Synthesis of Functionalized Arenes based on [3+3] Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes and related Transformations and Isolation of New Chemical Constituents of *Symplocos racemosa*

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Dekan : .....

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Affectionately Dedicated to

Ammar, Umar, Usman, Umair and Ayesha

"My beloved nephews and niece"

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In the name of Allah, Who is Ubiquitous, Omniscient, Worthy of all praise and Creator of all of us, Who guides in darkness and helps in difficulties. I do obeisance in thanks and gratitude for all His blessings, due to which I was able to accomplish this strenuous task.

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Muhammad Abid Rashid

Abbreviations

Ar	Aromatic
APT	Attached Proton Test
ATCC	American Type Culture Collection
*n*BuLi	*n*-Butylithium
DEPT	Distortionless Enhancement by Polarisation Transfer
EI	Electronic Ionization
ESI	Electrospray Ionization
EtOAc	Ethylacetate
HRMS	High Resolution Mass Spectroscopy
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
MS	Mass Spectrometry
Ph	Phenyl
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resolution
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Correlated Spectroscopy
NOESY	Nuclear Overhause and Exchange Spectroscopy
Me_3SiOTf	Trimethylsilyl trifluoro methanesulfonate
Me_3SiCl	Trimethylsilylchloride
mp.	Melting point
RCM	Ring Closing Metathesis
TBAI	Tetrabutyl amonium iodie
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
UV	Ultraviolet Spectroscopy

Summary

A significant part of this dissertation has recently been published (see list of publications at the end). The work embodied in this dissertation is concerned with the Synthesis of Functionalized Arenes based on [3+3] Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes and related Transformations and isolation of new chemical constituents of *Symplocos racemosa*.

This dissertation is split in two parts, **A** and **B**.

Part A

Synthesis of Functionalized Arenes based on [3+3] Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes and related Transformations

1. This chapter deals with the the cyclization of the dianions of 3-ketosulfones to synthesize the2-(sulfonylmethylidene)-tetrahydrofurans and 2-(sulfonylmethylidene)-5-vinyltetrahydrofurans which afforded ω-bromo-3-ketosulfones (**11&13)** after BBr_3-mediated cleavage. In addition synthesis of ω-bromo-3-ketonitriles (**16&18)** is also reported. Furthermore, this methodology was successfully applied to the synthesis of 2-(ω-haloalkyl)benzofurans (**22&25**)) based on the synthesis of 2-(sulfonylmethylidene) and 2-(cyanomethylidene)-tetrahydrofurans and their subsequent BBr_3-mediated cleavage.

2. Chapter two includes the synthesis of functionalized diarly sulfides and diaryl ethers based on formal $TiCl_4$ mediated [3+3] cyclization of masked dianions, methodology developed by Chan and coworkers.[64] Synthesis of 1,3-bis(sulfides) (**45e&45f**) was also carried out successfully. Here, *catalytic* [3+3] cyclizations (**43**) of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane are also reported. In addition, a convenient approach towards 2-thiophenoxybenzoates (**49**) containing a remote halide function by domino ′[3+3] cyclization / homo-Michael′ reaction has been reported. This chapter also deals with the synthesis of variety of benzophenones (**51**) by a domino 'Michael-retro-Michael-aldol' reaction of 1,3 bis-silyl enol ethers with 3-formyl benzopyrylium triflates. Furthermore, cyclization reactions of 1,3-bis (trimethylsilyloxy)-1,3-butadiene with chromone to afford biaryl lactones **54** is presented.

3. In this chapter, I have described the synthesis of functionalized 3-arylsalicylates by TMSOTf- (**62**) and $TiCl_4$- (**63**) mediated [3+3] cyclizations of novel 4-aryl-1,3-bis(silyloxy)-1,3-dienes with 3-silyloxy-2-en-1-ones. The biaryl skeleton is present in several natural products e.g cynandione A-C and dichamanetin. The methodology described here provides an easy and direct route for the synthesis of biaryls.

4. In chapter 4, I have reported the synthesis of 1-azaxanthones (**68**) by condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-(cyano)-benzopyrylium triflates and subsequent base-mediated domino 'retro-Michael–lactonization–aldol' reactions. This synthesis is carried out under mild conditions and the reactions proceed in acceptable yields with very good regio- and chemoselectivity.

5. This chapter includes the experimental section, spectroscopic data and full characterization of all new products has been described.

Part B

Isolation of New chemical constituents of *Symplocos racemosa*

The phytochemical investigation of *Symplocos racemosa* Roxb. resulted in the isolation of five new chemical constituents, out of these, two are phenolic glycosides of salirepin series, while other three are three benzylated glycosides. The new compounds include symplocuronic acid (**21**) and sympocemoside (**22**), locoracemosides A (**23**), locoracemosides B (**24**) and locoracemosides C (**25**). Locoracemosides A, B and C, benzylated glycosides, display inhibitory potential against the α-chymotrypsin enzyme.

In addition to these new chemical constituents, one new-source chemical constituent, salirepin (**26**), is reported. These isolated compounds were characterized by using various sophisticated spectroscopic techniques.

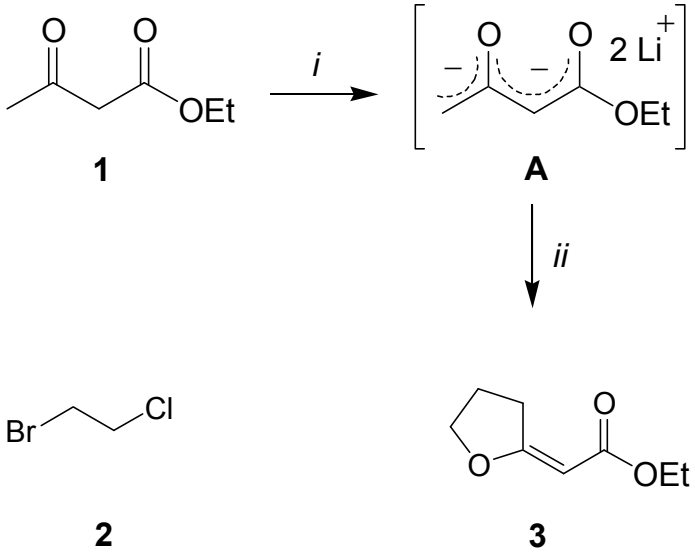
Part A

Synthesis of Functionalized Arenes based on [3+3] Cyclizations of 1,3-Bis(silyloxy)-1,3-butadienes and related Transformations

Introduction

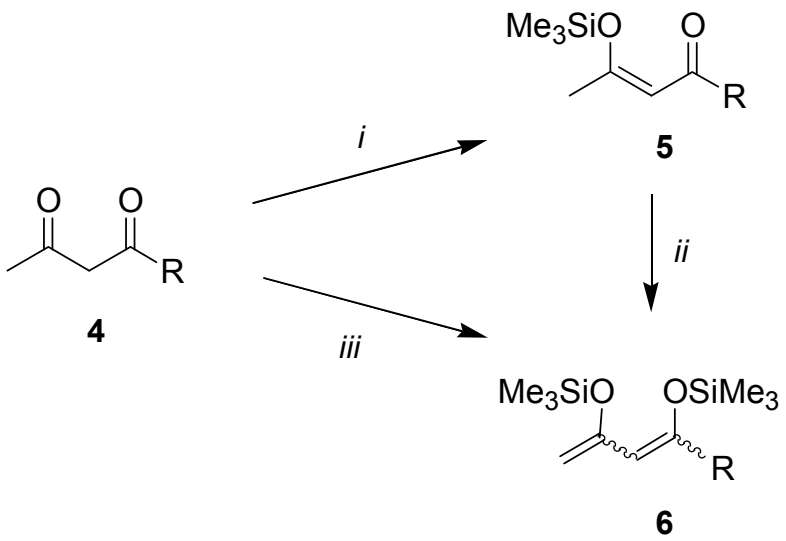
The synthesis of relevant organic compounds such as natural products and analogues, drugs, diagnostics, agrochemicals, and other kinds of material is a main topic in academic and industrial chemistry, and it is the connecting point of interdisciplinary research in chemistry, biology, and medicine. The view of synthesis has altered in recent years; there is clearly a change in paradigm. At the beginning, organic chemistry was considered a branch of natural sciences dealing with a specific type of compounds, mainly isolated from living organisms. Even today natural products continue to play an important role in discovery and development of new pharmaceuticals.[1] Since the discovery of penicillin, a large number of antibiotics have been isolated from scores of micro-organisms.[2] Natural products also provide a great help in chemotherapy of cancer. They are an integral part of anticancer drugs e.g. bleomycin, doxorubicin, mitomycin, and paclitaxel.[3] All this pharmacologically and biologically important stuff designed by Mother Nature was not available in bulk quantities which man demanded. Thus the development of new, highly selective methods is still being a main task, to get it in bulk amounts while following the foot steps of nature, but even more important is the search for more efficiency.[4] The relationship between structural complexity and the number of steps in a synthesis must be improved. In addition, synthetic methodology must be designed in a way that it allows access to diversified substance libraries in an automatized way.[5] A general way to improve synthetic eficciency and in addition to give access to a multitude of diversified molecules in solution is the development of multicompound domino reactions, which allow the formation of complex compounds starting from simple substrates. Domino reactions are defined as processes of two or more bond-forming reactions in which a subsequent trans-formation takes place by virtue of the functionalities introduced in a former transformation.[4a,5d,6] The development of cyclization reaction with free[7] and masked dianions,[8] for the development of biologically relevant ring systems, and natural substances,[9] is research priority in the working group prof. Langer.[10] Despite the simplicity of the idea that in the implementation dianions with 1-2 difunctional alkylhalides to cyclic systems, both dianions as many dielectrophiles represent highly reactive compounds, leading to adverse reactions, such as polymerization, reduction of dielectrophile,[11] monoalkylation,[12] eliminations[13] or SET reactions (SET = single-

electron-transfer).[14] These problems can be achieved through : (a) optimization of proper tuning of reactivity of dianion and dielectrophile and (b) the use of electroneutral dianions equalivalents (masked dianion) in Lewis acid catalyzed reactions. Masked dianion represent important building blocks. The regioselectivity observed for reactions of true and masked dianions is the same in most cases.



Scheme 1.. *i*: 2.5 equiv. LDA, THF, 0 °C, 1 h; *ii* $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h, then reflux, 14 h.

1,3-Bis(trimethylsilyloxy)-1,3-butadienes **6** are available from the respective 1,3-dicarbonyl compounds **4** in one or two steps. Following the procedures of Danishefsky, Chan and Molander, ester-derived bis-silyl enol ethers **6** can be prepared by treatment of the respective β-ketoester with NEt_3–Me_3SiCl to give the silyl enol ethers **5** Deprotonation of **2** with LDA and subsequent addition of Me_3SiCl afforded the dienes **6**.[15] Simchen et al. have reported that 1,3-diketone derived bis-silyl enol ethers can be prepared in one step by treatment of an ether solution of the diketone with NEt_3–Me_3SiOTf (2 equiv).[16]



Scheme 2.: *i*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; *ii*: LDA, THF, –78 → 20 °C, Me_3SiCl; *iii*: : Me_3SiCl (2.0 equiv), NEt_3, Et_2O, 20 °C

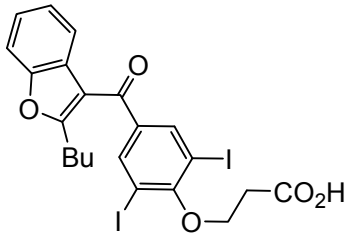
Bis-silyl enol ethers **6** can be stored in most cases at –30 °C for several months without decomposition.

My studies were focused on the synthesis of functionalized carbonyl compounds containing a halide group at a remote position and of pharmacologically relevant functionalized benzofurans followed by the synthesis of 2-alkyllidenetetrahydofurans by cyclization of free dianions. I was able to develop a new methodology for the synthesis of diarylsulfides and diaryl ethers. In addition, new applications of cyclization reactions of 1,3-bis-(trimethylsilyloxy)-1,3-butadienes with chromones and functionalized chromones are reported..

1. Regioselective Synthesis of ω-Bromo-3-ketosulfones, ω-Bromo-3-ktonitriles, and 2-(ω-Bromoalkyl)benzofurans based on a ′Ring-Closing / Ring-Opening′ Strategy

1.1 Introduction

Boron tribromide (BBr_3) represents a widely used reagent for the cleavage of methoxyarenes.[17] Besides this well-known application of BBr_3, other reactions have only scarcely been reported in the literature. ω-Bromoalcohols[18] and ω-halocarboxylic acids[19] were prepared by BBr_3 mediated ring opening of cyclic ethers and lactones, respectively.[19] Recently, Langer et al. reported the synthesis of 6-bromo-3-oxoalkanoates by reaction of BBr_3 with 2-alkylidenetetrahydrofurans.[20] The synthesis of benzofuran-3-carboxylic esters containing a remote bromide groups – based on a BBr_3 mediated ring transformation – has also been reported.[21] In my thesis, I developed a facile synthesis of ω-bromo-3-ketosulfones, ω-bromo-3-ketonitriles and 2-(ω-haloalkyl)benzofurans based on the synthesis of 2-(sulfonylmethylidene) and 2-(cyanomethylidene)-tetrahydrofurans and their subsequent BBr_3-mediated cleavage. The products repoted herein are not readily by other methods. Notably, functionalized benzofurans are of considerable pharmacological relevance and represent versatile synthetic building blocks in organic and medicinal chemistry.[22] For example, the benzofuran amiodarone **7** is used in the clinic as a potent antiarrythmic and antianginal drug.[23] Various benzofurans occur in natural products. This includes, for example, longicaudatin **8**,[24] the sessiliflorols A and B, cordigone **9**, flemistrictin E, tovophenone C, vismiaguianone C or piperaduncin B[25].



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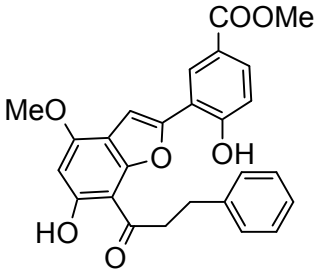

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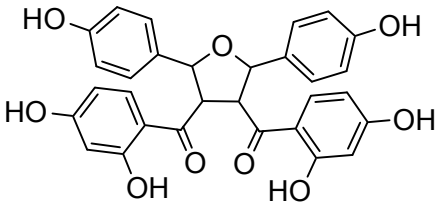

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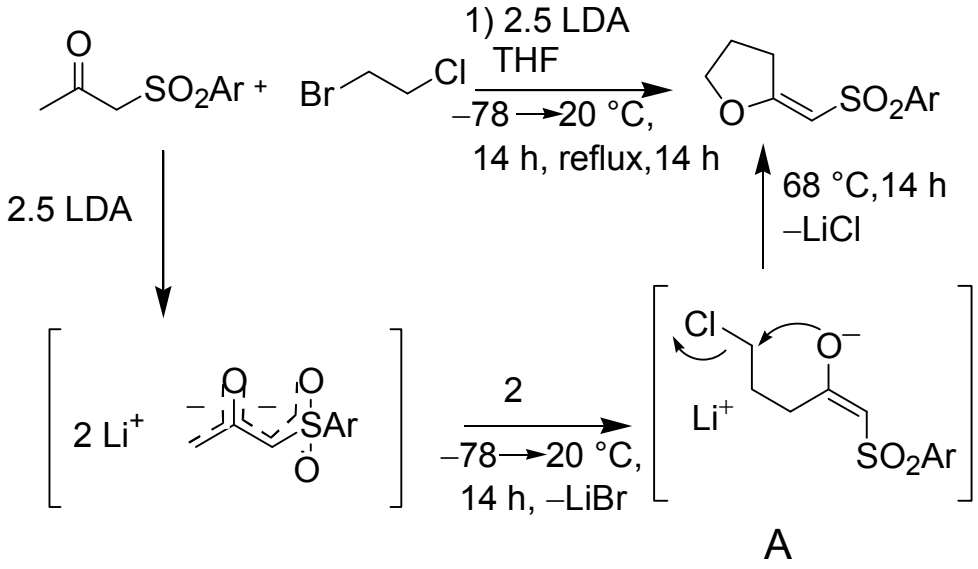
1.2 Results and Discussion

1.2.1. General mechanism for the cyclization of 1-bromo-2-chloroethane with 3-ketosulfone dianions

The terminal carbon atom of the dianion attacks the bromide group at low temperature to give intermediate **A**. Heating results in a regioselective attack of the enolate oxygen onto the chloride group of **A** to give the cyclizsation product.[26] The cyclization afforded the 2-(sulfonylmethylidene)tetrahydrofurans with very good *C/O* regioselectivity and *E*-diastereoselectivity which can be explained by (a) minimization of the dipole-dipole repulsion of the oxygen atoms in W-shaped intermediate **A**[27] and (b) by the higher thermodynamic stability of the *E*-diastereomer (Scheme 1.1).

2-(2-Oxoalkylidene)tetrahydrofurans are also available by cyclization[28] of 1,3-dicarbonyl dianions or 1,3-bis(silyl enol ethers) ('masked dianions') with various electrophiles, such as 1-bromo-2-chloroethane,[29] 1,4-dibromobut-2-ene,[30] or epoxides.[31] 2-(Sulfonylmethylidene)tetrahydrofurans were prepared, for example, from β-iodovinyl sulfones,[32] ω-halo and ω-hydroxy-β-ketosulfones,[33] or ω-hydroxypropargylic sulfones.[34]



Scheme 1.1 General mechanism for the cyclization of 1-bromo-2-chloroethane with 3-ketosulfone dianions

Another approach relies on the cyclization of 3-ketosulfone dianions with cyclic sulfates.[35] Some years ago, Langer et al. reported the synthesis of 7-sulfonyl-2,3,3a,4,5,6-

hexahydrobenzofurans, which can be regarded as bicyclic 2-(sulfonylmethylidene)tetrahydrofurans, by cyclization of cyclic 3-ketosulfone dianions with 1,4-dibromobut-2-ene.[30]

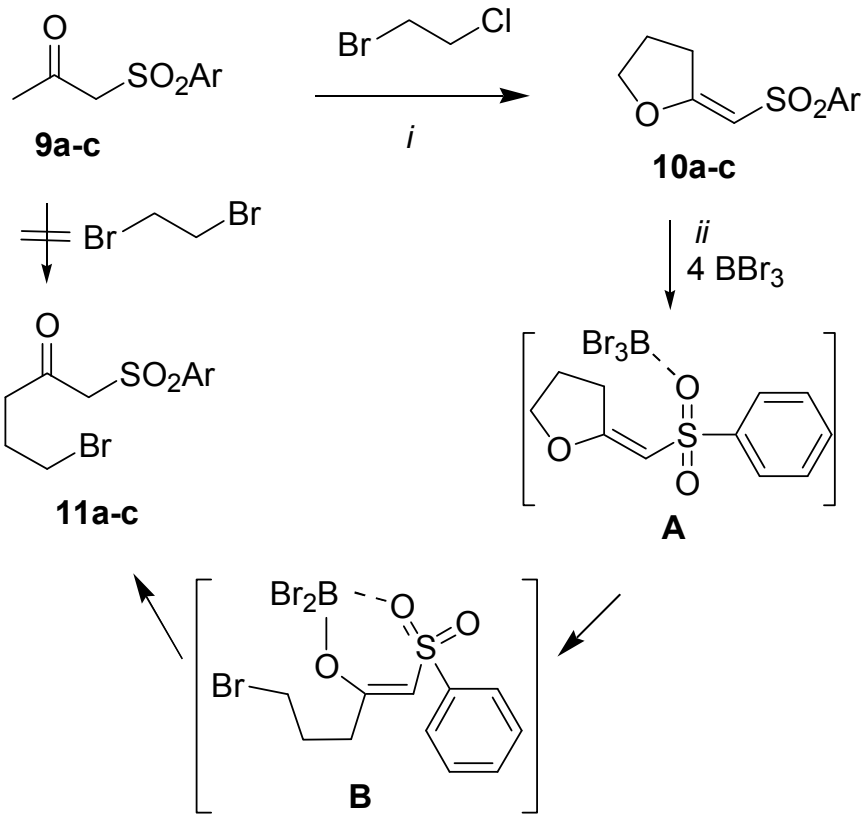
1.2.2. Synthesis of ω-Bromo-3-ketosulfones

The cyclization of the dianions of 3-ketosulfones **9a-c**, generated by LDA (2.5 equiv.), with 1-bromo-2-chloroethane afforded the 2-(sulfonylmethylidene)-tetrahydrofurans **10a-c** (Scheme 1.2, Table 1.1). The reaction of a CH_2Cl_2 solution of **10a-c** with BBr_3 and subsequent addition of water afforded the ω-bromo-β-ketosulfones **11a-c**. The formation of **11a-c** can be explained as follows: The interaction of BBr_3 with the sulfonyl group effects a dramatic increase of the electrophilicity of carbon atom C-5 of the tetrahydrofuran moiety. Nucleophilic attack of a BBr_3-derived bromide ion onto carbon C-5 results in ring-opening and formation of an open-chain boron enolate. The latter is subsequently protonated upon addition of water. During the optimization, the use of excess of BBr_3 proved to be important. Notably, products **11a-c** are not directly available by reaction of 3-ketosulfone dianions with 1,2-dibromoethane, due to a competing SET process (oxidative dimerization of the dianion and reduction of 1,2-dibromoethane to ethylene).[36]

Table 1.1. Synthesis of **11a-c**

10,11	Ar	% (**10**)[a]	*E/Z* (**10**)[b]	*%* (**11**)[a]
a	Ph	45	7:3	95
b	4-MeC_6H_4	45	7:3	92
c	4-ClC_6H_4	40	6:4	65

[a] Yields of isolated products; [b] by ^{1}H NMR



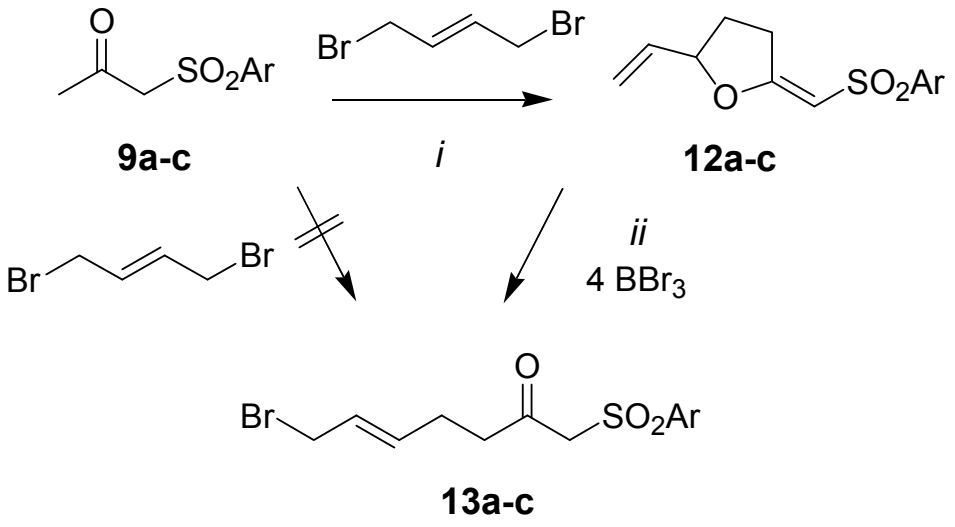
Scheme 1.2. Synthesis of ω-bromo-3-ketosulfones **11a-c**. *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h, then reflux, 14 h; *ii*: 1) 4.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 8 h; 2) H_2O

2-(Sulfonylmethylidene)-5-vinyltetrahydrofurans **12a-c** were prepared by cyclization of dilithiated 3-ketosulfones **9a-c** with 1,4-dibromobut-2-ene (Scheme 1.3, Table 1.2). The reaction of **12a-c** with BBr_3 afforded the ω-bromo-3-ketosulfones **13a-c**. The products were formed by cleavage of the 2-alkylidenetetrahydrofuran by a SN′ reaction. Notably, the products are not available by direct reaction of the dianions of **9a-c** with 1,4-dibromobut-2-ene, due to rapid cyclization.

Table 1.2. Synthesis of **13a-c**

12,13	Ar	% (**12**)[a]	*E/Z* (**12**)[b]	*%* (**13**)[a]
a	Ph	50	6:4	75
b	4-MeC_6H_4	38	6:4	75
c	4-ClC_6H_4	40	>98:2	70

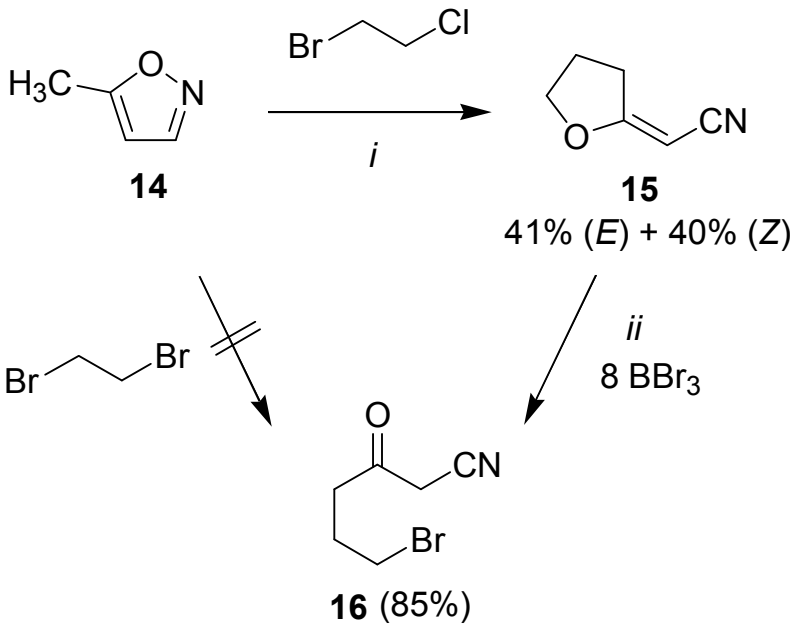
[a] Yields of isolated products; [b] by ^{1}H NMR



Scheme 1.3. *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) 1,4-dibromobut-2-ene, −78 → 20 °C, 20 h; *ii*: 1) 5.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 8 h; 2) H_2O

1.2.3. Synthesis of ω-Bromo-3-ketonitriles

Afterwards, I decided to extend the preparative scope of the methodology by its application to β-ketonitriles (Schemes 1.4 & 1.5). The known[29a] 2-alkylidenetetrahydrofuran **15** was prepared by cyclization of the dianion of cyanoacetone, generated by treatment of 5-methyl-isoxazole with LDA, with 1-bromo-2-chloroethane. Treatment of **15** with BBr_3 afforded 1-cyano-5-bromo-pentan-2-one (**16**) (Scheme 4). Despite its relatively low molecular weight, it was possible to independently confirm the structure of **16** by an X-ray crystal structure analysis (Figure 1.1).[97]



Scheme 1.4. Synthesis of 1-cyano-5-bromopentan-2-one (**16**). *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h, then reflux, 14 h; *ii*: 1) 8.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 8 h; 2) H_2O

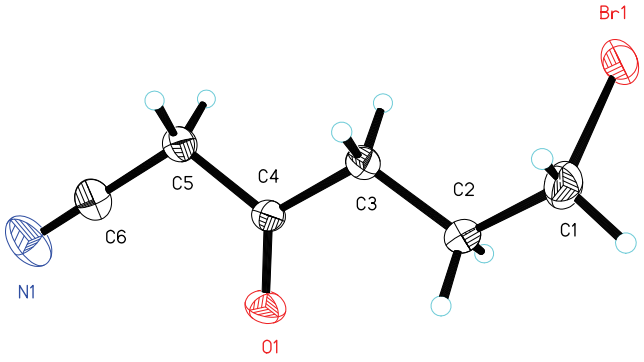
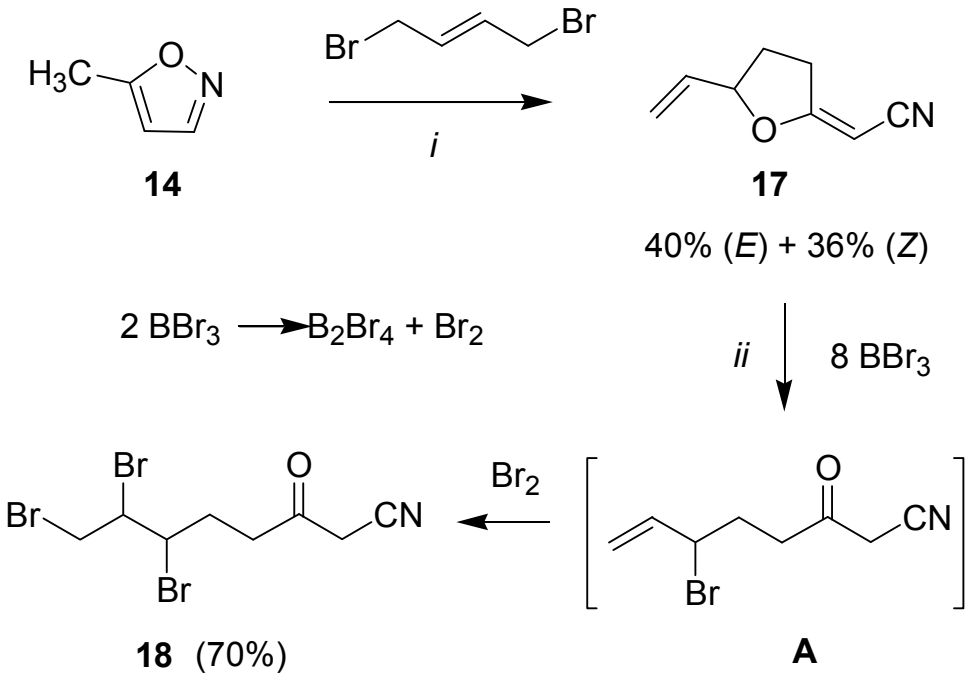


Figure 1.1. Ortep plot of **16**

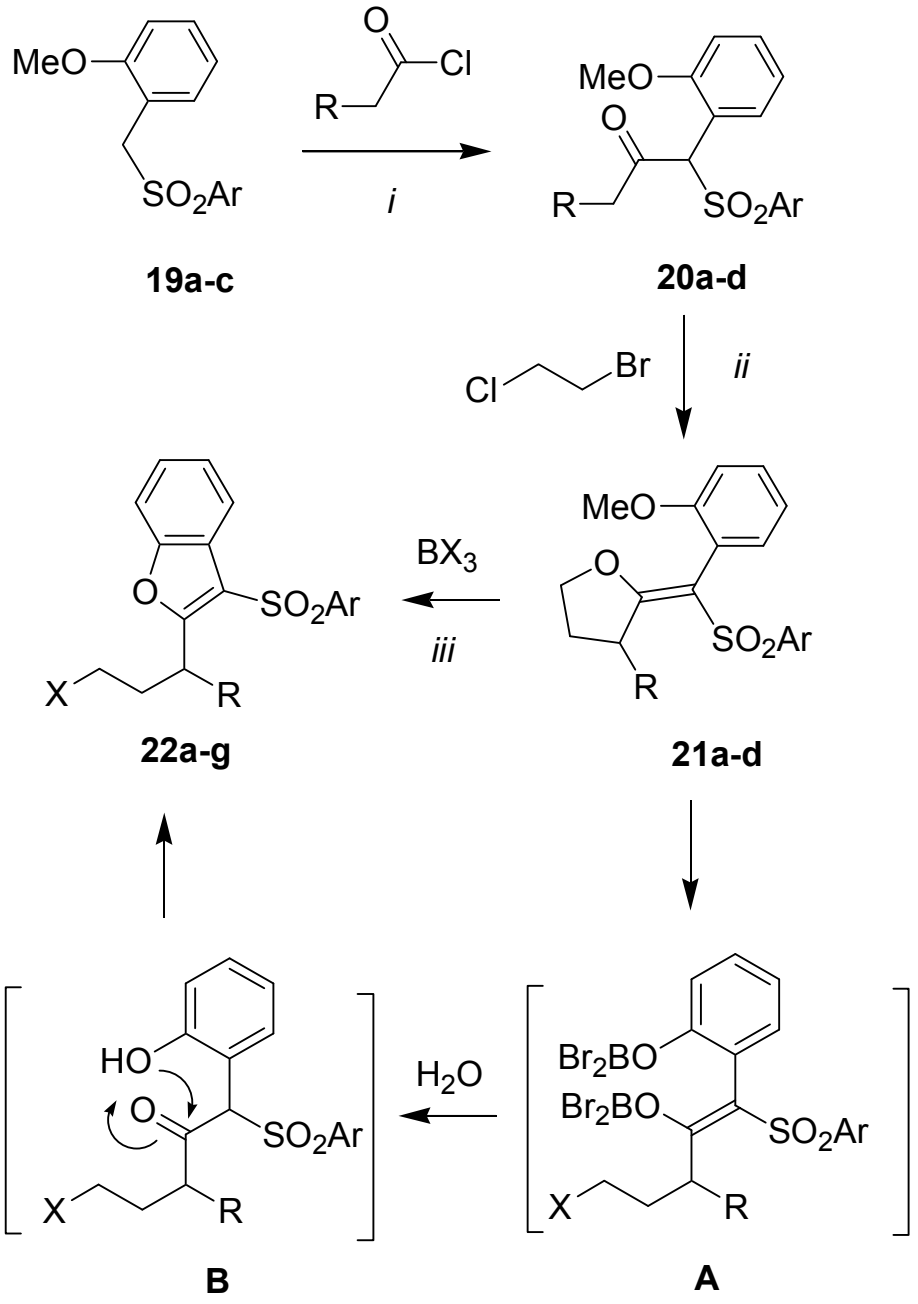
The cyclization of the dianion of cyanoacetone, generated by treatment of 5-methyl-isoxazole with LDA, with 1,4-dibromobut-2-ene afforded the known[29a] 2-alkylidenetetrahydrofuran **17**. Treatment of **17** with BBr_3 unexpectedtly afforded tribromide **18** (Scheme 1.5). Product **18** is presumably formed by BBr_3 mediated ring opening and formation of intermediate **A**. Subsequently, the double bond is brominated (by the action of bromine formed under the reaction conditions from BBr_3).



Scheme 1.5. *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) 1,4-dibromobut-2-ene, −78 → 20 °C, 20 h;; *ii*: 1) 8.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 6 h; 2) H_2O

1.2.4. Synthesis of 2-(ω-Bromoalkyl)benzofurans

The synthesis of benzofurans was studied next (Scheme 1.6 & 1.7). 3-Ketosulfones **20a-d** were prepared by acylation of aryl-[(2-methoxyphenyl)methyl]-sulfones **19a-c**. The cyclization of the dianions of **20a-c** with 1-bromo-2-chloroethane afforded the 2-alkylidenetetrahydrofurans **21a-d**. Treatment of **21a-d** with BBr_3 afforded the 2-(γ-bromoalkyl)-3-sulfonylbenzofurans **22a-d** (Scheme 3, Table 3). The reaction of **21a-c** with BCl_3 gave 2-(γ-hydroxypropyl)-3-sulfonylbenzofuran **22e-g**. The formation of benzofurans **22** can be explained by ring-opening of **21** and deprotection of the arylmethyl ether to give intermediate **A**, hydrolysis upon aqueous work-up (intermediate **B**) and subsequent acid mediated cyclization by attack of the hydroxy onto the carbonyl group. In case of **22e-g**, the chloride group was hydrolyzed.



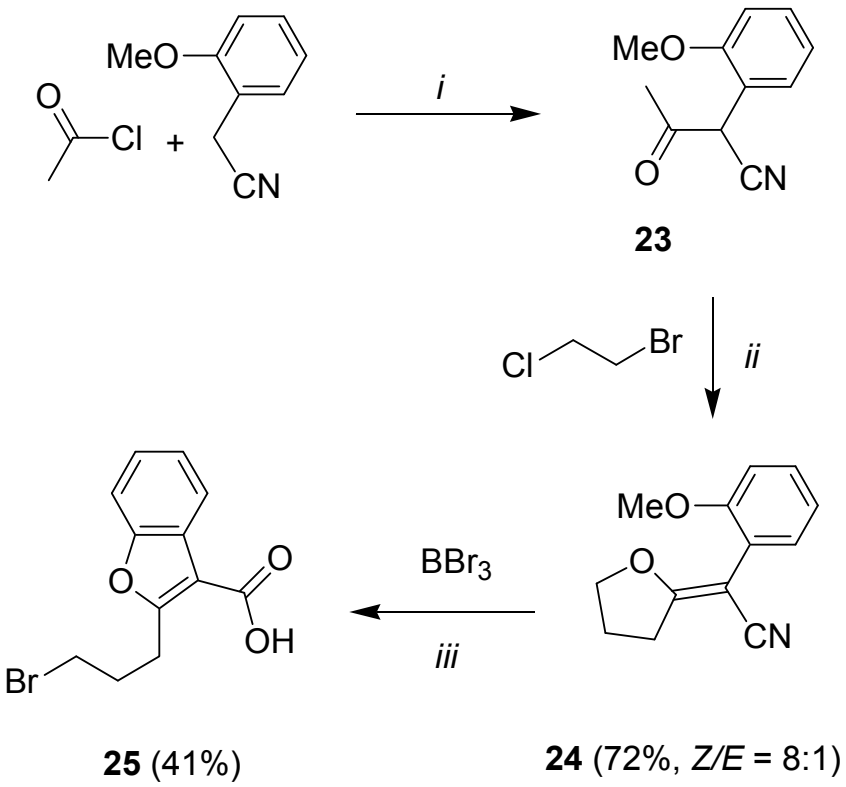
Scheme 1.6. Synthesis of benzofurans **22a-g**, *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 45 min, 2) acid chloride, −78 → 20 °C, 14 h; *ii*: 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h; then reflux, 14 h; *iii*: 1) 5.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 12 h; 2) H_2O

Table 1.2. Synthesis of benzofurans **22a-g**

20.21	**22**	Ar	R	X	% (**20**) [a]	% (**21**) [a, c]	*% (22)* [a]
a	**a**	Ph	H	Br	56	45 (*E*) + 22 (*Z*)	72
b	**b**	4-MeC_6H_4	H	Br	78	55 (*E*)	61
c	**c**	4-ClC_6H_4	H	Br	61	49 (*E*) + 19 (*Z*)	68
d	**d**	Ph	Me	Br	40	46 (*E/Z*= 8:1)	63
a	**e**	Ph	H	OH [b]	56	45 (*E*) + 22 (*Z*)	40
b	**f**	4-MeC_6H_4	H	OH [b]	28	55 (*E*)	34
c	**g**	4-ClC_6H_4	H	OH [b]	61	49 (*E*) + 19 (*Z*)	47

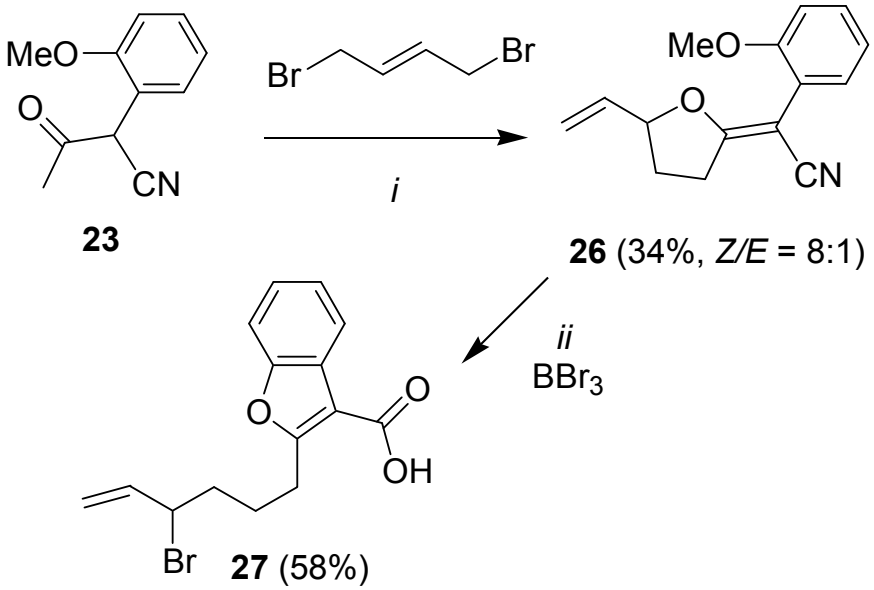
[a] Yields of isolated products;
[b] the product was formed when BCl_3 was used (by hydrolysis of the chloride group in the product);
[c] in brackets: configuration of the exocyclic double bond

The acylation of (2-methoxyphenyl) acetonitrile with acetyl chloride afforded β-ketonitrile **23**. The cyclization of the dianion of **23** with 1-bromo-2-chloroethane gave 2-alkylidenetetrahydrofuran **24**. Treatment of the latter with BBr_3 and subsequently with HBr (62%) afforded the 2-(γ-bromoalkyl)-3-carboxybenzofuran **25** (Scheme 1.7). During the optimization of this reaction, the addition of conc. hydrobromic acid proved to be important in order to induce a complete rearrangement. This was necessarry, since nitrile **23** proved to be less reactive than sulfones **21** in the reaction with BBr_3. This can be explained by the lower electron-withdrawing effect of the nitrile compared to the sulfone. The nitrile was hydrolyzed to a carboxylic acid group upon addition of conc. hydrobromic acid.



Scheme 1.7. Synthesis of benzofuran **25**, *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 45 min, 2) acid chloride, −78 → 20 °C, 14 h; *ii*: 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h; then reflux, 14 h; *iii*: 1) 7.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 72 h; 2) HBr (62%) 6.0 equiv. 20 °C, 20 h; 3) H_2O

The cyclization of the dianion of **23** with 1,4-dibromobut-2-ene gave 2-alkylidene-5-vinyltetrahydrofuran **26**. Treatment of the latter with BBr_3 and subsequently with HBr (62%) afforded the 2-(ω-bromoalkyl)-3-carboxybenzofuran **27** (Scheme 1.8). The nitrile was again hydrolyzed to a carboxylic acid group upon addition of conc. hydrobromic acid.



Scheme 1.8. Synthesis of benzofuran **27**, *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) 1,4-dibromobut-2-ene, −78 → 20 °C, 20 h;; *ii*: 1) 8.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 72 h; 2) HBr (62% , 6.0 equiv.), 20 °C, 20 h; 3) H_2O

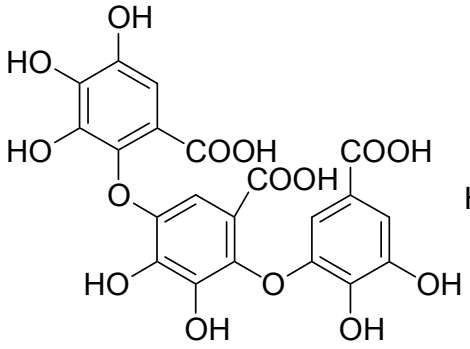
1.3. Conclusion

In conclusion, I developed an efficient approach to ω-bromo-3-ketosulfones, ω-bromo-3-ketonitriles, and 2-(ω-bromoalkyl)benzofurans based on one-pot cyclizations of 3-ketonitrile and 3-ketosulfone dianions and application of a ′ring-closing/ring-opening′ strategy.

2. Synthesis of Functionalized Diaryl Ethers and Sulfides based on Regioselective One-Pot Cyclizations of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes

2.1 Introduction

Functionalized diaryl ethers are of pharmacological relevance and occur in a variety of natural products.[37] This includes, for example, geodinhydrate methylester, methyl chloroasterrate,[38a,b] 1-desgalloylsanguiin,[39] dehydrotrigallic acid **28**,[40] epiphorellic acid **29**,[41] jolkianin,[42] remurin A,[43] and micareic acid **30**.[44] Diaryl sulfides (diaryl thioethers), the sulfur analogues of diaryl ethers, are also of considerable pharmacological importance and are present in various natural products. This includes, for example, cyclo(penta-1,4-phenylene sulfide), various dibenzothiophenes,[45] highly cytotoxic lissoclinotoxins (also known as varacins),[46] lissoclibadins **31**,[47] cyclotetra(*p*-phenylene sulfide),[48] and natural products isolated from *Streptomyces griseus* **32**.[49] Non-natural diaryl sulfides are also of considerable pharmacological relevance. For example, fluorinated diaryl sulfides have been reported to act as serotonin transporter ligands.[50] The most important approach to diaryl ethers relies on the Ullmann[51] and Buchwald-Hartwig[52] reaction and on related transformations.[53]



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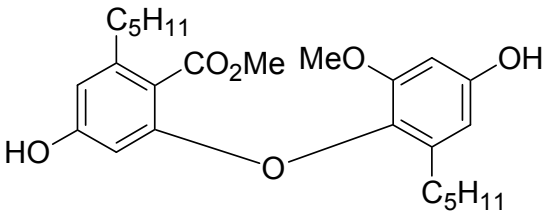

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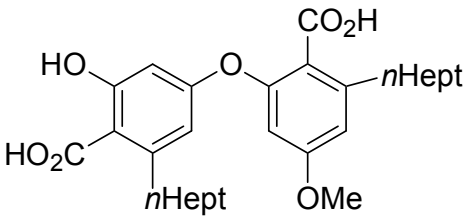

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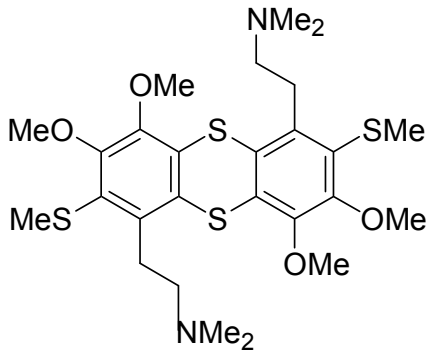
Although these methods are very important, the scope is limited by the availability of the starting materials, In fact, the synthesis of more complex aryl halides or triflates by regioselective functionalizations of arenes is often a difficult task. In addition, the transition metal catalyzed formation of diaryl ethers containing a sterically encumbered ether linkage is difficult. Most of the known synthetic approaches to diaryl sulfides are based on the formation of a carbon-sulphur bond. Classic syntheses[54] are often limited by their harsh conditions, low regioselectivity, narrow preparative scope or by the formation of polysulfides. In recent years, transition metal-catalyzed reactions for the synthesis of diaryl sulfides were developed which proceed under mild conditions (Buchwald-Hartwig reaction and related transformations).[55] Relatively mild metal-free reactions have also been reported.[56] However, the synthesis of highly substituted and sterically encumbered products by these methods is often difficult or not possible at all.



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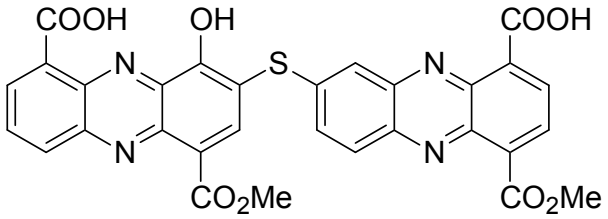


32

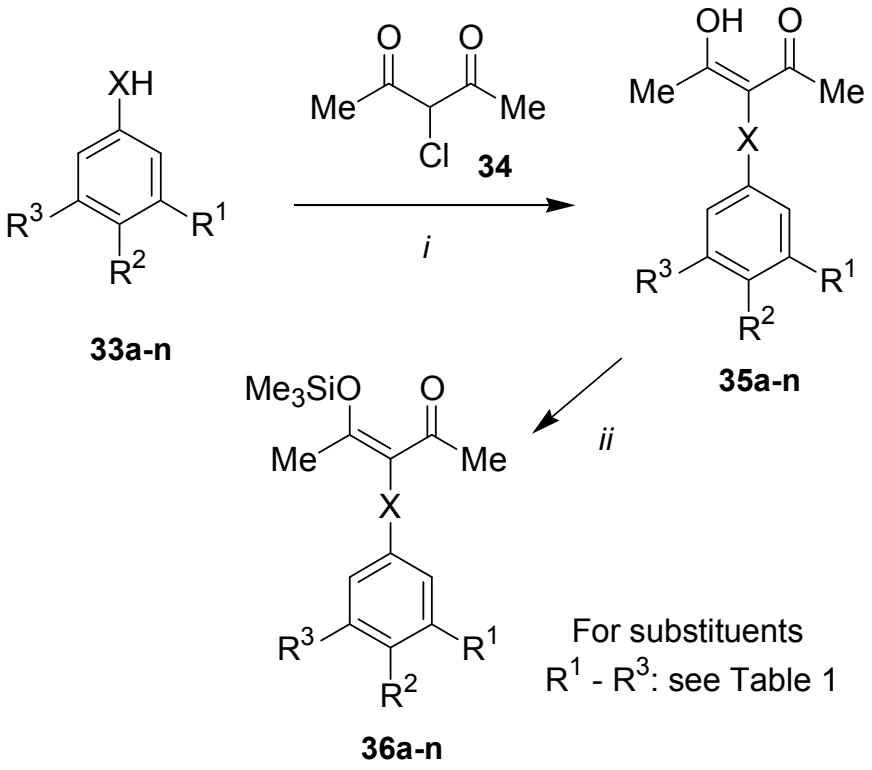
In addition, the synthesis of the starting materials, substituted arenes and thiophenols, can be a difficult task. An alternative approach to diaryl sulfides relies on cyclization reactions of thioaryloxy-containing building blocks. In contrast to other methods, this approach relies on the assembly of the arene moiety by formation of two carbon-carbon bonds. Only a few examples of this type of reaction have been reported to date. For example, Hilt and coworkers reported an efficient synthesis of diaryl sulfides by cobalt(I)-catalyzed [4+2] cycloaddition of alkynyl sulfides with 1,3-butadienes.[57] Chan *et al.* reported the synthesis of 2-(thiophenoxy)benzoates based on the cyclization of 1-methoxy-3-thiophenoxy-1-trimethylsilyloxy-1,3-butadiene with 3-siloxy-2-en-1-ones.[58] Dies-Alder reactions of this compound have also been reported.[59] Recently, Langer et al.

reported the synthesis of 5-aryloxysalicylates[60] and 5-thioaryloxysalicylates[61] based on reactions of 2-aryloxy- and 2-thioaryloxy-3-trimethylsilyloxy-2-en-1-ones, respectively (Scheme 2.2). In my thesis, I have studied full details of these cyclizations. In addition, I report the synthesis of diaryl ethers and diaryl sulfides based on [3+3] cyclizations of 4-aryloxy- and 4-thioaryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes (Scheme 2.4 & 2.5). These reactions provide a convenient and regioselective approach to sterically encumbered and functionalized diaryl sulfides and of diaryl ethers which are not readily available by other methods. Herein, full details of the methodology and a comprehensive study of its preparative scope are reported. In addition to the results reported in (Langer et al.) preliminary communication, I herein report the regioselective synthesis of functionalized 2-thiophenoxybenzoates by domino ′[3+3] cyclization / homo-Michael′ reactions of 1-trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 1,1-diacylcyclopropanes (Scheme 2.8) and synthesis of diaryl sulfides, diaryl ethers by cyclization of novel 4-thioaryloxy-1 and 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes with 1,1-diacetylcyclopropane (Scheme 2.6), 3-formylchromone (Scheme 2.9) and chromone (Scheme 2.11).

2.2 Results and Discussion

2.2.1. Synthesis of 5- Aryloxy and 5-Thioaryloxy Salicylates

3-(Thiophenoxy)- and 3-(phenoxy)pentane-2,4-diones **35a-n** were prepared, following a known procedure,[62] by reaction of 3-chloropentane-2,4-dione (**34**) with thiophenols and phenols respectively **33a-n** (Scheme 2.1, Table 2.1)**.** The silylation[63] of **35a-n** afforded the 2-thiophenoxy- and 2-phenoxy-3-silyloxy-2-en-1-ones **36a-n**. 1,3-Diones **35** are completely enolized in solution and in the solid state. The solid state structures of **35b** and **35c** were confirmed by X-ray crystal structure analyses (Figures 2.1 and 2.2).[97]



Scheme 2.1. Synthesis of **36a-n**: Reagents and conditions: *i*: method A: pyridine, MeOH, 0 → 20 °C, 6 h ; method B: piperidine, CH_2Cl_2, MeOH, 0 → 20 °C, 6 h (for X = S); K_2CO_3, acetone, 2 h, reflux (for X = O); *ii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h

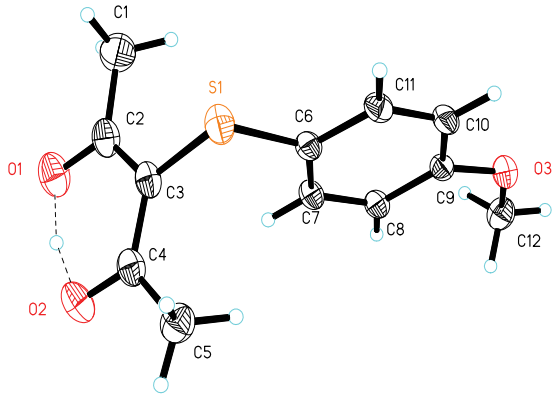


Figure 2.1. Ortep plot of **35b**

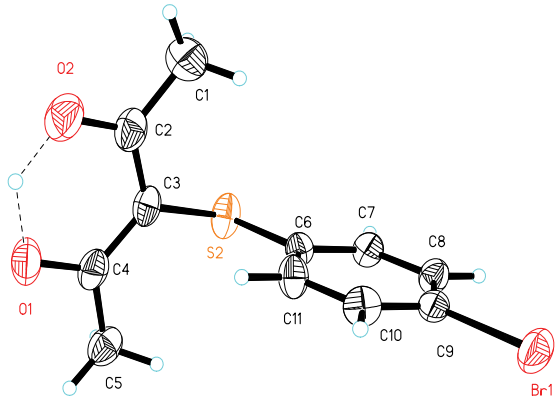


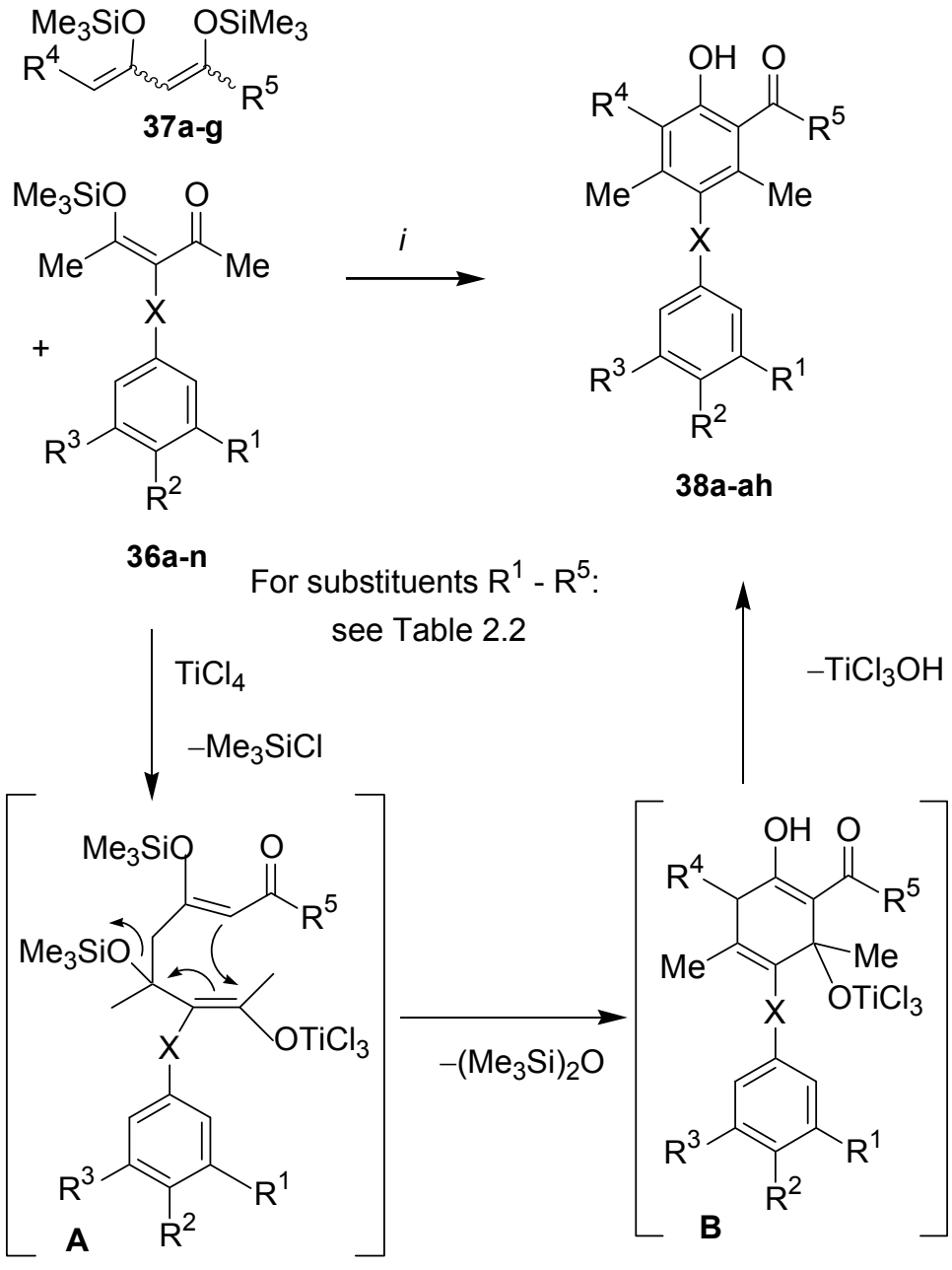
Figure 2.2. Ortep plot of **35c**

Table 2.1. Synthesis of **35a-n** and **36a-n**

35,36	X	R^1	R^2	R^3	% (**35**)[a]	% (**36**)[a]
a	S	H	H	H	72(A)	81
b	S	H	OMe	H	33(B)	90
c	S	H	Br	H	28(B)	79
d	S	H	Me	H	81(B)	92
e	S	OMe	H	H	73(B)	81
f	O	H	H	H	-[c]	91
g	O	Me	H	Me	20	94
h	O	H	Et	H	35	80
i	O	H	Cl	H	-[c]	96
j	O	H	OMe	H	24	95
k	O	OMe	OMe	H	40	97
l	O	H	Br	H	25	84
m	O	H	CN	H	25	82
n	O	H	CH_2CO_2Me	H	26	87

[a] Yields of isolated products; [b] in brackets: method for the synthesis of **35** (see experimental section); [c] commercially available

The $TiCl_4$ mediated [3+3] cyclization of **36a-n** with 1,3-bis(trimethylsilyloxy)-1,3-dienes **37a-g** – prepared from the corresponding 1,3-dicarbonyl compounds[64] – afforded the novel diaryl sulfides and diaryl ethers **38a-ah (**Scheme 2.2 Table 2.2). The structures of **38a** and **38b** were independently confirmed by X-ray crystal structure analyses (Figures 2.3 and 2.4).[97]



Scheme 2.2. Synthesis of **38a-ah**: Reagents and conditions: *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C,20h

The formation of salicylates can be explained by the mechanism depicted in Scheme 2.2: the $TiCl_4$-catalyzed attack of the terminal carbon atom of **37** onto **36** gave intermediate **A**. The subsequent cyclization afforded intermediate **B**, Extrusion of water from **B** afforded the final product.

Table 2.2. Synthesis of **38a-ah**

36	**37**	**38**	X	R^1	R^2	R^3	R^4	R^5	% (**38**)[a]
a	**a**	**a**	S	H	H	H	H	OMe	48
a	**b**	**b**	S	H	H	H	Me	OEt	40
a	**c**	**c**	S	H	H	H	Et	OEt	40
b	**d**	**d**	S	H	OMe	H	H	OEt	43
b	**b**	**e**	S	H	OMe	H	Me	OEt	35
b	**c**	**f**	S	H	OMe	H	Et	OEt	38
c	**a**	**g**	S	H	Br	H	H	OMe	36
d	**b**	**h**	S	H	Me	H	Me	OEt	33
e	**a**	**i**	S	OMe	H	H	H	OMe	32
e	**b**	**j**	S	OMe	H	H	Me	OEt	30
f	**d**	**K**	O	H	H	H	H	OEt	35
f	**b**	**l**	O	H	H	H	Me	OEt	30
f	**c**	**m**	O	H	H	H	Et	OEt	32
g	**d**	**n**	O	Me	H	Me	H	OEt	58
g	**b**	**o**	O	Me	H	Me	Me	OEt	39
h	**d**	**p**	O	H	Et	H	H	OEt	60
h	**b**	**q**	O	H	Et	H	Me	OEt	36
i	**a**	**r**	O	H	Cl	H	H	OMe	54

i	**b**	**s**	O	H	Cl	H	Me	OEt	49
i	**c**	**t**	O	H	Cl	H	Et	OEt	43
i	**e**	**u**	O	H	Cl	H	H	Me	35
j	**b**	**v**	O	H	OMe	H	H	OEt	30
k	**d**	**w**	O	OMe	OMe	H	H	OEt	58
k	**b**	**x**	O	OMe	OMe	H	Me	OEt	35
l	**d**	**y**	O	H	Br	H	H	OEt	58
l	**f**	**z**	O	H	Br	H	H	OCH_2Ph	59
m	**d**	**aa**	O	H	CN	H	H	OEt	50
m	**f**	**ab**	O	H	CN	H	H	OCH_2Ph	54
n	**d**	**ac**	O	H	CH_2CO_2Me	H	H	OEt	50
n	**f**	**ad**	O	H	CH_2CO_2Me	H	H	OCH_2Ph	65
n	**g**	**af**	O	H	CH_2CO_2Me	H	*n*Hex	OEt	54
n	**e**	**ag**	O	H	CH_2CO_2Me	H	H	Me	55
j	**b**	**ah**	O	H	OMe	H	Me	OEt	30

[a] Yields of isolated products

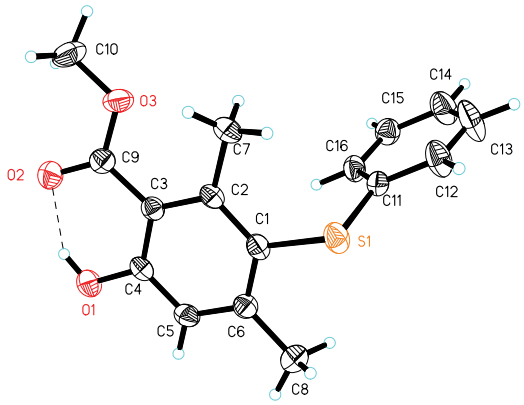


Figure 2.3. Ortep plot of **38a**

The best results were obtained when stoichiometric amounts of the starting materials and of $TiCl_4$ were used. The latter was added to a dichloromethane solution of the starting materials at –78 °C with subsequent warming of the mixture to 20 °C.

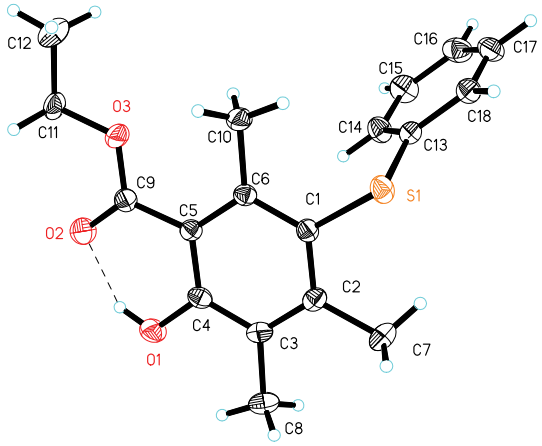


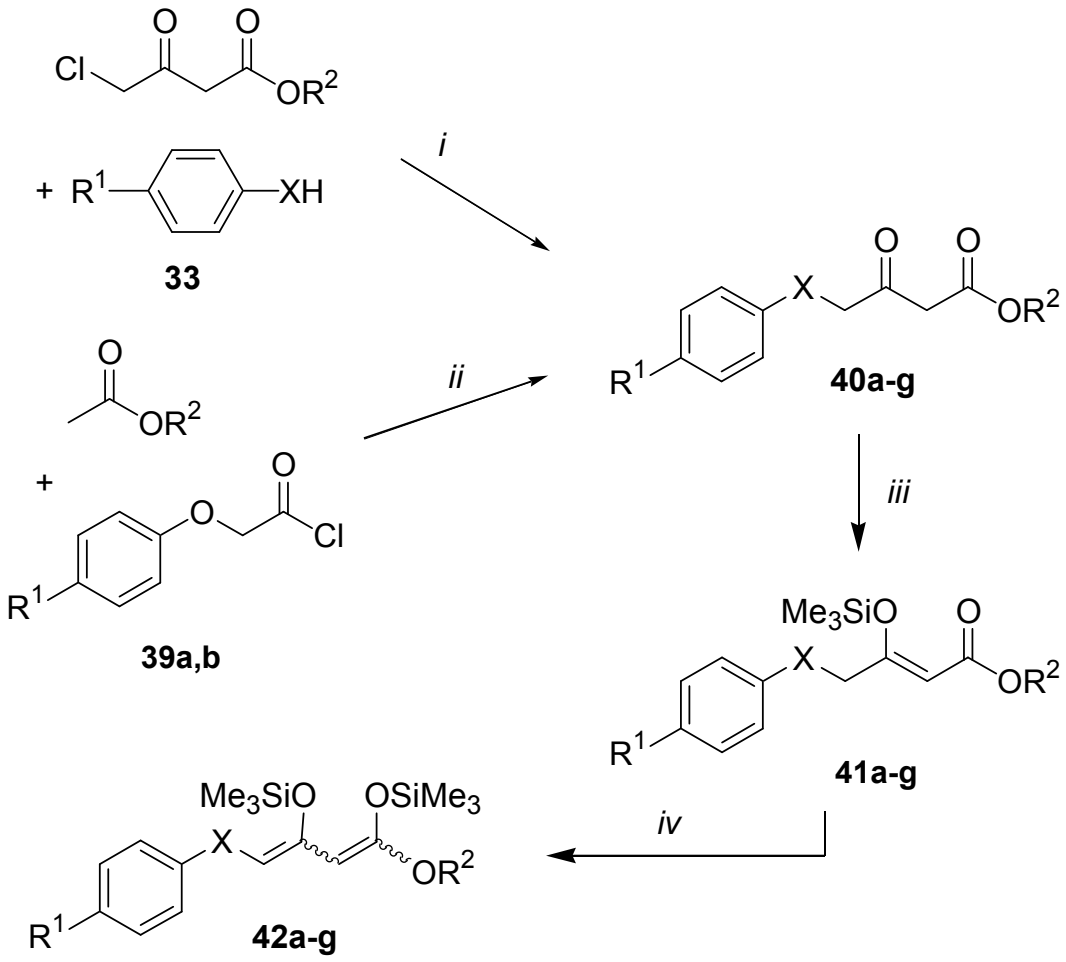
Figure 2.4. Ortep plot of **38b**

The high concentration of the solution (only 2 mL of solvent per 1 mmol of starting material) proved to be a very important parameter. The quality of the starting materials, reagents and solvent also played an important role. The use of Me_3SiOTf as the Lewis acid proved to be unsuccessful. All structures were established by spectroscopic methods. In most of the cyclization reactions, β-ketoester derived 1,3-bis(silyl enol ethers) were employed. However, the use of 1,3-bis(silyl enol ether) **37e**, prepared from acetylacetone, also proved to be successful. In contrast, employment of 1,3-bis(trimethylsilyloxy)-1-phenyl-1,3-butadiene (derived from benzoylacetone) resulted in the formation of complex mixtures. This can be explained by its lower reactivity compared to β-ketoester derived 1,3-bis(silyl enol ethers).

2.2.2. Synthesis of 3- Aryloxy and 3-Thioaryloxy Salicylates

In addition, the synthesis of 4-thiophenoxy- and 4-phenoxy-1,3-bis(silyloxy)-1,3-dienes and their application to the synthesis of functionalized diaryl sulfides and diaryl ethers has been studied. The novel 4-thiophenoxy- and 4-phenoxy-1,3-bis(silyloxy)-1,3-dienes **42a-g** were prepared from the esters **40a-g** (Scheme 2.3, Table 2.3)**.** The ethyl 4-thiophenoxyacetoacetates **40a,b,f,g** were prepared by reaction of ethyl 4-

chloroacetoacetate with thiophenols **33**. Ethyl 4-phenoxyacetoacetate (**35c**) was prepared by base mediated reaction of ethyl 4-chloroacetoacetate and phenol (**33f**). The methyl 4-phenoxyacetoacetates **40d,e** were prepared by Claisen condensation of methyl acetate with acid chlorides **39a,b**.



Scheme 2.3. Synthesis of **42a-g**: Reagents and conditions: i: NEt_3, CH_2Cl_2, 30 min, 0 °C (for X = S); KOH, DMSO, 5 h, 20 °C (for X = O); ii: LDA, THF, –78 → 20 °C, 14 h; iii: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; iv: LDA, THF, –78 → 20 °C

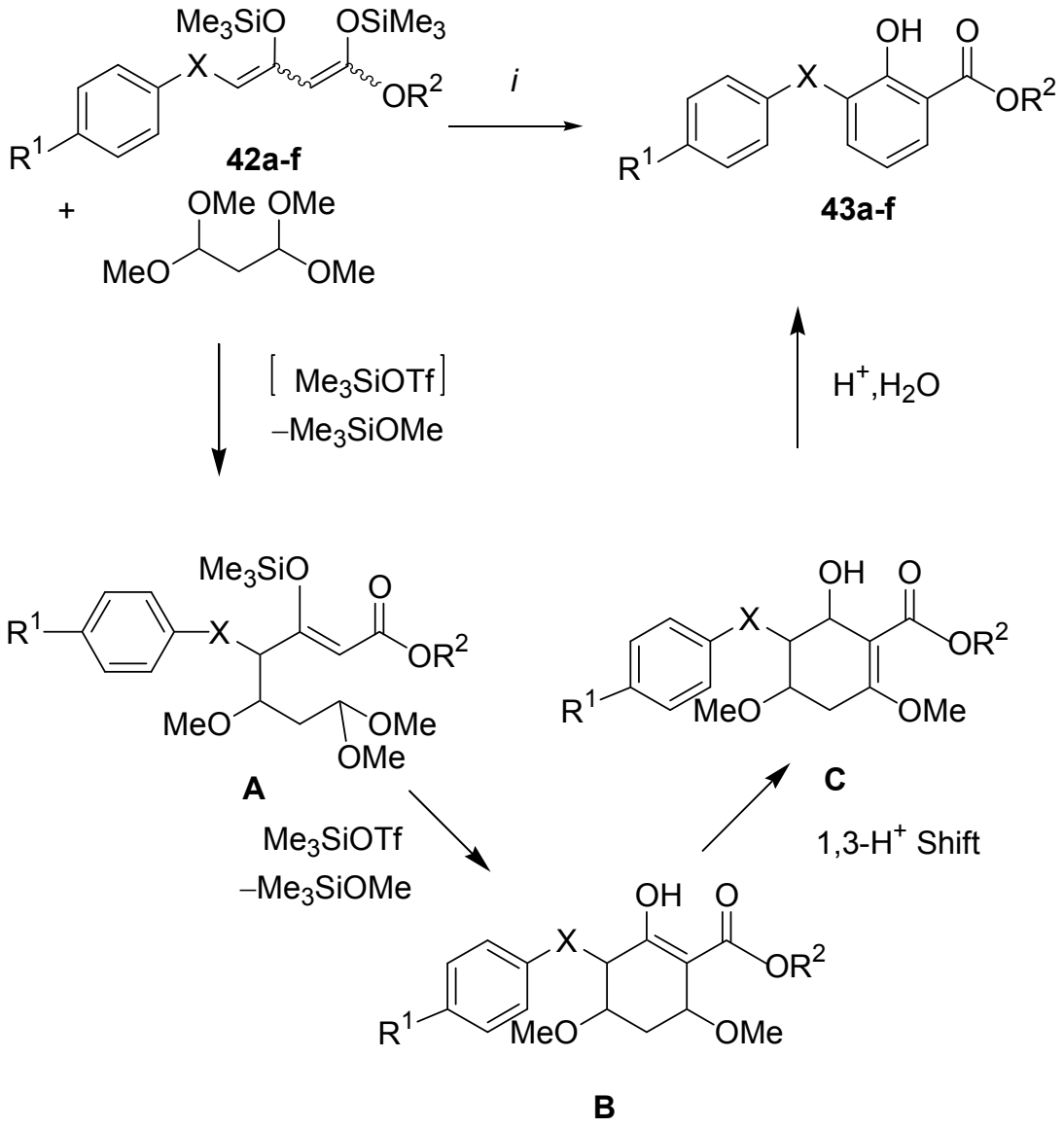
Table 2.3 Synthesis of **42a-g**

40-42	R^1	R^2	X	% (**40**)[a]	% (**41**)[a]	% (**42**)[a]
a	H	Et	S	80	84	89
b	OMe	Et	S	81	78	85
c	H	Et	O	60	91	82
d	Cl	Me	O	30	74	82
e	Me	Me	O	40	75	84
f	Me	Et	S	77	85	80
g	Cl	Et	S	84	90	87

[a] Yields of isolated products

The $TiCl_4$-mediated [3+3] cyclization of 4-thiophenoxy-1,3-bis(silyloxy)-1,3-dienes **42a,b** with 1,1,3,3-tetramethoxypropane afforded the 3-thiophenoxysalicylates **43a,b** in 30-31% yield (Scheme 2.4, Table 2.4). But the *catalytic* [3 + 3] cyclizations of 1,3-bis(silyl enol ethers) with 1,1,3,3-tetramethoxypropane gave a better yields (40-52%).These reactions provide a convenient approach to a variety of functionalized salicylates under mild conditions. Notably, the products are not directly and readily available by other methods. The trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) catalyzed condensation of silyl enol ethers with acetals, introduced by Noyori et al.,[65] has found a number of applications in organic synthesis.The Me_3SiOTf-catalyzed cyclization of 1,1,3,3-tetramethoxypropane with 4-phenoxy- and 4-thiophenoxy 1,3-bis(silyloxy)-1,3-dienes **42a-f** gave the 3-phenoxysalicylates **43a-f**. During the optimization the workup procedure (10% HCl), the temperature (-78 –20 °C, 6-12 h; then 20 °C, 2-6 h), and the concentration proved to be important parameters. The use of tetraethoxypropane proved to be unsuccessful. The use of trifluoroacetic acid (rather than Me3SiOTf) failed to give the desired product. The formation of salicylates by Me_3SiOTf-catalyzationcan can be explained by the mechanism depicted in Scheme 2.4: the Me_3SiOTf-catalyzed attack of the terminal carbon atom of **42** onto tetramethoxypropane gave intermediate **A**. The subsequent Me_3SiOTf-catalyzed cyclization afforded intermediate **B**, which

underwent a shift of the double bond to give intermediate **C**. Extrusion of water and methanol from **C** afforded the final product.



Scheme 2.4. Synthesis of **43a-f:** Reagents and conditions: *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h (method A); Me_3SiOTf (0.2 equiv.), CH_2Cl_2, –78 → 20 °C, 20 h (method B)

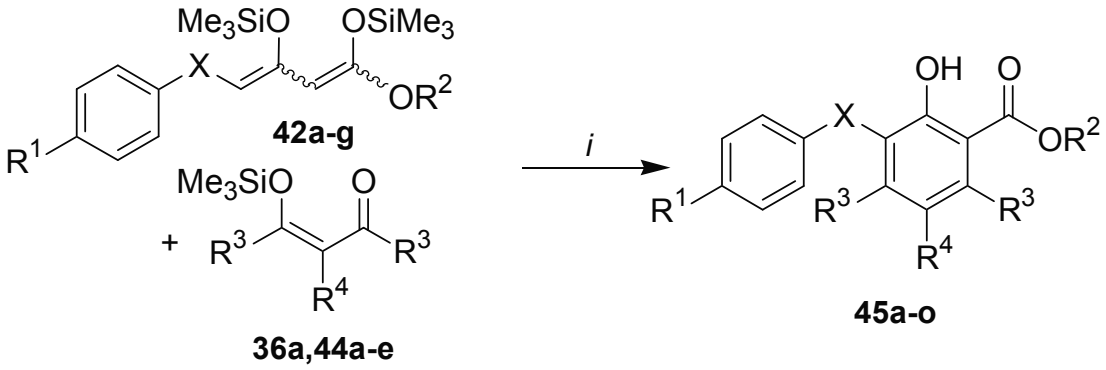
Notably, the formation of a 2-hydroxybenzoate was not observed, when 4-unsubstituted bis-silyl enol ether is used, which shows that water rather than methanol was selectively eliminated. This can be explained by the higher steric hindrance of the methoxy compared to the hydroxy group and the better leaving group ability of the latter. The

mechanism is supported by the isolation of a small amount of 3,5-dimethoxycyclohexanone. The formation of this side product can be explained by cleavage of the ester group of intermediate **B** and subsequent decarboxylation.

Table2.4. Synthesis of **43a-f**

43	R^1	R^2	X	% (**43**)[a]	% (**43**)[b]
a	H	Et	S	31	52
b	OMe	Et	S	30	42
c	H	Et	O	-[c]	45
d	Cl	Me	O	-[c]	46
e	Me	Me	O	-[c]	48
f	Me	Et	S	-[c]	40

[a] Isolated yields, method A: $TiCl_4$, CH_2Cl_2; [b] Isolated yields, method B: Me_3SiOTf (0.1 equiv.), CH_2Cl_2; [c] experiment was not carried out



Scheme 2.5. Synthesis of **45a-o:** Reagents and conditions**:** *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h

The $TiCl_4$-mediated [3+3] cyclization of 4-thiophenoxy-1,3-bis(silyloxy)-1,3-dienes **44a,b** and **44f,g** with 3-(silyloxy)-2-en-1-ones **36a** and **44a-d** afforded the 3-thiophenoxysalicylates **45a-f** and **45n,o** (Scheme 2.5, Table 2.5). Products **45e** and **45f** represent novel 1,3-bis(sulfides). The cyclization of 4-phenoxy-1,3-bis(silyloxy)-1,3-dienes **44c-e** with 3-(silyloxy)-2-en-1-ones **36a**, **44a** and **44c-e** afforded the 3-

phenoxysalicylates **45g-m**. During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution. In addition, the stoichiometry and the temperature are important parameters. The structure of **7g** was independently confirmed by X-ray crystal structure analysis (Figure 2.5).[97]

Table 2.5. Synthesis of **45a-o**

36a,44	**42**	**45**	X	R^1	R^2	R^3	R^4	% (**45**)[a]
44a	**a**	**a**	S	H	Et	Me	H	48
44b	**b**	**b**	S	OMe	Et	Et	H	35
44c	**a**	**c**	S	H	Et	Me	Cl	37
44d	**a**	**d**	S	H	Et	Me	Me	33
36a	**b**	**e**	S	OMe	Et	Me	PhS	34
36a	**a**	**f**	S	H	Et	Me	PhS	34
36a	**c**	**g**	O	H	Et	Me	PhS	30
44a	**c**	**h**	O	H	Et	Me	H	37
44c	**c**	**i**	O	H	Et	Me	Cl	38
44d	**c**	**j**	O	H	Et	Me	Me	43
44e	**c**	**k**	O	H	Et	Me	ArO [b]	30
44c	**d**	**l**	O	Me	Me	Me	Cl	40
44d	**e**	**m**	O	Cl	Me	Me	Me	40
44c	**f**	**n**	S	Me	Et	Me	Cl	30
44c	**g**	**o**	S	Cl	Et	Me	Cl	34

[a] Yields of isolated products; Ar [b] = 3,4-$(MeO)_2C_6H_3$

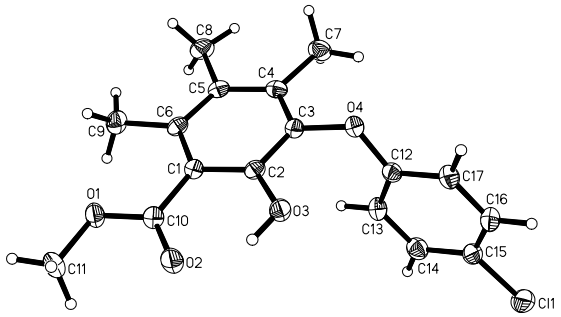
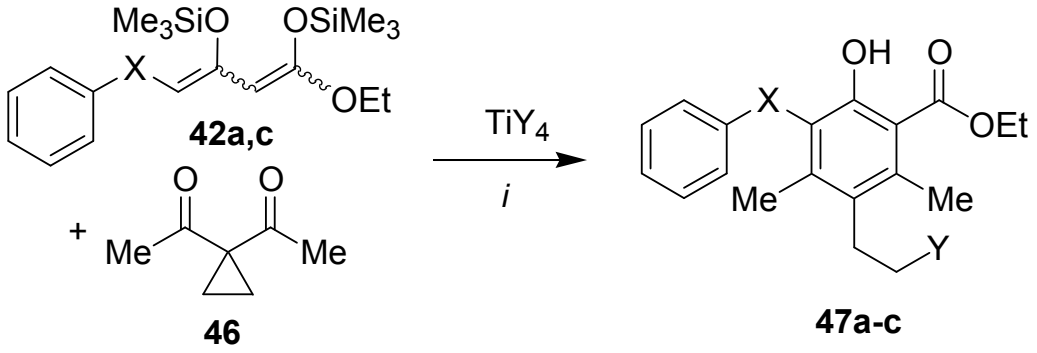


Figure 2.5. Ortep plot of **45m**



Scheme 2.6. Synthesis of **47a-c:** Reagents and conditions**:** *i*: TiY_4, CH_2Cl_2, –78 → 20 °C, 20 h

Table 2.6. Synthesis of **47a-c**

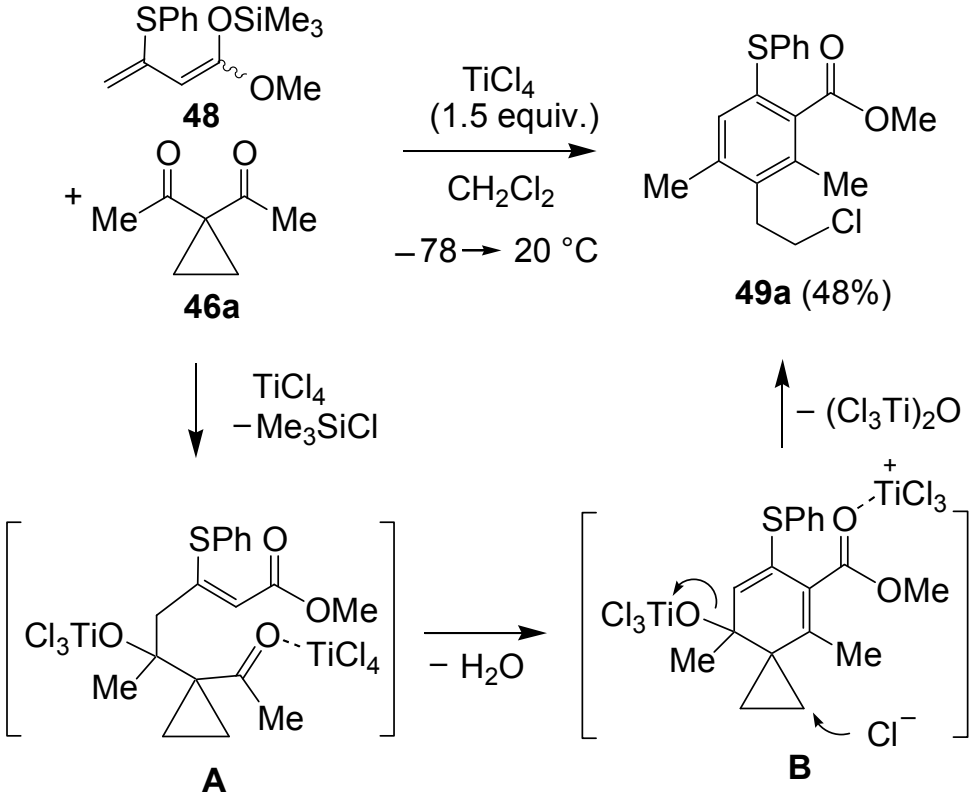
47	X	Y	% (**47**) [a]
a	O	Cl	40
b	O	Br	33
c	S	Br	45

[a] Isolated yields, method A: $TiCl_4$, CH_2Cl_2

The $TiCl_4$- and $TiBr_4$-mediated reaction of 4-thiophenoxy- and 4-phenoxy-1,3-bis(silyloxy)-1,3-dienes **42a** and **42c** with 1,1-diacetylcyclopropane (**46**) afforded the 3-thiophenoxy- and 3-phenoxysalicylates 4**7a-c** containing a remote halide function (Scheme 2.6, Table 2.6). The formation of the products can be explained by means of a domino cyclization-homo-Michael reaction.[66]

2.2.3. Regioselective Synthesis of Functionalized 2-Thiophenoxybenzoates by Domino ′[3+3] Cyclization /Homo-Michael′ Reactions

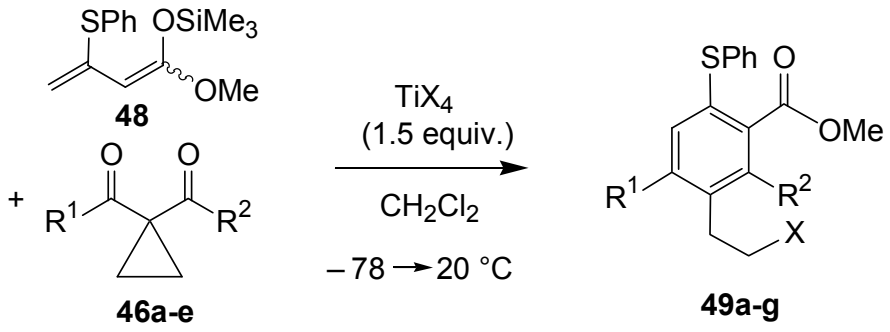
Afterwards, I decided to study the application of current methodology to 1-trimethylsilyloxy-3-thiophenoxy-1,3-butadienes. I developed what is, to the best of my knowledge, the first domino ′[3+3] cyclization / homo-Michael′ reactions of 1-trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 1,1-diacylcyclopropanes. These reactions provide a convenient and regioselective approach to sterically encumbered and functionalized 2-thiophenoxysalicylates which are not readily available by other methods. In contrast to the coupling reactions outlined before, this method relies on the assembly of one of the two arene moieties.



Scheme 2.7. Possible mechanism of the formation of **49a**

The $TiCl_4$-mediated cyclization of 1-methoxy-1-trimethylsilyloxy-3-thiophenoxy-1,3-butadiene **48**, readily available in two steps from methyl acetoacetate,[58] with 1,1-diacetylcyclopropane **46a** afforded the 2-thiophenoxybenzoate **49a** (Scheme 2.7). The

formation of **49a** can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **48** onto **46a** to give intermediate **A**, cyclization via the central carbon atom (intermediate **B**), and subsequent Lewis acid-assisted cleavage of the spirocyclopropane moiety and aromatization by attack of a chloride ion onto the cyclopropane.[67] The process can be regarded as a domino ′[3+3] cyclization / homo-Michael′ reaction.



Scheme 2.8. Synthesis of **49a-c:** Reagents and conditions**:** *i*: TiY_4, CH_2Cl_2, –78 → 20 °C, 14 h

The $TiCl_4$-mediated cyclization of 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** with 1,1-diacylcyclopropanes **46a-d** afforded the 5-chloroethyl-2-thioaryloxybenzoates **49a-d.**

Table 2.7. Synthesis of **49a-g**

48	**46**	**49**	R^1	R^2	X	% [a]
a	**a**	**a**	Me	Me	Cl	48
a	**b**	**b**	Me	Ph	Cl	47
a	**c**	**c**	Me	4-ClC_6H_4	Cl	43
a	**d**	**d**	Me	4-FC_6H_4	Cl	40
a	**e**	**e**	Et	Et	Br	28
a	**a**	**f**	Me	Me	Br	58
a	**b**	**g**	Me	Ph	Br	40

[a] Yields of isolated products

The cyclization of **48** with **46a,b** and **46e** in the presence of $TiBr_4$ afforded the 2-thioaryloxybenzoates **49e-f** containing a remote bromide function (Scheme 2.8, Table 2.7). Products **49** were formed with very good regioselectivity by attack of the terminal carbon atom of the diene onto the acetyl group.

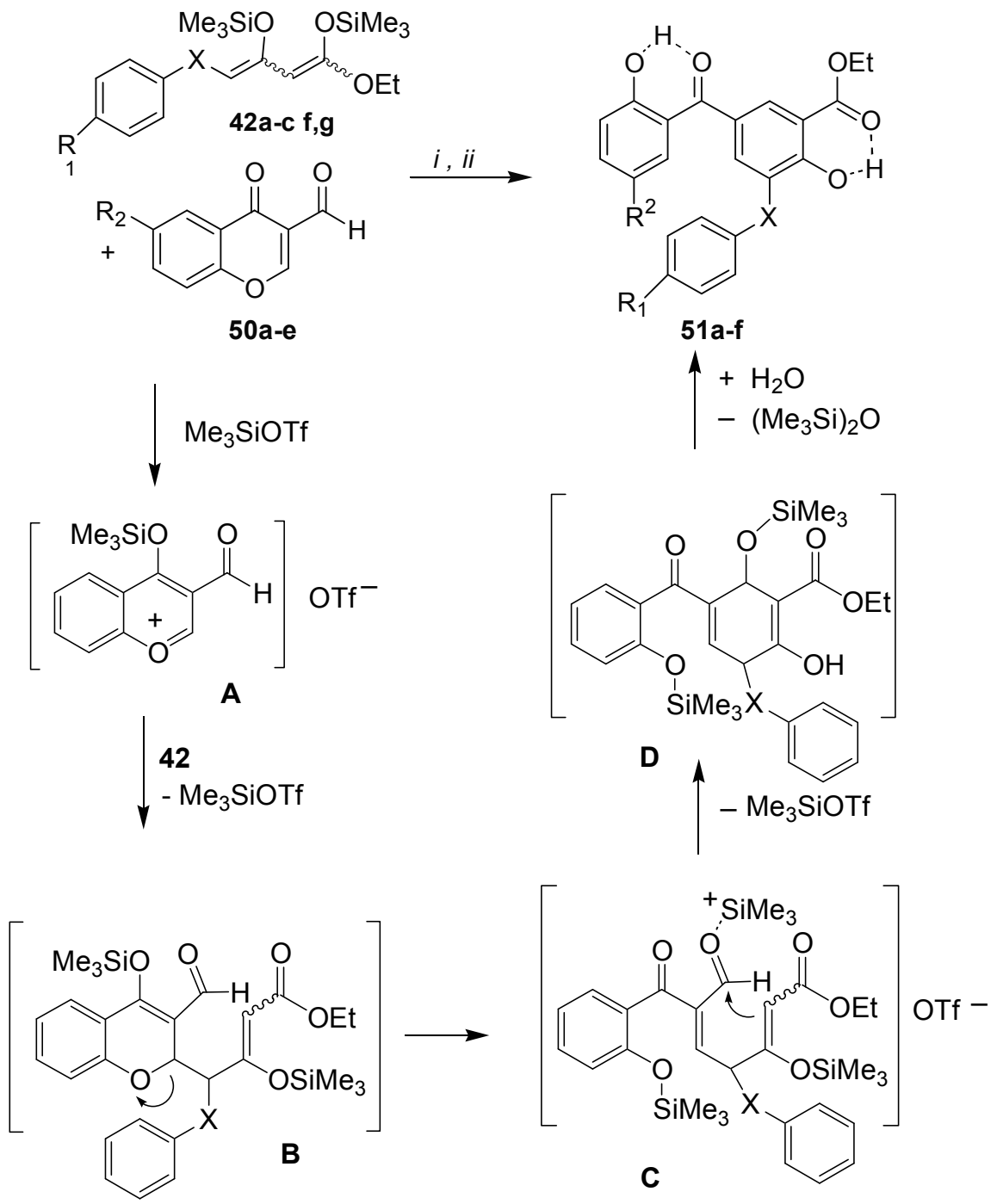
2.2.4. Synthesis of Thiophenoxy and Phenoxy substituted Benzophenones by Domino 'Michael-retro-Michael-aldol' Reactions

Functionalized benzophenones are of considerable interest as pharmacologically relevant natural products and natural product analogues and represent versatile synthetic building blocks.[68,69] Classical synthesis of benzophenone derivatives mainly rely on the Friedel–Crafts acylation.[70] However, unsatisfactory results are frequently obtained when this method is applied to the synthesis of functionalized or substituted derivatives. Major drawbacks result from the drastic reaction conditions and from the low chemo- and regioselectivity. Therefore there is a need for the development of alternative methods which allow the convenient and selective synthesis of a wide range of functionalized benzophenones under mild conditions.[71,72] My starting point was the development of a new method for the synthesis of the interesting thiophenoxy and phenoxy substituted benzophenone **51.**

Table 2.8. Synthesis of **51a-f**

42	**50**	**51**	X	R^1	R^2	% (**51**)[a]
a	**a**	**a**	S	H	Cl	47
b	**b**	**b**	S	OMe	Et	38
c	**c**	**c**	O	H	Me	35
f	**d**	**d**	S	Me	Br	45
g	**c**	**e**	S	Cl	Me	40
g	**e**	**f**	S	Cl	H	50

[a] Yields of isolated products



Scheme 2.9. Synthesis of **51a-f**: Reagents and conditions: *i*: Me_3SiOTf (0.3 equiv) 20 °C, 10 min; *ii*: 1) **42** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; 2) HCl (10%).

The Me_3SiOTf-catalyzed reaction of 4-phenoxy- and 4-thiophenoxy-1,3-bis(silyloxy)-1,3-dienes **42c** and **42a,b,f,g** with 3-formylchromones **50a-e**, following a procedure recently reported,[73] afforded the highly functionalized diaryl ethers and diaryl sulfides

51a-f (Scheme 2.9). The products are formed by a domino Michael–retro-Michael–Mukaiyama-Aldol reaction.The structure of **16b** was independently confirmed by X-ray crystal structure analysis (Figure 2.6).[97]

The formation of **51** can be explained by a domino 'Michael-retro-Michael-aldol' reaction (Scheme 1). The reaction of 3-formylchromone with TMSOTf afforded the benzopyrylium triflate **A**. The reaction of **A** with the terminal carbon atom of **42** gave intermediate **B** which underwent a retro-Michael reaction to give the polyketide **C**. An intramolecular aldol reaction afforded intermediate **D** which was transformed into the product **3a** by elimination of siloxane.

The Me_3SiOTf-catalyzed reaction of 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** with 3-formylchromones **50a**, afforded the highly functionalized diaryl sulfide **52**, in low yield (Scheme 2.10). The reaction of 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes with other 3-formylchromones did not work or afforded very low yield, particularly with 6-alkylated formylchromone. The effort to optimize the reaction conditions is in progress.

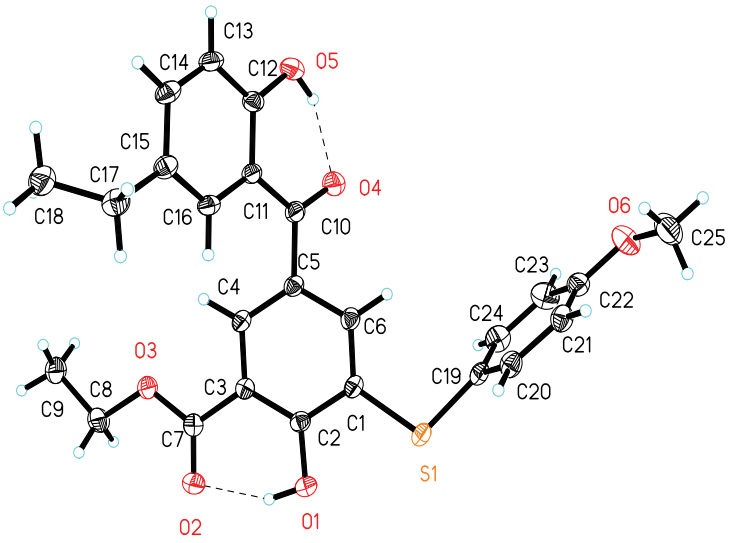
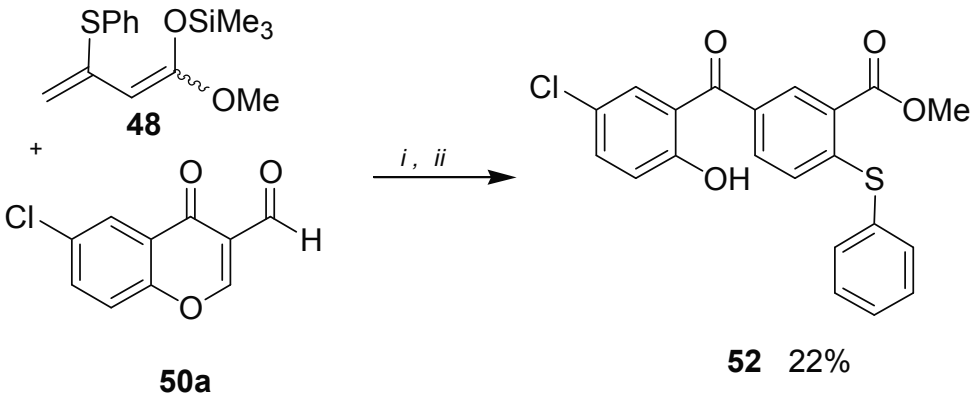


Figure 2.6. Ortep plot of **51b**



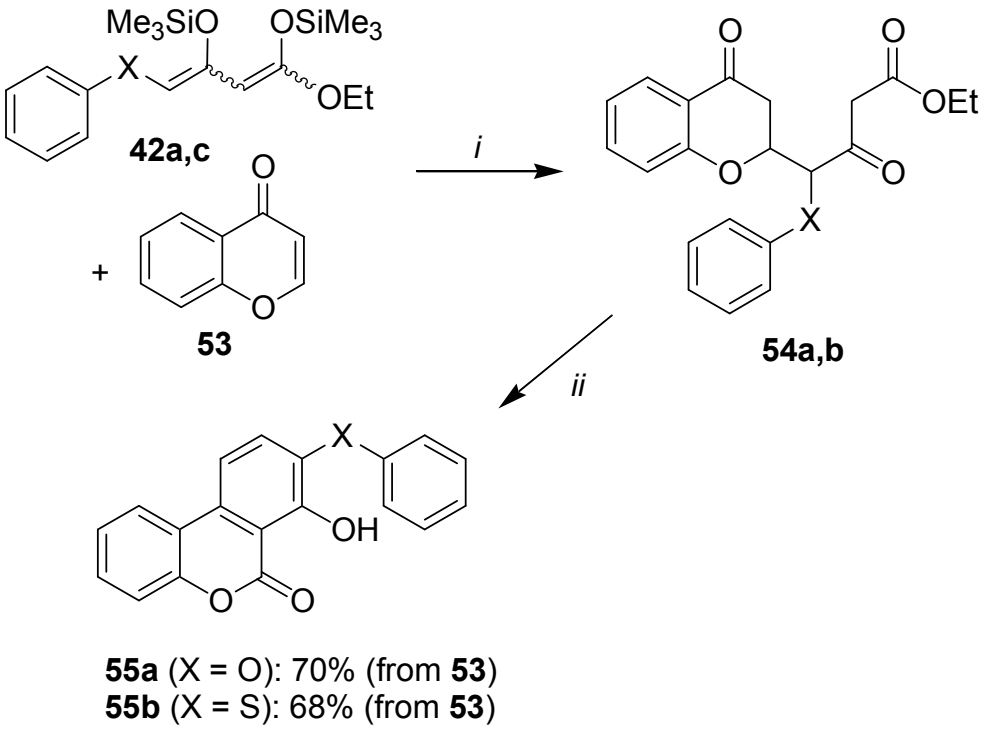
Scheme 2.10. Synthesis of **52**: Reagents and conditions: *i*: Me_3SiOTf (0.3 equiv) 20 °C, 10 min; *ii*: 1) **11a,c** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; 2) HCl (10%).

2.2.5. Synthesis of Fuctionalized Biaryl Lactones by Domino Michael-Retro-Michael-lactonization Reactions.

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo-[*b,d*]pyran-6-ones) are biaryl lactones which are present in a variety of pharmacologically relevant natural products. Autumnariol has been isolated from onions of *Eucomis autumnalis Greab.* (*Liliaceae*),[74]and a number of related natural products, such as autumnariniol[75] alternariol,[76]and altenuisoln [77] are known.[78] 6*H*-benzo[*c*]chromen-6-ones represent specific inhibitors of endothelic cell[79] and estrogen receptor[80] growth. The classic approach to the synthesis of 6*H*-benzo[*c*]chromen-6-ones relies on the cyclization of o-bromobenzoic acids with phenols; however, this method is limited to activated substrates and the yields are often low.[81] In my thesis, I studied the synthesis of functionalized 6*H*-benzo[*c*]chromen-6-ones by a new application of the condensation[82] of 1,3-bis-silyl enol ethers with 4-silyloxybenzopyrylium triflates, generated in situ from chromones, to give 2,3-benzopyrans; the latter were transformed into 7-hydroxy- 6*H*-benzo[*c*]chromen-6-ones by domino retro-Michael–aldol–lactonization reactions. [82]

The Me_3SiOTf-catalyzed reaction of **42a,c** with chromone (**53**) afforded products **54a,b** (2,3-benzopyrans) which were transformed (without purification) into diaryl ether **55a** and diaryl sulfide **55b** (Scheme 2.11). The transformation of **54a,b** into **55a,b** proceeds

by a domino Michael–retro-Michael–lactonization reaction. The structure of **55** was independently confirmed by X-ray crystal structure analysis (Figure 2.7).[97]



Scheme 2.11. Synthesis of **55a,b**. *i*: 1) Me_3SiOTf (1.3 equiv) 20 °C, 1 h; 2) **42a,c** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; 3) HCl (10%); *ii*: NEt_3 (2.0 equiv), EtOH, 20 °C, 12 h

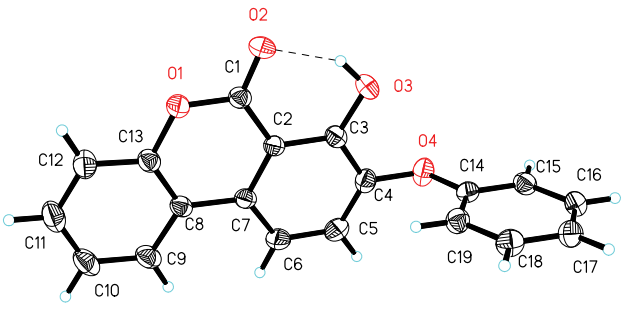


Figure 2.7. Ortep plot of **55a**

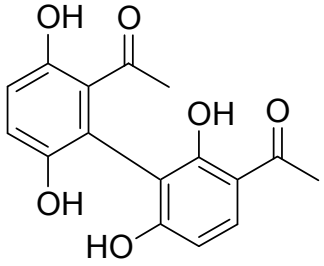
2.3. Conclusion

In conclusion, a new concept for the synthesis of a variety of functionalized diaryl sulfides and diaryl ethers based on [3+3] cyclizations of novel 1,3-bis(trimethylsilyloxy)-1,3-dienes was developed. The synthesis of novel 1,3-bis(sulfides) reported herein carries additional advantages. In addition, I developed the first domino ′[3+3] cyclization / homo-Michael′ reaction of 1-trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 1,1-diacylcyclopropanes. This reaction provides a convenient approach to 2-thiophenoxybenzoates containing a remote halide function. The reactions provide a regioselective access to sterically encumbered, highly functionalized products which are not readily available by other methods. A variety of benzophenones by a domino 'Michael-retro-Michael-aldol' reaction of 1,3 bis-silyl enol ethers with 3-formyl benzopyrylium triflates is also reported. This method allows a convenient procedure for the synthesis of these pharmacologically relevant compounds. Traditional methodologies rely on the Friedel–Crafts acylation which have many drawbacks in terms of yield and selectivity. The condensation of 1,3 bis-silyl enol ethers with benzopyrylium triflates, generated in situ by the reaction of chromone with Me_3SiOTf, afforded functionalized 2,3-dihydrobenzopyrans; treatment of the latter with NEt_3 resulted in a domino Michael–retro-Michael–lactonization reaction. This methodology allows for the convenient synthesis of 6*H*-benzo[*c*]chromen-6-ones

3. Regioselective Synthesis of Functionalized Biaryls based on Cyclizations of 4-Aryl-1,3-bis(trimethyl-silyloxy)-1,3-butadienes

3.1. Introduction

Functionalized biaryls containing a 3-arylsalicylate substructure occur in a variety of pharmacologically relevant natural products. The simple biaryls cynandione A-C **56** have been isolated from many plant sources and show a considerable in vitro activity against hepatocytes, human bladder carcinoma T-24 cells, epidermoid carcinoma KB cells, and human hepatoma PLC/PRF/5 cells.[83] A number of natural products, such as knipholone, 6'-*O*-methylknipholone or (+)-asphodelin, contain an anthraquinone moiety.[84] Other compounds, e. g. secalonic acid A or globulixanthone E, contain a bixanthenyl substructure.[85] 3-Arylsalicylates are also present in many flavones (e. g. 2,3-dihydroamentoflavone,[4a] bartramiaflavone,[86b] robustaflavone,[4c] dichamanetin).[86d,e] For some derivatives, inhibition of the human liver cathepsin B and K has been reported.[86f,g] The natural product anastatin A **57**, which contains a hydroxylated dibenzofuran moiety, shows hepatoprotective activity.[87]



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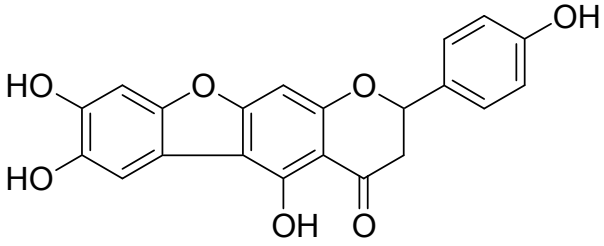


57

The most important synthetic approach to biaryls relies on palladium(0)-catalyzed cross-coupling reactions.[88] Although these reactions are broadly applicable, the synthesis of sterically encumbered products can be difficult or not possible at all. In addition, the regioselective synthesis of the required aryl halides or triflates can be a very difficult task. Some years ago, Chan *et al.* developed[58] a convenient approach to salicylates by formal [3+3] cyclizations[89] of 1,3-bis(trimethylsilyloxy)-1,3-dienes[10b] with 3-trimethylsilyloxy-2-en-1-ones. Recently, Langer et al. developed a catalytic variant of

this transformation.[90] In my thesis I studied, for the first time, the synthesis of 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-butadienes and their application to the synthesis of functionalized biaryls. The sterically encumbered and functionalized biaryls reported herein are not readily available by other methods.

3.2. Results and Discussion

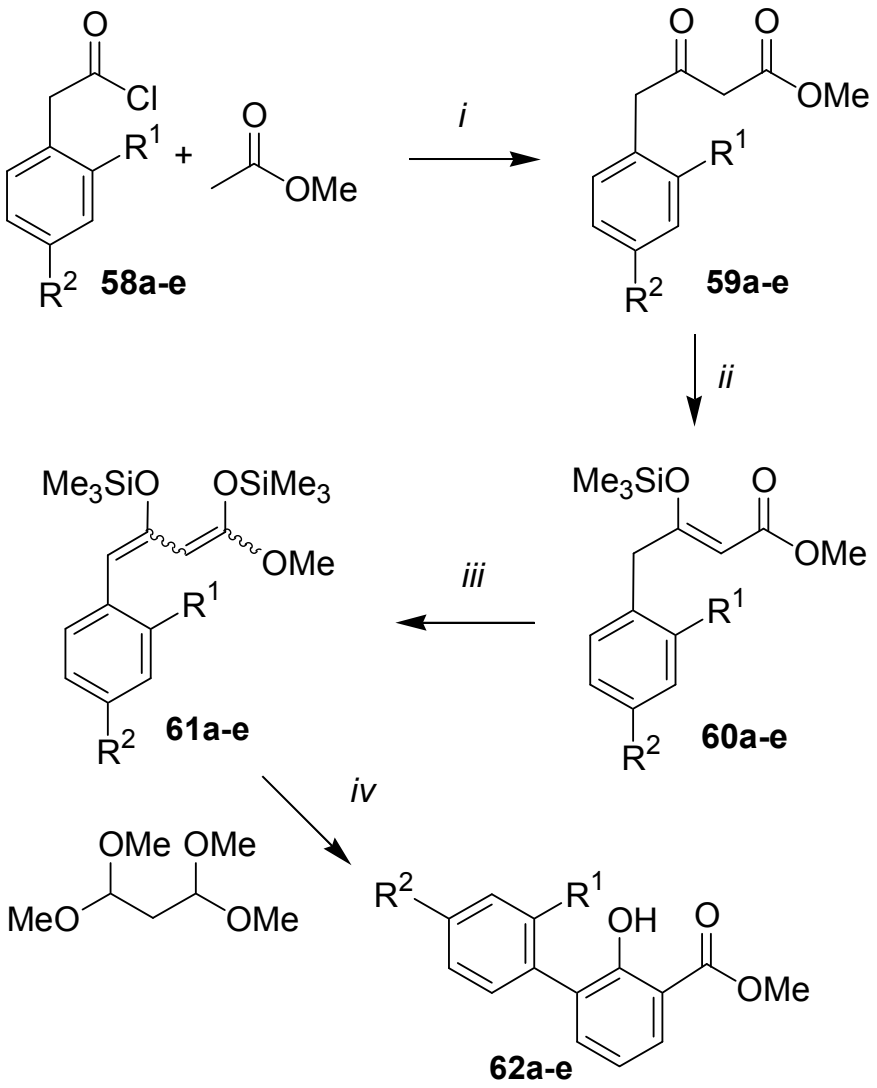
3.2.1. Synthesis of 3-Arylsalicylates

My aim was to synthesize 3-arylsalicylates using formal [3+3] cyclizations. The starting materials, 4-arylacetoacetates **59a-e**, were prepared by LDA-mediated reaction of methyl acetate with the α-arylacetyl chlorides **58a-e** (Scheme 3.1, Table 3.1). The silylation of **59a-e** afforded the 3-silyloxy-2-en-1-ones **60a-e**. The novel 4-aryl-1,3-bis(silyloxy)-1,3-dienes **61a-e** were prepared by deprotonation (LDA) of **60a-e** at −78 °C and subsequent addition of trimethylchlorosilane. The Me_3SiOTf-catalyzed cyclization of 4-aryl-1,3-bis(silyloxy)-1,3-dienes **61a-e** with 1,1,3,3-tetramethoxypropane, carried out following a recently reported procedure,[90] afforded the 3-arylsalicylates **62a-e**. The concentration and the stoichiometry proved to be important parameters during the optimization of this reaction. The structure of **62c** was independently confirmed by X-ray crystal structure analysis (Figure 3.1).[97]

Table 3.1. Synthesis of biaryls **62a-e**

2-5	R^1	R^2	% (**59**)[a]	% **60**)[a]	% (**61**)[a]	% (**62**)[a]
a	H	H	60	82	80	44
b	H	OMe	56	80	84	50
c	OMe	H	48	75	82	34
d	H	Cl	34	77	85	43
e	H	Me	45	81	86	36

[a] Isolated yields



Scheme 3.1. Synthesis of **62a-e**; *i*: LDA, THF, –78 → 20 °C, 14 h; *ii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; *iii*: LDA, THF, –78 → 20 °C; *iv*: Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C, 20 h

The $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-dienes **61a-e** with 3-silyloxy-2-en-1-ones **44a,c,d** afforded the 3-aryloxysalicylates **63a-j** (Scheme 3.2, Table 3.2). During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution.

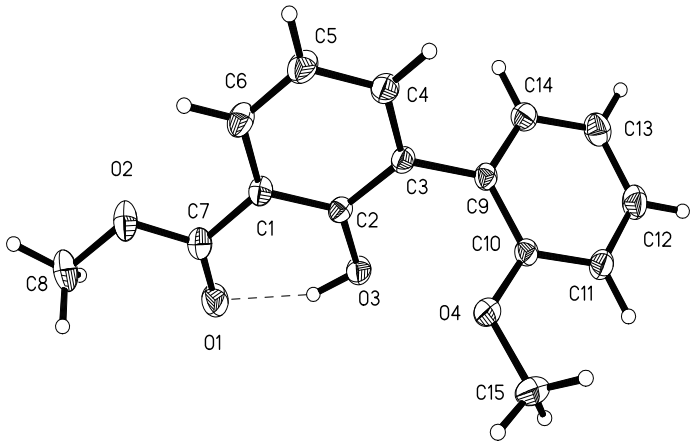
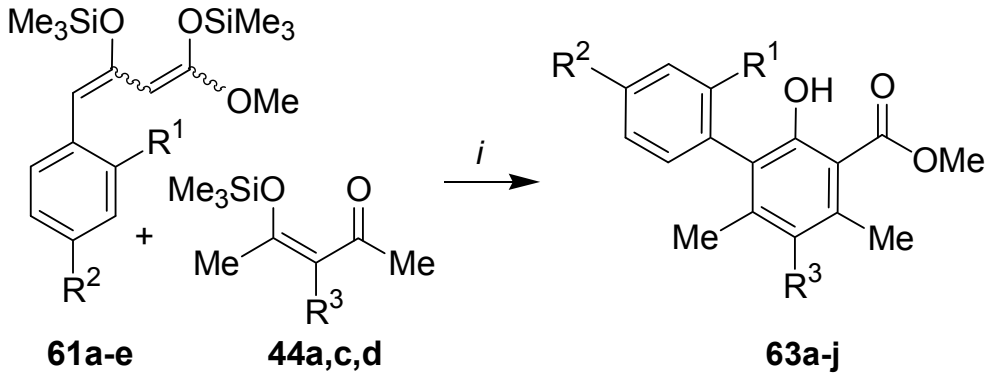


Figure 3.1. Ortep plot of **62c**



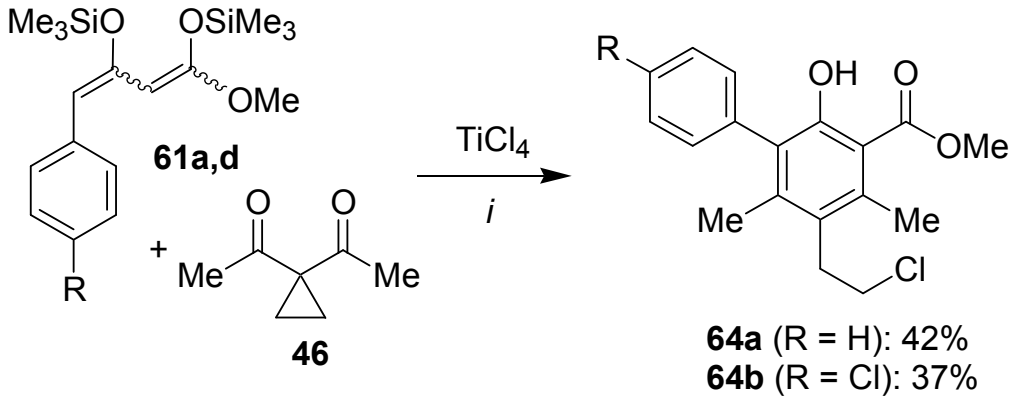
Scheme 3.2. Synthesis of **63a-j**; *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h

Table 3.2. Synthesis of biaryls **63a-j**

61	**44**	**63**	R^1	R^2	R^3	% (**63**)[a]
a	**a**	**a**	H	H	H	41
a	**c**	**b**	H	H	Cl	40
c	**a**	**c**	OMe	H	H	26
c	**c**	**d**	OMe	H	Cl	30
b	**c**	**e**	H	OMe	Cl	38
b	**a**	**f**	H	OMe	H	37
b	**d**	**g**	H	OMe	Me	38
a	**d**	**h**	H	H	Me	35
d	**c**	**i**	H	Cl	Cl	40
e	**c**	**j**	H	Me	Cl	30

[a] Isolated yields

The $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-dienes **61a** and **61d** with 1,1-diacetylcyclopropane (**46**) gave the 3-arylsalicylates **64a** and **64b**, respectively (Scheme 3.3)**.** Products **64a,b** are formed by a domino ′[3+3]-cyclization-homo-Michael′ reaction.[66]



Scheme 3.3. Synthesis of **64a,b**; *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h

3.3. Conclusion

In conclusion, a variety of functionalized, sterically encumbered biaryls were prepared by formal [3+3] cyclizations of novel 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-dienes. The products are not readily available by other methods.

4. Synthesis of 1-Azaxanthones by Condensation of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with 3-(Cyano)-benzopyrylium Triflates and Subsequent Domino ′Retro-Michael / Nitrile-Addition / Heterocyclization′ Reaction

4.1. Introduction

1-Azaxanthones (i. e. 5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridines) are of considerable pharmacological relevance. For example, they show antiinflammatory activity and represent inhibitors of the passive cutaneous anaphylaxis.[91] 1-Azaxanthones are available, based on pioneering work of Ghosh and coworkers,[92a] by base-mediated reaction of 3-cyanochromones with active methylene compounds.[92] Despite its preparative utility, the scope of this approach is limited to specific substrates and substitution patterns. 4-(Trimethylsilyloxy)benzopyrylium triflates can be readily generated by addition of trimethylsilyl-trifluoromethanesulfonate (TMSOTf) to chromones. Their reaction with nucleophiles allows the regioselective functionalization of carbon atom C-2 of the chromone moiety. The formal [4+2]-cycloaddition of 1,3-butadienes with 4-(trimethylsilyloxy)benzopyrylium triflates was first reported by Akiba and coworkers.[93] Later, the TMSOTf-mediated [4+2]-cycloaddition of 1,3-butadienes with 3-cyanochromone, via its 4-(trimethylsilyloxy)benzopyrylium triflate, has been reported.[94] In the course of their interest in the development of new domino reactions[4] of 4-(silyloxy)benzopyrylium triflates,[95] Langer et al. reported[96] the TMSOTf-mediated reaction of 3-cyanochromones with 1,3-bis(trimethylsilyloxy)-1,3-butadienes.[10] These reactions allow a convenient synthesis of functionalized 1-azaxanthones which are not readily available by other methods. During my thesis, I studied, based on previous work by Appel and Langer, [96] the scope of this methodology and a comprehensive study related to its preparative scope is reported.

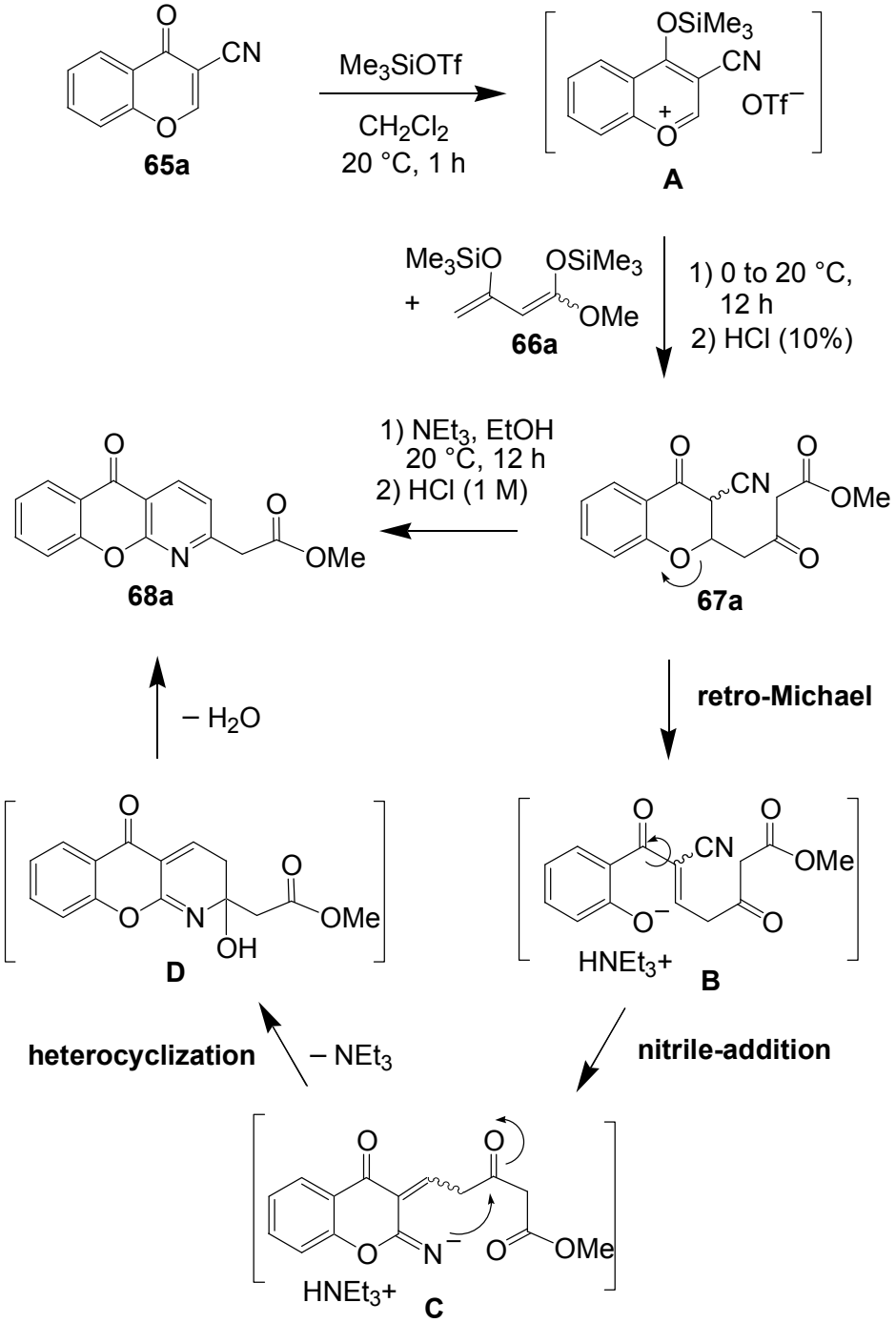
4.2. Results and Discussion

The TMSOTf-mediated reaction of **65a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **66a**, readily available in two steps from methyl acetoacetate,[15] afforded the condensation product **67a** by regioselective attack of the terminal carbon atom of **66a** onto carbon atom C-2 of **65a** and subsequent hydrolysis. Treatment of an ethanol solution of crude **67a** with triethylamine afforded 1-azaxanthone **68a** (Scheme 4.1). The formation of **68a** can be explained by a domino 'retro-Michael-lactonization-aldol' reaction. The base-mediated retro-Michael reaction of **67a** gave open-chained intermediate **B**. The attack of the hydroxy group onto the nitrile gave intermediate **C**. The attack of the imino nitrogen atom onto the carbonyl group (intermediate **D**) and subsequent aromatization by extrusion of water afforded **68a**. The transformation of **67a** into **68a** can be regarded as a domino 'retro-Michael / nitrile-addition / heterocyclization' reaction.

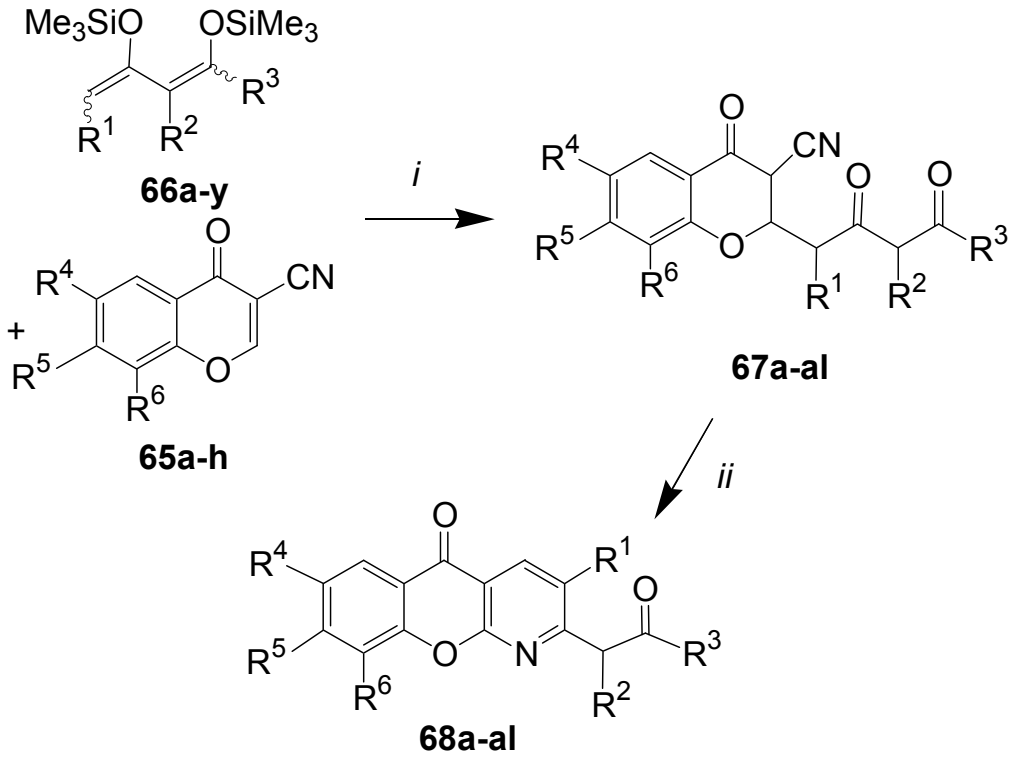
The reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **66a-c**, prepared from methyl, ethyl and isopropyl acetoacetate, with parent 3-cyanochromone (**65a**) and with the alkyl- and halogen-substituted 3-cyanochromones **65b-g** afforded products **67a-j** which were transformed, by reaction with NEt_3, into the 1-azaxanthones **68a-j** (Langer and Appel,[96] Scheme 4.2, Table 4.1). The reaction of parent 3-cyanochromone **65a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **66d**, prepared from methyl 3-oxopentanoate, afforded **67a**. Treatment of **67a** with triethylamine afforded dibenzo[*b*,*d*]pyran-6-one **69a** (Langer and Appel)[96] rather than the expected methyl-substituted azaxanthone **68k**. The formation of **69a** can be explained by a competing domino ′retro-Michael-aldol-lactonization′ reaction (Scheme 4.3).[82] In contrast, the reaction of **66e** (derived from ethyl 3-oxopentanoate) with chlorinated 3-cyanochromone **65e** afforded azaxanthone **68l** (via **67l**). The reaction of parent cyanochromone **65a** with 1,3-bis(silyl enol ether) **66f**, prepared from ethyl 3-oxohexanoate, afforded **67m**. Treatment of the latter with base resulted in formation of a separable mixture of ethyl-substituted azaxanthone **68m** and dibenzo[*b*,*d*]pyran-6-one **69b**.

In contrast, the exclusive formation of azaxanthones **68n,o** was observed when substituted cyanochromones **65e** and **65h** were employed. The propyl- and butyl-substituted dibenzo[*b*,*d*]pyran-6-ones **69c** and **69d** were isolated from the reaction of parent cyanochromone **65a** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **66g** and **66h**.

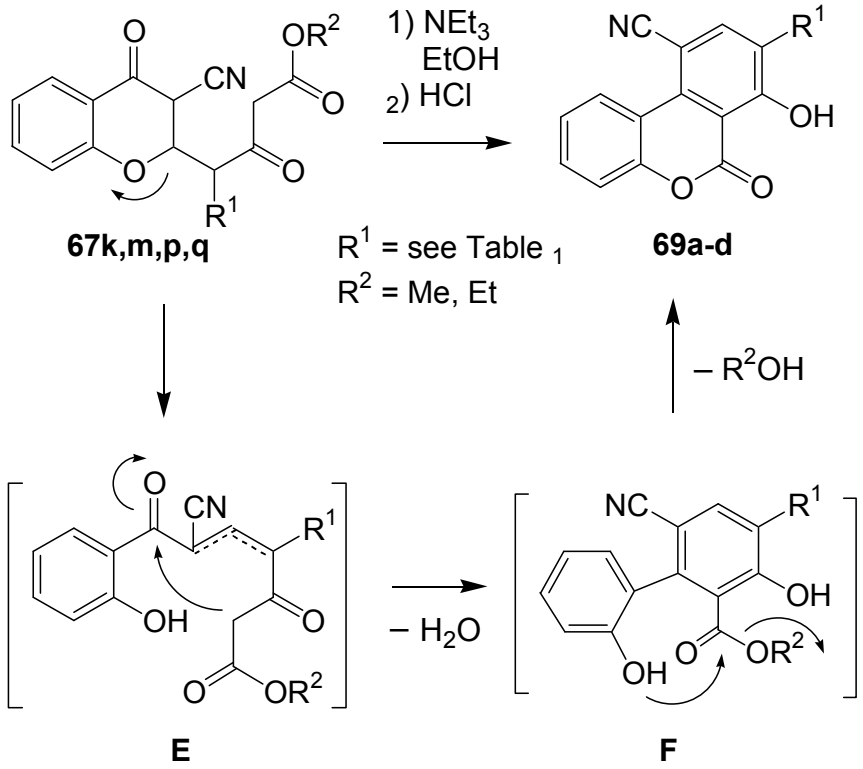
The reaction of **66i** with **65a** and **65e** exclusively afforded the heptyl-substituted azaxanthones **68r** and **68s**, respectively. The allyl-substituted azaxanthones **68t** and **68u** were prepared from **66j**. The reaction of 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-butadienes **66k-m** with 3-cyanochromones **65a,b,e** gave the products **67v-y** which were transformed into the 3-aryl-1-azaxanthones **68v-y**.



Scheme 4.1. Mechanism of the formation of **68a**



Scheme 4.2. Synthesis of 1-azaxanthones **68a-al** a: *i*: 1) **65a-h**, Me_3SiOTf, 1 h, 20 °C, 2) **66a-y**, CH_2Cl_2, 0 → 20 °C, 12 h, 3) HCl (10%); *ii*: 1) NEt_3, EtOH, 20 °C, 12 h, 2) HCl (1 M)



Scheme 4.3. Mechanism of the formation of **69a-d**

3-Methoxy-1-azaxanthone **68z** was prepared from 4-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **66n** which is available from methyl 4-methoxyacetoacetate. The reaction of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes **66o-q** with **65a,f,h** afforded the condensation products **67aa-ad** which were transformed into the 3-aryloxy-1-azaxanthones **68aa-ad**. Starting with 4-thioaryloxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes **66r-u**, the 3-thioaryloxy-1-azaxanthones **68ae-ah** were prepared. 1-Azaxanthones **68ai** and **68aj** were prepared from **65a** and from 2-methyl- and 2-ethyl-1,3-bis(trimethylsilyloxy)-1,3-butadienes **66v** and **66w**, respectively.

The reaction of **65a** with cyclohexanone-derived 1,3-bis(trimethylsilyloxy)-1,3-butadienes **66x** and **66y** gave **67ak** and **67al** which were transformed into the tetracyclic azaxanthones **68ak** and **68al**, respectively. The employment of 7- and 12-membered cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadienes **66z** and **66aa** proved to be unsuccessful.

The reaction of 3-cyanochromones with 1,3-diketone-derived 1,3-bis(silyl enol ethers), such as 1-phenyl-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**66ab**) or 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**66ac**), resulted in the formation of complex mixtures.

The structures of all products were proved by spectroscopic methods. The structure of **68t** was independently confirmed by X-ray crystal structure analysis (Figure 4.1).[97]

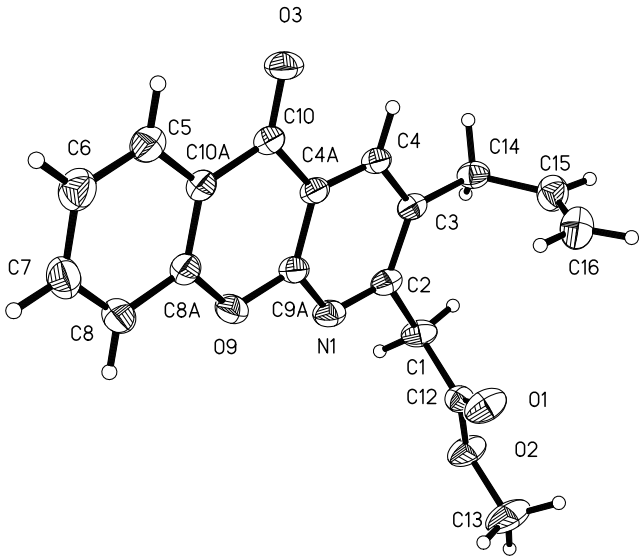


Figure 4.1. Ortep plot of **68t** (50% probability level)

Table 4.1. Products and yields

65	**66**	**68**	**69**	R^1	R^2	R^3	R^4	R^5	R^6	% **(68,69)**[a]
a	**a**	**a**		H	H	OMe	H	H	H	41
a	**b**	**b**		H	H	OEt	H	H	H	46
a	**c**	**c**		H	H	OiPr	H	H	H	42
b	**a**	**d**		H	H	OEt	Me	H	H	40
c	**c**	**e**		H	H	OiPr	Et	H	H	31
d	**a**	**f**		H	H	OEt	iPr	H	H	41
e	**a**	**g**		H	H	OEt	Cl	H	H	37
f	**a**	**h**		H	H	OEt	Cl	H	Cl	48
g	**a**	**i**		H	H	OEt	Br	H	H	34
g	**c**	**j**		H	H	OiPr	Br	H	H	32
a	**d**	**k**	**a**	Me	H	OMe	H	H	H	0 (34)[b]
e	**e**	**l**		Me	H	OEt	Cl	H	H	41
a	**f**	**m**	**b**	Et	H	OEt	H	H	H	17 (34)[b]
e	**f**	**n**		Et	H	OEt	Cl	H	H	46
h	**f**	**o**		Et	H	OEt	Me	Me	H	38
a	**g**	**p**	**c**	nPr	H	OMe	H	H	H	0 (37)[b]
a	**h**	**q**	**d**	nBu	H	OMe	H	H	H	0 (42)[b]
a	**i**	**r**		nHept	H	OEt	H	H	H	25
e	**i**	**s**		nHept	H	OEt	Cl	H	H	38
a	**j**	**t**		Allyl	H	OMe	H	H	H	38
e	**j**	**u**		Allyl	H	OMe	Cl	H	H	30
a	**k**	**v**		Ph	H	OMe	H	H	H	62
a	**l**	**w**		4-Cl(C_6H_4)	H	OMe	H	H	H	50
e	**m**	**x**		2-MeO(C_6H_4)	H	OMe	Cl	H	H	40
b	**m**	**y**		2-MeO(C_6H_4)	H	OMe	Me	H	H	32

a	**n**	**z**	MeO	H	OMe	H	H	H	31
a	**o**	**aa**	PhO	H	OEt	H	H	H	66
f	**o**	**ab**	PhO	H	OEt	Cl	H	Cl	44
h	**p**	**ac**	4-Cl(C_6H_4)O	H	OMe	Me	Me	H	33
f	**q**	**ad**	4-Me(C_6H_4)O	H	OMe	Cl	H	Cl	42
a	**r**	**ae**	PhS	H	OEt	H	H	H	51
h	**s**	**af**	4-Cl(C_6H_4)S	H	OEt	Me	Me	H	56
b	**t**	**ag**	4-Me(C_6H_4)S	H	OEt	Me	H	H	63
f	**u**	**ah**	4-MeO(C_6H_4)S	H	OEt	Cl	H	Cl	45
a	**v**	**ai**	H	Me	OEt	H	H	H	44
a	**w**	**aj**	H	Et	OEt	H	H	H	42
a	**x**	**ak**	$-(CH_2)_3-$		OEt	H	H	H	36
a	**y**	**al**	$-CH_2CHMeCH_2-$		OMe	H	H	H	32 [c]
a	**z**	**am**	$-(CH_2)_4-$		OMe	H	H	H	0
a	**aa**	**an**	$-(CH_2)_9-$		OMe	H	H	H	0
a	**ab**	**ao**	H	H	Ph	H	H	H	0
a	**ab**	**ap**	H	H	Ph	H	H	H	0

[a] Yields of isolated products **68** over two steps (based on **65**). [b] Yields in brackets refer to **69a-d** (structures see Scheme 3). [c] dr = 2:3

The overall yields of 1-azaxanthones **68a-al** are, in most cases, only moderate. However, it has to be taken into account that the yields refer to *two* steps. In fact, a 50% overall yield is obtained when each individual step proceeds in ca. 70% yield. The moderate yields can be explained by the fact that, for the first step, the conversion is often not complete. However, the yields could not be increased by employment of an excess of the 1,3-bis(trimethylsilyloxy)-1,3-butadiene or by longer reaction times.

The yields depend on the type of 1,3-bis(trimethylsilyloxy)-1,3-butadiene and 3-cyanaochromone employed. The synthesis of 3-alkyl-1-azachromones from parent 3-cyanochromone is problematic, due to the competing formation of dibenzo[*b*,*d*]pyran-6-ones which might be related to the steric influence of the alkyl group. In contrast, the synthesis of 3-alkyl-1-azachromones derived from substituted 3-cyanochromones proved

to be possible. Relatively good yields are observed for 1-azaxanthones **68w-y** prepared from the phenyl- and 4-chlorophenyl-substituted dienes **66k,l**. The yields dropped for products **68x,y** which were prepared from diene **66m** (containing the sterically more demanding 2-methoxyphenyl group). The yields of 1-azaxanthones **68aa-ah**, containing an aryloxy- or thioaryloxy-substituent, are again relatively good. These results can be explained by the assumption that, despite their steric effect, all these substituents exert an advantageous electronic effect in the first step (the addition of the diene onto the pyrylium salt) or in the second step (formation of intermediate **B** in Scheme 4.1). The yields of tetracyclic products **68ak** and **68al** are rather low and the synthesis of analogues containing larger annulated rings was not possible at all. This might be explained by steric effects. The failure of the synthesis of **67ao** and **67ap** (and, thus, of the corresponding 1-azaxanthones) can be explained by the generally lower reactivity of 1,3-diketone- compared to β-ketoester-derived 1,3-bis(trimethylsilyloxy)-1,3-butadienes.

4.3. Conclusion

In conclusion, a variety of 1-azaxanthones were prepared by TMSOTf-mediated condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-cyanochromones and subsequent base-mediated domino 'retro-Michael–lactonization–aldol' reaction. Noteworthy, the synthesis can be carried out under mild conditions and the reactions proceed in acceptable yields with very good regio- and chemoselectivity. The products are not readily available by other methods.

5. Experimental Section:

5.1. General: Equipment, chemicals and work technique

^{1}H NMR Spectroscopy:

Bruker: AM 250, Avance 250, AC 250 (250 MHz); ARX 300, Avance 300 (300 MHz); Varian VXR 500 S, Avance 500 (500 MHz); δ = 0.00 ppm for Tetramethylsilane; δ = 2.04 ppm for Acetone d-6; δ = 7.26 ppm for Deuterochloroform (CDCl3); Characterization of the signal fragmentations: s = singlet, d = doublet, dd = double of doublet, ddd = doublet of a double doublet, t = triplet, q = quartet, quint = quintet; sext = Sextet, sept = Septet, m = multiplet, br = broadly. Spectra were evaluated according to first order rule. All coupling constants are indicated as (*J*).

^{13}C NMR Spectroscopy:

Bruker: AM 250, Avance 250, AC 250 (62.9 MHz); ARX 300, Avance 300 (75 MHz); Varian VXR 500 S, Avance 500 (125 MHz); δ = 128.00 ppm for Acetone d-6; δ = 77.00 ppm for CDCl3. The multiplicity of the carbon atoms was determined by the DEPT 135 and APT technique (APT = Attached Proton Test) and quoted as CH3, CH2, CH and C for primary, secondary, tertiary and quaternary carbon atoms. Characterization of the signal fragmentations: quart = quartet the multiplicity of the signals was determined by the DEPT recording technology and/or the APT recording technology.

Mass Spectroscopy:

AMD MS40, AMD 402 (AMD Intectra), Varian MAT CH 7, MAT 731.

High Resolution mass spectroscopy: Finnigan MAT 95 or Varian MAT 311; Bruker FT CIR, AMD 402 (AMD Intectra).

Infrared spectroscopy (IR): Bruker IFS 66 (FT IR), Nicolet 205 FT IR; Nicolet Protege 460, Nicolet 360 Smart Orbit (ATR); KBr ,KAP, Nujol, and ATR; Abbreviations for signal allocations: w = weak, m = medium, s = strong, br = broad.

Elementary analysis: LECO CHNS-932, Thermoquest Flash EA 1112.

X-ray crystal structure analysis: Bruker X8Apex Diffractometer with CCD-Kamera (Mo-K_a und Graphit Monochromator, λ = 0.71073 Å).

Melting points: Micro heating table HMK 67/1825 Kuestner (Büchi apparatus); Melting points are uncorrected.

Column chromatography: Chromatography was performed over Merck silica gel 60 (0,063 -0,200 mm, 70 - 230 mesh) as normal and/or over mesh silica gel 60 (0,040 - 0,063 mm, 200 -400 mesh) as Flash Chromatography. All solvent were distilled before use.

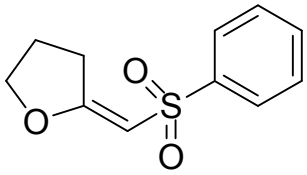
TLC: Merck DC finished foils silica gel 60 F_{254} on aluminum foil and Macherey finished foils Alugram® Sil G/UV_{254}. Detection under UV light with 254 nm and/or 366 nm without dipping reagent, as well as with anisaldehyde sulfuric acid reagent (1 mL anisaldehyde consisting in 100 mL stock solution of 85% methanol, 14% acetic acid and 1% sulfuric acid).

Chemicals and work technique: All solvents for using were distilled by standard methods. All reactions were carried out under an inert atmosphere, oxygen and humidity exclusion. All of the chemicals are standard, commercially available from Merck®, Aldrich®, Arcos® and others. The order of the characterized connections effected numerically, but does not correspond to the order in the main part of dissertation.

5.2 Procedures and Spectroscopic Data

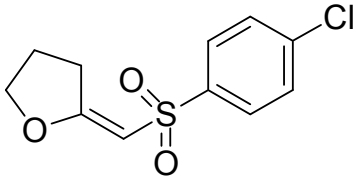
General Procedure for the Cyclization of 1-Bromo-2-chloroethane with Dianions: To a THF solution of LDA (prepared by addition of 5.0 mmol of *n*-BuLi, 2.5 M in hexane, to a solution of diisopropylamine (0.57 ml, 5.0 mmol) in 12 ml of THF, stirred for 30 min), was added 1-phenylsulfonyl-2-propanone (397 mg, 2.0 mmol) at 0 °C. The solution was stirred at 0 °C for 45 min. To this solution was added 1-bromo-2-chloroethane (0.17 ml, 2.1 mmol) at -78 °C. The temperature was allowed to rise to 20 °C during 14 h, and the solution was subsequently refluxed for 14 h. To the solution was added hydrochloric acid (1 M) and the mixture was subsequently extracted with EtOAc (3× 200 ml). The organic layers were dried and filtered, the solvent of the filtrate was removed in vacuo, and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane).

2 –[(Phenylsulfonyl)methylidene]tetrahydrofuran (10a):



Starting with 1-phenylsulfonyl-2-propanone **9a** (3.90 g, 19.76 mmol), and 1-bromo-2-chloroethane (1.8 ml, 21.74 mmol), **10a** was isolated as a highly viscos colourless oil (1.99 g, 45%, *E/Z* = 7:3); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92-2.09 (m, 2 ×2 H, CH_2, both isomers), 2.60 (dt, 2 H, *J* = 7.7 Hz, *J* = 1.2 Hz CH_2), 3.05 (dt, 2 H, *J* = 7.9 Hz, *J* = 1.8 Hz, CH_2), 4.15 (t, 2 H, *J* = 7.0 Hz, CH_2), 4.31 (t, 2 H, *J* = 6.8 Hz, CH_2), 5.39 (t, 1 H, *J* = 1.2 Hz, C=C*H*, *Z*-isomer), 5.67 (t, 1 H, *J* = 1.8 Hz, C=C*H*, *E*- isomer), 7.41-7.48 (m, 2 ×3 H, ArH, both isomers), 7.76-7.91 (m, 2 ×2 H, ArH, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 24.1, 29.8, 32.2, 72.9, 75.4 (CH_2), 98.8, 100.1 (CH), 126.7 (2C, CH), 127.3 (2C, CH), 128.6, 129.0 (CH), 129.4 (2C, CH), 132.8 (2C, CH), 143.9, 144.2, 170.1, 174.3(C); IR (neat): $\tilde{\nu}$ = 3086 (w), 3535 (w), 3061 (w), 2936 (m), 1720 (s), 1447 (s), 1402 (m), 1309 (s), 1153 (s), 688 (s), 528 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 224.1 (M^+, 100), 160 (15), 147 (18), 131 (24), 118(31), 89 (23), 77 (66), 51 (34); HRMS (ESI): calcd (%) for $C_{11}H_{12}O_3S$ ([M+1]) 224.05017, found 224.05017.

2[((4-Chhorophenyl)sulfonyl)methylidene]tetrahydrofuran (10c):

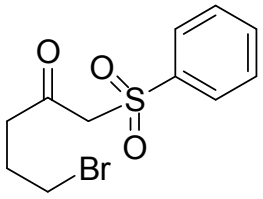


Starting with 1-(4-chlorophenyl)sulfonyl-2-propanone **9c** (1.50 g, 6.44 mmol), and 1-bromo-2-chloroethane (0.64 ml, 7.73 mmol), **10c** was isolated as a highly viscos colourless oil (668 mg, 40%, *E/Z* = 6:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21-2.34 (m, 2 ×2 H, CH_2, both isomers), 2.88 (dt, 2 H, dt, 2 H, *J* = 7.7 Hz, *J* = 1.2 Hz CH_2), 3.31 (dt, 2 H, *J* = 7.8 Hz, *J* = 1.7 Hz, CH_2), 4.42 (t, 2 H, *J* = 7.0 Hz, CH_2), 4.58 (t, 2 H, *J* = 6.9 Hz, CH_2), 5.65 (t, 1 H, *J* = 1.1 Hz, C=C*H*, *Z*-isomer), 5.91 (t, 1 H, *J* = 1.7 Hz, C=C*H*, *E*- isomer), 7.64, 7.73 (2×d, 4 H, *J* = 8.7 Hz, *J* = 8.5 Hz, ArH, both isomers), 7.98, 8.05 (2×d, 4 H, *J* = 8.7 Hz, *J* = 9.1, ArH, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.5, 24.1, 29.9, 32.2, 73.0, 75.5 (CH_2), 98.7, 99.8 (CH), 128.3 (2C, CH), 129.3 (2C, CH), 129.6 (2C, CH), 130.1 (2C, CH), 139.2, 139.4, 140.8, 142.2, 170.5, 174.7 (C); IR (neat): $\tilde{\nu}$ = 3090 (w), 2958 (m), 2933 (m), 1720 (m), 1627 (m), 1582 (m),

1394 (m), 1320 (s), 1155 (s), 1089 (s), 831 (m), 571 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 258 (M^+, 100), 241 (5), 194 (25), 192 (19), 175 (11), 152 (31), 147 (29), 131 (35), 111 (56), 89 (36), 75(44), 55 (37); HRMS (ESI): calcd (%) for $C_{11}H_{11}ClO_3S$ ([M+1]) 258.01082, found 258.01119.

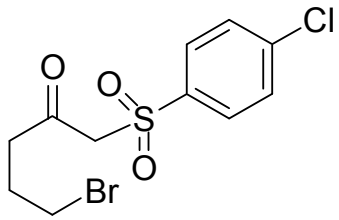
General Procedure for the Reaction of 2-(Alkylidene)-tetrahydrofurans with Borontribromide or Borontrichloride: To a CH_2Cl_2 solution (10 mL per 1 mmol of substrate) of 2-(alkylidene)tetrahydrofuran (1.0 equiv.) was added BBr_3 (4.0-8.0 equiv.) at 0 °C. The reaction mixture was allowed to warm to 20 °C during 12 h and was stirred for 12 h at 20 °C. Water (15 mL per 1 mmol of substrate) was slowly added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc).

5-Bromo-1-(phenylsulfonyl)-2-pentanone (11a):



Starting with **10a** (400 mg, 1.78 mmol) and BBr_3 (0.67 ml, 7.12 mmol), **11a** was isolated as a colourless solid (516 mg, 95%), mp. 77 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (quint, 2 H, *J* = 6.6 Hz, CH_2), 3.09 (t, 2 H, *J* = 6.8 Hz, CH_2), 3.58 (t, 2 H, *J* = 6.4 Hz, CH_2), 4.37 (s, 1 H, CH_2), 7.77 (m, 2H, ArH), 7.90 (m, 1H, ArH), 8.07 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4, 32.9, 42.8, 67.4 (CH_2), 127.4 (2C, CH), 128.6 (2C, CH), 134.8 (CH), 139.0, 197.4 (C); IR (KBr): $\tilde{\nu}$ = 2973 (m), 2925 (m), 1716 (s), 1445 (m), 1321 (s), 1297 (s), 1153 (s), 1009 (w), 688 (m), 525 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 306 (M^+, ^{81}Br, 0.30), 304 (M^+, ^{79}Br, 0.33), 242 (2), 240 (2), 198 (42), 151 (35), 149 (36), 141 (59), 77 (100), 51 (28), 41 (22); HRMS (ESI): calcd (%) for $C_{11}H_{13}BrO_3S$ ([M+1], ^{81}Br) 303.97709, found 303.97763.

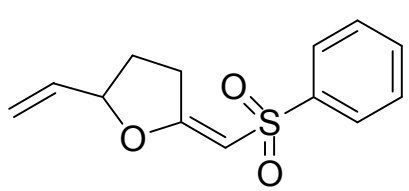
5-Bromo-1-[(4-chlorophenyl)sulfonyl]-2-pentanone (11c):



Starting with **10c** (274 mg, 1.05 mmol) and BBr_3 (0.39 ml, 4.2 mmol), **11c** was isolated as a colourless solid (234 mg, 65%), mp. 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (quint, 2 H, *J* = 6.4 Hz, CH_2), 2.87 (t, 2 H, *J* = 6.8 Hz, CH_2), 3.35 (t, 2 H, *J* = 6.4 Hz, CH_2), 4.10 (s, 1 H, CH_2), 7.48 (d, 2 H, *J* = 8.1 Hz, ArH), 7.77 (d, 2 H, *J* = 8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 32.7, 42.9, 67.2 (CH_2), 130.1 (2C, CH), 130.2 (2C, CH), 137.3, 141.7, 197.3 (C); IR (KBr): $\tilde{\nu}$ = 3090 (w), 2921 (w), 1717 (s), 1582 (m), 1322 (s), 1147 (s), 1088 (s), 827 (m), 530 (s), 460 (m) cm^{-1}; GC-MS (CI): *m/z* (%): 341 ([M+1]$^+$, ^{81}Br, 90), 339 ([M+1]$^+$, ^{79}Br, 86), 261 (40), 259 (100), 223 (5), 191 (13), 159 (5), 69 (8) (19); HRMS (CI): calcd (%) for $C_{11}H_{12}BrClO_3S$ ([M+1], ^{81}Br) 338.94510, found 338.94518.

General Procedure for the Cyclization of 1,4-Dibromo-2-butene with Dianions: A THF solution of LDA (2.5 equiv.) was prepared by addition of *n*-BuLi (1 ml, 2.5 mmol, 2.5 M solution in hexanes) to a THF solution (7 ml) of diisopropylamine (0.36 ml, 2.5 mmol) at 0 °C. After the solution was stirred for 30 min, 1-phenylsulfonyl-2-propanone (198 mg, 1.0 mmol) was added at 0 °C. After stirring for 45-60 min, to the solution was added a THF solution (4 ml) of 1,4-dibromo-2-butene (256 mg, 1.2 mmol) at -78 °C. The temperature was allowed to rise to 20 °C during 12-14 h, and the solution was stirred at 20 °C for 8-14 h. To the solution was added a diluted aqueous solution of HCl and the mixture was subsequently extracted with EtOAc (3×200 ml). The combined organic layers were dried and filtered, the solvent of filtrate was removed in vacuo, and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane).

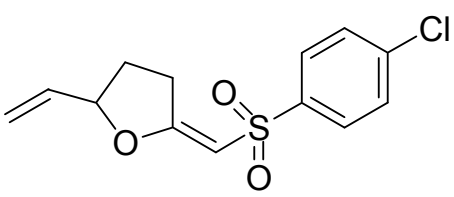
2-[(Phenyl)sulfonyl)methylidene]-5-vinyltetrahydrofuran (12a):



Starting with 1-(4-methylphenyl)sulfonyl-2-propanone **9a** (2.00 g, 10.0 mmol), and 1,4-dibromo-2-butene (2.60 g, 12.1 mmol), **12a** was isolated as a highly viscos colourless oil (1.26 g, 50%, *E/Z* = 6:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85-2.05 (m, 2×1 H, CH–CH_2, both isomers), 2.39-2.45 (m, 2×1 H,

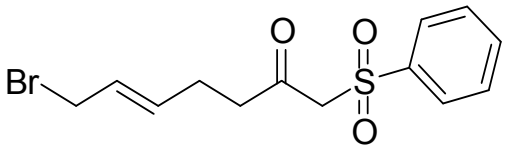
CH–CH_2, both isomers), 2.83 (dt, 1 H, J = 6.9 Hz, J = 1.1 Hz, CH_2–C), 3.43-3.46 (m, 1 H, CH_2–C), 3.43-3.54, 3.71-3.77 (2×m, 2 H, CH_2–C, *E-Z*), 4.95-5.02, 5.24-5.32 (2×m, 2 H, C*H*–CH_2), 5.38-5.49 (m, 4 H, CH_2=CH, both isomers), 5.66 (t, J = 1.1 Hz, C=C*H*, *Z* isomer), 5.93 (t, J = 1.7 Hz, C=C*H*, *E* isomer), 5.94-6.05 (m, 2 H, CH_2=C*H*, both isomers), 7.64, 7.84 (m, 2×3 H, ArH, both isomers), 8.01-8.17 (m, 2×2H, ArH, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 29.3, 29.8, 30.0 (CH_2), 85.1, 87.1, 99.5, 100.4 (CH), 116.5, 118.6 (CH_2), 126.8 (2C, CH), 127.7 (CH), 129.4 (2C, CH), 129.5 (2C, CH), 132.8, 135.3, 135.5 (CH), 143.8, 144.3, 169.1, 173.4 (C); IR (neat): $\tilde{\nu}$ = 3485(w), 2985 (w), 2940 (w), 2210 (w), 1750 (m), 1627 (s), 1447 (m), 1308 (s), 1151 (s), 1083 (m), 589 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 250 (M^+, 24), 183 (36), 141 (27), 125 (7), 109 (65), 91 (39), 77 (100), 67 (23), 51 (26); HRMS (ESI): calcd (%) for $C_{13}H_{14}O_3S$ ([M+1]) 250.06607, found 250.06582.

2-(*E*)–[((4-Chlorophenyl)sulfonyl)methylidene]-5-vinyltetrahydro-furan (12c):



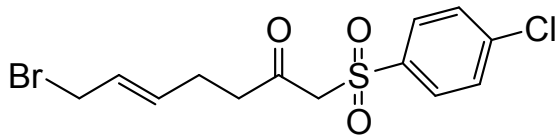
Starting with 1-(4-chlorophenyl)sulfonyl-2-propanone **9c** (1.00 g, 4.29 mmol), and 1,4-dibromo-2-butene (1.10 g, 5.15 mmol), **12c** was isolated as a highly viscos colourless oil (488 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73-1.85 (m, 1 H, CH–CH_2), 2.16-2.27 (m, 1 H, CH–CH_2), 2.89-2.95 (m, 1 H, CH_2–C), 3.17-3.25 (m, 1 H, CH_2–C), 4.73-4.80 (m, 1 H, C*H*–CH_2), 5.16-5.27 (m, 2 H, CH_2=CH), 5.67 (t, J = 1.7 Hz, C=C*H*), 5.70- 5.79 (m, 1 H, CH_2=C*H*), 7.40 (d, 2 H, J = 8.7 Hz, ArH), 7.73 (d, 2 H, J = 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.9, 30.0 (CH_2), 85.3, 100.0 (CH), 118.7 (CH_2), 128.3 (2C, CH), 129.7 (2C, CH), 135.4 (CH), 139.3, 142.8, 173.9 (C); IR (neat): $\tilde{\nu}$ = 3088(w), 3064 (w), 2946 (w), 1625 (s), 1582 (s), 1428 (m), 1319 (s), 1084 (s), 618 (s), 478 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 284 (M, 38), 217 (45), 175 (51), 111 (88), 109 (100), 91 (59), 67 (34), 53(19), 39 (17); elemental analysis: calcd (%) for $C_{13}H_{13}ClO_3S$ (208.0): C 54.83, H 4.60; found: C 54.82, H 4.77.

7-Bromo-1-(phenylsulfonyl)-5-hepten-2-one (13a):



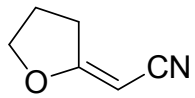
Starting with **12a** (200 mg, 0.94 mmol) and BBr_3 (0.44 ml, 4.7 mmol), **13a** was isolated as a highly viscos colourless oil (234 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (m, 2 H, CH_2), 2.76 (t, 2 H, *J* = 7.0 Hz, CH_2), 3.83 (d, 2 H, *J* = 6.6 Hz, CH_2), 4.08 (s, 2 H, CH_2), 5.63-5.66 (m, 2 H, C*H*=C*H*), 7.49-7.55 (m, 2 H, ArH), 7.60-7.63 (m, 1 H, ArH), 7.80 (dd, 2 H, *J* = 7.0, 1.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 25.8, 43.6, 67.3 (CH_2), 128.2 (CH), 128.6 (2C, CH), 129.8 (2C, CH), 133.8, 134.8 (CH), 139.0, 197.3 (C); IR (neat): $\tilde{\nu}$ = 3064 (m), 2991 (m), 2928 (s), 1731 (s), 1447 (s), 1309 (m), 1085 (s), 999 (m), 688 (m), 437 (w) cm^{-1}; GC-MS (CI): *m/z* (%): 333 ([M+H]$^+$, ^{81}Br, 7), 331 ([M+H]$^+$, ^{79}Br, 7), 253 (13), 252 (15), 251 (100), 143 (4), 127 (3), 111 (13), 109 (7), 79, (10), 71 (16), 69 (20); HRMS (CI): calcd (%) for $C_{13}H_{15}BrO_3S$ ([M+1], ^{81}Br) 330.99857, found 330.99980.

7-Bromo-1-[(4-chlorophenyl)sulfonyl]-5-hepten-2-one (13c):



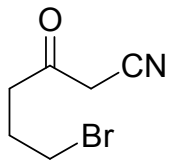
Starting with **12c** (105 mg, 0.37 mmol) and BBr_3 (0.17 ml, 1.84 mmol), **13c** was isolated as a highly viscos colourless oil (95 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56-2.56 (m, 2 H, CH_2), 3.02 (t, 2 H, *J* = 7.0 Hz, CH_2), 4.10 (m, 2 H, CH_2), 4.34 (s, 2 H, CH_2), 5.90-5.93 (m, 2 H, C*H*=C*H*), 7.75 (d, 2 H, *J* = 8.7 Hz, ArH)), 8.01 (d, 2 H, *J* = 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 33.0, 43.7, 67.1 (CH_2), 128.3 (CH), 130.1 (2C, CH), 130.2 (2C, CH), 133.6, (CH), 137.3, 141.6, 197.3 (C); IR (neat): $\tilde{\nu}$ = 3090 (w), 2927 (m), 2210 (w), 1721 (s), 1476 (s), 1154 (s), 969 (m), 815 (m), 763 (m), 469 (w) cm^{-1}; GC-MS (CI): *m/z* (%): 367 ([M+H]$^+$, ^{81}Br, 13), 465 ([M+H]$^+$, ^{79}Br, 10), 287 (39), 286 (14), 285 (100), 179 (2), 109 (6), 91 (3); HRMS (CI): calcd (%) for $C_{13}H_{14}BrClO_3S$ ([M+1], ^{81}Br) 364.96221, found 364.96083.

2-(Cyanomethylidene)tetrahydrofuran (15):



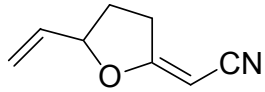
The synthesis of **15** has been previously reported.[11a] Starting with 5-methylisoxazole (3 ml, 36.82 mmol), 1-bromo-2-chloroethane (3.7 ml, 44.18 mmol), **15** (*E*-isomer) was isolated as a colourless oil (1.61 g, 41%) and **15** (*Z*-isomer) was isolated as a colourless oil (1.56 g, 40%). *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08 (quint, 2 H, *J* = 7.0 Hz, CH_2), 2.81 (t, 2 H, *J* = 7.0 Hz, CH_2), 4.26 (t, 2 H, *J* = 7.0 Hz, CH_2), 4.50 (s, 1 H, C*H*CN); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 30.6 (CH_2), 67.6 (*C*HCN), 74.6 (CH_2), 118.8 (CN), 178.0 (C); IR (neat): $\tilde{\nu}$ = 3086 (w), 2913 (s), 2211 (s), 1734 (w), 1429 (m), 1391 (s), 1186 (m), 1003 (s), 930 (m), 725 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 109 (M^+, 82), 80 (7), 68 (100), 52 (14), 42 (68), 38 (6); HRMS (ESI): calcd (%) for C_6H_7NO ([M+1]) 109.05188, found 109.05222. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (quint, 2 H, *J* = 7.0 Hz, CH_2), 2.90 (t, 2 H, *J* = 6.6 Hz, CH_2), 4.47 (s, 1 H, C*H*CN), 4.59 (t, 2 H, *J* = 6.8 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 31.2 (CH_2), 65.2 (*C*HCN), 74.4 (CH_2),117.2 (CN), 177.6(C); IR (neat): $\tilde{\nu}$ = 3086 (w), 2954 (m), 2854 (w), 1652 (s), 1458 (m), 1391 (s), 1186 (m), 1003 (s), 930 (m), 725 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 109 (M^+, 75), 80 (5), 68 (100), 52 (13), 42(71), 29 (3); HRMS (ESI): calcd (%) for C_6H_7NO ([M+1]) 109.05214, found 109.05222.

6-Bromo-1-cyano-3-oxopentane (16):



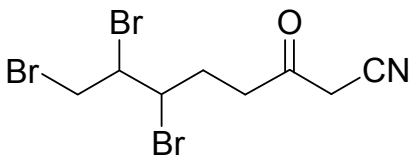
Starting with **15** (363 mg, 3.33 mmol) and BBr_3 (2.51 ml, 26.64 mmol), **16** was isolated as a colourless solid (538 mg, 85%), mp. 71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (quint, 2 H, *J* = 6.4 Hz, CH_2), 3.05 (t, 2 H, *J* = 6.8 Hz, CH_2), 3.68 (t, 2 H, *J* = 6.2 Hz, CH_2),3.74 (s, 2 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2, 32.6, 32.8, 40.5 (CH_2), 113.9 (CN), 196.8 (C); IR (KBr): $\tilde{\nu}$ = 2951 (m), 2920 (m), 2258 (w), 1719 (s), 1642 (m), 1405 (s), 1392 (s), 1328 (s), 977 (m), 581 (m) cm^{-1}; GC-MS (CI): *m/z* (%): 192 ($[M + H]^+$, ^{81}Br, 48), 190 ($[M + H]^+$, ^{79}Br, 59), 151 (9), 149 (9), 110 (100); elemental analysis: calcd (%) for C_6H_8BrNO (190): C 37.92, H 4.24; found: C 38.14, H 4.18.

2-(Cyanomethylidene)-5-vinyltetrahydrofuran (17):



The synthesis of **17** has been previously reported.[11a] Starting with 5-methylisoxazole (3 ml, 36.82 mmol), and 1,4-dibromo-2-butene (9.45 g, 44.18 mmol), **17** (*E*-isomer) was isolated as a colourless oil (1.96 g, 40%) and **17** (*Z*-isomer) was isolated as a colourless oil (1.77 g, 36%). *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78-1.98 (m, 1 H, CH–C*H*$_2$), 2.19-2.24 (m, 1 H, CH–C*H*$_2$), 2.75-2.91 (m, 2 H, CH_2),4.57 (t, 1 H, *J* = 1.5, C*H*CN),4.84-4.90(m, 1 H, C*H*–CH_2), 5.18-5.32(m, 2 H, C*H*$_2$=CH), 5.72-5.83(m, 1 H, CH_2=C*H*) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0, 30.6 (CH_2), 68.2, 86.8 (CH), 118.5 (CH_2),119.0 (CN), 135.4 (CH), 178.2 (C); IR (neat): $\tilde{\nu}$ = 3073 (w), 2988 (w), 2211 (s), 1641 (s), 1430 (m), 1217 (s), 1179 (s), 989 (m), 877 (m), 763 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 135 (M^+, 90), 134 (91), 120 (49), 106 (49), 92 (21), 79 (37), 67 (100), 53(50), 39 (53); HRMS (ESI): calcd (%) for C_8H_9NO ([M+1]) 135.06802, found 135.06787. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82-1.86 (m, 1 H, CH–CH_2), 2.10-2.22 (m, 1 H, CH–CH_2), 2.58-2.64 (m, 2 H, CH_2), 4.19 (s, 1 H, CHCN), 4.89-4.96 (m, 1 H, CH–CH_2), 5.18-5.33 (m, 2 H, CH_2=CH), 5.75-5.86 (m, 1 H, CH_2=CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.2, 31.0 (CH_2), 65.8, 86.4 (CH), 116.9 (CN), 118.3 (CH_2), 135.4 (CH), 176.4 (C); IR (neat): $\tilde{\nu}$ = 3085 (w), 2942 (w), 2212 (s), 1652 (s), 1430 (m), 1364 (m), 1187 (m), 989 (m), 934 (m), 730 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 135.1 (M^+, 83), 134.1 (92), 120.1 (51), 116.1 (10), 106.2 (42), 92.2 (21), 80.2 (34), 79.2 (39), 67.2 (100), 65.2 (19), 53.2 (52), 39.2 (51); HRMS (ESI): calcd (%) for C_8H_9NO ([M+1]) 135.06767, found 135.06787.

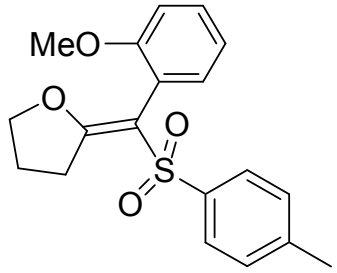
6,7,8-Tribromo-1-cyano-3-oxoheptane (18):



Starting with **17** (153 mg, 1.13 mmol) and BBr_3 (0.85 ml, 9.04 mmol), **18** was isolated as a highly viscos colourless oil (296 mg, 70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.10-2.16 (m, 1 H, Br–CH–XH_2), 2.43-2.48 (m, 1 H, Br–CH–CH_2), 2.81-2.84 (m, 2 H, CH_2CO), 3.45 (s, 2 H, CH_2CN),3.75-3.84 (m, 1 H, Br–CH_2), 3.99-4.05 (m, 1 H, Br–CH_2), 4.29-4.38 (m, 2 H, Br–CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.7, 32.5,

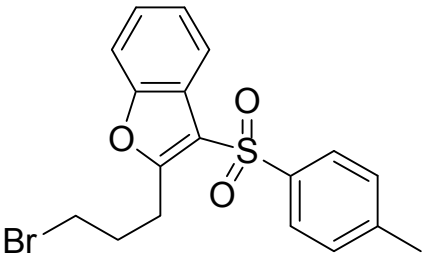
37.0, 40.1 (CH_2), 4.5, 55.5 (CH), 113.7 (CN), 196.3 (C); IR (neat): $\tilde{\nu}$ = 2951 (m), 2914 (m), 2260 (w), 1731 (s), 1403 (m), 1307 (m), 1185 (w), 1082 (m), 617 (w), 557 (w) cm^{-1}; GC-MS (CI): m/z (%): 378 ($[M+H]^+$, ^{81}Br, 42), 376 ($[M+H]^+$, ^{79}Br, 43), 337 (9), 335 (9), 298 (95), 296 (72), 257 (20), 255 (11), 218 (85), 216 (100), 136 (86), 95 (10), 67 (15); HRMS (CI): calcd (%) for $C_8H_{10}Br_3NO$ ([M+1], ^{81}Br) 373.83837, found 373.83853.

2-*(E)*(3-Phenyldihydro)-2(3*H*)-furanylidene-2-(2-methoxyphenyl)-(4-methylphenyl)sulfone (21b):



Starting with 1-(2-methoxyphenyl)-1-(4-methylphenylsulfonyl)acetone **20b** (1.20 g, 3.77 mmol), and 1-bromo-2-chloroethane (0.37 ml, 4.52 mmol), **21b** was isolated as a colourless solid (710 mg, 55%), mp. 132 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.82-1.93 (m, 2 H, CH_2), 2.30 (t, 2 H, *J* = 5 Hz, CH_2), 3.58(s, 3 H, OCH_3), 4.01-4.09 (m, 2 H, CH_2), 6.76-7.88 (m, 2 H, ArH), 7.13-7.19 (m, 3 H, ArH),7.20-7.26 (m, 1 H, ArH), 7.71-7.74 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 23.3, 31.8 (CH_2), 55.6 (OCH_3), 75.0 (CH_2), 108.0 (C), 111.3, 120.9 (CH), 122.9 (C), 128..2 (2C, CH), 129.1 (2C, CH), 130.5, 133.9 (CH), 141.0, 1.43.0, 158.5, 167.4 (C); IR (KBr): $\tilde{\nu}$ = 2970 (w), 2904 (w), 1634 (s), 1595 (m), 1491 (m), 1437 (s), 1306 (s), 1297 (s), 1139 (s), 1083 (m), 989 (m), 681 (m), 583 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 344 (M^+, 52), 208 (6), 189 (31), 91(26), 71 (100), 43 (24); HRMS (ESI): calcd (%) for $C_{19}H_{20}SO_4$ ([M+1]) 344.10768, found 344.107526.

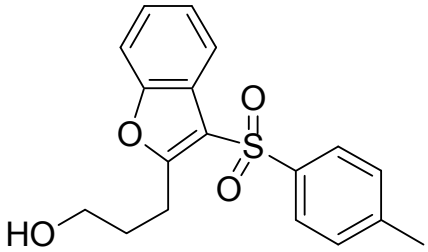
2-(3-Bromopropyl)-3-[(4-methylphenyl)sulfonyl]-benzofuran (22b):



Starting with **21b** (110 mg, 0.31mmol) and BBr_3 (0.15 ml, 1.5 mmol), **22b** was isolated as a highly viscous colourless oil (77 mg, 61%); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (quint, 2 H, *J* = 6.5 Hz, CH_2), 2.31 (s, 3 H, CH_3), 3.30 (t, 2 H, *J* = 7.2 Hz, CH_2), 3.42 (t 2H, *J* = 6.6 Hz, CH_2-Br), 7.22-7.27 (m, 4 H, ArH), 7.34-7.37 (m, 1 H, ArH), 7.80-7.86 (m, 3 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.5 (CH_3), 25.1, 29.9, 31.2

(CH_2), 110.3 (CH), 117.6 (C), 119.4 (CH), 123.1 (C), 123.4, 124.4, 125.7, 128.9 (CH), 138.4, 143.3, 152.3, 160 (C); IR (neat): $\tilde{\nu}$ = 3433 (m), 2984 (w), 2954 (m), 1595 (s), 1474 (s), 1326 (s), 1302 (s), 1255(s), 1090 (m), 1050 (m), 815 (m), 749 (s), 719 (s), 673 (s), 643 (m), 585 (m), 535 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 394 (M^+, ^{81}Br, 100), 392 (M^+, ^{79}Br, 95), 286 (35), 267 (9.07), 205 (14), 158 (19), 131 (41) 102 (28), 65 (16), 39 (7); HRMS (ESI): calcd (%) for $C_{!8}H_{17}BrO_3S$ ([M+1], ^{81}Br) 392.0.00763, found 392.0.00788.

2-(3-Hydroxypropyl)-3-[(4-methylphenyl)sulfonyl]-benzofuran (22f):



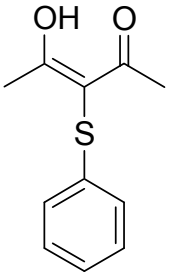
Starting with **21b** (335 mg, 0.97 mmol) and BCl_3 (0.77 ml, 4.8 mmol), **22f** was isolated as a highly viscos colourless oil (108 mg, 34%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (quint, 2 H, *J* = 6.8 Hz, CH_2), 2.32 (s, 3H, CH_3), 3.24 (t, 2 H, *J* = 7.0 Hz, CH_2), 3.63 (t 2 H, *J* = 5.9 Hz, C*H*$_2$-OH), 7.21-7.27 (m, 5 H, ArH), 7.34-7.37 (m, 1 H, ArH), 7.83 (d, 2 H, *J* = 8.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 23.9, 31.2, 61.2 (CH_2), 111.7 (CH), 119.1 (C), 120.8 (CH), 124.6 (C), 124.8 (CH), 125.8 (2C, CH), 127.1 (2C, CH), 130.3 (CH), 139.7, 144.8, 153.7, 163.5 (C); IR (Nujol): $\tilde{\nu}$ = 3420 (w), 1717 (m), 1597 (s), 1331 (s), 1154 (s), 1036 (s), 813 (m), 750 (s), 674 (s), 585 (s), 537 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 330.1 (M^+, 20), 281.1 (4), 207.1 (30), 175.1 (100), 131.1 (55), 115.1 (29), 91.1 (33) 65 (15), 39 (5); HRMS (ESI): calcd (%) for $C_{18}H_{18}O_4S$ ([M+1]) 330.09203, found 330.09203.

General procedure for the synthesis of 3-Thioaryloxy-2,4-pentanedione 35:

Method A: To a stirred solution of 3-chloro-2,4-pentanedione **34** (1.0 mmol) in pyridine (0.1ml) at 0°C was slowly added a solution of benzenethiol **33** (1.0 mmol) in methanol (0.1 ml). The mixture was stirred at room temperature for 6 h. Precipitated pyridine hydrochloride was removed by filtration and washed 3 times with 15 ml ether. The combined filtrate was washed with 25 ml water 5 times and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

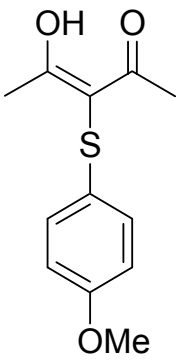
Method B: To a solution of 3-chloro-2,4-pentanedione **34** (1.0 mmol) and benzenethiol **33** (1.0 mmol) cooled to 0°C was added dropwise piperidine (1.0 mmol) in dichloromethane (0.1 ml) for 10 min. After the exothermic reaction ceased, MeOH (0.4 ml) was added to the mixture followed by further stirring for 6 h at room temperature. Successive treatment was identical with method A.

3-Thiophenoxy-4-hydroxy-3-penten-2one (35a):



Method A: Starting with 3-chloro-2,4-pentanedione (5.54ml, 48.91 mmol), thiophenol (5 ml, 48.91 mmol), pyridine (3.95 ml, 48.91mmol) and methanol (4.9 ml), **35a** was isolated as a colourless oil (7.3 g, 72%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.26 (s, 6 H, CH_3), 7.01 (dd, 2 H, *J* = 1.2, 8.2 Hz, ArH), 7.07 (m, 1 H, ArH), (m 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (2C, CH_3), 102.0 (C), 125.0 (2C, CH), 125.6 (CH), 129.6 (2C, CH), 138.1(C), 198.7 (2C); IR (neat): $\tilde{\nu}$ = 3072 (m), 2925 (m), 2853 (w), 1725 (m), 1582 (s), 1478 (s), 1259 (s), 1069 (m), 739 (s), 690 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 208.1 (M^+, 100), 166.1 (30), 147.1 (25), 123.1 (16), 103.1 (18), 88 (13), 43.1 (54); elemental analysis: calcd (%) for $C_{11}H_{12}O_2S$(208.0): C 63.43, H 5.81; found: C 62.9, H 6.40.

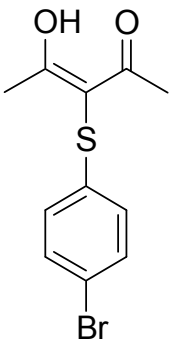
3-(4-methoxythiophenoxy)-4-hydroxy-3-penten-2one (35b):



Method B**:** Starting with 3-chloro-2,4-pentanedione (3.78 ml, 33.33 mmol), 4-methoxythiophenol (4.1 ml, 33.33 mmol), piperidine (3.3 ml, 33.33 mmol), CH_2Cl_2 (3 ml) and methanol (13.5 ml), **35b** was isolated as a colourless solid (2.8 g, 33%), mp. 88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 6 H, CH_3), 3.75 (s, 3 H, OCH_3), 6.81 (d, 2 H, *J* = 9.1 Hz, ArH), 7.01 (d, 2 H, *J* = 9.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (2C, CH_3), 55.2(CH_3), 102.9 (C), 114.8 (2C, CH), 126.8 (2C, CH), 128.3, 157.8 (C), 197.9 (2C); IR (KBr): $\tilde{\nu}$ = 2998 (m), 2961 (m), 2836 (w), 1492 (s), 1294 (s), 1172 (s), 1330 (s), 910 (w), 819 (s), 516 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z*

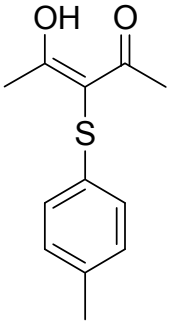
(%): 238 (M^+, 57), 196 (6), 151 (7), 108.1 (100), 59.1 (4), 43.1 (39); elemental analysis: calcd (%) for $C_{12}H_{14}O_3S$ (238.06): C 60.48, H 5.92; found: C 60.71, H 5.99.

3-(4-bromothiophenoxy)-4-hydroxy-3-penten-2one (35c):



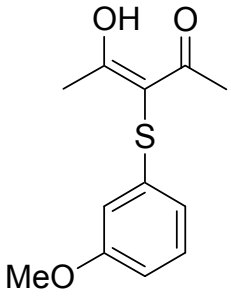
Method B**:** Starting with 3-chloro-2,4-pentanedione (1.5 ml, 13.22 mmol), 4-bromothiophenol (2.5 g, 13.22 mmol), piperidine (1.3 ml, 13.22 mmol), CH_2Cl_2 (1.3 ml) and methanol (5 ml), **35c** was isolated as a colourless solid (1.0 g, 28%), mp. 79 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.29 (s, 6 H, CH_3), 6.92 (d, 2 H, *J* = 8.8 Hz, ArH), 7.35 (d, 2 H, *J* = 8.9 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7 (2C, CH_3), 101.5, 119.2 (C), 126.6 (2C, CH), 132.6 (2C, CH), 137.4(C), 198.7 (2C); IR (KBr): $\tilde{\nu}$ = 3433 (w), 1557 (s), 1472 (s), 1386 (s), 1256 (w), 1020 (m), 909 (w), 809 (s), 479 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 288 (M^+, ^{81}Br, 98), 286 (M^+, ^{79}Br, 96), 246 (43), 244 (41), 192 (40), 164.1 (42), 117 (33), 88 (27), 43.1 (100); elemental analysis: calcd (%) for $C_{11}H_{11}BrO_2S$ (285.96): C 46.01, H 3.86; found: C 45.98, H 3.94

3-(4-methylthiophenoxy)-4-hydroxy-3-penten-2one (35d):



Method B**:** Starting with 3-chloro-2,4-pentanedione (9.1 ml, 80.51 mmol), 4-methylthiophenol (10 g, 80.51 mmol), piperidine (8 ml, 80.51 mmol), CH_2Cl_2 (6 ml) and methanol (30 ml), **35d** was isolated as a colourless solid (14.5 g, 81%), mp. 56 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_3), 2.31 (s, 6 H, CH_3), 6.96 (d, 2 H, *J* = 8.2 Hz, ArH), 7.07 (d, 2 H, *J* = 8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3 (2C, CH_3), 55.6 (CH_3), 101.1 (C), 110.9 (2C, CH), 117.3, 130.4 (CH), 139.6, 160.7(C), 198.7 (2C); IR (KBr): $\tilde{\nu}$ = 3073 (w), 2918 (w), 1576 (s), 1399 (s), 1259 (m), 1085 (w), 1016 (s), 909 (m), 806 (s), 506 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 222.1 (M^+, 100), 180.1 (27), 146.1 (17), 117.1 (25), 88.1 (27), 43.1 (51); elemental analysis: calcd (%) for $C_{12}H_{12}O_2S$ (222.07): C 64.83, H 6.35; found: C 64.94, H 6.31.

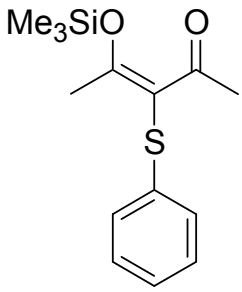
3-(3-methoxythiophenoxy)-4-hydroxy-3-penten-2one (35e):



Method B**:** Starting with 3-chloro-2,4-pentanedione (3.85 ml, 34.09 mmol), 3-methoxythiophenol (4.23 ml, 34.09 mmol), piperidine (3.38 ml, 34.09 mmol), CH_2Cl_2 (3 ml) and methanol (13 ml), **35e** was isolated as a colourless oil (5.9 g, 73%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 6.60 (m, 1 H, ArH), 6.63(br d, 1 H, J = 7.6 Hz, ArH), 6.66 (s, 1 H, ArH), 7.16 (t, 1 H, J = 7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1 (CH_3), 24.8 (2C, CH_3), 102.4 (C), 125.3 (2C, CH), 130.3 (CH), 134.5, 135.5(C), 198.6 (2C); IR (neat): $\tilde{\nu}$ = 3061 (w), 2958 (m), 2835 (m), 1590 (s), 1425 (s), 1182 (m), 857 (m), 686 (s), 534 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 238.1 (M^+, 100), 196.1 (50), 153.1 (32), 108.1 (24), 88.1 (18), 43.1 (9); elemental analysis: calcd (%) for $C_{12}H_{14}O_3S$(238.06): C 60.48, H 5.92; found: C 60.01, H 5.88.

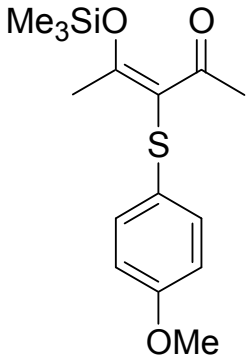
Typical procedure for the synthesis of silyl enol ethers 36 : The reaction was carried out analogously to a known procedure.[63] To a stirred benzene solution (2.5 ml) of **35** (1.0 mmol) was added triethylamine (1.6 mmol). After stirring for 2 h trimethylchlorosilane (1.8 mmol) was added. After stirring for 72 h, the solvent was removed *in vacuo* and to the residue was added Hexane (20 ml) to give a suspension. The latter was filtered under Argon atmosphere. The filtrate was distilled *in vacuo.* The compound was used directly after its preparation.

Synthesis of silyl enol ethers (36a) :



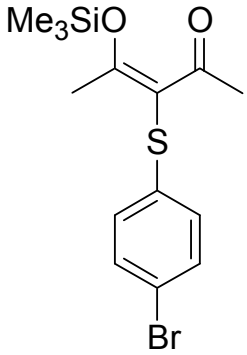
Starting with **35a** (8.0 g, 38.4 mmol), NEt3 (8.6 ml, 61.5 mmol), TMSCl (8.8 ml, 69.1 mmol) and benzene (100ml), **36a** was isolated as a yellow oil (8.7 g, 81%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 2.26 (s, 6 H, CH_3), 7.02-7.21 (m, 5 H, ArH).

Synthesis of silyl enol ethers (36b):



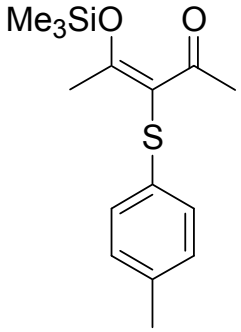
Starting with **35b** (2.36 g, 9.93 mmol), NEt3 (2.2 ml, 15.8 mmol), TMSCl (2.3 ml, 17.9 mmol) and benzene (25ml), **36b** was isolated as a yellow oil (2.8 g, 90%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 2.22 (s, 6 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.85 (d, 2 H, *J* = 8.7 Hz, ArH), 7.05 (d, 2 H, *J* = 8.5 Hz, ArH).

Synthesis of silyl enol ethers (36c):



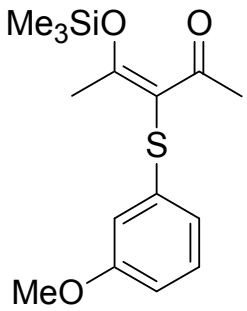
Starting with **35c** (986 mg, 3.43 mmol), NEt3 (0.77 ml, 5.48 mmol), TMSCl (0.78 ml, 6.18 mmol) and benzene (10ml), **36c** was isolated as a yellow oil (980 mg, 79%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 2.21 (s, 6 H, CH_3), 6.95 (d, 2 H, *J* = 8.5 Hz, ArH), 7.35 (d, 2 H, *J* = 8.5 Hz, ArH).

Synthesis of silyl enol ethers (36d):



Starting with **35d** (14 g, 62.97 mmol), NEt3 (14 ml, 100.7 mmol), TMSCl (113.34 ml, 14.3 mmol) and benzene (150ml), **36d** was isolated as a yellow oil (16 g, 92%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 2.21 (s, 6 H, CH_3),2.31 (s, 6 H, CH_3), 6.99 (d, 2 H, *J* = 8.4 Hz, ArH), 7.21 (d, 2 H, *J* = 8.5 Hz, ArH).

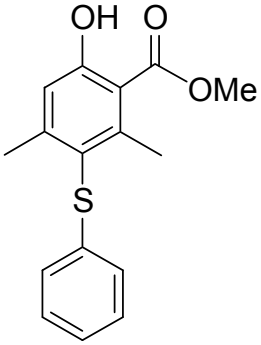
Synthesis of silyl enol ethers (36e):



Starting with **35e** (6.3 g, 26.2 mmol), NEt3 (5.9 ml, 42.0 mmol), TMSCl (47.2 ml, 6.0 mmol) and benzene (65ml), **36e** was isolated as a yellow oil (6.2 g, 81%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 2.15 (s, 3 H, CH_3), 3.41 (s, 3 H, OCH_3), 6.51-6.55 (m, 3 H, ArH), 6.81-6.87 (m, 1 H, ArH).

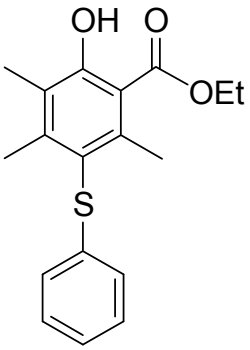
General procedure for the synthesis of diaryl Sufides and diaryl ethers 38 and 45: To a dichloromethane solution (2 mL/mmol) of **36** (1.0 mmol) and **37** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at –78 °C. The solution was allowed to warm to ambient temperature within 20 h. To the solution was added a saturated solution of $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 20 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane = 1:4).

Methyl 4,6-dimethyl-5-(thiophenoxy) salicylate (38a):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (200 mg, 0.71 mmol) 1,3-bis(silyl enol ether) **37a** (185 mg, 0.71 mmol), and $TiCl_4$ (0.08 ml, 0.71 mmol), **38a** was isolated as a colourless solid (99 mg, 48%), mp. 83 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 2.72 (s, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 6.89 (d, 2 H, *J* = 8.2 Hz, ArH), 6.76 (s, 1 H, ArH), 6.91 (s, 1 H, ArH), 7.05 (br t, 1 H, *J* = 7.2 Hz, ArH), 7.18 (br t, 1 H, *J* = 7.4 Hz, ArH),11.17 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 2.7, 52.3, (CH_3), 112.4 (C), 117.7 (CH), 122.7(C), 124.6 (CH), 125.2 (2C, CH), 128.9 (2C, CH), 138.2, 147.1, 151.4, 162.5, 171.8(C); IR (KBr): $\tilde{\nu}$ = 3061 (m), 2954 (m), 1663 (s), 1478 (s), 1360 (s), 1233 (s), 1187 (m), 1024 (m), 947 (w), 740 (s), 690 (m), 629 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 288.1 (M^+, 57), 256.1 (100), 185.1 (7), 91 (6); elemental analysis: calcd (%) for $C_{16}H_{16}O_3S$ (288.08): C 66.64, H 5.59; found: C 66.81, H 5.68.

Ethyl 3,4,6-trimethyl-5-(thiophenoxy) salicylate (38b):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (200 mg, 0.71 mmol) 1,3-bis(silyl enol ether) **37b** (204 mg, 0.71 mmol), and $TiCl_4$ (0.08 ml, 0.71 mmol), **38b** was isolated as a colourless solid (90 mg, 40%), mp. 122 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.42 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.24 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 2.74 (s, 3 H,

CH_3), 4.44(q, 2 H, J = 7.1 Hz, OCH_2), 6.90 (m, 2 H, ArH), 7.06 (br t, 1 H, J = 7.3 Hz, ArH), 7.18 (m, 2 H, ArH),11.52 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7, 14.1, 19.5, 21.6 (CH_3), 61.8 (CH_2), 112.0, 122.5, 123.9 (C), 124.5 (CH), 125.2 (2C, CH), 128.9 (2C, CH), 138.7, 143.7, 149.1, 160.6, 171.9(C); IR (KBr): $\tilde{\nu}$ = 3069 (m), 2980 (m), 1644 (s), 1548 (m), 1395 (s), 1343 (s), 1146 (s), 1083 (m), 1025 (s), 868 (w), 735 (s), 688 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 316 (M^+, 38), 270 (100), 242 (20), 165 (10), 77 (11); elemental analysis: calcd (%) for $C_{18}H_{20}O_3S$ (316.11): C 68.33, H 6.37; found: C 68.23, H 6.48

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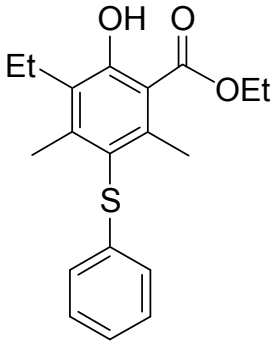
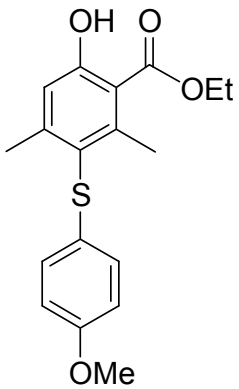
Ethyl 4,6-dimethyl-3-ethyl-5-(thiophenoxy) salicylate (38c):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (200 mg, 0.71 mmol) 1,3-bis(silyl enol ether) **37c** (214 mg, 0.71 mmol), and $TiCl_4$ (0.08 ml, 0.71 mmol), **38c** was isolated as a yellow highly viscous oil (90 mg, 40%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.04 (t, 3 H, J = 7.4 Hz, CH_3), 1.32 (t, 3 H, J = 7.1 Hz, CH_3), 2.40 (s, 3 H, CH_3), 2.64 (s, 3 H, CH_3), 2.68 (q, 2 H, J = 7.4 Hz, OCH_2), 4.35 (q, 2 H, J = 7.1 Hz, OCH_2), 6.82 (dd, 2 H, J = 1.5, 8.3 Hz, ArH), 6.97 (br t, 1 H, J = 7.3 Hz, ArH), 7.10 (br t, 2 H, J = 7.4 Hz, ArH), 11.38 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 13.1, 17.6 (CH_3), 19.4 (CH_2), 20.5 (CH_3), 60.8 (CH_2), 111.1, 121.6 (C), 123.4 (CH), 124.1 (2C, CH), 127.8 (2C, CH), 129.0, 137.7, 142.9, 147.4, 159.4, 170.9(C); IR (neat): $\tilde{\nu}$ = 3057 (m), 2970 (s), 2873 (m), 1732 (w), 1653 (s), 1583 (s), 1551 (s), 1439 (s), 1230 (s), 1084 (m), 866 (w), 813 (m), 689 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 330.2 (M^+, 63), 284.1 (100), 256.1 (24), 139 (9), 165.1 (7), 91.1 (8); HRMS (EI): calcd for $C_{19}H_{22}O_3S$ $[M]^+$: 330.12828, found 330.12842.

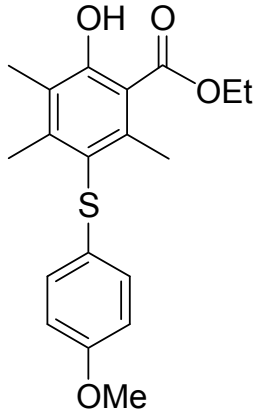
Ethyl 4,6-dimethyl-5-(4-methoxythiophenoxy) salicylate (38d):



Starting with 3-(siloxy)alk-2-en-1-one **36b** (300 mg, 0.96 mmol) 1,3-bis(silyl enol ether) **37d** (263 mg, 0.96 mmol), and $TiCl_4$ (0.1 ml, 0.96 mmol), **38d** was isolated as a colourless solid (138 mg, 43%), mp. 77 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.38 (t, 3 H, J = 7.0 Hz, CH_3), 2.39 (s, 3 H, CH_3), 2.73 (s, 3 H, CH_3), 3.71 (s, 3 H,

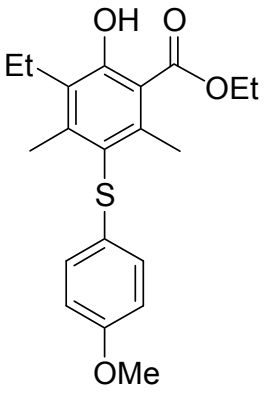
OCH_3), 4.40 (q, 2 H, J = 7.1 Hz, OCH_2), 6.73 (d, 2 H, J = 9.1 Hz, ArH), 6.81 (s, 1 H, ArH), 6.84 (d, 2 H, J = 9.1 Hz, ArH), 11.10 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 20.5, 22.1, 54.3 (CH_3), 60.8 (CH_2), 111.4 113.7 (2C, CH), 116.5 (CH), 123.0(C), 126.3 (2C, CH), 127.9, 145.8, 150.0, 156.5, 161.3, 170.3(C); IR (KBr): $\tilde{\nu}$ = 2991 (m), 2954 (m), 2833 (m), 1653 (s), 1558 (m), 1494 (s), 1450 (s), 1341 (s), 1286 (s), 1125 (w), 871 (m), 623 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 332.1 (M^+, 84), 286 (100), 243 (10), 218 (11), 178 (8) 139 (7), 91 (6); elemental analysis: calcd (%) for $C_{18}H_{20}O_4S$ (332.10): C 65.04, H 6.06; found: C 64.78, H 6.19.

Ethyl 3,4,6-trimethyl-5-(4-methoxythiophenoxy) salicylate (38e):



Starting with 3-(siloxy)alk-2-en-1-one **36b** (300 mg, 0.96 mmol) 1,3-bis(silyl enol ether) **37b** (277 mg, 0.96 mmol), and $TiCl_4$ (0.1 ml, 0.96 mmol), **38e** was isolated as a colourless oil (116 mg, 35%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.32 (t, 3 H, J = 7.1 Hz, CH_3), 2.14 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.66 (s, 3 H, CH_3), 3.66 (s, 3 H, OCH_3), 4.34 (q, 2 H, J = 7.0 Hz, OCH_2), 6.67 (d, 2 H, J = 8.8 Hz, ArH), 6.78 (d, 2 H, J = 8.8 Hz, ArH), 11.39 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7, 13.1, 18.6, 20.7, 54.2 (CH_3), 60.8 (CH_2), 110.9 113.6 (2C, CH), 122.8, 122.9 (C), 126.2 (2C, CH), 128.4, 142.3, 147.9, 156.3, 159.1, 170.9(C); IR (KBr): $\tilde{\nu}$ = 2978 (m), 2835 (m), 1645 (s), 1572 (s), 1491 (s), 1343 (s), 1287 (s), 1183 (s), 1099 (m), 868 (w), 800 (m), 621 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 346 (M^+, 83), 300 (100), 278 (14), 246 (23), 196 (26), 108 (36), 77 (14); elemental analysis: calcd (%) for $C_{19}H_{22}O_4S$ (345.11): C 65.87, H 6.40; found: C 65.71, H 6.59.

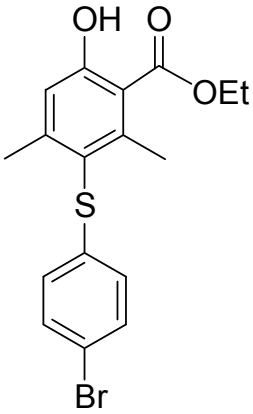
Ethyl 4,6-dimethyl-3-ethyl-5-(4-methoxythiophenoxy) salicylate (38f):



Starting with 3-(siloxy)alk-2-en-1-one **36b** (400 mg, 1.28 mmol) 1,3-bis(silyl enol ether) **37c** (387 mg, 1.28 mmol), and $TiCl_4$ (0.15 ml, 1.28 mmol), **38f** was isolated as a colourless highly viscous oil (175 mg, 38%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.09 (t, 3 H, J =

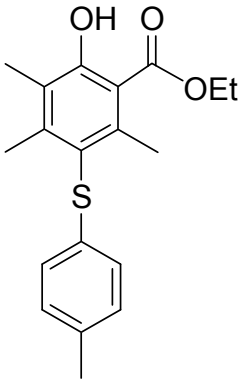
7.4 Hz, CH_3), 1.37 (t, 3 H, J = 7.0 Hz, CH_3) 2.47 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 2.73 (q, 2 H, J = 7.3 Hz, OCH_2), 3.71 (s, 3 H, OCH_3), 4.40 (q, 2 H, J = 7.1 Hz, OCH_2), 6.73 (d, 2 H, J = 9.1 Hz, ArH), 6.83 (d, 2 H, J = 9.1 Hz, ArH), 11.38 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.2, 14.1, 18.7 (CH_3), 20.4 (CH_2), 21.7, 55.2 (CH_3), 61.7 (CH_2), 112.1 (C),114.6 (2C, CH), 124.0 (C), 127.1 (2C, CH), 129.3, 129.9, 143.5, 148.2, 157.3, 160.2, 171.9 (C); IR (neat): $\tilde{\nu}$ = 2968 (m), 2834 (m), 1729 (w), 1652 (s), 1592 (s), 1437 (s), 1372 (s), 1260 (s), 1108 (s), 865 (w), 820 (s), 622 (m), 516 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 360 (M^+, 83), 300 (100), 286 (33), 271 (10), 178 (9), 57 (6); elemental analysis: calcd (%) for $C_{20}H_{24}O_4S$ (360.13): C 66.64, H 6.71; found: C 66.04, H 6.97.

Methyl 4,6-dimethyl-5-(4-bromothiophenoxy) salicylate (38g):



Starting with 3-(siloxy)alk-2-en-1-one **36c** (200 mg, 0.55 mmol) 1,3-bis(silyl enol ether) **37a** (144 mg, 0.55 mmol), and $TiCl_4$ (0.06 ml, 0.55 mmol), **38g** was isolated as a colourless solid (73 mg, 36%), mp. 114°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.62 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 6.68 (d, 2 H, J = 8.5 Hz, ArH), 6.80(s, 1 H, ArH), 7.20 (d, 2 H, J = 8.5 Hz, ArH), 11.10 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 21.9, 51.3 (CH_3), 11.5, 116.8 (C), 117.1(CH), 121.1 (C), 12.7 (2C, CH), 130.9 (2C, CH), 136.5, 146.1, 150.2, 161.7, 170.6(C); IR (KBr): $\tilde{\nu}$ = 3068 (w), 2953 (m), 1660 (s),1594 (s), 1472 (s), 1355 (s), 1230 (s), 1188 (m), 1005 (s), 944 (w), 824 (w), 807 (s), 503 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 368 (M^+, ^{81}Br, 49), 366 (M^+, ^{79}Br, 48), 336 (100), 334 (95), 184 (11), 127 (6), 91 (11); elemental analysis: calcd (%) for $C_{16}H_{15}BrO_3S$ (365.99): C 52.33, H 4.12; found: C 52.18, H 4.31.

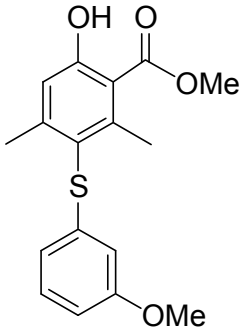
Ethyl 3,4,6-trimethyl-5-(4-methylthiophenoxy) salicylate (38h):



Starting with 3-(siloxy)alk-2-en-1-one **36d** (500 mg, 1.8 mmol) 1,3-bis(silyl enol ether) **37b**(520 mg, 1.8 mmol), and $TiCl_4$ (0.2 ml, 1.8 mmol), **38h** was isolated as a colourless solid (188 mg, 33%), mp. 75°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, J = 7.1 CH_3), 2.15 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 2.65 (s, 3 H,

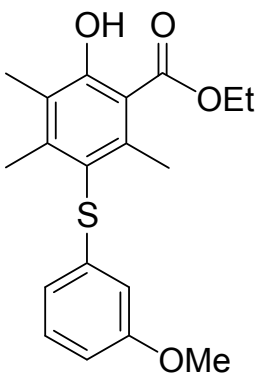
CH_3), 4.35 (q, 2 H, J = 7.3 OCH_2), 6.72 (d, 2 H, J = 8.2 Hz, ArH), 6.92 (d, 2 H, J = 8.2 Hz, ArH), 11.41 (s, 1 H, OH);^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.9, 14.3, 19.7, 20.9, 21.7 (CH_3), 61.9 (CH_2), 112.4, 123.3, 124.0 (C), 125.4 (2C, CH), 129.8 (2C, CH), 134.4, 135, 143.7, 149.2, 160.6, 172.1(C); IR (KBr): $\tilde{\nu}$ = 3015 (w), 2936 (m), 1647 (s),1551 (m), 1490 (s), 1392 (s), 1288 (s), 1185(s), 1100 (m), 1014 (m), 868 (w), 801 (s), 482 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 330.1 (M^+, 70), 284.1 (100), 256 (17), 241 (41), 165 (7), 91 (11); elemental analysis: calcd (%) for $C_{19}H_{22}O_3S$ (330.12): C 69.06, H 6.71; found: C 68.89, H 6.98

Methyl-4,6-dimethyl-5-(3-methoxythiophenoxy) salicylate (38i):



Starting with 3-(siloxy)alk-2-en-1-one **36e** (500 mg, 1.7 mmol) 1,3-bis(silyl enol ether) **37a**(455 mg, 1.7 mmol), and $TiCl_4$ (0.18 ml, 1.7 mmol), **38i** was isolated as a colourless solid (174 mg, 32%), mp. 78°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 2.60 (s, 3 H, CH_3), 3.59 (s, 3 H, OCH_3),3.83 (s, 3 H, OCH_3), 6.32 (m, 1 H, ArH), 6.37 (m, 1 H, ArH), 6.48 (br m, 1 H, ArH), 6.74 (s, 1 H, ArH), 6.97 (t, 1 H, J = 8.1 Hz, ArH) 11.01 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.4, 23.1, 52.4, 55.2 (CH_3), 109.8, 110.7 (CH), 112.2 (C), 117.4, 117.5 (CH), 122.3 (C), 129.5 (CH), 139.5, 147.0, 151.2, 159.9, 162.4, 171.6 (C); IR (KBr): $\tilde{\nu}$ = 3002 (w), 2947 (m), 1663 (s), 1591 (s), 1474 (s), 1357 (s), 1229 (s), 1110(m), 1046 (s), 877 (w), 847 (w), 768 (s), 686 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 318 (M^+, 59), 286(100), 256 (17), 225 (10), 179 (16), 91 (8) 57 (8); elemental analysis: calcd (%) for $C_{17}H_{18}O_4S$ (318.09): C 64.13, H 5.70; found: C 64.41, H 5.93.

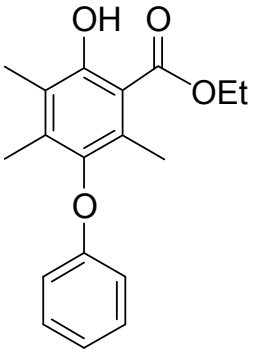
Ethyl-3,4,6-trimethyl-5-(3-methoxythiophenoxy) salicylate (38j):



Starting with 3-(siloxy)alk-2-en-1-one **36e** (500 mg, 1.7 mmol) 1,3-bis(silyl enol ether) **37b**(490 mg, 1.7 mmol), and $TiCl_4$ (0.18 ml, 1.7 mmol), **38j** was isolated as a colourless oil(177 mg, 30%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.33 (t, 3 H, J = 7.1 Hz, CH_3), 2.15 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 2.65 (s, 3 H, CH_3), 3.64 (s, 3 H, OCH_3), 4.35 (q, 2 H, J = 7.1 Hz, OCH_2), 6.38 (m, 1 H, ArH), 6.42 (m, 1 H,

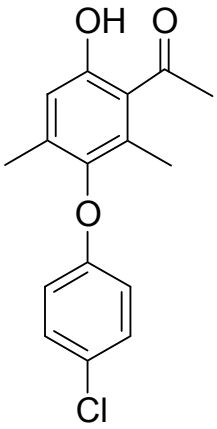
ArH), 6.52 (br m, 1 H, ArH), 7.02 (t, 1 H, J = 8.2 Hz, ArH) 11.44 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7, 13.1, 18.5, 20.5, 54.1 (CH_3), 60.8 (CH_2), 108.8, 109.9 (CH), 110.9 (C), 116.5 (CH), 121.2, 122.9 (C), 128.7(CH), 139.2, 142.8, 148.1, 159.0, 159.6, 170.9 (C); IR (KBr): $\tilde{\nu}$ = 3058 (w), 2933 (s), 1729 (w), 1652 (s), 1590 (s), 1475 (s), 1376 (s), 1283(s), 1242 (s), 1181 (s), 1045 (s), 860 (s), 686 (m), 566 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 346 (M^+, 80), 300(100), 256 (17), 257 (20), 164 (6), 69(13) 57 (5); elemental analysis: calcd (%) for $C_{19}H_{22}O_4S$ (346.12): C 65.87, H 6.40; found: C 65.47, H 6.64.

Ethyl-3,4,6-trimethyl-5-phenoxy salicylate (38i).



Starting with 1,3-bis(silyl enol ether) **37b** (400 mg, 1.3 mmol), 3-(siloxy)alk-2-en-1-one **36f** (367 mg, 1.3 mmol) and $TiCl_4$ (0.15 mL, 1.3 mmol), **38i** was isolated as a colourless solid (130 mg, 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, 3 H, J = 7.1 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 4.42 (q, 2 H, J = 7.1 Hz, OCH_2), 6.72-7.27 (m, 5 H, ArH), 11.51 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.9, 12.8, 13.1, 14.3 (CH_3), 60.6 (CH_2), 109.4 (C), 113.5 (2C), 120.3 (CH), 123.0 (C), 128.6 (2C, CH), 129.2, 137.1, 142.4, 156.8, 157.2, 170.9 (C); IR (KBr): $\tilde{\nu}$ = 3438 (w), 2937 (w), 1649 (s), 1396 (s), 1293 (s), 1222 (s), 1031 (m), 810 (m), 753 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 300.0 (M^+, 88), 254.0 (100), 226.0 (72), 211.0 (17); HRMS (EI): calcd. for $C_{18}H_{20}O_4$ $[M]^+$: 300.13563; found: 300.13561.

1-(3-(4-Chlorophenoxy)-6-hydroxy-2,4-dimethylphenyl)ethanone (38u).



Starting with 1,3-bis(silyl enol ether) **37e** (500 mg, 2.0 mmol), 3-(siloxy)alk-2-en-1-one **36i** (609 mg, 2.0 mmol) and $TiCl_4$ (2.04 mL, 2.0 mmol), **38u** was isolated as a yellow solid (205 mg, 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 6.69 (d, 2 H, J = 9.0 Hz, ArH), 6.76 (s, 1 H, ArH), 7.22 (d, 2 H, J = 9.0 Hz, ArH), 11.94 (s, 1 H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 17.2, 33.0 (CH_3), 115.7 (2C), 118.4 (CH), 120.9, 126.5 (C), 129.7 (2C, CH), 131.7, 140.2, 143.6, 156.4, 159.3, 205.3 (C); IR (KBr):

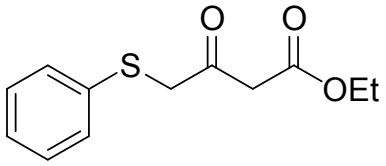
$\tilde{\nu}$ = 3341 (w), 2925 (w), 1629 (m), 1485 (s), 1296 (m), 1227 (s), 1091 (m), 827 (m) cm^{-1}; MS (EI, 70 eV): *m/z* (%): 290.0 (M^+, 95), 275.0 (100), 165.0 (43); HRMS (EI): calcd. for $C_{16}H_{15}ClO_3$ $[M]^+$: 290.07042; found: 290.07056.

General procedure for the synthesis of Ethyl-4-Thioaryloxyacetoacetate 40:A solution of 4-choloroacetoacetate (1.0 mmol), Et_3N (1.05 mmol) and thiophenol **33** (1.03 mmol) in CH_2Cl_2 (2 ml) was stirred at 0 °C for 30 min. The reaction mixture was diluted with EtOAc, washed with 1N NaOH, 1N HCl and brine, dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

General procedure for the synthesis of alkyl-4-aryloxyacetoacetate 40c-e:*Method A*:To a mixture of potassium hydroxide (2.0 mmol) in 2 ml of DMSO was added dropwise a solution of phenol (1.0 mmol) in 0.2 ml of DMSO. The mixture was stirred at room temperature for 30 min and then ethyl-4-chloracetoacetate (1.0mmol) was added. The mixture was stirred at room temperature overnight and then acidified with 4 M HCl and extracted with EtOAc, washed with water and brine, dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Method B: A THF solution of 2.3 equiv.LDA was prepared by addition of *n*-BuLi (0.93 ml, 2.3 mmole, 2.5 M in hexane) to a THF solution (6 ml) of diisopropylamine (0.32 ml, 2.3 mmole) at 0 °C. After the solution was stirred for 30 min, methylacetate (0.09 ml, 1.1 mmole) was added at 0 °C. After stirring for 45-60 min, to the solution was added a THF solution (4 ml)of acid chloride (205 mg, 1.0 mmole) at -78 °C. The temperature was allowed to rise to ambient during 5-6h, and the solution was stirred at 20 °C for 8 h.To the solution was added diluted HCl and mixture was extracted with EtOAc (3× 200 ml). The organic layers were dried and filtered, the solvent of filter was removed in vacuo, and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane).

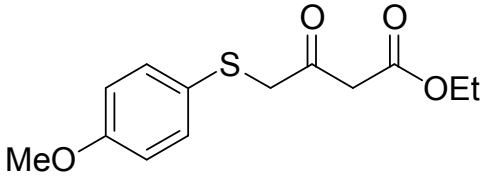
Ethyl-4-Thiophenoxyacetoacetate (40a):



Starting with 4-choloroacetoacetate (10 ml, 73 mmol), thiophenol (7.7 ml, 75.5 mmol), Et_3N (10.7 ml,

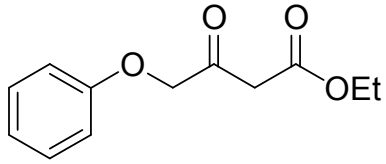
76.7mmol) and dichloromethane (146 ml), **40a** was isolated as a colourless oil (13.8 g, 80%); ^{1}H NMR (250MHz, $CDCl_3$): δ = 1.26 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.63 (s, 2 H, CH_2), 3.81 (s, 2 H, CH_2), 4.18 (q, 2 H, *J* = 7.1 Hz, OCH_2), 7.23-7.27 (m, 2H, ArH), 7.29-7.31(m, 1H, ArH), 7.32-7.37 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (CH_3), 44.3, 46.9, 61.9(CH_2), 127.6 (CH), 129.6 (2C, CH), 130.2(2C, CH) 134.4, 167.4, 198.3(C); IR (neat): $\tilde{\nu}$ = 3059 (w), 2982 (m), 2937(w), 1743 (s), 1716 (s), 1583 (m), 1439 (m), 1320 (s), 1188 (s), 1026 (s), 741 (s), 691 (s); *m/z* (%): 238 (M^+, 40), 192 (18), 166 (5), 150(53), 123 (100) , 110 (29), 77(16), 65(10); elemental analysis: calcd (%) for $C_{12}H_{14}O_3S$ (238): C 60.48, H 5.92; found: C 59.90, H 5.91.

Ethyl-4-(4-methoxythiophenoxy)acetoacetate (40b):



Starting with 4-choloroacetoacetate (3.3 ml, 24.2 mmol), thiophenol (3 ml, 25 mmol), Et_3N (3.6 ml, 25.5 mmol) and dichloromethane (50 ml), **40b** was isolated as a colourless oil (5.4 g, 81%); ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.11 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.48 (s, 2 H, CH_2), 3.52 (s, 2 H, CH_2), 3.62 (s, 3 H, OCH_3), 4.02 (q, 2 H, *J* = 7.0 Hz , OCH_2), 6.68 (d, 2 H, *J* = 8.9 Hz , ArH) , 7.1 (d, 2 H, *J* = 8.7 Hz, ArH) ; ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.4 (CH_3), 46.2, 46.9(CH_2), 55.6 (CH_3), 61.8(CH_2), 115.2 (2C, CH), 124.5(C) 134.3 (2C, CH) 159.2(C) , 167.7(C) , 198.2(C); IR (neat): $\tilde{\nu}$ = 2981 (m), 2939 (w), 2837(w), 1743 (s), 1714 (s), 1592 (s), 1495 (s), 1367 (m), 1284 (s), 1181 (s) 1029 (s), 828 (m), 638 (w), 525 (w): *m/z* (%): 268 (M^+, 24), 222 (16), 196 (26), 180(12), 153 (100) , 139 (28), 109(39), 96(10), 69(20); elemental analysis: calcd (%) for $C_{13}H_{16}O_3S$ (268): C 59.19, H 6.01; found: C 58.34, H 6.34.

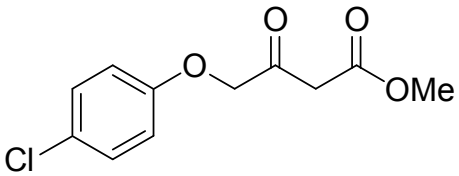
Ethyl-4-phenoxyacetoacetate (40 c):



Starting with 4-choloroacetoacetate (14.4 ml, 106.3 mmol), phenol (10 g, 106.3 mmol), KOH (11.8 g, 212.7 mmol) and DMSO (212 ml), **40c** was isolated as a

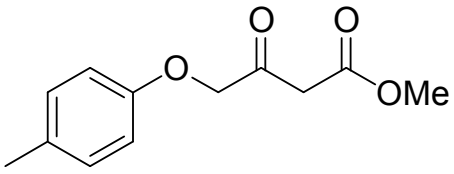
colourless oil (14.3 g, 60%); ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.29 (t, 3 H, *J* = 7.0 Hz, CH_3), 3.67 (s, 2 H, CH_2), 4.21 (q, 2 H, *J* = 7.0 Hz, OCH_2), 4.68 (s, 2 H, CH_2), 6.85-6.96 (m, 2H, ArH), 7.02-7.07 (m, 1H, ArH), 7.25-7.34 (m, 2H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_3), 46.5, 62.0, 72.8 (CH_2), 114.6 (2C, CH), 122.4 (CH), 129.9 (2C, CH) 157.4, 166.9, 200.7 (C); IR (neat): $\tilde{\nu}$ = 3043 (w), 2983 (m), 2937 (w), 1724 (s), 1599 (s), 1496 (s), 1322 (s), 1244 (s), 1175 (s), 1032 (s), 813 (m), 755 (s), 692 (s), 508 (w); *m/z* (%): 222 (M^+, 84), 176 (67), 134 (66), 129(72), 107 (100) , 94 (45), 77(97), 51(39); HRMS (EI): calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.08881, found 222.08866.

Methyl-4-(4-chlorophenoxy)acetoacetate (40d):



Starting with 2-(4-chlorophenoxy) acetyl chloride (5.0 g, 24.03 mmol), and methyl acetate (2.14 ml, 26.8 mmol l), **40d** was isolated as a colorless solid (2.0 g, 30%),mp. 57 °C; ^{1}H NMR (250MHz, $CDCl_3$): δ = 3.55 (s, 2 H, CH_2), 3.65 (s, 3 H, OCH_3), 4.55 (s, 2 H, CH_2), 6.74 (d, 2H, *J* = 9.1 Hz, ArH), 7.16 (d, 2H, *J* = 9.1 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 45.7 (CH_2), 52.4 (CH_3), 72.6 (CH_2), 115.8 (2C, CH), 126.6 (C), 129.4 (2C, CH) 156.0, 167.1, 199.6 (C); IR (KBr): $\tilde{\nu}$ = 3008 (w), 2958 (w), 2931 (w), 1737 (s), 1595 (m), 1493 (s), 1326 (s), 1233 (s), 1158 (s), 1024(s), 986 (m), 823 (s), 636 (m), 512 (m), 495 (w); *m/z* (%): 242 (M^+, 39), 210 (28), 168 (13), 141(76), 128 (17) , 115 (92), 101 (39), 85.9 (80),83.9 (100), 59 (23); HRMS (EI): calcd for $C_{11}H_{11}ClO_4$ $[M]^+$: 242.03335, found 242.03404.

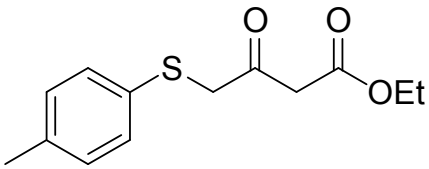
Methyl-4-(4-methylphenoxy)acetoacetate (40e):



Starting with 2-(4-methylphenoxy) acetyl chloride (10.0 g, 54.3 mmol), and methyl acetate (4.8 ml, 59.7 mmol), **40e** was isolated as a colorless oil (4.8 g, 40%); ^{1}H NMR (250MHz, $CDCl_3$): δ = 2.21 (s, 3 H, CH_3), 3.56 (s, 2 H, CH_2), 3.64 (s, 3 H, OCH_3), 4.52 (s, 2 H, CH_2), 6.70 (d, 2H, *J* = 8.6 Hz, ArH), 7.01 (distorted d, 2H, *J* = 8.6 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ =

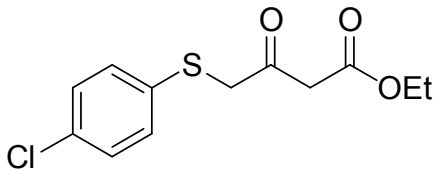
20.3 (CH_3), 46.1 (CH_2), 52.4 (CH_3), 72.6 (CH_2), 114.4 (2C, CH), 130.1 (2C, CH) 131.5,155.1, 167.3, 200.8 (C);); IR (neat): $\tilde{\nu}$ = 3030 (w), 2954 (w), 2926 (w), 1731 (s), 1613 (m), 1511 (s), 1437 (m), 1236 (s), 1178 (s), 1066(s), 1039 (m), 817 (s), 510 (w); *m/z* (%): 222 (M^+, 92), 206 (7), 190 (71), 148(34), 128 (55) , 121 (100), 101 (41), 86 (82),77 (49), 59 (28); HRMS (EI): calcd for $C_{12}H_{14}O_4$ $[M]^+$: 222.08869, found 222.08866.

Ethyl-4-(4-methylThiophenoxy)acetoacetate (40f):



Starting with 4-choloroacetoacetate (5.3 ml, 39 mmol), thiophenol (5 g, 40.2 mmol), Et_3N (5.7 ml, 41 mmol) and dichloromethane (78 ml), **40f** was isolated as a colourless oil (7.8 g, 77%); ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.16 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.22 (s, 3 H, CH_3), 3.53 (s, 2 H, CH_2), 3.65 (s, 2 H, CH_2), 4.07 (q, 2 H, *J* = 7.0 Hz , OCH_2), 7.01 (d, 2 H, *J* = 8.1 Hz , ArH) , 7.17 (d, 2 H, *J* = 8.2 Hz, ArH); ^{13}C NMR (75 MHz): δ =14.4 21.4(CH_3), 42.2, 43.6, 61.8 (CH_2), 130.4 (2C, CH), 130.8 (2C, CH) 131.5 , 137.9 , 167.4, 198.3(C); IR (neat): $\tilde{\nu}$ = 2981 (m), 2924 (w), 1744 (s), 1715 (s), 1652 (w), 1494 (m), 1320 (s), 1186 (s), 1030 (s) 942 (w), 800 (s), 733 (w), 501 (m): *m/z* (%): 252 (M^+, 30), 206 (15), 164 (28), 137(100), 119(9) , 91 (24), 77(7), 45(28); elemental analysis: calcd (%) for $C_{13}H_{16}O_3S$ (252.0): C 61.88, H 6.39; found: C 61.40, H 6.34.

Ethyl-4-(4-chloroThiophenoxy)acetoacetate (40g):

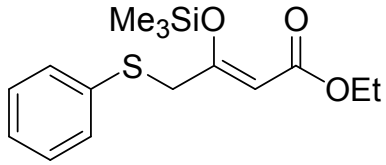


Starting with 4-choloroacetoacetate (13.8 ml, 101.1 mmol), 4-chlorothiophenol (15 g, 104.0 mmol), Et_3N (14.7 ml, 106.1 mmol) and dichloromethane (202 ml), **40g** was isolated as a colourless oil (23.8 g, 84%); ^{1}H NMR (250MHz, $CDCl_3$): δ = 1.21 (t, 3 H, *J* = 7.0 Hz, CH_3), 3.58 (s, 2 H, CH_2), 3.76 (s, 2 H, CH_2), 4.11 (q, 2 H, *J* = 7.4 Hz , OCH_2), 7.23 (m, 4 H, ArH); ^{13}C NMR (62 MHz): δ =14.1 (CH_3), 44.0, 46.5, 61.5 (CH_2), 129.3 (2C, CH), 130.8 (2C, CH) 132.7, 133.2, 172.2, 197.7 (C); IR (neat): $\tilde{\nu}$ = 2982 (m), 2937 (w), 1743 (s), 1716 (s), 1653 (w), 1478 (s), 1321 (s), 1250 (m), 1188 (m) 1095 (s), 815 (m), 744 (w), 489 (w):

m/z (%): 274 (M^+,^{37}Cl, 1), 272 (M^+,^{35}Cl, 3), 200 (5), 184 (3), 157 (13), 88 (29) , 86 (92), 84(100), 51 (74); HRMS (EI) calcd for $C_{12}H_{13}O_3ClS$ [M^+, ^{35}Cl]: 272.02660, found 272.02684.

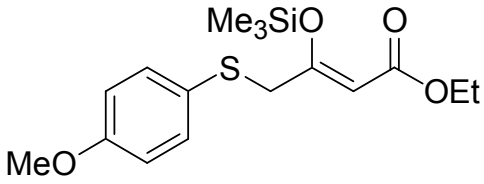
Typical procedure for the synthesis of silyl enol ethers 41 : The reaction was carried out analogously to a known procedure used for the synthesis of silyl enol ether **36**.

Synthesis of silyl enol ethers (41a) :



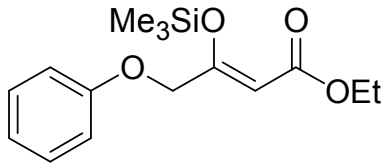
Starting with **40a** (12.50 g, 52.2 mmol), NEt3 (11.7 ml, 83.5 mmol), TMSCl (11.8 ml, 94.0 mmol) and benzene (130ml), **41a** was isolated as a yellow oil (13.5 g, 84%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 1.26 (t, 3 H, *J* = 7.2 Hz, CH_3), 3.79 (q, 2 H, *J* = 7.1 Hz, OCH_2), 3.92 (s, 2 H, CH_2), 4.92 (s, 1 H, =CH), 6.92-7.09 (m, 3H, ArH), 7.19-7.23(m, 2H, ArH).

Synthesis of silyl enol ethers (41b) :



Starting with **40b** (10.3 g, 38.6 mmol), NEt3 (8.5 ml, 61.7 mmol), TMSCl (8.7 ml, 69.4 mmol) and benzene (95ml), **41b** was isolated as a yellow oil (10.3 g, 78%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 1.26 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.62 (s, 3 H, OCH_3), 3.87 (q, 2 H, *J* = 7.1 Hz, OCH_2), 3.93 (s, 2 H, CH_2), 4.95 (s, 1 H, =CH), 6.62 (d, 2 H, *J* = 8.5 Hz, ArH), 7.02 (d, 2 H, *J* = 8.6 Hz, ArH).

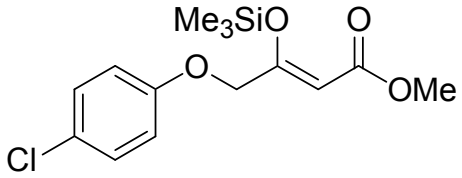
Synthesis of silyl enol ethers (41c) :



Starting with **40c** (6.2 g, 28.0 mmol), NEt3 (6.3 ml, 45.1 mmol), TMSCl (6.4 ml, 50.7 mmol) and benzene (70ml), **41c** was isolated as a yellow oil (7.6 g, 91%);^{1}H NMR (300MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 1.14 (t, 3 H, *J* = 7.0 Hz, CH_3), 3.80 (q, 2 H, *J*

= 7.1 Hz, OCH_2), 4.12 (s, 2 H, CH_2), 4.97 (s, 1 H, =CH), 6.62-6.78 (m, 3H, ArH), 7.01-7.19 (m, 2H, ArH).

Synthesis of silyl enol ethers (41d) :

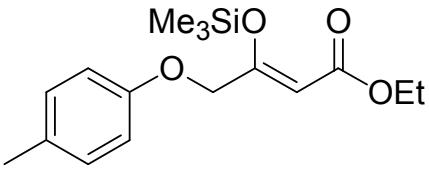


Starting with **40d** (1.6 g, 6.3 mmol), NEt3 (1.4 ml, 10.2 mmol), TMSCl (1.4 ml, 11.4 mmol) and benzene (16ml), **41d** was isolated as a yellow oil (1.5 g, 74%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.02 (s, 9 H, CH_3), 3.61 (s, 3 H, OC*H*$_3$), 4.18 (s, 2 H, CH_2), 5.01 (s, 1 H, =CH), 6.72 (d, 2 H, *J* = 8.3 Hz, ArH), 7.05 (d, 2 H, *J* = 8.5 Hz, ArH).

Synthesis of silyl enol ethers (41e) :

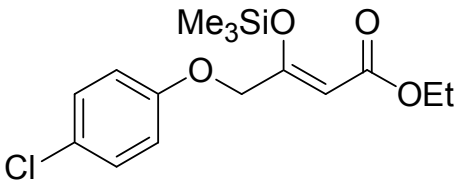
Starting with **40e** (3.7 g, 16.9 mmol), NEt3 (3.7 ml, 27.0 mmol), TMSCl (3.8 ml, 30.4 mmol) and benzene (45ml), **41e** was isolated as a yellow oil (3.7 g, 75%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 2.19 (s, 3 H, CH_3), 3.71 (s, 3 H, OC*H*$_3$), 4.17 (s, 2 H, CH_2), 4.93 (s, 1 H, =CH), 6.82 (d, 2 H, *J* = 8.6 Hz, ArH), 7.12 (d, 2 H, *J* = 8.7 Hz, ArH).

Synthesis of silyl enol ethers (41f) :



Starting with **40f** (5.5 g, 21.7 mmol), NEt3 (4.9 ml, 34.8 mmol), TMSCl (5.0 ml, 39.2 mmol) and benzene (60ml), **41f** was isolated as a yellow oil (6.0 g, 85%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 1.12 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.15 (s, 3 H, CH_3), 3.91 (q, 2 H, *J* = 7.2 Hz, OCH_2), 4.11 (s, 2 H, CH_2), 5.18 (s, 1 H, =CH), 7.18 (d, 2 H, *J* = 8.6 Hz, ArH), 7.31 (d, 2 H, *J* = 8.6 Hz, ArH).

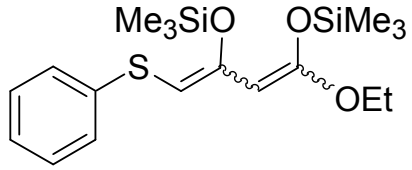
Synthesis of silyl enol ethers (41g) :



Starting with **40g** (23.7 g, 87.0 mmol), NEt3 (19.3 ml, 139.3 mmol), TMSCl (19.7 ml, 156.7 mmol) and benzene (217ml), **41g** was isolated as a yellow oil (27.0 g, 90%);[1]H NMR (300MHz, $CDCl_3$): δ = 0.07 (s, 9 H, CH_3), 1.11 (t, 3 H, *J* = 7.0 Hz, CH_3), 3.89 (q, 2 H, *J* = 7.2 Hz, OCH_2), 4.03 (s, 2 H, CH_2), 5.19 (s, 1 H, =CH), 6.94 (d, 2 H, *J* = 8.4 Hz, ArH), 7.21 (d, 2 H, *J* = 8.5 Hz, ArH).

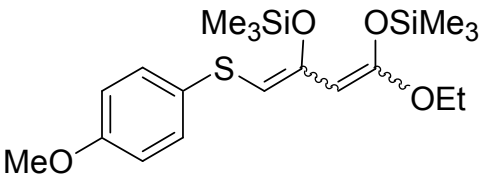
Typical procedure for the synthesis of 1,3-bis-silyl enol ethers (42): The reaction was carried out analogously to a known procedure.[63] To a stirred THF solution (2 ml) of LDA (1.5 equiv.) was added silyl enol ether (1.0 euiv.) at −78 °C. After stirring for 1 h, trimethylchlorosilane (1.8 equiv.) was added. The solution was allowed to warm to room temperature during 12 h with stirring. The solvent was removed *in vacuo* and to the residue was added Hexane (20 ml) togive a suspension. The latter was filtered under Argon atmosphere. The filtrate was distilled*in vacuo.* The compound was used directly after itspreparation. The spectroscopic data are identical with those reported.

Synthesis of 1,3-bis-silyl enol ether (42a):



Starting with **41a** (7.00 g, 22.5 mmol), LDA (33.7 mmol, 1.5 equiv.), TMSCl (5.2 ml, 40.5 mmol) and THF (75 ml), **42a** was isolated as a yellow oil (7.60 g, 89%).[1]H NMR (250MHz, $CDCl_3$): δ = 0.02 (s, 9 H, CH_3), 0.15 (s, 9 H, CH_3), 1.28 (t, 3 H, *J* = 7.2 Hz, CH_3), 3.79 (q, 2 H, *J* = 7.1 Hz, OCH_2), 4.92 (s, 1 H, =CH), 5.62 (s, 1 H, =CH), 6.91 (m, 1H, ArH), 7.12-7.23 (m, 2H, ArH), 7.25-7.29 (m, 2H, ArH).

Synthesis of 1,3-bis-silyl enol ether (42b):



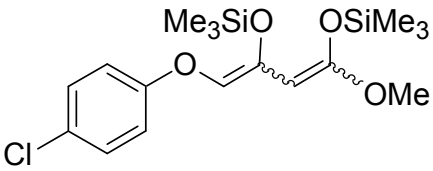
Starting with **41b** (12.5 g, 36.6 mmol), LDA (54.9 mmol, 1.5 equiv.), TMSCl (8.3 ml, 65.9 mmol) and THF (106 ml), **42b** was isolated as a yellow

oil (12.80 g, 85%).[1]H NMR (250MHz, $CDCl_3$): δ = 0.03 (s, 9 H, CH_3), 0.23 (s, 9 H, CH_3), 1.31 (t, 3 H, *J* = 7.2 Hz, CH_3), 3.52 (s, 3 H, OC*H*$_3$), 3.55 (q, 2 H, *J* = 7.3 Hz, OCH_2), 5.10 (s, 1 H, =CH), 5.59 (s, 1 H, =CH), 6.91 (d, 2 H, *J* = 8.7 Hz, ArH), 7.12 (d, 2 H, *J* = 8.7 Hz, ArH).

Synthesis of 1,3-bis-silyl enol ether (42c):

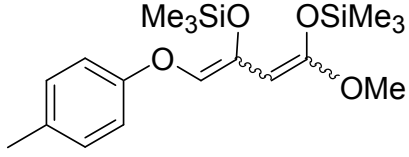
Starting with **41c** (3.00 g, 10.1 mmol), LDA (15.1 mmol, 1.5 equiv.), TMSCl (2.3 ml, 18.3 mmol) and THF (25 ml), **42c** was isolated as a yellow oil (3.0 g, 82%).[1]H NMR (300MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 0.25 (s, 9 H, CH_3), 1.19 (t, 3 H, *J* = 7.3 Hz, CH_3), 3.61 (q, 2 H, *J* = 7.4 Hz, OCH_2), 5.62 (s, 1 H, =CH), 6.34 (s, 1 H, =CH), 6.59-6.62 (m, 1H, ArH), 6.68-7.19 (m, 2H, ArH), 7.12-7.08 (m, 2H, ArH).

Synthesis of 1,3-bis-silyl enol ether (42d):



Starting with **41d** (1.5 g, 4.7 mmol), LDA (7.0 mmol, 1.5 equiv.), TMSCl (1.0 ml, 8.5 mmol) and THF (15 ml), **42d** was isolated as a yellow oil (1.50 g, 82%).[1]H NMR (250MHz, $CDCl_3$): δ = 0.08 (s, 9 H, CH_3), 0.25 (s, 9 H, CH_3), 3.54 (s, 3 H, OC*H*$_3$), 5.21 (s, 1 H, =CH), 6.23 (s, 1 H, =CH), 6.87 (d, 2 H, *J* = 8.5 Hz, ArH), 7.03 (d, 2 H, *J* = 8.5 Hz, ArH).

Synthesis of 1,3-bis-silyl enol ether (42e):

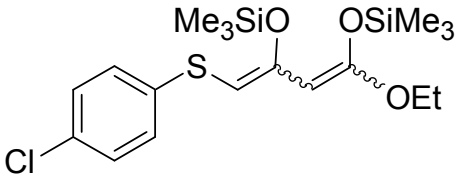


Starting with **41e** (3.0 g, 10.4 mmol), LDA (15.6 mmol, 1.5 equiv.), TMSCl (2.3 ml, 18.8 mmol) and THF (34 ml), **42e** was isolated as a yellow oil (3.1 g, 84%).[1]H NMR (250MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 0.18 (s, 9 H, CH_3), 2.21 (s, 3 H, CH_3), 3.70 (s, 3 H, OC*H*$_3$), 4.89 (s, 1 H, =CH), 5.92 (s, 1 H, =CH), 6.65 (d, 2 H, *J* = 8.3 Hz, ArH), 7.01 (d, 2 H, *J* = 8.5 Hz, ArH).

Synthesis of 1,3-bis-silyl enol ether (42f):

Starting with **41f** (2.0 g, 6.1 mmol), LDA (9.1 mmol, 1.5 equiv.), TMSCl (1.4 ml, 11.0 mmol) and THF (25 ml), **42f** was isolated as a yellow oil (1.95 g, 80%).^{1}H NMR (300MHz, $CDCl_3$): δ = 0.05 (s, 9 H, CH_3), 0.27 (s, 9 H, CH_3), 1.23 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.12 (s, 3 H, CH_3), 3.81 (q, 2 H, *J* = 7.4 Hz, OCH_2), 4.92 (s, 1 H, =CH), 5.61 (s, 1 H, =CH), 6.91 (d, 2 H, *J* = 8.7 Hz, ArH), 7.31 (d, 2 H, *J* = 8.5 Hz, ArH).

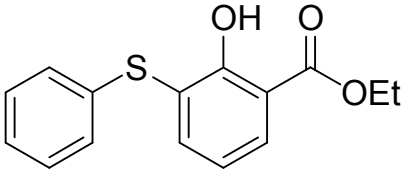
Synthesis of 1,3-bis-silyl enol ether (42g):



Starting with **41g** (25.0 g, 72.0 mmol), LDA (108 mmol, 1.5 equiv.), TMSCl (16.3 ml, 129.6 mmol) and THF (180 ml), **42g** was isolated as a yellow oil (26.2 g, 87%).^{1}H NMR (250MHz, $CDCl_3$): δ = 0.04 (s, 9 H, CH_3), 0.28 (s, 9 H, CH_3), 1.21 (t, 3 H, *J* = 7.4 Hz, CH_3), 3.78 (q, 2 H, *J* = 7.2 Hz, OCH_2), 4.86 (s, 1 H, =CH), 5.61 (s, 1 H, =CH), 6.78 (d, 2 H, *J* = 8.5Hz, ArH), 7.04 (d, 2 H, *J* = 8.5 Hz, ArH).

General procedure for the synthesis of diaryl ethers 43a-f: To a dichloromethane solution (2 mL / mmol of **42**) of **42** (1.0 mmol) and of tetramethoxypropane was added TMSOTf (0.1 mmol) at –78 °C. The solution was allowed to warm to 20 °C within 20 h. To the solution was added a saturated aqueous solution of HCL (15 mL). The organic and the aqueous layer were separated and the latter was extracted with dichloromethane (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo and the residue was purified by chromatography.

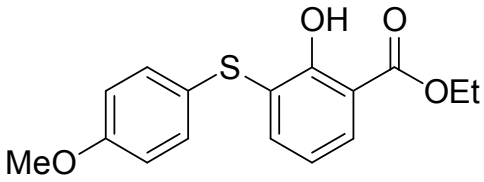
Ethyl-3- thiophenoxy salicylate (43a):



Starting with tetramethoxy (0.26 ml, 1.57 mmol) 1,3-bis(silyl enol ether) **42a** (600 mg, 1.57 mmol), and $TiCl_4$ (0.17 ml, 1.57 mmol), **43a** was isolated as a highly viscous oil (133 mg, 31%); ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.34 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.34(q, 2 H, *J* = 7.0 Hz, OCH_2), 6.74 (t, 1 H, *J*

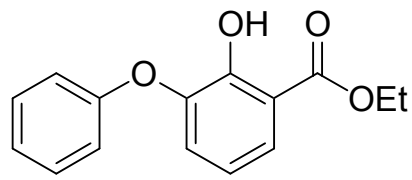
= 7.7 Hz,, ArH), 7.17-7.27 (m, 5 H, ArH), 7.29-7.31 (m, 1 H, ArH),), 7.69-7.73 (dd, 1 H, *J* = 1.5, 8.0 Hz, ArH),), 11.39 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, (CH_3), 60.7 (CH_2), 111.8 (C), 118.3 (CH), 123.0 (C), 126.2, 128.0 (CH), 128.2 (2C, CH), 130.2 (2C, CH), 133.0 (C), 136.8 (CH), 158.8, 169.1(C); IR (neat): $\tilde{\nu}$ = 3074 (w), 2983 (m), 2936 (w), 1669 (s), 1601 (m), 1428 (s), 1318 (s), 1251 (s), 1188 (s), 1023 (m), 752 (s), 690 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 274 (M^+, 66), 228 (100), 200 (14), 171(37), 139(5), 95(6), 51(4); elemental analysis: calcd (%) for $C_{15}H_{14}O_3S$ (274.07): C 65.67, H 5.14; found: C 65.23, H 5.13.

Ethyl-3-(4-methoxythiophenoxy) salicylate (43b):



Starting with tetramethoxy (0.26 ml, 1.57 mmol) 1,3-bis(silyl enol ether) **42b** (648 mg, 1.57 mmol), and $TiCl_4$ (0.17 ml, 1.57 mmol), **43b** was isolated as a highly viscous oil (143 mg, 30%); ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.23 (t, 3 H, *J* = 7.1 Hz, CH_3), 3.63 (s, 3 H, OCH_3), 4.23(q, 2 H, *J* = 7.2 Hz, OCH_2), 6.55 (t, 1 H, *J* = 7.8 Hz, ArH), 7.73 (d, 2 H, *J* = 8.9 Hz, ArH), 6.82-6.86 (dd, 1 H, , *J* = 2.1, 7.6 Hz, ArH),), 7.25 (d, 2 H, *J* = 8.7 Hz, ArH),), 7.47-7.50 (dd, 1 H, *J* = 1.7, 8.0 Hz, ArH),11.28 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 55.7 (CH_3), 62.3 (CH_2), 112.5 (C), 115.5 (2C, CH), 119.6 (C), 122.9, 127.6 (CH), 127.7 (CH), 134.6 (CH), 136.2 (2C, CH), 158.5, 160.4, 170.6 (C); IR (KBr): $\tilde{\nu}$ = 3074 (w), 2987 (m), 2942(w), 2835 (w), 1670 (s), 1569 (m), 1492 (s), 1372 (s), 1289 (s), 1180 (s), 1023 (s), 831 (s), 760 (s), 731 (m), 527 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 304.1 (M^+, 68), 258.1 (100), 243.1 (6), 215.1(9), 187.1(16), 159.1(4), 115.1(7), 95.1(6) 63.1 (3); elemental analysis: calcd (%) for $C_{16}H_{16}O_4S$ (304.08): C 63.14, H 5.30; found: C 63.14, H 5.37.

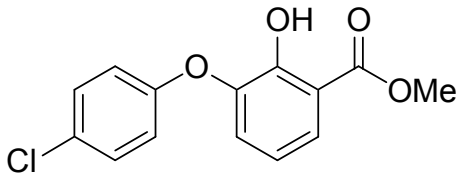
Ethyl-3-phenoxy salicylate (43c):



Starting with tetramethoxy (0.3 ml, 1.8 mmol) 1,3-bis(silyl enol ether) **42c** (660 mg, 1.8 mmol), and TMSOTf (0.03 ml, 0.18 mmol), **43c** was isolated as highly viscous oil (210 mg, 45%);^{1}H NMR (250 MHz,

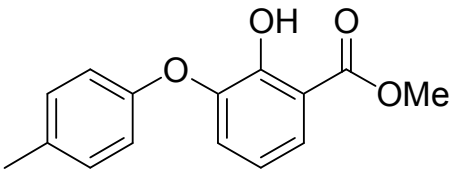
$CDCl_3$): δ =1.35 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.35 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6. 77 (t, 1H, *J* = 7.9 Hz, ArH), 6.91 (dd, 2H, *J* = 1.1, 8.6 Hz, ArH), 6.99 (m, 1 H, ArH), 7.11 (m, 1 H, ArH),7.20 (m, 2 H, ArH), 7.62 (dd, 1H, *J* = 1.5, 8.0 Hz, ArH), 10.95 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_3), 61.7 (CH_2) , 114.2 (C), 117.0 (2C, CH), 118.7, 122.7, 125.7, 126.7 (CH), 129.6 (2C, CH), 144.2, 154.0, 157.6, 170.0 (C) ; IR (neat): $\tilde{\nu}$ = 3072 (w), 2983 (w), 1674 (s), 1585 (s), 1460 (s), 1323 (s), 1253 (s), 1150 (s), 1025 (s), 854 (m), 752 (s), 690 (m), 580 (w), 498 (w); *m/z* (%): 258 (M^+, 65), 212 (100), 184 (46), 128 (13), 105 (31), 77 (15), 51 (12); elemental analysis: calcd (%) for $C_{15}H_{14}O_4$ (258): C 69.76, H 5.46 found: C 69.68, H 5.63.

Methyl -3-(4-chlorophenoxy) salicylate (43d):



Starting with tetramethoxy (0.25 ml, 1.5 mmol) 1,3-bis(silyl enol ether) **42d** (582 mg, 1.5 mmol), and TMSOTf (0.027 ml, 0.15 mmol), **43d** was isolated as higgly viscous oil (192 mg, 46%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =3.88 (s, 3 H, OC*H*$_3$), 6.81 (m, 3 H, ArH), 7.15 (m, 3 H, ArH), 7.61 (dd, 1 H, *J* = 1.5, 8.0 Hz, ArH), 10.23 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.5 (CH_3), 114.1 (C), 118.0 (2C, CH), 118.9,125.8, 127.0 (CH), 127.6 (C) 129.5 (2C, CH), 143.8, 153.9, 156.3, 170.3 (C) ; IR (neat): $\tilde{\nu}$ = 3099 (w), 2954 (m), 2854 (w), 1680 (s), 1583 (s), 1485 (s), 1329 (s), 1254 (s), 1007 (s), 824 (s), 662 (m), 499 (m), 441 (w); *m/z* (%):280(M^+, ^{37}Cl, 24), 278(M^+, ^{35}Cl, 71), 246 (100), 218 (26), 211 (50), 155(9), 139 (34), 107 (20), 75 (9); HRMS (EI): calcd for $C_{14}H_{11}ClO_4$ [M^+, ^{35}Cl] : 278.03435, found 278.03404.

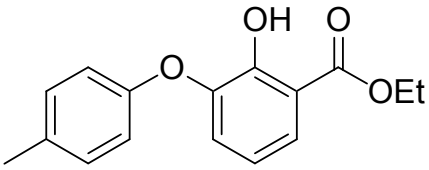
Methyl -3-(4-methylphenoxy) salicylate (43e):



Starting with tetramethoxy (0.25 ml, 1.5 mmol) 1,3-bis(silyl enol ether) **42e** (554 mg, 1.5 mmol), and TMSOTf (0.027 ml, 0.15 mmol), **43e** was isolated as higgly viscous oil (186 mg, 48%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =2.24 (s, 3 H, CH_3),3.89 (s, 3 H, OC*H*$_3$), 6.72-6.82 (m, 3 H, ArH), 7.02-7.09 (m, 3 H, ArH), 7.56 (dd, 1 H, *J* = 1.5, 8.0 Hz, ArH), 10.87 (s, 1H, OH);

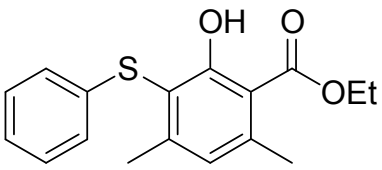
^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.5, 52.5 (CH_3), 112.8 (C), 116.2 (2C, CH), 117.7, 126.7, 127.5 (CH), 129.2 (2C, CH), 131.3, 143.9, 152.7, 154.1, 169.5 (C) ; IR (neat): $\tilde{\nu}$ = 2955 (w), 2924 (m), 2855 (w), 1680 (s), 1505 (s), 1440 (s), 1329 (s), 1252 (s), 11150 (s), 1006 (m), 815 (m), 718 (w), 501 (w); *m/z* (%): 258(M^+, 75), 226 (100), 198 (37), 119 (34), 107(14), 91 (11), 65 (8), 51 (5); HRMS (EI): calcd for $C_{15}H_{15}O_4$ $[M]^+$: 258.08868, found 258.08866.

Synthesis of ethyl-3-(4-methylthiophenoxy) salicylate (43f):



Starting with tetramethoxy (0.42 ml, 2.52 mmol) 1,3-bis(silyl enol ether) **42f** (1g, 2.52 mmol), and TMSOTf (0.05 ml, 0.257 mmol), **43f** was isolated as a gummy compound (291 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.34 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.27 (s, 3 H, CH_3), 4.33(q, 2 H, *J* = 7.0 Hz, OCH_2), 6.69 (t, 1 H, *J* = 7.8 Hz,, ArH), 7.06-7.09 (dd, 2 H, *J* = 0.57, 7.2 Hz, ArH), 7.10-7.13 (m, 2 H, ArH),), 7.24 (d, 1 H, *J* = 8.0 Hz, ArH),), 7.63-7.67 (dd, 1 H, *J* = 1.7, 8.0 Hz, ArH),11.39 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 20.1 (CH_3), 60.7 (CH_2), 111.5 (C), 118.2 (CH), 124.6 (C), 127.1 (CH), 127.5 (C), 129.1 (2C, CH), 131.5 (2C, CH), 135.2 (CH), 136.8, 158.1, 169.1(C); IR (KBr): $\tilde{\nu}$ = 2983 (m), 2916 (w), 1644 (s), 1667 (s), 1489 (m), 1399 (s), 1284 (s), 1245 (s), 1018 (s), 901 (w), 809 (s), 506 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 288 (M^+, 90), 242 (100), 213 (20), 185(18), 171(20), 152(6), 123(7), 63 (4); elemental analysis: calcd (%) for $C_{16}H_{16}O_3S$ (208.08): C 66.64, H 5.59; found: C 66.80, H 5.84.

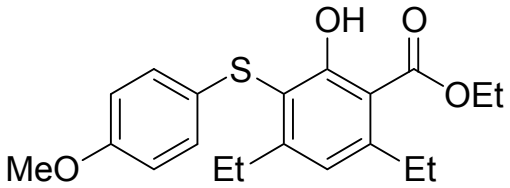
Ethyl-4,6-dimethyl-3-(thiophenoxy) salicylate (45a):



Starting with 3-(siloxy)alk-2-en-1-one **44a** (400 mg, 2.32 mmol) 1,3-bis(silyl enol ether) **42a** (887 mg, 2.32 mmol), and $TiCl_4$ (0.25 ml, 2.32 mmol), **45a** was isolated as a colourless solid (336 mg, 48%), mp. 79 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.34 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.33 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 4.35 (q, 2 H, *J* = 7.3 Hz, OCH_2), 6..66 (s, 1H, ArH), 6.94-6.97 (dd, 2 H, *J* = 1.5, 8.2 Hz, ArH); 7.01 (m, 1H, ArH), 7.09-7.13 (m, 2H, ArH), 11.75 (s, 1H, OH); ^{13}C NMR

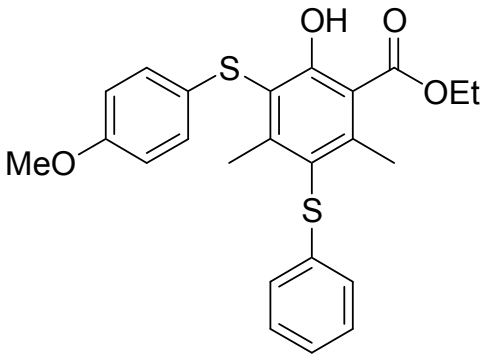
(62 MHz, $CDCl_3$): δ = 14.0, 21.5, 23.7 (CH_3), 61.6 (CH_2) , 111.5, 116.9(C), 124.8, 124.9 (CH), 125.9 (2C, CH), 128.6 (2C, CH), 137.2, 142.4, 150.2, 163.4, 172.4(C) ; IR (KBr): $\tilde{\nu}$ = 3054 (w), 2959 (w), 2935 (m), 2935 (m), 2809 (w), 2742 (w), 1639 (s), 1605 (s), 1476 (s), 1447 (s), 1376 (s), 1296 (s), 1259 (s), 1211 (s), 1108(w), 1015 (m), 820(m), 741(s), 459 (w); *m/z* (%): 302.1 (M^+, 61), 256.1 (100), 241.1 (22), 184.1 (14), 165.1 (5), 128 (5), 91.1 (7); elemental analysis: calcd (%) for $C_{17}H_{18}O_3S$ (302.1): C 67.52, H 6.00 found: C 67.48, H 6.24.

Ethyl-4,6-diethyl-3-(4-methoxythiophenoxy) salicylate (45b):



Starting with 3-(siloxy)alk-2-en-1-one **44b** (400 mg, 1.99 mmol) 1,3-bis(silyl enol ether) **42b** (824 mg, 1.99 mmol), and $TiCl_4$ (0.22 ml, 1.99 mmol), **45b** was isolated as a highly viscous oil (251 mg, 35%);^{1}H NMR (300 MHz, $CDCl_3$): δ =1.06-1.18 (m, 6 H, CH_3), 1.35 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.78-2.83 (m, 4 H, CH_2), 3.67 (s, 3H, OCH_3) 4.35 (q, 2 H, *J* = 7.2 Hz, OCH_2), 6.68 (d, 2 H, *J* = 8.9 Hz ArH), 6.99 (d, 2 H, *J* = 8.7 Hz ArH), 7.11 (s, 1 H, ArH), 11.07 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4, 15.5, 16.3 (CH_3), 28.7, 29.7 (CH_2), 55.7 (CH_3) 62.1 (CH_2) , 112.0 (C), 124.8 (CH), 114.9 (2C, CH), 117.4 (C), 122.5 (CH), 128.3 (C), 129.1 (2C, CH),148.4, 155.3, 158.3,162.5, 171.2 (C); IR (neat): $\tilde{\nu}$ = 3375 (w), 2963 (s), 2930(s), 2872 (m), 1728 (s), 1653 (s), 1595 (s), 1493 (s), 1374 (s), 1247 (s), 1107 (s), 1070 (m), 947 (w), 820 (m), 525(w); *m/z* (%): 360.2 (M^+, 65), 314.1 (100), 281.2 (10), 207 (7), 163 (13), 135 (15), 77 (7); HRMS (EI): calcd for $C_{20}H_{24}O_4S$ $[M]^+$: 360.13898, found 360.138235.

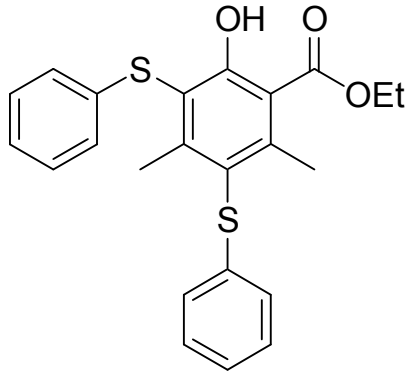
Ethyl-4,6-dimethyl-3-(4-methoxythiophenoxy)-5-thiophenoxy salicylate (45e):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (400 mg, 1.41 mmol) 1,3-bis(silyl enol ether) **42b** (582 mg, 1.41 mmol), and $TiCl_4$ (0.15 ml, 1.41 mmol), **45e** was isolated as a highly viscous oil (212 mg, 34%);^{1}H NMR (300 MHz, $CDCl_3$): δ =1.33 (t, 3

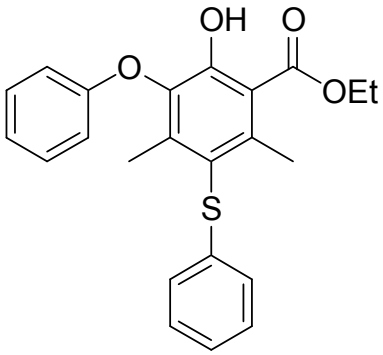
H, *J* = 7.1 Hz, CH_3), 2.34 (s, 3 H, CH_3), 2.68 (s, 3 H, CH_3), 3.71 (s, 3 H, OCH_3), 4.34 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.68 (d, 2 H, *J* = 8.9 Hz, ArH), 6.73-6.81 (m, 5H, ArH)), 7.32 (d, 2 H, *J* = 8.9 Hz, ArH), 11.12 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.5, 21.9, 24.8, 55.7 (CH_3), 62.2 (CH_2) , 112.9 (C), 115.1 (2C, CH), 118.0 (CH), 124.5 (C), 127.7 (2C, CH), 128.1, 128.8 (2C), 133.0 (2C, CH), 147.2, 151.4, 157.9, 160.3, 162.8, 171.7 (C); IR (Nujol): $\tilde{\nu}$ = 2954 (s), 2925 (s), 2855(s), 2932 (s), 1653 (m), 1591 (s), 1492 (s), 1461 (s), 1372 (s), 1245 (m), 1106 (m), 1034 (s),871 (s), 802 (w), 620 (w),522(m), 423 (w).

Ethyl-4,6-dimethyl-3-5-dithiophenoxy salicylate (45f):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (400 mg, 1.41 mmol) 1,3-bis(silyl enol ether) **42a** (539 mg, 1.41 mmol), and $TiCl_4$ (0.15 ml, 1.41 mmol), **45f** was isolated as a highly viscous oil (196 mg, 34%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.27 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.51 (s, 6 H, CH_3), 4.30 (q, 2 H, *J* = 7.1 Hz, OCH_2), 6.76-6.80 (dd, 2 H, *J* = 1.2, 8.2 Hz, ArH), 6.88-6.92 (m, 2 H, ArH), 6.94-7.09 (m, 6 H, ArH), 9.37 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 20.6, 21.4 (CH_3), 62.0 (CH_2) , 116.7, 116.8, 124.5 (C), 124.8 (CH), 125.2 (2C, CH), 125.6 (CH), 126.2 (2C, CH), 128.9 (2C, CH), 129.0 (2C, CH), 135.1, 137.7, 146.6, 154.2, 159.1, 169.2 (C); IR (KBr): $\tilde{\nu}$ = 3373 (s), 3057 (s), 2981(s), 2932 (s), 2869 (m), 1728 (s), 1653 (s), 1439 (s), 1121 (s), 998 (m), 857 (m), 738 (s), 689 (s), 582 (w), 471 (w), *m/z* (%): 410 (M^+, 69), 364 (100), 340 (44), 290 (18), 253 (12), 219 (12), 177 (74), 161 (48); 109 (35), 83 (56), 57 (93), 43 (54); HRMS (EI): calcd for $C_{23}H_{22}O_3S_2$ $[M]^+$: 410.10049, found 410.099732.

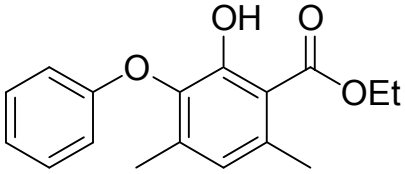
Ethyl 4,6-dimethyl-3-phenoxy-5-thiophenoxysalicylate (45g):



Starting with 3-(siloxy)alk-2-en-1-one **36a** (500 mg, 1.8 mmol), 1,3-bis(silyl enol ether) **42c** (647 mg, 1.8 mmol), and $TiCl_4$ (0.19 ml, 1.8 mmol), **45g** was isolated as a colourless solid (210 mg, 30%), mp. 103 °C; ^{1}H NMR (300

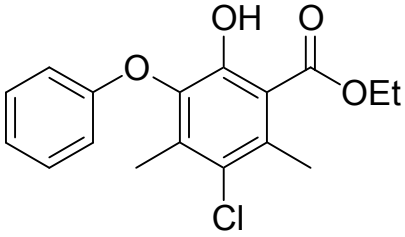
MHz, $CDCl_3$): δ = 1.34 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.26 (s, 3 H, CH_3), 2.69 (s, 3 H, CH_3), 4.37 (q, 2 H, *J* = 7.2 Hz, OCH_2), 6.77 (distorted d, 2 H, *J* = 7.8 Hz, ArH), 6.86 (dd, 2 H, *J* = 1.3, 8.1 Hz, ArH), 6.92-7.02 (m, 2H, ArH), 7.11-7.22 (m, 4H, ArH), 10.99 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 16.0, 21.1 (CH_3), 62.2 (CH_2), 114.0 (C), 114.6 (2C, CH), 121.9 (CH), 123.2 (C), 124.6, 124.8 (CH), 125.3 (2C, CH), 129.0 (2C, CH), 129.1 (2C, CH), 137.9, 139.5, 143.2, 144.2, 155.6, 157.5, 170.9 (C); IR (KBr): $\tilde{\nu}$ = 3069 (w), 2978 (w), 2928 (m), 2851 (m), 1662 (s), 1599 (s), 1476 (s), 1374 (s), 1244 (s), 1159 (s), 1077 (m), 752 (m), 686 (m), 488 (w); MS (EI, 70 eV): *m/z* (%): 394 (M^+, 93), 349 (37), 348 (100), 247 (22), 333 (16), 290 (5), 270 (7), 211 (10), 177 (28), 161 (19), 105 (28), 57 (31); HRMS (EI): calcd for $C_{23}H_{22}O_4S$ [M^+]: 394.12333, found 394.12343.

Ethyl 4,6-dimethyl-3-(phenoxy)salicylate (45h):



Starting with 3-(silyloxy)alk-2-en-1-one **44a** (600 mg, 3.48 mmol) 1,3-bis(silyl enol ether) **42c** (1.27 g, 3.48 mmol), and $TiCl_4$ (0.38 ml, 3.48 mmol), **45h** was isolated as a colourless solid (354 mg, 37%), mp. 69 °C; ^1H NMR (300 MHz, $CDCl_3$): δ =1.35 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.08 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 4.35 (q, 2 H, *J* = 7.0 Hz, OCH_2), 6.54 (s, 1 H, ArH), 6.78 (d, 2 H, *J* = 8.7 Hz, ArH); 6.90 (t, 1 H, *J* = 7.4 Hz, ArH), 7.18 (t, 2 H, *J* = 8.1 Hz, ArH), 11.43 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 16.3, 23.7 (CH_3), 61.6 (CH_2), 111.4 (C), 114.6 (2C, CH), 121.6, 124.3 (CH), 129.4 (2C, CH), 137.1, 138.1, 138.9, 155.9, 157.8, 171.2 (C); IR (KBr): $\tilde{\nu}$ = 2988 (m), 2930 (w), 1651 (s), 1590 (m), 1494 (s), 1377 (s), 1300 (s), 1213(s), 1164 (s), 1029 (m), 842 (w), 793 (s), 692 (s), 577 (w), 421 (w); MS (EI, 70 eV): *m/z* (%): 286 (M^+, 42), 240 (100), 211 (13), 197 (9), 135 (10), 105 (43), 77 (16); elemental analysis: calcd (%) for $C_{17}H_{18}O_4$ (286.1): C 71.31, H 6.43 found: C 71.18, H 6.66.

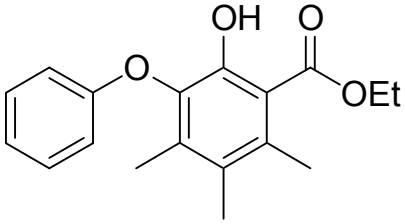
Ethyl 4,6-dimethyl-5-chloro-3-phenoxysalicylate (45i):



Starting with 3-(siloxy)alk-2-en-1-one **44c** (400 mg, 1.93 mmol), 1,3-bis(silyl enol ether) **42c** (707 mg, 1.93 mmol), and $TiCl_4$ (0.21 mL, 1.93 mmol), **45i** was

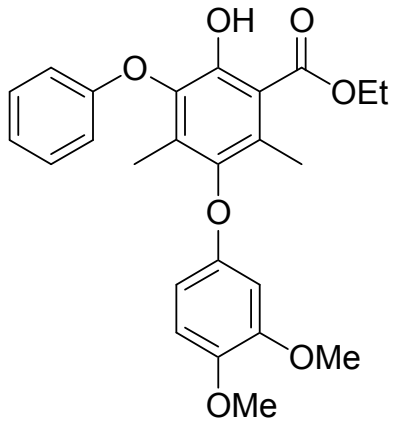
isolated as a colourless solid (234 mg, 38%), mp. 47 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.20 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 4.38 (q, 2 H, *J* = 7.1 Hz, CH_2), 6.75 (d, 2 H, *J* = 7.9 Hz, ArH), 6.91 (t, 1 H, *J* = 7.3 Hz, ArH), 7.18 (m, 2 H, ArH), 10.68 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.3, 14.0, 18.6 (CH_3), 61.1 (CH_2), 112.4 (C), 113.0 (2C, CH), 120.9 (CH), 125.7 (C) 128.5 (2C, CH), 133.3, 136.0, 138.3, 152.2, 156.5, 169.5 (C); IR (Nujol): $\tilde{\nu}$ = 3069 (w), 1664 (s), 1591 (m), 1490 (s), 1401 (s), 1376 (s), 1347 (m), 1246 (s), 1184 (s), 1074 (m), 854 (w), 749 (s), 686 (m), 433 (w); MS (EI, 70 eV): *m/z* (%):322 (M^+, ^{37}Cl, 15), 320 (M^+, ^{35}Cl, 43), 274 (100), 245 (15), 211 (13), 169 (8), 139 (34), 105 (43), 77 (21); elemental analysis: calcd (%) for $C_{17}H_{17}ClO_4$ (320.08): C 63.65, H 5.34; found: C 63.23, H 5.70.

Ethyl 4,5,6-trimethyl-3-phenoxysalicylate (45j):



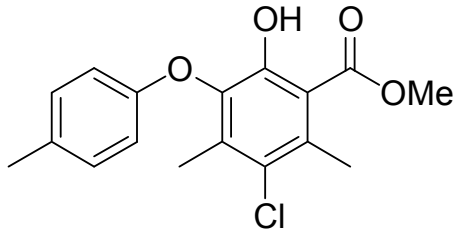
Starting with 3-(siloxy)alk-2-en-1-one **44d** (600 mg, 3.2 mmol), 1,3-bis(silyl enol ether) **42c** (1.18 g, 3.2 mmol), and $TiCl_4$ (0.35 mL, 3.2 mmol), **45j** was isolated as a colourless solid (414 mg, 43%), mp. 75 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.02 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 4.30 (q, 2 H, *J* = 7.0 Hz, OCH_2), 6.71 (dd, 2H, *J* = 1.1, 8.6 Hz, ArH), 6.84 (m, 1 H, ArH), 7.09-7.15 (m, 2 H, ArH), 10.08 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.8, 14.1, 15.8, 18.8 (CH_3), 61.7 (CH_2), 113.4 (C), 114.6 (2C, CH), 121.6 (CH), 127.7 (C), 129.5 (2C, CH), 134.3, 136.7, 138.4, 151.6, 158.0, 171.0 (C); IR (KBr): $\tilde{\nu}$ = 2992 (w), 2923 (w), 1663 (s), 1591 (s), 1414 (s), 1312 (s), 1251 (s), 1189 (s), 1018 (s), 801 (m), 753 (s), 693 (m), 507 (w), 418 (w); MS (EI, 70 eV): *m/z* (%): 300 (M^+, 46), 254 (100), 239 (27), 211 (15), 149 (15), 105 (57), 77 (22); elemental analysis: calcd (%) for $C_{18}H_{20}O_4$ (300.1): C 71.98, H 6.71 found: C 71.66, H 6.77.

Ethyl 4,6-dimethyl-3-phenoxy 5-(3,4-dimethoxyphenox)salicylate (45k):



Starting with 3-(siloxy)alk-2-en-1-one **44e** (600 mg, 1.83 mmol) 1,3-bis(silyl enol ether) **42c** (671 mg, 1.83 mmol), and $TiCl_4$ (0.2 ml, 1.83 mmol), **45k** was isolated as a highly viscous oil (207 mg, 30%); ^{1}H NMR (250 MHz, $CDCl_3$): δ =1.35 (t, 3 H, *J* = 7.1 Hz, CH_3), 1.95 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.75 (s, 3 H, O*C*H_3), 3.77 (s, 3 H, O*C*H_3), 4.36 (q, 2 H, *J* = 7.2 Hz, O*C*H_2), 6.02 (dd, 1H, *J* = 2.8, 8.6 Hz, ArH), 6.44 (d, 1H, *J* = 2.8 Hz, ArH), 6.64 (d, 1 H, *J* = 8.8 Hz, ArH), 6.77-6.81 (m, 2 H, ArH), 6.88-6.95 (m, 1 H, ArH), 7.16-7.23 (m, 2 H, ArH), 11.09 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 10.9, 14.1, 15.1, 55.9, 56.3 (CH_3), 62.0 (CH_2), 100.0, 104.1, 111.9 (CH), 112.0 (C), 114.5 (2C, CH), 121.8 (CH), 129.5 (2C, CH), 130.4, 133.8, 139.4, 143.7, 143.9, 150.1, 152.4, 153.1, 157.7, 171.1 (C); IR (neat): $\tilde{\nu}$ = 2999 (w), 2936 (w), 1601 (s), 1508 (s), 1452 (s), 1301 (s), 1261 (s), 1192 (s), 1027 (s), 833 (m), 753 (w), 653 (w), 475 (w); MS (EI, 70 eV): MS (EI, 70 eV): *m/z* (%): 438.1 (M^+, 100), 392.1 (87), 377.1 (49), 287.1 (3), 255 (3), 138 (13), 105 (59), 77 (16); HRMS (EI): calcd for $C_{25}H_{26}O_7$ [M^+]: 438.16708, found 438.16730.

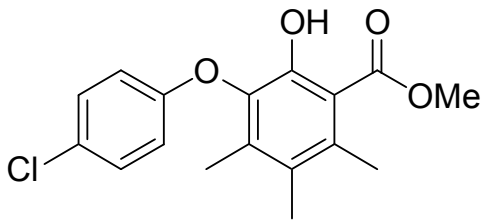
Methyl 4,6-dimethyl-5-chloro-3-(4-methylphenoxy)salicylate (45l):



Starting with 3-(siloxy)alk-2-en-1-one **44c** (400 mg, 1.9 mmol), 1,3-bis(silyl enol ether) **42d** (711 mg, 1.9 mmol), and $TiCl_4$ (0.21 mL, 1.93 mmol), **45l** was isolated as a highly viscous oil (248 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$): δ =2.20 (s, 6 H, CH_3), 2.53 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 6.65 (d, 2 H, *J* = 8.5 Hz, ArH), 6.97 (d, 2 H, *J* = 8.8 Hz, ArH), 10.55 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 18.6, 19.5, 51.5 (CH_3), 112.3 (C), 113.3 (2C, CH), 125.7 (C), 129.0 (2C, CH), 130.3, 133.0, 136.1, 138.5, 152.1, 154.4, 169.9 (C); IR (neat): $\tilde{\nu}$ = 297 (m), 2927 (m), 2871 (w), 1661 (s), 1506 (s), 1444 (s), 1248 (s), 1164 (s), 1040 (m), 846 (m), 707 (w), 612 (w), 503 (w); MS (EI, 70 eV): *m/z* (%):322 (M^+, ^{37}Cl,

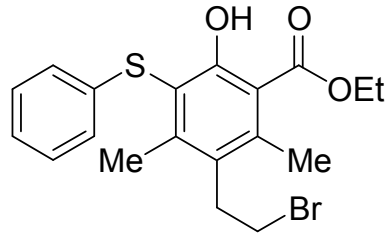
15), 320 (M^+, ^{35}Cl, 46), 288 (100), 273 (9), 259 (15), 169 (10), 119 (87), 91(22), 77 (18); HRMS (EI): calcd for $C_{17}H_{17}ClO_4$ [M^+, ^{35}Cl]: 320.08106, found 320.08099.

Methyl 4,5,6-trimethyl-3-(4-chlorophenoxy)salicylate (45m):



Starting with 3-(silyloxy)alk-2-en-1-one **44d** (400 mg, 2.1 mmol), 1,3-bis(silyl enol ether) **42e**(814 mg, 2.1 mmol), and $TiCl_4$ (0.23 mL, 2.1 mmol), **45m** was isolated as a colourless solid (272 mg, 40%), mp. 98 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 6.65 (d, 2 H, J = 8.9 Hz, ArH), 7.05 (d, 2 H, J = 8.8 Hz, ArH), 10.23 (s, 1H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.8, 15.9, 18.8, 52.3 (CH_3), 113.1 (C), 116.0 (2C, CH), 126.4, 127.8 (C), 129.4 (2C, CH), 134.7, 136.7, 138.3, 151.6, 156.6, 171.6 (C); IR (KBr): $\tilde{\nu}$ = 3005(w), 2952 (w), 2926 (w), 1667 (s), 1595 (m), 1485 (s), 1318 (s), 1248 (s), 1298 (s), 1064 (s), 994 (m), 823 (s), 626 (w), 457 (w); MS (EI, 70 eV): *m/z* (%):322 (M^+, ^{37}Cl, 21), 320 (M^+, ^{35}Cl, 62), 288 (70), 273 (13), 253 (71), 225 (11), 139 (100), 91 (13), 77 (18); elemental analysis: calcd (%) for $C_{17}H_{17}ClO_4$ (320.08): C 63.65, H 5.34 found: C 63.59, H 5.39.

Ethyl 4,6-dimethyl-5-(2-bromoethyl)-3-thiophenoxysalicylate (47c):

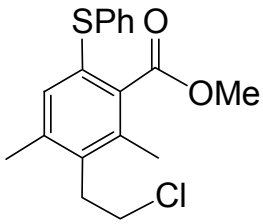


Starting 1,1-diacyclopropane **46** (500mg, 3.9 mmol) 1,3-bis(silyl enol ether) **42a** (2.2g, 5.5 mmol), $TiBr_4$ (1.4g, 3.9 mmol), and CH_2Cl_2 (110mL) **47c** was isolated as a yellowish highly viscous compound (715mg, 45%); ^1H NMR (250 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, J = 7.1 Hz, CH_3), 2.34 (S, 3 H, CH_3), 2.41 (S, 3 H, CH_3), 3.15 (m, 2 H, CH_2), 3.30 (m, 2 H, CH_2), 4.36 (q, 2 H, J = 7.1 Hz, CH_2), 6.92 (m, 2 H, ArH),.7.05 (m, 1H, ArH), 7.15 (m, 2 H, ArH), 8.67 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.2, 17.8, 18.5 (CH_3), 29.4, 34.2, 61.7 (CH_2), 116.3, 117.7 (C), 125.7 (CH), 126.2 (2C CH), 129.1 (2C CH),129.2 (C), 133.6, 138.5, 145.8, 156.4, 169.2 (C); IR (neat): $\tilde{\nu}$ = 3386 (s), 2979 (s), 2934 (m), 1728 (s), 1655 (s), 1582 (s), 1478 (s), 1373 (s), 1228 (s), 1048 (m), 739 (m) 690 (s) cm^{-1};

GC-MS (EI, 70 eV): *m/z* (%): 410 (M^+, ^{81}Br, 59), 408 (M^+, ^{79}Br, 57), 364 (100), 329 (18), 283 (85), 269 (24), 77 (12); HRMS (EI): calcd for $C_{19}H_{21}O_3BrS$ ($[M+1]^+$) 408.03893, found 408.03884.

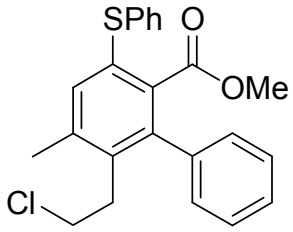
General procedure for the synthesis of diaryl sulfides 49a-g: To a dichloromethane solution (30 mL/mmol) of 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **1** (1.0 mmol) and 1,1-diacyclopropane **2** (1.5 mmol) was added TiX_4 (1.5 mmol) at –78 °C. The solution was allowed to warm to ambient temperature within 14 h. To the solution was added a diluted aqueous solution of HCL (25 mL). The organic and the aqueous layer were separated and the latter was extracted with dichloromethane (3 x 20 mL). The filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Methyl 4,6-dimethyl-5-(2-chloroethyl)-2-(thiophenoxy)benzoate (49a) :



Starting 1,1-diacyclopropane **46a** (378 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), $TiCl_4$ (0.33 ml, 3.0 mmol) and CH_2Cl_2 (60 mL) **49a** was isolated as highly viscous oil (322 mg, 48%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, CH_3), 2.21 (s, 3 H, CH_3), 3.09 (t, 2 H, *J* = 7.5 Hz , CH_2), 3.43 (t, 2 H, *J* = 7.1 Hz, CH_2), 3.76 (s, 3 H, OC*H*$_3$), 6.96 (s, 1 H, ArH), 7.11-7.21 (m, 5 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.8, 20.1 (CH_3), 33.0, 41.6 (CH_2), 52.2 (CH_3), 126.9.0 (CH), 129.04 (2C, CH), 130.3 (C), 130.5 (2C, CH),133.1 (CH), 134.1, 135.1, 136.0, 136.6, 138.9 (C), 169.3 (C=O); IR (ATR): $\tilde{\nu}$ = 2948 (w), 2871 (w), 1727 (s), 1579 (m), 1437 (m), 1268 (s), 1148 (s), 1039 (m), 1023 (m), 933 (w), 777 (w), 738 (s), 689 (s), 557 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):336 (M^+,^{37}Cl, 37), 334 (M^+,^{35}Cl, 100), 301 (61), 285 (56), 267 (36) 253 (66), 210 (13), 115 (8), 77 (9); elemental analysis: calcd (%) for $C_{18}H_{19}ClO_2S$ (334.86): C 64.56, H 5.72; found: C 64.59, H 5.84.

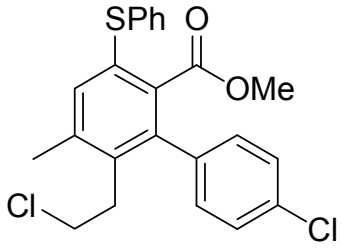
Methyl 4-methyl-5-(2-chloroethyl)-6-phenyl-2-(thiophenoxy)benzoate (49b) :



Starting 1,1-diacyclopropane **46b** (564 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0

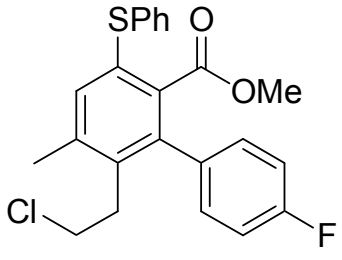
mmol), $TiCl_4$ (0.33 ml, 3.0 mmol) and CH_2Cl_2 (60 mL) **49b** was isolated as highly viscous oil (278 mg, 47%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 2.83 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.22 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.31 (s, 3 H, OC*H*$_3$), 7.03 (s, 1 H, ArH), 7.11-7.18 (m, 5 H, ArH), 7.23-7.30 (m, 4 H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.6 (CH_3), 32.1, 42.2 (CH_2), 51.7 (CH_3), 128.5, 128.7 (CH), 128.9 (2C, CH), 129.0 (2C, CH), 129.2 (2C, CH), 130.8 (C), 131.2 (2C, CH), 133.5 (CH), 133.9,135.2, 136.3 ,137.1, 138.5, 140.0 (C), 168.1 (C=O); IR (ATR): $\tilde{\nu}$ = 3022 (w), 2947 (w), 1729 (s), 1573 (m), 1438 (s), 1270 (s), 1137 (s), 1023 (m), 739 (s), 699 (s), 595 (m), 557 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):398 (M^+,^{37}Cl, 28), 396 (M^+,^{35}Cl, 75), 365 (7), 315 (100), 300 (10) 271 (23), 178 (8), 156 (6), 77 (2); HRMS (EI) calcd for $C_{23}H_{21}O_2ClS$ [M^+, ^{35}Cl]: 396.09453, found 396.09453.

Methyl 4-methyl-5-(2-chloroethyl)-6-(4-chlorophenyl)-2-(thiophenoxy)benzoate(49c) :



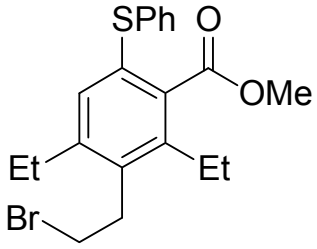
Starting 1,1-diacyclopropane **46c** (333 mg, 1.5 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (281 mg, 1.0 mmol), $TiCl_4$ (0.16 ml, 1.5 mmol) and CH_2Cl_2 (00 mL) **49c** was isolated as highly viscous oil (185 mg, 43%);^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 2.71 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.14 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.28 (s, 3 H, OC*H*$_3$), 6.94 (s, 1 H, ArH), 6.99 (d, 2 H, *J* = 8.4 Hz, ArH), 7.08-7.22 (m, 7 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.1 (CH_3), 33.1, 42.3 (CH_2), 51.9 (CH_3), 127.4 (CH), 128.3 (2C, CH), 129.1 (2C, CH), 130.6 (2C, CH), 131.4 (C), 131.5 (2C, CH), 133.7 (CH), 133.9, 134.0, 134.9, 135.3, 136.4, 139.3, 139.5 (C), 168.0 (C=O); IR (ATR): $\tilde{\nu}$ = 2996 (w), 2947 (w), 1729 (s), 1574 (m), 1438 (s), 1271 (s), 1191 (m), 1087 (s), 1001 (m), 836 (m), 739 (s), 598 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):435 ([M]$^+$, [2×^{37}Cl], 3), 433 ([M]$^+$, [^{37}Cl], [^{35}Cl], 15), 370 ([M]$^+$, [2×^{35}Cl], 23), 349 (100), 314 (16), 285 (10), 271 (24), 156 (10), 77 (3); elemental analysis: calcd (%) for $C_{23}H_{20}ClO_2S$ (431.37): C 64.04, H 4.67; found: C 63.79, H 4.86.

Methyl 4-methyl-5-(2-chloroethyl)-6-(4-fluorophenyl)-2-(thiophenoxy)benzoate(49d)



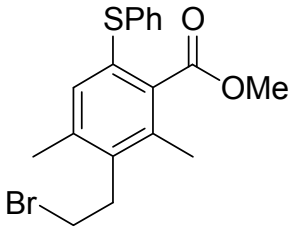
Starting 1,1-diacyclopropane **46d** (618 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), $TiCl_4$ (0.33 ml, 1.5 mmol) and CH_2Cl_2 (60 mL) **49d** was isolated as highly viscous oil (331 mg, 40%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 2.82 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.23 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.37 (s, 3 H, OC*H*$_3$), 7.01 (s, 1 H, ArH), 7.10 (d, 2 H, *J* = 8.6 Hz, ArH), 7.14-7.33 (m, 7 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.1 (CH_3), 33.3, 42.0 (CH_2), 51.8 (CH_3), 115.0, 115.3, 127.4 (CH), 129.2 (2C, CH), 130.9, 131.0 (CH), 131.3 (C), 131.5 (2C, CH), 133.6 (CH), 133.6, 134.3, 135.0, 135.5, 139.3, 139.7 (C), 162.1 (d, *J* = 274.2 Hz, CF), 168.1 (C=O); IR (ATR): $\tilde{\nu}$ = 2948 (w), 2923 (w), 1730 (s), 1590 (s), 1508 (s), 1438 (s), 1156 (s), 1023 (m), 785 (m), 690 (s), 605 (m), 558 (w) cm^{-1}; GC-MS (EI, 70 eV GC-MS (EI, 70 eV): *m/z* (%):416 (M^+,^{37}Cl, 24), 414 (M^+,^{35}Cl, 74), 383 (5), 333 (100), 318 (9) 289 (15), 197 (6), 163 (13), 57 (21); HRMS (EI) calcd for $C_{23}H_{20}O_2ClFS$ [M^+, ^{35}Cl]: 414.08518, found 141.08511.

Methyl 4,6-diethyl-5-(2-bromoethyl)-2-(thiophenoxy)benzoate (49e) :



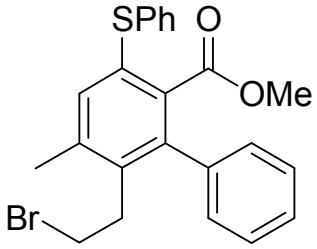
Starting 1,1-diacyclopropane **46e** (462 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), $TiBr_4$ (1.10 g, 3.0 mmol) and CH_2Cl_2 (60 mL) **49e** was isolated as highly viscous oil (228 mg, 28%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, , *J* = 7.4 Hz, CH_3), 1.13 (t, 3 H, , *J* = 7.5 Hz, CH_3), 2.54 (m, 4 H, 2× CH_2), 312 (m, 2 H, CH_2), 329 (m, 2 H, CH_2), 3.78 (s, 3 H, OC*H*$_3$), 6.98 (s, 1 H, ArH), 7.12-7.21 (m, 5 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 15.3, 15.9 (CH_3), 24.4, 25.9, 30.1, 32.5 (CH_2), 52.1 (CH_3), 126.8 (CH), 129.0 (2C, CH), 130.4 (2C, CH), 130.9 (C), 131.6 (CH), 134.6, 136.0, 136.1, 140.2, 145.0 (C), 169.3 (C=O); IR (ATR): $\tilde{\nu}$ = 2967 (w), 2874 (w), 1728 (s), 1578 (m), 1438 (m), 1476 (m), 1271 (s), 1145 (s), 1023 (m), 983 (w), 739 (s), 688 (s), 579 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):408 (M^+, ^{81}Br, 70), 406 (M^+, ^{79}Br, 69), 375 (100), 378 (88), 313 (19) 295 (37), 221 (8), 128 (13), 91 (5); elemental analysis: calcd (%) for $C_{20}H_{23}BrO_2S$ (407.06): C 58.97, H 5.69; found: C 59.55, H 6.04.

Methyl 4,6-dimethyl-5-(2-bromoethyl)-2-(thiophenoxy)benzoate (49f) :



Starting 1,1-diacyclopropane **46a** (378 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), $TiBr_4$ (1.101 g, 3.0 mmol) and CH_2Cl_2 (60 mL) **49f** was isolated as highly viscous oil (439 mg, 58%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 3.10 (m, 2 H, CH_2), 3.26 (m, 2 H, CH_2), 3.76 (s, 3 H, OC*H*$_3$), 6.95 (s, 1 H, ArH), 7.07-7.19 (m, 5 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.8, 20.0 (CH_3), 28.8, 33.5 (CH_2), 52.2 (CH_3), 126.9.0 (CH), 129.04 (2C, CH), 130.4 (C), 130.5 (2C, CH),133.1 (CH), 133.9, 136.0, 136.1, 136.6, 138.7 (C), 169.3 (C=O); IR (ATR): $\tilde{\nu}$ = 2947 (w), 2923 (w), 1727 (s), 1579 (m), 1436 (m), 1267 (s), 1147 (s), 1129 (m), 1045 (m), 812 (m), 738 (s), 688 (s), 591 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):380 (M^+, ^{81}Br, 100), 378 (M^+, ^{79}Br, 98), 347 (68), 345 (53), 299 (20) 285 (50), 253 (68), 115 (12), 77 (9); elemental analysis: calcd (%) for $C_{18}H_{19}BrO_2S$ (379.31): C 57.00, H 5.05; found: C 57.24, H 5.13.

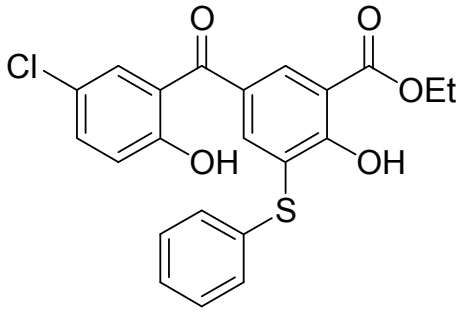
Methyl 4-methyl-5-(2-bromoethyl)-6-phenyl-2-(thiophenoxy)benzoate (49g) :



Starting 1,1-diacyclopropane **46b** (564 mg, 3.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), $TiBr_4$ (1.101 g, 3.0 mmol) and CH_2Cl_2 (60 mL) **49g** was isolated as highly viscous oil (353 mg, 40%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3), 2.85 (m, 2 H, CH_2), 3.07 (m, 2 H, CH_2), 3.31 (s, 3 H, OC*H*$_3$), 7.03 (s, 1 H, ArH), 7.11-7.19 (m, 5 H, ArH), 7.25-7.32 (m, 4 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.1 (CH_3), 29.5, 33.7 (CH_2), 51.7 (CH_3), 127.3, 127.8 (C), 128.1 (CH), 129.1 (2C, CH), 129.2 (2C, CH), 131.5 (2C, CH), 133.5 (C), 133.6 (2C, CH), 135.2, 135.3 (CH), 135.5, 137.9, 139.0, 140.7 (C), 168.2 (C=O); IR (ATR): $\tilde{\nu}$ = 3021 (w), 2846 (w), 1730 (s), 1573 (m), 1438 (m), 1268 (s), 1136 (s), 1089 (m), 1023 (m), 929 (w), 702 (s), 688 (s), 579 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):442 (M^+, ^{81}Br, 67), 440 (M^+, ^{79}Br, 64), 329 (15), 315 (100), 300 (10) 271 (24), 178 (11), 156 (10), 77 (3); elemental analysis: calcd (%) for $C_{18}H_{19}BrO_2S$ (441.38): C 62.59, H 4.80; found: C 62.73, H 4.98.

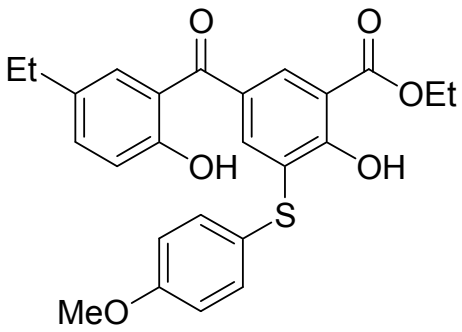
General procedure for the synthesis of benzophenones 51a-f: Me_3SiOTf (0.3 equiv) was added to 3-formylchromone (1.0 equiv) at 20°C. After stirring for 10 min CH_2Cl_2 (8 ml) was added, the solution was cooled to 0°C and the 1,3-bis-silyl enol ether (1.3 equiv) was addd. The mixture was stirred at 20°C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and aqueous layer was separated and lateral was extracted 3 times with 15 ml with CH_2Cl_2. The combined filtrate was washed with 25 ml and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Ethyl-5-(2-hydroxy-5-chlorobenzoyl)-3-thiophenoxysalicylate(51a):



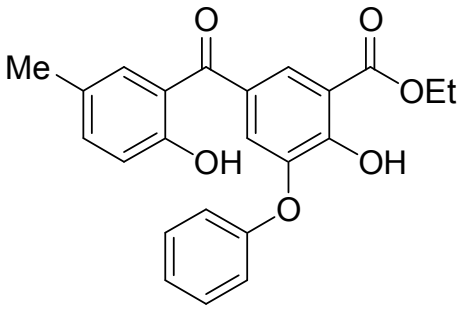
Starting with 3-formylchromone **50a** (400 mg, 1.91 mmol) 1,3-bis(silyl enol ether) **42a** (806 mg, 2.1 mmol), and Me_3SiOTf (0.1 ml, 0.57 mmol), **51a** was isolated as a solid (385 mg, 47%), mp. 104 °C; ^1H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.1 Hz, CH_3), 4.38 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.86 (dd, *J* = 0.8, 8.3 Hz, 1 H, ArH), 7.16-7.34 (m, 6 H, ArH), 7.41 (dd, *J* = 1.7, 8.2 Hz, 2 H, ArH), 8.02 (d, *J* = 2.2 Hz, 1 H, ArH), 11.53 (s, 1 H, OH), 11.89 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.9 (CH_3), 61.3 (CH_2), 111.2, 118.3 (C), 118.9 (CH), 122.2, 126.5, 127.2, 127.6 (C), 128.6 (CH), 128.7 (2C, CH), 130.0, 130.5 (CH), 132.4 (2C, CH), 133.8, 134.9 (CH), 160.2, 160.5, 168.4, 196.4 (C); IR (KBr): $\tilde{\nu}$ = 3073 (w), 2958(w), 2854 (w), 1661 (s), 1576 (s), 1473 (s), 1314 (s), 1290 (s), 1195 (m), 1022 (m), 864 (m), 787 (s), 690(s), 418 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):430(M^+,^{37}Cl, 40), 428 (M^+,^{35}Cl, 95), 382 (100), 302 (5), 228 (18) 200(10), 171 (17), 155 (21), 99 (5); HRMS (EI) calcd for $C_{22}H_{17}ClO_5S$ [M^+, ^{35}Cl]: 428.04744, found 428.04797.

Ethyl-5-(2-hydroxy-5-ethylbenzoyl)-3-(4-methoxyhiophenoxy)salicylate(51b):



Starting with 6-ethyl-3-formylchromone **50b** (500 mg, 2.47 mmol) 1,3-bis(silyl enol ether) **42b** (10.17 g, 2.47 mmol), and Me_3SiOTf (0.15 ml, 0.86 mmol), **51b** was isolated as a solid (422 mg, 38%), mp. 124 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.06 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.29 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.40 (q, *J* = 7.7 Hz, 2 H, CH_2), 3.6 (s, 3 H, OC*H*$_3$), 4.34 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.82 (m, 3 H, ArH), 7.13-7.25 (m, 3 H, ArH), 7.38 (d, *J* = 8.8 Hz, 2 H, ArH), 7.96 (d, *J* = 2.0 Hz, 1 H, ArH), 11.50 (s, 1 H, OH), 11.80 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 15.8 (CH_3), 27.9 (CH_2), 55.3 (CH_3), 62.1 (CH_2), 111.6 (C), 115.4 (2C, CH), 118.2 (CH), 118.5, 120.7 (C), 129.1 (CH), 129.1, 129.3 (C), 131.4, 133.5 (CH), 134.2 (C), 136.1 (CH), 136.5 (2C, CH), 160.5, 160.6, 161.0, 169.8, 198.6 (C); IR (ATR): $\tilde{\nu}$ = 2994 (w), 2912(w), 2839 (w), 1677(s), 1588 (s), 1349 (s), 1241 (s), 1217 (s), 1166 (s), 1019 (m), 833 (m), 810 (m), 670 (m), 567 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 452 (M^+,100), 406 (97), 258 (31), 230 (6), 177 (10), 149 (49), 111 (24), 83 (36), 57 (62); elemental analysis: calcd (%) for $C_{25}H_{24}O_6S$ (452.52): C 66.35, H 5.35; found: C 66.58, H 5.37.

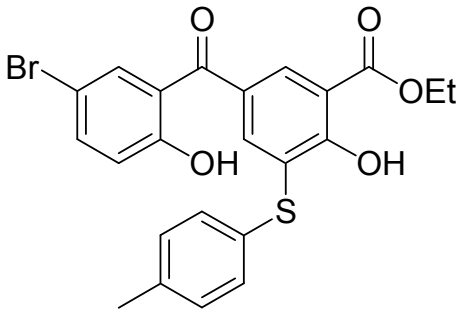
Synthesis of ethyl-5-(2-hydroxy-5-methylbenzoyl)-3-phenoxysalicylate (51c):



Starting with 3-formylchromone **50c** (411 mg, 2.2 mmol), 1,3-bis(silyl enol ether) **42c** (800 mg, 2.2 mmol), and Me_3SiOTf (0.65 mL, 1.2 mmol), **51c** was isolated as a highly viscous oil (300 mg, 35%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.35 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.17 (s, 3 H, CH_3), 4.39 (q, *J* = 7.1 Hz, 2 H, CH_2), 6.88 (m, 1 H, ArH), 6.94-7.06 (m, 3 H, ArH), 7.21-7.30 (m, 4 H, ArH), 7.44 (d, *J* = 2.1 Hz, 1 H, ArH), 8.02 (d, *J* = 2.2 Hz, 1 H, ArH), 11.45 (s, 1 H, OH), 11.49 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 20.4 (CH_3), 62.3 (CH_2), 113.8 (C),

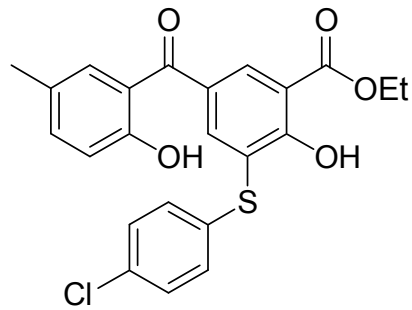
116.9 (C), 117.7 (2C, CH), 118.3 (CH), 118.5 (C), 123.6, 126.1, 127.0 (CH), 127.8, 128.6 (C), 129.8 (2C, CH), 132.5, 137.3 (CH), 144.8, 156.8, 156.9, 160.9, 169.6, 198.3 (C); IR (neat): $\tilde{\nu}$ = 2982 (w), 2926 (w), 2869 (w), 1678 (s), 1587 (s), 1401 (s), 1376 (s), 1212 (s), 1109 (m), 1028 (s), 827 (m), 788 (s), 691(m), 475 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 392 (M^+, 100), 347 (43), 258 (31), 212 (44), 184(13), 135(54), 105(24), 77 (27); HRMS (EI) calcd for $C_{23}H_{20}O_6$ [M^+]: 392.12554, found 392.12544.

Ethyl-5-(2-hydroxy-5-bromobenzoyl)-3-(4-methylthiophenoxy)salicylate(51d):



Starting with 6-bromo3-formylchromone **50d** (380 mg, 1.5 mmol) 1,3-bis(silyl enol ether) **42f** (594 mg, 1.5 mmol), and Me_3SiOTf (0.08 ml, 0.45 mmol), **51d** was isolated as a solid (329 mg, 45%), mp. 125 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.0 Hz, CH_3), 2.24 (s, 3 H, CH_3), 4.36 (q, *J* = 7.1 Hz, 2 H, CH_2), 6.81 (d, *J* = 9.4 Hz, 1H, ArH), 7.12 (d, *J* = 7.9 Hz, 2 H, ArH), 7.18 (d, *J* = 2.0 Hz, 1 H, ArH),7.32 (d, *J* = 10.1 Hz, 2 H, ArH), 7.41-7.45 (m, *J* = 10.1 Hz, 2 H, ArH), 7.98 (d, *J* = 2.2 Hz, 1 H, ArH), 11.47 (s, 1 H, OH), 11.86 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 11.9, 19.1 (CH_3), 60.2 (CH_2), 108.0, 110.0, 117.9 (C), 118.3 (CH), 124.7, 126.1, 126.7 (C), 127.0 (CH), 128.6 (2C, CH), 131.6 (CH), 132.2 (2C, CH), 132.5, 136.5 (CH), 137.1, 159.0, 159.6,167.5, 195.4 (C); IR (ATR): $\tilde{\nu}$ = 3017 (w), 2982(w), 2865 (w), 1627(s), 1568 (s), 1467 (s), 1398 (s), 1285 (s), 1163 (s), 1018 (s), 996 (m), 836 (m), 736 (s), 613 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):488 (M^+, ^{81}Br, 100), 486 (M^+, ^{79}Br, 92), 442 (87), 440 (78), 242 (25), 199 (20), 125 (12), 111 (20), 57 (45); elemental analysis: calcd (%) for $C_{23}H_{19}BrO_5S$ (486.01): C 56.68, H 3.93; found: C 56.12, H 4.40.

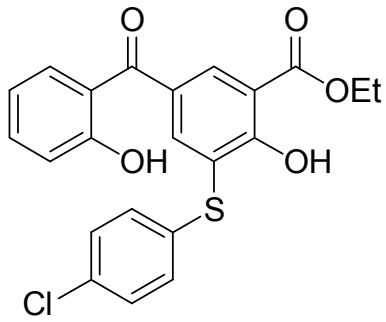
Ethyl-5-(2-hydroxy-5-methylbenzoyl)-3-(4-chlorothiophenoxy)salicylate(51e):



Starting with 6-methyl3-formylchromone **50c** (255 mg, 1.35 mmol) 1,3-bis(silyl enol ether) **42g** (566 mg, 1.35 mmol), and Me_3SiOTf (0.07 ml, 0.40 mmol), **51e** was isolated as a solid (240 mg, 40%), mp. 98 °C; ^{1}H NMR

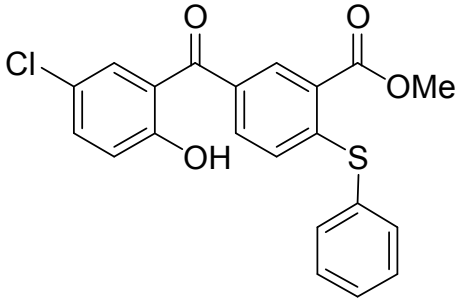
(250 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.13 (s, 3 H, CH_3), 4.38 (q, *J* = 7.1 Hz, 2 H, CH_2), 6.85 (d, *J* = 8.5 Hz, 1 H, ArH), 7.10 (d, *J* = 1.4 Hz, 1 H, ArH), 7.16-7.29 (m, 5 H, ArH), 7.51 (d, *J* = 2.0 Hz, 1 H, ArH), 8.09 (d, *J* = 2.2 Hz, 1 H, ArH), 11.47 (s, 1 H, OH), 11.86 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 21.4 (CH_3), 63.4 (CH_2), 113.5 (C), 119.2 (CH), 119.3, 126.3, 128.7, 130.2 (C), 130.6 (2C, CH), 131.7 (CH), 132.2 (C), 133.2 (CH), 134.5 (2C, CH), 135.2 (C), 138.2, 138.3 (CH), 161.9, 163.1, 170.6, 199.2 (C); IR (ATR): $\tilde{\nu}$ = 2994 (w), 2919(w), 2855 (w), 1628(s), 1581 (s), 1412 (s), 1377 (s), 1218 (s), 1190 (m), 1090 (m), 994 (m), 815 (m), 666(m), 536 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):444(M^+,^{37}Cl, 31), 442 (M^+,^{35}Cl, 86), 396 (100), 308 (10), 262 (40) 205 (10), 171 (10), 135 (42), 69 (50); HRMS (EI) calcd for $C_{23}H_{19}ClO_5S$ [M^+, ^{35}Cl]: 442.06469, found 442.06362.

Ethyl-5-(2-hydroxybenzoyl)-3-(4-chlorothiophenoxy)salicylate(51f):



Starting with 3-formylchromone **50e** (500 mg, 2.87 mmol) 1,3-bis(silyl enol ether) **42g** (12.01g, 2.87 mmol), and Me_3SiOTf (0.15 ml, 0.86 mmol), **51f** was isolated as a highly viscous oil (385 mg, 47%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.2 Hz, CH_3), 4.38 (q, *J* = 7.2 Hz, 2 H, CH_2), 6.74 (m, 1 H, ArH), 6.95 (dd, *J* = 0.9, 8.3 Hz, 1 H, ArH), 7.18-7.43 (m, 6 H, ArH), 7.50 (d, *J* = 1.8 Hz, 1 H, ArH), 8.09 (d, *J* = 2.0 Hz, 1 H, ArH), 11.57 (s, 1 H, OH), 11.85 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 15.0 (CH_3), 63.4 (CH_2), 113.4 (C), 119.5, 119.6 (CH), 119.7, 126.4, 130.0 (C), 130.6 (2C, CH), 131.7 (CH), 132.2 (C), 133.5 (CH), 134.5 (2C, CH), 135.2 (C), 137.3, 138.3 (CH), 163.2, 163.9, 170.5, 199.2 (C); IR (ATR): $\tilde{\nu}$ = 2979 (w), 2906(w), 2871 (w), 1670(s), 1623 (s), 1575 (s), 1338 (s), 1236 (s), 1184 (s), 1091 (m), 987 (m), 816 (m), 792(m), 561 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):430(M^+,^{37}Cl, 36), 428 (M^+,^{35}Cl, 81), 382 (100), 262 (16), 205 (9) 205 (10), 171 (11), 121 (71), 65 (14); HRMS (EI) calcd for $C_{22}H_{17}ClO_5S$ [M^+, ^{35}Cl]: 428.04840, found 428.04797.

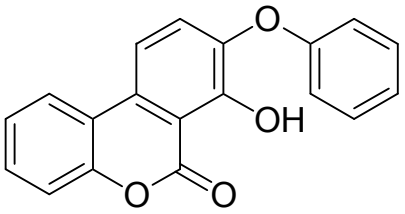
Methyl 5-(2hydroxy-5-chlorobenzoyl)-2-(thiophenoxy)benzoate(52):



Starting with 3-formylchromone **50a** (417 mg, 2.0 mmol) 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **48** (562 mg, 2.0 mmol), and Me_3SiOTf (0.11 ml, 0.65 mmol), **52** was isolated as a highly viscous oil (174 mg, 22%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.92 (s, 3 H, OC*H*$_3$), 6.82 (d, *J* = 8.5 Hz, 1 H, ArH), 6.95 (d, *J* = 8.2 Hz, 1 H, ArH), 7.35-7.47 (m, 6 H, ArH), 7.53-7.57 (m, 2 H, ArH), 8.28 (d, *J* = 2.0 Hz, 1 H, ArH), 11.64 (s, 1 H, OH);^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.5 (CH_3), 119.5 (C), 120.2 (CH), 123.5, 125.9 (C), 126.6, 129.9 (CH), 130.1 (2C, CH), 130.8 (C), 131.7. 132.2, 132.3 (CH), 132.7 (C), 136.0 (2C, CH),136.2 (CH), 150.1, 161.5, 165.8, 198.4 (C); IR (ATR): $\tilde{\nu}$ = 2952 (w), 2922(w), 1720 (s), 1629 (s), 1582 (s), 1463 (s), 1310 (m), 1263 (s), 1046 (s), 952 (m), 722 (s), 643 (m), 536 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):400 (M^+,^{37}Cl, 40), 398 (M^+,^{35}Cl, 100), 365 (44), 337 (33), 244 (33) 184 (23), 155 (27), 99 (13); HRMS (EI) calcd for $C_{21}H_{15}ClO_4S$ [M^+, ^{35}Cl]: 398.03687, found 398.03741.

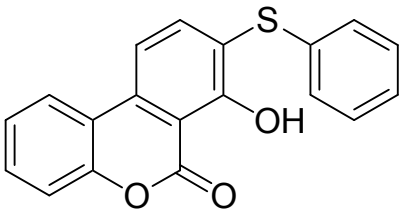
General procedure for the synthesis of 7-hydroxy-6*H*-benzo[c]chromen-6-one(55): Me_3SiOTf (1.3 equiv) was added to chromone (1.0 equiv) at 20°C. After stirring for 1h CH_2Cl_2 (8 ml) was added, the solution was cooled to 0°C and the 1,3-bis-silyl enol ether (1.3 equiv) was addd. The mixture was stirred at 20°C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and aqueous layer was separated and lateral was extracted 3 times with 15 ml with CH_2Cl_2 and dried over Na_2SO_4. The solvent was removed under reduced pressure to give crude product **54.** Et_3N (2.0 equiv) was added to the solution of **54** in EtOH (10 ml) and the mixture was stirred for 12 h at 20°C. After this HCl (1M) solution was added and extracted with EtOAc and dried over Na_2SO_4. The solvent was removed under reduced pressure and crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

8-Phenoxy-7-hydroxy-6*H*-benzo[c]chromen-6-one(55a):



Starting with chromone **53** (500 mg, 3.42 mmol) 1,3-bis(silyl enol ether) **42c** (1.62 g, 4.44 mmol) Me_3SiOTf (0.8 ml, 4.44 mmol), and Et_3N (0.95 ml, 6.84 mmol), **55a** was isolated as a colourless solid (728 mg, 70%),mp. 151 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.93 (dd, 2 H, , J = 1.1, 8.6 Hz, ArH), 7.03 (m, 1 H, ArH), 7.20-7.28 (m, 4 H, ArH), 7.32-7.36 (m, 2 H, ArH), 7.43 (distorted d, J = 8.6 Hz, 1 H, ArH), 7.86 (dd, J = 1.8, 8.6 Hz, 1 H, ArH), 11.42 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 107.5 (C), 112.2 (CH), 117.4 (2C, CH), 117.6 (CH), 118.1 (C), 122.9, 123.3, 125.3, 128.5 (CH), 129.7 (2C, CH), 130.2 (CH), 130.5, 143.6, 150.1, 153.9, 157.1, 165.3 (C); IR (KBr): $\tilde{\nu}$ = 3138 (w), 3070 (w), 2923 (w), 1684(s), 1586 (s), 1481 (s), 1318 (m), 1220 (s), 1128 (s), 1081 (m), 869 (m), 756 (s), 717 (m), 456 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 304 (M^+, 100), 287 (15), 199 (22), 171 (7) 115 (9), 77 (7), 51(4); HRMS (EI) calcd for $C_{19}H_{12}O_4$ $[M]^+$: 304.07316, found 304.07301.

8-Thiophenoxy-7-hydroxy-6*H*-benzo[c]chromen-6-one (55b):

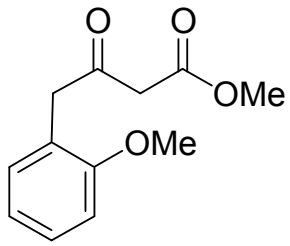


Starting with chromone **53** (310 mg, 2.1 mmol) 1,3-bis(silyl enol ether) **42a** (1.05 g, 2.7 mmol) Me_3SiOTf (0.48 ml, 2.7 mmol), and Et_3N (0.58 ml, 4.2 mmol), **55b** was isolated as a colourless solid (461 mg, 68%),mp. 178 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.20-7.28 (m, 5 H, ArH), 7.35-7.42 (m, 5 H, ArH), 7.86 (dd, J = 1.9, 8.5 Hz, 1 H, ArH), 11.8 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 105.9 (C), 112.5, 117.6 (CH), 118.1 (C), 123.1 (CH), 124.3 (C), 125.3, 127.9 (CH), 129.4 (2C, CH), 130.6 (CH), 132.2 (2C, CH), 132.9, 133.6 (C), 138.2 (CH), 150.4, 159.7, 165.4 (C); IR (KBr): $\tilde{\nu}$ = 3068 (w), 3046 (w), 1673 (w), 1606(s), 1555 (m), 1422 (s), 1320 (m), 1271 (s), 1150 (s), 1025 (w), 830 (m), 759 (s), 691 (m), 456 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 320 (M^+, 100), 302 (5), 288 (5), 258 (4) 215 (3), 143 (5), 77 (3); HRMS (EI) calcd for $C_{19}H_{12}O_3S$ $[M]^+$: 320.05025, found 320.05017.

General procedure for the synthesis of methyl 3-arylacetoacetates 59a-e:

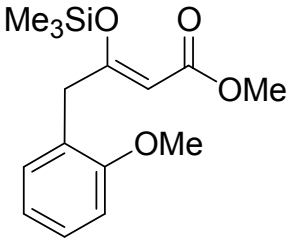
The synthesis was carried out according to the procedure given for the synthesis **40**(*method B)*.

Methyl 4-(2-methoxyphenyl)acetoacetate (59c):



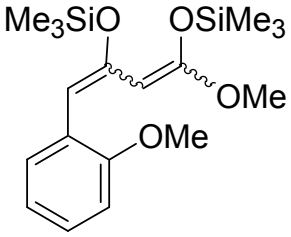
Starting with 2-(4-methoxyphenyl)acetyl chloride (5.00 g, 27.2 mmol) and methyl acetate (2.4 mL, 29.9 mmol), **59c** was isolated as a colorless oil (2.90 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (s, 3 H, OC*H*$_3$), 3.77 (s, 2 H, CH_2), 3.84 (s, 2 H, CH_2), 3.88 (s, 3 H, OC*H*$_3$), 6.94–7.02 (m, 2H, ArH), 7.21 (dd, 1 H, *J* = 1.7, 7.4 Hz, ArH), 7.32–7.37 (dt, 1 H, *J* = 1.7, 8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.7, 45.8 (CH_2), 50.0, 53.2 (CH_3), 118.4, 119.0 (CH), 121.7 (C), 126.8, 129.2 (CH) 155.3, 165.6, 198.8 (C). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3005 (w), 2953 (m), 2839 (w), 1749 (s), 1720 (s), 1602 (m), 1464 (s), 1317 (s), 1177 (s), 1027 (s), 756 (s), 519 (w). MS (EI, 70 eV): *m/z* (%): 222 (M^+, 38), 148 (37), 121 (100), 101 (10), 91 (75), 78 (18), 65 (30), 51 (11). Anal.: calcd (%) for $C_{12}H_{14}O_4$: C 64.85, H 6.35; found: C 64.87, H 6.47.

Synthesis of silyl enol ethers (60c) :



Starting with **59c** (2.90 g, 13.0 mmol), NEt3 (2.9 ml, 20.8 mmol), TMSCl (2.9 ml, 23.4 mmol) and benzene (35ml), **60c** was isolated as a yellow oil (2.90 g, 75%);^{1}H NMR (250MHz, $CDCl_3$): δ = 0.07 (s, 9 H, CH_3), 3.51 (s, 3 H, OC*H*$_3$), 3.71 (s, 3 H, OC*H*$_3$), 3.90 (s, 2 H, CH_2), 4.95 (s, 1 H, =CH), 6.92-7.21 (m, 4H, ArH).

Synthesis of 1,3-bis-silyl enol ether (61c):



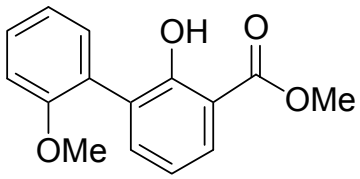
Starting with **60c** (2.85 g, 9.66 mmol), LDA (14.49 mmol, 1.5 equiv.), TMSCl (2.2 ml, 17.3 mmol) and THF (25 ml), **61c** was isolated as a yellow oil (2.91 g, 82%);^{1}H NMR (250MHz,

$CDCl_3$): δ = 0.02 (s, 9 H, CH_3), 0.19 (s, 9 H, CH_3), 3.55 (s, 3 H, OC*H*$_3$), 3.89 (s, 3 H, OC*H*$_3$), 5.01 (s, 1 H, =CH), 5.65 (s, 1 H, =CH), 6.97-7.19 (m, 4H, ArH).

General procedure for the synthesis of biaryls 62:

The synthesis was carried out according to the procedure given for the synthesis **43**.

Methyl 3-(2-methoxyphenyl)salicylate (62c):

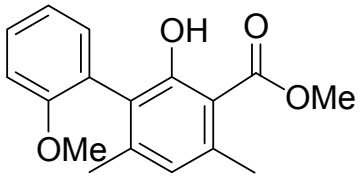


Starting with 1,1,3,3-tetramethoxy (0.3 mL, 1.8 mmol) 1,3-bis(silyl enol ether) **61c** (665 mg, 1.8 mmol), and TMSOTf (0.03 mL, 0.18 mmol), **62c** was isolated as colourless solid (158 mg, 34%), mp. 123 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.65 (s, 3 H, OC*H*$_3$), 3.81 (s, 3 H, OC*H*$_3$), 6.76–6.92 (m, 3 H, ArH), 7.10–7.26 (m, 2 H, ArH), 7.33 (dd, 1 H, *J* = 1.4, 7.1 Hz, ArH), 7.73 (dd, 1 H, *J* = 1.7, 8.0 Hz, ArH), 10.95 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.3, 55.7 (CH_3), 111.2 (CH), 112.2(C), 118.5, 120.4 (CH) 126.3, 127.6 (C), 129.1, 129.2, 131.3, 137.5 (CH), 157.0, 159.3, 170.9 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3049 (w), 2933 (w), 2835 (w), 1666 (s), 1597 (s), 1463 (s), 1367 (m), 1249 (s), 1152 (s), 1024 (s), 795 (m), 594 (w). MS (EI, 70 eV): *m/z* (%): 258 (M^+, 100), 226 (44), 209 (40), 195 (36), 181 (27), 139 (16), 97 (17), 57 (26). Anal.: calcd (%) for $C_{15}H_{14}O_4$ (258): C 69.76, H 5.46; found: C 69.85, H 5.42.

General procedure for the synthesis of biaryls 63:

The reaction was carried out analogously to a known procedure used for the synthesis of **45**.

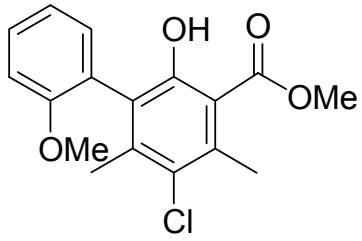
Methyl 4,6-dimethyl-3-(2-methoxyphenyl)salicylate (63c):



Starting with 3-(siloxy)alk-2-en-1-one **44a** (500 mg, 2.9 mmol), 1,3-bis(silyl enol ether) **61c** (1.07 g, 2.9 mmol), and $TiCl_4$ (0.31 mL, 2.9 mmol), **63c** was isolated as a colourless solid (216 mg, 26%), mp. 122 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 3.72 (s, 3 H, OC*H*$_3$), 3.90 (s, 3 H,

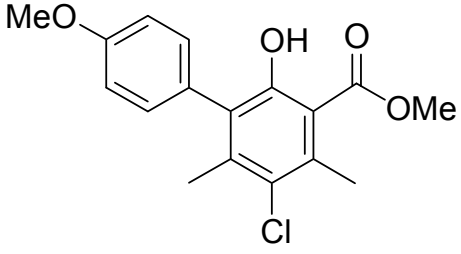
OC*H*$_3$), 6.64 (s, 1 H, ArH), 6.95–7.08 (m, 3 H, ArH), 7.29–7.36 (m, 1 H, ArH), 11.50 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 22.4, 25.8, 54.0, 57.4 (CH_3), 111.6 (C), 112.1, 122.4, 126.2 (CH), 127.3, 127.7 (C), 130.7, 133.2 (CH), 141.6, 146.0, 158.8, 162.2, 174.3 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (w), 2966 (w), 2833 (w), 1655 (s), 1449 (s), 1304 (s), 1257 (m), 1202 (s), 1048 (s), 1026 (m), 858 (w), 762 (s), 575 (w). MS (EI, 70 eV): *m/z* (%): 286 (M^+, 61), 254 (34), 239 (100), 223 (72), 181 (8), 165 (11), 127 (12), 69 (18). Anal.: calcd (%) for $C_{17}H_{18}O_4$: C 71.31, H 6.34; found: C 70.99, H 6.92.

Methyl 4,6-dimethyl-5-chloro-3-(2-methoxyphenyl)salicylate (63d):



Starting with 3-(siloxy)alk-2-en-1-one **44c** (500 mg, 2.4 mmol), 1,3-bis(silyl enol ether) **61c** (888 mg, 2.4 mmol), and $TiCl_4$ (0.26 mL, 2.4 mmol), **63d** was isolated as a colourless solid (217 mg, 30%), mp. 126 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.37 (s, 3 H, CH_3), 2.89 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 4.19 (s, 3 H, OCH_3), 7.25–7.33 (m, 3 H, ArH), 7.58–7.65 (m, 1 H, ArH), 10.93 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.6, 20.4, 52.6, 55.6 (CH_3), 111.4 (CH), 112.6 (C), 120.9 (CH), 125.5, 126.4, 127.5 (C), 129.5, 131.6 (CH), 136.9, 142.6, 157.2, 157.5, 171.8 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3008 (w), 2936 (w), 2840 (w), 1653 (s), 11595 (s), 1443 (s), 1362 (s), 1215 (s), 2024 (s), 959 (m), 811 (w), 755 (s), 610 (w). MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 13), 320 (M^+, ^{35}Cl, 44), 287 (14), 273 (100), 257 (39) , 165 (12), 144 (8), 69 (20). HRMS (EI, 70 eV): calcd for $C_{17}H_{17}ClO_4$ [M, ^{35}Cl]: 320.08069; found 320.08099.

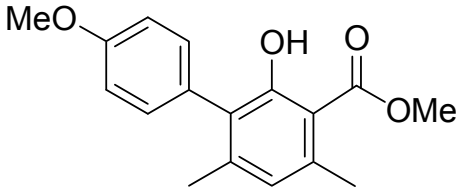
Methyl 4,6-dimethyl-5-chloro-3-(4-methoxyphenyl)salicylate (63e):



Starting with 3-(siloxy)alk-2-en-1-one **44c** (450 mg, 2.2 mmol), 1,3-bis(silyl enol ether) **61b** (806 mg, 2.2 mmol), and $TiCl_4$ (0.241 mL, 2.2 mmol), **63e** was isolated as a colourless solid (241 mg, 38%), mp. 94 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 6.89 (d,

2 H, *J* = 8.8 Hz, ArH), 7.03 (d, 2 H, *J* = 8.8 Hz, ArH), 10.54 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.0, 19.4 (CH_3), 51.4, 54.2 (OCH_3), 111.5 (C), 112.9 (2C, CH), 126.8, 127.6, 128.3 (C), 129.9 (2C, CH), 135.3, 140.8, 156.1, 157.8(C), 170.5 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3430 (m), 3050 (w), 3002 (w), 2959 (m), 2931 (m), 2837 (m), 1653 (s), 1607 (m), 1572 (w), 1514 (s), 1444 (s), 1373 (m), 1361 (s), 1297 (s), 1253(s), 1220(s), 1176 (m), 1092 (m), 1036 (m) 810(m) 686 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 16), 320 (M^+, 47), 288 (100), 260 (11), 245 (27), 225 (29), 181(7), 152 (12). HRMS (EI, 70 eV): calcd for $C_{17}H_{17}O_4Cl$ [M, ^{35}Cl]: 320.08099; found 320.08088.

Methyl 4,6-dimethyl-3-(4-methoxyphenyl)salicylate (63f):

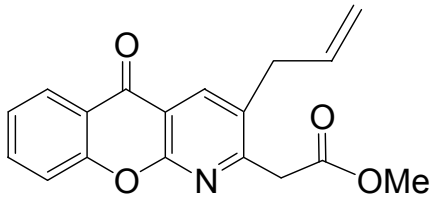


Starting with 3-(siloxy)alk-2-en-1-one **44a** (284 mg, 1.65 mmol), 1,3-bis(silyl enol ether) **61b** (604 mg, 1.65 mmol), and $TiCl_4$ (0.18 mL, 1.65 mmol), **63f** was isolated colourless solid (173 mg, 37%), mp. 66 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.00 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.59 (s, 1 H, ArH), 6.89 (d, 2 H, *J* = 7.5 Hz, ArH), 7.06 (d, 2 H, *J* = 8.8 Hz, ArH), 11.51 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.7, 22.9 (CH_3), 51.0, 54.1 (OCH_3), 108.7 (C), 112.7 (2C, CH), 123.5 (CH), 126.9 (C), 127.8 (C), 129.9 (2C, CH), 138.5, 142.6, 157.5, 159.5 (C), 171.5 (C=O). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3080 (w), 3061 (w), 3023 (w), 2957 (m), 1725 (w), 1650 (s), 1613(m), 1558 (w), 1430 (m), 1392 (m), 1360 (m), 1295 (s), 1255(s), 1197 (s), 1087 (m), 1066 (m), 955 (m), 807(s), 767 (s), 700 (s), 570 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 286 (M^+, 55), 254 (100), 226 (11), 211 (55), 153 (8), 127 (11). HRMS (EI, 70 eV): calcd for $C_{17}H_{18}O_4$ (M^+): 286.11996; found: 286.11977.

General procedure for the synthesis of azaxanthones 68a-al and dibenzo[*b*,*d*]pyran-6-ones 69a-d: To neat 3-cyanochromone **65** (1.0 equiv.) was added Me_3SiOTf (1.3 equiv.) and CH_2Cl_2 (1 mL) at 20 °C. After stirring for 1 h, CH_2Cl_2 and 1,3-bis(trimethylsilyloxy)-1,3-butadiene 2 (1.3 equiv.) were added at 0 °C. The mixture was stirred for 12 h at 20 °C and subsequently poured into hydrochloric acid (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3

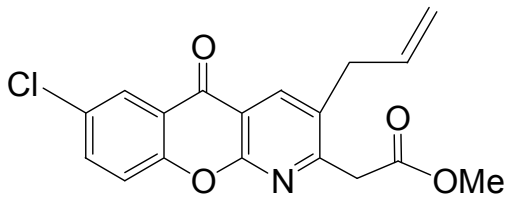
x 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was filtered through a pad of silica gel (EtOAc/hexane = 5:1) to give crude **67a-al**. To an ethanol solution (10 mL) of **67a-al** was added NEt_3 (2.0 equiv.) and the solution was stirred for 12 h at 20 °C. To the solution were subsequently added an aqueous solution of hydrochloric acid (1 M) and ether (50 mL). The organic and the aqueous layer were separated and the latter was extracted with ether (3 x 100 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, EtOAc/hexane).

Methyl 2-(3-allyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (68t):



Starting with 3-cyanochromone (**65a**) (400 mg, 2.33 mmol), **66j** (917 mg, 3.0 mmol), Me_3SiOTf (0.54 mL, 3.0 mmol), and NEt_3 (0.6 mL, 4.66 mmol), **68t** was isolated as a colourless solid (275 mg, 38%), mp. = 124 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.48 (d, ^3J = 6.1 Hz, 2 H, CH_2CHCH$_2$), 3.68 (s, 3 H, OCH_3), 3.96 (s, 2 H, CH_2), 4.98–5.16 (m, 2 H, CHCH_2), 5.86–5.96 (m, 1 H, CHCH$_2$), 7.32–7.38 (m, 1 H, ArH), 7.53 (dd, ^3J = 8.5 Hz, ^4J = 0.6 Hz, 1 H, ArH), 7.67–7.74 (m, 1 H, ArH), 8.23 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, ArH), 8.44 (s, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.8, 41.5 (CH_2), 52.4 (CH_3), 115.5 (C), 117.8 (CH_2), 118.4 (CH), 121.5 (C), 124.5, 126.6 (CH), 132.0 (C), 134.5, 135.5, 138.1 (CH), 155.6, 158.3, 158.8 (C), 169.6, 177.4 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3065 (w), 2995 (w), 2841 (w), 1738 (s), 1668 (s), 1609 (s), 1559 (m), 1429 (s), 1344 (s), 1269 (m), 1190 (s), 1165 (m), 997 (m), 916 (w), 766 (s), 670 (w). GC-MS (EI, 70 eV): *m/z* (%) = 309 (M^+, 85), 278 (11), 249 (100), 236 (35), 220 (16), 191 (5), 152 (5), 124 (6) 77 (8), 51 (3). Anal: calcd (%) for $C_{18}H_{15}NO_4$: C 69.89, H 4.89, N 4.53; found: C 6980, H 4.97, N 4.30.

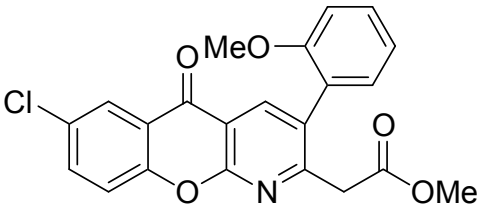
Methyl 2-(3-allyl-7-chloro-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (68u):



Starting with **65e** (200 mg, 0.97 mmol), **66j** (380 mg, 1.26 mmol), Me_3SiOTf (0.22 mL, 1.26 mmol), and NEt_3 (0.27 mL, 1.94 mmol), **68u**

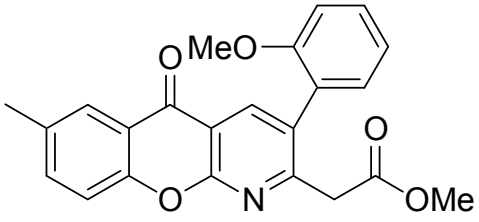
was isolated as a colourless solid (100 mg, 30%), mp. = 177 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.64 (d, ^3J = 6.3 Hz, 2 H, CH_2CHCH_2), 3.84 (s, 3 H, OCH_3), 4.12 (s, 2 H, CH_2), 5.14-5.34 (m, 2 H, CHCH_2), 5.98-6.12 (m, 1 H, CHCH_2), 7.65 (d, ^3J = 8.9 Hz, 1 H, ArH), 7.81 (dd, ^3J = 8.5 Hz, ^4J = 2.5 Hz, 1 H, ArH), 8.36 (d, ^4J = 2.3 Hz, 1 H, ArH), 8.59 (s, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.8, 41.5 (CH_2), 52.4 (CH_3), 115.2 (C), 117.9 (CH_2), 120.0(CH), 122.5 (C), 126.0 (CH), 130.4, 132.4 (C), 134.3, 135.6, 138.1 (CH), 154.0, 158.2, 159.2 (C), 169.5, 176.4 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2999 (w), 2950 (w), 1738 (s), 1667 (s), 1608 (s), 1475 (s), 1348 (s), 1311 (m), 1272 (s), 1169 (s), 1137 (m), 1000 (m), 639 (w). GC-MS (EI, 70 eV): *m/z* (%) = 345 (M^+, ^{37}Cl, 20), 343 (M^+, ^{35}Cl, 60), 285 (^{37}Cl, 43), 283 (^{35}Cl, 100), 270 (29), 248 (10), 219 (7), 178 (10) 149 (13), 97 (19), 69 (55), 57 (50). Anal: calcd (%) for $C_{18}H_{14}ClNO_4$: C 62.89, H 4.10, N 4.07; found: C 62.86, H 4.31, N 3.60.

Methyl 2-[7-chloro-3-(2-methoxyphenyl)-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl]acetate (68x):



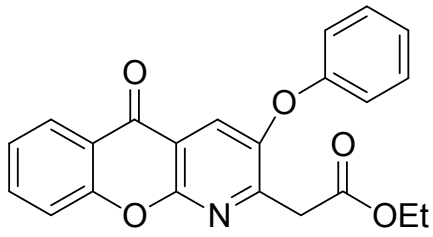
Starting with **65e** (200 mg, 0.97 mmol), **66m** (465 mg, 1.26 mmol), Me_3SiOTf (0.22 mL, 1.26 mmol), and NEt_3 (0.27 mL, 1.94 mmol), **68x** was isolated as a colourless solid (144 mg, 40%), mp. = 172 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 3.55 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.79 (s, 2 H, CH_2), 6.91–7.02 (m, 2 H, ArH), 7.15 (dd, ^3J = 7.4 Hz, ^4J = 1.8 Hz, 1 H, ArH), 7.33–7.39 (m, 1 H, ArH), 7.49 (d, ^3J = 8.8 Hz, 1 H, ArH), 7.64 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz, 1 H, ArH), 8.19 (d, ^4J = 2.3 Hz, 1 H, ArH), 8.45 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 42.2 (CH_2), 52.1, 52.3 (CH_3), 110.8 (CH), 114.9 (C), 120.2, 121.0 (CH), 122.5, 125.5 (C), 125.9, 130.4, 131.3 (CH), 132.8 (C), 135.5, 139.0 (CH), 154.0, 156.2, 158.7, 159.6 (C), 169.8, 176.4 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3067 (w), 2985 (w), 2939 (w), 1727 (s), 1662 (s), 1597 (s), 1471 (s), 1432 (s), 1309 (m), 1259 (s), 1025 (m), 828 (m), 631 (w), 538 (w). GC-MS (EI, 70 eV): *m/z* (%): GC-MS (EI, 70 eV): *m/z* (%) = 411 (M^+, ^{37}Cl, 8), 409 (M^+, ^{35}Cl, 26), 338 (^{37}Cl, 27), 336 (^{35}Cl, 100), 306 (9), 243 (2), 168 (3), 97 (10) 83 (13), 71 (11), 69 (20), 57 (21), 44 (25). HRMS (EI): calcd for $C_{22}H_{16}ClNO_5$ (M^+, ^{35}Cl): 409.07189, found 409.07115.

Methyl 2-[7-methyl-3-(2-methoxyphenyl)-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl]acetate (68y):



Starting with **65b** (200 mg, 1.08 mmol), **66m** (516 mg, 1.4 mmol), Me_3SiOTf (0.25 mL, 1.4 mmol), and NEt_3 (0.3 mL, 2.16 mmol), **68y** was isolated as a colourless solid (134 mg, 32%), mp. = 165 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.41 (s, 3 H, CH_3), 3.54 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.78 (s, 2 H, CH_2), 6.90–7.01 (m, 2 H, ArH), 7.15 (dd, ^3J = 7.4 Hz, ^4J = 1.7 Hz, 1 H, ArH), 7.32–7.39 (m, 1 H, ArH), 7.43–7.53 (m, 2 H, ArH), 8.02 (s, 1 H, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.8 (CH_3), 42.0 (CH_2), 52.0, 52.3 (CH_3), 110.7 (CH), 115.2 (C), 118.2, 120.9 (CH), 121.3, 125.8 (C), 126.0, 130.2, 131.4 (CH), 132.2, 134.4 (C), 136.7, 138.9 (CH), 153.9, 156.2, 159.0 (C), 169.9, 177.6 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 3046 (w), 2923 (w), 1742 (s), 1655 (s), 1488 (s), 1432 (s), 1253 (m), 1147 (s), 1020 (s), 834 (m), 794 (m), 630 (w), 542 (w). GC-MS (EI, 70 eV): *m/z* (%) = 389 (M^+, 35), 357 (9), 316 (100), 286 (11), 149 (8), 111 (18), 97 (32), 83 (41), 57 (65), 44 (90). HRMS (EI): calcd for $C_{23}H_{19}NO_5$ $[M]^+$: 389.12597, found 389.12577.

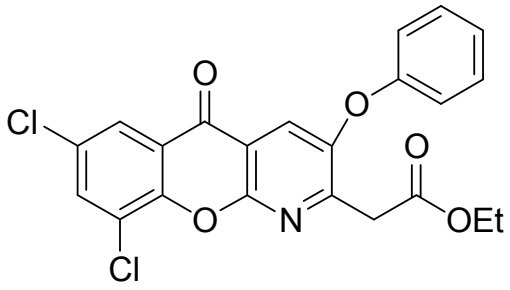
Ethyl 2-(5-oxo-3-phenoxy-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (68aa):



Starting with **65a** (400 mg, 2.62 mmol), **66o** (1.25 g, 3.41 mmol), Me_3SiOTf (0.62 mL, 3.41 mmol), NEt_3 (0.72 mL, 5.24 mmol), **68aa** was isolated as a colourless solid (595 mg, 66%), mp. = 144 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.13 (t, ^3J = 7.0 Hz, 3 H, CH_3), 4.01 (s, 2 H, CH_2), 4.09 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 6.98–7.00 (m, 2 H, ArH), 7.08–7.15 (m, 1 H, ArH), 7.26–7.33 (m, 3 H, ArH), 7.49 (dd, ^3J = 8.5 Hz, ^4J = 0.7 Hz, 1 H, ArH), 7.63–7.70 (m, 1 H, ArH), 7.95 (s, 1 H, ArH), 8.15 (dd, ^3J = 8.0 Hz, ^4J = 1.4 Hz, 1 H, ArH). ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_3), 39.5 (CH_2), 61.3 (OCH_2), 116.1 (C), 118.3 (CH), 119.2 (2C, CH), 120.9 (C), 123.1, 124.5, 124.8, 126.5 (CH), 130.2 (2C, CH), 135.5 (CH), 150.6, 152.5, 154.9, 155.5, 155.7 (C), 169.0, 177.1

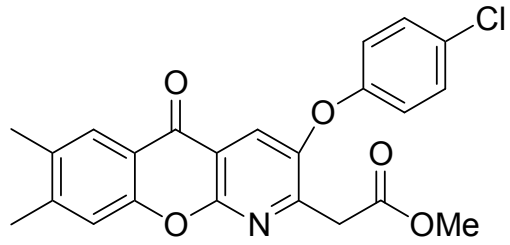
(C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3072 (w), 2985 (w), 2937 (w), 1730 (s), 1664 (s), 1470 (s), 1309 (s), 1220 (s), 1119 (m), 1024 (m), 771 (s), 757 (m), 689 (m), 498 (w). GC-MS (EI, 70 eV): *m/z* (%) = 375 (M^+, 100), 302 (10), 282 (12), 254 (88), 177 (44) 153 (13), 127 (54), 91(10), 51 (7). Anal: calcd (%) for $C_{22}H_{17}NO_5$: C 70.39, H 4.56, N 3.73; found: C 69.78, H 4.46, N 3.55.

Ethyl 2-(7,9-dichloro-5-oxo-3-phenoxy-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (68ab):



Starting with **65f** (125 mg, 0.52 mmol), **66o** (247 mg, 0.67 mmol), Me_3SiOTf (0.12 mL, 0.67 mmol), and NEt_3 (0.14 mL, 1.04 mmol), **68ab** was isolated as a colourless solid (102 mg, 44%), mp. = 147 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 (t, ^3J = 7.0 Hz, 3 H, CH_3), 4.07 (s, 2 H, CH_2), 4.09 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 7.01 (m, 2 H, ArH), 7.17 (m, 1 H, ArH), 7.35 (m, 2 H, ArH), 7.74 (d, ^4J = 2.6 Hz, 1 H, ArH), 7.90 (s, 1 H, ArH), 8.05 (d, ^4J = 2.6 Hz, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1 (CH_3), 38.6 (CH_2), 60.4 (OCH_2), 114.5 (C), 118.6 (2C, CH), 121.1 (CH), 121.7 (C), 123.5 (CH), 123.6 (C), 124.2 (CH), 129.0 (C), 129.4 (2C, CH), 134.4 (CH), 149.0, 150.6, 152.4, 153.2, 154.3 (C), 167.9, 174.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3073 (w), 2983 (w), 2916 (w), 1720 (s), 1671 (s), 1423 (s), 1225 (s), 1192 (s), 1120 (m), 1024 (m), 991 (m), 802 (m), 785 (s), 692 (m). GC-MS (EI, 70 eV): *m/z* (%) = 447 ($[M]^+$, [2×^{37}Cl], 1), 445 ($[M]^+$, [^{37}Cl], [^{35}Cl], 2), 443 ($[M]^+$, [2×^{35}Cl], 4), 400 (3), 398 (4), 352 (25), 350 (38), 324 (64), 322 (100), 294 (15), 266 (5), 174 (2), 94 (5), 65 (7). HRMS (EI): calcd for $C_{22}H_{15}Cl_2NO_5$ ($[M]^+$, [2×^{35}Cl]): 443.03114, found 343.03218.

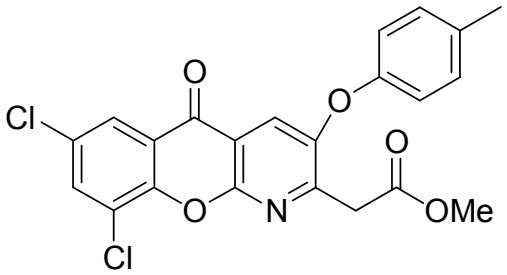
Methyl 2-[3-(4-chlorophenoxy)-7,8-dimethyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl]acetate (68ac):



Starting with **65h** (400 mg, 2.0 mmol), **66p** (1.00 g, 2.61 mmol), Me_3SiOTf (0.47 mL, 2.61 mmol), and NEt_3 (0.55 mL, 4.0 mmol), **68ac** was isolated as a colourless solid (280 mg,

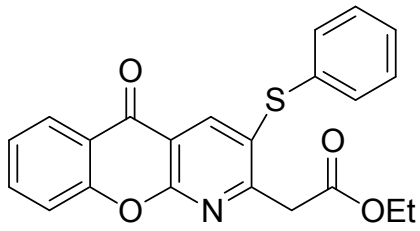
33%), mp. = 155 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.26 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 3.61 (s, 3 H, OCH_3), 3.99 (s, 2 H, CH_2), 6.91 (d, ^{3}J = 7.5 Hz, 2 H, ArH), 7.26 (d, ^{3}J = 7.3 Hz, 2 H, ArH), 7.86 (s, 1 H, ArH), 7.95 (s, 1 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 20.6 (CH_3), 39.2 (CH_2), 52.3 (OCH_3), 61.5 (OCH_2), 116.3, 118.4 (C), 118.7 (CH), 120.4 (2C, CH), 123.6, 126.1 (CH), 129.9 (C), 130.0 (2C, CH), 133.9, 146.6, 149.9, 151.8, 153.9, 154.0, 154.5 (C), 169.5, 176.7 (C=O). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3051(w), 2956 (w), 2847 (w), 1730 (s), 1607 (s), 1471 (s), 1410 (s), 1318 (s), 1209 (s), 1145 (s), 1087 (s), 994 (m), 873 (m), 672 (w). GC-MS (EI, 70 eV): *m/z* (%) = 425 (M^+, ^{37}Cl, 1), 423 (M^+, ^{35}Cl, 3), 392 (1), 364 (1), 296 (100), 266 (7), 238 (4), 127 (1), 99 (2). HRMS (EI): calcd for $C_{23}H_{18}ClNO_5$ (M^+, ^{35}Cl): 423.08620, found 423.08680.

Methyl 2-[7,9-dichloro-3-(4-methylphenoxy)-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl]acetate (68ad):



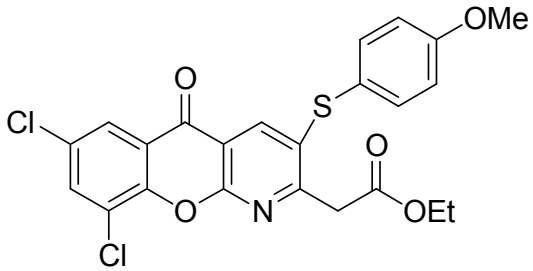
Starting with **65f** (400 mg, 1.66 mmol), **66q** (797 mg, 2.16 mmol), Me_3SiOTf (0.39 mL, 2.16 mmol), and NEt_3 (0.6 mL, 4.32 mmol), **68ad** was isolated as a colourless solid (294 mg, 42%), mp. = 194 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 2.31 (s, 3 H, CH_3), 3.65 (s, 3 H, OCH_3), 4.09 (s, 2 H, CH_2), 6.89 (d, ^{3}J = 8.5 Hz, 2 H, ArH), 7.14 (d, ^{3}J = 8.1 Hz, 2 H, ArH), 7.74 (d, ^{4}J = 2.6 Hz, 1 H, ArH), 7.85 (s, 1 H, ArH), 8.05 (d, , ^{4}J = 2.5 Hz, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.1 (CH_3), 39.3 (CH_2), 52.4 (OCH_3), 115.5 (C), 119.6 (2C, CH), 121.5 (CH), 122.6 (C), 124.5 (CH), 124.5, 130.0 (C), 130.9 (2C, CH), 135.1 (C), 135.3 (CH), 150.0, 152.1, 152.8, 152.9, 154.0 (C), 169.4, 175.7 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3068 (w), 2964 (w), 2924 (w), 1728 (s), 1666 (s), 1508 (s), 1429 (s), 1396 (s), 1272 (m), 1172 (m), 1016 (m), 787 (m), 718 (w), 527 (w). GC-MS (EI, 70 eV): *m/z* (%) = 447 ($[M]^+$, $[2\times^{37}Cl]$,7), 445($[M]^+$, $[^{37}Cl]$, $[^{35}Cl]$, 47),443 ($[M]^+$, $[2\times^{35}Cl]$,7), 77), 386 (17), 384 (26), 311 (13), 266 (12), 239 (4), 149 (7), 105 (12), 97 (17), 84 (10), 71 (25), 44 (100). HRMS (EI): calcd for $C_{22}H_{15}Cl_2NO_5$ ($[M]^+$, $[2\times^{35}Cl]$): 443.03085, found 343.03218.

Ethyl 2-[5-oxo-3-(phenylsulfanyl)-5*H*-chromeno[2,3-*b*]pyrid-2-yl]acetate (68ae):



Starting with **65a** (400 mg, 2.33 mmol), **66r** (1.18 g, 3.11 mmol), Me_3SiOTf (0.56 mL, 3.11 mmol), and NEt_3 (0.64 mL, 4.66 mmol), **68ae** was isolated as a colourless solid (465 mg, 51%), mp. = 88 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.30 (t, ^3J = 7.1 Hz, 3 H, CH_3), 4.27 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 4.65 (s, 2 H, CH_2), 7.04–7.13 (m, 3 H, ArH), 7.24–7.32 (m, 3 H, ArH), 7.47 (dd, ^3J = 8.3 Hz, ^4J = 0.6 Hz, 1 H, ArH), 7.62–7.69 (m, 1 H, ArH), 8.16 (dd, ^3J = 7.8 Hz, ^4J = 1.5 Hz, 1 H, ArH), 9.05 (s, 1 H, ArH). ^{13}C-NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_3), 40.0 (CH_2), 62.0 (OCH_2), 114.6 (C), 118.6 (CH), 121.6, 123.1 (C), 125.1, 126.7, 127.0 (CH), 128.8 (2C, CH), 131.0 (2C, CH), 134.4, 134.9 (C), 135.9, 141.0 (CH), 155.5, 164.6 (C), 165.4, 176.9 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3074 (w), 2982 (w), 2930 (w), 1725 (s), 1674 (s), 1600 (s), 1551 (m), 1310 (m), 1264 (s), 1159 (m), 765 (m), 689 (m), 528 (w), 508 (w). GC-MS (EI, 70 eV): *m/z* (%) = 391 (M^+, 100), 58 (10), 345 (40), 282 (13), 254 (94), 226 (17), 196 (12), 170 (4), 109 (13), 65 (8). HRMS (EI): calcd for $C_{22}H_{17}NO_4S$ $[M]^+$: 391.08738, found 391.08728.

Ethyl 2-{7,9-dichloro-3-[(4-methoxyphenyl)sulfanyl]-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl}acetate (68ah):



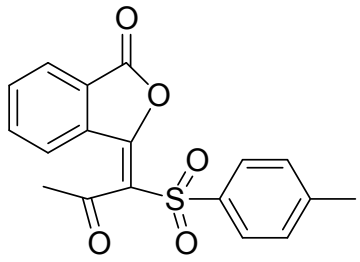
Starting with **65f** (400 mg, 1.66 mmol), **66u** (891 mg, 2.16 mmol), Me_3SiOTf (0.39 mL, 2.16 mmol), and NEt_3 (0.6 mL, 4.32 mmol), **68ah** was isolated as a colourless solid (366 mg, 45%), mp. = 153 °C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.28 (t, ^3J = 7.0 Hz, 3 H, CH_3), 3.83 (s, 3 H, OCH_3), 4.17 (s, 2 H, CH_2), 4.23 (q, ^3J = 7.1 Hz, 2 H, OCH_2), 6.91 (d, ^3J = 8.9 Hz, 2 H, ArH), 7.41 (d, ^3J = 8.9 Hz, 2 H, ArH), 7.77 (d, ^4J = 2.5 Hz, 1 H, ArH), 8.06 (d, ^4J = 2.5 Hz, 1 H, ArH), 8.20 (s, 1 H, ArH). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 42.5 (CH_2), 55.4 (OCH_3), 61.5 (OCH_2), 115.3 (C), 115.6 (2C, CH), 121.5, 123.2 (C), 124.5 (CH), 130.1, 134.8, 135.1 (C), 135.4 (CH), 135.5 (2C, CH), 137.2 (CH), 149.9, 157.3, 159.0, 160.6 (C), 168.7, 175.2 (C=O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3070 (w), 2985 (w), 2836 (w), 1727 (s), 1668 (s), 1591 (s), 1413 (s), 1387 (s), 1253 (s), 1176 (s), 1024 (s), 830 (m), 787 (m), 523 (w). GC-

MS (EI, 70 eV): *m/z* (%) = 493 ($[M]^+$, $[2\times^{37}Cl]$,7), 491 ($[M]^+$, $[^{37}Cl]$, $[^{35}Cl]$, 32), 489 ($[M]^+$, $[2\times^{35}Cl]$,46), 419 (10), 417 (17), 384 (13), 311 (8), 266 (8), 207 (3), 97 (15), 85 (11), 84 (10), 57 (34), 44 (100). Anal: calcd (%) for $C_{23}H_{17}Cl_2NO_5S$: C 56.34, H 3.49, N 2.86; found: C 56.33, H 3.46, N 2.87.

Manuscript in preparation

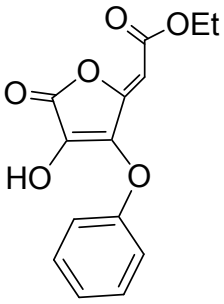
The following experimental data represent unpublished results from different projects.

Synthesis of 3-[2-oxo-1- (4-methylphenylsulfonyl) propylidene] -2- benzofuran -1-one (70):



Starting with phthaloyl dichloride (0.18 ml, 1.0 mmol), 2-(siloxy) -1-propenyl sulfone **71** (300 mg, 1.0 mmol), $TiCl_4$ (0.11 ml, 1.0 mmol) and CH_2Cl_2 (3 ml), **70** was isolated as a highly viscous oil (90 mg, 25%);^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 7.25-7.29(m, 2 H, ArH), 7.66-7.72 (m, 2 H, ArH), 7.81-7.94 (m, 3 H, ArH), 8.83-8.87 (m, 1 H, , ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 33.2 (CH_3), 126.3 (C), 126.6 (CH),126.9 (C) 128.2 (2C, CH), 129.0(CH), 130.3 (2C, CH),133.7 (CH), 134.7, 136.1, 138.4, 146.0, 152.0, 163.8, 195.0(C); IR (KBr): $\tilde{\nu}$ = 3128 (w), 2923 (m), 2853 (w), 1794 (s), 1701 (s), 1627 (s), 1594 (m), 1572 (m),1325 (s), 1306 (m),1153 (s), 701 (m) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 343 ($[M+H]^+$, 40), 301 (100), 278 (20), 236 (30), 155 (6); HRMS (ESI): calcd (%) for $C_{18}H_{14}O_5S$ ($[M+1]^+$) 342.05565, found 342.05513.

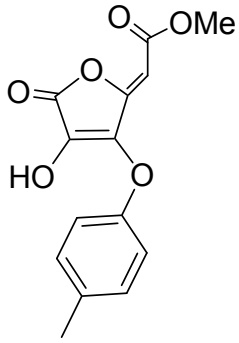
Synthesis of (*E*) Ethyl 2-[4-hydroxy-3-phenoxy-5-oxo-2(5*H*)-furanylidene]acetate (72):



Starting with oxalyl chloride (0.15 ml, 1.75 mmol) 1,3-bis(silyl enol ether) **42c** (640 mg, 1.75 mmol), TMSOTf (0.11 ml, 0.52 mmol) and CH_2Cl_2 (35 ml), **72** was isolated as a highly viscous oil (338 mg, 70%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.1 Hz, 3 H, CH_3), 4.11 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$), 5.49 (s, 1 H, C=C*H*), 6.95-7.00 (m, 2 H, ArH), 7.06-7.28 (m, 3 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1 (CH_3), 61.2 (CH_2), 96.3 (CH), 117.2 (2C, CH), 124.7 (CH), 128.3 (C), 129.7 (2C, CH), 137.0, 151.6, 154.3, 163.7, 163.9 (C); IR (ATR): $\tilde{\nu}$ = 3281 (m), 2980 (w), 2869 (w), 1778 (s), 1663 (s), 1489 (m), 1312 (s), 1183 (s), 1021 (s), 836 (m), 748 (s), 633 (w), 555 (w) cm^{-1}; GC-MS (CI): *m/z* (%): 277 ($[M + H]^+$, 100), 248 (10), 230 (23), 203

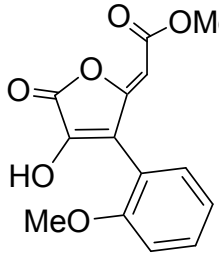
(43) 174 (4), 147 (4), 105 (8); HRMS (CI) calcd for $C_{14}H_{12}O_6$ $[M + H]^+$,: 277.07021, found 277.07066.

Synthesis of (*E*) Methyl 2-[4-hydroxy-3-(4-methylphenoxy)-5-oxo-2(5*H*)-furanylidene]acetate (73):



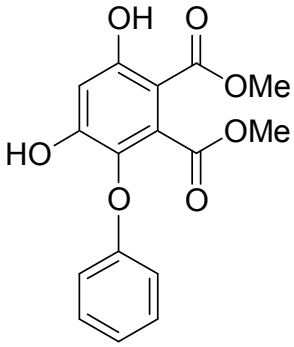
Starting with oxalyl chloride (0.15 ml, 1.75 mmol) 1,3-bis(silyl enol ether) **42e** (644 mg, 1.75 mmol), TMSOTf (0.11 ml, 0.52 mmol) and CH_2Cl_2(35), **73** was isolated as a highly viscous oil (348 mg, 72%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3), 3.71 (s, 3 H, OC*H*$_3$), 5.55 (s, 1 H, C=C*H*), 6.90 (d, *J* = 8.6 Hz, 2 H, ArH), 7.08 (distorted d, *J* = 8.2 Hz, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.7, 52.0 (CH_3), 96.2 (CH), 117.3 (2C, CH), 127.2 (C), 130.1 (2C, CH), 134.6, 137.5, 151.4, 152.1, 163.7, 164.0 (C); IR (ATR): $\tilde{\nu}$ = 3343 (m), 3029 (w), 2872 (w), 1776 (m), 1688 (s), 1504 (m), 1317 (s), 1283 (m), 1201 (s), 1029 (s), 821 (m), 696 (w), 535(w) cm^{-1}; GC-MS (CI): *m/z* (%): 277 ($[M + H]^+$, 100), 249 (28), 205 (12), 181 (6) 127 (29), 80 (27), 69 (38); HRMS (EI) calcd for $C_{14}H_{12}O_6$ $[M]^+$: 276.06329, found 276.06284.

(*E*) Methyl 2-[4-hydroxy-3-(2-methoxyphenyl)-5-oxo-2(5*H*)-furanylidene]acetate (74):



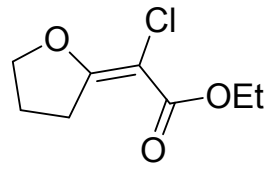
Starting with oxalyl chloride (0.30 ml, 3.5 mmol), 1,3-bis(silyl enol ether) **61c** (1.29 g, 3.5 mmol), TMSOTf (0.19 ml, 1.0 mmol) and CH_2Cl_2 (70 ml) **72** was isolated as a highly viscous oil (648 mg, 67%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70 (s, 3 H, OC*H*$_3$), 3.87 (s, 3 H, OC*H*$_3$), 5.36 (s, 1 H, C=C*H*), 6.99-7.06 (m, 2 H, ArH), 7.25 (dd, *J* = 7.7, 1.7 Hz, 1 H, ArH), 7.36-7.43 (m, 1 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.8, 55.6 (CH_3), 98.0, 112.2 (CH), 116.3, 121.4 (C), 121.7, 130.9, 131.4 (CH), 143.4, 155.8, 156.3, 163.2, 164.2 (C); IR (ATR): $\tilde{\nu}$ = 3337 (w), 3077 (w), 2839 (w), 1738 (m), 1492 (m), 1435 (s), 1239 (s), 1134 (s), 1013 (s), 928(m), 754 (s), 685 (w), 572 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 277 (M^+, 20), 248 (34), 206 (100), 181 (6) 148 (57), 121 (72), 69 (68); HRMS (EI) calcd for $C_{14}H_{12}O_6$ $[M]^+$: 276.06333, found 276.06284.

Dimethyl 4,6-dihydroxy-3-phenoxyphthalate (75):



Starting with dimethyl acetylene dicarboxylate (0.3 ml, 2.44 mmol) 1,3-bis(silyl enol ether) **42c** (893 mg, 2.44 mmol), **75** was isolated as a highly viscous oil (140 mg, 18%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.56 (s, 3 H, OC*H*$_3$), 3.77 (s, 3 H, OC*H*$_3$), 6.59 (s, 1 H, ArH), 6.78-6.82 (m, 2 H, ArH), 6.94-7.00 (m, 1 H, ArH), 7.16-7.23 (m, 3 H, ArH), 11.04 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.4, 52.7 (CH_3), 102.1 (C), 105.4 (CH), 115.2 (2C, CH), 123.1 (CH), 129.7 (2C, CH), 130.1, 132.0, 155.3, 157.4, 161.2, 166.1, 168.7 (C); IR (ATR): $\tilde{\nu}$ = 3040 (w), 2953 (w), 2849 (w), 1723 (m), 1667 (s), 1489 (s), 1437 (s), 1287 (s), 1195(s), 960(m), 749 (s), 688 (m), 536 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 318 (M^+, 100), 286 (76), 255 (91), 228 (20) 170 (7), 105 (30), 69 (21); HRMS (EI) calcd for $C_{16}H_{14}O_7$ $[M]^+$: 318.07354, found 318.07340.

Synthesis of (*Z*) Ethyl 2-chloro-2-dihydro-2(3*H*)-furanylideneacetate (76):



Starting with ethyl-2-chloro acetoacetate (5.0 ml, 36.1 mmol), 1-bromo-2-chloroethane (3.6 ml, 43.3 mmol), **76** was isolated as colourless solid (1.8 g, 26%);^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.32 (m, 2 H, CH_2), 3.31 (t, *J* = 7.8 Hz, 2 H, CH_2), 4.35 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$), 4.52 (t, *J* = 7.0 Hz, 2 H, CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.3 (CH_3), 24.6, 32.0, 61.0, 73.0 (CH_2), 95.5, 164.4, 170.0 (C); IR (ATR): $\tilde{\nu}$ = 2994 (w), 2935 (w), 2875 (w), 1690 (s), 1611 (s), 1422 (m), 1393 (m), 1294 (s), 1190(s), 1069 (s), 1036 (m), 953 (m), 872 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):192 (M^+,^{37}Cl, 15), 190 (M^+,^{35}Cl, 47), 162 (18), 144 (100), 120 (15) 103 (46), 69 (19), 53 (14); HRMS (EI) calcd for $C_8H_{11}ClO_3$ $[M]^+$: 190.03920, found 190.03912.

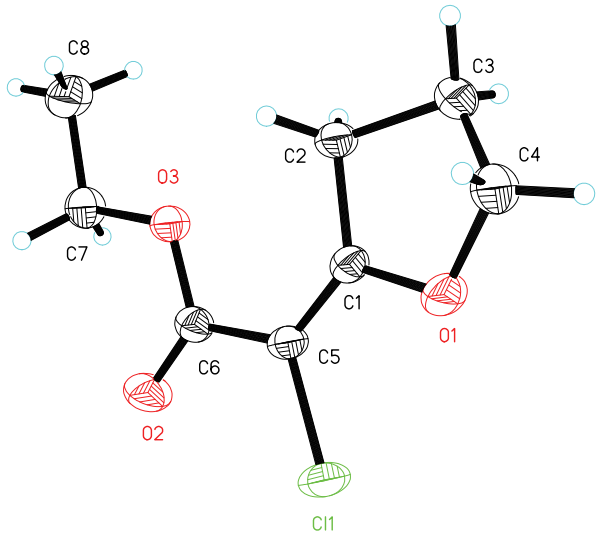
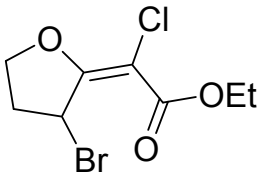


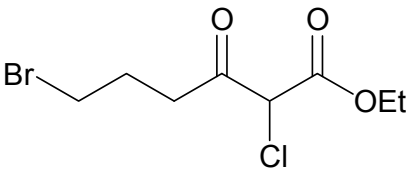
Figure 6.1. Ortep plot of **76**

Synthesis of (*E*) Ethyl 2-[3-bromodihydro-2(3*H*)-furanylidene]-2-chloroacetate (77):



Starting with **76** (930 mg, 4.8 mmol), NBS (1.10 g, 6.2 mmol), **77** was isolated as colourless solid (650 mg, 50%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.74-2.83 (m, 2 H, CH_2), 4.46-4.55 (m, 2 H, CH_2), 4.79-4.87 (m, 2 H, CH_2), 6.01 (d, *J* = 5.1 Hz, C*H*–Br); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 37.3 (CH_2), 44.8 (CH), 62.2, 71.3 (CH_2), 99.2, 163.3, 17.5 (C); IR (ATR): $\tilde{\nu}$ = 2980 (w), 2905(w), 2849 (w), 1698(s), 1621 (s), 1367 (m), 1274 (s), 1215 (s), 1179 (m), 1064 (s), 958 (s), 814 (m), 533 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):270 (M^+, ^{81}Br, 29), 268 (M^+, ^{79}Br, 22), 225 (13), 189 (50), 161 (100) 143 (30), 115 (22), 87 (15), 53 (19); HRMS (EI) calcd for $C_8H_{10}BrClO_3$ [M^+,^{81}Br] 267.94901, found 267.94964.

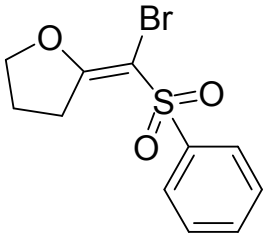
Synthesis of Ethyl 6-bromo-2-chloro-3-oxohexanoate (78):



Starting with **76** (326 mg, 1.69 mmol) and BBr_3 (0.60

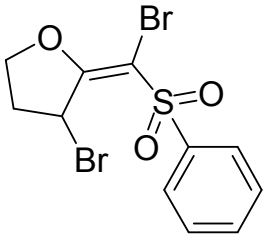
ml, 6.79 mmol) **78** was isolated as a highly viscous oil (401 mg, 87%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (t, *J* = 7.0 Hz, 3 H, CH_3), 2.33 (t, 2 H, *J* = 6.6 Hz, CH_2), 3.07 (m, 2 H, CH_2), 3.59 (t, 2 H, *J* = 6.4 Hz, CH_2), 4.41 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$), 4.94 (s, 1 H, CH–Cl); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.5 (CH_3), 26.6, 32.8, 37.3 (CH_2), 61.2 (CH), 63.7 (CH_2), 165.3, 198.4 (C); IR (ATR): $\tilde{\nu}$ = 2966 (w), 2909 (w), 2873 (w), 1724 (s), 1368 (m), 1299 (m), 1251 (s), 1176 (s), 1020 (s), 858 (m), 727 (w), 557 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):272 (M^+, ^{81}Br, 1), 270 (M^+, ^{79}Br, 1), 190 (3), 151 (100), 121 (25) 94 (7), 69 (14), 41 (43); HRMS (EI) calcd for $C_8H_{12}BrClO_3$ [M^+,^{81}Br] 269.96547, found 269.96529.

Synthesis of 5-[bromo(phenylsulfonyl)methylidene]dihydrofuran(79):



Starting with 2 –[(Phenylsulfonyl)methylidene]tetrahydrofuran **10a** (590 mg, 2.63 mmol), NBS (515 mg, 2.89 mmol), **79** was isolated as highly viscous oil (392 mg, 49%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.60 (quint, *J* = 7.0 Hz, 2 H, CH_2), 3.67 (t, *J* = 7.7 Hz, 3 H, CH_2), 4.70 (t, *J* = 7.0 Hz, 2 H, CH_2), 7.83-7.98 (m, 3 H, ArH), 8.24-8.29 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.9, 31.5, 73.3 (CH_2), 90.5 (C), 128.7 (2C, CH), 129.2 (2C, CH), 133.1 (CH), 139.1, 168.5 (C); IR (KBr): $\tilde{\nu}$ = 3084 (w), 2984 (w), 2929 (w), 1596 (s), 1551 (s), 1429 (s), 1304 (s), 1155 (s), 1101 (m), 1016 (m), 819 (m), 684 (s), 592 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):304 (M^+, ^{81}Br, 100), 302(M^+, ^{79}Br, 99), 238 (3), 193 (6), 168 (8) 131 (19), 77 (60), 51 (34); HRMS (EI) calcd for $C_{11}H_{11}BrO_3S$ [M^+,^{81}Br] 301.96130, found 301.96068.

Synthesis of 4-bromo-5-[bromo(phenylsulfonyl)methylidene]dihydrofuran(80):



Starting with 2 –[(Phenylsulfonyl)methylidene]tetrahydrofuran **10a** (590 mg, 2.63 mmol), NBS (515 mg, 2.89 mmol), **80** was isolated as colourless solid (340 mg, 35%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.75-2.84 (m, 1 H, CH_2), 2.89.3.02 (m, 1 H, CH_2), 5.00-5.17 (m, 2 H, CH_2), 5.38 (d, *J* = 5.8 Hz, 1 H, C*H*–Br), 7.86-8.03 (m, 3 H, ArH), 8.31-8.35 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 35.3

(CH_2), 47.9 (CH), 75.0 (CH_2), 96.1 (C), 127.9 (2C, CH), 128.9 (2C, CH), 133.6 (CH), 139.1, 168.5 (C); IR (KBr): $\tilde{\nu}$ = 3089 (w), 2974 (w), 2867 (w), 1598 (s), 1573 (s), 1413 (s), 1312 (s), 1123 (s), 1098 (s), 1016 (m), 812 (m), 676 (m), 590 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):372 (M^+, [2 × ^{81}Br], 11), 370 (M^+, [^{81}Br^{79}Br], 33), 368 (M^+, [2 × ^{79}Br], 12), 269 (11), 235 (65), 305 (100), 189 (19), 161 (25), 69 (20); Anal. calcd for $C_{10}H_{10}Br_2O_3S$ (370.06): C 32.46, H 2.72; found: C 32.50, H 2.70.

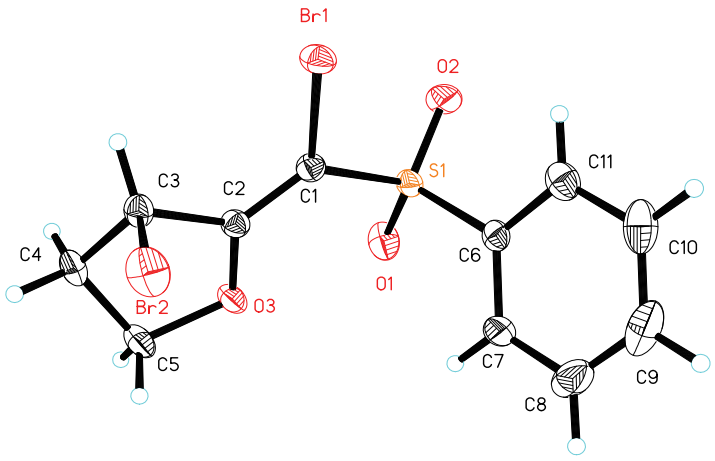


Figure 6.2. Ortep plot of **80**

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X-Ray Crystals Data

Data of compound 16 (chapter 1):

Table 1. Crystal data and structure refinement for mar125a.

Identification code	mar125a	
Empirical formula	C_6H_8BrNO	
Formula weight	190.04	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	$P2_1\ 2_12_1$	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 4.76520(10) Å	α= 90°.
	b = 8.1844(2) Å	β= 90°.
	c = 18.9671(5) Å	γ = 90°.
Volume	739.72(3) $Å^3$	
Z	4	
Density (calculated)	1.706 Mg/m^3	
Absorption coefficient	5.476 mm^{-1}	
F(000)	376	
Crystal size	0.98 x 0.09 x 0.08 mm^3	
Θ range for data collection	3.29 to 29.00°.	
Index ranges	$-6\leq h\leq 6$, $-11\leq k\leq 11$, $-25\leq l\leq 25$	
Reflections collected	11333	
Independent reflections	1959 [R(int) = 0.0323]	
Completeness to Θ = 29.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6563 and 0.0751	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1959 / 0 / 82	
Goodness-of-fit on F^2	1.065	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0200, wR2 = 0.0458	
R indices (all data)	R1 = 0.0216, wR2 = 0.0463	
Absolute structure parameter	0.013(10)	
Largest diff. peak and hole	0.288 and -0.539 $e.Å^{-3}$	

Data of compound 35b (chapter 2):

Table 1. Crystal data and structure refinement for mar40.

Identification code	mar40	
Empirical formula	$C_{12}H_{14}O_3S$	
Formula weight	238.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	$P2_12_12_1$	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 5.8084(2) Å	α= 90°.
	b = 7.3149(2) Å	β= 90°.
	c = 27.5137(8) Å	γ = 90°.
Volume	1169.00(6) $Å^3$	
Z	4	
Density (calculated)	1.354 Mg/m^3	
Absorption coefficient	0.266 mm^{-1}	
F(000)	504	
Crystal size	0.90 x 0.86 x 0.60 mm^3	
Θ range for data collection	2.96 to 38.49°.	
Index ranges	$-9\leq h\leq 9$, $-10\leq k\leq 12$, $-46\leq l\leq 47$	
Reflections collected	23003	
Independent reflections	6072 [R(int) = 0.0204]	
Completeness to Θ = 38.49°	94.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8569 and 0.7960	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6072 / 0 / 152	
Goodness-of-fit on F^2	1.075	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0290, wR2 = 0.0792	
R indices (all data)	R1 = 0.0309, wR2 = 0.0807	
Absolute structure parameter	0.00(4)	
Largest diff. peak and hole	0.303 and -0.226 $e.Å^{-3}$	

Data of compound 35c (chapter 2):

Table 1. Crystal data and structure refinement for mar41.

Identification code	mar41	
Empirical formula	C_{11} H_{11} Br O_2 S	
Formula weight	287.17	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	$P2_12_12_1$	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 5.6731(2) Å	α= 90°.
	b = 7.4057(2) Å	β= 90°.
	c = 27.7704(8) Å	γ = 90°.
Volume	1166.73(6) $Å^3$	
Z	4	
Density (calculated)	1.635 Mg/m^3	
Absorption coefficient	3.679 mm^{-1}	
F(000)	576	
Crystal size	0.68 x 0.54 x 0.20 mm^3	
Θ range for data collection	5.88 to 27.50°.	
Index ranges	-7≤h≤7, -9≤k≤9, -17≤l≤36	
Reflections collected	7929	
Independent reflections	2629 [R(int) = 0.0594]	
Completeness to Θ = 27.50°	97.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.5266 and 0.1887	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2629 / 0 / 142	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2σ(I)]	R1 = 0.0392, wR2 = 0.0977	
R indices (all data)	R1 = 0.0410, wR2 = 0.0986	
Absolute structure parameter	0.039(12)	
Largest diff. peak and hole	0.826 and -1.025 $e.Å^{-3}$	

Data of compound 38a (chapter 2):

Table 1. Crystal data and structure refinement for mar29.

Identification code	mar29	
Empirical formula	$C_{16}H_{16}O_3S$	
Formula weight	288.35	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 7.14290(10) Å	α= 90°.
	b = 8.1370(2) Å	β= 90.3340(10)°.
	c = 24.7865(5) Å	γ = 90°.
Volume	1440.61(5) $Å^3$	
Z	4	
Density (calculated)	1.329 Mg/m^3	
Absorption coefficient	0.229 mm^{-1}	
F(000)	608	
Crystal size	0.80 x 0.52 x 0.29 mm^3	
Θ range for data collection	2.63 to 27.50°.	
Index ranges	-8≤h≤9, -9≤k≤7, -32≤l≤32	
Reflections collected	10797	
Independent reflections	2889 [R(int) = 0.0201]	
Completeness to Θ = 27.50°	87.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9367 and 0.8382	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2889 / 0 / 186	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2σ(I)]	R1 = 0.0324, wR2 = 0.0882	
R indices (all data)	R1 = 0.0353, wR2 = 0.0917	
Extinction coefficient	0.0163(17)	
Largest diff. peak and hole	0.263 and -0.277 $e.Å^{-3}$	

Data of compound 38b (chapter 2):

Table 1. Crystal data and structure refinement for mar34.

Identification code	mar34	
Empirical formula	$C_{18}H_{20}O_3S$	
Formula weight	316.40	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 6.4052(2) Å	α= 75.9010(10)°.
	b = 11.1586(3) Å	β= 79.3640(10)°.
	c = 11.7113(4) Å	γ = 79.0220(10)°.
Volume	788.53(4) $Å^3$	
Z	2	
Density (calculated)	1.333 Mg/m^3	
Absorption coefficient	0.215 mm^{-1}	
F(000)	336	
Crystal size	0.32 x 0.20 x 0.10 mm^3	
Θ range for data collection	1.90 to 27.50°.	
Index ranges	$-8\leq h\leq 7$, $-14\leq k\leq 14$, $-15\leq l\leq 15$	
Reflections collected	12657	
Independent reflections	3514 [R(int) = 0.0250]	
Completeness to Θ = 27.50°	97.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9788 and 0.9343	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3514 / 0 / 204	
Goodness-of-fit on F^2	1.032	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0350, wR2 = 0.0941	
R indices (all data)	R1 = 0.0402, wR2 = 0.0982	
Largest diff. peak and hole	0.316 and -0.288 $e.Å^{-3}$	

Data of compound 45m (chapter 2):

```
data_ks717m

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_chemical_name_systematic
;
 ?
;
_chemical_name_common             ?
_chemical_melting_point           ?
_chemical_formula_moiety          ?
_chemical_formula_sum
 'C17 H17 Cl O4'
_chemical_formula_weight          320.76

loop_
 _atom_type_symbol
 _atom_type_description
 _atom_type_scat_dispersion_real
 _atom_type_scat_dispersion_imag
 _atom_type_scat_source
 'C'  'C'   0.0033   0.0016
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'H'  'H'   0.0000   0.0000
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'O'  'O'   0.0106   0.0060
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
 'Cl'  'Cl'   0.1484   0.1585
 'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

_symmetry_cell_setting            monoclinic
_symmetry_space_group_name_H-M    P2(1)/c

loop_
 _symmetry_equiv_pos_as_xyz
 'x, y, z'
 '-x, y+1/2, -z+1/2'
 '-x, -y, -z'
 'x, -y-1/2, z-1/2'

_cell_length_a                    14.384(3)
_cell_length_b                    14.157(3)
_cell_length_c                    15.968(3)
_cell_angle_alpha                 90.00
_cell_angle_beta                  108.64(3)
_cell_angle_gamma                 90.00
_cell_volume                      3081.1(11)
_cell_formula_units_Z             8
_cell_measurement_temperature     200(2)
_cell_measurement_reflns_used     all
_cell_measurement_theta_min       ?
_cell_measurement_theta_max       ?

_exptl_crystal_description        prism
_exptl_crystal_colour             colourless
_exptl_crystal_size_max           0.30
_exptl_crystal_size_mid           0.25
```

```
_exptl_crystal_size_min          0.22
_exptl_crystal_density_meas      ?
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_exptl_crystal_density_method    'not measured'
_exptl_crystal_F_000             1344
_exptl_absorpt_coefficient_mu    0.263
_exptl_absorpt_correction_type   none
_exptl_absorpt_correction_T_min  ?
_exptl_absorpt_correction_T_max  ?
_exptl_absorpt_process_details   ?

_exptl_special_details
;
 ?
;

_diffrn_ambient_temperature      200(2)
_diffrn_radiation_wavelength     0.71073
_diffrn_radiation_type           MoK\a
_diffrn_radiation_source         'fine-focus sealed tube'
_diffrn_radiation_monochromator  graphite
_diffrn_measurement_device_type  'STOE IPDS II'
_diffrn_measurement_method       ?
_diffrn_detector_area_resol_mean ?
_diffrn_standards_number         ?
_diffrn_standards_interval_count ?
_diffrn_standards_interval_time  ?
_diffrn_standards_decay_%        ?
_diffrn_reflns_number            43171
_diffrn_reflns_av_R_equivalents  0.0737
_diffrn_reflns_av_sigmaI/netI    0.0795
_diffrn_reflns_limit_h_min       -17
_diffrn_reflns_limit_h_max       17
_diffrn_reflns_limit_k_min       -17
_diffrn_reflns_limit_k_max       17
_diffrn_reflns_limit_l_min       -19
_diffrn_reflns_limit_l_max       19
_diffrn_reflns_theta_min         1.97
_diffrn_reflns_theta_max         26.00
_reflns_number_total             6055
_reflns_number_gt                2808
_reflns_threshold_expression     >2sigma(I)

_computing_data_collection       STOE-X-AREA
_computing_cell_refinement       ?
_computing_data_reduction        ?
_computing_structure_solution    'SHELXS-97 (Sheldrick, 1990)'
_computing_structure_refinement  'SHELXL-97 (Sheldrick, 1997)'
_computing_molecular_graphics    XP
_computing_publication_material  ?

_refine_special_details
;
 Refinement of F^2^ against ALL reflections.  The weighted R-factor wR
and
 goodness of fit S are based on F^2^, conventional R-factors R are
based
```

```
 on F, with F set to zero for negative F^2^. The threshold expression
of
 F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc.
and is
 not relevant to the choice of reflections for refinement.  R-factors
based
 on F^2^ are statistically about twice as large as those based on F,
and R-
 factors based on ALL data will be even larger.
;

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
 'calc w=1/[\s^2^(Fo^2^)+(0.0410P)^2^+0.0000P] where
P=(Fo^2^+2Fc^2^)/3'
_atom_sites_solution_primary      direct
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     mixed
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          6055
_refine_ls_number_parameters      405
_refine_ls_number_restraints      0
_refine_ls_R_factor_all           0.1002
_refine_ls_R_factor_gt            0.0363
_refine_ls_wR_factor_ref          0.0847
_refine_ls_wR_factor_gt           0.0741
_refine_ls_goodness_of_fit_ref    0.744
_refine_ls_restrained_S_all       0.744
_refine_ls_shift/su_max           0.000
_refine_ls_shift/su_mean          0.000
```

Data of compound 51b (chapter 2):

Table 1. Crystal data and structure refinement for 5-(3-Ethyl-2-hydroxy-benzoyl)-2-hydroxy-3-(4-methoxy-phenylsulfanyl)-benzoic acid ethyl ester (=mar212)

Identification code	mar212	
Empirical formula	$C_{25}H_{24}O_6S$	
Formula weight	452.50	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 14.8010(4) Å	α= 90°.
	b = 7.3353(2) Å	β= 109.574(2)°.
	c = 21.5310(6) Å	γ = 90°.
Volume	2202.52(10) $Å^3$	
Z	4	
Density (calculated)	1.365 Mg/m^3	
Absorption coefficient	0.187 mm^{-1}	
F(000)	952	
Crystal size	0.68 x 0.45 x 0.26 mm^3	
Θ range for data collection	2.85 to 30.00°.	
Index ranges	-20≤h≤20, -10≤k≤9, -30≤l≤30	
Reflections collected	30762	
Independent reflections	6399 [R(int) = 0.0200]	
Completeness to Θ = 30.00°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9530 and 0.8834	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6399 / 0 / 301	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2σ(I)]	R1 = 0.0342, wR2 = 0.0915	
R indices (all data)	R1 = 0.0420, wR2 = 0.1018	
Extinction coefficient	0.0025(8)	
Largest diff. peak and hole	0.377 and -0.227 $e.Å^{-3}$	

Data of compound 55a (chapter 2):

Table 1. Crystal data and structure refinement for mar158.

Identification code	mar158	
Empirical formula	$C_{19}H_{12}O_4$	
Formula weight	304.29	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 10.0265(3) Å	α= 90°.
	b = 9.7519(3) Å	β= 99.2720(10)°.
	c = 14.5748(3) Å	γ = 90°.
Volume	1406.47(7) $Å^3$	
Z	4	
Density (calculated)	1.437 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	632	
Crystal size	0.72 x 0.33 x 0.32 mm^3	
Θ range for data collection	2.52 to 30.00°.	
Index ranges	-14≤h≤13, -13≤k≤13, -20≤l≤18	
Reflections collected	16110	
Independent reflections	4070 [R(int) = 0.0238]	
Completeness to Θ = 30.00°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9683 and 0.9307	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4070 / 0 / 212	
Goodness-of-fit on F^2	1.051	
Final R indices [I>2σ(I)]	R1 = 0.0408, wR2 = 0.1070	
R indices (all data)	R1 = 0.0512, wR2 = 0.1175	
Largest diff. peak and hole	0.341 and -0.187 $e.Å^{-3}$	

Data of compound 62c (chapter 3):

Table 1. Crystal data and structure refinement for mar194.

Identification code	mar194	
Empirical formula	$C_{15}H_{14}O_4$	
Formula weight	258.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/c$	
Space group (Hall)	-P 2ybc	
Unit cell dimensions	a = 11.8116(2) Å	α= 90°.
	b = 7.36280(10) Å	β= 90.0980(10)°.
	c = 14.5840(3) Å	γ = 90°.
Volume	1268.32(4) $Å^3$	
Z	4	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	544	
Crystal size	0.85 x 0.85 x 0.18 mm^3	
Θ range for data collection	2.79 to 30.00°.	
Index ranges	$-16\leq h\leq 16$, $-10\leq k\leq 10$, $-20\leq l\leq 11$	
Reflections collected	9585	
Independent reflections	3669 [R(int) = 0.0159]	
Completeness to Θ = 30.00°	98.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9825 and 0.9212	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3669 / 0 / 179	
Goodness-of-fit on F^2	1.048	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0387, wR2 = 0.1079	
R indices (all data)	R1 = 0.0463, wR2 = 0.1166	
Extinction coefficient	0.000(2)	
Largest diff. peak and hole	0.400 and -0.196 $e.Å^{-3}$	

Data of compound 68t (chapter 4):

Table 1. Crystal data and structure refinement for mar197.

Identification code	mar197	
Empirical formula	$C_{18}H_{15}NO_4$	
Formula weight	309.31	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 5.1443(2) Å	α= 71.129(2)°.
	b = 12.0108(4) Å	β= 86.379(2)°.
	c = 13.0738(4) Å	γ = 78.594(2)°.
Volume	749.28(4) $Å^3$	
Z	2	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	324	
Crystal size	1.00 x 0.13 x 0.10 mm^3	
Θ range for data collection	2.82 to 30.00°.	
Index ranges	$-7\leq h\leq 7$, $-16\leq k\leq 16$, $-18\leq l\leq 18$	
Reflections collected	15822	
Independent reflections	4310 [R(int) = 0.0280]	
Completeness to Θ = 30.00°	98.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9903 and 0.9086	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4310 / 0 / 208	
Goodness-of-fit on F^2	0.995	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0488, wR2 = 0.1189	
R indices (all data)	R1 = 0.0670, wR2 = 0.1334	
Largest diff. peak and hole	0.427 and -0.282 $e.Å^{-3}$	

Data of compound 76 (**Manuscript in preparation**):

Table 1. Crystal data and structure refinement for mar141.

Identification code	mar141	
Empirical formula	$C_8H_{11}ClO_3$	
Formula weight	190.62	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	C2/m	
Space group (Hall)	-C 2y	
Unit cell dimensions	a = 17.0205(5) Å	α= 90°.
	b = 6.7961(2) Å	β= 119.9270(10)°.
	c = 8.7742(2) Å	γ = 90°.
Volume	879.61(4) $Å^3$	
Z	4	
Density (calculated)	1.439 Mg/m^3	
Absorption coefficient	0.398 mm^{-1}	
F(000)	400	
Crystal size	0.61 x 0.29 x 0.24 mm^3	
Θ range for data collection	2.68 to 29.99°.	
Index ranges	-23≤h≤22, -9≤k≤9, -12≤l≤12	
Reflections collected	7276	
Independent reflections	1380 [R(int) = 0.0211]	
Completeness to Θ = 29.99°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9106 and 0.7935	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1380 / 0 / 85	
Goodness-of-fit on F^2	1.099	
Final R indices [I>2σ(I)]	R1 = 0.0277, wR2 = 0.0755	
R indices (all data)	R1 = 0.0301, wR2 = 0.0785	
Largest diff. peak and hole	0.432 and -0.229 $e.Å^{-3}$	

Data of compound 80 (**Manuscript in preparation**):

Table 1. Crystal data and structure refinement for mar85c.

Identification code	mar85c	
Empirical formula	$C_{11}H_{10}Br_2O_3S$	
Formula weight	382.07	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	$P2_12_12_1$	
Space group (Hall)	P 2ac 2ab	
Unit cell dimensions	a = 6.7875(2) Å	α= 90°.
	b = 11.7052(3) Å	β= 90°.
	c = 16.1088(4) Å	γ = 90°.
Volume	1279.83(6) $Å^3$	
Z	4	
Density (calculated)	1.983 Mg/m^3	
Absorption coefficient	6.489 mm^{-1}	
F(000)	744	
Crystal size	0.56 x 0.37 x 0.18 mm^3	
Θ range for data collection	2.53 to 28.00°.	
Index ranges	$-8\leq h\leq 8$, $-15\leq k\leq 15$, $-14\leq l\leq 21$	
Reflections collected	11457	
Independent reflections	2888 [R(int) = 0.0271]	
Completeness to Θ theta = 28.00°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.3880 and 0.1219	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2888 / 0 / 154	
Goodness-of-fit on F^2	1.024	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0206, wR2 = 0.0449	
R indices (all data)	R1 = 0.0229, wR2 = 0.0454	
Absolute structure parameter	0.027(7)	
Largest diff. peak and hole	0.313 and -1.024 $e.Å^{-3}$	

Part B

Isolation of New Chemical Constituents of *Symplocos racemosa*

Intorduction

1. Taxonomy of the Family Symplocaceae

The family Symplocaceae was first recognized by D. Don. (Symplocineae, Prodr. Fl. Nepal. 144.1825, excluding *Schopfia*) but most authors including De Candolle (Prodr. 8: 244.1844), Bentham and Hooker (Gen. Pl. 2: 668.1876), Stewart and Brandis (For. Fl.299.1874) and C. B. Clarke in Hook. f. (Fl. Brit. Ind. 3: 572.1882) included it in family Styracaceae.

However, Miquel in Martius (Fl. Brass. 7: 22. 1842), Engler and Prantl (Pflanzenfam 4 (1): 168. 1890) following D. Don, treated it as a separate family. Lawrence (Taxon. Vasc. Pl. 665. 1951) and C. G. G. Van Steenis (Fl. Males. 4: 49. 1954) advocate its separate identity from Styracaceae on the basis of its inferior or semi-inferior, completely 2-5 loculed ovary, drupe crowned by persistent calyx lobes, 1-4 seriate or fasciculate (adelphous) stamens with ovoid-subglobose anthers and absence of stellate hairs or scales. Hutchison (Gen. Fl. Pl 2: 39.1968; Fam. Fl. Pl. 1: 171.1960) also treats it as a separate unigeneric family. The remarks of Shaw (in Willis Dict. Fl. Pl. and Ferns ed. 8.1093.1972) that Symplocaceae has not much in common with Styracaceae but is closely related to Theaceae are justified since it differs from Theaceae only in racemose inflorescence and inferior ovary, the characters found in some Theaceous genera (e.g., *Anneslea*, *Symplocarpon*).[1]

1.1 The Genus *Symplocos* **Jacq.** and **Linn**.

Being the only genus of family Symplocaceae, it has the same morphological characters and geographical distribution as the family.

1.1.1 Distribution

It is a large genus of trees and shrubs, widely distributed in the tropics and subtropics of Asia, Australia, and America. It consists of almost 290 species, about 68 species are found in India, of which only a few are of economic importance. In Pakistan only two species are found, namely *Symplocos chinensis* and *Symplocos racemosa*.[2,3]

1.1.2 Morphology

Trees or shrubs, usually glabrous. Leaves often turning yellow when dry, alternate, coriaceous or membranous, toothed or entire. Flowers usually white, in axillary spikes or racemes, sometimes reduced to few-flowered fascicles or to a single flower; bracteate, caduceous; bracteoles are 1-3 beneath the flower. Calyx-tube adnate, short when in flower, often enlarged in fruit; lobes 5, imbricate. Petals 5 in 1 series, or 6-10 in 2 series, free almost or entirely to the base, or obscurely connate (rarely connate into a tube), imbricate. Stamens are usually numerous, many seriate, adnate to the corolla-tube or to the petals, the outer ones longer; filaments filiform or flattened at the base; anthers short dehiscing longitudinally. Ovary inferior (in Indian species), 3- (rarely 2- or 4-) celled; ovules 2, pendulous from the inner angle of each cell; style usually filiform; stigma capitate or small, scarcely lobed. Drupe is ellipsoid or subglobose; stone usually woody, often ribbed, 1-3-seeded. Seeds oblong; embryo terete, straight or curved, in the centre of fleshy albumen; cotyledons much shorter than the radicle.[3]

1.2 The Species *Symplocos racemosa* Roxb.

1.2.1 History

This tree, in Sanskrit, was called Lodhra, Rodhra or Srimata meaning "propitious", and "Tilaka" because it was used in making the Tilaka mark on the forehead. The decoction of the bark was used for gargling when the gums were spongy and bleeding (Susruta). Roxburgh remarks that the bark was popular among the dyes of red in Calcutta and seemed to be used as a mordant only. In Europe it was formerly looked upon as a cinchona bark and had been known at various times as "Ecorce de lautour", "China nova", "China calafornica", "China brasilarsis", and "China paraquatan". It was also known as "Lotus bark".[4]

1.2.2. Distribution

It grows abundantly in the plains and lower hills throughout North and East India, ascending in the Himalayas up to an elevation of 1,400 m; southwards it extends up to Chota Nagpur. In Pakistan, it is found in the areas of Azad Kashmir and Abbottabad.[2]

1.2.3. Habitat

S. racemosa Roxb. is a small evergreen tree, stem up to 6 m high and 15 cm diameter. Bark dark grey, rough. Blaze 7.5-13 mm, shortly fibrous, pale yellow finely mottled with pale orange brown. Leaves 9-18 by 3.2-5 cm, elliptic-oblong or elliptic-lanceolate, apex acute, obtusely-acuminate or obtuse, serrulate obscurely crenate or rarely entire, base acute cuneate, coriaceous, glabrous above, pubscent beneath when young but ultimately glabrous or with scattered spreading hairs mainly on the midrib, glossy on both surfaces, dark green above; lateral nerves indistinct (distinct when dry) 5-9 pairs. Petiole 7.5-18 mm long. Flowers 1-1.3 cm diam., white fading yellow, in simple axillary pubescent racemes 1.3-9 cm long. Drupe 1-1.3 cm long, oblong, glabrous, purplish black, crowned with the persistent calyx, smooth and 1-3 seeded.[3]

1.2.4 Medicinal Impotance

Symplocos racemosa Roxb. (Lodh) is a medicinal plant widely used by the traditional practitioners against various diseases as single or in compound drug. It has a wide range of usage in Ayurveda and Unani medicines. Its bark is described as an emmenagogue tonic for the persons of plethoric constitution and is useful in bowel complaints and ulcers. Its decoction is used as a gargle for giving firmness to bleeding and spongy gums. It cures watery eyes, opthalmia and is good for all diseases of the eye. It also cures "Kapha" biliousness, diseases of the blood, dysentery, inflammations, vaginal discharges, leprosy, elephantiasis, filaria, and is useful in abortions, miscarriages and ulcers in the vagina. The bark in 20-grain doses mixed with sugar is given in menorrhagia due to relaxation of the uterine tissue; it should be given two or three times a day, for three or four days. It is also used for leucorrhoea. The bark is also prescribed in the treatment snake-bite and scorpion-sting. In snake-bite it is given internally in powder form or in the form of decoction.[3,5]

1.3 Phytochemicals: Their Role in the Modern Times

The word "phytochemical" means the chemicals derived from phyto or plant. Its study involves understanding the chemical composition of plants used in medicine. Phytochemicals produced in plants are secondary compounds responsible for metabolic activities and defense purpose. Phytochemicals are produced by specific biochemical pathways, which occur inside the plant cells. The phytochemicals can range from medicinally useful agents to deadly poisons. A number of phytochemicals isolated from plant material are used in the pharmaceutical drug industry today.

With the history of plant-based medicine in mind, one can conclude that in the early days, physicians were not aware of the chemical constituents in the plants. However, they did have knowledge of the active principles responsible for therapeutic activity. In Charaka–Samhita, the classical treatise on Ayurvedic medicine, the word, ***virya***, is similar to word, ***potency***. Drugs have been classified according to the pharmacological activities, but a comprehensive account of the mechanism of action was missing.

Ayurveda, the ancient healing system of India, flourished in the Vedic era in India. According to historical facts, the classical texts of Ayurveda, Charaka Samhita and Sushruta Samhita were written around 1000 B.C. The Ayurvedic Materia Medica includes 600 medicinal plants alongwith therapeutics. Herbs like turmeric, fenugreek, ginger, garlic and holy basil are an integral part of Ayurvedic formulations. These formulations either incorporate a single herb or more than one herb (i.e., polyherbal formulations).Before the availability of synthetic drugs; humans were completely dependent on medicinal herbs for prevention and treatment of diseases. The use of the medicinal herbs for curing disease has been documented in the history of all civilizations. The drugs were used in crude forms like expressed juice, powder, decoction or infusion. Although formulations mentioned in ancient texts are difficult to understand in terms of scientific parameters, some of them are still reputed for their curative values.

Ancient healers who developed formulations based on medicinal herbs were probably not aware of the chemical composition of these herbs. Nevertheless, the advancement they made despite the non-availability of scientific procedures is astonishing. The work on *Terminalia chebula* (myrobalan) mentioned in Charaka Samhita is quiet authentic and

modern studies have revealed that the purgative activity mentioned in Ayurveda is justified by the isolation of chebulic acid, the active constituent of myrobalan.

Medicinal plants are a significant source of synthetic and herbal drugs in India and China and have been on the forefront when we talk about history of herbal drugs. The traditional systems of medicines: Ayurveda, Siddha, Unani, Western Herbal Medicine, Traditional Chinese Medicine and Homeopathy have roots in medicinal herbs. The field of herbal medicine has produced a number of distinguished researchers and due to its accessibility to traditions; it is still practiced even by lay practitioners.

Sterner, who first isolated morphine from *Papaver somniferum* (opium poppy) showed to the medical profession that certain phytochemicals produced in plant cells are responsible for pharmacological activity. Later on, other alkaloids isolated from opium poppy were investigated for their pharmacological activities. Codeine showed anti-tussive activity and papaverine anti-spasmodic activity. The opium based extracts have been utilized for various pharmacological activities, and a number of alkaloids distributed in the plant have different pharmacological activities.

Scientific validation of herbal drugs always has been questioned, but with recent advances and publications of clinical trials, the researchers and the public are viewing herbal products with more respect. In the commercial market, medicinal herbs are used as raw drugs, extracts or tinctures. Isolated active constituents are used for applied research. There has been a dramatic rise in the sale of herbal products like *Allium sativum, Hypericum perforatum, Spirulina, Echinacea angustifolia, Ginkgo biloba* and *Silybum marianum*.

Before any herbal medicine is screened for testing, phytochemical investigations are essential because sometimes a critical constituent is missing from the herb due to reasons like storage, geographical distribution or processing. Today standardized extracts are used in herbal drug industry and their standard is based on the presence of marker compounds. The marker compounds may or may not have pharmacological activity.

A brief account of type of the phytochemicals distributed in plant flora is presented below:

1. Phenolic compounds are widely distributed in plant flora. A variety known as polyphenols is found in fruits of some plants. They occur as natural colour pigments and are responsible for the colour of the fruits.

2. Bitter principles are basically glycosides and are found commonly in plants of Genitiaceae. The bitters act on gustatory nerves, which results in increased flow of saliva and gastric juices and acts as appetizers.

3. Alkaloids are basically nitrogen containing bases and the most important class of phytochemicals. The amino acids act as building blocks for the biosynthesis of alkaloids.

4. Diarylheptanoids are rare compounds found in the family Zingiberaceae. Recent animal studies have shown diarylheptanoids to be potent anti-inflammatory agents.

5. Flavonoids are important group of polyphenols, widely distributed in plant flora. 4,000 flavonoids are known to exist and some of them are pigments in higher plants. Quercetin, kaempferol and quercitrin are common. Soya flavones have recently gained importance due to variety of pharmacological activities.

6. Furanocoumarins are photosensitizing agents used in the treatment of pigment disorders. Ayurveda, the ancient science of India, has described the use of bawachi (*Psoralia corylifolia*) for the treatment of leucoderma.

7. Furochromones are group of coumarins, derived from benzopyrone. They are related to furanocoumarins.

8. Hydroxycoumarins represents another group of coumarins.

9. Glycosides are water-soluble constituents, found in the cell sap. They are colourless, crystalline substances containing carbon, hydrogen and oxygen. Some glycosides are peculiar in having nitrogen and sulphur.

10. Napthodianthrones are derivatives of anthracene.

11. Neutral principles are bodies of unidentified character.

12. Acylphloroglucinols are group of phenolic compounds having significant antidepressant activity.

13. Resins are brittle, non-volatile, solid substances. Oleoresins are natural products of resin mixed with volatile oils. Gum- resins are plant exudates and are mixtures of gum

and resin and often volatile oils. Balsams are combinations of resins or oleoresins with aromatic acids.

14. Saponins are glycosides of triterpenes and steroids found in number of plants. Some are poisonous.

15. Sesquiterpene lactones constitute significant group of phytochemicals. They are formed by condensation of three isoprene molecules followed by oxidation.

16. Sterols are derivatives of steroids. Modern clinical studies have supported their role as anti-inflammatory and analgesic agents.

17. Tannins are widely distributed in plant flora. They are phenolic compounds of high molecular weight.

According to recent estimation, only 20 percent of the flora of Pakistan has been screened for drugs. Keeping in view the vast treasure of medicinal herbs, one can expect phytochemicals to play a significant role as modern science has limited options for diseases like diabetes mellitus, rheumatoid arthritis, Alzheimer's disease and Parkinson's disease. Work on the identification and isolation of phyochemicals is an ongoing process and herbal medicine is expected to play critical role in the future healthcare system.[6]

1.4 Diversity and Impotance of Phenolics in Plants

Phenolic constituents occurring in plants have a great diversity in their structures ranging from complex phenolic glycosides to simple salicylic acid. Several thousands phenolic compounds have been isolated from plant kingdom which make a considerable contribution to the nutritional quality of fruits and fruit products and play an important role in the daily diet. Phenols exhibit anti-inflammatory, antiseptic effects and antiviral properties. Protection against infection and feeding are the leading theories on why plants produce these compounds. They also play a key role in antioxidative defense mechanisms in biological systems and may have inhibitory effects on mutagenesis and carcinogenesis. Attention has turned to plant phenols because the use of synthetic antioxidants has been falling off due to their suspected action as cancer promoters.

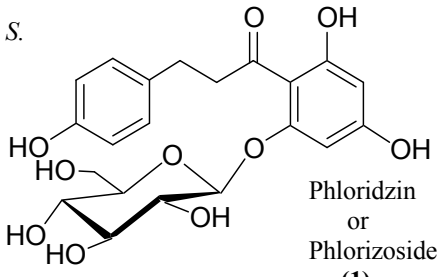
Polyphenols or multiphenolic complexes have an even wider range of biological activities. The red, blue and purple pigments found in fruits, vegetables, tea and herbs are due to their polyphenol contents. Specific examples include apples, blueberries, cranberries, egg plants, red currants, grapes, grape juice, purple bell peppers, raspberries, red wine, and green and black tea. They are considered to have antihistaminic, anti-inflammatory, antioxidant, anti-clotting, anti-tumor and vascular effects.

Natural phenolic acids belong to two different classes, hydroxybenzoic acids (HBA) and hydroxycinnamic acids (HCA). They are derived from two non-phenolic molecules, benzoic and cinnamic acids, respectively. Phenolic acids are widely represented in fruits, although their distribution may vary considerably according to species, cultivar, and physiological stage. Phenolic acids are also of great interest to man because they also contribute to the sensory and nutritional qualities.[7]

2. Chemical Constitutents of Genus *Symplocos*

According to the cited literature, the phytochemical investigation of the various species of the genus *Symplocos* Jacq. has resulted in the isolation of dihydrochalcone glucosides: [phloridzin (**1**), confusoside (**2**), trilobatin (**3**)],[8] flavanol glucosides: [symplocoside (**4**), symposide (**5**) , leucopelargonidin 3-glucoside (**6**), ellagic acid (**7**)],[9] flavonol glycoside: rhamnetin 3-digalactoside (**8**),[10] alkaloids: [isoboldine (**9**), caaverine (**10**)],[11] iridoid glucoside: verbenalin (**11**),[8] triterpenoids: [19α-hydroxyarjunolic acid-3,28-*O*-bis-β-glucopyranosides(**12**);[12] 19α-hydroxyasiatic acid-3,28-*O*-bis-β-glucopyranosides (**13**)),[12] 28-hydroxy-20α-urs-12, 18(19)-dien-3β-yl acetate (**14**), 24-hydroxyolean-12-en-3-one (**15**), 3-oxo-urs-20α-urs-12, 18(19)-dien-28-oic acid (**16**), betulin (**17**); oleanolic acid (**18**)][9c], β-sitosterol (**19**) and α-amyrin (**20**).[9b] An overview of all these compounds is given here in.

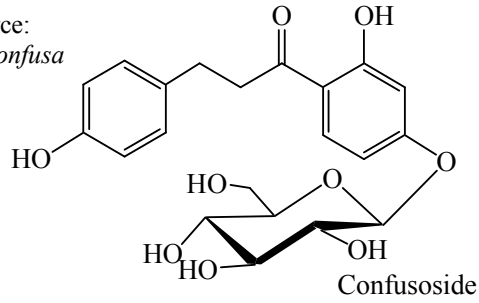
Source:
S. lancifolia S. spicata



Phloridzin
or
Phlorizoside
(1)

M. F. = $C_{21}H_{24}O_{10}$ M. W. = 436

Source:
S. confusa

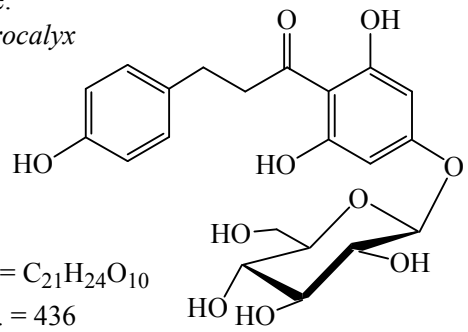


Confusoside (**2**)

M. F. = $C_{21}H_{24}O_9$ M. W. = 420

Source:
S. microcalyx

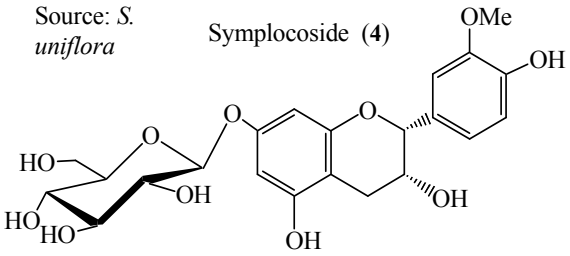
Trilobatin (**3**)



M. F. = $C_{21}H_{24}O_{10}$
M. W. = 436

Source: *S. uniflora*

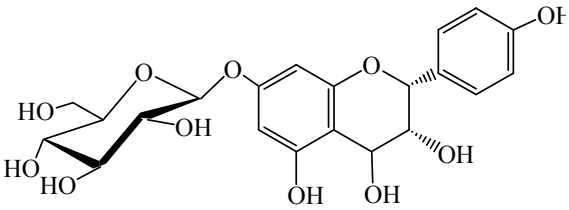
Symplocoside (**4**)



M. F. = $C_{22}H_{26}O_{11}$ M. W. = 466

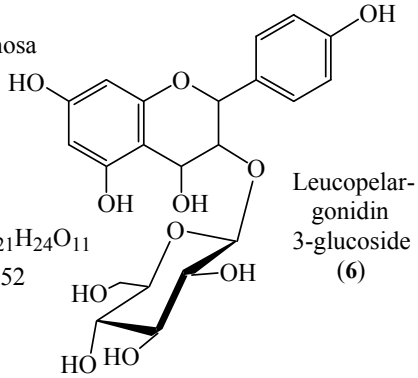
Source:
*S. ra*cemosa

Symposide (**5**)



M. F. = $C_{21}H_{24}O_{10}$ M. W. = 436

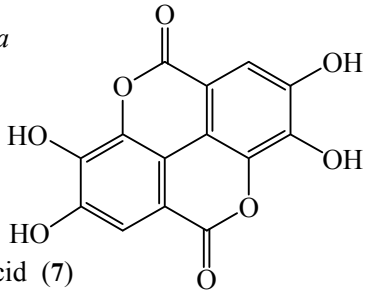
Source:
*S. ra*cemosa



Leucopelargonidin 3-glucoside (**6**)

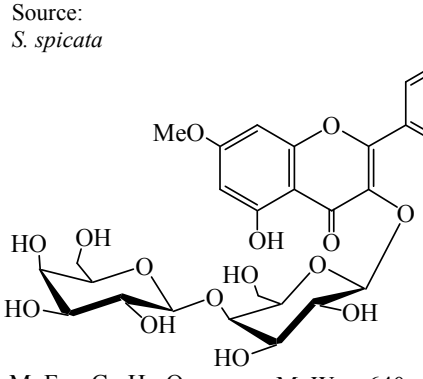
M. F. = $C_{21}H_{24}O_{11}$
M. W. = 452

Source:
S. racemosa



Ellagic acid (**7**)
M. F. = $C_{14}H_6O_8$
M. W. = 302

Source:
S. spicata

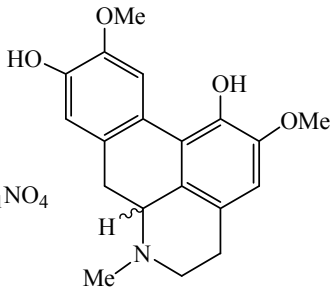


Rhamentin; 3-*O*-[β-D-galactopyranosyl-4-*O*-β-D-galactopyranoside (**8**)

M. F. = $C_{28}H_{32}O_{17}$ M. W. = 640

Source:

S. celastrinea



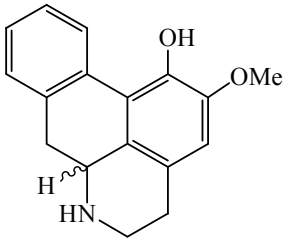
Isoboldine (**9**)

M. F. = $C_{19}H_{21}NO_4$

M. W. = 327

Source:

S. celastrinea



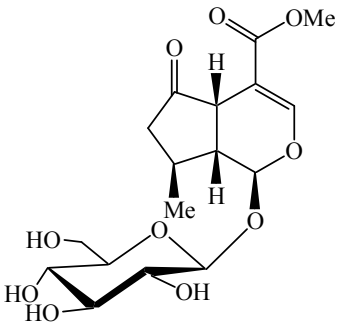
Caaverine (**10**)

M. F. = $C_{17}H_{17}NO_2$

M. W. = 267

Source:

S. glauca

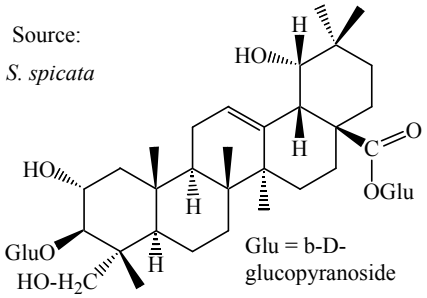


Verbenalin (**11**)

M. F. = $C_{17}H_{24}O_{10}$ M. W. = 388

Source:

S. spicata



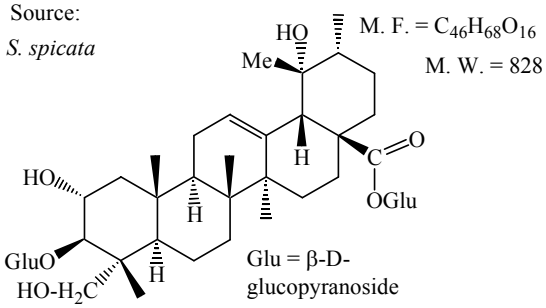
Glu = b-D-glucopyranoside

19α-Hydroxyarjunolic acid-3, 28-*O*-bis-β-glucopyranosides (**12**)

M. F. = $C_{42}H_{68}O_{16}$ M. W. = 828

Source:

S. spicata



Glu = β-D-glucopyranoside

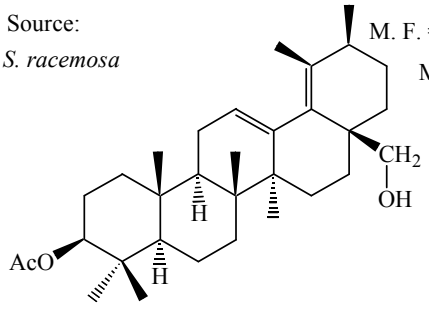
M. F. = $C_{46}H_{68}O_{16}$

M. W. = 828

19α-Hydroxyasiatic acid-3, 28-*O*-bis-β-glucopyranosides (**13**)

Source:

S. racemosa

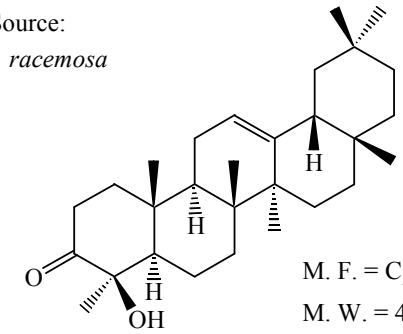


M. F. = $C_{32}H_{50}O_3$

M. W. = 482

28-Hydroxy-20α-urs-12,18(19)-dien-3β-yl acetate (**14**)

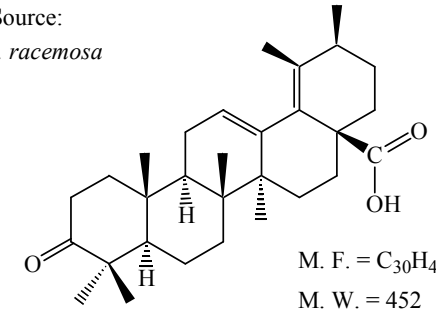
Source:
S. racemosa



M. F. = $C_{30}H_{48}O_2$
M. W. = 440

24-Hydroxyolean-12-en-3-one (**15**)

Source:
S. racemosa

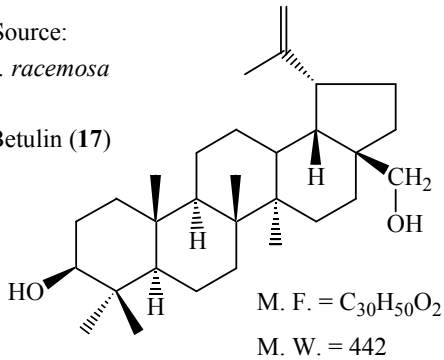


M. F. = $C_{30}H_{44}O_3$
M. W. = 452

3-Oxo-urs-20α-urs-12,18(19)-dien-28-oic acid (**16**)

Source:
S. racemosa

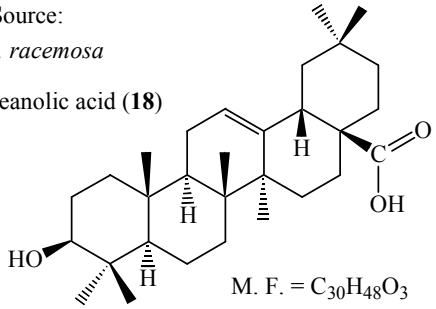
Betulin (**17**)



M. F. = $C_{30}H_{50}O_2$
M. W. = 442

Source:
S. racemosa

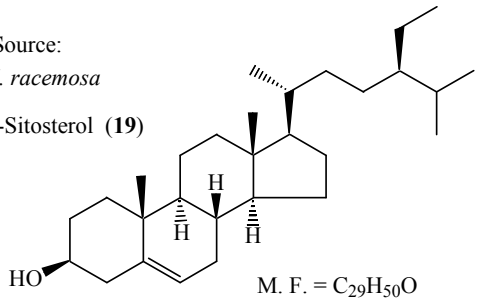
Oleanolic acid (**18**)



M. F. = $C_{30}H_{48}O_3$
M. W. = 456

Source:
S. racemosa

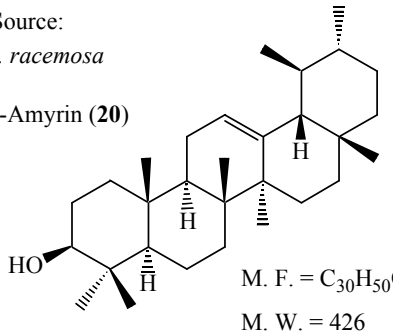
β-Sitosterol (**19**)



M. F. = $C_{29}H_{50}O$
M. W. = 414

Source:
S. racemosa

α-Amyrin (**20**)



M. F. = $C_{30}H_{50}O$
M. W. = 426

Results and Discussion

3. Present Work

The present work includes the phytochemical investigation and then re-investigation of the chemical constituents of the various fractions of *Symplocos racemosa*, the structure elucidation of the isolated constituents, and the screening of these constituents for various biological activities. For the convenience, the present work is divided into two categories; namely:

3.1. Structure elucidation of the chemical constituents of *Symplocos racemosa*

3.2. Bioactivity of the chemical constituents of *Symplocos racemosa*

Both these categories are discussed in detail, one after another.

3.1 Structure Elucidation of the Chemical Constitutents of *Symplocos racemosa*

This category of the present work highlights the characterization and identification of the chemical constituents, isolated from various fractions of *Symplocos racemosa*. The isolated constituents are divided into three sub-categories; namely:

3.1.1. New chemical constituents of *Symplocos racemosa*

3.1.2 New-source chemical constituents of *Symplocos racemosa*

A comprehensive account on these sub-categories is given below.

3.1.1. New Chemical Constitutents of *Symplocos racemosa*

The phytochemical investigation of the *n*-butanol soluble fraction of the bark of stem of *Symplocos racemosa* Roxb. yielded two new phenolic glycosides of salirepin series, symplocuronic acid (**21**) and sympocemoside (**22**) . Further investigation of the n-butanol solubles resulted in the isolation of three new benzyl derivatives, locoracemosides A, B and C (**23-25**). All the (five) new compounds are discussed, one by one, in detail.

3.1.1.1. Symplocuronic acid (21)

Symplocuronic acid (**21**) was isolated as an amorphous solid from the *n*-butanol fraction of the methanolic extract of the bark of *Symplocos racemosa* Roxb.

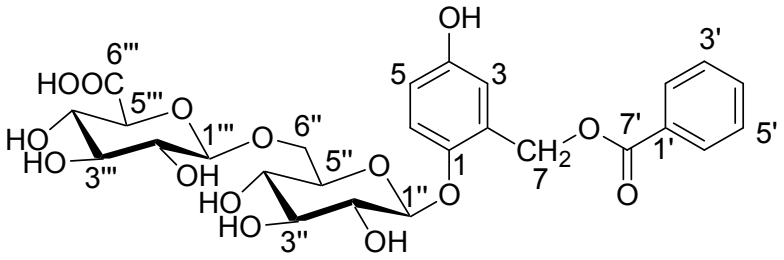


Fig. 3.1: Symplocuronic acid (**21**)

Its molecular formula $C_{26}H_{30}O_{15}$ was established through the HRFAB MS (+) showing a quasi-molecular ion $[M+H]^+$ peak at *m/z* 583.5089 which indicated 12 degrees of unsaturation. Its UV absorption band at λ_{max} 284 nm was characteristic of phenolic compounds and its IR spectrum showed specific absorptions at 3364-3025 (br) cm^{-1} and 1733 cm^{-1}, which could be ascribed to a carboxyl group. The intense IR absorption band at 1720 cm^{-1} revealed the presence of ester functionality while the broad C-O stretching band in the region of 1071 cm^{-1} suggested its glycosidic nature. The complete acid hydrolysis of **21** yielded various products and in the hydrolysate separated from the aglycone parts, the two sugars identified by the TLC comparison were found to be glucuronic acid and glucose and these were also supported by the loss of fragments in the FAB MS from the $[M]^+$ peak at *m/z* 582 to fragment ion peaks at *m/z* 406 [M – glucuronic acid]$^+$ and *m/z* 244 [M – glucuronic acid - glucose]$^+$. Its EI-MS spectrum also exhibited an ion at *m/z* 244 [M – glucuronic acid - glucose]$^+$ and the other characteristic fragments were observed at *m/z* 140 $[C_6H_3(OH)_2CH_2OH]^+$,123 $[C_6H_3(OH)_2CH_2]^+$,122 $[C_6H_5CO_2H]^+$,105 $[C_6H_5CO]^+$ and 77 $[C_6H_5]^+$ which indicated that the aglycone was exactly similar to that of reported salireposide[13-15] and this assignment was thoroughly supported by its ^{1}H-NMR data (Table 3.1). However, the remaining signals presumably belonged to two sugar moieties with two anomeric doublets at δ 4.72 (H-1″) and δ 4.75

(H-1‴) and the evidence for the β-configuration of these sugars was drawn from the coupling constants of J = 7.3 and J = 7.4 *Hz* for H-1″ and H-1‴ respectively. The ^{13}C-NMR spectrum corroborated the characteristic signals of a benzoyl residue, a substituted gentisyl alcohol unit and a glucose similar to that of known salireposide[13-15] but the additional signals were specific for a glucuronic acid moiety with the carboxy resonance at δ 173.7.[16,17] Its position in the molecule was deduced through the downfield shift of C-6″ to δ 65.4 as compared to the respective signal of salireposide[13-15] and HMBC correlations of H-1‴ with C-6″ and H-6″ with C-1‴. The important HMBC correlations are shown in figure 3.2.

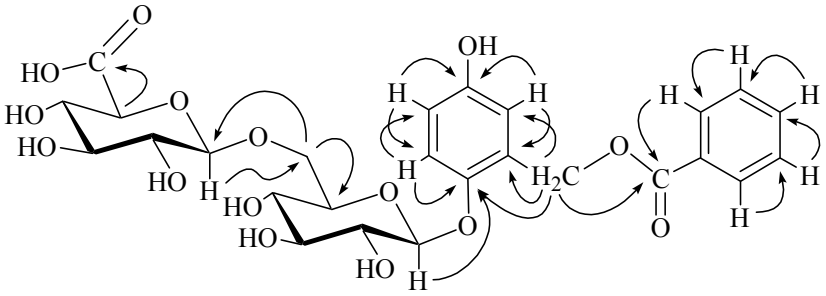


Fig. 3.2. Significant HMBC correlations of Symplocuronic acid (**21**)

Since only D-glucose and D-glucuronic acid are known in nature,[17] therefore, based upon the above cumulative evidences, **21** was identified as 2-[(benzoyloxy)methyl]-4-hydroxyphenyl O-β-D-glucuronopyranosyl (1→6)-β-D glucopy-ranoside.

Table:3.1 ^{13}C- (125 MHz) and ^{1}H-NMR (500 MHz) spectral data of Symplocuronic acid (**21**) correlated from 1D and 2D-NMR experiments in CD_3OD.

C. No.	Multiplicity (DEPT)	^{13}C-NMR (δ)	^{1}H-NMR (δ)	$^{1}J_{HH}$ (Hz)
1	C	149.8	-	-
2	C	133.2	-	-
3	CH	117.0	6.79	(d, *J* = 2.9)
4	C	154.2	-	-
5	CH	116.2	6.49	(dd, *J* = 2.9, 8.8)
6	CH	120.0	7.02	(d, *J* = 8.8)
7	CH_2	64.3	5.19	(d, *J* = 12.5)
			5.33	(d, *J* = 12.5)
1′	C	131.3	-	-
2′, 6′	CH	130.6	8.00	(d, *J* = 7.4)
3′, 5′	CH	129.6	7.49	(t, *J* = 7.6)
4′	CH	134.3	7.62	(t, *J* = 7.5)
7′	C	167.9	-	-
1″	CH	104.2	4.72	(d, *J* = 7.3)
2″	CH	74.4	3.45	(br t, *J* = 7.8)
3″	CH	78.3	3.49	m
4″	CH	72.0	3.41	m
5″	CH	75.5	3.86	(ddd, *J* =1.9, 8.9,11.3)
6″	CH_2	65.4	4.40	(dd, *J* = 7.7, 11.6)
			4.49	(dd, *J* = 1.9, 11.6)
1‴	CH	104.0	4.75	(d, *J* = 7.4)
2‴	CH	74.4	3.47	(br t, *J* = 7.7)
3‴	CH	78.1	3.52	m
4‴	CH	72.4	3.43	m
5‴	CH	75.0	4.02	(d, *J* = 9.3)
6‴	C	173.7	-	-

3.1.1.2. Sympocemoside (22)

Sympocemoside (**22**) was obtained also as an amorphous solid from the *n*-butanol fraction of the methanolic extract of the bark of *Symplocos racemosa* Roxb.

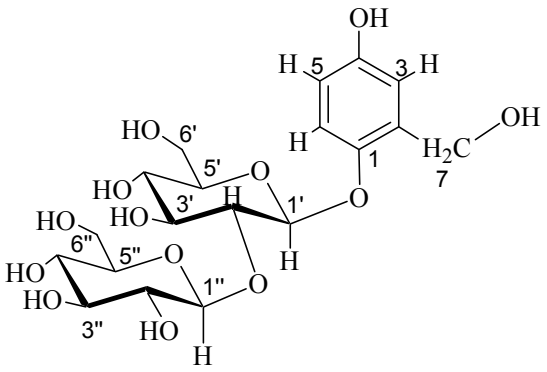


Fig. 3.3. Sympocemoside (**22**)

It was assigned a molecular formula $C_{19}H_{28}O_{13}$ on the basis of HRFAB MS (+) (*m/z* 465.4197 $[M+H]^+$, showing 6 degrees of unsaturation. It exhibited UV absorption band (λ_{max} 282 nm) typical of phenolic compounds. The IR absorption bands revealed the presence of hydroxyl groups (3357 br cm^{-1}), methines (2932 cm^{-1}), aromatic ring (1595-1416 cm^{-1}), ether linkage (1266, 1215 cm^{-1}) and the broad (C-O) stretching bands in the regions of 1115-1040 cm^{-1} accounted its glycosidic nature. The EI MS spectrum of **22** exhibited the following characteristic fragments; *m/z* 140 $[C_6H_3(OH)_2CH_2OH]^+$,123 $[C_6H_3(OH)_2CH_2]^+$, 122 $[C_6H_3(OH)_2CH_2OH - H_2O]^+$, which indicated the presence of a gentisyl alcohol moiety in the molecule. In the ^{1}H-NMR spectrum, the usual ABX spin system of the gentisyl alcohol group was readily identified by signals observed at δ 7.06 (1H, d, *J* = 8.7 *Hz*, H-6), 6.77 (1H, d, *J* = 3.0 *Hz*, H-3), and 6.65 (1H, dd, *J* = 8.7, 3.0 *Hz*, H-5) and the two anomeric doublets at δ 4.73 (*J* = 7.6 *Hz*, H-1′) and 4.70 (*J* = 7.8 *Hz*, H-1″) clearly ascertained the presence of two β-glucose moieties in the molecule. In addition to the similar signals of reported salirepin,[18] its ^{13}C-NMR spectrum also revealed the signals for an additional glucose unit and its position in the molecule was determined through the downfield shift of C-2′ (δ 77.9) and upfield shifts of C-1′ (δ 102.6) and C-3′

(δ 76.0) as compared to the respective signal of known salirepin (Table 3.2)**.** In the ^{1}H-^{1}H COSY spectrum of **22**, a broad triplet signal at δ 3.44 was assigned to H-2′ on the basis of a cross-peak with the anomeric proton H-1′ (δ 4.73) and there after the HMBC correlations of H-2′ with C-1″ and H-1″ with C-2′ confirmed that the additional glucose (II) was linked glycosidically to C-2′ of first glucose (I). The important HMBC correlations are shown in figure 3.4.

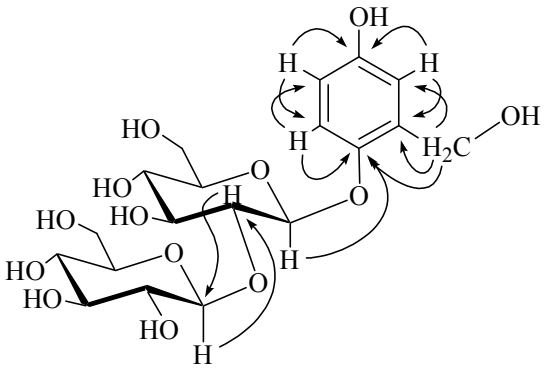


Fig. 3.4. Significant HMBC correlations of Sympocemoside (**22**)

Since only D-glucose is known in nature, therefore the structure of **2** was deduced as 2-(oxymethyl)-4-hydroxyphenyl O-β-D-glucopyranosyl (1→2)-β-D-glucopyranoside.

Table:3.2 ^{13}C- (125 MHz) and ^{1}H-NMR (500 MHz) spectral data of Sympocemoside (**22**) correlated from 1D and 2D-NMR experiments in CD_3OD.

C. No.	Multiplicity (DEPT)	^{13}C-NMR (δ)	^{1}H-NMR (δ)	$^{1}J_{HH}$ (Hz)
1	C	150.3	-	-
2	C	133.9	-	-
3	CH	116.4	6.77	(d, *J* = 3.0)
4	C	154.2	-	-
5	CH	115.8	6.65	(dd, *J* = 3.0, 8.7)
6	CH	119.5	7.06	(d, *J* = 8.7)
7	CH_2	61.1	4.68 4.50	(d, *J* = 13.0) (d, *J* = 13.0)
1′	C	102.6	4.73	(d, *J* = 7.6)
2′	CH	77.9	3.44	(br t, *J* = 7.7)
3′	CH	76.0	3.49	m
4′	CH	72.5	3.42	m
5′	C	77.7	3.85	m
6′	CH	62.6	4.38 4.46	m m
1″	CH	105.3	4.70	(d, *J* = 7.8)
2″	CH	75.2	3.46	(br t, *J* = 7.7)
3″	CH	78.2	3.51	m
4″	CH	72.3	3.41	m
5″	CH	75.9	3.85	m
6″	CH_2	62.4	4.38 4.46	m m

3.1.1.3. Locoracemoside A (23)

Locoracemoside A (**23**) was isolated as an amorphous solid. Its molecular formula $C_{25}H_{30}O_{12}$ was assigned on the basis of HRFABMS which showed a quasimolecular ion $[M+H]^+$ at m/z 523.5049. An intense band at 1719 cm^{-1} in its IR spectrum indicated an ester group.

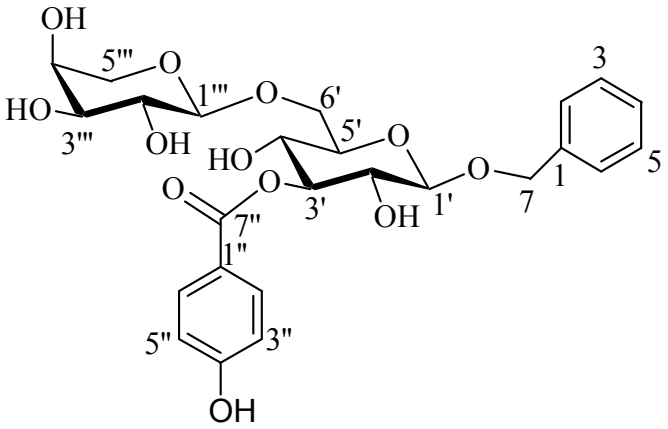


Fig. 3.5. Locoracemoside A (**23**)

The fragments at m/z 121 $[OHC_6H_4CO]^+$ and m/z 93 $[HOC_6H_4]^+$ in the EIMS were accounted for the presence of a hydroxybenzoyl group while the fragments at m/z 91 $[C_6H_5CH_2]^+$ and m/z 77 $[C_6H_5]^+$ could be ascribed for a benzyl moiety in the molecule. The ^{1}H NMR spectrum (Table 3.3) displayed a pair of anomeric resonances due to two sugar units [δ 4.50 (d, J = 8.0, H-1') and 4.39 (d, J = 7.4, H-1''')], a pair of A_2B_2 doublets due to p-hydroxyphenyl [δ 7.88 (2H, J = 8.7, H-2", H-6") and 6.85 (2H, J = 8.7, H-3", H-5")]. Additionally, a set of resonances characteristic for a mono-substituted phenyl [δ 7.41 (2H, distorted d, J = 7.3, H-2, H-6), 7.32 (2H, distorted t, J = 7.3, H-3, H-5), 7.25 (1H, distorted t, J = 7.3, H-4)][19] and two geminally coupled resonances for an isolated methylene [δ 4.87, 4.62 (1H each, both J = 11.8, CH_2-7)]. Out of 25 resonances appeared in its ^{13}C NMR spectrum (Table 3.3), 11 were attributed to a glucopyranosyl and an arabinopyranosyl that are in agreement with the corresponding signals of benzyl α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside [20] and confirmed by the downfield shift of C-6' (δ 67.6) and HMBC correlations of H-1''' with C-6' and CH_2-6' with C-1''' (Fig. 3.5). The HMBC correlations of H-2"/H-6" (δ 7.88) with C-4" (δ 163.5) and C-7" (δ 168.1) and of H-3"/H-5" (δ 6.85) with C-1" (δ 122.4) and C-4" (δ 163.5) supported the presence

of a para-hydroxybenzoyl group. Its position in the molecule was deduced through the downfield shift of C-3' (δ 79.8) and upfield shifts of C-2' (δ 73.5) and C-4' (δ 70.5) as compared to the respective signals of reported benzyl α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside and symponoside[20,21] and confirmed by HMBC correlation of H-3' (δ 5.32) with C-7'' (δ 168.1). The ^{1}H ^{1}H COSY correlations [CH_2-2, H-6 (δ 7.41)/H-3, H-5 (δ 7.32)/H-4 (δ 7.25)] and HMBC correlations [2H-7 (δ 4.87, 4.62)/C-2, C-6 (δ 128.7) and H-2, H-6 (δ 7.41)/C-7 (δ 71.9)] advocated a benzyl group. The position of benzyl unit at C-1' was confirmed by the HMBC correlations of CH_2-7 (δ 4.87, 4.62) with C-1' (δ 103.4) and H-1' (δ 4.50) with C-7 (δ 71.9).

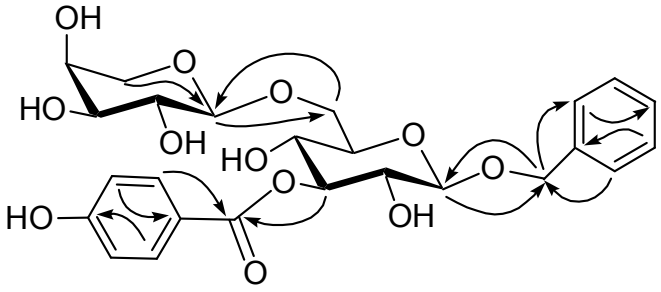


Fig. 3.6. Significant HMBC correlations of Locoracemoside A (**23**)

The sugars obtained after acid hydrolysis were identified as glucopyranose and arabinopyranose by comparing their Rf to those of the standard sugar samples on co-TLC. The absolute configurations of glucose and arabinose were determined as D and L respectively, by GC MS analysis of their acetylated thiazolidine derivatives.[22] Finally, **23** was established as benzyl O-(3'-O-p-salicyloyl-6'-O-α-L-arabinopyranosyl)-β-D-glucopyranoside.

Table:3.3 ^{13}C- (125 MHz) and ^{1}H-NMR (500 MHz) spectral data of Locoracemoside A (**23**) correlated from 1D and 2D-NMR experiments in CD_3OD.

C. No.	Multiplicity (DEPT)	^{13}C-NMR (δ)	^{1}H-NMR (δ)	$^{1}J_{HH}$ (Hz)
1	C	138.9	-	-
2,6	CH	128.7	7.41	(distorted d, J = 7.3)
3,5	CH	129.2	7.32	(distorted t, J = 7.3)
4	CH	129.1	7.25	(distorted t, J = 7.3)
7	CH_2	71.9	4.62 4.87	(d, J = 11.8) (d, J = 11.8)
1′	CH	103.4	4.50	(d, J = 8.0)
2′	CH	73.5	3.39	(br t, J = 8.2)
3′	CH	79.8	5.32	(br t, J = 9.3)
4′	CH	70.5	3.72	(br t, J = 8.6)
5′	CH	75.3	3.61	m
6′	CH_2	67.6	3.85 4.15	(dd, J = 5.6, 11.7) (dd, J = 1.6, 11.7)
1″	C	122.4	-	-
2″	CH	132.9	7.88	(d, J = 8.7)
3″	CH	116.4	6.85	(d, J = 8.7)
4″	C	163.5	-	-
5″	CH	116.4	6.85	(d, J = 8.7)
6″	CH	132.9	7.88	(d, J = 8.7)
7″	C	168.1	-	-
1‴	CH	105.6	4.39	(d, J = 7.4)
2‴	CH	71.6	3.54	(t, J = 8.5)
3‴	CH	73.4	3.68	(dd, J = 9.0, 3.2)
4‴	CH	69.2	3.93	m
5‴	CH_2	66.9	3.64 3.89	(br d, J = 11.9) (dd, J = 11.9, 2.4)

3.1.1.4. Locoracemoside B (24)

Locoracemoside B (**24**) was obtained as an amorphous solid, had a molecular formula, $C_{27}H_{32}O_{14}$ deduced from HRFABMS ($[M+H]^+$ at m/z 581.5398). Its IR spectrum possessed two intense absorption bands at 1731 cm^{-1} and 1720 cm^{-1} for a carboxylic acid and ester groups, respectively.

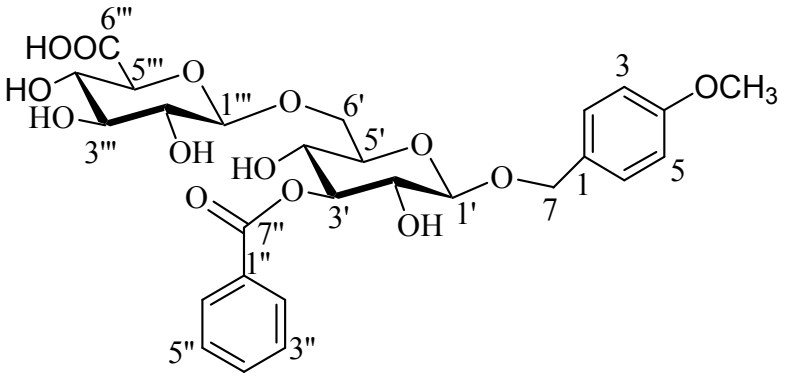


Fig. 3.7. Locoracemoside B (**24**)

The fragments in the EIMS at m/z 121 $[CH_3OC_6H_4CH_2]^+$ and 107 $[CH_3OC_6H_4]^+$ suggested an anisyl moiety while the fragments at m/z 105 $[C_6H_5CO]$ and 77 $[C_6H_5]^+$ clearly showed a benzoyl group in the molecule. When its ^1H and ^{13}C NMR data (Table 3.4) were compared to those of **23**, the resonances for an α-arabinose were missing showing instead for a β-glucuronic acid [δ 104.1 (C-1‴), 74.5 (C-2‴), 78.2 (C-3‴), 72.3 (C-4‴), 75.1 (C-5‴), 173.6 (C-6‴)].[23,24] Additionally, the resonances for a methoxyl were also observed [δ 55.0 (4-OCH_3) and δ 3.61 (3H, s, 4-OCH_3)]. The HMBC correlations of H-1''' with C-6' and CH_2-6' with C-1''' established the terminal position of the β-glucuronic acid which was also supported by a fragment ion at m/z 405 [M + H - glucuronic acid]$^+$ in the FABMS spectra. Similar to **23**, the NMR data of **24** corresponded to a mono-substituted and para-substituted phenyls. But the HMBC correlations of C-7" (δ 167.8) with H-2"/H-6" (8.10, dd, J = 1.4, 7.1) and H-3' (5.31, br t, J = 9.3) and that of C-7 (δ 70.4) with H-2/H-6 (7.45, d, J = 8.5) and H-1' (4.89, d, J = 7.5) revealed the position of benzoate at C-3' and of p-anisyl at C-1'.

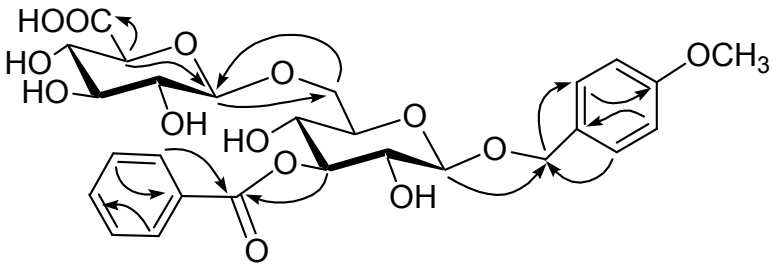


Fig. 3.8. Significant HMBC correlations of Locoracemoside B (**24**)

The D-glucopyranose was identified in a similar manner to that of **23**, whereas, the acetylated thiazolidine derivative of glucuronic acid was not detected in GC MS analysis. Ultimately, **24** was identified as 4-methoxybenzyl O-(3'-O-benzoyl-6'-O-β-glucuronopyranosyl)-β-D-glucopyranoside.

Table:3.4 ^{13}C- (125 MHz) and ^{1}H-NMR (500 MHz) spectral data of Locoracemoside B (**24**) correlated from 1D and 2D-NMR experiments in CD_3OD.

C. No.	Multiplicity (DEPT)	^{13}C-NMR (δ)	^{1}H-NMR (δ)	$^{1}J_{HH}$ (Hz)
1	C	130.6	-	-
2	CH	129.9	7.45	(d, J = 8.5)
3	CH	114.0	6.93	(d, J = 8.5)
4	C	159.5	-	-
5	CH	114.0	6.93	(d, J = 8.5)
6	CH	129.9	7.45	(d, J = 8.5)
7	CH_2	70.4	4.79 5.08	(d, J = 11.6) (d, J = 11.6)
1′	CH	103.5	4.89	(d, J = 7.5)
2′	CH	73.4	3.41	(br t, J = 8.1)
3′	CH	79.7	5.31	(br t, J = 9.3)
4′	CH	70.5	3.73	(br t, J = 8.4)
5′	CH	75.4	3.70	m
6′	CH_2	67.3	3.97 4.46	(dd, J = 7.3, 11.6) (dd, J = 1.8, 11.6)
1″	C	131.5	-	-
2″, 6″	CH	130.7	8.10	(dd, J = 1.4, 7.1)
3″, 5″	CH	129.6	7.51	(br t, J = 7.7)
4″	CH	134.4	7.63	(br t, J = 7.6)
7″	C	167.8	-	-
1‴	CH	104.1	4.74	(d, J = 7.4)
2‴	CH	74.5	3.45	(br t, J = 7.7)
3‴	CH	78.2	3.51	(br t, J = 7.6)
4‴	CH	72.3	3.43	(br t, J = 7.8)
5‴	CH	75.1	4.01	(d, J = 9.2)
6‴	C	173.6	-	-
4 -OCH_3	CH_3	55.0	3.61	s

3.1.1.5. Locoracemoside C (25)

Locoracemoside C (**25**) was purified as an amorphous solid. Its molecular formula $C_{29}H_{38}O_{18}$ was identified by a quasimolecular ion at m/z 675.6099 in HRFABMS.

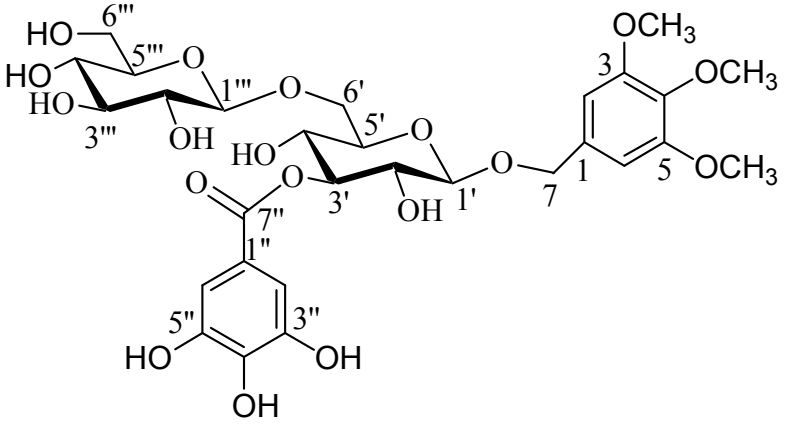


Fig. 3.9. Locoracemoside C (**25**)

The fragments in the EIMS at m/z 181 $[(CH_3O)_3C_6H_2CH_2]^+$ and 153 $[(OH)_3C_6H_2CO]^+$ suggested the presence of a trimethoxybenzyl and a galloyl units in the molecule. Its ^1H NMR spectrum (Table 3.5) exhibited the specific signals for a 3,4,5-trimethoxybenzyl moiety [δ 6.76 (2H, s, H-2, H-6), 4.85, 4.65 (1H each, both d, J = 13.1 each, CH_2-7), 3.84 (6H, s, 3,5-OCH_3), 3.75 (3H, s, 4-OCH_3)],[25] a galloyl group δ 7.14 (2H, s, H-2", H-6")[26] and two β-glucose units [δ 4.45 (1H, d, J = 7.6, H-1'), 4.68 (1H, d, J = 7.8, H-1''')]. The positions of the 3,4,5-trimethoxybenzyl, galloyl and terminal glucose were further confirmed by its long range HMBC correlations (Fig. 3.10). Similar to **1** and **2**, the absolute configuration of glucose was determined to be D. Accordingly, **3** was deduced as 3,4,5-trimethoxybenzyl O-(3'-O-galloyl-6'-O-β-D-glucopyranosyl)-β-D-glucopyranoside.

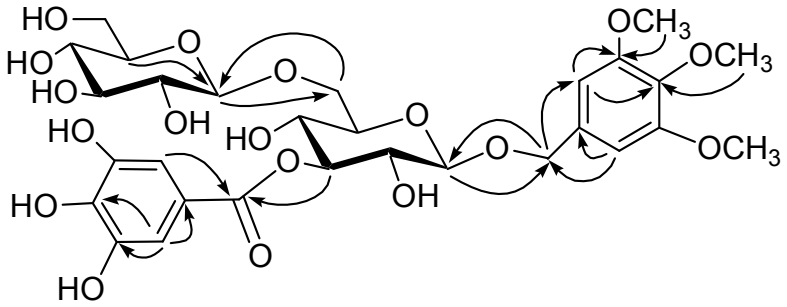


Fig. 3.10. Significant HMBC correlations
of Locoracemoside C (**25**)

Table:3.5 ^{13}C- (125 MHz) and ^{1}H-NMR (500 MHz) spectral data of Locoracemoside C (**25**) correlated from 1D and 2D-NMR experiments in CD_3OD.

C. No.	Multiplicity (DEPT)	^{13}C-NMR (δ)	^{1}H-NMR (δ)	$^{1}J_{HH}$ (Hz)
1	C	134.9	-	-
2	CH	106.2	6.76	s
3	CH	154.2	-	-
4	C	138.1	-	-
5	C	154.2	-	-
6	C	106.2	6.76	s
7	CH_2	71.3	4.65 4.85	(d, J = 13.1) (d, J = 13.1)
1′	CH	103.2	4.45	(d, J = 7.6)
2′	CH	73.5	3.42	(br t, J = 8.2)
3′	CH	79.7	5.33	(br t, J = 9.4)
4′	CH	70.4	3.73	(br t, J = 8.5)
5′	CH	75.5	3.69	m
6′	CH_2	67.5	3.96 4.23	(dd, J = 7.1, 11.5) (dd, J = 1.7, 11.5)
1″	C	121.4	-	-
2″	CH	110.0	7.14	7.14 s
3″	C	146.8	-	-
4″	C	140.1	-	-
5″	C	146.8	-	-
6″	CH	110.0	7.14	s
7″	C	168.3	-	-
1‴	CH	104.3	4.68	(d, J = 7.8)
2‴	CH	74.9	3.44	(br t, J = 7.7)
3‴	CH	78.1	3.50	(br t, J = 7.9)
4‴	CH	72.1	3.40	(br t, J = 7.8)
5‴	CH	77.8	3.69	m
6‴	CH_2	62.6	3.93 4.47	(dd, J = 6.9, 11.7) (dd, J = 1.8, 11.7)
3 -OCH_3	CH_3	56.5	3.84	s
4 -OCH_3	CH_3	58.0	3.75	s
5 -OCH_3	CH_3	56.5	3.84	s

3.1.2. New Source Chemical Constitutent of *Symplocos racemosa*

3.1.2.1 Salirepin (**26**)

Salirepin (**26**) was isolated , for the first time from this species, as a white powder from the *n*-butanol soluble part of the methanolic extract of *Symplocos racemosa* Roxb

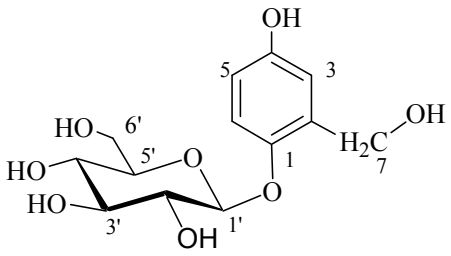


Fig. 3.11. Salirepin (**26**)

The FAB-MS of salirepin (**26**) showed a $[M]^+$ ion peak at *m/z* 302, corresponding with the molecular formula $C_{13}H_{18}O_8$, which indicated 5 degrees of unsaturation. It exhibited a UV absorption band (λ_{max} 285.8 nm) typical of phenolic compounds. The IR absorption bands observed at 3408 (OH), 2921 (C-H), 1665-1443, (C=C, Ar), 1268, 1215 (C-O-C), revealed the presence of hydroxyl groups, methines, aromatic double bonds and ether linkage while the broad (C-O) stretching bands in the region of 1084-1040 cm^{-1} suggested its glycosidic nature. The EI-MS spectrum of **26** exhibited the following characteristic fragments; $[C_6H_3(OH)_2CH_2OH]^+$ (*m/z* 140, 77.6 %), $[C_6H_3(OH)_2CH_2]^+$ (*m/z* 123, 36.5 %), [gentisyl alcohol – H_2O]$^+$ (*m/z* 122, 100 %), which indicated the presence of a gentisyl alcohol moiety in the molecule. In the ^{1}H-NMR spectrum, the usual ABX spin system of the gentisyl alcohol group was readily identified by signals observed at δ 7.07 (1H, d, *J* = 8.7 *Hz*, H-6), 6.78 (1H, d, *J* = 2.9 *Hz*, H-3), and 6.65 (1H, dd, *J* = 8.7, 2.9 *Hz*, H-5). The other signals observed were assignable to a β-D-glucose moiety. The ^{13}C-NMR spectrum and 2D-NMR experiments, confirmed the structure of **26** to be 2-[oxymethyl]-4-hydroxyphenyl-β-D-glucopyranoside.[27]

3.2. Bioactivity of the Chemical Constituents of *Symplocos racemosa*

Enzyme inhibition is an important area of pharmaceutical research since studies in this field have already led to the discovery of wide variety of drugs useful in a number of diseases. Specific inhibitors interact with enzymes and block their activity towards their corresponding natural substrates. The importance of enzyme inhibitors as drugs is enormous since these molecules have been used for treating a number of physiological conditions.[28] Owing to the manifold traditional activities of the plant *Symplocos racemosa*, we screened its constituents for α-chymotrypsin inhibition.

3.2.1. Chymotrypsin Inhibition

In all metazoan species, proteases play a prominent role in a wide array of physiological processes such as food digestion, blood clotting, embryogenesis, tissue reorganization (e.g. wound healing, regeneration, molting, metamorphosis etc.), defense mechanisms and immune responses. Many of these processes are proteolytic cascades, which, once set in action, lead very rapidly and irreversibly to a specific cellular response. Activation and inactivation of protease cascades have to be closely controlled at different regulatory levels being protease gene transcription, Mrna translation, zymogen activation, substrate specificity, enzyme kinetics and by means of enzyme-inhibitors. Most animal species synthesize a variety of protease inhibitors with different specificities, whose function is to prevent unwanted proteolysis. It follows that, -and evidence for this is accumulating-, proteases are involved in various disease states. For instance, the destruction of the extracellular matrix of articular cartilage and bone in arthritic joints is thought to be mediated by excessive proteolitic activity.[29] In emphysema, gingivitis, tumour invasion and inflammatory infections, it is suggested that tissue destruction is caused by proteases.[29] Among the enzymes involved in extracellular matrix degradation, a few serine proteases (elastase, collagenase, cathepsin G, chymotrypsin) are able to solubilize fibrous proteins such as elastin and collagen.[30,31] Given the specific recognition by proteases of defined amino acid sequences, it may be possible to inhibit these enzymes when they are involved in pathological processes. Potent inhibitors have the potential to be developed as new therapeutic agents. In vertebrates, serine protease inhibitors have

been studied for many years and they are known to be involved in phagocytosis, coagulation, complement activation, fibrinolysis, blood pressure regulation, etc. In the last decade, it became obvious that in invertebrates, serine proteases and their inhibitors are also involved in parallel physiological processes (e.g. blood clotting cascade in Limulus[32] and the innate immune response.[33] Moreover, some of the protease inhibitors isolated from invertebrate sources are quite specific towards individual mammalian serine proteases. This also offers huge opportunities for medicine. Thus, the development of non-toxic protease inhibitors extracted from natural sources for in vivo application may be quite important.[29] In the future, it is likely that numerous specific protease inhibitors will be tested clinically for the treatment of human disease such like emphysema, inflammation, dermitis and cancer. Since the current serine protease (like α-chymotrypsin) inhibitors are still far from perfection, the interests and efforts in the discovery of novel serine protease inhibitors are expected to continue in future. Locoracemosides A, B and C, three benzylated glycosides, isolated from the bark of the stem of *Symplocos racemosa*, displayed in vitro inhibitory potential against α-chymotrypsin enzyme. Their IC_{50} values are shown in table 3.6.

Table 3.6: In vitro inhibition of chymotrypsin by **23**-**25**

S.No.	Name of substance	IC50 ± SEM[a] (μM)
1	Locoracemoside A (**23**)	437.81 ± 2.11
2	Locoracemoside B (**24**)	11.95 ± 1.85
3	Locoracemoside C (**25**)	6.04 ± 0.31
4	Chymostatin (Standard)	7.21 ± 2.31

[a)] Standard mean error of 3-5 assays

3.2.2. Structure Activity Relationship

In continuation of our ongoing work on the chymotrypsin inhibition by natural products, we now describe the in vitro inhibitory activities of these three new benzylated glycosides (**23**-**25**) against this enzyme To the best of our knowledge such benzylated glycosides have rarely been reported as chymotrypsin inhibitors in the literature. As far as structure-activity relationship is concerned, the variations in the sugar core and benzoyl residues do not seem to be so much effectual but the good inhibitory potential of **24** as compared to **23** relative to chymostain (standard) can be attributed to the presence of a methoxy group on the benzyl moiety and in a similar way the substitution of three methoxy groups on the benzyl moiety in **25** further enhanced its inhibitory potential against this enzyme

Experimental

4. General

All chemical and instrumental analyses were performed at, H. E .J. Research Institute of Chemistry, University of Karachi, Pakistan. The commercially available solvents were distillated and used for thin layer and column chromatographic techniques. For column chromatography (CC), silica gel (70-230 mesh) and for flash chromatography (FC), silica gel (230-400 mesh) was used. TLC was performed on pre-coated silica gel G-25-UV_{254} plates. Detection was carried out at 254 nm, and by ceric sulphate or aniline phthalate reagent. For recycling HPLC (LC 908 W), a semi preparative (ODS-M80) was used. Purity of compounds was checked by TLC with different solvent systems using methanol, acetone, chloroform and hexane giving single spot. The optical rotations were measured on a Jasco-DIP-360 digital polarimeter. The UV and IR spectra were recorded on Hitachi-UV-3200 and Jasco-320-A spectrophotometer, respectively. GC was performed on Shimadzu 9-A, column 25 % Carbowax 20M on Chromosorb W 80/100 mesh, 145 ^{0}, FI detector. ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC and HMBC Spectra were run on Bruker spectrometers. The chemical shifts are given in δ in ppm and coupling constants in *Hz*. EI-MS and FAB–MS spectra were recorded on a JMS-HX-110 spectrometer, with a data system.

4.1. Spray Reagents

Ceric sulphate reagent was used for the detection of compounds and aniline phthalate reagent for sugar's detection.

4.1.1 Ceric Sulphate

Ceric sulphate (0.1 g) and trichloroacetic acid (1 g) were dissolved in 4 ml distilled water. The solution was boiled and conc. H_2SO_4 was added drop-wise until the disappearance of turbidity.

4.1.2 Aniline Phthalate

Aniline (0.93 g) and *o*-phthalic acid (1.66 g) were dissolved in 100 ml *n*-butanol saturated with H_2O.

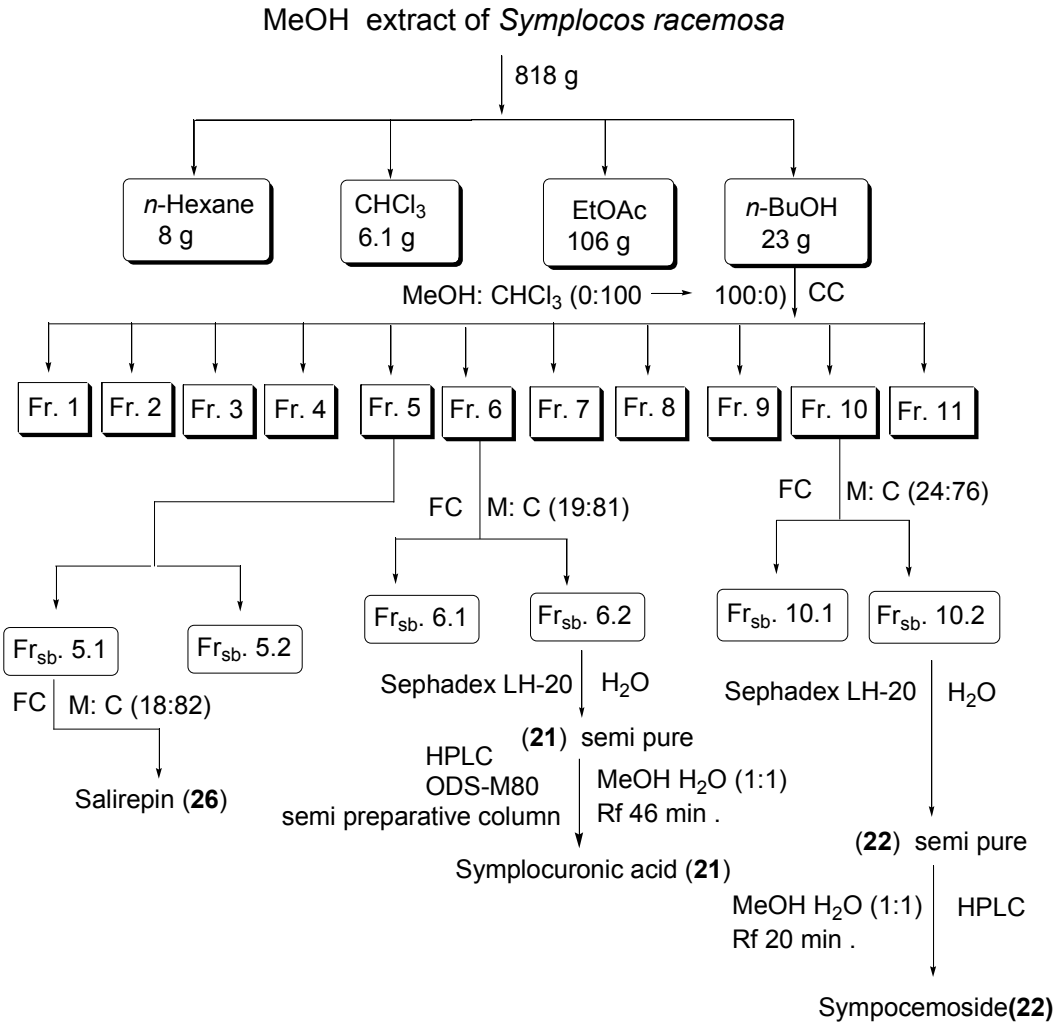
4.2 *Symplocos racemosa* Roxb.

4.2.1 Plant Material

The plant *Symplocos racemosa* (Symplocaceae) was collected from Abbottabad, Pakistan, and identified by Dr. Manzoor Ahmed (Taxonomist) at the Department of Botany, Post-Graduate College, Abbottabad, Pakistan, a voucher specimen (no. 6453) has been deposited.

4.2.2. Extraction and Purification.

The shade-dried ground bark (30 kg) was exhaustively extracted with methanol at room temperature. The extract was evaporated to yield a residue (818 g), which was dissolved in water and partitioned with hexane, chloroform, ethyl acetate and *n*-butanol successively. The *n*-butanol extract (23 g) was subjected to column chromatography over silica gel using $CHCl_3$ with gradient of methanol up to 100 %. Eleven fractions (Fr. 1-11) were collected. The fraction 5 was submitted to repeated FC (230-400 mesh) and eluted with MeOH: $CHCl_3$ (18:82) to get purified **26** (42.5 mg). The fraction 6 was loaded on flash silica gel and eluted with MeOH: $CHCl_3$ (19:81) to get two sub-fractions ($Fr_{sb.}$ 6.1 and $Fr_{sb.}$6.2). The $fraction_{sb.}$6.2 was then submitted to Sephadex LH-20 and eluted with pure water and the resulting impure **21** was finally purified on recycling HPLC [ODS-M80 semi preparative column, MeOH H_2O (1:1), flow rate (4 ml/ min), detection (UV and RI detectors), Rf 46 min (**21**, 12.9 mg)]. Similarly, the fraction 10 was subjected to FC and eluted with MeOH: $CHCl_3$ (24:76) to get two sub-fractions ($Fr_{sb.}$ 10.1 and $Fr_{sb.}$10.2). The $fraction_{sb.}$10.2 was then passed through Sephadex LH-20 and eluted with pure water and the resulting impure **22** was finally purified on recycling HPLC using a reverse phase semi preparative (M-80), eluting at a flow rate of 4 ml/ min. under isocratic conditions with MeOH: H_2O (1: 1) and the peak obtained at a retention time of 20 min. yielded the purified **22** (14.1 mg).

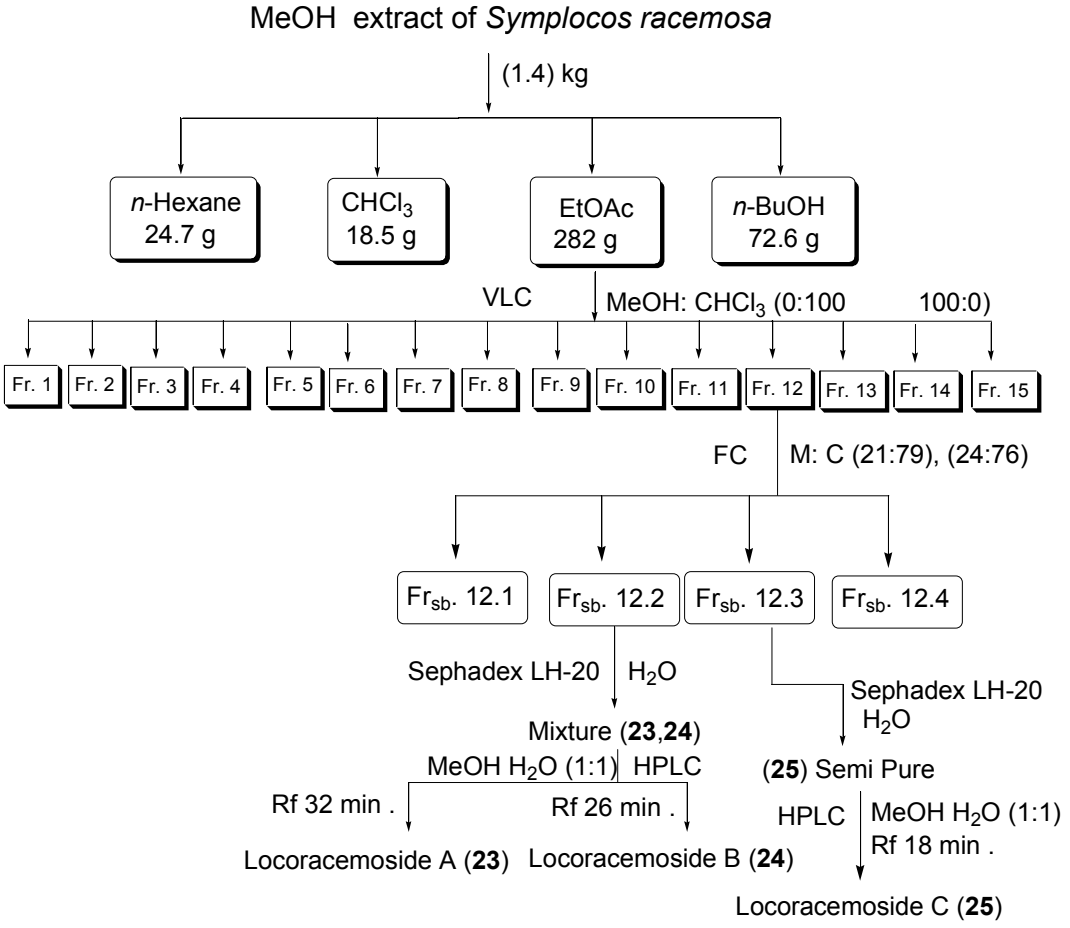


(Scheme 4.1): Extraction and isolation scheme of *Symplocos racemosa*

M = Methanol	Fr. = Fraction	FC=Flash chromatography
C = Chloroform	$Fr_{sb.}$ = Sub-fraction	

To get some minor constituents, the bark of the plant was collected again and in bulk quantity and the shade-dried ground bark of stem (40 kg) was exhaustively extracted with methanol (4 × 50 l × 48 h) at room temperature. The extract was evaporated to yield a residue (1.4 kg), which was dissolved in water (2.5 l) and partitioned with n-hexane, chloroform, ethyl acetate and n-butanol (each 3 l × 4). The n-butanol solubles (150 g) was subjected to VLC over silica gel using $CHCl_3$-MeOH gradient up to 100% methanol to obtain fifteen fractions (1-15). Fr. 12 was subjected to silica gel CC using MeOH $CHCl_3$ (21:79 and 24:76) followed by CC over Sephadex LH-20 with pure water to get

semi pure **23**-**25** which were finally purified on recycling HPLC [ODS-M80 semi preparative column, MeOH H_2O (1:1), flow rate (4 ml/ min), detection (UV and RI detectors), Rf 18 min (**25**, 11.1 mg), 26 min (**24**, 10.2 mg) and 32 min (**23**, 11.5 mg)].



(Scheme 4.2): Extraction and isolation (re-investigation)of *Symplocos racemosa*

4.3. Characterization of Compounds

4.3.1. Characterization of Symplocuronic acid (21) (=2-[(Benzoyloxy)methyl]-4-hydroxyphenyl O-β-D-glucuronopyranosyl (1→6)-β-D-glucopyranoside; **21**). Amorphous powder (12.9 mg): $C_{26}H_{30}O_{15}$; $[\alpha]^{23}_{D}$ + 16.66 (*c* = 0.028, MeOH); UV λ_{max} nm (log ε) (MeOH): 389.4 (2.81), 366 (2. 45), 343.2 (2.73), 339 (2.52), 284 (3.44), 256.6 (3.04), 227.4 (3.98), 212 (3.72), 199.8 (4.39) nm; IR ν_{max} (KBr): 3364-3025 br. (OH), 2928 (C-H), 1733 (C=O, acid), 1720 (C=O, ester), 1501-1453 (C=C, Ar), 1280 (C-O-C), 1071 (C-O), 894, 807, 715, 659 cm^{-1}; ^{1}H and ^{13}C NMR: Table 3.1; HRFAB-MS (+): *m/z* 583.5089 $[M+H]^+$ (calcd.for $C_{26}H_{31}O_{15}$, 583.5073) FAB MS (Positive mode) *m/z* 583 $[M+H]^+$, *m/z* 407 [M – glucuronic acid]$^+$, *m/z* 245 [M – glucuronic acid - glucose]$^+$.; FAB MS (Negative mode) *m/z* 581 $[M-H]^-$, *m/z* 405 [M – glucuronic acid]$^-$, *m/z* 243 [M – glucuronic acid - glucose]$^-$; EIMS: *m/z* (rel. int.): 244 [M – glucuronic acid - glucose]$^+$ (46.1), 140 $[C_6H_3(OH)_2CH_2OH]^+$ (32.3), 123 $[C_6H_3(OH)_2CH_2]^+$ (41.7), 122 $[C_6H_5COOH]$ (70.8), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (61.3).

4.3.2. Characterization of Sympocemoside (22) (= 2-(Oxymethyl)-4-hydroxyphenyl-*O*-β-D-glucopyranosyl (1→2)-β-D-glucopyranoside; **22**). Amorphous powder (14.1 mg): $C_{19}H_{28}O_{13}$; $[\alpha]^{23}_{D}$ - 57.89 (*c* = 0.038, MeOH); UV λ_{max} nm (log ε) (MeOH): 282 (3.51), 260 (3.25) nm; IR ν_{max} (KBr): 3357 br. (OH), 2932 (C-H), 1595-1416 (C=C, Ar), 1266, 1215 (C-O-C), 1115-1040 (C-O), 862, 663 cm^{-1}; ^{1}H and ^{13}C NMR: Table 3.2; HRFAB MS (+): *m/z* 465.4197 $[M+H]^+$ (calcd. for $C_{19}H_{29}O_{13}$) 465.4185; FAB MS (Positive mode): *m/z* 465 $[M+H]^+$, *m/z* 303 [M – glucose]$^+$, *m/z* 141 [M – glucose - glucose]$^+$; FAB MS (Negative ion mode): *m/z* 463 $[M-H]^-$, *m/z* 301 [M – glucose]$^-$, *m/z* 139 [M – glucose - glucose]$^-$; EIMS: *m/z* (rel. int.): 140 $[C_6H_3(OH)_2CH_2OH]^+$ (88.1), 123 $[C_6H_3(OH)_2CH_2]^+$ (65.9), 122 $[C_6H_3(OH)_2CH_2OH - H_2O]^+$ (100).

Acid hydrolysis of 21 - 22

A solution of (**21-22** separately) (8 mg) in MeOH (5 ml) containing 2 N HCl (4 ml) was refluxed for 4h, concentrated under reduced pressure, and diluted with H_2O (8ml). It was extracted with EtOAc and the residue recovered from the organic phase was found to be an inseparable mixture of products. The aqueous phase was neutralized with Ag_2CO_3,

filtered and evaporated *in vacuo*. The residue obtained showed the presence of glucose and glucuronic acid in **21** while only glucose in **22**, when compared with the authentic samples of these sugars on TLC (EtOAc: MeOH: AcOH: H_2O :: 11: 2: 2: 2) *via* visualizing the spots with aniline phthalate reagent.

4.3.3. Characterization of Locoracemoside A (**23**) [benzyl-α-L-arabinopyranosyl-(1→6)-β-D-glucopyranoside 3-(4-hydroxybenzoate)]*;* **23**. Amorphous solid (11.5 mg); $[\alpha]^{23}_{D}$ = + 21.1 (MeOH, *c* = 0.01) ; UV 280.3 (2.87), 253.6 (3.12), 232.1 (3.59), 224.9 (2.92); IR 3640-3139 (OH), 2965-2874 (CH), 1719 (C=O, ester), 1645, 1571, 1503 (C=C, Ar), 1283-1267 (C–O–C), 1102, 1056 (C–O); ^{1}H and ^{13}C NMR: Table 3.3; HR-FABMS (+) *m/z* 523.5049 (calcd. for $C_{25}H_{30}O_{12}$; 523.4982); FAB-MS (+) *m/z* 523 $[M+H]^+$, 391 [M-arabinose]$^+$; FAB-MS (–) 521 $[M-H]^-$, 389 [M-arabinose]$^-$; EI-MS *m/z* 138 $[HOC_6H_4COOH]^+$ (33.5), 121 $[HOC_6H_4CO]^+$ (100), 93 $[HOC_6H_4]^+$ (45.1), 91 $[C_6H_5CH_2]^+$ (65.9), 77 $[C_6H_5]^+$ (54.8).

4.3.4. **Characterization of Locoracemoside B (24)** [p-anisyl-β-D-glucuronopyranosyl-(1→6)-β-D-glucopyranoside 3-benzoate]; **24**]. Amorphous solid (10.2 mg); $[\alpha]^{23}_{D}$ = + 17.6 (MeOH, *c* = 0.01) ; UV 282.1 (2.94), 255.3 (3.23), 232.8 (3.28), 222.6 (2.78); IR 3636-3132 (OH), 2969-2870 (CH), 1731 (C=O, acid), 1720 (C=O, ester), 1648, 1575, 1509 (C=C, Ar), 1285-1263 (C–O–C), 1111, 1066 (C–O); ^{1}H and ^{13}C NMR: Table 3.4; HR-FABMS (+) *m/z* 581.5398 (calcd. for $C_{27}H_{32}O_{14}$; 581.5351); FAB-MS (+) *m/z* 581 $[M+H]^+$, 405 [M-glucuronic acid]$^+$; FAB-MS (–) *m/z* 579 $[M-H]^-$, 403 [M-glucuronic acid]$^-$; EI-MS *m/z* 122 $[C_6H_5COOH]^+$ (41.6), 121 $[CH_3OC_6H_4CH_2]^+$ (70.5), 107 $[CH_3OC_6H_4]^+$ (78.9), 105 $[C_6H_5CO]^+$ (100), 77 $[C_6H_5]^+$ (64.1).

4.3.5. Characterization of Locoracemoside C (25) [3,4,5-trimethoxybenzyl-β-D-glucopyranosyl-(1'''→6')-β-D-glucopyr-anoside 3-galloate; **25**]; $[\alpha]^{23}_{D}$ = + 19.4 (MeOH, *c* = 0.01); UV 275.4 (3.11), 251.8 (3.21), 230 (2.99), 227.5 (3.98), 215.3 (3.01); IR 3638-3052 (OH), 2970-2875 (CH), 1725 (C=O, ester), 1650, 1576, 1506 (C=C, Ar), 1288-1265 (C–O–C), 1108, 1070 (C–O); ^{1}H and ^{13}C NMR: Table 3.5; HR-FABMS (+)

m/z 675.6099 (calcd. for $C_{29}H_{38}O_{18}$; 675.6013); FAB-MS (+) *m/z* 675 $[M+H]^+$, 513 [M-glucose]$^+$; FAB-MS (–) *m/z* 673 $[M-H]^-$, 511 [M-glucose]$^-$; EI-MS *m/z* 181 $[(CH_3O)_3C_6H_2CH_2]^+$ (69.9), 170 $[(OH)_3C_6H_2COOH]^+$ (45.2), 167 $[(CH_3O)_3C_6H_2]^+$ (80.7), 153 $[(OH)_3C_6H_2CO]^+$ (100), 125 $[(OH)_3C_6H_2]^+$ (78.1).

Identification of sugars.(**23-25**)

The sugars obtained on usual acid hydrolysis of **23-25** (3 mg each) were identified as arabinose and glucose in **23**, glucose and glucuronic acid in **24** and glucose in **25** on silica gel co-TLC with the standards (Sigma-Aldrich) [EtOAc MeOH AcOH H_2O (11:2:2:2), detection (aniline phthalate reagent)]. The acetylated thiazolidine derivatives, formed with L-cysteine methyl ester hydrochloride (0.06mol/L), of the hydrolyzed sugars were prepared[22] as described by Ye and Zao (2002) and subjected to GC MS analysis [Conditions: Column (OV-17 column, 2 m × 3.1 mm), carrier gas (He, 50 ml/min), injection temperature (270 °C), detection temperature (280 °C), column temperature (170 °C to 210 °C at a rate 10 °C/min). The configurations were determined by comparing their retention times (t_R L-arabinose 6.2 min, t_R D-glucose 9.4 min) with acetylated thiazolidine derivatives prepared in a similar way from standard sugars (Sigma-Aldrich). The acetylated thiazolidine derivative of glucuronic acid was not detected in GC MS analysis.

4.3.6. Characterization of Salirepin (26) (= 2-(Oxymethyl)-4-hydroxyphenyl-β-D-glucopyranoside; **26**). White powder (42.5 mg): $C_{13}H_{18}O_8$; $[\alpha]^{23}_D$ – 45.1 (*c* = 0.0368, MeOH); UV λ_{max} nm (log ε) (MeOH): 285.8 (2.92), 251.2 (2.30), 225.6 (3.36) nm; IR ν_{max} (KBr): 3408 (OH), 2921 (C-H), 1665-1443, (C=C, Ar), 1268, 1215 (C-O-C), 1084, 1040 (C-O) 992, 671 cm^{-1}; ^{1}H-NMR (CD_3OD) (400 MHz) (δ ppm): 7.07 (1H, d, *J* = 8.7 *Hz*, H-6), 6.78 (1H, d, *J* = 2.9 *Hz*, H-3), 6.65 (1H, dd, *J* = 8.7, 2.9 *Hz*, H-5), 4.69 (1H, d, *J* = 13.0 *Hz*, H_β-7), 4.67 (1H, d, *J* = 6.9 *Hz*, H-1'), 4.51 (1H, d, *J* = 13.0 *Hz*, H_α-7), 3.88 (1H, dd, *J* = 11.8, 2.8 *Hz*, H_β-6'), 3.68 (1H, dd, *J* = 11.8, 7.2 *Hz*, H_α-6'), 3.46 (1H, m, H-5'), 3.43 (1H, t, *J* = 8.8 *Hz*, H-2'), 3.40 (1H, t, *J* = 8.6 *Hz*, H-3'), 3.35 (1H, t, *J* = 8.3 *Hz*, H-4'); ^{13}C-NMR (CD_3OD) (100 MHz) (δ ppm): 154.0 (C-4), 150.2 (C-1), 133.8 (C-2), 119.5 (C-6), 116.4 (C-3), 115.8 (C-5), 104.7 (C-1'), 78.1 (C-3'), 78.0 (C-5'), 75.1 (C-2'), 71.4 (C-4'), 62.6 (C-6'), 61.0 (C-7); FAB MS (Positive mode): *m/z* 303 $[M+H]^+$; FAB

MS (Negative mode): *m/z* 301 $[M-H]^-$; EIMS: *m/z* (rel. int.): 140 $[C_6H_3(OH)_2CH_2OH]^+$ (77.6), 123 $[C_6H_3(OH)_2CH_2]^+$ (36.5), 122 $[C_6H_3(OH)_2CH_2OH - H_2O]^+$ (100).

4.4. *In vitro* chymotrypsin assay.

The chymotrypsin inhibitory activity of the compounds was performed by the method of Cannell et al.[34] Chymotrypsin (9 units/ ml of 50 mM Tris-HCl buffer pH 7.6; Sigma Chemical Co. USA) was preincubated with the compounds for 20 min at 25 ^{0}C. 100 µL of substrate solution (N-succinyl-phenylalanine-p-nitroanilide 1 mg/ml of 50 mM Tris-HCl buffer pH 7.6) were added to start the enzyme reaction. The absorbance of released p-nitroaniline was continuously monitored at 410 nm until a significant color change had achieved. The final DMSO concentration in the reaction mixture was 7 %. The percentage (%) inhibition was calculated as follows (E – S)/ E x 100, where E is the activity of the enzyme without test compound and S is the activity of enzyme with test compound. The concentrations of test compounds that inhibited the hydrolysis of substrate up to 50 % (IC_{50}) were determined by monitoring the effect of various concentrations of these compounds in the assays on the inhibition values. The IC_{50} value was then calculated using the EZ-Fit Enzyme Kinetics program (Perrella Scientific Inc., Amherst, USA).

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Abstract

Teil A: Die Cyclisierung der Dianionen von 3-Ketosulfonen und von Cyanoaceton mit 1-Brom-2-chlorethan liefert 2-Alkylidentetrahydrofurane, die durch Umsetzung mit BBr_3 in funktionalisierte Ketosulfone und Ketonitrile überführt wurden. Diarylsulfide, Diarylether und Biaryle wurden basierend auf [3+3] Cyclisierungen von 1,3-Bis(silylenolethern) effizient hergestellt. Das präparative Potential einer neuen Methode zur Synthese von 1-Azaxanthonen wurde ausgebaut und eine Vielzahl neuer Verbindungen wurde auf effiziente Weise hergestellt. Weiterhin wurde eine neue Cyclisierungsreaktion von 3-Thiophenoxy-1,3-dienen mit 1,1-Diacylcyclopropanen entwickelt, die einen einfachen Zugang zu Diarylsulfiden ermöglicht. Teil B: Eine Reihe neuer Naturstoffe wurden aus *Symplocos racemosa* Roxb. und spektroskopisch charakterisiert.

Part A: The cyclization of the dianions of 3-ketosulfones and cynotacetone with 1-bromo-2-chloroethane gives 2-alkylidenetetrahydrofuran which afforded functionalized ketosulfones and ketonitrile after BBr_3-mediated cleavage. Diarlysulfides, diaryl ethers and biaryls were synthesized based on [3+3] cyclizations of 1,3-bis(silyl enol ethers) in an efficient way. The preparative scope of the new method for the synthesis of of 1-azaxanthones was expanded and a variety of new compounds were prepared in an efficient way. Furthermore, a new cyclization reaction of 3-thiophenoxy-1,3-diene with 1,1-diacylcyclopropanes was developed which provides a convenient approach to diarylsulfides containing a remote halide function. Part B: A number of new natural products were isolated from *Symplocos racemosa* Roxb and characterized by using various sophisticated spectroscopic techniques.

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Abstracts in Conferences:

1- **Muhammad Abid Rashid**, M. A. Abbasi, N. Rasool, M. Zubair and V. U. Ahmad, "New Salirepin Derivatives from *Symplocos racemosa'* , 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-158), Abstracts, page 266.

2- V. U. Ahmad, N. Rassol, M. A. Abbasi, **Muhammad Abid.Rashid**, F. Kousar, M. Zubair, A. Ejaz, M. I. Choudhary and R. B. Tareen, "Antioxidant Flavonoids from *Pulicaria undulate*" ., 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-161), Abstracts, page 269.

3- N. Shahzad, M. A. Abbasi, **Muhammad Abid.Rashid,** M. Zubair, N. Rassol, Z. Hassan, Aman Ullah, A.Zahoor, H. siddiqui, M. I. Choudhary and V. U. Ahmad, "Antioxidant and α Chymotrypsin Inhibiting Flavonoids from *Clematis orientalis"* 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-179), Abstracts, page 286.

4- Z. Fatima, A.Zahoor, M. A. Lodhi, **Muhammad Abid.Rashid,** M. Zubair, M. Qaisar, V. U. Ahmad and , M. I. Choudhary "Ethnobotanical , Biochemical and Chemical studies of *Enicostema hyssopifolium* (Willd) Verdoon of Gentianaceae from Tharparkar" 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-055), Abstracts, page 161.

Research Publications:

1- **Muhammad A. Rashid**, Nasir Rasool, Muhammad Adeel, Christine Fischer, Helmut Reinke, Peter Langer* *Tetrahedron* **2008**, 64, 529-535."Regioselective Synthesis of Diaryl Ethers based on One-Pot Cyclizations of 4-Aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes"

2- Nasir Rasool, **Muhammad A. Rashid,** Helmut Reinke, Christine Fischer, Peter Langer*. *Tetrahedron* **2008**, in press ."Synthesis and Reactions of Functionalized Spirocyclo-propanes by Cyclization of Dilithiated β-Ketosulfones and α-Cyanoacetone with 1,1-Diacetylcyclopropane".

3- Nasir Rasool, **Muhammad A. Rashid**, Helmut Reinke, Christine Fischer, Peter Langer*, *Tetrahedron* **2007**, (63) 11626 - 11635. "Regioselective Synthesis of ω-Bromo-3-ketosulfones, ω-Bromo-3-ketonitriles, and 2-(ω-Bromoalkyl)benzofurans based on a 'Ring-Closing / Ring-Opening' Strategy".

4- Nasir Rasool, Viqar U. Ahmad[*], Naseem Shahzad, **Muhammad A. Rashid**, Aman Ullah, Zahid Hassan[a], Muhammad Zubair[a] and Rasool B. Tareen *Natural product communications* **2008,** in press "New ent–kaurane type diterpene glycoside pulicaorside-B"

5- **Muhammad A. Rashid**, Helmut Reinke, and Peter Langer* *Tetrahedron letter* **2007,** (48) 2321-2323. "Regioselective Synthesis of Diaryl Sulfides by [3+3] Cyclizations of 1,3-Bis(Silyl Enol Ethers)"

6- Muhammad Sher, Zafar Ahmed**, Muhammad A. Rashid**, Christine Fischer, Anke Spannenberg and Peter Langer* *Tetrahedron **2007**,* (63) 4929- 4936 "Synthesis of Diaryl Ethers based on One-Pot [3 + 3] Cyclizations of 1,3-Bis(Silyl Enol Ethers)"

7- Muhammad Sher, T.H.Tam Dang, Zafar Ahmed, **Muhammad A. Rashid**, Christine Fischer, Peter Langer* *J. Org. Chem*. **2007**, (72) 6284- 6286 "First Catalytic [3+3] Cyclizations of 1,3-Bis(Silyl Enol Ethers)".

8- V. U. Ahmad*, **Muhammad Abid Rashid**, M. A. Abbasi, N. Rasool, M. Zubair; *J. Asian Nat. Prod. Res*. **2007**, 9 (3), 209-215. "New Salirepin Derivatives from Symplocos racemosa''

9- V.U. Ahmad*, Muhammad Zubair, M. A. Abbasi, F Kousar, **Muhammad Abid Rashid**, N Rasool and R. B. Tareen; *Nat. Prod. Res.* **2006,** 20(1), 69-74. "New Ceramides from Platytaenia multicaule"

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Karapetyan, Satenik Mkrtchyan, Helmut Reinke, Christine Fischer, and Peter Langer* *Tetrahedron* **2008,** submitted "Synthesis of 1-Azaxanthones by Condensation of 1,3- Bis (trimethy lsilyloxy) -1,3-butadieneswith-(Cyano)-benzopyryliumTriflates and Subsequent Domino ′Retro-Michael/Nitrile-Addition Heterocyclization"

18- Muhammad Adeel, **Muhammad A. Rashid**, Nasir Rasool, Rasheed Ahmad, Helmut Reinke, Christine Fischer, and Peter Langer* *Eur. J.O.C.* **2008,** submitted "Regioselective Synthesis of Functionalized Biaryls based on Cyclizations of 4-Aryl-1,3-bis(trimethyl-silyloxy)-1,3-butadienes."

19- Nasir Rasool, **Muhammad A. Rashid**, Muhammad Adeel, and Peter Langer* **2008,** *Tetrahedron Lett.* submitted "Synthesis and Reactions of Hydroxyspiro[5.2]cyclo-octenones based on the Cyclization of the Dianions of Acetone and Diethyl 2-Oxopropylphosphonate with 1,1-Diacylcyclopropanes"

20- Nasir Rasool, **Muhammad A. Rashid**, Inam Iqbal, Muhammad Imran and Peter Langer* *Tetrahedron* **2008,** submitted "Regioselective Synthesis of Functionalized 2-Thio-phenoxy-benzoates and Thioxanthones by Formal [3+3] Cyclizations of 1-Trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 3-Silyloxy-2-en-1-ones"

21- **Muhammad A. Rashid,** Nasir Rasool, Inam Iqbal, Muhammad Imran and Peter Langer* *Manuscript in preparation*. "Regioselective Synthesis of Functionalized 2-Thio-phenoxybenzoates by Domino ′[3+3] Cyclization / Homo-Michael′ Reactions of 1-Trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 1,1-Diacylcyclopropanes"

Declaration/Erklärung

Here by I declare that this work has so for neither submitted to the Faculty of Mathematics and Natural Sciences at the University of Rostock nor to any other scientific Institution for the purpose of doctorate. Further more, I declare that I have written this work by myself and that I have not used any other sources, other than mentioned earlier in this work.

Hiermit erkläre ich, daß diese Arbeit bisher von mir weder an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock noch einer anderen wissenschaftlichen Einrichtung zum Zwecke der Promotion

Eingereicht wurde.

Ferner erkläre ich, dass ich diese Arbeit selbständig verfasst und keine anderen als die darin angegebenen Hilfsmittel benutzt habe

I hereby apply irrevocably to take oral examination if the form of a private viva voce and a public presentation.

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Muhammad Abid Rashid