronics of these derivatives were examined by X-Ray crystallography and ^1H NMR, respectively.

Key words: electrocyclic reactions, ring closure, allenes, highly strained ring systems, metal-catalyzed cross-coupling

3,4-Bis(methylene)cyclobutene (**1**) is a highly-strained and air-sensitive isomer of benzene that was first detected in 1961 from the Hofmann elimination of 3,4-bis[(trimethylammonio)methyl]cyclobutene dihydroxide.¹ The relative thermal stability of derivatives of **1** initially came as a surprise due to the significant ring strain. As a result, there has been much fascination with the synthesis and reactivity of compounds bearing this core structure. Unsubstituted **1** can be generated quantitatively through the thermal rearrangement of 1,5-hexadiyne: an initial [3,3]-sigmatropic rearrangement affords hexa-1,2,4,5-tetraene, which undergoes conrotatory [2+2] electrocyclic ring closure to yield **1** (Scheme 1).²

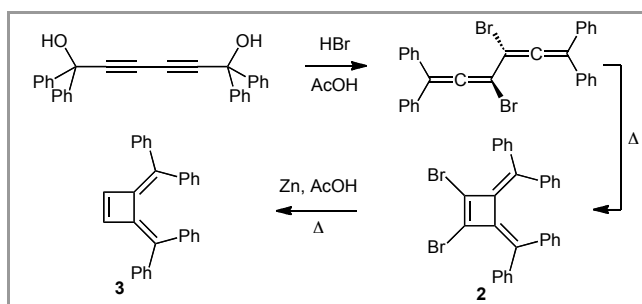


Scheme 1 Rearrangement of 1,5-hexadiyne to **1**.

Compound **1** has a significant dipole ($\mu = 0.616 \pm 0.002$ D) for a simple hydrocarbon, as increased electron density at C5 and C6 reduces the antiaromatic character of the ring.^{2c} Theoretical and experimental studies have shown that **1** is more similar to a cross-conjugated diene than to a triene. Additionally, the *exo*-methylene groups in **1** do not react as a Diels-Alder diene, as the resulting product would contain antiaromatic cyclobutadiene. The primary factor influencing the unique structure and reactivity of **1** is the energetic cost of antiaromaticity.³

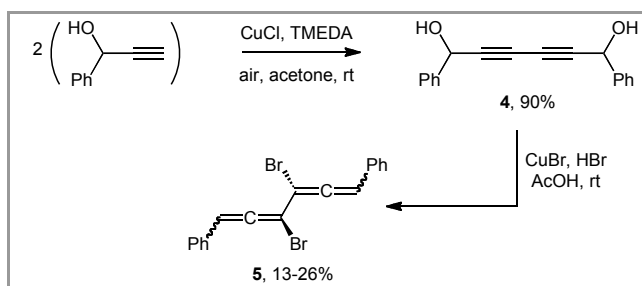
Although **1** is highly reactive, it is possible to synthesize air-stable analogs by installing electron-withdrawing groups, thereby reducing antiaromatic character.⁴ The most prominent example of this is 1,2-dibromo-3,4-bis(diphenylmethylene)cyclobutene (**2**),⁵

originally synthesized by Toda *et al.*⁶ The debrominated derivative (**3**) is readily available *via* reduction with zinc metal in acetic acid and is moderately air-stable as compared to **1** (Scheme 2).⁷ This synthetic scheme is limited in scope and functional group tolerance, due to its dependence on the use of tertiary propargyl alcohols, and harsh, acidic conditions. A new scheme is required to access less substituted derivatives and a wider range of functional groups.



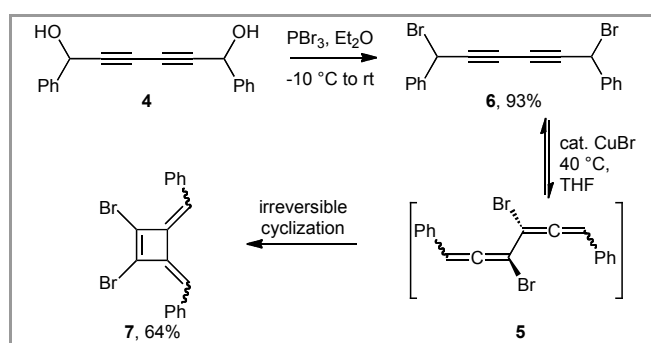
Scheme 2 Synthesis of **2** and **3** reported by Toda *et al.*

The rearrangement of propargyl alcohols to allenyl halides is a well-studied transformation.⁸ Glaser coupling of the corresponding terminal alkyne produces 1,6-Diphenyl-2,4-diyne-1,6-diol (**4**) on a large scale in good yield (100 g, 90%).⁹ Treatment of **4** with substoichiometric amounts of copper(I) bromide (CuBr) and concentrated hydrobromic acid (HBr) in acetic acid provides the desired 1,6-diphenyl-3,4-dibromo-1,2,4,5-tetraene (**5**, Scheme 3).¹⁰ Unfortunately, isolation of **5** is difficult, leading to decomposition and low yields (13-26%). Therefore, a synthesis that circumvents the direct isolation of **5** was pursued.



Scheme 3 Synthesis of intermediates **4** and **5**.

Copper(I) salts catalyze the reversible rearrangement of propargyl halides to allenyl halides.¹¹ Jacobs *et al.* reported a maximum conversion of alkyne to allene of 65% in the case of 3-bromopropyne. Interestingly, copper(I) salts have also been shown to catalyze the electrocyclic ring closure of diallenes to 3,4-bis(methylene)cyclobutenes.¹² The present system exploits the dual ability of copper(I) salts to achieve tandem rearrangement and irreversible electrocyclic ring closure (Scheme 4). Upon treatment with phosphorus tribromide (PBr₃), diol **4** is converted in high yield to dibromide **6**.¹³ As expected, upon heating to 40 °C in THF in the presence of 5 mol % CuBr, the crude product (**6**) was converted to a mixture of three isomers of 1,2-dibromo-3,4-bis(benzylidene)cyclobutene (**7**).



Scheme 4 Rearrangement and irreversible cyclization to form **7**.

The three isomers arise from the *E/Z* stereochemistry about the exocyclic double bonds and have been labeled as **7**(*in,out*), (*in,in*), and (*out,out*) referring to the position of the phenyl groups using nomenclature analogous to that used by Toda *et al.*¹⁴ The isomers of **7** are separable by column chromatography and the structure of each has been confirmed by X-ray crystallography (Figure 1).

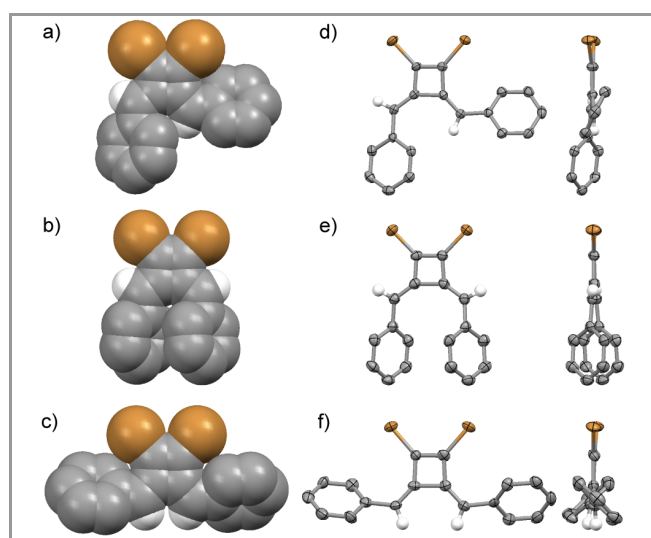


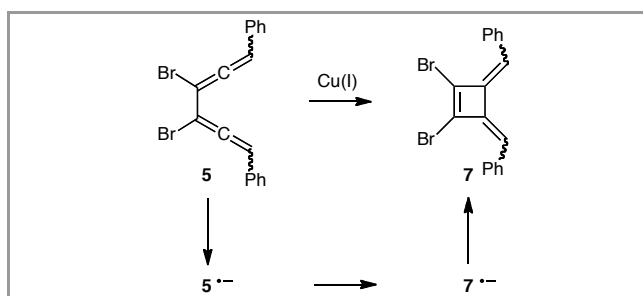
Figure 1 Space-filling (a-c) and front and side ellipsoid views (d-f) of X-Ray crystal structures of isomers of **7** (a,d) (*in,out*) (b,e) (*in,in*) (c,f) (*out,out*). Aromatic hydrogens omitted for clarity.

The formation of three isomers is consistent with the mechanism of the overall transformation. Starting from racemic 1-phenyl-2-propyn-1-ol, compounds **4** and **6** are a 1:1 mixture of the *rac* and *meso* stereoisomers, which rearrange to the corresponding isomers of **5**. The *meso* isomer then undergoes conrotatory cyclization to form exclusively **7**(*in,out*) while the *rac* isomers cyclize to either **7**(*in,in*) or **7**(*out,out*). Therefore, a 2:1:1 ratio of (*in,out*):(*in,in*):(*out,out*) isomers is expected. The distribution of products at different loadings of CuBr is listed in Table 1.¹⁵ The (*in,out*) isomer consistently accounts for approximately 50% of the product. When a pure sample of each isomer was irradiated with UV light,¹⁶ each isomerized to a mixture of approximately 67% (*in,out*), 23% (*in,in*), and 10% (*out,out*) isomers.¹⁵ This observation is consistent with calculations that predict the (*out,out*) isomer to be the highest in energy, although the differences are small.¹⁷

Table 1 Thermal distribution of isomers of **7**.

%CuBr	(<i>in,out</i>)	(<i>in,in</i>)	(<i>out,out</i>)
5	4.9 :	3.1 :	2.0
50	4.6 :	2.5 :	2.9
100	4.8 :	2.1 :	3.1
250	5.0 :	1.9 :	3.1

The increased energy of **7**(*out,out*) indicates the energetic cost of the phenyl groups twisting out of plane to reduce steric repulsion with the bromine atoms. The ability of the phenyl groups to π -stack is able to counterbalance the effect of steric repulsion and twisting in **7**(*in,in*). As shown in Table 1, the ratio of **7**(*out,out*) to **7**(*in,in*) increases with increased levels of the copper(I) source. Similarly, Pasto *et al.* found greater yields of sterically congested products with copper(I)-catalyzed ring closure of diallenes to 3,4-bisalkylidenecyclobutenes as compared to the strictly thermal process.^{12,18} It is proposed that the copper(I)-catalyzed cyclization occurs through a radical-anion process (Scheme 5). Theoretical investigation of the transformation of 1,2,4,5-hexatriene to **1** performed by Pasto *et al.* indicates that ring closure of the radical-anion is more exothermic than that of the neutral compound, creating an earlier transition state in which steric congestion (in the case of **7**(*out,out*)) or π -stacking (as in **7**(*in,in*)) in the product are less important.



Scheme 5 Copper(I)-catalyzed cyclization of **5** to **7** via radical anion intermediates.

Table 2 Structural information of **1** (B3LYP/6-31G**) and crystal structures of **7**. Redundant bond and torsion angles for symmetrical compounds have been omitted.

	1	7(in,out)	7(in,in)	7(out,out)	
Bond Length (Å)	C1 – C2	1.336	1.357	1.345	1.375
	C1 – C4	1.484	1.472	1.479	1.494
	C2 – C3	1.484	1.495	1.482	1.477
	C3 – C4	1.509	1.522	1.531	1.507
Distance (Å)	C5 – C6	3.409	3.508	3.679	3.340
Angle (°)	C1 – C2 – H(Br)	134	130	134	131
	C2 – C1 – H(Br)	-	133	-	-
	C2 – C3 – C6	137	131	130	139
	C1 – C4 – C5	-	140	-	-
Torsion (°)	C2 – C3 – C6 – Ph	0	29	43	42
	C1 – C4 – C5 – Ph	-	30	-	-

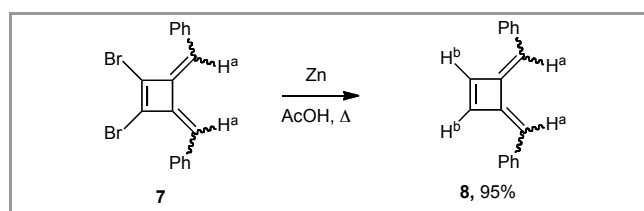
The structural differences between the isomers of **7** and the calculated structure of parent compound **1** (B3LYP/6-31G**) are summarized in Table 2. There is a notable deviation in internuclear distance between C5 and C6. This value is related to the bonding angle of C2-C3-C6 (and C1-C4-C5) and is determined by the steric interaction between either a phenyl ring and a bromine atom or between two phenyl rings. In the case of compound **1**, which lacks this steric interaction, the C5-C6 distance is 3.409 Å with a corresponding angle of 137°. The corresponding values of compound **7(out,out)** deviate the least from those of **1**, 0.069 Å and 2°, respectively. Compound **7(in,in)**, where the phenyl rings must twist in order to stack face-to-face and reduce steric repulsion, deviates the most from **1** with an increase in C5-C6 distance of 0.270 Å and a 7° decrease in the C2-C3-C6 angle.

The effects of steric bulk are also evident in variations of the angle defined by C1-C2-H(Br) (or C2-C1-H(Br)). In this regard, **7(in,in)** is the most similar to **1**. The angle is decreased by 3° in **7(out,out)** as the bromine atoms are forced closer together to accommodate the outward-pointing phenyl rings and minimize their twisting. As expected unsymmetrical **7(in,out)** exhibits both types of bond angles dependent on the position of the phenyl group.

Finally, and perhaps most significantly, is the difference in torsion angle caused by the twisting of the phenyl groups. In **7(in,out)** the phenyl groups only twist 29° and 30° out of plane whereas in **7(in,in)** and **7(out,out)** the corresponding values are 43° and 42°, respectively. Increased planarity (and therefore conjugation) of the benzylidene group in **7(in,out)** is a likely explanation for its favored formation in the photochemical isomerization.

Single isomers of **7** can be reduced to 3,4-bis(benzylidene)cyclobutene (**8**) with retention of the *E/Z* configuration by heating with zinc powder in

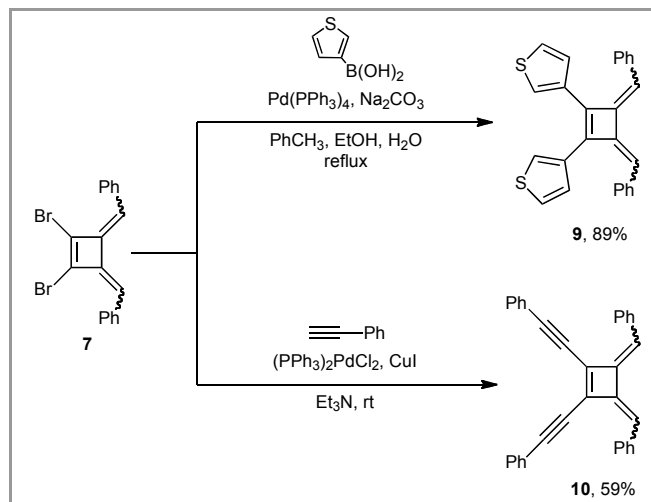
acetic acid (Scheme 6). Compound **8** is moderately stable, but decomposes slowly under air.¹⁹ A comparison of the ¹H NMR spectra of **7** and **8** is available in the supporting information (Figure S1). In the case of **8(in,in)** and **8(out,out)**, growth of the new H^b peak is evident. As expected from the dipole moment of parent compound **1**, the vinyl peaks for H^b are significantly deshielded and positioned downfield of the aromatic region. Previously, the synthesis of a single symmetrical isomer of **7** from the iron tricarbonyl complex of substituted cyclobutadiene was reported.²⁰ Based on our findings, however, it seems likely the authors had actually generated a mixture of symmetrical isomers (**8(in,in)** and **8(out,out)**).



Scheme 6 Reduction of single isomers of **7** to single isomers of **8** with retention of *E/Z* configuration.

Compound **7** can also be used as a coupling partner for metal-catalyzed cross-coupling reactions (Scheme 7). Coupling reactions were generally carried out using a single isomer of **7**, however no difference in efficiency of the reaction between isomers was observed. Two-fold Suzuki cross-coupling reaction between 3-thiophene boronic acid and **7** gave compound **9** in 89% yield. Attempts at oxidative cyclization between the thiophene rings of **9** to form benzodithiophene²¹ were unsuccessful due to the increased bond angles around the four-membered ring. Compound **7** also successfully participated in two-fold Sonogashira cross-coupling with phenylacetylene to produce **10** in 59% yield (Scheme 7). The absorption

and emission spectra of **10(out,out)** are shown in Figure 3; a difference in the optical characteristics between different isomers of **10** was not observed.



Scheme 7 Examples of metal-catalyzed cross-coupling of **7**.

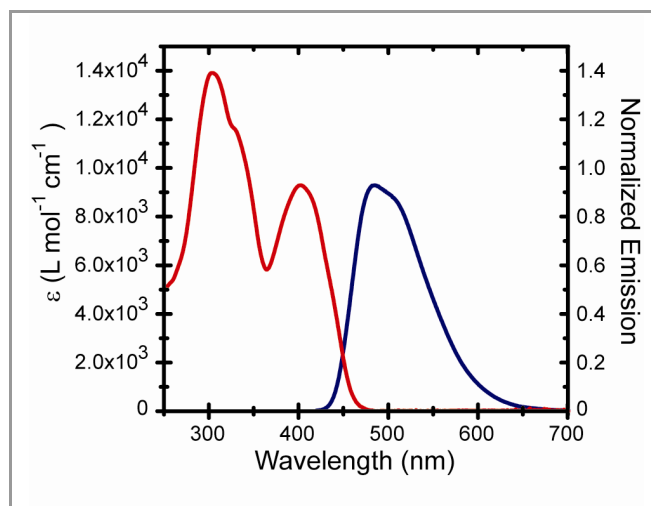


Figure 3 Absorption and emission curves of **10(out,out)** in chloroform ($\Phi_{em} = 0.63$, $t = 5.77$ ns).

In conclusion, we have developed a method for the synthesis of previously unknown 1,2-dibromo-3,4-bis(benzylidene)cyclobutene, **7**. Each of the three possible isomers of **7** were isolated and characterized by X-Ray crystallography. The utility of **7** as a starting material in the synthesis of additional highly strained molecules *via* reduction and metal-catalyzed cross-coupling has also been demonstrated.

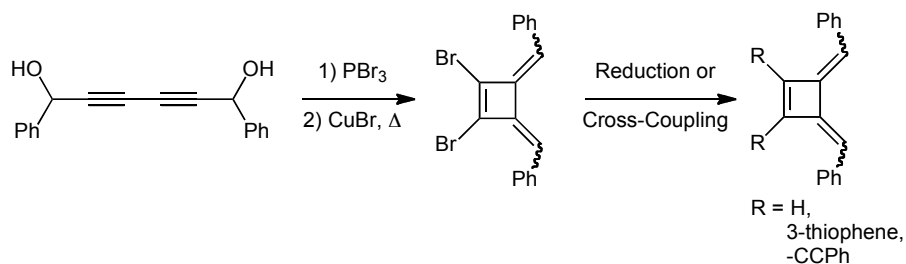
Supporting Information for this article is available online at <http://www.thieme-connect.de/ejournals/toc/synlett>.

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References

- (1) Blomquist, A. T.; Maitlis, P.M. *Proc. Chem. Soc. London*, **1961**, 332.
- (2) (a) Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1963**, *85*, 3308. (b) Huntsman, W. D.; Wristers, H. J. *J. Am. Chem. Soc.* **1965**, *89*, 342. (c) Collier, B. A. W.; Heffernan, M. L.; Jones, A. J. *Aust. J. Chem.* **1968**, *21*, 1807. (d) Hopf, H. *Angew. Chem. Int. Ed.* **1970**, *9*, 732.
- (3) Toda, F.; Garratt, P. *Chem. Rev.* **1992**, *92*, 1685.
- (4) Braverman, S.; Suresh Kumar, E. V. K.; Cherkinsky, M.; Sprecher, M.; Goldberg, I. *Tetrahedron*, **2005**, *61*, 3547.
- (5) For examples of the use of **2** see: (a) Toda, F.; Akagi, K. *J. Chem. Soc. D: Chem. Commun.* **1970**, 764. (b) Toda, F.; Akagi, K. *Tetrahedron*, **1971**, *27*, 2801. (c) Iyoda, M.; Kuwatani, Y.; Oda, M. *J. Am. Chem. Soc.* **1989**, *111*, 3761. (d) Toda, F.; Tanaka, K.; Sano, I.; Isozaki, T. *Angew. Chem.* **1994**, *106*, 1856. (e) Kuwatani, Y.; Yamamoto, G.; Iyoda, M. *Org. Lett.* **2003**, *5*, 3371. (f) Kuwatani, Y.; Yamamoto, G.; Oda, M.; Iyoda, M. *Bull. Chem. Soc. Jpn.* **2003**, *5*, 2188.
- (6) Toda, F.; Kumada, K.; Ishiguro, N.; Akagi, K. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3535.
- (7) Toda, F. *Chem. Commun.* **1969**, 1219.
- (8) Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes*. Elsevier Ltd.: Oxford, 2004; pp 235-265.
- (9) (a) Ulman, A.; Manassen, J. *J. Am. Chem. Soc.* **1975**, *97*, 6540. (b) Smith, C. D.; Tchabanenko, K.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron Lett.* **2006**, 47 3209.
- (10) Landor, S. R.; Demetriou, B.; Evans, R. J.; Grzeskowiak, R.; Devey, P. *J. Chem. Soc., Perkin Trans. 2.* **1972**, 1995.
- (11) Jacobs, T. L.; Brill, W. F. *J. Am. Chem. Soc.* **1953**, *75*, 1314.
- (12) (a) Kleveland, K.; Skattebøl, L. *J. Chem. Soc., Chem. Commun.* **1973**, 432. (b) Pasto, D. J.; Yang, S.-H. *J. Org. Chem.* **1989**, *54*, 3544.
- (13) Dibromide **6** was found to rearrange to **5** (~50%) and hydrolyze to **4** (~50%) upon chromatography on silica gel, and decomposed partially during recrystallization attempts.
- (14) Toda, F.; Tanaka, K.; Tamashima, T.; Kato, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 2724.
- (15) The distribution of isomers determined by ^1H NMR.
- (16) Photolysis experiments were conducted in hexane using a Hg pen-lamp, without the use of optical filters.
- (17) Spartan B3LYP/6-31+g*, relative E (kcal/mol): **7(in,out)** = -0.4487, **7(in,in)** = 0, **7(out,out)** = 0.0056.
- (18) Pasto, D. J.; Kong, W. *J. Org. Chem.* **1989**, *54*, 4028.
- (19) Attempts to purify compound **8** *via* column chromatography or recrystallization were unsuccessful due to its limited stability. Any impurities visible in Figure S1 are believed to be primarily high molecular weight decomposition products.
- (20) Roberts, B. W.; Wissner, A. *J. Am. Chem. Soc.* **1972**, *94*, 7168.
- (21) For examples of this methodology in the synthesis of polycyclic aromatic compounds see: (a) Tovar, J. D. Swager, T. M. *Adv. Mater.* **2001**, *13*(2), 1775. (b) Tovar, J. D.; Rose, A.; Swager, T. M. *J. Am. Chem. Soc.* **2002**, *124*, 7762.

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