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Studies on Thermal Reactivity of β-(1,2-Allenyl)butenolides and 2-Allyl-3-allenylcyclohex-2-enones

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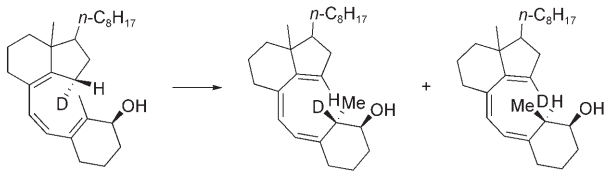
Abstract: A series of thermal pericyclic reactions of β-allenylfuranones have been studied. It was observed that β-allenylfuranones would undergo 1,5-hydrogen shift to afford a new type of trienes upon heating. Due to their high reactivity, these trienes would undergo subsequent pericyclic reactions based on the nature of the substituent group R: When R is an alkyl group, the intermediate **4a** or **4b** would undergo a further 1,7-hydrogen shift to afford a more stable conjugated triene **3**; with R being phenyl or cyclopropyl group, the 1,7-hydrogen shift was inhibited and the **4**-type conjugated triene would form a six-membered ring **5** via 6π-electrocyclization. Interestingly, introducing another C=C double bond into the triene intermediate (R = CH=CH_2), the **18**-type intermediate would undergo 8π-electrocyclization reaction to form an eight-membered ring. Such a transformation was also observed with 2-allyl-3-allenylcyclohex-2-enones. The deuterium-labeling mechanistic studies show that the alkyl groups at the allenyl moiety of **1** participated in the isomerization process via 1,7-hydrogen shifts between **18A**, **20A**, and **29A**.

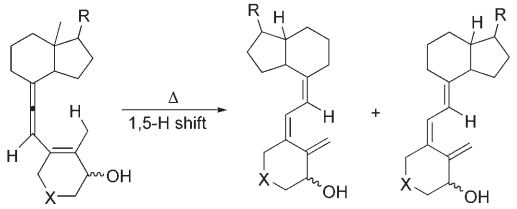
Keywords: allenes · cyclization · hydrogen shift · ketones · lactones

Introduction

Furanones are an important structural unit in natural products and useful intermediates in organic synthesis. The furanone-containing natural products usually exhibit interesting biological activities.[1,2] Thus, many methods for the synthesis of furanone derivatives have been developed.[3] Recently an efficient protocol has been developed in this group for the synthesis of β-allenylfuranones.[4] The interesting 1,3,4-triene within β-allenylfuranones has shown some synthetic potential, that is, the Diels–Alder reaction with electron-deficient alkynes for the synthesis of poly- or fully-substituted benzenes.[4] On the other hand, the sigmatropic hydrogen migration, which provides an efficient route to some not-readily-available structures, has been of great theoretical and practical interest.[5] For example, the classical thermal 1,7-hydrogen shift is considered to be a pivotal event in the metabolic production of vitamin D.[6] Hoeger et al. studied the stereochemistry of 1,7-H of the vitamin D-type compounds (Scheme 1).[6c] Okamura et al. and Jensen systematically studied the pericyclic reactions of vinylallenes, respectively (Scheme 2).[7] An interesting Alder–ene reaction between an



Scheme 1.



Scheme 2.

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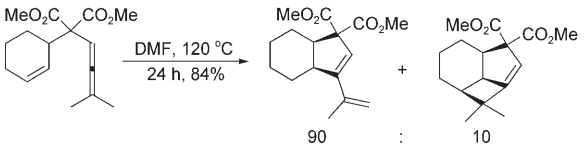
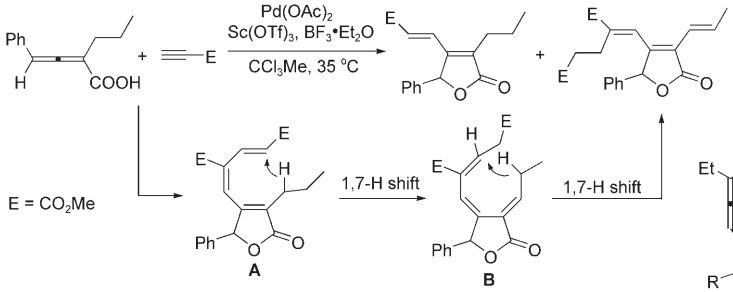
allene and an alkene was reported by Bäckvall et al.[8a] since allenes and alkenes preferentially form cyclobutanes via [2+2] cycloaddition rather than Alder–ene products (Scheme 3). Hashmi and Szeimies have also reported ene re-

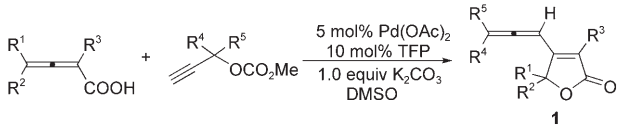


Scheme 3.

actions for intramolecular allenes.[8b] During the study of the cross-coupling reaction of 2,3-allenoic acids with methyl propionate, we have also observed an interesting π-bond migration, which may proceed through double 1,7-hydrogen shifts via the intermediates **A** and **B** (Scheme 4).[9] In this paper, we wish to report our observation on the thermal reactivities of β-allenylfuranones and 2-allyl-3-allenylcyclohex-2-enone.



Scheme 4.



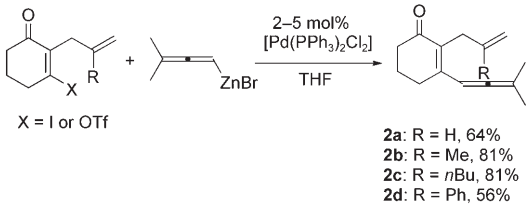
1a: R^1 = α-Naphthyl, R^2 = H, R^3 = *n*Pr, R^4 = R^5 = Et, 71%
1b: R^1 = Ph, R^2 = H, R^3 = *i*Bu, R^4 = R^5 = Me, 38%
1c: R^1 = Ph, R^2 = H, R^3 = *i*Bu, R^4 = R^5 = Et, 49%
1d: R^1 = Ph, R^2 = H, R^3 = Bn, R^4 = R^5 = Me, 39%
1e: R^1 = Ph, R^2 = H, R^3 = $CH_2CH(CH_2)_2$, R^4 = R^5 = Me, 45%
1f: R^1 = Ph, R^2 = H, R^3 = allyl, R^4 = R^5 = Et, 72%
1g: R^1 = Ph, R^2 = H, R^3 = allyl, R^4 = R^5 = Me, 60%
1h: R^1 = Ph, R^2 = H, R^3 = allyl, R^4,R^5 = -$(CH_2)_5$-, 63%
1i: R^1 = Me, R^2 = Me, R^3 = allyl, R^4 = R^5 = Et, 83%
1j: R^1 = Me, R^2 = Me, R^3 = allyl, R^4 = Et, R^5 = Me, 66%
1k: R^1 = Me, R^2 = Me, R^3 = allyl, R^4 = Me, R^5 = Ph, 79%
1l: R^1 = α-Nap, R^2 = H, R^3 = allyl, R^4 = R^5 = Et, 80%
1m: R^1 = α-Nap, R^2 = H, R^3 = allyl, R^4 = R^5 = Me, 63%
1n: R^1 = 4-BrC_6H_4, R^2 = H, R^3 = allyl, R^4 = R^5 = Et, 59%
1o: R^1 = 4-BrC_6H_4, R^2 = H, R^3 = allyl, R^4 = R^5 = Me, 46%
1p: R^1 = Et, R^2 = H, R^3 = allyl, R^4 = R^5 = Et, 72%
1q: R^1 = Et, R^2 = H, R^3 = allyl, R^4,R^5 = -$(CH_2)_5$-, 58%
1r: R^1 = Ph, R^2 = H, R^3 = allyl, R^4,R^5 = -$(CH_2)_4$-, 43%
1s: R^1 = Me, R^2 = Me, R^3 = allyl, R^4,R^5 = -$(CH_2)_4$-, 73%
1t: R^1 = 4-BrC_6H_4, R^2 = H, R^3 = allyl, R^4,R^5 = -$(CH_2)_4$-, 44%

Scheme 5.

Results and Discussion

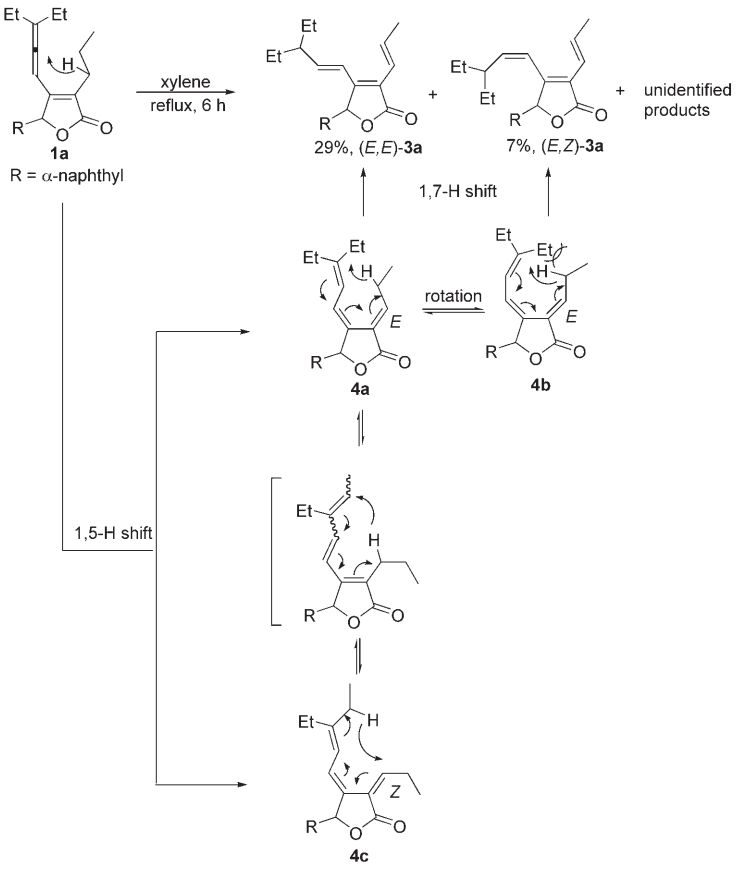
Preparation of starting materials: The β-allenylfuranone derivatives were synthesized via the palladium-catalyzed cross-coupling reaction of 2,3-allenoic acids with propargyl carbonates.[4] The results are listed in Scheme 5.

2-Allyl-3-allenylcyclohex-2-enone derivatives were prepared via the Negishi coupling of 2-allyl-3-(pseudo)halocyclohex-2-enone derivatives with the allenylic zinc reagent (Scheme 6).



Scheme 6.

Sequential 1,5-H shift and 1,7-H shift reactions of α-alkyl-β-allenylfuranones: The pericyclic reaction of **1a** was explored first. Interestingly, heating **1a** in xylene under reflux afforded two isomeric conjugated trienes (*E*,*E*)-**3a** and (*E*,*Z*)-**3a**



Scheme 7.

together with some unidentified products (Scheme 7). The structure of (*E*,*Z*)-**3a** was further confirmed by the X-ray diffraction analysis (Figure 1).[10] These results greatly encouraged us to further explore this reaction. We proposed that 1,5-hydrogen shift of **1a** would afford the intermediate **4**. The two conformers of **4**, that is, **4a** and **4b**, would give (*E*,*E*)-**3a** and (*E*,*Z*)-**3a** via 1,7-hydrogen shift, respectively.[9] To the best of our knowledge, the report on 1,7-hydrogen shift of acyclic triene via **4a**-type conformation is fairly rare.[6,7] Due to the steric hindrance, conformer **4a** should be favorable. Actually, when the more sterically hindered **1b** with an isobutyl group at α-position was used, (*E*)-**3b** was formed as the only isomer. Furthermore, under the same conditions, the reaction of **1c** afforded (*E*)-**3c** in 66% yield with 10% of the starting material remaining even with a prolonged the reaction time of 6 h (Scheme 8).

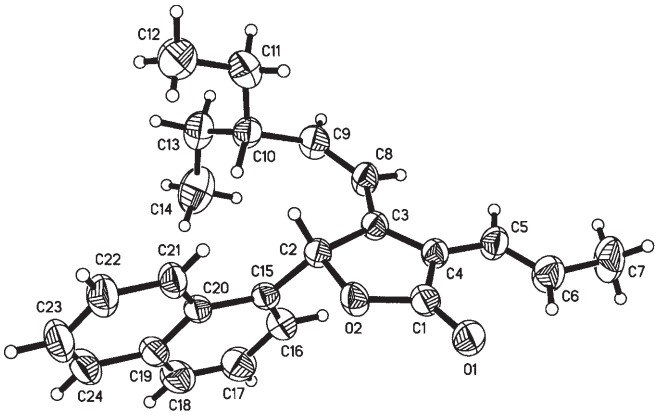
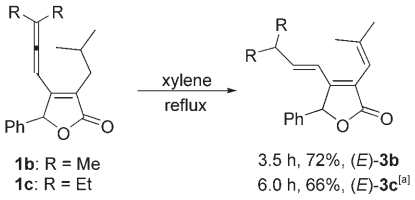
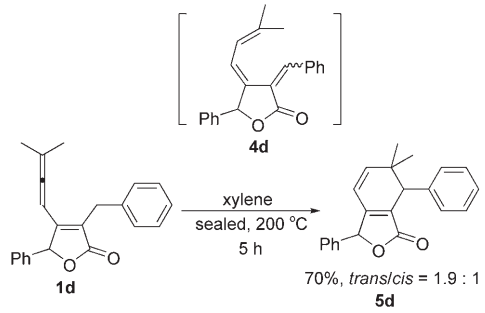


Figure 1. ORTEP representation of (*E*,*Z*)-**3a**.



Scheme 8. [a] 10% of **1c** was recovered.

Sequential 1,5-H shift and 6π-electrocyclization reaction of α-benzyl (or cyclopropylmethyl)-β-allenylfuranones: It was reasoned that if a benzyl group was introduced at the α-position of the starting butenolide, for example, **1d**, the subsequent 1,7-hydrogen shift of the 1,5-H shift product **4d** would be impossible, and may thus undergo a 6π-electrocyclization reaction to afford a new six-membered ring. In fact, such a transformation was observed at a higher temperatures: when heating **1d** at 200°C in xylene in a Schlenk tube with a screw cap, bicyclic lactone **5d** was formed in 70% yield with a diastereoselectivity of 1.9:1 (Scheme 9). The stereochemistry was established by the X-ray diffraction studies of



Scheme 9.

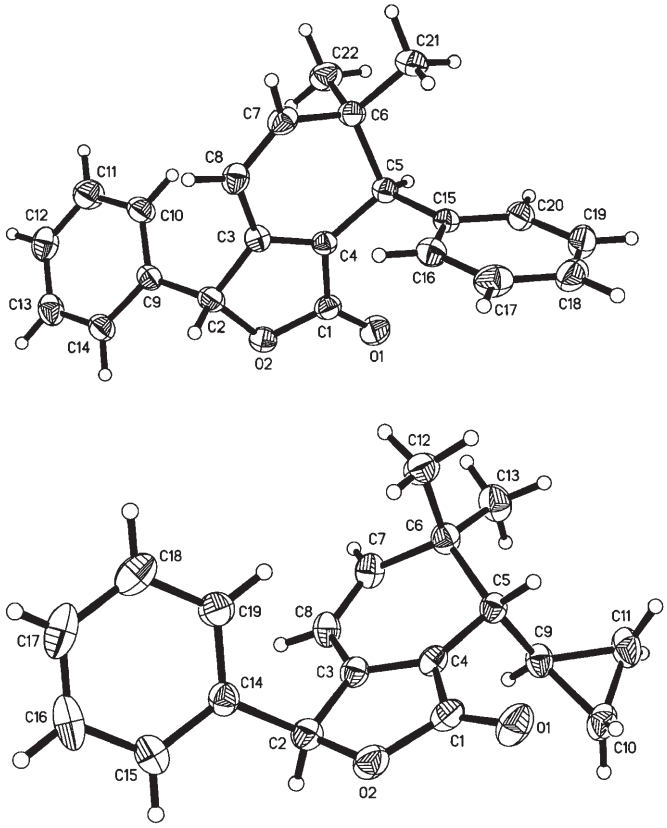
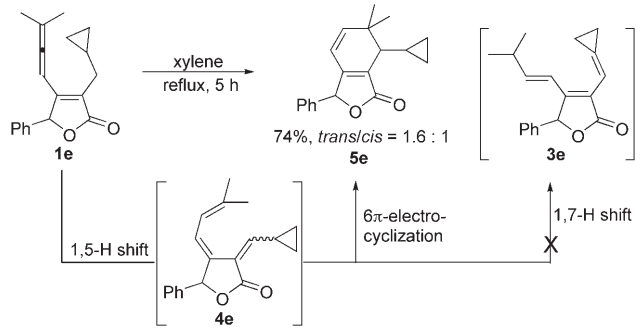


Figure 2. ORTEP representations of *trans*-**5d** (top) and *trans*-**5e** (bottom).

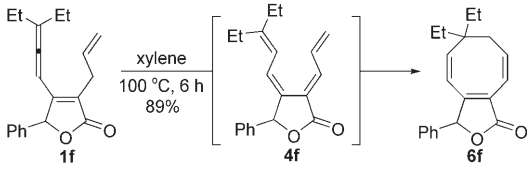
trans-**5d** (Figure 2, top).[11] Interestingly, even the reaction of **1e** did not form triene **3e** although there is a hydrogen in the intermediate **4e** for possible 1,7-hydrogen shift (Scheme 10). The formation of **5e** and its relative stereochemistry were further established by its X-ray diffraction study (Figure 2, bottom).[12]

Cycloisomerization of α-allyl-β-allenylfuranones: The results mentioned above encouraged us to develop a new reaction based on these α-allyl-β-allenylfuranones. It was reasoned that the intermediate **4f** may undergo 8π-electrocyclization reaction to afford an eight-membered ring.[13,14] Fortunately, it is interesting to observe that stirring the α-allyl substituted β-allenyl-butenolide **1f** under a milder condition (100°C,



Scheme 10.

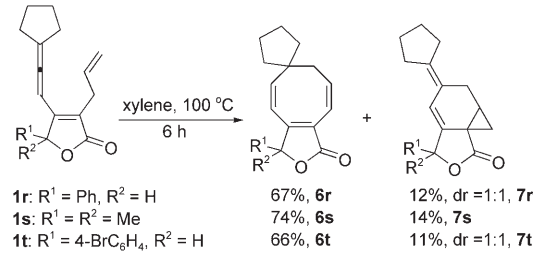
6 h) in xylene afforded the eight-membered product **6f** in 89% isolated yield (Scheme 11).[14] The importance of eight-membered cyclic compounds[15–18] has prompted us to conduct a comprehensive study on this isomerization reaction.



Scheme 11.

The general studies on the cycloisomerization reaction at 100 °C in xylene were listed in Table 1. The substituents R^1, R^2 at the 5-position of the furanones and R^3, R^4 at the allene moiety proved to be general.[14]

It is interesting to observe when R^3,R^4 is -$(CH_2)_4$-, besides the formation of the eight-membered products, we also isolated the intramolecular tricyclic Diels–Alder products **7** in 11–14% yield (Scheme 12). The structure of **7** was further established by the X-ray diffraction analysis of **7s** (Figure 3).[19]



Scheme 12.

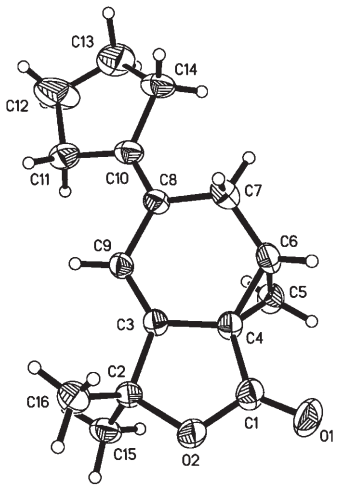
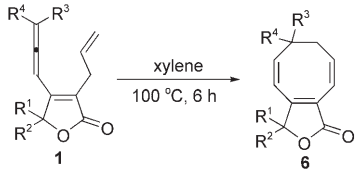


Figure 3. ORTEP representation of **7s**.

Table 1. Cycloisomerization reaction of α-allyl-β-allenylfuranones **1**.[a]



Entry	Substrate **1**				Yield of **6** [%]
	R^1	R^2	R^3	R^4	
1[b]	Ph	H	Me	Me (**1g**)	84 (**6g**)
2	Ph	H	-$(CH_2)_5$- (**1h**)		80 (**6h**)
3	Me	Me	Et	Et (**1i**)	83 (**6i**)
4	Me	Me	Me	Et (**1j**)	74 (**6j**)
5	Me	Me	Ph	Me (**1k**)	48 (**6k**)
6	α-naphthyl	H	Et	Et (**1l**)	97 (**6l**)
7	α-naphthyl	H	Me	Me (**1m**)	87 (**6m**)
8	*p*-BrC_6H_4	H	Et	Et (**1n**)	95 (**6n**)
9	*p*-BrC_6H_4	H	Me	Me (**1o**)	84 (**6o**)
10	Et	H	Et	Et (**1p**)	84 (**6p**)
11	Et	H	-$(CH_2)_5$- (**1q**)		89 (**6q**)

[a] Under an argon atmosphere, a solution of 0.15–0.25 mmol of **1** in 4 mL xylene was stirred at 100 °C for 6 h. [b] The reaction time was 7 h.

Cycloisomerization of 2-allyl-3-allenylcyclohex-2-enone derivatives: For a more general understanding of the scope of this cycloisomerization reaction, **2a**, which has a 2-cyclohexenone core, was synthesized. To our surprise, heating **8za** at 80 °C for 3 h in xylene, instead of forming the eight-membered product, we isolated two isomeric products **8aa** and **8ab**. The bromination of one of the isomers, that is, **8ab**, afforded two products **10aba** and **10abb** for structural determination. Thus, the identities of **8aa** and **8ab** have been successfully established by the X-ray diffraction studies of **10aba** (Figure 4, top).[20] Compounds **8aa** and **8ab** are obviously the intermolecular Diels–Alder products of two molecules of the possible tricyclic intermediate **9a** (Scheme 13).

Based on these results, another pathway for this isomerization shown in Scheme 14 has been proposed: [2+2] cycloaddition of allene–ene of **1** would afford tricyclic intermediate **11**. Subsequent 1,5-hydrogen shift of **11** would give **12**, which is likely to afford **5** via electrocyclic rearrangement. In order to trap the intermediate **9a**, some electron-deficient alkenes were added to the reaction mixture: upon heating of compound **2a** in the presence of **13** at 55 °C in xylene, products **14** were formed as the only diastereomer in moder-

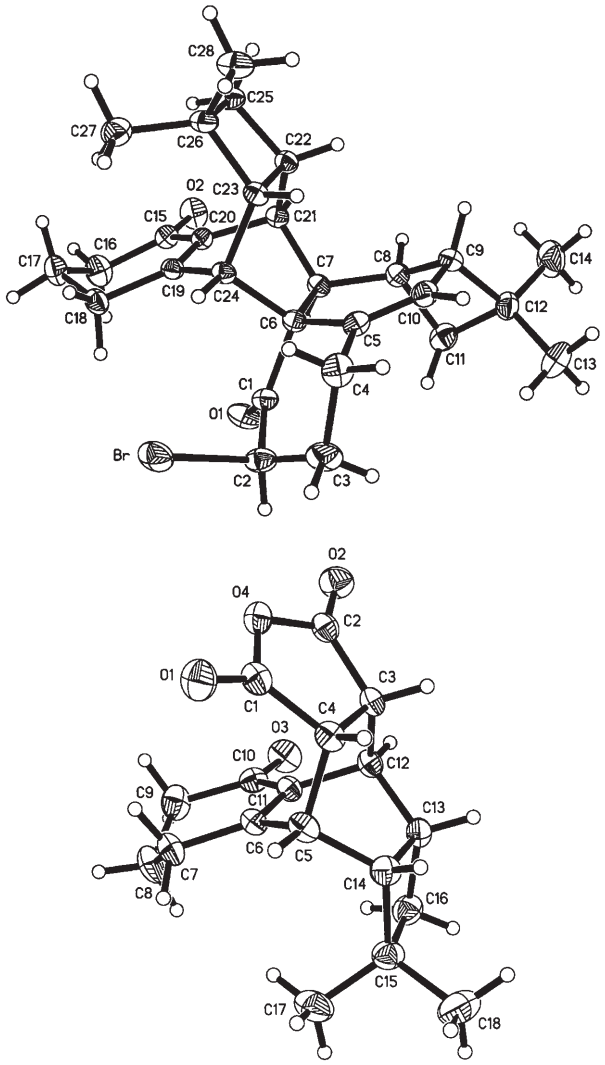


Figure 4. ORTEP representations of **10aba** (top) and **14aa** (bottom).

ate to high yields. The structure was also determined by the X-ray diffraction analysis of **14aa** (Figure 4, bottom).[21] The electron-deficient alkyne DMAD **13d** also reacted with **2a** to afford products **14ad** highly stereoselectively in 52% yield (Scheme 15).

In order to suppress the intermolecular Diels–Alder reaction, the more sterically demanding substrates **2b–d** were synthesized. To our delight, we obtained the expected eight-membered compounds **15b–d** in moderate yields by heating these compounds at 90°C for 2 h in xylene. Furthermore, we even isolated tricyclic product **9c** in 8% yield with R = *n*Bu, while the formation of product **9b** (R = Me) could be observed by ^{1}H NMR spectroscopy (Scheme 16).

Interestingly, reaction of (1,2,4*Z*,7)-tetraene **2e**, which was prepared in situ via the Claisen-type rearrangement reaction of **16** with $CH_3C(OEt)_3$, afforded tricyclic compound **9e** instead of the formation of eight-membered ring compound (Scheme 17).

Trapping of the intermediate **9**, however, is not enough to confirm the route shown in Scheme 14 since there may exist an equilibrium between bicyclic conjugated trienes **15** and tricyclic dienes **9** via the reversible 6π-pericyclic process.[22] As expected, heating the bicyclic ketone **15b** at 55°C in the presence of **13b** also afforded **14bb** in 53% yield, which confirmed that **15b** and **9b** did interconvert upon heating (Scheme 18).

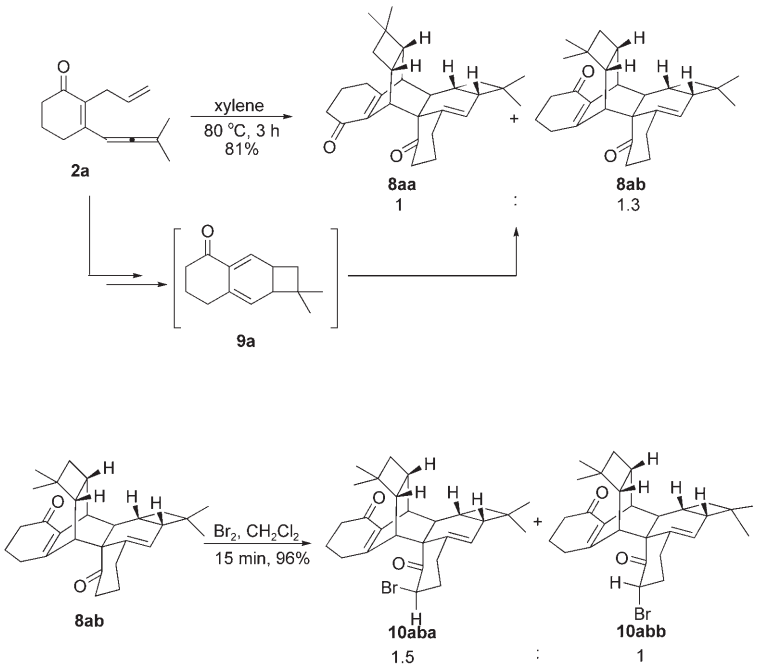
Mechanistic study of cycloisomerization of (1,2,4*Z*,7)-tetraenes: However, there still remains an important issue for this 1,5-H shift process: in principle, the 1,5-H shift of **1** would give two stereoisomers **18** and **20** via transition states **17** and **19**, respectively (Scheme 19). Furthermore, compound **20** would not give the eight-membered ring compounds via 8π-electrocyclization due to steric reasons.

To further confirm this 1,5-H shift process, we applied deuterium labeled α-allyl-β-allenylfuranones as mechanistic probes. Compound [D_5]-**1g**-(allyl) was synthesized according to the chemistry shown in Scheme 20. Based on the procedures established by Lebeau et al.,[23] we synthesized fully deuterated allyl mesylate [D_5]-**24**-(allyl). In the presence of CuI, allylic mesylate [D_5]-**24**-(allyl) coupled with 1-phenyl-prop-2-yn-1-ol to afford 4,4,5,6,6-pentadeutero-1-phenyl-2-hexyn-5-enol [D_5]-**25**-(allyl),[24] which was converted to 2,3-allenoic acid [D_5]-**26**-(allyl) under the catalysis of [Pd-(PPh_3)$_4$] in CO atmosphere.[25]

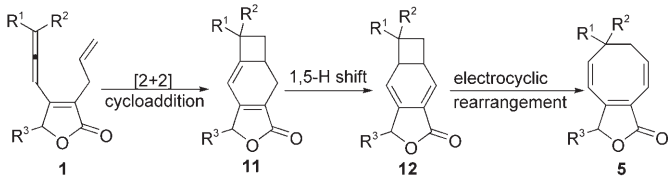
Compound [D_5]-**1g**-(allyl) was then prepared via the cross-coupling cyclization of [D_5]-**26**-(allyl) with methyl 2-methylbut-3-yn-2-yl carbonate.[4] Heating [D_5]-**1g**-(allyl) at 110°C for 6 h in xylene gave [D_5]-**6g** in 64% yield.[13] Based on careful ^{1}H NMR analysis, it was observed that the proton connected to the center carbon atom of the allene moiety in [D_5]-**1g**-(allyl) was 93% deuterated. In addition, to our surprise, only 82% [D] was incorporated at the 4-position of [D_5]-**6g** (Scheme 21). This means that ~18% of deuterium atom at the methenyl group of [D_5]-**1g**-(allyl) was lost during this cycloisomerization process. Further studies show that ~3% of D were incorporated into the two methyl groups (Figure 5a). These results prompted us to consider that the two methyl groups in [D_5]-**1g**-(allyl) may be involved in the isomerization process.

In order to clarify the mechanism further, butenolide [D_6]-**1g**-$(CD_3)_2$, where all the hydrogen atoms of the two methyl groups of the allenyl moiety were deuterated, was synthesized according to Scheme 22. The reaction of ethynylmagnesium bromide with CD_3COCD_3 produced [D_6]-**27**-$(CD_3)_2$-H(D), which can be easily converted to propargyl carbonate [D_6]-**28**-$(CD_3)_2$-H(D). The ^{1}H NMR spectra clearly show that the terminal alkyne was partially deuterated. The treatment of terminal alkyne [D_6]-**28**-$(CD_3)_2$-H(D) with *n*BuLi in THF at −78°C followed by quenching with water at this temperature produced [D_6]-**28**-$(CD_3)_2$. Compound [D_6]-**1g**-$(CD_3)_2$ was then synthesized via the palladium-catalyzed coupling reaction of 2-allyl-4-phenylbuta-2,3-dienoic acid with [D_6]-**28**-$(CD_3)_2$ in 54% yield with 95% of deuterium content.[4]

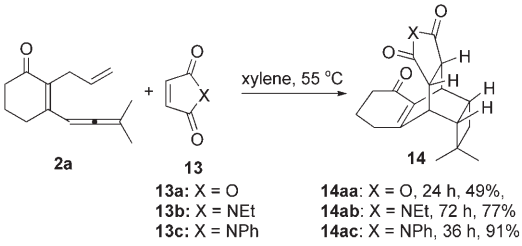
Under the same reaction conditions, [D_6]-**6g** was formed in 73% yield with 60% [D] incorporated at 4-position while

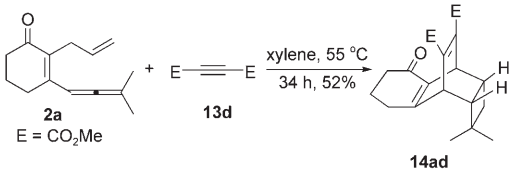


Scheme 13.



Scheme 14.

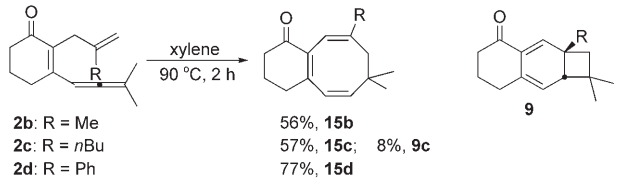




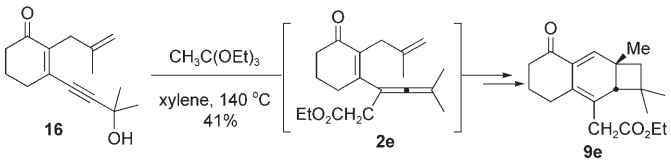
Scheme 15.

the deuterium incorporation at methyl group dropped from 95 to 85% (Scheme 23), which clearly indicates that the methyl groups were involved in the cycloisomerization process (Figure 5b).

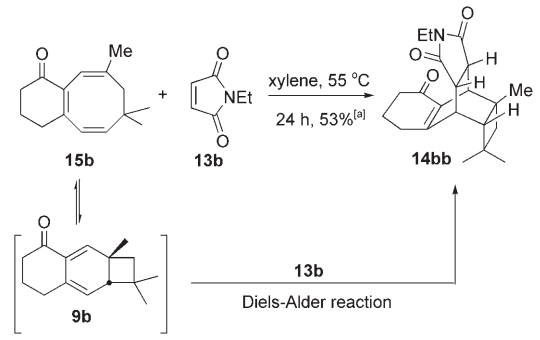
Taking all these experimental data into account as well as the stereochemistry shown in Scheme 19, we proposed the following reaction pathway (Scheme 24). First, 1,5-H shift of **1A** would afford two stereoisomers, **18A** and **20A**. However, tetraene **18A** would give the eight-membered ring compound **6A** via 8π-electrocyclization while **20A** could not due to the steric requirement of the 8π-electrocyclization.[13] However, 1,7-H shift of **20A** may afford intermediate **29A**, which could give **18A** or **20A** via another 1,7-H shift. The equilibrium of **18A** and **20A** upon heating via the intermediate **29A** was clearly supported the D-labeling results shown in Schemes 21 and 23.



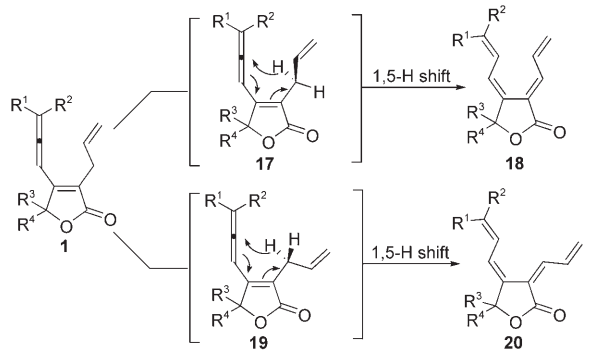
Scheme 16.



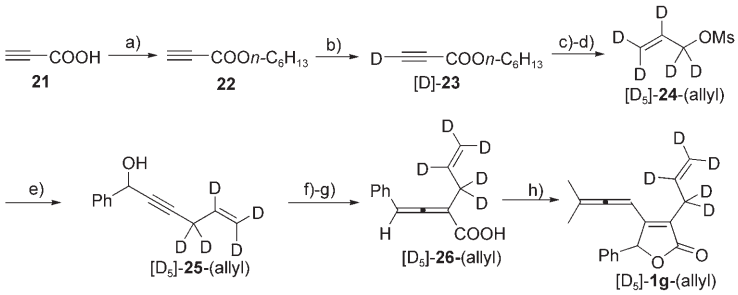
Scheme 17.



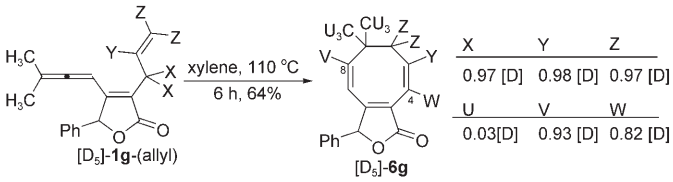
Scheme 18. [a] 28% of **15b** was recovered.



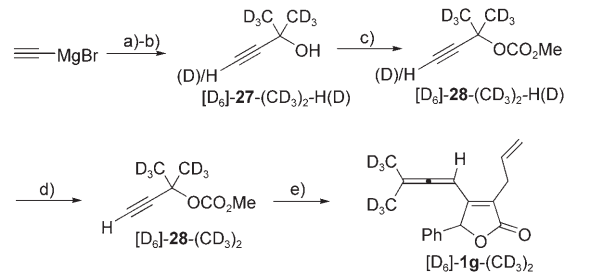
Scheme 19.



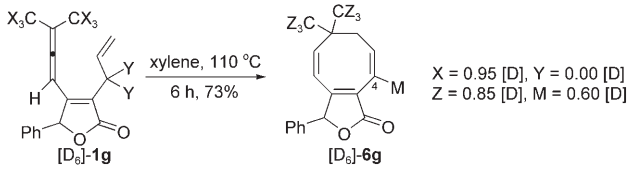
Scheme 20. Synthesis of $[D_5]$-**1g**-(allyl): a) n-$C_6H_{13}OH$, cat. pTsOH, benzene, 100%; b) D_2O, K_2CO_3, TBAB, repeat 4×, 96% [D]; c) $LiAlD_4$, Et_2O, then D_2O; d) MsCl, Et_3N, Et_2O, 39% for three steps; e) 1-phenylprop-2-yn-1-ol, CuI, K_2CO_3, DMF, 74%; f) nBuLi, LiBr, THF, −78°C, then pTsCl; g) $[Pd(PPh_3)_4]$, CO, THF, H_2O, 43% for two steps; h) methyl 2-methylbut-3-yn-2-yl carbonate, $Pd(OAc)_2$/TFP, K_2CO_3, DMSO, 62%.



Scheme 21. Cycloisomerization of $[D_5]$-**1g**-(allyl).



Scheme 22. Synthesis of $[D_6]$-**1g**-$(CD_3)_2$: a) C_2H_5Br, Mg, THF, then acetylene; b) CD_3COCD_3, 34%; c) NaH, Et_2O, then $ClCO_2Me$, 71%; d) nBuLi, Et_2O, −78°C; then H_2O, −78°C, 38%; e) 2-allyl-4-phenylbuta-2,3-dienoic acid, $Pd(OAc)_2$/TFP, K_2CO_3, DMSO, 54%.



Scheme 23. Isomerization of $[D_6]$**1g**$(CD_3)_2$.

Conclusion

We have studied the thermal reaction of β-allenylfuranones. It is interesting to observe that 1,5-hydrogen shift of β-allenylfuranones **1** is general upon heating, which would afford a new conjugated trienes, that is, **4** and **18**. Due to their high reactivity, these trienes would undergo subsequent pericyclic reaction based on the nature of the R group (Scheme 25): When R is an alkyl groups, the intermediate **4** would undergo a further 1,7-hydrogen shift to afford a more stable triene **3**; when R = phenyl or cyclopropyl group, triene **4d** or **4e** would form a six-membered ring via 6π-electrocyclization; Interesting 8π-electrocylization reaction of tetraene **18** forming eight-membered ring was observed when R is a vinyl group. Furthermore, not only the furanone derivatives,

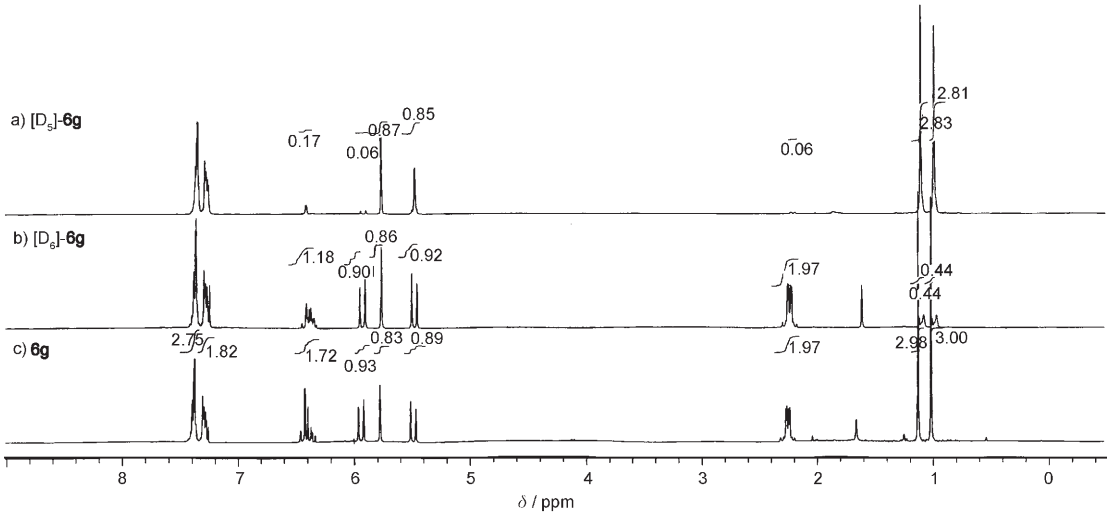
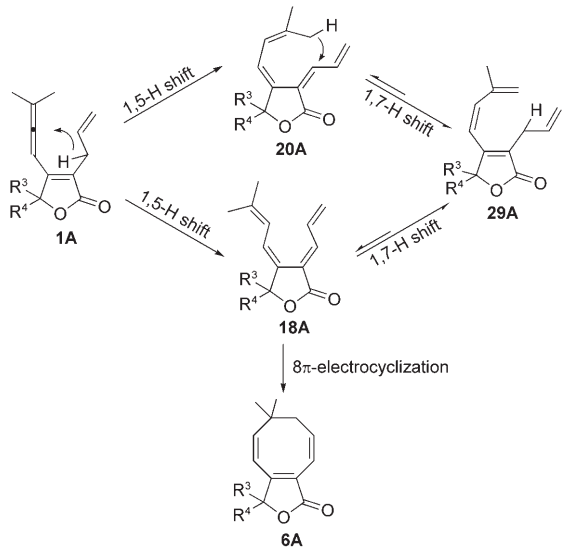
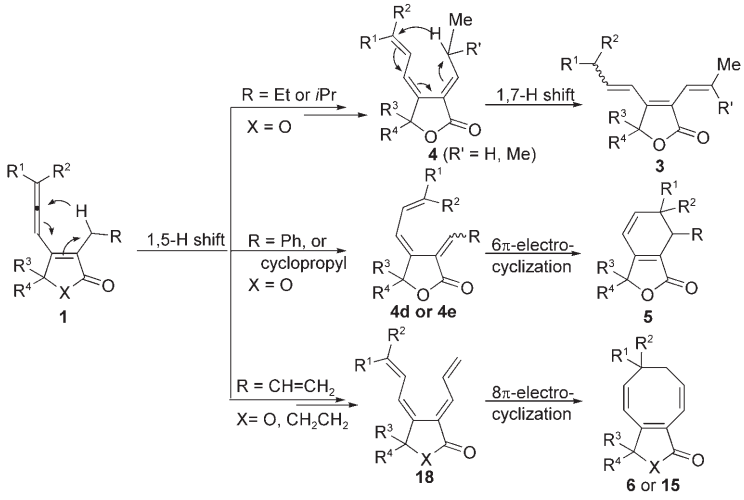


Figure 5. ^1H NMR spectrum of a) $[D_5]$-**6g**; b) $[D_6]$-**6g**; c) **6g**.



Scheme 24. Plausible pathway.



Scheme 25.

but also (1,2,4*Z*,7)-tetraenes bearing a 2-cyclohexenone core have been studied for the formation of eight-membered compounds. The deuterium-labeling experiments show that the alkyl groups at the allenyl moiety of α-allyl-β-furanones were involved in the isomerization process. The 1,7-hydrogen shifts may play an important role in the conversion from (*Z*)-tetraene **20** to (*E*)-tetraene **18**. Further studies in this area are being conducted in this laboratory.

Experimental Section

The analytic data of **1a**, **6f–r**, **6t**, **14ab**, **14bb**, and **15b**, as well as general methods have been published in the Supporting Information of references [4] and [15].

Synthesis of the starting materials β-allenylfuran-2(5*H*)-ones

3-Isobutyl-4-(3′-methylbuta-1′,2′-dienyl)-5-phenylfuran-2(5*H*)-one (1b): Under an argon atmosphere, a mixture of 2-isobutyl-4-phenylbuta-2,3-dienoic acid (217 mg, 1.00 mmol), methyl 2-methylbut-3-yn-2-yl carbonate (282 mg, 2.00 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), tri-2-furylphosphine (TFP) (23 mg, 0.10 mmol), and K_2CO_3 (138 mg, 1.00 mmol) in DMSO (4 mL) was stirred at 30 °C for 3 h. After complete consumption of the starting material as monitored by TLC, the mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 15:1) to afford **1b** (106 mg, 38 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 3H), 7.20–7.10 (m, 2H), 5.90 (heptet, J = 3.0 Hz, 1H), 5.68 (s, 1H), 2.35–2.19 (m, 2H), 2.11–1.91 (m, 1H), 1.63 (d, J = 3.0 Hz, 3H), 1.01 (d, J = 3.0 Hz, 3H), 0.963 (d, J = 6.3 Hz, 3H), 0.957 ppm (d, J = 6.3 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.8, 19.4, 22.4, 22.5, 27.9, 32.5, 83.0, 83.8, 99.7, 125.8, 127.5, 128.5, 128.9, 136.1, 155.9, 174.1, 208.0 ppm; IR (neat): $\tilde{\nu}$ = 1951, 1752, 1643, 1456, 1300, 1083, 1003 cm^{-1}; MS (EI): m/z (%): 282 (5.38) [M^+], 57 (100); HRMS: m/z: calcd for $C_{19}H_{22}O_2$: 282.1620 [M^+]; found: 282.1629.

Synthesis of 2-allylic 3-allenylic cyclohex-2-enone derivatives

2-Allyl-3-(3′-methylbuta-1′,2′-dienyl)cyclohex-2-enone (2a)—Typical Procedure for the preparation of 2-allylic 3-allenylic cyclohex-2-enone

a) Preparation of the allenyllic zinc reagent: To a flame dried Schlenk tube were added zinc (flame dried, 0.448 g, 7.0 mmol) and fleshly distilled (Na/benzophenone) THF (5 mL). To this suspension was added $BrCH_2CH_2Br$ (20 μL) followed by heating to gentle reflux. After cooling down to RT, TMSCl (20 μL) was added to the reaction mixture with stirring. After the formation of gray suspension, a solution of 1-bromo-3-methylbuta-1,2-diene[26] in THF (3 mL) was added dropwise to the reaction tube and allowed to stir at RT for 4 h to afford the zinc reagent needed for next step.

b) Palladium-catalyzed coupling of 2-allyl-3-iodocyclohex-2-enone with zinc reagent: The allenyl zinc reagent (0.625 mol L^{-1} in THF, prepared above) (1.60 mL, 1.00 mmol) was added to a mixture of $[Pd(PPh_3)_2Cl_2]$ (18 mg, 0.026 mmol), 2-allyl-3-iodocyclohex-2-enone[27] (130 mg, 0.5 mmol), and THF (4 mL) with stirring in a flame dried Schlenk tube. Then the mixture was stirred at RT for 1.5 h. After complete consumption of the starting material as monitored by TLC, THF was removed by evaporation and the residue was purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 25:1) to afford **2a** (64 mg, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.12 (heptet, J = 3.0 Hz, 1H), 5.82–5.68 (m, 1H), 5.00–4.88 (m, 2H), 3.14 (d, J = 6.0 Hz, 2H), 2.45–2.35 (m, 4H), 2.00–1.85 (m, 2H), 1.76 ppm (d, J = 3.0 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 19.8, 22.1, 27.6, 28.7, 37.9, 92.0, 98.7, 114.6, 132.0, 136.0, 151.7, 198.3, 207.5 ppm; IR (neat): $\tilde{\nu}$ = 1945, 1660, 1593, 1434, 1363, 1184 cm^{-1}; MS(EI): m/z (%): 202 (6.32) [M^+], 41 (100); HRMS: m/z: calcd for $C_{14}H_{18}O$: 202.1358 [M^+]; found: 202.1355.

Sequential 1,5-H shift and 1,7-H shift reactions of 3-alkyl-4-allenylfuran-2(5*H*)-ones

3-(Prop-1′(*E*)-enyl)-4-(3′-ethylpent-1′(*E*)-enyl)-5-(naphth-1′-yl)furan-2(5*H*)-one [(*E*,*E*)-3a] and 3-(prop-1′(*E*)-enyl)-4-(3-ethylpent-1′(*Z*)-enyl)-5-(naphth-1′-yl)furan-2(5*H*)-one [(*E*,*Z*)-3a]: Under an argon atmosphere, a solution of **1a** (140 g, 0.40 mmol) in xylene (6 mL) was stirred under reflux for 6 h. After complete consumption of the starting material as monitored by TLC, the mixture was directly purified via flash chromatography on silica gel to afford (*E*,*Z*)-**3a** (less polar, 10 mg, 7 %), (*E*,*E*)-**3a** (more polar, 41 mg, 29 %), and unidentified products (70 mg). (*E*,*Z*)-**3a**: Solid; m.p. 72–74 °C (Et_2O/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 9.0 Hz, 2H), 7.65–7.50 (m, 2H), 7.40 (t, J = 7.8 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.09 (dq, J = 6.9, 15.3 Hz, 1H), 6.80 (s, 1H), 6.32 (dd, J = 1.2, 15.3 Hz, 1H), 6.29 (d, J = 12.0 Hz, 1H), 5.49 (t, J = 12.0 Hz, 1H), 1.94 (d, J = 6.9 Hz, 3H), 1.82–1.68 (m, 1H), 1.40–1.18 (m, 1H), 1.12–0.90 (m, 2H), 0.74 (t, J = 7.5 Hz, 3H), 0.80–0.60 (m, 1H), 0.15 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 10.8, 11.7, 19.5, 26.9, 27.1, 42.9, 79.0, 118.4, 119.3, 122.6, 124.4, 125.2, 125.7, 126.0, 127.0, 128.9, 130.0, 131.3, 131.7, 133.8, 134.2, 145.4, 153.2, 171.9 ppm; IR (neat): $\tilde{\nu}$ = 1752, 1637, 1456 cm^{-1}; MS (ESI): m/z: 369 [M+Na$^+$], 347 [M^++H]; HRMS: m/z: calcd for $C_{24}H_{26}O_2$: 346.1933 [M^+]; found: 346.1928. (*E*,*E*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$):

δ = 8.29 (d, J = 8.7 Hz, 1H), 7.90 (t, J = 9.0 Hz, 2H), 7.68–7.51 (m, 2H), 7.42 (t, J = 7.8 Hz, 1H), 7.28 (dd, J = 1.2, 7.2 Hz, 1H), 6.81 (s, 1H), 6.30 (d, J = 16.2 Hz, 1H), 6.20–6.03 (m, 2H), 5.45 (dd, J = 9.3, 16.2 Hz, 1H), 1.90–1.72 (m, 4H), 1.37–1.15 (m, 2H), 1.15–1.00 (m, 1H), 0.96–0.77 (m, 1H), 0.72 (t, J = 7.2 Hz, 3H), 0.52 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 11.5, 11.7, 16.1, 26.9, 27.2, 47.6, 78.8, 118.3, 121.7, 123.0, 124.2, 125.0, 126.1, 126.3, 126.9, 128.9, 130.1, 131.8, 131.9, 133.6, 133.8, 147.9, 155.8, 172.6 ppm; IR (neat): $\tilde{\nu}$ = 1754, 1639, 1512, 1457, 1036 cm^{-1}; MS (ESI): m/z: 347 [M^++H]; HRMS: m/z: calcd for $C_{24}H_{26}O_2Na$: 369.1825 [M^++Na]; found: 369.1839.

Sequential 1,5-H shift and 6π-electrocyclization reaction of 3-benzyl (or cyclopropylmethylene)-4-allenylfuran-2(5*H*)-ones

6,6-Dimethyl-3,7-diphenyl-6,7-dihydroisobenzofuran-1(3*H*)-one (5d): Under an argon atmosphere, a mixture of **1d** (53 mg, 0.17 mmol) in xylene (4 mL) in a Schlenk tube with a screw cap was stirred at 200 °C for 5 h. The mixture was directly purified via flash chromatography on silica gel to afford *trans*-**5d** (less polar, 24 mg, 45%) and *cis*-**5d** (more polar, 13 mg, 25%). *trans*-**5d**: Solid, m.p. 157–159 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.37 (m, 3H), 7.36–7.18 (m, 7H), 6.06 (d, J = 9.3 Hz, 1H), 6.01 (d, J = 9.3 Hz, 1H), 6.00 (s, 1H), 3.60 (s, 1H), 1.22 (s, 3H), 0.89 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.4, 29.3, 38.0, 47.2, 82.2, 116.5, 125.7, 126.9, 127.4, 128.3, 129.0, 129.3, 134.5, 138.0, 149.0, 156.2, 172.4 ppm; IR (neat): $\tilde{\nu}$ = 1751, 1656, 1582, 1454, 1297, 1230, 1032 cm^{-1}; MS(EI): m/z (%): 316 (40.08) [M^+], 105 (100); HRMS: m/z: calcd for $C_{22}H_{20}O_2$: 316.1463 [M^+]; found: 316.1476. *cis*-**5d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.35 (m, 3H), 7.30–7.18 (m, 5H), 7.18–7.08 (m, 2H), 5.99 (d, J = 9.6 Hz, 1H), 5.94 (d, J = 9.6 Hz, 1H), 5.89 (s, 1H), 3.55 (s, 1H), 1.25 (s, 3H), 0.84 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 25.4, 29.5, 38.1, 46.7, 82.2, 116.2, 125.4, 126.8, 127.4, 128.2, 128.4, 129.0, 129.3, 134.7, 138.5, 148.9, 156.2, 172.6 ppm; IR (neat): $\tilde{\nu}$ = 1755, 1658, 1580, 1454, 1298, 1231, 1027, 1001 cm^{-1}; MS (EI): m/z (%): 316 (13.92) [M^+], 84 (100); HRMS: m/z: calcd for $C_{22}H_{20}O_2$: 316.1463 [M^+]; found: 316.1464.

Cycloisomerization of 3-allyl-4-allenylfuran-2(5*H*)-ones

(3a*Z*,4*Z*,8*Z*)-6,6-Tetramethylene-3-phenyl-6,7-dihydrocycloocta[*c*]furan-1(3*H*)-one (6r) and 7r: A solution of **1r** (52 mg, 0.178 mmol) in xylene (4 mL) was stirred at 100 °C for 6 h. After complete consumption of the starting material as monitored by TLC, the mixture was directly purified via flash chromatography on silica gel to afford **7r** (6 mg, 12%) and **6r**[14] (35 mg, 67%). **7r**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.28 (m, 5H), [6.16 (s), 5.60 (s), 6.12 (s), 5.98 (s), 2H], [2.75 (d, J = 6.0 Hz), 2.71 (d, J = 6.0 Hz), 1H], 2.49–2.37 (m, 1H), 2.35–2.08 (m, 5H), 1.79–1.70 (m, 1H), 1.70–1.50 (m, 4H), [1.20 (dd, J = 3.6, 6.9 Hz), 1.13 ppm (dd, J = 3.6, 6.9 Hz), 1H]; IR (neat): $\tilde{\nu}$ = 1777, 1292, 1139, 1101 cm^{-1}; MS (EI): m/z (%): 292 (20.94) [M^+], 84 (100); HRMS: m/z: calcd for $C_{20}H_{20}O_2$: 292.1463 [M^+]; found: 292.1465.

Cycloisomerization of 2-allyl-3-allenylcyclohex-2-enone

Compounds 8aa and 8ab: Under an argon atmosphere, a solution of **2a** (74 mg, 0.37 mmol) in xylene (4 mL) was stirred at 80 °C for 3 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 20:1 and 10:1) to afford **8aa** (26 mg, 35%) and **8ab** (34 mg, 46%). **8aa**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.55 (d, J = 2.4 Hz, 1H), 3.10 (d, J = 2.7 Hz, 1H), 3.00 (d, J = 4.5 Hz, 1H), 2.85–2.56 (m, 4H), 2.56–2.08 (m, 8H), 2.08–1.95 (m, 2H), 1.79–1.60 (m, 3H), 1.59–1.40 (m, 2H), 1.18–0.98 (m, 8H), 0.78 (s, 3H), 0.71 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.3, 23.9, 25.1, 27.4, 28.1, 31.8, 31.9, 32.0, 32.6, 33.2, 35.26, 35.29, 36.6, 37.0, 37.4, 37.6, 38.9, 39.6, 40.0, 45.1, 47.1, 60.6, 127.6, 136.4, 137.7, 161.8, 195.9, 210.3 ppm; IR (neat): $\tilde{\nu}$ = 1704, 1663, 1631, 1450, 1399, 1261, 1215 cm^{-1}; MS (EI): m/z (%): 404 (7.29) [M^+], 147 (100); HRMS: m/z: calcd for $C_{24}H_{28}O_2$: 348.2089 [M^+ −CH_2=C(Me)$_2$]; found: 348.2080. **8ab**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.71 (d, J = 2.4 Hz, 1H), 3.12–3.05 (m, 2H), 2.82–2.68 (m, 1H), 2.65–2.18 (m, 12H), 2.18–2.07 (m, 2H), 2.07–1.93 (m, 2H), 1.77–1.48 (m, 3H), 1.16 (s, 3H), 1.10–0.95 (m, 4H), 0.78 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.1, 23.9, 24.8, 26.2, 26.6, 28.2, 30.5, 31.0, 33.0, 33.4, 34.8, 35.3, 35.9, 37.2, 37.5, 38.8, 39.1, 39.3, 42.1, 45.1, 46.3, 56.0, 128.1, 135.5, 140.2, 159.9, 195.3, 209.4 ppm; IR (neat): $\tilde{\nu}$ = 1702, 1657, 1635, 1448, 1398, 1258, 1195 cm^{-1}; MS (EI): m/z (%): 292 [M^+−2[CH_2=C(Me)$_2$]], 118 (100); HRMS: m/z: calcd for $C_{20}H_{20}O_2$: 292.1463 [M^+−2[CH_2=C(Me)$_2$]]; found: 292.1464.

Compounds 10aba and 10abb: To a stirred solution of **8ab** (41 mg, 0.10 mmol) in CH_2Cl_2 (3 mL) was added Br_2 (1.0 mL, 0.188 mol L^{-1} in CH_2Cl_2) and stirred at RT for 15 min. After complete consumption of the starting material as monitored by TLC, an aqueous solution of $Na_2S_2O_3$ was added. The mixture was extracted with ether (50 mL), washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to afford **10aba** (less polar, 28 mg, 57%) and **10abb** (more polar, 19 mg, 39%). **10aba**: Solid, m.p. 154–155 °C (CH_2Cl_2/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (d, J = 2.7 Hz, 1H), 4.54 (t, J = 4.5 Hz, 1H), 3.44 (d, J = 3.3 Hz, 1H), 3.15–3.10 (m, 1H), 2.90–2.75 (m, 1H), 2.60–2.20 (m, 11H), 2.15 (s, 1H), 2.15–1.90 (m, 2H), 1.60–1.48 (m, 2H), 1.17 (s, 3H), 1.10–1.00 (m, 4H), 0.95 (t, J = 10.2 Hz, 1H), 0.79 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.3, 23.8, 24.9, 25.6, 28.0, 29.1, 31.0, 31.4, 33.6, 35.2, 35.5, 36.4, 37.3, 37.5, 38.8, 39.0, 39.2, 41.8, 46.3, 47.3, 49.9, 55.3, 128.8, 134.3, 140.3, 160.6, 195.6, 203.4 ppm; IR (neat): $\tilde{\nu}$ = 1700, 1662, 1451, 1398, 1261, 1192 cm^{-1}; MS-(ESI): m/z: 485 [(^{81}Br)M$^+$+H], 483 [(^{79}Br)M$^+$+H]; elemental analysis calcd (%) for $C_{28}H_{35}BrO_2$: C 69.56, H 7.30; found: C 69.17, H 7.23. **10abb**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.80 (d, J = 2.4 Hz, 1H), 5.19 (dd, J = 4.8, 12.3 Hz, 1H), 3.13 (t, J = 2.7 Hz, 1H), 3.03 (d, J = 3.0 Hz, 1H), 2.79–2.60 (m, 2H), 2.60–2.50 (m, 7H), 2.50–2.18 (m, 2H), 2.18–1.98 (m, 4H), 1.70–1.50 (m, 2H), 1.25–1.15 (m, 4H), 1.10–1.00 (m, 4H), 0.79 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.2, 23.8, 24.8, 26.2, 28.2, 30.3, 30.8, 33.3, 33.7, 35.3, 36.0, 36.1, 37.2, 37.4, 38.76, 38.80, 39.1, 42.2, 45.0, 46.8, 55.0, 56.7, 129.8, 133.5, 140.7, 158.7, 195.1, 200.3 ppm; IR (neat): $\tilde{\nu}$ = 1720, 1660, 1451, 1396, 1257 cm^{-1}; MS(ESI): m/z: 507 [(^{81}Br)M+Na$^+$], 505 [(^{79}Br)M+Na$^+$], 485 [(^{81}Br)M$^+$+H], 483 [(^{79}Br)M$^+$+H]; HRMS: m/z: calcd for $C_{28}H_{35}O_2BrNa$:: 505.1713 [(^{79}Br)M+Na$^+$]; found: 505.1702.

Preparation of 14aa via the Diels–Alder reaction of 2a with maleic anhydride 13a: Under an argon atmosphere, a solution of **2a** (40 mg, 0.20 mmol) and **13a** (98 mg, 1.00 mmol) in xylene (8 mL) was stirred at 55 °C for 24 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to afford **14aa** (29 mg, 49%). Solid, m.p. 172–174 °C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.87 (dd, J = 3.0, 4.2 Hz, 1H), 3.23 (t, J = 3.0 Hz, 1H), 3.16–3.02 (m, 2H), 2.78–2.58 (m, 2H), 2.55–2.37 (m, 3H), 2.18–1.98 (m, 3H), 1.66 (ddd, J = 2.1, 8.7, 10.2 Hz, 1H), 1.16 (s, 3H), 1.09 (dd, J = 6.6, 12.3 Hz, 1H), 0.85 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.0, 23.8, 30.4, 30.9, 31.9, 32.4, 35.5, 36.3, 37.0, 39.8, 44.2, 44.6, 48.6, 135.6, 161.8, 171.2, 171.8, 194.2 ppm; IR (KBr): $\tilde{\nu}$ = 1835, 1779, 1666, 1625, 1401, 1231, 1076 cm^{-1}; MS (ESI): m/z: 333 [M+MeOH+H$^+$], 318 [M+NH$_4^+$], 301 [M^++H]; elemental analysis calcd (%) for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.77, H 6.75.

Preparation of 14ac via the Diels–Alder reaction of 2a with *N*-phenylmaleimide 13c: Under an argon atmosphere, a solution of **2a** (41 mg, 0.20 mmol) and **13c** (69 mg, 0.40 mmol) in xylene (3 mL) was stirred at 55 °C for 36 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to afford **14ac** (69 mg, 91%). Solid, m.p. 221–223 °C (ethyl acetate/ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08–7.82 (m, 3H), 7.70–7.58 (m, 2H), 4.47 (d, J = 2.1 Hz, 1H), 3.83 (s, 1H), 3.60–3.40 (m, 2H), 3.40–3.13 (m, 2H), 3.13–2.80 (m, 3H), 2.78–2.41 (m, 3H), 2.21 (t, J = 10.5 Hz, 1H), 1.80–1.60 (m, 4H), 1.43 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.1, 23.9, 30.4, 31.5, 32.4, 35.4, 36.4, 37.2, 40.0, 43.7, 44.0, 49.0, 125.8, 128.4, 129.0, 131.4, 135.3, 162.0, 176.2, 176.3, 194.3 ppm; IR (KBr): $\tilde{\nu}$ = 1778, 1711, 1662, 1618, 1598, 1499, 1390, 1187 cm^{-1}; MS (ESI): m/z 398 [M+Na$^+$], 393 [M+NH$_4^+$], 376 [M^++H]; elemental analysis calcd (%) for $C_{24}H_{25}NO_3$: C 76.77, H 6.71, N 3.73; found: C 76.39, H 6.68, N 3.45.

Preparation of 14ad via the Diels–Alder reaction of 2a with dimethyl but-2-ynedioate 13d: Under an argon atmosphere, a solution of **2a** (41 mg, 0.20 mmol) and **13d** (114 mg, 0.80 mmol) in xylene (8 mL) was

stirred at 55 °C for 34 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 5:1) to afford **14ad** (36 mg, 52 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.53 (d, J = 4.5 Hz, 1H), 3.95 (d, J = 3.3 Hz, 1H), 3.73 (s, 6H), 2.72–2.48 (m, 3H), 2.48–2.28 (m, 2H), 2.12–1.98 (m, 3H), 1.57 (dd, J = 8.1, 12.0 Hz, 1H), 1.11 (s, 3H), 0.92–0.82 (m, 1H), 0.83 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 23.4, 23.7, 29.7, 31.6, 32.0, 32.6, 34.6, 36.9, 39.3, 46.8, 51.0, 52.2, 52.3, 138.9, 140.2, 144.7, 164.5, 165.4, 166.3, 194.3 ppm; IR (neat): $\tilde{\nu}$ = 1718, 1667, 1615, 1434, 1263, 1236, 1071 cm^{-1}; MS (ESI): m/z 362 [M+NH_4^+], 345 [M^++H]; HRMS: m/z: calcd for $C_{20}H_{24}O_5Na$: 367.1516 [M+Na^+]; found: 367.1514.

(4a*E*,5*Z*,9*Z*)-7,7-Dimethyl-9-butyl-3,4,7,8-tetrahydrocycloocta[*c*]cyclohexan-1(2*H*)-one (15c) and (2a,8a)-8a-butyl-2,2-dimethyl-1,2,2a,5,6,8a-hexahydrocyclobuta[*b*]naphthalen-7(4*H*)-one (9c): Under an argon atmosphere, a solution of **2c** (62 mg, 0.24 mmol) in xylene (4 mL) was stirred at 90 °C for 2 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 50:1) to afford **9c** (5 mg, 8 %) and **15c** (35 mg, 56 %). **9c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.68 (s, 1H), 5.28 (d, J = 6.0 Hz, 1H), 2.55 (d, J = 6.0 Hz, 1H), 2.51–2.42 (m, 2H), 2.42–2.32 (m, 2H), 1.94 (d, J = 11.7 Hz, 1H), 1.91–1.64 (m, 3H), 1.59–1.40 (m, 2H), 1.38–1.18 (m, 3H), 1.18–1.05 (m, 4H), 1.03 (s, 3H), 0.85 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.0, 21.4, 23.2, 25.3, 26.3, 30.6, 32.4, 35.5, 39.95, 40.04, 44.0, 47.6, 51.2, 120.1, 131.3, 131.7, 143.1, 198.5 ppm; IR (neat): $\tilde{\nu}$ = 1693, 1639, 1579, 1460, 1257, 1230 cm^{-1}; MS (ESI): m/z: 259 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{27}O$: 259.2056 [M^++H]; found: 259.2055. **15c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.23 (s, 1H), 5.63 (d, J = 13.5 Hz, 1H), 5.53 (d, J = 13.5 Hz, 1H), 2.42 (t, J = 6.6 Hz, 4H), 2.22 (t, J = 7.5 Hz, 2H), 2.15 (s, 2H), 2.08–1.95 (m, 2H), 1.53–1.40 (m, 2H), 1.40–1.21 (m, 2H), 1.08 (s, 6H), 0.90 ppm (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.0, 21.9, 22.5, 30.5, 31.4, 31.7, 37.7, 38.0, 38.8, 41.9, 122.6, 125.4, 131.9, 143.5, 146.9, 152.1, 199.0 ppm; IR (neat): $\tilde{\nu}$ = 1669, 1597, 1455, 1270, 1215, 1140, 1110 cm^{-1}; MS(ESI): m/z: 259 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{27}O$: 259.2056 [M^++H]; found: 259.2060.

(4a*E*,5*Z*,9*Z*)-7,7-Dimethyl-9-phenyl-3,4,7,8-tetrahydrocycloocta[*c*]cyclohexan-1(2*H*)-one (15d): Under argon atmosphere, a solution of **2d** (64 mg, 0.23 mmol) in xylene (4 mL) was stirred at 90 °C for 2 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 25:1) to afford **15d** (49 mg, 77 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.38 (m, 2H), 7.36–7.18 (m, 3H), 6.61 (s, 1H), 5.69 (d, J = 13.8 Hz, 1H), 5.57 (d, J = 13.8 Hz, 1H), 2.73 (s, 2H), 2.53–2.40 (m, 4H), 2.13–2.00 (m, 2H), 0.91 ppm (s, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.9, 31.4, 31.8, 37.9, 38.0, 40.9, 125.3, 125.9, 126.3, 127.0, 128.1, 132.3, 143.9, 144.4, 145.7, 152.9, 198.9 ppm; IR (neat): $\tilde{\nu}$ = 1666, 1639, 1592, 1451, 1360, 1270, 1187, 1132 cm^{-1}; MS (ESI): m/z: 279 [M^++H]; HRMS: m/z: calcd for $C_{20}H_{23}O$: 279.1743 [M^++H]; found: 279.1751.

(2a,8a)-2,2,8a-Trimethyl-3-(2′-ethoxycarbonylmethyl)-1,2,2a,5,6,8a-hexahydrocyclobuta[*b*]naphthalen-7(4*H*)-one (9e):[29] Under an argon atmosphere, a mixture of **16** (58 mg, 0.25 mmol) and $CH_3C(OEt)_3$ (162 mg, 1.00 mmol) in xylene (6 mL) was stirred at 140 °C with removal of ethanol by distillation. After 1 h, an additional amount of $CH_3C(OEt)_3$ (162 mg, 1.00 mmol) was added to the mixture and stirred for additional 2 h. After being cooling down to RT, the reaction mixture was directly purified via flash chromatography on silica gel (petroleum ether/ethyl acetate 20:1) to afford **9e** (31 mg, 41 %) together with other unidentified products. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.18 (d, J = 15.0 Hz, 1H), 2.70 (d, J = 15.0 Hz, 1H), 2.56 (s, 1H), 2.55–2.30 (m, 4H), 1.97 (d, J = 11.7 Hz, 1H), 1.93–1.75 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.14 (s, 6H), 0.94 ppm (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.2, 20.7, 24.4, 26.0, 29.3, 32.0, 33.2, 38.4, 38.9, 39.4, 51.5, 53.4, 60.6, 122.8, 128.4, 130.8, 143.0, 170.8, 198.6 ppm; IR (neat): $\tilde{\nu}$ = 1733, 1692, 1634, 1581, 1459, 1251, 1179, 1034 cm^{-1}; MS (EI): m/z (%): 302 (4.02) [M^+], 172 (100); HRMS: m/z: calcd for $C_{19}H_{26}O_3$: 302.1882 [M^+]; found: 302.1883.

Mechanistic study of cycloisomerization of 1,2,4*Z*,7-tetraenes

Synthesis of hexyl 3-deuteropropiolate ([D]-23):[23] Under an argon atmosphere, to a Schlenk tube was added hexyl propiolate (10.0 g, 65 mmol), D_2O (5.0 mL), K_2CO_3 (0.25 g, 1.8 mmol), TBAB (0.75 g, 2.3 mmol). After stirring at room temperature for 24 h, the aqueous layer was discarded. To the organic layer were added D_2O (5.0 mL), K_2CO_3 (0.25 g, 1.8 mmol), and TBAB (75 mg, 0.23 mmol). Then the mixture was stirred at RT for 24 h. After repeating this procedure for four times, the organic layer was dried over Na_2SO_4. This crude hexyl 3-deuteropropiolate ([D]-**23**) is pure enough for the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.19 (t, J = 6.6 Hz, 2H), 2.87 (s, 0.01 H), 1.75–1.60 (m, 2H), 1.42–1.20 (m, 6H), 0.89 ppm (t, J = 7.2 Hz, 3H).

1,1,2,3,3-Pentadeuteroallyl mesylate ([D$_5$]-24-(allyl)):[23] Under an argon atmosphere, to a three-necked flask containing $LiAlD_4$ (5.92 g, 141.0 mmol) and anhydrous Et_2O (180 mL) was added a solution of [D]-**23** (prepared above) in Et_2O (20 mL) over 1 h with the temperature below −10 °C. The reaction was allowed to warm up to RT and stirred for additional 6 h. After cooling to 0 °C, D_2O (6.0 mL, 300 mmol) was carefully added to the reaction mixture followed by stirring for 2 h. After the addition of 10 % NaOH (12 mL) and H_2O (18 mL), the reaction mixture was then filtered. The distillation of the filtrate afforded a mixture of 1,1,2,3,3-pentadeuteroallyl alcohol and ether for the next step.

The distillate and Et_3N (9.74 mL, 70 mmol) were added to a 250 mL flask. Then MsCl (5.4 mL, 8.02 g, 70 mmol) was added to the mixture with stirring at 0 °C over 20 min. The mixture was filtered and the filtrate was evaporated. The residue was purified via flash chromatography on silica gel to afford [D_5]-**24**-(allyl) (3.61 g, 39 % for three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.93 (0.02 H), 5.45–5.41 (m, 0.09 H), 5.36 (s, 0.02 H), 4.70 (s, 0.02 H), 3.00 ppm (s, 3H).

4,4,5,6,6-Pentadeutero-1-phenyl-2-hexyn-5-enol ([D$_5$]-25-(allyl)):[24] Under an argon atmosphere, a mixture of 1-phenylprop-2-yn-1-ol (1.32 g, 10.0 mmol), [D_5]-**24** (1.55 g, 11.0 mmol), CuI (0.19 g, 1.0 mmol), K_2CO_3 (2.76 g, 20.0 mmol), and DMF (30 mL) was stirred at 30 °C for 12 h. After complete consumption of the starting material as monitored by TLC, the reaction mixture was filtered through a short column on silica gel. The filtrate was diluted with water (100 mL) and extracted with Et_2O (50 mL × 3). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified via flash chromatography on silica gel to afford [D_5]-**25**-(allyl) (1.31 g, 74 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.52 (m, 2H), 7.46–7.28 (m, 3H), 5.82–5.80 (m, 0.01 H), 5.49 (d, J = 6.3 Hz, 1H), 5.32–5.30 (m, 0.04 H), 5.13–5.10 (m, 0.02 H), 2.22 ppm (d, J = 6.3 Hz, 1H).

2-(1′,1′,2′,3′,3′-Pentadeuteroallyl)-4-phenylbuta-2,3-dienoic acid ([D$_5$]-26)[25] [D_5]-**25**-(allyl) (1.06 g, 6.0 mmol) and THF (35 mL) was added to a dried 100 mL three-necked flask containing LiBr [dried from 0.63 g, (6.0 mmol) of LiBr?H_2O with a heating gun]. *n*BuLi (2.64 mL, 2.5 mol L^{-1} in hexanes, 6.6 mmol) was added dropwise at −78 °C with stirring. After the reaction mixture was stirred for 30 min at this temperature, *p*TsCl (1.26 g, 6.6 mmol) was added in one portion, then the mixture warmed up to RT and stirred at this temperature for 1.5 h. Then the mixture was transferred to autoclave followed by the addition of H_2O (1.2 mL) and [$Pd(PPh_3)_4$] (138 mg, 0.12 mmol). The mixture in autoclave was then stirred with a CO pressure of 300 psi at RT for 2 h. After carefully deflating the excess CO gas, the mixture was dried over Na_2SO_4. The solvent was evaporated and the residue was filtrated through a short column on silica gel. The crude product was purified via recrystallization to afford [D_5]-**26**-(allyl) (0.53 g, 43 %). Solid, m.p. 64–68 °C (Et_2O/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.17 (m, 5H), 6.63 (s, 1H), 5.88–5.83 (m, 0.01 H), 1.15–5.10 (m, 0.04 H), 3.13–3.05 ppm (m, 0.06 H).

3-(1′,1′,2′,3′,3′-Pentadeuteroallyl)-4-(3′-methylbuta-1′,2′-dienyl)-5-phenylfuran-2(5*H*)-one ([D$_5$]-1g-(allyl)): The reaction of [D_5]-**26**-(allyl) (123 mg, 0.60 mmol), methyl 2-methylbut-3-yn-2-yl carbonate (170 mg, 1.20 mmol), $Pd(OAc)_2$ (7 mg, 0.030 mmol), TFP (14 mg, 0.060 mmol), and K_2CO_3 (83 mg, 0.60 mmol) in DMSO (2.5 mL) afforded [D_5]-**1g**-(allyl) (86 mg, 53 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.18 (m, 3H), 7.18–7.02 (m, 2H), 5.88 (heptet, J = 3.0 Hz, 1H), 5.82 (s, 0.02 H), 5.64 (s, 1H), 5.15–5.01 (m, 0.10 H), 3.08 (s, 0.06 H), 1.58 (d, J = 3.0 Hz,

3H), 0.96 ppm (d, $J=3.0$ Hz, 3H); IR (neat): $\tilde{\nu}$ = 2212, 1950, 1752, 1643, 1456, 1301, 1152, 1102, 1103 cm^{-1}; MS(ESI): m/z: 272 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{13}D_5O_2Na$: 294.1513 [M+Na^+]; found: 294.1531.

[D_5]-6g: Under an argon atmosphere, a mixture of [D_5]-**1g**-(allyl) (72 mg, 0.27 mmol) in xylene (4 mL) was stirred at 110°C for 6 h. After complete consumption of the starting material as monitored by TLC, the mixture was directly purified via flash chromatography on silica gel to afford [D_5]-**6g** (46 mg, 64%) as well as unidentified products (10 mg). Solid, m.p. 114–118°C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.33 (m, 3H), 7.33–7.20 (m, 2H), 6.41 (s, 0.18H), 6.37 (s, 0.02H), 5.92 (d, $J=12.6$ Hz, 0.07H), 5.77 (s, 1H), 5.52–5.42 (m, 1H), 2.21 (d, $J=10.2$ Hz, 0.06H), 1.11 (s, 3H), 0.99 ppm (s, 3H); IR (neat): $\tilde{\nu}$ = 2239, 2196, 2135, 2082, 1741, 1699, 1622, 1494, 1457, 1331, 1141, 1018 cm^{-1}; MS(ESI): m/z: 294 [M+K]$^+$, 289 [M+Na^+], 272 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{14}D_5O_2$: 272.1693 [M^++H]; found: 272.1702.

[D_6]-28-(CD_3)$_2$-H(D): A solution of [D_6]-**28**-(CD_3)$_2$-H(D) (2.70 g, 30 mmol, prepared according to the literature[30] in Et_2O (5 mL) was added to a mixture of NaH (2.10 g, 60% in mineral oil, 51 mmol) and Et_2O (150 mL) in a 250 mL three-necked flask under stirring. After the addition, the mixture was stirred for 3 h under reflux. After cooling down to RT, a solution of $ClCO_2Me$ (3.48 mL, 45 mmol) in Et_2O (5 mL) was added over 30 min and stirred overnight. The reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the distillation of the residue afforded [D_6]-**28**-(CD_3)$_2$-H(D) (2.55 g, 71%). B.p. 49–50°C at 10 mm Hg; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 2.54 ppm (s, 0.16H).

Methyl 1,1-di(trideuteromethyl)prop-2-yn-1-yl carbonate ([D_6]-28-(CD_3)$_2$): Under an argon atmosphere, to a solution of [D_6]-**28**-(CD_3)$_2$-H(D) (1.51 g, 10.2 mmol) in Et_2O (30 mL) was added *n*BuLi (9.56 mL, 1.6 mol L^{-1} in hexane, 15.3 mmol) at −78°C with stirring over 50 min. After being stirred at −78°C for 20 min, the reaction mixture was quenched with H_2O at this temperature. The mixture was allowed to warm up to RT spontaneously. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed by evaporation and the residue was purified via flash chromatography on silica gel (pentane/Et_2O 50:1) to afford [D_6]-**28**-(CD_3)$_2$ (0.58 g, 38%), which was used directly for the next step without further characterization. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 2.56 ppm (s, 1H).

3-Allyl-4-[3′,3′-di(trideuteromethyl)propa-1′,2′-dienyl]-5-phenylfuran-2(5*H*)-one ([D_6]-1g-(CD_3)$_2$): The reaction of 2-allyl-4-phenylbuta-2,3-dienoic acid (150 mg, 0.75 mmol), [D_6]-**28**-(CD_3)$_2$) (221 mg, 1.50 mmol), Pd(OAc)$_2$ (5 mg, 0.020 mmol), TFP (9 mg, 0.040 mmol), and K_2CO_3 (104 mg, 0.75 mmol) in DMSO (3 mL) afforded [D_6]-**1g**-(CD_3)$_2$ (110 mg, 54%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 3H), 7.22–7.15 (m, 2H), 6.00–5.85 (m, 2H), 5.72 (s, 1H), 5.22–5.08 (m, 2H), 3.19 (d, $J=$ 6.3 Hz, 2H), 1.68–1.61 (m, 0.16H), 1.05–1.00 ppm (m, 0.15H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 18.1 (heptet), 27.6, 83.0, 83.5, 99.4, 116.3, 123.7, 127.5, 128.5, 128.8, 133.4, 135.8, 156.2, 173.5, 208.2 ppm; IR (neat): $\tilde{\nu}$ = 2237, 2203, 2107, 1949, 1752, 1642, 1456, 1355, 1302, 1084, 1005 cm^{-1}; MS(EI): m/z (%): 273 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{12}D_6O_2$: 272.1683 [M^+]; found: 272.1683.

[D_6]-6g: A solution of [D_6]-**1g**-(CD_3)$_2$ (90 mg, 0.33 mmol) in xylene (4 mL) was stirred at 110°C for 6 h. After complete consumption of the starting material as monitored by TLC, the mixture was directly purified via flash chromatography on silica gel to afford product [D_6]-**6g** (76 mg (76 mg). The product was further purified by one recrystallization from ethyl acetate and petroleum ether (66 mg, 73%). Solid, m.p. 116–118°C (ethyl acetate/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.35 (m, 3H), 7.35–7.22 (m, 2H), 6.46–6.32 (m, 1.22H), 5.93 (d, $J=$ 13.2 Hz, 1H), 5.77 (s, 1H), 5.48 (d, $J=13.2$ Hz, 1H), 2.32–2.17 (m, 2H), 1.15–1.05 (m, 0.45H), 1.03–0.96 ppm (m, 0.45H); IR (neat): $\tilde{\nu}$ = 2215, 1743, 1624, 1495, 1457, 1265, 1125, 1035, 1003 cm^{-1}; MS(ESI): m/z: 290 [M+NH_4^+], 273 [M^++H]; HRMS: m/z: calcd for $C_{18}H_{12}D_6O_2$: 272.1683 [M^+]; found: 272.1679.

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10364/3780 (R_{int} = 0.1251); number of observations [$I > 2\sigma(I)$] 1154, parameters: 239. CCDC 647592 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[11] Crystal data for *trans*-**5d**: $C_{22}H_{20}O_2$, M_W = 316.38, monoclinic; space group $P2(1)/n$, a = 9.5944(10), b = 12.7764(13), c = 13.7255(14) Å, α = 90, β = 96.046(2), γ = 90°, V = 1673.1(3) Å^3, T = 293(2) K, Z = 4, $Mo_{K\alpha}$ final R indices [$I > 2\sigma(I)$], $R1$ = 0.0598, $wR2$ = 0.1530; R indices (all data): $R1$ = 0.0759, $wR2$ = 0.1652; reflections collected/unique: 9684/3645 (R_{int} = 0.1342); number of observations [$I > 2\sigma(I)$] 2656, parameters: 228; CCDC 647595 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[12] Crystal data for *trans*-**5e**: $C_{19}H_{20}O_2$, M_W = 280.35, monoclinic; space group $P2(1)$, a = 8.4041(9), b = 7.7989(9), c = 11.9701(13) Å, α = 90, β = 103.336(2), γ = 90°, V = 763.40(15) Å^3, T = 293(2) K, Z = 2, $Mo_{K\alpha}$, final R indices [$I > 2\sigma(I)$], $R1$ = 0.0424, $wR2$ = 0.1055; R indices (all data): $R1$ = 0.0442, $wR2$ = 0.1070; reflections collected/unique: 4491/1785 (R_{int} = 0.0864); number of observations [$I > 2\sigma(I)$] 1670, parameters: 205; CCDC 647594 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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[20] Crystal data for **10aba**: $C_{28}H_{35}BrO_2$, MW = 483.47, monoclinic; space group $P2(1)/n$, a = 9.6751(11), b = 18.841(2), c = 13.5790(15) Å, α = 90, β = 106.572(2), γ = 90°, V = 2372.4(5) Å^3, T = 293(2) K, Z = 4, $Mo_{K\alpha}$, final R indices [$I > 2\sigma(I)$], R1 = 0.0404, wR2 = 0.0777; R indices (all data): $R1$ = 0.0787, $wR2$ = 0.0840; reflections collected/unique: 13970/5361 (R_{int} = 0.0814); number of observations [$I > 2\sigma(I)$] 2959, parameters: 292; CCDC 647590 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

[21] Crystal data for **14aa**: $C_{18}H_{20}O_4$, M_W = 300.34, monoclinic; space group $P2(1)/c$, a = 12.2043(14), b = 11.8230(14), c = 10.7171(12) Å, α = 90, β = 92.944(2), γ = 90°, V = 1544.3(3) Å^3, T = 293(2) K, Z = 4, $Mo_{K\alpha}$, final R indices [$I > 2\sigma(I)$], $R1$ = 0.0491, $wR2$ = 0.1266; R indices (all data): $R1$ = 0.0633, $wR2$ = 0.1348; reflections collected/unique: 8749/3359 (R_{int} = 0.0777); number of observations [$I > 2\sigma(I)$] 2642, parameters: 226. CCDC 647591 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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