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Copper(I) mediated Highly Diastereoselective Conjugate Addition of Grignard Reagents to 2-Silyloxycyclopentenecarboxylates.

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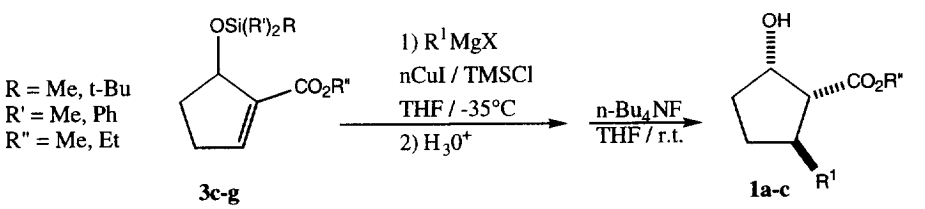
***Abstract** : The conjugate addition of magnesium cuprates to 2-silyloxycyclopentenecarboxylates leads, after desilylation, to 5-substituted-2-hydroxycyclopentanecarboxylates in high yields and diastereoselectivities. The 2-silyloxy derivatives avoid the formation of the SN_2' reaction by-products. No loss of selectivity is also observed when a catalytic amount of cuprous salt is used.*

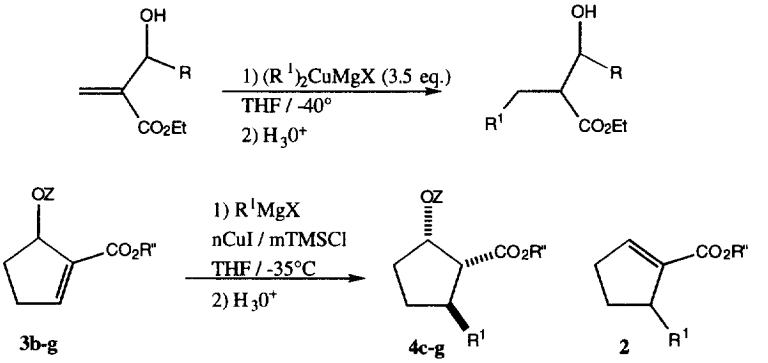
Since it allows C-C bond formation, addition of organometallic reagents to carbon electrophiles is one of the fundamental processes of organic synthesis. Among the variety of organic elements used for this purpose (Li, Mg, Zn, ...), copper received a particular interest by enabling conjugate and Michael-type addition reactions to α,β-unsaturated carbonyl derivatives[1-2]. Recently, Urban *et al.* have described the conjugate addition of lithium dialkylcuprates to 2-oxocyclohexenecarboxylates[3] and 2-oxocyclopentenecarboxylates[4]. We focused our attention on the conjugate addition of magnesium dialkylcuprates, generated *in situ*, to 2-trialkylsilyloxycyclopentenecarboxylates, leading to 5-substituted-2-hydroxycyclopentanecarboxylates **1a-c** in good diastereoselectivities and yields (scheme 1).



3c-g **1a-c**

Scheme 1

A few years ago, we have reported the conjugate addition of excess (3 eq.) magnesium cuprates to functionalized *acyclic* alkenols[5]. Nevertheless, such a method could not be applied to 5- and 6-membered ring analogs without exclusive formation of the SN_2' reaction type products **2** wich probably proceeds via addition/β-elimination[6]. Several attempts were tried in order to avoid that problem starting from the **3c-g** derivatives and using an excess of trimethylsilyl (TMS) halide to trap the intermediate ester enolate[7] (Scheme 2 and Table 1). In all cases the reactions proceeded quantitatively (no cyclopentenol was recovered). The crude product consisted on a mixture of **4** and **2**.



Scheme 2

Table 1. CuI mediated conjugate addition of Grignard reagents to cyclopentenes **3a-g**.

Cyclopentene **3**	Z	R''	R^1MgX	TMS halide (2.50 eq.)	**4 / 2** [a]	CuI amount/eq
a	H	Et	*n*BuMgBr	Me_3SiCl	0 / 100	1
b	CH_3CO	"	"	"	0 / 100	1
c	$SiMe_3$	"	"	"	75 / 25	0.1
d	$SiMe_2tBu$	"	"	"	90 / 10	1
"	"	"	"	"	90 / 10	0.1
e	"	Me	"	"	90 / 10	0.1
f	$SiPh_2tBu$	Et	"	"	95 / 5	1
"	"	"	"	"	95 / 5	0.1
g	"	Me	"	"	95 / 5	0.1
f	"	Et	"	-	0 / 100	1
e	$SiMe_2tBu$	Me	MeMgBr	Me_3SiCl	90 / 10	0.1
"	"	"	EtMgBr	"	90 / 10	0.1
"	"	"	*i*PrMgCl	"	60 / 40	0.1
"	"	"	"	Me_3SiBr	52 / 48	0.1

[a] The **4 / 2** ratio was calculated with ^{1}H-NMR by relative integration of the H-2 of **4** and the olefinic proton of **2**.

As shown in Table 1, it is obvious that the *TMSCl is essential for the access* to **4c-g** derivatives. The rate of the O-silylation vs β-elimination of the intermediate magnesium enolate probably explains these results. Although it is known as a better electrophile, the trimethylsilyl bromide is less effective in our method. Concerning the nature of the Z group of **3**, it can be inferred that the bulkiness of the silyl derivatives seems to greatly favor the

production of **4**. Furthermore, we have not observed any influence of the R'' chain and of the halogen or the solvent of the Grignard reagent. No improvement occured also while the experiment was carried out with one eq. of HMPA as a co-solvent. Finally, we have found that the use of **a catalytic amount of cuprous iodide is best suited for the chemio- and stereoselectivity of our method.**

The desilylation[8] of **4d-g** derivatives leads to **1a-c** in moderate to good yields (calculated from the **3** compounds ; Table 2). Nevertheless, this last step needs to be improved since we have met some difficulties with the t-butyldiphenylsilyloxy moiety[9].

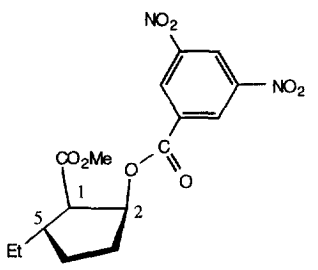
Table 2.

R''	R^1	Yield[a] %	d.e.[b] %	Cyclopentanol
Me	*n*-Bu	77	86	**1a**
Me	Me	50	> 99	**1b**
Me	Et	42	> 99	**1c**

[a] Yields are those of chromatographied compounds for the **3**-to-**1** steps.

[b] Calculated by MS-Gas Chromatography coupling.

Consequently to those results we have showed that the alcohols **1a-c** were obtained with high diastereoselectivities. Indeed only one signal for $H\text{-}C_1$ (dd around 2,2 ppm ; $^3J_{cis}$ ~ 5 Hz and $^3J_{trans}$ ~ 10 Hz) was oberved in ^{13}C and ^1H NMR (400 MHz) spectroscopy in almost cases. Besides, the analysis by gas-chomatography coupled mass spectrometer have confirmed our presumptions. Finally, a crystal structure of **5** (obtained with a DMAP mediated esterification[10] with 3,5-dinitrobenzoyl chloride) has permitted to establish the relative configuration of $H_1\text{-}C\text{-}C\text{-}H_2$ (*syn*) and $H_1\text{-}C\text{-}C\text{-}H_5$ (*anti*) with no ambiguity (scheme 3).



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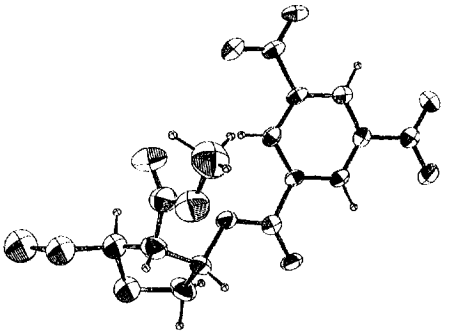
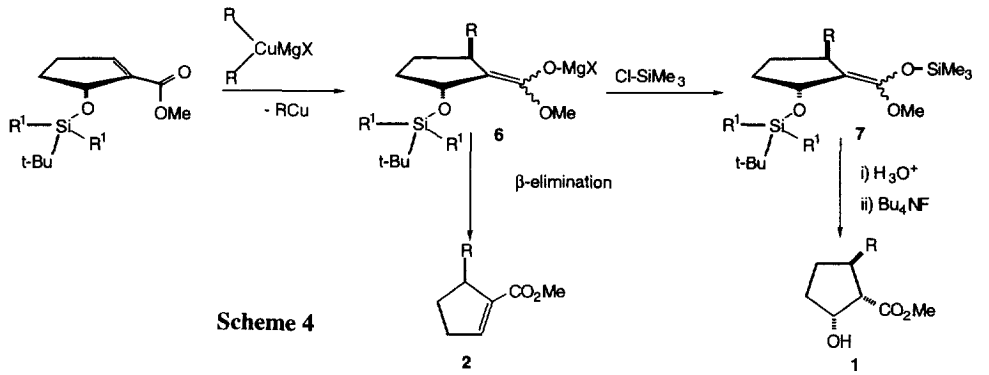


Scheme 3

From these results, it is evident that the addition of the magnesium cuprate takes place from the less hindered face of the substrate leading to the ester enolate **6** (Scheme 4) wich reacts preferentially with TMSCl to give **7**. The resulting silylated alkylidenecyclopentane is then stereoselectively hydrolysed to afford **1** (see Table 2). In this last step, the stereoselection is, once again, probably due to the 2-silyloxy bulky moiety.

Following our set of experiments[11], several studies are now in progress, concerning the addition of lithium cuprates to various analogs (replacing the ester group by CN, COR, CONRR', ...) and to related cyclohexenols.



Scheme 4

This stereoselective addition of organometallic reagent to α-functional cyclopentenols can be considered as a new opportunity for the preparation of chiral cyclic β-hydroxyesters which could be obtained by stereoselective cyclic aldolisation, as described by Pinto *et al.* for the synthesis of enantiomeric Gibberellin analogues from natural isopimarenes[12].

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References and notes

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8. E.J. Corey, B.B. Snider, *J. Am. Chem. Soc.*, **94**, 2549-2550 (1972).
9. In our attempts to cleave the t-butyldiphenylsilyl ethers we have observed the formation of a significant amount of tri-*n*-butylamine after 48 hours at room temperature while the desilylation was far from complete. A partial epimerization of C_1 also occured for longer reaction times.
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11. **Typical procedure :** cuprous iodide (0.5 to 5 mmol) and trimethylsilyl halide (12.5 mmol) were added under nitrogen to a solution of **3c-g**[13] (5 mmol) in anhydrous THF (40 mL) at -50°C. Then a solution of the Grignard reagent (10 mmol) was added slowly (15-20 min.). After stirring for two hours at -35°C, the mixture was worked-up (-50°C) by aqueous NH_4Cl, extracted with ether and the organic layer was washed with brine. Drying ($MgSO_4$) and concentration afforded a mixture of **4c-g** and **2**. After determination of the ratio of the latter by ^{1}H-NMR (see Table 1), the crude product was desilylated as described before[8].
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