

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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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 allenyne,¹⁰ and allene–allene¹¹ 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 bicyclo[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**

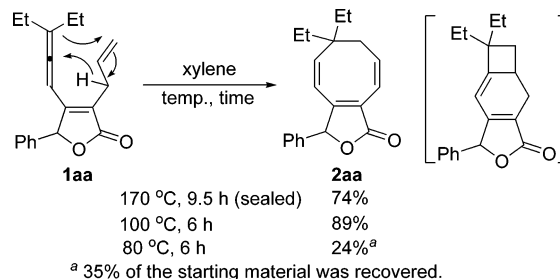


Table 1. The Thermal Cyclization Reaction of (1,2,4Z,7)-Tetraenes **1**^a

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

^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

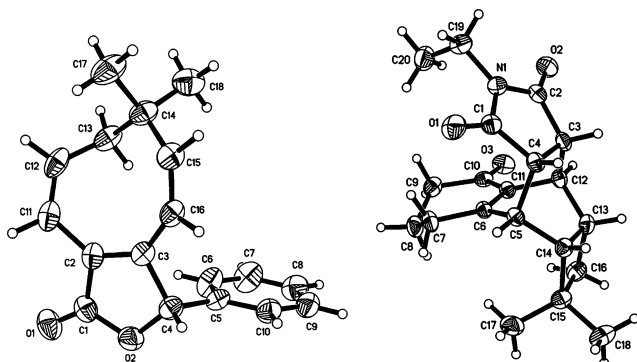
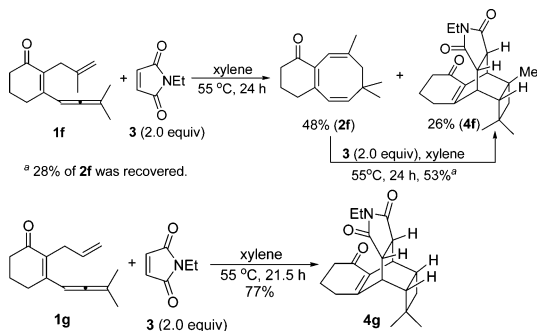
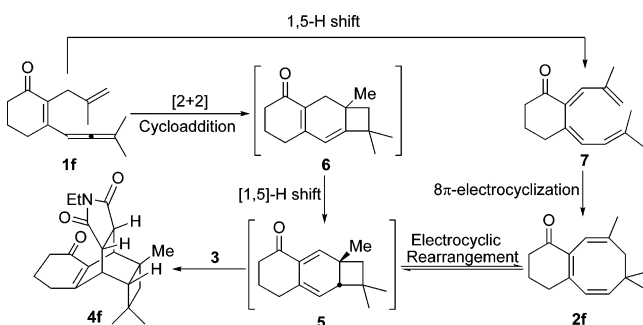


Figure 1. ORTEP representations of **2ab** (left) and **4g** (right).

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.

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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>.

References

- (1) (a) Landor, S. R., Ed. *The Chemistry of the Allenes*; Academic Press: London, 1982; Vol. 1. (b) Krause, N.; Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2.

- (2) (a) Zimmer, R. C.; Dinesh, U.; Nandan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (b) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (c) Reissig, H.-U.; Schade, W.; Amombo, M. O.; Pulz, R.; Hausherr, A. *Pure Appl. Chem.* **2002**, *74*, 175. (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829 and references therein.
- (3) For some of the typical reactions of allenenes, see: (a) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50. (b) Chang, K.-J.; Rayabarapu, D. K.; Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2005**, *127*, 126. (c) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320. (d) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186. (e) Hamaguchi, H.; Kosaka, S.; Ohno, H.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1513.
- (4) Brummond, K. M.; Chen, H. *Allenenes in Natural Product Synthesis*. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1 and 2 and references therein.
- (5) For reviews on synthesis of cyclooctanoids, see: (a) Sieburth, S. M.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (c) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.
- (6) (a) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (b) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782. (c) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904. (d) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (e) Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876. (f) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. (g) Snapper, M. L.; Tallarico, J. A.; Randall, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 1478.
- (7) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
- (8) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
- (9) (a) Makino, T.; Itoh, K. *Tetrahedron Lett.* **2003**, *44*, 6335. (b) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395.
- (10) (a) Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295. (b) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186. (c) Cadran, N.; Cariou, K.; Herve, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* **2004**, *126*, 3408.
- (11) (a) Kang, S.-K.; Baik, T.-G.; Kulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529. (b) Ma, S.; Lu, P.; Lu, L.; Hou, H.; Wei, J.; He, Q.; Gu, Z.; Jiang, X.; Jin, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 5275.
- (12) Ma, S.; Gu, Z.; Deng, Y. *Chem. Commun.* **2006**, 94.
- (13) (a) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. (b) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealton, S. *J. Am. Chem. Soc.* **1979**, *101*, 5283. (c) Kirk, B. E.; Taylor, D. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1844. The silyl group in the substrates is important for the allene to undergo the ene reaction rather than [2 + 2] cycloaddition. See: (d) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.
- (14) Crystal data for **2ab**: $C_{18}H_{18}O_2$, MW = 266.32, monoclinic, space group $P2(1)/c$. Final R indices [$I > 2\sigma(I)$], $R_1 = 0.0586$, $wR_2 = 0.1363$, R indices (all data) $R_1 = 0.0894$, $wR_2 = 0.1517$, $a = 6.7357(8)$ Å, $b = 19.494(2)$ Å, $c = 11.5301(14)$ Å, $\beta = 101.969(2)^\circ$, $V = 1481.1(3)$ 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 [$I > 2\sigma(I)$], $R_1 = 0.0548$, $wR_2 = 0.1360$, R indices (all data) $R_1 = 0.0727$, $wR_2 = 0.1464$, $a = 13.6546(10)$ 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.
- (17) The regioselectivity of [2 + 2] cycloaddition of 1,7-allenene can afford distal or proximal adducts. For distal adducts, see: (a) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1995**, *117*, 7071. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, *5*, 3795. (c) Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5113. For proximal adducts, see: (d) Becker, D.; Harel, Z.; Nagler, M.; Gillon, A. *J. Org. Chem.* **1982**, *47*, 3297. (e) Dauben, W. G.; Rocco, V. P.; Shapiro, G. *J. Org. Chem.* **1985**, *50*, 3155. (f) Shepard, M. S.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597. (g) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238.
- (18) (a) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (b) Roth, W. R.; König, J. Stein, K. *Chem. Ber.* **1970**, *103*, 426. (c) Doering, W. v. E.; Keliher, E. J.; Zhao, X. *J. Am. Chem. Soc.* **2004**, *126*, 14206.
- (19) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag-Chemie/Academic Press: Weinheim/Bergstr., Germany and New York, 1970. (b) Glass, D. S.; Watthey, J. W. H.; Winstein, S. *Tetrahedron Lett.* **1965**, 377. (c) Rahman, M. M.; Secor, B. A.; Morgan, K. M.; Shafer, P. R.; Lemal, D. M. *J. Am. Chem. Soc.* **1990**, *112*, 5986.
- (20) For the formation of the cyclooctanoid compounds via the 8π -electrocyclization of 1,3,5,7-tetraenes, see: (a) Kerr, D. J.; Willis, A. C.; Flynn, B. L. *Org. Lett.* **2004**, *6*, 457. (b) Brückner, S.; Baldwin, J. E.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Tetrahedron* **2004**, *60*, 2785. (c) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130. (d) Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235.

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