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Torquoselective Ring Opening of Fused Cyclobutenamides: Evidence for a *Cis,Trans*-Cyclooctadienone Intermediate

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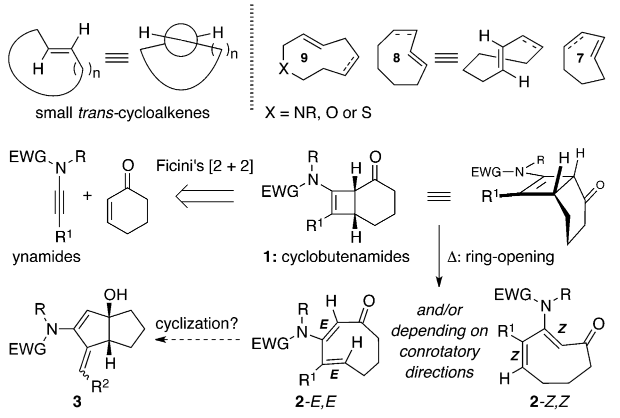
Supporting Information

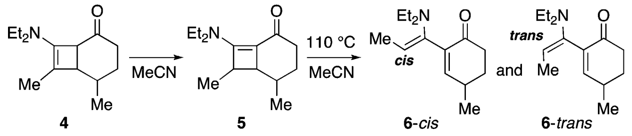
ABSTRACT: Electrocyclic ring opening of 4,6-fused cyclobutenamides **1** under thermal conditions leads to *cis,trans*-cyclooctadienones **2**-*E,E* as transient intermediates, en route to 5,5-bicyclic products **3**. Theoretical calculations predict that 4,5-fused cyclobutenamides should likewise undergo thermal ring opening, giving *cis,trans*-cycloheptadienones, but in this case conversion to 5,4-bicyclic products is thermodynamically disfavored, and these cyclobutenamides instead rearrange to vinyl cyclopentenones.

Small *trans*-cycloalkenes have unique reactivities and structural features, including inherent planar chirality, which have been the focus of many elegant experimental and seminal theoretical studies,[1−6] and have recently attracted increasing interest relating to their applications in bioconjugate chemistry.[1d] Accommodating a *trans* olefin within a ring size of 7, 8, or 9 engenders significant ring strain, which may be alleviated if the ring contains heteroatoms such as N, O, or S but is exacerbated when the ring contains additional sp^2-hybridized atoms.[3−5] We report here the discovery of a new entry point into the chemistry of all-carbon *trans*-cycloalkenones, uncovered during our studies of cyclobutenamides **1** (Scheme 1).[7−9] Under thermal conditions, 4,6-fused cyclobutenamides **1** undergo rearrangement to products whose structures are consistent with the intermediacy of the cyclooctadienone **2**-*E,E*, containing one *cis* and one *trans* olefin, derived from cyclobutene ring opening. Small-ring *trans*-cycloalkenes are expected to be metastable intermediates that should undergo facile inter- or intramolecular transformations, and in the case of **2**-*E,E*, this is manifested in a transannular cyclization leading to the 5,5-bicyclic product **3**. This outcome is surprising as it is in direct contrast to previous studies of the related 4,6-fused cyclobutenamine **4** (Scheme 2), which showed no evidence for cycloalkadienone formation. Thermal rearrangement of **4** gave instead the dienes **6**-*cis* and **6**-*trans*.[9,10] The sole difference is the amino group in **4** versus the amide in **1**. Here we report our experimental and theoretical studies of the generation and fate of *cis,trans*-cyclooctadienones **2** from 4,6-fused cyclobutenamides **1** and the contrasting behavior of the corresponding 4,5-fused cyclobutenamides.

Scheme 1. Ring-Fused Cyclobutenamides as Potential Precursors to Small *Cis,Trans*-Cycloalkadienones



Scheme 2. Ficini's Thermal Rearrangement of a Fused Cyclobutenamine[10]



Our experiments on the thermal rearrangements of cyclobutenamides **1** are summarized in Table 1. When heated at 100−120 °C in toluene, 4,6-fused cyclobutenamides **1** rearranged to the synthetically useful pentalanes **3** in 45−62% yield. The choice of appropriate conditions was crucial: no reaction took place either in DMF or chloroform (entries 1 and 2), or in the presence of base or 4 Å molecular sieves (entries 4 and 5). Yields were slightly higher when the reaction was conducted at 120 °C than at 100 °C (e.g., entry 3 vs 6) and were higher when lower concentrations of cyclobutenamide were used (e.g., entries 7, 8, 10), but in no case could the reaction be driven to completion.

The scope and generality of this fascinating cascade are accentuated in Figure 1. Variation of substituents on the nitrogen atom and/or the *β*-carbon of the starting cyclo-

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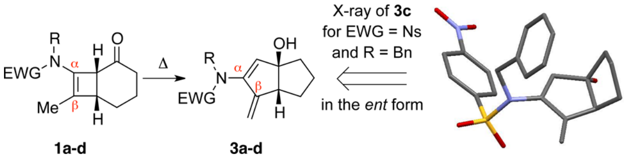
Table 1. Thermal Rearrangements of 4,6-Fused Cyclobutenamides 1



entry	EWG =	R =	solvent [concn *M*]	additive [equiv]	temp [°C]	time [h]	yield [%]^a	1^b
1	**1a:** Mbs^c	Bn	DMF [0.10]	--	100	33	**3a:** 0^d	100
2	Mbs	Bn	$CHCl_3$ [0.10]	--	100	12	0	100
3	Mbs	Bn	Toluene [0.10]	--	100	36	47	30
4	Mbs	Bn	Toluene [0.10]	DBU [1.0]	100	23	0	100
5	Mbs	Bn	Toluene [0.10]	4Å MS	100	47	0	100
6	Mbs	Bn	Toluene [0.10]	--	120	34	56	12
7	Mbs	Bn	Toluene [0.050]	--	100	32	45	40
8	Mbs	Bn	Toluene [0.033]	--	100	34	53	27
9	Mbs	Bn	Toluene [0.033]	--	120	33	56	0
10	Mbs	Bn	Toluene [0.025]	--	100	32	56	22
11	**1b:** Ts	Bn	Toluene [0.025]	--	100	32	**3b:** 62	0
12	**1c:** Ns	Bn	Toluene [0.025]	--	100	32	**3c:** 56	19
13	**1d:** Ts	allyl	Toluene [0.025]	--	100	32	**3d:** 57	19

^{a}All are isolated yields. ^{b}Recovered starting **1**. ^{c}Mbs = *para*-methoxy-benzene-sulfonyl; Ns = *para*-nitro-benzene-sulfonyl. ^{d}Complete recovery of **1**.

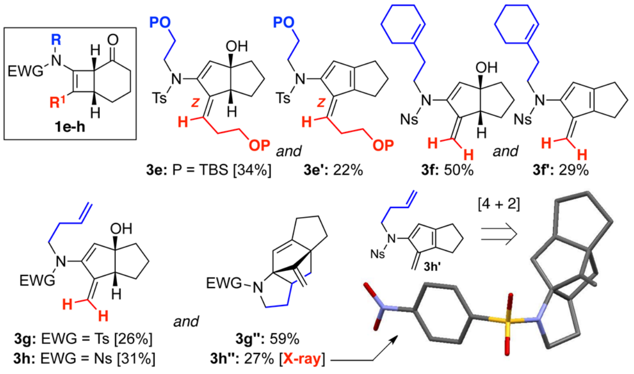
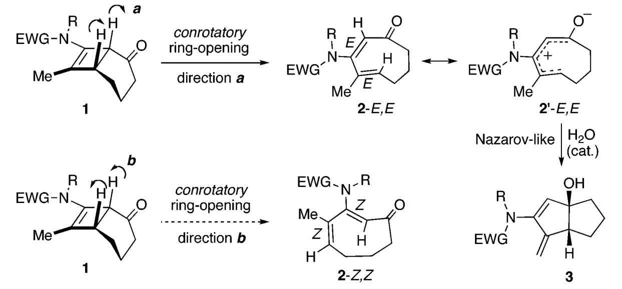


Figure 1. Structurally diverse products accessed through thermal rearrangements of cyclobutenamides **1**.

butenamides led to the pentalanes **3d** (Table 1) and **3e−h** (Figure 1). The initially formed hydroxypentalanes could undergo *syn*-dehydration to fulvenes, which may be isolated (**3e′** and **3f′**) or trapped by an intramolecular [4 + 2] cycloaddition onto a tethered alkene to give tetracycles (**3h″** and **3g″**). These last two examples reveal the synthetic potential of this rearrangement for the rapid assembly of structural complexity. It is also noteworthy that, in the case of **3e**/**3e′**, only the *Z* exocyclic olefin was found.

Having uncovered this novel cascade reaction, we were intrigued by its mechanism and distinct contrast to Ficini's observations on the 4,6-fused cyclobutenamines **4**.[10] We propose that the rearrangement of **1** to **3** follows the mechanism shown in Scheme 3. The details of the mechanism were established with the aid of density functional theory calculations,[11] performed at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory (Figure 2).[12] The 4π electrocyclic ring opening of **1** predictably[13] favors the conrotatory mode in which the cyclohexanone alkyl group rotates outward and the carbonyl rotates inward (direction *a*) leading to **2**-*E,E*. This intermediate lies 9.4 kcal/mol above **1**. The computed torquoselectivity ($\Delta\Delta G^{\ddagger}$) is 9.8 kcal/mol.

Scheme 3. Proposed Mechanism for Thermal Rearrangement of 1 to 3



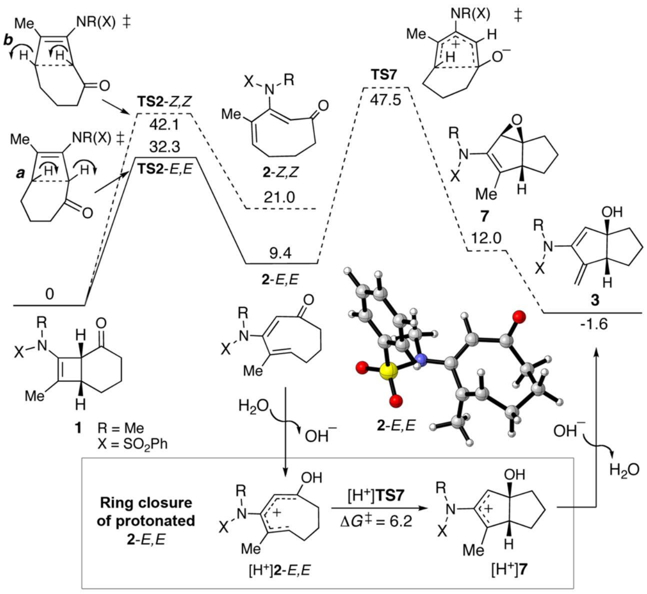
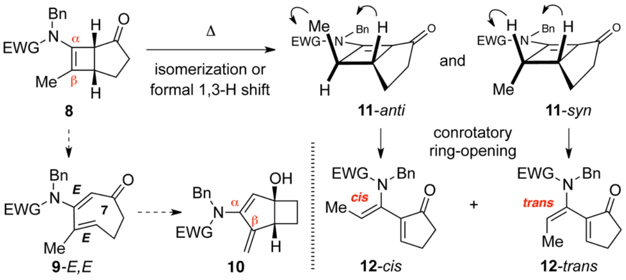


Figure 2. Free energy profile for thermal rearrangement of **1** to **3** in toluene, calculated at the M06-2X/6-311+G(d,p)//B3LYP/6-31G(d) level of theory with SMD solvent corrections. ΔG in kcal/mol.

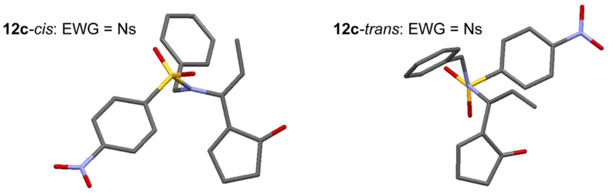
The *E,E* isomer of **2** is not only kinetically favored but also the only isomer possessing an appropriate geometry for cyclization in the 5,5 mode to give **3** (in **2**-*Z,Z*, the carbonyl group and diene terminus are too far apart to form a bond). Ring closure of **2**-*E,E* resembles a Nazarov cyclization (cf. resonance structure **2′**-*E,E*, Scheme 3). Starting from the neutral cyclooctadienone, 5,5 ring closure leading to epoxide **7** (the result of barrierless collapse of a 5,5-bicyclic zwitterion) has a very high barrier (**TS7**, 47.5 kcal/mol), too high to be feasible at 100−120 °C. However, protonation of the carbonyl group (Figure 2 inset) lowers the energy of the Nazarov TS significantly, such that it lies only 6.2 kcal/mol above protonated **2**-*E,E*.[14,15] Based on this result, together with the lack of reaction in the presence of 4 Å molecular sieves (Table 1, entry 5), we propose that the cyclization step is catalyzed by adventitious water acting as an acid catalyst.[15] Unfortunately, the yield of **3** could not be improved by deliberate addition of an acid catalyst; for example, addition of camphorsulfonic acid (CSA, 0.4 equiv) brought about severe decomposition.[16]

The 4,5-fused cyclobutenamides **8** behaved differently from **1**, instead echoing the behavior of **4** observed by Ficini (Scheme 2).[10] As shown in Table 2, no products were identified that could be traced to the *cis,trans*-cycloheptadienone intermediate **9**-*E,E*. Instead, 4,5-fused cyclobutenamides **8** rearranged to amido-dienes **12** as *cis*/*trans* mixtures.[17] The

Table 2. Thermal Rearrangements of 4,5-Fused Cyclobutenamides 8



entry	EWG =	solvent [concn *M*]	temp [°C]	time [h]	yield **12** [%]^{a}:	*cis*	*trans*	*cis:trans*
1	**8a:** Mbs	toluene [0.025 M]	140	32	**12a:**	8^{b}	0	--
2	Mbs	xylenes [0.025 M]	195	36		54	16	3:1
3	**8b:** Ts	xylenes [0.025 M]	195	36	**12b:**	46	16	3:1
4	**8c:** Ns	xylenes [0.025 M]	195	36	**12c:**	51^{c}	22	2:1


12c-*cis*: EWG = Ns

12c-*trans*: EWG = Ns

^{a}All are isolated yields. ^{b}72% recovered **8a**. ^{c}16% recovered **8c**.

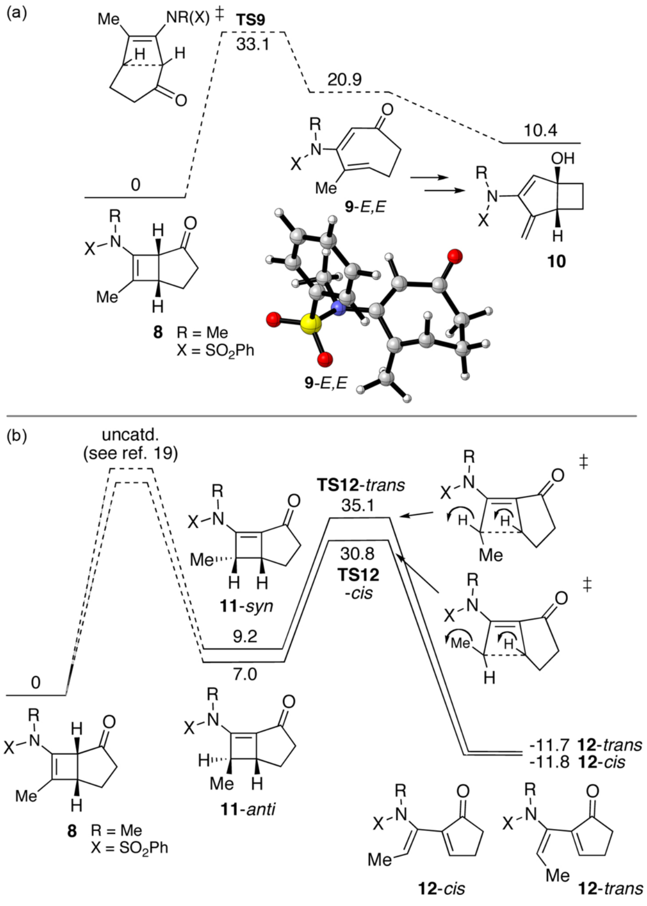


Figure 3. Free energy profiles for thermal rearrangements of **8** to (a) **10** and (b) **12** in toluene.

rearrangements involving the 4,5-fused series required much higher temperatures (195 °C) than those in the 4,6-fused series (100−120 °C).

The rearrangement of **8** to **12** is proposed to commence with formation of the conjugated cyclobutenone **11** (*syn*/*anti*), as previously observed by Ficini[10c] for **4** (Scheme 2). 4π electrocyclic ring opening of **11** gives **12**. Each isomer of **11** undergoes ring opening with complete torquoselectivity, avoiding unfavorable inward rotation by the cyclopentanone alkyl group that would lead to a highly strained *trans*-cyclopentenone. Thus, **12**-*cis* is derived from **11**-*anti* and **12**-*trans* from **11**-*syn*.

Why does **8** rearrange to **12**, rather than to **10**? Theoretical calculations (Figure 3a) in fact predict that the *cis,trans*-cycloheptadienone **9**-*E,E*, which would be the precursor of **10**, can be accessed from **8** with a barrier of 33.1 kcal/mol (**TS9**). This value is only 0.8 kcal/mol higher than the barrier for formation of **2**-*E,E* from **1**. It is therefore likely that some **9**-*E,E* is formed transiently during the course of the reaction at 195 °C. The transient formation of **9**-*E,E* is not reflected in the final product distribution, however, because the transannular cyclization product **10** is higher in energy than the starting cyclobutenamide (Δ*G* = 10.4 kcal/mol).[18] Given the thermodynamic driving force against the formation of **10**, the *cis,trans*-cycloheptadienone **9**-*E,E* reverts to **8** which rearranges by the alternative pathway shown in Figure 3b to **12**. Conversion of **8** to the *α,β*-unsaturated intermediate **11** is likely to be acid catalyzed.[19] Formation of **12**-*cis* and **12**-*trans* from **8** has Δ*G* ≈ −12 kcal/mol.

We have documented here the thermal rearrangements of 4,6-fused and 4,5-fused cyclobutenamides **1** and **8** and the discovery of contrasting mechanistic pathways. Theory predicts that **1** and **8** undergo electrocyclic ring opening to *cis,trans*-cyclooctadienone **2**-*E,E* and *cis,trans*-cycloheptadienone **9**-*E,E*, respectively. For **2**-*E,E*, Nazarov-like ring closure leads to 5,5-bicyclic amido-dienes **3**, but for **9**-*E,E*, Nazarov cyclization is thermodynamically disfavored and an alternative rearrangement leads to monocyclic amido-dienes **12**. The differing behavior between **1** and Ficini's 4,6-fused cyclobutenamines **4** likely reflects the lower basicity of **1**, which inhibits the isomerization to a conjugated cyclobutenamide (cf. **5**) that would trigger rearrangement to monocyclic amido-dienes. Further synthetic and mechanistic studies and development of an asymmetric variant are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterizations, NMR spectra, X-ray data, computational methods and data, supporting mechanistic discussion, and a complete citation for ref 11. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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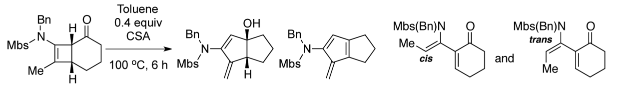
(14) In contrast, H-bonding catalysis by a water molecule lowers the barrier of the Nazarov cyclization by only 5.8 kcal/mol.

(15) *O*-Protonation of cyclobutenamide **1** (R = Me, X = SO_2Ph) lowers the barrier for cyclobutene ring opening to 21.3 kcal/mol.

(16) When **1a** was heated at 100 °C in the presence of 0.4 equiv of CSA, we obtained a complex mixture due to decomposition of **1a**. However, we were able to identify from the mixture all four products including those corresponding [see **i**] to Ficini's observations.



1a **3a:** 7% **3a':** 8% **i**-*cis* 26%; *dr* 2:1 **i**-*trans*

(17) Amido-dienes **12**-*cis* and **12**-*trans* interconvert under the reaction conditions but do not fully equilibrate during the time scale of the synthetic experiments. The *cis*/*trans* ratios of **12** in Table 2 do not reflect thermodynamic control but are determined by the rates of isomerization of **8** to **11**-*syn* and **11**-*anti*, which are rate-determining under thermal conditions.[19]

(18) It is noteworthy that, in the calculations on the 4,6 series (Figure 2), the final product **3** is only 1.6 kcal/mol lower in energy than the reactant **1**. This likely explains our observation that these reactions could not be driven to completion in the laboratory.

(19) Isomerization of **8a**−**c** to **11a**−**c** (*syn*/*anti*) appears to be catalyzed by adventitious acid. In the presence of 0.4 equiv of CSA, amido-dienes **12a**−**c** were obtained (85%−92% yield) after only 6 h, as compared with 36 h in the absence of CSA. Further discussion of the mechanism of conversion of **8** to **11** is provided in the Supporting Information.