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ENYNONES IN ORGANIC SYNTHESIS. I. SPIROANNULATION BY TANDEM OXY-COPE REARRANGEMENT-ELECTROCYCLIC RING CLOSURE

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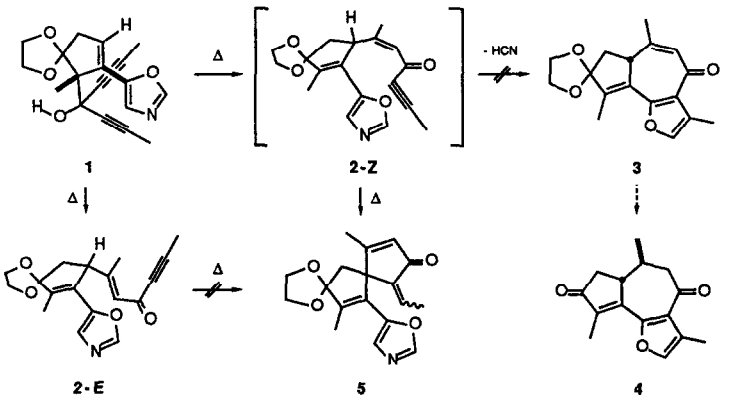
Summary: *Bis-acetylenic alcohols of proper design undergo a facile oxy-Cope rearrangement to afford mixtures of E- and Z-enynones. These latter compounds afford methylenecyclopentenones upon enolization and electrocyclic ring closure.*

During the course of studies directed toward the total synthesis of gnididione (**4**),[1g] we briefly explored the possibility that dehydrognididione ketal (**3**) might be derived from the acetylenic enone **2-Z** by a straightforward extension of the oxazole-Diels-Alder methodology which we have employed for the synthesis of various furanosesquiterpenes (Scheme 1).[1] This approach was attractive because it offered the possibility that **2-Z** might be

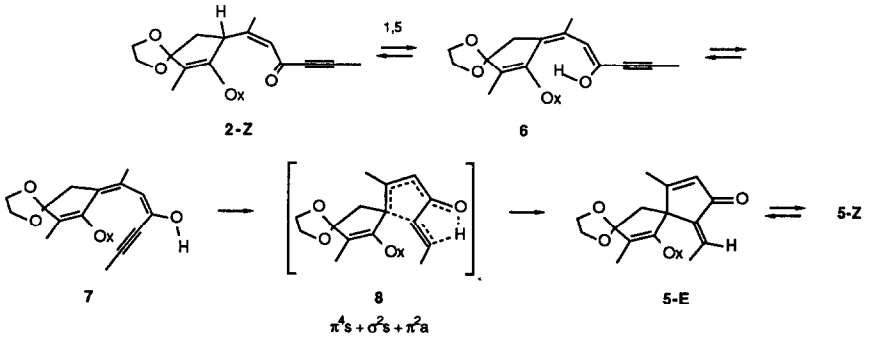


Scheme 1

conveniently prepared by an oxy-Cope rearrangement of the tertiary alcohol **1**,[2] itself available in multigram quantities from the corresponding ester. In fact, thermolysis of **1** provided an excellent yield of the expected mixture of **2-Z** and **2-E** at temperatures between 80 - 90° C. At higher temperatures, however, we were surprised to find that **2-Z** gave none

of the desired furan **3**, but rather was cleanly converted to the spirocyclic methylenecyclopentenone **5**, which was isolated as an equilibrium mixture of E- and Z-isomers (E:Z ~1:1, >90% yield, 110° C, toluene, reflux).[3] Acetylenic enone **2-E**, in contrast, was totally unreactive at temperatures up to 160° C and slowly decomposed at temperatures above 200°. At the time, transformations of the type **2-Z** ---> **5** were unprecedented, although Dreiding *et al.* have since reported on similar conversions occurring in low yield in the vapor phase at 600-800°,[4] and Agosta *et al.* have described a related photochemical reaction of mesityl ketones.[5]

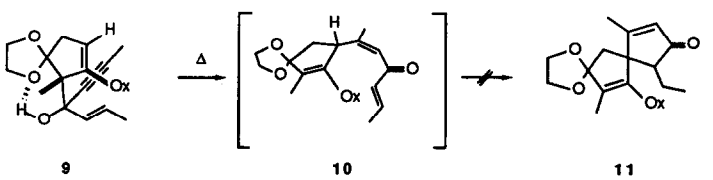
The cyclization of **2-Z** to **5** is not inhibited by radical scavengers, and most attempts at acid or base catalysis caused extensive decomposition (see below, however). These observations, taken together with the unreactive nature of **2-E**, are strongly suggestive of a mechanism involving a thermal 1,5-prototropic shift to give the enolized species **6**, which might then equilibrate to the more stable enol **7** (Scheme 2).[5b] Enol **7**, in turn, could afford **5-E** *via* a concerted



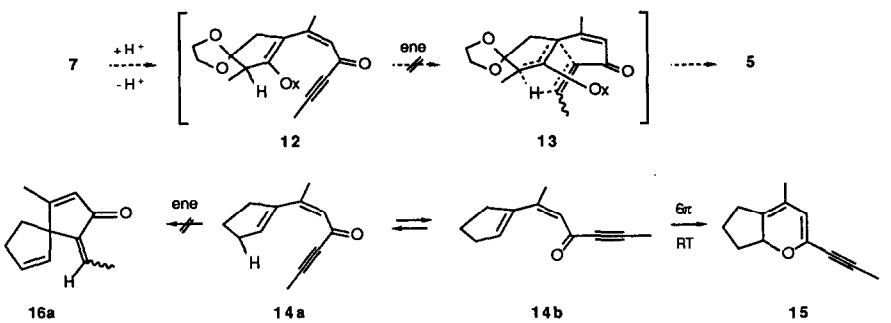
Scheme 2

($\pi^4s + \sigma^2s + \pi^2a$) electrocyclic reaction, a pathway which would be facilitated by the nucleophilicity of the terminus of the dienol and the electrophilicity of the acetylene.[6] In support of the concerted process, in model studies we have shown that the E-methylenecyclopentenone is the product of kinetic control, with the Z-isomer forming by equilibration.[7] However, we should caution that the kinetic bias in the cyclization **2-Z** ---> **5** could not be determined, due to rapid equilibration of **5-E** and **5-Z** under the reaction conditions employed.

As predicted by the electrocyclic mechanism, the in-plane orbitals of the acetylene are required for spiroannulation (*cf.* transition state **8**). Thus, alkene **10**, derived by chemoselective oxy-Cope rearrangement of the tertiary alcohol **9**,[1g] showed no inclination for undergoing conversion to the ethylcyclopentenone **11**, in contrast to the results obtained with the closely related species **2-Z**. Finally, an alternative mechanism, involving an ene reaction of the fully conjugated

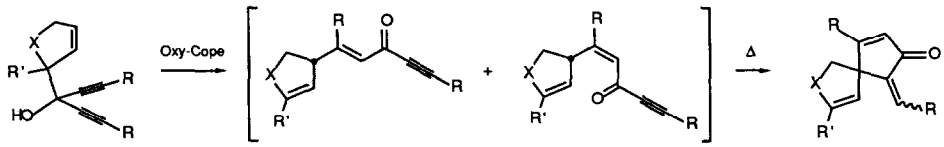


dienone **12**, has been ruled out on the basis of results obtained with the closely related dienone **14** (Scheme 3, following page), as well as studies described in the paper which follows.[7] Thus, **14** reacted exclusively through conformation **14b** to afford the pyran **15**, the product of 6π-electrocyclization, and no trace of the methylenecyclopentenone **16a** could be detected.[8]



Scheme 3

That conversions of the type **1** ---> **5** are reasonably general in nature is indicated by the examples given in Table 1. Thus, cyclopentene derivatives **17a** and **17b** gave mixtures of the corresponding enynones **18-E** (15-25%) and spirocyclic methylenecyclopentenones **16** (35-45%) upon heating in toluene or mesitylene at 250° C for 12-16 h (conditions *a*). Under these conditions, little if any of the isomeric enynones **18-Z** could be isolated. In identical fashion, cyclohexene derivatives **17c** and **17d** afforded the methylenecyclopentenones **16c** (18%) and **16d** (29%), together with the enynones **18-Ec** (10%) and **18-Ed** (17%). Some degree of latitude was also possible in the nature of the acetylenic substituent R. For example, **17e** (R = Ph) gave a 9% yield of **16e** after 6 h at 230°, in addition to 18% of recovered starting material. However, the terminal acetylenic derivative **17f** gave only trace amounts of the spiroannulation product **16f**, apparently due to decomposition during the oxy-Cope process.



a : X = CH_2, R' = H, R = Me	(25%)[a] (0%)[b]	0%	(43%)[a] (81%)[b]
b : X = CH_2, R' = Me, R = Me	(14%)[a] (0%)[b]	0%	(37%)[a] (79%)[b]
c : X = $(CH_2)_2$, R' = H, R = Me	(10%)[a] (0%)[b]	0%	(18%)[a] (55%)[b]
d : X = $(CH_2)_2$, R' = Me, R = Me	(17%)[a] (0%)[b]	0%	(29%)[a] (66%)[b]
e : X = CH_2, R' = H, R = Ph	(00%)[a] (0%)[b]	0%	(09%)[a] (70%)[b]
f : X = CH_2, R' = H, R = H	(00%)[a] (0%)[b]	0%	(<1%)[a] (<1%)[b]

(a) toluene or mesitylene Δ. (b) toluene, Δ, 4-*t*-butylcatechol.

Table 1

Interestingly, both the yield and rate for the conversions of 17 to 16 were substantially increased in the presence of excess 4-t-butylcatechol (TBC). Catalytic activity was roughly proportional to the concentration of TBC. Thus, **17a** gave an 81% yield of **16a** after 6 h at 250° with 1.1 eq of TBC (0.05 N) (conditions *b*), while the same reaction required 12 h to give a 43% yield of **16a** in the absence of TBC (conditions *a*). Also, enynone **18-Ea** was totally consumed. Similar results were obtained with acetylenic alcohols **17b - 17e**, with **17e** providing a particularly dramatic contrast between conditions *a* and *b* (9% vs 70%). In part, these rate enhancements are probably due to TBC functioning as a mild acid catalyst in the enolization of both **18-E** and **18-Z** which is required for spirocyclization (*cf.* Scheme 2). However, it is also possible that more substantive effects are involved, as discussed in the paper which follows.[7,9]

References and Notes

1. (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (b) Jacobi, P. A.; Ueng, S. N.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042. (c) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (d) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (e) Jacobi, P. A.; Frechette, R.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (f) Jacobi, P. A.; Weiss, K.; Egbertson, M. *Heterocycles* **1984**, *22*, 281. (g) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (h) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, 4859. (i) Jacobi, P. A.; Frechette, R. F. *Tetrahedron Lett.* **1987**, 2937. (j) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475. (k) Jacobi, P. A.; Egbertson, M.; Frechette, R. F.; Miao, C. K.; Weiss, K. T. *Tetrahedron* **1988**, *44*, 3327.
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3. All yields refer to isolated and purified materials. Physical and chemical data for representative compounds: (a) **1:** colorless crystalline solid, mp 156-57° C, Rf 0.43 (ether, silica gel); mass spectrum, m/e 313 (M+); IR(KBr) 3420 br, 2910, 2235 cm^{-1}; NMR($CDCl_3$) δ 1.53 (s, 3H), 1.72 (s, 3H), 1.75 (s, 3H), 2.29 (dd, 1H, J = 4.0, 17.5 Hz), 3.08 (dd, 1H, J = 2.5, 17.5 Hz), 4.03 (m, 4H), 6.36 (dd, 1H, J = 2.5, 4.0 Hz), 7.10 (s, 1H), 7.75 (s, 1H). **Anal.** Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.46. Found: C, 68.79; H, 5.86; N, 4.30. (b) **2-E:** amorphous solid, Rf 0.51 (ether, silica gel); mass spectrum, m/e 313 (M+); IR($CHCl_3$) 2222, 1650, 1603, 1493 cm^{-1}; NMR($CDCl_3$) δ 1.88 (dd, 1H, J = 4.0, 14.0 Hz), 1.94 (s, 3H), 1.96 (s, 3H), 1.99 (s, 3H), 2.38 (dd, 1H, J = 9.0, 14.0 Hz), 3.63 (m, 1H), 3.99 (m, 4H), 6.21 (s, 1H), 7.03 (s, 1H), 7.83 (s, 1H). (c) **2-Z:** pale yellow oil, Rf 0.56 (ether, silica gel); mass spectrum, m/e 313 (M+); IR($CHCl_3$) 2222, 1645, 1601, 1493 cm^{-1}; NMR($CDCl_3$) δ 1.64 (s, 3H), 1.78 (dd, 1H, J = 3.0, 14.0 Hz), 1.94 (s, 3H), 1.99 (s, 3H), 2.52 (dd, 1H, J = 9.0, 14.0 Hz), 4.01 (m, 4H), 5.25 (m, 1H), 6.17 (br s, 1H), 7.04 (s, 1H), 7.84 (s, 1H). (d) **5-E:** pale yellow crystalline solid, mp 130-31° C, Rf 0.39 (ether, silica gel); mass spectrum, m/e 313 (M+); IR($CHCl_3$) 1696, 1654, 1616, 1496 cm^{-1}; NMR($CDCl_3$) δ 1.68 (d, 3H, J = 8.0 Hz), sharpens to a singlet upon irradiation at 6.56, 1.90 (d, 3H, J = 1.0 Hz), sharpens to a singlet upon irradiation at 6.13, 2.00 (s, 3H), 2.27 (d, 1H, J = 15 Hz), 2.47 (d, 1H, J = 15 Hz), 4.09 (m, 4H), 6.13 (br s, 1H), 6.56 (q, 1H, J = 8.0 Hz), collapses to a singlet upon irradiation at 1.68, 6.85 (s, 1H), 7.78 (s, 1H). **Anal.** Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.46. Found: C, 68.25; H, 6.07; N, 4.20. (e) **5-Z:** pale yellow oil, Rf 0.44 (ether, silica gel); mass spectrum, m/e 313 (M+); IR($CHCl_3$) 1690, 1649, 1616, 1495 cm^{-1}; NMR($CDCl_3$) δ 1.84 (d, 3H, J = 1.0 Hz), 1.98 (s, 3H), 2.12 (d, 3H, J = 8.0 Hz), 2.14 (d, 1H, J = 14 Hz), 2.29 (d, 1H, J = 14 Hz), 4.01 (m, 4H), 6.04 (q, 1H, J = 8.0 Hz), 6.11 (q, 1H, J = 1.0 Hz), 6.84 (s, 1H), 7.78 (s, 1H). (f) **16a-Z:** pale yellow oil, Rf 0.45 (10% EtOAc/hexane, silica gel); mass spectrum, m/e 174 (M+); IR($CHCl_3$) 1688, 1645 cm^{-1}; NMR($CDCl_3$) δ 1.91 (s, 3H), 2.08 (m, 2H), 2.17 (d, 3H, J = 7.2 Hz), 2.31 (m, 2H), 5.25 (m, 1H), 5.89 (q, 1H, J = 7.2 Hz), 5.58 (m, 2H). **Anal.** Calcd for $C_{12}H_{14}O$: C, 82.70; H, 8.11. Found: C, 82.72; H, 8.15.
4. Koller, M.; Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1986**, 19; *ibid., Helv. Chim. Acta.* **1986**, *69*, 560.
5. (a) Rao, V. B.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 521. (b) Agosta, W. C.; Caldwell, R. A.; Jay, J.; Johnston, L. J.; Venepalli, B. R.; Scaiano, J. C.; Singh, M.; Wolff, S. *J. Am. Chem. Soc.* **1987**, *109*, 3050.
6. We are grateful to Professor Kendall Houk, of the University of California, Los Angeles, for helpful discussions regarding the mechanism of this reaction. *A priori*, we cannot rule out the possibility that **5-E** is formed directly from **2-Z** *via* a $\sigma^2s + \pi^2a$ addition of the γ-(C-H) bond across the acetylenic π-system (*cf.*, for example, references 2 and 4). However, this possibility seems remote in view of the mildness of the conditions employed and the catalytic studies reported in the paper which follows.[7]
7. Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J., following paper in this series.
8. For a closely related example, see (a) Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034. See also, (b) Marvell, E.N. "Thermal Electrocyclic Reactions", Academic Press : New York, 1980, p 305-319. Enynone **14** was generated *in situ* by addition of propynyl magnesium bromide to the corresponding Weinreb amide (*cf.* reference 1j).

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