Isomerizations of Propargyl 3-Acylpropiolates via Reactive Allenes

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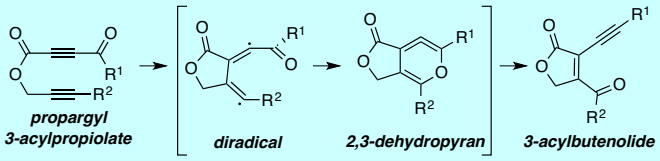
Supporting Information Placeholder

ABSTRACT: Thermal isomerizations of various propargyl 3-acylpropiolates are described. Many result in the formation of 3-acylbutenolides. These reactions appear to proceed through intermediate 2,3-dehydropyrans (strained cyclic allenes), which then isomerize in a previously unobserved fashion. Competitive processes that provide additional mechanistic insights are also described.



Thermal reactions of alkyne-containing substrates often proceed because of the inherently high potential energy of the C–C triple bond.[1] Rearrangements of conjugated ynones are no exception. Wills and Danheiser reported[2] the cycloisomerization of a series of conjugated ynones **1** to efficiently provide the isomerized furan products **4** (Figure 1a). The exergonicity of this transformation is a reflection of the consumption of two alkynes with overall concomitant generation of substructural units comprised of more stable bonding arrangements, including the heteroaromatic character in furan **4**. These researchers proposed and provided compelling evidence that the reactions proceed through reactive intermediates **2** and **3**. Thus, the alkynes in **1** are capable of powering the formation of the strained allene in the 2,3-dehydropyran **2** as well as that of the free carbene **3**. Related, strained, all-hydrocarbon analogs of these cyclic allenes are produced in the cycloisomerization reactions of conjugated dienynes.[3] We have computed the free energies of **1**-**4** [SMD(toluene)/UB3LYP-D3BJ/6-311+G-(d,p)] for the example in which Z = CH_2 and R = $SiMe_3$ and these are given in Figure 1a. Notably, the strained allene in **2** and free carbene in **3** are only uphill in energy by ≤10 kcal•mol^{-1} from **1** and, as such, are viable intermediates.

We have studied and report here alternative and complementary reactivities of substrates containing a modified alkynyl ynone motif. Specifically, when the ynone bears a second carbonyl functional group (cf. **5**, which is a propargylic ester of a 3-acylpropiolic acid), the (presumed) 2,3-dehydropyran intermediates **6** take a different reaction course—electrocyclic ring-opening to produce 3-acylbutenolides **7**.[4] We performed an analogous set of DFT calculations, and the free energies for **5**-**7** as well as the carbene **8** (R^1 = CH_3, and R^2 = ^{t}Bu) are given in Figure 1b. A fuller description of this pathway and its energetics is discussed below (Figure 2). We will refer here to this new reaction pathway, informally, as an "ynedione" rearrangement. A related process involving an all-hydrocarbon substrate (2-methylnona-1-en-3,8-diyne) is known.[5]

Seven examples of substrates **5** and their conversions to products **7** are shown in Table 1. The isolated yields are generally

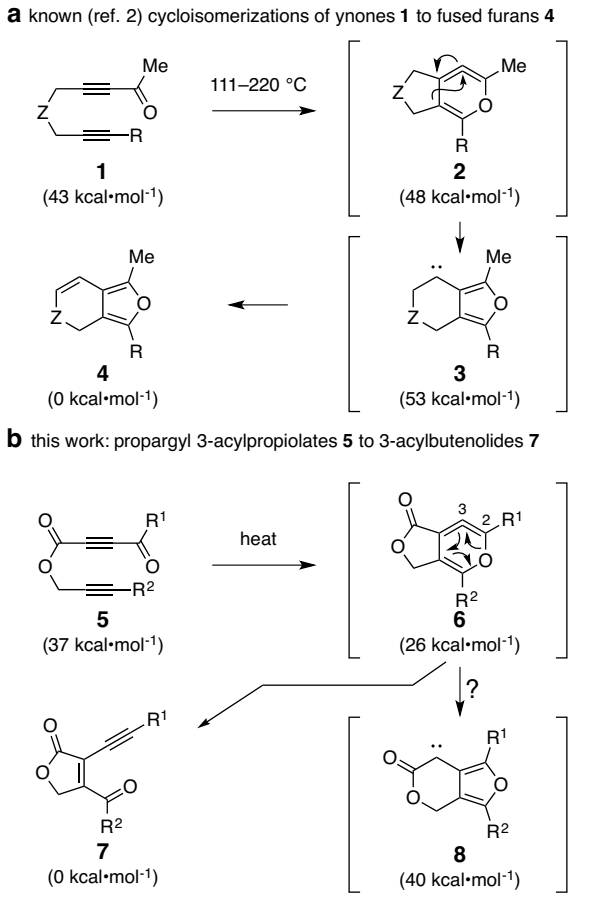
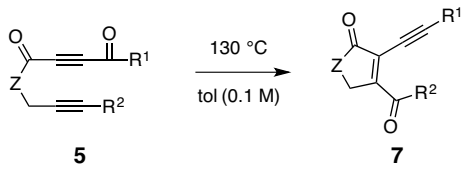


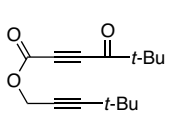
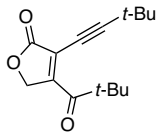
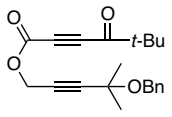
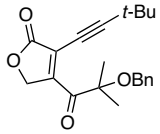
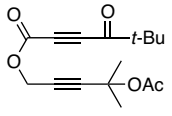
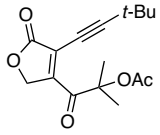
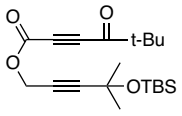
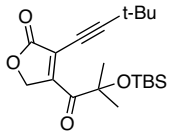
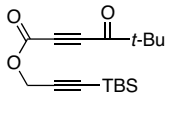
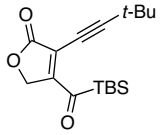
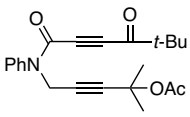
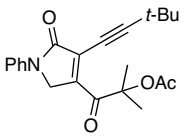
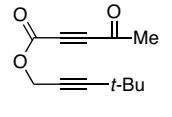
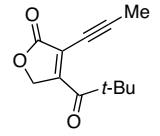
Figure 1. (a) Known rearrangements of conjugated ynones **1** to fused furans **4** via 2,3-dehydropyrans **2** and carbenes **3**. (b) New rearrangements of propargylic 3-acylpropiolates **5** to 3-acylbutenolides **7** via cycloallene intermediates **6**. The relative energies of these species from DFT calculations [see Supporting Information (SI)] are given in parentheses.

very good, and the NMR spectrum of the crude product mixture suggested that in every case the reaction itself was highly efficient. The example in entry 6 demonstrates that an ***N***-propargylated amide will also undergo transformation to an analogous lactam product (**7f**).

Table 1. 3-Acylbutenolide-like products 7 from thermal rearrangement of propargyl 3-acylpropiolate-like substrates 5.



5 **7**

entry	diyne substrate	product (isolated yield)
1	 **5a**	 **7a** (72%)
2	 **5b**	 **7b** (89%)
3	 **5c**	 **7c** (73%)
4	 **5d**	 **7d** (72%)
5	 **5e**	 **7e** (91%)
6	 **5f**	 **7f** (93%)
7	 **5g**	 **7g** (90%)

To gain support for the mechanistic framework shown in Figure 1b, we also identified transition structure energies by DFT for the conversion of **5g** to **7g.** These results are summarized in Figure 2. Overall, the reaction is exergonic by 37 kcal•mol^{-1}. We were not successful in locating a transition structure corresponding to a concerted cyclization converting **5g** to the intermediate **5g-allene**. However, a stepwise process proceeding through **5g-diradical** was found; the initial, rate-limiting step was computed to have an activation energy of 29 kcal•mol^{-1}, and **5g-diradical** was computed to cyclize to **5g-allene** with a very low free energy barrier ($\Delta G^{\ddagger}$ = 2 kcal•mol^{-1}). The final electrocyclic ring-opening of **5g-allene** to the product **7g** accounts for the majority of the overall ergonicity and was computed to proceed with a small barrier of just 6 kcal•mol^{-1}.

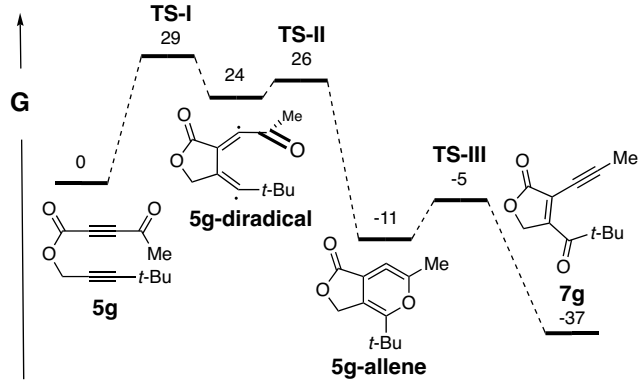
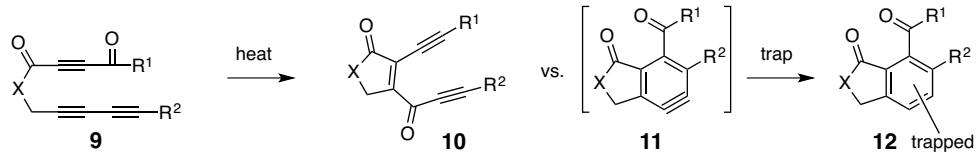


Figure 2. DFT computation [SMD(toluene)/UB3LYP-D3BJ/6-311+G-(d,p)] of the reaction of diyne **5g** to give the 3-acylbutenolide **7g**. The free energy of each minimum and transition state structure is given (in kcal•mol^{-1}) above the bold line corresponding to each of these geometries.

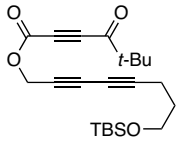
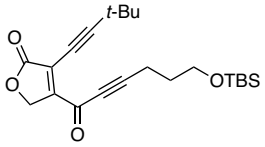
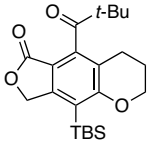
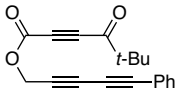
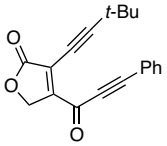
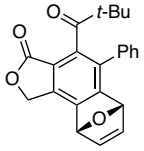
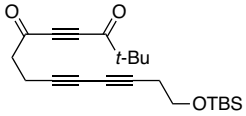
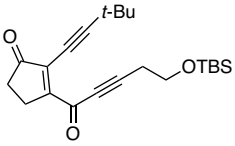
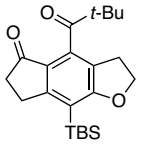
We also have examined several triyne substrates (cf. **9**, Table 2) to address whether they would proceed by this new rearrangement pathway (i.e., to give **10**) or cycloisomerize to benzynes via the hexadehydro-Diels-Alder (HDDA) process (i.e., to trapped products **12** via **11**).[6] In each of the three substrates, the two pathways are competitive. The sum of the yields of the two products coming from the ynedione rearrangement (blue) and the HDDA (red) processes are quite similar for each of the three entries. In addition, there is only a slight (energetic) difference for the two competitive pathways, as judged from the observed product ratios of **10**:**12**.

The mechanism for both HDDA cycloisomerization[7] as well as the ynedione rearrangement (Figure 2) is computed to involve initial formation of a diradical intermediate. Thus, we were not surprised to see that DFT calculations [SMD(chloroform)/UB3LYP-D3BJ/6-311+G-(d,p)] using a truncated analog of the ester-linked triynes **9a** and **9b**—namely, **9d** (Figure 3[8])—suggested that the diradical intermediate **9d-diradical** was common to both pathways. The activation energy for its formation (**TS-I**) was calculated to be 22 kcal•mol^{-1}, which is consistent with the faster cyclization of **9a** or **9b** vs. that of **5g** (Figure 2, E_{act} = 29 kcal•mol^{-1}). The two pathways then diverge through different cyclizations, respectively leading to intermediate **9d-allene** or benzyne **11d**. The activation barriers for each pathway are computed to be quite similar ($\Delta\Delta G^{\ddagger}$ = 1 kcal•mol^{-1}), which is consistent with the formation of comparable amounts of both types of products in entries 1-3 in Table 2. We also computed the activation barriers for the reaction of the initial diradical arising from a truncated analog of the ketone-linked substrate **9c**. The

Table 2. Competition between ynedione rearrangement and hexadehydro-Diels-Alder (HDDA) processes.



9 **10** **11** **12**

entry (time)	ynedione substrate	reaction condition	butenolide product (isolated yield)	HDDA product (isolated yield)	butenolide:HDDA
1	 **9a**	@ 80 °C chloroform 2 h	 **10a** (61%)	 **12a** (20%)	3:1
2	 **9b**	10 equiv furan @ 80 °C chloroform 2 h	 **10b** (70%)	 **12b** (17%)	4:1
3	 **9c**	@ 80 °C chloroform 48 h	 **10c** (21%)	 **12c** (58%)	1:3

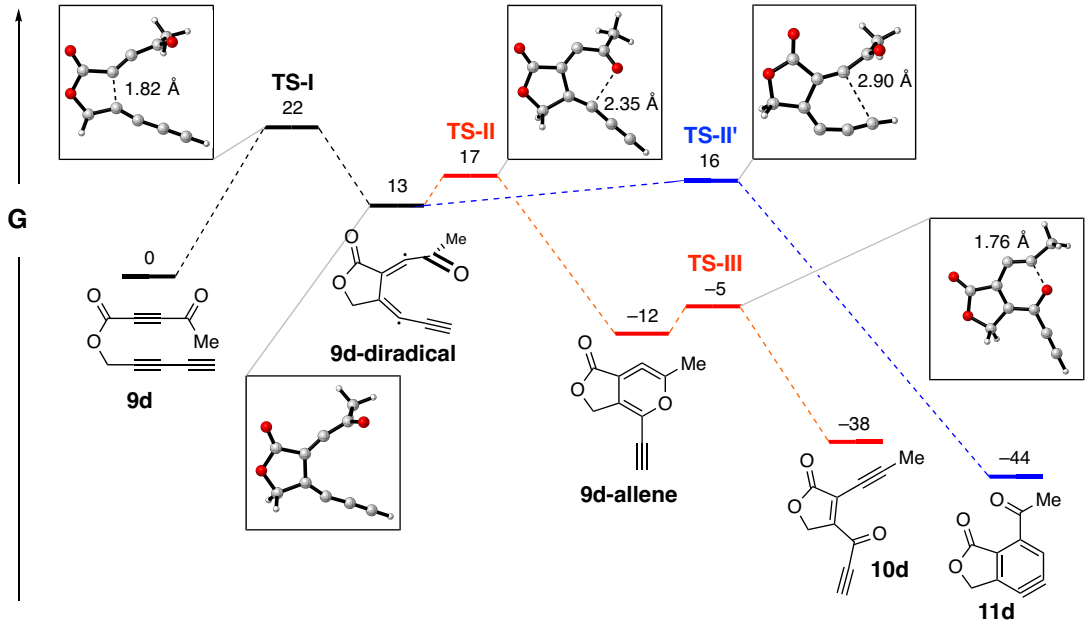


Figure 3. Reaction profile from DFT computations [SMD(chloroform)/UB3LYP-D3BJ/6-311+G-(d,p)] for the reaction of (the model, truncated) triyne **9d** via competitive exiting from the common initial intermediate **9d-diradical** (via TS-II vs. TS-II') to give either **9d-allene** or benzyne **11d**. The free energy of each minimum and transition structure is given (in kcal•mol^{-1}) above the bold line corresponding to each of these geometries.

difference in activation energies for the competing processes was, again, small[$\Delta\Delta G^{\ddagger}$ = 2 kcal•mol^{-1}; see Figure S1 in the Supporting Information (SI) for details]

Several additional substrates were studied that react by alternative pathways either (i) to the exclusion of (Figure 4) or (ii) in competition with (Figures 5 and 6) the ynedione rearrangement. The methyl group at the remote alkyne terminus in ynedione **14** bears a propargylic hydrogen atom. Upon being warmed, it was observed to react at a lower temperature than the analogous substrates in Table 1, none of which contain such a feature. None of the expected butenolide product was observed (cf. **7a-g**). Instead, the only isolable product was a dimer whose structure was deduced by NMR studies to have the constitution of **16**, the stereochemical features of which were revealed by single crystal X-ray diffraction analysis. We propose that this arose from an initial propargyl ene reaction to produce the allene **15**, which then dimerized in the [4+2] fashion suggested by the dashed lines. Assuming that diradical formation in the mechanism of the ynedione rearrangement is rate-limiting (cf. **5-g** to **5g-diradical** in Figure 2), this faster conversion of **14** strongly implies that the propargyl ene reaction is concerted; the alternative stepwise mechanism would proceed through the same initial diradical involved in the rearrangements leading to the 3-acylbutenolide products. A similar diyne-to-allene-to-dimer was reported for the gas-phase flow thermolysis of **13** at 440 °C.[9] At higher temperatures, the intermediate allene isomerizes unimolecularly in the gas phase before it can dimerize.[10]

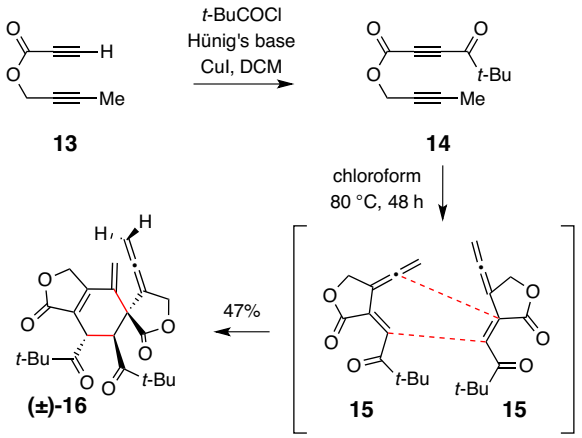


Figure 4. Me-substituted ynedione substrate **14** gives the Diels-Alder dimer **16** via the allene **15**.

Heating the benzoyl-containing substrate **17** (Figure 5, 130 °C, 24 h) revealed yet another type of reaction, this time in the form of a further conversion of the primary butenolide product. We initially observed formation of essentially identical amounts of two products (Figure 5). The first was the expected acylbutenolide **18**. The second was not at all obvious from its NMR spectral data and was only revealed to be the hydroxynaphthaldehyde **19** following an X-ray diffraction analysis of its ***p***-bromobenzoate ester derivative (see SI). Further investigation confirmed that **18** can be cleanly and fully converted to **19** by extended heating at 130 °C (^{1}H NMR, PhMe-d_8; half-life of ca. 24 h). We propose that this deep-seated bond reorganization proceeds by an initial shuttling of one of the butenolide methylene protons by the ketone carbonyl oxygen to the remote alkyne carbon (i.e., **18** to the allene **21** via the furan zwitterion rotamers **20** and **20'**). A peripheral electrocyclization in **21** would give the ketene **22**, within which a 6π-electrocyclization would afford the ketone **23**, a tautomer of the naphthol **19**.

A reviewer has suggested two variants (Figure 5b) on the panel a pathway: i) the butenolide **18** first tautomerizes to the hydroxyfuran **18-taut**, which then converts to the allene **21** by a 1,5-hydrogen atom migration and ii) **21**, regardless of its origin, could proceed to **22** by way of the zwitterionic intermediate **21-zwit** as an alternative to the concerted conversion of **21** to **22** depicted in panel a. Variation i) avoids the unorthodox intermediate **20** but introduces the need to catalyze the initial butenolide to hydroxyfuran tautomerization.

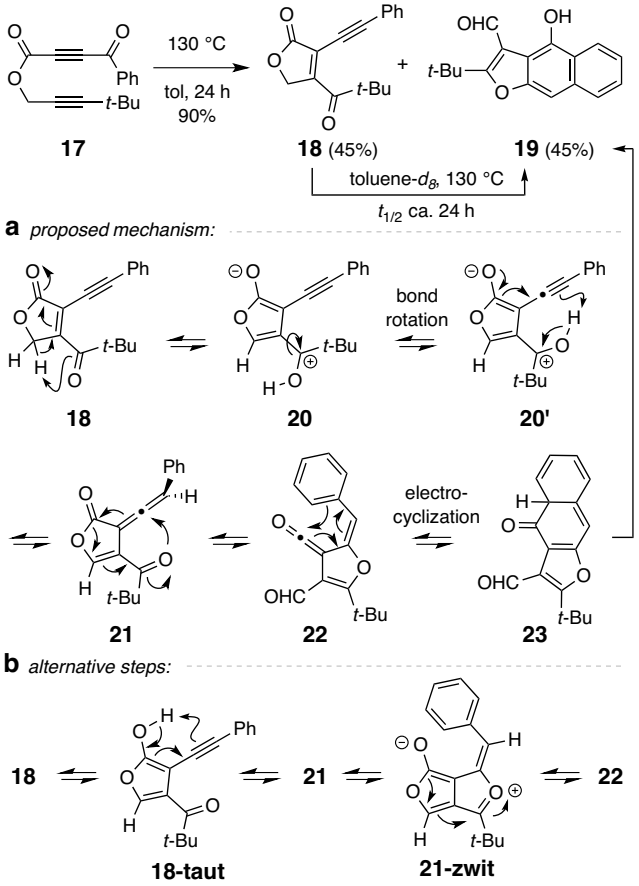


Figure 5. Formation of a secondary product, the naphthaldehyde derivative **19**, upon heating the benzoylated diyne **17**.

We examined two propargyl propiolates containing an aromatic ring on the terminus of the propargyl moiety as the final substrate variation (Figure 6). This was designed to probe the possibility for competition between the ynedione rearrangement and a potential tetradehydro-Diels-Alder [11] (TDDA) reaction. Indeed, from the phenyl-containing substrate **24** (Figure 6a), the mixture of **25**–**27** was produced. This suggested that initial formation of the TDDA allene product **28** and the now-familiar cyclic allene (not shown) were indeed competitive, perhaps even arising from a common diradical intermediate. The further conversion of strained allenes such as **28** to a mixture of both linear and angular naphthalene products analogous to **26** and **27** is known and has been rationalized to occur by way of initial electrocyclic ring-opening (**28** to **29**) followed by ***E***- to ***Z***-alkene isomerization, electrocyclic ring-closure, and final 1,5-hydrogen atom migration (the analog of **28** to **26**).[12] This TDDA pathway can be avoided by using an aryl group with non-hydrogen atom substituents in the

ortho-positions. For example, and as shown in Figure 6b, the pentafluorophenyl-containing substrate **30** gave the butenolide **31** as the only observed and isolable product.

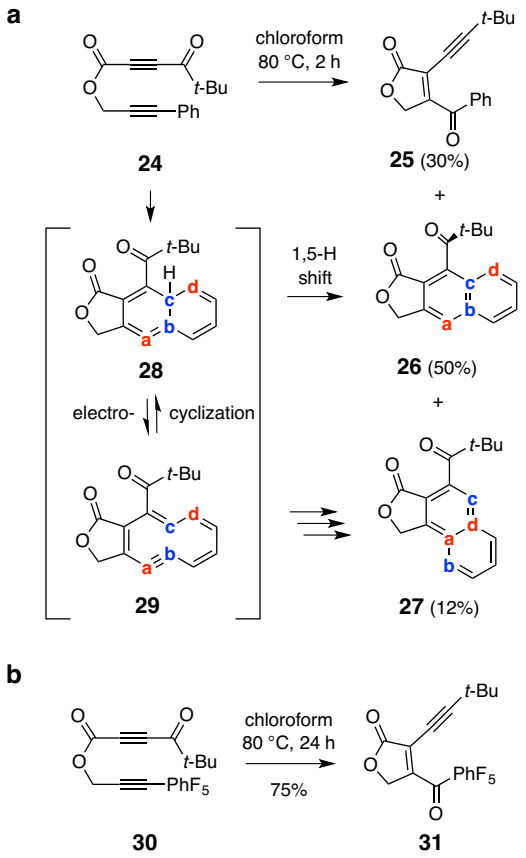


Figure 6. (a) The phenyl-substituted ynedione substrate **24** gives the butenolide **25** together with the TDDA products, naphthalenes **26** and **27**. (b) The F_5Ph-ynedione **30** gives only the butenolide **31**.

In conclusion, a novel rearrangement pathway for propargyl 3-acyclpropiolates has been discovered. It involves their conversion to strained 2,3-dehydropyrans **6** that undergo ring-opening to butenolide products **7** (Table 1). Computational studies suggest that the initial cyclization proceeds through a diradical intermediate rather than a concerted [4+2] cycloaddition. The rearrangement of the primary 3-benzoylbutenolide product **18** to the highly reorganized naphthofuranone **19** is also a new type of transformation.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Details for compound preparation, structural characterization, computational studies, and X-ray diffraction data (for 1844984.cif, 1844985.cif, and 1844986.cif). Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of all new compounds (PDF).

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The authors have no competing financial interests to declare.

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