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Unexpected stereoselectivity in the anionic oxy-Cope rearrangement of acyclic enol ethers

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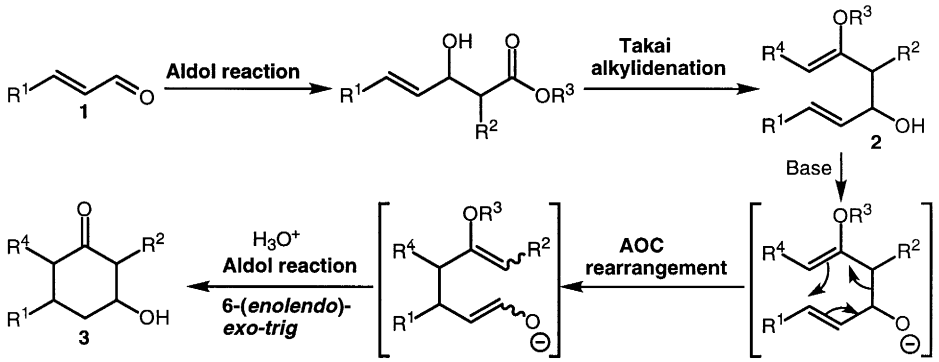
Abstract

The anionic oxy-Cope rearrangement of alkoxides derived from (1*E*,5*Z*)-4-methyl-5-alkoxy-1-phenyl-1,5-heptadien-3-ols proceeds via a chair-like transition state with the oxyanion axial, even when there is a 3,4-*syn*-relationship between the methyl group and the oxyanion so that both groups are axial in the transition state of the [3,3]-sigmatropic rearrangement. We believe that this is the first example of chelation control in the AOC rearrangement. The reaction forms the basis of a stereoselective synthesis of β-hydroxycyclohexanones containing four chiral centres.

Keywords: rearrangements; stereocontrol; chelation; cyclohexanones.

We have recently developed a general method for the stereocontrolled synthesis of β-hydroxycyclohexanones from α,β-unsaturated aldehydes **1** using four key reactions:[1] the aldol reaction, Takai alkylidenation,[2] anionic oxy-Cope (AOC) rearrangement of acyclic enol ethers and intramolecular aldol reaction (Scheme 1). By rearranging and cyclising alcohols **2** (R^2=H), we made racemic β-hydroxycyclohexanones **3** with up to three chiral centres in a stereocontrolled way.



Scheme 1.

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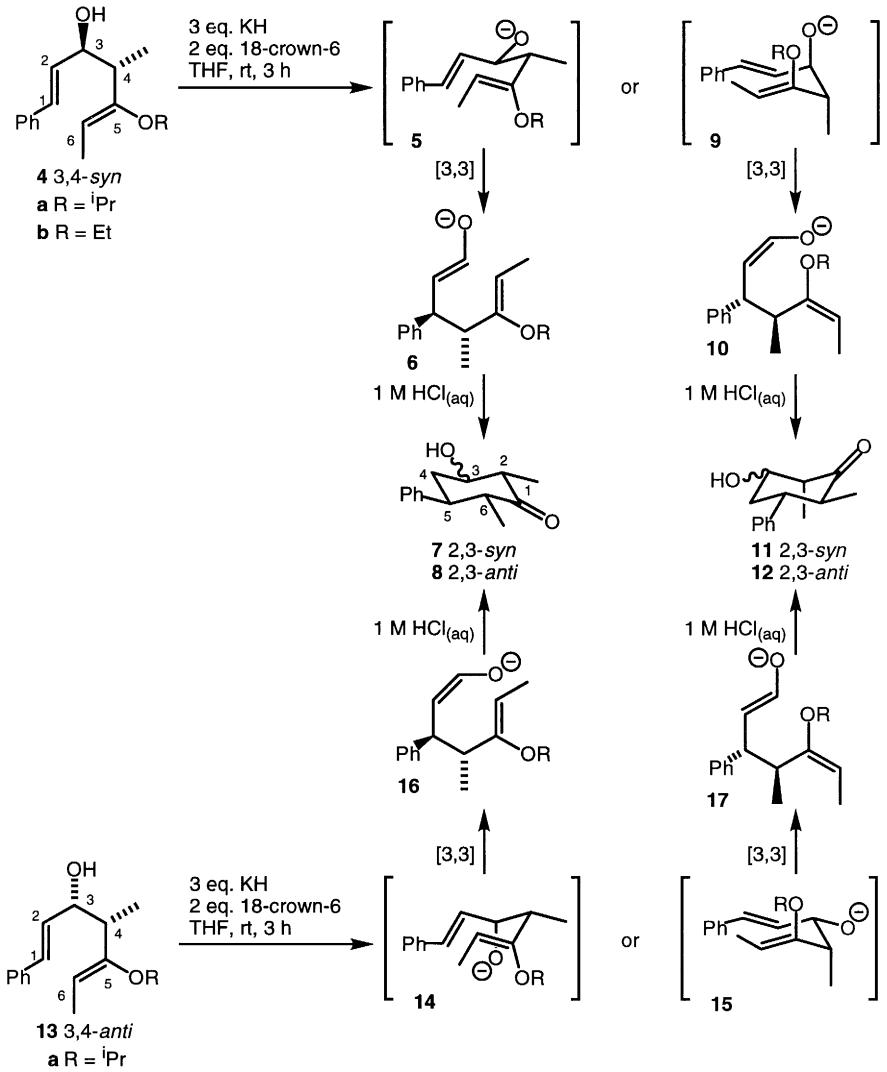
We now report the synthesis of β-hydroxycyclohexanones **3** (R^2=Me) with four chiral centres and the surprising and unprecedented stereoselectivity that results from the presence of the enol ether in alcohols **2** (R^2=Me).

The stereochemical outcome of the AOC rearrangement of acyclic compounds depends on the orientation of the oxyanion in the chair-like transition state.[3–6] In the absence of steric effects, there is little difference in energy between the axial and equatorial orientations of the oxyanion.[3,4] However, faithful transfer of chirality occurs when the oxyanion at C-3 and a substituent at C-4 of the 1,5-hexadien-3-oxide system are *syn* to each other, because both substituents lie equatorial in the transition state.[5,6] We concluded from this precedent that 3,4-*syn* alcohol **4** would rearrange exclusively via reacting conformation **5** to give *Z*-enol ether **6**, which would cyclise in acid to give cyclohexanones **7** and **8** (Scheme 2). We reasoned that electrostatic repulsion between the oxyanion and the enol ether oxygen atom would combine with steric factors to completely disfavour reacting conformation **9**, which leads to the formation of *E*-enol ether **10** and ultimately to cyclohexanones **11** and **12**. On the other hand, we expected 3,4-*anti* enol ether **13** to rearrange by both of the two chair-like conformations **14** and **15** to give



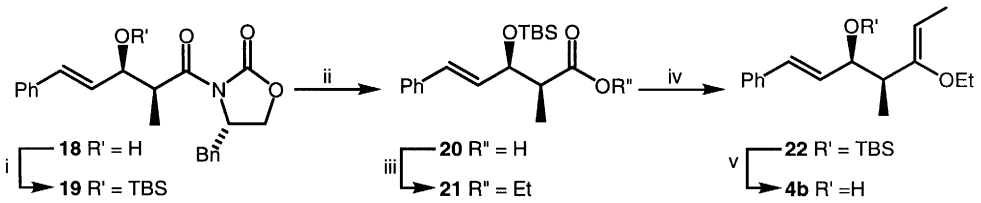
Scheme 2.

enolates **16** and **17**. When quenched with aqueous acid, enolate **16** should cyclise to give cyclohexanones **7** and **8**, while enolate **17** should give cyclohexanones **11** and **12**.

The 5,6-*anti* stereochemistry in cyclohexanones **7**, **8**, **11** and **12** arises from a chair-like transition state in the AOC rearrangement. Stereoselectivity in the intramolecular aldol reaction determines the configuration at C-3 and the stereochemistry at C-2 should arise stereospecifically from the enol ether geometry in enolates **6**, **10**, **16** and **17** (assuming a chair-like transition state).

First we synthesised, using our standard route (Scheme 1), an inseparable 1:1 mixture of 3,4-*syn* and 3,4-*anti* alcohols **4a** and **13a** in 33% yield from isopropyl propionate. The mixture underwent AOC rearrangement followed by acid-induced cyclisation to give a 7:8:3:1 mixture of cyclohexanones **7**, **11** and **12** and a minor isomer in 100% crude yield (reaction conditions shown in Scheme 2). Flash chromatography gave the pure cyclohexanones in 56% yield.

The 3,4-*syn* enol ether **4b** was then synthesised unambiguously from imide **18** (Scheme 3).[7] Alcohol **18** was protected as the *tert*-butyldimethylsilyl ether **19** and the chiral auxiliary was removed[8] to give acid **20**. Esterification under Mitsunobu[9] conditions proved superior to methods based on activation of the carboxylic acid. Alkylidenation[2] of the resulting ester **21** gave only the *Z*-enol ether **22** (*Z*:*E* >98:2), which was deprotected to give the desired alcohol **4b**.



Scheme 3. Reagents and conditions: (i) TBSCl, $^{i}Pr_2NEt$, DMF, rt, 17 h (93%); (ii) (a) H_2O_2, LiOH, THF–H_2O (10:1), 0°C to rt, 4 h; (b) $Na_2SO_{3(aq)}$ (83%); (iii) PPh_3, DEAD, EtOH, −40°C then rt, 17 h (79%); (iv) $TiCl_4$, TMEDA, Zn, $PbCl_2$, $MeCHBr_2$, THF, rt, 14 h (81%); (v) Bu_4NF, THF, 4 Å MS, rt, 1 h (63%)

To our surprise, alcohol **4b** underwent AOC rearrangement/aldol reaction to give an 8:3:1 mixture of cyclohexanones **11** and **12** (resulting from reacting conformation **9**!) and a minor isomer in 64% yield after work-up. Cyclohexanones **11** and **12** arise from cyclisation of aldehyde **23b** (Fig. 1). We have previously shown that the R group has little effect on the stereochemical outcome of such cyclisations;[1] consequently, **11** and **12** are formed in the same 8:3 ratio by cyclisation of **23a**, produced by the rearrangement of the 1:1 mixture of alcohols **4a** and **13a**. However, the overall product composition is very different for the two rearrangements, showing that the ratio of diastereomeric cyclohexanones is not the result of epimerisation. This is completely supported by our previously-reported, deuterium-labelling experiments.[1]

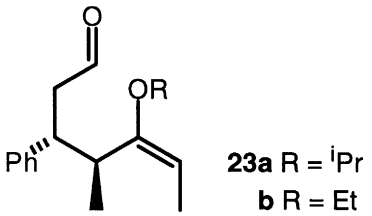


Fig. 1.

Cyclohexanone **7** is one of the major products from AOC rearrangement/cyclisation of the 1:1 mixture of alcohols **4a** and **13a**, and so it is clear that the 3,4-*anti* isomer **13a** also rearranges predominantly by a reacting conformation **14** that has an axial oxyanion.

We propose that the potassium cation is chelated between the oxyanion and the oxygen atom of the enol ether during the AOC rearrangement. Thus, reacting conformation **9** would be more properly represented

as chelate **24** (Fig. 2). The pre-ordering of the ground state may accelerate the reaction (even if the oxyanion is less naked as a result). Recently, a similar chelation model has been used to explain the rapid AOC rearrangement that occurs when an oxyanion is in a 1,3-relationship with a methoxy substituent of an aromatic ring participating in the [3,3] sigmatropic rearrangement.[10]

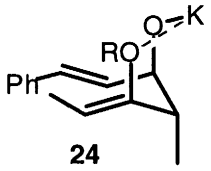


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Fig. 2.

The relative stereochemistry of cyclohexanones **7**, **11** and **12** was assigned from the coupling constants in their ^{1}H NMR spectra (Fig. 3). $J_{5,6}$ is 11–13 Hz in each case, confirming the 5,6-*anti* stereochemistry. H^3 (δ_H 4.12) of cyclohexanone **11** shows a large axial–axial coupling (10 Hz) and two smaller axial–equatorial couplings (5 Hz), showing that the methyl group is axial and the hydroxyl group is equatorial. $J_{2,3}$ is 3 Hz for the cyclohexanone that is assigned as **7** and 2 Hz for the cyclohexanone that is assigned as **12**; in each case, H^3 shows no axial–axial coupling so the hydroxyl group is axial. Although axial–equatorial couplings are usually 1 Hz larger than equatorial–equatorial couplings, we cannot be certain which of the two cyclohexanones has structure **7** and which has structure **12** from the coupling constants alone. However, since cyclohexanone **7** is a major component of one product mixture and completely absent from the other, the reverse assignment can be ruled out on mechanistic grounds: enolates **10** and **17** produce the same aldehyde **23**, which cyclises to give cyclohexanones **11** and **12**, so the ratio of **11**:**12** should be independent of the ratio of alcohols **4**:**13** used (R has little effect on the stereochemical outcome of such cyclisations[1]).

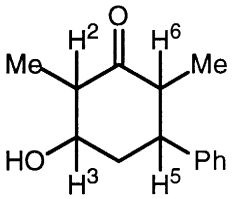

Fig. 3.

Prior to our work, only five examples of AOC rearrangement of enol ethers had been reported;[11,12] all were cyclic, with the orientation of the oxyanion controlled by the ring(s) present in the substrates, and only two had our 1,3-relationship between the enol ether and the oxyanion.[12] We are the first to report the significant effect of an enol ether oxygen atom on the stereochemical outcome of the AOC rearrangement.

Acknowledgements

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References

1. Rutherford, A. P.; Gibb, C. S.; Hartley, R. C. *Tetrahedron Lett.* **1998**, *39*, 685–688.
2. Takai, K.; Kataoka, Y.; Miyai, J.; Okazoe, T.; Oshima, K.; Utimoto, K. *Org. Synth.* **1996**, *73*, 73–84.
3. Paquette, L. A.; Maynard, G. D. *J. Am. Chem. Soc.* **1992**, *114*, 5018–5027.

4. Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444–1456.
5. Wei, S.-Y.; Tamooka, K.; Nakai, T. *Tetrahedron* **1993**, *49*, 1025–1042.
6. Greeves, N.; Lee, W.-M. *Tetrahedron Lett.* **1997**, *35*, 6445–6448, and references 10 and 11 therein.
7. Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
8. Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
9. Hughes, D. L. *Org. React. (NY)* **1992**, *42*, Ch. 2.
10. Seki, K.; Tooya, M.; Sato, T.; Ueno, M.; Uyehara, T. *Tetrahedron Lett.* **1998**, *39*, 8673–8676.
11. Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. *Tetrahedron* **1988**, *44*, 3139–3148; Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331–2332; Maleczka Jr., R. E.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 6538–6546.
12. Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576–4581; Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. *Tetrahedron* **1996**, *52*, 3075–3094.