Diastereoselective Synthesis of Enantiomerically Pure *syn*- or *anti*-β-Alkyl γ-Alkoxyesters by Addition of Organometallic Compounds to α-Alkoxy Isopropylidene Alkylidenemalonates

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The stereochemistry of the conjugate addition of organometallic compounds R^2M (M = Li or Mg) to O-protected α-hydroxy alkylidene isopropylidenemalonates is highly dependent on the nature of the protecting group; in the case of the MEM group, *syn*-compounds were obtained almost exclusively with Grignard compounds whereas the use of a non-chelating protecting group such as Bu^tPh_2Si afforded nearly pure *anti*-compounds with organolithium compounds in the presence of 12-crown-4.

A properly positioned hydroxy or alkoxy function can exert a high degree of stereocontrol on the delivery of a reagent to a second reactive site. While such a directing effect has been well documented for the reaction of electrophiles with electron-rich molecules, little is available about the directed Michael additions of nucleophiles on an activated double bond.[1] Good diastereoselectivity was observed in the case of vinylic sulphones[1a,b] although restricted to the production of *syn*-isomers in the acyclic systems. Some additions on γ-alkoxy α,β-unsaturated esters have also been reported[1c,e] and results were shown to be dependent on the stereochemistry of the double bond.[1f,g]

We report here that we have succeeded in controlling the stereochemistry of the 1,4 addition of organometallic compounds to α-alkoxy activated double bonds and thus we have prepared either *syn* or *anti* optically active β-alkyl γ-alkoxyesters by changing the alkoxy group.

During the addition of nucleophiles to α,β-unsaturated compounds, the main problem is to use a sufficiently activated double bond to obtain the Michael 1,4 addition even with reagents such as organolithium compounds. Thus, we selected the alkylidenemalonates derived from Meldrum's acid.[2] Owing to its high acidity, it is possible to prepare compounds (**1**) in high yield by a Knoevenagel reaction with protected α-hydroxyaldehydes,† the preparation of which in optically pure form we have previously described.[3] Moreover, the alkylated substrates (**2**) and (**3**) may be easily decarboxylated in neutral medium by heating in a 1/1 mixture of pentan-3-one/water.

The MEM protected alkylidene malonates (**1a**), when treated with a Grignard compound (Scheme 1) afforded nearly quantitative yields of 1,4 addition adducts as a single diastereoisomer (**2a**) [the (**3a**) *anti*-isomer was however observed with lactate derivative: Table 1, entry 1]. The stereochemistry was established by decarboxylation and cyclisation into lactones (**4**) followed by g.l.c. and n.m.r. analysis.

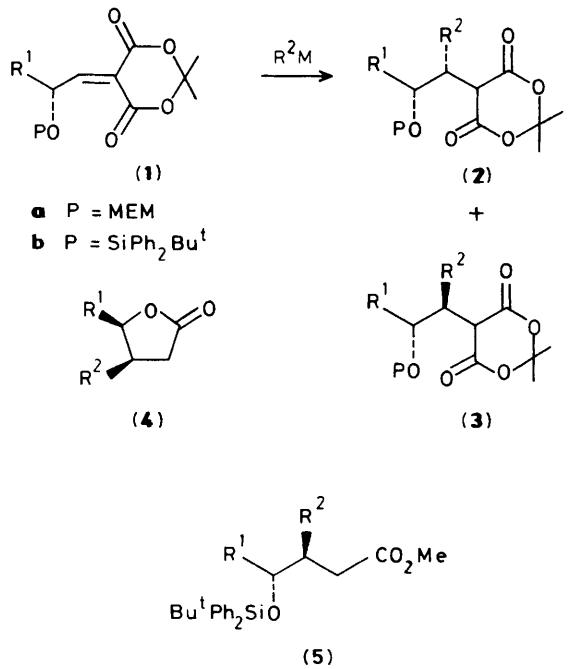
The reaction with methyl-lithium also led to 1,4 addition predominantly, but the *syn* : *anti* ratio was only 70 : 30 (entry 4). We thought that by changing the protecting group, it would perhaps be possible to obtain the *anti*-isomer. Indeed, the reaction of methyl-lithium with Bu^tPh_2SiO-protected isopropylidenemalonates (**1b**) provided this isomer as the major one. In order to enhance the selectivity of the reaction, we

† In all cases, the yields of purified (**1**) are better than 80%. Crude products may also be used for the Michael addition.

Table 1. Diastereoselective conjugate addition to (**1**).

Entry	R^1	P	R^2M	Solvent	(**2**) *syn*: (**3**) *anti*	Yield, %[a]
1	Me	MEM	BuMgBr	THF[b]	89:11	—[c]
2	Pr	MEM	MeMgBr	THF	>99:<1	—[c]
3	Hexyl	MEM	MeMgBr	THF	>99:<1	—[c]
4	Pr	MEM	MeLi	Et_2O[d]	70:30	—[c]
5	Me	Bu^tPh_2Si	MeMgBr	THF	80:20	84
6	Me	Bu^tPh_2Si	EtMgBr	THF	15:85	71
7	Me	Bu^tPh_2Si	MeLi	Et_2O + 12-C-4 (1 equiv.)	1:99	62
8	Bu	Bu^tPh_2Si	MeLi	Et_2O + 12-C-4 (1 equiv.)	5:95	79
9	Me	Bu^tPh_2Si	BuLi	Et_2O	1:99	47
10	Hexyl	Bu^tPh_2Si	MeLi	Et_2O	15:85	88
11	Hexyl	Bu^tPh_2Si	MeLi	Et_2O + 12-C-4 (1 equiv.)	8:92	92
12	$Me_2C{=}CH{-}CH_2$	Bu^tPh_2Si	MeLi	Et_2O + 12-C-4 (1 equiv.)	2:98	94

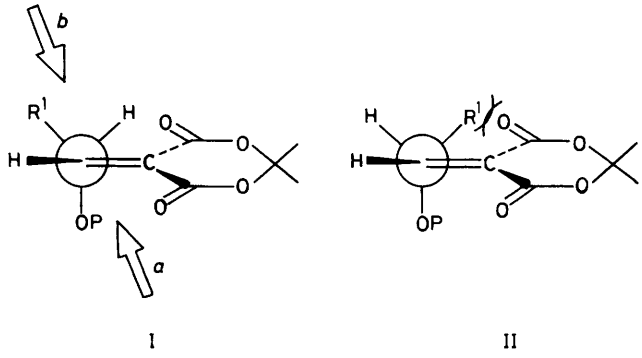
[a] Typical procedure: organometallic compound (5 mmol) is added to a solution of (**1**) (5 mmol) in the appropriate solvent under an atmosphere of dry argon at −70 °C, stirred for 5 h, and worked up with a solution of tartaric acid in water (1/1, w/w). [b] Tetrahydrofuran. [c] MEM substituted malonates (**2a**) are not stable on silica gel; they are directly decarboxylated by heating in a 1/1 mixture of water and pentan-3-one (20 ml) at 160 °C under pressure for 3 h, deprotected (pyridinium tosylate, 3 equiv., EtOH, reflux 8 h), and cyclised into lactones (cat. TsOH Ts=*p*-$MeC_6H_4SO_2$), benzene, reflux). Total yields from (**1**): 52, 62, 61, and 49% (entries 1, 2, 3, and 4). [d] 2 Equiv. of TMEDA were added.



Scheme 1. MEM = $MeOCH_2CH_2OCH_2$.

attempted to minimize the chelation between the incoming nucleophile and the O-protected hydroxy function by adding an external complexing agent. Tetramethylethylenediamine (TMEDA) was rather inefficient; in contrast, the addition of 12-crown-4 led almost exclusively to the *anti*-isomer without any loss in the yield (Table 1). We observed the same result with butyl-lithium; however, presumably owing to some 1,2 addition occurring, the yield was slightly lower. These *anti*-adducts may also be decarboxylated and cyclised after deprotection into *trans*-lactones; alternatively, the γ-alkoxy-esters (**5**) can be isolated after diazomethane esterification of the decarboxylated monoacids.

The diastereoselectivity may be interpreted as arising *via* addition to conformer **I**. In the presence of a chelating protective group such as MEM, the approach of the nucleophile follows path *a* to give the *syn*-isomer; in contrast, with a non-chelating group, the addition takes place *via* path *b* leading to the *anti*-isomer.

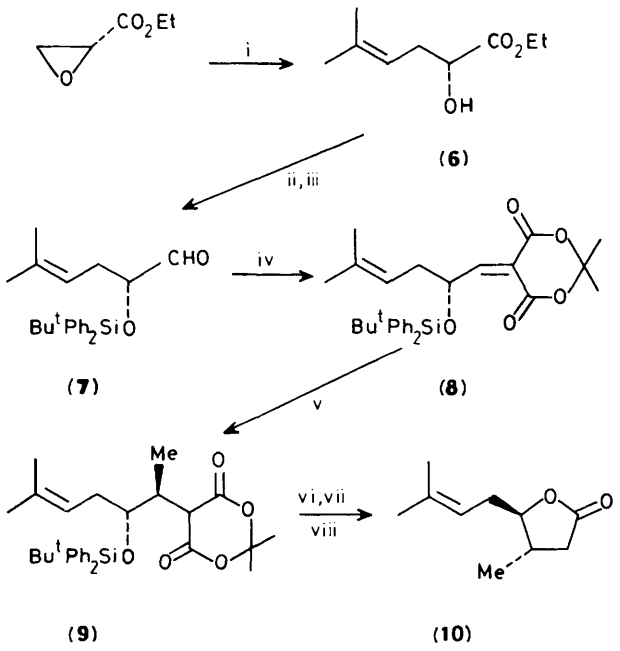


Indeed, it is generally assumed for α-substituted carbonyl compounds that in the absence of a chelating effect, the ligand with the lowest σ* orbital is perpendicular to the carbonyl plane (Felkin–Anh model)[4] and that the stereo-differentiation arises from differential interactions of the attacking nucleophile with the small and medium ligands rather than from a difference in energy of the two conformers.

However, in the case of the alkylidenemalonates, it appears that the existence of a strong interaction between the carbonyl function and the R^1 group destabilizes the conformer **II** and favours the conformer **I**. It should be noted that this interaction may explain the change of stereochemistry which was previously observed for substrates which presents a *cis*- and *trans*-stereochemistry, the **II** conformer being specially disfavoured for the *Z* isomer.[1g]

All the results in Table 1 are in accordance with the proposed model except the addition of MeMgBr to the Bu^tPh_2SiO-protected alkylidenemalonate derived from lactaldehyde which affords predominantly the *syn*-isomer (entry 5). This result may be explained by a residual chelating effect between the silyl ether oxygen and the Grignard compound which is sufficiently small to allow such a chelation.

The potential utility of this methodology was demonstrated in the synthesis of optically pure eldanolide (**10**), the sexual pheromone of *Eldana saccharina*, whose absolute configuration we established some years ago (Scheme 2).[5]



Scheme 2. *Reagents and conditions:* i, $(Me_2C{=}CH)_2CuLi$, ether, −60 °C, 1 h; ii, Bu^tPh_2SiCl, imidazole, dimethylformamide (DMF); iii, Bu^i_2AlH, hexane, −78 °C, 4 h; iv, Meldrum's acid, benzene, 5 °C, piperidinium acetate (catalytic amount), 1 h; v, MeLi, ether, 12-crown-4 (1 equiv.), −78 °C, 4 h; vi, H_2O, pentan-3-one, 160 °C, 3 h; vii, 40% HF, MeCN, 20 °C, 12 h; viii, benzene, reflux, TsOH(Ts = p-$MeC_6H_4SO_2$) (catalytic amount).

The α-hydroxyester (**6**) was prepared from (*R*)-(+)-glycidic ethyl ester in 90% yield.[3] After protection as the Bu^tPh_2Si ether, it was reduced to the aldehyde (**7**), $[\alpha]_D^{20}$ −10.7° (*c* 7.6, MeOH); yield 90%. This compound was treated with Meldrum's acid in the presence of a catalytic amount of piperidinium acetate to give the alkylidenemalonate (**8**) in 84% yield after purification, $[\alpha]_D^{20}$ 5.0° (*c* 7.3, MeOH). Reaction with methyl-lithium in ether in the presence of one equivalent of 12-crown-4 afforded the isopropylidenemalonate (**9**) (yield 94%) which was directly decarboxylated in pentan-3-one–water (1:1) at 160 °C under pressure. The γ-alkoxy acid was then deprotected and cyclised into (3*S*,4*R*)-eldanolide {total yield from (**9**): 55%, $[\alpha]_D^{20}$ 53.1° (*c* 1.61, MeOH)} which was identical in all respects including optical rotation ($[\alpha]_D^{21}$ 52.4°) with the natural product reported in the literature.[5]

In summary, we have demonstrated that high degrees of regio- and stereo-control can be achieved through the 1,4 addition of organometallics to α-alkoxy isopropylidenemalonates.

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