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# Evidence for Atropisomerism in Polycyclic γ-Butenolides: Synthesis, Scope, and Spectroscopic Studies

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**Abstract:** Design and development of a domino cyclative approach for the synthesis of new polycyclic γ-butenolides from β-aryl-*Z*-enoate propargylic alcohols, through the interception of an intermediate of the *Z*-enoate-assisted Meyer–Schuster rearrangement, has been reported. A systematic NMR analysis of various derivatives of this class revealed and supported the potential atropisomerism associated with them. These molecules represent first examples of butenolide ring-based atropisomeric compounds in organic chemistry. The synthetic process involves a synchronous construction of both rings with concurrent creation of the potential stereogenic rotational axis.

Discovery of new classes of atropisomeric compounds is a hot area of research as they have tremendous applications.[1] They are frequently encountered in pharmaceuticals,[2] bioactive natural products,[3] and as chiral ligands in asymmetric synthesis.[4] The most explored atropisomeric structures possess six-membered rings (carbocycles as well as heterocycles).[5] In contrast, synthesis and study of atropisomeric units possessing at least one five-membered ring (either carbocyclic or heterocyclic) are less explored.[6] Therefore, the design and development of synthetic strategies to access the class of five-membered atropisomeric structures, especially heterocycle-based ones, are highly desirable.

The γ-butenolides (five-membered cyclic esters) have been recognized as important structures as they represent the core framework of many natural products and potential drugs.[7] They have also been utilized as building blocks for the generation of structurally diverse complex molecules.[8] However, employing butenolides as one of the rings in atropisomeric compounds are unprecedented till date.

Recently, we developed a new variant of the classical Meyer–Schuster (M–S) rearrangement[9] (Scheme 1 A), employing the *Z*-enoate-attached propargylic alcohol **1a** for the nucleophiliation of allene intermediates **2**.[10] Various nucleophiles such as Ar–H, $MsO^-$, $TsO^-$, $Cl^-$, and $H_2O$ have efficiently been added for the synthesis of α-functionalized 1,4-enone-esters **3a** and 1,2-diketones **3b**. Both unsubstituted (R = H) as well as β-alkyl-substituted *Z*-enoates have been successfully employed in this reaction. According to the proposed mechanism, the possible intermediates are alkoxyfuranyl allene **2** and cyclic orthoester **4a**. The orthoester **4a** upon ring-opening will lead to the products **3a** and **3b**.

In continuation of our efforts in exploring this versatile transformation, we aimed to develop an approach for the prototypical synthesis of potential γ-butenolide-based atropisomeric compounds **5** through the competitive ethanol elimination from the cyclic orthoester **4b** (Scheme 1 B) over the usual ring-opening (Scheme 1 A). These structures **5** represent a novel and unprecedented class of polycyclic butenolides and may exhibit atropisomerism due to the restricted rotation across the C–C bond connecting the butenolide and the bicyclic system. To promote the elimination of ethanol from **4b** over the competitive ring-opening (as is the case with unsubstituted as well as β-alkyl-substituted substrates (**4a**), Scheme 1 A), we proposed to place an aryl substituent on the β-carbon of the *Z*-enoate linker of a propargylic alcohol with an intramolecular arene nucleophile such as **1b**. According to our design, the +mesomeric (+M) effect of the β-aryl ring would decline ring opening of the cyclic orthoester **4b** and promote the elimination of ethanol.

To test this hypothesis, we began our investigation with β-phenyl *Z*-enoate propargylic alcohol **6a** (possessing phenyl as an intramolecular nucleophile). Treatment of **6a** with MsOH (1.3 equiv) in $CH_2Cl_2$ at 0 °C to RT, gave the expected polycyclic butenolide **7a** in 65% yield after 12 h (entry 1, Table 1). Reaction with *p*TSA (*p*-toluenesulfonic acid, entry 2) also gave the product **7a** after 12 h at 55 °C (at 0 °C, no reaction was observed) but in poor yield (51%). With TfOH (trflic acid, 1.3 equiv) in $CH_2Cl_2$, the reaction was slower (24 h) at 0 °C to RT but efficient (70% of **7a**) and also gave 7% of 1,4-ketoester **8a** (entry 3).[10b] Employing Lewis acids such as $BiCl_3$ and $BF_3{\cdot}Et_2O$ (entries 4 and 5) did not show any improvement in the reaction outcome. We next screened various solvents (entries 6–9) such as acetonitrile, 1,2-dichloroethane, toluene, and nitromethane against TfOH (1.3 equiv). Among them, nitromethane (entry 9) was found to be the best to yield the butenolide **7a** in 85%, along with 7% of **8a** within 3 h at RT. Decreasing the amount of TfOH (entries 10 and 11) resulted in an inefficient process. In almost all experiments with TfOH, the 1,4-ketoester **8a** was associated in varying amounts. Formation of **7a** (path b) and **8a** (path a) can be explained via two competitive processes, that is, ethanol elimination versus ring opening, from the cyclic orthoester intermediate **9a**.

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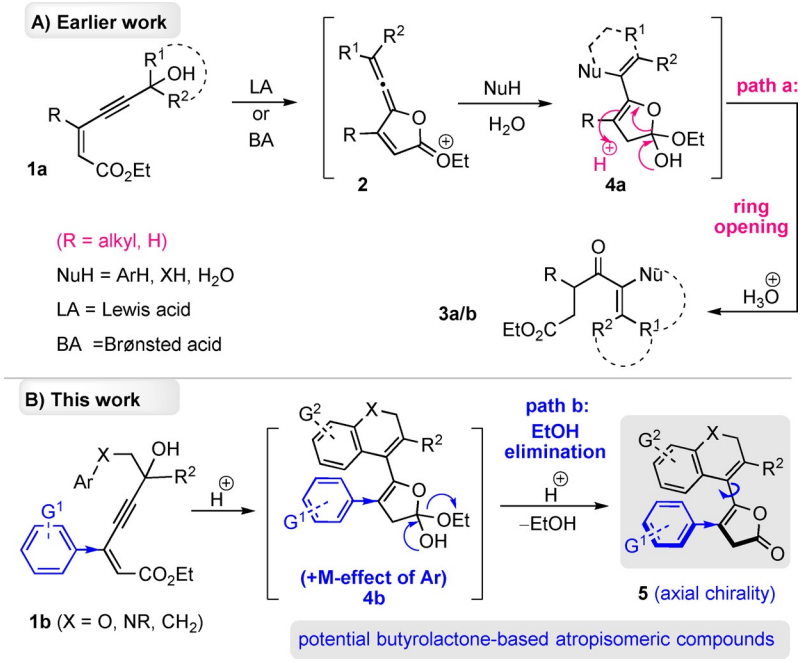
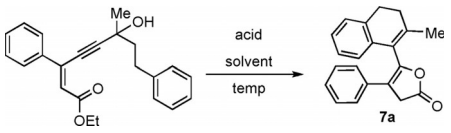
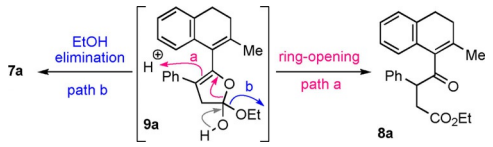



**Scheme 1.** A) Earlier work: the *Z*-enoate-assisted Meyer–Schuster rearrangement of *Z*-enoate propargylic alcohols.[10] B) This work: Design for the prototypical generation of potential γ-butenolide based atropisomeric compounds ($G^1$ = H, alkyl, aryl, OH, and OMe; and $G^2$ = H, alkyl, and OMe).

**Table 1.** Reaction optimization.[a]




| Entry | Acid | Equiv. | Solvent | *T* [°C] | Time [h] | Yield[b] **7a** [%] |
|---|---|---|---|---|---|---|
| 1 | MsOH | 1.3 | $CH_2Cl_2$ | 0 to RT | 12 | 65 |
| 2 | $_p$TSA | 1.3 | $CH_2Cl_2$ | 55 | 12 | 51 |
| 3 | $CF_3SO_3H$ | 1.3 | $CH_2Cl_2$ | 0 to RT | 24 | 70[c] |
| 4 | $BiCl_3$ | 1.3 | $CH_2Cl_2$ | 0 to RT | 4 | 60 |
| 5 | $BF_3OEt_2$ | 1.3 | $CH_2Cl_2$ | 0 to RT | 5 | 45 |
| 6 | $CF_3SO_3H$ | 1.3 | $CH_2Cl_2$ | 0 to RT | 3.5 | 10 |
| 7 | $CF_3SO_3H$ | 1.3 | 1,2-DCE | 0 to RT | 12 | 60[d] |
| 8 | $CF_3SO_3H$ | 1.3 | toluene | 0 to RT | 7 | 60[e] |
| 9 | $CF_3SO_3H$ | 1.3 | $CH_3NO_2$ | 0 to RT | 3 | 85[f] |
| 10 | $CF_3SO_3H$ | 0.6 | $CH_3NO_2$ | 0 to RT | 6 | 56[g] |
| 11 | $CF_3SO_3H$ | 0.1 | $CH_3NO_2$ | 0 to RT | 12 | 35 |




[a] All reactions were carried out in 0.2 mmol of **6a** in 5 mL of solvent. [b] Yields are after chromatographic purification. [c] 7% of **8a**. [d] 11% of **8a**. [e] 15% of **8a**. [f] 7% of **8a**. [g] 17% of **8a**.

Subsequently, we performed a scope study by employing various β-aryl-*Z*-enoate propargylic alcohols for the generation of structurally divergent butenolide-based potential atropisomeric compounds (Figure 1). Various intramolecular arene nucleophiles, propargylic alcoholic substituents, and β-aryl groups were screened. All substrates **6b–6p** smoothly underwent the domino-double cyclization under standard reaction conditions (entry 9, Table 1) and afforded the corresponding products **7b–7p** in good yields (70–91%). In case of **6d** and **6e**, we also isolated minor amounts of the corresponding 1,4-ketoesters **8d** (10%) and **8e** (11%), respectively, along with **7d** (75%) and **7e** (78%).

Interestingly, $^1$H NMR spectra of all these tetracyclic compounds **7a–7p** exhibited a unique diastereotopic character at the methylene group present in the butenolide ring. Typical AB-quartet (3.86, 3.71 ppm, 2H, ABq, $J$ = 22.4 Hz, for **7a**) with a very strong geminal coupling (of $^2J_{H-H}$ = 23.4 Hz) was observed for these two protons in all products (in Figure 2A, the $^1$H NMR spectrum of compound **7a** is depicted). This may be due to the presence of a chiral axis in these molecules because of restricted rotation across the C–C bond connecting the butenolide and dihydronaphthalene rings. Furthermore, single-crystal X-ray diffraction analysis of compound **7b** (Figure 2B) unambiguously confirmed the presence of the β-aryl-γ-butenolide–dihydronaphthyl framework. This also supported our hypothesis that presence of a chiral rotational axis is due to restricted rotation as the dihedral angle between butenolide and dihydronaphthalene is close to 90°.[11]

Encouraged by the observed atropisomerism in butenolide–dihydronaphthyl systems, we next synthesized analogous 3-arylbutenolide-dihydroquinolines (**7q–7s**) as well as 3-arylbutenolide-chromenes (**7t**, **7u**) by changing the linker from –$(CH_2)_2$– to [–$CH_2$-N(Ts)–] and [–$CH_2$–O–], respectively (Figure 3) to understand the influence of heteroatoms on the atropisomeric behavior. For all these compounds (**7q–7u**) a better diastereotopic behavior of butenolide methylene protons was observed. In case of dihydroquinoline products **7q–7s**, the 'N–$CH_2$' protons also exhibited two distinct doublets. This behavior suggests that these two protons are also in mag-

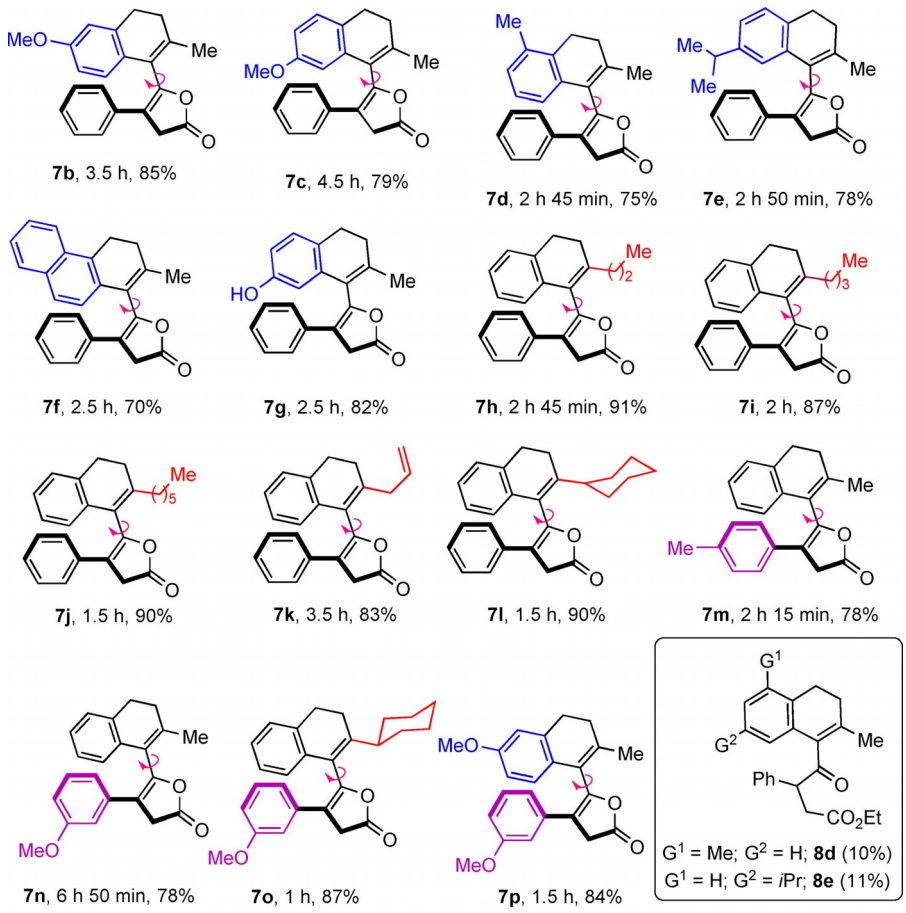



**Figure 1.** Scope study for divergent butanolide-based potential atropisomeric compounds; conditions: TfOH (1.3 equiv), $CH_3NO_2$, 0 °C to RT.

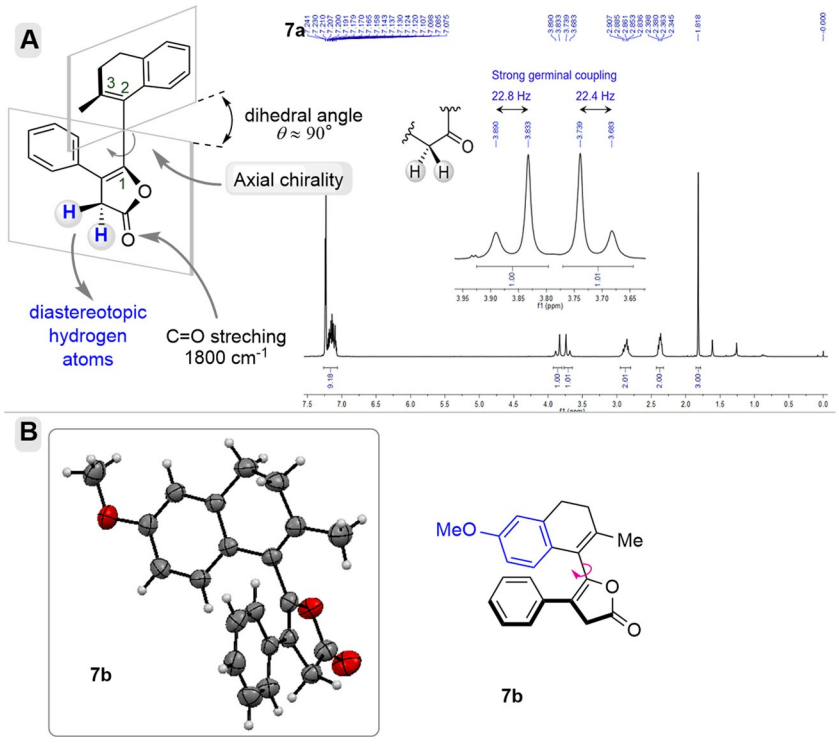



**Figure 2.** A) Observation of possible butyrolactone-based atropisomerism through the analysis of $^1$H NMR spectrum of **7a**; B) ORTEP diagram for compound **7b**.

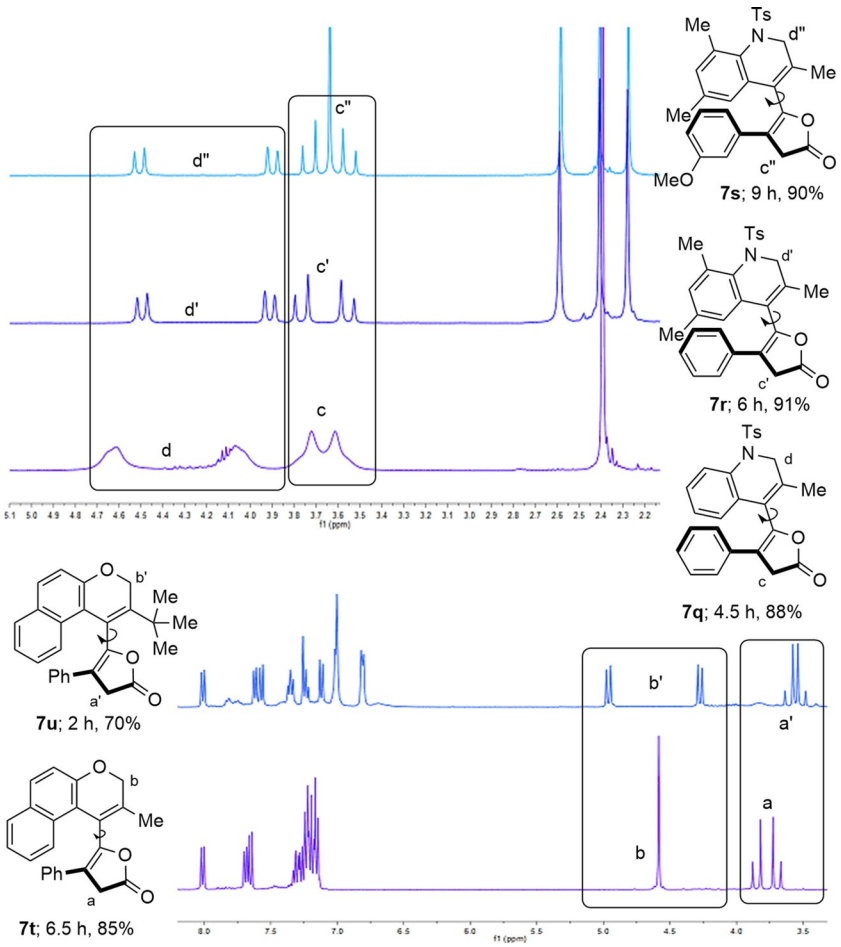



**Figure 3.** Designed dihydroquinoline and naphthopyran substrates to understand the heteroatom effect on the atropisomerism of γ-butenolide derivatives.

netically distinct environments, which supports the proposed atropisomerism. The $^1$H NMR spectrum of compound **7q** exhibits its diastereotopicity with very broad signals for all protons; this may be due to the lower rotational barrier compared to more sterically crowded **7r** and **7s**. The two naphthopyran–butenolides **7t** and **7u** that differ in 'methyl vs. *tert*-butyl' on the pyran ring were also studied. The $-OCH_2-$ protons of the methyl-substituted chromene derivative **7t** shows only a 2H singlet at 4.58 ppm and an AB-quartet (diastereotopicity) for the butenolide methylene (3.85, 3.70 ppm; 2H, ABq, $J = 23.5$ Hz). On the other hand, the *tert*-butyl derivative **7u** exhibited two doublets for $-OCH_2-$ protons (at 4.30 and 5.05 ppm; diastereotopic behavior) as well as AB quartet for the butenolide methylene protons. This suggests that higher the steric hindrance, higher the rotational barrier and hence stronger the atropisomerism.

Next, we aimed at the separation of the enantiomers of these hypothetical atropisomers as corresponding diastereomers by attaching a chiral entity (point chirality) such as chiral camphor sulfonic acid (Figure 4).[12] Accordingly, the butenolide **7g**, which exhibits atropisomeric behavior (see i, Figure 4A), was treated with (1*S*,4*R*)-10-camphorsulfonyl chloride in the presence of DMAP (4-dimethylaminopyridine) and TEA (triethylamine) in dichloromethane at ice-cold temperature to generate the corresponding sulfonate **9** in 82% yield. However, the $^1$H NMR spectrum of **9** shows the presence of only a single product instead of a mixture of diastereomers. Furthermore, **9** does not exhibit any atropisomerism as the butenolide–methylene appears as a singlet at RT instead of AB quartet (compare i and ii; Figure 4A). It appears that the addition of the sulfonic acid moiety reduced the barrier for the restricted rotation by moving away from the phenyl ring on the butenolide in comparison to **7g**. Single-crystal X-ray diffraction analysis of compound **9** confirmed the distal location of the camphor moiety and also the structure of **9** (Figure 4B).[13] However, to reinforce the atropisomeric behavior of **9**, we performed a variable-temperature (VT) NMR study (Figure 4A). Accordingly, $^1$H NMR spectra were recorded from 0 to −50 °C with intervals of 10 °C. The atropisomeric (diastereotopic) behavior of butenolide–methylenes began to reappear only at −40 and −50 °C (vii & viii; Figure 4A). This supported the proposal of poor rotational barrier for **9** compared with **7g**.

In continuation, we have also oxidized few of the dihydronaphthalenes **7d**, **7e**, and **7p** to the corresponding naphthalenes **10d**, **10e**, and **10p** by treating with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in refluxing toluene and analyzed their $^1$H-NMR spectra (Scheme 2). Both **10e** and **10p** exhibited the loss of diastereotopic character, that is, atropiso-

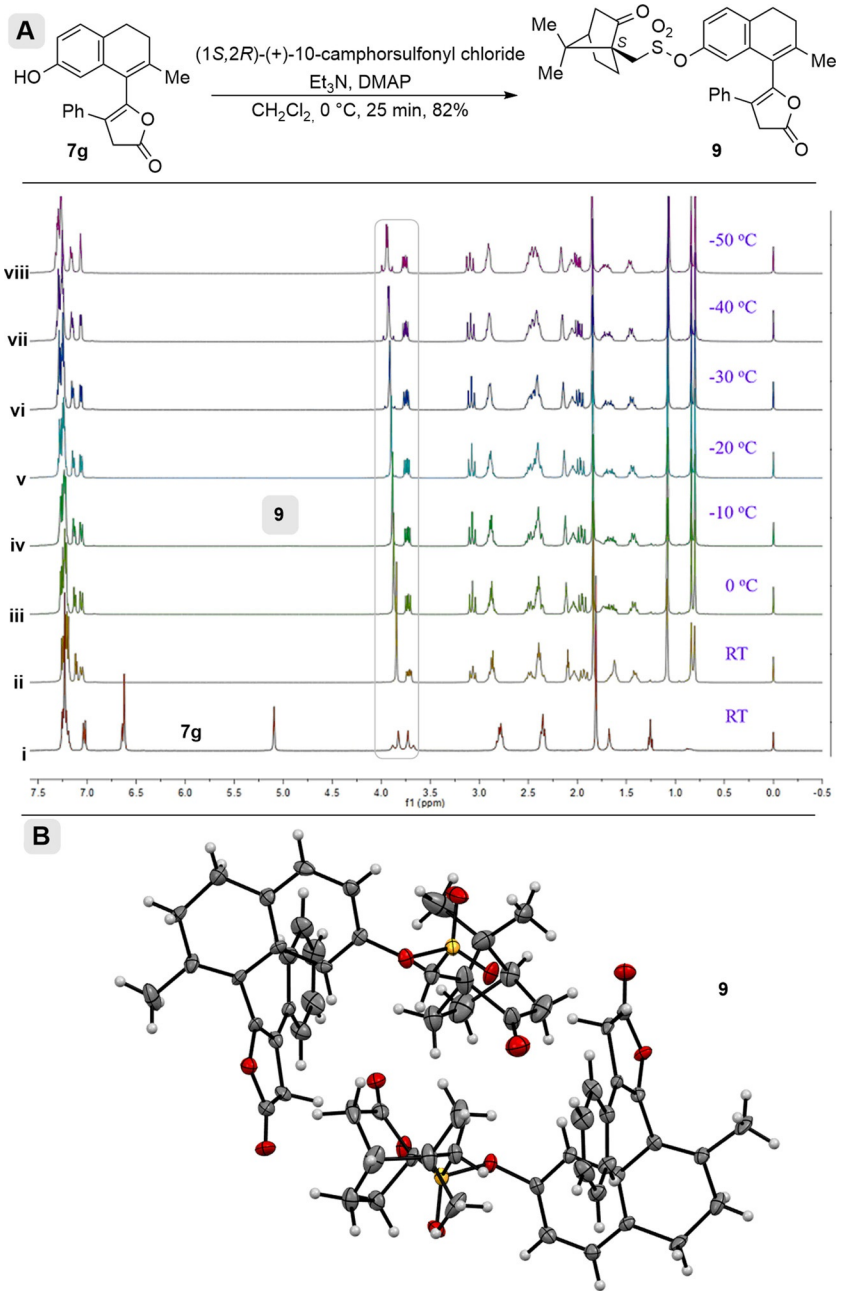
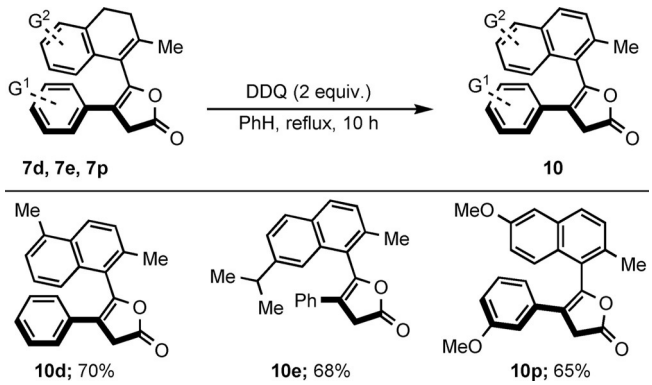


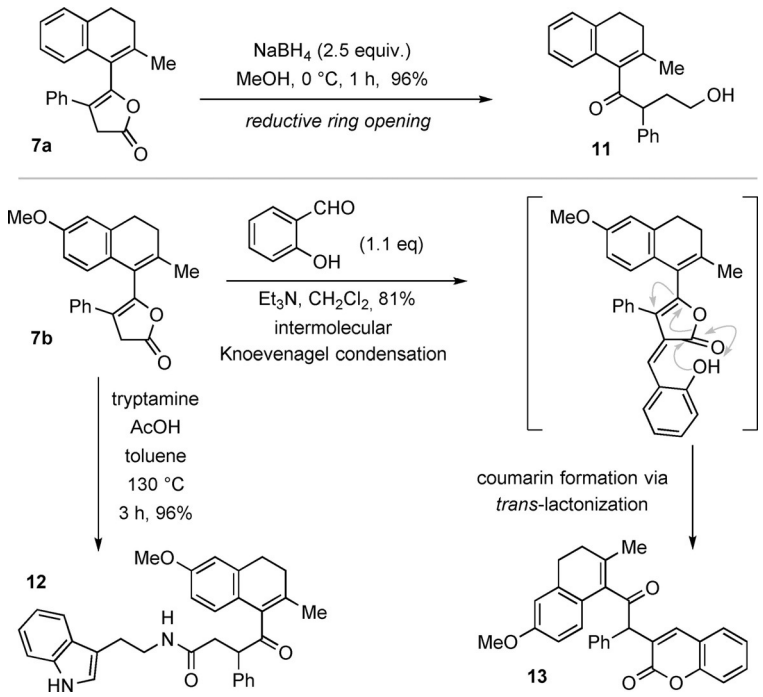

**Figure 4.** A) Variable temperature (VT) $^{1}$H NMR analysis of compound **9**; B) ORTEP diagram for compound **9**.




**Scheme 2.** Aromatization of dihydronaphthalenes.

merism, whereas **10 d** showed a weak AB quartet (see the Supporting Information for $^{1}$H NMR spectra). At this stage, we do not have any other evidence to support the observed atropisomerism in our polycyclic γ-butenolide frameworks.

Apart from exhibiting prototypical atropisomerism, this new class of butenolides can also be useful as building block for the synthesis of various functionalized polycyclic systems (Scheme 3). Treatment of **7 a** with $NaBH_4$ in MeOH gave the hydroxyketone **11** in 96% yield via a reductive ring opening. Similarly, refluxing **7 b** and tryptamine in acetic acid (AcOH) and toluene gave the ketoamide **12**. On the other hand, reaction of **7 b** with salicylaldehyde in the presence of $Et_3N$ afforded the




**Scheme 3.** Synthetic transformations of 4-(dihydronaphthyl)-3-arylbutenolides.

polycyclic coumarin **13** in 81% yield through a domino Knoevenagel condensation–*trans*-lactonization reaction sequence.

In conclusion, we have discovered a domino cyclization approach for the synthesis of a new class of γ-butenolide derivatives from β-aryl-*Z*-enoate propargylic alcohols through the interception of an intermediate of the *Z*-enoate-assisted Meyer–Schuster rearrangement. A systematic NMR analysis of various derivatives of this class of molecules revealed the potential atropisomerism associated with them. These molecules represent a first example of atropisomeric compounds consisting of butenolide ring in organic chemistry. The synthetic process involves a synchronous construction of both rings with the concurrent creation of the potential stereogenic rotational axis. The synthetic utility of these polycyclic butenolides has also been demonstrated.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** atropisomerism · butenolides · domino cyclization · Meyer–Schuster rearrangement · propargylic alcohols

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[11] Deposition Number 1881525 contains the supplementary crystallographic data for this paper. These data are provided free of charge by

the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[12] We attempted the enantiomeric separation of some of these atropisomeric compounds on a chiral-HPLC. But all attempts with a combination of several solvent mixtures against different chiral columns failed to provide separation for any of these compounds.

[13] Deposition Number 2039430 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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