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Synthesis of Diastereoisomerically Pure 5-Substituted 5-(*l*-Menthyloxy)-4-(Pyrrolidin-1-yl)furan-(5*H*)-ones

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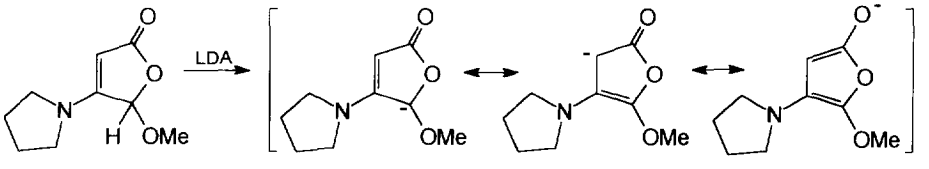
Abstract: Reactions of lithium enolate **2**, generated from (5*S*)-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (**1a**) or from the mixture of epimers at C-5 (**1a, 1b**), with different sort of electrophiles, such as alkylating agents, aldehydes, acyl chlorides, dimethyl carbonate and a Michael acceptor, occur regioselectively and stereoselectively from the *Re* face of the enolate to give the corresponding 5-substituted derivatives in synthetically useful yields. The stereoselectivity of the reactions is influenced by the nature and steric bulk of the substituents on the reactive center of the electrophile.

Considerable effort has been made in the development of generally applicable synthetic routes for the construction of functionalized furan-2(5*H*)-ones, due to their versatility as intermediates in organic synthesis. A convenient approach to the title compounds could be the reaction with electrophiles of the enolate anions generated from simple furanone derivatives, since in the literature it has been reported that the presence of an electron-releasing group, as alkoxy[1-3] or alkylamino,[4-9] at the 4-position favours the formation of the C-5 substituted derivatives. Thus, we have previously reported that 5-methoxy-4-(pyrrolidin-1-yl)furan-2(5*H*)-one is readily deprotoned by lithium diisopropylamide (LDA) to its anion and this species, although it could act as tridentate anion (scheme 1), reacts with different types of



Scheme 1

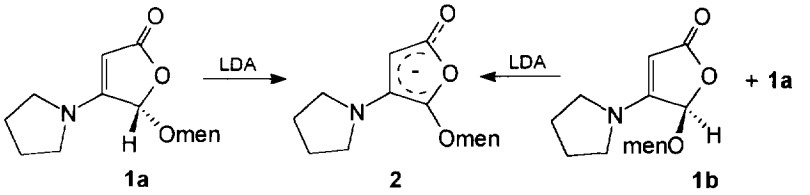
electrophiles exclusively at the C-5 position.[7] However, there are few reports dealing with the stereoselective introduction of the substituents at C-5 of vinylogous urethane furanones by the above methodology.[5,6,8,9] All reported cases refer to reactions of enolates, in which the chiral auxiliary group is

a pyrrolidine derivative at the C-4 position, and the electrophile is an alkyl halide or propionaldehyde. In contrast, there are no antecedents of the above reactions starting from 4-enaminofuranones with the chiral group at the 5-position of the furanone ring. This fact and the interest of homochiral tetronic acids derivatives, prompted us to carry out the reactions with electrophiles of different types with the lithium enolate derived from the 5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (**1**) recently synthesized by us.[10]

In this paper we report the generation of enolate **2** either from **1a** or from a mixture of **1a** and **1b**, and its regioselective and stereoselective reactions with electrophiles such as alkyl halides, acyl chlorides, aldehydes, dimethyl carbonate and 3-bromo-5-methoxyfuran-2(5*H*)-one. The above reactions are an attractive way to obtain enantiomerically pure 5-alkyl-, 5-acyl-, 5-hydroxyalkyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones.

RESULTS AND DISCUSSION

Lithium enolate **2** is readily generated from **1a** or a mixture of **1a** and **1b** by treatment with LDA, in THF at -70 °C for 15 min (scheme 2). Immediate quenching of **2** with water gives a mixture of epimers

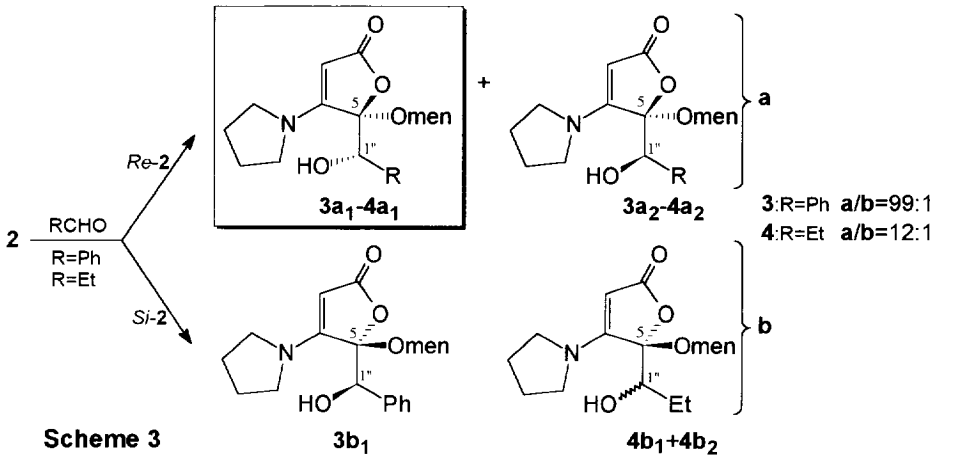


Scheme 2

at C-5 **1a** and **1b**. The same ratio **a**/**b** (55:45) is obtained starting from **1a** or from the epimeric mixture **1a** + **1b**. The lack of stereoselectivity in the protonation of **2** was not surprising, taking into account the results reported by Schlessinger for the protonation of analogous enolates.[5,8]

Additions to C=O bonds

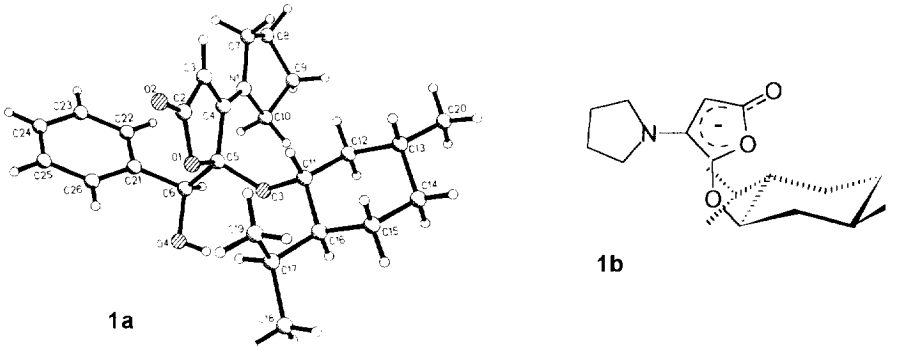
Lithium enolate **2** reacts with an excess of benzaldehyde, at -70 °C for 3 min., to give in regioselective manner the alcohol **3**,[11] as a mixture of the diastereoisomers $\mathbf{3a_1}$,$\mathbf{a_2}$,$\mathbf{b_1}$ in a 90:9:1 ratio (scheme 3). The major isomer $\mathbf{3a_1}$ was isolated in 77% yield by column chromatography on silica gel. The stereoselectivity in the addition of enolate **2** to propionaldehyde was lower than observed with benzaldehyde. The four possible diastereoisomers ($\mathbf{a_1}$,$\mathbf{a_2}$,$\mathbf{b_2}$,$\mathbf{b_1}$) of the 5-hydroxypropyl derivative **4** were obtained in a c.a 19:12:2:1 ratio.[12] In this case, by chromatography, only mixtures of $\mathbf{4a_1}$+$\mathbf{4b_2}$ and $\mathbf{4a_2}$+$\mathbf{4b_1}$ can be isolated. Enantiomerically pure $\mathbf{4a_2}$ was achieved by filtration, after trituration of the mixture $\mathbf{4a_2}$–$\mathbf{4b_1}$ with hexane. Although with both aldehydes the diastereoisomers of type **a** were the major



Scheme 3

products, the different **a**/**b** ratio observed, for benzaldehyde and propionaldehyde shows clearly the steric effect of the substituent R upon the stereoselectivity of the addition of **2** to the aldehyde group.

The absolute configuration of $\mathbf{3a_1}$ (5*R*, 1''*S*), determined by X-ray analysis (figure 1a),[13] reveals that the attack of enolate **2** occurs preferentially from its *Re* face to the *Re* face of electrophile. The fashion of approach of reagents suggests that the reactive conformation of the enolate **2** should be the one shown in figure 1b, in which the attack of benzaldehyde on *Si* face is inhibited by the isopropyl group of the chiral auxiliary.

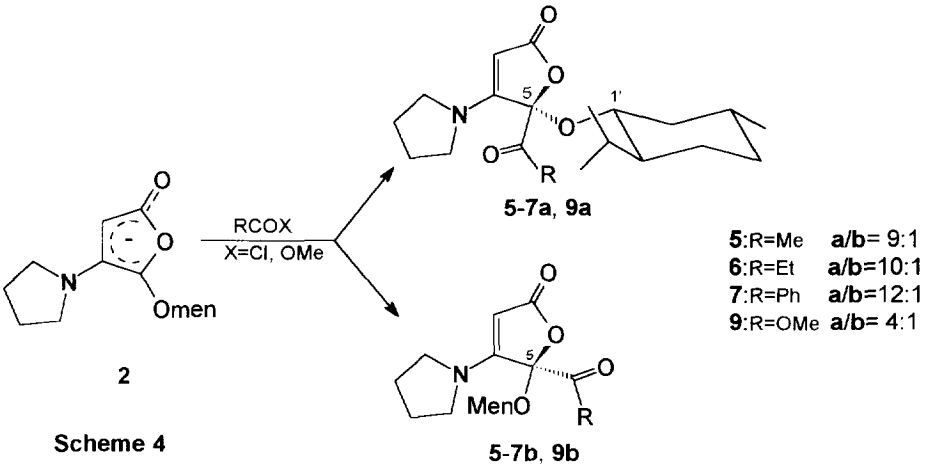


1a 1b

Figure 1

Additions of **2** to acetyl, propionyl or benzoyl chlorides were carried out under similar conditions to those used for aldehydes. The reactions proceed at a lower rate than those of the aldehydes, affording the corresponding C-5 acyl compounds **5-7** (scheme 4), as a mixture of epimers at C-5 (**a** and **b**), along with substantial amounts of **1** (35, 15 and 14% respectively). In the case of benzoyl chloride a trace of 3-benzoyl-5 -(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (**8**) was detected.

Finally, the reaction of enolate **2** with dimethyl carbonate afforded the 5-methoxycarbonylfuranones **9a** and **9b** in a c.a. 4:1 ratio. This stereoselectivity is the lowest obtained with the electrophiles studied



Scheme 4

in this paper.

The isomers of type **a**, obtained as major products with carboxylic acid derivatives and enolate **2**, were isolated diastereoisomerically pure by filtration after the trituration of epimeric mixtures with hexane or pentane.

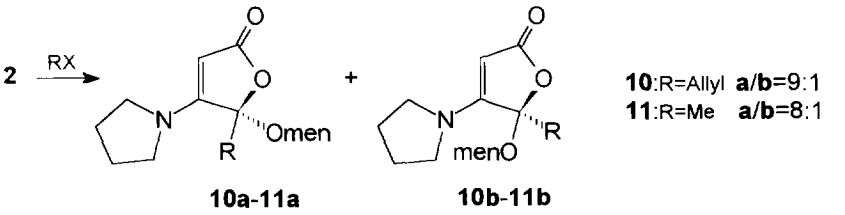
In order to verify that configuration at C-5 of the major stereoisomers (**a**) of acyl- and hydroxyalkylfuranones is the same, the acylfuranones **6a** and **7a** were subjected to sodium borohydride reduction. The formation of alcohols $\mathbf{4a_1}$+$\mathbf{4a_2}$ and $\mathbf{3a_1}$+$\mathbf{3a_2}$ from **6a** and **7a** respectively, confirms that the attack of acyl chlorides to the carbon bearing the menthyloxy group occurs also predominantly from the *Re* face of the enolate. On the other hand, the formation of alcohols $\mathbf{3a_1}$+$\mathbf{3a_2}$ from the benzoyl compound **7a**, and the configuration of $\mathbf{3a_1}$ allow to assign unequivocally the configurations (5*R*, 1"*R*) to $\mathbf{3a_2}$, (5*S*) to $\mathbf{3b_1}$ and (5*R*) to **7a**. The *R* configuration at C-5 of **4a-6a** and **9a** is based on the preferential mode of approach of the electrophile to the enolate. According to the proposed configurational assignment, the chemical shifts of C-1' in all **a** epimers appear at lower δ values than those of the corresponding stereoisomer **b**.

The configuration *R* at the carbon bearing the hydroxyl group for $\mathbf{3b_1}$, was assigned taking into account that the less hindered approach to the *Si* face of **2** is from the *Si* face of aldehyde. On the basis of the preferential approach *Re-Re* of aldehyde to enolate, we proposed the structures indicated on the scheme 3 for the stereoisomers $\mathbf{4a_1}$ and $\mathbf{4a_2}$. However, it was not possible to assign the configuration at the C-1" for $\mathbf{4b_1}$ and $\mathbf{4b_2}$, since the face stereoselectivity in the addition to propionaldehyde is poor and the ratio of isomers can not be accurately determined.[12]

The stereochemical results of the reactions reported in this section, make evident the influence, of the electronic nature and steric bulk, of the groups attached to C=O upon the stereoselectivity in the additions of the enolate **2**.

Reactions with alkyl halides and Michael acceptors

From the reaction with enolate **2** and allyl bromide was obtained a mixture of 5-allylfuranones **10a**, **10b** and the unalkylated furanone **1**, in a approximately 72:8:20 ratio (scheme 5). The enolate **2** reacts



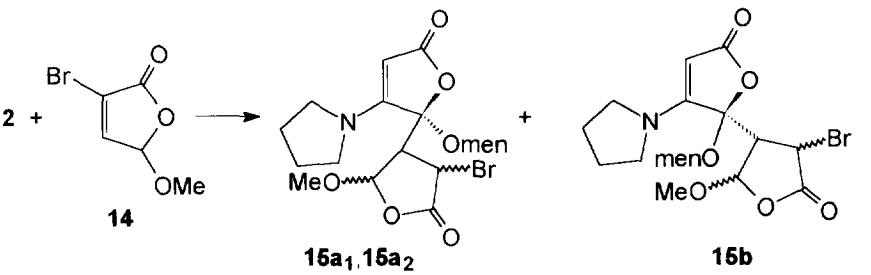
10a-11a **10b-11b**

Scheme 5

with methyl iodide to afford the furanone methylated at 5-position **11**, as epimeric mixture (**a**/**b**=8) in 55% combined yield. However in this case, besides the furanones **11a**,**b** and **1**, also were isolated, although in very low yield, the 3-methyl- and 3,5-dimethyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (**12** and **13**).[14]

The stereochemistry **a** or **b** to epimeric alkyl furanones **10** and **11** was assigned by the same bases used for the acylfuranones.[15]

Taking into account that the enolates derived from 5-methoxy- and 5-ethylthio-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones, do not react with acrylonitrile neither methyl acrylate,[7] but react with the racemic mixture of the 3-bromo-5-methoxyfuran-2(5*H*)-one[16] (**14**), we carried out the addition of enolate **2** to the furanone **14**. In the crude reaction mixture were observed only three diastereoisomers **15a**$_1$,**a**$_2$,**b** (55:28:17



14 **15a$_1$,15a$_2$** **15b**

Scheme 6

ratio) of the sixteen possible Michael adducts. By chromatography on silica gel, we could not achieve every pure adduct, only a mixture of **15a**$_1$+**15b** and **15a**$_2$ with traces of **1** were isolated. The *S* configuration at C-5, as result of the approach of the electrophile to the *Re* face of enolate, was assigned to the major isomers **a**$_1$ and **a**$_2$, by analogy with the results observed for the other electrophiles. This assignment was supported by the chemical shifts of C-1' and C-5, that in **15b** is higher than those of **15a**$_1$ and **15a**$_2$. The arrangement of the three substituents on the saturated lactone ring was not determined,

because the coupling constants display higher values that those reported for all *trans* 5-alkoxy-3,4-dihydrofuran-2(5*H*)-ones substituted at C-3 and C-4, obtained as sole or major isomer in conjugate addition to 5-alkoxyfuran-2(5*H*)-ones.[17-19]

EXPERIMENTAL

Column chromatography was performed on 230-400 mesh silica gel (Merk) and analytical TLC on Merk DC-Alufolien with F_{254} silica gel 60. Melting points were determined on a Gallenkamp apparatus on open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker-WM-200 instrument in $CDCl_3$. J values are given in Hz. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded on a Perkin-Elmer model 681 spectrophotometer, ν values in cm^{-1}. Mass spectra were recorded on a VG 12-250 spectrometer using electron impact at 70 eV. Optical rotation were measured with a Perkin-Elmer 241 polarimeter, concentrations are given in g/100 ml. Microanalyses were performed with a Heraus analyzer. The X-ray analysis of compound **3a$_1$** is described separately.[13]

Generation of 2a and Reaction with Electrophiles.

General Procedure. To a solution of diisopropylamine (1.9 mmol) in dry tetrahydrofuran (1 ml) at -70 °C, under an argon atmosphere, was added a solution of n-butyllithium (1.7 mmol). After 15 min a solution of furanone **1a** (1.6 mmol) in dry tetrahydrofuran (9 ml) was added and stirred for additional 15 min at -70 °C. Then, the electrophile was added, and the reaction mixture was kept under the conditions indicated in each case (Table 1). The resulting solution was poured into satured aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (the eluent is indicated in each case). The minor isomer could not be isolate in the pure form.

5-Hydroxybenzyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (3).

(Hexane/acetone:3/1).

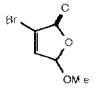
(5*R*, 1"*S*) **3a$_1$**: 77% yield. M.p. 185-6 °C. $[\alpha]_D$= - 37.67 (c=0.43, $CHCl_3$). IR(Nujol) : 3570, 1745, 1610. ^1H NMR: 7.4-7.2 (m, 5H arom.), 5.10 (d, 1H, $H_{1"}$, J=3.5), 4.2 (m, 1H, CH_2N), 4.14 (s, 1H, H_3), 3.65 (dt, 1H ment., J=10.6, J=4.3), 3.5 (m, 1H, CH_2N), 3.08 (d, 1H, OH, J=3.5), 3.1-2.9 (m, 2H, CH_2N), 2.5-0.6 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 170.8 (s), 164.3 (s), 136.3, 128.6, 128.0, 127.3 (C arom.), 104.3 (s), 84.7 (d), 75.8 (d), 73.7 (d), 50.1 (t), 48.6 (d), 48.6 (t), 41.8 (t), 33.9 (t), 31.4 (d), 26.1 (t), 25.3 (d), 24.2 (t), 22.8 (t), 22.4 (q), 21.4 (q), 15.3 (q). MS, m/z (relative intensity): 258 (M^+-155, 11), 185 (6), 168 (100), 140 (31), 107 (12), 105 (23), 77 (12). Analysis Calcd. for $C_{25}H_{35}O_4N$: C, 72.61; H, 8.53; N, 3.39. Found: C, 72.91; H, 8.75; N, 3.45.

(5*R*, 1"*R*) **3a$_2$**: M.p. 188-90 °C. $[\alpha]_D$= - 11.3 (c=0.33, $CHCl_3$). ^1H NMR: 7.43 (m, 2H arom.), 7.38 (m, 3H arom.), 5.00 (d, 1H, $H_{1"}$, J=5.5), 4.46 (s, 1H, H_3), 4.2 (m, 1H, CH_2N), 3.6 (m, 1H, CH_2N), 3.45 (dt, 1H ment., J=10.6, J=4.1), 3.3 (m, 1H, CH_2N), 3.1 (m, 1H, CH_2N), 2.9 (m, 1H, OH), 2.2-0.4 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 171.8 (s), 165.4 (s), 137.6, 128.1, 127.6 (C arom.), 104.2 (s), 84.0 (d), 75.3 (d),

73.0 (d), 50.5 (t), 48.4 (d), 48.2 (t), 41.8 (t), 34.0 (t), 31.4 (d), 26.2 (t), 24.2 (t), 23.9 (d), 22.6 (t), 22.4 (q), 21.2 (q), 15.3 (q).

(5*S*, 1"*R*) **3b$_1$**: ^{1}H NMR: 4.22 (s, 1H, H_3), (characteristic signal).[20]

Table 1: Reactions of lithium enolate 2 with eletrophiles

Electrophile	Equiv.	Temp.,°C	Time	Products (% yield)[a]	Diastereomers ratio[b]
H_2O	exc.	-70	1min	**1**	**1a**:**1b** 55:45
PhCHO	1.3	-70	3 min	**3** (85)	**3a$_1$**:**3a$_2$**:**3b$_1$** 90:9:1
EtCHO	1.5	-70→+20	5 min	**4** (87)	**4a$_1$**:**4a$_2$**:**4b$_1$**:**4b$_2$** 56:35:6:3
	1.5	-70	10 min	**4** (87)	
MeCOCl	1.2	-70	2 h	**5** (50), **1**(35)	**5a**:**5b** 90:10
EtCOCl	2.0	-70	3 h	**6** (50), **1** (15)	**6a**:**6b** 91:9
PhCOCl	1.1	-70→+20	3 h	**7** (72), **8** (3) **1** (14)	**7a**:**7b** 92:8
$CO(OMe)_2$	1.1	-70	3 h	**9** (60), **1** (9)	**9a**:**9b** 81:19
CH_2=$CHCH_2Br$	2.0	-70	3 h	**10** (60), **1** (15)	**10a**:**10b** 90:10
MeI	2.5	-70	2h	**11** (55), **12** (7) **13** (9), **1** (10)	**11a**:**11b** 89:11
	1.3	-70	2 h	**15** (65), **1** (14)	**15a$_1$**:**15a$_2$**:**15b** 55:28:17

[a] Isolated yield, non optimized. [b] Determined by ^{1}H NMR.

5-(1-Hydroxyprop-1-yl)-5-(l-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (4).

A first column chromatography (ethyl acetate/hexane:4/1) afforded mixtures of **4a$_1$**+**4b$_2$**+**1**, and **4a$_2$**+**4b$_1$**. **4a$_1$**+**4b$_2$**: A c.a. 80:20 mixture was achieved by a second column chromatography (ether). M.p. 168-82 °C.

IR($CHCl_3$): 3560, 1730, 1610. MS, m/z (relative intensity): 366 (M^++1, 36), 365 (M^+, 13), 306 (10), 210 (23), 168 (100), 140 (43), 95 (40), 70 (22). Analysis Calcd. for $C_{21}H_{35}O_4N$: C, 69.01; H, 9.65; N, 3.83. Found: C, 68.91; H, 9.71; N, 3.68.

(5*R*, 1''*S*) **4a$_1$**: ^{1}H NMR: 4.50 (s, 1H, H_3), 4.14 (m, 1H, CH_2N), 3.91 (m, 1H, $H_{1''}$), 3.54 (dt, 1H ment., J=10.5, J=4.4), 3.4-3.0 (m, 3H, CH_2N), 2.4-0.6 (m, 18H ment., 4H pyrro., 2H, $H_{2''}$), 2.28 (d, 1H, OH, J=6.5), 1.01 (t, 3H, $H_{3''}$, $J_{2'',3''}$=7.3). ^{13}C NMR: 171.2 (s), 164.9 (s), 104.7 (s), 83.7 (d), 74.9 (d), 72.7 (d), 50.3 (t), 48.6 (d), 48.3 (t), 41.9 (t), 33.9 (t), 31.4 (d), 26.0 (t), 24.9 (d), 24.2 (t), 23.6 (t), 22.7 (t), 22.4 (q), 21.4 (q), 15.5 (q), 10.2 (q).

4b$_2$: ^{1}H NMR: 4.51 (s, 1H, H_3), 4.0 (m, 1H, $H_{1''}$), 3.45 (dt, 1H ment., J=10.4, J=4.4), 2.28 (d, 1H, OH, J=6.5). ^{13}C NMR: 170.1 (s), 164.3 (s), 106.0 (s), 83.3 (d), 74.3 (d), 74.1 (d), 50.0 (t), 48.7 (t), 47.6 (d), 44.1 (t), 34.0 (t), 25.3 (d), 24.0 (t), 23.7 (t), 22.6 (t), 22.0 (q), 15.9 (q), (characteristic signals).[20]

(5*R*, 1''*R*) **4a$_2$**: Isolated in pure form after washing with hexane the **4a$_2$**+**4b$_1$** isomeric mixture. 26% yield. M.p. 209-13 °C. $[\alpha]_D$= - 5.3 (c=0.76, $CHCl_3$). IR(Nujol): 3320, 1715, 1610. ^{1}H NMR: 4.51 (s, 1H, H_3), 4.04 (m, 1H, CH_2N), 3.82 (dd, 1H, $H_{1''}$, J=10.1, J=2.5), 3.53 (dt, 1H ment., J=10.5, J=4.4), 3.5-3.3 (m, 2H, CH_2N), 3.09 (m, 1H, CH_2N), 2.3-0.6 (m, 18H ment., 4H pyrro., 2H, $H_{2''}$), 1.05 (t, 3H, $H_{3''}$, $J_{2'',3''}$=7.4). ^{13}C NMR: 172.1 (s), 165.7 (s), 105.2 (s), 83.7 (d), 74.6 (d), 73.2 (d), 50.4 (t), 48.6 (d), 48.2 (t), 41.9 (t), 34.1 (t), 31.5 (d), 26.1 (t), 25.0 (d), 24.2 (t), 24.0 (t), 22.8 (t), 22.5 (q), 21.4 (q), 15.5 (q), 10.5 (q).

4b$_1$: ^{1}H NMR: 4,52 (s, 1H, H_3), (characteristic signal).[20]

5-Acetyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (5).

(Hexane/ethyl acetate:3/1.5). The mixture **5a**+**5b** was washed with pentane and the resulting solid was filtered to yield pure isomer **5a**.

(5*R*) **5a**: 35% yield. M.p. 139-40 °C. $[\alpha]_D$= - 104 (c=0.55, $CHCl_3$). IR($CHCl_3$): 1730, 1620. ^{1}H NMR: 4.56 (s, 1H, H_3), 3.8-3.6 (m, 1H ment., 1H, CH_2N), 3.4-3.0 (m, 3H, CH_2N), 2.4-0.6 (m, 18H ment., 4H pyrro.), 2.37 (s, 3H, $H_{2''}$). ^{13}C NMR: 199.5 (s), 170.7 (s), 163.8 (s), 101.8 (s), 82.7 (d), 73.7 (d), 49.8 (t), 48.2 (d), 48.1 (t), 41.3 (t), 33.7 (t), 31.3 (d), 25.6 (t), 25.0 (d), 24.7 (q), 24.2 (t), 22.5 (t), 22.2 (q), 21.2 (q), 15.3 (q). Analysis Calcd. for $C_{20}H_{31}O_4N$: C, 68.74; H, 8.94; N, 4.01. Found: C, 69.01; H, 8.69; N, 3.94.

(5*S*) **5b**: ^{1}H NMR: 4.58 (s, 1H, H_3), 2.36 (s, 3H, $H_{2''}$). ^{13}C NMR: 82.5 (d), 75.8 (d), 15.7 (q), (characteristic signals).[20]

5-(*l*-Menthyloxy)-5-propinoyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (6).

(Ether/hexane:2/1). The mixture **6a**+**6b** was washed with hexane and the resulting solid was filtered to yield pure isomer **6a**.

(5*R*) **6a**: 37% yield. M.p. 86-8 °C. $[\alpha]_D$= - 93.6 (c=0.70, $CHCl_3$). IR(Nujol): 1760, 1730, 1620. ^{1}H NMR: 4.56 (s, 1H, H_3), 3.8-2.9 (m, 1H ment., 4H, CH_2N), 2.8 (m, 2H, $H_{2''}$), 2.4-0.6 (m, 18H ment., 4H pyrro.), 1.08 (t, 3H, $H_{3''}$, $J_{2'',3''}$=7,2). ^{13}C NMR: 202.4 (s), 170.9 (s), 164.2 (s), 102.0 (s), 82.8 (d), 73.7 (d), 49.9 (t), 48.3 (d), 48.1 (t), 41.4 (t), 33.8 (t), 31.4 (d), 30.0 (t), 25.7 (t), 25.1 (d), 24.3 (t), 22.6 (t), 22.3 (q), 21.3 (q), 15.4 (q), 7.0 (q). MS, m/z (relative intensity): 364 (M^++1, 21), 306 (27), 208 (20), 168 (100), 140

(48), 96 (14), 95 (32), 81 (21), 70 (20). Analysis Calcd. for $C_{21}H_{33}O_4N$: C, 69.39; H, 9.15; N, 3.85. Found: C, 69.42; H, 9.40; N, 3.74.

(5*S*) **6b**: ^{1}H NMR: 4,57 (s, 1H, H_3). ^{13}C NMR: 82.7 (d), 75.8 (d), (characteristic signals).[20]

5-Benzoyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (7).

(Hexane/ethyl acetate:3/1). The mixture **7a**+**7b** was washed with pentane and the resulting solid was filtered to yield pure isomer **7a**.

(5*R*) **7a**: 53% yield. M.p. 110-1 °C. $[\alpha]_D$= - 272.7 (c=1, $CHCl_3$). IR(KBr pellet): 1760, 1690, 1622. ^{1}H NMR: 8.1-8.0 (m, 2H arom.), 7.6-7.4 (m, 3H arom.), 4.62 (s, 1H, H_3), 3.89 (dt, 1H ment., J=10.6, J=4.6), 3.8 (m, 1H, CH_2N), 3.45 (m, 1H, CH_2N), 3.21 (m, 2H, CH_2N), 2.3-0.8 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 191.7 (s), 170.8 (s), 165.3 (s), 134.3, 133.1, 130.0, 127.8, (C arom.), 103.5 (s), 82.4 (d), 74.7 (d), 50.0 (t), 48.4 (t), 48.1 (d), 41.2 (t), 33.7 (t), 31.3 (d), 25.6 (t), 24.7 (d), 24.2 (t), 22.6 (t), 22.2 (q), 21.0 (q), 15.5 (q). MS, m/z (relative intensity): 306 (M^+-105, 0.7), 256 (M^+-155, 1), 168 (100), 140 (18), 105 (14), 83 (20), 77 (10), 70 (11), 55 (16). Analysis Calcd. for $C_{25}H_{33}O_4N$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.88; H, 7.99; N, 3.58.

(5*S*) **7b**: ^{1}H NMR: 4.69 (s, 1H, H_3). ^{13}C NMR: 104.9 (s), 83.2 (d), 77.3 (d), 48.8 (t), 47.9 (d), 43.9 (t), 31.5 (d), 25.0 (d), 24.0 (t), 22.1 (q), 20.5 (q), 16.1 (q), (characteristic signals).[20]

3-Benzoyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (8).

The title compounds were characterized from a 39:52:8 mixture of $\mathbf{8_1}$, $\mathbf{8_2}$ and **7a**. ^{1}H NMR: 8.1-7.4 (m, 5H arom.), 5.92 and 5.84 (2s, 1H, H_5), 4.0-3.2 (m, 1H ment., 4H pyrro.), 2.3-0.8 (m, 18H ment., 4H pyrro.).

5-(*l*-Menthyloxy)-5-methoxycarbonyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (9).

(Hexane/ethyl acetate:1.2/1). The mixture **9a**+**9b** was washed with pentane and the resulting solid was filtered to yield pure isomer **9a**.

(5*R*) **9a**: 42% yield. M.p. 93-5 °C. $[\alpha]_D$= + 12.9 (c=0.07, $CHCl_3$). IR($CHCl_3$): 1755, 1745, 1625. ^{1}H NMR: 4.58 (s, 1H, H_3), 3.83 (s, 3H, OCH_3), 3.8 (m, 1H, CH_2N), 3.64 (dt, 1H ment., J=10.5, J=4.4), 3.3 (m, 1H, CH_2N), 3.2-3.1 (m, 2H, CH_2N), 2.4-0.7 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 171.0 (s), 165.9 (s), 163.8 (s), 99.3 (s), 82.4 (d), 74.3 (d), 53.3 (q), 50.0 (t), 48.3 (d), 47.6 (t), 41.7 (t), 33.9 (t), 31.5 (d), 25.8 (t), 24.8 (d), 24.3 (t), 22.9 (t), 22.3 (q), 21.3 (q), 15.7 (q). Analysis Calcd. for $C_{20}H_{31}O_5N$: C, 65.71; H, 8.55; N, 3.83. Found: C, 65.78; H, 8.80; N, 3.95.

(5*S*) **9b**: This compound was characterized from a 60:40 mixture of **9a** and **9b**. ^{1}H NMR: 4.55 (s, 1H, H_3), 3.82 (s, 3H, OCH_3). ^{13}C NMR: 170.9 (s), 166.7 (s), 163.9 (s), 99.8 (s), 81.6 (d), 76.6 (d), 53.2 (q), 48.0 (d), 47.9 (t), 43.1 (t), 34.0 (t), 25.3 (t), 22.1 (q), 15.9 (q), (characteristic signals).[20]

5-Allyl-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (10).

(Hexane/ethyl acetate:3/2). The mixture **10a**+**10b** was washed with hexane and the resulting solid was filtered to yield pure isomer **10a**.

(5*S*) **10a**: 48% yield. M.p. 118-9 °C. $[\alpha]_D$= + 2.6 (c=1, $CHCl_3$). IR(Nujol): 1740, 1610. ^{1}H NMR: 5.7 (m,

1H, $H_{2'}$), 5.15 (m, 2H, $H_{1''}$), 4.45 (s, 1H, H_3), 4.1 (m, 1H, CH_2N), 3.52 (dt, 1H ment., J=10.4, J=4.4), 3.4-3.2 (m, 2H, CH_2N), 3.1 (m, 1H, CH_2N), 2.86 (dd, 1H, $H_{1'''}$, J=14.1, J=8.0), 2.65 (dd, 1H, $H_{1'''}$, J=14.5, J=8.0), 2.3-0.7 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 171.2 (s), 165.1 (s), 130.0 (d), 119.1 (t), 103.7 (s), 82.9 (d), 72.3 (d), 49.8 (t), 48.2 (d), 47.4 (t), 41.6 (t), 40.4 (t), 33.7 (t), 31.1 (d), 25.7 (t), 24.6 (d), 24.0 (t), 22.6 (t), 22.1 (q), 21.0 (q), 15.5 (q). MS, m/z (relative intensity): 347 (M^+, 0.4), 209 (20), 192 (29), 182 (10), 168 (100), 140 (40), 136 (38), 57 (68), 83 (42), 81 (13), 69 (46), 55 (57). Analysis Calcd. for $C_{21}H_{33}O_3N$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.56; H, 9.50; N, 4.20.

(5*R*) **10b**: ^1H NMR: 4.44 (s, 1H, H_3); ^{13}C NMR: 171.2 (s), 164.6 (s), 130,3 (d), 118.9 (t), 104.7 (s), 82.9 (d), 74.1 (d), 47.8 (d),43.9 (t), 24.8 (d), 22.1 (q), (characteristic signals).[20]

5-(*l*-Menthyloxy)-5-methyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (11).

(Ether/hexane:10/1).

(5*S*) **11a**: 32% yield. M.p. 150-1 °C. $[\alpha]_D$ = + 24.78 (c=0.23, $CHCl_3$). IR($CHCl_3$): 1715, 1600. ^1H NMR: 4.43 (s, 1H, H_3), 4.07 (m, 1H, CH_2N), 3.48 (dt, 1H ment., J=10.4, J=4.3), 3.30 (m, 2H, CH_2N), 3.12 (m, 1H, CH_2N), 2.3-0.8 (m, 18H ment., 4H pyrro.), 1.72 (s, 3H, CH_3). ^{13}C NMR: 171.3 (s), 166.6 (s), 102.4 (s), 81.8 (d), 72.6 (d), 49.9 (t), 48.3 (d), 47.4 (t), 41.7 (t), 33.9 (t), 31.2 (d), 25.9 (t), 24.9 (d), 24.1 (t), 23.6 (q), 22.8 (t), 22.2 (q), 21.2 (q), 15.7 (q). Analysis Calcd. for $C_{19}H_{31}O_3N$: C, 70.99; H, 9.72; N, 4.36. Found: C, 70.99; H, 10.00; N, 4.37.

(5*R*) **11b**: This compound was characterized from a 60:40 mixture of **11a** and **11b**. ^1H NMR: 4.40 (s, 1H, H_3), 4.00 (m, 1H, CH_2N), 3.58 (dt, 1H ment., J=10.4, J=4.3), 3.4-3.1 (m, 3H, CH_2N), 1.75 (s, 3H, CH_3). ^{13}C NMR: 81.4 (d), 74.4 (d), 48.0 (d), 47.6 (t), 34.1 (t), 31.3 (d), 24.0 (t), 23.1 (q), 22.7 (t), 22.0 (q), 15.7 (q), (characteristic signals).[20]

5-(*l*-Menthyloxy)-3-methyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (12).

M.p. 80-6 °C. $[\alpha]_D$= + 63.64 (c=0.63, $CHCl_3$). IR($CHCl_3$): 1720, 1620. ^1H NMR: 5.65 (s, 1H, H_5), 3.8-3.5 (m, 1H ment., 4H, CH_2N), 2.3-0.7 (m, 18H ment., 4H pyrro.), 1.96 (s, 3H, CH_3). ^{13}C NMR: 174.4 (s), 158.4 (s), 97.5 (d), 89.6(s), 79.8 (d), 48.8 (t), 48.2 (d), 42.4 (t), 34.0 (t), 31.6 (d), 25.1 and 25.0 (d and t), 22.7 (t), 22.2 (q), 21.2 (q), 15.7 (q), 8.6 (q). MS, m/z (relative intensity): 321 (M^+, 18), 183 (29), 166 (63), 155 (87), 138 (51), 109 (100), 70 (11).

5-(*l*-Menthyloxy)-3,5-dimethyl-4-(pyrrolidin-1-yl)furan-2(5*H*)-one (13).

White solid of m.p. 131-5 °C. $[\alpha]_D$= + 17.78 (c=0.09, $CHCl_3$). IR($CHCl_3$): 1715, 1610. ^1H NMR: 3.99 (m, 2H, CH_2N), 3.6-3.3 (m, 1H ment., 2H, CH_2N), 2.3-0.7 (m, 18H ment., 4H pyrro.), 1.97 (s, 3H, CH_3-C_3), 1.69 (s, 3H, CH_3-C_5). ^{13}C NMR: 173.4 (s), 161.4 (s), 102.1 (s), 89.6 (s), 72.6 (d), 49.2 (t), 48.6 (d), 42.1 (t), 34.2 (t), 31.4 (d), 25.0 (d), 24.2 (q), 23.0 (t), 22.5 (q), 21.4 (q), 15.9 (q), 9.1 (q). MS, m/z (relative intensity): 335 (M^+, 12), 180 (44), 109 (100), 70 (8).

5-(3'-Bromo-5'-methoxy-2'-oxotetrahydrofuran-4'-yl)-5-(*l*-menthyloxy)-4-(pyrrolidin-1-yl)furan-2(5*H*)-ones (15). By column chromatography (hexane/ethyl acetate:3/1) was isolated a mixture of **15a$_1$**+**15b** and the diastereoisomer **15a$_2$** with some impurities of furanone **1**.

(15a$_1$+15b): M.p. 158-66 °C. IR(Nujol): 1800, 1760, 1615. MS, m/z (relative intensity): 501-499 (M^+, 1), 458-456 (3), 392 (12), 364-362 (12), 258-256 (9), 169 (100), 141 (90), 70 (28). Analysis Calcd. for $C_{23}H_{34}O_6NBr$: C, 55.20; H, 6.85; N, 2.80. Found: C, 55.50; H, 7.00; N, 2.69.

(15a$_1$): ^{1}H NMR: 5.67 (d, 1H, $H_{5''}$, $J_{4'',5''}$=4.4), 4.60 (s, 1H, H_3), 4.20 (d, 1H, $H_{3''}$, $J_{3'',4''}$=8.2), 4.1 (m, 1H, CH_2N), 3.7-3.0 (m, 1H, ment., 3H, CH_2N), 3.62 (dt, 1H, ment., J=10.5, J=4.4), 3.57 (s, 3H, OCH_3), 3.26 (dd, 1H, $H_{4''}$, J=8.2, J=4.4), 2.3-0.5 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 169.7 (s), 169.2 (s), 163.2 (s), 104.6 (d), 102.0 (s), 83.6 (d), 74.0 (d), 57.8 (q), 56.4 (d), 50.4 (t), 48.2 (d), 48.1 (t), 41.3 (t), 37.1 (d), 33.7 (t), 31.3 (d), 25.9 (t), 24.8 (d), 24.0 (t), 22.5 (t), 22.3 (q), 21.1 (q), 15.2 (q).

(15b): ^{1}H NMR: 5.61 (d, 1H, $H_{5''}$, $J_{4'',5''}$=3.4), 4.63 (s, 1H, H_3), 4.2-3.0 (m, 1H, $H_{4''}$, 1H ment., 4H, CH_2N), 3.61 (s, 3H, OCH_3). ^{13}C NMR: 162.3 (s), 105.0 (d), 103.4 (s), 83.7 (d), 75.2 (d), 57.8 (q), 56.2 (d), 48.5 (t), 47.3 (d), 36.4 (d), 25.2 (d), 23.9 (t), 22.0 (q), 21.3 (q), 15.8 (q).

15a$_2$: IR($CHCl_3$): 1780, 1740, 1610. ^{1}H NMR: 5.02 (d, 1H, $H_{5''}$, $J_{4'',5''}$=5.1), 4.87 (d, 1H, $H_{3''}$, $J_{3'',4''}$=7.5), 4.58 (s, 1H, H_3), 4.1 (m, 1H, CH_2N), 3.56 (dt, 1H ment., J=10.5, J=4.5), 3.47 (s, 3H, OCH_3), 3.5-3.1 (m, 3H, CH_2N), 3.34 (dd, 1H, $H_{4''}$, J=7.5, J=5.1), 2.4-0.6 (m, 18H ment., 4H pyrro.). ^{13}C NMR: 169.9 (s), 169.7 (s), 163.3 (s), 103.6 (d), 102.3 (s), 83.4 (d), 73.7 (d), 58.3 (q), 57.1 (d), 50.6 (t), 48.3 (t), 47.9 (d), 41.6 (t), 37.1 (d), 33.8 (t), 31.5 (d), 26.0 (t), 25.2 (d), 24.2 (t), 22.6 (t), 22.4 (q), 21.4 (q), 15.4 (q).

Reduction of furanones 6a and 7a

To a solution of furanone **6a** or **7a** (0.13 mmol) in dry tetrahydrofuran (2 ml) was added sodium borohydride (0.65 mmol). The mixture was stirred at room temperature for 4 hours. The evolution of reaction was followed by TLC. After evaporation of THF, the residue was dissolved in dichloromethane and then washed with water. The aqueous layer was extracted several times with dichloromethane. The combined organic layers were dried and the solvent evaporated to dryness.

The reduction of propionylfuranone **6a** afforded, in cuantitative yield, a 58:42 mixture of diastereoisomeric hydroxypropylfuranones **4a$_1$** and **4a$_2$**.

The reduction of **7a** gave a 61:39 mixture of diastereoisomeric hydroxybenzylfuranones **3a$_1$** and **3a$_2$**, and traces of **1**. From this mixture the pure isomers (5*R*,1''*S*) **3a$_1$** and (5*R*, 1''*R*) **3a$_2$** were isolated by column chromatography (Hexane/ethyl acetate: 1/1), in 58 and 35% yield respectively.

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REFERENCES AND NOTES

1. T. Yamada, H. Hagiwara and H. Uda, *J. Chem. Soc. Chem Comm.*, **1980**, 838.
2. A. Pelter, R. I. H. Al-Bayati, M. T. Ayoub, W. Lewis and P. Pardasani, *J. Chem. Soc. Perkin Trans. I*, **1987**, 717.
3. T. Honda, T. Hayakawa, H. Kondoh, A. Okuyama and M. Tsubuki, *Chem. Letters*, **1991**, 1861.

4. S. C. M. Fell, J. Heaps and J. S. E. Holker, *J. Chem. Soc. Chem. Comm.*, **1979**, 81.
5. R. H. Schlessinger, E. J. Iwanowicz and J. P. Springer, *Tetrahedron Lett.*, **1988**, *29*, 1489.
6. H. Jatzke, U. Evertz and R. R. Schmidt, *Synlett*, **1990**, 191.
7. B. de Ancos, F. Fariña, M. C. Maestro, M. R. Martin and M. M. Vicioso, *Tetrahedron*, **1991**, *47*, 3171.
8. R. H. Schlessinger, A. M. M. Mjalli, A. D. Adams, J. P. Springer and K. Hoogsteen, *J. Org. Chem.*, **1992**, *57*, 2992
9. K. Nishide, A. Aramata, T. Kamanaka and M. Node, *Heterocycles*, **1993**, *36*, 2237.
10. M. R. Martin and A. I. Mateo, *Tetrahedron: Asymmetry*, **1994**, *5*, 1385.
11. The regiochemical assignments of the new 5,5-disubstituted furanones were based on the spectral data obtained for each compound. Thus, the ^{1}H-NMR spectra of these compounds lacked resonances corresponding to the acetal-type protons at C-5, but exhibited signals assignable to the olefinic proton at 3-position. Furthermore, ^{13}C-NMR spectra displayed signals assignable to C-5 quaternary carbon that show differences in chemical shifts in accord with the nature of the new substituent introduced.
12. The ratio is only approximate, because the signals of four diastereoisomers appear very close.
13. I. Alonso, I. Lopéz-Solera, P. R. Raithby, *Acta Crystallogr.*, **1995** to be published.
14. For these compounds the configuration at C-5 has not been unequivocally determined. However, from mechanistic considerations and comparation of their ^{13}C NMR data with those of furanones **1** and **11**, we tentatively propose the (5*S*) configuration for furanones **12** and **13**.
15. The stereochemistry **a** or **b** to the alkylated furanones was assigned, besides by the preferential mode of the reagents approach, by ^{13}C-NMR. Thus, the chemical shifts of C-1' in **a** epimers appear at lower δ values than those of the corresponding stereoisomers **b**.
16. F. Fariña, M. R. Martin and M. V. Martin, *An. Quim.*, **1978**, *74*, 799.
17. a) F. Fariña, M. C. Maestro, M. R. Martin, M. V. Martin and F. Sánchez, *Heterocycles*, **1983**, *20*, 1761. b) F. Fariña, M. C. Maestro, M. R. Martin, M. V. Martin and F. Sánchez, *J. Chem. Research* (S), **1984**, 44; (M), **1984**, 534.
18. A. Pelter, R. S. Ward, D. M. Jones and P. Maddocks, *J. Chem. Soc. Perkin Trans 1*, **1993**, 2621 and references cited therein.
19. a) B. de Lange, F. van Bolhuis and B. L. Feringa, *Tetrahedron*, **1991**, *45*, 6799. b) J. F. G. A. Jansen, C. Jansen and B. L. Feringa, *Tetrahedron: Asymmetry*, **1991**, *2*, 109 and references cited therein.
20. The remaining signals were not included, because either they overlap with other signals or were not detected due to the low concentration of this isomer in the mixture.

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