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DIRECT LITHIATION OF FUNCTIONALLY SUBSTITUTED ACRYLIC ACID DERIVATIVES

LITHIATION OF β-(2-FURANYL)- AND β-(2-THIENYL)-ACRYLIC ACIDS[1]

R. R. SCHMIDT* and R. HIRSENKORN
Fakultät Chemie, Universität Konstanz D-7750, Konstanz, Germany

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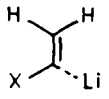
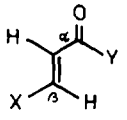
Abstract—Direct C-lithiation of β-functionally-substituted acrylates yields versatile building units for syntheses of butenolides, tetronates, cyclopentenones and derivatives, which are portions of many natural products. A wide variety of α- and β-substituents are compatible with this lithiation: alkyl-, aryl- and electron donating substituents in α-position or for instance an electron withdrawing ester group in β-position. Lithiation of aminomethylene malonitrile derivative **17** led to a new azafulvene **18**.

β-(2-Furanyl)- and β-(2-thienyl)-acrylates (**23–30**) were directly C-lithiated in α-, β-, or 5-position and α- or 5-position, respectively. Reactions with different electrophiles were carried out. The presence of the unprotected electrophilic carboxylic group allows for interesting ring closure reactions, for instance with carbonyl compounds to butenolides **42** and **43**. The three vinylic positions (α, β and C-5) are accessible to a highly site-selective successive lithiation and reaction with electrophiles, as demonstrated for the transformation of **25** to **45** via **42** and **44**.

Functionally substituted vinyllithium compounds **1** are of great interest as reactive intermediates especially if other unprotected groups are also present. Our investigations with β-substituted acrylic acids and derivatives **2–4** have demonstrated, that these compounds are accessible to direct lithiation of the α and/or β-position without previous protection of the carboxylic functionality.[2-15] This means that the generation of stable vinyllithium derivatives prevails over the expected 1,2- or 1,4-addition of the lithiating agent to acrylate system. This possible twofold lithiation of **2–4** leads to a preparative versatility, which for structural reasons is not accessible to aryl- and hetaryl systems.

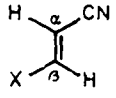


1



2 : Y = OR

3 : Y = NR_2



A : X = OR

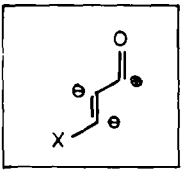
B : X = $N\langle^{R^1}_{R^2}$

C : X = SR

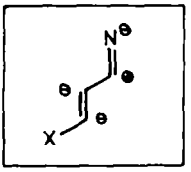
4

The regioselectivity of lithiation is mainly determined by the β-alkoxy, β-dialkylamino, β-N-acyl-N-alkylamino and β-alkylmercapto groups on one side and the carboxylic functionality on the other side.[7,11] In addition, some acrylic acid derivatives could be lithiated selectively in either the α- or β-positions by use of kinetic or thermodynamic control.[4,7,11] Table 1 contains typical vinyllithium derivatives, which were generated as intermediates in solution, in most cases quantitatively.[2-18] Table 1 demonstrates, that alkyl and aryl groups and electron donating substituents in the α-position are compatible with the β-lithiation (see the generation of **2Ab-β**, **2Ac-β**, **2Bb-β** – **2Bd-β**, **2Cb-β** – **2Cd-β** and **4Bb-β**).[19]

Reaction with electrophiles and especially with electrophilic–nucleophilic compounds (aldehydes, ketones, azomethines, esters, α,β-unsaturated carbonyl compounds, cumulenes, etc.) afforded numerous interesting products,[3-16] which are schematically compiled (Scheme 1). The multifunctionality and synthetic versatility of the lithiated intermediates are demonstrated by these reactions. Thus from **2–4** in stepwise reaction the valuable synthons I and II are generated, which are structural units of many natural products.



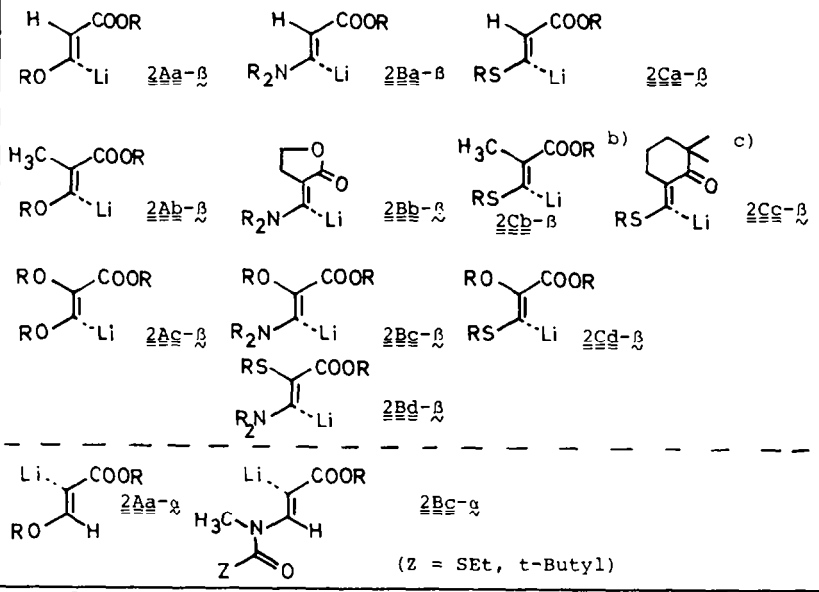
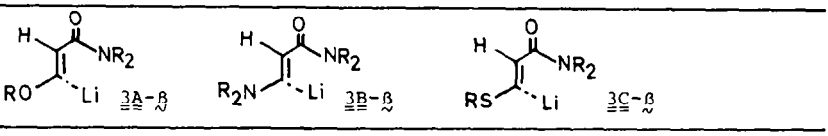
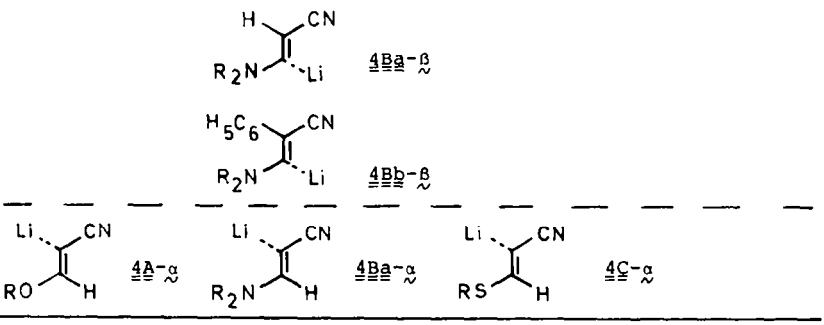
(I)



X = OR, NR_2, SR

(II)

Table 1. Typical functionalized vinyllithium intermediates[a])

Esters	
Amides	
Nitriles	

[a]) Further examples and comments, see ref. 2-16; R = Alkyl.

[b]) See ref. 17. [c]) See ref. 18. [d]) See ref. 16.

TETRONATE SYNTHESES

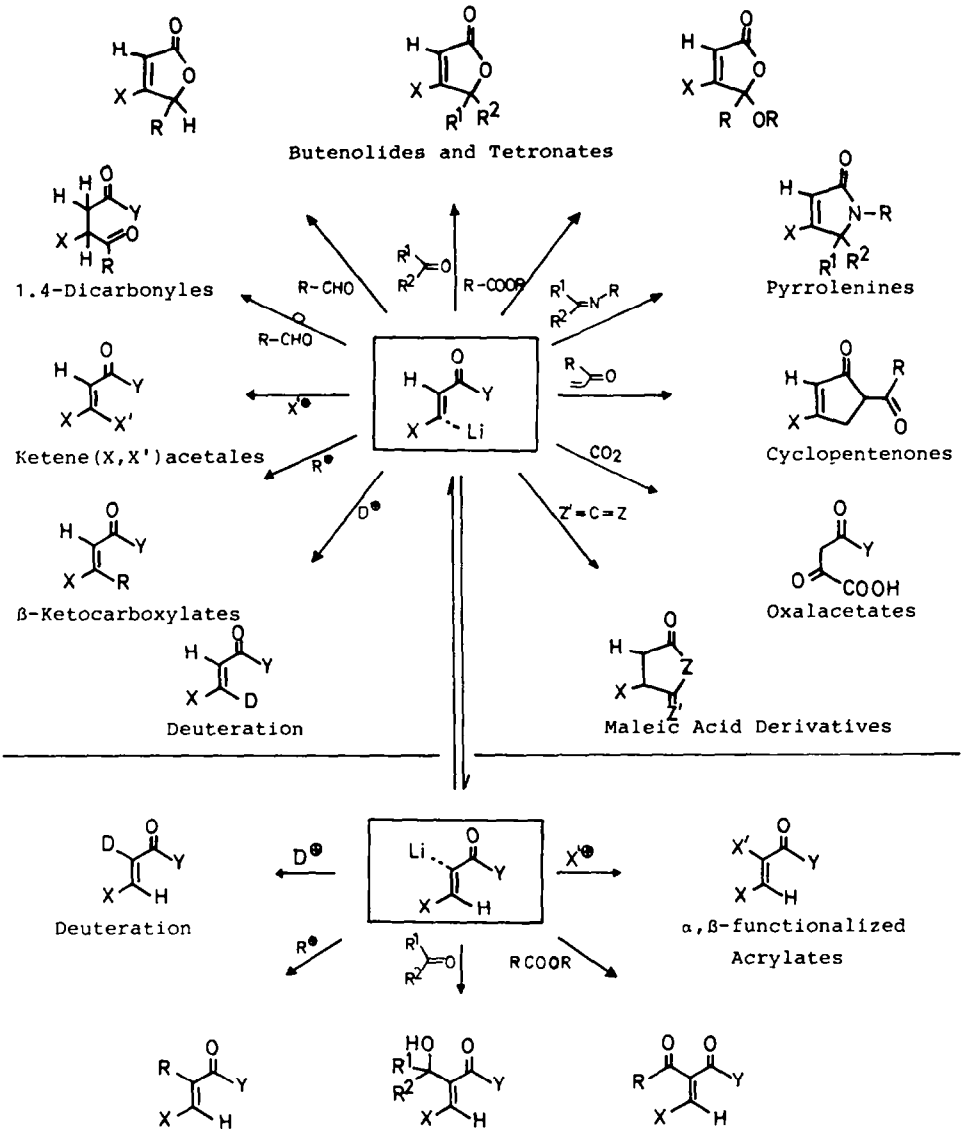
The kinetically selective lithiation of **2A** to generate **2Aa-β** enables a regiospecific reaction with electrophiles and because of the electrophilicity of the carboxylate group in **2Aa-β** — also with electrophilic-nucleophilic compounds. Using carbonyl compounds as the electrophilic-nucleophilic components results in the one-step formation of γ-substituted tetronates **5–9**[14] (Scheme 2). **5** is an interesting intermediate for a synthesis of fadyenolide.[21]

Direct lithiation of the γ-disubstituted tetronates **5–7** (→**5-α-7-α**) was performed under standard conditions and shown to be quantitative by deuteration. Reaction with various electrophiles led to α, γ-substituted tetronates in good yields.[14]

This efficient method for the preparation of substituted tetronates is applicable to the synthesis of naturally occurring examples of this class of compounds. Our interest was devoted to the antibiotically active aspertetronins and gregatins,[22] for which structures **12a-d** were proposed.[23] Reaction of **2Aa-β** with (*E*, *E*)-3,5-octadien-2-one gave the expected tetronate **10**. α-Lithiation with LDA delivered **10-α** and reaction with acetic anhydride led to tetronate **12a** in an overall two-step reaction. However, by these investigations it was demonstrated that the natural gregatin B is isomeric to **12a** and has structure **13a**.[24]

Pelter *et al.*[25] reported that γ-unsubstituted tetronate **8c** reacts in aprotic solvent with strong base and an electrophile at C-γ or at the carbonyl O atom. Surprisingly in our hands α-substituted tetronates **14a,b** were obtained from **9a,b**, LDA in THF, and various electrophiles. Investigations with deuterated compounds clearly indicated, that the α-vinyl-lithium species **8a-α**, **8b-α**, and not **11a,b** are intermediates in these reactions.[15]

Thus it is established that under the LDA/THF conditions the kinetic acidity of the α-vinylic proton is higher than the acidity of the carbonyl activated γ-methylene protons, even though a resonance sta-



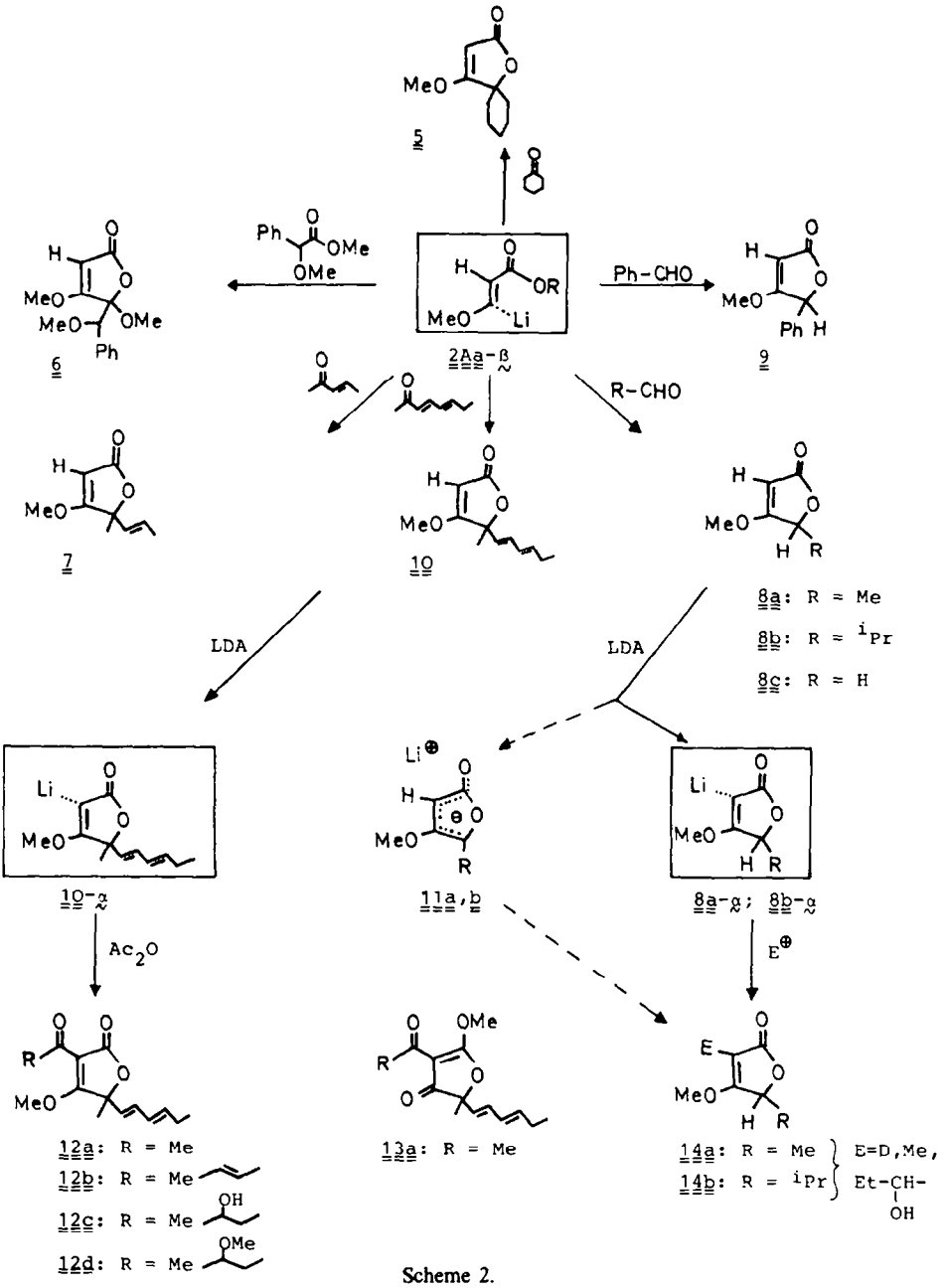
Scheme 1.

bilized oxapentadienyl anion would be generated in **11a,b**. This finding emphasizes the importance of the direct and directed deprotonation of vinylic methine groups, which are activated by inductive effects and intramolecular complexation in the metallated species.[7]

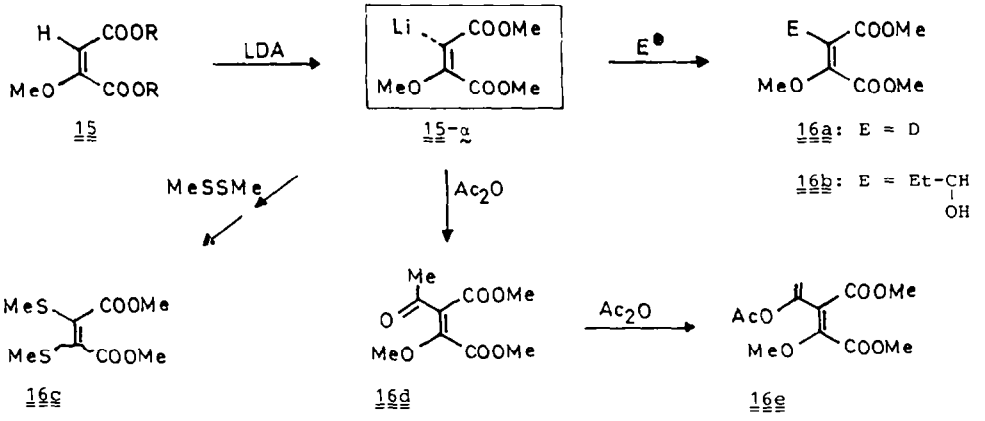
Electron-withdrawing substituents

The introduction of a further electron withdrawing functional group is also compatible with direct lithiation of acrylic systems. For instance, the (*E*)-β-methoxy-methoxycarbonyl acrylate **15** was transformed into the α-lithiated species **15-α**, almost quantitatively (Scheme 3). Reactions with electrophiles were carried out. Methanol-O-d and propionaldehyde delivered **16a,b**; dimethyl disulfide after sulfenylation and methoxide/methylthio exchange led to **16c**; with acetic anhydride as electrophile the acylation product **16d** was obtained, which was O-acetylated under the reaction conditions to give diene **16e**. Vinyl carbanions of type **15-α** have been postulated as intermediates in many addition reactions of nucleophiles to acetylenedicarboxylate.[27]

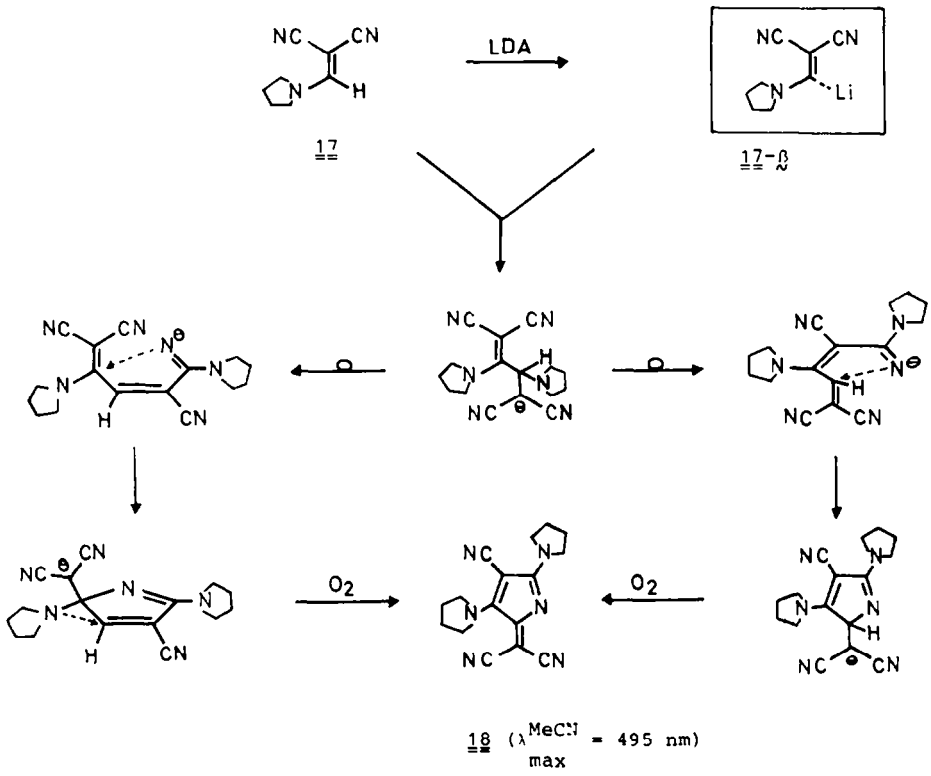
An interesting result was obtained on lithiation of **β-amino-α-cyano acrylonitrile 17**.[16] The increased electron polarisation in this system does not prevent **β**-lithiation to **17-β**; however, nucleophilic addition to the starting material **17** is enhanced. Therefore, Michael-addition of **17-β** to **17** preponderates. Via some unknown intermediates (Scheme 4) a colorless compound is obtained, which is quantitatively oxidized by air to the push-pull stabilized azafulvene **18**, whose structure was determined by X-ray analysis.[28]



Scheme 2.



Scheme 3.



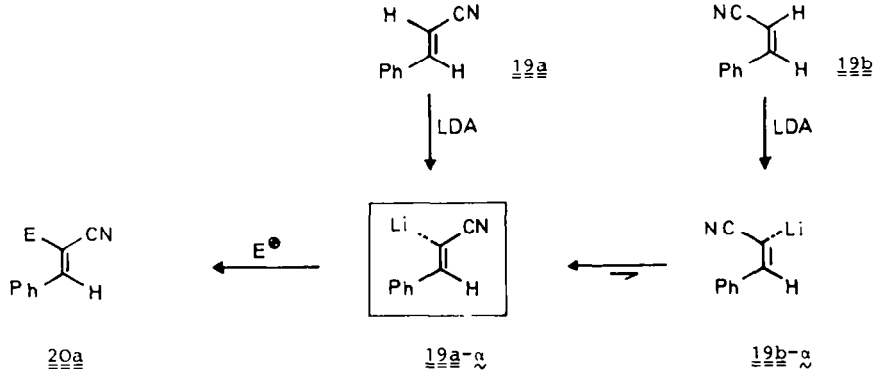
Scheme 4.

Cinnamic acid derivatives

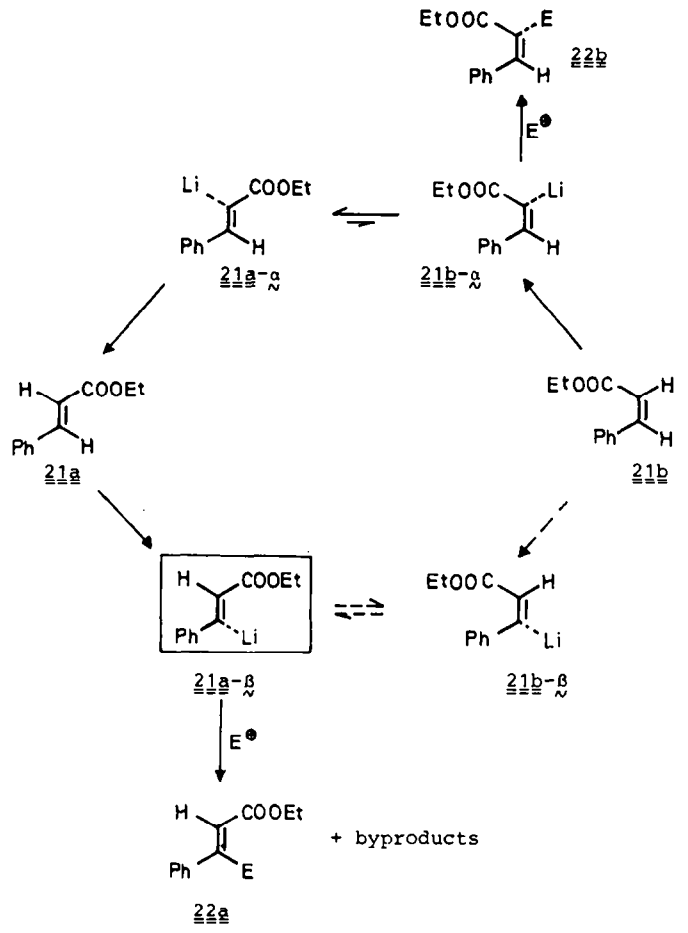
The strong influence of inductive effects and intramolecular complexation on the regioselectivity of the direct lithiation of acrylates **2–4** raises the question of whether β-aryl and β-hetaryl substituted acrylates are still directly lithiated. β-Phenyl substituted acrylates (cinnamates) are much more prone to Michael addition than **2–4** and the inductive activation of the lithiation is diminished. However, *trans*- and *cis*-cinnamonitriles **19a,b** were lithiated in α-position almost quantitatively and transformed successfully with electrophiles.[6,10] Due to the inversion of configuration of *cis*-anion **19b-α** to *trans*-anion **19a-α**, the *trans*-products **20b** were obtained almost exclusively (Scheme 5). The faster and more complete lithiation of **19b** compared with **19a** is ascribed to steric effects. Therefore, from a preparative point of view the generation of **19a-α** from **19b** should be preferred.

trans-Cinnamate **21a**, due to lower α-inductive activation and increased β-intramolecular complexation, led to β-lithiated species **21a-β**[9]. The conversion of **21a** to **21a-β** at low temperatures in THF is, however, less than 50% and thus the yields of products of type **22a** on reaction with electrophiles are low. Again Michael addition of **21a-β** to **21a** and subsequent reactions led to the formation of oligomers and dimers.

Comparable results were obtained with *cis*-cinnamate **21b**, the products being *trans*-compounds **22a**.[9] Due to the increased α-intramolecular complexation it was not surprising, that products **22b** derived from the α-lithiated species **21b-α** were obtained on quenching with methanol-O-d. Therefore it is as-



Scheme 5.

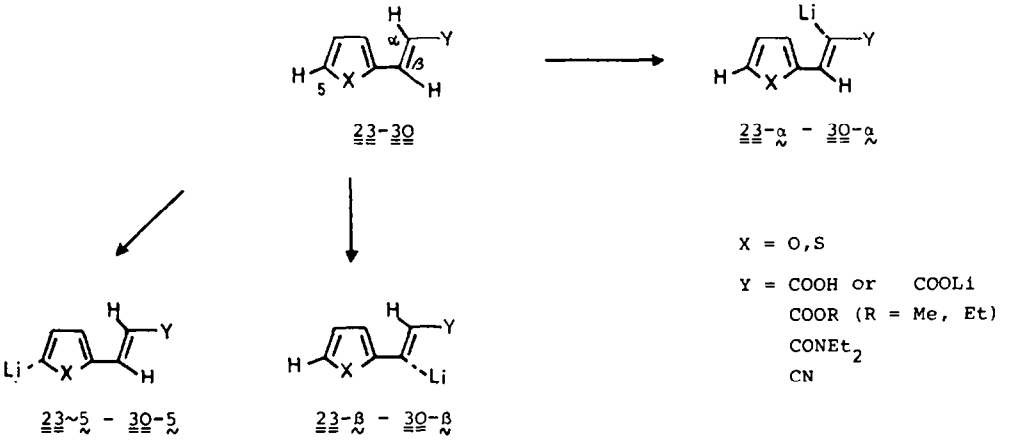


Scheme 6.

sumed, that the *trans*-products **22a** are obtained via inversion of configuration of **21b-α** to **21a-α**, formation of **21a**, lithiation to **21a-β**, and reaction with the electrophile (Scheme 6). There were no indications of formation of **21b-β**. Not unexpectedly, with unsubstituted acrylates the available concentrations of α- or β-lithiated species were even lower under the conditions used.

β-(2-Furanyl)-and β-(2-Thienyl)-acrylates

A most versatile method for the substitution of furans and thiophenes is by reaction of metallated derivatives with electrophiles. These metallated species can be formed either by metal–halogen exchange[29,30] or by direct metallation[30,31] of these heterocycles. In the latter case metallation occurs at the 2- or 5-position.

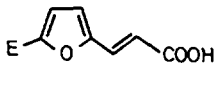


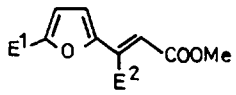
Scheme 7.

The easily available β-(2-furanyl)- and β-(2-thienyl)-acrylates **23–30**, which combine a heterocycle with the acrylate moiety are interesting targets for lithiations. Depending on the reaction conditions on the lithiating agent, and on the carboxylate derivative, directed lithiation at the α-, β-, or 5-position has been achieved[32] (Scheme 7).

Experimental verification is given in Table 2: the furanyl-acrylate derivatives **23–26** are directly lithiated at α-, β- and 5-position. As expected and as independently reported[33] treatment of furanylacrylic acid with two equivalents of base resulted only in C-5 lithiation to give **23–5**. While **24**, which contains the inductively more activating ester group, was lithiated by LDA in the 5-position (→**24-5**), with LTMP lithiation was directed to the β-position (→**24-β**). With amides, because of favored intramolecular complexation, generally β-lithiation has been observed; this is also true for **25**, which delivered **25-β** when LTMP was used as base. With LDA as base no site-specificity was obtained. The nitrile group in furanylacrylonitrile **26** led with LDA as base to exclusive formation of the α-lithiated species **26-α**, which is configurationaly labile.

These results were not only obtained from deuteration studies, but also by reaction with methyl iodide and other electrophiles. Compounds **31a-35c** were isolated. The higher yields, obtained with methylation than with deuteration, demonstrate, that the yields of lithiated species are higher than the values in Table 2, which are derived from deuteration experiments. The reason for this observation is partial protonation by the amine base.





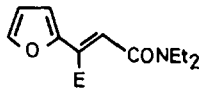
31a : E = D

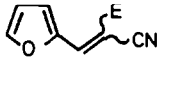
31b : E = CH_3

32a : E^1 = D, E^2 = H

32b : E^1 = CH_3, E^2 = H

33a : E^1 = H, E^2 = D





34a : E = D

34b : E = CH_3

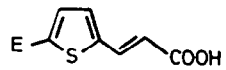
34c : E = ^{n}Pr-CH(OH)-

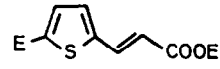
35a : E = D

35b : E = CH_3

35c : E = SCH_3

The ability of sulfur to stabilize an adjacent negative charge[34,35] accounts for the importances of the direct metallation of thiophenes in organic synthesis.[30] Direct lithiation of enethiol and enedithiol ethers has been found to be similarly facile.[8] It is therefore reasonable, that the lithiation of thienylacrylic acid **27**, of the ester **28**, and of the amide **29** took place preferably at C-5 to generate **27-5** – **29-5**, respectively (Table 2). Apart from the formation of some Michael adduct, no other products were obtained in these reactions. Thienyl acrylonitrile **30**, however, yielded only the α-lithiated species **30-α**, which again is configurationally labile. The site selectivity of these lithiations was assigned on the basis of deuteration and methylation experiments, which led to **36a,b** – **39a,b**. Addition of two equivalents of base to **30** generated dianion **30-5**, α which gave with methyl iodide the dimethylated derivative **39c**.

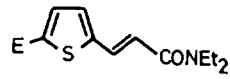


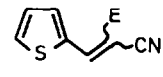


36a,b

37a,b

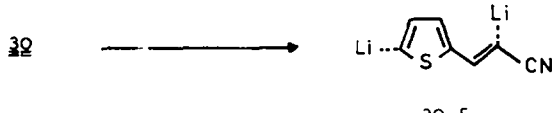
a : E = H; **b** : E = Me





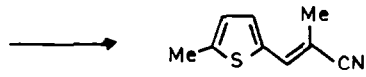
38a,b

39a,b



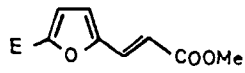
30

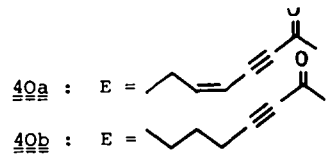
30-5,α



39c

The vinyllithium derivatives **23–5**, **24–5**, **24–β**, **25–β**, **26–α**, **27–5**, **28–5**, **29–5**, **30–α** and **30–5**, α are versatile intermediates for syntheses. The recently published synthesis of the phytoalexins wyerone (**40a**) and dihydrowyerone (**40b**) featured **23–5** as a key intermediate.[36] We have prepared butenolides starting from **25–β**. For instance, reaction with n-butanal





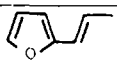
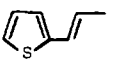
40a : E =

40b : E =

and cyclohexanone yielded the 2-furanylbutenolides **42** and **43**, respectively, (Scheme 8), which contain structural units found in many terpenoids[20,37]

It was also demonstrated, that stepwise base treatment allows for a direct metallation at all three positions: LDA treatment of **42** and subsequent addition of methyl iodide gave mainly the 5-methylated product **44**, proving the preferred formation of **42–5**. Surprisingly, LDA treatment of **44** did not lead to deprotonation of the newly intro-

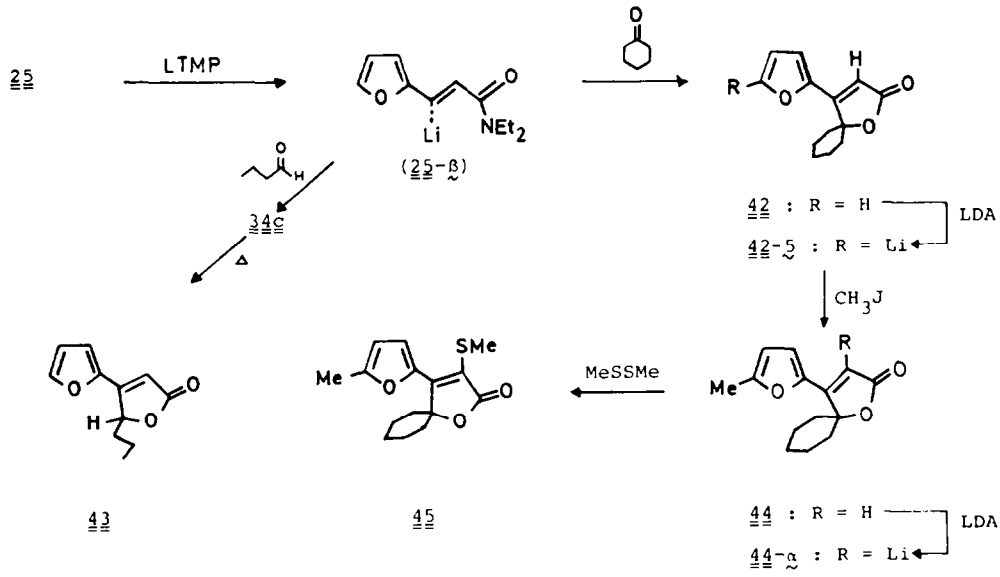
Table 2. Lithiation of β-(2-Furanyl)- and β-(2-Thienyl)-acrylic acid and derivatives **23–30**[a]

Compound	Lithiation Conditions (Base, Temp. [°C], Time [min] [b]				
	LDA, -115, 30	LDA, -90, 30	LDA, -80, 60	LTMP, -115, 30	LTMP, -90, 30
 [c] (23)	-	23-5 (45 %)	-	-	-
(24) -COOMe	24-5 (48 %)	24-5 (46 %) MA (20 %)	-	24-β (38 %)	24-β (44 %)
(25) -$CONEt_2$	25-β (25 %) 25-5 (53 %) MA (11 %)	25-β (11 %) 25-5 (23 %) MA (23 %)	MA (90 %)	-	25-β (60 %)
(26) -CN	26-α (32 %) 26-β (7 %) 26-5 (14 %)	26-α (48 %)	26-α (40 %)	-	-
 (27)	-	27-5 (45 %)	27-5 (35 %)	-	-
(28) -COOEt	-	28-5 (48 %) MA (9 %)	28-5 (45 %) MA (7 %)	-	28-5 (50 %)
(29) -$CONEt_2$	-	29-5 (61 %) MA (7 %)	-	-	29-5 (72 %)
(30) -CN	-	30-α (52 %)	-	-	-

[a] Determined through isolated yields of C-deuterated compounds 31a-39a; see Experimental; MA = Michael adducts of the base to the acrylate system; the other material was mainly or exclusively starting material.

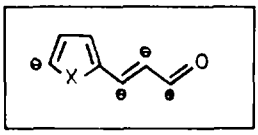
[b] Reaction in tetrahydrofuran; general procedure: see Experimental part. LDA = Lithiumdiisopropylamide, LTMP = Lithium 2.2.6.6-tetraemthylpiperidide.

[c] See ref. 33.

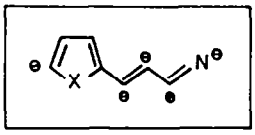


Scheme 8.

duced Me group; treatment with dimethyl disulfide resulted in the formation of **45**, indicating that the α-proton has the highest kinetic acidity. In this way it is demonstrated that **23–30** are synthetic equivalents of the synthons III and IV.



III



X = O,S

IV

Further reactions such as transformation of γ-substituted butenolides into furans via base-catalyzed O-silylation or reduction of the CO group,[20,25,32] and subsequent inter- and intramolecular cycloaddition reactions of these furans[25] enhance the synthetic importance of the functionally substituted vinyllithium derivatives described in this paper.

EXPERIMENTAL

The solvents were purified by conventional methods. Mp were carried out in a metal block and are uncorrected. ^{1}H-NMR spectra: Bruker CP 80 CW; chemical shifts are reported in ppm (δ) with TMS as internal reference. Column chromatography: Silica Gel (Fa. Macherey and Nagel, size 0.05 0.2 mm). TLC: Silica Gel, 0.25 mm layer with fluorescence indicator (Fa. Macherey and Nagel, "Polygram" SIL G UV_{254}), 4 × 8 cm; Eluents: see experimental description.

2-Cyano-3-pyrrolidino-2-propenenitrile (**17**). To a soln of (*E*)-3-chloro-2-cyano-2-propenenitrile[38] (5.62 g, 50 mmol) in THF (40 ml) was added at − 35° pyrrolidine (7.1 g, 0.1 mole). After the vigorous reaction had ceased, the mixture was warmed to room temp and then extracted with a water–chloroform mixture. The organic layer was washed with water, dried, and the solvent evaporated. The resulting slightly yellowish product (7.43 g) was recrystallized from a mixture of petroleum ether (300 ml, b.p. 50–70°) and benzene (40 ml) to give colorless crystals of **17** (6.3 g, 86%). m.p. 90°. analy. Calc for $C_8H_9N_3$ (147.2): C, 65.29; H, 6.16; N, 28.55, Found: C, 65,45; H, 6.12; N, 28.38.

4-Cyano-2-dicyanomethylene-3,5-di(1-pyrrolidinyl)-2H-pyrrole (**18**). **17** (0.59 g, 4 mmole) dissolved in dry THF (10 ml) was added to a cooled (− 82°) soln of LDA (5.3 mmole) in THF (70 ml). After 4 min the mixture was treated with MeOH (1 ml) and then warmed to room temp. 1 hr later this almost colorless mixture was extracted with water–$CHCl_3$. The organic layer, which upon exposure to air took a red color, was washed with water, dried with Na_2SO_4, and the solvent evaporated. The residue was purified by column chromatography (silica gel, EtOAc), yield 0.27 g (46%). TLC (silica gel, EtOAc) R_f 0.71. UV: λ_{max} (CH_3CN): 495 nm. anal. Calc for $C_{16}H_{16}N_6$ (292.3): C, 65.73: H, 5.51; N, 28.75; Found: C, 65.89; H, 5.44; N, 28.76.

Lithiation of compounds **23–30** *and reaction with electrophiles*:

General procedure. Compounds **23–30** are either commercially available (**23**, **26**, **27**) or were synthesized according to known procedures (**24**, Ref. 39; **25**, Ref. 40; **28**, Ref. 41; **29**, Ref. 42; **30**, Ref. 43).

The experimental conditions and the results are given for

Table 3. Reaction of lithiated acrylates with electrophiles

Lithiated Species [a]	Electrophile (mmole)	Reaction Conditions T_2 [°C]	t_2 [min]	Method	Product	Yield [b] [%]	B.P. [°C/torr]	TLC [c] (R_f)
23-5	CH_3J (6.0)	-80	60	A	31b	49	[d]	(0.39)
24-5	CH_3J	-90	60	B [c]	32b	24	140/15	(0.31)
25-8	CH_3J	-90	90	B [c]	34b	53	140/0.02	(0.62)
25-8		-90	60	B [c]	34c	55	oil [e]	(0.55)
26-α	CH_3J	-80	60	B [c]	35b	53	160/15	(0.44)
26-α	CH_3SSCH_3	-80	90	B [c]	35c	48	170/15	(0.59)
27-5	CH_3J	-80	60	A	36b	81	[d]	(0.35)
28-5	CH_3J	-80	100	B [c]	37b	38	145/15	(0.31)
29-5	CH_3J	-90	90	B [c]	38b	67	180/0.02	(0.30)
30-α	CH_3J	-80	60	B	39b	44	140/0.02	(0.35)

[a] Generated according to the General Procedure. [b] Isolated yields.

[c] Eluents: Petroleumether/ethylacetate: 31b (7:3); 32b (9:1); 34b (7:3); 34c (7:3); 35b (85:15); 35c (7:3) 36b (1:1); 37b (9:1); 38b (7:3); 39b (85:15). [d] Solid compound; m.p.: 36b: 164°C.

[e] Distillation at 160°C/0.02 torr yields partial ring closure to 43.

Table 4. Elemental analyses and ^{1}H-NMR data of compounds **31b, 32b, 31b,c, 32b,c, 36b–39b**

Compound	Formula (M.W.)	Analysis C	H	X	^{1}H-NMR ($CDCl_3$)
(E)-3-(5-Methyl-2-furanyl)-2-propenoic acid (31b)	$C_8H_8O_3$ (152.1)	C.: 63.15 F.: 63.27	5.30 5.34	- -	11.55(s,1H,COOH); 7.53(d,1H,H-β) 6.63(d,1H,H-3); 6.28(d,1H,H-α) 6.15(d,1H,H-4); 2.37(s,3H,CH_3).
Ethyl (E)-3-(5-Methyl-2-furanyl)-2-propenoate (32b)	$C_{10}H_{12}O_3$ [a] (180.2)				7.44(d,1H,H-β); 6.55(d,1H,H-3) 6.27(d,1H,H-α); 6.12(d,1H,H-4) 4.27(q,2H,$\underline{CH_2}CH_3$); 2.35(s,3H,CH_3) 1.30(t,3H,$CH_2\underline{CH_3}$)
(E)-3-(2-Furanyl)-2-butenoic acid diethylamide (34b)	$C_{12}H_{17}NO_2$ (207.3)	C.: 69.54 F.: 69.20	8.27 8.50	- -	7.47(d,1H,H-5); 6.64(d,1H,H-α) 6.51(d,1H,H-3); 6.49(dd,1H,H-4) 3.47(m,4H, $N\underline{CH_2}CH_3$); 2.27(d,3H,CH_3); 1.19(t,6H,$NCH_2\underline{CH_3}$)
(E)-3-(2-Furanyl)-4-hydroxy-2-heptenoic acid diethylamide (34c)	$C_{15}H_{23}NO_3$ [a] (265.4)				7.52(d,1H,H-5); 6.71(d,1H,H-α); 6.67(d,1H,H-3); 6.50(dd,1H,H-4) 6.20(s,1H,OH); 4.61(m,1H,H-γ) 3.50(m,4H,$N\underline{CH_2}CH_3$); 2.1-0.8(m,13 H, $NCH_2\underline{CH_3}$ + ^{n}Pr.)
(E)-3-(2-Furanyl)-2-methyl-2-propenenitrile (35b)	C_8H_7NO (133.2)	C.: 72.17 F.: 71.97	5.30 5.41	10.52 10.32	7.63(d,1H,H-5); 6.95(d,1H,H-β) 6.65(d,1H,H-3); 6.56(dd,1H,H-4) 2.26(d,3H,CH_3)
(E+Z)-3-(2-Furanyl)-2-methylthio-2-propenenitrile (35c)	C_8H_7NOS [a] (165.2)				7.60(d,1H,H-5); 7.11(d,1H,H-3) 6.98(dd,1H,H-4); 6.58(s,1H,H-β) 2.54+2.49(2s,3H,SCH_3)
(E)-3-(5-Methyl-2-thienyl)-2-propenoic acid (36b)	$C_8H_8O_2S$ (168.2)	C.: 57.12 F.: 56.92	4.79 4.66	19.06[b] 19.11	10.50(s,1H,COOH); 7.89(d,1H,H-β) 7.19(d,1H,H-3); 6.81(d,1H,H-4) 6.16(d,1H,H-α); 2.53(s,3H,CH_3)
Ethyl (E)-3-(5-Methyl-2-thienyl)-2-propenoate (37b)	$C_{10}H_{12}O_2S$ [a] (196.3)				7.77(d,1H,H-β); 7.11(d,1H,H-3) 6,77(d,1H,H-4); 6.15(d,1H,H-α) 4.27(q,2H,$COO\underline{CH_2}CH_3$); 2.50(s,3H, CH_3) 1.32(t,3H,$COOCH_2\underline{CH_3}$)
(E)-3-(5-Methyl-2-thienyl)-2-propenoic acid diethylamide (38b)	$C_{12}H_{17}NOS$	C.: 64.54 F.: 64.29	7.67 7.59	6.27[c] 6.42	7.81(d,1H,H-β); 7.05(d,1H,H-3) 6.72(dd,1H,H-4); 6.55(d,1H,H-α) 3.46(q,4H,$N\underline{CH_2}CH_3$); 2.46(s,3H,CH_3) 1.20(t,6H,$NCH_2\underline{CH_3}$)
(E)-2-Methyl-3(2-thienyl)-2-propenenitrile (39b)	C_8H_7NS (149.2)	C.: 64.40 F.: 64.16	4.73 4.73	9.39[c] 9.15	7.62(dd,1H,H-5); 7.38(d,1H,H-β) 7.32(dd,1H,H-3); 7.20(dd,1H,H-4) 2.19(d,1H,CH_3)

[a] M^+ (m/e) : 32b : 180; 34c : 165; 35c : 165; 37b : 196

[b] X = S;

[c] X = N;

each experiment in Tables 2 – 4. The lithium amide used as base (4.5 mmole LDA or LTMP for **24–26**, **28–30** and 8.5 mmole for **23** and **27**) was prepared by adding an equimolar amount of n-BuLi or t-BuLi (dissolved in hexane) into the diisopropylamine or 2,2,6,6-tetramethylpiperidine dissolved in THF (20 ml) cooled already to the temperature given in Table 2. The acrylate derivative (**23–30**, 4 mmol) dissolved in THF (20 ml) was added to this mixture. All the manipulations and the lithiation itself (reaction time: see Table 2) were carried out under N_2 and anhydrous conditions.

Deuteration (to give **31a–39a**) was carried out by adding MeOH-O-d (0.2 ml, 5 mmole) to the mixture. After 15 min this mixture was extracted with water–$CHCl_3$. (For **31a** and **36a** the mixture was acidified to pH 1 for the extraction). The organic layer was washed with water, dried and evaporated. The resulting residue was worked up as applied for the corresponding compounds **23–30**. Deuteration was determined by ^{1}H-NMR spectroscopy. Isolated yields of deuterated compounds, see Table 2.

For other electrophiles (to yield **31b, 32b, 34b, C, 35b, C, 36b–39b**) the reaction conditions (molar quantity, reaction temp T_2 and time t_2) and the results are given in Tables 3 and 4. The mixture was extracted with water–$CHCl_3$ (for **31b** and **36b** the mixture was acidified to pH 1 for extraction). The organic layer was washed with water, dried and evaporated. The resulting residue was either recrystallized (method A, Table 3) or chromatographed on silica gel (method B; for eluent, see Table 3).

(E)-2-*Methyl*-3-(5-*Methyl*-2-*thienyl*)-2-*propenenitrile* (**39c**). **30** (0.675 g, 5 mmole) dissolved in dry THF (20 ml) was added to a cooled (– 80°) sol of LDA (11 mole) in THF (20 ml). After 60 min MeI (0.75 ml, 12 mmole) was added. The mixture was worked up 60 min later by water–$CHCl_3$ extraction. The organic layer was washed with water, dried with K_2CO_3, and evaporated. The solid residue was chromatographed on silica gel (petroleum ether: EtOAc = 9 : 1); 0.55 g (67%); m.p. 88°. TLC (petroleum ether–EtOAc = 8.5:15) R_f 0.48. ^{1}H-NMR ($CDCl_3$): δ7.28 (s, 1H, H-β); 7.09 (d, 1H, H-3); 6.93 (d, 1H, H-4); 2.55 (s, 3H, CH_3 – 5); 2.17 (s, 3H, CH_3-α). Found: C, 66.23; H, 5.56; N, 8.68; S, 19.49. anal. Calc for C_9H_9NS (163.2): C, 66.22; H, 5.56; N, 8.58; S, 19.64.

4-(2-*Furanyl*)-5,5-*pentamethylene*-2(5H)-*furanone* (**42**). **25** (0.54 g, 2.8 mmole) dissolved in dry THF (20 ml) was added to a cooled (– 100°) soln of LTMP (3.2 mmole) in THF (20 ml). After 30 min cyclohexanone (0.41 ml, 4 mmole) dissolved in THF (5 ml) was added. The mixture was worked up 60 min later by extraction with water–CH_2Cl_2, as usual. The crude product was chromatographed on silica gel (petroleum ether–EtOAc = 1 : 1): 0.33 g (55%); m.p. 149° (dec). TLC (petroleum ether–EtOAc = 1 : 1) R_f = 0.68. ^{1}H NMR ($CDCl_3$): δ7.60 (d, 1H, H-5); 6.80 (d, 1H, H-3); 6.54 (dd, 1H, H-4); 6.12 (s, 1H, H-α); 2.2–0.9 (n, 10H, $5CH_2$).

This material was immediately used for the synthesis of **44**.

Byproduct in this reaction was a small amount of thienyl-C-5 substituted material.

4-(2-*Furanyl*)-5-*propyl*-2(5H)-*furanone* (**43**) **25** (0.96 g, 5 mmole dissolved in dry THF (20 ml) was added to a cooled (– 90°) soln of LTMP (5.5 mmole) in THF (20 ml). After 30 min n-butyraldehyde (0.54 ml, 6 mmole) was added and then the mixture warmed to 0°. After 60 min, this mixture was extracted with water–$CHCl_3$, the organic layer was washed with water, dried with K_2CO_3, and evaporated. The residue (**34c**) was heated in petroleum ether (b.p. 100–140°) for ring closure (1 hr) and then chromatographed on silica gel (petroleum ether–EtOAc = 7 : 3): 0.59 g (61%); m.p. 55°; TLC (petroleum ether: EtOAc = 7 : 3) R_f 0.68. ^{1}H NMR ($CDCl_3$): δ 7.69 (d, 1H, H-5); 6.86 (d, 1H, H-3); 6.63 (dd, 1H, H-4); 6.22 (d, 1H, H-α); 5.35 (m, 1H, H-γ); 2.3–0.8 (m, 7H, ^{n}Pr). Found: C, 68.32; H, 6.37. anal. Calc for $C_{11}H_{12}O_3$ (192.2): C, 68.73; H, 6.29.

4-(5-*Methyl*-2-*furanyl*)-5,5-*pentamethylene*-2(5*H*)-*furanone* (**44**). **43** (0.44 g, 2 mmole) dissolved in dry THF (20 ml) was added to a cooled (– 90°) soln of LDA (2.2 mmole) in THF (20 ml). After 30 min, MeI (0.16 ml, 2.5 mmole) was added and the reaction kept at – 90° for 1 hr. The mixture was extracted with water-CH_2Cl_2, the organic layer washed with water, dried, and evaporated. The residue was chromatographed on silica gel (petroleum ether–EtOAc = 7:3): 0.22 g (48%); m.p. 176°. TLC (petroleum ether–EtOAc = 7 : 3) R_f 0.53. ^{1}H NMR ($CDCl_3$): δ 6.82 (d, 1H, H-3); 6.28 (d, 1H, H-4); 6.14 (s, 1H, H-α); 2.42 (s, 3H, CH_3); 2.3–1.2 (m, 10H, $5CH_2$).

This material was immediately used for the synthesis of **45**. Byproduct in this reaction was a small amount of α-substituted product.

4-(5-*Methyl*-2-*Furanyl*)-3-*methylthio*-5,5-*pentamethylene*-2(5H)-*furanone* (**45**). **44** (0.13 g, 0.55 mmole) dissolved in dry THF (20 ml) was added to a cooled (– 90°) soln of LDA (1 mmole) in THF (20 ml). After 30 min, Me_2S_2 (0.14 ml, 1.5 mmole) was added and the reaction kept at – 90° for 1 hr. The mixture was extracted with water-CH_2Cl_2, the organic layer was washed with water, dried with Na_2SO_4, and evaporated. The residue was filtered through silica gel (toluene: EtOAc = 9 : 1) : 0.12 g (78%); m.p. 79° TLC (toluene–EtOAc = 9:1) R_f 0.65. ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1H, H-3; 6.35 (d, 1H, H-4); 2.67 (s, 3H, S-CH_3); 2.43 (s, 3H, C-CH_3); 2.5–1.2 (m, 10H, 5 CH_2). Found: C, 64.20; H, 6.79. Anal. Calc for $C_{15}H_{18}O_3S$ (278.4): C, 64.72; H, 6.52).

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