Sequential Rearrangement of 1,2,4Z,7-Tetraenes Involving [1,5]-Hydrogen Migration and Electrocyclization: An Efficient Synthesis of Eight-Membered Cyclic Compounds

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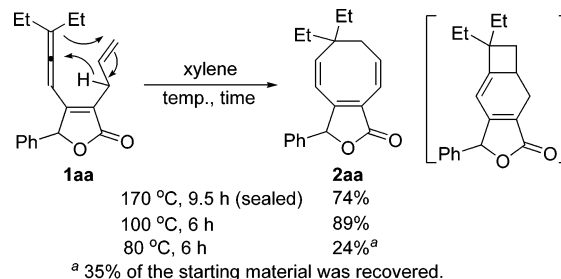
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Allenes, an important class of compounds, have demonstrated unique reactivity and stereoselectivity due to the two mutually perpendicular π-orbitals.[1–3] In many cases, it is advantageous to use an allene as a retrosynthetic fragment.[4]

During the evolution of alicyclic chemistry, medium rings, particularly eight-membered cyclic compounds, have aroused considerable interest and attention.[5,6] Until now, more than 100 cyclooctanoid-containing natural products have been isolated from plants, marine organisms, and insects, etc., many of which exhibit an exceptional and broad range of biological activity.[7] However, the synthesis of eight-membered cyclic compounds remains difficult due to unfavorable entropic and enthalpic factors.[8] The transition-metal-catalyzed cycloisomerization reactions of allenene,[9] al-lenyne,[10] and allene−allene[11] are powerful protocols for the construction of four- to seven-membered mono-, bi-, and even tetracyclic compounds in one pot. To the best of our knowledge, there is no report on the cycloisomerization reaction of 1,2,4Z,7-tetraene compounds. Herein we report an efficient synthesis of cyclooctanoid compounds from 1,2,4Z,7-tetraenes.

Our initial investigation was based on the reaction of 3-allyl-4-(3′-ethylpenta-1′,2′-dienyl)-5-phenylfuran-2(5H)-one (**1aa**), which was easily prepared from the cross-coupling cyclization of 2,3-allenoic acids and propargylic carbonates developed recently in this group.[12] To our surprise, when **1aa** was stirred in xylene at 170 °C for 9.5 h, instead of forming the expected [2 + 2] cycloaddition product, we isolated 74% yield of **2aa**, which was the formal Alder-ene-type product (Scheme 1). Since allenes preferentially form cyclobutanes with alkenes through [2 + 2] cycloaddition rather than the Alder-ene products,[13] we show great interests in this type of reaction. Further studies show that a higher yield of **2aa** can be achieved in xylene at 100 °C for 6 h (Scheme 1).

The optimized reaction conditions (100 °C, 6 h, in xylene) were then applied to the cyclization of 1,2,4Z,7-tetraenes **1** (Table 1). The substituent of the 5-position of the furanone proved to be general for this reaction. 5-Aryl- (entries 1−9, Table 1), alkyl- (entries 13 and 14, Table 1), or dimethyl (entries 10−12, Table 1)-substituted furanones can efficiently afford the bicycle[6.3.0]-lactones **2**. With R¹ and R² being the tetramethylene group (entries 4 and 9, Table 1), the reaction afforded the products in relatively lower yields. The yield is also lower when R¹ is a phenyl group (entry 12, Table 1). Furthermore, **1f**, which has a 2-cyclohexenone core, can also smoothly form bicylco[6.4.0]ketone **2f** (entry 15, Table 1). The structure of the products **2** was further established by the X-ray diffraction studies of **2ab** (Figure 1, left).[14]

To determine the possible mechanism for this reaction, a control experiment was conducted. When a solution of **1f** and the dienophile **3** in xylene was stirred at 55 °C for 24 h, we isolated two products, **2f** and **4f** (Scheme 2), indicating the intermediacy of tricyclic diene **5** (Scheme 3). Furthermore, heating **2f** at 55 °C in the presence of **3** yielded 53% of **4f** with 28% of **2f** remaining, indicating that **2f**

Scheme 1. Cycloisomerization of **1aa**

170 °C, 9.5 h (sealed)	74%
100 °C, 6 h	89%
80 °C, 6 h	24%ᵃ

ᵃ 35% of the starting material was recovered.

Table 1. The Thermal Cyclization Reaction of (1,2,4Z,7)-Tetraenes **1**ᵃ

entry	reactant	product
1	R¹ = R² = Et, **1aa**	89% (**2aa**)
2ᵇ	R¹ = R² = Me, **1ab**	84% (**2ab**)
3	R¹, R² = -(CH₂)₅-, **1ac**	80% (**2ac**)
4ᶜ	R¹, R² = -(CH₂)₄-, **1ad**	67% (**2ad**)
5	R¹ = R² = Et, **1ba**	97% (**2ba**)
6	R¹ = R² = Me, **1bb**	87% (**2bb**)
7	R¹ = R² = Et, **1ca**	95% (**2ca**)
8	R¹ = R² = Me, **1cb**	84% (**2cb**)
9ᶜ	R¹, R² = -(CH₂)₄-, **1cd**	66% (**2cd**)
10	R¹ = R² = Et, **1da**	83% (**2da**)
11	R¹ = Et, R² = Me, **1de**	74% (**2de**)
12	R¹ = Ph, R² = Me, **1df**	48% (**2df**)
13	R¹ = R² = Et, **1ea**	84% (**2ea**)
14	R¹, R² = -(CH₂)₅-, **1ec**	89% (**2ec**)
15ᵈ	**1f**	56% (**2f**)

ᵃ Under argon atmosphere, a solution of 0.15−0.25 mmol of **1** in 4 mL of xylene was stirred at 100 °C for 6 h. ᵇ The reaction time was 7 h. ᶜ An unidentified product was also isolated in about 10% yield by weight. ᵈ The reaction was carried at 90 °C for 2 h.

and **5** exist in equilibrium upon heating.[15] When **1g** with a monosubstituted terminal C═C bond was used as the substrate in the presence of **3**, Diels−Alder product **4g** was isolated in 77% yield as the only product. The structures of **4f** and **4g** were further determined by the X-ray diffraction studies of **4g** (Figure 1, right).[16]

Due to the nature that an allene favors [2 + 2] cycloaddition rather than ene reaction,[13d] we proposed two additional mechanistic pathways shown in Scheme 3. Compound **1f** is first postulated to undergo a thermal [2 + 2] cycloaddition between the terminal C═C double bond and the allene functionality to form intermediate **6**.[17] Due to the high strain in the four-membered ring with an
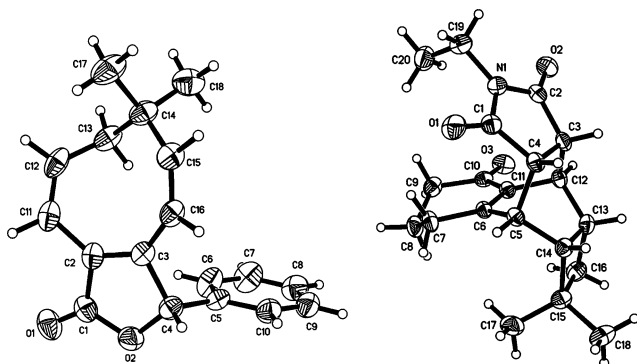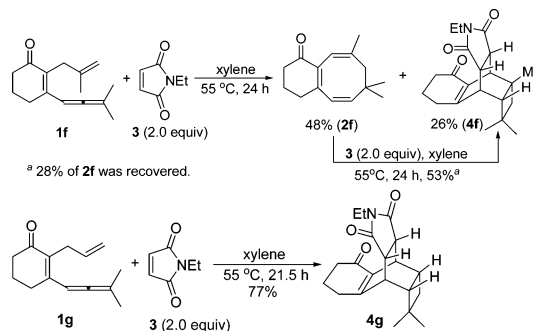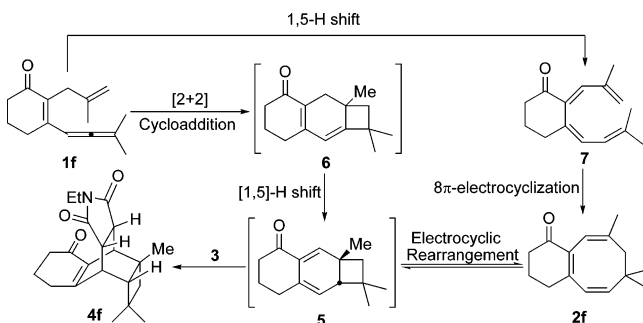
Figure 1. ORTEP representations of **2ab** (left) and **4g** (right).

Scheme 2. Mechanistic Evidence

Scheme 3. The Plausible Mechanism

exocyclic double bond, [1,5]-H migration of **6** would form tricyclic intermediate **5**.[18] Then the intermediate **5** would undergo an electrocyclic rearrangement to form the eight-membered bicyclic product **2f**.[19] The second pathway is the 1,5-H shift of **1f** forming tetraene **7**, which would undergo 8π-electrocyclization to afford **2f**.[15,20] In the presence of dienophile **3**, the intermediate **5** may undergo Diels–Alder reaction to afford **4f**.

In conclusion, we have described an efficient protocol for the synthesis of eight-membered bicyclic compounds through 1,2,4Z,7-tetraenes. The reaction may proceed via the sequential [2 + 2] cycloaddition, [1,5]-H migration, and electrocyclic rearrangement or the sequential 1,5-H shift and 8π-electrocyclization reaction. Further studies in this area are being pursued in our laboratory.

Supporting Information Available: Experimental procedures and characterization data of all new products **2** and **4** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystal data for **2ab**: $C_{18}H_{18}O_2$, MW = 266.32, monoclinic, space group $P2(1)/c$. Final R indices [$I > 2\sigma(I)$], R1 = 0.0586, wR2 = 0.1363, R indices (all data) R1 = 0.0894, wR2 = 0.1517, a = 6.7357(8) Å, b = 19.494(2) Å, c = 11.5301(14) Å, β = 101.969(2)°, V = 1481.1(3) Å³, T = 293(2) K, Z = 4. Reflections collected/unique: 8643/3238 (R_{int} = 0.1579), number of observations [$>2\sigma(I)$] 1964; parameters, 204. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 278334.

(15) We thank one of the referees for the suggestion of this experiment and adding the pathway involving intermediate **7** (Scheme 3).

(16) Crystal data for **4g**: $C_{20}H_{25}NO_3$, MW = 327.41, orthorhombic, space group *Pbca*. Final R indices [$I > 2\sigma(I)$], R1 = 0.0548, wR2 = 0.1360, R indices (all data) R1 = 0.0727, wR2 = 0.1464, a = 13.6546(10) Å, b = 12.7382-(9) Å, c = 19.7605(14) Å, V = 3437.0(4) Å³, T = 293(2) K, Z = 8. Reflections collected/unique: 19111/3730 (R_{int} = 0.1297), number of observations [$>2\sigma(I)$] 2717, parameters, 245. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 290061.

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