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CHIRALITY TRANSMISSION VIA TANDEM SIGMATROPIC REARRANGEMENT REGIO- AND STEREOCHEMICAL OUTCOME IN THE TANDEM WITTIG—OXY-COPE SEQUENCE OF ALLYL *cis*-5-METHYL-2-CYCLOHEXENYL ETHER

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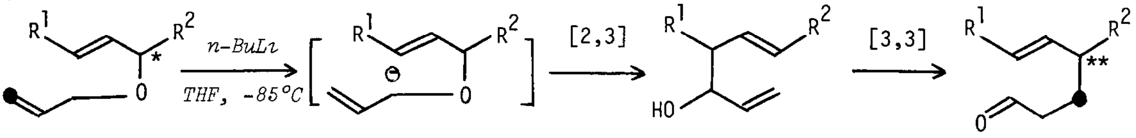
The titled sigmatropic sequence proceeds with complete net retention of configuration, and surprisingly, suffers from a regiochemical complication arising mainly from the unexpected competition of the [2,3]- vs. [1,2]-shift in the Wittig process, as revealed by the use of the deuterium-labeled substrate

The regio- and stereochemistry of carbon-carbon bond formations with allylic substrates have received much attention from physical and synthetic organic chemists[1] Recently we have developed a novel "net S_N2 displacement" process[2] which involves the regiospecific [2,3]-Wittig rearrangement[3] of acyclic bis-allylic ethers followed by the oxy-Cope rearrangement (Scheme I) The sigmatropic sequence is of synthetic value since the net effect allows the allyloxy moiety to serve as a homoenolate ion equivalent, providing a convenient entry to δ,ε-unsaturated carbonyl compounds

Scheme I



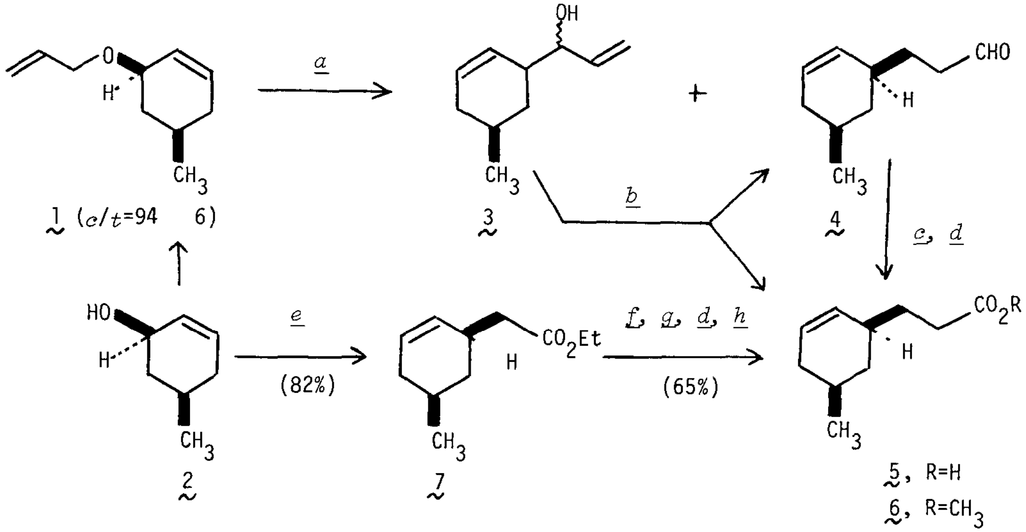
While the sigmatropic sequence is attractive in terms of the regioselectivity, many questions concerning stereochemical courses must, of course, be elucidated Particularly, the question how effectively the substrate chirality (*) could be transmitted to the product chirality (**) (see Scheme I) is crucial for its application in synthesis In view of the suprafacial character of [2,3]- and [3,3]-sigmatropic shifts in principle, it is highly likely that the present sequence achieves otherwise difficult "net *syn*-S_N2-displacement "[4] In order to establish this point unambiguously, we have now examined the stereochemistry of the sigmatropic sequence by choosing allyl *cis*-5-methyl-2-cyclohexenyl ether (1) as a stereochemically defined substrate[5] (see Scheme II).

Substrate **1** (*cis/trans*= 96:4)6) was prepared via etherification of (±)-*cis*-alcohol **2**.7) The Wittig rearrangement of **1** under the standard condition gave a stereoisomeric mixture of **3**8) in 62% isolated yield, along with 14% of the abnormal product (**4**).9,10) At this stage, any attempts were not made to assign the stereochemistry of these products. After separation of **3** from **4** by column chromatography (silica gel), the stereomixture of **3** was subjected to the anionic oxy-Cope rearrangement11,12) to afford aldehyde **4**9) and its oxidation product (**5**)13,14) in 85% combined yield. The stereochemistry of the oxy-Cope product(s) was determined to be >95% *cis* through nmr and vpc comparisons of its methyl ester (**6**)15) with an authentic *cis*-isomer of **6** (>95% *cis*) which was independently prepared via the orthoester Claisen rearrangement16) followed by the Arndt-Eistert homologation sequence as shown in Scheme II. It should be emphasized here that the *cis* configuration of **7** (and thus the authentic **6**) is well secured because the Claisen rearrangement has been well established to proceed with complete retention of configuration.17) In a similar manner, the abnormal product (**4**) formed in the Wittig process was also found to possess exclusively the *cis* configuration.

The stereochemical outcome clearly indicates that the sigmatropic shifts involved in the present sequence, including the unusual one directly leading to **4**, proceed without loss of configurational purity to afford the corresponding *syn*-product. The unexpected formation of **4** in the Wittig process, however, raised the question whether the present cyclohexenyl substrate, like acyclic ones,3) undergoes the rearrangement exclusively in the [2,3]-sigmatropic fashion. Thus, to probe this point, we have next ascertained the regiochemistry of the Wittig process using the deuterium-labeled substrate (**1**-α-*d*)18)(see Scheme III). The Wittig process of **1**-α-*d* under identical conditions gave, after chromatographic separation, alcohol **3**-*d* and aldehyde **4**-*d* in 62% and 14% yield. Careful nmr analysis19) indicated that **3**-*d* was a 66:34 mixture of **3γ** and **3α** whereas **4**-*d* was the sigle regioisomer (**4α**) without detectable contamination with **4γ**. The somewhat unexpected regiochemical outcome reveals that the [2,3]-Wittig shift of the present substrate leading to **3γ** does compete considerably with the [1,2]- (**3α**) and [1,4]-shift (**4α**) in contrast to the exclusive [2,3]-shift observed with acyclic substrates.3)

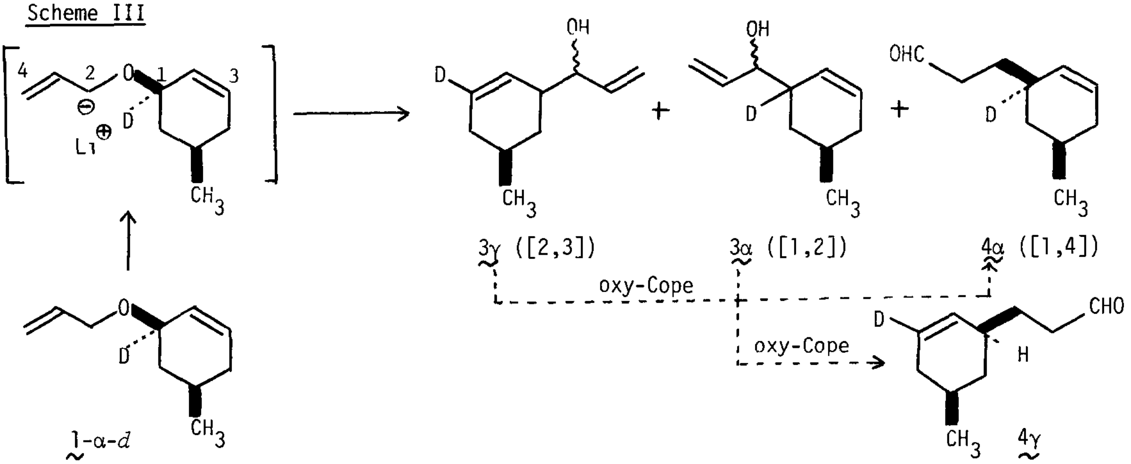
In summary, combination of the regio- and stereochemical outcomes outlined here suggests that the present sigmatropic sequence of unsymmetrical cyclohexenyl systems like **1**-α-*d* would ventually lead to a mixture of "net *syn*-S_N2 and *syn*-S_N2' displacements." Noteworthy is the regio- and stereochemical outcomes of the unusual [1,4]-shift which are exactly the same as

Scheme II



a *n-BuLi, THF, -85°C,* *b* *KH, 18-Crown-6, DME, reflux,* *c* *Ag_2O, aq EtOH, reflux,* *d* *CH_2N_2, Et_2O,* *e* *$CH_3C(OEt)_3$, 2,6-diemthylphenol, 190°C,* *f* *KOH, aq EtOH, reflux,* *g* *$SOCl_2$, PhH, reflux,* *h* *Ag_2O, aq MeOH, 60°C*

Scheme III



those of the tandem [2,3]-Wittig—oxy-Cope sequence In spite of the serious drawback to the synthetic utility of the present sequence, the results of this work point out mechanistically interesting aspects of sigmatropic rearrangements concerned We are now investigating not only the detailed mechanism of the Wittig process of cyclohexenyl ether systems but also the chirality transmission within acyclic chiral frameworks

References and Notes

1) For an excellent review, see R M Magid, *Tetrahedron*, **36**,1901 (1980)

2) K Mikami, S Taya, T Nakai, and Y Fujita, *J Org Chem* , **46**, 5447 (1981)

3) T Nakai, K Mikami, S Taya, and Y Fujita, *J. Am Chem Soc.*, **103**, 6492 (1981)

4) For previous examples of "net *syn*-S_N2 displacement", see (a) Pd-mediated method B M Trost and T R Verhoeven, *J Org Chem* , **41**, 3215 (1976), J C Fiaud and J L Malleron, *Tetrahedron Lett* , **22**, 1399 (1981),(b) double Claisen-Cope sequence A F Thomas and G Ohloff, *Helv Chim Acta*, **53**, 1145 (1970)

5) This type of cyclohexenyl system has been employed most extensively for regio- and stereochemical studies on S_N2 vs S_N2' and often called the Goering's sytem (*cf* ref 7)

6) Yield, 84%, bp 30-35°C/0 1 mmHg, nmr (CCl_4, TMS), δ 6 10-5 57 (m, 3H), 5 33-4 95 (m, 2H), 4 07-3 77 (m, 3H), 2 17-0 73 (m, 5H), 0 95 (d, J=6 0 Hz, 3H), vpc (PEG 20M, 150°C), t_R= 9 1 and 10 4 (4 96)

7) H L Goering, T D Nerrit, E F Silversmith, *J Am Chem Soc* , **77**, 4042 (1955)

8) Bp 50-55°C/0 1 mmHg, ir (film), 3360 cm^{-1}(OH), nmr (CCl_4), δ 6 13-5 47 (m, 3H), 5 40-5 07 (m, 2H), 4 10-3 80 (m, 1H), 2.60-0 07 (m, 7H), 1 00 (d, J=6 0 Hz, 3H)

9) Bp 45-50°C/0 1 mmHg, ir (film), 1725 cm^{-1}(C=O), nmr (CCl_4), δ 9 73 (t, J=1 5 Hz, 1H), 5 77-5 30 (m, 2H), 2 40 (t,d, J=6 8 and 1 5 Hz, 2H), 2 50-0 40 (m, 8H), 1 00 (d, J=6 0 Hz, 1H)

10) Control experiment showed that **4** was not formed from **3** via the in situ oxy-Cope rearrangement, but directly from **1** via an unusual shift during the carbanion rearrangement

11) D A Evans and A. M Golob, *J. Am Chem Soc* , **97**, 4765 (1975)

12) In the absence of the crown ether, the oxy-Cope rearrangement not only required a longer time (50 h) for completion but also decreased the combined yield to 72% The attempted siloxy-Cope rearrangement resulted in the quantitative recovery of the silyl ether of **3**

13) Control experiment demonstrated that aldehyde **4** once formed was considerably oxidized (presumably with air) under the anionic oxy-Cope conditions We separately found that treatment of pentanal under identical conditions for 10 h afforded pentanoic acid in 92%

14) The ir and nmr spectra of this compound were in agreement with the assigned structure

15) Bp 55-57°C, ir (film), 1740 cm^{-1}(C=O), nmr (CCl_4), δ 5 73-5 27 (m, 2H), 3.60 (s, 3H), 2 33-0 60 (m, 8H), 2.27 (t, J=7 0 Hz, 2H), 0 95 (d, J=6 0 Hz, 3H), vpc (SE 30, 150°C), t_R=11 1 min

16) W S Johnson, L Werthemann, W R Bartlett, T J Li, D J Faulkner, and M R Petersen, *J Am Chem Soc* , **92**, 741 (1970), **7** ir (film), 1738 cm^{-1}(C=O), nmr (CCl_4), δ 5 77-5 30 (m, 2H), 4 05 (q, J=7 0 Hz, 2H), 2 80-0 60 (m, 8H), 1 27 (t, 3H), 0 95 (d, J=6 0 Hz, 3H)

17) For examples of cyclohexenyl systems, see R K Hill and A G Edwards, *Tetrahedron Lett* , **1964**, 3239, R K Hill and M E Synerholm, *J Org Chem* , **33**, 925 (1968), also see ref 4b

18) Prepared from **2**-α-*d* which was prepared via reduction of 5-methyl-2-cyclohexenone with $LiAlD_4$ according to the Goering's procedure (ref 7)

19) The regioisomeric ratio was calculated from the nmr integral of the olefinic peaks relative to that of the peak due to the methin α to the hydroxy group for **3**-*d* and realtive to that of the formyl peak for **4**-*d* Thus the errors inherent in this method are of the order of at least ± 5 0%

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