

Michael Reaction of Functionalized Chiral Cyclanone Imines. Enantioselective Synthesis of C_2 -Symmetric *cis*-(1*R*,6*R*)-1,6-Dimethylbicyclo[4.4.0]decane-3,8-dione

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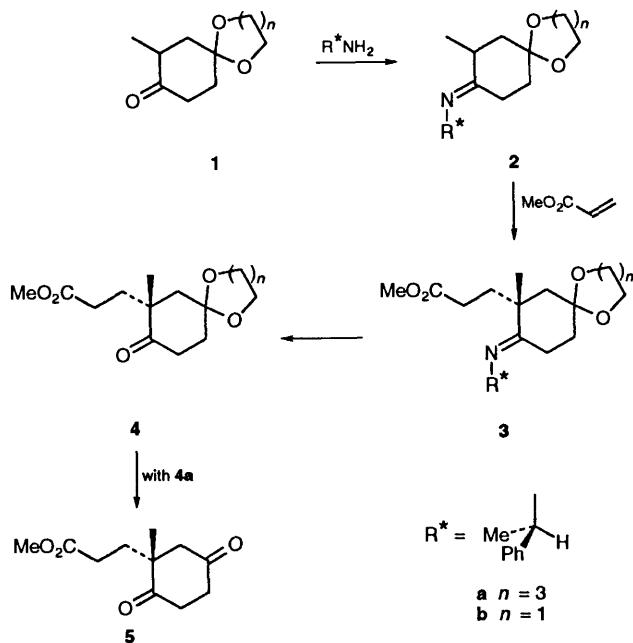
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Enantioselective Michael reaction of methyl acrylate or methyl vinyl ketone with a chiral imine of 2-methylcyclohexanone having a protected carbonyl function in the 4-position **2** led to monoprotected keto ester **4** or dione **6**. The latter was converted into the title compound **10**.

The scope and limitations of the diastereoselective Michael reaction with chiral 2-substituted cyclic ketimines¹ so far investigated, concern the nature of the starting cyclanone (five- and six-membered carbo- and hetero-cyclanones), that of its 2-substituent and that of the electrophilic olefin.²

In this communication we report that the reaction can be extended to cyclohexanones functionalized at the 4-position, thus, allowing the preparation of a new kind of chiral building block.

2-Methylcyclohexane-1,4-dione, monoprotected at the 4-position, was used as the starting compound **1a**. Methyl acrylate addition to the corresponding chiral imine **2a** led to the alkylated compound **3a**, the imine function of which was then hydrolysed[†] to key intermediate **4a** in 76.5% overall yield from keto ketal **1a** in a one-pot procedure (Scheme 1).



Gas-liquid chromatography-mass spectra (GLC-MS) determinations at any stage of the Michael reaction show the presence of only imine **3a** and its diastereoisomer in a constant ratio (no reversibility observed) of 98.5:1.5, thus, allowing a

direct measurement (independent of the optical purity of the chiral amine used) of the high reaction enantioselectivity leading to compound **4a** [enantiomeric excess (ee) 97%].

Hydrolysis of ketal **4a** gave diketo ester **5** in 88% yield after purification by flash chromatography.

Although no chemical correlation was undertaken to obtain a formal proof of the absolute configuration of diketo ester **5** (and **3a**, **4a**), the one depicted can be given with a high level of confidence by analogy with the absolute configuration of dione **7** (*vide infra*). This assignment is also in accordance with that which can be anticipated according to the general model^{1b} and all the preceding examples of the use of chiral imines in Michael reactions.²

Methyl vinyl ketone (MVK) addition to chiral imine **2a** derived from ketone **1a**, led to the alkylated compound, the imine function of which was then hydrolysed and the corresponding dione cyclized to give key intermediate **6a** in 72% overall yield from keto ketal **1a** in a one-pot procedure (Scheme 2).

In this instance, GLC-MS could not be used to determine the ratio of the alkylated imine diastereoisomers since these compounds are partially cyclized during the reaction. Instead, chiral GLC of oily compound **6a** was performed to determine the reaction enantioselectivity (ee = 90.5%), which is of the same order as that observed in the usual reaction with non-functionalized cyclanones (ee = 89–96%).^{1a,d,2}

Hydrolysis of keto ketal **6a** gave dione **7** in 63% yield after purification by flash chromatography.[‡]

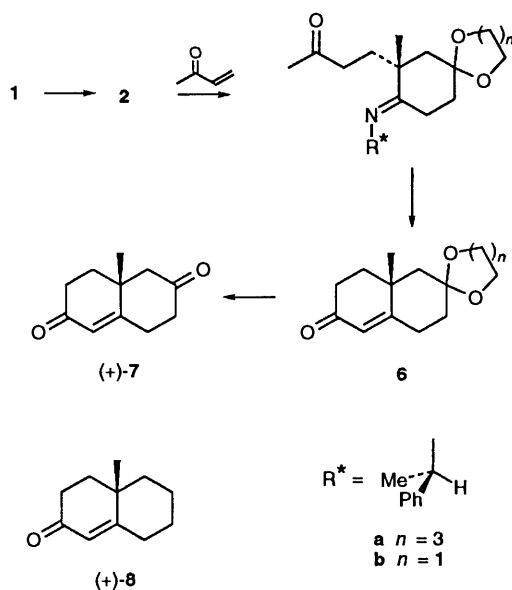
The *R* absolute configuration of dione **7** (and **6a**) was determined by chemical correlation with the known^{1a,d} corresponding (+)-methyloctalone **8** through reduction of the non-conjugated carbonyl group in compound **7**, formation of the phenyl thiocarbonate ester and radical reduction.⁴

To check the influence of the size of the protecting group in imines of type **2** on the enantioselectivity of the reaction, the procedures depicted for ketone **1a** in Schemes 1 and 2 were also performed with the five-membered ring protected compound **1b**. No significant differences are observed (ee = 97% for **4b** and ee = 88% for **6b**). From a practical point of view, the seven-membered ring monoprotected dione can be used preferentially for obtaining diketo ester **5** (easy procedure for selective hydrolysis of ketal ester **4a**) and the five-membered ring monoprotected dione for obtaining a stable solid monoprotected dione **6b**.

Chiral molecules having a C_2 -symmetry axis are a useful class of compounds for their chiroptical properties⁵ as well as for their potentially efficient use as chiral auxiliaries for asymmetric induction.⁶

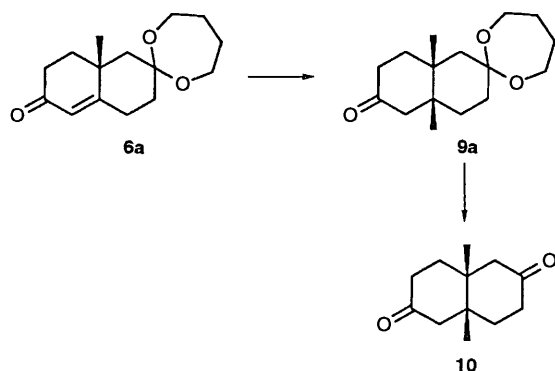
[†] In contrast to the general case with non-functionalized imino-adducts,^{1a,d,2} hydrolysis leading to the monoprotected keto ester **4a** (or **4b**, **6a**, **6b**, *vide infra*) cannot be performed in an acidic medium, thus impeding a straightforward recovery of the chiral amine.

[‡] Racemic dione **7** has been prepared from 4,4-(ethylenedioxy)-2-methylcyclohexanone **1b** in 18% overall yield.³



Scheme 2

An example of the use of monoprotected building blocks of type **6** is provided by the straightforward synthesis of a chiral C_2 -symmetric dione, *cis*-(1*R*,6*R*)-1,6-dimethylbicyclo[4.4.0]decane-3,8-dione **10**, obtained in 61% overall yield through 1,4-addition of Me_2CuLi to compound **6a**, followed by hydrolysis of the ketal function of compound **9a** (Scheme 3).



Scheme 3

Experimental

General.—Compounds **1**, **2**, **4–8** exhibited spectral properties in accordance with the assigned structures.

(R)-(–)-2-(2-Methoxycarbonyl)ethyl)-2-methylcyclohexane-1,4-dione **5**.—Standard procedure (lithium diisopropylamide–MeI) for methylation of 4,4-(tetramethylenedioxy)cyclohexanone⁷ afforded compound **1a** in 70% yield. Azeotropic imination (15 h in 7 cm³ of toluene) of ketone **1a** (0.93 g, 4.70 mmol) with **(R)**-(+)-1-phenylethylamine (0.63 g, 5.17 mmol, 1.1 equiv.) was followed by evaporation of the solvent under reduced pressure. Methyl acrylate (0.49 g, 5.64 mmol, 1.2 equiv.) was added to crude imine **2a** and the mixture was heated at 70 °C for 48 h, during which time GLC–MS measurements showed a constant ratio of *ca.* 98.5:1.5 for the diastereoisomers **3a**. Hydrolysis of the imine function was performed on the crude mixture with water (2 cm³) and methanol (25 cm³) at room

temp. for 36 h. After solvent concentration and flash chromatography (FC), distillation yielded keto ester **4a** (1.02 g, 76.5%); $[\alpha]_D^{20} + 9$ (*c* 3 in EtOH).^{*} Deacetalization⁸ of mono-protected diketo ester **4a** (0.70 g, 2.46 mmol) followed by FC yielded diketo ester **5** (0.46 g, 88%), m.p. 57.5 °C (Found: C, 62.1; H, 7.6. $\text{C}_{11}\text{H}_{16}\text{O}_4$ requires C, 62.25; H, 7.60%); $[\alpha]_D^{20} - 26$ (*c* 2 in EtOH).

(R)-(+)-6-Methylbicyclo[4.4.0]dec-1-ene-3,8-dione **7**.—Crude imine **2a** was obtained as above from ketone **1a** (6.74 g, 34 mmol). MVK (2.86 g, 40.8 mmol, 1.2 equiv.) was added under nitrogen and the mixture was heated at 40 °C for 24 h. Then, methanol (50 cm³) and KOH solution (10%) were successively added and the mixture heated at 50 °C for 24 h. After concentration, addition of water, diethyl ether extraction and FC, distillation yielded keto ketal **6a** (6.12 g, 72%). Chiral GLC of oily keto ketal **6a** showed an 85.8% optical purity (o.p.), *i.e.*, ee = 90.5% (o.p. of the chiral auxiliary amine: 94.8%). Deacetalization⁸ of keto ketal **6a** (2.0 g, 8.0 mmol) followed by FC yielded dione **7** (0.9 g, 63%), m.p. 91–92 °C; $[\alpha]_D^{20} + 108$ (*c* 4 in EtOH) (lit.⁹ for *ent*-**7**, m.p. 90–91 °C, laevorotatory; ¹H NMR, identical spectrum).

Experiments with Monoprotected Dione 1b.—The procedures used with dione **1a** were applied to dione **1b** [from commercial 4,4-(ethylenedioxy)cyclohexanone] with similar results. Keto ester **4b** was obtained in 81% yield. Keto ketal **6b** was obtained in 60% yield, m.p. 80 °C; $[\alpha]_D^{20} + 176$ (*c* 2 in EtOH). Deacetalization of compound **6b** was performed with HCl solution (10%) in this case, yielding dione **7** (82%), m.p. 92–93 °C.

(1*R*,6*R*)-(+) -1,6-Dimethylbicyclo[4.4.0]decane-3,8-dione 10.—The standard procedure for 1,4-addition of Me_2CuLi was carried out with enone **6a** (10.5 g, 41.9 mmol), followed by FC, yielding crude keto ketal **9a**. Hydrolysis in HCl solution (10%) yielded after FC purification, dione **10** (4.99 g, 61%), m.p. 195 °C (Found: C, 74.0; H, 9.3. $\text{C}_{12}\text{H}_{18}\text{O}_2$ requires C, 74.19; H, 9.34%); $[\alpha]_D^{20} + 26.8$ (*c* 1.5 in EtOH).

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* $[\alpha]_D$ Values are given in units of 10⁻¹ deg cm² g⁻¹.