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Synthesis of 3-(1-Hydroxyalkyl)-5*H*-furan-2-ones: Study of their Reaction with Halogens

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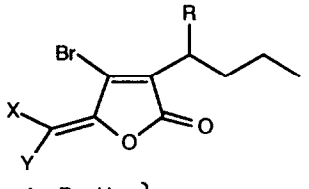
Key words: 3-(1-hydroxyalkyl)-5*H*-furan-2-ones; bromination; bromine chlorination

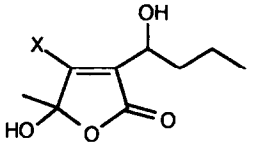
Abstract: The synthesis of 3-(1-hydroxyalkyl)-5*H*-furan-2-ones, **4a-c**, is reported. The reaction of lactones **4a** and **4b** with bromine under typical ionic bromination conditions gives as major product the unexpected substitution of the allylic hydroxyl group. Only the less hindered double bond in **4c** gives some proportion of the normal addition product. The bromine chloride addition to **4c** proceeds with 55% yield, while lactone **4a** does not add BrCl. All these results point to the fact that halogen addition to the double bond of **4** suffers at least from steric hindrance.

INTRODUCTION

In 1977 a family of secondary metabolites with the basic structure of γ-yliden-α,β-butenolide, named as fimbrolides, was isolated and identified from the dichloromethane extract of the red algae *Delisea fimbriata* (Bonnemaisoniaceae).[1] All these unsaturated lactones possess a bromine atom attached at the β-carbon and one or two additional halogen atoms at the exocyclic methylene group. Moreover, a butyl chain with different functionalization is also always linked at the α-carbon, giving raise to fimbrolides (**1a**, R = H), hydroxyfimbrolides (**1b**, R = OH), and acetoxyfimbrolides (**1c**, R = OAc) (Scheme 1). The same year K. Ohta[2] identified two related substances, named bromobeckerelide (**2a**, X = Br) and chlorobeckerelide (**2b**, X = Cl), from the red algae *Beckerella subcostatum*. Later on, six new compounds related with the structure of fimbrolides have been isolated from *Delisea elegans*.[3] Some of these substances have a cyclobutanic structure derived from a [2+2] cycloaddition of the exocyclic double bond.



1a: R = H
1b: R = OH
1c: R = OAc
} X,Y = H, Cl, Br, I



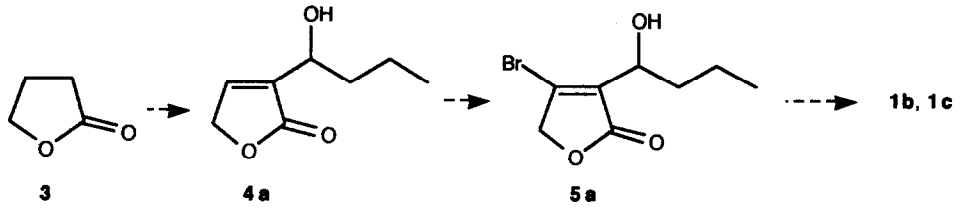
2a: X = Br
2b: X = Cl

Scheme 1

Since all these compounds were shown to have interesting antifungal and antimicrobial properties, *in vitro* as well as *in vivo*, several attempts to synthesize these novel highly functionalized secondary metabolites have been described, but until now very little success has been achieved. No synthesis of hydroxy- nor acetoxyfimbrolides has been yet reported and only two synthesis of fimbrolides, **1a**,[4] and one of bromobeckerelide[5] have been described. In relation to our research on structurally simple α,β-butenolides we initiated some years ago a program with the final goal to open a new general access to hydroxyfimbrolides and acetoxyfimbrolides. In this paper we want to give the full results, a preliminary note being already published,[6] derived from our first approach.

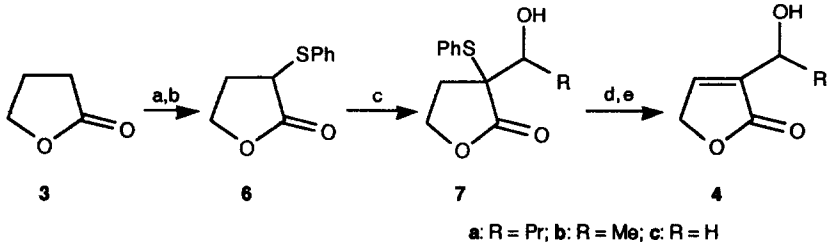
RESULTS AND DISCUSSION

A first and rapid retrosynthetic approach to **1b** and **1c** conducted us to γ-butyrolactone, **3**, as starting material, in such a way that the different substituents present in the fimbrolides would be incorporated successively: i) the butyl chain, **4a**; ii) the bromine atom at the β-carbon, **5a**; and iii) the halogenated methylene group (Scheme 2).



Scheme 2

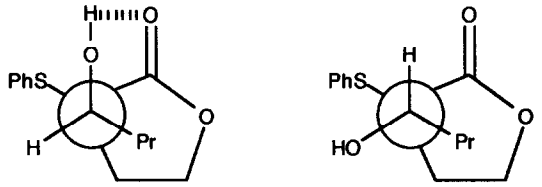
After several attempts,[6a] we prepared 3-(1-hydroxybutyl)-5*H*-furan-2-one, **4a**, by the sequence showed in Scheme 3. Thioether **6** was best prepared through α-bromination of butyrolactone[7] and subsequent reaction with sodium thiophenolate.[8] Direct reaction of the lithium enolate of **3** with diphenyldisulfide gave lower yields.[9] Condensation of the anion of **6** with *n*-butanal afforded butanolide **7a** as a 1:1 diastereomeric mixture in 88% yield. The use of Lewis acid catalysts[10] or the addition of HMPA[9] did not improve the yield. Both isomers were separated by column chromatography and we assigned the relative stereochemistry (3*RS*,1'*RS*) to the first eluted product (Figure 1). This less polar isomer presents an intramolecular hydrogen bond as indicated by its ^{1}H nmr spectrum and its ir spectrum at different concentrations. Another spectral difference between both stereoisomers is the absorption of the methylene protons at the β-carbon. In (3*RS*,1'*RS*)-**7a**



a) Br_2; b) PhSNa, THF; c) LDA, RCHO; d) *m*-CPBA or $NaIO_4$; e) pyrolysis

Scheme 3

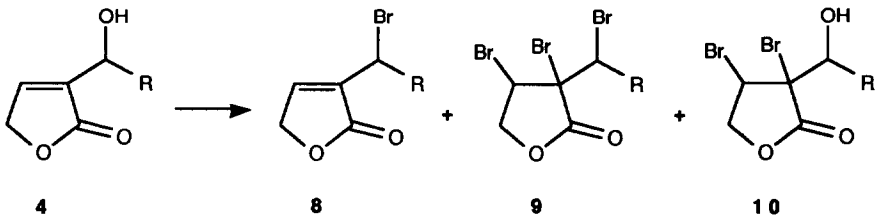
these protons resonate at δ 2.11 and 2.55, while in the other isomer they absorb more separated at δ ≈ 2.00 and 2.76. This difference has been also observed by Hoye *et al.*[10] and it may be due to the spatial situation and influence of the lone electron pairs of the hydroxyl group. Oxidation of crude **7a** with *m*-chloroperbenzoic acid or sodium periodate and elimination of phenylsulfenic acid gave butenolide **4a** in 62-77% yield.



(3*RS*,1'*RS*)-**7a** (3*RS*,1'*SR*)-**7a**

Figure 1

Our next synthetic goal was bromolactone **5a**, that we expected to prepare by bromination and subsequent dehydrobromination of **4a** (Scheme 2). Analogous transformations on butenolides had been already described.[11] To our surprise, when lactone **4a** was submitted to the conventional ionic bromination conditions (1 equiv of puriss bromine, purchased from Fluka AG, at room temperature in CCl_4), we isolated as major product the new 3-(1-bromobutyl)-5*H*-furan-2-one, **8a**, which results from the substitution of the hydroxyl group by the bromine atom leaving the double bond unmodified (Scheme 4, Table 1). The structural assignment of the bromo derivative **8a** was unambiguous since it gave satisfactory elemental analysis, the ir spectrum presented no absorption in the region 3600-3050 cm^{-1}, the ^1H nmr spectrum showed a broad singlet at δ 7.47, and the chemical ionization (NH_3) mass spectrum indicated molecular ions at *m/e* 238-236 $(C_8H_{11}BrO_2 + 18)^+$.



4 **8** **9** **10**

a: R = Pr; **b**: R = Me; **c**: R = H

Scheme 4

Note from Table 1 that starting material was always recovered in fair yields and that when the reaction time was highly prolonged the tribromo derivative **9a** was isolated in 14% yield, indicating its formation from **8a**, as was confirmed by independent bromination of this compound (Table 1, entries 9 and 10). All the spectral data are also in agreement with the structure of **9a**. Changing the reaction conditions between **4a** and bromine (solvent and time, Table 1) never did give rise to the desired addition product **10a**.

At this stage we decided to try other bromination reagents. The reaction of lactone **4a** with 4-(dimethylamino)pyridinium tribromide (DMAPHBr$_3$)[12] in acetic acid allowed the isolation and identification of three compounds: the brominated acetoxy compound **11** (12%), the described bromo derivative **8a** (4%), and the acetylated product **12** (55%) (Schemes 5 and 6). The structural assignment of **11** was not easy: the chemical

Table 1. Bromination reactions

entry	compd	solvent	reagent	time (h)	starting mat (%)[a]	**8** (%)[a]	**9** (%)[a]	Br_2 add (%)[a]	others (%)[a]
1	**4a**	CCl_4	Br_2	19	**4a** (21)	**8a** (52)			
2	**4a**	CCl_4	Br_2	48	**4a** (7)	**8a** (50)	**9a** (14)		
3	**4a**	CH_2Cl_2	Br_2	80	**4a** (trace)	**8a** (44)			
4	**4a**	benzene	Br_2	19	**4a** (30)	**8a** (46)			
5	**4a**	acetic acid	$DMAPHBr_3$	72		**8a** (4)			**11** (12), **12** (55)
6	**4a**	dioxane	TMPAP	84		**8a** (28)			**13** (51), **14** (17)
7	**4b**	CH_2Cl_2	Br_2	19		**8b** (42)			
8	**4c**	CH_2Cl_2	Br_2	19	**4c** (2)	**8c** (12)	**9c** (24)	**10c** (38)	
9	**8a**	CCl_4	Br_2	80	**8a** (18)		**9a** (69)		
10	**8a**	CH_2Cl_2	Br_2	80	**8a** (60)		**9a** (12)		
11	**12**	CCl_4	Br_2	120	**12** (10)	**8a** (25)	**9a** (20)	**18** (25)	
12	**16**	CCl_4	Br_2	55		**8a** (16)	**9a** (17)	**19** (6)	**13** (7)
13	**17**	CCl_4	Br_2	74	**16** (trace)	**8a** (30)		**20** (20)	

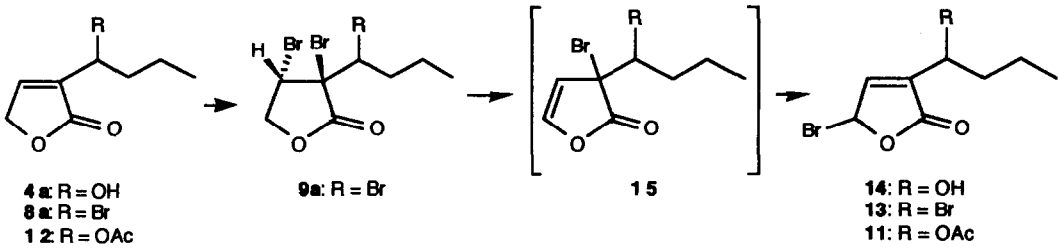
[a] Isolated yield

ionization mass spectrum with ammonia (*m/e*=296-294, $C_{10}H_{13}BrO_4 + 18)^+$ indicated the incorporation of a bromine atom and an acetyl group; the ^1H nmr spectrum revealed the absence of the methylene group in the γ position since there was no absorption in the region δ 4.70-4.90 and the presence of two singlets at δ 6.83 and 7.33 corresponding to the protons at C-5 and C-4 respectively. All these data are consistent with the structure of a 5-bromo-5*H*-furan-2-one. When the reaction with $DMAPHBr_3$ was run in CCl_4 only starting lactone **4a** was recovered. We used this bromination reagent since its reaction with 3-phenyl-2-propen-1-ol is reported to give quantitatively the normal addition product without substitution[12] (*vide infra*).

We still tried the synthesis of **10a** employing other previously reported bromination reagents, such as tetrabutylammonium tribromide (TBAT),[13] tetrabutyl-ammonium bromine iodide,[14] 1,8-diazabicyclo[5.4.0]-undec-7-ene hydrobromide ($DBUHBr_3$) without catalyst or in the presence of $HgCl_2$,[15] and trimethylphenyl-ammonium perbromide (TMPAP) in methanol and dioxane.[14,16] The last reagent has been already satisfactorily used in the addition of bromine to α-methylenebutyrolactones, reaction in which other reagents also failed.[16] In all these experiments, excepting one the starting material was recovered. Only in the reaction with TMPAP in dioxane we could isolate three products: 5-bromo-3-(1-bromobutyl)-5*H*-furan-2-one, **13** (51%), **8a** (28%), and 5-bromo-3-(1-hydroxybutyl)-5*H*-furan-2-one, **14** (17%). We assume (Scheme 5) that compounds **11**, **13**, and **14**, all with a bromine atom in 5-position (^1H nmr δ ≈ 6.85 for the proton at C-5), derive from the addition of bromine to the double bond of lactones **12**, **8a**, and **4a** respectively. The resulting addition products eliminate hydrogen bromide between positions 4 and 5 giving the non-conjugated bromolactones of type **15**. Bromine allylic rearrangement should account for the final products **11**, **13**, and **14**. We have already described analogous transpositions in five[17] and six membered lactones.[18]

As mentioned before the bromination of **8a** gave the bromine addition product **9a**. With this compound in our hands we decided to study the pyrolytic elimination of hydrogen bromide.[11] The only identified product from this reaction was **13** (22%). This result supports our assumption displayed in Scheme 5.

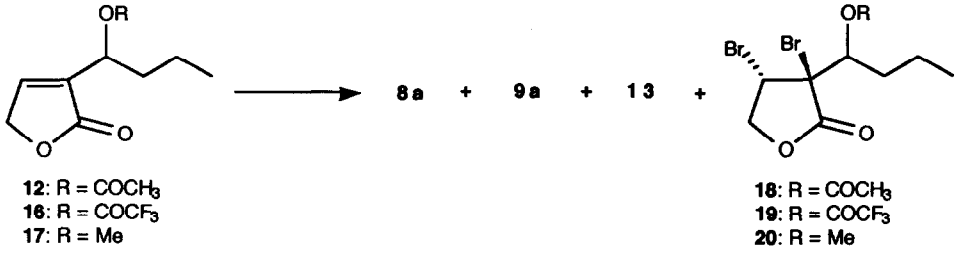
Due to the unexpected substitution reaction in the allylic alcohol **4a** by bromine, we decided to study in more detail this bromination process. The only described substitution reactions of the hydroxyl group for



Scheme 5

bromine are, to the best of our knowledge, the cases of 3-phenyl-2-propen-1-ol (*vide supra*) and 1-phenyl-2-propen-1-ol, in which the tribromoderivatives were obtained in poor yields.[19] No explanation for these results was given. In addition, the bromination of the **4a** analogous compound, 3-butyl-5*H*-furan-2-one[20] and **8a** (as indicated in this work), both derivatives without the allylic hydroxyl group, takes place under standard reaction conditions yielding the normal addition product.

In view of the described results we decided to protect the hydroxyl group and we prepared by conventional methods several derivatives of **4a**: the acetate **12**, the trifluoroacetate **16**, and the methyl ether **17**. These products were submitted to bromination using bromine in CCl_4 (Table 1, entries 11-13). In all the cases the compounds derived from O-substitution were again the main isolated products, but the normal addition compound was formed now to some extent (Scheme 6). The dibromoacetate **18** was isolated in a 25% yield and both diastereomers could be separated. The mixture of trifluoroacetates **19**, that was obtained in only 6% yield, could be identified by its ir, ^1H nmr, and mass spectra and compound **20** could not be obtained in pure form and it was only characterized by its mass spectrum.

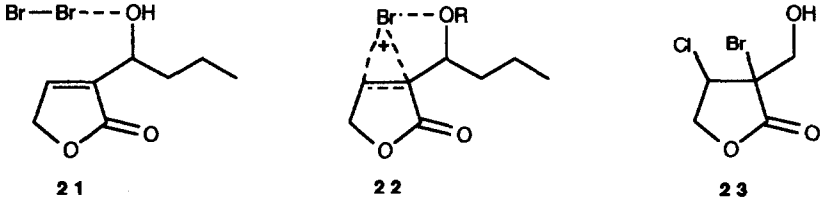


Scheme 6

In order to study the influence of the alkyl chain in the bromination reaction we also synthesized lactones **4b**[21] and **4c** using the same sequence employed in the case of **4a** (Scheme 3). The overall yields were 31% and 46% respectively from lactone **6**. When lactone **4b** was brominated (Table 1, entry 7) the only isolated product was again the bromine substituted derivative **8b**. Its structural assignment is based on its satisfactory elemental analysis, its mass spectrum, the absence of hydroxyl group absorption in its ir spectrum, and the presence of a signal at δ 7.46 in the proton nmr spectrum due to the vinylic proton. However, the bromination of **4c** (Table 1, entry 8) gave a mixture of compounds, from which **4c**, **8c**,[22] **9c**, and the desired **10c** (38%) could be isolated and identified.

The results that **4a** and **4b** undergo substitution, while **4c** partially undergoes bromine addition and substitution, point to the fact that bromine addition to the double bond of 3-(1-hydroxyalkyl)-5*H*-furan-2-ones, **4**, suffers at least from steric hindrance. These olefins have three electron-withdrawing substituents and

therefore are poor nucleophiles and the reaction progress with an electrophilic reagent like bromine should be very slow,[23] as is indeed experimentally observed. Following Bellucci's studies[24] we have also postulated[6] the formation of a complex between bromine and the hydroxyl group, **21**, and the intramolecular transfer of bromine to the double bond with the final formation of the intermediate **22** (Figure 2). Now, the nucleophilic opening of the bromonium ion **22** is influenced and strongly decelerated by the hydroxyl group[24], the lactone oxygen,[24] and the carbonyl group,[25] and if it is produced it should occur at the α-position.[6] Then, in the cases where bulky alkyl chains are present at this position, the reaction proceeds, although slowly, through other pathway giving rise to the substitution of the hydroxyl group. The ether **17** is a stronger Lewis base then the hydroxyl group and would favor the formation of bromonium ion **22**, but it is not a good leaving group, and this could explain the formation of both substitution and addition products. In the cases of esters **12** and **16** the effects are opposite to the methoxy group giving rise also to both types of reaction.



21 **22** **23**

Figure 2

In a further attempt to obtain information on the mechanism of addition of halogens to 3-(1-hydroxyalkyl)-5*H*-furan-2-ones, **4**, we studied the reaction of these lactones with bromine chloride, prepared by the method described by Heasley and co-workers.[25a] Although the reaction of **4c** with this reagent was also slow (40 h), we were able to isolate the addition product **23**, 3-bromo-4-chloro-4,5-dihydro-3-hydroxymethyl-3*H*-furan-2-one, in 55% yield (Figure 2). Its structural assignment is based on comparison of its ^{13}C nmr spectrum with that of the dibromo derivative **10c**: the quaternary carbon C-3 absorbs in both cases at $\delta \approx 59$, while C-4 resonates at δ 62.0 and 50.1 for **23** and **10c** respectively. From the reaction of lactone **4a** with bromine chloride in methylene chloride or carbon tetrachloride no addition product could be isolated. Since BrCl is more polar than bromine it might be that for substrate **4c** -with less steric hindrance- no hydroxyl anchimeric polarization assistance is needed, allowing the formation of a classic bromonium ion and its opening by Cl^- at the β-position.

We may conclude from all these experiments, that for lactone **4c**, in which the steric effect of the alkyl chain is negligible, two mechanisms are operative: either the formation of a classic bromonium ion, or the participation of the hydroxyl group giving rise to the formation of a bromonium ion analogous to **22**. Substrates **4a** and **4b** seem to behave different and we have to accept that the size of the alkyl chain has a determinant effect on the mechanism of the addition of halogens to 3-(1-hydroxyalkyl)-5*H*-furan-2-ones, **4**.

It is evident that these results make the synthetic route outlined in Scheme 2 useless for the preparation of hydroxy- and acetoxyfimbrolides. In our laboratories we are searching for other strategies that would allow us the synthesis of these secondary metabolites.[26]

EXPERIMENTAL SECTION

Commercial TBAP and TMPAP were used. The ir spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. The 80 MHz pmr and 20 MHz cmr spectra were recorded on a Bruker WP80SY

spectrometer from deuterated chloroform solutions; chemical shifts are given in ppm relative to TMS (δ values). Distillation of small amounts were effected on a Büchi KRV 65/30 rotational distillator (only oven temperature given). Mass spectra and gc-ms analyses (70 eV for electron impact and ammonia as reagent gas for chemical ionization) were recorded on a Hewlett-Packard 5985B gc-ms system; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

*4,5-Dihydro-3-phenylthio-3*H*-furan-2-one*, **6**

This lactone was prepared in 36% yield by reaction of the enolate of γ-butyrolactone with diphenyldisulphide following the method described by Kido *et al.*[9] Better results (47% overall yield) were obtained by transformation of γ-butyrolactone into α-bromo-γ-butyrolactone (55%)[7] and subsequent reaction with sodium thiophenolate (85%).[8]

*4,5-Dihydro-3-(1-hydroxybutyl)-3-phenylthio-3*H*-furan-2-one*, **7a**

To a stirred solution of 55.7 mmol of lithium diisopropylamide (LDA), prepared from 7.8 mL of diisopropylamine and 34.9 mL of 1.6 M *n*-BuLi in hexane, in 33 mL of anhydrous THF at -78 °C, a solution of lactone **6** (9.0 g, 46.4 mmol) in THF (47 mL) was slowly added over a period of 15 minutes. The temperature was raised to -50 °C and the solution was stirred for 1 h. Then, a solution of butyraldehyde (4.0 g, 4.9 mL, 55.7 mmol) in THF (33 mL) was added. The crude mixture was left at -50 °C for a further 2 h and it was poored over 270 mL of cold saturated ammonium chloride solution. The ether extracts (4x135 mL) were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield 12.3 g of an orange oil. This crude was purified by column chromatography through silica gel (70-230 mesh) using hexane-ethyl acetate (2:1) as eluent. This process allowed the isolation of 10.87 g (88% yield) of lactone **7a**. Repeated chromatography of a portion of this material using methylene chloride-ethyl acetate (19:1) as eluent afforded pure (3*RS*,1'*RS*)-**7a** and (3*RS*,1'*SR*)-**7a** in elution order.

(3*RS*,1'*RS*)-**7a**: mp 66-8 °C (hexane-ethyl acetate); ir (KBr) 3440, 3060, 2950, 2920, 2860, 1740, 1370, 1300, 1280, 1210, 1170, 1060 cm^{-1}; ^1H nmr 0.9 (t, J = 6.2 Hz, 3 H), 1.21-1.63 (m, 4 H), 2.11 (ddd, J = 14.0 Hz, J' = 6.5 Hz, J'' = 2.5 Hz, 1 H), 2.55 (dt, J = 14.0 Hz, J' = 8.0 Hz, 1 H), 3.18 (br s, 1 H), 3.82 (br d, 1 H), 4.21 (m, 2 H), 7.24-7.45 (m, 3 H), 7.51-7.64 (m, 2 H); ^{13}C nmr 13.8, 19.6, 31.2, 33.8, 59.2, 65.4, 72.6, 128.8, 129.0, 130.1, 137.2, 175.3; ms *m/e* 266 (M^+, 1.4), 249 (0.7), 194 (100), 121 (24), 117 (33), 109 (36), 65 (32), 55 (28), 43 (41), 41 (49). Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.30; H, 6.61.

(3*RS*,1'*SR*)-**7a**: 81-3 °C (hexane-ethyl acetate); ir (KBr) 3500, 3060, 2960, 2920, 2885, 2865, 2845, 1750, 1470, 1370, 1210, 1180, 1170, 1060, 1040, 1000 cm^{-1}; ^1H nmr 1.0 (t, J = 6.2 Hz, 3 H), 1.15-2.24 (m, 6 H), 2.76 (dt, J = 13.5 Hz, J' = 9.7 Hz, 1 H), 3.88 (br d, 1 H), 4.27 (m, 2 H), 7.24-7.60 (m, 5 H); ^{13}C nmr 13.8, 19.3, 28.9, 32.3, 58.2, 65.4, 70.6, 128.5, 128.9, 130.0, 137.0, 175.6; ms *m/e* 266 (M^+, 4), 249 (1), 194 (100), 121 (26), 117 (30), 109 (30), 91 (20), 65 (27), 55 (29), 43 (39), 41 (41). Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 63.39; H, 6.75.

*4,5-Dihydro-3-(1-hydroxyethyl)-3-phenylthio-3*H*-furan-2-one*, **7b**

To a stirred solution of 12.5 mmol of lithium diisopropylamide (LDA), prepared from 1.7 mL of diisopropylamine and 7.8 mL of 1.6 M *n*-BuLi in hexane, in 7.5 mL of anhydrous THF at -78 °C, a solution of lactone **6** (2.02 g, 10.4 mmol) in THF (47 mL) was slowly added over a period of 15 minutes. The temperature was raised to -50 °C and the solution was stirred for 1 h. Then, a solution of acetaldehyde (0.55 g, 0.7 mL, 12.5 mmol) in THF (7.5 mL) was added. The crude mixture was left at -50 °C for a further 2 h and it

was poored over 50 mL of cold saturated ammonium chloride solution. The ether extracts (3x50 mL) were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield 2.29 g of an orange oil. This crude was purified by column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (1:1) as eluent. This process allowed the isolation of 1.92 g (77% yield) of lactone **7b** as a 1:1 mixture of diastereomers:[10,21] ^{1}H nmr 1.28 (d, J = 7.0 Hz) and 1.39 (d, J = 7.0 Hz) (3 H), 1.90-2.77 (m, 3 H), 4.00-4.26 (m, 3 H), 7.20-7.26 (m, 5 H); ms *m/e* 238 (M^+, 8), 194 (100), 121 (24), 91 (21).

*4,5-Dihydro-3-(1-hydroxymethyl)-3-phenylthio-3*H*-furan-2-one*, **7c**

To a stirred solution of 54.8 mmol of lithium diisopropylamide (LDA), prepared from 7.6 mL of diisopropylamine and 33.7 mL of 1.6 M *n*-BuLi in hexane, in 12 mL of anhydrous THF at -78 °C, a solution of lactone **6** (8.0 g, 41.2 mmol) in THF (24 mL) was slowly added over a period of 15 minutes. The temperature was raised to -50 °C and the solution was stirred for 1 h. Then, a solution of formaldehyde (generated by pyrolysis of 6.0 g, 0.2 mmol, of paraformaldehyde at 200 °C) in argon is added to the reaction vessel over a period of 30 min. The crude mixture was left at -50 °C for a further 2 h and it was poored over 100 mL of cold saturated ammonium chloride solution and it was acidified to pH 5 with diluted HCl. The ether extracts (4x50 mL) were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield 8.3 g of an orange oil. Column chromatography through silica gel (230-400 mesh) of this material using hexane-ethyl acetate (2:1) as eluent gave **7c** (6.83 g 74% yield): mp 47-9 °C (hexane-ethyl acetate); ir (KBr) 3600-3200, 3060, 2960, 2920, 1760, 1440, 1230, 1180, 1060, 1020 cm^{-1}; ^{1}H nmr 1.90-2.30 (m, 2 H), 2.77 (dt, J = 12.9 Hz, J' = 9.0 Hz, 1 H), 3.72 (dd, J = 12.5 Hz, J' = 6.8 Hz, 1 H), 3.94 (dd, J = 10.7 Hz, J' = 6.8 Hz, 1 H), 4.21-4.49 (m, 2 H), 7.25-7.61 (m, 5 H); ^{13}C nmr 30.9, 54.6, 63.8, 65.3, 128.3, 128.9, 129.9, 137.0, 175.3; ms *m/e* 224 (M^+, 100), 194 (81), 149 (25), 147 (29), 135 (26), 121 (39), 117 (25), 115 (35), 110 (86), 109 (68), 105 (27), 103 (23), 91 (39), 77 (31), 71 (41), 69 (35), 66 (21), 65 (27), 58 (43), 57 (59), 41 (40). Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; S, 14.30. Found: C, 58.61; H, 5.31; S, 14.10.

*3-(1-Hydroxybutyl)-5*H*-furan-2-one*, **4a**

A) To a magnetically stirred solution of thioether **7a** (740 mg, 2.8 mmol) in methanol (8 mL) at 0 °C, a water solution (8 mL) of sodium periodate (720 mg, 3.3 mmol) was slowly added during 30 min. The solution was kept for 1 h at 0 °C and overnight at room temperature. The precipitate was filtered off and methylene chloride (20 mL) was added. The resulting organic phase was washed successively with $NaHCO_3$ solution and water, dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to afford 580 mg of crude sulphoxides. This material was dissolved in toluene (10 mL) and was heated at reflux during 90 min. Removal of the solvent by vacuum distillation gave a yellow oil, which was chromatographed through a silica gel column (70-230 mesh). With hexane-ethyl acetate (3:2) as eluent 335 mg (77% yield) of a pale yellow oil identified as **4a** were obtained:[27] ^{1}H nmr 0.9 (t, J = 6.2 Hz, 3 H), 1.08-1.98 (m, 4 H), 2.18 (br s, 1 H), 4.50 (m, 1 H), 4.76 (br s, 2 H), 7.24 (br s, 1 H); ^{13}C nmr 13.5, 18.2, 37.4, 66.5, 70.3, 136.6, 145.0, 173.1.

B) When the oxidation was carried out with *m*-chloroperbenzoic acid in methylene chloride at 0 °C for 1 h the yield of **4a** was 62%.

*3-(1-Hydroxyethyl)-5*H*-furan-2-one*, **4b**

An analogous oxidation (method A) and pyrolysis procedure described for **4a** was applied to lactone **7b** (1.85 g, 7.7 mmol). The toluene solution of the crude sulphoxides was refluxed in this case for 3 h. Column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (3:1) as eluent afforded

following fractions in elution order: i) starting material (79 mg, 4%); ii) 5*H*-furan-2-one (142 mg, 22%); iii) 476 mg of impure 3-(1-hydroxyethyl)-5*H*-furan-2-one, **4b**.[21] Distillation of this material gave 390 mg (40% yield) of pure **4b**: bp 165-6 °C/12 torr; ^{1}H nmr 1.49 (d, J = 6.2 Hz, 3 H), 2.15 (br s, 1 H), 4.69 (m, 1 H), 4.83 (m, 2 H), 7.30 (m, 1 H); ^{13}C nmr 21.3, 62.6, 70.3, 137.2, 144.9, 173.0.

3-(1-Hydroxymethyl)-5H-furan-2-one, **4c**

An analogous oxidation (method A) and pyrolysis procedure described for **4a** was applied to lactone **7c** (4.61g, 20.6 mmol). The toluene solution of the crude sulphoxides was refluxed in this case for 2 h. Column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (1:1) as eluent allowed the isolation of **4c** as a colorless oil (1.45 g, 62% yield): bp 104-6 °C/0.3 torr; ir ($CHCl_3$) 3620, 3560-3300, 3020, 2940, 2870, 1750, 1660, 1440, 1350, 1080, 1050, 1010, 830 cm^{-1}; ^{1}H nmr 2.75 (br s, 1 H), 4.45 (m, 2 H), 4.86 (m, 2 H), 7.43 (m, 1 H); ^{13}C nmr 56.2, 70.7, 133.2, 146.6, 173.3; ms *m/e* 113 (M^+-1, 5.7), 96 (19), 85 (100), 68 (21), 55 (20); ms (CI, NH_3) *m/e* 149 (M^++35), 132 (M^++18). Anal. Calcd. for $C_5H_6O_3$: C, 52.63; H, 5.30. Found: C, 52.75; H, 5.59.

Bromination reactions of lactone **4a**

A) To a light protected and stirred solution of lactone **4a** (170 mg, 1.1 mmol) in CCl_4 (2 mL) at 0 °C a solution of puriss. bromine (174 mg, 1.1 mmol) in the same solvent (1 mL) was slowly added over a period of 45 min. The mixture was kept at room temperature for 48 h. The crude mixture was diluted with $CHCl_3$ (10 mL) and it was successively washed with saturated sodium bisulphite solution and water. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield 320 mg of a yellow oil. Column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent afforded the following fractions: i) 52 mg (14% yield) of 3,4-dibromo-3-(1-bromobutyl)-4,5-dihydro-3*H*-furan-2-one, **9a**, as a diastereomeric mixture; ii) 120 mg (50% yield) of 3-(1-bromobutyl)-5*H*-furan-2-one, **8a**, as a colorless oil; and iii) 12 mg (7% yield) of starting material **4a**.

9a: Spectral data described bellow.

8a: bp 95-8 °C/0.05 torr; ir ($CHCl_3$) 2970, 2940, 2880, 1760, 1710, 1450, 1110, 1070, 1040 cm^{-1}; ^{1}H nmr 1.00 (t, J = 6.2 Hz, 3 H), 1.25-1.73 (m, 2H), 1.90-2.21 (m, 2 H), 4.70 (t, J = 6.7 Hz, 1 H), 4.80 (m, 2 H), 7.47 (br s, 1 H); ^{13}C nmr 12.9, 20.7, 38.8, 43.0, 69.8, 135.2, 147.0, 170.9; ms *m/e* 219-217 (M^+-1, 0.7, 1), 139 (100), 93 (45), 77 (28), 53 (30), 41 (30); ms (CI, NH_3) *m/e* 238-236 (M^++18). Anal. Calcd. for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06. Found: C, 44.03; H, 5.11.

B) Only lactone **8a** (25-46% yield) was obtained when lactone **4a** and bromine were allowed to react in CH_2Cl_2 or benzene during 10-80 h.

C) To a stirred solution of lactone **4a** (245 mg, 1.6 mmol) in acetic acid (5 mL) at room temperature 4-(dimethylamino)pyridinium tribromide[12] (680 mg, 1.9 mmol) was added. The mixture was stirred for 72 h, it was diluted with CH_2Cl_2 (20 mL), and it was successively washed with $NaHCO_3$ solution and water. The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to yield 370 mg of a red oil. Column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent afforded the following fractions: i) 52 mg (12% yield) of 3-(1-acetoxybutyl)-5-bromo-5*H*-furan-2-one, **11**, as a diastereomeric mixture; ii) 14 mg (4% yield) of **8a**; and iii) 175 mg (55% yield) of 3-(1-acetoxybutyl)-5*H*-furan-2-one, **12**.

11: ir (film) 3090, 2950, 2920, 2860, 1770, 1730, 1360, 1230, 1200, 1100, 1060, 960, 940 cm^{-1}; ^{1}H nmr 0.96 (t, J = 6.2 Hz, 3 H), 1.26-1.90 (m, 4 H), 2.13 (s, 3 H), 5.66 (br t, J = 5.7 Hz, 1 H), 6.83 (s, 1 H), 7.33 (s, 1 H); ms (CI, NH_3) *m/e* 296-294 (M^++18).

12: spectral data described below.

D) A solution of lactone **4a** (200 mg, 1.3 mmol) and trimethylphenylammonium perbromide (TMPAP, 723 mg, 1.9 mmol) in dioxane (4 mL) at room temperature was stirred during 84 h. Ether (15 mL) was added and the formed precipitate was filtered off. The solvent was removed under reduced pressure to yield 450 mg of a yellow oil. Column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (3:2) as eluent afforded the following fractions: i) 192 mg (51% yield) of dibromo derivative **13**; ii) 78 mg (28% yield) of bromo compound **8a**; and iii) 52 mg (17% yield) of 5-bromo-3-(1-hydroxybutyl)-5*H*-furan-2-one, **14**.

13: Spectral data described below.

14: ir (film) 3600-3300, 2950, 2925, 2865, 1775, 1460, 1315, 1200, 1110, 1065, 1030, 955 cm^{-1}; ^1H nmr 0.9 (t, J = 6.2 Hz, 3 H), 1.3-1.9 (m, 4 H), 2.20 (br s, 1 H), 4.55 (m, 1 H), 6.83 (s, 1 H), 7.33 (s, 1 H); ^{13}C nmr 13.5, 13.6, 18.0, 18.2, 37.1, 66.2, 66.5, 74.2, 74.4, 136.9, 137.0, 146.9, 147.0, 169.0; ms (CI, NH_3) *m/e* 254-252 (M^++18).

E) From the reaction of lactone **4a** with TMPAP in methanol, *n*-Bu_4NBr_3, *n*-Bu_4NIBr_2, DBUHBr_3, or DBUHBr_3/$HgCl_2$ only starting material could be isolated.

Reaction of lactone **4b** *with bromine*

Lactone **4b** (150 mg, 1.2 mmol) was allowed to react with bromine (187 mg, 1.2 mmol) in methylene chloride (3 mL) at room temperature during 19 h. Column chromatography of the crude product through silica gel (230-400 mesh) using hexane-CH_2Cl_2 (3:7) as eluent afforded 3-(1-bromoethyl)-5*H*-furan-2-one, **8b**, as a colorless oil (94 mg, 42% yield): bp 82-3 °C/0.05 torr; ir ($CHCl_3$) 3020, 2930, 2870, 1760, 1445, 1100, 1070, 1050, 1020 cm^{-1}; ^1H nmr 1.95 (d, J = 7.4 Hz, 3 H), 4.81 (m, 3 H), 7.46 (s, 1 H); ^{13}C nmr 24.4, 37.0, 69.7, 136.6, 146.3, 170.7; ms *m/e* 192-190 (M^+, 0.5, 0.5), 111 (100), 83 (23), 55 (24); ms (CI, NH_3) *m/e* 227-225 (M^++35), 210-208 (M^++18). Anal. Calcd. for $C_6H_7BrO_2$: C, 37.72; H, 3.69. Found: C, 37.41; H, 3.29.

Reaction of lactone **4c** *with bromine*

Lactone **4c** (385 mg, 3.4 mmol) was allowed to react with bromine (540 mg, 3.4 mmol) in methylene chloride (3 mL) at room temperature for 19 h. Column chromatography of the crude product through silica gel (230-400 mesh) using hexane-ethyl acetate (1:3) as eluent afforded following fractions: i) a diastereomeric mixture of 3,4-dibromo-3-bromomethyl-4,5-dihydro-3*H*-furan-2-one, **9c**, as a yellowish oil (274 mg, 24% yield); ii) 3,4-dibromo-4,5-dihydro-3-hydroxymethyl-3*H*-furan-2-one, **10c**, as a diastereomeric mixture (350 mg, 38% yield); iii) 3-bromomethyl-5*H*-furan-2-one, **8c**,[22] as a colorless oil (70 mg, 12% yield); and iv) starting material (7 mg, 2% yield).

9c: ir ($CHCl_3$) 3020, 2960, 1785, 1160, 1040, 1020 cm^{-1}; ^1H nmr 3.85 (d, J = 6.3 Hz, 1 H), 4.00 (d, J = 6.3 Hz, 1 H), 4.51 (d, J = 11.2 Hz, 1 H), 4.73 (d, J = 3.7 Hz, 1 H), 4.95 (dd, J = 11.2 Hz, J' = 3.7 Hz, 1 H), small absorptions corresponding to a diastereomer were also observed; ms (CI, NH_3) *m/e* 375-373-371-369 (M^++35), 358-356-354-352 (M^++18).

10c: mp 65-7 °C (hexane-ethyl acetate); ir (KBr) 3600-3100, 3020, 2940, 1775, 1220, 1160, 1080, 1040, 1020, 1000, 960 cm^{-1}; ^1H nmr 2.15 (br s, 1 H), 4.24 (s, 2 H), 4.57 (d, J = 10.3 Hz, 1 H), 4.81 (d, J = 4.8 Hz, 1 H), 5.00 (dd, J = 10.3 Hz, J' = 4.8 Hz, 1 H); ^{13}C nmr 50.1, 59.1, 66.0, 74.3, 170.4; ms (CI, NH_3) *m/e* 311-309-307 (M^++35), 294-292-290 (M^++18).

8c: ir ($CHCl_3$) 3040, 2980, 2960, 1760, 1350, 1070, 1050, 830 cm^{-1}; ^1H nmr 4.03 (m, 2 H), 4.77 (m, 2 H), 7.46 br s, 1 H); ^{13}C nmr 20.6, 70.0, 131.1, 148.7, 171.2; ms *m/e* 178-176 (M^+, 21, 17), 97 (100).

*3,4-Dibromo-3-(1-bromobutyl)-4,5-dihydro-3*H*-furan-2-one*, **9a**

To a light protected and stirred solution of bromolactone **8a** (170 mg, 0.8 mmol) in CCl_4 (2 mL) at 0 °C a

solution of bromine (124 mg, 0.8 mmol) in the same solvent (1 mL) was slowly added over a period of 30 min. The mixture was kept at room temperature for 80 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent. This process allowed the isolation of 202 mg (69% yield) of diastereomers **9a** and 30 mg (18% yield) of starting material **8a**. Recrystallization of **9a** from hexane afforded 65 mg of one diastereomer of **9a** in pure form: mp 87-9 °C.

Mixture of **9a**: ^{1}H nmr 1.00 (t, J = 7.2 Hz, 3 H), 1.25-3.06 (m, 4 H), 4.20-5.25 (m, 4 H); ms (CI, NH_3) *m/z* 417-415-413-411 (M^++35), 400-398-396-394 (M^++18). Pure diastereomer of **9a**: ir (KBr) 2940, 2920, 2860, 1770, 1450, 1250, 1210, 1180, 1160, 1040, 1030 cm^{-1}; ^{1}H nmr 1.00 (t, J = 7.2 Hz, 3 H), 1.25-2.17 (m, 3H), 2.63-3.06 (m, 1 H), 4.36 (dd, J = 9.7 Hz, J' = 2.4 Hz, 1 H), 4.54 (d, J = 11.0 Hz, 1 H), 4.84 (d, J = 3.0 Hz, 1H), 5.09 (dd, J = 11.0 Hz, J' = 3.0 Hz, 1 H); ^{13}C nmr 13.2, 20.8, 37.0, 55.4, 58.1, 64.9, 73.1, 167.3; ms *m/e* 301-299-297 (M^+-Br, 18, 39, 20), 139 (36), 137 (20), 93 (100), 91 (50), 81 (30), 79 (33), 77 (50), 67 (26), 66 (24), 65 (37), 55 (35), 53 (44), 51 (50), 41 (56).

The same reaction run in methylene chloride at room temperature for 80 h allowed the isolation of **9a** (12% yield) and 60% of starting material.

Pyrolysis of tribromolactone **9a**

Lactone **9a** (257 mg, 0.7 mmol) was pyrolysed and distilled in a rotational distillator at 135 °C/19 torr during 2 h. Column chromatography of the distilled material (82 mg) through silica gel (230-400 mesh) using CCl_4-ethyl acetate (19:1) yielded a diastereomeric mixture of 5-bromo-3-(1-bromobutyl)-5*H*-furan-2-one, **13**, (45 mg, 22% yield): ir (film) 3080, 2940, 2920, 2860, 1770, 1625, 1200, 1060, 1030, 950 cm^{-1}; ^{1}H nmr 1.00 (t, J = 6.2 Hz, 3 H), 1.20-1.78 (m, 2 H), 1.93-2.23 (m, 2 H), 4.73 (t, J = 6.4 Hz, 1 H), 6.86 (s, 1 H), 7.64 (s, 1 H); ^{13}C nmr 13.1, 20.7, 20.8, 38.6, 38.8, 41.5, 41.7, 73.8, 73.9, 135.5, 135.7, 148.6, 148.8, 167.1; ms (CI, NH_3) *m/e* 335-333-331 (M^++35), 318-316-314 (M^++18).

3-(1-Acetoxybutyl)-5H-furan-2-one, **12**

To a stirred solution of lactone **4a** (190 mg, 1.2 mmol) in CH_2Cl_2 (10 mL) at room temperature, acetic anhydride (186 mg, 1.8 mmol) and pyridine (144 mg, 1.8 mmol) were added. After 120 h the solution was slightly acidified with 0.5 N HCl. The organic phase was washed with saturated solution of $NaHCO_3$, dried over anhydrous sodium sulphate, and the solvent was removed under reduced pressure yielding a red oil (230 mg). This material was purified by column chromatography through silica gel (230-400 mesh) using CH_2Cl_2 as eluent. This process allowed the isolation of 195 mg (81% yield) of **12**.

12: bp 80-2 °C/0.05 torr; ir (film) 3060, 2940, 2920, 2860, 1760, 1740, 1360, 1230, 1200, 1060, 1030, 1020 cm^{-1}; ^{1}H nmr 0.94 (t, J = 6.2 Hz, 3 H), 1.15-1.59 (m, 2H), 1.65-1.97 (m, 2 H), 2.09 (s, 3 H), 4.78 (m, 2 H), 5.62 (br t, J= 5.9 Hz, 1 H), 7.28 (m, 1 H); ^{13}C nmr 13.4, 18.1, 20.6, 34.7, 68.5, 70.0, 133.5, 146.1, 169.7, 171.4; ms *m/z* 155 (M^+-43, 20), 138 (36), 123 (28), 113 (38), 93 (29), 43 (100); ms (CI, NH_3) *m/z* 216 (M^++18). Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.08; H, 6.78.

3-(1-Trifluoroacetoxybutyl)-5H-furan-2-one, **16**

A solution of lactone **4a** (400 mg, 2.6 mmol) in trifluoroacetic anhydride (1.8 mL, 13 mmol) was kept at room temperature overnight. Ether (10 mL) was added and the organic phase was washed with saturated solution of $NaHCO_3$, and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the crude was chromatographed through silica gel (230-400 mesh) using hexane-ethyl acetate (1:1) as eluent giving the following fractions: i) 3-(1-trifluoroacetoxybutyl)-5*H*-furan-2-one, **16**, as a colorless

oil (309 mg, 48% yield); and ii) starting lactone **4a** (120 mg, 30% yield).

16: bp 95-6 °C/0.3 torr; ir (film) 2960, 2930, 2870, 1775, 1750, 1220, 1150, 1070, 1040 cm^{-1}; ^1H nmr 0.93 (t, J = 6.2 Hz, 3 H), 1.19-1.66 (m, 2 H), 1.80-2.16 (m, 2 H), 4.83 (m, 2 H), 5.80 (m, 1 H), 7.36 (m, 1 H); ^{13}C nmr 13.1, 17.8, 34.3, 70.3, 72.7, 114.3 (q, J = 284 Hz), 131.3, 147.7, 156.4 (q, J = 42 Hz), 170.9; ms *m/e* 253 (M^++1, 0.7), 233 (0.5), 210 (2), 139 (32), 123 (55), 113 (38), 108 (28), 96 (55), 95 (28), 93 (100), 85 (29), 81 (52), 77 (25), 69 (93), 68 (63), 67 (26), 55 (46), 53 (54), 43 (65), 41 (59); ms (CI, NH_3) *m/e* 287 (M^++35), 270 (M^++18). Anal. Calcd. for $C_{10}H_{11}F_3O_4$: C, 47.63; H, 4.39. Found: C, 47.81; H, 4.78.

3-(1-Methoxybutyl)-5H-furan-2-one, **17**

To a light protected and stirred solution of lactone **4a** (200 mg, 1.3 mmol) in methyl iodide (10 mL) at room temperature, silver oxide (593 mg, 2.6 mmol) was added and the mixture was left to react during 55 h. The silver salts were filtered off through a small silica gel (70-230 mesh) column affording a crude oil (210 mg). This material was purified by column chromatography through silica gel (230-400 mesh) using hexane-ethyl acetate (2:1) as eluent giving methyl ether **17** as a colorless oil (110 mg, 50% yield) and starting material (52 mg, 26% yield).

17: bp 70-1 °C/0.2 torr; ir (film) 2940, 2920, 2860, 2820, 1740, 1440, 1340, 1190, 1120, 1080, 1050, 1030 cm^{-1}; ^1H nmr 0.90 (t, J = 6.2 Hz, 3 H), 1.23-1.77 (m, 4 H), 3.32 (s, 3 H), 4.06 (m, 1 H), 4.80 (m, 2 H), 7.30 (m, 1 H); ^{13}C nmr 13.6, 18.0, 36.1, 57.1, 70.1, 75.8, 135.0, 145.7, 172.6; ms *m/e* 171 (M^++1, 33), 155 (2), 139 (30), 127 (77), 99 (100), 53 (18), 41 (44). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.22; H, 8.40.

Reaction of lactone **12** *with bromine*

Lactone **12** (100 mg, 0.5 mmol) was allowed to react with bromine under the same reaction conditions described for product **4a** (method A), except that the reaction time was 5 d. Column chromatography of the crude product through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent afforded the following fractions: i) tribromolactone **9a** (73 mg, 38% yield); ii) a diastereomeric mixture of 3-(1-acetoxybutyl)-3,4-dibromo-4,5-dihydro-3*H*-furan-2-one, **18**, as a colorless oil (44 mg, 25% yield); iii) monobromolactone **8a** (28 mg, 25% yield); and iv) starting material **12** (10 mg, 10% yield). Analytical samples of both diastereomers of **18** were obtained by column chromatography using hexane-chloroform (1:2) as eluent.

18: ms (CI, NH_3) *m/z* 378-376-374 (M^++18).

Less polar isomer of **18**: ir (film) 3000, 2940, 2920, 2860, 1770, 1730, 1450, 1360, 1210, 1160, 1040, 1015 cm^{-1}; ^1H nmr 1.00 (t, J = 6.2 Hz, 3 H), 1.20-1.76 (m, 4 H), 2.13 (s, 3 H), 4.40 (d, J = 10.6 Hz, 1 H), 4.73 (d, J = 3.2 Hz, 1 H), 5.06 (dd, J = 10.6 Hz, J' = 3.2 Hz, 1 H), 5.36 (dd, J = 9.3 Hz, J' = 2.6 Hz, 1 H).

More polar isomer of **18**: ir (film) 3000, 2940, 2920, 2860, 1775, 1730, 1450, 1360, 1220, 1160, 1070, 1020 cm^{-1}; ^1H nmr 1.00 (t, J = 6.2 Hz, 3 H), 1.26-1.83 (m, 4 H), 2.16 (s, 3 H), 4.53 (d, J = 10.6 Hz, 1 H), 4.60 (d, J = 3.2 Hz, 1 H), 5.00 (dd, J = 10.6 Hz, J' = 3.2 Hz, 1 H), 5.56 (dd, J = 10.5 Hz, J' = 2.6 Hz, 1 H).

Reaction of lactone **16** *with bromine*

Lactone **16** (114 mg, 0.45 mmol) was allowed to react with bromine under the same reaction conditions described for product **4a** (method A), except that the reaction time was 9 d. Column chromatography of the crude product through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent afforded the

following fractions: i) tribromolactone **9a** (30 mg, 17% yield); ii) a diastereomeric mixture of 3,4-dibromo-3-(1-trifluoroacetoxybutyl)-4,5-dihydro-3*H*-furan-2-one, **19**, (12 mg, 6% yield); iii) dibromolactone **13** (10 mg, 7% yield); and iv) **8a** (16 mg, 16% yield).

19: ir (film) 2960, 2920, 2860, 1780, 1220, 1170, 1140, 1110 cm^{-1}; ^1H nmr 1.00 (m, 3 H), 1.26-2.66 (m, 4 H), 4.60 (d, J = 10.6 Hz, 1 H), 4.73 (d, J = 3.4 Hz, 1 H), 5.10 (dd, J = 10.6 Hz, J' = 3.4 Hz, 1 H), 5.53 (dd, J = 8.5 Hz, J' = 2.6 Hz, 1 H); ms (CI, NH_3) *m/e* 432-430-428 (M^++18).

Reaction of lactone **17** *with bromine*

Lactone **17** (30 mg, 0.17 mmol) was allowed to react with bromine under the same reaction conditions described for product **4a** (method A), except that the reaction time was 55 h. Column chromatography of the crude product through silica gel (230-400 mesh) using hexane-ethyl acetate (4:1) as eluent afforded the following fractions: i) a diastereomeric mixture of 3,4-dibromo-4,5-dihydro-3-(1-methoxybutyl)-3*H*-furan-2-one, **20**, (11 mg, 20% yield, not pure material); and ii) **8a** (11 mg, 30% yield).

20: ms (CI, NH_3) *m/e* 350-348-346 (M^++18).

Reaction of lactone **4a** *with bromine chloride*

When lactone **4a** was allowed to react with bromine chloride either in CCl_4 or CH_2Cl_2 the desired addition product could not be detected. Gc analysis of the crude indicated a very complex mixture, from which only starting material and monobromolactone **8a** could be isolated.

Reaction of lactone **4c** *with bromine chloride*

To a light protected and stirred solution of lactone **4c** (306 mg, 2.7 mmol) in CH_2Cl_2 (6 mL) at 0 °C a 1.5 M solution of bromine chloride[25a] (1.8 mL, 2.7 mmol) in the same solvent was slowly added over a period of 9 min. The mixture was kept at room temperature for 40 h and the solvent was removed under reduced pressure yielding an oil (550 mg). Column chromatography of this oil through silica gel (230-400 mesh) using hexane-ethyl acetate (1:1) as eluent afforded 3-bromo-4-chloro-4,5-dihydro-3-hydroxymethyl-3*H*-furan-2-one, **23** (340 mg, 55% yield): mp 72-4 °C (hexane-ethyl acetate); ir (KBr) 3600-3100, 2960, 1750, 1460, 1370, 1230, 1170, 1080, 1050, 1030, 1000, 980 cm^{-1}; ^1H nmr 2.33 (br s, 1 H), 4.23 (br s, 2 H), 4.53 (d, J = 10.6 Hz, 1 H), 4.86-5.05 (m, 2 H); ^{13}C nmr 60.4, 62.0, 65.3, 75.1, 171.9; ms *m/e* 233-231-229 (M^++1, 0.2, 1, 0.8), 202-200-198 (0.1, 0.9, 0.6), 69 (29), 41 (100); ms (CI, NH_3) *m/e* 267-265-263 (M^++35), 250-248-246 (M^++18). Anal. Calcd. for $C_5H_6BrClO_3$: C, 26.17; H, 2.63; Br, 34.82; Cl, 15.45. Found: C, 26.17; H, 2.34; Br, 34.61; Cl, 15.44.

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REFERENCES

1. a) Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. *Tetrahedron Lett.* **1977**, 37-40; b) Pettus, J.A., Jr.; Wing, R.M.; Sims, J.J. *Tetrahedron Lett.* **1977**, 41-44.
2. Ohta, K. *Agric. Biol. Chem.* **1977**, *41*, 2105-2106.
3. McCombs, J.D.; Blunt, J.W.; Chambers, M.V.; Munro, M.H.; Robinson, W.T. *Tetrahedron* **1988**, *44*, 1489-1502.
4. a) Beechan, C.M.; Sims, J.J. *Tetrahedron Lett.* **1979**, 1649-1652; b) Caine, D.; Ukachukwu, V.C. *J. Org. Chem.* **1985**, *50*, 2195-2198.

5. Jefford, C.W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1989**, *30*, 1237-1240.
6. a) Calderón, A.; Font, J.; de March, P. *J. Org. Chem.* **1987**, *52*, 4631-4633; b) Calderón, A.; Font, J.; Gracia, A.; de March, P. *Industrial Chemistry Library I*, Vol. 3, *Advances in Organobromine Chemistry I*; Elsevier: Amsterdam 1991, pp 51-60.
7. Price, C.; Judge, J.M. *Org. Synth.* Coll. Vol. 5, 255-258.
8. a) Iwai, K.; Kosugi, H.; Uda, H.; Kawai, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 242-247; b) Detty, M.R.; Wood, G.P. *J. Org. Chem.* **1980**, *45*, 80-89.
9. Kido, F.; Noda, Y.; Maruyama, T.; Kabuto, C.; Yoshikoshi, A. *J. Org. Chem.* **1981**, *46*, 4264-4266.
10. a) Hoye, T.R.; Kurth, M.J. *J. Org. Chem.* **1980**, *45*, 3549-3553; b) Hoye, T.R.; Caruso, A.J.; Magee, A.S. *J. Org. Chem.* **1982**, *47*, 4152-4156.
11. a) Escobar, C.; Fariña, F.; Sañudo, J.M. *Anales Quím.* **1971**, *67*, 43-57; b) Fariña, F.; Martín, M.V.; Martín, M.R.; Sánchez, F. *Synthesis* **1977**, 642-644; c) Fariña, F.; Martín, M.R.; Martín, M.V. *Anales Quím.* **1978**, *74C*, 799-805; d) Fariña, F.; Martín, M.V.; Martín-Aranda, R.M.; Martínez de Guereñu, A. *Synth. Commun.* **1993**, *23*, 459-472.
12. Arrieta, A.; Ganboa, I.; Palomo, C. *Synth. Commun.* **1984**, *14*, 939-945.
13. Berthelot, J.; Benammar, Y.; Lange, C. *Tetrahedron Lett.* **1991**, *32*, 4135-4136.
14 a) Collado, I.G.; Massanet, G.M.; Alonso, M.S. *Tetrahedron Lett.* **1991**, *32*, 3217-3220; b) Popov, A.I.; Buckles, R.E. *Inorg. Synth.* Vol. 5, 167-175.
15. Muathen, H.A. *J. Org. Chem.* **1992**, *57*, 2740-2741.
16. a) Collado, I.G.; Fraga, B.M.; Hanson, J.R.; Hitchcock, P.; Tellado, F.G. *J. Chem. Soc. Perkin Trans 1* **1988**, 105-110; b) Collado, I.G.; Madero, J.G.; Massanet, G.M.; Luis, F.R. *Tetrahedron Lett.* **1990**, *31*, 563-566.
17. Font, J.; Gracia, A.; de March, P. *Tetrahedron* **1990**, *46*, 4407-4416.
18. de March, P.; Moreno-Mañas, M.; Roca, J.L. *J. Org. Chem.* **1988**, *53*, 5149-5151.
19. a) Klages, A.; Klenk, K. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2552-2555; b) Arcus, C.L.; Strauss, H.E. *J. Chem. Soc.* **1952**, 2669-2671.
20. a) Gryff-Keller, A.; Kolodziejk, W.; Prejzner, J. *Org. Magn. Reson.* **1983**, *21*, 157-162; b) Prejzner, J. *Pol. J. Chem.* **1979**, *53*, 785-790; *Chem. Abstr.* **1979**, *91*, 175096s.
21. a) Trost, B.M.; Mao, M.K.T. *Tetrahedron Lett.* **1980**, *21*, 3523-3526; b) Trost, B.M.; Mao, M.K.T.; Balkovec, J.M.; Buhlmayer, P. *J. Am. Chem. Soc.* **1986**, *108*, 4965-4973; c) Brown, D.W.; Campbell, M.M.; Taylor, A.P.; Zhang, X. *Tetrahedron Lett* **1987**, *27*, 985
22. Chapleo, C.B.; Svanholt, K.L.; Martin, R.; Dreiding, A.S. *Helv. Chim. Acta* **1976**, *59*, 100-107.
23. Dubois, J.E.; Goetz, E. *Tetrahedron Lett.* **1963**, 303-308.
24. a) Barili, P.L.; Bellucci, G.; Berti, G.; Golfarini, M.; Marioni, F.; Scartoni, V. *Gazz. Chim. Ital.* **1974**, *104*, 107-125; b) Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital.* **1976**, *106*, 955-966.
25. a) Heasley, V.L.; Spaite, D.W.; Shellhamer, D.F. *J. Org. Chem.* **1979**, *44*, 2608-2611; b) Herr, R.W.; Wieland, D.M.; Johnson, C.R. *J. Am. Chem. Soc.* **1970**, *92*, 3813-3814; c) Chong, J.M.; Sharpless, K.B. *Tetrahedron Lett.* **1985**, *26*, 4683-4686; d) Ortuño, R.M.; Cardellach, J.; Font, J. *J. Heterocycl. Chem.* **1987**, *24*, 79-84.
26. Font, J.; Gracia, A.; de March, P. *Tetrahedron Lett.* **1990**, *31*, 5517-5520.
27. Watanabe, M.; Shirai, K.; Kumamoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3318-3320.

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