

## Sequential cross-coupling reactions as a versatile synthetic tool

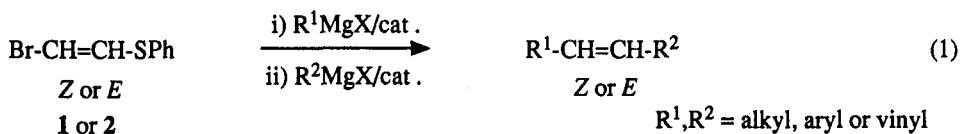
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**Abstract** - Recent developments of our stereospecific procedure for the synthesis of olefins will be reported. Stereodefined 1-silylated 1,3-dienes with a *E-E* or *E-Z* configuration have been prepared. 1,4-Disilylated *E,E*-1,3-diene and 1,6-disilylated *E,E,E*-1,3,5-triene have been also obtained and the highly chemoselective substitution of the silyl group with acyl chlorides in the presence of aluminum trichloride has led to silylated ketones and dicarbonyl compounds with a conjugated (all *E*) diene and triene structure. Furthermore, using a variation of the procedure, insect sex pheromones presenting a *E-Z* or *Z-E* conjugated diene structure have been prepared with high stereoselectivity. *Z*- or *E*-1-Bromo-2-arylsulfinylethenes, when reacted with Grignard reagents or with cuprates, produced different compounds, leading to aryl alkyl sulfoxides or aryl alkenyl sulfoxides respectively. Optically active 1-bromo-1-*p*-tolylsulfinylethene reacted with Grignard reagents with inversion of configuration, leading to chiral sulfoxides with high optical purities. Finally, the sequential cross-coupling approach has been also applied to the synthesis of carbonyl compounds, such as ketones, 1,4-ketoaldehydes, and 1,4-diketones, starting from *S*-phenyl carbonochloridothioate and Grignard reagents in the presence of Ni(II) or Fe(III) as catalysts. The versatility of the ketone synthesis has been demonstrated by the preparation of natural products, such as *Z*-jasmone and dihydrojasmone. By means of di-Grignard reagents a simple route to 1,*n*-diketones ( $n \geq 8$ ) and long chain  $\alpha,\omega$ -dicarboxylic acid thiol esters has been also devised.

### INTRODUCTION

In spite of the large number of methods for the synthesis of 1,2-disubstituted olefins, when stereoselectivity is required, the synthetic task becomes much more difficult. An important contribution to the synthesis of vinyl derivatives is represented by the cross-coupling reaction of unsaturated halides with organometallic compounds, in the presence of nickel or palladium catalysts (ref. 1), leading to the stereoselective formation of the carbon-carbon bond. In recent years we reported a highly stereospecific route to *Z*- or *E*-1,2-disubstituted ethenes (refs. 2, 3), based upon sequential cross-coupling reactions of Grignard reagents with *Z*- or *E*-1-bromo-2-phenylthioethene (**1** or **2**) in the presence of transition metal catalysts, as in eq. 1:

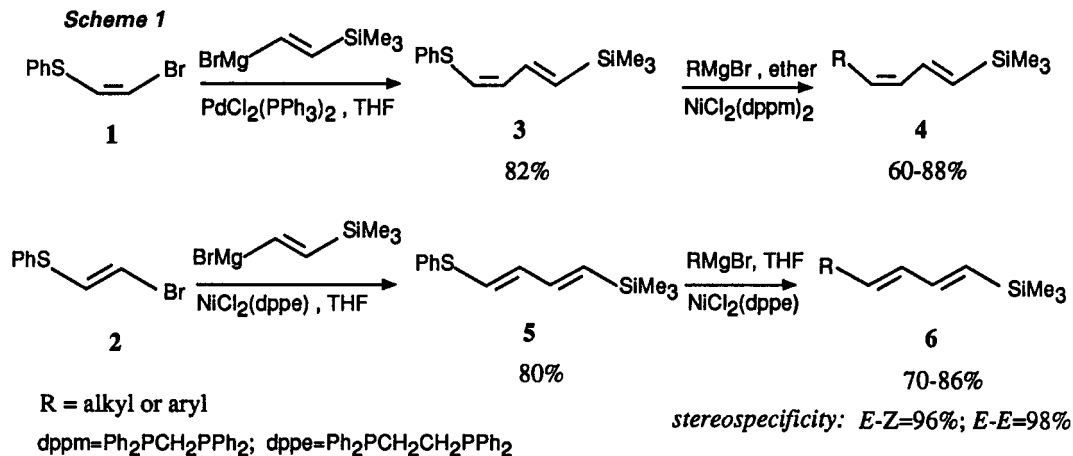


A variety of synthetic applications have been already described (ref. 3). In this paper we report the recent developments of the method, regarding mainly the synthesis of stereodefined conjugated dienes or trienes, the preparation of chiral sulfoxides, and the extension of the sequential cross-coupling approach to the synthesis of carbonyl compounds.

## 1. SYNTHESIS OF CONJUGATED DIENES AND TRIENES

## 1.1 1-Silylated 1,3-dienes

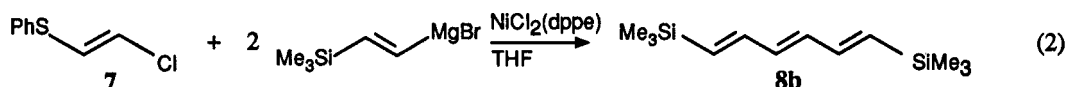
A highly stereospecific synthesis of doubly stereodefined conjugated 1-silylated dienes, a class of compounds of considerable interest in cycloaddition reactions (ref. 4), was performed by means of two sequential cross-coupling reactions between *Z*- or *E*-1-bromo-2-phenylthioethene **1** or **2** and Grignard reagents, in the presence of transition metal catalysts (ref. 5), as reported in Scheme 1:



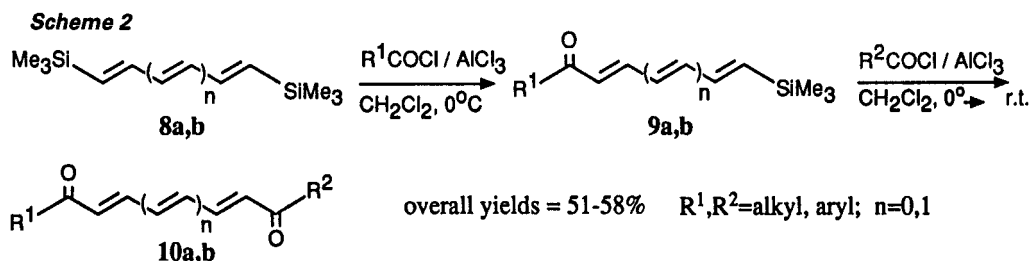
The coupling of compound **1** with *E*-2-trimethylsilyl-1-butenylmagnesium bromide in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as a catalyst, or the coupling of compound **2** with the same reagent in the presence of catalytic amounts of NiCl<sub>2</sub>(dppe), led to the dienylyl sulfide **3** or **5**, with stereoisomeric purity of 96% and 98% respectively. Various *1E,3Z*- or *1E,3E*-1-trimethylsilyl-1,3-dienes, **4** or **6**, were obtained by reacting the intermediate **3** or **5** with different Grignard reagents, in the presence of Ni-phosphine catalysts.

## 1.2 Silylated ketones and dicarbonyl compounds with a conjugated diene and triene structure

Due to our interest in the synthesis of stereodefined unsaturated organosilicon compounds, we prepared disilylated compounds **8**, namely (*1E,3E*)-1,4-bis(trimethylsilyl)-1,3-butadiene **8a**, by a known coupling process involving *E*-2-trimethylsilyl-1-butenylmagnesium bromide (ref. 6), and (*1E,3E,5E*)-1,6-bis(trimethylsilyl)-1,3,5-hexatriene **8b**, by means of cross-coupling reactions between the readily available *E*-1-chloro-2-phenylthioethene **7** (ref. 7) and the same Grignard reagent, as in eq. 2:



In this section we now describe some relevant results regarding a new synthetic approach to stereodefined (all *E*) silylated ketones and dicarbonyl compounds (ref. 8). As depicted in Scheme 2, the highly chemoselective substitution of a trimethylsilyl group of **8a** (*n*=0) or **8b** (*n*=1) with acyl chlorides in the presence of AlCl<sub>3</sub> affords silylated ketones **9a,b**. Subsequent substitution of the second silyl group with an other acyl chloride in the same reaction flask leads to the diketones derivatives **10a,b**.

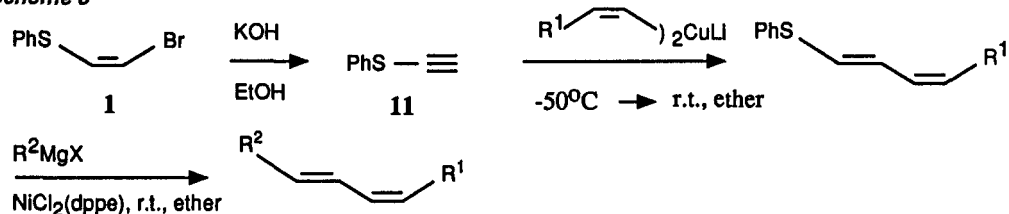


Both compounds **9** and **10** present several interesting features owing to the possibility of elaborating the silicon and/or the carbonyl functionality for further transformations. Following this procedure we are performing the synthesis of several natural compounds having a polyene structure.

1.3 Insect pheromones with a *E-Z* or *Z-E* configuration

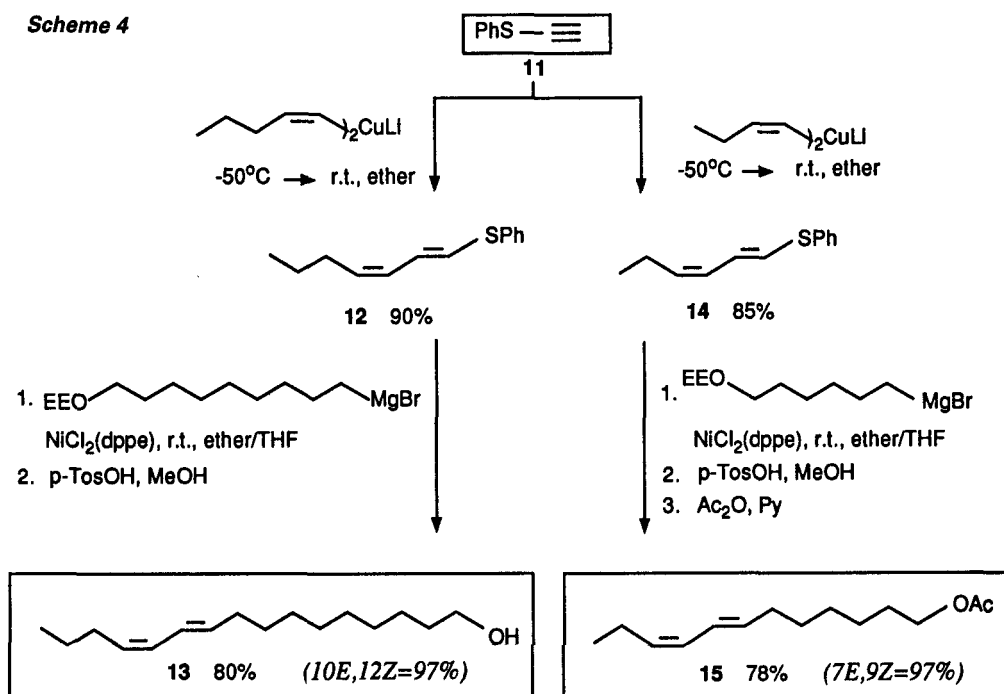
When we attempted to carry out the coupling reaction of **1** or **2** with *Z*-dialkenyl cuprates in the conditions adopted for vinyl halides (ref. 9), unsatisfactory results were obtained. Nevertheless, adopting a variation of our procedure, conjugated dienes with a *E-Z* or *Z-E* configuration were obtained with high stereoselectivity. Phenylthioacetylene **11**, easily prepared from *Z*-1-bromo-2-phenylthioethene **1** (ref. 10), was subjected to addition reactions of *Z*-dialkenyl cuprates, obtaining stereodefined alkadienyl sulfides. The cross-coupling reaction of these intermediates with Grignard reagents, in the presence of a Ni(II) complex, led to the desired dienes (ref. 11) (Scheme 3).

Scheme 3



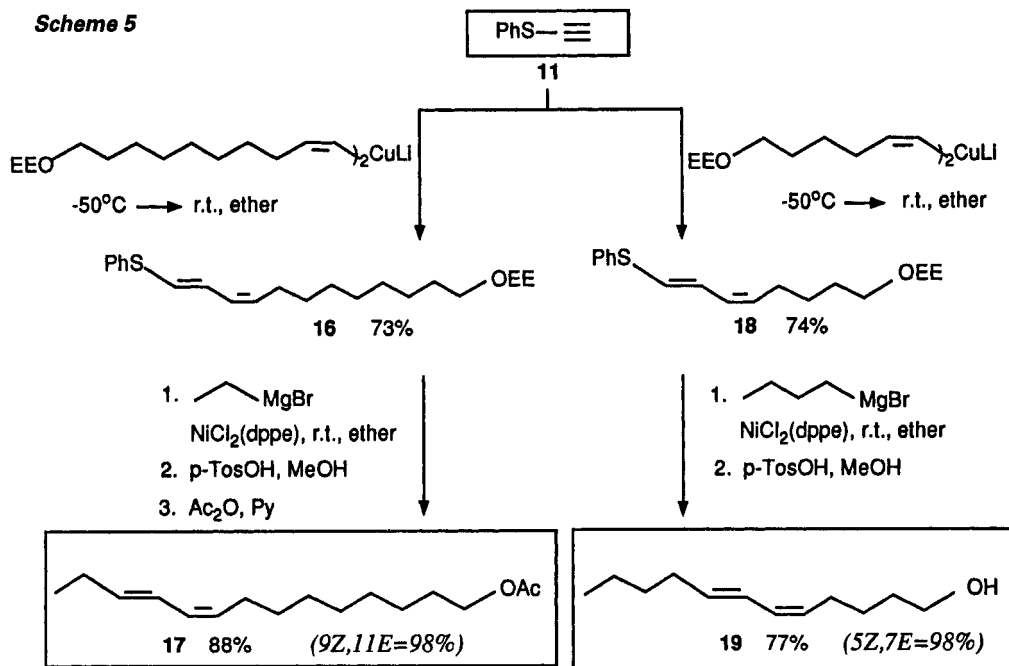
Insect sex pheromones of *E-Z* configuration (ref. 12), such as (10*E*,12*Z*)-hexadeca-10,12-dien-1-ol **13**, bombykol, the pheromone of *Bombyx mori*, the silkworm moth, and (7*E*,9*Z*)-dodeca-7,9-dien-1-yl acetate **15**, the pheromone of *Lobesia botrana*, the european grape vine moth, were prepared with this procedure (Scheme 4). Compounds having a *Z-E* configuration, such as (9*Z*,11*E*)-tetradeca-9,11-dien-1-yl acetate **17**, the pheromone of *Spodoptera littoralis* (ref. 12), the Egyptian cotton leafworm, and (5*Z*,7*E*)-dodeca-5,7-dien-1-ol **19**, the pheromone of *Malacosoma disstria* (ref. 13), the forest tent caterpillar, were synthesized in an equally straightforward manner (Scheme 5).

Scheme 4



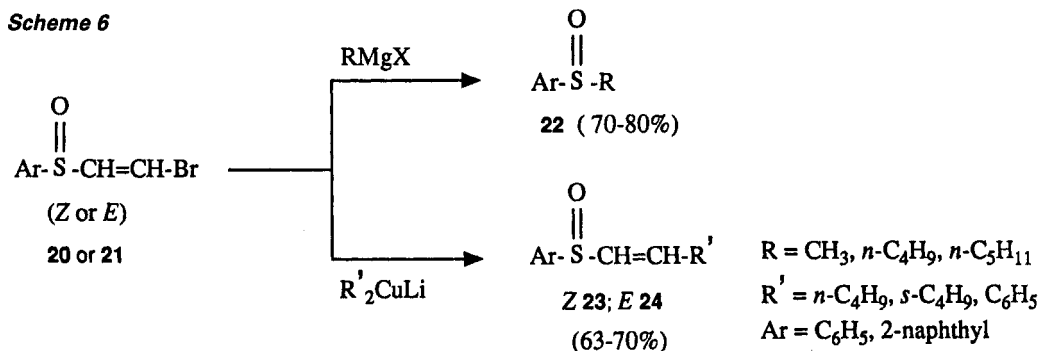
In particular, to obtain pheromones with a *E-Z* conjugated diene structure, a *Z*-dialkenylcuprate was reacted with phenylthioacetylene **11**, leading to the dienyl sulfides **12** or **14** with 97% stereoisomeric purity. The coupling reaction with a suitable functionalized Grignard reagent, followed by removal of the protecting group, afforded the pheromone **13**, or the pheromone **15**, after the deprotection and the acetylation steps.

In order to prepare pheromones with a *Z-E* configuration, a functionalized *Z*-dialkenyl cuprate was added to phenylthioacetylene **11** and the sulfide intermediate (**16** or **18**) was allowed to react with the appropriate Grignard reagent. After removal of the protecting group and acetylation, the pheromone **17** or, after a simple deprotection step, the pheromone **19**, both with 98% stereoisomeric purity, were obtained.

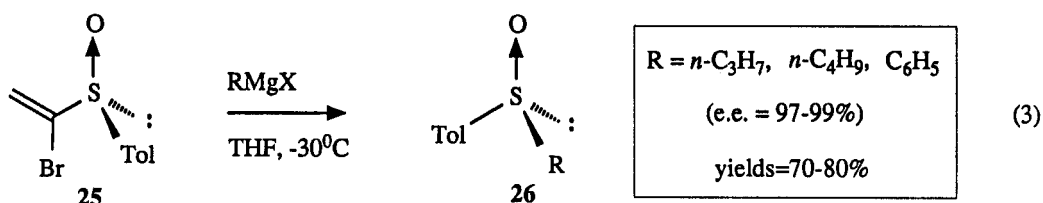


## 2. SYNTHESIS OF CHIRAL SULFOXIDES (ref. 14)

It was considered of interest to compare the reactions between *Z*- or *E*-1-bromo-2-arylsulfinylethene (**20** or **21**) and organometallic reagents with the reactions of the corresponding sulfides. It is worth noting that, in principle, the sulfoxides could offer the advantage of the presence of a chiral centre in the first cross-coupling step and could be easily reduced for the second cross-coupling reaction. However, we found that different types of products can be obtained, depending on the organometallic reagent. Indeed, as depicted in Scheme 6, if the reaction was carried out with Grignard reagents, formation of the carbon-sulfur bond was observed with production of the sulfoxides **22**. On the contrary, using diorgano cuprates as organometallic reagents, formation of the carbon-carbon bond was found to occur with production of alkenyl sulfoxides (**23,24**).

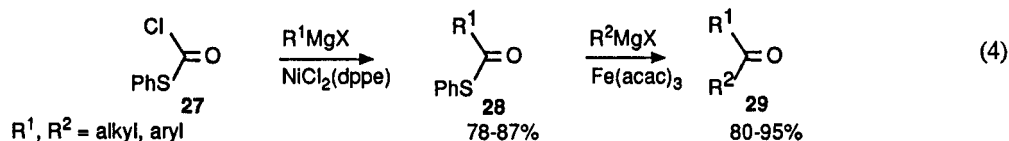


Moreover, relevant results were obtained in the case of optically active 1-bromo-1-*p*-tolylsulfinylethene **25**, prepared by the Andersen method (ref. 15), which reacts with Grignard reagents with inversion of configuration, leading to sulfoxides **26** with high optical purities (eq. 3). We are currently investigating the scope of this new synthesis of chiral sulfoxides.

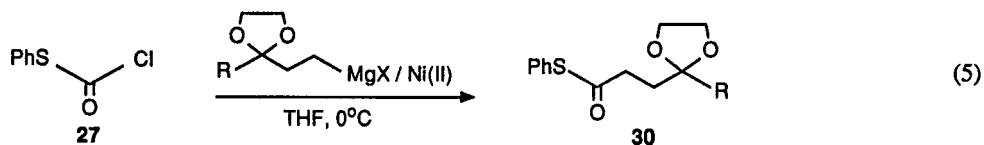


### 3. SYNTHESIS OF CARBONYL COMPOUNDS

Recently, we found that acyl chlorides can be successfully reacted with Grignard reagents, in the presence of Fe(III) catalyst (ref. 16), to give ketones in high yields without side reactions. On the basis of this finding, we devised a general procedure for the synthesis of the title compounds, by employing the same sequential cross-coupling approach. In fact, starting from the commercially available *S*-phenyl carbonochloridothioate **27**, it is possible to substitute selectively the chlorine atom with Grignard reagents, in the presence of catalytic amounts of a Ni(II)-phosphine complex, without concomitant displacement of the phenylthio group. The *S*-phenyl carbothioate intermediate **28** can be reacted with several Grignard reagents in the presence of a Fe(III) catalyst to give aliphatic and aromatic ketones **29** in high yields (ref. 17) (eq. 4).

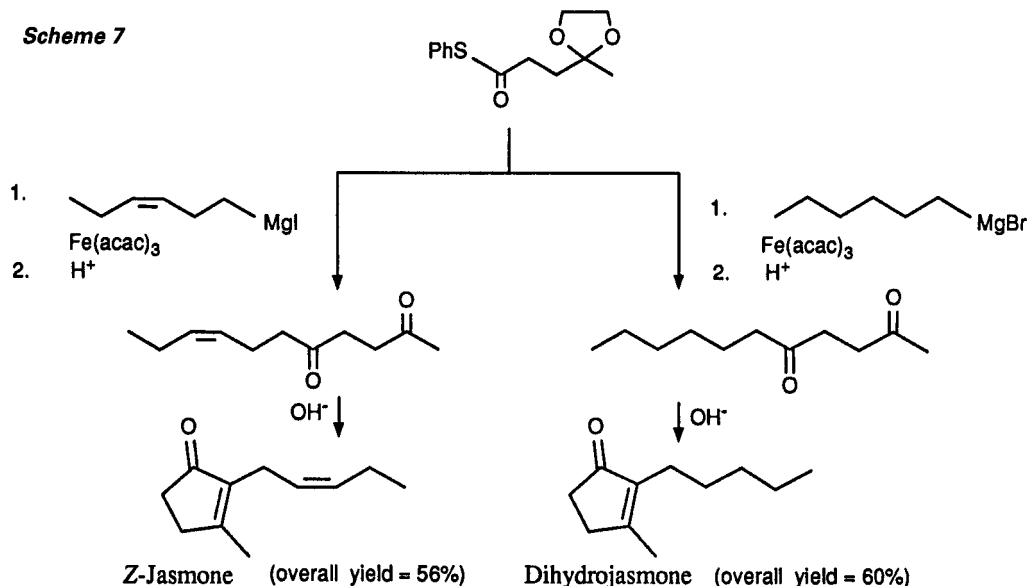


In order to prepare 1,4-ketoaldehydes or 1,4-diketones (ref. 18), it is sufficient to use, in the first cross-coupling reaction, the appropriate functionalized Grignard reagent, in the presence of NiCl<sub>2</sub>(dppe), to obtain the *S*-phenyl carbothioate intermediate **30** (R=H or Me) (eq. 5).

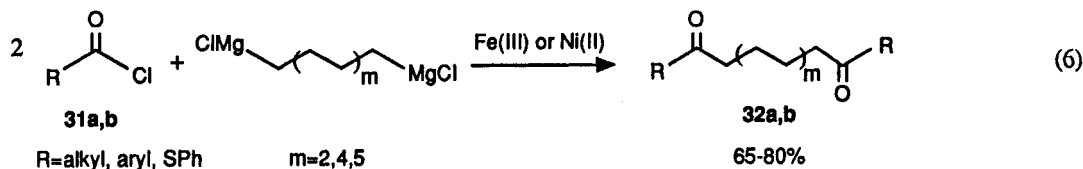


The subsequent reaction of compound **30** with several Grignard reagents, in the presence of Fe(acac)<sub>3</sub>, gives, after the deprotection step, various 1,4-ketoaldehydes or 1,4-diketones in high isolated yields (86-95%). The synthesis of 1,4-diketones, which can be easily transformed in *Z*-jasmane or dihydrojasmane, important perfumery constituents (ref. 19), is reported in Scheme 7.

Scheme 7



Using di-Grignard reagents, a new one-step strategy for the synthesis of symmetrical 1,n-diketones **32a** ( $n \geq 8$ , R=alkyl, aryl) and long-chain dicarboxylic thiol esters **32b** ( $n \geq 8$ , R=SPh) was devised (ref. 20) (eq. 6).



Among the various diketones **32a**, 2,15-hexadecanedione (R=Me, m=5), well known precursor of the naturally occurring fragrant compound with musk odor, muscone (ref. 21), was prepared in 80% yield.

#### Acknowledgement

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