Synthesis of (*R*)-(−)- and (*S*)-(+)-Muscone of 100% Optical Purity by Conjugate Addition of Chiral Methylcuprate to (*E*)-Cyclopentadec-2-enone

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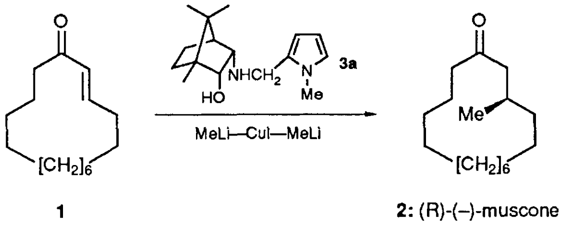
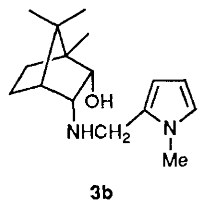
Synthesis of (*R*)-(−)- and (*S*)-(+)-muscone of essentially 100% enantiomeric excess (e.e.) by the conjugate addition of chiral methylcuprate to (*E*)-cyclopentadec-2-enone was accomplished by adding small amounts of tetrahydrofuran (THF) as an external ligand to a toluene solution of the chiral methylcuprate.

Previous studies in our laboratory have resulted in the development of efficient chiral ligands for the enantioselective conjugate addition of methylcuprate to (*E*)-cyclopentadec-2-enone to afford (*R*)-(−)-muscone in 89% e.e.[1] The realization of 100% enantioselectivity in the organocopper conjugate addition reaction remains a challenge.[2] The difficulty in developing such a process stems from the fact that the extent of asymmetric induction and the absolute stereochemistry of the product are influenced by various factors such as substrate structure, cuprate reagent, cuprate composition, solvent, concentration of the reagents, presence of salts and temperature.[3] This communication describes the realization of essentially 100% enantioselectivity in the conjugate addition of chiral methyl(hetero)cuprate to (*E*)-cyclopentadec-2-enone **1**.

Table 1 shows the influence of the solvent on the enantioselectivity. The reaction of **1** with the chiral methyl cuprate derived from **3a** in diethyl ether gave (*R*)-muscone[4] in 99% e.e., but the yield was moderate (entry 5). In toluene, the addition of THF showed a dramatic effect on the enantioselectivity. The sensitivity to this additive is strongly dependent upon the chiral ligand employed. The use of chiral ligand **4** in



1 **2**: (R)-(−)-muscone



3b

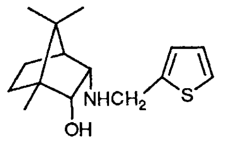


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Table 1 Conjugate addition of chiral methylcuprate to (*E*)-cyclopentadec-2-enone

Entry	Chiral ligand	Solvent[a]	Additive	Yield[b] (%)	E.e.[c] (%)	Config.
1	**3a**	Toluene	None	85	89	*R*[d]
2	**3a**	Toluene	THF (2 equiv.)	89	100	*R*
3	**3a**	Toluene	THF (4 equiv.)	94	99	*R*
4	**3a**	Toluene	THF (10 equiv.)	93	100	*R*
5	**3a**	Ether	None	57	99	*R*
6	**3b**	Toluene	THF (2 equiv.)	90	100	*S*
7	**4**	Toluene	None	84	86	*R*[d]
8	**4**	Toluene	THF (10 equiv.)	80	95	*R*

[a] The reaction was carried out by using chiral ligand (11 mmol), MeLi (11 mmol), CuI (5.5 mmol) and MeLi (11 mmol) in dry solvent (90 ml). [b] Yields are based upon isolated products purified by chromatography on silica gel. [c] Optical yields were determined from measurements of the optical rotation of the distilled product after the chromatography. [d] Reported result; see ref. 1.

the presence of 10 equiv. of THF afforded (*R*)-muscone in 95% optical yield (entry 8). Essentially 100% optical yield was obtained by employing the methyl(hetero)cuprate derived from **3a** (entries 2 and 4).†

The increase in enantioselectivity when THF is added may be due to the incorporation of THF molecules as external ligands in the cuprate structure. However, the use of THF as the solvent produced racemic muscone in 47% yield. Excess of this additive may promote structural changes of the effective cuprate cluster for the enantioselective conjugate addition.

In order to check the reproducibility of this highly enantioselective conjugate addition, we prepared **3b** from L-camphor using the procedure followed for **3a**. The reaction of the enone **1** with the chiral methylcuprate derived from **3b** in the presence of THF (2 equiv.) afforded (*S*)-(+)-muscone in 90% yield and with an optical purity of 100%.

In conclusion, we have developed, for the first time, essentially 100% enantioselectivity in the conjugate addition of methylcuprate to (*E*)-cyclopentadec-2-enone. Since both the enantiomers of the ligand are readily available from camphor, either isomer of muscone can be synthesized. We are currently investigating the cuprate conjugate addition using other macrocyclic enones.

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† *General Procedure*: for the preparation of (*R*)-(−)-muscone of essentially 100% optical purity in gram amounts. To a solution of the chiral methylcuprate prepared from **3a** (2.89 g, 11.0 mmol), methyllithium (11.0 mmol), copper(I) iodide (1.048 g, 5.50 mmol), and methyllithium (11.0 mmol) in dry toluene (90 ml) at −78 °C[1] was added dry THF (4.1 ml, 50 mmol); the solution was stirred for 15 min at −78 °C. A solution of **1** (1.112 g, 5.00 mmol) in dry toluene (10 ml) was added dropwise at −78 °C and the mixture was stirred overnight at −78 °C. After quenching at −78 °C by the addition of a 1 : 1 mixture of saturated ammonium chloride–30% ammonium hydroxide (12 ml) followed by extraction with diethyl ether, the organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Chromatography on silica gel (hexane–ethyl acetate, 45 : 1) afforded (*R*)-muscone (1.11 g, 93%) as a colourless oil. Distillation of the oil gave pure (*R*)-muscone (1.05 g, 88%), $[\alpha]_D^{18}$ − 12.5 ° (*c* 5.00 in MeOH) {lit.[4a] $[\alpha]_D$ −11.7° (*c* 0.80 in MeOH)}.

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