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Stereoselective Synthesis of β-Hydroxycyclohexanones

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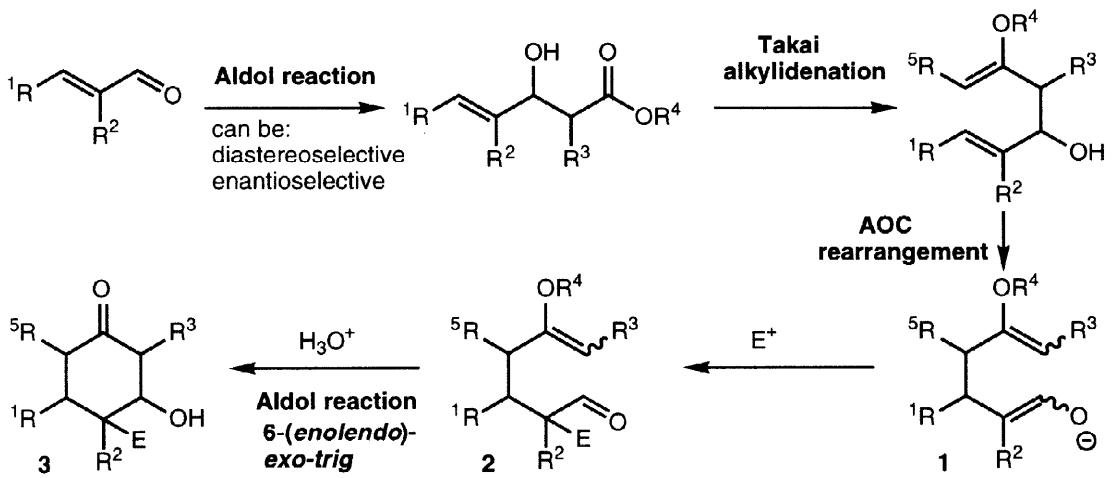
Abstract: We have developed a stereoselective route to β-hydroxycyclohexanones using the aldol reaction, the Takai alkylidenation, a novel anionic oxy-Cope rearrangement of acyclic enol ethers and an intramolecular aldol reaction. The stereoselectivity of the acid-induced, 6-(enolendo)-exo-trig, intramolecular, aldol reaction between an aldehyde and an enol ether has been investigated. The strong preference for an axial hydroxyl in the β–hydroxycyclohexanone products is explained in terms of an electrostatic interaction in the oxonium ion intermediate.

We are developing a general method for the stereocontrolled synthesis of polyfunctionalised ring systems using four key reactions: the aldol reaction, Takai alkylidenation, a novel anionic oxy-Cope (AOC) rearrangement of acyclic enol ethers and a new intramolecular aldol reaction (*scheme 1*). The aldol reaction is chosen as the first step in the synthesis as it is reliable and has many diastereoselective and enantioselective variants.[1] *Z*-Selective Takai alkylidenation[2] introduces further stereochemical information. The AOC rearrangement moves this 'information' into positions that are less accessible by 'direct' synthesis, and it may also increase the stereochemical complexity of the system. The product enolate **1** is quenched with an electrophile to give an aldehyde/enol ether **2**. The AOC rearrangement of rigid cyclic substrates is well known to give high levels of stereocontrol and is widely used.[3] Our method employs the rarer AOC rearrangement of acyclic substrates.[4] Acid-induced cyclisation of the aldehyde **2** to give a β-hydroxycyclohexanone **3** produces up to two new chiral centres. Similar 6-(*Enolendo*)-*exo-trig* intramolecular aldol reactions are some of the most important synthetic (e.g. the Robinson annulation) and biological transformations (e.g. aromatic ring formation in polyketide synthesis). It is surprising therefore that, prior to our work, there has been no systematic study of the stereochemical aspects of this highly favoured process.[5]



Scheme 1

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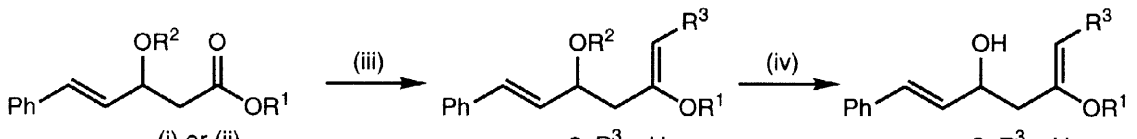
Here we report our first successes with the above route using simple racemic compounds. Reaction of cinnamaldehyde with the appropriate lithium enolates gave aldols **4a-c** in quantitative yield, while a boron trifluoride induced Mukaiyama aldol[6] with the trimethylsilyl enol ether of phenyl acetate gave aldol **4d** in 52% yield (*scheme 2*). Protection of the aldols as silyl ethers **5**, followed by Takai alkylidenation to give enol ethers **6** and **7** and removal of the silyl protecting groups gave alcohols **8** and **9** in 25-55% overall yield from the corresponding aldols. Protection of the hydroxyl is vital to the success of the alkylidenation reaction. *Tert.*-butyldimethylsilyl (TBS), triethylsilyl (TES) and trimethylsilyl groups (TMS) were all effective. We prefer the TMS group as it is easiest to remove and there is no need to purify intermediates **5** and **6** by chromatography. Alkylidenation with 1,1-dibromoethane gave mixtures of *Z* and *E* enol ethers with the *Z* isomers predominating (81-85% *Z*, assignment[7] by ^{13}C NMR). The isomers were separated after desilylation. Much higher *Z*-selectivity has been observed with esters having a branch alpha to the carbonyl group.[2b]



4a, R^1 = Me, **b**, R^1 = Et, **c**, R^1 = ^{i}Pr, **d**, R^1 = Ph,

5a, R^1 = Me, R^2 = TBS; **b**, R^1 = Et, R^2 = TMS; **c**, R^1 = ^{i}Pr, R^2 = TBS; **d**, R^1 = Ph, R^2 = TMS

6a, R^1 = Me, R^2 = TBS; **c**, R^1 = ^{i}Pr, R^2 = TBS; **d**, R^1 = Ph, R^2 = TMS; **7b**, R^1 = Et, R^2 = TMS; **c**, R^1 = ^{i}Pr, R^2 = TBS

8a, R^1 = Me, **c**, R^1 = ^{i}Pr, **d**, R^1 = Ph, **9b**, R^1 = Et, **c**, R^1 = ^{i}Pr,

Reagents

(i) TBSCl, EtN^iPr_2, DMF (ii) TMSCl, EtN^iPr_2, THF

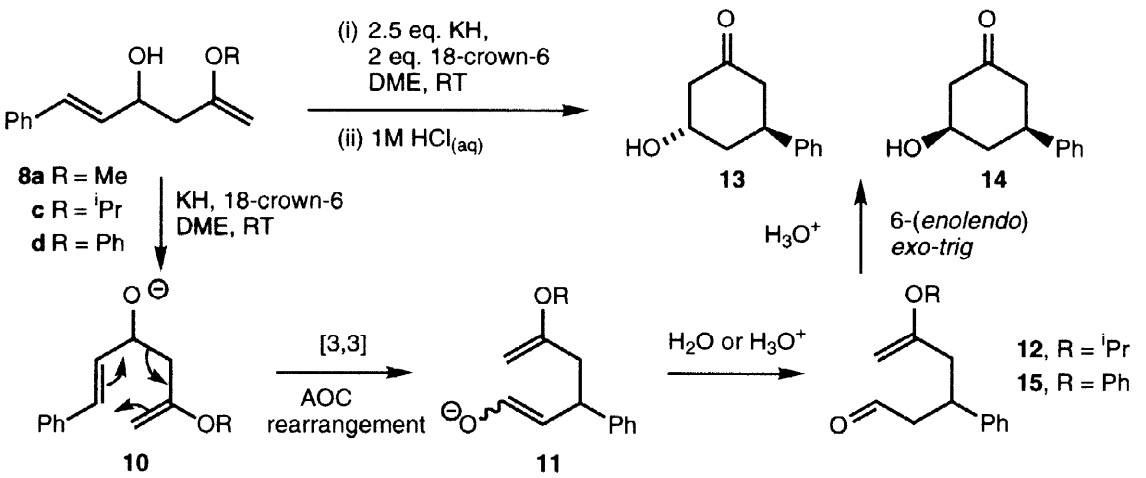
(iii) $TiCl_4$, TMEDA, Zn, R^3CHBr_2, THF (iv) Bu_4NF, THF, 4 Å MS (no MS when R^2 = TMS)

Scheme 2

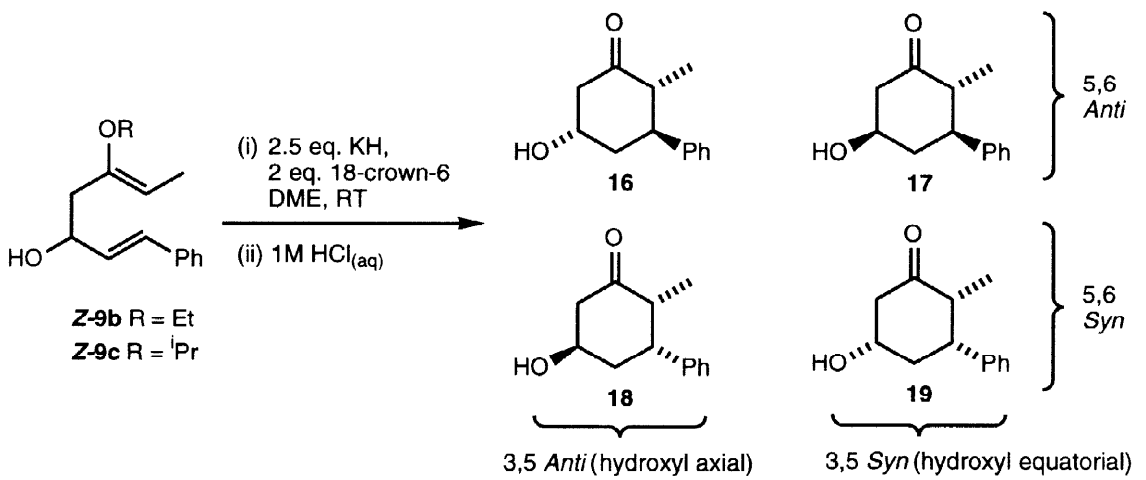
The methyl enol ether **8a** gave a complex mixture of products under a variety of conditions for the AOC rearrangement. However, *iso*-propyl enol ether **8c** reacted with potassium hydride and 18-crown-6 in DME to give a naked alkoxide **10** which underwent AOC rearrangement to enolate **11** (*scheme 3*). This was quenched with 1M aqueous hydrochloric acid to generate the desired aldehyde **12** which cyclised under these acid conditions to give a 94:6 ratio of 3,5-*anti* and 3,5-*syn* β-hydroxycyclohexanones **13** and **14** (no dehydration).[8] Pure β-hydroxycyclohexanone **13** was obtained in 43% yield by crystallisation. In the same way the phenyl enol ether **8d** rearranged and cyclised to give a 78:11:11 ratio of β-hydroxycyclohexanones **13** and **14** and cyclohexenone resulting from dehydration. The intermediate aldehyde **15** was isolated in 61% yield (minor impurities) by using saturated aqueous sodium bicarbonate instead of acid to quench the enolate. This is the first example of a compound containing an aldehyde and an enol ether in a 1,5 relationship. Its relative stability is due to the electron withdrawing effect of the phenyl group.

AOC rearrangement of *Z iso*-propyl enol ether **9c** followed by acid quench gave a 78:11:10:1 mixture of the three β-hydroxycyclohexanones **16**, **17**, and **18** and cyclohexenones resulting from dehydration (*scheme 4*). The all *syn* diastereomer **19** was not detected. The major isomer **16** was isolated by crystallisation in 31% yield. Diastereomers **17** and **18** were identified from their C*H*OH signal in the ^1H NMR spectrum of the crude mixture, and by TBS protection and isolation of their TBS derivatives. A similar ratio of products resulted from

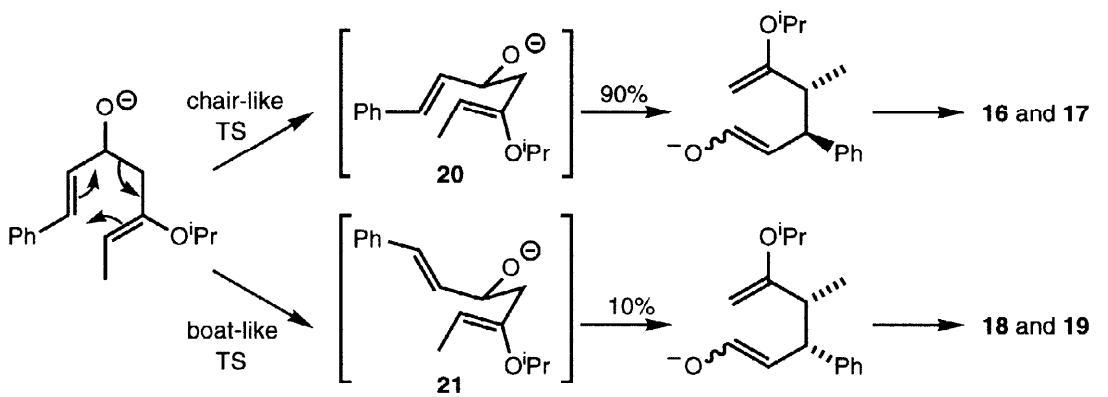
the rearrangement of the *Z* isomer of ethyl enol ether **9b** (*scheme 4*). When enol ether **9b** was rearranged and quenched with 1 M DCl in D_2O the label was incorporated at C-4 of β-hydroxycyclohexanone **16** but not at C-6. This confirms that the 5,6 stereochemistry reflects whether the transition state of AOC rearrangement is chair-like or boat-like and is not the result of epimerisation.



Scheme 3

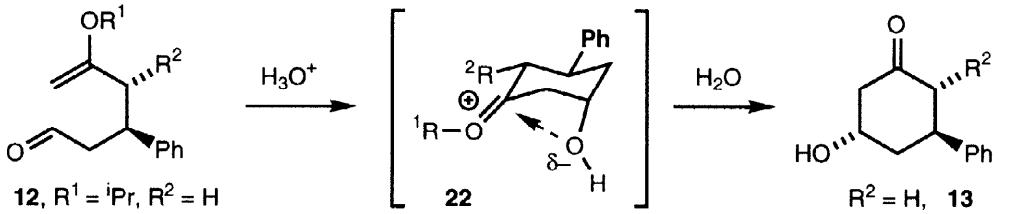


Scheme 4



Scheme 5

5,6-*Anti* β-hydroxycylclohexanones **16** and **17** were the major products when *Z* enol ether **9c** was rearranged and cyclised. These arise from the expected chair-like transition state **20** for the AOC rearrangement (*scheme 5*). The 5,6-*syn* β-hydroxycylclohexanones **18** and **19** arise from a boat-like transition state **21**. The oxy-anion is assumed to be equatorial in transition states **20** and **21** to avoid a 1,3 pseudo-diaxial interaction with the electron rich oxygen of the enol ether.



12, R^1 = ^{i}Pr, R^2 = H
15, R^1 = Ph, R^2 = H
23, R^1 = ^{i}Pr, R^2 = Me

R^2 = H, **13**
R^2 = Me, **16**

Scheme 6

The major products **13** and **16** of cyclisation have an axial hydroxyl. We propose that the oxonium ion **22** with an axial hydroxyl is stabilised by the electrostatic interaction shown in *scheme 6*, and that either there is a rapid equilibration in favour of this oxonium ion by a retro-aldol/aldol reaction prior to hydrolysis or the transition state leading to ion **22** is stabilised by the developing electrostatic interaction. Calculations[9] on unsubstituted β-hydroxycyclohexanone indicate that there is a preference for an axial hydroxyl in a vacuum and that this preference is reinforced in the oxonium ion.

In summary, we have demonstrated a new stereoselective route to β-hydroxycyclohexanones, reported the previously unknown 6-(*enolendo*)-*exo-trig* cyclisation of enol ethers onto aldehydes, and explained the high selectivity for an axial hydroxyl in the product β-hydroxycyclohexanones. Similar β-hydroxycyclohexanones are known to be plant growth regulators.[10]

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