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New Homochiral Ketoalcohols from Aldol Reactions of (+)-Isomenthone and Reversal of Diastereoselectivity

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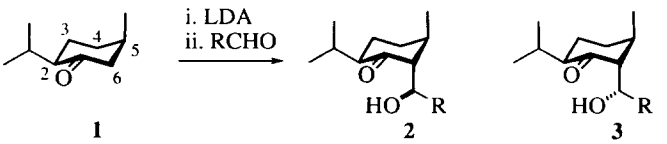
Abstract: Aldol reaction of (+)-isomenthone lithium enolate with aryl and alkyl aldehydes proceeds with complete diastereocontrol at the α-carbon (C6), but the stereochemical outcome at the secondary alcohol stereocentre (established by X-ray crystal structure determinations) can be unexpectedly *reversed* by changing reaction quenching temperature. This provides a route to a range of new homochiral ketoalcohols.

Terpenes are a chiral pool source[1] providing a number of valuable chiral auxiliaries (e.g. 8-phenylmenthol[2]), reagents (e.g. isopinocamphenyl boranes,[3a] carenyl allyl boranes[3b]) and also a number of chiral catalysts.[4] While menthol derivatives have been important in these areas, applications of isomenthol derivatives of (+)-isomenthone **1**, epimeric with (+)-menthone at C5, for synthesis of chiral controllers appears essentially unexplored. As part of a project developing C_2 or '*pseudo*-C_2' symmetric cyclic ketones as precursors of homochiral dioxiranes, we proposed evaluating several terpenone- and carbohydrate-derived ketones of the latter type. We reasoned that isomenthone might be suitable for construction of '*pseudo*-C_2' chiral cyclohexanones, since it seemed apparent that (+)-isomenthone should undergo highly diastereoselective C-C bond formation *via* the kinetic enolate, *anti* to the C5 methyl group. Although therefore we anticipated that *aldol additions* of (+)-isomenthone should be stereospecific at ring substitution (i.e. at C6), either of the two diastereomeric products, **2** and **3**, could be formed and we were unaware of precedents for predicting the outcome. [Aldol products were also of interest as precursors to various other new bifunctional chiral derivatives of (+)-isomenthone.]



1 **2** **3**

The diastereoselectivity of aldol reactions of cyclohexanone was originally reported to be low,[5] though later investigations evidenced the expected *threo* selectivity, and solvent and conditions dependances.[6] An interesting study of the influence of ring structure in substituted cyclohexanone and cyclohexenone is also of relevance,[6c]

while there are several examples of diastereoselective aldols of cyclic ester[7a] or amide enolates.[7b,c] The only recent precedent for aldol products specifically derived from isomenthone we are aware of arose from studies using (-)-menthone, where, under equilibrating conditions, aldol reaction (of (-)-menthone) with 4-biphenylcarboxaldehyde gave products equivalent to aldol reaction of *(+)-isomenthone* (*via* C2 epimerization),[8] while under kinetic conditions (-)-menthone derivatives were obtained as a *mixture* of C6 diastereomers.[9]

We sought therefore to establish the diastereoselectivity of direct aldol reactions of (+)-isomenthone, with respect to both C6 and the secondary alcohol centre. Thus, aldol reactions of (+)-isomenthone (lithium enolate) with a range of alkyl and aromatic aldehydes were carried out at -78 °C, either with immediate quenching (aq. NH_4Cl), or by allowing the reaction to warm to 0 °C (equilibrating conditions) for 30 min prior to quenching. Gratifyingly, all the aldol reactions undertaken using (+)-isomenthone enolate proved to be *completely diastereoselective at C6*, independent of the reaction quench temperature. However, the enantiofacial preference for attack on the *aldehyde carbon* was unexpectedly reversed (from *Si* to *Re*) by allowing reactions to warm to 0 °C before quenching. In most cases, diastereomers were readily separated by chromatography or crystallization. Aldol reaction with ethanal at -78 °C, with quenching at -78 °C, afforded a 74:26 mixture of diastereomers **2** and **3** [R=Me] [**Table 1**, Entry 1], exhibiting thus a 3:1 preference for *Si* face addition to the aldehyde (*threo* product).[10] Similarly, aldol addition to propanal quenched at -78 °C proceeded with the same sense of diastereoselectivity, affording an 80:20 mixture of diastereomers **2** and **3** [R=Et] [**Table 1**, Entry 2]. Several diastereomeric products from aldol reactions using alkanals were low melting solids (i.e. oils at ambient temperature: aromatic aldehyde derived aldol products were crystalline at room temperature) and structures of three of these have now been obtained at 100 K.[11] Low temperature crystal structure analyses established both the major product as **2** [R=Et] (**Figure 1**) and the minor as **3** [R=Et],[10] respectively. However, when the reaction was warmed to 0 °C prior to quenching, the diastereomeric ratio unexpectedly *reversed* to afford a 31:69 mixture of **2** and **3** [R=Et] [**Table 1**, Entry 3]. The kinetic selectivity for the formation of **2** was even higher with bulkier alkanals, 2-methylpropanal [**Table 1**, Entry 4] and cyclohexanecarboxaldehyde [**Table 1**, Entry 5], both giving essentially one diastereoisomer when reactions were quenched at -78°C (≥97% d.e.).

Table 1: Diastereomeric Outcome of Aldol Reactions of (+)-Isomenthone with RCHO.[12]

Entry	R	Quench Temp °C	**2** : **3**
1	Me	-78	74 : 26[a]
2	Et	-78	80 : 20[a]
3	Et	0	31 : 69[a]
4	$CHMe_2$	-78	>97 : 3[a]
5	C_6H_{11}	-78	>97 : 3[a]
6	Ph	-78	62 : 38[b]
7	Ph	0	12 : 88[c]
8	Naph	-78	82 : 18[c]

[a]From hplc. [b]From 300 MHz ^{1}H NMR of acetate derivatives. Key diastereomeric peaks. **4**: δ 6.23 (1H, d, *J* 10.1Hz). Acetate of **2** [R=Ph]: δ 6.22 (1H, d, *J* 11.1Hz). [c]From 300 MHz ^{1}H NMR.

When the aldol reaction was carried out using the *aromatic* substrate benzaldehyde, quenching directly at -78°C afforded a 62:38 ratio of diastereomers **2** and **3** [R=Ph] [**Table 1**, Entry 6], showing the same *sense* of selectivity as for alkanals. When this reaction was quenched after warming to 0°C, selectivity was once again *reversed* to afford a 12:88 mixture of diastereomers **2** and **3** [R=Ph] [**Table 1**. Entry 7]. The relative stereochemistry was confirmed by crystal structure analyses of **2** [R=Ph][10] and of the acetate derivative of **3** [R=Ph], namely **4** (**Figure 2**). In addition, aldol reaction with naphthaldehyde quenched directly at -78°C afforded an 82:18 mixture of diastereomers **2** and **3** [R=Naph] [**Table 1**, Entry 8], showing again the same kinetic *Si* preference giving *threo* aldol (in this case with a higher *Si*:*Re* ratio of ~4.5 than for benzaldehyde).

Figure 1
X-ray structure of diastereoisomer **2** [R=Et].

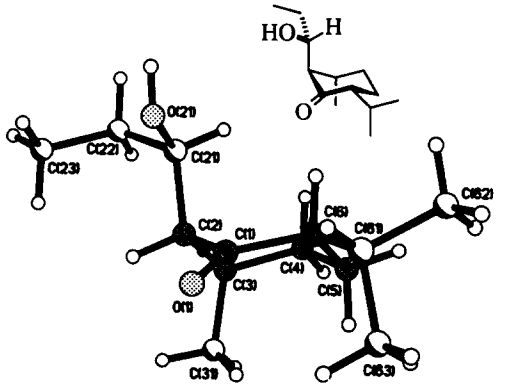
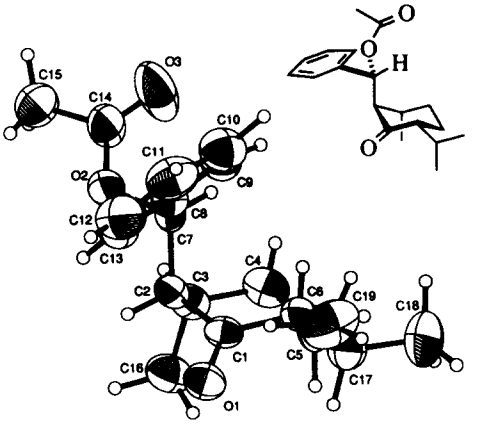
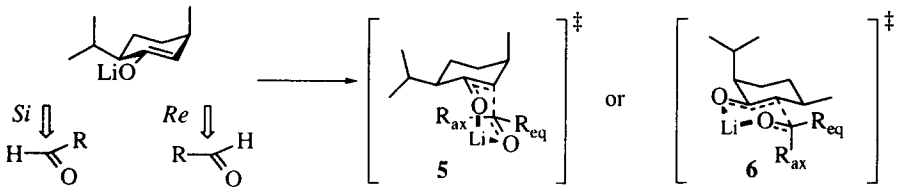


Figure 2
ORTEP[13] drawing from the X-ray crystal structure of diastereoisomer **4**.



Thus these aldol reactions of (+)-isomenthone all proceeded with *complete diastereocontrol at the ring carbon (C6)*, and all showed *Si* preference under kinetically-controlled conditions (quenching directly at -78 °C), but for both the alkyl and aryl examples determined, selectivity was reversed on quenching reactions after warming to 0 °C. Presumably, this reversal occurs *via* retroaldol-re-aldol under the latter conditions. [Notably, no enolate equilibration was apparent: no C2-alkylated products or unalkylated (-)-menthone were detected.]

Figure 3: Enantiofacial selectivities for aldol additions and Zimmerman-Traxler transition states.



The *cis*-decalin type Li-chelated Zimmerman-Traxler transition state **5** giving rise to the requisite stereospecificity at C6, requires *axial* location of the aldehyde R group (R_{ax}) [**Figure 3**] for *Re* addition, and sterically unfavourable *endo* location of this group, interacting with the axial protons at C2 and C4. This

transition state would thus suggest kinetic preference for *Si* face addition, consistent with our observed kinetic selectivities, since this locates the aryl/alkyl group equatorial (R_{eq}) [**Figure 3**]. The alternative *trans*-decalin type transition state **6** leads to the *same relationship* between *Si* face addition and equatorial location of the R group, and on those grounds would also be consistent with the observed selectivities. However, 1,3-strain between the equatorial group and the ring (C5) methyl group would be expected to disfavour this transition state relative to **5**. The change of selectivity on equilibrating must be explained, therefore, by conformer and rotamer stabilities of the lithium alkoxide aldol product.[14]

In summary, we have established that aldol additions to (+)-isomenthone proceed with universal diastereospecificity for C-C bond formation at C6. Unambiguous assignment of diastereomeric structures by X-ray analyses shows that kinetic conditions lead to predominantly to threo products through *Si* face addition to the aldehyde, while equilibration at 0 °C prior to quenching leads to unexpected *reversal* of facial selectivity favouring *Re* face addition. Keto alcohol products **2** and **3** are routinely separable, and should be useful intermediates for construction of novel bifunctional chiral compounds derived from a readily available, and under-explored, chiral pool source. Elaboration these new keto alcohols will be reported elsewhere.[15]

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10. Structures of **2** [R=Me, Ph] and **3** [R=Et] have also been confirmed by X-ray: Chughtai, J. H.; Gardiner, J. M.; Harris, S. G.; Parsons, S.; Rankin, D. W. H.; Schwalbe, C. H. *manuscript in preparation*, **1997**.
11. A liquid sample was held in a glass capillary and mounted on a Stoe Stadi-4 four circle diffractometer equipped with an Oxford Cryosystems low-temperature device. Crystal growth was effected by first establishing a solid-liquid boundary at 303 K and then cooling at a rate of 10 K hr^{-1}. Compound **2** [R=Et] crystallizes in space group P212121: the absolute configuration is established from the known (unchanged) C2 configuration.
12. HPLC and NMR ratios on crude reaction mixtures: 86-97% yields.
13. Thermal ellipsoids are drawn at 50% probability level. C. K. Johnson, 'ORTEP. Oak Ridge Thermal-Ellipsoid Plot Program' (**1976**), Oak Ridge National Laboratory, Tennessee, U.S.A.
14. Notably, all the crystal structures (including those to be reported) indicate a ground state preference for *trans* diaxial configurations of the ring methyl and hydroxyalkyl groups.
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