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Synthesis of Homochiral α-Cyperone via Enantioselective Catalysis

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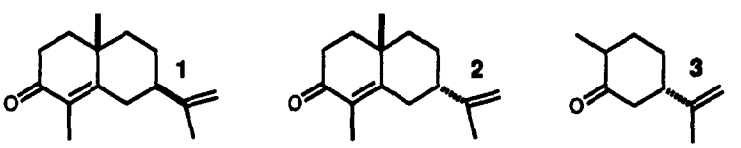
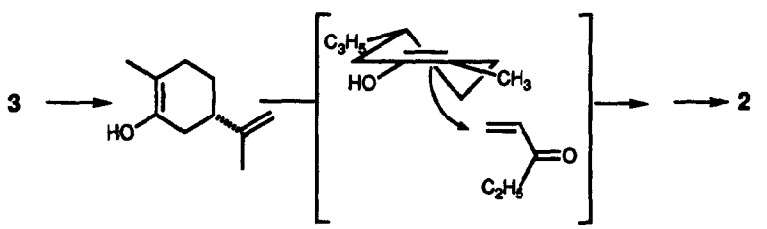
Abstract: The title sesquiterpene was obtained in a five-step synthesis starting from an achiral substrate: oxycarvone. Enantioselectivity is due to a phenylalanine-catalyzed intramolecular aldol reaction.

α-Cyperone **1** and α-epicyperone **2** are widely used chiral materials for the synthesis of other eudesmane sesquiterpene derivatives.[1] Whereas (-)-α-epicyperone can be very easily synthesized[2] from (+)-dihydrocarvone **3**, there are but a few synthetic methods yielding α-cyperone, all involving diastereoselective transformations of chiral building blocks.[3]

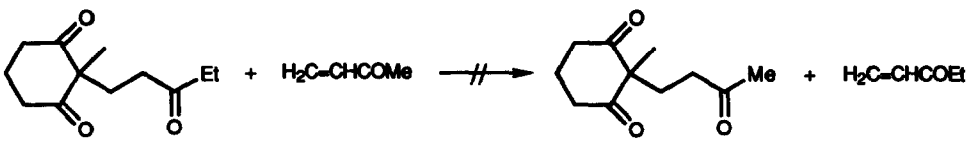


As already emphasized,[4] there is a pitfall when starting from dihydrocarvone **3**, which stands as the obvious starting point, since Robinson annelation invariably leads, through axial attack onto the enolate double bond, almost exclusively to octalones exhibiting a *trans* relationship between the ring substituents, thus providing direct access to epicyperone **2** but not to cyperone **1**:



Compared with previous reports, the five-step synthesis (cf. Scheme 1) we present here shows two original and useful features: (i) the synthesis of cyperone begins with an achiral substrate: oxycarvone **4**, (ii) chiral catalysis is responsible for the enantioselective formation of the target-molecule.

Oxycarvone **4**[5] was reacted with 1-penten-3-one (50°C, H_2O/MeOH 3/1,48h, 81%) and the addition yielded both adducts **5** and **6** in a 60/40 relative ratio. This stereochemical course cannot be attributed to a thermodynamical control because no exchange reaction was observed when the ethyl vinyl ketone adduct of 2-methyl-1,3-cyclohexanedione was treated with methyl vinyl ketone (5 equiv) under the same experimental conditions as above:



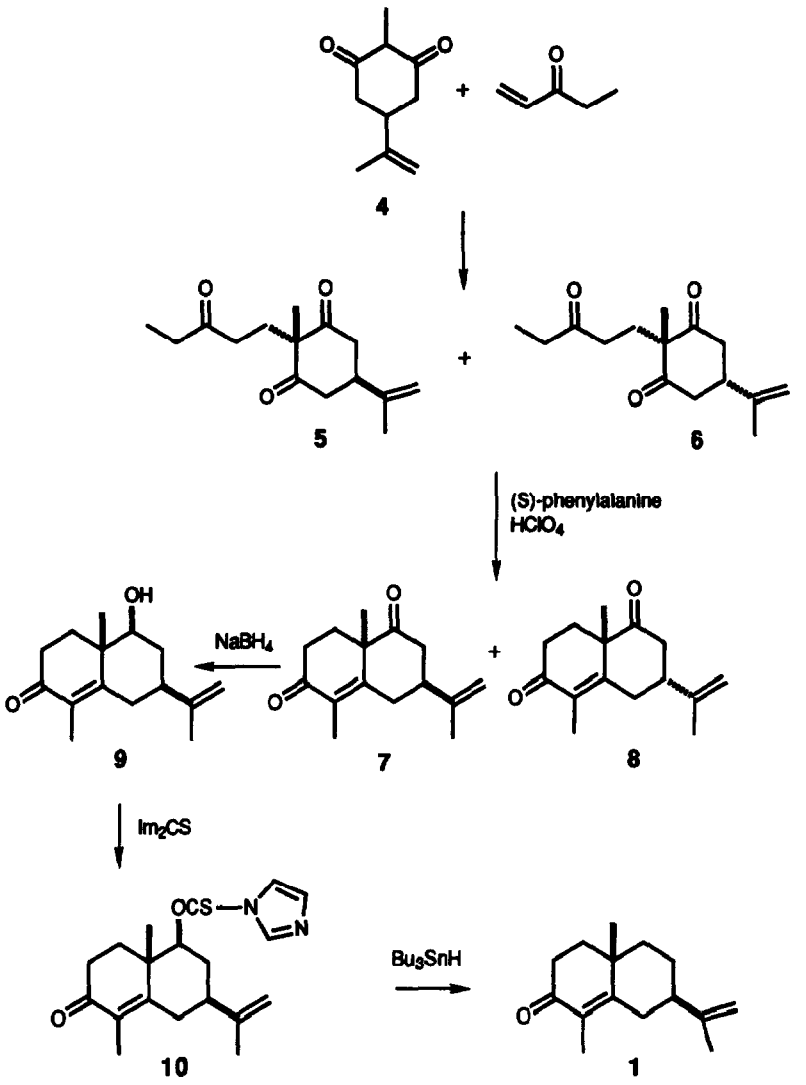
Most likely, the contrast between the reactivity of the enol forms of dihydrocarvone **3** and oxycarvone **4** should be attributed to conformational differences; for instance, the alkyl-3 ketone effect[6] comes into play in the case of substrate **4** and might be responsible for the observed absence of stereoselectivity. Anyhow this stereochemical outcome is greatly beneficial since it makes the adduct with the *cis* relationship between the ring substituents now available.

We described[7] previously the enantioselective intramolecular aldol reaction which occurs when triketones **5** and **6** are heated in the presence of (S)-phenylalanine[8] and 1N $HClO_4$ in acetonitrile (reflux, 6 days, 90%). Enediones **7** and **8** were separated by silica gel column chromatography (pentane/ether 80/20) and showed enantiomeric excesses about 90-95% (^1H NMR measurements with Eu(hfc)$_3$).[9] Compound **7** {(mp 60°C, $[\alpha]^D_{20}$ = +31.3 (c=0.7, dioxane)} was obtained in enantiomerically pure form after one crystallization from pentane. Enedione **7** (5.6 mmol) was thus treated with sodium borohydride (2.1 mmol) (0°C, EtOH, 91%) and yielded alcohol **9** {(mp 39°C, $[\alpha]^D_{20}$ = +78.7 (c=0.5, dioxane)}.

Deoxygenation of alcohol **9** was first attempted by reducing its tosylate derivative. To this end, compound **9** (R = OH) was treated with *p*-toluenesulfonic chloride in pyridine and transformed in the corresponding *p*-toluene sulfonate {(mp 121°C, $[\alpha]^D_{20}$ = +42.5 (c=1, dioxane)}. However reduction of this tosylate either by the Zn/NaI[10] system or by $LiAlH_4$[11] was unsuccessful.

Finally alcohol **9** was conveniently deoxygenated by using the method described by Barton and Mc Combie[12]: reduction of thiocarbonylimidazole derivatives by tributyltin hydride. An attempt of deoxygenate alcohol **9** via its S-methyldithiocarbonate was unsatisfactory because the preparation of this derivative required very basic conditions and therefore led to formation of many isomers which are likely to result from double bond migration and/or epimerization of the isopropenyl-bearing stereogenic center.

Alcohol **9** reacted with 1,1'-thiocarbonyldiimidazole (2 eq.) in 1,2-dichloroethane (reflux, 3h, 86%) and afforded imidazolide **11** {(mp 88°C, $[\alpha]^D_{20}$ = +80.2 (c=0.5, $CHCl_3$)}. Reduction by tributylstannane proceeded smoothly to give the desired sesquiterpene.[13] Thus (+)-α-cyperone **1** resulted from treatment of imidazolide **10** by tributyltin hydride (1.5 equiv, toluene, reflux, 2h, 82%) and was obtained in an optically pure form : $[\alpha]^D_{20}$ = +87.9 (c=1.5, $CHCl_3$) and +79.2 (c=1, dioxane), lit.: $[\alpha]^D_{20}$ = +91.1 (c=0.7, $CHCl_3$)[3a] and +81 (c=0.09, dioxane)[14].



Scheme 1

Owing to the good overall yield and convenience of the procedures described here, this first example of a genuinely enantioselective synthesis of (+)-α-cyperone **1** should make this sesquiterpene a still more useful starting chiral block for asymmetric syntheses.

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8. As regards enantioselectivity, phenylalanine is a much better catalyst than proline when the intramolecular aldol reaction involves an ethyl ketone moiety; for an explanation based on the intermediacy of an enamine, see p.502 in: Agami, C., *Bull. Soc. Chim. Fr.*, **1988**, 499.
9. Absolute configuration of enedione **7** was previously assigned on the basis of circular dichroism data.[6] The present synthesis of the known (+)-α-cyperone **1** from compound **7** definitely confirm this assignment.
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