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Reaction of Iodoalkylidene Lactones with Nucleophiles

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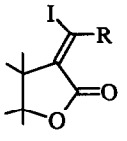
ABSTRACT - *Nucleophilic replacement of iodide from iodoalkylidene lactones provides a route to a variety of substituted alkylidene lactones. Trifluoromethyl, azido and phenylthio substituted systems are particularly accessible and reaction generally proceeds with predominant retention of the double bond configuration. A detailed GLC study of the stereoselectivity of phenylthiomethylene substitution is described. Reaction with dithiols leads to cyclic thioacetals.*

INTRODUCTION

We have now established simple synthetic routes from alkenes to both (*E*)- and (*Z*)-iodoalkylidene butyrolactones (1) and (2)[1,2].



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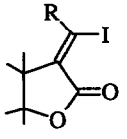

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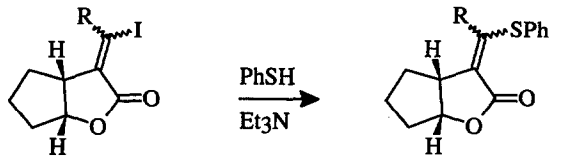
Nucleophilic attack on α,β-unsaturated esters or enones which bear leaving groups in the β-position, generally proceeds by initial conjugate addition, followed by extrusion of the leaving group. This results in an overall substitution reaction For example, treatment of a β-iodo enone with a cuprate reagent has been reported to proceed to a β-alkylated enone[3]. Reactions of this type, conducted on substrates such as (1) or (2) could be particularly useful in synthesis, especially if they proved to be stereoselective. Our previous work on structural modification of these compounds with lithium dialkylcuprates[4] has indeed revealed reactions which proceed with a high degree of retention of stereochemistry. In this paper we describe reactions with a selection of other nucleophilic systems.

SULFUR NUCLEOPHILES

Thiols add readily to methylene lactones. This process has been suggested as the mode by which the bioactive sesquiterpene methylene lactones interact with living systems, and model reactions with simple systems have been studied[5]. The iodoalkylidene lactones (1) and (2) have the potential to react similarly, but departure of iodide should generate a new enone system. This has the capacity to react in a further addition of a thiol.

We have previously reported the synthesis of a series of cyclopentyl fused iodoalkylidene lactones with various alkyl substituents in the β-position[1,2]. These compounds were used in this study to examine the reaction with thiophenoxide ion in a systematic fashion. Reactions were conducted by treatment with thiophenol

in the presence of triethylamine (Scheme 1), and the reactions were monitored by GLC. Results from these experiments, and from preparative scale reactions are summarised in Table 1.



(3) (*E*)-isomer
(5) (*Z*)-isomer

(4) (*E*)-isomer
(6) (*Z*)-isomer

(a) R = H
(b) R = CH_3
(c) R = CH_3CH_2
(d) R = $(CH_3)_2CH$
(e) R = $(CH_3)_3C$

Scheme 1.

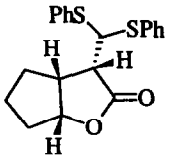
Table 1. Reaction of Iodoalkylidene Lactones with Thiophenol

Reactant		Reaction Conditions		State at Reactant Half-Life†		Isolated Yields (%)	
R =	Compound	Solvent	Temp (°C)	Time (h)	(*E*):(*Z*) Product Ratio	(*E*)	(*Z*)
H	(*E*) (3a)	Et_2O	20	0.10	40:1	(4a) 81	-
	(*Z*) (5a)	Et_2O	20	0.02	1:80	-	(6a) 56
CH_3	(*E*) (3b)	Et_2O	34	11.0	19:3	(4b) 76	-
	(*Z*) (5b)	Et_2O	34	2.0	1:18	-	(6b) 53
CH_3CH_2	(*E*) (3c)	Et_2O	34	>60	20:1	(4c) 55	-
	(*Z*) (5c)	Et_2O	34	12.0	1:4	(4c) 7	(6c) 37
$(CH_3)_2CH$	(*E*) (3d)	EtOH	78	1.1	80:1	(4d) 63	-
	(*Z*) (5d)	EtOH	78	0.6	1:1	(4d) 26	(6d) 28
$(CH_3)_3C$	(*E*) (3e)	EtOH	78	1.0	40:3	(4e) 57	(6e) 6
	(*Z*) (5e)	EtOH	78	1.0	10:27	(4e) 26	(6e) 53

† Half lives and product compositions estimated from GLC data.

As expected, the iodomethylene compounds (3a) and (5a) reacted more rapidly than did the alkyl substituted derivatives. Both (3a) and (5a) reacted at reasonable rates in ether at 20°C, but the methyl and ethyl substituted compounds (3b), (5b), (3c) and (5c) required the temperature to be raised to the boiling point. The isopropyl and *tert*-butyl substituted derivatives (3d), (5d), (3e) and (5e) required heating in boiling ethanol. With the exception of the *tert*-butyl substituted pair (3e) and (5e), the (*Z*)-isomers reacted appreciably faster than did the (*E*). These reactivity differences may result from differences in LUMO energies. Such a conjecture is supported by UV data. All of the (*E*)-isomers, with the exception of (3e) have λ_{max} in the range 252 - 255 nm, while the corresponding values for the (*Z*)-isomers are in the range 262 - 265[2]. The *tert*-butyl compound with the (*E*)-geometry (3e) has λ_{max} 264 nm, very similar to that for its (*Z*)-isomer (5e).

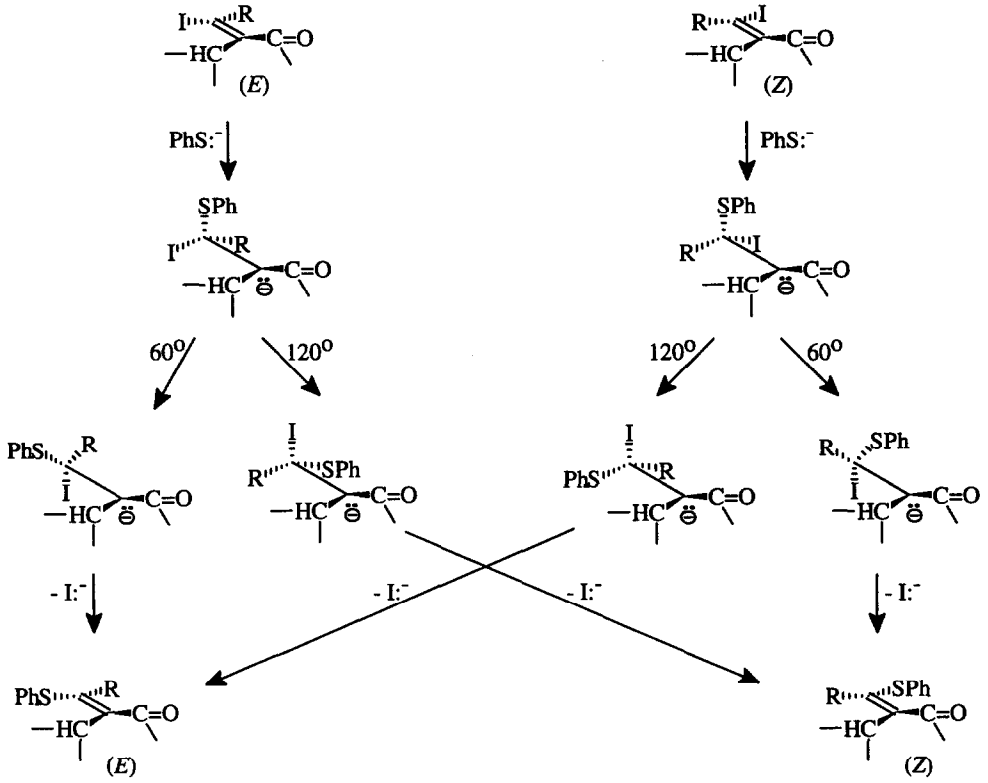
In only one case was there any observable change in the (*E*) : (*Z*) ratio over the duration of the reaction. This was with the most reactive system, the (*Z*)-iodomethylene lactone (5a) where the product (*E*) : (*Z*) ratio gradually increased with time. This observation, coupled with the fact that decidedly different product mixtures resulted from the two geometric isomers in each case, suggested that the reactions were not operating reversibly. With (5a), prolonged reaction also resulted in the formation of appreciable amounts of a thioacetal (7) (stereochemistry assigned by comparison with other similar thioacetals - see later).



(7)

In general, the reactions proceeded with predominant retention of stereochemistry. Stereoselectivity tended to be lower for the reactants with a (*Z*)-geometry, particularly those with larger alkyl groups in the β-position. The (*E*)-compounds reacted to give mainly the (*E*)-thiophenyl derivatives.

Nucleophilic substitution reactions of similar electron deficient systems have been studied in considerable detail[6]. In general terms, the mechanism for thiophenoxide attack on an iodoalkylidene lactone can be illustrated as in Scheme 2. Attack is most likely from the less hindered convex face of the molecule, but analysis leads to the same conclusions whichever face is considered.



Scheme 2

Nucleophilic attack generates a carbanionic species. For stereoelectronic reasons, the expulsion of X^- requires the carbanionic orbital and the C-X bond to be parallel. Thus a 60^o rotation gives a conformer which can lose X^- with retention of configuration, while a 120^o rotation leads to inversion. Rate constants for both rotation (k_{rot}) and expulsion of X^- (k_{exp}) are relevant to the final stereochemistry[6].

When rotation is faster than elimination, ($k_{rot} > k_{exp}$), both precursors will give the same ratio of

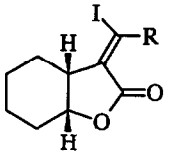
products (or a single product) and complete stereoconvergence will be observed. However, when $k_{exp} > k_{rot}$, the isomeric ratio of the product mixture is determined by competition between 60° and 120° rotations. Factors controlling the rotational barriers have been identified as steric and hyperconjugative[6]. The latter generally favours the 60° rotation, while the steric barrier favours the rotation which proceeds with minimal steric interaction between eclipsing vicinal substituents. If $k_{rot} \approx k_{exp}$, both rotational barriers and elimination rates influence the product ratios and partial stereoconvergence is observed.

The stereochemistry of substitution therefore depends to a considerable extent on the nature of the leaving group. Poor leaving groups give rise to long-lived carbanion intermediates which leads to stereoconvergence. In the reactions of the iodoalkylidene lactones in this study, the iodide leaving group should depart rapidly and the product ratio should be dominated by the rotational barriers. The experimental results generally indicated a preference for a 60° rotation and subsequent retention of stereochemistry. As R increased in bulk, 120° rotation became more pronounced, particularly with the (*Z*)-isomers. For 120° rotations both I and SPh must eclipse adjacent groupings, but the R group eclipses none (Table 2). However, for 60° rotations the R group passes through eclipsing arrangements with the carbonyl {(*E*)-isomer} or with the ring junction methine {(*Z*)-isomer}. Therefore, increasing the bulk of the R group will increase the barrier to 60° rotation but the 120° rotation will be essentially unaffected. Models show that close approach between the R grouping and a ring methylene is likely to be particularly significant, in accordance with the increased sensitivity to the size of R which has been observed in the reactions of the (*Z*)-isomers.

Table 2. Eclipsing Interactions During Rotation of Intermediates from Thiophenoxide Addition

Reactant Stereochemistry	Eclipsing Interaction	
	60° rotation	120° rotation
(*E*)	R / C=O	I / CH & PhS / C = O
(*Z*)	R / CH	I / C = O & PhS / CH

Reaction of the cyclohexyl fused iodoalkylidene lactones were also investigated. Here the (*E*)-isomers (8a) and (8b) reacted with Et_3N/PhSH with retention of stereochemistry. The trimethylsilyl derivative (8f) reacted very slowly to give a 1 : 1 ratio of (10f) and (11f). Stereoselectivity was improved in this instance by using sodium thiophenoxide in ethanol. All the (*Z*)-isomers gave isomeric mixtures with a predominance of the (*Z*)-phenylthioalkylidene derivative.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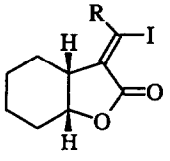
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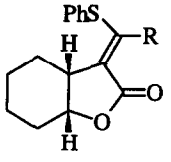
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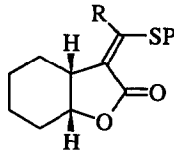
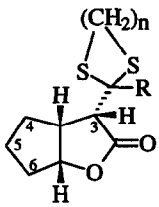
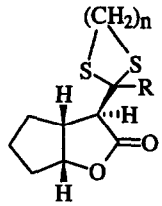

(11)

(a) R = H
(b) R = CH_3
(f) R = $(CH_3)_3Si$

Formation of the thioacetal (7) demonstrates that reaction of the iodoalkylidene lactones with two equivalents of a nucleophile is possible. Reaction with dithiols was therefore investigated as a route to cyclic thioacetals. Reaction of the (*E*)-iodomethylene lactone (3) with ethanedithiol and triethylamine resulted in the formation of two products in a 5 : 7 ratio. The IR spectra of both compounds indicated a loss of conjugation, while the ^1H NMR spectra featured methylene proton signals consistent with a dithiane ring. The loss of the double bond was confirmed by ^{13}C NMR. Data were consistent with the expected thioacetal structures (12a) and (13a).



(12) n = 2
(14) n = 3



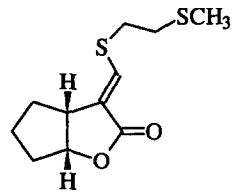
(13) n = 2
(15) n = 3

(a) R = H
(b) R = CH_3

The minor isomer was assigned structure (12a) on the basis of ^1H NMR coupling constants. The thioacetal proton signal appeared as a doublet at δ 4.57 with a coupling constant of 11 Hz, while the C-3 proton signal was a double doublet at δ 3.16 (*J* 9, 11 Hz). These coupling constants matched those calculated from an energy minimised structure (7, 12 Hz respectively)[7]. Observed coupling constants for the major isomer were equally well in agreement with calculated values for structure (13a). Here the H-3 resonance appeared at δ 2.77 (*J* 4, 4 Hz). Calculated coupling constants were both 3 Hz. The thioacetal proton signal for this isomer was a doublet at δ 5.04 (*J* 4 Hz). Data for the previously discussed thioacetal (7) matched those for (12a) closely.

Reaction of (3a) with 1,3-propanedithiol again resulted in the formation of two isomers in a 9 : 1 ratio. As the major isomer displayed similar coupling constants to those found in (12a), and values for the minor isomer matched those of (13a), they were assigned structures (14a) and (15a) respectively. In a similar fashion. the iodoethylidene lactone (3b) with ethanedithiol gave two thioacetals in a 1 : 2 ratio. These were assigned structures (12b) and (13b) respectively on the basis of their H-3/H-3a coupling constants.

The lactone thioacetal (12a) possesses two sites that could be deprotonated for further structural modification. When (12a) was treated with lithium isopropylcyclohexyl amide, followed by iodomethane, a new compound was obtained along with a small amount of unchanged (12a). IR and ^1H and ^{13}C NMR spectra of the new compound showed considerable similarities to those of the previously synthesised phenylthiomethylene lactones. In particular, the ^1H NMR spectrum showed an olefinic proton signal at δ 7.44, and two ring junction proton peaks at δ 3.36 and 4.99. The IR spectrum featured C=O and C=C stretches (1740, 1610 cm^{-1}), consistent with a conjugated lactone. The presence of a three proton singlet at δ 2.17, coupled with appropriate microanalytical data, suggested the vinyl sulfide structure (16). Formation of this compound may be rationalised by deprotonation at C-3 followed by opening of the thioacetal ring and subsequent methylation of the ensuing thiolate. A nuclear Overhauser enhancement (NOE.) experiment was inconclusive, but consistent with the premise that ring opening had occurred to give the (*E*)-isomer. Irradiation of the olefinic proton resonance at δ 7.44 gave only gave only enhancement of the SCH_2 signals. The low-field position of this vinylic proton signal is also consistent with the (*E*)-stereochemistry (*c.f.* (*E*)- and (*Z*)-thiophenylmethylene lactones (3a) and (5a) with values of δ 7.64 and 7.09 respectively).



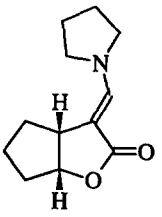
(16)

NITROGEN NUCLEOPHILES

It has been documented previously that nucleophilic substitution reactions on activated vinyl halides by amines proceed non-stereospecifically[8,9]. The initial displacement has been shown to proceed with retention of stereochemistry, but facile post reaction isomerisation results in the more stable product. The isomerisation can be a thermal process[10-13] or the result of acid catalysis[14,15]. Replacement of the tosyloxy group of a tosyloxymethylene lactone with amines has also given the more stable isomer[16].

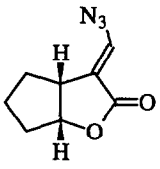
Reaction of the (*E*)-iodomethylene lactone (3a) with pyrrolidine in ethanol gave a single product (17) in 76% yield. The ^1H NMR spectrum exhibited ring junction proton resonances at δ 3.63 and 4.85 and an olefinic proton signal at δ 7.33, consistent with retention of a monosubstituted methylene lactone system. It also featured

the methylene proton resonances of the pyrrolidine ring system at δ 1.96 and 3.51. N.O.e. experiments provided no conclusive proof of an (*E*)-stereochemistry, but irradiation of the olefinic proton signal gave no enhancement of the cyclopentyl ring proton signals while enhancing the pyrrolidine ring proton resonance at δ 3.51. Once again, the chemical shift of the olefinic proton signal (δ 7.33) favoured an (*E*)-geometry. When the reaction was repeated with the (*Z*)-iodomethylene lactone (5a), the ^{1}H NMR spectrum of the crude product showed only signals for (17) with no evidence for a significant amount of its (*Z*)-isomer. This suggested that thermal isomerisation occurs to produce the more stable *trans* product. Isomerisation by acid catalysis is unlikely, as work up consisted solely of removal of excess pyrrolidine and ethanol *in vacuo*.



(17)

Treatment of simple isomeric tosyloxymethylene lactones with sodium azide has been shown to result in the stereoselective formation of the (*E*)- and (*Z*)-azidolactones[16]. It was noted in this latter study that the (*Z*)-azidolactone slowly isomerised to the (*E*)-form at room temperature. Reaction of the (*E*)-iodomethylene lactone (3a) with sodium azide in aqueous ethanol resulted in a crystalline solid (18) whose IR spectrum displayed a distinctive azide stretch at 2125 cm^{-1}. The ^{1}H NMR spectrum revealed the typical features of a substituted methylene lactone including an olefinic proton resonance at δ 7.35, consistent with retention of the (*E*)-geometry.



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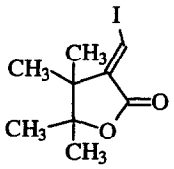

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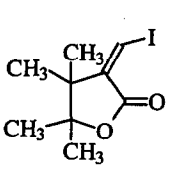

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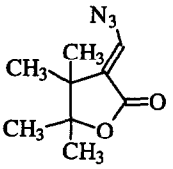

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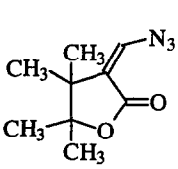
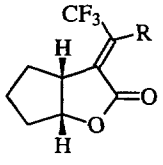


(22)

To investigate possible post reaction isomerisation, two isomeric iodolactones (19) and (20) were separately treated with sodium azide. Each gave a single product whose IR spectrum featured an azide stretch. The ^{1}H NMR spectrum of the product from iodolactone (19) displayed an vinylic proton resonance at δ 7.38 while the vinylic proton resonance in that from (20) was observed at δ 6.54. This is consistent with the (*E*)- and (*Z*)-azidomethylene lactones (21) and (22) respectively. No (*E*)/(*Z*) isomerisation was observed although both azides decomposed over 1-2 days at room temperature.

TRIFLUOROMETHYLATION

Preliminary results of the formation of trifluoromethylalkylidene lactones by reaction of iodoalkylidene lactones with an organocopper based reagent[17] have already been published[18]. Full details of the synthesis of the trifluoromethyl derivatives (23a), (23b), (24a), (24b), (25) and (26) are included in this paper.



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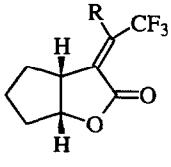

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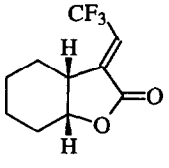

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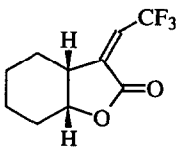

(26)

(a) R = H
(b) R = CH_3

A noteworthy feature of this transformation is that it proceeds stereospecifically with retention of stereochemistry. Yields are high (75-95%). The iodomethylene lactones (3a) and (5a) react more readily than do the iodoethylidene compounds (3b) and (5b), in parallel with the observations made earlier in relation to the reaction with thiophenoxide. This process is not suitable for preparation of trimethylsilyl derivatives as reaction

of the iodotrimethylsilylmethylene lactone (8f) yields the de-silylated trifluoromethylene derivative (25a), presumably as a result of fluoride ion present in the reaction medium. Overall, this synthesis provides a general access to a new and interesting class of organofluorine derivative.

CONCLUSIONS

The iodoalkylidene lactones which may be synthesised readily from a variety of alkenes, and which are now available in either the (*E*)- or (*Z*)-form[1,2], react readily with a variety of nucleophiles to provide facile access to a range of substituted alkylidene lactone derivatives. Replacement of iodide by the trifluoromethyl group has been achieved by way of reaction with an organocuprate reagent. This adds to the already reported alkylation with lithium dimethylcuprate[4]. Thiolates, amines and azides also react readily.

Replacement reactions proceed with varying degrees of stereoselectivity. Azide and trifluoromethyl substitutions give high degrees of retention of stereochemistry, while thiophenoxide reacts with moderate to high retention of configuration. Amine replacement with pyrrolidine gives enamine derivatives which appear to revert readily under the reaction conditions to the more stable geometric isomer.

Iodoalkylidene lactones have the capacity to undergo first a nucleophilic replacement reaction, followed by a nucleophilic addition. Thus, ring systems may be created if a reagent with two nucleophilic centres is used. Formation of cyclic thioacetals by reaction with dithiols demonstrates that this potential can be realised.

EXPERIMENTAL

General

General experimental details are as described in ref. 2. Iodoalkylidene lactone syntheses have been described in refs. 1 and 2.

Phenylthioalkylidene Lactone Preparations

Method A. Thiophenol (2 mmol), followed by Et_3N (1.5 mmol), was added to a solution of the iodoalkylidene lactone (1 mmol) in the specified solvent. After reaction, the solvent was removed and the residue was taken up into Et_2O. The ethereal solution was washed with NaOH (2 M), HCl (1 M), then H_2O, dried ($MgSO_4$) and evaporated. Reactions were sampled at regular intervals and compositions determined by gas chromatography.

Method B. NaH (50% dispersion in oil, pre-washed with dry Et_2O, 1 mmol), was reacted with half the specified volume of EtOH. The solution was cooled to 0°C and thiophenol (1 mmol) was added, followed by a solution of the iodolactone (1 mmol) in the remaining EtOH. After reaction, H_2O (2 ml) was added and the mixture was acidified with 1M HCl to pH 2. The aqueous layer was extracted with Et_2O and the organic extracts were washed with 5% NaOH and dried ($MgSO_4$).

Preparations are reported according to the convention : method, iodoalkylidene lactone (mass, amount), solvent (volume), reaction conditions, experimental data.

(3E,3aα,6aα)-Hexahydro-3-(phenylthiomethylene)-2H-cyclopenta[b]furan-2-one (4a). Method A, (3a) (0.150 g, 0.57 mmol), Et_2O (5 ml), 20°C, 1 h, PLC (60% Et_2O/hexanes) gave (4a) as an oil (0.114 g, 81%), distilled 118°C (block)/0.027 mm; IR (film): 1745, 1190 (lactone), 1615 (C=C), 1580, 740, 690 (phenyl); ^1H NMR : 1.5-1.9 (m, 4H); 1.97 (m, $W_{h/2}$ 19 Hz, 1H); 2.12 (m, $W_{h/2}$ 26 Hz, 1H); 3.46 (m, $W_{h/2}$ 19 Hz, 1H); 5.03 (m, $W_{h/2}$ 11 Hz, 1H); 7.3-7.4 (m, 3H); 7.4-7.5 (m, 2H); 7.64 (d, *J* 2 Hz, 1H); ^{13}C NMR : 23.5 (CH_2), 31.3 (CH_2), 34.1 (CH_2), 42.9 (CH), 83.7 (CH), 126.8 (C), 128.5 (CH), 129.6 (2 x CH), 130.9 (2 x CH), 133.0 (C), 139.5 (CH), 169.8 (C); Anal. Found : C, 68.0; H, 5.7; S, 13.2; Calc. for $C_{14}H_{14}O_2S$: C, 68.3; H, 5.7; S, 13.0%.

(3E,3aα,6aα)-Hexahydro-3-[1-(phenylthio)ethylidene]-2H-cyclopenta[b]furan-2-one (4b). Method A, (3b) (0.081 g, 0.29 mmol), Et_2O (1 ml), 20°C, 22 h, PLC (50% Et_2O/hexanes) gave (4b) as a colourless oil (0.058 g, 76%). Distilled 120°C (block)/0.030 mm; IR (film) : 1730, 1235 (lactone), 1615 (C=C), 1580, 750, 690 (phenyl); ^1H NMR: 1.5-1.8 (m, 3H); 1.8-2.0 (m, 2H); 2.11 (m, $W_{h/2}$ 16 Hz, 1H); 2.22 (d, *J* 2 Hz, 3H), 3.56 (m, $W_{h/2}$ 18 Hz, 1H), 4.94 (m, $W_{h/2}$ 11 Hz, 1H); 7.3-7.45 (m, 3H); 7.45-7.55 (m, 2H); ^{13}C NMR : 17.5 (CH_3), 23.6 (CH_2), 32.8 (CH_2), 34.2 (CH_2), 45.0 (CH), 82.3 (CH), 123.3 (C), 129.4 (2 x CH), 129.5 (C); 129.6 (CH); 135.6 (2 x CH), 152.5 (C), 169.3 (C); Anal. Found : C, 69.0; H, 6.4; S, 12.5; Calc. for $C_{15}H_{16}O_2S$: C, 69.2; H, 6.2; S, 12.3%.

(3E,3aα,6aα)-Hexahydro-3-[1-(phenylthio)propylidene]-2H-cyclopenta[b]furan-2-one (4c). Method A, (3c) (0.117 g, 0.41 mmol), Et_2O (1.5 ml), reflux, 40 h, PLC (40% Et_2O/hexanes) gave (4c) as a white crystalline solid (0.060 g, 55%). Distilled 140°C (block)/0.07 mm; MP 86°C; IR (film) : 1720, 1230 (lactone), 1600 (C=C), 1580, 750, 695 (phenyl); ^1H NMR : 0.95 (t, *J* 7, 3H), 1.5-1.8 (m, 3H); 1.8-2.0 (m, 2H); 2.12 (m, $W_{h/2}$ 16 Hz, 1H); 2.61 (dq, *J* 7, 14 Hz, 1H); 2.85 (dq, *J* 7, 14 Hz, 1H); 3.55 (m, $W_{h/2}$ 19 Hz, 1H), 4.94 (m, $W_{h/2}$ 12 Hz, 1H); 7.4-7.45 (m, 3H); 7.45-7.55 (m, 2H); ^{13}C NMR : 14.4 (CH_3), 23.0 (CH_2), 23.5 (CH_2), 33.1 (CH_2), 34.2 (CH_2), 45.0 (CH), 82.2 (CH), 123.5 (C), 129.4 (3 x CH), 129.8 (C), 135.2 (C), 158.8 (C), 168.7 (C); Anal. Found : C, 69.8; H, 6.6; S, 11.5; Calc. for $C_{16}H_{18}O_2S$: C, 70.0; H, 6.6; S, 11.7%.

(3E,3aα,6aα)-Hexahydro-3-[1-(phenylthio)-2-methylpropylidene]-2H-cyclopenta[b]furan-2-one (4d). Method A, (3d) (0.081 g, 0.26 mmol), EtOH (1 ml), reflux, 3 h, PLC (40% Et_2O/hexanes) gave (4d) as a white crystalline solid (0.048 g, 63%). Sublimed 90°C (block)/0.030 mm; IR (film) : 1740, 1220 (lactone), 1585 (C=C), 1580, 745, 690 (phenyl); ^1H NMR : 1.14 (d, *J* 7, 3H), 1.20 (d, *J* 7 Hz, 3H), 1.5-1.9 (m, 5H); 1.98 (m, $W_{h/2}$ 15 Hz, 1H); 2.92 (m, $W_{h/2}$ 15 Hz, 1H), 4.45 (sept, *J* 7 Hz, 1H), 4.69 (m, $W_{h/2}$ 12 Hz, 1H); 7.2-7.4 (m, 5H); ^{13}C NMR : 20.8 (CH_3), 21.7 (CH_3), 23.5 (CH_2), 30.9 (CH), 32.8 (CH_2), 34.1 (CH_2), 45.0 (CH), 82.0 (CH), 127.5 (CH), 129.4 (2 x CH), 131.0 (2 x CH), 131.1 (C), 133.9 (C), 160.8 (C), 169.0 (C); Anal. Found : C, 70.5; H, 7.0; S, 10.9; Calc. for $C_{17}H_{20}O_2S$: C, 70.8; H, 7.0; S, 11.1%.

(3E,3aα,6aα)-Hexahydro-3-[1-(phenylthio)-2,2-dimethylpropylidene]-2H-cyclopenta[b]furan-2-one (4e). Method A, (3e) (0.070 g, 0.22 mmol), EtOH (1 ml), reflux, 22 h, PLC (40% Et_2O/hexane) gave : (i) at higher R_f, (4e) as a white crystalline solid (0.038 g, 57%). Distilled 145°C (block)/0.070 mm; MP 125°C; IR (film) : 1750, 1190 (lactone), 1580 (C=C), 1570, 740, 690 (phenyl); ^1H NMR : 1.40 (s, 9H), 1.5-1.9 (m, 5H); 2.03 (m, $W_{h/2}$ 18 Hz, 1H); 3.45 (m, $W_{h/2}$ 19 Hz, 1H) 4.77 (m, $W_{h/2}$ 11 Hz, 1H); 7.2-7.4 (m, 5H); ^{13}C NMR : 23.6 (CH_2), 30.2 (3 x CH_3), 33.9 (CH_2), 34.0 (CH_2), 40.8 (C), 49.7 (CH), 81.8 (CH), 126.7 (CH), 128.2 (2 x CH), 129.4 (2 x CH), 136.6 (C), 138.5 (C), 160.3 (C), 167.5 (C); Anal. Found : C, 71.4; H, 7.7; S, 10.9; Calc. for $C_{18}H_{22}O_2S$: C, 71.5; H, 7.3; S, 10.6%; (ii) at lower R_f, (6e) (0.004g, 6%).

(3Z,3aα,6aα)-Hexahydro-3-(phenylthiomethylene)-2H-cyclopenta[b]furan-2-one (6a). Method A, (5a) (0.101 g, 0.38 mmol), Et_2O (1 ml), 20°C, 0.5 h, PLC (50% Et_2O/hexanes) gave (6a) as a white crystalline solid (0.053 g, 56%). Distilled 126°C (block)/0.031 mm; IR (film) : MP 119°C; 1730, 1180 (lactone), 1600 (C=C), 1580, 755, 695 (phenyl); ^1H NMR : 1.5-1.8 (m, 4H); 1.87 (m, $W_{h/2}$ 25 Hz, 1H); 2.09 (m, $W_{h/2}$ 15 Hz, 1H); 3.46 (m, $W_{h/2}$ 17 Hz, 1H); 5.03 (m, $W_{h/2}$ 11 Hz, 1H); 7.09 (d, *J* 2 Hz, 1H); 7.3-7.45 (m, 3H); 7.45-7.55 (m, 2H); ^{13}C NMR : 23.2 (CH_2), 34.0 (CH_2), 35.9 (CH_2), 44.6 (CH), 84.0 (CH), 125.0 (C), 128.3 (CH), 129.5 (2 x CH), 131.1 (2 x CH), 135.9 (C), 142.0 (CH), 170.8 (C); Anal. Found : C, 68.4; H, 5.8; S, 13.1; Calc. for $C_{14}H_{14}O_2S$: C, 68.3; H, 5.7; S, 13.0%.

(3α,3aβ,6aβ)-Hexahydro-3-[di(phenylthio)methyl]-2H-cyclopenta[b]furan-2-one (7). Method A, (5a) (0.185 g, 0.70 mmol), Et_2O (5 ml), 20°C, 50 h, PLC (50% Et_2O/hexanes) gave : (i) at higher R_f, (7) as a white crystalline solid (0.050 g, 22%); MP 74°C; IR (nujol): 1765, 1180 (lactone), 1580, 745, 690 (phenyl); ^1H NMR : 1.4-2.1 (m, 6H); 2.81 (t, *J* 4 Hz, 1H), 3.11 (m, $W_{h/2}$ 21 Hz, 1H), 4.86 (d, *J* 4 Hz, 1H); 5.11 (dd, *J* 6,

6 Hz, 1H); 7.2-7.3 (m, 6H); 7.39 (m, $W_{h/2}$ 10 Hz, 2H); 7.48 (m, $W_{h/2}$ 10 Hz, 2H); ^{13}C NMR: 23.5 (CH_2), 33.8 (CH_2), 34.5 (CH_2), 41.0 (CH), 53.7 (CH), 61.1 (CH), 85.8 (CH), 128.5 (2 x CH); 129.2 (2 x CH); 129.4 (2 x CH); 133.0 (C); 133.2 (4 x CH); 133.5 (C); 181.3 (C); Anal. Found : C, 67.7; H, 5.8; S, 18.1; Calc. for $C_{20}H_{20}O_2S$: C, 67.4; H, 5.7; S, 18.0%; (ii) at lower R_f, (4a) (0.104 g, 60%).

(3Z,3aα,6aα)-Hexahydro-3-[1-(phenylthio)ethylidene]-2H-cyclopenta[b]furan-2-one (6b). Method A, (5b) (0.028 g, 0.10 mmol), Et_2O (0.5 ml), reflux, 12h, PLC (50% Et_2O / hexane) gave (6b) as a colourless oil (0.014 g, 53%), distilled 120°C(block)/0.03 mm; IR (film) : 1730 (lactone), 1590 (C=C); 755, 695 (phenyl); ^{1}H NMR: 1.6-2.0 (m, 5H); 1.84 (s, 3H), 2.10 (m, $W_{h/2}$ 14 Hz, 1H); 3.45 (m, $W_{h/2}$ 15 Hz, 1H), 4.96 (m, $W_{h/2}$ 12 Hz, 1H); 7.3-7.45 (m, 3H); 7.45-7.6 (m, 2H); ^{13}C NMR: 21.7 (CH_3), 23.4 (CH_2), 33.8 (CH_2), 34.2 (CH_2), 44.8 (CH), 82.9 (CH), 121.9 (C), 129.2 (2 x CH), 129.5 (CH), 130.8 (C), 136.2 (2 x CH), 151.2 (C), 171.2 (C); Anal. Found: C,69.1; H,6.2; S,12.4; Calc. for $C_{15}H_{16}O_2S$: C,69.2; H,6.2; S,12.3%.

(3Z,3aα,6aα)-Hexahydro-3-[1-(phenylthio)propylidene]-2H-cyclopenta[b]furan-2-one (6c). Method A, (5c) (0.029 g, 0.10 mmol), Et_2O (0.5 ml), reflux, 40 h, PLC (40% Et_2O/hexanes) gave : (i) at higher R_f, (4c) as a white crystalline solid (0.002 g, 7%); (ii) At lower R_f, (6c) as a yellow oil (0.010 g, 37%). IR (film) : 1730, 1230, 1150 (lactone), 1595 (C=C), 755, 665 (phenyl); ^{1}H NMR : 0.91 (t, *J* 7, 3H), 1.5-1.8 (m, 4H); 1.95 (m, $W_{h/2}$ 28 Hz, 1H); 2.10 (m, $W_{h/2}$ 13 Hz, 1H); 2.2-2.4 (m, 2H) 3.45 (m, $W_{h/2}$ 19 Hz, 1H), 4.95 (m, $W_{h/2}$ 11 Hz, 1H); 7.3-7.4 (m, 3H); 7.5-7.6 (m, 2H); ^{13}C NMR: 13.5 (CH_3), 23.7 (CH_2), 26.9 (CH_2), 34.0 (CH_2), 34.6 (CH_2), 44.5 (CH), 82.9 (CH), 122.1 (C), 129.1 (2 x CH), 129.3 (CH), 130.7 (C), 136.0 (2 x CH), 156.7 (C), 170.3 (C); MS : *m/z* 274.1039; Calc. for $C_{16}H_{18}O_2S$: 274.1028.

(3Z,3aα,6aα)-Hexahydro-3-[1-(phenylthio)-2-methylpropylidene]-2H-cyclopenta[b]furan-2-one (6d). Method A, (5d) (0.028 g, 0.092 mmol), EtOH (0.5 ml), reflux, 4 h, PLC (40% Et_2O/hexanes) gave : (i) at high R_f, (4d) (0.007 g, 26%); (ii) at lower R_f, (6d) (0.008g, 30%) as a yellow oil. IR (film) : 1740, 1220 (lactone), 1580 (C=C); ^{1}H NMR : 1.18 (d, *J* 7 Hz, 6H), 1.5-1.8 (m, 4H); 1.9-2.2 (m, 2H); 2.99 (sept, *J* 7 Hz, 3H), 3.59 (m, $W_{h/2}$ 20 Hz, 1H), 4.85 (m, $W_{h/2}$ 11 Hz, 1H); 7.15-7.5 (m, 5H); ^{13}C NMR : 20.6 (CH_3), 21.1 (CH_3), 23.5 (CH_2), 33.8 (CH_2), 34.8 (CH_2), 35.9 (CH), 44.7 (CH) 81.7 (CH), 126.8 (CH), 128.9 (2 x CH), 129.2 (C), 130.3 (2 x CH), 135.9 (C), 155.8 (C), 168.0 (C); Anal. Found : C, 70.6; H, 6.9; S, 11.0; Calc. for $C_{17}H_{20}O_2S$: C, 70.8; H, 7.0; S, 11.1%.

(3Z,3aα,6aα)-Hexahydro-3-[1-(phenylthio)-2,2-dimethylpropylidene]-2H-cyclopenta[b]furan-2-one (6e). Method A, (5e) (0.028 g, 0.088 mmol), EtOH (0.5 ml), reflux, 22 h, PLC (40% Et_2O/hexanes) gave : (i) at higher R_f, (4e) (0.007 g, 26%); (ii) at lower R_f, (6e) as a white crystalline solid (0.014 g, 53%). Sublimed 160°C (block)/0.070 mm; MP 167°C; IR (film) : 1740, 1185, 1140 (lactone),. 1580 (C=C), 740, 690 (phenyl); ^{1}H NMR : 1.44 (s, 9H), 1.5-1.9 (m, 4H); 2.0-2.2 (m, 2H); 3.78 (m, $W_{h/2}$ 20 Hz, 1H), 4..63 (m, $W_{h/2}$ 9 Hz, 1H); 7.0-7.15 (m, $W_{h/2}$ 17 Hz, 1H); 7.11 (m, 4H) ^{13}C NMR : 23.4 (CH_2), 30.2 (3 x CH_3), 33.1 (CH_2), 35.0 (CH_2), 41.7 (C), 46.3 (CH), 81.3 (CH), 126.0 (CH), 128.5 (2 x CH), 128.9 (2 x CH), 132.8 (C), 139.4 (C), 158.9 (C), 168.8 (C); Anal. Found : C, 71.3; H, 7.3; S, 10.7; Calc. for $C_{18}H_{22}O_2S$: C, 71.5; H, 7.3; S, 10.6%.

(3E,3aα,7aα)-Hexahydro-3-[(phenylthio)methylene]-2(3H)-benzofuranone (10a). Method A, (8a) (0.082 g, 0.29 mmol), Et_2O (3 ml), 20°C, 2 h, radial chromatography (35% Et_2O/hexanes) gave (10a) (0.056 g, 73%). Distilled 80°C (block)/0.04 mm; IR (film) : 1745, 1200, 1180 (lactone), 1620 (C=C), 1585, 750, 690 (phenyl); UV (MeOH) : 285 (ε 9450); ^{1}H NMR : 1.2-1.8 (m, 6H); 2.0-2.2 (m, 2H); 2.08 (m, $W_{h/2}$ 38 Hz, 2H); 3.05 (m, $W_{h/2}$ 22 Hz, 1H); 4.51 (m, $W_{h/2}$ 14 Hz, 1H); 7.3-7.4 (m, 3H); 7.4-7.5 (m, 2H); 7.55 (d, *J* 2 Hz, 1H); ^{13}C NMR : 19.3 (CH_2), 22.0 (CH_2), 25.1 (CH_2), 27.3 (CH_2), 38.9 (CH), 76.6 (CH), 128.4 (CH), 129.5 (2 x CH + s), 130.7 (2 x CH), 133.0 (C), 137.4 (CH), 169.8 (C); MS : m/z 260 (M^+), 151, 147, 110, 109; Anal. Found : C, 69.2; H, 6.1; Calc. for $C_{15}H_{16}O_2S$: C, 69.2; H, 6.2%.

(3Z,3aα,7aα)-Hexahydro-3-[(phenylthio)methylene]-2(3H)-benzofuranone (11a). Method A, (9a) (0.055 g, 0.20 mmol), Et_2O (3 ml), 20°C, 50 h, multiple run PLC (20% Et_2O/hexanes) gave : (i) at higher R_f, (*E*)-thiomethylene lactone (10a) (0.020 g, 39 %); (ii) at lower R_f, (*Z*)-thiomethylene lactone (11a) (0.006 g, 12 %). Distilled 85°C (block)/0.04 mm; IR (film) : 1740, 1175 (lactone), 1612 (C=C), 1590, 740, 695 (phenyl); UV (MeOH) : 254, sh (ε 2770), 294 (ε 5580); ^1H NMR : 1.2-1.9 (m, 8H); 3.04 (ddd, *J* 14, 6, 2 Hz, 1H); 4.57 (ddd, *J* 6 , 6, <1 Hz, 1H); 6.94 (d, *J* 2 Hz, 1H); 7.3-7.4 (m, 3H); 7.4-7.5 (m, 2H); ^{13}C NMR : 20.3 (CH_2), 21.4 (CH_2), 27.3 (CH_2), 28.6 (CH_2), 40.9 (CH), 77.8 (CH), 125.4 (C), 128.3 (CH), 129.5 (2 x CH), 131.1 (2 x CH), 135.7 (C), 138.8 (CH), 170.4 (C); MS : *m/z* 274 (M^+), 197, 181, 165, 147; Anal. Found : C, 69.4; H, 6.0; Calc. for $C_{15}H_{16}O_2S$: C, 69.2; H, 6.2%.

(3E,3aα,7aα)- and (3Z,3aα,7aα)-Hexahydro-3-[1-(phenylthio)ethylidene]-2(3H)-benzofuranone (10b) and (11b). (a) Method B, (8b) (0.095 g, 0.33 mmol), EtOH (2 ml), 0°C, 6.5 h, PLC (25% Et_2O/hexanes) gave : (i) at higher R_f, (*E*)-thiomethylene lactone (10b) (0.045 g, 50 %). Distilled 110°C (block)/0,04 mm; IR (film) : 1740, 1240, 1220 (lactone), 1620 (C=C), 1585, 755, 695 (phenyl); UV (MeOH) : 290 (ε 10170); ^1H NMR : 1.1-1.8 (m, 6H); 2.1-2.3 (m, 2H); 2.19 (d, *J* 0.5 Hz, 3H); 3.17 (m, $W_{h/2}$ 22 Hz, 1H); 4.45 (m, $W_{h/2}$ 11 Hz, 1H); 7.3-7.4 (m, 3H); 7.4-7.5 (m, 2H); ^{13}C NMR : 18.0 (CH_3), 19.5 (CH_2), 22.9 (CH_2), 25.8 (CH_2), 27.2 (CH_2), 41.2 (CH), 75.5 (CH), 127.9 (C), 129.3 (3 x CH), 129.8 (C), 135.0 (2 x CH), 149.3 (C), 169.3 (C); MS : *m/z* 274 (M^+), 236, 167, 165, 139, 138; Anal. Found : C, 70.1; H, 6.7; Calc. for $C_{16}H_{18}O_2S$: C, 70.0; H, 6.6%. (ii) at lower R_f, (*Z*)-thiomethylene lactone (11b) (0.021 g, 23%). Distilled at 115°C (block)/(0.05 mm); IR (film) : 1735, 1160, 1130 (lactone), 1610 (C=C), 1590, 755, 675 (phenyl); ^1H NMR : 1.82 (s, 3H); 2.91 (m, $W_{h/2}$ 22 Hz, 1H); 4.46 (m, $W_{h/2}$ 11 Hz, 1H); 7.3-7.45 (m, 3H); 7.5-7.6 (m, 2H); ^{13}C NMR : 19.5 (CH_2), 21.0 (CH_3), 23.0 (CH_2), 27.3 (2 x CH_2), 41.0 (CH), 76.2 (CH), 125.1 (C), 129.2 (2 x CH), 129.4 (CH), 130.8 (C), 136.1 (2 x CH), 148.4 (C), 169.9 (C); MS : *m/z* 274 (M^+), 197, 165, 147, 119, 109; Anal. Found : C, 70.0; H, 6.8; Calc. for $C_{16}H_{18}O_2S$: C, 70.0; H, 6.6%.

(b) Method A, (8b) (0.074 g, 0.25 mmol), Et_2O (3 ml), 20°C, 40 h, ^1H NMR showed the presence of starting material and (*E*)-isomer (10b) in the ratio of 1 : 3 with no detectable amounts of the (*Z*)-isomer (11b).

(c) Method A, (9b) (0.035 g, 0.12 mmol), Et_2O (2 ml), 20°C, 48 h, ^1H NMR showed the presence of starting material and the (*E*)- and (*Z*)-phenylthiomethylene lactones (10b) and (11b) in the ratio of 22 : 1 : 11.

(3E,3aα,7aα)- and (3Z,3aα,7aα)-Hexahydro-3-[(phenylthio)(trimethylsilyl)methylene]-2(3H)-benzofuranone (10f) and (11f). (a) Method B, (8f) (0.108 g, 0.31 mmol), EtOH (5 ml), 20°C, 21 h, PLC (25% Et_2O/hexanes) gave : (i) at higher R_f, the (*E*)-thiomethylene lactone (10f) (0.092 g, 89%). Distilled 115°C (block)/0.04 mm; MP 102-3°C. IR (film) : 1755, 1200 (lactone), 1580, 740, 690 (phenyl); ^1H NMR : 0.14 (s, 9H); 1.2-1.7 (m, 6H); 1.98 (br. m, $W_{h/2}$ 22 Hz, 1H); 2.12 (br.d, *J* 12 Hz, 1H); 3.29 (m, $W_{h/2}$ 8 Hz, 1H); 4.50 (m, $W_{h/2}$ 10 Hz); 7.1-7.3 (m, 5H, aromatic); ^{13}C NMR : 0.5 (3 x CH_3), 19.3 (CH_2), 22.9 (CH_2), 26.6 (CH_2), 27.2 (CH_2), 42.7(CH), 76.1 (CH), 126.5 (CH), 128.8 (2 x CH), 129.0 (2 x CH), 137.0 (C), 149.7 (C), 151.4 (C), 168.7 (C); Anal. Found : C, 65.2; H, 7.1; Calc. for $C_{18}H_{24}O_2SSi$: C, 65.0; H, 7.28%; (ii) at lower R_f, the (*Z*)-thiomethylene lactone (11f) (0.010 g, 10%). Distilled 115°C (block)/0.04 mm; MP 96-7°C; ^1H NMR : 1.24 (s, 9H), 3.31 (m, $W_{h/2}$ 22, 1H), 4.53 (m, $W_{h/2}$ 12, 1H), 7.23 (s, 5H, aromatic); ^{13}C NMR : 1.3 (3 x CH_3), 19.2 (CH_2), 23.3 (CH_2), 27.3 (CH_2), 27.7 (CH_2), 43.7 (CH), 75.5 (CH), 126.4 (CH), 128.8 (CH), 129.7 (CH), 137.4 (C), 145.5 (C), 148.0 (C), 167.8 (C); Anal. Found : C, 65.2; H, 7.0; Calc. for $C_{18}H_{24}O_2SSi$: C, 65.0; H, 7.3%.

(b) Method A, (8f) (0.064 g, 0.20 mmol), Et_2O (3 ml) 20°C, 140 h, ^1H NMR showed the presence of the (*E*)- and (*Z*)-thiomethylene lactones (10f) and (11f) in addition to starting material in the ratio 1 : 1 : 4 respectively.

(c) Method A, (9f) (0.040 g, 0.13 mmol), Et_2O (1.8 ml) 20°C, 48 h, ^1H NMR showed the presence of the (*E*)- and (*Z*)-thioalkylidene lactones (10f) and (11f) in the ratio 1 : 6.

Phenylthioalkylidene Lactone Formation - GLC Studies

Thiophenol (0.4 mmol) was added to a solution of the iodoalkylidene lactone (0.2 mmol), tetradecane (0.1 mmol) and Et_3N (0.3 mmol) in the chosen solvent (1 ml). Reactions were conducted at either 20°C or at the boiling point of the solvent. Aliquots (100 µl) were removed at intervals, diluted with Et_2O (1 ml) and analysed by GLC on a 10 m DB-1 column (J&W Scientific). The oven temperature was programmed from 60°C to 160°C at a linear rate of 5° min^{-1}. Results are summarised in Table 1.

Thioacetal Preparations

The thiol, followed by Et_3N was added to a solution of the iodoalkylidene lactone in dry solvent under an atmosphere of N_2. After reaction, H_2O (30 ml) was added and the mixture was extracted with Et_2O (2 x 30 ml). The combined ethereal extracts were washed with NaOH (50 ml, 2M), HCl (50 ml, 0.5 M) and H_2O (50 ml), dried ($MgSO_4$) and evaporated.

Preparations are reported according to the convention : iodoalkylidene lactone (mass, amount), solvent (volume), thiol (mass, amount), Et_3N (mass, amount), reaction conditions, experimental data.

(3α,3aβ,6aβ)- and (3β,3aβ,6aβ)-Hexahydro-3-(1,3-dithiolan-2-yl)-2H-cyclopenta[b]furan-2-one (12a) and (13a). (3a) (0.300 g, 1.14 mmol), Et_2O (10 ml), ethanedithiol (0.214 g, 2.28 mmol), Et_3N (0.277 g, 2.74 mmol), stirred at 20°C for 96 h. Multiple run PLC (50% Et_2O/hexanes) gave : (i) at high R_f, (12a) as a yellow oil (0.091 g, 35%). Distilled 110°C (block)/0.032 mm; IR (film) 1755, 1180 (lactone); ^1H NMR : 1.5-2.1 (m, 6H); 2.77 (dd, *J* 4, 4 Hz, 1H), 2.95 (m, $W_{h/2}$ 25 Hz, 1H), 3.2-3.4 (m, 4H), 5.01 (m, $W_{h/2}$ 20 Hz, 1H); 5.04 (d, *J* 4 Hz, 1H); ^{13}C NMR : 23.5 (CH_2), 33.7 (CH_2), 34.1 (CH_2), 39.5 (CH_2), 39.8 (CH_2), 42.1 (CH), 53.9 (2 x CH), 85.3 (CH), 176.8 (C); Anal. Found : C, 52.3; H, 6.3; S, 27.2; Calc. for $C_{10}H_{14}O_2S_2$: C, 52.1; H, 6.1; S, 27.8%; (ii) at lower R_f, (13a) as a white solid (0.135 g, 52%). Distilled 110°C (block)/0.032 mm; MP 102°C; IR (film): 1760, 1160 (lactone); ^1H NMR : 1.5-2.1 (m, 6H); 2.93 (dddd, *J* 5, 8, 8, 9 Hz, 1H), 3.16 (dd, J 9, 11 Hz, 1H), 3.1-3.3 (m, 4H), 4.57 (d, *J* 11 Hz, 1H), 4.85 (ddd, *J* 2, 5, 5 Hz, 1H); ^{13}C NMR : 24.6 (CH_2), 26.1 (CH_2), 32.3 (CH_2), 38.2 (CH_2), 39.2 (CH_2), 45.7 (CH), 50.4 (CH), 53.2 (CH), 84.4 (CH), 175.5 (C); Anal. Found : C, 52.2; H, 6.1; S, 27.5; Calc. for $C_{10}H_{14}O_2S_2$: C, 52.1; H, 6.1; S, 27.8%.

(3α,3aβ,6aβ)- and (3β,3aβ,6aβ)-Hexahydro-3-(1,3-dithian-2-yl)-2H-cyclopenta[b]furan-2-one (14a) and (15a). (3a) (0.100 g, 0.38 mmol), EtOH (2 ml), 1,3-propanedithiol (0.082 g, 0.76 mmol), Et_3N (0.092 g, 0.91 mmol), reflux 1h. PLC (70% Et_2O/hexanes) gave : (i) at higher R_f, (14a) as a solid (0.058 g, 63%). IR (nujol): 1770, 1180 (lactone); ^1H NMR : 1.5-2.2 (m, 8H); 2.71 (dd, *J* 4, 4 Hz, 1H), 2.8-3.2 (m, 5H), 4.61 (d, *J* 4 Hz, 1H), 4.99 (m, $W_{h/2}$ 14 Hz, 1H); ^{13}C NMR : 23.4 (CH_2), 25.1 (CH_2), 30.4 (CH_2), 31.0 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 41.0 (CH), 49.5 (CH), 53.5 (CH), 85.9 (CH), 176.4 (C); Anal. Found : C, 54.5; H, 6.5; S, 26.1; Calc. for $C_{11}H_{16}O_2S_2$: C, 54.1; H, 6.6; S, 26.1%; (ii) at lower R_f, (15a) as a yellow oil (0.008 g, 9%). IR (film): 1770, 1155 (lactone); ^1H NMR : 1.5-2.2 (m, 8H); 2.8-3.1 (m, 5H), 3.19 (dd, *J* 9, 8 Hz, 1H), 4.38 (d, *J* 9 Hz, 1H), 4.82 (m, $W_{h/2}$ 12 Hz, 1H); ^{13}C NMR : 24.4 (CH_2), 25.5 (CH_2), 26.5 (CH_2), 30.3 (CH_2), 30.7 (CH_2), 32.2 (CH_2), 44.0 (CH), 45.1 (CH), 49.0 (CH) 84.7 (CH), 174.1 (C); MS : *m/z* 244.0599; Calc. for $C_{11}H_{16}O_2S_2$: 244.0592.

(3α,3aβ,6aβ)- and (3β,3aβ,6aβ)-Hexahydro-3-(2-methyl-1,3-dithiolan-2-yl)-2H-cyclopenta[b]furan-2-one (12b) and (13b). (3b) (0.140 g, 0.50 mmol), EtOH (2 ml), ethanedithiol (0.096 g, 1.0 mmol), Et_3N (0.123g, 1.22 mmol), reflux, 3 h. Multiple run PLC (50% Et_2O/hexanes) gave : (i) at higher R_f, (12b) as an oil (0.025 g, 20%). Distilled 95°C (block)/0.035 mm; IR (film): 1760, 1180 (lactone); ^1H NMR : 1.5-2.1 (m, 6H); 1.93 (s, 3H); 2.82 (d, *J* 4 Hz, 1H); 2.95 (m, $W_{h/2}$ 25 Hz, 1H); 3.3-3.5 (m, 4H); 4.95 (m, $W_{h/2}$ 15 Hz, 1H); ^{13}C NMR : 23.4 (CH_2), 31.7 (CH_3), 33.8 (CH_2), 34.5 (CH_2), 40.2 (CH_2), 40.6 (CH_2), 44.7 (CH), 60.0 (CH), 67.5 (C), 84.0 (CH), 175.9 (C); Anal. Found : C, 54.2; H,6.9; Calc. for $C_{11}H_{16}O_2S_2$: C, 54.1; H, 6.6%; (ii) at lower

R_f, (13b) as an oil (0.051 g, 41%). Distilled 95°C (block)/0.035 mm; IR (film): 1760, 1160 (lactone); ^{1}H NMR : 1.5-2.1 (m, 6H); 1.93 (s, 3H); 2.94 (m, $W_{h/2}$ 28 Hz, 1H); 3.3-3.5 (m, 4H); 3.54 (d, *J* 8 Hz, 1H); 4.77 (m, $W_{h/2}$ 12 Hz, 1H); ^{13}C NMR : 25.4 (CH_2), 26.7 (CH_2), 31.6 (CH_2), 33.1 (CH_3), 39.6 (CH_2), 40.7 (CH_2), 46.5 (CH), 57.0 (CH), 64.0 (C), 83.9 (CH), 174.2 (C); Anal. Found : C, 54.1; H, 6.8; Calc. for $C_{11}H_{16}O_2S_2$: C, 54.1; H, 6.6%.

(3E,3aα,6aα)-Hexahydro-3-{[2-(methylthio)ethylthio]methylene}-2H-cyclopenta[b]furan-2-one. (16).

Butyl lithium (0.522 mmol, 1.4 M in hexanes) was added to isopropylcyclohexylamine (0.074 g, 0.52 mmol) under nitrogen. The mixture was stirred at 0°C for 1 h then cooled to -78°C. (13a) (0.120 g, 0.52 mmol) in THF (2 ml) was added and the reaction mixture was stirred at -78°C for 2 h. After the addition of CH_3I (0.099 g, 0.70 mmol) the reaction mixture was allowed to come to room temperature. The mixture was poured into H_2O (20 ml) and extracted with CH_2Cl_2 (2 x 30 ml). The organic extracts were washed with H_2O (50 ml), dried ($MgSO_4$) and evaporated. Multiple PLC (50% Et_2O/hexanes) gave : (i) at high R_f, unchanged (13a) (0.020 g, 17%); (ii) at lower R_f, (16) as an oil (0.063 g, 49%). Distilled 105°C (block)/0.035 mm; IR (film): 1740, 1190 (lactone), 1610 (C=C); ^{1}H NMR : 1.4-2.0 (m, 5H); 2.09 (m, $W_{h/2}$ 25 Hz, 1H); 2.17 (s, 3H), 2.80 (dd, *J* 6, 10 Hz, 2H), 3.08 (dd, *J* 6, 10, 2H), 3.36 (m, $W_{h/2}$ 16 Hz, 1H), 4.99 (m, $W_{h/2}$ 12 Hz, 1H), 7.44 (d, *J* 2 Hz, 1H); ^{13}C NMR : 15.6 (CH_3), 23.4 (CH_2), 30.9 (CH_2), 34.0 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 42.8 (CH), 83.5 (CH), 126.6 (C), 139.5 (CH), 169.7 (C); Anal. Found : C, 54.0; H, 6.8; S, 26.4; Calc. for $C_{11}H_{16}O_2S_2$: C, 54.1; H, 6.6; S, 26.2%.

(3E,3aα,6aα)-Hexahydro-3-(pyrrolidynomethylene)-2H-cyclopenta[b]furan-2-one (17).

Pyrrolidine (0.026 g, 0.40 mmol) was added to a solution of the (*E*)-iodomethylene lactone (3a) (0.050 g, 0.19 mmol) in EtOH (2 ml) and the reaction mixture was heated under reflux for 0.5 h. Removal of EtOH and excess pyrrolidine under reduced pressure followed by PLC (Et_2O) gave (17) as an oil (0.030 g, 76%). Distilled 147°C (block)/0.028 mm; IR (film) : 1720, 1215, 1140 (lactone), 1620 (C=C); ^{1}H NMR : 1.0-1.6 (m, 5H), 1.93 (m, $W_{h/2}$ 14 Hz, 4H); 2.05 (m, $W_{h/2}$ 10 Hz, 1H); 3.51 (m, $W_{h/2}$ 12 Hz, 4H); 3.63 (m, $W_{h/2}$ 16 Hz, 1H); 4.85 (m, $W_{h/2}$ 11 Hz, 1H); 7.33 (s, 1H); ^{13}C NMR : 22.9 (CH_2), 25.4 (CH_2), 34.1 (CH_2), 37.0 (CH_2), 41.6 (CH), 50.3 (2 x CH_2, broad), 82.2 (CH), 94.5 (C), 143.1 (CH), 175.8 (C); Anal. Found : C, 69.3; H, 8.4; N, 6.5; Calc. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8%.

Repetition of this reaction with the (*Z*)-iodomethylene lactone (5a) gave a crude mixture which consisted primarily of (17) (^{1}H NMR).

Azidomethylene Lactone Preparations

A solution of NaN_3 in H_2O (1 ml) was added to a solution of the iodomethylene lactone in absolute EtOH (2 ml). The mixture was heated under reflux. H_2O (5 ml) was added and the aqueous solution was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with H_2O (20 ml), dried ($MgSO_4$), evaporated and purified by PLC (50% Et_2O/hexanes).

Preparations are reported according to the convention : iodomethylene lactone (mass, amount), NaN_3 (mass, amount), reaction time, experimental data.

(3E,3aα,6aα)-Hexahydro-3-(azidomethylene)-2H-cyclopenta[b]furan-2-one (18). (3a) (0.054 g, 0.20 mmol), NaN_3 (0.082 g, 1.3 mmol), 0.25 h, white crystalline solid (0.033 g, 90%). IR (nujol) : 2125 (N_3), 1730 1210 (lactone), 1650 (C=C); ^{1}H NMR : 1.4-1.8 (m, 5H); 2.07 (m, $W_{h/2}$ 17 Hz, 1H); 3.44 (m, $W_{h/2}$ 20 Hz, 1H), 4.98 (m, $W_{h/2}$ 12 Hz, 1H), 7.35 (d, *J* 2 Hz, 1H); ^{13}C NMR : 23.3 (CH_2), 32.9 (CH_2), 34.0 (CH_2), 41.2 (CH), 84.0 (CH), 120.1 (C), 135.9 (CH), 171.2 (C); MS : *m/z* 179.0704; Calc. for $C_8H_9N_3O_2$: 179.0695.

(E)-Dihydro-3-(azidomethylene)-4,4,5,5-tetramethyl-2(3H)-furanone (21). (19) (0.119 g, 0.42 mmol), NaN_3 (0.151 g, 2.3 mmol), 0.5 h, pale yellow oil (0.064 g, 77%). IR (film) : 2120 (N_3), 1750, 1220 (lactone), 1650 (C=C); UV (MeOH) : 267 (ε 4080); ^{1}H NMR : 1.21 (s, 6H), 1.28 (s, 6H), 7.38 (s, 1H); ^{13}C NMR : 22.3 (2 x CH_3), 23.6 (2 x CH_3), 45.3 (C), 87.3 (C), 128.2 (C), 135.5 (CH), 156.7 (C); MS : *m/z* 195.1009; Calc. for $C_9H_{13}N_3O_2$: 195.1008.

(Z)-Dihydro-3-(azidomethylene)-4,4,5,5-tetramethyl-2(3H)-furanone (22). (20) (0.093 g, 0.33 mmol), NaN_3 (0.116 g, 1.8 mmol), 0.75 h, pale yellow oil (0.048 g, 74%). IR (film) : 2120 (N_3), 1750, 1265, 1210 (lactone), 1650 (C=C); UV (MeOH) : 272 (ε 7918); ^{1}H NMR : 1.15 (s, 6H), 1.29 (s, 6H), 6.54 (s, 1H); ^{13}C NMR : 23.3 (2 x CH_3), 23.8 (2 x CH_3), 45.2 (C), 86.7 (C), 125.6 (C), 132.8 (CH), 167.0 (C); MS : *m/z* 195.1015; Calc. for $C_9H_{13}N_3O_2$: 195.1008.

Trifluoromethylalkylidene Lactone Preparations.

An approximately 1 M solution of "$ZnCF_3$" was prepared by adding CF_2Br_2 (2.0 ml, 21.9 mmol) in portions to activated zinc dust (2.86 g, 43.8 mmol) in DMF (10 ml), allowing a small degree of reflux to occur, followed by stirring for 2 h at room temperature. Filtration *via* a Schlenk funnel under N_2 gave a thick brown solution of the organozinc reagent.

To a solution of 1 M "$ZnCF_3$" at 0°C was added CuBr (2 equiv) and an equivalent volume of HMPA. After stirring for 5 min, a solution of the iodovinylidene lactone in DMF was added and then stirred for 1 h at room temperature and 1 h at 60°C. The resulting dark brown solution was diluted with Et_2O, washed with H_2O, dried ($MgSO_4$), evaporated *in vacuo* and filtered through silica (1 : 1, Et_2O/hexanes) to yield the crude product. Further purifications were carried out if required by using column chromatography on silica with 25% Et_2O/hexanes as eluent. Purification of trifluorinated lactones from unreacted starting material could be achieved by fractional evaporation of the fluorinated material under vacuum (30 °C/0.1 mm).

The trifluoromethylations are reported according to the convention : "$ZnCF_3$" reagent (volume), CuBr (mass), iodovinylidene lactone (mass, amount) in DMF (volume), experimental data.

(3E,3aα,6aα)-Hexahydro-3-[(trifluoromethyl)methylene]-2H-cyclopenta[b]furan-2-one (23a). (1.5 ml), (0.137 g), (3a) (0.127 g, 0.48 mmol), (0.5 ml). Fractional sublimation gave (23a) as a white, low melting point solid (0.94 g, 95%). IR (film) : 1766, 1220, 1130 (lactone); ^{1}H NMR : 1.5-1.8 (m, 4H); 2.0-2.2 (m, 2H); 3.69 (tm, J 3 Hz, 1H); 5.04 (br. d, *J* 6 Hz, 1H); 6.61 (qd, *J* 8, 3 Hz, 1H); ^{19}F NMR : -61.6 (dd, *J* 8, 3 Hz); ^{13}C NMR : 23.4 (CH_2), 33.5 (CH_2), 34.4 (CH_2), 42.0 (CH), 84.4 (CH), 122.6 (CF_3), 122.9 (CH), 142.1 (C), 169.5 (C); m/z 206 (M^+); Anal. Found : C, 52.6; H, 4.5; Calc. for $C_9H_9O_2F_3$: C, 52.4; H, 4.4%.

(3Z,3aα,6aα)-Hexahydro-3-[(trifluoromethyl)methylene]-2H-cyclopenta[b]furan-2-one (24a). (0.5 ml), (0.024 g), (5a) (0.023 g, 0.09 mmol), (0.5 ml). Fractional sublimation gave (24a) as a white, low melting point solid (0.016 g, 90%). IR (film) : 1770, 1120 (lactone); ^{1}H NMR : 1.5-1.8 (m, 4H), 2.0-2.2 (m, 2H), 3.47 (m, $W_{h/2}$ 16 Hz, 1H); 5.04 (m, $W_{h/2}$ 13 Hz, 1H); 6.13 (qd, *J* 9, 2 Hz, 1H); ^{19}F NMR : -57.8 (d, *J* 9 Hz); ^{13}C NMR : 23.3 (CH_2), 33.7 (CH_2), 35.6 (CH_2), 44.8 (CH), 83.4 (CH), 120.9 (CF_3), 125.6 (CH), 143.5 (C), 165.4 (C); MS : *m/z* 206 (M^+); Anal. Found : C, 52.4; H, 4.4; Calc. for $C_9H_9O_2F_3$: C, 52.4; H, 4.4%.

(3E,3aα,6aα)-Hexahydro-3-[1-(trifluoromethyl)ethylidene]-2H-cyclopenta[b]furan-2-one (23b). (1.0 ml), (0.125 g), (3b) (0.100 g, 0.36 mmol), (0.5 ml). Fractional sublimation gave (23b) as a white, low melting point solid (0.070 g, 89%). IR (film) : 1760, 1210, 1115 (lactone); ^{1}H NMR : 1.6-1.8 (m, 4H), 2.0-2.2 (m, 2H), 2.32 (d, *J* 2 Hz, 3H); 3.68 (m, $W_{h/2}$ 20 Hz, 1H); 4.89 (ddd, *J* 2, 2, 2 Hz, 1H); ^{19}F NMR -65.6 (d, *J* 3 Hz, 3F); ^{13}C NMR : 12.5 (CH_3), 23.3 (CH_2), 33.5 (CH_2), 34.7 (CH_2), 43.7 (CH), 83.1 (CH), 123.7 (CF_3), 134.6 (C), 136.2 (C), 169.8 (C); MS : *m/z* 220 (M^+); Anal. Found : C, 54.6; H, 5.1; Calc. for $C_{10}H_{11}O_2F_3$: C, 54.6; H, 5.0%.

(3Z,3aα,6aα)-Hexahydro-3-[1-(trifluoromethyl)ethylidene]-2H-cyclopenta[b]furan-2-one (24b). (1.0 ml), (0.095 g), (5b) (0.092 g, 0.33 mmol), (0.5 ml). Fractional sublimation gave (24b) as a white, low melting point solid (0.068 g, 94%). IR (film) : 1765, 1162 (lactone); ^{1}H NMR : 1.5-1.9 (m, 4H), 2.0-2.2 (m, 2H), 2.06 (d, *J* 2 Hz, 1H); 3.45 (m, $W_{h/2}$ 20 Hz, 1H); 4.95 (m, $W_{h/2}$ 13 Hz, 1H); ^{19}F NMR -60.8 (q, *J* 2 Hz, 3F); ^{13}C NMR : 17.2 (CH_3), 23.5 (CH_2), 33.0 (CH_2), 39.9 (CH_2), 44.6 (CH), 82.5 (CH), 121.9 (CF_3), 135.4 (C), 136.9 (C), 165.4 (C); MS : *m/z* 220 (M^+); Anal. Found : C, 54.3; H, 5.1; Calc. for $C_{10}H_{11}O_2F_3$: C, 54.6; H, 5.0%.

(3E,3aα,7aα)-Hexahydro-3-[(trifluoromethyl)methylene]-2(3H)-benzofuranone (25a). (a) (1.5 ml), (0.140 g), (8a) (0.100 g, 0.36 mmol), (0.5 ml). Gave (25a) as a white, low melting point solid (0.095 g, 95%). IR (film) : 1775, 1245, 1210, 1185, 1130 (lactone); ^{1}H NMR : 1.1-1.9 (m, 7H), 2.21 (br.d, *J* 14 Hz, 1H), 3.21 (br.m, $W_{h/2}$ 24 Hz, 1H); 4.45 (br. q, *J* 4 Hz, 1H); 8.06 (qd, *J* 8, 2 Hz, 1H); ^{19}F NMR : -65.6 (d, *J* 8 Hz); ^{13}C NMR : 10.8 (CH_2), 22.8 (CH_2), 26.9 (CH_2), 29.8 (CH_2), 38.6 (CH), 77.3 (CH), 120.9 (CH), 122.6 (CF_3), 144.1 (C), 169.5 (C); MS : *m/z* 220 (M^+); Anal. Found : C, 54.5; H, 5.0; Calc. for $C_{10}H_{11}O_2F_3$: C, 54.6; H, 5.0%.

(b) (1.0 ml), (0.047 g), (8f) (0.057 g, 0.16 mmol), (1.0 ml). Gave (25a) (0.034 g, 97%).

(3Z,3aα,7aα)-Hexahydro-3-[(trifluoromethyl)methylene]-2(3H)-benzofuranone (26a). (0.5 ml), (0.050 g), (9a) (0.026 g, 0.093 mmol), (0.5 ml). Gave (26a) as a white, low melting point solid (0.017 g, 84%). IR (film) : 1765, 1140 (lactone); ^{1}H NMR : 1.4-1.9 (m, 8H), 3.06 (m, $W_{h/2}$ 9 Hz, 1H); 4.58 (q, *J* 6 Hz, 1H); 5.97 (qd, *J* 8, 2 Hz, 1H); ^{19}F NMR : -57.8 (d, *J* 9 Hz); ^{13}C NMR : 20.2 (CH_2), 21.3 (CH_2), 26.0 (CH_2), 28.8 (CH_2), 41.7 (CH), 76.6 (CH), 122.2 (CF_3), 122.8 (CH), 142.8 (C), 165.3 (C); MS : *m/z* 220 (M^+); Anal. Found : C, 54.6; H, 4.9; Calc. for $C_{10}H_{11}O_2F_3$: C, 54.6; H, 5.0%.

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REFERENCES

1. Haaima, G.; Lynch, M-.J.; Routledge, A.; Weavers, R.T. *Tetrahedron* **1993**, *49*, 4229-4252.
2. Haaima, G.; Hanton, L.R.; Lynch, M-. J.; Mawson, S.D.; Routledge, A.; Weavers, R.T. *Tetrahedron* submitted for publication.
3. Piers, E.; Ruediger, E.H. *J. Chem. Soc., Chem. Commun.* **1979**, 166-167.
4. Haaima, G.; Lynch, M-.J.; Routledge, A.; Weavers, R.T. *Tetrahedron* **1991**, *47*, 5203-5214.
5. Kupchan, S.M.; Fessler, D.C.; Eakin, M.A.; Giacobbe, T.J. *Science* **1970**, *168*, 376-378.
6. Avramovitch, B.; Rappoport, Z. *J. Am. Chem. Soc.* **1988**, *110*, 911-922 and references therein.
7. PCMODEL-PI, Version 3.2, Serena Software, Box 3076, Bloomington, IN 47402-3076, U.S.A. J values are calculated according to the algorithm described by Haasnoot, C.A.G.; de Leeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783-2792.
8. Scotti, F.; Frazza, E.J. *J. Org. Chem.* **1964**, *29*, 1800-1808.
9. Ghersetti, S.; Lugli, G.; Melloni, G.; Modena, G.; Todesco, P.E.; Vivarelli, P. *J. Chem. Soc.* **1965**, 2227-2235.
10. Truce, W.E.; Brady, D.G.; *J. Org. Chem.* **1966**, *31*, 3543-3550.
11. Shvo, Y.; Shanan-Atidi, H. *J. Am. Chem. Soc.* **1969**, *91*, 6683-6689.
12. Shvo, Y.; Shanan-Atidi, H. *J. Am. Chem. Soc.* **1969**, *91*, 6689-6696.
13 Shvo, Y.; Belsky, I. *Tetrahedron* **1969**, *25*, 4649-4665.
14 Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526-2545.
15 Herbig, K.; Huisgen, R.; Huber, H. *Chem. Ber.* **1966**, *99*, 2546-2555.
16. Mazal, C.; Jurka, Z.; Jonas, J. *Coll. Czech. Chem. Commun.* **1984**, *49*, 2509-2519.
17. Burton, D.J.; Wiemers, D.M. *J. Am. Chem. Soc.* **1985**, *107*, 5014-5015.
18. Mawson, S.D.; Weavers, R.T. *Tetrahedron Lett.* **1993**, *34*, 3139-3140.

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