Sulfine-based Synthesis of Four-, Five- and Six-Membered Heterocycles

Een wetenschappelijke proeve op het gebied van de Natuurwetenschappen, Wiskunde en Informatica

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Katholieke Universiteit Nijmegen,
op gezag van de Rector Magnificus Prof. Dr. C. W. P. M. Blom,
volgens het besluit van het College van Decanen in het openbaar te verdedigen op
dinsdag 4 november 2003 des namiddags om 15.00 uur precies

door

Andreas Christianus Bernardus Lucassen

Geboren op 3 september 1970 te Nijmegen

Promotor: Prof. Dr. B. Zwanenburg

Manuscriptcommissie:

Prof. Dr. S. Braverman (Bar-Ilan University, Israel)
Prof. Dr. P. Metzner (UMR du CNRS, ISMRA-University, Caen, France)
Prof. Dr. T. Saito (Tokyo University of Science, Tokyo, Japan)

The research described in this Ph.D. thesis was supported by the Netherlands Foundation for Chemical Research (NWO/CW) with financial aid from the Netherlands Organisation for Scientific Research (NWO).

ISBN 90-9017389-7

Omslagontwerp en realisatie:
Lidwien van der Horst, Afdeling Grafische Vormgeving en Fotografie, K.U. Nijmegen

"*The appropriate demeanor for a human is to feel lucky that he is alive and to humble himself in the face of the immensity of things and have a beer. Relax. Welcome to Earth. It's a little confusing at first. That's why you have to come back over and over again before you learn to really enjoy yourself.*
The sky is not falling."

Kary Mullis

CONTENTS

CHAPTER 1

Introduction

1.1 Sulfines, general characteristics

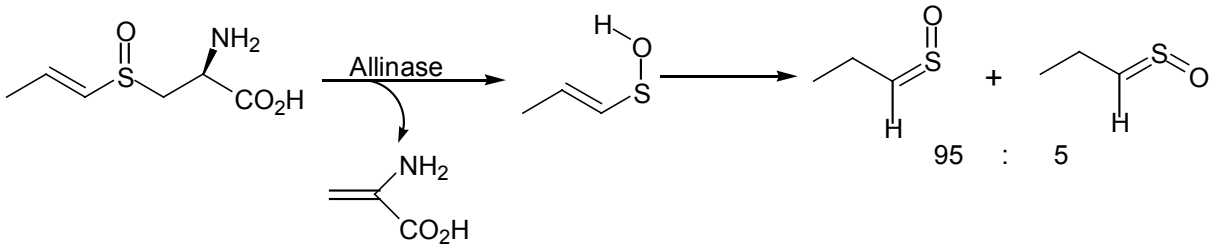
Sulfines **1a** are the *S*-mono oxides of thiocarbonyl compounds. The name sulfines was introduced by Sheppard and Dieckmann[1] to demonstrate the analogy with sulfenes (thiocarbonyl *S*,*S*-dioxides). These sulfur-centered heterocumulenes possess a non-linear structure as expected for molecules with the general structure X-Y-Z and 18 valence electrons.[2] Measurements of the dipole moments,[3] microwave spectroscopy,[4] ^{1}H-NMR[3c,5] studies and X-ray[6] structure determinations confirmed the non-linearity of sulfines. Recently, magnetic properties[7], vibrational frequencies[8] and ionization energies[9] of the parent sulfine were determined by spectroscopic methods. A theoretical study has been reported on the electronic structure, electronically excited states and UV-VIS absorptions of a number of aliphatic and aromatic sulfines.[10] The results suggested structure **1b** to be the predominant one in all cases. In spite of this, in the thesis the structure of sulfines is drawn as shown in **1a** in order to be consistent with previous publications.

1a **1b**

Figure 1

Because of this non-linearity, sulfines with two different substituents at the carbon atom can exist as two geometrical isomers. Several examples of stable isomers are known.[11] Geometrical isomerisation is possible by light[12], heating[3a,b], electrochemical procedures[13] or treatment with base[14,64]. Calculations of the charge distribution have been carried out for differently substituted sulfines. The charge on oxygen and sulfur of the parent sulfine (figure 1,R^1=R^2=H) and some mono- and dihalogen derivatives showed little variation. However, the electron density at the sulfine carbon differs greatly for different substituents.[15] As a consequence the stability of sulfines is strongly influenced by their substituents. In general, sulfines with aromatic substituents are more stable than those with aliphatic substituents. Electron-withdrawing substituents decrease the stability, whereas electron-donating substituents have a stabilizing effect.[11]

The principle lachrymatory factor in onions was shown to be *Z*-ethylsulfine, formed by the enzymatic degradation of *trans*-(+)-*S*-(1-propenyl)-*L*-cysteine *S*-oxide by allinase (Scheme 1). Allinase is activated when the onions is damaged (cutting), the initially formed 1-propenesulfenic acid tautomerises to *Z*-ethylsulfine.[16]

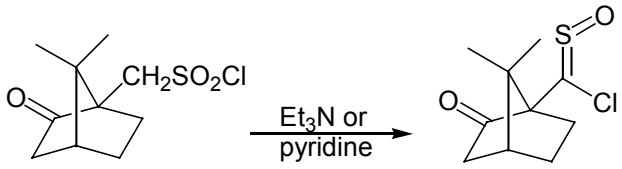


Scheme 1

1.2 Synthesis of sulfines

In this section a brief overview of the most versatile methods for the preparation of sulfines will be given with emphasis on those methods that will be used in the chapters 2-4.

Although Staudinger reported attempts to prepare sulfines,[17] the first stable sulfine was obtained by Wedekind in 1928 by treatment of camphor-10-sulfonyl chloride with pyridine or triethylamine (Scheme 2).[18]

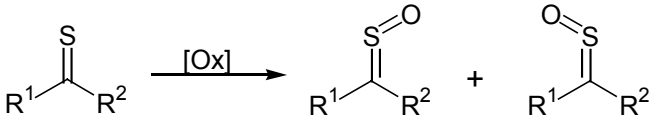


Scheme 2

Definite proof of this structure was given many years later by King and Durst by spectroscopic evidence[19] and in 1986 by the Nijmegen group by an X-ray crystal structure.[6h]

1.2.1 Oxidation of thiocarbonyl compounds

The first general method for the preparation of several different types of sulfines is the oxidation of thiocarbonyl compounds (Scheme 3).

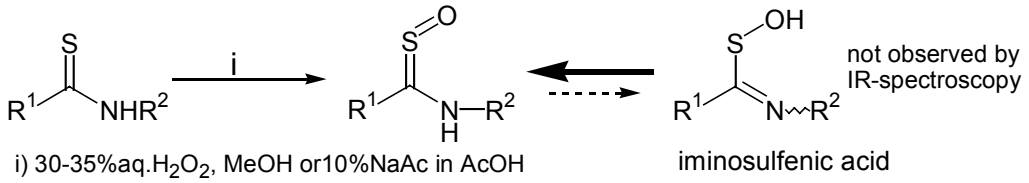


Scheme 3

Although used already in 1938 (see below), only since the sixties thiocarbonyl oxidation received real attention. Since then a great variety of thiocarbonyl derivatives has been transformed into the corresponding *S*-oxides, examples include aromatic- and non-enethiolizable aliphatic thiones[20], thioamides[21,33,34] , thiophosgene[22], thioacyl silanes[23], trithiocarbonates[24], thioacyl chlorides[25] , dithiocarboxylic esters[3c,24d,26], thiono esters[27] and xanthates.[28] Oxidation reagents that have been applied include hydrogen peroxide (thioamides, see below), peroxycarboxylic acids[11,26d,27,29], (camphorsulfonyl)-oxaziridine[30], and dimethyl dioxirane[31]. Recently, also trimethyloxyrehnium was employed as catalyst in the hydrogen peroxide oxidation of several thiobenzophenones.[32]

As aminosulfines are the subject of research in chapter 2, some more details about their oxidative preparation will be given. These sulfines are formed by *S*-mono-oxidation of thioamides and constitute a class of sulfines with different characteristics when compared to

other sulfines. The first example of an aminosulfine was reported by Kitamura as early as 1938, who however assumed to have prepared the tautomeric iminosulfenic acid (Scheme 4).[33] This tautomeric form could not be confirmed by spectroscopic studies.[34e,f]



Scheme 4

In the sixties and seventies Walter and coworkers studied the synthesis and physical properties of these aminosulfines in great detail.[34] The stability of aminosulfines was shown to decrease going from primary to tertiary derivatives. This can be attributed to the ability of primary- and secondary aminosulfines to form a hydrogen bond between the sulfine-oxygen and the proton on the nitrogen atom, tertiary derivatives obviously lack this possibility. Because of this hydrogen bonding, primary and secondary aminosulfines exist exclusively in the *Z*-form.[34] Also the nature of the substituents R^1 and R^2 (Figure 2) has a strong influence on the stability. As with other sulfines, electron-withdrawing groups (either R^1 or R^2) reduce the stability, while electron-releasing groups and aromatic substituents enhance the stability.[34c]

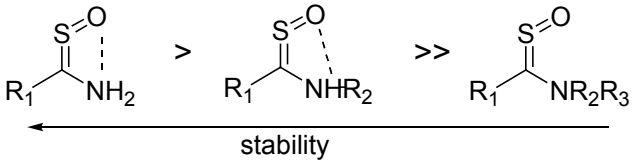


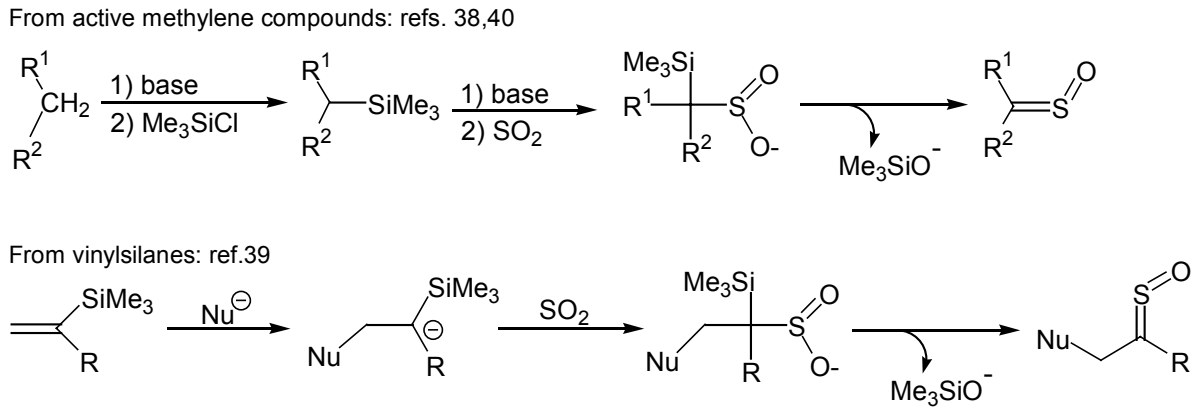
Figure 2

Oxidation of primary and secondary thioamides is usually carried out with aqueous hydrogen peroxide in methanol or DMF. Tertiary aminosulfines were very difficult to prepare in this way, over-oxidation and the low stability of these sulfines being the main problems.[34] The fact that aminosulfines form colored complexes with aqueous iron(III) chloride was used as an indication for their formation, even when isolation was not successful.[34] Further studies by Walter *et al.* showed that a buffer system of 10 % sodium acetate in acetic acid increases the rate of mono-oxidation while it slows down the second oxidation to the aminosulfenes (thioamide *S*,*S*-dioxides), which are highly unstable and immediately decompose.[34] Using this buffer system, a number of tertiary aminosulfines was prepared and isolated.[34e] Later, Lenz *et al.* used this procedure for the preparation of several secondary aminosulfines.[35] (See also chapter 2 of this thesis, where the preparation of a number of new derivatives is described, using this method.)
Finally, it should be noted that several *S*-oxides of known thioamides were identified as metabolites of the latter and are believed to be amongst the actual carcinogenic metabolites of thioamides.[36]
For reactions of aminosulfines, see section 1.3 and chapter 2.

1.2.2 Alkylidenation of sulfur dioxide

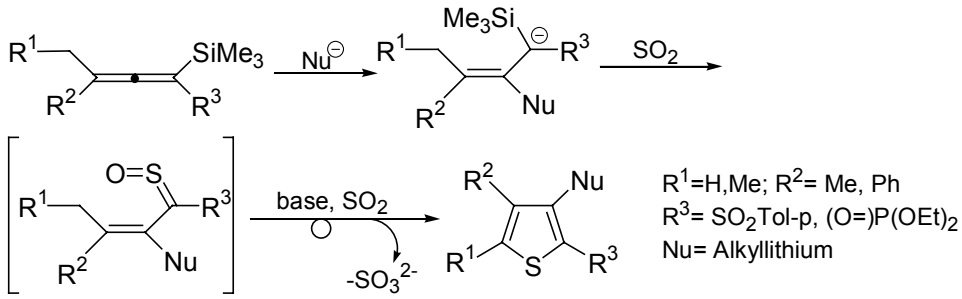
Sulfines can in principle be regarded as the alkylidene derivatives of sulfur dioxide and it was first shown by Van der Leij *et al.* that a modified Peterson reaction[37] of α-silyl carbanions with sulfur dioxide indeed constitutes a versatile route to sulfines. This method is of special

interest for those sulfines that cannot be prepared by oxidation of thiocarbonyl compounds.[38] The α-silyl carbanions can be prepared by silylation of active methylene compounds[38,40] or by nucleophilic addition to vinyl silanes[39] (Scheme 5).



Scheme 5

Later work by Hermans and Van der Linden further broadened the scope of this method.[40] When allenylsilanes were used instead of vinylsilanes, the corresponding α,β-unsaturated sulfines underwent a sulfur dioxide mediated ring-closure to yield some new 2-sulfonyl- and 2-phosphonate substituted thiophenes (scheme 6).[40b,41,42]

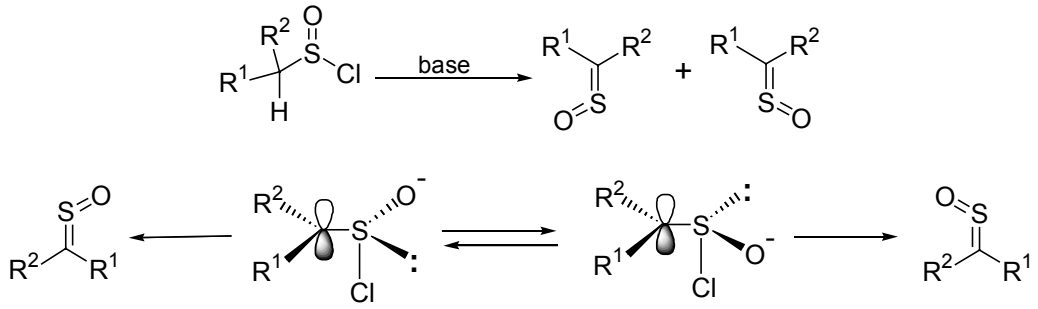


Scheme 6

As a second option the Wittig-alkylidenation could be applied for sulfur dioxide also leading to sulfines, although the scope of this procedure was limited.[38b, 43]

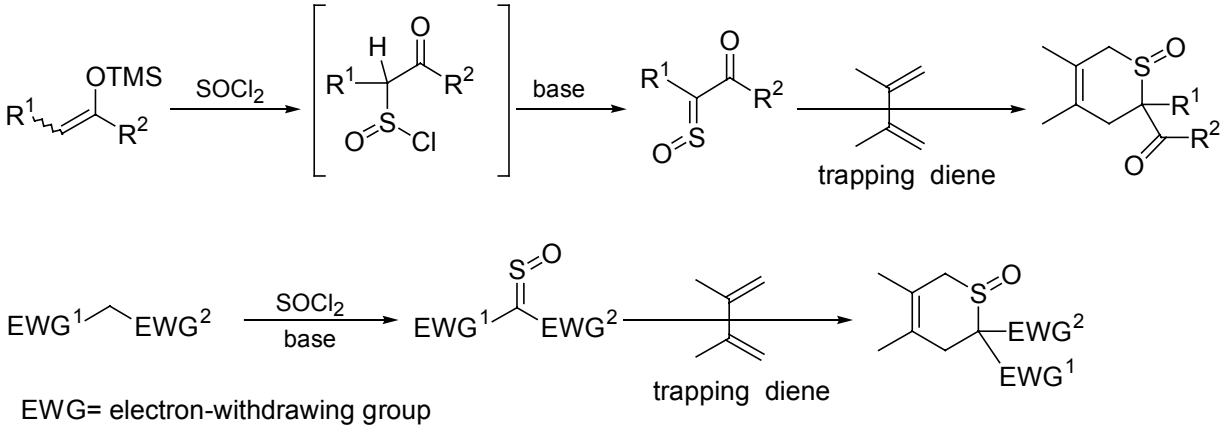
1.2.3 Dehydrochlorination of sulfinyl chlorides

One of the first routes to stable sulfines constitutes the dehydrochlorination of sulfinyl chlorides (scheme 7).[1,16a,b,44] The elimination of hydrogen chloride also provided access to aliphatic sulfines, which were hardly accessible by oxidation of the corresponding thiones. The main drawback of the procedure is the limited number of available β-sulfinyl chlorides, combined with their limited stabilities. The finding that reactive β-sulfinyl chlorides are formed by the reaction of silyl enol ethers or active methylene compounds with thionyl chloride can be regarded as a major leap forward in sulfine synthesis (scheme 8).[35a,45,46,47,48] These sulfinyl chlorides eliminate hydrogen chloride either spontaneously or upon treatment with base, affording α-oxo sulfines. Being quite sensitive towards reductive hydrolysis (although some stable derivatives have been prepared), these sulfines were usually trapped by Diels-Alder reaction with 1,3-butadienes giving rise to



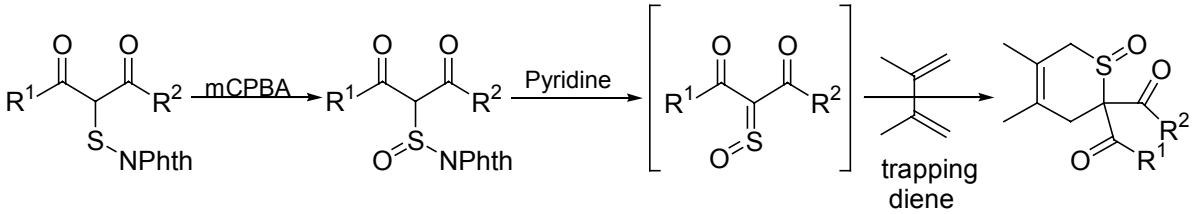
Scheme 7

numerous new thiopyran derivatives (see section 1.3).[35a,45-47] Recently, work by Damen in the Nijmegen group showed that by a careful choice of reaction conditions (solvent, base, temperature, addition of reagents) a clean formation of sulfines can be accomplished, allowing the isolation of several α-oxosulfines that previously were believed to be too unstable.[49,50] Chapter 3 of this thesis deals with some new examples of this method.



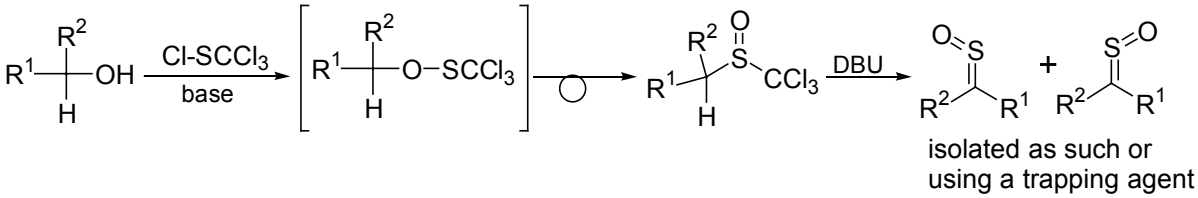
Scheme 8

In the past decade also 1,2-eliminations from other β-sulfinyl derivatives have been developed as versatile approaches to various types of sulfines. For example, Capozzi and Menichetti used *N*-sulfinyl phthalimides as precursors for the synthesis of α-oxo- and α,α'-dioxo-sulfines which were trapped e.g. with a 1,3-diene (Scheme 9).[51]



Scheme 9

Bravermann *et al.* reported the base-induced β-elimination of chloroform from trichloromethyl sulfoxides as a convenient approach to α,β-unsaturated mono- and disubstituted sulfines (Scheme 10).[52]



Scheme 10

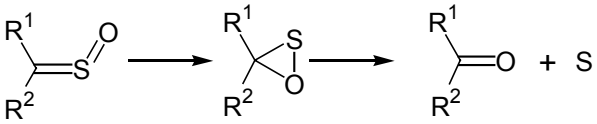
Another recent example involves the thermal elimination reaction of hetero-aromatically substituted sulfoxides.[53]

1.3 Reactions of sulfines

The reactions of sulfines have been studied in detail for several decades now in the Nijmegen- and other groups and (recent) literature reviews provide a good overview.[11,29,54] A brief overview of the most important reactions with some illustrative examples is given below.

1.3.1 Degradation reactions

The stability of sulfines ranges from stable, crystalline solids to representatives that can only be formed *in situ* and be isolated as trapping products. Many sulfines are known to decompose thermally and under photolytic conditions via an oxathiirane intermediate to form ketones and elemental sulfur (Scheme 11).[11,55]

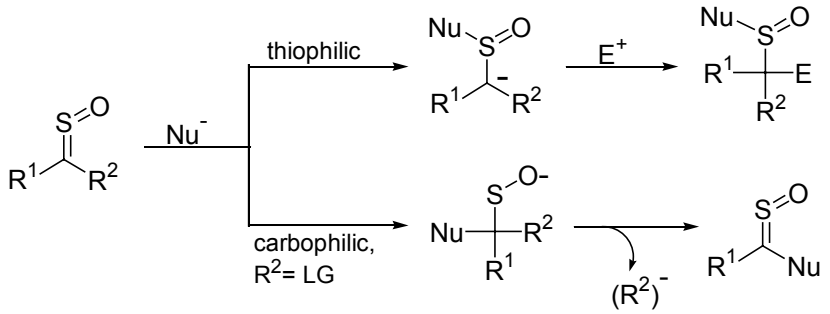


Scheme 11

Sulfines are also sensitive to hydrolytic conditions, especially acid-catalysed hydrolysis. Depending upon the type of sulfine, the hydrolysis products are either ketones (from dialkyl-, alkyl/aryl or diaryl sulfines) or the corresponding methylene compounds (sulfines with electron-withdrawing substituents).[11, 56] The latter reaction is referred to as reductive hydrolysis.

1.3.2 Reactions with nucleophilic reagents

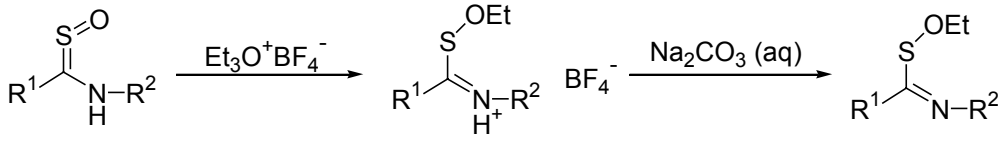
Sulfines can react with nucleophiles to give either thiophilic- or carbophilic addition products [57], the former being the most common ones. Especially the addition of alkyllithiums has received much attention, giving mostly sulfoxides by a thiophilic addition reaction (Scheme12).[11,55a,b,58,59] A carbophilic reaction is only observed when one of the substituents at carbon is a good leaving group, allowing an addition-elimination reaction to take place (Scheme 12).[57]



Scheme 12

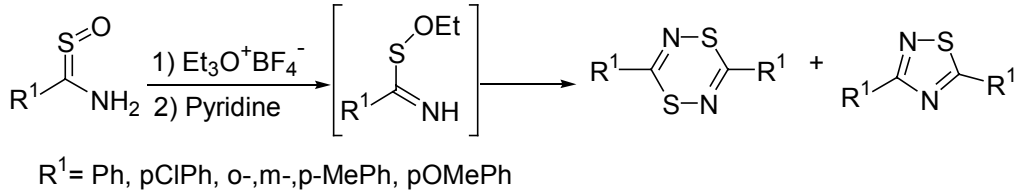
1.3.3 Reactions with electrophilic reagents

Diphenylsulfine[60] and mesityl(methylthio)sulfine[61] were shown to give *O*-alkylation by treatment with Meerwein's reagent. The *O*-alkylation of aminosulfines with Meerwein's reagent was studied by Lenz[35]. The initially formed iminium salts could be deprotonated to yield the corresponding isolable iminosulfenates (Scheme 13).



Scheme 13

These iminosulfenates reacted with amines to result in the formation of α-iminosulfenamides. When R^2=H, treatment of the iminium salt with pyridine led to the formation of 1,4,2,5-dithiadiazines and in some cases also to 1,2,4-thiadiazoles (Scheme 14).[35a,c]

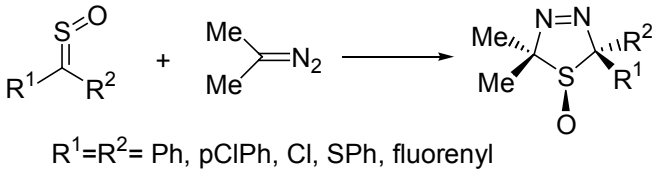


Scheme 14

The reaction of aminosulfines with trialkylsilyl triflates and use of the thus formed *O*-silyl α-iminosulfenates is the subject of chapter 2 of this thesis.

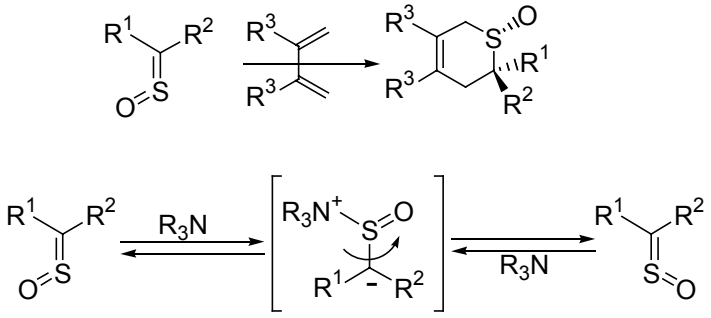
1.3.4 Cycloaddition reactions

Several examples of sulfines reacting as 1,3-dipolarophiles have been reported. A typical example is shown in Scheme 15.[62,11]



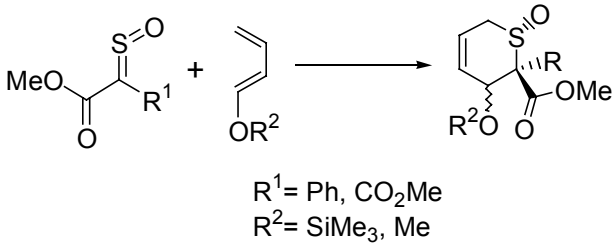
Scheme 15

The Diels-Alder reaction of sulfines with 1,3-dienes has been studied in great detail over the years. Numerous sulfines and 1,3-dienes were successfully applied, providing access to a large variety of 3,6-dihydro-2*H*-thiopyran *S*-oxides.[11, 35, 40a, 45-52, 68, 69, 63] Sulfines bearing one or two electron-withdrawing groups are the most reactive ones, the HOMO's of electron-rich dienes showing strong interaction with the LUMO's of these electron-poor dienophiles. As the cycloaddition is a concerted process, the stereochemistry of the sulfine is usually retained in the cycloadduct (Scheme 16, top line). In reported cases were *E*/*Z*-mixtures of cycloadducts were obtained, this could be explained by a base-mediated isomerization of the sulfine prior to the cycloaddition reaction (Scheme, 16 bottom line). It was also found that for mono-substituted sulfines, the *E*-isomer is far more reactive in the [4+2]-cycloaddition reaction than the *Z*-isomer.[52,64] Results from a recent theoretical study are in agreement with these findings.[65]



Scheme 16

Especially sulfines with electron-withdrawing substituents (e.g. α-oxo sulfines) are reactive dienophiles in the reaction with common electron-rich dienes, such as 2,3-dimethyl-1,3-butadiene or 1-oxy-substituted 1,3-dienes. When 1-methoxy- and 1-silyloxy-1,3-butadiene were applied as dienes, regioselective formation of 3-oxy-substituted 3,6-dihydro-2*H*-thiopyrans was observed[49] (Scheme 17). This implies that the largest LUMO-coefficient of α-oxo sulfines is on the sulfur atom and the largest HOMO-coefficient of the 1-methoxy- and 1-trimethylsilyoxy dienes resides on C-4. This is in contrast with the 6-substituted cycloadducts obtained for carbonyl dienophiles.[66]

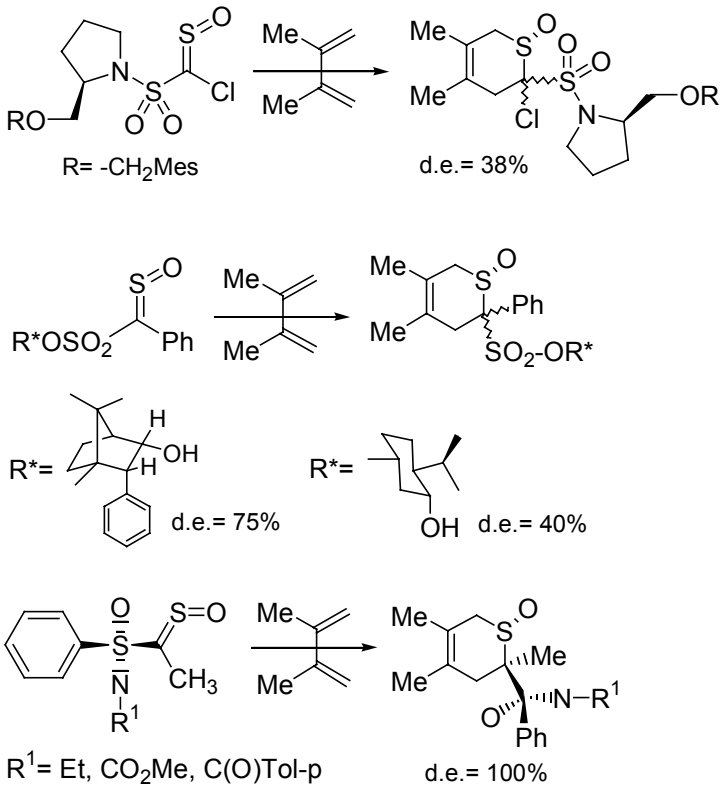


Scheme 17

With different substituents R^2 on the dienes (carbonate and carbamate derivatives), also the other regioisomers were obtained as minor products.[49]

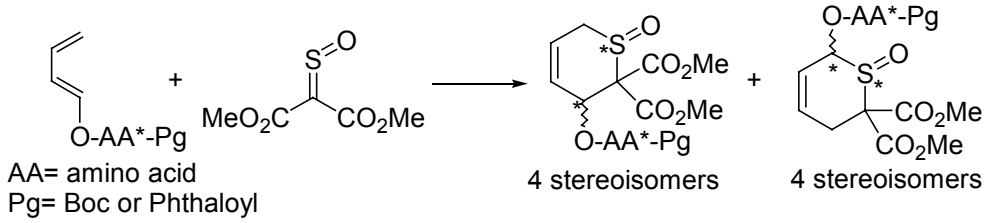
When the Diels-Alder cycloadducts of α-oxo sulfines contain a proton on C-2, acid- (during chromatography over silica gel) or base-induced epimerisation at the sulfine unit may occur.[35a,49,67] Additional examples of base-induced C-2-epimerisation reactions will be reported in chapter 3 of this thesis.

The Diels-Alder reaction also has been performed with chiral sulfines and chiral dienes with the aim to achieve chiral induction. Chiral auxiliaries as sulfine substituents were derived from proline[38e, 68] and terpenols.[40a] Only moderate to poor d.e's were observed, the use of chiral α-sulfoximido sulfines resulted in a completely diastereoselective formation of 3,6-dihydrothiopyran *S*-oxides.[38c, f ,g] The best results are depicted in scheme 18.



Scheme 18

Damen has employed chiral dienes, including 'Trost' diene (derived from mandelic acid) and several new 1-acyloxydienes derived from α-amino acids (phenylglycine, proline, alanine, phenylalanine and indoline-2-carboxylic acid).[49]



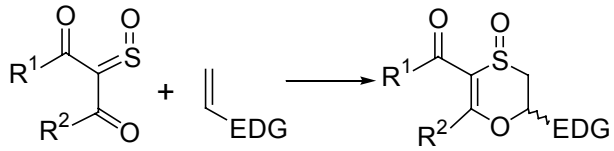
Scheme 19

Cycloaddition reactiones of these chiral dienes with *N*-ethyl maleimide was regioselective and the obtained *endo*-isomers showed moderate d.e-values (up to 43%). However, with the α,α-dioxo sulfine derived from dimethyl malonate, a mixture of *exo*/*endo*-, regio- and diastereomers was obtained, although the overall yields of cycloadducts were good.

Finally, attempts to induce chirality transfer by using a number of known chiral Lewis acid catalysts have been undertaken, but without success so far.[49]

1.3.5 α-Oxo sulfines as heterodienes

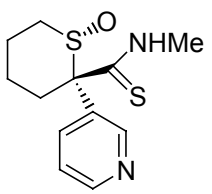
Apart from being dienophiles, α-oxo sulfines can also serve as 1,3-heterodienes in reverse electron-demand Diels-Alder reactions with electron-rich alkenes. Early examples from the Nijmegen laboratory were reported by Lenz[35a] and Rewinkel[46] (Scheme 20). Recently, Capozzi and Menichetti *et al.* elegantly extended the scope of these cycloadditions.[69]



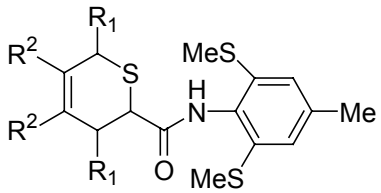
Scheme 20

1.4 Aim and outline of the thesis

After four fruitful decades of sulfine chemistry one may wonder what remains to be investigated in this field. The development of several different synthetic methodologies allows the preparation of various types of sulfines. The chemical behaviour towards several types of reagents was studied to quite an extent. Especially, the [4+2]-cycloaddition with 1,3-butadienes has yielded dozens of new dihydrothiopyran *S*-oxides which themselves have been transformed into a variety of (hetero)cyclic compounds. Despite of this, some areas of sulfine chemistry have received less attention, the synthetic applications of aminosulfines being an example. In addition, a number of reports on biologically active (dihydro)thiopyrans have appeared during the past decade[70], amongst these were publications on potassium channel openers[70a,71] (e.g. Aprikalim, a potential candidate as an anti-hypertensive and anti-anginal agent) and inhibitors of the enzyme Acyl-CoA:cholesterol acyl transferase (ACAT) that could proof useful in slowing down, or even in reversing, the artherosclerotic process.[72] (Figure 3).



Aprikalim



R^1= C_1-C_8alkyl; R^2=H
or R^2= C_1-C_8alkyl; R^1=H

Figure 3

Also a growing interest in thiosugars and thionucleosides as interesting sulfur-analogs could be noticed.[73]
Regarding these developments, a synthetic study on the application of sulfines in the synthesis of some heterocyclic analogs of biologically active compounds would be of interest.

The main goals of the work in this thesis were the following:

- Study of the synthetic potential of aminosulfines for the preparation of new β-lactam derivatives. (Chapter 2)
- The synthesis and use of new α-oxo sulfines in the preparation of some structural analogs of Aprikalim and ACAT-inhibitors. (Chapter 3)
- Study of the functionalization of the olefinic bond of 3,6-dihydro-2H-thiopyrans by means of some cohalogenation procedures. (Chapter 4)

In chapter 2 the synthesis of some new 4-silylsulfenate substituted β-lactams by a one-pot procedure from aminosulfines via silyl esters of iminosulfenic acids is described. Chapter 3 deals with the preparation of 2-carboxamido- and 2-thiocarboxamido-thiopyran *S*-oxides, respectively from thioloester- and dithioester-derived α-oxo sulfines and α-thioxo sulfines. In chapter 4 the reaction of some dihydrothiopyrans with *N*-iodo-succinimide and carboxylic acids leading to new functionalized tetrahydrothiophenes is described.

1.5 References

1] W. A. Sheppard and J. Dieckmann, *J. Am. Chem. Soc.* **86**, 1891 (1964).

2] A. D. Walsh, *J. Chem. Soc.* 2266 (1953).

3] **a**] J. F. King and T. Durst, *J. Am. Chem. Soc.* **85**, 2676 (1963).

b] J. F. King and T. Durst, *Can. J. Chem.* **44**, 819 (1966).

c] B. Zwanenburg, L. Thijs and J. Strating, *Recl. Trav. Chim. Pays-Bas* **90**, 614 (1971).

d] A. Tangerman and B. Zwanenburg, *J. Chem. Soc. Perkin Trans II*, 1413 (1974).

4] E. Block, R.E. Penn, R. J. Olsen and P.F. Sherwin, *J. Am. Chem. Soc.* **98**, 1264 (1976).

5] B. Zwanenburg and J. Tangerman, *Tetrahedron* **27**, 1731 (1971).

6] **a**] Th.W.A. Hummelink, *J. Cryst. Mol. Struct.* **4**, 87 (1974).

b] Th.W.A. Hummelink, *Cryst. Struct. Commun.* **4**, 441 (1975).

c] Th.W.A. Hummelink, *Cryst. Struct. Commun.* **5**, 169 (1976).

d] T.C. Britton, T.J. Lobl and C.G. Chidester, *J. Org. Chem.* **49**, 4773 (1984).

e] D. St.C. Black, C.D. Fallon, B.M. Gatehouse and J.D. Wishart, *Austr. J. Chem.* **37**, 777 (1984).

f] S. Kosack, G. Himbert and G. Maas, *Angew. Chem.* **98**, 443 (1986).

g] R.J.F. Jans, G. van Koten, R.R. Andréa, K. Vreize, A.L. Spek, B. Kojic-Prodic and J.L. de Boer, *Recl. Trav. Chim. Pays-Bas* **105**, 317 (1986).

h] P.T. Beurskens, R.C. Haltiwanger, P.A.T.W. Porskamp and B. Zwanenburg, *J. Cryst. Spectrosc. Res.* **16**, 71 (1986).

7] A. Klesing and D.H. Sutter, *J. Mol. Struct*., **352/353**, 357 (1995).

8] **a**] D.J. Clouthier and J.M. Vollmer, *J. Mol. Struct*., **354**, 49 (1995).

b] E. Suzuki and F. Watari, *Spectrochim. Acta* A, **51**, 779 (1995).

9] E.Block, H. Bock, S. Mohmand, P. Rosmus and B. Solouki, *Angew. Chem.* **88**, 389 (1976).

10] M. Petiau, J. Fabian and P. Rosmus, *Phys. Chem. Chem. Phys*. **1**, 5547(1999).

11] B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **101**, 1 (1982) and references cited therein.

12] **a**] A.G. Schulz and R.H. Schlessinger, *J. Chem. Soc. Chem. Commun.* 1483 (1969).

b] A.G. Schulz and R.H. Schlessinger, *Tetrahedron Lett.* **17** 4513 (1976).

13] K. Nakamura, Y. Shizume, T. Sugiyama, A. Ohno and S. Oka, *Phosphorous and Sulfur* **16**, 153 (1983).

14] **a**] B. F. Bonini, G. Maccagnani, G. Mazzanti, L. Thijs, G.E. Veenstra and B. Zwanenburg, *J.Chem. Soc. Perkin Trans.* I, 1218 (1978).

b] P.A.T.W. Porskamp, R. Haltiwanger and B. Zwanenburg, *Tetrahedron Lett.* **24**, 2035 (1983).

15] **a**] J. van Lierop, A. van der Avoird and B. Zwanenburg, *Tetrahedron* **33**, 539 (1977).

b] S.N. Lyashchuk, N.V. Vasileva and Y.G. Skrypnik, *Zh. Org. Khim.* **32**, 509 (1996).

16] **a**] M.H. Brodnitz and J.V. Pascale, *J. Agr. Food. Chem.* **19**, 269 (1971).

b] E. Block, L.K. Revelle and A.A. Bazzi, *Tetrahedron Lett.* **21** 1277 (1980).

c] E. Block, *Angew. Chem.* **104**, 1158 (1992).

d] E. Block, J.Z. Gillies, A.A. Bazzi, D. Putman, L.K. Revelle, D. Wang and X. Zhang, *J. Am. Chem. Soc.* **118**, 7492 (1996).

17] **a**] H. Staudinger and F. Pfenniger, *Ber. Dtsch. Chem. Ges.* **49**, 1941, (1916).

b] H. Staudinger and W. Braunholtz, *Helv. Chim. Acta* **4**, 847 (1921).

18] E. Wedekind, D. Schenk and R. Strüsser, *Ber. Dtsch. Chem. Ges.* **56**, 633 (1923).

19] J. F. King and T. Durst, *Tetrahedron Lett.* **4**, 585 (1963).

20] **a**] J. Strating, L. Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **86**, 577 (1967).

b] B. Zwanenburg, A. Wagenaar, T. Thijs and J. Strating, *J. Chem. Soc. Perkin I*, 73 (1973).

c] S. Ghersetti, L. Lunazzi, G. Maccagnani and A. Mangini, *J. Chem. Soc. Chem. Commun.* 834 (1969).

d] M.S. Raasch, *J.Org. Chem.* **44**, 632 (1979).

e] W. Kappert, W. Sander and C. Landgrafe, *Liebigs Ann./ Recueil* 2519 (1997).

f] N. Pelleoux-Leon, F. Minassian, J. Levillain, J.-L. Ripoll and Y. Vallée, *Tetrahedron Lett.* **39**, 4823 (1998).

21] **a**] T. Saito, A. Koide, Y. Kikuchi and S. Motoki, *Phosphorous and Sulfur* **17**, 153 (1983).

22] J. Strating, L. Thijs and B. Zwanenburg, *Tetrahedron Lett.* **10**, 4461 (1969).

23] **a**] B.F. Bonini, G. Mazzanti, P.Zani, G. Maccagnani, G. Barbaro, A. Battaglia and P. Giorgianni, *J. Chem. Soc. Chem. Commun.* 964 (1986).

b] B.F. Bonini, G. Mazzanti, P.Zani, G. Maccagnani, *J. Chem. Soc. Chem. Commun.* 365 (1988).

c] G. Barbaro, A. Battaglia and P. Giorgianni, B.F. Bonini, G. Maccagnani, P.Zani, *J. Org. Chem.* **55**, 3744 (1990).

24] **a**] E. Klingsberg, *J. Am. Chem. Soc.* **86**, 5290 (1964).

b] W.M. Doane, B.S. Shasha, C.R. Russel and C.E. Rist, *J. Org. Chem.* **30**, 3071 (1965).

c] T.J. Adley, A.K.M. Anisuzzaman and L.N. Owen, *J. Chem. Soc. C*, 807 (1967).

d] B. Zwanenburg, L. Thijs and J. Strating, *Tetrahedron Lett.* **8**, 3453 (1967).

e] H.C. Hansen, A. Senning and R.G. Hazell, *Tetrahedron* **41**, 5145 (1985).

f] C. Leriverend, P. Metzner, A. Capperucci and A. Degl'Innocenti, *Tetrahedron* **53**, 1323 (1997).

25] **a**] G.E. Veenstra, N.M. Bronold, J.F.M. Smits, A. Tangerman and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **96**, 139 (1977).

b] A. Capperucci, A. Degl'Ínnocenti, C. Levirend and P. Metzner, *J. Org. Chem.* **61**, 7174 (1996).

26] **a**] B. Zwanenburg, L. Thijs and J. Strating, *Tetrahedron Lett*. **9**, 2871 (1968).

b] G.E. Veenstra and B. Zwanenburg, *Tetrahedron* **34**, 1585 (1978).

c] B. Zwanenburg, H.J. G. Broxterman and J.B. van der Linden, *Phosphorus, Sulfur and Silicon* **95/96**, 405 (1994).

d] F. Cerreta, A.-M. Le Nocher, C. Leriverend, P. Metzner and T.N. Pham, *Bull. Soc. Chim. Fr.* **132**, 67 (1995).

27] M. Lemarié, P. Metzner and T.N. Pham, *Tetrahedron Lett.* **32**, 7411 (1991).

28] E. Marrière, D. Chevrie and P. Metzner, *J. Chem. Soc., Perkin Trans. I*, 2019 (1997).

29] B. Zwanenburg, *Phosphorus, Sulfur and Silicon* **43**, 1 (1989).

30] F.A. Davies, R. Thimma Reddy and M.C. Weismiller, *J. Am. Chem. Soc.* **111**, 5964 (1989).

31] **a**] H.J.F. Philipse, *Ph.D. Thesis*, University of Nijmegen, (2003).

b] R. Tripolt and E. Nachbaur, *Phosphorus, Sulfur and Silicon* **65**, 173 (1992).

32] R. Huang and J.H. Espenson, *J. Org. Chem.* **64**, 6935 (1999).

33] R. Kitamura*, J. Pharm. Soc. Jpn.* **58**, 246 (1938).

34] **a**] W. Walter and J. Curts, *Chem. Ber.* **93**, 1511 (1960).

b] W. Walter, J. Curts and H. Pawelzik, *Liebigs Ann. Chem.* **643**, 29 (1961).

c] W. Walter and K-D. Bode, *Liebigs Ann Chem.* **698**, 131 (1966).

d] W. Walter and G. Maerten, *ibid.* **712**, 46 (1968).

e] W. Walter and O.H. Bauer, *Liebigs Ann Chem.* 1584 (1976).

f] W. Walter and O.H. Bauer, *Liebigs Ann Chem.* 428 (1977).

g] W.Walter in *Organosulfur Chemistry*, M.J. Janssen (Ed.), Interscience Publ. 1967, Chapter 14 and references cited therein.

35] **a**] B.G. Lenz, *Ph.D. Thesis* University of Nijmegen, (1984).

b] B.G. Lenz and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **103**, 342 (1984).

c] B.G. Lenz and B. Zwanenburg,, *J. Chem. Soc. Chem. Comm.* 1386, (1984).

36] J. R. Cashman and R. P. Hanzlik, *J. Org. Chem*. **47**, 4645 (1982) and references therein.

37] D.J. Peterson, *J. Org. Chem.* **33**, 780 (1968).

38] **a**] M. van der Leij, P.A.T.W. Porskamp, B.H.M. Lammerink and B. Zwanenburg, *Tetrahedron Lett.* **19**, 811 (1978).

b] M. van der Leij, *Ph.D. Thesis,* University of Nijmegen, (1979).

c] P.A.T.W. Porskamp, M. van der Leij, B.H.M. Lammerink and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **102**, 400 (1983).

d] P.A.T.W. Porskamp, B.H.M. Lammerink and B. Zwanenburg, *J. Org. Chem.* **49**, 263 (1984).

e] L.A.G.M. van den Broek, P.A.T.W. Porskamp, R.C. Haltiwanger, B.H.M. Lammerink and B. Zwanenburg, *J. Org. Chem.* **49**, 1691 (1984).

f] P.A.T.W. Porskamp, R.C. Haltiwanger, B.H.M. Lammerink and B. Zwanenburg, *Tetrahedron Lett.* **24**, 2035 (1983).

g] P.A.T.W. Porskamp, *Ph.D. Thesis*, University of Nijmegen ,(1983).

39] **a**] M. van der Leij and B. Zwanenburg, *Tetrahedron Lett*., 3383 (1978).

b] P.A.T.W. Porskamp, A.M. van de Wijdeven and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **102**, 506 (1983).

40] **a**] P.A. Hermans, *Ph.D. Thesis*, University of Nijmegen, (1990).

b] J.B. van der Linden, *Ph.D. Thesis*, University of Nijmegen, (1994).

41] S. Braverman, P.F.T.M. van Asten, J.B. van der Linden and B. Zwanenburg, *Tetrahedron Lett*. **32**, 3867 (1991).

42] J.B. van der Linden, A.C.B. Lucassen and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **113**, 457 (1994).

43] B.Zwanenburg, C.G. Venier, P.A.T.W. Porskamp and M. van der Leij, *Tetrahedron Lett*. 807 (1978).

44] **a**] J. Strating, L.Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **83**, 631 (1964).

b] J. Buter and R.M. Kellogg, *J. Org. Chem.* **42**, 973 (1977).

c] L.A. Carpino and J.R. Williams*, J. Org. Chem*. **44**, 1177 (1979).

45] **a**] B.G. Lenz, H. Regeling and B. Zwanenburg, *Tetrahedron Lett*. **25**, 5947 (1984).
b] B.G. Lenz, H. Regeling, H.L.M. van Rozendaal and B. Zwanenburg, *J. Org. Chem.* **50**, 2930 (1985).
c] J.B.M. Rewinkel and B. Zwanenburg, *Recl.Trav. Chim. Pays-Bas* **109**, 190 (1990).

46] J.B.M. Rewinkel, *Ph.D. Thesis*, University of Nijmegen (1989).

47] R.C. De Laet, *Ph.D. Thesis*, University of Nijmegen (1995).

48] **a**] I.W.J. Still and F.J. Ablenas, *J. Chem. Soc., Chem Commun.* 524 (1985).
b] I.W.J. Still, *Phosphorus, Sulfur and Silicon* **58**, 129 (1991).
c] I.W.J. Still and D.K.T. Wilson, *Can. J. Chem.* **70**, 964 (1992).

49] T.J.G. Damen, *Ph.D. Thesis*, University of Nijmegen (2002).

50] T.J.G. Damen and B. Zwanenburg, *Phosphorus, Sulfur and Silicon* **153/154**, 119 (1999).

51] **a**] G. Capozzi, A. Corti, S. Menichetti and C. Nativi, *Phosphorus, Sulfur and Silicon* **120/121**, 317 (1997).
b] G. Capozzi, A. Corti, S. Menichetti and C. Nativi, *Tetrahedron Lett.* **38**, 5041 (1997).

52] **a**] S. Braverman, D. Grinstein and H.E. Gottlieb, *Tetrahedron Lett.* **35**, 953 (1994).
b] S. Braverman, D. Grinstein, *Phosphorus, Sulfur and Silicon* **95/96**, 321 (1994).
c] S. Braverman, D. Grinstein and H.E. Gottlieb, *Tetrahedron* **53**, 13933 (1997).
d] S. Braverman, D. Grinstein and H.E. Gottlieb, *J. Chem. Soc., Perkin Trans I*, 103 (1998).

53] H. Morita, M. Takeda, T. Yoshimura, T. Fujii, S. Ohno and C. Shimazaki, *J. Org. Chem*. **64**, 6730 (1999).

54] B. Zwanenburg, T.J.G. Damen, H.J.F. Philipse, R.C. De Laet and A.C.B. Lucassen, *Phosphorus, Sulfur and Silicon* **153/154**, 119 (1999).

55] **a**] A.G. Schultz and R.H. Schlessinger, *J. Chem. Soc. D*, 1483 (1969).
b] A.G. Schultz and R.H. Schlessinger, *Tetrahedron Lett.* **10**, 4513 (1969).
c] L. Carlsen, N. Harrit and A. Holm, *J. Chem. Soc., Perkin I*, 1404 (1976).
d] L. Carlsen, A. Holm, E. Kochi and B. Stilkerieg, *Acta Chem. Scand.* **B 31**, 679 (1977).

56] J. Strating, L. Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas **86***, 641 (1967).

57] **a**] J. Strating, L. Thijs and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **89**, 687 (1970).
b] J.A. Loontjes, M. van der Leij and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **99**, 39 (1980).
c] L. Carlsen, A. Holm, J.P. Snyder, E. Kochi and B. Stilkerieg, *Tetrahedron* **33**, 2231 (1977).

58] **a**] J.B.M. Rewinkel, P.A.T.W. Porskamp and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **107**, 563, (1988).
b] C. Alayrac, F. Cerreta, I. Chapron, F. Corbin and P. Metzner, *Tetrahedron Lett.* **37**, 4507 (1996).
c] P. Metzner, *Pure & Appl. Chem.* **68**, 863 (1996).

59] **a**] A.Capperucci, A. Degl'Innocenti, C. Leriverend and P. Metzner, *J. Org. Chem.* **61**, 7174 (1996).
b] F. Cerreta, Leriverend and P. Metzner, *Tetrahedron Lett.* **34**, 6741 (1993).
c] J.-B. Baudin, M.-G. Commenil, S.A. Julia, R. Lorne and O. Ruel, *Bull. Soc. Chim. Fr.* **133**, 1127 (1996).

60] L. Carlsen and A. Holm, *Acta Chem. Scand.* **B30**, 277 (1976).

61] M.A. Pérez and G. Kresze, *Justus Liebigs Ann. Chem.* 1505 (1981).

62] **a**] E. Block, A.A. Bazzi and I.K. Revelle, *J. Am. Chem. Soc.* **102**, 2490 (1980).
b] R. Huisgen, G. Mloston, K. Polborn, R. Sustmann and W. Sicking, *Liebigs Ann./ Recueil* 179 (1997).
c] W. Adam and S. Weinkötz, *J. Am. Chem. Soc.* **120**, 4861 (1998).

63] B. Zwanenburg, L. Thijs, J.B. Broens and J. Strating, *Recl. Trav. Chim. Pays-Bas* **91**, 443 (1972).

64] B.F. Bonini, G. Maccagnani, P. Zani, G. Barbaro, A. Battaglia and P. Giorgianni, *J. Org. Chem.* **56**, 2512 (1991).

65] M. Manoharan and P. Venuvanalingam, *J. Phys. Org. Chem.* **10**, 768 (1997).

66] **a**] S.M. Weinreb and R.R. Staib, *Tetrahedron* **38**, 3087 (1982).

b] L.F. Tietze and G. Kettschau, *Topics in Current Chemistry* **189**, 1 (1997).

c] R. Sustmann, S. Tappanchai and H. Bandmann, *J. Am. Chem. Soc.* **118**, 12555 (1996).

d] Y. Tamaru, H. Harayama, H. Sakata, H. Konishi, K. Fugami, S. Tanaka, T. Okajima and Y. Fukazawa, *Lieibigs Ann./Recueil* 907 (1997).

67] P. Kiełbasiński, B. Zwanenburg, T.J.G. Damen, M.W. Wieczorek, W.R. Majzner and G.D. Bujacz, *Eur. J. Org. Chem.* 2573 (1999).

68] P.A.T.W. Porskamp, *Ph.D. Thesis*, University of Nijmegen (1983).

69] **a**] G. Capozzi, P. Fratini, S. Menichett and C. Nativi, *Tetrahedron Lett.* **36**, 5089, (1995).

b] G. Capozzi, R.W. Franck, M. Mattioli, S. Menichetti, C. Nativi and G. Valle, *J. Org. Chem*, **60**, 6416 (1995).

c] G. Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron* **52**, 12233 (1996).

d] G. Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron* **52**, 12247 (1996).

e] G. Capozzi, S. Menichetti, C. Nativi and C. Vergamini, *Synthesis* 915 (1998).

f] G. Capozzi, S. Menichetti, C. Nativi and A. Provenzani, *Eur. J. Org. Chem*. 3721 (2000).

70] **a**] I.L. Pinto, D.R. Buckle, H.K. Rami and D.G. Smith, *Tetrahedron Lett.* **33**, 7597 (1992).

b] B. Heuzé, R. Gasparova, M. Heras and S. Masson, *Tetrahedron Lett.* **41**, 7327 (2000).

c] J. Prabhakaran, H. Lhermitte, J. Das, T.K. Sasi-Kumar and D.S. Grierson, *Synlett* **5**, 658 (2000).

d] E. Fritz-Langhals, *Angew. Chem.* **105**, 5, 785 (1993).

e] Unterhalt, B. Krebs, M. Laege and B. Nocon, *Arch. Pharm.* **327**, 12, 799 (1994).

f] X.-F. Yang and C.-J. Li, *Tetrahedron Lett.* **41**, 1321 (2000).

71] T.J. Brown, R.F. Chapman, D.C. Cook, T.W. Hart, I.M. McLay, R. Jordan, J.S. Mason, M.N. Palfreyman, R.G.A. Walsh, M.T. Withnall, J.-C. Aloup, D.D. Farge, C. James and S. Mondot, *J. Med. Chem*. **35**, 3613 (1992) and references cited therein.

72] R.G. Wilde, J.T. Billheimer, S.J. Germain, E.A. Hausner, P.C. Meunier, D.A. Munzer, J.K. Stoltenborg, P.J. Gillies, D.L. Burcham, S.-M. Huang, J.D. Klaczkiewicz, S.S. Ko and R.R. Wexler, *Bioorg & Med. Chem.* **4**, 1493 (1996).

73] **a**] N.A.L Al-Masoudi and N.A. Hughes, *J. Chem. Soc. Perkin Trans. I*, 695 (1986).

b] N.A. Hughes and C.J. Woody, *J. Chem. Soc. Perkin Trans. I*, 2061 (1987).

c] M. Baudry, V. Barberousse, G. Descotes, R. Faure, J. Pires and J.-P. Praly, *Tetrahedron* **54**, 7431 and 7447 (1998).

d] H.J. Altenbach and G.F. Merhof, *Tetrahedron Asymmetry* **7**, 3087 (1996).

e] J.A. Miller, A.W. Pugh and M. Ullah , *Tetrahedron Lett.* **41**, 3265 (2000) and references cited therein.

CHAPTER 2

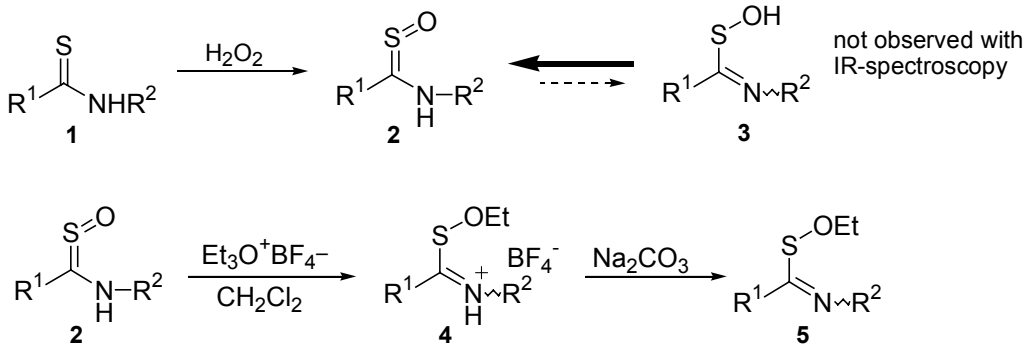
Silyl esters of iminosulfenic acids as intermediates in the synthesis of new 4-*O*-silyl sulfenate substituted β-lactams

A one-pot synthesis of β-lactams from aminosulfines

2.1 Introduction

2.1.1 Aminosulfines

The preparation of *S*-mono-oxide analogues **2** of thioamides, known as thioamide-*S*-oxides or aminosulfines has been studied in detail by Walter and coworkers[1]. They prepared a large number the *S*-oxides by oxidation of the corresponding thioamides with aqueous hydrogen peroxide (Scheme 1).[1] The general stability pattern of these compounds showed a decrease in going from primary to tertiary amide derivatives.[1] While primary and secondary aminosulfines are often stable, crystalline solids[1,2], the tertiary amide congeners are far less stable; most likely because they lack the possibility to form a hydrogen bond between the sulfine oxygen and an amide proton.[3] The stability is also negatively influenced by electron-withdrawing substituents on either the nitrogen atom or alpha to the thiocarbonyl moiety.[1] Thioformamide derived aminosulfines showed a limited stability, although thioformanilide *S*-oxide was isolated in 48% yield.[1] Walter and coworkers reported that the iminosulfenic acid form **3** of aminosulfines is not detectable in the IR-spectra of thioamide derived aminosulfines.[4] They mentioned one example of *O*-methylation of a secondary aminosulfine, in all other cases *N*-methylation was observed.[5,6] Later work by Lenz and Zwanenburg[7] revealed that the *O*-ethyl esters of iminosulfenic acids **5** can be obtained by treatment of primary and secondary aminosulfines with triethyloxonium tetrafluoroborate (Meerwein's reagent) followed by treatment of the formed iminium salts **4** with aqueous sodium carbonate (Scheme 1). A number of these derivatives has been isolated and were found to be remarkably stable compounds.



R_1= cinnamyl, Me, aryl; R_2= H, aryl

Scheme 1

Because of the commercial availability of a large variety of silylating agents with varying reactivities and different levels of steric stabilization it was a feasible option to investigate the synthesis of *O*-silyl esters of iminosulfenic acids. The resulting silyl esters **6** can be regarded as bifunctional intermediates with possibilities for further synthetic elaboration (Figure 1).

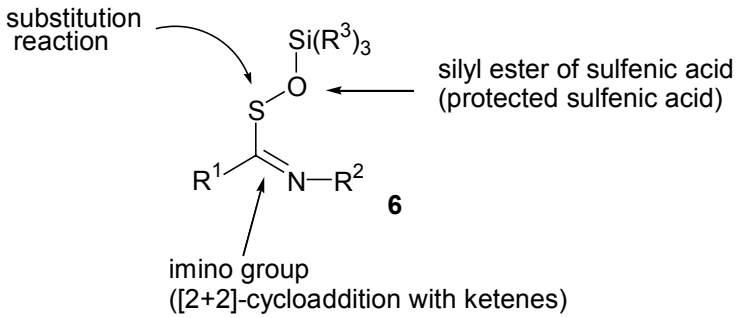
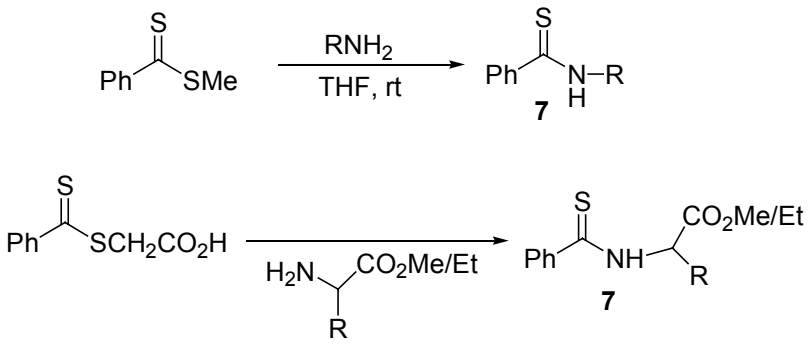


Figure 1

Especially the [2+2]-cycloaddition of these iminosulfenic acid derivatives **6** with ketenes leading to β-lactams having a sulfenic acid silyl ester on the C-4 position is attractive. This silyl sulfenate unit can be envisaged as an appendage for subsequent inter- or intramolecular reactions.[17]

2.2 Synthesis of new aminosulfines

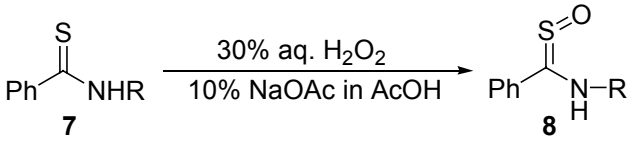
The thioamides **7** were prepared either by reaction of the amine with methyl dithiobenzoate in THF at room temperature (**7a-e**) (liberated methanethiol was removed by a slow stream of nitrogen) or by reaction of the amino acid esters with *S*-thiobenzoyl-thioglycolic acid (**7f-h**).[8, 9] The thiobenzoyl derivatives were chosen because of their favorable stability. Also the known thioformanilide *S*-oxide and thioacetanilide *S*-oxide were used in this study.



Scheme 2

New aminosulfines were prepared by oxidation of the corresponding thioamides (Table 1).
The yields for the new derivatives **8a-h** are shown in table1. The best yields were obtained when the oxidation was performed in a buffer of 10 % sodium acetate in acetic acid.[1b] For the aminosulfines **8e-h** this was the only successful approach. The oxidation reactions were quenched by adding dichloromethane to the reaction mixture, followed by careful addition of saturated sodium hydrogen carbonate solution. In most cases, the reaction was quenched before all thioamide had been consumed as otherwise over-oxidation of the sulfine took place resulting in formation of the corresponding amide by loss of sulfur.

Table 1 Synthesis of new aminosulfines



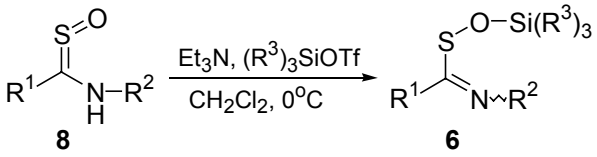
8	R	color with $FeCl_3$	yield %
a	P(MeO)Bn	dark blue	44
b	pClBn	blue	87
c	allyl	blue/purple	80
d	cinnamyl	blue	75
e	α-MeBn	red-brown	84
f	$-CH_2CO_2Et$	purple	75
g	$-CH(iPr)CO_2Me$	red-brown	71
h	$CH(CH_2Ph)CO_2Me$	red-brown	85

Whereas derivatives **8a-d** were stable crystalline solids, **8e** was obtained as a very viscous yellow oil that decomposed overnight even when stored at –20°C. The amino acid derived compounds **8f-h** were isolated as viscous yellow oils that could be kept at –20°C for several days before signs of decomposition were noticed. The aminosulfines **8e-h** were used immediately for further reactions. All aminosulfines showed the characteristic formation of colored complexes when treated with aqueous iron(III)chloride[1,5] (sometimes aqueous acetone solutions were used due to solubility problems). Colors ranged from red-brown to purple and blue (Table 1). The ^{13}C-NMR signal around 193 ppm for the sulfine carbon atom was very characteristic for all derivatives **8**.

2.3 *O*-Silylation of aminosulfines

Attempts to silylate aminosulfines with trimethyl- and triethylsilyl chloride in the presence of triethylamine were not successful. With trialkylsilyl triflates however, silylation was almost instantaneous upon addition of the triflates to a solution of aminosulfine and triethylamine. A first indication of a reaction was the immediate disappearance of the typical bright yellow color of the aminosulfines and the solutions becoming faintly yellow or colorless.

Table 2 *O*-silylation of aminosulfines with trialkylsilyl triflates



9	R^1	R^2	R^3	^{13}C=N (ppm)
a	Ph	Ph	iPr	169
b	Ph	Ph	TBDMS	n.d.
c	pClPh	mClPh	iPr	172
d	Ph	allyl	iPr	n.d.

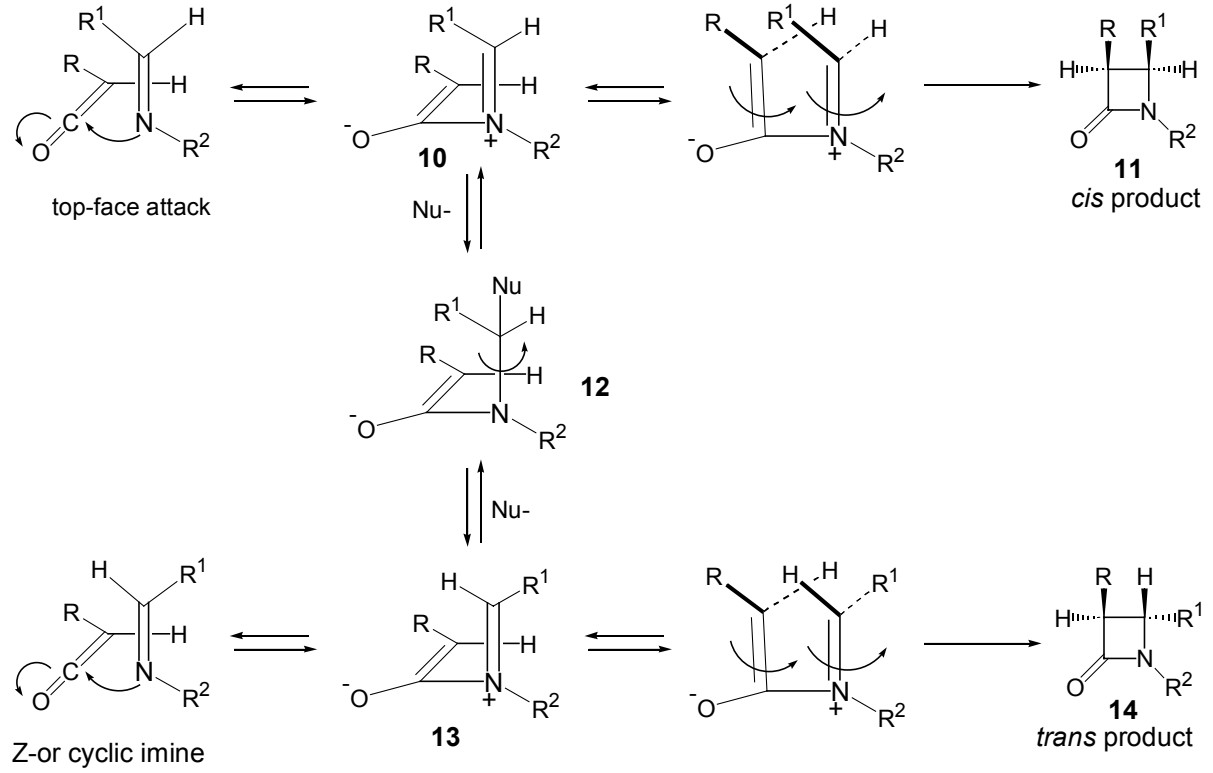
The use of an aqueous work-up[7] by quenching the reaction with 5% sodium carbonate solution, followed by extraction, also gave the silyl esters but these were usually contaminated with substantial amounts of aminosulfine starting material, thioamide/amide and sulfur from hydrolysis and/or decomposition. *O*-silyl esters **9a** and **c** could be isolated in reasonable purity as light yellow oils by a non-aqueous work-up procedure involving direct removal of the dichloromethane from the reaction mixture, followed by separation of the

product from the triflate salt by precipitation of the latter with dry ether. Evaporation then gave the products as slightly turbid light yellow oils that immediately were used for NMR analysis. In the ^{1}H-NMR spectra the signal of the thioamide *S*-oxide amide proton had (largely) disappeared and of course the signal for the isopropyl protons (at 0.88 ppm and 1.15 ppm) were present. The compounds slowly hydrolysed/decomposed in a few hours even at –20°C. Only from silyl ester **9c** a mass spectrum (EI) could be obtained, clearly showing an M^+-peak at m/e=385. Other silyl esters were not isolated because of their sensitivity towards hydrolysis and were prepared *in situ* and trapped by the [2+2]-cycloaddition reaction with ketenes.

2.4 Synthesis of β-lactams

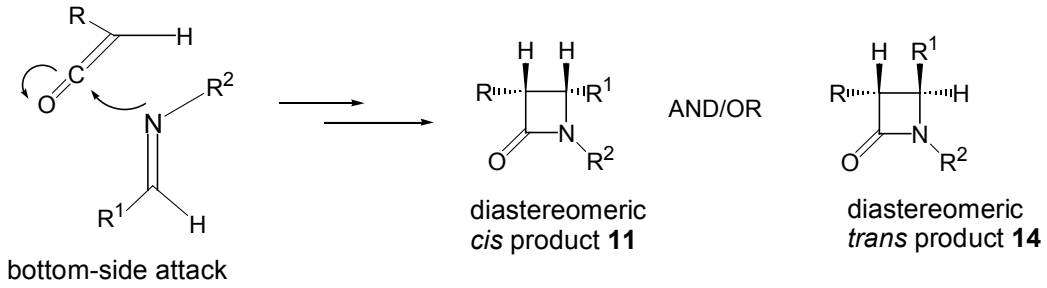
2.4.1 Background

The [2+2]-cycloaddition of imine derivatives with *in situ* prepared ketenes is one of the most versatile and well-studied synthetic approaches to β-lactams.[10] Although the net result of the reaction is a [2+2]-cycloaddition, the reaction is not concerted but is believed to proceed via a two-step zwitterionic pathway. Still, this leaves two possible mechanisms in cases where acid chlorides are used as ketene precursors. The first possible route involves initial formation of the ketene by reaction of the acid chloride with the base (Scheme 3). It is then believed that the LUMO of the ketene carbonyl (which is coplanar to the ketenes substituents) is attacked by the imine nitrogen in an orthogonal fashion. The imine is assumed to possess the *E*-stereochemistry. This leads to intermediate **10** in which the enolate and the iminium groups are positioned perpendicular to each other. The substituent of the ketene is assumed to point away from the attacking imine.



Scheme 3

The formation of the β-lactam is then explained by a conrotatory ring closure of **10**, leading in this case to the energetically less favorable *cis*-β-lactam **11**. The formation of the more favorable *trans*-β-lactam **14** will result from attack of a nucleophile (Cl- or excess base) on intermediate **10** to form **12**. In **12** bond rotation is possible, leading, after loss of the nucleophile, to **13**, which upon conrotatory ring closure leads to *trans* derivative **14**. In case of cyclic imines, with inherent Z-stereochemistry of the imine, *trans* β-lactams are expected as attack on the ketene leads directly to intermediate **13**. Attack can also take place from the bottom side of the ketene, this leads in an analogous way to the diastereomers of **11** and **14**, respectively (Scheme 4).

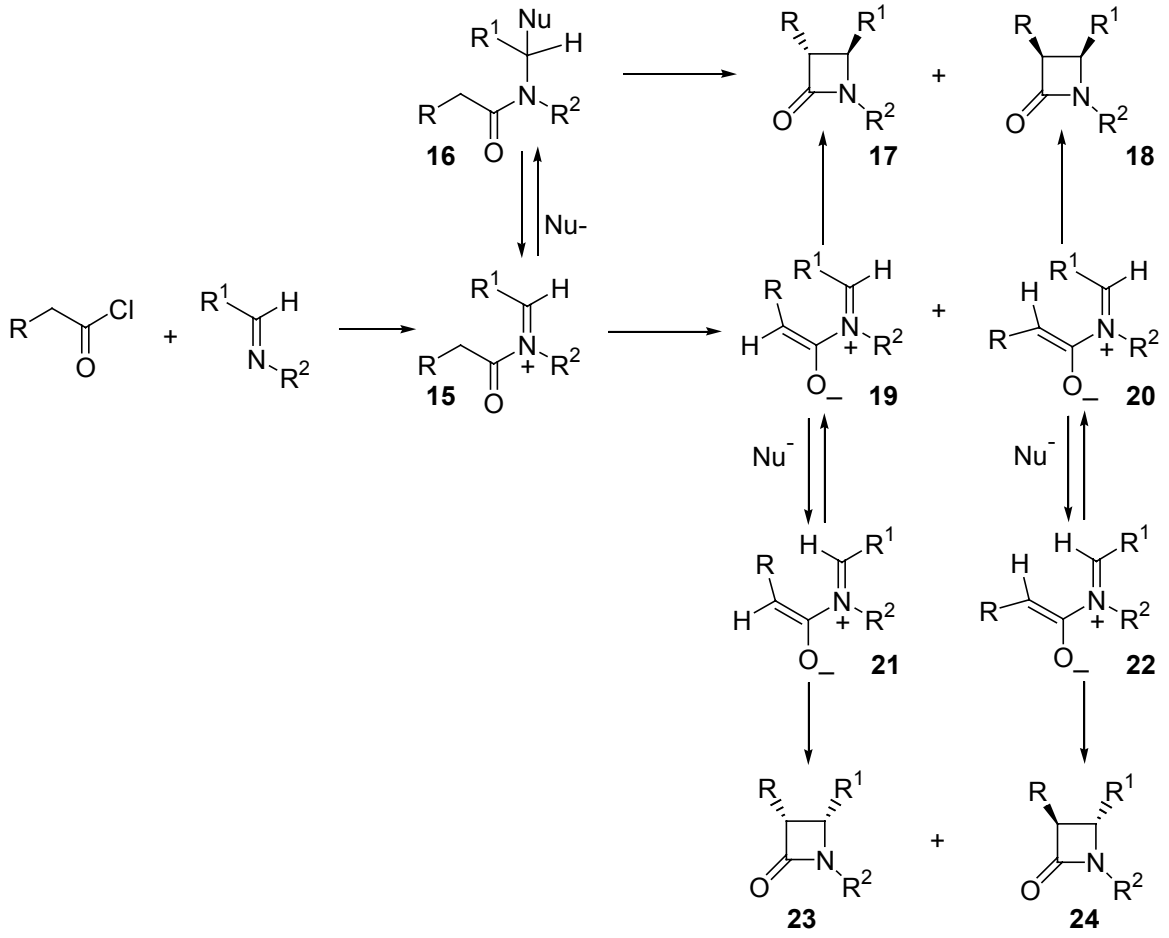


Scheme 4

Chiral induction in this ketene-imine cyclization pathway is explained by energetic preference for either top or bottom face attack.

The second proposed route for the formation of β-lactams assumes that, instead of formation of the ketene and subsequent attack by the imine, the acid chloride acylates the imine to form an *N*-acyliminium chloride **15** (Scheme 5). Intermediate **15** now has two possibilities that can lead to β-lactams. The first option involves the addition of a nucleophile, e.g. a chloride anion to the carbon of the iminium species to give amide **16**, deprotonation α to the amide carbonyl gives the corresponding enolate which by a S_N2 substitution leads to β-lactams **17** and **18**. The stereochemistry of the β-lactam is then determined by the enolate stereochemistry. The second option is enolization of the carboxamide before nucleophilic attack by a nucleophile on the iminium group. This leads to the same zwitterionic intermediates **19** and **20** as shown in the ketene-imine mechanism. Now, enolization can produce two different isomers directly. Conrotatory ring closure leads to either *trans*- or *cis*-β-lactams **17** and **18**, respectively. Both **19** and **20** can again react with a nucleophile (Cl- or base) allowing isomerization of the imininium moiety leading to **21** and **22**, respectively. Subsequent conrotatory ring closure then gives the diastereomeric *cis*- and *trans*-β-lactams. The same mechanism can of course be applied to *Z*-imines.

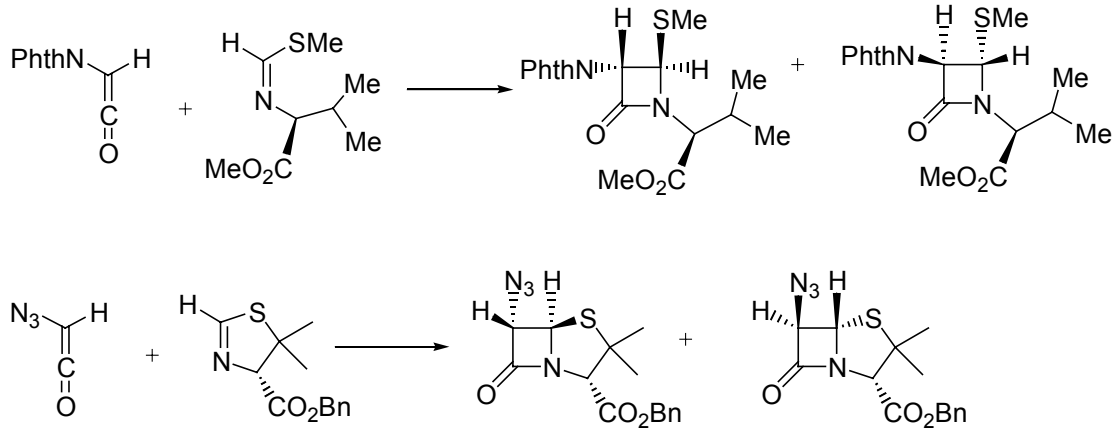
It has been shown that the stereochemical outcome of the β-lactam formation depends on the reaction conditions used. Formation of the ketene *in situ* followed by addition of the imine gives results different from the addition of the corresponding acid chloride to a mixture of the imine and base.[10b] This is a clear indication that in the latter case the reaction proceeds



Scheme 5

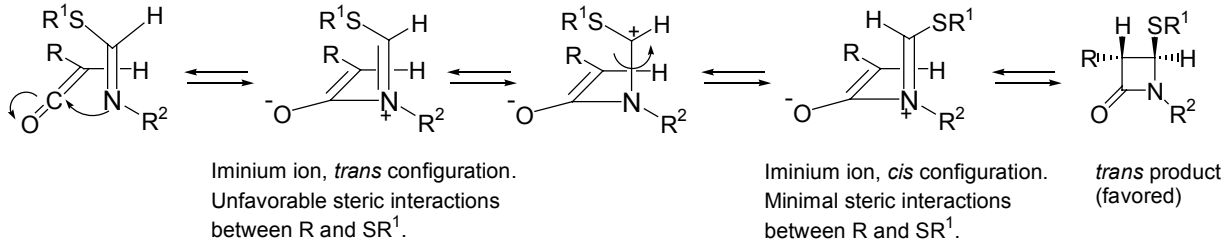
through the acid chloride-imine mechanism instead of via the ketene-imine route. Also the nature of the ketene can strongly influence the stereochemistry of the resulting β-lactam. Ketenes have been classified in three groups:[10b]
i.) Bose-Evans ketenes, with small-size substituents (e.g. O-aryl, O-alkyl, NHCOR, OCOR) or substituents that possess dipole interactions (F, N_3).
ii.) Sheehan ketenes with medium-size substituents (e.g. allyl, phthaloyl) and
iii.) Moore ketenes with large-size substituents (e.g. Br, Cl, alkyl, aryl or $S(O)_nR$ n=0-2).

As the used *O*-silyl esters of iminosulfenic acids **9** (with some caution, as internal charge distribution is probably different) can be regarded as derivatives of thioimidates, the features of these imines in the ketene-imine cyclization will be briefly discussed. This chemistry of thioimidates has been the subject of several studies.[11] The stereochemical outcome of the [2+2]-cycloaddition with thioimidates is generally *trans* with respect to C-3 and C-4 of the β-lactam ring, regardless of the ketene used.[10, 12, 13] Illustrative examples are given in Scheme 6.



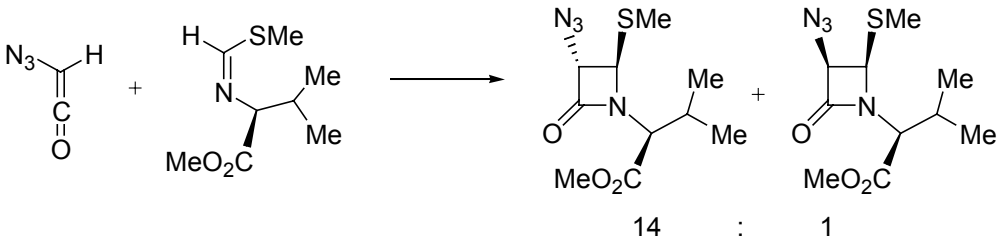
Scheme 6

The stereochemistry can be explained by the electron-donating ability of the thioimidate sulfur atom which can stabilize the zwitterionic intermediate of the [2+2]-cycloaddition by inductive or mesomeric effects. This allows isomerisation to the iminium-ion intermediate with the *cis*-configuration which is sterically more favorable with regard to the ketene substituent R and the thioimidate group, than the corresponding intermediate with the *trans* structure. Conrotatory ring closure then leads to a *trans* β-lactam (Scheme 7).[10]



Scheme 7

A rare example of the formation of a small amount of *cis*-β-lactam was reported by Bachi *et al.* for the use of azidoketene[14].



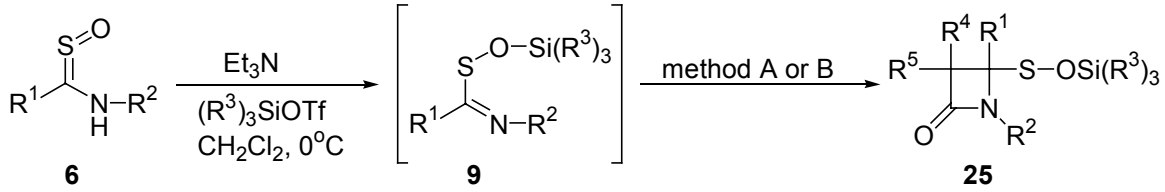
Scheme 8

2.4.2 Synthesis of β-Lactams from *O*-silyl esters of iminosulfenic acids

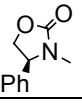
For the [2+2]-cycloaddition the *O*-silyl iminosulfenates **9** were prepared *in situ* at 0°C. The cycloaddition was performed in two ways. Method A: first addition of an excess of triethylamine to a solution of *in situ* prepared *O*-silyl iminosulfenate, followed by slow dropwise addition of a solution of the corresponding acid chloride at –78°C. Upon completion of the reaction the temperature was raised slowly to 0°C (see experimental). Method B: Transfer of a cooled (-78°C) solution of silyl sulfenate to a solution of *in situ* prepared ketene

at –78°C, followed by slowly raising the temperature to 0°C. The results are collected in Table 3. The data shown in Table 3 reveal that a series of different ketenes cyclizes with compounds **9** to give good to moderate yields of β-lactams **25**. The yields for the β-lactams **25l** and **25m** were rather poor. The reaction seems to be limited to aminosulfines **8** with R^1=Ar because *N*-phenylthioformamide *S*-oxide (R^1=H) and thioacetanilide *S*-oxide (R^1=Me) did not give any β-lactams with phenoxy-, dichloro- and phthaloyl ketene.

Table 3 Synthesis of β-lactams from aminosulfines **8** via O-Silyl iminosulfenic acids **9**.



6 **9** **25**

25	R^1	R^2	R^3	R^4	R^5	method	yield (%)[a]
a	Ph	Ph	iPr	PhO	H	A, B	62, 71
b	Ph	Ph	iPr	PhtN	H	B	54
c	Ph	Ph	Et	PhtN	H	A, B	65, 73
d	Ph	Ph	Et	PhtN	CH_2Ph	B	28
e	Ph	Ph	iPr	Cl	Cl	A	80
f	pClPh	mClPh	iPr	PhtN	H	A	42
g	Ph	Ph	iPr	N_3	H	A, B	24, 41[b]
h	Ph	allyl	Et	PhtN	H	B	52
i	Ph	d-(+)-MeBn	iPr	PhO	H	B	76[c]
j	Ph	pOMeBn	iPr	PhO	H	A	78
k	Ph	pClBn	iPr	PhO	H	A	63
l	Ph	-CH=CHPh	Et	PhtN	H	B	17
m	Ph	Ph	Et		H	B	10-12

a) yield calculated on aminosulfine. b) obtained as a 9:1 mixture of *cis* and *trans* isomers. c) obtained as a 1:1 mixture of diastereomers.
Method A: Acid chloride (1.5 eq) is added dropwise to solution of *in situ* prepared **9** and 2.5 equiv. of Et_3N at –78°C. **Method B:** A solution (-78°C) of *in situ* prepared **9** is added via a canulla to a solution of *in situ* prepared ketene (-78°C).

It should be emphasized that the above prepared β-lactams **25** are the first examples of β-lactams with an *O*-silyl sulfenate function of C-4 that are not derived from penicillin *S*-oxide.[21] The ^{1}H-NMR spectra showed that only one isomer had been formed, except for **25h** where a *cis/trans* mixture was obtained in a 9:1 ratio (^{1}H-NMR) using azidoketene, (the C-3 proton signal of the main isomer appeared at 5.2 ppm, that of the minor isomer at 4.9 ppm). Both methods gave the same ratio of products, however, method B gave a considerably better yield. As shown in Scheme 8, azidoketene led to the formation of the second possible isomer in other cases.[14] Reaction with the chiral ketene introduced by Evans[15] was very sluggish, even after stirring overnight at room temperature only 10-12% of **25m** could be isolated as a white solid. The ^{1}H-NMR spectrum showed the presence of one diastereoisomer. The low yield in this case is not too surprising as the related imidates also gave low yields with this class of ketenes.[10] With the chiral aminosulfine **8i** a 1:1 mixture of diastereoisomers was obtained. Establishing the stereochemistry of the β-lactams turned out to be difficult with ^{1}H-NMR-techniques because of the lack of a C-4 hydrogen atom which results in a rather 'isolated' position of the C-3 proton. Also 400 MHz NOESY spectra did not provide sufficient information. However, an X-ray crystal structure analysis of **25c**, clearly showed a *trans* relationship between the silyl sulfenate and the phthaloyl moiety (figure 2).

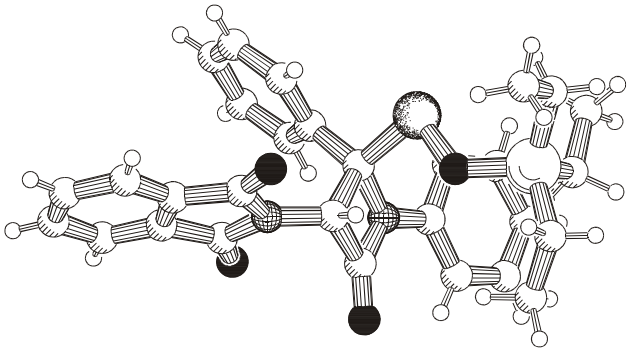
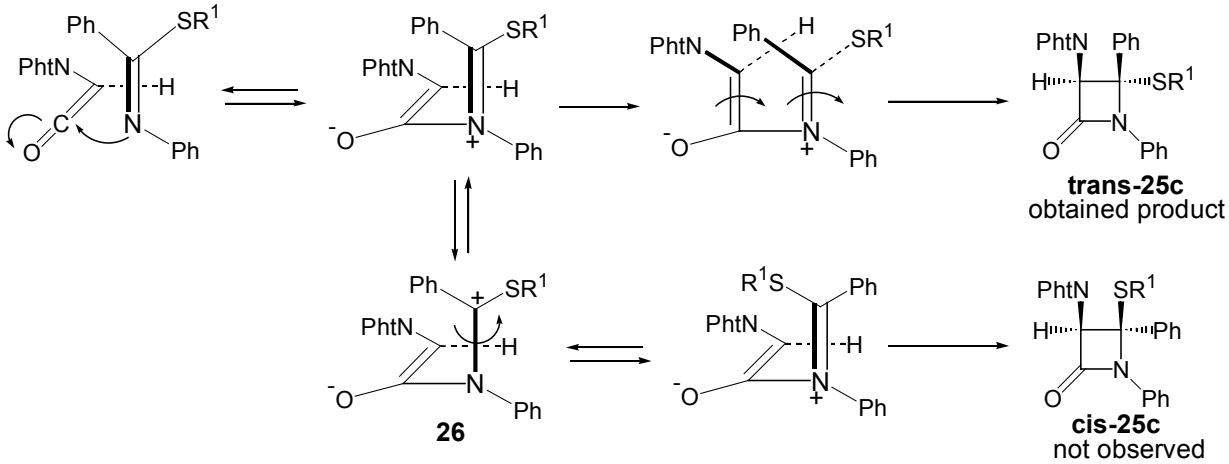


Figure 2. X-ray structure of **25c**

The product **25c** used for the crystallographic analysis was prepared by method A. This β-lactam **25c** was also prepared by method B. The product had exactly the same ^{1}H- and ^{13}C-NMR spectra, thus the stereochemical outcome is the same for the different reaction conditions in this case. It should be noted that a different stereochemistry certainly would have an effect on the chemical shift of the proton of C-3 and on the ^{13}C-signals of C-3 and C-4, respectively, as was observed for **25g**. Although the structure of **25c** perse does not provide information about the stereochemistry of the other β-lactams, it can be regarded as a good indication that these thioimidates usually give the same stereochemical outcome irrespective of the ketene used. From the fact that for **25a** and **25c** the stereochemistry is independent of the reaction conditions used, a similar stereochemistry for the other β-lactam products might be expected.

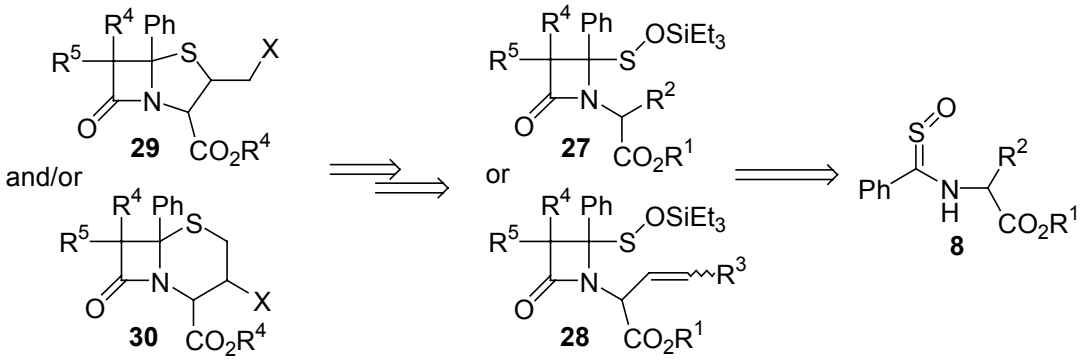
The stereochemistry of **25c** can be rationalized by using the mechanisms shown in Schemes 3, 4, 5 and 7. For method A it cannot be said which pathway (ketene-imine or acid chloride-imine) is followed. Method B clearly involves the ketene-imine route. In the *O*-silyl iminosulfenate **9** the aromatic rings most likely are positioned *anti* with respect to each other. Assuming that the sulfur atom would be able to stabilize the intermediate carbocation **26**, then this would lead to the formation of the *cis*-product **25c**, which however is not observed.



Scheme 9

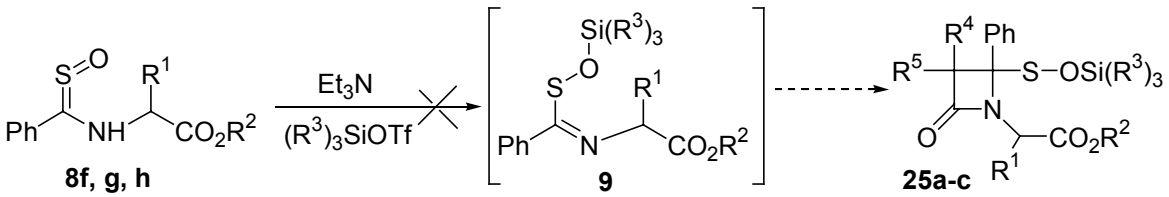
Consequently, the synthesis by method B involves attack of the imine nitrogen on the ketene followed by conrotatory ring closure to give the *trans*-isomer of **25c** (Scheme 9, topline). Analogously, the bottom face attack would lead to the enantiomer of **25c**. It is relevant to note that if the imine would have a different configuration, with the two phenyl groups positioned *syn*, then the product formation to *trans*-**25c** must take place in the opposite manner, namely

via isomerization of the zwitter-ion via the cationic intermediate **26** to bring the groups in the proper position prior to the conrotatory ring closure.
After the promising results with relatively simple aminosulfines, the preparation of β-lactams **27** and **28** was considered as that could provide an entry to new penam and/or cepham derivatives **29** and **30**. The corresponding aminosulfines then will be the *S*-oxides of *N*-thiobenzoylated amino acid esters **8**. A retrosynthetic analysis is depicted in Scheme 10.



Scheme 10

The amino acid derived amino sulfines could be prepared in good yields (**8f**,**g**,**h** in Table 1). These substrates then were subjected to the [2+2]-cycloaddition reaction with ketenes. Disappointingly however, these aminosulfines did not yield any β-lactams upon reaction with phthaloyl- phenoxy- or dichloroketene. This failure probably can be attributed to the presence of an ester group that introduces another side for possible silylation (to form a *O*-silyl ketene acetal[16]) and that would interfere with *O*-silylation of the aminosulfine. The use of two equivalents of base and silylating agent was also unsuccessful (Scheme 11).



R^1= H (R^2=Et) or Bn, iPr (R^2=Me), R^3=iPr,Et.

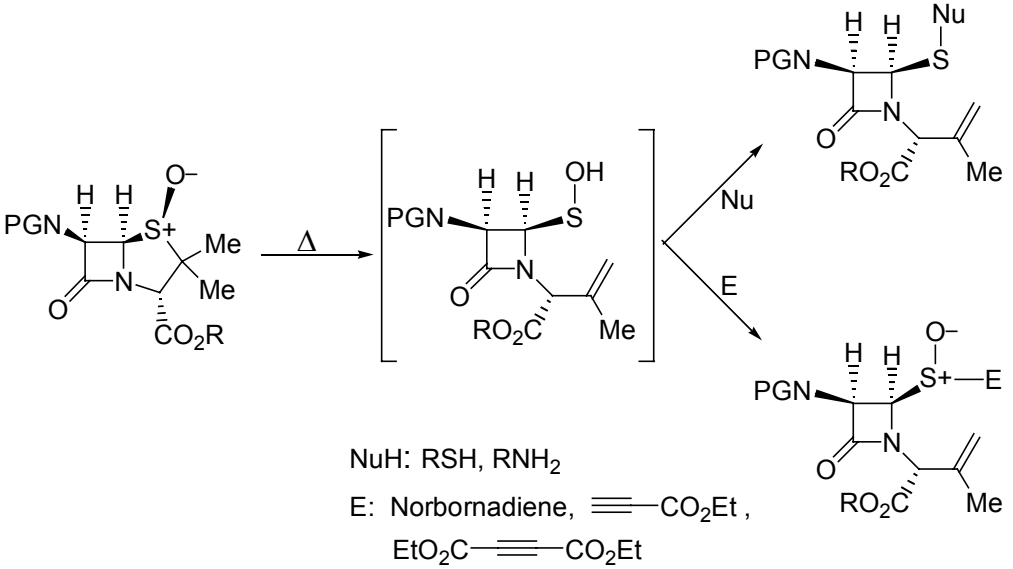
Scheme 11

Considering the fact that *S*-alkyl thioimidate analogues have been shown to form β-lactams (Schemes 6 and 8),[10,11] it is reasonable to assume that problems regarding the formation of the imino silylsulfenates are indeed responsible for the failure of β-lactam formation. If formed, the iminosulfenates would have reacted with the ketenes in the expected manner.

2.5 Reactions of the silyl sulfenate moiety

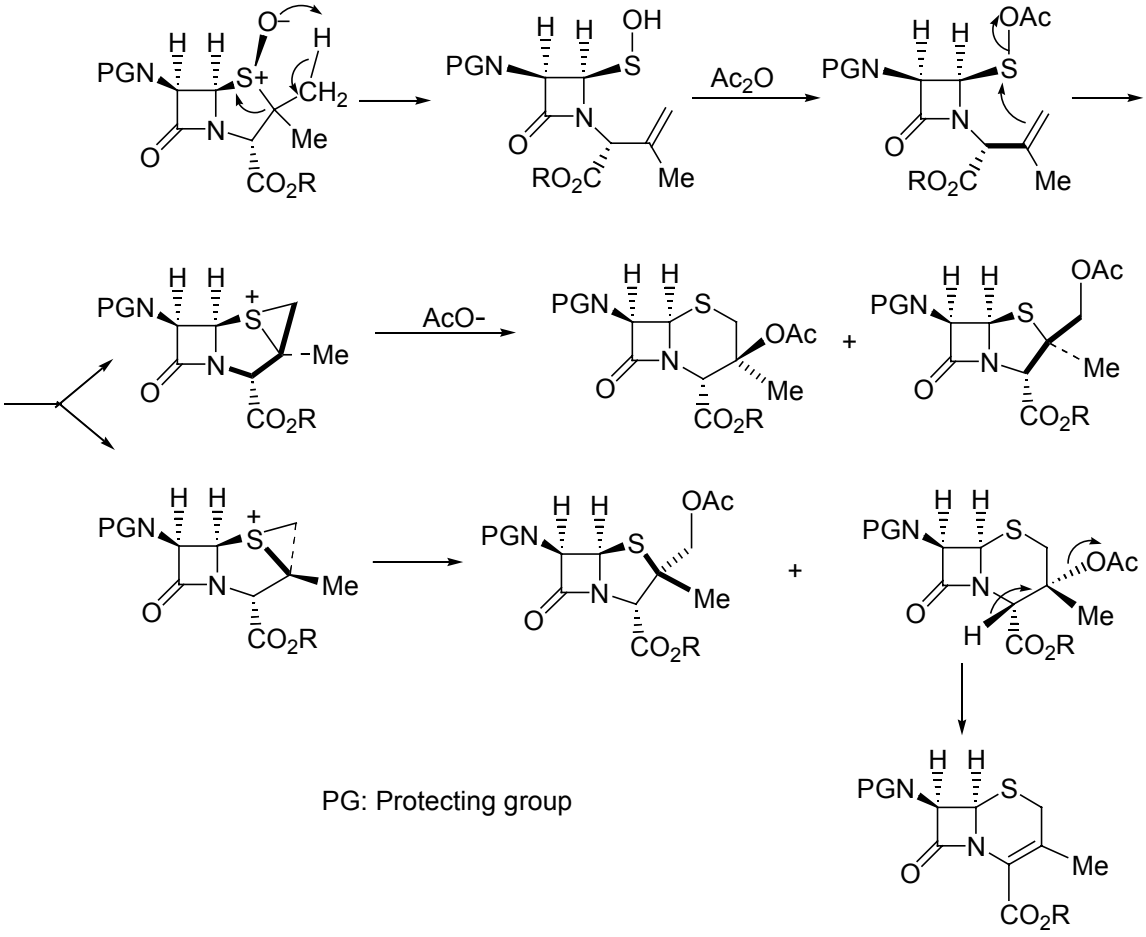
2.5.1 Background

The use of sulfenic acid intermediates has received considerable attention in β-lactam chemistry.[17-24] Sulfenic acid derivatives of azetidinones have been shown to react inter- or intramolecularly with olefenic[17] and acetylenic[18] bonds. The sulfenic acid is generated by a thermal rearrangement of penicillin *S*-oxides as outlined in Scheme 12.



Scheme 12

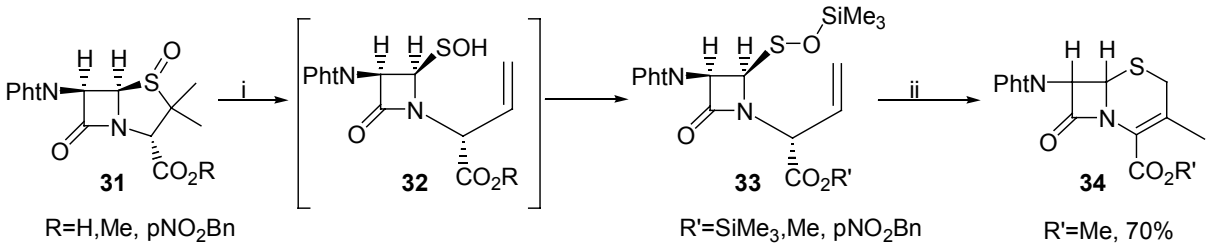
The intramolecular reaction has been used extensively in the rearrangement of penicillin derivatives into cephalosporins.[17-24] Scheme 13 shows an example in which the sulfenic acid is activated by formation of its acetate.[19]



Scheme 13

Examples of the use of silyl sulfenate-substituted β-lactams in this rearrangement have been reported by Chou.[17,21] The sulfenic acid **32** was trapped as the *O*-trimethylsilyl ester by

heating the penicillin *S*-oxide in the presence of trimethylsilyl chloride/hexamethyldisilazane in benzene (Scheme 14).



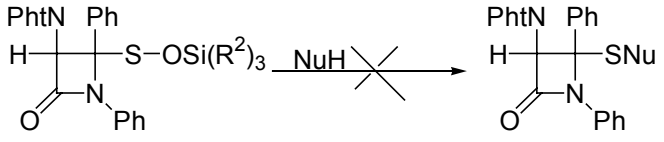
Conditions: i) TMSCl/HMDS=2:1 2eq. C_6H_6, Δ. ii) $MeSO_3H$, C_6H_6/dimethylacetamide

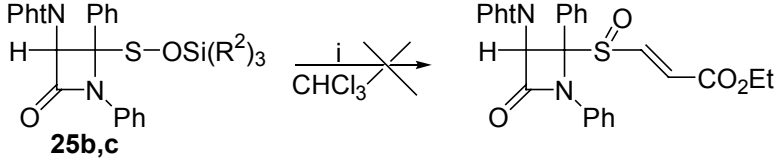
Scheme 14

This silylsulfenate **33** then could be converted into cephalosporin derivative **34** by subsequent treatment with methanesulfonic acid in benzene/dimethylacetamide. When the formation of the silyl sulfenate was carried out in the presence of a catalytic amount of triethylamine, the double bond in **33** isomerized to form the corresponding conjugated ester derivatives. It should be noted that the two sulfenic acids **32** (R=Me, pNO_2Bn) and the conjugated (α,β)-isomer with R'=Me were isolated as crystalline solids,[17] constituting examples of the rather small class of stable sulfenic acids.[20]

2.5.2 Results

The silyl sulfenate substituted β-lactams **25**, which can be regarded as silyl-protected sulfenic acids,[21] were subsequently reacted with different nucleophiles and electrophiles in order to obtain new β-lactam derivatives (Scheme 15). In the reaction with nucleophiles the trimethylsilanoate anion should act as the leaving group. However, reaction of **25b** and **25c** with excess thiophenol or ethanethiol in dichloromethane did not produce the desired disulfides. The presence of base (Et_3N or K_2CO_3) did not affect the outcome. Attempted reactions of the liberated sulfenic acid with methanol by stirring a methanolic solution with a catalytic or equimolar amounts of *p*-toluenesulfonic acid or PPTS gave either no reaction (0°C) or a mixture of unidentifiable products (room temperature or 60°C). Also reaction with ethyl propiolate in the presence of these acids[17] or even dilute HCl gave no products.



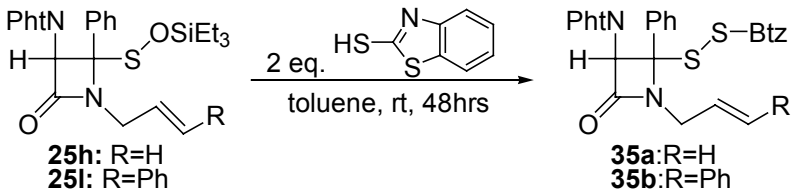


i) ethyl propiolate (10-20 eqiuv), pTosOH or PPTS

Scheme 15

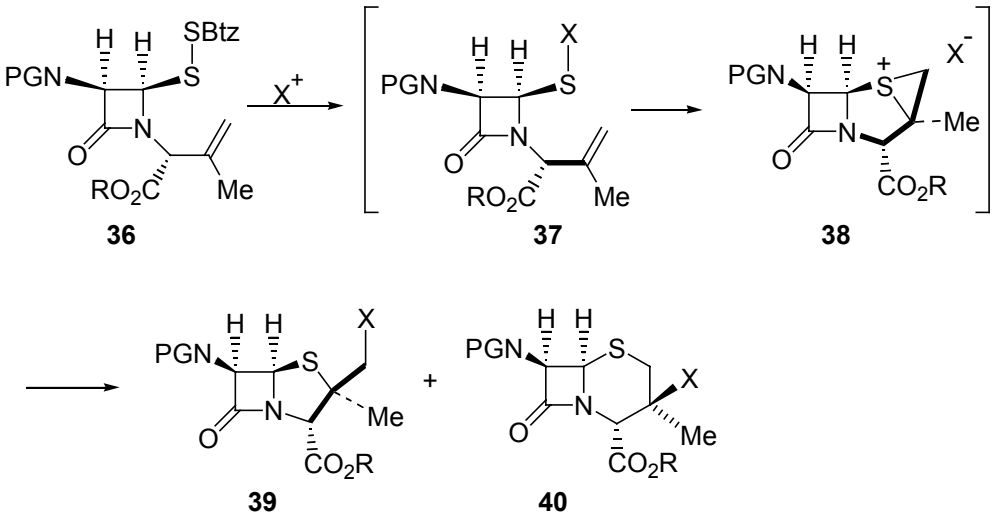
It should be mentioned that compound **25b** showed a remarkable stability towards hydrolysis, even when stirred overnight in a mixture of 5% HCl (aq) and methanol the compound was largely in tact. Attempts to activate the silyl sulfenate using TBAF or cesium fluoride in

tetrahydrofuran in the presence of excess ethyl propiolate (with or without water) on the other hand resulted in complete destruction of the β-lactam. Treatment of **25n** under the conditions of Chou[17a,21] (Scheme 14) resulted in complex mixtures, even when the reaction was performed at room temperature.
However, when **25h** and **25l** were treated with two equivalents of 2-mercaptobenzothiazole (BtzSH) in toluene at room temperature (Scheme 16) for 48 hours, the corresponding unsymmetrical disulfides **35a** and **35b** were obtained in yields of 83 and 85%, respectively.



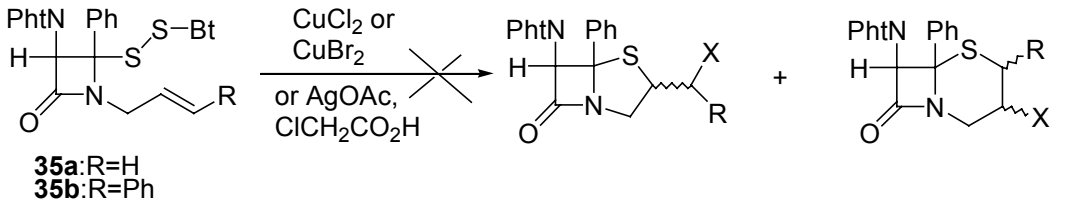
Scheme 16

This type of unsymmetrical disulfides have received considerable attention as intermediates in the synthesis of various penam and cepham derivatives from penam *S*-oxides (Scheme 17).[23] Reaction of compound **36** with a halonium species is believed to give the corresponding sulfenyl halide **37**. Subsequently, the sulfenyl halide reacts with the olefinic double bond to form an episulfonium ion **38** which, upon reaction with the halide ion, yields the penam and/or cepham derivatives **39** and **40,** respectively. Among the various reagents employed the method using copper(II)halides under heterogenous conditions looked particularly appealing.[23g, 22]



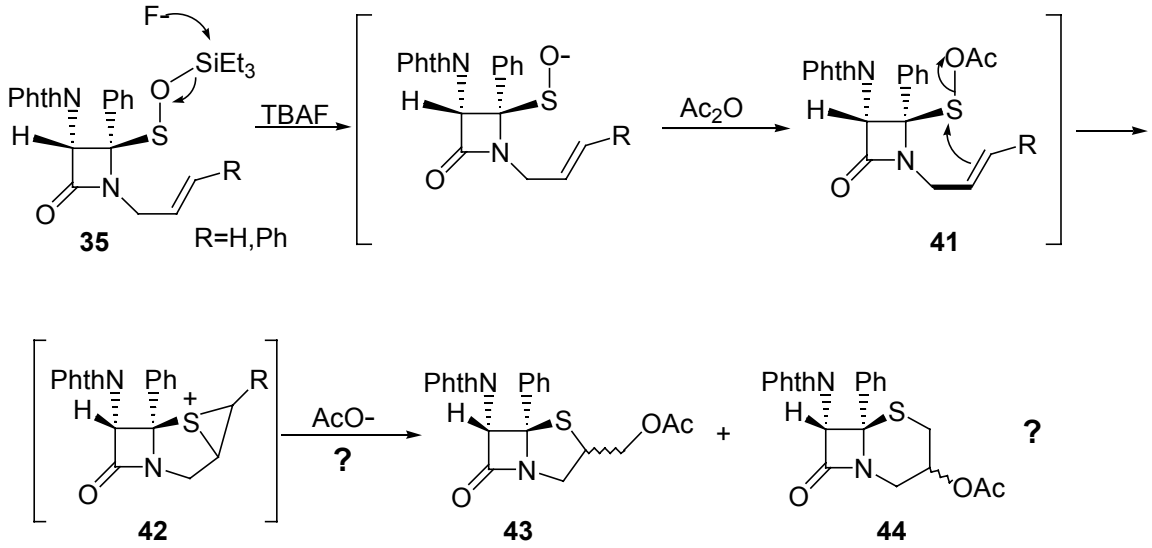
Scheme 17

Another interesting approach by Baldwin involves the use of silver salts of carboxylic acids and leads to the corresponding penam- and cepham-acetates.[23b]
Thus, **35a** and **35b** were subsequently employed in reactions with the above mentioned reagents for ring closures of penicillin-derived mixed disulfides.[23]



Scheme 18

The reagents tested included bromine, iodine, copper(II) bromide, copper(II) chloride and silver acetate/chloroacetic acid according to literature procedures.[23, 24] However, the results were disappointing as in no case the desired penam/cepham products were obtained. Instead, only unidentifiable products were obtained. In a final attempt **25h** and **25l** were treated with TBAF in the presence of 1 or 5 equivalents of acetic anhydride, in the hope to produce the sulfenic acetate **41** (Scheme 19). Reaction of the olefinic bond with this acetate would then yield acetate **43** and/or acetate **44** analogous to the penicillin-cephalosporin rearrangement shown in Scheme 13.



Scheme 19

In all cases however, complete destruction of the starting materials into various products was observed. A possible explanation for these disappointing results cannot be given.
The formation of the benzothiazole derived mixed disulfides is remarkable. The successful formation of disulfides **35a** and **35b** probably can be attributed to the enhanced nucleophilicity of 2-mercaptobenzothiazole compared to the other nucleophiles, as steric hindrance related to the presence of the C-4 phenyl group should be experienced more strongly by 2-mercaptobenzothiazole than by any of the other nucleophiles used.
The absence of an ester group in derivatives **25** and **35a,b** is not expected to have a large influence on reactions involving episulfonium ions. It would make elimination of HX from any formed 3-halocepham far more unlikely.

2.6 Conclusions

It has been demonstrated that *O*-silyl esters of iminosulfenic acids can be obtained *in situ* from aminosulfines (thioamide *S*-oxides) by treatment with trialkylsilyl triflates in the presence of triethylamine. Isolation of these esters proved difficult as they are prone to

hydrolysis. When formed *in situ* however, they can be converted into new β-lactams upon reaction with ketenes in essentially a one-pot procedure from aminosulfines. The yields were good to acceptable in most cases. This constitutes the first synthesis of β-lactams containing a silyl sulfenate moiety on C-4 that is not derived from penicillin *S*-oxide derivatives. Aminosulfines derived from amino acid esters failed to give a β-lactam, probably due to the presence of the ester function which interferes with the formation of the iminosulfenic acid *O*-silyl esters **9**. Further reaction of the *O*-silyl sulfenates of derivatives **25** proved problematic. The only successful conversion of the silyl sulfenate moiety was achieved by reaction of **25h**,**l** with 2-mercaptobenzothiazole to form the corresponding unsymmetrical disulfides **35a,b**. However, all attempts to accomplish a ring-closure reaction to give new penam derivatives were unsuccesful.

2.7 Experimental

General remarks

All cycloaddition reactions were carried out under a dry argon atmosphere. Optical rotations were measured using a Perkin Elmer 241 MC automatic polarimeter. Melting points were determined with a Reichert Thermopan microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with Bruker AC 100 MHz and AC 300 MHz FT spectrometers. Mass spectra were obtained with a VG7070E spectrometer. Elemental analyses were obtained using a Carlo Erba EA 1108 element analyser. Thin layer chromatography was carried out on Merck silica gel 60 F-254 plates. Spot were visualised with UV or by dipping in a coloring solution (6.2% sulfuric acid aqueous solution, containing 42g ammonium molybdate and ceric ammonium sulfate per liter) followed by charring. Column chromatography was carried out using Silica gel 60 (Baker).

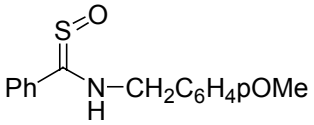
Solvents

Dichloromethane was freshly distilled from phosphorous pentoxide. Tetrahydrofuran was distilled from sodium benzophenone ketyl or lithium aluminium hydride. Triethylamine was distilled from potassium hydroxide and stored under argon over potassium hydroxide pellets.

Preparation of new aminosulfines 8:

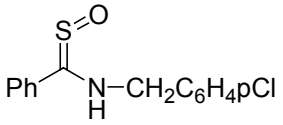
The method reported by Walter et al.[4b] for the preparation of tertiary aminosulfines was used. Reactions were performed on a 2 mmol scale unless stated otherwise. Upon addition of the hydrogen peroxide the reaction was monitored closely by TLC (every minute a new TLC, visualization by UV followed by staining with aqueous Fe(III)chloride). The reaction was stopped when most of the starting material was consumed and when over-oxidation became visible (TLC and precipitation of sulfur started). The reaction was quenched by adding 50ml of dichloromethane followed by the careful addition (strong CO_2 evolution!) of a saturated sodium hydrogen carbonate solution. The reaction should be performed in a large enough flask (at least 250 ml) to prevent overflow upon addition of the base. After extraction and drying ($MgSO_4$) the products were purified by column chromatography with chloroform to chloroform/methanol (9:1) gradient over silica gel.

***N*-thiobenzoyl p-methoxybenzylamine *S*-oxide (8a)**



Obtained as a bright yellow crystalline solid, after chromatography, 240 mg, 44 %. Mp. 97-99 °C (dec). Color with aq. Fe(III)Cl_3 :dark blue. ^{1}H-NMR (300MHz) d: 3.79 (s, 3H, OC**H**$_3$), 4.53 (AB, 2H, **H**$_2$C-PhpOMe), 6.84 (m, 2H, Ar), 7.10 (m, 2H, Ar), 7.30-7.55 (m, 5H, Ar), 7.87 (br.s., 1H, N**H**). ^{13}C-NMR (75 MHz) d: 48.4, 55.25, 114.2, 126.6, 127.6, 128.4, 128.7, 129.0, 131.4, 159.4, 192.7 (**C**=S=O). Mass (EI): m/e 273 (M^+), 257 (M^+-O), 224 (M^+-HSO).

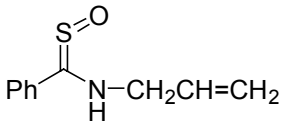
***N*-thiobenzoyl p-chlorobenzylamine *S*-oxide (8b)**



Obtained as a bright yellow crystalline solid, after chromatography, 481mg, 87%. Mp. 115-116°C (dec). Color with aq. Fe(III)Cl_3: blue. ^{1}H-NMR (300MHz) d: 4.57 (s, 2H, **H**$_2$C-PhpCl), 7.12 (m, 2H, Ar), 7.28-7.35 (m, 4H,

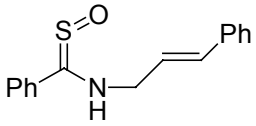
Ar), 7.43-7.56 (m, 3H, Ar), 7.97 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 48.1, 126.4, 127.6, 128.5, 129.1, 129.2, 131.6, 134.0, 135.1, 193.1 (**C**=S=O). Mass (EI): m/e 277 (M^+), 261 (M^+-O), 228 (M^+-HSO).

***N*-thiobenzoyl allylamine *S*-oxide (8c)**



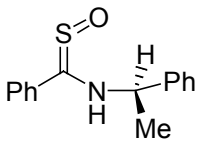
Obtained as a bright yellow crystalline solid, after chromatography, 310 mg, 80%. Mp. 82-84 °C. Color with aq. Fe(III)Cl_3: blue/purple. ^{1}H-NMR (300MHz) d: 4.05 (br. d, 2H, J= 5.0 Hz, N-C**H$_2$**-CH=CH_2), 5.16-5.35 (m, 2H, N-CH_2-CH=C**H$_2$**), 5.68-6.08 (m, 1H, N-CH_2-C**H**=CH_2), 7.25-7.58 (m, 5H, arom.), 7.79 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 47.2 (t, N-**C**H_2-CH=CH_2), 117.5 (t, N-CH_2-CH=**C**H_2), 126.7, 127.4, 128.9, 131.1, 131.4, 133.0 (**C**-arom. + N-CH_2-**C**H=CH_2), 193.0 (**C**=S=O). Mass (CI): m/e 193 (M^+), 176 (M^+-O), 143 (M^+-HSO). Elemental analysis: calcd. for $C_{10}H_{11}NOS$, C 62.15, H 5.74, S 16.59, N 7.25 %. Found: C 61.93, H 5.75, S 15.78, N 7.27 %.

***N*-Thiobenzoyl cinnamylamine *S*-oxide (8d)**



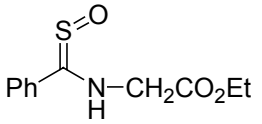
Obtained as a bright yellow crystalline solid, after chromatography, 1.0 mmol scale, 147 mg, 55%. Mp. 90°C (dec). Color with aq. Fe(III)Cl_3 : blue. ^{1}H-NMR (300MHz) d: 4.25 (m, 2H, NHC**H$_2$**), 6.22-6.79 (m, 2H, **H**C=C**H**), 7.31-7.78 (m, 11H, Ar and NH). ^{13}C-NMR (75 MHz) d: 48.9 (NH**C**H_2), 123.6, 126.7 ,127.0, 127.5, 127.7, 128.1, 128.8, 129.5, 131.4, 192.5 (**C**=S=O). Mass (EI): m/e 269 (M^+), 252 (M^+-O), 220 (M^+-SO).

***N*-thiobenzoyl α-(+)-methylbenzylamine *S*-oxide (8e)**



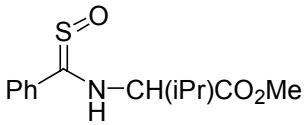
Obtained as a viscous yellow oil, after chromatography, 431 mg, 84%. It was used immediately for further reactions as it easily decomposed giving off sulfur. Color with aq. Fe(III)Cl_3 : red/brown. ^{1}H-NMR (300MHz) d: 1,61 (d, 3H, C**H$_3$**), 4.88 (br.s, 1H, **H**C-CH_3), 7.15-7.51 (m, 10H, Ar), 7.79 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 23.5 (**C**H_3), 54.6 (**C**HCH_3), 125.5, 126.7, 127.5, 127.6, 128.8, 131.2, 142.2, 192.2 (**C**=S=O). Mass (EI): m/e 257 (M^+), 241 (M^+-O), 208 (M^+-HSO).

***N*-thiobenzoyl glycine ethyl ester *S*-oxide (8f)**



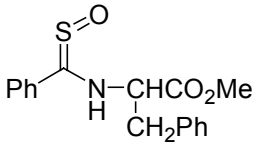
Obtained as a viscous yellow oil, after chromatography, 358 mg, 75%. Color with aq. Fe(III)Cl_3 : purple. ^{1}H-NMR (300MHz) d: 1.26 (t, 3H, C**H$_3$**), 4.17-4.25 (m, 4H, NH-C**H$_2$** and O-C**H$_2$**-CH_3), 7.30-7.56 (m, 5H, Ar), 8.18 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.0 (**C**H_3), 46.0 (O**C**H_2CH_3), 61.8 (NH-**C**H_2C=O), 127.6, 129.1, 131.5, 168.2 (**C**=O), 192.8 (**C**=S=O). Mass (EI): m/e 239 (M^+), 223 (M^+-O), 190 (M^+-HSO).

***N*-thiobenzoyl valine methyl ester *S*-oxide (8g)**



Obtained as a viscous yellow oil, after chromatography, 380 mg, 71%. Color with aq. Fe(III)Cl_3 : red/brown. ^{1}H-NMR (300MHz) d: 0.83 (d, H, (C**H$_3$**)-CH)), 0.87 (d, H, (C**H$_3$**)-CH)),2.24 (m, 1H, $(CH_3)_2$-C**H**)), 3.77 (s, 3H, OC**H$_3$**), 4.13 (m, 1H, N-C**H**-C=O), 7.31-7.60 (m, 6H, Ar and N**H**). ^{13}C-NMR (75 MHz) d: 13.9 (CH**C**H_3), 14.0 (CH**C**H_3), 31.6, (**C**HMe_2), 52.3 N-**C**H-C=O), 62.6 (O**C**H_3), 127.4, 129.0, 131.4, 170.9 (**C**=O), 192.7 (**C**=S=O). Mass (EI): m/e 267 (M^+), 251 (M^+-O), 218 (M^+-HSO).

***N*-thiobenzoyl phenylalanine methyl ester *S*-oxide (8h)**



Obtained as a viscous yellow oil, after chromatography, 535 mg, 85%. Color with aq. Fe(III)Cl_3 : red/brown.^{1}H-NMR (300MHz) d: 3.26 + 3,55 (AB of dd's, 2H, **H$_2$**C-Ph), 3.75 (s, 3H, OC**H$_3$**), 5.53 (m, 1H, HN-C**H**-C=O), 7.10-7.45 (m, 8H, Ar), 7.68 (m, 2H, Ar), 8.01 (br.d, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 35.9 (O**C**H_3), 52.4, 58.8, 126.5, 127.2, 128.3, 128.5, 129.1, 131.2, 171.2 (**C**=O), 192.4 (**C**=S=O). Mass (EI): m/e 315 (M^+), 299 (M^+-O), 366 (M^+-HSO).

Synthesis of silyl esters of iminosulfenic acids (general procedure)

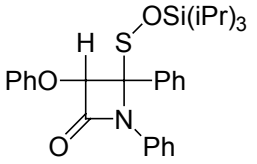
To a cooled (0°C) solution of aminosulfine (1.0 mmol) in 8 ml dry dichloromethane was added of dry triethylamine (1.1 mmol; 0.15 ml; 1.1eq.) by syringe through a septum. Then trialkylsilyl triflate (1.05 mmol) was added dropwise in the same manner. During the addition of the triflate the bright yellow color of the sulfine solution faded to slighty yellow or colorless. Isolation: After stirring for one minute, the dichloromethane was removed *in vacuo* and 10 ml of dry ether or pentane was added under an argon atmosphere causing precipitation of the triethylamine triflate salt. The solution of crude iminosilyl sulfenate was quickly transferred to an argon flushed oven dried flask and the solvent was removed *in vacuo* (water bath, room temperature). The crude product was kept under argon and was used immediately for NMR purposes.

Synthesis of β-lactams 25 (general procedures):

Method A: An *in situ* prepared solution of imino silylsulfenate (1.0 mmol) (see above) was cooled to –78°C. Then triethylamine (2.0 mmol; 0.27 ml) was added by a syringe through a septum, followed by the dropwise addition of a solution of acid chloride (1.3 mmol) in 10 ml of dichloromethane over 30 minutes. After completion of the addition, the reaction mixture was stirred at –78°C for 1-2 h (see below) and subsequently allowed to reach 0°C, at which stirring was continued for 1-2 h (see below). In some cases, the mixture was then also stirred at room temperature. The reaction mixture was poured into a 5% aqueous sodium carbonate solution, the layers were separated and the aqueous layer was extracted four times with 20 ml of dichloromethane. The combined organic fractions were dried ($MgSO_4$) and the solvent was removed *in vacuo*. This gave dark yellow viscous oils that sometimes partly solidified. The crude product was purified by column chromatography over silica gel. Solid β-lactams were then crystallized, while a second chromatography step was necessary to obtain the oily products in pure state. The reaction was performed up to 20 mmol scale for β-lactam **25c**).

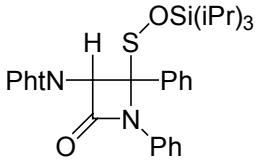
Method B: A solution of ketene was prepared by the addition of triethylamine (1.7 mmol, 0.23 ml) using a syringe to a cooled (-78°C) solution of the acid chloride (1.5 mmol) in 10 ml of dichloromethane, followed by stirring for 15-20 min. Then the *in situ* prepared solution of imino silylsulfenate (1.0 mmol) (see above) was cooled from 0° t0 –78°C and added by a canulla using argon pressure. From hereon the procedure was the same as in method A.

1-Phenyl-3-phenoxy-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25a)



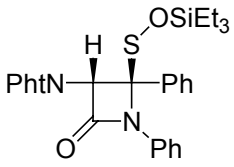
Obtained as a very viscous colorless oil, after 2x column chromatography (EtOAc : Hexane = 3:1), 368 mg (71%). ^{1}H-NMR (300MHz) d:0.88-1.03 (m, 21H, 3 (**H**$_3$C)$_2$C**H**-), 5.92 (s, 1H, **H**C-3 β-lactam), 6.81-7.83 (m, 15H, arom). ^{13}C-NMR (75 MHz) d: 12.2 (d, 3 (H$_3$C)$_2$**C**H-), 17.5 (q, 3 (H$_3$**C**)$_2$CH-), 83.0 (s, **C**-4 β-lactam), 84.6 (d, **C**-3 β-lactam), 115.5, 118.8, 122.0, 124.6, 127.2, 128.6, 129.2, 129.3 (d, **C**-arom.), 130.0 (Cipso), 136.1 (s, **C**$_{ipso}$-N), 157.0 (**C**$_{ipso}$-O), 161.6 (**C**=O). Mass (EI): m/e 519 (M^+). HRMS: calcd for $C_{30}H_{37}NO_3SSi$ 519.2263. Found 519.2267.

1-Phenyl-3-phthalimido-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25b)



Obtained as a colorless viscous oil, after column chromatography (hexane: ethyl acetate = 4:1), 310 mg (54%). It slowly crystallized upon storage at –20°C. Mp. 148-149°C. ^{1}H-NMR (300MHz) d: 0.90-1.20 (m, 21H, 3 (H$_3$C)$_2$CH-), 6.19 (s, 1H, HC-3 β-lactam), 7.02-7.95 (m, 14H, arom). ^{13}C-NMR (75 MHz) d: 12.4 (3 Me$_2$CH-), 17.5 (3 Me$_2$CH-), 62.3 (C-3 β-lactam), 83.4 (C-4 β-lactam), 118.7 , 123.4, 124.6, 127.7, 128.5, 129.4, 134.2 (d, arom.), 129.6, 131.2, 137.2 (s, arom.), 160.2 (C=O, β-lactam), 166.3 (2 C=O, phthaloyl). Mass (EI): m/e 573 (MH^+), 367 (MH^+- SOSi(iPr)$_3$, 56.1%).Elemental analysis: calcd. For $C_{32}H_{36}N_2O_4SSi$, C 67.10, H 6.33, N 4.89%. Found: C 67.38, H 6.19, N 4.70%.

1-Phenyl-3-phthalimido-4-phenyl-4-(*O*-triethylsilyl sulfenato)-azetidin-2-one (25c)



Obtained as white solid, after column chromatography (hexane: ethyl acetate = 4:1), 385 mg (73%). Colorless small needles after crystallization from diisopropyl ether. Mp. 163-164°C. ^{1}H-NMR (300MHz) d: 0.46-0.60 (m, 9H, 3 **H$_3$**C-CH$_2$-), 0.86-0.97 (t, 6H, 3 H$_3$C-C**H$_2$**-), 6.13 (s, 1H, **H**C-3 β-lactam), 7.14-7.90 (m, 14H, arom.). ^{13}C-NMR (75 MHz) d: 4.9 (t, 3 H$_3$C-**C**H$_2$-), 6.4 (q, 3 H$_3$**C**-CH$_2$-), 62.4 (d, C-3 β-lactam), 83.2 (s, C-4 β-lactam), 118.8, 123.4, 124.6, 127.8, 128.5, 128.7, 129.3, 134.1 (s, C-arom.), 129.5 131.2, 137.2 (s, C-arom), 160.2 (2 C=O, phthaloyl), 166.3 (C=O β-lactam). Mass (CI): m/e 531 (MH^+). HRMS: Calculated for $C_{29}H_{30}N_2O_4SiS$: 530.16956. Found 530.17028. Elemental analysis: calcd. for $C_{29}H_{30}N_2O_4SiS$: C 65.63, H 5.70, N 5.28%. Found: C 65.78, H 5.04, N 5.10%.

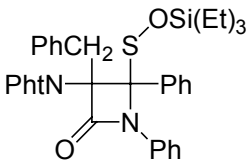
Crystals of **25c** suitable for X-ray diffraction studies were obtained from diisopropyl ether by slow cooling of a warm saturated solution. A single crystal was mounted in air on a glass fibre. Intensity data were collected at a temperature of -65°C. An Enraf-Nonius CAD4 single-crystal diffractometer was used, Cu-Kα radiation, θ-2θ scan mode. Unit cell dimensions were determined from the angular setting of 25 reflections. Intensity data were corrected for Lorentz and polarization effects. Semi-empirical absorption correction (Ψ-scans)[25] was applied. The structure was solved by the program CRUNCH[26] and was refined with standard methods (refinement against F^2 of all reflections with SHELXL97 [27] with anisotropic parameters for the non hydrogen atoms. All hydrogens were initially placed at calculated positions and were freely refined subsequently.

Crystal data and structure refinement for **25c**.

Crystal color	transparent colorless
Crystal shape	very regular rod
Crystal size	0.36 x 0.14 x 0.13 mm
Empirical formula	$C_{29}H_{30}N_2O_4SSi$
Formula weight	530.70
Temperature	208(2) K
Radiation / Wavelength	CuKα(graphite mon.) / 1.54184 Å
Crystal system, space group	Monoclinic, P21/n
Unit cell dimensions	a, α= 9.7392(3) Å, 90°
(25 reflections 40.313 < θ < 46.227)	b, β= 17.9410(3) Å, 99.447(3)°
	c, γ= 15.9856(4) Å, 90°
Volume	2755.29(12) Å^3
Z, Calculated density	4, 1.279 Mg/m^3
Absorption coefficient	1.761 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / θ-2θ
F(000)	1120
θ-range for data collection	3.73 to 69.92°
Index ranges	-11<=*h*<=0, -21<=*k*<=0, -19<=*l*<=19
Reflections collected / unique	5533 / 5214 [R_{int} = 0.0503]
Reflections observed	4504 ([I_o>2σ(I_o)])
Absorption correction	Semi-empirical from Ψ-scans
Range of relat. transm. factors	1.122 and 0.915
Refinement method	Full-matrix least-squares on F^2

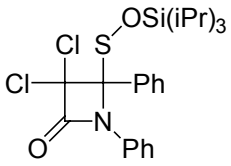
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	5214 / 0 / 454
Goodness-of-fit on F^2	1.111
SHELXL-97 weight parameters	0.059900 1.546200
Final R indices [I>2σ(I)]	R_1 = 0.0433, wR_2 = 0.1163
R indices (all data)	R_1 = 0.0513, wR_2 = 0.1229
Largest diff. peak and hole	0.477 and -0.431 e.Å^{-3}

1-Phenyl-3-phthalimido-3-benzyl-4-phenyl-4-(*O*-triethylsilyl sulfenato)-azetidin-2-one (25d)



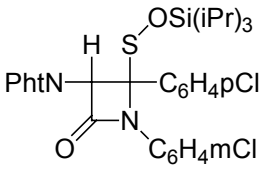
Obtained as a white solid, after column chromatography (hexane: ethyl acetate = 6:1), 154 mg (28%, method B). mp.: >200°C (dec.) ^{1}H-NMR (300MHz) d: 0.48-0.71 (m, 21H, 3 (**H$_3$**C)$_2$C**H**-), 2.92 (d, 1H, B of AB, J_{AB}= 14.8 Hz, benzylic), 3.39 (d, 1H, A of AB, J_{AB}= 14.8 Hz, benzylic), 7.00-7.90 (m, 19H, arom.). ^{13}C-NMR (75 MHz) d: 12.3 (d, 3 (H$_3$C)$_2$**C**H-), 17.3, 17.5, 17.6 (q, 3 (H$_3$**C**)$_2$CH-), 38.3 (t, Ph**C**H$_2$-), 78.2 (s, **C**-4 β-lactam), 85.7 (d, **C**-3 β-lactam), 119.1, 122.8, 123.4, 124.5, 126.7, 126.9, 128.0, 128.5, 128.7, 129.0, 130.1, 133.7, 133.9 (**C**-arom.), 131.5, 131.8, 131.9, 134.9, 137.0 (**C**$_{ipso}$), 161.5, 165.4, 168.7 (**C**=O, phthaloyl and β-lactam).Mass (CI): m/e 663 (MH$^+$). HRMS: Calcd for (M+-iPr): $C_{36}H_{35}N_2O_4SiS$: 619.20868. Found: 619.20811. Calcd for (M$^+$-O=C-N-Ph), $C_{32}H_{37}NO_3SiS$: 543.22635. Found: 543.22781.

1-Phenyl -3,3-dichloro-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25e)



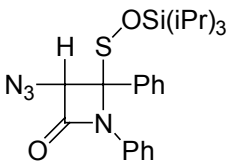
Obtained as a slightly yellow viscous oil after column chromatography (hexane: ethyl acetate= 6:1) 398 mg (80%). It crystallized slowly after several months of storage at –20°C. Mp. 57-60°C. ^{1}H-NMR (300MHz) d: 0.85-1.14 (m, 21H, 3 (**H$_3$**C)$_2$C**H**-), 7.15-7.42 (m, 8H, arom), 7.82-7.86 (m, 2H, arom). ^{13}C-NMR (75 MHz) d: 12.2 (3 (H$_3$C)$_2$**C**H-), 17.4 (3 (H$_3$**C**)$_2$CH-), 90.4 (C-4 β-lactam), 91.4 (C-3 β-lactam), 119.0, 125.4, 125.9, 128.8, 129.0, 130.0, 131.1(**C**$_{ipso}$), 136.6 (**C**$_{ipso}$-N), 158.6 (**C**=O). Mass (EI): m/e 495, 465 (M$^+$). HRMS: calcd for $C_{24}H_{31}NO_2SiSCl_2$: 495.12219. Found: 495.12197.

1-(3-Chlorophenyl)-3-phthalimido-4-(4-chlorophenyl)-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25f)



Obtained as a slightly yellow viscous oil, after column chromatography (hexane: ethyl acetate = 6:1) 250 mg (42%). It crystallized upon standing at –20°C. Mp. 196-199°C. ^{1}H-NMR (300MHz) d: 0.90-1.00 (m, 21H, 3 (H$_3$C)$_2$CH-), 6.18 (s, 1H, HC-3 β-lactam), 7.13-7.37 (m, 6H, arom), 7.70-7.92 (m, 6H, arom). ^{13}C-NMR (75 MHz) d: 12.2 (3 Me$_2$CH-), 17.4 (3 Me$_2$CH-), 62.2 (C-3 β-lactam), 83.1 (C-4 β-lactam), 116.5, 118.4, 123.5, 124.7, 128.8, 128.9, 129.7, 134.3 (d, arom.), 127.7, 131.0, 135.6, 137.8 (s, arom.), 160.1 (C=O, β-lactam), 166.1 (2 C=O, phthaloyl). Mass (CI): m/e 641(M$^+$), 597 (M$^+$-iPr). HRMS: measured on fragment 597: Calcd for $C_{29}H_{27}N_2Cl_2O_4SiS$: 597.08379. Found: 597.08414.

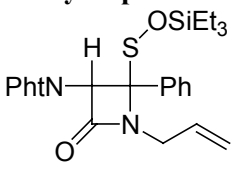
1-Phenyl-3-azido-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one 25g



Obtained as a light yellow viscous oil, after column chromatography (hexane: ethyl acetate = 8:1) 193 mg (41%, method B).
^{1}H-NMR (300MHz) d: 0.85-0.98 (m, 21H, 3 (**H$_3$**C)$_2$C**H**-), 4.79 (s, **H**C-3 β-lactam minor isomer), 5.19 (s, 1H, **H**C-3 β-lactam major isomer), 6.95-7.68 (m, 10H, arom). ^{13}C-NMR (75 MHz) d: 12.4 (3 (CH$_3$)$_2$**C**H-), 17.4 (3 (**C**H$_3$)$_2$CH-), major isomer: 71.8 (C-3 β-lactam), 83.1 (C-4 β-lactam), 118.7, 124.8, (**C**-arom.) 132.8, 136.3 (**C**$_{ipso}$), 160.2 (**C**=O). minor isomer: 75.6 (C-3 β-lactam), 82.5 (C-4 β-lactam), 118.5, 124.7 (C-arom), 134.0, 136.7 (**C**$_{ipso}$), 160.9 (**C**=O). Further arom. signals: 126.9, 127.2, 127.6, 128.1,

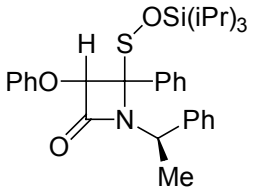
128.3, 128.6, 128.8, 128.9, 129.4, 129.9. Mass (CI): m/e 469 (MH^+). HRMS:Calcd for $C_{24}H_{33}N_4O_2SiS$ (MH+): 469.20935. Found: 469.21001

1-Allyl-3-phthalimido-4-phenyl-4-(*O*-triethylsilyl sulfenato)-azetidin-2-one (25h)



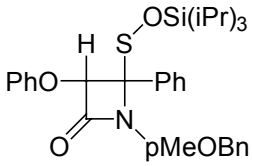
Obtained as a slightly yellow viscous oil, after column chromatography (hexane: ethyl acetate = 3:1), 255 mg (52%, method B).
^{1}H-NMR (300MHz) d: 0.80 (q, 9H, 3 **H$_3$**C-CH$_2$-), 1.06 (t, 6H, 3 H$_3$C-C**H$_2$**-), 4.13 (dd, B of AB each splitt in multiplet, 1H, $J_{AB}\approx$ 18Hz, -CH**H**-CH=CH$_2$), 4.13 (A of AB each splitt in multplet, 1H, $J_{AB}\approx$ 18Hz, -C**H**H-CH=CH$_2$), 5.41 (dd, 1H, J= 9Hz, 1.2 Hz, -CH$_2$-CH=CH**H**$_{cis}$), 5.67 (dd, 1H, J=16.5Hz, 1.2 Hz, -CH$_2$-CH=CH**H**$_{trans}$), 5.83 (s, 1H, **H**C-3 β-lactam), 6.21 (m, 1H, -CH$_2$-C**H**=CH$_2$), 7.14-7.90 (m, 9H, H-arom.). ^{13}C-NMR (75 MHz) d: 4.9 (t, 3 H$_3$C-**C**H$_2$-), 6.6 (q, 3 H$_3$**C**-CH$_2$-), 44.2 (d, -**C**H$_2$-CH=CH$_2$), 62.3 (d, C-3 β-lactam), 83.8 (s, C-4 β-lactam), 116.4 (t, -CH$_2$-CH=**C**H$_2$), 123.4, 127.3, 128.5, 129.3, 131.7, 134.2 (d, **C**-arom + -CH$_2$-**C**H=CH$_2$), 130.1, 131.2 (s, **C**-arom), 163.4 (s, 2 **C**=O phthaloyl), 166.5 (**C**=O β-lactam). Mass (CI): m/e 495 (MH^+). HRMS: Calcd for $C_{26}H_{30}N_2O_4SiS$: 494.16956. Found: 494.16999.

1-[α-(+)-Methylbenzyl]-3-phenoxy-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25i)



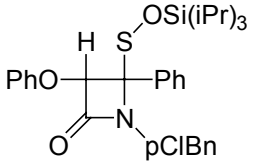
Obtained as a colorless viscous oil, after column chromatography (hexane: ethyl acetate = 4:1), 413 mg (76%, method B), 1:1 mixture of diasteromers.
^{1}H-NMR (300MHz) d: 0.97 (m, 6H, 2x3 (CH$_3$)$_2$C**H**-), 1.06 (m, 36H, 2x3 C**H$_3$**)$_2$CH-), 1.89 (d, 3H, J= 7.2Hz, **H$_3$**C-CHPh), 1.98 (d, 3H, J= 7.2Hz, **H$_3$**C-CHPh), 4.48-4.58 (overlapping quartets, 2H, 2x H$_3$C-C**H**Ph), 5.62 (s, 1H, **H**C-3 β-lactam), 5.78 (s, 1H, **H**C-3 β-lactam), 6.85-7.60 (m, 15H, arom.). ^{13}C-NMR (75 MHz) d: 12.2, 12.4, 12.6 (3 Me$_2$**C**H-), 17.7, 17.8, 17.9 (3 **Me**$_2$CH-), 21.5, 21.9 (2 H$_3$**C**-CHPh), 54.7, 54.8 (2 H$_3$C-**C**HPh), 83.3, 85.0 (s, C-4 β-lactam), 84.4, 84.8 (d, C-3 β-lactam), 116.0, 116.1, 122.0, 122.1, 127.2, 127.3, 127.4, 127.6, 127.8, 128.3, 128.4, 128.7, 129.0, 129.4, 130.3, 131.3 (C-arom), 142.5, 142.8 (C-ipso), 157.1, 157.3 (**C**$_{ipso}$-O), 164.4, 164.6 (**C**=O). Mass (EI): m/e 547(M^+), 342 (M^+-SOSi(iPr)$_3$, 59.9%). HRMS: Calcd for $C_{32}H_{41}NO_3SiS$: 547.25764. Found: 547.25750.

1-(p-Methoxybenzyl)-3-phenoxy-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25j)



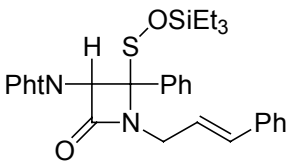
Obtained as a colorless viscous oil, after column chromatography (hexane: ethyl acetate = 4:1) 439 mg (78%). ^{1}H-NMR (300MHz) d:1.05-1.23 (m, 21H, 3 (C**H$_3$**)$_2$C**H**-), 3.78 (s, 3H, **H$_3$**CO-), 4.30 (d, 1H, B of AB, J=15.0 Hz, benzylic), 4.75 (d, 1H, A of AB, J=15.0 Hz, benzylic), 5.78 (s, 1H, **H**C-3 β-lactam), 6.78-7.41 (m, 14H, arom.). ^{13}C-NMR (75 MHz) d: 12.2, 12.3 (3 Me$_2$**C**H-), 17.6, 17.7 (3 **Me**$_2$CH-), 44.0 (Ph**C**H$_2$N-), 55.2 (H$_3$**C**O-), 84.4 (C-4 β-lactam), 85.6 (C-3 β-lactam), 113.8, 115.8, 122.0, 125.7, 127.5, 128.1, 129.3, 130.6 (C-arom), 157.2, 159.1 (**C**$_{ipso}$-O), 165.0 (C=O). Mass (CI): m/e 564 (MH^+). HRMS: calcd for $C_{32}H_{41}NO_4SiS$: 563.25256. Found: 563.25113

1-(p-Chlorobenzyl)-3-phenoxy-4-phenyl-4-(*O*-triisopropylsilyl sulfenato)-azetidin-2-one (25k)



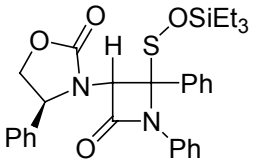
Obtained as a colorless viscous oil, after column chromatography (hexane: ethyl acetate = 6:1) 358 mg (63%). ^{1}H-NMR (300MHz) d: 1.05-1.25 (m, 21H, 3 (H$_3$C)$_2$CH-), 4.38 (d, 1H, J=14.7 Hz, B of AB, PhC**H**HN-), 4.70 (d, 1H, J=14.7 Hz, A of AB, PhCH**H**N-), 5.78 (s, 1H, HC-3 β-lactam), 6.90-6.95 (m, 4H, arom), 7.09-7.40 (m, 12H, arom). ^{13}C-NMR (75 MHz) d: 12.2 (3 Me$_2$**C**H-), 17.6 (3 **Me**$_2$CH-), 44.1 (Ph**C**H$_2$N-), 84.4 (C-4 β-lactam), 85.6 (C-3 β-lactam), 115., 122.4, 127.8, 128.7, 129.3, 129.7 (C-arom.) 133.6, 134.6 (s, C-arom.), 157.1 (s, C$_{ipso}$-O) 165.1 (s, C=O). Mass (CI): m/e 568 (MH^+). HRMS: Calcd for $C_{31}H_{38}NO_3SiSCl$: 567.20302. Found: 567.20332.

1-Cinnamyl-3-phthalimido-4-phenyl-4-(*O*-triethylsilyl sulfenato)-azetidin-2-one (25l)



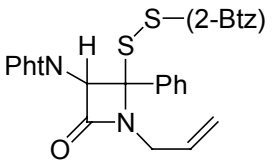
Obtained as a slightly yellow viscous oil, after column chromatography (hexane: ethyl acetate = 6:1), 96 mg (17%, method B). ^{1}H-NMR (300MHz) d: 0.78-0.90 (m, 6H, 3 $CH_3C\mathbf{H_2}$-), 1.03-1.10 (m, 9H, 3 $C\mathbf{H_3}CH_2$-), 4.37 (m, 2H, N-$C\mathbf{H_2}$-CH=CHPh), 5.83 (s, 1H, **H**C-3 β-lactam), 6.55 (m, 1H, N-CH_2-C**H**=CHPh), 6.86 (d, 1H, J=15.9Hz, N-CH_2-CH=C**H**Ph), 7.14-7.75 (m, 14H, arom.). ^{13}C-NMR (75 MHz) d: 4.9 (t, 3 H_3C-$\mathbf{C}H_2$-), 6.6 (q, 3 $H_3\mathbf{C}$-CH_2-), 43.7 (N-$\mathbf{C}H_2$-CH=CHPh), 62.4 (C-3 β-lactam), 83.8 (C-4 β-lactam), 123.4, 126.6, 127.3, 127.6, 128.4, 128.5, 129.3, 130.1, 131.2, 133.5 (C-arom.), 134.2 (2 $\mathbf{C}_{ipso}$ phthaloyl), 136.7 ($\mathbf{C}_{ipso}$), 163.2 (**C**=O phthaloyl and β-lactam, overlapping). Mass (EI): m/e 570 (M^+). HRMS: m/e calcd for $C_{32}H_{43}N_2O_4SSi$: 570.20000. Found: 570.19885.

(4*S*)-3-[1-Phenyl-2-oxo-4-phenyl-4-(*O*-triethylsilyl sulfenato)-azetidinyl]-4-phenyl-2-oxazolidinone (25m)



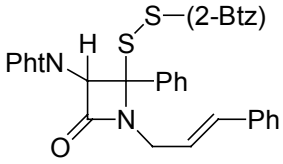
Obtained as a white amorphous solid, after column chromatography (hexane: ethyl acetate = 2:1) followed by trituration with n-hexane, 62 mg (11%, method B). ^{1}H-NMR (300MHz) d: 0.28-0.36 (m, 6H, 3 $CH_3C\mathbf{H_2}$-), 0.68-0.73 (m, 9H, 3 $C\mathbf{H_3}CH_2$-), 4.07 (dd, 1H, J= 6.9 Hz, 8.7 Hz, O-C**H**HCHPh), 4.43 (t, 1H, J= 8.7 Hz, O-CH_2C**H**Ph), 4.95 (dd, 1H, J= 6.9 Hz, 8.7 Hz, O-CH**H**CHPh), 5.18 (s, 1H, **H**C-3 β-lactam), 7.10-7.40 (m, 13H, arom.), 7.70-7.75 (m, 2H, arom.). ^{13}C-NMR (75 MHz) d: 4.5 (3 H_3C-$\mathbf{C}H_2$-), 6.3 (3 $H_3\mathbf{C}$-CH_2-), 59.9, 66.3, 70.5, 83.3 (C-4 β-lactam), 118.8, 124.5, 127.4, 128.0, 128.5, 128.7, 129.1, 129.4, 129.6,136.8, 136.9, 156.6 (**C**=O), 160.1(**C**=O). Mass (CI): m/e 547 (MH^+), 517 (M^+-Et, 18.6 %). Elemental analysis: calcd. for $C_{30}H_{34}N_2O_4SSi$, C 65.90, H 6.27, S 5.86, N 5.12%. Found C 65.96 , H 6.56, S 5.35, N 5.11%.

1-Allyl-3-phthalimido-4-phenyl-4-[(2-dithiobenzothiazolo)]-azetidin-2-one (35a)



To a stirred solution of **25h** (mg, 0.10 mmol) in anhydrous toluene (2 ml) at 0^{o}C was added 2-mercaptobenzothiazole (25 mg, 0.15 mmol). After 5 min. The reaction mixture was allowed to reach room temperature and was left stirring until TLC (heptane : ethyl acetate = 1:1) indicated complete consumption of starting material (24 h). After removal of the toluene *in vacuo*, the crude product was purified by column chromatography (heptane : ethyl acetate = 3:1) to give **35a** 45 mg (83%) product as a light yellow solid. Mp. >85^{o}C (dec.) ^{1}H-NMR (300MHz) d: 4.12 (m, 2H, N-$C\mathbf{H_2}$-), 5.42 (d, J= 9.6Hz, 1H, **H**HC=CH-), 5.63 (d, J= 17.4Hz, 1H, H**H**C=CH-), 5.96 (s, 1H, **H**-C-3 β-lactam), 6.20 (m, 1H, H_2C-C**H**=CH_2), 7.18-7.75 (m, 11H, arom.), 7.92 (d, J= 7.5 Hz, 2H, arom), 8.02 (d, J= 7.5Hz, 2H, arom). ^{13}C-NMR (75 MHz) d: 45.1 (**C**H_2-CH=CH), 64.7 (H-**C**-C(=O)-N), 81.8 (O=C-N-**C**-S), 119.2, 121.3, 122.8, 123.4, 125.3, 126.5, 126.9, 127.2, 128.7, 129.4, 130.8, 131.0, 132.9, 134.2, 136.4, 144.1, 162.7 (C=O), 167.8 (C=O). Mass (CI): m/e 529 (MH^+), 363 (M^+-BtZS$^-$, 100%). HRMS: m/e calcd for $C_{27}H_{19}N_3O_3S_3$: 529.05885. Found 529.05824.

1-Cinnamyl-3-phthalimido-4-phenyl-4-[(2-dithiobenzothiazolo)]-azetidin-2-one (35b)



Prepared according to procedure for **35a** from **25l** (33 mg, 0.054 mmol) was obtained 28 mg **35b** (85%) product as a light yellow solid. Mp.>96^{o}C (dec.). ^{1}H-NMR (300MHz) d: 4.36 (d, J= 5.9 Hz, 2H, N-$C\mathbf{H_2}$-), 5.95 (s, 1H, **H**-C-3 β-lactam), 6.47-6.57 (doublet of triplets, J= 5.9 Hz and 16 Hz, 1H, CH_2-C**H**=CH-Ph), 6.83 (d, J= 16 Hz, 1H, Ph-C**H**=CH-CH_2), 7.17-7.60 (m, 16H, arom.), 7.90-8.00 (m, 2H, arom). ^{13}C-NMR (75 MHz) d: 44.6 (**C**H_2-CH=CH), 64.8 (H-**C**-C(=O)-N), 81.7 (O=C-N-**C**-S), 121.3, 122.0, 122.8, 123.5, 125.2, 126.5, 126.7, 127.3, 128.0, 128.5, 128.7, 129.5, 131.0, 133.0, 134.2, 134.4, 136.2, 136.4, 148.3, 162.3 (C=O), 165.5 (C=O). Mass (CI): m/e 606 (MH+), 438 (M^+-BtzS$^-$, 100%). HRMS: m/e calcd for $C_{33}H_{23}N_3O_3S_3$: 605.09015. Found:605.09004

2.8 References

1] B. Zwanenburg and B. G. Lenz in Houben-Weyl, *Methoden der Organischen Chemie Band. E-11/2*, pp 911– 949 Georg Thieme, Stuttgart 1985 and references cited therein.

2] J.R. Cashman and R.P. Kubersky, *J. Org. Chem.* **47**, 4645 (1982).

3] W. Walter and M. Steffen, *Justus Liebigs Ann. Chem.* **742**, 53 (1968).

4] **a**] W. Walter and J.Voss in "*Organosulfur Chemistry*", ed. M.J. Janssen, Interscience, New York, 1967, **b**] W. Walter and O.H. Bauer, *Justus Liebigs Ann. Chem*. 1584 (1976) and 428 (1977).

5] W. Walter and J. Curts, *Justus Liebigs Ann. Chem.* **643**, 29 (1961).

6] *O*-alkylation of other sulfines by treatment with Meerwein's reagent has been reported for diphenylsulfine and (2,4,6-trimethylphenyl)(methylthio)sulfine:
a] L. Carlsen and A. Holm, *Acta Chem. Scand.* **B**30, 277 (1976).
b] M.A. Perez and G. Kresze, *Justus Liebigs Ann. Chem.*1505, (1981).

7] B.G. Lenz and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **103**, 342-347 (1984).

8] Cinnamyl azide was obtained from cinnamyl chloride by stirring overnight with 1.05 eq. of sodium azide in dry *N*,*N*-dimethylformamide followed by quenching with water and extraction with ether. The combined ether fractions were washed with brine and dried ($MgSO_4$). The crude product was chromatographed over silicagel using pentane as the eluent (84% yield). The amine was obtained by reduction of the azide: I. Bosch, A.M. Costa, M. Martin, F. Urpi and J. Vilarrasa, *Organic Lett.* **2**, 397 (2000). It was used immediately after its isolation.

9] Thiobenzoylated amino acids and -esters:
a] W. Bauer and K. Kühlein in Houben Weyl, *Methoden der Organischen Chemie Band.E-5/2* pp.1250, Georg Thieme, Stuttgart 1985 and references therein.
b] K.M. Doyle and F. Kurzer, *Chem. & Industry*, 803 (1974) and references therein.
c] A. Kjær, *Acta Chem. Scand*. **6**, 327 (1952); *ibid.* **4**, 1347 (1950).

10] **a**] J.Mattay, R.Conrads and R.Hoffmann in Houben-Weyl, *Methoden der Organischen Chemie* Band E-21, pp. 3070, Georg Thieme, Stuttgart 1995 and references therein.
b] G. I. Georg and V. T. Ravikumar in "*The Organic Chemistry of β-lactams*" Chapter 6, ed. G.I. Georg, VCH, New-York (1992).

11] **a**] D.R. Wagle, C.Garai, J.Chiang, M.G. Monteleone, B.E. Kurys, T.W. Strohmeyer, V.R. Hegde, M.S.Manhas and A.K. Bose, *J.Org.Chem.* **53**, 4227 (1988).
b] A.K. Bose, M.S. Manhas, J.M. van der Veen, S.G. Amin, I.F. Fernandez, K.Gala, R.Gruska, J.C.Kapur, M.S. Khajavi, J. Kreder, L.Mukkavilli, B.Ram, M.Seguira and J.E.Vincent, *Tetrahedron* **37**, 2321 (1981).
c] A.K. Bose, G.Spiegelman and M.S.Manhas, *J.Am.Chem.Soc.* **90**, 16, 4506 (1968).
d] H. Vanderhaeghe and J.Thomis, *J. Med. Chem.* **18**, 5 (1975).

12] D.R. Wagle, C.Garai, J.Chiang, M.G.Monteleone, B.E.Kurys, T.W.Strohmeier, V.R.Hegde, M.S.Manhas and A.K.Bose, *J.Org.Chem.* **53**, 4227 (1988).

13] R.A. Firestone, N.S. Maciejewicz, R.W.Ratcliffe and B.G.Christensen, *J.Org.Chem.* **39**, 437 (1974).

14] M.Bachi and J.Vaya, *J.Org.Chem.* **44**, 4393 (1979).

15] D. A. Evans and E.B. Sjogren, *Tetrahedron Lett.* **26**, 32, 3783 (1985).

16] G.Simchen and W. West, *Synthesis* 247 (1977).

17] **a**] T.S. Chou, J.R. Burgtorf, A.L. Ellis, S.R. Lammert and S.P. Kukolja, *J. Am. Chem. Soc.* **96**, 1609 (1974).

b] T. S. Chou, G.A. Koppel, D.E. Dorman and J.W. Paschal, *J. Am. Chem. Soc.* **98**, 7864 (1976).

c] D.H.R. Barton, F.Comer, D.G.T. Greig, P.G. Sammes, C.M. Cooper, G. Hewitt and W.G.E. Underwood, *J. Chem. Soc. C*, 3540 (1971).

d] M.J.V. de Oliviera Baptista, A.G.M. Barret, D.H.R. Barton, M. Girijavallabhan, R.C. Jennings, J. Kelly, J. Papadimitriou, J.V. Turner and N.A. Usher, *J.Chem. Soc. Perkin I*, 1477 (1977).

e] G.A. Koppel and S. Kukolja, *J. Chem. Soc. Chem. Commun.* 57 (1975).

f] M.D. Bachi, O. Goldberg and A. Gross, *Tetrahedron Lett.* **43**, 4167 (1978).

g] D.H.R. Barton, I.H. Coates and P.G. Sammes, *J.Chem. Soc. Chem. Commun.* 303 (1973).

h] D.H.R. Barton, I.H. Coates, P.G. Sammes and C.M. Cooper, *ibid*. 1459 (1974).

i] R.B. Morin, B.G. Jackson, R. A. Mueller, E.R. Lavagnino, W.B. Scanlon and S. L. Andrews, *J. Am. Chem. Soc.* **85**, 1896 (1976).

j] D.O. Spry, *ibid.* **92**, 5006 (1970). k) P.G. Sammes, *Chem. Rev.* **76**, 113 (1976).

k] G. Francheschi, M. Alpegiani, C. Battistini, A. Bedeschi, E. Perrone and F. Zarini, *Pure & Appl. Chem.* **59**, 467 (1987).

l] S.N. Maiti, P. Spevak, K. Ogawa and R.G. Micetich, *J. Org. Chem*. **53**, 3803 (1988).

m] J.Verweij and E. de Vroom, *Recl. Trav. Chim. Pays-Bas* **112**, 66-81 (1993).

n] P.A.M. van der Klein, J. Castelijns, H.G.J. Hirs, J. Verweij and E. de Vroom, *Recl. Trav. Chim. Pays-Bas* **115**, 185 (1996).

o] H. Tanaka, Y. Yamaguchi, S. Sumida and S. Torii, *J. Chem. Soc. Chem. Commun.* 2705, (1996).

18] J.E. Arrowsmith and C.W. Greengrass, *Tetrahedron Lett.* **23**, 3, 357-360 (1982).

19] R. B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon and S.L. Andrews, *J. Am. Chem. Soc.* **91**, 1401 (1969).

20] **a**] F.A. Davies, R.H. Jenkins Jr., S.Q.A. Rizvi and S.G.Yocklovich, *J.Org.Chem.* **46**, 3467 (1981) and references therein.

b] J.R. Shelton and K.E. Davies, *J. Am. Chem. Soc.* **89**, 718 (1967).

21] T.S.Chou, *Tetrahedron Lett.* **9**, 725-728 (1974).

22] R.G. Micetich, S. Betageri, R. Singh and P.Payne, *J.Org.Chem.* **52**, 915 (1987).

23] **a**]Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, *Tetrahedron Lett.* **32**, 3001 (1973).

b] J.E. Baldwin and P. Singh, *Tetrahedron Lett.* **39**, 3757 (1979).

c] T. Kamiya, T. Teraji, M. Hashimoto, O. Nakaguchi and T. Oku, *J. Am. Chem. Soc.* **97**, 5020 (1975).

d] R.G. Micetich, S. Betageri, R. Singh and P. Payne, *J.Org. Chem*. **52**, 915-918 (1987).

e] A. Balsamo ,P.M. Benedini, B. Macchi and A. Rosselo, *J. Chem. Soc. Perkin I*, 413 (1984).

f] R.G. Micetich and R.B. Morin, *Tetrahedron Lett*. **13**, 979 (1976).

g] M. Alpegiani, F. Giudici and D. Borghi, *Tetrahedron Lett.* **31**, 3509 (1990).

h] R.G. Micetich, S.N. Maiti and P. Spevak, *Synthesis* 292 (1986).

i] J.E. Baldwin, R.M. Adlington, T.W. Kang, E, Lee and C. J. Schofield, *J. Chem. Soc. Chem. Commun.* 104 (1987).

j] J. Kant and D.G. Walker in " *The Organic Chemistry of β-lactams*" Chapter 3, ed. G.I. Georg, VCH, New-York (1992).

24] J.E. Baldwin, J.E.Cobb and L.N. Sheppard, *Tetrahedron* **43**, 5, 1003 (1987).

25] A.C.T.North, D.C.Philips and F.S. Mathews, *Acta Crystallogr.* **A24**, 351 (1968).

26] R. de Gelder, R.A.G. de Graaff and H. Schenk, *Acta Crystallogr.* **A49**, 287 (1993).

27] Sheldrick, G.M. SHELXL-97. Program for the refinement of crystal structures; University of Göttingen: Germany, 1997.

CHAPTER 3

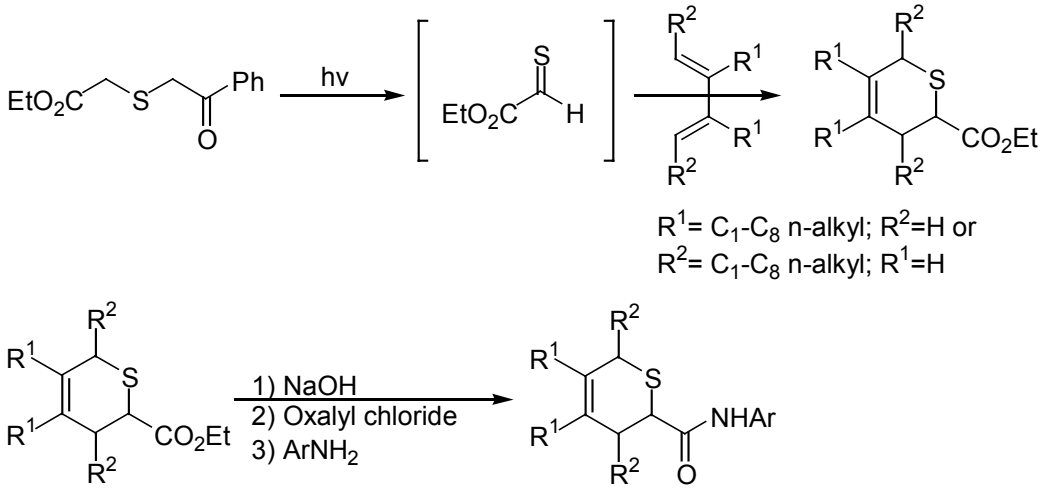
2-Carboxamido- and 2-thiocarboxamido-3,6-dihydro-2*H*-thiopyran *S*-oxides

Synthesis and reactions of sulfines derived from *O*-silyl-monothioketene- and *S*-silyl-dithioketene acetals

---

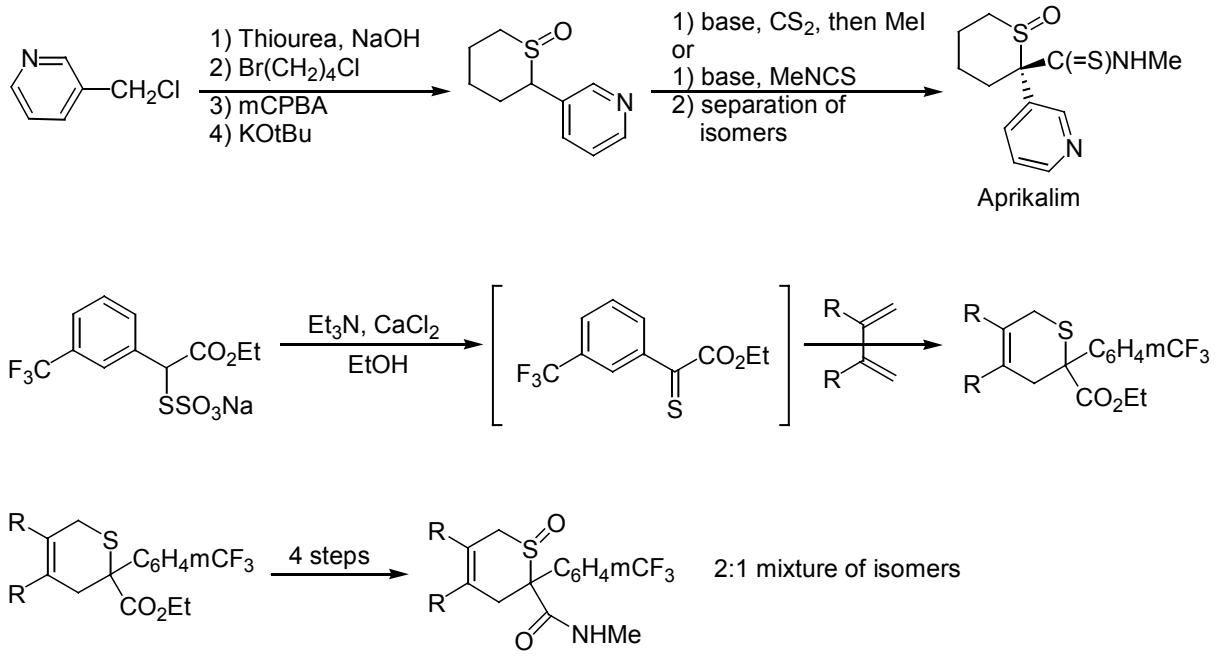
3.1 Introduction

In recent years the synthesis of 3,6-dihydro-2*H*-thiopyran derivatives have received considerable attention.[1] In some cases these dihydrothiopyran derivatives showed interesting biological activities.[1,2] Wilde and coworkers[2a] prepared a number of 4,5- (and 3,6-) dialkyl substituted dihydrothiopyran-2-carboxamides (Scheme 1), some of which showed activity in the systemic inhibition of the enzyme Acyl-CoA: cholesterol acyl transferase (ACAT). Such compounds are believed to slow down or even reverse the artherosclerotic process. Their dihydrothiopyran synthesis involved the cycloaddition of photochemically *in situ* generated thioaldehydes with 2,3-dialkyl-1,3-butadienes and 1,4-dialkyl-1,3-butadienes. In a second step the ester function was converted into the carboxamide in the manner indicated.



Scheme 1

An example of a biologically active thiane derivative is Aprikalim®, which is a promising candidate as an anti-hypertensive and anti-anginal agent. Brown and coworkers prepared Aprikalim® and a number of analogues starting from 3-(chloromethyl)-pyridine and other chloromethyl-heteroaromatics whereby the six-membered sulfur heterocycle was prepared by a conventional ring-closure reaction (Scheme 2).[1a,2b]

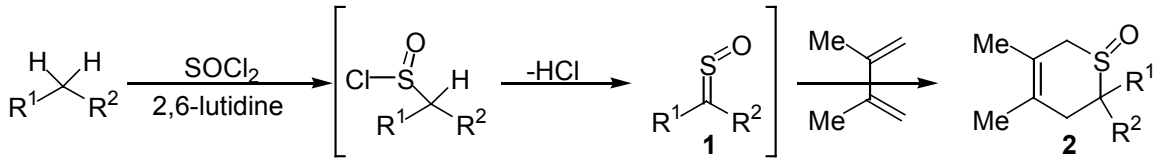


Scheme 2

It was shown that for biological activity a *trans*-relationship between the sulfoxide and the thioamide functions is a prerequisite. Pinto et al.[1a] reported the synthesis of dihydrothiopyran carboxamido derivatives by the hetero-Diels-Alder reaction of *in situ* prepared α-thiocarbonyl-esters with different 1,3-dienes, followed by transformation of the ester function into the *N*-methyl amide (Scheme 2). It should be emphasized here that the synthesis depicted in scheme 2 leads to *cis*/*trans* mixtures of products that need to be separated as only the isomers with a *trans*-configuration of the sulfoxide and the (thio)carboxamide substituents are desired.

The brief survey presented above clearly suggests that the hetereo-Diels-Alder reaction of thiocarbonyl compounds with 1,3-dienes is a convenient method for the synthesis of 3,6-dihydro-2*H*-thiopyrans derivatives. However, it should be noted that the scope of this reaction is seriously limited by the availability of suitable thiocarbonyl compounds, which in many cases must be generated *in situ*. Therefore, sulfines (thiocarbonyl *S*-oxides) are a welcome synthetic equivalent for these dienophiles. It is well documented that sulfines can undergo a Diels-Alder type cycloaddition with a variety of 1,3-dienes to give the corresponding 3,6-dihydro-2*H*-thiopyran *S*-oxides in good yields,[3,4] which can be readily deoxygenated by reaction with sodium iodide and trifluoroacetic anhydride[5] to produce the dihydrothiopyrans. Sulfines can be prepared by a variety of methods. [3,4,7,6] A wide range of sulfines can thus be made available, including those that have electron-withdrawing substituents at the sulfine carbon atom required for a high reactivity in the [4+2]-cycoaddition reactions with 1,3-dienes. In this manner, dihydrothiopyrans with a wide selection of substituents can be obtained. The α-oxo-sulfines **1** are of particular interest as they can be readily prepared, either *in situ* or as such, from doubly-activated methylene compounds or enol silyl ethers by reaction with thionyl chloride in the presence of a suitable tertiairy base, such as 2,6-lutidine, triethylamine or diisopropylethylamine.[7,6] Elimination of hydrogen chloride from the initially formed sulfinyl chlorides by base generates the α-oxo-sulfines in good to excellent yields. Subsequent reaction with appropriate 1,3-dienes then leads to 3,6-dihydro-2*H*-thiopyran *S*-oxides **2**. An illustrative series of such compounds obtained from doubly-activated methylene compounds is depicted in Table 1.

Table 1 Synthesis of α-oxo sulfines from doubly-activated methylene compounds and their subsequent trapping with 2,3-dimethyl-1,3-butadiene.

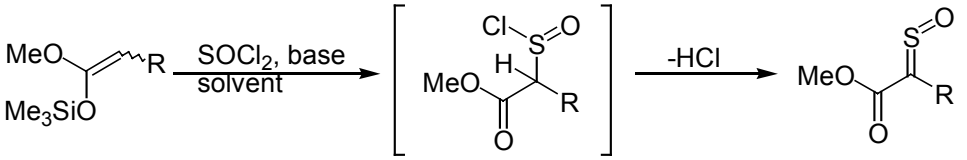


R^1	R^2	T (°C)	yield (%)	ref	R^1	R^2	T (°C)	yield (%)	ref
PhC(=O)	C(=O)Ph	-18	85	6,7	EtO_2C	$(O=)P(OEt)_2$	20	92[a,b]	6,7
MeC(=O)	CO_2Et	-18	48[a]	6,7	EtO_2C	SO_2Ph	0	93	6,7
PhC(=O)	SPh	20	31[b]	6,7	SO_2Ph	NO_2	0	66	6,7
PhC(=O)	SO_2Ph	-18	68	6,7	NC	$(O=)P(OEt)_2$	0	75	6,7
EtO_2C	CO_2Et	0	75	6,7	NC	SO_2Ph	0	93	6,7
EtO_2C	CN	0	96	6,7	NC	CN	0	92	6,7

a) Obtained as mixtures of diastereomers.
b) Triethylamine was used as the base.

Examples of α-oxo sulfines **3** derived from *O*-silyl ketene acetals are shown in Table 2. These sulfines have been isolated as such,[7] or alternatively were trapped by 2,3-dimethyl-1,3-butadiene as 3,6-dihydro-2*H*-thiopyran *S*-oxides.[6, 7]

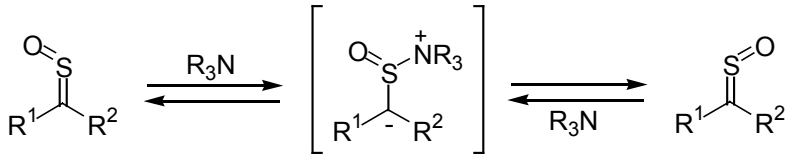
Table 2 Synthesis and isolation of α-oxo sulfines derived from silyl ketene acetals.[7]



R	Base:solvent	T (°C)	yield(%)	R	Base:solvent	T (°C)	yield(%)
H	DIPEA:CH_2Cl_2	-50→rt	---[a]	$PhCH_2CH_2$	DIPEA:Et_2O	-78→rt	95
Me	DIPEA:Et_2O	-78→rt	66[b]	$C_{16}H_{35}$	Et_3N:CH_2Cl_2	-50→rt	81
Ph	DIPEA:Et_2O	-78→rt	96	MeO	Et_3N:CH_2Cl_2	-50	93
Bn	Et_3N:Et_2O	-78→rt	93	PhO	Et_3N:CH_2Cl_2	-50	97

a) could not be isolated, b) yield after distillation

An important feature of the Diels-Alder reaction of sulfines is that the stereochemistry of this heterocumulene is retained in the cycloadduct. [6,7,8] There are however, a few exceptions to this rule. The formation of the then obtained mixture of stereomeric cycloadduct can be explained by an isomerisation of the sulfines induced by base prior to the cycloaddition as depicted in Scheme 3.[9]



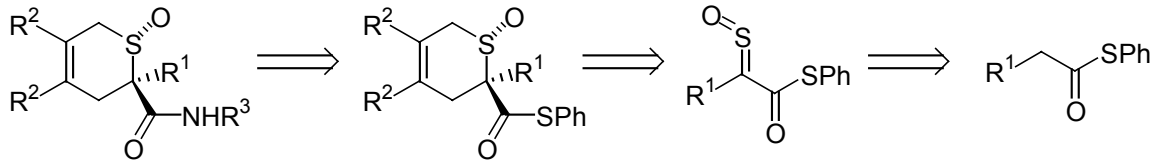
Scheme 3

In view of the fact that dihydrothiopyrans having a 2-carboxamide substituent show interesting biological properties, the question arose whether such compounds could be prepared via an α-oxo sulfine. [10] In principle, the shortest route would be a [4+2]-cycoaddition reaction of α-carboxamido sulfines with 1,3-dienes. Sofar, there are only two

reports on a-carboxamido sulfines, namely the one by Himbert et al[11] and that by Rewinkel.[6e] In both cases, these sulfines were derived from tertiairy carboxamides, viz. *N*,*N*-dimethyl[11] and morpholine[6d] derivatives. However, from previous work it was known that α-oxo sulfines derived from secondary amides are not accessible in a direct manner.[6d] Therefore, a detour was considered for the preparation of the cycloadducts of such sulfines. This chemistry is the subject of this chapter.

3.2 Results

The synthetic plan for the synthesis of 3,6-dihydrothiopyran *S*-oxides having a carboxamide substituent at C2 is shown in Scheme 4 in a retrosynthetic fashion. Thiophenoxy esters have been used as precursors for amides. [12]

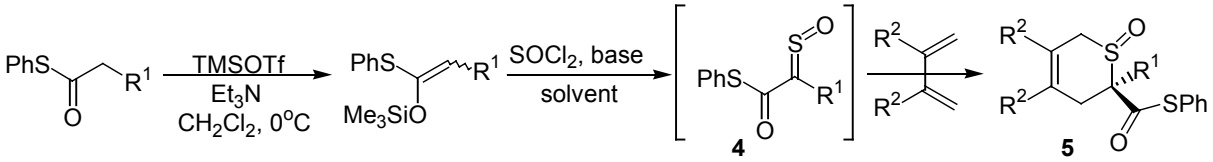


Scheme 4

3.2.1 Synthesis of thiolo ester substituted 3,6-dihydro-2*H*-thiopyran *S*-oxides.

The required starting materials viz. thiophenoxy esters were readily accessible by reaction of the corresponding acid chloride with thiophenol in the presence of triethylamine in ether at 0°C. These compounds were converted into *O*-silyl thioketene acetals using trimethylsilyl triflate analogous to a literature procedure.[13] The thus obtained derivatives were treated with thionyl chloride in the presence of triethylamine in ether at –78°C. Experimentally, this method was similar to the previous preparation of α-oxo sulfines from *O*-silyl ketene acetals.[7b] The oxo-sulfines were trapped *in situ* with 1,3-dienes to give the expected 4,5-dialkyl-3,6-dihydro-2*H*-thiopyran *S*-oxides **5** in moderate to good yields. The results are collected in Table 3. The data in Table 3 reveal that the cycloaddition with 1,3-dienes having long chain alkyl substituents proceeds in a lower yield than that with 2,3-dimethyl-1,3-butadiene, which is the usual standard.

Table 3 Synthesis of new 3,6-dihydro-2*H*-thiopyran *S*-oxides **5**.



product	R_1	R_2	T (°C)*	yield(%)
5a	H	Me	-78	69
5b	H	C_6H_{13}	-20	55
5c	H	$C_{10}H_{21}$	-10	35
5d	Me	Me	-78	77
5e	Me	C_5H_{11}	-30	62
5f	Me	C_6H_{13}	-20	53

*temperature diene addition.

In the case of 2,3-didecyl-1,3-butadiene (entry 3) the cycloaddition reaction had to be carried out at a temperature between –10 and 0°C in order to avoid solidification of the reaction

mixture because of the melting point of this diene (~ +10°C). In spite of the higher reaction temperature, a rather long reaction time was needed for this diene. The sluggish reactivity and the rather low yield of **5c** may be attributed to the instability of the sulfine **4** under these conditions and the steric influence of the alkyl substituents on the diene in adopting the required *s-cis* conformation for the concerted [4+2]-cycloaddition to take place. The yields of **5b**,**e** and **f** were only slightly lower than for the standard diene (entries 1 and 4), in spite of the fact that the reaction had to be carried out at –20°C (entries 2 and 6) and –30°C (entry 5) to avoid solidification of the reaction mixture. The reaction rate for 2,3-dipentyl and 2,3-dihexyl-1,3-butadiene is considerably lower than that for the standard diene due to the hindrance in adopting the *s-cis* conformation.The cycloadditions took place in a completely stereoselective manner. The relative position of the sulfoxide oxygen and the thiolo ester group was established to be *anti* as was deduced from an X-ray diffraction analysis of the cycloadduct **5a**. (Fig.1) This observation implies that the oxo sulfine **4** had the *E*-geometry. This conclusion is in accordance with the expected geometry (see Chapter 1, Scheme 16). [6,7]

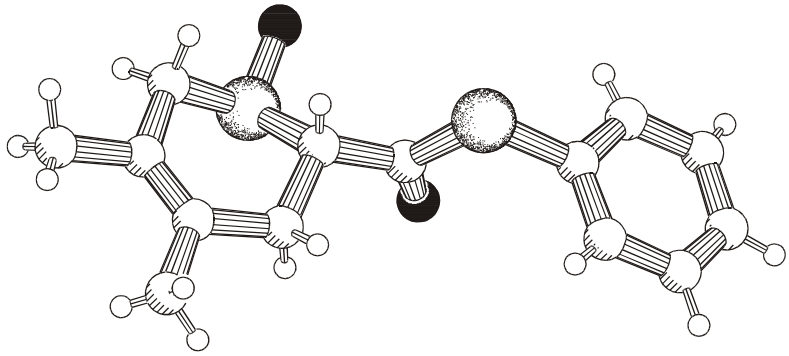
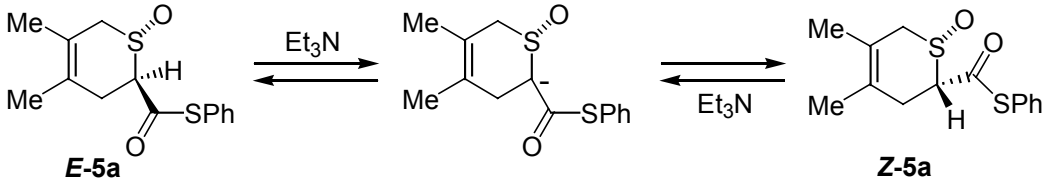


Figure 1. X-ray crystal structure of ***E*-5a**

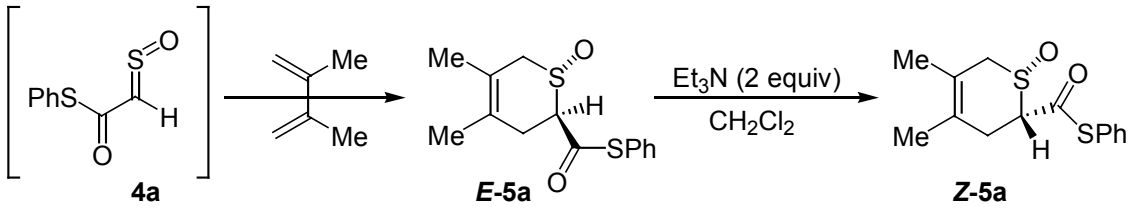
An interesting observation was made when the crude reaction mixture was allowed to stand overnight, viz. that partial *E* to *Z*-isomerization had occurred as was concluded from ^{1}H-NMR analysis. This isomerization can be rationalized by invoking a reaction with some residual triethylamine; namely a deprotonation-protonation reaction as shown in Scheme 5.



***E*-5a** ***Z*-5a**

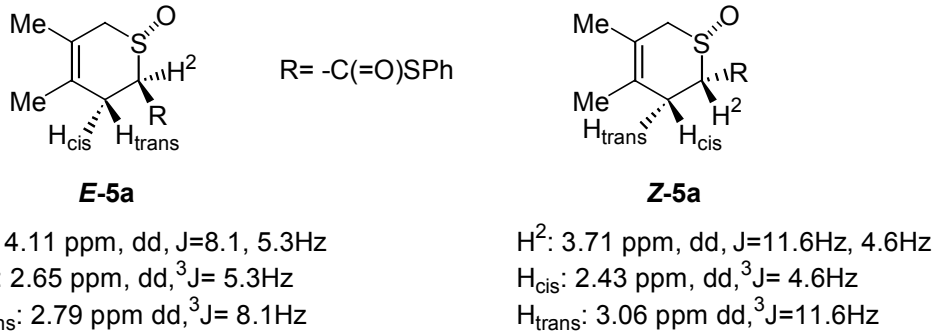
Scheme 5

This isomerization could be prevented by chromatographing the crude product immediately after work-up. In the ^{1}H-NMR spectrum the proton signals for C-2, C-3 and C-6 could be assigned by using data from previous work on similar derivatives[6a-d,7] and by recording a C,H-correlation spectrum of ***E*-5a.** It was shown that *E*-**5a** isomerizes completely to its *Z*-isomer upon treatment with two equivalents of triethylamine in dichloromethane at room temperature for 16 hrs.



Scheme 6

The ^{1}H-NMR spectrum of the *Z*-isomer showed a clear change in shift and coupling pattern of the thiopyran ring protons. The C-2 proton in the initial *E*-isomer *E*-**5a** showed a double doublet at 4.11 ppm, whereas in *Z*-**5a** this signal had shifted to 3.71 ppm, while the doublets are more clearly separated (Fig.2).



***E*-5a**

H^2: 4.11 ppm, dd, J=8.1, 5.3Hz
H_{cis}: 2.65 ppm, dd, ^{3}J= 5.3Hz
H_{trans}: 2.79 ppm dd, ^{3}J= 8.1Hz

***Z*-5a**

H^2: 3.71 ppm, dd, J=11.6Hz, 4.6Hz
H_{cis}: 2.43 ppm, dd, ^{3}J= 4.6Hz
H_{trans}: 3.06 ppm dd, ^{3}J=11.6Hz

Figure 2

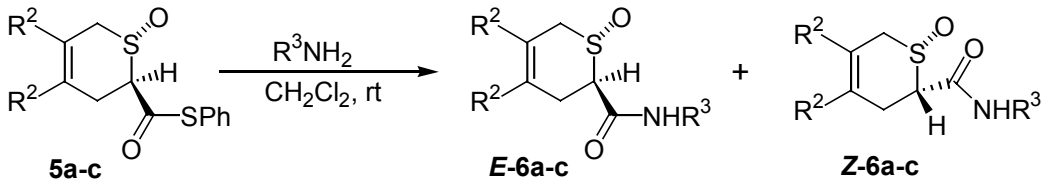
In *E*-**5a** the C-3-protons showed two double doublets (AB of ABX-system) at 2.65 and 2.79 ppm, respectively. *Z*-**5a** showed a double doublet at 2.43 ppm and a double doublet at 3.06 ppm. The C-6 protons next to the sulfoxide group in *E*-**5a** appeared as two doublets at 3.38 and 3.55 ppm, respectively, with a light roof effect (towards an AB-type pattern). In *Z*-**5a** this had changed into a broad singlet (A_2-type pattern) at 3.38 ppm. These differences in chemical shift- and coupling patterns for the C-3 and the C-6 protons proved useful in establishing the stereochemistry of the amide derivatives (see below).

The stereochemistry of the cycloadducts **5b** and **5c** was determined by comparing the spectral features (chemical shifts and coupling pattern) with those of product *E*-**5a**. Also these two cycloadducts had the *E*-stereochemistry as was apparent from the strong resemblance of these spectral data. Compounds **5b** and **5c** slowly isomerized partly into the *Z*-isomer on standing at low temperature (-18^{o}C) for several days, even when these compounds had been purified by column chromatography over neutral aluminium oxide. Attempts to separate the isomers by chromatography or crystallization were unsuccessful. Treatment with triethylamine in dichloromethane resulted in an isomerization to the *Z*-isomers. In the case of **5c** the material also showed signs of degradation during this base treatment. It should be mentioned that the cycloadducts **5b** and **5c** isomerized to 1:1 mixtures when chromatographed over silica gel, indicating that these compounds are prone to isomerization under basic as well as acidic conditions. The ^{1}H-NMR spectra of *Z*-**5b** and *Z*-**5c** were similar to that of *Z*-**5a**. When crystalline, *E*- and *Z*-**5a** do not undergo any change for a period of at least 8 months. The compounds **5b** and **5c** were obtained as amorphous solids which slowly colorize from off-white to yellow and have a faint smell of thiophenol, even shortly after chromatography. As a consequence, the elemental analyses of these compounds were not satisfactory.

The cycloadducts **5d-f** derived from the α-oxo sulfines with R^1=Me, thus from *O*-silyl ketene acetal **3b**, cannot isomerize because the hydrogen atom at C2 is now replaced by a methyl group. The formation of these cycloadducts requires a longer reaction time than was observed for the **5a-c**. The stereochemical structure of **5d** was established indirectly by correlation with the structure of **6j** that was determined by an X-ray diffraction analysis (see below). This correlation showed that **5d**, and similarly **5e** and **5f**, had the *E*-configuration. The cycloadducts **5d-f** were obtained as slightly yellow oils that could be kept unchanged at 4°C for several months.

3.2.2 Conversion of thiolo esters into carboxamides

Preparation of the aliphatic amides **6** was accomplished in a convenient manner by reaction of **5a-c** with several amines in dichloromethane at room temperature (Scheme 7). For *N*-methyl derivatives the reaction was performed in aqueous tetrahydrofuran.



Scheme 7

The cycloadducts ***E*-5a-c** have a hydrogen at C2 and are sensitive to isomerization under basic conditions (*vide supra*) and accordingly, it was expected that such an isomerization would occur during the treatment with primary amines. Indeed, the carboxamides **6a,b** and **d** were obtained as 1:1 mixtures of isomers that could not be separated by column chromatography.

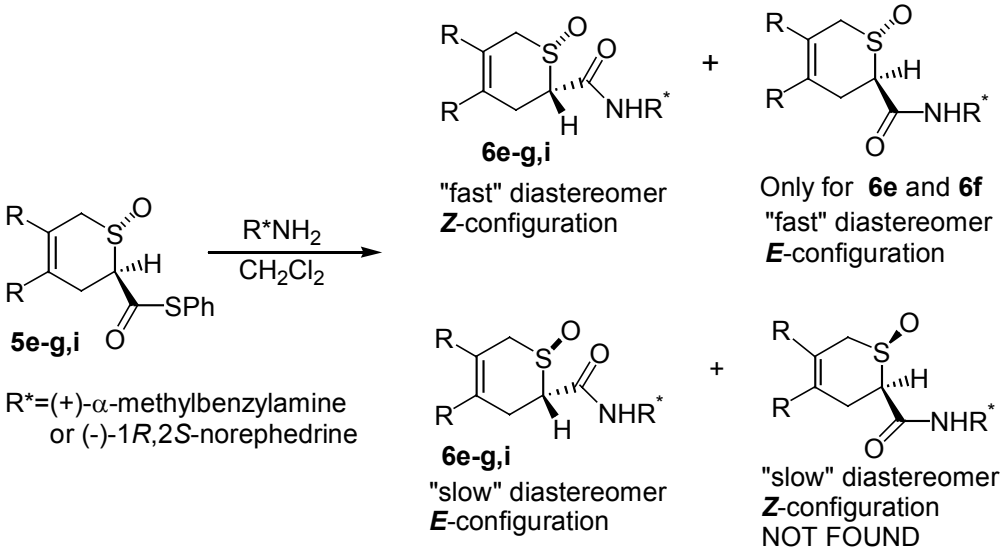
Table 4 Synthesis of amides **6a-i**.

product	R^1	R^2	R^3	E:Z	yield (%)
6a	H	Me	Bn	1:1[a]	92
6b	H	Me	allyl	1:1[a]	94
6c	H	Me	$C_{12}H_{25}$	9:1	87
6d	H	Me	CH_2CH_2OH	1:1[a]	89
6e	H	Me	α(+)MeBn	1:1[c]	82
6f	H	Me	(-)1S,2R n.eph.[b]	1:1[c]	81
6g	H	C_6H_{13}	(-)1S,2R n.eph.[b]	1:1[c]	83
6h	H	C_6H_{13}	CH_2CH_2OH	0:100[d]	86
6i	H	$C_{10}H_{22}$	(-)1S,2R n.eph.[b]	1:1	81

a) Washing of a dichloromethane solution of the compound with 0.1N NaOH gave complete isomerization to the *Z*-isomer.
b) (-)1*S*,2*R*-norephedrine.
c) Fast diastereomer isomerised to *Z*-configuration.
d) Probably *Z*, difficult to see due to overlapping signals in ^{1}H-NMR.

However, washing a solution of the product in dichloromethane with aqueous 0.1N NaOH resulted in a complete isomerisation to the *Z*-isomers.
The structural assignment was made on the basis of a comparison with the spectral characteristics of starting materials **5a-c**. The signals for the C3 and C6 protons of the ***Z*-6** isomers closely resembled those of ***Z*-5a**. The signals attributable to the carboxamides with the *E*-configuration were completely absent. The carboxamide **6c** was obtained as an *E*:*Z*

mixture in a 9:1 ratio, apparently isomerization is more sluggish in this case. The isomers of **6c** could be separated by column chromatography.When the chiral amines (+)-α-methylbenzylamine and (-)1*R*,2*S*-norephedrine were employed, isomerisation was observed for only one of the diastereomers (Scheme 8). For **6e** and **f** the faster running spot on TLC was shown (after column chromatography) to contain a mixture of *E*- and *Z*-isomers in ratios of *E*:*Z*=1:6 and *E*:*Z*=1:3, respectively (^{1}H-NMR). Attempts to separate the isomers of **6f** by crystallization from diisopropyl ether/ethyl acetate failed.



Note: The absolute configuration only applies for **6g**

Scheme 8

However, a small amount of the *E*-isomer of **6f** could be separated in approximately 90% isomeric purity by careful chromatography of the mixture which was sufficient for an NMR analysis. The proton spectrum clearly showed the expected pattern for an *E*-configuration. In the ^{13}C-NMR spectrum of the original mixture the peaks of both the isomers could be assigned. The ^{1}H-NMR of the "slower" products of **6e** and **6f** only showed signals corresponding with an *E*-configuration.

For **6g** and **6i** the ^{1}H-NMR data suggested that the "fast running" product had the *Z*-configuration while the "slower running" diastereomers showed proton signals corresponding with an *E*-configuration. In order to obtain certainty about the stereochemistry and the absolute configuration of the different isomers an X-ray diffraction analysis was considered. Attempts to obtain suitable crystals were only successful for the "slower" isomer of **6g** (crystallized slowly from dilute diisopropyl ether solutions[14]) and was unambiguously shown to possess the *E*-configuration. Furthermore, by using the known chirality of (-)1*R*,2*S*-norephedrine the absolute configuration could be established.(Fig. 3).

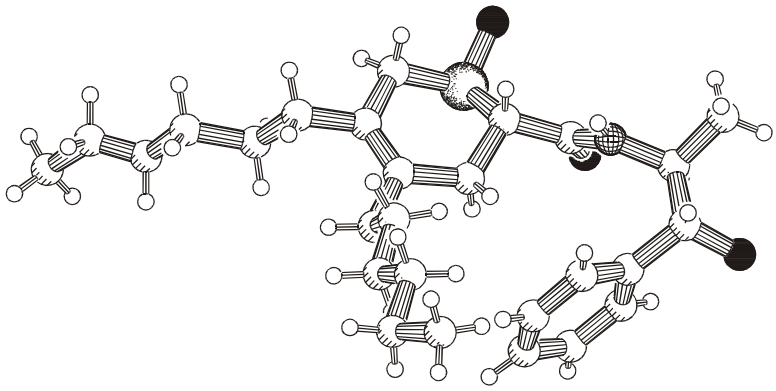
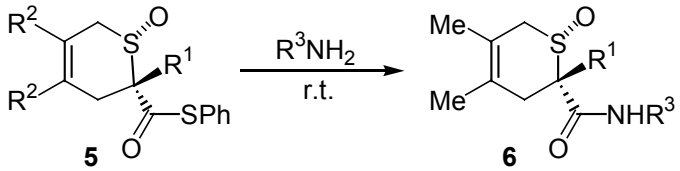


Figure 3. X-ray crystal structure of **6g** ("slow" *E*-diastereomer)

Knowing the structure of **6g**, the ^{1}H-NMR spectra of the respective isomers of **6** could be interpreted and it was found that the signals for the C3 and C6 positions indeed could be reliably used for assigning the relative configuration of the C2 substituent with respect to the sulfoxide function in the carboxamides **6a-i**.
The conversion into carboxamides was also investigated for the thiolo esters **5d-f** having a methyl group at C2 which precludes isomerization reactions of these cycloadducts with primary amines. This led, as expected, to the corresponding carboxamides **6j-n**.

Table 5 Synthesis of derivatives **6j-n**.



product	R^1	R^2	R^3	E:Z	Yield(%)
6j	Me	Me	Me	100 : 0	94
6k	Me	Me	$CH_2PhpOMe$	100 : 0	93
6l	Me	Me	(-)1S,2R n.eph.[a]	100 : 0[b]	88
6m	Me	C_5H_{11}	(-)1S,2R n.eph.[a]	100 : 0[b]	87
6n	Me	C_6H_{13}	$CH_2PhpOMe$	100 : 0	91

a) (-) 1S,2R-norephedrine
b) 1:1 mixture of diastereomers

An X-ray diffraction analysis of product **6j** (Fig. 4) revealed that this compound indeed had the *E*-configuration. In analogy, the products **6k-n** also were assigned as the *E*-isomers.

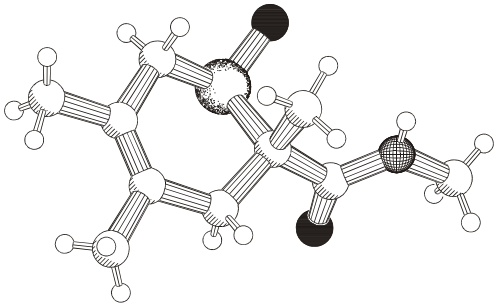
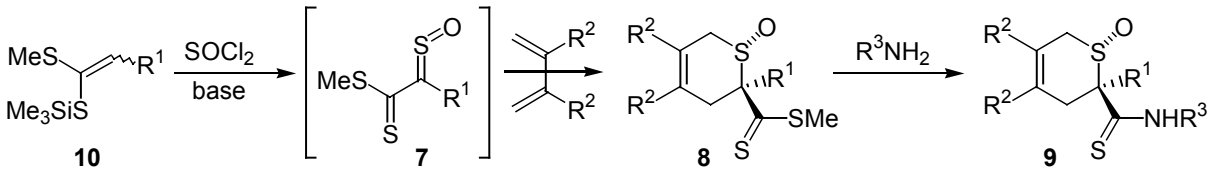


Figure 4. X-ray crystal structure of **6j**.

The reaction of **5d** with (-)1*R*,2*S*-norephedrine gave **6l** as a mixture of diastereomers that could not be separated by chromatography or crystallization. For **6m** the obtained diastereomers could not be separated by column chromatography, however recrystallisation from diisopropyl ether/ethyl acetate gave one diastereomer in pure form.
The reaction of the thiolo esters with aromatic primary amines failed. Treatment of **5d** with aniline or 4-methoxyaniline in dichloromethane, THF or toluene, using reflux conditions did not lead to any new product. (In refluxing toluene slow decomposition was observed).

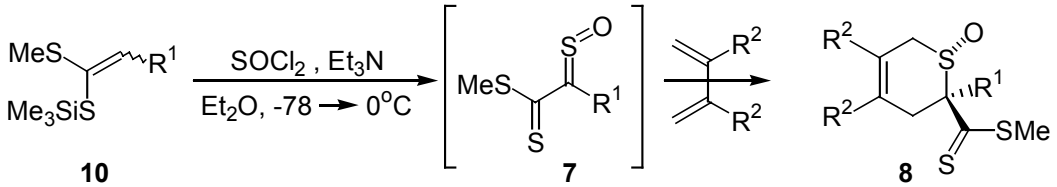
3.2.3 Synthesis of dithioester substituted 3,6-dihydro-2*H*-thiopyran *S*-oxides

A dithioester substituent at the dihydrothiopyran C2 would allow the conversions into other functions, e.g. thiocarboxamides. Such compounds may be of interest because of their biological properties.[2] An example is Aprikalim® (see section 3.1 Scheme 2). The shortest route to such dithioester substituted dihydrothiopyrans would be the cycloaddition of dithioester substituted sulfine **7** with an appropriate 1,3-diene. The required starting material for the preparation of sulfine **7** is a *S*-silyl dithioketene acetal **10**.[15] The entire sequence of reactions is outlined in scheme 9. The stereochemical features are included in this scheme as well. The stereochemistry with respect to the sulfoxide and the dithioester substituent in the cycloadducts is expected to be *trans*[7,6] as desired.[1,2]



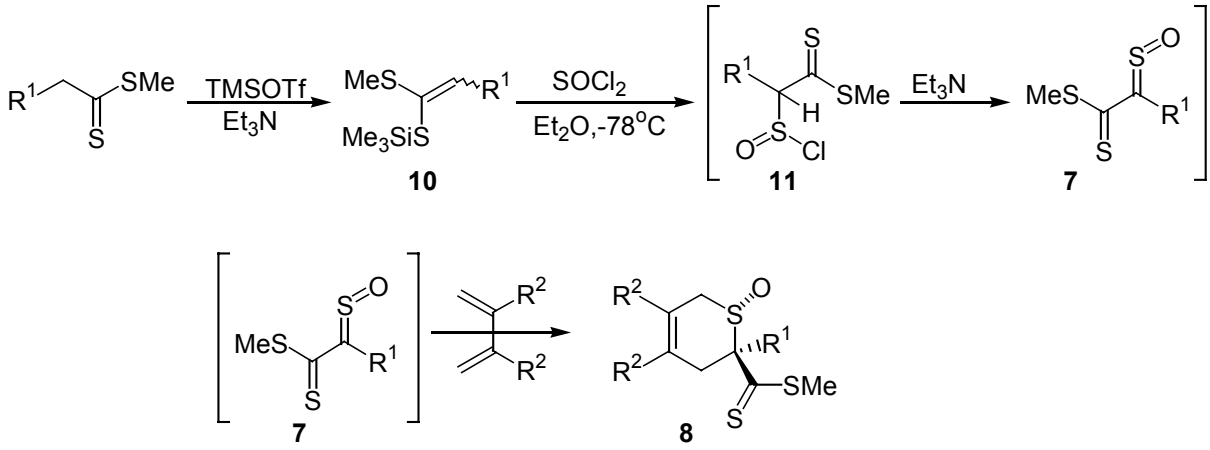
Scheme 9

One example of the preparation of a cycloadduct **8** was reported previously by Rewinkel[6], viz. **8a** (R=R[1]=Me) which was obtained in 17% yield by the addition of a solution of silyl dithioketene acetal and triethylamine to a cooled (-20°C) solution of thionyl chloride in dichloromethane in the presence of a large excess of 2,3-dimethyl-1,3-butadiene. Since this first preparation improved conditions for the reaction of silyl enol ethers with thionyl chloride have been developed, e.g. lower reaction temperature (-78°C), diethyl ether as the solvent and triethylamine or diisopropylethylamine as the base.[7b,c] Therefore, attempts were made to improve the yield for the preparation of sulfines **7** and their concurrent cycloaddition (Scheme 10). The *S*-silyl dithioacetals **10** were readily obtainable from the corresponding dithioesters following a literature procedure.[15] The results of the attempt to improve the yield by modifying the conditions are collected in Table 6. Disappointingly, the yields were still low.
Table 6 Synthesis of 2-dithiocarboxylate substituted 3,6-dihydro-2*H*-thiopyran *S*-oxides **8**.



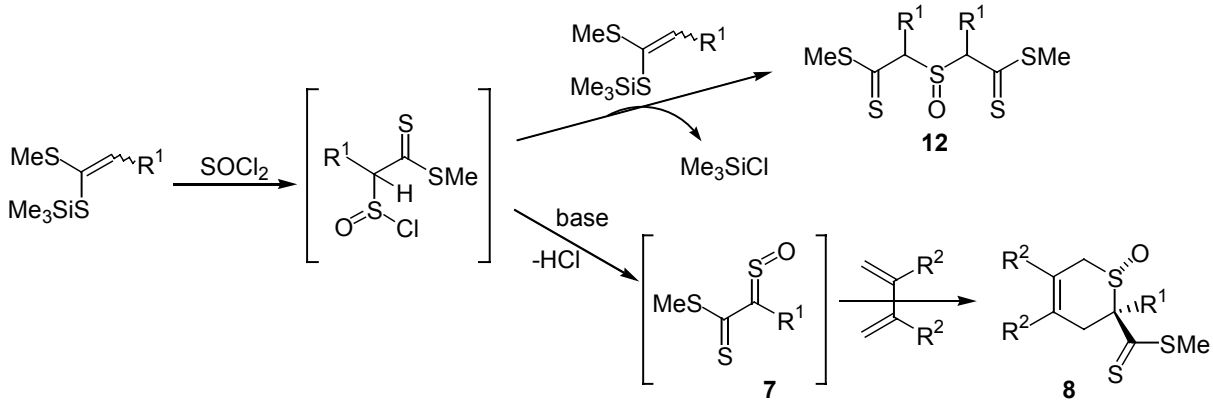
product	R	R^1	yield (%)
8a	Me	Me	33
8b	Me	nC_3H_7	40
8c	Me	Ph	12

Addition of a solution of silyl dithioketene acetal and triethylamine to a solution of thionyl chloride and excess 2,3-dimethyl-1,3-butadiene first led to a dark red-brown reaction mixture, which changed to bright yellow when the temperature was raised to 0°C, then the color changed slowly to darker yellow. Monitoring the reaction by TLC showed no sign of cycloadduct formation when the color had just changed to bright yellow, later in the process the product appeared. This observation suggests that the initial dark red-brown color belongs to the intermediate sulfinyl chloride **11**, the bright yellow color corresponds with the sulfine **7**, which is then slowly converted into the dark-yellow cycloadduct **8**.



Scheme 10

The low efficiency of this process may be due to the rather low reactivity of sulfine **7** in the hetero-Diels-Alder reaction. It is well documented that at least one electron-withdrawing group next to the sulfine group is required for an appreciable activity in [4+2]-cycloaddition reactions. The performance of the dithioester unit in this respect will be considerably lower than that of a regular ester group. Consequently, unwanted side reactions may compete with the cycloaddition reaction. Although no by-products were isolated, it may be speculated that side reactions may take place similar to those that were observed previously (Scheme 11), e.g. the formation of β,β'- dioxo sulfoxides **12**.[6d]



Scheme 11

It was also attempted to use 1,3-butadiene, 2,3-dihexyl-1,3-butadiene and 1-trimethylsilyloxy-1,3-butadiene (The latter was added to the reaction mixture after the supposed formation of the sulfine, because it reacts itself with thionyl chloride.) No products were obtained however.

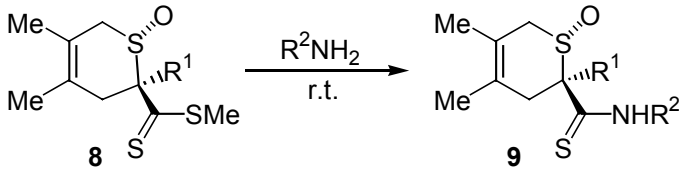
The cycloaddition reaction shown in Scheme 10 could however be performed on a multigram scale, allowing the preparation of reasonable quantities (largest prepared batch was 2.54gr. of

8b) of thiopyrans **8a**,**b** and **8c**. The cycloadducts were isolated as dark yellow viscous oils after column chromatography over silica gel and when pure, they could be kept at –20°C for at least several weeks without signs of decomposition products. Although the yield for **8a** (33%) is rather low, it is twice that of the earlier attempt.[6d] Moreover, the product could be obtained in pure form. The crude compounds **8** contained substantial amounts of decomposition products and some dithioester (starting material), which can either be formed by hydrolysis of the *S*-silyl dithioketene acetal or by hydrolytic decomposition of sulfine **7**. Attempts to isolate the sulfines, by filtering off the formed triethylamine salts followed by direct removal of the solvent *in vacuo* (cold water bath) or quick aqueous work-up (washing with ice-water, drying with $MgSO_4$ and evaporation of solvent using a cold water bath) were unsuccessful and gave some starting dithioester together with decomposition products.

3.2.4 Conversion of dithioesters into thiocarboxamides

Next the dithioester substituted cycloadducts **8** were transformed into the corresponding thioamides **9** by reaction with a variety of primary amines. The reactions all took place in high yields.

Table 7 Preparation of 2-thiocarboxamide substituted 3,6-dihydro-2*H*-thiopyran *S*-oxides **9**.

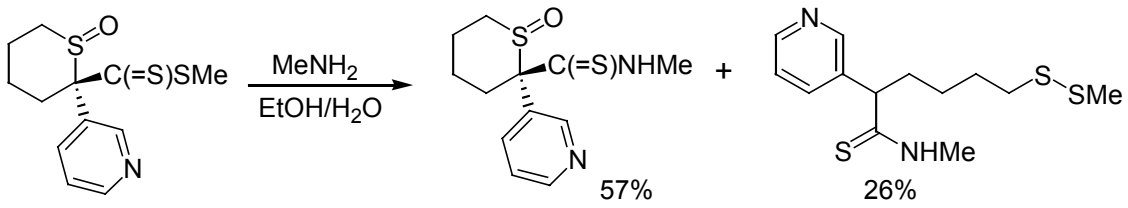


Entry	product	R^1	R^2	time(min)	yield (%)	yield (%)[c]
1	**9a**	Me	H	10	92[a]	30
2	**9b**	Me	Me	30	91[a]	30
3	**9c**	Me	Bn	40	89	29
4	**9d**	Me	4-ClBn	40	85	28
5	**9e**	nC_3H_7	Me	180	85[a]	34
6	**9f**	nC_3H_7	4-ClBn	16 hrs	90	36
7	**9g**	Ph	Me	30	84[a]	10
8	**9h**	Ph	4-ClBn	60	81	9.7

a) THF as solvent b) dichloromethane as solvent c) overall yield from silyl dithioketene acetal.

The reactions with ammonia (entry 1, Table 7) and methylamine (entries 2,5 and 7) were conducted in THF, while the others were carried out in dichloromethane. The reaction of the cycloadduct of sulfine **8b** was rather sluggish, probably due to the steric effect of the n-propyl group at C2. All products **9** are stable solids that could be stored a 4°C for at least several months without any signs of decomposition. The results are collected in Table 7.
All derivatives are stable solids that can be kept at 4°C for at least several months when pure.

It should be noted that this reaction of the dithioesters with methylamine contrasts with that of thiane *S*-oxides, where deoxygenation of the sulfoxide and ring-opening reactions were reported as unwanted side-reactions (Scheme12).[16]



Scheme 12

3.3 Concluding remarks

The results described in the preceding sections show that 2-carboxamido-4,5-dialkyl-3,6-dihydrothiopyran *S*-oxides can be prepared in a convenient manner by a [4+2]-cycloaddition reaction of *in situ* generated thiolo ester derived α-oxo sulfines with various 3,4-dialkyl-1,3-butadienes, followed by a reaction with primary aliphatic amines. The yields of the cycloaddition reactions were shown to decrease with the increasing chain length of the alkyl group in the 1,3-dienes. Cycloadducts having a hydrogen atom at C2 are prone to isomerize from the *E*-form to the *Z*-form upon treatment with triethylamine. The amination reaction with cycloadducts having a C2-hydrogen was accompanied by isomerization of *E*- to *Z*-isomers. Treatment of *E*-carboxamide products with base lead to complete isomerization into the *Z*-isomers, thus showing that this configuration is the thermodynamically more stable one. Cycloaddition products with a methyl group at C2 were not encumbered by any isomerization during the formation of the carboxamides.

The preparation of dithioester substituted 3,6-dihydro-2*H*-thiopyran *S*-oxides by the reaction of *S*-silyl dithioketene acetals with thionyl chloride was low yielding. However, the subsequent conversion into the corresponding thioamides took place in high yields.

The results described in this chapter also provided insight into the relative stability of a series of structurally related substituted sulfines (Fig.5). Compound **13** with an ester substituent is a stable crystalline solid, [7] whereas thiolo ester substituted sulfine **14** is only stable for a short period.[17] The sulfine **7** having a dithioester substituent cannot be isolated at all.

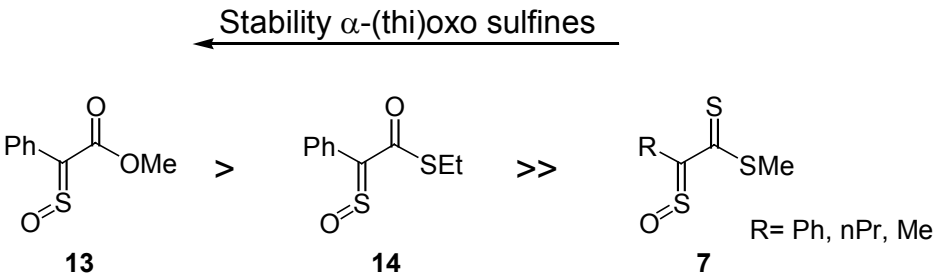


Figure 5 Stablity pattern for α-(thi)oxo sulfines

In summary, the chemistry in this chapter describes the synthesis of a series of new 3,6-dihydro-2*H*-thiopyran *S*-oxides with a carboxamide and thiocarboxamide substituents. Such compounds may be of interest for their biological properties.

3.3 Experimental

All cycladdition reactions were carried out under a dry argon atmosphere. Thiol esters and *O*-silyl thioketene acetals were prepared according to literature procedures.[13] 2,3-dimethyl-1,3-butadiene was purchased from Aldrich, other dienes were synthesized according to literature procedures using a slightly modified work up procedure (see below). Optical rotations were measured using a Perkin Elmer 241 MC automatic polarimeter.

Melting points were determined with a Reichert Thermopan microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with Bruker AC 100 MHz, Bruker AC 300 MHz FT and Varian Unity Inova 400 HR spectrometers. Mass spectra were obtained with a VG 7070E spectrometer. Elemental analyses were obtained using a Carlo Erba EA 1108 element analyser. Thin layer chromatography was carried out on Merck silica gel 60 F-254 plates. Spot were visualised with UV or by dipping in a coloring solution (6.2% sulfuric acid aqueous solution, containing 42g. ammonium molybdate and ceric ammonium sulfate per liter) followed by charring. Column chromatography was carried out on Silica 60 (Baker) or neutral aluminum oxide.

Solvents
Tetrahydrofuran was distilled from sodium benzophenon ketyl or lithium aluminium hydride. Diethyl ether was distilled from sodium hydride. Dichloromethane and acetonitril were distilled from P_2O_5. Ethyl acetate was distilled from K_2CO_3 and heptane from CaH_2. Triethylamine was distilled from potassium hydroxide and stored under argon over potassium hydroxide pellets. Thionyl chloride was distilled from triphenyl phosphite and stored under argon. Diisopropyl ether (p.a., Fluka) was used as received.

Modified work up for dienes: The procedure of Wilde and coworkers[2a,18] was followed. After isopropyl alcohol was added, most of the solvents were evaporated under reduced pressure and the crude, gummy mixture was triturated four times (each 20-30 min) with 200 ml portions of pentane which were carefully decanted. The combined pentane fractions were concentrated *in vacuo* giving light yellow turbid oils. These were purified by column chromatography (silica gel; pentane) and obtained as clear colorless oils. The ^{1}H-NMR spectra of 2,3-di-(n-pentyl)- and 2,3-di-(n-hexyl)-1,3-butadiene were in accordance with the literature data.

2,3-Di-(n-decyl)-1,3-butadiene:
Obtained as colorless oil (68%) that solidified below 5°C. ^{1}H-NMR (300MHz) d: 0.75-0.90 (m, 6H), 0.95-1.45 (m, 32H), 2.1-2.1 (m, 4H), 5.1-5.25 (m, 4H vinylic).

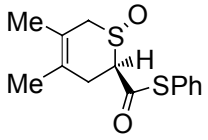
Ketene-*O*-trimethylsilyl-*S*-phenyl mono-thioacetals[13]

1-(Phenylsulfanyl)vinyl-*O*-trimethylsilyl ether
Obtained as a colorless oil after vacuum distillation. Bp. 125-128 °C (13 mmHg) in 69 % yield. ^{1}H-NMR (300MHz) d: 0.00 (s, 9H, Si(C**H**$_3$)$_3$), 4.35 (m, 2H, **H**$_2$C=C), 7.06-7.36 (m, 5H, **H**$_{arom}$). ^{13}C-NMR (75 MHz) d: 0.00,126.7, 129.1, 132.6, 134.4, 152.9.

(*E*/*Z*)-1-(Phenylsulfanyl)-1-propenyl-*O*-trimethylsilyl ether
Obtained as a colorless oil after vacuum distillation, approximately 6:1 mixture of isomers (^{1}H-NMR). Bp. 80-90°C (4 mmHg), 80% yield. ^{1}H-NMR (300MHz) d: Minor isomer, 0.12 (s, 9H, Si(C**H**$_3$)$_3$), 1.86 (d, 3H, J= 6.9 Hz, **H**$_3$CCH=C-O), 2.72 (q, 1H, overlap with major isomer, H$_3$CC**H**=C-O), 7.20-7.45 (m, 5H, H-arom, overlap with major isomer). Major isomer: 0.19 (s, 9H, Si(C**H**$_3$)$_3$), 1.73 (d, 3H, J= 6.9 Hz, **H**$_3$CCH=C-O), 5.37 (q, 1H, J= 6.9 Hz, H$_3$CC**H**=C-O), 7.20-7.45 (m, 5H, H$_{arom}$). ^{13}C-NMR (75 MHz) d: 0.00, 12.2, 115.2, 125.9, 128.5, 128.7, 129.7, 135.2, 141.8 (major isomer).

Cycloaddtion reactions

***S*-Phenyl 4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (*E*-5a)**



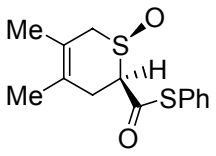
A solution of 1-(phenylsulfanyl)vinyl trimethylsilyl ether (10 mmol) and triethylamine (10 mmol) in 20ml diethyl ether was slowly added to a cooled (-78° C) solution of thionyl chloride (10 mmol) and 2,3-dimethyl-1,3-butadiene (10 equiv.) in 10ml of diethyl ether. After the addition was complete, the reaction mixture was kept at –78°C for 30 min, then it was slowly warmed to 0°C and kept at this temperature for 2 h, followed by 30 min at room temperature. The reaction mixture is poured into 50 ml of water. The layers are separated and the aqueous layer was extracted four times with 25ml dichloromethane. The combined organic fractions are dried ($MgSO_4$), filtered and the solvents are removed *in vacuo*. This gave 2.72 g crude product as a light brown oil. Purification by column chromatography (silica gel, hexane: ethyl acetate= 2:1) gave 1.93 g (69 %) of a light yellow oil that crystallized upon standing. This product was sufficiently pure for further use. It was further purified

by a second chromatography step to obtain an analytically pure sample (white to off-white crystalline solid) that could be crystallized from warm diisopropyl ether (small colorless crystals, used for X-ray diffraction analysis). Mp.93-94°C. ^{1}H-NMR (300MHz) d: 1.75 (s, 6H, $2CH_3$, $\mathbf{H_3}C{=}CC\mathbf{H_3}$), 2.64 A of ABX (dd, 1H, J_{AB}= 18Hz, **H**HC-CH-S=O), 2.79 B of ABX (dd, 1H, J_{AB}= 18Hz, H**H**C-CH-S=O), 3.38 A of AB (d, 1H, J_{AB}=16.5 Hz, **H**HC-S=O), 3.55 B of AB (d, 1H, J_{AB}= 16.5Hz, H**H**C-S=O), 4.10 X of ABX (dd, 1H, O=SC**H**C=O), 7.43 (m, 5H arom). ^{13}C-NMR (75 MHz) d:19.4 (H_3**C**CC=C), 20.0 (H_3**C**CC=C), 31.0 (H_2**C**-CH-S=O), 53.1 (H_2**C**-S=O), 69.6 (O=S**C**HC=O),117.6 (H_3C**C**=C), 126.2 (H_3C**C**=C), 126.9, 129.4,129.9 (C arom), 134.4 (C-ipso), 193.2 (S**C**=O). Mass (EI): m/e 280 (M^+), 232 (M^+-SO,41%) ,171(M^+-SPh, 47%), 95 (C_7H_{11}, 100%). Elemental analysis: calcd for $C_{14}H_{16}O_2S_2$: C 59.97, H 5.75, S 22.87 %. Found: C 60.39, H 5.77, S 24.70 %.

Crystal data and structure refinement for *E*-5a.

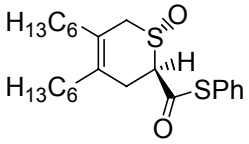
Crystal color	transparent colorless
Crystal shape	regular rod
Crystal size	0.54 x 0.18 x 0.15 mm
Empirical formula	$C_{14}\ H_{16}\ O_2\ S_2$
Formula weight	280.39
Temperature	293(2) K
Radiation / Wavelength	CuK_α (graphite mon.) / 1.54184 Å
Crystal system, space group	Monoclinic, P 21/n
Unit cell dimensions	a, α= 7.0451(17) Å, 90°
(14 reflections 7.603 < θ < 40.408)	b, β = 15.955(2) Å, 91.85(4)°
	c, γ = 12.779(4) Å, 90°
Volume	1435.6(6) Å^3
Z, calculated density	4, 1.297 Mg/m^3
Absorption coefficient	3.293 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / θ-2θ
F(000)	592
θ-range for data collection	4.43 to 55.19°
Index ranges	-7<=*h*<=0, 0<=*k*<=16, -13<=*l*<=13
Reflections collected / unique	1991 / 1821 [R_{int} = 0.0202]
Reflections observed	1602 ([I_o>2σ(I_o)])
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	1821 / 0 / 227
Goodness-of-fit on F^2	1.092
SHELXL-97 weight parameters	0.044700 0.851100
Final R indices [I>2σ(I)]	R_1 = 0.0402, wR_2 = 0.0964
R indices (all data)	R_1 = 0.0459, wR_2 = 0.1006
Largest diff. peak and hole	0.249 and -0.196 e.Å^{-3}

Isomerisation of *E*-5a into *Z*-5a:



E-**5a** (2.0 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (4.0 mmol) was added. After stirring at room temperature for 16 h the solvent and triethylamine were removed *in vacuo* to give *Z*-**5a** (2.0 mmol) which could be crystallized from diisopropyl ether as colorless small needles (1.72 mmol, 86%). Mp.>135°C (dec). ^{1}H-NMR (300MHz) d: 1.75 (s, 3H, C**H$_3$**), 1.79(s, 3H, C**H$_3$**), 2.43 A of ABX (dd , 1H, J_{AB}= 18Hz, J_{AX}≈ 3.9Hz, **H$_{cis}$**HC-CH-S=O), 3.06 B of ABX (dd, 1H, J_{AB}=18Hz, J_{BX}≈16Hz, **H$_{trans}$**HC-CH-S=O), 3.37(br.s, 2H, **H$_2$**C-S=O), 3.70 X of ABX (dd, 1H, J_{AX}≈ 3.9Hz, J_{BX}≈ 16Hz, O=SC**H**C=O), 7.43 (m, 5H arom). ^{13}C-NMR (75 MHz) d: 19.67 (**C**H$_3$C=C), 19.85 (**C**H$_3$C=C), 25.8(**C**H$_2$CH-S=O), 52.3 (**C**H$_2$-S=O), 64.8 (O=S**C**HC=O), 115.7 (**C**=C), 126.2 (**C**=C), 126.7- 134,4 (4x**C$_{arom}$**),192.7 (**C**=O). Mass (EI): m/e 280 (M^+), 232 (M^+-SO,44%) ,171(M^+-SPh, 66%), 95 (C_7H_{11}, 100%). Elemental analysis: calcd for $C_{14}H_{16}O_2S_2$; C 59.97, H 5.75, S 22.87 %. Found: C 60.38, H 5.78, S 24.02 %.

***S*-Phenyl 4,5-dihexyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (*E*-5b)**

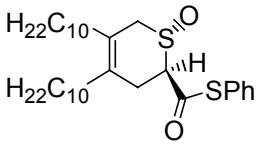


A solution of 1-(phenylsulfanyl)vinyl trimethylsilyl ether (10 mmol) and triethylamine (10 mmol) in 20ml diethyl ether was slowly added to a cooled (-78°C) solution of thionyl chloride (10 mmol) in 15ml diethyl ether. After addition was complete, the reaction mixture was kept at –78°C for 20 min, then it was slowly warmed to -20°C and 2,3-dihexyl-1,3-butadiene (3 equiv.) was added slowly. The reaction mixture was kept at this temperature for 3 h followed by 3 h at 0°C. Standard work-up (**5a**) and column chromatography over neutral aluminum oxide (heptane/ethyl acetate = 6:1) gave 2.31g. **5b** (55 %) as a light yellow amorphous solid with a faint smell of thiophenol, which slowly melts above 35°C. ^{1}H-NMR (100MHz) d: 0.85 (m, 6H, 2C**H$_3$**), 1.28 (m, 16H, 8 C**H$_2$**), 2,73 (m, 2H, C**H$_2$**CHS=O), 3.40 A of AB (d, 1H, J_{AB}= 15Hz, **H**HCS=O), B of AB (d, 1H, J_{AB}= 15Hz, H**H**CS=O), 4.00 (dd, 1H, ^{3}J= 7.0 Hz, ^{3}J= 5.7Hz, O=SC**H**C=O), 7.43 (m, 5H, **arom**). ^{13}C-NMR (75 MHz) d: 14.0 (2x CH3), 22.5-33.5 (alkyl chain, + **C**H$_2$CHS=O), 50.9 (**C**H$_2$S=O), 64.8 (O=S**C**HC=O), 120.6 (**C**=C), 129.3 (C=**C**), 129.8, 131.6,134.6 (**C**-arom), 193.4 (**C**=O). Mass: No M^+-peak was found, although M^+-SO (m/e=372) was present. No satisfactory elemental analysis could be obtained because the product slowly decomposed on standing.

NMR data *Z*-5b: Phenyl-4,5-dihexyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (*Z*-**5b**)

^{1}H-NMR (300MHz) d: 0.87 (m, 6H, 2C**H$_3$**), 1.29 (m, 16H, 8 C**H$_2$**), 2.48 (dd, 1H, ^{2}J= 15Hz, ^{3}J= 4.5Hz, H**H**CCHS=O), 3.03 (dd, 1H, ^{2}J=15Hz, ^{3}J=11.1Hz, H**H**CCHS=O), 3.71 (dd, 1H, ^{3}J= 4.5Hz, ^{3}J= 11.1Hz, O=SC**H**C=O), 7.41 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 14.0 ( ), 22.5-33.5 (alkyl chain, + **C**H$_2$CHS=O), 50.9 (**C**H$_2$S=O), 64.8 (O=S**C**HC=O), 120.6 (**C**=C), 129.3 (C=**C**), 129.8, 131.6,134.6 (**C**-arom), 192.7(**C**=O).

***S*-Phenyl 4,5-didecyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (5c)**

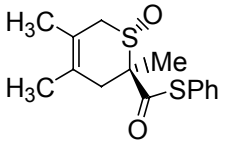


A solution of 1-(phenylsulfanyl)vinyl trimethylsilyl ether (10 mmol) and triethylamine (10 mmol) in 20 ml diethyl ether was slowly added to a cooled (-78°C) solution of thionyl chloride (10 mmol) in 15ml diethyl ether. After addition was complete, the reaction mixture was kept at -78°C for 20 min, then it was allowed to warm up to -5°C and 2,3-didecyl-1,3-butadiene (4 equiv. in 15 ml of ether) was added. The reaction mixture was kept at this temperature for 6 h. Standard work-up (**5a**) and column chromatography over neutral aluminum oxide (heptane/ethyl acetate = 9:1) gave 1,88 g **5c** (35%) as a light yellow amorphous solid with a faint smell of thiophenol. ^{1}H-NMR (300MHz) d: 0.88 (m, 6H, 2CH$_3$), 1.26 (m., 32H, 2 (C**H$_2$)$_8$**), 2.08 (m, 4H, 2 C**H$_2$**), 2.67 (dd, 1H, ^{3}J= 9.6Hz, ^{2}J= 17.7Hz, **H$_{trans}$**CCH-S=O), 2.81 (dd, 1H, ^{3}J= 5.1Hz, ^{2}J= 17.7Hz, **H$_{cis}$**CCH-S=O), 3.40 A of AB (d, 2H, J_{AB}= 15.6Hz, **H**HC-S=O), 3.58 B of AB(d, 2H, J_{AB}= 15.6Hz, **H**HC-S=O), 4.00 (dd, 1H, ^{3}J= 5.1Hz, ^{3}J= 9.6Hz, O=C-C**H**-S=O), 7.43 (br s, 5H, **arom**). ^{13}C-NMR (75 MHz) d: 14.1 (**C**H$_3$), 22.6 (**C**H$_2$), 28.0-33.3 (C-alkyl chains+ H$_2$CCHS=O), 52.3 (H$_2$**C**S=O), 70.9 (O=C**C**HS=O), 122.9 (**C**=C), 129.9 (**C**=C), 126.3, 129.3, 132.1 (C-arom), 134.4 (C-ipso), 193.5 (**C**=O). Mass: No M^+-peak was found, although M^+-SO (m/e = 484) was present. No satisfactory elemental analysis could be obtained because the product slowly decomposed on standing.

NMR-data *Z*-5c:

^{1}H-NMR (300MHz) d: 0.88 (m, 6H, 2CH_3), 1.26 (m., 32H, 2(CH_2)$_8$), 2.08 (m, 4H, 2CH_2), 2.47 (d, 1H, J≈ 15Hz, H_{cis}CCH-S=O), 3.03 (dd, 1H, ^{3}J= 11.1Hz, ^{2}J≈ 15Hz, H_{trans}HCCH-S=O), 7.0 (dd, 1H, ^{3}J= 5.2Hz, ^{3}J= 11.1Hz, O=C-C**H**-S=O), 7.43 (br s, 5H, **arom**). ^{13}C-NMR (75 MHz) d: 14.0 (CH_3), 22.5 (CH_2), 28.0-33.3 (C-alkyl chains+ H_2CCHS=O), 50.8 (H_2CS=O), 64.7 (O=CCHS=O), 120.5 (**C**=C), 129.6 (**C**=C), 129.2, 129.9, 132.1 (C-arom), 134.4 (C-ipso), 192.5 (**C**=O).

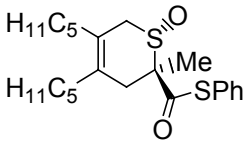
***S*-Phenyl 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (5d)**



A solution of 1-(phenylsulfanyl)-1-propenyl trimethylsilyl ether (10 mmol) and triethylamine (10 mmol) in 20ml of diethyl ether was slowly added to a cooled (-78°C) solution of thionyl chloride (10 mmol) and 2,3-dimethyl-1,3-butadiene (10 equiv.) in 10ml of diethyl ether. After addition was complete, the reaction mixture was kept at –78°C for 20 min, then it was slowly warmed to 0°C and kept at this temperature for 6 h followed by 14 h at room temperature. Standard work-up (**5a**) and column chromatography (silica gel, heptane: ethyl acetate = 6:1) gave 2,26 g **5d** (77 %) as a slightly yellow viscous oil. ^{1}H-NMR (300MHz) d: 1.68 (s, 6H, **H**$_3$CC=CC**H**$_3$), 1.77 (s, 3H, **H**$_3$CCH-S=O), 2.49 A of AB (d, 1H, J= 18Hz, **H**HCCH-S=O), 2.68 B of AB (d, 1H, J= 18Hz, **H**HCCH-S=O), 3.15 A of AB (d, 1H, J= 18Hz, **H**HCCH-S=O), 3.42 B of AB (d, 1H, J= 18Hz, **H**HCCH-S=O), 7.26-7.40 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 19.2 (H_3**C**C=CCH_3), 20.0 (H_3CC=C**C**H_3), 20.8 (O=SCC**H**$_3$), 49,8 (**H**$_2$C-S=O), 67.5 (O=S**C**CH_3), 116.3 (**C**=C), 125.6 (C=**C**), 126.0, 129.2 and 129.6 (**C** arom), 134.5(**C**-ipso), 198.0 (**C**=O). mass (EI): m/e 294 (M^+), 246 (M^+-SO, 27%), 109 ($C_8H_{13}^+$and SPh, 100%). HRMS: calcd for $C_{15}H_{18}O_2S_2$: 294.074825. Found: 294.074530.

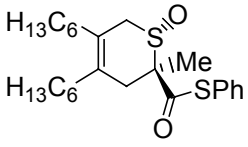
***S*-Phenyl 4,5-di-(n-pentyl)-2-methyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (5e)**

A solution of 1-(phenylsulfanyl)-1-propenyl trimethylsilyl ether (5,0 mmol) and triethylamine (5,0 mmol) in 20 ml of diethyl ether was slowly added to a cooled (-78°C) solution of thionyl chloride (5,0 mmol) in 10ml of diethyl ether. After completion of addition the reaction mixture was kept at -78°C for 20 min, then it was slowly warmed to -30°C and 2,3-dipentyl-1,3-butadiene (5 equiv. in 10 ml of ether) was added slowly. The reaction mixture was kept at this temperature for 2 h followed by 6h at 0°C and 16h at room temperature. Standard work-up (**5a**) and column chromatography (silica gel, heptane: ethyl acetate = 6:1) gave 1,26 g **5e** (62 %) as a slightly yellow oil.



^{1}H-NMR (300MHz) d: 0.83-0.92 (m, 6H, 2 C**H**$_3$(CH_2)$_4$), 1.20-1.45 (m, 12H, 2x CH_3(C**H**$_2$)$_3$$CH_2$-), 1.70 (s, 3H, O=SC-C**H**$_3$), 1.99-2.18 (m, 4H, CH_3(CH_2)$_3$C**H**$_2$-), 2.58 A of AB (d, 1H, J= 17.7Hz, **H**HCCH-S=O), 2.72 B of AB (d, 1H, J= 17.7Hz, **H**HCCH-S=O), 3.19 A of AB (d, 1H, J= 17.4Hz, **H**HC-S=O), 3.53 B of AB (d, 1H, J= 17.4Hz, **H**HC-S=O), 7.30-7.45 (m, 5H, aromatic). ^{13}C-NMR (75 MHz) d: 13.9 (CH_2C**H**$_3$), 14.0 (CH_2C**H**$_3$), 20.4 (O=SCC**H**$_3$), 22.5, 27.6, 27.8 , 31.5, 31.9, 32.8, 32.9, 33.9, 48.9 (**H**$_2$C-S=O), 67.8 (O=S**C**CH_3), 121.8 (C=**C**), 125.8 (C=**C**), 129.3, 129.8 and 130.8 (**C** arom), 134.7(**C**-ipso), 198.4 (**C**=O). Mass (EI): m/e 407 (M^++1), 358 (M^+-SO). HRMS: calcd for $C_{23}H_{34}O_2S_2$: 406.20003. Found: 406.19970.

***S*-Phenyl 4,5-di-(n-hexyl)-2-methyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioate (5f)**



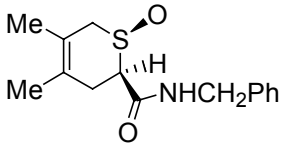
A solution of 1-(phenylsulfanyl)-1-propenyl trimethylsilyl ether (10 mmol) and triethylamine (10 mmol) in 20ml of diethyl ether was slowly added to a cooled (-78°C) solution of thionyl chloride (10,0 mmol) in 10ml of diethyl ether. After addition was complete, the reaction mixture was kept at –78°C for 20 min, then it is slowly warmed to -20°C and 2,3-dipentyl-1,3-butadiene (5 equiv. in 10 ml of diethyl ether) is added slowly. The reaction mixture was kept at this temperature for 1 h followed by 4 h at 0°C and 16h at room temperature. Standard work-up (**5a**) and column chromatography (silica gel, heptane: ethyl acetate = 9:1) gave 2,30 g **5f** (53%) as a slightly yellow viscous oil. ^{1}H-NMR (300MHz) d: 0.85-0.92 (m, 6H, 2 **H**$_3$C-CH_2-), 1.24-1.38 (m, 14H, 7 C**H**$_2$), 1.49 (m, 2H), 1.70 (s, 3H, C**H**$_3$), 1.94-2.20 (m, 4H), 2.57 A of AB (d, 1H, J= 18Hz, **H**HC-C-S=O), 2.70 B of AB (d, 1H, J= 18Hz, **H**HC-C-S=O), 3.18 A of AB (d, 1H, J= 17.4Hz, **H**HC-S=O), 3.53 B of AB (d, 1H, J= 17.4Hz, **H**HC-S=O), 7.27-7.44 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 14.0(2 CH_2C**H**$_3$) , 20.4(O=SCC**H**$_3$), 22.5, 22.6, 27.9, 28.0, 29.1, 29.4, 31.7, 32.8, 33.0 and 33.9 (alkyl **C**'s + H_2**C**-C-S=O), 49.0(H_2**C**-S=O),

67.8(Me-**C**-S=O), 121.8(**C**=C), 125.9(C=**C**), 129.3, 129.8 and 130.8(**C** arom), 134.8 (**C**-ipso), 198.4 (**C**=O). Mass (EI): m/e 434 (M^+), 386 (M^+-SO), 249($C_{18}H_{33}^+$, 100%). HRMS: calcd for $C_{25}H_{38}O_2S_2$: 434.231326. Found: 434.231190.

General procedure for synthesis of carboxamides. (except *N*-methyl amide)

A solution of amine (2.1 mmol) in dichloromethane (5ml) was added to a solution of thiolo ester **5** (2,0 mmol) in 5ml of dichloromethane at room temperature. The reaction was monitored by TLC (heptane: ethyl acetate = 1:1 or pure ethyl acetate). After completion of the reaction the dichloromethane was removed *in vacuo* and the crude product was chromatographed over silica gel. For **6a**, **6b** and **6d** completely isomerised Z-isomers were obtained by adding 10ml of 0.1N NaOH to the reaction mixture followed by extraction with dichloromethane, drying ($MgSO_4$) and evaporation of the solvent *in vacuo*. Some products were further purified by crystallization (see below). In several cases other amounts of starting materials were used, this is indicated in the text. Using this procedure the following derivatives were prepared:

***N*-Benzyl 4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (*Z*-6a)**



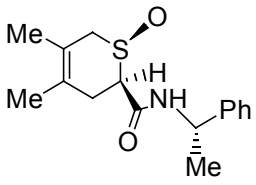
Obtained as a white crystalline solid after column chromatography (ethyl acetate: heptane= 1:1 gradient to 100% ethyl acetate), 510 mg. (92 %). Mp. 165-166°C (Crystallized from diisopropyl ether/ethyl acetate). ^{1}H-NMR (300MHz) d: 1.69 (s, 3H, **H**$_3$CC=C), 1.71 (s, 3H, **H**$_3$CC=C), 2.43 (dd, 1H, ^{2}J= 17.4Hz, ^{3}J= 1.8Hz **H**$_{cis}$CCH-S=O), 2.98 (dd, 1H, ^{2}J= 17.4Hz, ^{3}J= 6.3Hz, **H**$_{trans}$CCH-S=O), 3.36 from AB to A_2 (br.s, 2H, **H**$_2$C-S=O), 3.63 AB middle peaks overlapping (t, 1H, ^{3}J= 5.4Hz, H_2CC**H**-S=O), 4.50 (d, 2H, J= 5.7Hz, **H**$_2$CPh), 7.20-7.35 (m, 5H, **arom**), 7.58 (br.s, 1H, N**H**).^{13}C-NMR (75 MHz) d: 19.5 (H_3**C**C=C), 19,9 (H_3**C**C=C), 29.4 (H_2**C**CH-S=O), 43.4 (H_2**C**Ph), 50.1 (H_2**C**-S=O), 55.2 (H_2C**C**H-S=O), 116.2 (**C**=C), 127.4 (**C**=C), 127.7, 127.8 and 128.6 (C arom), 138.0 (C-ipso),166.9 (**C**=O). Mass (EI): m/e 277 (M^+), 229 (M^+ -SO, 31%), 95 ($C_7H_{11}^{+\cdot}$). Elemental analysis: calcd for $C_{15}H_{19}NO_2S$, C 64.95, H 6.90, S 11.56, N5.05 %. Found: C 64.92, H 6.86, S 12.15, N 5.07 %.

***E*-6a:** protons thiopyran ring: ^{1}H-NMR (300MHz) d: 2.69 AB system, almost A_2 (2H, **H**$_2$CCH-S=O), 3.41 A of AB (d, 1H, J_{AB}= 15.3Hz, **H**HC-S=O), 3.65 B of AB (d, 1H, J_{AB}= 15.3Hz, H**H**C-S=O), 3.57 (dd, 1H, ^{2}J= 9.6 Hz, ^{3}J= 6.9Hz, H_2CC**H**-S=O). Mass (*E*/*Z*-mixture)(EI): m/e 277 (M^+), 229 (M+-SO).

***N*-[(1*R*)-1-Phenylethyl]-4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6e) (2 isomers)**

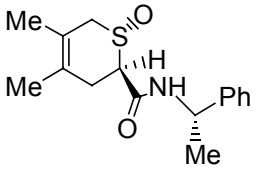
Obtained as a white crystalline solid after column chromatography (ethyl acetate: heptane= 1:1 gradient to 100% ethyl acetate), *Z*/*E* = 6:1 mixture of isomers, 242 mg. (42 %). Mp.>130°C (dec). $[\alpha]_D^{22}$ = -75.2°

***Z*-isomer:**



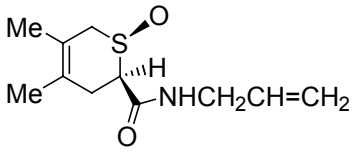
^{1}H-NMR (300MHz) d:1.51 (d, 3H, J= 6.9 Hz, **H**$_3$CC-Ph), 1.72 (s, 6H, **H**$_3$CC=C**H**$_3$), 2.38 (dd, 2H, J= 5.7 Hz, 16.8 Hz, H**H**C-C-S=O), 2.97 (dd, 1H, J= 5.7Hz, 16.8 Hz, H**H**C-C-S=O), 3.42 (br.s, 2H, **H**$_2$C-S=O), 3.66 (m, 1H overlap with signals other isomer, O=C-C**H**-S=O), 5.14 (m, 1H overlap with signals other isomer, **H**C-Ph), 7.20-7.40 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 19.4 (**C**H_3C=C), 20.0 (**C**H_3C=C), 22.5 (**C**H_3CH-Ph), 29.6 (**C**H_2CHS=O), 49.3 (H**C**-Ph), 54.9 (H_2**C**-S=O), 61.9 (O=S-**C**H-C=O), 116.2 (**C**=C), 127.6 (**C**=C), 127.3, 128.7 (C **arom**), 143.1 (C-ipso), 165.9 (**C**=O). **E-isomer:** ^{1}H-NMR (300MHz) d: 1.48 (d, 3H, J= 6.9 Hz, **H**$_3$CC-Ph), 1.63(s, 6H, **H**$_3$CC=C**H**$_3$), 2.67 (d, 2H, J= 10.8 Hz, **H**$_2$C-C-S=O), 3.22 (AB, 1H, J= 15 Hz, H**H**C-S=O), 3.67 (d, 1H, overlap with signals of other isomer, H**H**C-S=O), 3.66 (m, 1H overlap with signals of other isomer, O=C-C**H**-S=O), 5.14 (m, 1H overlap with signals of other isomer, **H**C-Ph), 7.20-7.40 (m, 5H overlap with signals of other isomer, **arom**). ^{13}C-NMR (75 MHz) d: 19.8 (**C**H_3C=C),19.9 (**C**H_3C=C), 22.6 (**C**H_3CH-Ph), 31.9 (**C**H_2CHS=O), 49.7 (H**C**-Ph), 54.8 (H_2**C**-S=O), 56.0 (O=S-**C**H-C=O), 116.2 (**C**=C), 127.5 (**C**=C), 127.6, 128.3 (C **arom**), 144.0 (C-ipso), 166.1 (**C**=O). Mass (EI): m/e 291 (M+), 243 (M+-SO, 17%), 105 ($PhCH^{+\cdot}CH_3$, 100%), 95 ($C_7H_{11}^{\cdot+}$, 54%). Elemental analysis: calcd for $C_{16}H_{21}NO_2S$, C 65.95, H 7.26, S 11.00, N 4.81. Found: C 65.33, H 7.23 ,S 11.32, N 4.74%.

"Slow moving" diastereomer (*E*-isomer):



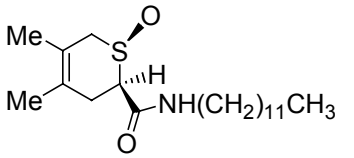
Obtained as a white crystalline solid after column chromatography (ethyl acetate: heptane= 1:1 gradient to 100% ethyl acetate), 238 mg. (40 %) of a white solid. Mp.140-142 °C. $[\alpha]_D^{22}$ = +270° ; ^{1}H-NMR (300MHz) d: 1.53 (d, 3H, J= 6.9Hz, **H**$_3$CCHPh), 1.69 (s, 3H, **H**$_3$CC=C), 1.73 (s, 3H, **H**$_3$CC=C), 2.66 from AB to nearly A_2 (br.s, 2H, **H**HCCHS=O), 3.41(d, 1H, J= 16.0Hz, **H**HCS=O), 3.52 (dd, 1H, ^{2}J= 8.9Hz, ^{3}J= 6.9Hz, O=CC**H**S=O), 3.67 (d, 1H, J= 16.0Hz, **H**HCS=O), 5.14 (m,1H, H$_3$CC**H**Ph), 7.20-7.37 (m, 5H, arom).^{13}C-NMR (75 MHz) d: 19.1(H$_3$**C**CC=C), 19.2 (H$_3$**C**CC=C), 22.2 (H$_3$**C**CHPh), 31.9 (**C**H$_2$CHS=O), 49.6 (H**C**-Ph), 56.1 (H$_2$**C**-S=O), 62.1 (O=C**C**HS=O), 117.2 (**C**=C),126.1 (**C**=C), 127.4, 128.6 and 128.7 (**C**-arom), 143.0 (**C**-ipso), 165.7 (**C**=O). Mass (EI): m/e 291 (M^+), 243 (-SO, 18%), 105 (PhCH$^+$CH$_3$,100%).
Elemental analysis: calc. for $C_{16}H_{21}NO_2S$, C 65.95, H 7.26, S 11.00, N 4.81 %. Found: C 66.12, H 7.20, S 11.47, N 4.85 %.

***N*-Allyl 4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (*Z*-6b)**



Obtained as a white crystalline solid after column chromatography (ethyl acetate: heptane= 1:1), 426 mg. (94 %). Mp.166-168°C (diisopropyl ether/ethyl acetate). ^{1}H-NMR (300MHz) d: 1.71 (br.s, 6H, **H**$_3$CC=CC**H**$_3$), 2.43 (dd, 1H, ^{2}J=19.2Hz, **H**$_{cis}$CCH-S=O), 2.97 (dd, 1H, ^{2}J= 19.2Hz, ^{3}J= 5.4Hz, **H**$_{trans}$CCH-S=O), 3.39 from AB to nearly A_2 (br.s, 2H, **H**$_2$C-S=O), 3.60 (1H, ^{3}J= 6.0Hz, O=CC**H**-S=O), 3.94 (m, 2H, **H**$_2$CCH=CH$_2$), 5.12-5.27 (m, 2H, **H**$_2$C=CHCH$_2$), 5.85 (m, 1H, H$_2$CC**H**=CH$_2$), 7.27 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 19.5 (H$_3$**C**CC=CCH$_3$), 20.0 (H$_3$CC=C**C**H$_3$), 29.3 (H$_2$**C**CH-S=O), 41.9 (H$_2$C=CH**C**H$_2$), 50.2 (H$_2$**C**-S=O), 55.3 (O=CC**H**-S=O), 116.1, 116.5, 127.5 and 133.6 (vinylic **C**'s), 167.0 (C=O). Mass (EI): m/e 227 (M^+), 179 (M^+-SO, 54%), 95 (1,2-dimethylcycopentene cation, 100%). Elemental analysis: calcd for $C_{11}H_{17}NO_2S$, C 58.12, H 7.54, S 14.11, N 6.16 %. Found: C 58.13, H 7.37, S 14.83, N 6.11 %.

***N*-Dodecyl 4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6c)**

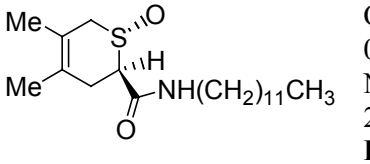


Obtained from 1.0 mmol of **5a** as an off white solid (E:Z ≈ 9:1), isomers were separated by column chromatography (EtOAc:heptane= 1:1).

(*Z*)-6c ("fast" isomer)

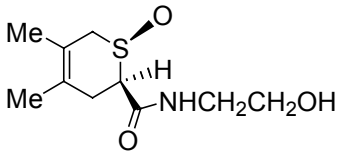
White needles, 31 mg. (8.7 %). Mp. 126-129°C (diisopropyl ether/ ethyl acetate). ^{1}H-NMR (300MHz) d:0.85 (m, 3H, -CH$_2$C**H**$_3$), 1.20-1.33(m, 18H, (C**H**$_2$)$_9$), 1.53 (m, 2H, NCH$_2$C**H**$_2$), 1.71 (s, 6H, **H**$_3$CC=CC**H**$_3$), 2.40 (dd, 1H, ^{2}J= 17.7Hz, **H**$_{cis}$HCCH-S=O), 2.95 (dd, 1H, ^{2}J= 17.7Hz, ^{3}J= 6.3Hz, **H**$_{trans}$HCCH-S=O), 3.27 (m, 2H, NHC**H**$_2$), 3.37 A_2 system (s, 2H, C**H**$_2$-S=O), 3.55 (dd, 1H, ^{2}J= 6.4Hz, ^{3}J= 6.3Hz, O=CC**H**-S=O), 7.16 (m, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.1 (H$_3$CCH$_2$-), 19.5 (H$_3$**C**CC=C), 19.9 (C=C**C**H$_3$), 22.7, 26.9, 29.2, 29.3, 29.4, 29.5, 29.55, 29.6 and 31.9 (10 **C**H$_2$ some peaks overlapping and **C**H$_2$CH-S=O), 39.7 (HN**C**H$_2$-), 50.2 (**C**H$_2$-S=O), 55.3 (O=C**C**H-S=O), 116.1 (**C**=C), 127.5 (C=**C**), 167.0 (**C**=O). Mass (EI): 355 (M^+), 307 (-SO, 87%), 95 (C7H11, 100%). Elemental analysis: calcd for $C_{20}H_{37}NO_2S$, C 67.56, H 10.49, S 9.02, N 3.94 %. Found: C 67.28, H 10.45, S 9.25, N 4.01 %.

(*E*)-6c slow isomer



Off white solid, 309 mg. (78 %). Mp. ±35°C. ^{1}H-NMR (300MHz) d: 0.87 (m, 3H,C**H**$_3$), 1.20-1.33(m, 18H, (C**H**$_2$)$_9$), 1.52 (m, 2H, NCH$_2$C**H**$_2$), 1.70 (s, 3H, **H**$_3$CC=C), 1.73 (s, 3H, **H**$_3$CC=C), 2.66 (br.s, 2H, **H**$_2$CCH-S=O), 3.29 (m, 2H, NC**H**$_2$CH$_2$), 3.43 (d, 1H, J= 15.3Hz, **H**HC-S=O), 3.58 (dd, 1H, ^{2}J= 9.3Hz, ^{3}J= 6.9Hz,O=C**C**H-S=O), 3.65 (d, 1H, J= 15.3Hz, **H**HC-S=O), 6.99 (m, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.1 (**C**H$_3$), 19.1 (H$_3$CC=C), 19.8 (H$_3$**C**C=C), 22.6, 26.8, 29.2, 29.5, 29.6, 31.9, 32.2 (10 **C**H$_2$ some peaks overlapping and **C**H$_2$CH-S=O), 40.0 (N**C**H$_2$CH$_2$), 55.6 (H$_2$**C**-S=O), 62.3 (O=C**C**H-S=O), 117.0 (C=**C**), 128.6 (C=**C**), 166.5 (**C**=O). Mass (EI): m/e 355 (M^+), 307 (-SO, 69%), 95 ($C_7H_{11}^+$, 100%). Elemental analysis: calcd for $C_{20}H_{37}NO_2S$, C 67.56, H 10.49, S 9.02, N 3.94 %. Found: C 67.11, H 10.41, S 9.18, N 3.88 %.

***N*-(2-Hydroxyethyl) 4,5-dimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6d)**

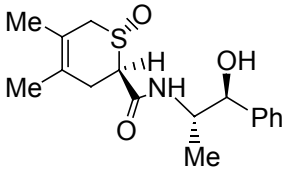


Obtained from 1.0 mmol of **5a** as a crystalline white solid, 205 mg. (89 %). Colorless needles from ethyl acetate. Mp.145°C (dec). ^{1}H-NMR (300MHz) d:1.69 (s, 3H, **H$_3$**CC=C), 1.74 (s, 3H, **H$_3$**CC=C), 2.58 (dd, 1H, J= 4.5 Hz, J= 18.3 Hz, **H**$_{cis}$CHCH-S=O), 2.75 (dd, 1H, J= 11.1Hz, J= 18.3 Hz, **H**$_{trans}$CHCH-S=O), 3.20-3.36 (m, 2H, O**H** and 1 proton from ethanol amine), 3.46 (d, 1H, J= 15.3Hz, **H**HC-S=O), 3.35-3.78 (m, 5H, **H**HC-S=O + O=CC**H**-S=O + 3 protons ethanol amine), 7.50 (t, 1H, J= Hz, N**H**). ^{13}C-NMR (75 MHz) d:19.1 (H$_3$**C**C=C), 19.9 (H$_3$**C**C=C), 32.8 (**C**H$_2$CH-S=O), 42.8 (N**C**H$_2$-), 55.2 (H$_2$**C**-S=O), 61.1, 64.1 (H$_2$C-S=O and H$_2$C-OH), 117.1 (**C**=C), 128.5 (C=**C**), 167.5 (**C**=O). Mass (EI): m/e 231(M$^+$), 183 (M$^+$-SO, 67%), 95 (C$_7$H$_{11}$, 100%). Elemental analysis: calcd for $C_{10}H_{17}NO_3S$, C 51.92, H 7.41, S 13.86, N6.06 %. Found: C 51.62, H 7.41, S 13.34, N 6.07 %.

***N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl] 4,5-dimethyl-1-oxo-3,6-dihydro-2H-thiopyran-2-carboxamide (6f)**

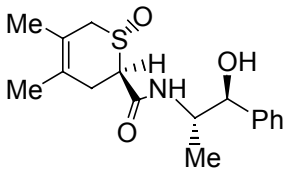
Obtained from 1.0 mmol of **E-5a**, 260 mg (81 %) of a white solid that showed three spots on TLC (ethyl acetate), these consisted of a pair of diastereomers of which the fastest had partially isomerized. The minor spot of the latter two (a small amount for NMR purposes was obtained in 90% purity after two chromatography steps (ethyl acetate:heptane=1:1 to 100% ethyl acetate) and was shown to belong to the initial fast *E*-isomer (^{1}H-NMR). The *Z*-isomer (H-NMR) was obtained in 90% purity after crystallization from ethyl acetate. The third (slowest) spot corresponded with the second diastereomer and its ^{1}H-NMR spectrum indicated an *E*-configuration.

"Fast" diastereomer:



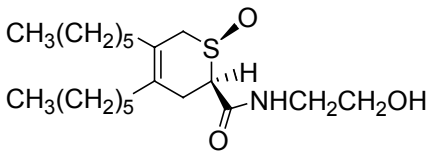
E-isomer, 10 mg (containing ±10% of *Z*-isomer): ^{1}H-NMR (300MHz) d: 0.97 (d, 3H, J= 6.9Hz, **H$_3$**CCHNH), 1.71 (s, 3H, **H$_3$**CC=CCH$_3$),1.74 (s, 3H, H$_3$CC=C**CH$_3$**), 2.58 (dd, 1H, ^{2}J=18.0Hz, ^{3}J= 4.8Hz, **H**HCCHS=O), 2.83 (dd, 1H, ^{2}J= 18.0 Hz, ^{3}J= 11.4Hz, **H**HCCHS=O), 3.45 (d, 1H, J= 13.0Hz, **H**HCS=O), 3.52 (dd, 1H, ^{3}J= 11.4Hz, ^{3}J= 4.8Hz, O=CC**H**S=O), 3.69 (d, 1H, J= 13.0Hz, **H**HCS=O) overlapping with 3.71 (br.s, 1H, O**H**), 4.33 (m, 1H, HNC**H**CH$_3$), 4.98 (d, 1H, J= 3.0Hz, HOC**H**Ph), 6.64 (d, 1H, N**H**), 7.31-7.41 (m, 4H, **arom**). ^{13}C-NMR (75 MHz) d: 12.9 (H$_3$**C**CHNH), 19.2 (H$_3$**C**C=CCH$_3$), 19.9 (H$_3$CC=C**C**H$_3$), 32.1 (H$_2$**C**CHS=O), 51.9 (HN**C**HCH$_3$), 55.8 (H$_2$**C**-S=O), 63.9 (O=C**C**HS=O), 74.2 (HO**C**HPh), 117.0 (**C**=C), 125.9, 127.2, 128.1 (aromatic), 128.6 (C=**C**), 140.6 (**C**-ipso), 166.3 (**C**=O). **Z-isomer**: 122 mg (38%); ^{1}H-NMR (300MHz) d: 1.06 (d, 3H, J= 6.9Hz, **H$_3$**CCHNH), 1.70 (s, 3H, **H$_3$**CC=CCH$_3$), 1.72 (s, 3H, H$_3$CC=C**CH$_3$**), 2.39 (dd, 1H, ^{2}J= 17.7 Hz, **H**HCCHS=O), 2.92 (dd, 1H, ^{2}J= 17.7Hz, ^{3}J= 6.0Hz, **H**HCCHS=O), 3.34 (two broad singlets overlapping, 1H, O**H** and 2H, **H$_2$**CS=O), 3,54 (t, 1H, ^{3}J= 6.0Hz, O=CC**H**S=O), 4.33 (m,1H, HNC**H**CH$_3$), 4.88 (d, 1H, J= 3.3Hz, HOC**H**Ph), 7.23-7.42 (m, 6H, N**H**, **arom**). ^{13}C-NMR (75 MHz) d: 14.3 (H$_3$**C**CHNH), 19.5 (H$_3$**C**C=CCH$_3$), 19.9 (H$_3$**C**C=CCH$_3$), 29.1 (H$_2$**C**CHS=O), 50.2 (H$_2$**C**-S=O), 51.5 (HN**C**HCH$_3$), 55.5 (O=C**C**HS=O), 76.0 (HO**C**HPh), 116.0 (**C**=C), 126.2(**C**=C), 127.4, 127.6 and 128.2 (**C**-arom), 140.9 (**C**-ipso), 167.2(**C**=O).

"Slow" diastereomer (*E*-isomer):



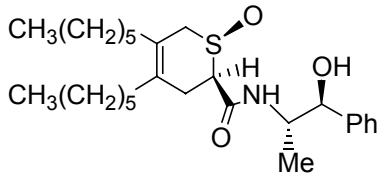
White crystalline solid 125 mg (39%). Mp.184-185°C. ^{1}H-NMR (300MHz) d: 1.08 (d, 3H, J= 6.9Hz, **H$_3$**CCHNH), 1.71 (s, 3H, **H$_3$**CC=CCH$_3$), 1.73 (s, 3H, H$_3$CC=C**CH$_3$**), 2.66 (m, 2H, **H$_2$**CCHS=O), 3.29 (br.s, 1H, O**H**), 3.39 (d, 1H, J=15.5Hz , **H**HCS=O), 3.53 (dd, 1H, ^{3}J= 9.6 Hz, ^{3}J= 3.3Hz, O=CC**H**S=O), 3.64 (d, 1H, J= 15.5Hz , **H**HCS=O), 4.33 (m,1H, HNC**H**CH$_3$), 4.88 (d, 1H, J= 3.0Hz, HOC**H**Ph), 6.99 (d, 1H, J= 7.5Hz, N**H**), 7.23-7.42 (m, H, **arom**). ^{13}C-NMR (75 MHz) d: 14.2 (H$_3$**C**CHNH), 19.2 (H$_3$**C**C=CCH$_3$), 19.8 (H$_3$**C**C=CCH$_3$), 32.2 (H$_2$**C**CHS=O), 51.8 (HN**C**HCH$_3$), 55.7 (H$_2$**C**-S=O), 62.6 (O=C**C**HS=O), 76.2 (HO**C**HPh), 117.2 (**C**=C), 126.2, 127.6 and 128.2 (**C-arom**), 128.4 (**C**=C), 140.7 (**C**-ipso), 167.0 (**C**=O). Mass (EI): m/e 321 (M$^+$), 214 (M+-PhCHO, 71.3%). HRMS: calcd for $C_{17}H_{23}NO_3S$: 321.13987. Found: 321.14006.

***N*-(2-Hydroxyethyl) 4,5-di-(n-hexyl)-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6h)**



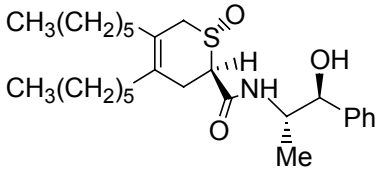
Obtained from 0.5 mmol **5b** after column chromatography (heptane:ethyl acetate=1:1). 160 mg. (86%), small white needles from ethyl acetate. Mp.85-94 °C. ^{1}H-NMR (400MHz) d: 0.88 (m, 6H, 2 $\mathbf{H_3}CCH_2$-), 1.20-1.40 (m, 16H, 2 ($C\mathbf{H_2})_4$), 1.98-2.07 (m, 4H, -$\mathbf{H_2}CC{=}CC\mathbf{H_2}$-), 2.50-2.75 (br.s, 1H, O**H**) overlapping with two double doublets which form AB system: 2.66 (dd, 1H, ^{2}J= 14.1Hz, ^{3}J= 4.2Hz, $\mathbf{H_{cis}}$HCCHS=O) and 2.77 (dd, 1H, ^{2}J= 14.1Hz, ^{3}J= 8.1Hz, $\mathbf{H_{trans}}$HCCHS=O), 3.35 (m, 1H, ethanolamine), 3.43 (d, 1H, J= 10.8Hz, H**H**CS=O), 3.56-3.78 (m, 5H, O=SC**H**C=O, H**H**CS=O and three protons from ethanol amine), 7.21 (br.s. 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.0 (2 $H_3\mathbf{C}CH_2$-), 22.6, 27.9, 28.3, 29.1, 29.3, 30.9, 31.6, 33.4, 42.9 (-HN$\mathbf{C}H_2CH_2OH$), 54.2 ($H_2\mathbf{C}$-S=O), 61.4, 64.1 (HO$\mathbf{C}H_2$- and O=S**C**HC=O), 121.9 (C=**C**), 133.3 (**C**=C), 167.7 (**C**=O). Mass (EI): m/e 371 (M^+), 353 (M^+-H_2O, 22%), 323 (M^+- SO, 64%). HRMS: calcd for $C_{20}H_{37}NO_3S$: 371.24942. Found: 371.24947.

***N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]-4,5-di-(n-hexyl)-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6g) ("fast" diastereomer; *Z*-configuration)**



Obtained from 1.0 mmol of **5b** as an off-white sticky solid after columnchromatography (ethyl acetate:heptane=1:1), 184 mg (40 %). Mp. 146-148°C. $[\alpha]_D^{22}$ = -106°. ^{1}H-NMR (300MHz) d: 0.87-0.93 (m, 6H, 2 $\mathbf{H_3}$CCH2-), 1.06 (d, 3H, J= 6.9Hz, $\mathbf{H_3}$CCHN), 1.23-1.40 (m, 16H, 2 ($C\mathbf{H_2})_4$), 2.04 (m, 4H, -$\mathbf{H_2}CC{=}CC\mathbf{H_2}$-), 2.42 (dd, 1H, ^{2}J=17.7Hz, ^{3}J= 4.8Hz, H$\mathbf{H_{cis}}$CCHS=O), 2.94 (dd, 1H, ^{2}J= 17.7Hz, ^{3}J= 6.9Hz, H$\mathbf{H_{trans}}$CCHS=O), 3.10-3.40 (br.s. 1H, O**H**), 3.33 A of AB (d, 1H, J_{AB}= 16.5Hz, H**H**CS=O), 3.38 B of AB (d, 1H, J_{AB}= 16.5Hz, H**H**CS=O), 3.53 (t from dd, 1H, O=SC**H**C=O), 4.25-4.40 (m,1H, **H**CNH), 4.88 (d, 1H, J= 3.3Hz, **H**CPh), 7.24-7.40 (m, 6H, N**H** + arom). ^{13}C-NMR (75 MHz) d: 14.1(2 $H_3\mathbf{C}CH_2$-), 14.3 ($H_3\mathbf{C}$CHNH-), 22.5, 22.6, 27.4, 27.9, 28.2, 29.4, 31.7 and 33.3 ($\mathbf{C}H_2$ some peaks overlapping and $\mathbf{C}H_2$CH-S=O), 48.8 ($H_2\mathbf{C}$-S=O), 51.5 (HN$\mathbf{C}HCH_3$), 55.5(O=C**C**HS=O), 76.1(HO**C**HPh), 121.0 (**C**=C), 126.2, 127.6 and 128.2 (C-arom), 132.1(C=**C**), 140.8 (**C**-ipso), 167.3 (**C**=O).Mass (EI): m/e 461 (M+), 354 (M+-PhCHO, 51%), 311 (M^+-NHCH(Me)CHOHPh, 59%). HRMS: calcd for $C_{27}H_{43}NSO_3$: 461.29636. Found: 461.29581.

***N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl]-4,5-di-(n-hexyl)-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6g) ("slow" diastereomer, *E*-conformation)**



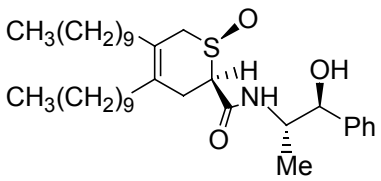
Obtained as an off-white sticky solid after columnchromatgraphy (ethylactate:heptane=1:1), 203 mg (44 %); was crystallized from dilute diisopropyl ether. Mp. 127-128°C. $[\alpha]_D^{22}$ = -90.4°; ^{1}H-NMR (300MHz) d: 0.87 (m, 6H, 2 $\mathbf{H_3}CCH_2$-), 1.07 (d, 3H, J= 6.9Hz, $\mathbf{H_3}$CCHN), 1.25-1,43 (m, 16H, 2 ($C\mathbf{H_2})_4$), 2.05 (m, 4H,-$\mathbf{H_2}CC{=}CC\mathbf{H_2}$-), 2.69 from AB to nearly A_2 (d, 2H, $\mathbf{H_2}$CCHS=O), 3.25-3.50 (br.s, 1H, O**H**) overlapping with: 3.37 (d, 1H, J=15.0Hz, H**H**C-S=O) and 3.47 triplet from dd (t, 1H, ^{3}J= 8.2Hz, O=SC**H**C=O), 3.66 (d, 1H, J= 15.0Hz, H**H**C-S=O), 4.29-4.39 (m, 1H, NHC**H**), 4.89 (d, 1H, J= 3.3Hz, HOC**H**Ph), 7.04 (m, 1H, N**H**), 7.24-7.36 (m, 5H, arom).^{13}C-NMR (75 MHz) d: 14.0 ($H_3\mathbf{C}$), 14.1 ($H_3\mathbf{C}$), 22.6, 27.9, 28.4, 29.1, 29.4, 30.6, 31.6, 33.0 and 33.3 (10 $\mathbf{C}H_2$ with some peaks overlapping and $\mathbf{C}H_2$CH-S=O), 51.8 (HN$\mathbf{C}HCH_3$), 54.4($H_2\mathbf{C}$-S=O), 63.1(O=C**C**HS=O), 76.2 (HO**C**HPh), 122.1(**C**=C), 126.2, 127.6 and 128.2 (C-arom), 133.3(C=**C**), 140.8, (**C**-ipso), 167.3(**C**=O). MS: m/e 461 (M^+), 355 (M^+-PhCHOH, 22%), 311 (M^+-NHCH(Me)CHOHPh, 21%). HRMS: calcd for $C_{27}H_{43}NSO_3$: 461.29636. Found: 461.29608.

Crystal data and structure refinement for 6g ("slow" diastereomer).

Crystal color	transparent colorless

Crystal shape	regular needle
Crystal size	0.36 x 0.12 x 0.06 mm
Empirical formula	$C_{27}\ H_{42}\ N\ O_3\ S$
Formula weight	460.68
Temperature	293(2) K
Radiation / Wavelength	MoK_α (graphite mon.) / 0.71073 Å
Crystal system, space group	Monoclinic, P 21
Unit cell dimensions	a, α = 9.461(2) Å, 90°
(14 reflections 3.974 < θ < 6.826)	b, β = 29.814(9) Å, 95.40(3)°
	c, γ = 10.011(2) Å, 90°
Volume	2811.4(12) $Å^3$
Z, calculated density	4, 1.088 Mg/m^3
Absorption coefficient	0.140 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / θ-2θ
F(000)	1004
θ-range for data collection	2.56 to 24.62°
Index ranges	-11<=*h*<=10, 0<=*k*<=32, -10<=*l*<=0
Reflections collected / unique	4261 / 4011 [R_{int} = 0.0644]
Reflections observed	1326 ([I_o>2σ(I_o)])
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	4011 / 1 / 579
Goodness-of-fit on F^2	1.031
SHELXL-97 weight parameters	0.018300 0.129100
Final R indices [I>2σ(I)]	R_1 = 0.0844, wR_2 = 0.0793
R indices (all data)	R_1 = 0.2830, wR_2 = 0.1162
Largest diff. peak and hole	0.181 and -0.186 e.$Å^{-3}$

_N_-[(1_S_,2_R_)-2-Hydroxy-1-methyl-2-phenylethyl] 4,5-di-(n-decyl)-1-oxo-3,6-dihydro-2_H_-thiopyran-2-carboxamide (6i)



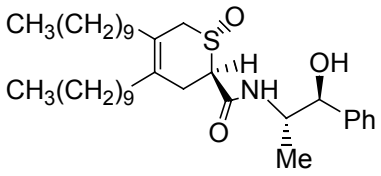
From 1.0 mmol of **E-5a**, obtained as an off-white solid, 1:1 mixture of isomers that was separated by column chromatography (heptane:ethyl acetate =1:1).

6i _Z_-conformation

229 mg (40 %), Mp. 124-126°C. $[\alpha]_D^{22}$ = +42.3°. ^{1}H-NMR (300MHz) d: 0.85-0.90 (m, 6H, 2 **H**$_3$CCH$_2$-), 1.06 (d, 3H, J= 6.9Hz, **H**$_3$CCHN), 1.20-1,45 (m, 32H, alkyl chain), 1.96-2.08 (m, 4H, -**H**$_2$CC=CC**H**$_2$-), 2.42 (dd, 1H, J= 18.0Hz, ^{3}J= 4.8Hz, H**H**$_{cis}$CCHS=O), 2.94 (dd, 1H, ^{2}J= 18.0Hz, ^{3}J= 7.0Hz, H**H**$_{trans}$CCHS=O), 3.33 A of AB (d, 1H, J_{AB}= 16.5Hz, H**H**C-S=O), 3.40 B of AB (d, 1H, J_{AB}= 16.5Hz, H**H**C-S=O), 3.53 dd that became triplet (t, 1H, O=S-C**H**-C=O), 4.34 (m,1H, HNC**H**Me), 4.88 (d,1H, J= 3.3Hz, HOC**H**Ph), 7.22-7.39 (m,6H, N**H** + arom).^{13}C-NMR (75 MHz) d: 14.1 (H$_3$**C**CHN-), 14.3 (2 **C**H$_3$CH$_2$-), 22.7, 27.4, 28.0, 28.2, 29.3, 29.5, 29.6, 29.7, 29.8, 31.9 and 33.3 (18 **C**H$_2$ with some peaks overlapping and **C**H$_2$CH-S=O) , 48.8 (H$_2$**C**-S=O), 51.5 (HN**C**HCH$_3$), 55.5 (O=C**C**HS=O), 76.1 (HO**C**HPh), 121.0

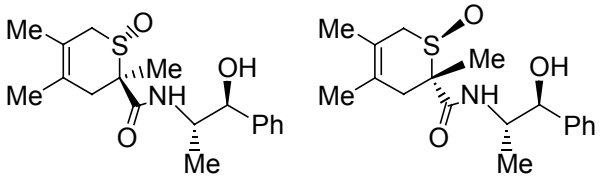
(**C**=C), 126.2, 127.5, 128.2, 132.1 (**C**=C), 140.8 (C-ipso), 167.3 (**C**=O). Mass (EI): m/e 573 (M^+), 555 (M^+-H_2O, 11%), 448 (M^+- $PhCH_2O$, 47%). HRMS: calculated for $C_{35}H_{59}NO_3S$: 573.42157. Found: 573.42161. Elemental analysis: calc. for $C_{35}H_{59}NSO_3$: %C 73.25, %H 10.36, %N 2.44. Found %C 72.91, %H 10.36, %N 2.57.

6i *E*-conformation



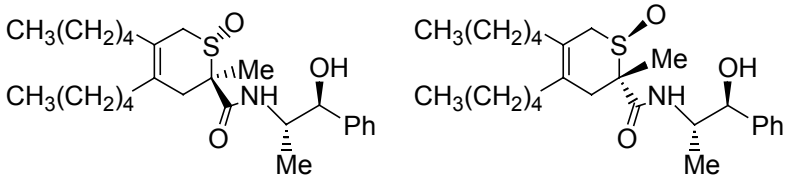
Obtained after column chromatography (ethyl acetate:heptane=1:1), 234 mg (41 %) as an amorphous solid that stuck as a film to the surface of the flask. The compound melted slowly above 35 °C, crystallisation failed because of gel formation upon cooling warm solutions in heptane/ethyl acetate, chloroform or diisopropyl ether. $[\alpha]_D^{22}$ = -98.3° . ^{1}H-NMR (300MHz) d: 0.88 (m, 6H, 2x **H**$_3$CCH$_2$-), 1.06 (d, 3H, J= 6.9Hz, NCHC**H**$_3$), 1.20-1.40 (br. m, 32H, 2 -(C**H**$_2$)$_8$-), 2.03 (m, 4H, -**H**$_2$CC=CC**H**$_2$-), 2.68 (m, 2H, C**H**$_2$-S=O), 3.34 (d, 1H, J= 18.0 Hz, **H**$_{trans}$CCH-S=O), 3.46 (dd, 1H, J= 6.9 Hz, Hz, O=S-C**H**-C=O), 3.63 (d, 1H, J= 18.0 Hz, **H**$_{cis}$CCH-S=O), 4.32 (m, 1H, HN-C**H**(Me)-), 4.89 (d, 1H, J= 3.0 Hz, Ph-C**H**(OH)-), 7,17 (br.d, 1H, J= 8.3 Hz, N**H**), 7.25-7.35 (m, 5H, **arom**). ^{13}C-NMR (75 MHz) d: : 14.0 (H$_3$**C**CHN-), 14.1 (2 **C**H$_3$CH$_2$-), 22.7, 28.0, 29.3, 29.5, 29.6,29.7, 30.6, 31.9, 33.0 and 33.3 (18 **C**H$_2$ with some peaks overlapping and **C**H$_2$CH-S=O), 51.8 (HN**C**HCH$_3$), 54.2 (H$_2$**C**-S=O), 63.3 (O=C**C**HS=O), 76.0 (HO**C**HPh), 122.1 (**C**=C), 126.2, 127.5 and 128.2 (**C**-arom), 133.3(**C**=C), 140.8 (**C**-ipso), 167.1(**C**=O). Mass (EI): m/e 573 (M^+), 555 (M^+-H_2O, 22%), 449 (M^+- PhCHO, 15%). HRMS: calcd for $C_{35}H_{59}NO_3S$: 573.42157. Found: 573.42258.

***N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl] 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6l)**



Obtained as white foam after column chromatography (ethyl acetate: heptane = 1:1 to 100% ethyl acetate), 590 mg (88%), 1:1 mixture of diastereomers. ^{1}H-NMR (300MHz) d: 0.98 (d, 3H, J= 6.9Hz, C**H**$_3$CNH), 1.06 (d, 3H, J= 6.9Hz, C**H**$_3$CNH), 1.45 (s, 3H, C**H**$_3$C-S=O), 1.51 (s, 3H, C**H**$_3$C-S=O), 1.70 (m, 12H, 2x C**H**$_3$C=CC**H**$_3$), 1.90 (br.s, 1H, O**H**), 2.53 (br.s A_2 from AB, 2H, C**H**$_2$S=O), overlapping with AB-system: A-part 2.51 (d, 1H, J_{AB}= 17.7 Hz, **H**HCCHS=O), B-part 2.61(d, 1H, J_{AB}= 17.7Hz, **H**HCCHS=O), 3.15 A-part of AB-system (d, 1H, J_{AB}=17.4Hz, **H**HC-S=O), B-part of AB-system 3.48 (d, 1H, J_{AB}= 17.4Hz, **H**HC-S=O), latter AB-system overlaps with A_2-system at 3.46 (br.s, 2H, **H**$_2$C-S=O), 4.28 (m, 2H, 2 HNC**H**CH$_3$), 4.77 (br.s, 1H, HOC**H**Ph), 4.84(br.s, 1H, HOC**H**Ph), 6.65 (d, 1H, J= 4.2Hz, N**H**), 6.74 (d, 1H, J= 4.2Hz, N**H**), 7.28-7.38 (m, 10H, arom). ^{13}C-NMR (75 MHz) d: 13.7, 14.8, 15.3 and15.9 (O=S-C-**C**H$_3$ and HNCH**C**H$_3$), 19.4 (H$_3$**C**CC=C), 19.8 (H$_3$**C**CC=C), 36.4 (2 **C**H$_2$C(Me)-S=O), 50.1 (H$_2$**C**-S=O), 50.3 (H$_2$**C**-S=O), 51.2 (2 HN**C**HCH$_3$), 58.6 (O=C-**C**-S=O), 59.0 (O=C-**C**-S=O), 75.3 (HO**C**HPh), 76.4 (HO**C**HPh), 116.9 (**C**=C), 117.0 (**C**=C), 126.6 (C=**C**), 126.7(C=**C**), 126.1, 126.3, 127.5, 127.7 and 128.2 (**C**-arom), 140.6 (**C**-ipso), 140.8 (**C**-ipso), 170.9 (**C**=O), 171.6 (**C**=O). Mass (EI): m/e 335 (M^+), 287 (M^+-SO, 23%), 109 (C_8H_{13}+, 100%). HRMS: calcd for $C_{18}H_{25}NO_3S$: 335.15551. Found: 335.15562.

***N*-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethyl] 2-methyl-4,5-di-(n-pentyl)-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6m)**

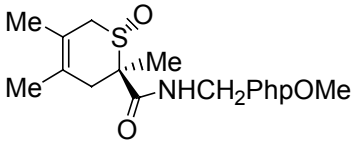


Obtained from 2 mmol of **5e** as a mixture of diastereomers after column chromatography (ethyl acetate: heptane=1:1). White foam that turned to viscous syrup upon warming, 778 mg (87%). One diastereomer was obtained in pure form by crystallisation from diisopropyl ether/ethyl acetate. **Crystalline diastereomer**: Mp.169-170°C. $[\alpha]_D^{22}$ = 61.1°. ^{1}H-NMR (300MHz) d: 0.90 (m, 6H, 2 C**H**$_3$CH$_2$-), 0.99 (d, 3H, J=6.9Hz, C**H**$_3$CNH), 1.20-1.40 (m, 12H, 2 CH$_3$(C**H**$_2$)$_3$-CH$_2$-), 1.49 (s, 3H, **H**$_3$C-C-S=O), 1.97-2.05 (m, 4H, -**H**$_2$CC=CC**H**$_2$-), 2.54 A of AB (d, 1H, J_{AB}= 18.6Hz, **H**HCCHS=O), 2.64 B of AB (d, 1H, J_{AB}= 18.6Hz, **H**HCCHS=O), 2.81 (br.s, 1H, O**H**), 3.13 (d, 1H, J= 16.5Hz,

HHCS=O), 3.49 (d, 1H, J= 16.5Hz, **H**HCS=O), 4.28 (m, 1H, HNC**H**CH_3), 4.86 (d, 1H, J= 3.3Hz, HOC**H**Ph), 6.73 (d, 1H, J= 4.2Hz, NH), 7.26-7.40 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 13.7, 14.0, 14.6 (O=S-C-**C**H_3, HNCH**C**H_3 and two overlapping **C**H_3CH_2-), 2x 22.5, 27.4, 28.0, 31.7, 31.8, 33.0 and 33.3 (two -(**C**H_2)$_4$-), 34.5 (H_2**C**-C(Me)-S=O), 48.9 (H_2**C**-S=O), 51.3 (HN**C**HCH$_3$), 58.7 (O=C-**C**-S=O), 75.4 (HO**C**HPh), 122.1 (**C**=C), 131.4 (C=**C**), 126.1, 127.4 and 128.2 (**C**-arom), 140.8 (**C**-ipso), 171.2 (**C**=O). Mass (diast. mixture) (EI): m/e 447 (M^+), 340 (M^+-PhCHO, 13.5%), 107 (PhCHO, 100%). Elemental analysis: calc. for $C_{26}H_{41}NO_3S$: C 69.76, H 9.23, N 3.13, S 7.16 %. Found: C 69.96, H 9.33, S 7.20, N 3.18 %.

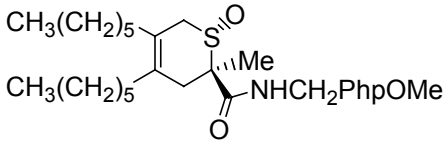
Non-crystalline diastereomer: ^{1}H-NMR (300MHz) d: 0.89 (m, 6H, 2 C**H$_3$**CH$_2$-), 1.07 (d, 3H, J=6.9Hz, C**H$_3$**CNH), 1.20-1.40 (m, 12H, 2 CH$_3$(C**H$_2$**)$_3$-CH$_2$-), 1.40 (s, 3H, **H$_3$**C-C-S=O), 1.97-2.05 (m, 4H, -**H$_2$**CC=CC**H$_2$**-), 2.56 (A$_2$-system s, 2H, **H$_2$**CCHS=O), 3.14 (d, 1H, J=16.5Hz, **H**HCS=O), 3.53 (d, 1H, J= 16.5Hz, **H**HCS=O), 4.28 (m, 1H, HNC**H**CH$_3$), 4.77 (d, 1H, J= 3.6Hz, HOC**H**Ph), 6.91 (d, 1H, J= 3.9Hz, NH), 7.22-7.36 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 13.5, 13.9, 14.7, 14.8 (O=S-C-**C**H$_3$, HNCH**C**H$_3$ and two **C**H$_3$CH$_2$-), 22.4, 27.7, 27.9, 32.8, 32.9 (two -(**C**H$_2$)$_4$-), 35.1(H_2**C**-C(Me)-S=O), 48.7 (H_2**C**-S=O), 51.2 (HN**C**HCH$_3$), 58.3 (O=C-**C**-S=O), 76.2 (HO**C**HPh), 122.0(**C**=C), 131.3 (C=**C**), 126.3, 127.3 and 128.1 (**C**-arom), 141.1(**C**-ipso), 170.9(**C**=O).

***N*-(4-Methoxybenzyl) 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6k)**



Obtained from 1.0 mmol of **5d** as a slightly yellow viscous oil after column chromatography (ethyl acetate/heptane=1:1) that solidified on standing, 298 mg (93%). Mp.168-169^{o}C. ^{1}H-NMR (300MHz) d:1.53 (s, 3H, CC**H$_3$**), 1.69 (s, 6H, **H$_3$**CC=CC**H$_3$**), 2.59 (br.s., 2H, **H$_2$**CCHS=O) 3.18 A of AB (d, 1H, J_{AB}= 17.1Hz, **H**HCS=O), 3.50 B of AB (d, 1H, J_{AB}= 17.1Hz, **H**HCS=O), 3.79 (s, 3H, **H$_3$**C-O), 4.29 A of AB (dd, 1H, ^{2}J= 14.7Hz, ^{3}J= 5.4Hz, HNC**H**HPh), 4.48 B of AB (dd, 1H, ^{2}J= 14.7Hz, ^{3}J= 6.0Hz, NC**H**H), 6.85 (m, 2H, **arom**), 6.97 (t, 1H, N**H**), 7.16 (m, 2H, **arom**). ^{13}C-NMR (75 MHz) d: 15.7 (**H$_3$**CC), 19.4 (**H$_3$**CC=C), 19.4 (**H$_3$**CC=C), 36.6 (H_2**C**-C(Me)-S=O), 43.0 (**H$_3$**C-O), 50.4 (H_2**C**-S=O), 55.2 (N-H_2**C**PhpOMe), 58.5 (O=C-**C**-S=O), 114.0 (Ph **C-3**), 117.1 (**C**=C), 126.8 (C=**C**), 128.7, 129.9, 158.9 (Ph **C**-4), 171.2 (**C**=O). Mass (EI): m/e 321 (M^+), 273 (M^+-SO, 16.3 %), 121 (corr.to pMeOBn-group, 100%), 109 ($C_8H_{13}^+$, 57.0 %). Elemental analysis: calcd for $C_{17}H_{23}NO_3S$: C 63.52, H 7.21, N 4.36 , S 9.98 %. Found: C 63.33, H 7.17, N 4.42, S 9.23 %.

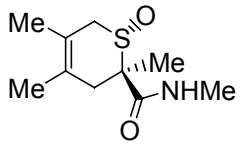
***N*-(4-Methoxybenzyl) 2-methyl-1-oxo-4,5-di-(n-hexyl)-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6n)**



Obtained from 1.0 mmol of **5e** after column chromatography (ethyl acetate/heptane = 1:1) as slightly yellow oil which turned pink, 420 mg (91%) ^{1}H-NMR (300MHz) d: 0.89 (m, 6H, 2CH$_2$C**H$_3$**), 1.26 (m, 16H, 2Me(C**H$_2$**)$_4$CH$_2$), 1.51 (s, 3H, CC**H$_3$**), 2.01 (m, 4H, -**H$_2$**CC=CC**H$_2$**-), 2.56 A of AB (d, 1H, J_{AB}= 18.9Hz, H**H**CCHS=O), 2.64 B of AB (d, 1H, J_{AB}= 18.9Hz, H**H**CCHS=O), 3.17 (d, 1H, J= 16.5Hz, **H**HCS=O), 3.56 (d, 1H, J= 16.5Hz, **H**HCS=O), 3.79 (s, 3H, **H$_3$**C-O), 4.31 A of AB (dd, 1H, ^{2}J= 14.6Hz, ^{3}J= 5.4Hz, NC**H**HPh), 4.46 B of AB (dd, 1H, ^{2}J= 14.6Hz, ^{3}J= 6.0Hz, NC**H**H), 6.84 (m, 2H, **arom**), 7.06 (t, 1H, N**H**), 7.19 (m, 2H, **arom**).^{13}C-NMR (75 MHz) d:14.0 (C**H$_3$**-C-S=O), 14.9 (two C**H$_3$**CH$_2$-), 22.5, 28.0, 28.2, 29.1, 29.3, 31.6, 31.6, 33.0 and 33.3 (two -(**C**H$_2$)$_5$-), 35.1(H_2**C**-C(Me)-S=O), 43.1(**H$_3$**C-O), 49.1(H_2**C**-S=O), 55.2 (N-H_2**C**PhpOMe), 58.2 (O=C-**C**-S=O), 114.0 (Ph **C-3**), 122.4 (**C**=C), 128.8, 129.9, 131.5, 158.9 (Ph **C-4**), 171.3 (**C**=O).Mass (EI): m/e 461 (M^+), 412 (M^+-SO, 10%), 249 ($C_{18}H_{33}^+$, 14.7 %), 121 (pMeObenzyl-group, 100%). HRMS: Calcd for $C_{27}H_{43}NO_3S$: 461.29637. Found: 461.29626.

***N*-Methyl-(2,4,5-trimethyl)-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (6j)**

To a solution of **5d** (2,0 mmol) in 10ml tetrahydrofuran was added a 40% aqueous solution of methylamine in 0.25 ml portions with 10 min intervals. The reaction was monitored by TLC (heptane: ethyl acetate = 1:1). Upon completion of the reaction the solvent was evaporated and the product was chromatographed over a short path of silica gel (heptane: ethyl acetate= 1:1) yielding 202 mg (94 %) **6j** as colorless oil that crystallised upon standing. Crystallization from diisopropylether gave small



transparant platelets. Mp. 87-88°C. ^{1}H-NMR (300MHz) d:1.46 (s, 3H, C**H$_3$**), 1.71 (s, 6H, **H$_3$**CC=CC**H$_3$**), 2.58 (AB nearly A_2, 2H, J_{AB}= 20.1Hz, **H$_2$**CCHS=O), 2.82 (m, 3H, **H$_3$**CNH), 3.20 (d, 1H, J= 16.5Hz, **H**HCS=O), 3.56 (d, 1H, J= 16.5Hz, H**H**CS=O), 6.87 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 15.4 (O=SC**C**H$_3$), 19.3 (H$_3$**C**C=CCH$_3$), 19.6 (H$_3$CC=C**C**H$_3$), 26.4 (HN**C**H$_3$), 36.6 (H$_2$**C**-C(Me)-S=O), 50.2 (H$_2$**C**-S=O), 58.4 (O=C-**C**-S=O), 116.8 (**C**=C), 126.7 (C=**C**), 171.8 (**C**=O). Mass (EI): m/e 215 (M^+), 167 (M^+-SO, 36,7 %), 109 ($C_8H_{13}^+$, 100%). HRMS: Calcd for $C_{10}H_{17}NO_2S$: 215.09780. Found 215.09764.

Crystal data and structure refinement for 6j.

Crystal color	colorless transparant
Crystal shape	regular platelet
Crystal size	0.37 x 0.37 x 0.09 mm
Empirical formula	C_{10} H_{17} N O_2 S
Formula weight	215.31
Temperature	293(2) K
Radiation / Wavelength	MoK_α (graphite mon.) / 0.71073 Å
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a, α = 5.7348(9) Å, 101.886(16)°
(23 reflections 10.315 < θ < 14.418)	b, β = 7.5724(8) Å, 99.871(12)°
	c, γ = 13.4096(19) Å, 93.456(9)°
Volume	558.64(13) Å^3
Z, calculated density	2, 1.280 Mg/m^3
Absorption coefficient	0.266 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / Ω
F(000)	232
θ range for data collection	5.32 to 27.47°
Index ranges	-7<=*h*<=0, -9<=*k*<=9, -17<=*l*<=17
Reflections collected / unique	2792 / 2544 [R_{int} = 0.0458]
Reflections observed	1434 ([I_o>2σ(I_o)])
Absorption correction	Semi-empirical from Ψ-scans
Range of relat. transm. factors	1.023 and 0.984
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	2544 / 0 / 195
Goodness-of-fit on F^2	1.041
SHELXL-97 weight parameters	0.046500 0.245100
Final R indices [I>2σ(I)]	R_1 = 0.0613, wR_2 = 0.1135
R indices (all data)	R_1 = 0.1322, wR_2 = 0.1374
Largest diff. peak and hole	0.273 and -0.213 e. Å^{-3}

Dithioesters and thioamides

Methyl propanedithioate and methyl pentanedithioate were prepared by Grignard reaction of ethylmagnesium bromide and 1-n-butylmagnesium bromide, respectively, with carbondisulfide followed by treatment with methyl iodide.[19a] Methyl phenylmethanedithioate was prepared in two steps from phenylacetyl chloride by successive reaction with methanethiol and Lawesson's reagent.[19b]

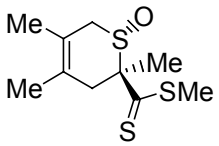
Trimethyl[(*E*)-1-(methylsulfanyl)-1-propenyl]sulfanylsilane [15c]
Prepared according to literature procedure.[13] Obtained in 64% yield as a yellow liquid after distillation *in vacuo*. Bp. 54-57°C, 0.1mmHg. *E/Z*-mixture (approximately 6:1) ^{1}H-NMR (300MHz) major isomer d: 0.27 (s, 9H, 3x C**H$_3$**), 1.82 (d, 3H, J=6.6Hz, C=CC**H$_3$**), 2.22 (s, 3H, SC**H$_3$**), 5.80 (q, 1H, J= 6.7Hz, **H**-C=C).

Trimethyl[(*E*)-1-(methylsulfanyl)-1-pentenyl]sulfanylsilane[15b]
Prepared according to literature procedure.[13] Obtained in 73% yield as a yellow liquid after distillation *in vacuo*. Bp. 83-87°C, 0.1 mmHg. *E/Z*-mixture (approximately 8:1). ^{1}H-NMR (300MHz) d:0.36 (s, 9H, 3x C**H$_3$**), 0.92 (t, 3H, J= 7.2 Hz, C**H$_3$**CH$_2$-) 1.41 (m, 2H, CH$_3$C**H$_2$**-), 2.26 (s, 3H, SC**H$_3$**) overlapping with (m, 2H, -C**H$_2$**C=C-), 5.77 (t, 1H, J= 7.0Hz, **H**-C=C).

Trimethyl[(*E*)-1-(methylsulfanyl)-2-phenyl-1-ethenyl]sulfanylsilane[15c]
Prepared according to literature procedure.[13] Obtained in 55% yield after distillation *in vacuo*. Bp. 125-128°C, 0.9 mmHg. *E/Z*-mixture (approximately 1:1). ^{1}H-NMR (300MHz) d: 0.28 and 0.40 (s, 9H, 3x C**H$_3$**), 2.39 and 2.40 (s, 3H, SC**H$_3$**), 6.64 and 7.00 (s, 1H, **H**-C=C), 7.15-7.70 (m, 5H, **arom**).

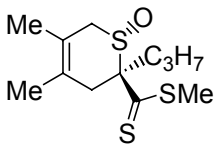
Cycloaddition reactions:

***S*-Methyl 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbodithioate (8a)**



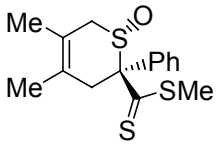
A solution of dithioketene acetal (20 mmol, 3.84 gr) and triethylamine (21 mmol, 2.90ml) in 20ml of diethyl ether was added dropwise over 20 min to a cooled (-78°C) solution of thionyl chloride (20 mmol, 1.45 ml) and 2,3-dimethyl-1,3-butadiene (10 equiv.) in 20 ml of diethyl ether. The reaction mixture was stirred at this temperature for 30 min and was then allowed to warm up to 0°C and was stirred for 3h followed by 14h at room temperature. The reaction mixture was then poured into 75ml of water. The layers were separated and the aqueous layer was extracted four times with 50 ml portions of diethyl ether. The combined ether fractions were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by column chromatography (heptane:ethyl acetate=2:1) gave the product as a dark yellow viscous oil, 1.63 g (33%). ^{1}H-NMR (300MHz) d: 1.57 (s, 3H, **H$_3$**CCS=O), 1.67 (s, 3H, **H$_3$**CC=C),1.69 (s, 3H, **H$_3$**CC=C), 2.54 (s, 3H, **H$_3$**C-S), 2.70 B of AB (d, 1H, J_{AB}= 18.3Hz, **H**HC-C-S=O), 2.78 (d, A of AB, 1H, J_{AB}= 18.3Hz, **H**HC-C-S=O), 2.97 (d, 1H, J=17.7Hz, **H**HC-S=O), 3.31 (d, 1H, J=17.7Hz, H**H**CS=O). ^{13}C-NMR (75 MHz) d: 19.4 (H$_3$**C**), 19.5 (H$_3$**C**), 19.9 (H$_3$**C**), 26.0 (S-**C**H$_3$), 35.8 (H$_2$**C**-C-S=O), 48.6 (H$_2$**C**-S=O), 72.4 (H$_3$C-**C**-S=O), 115.7 (**C**=C), 126.2 (C=**C**), 237.0 (**C**=S). Mass (EI): m/e 248 (M^+), 200 (M^+-SO, 71%), 109 (M^+-SO-Me-CS_2, 100%).

***S*-Methyl 4,5-dimethyl-1-oxo-2-(n-propyl)-3,6-dihydro-2*H*-thiopyran-2-carbodithioate (8b)**



Following the procedure of **8a**, 2.21g (40%) of **8b** was obtained as a dark yellow viscous oil after column chromatography (heptane: ethyl acetate = 2:1). ^{1}H-NMR (300MHz) d: 0.90 (m, 3H, H$_3$C(CH$_2$)$_2$-), 1.20-1.35 (m, 2H, H$_3$CC**H$_2$**CH$_2$-), 1.65 (s, 3H, **H$_3$**CC=C), 1.80 (s, 3H, **H$_3$**CC=C), 2.08 (m, 1H, H$_3$CCH$_2$CH**H**-), 2.28 (m, 1H, H$_3$CCH$_2$CH**H**-), 2.63 (br.s., 3H, **H$_3$**CS-), 2.76 (d, B of AB, 1H, J_{AB}= 18.9 Hz), 2.91 (d, A of AB, 1H, J_{AB}= 18.9 Hz), 3.03 (d, B of AB, 1H, J_{AB}= 18.3Hz), 2.34 (d, A of AB, 1H, J_{AB}= 18.3 Hz). ^{13}C-NMR (75 MHz) d: 14.0 (H$_3$**C**CH$_2$-), 16.3 (H$_3$C**C**H$_2$CH$_2$-), 19.4 (C=C**C**H$_3$), 20.0 (C=C**C**H$_3$), 22.4 (SCH$_3$), 32.8, 42.2, 47.9, 75.6 (S=C-**C**-S=O), 115.3 (**C**=C), 125.7 (C=**C**), 235.1 (C=S). Mass (EI): m/e 276 (M^+), 228 (M^+-SO). HRMS: calcd for $C_{12}H_{20}OS_3$: 276.06763. Found: 276.06725.

***S*-Methyl 4,5-dimethyl-1-oxo-2-phenyl-3,6-dihydro-2*H*-thiopyran-2-carbodithioate (8c)**



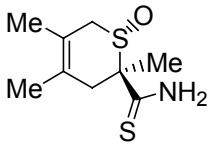
Following the procedure of **8a**, 744 mg (12%) of **8c** was obtained as a dark yellow sticky oil after column chromatography (heptane:ethyl acetate =2:1). ^{1}H-NMR (300MHz) d: 1.65 (s, 3H, C**H$_3$**C=C), 1,82 (s, 3H, C**H$_3$**C=C), 2.57 (s, 3H, SC**H$_3$**), 2.75 (d, 1H, J= 16.8Hz, **H**HC-C-S=O), 3.13 B of AB (d, 1H, J_{AB}= 18.2Hz, **H**HC-S=O), 3.27 A of AB (d, 1H, J_{AB}=18.2Hz, **H**HC-S=O), 3.41 (d, 1H, J= 16.8Hz, **H**HC-C-S=O), 7.36-7.56 (m, 5H, **arom**). ^{13}C-NMR (75 MHz) d:19.6, 19.8 and 19.9 (C**H$_3$**C=CC**H$_3$** and SC**H$_3$**), 38.9 (H$_2$**C**-C-S=O), 50.5 (H$_2$**C**-S=O), 79.6 (Ph-**C**-S=O), 118.4 (**C**=C), 126.4, 128.3 ,128.8 and 135.3 (2nd vinyl-C and C-arom), 237.1 (**C**=S).Mass (EI): m/e 310 (M^+), 262 (M^+-SO, 51%), 247 (M^+-SO-Me, 28%), 171 (M^+-SO-Me-CS_2, 100%). HRMS: calcd for $C_{15}H_{18}OS_3$: 310.05198. Found: 310.05139.

Thioamides

***N*-methyl thioamides**: To a solution of the dithioester (1.0 mmol) in 10 ml of tetrahydrofuran at room temperature was gradually added 40% aqueous solution of methylamine in 0.1ml portions with 10 min intervals. During the reaction a slow stream of nitrogen was passed over the reaction mixture to remove the formed methanethiol more efficiently, leading to shorter reaction times. After every addition the reaction was monitored by TLC (ethyl acetate or ethylacetate/heptane = 1:1). After completion of the reaction the solvent was evaporated *in vacuo* and the residue was purified by column chromatography over a short path of silica gel.

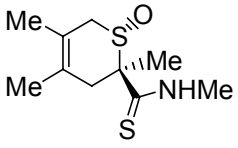
Other thioamides: To a solution of the dithioester (1.0 mmol) in 5 ml of dichloromethane was gradually added a solution of the amine (1.0 mmol) in 5 ml of dichloromethane at room temperature. During the reaction a slow stream of nitrogen was passed over the reaction mixture to remove the formed methanethiol more efficiently. The reaction was monitored by TLC ethyl acetate or ethylacetate/heptane = 1:1 or 2:1). After completion of the reaction the solvent was evaporated *in vacuo* and the residue was purified by column chromatography over silica gel. Analytical samples were obtained by crystallization from the appropriate solvent(s).

2,4,5-Trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9a)



200 mg (92%) off a light yellow crystalline solid after column chromatography (ethyl acetate: heptane = 1:1). Small light yellow needles from diisopropyl ether/ ethyl acetate. Mp. 150-160°C (dec). ^{1}H-NMR (300MHz) d: 1.65 (s, 3H, CC**H$_3$**), 1.73 (br. s, 6H, **H$_3$**CC=CC**H$_3$**), 2.78 A_2-system (br.s, 2H, **H$_2$**CC(Me)-S=O), 3.24 (d,1H, J=16.6Hz, **H**HC-S=O), 3.63 (d, 1H, J= 16.6Hz, **H**HC-S=O), 7.74 (s, 1H, **H**HN-C=S). ^{13}C-NMR (75 MHz) d: 17.9 (**C**H$_3$C-S=O), 19.4 (**C**H$_3$C=C), 19.9 (**C**H$_3$C=C), 40.1 (H$_2$**C**-C-S=O), 51.1 (H$_2$**C**-S=O), 62.6 (S=C-**C**-S=O),117.2 (**C**=C),127.1 (**C**=C), 208.0 (**C**=S). Mass (EI): m/e 217 (M^+), 169 (M^+-SO). HRMS: calcd for $C_9H_{15}NOS_2$: 217.05951. Found: 217.0602.

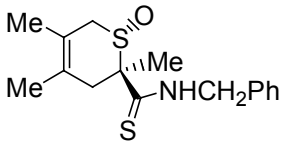
***N*-Methyl 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9b)**



Obtained as a white microcrystalline solid, 210 mg (91%) after column chromatography (heptane: ethyl acetate = 1:1). Small colorless crystals from diisopropyl ether. Mp. 130-135°C (dec). ^{1}H-NMR (300MHz) d: 1.61 (s, 3H, **H$_3$**CC), 1.73 (br, 6H, **H$_3$**CC=CC**H$_3$**), 2.83 (br s, 2H, **H$_2$**CC(Me)-S=O), 3.18 (d, 3H, J= 4.8Hz, **H$_3$**CNH-), 3.24 (d, B of AB, 1H, J_{AB}= 16.5Hz, **H**HC-S=O), 3.60 (d, B of AB, 1H, J_{AB}= 16.5Hz, **H**HC-S=O), 8.90 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 17.4 (**C**H$_3$C-S=O), 19.3 (C=C**C**H$_3$), 19.9 (C=C**C**H$_3$), 33.6 (N**C**H$_3$), 40.7 (H$_2$**C**-C-S=O), 51.4 (H$_2$**C**-S=O), 62.1 (H$_2$C-**C**-S=O), 117.1 (**C**=C), 127.4(**C**=C), 204.2 (**C**=S). Mass (EI): m/e 231 (M^+), 183 (M^+-SO). HRMS: calcd for $C_{10}H_{17}NOS_2$: 231.07516. Found: 231.07481.

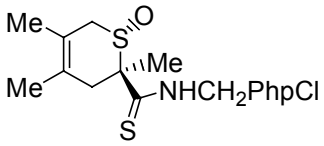
***N*-Benzyl-2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9c)**

Obtained as a yellow solid after column chromatography (heptane: ethyl acetate = 2:1 to 1:1), 273 mg (89%). Yellow crystals from diisopropyl ether. Mp. >140°C (dec). ^{1}H-NMR (300MHz) d: 1.65 (s,3H, CC**H$_3$**); 1.68 (s,3H, C=CC**H$_3$**); 1.71 (s,3H, C=CC**H$_3$**); 2.73 B of AB (d, 1H, J_{AB}= 18.9Hz, H**H**C-C(Me)-S=O), 2.85 A of AB (d, 1H, J_{AB}= 18.9Hz, **H**HC-C(Me)-S=O), 3.17 (d, B of AB, 1H, J_{AB}= 16.8Hz, **H**C-C-C=S); 3.55 (d, A of AB, 1H, J_{AB}=16.8Hz, **H**C-C-C=S); 4.71



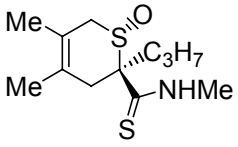
(dd, 1H, ^{2}J= 15.0Hz, ^{3}J= 4.5Hz, **H**C-Ph), 4.97 (dd, 1H, ^{2}J= 15.0Hz, ^{3}J= 5.7Hz, **H**C-Ph), 7.2-7.4 (m, 5H, arom), 8.81 (br. s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 18.8 (H_3**C**-C-S=O), 19.3 (H_3**C**C=C), 19.9 (H_3**C**C=C), 39.3 (H_2**C**-C-S=O), 50.3 (H_2**C**-Ph), 50.9 (H_2**C**-S=O), 63.0(S=C-**C**-S=O), 117.4 (**C**=C), 126.8, 127.8, 128.0, 128.9,135.8 (C-ipso), 202.6 (**C**=S). Mass (EI): m/e 307 (M^+), 259 (M^+-SO). HRMS: calcd for $C_{16}H_{21}NOS_2$: 307.10646. Found: 307.10639

***N*-4-Chlorobenzyl 2,4,5-trimethyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9d)**



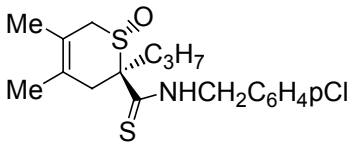
Obtained as yellow solid after columnchromatography (heptane: ethyl acetate = 1:1), 290 mg (85%).Yellow crystals from diisopropyl ether/ ethyl acetate. Mp. 142-143°C (dec). ^{1}H-NMR (300MHz) d: 1.63 (s, 3H, CC**H$_3$**), 1.70 (s, 6H, C**H$_3$**C=CC**H$_3$**), 2.77 B of AB (d, 1H, J_{AB}≈19.5Hz, **H**HC-C(Me)-S=O), 2.85 A of AB (d, 1H, J≈ 19.5Hz, **H**HC-C(Me)-S=O), 3.21 (d, B of AB, 1H, J_{AB}= 16.5 Hz, **H**HC-S=O), 3.57 (d, A of AB, 1H, J_{AB}= 16.5Hz, **H**HC-C-S=O), 4.74 (dd, 1H, ^{2}J≈15.6 Hz, ^{3}J= 4.8Hz, **H**HC-Ph), 4.91 (dd, 1H, ^{2}J≈15.6 Hz, ^{3}J= 5.4Hz, **H**HC-Ph), 7.28 (m, 4H, **arom**), 9.01 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 17.9 (O=S-C**C**H$_3$), 19.3 (H_3**C**C=C) 19.9 (H_3**C**C=C), 40.2 (H_2**C**-C-S=O), 49.4 (H_2**C**-Ph**),** 51.2 (H_2**C**-S=O**),** 62.3 (S=C-**C**-S=O), 117.2 (**C**=C),127 (C=**C**), 129.0 , 129.2, 134 .4 (**C**-ipso), 203.2 (**C**=S). Mass (EI): m/e 341 (M^+), 293 (M^+-SO). HRMS: calcd for $C_{16}H_{20}NOS_2Cl$: 341.06748. Found: 341.06731.

***N*-Methyl 2,4,5-trimethyl-1-oxo-2-(n-propyl)-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9e)**



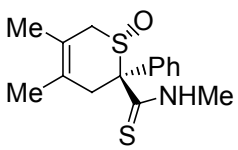
Obtained after column chromatography (heptane:ethyl acetate=1:1) as a white solid, 220 mg (85%). Small colorless crystals from diisopropyl ether/ethyl acetate. Mp.>150°C (dec). ^{1}H-NMR (300MHz) d: 0.94 (t, 3H, J= 7.2Hz, **H$_3$**CCH$_2$-), 1.15-1.40 (m, 2H, H$_3$CC**H$_2$**CH$_2$-), 1.72 (s,3H, C=CC**H$_3$**), 1.76 (s,3H, C=CC**H$_3$**), 1.79 (m, 1H, H$_3$CCH$_2$C**H**H-), 2.23 (m, 1H, H$_3$CCH$_2$C**H**H-), 2.68 (d, B of AB, 1H, J_{AB}= 18.9Hz,), 2.80 (d, A of AB, 1H, J_{AB}= 18.9Hz), 3.18 (d, 3H, J= 4.8Hz, **H$_3$**CNH-) partly overlapping with 3.21(d, B of AB, 1H, J_{AB}= 17.0Hz), 3.55 (d, A of AB, 1H, J_{AB}= 17.0Hz), 8.40 (br.s., 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.3 (H_3**C**CH$_2$-), 16.8 (H_3C**C**H$_2$CH$_2$-), 19.5 (C=C**C**H$_3$), 20.1 (C=C**C**H$_3$), 33.4, 34.2, 35.6, 50.2 (H_2**C**-S=O), 66.3 (S=C-**C**-S=O), 117.4 (**C**=C), 126.3 (C=**C**), 201.4 (C=S). Mass (EI): m/e 259 (M^+), 211 (M^+-SO). Elemental analysis: calcd for $C_{12}H_{21}NOS_2$: C 55.56, H 8.16, N 5.40%. Found: C 55.76, H 8.21, N 5.24%.

***N*-(4-Chlorobenzyl) 4,5-dimethyl-1-oxo-2-(n-propyl)-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9f)**



Obtained as a white solid, 332 mg (90%) after washing the crude product with several small portions of diisopropyl ether. Small colorless crystals from diisopropyl ether/ethyl acetate. Mp. 170-171°C. ^{1}H-NMR (300MHz) d: 0.93 (t, 3H, J= 7.2Hz, **H$_3$**CCH$_2$-), 1.20-1.40 (m, 2H, H$_3$CC**H$_2$**CH$_2$-), 1.67 (s,3H, C=CC**H$_3$**), 1.72 (s,3H, C=CC**H$_3$**), 1.82 (m, 1H, H$_3$CCH$_2$C**H**H-), 2.25 (m, 1H, H$_3$CCH$_2$C**H**H-), 2.61 (d, B of AB, 1H, J_{AB}= 18.9Hz,), 2.82 (d, A of AB, 1H, J_{AB}= 18.9Hz), 3.15 (d, B of AB, 1H, J_{AB}= 17.1Hz), 3.49 (d, A of AB, 1H, J_{AB}= 17.1Hz), 4.67 (dd, B of AB, 1H, J_{AB}≈ 15.3Hz, HNC**H**HPhpCl), 4.97 (dd, A of AB, 1H, J_{AB}≈ 15.3Hz, HNC**H**HPhpCl), 7.21 (d, 2H, **H**$_{arom}$), 7.32 (d, 2H, **H**$_{arom}$), 8.43 (br.s., 1H, N**H**). ^{13}C-NMR (75 MHz) d: 14.3 (H_3**C**CH$_2$-), 16.8 (H_3C**C**H$_2$CH$_2$-), 19.4 (C=C**C**H$_3$), 20.1 (C=C**C**H$_3$), 34.5 (C=C-**C**H$_2$-C-C=S), 35.1 (CH$_2$-**C**H$_2$-C-C=S), 49.2 (H_2C-Ph), 50.1 (**C**H$_2$-S=O), 66.8 (S=C-**C**-S=O), 117.8 (**C**=C), 126.1 (C=**C**), 129.0, 129.3 and 134.4 (C$_{arom}$), 200.7 (C=S). Peaks at resp. 34.5, 35.1, 49.2 and 50.1 ppm were assigned by a H,C-correlation experiment. Mass (EI): m/e 369 (M^+), 321 (M^+-SO). Elemental analysis: calcd for $C_{18}H_{24}NOS_2Cl$: C 58.44, H 6.54, N 3.79 %. Found: C 58.74, H 6.50, N 3.55 %.

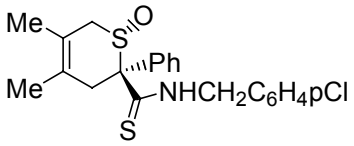
***N*-Methyl 4,5-dimethyl-1-oxo-2-phenyl-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9g)**



Obtained as a white microcrystalline solid after column chromatography (ethyl acetate: heptane = 3:1 to 2:1) 246 mg (84%). Mp. 181-183°C (dec). ^{1}H-NMR (300MHz) d: 1.61 (s, 3H, **H$_3$**CC=C), 1.78 (s, 3H, **H$_3$**CC=C), 2.48 (d, 1H, J= 15.9Hz, **H**HC-C(Ph)-S=O), 3.14 (d, 3H, J= 4.5Hz, **H$_3$**CNH-) overlapping with 3.02-3.28 (m, 3H, (d and AB-system overlapping), 7.39-7.45 (m, 5H, **arom**), 8.05 (br.s, 1H, N**H**). ^{13}C-NMR (75 MHz) d: 19.2 (H_3**C**C=C), 19.7 (H_3**C**C=C), 33.4 (N**C**H$_3$), 41.3

(H_2**C**-C-S=O), 51.2 (H_2**C**-S=O), 74.0 (S=C-**C**-S=O), 119.0 (**C**=C), 127.0, 128.5, 128.6, 132.7, 203.1 (**C**=S). Mass (EI): m/e 293 (M^+), 245 (M^+-SO). HRMS: calcd for $C_{15}H_{19}NOS_2$: 293.09081. Found: 293.09131.

***N*-(4-Chlorobenzyl)-4,5-dimethyl-1-oxo-2-phenyl-3,6-dihydro-2*H*-thiopyran-2-carbothioamide (9h)**



Obtained as a yellow crystalline solid after column chromatography (heptane: ethyl acetate = 2:1), 326 mg (81%). Mp.180-181°C. ^{1}H-NMR (300MHz) d: 1.61 (s, 3H, **H**$_3$CC=C), 1.78 (s, 3H, **H**$_3$CC=C), 2.55 (d, 1H, J= 15.9 Hz), 3.04 (d, J= 15.9Hz), 3.26 (dd appearing as triplet, 1H, J= 18.6Hz), 4.82 (d from two double doublets AB to nearly A_2 , 2H, HNC**H**$_2$Ph), 7.10-7.14, 7.25-7.29, 7.37-7.47 (m, 4H, arom), 8.21 (br.t., 1H, N**H**). ^{13}C-NMR (75 MHz) d: 19.4 (H_3**C**CC=C), 19.7 (H_3**C**CC=C), 40.8 (H_2**C**-C-S=O), 49.3(**C**H_2NH), 51.3 (H_2**C**-S=O), 73.7 (S=C-**C**-S=O), 119.2 (**C**=C), 126.9, 128.4, 128.7, 129.0, 129.2, 129.3, 132.8, 133.8, 134.2, 202.6 (**C**=S). Mass (EI): m/e 403 (M^+), 355 (M^+-SO). HRMS: calcd for $C_{21}H_{22}NOS_2Cl$: 403.08314. Found: 403.08310.

3.4 References

1] **a**] I.L. Pinto, D.R.Buckle, H.K. Rami and D.G.Smith, *Tetrahedron Lett.* **33**, 7597 (1992).

b] B. Heuzé, R. Gasparova, M.Heras and S. Masson, *Tetrahedron Lett.* **41**, 7327 (2000).

c] J. Prabhakaran, H.Lhermitte, J.Das, T.K. Sasi-Kumar and D.S. Grierson, *Synlett.* **5**, 658 (2000).

d] E. Fritz-Langhals, *Angew. Chem.* **105**, 785 (1993).

e] B. Unterhalt, B. Krebs, M. Laege and B. Nocon, *Arch. Pharm.* **327**, 799 (1994).

f] X-F.Yang and C-J. Li, *Tetrahedron Lett.* **41**, 1321 (2000).

2] **a**] R.G.Wilde, J.T. Billheimer, S.J.Germain, E.A. Hausner, P.C. Meunier, D.A. Munzer, J.K. Stoltenborg, P.J. Gillies, D.L. Burcham, S-M. Huang, J.D. Klaczkiewicz, S.S. Ko and R.R. Wexler, *Bioorg. & Med. Chem*. **4**, 1493 (1996).

b] T.J. Brown, R.F. Chapman, D.C. Cook, T.W. Hart, I.M. McLay, R. Jordan, J.S. Mason, M.N. Palfreyman, R.G.A. Walsh, M.T. Withnall, J-C. Aloup, I. Cavero, D. Farge, C. James and S.Mondot, *J.Med. Chem.* **35**, 3613 (1992) and references therein.

c] J-C. Aloup, D. Farge, C. James, S. Mondot and I. Cavero *Drugs of the Future* **15**, 1097, (1990).

d] J-C. Aloup, J. Bouchaudon, D. Farge, C. James, J. Deregnaucourt and M. Hardy-Houis, *J.Med. Chem.* **30**, 24 (1987).

3] **a**] G.Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron* **52**, 12233 (1996).

b] G.Capozzi, S. Menichetti, C. Nativi and A. Rossi, *Tetrahedron Lett.* **34**, 4253 (1993).

4] **a**] A.R. Maguire, P.G. Kelleher, G.Fergueson and J.F. Gallagher, *Tetrahedron Lett.* **39**, 3849 (1998).

b] H.Morita, M.Takeda, T.Yoshimura, T. Fjii, S.Ono and C.Shimazaki, *J.Org.Chem.* **64**, 6730 (1999).

5] J. Drabowicz and S. Oae, *Synthesis* 404 (1977).

6] **a**] B.G.Lenz, H. Regeling, H.L.M. van Rozendaal and B. Zwanenburg, *J. Org. Chem*. **50**, 2930 (1985).

b] J.B.M. Rewinkel and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **109**, 190 (1990).

c] R.C. de Laet, A.J.J.M. van Breemen, A.J. Derksen, M. van Klaveren and B.Zwanenburg, *Phosphorous, Sulfur and Silicon* **74**, 371 (1993).

d] I.J.W. Still and D.K.T. Wilson, *Can. J. Chem.* **70**, 964 (1992).

e] J.B.M. Rewinkel, *Ph.D. Thesis*, University of Nijmegen (1989).

7] **a**] B. Zwanenburg, T.J.G. Damen, H.J.F. Philipse, R.C. deLaet and A.C.B. Lucassen *Phosphorous, Sulfur and Silicon* **153-154**, 119 (1999).

b] T.J.G. Damen and B. Zwanenburg *Phosphorous, Sulfur and Silicon* **120/121**, 319 (1997).

c] T.J.G. Damen, *Ph.D. Thesis*, University of Nijmegen, (2002).

8] B. Zwanenburg, L.Thijs, J.B. Broens and J. Strating *Recl.Trav. Chim. Pays-Bas* **91**, 443 (1972).

9] B.F. Bonini, G. Maccagnani, P. Zani, G. Barbaro, A. Battaglia and P. Georgianni *J. Org. Chem.* **56**, 2512 (1991).

10] A previous attempt to prepare Aprikalim® was not completed; R.C. de Laet, *Ph.D. Thesis*, University of Nijmegen (1995).

11] **a**] S. Kosack and G. Himbert *Chem. Ber.* **121**, 833 (1988).

b] K-P. Pfeifer and G. Himbert *Tetrahedron Lett.* **31**, 5725 (1990).

12] **a**] I.Lee, C.S. Shim and H.W. Lee *J.Chem. Res. Miniprint* **3**, 769 (1992).

b] F.Weygand and W. Steglich *Chem. Ber.* **93**, 2983 (1960).

c] T.Wieland and G.Hörlein *Justus Liebigs Ann. Chem.* **591**, 192 (1955).

13] G.Simchen and W. West, *Synthesis* 247 (1977).

14] It should be mentioned that the slow diastereomers of both **4g** and **4i** showed gelating properties. When hexane/ethyl acetate solutions of these compounds were evaporated or cooled to room temperature for crystallisation, stable gels were formed indicating aggregational properties for these compounds.

15] **a**] K. Hartke and O. Kunze, *Liebigs Ann. Chem.* 321 (1989).

b] R.S. Sukhai and L. Brandsma, *Synthesis* 455, (1979).

c] P. Beslin and P. Marion, *Tetrahedron Lett.* **33**, 935 (1992).

16] H.J. Schostarez and T.M. Schwartz, *J. Org. Chem.* **61**, 8701 (1996).

17] A.C.B. Lucassen and B. Zwanenburg, unpublished results.

18] S. Araki, M. Ohmura and Y.Butsugan, *Synthesis* 963 (1985**)**.

15] **a**] J.Meyer, P. Vermeer and L.Brandsma, *Recl.Trav.Chim Pays-Bas* **92**, 601 (1973).

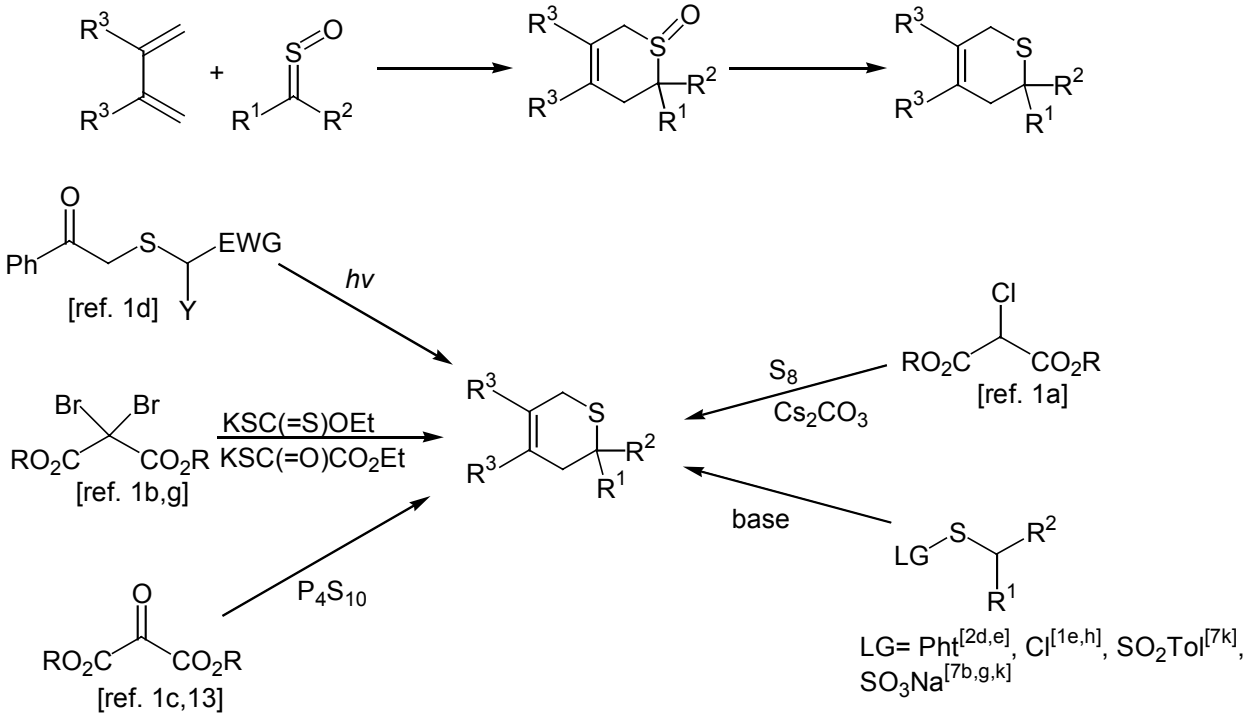
b] J.B. van der Linden, *Ph.D. Thesis*, University of Nijmegen, (1994).

CHAPTER 4

Ring contraction of 3,6-dihydro-2*H*-thiopyrans to thiolanes by an iodo oxyacylation reaction

4.1 Introduction

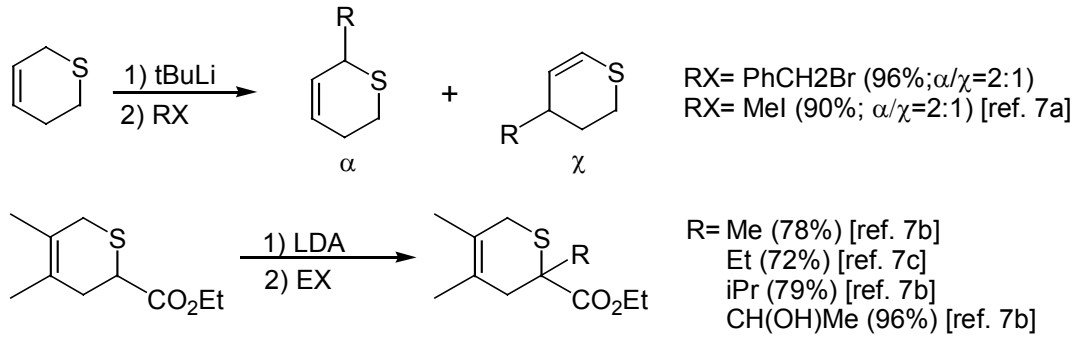
A commonly used synthesis of 3,6-dihydro-2*H*-thiopyrans is the [4+2]-cycloaddition reaction of thiocarbonyl compounds with 1,3-dienes.[1] The required thiones are stable in a limited number of cases, mostly they are prepared *in situ* in the presence of the trapping 1,3-dienes (Scheme 1). In the past two decades the scope for these syntheses of 3,6-dihydrothiopyrans has been substantially extended [2]. An attractive alternative for the synthesis of these sulfur heterocycles involves the [4+2]-cycloaddition reaction of sulfines (thione *S*-oxides) with 1,3-dienes.[3] The thus formed dihydrothiopyran *S*-oxides can readily be deoxygenated to give dihydrothiopyrans.[4] In fact, sulfines serve as synthetic equivalents of thiocarbonyl compounds.[3a] Various methods are available for the preparation of a large variety of substituted sulfines, such as oxidation of thiocarbonyl compounds with percarboxylic acids, alkylidenation of sulfur dioxide with α-silyl carbanions and dehydrohalogenation of suitably substituted sulfinyl chlorides.[3a,c,h ,5]



Scheme 1

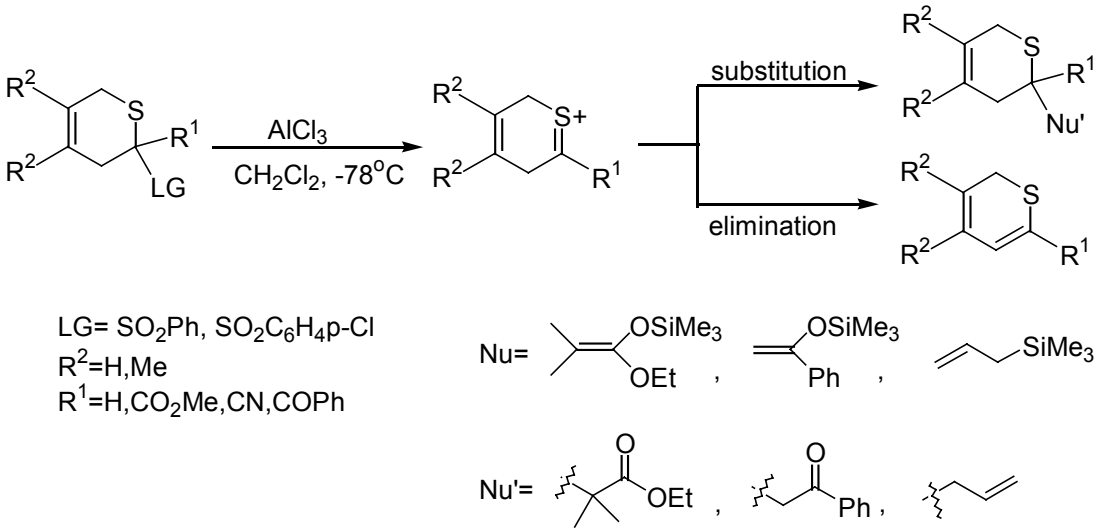
The reaction of silyl enol ethers [3a, c, 5] or doubly-activated methylene compounds [3a,h, 6] with thionyl chloride in the presence of a tertiary amine base is particularly attractive for the preparation of α-oxo sulfines, because of its simplicity and its versatility.[3a]

The chemical behaviour of 3,6-dihydrothiopyrans received only little attention in the literature. Base induced ring contractions of 2,2-disubstituted dihydrothiopyrans were observed and explained by a ring opening ring closure mechanism.[7] Electrophilic alkylation at the 2-position was achieved for 2-carboethoxy-4,5-dimethyl-3,6-dihydro-2*H*-thiopyrans by treatment with LDA followed by an alkylating agent.[7a-c]



Scheme 2

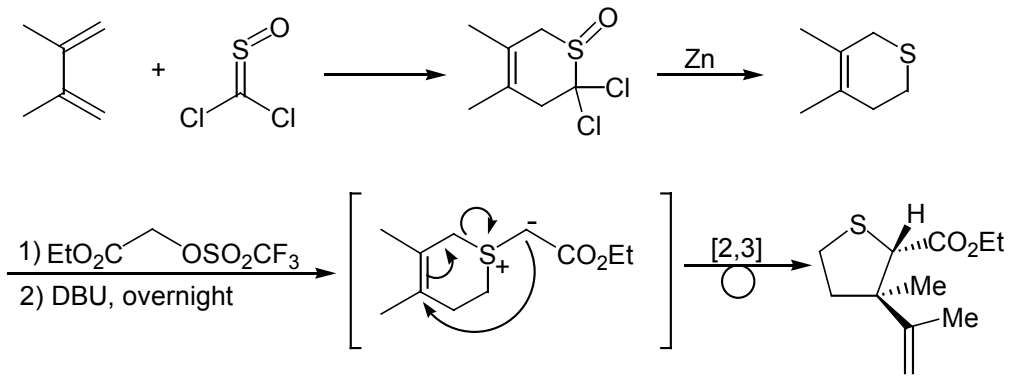
A remarkable Lewis acid mediated nucleophilic substitution involving the intermediacy of a thioxonium ion was observed by De Laet and Derksen.[5]



Scheme 3

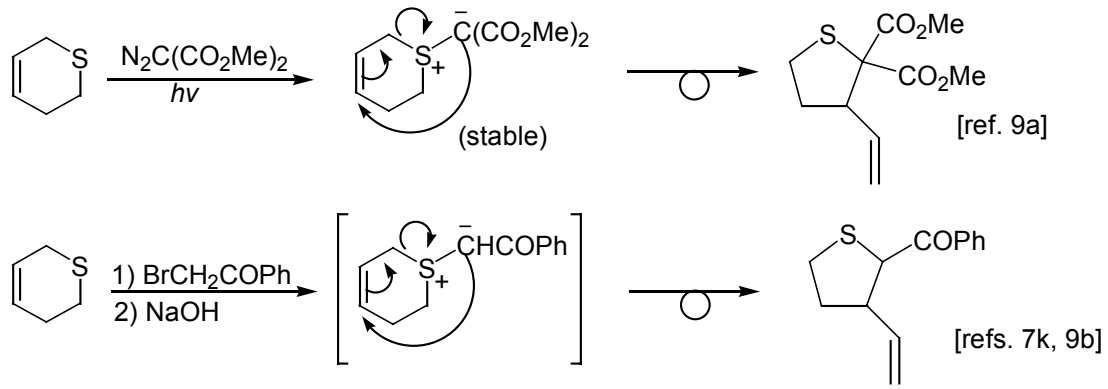
In these reactions the presence of an arylsulfonyl group to serve as a leaving group is necessary.

Conversion into a sulfur ylide by treatment with carbethoxymethyl trifluoromethanesulfonate and subsequent reaction with DBU gave thiolane derivatives (Scheme 4).[6]



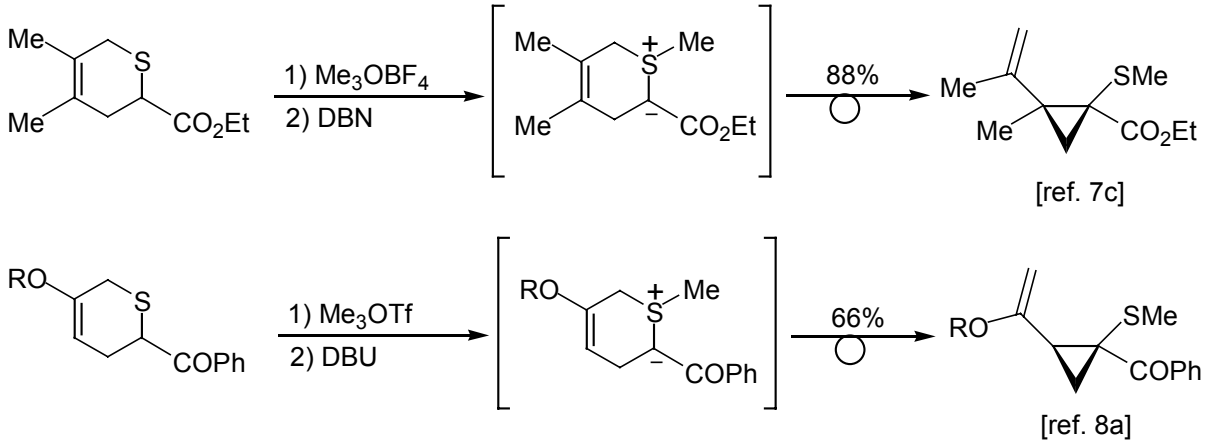
Scheme 4

Some related ring contractions are shown in schemes 5 and 6.[7j, 9]



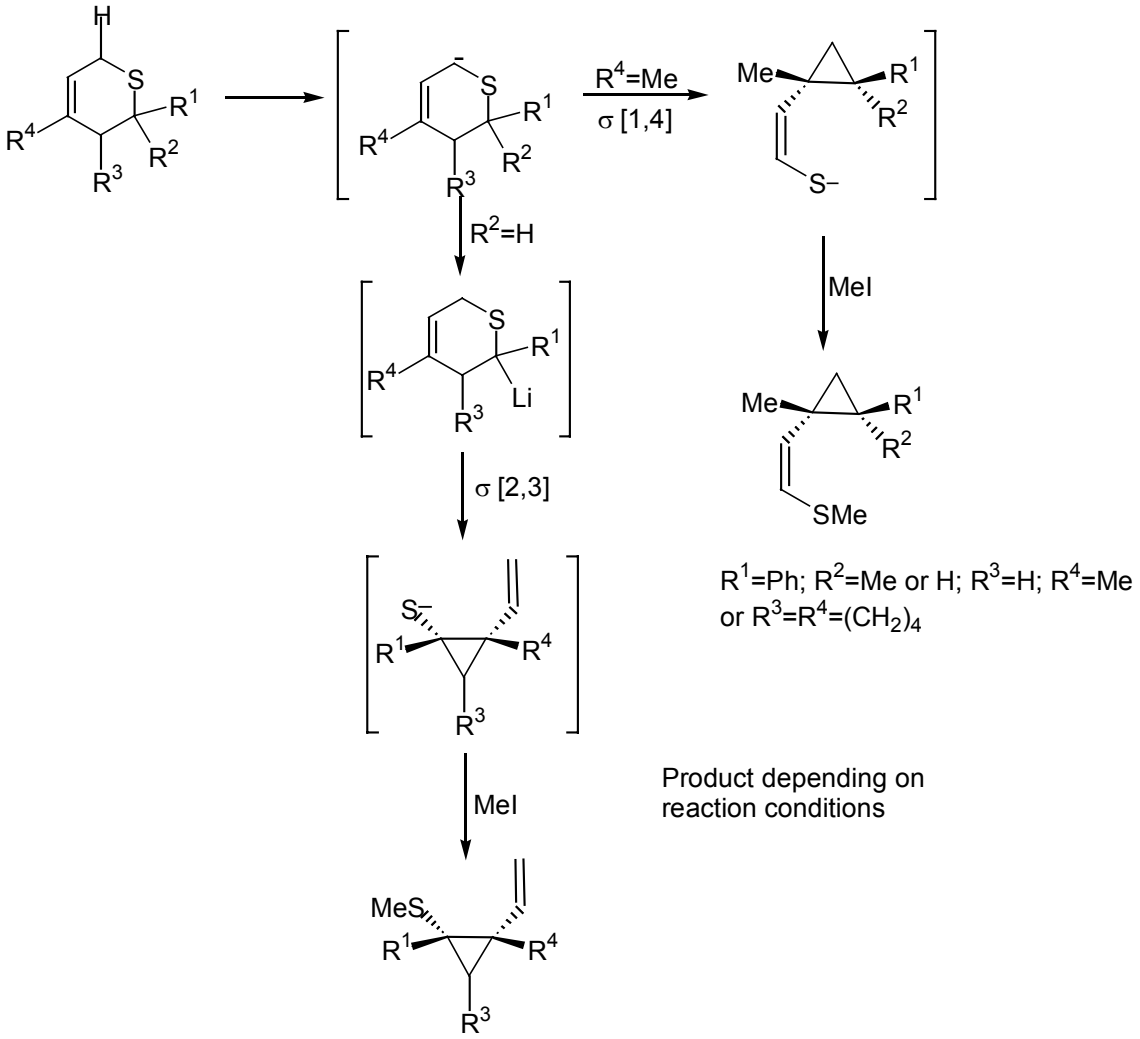
Scheme 5

Endocyclic sulfonium ylides with the ylid as part of the ring undergo a [2,3]-sigmatropic rearrangement yielding cyclopropane derivatives when six-membered rings are used (Scheme 6).[7c, 8a]



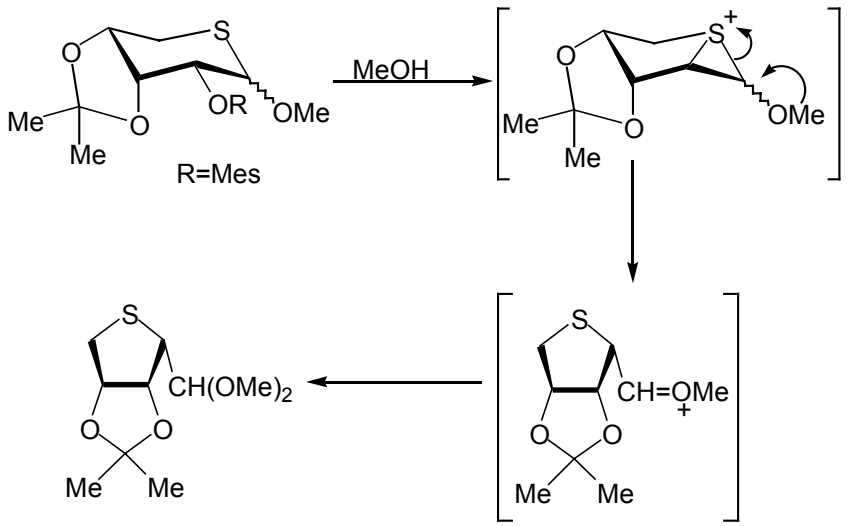
Scheme 6

Sigmatropic rearrangements of sulfonium ylides derived from 3,6-dihydro-2*H*-thiopyrans give rise to ring contraction reactions yielding vinylcyclopropanes (Scheme 7).[7a-c,g-i, 8, 9]



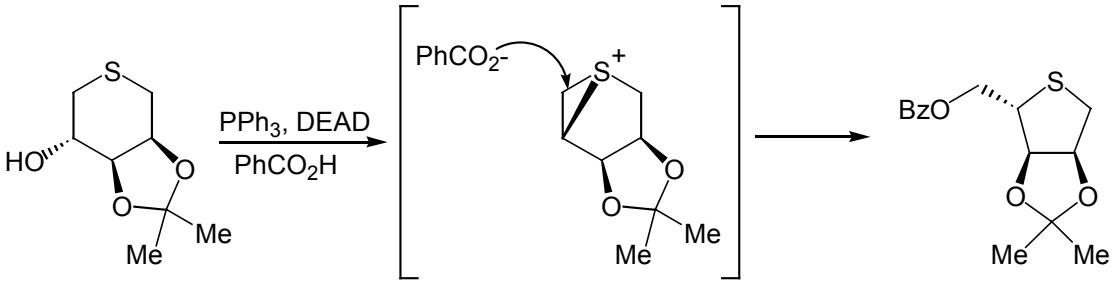
Scheme 7

Hughes[10] reported ring contractions of thiopyranosides (5-thio-D-ribose and 5-thio-D-xylose) where the 4-hydroxyl groups were converted into the corresponding methanesulfonates that serve as leaving group upon attack of sulfur (Scheme 8).



Scheme 8

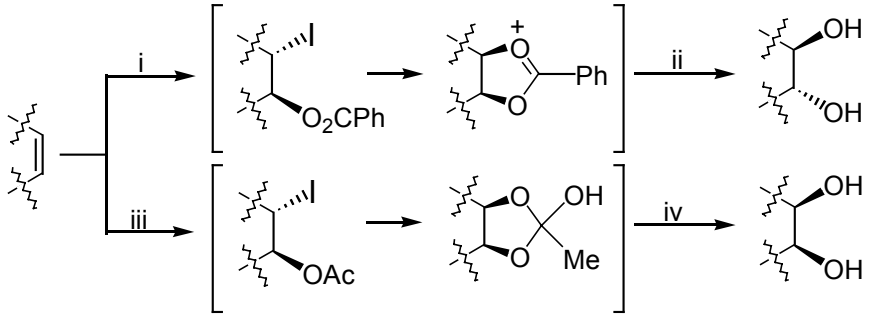
Altenbach[11] reported a ring contraction of a 3,4,5-trihydroxy-tetrahydrothiopyran derivative (prepared from D-arabitol) by activation of the hydroxyl group using Mitsunobu conditions (Scheme 9). The intermediate episulfonium-ion reacts with benzoate to give the thiolane.



Scheme 9

Selective hydrogenation of the olefinic bond has also been accomplished.[5a] The selective *cis*-dihydroxylation of the olefinic bond has been accomplished using osmium tetroxide and an osmium trichloride system[2, 12], although the success is highly dependent on the substitution pattern of the sulfur heterocycle.[13] It is relevant to mention that selective epoxidation of this bond failed due to concurrent oxidation of sulfur.[14]

In this chapter an alternative method of dihydroxylation is considered, viz. the so-caled cohalogenation involving the initial halogenation of the olefinic bond to a halonium ion (or π-complex) followed by a reaction with a carboxylate anion as a nucleophile and finally base mediated hydrolysis to give 1,2-diols (Scheme 10).[15]

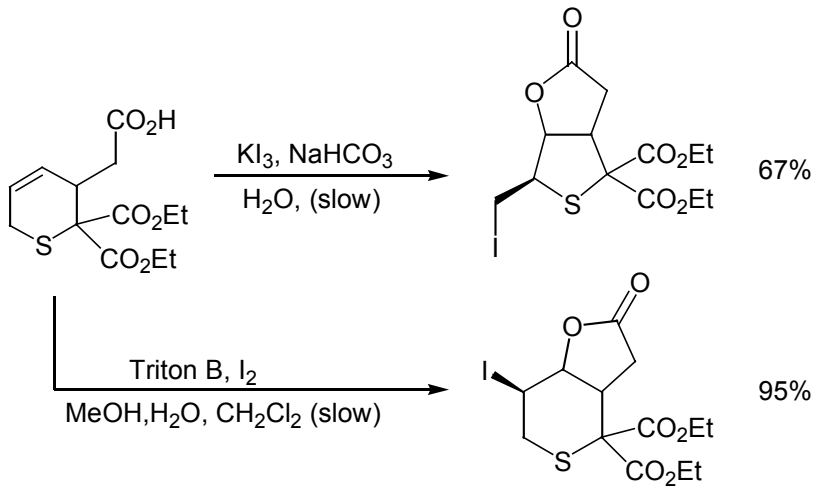


i) 2 eq. $PhCO_2Ag$, 1eq. I_2, benzene. ii) OH^-.
iii) I_2, AcOAg, AcOH/water. iv) OH^-.

Scheme 10

Mechanistically, this cohalogenation process is related to the halolactonization reaction.

Sofar, this approach to the dihydroxylation of dihydro-2*H*-thiopyrans has not been investigated. The more common iodolactonization has been studied by Sutherland *et al*.[16] for dihydrothiopyrans bearing a CH_2CO_2H substituent at the allylic 3-position. In one case a deviating course of the reaction was observed, namely treatment of these substrates with KI_3/ $NaHCO_3$ in water gave a ring contraction product identified as a thiolane derivative in 67% yield (Scheme 11).



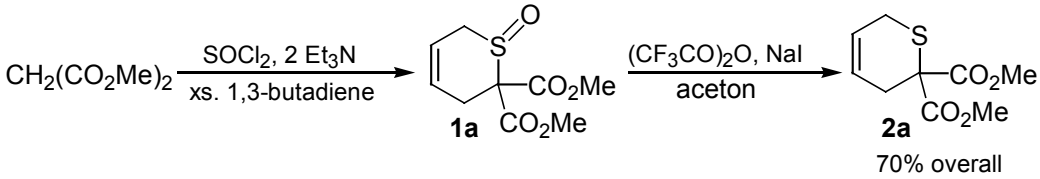
Scheme 11

The formation of this unwanted product was explained by invoking initial complexation of the sulfur atom with iodine.[16] In the present study the cohalogenation of dihydrothiopyran **2a** (Scheme 12) is investigated with *N*-iodosuccinimide in the presence of a carboxylic acid. Although the initial aim was to accomplish a selective reaction at the olefinic bond, it will be shown that actually a ring contraction to thiolanes took place exclusively.

4.2 Results

4.2.1 Reactions of symmetrical thiopyrans

In this chapter the focus will be on the use of 3,6-dihydrothiopyrans prepared from sulfines derived from active methylene compounds. The reaction of diethyl malonate with thionyl chloride in the presence of triethylamine and 1,3-butadiene as the trapping diene conveniently leads to cycloadduct **1a** in good yield[3a,5a,6] (Scheme 12). Subsequent removal of the sulfoxide oxygen by treatment with sodium iodide and trifluoroacetic anhydride in acetone[4] then produces the 3,6-dihydrothiopyran **2a** in an overall yield of 70% (Scheme 12).



Scheme 12

Treatment of a solution of substrate **2a** in chloroform with *N*-iodosuccinimide as the source of electrophilic halogen in the presence of an excess of diphenylacetic acid gave a single crystalline product in 84% yield. Comparison of the NMR spectral data of this product with those of known thiane derivatives[3h,i] clearly revealed that no six-membered sulfur heterocycle had been obtained, although the molecular composition was the same as expected for an iodo oxygenation of the olefinic bond. The structure of the newly formed product was elucidated by an X-ray diffraction analysis[17,18] and shown to be iodothiolane **3a** (Fig 1).

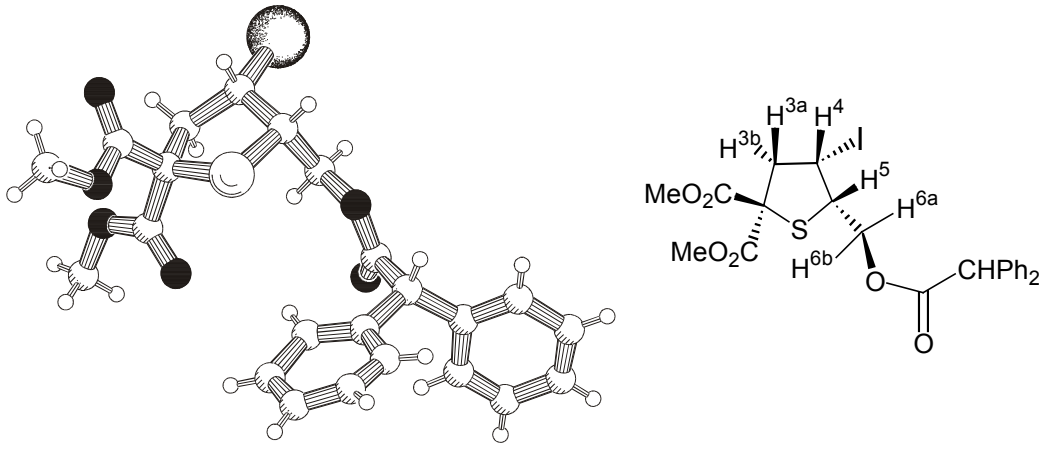
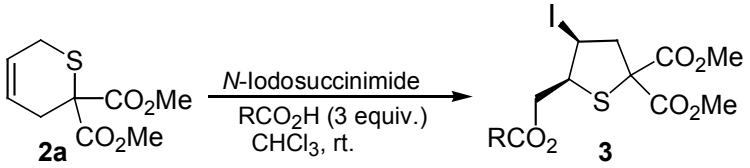


Figure 1 X-ray crystal structure of **3a**

The iodine substituent at C-4 is positioned *cis* with respect to the substituent at C-5. Thus, a ring contraction to thiolane had taken place (Table 1). Having in hand the correct structure of the product, the signals in the ^{1}H and the ^{13}C-NMR spectra could be assigned using DEPT- and H,C-correlation methods. The 400 MHz proton NMR-spectrum of **3a** showed two double doublets for H_{3a} and H_{3b} with geminal coupling constants $J(H_{3a},H_{3b})$= 11.4Hz and $J(H_{3a},H_4)$= 5.6 Hz. The coupling between H4 and H5 could not be clearly identified by saturation of either of their signals because their signals are insufficiently separated. It is reasonable to assume however that $J(H_4,H_5)$ will be in the same range as $J(H_{3a},H_4)$ (5.6 Hz). The signals for H6a and H6b appear as two double doublets resembling an AB-type spectrum, with approximate coupling constants $J(H_{6a}, H_{6b})$= 11.5 Hz, $J(H_{6a},H_5)$= 6.7 Hz and $J(H_{6b},H_5)$= 4.8Hz. This spectral analysis is important for the structure determination of other thiolane products mentioned below.

Table 1 Synthesis of thiolanes from 3,6-dihydrothiopyran **2a**

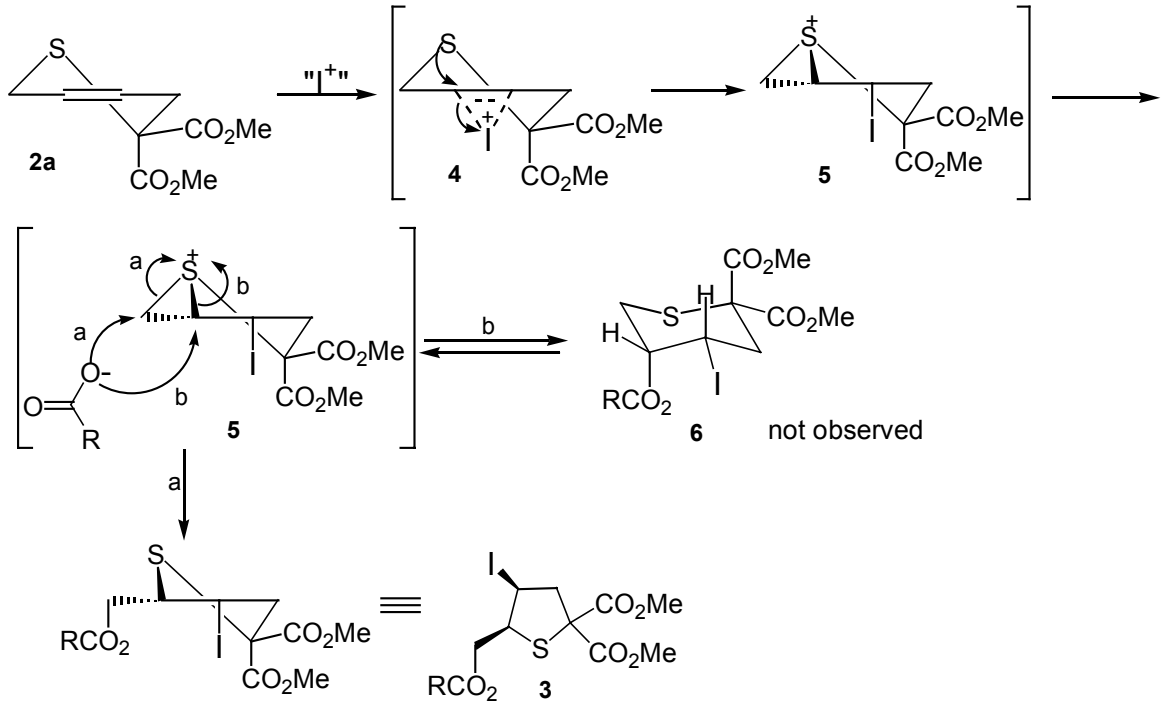


entry	Product	R	time (hrs)	yield (%)
1	**3a**	Ph_2CH-	16	84
2	**3b**	Me	5	90
3	**3c**	Cl_3C	2	97
4	**3d**	HC≡C-	1.5	94
5	**3e**	H	1.5	98
6	**3f**	4-$MeOC_6H_4CH_2$	30	68
7	**3g**	$MeOCH_2$-	3	92
8	**3h**	2-MeOPh	96	56[c]
9	**3i**	3,4,5$(MeO)_3$Ph	72	72[c]
10	**3j**	mandelic acid	2	92[a]
11	**3k**	[b]	24	35[c]
12	**3l**	Ph	7 days	0

a) 2:3 mixture of diastereomers. b) OH instead of RCO_2
c) incomplete conversion

The reaction time for the ring contraction using diphenylacetic acid is rather long (16 hrs). The influence of the carboxylic acid on the reaction rate was tested by studying a series of acids as shown in Table 1. In all cases ring contracted thiolanes were obtained as the sole product. In most cases the yields are excellent. The reaction time indeed depends on the nature of the acid, the stronger the acid the faster the reaction. Benzoic acid failed to react even after 7 days, but 2-methoxybenzoic acid gave the expected product after 4 days in 56% yield. The scope of this novel ring contraction is quite substantial. In all cases the ^{1}H-NMR spectra reveal that the C_4-C_5 *cis* product is obtained exclusively. Due to the stereogenic center in mandelic acid, two diastereomeric products are obtained (ratio 2:3). The products **3** are stable compounds that can be stored at ambient temperature. In most cases the initially obtained oily products crystallized on standing at –20^{o}C, sometimes after several months.

The formation of the ring contracted products can be rationalized by assuming an initial reaction of the electrophilic iodo succinimide with the olefinic bond to give an iodonium ion **4**. By an intramolecular reaction of sulfur this ion **4** is transferred to bicyclic thiiranium ion **5**. This reaction must take place in a stereocontrolled manner because of the steric restrictions imposed by the six-membered sulfur heterocycle. In a subsequent step the carboxylate anion, formed by the reaction of the carboxylic acid with the succinimide anion released during the iodination with NIS, will attack from the least hindered side (route **a** in Scheme 13) to give the final product **3**. This sequence leads to the observed *cis*-relationship of the iodine substituent and the group at C5 (scheme 13). The alternative ring opening of species **5** following the sterically more encumbered route **b**, would lead to the six-membered product **6**. This compound was experimentally not observed.

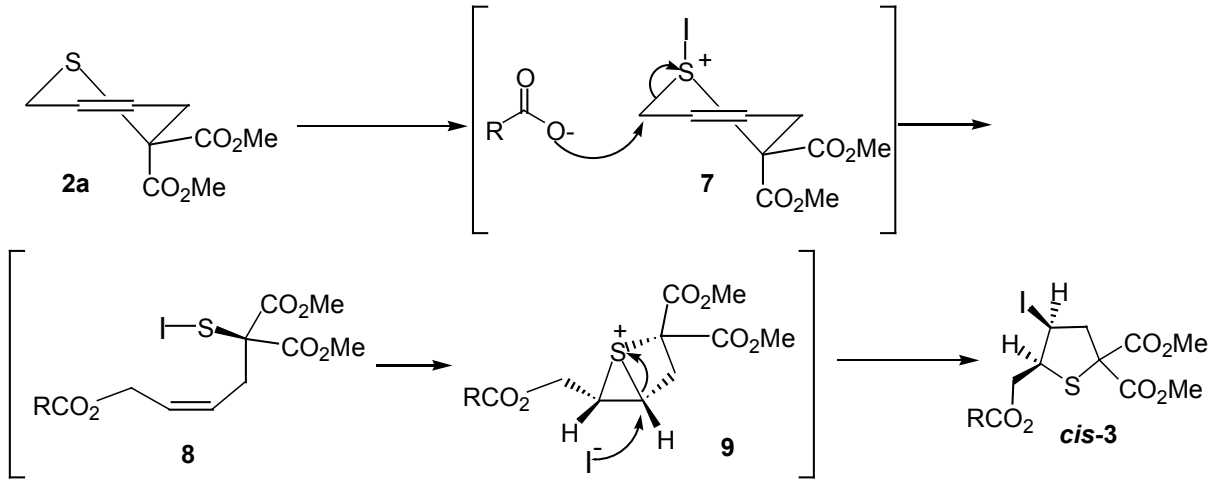


Scheme 13

This mechanism is similar to the one suggested by Hughes[10] and Altenbach[11] in their work on ring contractions of (thio)sugar derived thiopyrans. In contrast to their work, the leaving group that is involved during the attack by sulfur (iodide in our case) remains part of the product, thus resulting in the introduction of two functionalities with simultaneous ring contraction.

An alternative explanation involves initial iodination of the sulfur atom to sulfonium species **7**, which on reaction with carboxylate anion opens up to sulfanyl iodide **8**. It then

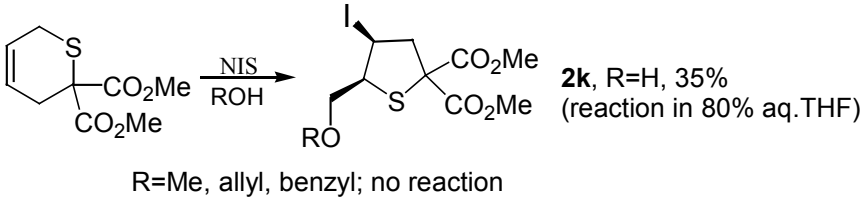
must be assumed that an intramolecular reaction occurs with the olefinic bond resulting in thiiranium ion **9**. Cleavage of the three-membered ring by opening the central bond in **9** by an iodide ion then leads to product **3**. Cyclizations of alkenylsulfanyl halides are indeed believed to occur by an electrophilic addition to the double bond giving a thiiranium intermediate.[19] For substrates having short tethers, as in the present case, the formation of the bicyclic species (here **9** is a [2.1.0]-system) may be difficult due to strain effects.[16] Furthermore, the stereoelectronic alignment for the 5-endo-trig closure of of **8** to **9** may be sterically considerable hampered.[16] For these reasons this alternative mechanism is considered unlikely.



Scheme 14

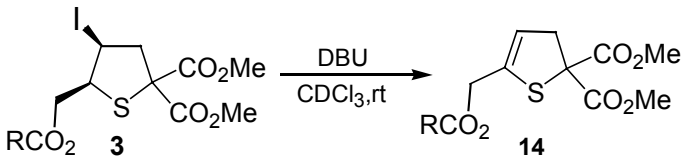
It should be noted that Sutherland *et al.*[16] explained the deviant formation of a ring-contracted product (a thiolane) during the iodolactonization of a dihydrothiopyran with a CH_2CO_2H substituent, by invoking a bicyclic thiiranium ion resembling structure **5** in scheme 13, although its formation was not clearly specified.

By monitoring the reaction of **2a** with NIS and acetic acid with ^{1}H-NMR it was attempted to spot any intermediate in this ring contraction process. However, only the appearance of product **3b** and the disappearance of the substrate **2a** was observed. The use of molecular iodine as iodination agent was also tried.[16, 19a] No reaction was observed even after several days. This was somewhat surprising as alkenyl sulfides undergo a cyclization reaction to thiolanes and/or thianes upon treatment with iodine or bromine.[19a] Attempts to accomplish a reaction with *in situ* generated IN_3 from NIS and NaN_3, ICl and NaN_3 or NIS and HN_3 did not lead to any product at all, the substrate was recovered quantitatively. When *N*-bromosuccinimide or *N*-bromoacetamide were used instead of NIS hardly any reaction was detected. Replacement of the carboxylic acid by alcohols (such as allyl-, benzyl- and methyl alcohol) resulted in complete failure of the reaction. Only with 80% aqueous THF using two equiv. of NIS the corresponding iodo alcohol **3k** was obtained albeit in only modest yield (35%) after 24 hours (Scheme 15).



Scheme 15

Unfortunately, attempts to substitute the iodide functionality in **3a** with an azide group failed, treatment of **3a** with sodium- or lithium azide in DMSO, DMF or acetonitrile only lead to HI-elimination giving derivative **14a**. Treatment of **3a-c**,**e** and **g** with DBU in $CDCl_3$ was monitored by ^{1}H-NMR and as expected showed the formation of derivatives **14a-c,e** and **g**, respectively (Scheme 16).



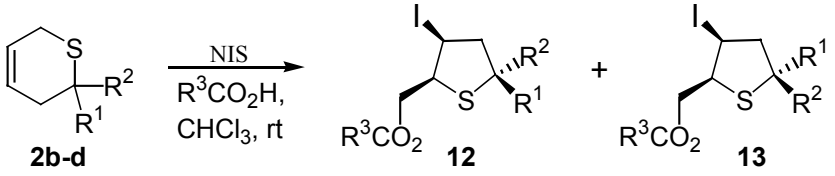
R=Ph_2CH, Me, Cl_3C, H, $MeOCH_2$.

Scheme 16

4.2.2 Reactions of unsymmetrical thiopyrans

As mentioned in the introduction, the reaction of doubly-activated methylene compounds with thionyl chloride in the presence of triethylamine and a trapping 1,3-diene is an effective way to prepare dihydrothiopyran *S*-oxides.[3] This method was applied for methyl phenylacetate, ethyl cyanoacetate and diethyl cyanomethane phosphonate. Subsequent deoxygenation then gives the dihydrothiopyrans shown in Table 2. These unsymmetrically substituted sulfur heterocycles were subjected to the optimal ring contraction conditions with NIS as the electrophilic reagent. The expected thiolanes were obtained as a 1:1 mixture of isomers **12** and **13** (table 2). The reaction with diphenyl acetic acid as the carboxylate was slow for substrate **2b** and failed for the substrates **2c** and **2d**. The more reactive acids acetic acid, formic acid and propiolic acid gave good to excellent yields of thiolanes (table 2).

Table 2 Synthesis of thiolanes from unsymmetrically substituted 3,6-dihydrothiopyrans



entry	R^1	R^2	R^3	products **12** + **13**	yield (%)
1	CO_2Me	Ph	Ph_2CH-	**a**	52
2	CO_2Me	Ph	Me	**b**	74
3	CO_2Et	CN	Ph_2CH-	**c**	--
4	CO_2Et	CN	H	**d**	91
5	CO_2Et	CN	HC≡C-	**e**	93
6	CN	$(EtO)_2P(O)$-	Ph_2CH-	**f**	--
7	CN	$(EtO)_2P(O)$-	H	**g**	88
8	CN	$(EtO)_2P(O)$	HC≡C-	**h**	93

During the reaction of **2b** with NIS and acetic acid some by-products were also formed. These minor products showed a vinylic proton signal at ca 6.3 ppm, suggesting that elimination of HI had taken place. However, the structure of these by-products remained obscure. In the case of products **12/13e,g**,and **h**, separation of isomers could be achieved by chromatography. The structures of the obtained products could be deduced from the NMR spectral characteristics. The overall patterns closely resembled those of product **3b** obtained from the substrate **2a**. The substituents at C-4 and C-5 have a *cis*-relationship as is apparent from the coupling

constant $J(H_4,H_5)$. All other signals could be properly assigned. The structures of **12e** and **12h** were established unambiguously by means of an X-ray diffraction analysis (Fig. 2).

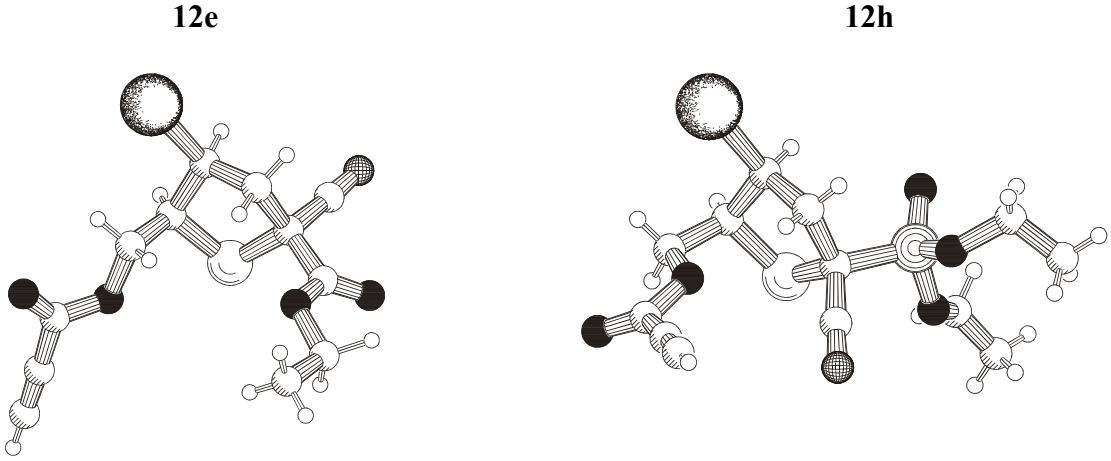
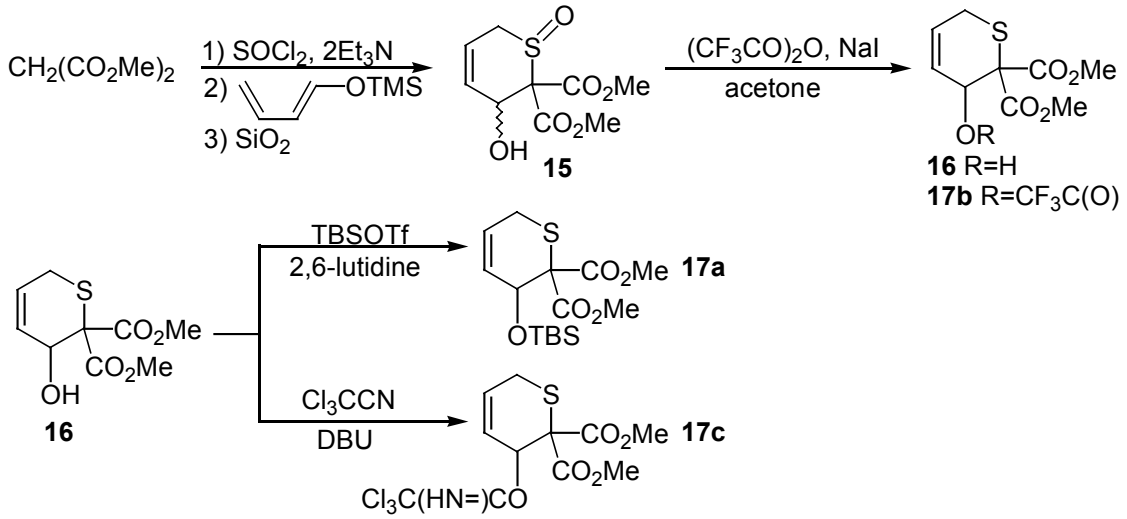


Figure 2 X-ray crystal structures of **12e** and **12h**

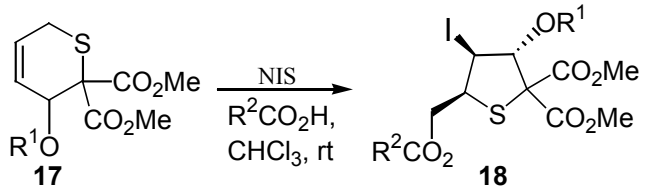
The sulfine derived from diethyl malonate was also trapped with 1-trimethylsilyloxy-1,3-butadiene. The resulting 3-OTMS derivative (mixture of isomers) was deprotected by stirring overnight with silica gel in ethyl acetate to give **15**. Subsequent deoxygenation with trifluoracetic anhydride and sodium iodide gave **16** together with variable amounts of trifluoroacetate **17b**. Treatment of **16** with $tBuMe_2SiOTf$ in the presence of 2,6-lutidine produced **17a** in 82% yield while reaction with trichloroacetonitrile and DBU lead to **17c** in 92% yield (Scheme 17).



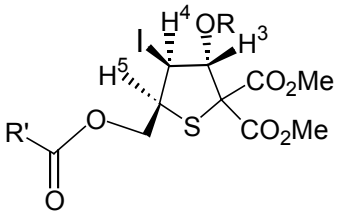
Scheme 17

The ring contraction with NIS in the presence of a carboxylic acid now produces penta-substituted thiolanes **18**. The reaction with diphenylacetic acid is sluggish and low yielding, but with propiolic acid the yield of **18b** was excellent. The trifluoroacetyl protected substrate **17c** failed to react possibly due to a deactivating effect of this substituent on the olefinic bond.

Table 3 Synthesis of pentasubstituted thiolanes



entry **17**	R^1	R^2	yield **18** (%)
a	TBDMS	Ph_2CH-	20
a	TBDMS	HC≡C-	95
b	$CF_3C(=O)$-	HC≡C-	0



18a: R'= Ph_2CH; $J(H_3,H_4)$= 9.9 Hz

18b: R'=HC≡C; $J(H_3,H_4)$= 9.7 Hz

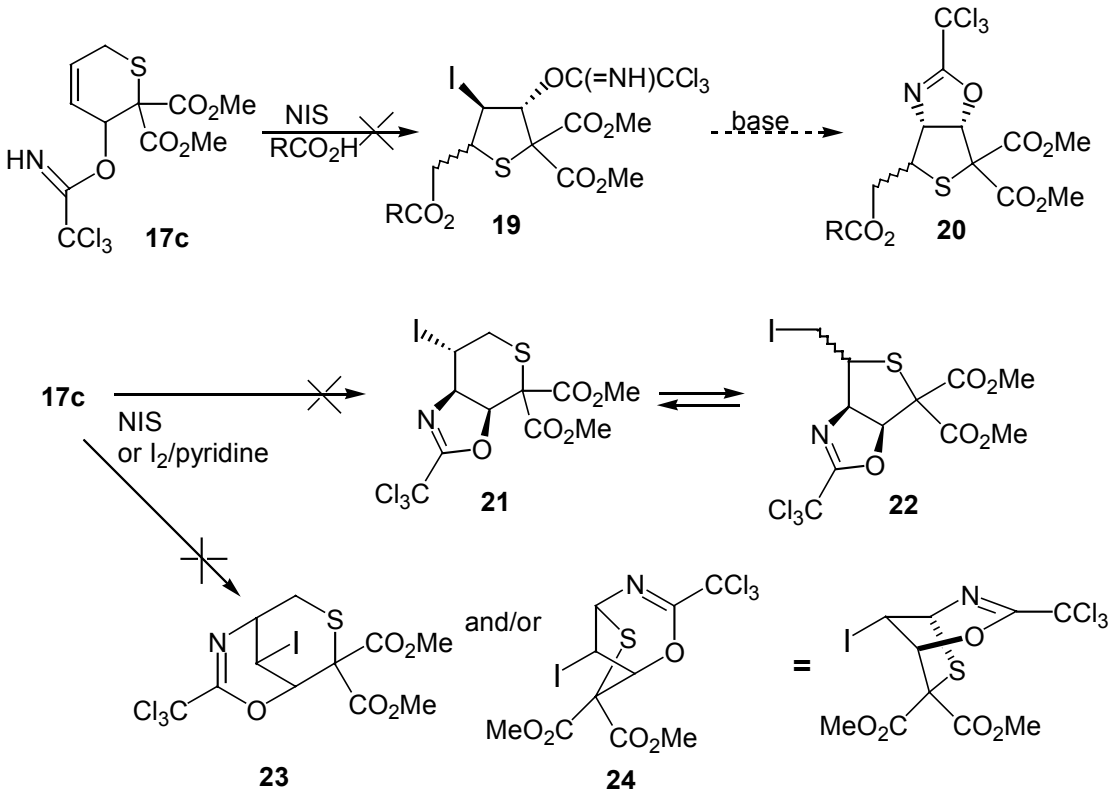
J(H4,H5)= 7.2Hz

R=TBDMS

The products **18a** and **18b** were obtained as single isomers. It may be assumed that the substituents at C-4 and C-5 are positioned in a *cis* manner, although the $J(H_4,H_5)$ of 7.2 Hz is a little high. H-3 and H-4 have a *trans* relationship as is apparent from the $J(H_3,H_4)$ of 9.9 and 9.7 Hz, respectively.

In the case of trichloroimidate **17c**, both the sulfur and the imidate-nitrogen are nucleophiles and it would be interesting to see which one would react with the intermediate iodonium ion. (Several examples of iodo-imidation with similar derivatives, without sulfur in the ring but either carbon or oxygen in this position, are known.)[15f] The presence of a carboxylic acid could result again in thiolane formation (**19**), however attack of the imidate nitrogen instead, would result in formation of either **23** or **24** depending on the position of attack. Straightforward iodo-imidation (in absence of a carboxylic acid) would give thiopyran **21** (possibly in equilibrium with thiolane **22**). In any case, the obtained products would be highly functionalized derivatives with ample opportunity for further synthetic elaboration (e.g. to **20**).

Disappointingly however, reaction of **17c** with NIS with or without the presence of carboxylic acids gave no products at all, only starting material was recovered. Also reaction with iodine/pyridine in THF showed no reaction at all even after ten days.



Scheme 18

In summary, the ring contraction of 3,6-dihydrothiopyrans derived from doubly-activated methylene compounds via a sulfine intermediate, can be readily accomplished by treatment with *N*-iodo succinimide in the presence of a range of carboxylic acids. In most cases the yields are high. This reaction proceeds in a stereocontrolled manner to give thiolanes with the substituents at C-4 and C-5 in a *cis*-relationship. Mechanistically, this ring contraction takes place by an initial iodination of the olefinic bond, followed by an intramolecular reaction of the ring sulfur atom to give a thiiranium ion as the key intermediate, which then opens up to produce the five-membered ring products. The availability of a large variety of 3,6-dihydrothiopyrans should allow for the preparation of many other new thiolane derivatives.

4.3 Experimental

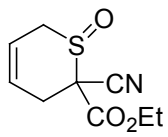
General remarks

Melting points were determined with a Reichert Thermopan microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with Bruker AC 300 MHz and Varian Unity Inova 400 HR spectrometers. Mass spectra were obtained with a VG 7070E spectrometer. Elemental analyses were obtained using a Carlo Erba EA 1108 element analyser. Thin layer chromatography was carried out on Merck silica gel 60 F-254 plates. Spots were visualised with UV and by dipping in a staining solution (6.2% sulfuric acid aqueous solution, containing 42g ammonium molybdate and ceric ammonium sulfate per liter) followed by charring. Gravity column chromatography was carried out on Silica 60 (Baker).

Solvents

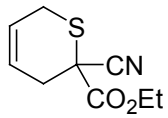
The rearrangement reactions were performed in chloroform (p.a.), Dichloromethane and acetonitril were distilled from P_2O_5, ethyl acetate was distilled from K_2CO_3 and heptane from CaH_2. Thionyl chloride was distilled from triphenyl phosphite and stored under argon. Diisopropyl ether (p.a., Fluka) was used as received.

Ethyl 2-cyano-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxylate (1c)[6]



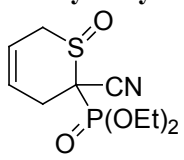
Under an argon atmosphere a solution of ethyl cyanoacetate (4.52 g, 40 mmol) and triethylamine (8.5 g, 84 mmol, 2.1 eq.) in 100 ml diethyl ether was added drop wise over 45 minutes to a cooled (-78°C) solution of thionyl chloride (2.98 ml, 41 mmol) in diethyl ether (100 ml) into which an excess of 1,3-butadiene had been condensed. After completion of addition the reaction mixture was stirred for 30 minutes at –78°C after which the temperature was allowed to reach 0°C. After stirring for 3 hrs the temperature was raised to room temperature and stirring was continued overnight under a slow stream of argon. The reaction mixture was poured into a 500 ml separatory funnel containing 150 ml of water. The layers were separated and the aqueous layer was extracted with dichloromethane (3x75 ml), the combined organic fractions were dried ($MgSO_4$) and filtered. Removal of the solvents *in vacuo* gave 8.35 g of crude product as a dark yellow to brownish oil. Purification by column chromatography (silica gel, ethyl acetate: heptane = 1:1) yielded 6.91g (81%) of yellow oil that crystallized upon standing. Mp. 98-101°C. ^{1}H-NMR (300MHz) d: 1.37 (t, 3H, J= 7.2 Hz, -C**H$_3$**), 3.0 (br.s, 2H, **H$_2$**C-C-S=O), 3.72 (br.d, 1H, **H**HC-S=O), 3.94 (dd, 1H, J= 6.2, 20.2Hz, **H**HC-S=O), 4.40 (q, 2H, J= 7.2Hz, OC**H$_2$**-), 5.66-5.86 (m, 2H, **H**C=C**H**). ^{13}C-NMR (75 MHz) d: 13.9 (**C**H$_3$), 32.4 (H$_2$**C**-C-S=O), 49.0 (H$_2$**C**-S=O), 63.9 (NC**C**-S=O), 64.6 (O**C**H$_2$-), 112.9 (**C**N), 118.7, 125.2 (H**C**=**C**H), 164.1 (**C**=O).
Mass (EI): m/e 213(M^+).

Ethyl 2-cyano-3,6-dihydro-2*H*-2-thiopyran-2-carboxylate (2c)



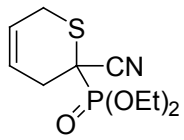
Prepared by reduction of the *S*-oxide according to a literature procedure[4]
Obtained from *S*-oxide (2.13 g., 10.0 mmol) as viscous yellow oil (1.67 g, 85%) after column chromatography (ethyl acetate : heptane = 1:4). ^{1}H-NMR (300MHz) d: 1.35 (t, 3H, J= 7.2 Hz, -C**H$_3$**), 2.82 (m, 2H, **H$_2$**C-C-S), 3.25 (dd, 1H, J= 4.0, 18.0 Hz, **H**HC-S), 3.71 (br.d, 1H, J= 18.0 Hz, **H**HC-S), 4.32 (q, 2H, J=7.2Hz, OC**H$_2$**-), 5.80-6.04 (m, 2H, **H**C=C**H**). ^{13}C-NMR (75 MHz) d: 13.7 (**C**H$_3$), 32.1 (H$_2$**C**-C-S), 42.5 (H$_2$**C**-S), 60.1(NC**C**-S), 63.7 (O**C**H$_2$-), 116.0 (**C**N), 123.3,123.6 (H**C**=**C**H), 165.4 (**C**=O). Mass (EI): m/e 197 (M^+).

Diethyl 2-cyano-1-oxo-3,6-dihydro-2*H*-thiopyran-2-phosphonate (1d)



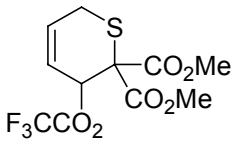
Prepared according to procedure for **1c** from *O*,*O*-diethyl- cyanomethylphosphonate (20.0 mmol, 3.54 g) . Obtained as viscous yellow oil (4.32 g, 78 %) after column chromatography (ethyl acetate : heptane = 1:1), sufficiently pure for *S*-oxide reduction (proton NMR showed the presence of a small amount of O,O-diethyl cyanomethylphosphonate). ^{1}H-NMR (300MHz) d: 1.43 (m, 6H, P(OCH$_2$C**H$_3$**)$_2$), 2.93 (m, 2H, **H$_2$**CC-S=O), 3.71 (br.d, 1H, J= 16.5 Hz, **H**HC-S=O), 3.98 (d of triplets, 1H, J= 16.5, 4.8 Hz, **H**HC-S=O), 4.30-4.40 (m, 4H, P(OC**H$_2$**CH$_3$)$_2$), 5.75-5.83 (m, 2H, **H**C=C**H**).^{13}C-NMR (75 MHz) d: 16.2 (d, J= Hz, 2x -**C**H$_3$), 31.0 H$_2$**C**C-S=O), 48.8 (H$_2$**C**-S=O), 65.0, 65.4 (d, J= 30Hz, O**C**H$_2$CH$_3$)$_2$, 119.2 (**C**N), 125.2, 125.4 (H**C**=**C**H). Mass (EI): m/e 277 (M^+).

Diethyl 2-cyano-3,6-dihydro-2*H*-thiopyran-2-phosphonate (2d)



Prepared by reduction of the *S*-oxide according to a literature procedure.[4] Obtained from the *S*-oxide (2.77 g, 10.0 mmol) as yellow oil (2.14 g, 82%). ^{1}H-NMR (300MHz) d: 1.42 (t, 6H, J= Hz, P(OCH$_2$C**H$_3$**)$_2$), 2.80 (AB of multiplets, 2H, **H$_2$**CC-S), 3.21 (d of multiplets, 1H, J= 17.7 Hz, **H**HCC-S), 3.71 (d of multiplets, 1H, J= 17.7 Hz, **H**HCC-S), 4.29-4.40 (m, 4H, P(OC**H$_2$**CH$_3$)$_2$), 5.85 (m, 1H, **H**C=CH), 6.00 (m, 1H, HC=C**H**).^{13}C-NMR (75 MHz) d: 16.2, 16.3 (P(OCH$_2$**C**H$_3$)$_2$), 25.0 (d, J= 5.3Hz, H$_2$**C**C-S), 30.6 (d, J= 3 Hz, H$_2$**C**-S), 35.5+37.3 (d, J_{PC}= 135Hz, P-**C**-S), 65.0, 65.4 (2x d, J_{PC}= 7.5Hz, P(O**C**H$_2$CH$_3$)$_2$), 116.4 (d, J_{PC}= 7.5Hz, **C**N), 123.5 (H**C**=CH), 123.8 (HC=**C**H). Mass (EI): m/e 261 (M^+).

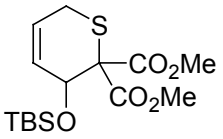
Dimethyl 3-[trifluoroacetyl)oxy]-3,6-dihydro-2*H* thiopyran-2,2-dicarboxylate (17b)



Obtained together with hydroxy-derivative **10a** from the reduction of the thiopyran *S*-oxide in varying amounts (0-35%) as a white crystalline solid. (Separated from **10a** during column chromatography.)
Mp. 105-106°C. ^{1}H-NMR (300MHz) d: 3.25 (m, 2H, C**H$_2$**S), 3.81 (s, 6H, 2 – CO$_2$C**H$_3$**), 5.93-6.04 (m, 2H, C=C**H**-C**H**OC(=O)CF$_3$), 6.23-6.29 (m, 1H,

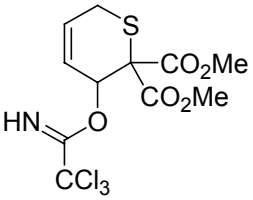
$CH_2C\mathbf{H}$=CH-). ^{13}C-NMR (75 MHz) d: 24.4 (**C**H_2S), 53.8 (2 –$CO_2\mathbf{C}H_3$), 58.3 (C=CH-**C**HOC(=O)CF_3), 69.1 (S-**C**$(CO_2Me)_2$), 122.8 (HC=**C**H-CHOC=OCF_3), 130.3 (H**C**=CH-CHOC=OCF_3), 165.6 (2 **C**=O methylester), 166.3 (F_3C**C**(=O)-O-). Mass (EI): m/e 328(M^+). Elemental analysis: calcd for $C_{11}H_{11}IO_6SF_3$: C 40.25, H 3.78 %. Found: C 40.21, H 3.51 %.

Dimethyl 3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-3,6-dihydro-2*H* thiopyran-2,2-dicarboxylate (17a)



Under an argon atmosphere a solution of *tert*-butyldimethylsilyl triflate (0.48ml, 2.1 mmol) in 10ml dichloromethane was added dropwise to a solution of 3-hydroxy-di-carbomethoxy-4,5-dehydrothiopyran[6] (464 mg, 2.0 mmol) and 2,6-lutidine (0.25 ml, 2.1 mmol) in dichloromethane (10 ml) at 0°C. After completion of the reaction (TLC ethyl acetate/ heptane = 1:1) the reaction mixture was poured into a separating funnel with water (25ml), the layers were separated and the water layer was extracted with dichloromethane (2x20 ml). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by column chromatography over silica gel (ethyl acetate: heptane = 1:2) gave 567 mg (82%) **17a** as a white crystalline solid.
Mp. 72-74°C. ^{1}H-NMR (300MHz) d: 0.00 (s, 3H, **H$_3$**CSiMetBu), 0.04 (s, 3H, **H$_3$**CSiMetBu), 0.78 (s, 9H, (**H$_3$**C)$_3$CSiMe$_2$), 3.04 (m, 2H, C**H$_2$**S), 3.68 (s, 3H, –$CO_2C\mathbf{H}_3$), 3.71 (s, 3H, –$CO_2C\mathbf{H}_3$), 4.75 (d, 1H, J= 3.6 Hz, C=CH-C**H**OTBS), 5.88-6.00 (m, 2H, -C**H**=C**H**-). ^{13}C-NMR (75 MHz) d: -4.8 (H_3**C**SiMetBu), -3.5 (H_3**C**SiMetBu), 17.9 (Si**C**$(Me)_3$), 25.3 (**C**H_2S), 25.6 (SiC(**C**$H_3)_3$), 53.1 (2 –CO_2**C**H_3), 64.8 (**C**-OSi), 125.3, 129.3 (-H**C**=**C**H-), 168.0 (2 O=**C**-OMe). Mass (EI): m/e 346 (M^+).

Dimethyl 3-[trichloroethanimidoyl)oxy]-3,6-dihydro-2*H* thiopyran-2,2-dicarboxylate (17c)

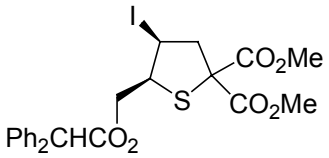


To a cooled (0°C) solution of 3-hydroxy-2,2-dicarbomethoxy 4,5-dehydrothiopyran (232 mg, 1.0 mmol) and trichloroacetonitrile (1.0 ml, 10.0 mmol) in 5.0 ml dichloromethane was added DBU (0.05 ml, 0.3 mmol, 0.3 eq.). The reaction was almost instantaneous (TLC). After stirring for ten minutes the reaction mixture was poured into a separating funnel containing water (25ml). The layers were separated and the water layer is extracted with dichloromethane (2x15ml). The combined organic fractions were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by column chromatography over silica gel (ethyl acetate: heptane = 1:1) gave 345 mg (92%) of **17c** as a white crystalline solid. Upon storage at –20°C for three months, the compound showed some signs of decomposition (TLC).
Mp. 87-90°C. ^{1}H-NMR (300MHz) d:3.22 (m, 2H, C**H$_2$**S), 3.80 (s, 6H, –$CO_2C\mathbf{H}_3$), 5.97 (br.d, 1H, J= 3.3 Hz, C=CH-C**H**OC(=NH)CCl_3), 6.15-6.25 (m, 2H, -C**H**=C**H**-), 8.46 (br.s., 1H, C=N**H**). ^{13}C-NMR (75 MHz) d: 25.4 (**C**H_2S), 53.5, 53.6 (2 –CO_2**C**H_3), 59.1 (**C**$(CO_2Me)_2$), 69.4 (**C**-O-C=N), 91.2 (**C**Cl_3), 122.9, 128.6 (-H**C**=**C**H-), 161.1 (**C**=NH), 166,1, 166.8 (O=**C**-OMe). Mass (EI): m/e 375(M^+). HRMS: calcd for $C_{11}H_{12}NO_5Cl_3SI$ 374.95018. Found: 374.95021.

Synthesis of 4-iodotetrahydrothiolanes, general procedure:
To a solution of the thiopyran (1.0 mmol) and 3.0 mmol of carboxylic acid in 6 ml of chloroform was added N-iodosuccinimide (270 mg, 1.2 mmol, 1.2 eq.) in three portions with appox. 10 min intervals. The reaction was monitored by TLC, after completion of the reaction (table 1) chloroform (15 ml) was added and the solution was poured into a separating funnel containing 10% sodium thiosulfate (25 ml). The layers were separated and the aqueous layer was extracted with chloroform (2x 20ml). The combined organic fractions were washed with 3% sodium bicarbonate solution and then with water. Drying ($MgSO_4$), filtration and removal of the solvent *in vacuo* yielded the crude product. Column chromatography over silica gel gave the pure products.

According to this procedure, the following derivatives were prepared:

Dimethyl (4,5-*cis*)-5-[(2,2-diphenylacetyl)oxy]methyl-4-iodotetrahydrothiophene-2,2-dicarboxylate (3a)
Obtained as a white crystalline solid (465 mg, 84%) after column chromatography (ethyl acetate : heptane = 1:3), crystallization from diisopropyl ether gave small transparent needles suitable for X-ray structure determination.

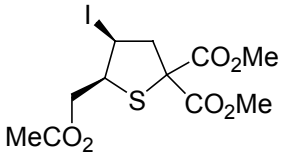


Mp. 109-110°C. ^{1}H-NMR (300MHz) d: 2.73 (dd, 1H, J= 13.7 ,11.5 Hz, $\mathbf{H}_{trans}$HCC(CO_2Me)$_2$), 3.04 (dd, 1H, J= 13.7, 5.7 Hz, $\mathbf{H}_{cis}$HCC(CO_2Me)$_2$), 3.57 (m, 1H, **H**C-S), 3.74 (s, 3H, $CO_2C\mathbf{H_3}$), 3.76 (s, 3H, $CO_2C\mathbf{H_3}$), 4.37 (dd, 1H, J= 11.5, 6.7Hz, O-C$\mathbf{H}_{trans}$H-CH-S), 4.48 (dd, 1H, J= 11.5 , 4.8Hz partial overlap with multiplet CH-**H**C-I), 5.05 (s, 1H, $Ph_2C\mathbf{H}$-), 7.23-7.33 (m, 5H, arom.). ^{13}C-NMR (75 MHz) d: 22.5 (d, **C**-I), 46.6 (t, $H_2\mathbf{C}$-C(CO_2Me)$_2$), 51.1 (d, OCH_2-**C**H-S), 53.7 (2x $CO_2\mathbf{C}H_3$), 56.9 ($Ph_2\mathbf{C}$H-), 64.5 (s, S-**C**(CO_2Me)$_2$), 68.7 (t, O$\mathbf{C}H_2$-CH-S), 127.2, 127.3, 128.5, 2x128.6, 128.7 (C-arom), 138.2 (C-ipso), 168.7, 170.0, 171.9 (s, **C**=O). Mass (EI): m/e 554(M^+). Elemental Analysis: calcd for $C_{23}H_{23}IO_6S$: C 49.83, H 4.18 %. Found: C 49.82, H 4.09 %.

Crystal data and structure refinement for **3a**.

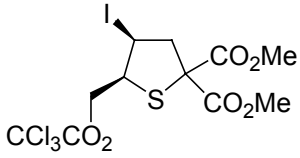
Crystal colour	transparent colorless
Crystal shape	regular fragment
Crystal size	0.29 x 0.21 x 0.15 mm
Empirical formula	C_{23} H_{23} I O_6 S
Formula weight	554.37
Temperature	293(2) K
Radiation / Wavelength	MoK_α (graphite mon.) / 0.71073 Å
Crystal system, space group	Monoclinic, Pn
Unit cell dimensions	a, α= 10.7956(16) Å, 90^o
(25 reflections, 10.523 < θ< 14.466)	b, β= 12.1197(15) Å, 92.054(19)^o
	c, γ= 17.677(3) Å, 90^o
Volume	2311.4(6) Å^3
Z, Calculated density	4, 1.593 Mg/m^3
Absorption coefficient	1.512 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / Ω
F(000)	1112
θ range for data collection	3.36 to 27.48^o
Index ranges	0<=*h*<=14, -15<=*k*<=0, -22<=*l*<=22
Reflections collected / unique	5554 / 5554
Reflections observed	2607 ([I_o>2σ(I_o)])
Absorption correction	Semi-empirical from Ψ-scans
Range of relat. transm. factors	1.169 and 0.814
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	5554 / 2 / 563
Goodness-of-fit on F^2	1.043
SHELXL-97 weight parameters	0.112600 0.000000
Final R indices [I>2σ(I)]	R_1 = 0.0922, wR_2 = 0.1954
R indices (all data)	R_1 = 0.2030, wR_2 = 0.2513
Largest diff. peak and hole	1.500 and -0.781 e.Å^{-3}

Dimethyl (4,5-*cis*)-5-[(acetyloxy)methyl]-4-iodotetrahydrothiophene-2,2-dicarboxylate (3b)



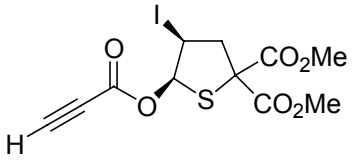
Obtained as a white crystalline solid (360 mg; 90 %) after column chromatography (ethyl acetate: heptane = 1:3), crystallization from diisopropyl ether gave long transparent needles.
Mp.120-121°C. ^{1}H-NMR (300MHz) d: 2.08 (s, 3H, **H$_3$**C-CO$_2$-), 2.87 (dd, 1H, J= 11.7, 13.5 Hz, **H**$_{trans}$HCC(CO$_2$Me)$_2$), 3.16 (dd, 1H, J= 5.7, 13.5 Hz, **H**$_{cis}$HCC(CO$_2$Me)$_2$), 3.60 (m, 1H, **H**C-S), 3.79 (s, 3H, CO$_2$C**H$_3$**), 3.80 (s., 3H, CO$_2$C**H$_3$**), 4.24 (dd, 1H, J= 6.9, 11.7 Hz, O-C**H**$_{trans}$H-CH-S), 4.49 (dd, 1H, J= 4.5, 11.7 Hz, O-C**H**$_{cis}$H-CH-S), 4.58 (m, 1H, I-C**H**-CH-S). ^{13}C-NMR (75 MHz) d: 20.9 (H$_3$**C**-CO$_2$-), 22.6 (I-**C**H-), 46.9 (t, H$_2$**C**-C(CO$_2$Me)$_2$), 51.3 (d, OCH$_2$-**C**H-S), 53.8 (2q, 2 CO$_2$**C**H$_3$), 64.5 (s, S-**C**(CO$_2$Me)$_2$), 68.2 (t, MeCO$_2$-**C**H$_2$-), 168.8, 170.0, 170.3 (**C**=O). Mass (EI): m/e 402(M$^+$). Elemental Analysis: calcd for C$_{11}$H$_{15}$IO$_6$S: C 32.85, H 3.76 %. Found: C 32.80, H 3.71 %.

Dimethyl (4,5-*cis*)-4-iodo-5-[trichloroacetyloxy]methyltetrahydrothiophene-2,2-dicarboxylate (3c)



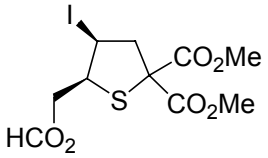
Obtained as a colorless oil (488 mg, 97%) after column chromatography (ethyl acetate: heptane = 1:3) which slowly crystallised at –20°C. Crystallization from diisopropyl ether gave small white needles.
Mp.83-85°C. ^{1}H-NMR (300MHz) d: 2.89 (dd app. as triplet, 1H, J= 13.5, 13.5 Hz, **H**$_{trans}$HCC(CO$_2$Me)$_2$), 3.16 (dd, 1H, J= 5.7, 13.5 Hz, **H**$_{cis}$HCC(CO$_2$Me)$_2$), 3.79 (m, 7H, **H**C-S and 2 CO$_2$C**H$_3$**), 4.58-4.71 (m, 3H, MeCO$_2$-C**H$_2$**- and I-C**H**-). ^{13}C-NMR (75 MHz) d: 21.4 (**C**-I), 46.6 (H$_2$**C**-C(CO$_2$Me)$_2$), 50.3 (**C**H-S), 2x 53.7 (2 CO$_2$**C**H$_3$), 64.5 (S-**C**(CO$_2$Me)$_2$), 72.4 (Cl$_3$CCO$_2$-**C**H$_2$-),161.1 (Cl$_3$C-**C**=O), 168.1, 168.6 (**C**=O). Mass (EI): m/e 504(M$^+$). HRMS: calcd for C$_{11}$H$_{12}$O$_6$Cl$_3$SI, 503.8466. Found: 503.8468.

Dimethyl (4,5-*cis*)-4-iodo-5-[(propioloyloxy)methyl]tetrahydrothiophene-2,2-dicarboxylate (3d)



Obtained as a colorless oil (387 mg, 94 %) after column chromatography (ethyl acetate: heptane = 1:3) which slowly crystallized at –20°C. Crystallization from diisopropyl ether gave small white needles.
Mp. 96-98 °C. ^{1}H-NMR (300MHz) d: 2.84 (dd, 1H, J= 13.7, 11.7 Hz, **H**$_{trans}$HCC(CO$_2$Me)$_2$), 2.97 (s, 1H, **H**C≡C-), 3.20 (dd, 1H, J= 13.7, 5.8Hz, **H**$_{cis}$HCC(CO$_2$Me)$_2$), 3.64 (m, 1H, **H**C-S), 3.79 (br.s, 6H, 2x CO$_2$C**H$_3$**), 4.37 (dd, J= 11.5, 7.0Hz, 1H, O-C**H**H-CH-S), 4.56-4.64 (m, 3H, C≡C-CO$_2$-C**H$_2$**- (dd, J≈5.0, 11.5 Hz) overlapping with m, 1H, CH-**H**C-I). ^{13}C-NMR (75 MHz) d: 22.0 (H**C**-I), 46.7 (H$_2$**C**-C(CO$_2$Me)$_2$), 50.9 (**C**H-S), 2x 53.8 (2 CO$_2$**C**H$_3$), 64.5 (S-**C**(CO$_2$Me)$_2$), 69.6 (HC≡C-CO$_2$-**C**H$_2$-), 74.2 (HC≡**C**-C), 75.6 (HC≡C), 151.8 (HC≡C-**C**=O), 168.6, 170.0 (**C**O$_2$Me). Mass (EI): m/e 412(M$^+$). HRMS: calcd for C$_{12}$H$_{13}$O$_6$SI: 411.9478. Found: 411.9478.

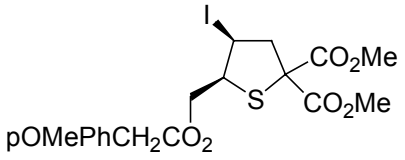
Dimethyl (4,5-*cis*)-5-(formyloxymethyl)-4-iodotetrahydrothiophene-2,2-dicarboxylate (3e)



Obtained as a colorless oil (380 mg, 98 %) after column chromatography (ethyl acetate: heptane = 1:3). ^{1}H-NMR (300MHz) d: 2.86 (dd, 1H, J= 13.7, 11.6Hz, H$_{trans}$HCC(CO$_2$Me)$_2$), 3.18 (dd, 1H, J= 13.7, 5.7 Hz, H$_{cis}$HCC(CO$_2$Me)$_2$), 3.66 (m, 1H, HC-S), 3.79 (br.s, 6H, 2x CO$_2$CH$_3$), 4.31 (dd, 1H, J= 11.5, 7.3Hz, O-CHH-CH-S), 4.57-4.66 (m, 2H, HC-I, overlapping with dd, 1H, O-CHH-CH-S), 8.09 (s, 1H, H-C(O)O-).^{13}C-NMR (75 MHz) d: 22.2 (HC-I), 46.5 (H$_2$C-C(CO$_2$Me)$_2$), 50.9 (CH-S), 53.6, 53.7 (2 CO$_2$CH$_3$), 64.3 (S-C(CO$_2$Me)$_2$), 67.3 (HC≡C-CO$_2$-CH$_2$), 160.0 (H-C=O), 168.5, 169.6 (-CO$_2$Me).Mass (EI): m/e 388(M$^+$). HRMS: Calcd for C$_{10}$H$_{13}$O$_6$SI : 387.9478. Found: 387.94770.

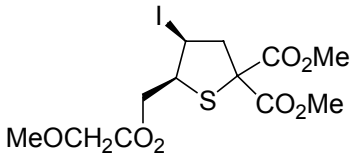
Dimethyl (4,5-*cis*)-4-iodo-5-([2-(4-methoxyphenyl)acetyl]oxymethyl)tetrahydrothiophene-2,2-dicarboxylate (3f)

Obtained as a colorless oil (345 mg, 68 %) after column chromatography (ethyl acetate: heptane = 1:3). ^{1}H-NMR (300MHz) d: 2.81 (dd, 1H, J= 13.7, 11.5 Hz, H$_{trans}$HCC(CO$_2$Me)$_2$), 3.12 (dd, 1H, J= 13.7, 5.7 Hz, H$_{cis}$HCC(CO$_2$Me)$_2$), 3.58 (m, 3H, PhCH$_2$- and HC-S), 3.79 (br.s, 9H, 2x CO$_2$CH$_3$ and



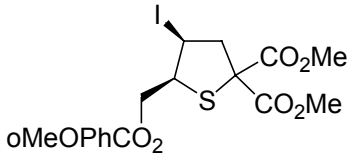
H_3C-O), 4.26 (dd, 1H, J= 11.5, 6.7 Hz, O-CH_{trans}H-CH-S), 4.44-4.60 (m, 2H, dd. J= 11.5, 4.7Hz, O-CH_{cis}H-CH-S, partial overlap with multiplet CH-HC-I), 6.86 (m, 2H, arom.), 7.20 (m, 2H, arom.).
^{13}C-NMR (75 MHz) d: 22.5 (C-I), 40.2 (-**C**H_2PhpOMe), 46.8 (H_2**C**-C$(CO_2Me)_2$), 51.1 (**C**H-S), 2x 53.7 (2 -CO_2**C**H_3), 55.2 (H_3**C**-O), 64.5 (S-**C**$(CO_2Me)_2$), 68.4 (O=C-O-**C**H_2-), 114.0 (C-3 arom), 125.6 (CH_2-**C**-ipso), 130.3 (**C**-2 arom.), 158.7 (O-**C**-ipso), 168.7, 170.0, 171.2 (**C**=O).
Mass (EI): m/e 508(M^+).

Dimethyl (4,5-*cis*)-4-iodo-5-[(2-methoxyacetyl)oxy]methyltetrahydrothiophene-2,2-dicarboxylate (3g)



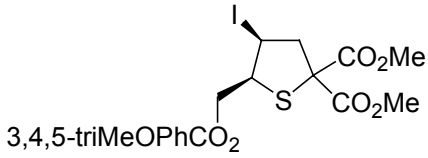
Obtained as a colorless oil (397 mg, 92 %) after column chromatography (ethyl acetate: heptane = 1:3) which slowly crystallized at –20°C.
Mp. 88-89°C. ^{1}H-NMR (300MHz) d: 2.85 (dd, 1H, J= 13.6, 11.9 Hz, **H**$_{trans}$HCC$(CO_2Me)_2$), 3.16 (dd, 1H, **H**$_{cis}$HCC$(CO_2Me)_2$), 3.45 (d, 3H, J= 2.1Hz, **H**$_3$C-O-), 3.65 (m, 1H, **H**C-S), 3.78, 3.79 (2xs, 6H, 2x CO_2C**H**$_3$), 4.05 (AB, 2H, MeO-C**H**$_2$-), 4.36 (dd, 1H, J= 11.5, 6.6 Hz, O=C-O-C**H**H-), 4.56-4.64 (m, 2H, O=C-O-C**H**H- and I-C-**H**).^{13}C-NMR (75 MHz) d: 22.4 (**C**-I), 46.6 (H_2**C**-C$(CO_2Me)_2$), 50.9 (**C**H-S), 2x 53.8 (2 -CO_2**C**H_3), 59.2 (H_3**C**-O), 64.3 (S-**C**$(CO_2Me)_2$), 68.1, 69.4, 168.4, 169.5, 169.7 (**C**=O).
Mass (CI): m/e 432 (M^+). Elemental analysis: Calcd for $C_{12}H_{17}O_7SI$: C 33.35, H 3.96 %. Found: C 33.14, H 3.86 %.

Dimethyl (4,5-*cis*)-4-iodo-5-[(2-methoxybenzoyl)oxy]methyltetrahydrothiophene-2,2-dicarboxylate (2h)



Obtained as a colorless oil (276 mg, 56 %) after column chromatography (ethyl acetate: heptane = 1:3). ^{1}H-NMR (300MHz) d: 2.98 (dd, 1H, J= 13.7, 11.1Hz, H_{trans}HCC$(CO_2Me)_2$), 3.12 (dd, 1H, J= 13.7, 5.7 Hz, H_{cis}HCC$(CO_2Me)_2$), 3.65 (s, 3H, 2-H_3C-O-Ph), 3.72 (m, 1H, HC-S-), 3.78 (s, 3H, -CO_2CH_3), 3.90 (s, 3H, -CO_2CH_3), 4.43 (dd, 1H, J= 11.5, 6.8Hz, O=C-O-CHH-), 4.63-4.76 (m, 2H, O=C-O-CHH- overlap with HC-I), 6.99 (m, 2H, arom), 7.48 (m, 1H, arom), 7.82 (m, 1H, arom). ^{13}C-NMR (75 MHz) d: 23.3 (C-I), 46.7 (H_2C-C$(CO_2Me)_2$), 51.5 (CH-S), 53.6, 53.7 (2 -CO_2CH_3), 55.8 (H_3CO-), 64.5 (S-C$(CO_2Me)_2$), 68.5 (O=C-O-CH_2-),111.9, 119.4, 120.0, 131.8, 133.8 (C-arom.),159.2 (O-C_{ipso}), 165.4, 168.7, 170.0 (C=O).Mass (CI): m/e 494 (M^+). HRMS: Calcd for $C_{18}H_{21}O_7SI$: 493.98962. Found: 493.98973.

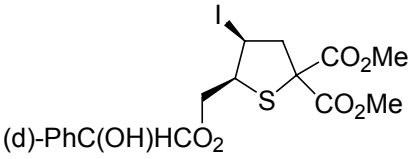
Dimethyl (4,5-*cis*)-4-iodo-5-[(3,4,5-trimethoxybenzoyl)oxy]methyltetrahydrothiophene-2,2-dicarboxylate (3i)



Obtained as a viscous colorless oil (400 mg, 72%) after column chromatography (ethyl acetate: heptane = 1:3). ^{1}H-NMR (300MHz) d: 2.91(dd, 1H, J= 13.5, 13.5Hz, H_{trans}HCC$(CO_2Me)_2$), 3.24 (dd, 1H, J= 13.5, 5.2 Hz, H_{cis}HCC$(CO_2Me)_2$), 3.70 (m, 1H, HC-S-), 3.73 (s, 3H, (O=C)-OCH_3), 3.79 (s, 3H, (O=C)-OCH_3), 3.92 (s, 9H, 3x OCH_3), 4.37-4.83 (m, 3H, O=C-O-CH_2- overlap with HC-I), 7.31 (s, 2H, arom). ^{13}C-NMR (75 MHz) d: 22.1 (C-I), 46.9 (H_2C-C$(CO_2Me)_2$), 51.2 (CH-S), 2x 53.7 (-CO_2CH_3), 56.2 (2x H_3C-O), 60.8 (H_3C-O), 64.3 (S-C$(CO_2Me)_2$), 68.4 (O=C-O-CH_2-), 106.9 (C-2 arom.), 124.5 (C-1 arom.), 142.3 (C-4 arom.), 152.8 (C-3 and C-5 arom.), 165.4, 168.6, 169.8 (C=O).Mass (EI): m/e 554(M^+).

Dimethyl (4,5-*cis*)-5-([(2*R*)-2-hydroxy-2-phenylethanoyl]oxymethyl)-4-iodotetrahydrothiophene-2,2-dicarboxylate (3j, mixture of diastereomers)

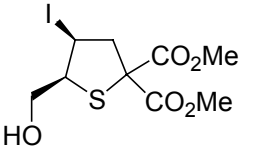
Obtained as colorless viscous oil, approx. 2:3 mixture of diastereomers (455 mg, 92 %).
Major isomer: ^{1}H-NMR (300MHz) d: 2.68 (dd, 1H, J= 12.8, 12.8 Hz, **H**$_{trans}$HCC$(CO_2Me)_2$), 2.97 (dd, 1H, J= 12.8, 6.0 Hz, **H**$_{cis}$HCC$(CO_2Me)_2$), 3.62 (br. s, 1H, O**H** overlapping with OH of minor diastereomer), 3.77 (2x s, 6H, -CO_2C**H**$_3$, overlapping with minor diastereomer), 4,35-4.51 (m, 3H,



O=C-O-C**H**$_2$- and **H**C-I overlapping with minor diastereomer), 5.18 (br.s., PhC**H**(OH)), 7.29-7.44 (m, 5H, arom. overlapping). ^{13}C-NMR (75 MHz) d: 22.2 (**C**-I), 46.5 (H_2**C**-C(CO_2Me)$_2$), 50.7 (**C**H-S), 53.6, 53.7 (2x -CO_2**C**H_3), 64.5 (S-**C**(CO_2Me)$_2$), 69.2 (O=C-O-C**H**$_2$-), 73.0 (Ph**C**H(OH)), 126.7, 128.5 (C-arom), 173.8 (C-ipso), 168.6, 169.8, (2x2 -**C**O_2Me), 172.9 (C=O, mandelic ester).

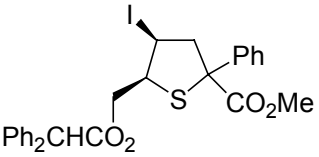
Minor isomer: ^{1}H-NMR (300MHz) d: 2.79 (dd, 1H, J= 13.5, 11.7 Hz, **H**$_{trans}$HCC(CO_2Me)$_2$), 3.12 (dd, 1H, J= 13.5, 5.7 Hz, **H**$_{cis}$HCC(CO_2Me)$_2$), 3.54 (m, 2H, 2x **H**C-S-), 3.60 (br.s., 2H, 2x O**H**), 3.77 (br.s., 6H, 2x -CO_2C**H**$_3$), 4.32 (m, 3H, O=C-O-C**H**$_2$- and **H**C-I), , 5.23 (br.s., PhC**H**(OH), minor isomer), 7.29-7.44 (m, 5H, arom). ^{13}C-NMR (75 MHz) d: 21.4 (**C**-I), 46.6 (H_2**C**-C(CO_2Me)$_2$), 50.8 (**C**H-S), 53.7, 53.8 (2x -CO_2**C**H_3), 64.3 (S-**C**(CO_2Me)$_2$), 69.3 (O=C-O-C**H**$_2$-), 73.0 (Ph**C**H(OH)), 126.5, 128.4 (C-arom), 137.7 (C-ipso),168.8, 169.7 (2x-**C**O_2Me), 172.6 (C=O, mandelic ester). Mass (EI): m/e 494 (M^+). HRMS: Calcd for $C_{17}H_{19}O_7SI$: 493.98962. Found: 493.98956.

Dimethyl (4,5-*cis*)-5-(hydroxymethyl)-4-iodotetrahydrothiophene-2,2-dicarboxylate (3k)



Obtained as a colorles viscous oil (125 mg, 35%) after column chromatography (ethyl acetate: heptane = 1:3). (Slowly turned yellow, even stored at –20°C.) ^{1}H-NMR (300MHz) d: 2.45 (br.s., 1H, O**H**), 2.76 (dd appearing as triplet, 1H, J= 12.9, 12.9Hz, **H**$_{trans}$HCC(CO_2Me)$_2$), 3.21 (dd, 1H, J= 12.9, 6.0Hz, **H**$_{cis}$HCC(CO_2Me)$_2$), 3.56 (m, 1H, **H**C-S-), 3.79 (br.s., 6H, 2 -CO_2C**H**$_3$), 3.88-4.05 (m, 2H, O=C-O-C**H**$_2$-), 4.57 (m,1H, **H**C-I). ^{13}C-NMR (75 MHz) d: 23.2 (**C**-I), 47.0 (H_2**C**-C(CO_2Me)$_2$), 53.6, 54.0 (2 -CO_2**C**H_3), 55.4(**C**H-S), 64.8, (S-**C**(CO_2Me)$_2$), 66.3 (O=C-O-C**H**$_2$-), 169.6, 169.7 (**C**=O). Mass (EI): m/e 360(M^+). Exact mass: Calcd for $C_9H_{13}O_5SI$ 359.9529. Found: 359.95293.

Methyl (4,5-*cis*)-5-[(2,2-diphenylacetyl)oxy]methyl-4-iodo-2-phenyltetrahydrothiophene-2-carboxylate (12a)

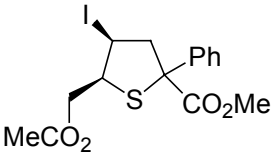


Obtained as a colorless oil (295 mg, 52 %, ca. 9:1 mixture of isomers) after column chromatography (ethyl acetate: heptane = 1:3) which crystallised upon standing. Recrystallisation from diisopropyl ether gave small transparent needles (mixture of isomers).
Mp.144-149 °C.

Major isomer: ^{1}H-NMR (300MHz) d: 2.21 (dd app. as triplet, 1H, J= 13.2, 13.2Hz, S-C-C**H**^{3a}H), 3.39 (dd, 1H, J= 13.2, 5.7Hz, S-C-C**H**^{3b}H), 3.68 (s, 3H, OC**H**$_3$), 3.72 (m, 1H, **H**^{5}C-S), 4.37 (dd, 1H, J= 11.6 , 6.6 Hz, OC**H**^{6a}H-CH-S), 4.50 (dd, 1H, J= 11.6, 4.2 Hz, OC**H**^{6b}H-CH-S), 4.64 (m, 1H, **H**-C-I), 4.80 (s, 1H, Ph_2C**H**-), 7.18-7.40 (m, 15H, arom.). ^{13}C-NMR (75 MHz) d: 22.1 (H-**C**-I), 50.4 (S-C-**C**H_2-), 50.7 (H-**C**-S), 53.2 (2x O-**C**H_3), 56.9 (Ph_2**C**H), 65.4 (S-**C**-CO_2Me), 69.4 (O**C**H_2-CH-S), 126.3, 126.5, 127.8, 128.2, 128.5, 128.7, 128.8, 129.0 (**C**-arom), 138.0 , 140.0 (**C**-ipso), 171.9, 173.5 (**C**=O).

Minor isomer:
^{1}H-NMR (300MHz) d: 2.65 (dd, 1H, J≈ 5-6, ≈13 Hz, S-C-C**H**^{3b}H), 3.44 (dd app. as triplet, 1H, J≈ 13 Hz, S-C-C**H**^{3a}H), 3.62 (s, 3H, OC**H**$_3$), 4.20 (m, 1H, **H**-C-I), 5.10 (s, 1H, Ph_2C**H**-), signals for other protons are overlapped by main isomer. ^{13}C-NMR (75 MHz) d: 21.9 (H-**C**-I), 50.1 (S-C-**C**H_2-), 51.0 (H-**C**-S), 53.3 (2x O-**C**H_3), 56.9 (Ph_2**C**H), 65.3 (S-**C**-CO_2Me), 69.4 (O**C**H_2-CH-S), 126.5, 127.8, peaks overlapped by main isomer (C-arom), 138.1 , 140.8 (C-ipso), 172.0, 173.5 (C=O).
Mass (EI): m/e 572(M^+). Elemental Analysis: calcd for $C_{27}H_{25}IO_4S$: C 56.65, H 4.40 %. Found: C 56.57, H 4.26 %.

Methyl (4,5-*cis*)-5-[(acetyloxy)methyl]-4-iodo-2-phenyltetrahydrothiophene-2-carboxylate (12b)

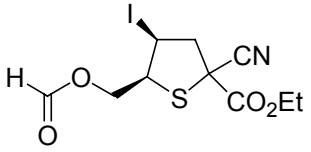


Obtained as a colorless oil (310 mg, 74 %, ca. 3:1 mixture of isomers) after column chromatography (ethyl acetate: heptane = 1:3).

Major isomer:
^{1}H-NMR (300MHz) d: 1.87 (s, 3H, **H**$_3$C-C(=O)O-), 2.46 (dd, 1H, J=13.0, 13.0 Hz, S-C-C**H**^{3a}H), 3.54 (dd, 1H, J= 13.0, 5.6Hz, S-C-C**H**^{3a}H), 3.71 (s, 3H, O=C-OC**H**$_3$), 3.74 (m, 1H, **H**^{5}C-S), 4.25 (dd, 1H, J= 11.6, 6.2Hz, OC**H**^{6a}H-CH-S), 4.56 (dd, 1H, J= 11.6, 4.2 Hz, OC**H**^{6b}H-CH-S), 4.72 (m, 1H, H-**C**-I), 7.28-7.48 (m, 5H, arom.). ^{13}C-NMR (75 MHz)

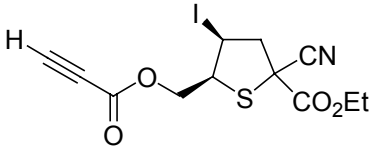
d: 20.7 (H_3**C**-C(=O)O-), 22.7 (H-**C**-I), 50.6 (S-**C**-CH_2-), 51.2 (H-**C**-S), 53.2 (O=C-O**C**H_3), 65.4 (S-**C**-CO_2Me), 68.4 (O**C**H_2-CH-S), 126,4, 127.8, 128.5 (**C**-arom), 140.1 (**C**-ipso),170.3, 173.5 (**C**=O).
Minor isomer:
^{1}H-NMR (300MHz) d: 2.10 (s, 3H, **H$_3$**C-C(=O)O-), 2.74 (dd, 1H, J= 12.9, 5.2 Hz, S-C-C**H^{3b}**H), 3.51 (dd app. as triplet, 1H, J= 12.9 Hz, S-C-C**H^{3a}**H), other signals overlapped by main product. ^{13}C-NMR (75 MHz) d: : 20.9 (H_3**C**-C(=O)O-), 21.9 (H-**C**-I), 50.1 (S-C-**C**H_2-), 51.1 (H-**C**-S), 53.3 (O=C-O**C**H_3), 65.2 (S-**C**-CO_2Me), 68.9 (O**C**H_2-CH-S), 126.6, 127.9, 128.6 (**C**-arom), 140.8 (**C**-ipso),170.5, 172.2 (**C**=O). Mass (EI): m/e 420 (M^+), 293 (M^+-I). HRMS: Calcd for $C_{15}H_{17}O_4SI$: 419.98923. Found: 419.98918.

Ethyl (4,5-*cis*)-2-cyano-5-(formyloxymethyl)-4-iodotetrahydrothiophene-2-carboxylate (12d)



Obtained as a colorless oil (335 mg, 91%, ca. 1:1 mixture of isomers) after column chromatography (ethyl acetate: heptane = 1:3) which only partly crystallised upon standing.
Fast isomer:
^{1}H-NMR (300MHz) d: 1.36 (t, 3H, J= 7.2Hz, C**H$_3$**), 2.98 (dd, 1H, J= 14.0, 5.6 Hz, S-C-C**H^{3b}**H), 3.19 (dd appearing as triplet, 1H, J=14.0, 14.0 Hz, S-C-C**H^{3a}**H), 3.91 (m, 1H, **H^5**C-S), 4.30 (dd of doublets, 1H, J= 11.6, 7.6, 0.8 Hz, OC**H^{6a}**H-CH-S) partial overlap with 4.32 (m, 2H, OC**H$_2$**CH_3), 4.65 (m, 1H, **H**-C-I), 4.71 (dd of doublets, 1H, J= 11.6, 4.0, 0.8 Hz, OC**H^{6b}**H-CH-S), 8.07 (s, 1H, **H**-CO_2-). ^{13}C-NMR (75 MHz) d: 13.7 (OCH_2**C**H_3), 18.6 (H-**C**-I), 47.9 (S-C-**C**H_2-), 50.4 (S-**C**-C≡N), 51.5 (H-**C**-S), 64.3 (O**C**H_2CH_3), 66.9 (O-**C**H_2CH-S), 118.2 (C≡N), 159.9 (H-**C**=O), 164.9 (O=**C**-OEt).
Slow isomer:
^{1}H-NMR (300MHz) d: 1.36 (t, 3H, J=7.2Hz, C**H$_3$**), 2.92 (dd, 1H, J= 13.5, 11.7 Hz, S-C-C**H^{3a}**H), 3.27 (dd, 1H, J= 13.5, 6.0 Hz, S-C-C**H^{3b}**H), 3.77 (m, 1H, **H^5**C-S), 4.32 (m, 2H, OC**H$_2$**CH_3), 4.47 (dd, 1H, J= 12.0, 5.3 Hz, OC**H**H-CH-S), 4.68-4.75 (m, 2H, OC**H**H-CH-S and **H**-C-I), 8.16 (s, 1H, **H**-CO_2-).
^{13}C-NMR (75 MHz) d: 13.7 (OCH_2**C**H_3), 21.6 (H-**C**-I), 48.2 (S-C-**C**H_2-), 49.5 (S-**C**-C≡N), 52.4 (H-**C**-S), 64.1 (O**C**H_2CH_3), 66.9 (O-**C**H_2CH-S), 117.3 (**C**≡N), 159.9 (H-**C**=O), 166.4 (O=**C**-OEt).
Mass (EI): m/z 369 (M^+). HRMS: calcd for $C_{10}H_{12}NO_4SI$: 368.95318. Found: 368.95310.

Ethyl (4,5-*cis*)-2-cyano-4-iodo-5-[(propioloyloxy)methyl]tetrahydrothiophene-2-carboxylate (12e)

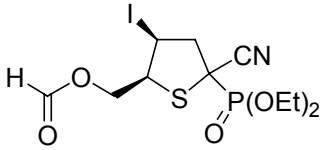


Isomers were separated by careful column chromatography (ethyl acetate: heptane = 1:3).
Fast isomer
Colorles oil (197 mg, 50 %) which crystallized upon standing, recrystallization from diisopropyl ether gave small transparent needles for X-ray diffraction analysis. Mp.38-40°C. ^{1}H-NMR (400MHz) d: 1.36 (t, 3H, J= 7.2Hz, OCH_2C**H$_3$**), 3.00 (dd, 1H, J= 13.6, 5.6 Hz, S-C-C**H^{3b}**H) overlapping with 3.00 (s, 1H, **H**-C≡C-), 3.14 (dd appearing as t, 1H, J= 13.6, 13.6Hz, S-C-C**H^{3a}**H), 3.91 (m, 1H, **H^5**C-S), 4.26-4.41 (m, 3H, O-C**H^{6a}**H-CH-S overlapping with OC**H$_2$**CH_3), 4.62 (m, 1H, **H^4**-C-I), 4.71 (dd, 1H, J= 11.4, 4.4 Hz, O-C**H^{6b}**H-CH-S). ^{13}C-NMR (75 MHz) d: 13.8 (OCH_2**C**H_3), 18.0 (H-**C**-I), 47.9 (S-C-**C**H_2-), 50.5 (S-**C**-C≡N), 51.2 (H-**C**-S), 64.4 (O**C**H_2CH_3), 69.2 (O-**C**H_2CH-S), 74.0 (-**C**≡CH), 76.4 (-C≡**C**H), 118.2 (**C**≡N), 151.7 (HC≡C**C**O_2-), 164.8 (-**C**O_2Et). Mass (EI): m/e 393 (M^+). Elemental analysis: Calcd for $C_{12}H_{12}NO_4SI$: C 36.66, H 3.08, N 3.56 %. Found: C 36.49, H 3.11, N 3.49 %.
Slow isomer
Obtained as colorles oil (170 mg, 43 %). ^{1}H-NMR (300MHz) d: 1.36 (t, 3H, J= 7.2Hz, OCH_2C**H$_3$**), 2.90 (dd, 1H, J= 13.3, 11.7 Hz, S-C-C**H^{3a}**H), 3.02 (s, 1H, **H**-C≡C-), 3.27 (dd, 1H, J= 13.3, 6.0 Hz, S-C-C**H^{3b}**H), 3.75 (m, 1H, **H^5**C-S), 4.24-4.37 (m, 2H, OC**H$_2$**CH_3), 4.51 (dd, 1H, J= 9.0, 5.8Hz, O-C**H^{6a}**H-CH-S), 4.64 (dd, 1H, J= 9.0, 4.1Hz, O-C**H^{6b}**H-CH-S), 4.72 (m, 1H, **H^4**-C-I). ^{13}C-NMR (75 MHz) d: 13.8 (OCH_2**C**H_3), 21.1 (H-**C**-I), 48.2 (S-C-**C**H_2-), 49.4 (S-**C**-C≡N), 52.0 (H-**C**-S), 64.2 (O**C**H_2CH_3), 69.2 (O-**C**H_2CH-S), 73.8 (-**C**≡CH), 76.4 (-C≡**C**H), 117.0 (**C**≡N), 151.7 (C≡C**C**O_2-), 166.5 (-**C**O_2Et). Mass (EI): m/e 393(M^+).

Crystal data and structure refinement for **12e**.

Crystal colour	transparent colorless
Crystal shape	rather regular rod
Crystal size	0.44 x 0.19 x 0.13 mm
Empirical formula	C_{12} H_{12} I N O_4 S
Formula weight	393.19
Temperature	293(2) K
Radiation / Wavelength	MoK_α (graphite mon.) / 0.71073 Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a, α = 12.9002(19) Å, 90°
(25 reflections 10.359 < θ < 12.704)	b, β = 6.9645(7) Å, 95.485(8)°
	c, γ = 16.202(2) Å, 90°
Volume	1449.0(3) $Å^3$
Z, Calculated density	4, 1.802 Mg/m^3
Absorption coefficient	2.362 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / Ω-2θ
F(000)	768
θ range for data collection	2.53 to 27.48°
Index ranges	-16<=*h*<=16, 0<=*k*<=9, -21<=*l*<=0
Reflections collected / unique	3426 / 3307 [R_{int} = 0.0427]
Reflections observed	2867 ([I_o>2σ(I_o)])
Absorption correction	Semi-empirical from Ψ-scans
Range of relat. transm. factors	1.288 and 0.813
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	3307 / 0 / 205
Goodness-of-fit on F^2	1.150
SHELXL-97 weight parameters	0.102000 0.761400
Final R indices [I>2σ(I)]	R_1 = 0.0463, wR_2 = 0.1426
R indices (all data)	R_1 = 0.0531, wR_2 = 0.1484
Largest diff. peak and hole	1.409 and -1.754 e. $Å^{-3}$

Diethyl [(4,5-*cis*)-2-cyano-5-(formyloxymethyl)-4-iodotetrahydro-2-thiophenyl]phosphonate (12g)



Isomers were separated by column chromatography (ethyl acetate: heptane = 1:3).

Fast isomer: Obtained as olorless oil (180 mg, 42 %).

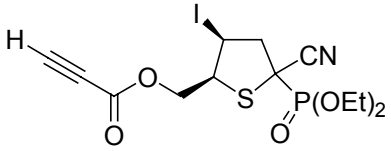
^{1}H-NMR (300MHz) d: 1.40 (t of doublets, 6H, J= 6.9, 1.8Hz, $P(OCH_2C\mathbf{H_3})_2$), 2.93 (m, 1H, S-C-C**H**H), 2.95-2.99 (m, 1H, S-C-C**H**H), 3.91 (m, 1H, $\mathbf{H^5}$C-S), 4.20 (dd, 1H, J= 11.3, 8.0Hz, O-C$\mathbf{H^{6a}}$H-CH-S), 4.25-4.37 (m, 4H, $P(OC\mathbf{H_2}CH_3)_2$), 4.58 (m, 1H, $\mathbf{H^4}$-C-I), 4.74 (dd of doublets, 1H, J= 11.3, 4.0, 0.8Hz, O-C$\mathbf{H^{6b}}$H-CH-S), 8.10 (s, 1H, **H**-CO_2-). ^{13}C-NMR (75 MHz) d: 16.2, 16.3 ($P(OCH_2\mathbf{C}H_3)_2$), 17.9 (d, I-**C**-H, J= 11.8Hz), 44.8 (d, S-**C**-P, J= 159 Hz), 46.5 (S-C-$\mathbf{C}H_2$-), 50.6 (d, J=2.2Hz, H-**C**-S), 65.4 (d, $P(O\mathbf{C}H_2CH_3)_2$, J=

7.0Hz), 65.6 (d, P(O**C**$H_2CH_3)_2$, J=7.0Hz), 67.1 (O-**C**H_2CH-S), 118.2 (C≡N), 160.1 (H-**C**O_2-). Mass (EI): m/e 433 (M^+), HRMS: calcd for $C_{11}H_{17}NO_5PSI$: 433.96098. Found: 433.96104.

Slow isomer:

Obtained as colorles oil (200 mg, 46 %) which crystallized upon standing, recrystallization from diisopropyl ether gave small transparent needles. Mp.46-47°C. ^{1}H-NMR (300MHz) d: 1.40 (t, 6H, J= 6.9 Hz, P(OCH_2C**H$_3$)$_2$**), 2.91-3.20 (m, 2H, S-C-C**H$_2$**-CHI), 3.70 (m, 1H, **H^5**C-S), 4.32 (m, 4H, P(OC**H$_2$**$CH_3)_2$), 4.47 (dd, 1H, J= 11.9 , 5.2 Hz, O-C**H**H-CH-S), 4.66-4.79 (m, 2H, O-C**H**H-CH-S and I-C-**H**), 8.16 (**H**-CO_2-). ^{13}C-NMR (75 MHz) d: 16.3 (2x doublet appearing as triplet, J=6.0 Hz, P(OCH_2**C**$H_3)_2$), 22.1 (d, J= 2.5Hz, I-**C**-H), 43.9 (d, J= 159 Hz, S-**C**-P), 47.0 (d, J=2.5 Hz, S-C-**C**H_2-CHI), 52.1 (H-**C**-S), 65.2 (d, J= 7.3 Hz, P(O**C**$H_2CH_3)_2$), 66.1 (d, J= 7.3 Hz, P(O**C**$H_2CH_3)_2$), 67.0 (O-**C**H_2CH-S), 117.6 (**C**≡N), 159.8 (H-**C**O_2-). Mass (EI): m/e 433 (M^+). Elemental analysis: Calcd for $C_{11}H_{17}NO_5PSI$: C 30.50, H 3.96, N 3.23 %. Found: C 30.31 , H 3.86, N 3.30 %.

[(2,3-*cis*)-5-cyano-5-(diethoxyphosphoryl)-3-iodotetrahydro-2-thiophenyl]methyl propiolate (12h)



Fast isomer:

Obtained as colorless oil (220 mg, 48 %) after column chromatography (ethyl acetate : heptane = 1:2)

^{1}H-NMR (300MHz) d: 1.40 (triplet of doublets, 6H, J= 2.7, 8.4Hz, P(OCH_2C**H$_3$)$_2$**), 2.82 (m, 1H,S-C-C**H**H-CHI), 2.97 (dd of doublets, 1H, J= 12.8, 5.3, 1.1Hz , S-C-C**H**H-CHI), 3.07 (s, 1H, **H**-C≡C-), 3.97 (m, 1H, **H^5**C-S), 4.20-4.38 (m, 5H, P(OC**H$_2$**$CH_3)_2$ overlapping with O-C**H**H-CH-S), 4.56 (m, 1H, I-C-**H^4**), 4.66 (dd, 1H, J= 11.4, 4.3 Hz, O-C**H**H-CH-S). ^{13}C-NMR (75 MHz) d: 16.2 (d, J= 2.5Hz, P(OCH_2**C**H_3)), 16.3 (d, J= 2.1Hz, P(OCH_2**C**H_3)), 17.1 (d, J= 11.6Hz, I-**C**-H), 44.9 (d, J= 159Hz, S-**C**-P), 46.5 (d, J= 2.0Hz, S-C-**C**H_2-CHI), 50.1 (H-**C**-S), 65.5 (d, J=6.5 Hz, P(O**C**$H_2CH_3)_2$), 69.5 (O-**C**H_2CH-S), 73.9 (-**C**≡CH), 76.1 (C≡**C**H), 118.1 (**C**≡N), 151.7 (**C**=O). Mass (EI): m/e 457(M^+). Exact mass: calcd for $C_{13}H_{17}NO_5PSI$: 457.9610. Found: 456.9610.

Slow isomer:

Obtained as colorles oil (205 mg, 45 %) which crystallized upon standing. Crystallization from diisopropyl ether gave small transparent needles suitable for X-ray diffraction analysis.

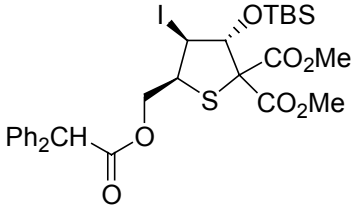
Mp. 137-140°C. ^{1}H-NMR (300MHz) d: 1.42 (triplet of doublets, 6H, J= 8.4Hz, P(OCH_2C**H$_3$)$_2$**), 2.90-3.20 (m, 2H, S-C-C**H$_2$**-CHI), 3.02 (s, 1H, **H**-C≡C-), 3.69 (m, 1H, **H^5**C-S), 4.25-4.41 (m, 4H, P(OC**H$_2$**$CH_3)_2$), 4.51 (dd, 1H, J= 12.0, 5.7Hz, O-C**H^{6a}**H-CH-S), 4.63 (dd, 1H, J= 12.0, 4.2Hz, O-C**H^{6b}**H-CH-S), 4.77 (m, 1H, I-C-**H^4**). ^{13}C-NMR (75 MHz) d: 16.3 (d, J≈ 7Hz, P(OCH_2**C**H_3)), 16.4 (d, J≈ 7Hz, P(OCH_2**C**H_3)), 21.6 (d, J= 2.6 Hz, I-**C**-H), 43.9 (d, J= 159 Hz, S-**C**-P), 47.1 (d, J= 2.5 Hz, S-C-**C**H_2-CHI), 51.8 (H-**C**-S), 65.2 (d, J= 7.4Hz, P(O**C**H_2CH_3)), 66.3 (d, J= 7.9 Hz, P(O**C**H_2CH_3)), 69.3 (O-**C**H_2CH-S), 73.9 (**C**≡CH), 76.3 (C≡**C**H), 117.4 (**C**≡N), 151.7 (**C**=O). Mass (EI): m/e 457 (M^+). Elemental analysis: Calcd for $C_{13}H_{17}NO_5PSI$: C 34.15, H 3.75, N 3.06%. Found: C 34.36, H 3.69, N 3.04 %.

Crystal data and structure refinement for **12h**

Crystal colour	transparent colorless
Crystal shape	regular rod
Crystal size	0.60 x 0.16 x 0.14 mm
Empirical formula	C_{13} H_{17} I N O_5 P S
Formula weight	457.21
Temperature	293(2) K
Radiation / Wavelength	MoK_α(graphite mon.) / 0.71073Å
Crystal system, space group	Monoclinic, P21/c
Unit cell dimensions	a, α= 8.2923(6) Å, 90°
(25 reflections 10.243 < θ < 12.761)	b, β= 17.8310(13) Å, 91.743(8)°

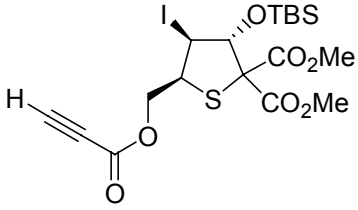
	c, γ= 12.2414(11) Å, 90°
Volume	1809.2(2) $Å^3$
Z, Calculated density	4, 1.679 Mg/m^3
Absorption coefficient	1.993 mm^{-1}
Diffractometer / scan	Enraf-Nonius CAD4 / Ω-2θ
F(000)	904
θ-range for data collection	2.71 to 27.41°
Index ranges	-10<=*h*<=10, -23<=*k*<=0, -15<=*l*<=0
Reflections collected / unique	4294 / 4106 [R_{int} = 0.0242]
Reflections observed	3097 ([I_o>2σ(I_o)])
Absorption correction	Semi-empirical from Ψ-scans
Range of relat. transm. factors	1.066 and 0.972
Refinement method	Full-matrix least-squares on F^2
Computing	SHELXL-97 (Sheldrick, 1997)
Data / restraints / parameters	4106 / 0 / 229
Goodness-of-fit on F^2	1.055
SHELXL-97 weight parameters	0.058600 1.847500
Final R indices [I>2σ(I)]	R_1 = 0.0432, wR_2 = 0.1085
R indices (all data)	R_1 = 0.0624, wR_2 = 0.1201
Largest diff. peak and hole	0.981 and -0.694 e. $Å^{-3}$

Dimethyl (3,4-*trans*-4,5-*cis*)-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-5-[(2,2-diphenylacetyl)oxy]methyl-4-iodotetrahydrothiophene-2,2-dicarboxylate (18a)



Compound (350 mg; ca.52%) could not be separated from an unknown impurity. ^{1}H-NMR (300MHz) d: 0.05 (s, 3H, **H$_3$**CSiMetBu), 0.22 (s, 3H, **H$_3$**CSiMetBu), 0.90 (s, 9H, (**H$_3$**C)$_3$CSiMe$_2$), 3.53 (m, 1H, **H**-C-S), 3.68 (s, 3H, $CO_2C\mathbf{H_3}$), 3.74 (s, 3H, $CO_2C\mathbf{H_3}$), 4.47 (d, 2H, J=4.5 Hz, -O-C**H$_2$**-CH-S), 4.80 (dd, 1H, J= 7.2, 9.7 Hz), 5.15 (s, 1H, $Ph_2C\mathbf{H}C{=}O$), 5.26 (d, 1H, J= 9.7 Hz, **H**-C-OTBDMS), 7.18-7.35 (m, aromatic). ^{13}C-NMR (75 MHz) d: -4.7 (H$_3$**C**SiMetBu), -4.2 (H$_3$**C**SiMetBu), 18.1 ((H$_3$C)$_3$**C**SiMe$_2$), 26.3 ((H$_3$**C**)$_3$CSiMe$_2$), 33.7 (**C**-I), 44.6 (H-**C**-S), 53.2 (2x O=C-O**C**H$_3$), 63.9 (S-**C**-(CO$_2$Me)$_2$), 69.0 (O-**C**H$_2$CH-S), 82.4 (H**C**-OSiMe$_2$tBu), aromatic C's overlap with impurity, 138.4, 139.8 (2x **C**-ipso), 168.6 ($Ph_2CH\mathbf{C}O_2$-), 171.3, 171.9 (2x O=**C**-OMe). Mass: (CI) m/e 685 (M+).

Dimethyl (3,4-*trans*-4,5-*cis*)-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4-iodo-5-[(propioloyloxy)methyl]tetrahydrothiophene-2,2-dicarboxylate(18b)



Obtained as white solid (515 mg, 95 %), attempts to obtain suitable crystals for X-ray diffraction analysis failed. Mp.108-110°C (dec). ^{1}H-NMR (400MHz) d: 0.08 (s, 3H, **H$_3$**CSiMetBu), 0.32 (s, 3H, **H$_3$**CSiMetBu), 0.90 (s, 9H, (**H$_3$**C)$_3$CSiMe$_2$), 3.00 (s, 1H, **H**C≡C-), 3.60 (m, 1H, **H**-C-S), 3.77 (s, 3H, $CO_2C\mathbf{H_3}$), 3.80 (s, 3H, $CO_2C\mathbf{H_3}$), 4.42 (dd, 1H, J=11.6, 6.0Hz, O=C-O-C**H^{6a}**H-), 4.57 (dd, 1H, J= 11.6 ,3.6Hz, O=C-O-C**H^{6b}**H-), 4.84 (dd, 1H, J=7.2, 9.9Hz, **H**-C-I), 5.20 (d, 1H, J= 9.9 Hz, **H**-C-OTBS). ^{13}C-NMR (75 MHz) d: -4.9 (H$_3$**C**SiMetBu), -4.2 (H$_3$**C**SiMetBu), 18.2 ((H$_3$C)$_3$**C**SiMe$_2$), 26.1 ((H$_3$**C**)$_3$CSiMe$_2$), 32.7 (**C**-I), 43.9 (H-**C**-S), 53.2, 53.3 (2x O=C-O**C**H$_3$), 63.6 (S-**C**-(CO$_2$Me)$_2$), 70.2 (O-**C**H$_2$CH-S), 74.1 (**C**≡CH), 75.7 (C≡**C**H), 82.4 (H**C**-OSiMe$_2$tBu), 151.8

(HC≡C-**C**=O), 168.1, 168.6 (O=**C**-OMe). Mass (CI): m/e 543 (M^++H). Elemental analysis: Calcd for $C_{18}H_{27}O_7SSiI$: C 39.85, H 5.02%. Found: C 39.53, H 5.12 %.

4.4 References

1] **a**] M.M. Abelman, *Tetrahedron Lett.* **32**, 7389 (1991).

b] K. Beelitz, G. Höhne and K. Praefcke, *Z. Naturforsch.* **33b**, 417 (1978).

c] G. W. Kirby and W.M. Mc Gregor, *J. Chem. Soc. Perkin Trans I*, 3175 (1990).

d] E. Vedejs, T.H. Eberlein, D. J. Mazur, C.K. McClure, D.A.Perry, R. Ruggeri, E. Schwarz, J.S. Stults, D.L. Varie, R.G. Wilde and S. Wittenberger, *J. Org. Chem*. **51**, 1556 (1986).

e] C.M. Bladon, I.E.G. Ferguson, G.W. Kirby, A.W. Lochead and D.C. McDougall, *J. Chem. Soc. Perkin Trans I*, 1541 (1985).

f] G. Capozzi, R.W. Franck, M.Mattioli, S. Menichetti, C. Nativi and G. Valle, *J. Org. Chem*. **60**, 6416 (1995) and references therein.

g] J.L. Hermann, G.R. Kieczykowsky and R.H. Schlessinger, *Tetrahedron Lett*. 2433 (1973).

h] C.M. Bladon, I.E.G. Ferguson, G.W. Kirby, A.W. Lochead and D.C. McDougall, *J. Chem. Soc., Chem. Commun.* 423 (1983).

2] **a**] B. Heuzé, R. Gasparova, M.Heras and S. Masson, *Tetrahedron Lett.* **41**, 7327-7331 (2000).

b] J. Prabhakaran, H. Lhermitte, J.Das, T.K. Sasi-Kumar and D.S. Grierson, *Synlett*. **5**, 658 (2000).

c] D. Adam, A. A. Freer, N. W. Isaacs, G. W. Kirby, A. Littlejohn and M.S. Rahman, *J. Chem. Soc. Perkin Trans. I*, 1261 (1992) and refs therein.

d] G. W. Kirby, and A.W. Lochead, *J.Chem. Soc., Chem. Commun.* 1325 (1983).

e] G. Capozzi, S. Menichetti, C. Nativi, A. Rossi and G. Valle, *Tetrahedron* **48**, 9023 (1992).

3] **a**] B.Zwanenburg, T.J.G. Damen, H.J.F. Philipse, R.C. de Laet and A.C.B. Lucassen, *Phosphorous, Sulfur and Silicon* **153-154**, pp 119-136, (1999).

b] B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **101**, 1, (1982).

c] B. Zwanenburg, *Phosphorous, Sulfur and Silicon* **43**, 1, (1989).

d] G.Capozzi, P. Fratini, S. Menichetti and C. Nativi, *Tetrahedron* **52**, 37, 12233 (1996).

e] G.Capozzi, S. Menichetti, C. Nativi and A. Rossi, *Tetrahedron Lett.* **34**, 4253 (1993).

f] A.R. Maguire, P.G. Kelleher, G.Fergueson and J.F. Gallagher *Tetrahedron Lett.* **39**, 3849 (1998).

g] H.Morita, M.Takeda, T.Yoshimura, T. Fjii, S.Ono and C.Shimazaki, *J.Org.Chem.* **64**, 6730 (1999).

h] B.G.Lenz, H. Regeling, H.L.M. van Rozendaal and B. Zwanenburg, *J. Org. Chem*. **50**, 2930 (1985).

i] J.B.M. Rewinkel and B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **109**, 190 (1990).

j] I.J.W. Still and D.K.T. Wilson, *Can. J. Chem.* **70**, 964 (1992).

4] J. Drabowicz and S. Oae, *Synthesis* 404, (1977).

5] **a**] R. C. DeLaet, *Ph.D. Thesis*, University of Nijmegen 1995).

b] J. B. M. Rewinkel, *Ph.D. Thesis*, University of Nijmegen (1992).

6] T.J.G. Damen, *Ph.D. Thesis*, University of Nijmegen, (2002).

7] **a**] J.F Biellmann, J.B. Ducep and J.J. Vicens, *Tetrahedron*, **32**, 1801 (1976).

b] S.D. Larsen , P.V. Fisher, B.E. Libby, R.M. Jensen, S.A. Mizsak and W. Watt, *J. Org. Chem.*, **61**, 4725 (1996).

c] G. W. Kirby, M.P. Mahajan, and M.S. Rahman, *J. Chem. Soc. Perkin Trans I*, 2033 (1991).

d] E. Block and A. Wall, *Tetrahedron Lett.* 26, 1425 (1985).

e] E. Block, A. Wall and J. Zubieta, *J. Am. Chem. Soc.*,**107**, 1783 (1985).

f] E. Block and A. Wall, *J. Org. Chem.*, **52**, 809 (1987).

g] S.D. Larsen, *J. Am. Chem. Soc.*, **110**, 5932 (1988).

h] M. Reglier and S.A. Julia, *Tetrahedron Lett.*, **26**, 2319 (1985).

i] W. Ando, M. Yamada, E. Matsuzaki and T. Migita, *J. Org. Chem.*, **37**, 3791 (1972).

j] S. Mageswaran, W.D. Ollis and I.O., Sutherland, *J. Chem. Soc. Perkin Trans I*, 1953 (1981).

k] G.W. Kirby, A.W. Lochead and G.N. Sheldrake, *J. Chem. Soc.Chem. Commun.* 922 (1984).

8] **a**] E. Vedeis, T.H. Eberlein and D.L. Varie, *J. Am. Chem. Soc.* **104**, 1445 (1982).

b] H. Ishibashi, Y. Kitano, M. Okada and M. Ikeda, *Tetrahedron Lett.* **25**, 4231 (1984).

c] E.J. Corey and S.W. Walinski, *J. Am. Chem. Soc.* **94**, 8932 (1972).

d] T. Kataoka, T. Iwama, T. Tsutsumi, Y. Nakamura, H. Matsumoto, H. Shimizu and M. Hori, *J. Chem. Res. (S)*, 393 (1992).

9] **a**] W. Ando, S. Kondo, K. Nakayama, K. Ichibori, K. Kohda, H. Yamamoto, I. Imai, S. Nakaido and T. Migita, *J. Am. Chem. Soc.* **94**, 3870 (1972).

b] S. Mageswaran, W.D. Ollis and I.O., Sutherland, *J. Chem. Soc.Chem. Commun.,* 656 (1973).

10] N.A. Hughes and C.J. Wood, *J. Chem. Soc. Perkin Trans I,* 695 (1986).

11] H-J. Altenbach and G.F. Merhof, *Tetrahedron Asymm.*, **7**, 3087 (1996).

12] D.M. Vyas and G.W. Hay, *Can. J. Chem.* **53**, 1362 (1975).

13] T.J.G. Damen and B. Zwanenburg, unpublished results.

14] **a**] K. Eichinger, H. Berbalk, E. Machat and J. Winner, *J. Chem. Res*. 1625 (1983).

b] M. Schwab and W. Sundermeyer, *Chem. Ber.* **119**, 2485 (1986).

c] H. Fritz and W. Sundermeyer, *Chem. Ber*. **122**, 1757 (1989).

d] D.G. Smith, *J. Chem. Soc. Perkin Trans. I*, 3187 (1990).

15] **a**] R.B. Woodward, F.V.J. Brutcher Jr, *J. Am. Chem. Soc.*, **80**, 209 (1958).

b] L. Magnoni, M. Adolfini, G. Barone and M. Parrilli, *Tetrahedron Lett.* **14**, 1581 (1976).

c] D. Jasserand, J.P. Girard and R. Granger, *Tetrahedron Lett.* **17**, 4485 (1976).

d] G. Cardillo and M. Orena, *Tetrahedron*, **46**, 3321 (1990).

e] J. Rodriguez, J-P. Dulcère, *Synthesis* 1177 (1993).

f] S. Knapp, *Chem. Soc. Rev.* **28**, 61 (1999).

g] Houben Weyl, *Methoden der Organischen Chemie*, Band E-21, Chapter 7, p.5337, Stuttgart/New York (1995) and references therein.

16] K.R. Lawson, B.P. McDonald, O. S. Mills, R.W. Steele, J. K. Sutherland, T.J. Wear, A. Brewster and P. R. Marsham, *J. Chem. Soc. Perkin Trans. I*, 663 (1988).

17] Suitable crystals were obtained by slow crystallisation of **2a** from dilute solutions in diisopropyl ether.

18] The structure contains two independent molecules in the asymmetric unit. These molecules are related by a non-crystallographic center of symmetry.

19] **a**] X-F. Ren, M. I. Konaklieva, E. Turos, L.M. Krajkowsky, C.H. Lake, T.S. Janik and M. R. Churchill, *J. Org. Chem*. **60**, 6484 (1995) and references therein.

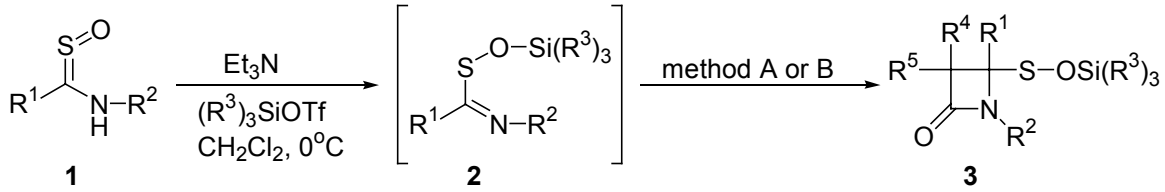
b] K.C. Nicolaou, W.E. Barnette and R.L. Magolda, *J. Am. Chem. Soc.* **103**, 3472 and 3486 (1981).

Summary

Subject of this thesis was the use of sulfines as starting materials for the synthesis of heterocyclic derivatives.

Chapter 1 gives a brief overview of the different classes of sulfines, their properties and the most important methods for their synthesis.

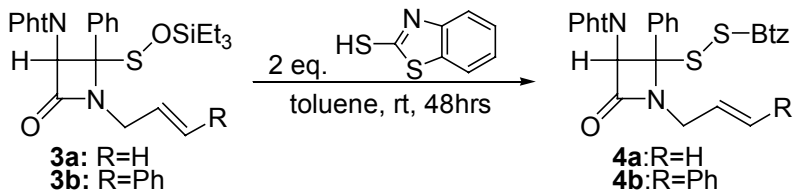
Chapter 2 deals with the use of aminosulfines **1** as starting materials for the preparation of new β-lactam derivatives (Scheme 1). This was achieved by treating aminosulfines with trialkylsilyl triflates in the presence of triethylamine to produce *O*-silyl esters of iminosulfenic acids **2**. These compounds were found to be very sensitive to hydrolysis during isolation. When kept *in situ* they were shown to undergo [2+2] ketene/imine cyclization yielding new β-lactam derivatives **3** with an *O*-silyl sulfenate moiety on the 4-position of the β-lactam ring in a one-pot procedure.



Method A: Acid chloride (1.5 eq) is added to *in situ* prepared **2** and 2.5equiv. of Et_3N at –78°C.
Method B: Solution of *in situ* prepared **2** is added via canulla to *in situ* prepared ketene at -78°C.

Scheme 1

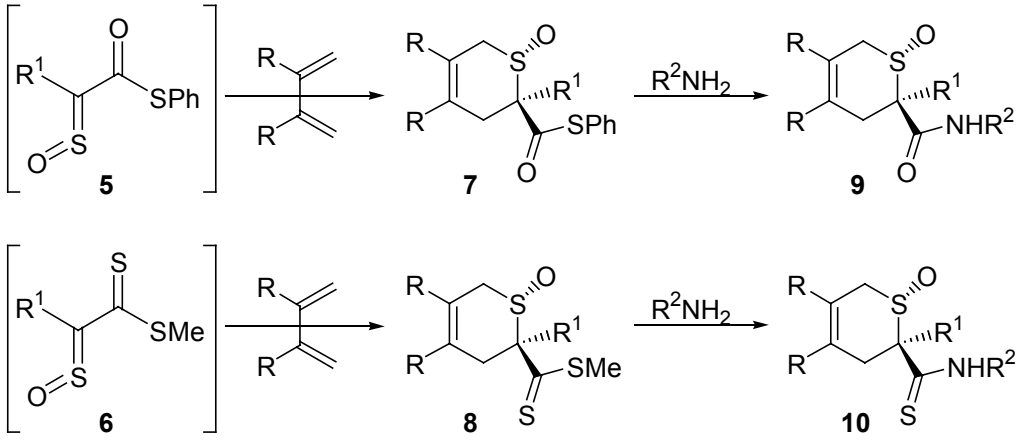
This is the first example of the synthesis of β-lactams containing a silyl sulfenate moiety on C-4 of the ring that does not start from penicillin *S*-oxides.
Attempts to modify the silylsulfenate moiety of the β-lactams was very problematic. Only the reaction with 2-mercaptobenzothiazole worked to give the corresponding unsymmetrical disulfides **4** (Scheme 2).



Scheme 2

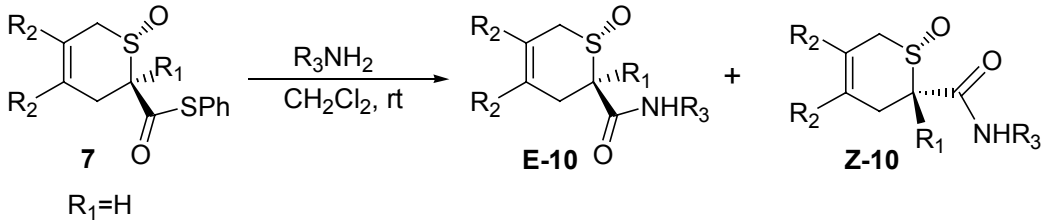
Attempts to perform ring-closure reactions with the latter to obtain bicyclic penam and/or cepham derivatives failed.

In **chapter 3** the synthesis of some new 3,6-dihydro-2*H*-thiopyran *S*-oxides **9** and **10** containing a secondary or primary amide or thioamide function in the 2-position were prepared. The key step in their synthesis involved the [4+2]-cycloaddition with several 1,3-butadienes of new α-oxo and α-thioxo sulfines **5** and **6** (obtained from thiolesters and dithioesters) giving **7** and **8**, respectively. Yields for derivatives **7** were good to acceptable for several 2,3-dialkyl-butadienes (R= Me, C_5H_{11}, C_6H_{13}, $C_{10}H_{21}$), whereas yields of products **8** were between 12% (R^1=Ph) and 40% (R^1=C_4H_9) and only 2,3-dimethyl-1,3-butadiene gave cycloadducts. Subsequent reaction of the latter with amines then lead to **9** and **10** (Scheme 3).



Scheme 3

Thiopyran *S*-oxides **7** with a proton on C-2 carbon (R^1=H) showed isomerisation upon reaction with amines to *E*- and *Z*-**10** (Scheme 4).



R_1=H

Scheme 4

Compounds **9** and **10** can be regarded as analogues of derivatives **11** (Aprikalim®) and **12** that were shown to have interesting biological activities; **11** has anti-hypertensive and anti-anginal properties and derivatives of **12** were shown to possess activity in the systemic inhibition of the enzyme Acyl-CoA: cholesterol acyl transferase (ACAT). Such compounds are believed to slow down or even reverse the artherosclerotic process.

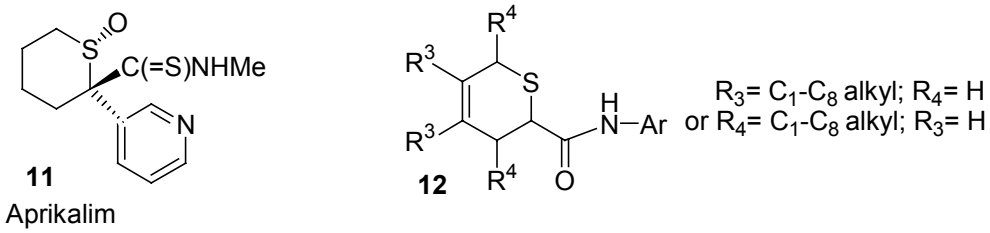
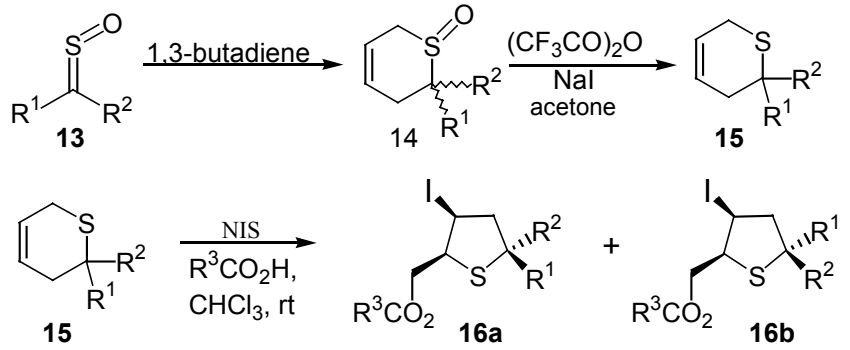


Figure 1

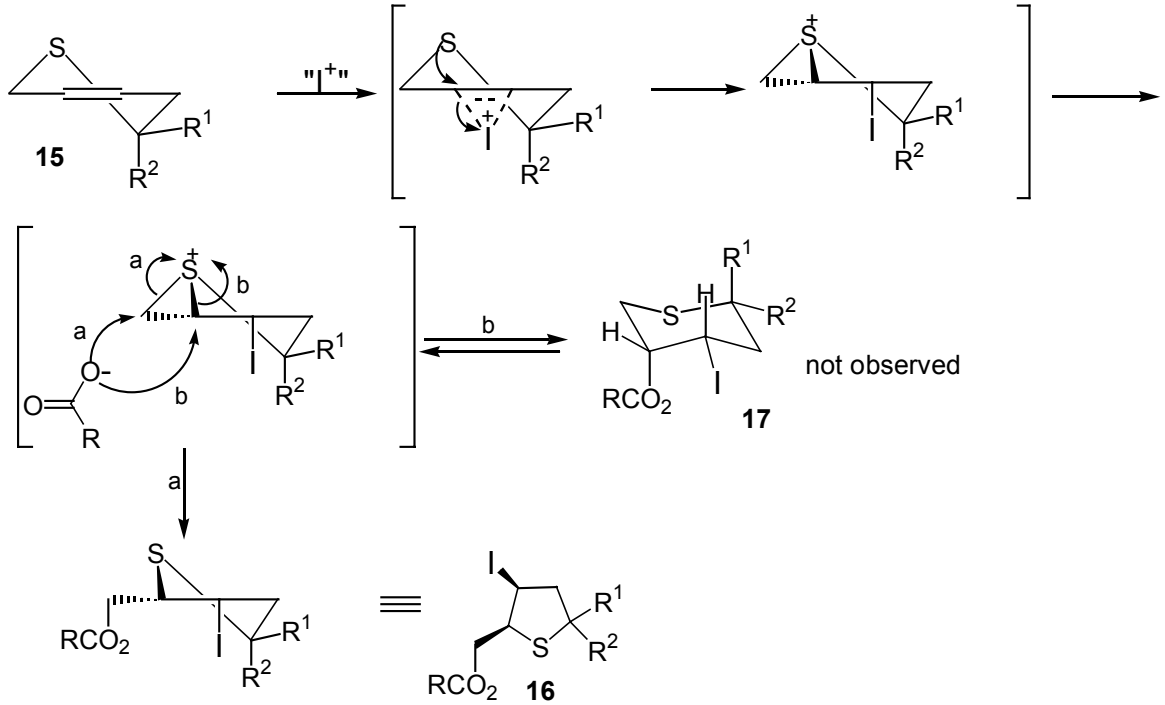
In **chapter 4** sulfines **13** form the basis for dihydrothiopyrans **15**. Upon treatment with *N*-iodosuccinimide in the presence of three equivalents of a carboxylic acid these thiopyrans underwent an iodo-oxyacylation with simultaneous ring contraction resulting in the formation of new tetrahydrothiophenes (thiolanes) **16** in good to excellent yields (Scheme 5).



Scheme 5

Increasing acid strength lead to higher reaction rates. The lower limit in acid strength was benzoic acid that failed to react. Treatment of unsymetrically substituted dihydrothiopyrans ($R^1 \neq R^2$) gave 1:1 mixtures of isomers.

It was shown that the ring contraction proceeds in a stereoselective fashion giving only derivatives of **16** with a *cis*-relationship regarding C-4 and C-5 of the ring (Scheme 6). This selectivity can be attributed to the stereochemical restrictions imposed by the cyclic structure of the dihydrothiopyrans (Scheme 6).



Scheme 6

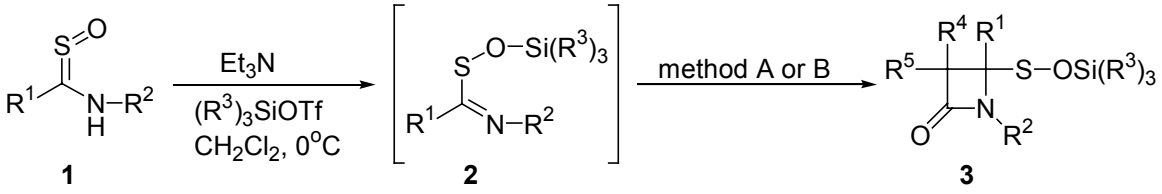
The formation of tetrahydrothiopyran derivatives **17** was not observed. Monitoring of the reaction by ^{1}H-NMR did not show any presence of **17** as intermediates either, only formation of **16** at the expense of **15** was seen.

Samenvatting

Het onderzoek in dit proefschrift had tot doel het gebruik van sulfinen (thiocarbonyl *S*-oxiden) als uitgangsstoffen voor de synthese van nieuwe heterocyclische verbindingen te onderzoeken.

Hoofdstuk 1 geeft een kort overzicht van de verschillende klassen van sulfinen, enkele belangrijke eigenschappen en synthesemethoden.

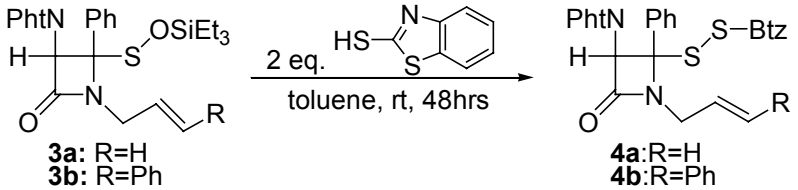
Hoofdstuk 2 richt zich op het gebruik van aminosulfinen **1** als uitgangsstoffen voor de synthese van nieuwe β-lactam derivaten (Schema 1). Behandeling van aminosulfinen met trialkylsilyltriflaten in de aanwezigheid van triethylamine leidde tot de vorming van *O*-silyl esters van iminosulfeenzuren **2**. Deze verbindingen bleken zeer gevoelig voor hydrolyse en isolatie was erg problematisch. Indien verbindingen **2** *in situ* werden bereid en vervolgens werden behandeld met (eveneens *in situ* bereidde) ketenen werden via een [2+2]-keteen/imine cyclisatie nieuwe β-lactam derivaten **3** verkregen met een *O*-silyl sulfenaat functie op de 4-positie van de β-lactam ring. Dit is de eerste synthese van dergelijke β-lactamen die niet uitgaat van peniciline *S*-oxiden.



Methode A: Zuurchloride (1.5 eq) wordt toegevoegd aan *in situ* bereid **2** en 2.5equiv. Et_3N bij –78°C.
Methode B: Oplossing van *in situ* bereid **2** wordt toegevoegd via canulla aan *in situ* bereid keteen bij -78°C.

Schema 1

Derivatiseren van de *O*-silyl sulfenaat groep was problematisch, alleen de reactie met 2-mercaptobenzothiazool leverde isoleerbare disulfiden **4** op (Schema 2).

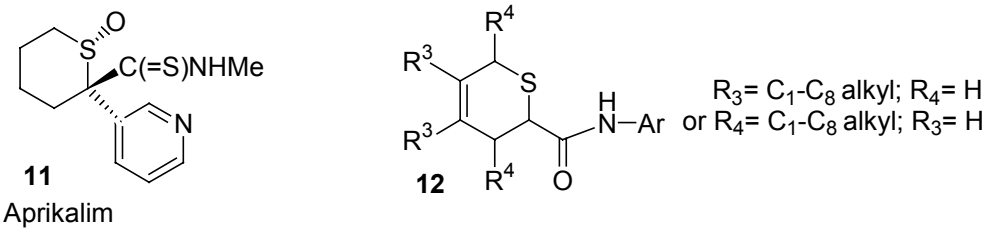


Schema 2

Pogingen om ringsluitingsreacties met derivaten **4** te bewerkstelligen met als doel de vorming van penam/cepham verbindingen, leverde geen resultaten op.

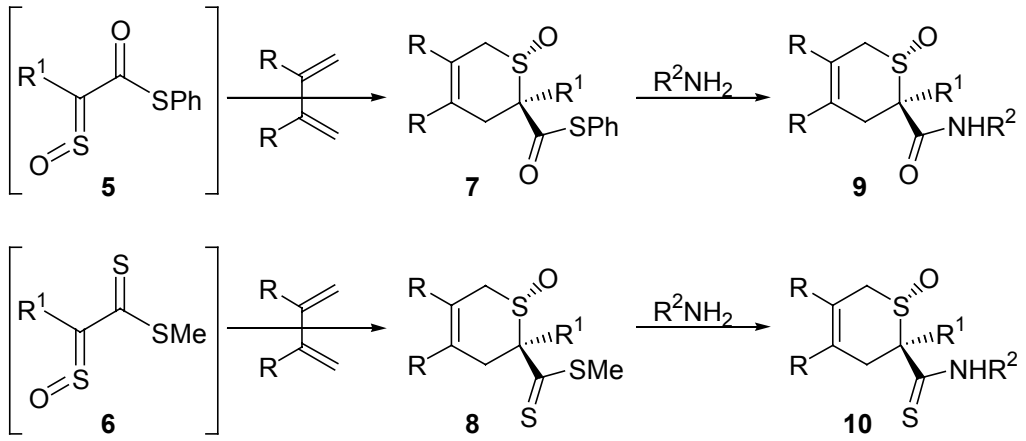
Hoofdstuk 3 beschrijft de bereiding van nieuwe 3,6-dihydro-2H-thiopyran *S*-oxiden **9** en **10** met respectievelijk een carboxamide- en een thiocarboxamidefunctie op de 2-positie.

Verbindingen **9** en **10** kunnen worden beschouwd als analoga van **11** (Aprikalim®) en **12** (Figuur 1), deze vertonen interessante biologische eigenschappen. Aprikalim® heeft anti-hypertensieve eigenschappen en van derivaten van **12** is aangetoond dat ze activiteit bezitten voor systemische inhibitie van het enzym Acyl-CoA:cholesterol acyl transferase (ACAT). Van dergelijke verbindingen zouden het artherosclerotische process kunnen remmen of eventueel zelfs kunnen omdraaien.



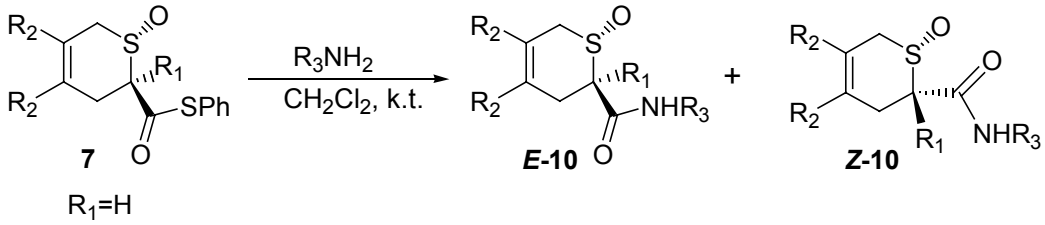
Figuur 1

De belangrijkste stap in de synthese van **9** en **10** was de Diels-Alder-reactie van de nieuwe, *in situ* bereide sulfinen **5** en **6** (op hun beurt bereid uit thiolesters en dithioesters) met verschillende 2,3-dialkyl-1,3-butadienen (Schema 3). Dit gaf respectievelijk de cycloadducten **7** en **8**, de opbrensten voor verbindingen **7** waren acceptabel tot goed. De verbindingen **8** werden slechts in matige tot teleurstellende opbrensten verkregen. Reactie van **7** en **8** met verschillende primaire aminen en ammonia leverde de gewenste producten **9** en **10** in goede opbrengsten.



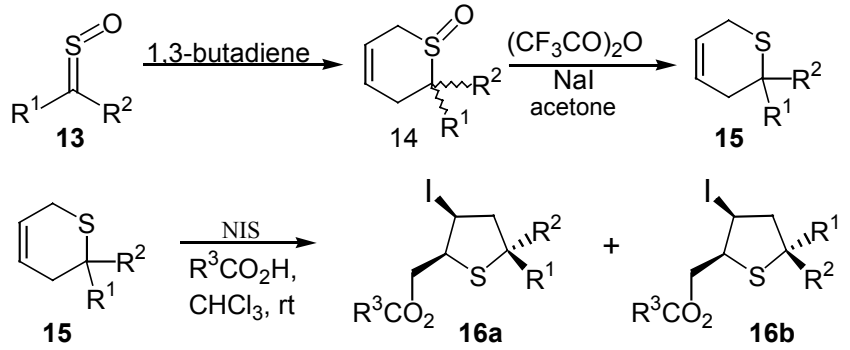
Schema 3

Dihydrothiopyran *S*-oxiden **7** met een proton op C-2 van de ring isomeriseerden in de reactie met aminen (Schema 4), waarbij *E*- en *Z*-**10** werden verkregen.



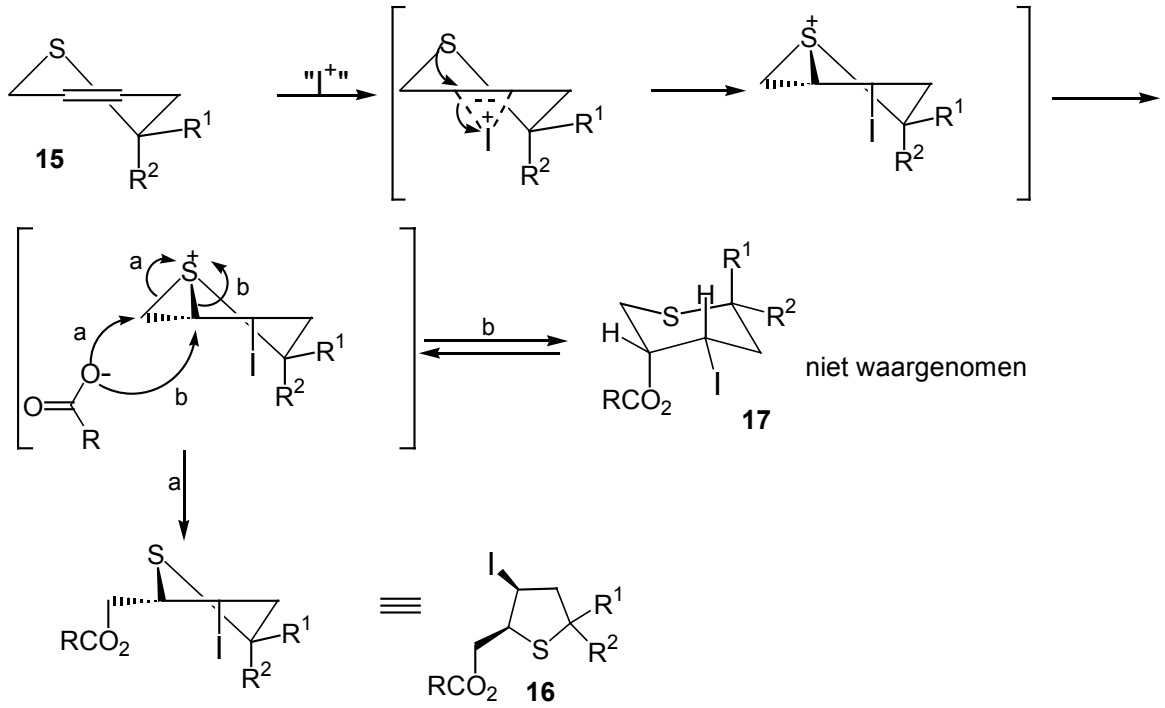
Schema 4

In **hoofdstuk 4** vormen sulfinen de uitgangsstoffen voor dihydrothiopyran derivaten **15**. Hier werd aangetoond dat reactie van verbindingen **15** met *N*-iodosuccinimide i.a.v. drie equivalenten carbonzuur leidde tot de vorming van nieuwe gefunctionaliseerde tetrahydrothiofenen (thiolanen) **16** via een zogenaamde iodo-oxyacylerings-reactie en simultane ringcontractie (Schema 5). De opbrengsten waren in veel gevallen erg goed.



Schema 5

Het bleek dat een hogere zuursterkte van de carbonzuren leidde tot snellere reactie en hoge opbrengsten. Mierenzuur en trichloorazijnzuur vertoonden de hoogste reactiviteit, de ondergrens qua reactiviteit werd bereikt bij benzoëzuur waarmee geen product werd gevormd. Indien niet-symmetrisch gesubstitueerde 3,6-dihydro-2*H*-thiopyranen **15** ($R^1 \neq R^2$) werden gebruikt, leverde dit 1:1 mengsels van isomeren (Schema 5). Verder werd aangetoond dat deze ringcontractie stereoselectief verliep, alle verkregen tetrahydrothiofenen vertoonden een *cis*-relatie m.b.t. de substituenten op C-4 en C-5 van de ring (Schema 5). Deze selectiviteit kon worden toegeschreven aan de stereochemische beperkingen die worden veroorzaakt door de cyclische structuur van de 3,6-dihydro-2*H*-thiopyranen **15** (Schema 6).



Schema 6

De vorming van thiopyran derivaten **17** werd niet waargenomen, volgen van de reactie m.b.v. ^{1}H-NMR gaf geen aanwijzingen dat **17** als eventueel intermediair aanwezig was. Slechts vorming van **16** en verdwijnen van **15** werd waargenomen.

Publications and presentation

Publications

J.B. van der Linden, A.C.B. Lucassen and B.Zwanenburg, '*Synthesis of thiophene-2-phosphonates via α,β-unsaturated sulfines as intermediates*', *Recl. Trav. Chim. Pays Bas* **113**, 547 (1994).

B.Zwanenburg, T.J.G. Damen, H.J.F. Philipse, R.C. de Laet and A.C.B. Lucassen; '*Advances in sulfine chemistry*', *Phosphorous, Sulfur & Silicon*, **1999**, Vol. 153-154, pp 119-136.

A.C.B. Lucassen and B.Zwanenburg, '*Silyl esters of iminosulfenic acids*', *Phosphorus, Sulfur & Silicon*, **1999**, Vol. 153-154, pp 389-390.

A.C.B. Lucassen and B. Zwanenburg, '*Ring contraction of 3,6-dihydro-2H-thiopyrans to thiolanes by a iodo oxyacetylation reaction*' Accepted for publication in *Eur. J. Org. Chem.*

A.C.B. Lucassen and B. Zwanenburg. '*Synthesis of 2-Carboxamido- and 2-thiocarboxamido-3,6-dihydro-2H-thiopyran S-oxides* ' To be submitted.

A.C.B. Lucassen and B. Zwanenburg, '*A one-pot synthesis of new β-lactam derivatives from thioamide S-oxides*' To be submitted.

Presentations

A.C.B. Lucassen and B.Zwanenburg, '*Sulfine based synthesis of new functionalised thiopyrans and tetrahydrothiophenes*', 19th International Symposium on the Organic Chemistry of Sulfur (ISOCS 19) 2000, Sheffield, United Kingdom, Oral- and Poster Communication.

A.C.B. Lucassen and B.Zwanenburg, '*New chemistry of amino- and α-oxo-sulfines*' Symposium University of Sydney 1999, Sydney, Australia. Oral- and Poster Communication.
During the study tour of the research group to Australia.

A.C.B. Lucassen and B.Zwanenburg, '*Silyl esters of iminosulfenic acids*' 18th International Symposium on the Organic Chemistry of Sulfur (ISOCS 18) 1998, Florence, Italy, Oral Communication.

A.C.B. Lucassen and B.Zwanenburg, '*β-lactams from aminosulfines, first results*' Bologna/Nijmegen Minisymposium BONIMI V, 1996, Camerino, Italy. Oral Communication.

Dankwoord

Als eerste wil ik Prof. Dr. Binne Zwanenburg bedanken om mij de mogelijk te geven om met grote vrijheid mijn promotie onderzoek in zijn groep te verrichten. Buiten dit wil ik mijn promotor ook bedanken voor een aantal zaken die een zeer positieve invloed op mijn priveleven hebben gehad.

I want to thank especially Martijn Doesborgh, Dennis Fiorini and Floriana Umani for their great efforts in the sometimes rather tricky chemistry of sulfines and β-lactams. Despite these difficulties you were always in a good mood and contributed to a good atmosphere inside and outside the laboratory.

Altijd aanspreekbaar voor problemen van chemische aard waren Bertus Thijs, Gerry Ariaans, Ton Klunder, Gordon Chittenden en Gerard Nefkens.
Zonder secretaresses promoveert niemand; Jacky Versteeg en Sandra Tijdink, jullie zorgden altijd perfect voor het regelen van afspraken, papierwerk en talloze andere kleine en grotere zaken.

Een organisch syntheticus wil vooral één ding: uitgangsstoffen omzetten (liefst) in gewenste producten. Voor de soepele aanlevering van deze uitgangsstoffen (en andere benodigdheden) wil ik Wim van Luyn en Chris Kroon bedanken. Voor de analyses van de (gewenste en ongewenste) producten bedank ik Ad Swolfs (NMR), Peter van Galen (Massa) en Heleen Amatdjais-Groenen (Element Analyse) en René de Gelder (Röntgen Analyse). Voor het oplossen computer- en andere technische problemen kon ik altijd terecht bij Gerry Ariaans en Pieter van der Meer.

Tijdens het promotieonderzoek waren er goede en slechte perioden wat betreft de chemie, maar altijd goed was de sfeer in de groep. Bij deze wil ik iedereen bedanken voor zijn/haar bijdrage hieraan tijdens werkuren, koffiepauzes, borrels en studiereizen. Wat betreft de “339-tijd” zorgden Jelle de Vries en Jeroen Ledeboer (team 91.1), René Schouwstra, Marie-José Vullers-Heldens en Nieves Martin-Laso voor unieke momenten. Mijn collega-promovendi op lab 339, Eddy Damen (korte en langere pauzes, en sportieve inspanningen met Ruud Titulaer) en Sander Hornes (alleen Gerry weet meer van PC’s) stonden ook altijd garant voor goede sfeer. Met Peter ten Holte en Corrine Lawrence was het later ook altijd goed toeven in 351/353.

En dan was er ook nog een leven buiten de werkvloer. Jacco van Kuik en Fred van der Logt; de vele ‘dart-avonden’ en ‘playstation-sessies’ zorgden altijd weer voor de nodige ontspanning. Ook dank aan de ex-Biezenstraters voor een goede tijd voor- en tijdens de promotie-periode.

Verder kon ik altijd terecht bij m’n familie en in het bijzonder bij jou Mam, jouw eindeloos geduld en doorzettingsvermogen zijn altijd m’n voorbeeld geweest. Dat voorbeelden niet altijd makkelijk te volgen zijn weet iedereen; Anat, zonder jou zou het allemaal zoveel moeilijker zijn geweest!

André

CURRICULUM VITAE

André Lucassen werd geboren op 3 september 1970 in Nijmegen. Na het behalen van het HAVO-diploma in 1987 aan het Canisius College Mater Dei in Nijmegen, gevolgd door één jaar 5 VWO, begon hij in 1988 aan een studie Hoger Laboratorium Onderwijs (HLO) aan de Hogeschool Arnhem/Nijmegen. Na behalen van het HLO-diploma in de afstudeerrichting Organische Chemie in 1992, startte hij in datzelfde jaar met een verkort doctoraal programma Scheikunde aan de Katholieke Universiteit Nijmegen. Het doctoraalexamen werd in augustus 1995 behaald met als hoofdrichting Organische Chemie (Prof. Dr. B. Zwanenburg). Een buitenlandstage aan de Bar-Ilan University in Ramat Gan in Israël (Prof. Dr. S. Braverman) van januari tot en met juli 1995 maakte deel uit van de studie. Van november 1995 tot en met september 1996 was hij werkzaam als Junior Onderzoeker in de onderzoeksgroep van Prof. Dr. B. Zwanenburg. Vanaf 1 oktober 1996 tot 1 oktober 2000 was hij werkzaam als Onderzoeker in Opleiding (OIO) in diezelfde onderzoeksgroep en werd het onderzoek verricht dat beschreven staat in dit proefschrift. Van mei 2001 tot mei 2003 was hij werkzaam als Postdoctoral Fellow (EU-project "Molecular Level Devices and Machines") aan het Weizmann Institute of Science (Rehovot, Israel) in de group van Prof. Dr. A. Shanzer. Sinds juni 2003 is hij Postdoctoral Fellow, eveneens aan het Weizmann Institute of Science, in de groep van Dr. M. van der Boom.