5-Alkoxy-2(5H)-furanones in asymmetric synthesis

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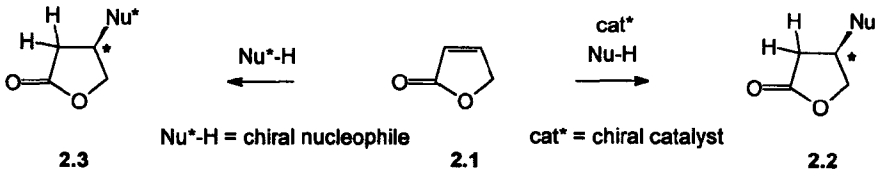
Chapter 2

Michael additions to 5-alkoxy-2(5*H*)-furanones

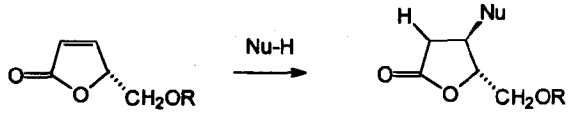
2.1 Introduction

The α,β-unsaturated moiety of 5-alkoxy-2(5*H*)-furanones serves as an excellent Michael acceptor.[1] Soft nucleophiles will add in a 1,4-fashion to give the 4-substituted 2(5*H*)-furanones, while harder nucleophiles usually result in addition to the carbonyl functionality (1,2-addition). The Michael addition to α,β-unsaturated esters is a well known reaction and many methods have been developed for the stereoselective addition of nucleophiles at the β-position of an α,β-unsaturated ester.[2] Cyclic esters, like unsubstituted 2(5*H*)-furanone have been used as substrates in this type of reaction,[3] because it is an attractive functionalized four carbon synthon, which can be transformed into a number of products. Stereoselectivity in a 1,4-addition to unsubstituted 2(5*H*)-furanone can be achieved by using a chiral nucleophile[4] or by performing the reaction with a chiral catalyst[5] (Scheme 2.1).



Scheme 2.1

2(5*H*)-Furanone as a substrate in itself is not a chiral molecule. This changes with the introduction of a substituent at C_5 of the furanone. Now there is a stereogenic center in the molecule, that can effect a stereoselective addition of the nucleophile to the double bond. Because of the rigidity and near planarity of the furanone ring, the substituent at C_5 can effect efficient π-face shielding, forcing the nucleophile to approach the double bond from the opposite side. Nucleophilic attack results in most cases in a stereospecific addition, giving only a *trans* 4,5-disubstituted furanone. Much work has been done on Michael additions to derivatives of 5-(hydroxymethyl)-2(5*H*)-furanone **2.4** (Scheme 2.2).[6] Especially



Scheme 2.2

bulky protecting groups on the hydroxyl moiety, such as trityl or TBDMS give good results with respect to the stereoselectivity of the nucleophilic addition. Also other 5-alkyl-2(5*H*)-furanones undergo highly stereoselective Michael additions with a number of nucleophiles.[7]

2.2 Nucleophilic additions to 5-alkoxy-2(5*H*)-furanones

5-Alkoxy-2(5*H*)-furanones are multifunctional four carbon synthons. They provide the same number of carbon atoms as unsubstituted 2(5*H*)-furanone, but they carry a stereocenter at C_5. Because of the possibility to obtain each of the enantiomers of the 5-alkoxy-2(5*H*)-furanone separately, by using one of the methods mentioned in Chapter 1, they are attractive starting materials in asymmetric synthesis. The most frequently used method so far, to prepare (5*S*)- or (5*R*)-menthyloxy-2(5*H*)-furanone, is based on *d*- or *l*-menthol, respectively, as a chiral auxiliary. The bulky menthyloxy group at C_5 effects efficient π-face shielding in Michael additions to this substrate. As demonstrated by Jansen,[1] a variety of nucleophiles add to 5-menthyloxy-2(5*H*)-furanone to give *trans* 1,4-addition products. In this section some of the reactions described by Jansen will be discussed briefly, because they provide useful information for the remainder of this chapter.

2.2.1 Base-catalyzed addition of nucleophiles

Activated methylene compounds such as nitroalkanes or β-dicarbonyl compounds can undergo a base-catalyzed Michael addition to 5-menthyloxy-2(5*H*)-furanone.[1] The reaction takes place under thermodynamic control and the stereoselectivity at the exocyclic stereocenter, when a prochiral nucleophile is used, is usually very low. Stereocontrol over C_4 in the furanone ring is generally high and in most cases only the *trans* addition product is observed.

2.2.2 Addition of lithium enolates

Lithium enolates, prepared via deprotonation of enolizable carbonyl compounds with LDA at low temperatures, give Michael adducts with 5-alkoxy-2(5*H*)-furanones.[1] The reaction takes place under kinetic control and the stereochemistry of the prochiral enolate determines the stereochemistry at the exocyclic center of the product. Again the addition of the nucleophile to the substrate is a highly stereoselective process and generally only *trans* addition products are obtained.

2.2.3 Addition of lithiated dithianes

Dithianes are easily deprotonated with *n*-BuLi and the resulting lithiated dithianes are excellent Michael donors.[8] With 5-alkoxy-2(5*H*)-furanones, 4,5-*trans* disubstituted 2(3*H*)-dihydrofuranones are formed.

2.2.4 Addition of heteroatom nucleophiles

Nitrogen, sulfur, and phosphorus nucleophiles have been added under various conditions to

5-alkoxy-2(5*H*)-furanones. Only *trans* addition products were observed.[9]

2.2.5 Michael additions followed by quenching of the resulting lactone enolates with electrophiles

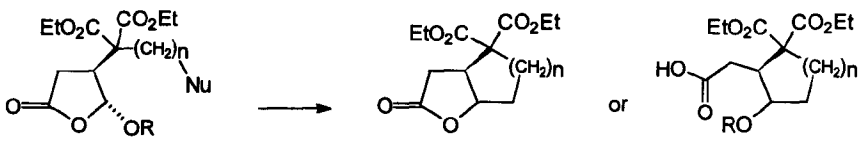
When lithium enolates or lithiated dithianes are added at low temperature to 5-alkoxy-2(5*H*)-furanones, a lactone enolate anion is formed as intermediate. At higher temperatures these enolates can undergo self-condensation reactions, but below -50°C they are stable and can be quenched with electrophiles to give 3,4,5-trisubstituted 2(5*H*)-furanones.[1] Addition of an electrophile to the lactone enolate occurs with high stereoselectivity, resulting in C_3,C_4-*trans* stereochemistry. By using a prochiral electrophile, such as an aldehyde, an exocyclic stereocenter is created. Stereoselectivity at the exocyclic center, resulting from the addition of the lactone enolate anion to the aldehyde depends on the substrates used, but in many cases one diastereoisomer is formed. The stepwise addition of a prochiral nucleophile followed by quenching of the lactone enolate anion with a prochiral electrophile thus results in the formation of four new stereocenters in a one-pot process. In selected cases complete stereocontrol over all four stereocenters was observed.[1]

2.2.6 Organometallic nucleophiles

Organometallic reagents that are known to give 1,4-addition products with α,β-unsaturated esters,[3] such as organocopper, organonickel, or organozinc reagents, did not give 1,4-addition products with 5-alkoxy-2(5*H*)-furanones.[1] The method used so far to introduce alkyl groups at C_4 has been via the addition of lithiated dithianes or trithianes followed by reductive desulfurization. The direct introduction of alkyl groups in a stereoselective manner, however, would be highly attractive (see Chapter 2.5).

2.3 Base-catalyzed addition of substituted malonates

In order to explore the reactivity of the acetal functionality in 5-alkoxy-2(3*H*)-dihydrofuranones towards Lewis acid-mediated cyclizations (see Chapter 4), we decided to synthesize substrates with a nucleophilic moiety at C_4 (Scheme 2.3).

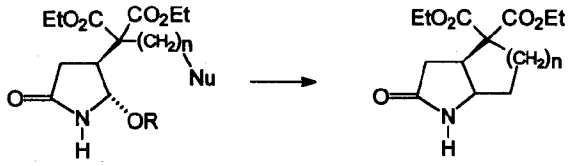


2.6 **2.7** **2.8**

Scheme 2.3

Because of the facile preparation of mono substituted diethylmalonates and because these

malonates are good Michael donors, we used this system for the introduction of a number of nucleophilic substituents (see Chapters 4 and 5). For the corresponding 5-alkoxy-pyrrolidinones **2.9** this synthetic strategy has been highly successful and gave the cyclized products **2.10** in good yields (Scheme 2.4).[10]

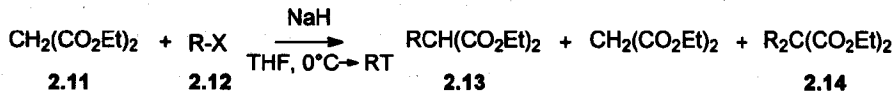


2.9 **2.10**

Scheme 2.4

2.3.1 Monosubstituted diethylmalonates

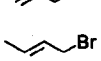
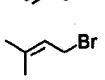
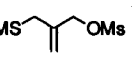
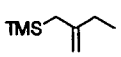
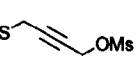
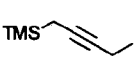
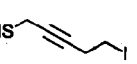
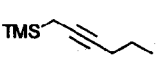
The monofunctionalization of diethylmalonate is a well known reaction and allows the introduction of a variety of functional groups via a S_N2 substitution reaction with an electrophile.[11] Deprotonation of diethylmalonate can be achieved with sodium in ethanol, with NaH in THF, with KO*t*-Bu in THF, or under phase transfer conditions,[12] to mention a few methods. Addition of diethylmalonate anions to electrophiles usually results in mixtures of O-alkylated products, and non-, mono- and disubstituted diethylmalonates. A number of monosubstituted diethyl malonates was prepared via alkylation using NaH as base (Scheme 2.5). Our results of these reactions are summarized in Table 2.1.



2.11 **2.12** **2.13** **2.14**

Scheme 2.5

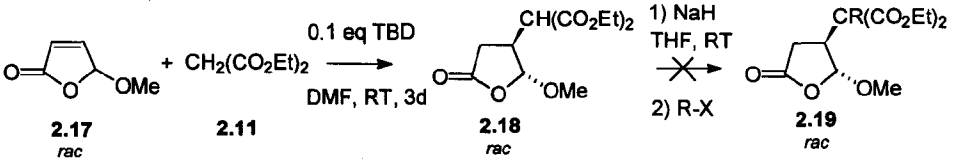
Table 2.1: Synthesis of monosubstituted diethylmalonates **2.13**

Entry	R-X		product	R =	yield[a] %
1	**2.12a**		**2.13a**[27]		52
2	**2.12b**		**2.13b**[27]		55
3	**2.12c**		**2.13c**[27]		62
4	**2.12d**[24]		**2.13d**		53
5	**2.12e**[25]		**2.13e**		64
6	**2.12f**[26]		**2.13f**		78

[a] *Isolated yields after distillation.*

2.3.2 Michael additions of diethylmalonates to *rac* 5-methoxy-2(5*H*)-furanone

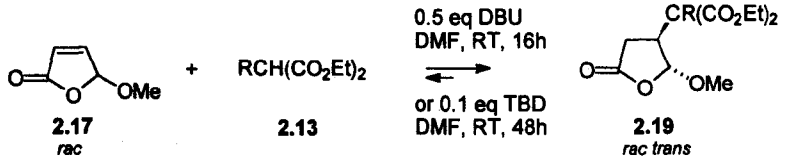
The introduction of nucleophilic functional groups (see Chapter 4) was attempted by performing an alkylation of **2.18** (Scheme 2.6). This method would allow the introduction of a variety of substituents from one precursor **2.18** in a single step. To explore whether this procedure could be applied, the diethylmalonate substituted 5-methoxy-2(3*H*)-dihydrofuranone (**2.18**) was synthesized (Scheme 2.6).



2.17 *rac* **2.11** **2.18** *rac* **2.19** *rac*

Scheme 2.6

Addition of diethylmalonate (**2.11**) to 5-methoxy-2(5*H*)-furanone (**2.17**) was catalyzed by triazabicyclodecene (TBD). After 3 days the reaction mixture was quenched with water and the product was purified by chromatography. The isolated yield of 44% is not very high, due to the formation of disubstituted and unsubstituted diethylmalonate and probably a retro-Michael reaction is taking place during work-up. When **2.18** was reacted with alkyl halides, after deprotonation with NaH, an indistinct mixture of products was formed containing only small amounts of the desired alkylated products **2.19**. Retro Michael reaction and alkylation at C_3 of the furanone are possible side reactions, as concluded from ^{1}H NMR spectra of the crude products. Apparently, the route of Scheme 2.6 was not successful and therefore compounds **2.19** were prepared via a Michael addition of the preformed monoalkylated diethyl malonates **2.13** to 5-methoxy-2(5*H*)-furanone, as depicted in Scheme 2.7.



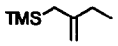
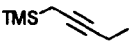
2.17 *rac* **2.13** **2.19** *rac trans*

Scheme 2.7

Monosubstituted malonates **2.13** were added to racemic 5-methoxy-2(5*H*)-furanone using 0.1 eq of TBD or 0.5 eq of diazabicycloundecene (DBU) as catalyst and DMF as solvent. The reactions never seemed to go to completion, probably due to an equilibrium between **2.19** and **2.17** and smaller amounts of catalyst caused a decrease in the reaction rate. Isolated yields of the Michael addition products **2.19** after work-up, followed by column

chromatography, are given in Table 2.2. Only *trans* addition products were obtained. The *trans* configuration of the substituents at C_4 and C_5 was deduced from the small coupling constant in the ^1H NMR spectrum ($^3J_{H4\text{-}H5} < 2.0$ Hz).[13]

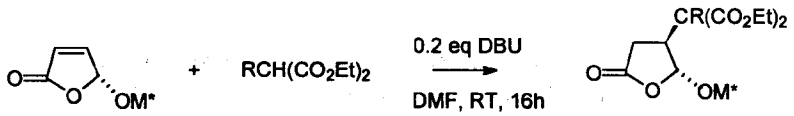
Table 2.2: Michael addition of monosubstituted diethylmalonates **2.13** to 5-methoxy-2(5*H*)-furanone (**2.17**)

Entry	R	method [a]	product	yield [b] %
1		A	**2.19a**	61
2		A	**2.19b**	70
3		A	**2.19c**	67
4		A	**2.19d**	71
5		A	**2.19e**	72
6		A	**2.19f**	67
7	Ph	B	**2.19g**	72
8	$PhCH_2$	B	**2.19h**	76
9	H	B	**2.18**	44

[a] *Method A: DMF, 0.5 eq DBU, 16h ; Method B: DMF, 0.1 eq TBD, 48h*
[b] *Isolated yields after chromatography*

2.3.3 Michael additions of diethylmalonates to (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone

(5*R*)-(*l*-Menthyloxy)-2(5*H*)-furanone (**2.16**) is a good Michael acceptor for diethylmalonates. By using the same procedure as described for racemic 5-methoxy-2(5*H*)-furanone, (4*S*)(5*R*)-disubstituted lactones **2.20** are obtained in modest to good yields (Scheme 2.8, Table 2.3). Again *trans* addition products are formed exclusively as can be deduced from NMR data. The newly formed stereocenter at C_4 can be used to induce stereoselectivity in subsequent reactions. The chirality of the auxiliary menthol has been "transferred" to the substituted furanone. The results of the addition of various substituted diethylmalonates to (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone **2.16** are summarized in Table 2.3.

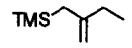
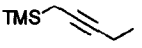


2.16 **2.13** **2.20**

OM*= *l*-menthyloxy

Scheme 2.8

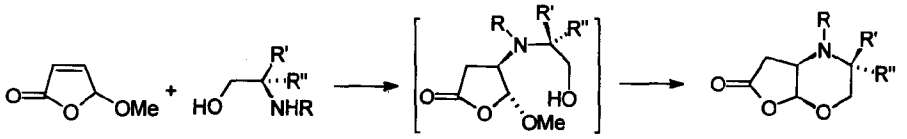
Table 2.3: Michael additions of monosubstituted diethylmalonates **2.13** to (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone (**2.16**)

Entry	R	product	yield[a] %
1		**2.20a**	69
2		**2.20b**	78
3	$PhCH_2$	**2.20c**	82

[a] *Isolated yields after chromatography.*

2.4 Additions of aminoalcohols to 5-alkoxy-2(5*H*)-furanones

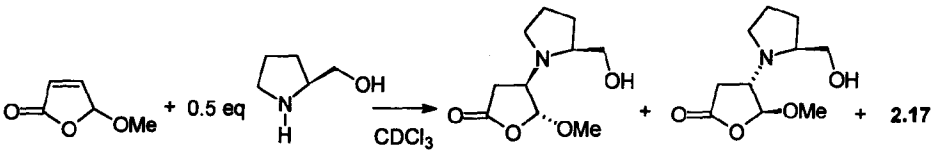
Many examples are known of the addition of heteroatom nucleophiles to 5-alkoxy-2(5*H*)-furanones.[14] We were interested in the addition of aminoalcohols to **2.17**, since Michael addition of chiral aminoalcohols to racemic 5-methoxy-2(5*H*)-furanone might result in a kinetic resolution of the furanone. Furthermore, addition of aminoalcohols to 5-alkoxy-2(5*H*)-furanones would give interesting, highly functionalized bicyclic compounds if the amine addition could be followed by a transacetalization (Scheme 2.9).



2.17 *rac* **2.21** **2.22** **2.23**

Scheme 2.9

Although the addition of secundary and primary amines to **2.17** is a very fast, high yield and stereoselective reaction,[15] the addition of β-amino alcohols somehow causes problems. Some amino alcohols did give a fast addition reaction to 5-methoxy-2(5*H*)-furanone, as could be observed by NMR spectroscopy of the crude reaction mixtures, but isolation of the addition products proved to be difficult, whereas other amino alcohols did not form the addition products at all. No kinetic resolution was observed in the addition of S-prolinol to

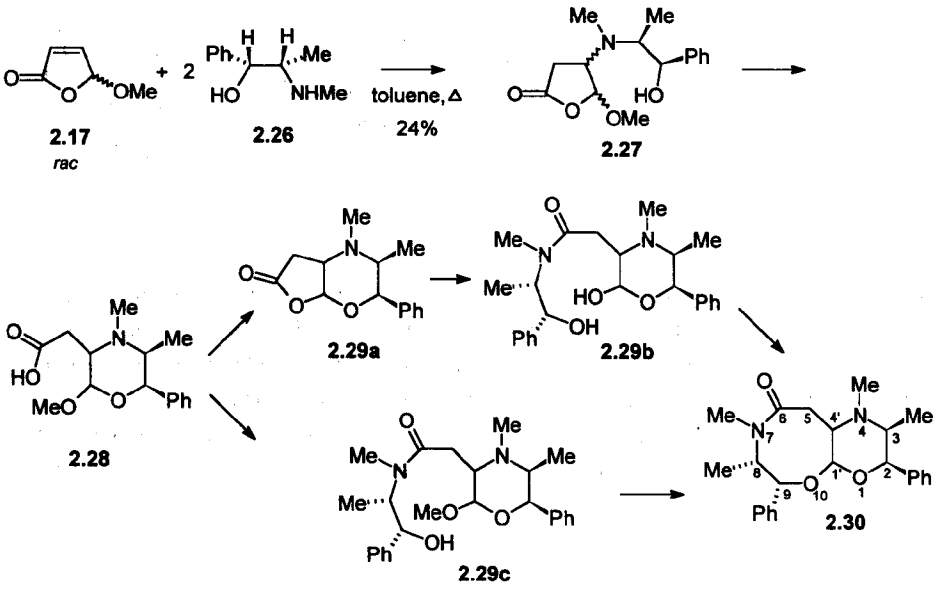


2.17 *rac* **2.24** **2.25a** 1 : **2.25b** 1

Scheme 2.10

rac-5-methoxy-2(5*H*)-furanone (Scheme 2.10). When a 2:1 mixture of *rac*-5-methoxy-2(5*H*)-furanone and *S*-prolinol in $CDCl_3$ was kept at RT for 1h, 40% conversion was found, but unfortunately the addition product was obtained as a mixture of diastereomers in a 1:1 ratio.

After several attempts to perform a Michael addition of ephedrine (**2.26**) to 5-methoxy-2(5*H*)-furanone, it was found that the reaction of **2.26** and **2.17** in refluxing toluene for 24 h gave, upon cooling, a white crystalline material. After addition of ether more crystalline product separated and this product was characterized to be a new heterocyclic compound **2.30**. The structure of this unexpected product was determined by analytical and spectroscopic techniques. The mass spectrum showed that two nitrogen atoms (this means two ephedrine moieties) were present. From the IR spectrum it was concluded that **2.30** contained an amide functional group (C=O absoption at 1642 cm^{-1}). From the ^1H NMR spectrum it was evident that the methoxy group had disappeared. ^{13}C NMR and elemental analysis were in accordance with the proposed structure **2.30**. The stereochemistry of **2.30** could not be unequivocally established. From NOE experiments it was deduced that $H_{1'}$ and $H_{4'}$ have a *cis* relationship, but the absolute stereochemistry at $C_{1'}$ and $C_{4'}$ could not be determined. The stereochemistry at C_2, C_3, C_8 and C_9 is the same as in (-)-ephedrine (**2.26**). The proposed mechanism for the formation of **2.30** is depicted in Scheme 2.11.



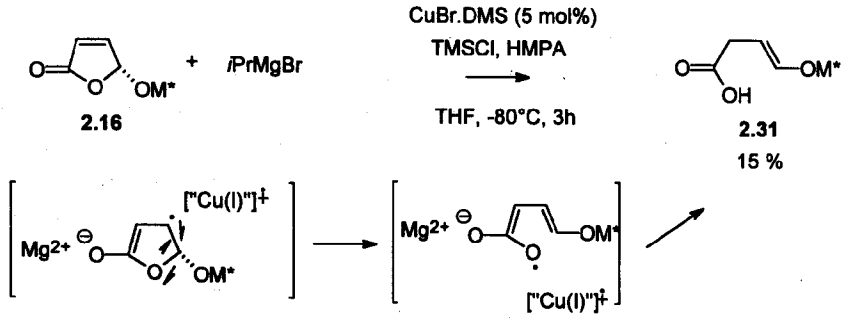
Scheme 2.11

First a Michael addition of the amine **2.26** to 5-methoxy-2(5*H*)-furanone takes place followed by transacetalization to give the intermediate carboxylic acid **2.28**. The opening of the furanone ring in this fashion is also observed in Lewis acid mediated nucleophilic additions to oxycarbenium ions derived from 5-methoxy-2(3*H*)-dihydrofuranones, as described in chapter 4. From **2.28** there are two possible routes towards **2.30**; (i) **2.28** undergoes ring closure to give **2.29a** which forms with a second molecule of ephedrine amide **2.29b**, that cyclizes to the bicyclic compound **2.30**; (ii) **2.28** forms with a second molecule of ephedrine amide **2.29c**, which cyclizes to the bicyclic compound **2.30** upon elimination of methanol. It was found that the ratio of the reactants hardly influenced the yield of this product, which was isolated in maximal 24% based on 5-methoxy-2(5*H*)-furanone. The remaining mother liquor contained some more **2.30** together with a number of undefined products. It should be noted that **2.30** was isolated as a single diastereomer as determined by ^{1}H NMR and ^{13}C NMR. The byproducts in this reaction could be, amongst others, the other diastereomers which might be formed in this reaction and also the intermediate products as depicted in Scheme 2.11. In this case we were fortunate that one of the many products crystallized from the reaction mixture. Attempts to perform the same reaction with prolinol (**2.24**) led to a mixture of products, but none could be crystallized directly from the mixture. No attempts were made to separate the mixture by other means.

2.5 Addition of organometallic reagents

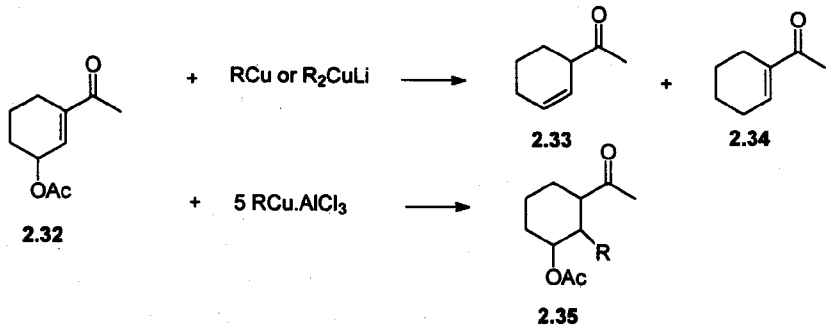
The introduction of alkyl substituents at C_4 via the nucleophilic addition of an organometallic reagent to 5-alkoxy-2(5*H*)-furanones is highly desirable. 4-Alkyl substituted 2(3*H*)-dihydrofuranones are frequently found as natural products.[16] Examples are: lignans (see chapter 3), (+)-pilocarpine,[17] a number of 3-methylene-2(3*H*)-dihydrofuranones,[18] flavor components,[19] and pheromones.[20] Not discouraged by the findings of Jansen[1] that the addition of organocuprates or organozincates to 5-alkoxy-2(5*H*)-furanones were unsuccessful, we decided to reinvestigate this reaction. Attempts to perform the addition of organocopper reagents to 5-alkoxy-2(5*H*)-furanones in the presence of a number of additives initially failed and either starting materials or undefined mixtures of products were obtained, but never more than 5 % of the 1,4-addition product was detected.

The reaction of (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone (**2.16**) with isopropylmagnesium bromide catalyzed by CuBr.DMS with trimethylsilylchloride and hexamethylphosphoramide as additives, however, gave a clean reaction to one major product, which was isolated in low yield and was characterized to be enol ether **2.31** (Scheme 2.12). This enol ether probably is the result of reductive elimination of the acyloxy group from the intermediate enone-copper adduct,[21] as depicted in Scheme 2.12.



Scheme 2.12

A literature survey showed that this is not an uncommon reaction for γ-acyloxy-α,β-unsaturated ketones and that the addition of Lewis acids such as $AlCl_3$ prevents the undesired elimination reaction (Scheme 2.13).[22]

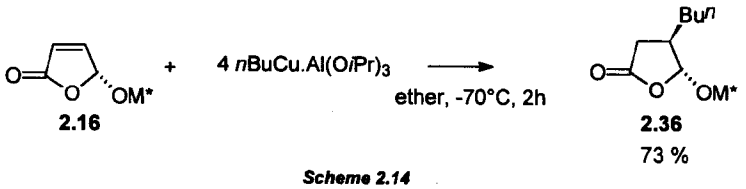


Scheme 2.13

A further problem with 5-alkoxy-2(5*H*)-furanones, however, is the presence of an acid sensitive acetal moiety in the molecule. Strong Lewis acids, such as $AlCl_3$, may cause activation of the acetal and subsequent nucleophilic additions at the C_5-position (see Chapters 4 and 5).

A solution to these problems was found by employing a milder Lewis acid in combination with an organocopper reagent. Thus instead of $AlCl_3$, $Al(OiPr)_3$ was used. *n*-Butylcopper was prepared *in situ* from *n*-butyllithium and CuI. After addition of $Al(OiPr)_3$, (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone (**2.16**) was added to give a clean 1,4-addition to furnish the 4,5-*trans* disubstituted lactone **2.36** in 73 % isolated yield (Scheme 2.14).

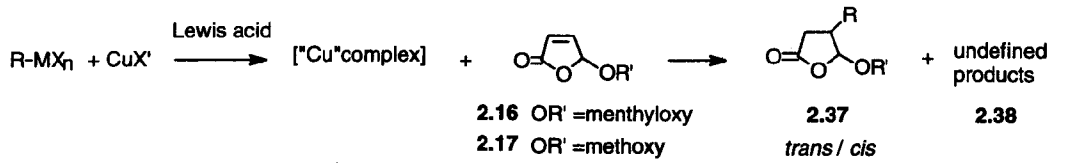
The 4,5-*trans* relationship of the substituents is evident from the ^1H NMR spectrum, where the proton at C_5 gives clearly distinguishable absorptions for the *cis* and the *trans* products (*trans*: δ 5.35 and J = 2.1 Hz; *cis*: δ 5.46 and J = 8.1 Hz). The temperature had a distinctive



Scheme 2.14

influence on the stereoselectivity of the reaction; at temperatures below -70°C only the *trans* addition product was detected, while at higher temperatures also the *cis* addition product was formed. When the reaction was performed at -20°C the ratio of *trans* and *cis* furanones **2.36** was 9:1. Also, the ratio of the reactants had an influence on the stereoselectivity of the addition. When a 2.5:1 ratio of *n*-BuCu.Al(O*i*Pr)$_3$: (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone was used, **2.36** was obtained in 50% crude yield as a 3:1 mixture of *trans* and *cis* furanones **2.36**. An explanation for the lower stereoselectivity might be a competition between copper and aluminum for complexation with **2.16**. In the first case the copper is expected to coordinate to the double bond of **2.16** from the opposite side of the menthyloxy group, resulting in an alkyl transfer to give the *trans* addition product. In the second case aluminum can coordinate to the furanone oxygen atom, at the opposite side from the menthyloxy group. The alkylcopper reagent has to enter from the same side as the menthyloxy substituent and after the alkyl transfer the *cis* addition product is obtained. It should be noted that the product **2.36** is stable towards Al(O*i*Pr)$_3$, because after stirring a mixture of **2.36** and Al(O*i*Pr)$_3$ in ether at RT for 1 h no epimerization was observed. Only diethyl ether appeared to be a good solvent for this reaction and it only seemed to work well with butylcopper prepared from butyllithium. The addition of methylcopper, prepared from methyllithium and CuI usually resulted in no more than 10% of the 1,4-addition product. Only at a prolonged reaction time of 20 h, 30% conversion to the 1,4-adduct was observed (Table 2.4, Entry 6). Various organocopper reagents were prepared in situ from the corresponding organomagnesium compounds and then subjected to the reaction conditions as described before. Only low yields of the 1,4-addition products were detected in the crude reaction mixtures and mixtures of *trans* and *cis* addition products were obtained. An exception is the addition of isopropylcopper, prepared from isopropylmagnesium bromide and catalytic amounts of CuBr.SMe$_2$ and Al(O*i*Pr)$_3$ (Table 2.4, Entry 5); this combination of reagents gave the 1,4-addition product **2.37** in good yield, but the stereoselectivity was very poor (*trans*/*cis*, 4:1). In Table 2.4 some examples are listed.

Furthermore, it was found that **2.16** was not stable under the reaction conditions (with organocopper reagents derived from Grignard reagents), because the recovered starting material was a mixture of epimers at C_5 as was easily determined by ^{1}H NMR.[23] The last observation is in contrast with the results using organocopper reagents derived from



Scheme 2.15

Table 2.4: attempted conjugate addition reactions of *in situ* prepared alkylcopper reagents to 5-alkoxy-2(5H)-furanones **2.16** or **2.17**

								products (ratio [a]%)		
Entry	st. mat	R-MX_n (eq)	CuX' (eq)	Lewis acid (eq)	T (°C)	time(min)	solvent	**2.16/2.17**	**2.37** (trans:cis)	**2.38**
1	**2.17**	*n*-BuLi (7)	CuI (7)	$AlCl_3$ (7)	-70	30	ether	<10	20 (2:1)	70
2	**2.17**	*n*-BuLi (3)	CuI (3)	$Al(OiPr)_3$ (3)	-70→-30	30	ether	<10	60 (9:1)	30
3	**2.16**	MeLi (5)	CuI (5)	$Al(OiPr)_3$ (5)	-70→-30	30	ether	80	7 (5:1)	13
4	**2.16**	MeLi (10)	CuI (5)	$Al(OiPr)_3$ (5)	-70→-30	30	ether	70	<10 (3:1)	20
5	**2.17**	*i*PrMgBr (3)	$CuBr.SMe_2$ (0.3)	$Al(OiPr)_3$ (0.6)	-70→-30	30	THF/ether	15	70 (4:1)	15
6	**2.16**	MeLi (5)	CuI (5)	$Al(OiPr)_3$ (5)	-40	1200	ether	40	30 (3:1)	30
7	**2.16**	EtMgBr (5)	CuI (5)	$Al(OiPr)_3$ (5)	-70→-40	140	ether	65	25 (6:1)	10
8	**2.16**	BuMgBr (5)	$CuBr.SMe_2$ (0.1)	$Al(OiPr)_3$ (5)	-70	100	ether	30	30 (10:1)	40

[a] *Ratio determined by ^1H NMR of the crude product.*

alkyllithium compounds, which caused no epimerization of the starting material. It appears that also the size of the organocopper reagent is crucial for the success of the reaction. The small methylcopper gave the 1,4-addition product **2.37** in < 10 % yield while ethylcopper gave the 1,4 addition product in 25 % yield and butylcopper gave a 73 % yield of the 1,4-addition product. The yields could be improved somewhat by raising the temperature to −30°C, but this resulted in a drop of stereoselectivity. Since the reaction mixture is heterogeneous it is assumed that the solubility of the organocopper.Al(O*i*-Pr)$_3$ complex is important for the addition reaction. Because in many of the reactions that were investigated, the starting 5-alkoxy-2(5*H*)-furanone was recovered in good yield apparently no reaction had occurred. It is likely that the larger alkylcopper reagents are better soluble than the smaller ones, which is in agreement with the results described here. Unfortunately, the scope of this method is limited. However, the use of less acid sensitive substrates, such as 5-acyloxy-2(5*H*)-furanones or the use of different solvents, copper salts, aluminum salts, organometallic precursors or the addition of additives might broaden the scope of this reaction.

2.6 Addition of lithiated dithianes or tris(methylthio)methane

An alternative to the organometallic reagents mentioned in the previous section, are lithiated dithianes. These are soft nucleophiles and react with most α,β-unsaturated carbonyl compounds, to furnish 1,4-addition products. After the addition reaction the dithiane moiety can be reduced to the corresponding alkyl moiety or it can be hydrolyzed to the ketone, as reported by Jansen.[1] Although one more synthetic step is required it is a relatively simple method and since thioacetals are easily prepared from the corresponding aldehydes and thiols, a large variety of substituents can be introduced at C_4 of the furanone. An important application of the 1,4-addition of lithiated dithianes to 5-menthyloxy-2(5*H*)-furanone is found in the synthesis of lignans as will be described in the next Chapter.

2.7 Summary

The Michael addition of a number of nucleophiles to 5-alkoxy-2(5*H*)-furanones proceeds in most cases with excellent *trans* diastereoselectivity. In addition to the results described by Jansen in his thesis,[1] new examples of this reaction are presented here. Via the addition of monosubstituted malonates or lithiated di- or trithianes (see Chapter 3) to 5-alkoxy-2(5*H*)-furanones a number of substituents can be introduced at C_4. The direct introduction of alkyl substituents via a Michael addition of organocuprates to 5-alkoxy-2(5*H*)-furanones would be attractive for the synthesis of many natural products. Unfortunately only the addition of *n*-butylcopper to (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone proceeds with acceptable yield and excellent diastereoselectivity.

Acknowledgments: Edzard Geertsema, Mariël Zwaagstra, Kirsten Daniel and Chiu Leung are gratefully acknowledged for their contributions to this Chapter.

2.8 Experimental

General

All solvents were reagent grade and distilled before use, following standard procedures. Reagents were purchased from Acros Chimica, Aldrich or Fluka and used without purification unless stated otherwise. 5-Hydroxy-2(5*H*)-furanone, 5-methoxy-2(5*H*)-furanone **2.17** and (5*R*)-(*l*-menthyloxy)-2(5*H*)-furanone **2.16** were prepared following our standard procedure.[23] Alkylating agents **2.12** were commercially available or prepared following literature procedures: **2.12d**,[24] **2.12e**[25] and **2.12f**[26]. Mono alkylated diethylmalonates **2.13a,b,c**[27] were prepared following a modified literature procedure.[28] Melting points (uncorrected) were determined on a Mettler FP21 melting point apparatus equiped with a Mettler FP2 microscope. Optical rotations were measured at ambient temperatures using a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 841 spectrometer. ^{1}H NMR spectra were recorded on a Varian Gemini 200 or a Varian VXR 300 spectrometer. Chemical shifts are denoted in δ units (ppm) relative to tetramethylsilane or residual solvent peaks. $CDCl_3$ was used as solvent unless stated otherwise. Coupling constants are given in Hz and the splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and bs (broad singlet). ^{13}C NMR spectra were recorded on a Varian Gemini 200 (50.32 MHz) or a Varian VXR 300 (75.48 MHz) spectrometer. Chemical shifts are denoted in δ units (ppm) relative to δ ($CDCl_3$) = 76.91 ppm. High resolution mass spectra were recorded on a AEI-MS-902 mass spectrometer (E.I.) by Mr. A. Kiewiet. Elemental analyses were performed in the microanalytical department of this laboratory by Mr. H. Draaijer, Mr J. Ebels and Mr. J. Hommes.

Methanesulfonic acid 2-(2-trimethylsilylmethyl)allyl ester (2.12d)

To a solution of 0.83 g (5.8 mmol) of 2-(trimethylsilylmethyl)prop-2-enol[24] in 25 mL of CH_2Cl_2 was added 0.84 ml (6.1 mmol) of triethylamine. After cooling to 0°C methanesulfonyl chloride (0.47 mL, 6.1 mmol) was added and the mixture was stirred for 30 min at room temperature. Quenching with water was followed by extraction with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with water (1 x 15 mL), dried (K_2CO_3) and concentrated in vacuo. 1.27 g (5.7 mmol, 99%) of **2.12d** was obtained as a yellowish oil. Crude **2.12d** was used for the synthesis of malonate **2.13d**.

^{1}H NMR : δ 5.04 (s, 1H) 4.86 (s, 1H) 4.58 (s, 2H) 3.02 (s, 3H) 1.61 (s, 2H) 0.05 (s, 9H) ^{13}C NMR: δ 139.98 (s) 112,78 (t) 73.38 (t) 37.92 (q) 22.90 (t) -1.53 (q).

2-[(2-Trimethylsilylmethyl)allyl]malonic acid diethyl ester (2.13d)

To a solution of 0.61 g (3.8 mmol) diethylmalonate in 25 mL of THF was added at 0°C 96 mg (4.0 mmol) of sodium hydride. After 15 min 0.85 g (3.8 mmol) of **2.12d** was added and the mixture was stirred overnight. 1 N HCl (aq) was added and the mixture was extracted with ether (3 x 20 mL) and the combined organic layers were washed with water (1 x 15 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the residu gave 0.58 g (2.0 mmol, 53%) of **2.13d** as a colorless oil. Bp.

145°C (0.5 mmHg).
^{1}H NMR: δ 4.60 (m, 2H) 4.20 (q, 4H, J=7.3) 3.60 (t, 1H, J=7.7) 2.58 (d, 2H, J=7.7) 1.55 (d, 2H, J=0.9) 1.27 (t, 6H, J=7.3) 0.04 (s, 9H) ^{13}C NMR: δ 169.10 (s) 143.80 (s) 108.53 (t) 61.41 (t) 51.83 (d) 36.71 (t) 26.82 (t) 16.16 (q) -1.51 (q). HRMS calcd for $C_{14}H_{26}O_4Si$: 286.160; found: 286.160

2-(4-Trimethylsilylbut-2-ynyl)malonic acid diethyl ester (2.13e)
To a solution of 2.20 g (13.8 mmol) of diethylmalonate **2.11** in 35 mL of THF was added at 0°C 0.35g (14.6 mmol) of sodium hydride. After stirring for 30 min at room temperature, 2.30 g (10.5 mmol) of 4-methylsulfonyl-(1-trimethylsilyl)-2-butyne was added. The reaction mixture was stirred for 3 h and quenched with 1N HCl (aq). The mixture was extracted with ether (3 x 25 mL) and the combined organic layers were washed with water (20 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the residu gave 1.92 g (6.8 mmol, 64%) of **2.13e** as a colourless oil. Bp. 140°C (0.5 mmHg).
^{1}H NMR : δ 4.20 (q, 4H, J=7.3) 3.51 (t, 1H, J=7.9) 2.78 - 2.72 (m, 2H) 1.41 (m, 2H) 1.26 (t, 6H, J=7.3) 0.07 (s, 9H) ^{13}C NMR : δ 168.23 (s) 79.85 (s) 74.19 (s) 61.48 (t) 19.00 (t) 13.99 (q) 6.86 (t) −2.25 (q) HRMS calcd for $C_{14}H_{24}O_4Si$: 284.144 found: 284.144 .

2-(5-Trimethylsilylpent-3-ynyl)propanedioic acid diethyl ester (2.13f)
To a solution of 0.72 g (4.5 mmol) diethylmalonate in 25 mL of THF was added at 0°C 0.11 g (4.6 mmol) of sodium hydride. After 10 min 0.80 g (3.0 mmol) of 5-iodo-(1-trimethylsilyl)-2-pentyne was added and the mixture was stirred overnight. 1N HCl (aq) was added and the mixture was extracted with ether (3 x 20 mL) and the combined organic layers were washed with water (15 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the residu gave 0.70 g (2.3 mmol, 78%) of **2.13f** as a colorless oil. Bp. 150°C (0.5 mmHg).
^{1}H NMR: δ 4.26 - 4.15 (m, 4H) 3.60 (t, 1H, J=7.1) 2.29 - 2.18 (m, 2H) 2.11 - 2.00 (m, 2H) 1.42 (t, 2H, J=2.7) 1.28 (t, 6H, J=7.1) 0.10 (s,9H) ^{13}C NMR: δ 169.27 (s) 79.08 (s) 76.54 (s) 61.31 (t) 50.59 (d) 28.34 (t) 16.92 (t) 14.00 (t), 6.89 (t) -2.16 (q) HRMS calcd for $C_{15}H_{26}O_4Si$: 298.160 found: 298.160 .

General procedure for the Michael additions: synthesis of 2.19a-f
Mono alkylated diethylmalonate **2.13** (1eq.) and 5-methoxy-2(5*H*)-furanone (**2.17**, 1.1 eq.) were dissolved in DMF. After adding 0.5 equiv. of DBU the mixture was stirred for 16 h at RT. Then 1 N HCl (aq) was added and the mixture was extracted with ether (3 x 30mL). The combined organic extracts were washed with water (2 x 30 mL), dried (Na_2SO_4) and concentrated in vacuo. The residu was purified by column chromatography.

4-(1-(1,1-Diethoxycarbonyl-3-butenyl))-5-methoxy-2(3H)-dihydrofuranone (2.19a)
Prepared from 1.0g (5.0 mmol) of **2.13a**, 0.57g (5.0 mmol) of **2.17** and 0.38 mL (2.5 mmol) of DBU in 25 mL of DMF. After chromatography (silica gel hexane/ether 1:1) there was obtained 0.96g (3.1 mmol, 61%) of **2.19a** as a colorless oil.
^{1}H NMR: δ 5.72-5.36 (m, 1H) 5.36 (s ,1H) 5.17-5.08 (m, 2H) 4.30-4.13 (m ,4H) 3.48 (s, 3H) 2.94-

2.53 (m, 5H) 1.30-1.21 (m, 6H) ^{13}C NMR: δ 175.35 (s) 169.14 (s) 131.22 (d) 120.36 (t) 62.02 (t) 58.26 (s) 56.83 (q) 44.28 (d) 37.80 (t) 30.46 (t) 13.87 (q)

4-(1-(1,1-Diethoxycarbonyl-3-pentenyl))-5-methoxy-2(3H)-dihydrofuranone (2.19b)

Prepared from 0.46 g (2.1 mmol) of **2.13b** (a mixture of E and Z-crotyl bromide), 0.25 g (2.2 mmol) of **2.17** and 0.16 mL (1.1 mmol) of DBU in 25 mL of DMF. After chromatography (silica gel hexane/ether 1:1) there was obtained 0.48g (1.5 mmol, 68%) of **2.19b** as a colorless oil, as a mixture of E- and Z-isomers.

^{1}H NMR: δ 5.70-5.45 (m, 1H) 5.36 (d, 1H, J=1.4) 5.30-5.16 (m, 1H) 4.27-4.12 (m, 4H) 3.47 (s, 3H) 2.89-2.52 (m, 5H) 1.62 (s, 3H) 1.29-1.16 (m, 6H) ^{13}C NMR: δ 175.52 (s) 169.59 (s) 131.19 (d) 129.00 (d) 123.51 (d) 122.43 (d) 106.21 (d) 61.95 (t) 58.49 (s) 56.84 (q) 44.14 (d) 30.40 (t) 17.99 (q) 13.87 (q) HRMS calcd for $C_{16}H_{24}O_7$: 328.152 found: 328.152

4-(1-(1,1-Diethoxycarbonyl-4-methyl-3-pentenyl))-5-methoxy-2(3H)-dihydrofuranone (2.19c)

Prepared from 2.51 g (11.0 mmol) of **2.13c**, 1.40 g (22.2 mmol) of **2.17** and 0.91 mL (6.1 mmol) of DBU in 25 mL of DMF. After chromatography (silica gel hexane/ether 1:1) there was obtained 2.51 g (7.3 mmol, 67%) of **2.19b** as a colorless oil.

^{1}H NMR: δ 5.36 (d, 1H, J=1.2) 4.98-4.87 (m, 1H) 4.27-4.12 (m, 4H) 3.47 (s, 3H) 2.90-2.54 (m, 5H) 1.69 (s, 3H) 1.60 (s, 3H) 1.30-1.21 (m, 6H) ^{13}C NMR: δ 175.68 (s) 169.78 (s) 169.52 (s) 136.87 (d) 116.56 (s) 106.25 (d) 61.95 (t) 58.33 (s) 56.77 (q) 44.14 (d) 31.99 (t) 30.50 (t) 26.02 (q) 17.90 (q) 13.84 (q) HRMS calcd for $C_{17}H_{26}O_7$: 342.168 found: 342.168

4(1-(1,1-Diethoxycarbonyl-3-methylene-4-trimethylsilylbutanyl))-5-methoxy-2(3H)-dihydrofuranone (2.19d)

Prepared from 0.61 g (2.1 mmol) of **2.13d**, 0.27 g (2.3 mmol) of **2.17** and 0.15 mL (0.98 mmol) of DBU in 30 mL of DMF. After chromatography (silica gel hexane/ether 3:1) there was obtained 0.60 g (1.5 mmol, 71%) of **2.19d** as a colorless oil.

^{1}H NMR: δ 5.34 (d, 1H, J=0.9) 4.69 (s, 1H) 4.60 (d, 1H, J=0.9) 4.22 - 4.07 (m, 4H) 3.45 (s, 3H) 3.08 - 2.51 (m, 5H) 1.37 (s, 2H) 1.29 - 1.20 (m, 6H) -0.01 (s, 9H) ^{13}C NMR: δ 175.75 (s) 169.72 (s) 169.50 (s) 140.84 (s) 113.64 (t) 106.19 (d) 61.99 (t) 57.91 (s) 56.64 (d) 43.78 (q) 40.69 (t) 30.37 (t) 27.07 (t) 13.71 (q) -1.65 (q). HRMS calcd for $C_{19}H_{32}O_7Si$: 400.192, found: 400.192.

4-(1-(1,1-Diethoxycarbonyl-5-trimethylsilylpent-3-ynyl))-5-methoxy-2(3H)-dihydrofuranone (2.19e)

Prepared from 0.28 g (1.0 mmol) of **2.13e**, 0.12 g (1.1 mmol) of **2.17** and 0.08 mL (0.5 mmol) of DBU in 25 mL of DMF. After chromatography (silica gel hexane/ether 3:1) there was obtained 0.29 g (0.72 mmol, 72%) of **2.19e** as a colorless oil.

^{1}H NMR: δ 5.43 (d, 1H, J=1.7) 4.28 - 4.14 (m, 4H) 3.49 (s, 3H) 3.23 - 3.16 (m, 1H) 2.98 - 2.62 (m, 5H) 1.40 (t, 2H, J=3.0) 1.30 - 1.22 (m, 6H) 0.07 (s, 9H) ^{13}C NMR: δ 175.70 (s) 168.98 (s) 168.80 (s) 106.01 (d) 82.21 (s) 71.71 (s) 62.04 (t) 57.88 (s) 56.40 (q) 40.23 (d) 30.08 (t) 24.08 (t) 13.91 (q) 6.83 (t) -2.01 (q). HRMS calcd for $C_{19}H_{30}O_7Si$: 398.176, found: 398.176

4(1-(1,1-Diethoxycarbonyl-6-trimethylsilylhex-4-ynyl))-5-methoxy-2(3H)-dihydrofuranone (2.19f)

Prepared from 0.35 g (1.2 mmol) of **2.13f** and 0.16 g (1.4 mmol) of 5-methoxy-2[5H]-furanone (**2.17**) and 0.10 mL (0.7 mmol) of DBU in 25 mL of DMF. After work-up and purification 0.33 g (0.8 mmol, 68%) of **2.19f** was obtained as a colorless oil. R_f 0.37 (ether/hexane 1:3, silica gel).
^{1}H NMR : δ 5.34 (t, 1H, J=0.9) 4.29 - 4.13 (m, 4H) 3.48 (s, 3H) 2.97 - 2.79 (m, 2H) 2.65 - 2.35 (m, 1H) 2.20 - 2.09 (m, 2H) 1.41 - 1.38 (m, 2H) 1.26 (m, 6H) 0.07 (s) ^{13}C NMR : δ 175.17 (s) 169.40 (s) 169.24 (s) 106.12 (d) 78.76 (s) 76.64 (s) 62.04 (t) 57.92 (s) 56.87 (q) 44.65 (d) 33.23 (t) 30.59 (t) 14.54 (t) 13.81 (q) 6.86 (t) -2.13 (q).

4((1,1-Diethoxycarbonyl)phenylmethyl)-5-methoxy-2(3H)-dihydrofuranone (2.19g)

To a solution of 3.90g (34 mmol) of **2.17** and 8.06g (34 mmol) of diethylphenyl malonate in 30 mL of DMF was added 480 mg (3.4 mmol) of TBD (1,5,7-triazabicyclo[4,4,0]dec-5-ene). The reaction mixture became dark brown and warm. It was stirred at RT for 48 h and then 50 mL of ice cold 1 N HCL was added and the mixture was extracted with ether (1 × 75 and 2 × 30 mL). The combined organic layers were washed with ice cold 0.5 N HCl (3 × 50 mL) , 50 mL ice cold 5 % $NaHCO_3$, 50 mL ice cold water and brine and dried (Na_2SO_4). Concentration in vacuo afforded 10.1 g yellow oil which was purified by chromatography (silica gel, ether/pentane 1:1) to give 8.60g (24.6 mmol, 72%) of **2.19g** as a colorless oil.
^{1}H NMR: δ 7.34-7.31 (m,5H) 5.34 (d,1H,J=1.5) 4.29-4.18 (m,4H) 3.39 (s,3H) 3.50 (ddd,1H,J=10.1,J=3.4,J=1.5) 2.90(dd,1H,J=18.7,J=10.1) 2.49 (dd,1H,J=18.7,J=3.4) 1.35-1.20 (m,6H) ^{13}C NMR: δ 175.51 (s) 169.25 (s) 169.07 (s) 134.97 (s) 128.47 (d) 128.13 (d) 127.83 (d) 106.28 (d) 63.97 (s) 62.25 (t) 56.65 (q) 46.41 (d) 31.10 (t) 13.50 (q) Anal. Calcd. for $C_{18}H_{22}O_7$: C: 61.69; H: 6.33 Found C: 61.26; H: 6.44

4(1-(1,1-Diethoxycarbonyl)-2-phenylethyl)-5-methoxy-2(3H)-dihydrofuranone (2.19h)

Same procedure as for **2.19g** 86% yield, colorless crystals, mp. 55.7-56.5°C (pentane).
^{1}H NMR: δ 7.30-7.06 (m,5H) 5.37 (s,1H) 4.30-4.11 (m,4H) 3.48 (s,3H) 3.30 (s,2H) 2.88-2.57 (m,3H) 1.31-1.21 (m,6H) ^{13}C NMR: δ 175.52 (s) 169.50 (s) 169.02 (s) 134.44 (s) 130.01 (d) 128.48 (d) 127.47 (d) 106.02 (d) 62.11 (t) 62.01 (t) 59.60 (s) 56.69 (q) 43.55 (d) 39.98 (t) 30.54 (t) 13.72 (q) HRMS calcd: 364.152 found: 364.152 Anal. Calcd for $C_{19}H_{24}O_7$: C: 62.61; H: 6.64 Found: C: 62.62; H: 6.60

(4*S*)(5*R*)-4(1-(1,1-Diethoxycarbonyl-3-methylene-4-trimethylsilylbutanyl))-5-(*l*-menthyloxy)-2(3H)-dihydrofuranone (2.20a)

Same procedure as for **2.19a-f**; 69 % yield.
^{1}H NMR: δ 5.61 (s,1H), 4.69 (d,2H,J=17.4) 4.28-4.10 (m,4H) 3.50 (dt,1H,J=10.6,J=4.4) 3.10-2.62 (m,5H) 2.18-2.00 (m,2H) 1.72-0.74 (m,24H) 0.03 (s,9H)

(4*S*)(5*R*)-4-(1-(1,1-Diethoxycarbonyl-5-trimethylsilylpent-3-ynyl))-5-(*l*-menthyloxy)-2(3H)-dihydrofuranone (2.20b)

Same procedure as for **2.19a-f**; 78 % yield.
^{1}H NMR: δ 5.62 (d,1H,J=1.0) 4.08 (q,4H,J=7.3) 3.44 (dt,1H,J=10.3,J=3.8) 3.25-3.13 (m,1H) 2.99-2.78 (m,3H) 2.70-2.57 (m,1H) 2.18-1.95 (m,2H) 1.69-1.53 (m,2H) 1.41-1.35 (m,2H) 1.26 (t,6H,J=7.3) 1.38-1.10 (m,2H) 1.02-0.65 (m,12H) 0.04 (s,9H) ^{13}C NMR: δ 175.81 (s) 168.89 (s) 168.67 (s) 101.23 (d) 82.36 (s) 76.73 (d) 71.43 (s) 62.05 (t) 57.69 (s) 47.69 (d) 44.25 (d) 39.40 (t) 34.30 (t) 31.29 (d) 30.50 (t) 25.36 (d) 24.12 (t) 23.04 (t) 22.21 (q) 20.82 (q) 15.53 (q) 13.82 (q) 6.98 (t) -2.15 (q). HRMS: calcd for $C_{28}H_{46}O_7Si$: 522.301 found: 522.301.

(4*S*)(5*R*)-4-(1-(1,1-Diethoxycarbonyl-2-phenyl ethyl))-5-(*l*-menthyloxy)-2(3H)-dihydrofuranone (2.20d)
Same procedure as for **2.19a-f**; 82 % yield.
^{1}H NMR: δ 7.30-7.06 (m,5H) 5.66 (s,1H) 4.28-4.07 (m,4H) 3.50 (dt,1H,J=10.4,J=4.3) 3.39-3.21 (m,2H) 2.94-2.58 (m,3H) 2.18-1.96 (m,2H) 1.69-0.73 (m,22H) ^{13}C NMR: δ 175.84 (s) 169.58 (s) 169.05 (s) 134.56 (s) 130.14 (d) 128.49 (d) 127.41 (d) 101.11 (d) 76.62 (d) 62.17 (t) 61.92 (t) 59.60 (s) 47.73 (d) 43.37 (d) 39.60 (t) 38.80 (t) 34.24 (t) 31.31 (d) 31.00 (t) 25.32 (d) 22.97 (t) 22.22 (q) 20.88 (q) 15.42 (q) 13.78 (q) Anal. Calcd. for $C_{28}H_{40}O_7$: C: 68.83 H: 8.25 found: C:68.59 H: 8.18

Attempted kinetic resolution of *rac*-5-methoxy-2(5*H*)-furanone via addition of *S*-prolinol
To a solution of 15 mg (0.13 mmol) of **2.17** in 0.5 mL of $CDCl_3$ was added 6 mg (0.06 mmol) of **2.24**. The reaction was followed by ^{1}H NMR. After 1 h, 40% conversion to **2.25a** and **2.25b** in a 1:1 ratio was observed. The ratio of **2.25a** and **2.25b** could be determined by integration of the signals of the acetal protons in the ^{1}H NMR spectrum.
2.25a: ^{1}H NMR: δ 5.30 (d,1H,J=2.0) **2.25b**: ^{1}H NMR: δ 5.25 (d,1H,J=1.8)

3,4,7,8-Tetramethyl-2,9-diphenyl-hexahydro-1,10-dioxa-4,7-diazabenzocyclooctan-6-one (2.30)
A solution of 0.57g (5 mmol) of **2.17** and 0.83g (10 mmol) of (-)-ephedrine in 25 mL of toluene was heated ro reflux for 24 h. After cooling to RT a white crystalline precipitate had formed. Upon addition of 30 mL ether, additional crystalline product precipitated, which was collected by filtration and washed with ether to give 0.47g (1.2 mmol, 24%) of **2.30**. Two crystallizations from $CHCl_3$ afforded analytically pure **2.30**, mp. 229-231°C.
^{1}H NMR: δ 7.47-7.26 (m,10H) 5.43 (s,1H) 4.73 (s,1H) 4.67 (d,1H,J=7.4) 3.40 (q,1H,J=6.8) 3.13-3.0 (m,1H) 3.04 (d,2H,J=3.8) 2.58 (s,3H) 2.30-2.20 (m,1H) 2.20 (s,3H) 1.14 (d,3H,J=6.6) 1.03 (d,3H,J=6.8) ^{13}C NMR: δ 169.50 (s) 144.17 (s) 138.02 (s) 128.36 (d) 127.80 (d) 127.07 (d) 126.24 (d) 125.64 (d) 87.58 (d) 77.45 (d) 75.41 (d) 66.99 (d) 61.70 (t) 61.42 (d) 38.58 (q) 35.95 (q) 8.15 (q) 6.79 (q) IR (KBr): 1642 cm^{-1} (CO) HRMS Calcd: 394.226 Found 394.226. Anal. Calcd. for $C_{24}H_{30}N_2O_3$: C:73.07; H: 7.66; N: 7.10 Found: C: 72.60; H: 7.63; N: 7.14.

4-Menthyloxy-but-3-enoic acid (2.31)
A solution of isopropylmagnesium bromide in THF (1.2M, 7 mL) was cooled to -80°C and 85 mg (0.4 mmol) of CuBr.DMS was added followed by 2.1 mL of HMPA. A solution of 1.43 g (6 mmol) 5-menthyloxy-2(5*H*)-furanone **2.16** and 1.5 mL of TMSCl in 20 mL of THF was added dropwise in 40 min. The mixture was stirred at -80°C for 3 h and then poured into 150 mL of sat. NH_4Cl solution. After extraction with 3 × 50 mL ether, the combined organic layers were washed with

respectively 0.2 N HCl and water (2 × 50 mL) and dried (Na_2SO_4). Concentration in vacuo afforded 1.76 g of a yellow oil, which was purified by chromatography (silica gel, first CH_2Cl_2 followed by ether) to give 220 mg (0.92 mmol, 15%) of **2.31** containing <5% impurities.
^{1}H NMR: δ 6.24 (d, 1H,J=12.4) 4.94 (dt, 1H,J=7.7,J=12.4) 3.55-3.42 (m,1H) 2.97 (dd,2H,J=0.9,J=7.7) 2.16-2.01 (m,3H) 1.71-1.62 (m,2H) 1.40-1.27 (m,2H) 1.09-0.68 (m,18H) ^{13}C NMR: δ 177.71 (s) 148.58 (d) 96.25 (d) 47.69 (d) 40.93 (t) 34.29 (d) 33.09 (d) 31.45 (d) 25.70 (d) 23.36 (t) 22.08 (q) 20.72 (q) 16.28 (t) HRMS calcd. for $C_{14}H_{24}O_3$: 240.173 Found: 240.173.

(4*R*)(5*R*)-4-(*n*-Butyl)-5-(*l*-menthyloxy)-2(3H)-dihydrofuranone (2.36)
A suspension of CuI (1.90 g, 10 mmol) in 15 mL of ether was cooled to -30°C and 4.1 mL 2.4 N (10 mmol) nBuli in hexanes was added via syringe in 5 min. The brown suspension was stirred at −30°C for 45 min, cooled to -70°C and 2.04 g (10 mmol) of $Al(OiPr)_3$ was added at once. The resulting heterogeneous mixture was stirred at -70°C for 20 min and a solution of 0.48 g (2.0 mmol) (5*R*)-menthyloxy-2(5*H*)-furanone in 10 mL ether was added dropwise in 15 min. Stirring at −70°C was continued for 80 min and the mixture was poured into a stirred saturated NH_4Cl solution (100 mL). The mixture was stirred for 15 min and filtered over Celite, rinsed several times with ether and the filtrate layers separated. The water layer was extracted with 2 x 30 mL ether and the combined organic layers were washed with brine and dried (Na_2SO_4). Concentration in vacuo gave 0.58 g of a slightly yellow oil. ^{1}H NMR of the crude product shows a mixture of *trans* 1,4-addition product **2.36**, starting material (<10%) and an aldehyde (<10%). The product was purified by bulb-to-bulb distillation (130°C, 0.01 mmHg) to give 0.435 g (1.5 mmol, 73%) of **2.36** as a white solid. Analytically pure product was obtained by crystallization from hexanes at -18°C; mp 66.8-68.6°C
^{1}H NMR: δ 5.35 (d,1H,J=2.1) 3.50 (dt,1H,J=10.4,J=4.3) 2.80 (dd,1H,J=7.7,J=7.1) 2.30-2.01 (m,4H) 1.70-0.76 (m,25H) ^{13}C NMR: δ 176.08 (s) 104.99 (d) 76.84 (d) 47.65 (d) 41.46 (d) 39.75 (t) 34.19 (t) 33.78 (t) 31.50 (t) 31.24 (d) 29.02 (t) 25.31 (d) 22.96 (t) 22.36 (t) 22.13 (q) 20.78 (q) 15.50 (q) 13.79 (q) HRMS calcd: 296.235 found 296.235 Anal. Calcd for $C_{18}H_{32}O_3$: C: 72.98; H: 10.89 Found C: 72.89; H: 11.09. $[\alpha]^{23}_D$ -156 (c 0.50, $CHCl_3$)

***rac* 4-(n-Butyl)-5-methoxy-2(3*H*)-dihydrofuranone (2.37 R = n-butyl, OR' = OCH_3)**
Prepared from 0.34 g (3.0 mmol) of **2.17**, 1.90 g (10 mmol) of CuI, 2.04 g (10 mmol) of $Al(OiPr)_3$ and 4.1 mL of 2.4N *n*BuLi in hexanes, following the procedure for **2.36**. The crude product (0.29 g) concisted of isopropanol, starting material (<10%), several unidentified by products (<30%) and **2.37** as a mixture of *trans* and *cis* substituted furanones, ratio 9 : 1, according to the ^{1}H NMR spectrum. The product was not further purified.
^{1}H NMR: δ *trans*: 5.05 (d,1H,J=2.1) 3.47 (s,3H) 2.77 (dd,1H,J=17.5,J=8.1) 2.15 (dd,1H,J=17.5,J=4.3) 1.60-1.18 (m,7H) 0.89 (t,3H,J=6.8) *cis*: 5.25 (d,1H,J=4.7) 3.45 (s,3H) 2.49-2.19 (m,2H) 1.60-1.18 (m,7H) 0.89 (t,3H,J=6.8)

General procedures for the conjugate addition of organocopper reagents derived from Grignard reagents: (See Table 2.4)
Method 1; stoichiometric amounts of Cu(I)-salts: To a suspension of CuI in ether was added at

−20°C a solution of the organomagnesium reagent in ether or THF. Stirring was continued for 30 min and the mixture was cooled to -70°C. Then $Al(OiPr)_3$ was added at once and after stirring for 20 min at -70°C, a solution of **2.16** or **2.17** in ether was added dropwise keeping the temperature below -70°C. Stirring was continued for the time indicated in Table 2.4 at the given temperature and the reaction mixture was poured into sat NH_4Cl (aq). The work up procedure described for **2.36** was followed and the crude product analyzed by ^1H NMR.

Method 2; catalytic amounts of Cu(I)-salts: A solution of a Grignard reagent in ether or THF was cooled to -20°C and a catalytic amount of a Cu(I)-salt was added. Stirring at -20°C was continued for 30 min and the mixture was subsequently cooled to -70°C. $Al(OiPr)_3$ was added at once and the mixture was stirred for 20 min at -70°C followed by dropwise addition of a solution of **2.16** or **2.17** in ether. Stirring was continued for the time indicated in Table 2.4 at the given temperature and the reaction mixture was poured into sat NH_4Cl (aq). The work up procedure described for **2.36** was followed and the crude product analyzed by ^1H NMR.

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