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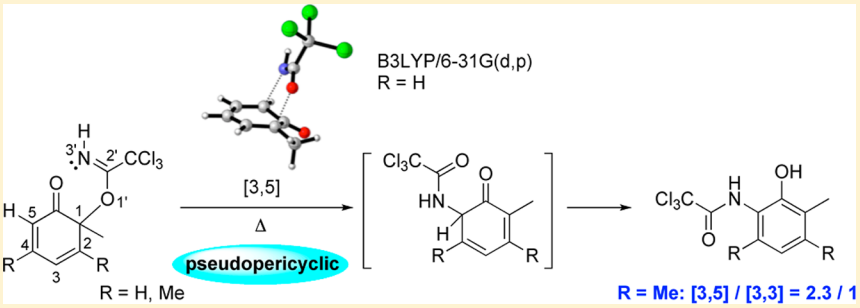
Competitive Pseudopericyclic [3,3]- and [3,5]-Sigmatropic Rearrangements of Trichloroacetimidates

Shikha Sharma, Trideep Rajale, Daniel K. Unruh, and David M. Birney*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

Supporting Information



ABSTRACT: The Woodward–Hoffmann rules predict whether concerted pericyclic reactions are allowed or forbidden based on the number of electrons involved and whether the cyclic orbital overlap involves suprafacial or antarafacial orbital overlap. Pseudopericyclic reactions constitute a third class of reactions in which orthogonal orbitals make them orbital symmetry allowed, regardless of the number of electrons involved in the reaction. Based on the recent report of eight-centered ester rearrangements, it is predicted that the isoelectronic eight-centered rearrangements of imidates would also be allowed. We now report that these rearrangements occur, and indeed, an eight-centered rearrangement is slightly favored in at least one case over the well-known six-centered Overman rearrangements, in a trichloroacetimidoylcyclohexadienone, a molecular system where both rearrangements are possible.

INTRODUCTION

It would be difficult to overstate the importance of the Woodward–Hoffmann rules in modern organic chemistry.[1] This triumph of molecular orbital theory led to clear and consistent explanations of pericyclic reactions and codified the application of the conservation of orbital symmetry to a wide range of reactions. Quite simply, the rules predict whether the reaction is allowed or forbidden based on the number of electrons involved and whether the cyclic orbital overlap is suprafacial or antarafacial.

However, not long after the publication of the rules, Lemal recognized a third possibility.[2] If bonding and nonbonding orbitals on the same atom exchange roles during a pericyclic reaction, then these orthogonal orbitals can result in a transition-state geometry that lacks cyclic orbital overlap around the ring of atoms that undergo bonding changes. Lemal described such reactions as pseudopericyclic and recognized that all such reactions with this orbital topology would be allowed by orbital symmetry, regardless of the number of electrons involved.[3,4]

Since that time, there have been extensive efforts from our laboratory,[5−10] along with numerous insightful studies from other groups, both experimental[11,12] and computational,[13−26] exploring the scope of pseudopericyclic reactions. Aspects of this work have recently been reviewed,[27,28] and so only leading references to the extensive literature on these reactions are provided.[5−26] Four general characteristics have been suggested for pseudopericyclic reactions:[2,5,8] (1) planar, or close to planar transition states[5−7,13−16] (2) low, or even nonexistent barriers, particularly when the transition state geometry is favorable,[2,5−7,13−26] (3) nonaromatic transition states,[15,18,20,26] and (4) perhaps most significantly and the focus of this work, no pseudopericyclic reaction can be forbidden.[5−7,9,11] In particular, we have predicted[6,7] and subsequently experimentally demonstrated[8,10] examples of concerted thermal reactions of esters that proceed via eight-centered cyclic transition states. These reactions would be forbidden by the Woodward–Hoffmann rules[1] but are orbital-symmetry-allowed with a pseudopericyclic orbital topology.[2]

Acetoxycyclohexadienones (e.g., **1**) have long been known to undergo formal [3,5]-sigmatropic thermal rearrangements, beginning with the pioneering work of Wessely.[29] Two mechanisms were suggested for the formation of **4** and **5**, either two sequential Woodward–Hoffmann-allowed [3,3]-rearrangements via **3** and **2** or a direct [3,5]-rearrangement via **2** (Scheme 1) followed by tautomerization. The latter would be unable to achieve a [3s,5a] transition-state geometry, and a

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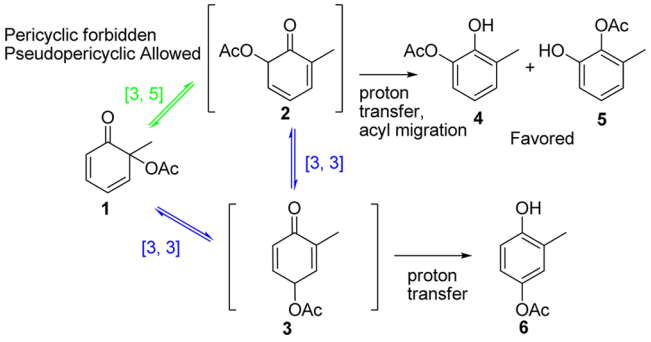
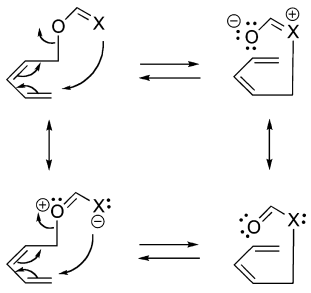
Scheme 1. Rearrangements of 2-Acetoxy-2-methyl-3,5-cyclohexadienone (1)



[3s,5s] transition state would be predicted to be forbidden by the Woodward–Hoffmann rules.[1]

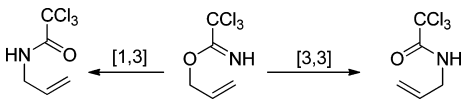
More recent qualitative theory has suggested that participation of ester lone pairs renders all thermal reactions of esters allowed via pseudopericyclic transition states.[6−8,10] Indeed, experimental studies from this laboratory on the thermal rearrangement of acetoxycyclohexadienone (**1**) have recently shown that **4** and **5** are the major products and **6** is the minor product, extrapolated to time zero.[10] This demonstrates that the [3,5]-sigmatropic rearrangement occurs in preference to the [3,3]-rearrangement.[10] Computations suggested that the [3,5]-rearrangement proceeds by a lower barrier pseudopericyclic transition state in agreement with the experimental preference.[6,7,10] To extend the scope of these rearrangements, we have proposed the design and synthesis of isoelectronic[26,30] trichloroacetimidate derivatives (Scheme 2) that can undergo similar pseudopericyclic [3,3]- and [3,5]-sigmatropic rearrangements to give the corresponding trichloroacetamide derivatives.

Scheme 2. Acetate (X = O) and Imidate (X = NH) [3,5]-Rearrangements Are Isoelectronic and Pseudopericyclic, with Orbital Disconnections at the Breaking and Forming σ-Bonds



The Overman rearrangement of allylic imidates is a synthetically useful method for the synthesis of allylic amines, amino acids, and other organic scaffolds with transposition of the functional groups[30−33] (Scheme 3). The calculated transition states for imidate [1,3]- and [3,3]-sigmatropic rearrangements have been recognized as pseudopericyclic,[26] based on analyses showing localized electron density in the transition state, in contrast to the cyclic delocalization in pericyclic reactions.[1] The calculated barrier for the thermal [1,3]-rearrangement is substantially higher than for the [3,3]; this is consistent with the experimental observation of exclusive [3,3]-rearrangement.[26] This is arguably due to angle strain in the four-centered transition state. In contrast, pseudopericyclic [3,5]-rearrangements of esters are favored over the more familiar [3,3]-rearrangements (Scheme 1);[10] there is presumably less strain in an eight-centered transition state. Therefore, it is anticipated that a pseudopericyclic [3,5]-rearrangement would also be allowed and might be observable in the case of imidates as well.

Scheme 3. Overman Rearrangement of Imidates



We first proposed the study of imidate **8** (Scheme 4), which possesses a dienyl moiety in a conformation suitable for either [3,3]- or [3,5]-sigmatropic rearrangements.[34] Hence, we anticipated that it could rearrange into either or both intermediates **9** and **11** via facile [3,5]- and [3,3]-rearrangements, respectively, followed by tautomerization to the corresponding phenols **10** and **12**. A second [3,3]-rearrangement of the amide **11** to form imidate **13** and then **14** would not be expected to be favored simply because amides are much more stable than imidates. In any case, the [3,3]-, direct [3,5]-, and sequential [3,3]-rearrangement mechanisms would give readily distinguishable isomeric structures **10**, **12**, and **14**. Identification of products would answer the question of whether the [3,5]-rearrangement occurs or not. Computational studies (B3LYP/6-31G(d,p)) reported below concur with the qualitative theory and suggest that both of the [3,3]- and [3,5]-rearrangements would be allowed.

RESULTS AND DISCUSSION

Synthetic Approaches to Trichloroacetimidate 8. However, synthetic access to **8** proved challenging. Wessely oxidation[29] of *o*-cresol using $Pb(OAc)_4$/AcOH yields the acetate **1** as a yellow solid in reasonable yield.[10,35−38] Ester hydrolysis of **1** may occur under some conditions, but the corresponding alcohol (**7**) could not be isolated.[35−38] Hydrolysis of **1** in basic methanol is known to give the ring-opened keto ester (Scheme 5).[35] Hydrolysis under acidic conditions led to the formation of **15** via the well-precedented Diels–Alder dimerization of alcohol **7**.[36−38]

The known propensity of sterically unencumbered cyclohexadienones to undergo Diels–Alder reactions[36−38] suggested **8** could be accessed via protection/deprotection approach, as shown in Schemes 6 and 7. Pyrolysis of **18** could lead to **8** via a retro-Diels–Alder reaction. Under the pyrolysis conditions, **8** would be expected to then undergo the thermal rearrangements outlined in Scheme 4 and Scheme 7. For the synthesis of **18** (Scheme 6), acetate **1** was refluxed with freshly cracked cyclopentadiene[39] in xylene to yield the [4 + 2] cycloaddition product **16**. This Diels–Alder adduct was smoothly hydrolyzed to the corresponding alcohol **17** using 10% $NaOH_{(aq)}$. Alcohol **17** was then treated with KH as base, followed by addition of trichloroacetonitrile in dry THF. The expected trichloroacetimidate **18** was not obtained under these standard conditions.[40,41] Instead, the tetracyclic adduct **19** was obtained, presumably via the intermediacy of the less stable isomer **18**. The structure of **19** was confirmed by ^1H and ^{13}C NMR as well as an X-ray crystal structure (Figure 1). Authentic samples of compounds **10** and **12** (to serve as GC standards) were synthesized from the corresponding anilines by treatment with hexachloroacetone in hexane at 65–70 °C.

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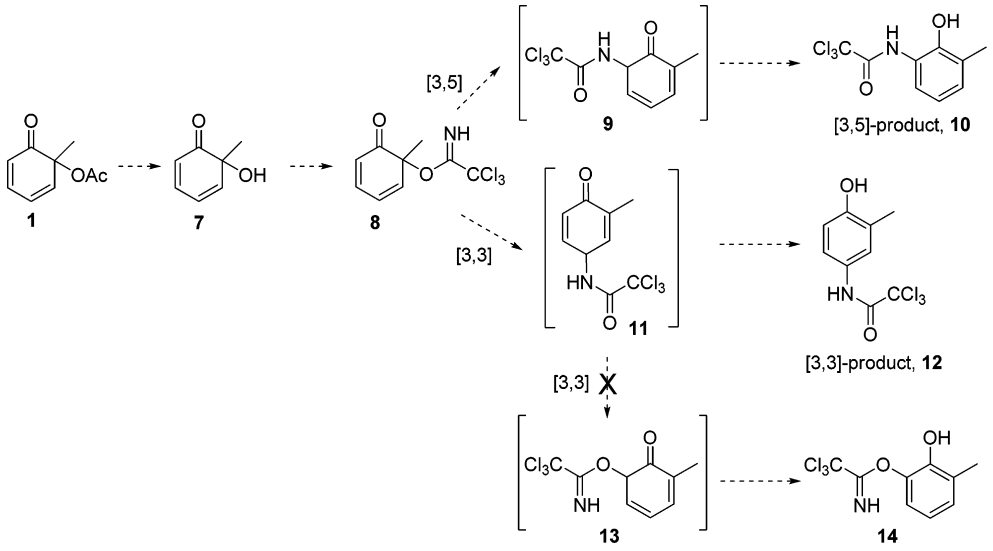
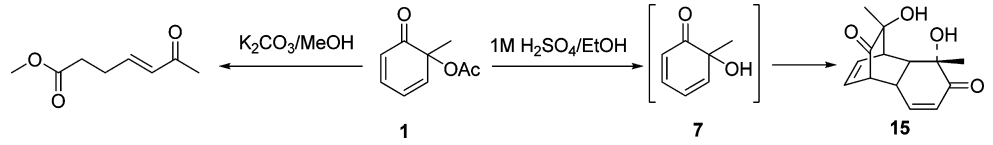
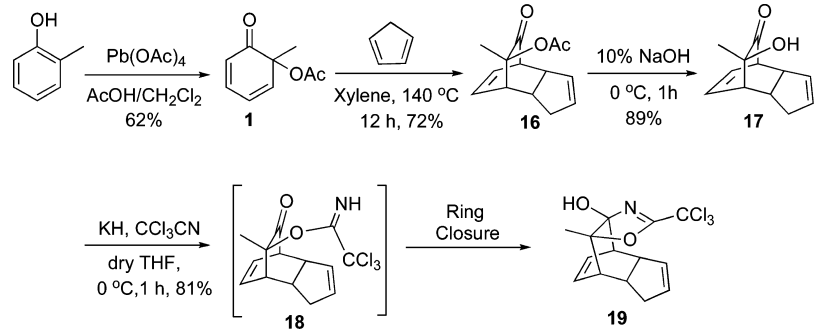
Scheme 4. Proposed Rearrangements of Cyclohexadienyl Trichloroacetimidate (8)



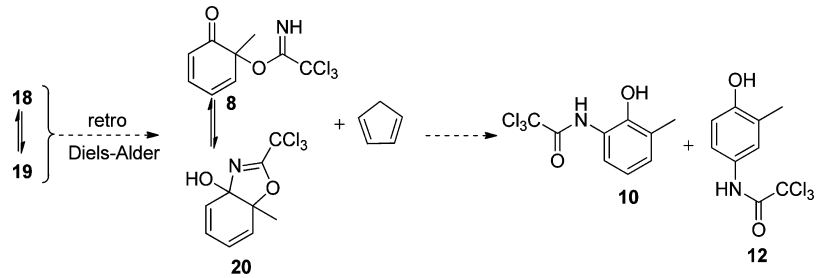
Scheme 5. Attempted Hydrolysis of Acetate 1



Scheme 6. Synthesis of 19



Scheme 7. Anticipated Thermolysis Products of 19



Flash Vacuum Pyrolysis of 19. Flash vacuum pyrolysis (FVP) proved to be extremely useful in studying the mechanism of [3,3]- and [3,5]-sigmatropic rearrangements in acetoxycyclohexadienone **1**.[10] Despite our initial disappointment that **18** could not be isolated, **19** was nevertheless subjected to FVP (details in the Supporting Information) between a temperature range of 400−550 °C. The product mixture was collected in a cold trap. The results of the FVP are summarized in Table 1.

FVP of **19** at these high temperatures gave a complex mixture of products, most of which were not identified. However, the amide **10** expected from [3,5]-rearrangement of **8** was identified in this mixture by GC, GC−MS, and ^{1}H NMR comparison to an authentic sample. There is no evidence as to whether the retro-Diels−Alder reaction or the ring opening

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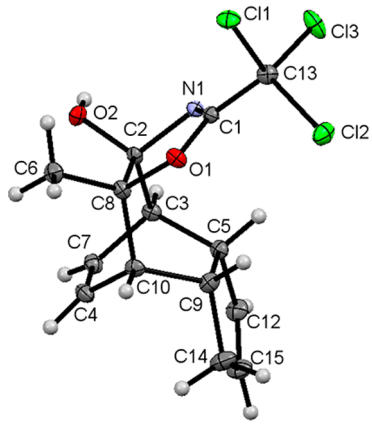


Figure 1. X-ray diffraction crystal structure of **19**. Thermal ellipsoids are represent at 50% probability.

Table 1. Flash Vacuum Pyrolysis of 19[a]

temp (°C)	% **19**	% [3,5]-product **10**	% unidentified products
400	98	0	2
450	79	2	19
500	0	7	93
550	0	8	92

[a]Note: The FVP was carried out using 50 mg of **19** and was performed according to the general procedure described in the Supporting Information. The percentages of products are based on uncorrected GC integrations.

occurred first, i.e., whether the reaction occurred as **19** to **18** to **8** or occurred as **19** to **20** to **8**, but the formation of **10** seems to require the intermediacy of **8**.

FVP at 400 °C resulted in only 2% conversion of **19**, indicating that the retro-Diels–Alder reaction required higher temperatures. (The barrier for the [3,3]- and [3,5]-rearrangement of trichloroacetimidates is expected to be lower than the retro-Diels–Alder.[26,30−33]) When the temperature was raised to 450 °C, about 79% of **19** was unreacted, but cyclopentadiene was observed in the ^{1}H NMR, indicating that the retro-Diels–Alder reaction occurred. Approximately 2% of the [3,5]-rearranged product **10** was observed as indicated by GC and GC–MS. The remaining peaks were unidentified. At 500 and 550 °C, there was no starting compound **19** left in the pyrolysis mixture. A modest amount of the product **10** from [3,5]-rearrangement was observed (7% at 500 °C and 8% at 550 °C).

The amide **12** anticipated from the [3,3]-rearrangement of **8** was not observed in the complex product mixtures obtained from FVP at any temperatures (400–550 °C). It may be that **12** was not formed, but it also might be that **12** underwent a subsequent reaction under these harsh conditions. It could also be that the keto tautomer **11** from the [3,3]-rearrangement was the species that decomposed, while **9** from the [3,5]-rearrangement underwent intramolecular tautomerization to the stable phenol **10** (see calculations and Figure 3, below), in analogy to the reactions calculated for **1**.[10]

Among the unidentified peaks in the GC–MS was one that showed a molecular ion and fragmentation pattern similar to **10** and **12**, but at a different retention time. Based solely on this limited GC–MS data, this might have been **20**. This would require the retro-Diels–Alder of **19** to directly form **20** and the survival of **20** unchanged during the FVP. If **8** were formed in the FVP, it would be expected to rapidly rearrange to **10** or **12**.

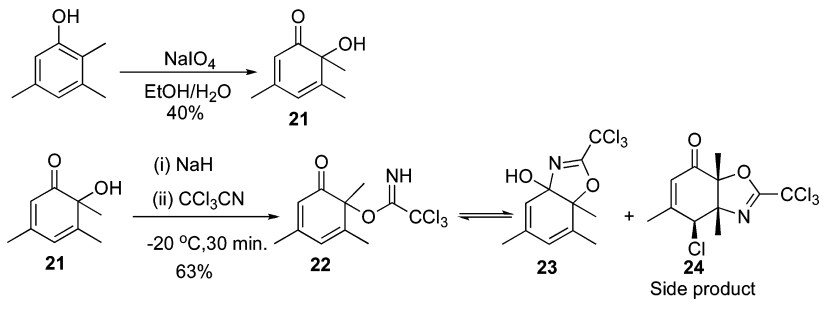
Synthesis of 22. The observation of the [3,5]-rearrangement product **10** was encouraging. However, in light of the complex product mixture obtained from FVP of **19**, we sought a structurally similar molecular system that was simpler and might be expected to give a cleaner product mixture. The complication with the imidate **8** was the dimerization of the dienone alcohol **7**. Thus, we sought a dienone alcohol that would not undergo Diels–Alder dimerization.

There is precedent that monomeric cyclohexadienone alcohols can be isolated if the system is sufficiently crowded. The [4 + 2]-Diels–Alder dimerization can be blocked merely by introducing a small alkyl or alkoxy substituent to the C-5 position of the 2,4-cyclohexadienone system.[42,43] Oxidative dearomatization of 2,3,5-trimethylphenol has been reported using SIBX as the oxidant, albeit in only 12% isolated yield of the desired alcohol **21**.[43]

The hydroxytrimethylcyclohexadienone **21** has also been prepared in modest (35%) yield by periodate oxidation.[42] In our hands, **21** was obtained in 40% yield (Scheme 8 and Figure 2a). We anticipated that subsequent formation of the imidate **22** would be straightforward when **21** was subjected to standard conditions for the formation of trichloroacetimidates.[40,41] ^{1}H and ^{13}C NMR of the product in $CDCl_3$ showed **22**, along with the ring-closed isomer **23**, in analogy to **19**.[44] When the mixture of **22** and **23** was crystallized from pentane as solvent, X-ray diffraction showed that the crystals consisted solely of **23** (Figure 2b).

Dissolution of crystalline **23** in $CDCl_3$ gave the original mixture of **22** and **23**. ^{1}H NMR spectra were then obtained in three other solvents of varying polarity (CCl_4, benzene-d_6, and acetone-d_6). The proportion of **22** in each solvent is presented in Table 2. With the increase in dielectric constant of the solvents CCl_4, benzene-d_6, and $CDCl_3$ there is an increase in the percentage of ring-opened isomer **22**. However, in the case of deuterated acetone which has a dielectric constant of 20.7, only the ring-closed isomer **23** was observed. This can be

Scheme 8. Synthesis of 22, 23, and the Byproduct 24



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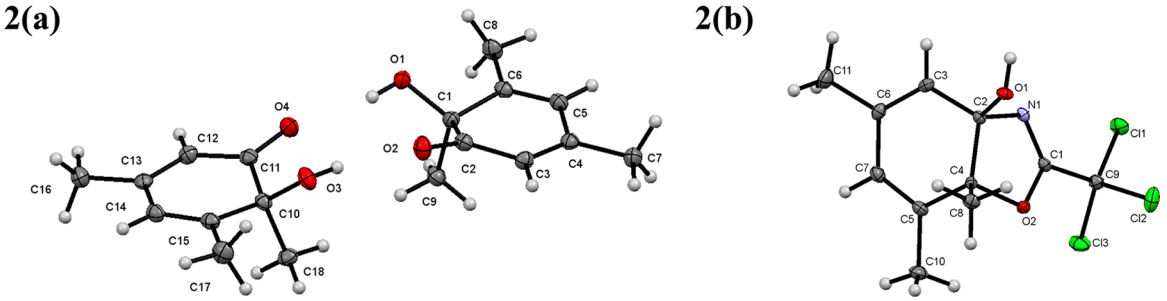


Figure 2. (a) Crystal structure of **21**. (b) Crystal structure of **23**. Thermal ellipsoids are represent at 50% probability.

Table 2. Percentage of 22 in Equilibrium with 23 in Different solvents by ^{1}H NMR

^{1}H NMR Solvents	% **22**	dielectric constant
CCl_4	28	2.24
benzene-d_6	37	2.27
$CDCl_3$	69	4.87
acetone-d_6	0	20.7

rationalized by assuming that acetone can hydrogen bond with the hydroxyl group present in **23** and thus stabilize the ring-closed isomer. We calculated the relative energies of the two isomers at the B3LYP/6-31G(d,p) level to assess the energies of **22** and **23** using the SCRF polarizable continuum model for these solvent dielectric constants, and a similar trend in the stability of ring opened **22** and ring closed **23** was observed, where a higher dielectric constant stabilized the ring-opened form **22** (see the Supporting Information).

Thermal Rearrangements of 22. To study the [3,3]- and [3,5]-rearrangements of **22** and/or **23**, we conducted gas-phase FVP studies as well as thermolysis in benzene-d_6 solution; the results are summarized in Scheme 9 and Table 3. FVP was conducted at 300 and 400 °C. The product mixtures were analyzed by ^{1}H NMR, GC, and GC−MS. Both these FVP reactions were clean and generated only **25** ([3,5]-rearranged product) and **26** ([3,3]-rearranged product) with no starting material remaining by ^{1}H NMR. The product distribution was analyzed by GC; comparison with authentic samples showed a 1.5:1 ratio of **25** to **26** at 300 °C, favoring the [3,5]-rearrangement (see the Supporting Information for GC conditions). Control experiments showed that these amides (**25** and **26**) are stable under the GC conditions. But the barrier for the [3,3]-rearrangements of imidates[26,30,31] is lower than for ester rearrangements,[10] so it was not surprising that control experiments showed that the starting compound **23** rearranged

Table 3. Thermolysis and FVP of 23

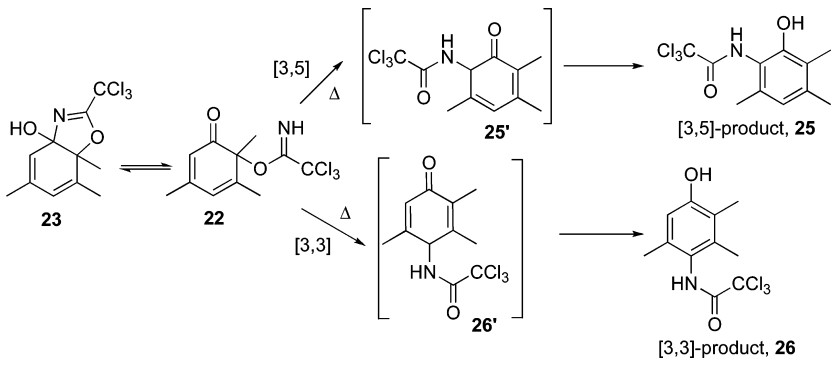
temp (°C)	% **23**	% **25**	% **26**	ratio **25**:**26**
60 (18 h)[a]	80	14	6	2.3:1[d]
70 (15 h)[a]	0	69	31	2.2:1[c]
80 (12 h)[a]	0	65	35	1.9:1[d]
300[b]	0	60	40	1.5:1[c]
400[b]	0	58	42	1.4:1[d]

[a]Thermolysis in benzene-d_6. [b]Flash vacuum pyrolysis. [c]Ratios are based on GC integration. [d]Ratios are based on ^{1}H NMR integration.

under the GC conditions (injector temperature of 160 °C). This suggested that much lower temperatures could still lead to the rearrangements. Indeed, heating **23** at 80 °C in benzene-d_6 for 12 h resulted in complete conversion of **23** into **25** and **26** in a 1.9:1 ratio by ^{1}H NMR integration. Heating a sample in benzene-d_6 at 60 °C for 18 h led to 20% conversion to **25** and **26** in a 2.3:1 ratio by ^{1}H NMR integration. Continued heating of this sample at 70 °C for an additional 15 h led to complete disappearance of **23** and formation of **25** and **26** in a 2.2:1 ratio by GC analysis.[45]

Computational Details. To complement the experimental studies and to shed light on the mechanism of the rearrangements, a brief computational study was undertaken. Most of the calculations were carried out using the Gaussian09 suite of programs.[46] The geometries of the reactants, intermediates, transition states, and products were optimized with the B3LYP functional[47] using the 6-31G(d,p) basis set.[48] Transition states and minima were verified by frequency calculations. Multiple conformations of **8**, **9**, and **11** were calculated. The relative energies of the lowest energy conformations and transition states are presented graphically in Figure 3, and the energies discussed in the text are the B3LYP/6-31G(d,p) free energies unless otherwise noted. Transition states [**3,5**]-**TS2** and [**3,3**]-**TS1** are for the [3,5]-

Scheme 9. Thermal [3,3]- and [3,5]-Rearrangement of 23



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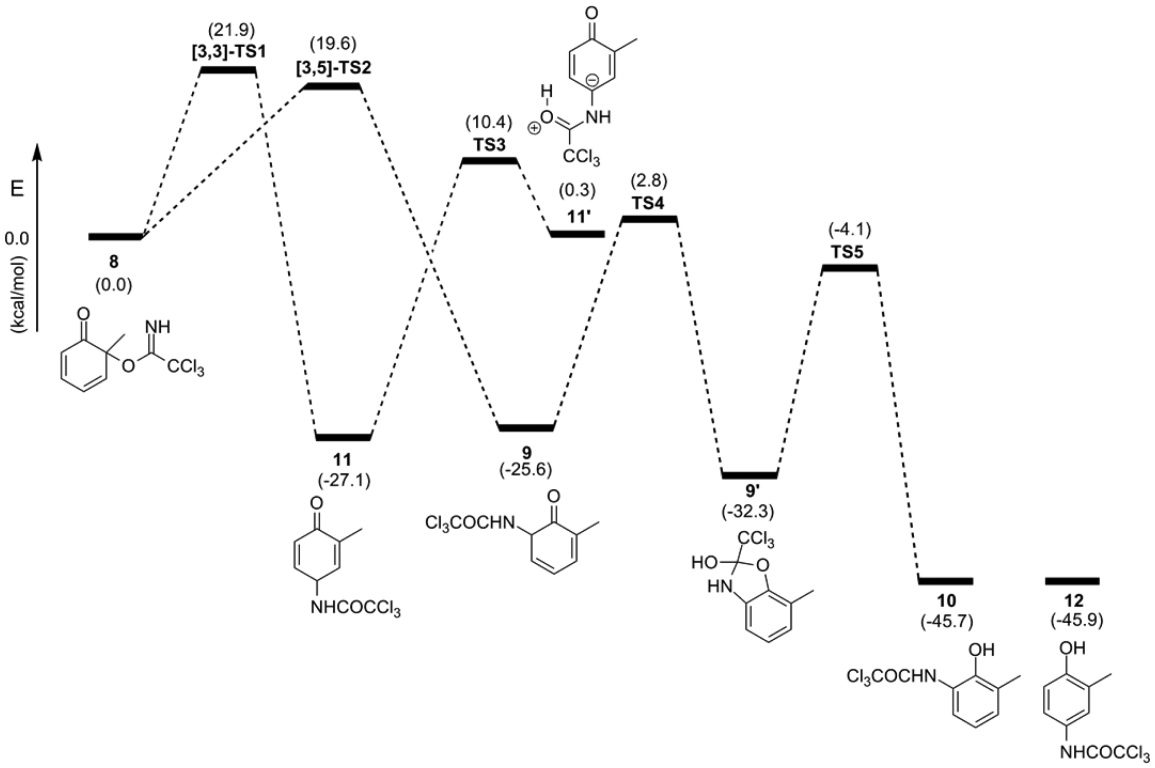

Figure 3. Free energy profile, ΔG_{gas}, for the [3,3]- and [3,5]-sigmatropic rearrangements of compound **8** at the B3LYP/6-31G(d,p) level of theory at 723.15 K.

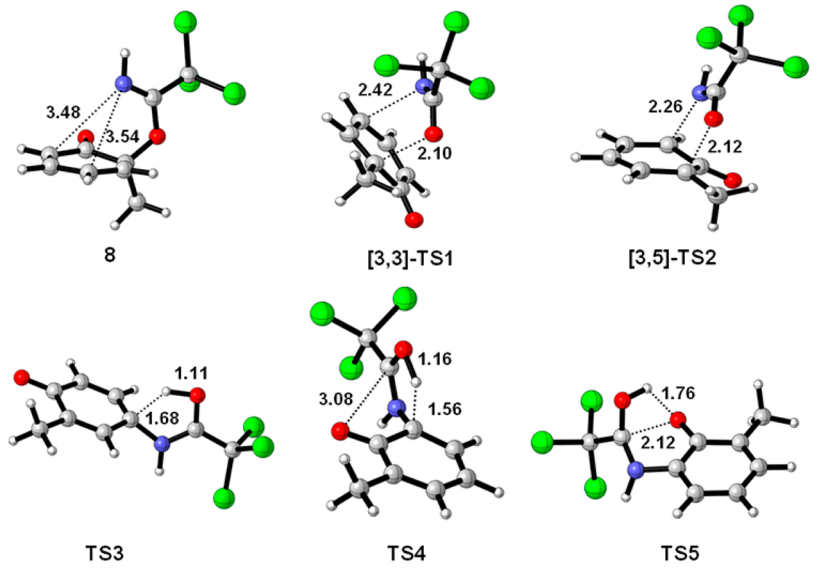

Figure 4. Transition-state geometries calculated at the B3LYP/6-31G(d,p) level of theory for thermal reactions of **8**. Distances of breaking and forming bonds in angstroms.

and [3,3]-rearrangement of **8** to **9** and **11**, respectively. Additionally, **22** and **23** were optimized at the B3LYP/6-31G(d,p) level and single-point energies were calculated using the polarizable dielectric continuum model.[49] Further computational details and geometries of all structures are provided in the Supporting Information. Additional computational studies are in progress.

Computational Results. In our earlier work, we have shown that the [3,5]-sigmatropic rearrangement of esters is allowed via a low energy, concerted pseudopericyclic pathway.[10] The [3,5]-rearrangements of esters are favored over the more familiar [3,3]-rearrangement, both experimentally and computationally. Since the imidates are isoelectronic with esters, we undertook the DFT calculations to study the [3,3]- and [3,5]-sigmatropic rearrangement of trichloroacetimidate **8**. Experimentally, we have shown above that the [3,5]-rearrangement of **8** occurs, and the [3,5]-rearrangement of **22** is favored over the [3,3]-rearrangement.

Figure 3 shows the calculated free energy (ΔG) profile at 450 °C (723.15K) for the [3,3]- and [3,5]-sigmatropic rearrange-

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ments of trichloroacetimidate **8** and for the subsequent tautomerization to **10** and **12**. The calculated barriers for both rearrangements are similar (ΔG = 21.9 and 19.6 kcal/mol for [**3,3**]-**TS1** and [**3,5**]-**TS2**, respectively). While this energy difference is below the computational accuracy of this level of theory, it is consistent with the observation of **12** from the pyrolysis of **19** and is in agreement with the experimental preference for the [3,5]-rearrangement of the trimethyl imidate **22**. It provides a reasonable mechanism for the formation of **10** from the **8**. Interestingly, it seems to be the calculated entropies of the two transition states ([**3,3**]-**TS1** and [**3,5**]-**TS2**) that favors the latter by 4.8 kcal/mol at 450 °C ($T\Delta S$), although the former has a lower B3LYP electronic energy. The calculated enthalpic corrections are less than 0.2 kcal/mol, favoring [**3,5**]-**TS2** as well. As expected, the amides **9** and **11** are significantly more stable than the imidate **8**, so subsequent equilibration is not likely. An intramolecular pathway was calculated for the tautomerization of **9** to **10**. Analogously to what was calculated in the case of ester rearrangements of **1**,[10] an intramolecular transition state **TS4** is found, connecting **9** to the aromatized isomer **9′**. This has only a modest barrier (ΔG = 28.4 kcal/mol) from **9**, so the reaction would be accessible under the conditions for thermolysis of **19**. A second intramolecular transition state, **TS5** leads to the observed product, **10**. The pathway through **TS4** and **TS5** provides an intramolecular pathway for the formation of the stable amidophenol **10**. An intramolecular process from **11** to **11′** is not energetically viable, so it is unlikely that the equally stable isomer **12** is formed in the gas-phase pyrolysis of **8** (from **19**). The direct formation of **10**, but not **12** could offer a speculative explanation as to why **10**, but not **12** is observed in the FVP of **19**. If the tautomers **11** (nonaromatic) or **11′** (zwitterionic) were formed, each would be expected to be more reactive and so would not survive for subsequent analysis. In summary, the product distribution from **8** is calculated to be controlled by the competition between the two unimolecular reactions via [**3,3**]-**TS1** and [**3,5**]-**TS2** to ultimately give **10** as observed, and possibly **12** (not observed).

Figure 4 shows the calculated geometries of **8** and of the transition states. Although the trichloroacetimidate **8** was not isolated, the calculated geometry shows that the imidate nitrogen is over the dienone ring, positioned to bond to the carbons for either the [3,3]- or [3,5]-rearrangement, but slightly closer to the carbon involved in the [3,5]-rearrangement.

The transition-state geometries for the rearrangements are qualitatively similar to those calculated for the isolectronic ester rearrangements of **1**.[10] Specifically, [**3,3**]-**TS1** is a flattened boat geometry, as was also calculated for ester rearrangement of **1** to **3**. This geometry can be considered as resulting from state mixing of two allowed transition states of the same symmetry: (1) an all-π pericyclic one with (2) a pseudopericyclic one where σ-bond breaking and forming would be in the plane of the imidate. The breaking and forming bonds in [**3,3**]-**TS1** are relatively long, 2.10 and 2.42 Å, respectively. The subsequent transition states **TS3**, **TS4**, and **TS5** are all similar to the isoelectronic ones calculated in the ester rearrangement sequence.[10]

For the [3,5]-rearrangement, a suprafacial all-π transition state would be forbidden, as discussed above, but the pseudopericyclic one would be allowed. The calculated transition state [**3,5**]-**TS2** reflects this; the breaking and forming σ-bonds are in the plane of the imidate, as expected for a purely pseudopericyclic orbital topology. These calculations are in qualitative agreement with the experiments, in that the [3,3]- and [3,5]-rearrangements are calculated to have similar barrier heights and the [3,5]-rearrangement proceeds through a purely pseudopericyclic transition state. The breaking and forming bonds (2.12 and 2.26 Å) are calculated to be slightly shorter in [**3,5**]-**TS2** than in [**3,3**]-**TS1**.

The ring-opened and ring-closed isomers **22** and **23** were studied at the B3LYP/6-31G(d,p) level. Geometry optimization gave a structure of **23** that was similar to the X-ray crystal structure. At this admittedly approximate level, **22** was calculated to be more stable (gas phase) than **23** by 2.9 kcal/mol in the gas phase.

The ratio of **22** to **23** is solvent dependent by ^{1}H NMR. To estimate the effects of solvent polarity, single-point energy calculations were performed on **22** and **23** using the SCRF-PCM dielectric constant model for solvation.[49] As the dielectric constant increased from CCl_4 to benzene-d_6, to $CDCl_3$, the energetic preference for **23** decreased (see Table S1). This trend is in accord with the NMR results in Table 2, even though the calculated energy differences are not realistic. This argues that the experimental trend in the equilibrium distribution of **22** and **23** reflects the stabilization of **22** by polar solvents. Acetone does not fit this trend, arguably because of hydrogen bonding that is not reproduced in the dielectric continuum model calculations.

CONCLUSIONS

The tetracyclic compound **19** has been synthesized and characterized by X-ray crystallography and NMR. It may be a thermal precursor to the trichloroimidate **8**. Flash vacuum pyrolysis of **19** led to a low yield of the trichloroacetamide (**10**), presumably formed via a retro-Diels–Alder reaction to give either **8** or **20** (in equilibrium), followed by a thermal [3,5]-rearrangement of **8** to **9** and subsequent tautomerization to **10**. The product anticipated from [3,3]-rearrangement of **8** and subsequent tautomerization (**12**) was not observed.

The dienyl trichloroacetimidate **22** (in equilibrium with the ring-closed isomer **23**) has been synthesized and characterized by NMR spectroscopy (and **23** by X-ray crystallography). Its geometry is appropriate for either a [3,5]- or a [3,3]-sigmatropic rearrangement, and indeed, **25** and **26** are the major products observed upon FVP or thermolysis in benzene-d_6. The product (**25**) from the [3,5]-rearrangement is (slightly) favored over the [3,3]-product (**26**) by a 2.3:1 ratio at 60 °C in benzene-d_6.

The [3,5]-rearrangements are geometrically prevented from achieving a suprafacial/antarafacial transition state geometry and so would be forbidden under the Woodward–Hoffmann rules. They are orbital symmetry allowed with a pseudopericyclic transition state orbital topology, however. This qualitative analysis is supported by B3LYP/6-31G(d,p) transition state calculations, which show a planar geometry on the imidate in the calculated transition state for the [3,5]-rearrangement, [**3,5**]-**TS2**. These results add an additional example to the small number of experimental systems where six-centered and eight-centered concerted reactions are competitive because of the pseudopericyclic nature of the transition states.

EXPERIMENTAL SECTION

General Experimental Information. All reactions were carried out in oven-dried glassware under an inert atmosphere of dry nitrogen.

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All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise specified. ^{1}H and ^{13}C NMR spectra were measured on 400 MHz spectrometers. High-resolution mass spectrometry (HRMS) was performed under positive-mode electrospray ionization (ES) conditions. GC data were obtained on a capillary column with FID or MS detection, and integrations are uncorrected. Melting points were measured on a capillary melting point apparatus and are uncorrected.

General Procedure for Flash Vacuum Pyrolysis. The FVP of **19** and **23** was carried out on recrystallized solid samples. The compound to be pyrolyzed (**19** or **23**) was transferred into a quartz tube (65 cm long and 2 cm diameter) either directly as solid crystals or as a solution in diethyl ether (**23**) or acetone (**19**; due to its better solubility in acetone). The solvent was evaporated, and the compound was dried under high vacuum followed by purging the tube with nitrogen gas. The quartz tube was connected to a U-shaped product trap that was cooled with liquid nitrogen, and the entire setup was kept under vacuum (0.01 mmHg). The end of the quartz tube bearing the sample was initially placed outside the circular furnace and when the temperature of the furnace reached the desired temperature for pyrolysis the quartz tube was gradually moved through the hot zone of quartz tube maintained at a specific temperature (ranging from 300 to 500 °C). The temperature was recorded using a thermocouple that was held in place using a custom-made holder to ensure reproducibility of results. The rearranged product mixture was collected at the cooler region at the end of the quartz tube. More volatile components were trapped in the U-shaped product trap cooled under liquid nitrogen bath. The rearranged product mixture was collected from the quartz tube and U-shaped tube by dissolving in dichloromethane. The samples were then analyzed by ^{1}H NMR, GC–MS, and GC–FID and by comparison to authentic materials.

Synthesis and Characterization of Substrates. *9-Methyl-8-oxo-3a,4,7,7a-tetrahydro-3H-4,7-ethanoinden-9-yl Acetate* ***16***. Compound **16** was synthesized from **1** (1.0 g, 6.0 mmol) according to the procedure described in the literature.[50] The compound was purified by column chromatography to yield **16** as a white solid (1.0 g, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.26 (t, J = 7.3 Hz, 1H), 6.06 (t, J = 7.1 Hz, 1H), 5.68–5.66 (m, 1H), 5.43–5.42 (m, 1H), 3.90–3.88 (m, 1H), 3.27–3.25 (m, 1H), 3.20–3.18 (m, 1H), 2.75–2.69 (m, 1H), 2.56–2.49 (m, 1H), 2.06 (s, 1H), 1.99–1.95 (m, 1H),1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 170.2, 133.9, 133.5, 129.9, 128.8, 81.1, 51.3, 49.4, 45.6, 38.6, 34.2, 22.0, 21.4.

Compound **17** was synthesized from **16** (600 mg, 2.6 mmol) according to the procedure described in literature[50] to yield the desired alcohol as a white solid (437 mg, 89%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (t, J = 7.3 Hz, 1H), 6.02 (t, J = 7.4 Hz, 1H), 5.67 (m, 1H), 5.42 (m, 1H), 3.21–3.16 (m, 3H), 2.98–2.96 (m, 1H), 2.57–2.52(m, 2H), 1.98–1.94 (m, 1H), 1.29 (s, 3H) [the literature ^{1}H NMR data seems inconsistent with the structure; lit.[50] ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, s), 5.36–5.50 (1H, m), 5.64–5.76 (1H, m), 6.04 (1H, dt, J = 7, 1 Hz), 6.32 (1H, dt, J = 7, 1 Hz); the literature elemental analysis is consistent with the structure]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 133.9, 133.7, 130.0, 128.1, 73.2, 51.7, 51.0, 49.2, 38.5, 33.5, 26.2.

8a-Methyl-2-(trichloromethyl)-4,4a,7,7a,8,8a-hexahydro-3aH-4,8-ethenoindeno[5,6-d]oxazol-3a-ol ***19***. To a solution of alcohol **17** (100 mg, 0.53 mmol) in dichloromethane (~10 mL) was added DBU (~16 μL, 0.11 mmol) dropwise at 0 °C. The mixture was allowed to stir at 0 °C for about 20 min, and then trichloroacetonitrile (~58.0 μL, 0.578 mmol) was added to the mixture at 0 °C. The reaction mixture turned reddish brown in color. The reaction was then allowed to stir at room temperature for about 1 h. The TLC showed the disappearance of alcohol **17**. The solvent was evaporated under reduced pressure to yield a brown oil. The brown residue was purified by column chromatography, and the compound was crystallized in ethanol to yield colorless crystals of **19** (130 mg, 74%, mp 248–250 °C) which were used for X-ray diffraction studies.

Note: The above reaction was also repeated using 200 mg of **17** and KH as a base, and we obtained 285 mg (81%) of similar quality crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23–6.15 (m, 2H), 5.57–5.55 (m, 1H), 5.40–5.38 (m, 1H), 3.31 (bs, 1H), 3.01–2.96 (m, 3H), 2.77–2.70 (m, 1H), 2.53–2.46 (m, 1H), 1.94–1.88 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 132.7, 132.0, 131.5, 129.2, 101.4, 95.5, 48.1, 47.2, 45.2, 38.6, 32.5, 21.4.

Synthesis of 6-Hydroxy-3,5,6-trimethylcyclohexa-2,4-dienone ***21***. Compound **21** was synthesized from 2,3,5-trimethylphenol (1.0 g, 7.4 mmol) according to the procedure described in literature.[42] This gave **21** (446 mg, 40%) as a yellow-colored low-melting crystalline solid. The ^{1}H NMR and ^{13}C NMR of **21** agreed with those reported in literature.[42,43]

*Synthesis of 1,2,4-Trimethyl-6-oxocyclohexa-2,4-dien-1-yl 2,2,2-trichloroacetimidate (**22**) and 5,7,7a-Trimethyl-2-(trichloromethyl)-3a,7a-dihydrobenzo[d]oxazol-3a-ol (**23**).* To a suspension of sodium hydride (~27 mg, 1.05 mmol, 95% w/w) in dry THF (3 mL) was added a solution of starting alcohol **21** (200 mg, 1.32 mmol) in dry THF (2 mL) at −20 °C, and the mixture was allowed to stir at −20 °C for about 30 min. Trichloroacetonitrile (198 μL, 1.97 mmol) was then added to the mixture dropwise, and the resulting mixture was stirred at −20 °C for about 30 min. The reaction was monitored by removing small aliquots for ^{1}H NMR spectroscopy. Upon completion, the reaction was quenched with ammonium chloride solution, THF was evaporated, and the aqueous layer was extracted with three 10 mL portion of ethyl acetate. The organic layer was then washed with brine, dried over anhydrous sodium sulfate, and concentrated using a rotavap. The resulting residue was purified by column chromatography (silica gel, 15% ethyl acetate in hexane) to yield the desired compound as a yellow gummy solid. The compound was crystallized in ether/pentane solvent system to yield colorless crystals (246 mg, 63%) of **23**, which equilibrates with **22** in solution as indicated by ^{1}H NMR studies in CCl_4, benzene-d_6, $CDCl_3$ and acetone-d_6. These crystals were suitable for X-ray diffraction studies.

Note: Side product **24** was obtained when 1.5 equiv of trichloroacetonitrile was used.[44] We were able to avoid the formation of **24** by adding only 1 equiv of trichloroacetonitrile.

^{1}H NMR of **22** and **23** in CCl_4 as read from an equilibrated mixture of **22** and **23**: ^{1}H NMR of the major isomer **23** (72%) (400 MHz, CCl_4) 5.62 (s, 1H), 5.57 (bt, J = 1.4 Hz, 1H), 5.11 (bs,1H), 1.96 (s, 3H), 1.84 (s, 3H), 1.66 (s, 3H); ^{1}H NMR of the minor isomer **22** (28%) 8.23 (bs, 1H), 5.88 (s, 2H, 2 −CH), 2.09 (s, 3H), 1.95 (s, 3H), 1.50 (s, 3H).

^{1}H NMR of **22** and **23** in $CDCl_3$ in an equilibrated mixture: ^{1}H NMR of the major isomer **22** (69%) (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 5.99 (s,1H), 5.97 (s, 1H), 2.07 (s, 3H), 1.94 (s, 3H), 1.52 (s, 3H); ^{1}H NMR of the minor isomer **23** (31%) δ 5.57 (s, 1H), 5.54 (s, 1H), 2.99 (s, 1H), 1.91 (s, 3H), 1.78 (s, 3H), 1.64 (s, 3H); ^{13}C NMR of the mixture of **22** and **23** (100 MHz, $CDCl_3$) δ 197.9, 165.2, 159.7, 153.7, 151.7, 136.1, 133.4, 124.7, 123.5, 122.1, 120.9, 96.9, 94.7, 90.76, 84.19, 24.79, 23.17, 21.51, 17.52, 17.48, 16.90.

^{1}H NMR of **22** and **23** in benzene-d_6 in an equilibrated mixture: ^{1}H NMR of the major isomer **23** (63%) (400 MHz, C_6D_6) δ 5.74(s, 1H), 5.17 (s, 1H), 4.65 (s, 1H), 1.69 (s, 3H), 1.68 (s, 3H), 1.43 (s, 3H); ^{1}H NMR of the minor isomer **22** (37%) 8.28 (s, 1H), 5.99 (s, 1H), 5.45 (s, 1H), 1.69 (s, 3H), 1.43 (s, 3H), 1.36 (s, 3H); ^{1}H NMR of **23** (100%) in acetone-d_6 (400 MHz, CD_3COCD_3) δ 5.59 (s, 1H), 5.51 (bs, 1H), 5.49 (s, 1H), 1.87, (s, 3H), 1.73 (s, 3H), 1.57 (s, 3H).

Compound **24** was obtained (70 mg, 16%) as a less polar impurity formed in the above reaction starting from 200 mg of **21**. It is a colorless crystalline solid (mp 74–76 °C). The structure of **24** was confirmed by X-ray crystallography. The ^{1}H and ^{13}C NMR spectra are in accord with this structure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1H), 4.63 (s, 1H), 2.16 (s, 3H), 1.76 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 162.4, 158.4, 128.0, 90.0, 86.0, 75.0, 59.2, 22.8, 21.8, 17.3.

2,2,2-Trichloro-N-(2-hydroxy-3-methylphenyl)acetamide ***10***. As shown in Scheme S1 (Supporting Information), compound **10** was synthesized in three steps. Nitration of *o*-cresol with HNO_3/AcOH yielded 6-nitro-*o*-cresol.[51] This (200 mg) was reduced using H_2 and 10% Pd/C to yield the corresponding amino phenol (143 mg, 89%).[51] The aminophenol (80 mg, 0.65 mmol) was then treated with hexachloroacetone in hexane and the reaction mixture was refluxed for

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6 h, to yield the desired trichloroacetamide **10** as a white solid (141.06 mg, 86%):[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (bs, 1H), 7.71 (d, J = 6.8 Hz, 1H), 7.03 (d, J = 6.8 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 5.72 (bs, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 144.9, 128.3, 125.4, 124.4, 121.3, 119.2, 92.17, 29.8,16.0; EIMS m/z (relative abundance) 269 (4), 267 (4), 150 (100), 122 (24); HRMS (ESI) calcd for $[C_9H_8Cl_3NO_2 + H]^+$ 267.9693 found 267.9688.

2,2,2-Trichloro-N-(4-hydroxy-3-methylphenyl)acetamide ***12*** *(Scheme S1, Supporting Information).* Compound **12** was synthesized by treating commercially available 4-amino-*o*-cresol (100 mg, 0.812 mmol) with hexachloroacetone in hexane at 65−70 °C for about 4 h[52] and was obtained as a white solid (189 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (bs, 1H), 7.33 (d, J = 2.6 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 6.79 (d, J = 8.7 Hz, 1H), 4.77 (bs, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 152.1, 128.9, 125.0, 123.8, 119.9, 115.5, 93.0, 16.0; EIMS m/z (relative abundance) 271(6), 269 (18), 267 (18), 150 (30), 122 (100). Anal. Calcd for $C_9H_8Cl_3NO_2$: C, 40.26; H, 3.00; N, 5.22. Found: C, 40.14; H, 2.75; N, 5.15.

Compounds **30**, **31**, **32**, **33**, **25**, and **26** were synthesized as described in Scheme S2 (Supporting Information).

*Synthesis of 2,3,5-Trimethyl-6-nitrophenol (****30****) and 2,3,5-Trimethyl-4-nitrophenol (****31****).* 2,3,5-Trimethylphenol (5.0 g, 37 mmol was nitrated as described in the literature.[53] ^{1}H and ^{13}C NMR spectra of **30** (2.2 g, 33%) were in agreement with the literature.[54] The authors reported but did not isolate the minor product **31**; however, we were able to isolate **31** as a yellow crystalline solid (1.8 g, 27%, mp 79−81 °C) and characterized it by ^{1}H and ^{13}C NMR: ^{1}H NMR of **31** (400 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.48 (bs, 1H), 2.21 (s, 3H), 2.17 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 146.6, 130.3, 128.2, 121.9, 114.6, 17.5, 15.1, 11.8; EIMS m/z (% relative abundance) 181 (100), 164 (76), 91 (82), 79 (36).

Synthesis of 2-Amino-3,5,6-trimethylphenol ***32****.*[55] To a solution of **30** (160 mg, 0.88 mmol) in THF (∼5 mL) was added 10% Pd/C (∼16 mg, 0.088 mmol) at room temperature, and the mixture was allowed to stir under H_2 atmosphere (H_2 balloon) for about 6 h. The TLC showed the appearance of a more polar spot (20% ethyl acetate/hexane). The reaction mixture was poured over a bed of Celite, which was washed with ethyl acetate (3 × 5 mL). The filtrate was then concentrated and dried under high vacuum pump to yield the desired amine as an off-white solid (134 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 3.57 (bs, 2H), 2.18 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 129.4, 128.7, 123.6, 123.3, 119.6, 19.6, 17.3, 11.9; EIMS m/z (relative abundance) 152 (10), 151 (100), 136 (60), 106 (22), 91 (20).

2,2,2-Trichloro-N-(2-hydroxy-3,4,6-trimethylphenyl)acetamide ***25****.* Compound **25** was synthesized according to the general procedure described in the literature[52] The aminophenol **32** (150 mg, 0.99 mmol) was taken up in hexane, and hexachloroacetone (166 μL, 1.09 mmol) was added to it at room temperature. The mixture was then heated at 65−70 °C for about 6 h. TLC showed the disappearance of the starting aminophenol **32** and formation of a new less polar spot. The solvent was evaporated, and the residue was purified by column chromatography to yield **25** as an off-white solid (132 mg, 45%, mp 150−152 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (bs, 1H), 6.66 (s, 1H), 6.38 (s, 1H), 2.24 (s, 6H), 2.18 (s, 3H); ^{1}H NMR (400 MHz, C_6D_6) δ 7.53 (bs, 1H), 6.62 (s, 1H), 6.41 (s, 1H), 2.12 (s, 3H), 2.01 (s, 3H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 148.5, 137.7, 129.3, 124.7, 124.3, 119.8, 92.3, 20.1, 17.7, 12.1; EIMS m/z (relative abundance) 297 (4), 295 (4), 178 (100), 150 (14); HRMS (ESI) calcd for $[C_{11}H_{12}Cl_3NO_2 + H]^+$ 296.0012 found 296.0004.

4-Amino-2,3,5-trimethylphenol ***33****.*[56] Compound **33** was synthesized according to the general procedure described in the literature.[57] To a solution of **31** (200 mg, 1.1 mmol) in methanol at 0 °C was added 10% Pd/C (0.1 mmol). Then a solution of $NaBH_4$ (125 mg, 3.31 mmol) in water (∼2 mL) was added dropwise to the above solution. The reaction mixture was allowed to stir at room temperature for about 30 min. The TLC showed the formation of a new more polar spot. The mixture was filtered through a Celite bed, and the Celite bed was washed with ethyl acetate. The filtrate was treated with water, followed by brine, and then dried over sodium sulfate. It was then filtered and concentrated to yield a red/brown solid that was purified by column chromatography to yield **33** as a pale brown solid (129.7 mg, 78%, mp 149−151 °C). Note: The above reduction did not work with H_2 (balloon) and 10% Pd/C at room temperature; hence, we reduced the nitro compound using $NaBH_4$/MeOH and 10% Pd/C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 1H), 4.33 (bs, 1H), 3.33 (bs, 2H), 2.17 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 136.2, 122.5, 120.8, 120.5, 114.8, 17.8, 13.7, 12.2; MS (EI) m/z 151, 136, 106, 91; EIMS m/z (relative abundance) 152 (10), 151 (100), 136 (65), 106 (62), 91 (38), 77 (40); HRMS (ESI) calcd for $[C_9H_{13}NO + H]^+$ 152.1075 found 152.1069.

2,2,2-Trichloro-N-(4-hydroxy-2,3,6-trimethylphenyl)acetamide ***26****.* To a solution of **29** (100 mg, 0.66 mmol) in dichloromethane was added trichloroacetic anhydride (133 μL, 0.73 mmol) at 0 °C, and the mixture was allowed to stir at room temperature under N_2 for 3 h. The reaction was monitored by TLC. Upon completion of reaction, the solvent was evaporated, and the residue was purified by column chromatography to yield the desired **26** as a pale yellow solid (180 mg, 92%; mp 216−218 °C; the compound turned brown at 180 °C): ^{1}H NMR (400 MHz, $CDCl_3$, sparingly soluble) δ 7.87 (bs, 1H), 6.44 (s, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H); ^{1}H NMR (400 MHz, C_6D_6) δ 6.94 (bs, 1H), 5.99 (s, 1H), 2.01 (s, 3H), 1.94 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 153.6, 135.8, 133.6, 124.4, 121.5, 114.8, 93.0, 18.0, 14.8, 12.1; EIMS m/z (relative abundance) 299 (2), 297 (6), 295 (6), 178 (32), 150 (100), 117 (24), 107 (36), 91 (42), 77(65); HRMS (ESI) calcd for $[C_{11}H_{12}Cl_3NO_2 + H]^+$ 296.0006, found 296.0000.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01355.

Synthetic schemes for the preparation of authentic standards **10**, **12**, **25**, and **26**, GC conditions, a representative GC trace and ^{1}H NMR spectrum of pyrolysis products, ^{1}H and ^{13}C NMR spectra of all new compounds, and computational information, including energies, pictures, and Cartesian coordinates of all conformations of all calculated structures(PDF)

X-ray crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: david.birney@ttu.edu.

Notes

The authors declare no competing financial interest.

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