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Direct Generation of Lithium Homoenolates from 3-Aryl α,β-Unsaturated Ketones or Esters by an Arene-Catalysed Lithiation: Synthesis of Substituted Tetrahydrofurans and γ-Butyrolactones

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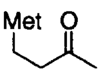
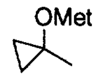
Abstract: The reaction of α,β-unsaturated ketones **1** with an excess of lithium powder, a catalytic amount of naphthalene (4 %) and different carbonyl compounds in the presence of boron trifluoride in THF at -78 - 0°C yields, after treatament with silyl nucleophile and final hydrolysis, the expected substituted tetrahydrofurans **5**. Similar methodology applied to β-aryl acrylic esters **6**, but without using boron trifluoride or silyl reagents yields the corresponding lactones **7**.

INTRODUCTION

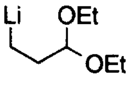
Metal homoenolates[1] of type **I** are important intermediates in synthetic organic chemistry because in their reaction with electrophiles it is possible to introduce an electrophilic fragment at the β-position with respect to the carbonyl functionality; when the electrophile is a carbonyl compound the reaction can be considered as a homoaldol process.[2] Such "umpolung synthons"[3] are very unstable when the metal is electropositive: for instance, the lithium derivative undergoes intramolecular S_N reaction giving a cyclopropanolate of type **II** even at low temperature.[4] Some synthetic alternatives to metal intermediates of type **I**[5] with Met = Li are shown in the structures **III**,[6] **IV**,[2] **V**[7] and **VI**[8] prepared either by deprotonation[2] or chlorine-[6,8a] or tin-lithium[7,8b] exchange. We have used successfully an arene-catalysed lithiation[9] under very mild conditions in order to prepare very reactive functionalised organolithium compounds[10] (from chlorinated precursors[11] or heterocyclic compounds[12]) or polylithium synthons.[13] In this paper we apply the arene-catalysed lithiation to the preparation of lithium homoenolates derived from α,β-unsaturated ketones or esters, combining this methodology with the use of Barbier-type reaction conditions.[14]



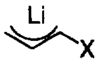
I



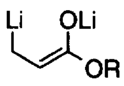
II



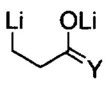
III



IV (X = OR, NR$_2$, ...)



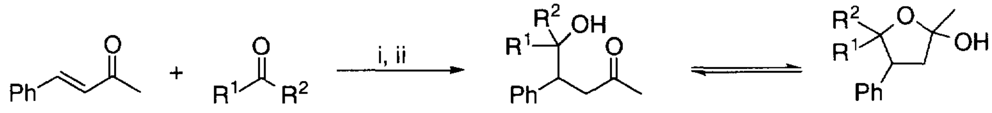
V



VI (Y = O, NR)

RESULTS AND DISCUSSION

The reaction of benzylideneacetone (**1a**) with cyclopentanone (1:1.2 molar ratio) in the presence of an excess of lithium powder (1:14 molar ratio) and a catalytic amount of naphthalene (1:0.08 molar ratio; 4 mol %) in THF at temperatures ranging between -78 and 0°C led, after hydrolysis with water, to the corresponding hydroxyketone **3** in 38% GLC yield (Scheme 1 and Table 1, entry 1). The use of different Lewis acids as catalysts (LiCl, $TiCl_4$, $SnBu^n_4$, $SnCl_4$, BF_3) gave variable yields, the best results being obtained (55% GLC yield) using boron trifluoride etherate (Table 1, entries 2-6). When the BF_3 catalysed reaction was applied to pivalaldehyde the corresponding diastereomeric mixture (1.5:1, *syn/anti*) was obtained in 70% GLC yield (Scheme 1 and Table 1, entry 7). The existence of an equilibrium between the hydroxyketone **3** and the corresponding hemiketal **3'** made the spectroscopic characterization of compounds **3/3'** difficult, so the mixture was studied by tandem GLC-MS. Anyhow, the existence of hydroxyketone **3a** was demonstrated by trapping the product resulting from the reaction with cyclopentanone with an excess of methyllithium, so the expected diol **4** was isolated, after final hydrolysis with water, in 30% overall yield (Scheme 2).



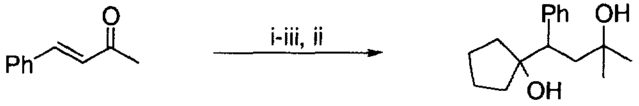
1a **2** **3** **3'**

Scheme 1. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (4 mol%), Lewis acid, THF, -78 to 0°C; ii, H_2O.

Table 1. Preparation of Compounds **3/3'** from Benzylideneacetone (**1a**)

	Carbonyl Compound **2**			Product[a]	
Entry	R^1	R^2	Lewis acid	No.	Yield (%)[b]
1	$-(CH_2)_4-$		-	**3a**	38
2	$-(CH_2)_4-$		LiCl	**3a**	25
3	$-(CH_2)_4-$		$TiCl_4$	**3a**	12
4	$-(CH_2)_4-$		$SnBu^n_4$	**3a**	13
5	$-(CH_2)_4-$		$SnCl_4$	**3a**	47
6	$-(CH_2)_4-$		BF_3	**3a**	55
7	Bu^t	H	BF_3	**3b**	70[c]

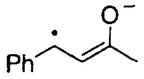
[a] Products **3/3'** were >90% pure and were characterised by tandem GLC/MS. [b] GLC yield. [c] 1.5/1 *syn/anti* diastereoisomers mixture (GLC).



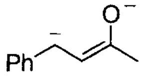
1a **4** (30 %)

Scheme 2. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (4 mol%), $(CH_2)_4CO$, BF_3, THF, -78 to 0°C; ii, H_2O; iii, MeLi (4 eq), -78 to 20°C.

From a mechanistic point of view, we think that the reaction shown in Schemes 1 and 2 starts from a single electron transfer from the naphthalene radical anion (or the corresponding dianion) to the starting enone yielding a radical anion **VII**, which can take a second electron giving a dianion **VIII**, which in the presence of electrophile (Barbier-type conditions) reacts to afford the final product **3/3'**. Actually, when the process was carried out in absence of the electrophile (two-step process) the reaction did not work. On the other hand, the presence of phenyl group stabilising the radical and the negative charge on the adjacent carbon (benzylic position) is necessary, because for aliphatic derivatives or non-substituted unsaturated ketones (*ie.* methyl vinyl ketone) the reaction failed.[15]

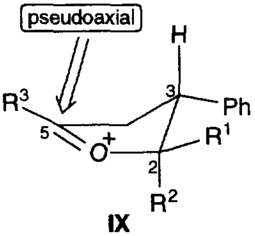


VII

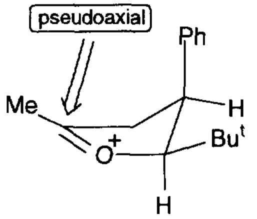


VIII

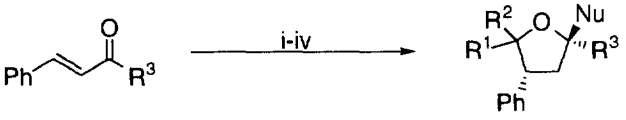
We then combined the reaction shown in Scheme 1 with the BF_3-assisted nucleophilic substitution of lactols by silylated species.[16] Thus, once the corresponding compounds **3/3'** were obtained following the above mentioned methodology, the crude products were treated with different silicon-containing nucleophiles in the presence of boron trifluoride in methylene chloride at temperatures ranging between -78 and 20°C, giving the expected substituted products **5** (Scheme 3 and Table 2). In this way the allyl group, a hydrogen and cyano group were introduced instead of the hydroxy group of the lactol **3'**. For symmetric ketones (3-pentanone, cyclopentanone or cyclohexanone) only the diastereoisomer shown in Scheme 3 was detected, except in the case of using cyanide derivative (Table 2, entry 6).[17] The obtained stereochemistry was assigned according to the literature data[17] and by n.O.e. experiments (see Experimental Part) and can be explained considering that the nucleophilic attack takes place at the upper face of the most stable cationic intermediate of the type **IX**, which contains the phenyl group in a pseudoequatorial position.[16a] In the case of the pivalaldehyde derivative the most stable conformation for the *trans* cationic intermediate contains both groups in pseudoequatorial positions (**IX**, $R^1 = Bu^t$, $R^2 = H$) yields the corresponding product with 2*S**,3*R**,5*S** relative stereochemistry resulting from a pseudoaxial (upper) attack. For the *cis* intermediate the corresponding conformers (**IX**, $R^1 = H$, $R^2 = Bu^t$ and **X**) compete in the reaction with the nucleophile, so the expected upper attack yields a mixture of products with a relative 2*R**,3*R**,5*S** and 2*R**,3*R**,5*R** stereochemistry (2:1 molar ratio).



IX



X



1a: R^3 = Me
1b: R^3 = Ph

5

Scheme 3. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (4 mol %), R^1COR^2, BF_3, THF, -78 to 0°C; ii, H_2O; iii, $R^4{}_3SiNu$, BF_3, CH_2Cl_2, -78 to 20°C; iv, $NaHCO_3$-H_2O.

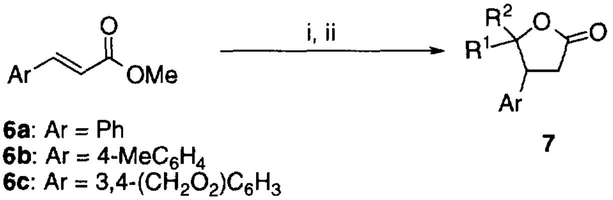
Table 2. Preparation of Compounds **5**

	Starting	Carbonyl Compound **2**			Product[a]	
Entry	Enone	R^1	R^2	$R^4{}_3SiNu$	No.	Yield (%)[b]
1	**1a**	$-(CH_2)_4-$		$Me_3SiCH_2CH=CH_2$	**5a**	43
2	**1a**	Et	Et	$Me_3SiCH_2CH=CH_2$	**5b**	31
3	**1a**	$-(CH_2)_5-$		$Me_3SiCH_2CH=CH_2$	**5c**	42
4	**1a**	Bu^t	H	$Me_3SiCH_2CH=CH_2$	**5d**	51[c]
5	**1a**	$-(CH_2)_5-$		Et_3SiH	**5e**	51
6	**1a**	$-(CH_2)_5-$		Me_3SiCN	**5f**	23[d]
7	**1b**	$-(CH_2)_5-$		$Me_3SiCH_2CH=CH_2$	**5g**	24

[a] All products **5** were >95% pure (GLC and 300 MHz ^1H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting enone **1**. [c] 2:2:1 diastereoisomers mixture (see text), deduced by GLC and 300 MHz ^1H NMR. [d] 4:1*trans/cis* diastereoisomers mixture (see text), deduced by GLC and 300 MHz ^1H NMR.

In the last part of this study we applied the reaction shown in Scheme 1 to methyl β-arylacrylic esters and obtained lactones **7** using ketones as electrophiles (Scheme 4 and Table 3). Some special remarks concerning this reaction should be pointed out: (a) the reaction gives higher yield in absence of Lewis acid catalyst (with BF_3, LiCl, or Me_3SiCl as additives the yields were poorer); (b) the process failed when aldehydes (Bu^tCHO, PhCHO) were used as electrophiles, intractable mixtures of products being obtained;[18] (c) in many cases neutral alumina should be used in the chromatographic purification, in order to avoid decomposition of the reaction product **7** (Table 3, entries 1, 2, 6 and 7, and footnotes b and c). In the case of using propiophenone a 1.6/1 *trans/cis* mixture was obtained (Table 3, entry 4), the stereochemistry being deduced by n.O.e experiments.

Mechanistically, the reaction involving β-aryl acrylic esters **6** could follow the same pathway as for the ketones **1**, mentioned above, that is, the formation of a radical anion following by the generation of a stabilised dianion which reacts *in situ* with the electrophile present in the reaction medium.[15]



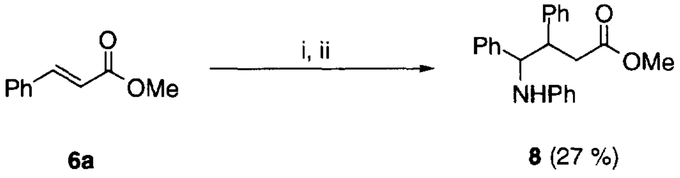
Scheme 4. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (4 mol%), R^1COR^2, THF, -78 to 0°C; ii, H_2O.

Table 3. Preparation of Compounds **7**

Entry	Starting Ester	Carbonyl compound R^1	R^2	Product[a] No.	Yield (%)[b]
1	**6a**	Et	Et	**7a**	86
2	**6a**	Pr^i	Pr^i	**7b**	43
3	**6a**	$-(CH_2)_4-$		**7c**	36[c]
4	**6a**	Ph	Et	**7d**	37[c,d]
5	**6a**	Ph	Ph	**7e**	60[c]
6	**6b**	Et	Et	**7f**	47
7	**6c**	Et	Et	**7g**	60

[a] All products **7** were >91% pure (GLC and 300 MHz ^1H NMR). [b] Isolated yield after column chromatography (neutral alumina, unless otherwise stated; hexane/ ethyl acetate) based on the starting ester **6**. [c] Silica gel was used in the chromatographic purification. [d] 1.6:1 *trans/cis* diastereoisomers mixture (GLC and 300 MHz ^1H NMR).

Finally, we used the reaction shown in Scheme 4 but using an imine, benzylideneaniline, as electrophilic reagent to obtain a 3/1 diastereoisomers mixture of the expected γ-aminoester **8** in poor isolated yield.



Scheme 5. *Reagents and conditions*: i, Li powder, $C_{10}H_8$ cat. (4 mol%), PhCH=NPh, THF, -78 to 0°C; ii, H_2O.

As a conclusion, we have described in this paper a new way to prepare *in situ* β-aryl substituted lithium homoenolates by direct napthalene-catalysed lithiation of β-arylsubstituted α,β-unsaturated ketones or esters, which under Barbier-type reaction conditions react with electrophiles, mainly carbonyl compounds, to give the corresponding reaction products. Due to the equilibrium between the obtained hydroxyketone with the corresponding lactols the reaction is connected with a silicon-promoted nucleophilic substitution in the presence of BF_3 to give substituted tetrahydrofurans; starting from β-aryl acrylic esters, and without using a Lewis acid, the reaction afforded directly substituted lactones.

EXPERIMENTAL PART

General.- For general information, see reference 19. Starting compounds **1** and **6a** were commercially available (Aldrich) and used as received. The other compounds **6b**[20] and **6c**[21] were prepared from the corresponding commercially available (Aldrich) acids by subsequent reaction with oxalyl chloride[22] in CH_2Cl_2 and methanol according to the literature procedures.[23]

Naphthalene-Catalysed Lithiation of Benzylideneacetone in the Presence of Electrophiles. Isolation of Compounds **3/3'**. *General Procedure.*- To a green suspension of lithium powder (100 mg, 14 mmol) and naphthalene (10 mg, 0.08 mmol) in THF (5 ml) was slowly added (*ca.* 10 min) a solution of α,β-unsaturated ketone **1a** (1 mmol), electrophile (1.2 mmol) and Lewis acid (1.2 mmol, see Table 1 and text) in THF (2 ml) at -78°C under an argon atmosphere. Stirring was continued for 2 h allowing the temperature to rise to 0°C. The resulting mixture was then hydrolysed with water (5 ml) and extracted with diethyl ether (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4, the solvents were removed (15 Torr) and the resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to give the corresponding products **3/3'**. Yields are reported in Table 1. GLC-MS data follow.

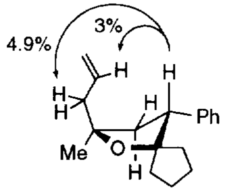
4-(1'-Hydroxycyclopentyl)-4-phenyl-2-butanone (**3a/3a'**): t_r 11.37 min; *m/z* 214 (M^+-18, 39%), 172 (10), 171 (59), 157 (12), 156 (12), 143 (15), 130 (17), 129 (87), 128 (27), 117 (10), 103 (13), 91 (45), 77 (19), 67 (19), 55 (11), 51 (13), 44 (15), 43 (100), 41 (17).

6,6-Dimethyl-5-hydroxy-4-phenyl-2-heptanone (**3b/3b'**): t_r 10.04 and 10.10 min; *m/z* 216 (M^+-18, 11%), 159 (17), 131 (16), 129 (13), 115 (11), 57 (18), 43 (100).

Naphthalene-Catalysed Lithiation of Benzylideneacetone in the Presence of Cyclopentanone. In Situ *Reaction of Hydroxyketone* **3a/3a'** *with Methyllithium. Isolation of 1-(3-Hydroxy-3-methyl-1-phenylbutyl)-1-cyclopentanol* (**4**).- Once the compound **3** was obtained, as described above, the crude product **3a/3a'** was dissolved in dry ether (10 ml) and cooled at -78°C and to the resulting solution was added MeLi (4 mmol, 1.6 M solution in ether). The mixture was stirred overnight allowing the temperature to rise to 20°C. Then, it was hydrolysed with water (5 ml), and extracted with ether (2x20 ml) and the organic layer dried over Na_2SO_4. Solvents were removed *in vacuo* (15 Torr) and the resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to give the corresponding diol **4**. Yield is given in Scheme 2. R_f 0.18 (hexane/ethyl acetate: 2/1); t_r 12.69 min; ν (film) 3403 (OH), 3060, 3023, 1601, 1494 cm^{-1} (HC=C); δ_H 1.07, 1.14 (3H and 3H, respectively, 2s, 2xCH_3), 1.55-1.85 [10H, m, $(CH_2)_4$, 2xOH], 2.06, 2.18 (1H and 1H, respectively, 2dd, *J*=14.3, 2.7 and 14.3, 9.5, respectively, C*H*$_2$CHPh), 2.91 (1H, dd, *J*=9.5, 2.7, C*H*Ph), 7.20-7.35 (5H, m, Ph); δ_C 23.45, 23.6, 38.6, 38.65 $(CH_2)_4$, 29.5, 30.5 (2xCH_3), 44.55 (*C*H$_2$CHPh), 50.95 (*C*HPh), 126.6, 128.35, 129.2, 143.45 (Ph); *m/z* 212 (M$^+$-36, 8%), 157 (18), 146 (72), 132 (12), 131 (100), 129 (28), 128 (11), 115 (16), 104 (10), 91 (46), 85 (24), 77 (12), 67 (18), 59 (29), 55 (14), 43 (27).

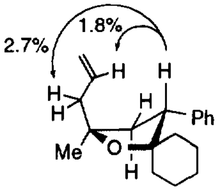
Naphthalene-Catalysed Lithiation of α,β-Unsaturated Ketone Derivatives in the Presence of Electrophiles. In Situ *Reaction of Hydroxytetrahydrofurans with Silyl Derivatives. Isolation of Compounds* **5**. *General Procedure.-* Once the compound of type **3** was obtained, as described above, the crude product of type **3/3'** was dissolved in dry CH_2Cl_2 (10 ml) and cooled at -78°C, and to the resulting solution was added triethylsilane, trimethylsilyl cyanide or allyltrimethylsilane (2 mmol) and $BF_3.Et_2O$[16b] (3 mmol). The mixture was stirred for 1h at the same temperature and overnight allowing the temperature to rise to 20°C. Then, it was hydrolysed with saturated aqueous $NaHCO_3$ (10 ml), and extracted with diethyl ether (2x20 ml) and the organic layer dried over Na_2SO_4. Solvents were removed *in vacuo* (15 Torr) and the resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate) to give the corresponding tetrahydrofurans **5**. Yields are reported in Table 2. Spectroscopic and analytical data follow.

2-Allyl-2-methyl-4-phenyl-1-oxaspiro[4,4]nonane (**5a**): R_f 0.37 (hexane); t_r 13.47 min; ν (film) 3070, 3032, 1639, 1602 cm^{-1} (HC=C); δ_H 1.10-1.85, 2.15-2.25, 2.32 [14H, 2H and 1H, respectively, m with s at 1.36, m and dd, respectively, *J*=7.3, 3.7, $(CH_2)_5$, CH_3, C*H*$_2$CHPh, C*H*$_2$CH=C], 3.45 (1H, dd, *J*=12.1, 8.1, C*H*Ph), 5.04-5.10 (2H, m, 2xCH_2=C), 5.80-6.00 (1H, m, C*H*=CH_2), 7.15-7.35 (5H, m, Ph); for n.O.e. data see the follow formula; δ_C 23.0, 23.95, 34.6, 37.5 $(CH_2)_4$, 28.9 (CH_3), 42.0 (*C*H$_2$CHPh), 47.1 (*C*H$_2$CH=C), 51.65 (*C*HPh), 80.8 (*C*CH$_3$), 94.0 (*C*CHPh), 117.45, 126.65, 128.1, 128.75, 135.2, 139.0 (Ph, HC=C); *m/z* 216 (M$^+$-40, 4%), 215 (M$^+$-41, 26), 172 (10), 157 (58), 132 (10), 131 (100), 129 (27), 115 (12), 91 (35), 55 (11), 43 (87) (Found: M$^+$-41, 215.1436. $C_{15}H_{19}O$ requires 215.1436).

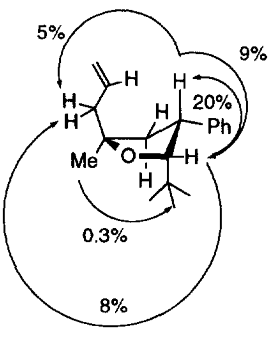


5-Allyl-2,2-diethyl-5-methyl-3-phenyltetrahydrofuran (**5b**): R_f 0.32 (hexane); t_r 13.15 min; ν (film) 3063, 3018, 1716, 1645 cm^{-1} (HC=C); δ_H 0.72, 1.04 (3H and 3H, respectively, 2t, *J*=7.3, 7.3, respectively, 2xC*H*$_3$CH$_2$), 0.80-0.95, 1.30-1.45 (1H and 4H, m and m with s at 1.36, respectively, C*H*$_2$CH$_3$, CH_3CO), 1.45-1.60, 1.75-1.90 (1 and 1H, respectively, 2m, C*H*$_2$CH$_3$), 2.13, 2.30-2.40 (1 and 3H, respectively, dd and m, *J*=12.5, 7.0, C*H*$_2$CHPh, C*H*$_2$CH=C), 3.54 (1H, dd, *J*=13.1, 7.0, C*H*Ph), 5.05-5.10 (2H, m, C*H*$_2$=C), 5.80-6.00 (1H, m, C*H*=CH$_2$), 7.15-7.35 (5H, m, Ph); δ_C 7.35, 7.95 (2x*C*H$_3$CH$_2$), 27.25, 28.6 (2x*C*H$_2$CH$_3$), 28.7 (*C*H$_3$CO), 40.35 (*C*H$_2$CHPh), 47.15 (*C*H$_2$CH=C), 48.4 (*C*HPh), 79.6 (*C*CH$_3$), 86.7 (*C*CHPh), 117.6, 126.55, 128.1, 128.4, 135.1, 138.8 (Ph, HC=C); *m/z* 229 (M$^+$-29, 2%), 217 (10), 172 (11), 159 (18), 132 (13), 131 (100), 117 (16), 91 (29), 57 (23), 44 (12), 43 (75) (Found: M$^+$-29, 229.1586. $C_{16}H_{21}O$ requires 229.1592).

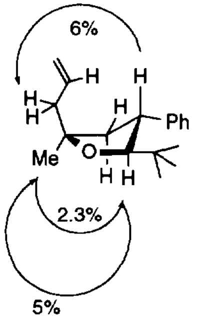
2-Allyl-2-methyl-4-phenyl-1-oxaspiro[4,5]decane (**5c**): R_f 0.39 (hexane); t_r 14.21 min; ν (film) 3061, 3027, 1741, 1602 cm^{-1} (HC=C); δ_H 1.20-1.75 [13H, m with s at 1.37, $(CH_2)_5$, CH_3], 2.12, 2.25-2.40 (1H and 3H, respectively, dd and m, respectively, *J*=12.5, 7.0, C*H*$_2$CHPh, C*H*$_2$CH=C), 3.15 (1H, dd, *J*=13.4, 7.0, C*H*Ph), 5.00-5.10 (2H, m, C*H*$_2$=C), 5.85-6.00 (1H, m, C*H*=C), 7.15-7.35 (5H, m, Ph); for n.O.e. data see the follow formula; δ_C 21.45, 23.2, 25.65, 33.1, 37.85 $(CH_2)_5$, 29.1 (CH_3), 40.75 (CH_2CHPh), 47.5 ($CH_2CH{=}C$), 55.1 ($CHPh$), 79.8 (CCH_3), 83.7 ($CCHPh$), 117.2, 126.6, 128.0, 128.65, 135,45, 139.0 (Ph, HC=C); *m/z* 230 (M^+-40, 3%), 229 (M^+-41, 18), 172 (13), 171 (26), 132 (11), 131 (100), 129 (17), 91 (26), 55 (10), 43 (59) (Found: M^+-41, 229.1592. $C_{16}H_{21}O$ requires 229.1592).



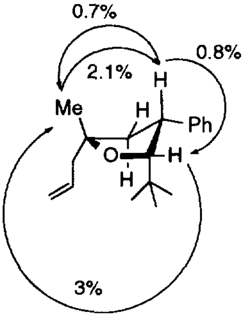
*5-Allyl-2-*tert*-butyl-3-phenyltetrahydrofuran* (**5d**): R_f 0.36 (hexane); t_r 11.61, 11.68, 12.10 min; ν (film) 3074, 3028, 1603, 1495 cm^{-1} (HC=C); δ_H (2*R**,3*R**,5*S**) 0.69 (9H, s, $3xCH_3$), 1.48 (3H, s, CH_3CO), 1.92, 2.20-2.55 (1H and 3H, respectively, dd and m, respectively, *J*=13.1, 4.9, CH_2CHPh, $CH_2CH{=}C$), 3.40-3.45 (1H, m, $CHPh$), 3.78 (1H, d, *J*=6.1, CHO), 5.05-5.15 (2H, m, $CH_2{=}C$), 5.80-6.00 (1H, m, CH=C), 7.10-7.35 (5H, m, Ph); (2*S**,3*R**,5*S**) 0.78 (9H, s, $3xCH_3$), 1.32 (3H, s, CH_3CO), 1.80, 2.20-2.55 (1H and 3H, respectively, dd and m, respectively, *J*=12.8, 11.0, CH_2CHPh, $CH_2CH{=}C$), 3.10-3.25 (1H, m, $CHPh$), 3.87 (1H, d, *J*=10.1, CHO), 5.05-5.15 (2H, m, $CH_2{=}C$), 5.80-6.00 (1H, m, CH=C), 7.10-7.35 (5H, m, Ph); (2*R**,3*R**,5*R**) 0.77 (9H, s, $3xCH_3$), 1.23 (3H, s, CH_3CO), 2.00-2.10, 2.20-2.55 (1H and 3H, respectively, 2m, CH_2CHPh, $CH_2CH{=}C$), 3.10-3.25 (1H, m, $CHPh$), 3.84 (1H, d, *J*=9.8, CHO), 5.05-5.15 (2H, m, $CH_2{=}C$), 5.80-6.00 (1H, m, CH=C), 7.10-7.35 (5H, m, Ph); for n.O.e. data see the follow formula; δ_C 25.95, 26.6, 26.75, 27.3, 27.45, 27.65 (CH_3), 34.1, 34.2 (CCH_3), 44.85, 46.15, 46.65, 49.05, 49.25 (CH_2CHPh, $CH_2CH{=}C$), 46.75, 47.05, 48.3 ($CCHPh$), 79.8, 80.2 (CH_3CO), 88.05, 91.25, 92.15 (CHO), 117.3, 117.35, 117.45 ($CH_2{=}CH$), 126.1, 126.15, 127.7, 127.9, 128.45, 129.9, 135.1, 135.2, 143.25, 143.35, 143.6 (Ph); *m/z* 218 (M^+-40, 2%), 217 (11), 131 (80), 91 (15), 43 (100) (Found: M^+-41, 217.1588. $C_{15}H_{21}O$ requires 217.1592).



(2*R**,3*R**,5*S**)



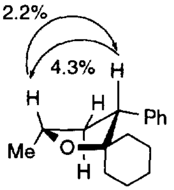
(2*S**,3*R**,5*S**)



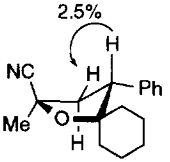
(2*R**,3*R**,5*R**)

2-Methyl-4-phenyl-1-oxaspiro[4,5]decane (**5e**): R_f 0.43 (hexane); t_r 12.19 min; ν (film) 3083, 3061, 3028, 1740, 1603 cm^{-1} (HC=C); δ_H 1.20-1.70 [13H, m with d at 1.37, *J*=7.3, $(CH_2)_5$, CH_3], 1.90-2.05, 2.25-2.35

(1H and 1H, respectively, 2m, C*H*$_2$CHPh), 3.01 (1H, dd, *J*=11.3, 7.0, C*H*Ph), 4.00-4.25 (1H, m, CHO), 7.10-7.35 (5H, m, Ph); for n.O.e. data see follow formula; δ_C 22.05 (CH_3), 21.9, 23.2, 25.6, 34.4, 36.95 $(CH_2)_5$, 39.85 (*C*H$_2$CH), 55.9 (*C*HPh), 72.3 (CHO), 83.4 (*C*CHPh), 126.45, 128.0, 128.65, 140.5 (Ph); *m/z* 230 (M$^+$, 2%), 133 (13), 132 (90), 131 (12), 118 (15), 117 (100), 115 (16), 91 (26), 55 (26), 43 (16) (Found: M$^+$, 230.1660. $C_{16}H_{22}O$ requires 230.1670).

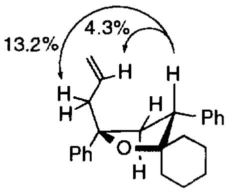


(2R*,4S*)-*2-Methyl-4-phenyl-1-oxaspiro[4,5]-dec-2-yl Cyanide* (*trans*-**5f**): R_f 0.64 (hexane/ethyl acetate: 6/1); t_r 13.78 min; ν (film) 3061, 3029, 1602, 1496 (HC=C), 2211 (CN), 1102 cm^{-1} (CO); δ_H 1.41-1.67 [10H, m, $(CH_2)_5$], 1.75 (3H, s, CH_3), 2.40-2.55, 2.60 (1H and 1H, respectively, m and dd, respectively, *J*=12.7, 6.3, C*H*$_2$CHPh), 3.51 (1H, dd, *J*=13.3, 6.3, C*H*Ph), 7.15-7.40 (5H, m, Ph); for n.O.e. data see follow formula; δ_C 21.4, 22.95, 25.15, 34.45, 37.1 $(CH_2)_5$, 26.95 (CH_3), 43.35 (*C*H$_2$CCH$_3$), 54.95 (*C*HPh), 73.35 (*C*CH$_3$), 86.7 (*C*CHPh), 122.7 (CN), 127.3, 128.35, 128.4, 137.1 (Ph); *m/z* 229 (M$^+$-26, 1%), 228 (M$^+$-27, 3), 158 (13), 157 (100), 156 (70), 142 (20), 129 (14), 115 (21), 99 (34), 91 (15), 81 (13), 55 (18), 43 (24).



(2S*,4S*)-*2-Methyl-4-phenyl-1-oxaspiro[4,5]-dec-2-yl Cyanide* (*cis*-**5f**): R_f 0.48 (hexane/ethyl acetate: 6/1); t_r 13.87 min; ν (film) 3061, 3029, 1602, 1496 (HC=C), 2211 (CN), 1102 cm^{-1} (CO); δ_H 1.40-1.70 [10H, m, $(CH_2)_5$], 1.67 (3H, s, CH_3), 2.38, 3.00-3.15 (1H and 2H, respectively, dd and m, respectively, *J*=10.1, 4.9, C*H*$_2$C*H*Ph), 7.20-7.40 (5H, m, Ph); δ_C 21.2, 22.85, 25.4, 29.95, 36.85 $(CH_2)_5$, 28.8 (CH_3), 42.65 (*C*H$_2$CCH$_3$), 54.35 (*C*HPh), 71.15 (*C*CH$_3$), 87.65 (*C*CHPh), 123.45 (CN), 127.4, 128.35, 128.6, 136.35 (Ph); *m/z* 229 (M$^+$-26, 1%), 228 (M$^+$-27, 3), 158 (13), 157 (100), 156 (70), 142 (20), 129 (14), 115 (21), 99 (34), 91 (15), 81 (13), 55 (18), 43 (24).

2-Allyl-2,4-diphenyl-1-oxaspiro[4,5]decane (**5g**): R_f 0.54 (hexane); t_r 16.97 min; ν (film) 3061, 3027, 1741 cm^{-1} (HC=C); δ_H 1.52-1.86 [10H, m, $(CH_2)_5$], 2.51-2.61, 2.70-2.80 (3H and 1H, respectively, 2m, C*H*$_2$CHPh, C*H*$_2$CH=C), 3.30 (1H, dd, *J*=13.1, 7.0, C*H*Ph), 4.90-5.00 (2H, m, C*H*$_2$=C), 5.70-5.85 (1H, m, C*H*=C), 7.19-7.50 (10H, m, Ph); for n.O.e. data see the follow formula; δ_C 22.0, 23.4, 25.65, 31.9, 37.75, 41.6, 49.6 [$(CH_2)_5$, *C*H$_2$CHPh], 55.25 (*C*HPh), 83.55, 84.45 (2xCO), 117.4 (*C*H$_2$=C), 125.2, 126.15, 126.7, 127.7, 128.05, 128.75, 134.7, 138.65, 149.45 (*C*H=C, Ph); *m/z* 291 (M$^+$-41, 59%), 234 (12), 193 (54), 172 (15), 171 (100), 143 (12), 130 (22), 129 (45), 128 (14), 117 (13), 115 (54), 105 (93), 91 (58), 77 (48), 55 (18) (Found: M$^+$-41, 291.1740. $C_{21}H_{23}O$ requires 291.1749).



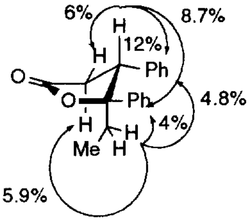
Naphthalene-Catalysed Lithiation of Cinnamic Ester Derivatives in the Presence of Electrophiles. Isolation of Compounds **7** *and* **8**. *General Procedure.-* To a green suspension of lithium powder (100 mg, 14 mmol) and naphthalene (10 mg, 0.08 mmol) in THF (5 ml) was slowly added (*ca.* 10 min) a solution of the cinnamic derivative **6** (1 mmol) and the electrophile (1.2 mmol) in THF (2 ml) at -78 °C under an argon atmosphere. Stirring was continued for 3 h allowing the temperature to rise to 0 °C. The resulting mixture was then hydrolysed with water (5 ml) and extracted with diethyl ether (2x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvents were removed (15 Torr) to give a residue which was purified by column chromatography (silica gel or neutral aluminum oxide; hexane/ethyl acetate, see footnotes b and c in Table 3 and text) to give the corresponding lactones **7** and aminoester **8**. Yields are included in Table 3 and Scheme 5. Spectroscopic and analytical data as well as literature references for known compounds follow.

5,5-Diethyl-4-phenyltetrahydro-2-furanone (**7a**): R_f 0.2 (hexane/ethyl acetate: 6/1); t_r 13.30 min; ν (film) 3061, 3030, 1602, 1497 (HC=C), 1768 cm^{-1} (C=O); δ_H 0.73, 1.05 (3H and 3H, respectively, 2t, J=7.5, 7.5 respectively, $2xCH_3$), 1.10-1.38, 1.40-1.60, 1.70-1.85, 1.85-2.00 (1H, 1H, 1H and 1H, respectively, 4m, $2xCH_2CH_3$), 2.90, 2.98 (1H and 1H, respectively, 2dd, J=17.7, 8.5 respectively, CH_2CHPh), 3.65 (1H, t, J=8.5, C*H*Ph), 7.10-7.40 (5H, m, Ph); δ_C 7.65, 7.95 ($2xCH_3$), 27.1, 28.4 ($2xCH_2CH_3$), 35.3 (CH_2CHPh), 46.95 (*C*HPh), 91.6 (*C*CHPh), 127.55, 128.1, 128.65, 137.75 (Ph), 175.95 (C=O); *m/z* 218 (M^+, 1%), 118 (50), 117 (16), 105 (10), 104 (100), 91 (10), 57 (24).

5,5-Diisopropyl-4-phenyltetrahydro-2-furanone (**7b**): R_f 0.34 (hexane/ethyl acetate: 6/1); t_r 13.86 min; ν (film) 3037, 3035, 1601, 1473 (HC=C), 1767 cm^{-1} (C=O); δ_H 0.69, 1.16 (3H and 3H, respectively, 2t, J=7.0, 7.0, respectively, $2xCH_3$), 0.80, 1.10 (3H and 3H, respectively, 2t, J=6.7, 6.7, respectively, $2xCH_3$), 2.05-2.15, 2.30-2.45 [1 and 1H, respectively, 2m, $2xCH(CH_3)_2$], 2.85, 3.07 (1H and 1H, respectively, 2dd, J=18.1, 9.8 and 18.1, 10.1, respectively, CH_2CHPh), 3.90-4.00 (1H, m, C*H*Ph), 7.25-7.40 (5H, m, Ph); δ_C 17.8, 18.15, 18.35, 18.4 ($4xCH_3$), 32.45, 32.8 [$2xCH(CH_3)_2$], 35.6 (CH_2), 43.95 (*C*HPh), 127.35, 128.45, 128.65, 137.55 (Ph), 176.05 (C=O); *m/z* 218 (M^+-28, 3%), 203 (35), 131 (26), 105 (24), 104 (100), 103 (15), 91 (15), 78 (11), 77 (11), 71 (21), 55 (12), 44 (12), 43 (71).

4-Phenyl-1-oxaspiro[4,4]nonan-2-one (**7c**):[24] R_f 0.32 (hexane/ethyl acetate: 6/1); t_r 13.79 min; ν (film) 3061, 3030, 1603, 1497 (HC=C), 1771 cm^{-1} (C=O); δ_H 1.40-2.15 [8H, m, $(CH_2)_4$], 2.89, 2.96 (1H and 1H, respectively, 2dd, J=17.4, 8.5 and 17.4, 8.2, respectively, CH_2CHPh), 3.62 (1H, t, J=8.4, C*H*Ph), 7.15-7.40 (5H, m, Ph); δ_C 23.05, 23.35, 33.95, 36.2, 38.05 ($5xCH_2$), 48.7 (*C*HPh), 98.45 (*C*CHPh), 127.65, 127.9, 128.75, 138.05 (Ph), 175.85 (C=O); *m/z* 216 (M^+, 2%), 105 (16), 104 (100), 103 (13), 78 (11), 77 (10), 43 (10).

(4R,5S*)-5-Ethyl-4,5-diphenyltetrahydro-2-furanone* (*trans*-**7d**): R_f 0.40 (hexane/ethyl acetate: 6/1); t_r 14.85 min; ν (film) 3061, 3023, 1713, 1497 (HC=C), 1771 cm^{-1} (C=O); δ_H 0.63 (3H, t, J=7.3, CH_3), 1.55-1.70 (2H, m, CH_2CH_3), 2.82, 2.90 (1H and 1H, respectively, 2dd, J=17.7, 6.6, and 17.7, 7.8, respectively, CH_2CHPh), 3.74 (1H, dd, J=7.8, 6.6, C*H*Ph), 7.15-7.45 (10H, m, Ph); for n.O.e. experiments see the follow formula; δ_C 8.11 (CH_3), 30.15 (CH_2CH_3), 35.55 (CH_2CHPh), 53.15 (*C*HPh), 92.5 (*C*CHPh), 124.9, 127.55, 127.85, 128.45, 128.55, 128.7, 137.65, 142.25 (Ph), 176.35 (C=O); *m/z* 266 (M^+, 1%), 135 (11), 105 (22), 104 (100), 78 (10), 77 (17) (Found: M^+, 266.1298. $C_{18}H_{18}O_2$ requires 266.1306).



(4R,5R*)-5-Ethyl-4,5-diphenyltetrahydro-2-furanone* (*cis*-**7d**): R_f 0.43 (hexane/ethyl acetate: 6/1); t_r 15.25 min; ν (film) 3061, 3023, 1713, 1497 (HC=C), 1771 cm^{-1} (C=O); δ_H 0.86 (3H, t, *J*=7.3, CH$_3$), 1.65-1.80 (2H, m, C*H*$_2$CH$_3$), 2.75-2.95 (2H, m C*H*$_2$CHPh), 3.75-3.85 (1H, m, C*H*Ph), 7.10-7.40 (10H, m, Ph); δ_C 8.35 (CH$_3$), 27.65 (*C*H$_2$CH$_3$), 33.5 (*C*H$_2$CHPh), 52.35 (*C*HPh), 92.9 (*C*CHPh), 126.1, 127.1, 127.6, 128.1, 128.3, 128.5, 137.55, 140.3 (Ph), 176.0 (C=O); *m/z* 266 (M$^+$, 1%), 135 (11), 105 (22), 104 (100), 78 (10), 77 (17).

4,5,5-Triphenyltetrahydro-2-furanone (**7e**):[25] R_f 0.32 (hexane/ethyl acetate: 6/1); t_r 17.62 min; ν (KBr) 3087, 3061, 3033, 1602, 1496 (HC=C), 1782 (C=O), 1134 cm^{-1} (CO); δ_H 2.78, 2.98 (1H and 1H, respectively, 2dd, *J*=17.4, 4.6 and 17.4, 7.9, respectively, CH$_2$), 4.48 (1H, dd, *J*=7.9, 4.6, C*H*Ph), 7.00-7.65 (15H, m, Ph); δ_C 37.4 (CH$_2$), 50.95 (*C*HPh), 92.9 (*C*Ph$_2$), 126.05, 126.2, 127.15, 127.3, 128.1, 128.3, 128.5, 128.65, 138.45, 139.9, 143.1 (Ph), 175.75 (C=O); *m/z* 298 (M$^+$-60, 3%), 211 (28), 184 (14), 183 (100), 105 (93), 104 (53), 91 (60), 78 (13), 77 (65), 51 (23), 44 (32).

5,5-Diethyl-4-(4'-methylphenyl)tetrahydro-2-furanone (**7f**): R_f 0.38 (hexane/ethyl acetate: 6/1); t_r 14.10 min; ν (film) 3024, 1516 (HC=C), 1770 cm^{-1} (C=O); δ_H 0.73 (3H, t, *J*=7.3, C*H*$_3$CH$_2$), 1.03 (3H, t, *J*=7.5, C*H*$_3$CH$_2$), 1.10-1.25, 1.40-1.60, 1.65-1.80, 1.85-2.00 (1H, 1H, 1H and 1H, respectively, 4m, 2xC*H*$_2$CH$_3$), 2.34 (3H, s, C*H*$_3$Ph), 2.86, 2.93 (1 and 1H, respectively, 2dd, *J*=17.7, 8.6 and 17.7, 8.6, respectively, C*H*$_2$CHPh), 3.61 (1H, t, *J*=8.6, C*H*Ph), 7.05-7.15 (4H, m, Ph); δ_C 7.6, 7.9 (2x*C*H$_3$CH$_2$), 20.95 (*C*H$_3$Ph), 27.0, 28.35 (2x*C*H$_2$CH$_3$), 35.35 (*C*H$_2$CHPh), 46.55 (*C*HPh), 91.6 (*C*CHPh), 127.9, 129.25, 134.6, 137.2 (Ph), 176.0 (C=O); *m/z* 232 (M$^+$, 2%), 119 (10), 118 (100), 117 (20).

*4-{Benzo[*d*][1,3]dioxol-5-yl}-5,5-diethyltetrahydro-2-furanone* (**7g**): R_f 0.39 (hexane/ethyl acetate: 2/1); t_r 15.80 min; ν (film) 1767 (C=O), 1610 (HC=C), 925 cm^{-1} (CO); δ_H 0.76, 1.03 (3H and 3H, respectively, 2t, *J*=7.5, 7.5, respectively, 2xCH$_3$), 1.15-1.30, 1.45-1.60, 1.60-1.80, 1.80-2.00 (1H, 1H, 1H and 1H, respectively, 4m, 2xC*H*$_2$CH$_3$), 2.82, 2.94 (1 and 1H, respectively, 2dd, *J*=17.9, 8.6, respectively, CH$_2$C=O), 3.57 (1H, t, *J*=8.6, C*H*Ph), 5.97 (s, 2H, CH$_2$O), 6.60-6.65, 6.75-6.80 (2 and 1H, respectively, 2m, Ph); δ_C 7.7, 7.9 (2xCH$_3$), 26.95, 28.3 (2x*C*H$_2$CH$_3$), 35.5 (*C*H$_2$CHPh), 46.65 (*C*HPh), 91.6 (*C*CHPh), 101.2 (CH$_2$O), 108.25, 121.3, 131.4, 146.95, 147.95 (Ph), 175.8 (C=O); *m/z* 263 (M$^+$+1, 1%), 262 (M$^+$, 5), 149 (10), 148 (100) (Found: M$^+$, 262.1199. $C_{15}H_{18}O_4$ requires 262.1205).

Methyl 3,4-Diphenyl-4-phenylaminobutanoate (**8**): R_f 0.36 (hexane/ethyl acetate: 6/1); t_r 18.60 min; ν (film) 3400 (NH), 3085, 3059, 3028, 1601, 1503 (HC=C), 1735 cm^{-1} (C=O); δ_H 2.67, 2.78 (1H and 1H, respectively, 2dd, *J*=16.1, 8.2 and 16.1, 6.4, respectively, C*H*$_2$CHPh), 3.50-3.60 (4H, m with s at 3.50, C*H*CH$_2$, CH$_3$), 4.56 (1H, d, *J*=6.7, CHN), 6.35-6.40, 6.55-6.65, 6.95-7.30 (2H, 1H and 12H, respectively, 3m, Ph); δ_C 37.65 (CH$_2$), 48.75 (CH$_3$), 51.55 (*C*HCH$_2$), 61.6 (CN), 113.7, 117.6, 127.35, 127.4, 128.35, 128.4, 128.6, 139.4, 141.7, 147.2 (Ph), 172.5 (C=O); *m/z* 345 (M$^+$, 1%), 183 (17), 182 (100), 104 (14), 77 (27).

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