Photochemistry

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The Profound Effect of the Ring Size in the Electrocyclic Opening of Cyclobutene-Fused Bicyclic Systems**

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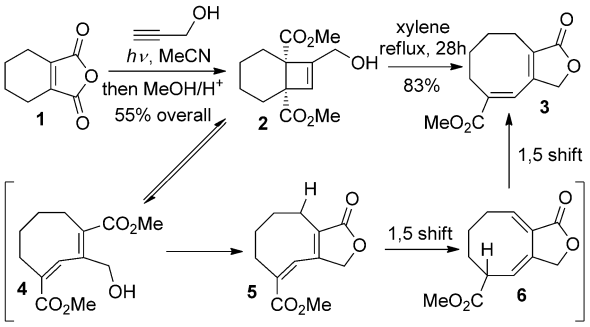
Abstract: *Fused cyclobutenes, prepared by the photocycloaddition of propargyl alcohols to cyclic anhydride chromophores, undergo facile thermochemical ring opening to fused γ-lactones. The size of the fused ring profoundly influences the temperature that is required to facilitate the ring opening (from 50 °C to 180 °C) and the nature of the product that is formed. Our studies provide new insights into the mechanistic course of these reactions and have been extended to facilitate the preparation of lactams fused to medium-sized rings.*

Medium to large carbocyclic rings are of great importance in organic chemistry and are commonly found as structural cores in an enormous range of biologically relevant natural products, including phorbol (7),[1] taxol (8),[2] byssochlamic acid (9),[3] eleutherobin (10).[4] Both strain and unfavorable entropic factors[5] mean that the synthesis by direct cyclization is often very difficult. It is especially acute in the formation of 8-, 9-, and 10-membered rings, often necessitating indirect methods such as ring expansion by rearrangement or fragmentation reactions. Such strategies involving 4-membered rings have proved to be a useful tool in total synthesis.[6]

We have reported[7] extensively on the photocycloaddition reactions of maleimide and maleic anhydride derivatives and their use in synthesis. Ring opening and ring expansion of cyclobutanes, cyclobutenes, and cyclobutanones[8] has proved useful, for example, in the synthesis of the cyclooctane terpenoids asteriscanolide[9] and pachylactone.[10] Specifically we found that photocycloaddition of tetrahydrophthalic anhydride **1** (THPA) with propargyl alcohol led, after alcoholysis, to the bicyclo[4.2.0]cyclooctene **2** (Scheme 1). Thermolysis of this cyclobutene provided bicyclic lactone **3** by way of an electrocyclic ring-opening/lactonization sequence.[10] In this particular case, the cyclooctadiene **3** was obtained with the *cis,cis*-diene geometry that formally represents a thermally forbidden process[11] through a disrotatory mode of ring opening. Although this method provides a valuable route to cyclooctanoids, the synthetic value of the overall process is somewhat limited because of the high temperatures that are required. Both the thermal and photochemical ring-opening reactions of cyclobutenes to medium and macrocyclic dienes have been the subject of previous mechanistic studies.[12] In 1969, McConaghy and Bloomfield[13] showed that the parent bicyclo[4.2.0]octene could undergo a conrotatory ring opening at temperatures as low as 110 °C. However, the putative *cis,trans*-cyclooctadiene rapidly reverts back to the starting material, thus preventing its isolation. We proposed that our "forbidden" sequence was initially proceeding through an allowed conrotatory ring opening to the *cis,trans*-cyclooctadiene **4**. A lactonization event leads to **5**, which is less likely to undergo reversion to a cyclobutene because of strain. Two sequential 1,5-sigmatropic shifts then occur, leading first to diene **6** before proceeding to the *cis,cis*-diene **3** (Scheme 1).



Scheme 1. Formation of a fused cyclooctadiene lactone by a "forbidden" conrotatory electrocyclic ring-opening/lactonization sequence.

Subsequently, Baldwin and Leber[14] carried out kinetic isotope experiments on simpler systems, which indicated that the disrotatory electrocyclic ring opening of cyclobutenes may be possible at extreme temperatures of 250 °C. A detailed computational study by de Lera[15] provided evidence for conrotatory ring opening followed by *trans*-to-*cis* isomerization. Very recently, Krenske, Houk, and Hsung[16] published convincing experimental and computational evidence for the transient formation of *cis,trans*-cyclooctadieneones during the thermally induced electrocyclic ring opening of cyclobutenamides. Houk has published[17] extensively on the torquoselectivity observed in monocyclic cyclobutenes.

The focus of our current study was the synthesis of a range of [*n*.2.0] ring systems and the exploration of their thermal

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ring opening in order to generalize the above sequence for the formation of bicyclic systems containing medium and macrocyclic rings fused to lactones. Of particular interest was the hypothesis that the ring opening of larger [*n*.2.0] substrates would lead to isolable *cis*,*trans*-bicyclic lactones (see compound **5**), thus confirming the conrotatory mode of ring opening in these fused systems.

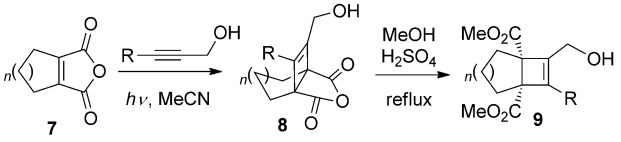
While the 6-membered anhydride **1** and its 5-membered homologue are readily obtainable, none of the higher members were commercially available. Fortunately, we were able to exploit the versatile methodology of Tanaka[18] to synthesize a range of cyclic anhydride derivatives. This method involved subjecting β-keto-ester-derived enol-triflates to a palladium-catalyzed carbonylation sequence, and gave us access to a number of isolated anhydrides **7** in good yields. These were then subjected to [2+2] photocycloaddition with propargyl alcohols using a medium-pressure 400 W Hg lamp in a water-cooled pyrex immersion well.

Generally, the photocycloadditions proceeded smoothly, allowing the isolation of the corresponding cyclobutenes **8** in moderate to good yields and in multigram quantities. Further scale-up could be achieved using our flow photochemistry techniques,[19] which allowed for example the synthesis of **8b** with a productivity of 1.3 $g\,h^{-1}$. Exceptions were observed with the 9- and 12-membered examples **7f** and **7g**, respectively. Both anhydrides were photochemically very active and were rapidly consumed upon irradiation to mainly unidentifiable side products. However, a sufficient amount of the cyclobutene could be synthesized for further study. Unfortunately, a lack of suitable routes to the corresponding 10- and 11-membered anhydrides prevented their study. Rather surprisingly, cycloaddition yields increased again with the 15-membered anhydride **7h**. Once suitable quantities of the cyclobutene anhydrides **8** were obtained, they were converted to the substrates required for thermolysis (**9**) by simple acid-catalyzed methanolysis (Table 1).

With a range of [*n*.2.0] bicyclic ring systems in hand, we were now in a position to undertake a systematic study of the thermolysis to see how the rate of electrocyclic ring opening is influenced by the size of the appended ring (Table 2). Although the thermolysis of diesters **9a** and **2** had been studied in our previous work, we were able to optimize them further. Thus, when the 5-membered system **9a** (Table 2, entry 1; R = H) was heated neat at 180 °C, it gave the ring-opened product in 25% yield (previously 6%) with high recovery of the starting cyclobutene. Prolonged heating, however, resulted in a reduced yield and extensive decomposition. The 6-membered example (**2**, Table 2, entry 2, R = H) also underwent slow but effective ring opening at 140 °C in xylenes to give the isolated *cis*,*cis*-cyclooctadiene **3** in an improved yield of 95%. Heating **2** neat at 180 °C for a shorter period of time resulted in extensive decomposition before maximum conversion could be achieved. The prolonged reaction times and high temperatures needed for these examples are undoubtedly linked to the highly strained nature of the *cis*,*trans*-diene intermediates (see **5**) formed by conrotatory ring opening en route to the 7- and 8-membered ring-opened systems.

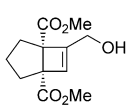
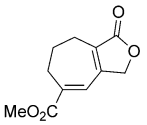
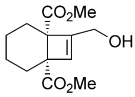
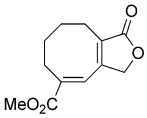
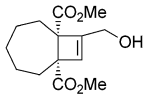
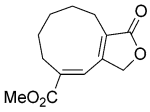
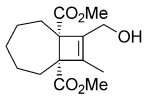
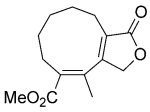
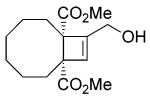
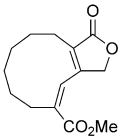
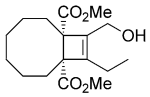
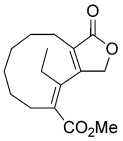
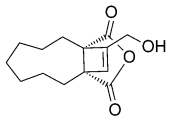
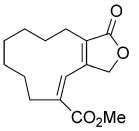
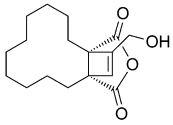
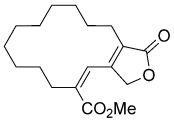
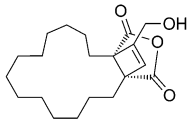
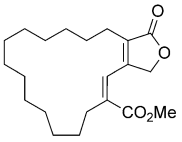
It was pleasing, therefore, to observe the comparatively rapid ring opening of the 7-membered homologue **9b** at 140 °C in xylene (Table 2, entry 3, R = H), which showed about 40% conversion after 6 h. The optimization of this reaction was achieved by simply heating **9b** neat at 180 °C, which resulted in the formation of the *cis*,*cis*-diene product in excellent yield (86%) in only 3 h. Interestingly, the methyl-substituted example **9c** underwent a similarly rapid ring-opening/lactonization sequence. Previously we found that the lower 6-membered homologue of this substrate failed to undergo ring opening, which we attributed to unfavorable transannular interactions in the initial *cis*,*trans*-cyclooctadiene, a factor that is clearly less of an issue with the larger compound **9c**. Increasing ring size led to a very significant lowering of the activation energy, allowing the ring-opening/lactonization sequence to **10d** to occur at just 90 °C in 24 h (Table 2, entry 5). A highly significant observation was that, for the first time, the ring-opened product **10d** had the *cis*,*trans*-diene geometry, which was confirmed by X-ray crystallography (see the Supporting Information). This observation clearly indicates a conrotatory ring opening and that the 10-membered ring readily accommodates a *trans*-alkene, thus obviating the need for it to undergo an isomerization as would appear to be the case in the lower homologues. The ethyl-substituted analogue **9e** also underwent the sequence at much lower temperatures (Table 2, entry 6). Very surprisingly, the ring opening of the 9-, 12-, and 15-membered-ring anhydrides **9f–h** occurred during the esterification process at just 50 °C, and none of the cyclobutene diesters could be isolated. These anhydrides gave the corresponding ring-expanded lactones **10f–h** in reasonable to good overall yields for one-pot, two-step processes. Once again, these larger ring systems were obtained with the *cis*,*trans*-diene geometry. Remarkably, the macrocyclic anhydride **9g** was found to undergo the electrocyclic ring-opening/lactonization sequence in 30% yield after 10 days at 0 °C in the refrigerator! The high reactivity of the cyclobutene ring in these macrocyclic fused systems is similar to some of the monocyclic cyclobutenes studied previously by Houk.[17]

Table 1: Preparation of [*n*.2.0]-fused bicyclic cyclobutenes for thermal electrocyclic ring opening.



Entry	Anhydride		R	Yield **8** [%]	Yield **9** [%]
1	**7a**	*n* = 1	H	70	74
2	**1**	*n* = 2	H	67	84
3	**7b**	*n* = 3	H	60	80
4	**7c**	*n* = 3	Me	55	77
5	**7d**	*n* = 4	H	62	80
6	**7e**	*n* = 4	Et	57	42
7	**7f**	*n* = 5	H	18	see Table 2
8	**7g**	*n* = 8	H	21	see Table 2
9	**7h**	*n* = 11	H	50	see Table 2

Table 2: Thermal electrocyclic ring opening of [*n*.2.0]-fused bicyclic cyclobutenes.

Ent.	Cyclobutene[a]		Cond.	Product		Yield [%]
1		**9a**	180 °C 24 h neat		**10a**	25
2		**2**	140 °C 48 h xylenes		**3**	95
3		**9b**	180 °C 3 h neat		**10b**	86
4		**9c**	180 °C 3 h neat		**10c**	70
5		**9d**	90 °C 24 h toluene		**10d**	79
6		**9e**	110 °C 16 h Toluene		**10e**	57
7		**9f**	50 °C 16 h H_2SO_4 MeOH		**10f**	37
8		**9g**	50 °C 16 h H_2SO_4 MeOH		**10g**	57
9		**9h**	50 °C 16 h H_2SO_4 MeOH		**10h**	48

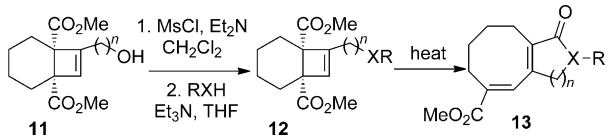
[a] All cyclobutene substrates were racemic.

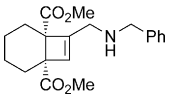
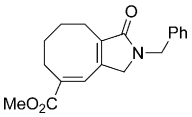
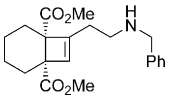
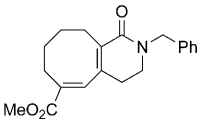
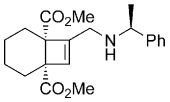
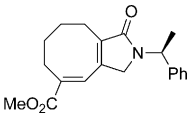
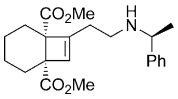
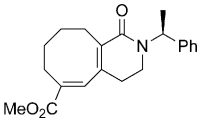
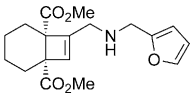
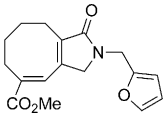
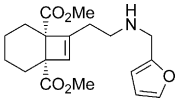
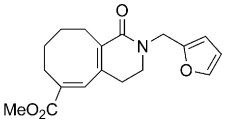
Modification of previously obtained cyclobutenes provided ready access to substrates for a thermal-ring-opening/lactamization sequence. For example, the formation of the mesylate of **2**, followed by amination with benzylamine gave the amino-substituted cyclobutene **12a** (R = CH_2Ph, $n = 1$). Thermolysis of **12a** gave the corresponding *cis*,*cis*-cyclooctadiene fused 5-membered lactam **13a** (R = CH_2Ph, $n = 1$; Table 3, entry 1). Notably, the product was formed in good yield at just 100 °C, which was significantly lower than the 140 °C required for the production of the corresponding lactone **2**. We attribute this observation to a faster rate for the lactamization compared to the lactonization during trapping of the highly strained *cis*,*trans*-cyclooctadiene intermediate (see **4** to **5**). The furyl-substituted derivatives behaved similarly and gave the lactam products **12e** and **12f** in good yield. Both benzyl- and furyl-substituted substrates underwent the thermal-ring-opening/lactamization sequence with good overall yields. Although the benzyl-substituted derivatives required the same temperature as **2**, they needed only half the reaction time to be completely lactamized. The furyl-substituted example underwent the formation of the 6-membered lactam at both a lower temperature and with a shorter reaction time.

In order to probe the mechanistic hypothesis in Scheme 1, we investigated the effect of additives on the slow conversion of **2** to **3** at high temperatures (Scheme 1). In particular, we were keen to demonstrate the reversible formation of the *cis*,*trans*-cycloctadiene **4** and its conversion to **5**. Running the thermolysis at a lower temperature of 110 °C in toluene resulted in an incomplete conversion (49 %) of **2** to product **3** after 100 h (Figure 1). Repeating the reaction with 20 mol % of added iodine gave a 92 % conversion after just 43 h. This dramatic acceleration can almost certainly be attributed to an iodine-assisted *trans*-to-*cis* isomerization of **4**, thus facilitating a direct lactonization to **3.** It could of course be argued that iodine initiates an alternative mode of cyclobutene ring opening. However, this seems unlikely, as repeating the same iodine-catalyzed sequence for the 4,5-membered-ring system **9a** at 110 °C and 140 °C showed no reaction and the starting material could be recovered. Thus, the iodine-catalyzsed ring opening did not occur at these lower temperatures (180 °C were required for the non-catalyzed process). Equally revealing was the thermolysis of **2** in toluene with 10 % *w*/*v* of added methanol. Here we observed that the sequence was significantly slower, giving just 14 % conversion after 93 h. This result adds weight to our initial proposal that the lactonization of **4** to **5** "locks out" the high energy *cis*,*trans*-cycloctadiene and prevents the cyclization back to **2** (Scheme 1). This slower overall conversion can be rationalized by the fact that a raised concentration of MeOH is likely to assist in the equilibration of lactone **5** back to cyclooctadiene **4** (Scheme 1).

This study has demonstrated that photochemically derived cyclobutenes readily undergo thermal electrocyclic ring opening, leading to γ-lactones fused to cyclic dienes with ring sizes ranging from 7 to 17 members. Overall, the three-step sequence utilizes only light, heat, and MeOH/H^+ to convert known cyclic anhydrides into a range of multifunctional bicyclic compounds. Critically, as the size of the ring fused to the cyclobutene increases, the activation energy for the thermal electrocyclic ring opening decreases, so that with the larger ring systems efficient ring opening occurred at 50 °C

Table 3: Lactam formation during conrotatory ring opening of bicyclo[4.2.0]octenes.



Ent.	Cyclobutene[a]	Cond.	Product	Yield [%]
1	 **12a**	100 °C 64 h toluene	 **13a**	82
2	 **12b**	140 °C 24 h xylenes	 **13b**	81
3	 **12c**	140 °C 24 h xylenes	 **13c**	67
4	 **12d**	140 °C 24 h xylenes	 **13d**	55
5	 **12e**	110 °C 52 h toluene	 **13e**	76
6	 **12f**	110 °C 24 h toluene	 **13f**	72

[a] All cyclobutene substrates were racemic except for **12c** and **12b**, which were obtained as a 1:1 mixture of diastereomers from photocycloaddition.

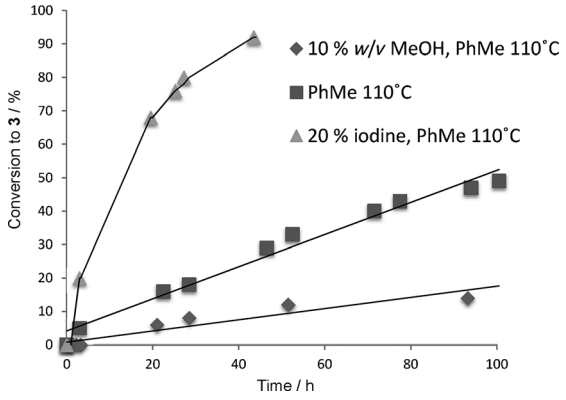


Figure 1. Comparison of the thermal conversion of **2** to **3** in the presence of additives.

and below to give macrocyclic *cis*,*trans*-dienes. Ring-opening reactions to generate lactones fused to medium-sized ring systems (7–9 members) gives products with a *cis*,*cis*-diene geometry. It seems likely that these ring openings proceed through a conrotatory mode, followed by the isomerization of the resulting *cis*,*trans*-diene. Experimental evidence in support of this hypothesis is strong. Finally, a study of related amino-substituted cyclobutenes has uncovered a useful extension of this sequence for the formation of medium-sized-ring dienes fused to 5- or 6-membered lactams.

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