On the thermodynamic control of ring-opening of 4-substituted 1,3,3-*tris*-carbethoxycyclobutene and the role of the C-3 substituent in masking the kinetic torquoselectivity

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Abstract. The predominant transformations of 4-methyl- and 4-phenyl-1,3,3-*tris*-carbethoxycyclobutenes to s-*trans*-*trans*-1,1,3-*tris*-carbethoxy-4-methyl- and 4-phenyl-1,3-butadienes, respectively, proceed through pathways entailing heterolytic cleavage of the σ_{C3C4} bond rather than the usual four-electron conrotatory ring opening following the rules of torquoselectivity. The adventitious or in situ generated halogen acid from $CDCl_3$ catalyzes the reaction of 4-methyl-1,3,3-*tris*-carbethoxycyclobutene by protonation of one of the two ester groups on C3 and, thereby, weakening the σ_{C3C4} bond to allow its heterolytic S_N2 cleavage by the chloride ion. This is followed by *cisoid*→*transoid* isomerization and loss of the elements of the halogen acid to form the products. In the Lewis acid-catalyzed reaction of 4-phenyl-1,3,3-*tris*-carbethoxycyclobutene in CH_2Cl_2, coordination of the Lewis acid with one of two ester groups on C3 is followed by heterolytic cleavage of the σ_{C3C4} bond. The resultant species subsequently undergoes *cisoid*→*transoid* isomerization before losing the Lewis acid to form the products.

KEYWORDS. 1,3,3-*tris*-carbethoxy-4-methylcyclobutene, 1,3,3-*tris*-carbethoxy-4-phenylcyclobutene, torquoselectivity, quantum chemical calculation, heterolytic ring cleavage, solvent effects

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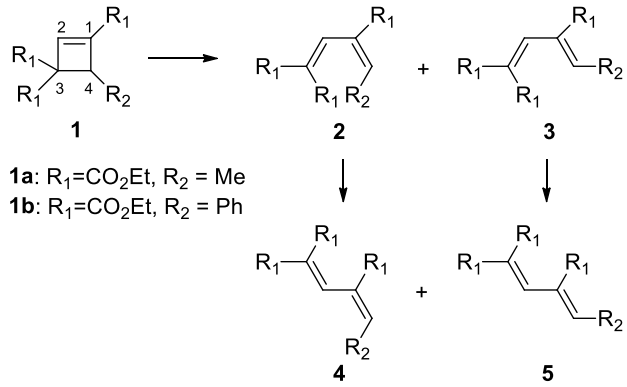
Introduction. Cyclobutene bearing an electron-donating substituent undergoes conrotatory ring-opening[1] such that the substituent rotates outward to reside *trans* on the double bond.[2,3] There were no known exceptions to this general rule until a research group reported inward rotation of methyl and phenyl groups from the reactions of the triester-substituted cyclobutenes **1a** and **1b**, respectively, Scheme 1.[4] A solution of **1a** in deuterated chloroform ($CDCl_3$) was heated to 80 °C for 36 h to obtain a 4.5:1 mixture of **4a** and **5a**. In comparison, the reaction of **1b** was very facile as it occurred at room temperature in less than 5 min to exclusively form **4b** on mixing with 5 mol% $AgOCOCF_3$ in methylene chloride (CH_2Cl_2). The first formed *cisoid* dienes **2** and **3** isomerized subsequently to the *transoid* dienes **4** and **5**, respectively, under the reaction conditions. Such isomerizations under thermal conditions are common knowledge and routinely considered in the Diels-Alder chemistry.[5]



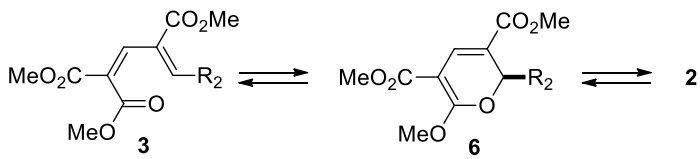
Scheme 1. Inward and outward ring-openings of the cyclobutenes **1a** and **1b**

Houk and co-workers explained the predominant formation of **4**/**2** as a consequence of double bond isomerization in **5**/**3**.[4] The species **3**, formed from outward ring-opening in **1** following the rules of torquoselectivity,[6] was considered to generate **4** by first conformational isomerization to **5** (**3**⟶**5**) and then double bond isomerization to **4** (**5**⟶**4**) under thermodynamic control. Thus, the overall pathway suggested for the reaction was **1**⟶**3**⟶**5**⟶**4**. The activation energy for the isomerization **5**⟶**4** was estimated to be significantly higher than the activation energy for ring-opening **1**⟶**3**. The significantly higher barrier for double bond isomerization and also the well-established fact that such an isomerization has seldom been observed under the thermal conditions of the Diels-Alder reaction led us to re-investigate the reaction.

We report herein that the present ring-opening proceeds by heterolytic cleavage of the $\sigma_{C3\text{-}C4}$ bond which is rendered labile by the two electron-withdrawing ester groups on C3. The heterolytic cleavage is additionally facilitated by the Brønsted acid HCl, adventitious or generated in situ from the decomposition of chloroform on heating, and also the Lewis acid $AgOCOCF_3$, added externally to the reaction mixture.

In computational modelling of the ethyl ester by methyl ester,[4] Houk and Tang discovered that the transition state (TS) for outward rotation of R_2 had 6−8 kcal/mol less energy barrier than inward rotation in following the rules of torquoselectivity.[6] The observed discrepancy between the theory and experiment was allayed to double bond isomerization under thermodynamic control under the reaction conditions. The diene **4a** was estimated to be 1.0 kcal/mol more stable than **5a**. For this energy difference, **4a**:**5a** thermodynamic equilibrium distribution will be estimated at 5:1, which goes well with the experimentally observed 4.5:1 distribution. However, the double bond isomerization **5**⟶**4** was calculated to pass through a barrier that was 8−10 kcal/mol higher than the outward ring-opening **1**⟶**3** and, thus, it cannot be considered as a plausible route to the predominant formation of **4**.

The disrotatory 6π-electrocyclization[7] **3**⟶**6** and further inward opening **6**⟶**2**, Scheme 2, was also not feasible. While the barrier for **3**⟶**6** transformation was about 17 kcal/mol lower than **1**⟶**3** transformation, the inward opening **6**⟶**2** was still lower, 13.4−16.0 kcal/mol. It is significant to note that the previous authors[4] did not investigate the barrier for outward opening **6**⟶**3** which, in fact, is further lower than the inward opening (our calculations) in keeping with the rules of torquoselectivity. Thus, **3** may convert to **6** soon after it is formed, **6** will open outward to **3** in preference to **2**. In other words, the transformation **1**⟶**3**⟶**6**⟶**3** is more facile than **1**⟶**3**⟶**6**⟶**2**. The cause for the predominant formation of **2** was, therefore, not resolved.



Scheme 2. The 6π electrocyclization of **3**⟶**6** and further opening **6**⟶**2/3**

Computational methods. The ethyl ester and D^+ were modelled computationally by methyl ester and H^+, respectively. The geometry optimizations and TS searches were carried out using the hybrid meta-GGA M06-2X density functional[8] and 6-31G(d) basis set embedded in the Gaussian 09 suite of programs.[9] The previous researchers have used B3LYP density functional instead, and the same basis set.[4] The optimized structures were verified as minima or first order saddle points by harmonic vibrational frequency analysis. The solvent effects of $CHCl_3$ and CH_2Cl_2 on the potential energy profiles were estimated using the Conductor Polarized Continuum Model (CPCM).[10] The estimated coordinates of geometries, Gibbs' free energies, activation energies and single imaginary frequencies are given in the Supplementary Information.

Results and Discussion. We have investigated the reaction to seek a plausible answer to the predominant transformation **1**⟶**2/4**. The outward opening **1**⟶**3** of both **1a** and **1b** is a significantly lower energy event than the corresponding inward opening **1**⟶**2** and, thus, both conform to the rules of TS-torquoselectivity in as much as an electron-donating or electron-rich substituent is required to rotate outward. The activation energies of the reactions **1**⟶**2** and **1**⟶**3** are collected in Table 1. **1**⟶**2**

Table 1. Calculated Gibbs' free energies of activation (kcal/mol) for the ring-opening of **1a** and **1b**

Substrate	$\Delta G^{\ddagger}_{(\mathbf{1}\rightarrow\mathbf{2})}$	$\Delta G^{\ddagger}_{(1\rightarrow\mathbf{3})}$	$\Delta G^{\ddagger}_{(\mathbf{1}\rightarrow\mathbf{2})} - \Delta G^{\ddagger}_{(1\rightarrow\mathbf{3})}$
1a	37.0	30.9	6.1
1b	33.6	25.4	8.2

The activation energy of the reaction **3a**⟶**6a** was estimated to be 3.6 kcal/mol lower than the reaction **2a**⟶**6a**. In close analogy, the activation energy of the reaction **3b**⟶**6b** was also 4.1 kcal/mol lower than the reaction **2b**⟶**6b**. Two significant points emerge: (a) The 6π ring-closing reaction **3**⟶**6** is more facile than **2**⟶**6** and (b) both the ring-closing reactions **3**⟶**6** and **2**⟶**6** are sufficiently more facile than the ring-opening reactions **1**⟶**2** and **1**⟶**3**. Thus, both **2** and **3** must ring-close to **6** as soon as they are formed. The TS-torquoselectivity of **1** therefore effectively translates into the TS-torquoselectivity of **6**. The activation energies of the reactions **2/3**⟶**6** are collected in Table 2.

Table 2. Calculated Gibbs' free energies of activation (kcal/mol) for the 6π ring-closing reactions **2**/**3**→**6**

Reaction	$\triangle G^{\ddagger}$
2a→**6a**	18.8
3a→**6a**	15.2
2b→**6b**	21.2
3b→**6b**	17.1

Consequently, we investigated the disrotatory six-electron ring-opening of **6** and discovered that the outward opening reactions **6a**→**3a** and **6b**→**3b** were, respectively, 3.7 and 0.6 kcal/mol more facile than the corresponding inward opening reactions **6a**→**2a** and **6b**→**2b**. These activation energies are collected in Table 3. On putting together the events **1**→**2**/**3**, **2**/**3**→**6** and **6**→**2**/**3**, and also noting that **6**→**2**/**3** is the actual torquoselectivity control event, **6a**→**3a** transformation will predominate over **6a**→**2a** for the 3.7 kcal/mol activation energy difference in favor of the former. Likewise, **6b** will be expected to form an approximately 1:3 equilibrium mixture of **2b** and **3b** for the 0.6 kcal/mol difference in the activation energies of **6b**→**2b** and **6b**→**3b**. Neither activation energy-based predictions is supported by the experiments. The energy profile for the changes **1**→**3**→**6**→**3** is shown in Figure 1.

Table 3. Calculated Gibbs' free energies of activation (kcal/mol) for the 6π ring-opening reactions **6**→**2**/**3**

Reaction	$\triangle G^{\ddagger}$
6a→**2a**	20.9
6a→**3a**	17.2
6b→**2b**	19.6
6b→**3b**	19.0

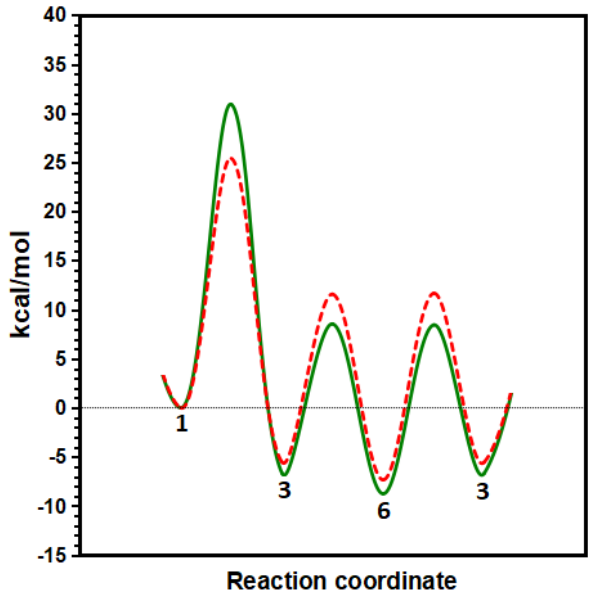


Figure 1. The Gibbs' free energy profiles for the transformations **1a**→**3a**→**6a**→**3a** (solid green line) and **1b**→**3b**→**6b**→**3b** (dotted red line)

From the above discussion, **1a**→**3a**→**6a**→**3a** and **1b**→**3b**→**6b**→**3b** emerge as the predominant routes. The rationale to the observed predominance of **2**/**4** is, therefore, still eluding.

We next considered **3**→**2** or **5**→**4** isomerization, as also pointed out by the previous investigators,[4] for the predominant formation of **2** or **4**, respectively. Numerous attempts at locating the TS structure for **3a**→**2a** double bond isomerization led to the pyran species **6a**. Also, calculation of the activation energy of **5a**→**4a** double bond isomerization always collapsed to either an oxetene (see below) or structures resembling **5a** or **4a** with a weak vibration elsewhere in the molecule. The issue was resolved from conformational scan, wherein the torsion angle of the methyl group on the double bond with the carbonyl carbon of the adjacent ester group was varied by 5° at a time, with everything else relaxed, to achieve the highest energy point and then refined around it by 1° change at a time to arrive at $\triangle G^{\ddagger}$ = 60.7 kcal/mol for the double bond isomerization **5a**→**4a**. From a similar exercise, the $\triangle G^{\ddagger}$ for the double bond isomerization **5b**→**4b** was estimated at 64.0 kcal/mol. The activation energy for double bond isomerization is too high to compete any of the processes discussed above. The argument holding **5**→**4** isomerization responsible for the predominant formation of **4** is therefore erroneous.[11] The

estimated reaction profiles for the transformations **1a**→**3a**→**5a**→**4a** and **1b**→**3b**→**5b**→**4b** are shown in Figure 2.

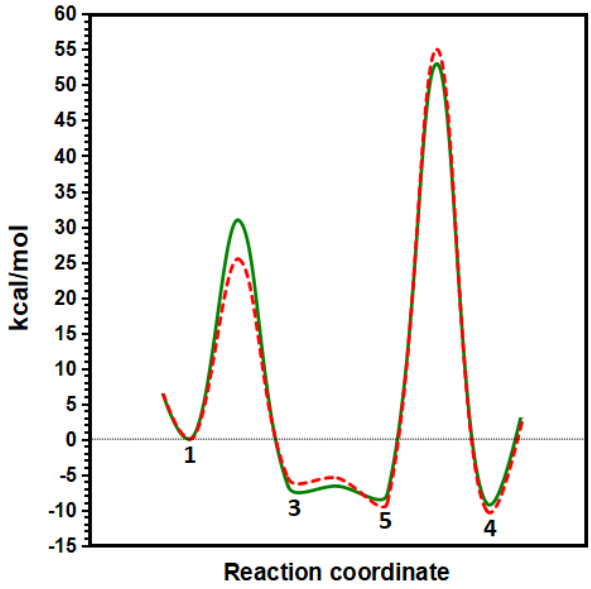
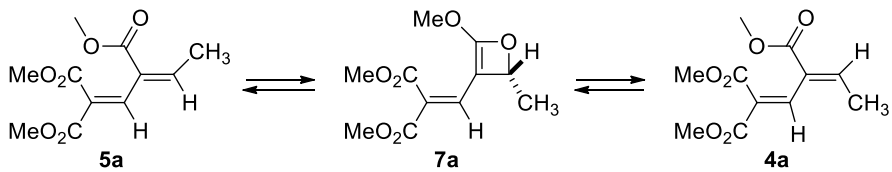


Figure 2. The Gibbs' free energy profiles for the transformations **1a**→**3a**→**5a**→**4a** (solid green line) and **1b**→**3b**→**5b**→**4b** (dotted red line)

The electrocyclization **5a**→**7a**, Scheme 3, followed by conrotatory ring-opening in **7a** was also investigated. While the outward opening **7a**→**4a** ($\triangle G^{\ddagger}$ = 18.9 kcal/mol) is favored over the inward opening **7a**→**5a** ($\triangle G^{\ddagger}$ = 24.8 kcal/mol), the activation energy of the initial **5a**→**7a** transformation, 55.7 kcal/mol (the corresponding energy for the transformation **3a**→**7a** is 49.2 kcal/mol), is way above the activation energies of the **6a**→**2a**/**3a** and also **1a**→**2a**/**3a** transformations. The predominant **1**→**2**/**4** reaction, therefore, continues to elude an explanation. The reaction profiles for the transformations **7a**→**4a** and **7a**→**5a** are collected in Figure 3.



Scheme 3. Four-electron ring-closing reaction **5a**→**7a** and the ring-opening reactions **7a**→**4a** and **7a**→**5a**

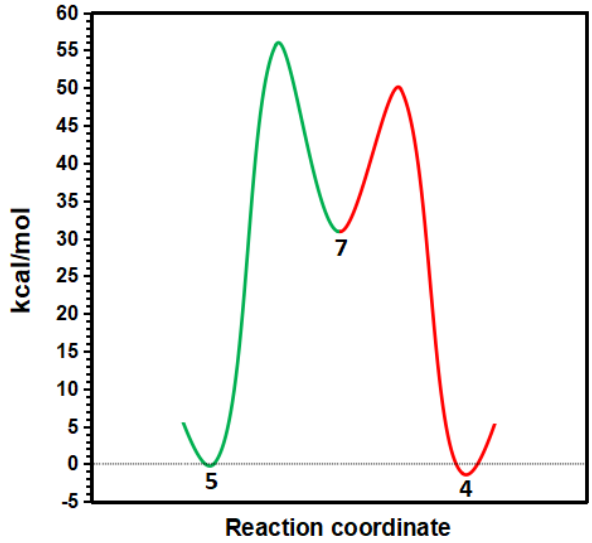
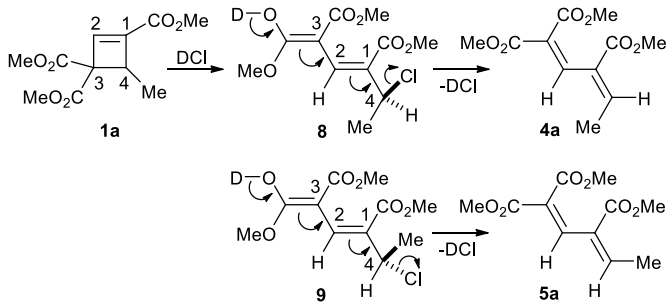


Figure 3. Gibbs' free energy profiles for the transformations **7a**⟶**5a** (green line) and **7a**⟶**4a** (red line)

DCl, adventitious or formed in situ from $CDCl_3$ on heating,[12] may conceivably protonate one of the two ester groups on C3 and weaken the σ_{C3C4} bond to allow its heterolytic S_N2 cleavage by chloride ion to the species **8** and **9** after *cisoid*⟶*transoid* isomerization, as shown in Scheme 4. The species **8** reorganizes by losing the elements of DCl in the manner shown to form the predominantly observed product **4a**. Elimination through the conformer **9** will form the minor product **5a**.



Scheme 4. Proposed cleavage of **1a** under DCl-catalysis

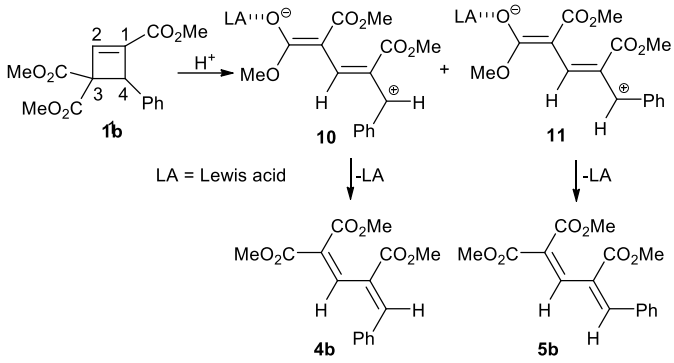
The σ_{CCl} bond must align parallel to the *p* orbitals of the diene system for maximum overlap for elimination of DCl from **8** and **9**. These conformations actually resemble the TS structures for the said elimination. Indeed, after having constrained the geometry by fixing the torsion angle C2-

C1-C4-Cl at 90°, the conformer **8** was estimated to be 1.0 kcal/mol more stable than **9** under the solvent effect of chloroform at 298.15 K. The relationship ΔG = -RT lnK translates this energy difference to **8**:**9** = 5.4:1 equilibrium distribution. Having assumed that the facility of DCl elimination from both the species is equal, the resultant **4a**:**5a** distribution will also be the same and may lower further close to the experimental 4.5:1 distribution on temperature correction.[13] The geometries of **8** and **9** after imposing the torsion angle-constraint are given in the Supplementary Information.

It is interesting to note that with no restriction on the C2-C1-C4-Cl torsion angle, the species **8** is less stable than **9** by 0.22 kcal/mol under the solvent effect of $CHCl_3$. It is only on imposition of the torsion angle-constraint required for DCl elimination that the relative stability reversed in favor of **8**. Thus, the solvent in combination with the definitive TS geometry requirement for elimination plays a crucial role in the determination of product composition.[14]

The Gibbs' free energy of activation for the nucleophilic cleavage of protonated-**1a** (**1a**-$\mathbf{H^+}$) by chloride ion was estimated at -72.4 kcal/mol (Imaginary Frequency = -446.18) in the gas phase. Such a reaction profile with negative activation energy is common for S_N2 reactions.[15] On inclusion of solvent effects of chloroform, the activation free energy was estimated at 3.02 kcal/mol (Imaginary Frequency = -447.57).

The ring-opening in **1b** was very facile as it occurred at room temperature in less than 5 min to exclusively form **4b** on mixing with 5 mol% $AgOCOCF_3$, a Lewis acid, in CH_2Cl_2 as the reaction medium. The heterolytic cleavage of σ_{C1C4} bond after coordination of one of the two ester groups on C3 with the Lewis acid to generate the zwitter ions **10** and **11**, Scheme 5, will be expected to be rapid for the enhanced stability of the cation due to its benzylic character. However, the large steric interaction of phenyl with the adjacent ester group in **11** may guarantee large bias for the zwitter ion **10** and, thus, lead exclusively to **4b** on loss of the Lewis acid.

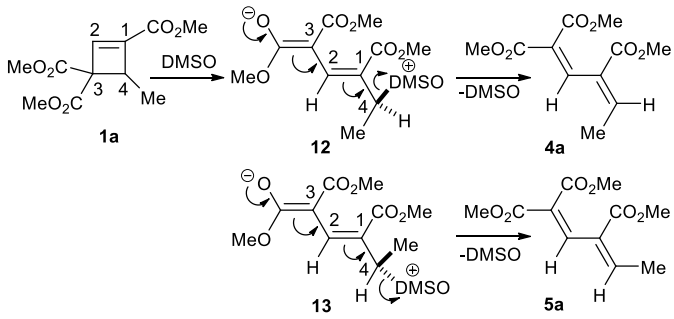


Scheme 5. Lewis acid-catalysed cleavage of **1b** leading to **4b** and **5b**

We have computationally modelled the Lewis acid $AgOCOCF_3$ by H^+ and discovered that the species **10** is indeed more stable than **11** by 3.62 kcal/mol under the solvent effect of CH_2Cl_2. This energy difference predicts exclusive formation of **10** and, thus, **4b** as indeed observed from the experiment. The computed 3D geometries of **10** and **11** are given in the Supplementary Information.

The previous investigators have also reported that when either **1a** or a 4.5:1 mixture of the dienes **4a** and **5a** was heated in DMSO-*d*6 at 80 °C for 12 h, a 3:1 mixture of **4a**:**5a** was obtained.[4] Following the rules of TS-torquoselectivity, **1a** is estimated to prefer outward to inward opening by a margin of 7.0 kcal/mol under the solvent effects of DMSO. The larger concentration of the apparently inward opened product in this instance also required a suitable explanation.

DMSO is a nucleophilic solvent.[16] Analogous to the ring opening by chloride ion, S_N2 attack of DMSO on C4 at an elevated temperature (80 °C) opens the ring to form the dienolates **12** and **13** after *cisoid*→*transoid* isomerization as shown in Scheme 6. Like in the instances of **8** and **9**, the torsion angle-constrained conformer **12** is 0.93 kcal/mol more stable than **13** under the solvent effects of DMSO at 298.15 K. This energy difference corresponds to 4.8:1 distribution of **12**:**13** and, hence, also **4a**:**5a**. This distribution will also lower and match better with the experimental 3:1 distribution at the experimental 353.15 K temperature. DMSO can also add to the dienes **4** and **5** in conjugate manner to generate the same species **12** and **13**.



Scheme 6. DMSO-initiated S_N2 cleavage pathway to **4a** and **5a**

Conclusion. The ring-opening of **1** is argued to follow a heterolytic pathway under the electron-withdrawing influence of the two ester groups on C3 rather than the usual conrotatory ring-opening following the rules of torquoselectivity. The reaction of **1a** is catalyzed by the adventitious or in situ formed DCl from $CDCl_3$ on heating at 80 °C over 36 h. Protonation of one of the two ester groups on C3 weakens the σ_{C3C4} bond and allows it's S_N2 cleavage by chloride ion. This is followed by *cisoid→transoid* isomerization and elimination of the elements of DCl to form the products.

In the instance of **1b**, the ring opens on coordination of $AgOCOCF_3$ to one of the two ester groups on C3. The resultant cation is benzylic and, thus, significantly stable. This is followed by *cisoid→transoid* isomerization and loss of $AgOCOCF_3$ to form the products.

The transformation of **1a** into 3:1 mixture of **4a**:**5a** on heating for 12 h in DMSO at 80 °C is also argued to proceed by heterolytic S_N2 ring cleavage by DMSO to result into dienolates. The same dienolates may also form from conjugate addition of DMSO to the dienes **4a** and **5a**. These dienolates then eject DMSO from the TS-resembling conformers to form a mixture of **4a** and **5a**.

Overall, both the reactions proceed via heterolytic ring-cleavage under the combined steric control of the methyl or phenyl substituent and the ester group on C1. The rules of torquoselectivity do not apply to the substrates **1a** and **1b** because they react by heterolytic pathways rather than the usual conrotatory ring-opening.

ASSOCIATED CONTENT

Supporting Information

Coordinates of the geometries, Gibbs' free energies, Gibbs' activation free energies, and imaginary frequencies of the transition state structures

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Notes

The authors declare no competing financial interests.

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The transformations of 4-methyl- and 4-phenyl-1,3,3-*tris*-carbethoxycyclobutenes to s-*trans*-*trans*-1,1,3-*tris*-carbethoxy-4-methyl-1,3-butadiene and 4-phenyl-1,3-butadiene, respectively, proceed through heterolytic cleavage of the σ_{C3C4} bond rather than the usual four-electron conrotatory ring opening.