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Stereoselectivity in the anionic oxy-Cope rearrangement of acyclic vinyl sulfides

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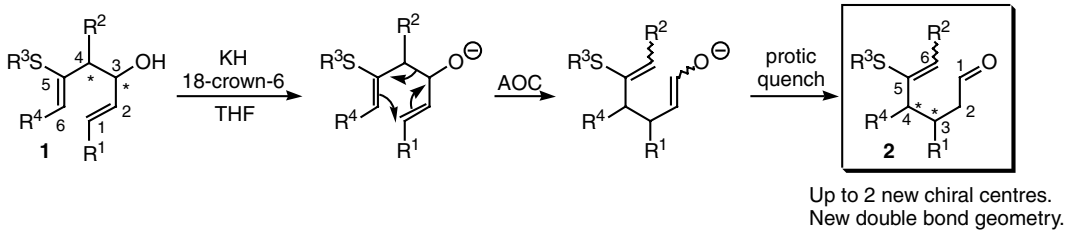
Abstract—Novel anionic oxy-Cope (AOC) rearrangements of substituted 5-alkylthio-1,5-dien-3-ols were studied. Aqueous quench gave new access to compounds with a nucleophilic vinyl sulfide and an electrophilic aldehyde in a 1,5 relationship. 3,4-*Anti* and 3,4-*syn* 1*E*,5*Z*-5-hexylthio-4-methyl-1-phenylhepta-1,5-dien-3-ols were synthesised separately by stereoselective aldol reaction, thioesterification and alkylidenation of the resulting thioesters to give *Z*-vinyl sulfides with $\geqslant 90\%$ stereoselectivity. AOC rearrangement of the 3,4-*syn* substrate gave predominantly 3,4-*syn* *Z*-vinyl sulfide while the 3,4-*anti* substrate gave mostly 3,4-*syn* *E*-vinyl sulfide, via chair-like transition states with the oxyanion pseudo-equatorial. Stereochemistry was assigned by NOE taking advantage of the conformational stability of the products.

Anionic oxy-Cope (AOC) rearrangement[1,2] (rapid [3,3]-sigmatropic rearrangement of an alkoxide generated by deprotonating a 1,5-dien-3-ol with a strong base) of cyclic substrates is commonly used in target-oriented synthesis[3] because it often proceeds with good stereocontrol[4] and complex frameworks can be accessed easily. On the other hand, stereocontrol in the AOC rearrangement of acyclic substrates remains a challenge since in the absence of steric factors, there is little difference in energy between a chair-like transition state with a *pseudo*-axial oxyanion and one with a *pseudo*-equatorial oxyanion.[5,6] In 1978, Evans et al. noted the particularly rapid AOC rearrangement of alkoxides derived from 4-phenylthio-1,5-dien-3-ols.[7] Recently, Paquette and co-workers have shown that 6-alkylthio groups have a similar effect, and have concluded from theoretical studies that the sulfur atom in these substrates stabilises an allyl anion favouring a stepwise mechanism for the reaction.[8] However, there are very few other examples of AOC rearrangement of alkylthio-substituted 1,5-dien-3-ols,[9] and none with an alkylthio group at C-5 (Scheme 1).[10]

We decided to investigate AOC rearrangement of 5-alkylthio-1,5-dien-3-ols **1** since they would give compounds **2** that have a useful combination[11] of a



Scheme 1.

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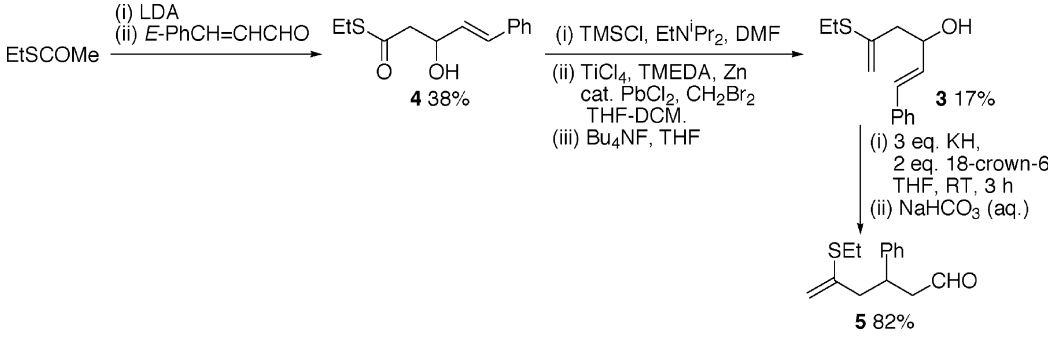
nucleophilic vinyl sulfide and an electrophilic aldehyde in a 1,5 relationship (Scheme 1). Unlike 6-alkylthio groups, 5-alkylthio groups would not be expected to promote a stepwise mechanism that could reduce stereocontrol and scramble the carbon framework, and the group might control the orientation of the oxyanion in the transition state of the rearrangement. Furthermore, spontaneous cyclisation of vinyl sulfides **2** would be expected to be slow, relative to the cyclisation of the more nucleophilic enol ethers that we have investigated previously.[12,13] Consequently, it might be possible to manipulate the two functional groups independently and determine the stereochemical outcome of rearrangement directly, without the complication of an intramolecular aldol reaction.

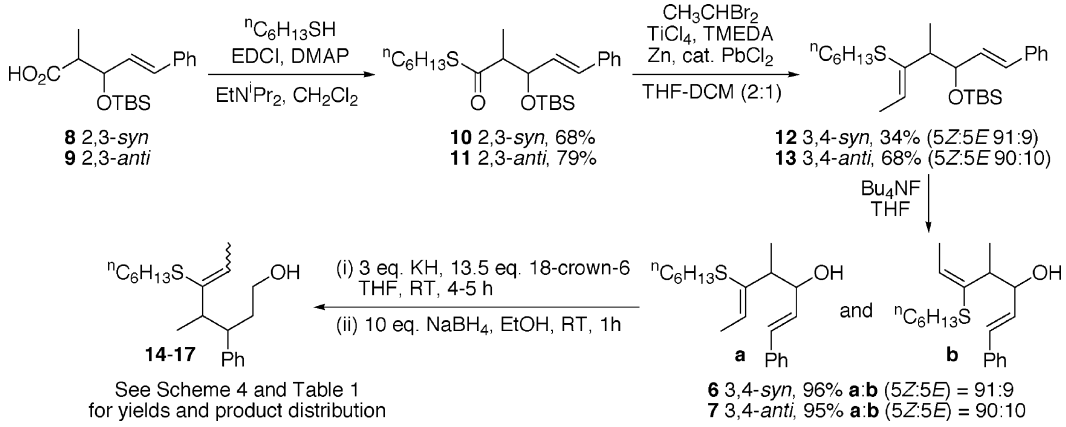
Initially, we synthesised a simple vinyl sulfide **3** to test the viability of the AOC rearrangement (Scheme 2). Aldol reaction between ethyl thioacetate and cinnamaldehyde gave thioester **4**. TMS protection, Takai methylenation[14] and deprotection then gave vinyl sulfide **3**. Treatment with base and aqueous quench gave a good yield of aldehyde **5**.[15] However, the vinyl sulfide decomposed over 48 h.

We then synthesised alcohol substrates **6** and **7** according to Scheme 3. 2,3-*syn* Carboxylic acid **8** was prepared using Evans' oxazolidinone chiral auxiliary as described previously.[12] 2,3-*anti* Carboxylic acid **9** was prepared by Heathcock's diastereoselective aldol reaction using 2,6-dimethylphenyl propionate,[16] then ester hydrolysis and silyl protection. Carboxylic acids **8** and **9** were converted into the corresponding thioesters **10** and **11**, which were then alkylidenated using Takai's procedure[14] to give predominantly *Z*-vinyl sulfides **12** and **13**. The *Z*-selectivity was $\geqslant$90%, but *E* and *Z* isomers could not be separated. Alkylidenations of thioesters are rare[17] and proceed with lower *Z*-stereoselectivity than alkylidenations of similar esters.[12] Deprotection then gave *Z*-vinyl sulfides **6a** and **7a**, contaminated by the corresponding 5*E*-isomers **6b** and **7b**. The *Z*-vinyl sulfide geometry of **6a** and **7a** was confirmed by NOE.

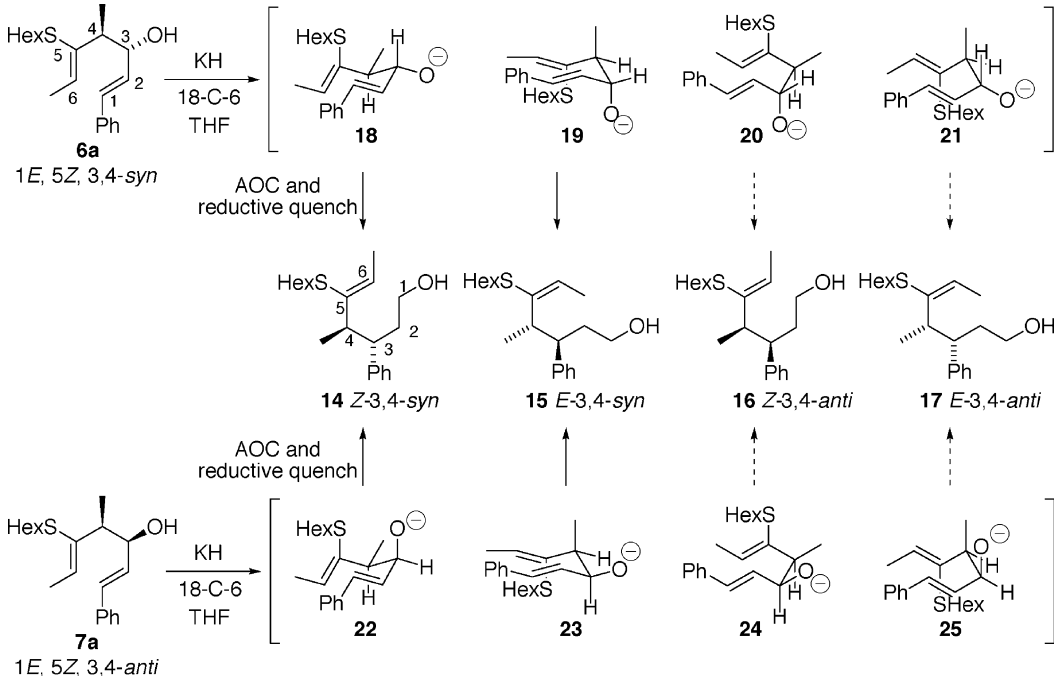
Deprotonation of 3,4-*syn* alcohols **6** led to AOC rearrangement, which was quenched by syringing the reaction mixture into a rapidly stirred solution of sodium borohydride in ethanol to give stable alcohols[18] **14**–**16** in very high yield (Scheme 4, Table 1, entry 1). As expected,[4] the major product **14** and a minor product **15** are those that would result from rearrangement of *Z*-vinyl sulfide **6a** via chair-like reacting conformations **18** and **19**. The formation of 3,4-*anti* isomer **16** can largely be explained as arising from AOC rearrangement of the small amount of the 5*E* alcohol **6b** present via a chair-like transition state. Assuming this is the case, only 1% of *Z*-vinyl sulfide **6a** rearranges via a boat-like conformation **20**. The remaining 99% rearranges via chair-like conformations **18** and **19** with a 93:7 preference for conformation **18** that has both the oxyanion and the methyl group *pseudo*-equatorial.



Scheme 2.



Scheme 3.



Scheme 4.

Table 1

Substrate	Combined yield (%)	Product ratio (%)			
		14 *Z*-3,4 *syn*	**15** *E*-3,4-*syn*	**16** *Z*-3,4-*anti*	**17** *E*-3,4-*anti*
6 3,4-*syn* **a**:**b** (5*Z*:5*E*) 91:9	99	84	6	10	0
7 3,4-*anti* **a**:**b** (5*Z*:5*E*) 90:10	75	18	64	9	9

When the 3,4-*anti* alcohols **7** were rearranged (Scheme 4, Table 1), they gave a mixture of all four isomeric alcohols **14**–**17** following reductive quench. Again 3,4-*syn* products **14** and **15** predominated showing that chair-like reacting conformations **22** and **23** are favoured. However, in this case at least half the total quantity of 3,4-*anti* products **16** and **17** formed must arise from rearrangement of *Z*-vinyl sulfide **7a** via boat-like reacting conformations **24** and **25**. The remainder is formed by rearrangement of the small amount of *E*-vinyl sulfide substrate **7b** via chair-like transition states. It is very unlikely that any *E*-vinyl sulfide **15** is produced by rearrrangement of *E*-vinyl sulfide substrate **7b**, as this would involve a boat-like transition state with all except the phenyl group *pseudo*-axial. Thus there is a >78:22 preference for a *pseudo*-equatorial oxyanion rather than a *pseudo*-equatorial methyl group when vinyl sulfide **7a** rearranges via a chair-like transition state.

By comparing our data with those in the literature (Fig. 1, Table 2), we can establish whether the 5-alkylthio group influences the orientation of the oxyanion when rearrangement occurs via chair-like transition states. Unlike the oxygen atom of enol ethers,[12] there is no evidence that the sulfur atom of vinyl sulfides **6** and **7** promotes conformations **19** and **22** by co-ordinating the potassium counterion and pre-ordering the substrate for rearrangement. Indeed, quite the opposite is true, it would seem that steric or electrostatic repulsion between the C-5 alkylthio group and the *pseudo*-axial oxyanion disfavours these conformations, and rearrangement occurs predominantly via conformations **18** and **23** with

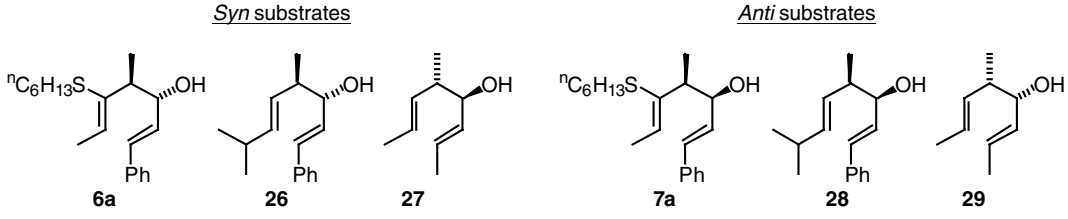


Figure 1. Alcohol substrates for AOC rearrangement.

Table 2

Substrate	Transition states		Orientation of oxyanion in chair-like TS's		Reference
	% Chair-like	% Boat-like	% Equatorial	% Axial	
6a *syn*	99	1	93	7	This work[a]
26 *syn*	92	8	84	16	19
27 *syn*	100	0	100	0	20
7a *anti*	91	9	78	22	This work[a]
28 *anti*	88	12	64	36	19
29 *anti*	90	10	53	47	21

[a] Ratios calculated assuming *E*-vinyl sulfides **6b** and **7b** rearrange exclusively via chair-like transition states.

the oxyanion *pseudo*-equatorial. The effect is less pronounced in the rearrangement of 3,4-*syn* alcohol **6a** where the *pseudo*-equatorial orientation of the methyl group also favours reacting conformation **18**. Although in this case the preference for a chair-like transition state with a *pseudo*-equatorial oxyanion is higher than that reported for AOC rearrangement[19] of analogue **26** that lacks a substituent at C-5, it is lower than that reported for rearrangement of alcohol **27** (Fig. 1, Table 2).[20] However, a C-1 phenyl group is known to favour a *pseudo*-axial oxyanion more strongly than a C-1 methyl group.[6] Although the stereoselectivity in AOC rearrangement of 3,4-*anti* alcohol **7a** is lower than that in the rearrangement of 3,4-*syn* alcohol **6a**, it is more significant. The C-4 methyl group and C-3 oxyanion compete for the *pseudo*-equatorial orientation in the rearrangement of 3,4-*anti* alcohol **7a** and the C-5 alkylthio substituent clearly favours formation of *E*-vinyl sulfide **15** via conformation **23**. The preference for a *pseudo*-equatorial oxyanion is significantly greater than in the AOC rearrangement of related alcohols **28**[19] and **29**[21] that lack a C-5 substituent (Fig. 1, Table 2).

In summary, we have synthesised vinyl sulfide substrates for AOC rearrangement by stereoselective aldol reaction, thioesterification and a rare *Z*-selective alkylidenation of the resulting thioesters. We have used the AOC rearrangement as a new access to aldehydes that have a vinyl sulfide group and the carbonyl group in a 1,5-relationship. Finally, we have shown that a 5-alkylthio group assists stereocontrol in the AOC rearrangement of 3,4-*anti* vinyl sulfides by discouraging a *pseudo*-axial oxyanion.

Acknowledgements

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$CH_cH_dC{=}CH_2$ and SCH_2CH_3), 2.43–2.32 (2H, m, CH_2CHO) and 1.13 (3H, t, J 7.6 Hz, SCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 202.1 (CH), 143.5 (C), 143.1 (C), 129.0 (CH), 127.8 (CH), 127.2 (CH), 108.7 (CH_2), 49.3 (CH_2), 45.3 (CH_2), 39.3 (CH), 25.7 (CH_2) and 13.7 (CH_3); ν_{max} ($CDCl_3$)/cm^{-1} 1729 (C=O); m/z (EI) 234 ($M^{+\cdot}$, 7%), 205 [$(M-C_2H_5^{\cdot})^+$, 10%], 174 (65), 105 (100); Found: M^+, 234.1079. $C_{14}H_{18}OS$ requires M, 234.1078.

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