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LETTERS

C(1)-Substituted Menthol Derivatives: Self-Removing Chiral Auxiliaries for Asymmetric Conjugate Additions to Cycloalkenones

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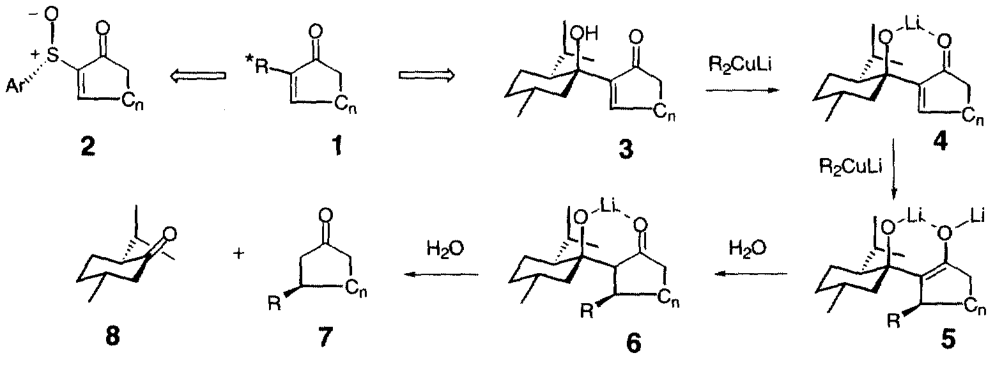
Abstract: C(1)-substituted (-)-menthone derivatives **3** were prepared by the stereoselective addition of the alkenyllithium reagents **9** to menthone (**8**) and subsequent acid catalyzed hydrolysis of the dioxolane protecting groups. Conjugate addition of cuprate reagents to enones **3a,b** followed by a methanol quench directly gave the β-alkylcycloalkanones **7** via retro-aldol reactions in 80-91% ee.

The asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is a potentially important source of chiral building blocks.[1] While a general, efficient catalyst for this important transformation remains elusive,[2] many auxiliary-based strategies have been developed.[1] By far, the most commonly studied examples involve conjugate additions to chiral unsaturated amides or esters due, in part, to their accessibility by acylation of chiral amines or alcohols, respectively. In contrast, auxiliary-mediated asymmetric conjugate additions to enones are much less common since the introduction and removal of the auxillary is not as straightforward. Attachment of the auxiliary at C(2) of the enone as shown in the general structure **1** is preferred due to its proximity to both the incipient stereogenic center and the adjacent carbonyl which can facilitate its eventual removal. Indeed, Posner documented the value of this approach in his pioneering investigation of the stereoselective conjugate addition reactions of organometallic reagents to chiral 2-*p*-(tolylsulfinyl)-2-cycloalkenones **2**, albeit, with destruction of the auxiliary during its reductive removal.[3a] We desired an auxiliary R* that could be easily introduced to furnish conjugate addition substrates **1** and, moreover, removed in the same reaction flask employed for the asymmetric conjugate addition.[4] Thus, it was envisaged that the readily available C(1) menthone derivative **3**,[5] *vida infra*, would undergo highly steroeselective addition reactions of organocuprates to the β-face of intermediate chelate **4** and provide the Michael adduct **5** which, upon an aqueous quench of the reaction mixture, would afford the desired β-alkylcycloalkanone **7** and the auxiliary menthone (**8**) by a facile retro-aldol reaction of the sterically congested alkoxide intermediate **6**. We report herein our preliminary results which substantiate this overall scheme.



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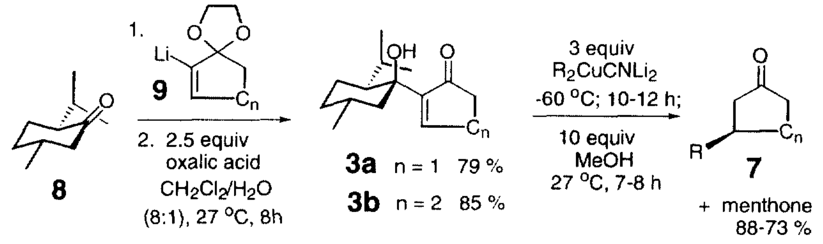
The syntheses of the conjugate addition substrates **3** were readily accomplished using the enone α-carbanion synthons **9** developed by Smith.[6] Thus, stereoselective addition of vinyl anions **9** to (-)-menthone (**8**) and subsequent hydrolysis of the crude reaction mixtures afforded enones **3** as single stereoisomers.[7] Conjugate addition of the cuprate reagents (3 equiv) derived from CuCN and 2 equiv RLi proceeded smoothly at -60 °C. The disappearance of the enone was followed by TLC and when the reaction was judged to be complete, methanol was added (10 equiv) and the solution was brought up to room temperature overnight. Column chromatography of the reaction mixture afforded recovered menthone and the anticipated (R)-3-alkylcycloalkanones **7** in high enantiomeric excesses.[8]



	n	R	% Y	% ee
a	1	Ph	73	80
b	1	Bu	66	85
c	2	Ph	81	91
d	2	Bu	85	90

In summary, we have demonstrated that the asymmetric conjugate addition, retroaldol sequence employing C(1)-substituted menthol derivatives **3** constitutes a useful route to chiral 3-alkylcyloalkanones. Efforts to improve the enantioselectivities observed herein and, more importantly, apply this novel strategy for asymmetric synthesis in other reaction sequences, eg., aldol/retroaldol; dioxy-Cope/retroaldol; etc., will be reported in due course.

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8. The absolute configurations were assigned based upon comparison of the specific rotations with previously reported values.[2,3b] The enantiomeric excesses were determined by gas chromatography on a Supelco α-dex 120 column (30 m, .25 mm ID). We thank Professor Xumu Zhang for the use of his instrument.