Studies on the Preparation of Dihydro-1,4-oxathiines. Computer-Assisted Evaluation of the Results of Retrosynthetic Analysis Verified by Synthetic Experiments and By-Product Analyses. Synthetic Pathways Involving α-Sulfenylated Ketones and 1,3-Oxathiolanes of α-Halo and α-Hydroxy Ketones

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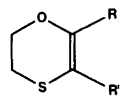
The preparation of 2- and 2,3-substituted 5,6-dihydro-1,4-oxathiines has been studied by computer simulation and by experiment. Three major synthetic pathways, involving 2-(1-hydroxyalkyl)-1,3-oxathiolanes, 2-(1-haloalkyl)-1,3-oxathiolanes, 2-hydroxyethylthiomethyl ketones, methanesulfonates of 2-hydroxyethylthiomethyl ketones and 2-chloroethylthiomethyl ketones as intermediates, were evaluated, by running the program CAMEO, and by experiment. The results of the two approaches were compared and the major by-products of the reactions were identified by GLC/MS.

The preparation and properties of dihydro-1,4-oxathiines **1** have been of interest to synthetic chemists for the last two decades.[1–15] Dihydro-1,4-oxathiines are active antifungal compounds. Lately, the synthetic efforts have been concentrated on the further development of old methods,[3] though some new methods have been introduced as well.[2,13–15] Our approach has been to scrutinise as many preparative methods for **1** as possible, investigating both new, previously demonstrated but not yet widely applied methods,[1] and more conventional methods.

This broad approach was attractive to us, since we have tried to devise potential synthetic routes to **1** by analysing the problem in a retrosynthetic manner and assessing the results by a computer program, CAMEO.[16] The performance of the methods suggested by the retrosynthetic analysis and computer evaluation was also examined experimentally: products were determined by GLC/MS and the results were compared with those provided by CAMEO. Studies are described on the synthesis of a total of seven dihydro-1,4-oxathiines **1a–g** by three synthetic methods, suggested by the retrosynthetic analysis of **1**.



1

1	R	R'
a	Me	H
b	Me	Me
c	Ph	H
d	Me	CO_2Me
e	Me	CO_2Et
f	Me	CONHPh
g	Me	CO_2H

Synthetic analysis and generation of the synthetic plan

The manual retrosynthetic analysis of **1** was carried out using short mechanistic steps in preference to entire conventional transformations. The most important results of the analysis are shown in Scheme 1.

The retrosynthetic scheme comprises three pathways, initiated by the generation of reactive intermediates **A**, **B** and **C**, respectively. These intermediates were converted into the neutral and more stable precursors **2**, **3** and **4**, which were processed further to obtain the synthons **D–H**.

The synthetic methods investigated comprise both new and old synthetic chemistry. Recently, we briefly described the performance of two synthetic methods making use of the pathway **1** ⇒ **A** ⇒ **2**: elimination of water from 2-(1-hydroxyalkyl)-1,3-oxathiolanes (**2**, X = OH) involving a rearrangement (method A1, Scheme 1),[13] and *in situ* generation of 2-(1-haloalkyl)-1,3-oxathiolanes (**2**, X = Cl, Br) followed by elimination of halide, rearrangement and

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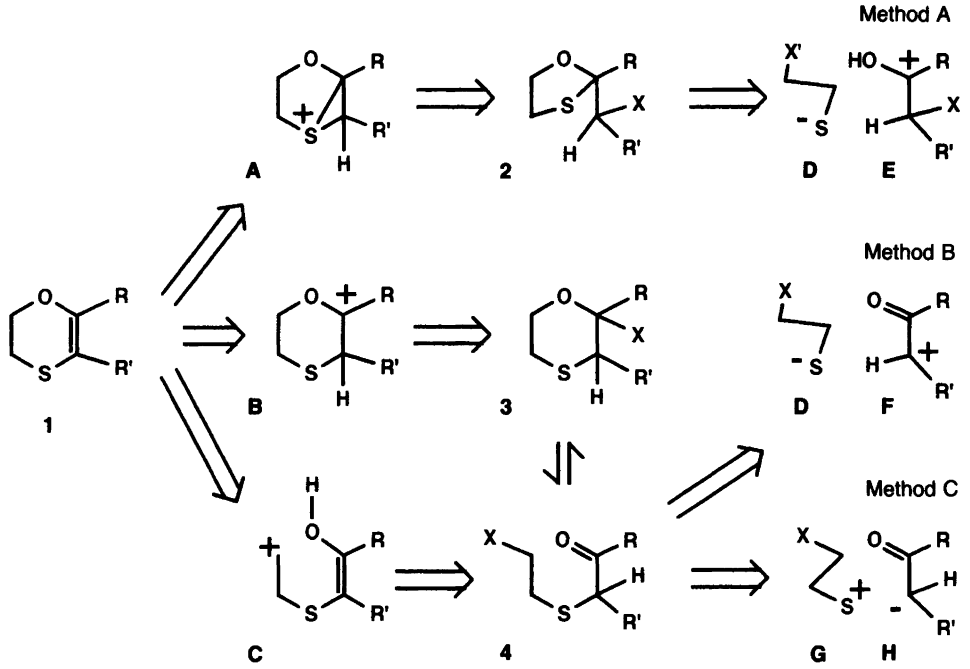
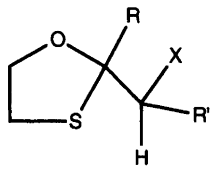


Scheme 1. Mechanistic steps in the retrosynthetic analysis of dihydro-1,4-oxathiine **1**. *Method A:* two modifications of the method were studied. *Method A1:* the use of **2** (X = OH) which was prepared and purified before its conversion into **1**. *Method A2:* the *in situ* generation of **2** (X = Cl, Br). The reagents for the synthons **D** and **E** were the thiol **5a** and the ketones **6** (X = Cl, Br). *Method B:* the reagents for the synthon **F** were the ketones **6** (X = halogen). *Method C:* the reagents for the synthons **G** and **H** were the compounds **5b,c** (X = acetate or methyl sulphonate), prepared *in situ* from **7a** (by functional group interconversions) and **9** (R′ = withdrawing group). In the conversion of **4** into the synthons **D** and **F**, two distinct methods were studied: one method making use of **3**, in which case the substituent X of **4** is the same as that of **3** and **D** (i.e. X = OH; *Method B1*), and another method in which there was an FGI before the actual conversion of **4** into **D** and **F** [i.e. retrosynthetic conversion of **4** (X = Cl or OSO_2Me) into **4** (X = OH) which was further broken down into **D** and **F**; *Method B2*].



2

2	R	R′	X
a	Me	Me	OH
b	Me	H	Cl
c	Ph	H	Br
d	Me	CO_2Me	Cl
e	Me	CO_2Et	Cl
f	Me	CONHPh	Cl
g	Me	H	OCOMe
h	Me	H	SCH_2CH_2OH
i	Me	H	SCH_2CH_2Cl

neutralisation by loss of a proton (method A2, Scheme 1).[14] A related study on method A2 has recently been reported by Mattay and Dittmer (only for two compounds which are not included in this study).[2]

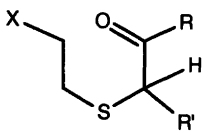
The cyclisation of **4** to give **1** might be performed in two ways. The conventional method would be to run the reaction through the ring-chain isomers of **4**, i.e. through the cyclic hemiacetals (**3**, X = OH), in which easy, acid-catalysed, elimination of water could occur (method B1, Scheme 1).[5–7,9–12] The second way would be to induce an S_Ni reaction in the enol tautomer of **4** (X = OSO_2Me, Cl or OAc) (method B2, Scheme 1). This pathway looks promising because there is a sulphide group β to the leaving group potentially contributing to the success of the substitution reaction. Support for the β-sulfide-assisted cyclodehydrohalogenation has recently been provided by Murray, who obtained 1,4-oxathianes by cyclodehydration of 2-hydroxyalkyl sulfide derivatives.[17] A single example of the cyclodehydrohalogenation of an 2-chloroethylthiomethyl ketone derivative has been presented.[18]

We investigated two methods of preparing **4**. In the preparation of the compounds **4** (X = OH), the reagents, corresponding to the synthons **D** and **F**, were the thiol **5a** and the α-halo ketones **6a–f** (Scheme 1).

This is a conventional preparative method for α-sulfenylated ketones.[5–7,9–12] In a second method, the preparation of **4** (X = OSO_2Me, OAc) was based on **G** and **H** (i.e. method C, Scheme 1). The reagent corresponding to the synthon **G** can be a sulfenyl chloride, such as **5b** or **5c**, generated *in situ* from **7a** or **7b**.

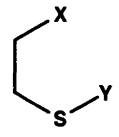
To our knowledge, the pathway from **G** and **H** through **4** to **1**, if successful, would constitute a novel method for the preparation of the title compounds. Moreover, the use of **5b** or **5c** in the above manner might allow a one-pot generation of **1**.

Compounds **2–20** were involved in this study either as



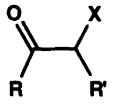
4

4	R	R'	X
a	Me	H	OH
b	Me	Me	OH
c	Ph	H	OH
d	Me	CO_2Me	OH
e	Me	CO_2Et	OH
f	Me	CONHPh	OH
g	Ph	H	OSO_2Me
h	Me	CO_2Et	OSO_2Me
i	Ph	H	Cl
j	Me	H	Cl
k	Me	CO_2Me	Cl
l	Me	CO_2Me	OCOMe
m	Me	Me	Br
n	Me	Me	Cl
o	Me	Me	OCOMe



5

5	X	Y
a	OH	H
b	OCOMe	Cl
c	OSO_2Me	Cl



6

6	R	R'	X
a	Me	H	Cl
b	Ph	H	Br
c	Me	CO_2Me	Cl
d	Me	CO_2Et	Cl
e	Me	CONHPh	Cl

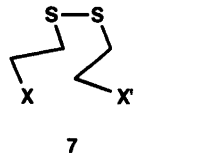
starting materials, reactive intermediates or as by-products. Compounds **2a**, **4a–f**, **5a**, **6a–e** and **7a–b** were used as starting materials. Compounds **2g–i**, **3**, **4i–k** and **4m–o** were expected as reactive intermediates. Compounds **2b–f**, **4g–h**, **4l**, **7c–f**, **8a–c**, **9a–e**, **10a–b**, **11a–b**, **12a–e**, **13a–c**, **14a–b**, **15**, **16a–b**, **17a–b** and **18–20** were detected as by-products.

The evaluation of synthetic pathways by use of the CAMEO program

The computer program CAMEO, developed by Jorgensen *et al.*, is an interactive computer program that predicts the products of organic reactions for starting materials and conditions specified by the user.[16,19] More broadly, it can be used to evaluate synthesis plans, i.e. to assess the potential performance of synthetic reactions of interest, and to suggest side-reactions, which are easily taken care of by proper adjustment of reaction conditions, or which are so major as to indicate that the synthetic method in question should be abandoned.

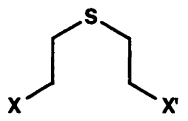
CAMEO was used to assess the potential performance of methods A, B and C (see Scheme 1). The version of CAMEO released in 1988 was used. The reactions evaluated by CAMEO were as follows: the preparation of **4d** from **5a** and **6c** under basic conditions (see Scheme 2); an acid-catalysed cyclisation of **4d** to obtain **1d**; the *in situ* generation of **2c** and its subsequent conversion into **1c**; the sulfenylation of the ketone **9c** by **5c** to obtain **4h**; the concomitant cyclisation of **4h** to obtain **1d**; and finally, the acid-catalysed rearrangement and elimination of water from **2a**. These reactions were suitable for a study by CAMEO because we had available a considerable amount of experimental data on the by-products of these reactions, which could be compared with the results provided by CAMEO.

In the case of the α-sulfenylation of **6c**, shown in Scheme 2, CAMEO generated the structures **4d** and **21–28**. The negative enthalpy change of the reaction giving rise to **4d** (ΔH = −149 kJ mol^{-1} when the reaction conditions



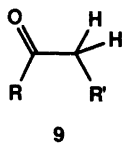
7

7	X	X'
a	OH	OH
b	OCOMe	OCOMe
c	Cl	Cl
d	Cl	OCOMe
e	Br	Br
f	Br	OH



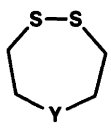
8

8	X	X'
a	Br	Br
b	Br	OH
c	Cl	Cl



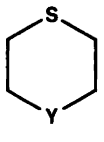
9

9	R	R'
a	Me	H
b	Ph	H
c	Me	CO_2Me
d	Me	CO_2Et
e	Me	CONHPh



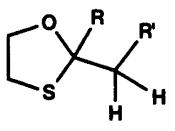
10

10	Y
a	S
b	O



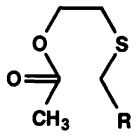
11

11	Y
a	S
b	O



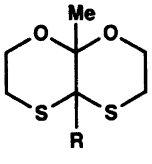
12

12	R	R'
a	Me	H
b	Me	Me
c	Ph	H
d	Me	CO_2Me
e	Me	CO_2Et



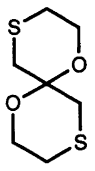
13

13	R
a	CO_2Me
b	CO_2Et
c	COMe



14

14	R
a	H
b	Me



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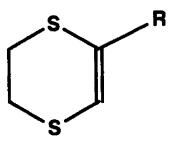
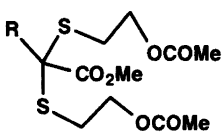


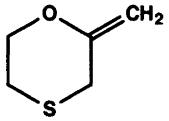
16

16	R
a	Ph
b	Me

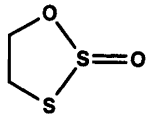


17

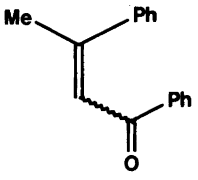
17	R
a	H
b	COMe



18



19



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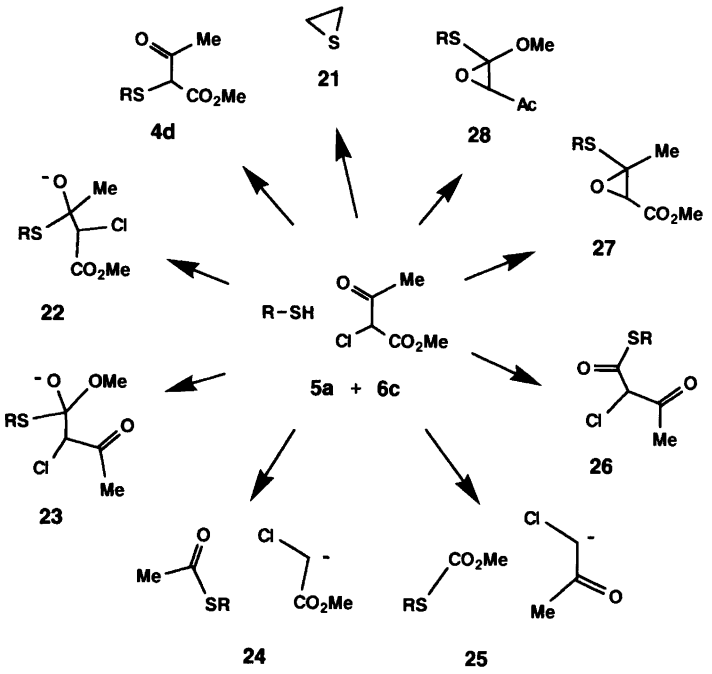


Conditions: KOH / H_2O									
Products:	**4d**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
ΔH (kJ mol^{-1})	−149	+37	−20	+37	+15	+3	+60	–	–
Conditions: NEt_3									
Products:	**4d**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
ΔH (kJ mol^{-1})	−102	–	+43	+106	+56	+44	–	−5	+59

Scheme 2. Results of CAMEO runs for the mixture of 2-mercaptoethanol **5a** and α-chloromethylacetoacetate **6c** under basic conditions.

were KOH/H_2O) suggests that **4d** would be the preferred product, which appears to be consistent with the experimental results discussed later.

The by-products **24** and **25** suggested by CAMEO imply that a cleavage of the β-keto ester system of **6c** via a reversed ester condensation could take place. However, that could also occur in the case of the desired product **4d**, either intramolecularly, giving rise to **13a**, or intermolecularly, giving rise to esters of 2-hydroxyethylthiomethylcarboxylic acids or 2-hydroxyethylthiomethyl ketones along with their *O*-acetylated derivatives. To take advantage of the warnings of CAMEO about these side-reactions, one should avoid lengthy exposure of the mixture of **4d** or **6c**, and 2-mercaptoethanol to a strong base.

Addition of 2-mercaptoethanol to the ketone carbonyl of **6c** and an accompanying epoxide (**27**) formation (see Scheme 2) was suggested by CAMEO. If the epoxide **27** were formed in the reaction mixture, it could be converted via cyclisations into 3-hydroxy-1,4-oxathiane derivatives or 2-(1-hydroxyalkyl)-2-methyl-1,3-oxathiolane derivatives. The latter could be converted into **1d** under cyclodehydration conditions, assuming that the hydroxyalkyl-1,3-oxathiolane in question behaved like **2a**.[14] Therefore, even if some of **5a** were to react with **6c** to give rise to **27**, this is not necessarily harmful because the desired end product **1d** can also be obtained in this way.

Although CAMEO is a useful reminder to the user of most of the potential side-reactions, the program did not reveal that α-halo carbonyl compounds could be dehalogenated in the presence of thiols (the thiols would be oxidised to the corresponding disulfides).[15,20–24]

In the case of the acid-catalysed cyclodehydration of **4d**, CAMEO predicted the formation of three products **1d** (ΔH = 10 kJ mol^{-1}), tosylate of **4d** (ΔH = −7 kJ mol^{-1}), methyl 2-vinylthioacetoacetate (ΔH = 32 KJ mol^{-1}) and methyl 2-(1-tosylethylthio)acetoacetate (ΔH = −27.5 kJ mol^{-1}). The last product would be formed via methyl 2-vinylthioacetoacetate which has the least favourable enthalpy of formation. Therefore, one could predict that the two last products predicted by CAMEO would not be formed under real reaction conditions.

For the acid-catalysed condensation of α-bromoacetophenone with 2-mercaptoethanol, HBr was selected as a catalyst because HBr would be the acid present in high concentration in the actual reaction mixture (HBr is produced in the reaction). CAMEO predicted the primary products **2c** (ΔH = −26 kJ mol^{-1}), **4c** (ΔH = −64 kJ mol^{-1}), α-(2-mercaptoethoxy)acetophenone (ΔH = 16 kJ mol^{-1}), α-(2-hydroxyethylthio)acetophenone (ΔH = 47 kJ mol^{-1}) and the enol and thioenol ethers of α-bromoacetophenone (ΔH = 57 and 48 kJ mol^{-1}). Further acid-catalysed reactions of all these primary products were

predicted to give rise to either **1c** or 3-phenyldihydro-1,4-oxathiine.

In this reaction system there is a question arising from competition between the formation of **2c** and **4c**. In the case of carbonyl compounds, the equilibrium constants for hydration are generally unfavourable, except for formaldehyde and compounds which are activated by electron-withdrawing substituents, but the equilibrium between hydrates and the corresponding carbonyl compounds has been proved to be fast (hydration is also facilitated by the presence of an acid or base).[25] Also, in the case of ketones, α-halogen substituents have been shown to increase the equilibrium constants for the hydrate formation.[26] The results provided by CAMEO indicate that the method in question could work. In this case the side-reactions would be more difficult to prevent than with method B1 owing to the methods generally utilised in the preparation of 1,3-oxathiolanes.[27]

For the α-sulfenylation of **9c** using the sulfenyl chloride **5c**, CAMEO predicted *C*2-sulfenylation of **9c** ($\Delta H = -143$ kJ mol^{-1}), *C*2-alkylation of **9c** ($\Delta H = -106$ kJ mol^{-1}), *O*-sulfenylation the ketone carbonyl of **9c** ($\Delta H = -20$ kJ mol^{-1}), *O*-alkylation of the ketone carbonyl of **9c** ($\Delta H = -37$ kJ mol^{-1}), *O*-sulfenylation the ester-carbonyl of **9c** ($\Delta H = 52$ kJ mol^{-1}), *O*-alkylation of the ester-carbonyl of **9c** ($\Delta H = 39$ kJ mol^{-1}), and the formation of vinylsulfenyl chloride ($\Delta H = -26$ kJ mol^{-1}). On the basis of the enthalpies only, the desired *C*2-sulfenylation could be the major reaction and the *C*2-alkylation a side-reaction.

In the case of the further base-catalysed reactions of the methyl 2-(2-methylsulfonyloxyethylthio)acetoacetate, CAMEO predicted the formation of **1d** ($\Delta H = -47$ kJ mol^{-1}) along with methyl 2-vinylthioacetoacetate ($\Delta H = -25$ kJ mol^{-1}), methyl 2-thioxoacetoacetate ($\Delta H = -47$ kJ mol^{-1}), methyl ester of 1-acylthietane-1-carboxylic acid ($\Delta H = -22$ kJ mol^{-1}) and 2-methoxy-3-acyl-5,6-dihydro-1,4-oxathiine ($\Delta H = -25$ kJ mol^{-1}). On the basis of these results one could assume methods B2 and C (see Scheme 1) to be worthy of further work (i.e. an experimental verification of their performance).

The products of the *p*-toluenesulfonic acid-catalysed reactions of **2a** suggested by CAMEO were **1b** ($\Delta H = 49$ kJ mol^{-1}), **4b** ($\Delta H = 15$ kJ mol^{-1}), 2-(2-hydroxyethylthio)-3-hydroxy-2-tosyloxybutene ($\Delta H = 19$ kJ mol^{-1}) and an epoxide of 2-(2-hydroxyethylthio)-2-butene ($\Delta H = 112$ kJ mol^{-1}). These results could be used to predict that the conversion of **2a** into **4b** would be the most likely reaction in the system in question. Also, the formation of **1b** from **2a** appears interesting in that **1b** could arise either from the further reactions of **4b** or through the intermediate A (Scheme 1).

The computer-assisted evaluation of syntheses, as discussed above, suggested methods A1 and B1 (see Scheme 1) to be the most promising pathways for the preparation of dihydro-1,4-oxathiines. Although some side-reactions were predicted, none of them should be impossible to control. The predicted success of methods B1 and A2 (see Scheme 1) are consistent with the previous reports of the preparation of dihydro-1,4-oxathiine derivatives.[2,5–7,9–12] The CAMEO runs also indicated the potential usefulness of methods B2 and C (see Scheme 1), though some problems that could only be solved by experiments, were pointed out.

Synthetic results

The synthetic experiments are summarised in Table 1. The best yields of **1** were obtained by method B1 (see Scheme 1), except for dihydro-1,4-oxathiines where the double bond of the heterocyclic ring is not stabilised by conjugation.

For these compounds method A1 (see Scheme 1) through 1,3-oxathiolanes of α-hydroxy ketones was better. Method A1 gave rise to **1b** in a yield of 40–85 % depending on the conditions used. Method B1 and A2 (see Scheme 1) failed to give **1a**.

In the case of the intermediates **2c–f**, method A2 gave **1c–g** in yields of 42–90 %. The *in situ* generation of **2c** and its subsequent conversion into **1c** was exceptional in that the performance of the reaction depended on the initial concentrations of the reagents. A modification of method A2 involving generation of the reactive halo-1,3-oxathiolanes via oxathiolane transfer reactions (e.g. experiments 9 and 10) afforded the desired products, but unfortunately in low yields only.

Method B2 (see Scheme 1) did not work as well as B1. The dihydro-1,4-oxathiine **1c** was obtained in a yield of 68 % when **4c** was treated with thionyl chloride in the presence of triethylamine, whereas method B1 gave **1c** in a yield of 91 %. When **4c** was treated with methanesulfonyl chloride, in the presence of triethylamine, **1c** was obtained in a yield of 28 %. On the basis of these results, one could expect that method B2 would work better for **4d** and **4e** than for **4c**. The formation of an enol of **4h** should be much easier than the formation of an enol of **4g**, and on that basis one could predict that the subsequent ring-closure step should proceed more smoothly. However, when **4e** was treated in the same way as **4c**, **1e** was produced in only a very low yield, and a complicated mixture of products appeared.

One reason for the poor yield with method B2 (see Scheme 1) could be a lack of chemoselectivity in the reactions of methanesulfonyl chloride with **4e**, i.e. competing reactions of the enol moiety of **4e** could take place, or one molecule of **4e** could react with two equivalents of methanesulfonyl chloride. Another reason could be the formation of the enol of **4e** in which the hydroxy group of the enol is hydrogen-bonded to the carbonyl group. In that case there is no conceivable way for the intramolecular substitution to occur. This last explanation is also reasonable in the light of the preparation of **1c** through **4g**, because the enol of **4g** would be more likely to exist in a form that would make the cyclisation step possible.

Method C (see Scheme 1) was studied for the synthesis of

Table 1. Summary of syntheses of dihydro-1,4-oxathiines **1a–g**.

Exp. No.	Method	Summary of starting materials and reaction conditions used	Product	Yield (%)
1	A1	**2a** + HBr (1:1) in CH_2Cl_2[a]	**1b**	70[b]
2	A1	**2a** + TsOH in CH_2Cl_2[a,c]	**1b**	40[b]
3	A1	**2a** + TsOH in toluene[a]	**1b**	85[b]
4	A1	**2a** + $SOCl_2$ (1:1) in EtOAc + Et_3N then reflux	**1b**	55[b]
5	A1	**2a** + $MeSO_2Cl$ (1:1) in CH_2Cl_2 + Et_3N then reflux	**1b**	85[b]
6	A2	**5a** + **6b** (50 mmol dm^{-3} in $CHCl_3$) (1:1) + TsOH[a]	**1c**	90[b]
7	A2	**5a** + **6b** (250 mmol dm^{-3} in $CHCl_3$) (1:1) + TsOH[a]	**1c**	1[b]
8	A2	**5a** + **6b** (1:1) TsOH,[a] no solvent	**1c**	0[b]
9	A2	**6b** + **12a** (1:3) + TsOH, no solvent, RT	**1c**	18[b]
10	A2	**6c** + **12a** (1:3) + TsOH, no solvent, RT	**1d**	11[b]
11	A2	**5a** + **6a** (1:1) in $CHCl_3$ or CH_2Cl_2 + TsOH[a]	**1a**	tr[b]
12	A2	**5a** + **6e** (1:1) in toluene + petr. spirit + TsOH[a]	**1f**	50[d]
13	A2	**5a** + **6c** (1:1) in toluene + petr. spirit + TsOH,[a] then NaOH(aq) / EtOH	**1g**	45
14	A2	**5a** + **6c** (1:6:1) in toluene + petr. spirit + TsOH,[a] then NaOH(aq) / EtOH	**1g**	45
15	A2	**5a** + **6c** (1:1) in $CHCl_3$ + TsOH,[a] then NaOH(aq) / EtOH	**1g**	42
16	A2	**5a** + **6d** (1:1) in toluene + petr. spirit + TsOH,[a] then NaOH(aq) / EtOH	**1g**	45
17	B1	**5a** + **6a** (1:1) + $NaHCO_3$ in $CHCl_3$ then TsOH[a]	**1a**	0[b]
18	B1	**5a** + **6b** (1:1) + NaOH (aq) in MePh then TsOH[a]	**1c**	91
19	B1	**5a** + **6c** (1:1) + $NaHCO_3$ in MePh then TsOH[a]	**1d**	70–75
20	B1	**5a** + **6d** (1:1) + $NaHCO_3$ in MePh then TsOH[a]	**1e**	70–75
21	B1	**5a** + **6c** (1:1) + $NaHCO_3$ in MePh then TsOH,[a] then NaOH(aq) / EtOH	**1g**	60–65
22	B1	**5a** + **6d** (1:1) + $NaHCO_3$ in MePh then TsOH,[a] then NaOH(aq) / EtOH	**1g**	60–65
23	B1	**5a** + **6e** (1:1) + $NaHCO_3$ in MePh then TsOH[a]	**1f**	70–75
24	B2	**4c** + $SOCl_2$ / NEt_3 in MePh	**1c**	68[b]
25	B2	**4c** + $MeSO_2Cl$ / NEt_3 in MePh	**1c**	28[b]
26	B2	**4e** + $MeSO_2Cl$ / NEt_3 in MePh	**1e**	3[b]
27	C	**7a** + $MeSO_2Cl$ / NEt_3 in CH_2Cl_2 then SO_2Cl_2 at −15 °C and then **9c**	**1d**	tr[b]
28	C	**7b** + SO_2Cl_2 at −15 °C then **9c**	**1d**	23[b]

[a]Azeotropic removal of water by using a conventional Dean–Stark separator. [b]Determined by GLC. Yields less than 1 % are marked as tr. [c]TsOH = *p*-$MeC_6H_4SO_3H$. [d]The yield is based on the NMR spectra.

1d. This method offers another pathway to the sulfonate **4h**, via an α-sulfenylation of the ketone **9c** by **5c**. Method C through the *in situ* formed sulfonate **4h** failed to afford **1e**. In fact, this result provides further support for the mechanism assumed and for the importance of the geometry of the enol required in a successful cyclisation of the sulfonates in question.

By contrast, method C (see Scheme 1) via an α-sulfenylation of the ketone **9c** by **5b** provided **1d** in a yield of 23 %. This result is interesting in the light of the unsuccessful cyclisation using **4h**. The cyclisation of the acetate **4l** should work even worse because acetate is a poorer leaving group than methyl sulfonate. There are, of course, several reaction mechanisms which could explain the conversion of **4l** into **1d** in the presence of dry HCl in a dichloromethane solution (i.e. the conditions under which the *in situ* generation of **5b** and the subsequent reaction of **5b** with **9c** were carried out).

Computer-assisted evaluation of reactions and experimental findings on the formation of products

Several product mixtures of reactions were analysed by GLC to determine the by-products of the reactions. The analyses are summarised in Table 2 (data organised according to Table 1).

The reactions predicted by CAMEO on the conversion of **2a** into **1b** are consistent with the experimental findings shown in Tables 1 and 2 (i.e. the formation of products in the experiments 1–5). According to CAMEO, **4b** should be the most thermodynamically favoured product of acid-catalysed reactions of **2a**. Also, rearrangements of thiiranes are reported to result in the formation of ketones.[28] In fact, **4b** was the main product when **2a** was treated with TsOH in boiling dichloromethane solution. At higher temperatures, the major product appeared to be **1b** (see Table 2).

It is not obvious how the formation of **1b** from **2a** occurs under acidic conditions but, in addition to our proposed pathway through the intermediate A (see Scheme 1), explanations analogous to those provided for the acid-catalysed reactions of α-hydroxybis(phenylthio)alkanes,[29] could apply. Since the formation of **4b** from **2a** has been proved, the by-products **4m–o** could arise from further reactions of **4b**. EtOAc was used in experiment 4 (see Table 2) in order to trap hydroxylic side-products by transesterification.

GLC/MS analysis of the products of the treatment of **2a** with methanesulfonyl chloride showed two isomers of the same molecular weight $m/z = 130$. One of these was **1b** and

Table 2. Summary of the by-products determined in the synthesis of dihydro-1,4-oxathiines **1a–g**.

Exp. No.[a]	By-product / abundance (%)[b]
1	**4m** (29)
2	**4b** (60)
4	**4n** (7), **40** (9), **7b** (tr), **7c** (tr), **7d** (tr), **10b** (tr), **11a** (tr), **14b** (3), **19** (15)
5	**4n** (5), **18** (9)
7	**7a** (tr), **7e** (6), **7f** (3), **8a** (tr), **8b** (tr), **9b** (79), **10a** (tr), **16a** (3), **20** (10)
8	**7e** (57), **7f** (6), **8a** (2), **9b** (7), **10a** (tr), **16b** (tr), **20** (25)
9	**1a** (1), **7e** (13), **9b** (34), **12c** (10)
10	**1a** (1), **4j** (5)
13–16	Derivatives of **2h** and **2i**
17	**2h** (11), **2i** (tr), **7a** (tr), **12a** (tr), **14a** (tr), **15** (tr)
19–20	**1a** (2–20), **2g** (1), **4j** (0–3), **7a,b** (0–5), **9c,d** (1–11), **10a,b**, **11a,b** (0–5), **12a** (tr), **12d–e** (0–6), **13a,b** (2–8), **13c** (0–3), **14a** (tr), **15** (tr), **16b** (tr)
27	**7c**, **8c**, **10a**, **11a**
28	**41** (8), **7b** (44), **13a** (4), **13c** (4), **17a** (tr), **17b** (14)

[a]See Table 1. [b]Determined by GLC. Abundances less than 1 % are marked as tr.

the other was characterised as **18** on the basis of its mass spectrum.[13] If **18** was also formed in the treatment of **2a** with acids, it would have been converted into the more stable isomer (the stability difference between **1b** and **18** is 13 kJ mol^{-1} calculated from the heats of formation given by CAMEO) and thus would not be found in the reaction mixture.

The formation of **19** in experiment 4 (see Table 2) implies that $SOCl_2$ can give rise to a cleavage of the 1,3-oxathiolane ring. Although it is known that **19** can be prepared from $SOCl_2$ and 2-mercaptoethanol,[30] its formation from free 2-mercaptoethanol released from **2a** under the conditions of experiment 4 (i.e. in the absence of water) seems unlikely. More likely, the loss of the oxathiolane moiety of **2a** takes place through an *O*-chlorosulfinyl derivative of the epoxide of 2-(2-hydroxyethylthio)-2-butene, from which, via an addition of any nucleophile to the epoxide derivative, an α-functionalised ketone and **19** would be obtained. Reactions of related epoxide derivatives with nucleophiles are known to proceed in this way.[31,32]

The formation of small amounts of disulfides **7b–d** and **10b** (see Table 2) when **2a** was treated with $SOCl_2$ in the presence of NEt_3 implies that disproportionation reactions involving the sulfur moieties occur to minor extent only. No disulfides were obtained when **2a** was treated with acids. This result is interesting in light of the work of Blatcher and Warren who found that either α-sulfenylated or non-sulfenylated ketones could be obtained in good yield by treating α-hydroxybis(phenylthio)alkanes with TsOH or trifluoroacetic acid.[29]

In the case of method A2 (see Scheme 1), the results of CAMEO were not consistent with the experimental findings in that the dehalogenation of the α-halo ketones by mercaptoethanol was not taken into account at all. There are examples of the dehalogenation or desulfenylation of α-halogenated or sulfenylated carbonyl compounds or sulfones by thiols, under both acidic and basic conditions.[15,20–24,33] We have recently shown that, under acidic conditions, the feasibility of dehalogenation reactions increases with the increasing initial concentration of the reacting halo ketone and thiol.[15,33] In this way, it is possible to produce dihydro-1,4-oxathiines straight from α-halo ketones and 2-mercaptoethanol by an acid-catalysed condensation, in one pot.

The formation of **14b** in experiment 4 suggests that **2a** was oxidised with $SOCl_2$, although direct oxidation products of **2a** were not found. The formation of **14b** could be explained by involving 2-acyl-2-methyl-1,3-oxathiolane, formed by elimination of SO_2 from the symmetric sulfite of **2a**. Even though we did not find 2-acyl-2-methyl-1,3-oxathiolane in any reaction mixtures analysed, we have observed that this compound reacts with 2-mercaptoethanol in the presence of an acid catalyst, giving rise to **14b** and 2-methyl-2-(2-methyl-1,3-oxathiolanyl)-1,3-oxathiolane. These types of cyclic isomers are easily distinguished on the basis of their mass spectra.[34]

Formation of almost all the products of the experiments 7 and 8 can be explained by disproportionation reactions typical of sulfur compounds.[15] The disulfides **7a**, **7e**, **7f** and **10a**, along with the ketones **9b** and **20**, all arise from the dehalogenation of the α-bromoacetophenone (see Table 2).

When method A2 (Scheme 1) was applied to the preparation of **1g**, using **6c** or **6d** as the starting material to obtain the esters **1d** or **1e**, which were then hydrolysed to **1g**, the yield of **1g** remained around 45 % despite efforts to optimise the reaction conditions. The dehalogenation reactions occurred only to minor extent in the acid-catalysed reactions of **5a** with **6c** or **6d**. However, an annoying side-reaction, the addition of **5a** to the newly formed **1d** or **1e** took place.

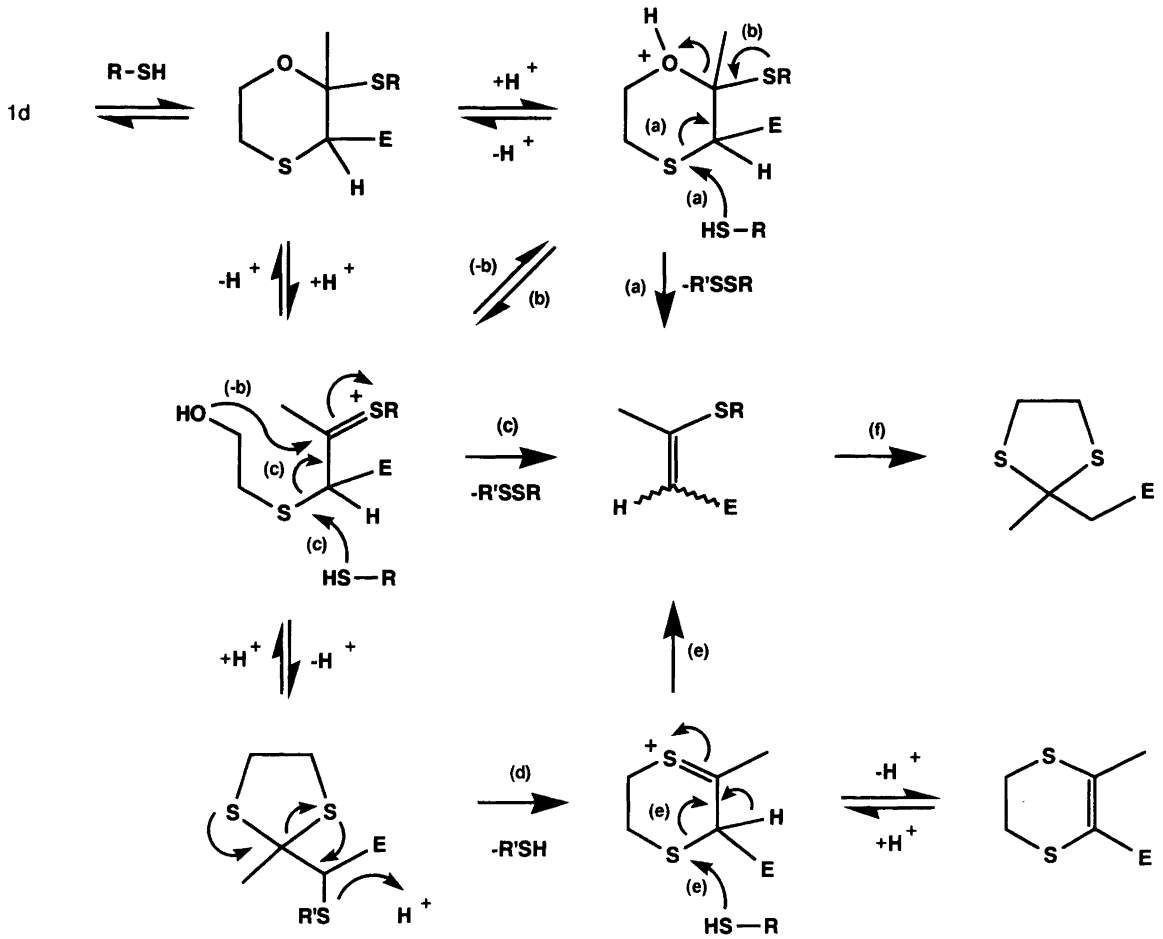
These side reactions were studied by treating pure **1d** and **1e** with **5a** and 1,2-ethanedithiol in the presence of TsOH, or by trapping of the side products via transesterification (i.e. by carrying out the experiments in the presence of a mild acetylating agent). The acid-catalysed reactions of **5a** with **1d** were also studied by running CAMEO. The results imply that when **5a** reacts with **1d** in the presence of an acid, three types of reactions would be possible: a transesterification, a nucleophilic addition of the thiol group of **5a** to the double bond of the heterocyclic ring, and an electrophilic addition of a thiirane (formed from **5a** by an acid-catalysed elimination of water) to the double bond of the heterocyclic ring.

The reaction of **1e** with **5a** in boiling dichloromethane gave a mixture of **1e** and the oxathiolanes **2h**, **12a** and **12d** (see Table 2). If **1d** or **1e** were heated with **5a** in the presence of TsOH (in the absence of a solvent), it disappeared completely and several 1,3-oxathiolane derivatives were produced (see Table 2). Also, when **1d** or **1e** was heated at 150 °C (to facilitate the side reactions that could occur) with

1,2-ethanedithiol and TsOH for 15–30 min in the absence of a solvent, 1,3-dithiolane derivatives were produced. These conclusions were drawn from the ^{13}C NMR data collected on reaction mixtures. The shifts of the starting materials disappeared and the characteristic singlet (several singlets between 93 and 98 ppm) of C-2 of the 1,3-oxathiolane ring, and the doublet (several doublets between 53 and 57 ppm) of C-2 of the α-sulfenylated acetoacetate moieties of 1,3-oxathiolane derivatives of **4d** appeared. Also, several signals characteristic for ester groups arose. The area in which characteristic signals of esters of thiocarboxylic acids generally appear was quite clean. In the case of the reaction of 1,2-ethanedithiol with **1d**, the shifts of **1d** disappeared and the characteristic shifts of 1,3-dithiolanes appeared (e.g. several singlets between 67.4 and 66.3 ppm arising from C-2 of the 1,3-dithiolane rings; several doublets between 60.7 and 60.0 ppm arising from the α-sulfenylated carbon-2 of the 1,3-dithiolanes of the 3-oxobutanoates; several triplets between 42.0 and 38.2 arising from C-4 and C-5 of the 1,3-dithiolane rings). Also the occurrence of the triplets arising from the CH_2O groups was low when **1d** was heated with 1,2-ethanedithiol, which implies that the newly formed β-hydroxy sulfide groups arising from the cleavage of the dihydro-1,4-oxathiine ring system were further sulfenylated. The ^{13}C NMR spectroscopic study on the products of the reaction of **1f** with 1,2-ethanedithiol gave results completely consistent with these of **1d** and **1e**.

When the pale yellow oil, provided by heating **1d** with 1,2-ethanedithiol in the presence of TsOH as described above, was analysed by GLC/MS, several products were found along with **1d**. The most abundant of these were 2,2-dimethyl-1,3-dithiolane, 5,6-dihydro-2-methyl-1,4-dithiine, **1d**, the 1,3-dithiolane of methyl acetoacetate and the methyl ester of 5,6-dihydro-2-methyl-1,4-dithiine-3-carboxylic acid, which were found in the ratio 2.5 : 2 : 1.5 : 1 : 3. The same compounds, except for **1d**, were observed when 1,2-ethanedithiol was heated with **6c** in the presence of TsOH under a conventional Dean–Stark water separator.[33] The MS identification was based on our lately reported fragmentation analysis of 1,3-dithiolanes,[35] dihydro-1,4-dithiines[36] and dihydro-1,4-oxathiines.[37]

The formation of the products in the above acid-catalysed condensations of dihydro-1,4-oxathiines with thiols can be realised on the basis of reactions depicted in Scheme 3. Formation of desulfenylated products could



Scheme 3. Acid-catalysed reactions of the methyl ester of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid (**1d**) with 1,2-ethanedithiol.

occur via the reaction steps (a) or (b) and (c) or even via the steps (b), (d) and (e) from which the pathways via (d) explain also the formation of dihydro-1,4-dithiine derivatives observed in the reaction mixtures.

There are many pathways which could explain the formation of decarboxylated products in these reactions. A number of them involve intermediates related to those shown in Scheme 3.

To ensure that these products really arose from the reactions in question, blind experiments were carried out by heating **5a**, 1,2-ethanedithiol, **1d** and **1e** in turn under the same conditions. The experiments confirmed that none of the ^{13}C NMR shifts discussed above arose from acid-catalysed reactions between the same type of molecules but were due to the presence of the above products.

The other focus in the study on the side reactions hampering the utilisation of method A2 (see Scheme 1) was the reaction of **6c** with **5a** (1.6 mol equiv.) in the presence of a catalytical amount of TsOH (according to experiment 14) carried out in a boiling mixture of toluene, petroleum spirit (fraction boiling at 80–100 °C) and EtOAc, under a conventional Dean–Stark water separator. The experiment was run for 3 days to allow all possible reactions to occur, and the final mixture was analysed by a GC/MS method. The major single constituents of the mixture were the esters **1d** and **1e** (total abundance about 47 %) and the methyl and ethyl esters of α-(2-methyl-1,3-oxathiolanyl)-α-(2-acetoxyethylthio)acetic acid (total abundance about 20 %) along with 2-methyl-2-(2-acetoxyethylthiomethyl)-1,3-oxathiolane (about 8 %). Small amounts of **1a**, **6c**, methyl α,α-dichloroacetoacetate, **12d**, **12e**, 2-acetoxyethylthiomethyl methyl ketone, **2i**, and **7b** were detected as well.

The complete separation and purification of the constituents of the above complex reaction mixture was not undertaken, but the oxathiolane derivatives of α-sulfenylated acetoacetates and acetones were identified by comparing their EI-fragmentations with those of **2a** and **12a–e** investigated earlier.[38] Also, the fragmentation of **2h** was used as a guide in the deduction of the structures of the more functionalised 1,3-oxathiolanes. (**2h** appeared as the most prominent by-product of experiment 17 and was purified and characterised by ^1H NMR and ^{13}C NMR spectroscopy and mass spectrometry.)

It was not possible to determine the elemental composition of the 1,3-oxathiolane derivatives by high resolution mass spectrometry because the abundance of molecular ions was very low. However, information on the elemental composition of the characteristic fragment ions was used to confirm the deduced structures.

Fragmentation of all these 1,3-oxathiolanes gave rise to a characteristic cation at $m/z = 103$, corresponding to the formulae $[C_4H_7OS]^+$ (i.e. the 2-methyl-1,3-oxathiolane 2-cation). This was also the base peak of their mass spectra. α-Sulfenylated acetoacetates gave the fragments $[CH_2CH_2SCHCO_2R]^{+\cdot}$. The fragmentation of the oxathiolane derivatives of the α-sulfenylated acetones gave rise to ions at $m/z = 116$ and 117, corresponding to the formulae $[C_5H_8OS]^{+\cdot}$ and $[C_5H_9OS]^{+\cdot}$. These ions arise from the loss of the α-sulfenyl substituents. In the case of **2i**, the chlorine-containing fragment ions at $m/z = 109/111$ and 63/65 corresponding to the characteristic fragments $[CH_2SCH_2CH_2Cl]^+$ and $[CH_2CH_2Cl]^+$ were produced as well. The fragmentation of both **2h** and its acetate gave an ion at $m/z = 74$ corresponding to the fragment $[CH_2SCH_2CH_2]^+$.

Method B1 (see Scheme 1) gave the best yields of conjugatively stabilised dihydro-1,4-oxathiines **1c–g**. The reactions of **5a** with **6c** in the presence of a base and the acid-catalysed cyclodehydration of the intermediate **4d** were investigated by running the CAMEO program. CAMEO suggested that the cleavage of the β-keto ester system of **6c–e** and/or **4d–f** via a retro ester condensation would occur, and in fact, it was one of the side reactions observed. Also, an intramolecular acyl migration, along with a loss of the acyl moiety, was found to take place for the compounds **4d–f**. These side reactions gave rise to methyl and ethyl esters of 2-acetoxyethylthioacetic (**13a** and **13b**) and 2-hydroxyethylthioacetic acids, or in the case of **4f** to the corresponding amides. The loss of the ester moiety of **4d–e** also could have occurred, since **13c** was found among the by-products of experiments 19 and 20 (see Table 2).

As in the case of method A2, dehalogenation of the α-halocarbonyl compounds occurred. However, when the reaction conditions were properly adjusted, the harm caused by the dehalogenation was not significant (the disulfides **7a,b** and **10a,b**, as well as the other products of the dehalogenation reactions, i.e. **9c,d**, **12a** and **12d,e**, were minor constituents in the reaction mixtures of experiments 19 and 20, see Table 2). In addition to dehalogenation, desulfenylation of **4d–f** also occurred when these compounds were treated with **5a** in the presence of a strong base. This implies that the 'dehalogenation' of **6c–e** under basic conditions occurs preferentially through **4d–f** but does not exclude the pathway through the sulfenyl halides. Furthermore, the sulfenylated and desulfenylated β-keto carbonyl compounds formed were found to be in equilibrium; for example, when **9e** was treated with **7a** in a KOH – water solution, a mixture of **4f**, **7a**, **9e** and *N*-phenyl-2-hydroxyethylthioacetamide was provided. Even though the equilibrium constants of these reactions were not determined, the equilibrium was found to favour the disulfide – desulfenylated ketone system in the KOH – water solution (namely 5–7 mol equiv. of **7a** were required to provide a mixture containing detectable amounts of **4f**). These types of sulfenylation reactions may explain the formation of **14** and **15** in experiments 19 and 20. We also tried to prepare **4f** from **6e** and **7a** under basic conditions (KOH – water solutions) but we always obtained mixtures of **4f** and *N*-phenyl-2-hydroxyethylthioacetamide and the yields of **4f** were poor.

The experiments did not clarify the role of the thiiranes **27** and **28**, suggested by CAMEO as potential intermediates in the reaction between **5a** and **6c** under basic

conditions (see Scheme 2). However, the formation of 2-acetoxymethyl-2-methyl-1,3-oxathiolane (**2g**) in experiments 19 and 20 could easily be explained by considering the epoxide **27** as a reactive intermediate.

With refluxing under a conventional Dean–Stark water separator, the acid-catalysed cyclisation of the intermediates **4c–f** proceeded smoothly giving rise to the dihydro-1,4-oxathiines **1c–f**. The most prominent side product was **1a** which could have been produced via several pathways, i.e., via a Grob-type fragmentation taking place on the hydrated ester group of **4d–e** (water is produced by the cyclisation reaction), via cyclisation of **4a** (decarboxylation of **4d–e** would give rise to **4a**), and so on.

Method B2 (see Scheme 1) was studied by CAMEO for the case of the cyclisation of the sulfonate of **4d**. When the cyclisation of this type of sulfonate was investigated experimentally, the procedure was found to work in the preparation of **1c** but not **1d–e**. Similarly, when method C (see Scheme 1) was utilised to prepare and cyclise the sulfonate of **4d**, only traces of the desired product **1d** were found in the reaction mixture, as shown in Table 1. The compositions of the reaction mixtures provided by the experiments 26–28 were complex and only a limited amount of data on the by-products was produced. Experiment 28 was the most revealing in its by-products and side reactions (see Table 2). In this experiment the desired sulfenylation occurs, giving rise to **4l**, but a further sulfenylation then seems to take place, resulting in the formation of **17b**. This was something that could be expected from the first sulfenylation step predicted by CAMEO (see Scheme 2).

Conclusions

Method B1, i.e. the acid-catalysed cyclodehydration of 2-hydroxyethylthiomethyl ketones prepared from the corresponding α-halo carbonyl compounds and 2-mercaptoethanol in the presence of a base, gave conjugatively stabilised dihydro-1,4-oxathiines in good yield but did not work in the case of compounds that were not stabilised by conjugation or substitution. Method A2, i.e. the *in situ* generation of 1,3-oxathiolanes of α-halo ketones and subsequent elimination of hydrogen halide, gave the title compounds in high yields, but only in a few cases. Method A1 appeared promising in the preparation of dihydro-1,4-oxathiines not stabilised by conjugation. Method B2 worked in some cases and might be useful in the preparation of dihydro-1,4-oxathiines with a fusion bond between C-5 and C-6.

The performance of the program CAMEO was encouraging, suggesting that it would be a useful tool for anybody working on synthetic problems. In many cases CAMEO correctly suggested the most likely products of reactions, and even though the experimentally observed products were not always immediately displayed, intermediates were generated which, under the actual reaction conditions, would be converted into the experimentally observed products. Considering the results in this manner, the experimental results were logically consistent with those provided by CAMEO.

Experimental

The mass spectra were run on a Jeol JMS-D300 mass spectrometer equipped with a Jeol JMA-2000H data system. The volatile reaction products were separated with a Carlo Erba Fractovap 4160 gas chromatograph equipped with a fused silica SE-52 column connected to the mass spectrometer. Quantitative analyses were performed using a Jeol JGC-20K gas chromatograph equipped with an OV-30 column. The ^{1}H NMR spectra were recorded with a Jeol JNM-PMX60 spectrometer and the ^{13}C spectra with a Bruker AM250/Aspect 3000 FT-NMR system. References were 1 % Me_4Si (0 ppm) (^{1}H) and $CDCl_3$ (77 ppm) (^{13}C). The GLC data were used without detector response corrections to calculate the relative proportions of the products shown in Tables 1 and 2.

The chloro ketones **6c–e** were prepared as described in the literature (the purity of distilled **6c–d**, >98 %, was checked by GLC).[39] Commercially available chloroacetone and α-bromoacetophenone were used as such. The purity of 2-mercaptoethanol was checked by NMR spectroscopy. The 2-(1-hydroxyethyl)-2-methyl-1,3-oxathiolane (**2a**) was prepared from 2-acyl-2-methyl-1,3-oxathiolane (prepared by an acid-catalysed condensation of butane-2,3-dione and 2-mercaptoethanol) by $NaBH_4$ reduction.

Reaction simulations were performed by use of the 1988 release of CAMEO. The following modules were used: acidic/electrophilic for reactions occurring in acidic conditions, basic/nucleophilic modules for reactions taking place under basic conditions and heterocyclic modules for all reactions in which heterocycles were assumed to be produced (reactions occurring under acidic and/or basic conditions).

*Method A1. The acid-catalysed conversion of 2-(1-hydroxyethyl)-2-methyl-1,3-oxathiolane (**2a**).* A solution of **2a** (0.25 g, 1.7 mmol) and a few crystals of *p*-toluenesulfonic acid (a catalytic amount) in 10 ml of toluene were refluxed under a conventional Dean–Stark water separator (in addition the separator was filled with dry calcium chloride and toluene). After 2 h the resulting mixture was washed with dilute sodium carbonate and water. The toluene solution was dried with magnesium sulfate and after filtration the solvent was removed under reduced pressure. The results of NMR spectroscopy and GLC showed the residue (0.27 g) to contain toluene and 1-(2-hydroxyethylthio)ethyl methyl ketone **4b** along with **1b**. The GLC analysis of the residue showed an 85 % yield of 5,6-dihydro-2,3-dimethyl-1,4-oxathiine (**1b**).

*Method A1. The reaction of 2-(1-hydroxyethyl)-2-methyl-1,3-oxathiolane (**2a**) with methanesulfonyl chloride.* A solution of methanesulfonyl chloride (0.21 g, 1.8 mmol) in dichloromethane (10 ml) was added dropwise to a solution

of **2a** (0.25 g, 1.7 mmol) and triethylamine (0.36 g, 3.6 mmol) in 25 ml of dichloromethane under stirring, at 0 °C. The mixture was stirred overnight at room temperature and then refluxed for 2 h. The resultant mixture was washed with water, dilute sodium carbonate and water and dried with magnesium sulfate. The solvent was removed under reduced pressure to give an oily residue (0.24 g). The GLC analysis of the oil showed an 85 % yield of 5,6-dihydro-2,3-dimethyl-1,4-oxathiine (**1b**).

General procedure for the method A2. Acid-catalysed condensation of α-halo ketones **6c–e** *with 2-mercaptoethanol.* A solution of α-halo ketone **6c–e** (60 mmol), 2-mercaptoethanol (4.70, 60 mmol) and TsOH (a catalytic amount) in a mixture of toluene and light petroleum (fraction boiling 80–100 °C, 250 ml) was refluxed for 2–3 h under a conventional Dean–Stark water separator. A small sample was taken for GLC and spectroscopic studies. In the case of the ethyl and methyl esters of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid, the solvents were removed from the rest of the solution under reduced pressure and the resultant light yellow oil was refluxed in water–ethanol solution containing 20 % NaOH for 3 h. The ethanol was removed by distillation and the residue was washed twice with diethyl ether. Concentrated hydrochloric acid was added to the water portion containing the salt of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid until a pH of ca. 3 was achieved. The white precipitate that formed was filtered, washed with ethanolic water and dried at room temperature to give the pure 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid (**1g**) in a yield of 45 % (based on α-halo ketones **6c** and **6d**).

Method A2. The concentration dependence of reactions of α-bromoacetophenone with 2-mercaptoethanol. A series of solutions, each containing α-bromoacetophenone (0.76 g) and *p*-toluenesulfonic acid (0.05 g) in chloroform (20, 40, 50 and 85 ml), was prepared and 2-mercaptoethanol (0.30 g) was added to each solution with stirring. After 3–7 days the mixtures were refluxed for 2 h under a Dean–Stark water separator filled with chloroform and dry calcium chloride, washed with dilute sodium carbonate and water and dried over $MgSO_4$. The solvent was distilled off under normal pressure and finally under reduced pressure at 40 °C. The residues were analysed using GLC/MS. The above experiment, in which 85 ml of chloroform were used, gave 5,6-dihydro-2-phenyl-1,4-oxathiine (**1c**) in a yield of 90 %.

Method A2. The general procedure for the generation of halo-1,3-oxathiolanes by oxathiolane transfer. A solution of α-halo ketone (10 mmol), 2,2-dimethyl-1,3-oxathiolane (3.54 g, 30 mmol) and *p*-toluenesulfonic acid (0.01 g) in chloroform (50 ml) was stirred for 3–7 days at room temperature. The solution was refluxed for 2 h under a Dean–Stark water separator filled with chloroform and dry calcium chloride. The solvent was removed under reduced pressure. Because of the low yields (11–18 %), isolation of the desired dihydro-1,4-oxathiines was not undertaken, but a small sample of the reaction mixture was taken and analysed by GLC/MS.

General procedure for method B1. Sulfenylation of α-halo ketones (6) and subsequent cyclodehydration. A solution of α-halo ketone (48 mmol) in toluene (20 ml) was added dropwise to a mixture of 2-mercaptoethanol (3.76 g, 48 mmol) and $NaHCO_3$ in toluene (or 20 % NaOH in water–toluene) (20 ml) with stirring at room temperature over a period of 10 min and the resultant mixture was stirred for a further 1–2 h at 40 °C. The solids were removed by filtration (or separation of the toluene phase when the sulfenylation was carried out in the water – toluene solution), and the toluene solution was refluxed under a Dean–Stark water separator in the presence of a catalytic amount of *p*-toluenesulfonic acid until no more water separated. The resultant light brown solution was washed with concentrated Na_2CO_3, dilute hydrochloric acid and water, and dried with $MgSO_4$. After filtration (a small sample was taken for GLC/MS studies), the solvent was removed under reduced pressure to obtain dihydro-1,4-oxathiines in a yield of 70–91 % (based on the α-halo ketones **6**). 5,6-Dihydro-2-phenyl-1,4-oxathiine (**1c**) was obtained almost without impurities, based on GLC and NMR measurements. The methyl ester of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid (**1d**) was purified by crystallisation (the raw product crystallised after 3–4 weeks in a refrigerator). The ethyl ester of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid (**1e**) was purified by distillation (b.p. 136 °C / 8 mmHg) and *N*-phenyl-5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxamide (**1f**) was purified by recrystallisation from petroleum ether–ethyl acetate (m.p. 91–93 °C). The methyl and ethyl esters of 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid were also hydrolysed to the acid (**1g**) by refluxing the raw product in a water–ethanol solution containing 20 % NaOH. The ethanol was removed by distillation and concentrated hydrochloric acid was added to the remaining solution until pH 3 was achieved. The white precipitate that formed was filtered, washed with ethanolic water and dried at room temperature to give the pure 5,6-dihydro-2-methyl-1,4-oxathiine-3-carboxylic acid (**1g**) in a yield of 60–65 % (based on α-halo ketones **6d** and **6e**).

General procedure for method B2. Preparation of methanesulfonates of 2-hydroxyethylthiomethyl ketones, and their subsequent conversion into dihydro-1,4-oxathiines. A solution of methanesulfonyl chloride (0.58 g, 5 mmol) in dichloromethane (10 ml) was added dropwise to a solution of 2-hydroxyethylthiomethyl ketone (5 mmol, **4c–e**) and triethylamine (1.52 g, 15 mmol) in dichloromethane (10 ml) with stirring at room temperature over a period of 10 min (isolation of the sulfonates was not undertaken). The mixture was stirred for 1 h and then refluxed for an additional 2 h. The resultant mixture was washed with

dilute hydrochloric acid and water and dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure.

Preparation of 2-chloroethylthiomethyl phenyl ketone and subsequent cyclodehydrohalogenation (method B2). A solution of thionyl chloride (0.60 g, 5 mmol) in dichloromethane (10 ml) was added dropwise to a solution of 2-hydroxyethylthiomethyl phenyl ketone (**4c**) (5 mmol) and triethylamine (1.52 g, 15 mmol) in dichloromethane (10 ml) with stirring at room temperature over a period of 10 min. The mixture was stirred for 1 h and then refluxed for an additional 2 h. The resultant mixture was washed with dilute hydrochloric acid and water and dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure.

General procedure for method C. Preparation of methyl α-(2-acetoxyethylthio)acetoacetate and subsequent ring closure. A solution of sulfuryl chloride (0.68 g, 5 mmol) in carbon tetrachloride (5 ml) was added dropwise to a solution of 2-acetoxyethyl disulfide (**7b**) (1.19 g, 5 mmol) in dichloromethane (10 ml) with stirring at −15 °C over a period of 10 min, and the resultant solution was stirred for an additional 30 min. The solution was placed into a precooled dropping funnel and added dropwise to a solution of methyl acetoacetate (0.58 g, 5 mmol) in dichloromethane (10 ml) with stirring at −15 °C over a period of 10 min. After 40 min, the mixture was allowed to warm to room temperature and finally the solution was refluxed for 30 min. The solvent was removed under reduced pressure to give 1.58 g of yellow oil. A small sample of the resultant oil was investigated by GLC/MS.

The spectroscopic data (supplementary material, 6 pages) used to identify the compounds are available upon request from V.N. (i.e. compounds **1–20**; data of **6**, **9** and **12**, which are well known, are excluded). The α-sulfenylated carbonyl compounds (**4a–i**) were not isolated but cyclised to the corresponding dihydro-1,4-oxathiines. Also, the isolation of the reactive sulfenyl chlorides **5b–c** was not undertaken.

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