

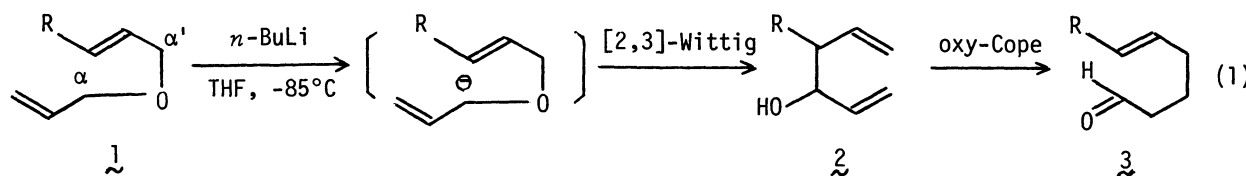
APPLICATIONS OF THE TANDEM [2,3]-WITTIG-OXY-COPE REARRANGEMENT TO SYNTHESSES OF  
*exo*-BREVICOMIN AND OXOCRINOL. THE SCOPE AND LIMITATION OF THE SIGMATROPIC  
 SEQUENCES AS A SYNTHETIC METHOD FOR  $\delta,\epsilon$ -UNSATURATED KETONES

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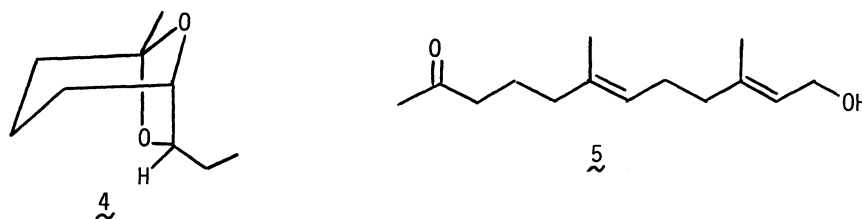
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The synthetic utility of the title sigmatropic sequence is illustrated in the syntheses of (*E*)-6-nonen-2-one, a precursor of *exo*-brevicomine, and oxocrinol. The scope and limitation of this sequence as a synthetic method for  $\delta,\epsilon$ -unsaturated ketones are also discussed.

Recently we have reported the tandem [2,3]-Wittig-oxy-Cope rearrangement which permits ready access to (*E*)- $\delta,\epsilon$ -unsaturated aldehydes (eq 1).<sup>1)</sup> This sequence possesses synthetically valuable features; (a) the [2,3]-Wittig process of the type of  $\downarrow$  affords the single regioisomer of 1,5-dien-3-ol ( $\underline{2}$ ) arising from the regiospecific lithiation on the less substituted allylic moiety ( $\alpha$ )<sup>2)</sup> and (b) the oxy-Cope process of  $\underline{2}$ , when carried out in refluxing decane,<sup>3)</sup> proceeds with a high *E* selectivity (90-95%), irrespective of the stereochemistry (threo/erythro) of  $\underline{2}$ .

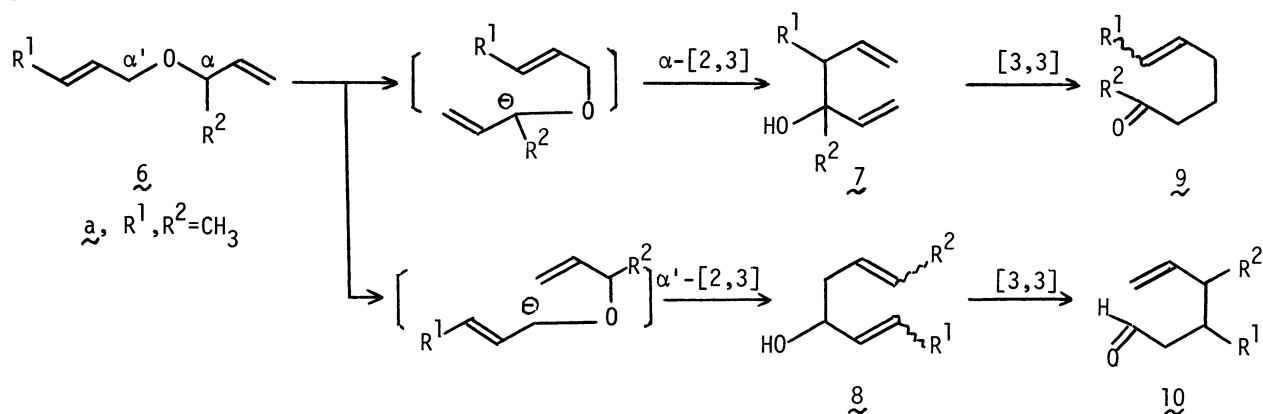


To expand the synthetic scope of the sigmatropic sequence, our efforts have now been directed toward its extension to preparations of  $\delta,\epsilon$ -unsaturated ketones which are frequently found in natural products and synthetic intermediates thereof. This communication not only illustrates the synthetic utility of the present sequence in the syntheses of *exo*-brevicomine ( $\underline{4}$ ) and oxocrinol ( $\underline{5}$ ) but also describes its scope and limitation as a synthetic method for  $\delta,\epsilon$ -unsaturated ketones.



In order to establish the feasibility of such an approach to  $\delta,\epsilon$ -enones (see Scheme I), the two questions must be elucidated whether the regiospecific formation of the desired  $\alpha$ -[2,3]-product (7) is possible in the Wittig process of  $\alpha,\gamma'$ -disubstituted substrates (6) and whether a high *E* selectivity can be obtained in the oxy-Cope process of 7. Thus, to probe these points, we first

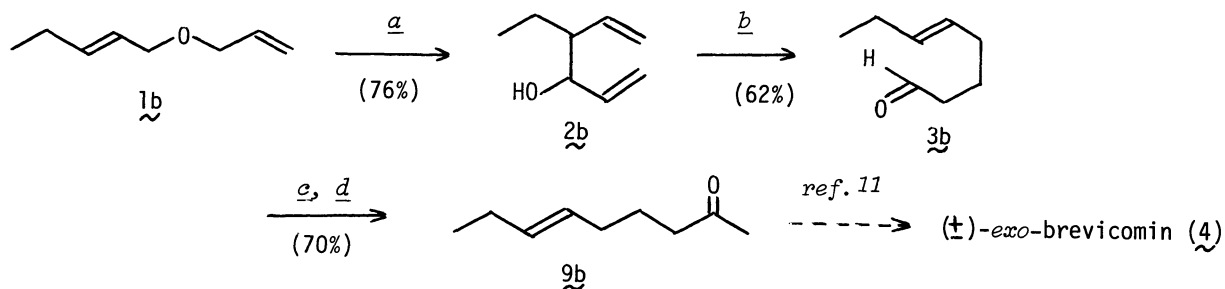
Scheme I



examined the regiochemistry of the Wittig process of 6a.<sup>4)</sup> Treatment of 6a with a hexane solution of butyllithium in various solvents at  $-85^\circ\text{C}$  gave regioisomeric mixtures<sup>5)</sup> of 7a and 8a in 82-93% combined yields with the ratios ranging from 66 : 34 (THF) to 77 : 23 (*N,N,N',N'*-tetramethylethylenediamine (TMEDA)). The 66 : 34 mixture was then refluxed in decane<sup>3)</sup> giving ketone 9a<sup>6)</sup> in 58% isolated yield, surprisingly, *without detectable contamination with aldehyde 10a to be derived from 8a*.<sup>7)</sup> Unfortunately, however, the *E/Z* ratio of 9a was found to be 77 : 23 (by vpc assay).<sup>6)</sup> Thus these results suggest the general scope of the present approach to  $\delta,\epsilon$ -enones: the tandem sequence performed on the type of 6, despite the regiochemical complication in the Wittig process, eventually affords the corresponding ketone (9) as the sole isolable carbonyl product in a moderate yield with a lower *E* selectivity than previously reported for  $\delta,\epsilon$ -enals (3).

With the scope and limitation of the present approach to  $\delta,\epsilon$ -unsaturated carbonyl compounds in mind, we next set out to illustrate its potential in the area of natural product synthesis. As an example, we carried out the stereocontrolled formal synthesis of ( $\pm$ )-*exo*-brevicomins (4) identified as the principal aggregation pheromone of *Dentroctonus brevicomis*<sup>8)</sup> (see Scheme II). It should be noted here that application of the sequence depicted in Scheme I, though more straightforward, was avoided in view of the expected lower stereoselectivity. The standard Wittig process of 1b ( $R = \text{CH}_2\text{CH}_3$ ) (bp  $60-62^\circ\text{C}/16 \text{ mmHg}$ )<sup>4)</sup> afforded a diastereomeric mixture of 2b (bp  $56-60^\circ\text{C}/10 \text{ mmHg}$ )<sup>4)</sup> which was then refluxed in decane giving aldehyde 3b.<sup>9)</sup> Nmr analysis confirmed that the geometry of 3b was *E* (>95%).<sup>9)</sup> The reaction of 3b with methyllithium followed by oxidation gave the desired (*E*)-6-nonen-2-one (9b)<sup>10)</sup> which has been reported to serve as a precursor of *exo*-brevicomins (4).<sup>11)</sup>

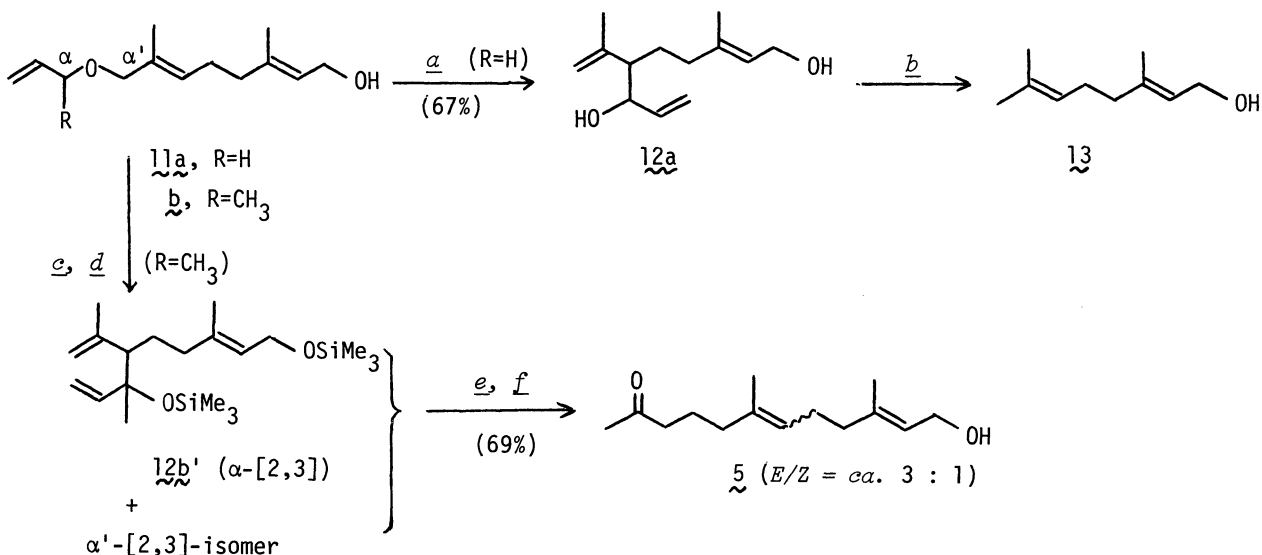
## Scheme II



a: *n*-BuLi, THF,  $-85^{\circ}\text{C}$ ; b: reflux, decane, 45 h; c: MeLi, THF; d:  $\text{CrO}_3 \cdot \text{pyr} \cdot \text{HCl}$  (PCC),  $\text{CH}_2\text{Cl}_2$

To exemplify further our approach, we also carried out the synthesis of oxocrinol (**5**) isolated from a Mediterranean algae<sup>12)</sup> (see Scheme III). By taking the regio- and stereochemical aspects into account, we initially attempted the sequence represented by eq 1 starting with the bis-allylic ether (**11a**)<sup>13)</sup> of which the Wittig process actually raised no problem of regioselectivity; however, the oxy-Cope process of **12a**<sup>4)</sup> failed, instead leading to the retro-ene product (**13**). Thus we applied the sequence depicted in Scheme I to ether **11b**.<sup>13)</sup> Treatment of **11b** with a hexane solution of butyllithium in TMEDA followed by quenching the chlorotrimethylsilane afforded a 3 : 1 mixture<sup>4)</sup> of the silyl ether (**12b'**) and its  $\alpha'$ -[2,3]-counterpart. Thermolysis of the mixture followed by column chromatography (silica gel) gave a geometric mixture of the desired ketone **5**<sup>14)</sup> in 69% overall yield from **11b**. The nmr spectrum of **5** indicated that the *E/Z* ratio was ca. 3 : 1.<sup>14)</sup>

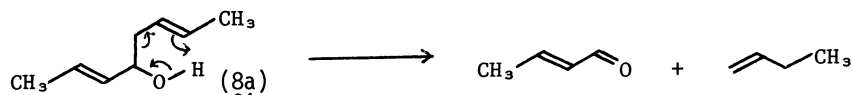
## Scheme III



a: *n*-BuLi, THF,  $-85^{\circ}\text{C}$ ; b: reflux, decane, 45 h; c: *n*-BuLi, TMEDA,  $-78^{\circ}\text{C}$ ; d:  $\text{Me}_3\text{SiCl}$  (3 equiv);  
e:  $180^{\circ}\text{C}$ , neat,  $\text{N}_2$ ; f:  $\text{SiO}_2$ , hexane/ether.

## References

- 1) K. Mikami, S. Taya, T. Nakai, and Y. Fujita, *J. Org. Chem.*, **46**, 5447 (1981).
- 2) T. Nakai, K. Mikami, S. Taya, and Y. Fujita, *J. Am. Chem. Soc.*, **103**, 6492 (1981).
- 3) Applications of other oxy-Cope procedures (thermolysis in *N*-methylpyrrolidone and the anionic oxy-Cope and the siloxy-Cope modifications) to 2a (R=CH<sub>3</sub>) resulted in lower *E* selectivities ranging from 67% to 79% (see ref 1).
- 4) This compound showed spectral (ir and nmr) data in accord with the assigned structure.
- 5) Bp 52-60°C/14 mmHg; vpc (PEG 20 M, 100°C),  $t_R$ =22.9, 25.7, 69.3 min; the diastereomers of 7a and 8a were separated by preparative vpc and each exhibited spectral (ir and nmr) properties in accord with the assigned structure.
- 6) Isolated by column chromatography (SiO<sub>2</sub>, hexane/ether); ir (film), 1720, 970, 702 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>, TMS),  $\delta$  1.25-1.78 (m, 5H), 1.78-2.20 (m, 2H), 2.03 (s, 3H), 2.37 (t, J=4.8 Hz, 2H), 5.20-5.73 (m, 2H); vpc (PEG 20M, 120°C),  $t_R$ =19.8, 21.2 min (77 : 23).
- 7) The absence of 10a in the product mixture is reasonably explained by the retro-ene cleavage of 8a depicted below. It is well-known that the oxy-Cope rearrangement is often accompanied by this type of side reaction: E. N. Marvell and W. Whalley, "Chemistry of The Hydroxy Group", Vol. 1, ed. by S. Patai, Interscience, New York, 1971, Chapter 13.



- 8) Isolation: R. M. Silverstein, R. G. Brownlee, T. E. Bellas, D. L. Wood, and L. E. Browne, *Science*, **159**, 889 (1968). For recent syntheses, see: K. Mori, "The Total Synthesis of Natural Products," Vol.4, ed. by J. ApSimon, John Wiley, New York, 1981, p.69-74.
- 9) Ir (film), 1725, 970 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>),  $\delta$  9.92 (br.s, 1H) for CHO. Decoupling experiment indicated that 3b was geometrically homogeneous and its coupling constant between the olefinic protons was 15.0 Hz.
- 10) Isolated by column chromatography (SiO<sub>2</sub>, hexane/ether); ir (film), 1720, 970 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>),  $\delta$  0.97 (t, J=7.2 Hz, 3H), 1.13-2.20 (m, 6H), 2.00 (s, 3H), 2.33 (t, J=7.2 Hz, 2H), 5.07-5.67 (m, 2H); vpc (PEG 20M, 130°C),  $t_R$ =26.4 min; the data is consistent with the reported one (ref 11).
- 11) J. Knolle and J. J. Schäfer, *Angew. Chem. Int. Ed. Engl.*, **14**, 758 (1975).
- 12) E. Fattorusso, S. Magno, L. Mayol, C. Santacroce, D. Sica, V. Amico, G. Oriente, M. Piattelli, and C. Tringali, *Tetrahedron Lett.*, **1976**, 937. For the first total synthesis, see: T. Kato, H. Takayanagi, T. Uyehara, and Y. Kitahara, *Chem. Lett.*, **1977**, 1009.
- 13) Ethers 11a and 11b were prepared from (*E*)-8-bromogeranyl acetate via the Williamson reaction using the sodium salt of the corresponding allylic alcohol (2 equiv); 11a, 63%; 11b, 67%; bp 107-112°C/0.01 mmHg.
- 14) Ir (film), 3400 (OH), 1720 cm<sup>-1</sup> (C=O); nmr (CCl<sub>4</sub>),  $\delta$  1.58 (s, 2.25H), 1.64 (s, 3.75H), 2.02 (s, 3H), 2.30 (t, J=7.0 Hz, 2H), 1.67-2.50 (m, 9H), 3.98 (d, J=7.0 Hz, 2H), 5.06 (br. t, J=6.0 Hz, 1H), 5.30 (br. t, J=7.0 Hz, 1H): cf. R. B. Bates, D. M. Gala, and B. J. Gruner, *J. Org. Chem.*, **28**, 1086 (1963).

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