

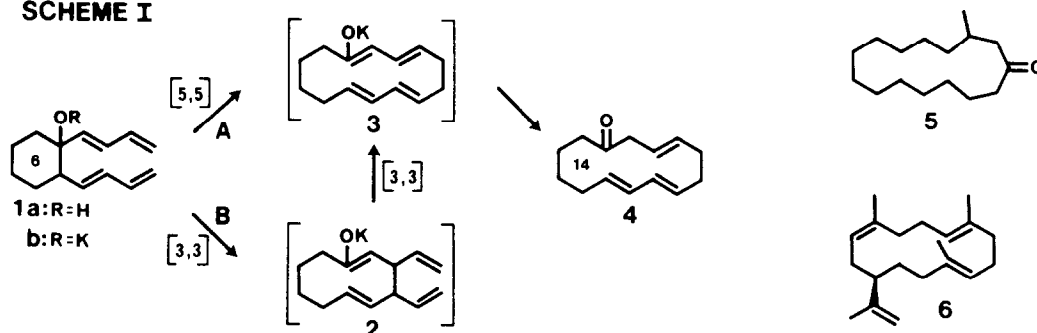
An Enolate-Accelerated Cope Rearrangement¹

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Abstract: The first example of an enolate accelerated Cope rearrangement is described along with its importance in the rearrangement of 5-alkoxy-deca-1,3,7,9-tetraenes.

We recently introduced a macroexpansion method¹ for the synthesis of large ring compounds, exemplified by the conversion of **1** into **4** (Scheme I) which has resulted in straightforward syntheses of (+)-muscone (**5**)^{1c} and (-)-3 β -cembrene A (**6**)^{1d}. While the precise mechanism for this rearrangement could not be

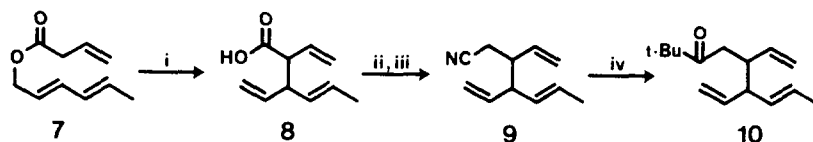
SCHEME I



established with the data available from these preliminary studies, the enolate **3** produced in this reaction presumably originates from a concerted [5,5] sigmatropic rearrangement (path A) or from two sequential [3,3] shifts (path B). It is interesting to note that, if the latter path were followed, intermediate **2** would be required to undergo a particularly rapid Cope rearrangement since the conversion of **1** into **3** is complete in less than one hour at room temperature and **2** does not accumulate under the mild reaction conditions. This path can not be ruled out on this basis alone, however, since there exists an intriguing possibility that rearrangement of triene enolate **2** could be facilitated by its enolate subunit² in a fashion similar to that first reported by Evans and coworkers³ for the vinylogously-related alkoxide functionality. The studies described herein were undertaken to determine the effect of an enolate subunit on the facility of the Cope rearrangements of triene enolates related to **2** and whether such intermediates intervene in the rearrangement of 5-alkoxy-deca-1,3,7,9-tetraenes.

In order to eliminate uncertainties associated with ring strain, enolate solvation, and enolate regiochemistry, enolate **11a** (Scheme III), the acyclic counterpart of **2**, was selected for investigation. An expeditious entry into this system via trienone **10** (Scheme II) was realized when the trimethylsilyl

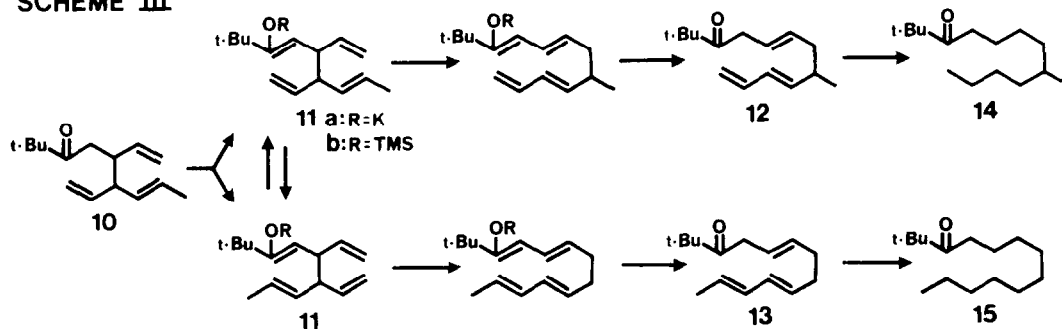
SCHEME II



i) LDA, TMSCl, Δ (80%); ii) LiAlH₄ (90%); iii) a: TsCl, pyr. b: KCN, DMF (84%); iv) a: t-BuLi, b: H₂SO₄ (40%)

derivative of the enolate of **7** was found to rearrange⁴ cleanly to triene acid **8** (80%).⁵ Subsequent conversion of this acid (**8**) to **10** proceeded in a conventional manner and in 30% overall yield. For the purpose of testing the facility of the enolate rearrangement, trienone **10** (1:1 mixture of diastereomers) was stirred in THF solution at room temperature with potassium hydride⁶ for 17 hours, during which time it was completely consumed and ketones **12** and **13** were produced in a ratio of 1:1.2 (73%; each a mixture of isomers).⁷

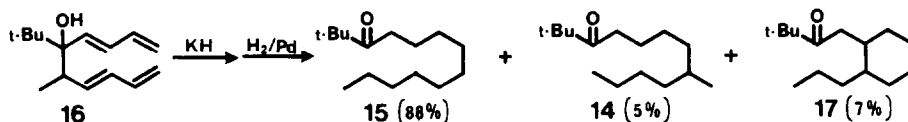
SCHEME III



The identities of these products were established by their reduction to ketones **14** and **15** (1:1.2, respectively) which proved to be identical with independently prepared samples.⁸ Further studies revealed that the conversion of **10** into **12** and **13** occurred with a half-life of 62.8 minutes at 25°.¹¹ For calibration on the facility of this rearrangement,⁹ under conditions (THF, 10h, 25°) which would have led to a 99.9% conversion of enolate **11a** into **12** and **13**, the corresponding silyl enol ether **11b** remained unchanged.¹⁰ The same result was

obtained when **11b** was heated (65°) for 4 hours in THF. Rearrangement of **11b** was eventually achieved but only when it was heated in toluene at reflux (111°; $t_{1/2}$ = 19 minutes).¹¹ The resultant products were again characterized by hydrolysis and hydrogenation which gave compounds **12** and **13**, identical to the products derived from **11a**, but in a slightly different ratio (1.3:1, respectively).

Having established that enolate substitution at C-3 of a hexa-1,5-diene can indeed facilitate its Cope rearrangement, we next set out to determine whether this process occurs in the rearrangement of the potassium salt of **16**,¹² a system analogous to tetraene **1**. Rearrangement of **16** by way of consecutive [3,3] shifts



would produce the same enolate (**11a**) prepared previously (vide supra) which would be expected to provide ketones **12** and **13**. A single [5,5] rearrangement pathway, however, would be expected to give only ketone **13**. In the event, treatment of alcohol **16** with potassium hydride in THF at room temperature for one hour followed by hydrolysis and hydrogenation of the reaction mixture gave ketone **15** (88%), in addition to ketones **14** (5%) and **17** (7%). These results are consistent with a rearrangement in which both [5,5] and consecutive [3,3] pathways are operative, with the former being favored. While other pathways, including a cleavage-recombination mechanism, can not be excluded on the basis of these results, this study establishes that a high degree of positional selectivity can be obtained in the rearrangement of 5-hydroxy-deca-1,3,7,9-tetraenes, a finding which provides a foundation for further synthetic applications. Moreover, while the mechanistic interpretation derived from the above acyclic systems might differ from the macroexpansion processes due to structural variations, it is again clear that in these latter reactions (e.g., **1** → **4**) high, if not complete, positional selectivity can be realized. Finally, the rate acceleration observed for the rearrangement of enolate **11a** relative to its enol ether derivative suggests a broader role for the enolate functionality in rate modulation of sigmatropic reactions.

Acknowledgment. This investigation was supported by grant CA31845 awarded by the National Cancer Institute, DHHS and funds from Eli Lilly and Company.

References and Notes

1. Part V in a series on macroexpansion methodology taken in part from the Ph.D. thesis of S. McN. Sieburth, Harvard University, 1982. For previous studies, see: a) Wender, P.A.; Sieburth, S. McN. *Tetrahedron Lett.* **1981**, *22*, 2471; b) Wender, P.A.; Sieburth, S. McN.; Petraitis, J.J.; Singh, S.K. *Tetrahedron* **1981**, *37*, 3967; c) Wender, P.A.; Holt, D.A.; Sieburth, S. McN. *J. Am. Chem. Soc.* **1983**, *105*, 3348; d) Wender, P.A.; Holt, D.A., *J. Am. Chem. Soc.* **1985**, *107*, 0000.

2. a) For a recent study on anion accelerated rearrangements and lead references, see: Denmark, S.E.; Harmata, M.A. *J. Am. Chem. Soc.* **1982**, *104*, 4972 and indem., *Tetrahedron Lett.* **1984**, *25*, 1543. b) For a theoretical overview on substituent induced rate changes, see: Carpenter, B.K. *Tetrahedron* **1978**, *34*, 1877.

3. Evans, D.A.; Golob, A.M. *J. Am. Chem. Soc.* **1975**, *97*, 4765; Evans, D.A.; Baillargeon, D.J.; Nelson, J.V. *J. Am. Chem. Soc.* **1978**, *100*, 2242.

4. Ireland, R.E.; Mueller, R.H.; Willard, A.K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

5. Satisfactory NMR, IR and MS data and either elemental or exact mass analyses were obtained on purified samples of all new compounds.

6. Brown, C.A., *J. Org. Chem.* **1974**, *39*, 3913.

7. The presence of two distinct vinyl groups on the "lower half" of **11** would be expected to result in the formation of two different Cope products assuming that free rotation about the C₃-C₄ bond is facile. This assumption is reasonable when one considers the calculated and measured rotational barriers of 2,3-dimethylbutane (3.1-4.3 kcal/mol and 5.0 kcal/mol for the anti-gauche and gauche-gauche barriers, respectively; Osawa, E.; Shirahama, H.; Matsumoto, T., *J. Am. Chem. Soc.* **1979**, *101*, 4824.

8. Authentic samples of **14** and **15** were prepared as follows:

14: Treatment of δ -valerolactone with one equivalent each of n-butyl lithium and methyllithium resulted in an acyclic diol which was selectively dehydrated and hydrogenated to yield 5-methyl-1-nonanol. Tosylation and cyanide displacement followed by t-butyllithium addition and hydrolysis gave ketone **14**.
15: 1-Iododecane was treated with potassium cyanide in DMF. Addition of t-butyllithium to the nitrile product and hydrolysis of the resulting imine gave **15**.

9. For a related comparison and lead references, see: Lutz, R.P.; Berg, H.A.J., *J. Org. Chem.* **1980**, *45*, 3915.

10. The charge densities in silyl enol ethers and metal enolates have been estimated from ¹³C measurements. See House, H.O.; Prabhu, A.V.; Phillips, W.V. *J. Org. Chem.* **1976**, *41*, 1209; Letendre, L.J., Doctoral Thesis, Harvard University, 1981; and references therein.

11. The reaction rate, as defined by conversion of starting material, was followed by GC and measured against an adamantane internal standard.

12. Compound **16** was prepared from the adduct of 2-chloropropionyl chloride with 1-lithio-3-buten-1-yne using recently developed reduction-rearrangement chemistry (ref. 1c). Oxidation of the intermediate alcohol gave tetraenone **19**. Reaction of **19** with t-butyllithium gave **16** in low yield.

