Synthesis of Pharmacologically Relevant Arenes by [3+3] Cyclizations And Phytochemical Investigation of *pulicaria undulata*

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2. Gutachter : ....

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Dedicated to my Father, Mother, sister, brother in laws, Midhat and Riyan"

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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
NEt3	Triethylamine
NMR	Nuclear Magnetic Resolution
HMQC	Heteronuclear Multiple Quantum Coherence
HMBC	Heteronuclear Multiple Bond Correlation
COSY	Correlated Spectroscopy
NOESY	Nuclear Overhause and Exchange Spectroscopy
Me3SiOTf	Trimethylsilyl trifluoro methanesulfonate
Me3SiCl	Trimethylsilylchloride
mp.	Melting point
RCM	Ring Closing Metathesis
TBAI	Tetrabutyl amonium iodie
TFA	Trifluoroacetic acid
Tf2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofurane
TLC	Thin Layer Chromatography
TMS	Trimethylsilane
UV	Ultraviolet spectroscop

Summary

Dissertation can be summarized as following.

1. Chapter 1 deals with the cyclization of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1, 1-diacetylcyclopropane. These reactions afford 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones which were transformed, by reaction with tetrabutylammonium halides, into functionalized phenols.

2. Chapter 2 includes the cyclization of the dianions of diethyl 2-oxopropylphosphonate and of acetone with 1, 1-diacylopropanes. These reactions afforded hydroxyspiro[5.2]cyclooctenones which were transformed, by homo-Michael reactions with tetrabutylammonium halides, into various functionalized phenols or their dimmers.

3. In chapter 3 we have described the chemo- and regioselective synthesis of ω-bromo-3-ketosulfones, ω-bromo-3-ketonitriles and various functionalized 2-(ω-bromoalkyl)benzofurans by application of a ′ring-closing/ring-opening′ strategy. The cyclization of 3-ketosulfone and 3-ketonitrile dianions with 1-bromo-2-chloroethane or 1,4-dibromobut-2-ene afforded functionalized 2-alkylidenetetrahydrofurans which were subsequently cleaved by reaction with boron tribromide or boron trichloride.

4. In chapter 4 we have reported sterically encumbered diaryl ethers which are prepared based on formal [3+3] cyclizations of novel 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes.

5. In chapter 5 we have studied fuctionalized 1-azaxanthones (5-oxo-5*H*-[1]-benzopyrano[2,3-*b*]pyridines) which were prepared by TMSOTf-mediated reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with cyanochromones and subsequent base-mediated domino retro-Michael / nitrile-addition / heterocyclization reactions.

6. In chapter 6 we have reported sterically encumbered biaryls which are regioselectively prepared based on formal [3+3] cyclizations of novel 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-dienes.

7. Chapter 7 deals with the regioselective synthesis of functionalized thiophenoxybenzoates by domino [3+3] cycllization / homo Michael reactions of 1-trimethylsilyloxy-3-thiophenoxy-1, 3-butadienes with 1,1-diacylcyclopropanes.

8. In chapter 8 we studied the synthesis of various tetraarylthiophenes based on Suzuki reactions of tetrabromothiophene.

9. In chapters 9 to 12 our studies were focused on the isolation and characterization of new chemical constituents from *Pulicaria undulata.* During these studies we have isolated and structurally elucidated different chemical constituents that belong to flavonoid and *ent*-kaurane-type diterpenes, to two new flavonoid glycosides, pulicaroside, undulatoside and one new flavonoid undulol. In addition, four known flavonones – one new *ent*-kaurane-type diterpene glycoside, pulicaroside-B together with three known compounds paniculosides-IV, roseoside and corchionol C which are derivatives of α-ionol – were isolated. The structures of the new and known compounds were elucidated by 1D- and 2D-NMR techniques, along with other spectral evidences and comparison of the spectral data with those of closely related compounds. All the flavonoids (**1-6**) that are discussed in chapter 11 exibited superoxide anion scavenging activity.

PART- A

Synthesis of Pharmacologically Relevant Arenes by [3+3] Cyclizations

General Introduction

Methods in Organic Synthesis are an alerting service covering the most important current developments in organic synthesis. It is designed with the synthetic organic chemist in mind, providing informative reaction schemes and covering new reactions and new methods. 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 discoveries of penicillin, a large number of antibiotics have been isolated from scores of micro-organisms.[2] Natural products also provide a great help ic chemotherapy of cancer. They are integral part of anticancer drugs e.g. bleomycin, doxorubicin, mitomycine, and paclitaxel.[3] All this pharmacologically and biologically important stuff designed by Mother Nature was not available in bulk quantities which man demanded. This forced scientists to look for alternate way to get it in bulk amounts while following to foot step of nature. That gradually resulted in the form of modern synthetic organic chemistry. The spirocycloprapane moiety is present in many cytotoxic compounds which play an important role an therapeutic agent in the treatment of cancer and systemic chemotherapy.[4] Most of the chemotherapeutic agents used today belong to alkylating compounds, such as chlorambucil, melphalan, thiotepa and busulfan.[5] New cytotoxic compounds are an important target in medicinal chemistry, as many natural products with cytotoxic properties were identified as poisonous components in fungi. The isolation of the illudins S and M as cytotoxic constituents of *O. illudens* was reported in 1950.[6] The synthesis of illudin analogs is of considerable pharamacological relevance, due to their cytotoxic and cancerostatic activity. Padwa and coworkers reported an interesting and efficient synthesis of illudin based on cyclization reactions of diazo compounds.[7] In addition, spirocyclopropanes are present in a number of pharmacologically interesting natural products, such as CC-1065 and duocarmycin SA[8], which exhibit a considerable antiproliferative activity against human leukaemia HL60 cells.[9] Benzofurans represent important synthetic bulding blocks and occur in a variety of pharmacologically relevant natural products, such as diazonamide A, anigopreissinA, euparin, coumestrol, dehydrotremetone,or cicerfuran.[10] Synthetic amiodarine represents a potent antiarrthmic and antianginal drug that is used in the clinic.[11] Functionalized diaryl ethers occur in a variety of natural products which show strong pharmacological activties.[12] This includes, for example, geodinhydrate methylester, methyl chloroasterrate,[13a,b] 1-desgalloylsanguiin,[13c] dehydrotrigallic acid,[13d] epiphorellic acid,[13e] jolkianin,[13f] remurin A,[13g] and micareic acid. Azaxanthones are also of considerable pharmacological relevance. For example, they show antiinflammatory activity and represent inhibitors of the passive cutaneous anaphylaxis.[14] Biaryls containing a 3-arylsalicylate substructure occur in a variety of pharmacologically relevant natural products. The simple biaryls cynandione A-C 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.[15] A number of natural products, such as knipholone, 6'-*O*-methylknipholone or (+)-asphodelin, contain an anthraquinone moiety.[16]

My own studies were focussed on the synthesis of different spirocyclopropanes and their reactions. I synthesized different types of benzofurans which are versatile synthetic bulding block in organic chemistry. I also contributed to the development of a new methodology for the synthesis of diaryl ethers, azaxanthones, and biaryls which are all important parts or analogues of different natural products.

Note: The text of the individual chapters were generally directly taken from the publications without change.

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Chapter 1

Synthesis and Reactions of Functionalized Spirocyclo-propanes by Cyclization of Dilithiated β-Ketosulfones, α-Cyanoacetone and Diethyl 2-Oxopropylphosphonate with 1,1-Diacetylcyclopropane

Tetrahedron **2008**, accepted

1.1 Introduction

1.1. Cytotoxic natural products are important lead structures for the synthesis of new anticancer agents.[1] Notably, the search for new cytotoxic compounds is of ongoing importance since tumours, similar to bacteria, may become resistant to known chemotherapeutics.[2] In addition, several types of tumours have not yet been efficiently addressed by chemotherapeutic methods. Spiro [2.5] cycloocta-4, 7-dien-6-ones and related spirocyclopropanes constitute an important structural motif of cytotoxic and cancerostatic natural and non-natural products. This includes, for example, the illudins S and M (Figure 1) which possess a 1-hydroxyspiro [5.2] cyclooct-4-en-2-one skeleton.[3] The cytotoxic natural products CC-1065 and duocarmycin SA contain a spiro[2.5]cycloocta-4,7-dien-6-one moiety containing aromatic rings fused to a heterocyclic ring system.[4] Most of the chemotherapeutic agents used today belong to alkylating compounds (chlorambucil, melphalan, thiotepa and busulfan), platinum derivatives (cisplatin,carboplatin), inhibitors of topoisomerases (camptothecin, etoposide, doxorubicin), antimetabolic compounds (5-fluoruracil, methotrexate, hydroxyurea) or inhibitors of mitosis (taxol, vinblastine). The illudins belong to the group of alkylating agents: The reaction of a nucleophile (such as glutathione) with the unsaturated ketone moiety results in formation of a cyclohexadiene which rapidly undergoes an aromatization with concurrent ring opening of the cyclopropane moiety and alkylation of the DNA.[3]

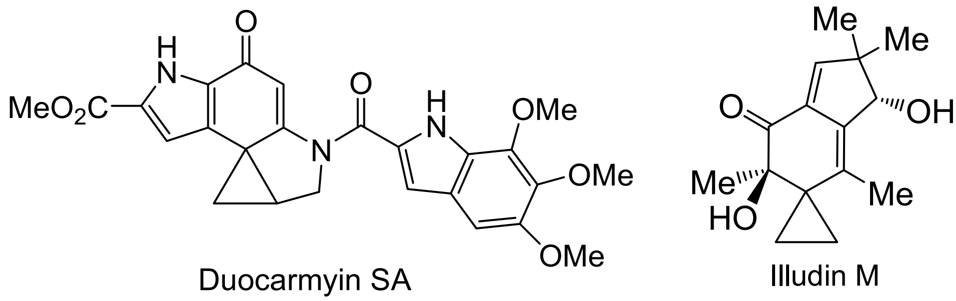


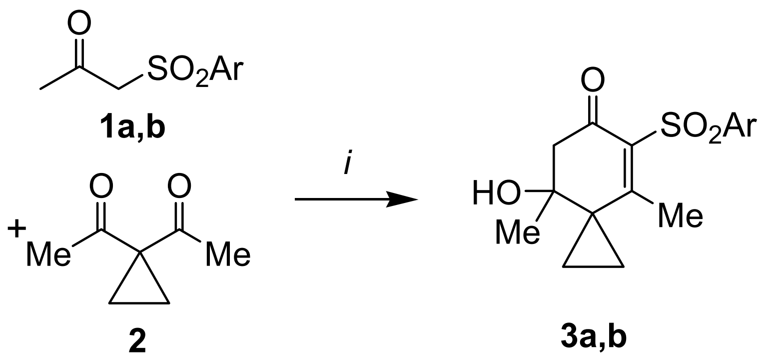
Chart 1. Natural cancerostatic spirocyclopropanes

In their pioneering work, Baird and Winstein studied the synthesis of spiro[2.5]cycloocta-4,7-dien-6-ones and their reaction with various nucleophiles.[5] Padwa and coworkers reported interesting cyclization reactions of diazo compounds which allow a convenient synthesis of illudins.[6] We reported[7] the synthesis of ester-substituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones based on cyclization reactions of 1,3-dicarbonyl dianions. Noteworthy, the products showed a considerable antiproliferative activity against human leukemia HL60cells. Herein, we report the synthesis and reactions of novel spirocyclopropanes based on cyclizations of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1,1-diacetylcyclopropane. These reactions provide a convenient access to functionalized phenols, which are not readily available by other methods.

1.2 Results and Discussion

1.2.1 β-Ketosulfones

1.2. Dianions of β-ketosulfones are useful synthetic building blocks, which have been previously used in cyclization reactions. This includes, for example, the synthesis of 2-(sulfonylmethylidene) tetrahydrofurans[8] and 7-sulfonyl-2, 3,3a, 4,5,6-hexahydro benzofurans[9] by cyclization of β-ketosulfone dianions with cyclic sulfates and 1,4-dibromobut-2-ene, respectively. The cyclization of the dianions of β-ketosulfones **1a,b**, generated by means of LDA (2.0 equiv.), with 1,1-diacetylcyclopropane (**2**) afforded the 1-hydroxyspiro [5.2] cyclooct-4-en-3-ones **3a,b** (Scheme 1, Table 1). The relatively low isolated yields can be explained by the fact that the products are, due to their high reactivity, rather unstable and readily decompose during the chromatographic purification. However, it proved possible to directly use the crude spirocyclopropane for the next synthetic step (vide infra) without chromatographic purification.



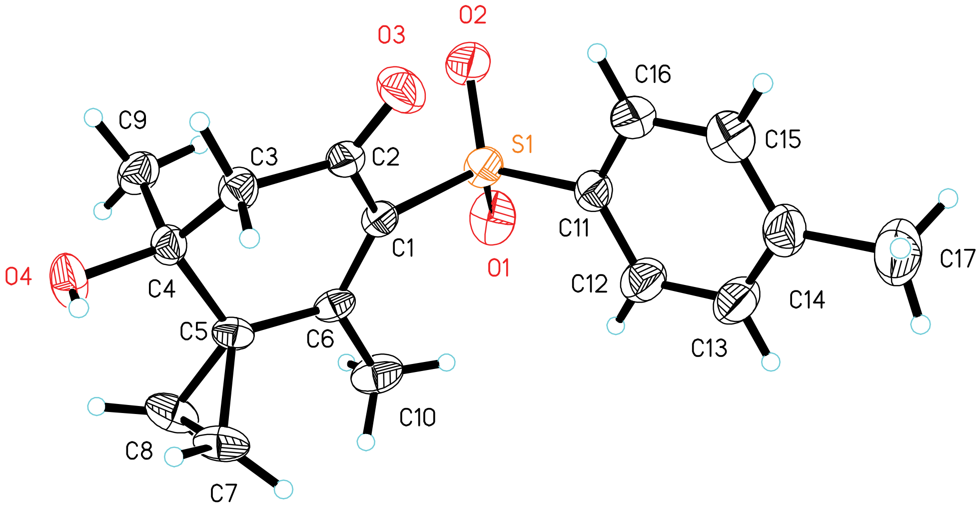
Scheme 1. Synthesis of **3a,b**; *i*: 1) LDA (2.0 equiv), **1a,b** (1.0 equiv), THF, 1 h 0 °C, 2) **2** (1.0 equiv), −78 → 20 °C, 14 h

Table 1. Synthesis of **3a,b**

3	Ar	% [a]
a	Ph	30
b	4-MeC_6H_4	32

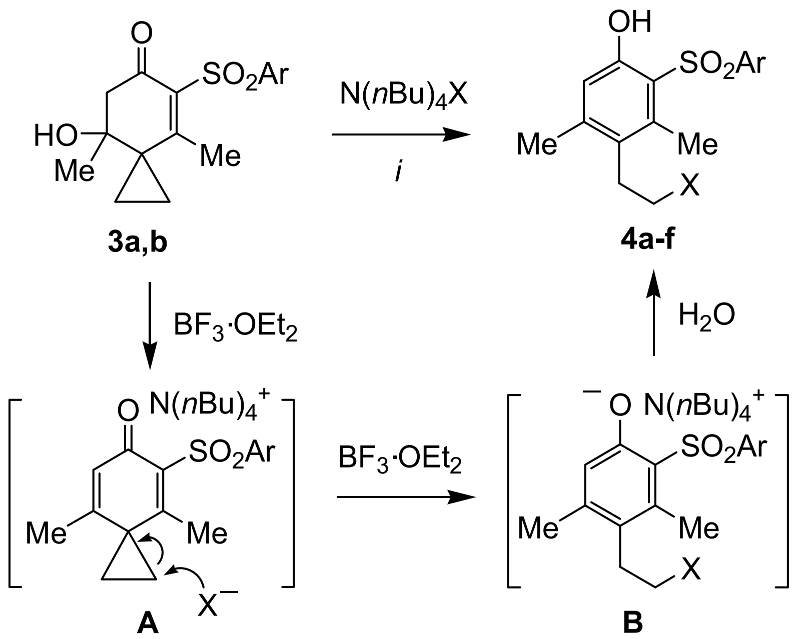
[a] Yields of isolated products

Despite its unstable nature, it proved to be possible to grow a single crystal of spirocyclopropane **3b** and to independently confirm its structure by X-ray crystal structure analysis (Figure 1).[10]



1.3. Figure 1. Ortep plot of **3b**

The $BF_3 \cdot OEt_2$-mediated reaction of pure **3a,b** with tetrabutylammonium halides afforded the sulfonyl-substituted phenols **4a-f** containing a remote chloride, bromide, and iodide group (Scheme 2, Table 2). Alternatively, the crude material could be successfully employed (vide supra). Products **4a-f** were presumably formed by Lewis acid mediated elimination of water to give a highly reactive spiro[2.5]cycloocta-4,7-dien-6-one (intermediate **A**). The cyclopropane moiety is subsequently cleaved by Lewis acid mediated attack of the halide ion to give a phenolate (intermediate **B**), which is protonated upon addition of water (aqueous work-up). The structure of **4f** was independently confirmed by X-ray crystal structure analysis (Figure 2).



Scheme 2. Synthesis of **4a-f**; *i*: BF_3·OEt_2, CH_2Cl_2, –78 → 20 °C, 6 h, then 20 °C, 6 h

Table 2. Reaction of **3a,b** with N(*n*Bu)$_4$

4	Ar	X	% [a]
a	Ph	Cl	80
b	Ph	Br	75
c	Ph	I	81
d	4-MeC_6H_4	Cl	78
e	4-MeC_6H_4	Br	68
f	4-MeC_6H_4	I	84

[a] Yields of isolated products

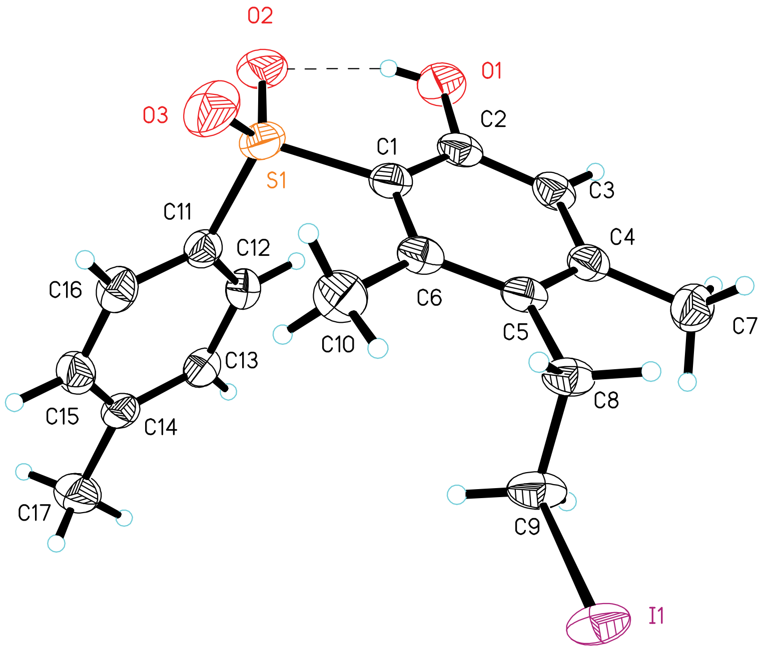
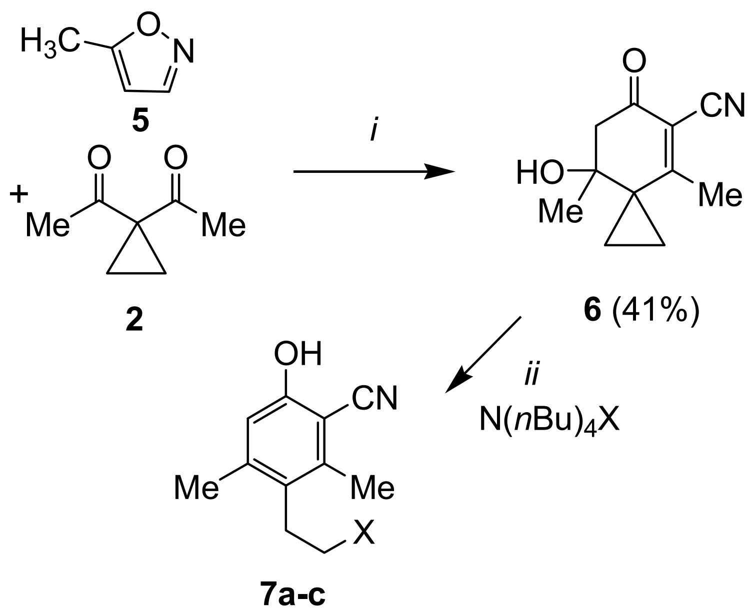


Figure 2. Ortep plot of **4f**

1.2.2 α-Cyanoacetone

The cyclization of **2** with the dianion of α-cyanoacetone, generated by treatment of 5-methylisoxazole (**5**) with LDA,[11] afforded 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **6** (Scheme 3). The $BF_3{\cdot}OEt_2$-mediated reaction of **6** with tetrabutylammonium halides gave the 2-cyanophenols **7a-c** containing a remote halide group (Scheme 3, Table 3). The formation of **7a-c** can be explained by a similar mechanism as discussed for **4a-f**. The structure of **7b** was independently confirmed by X-ray crystal structure analysis (Figure 3).[10]

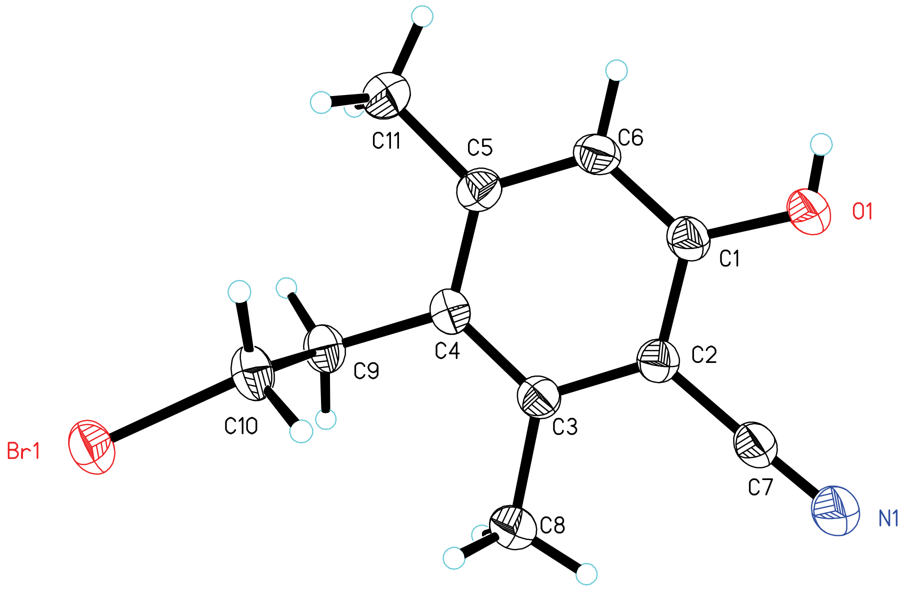


Scheme 3. Synthesis of **7a-c**; *i*: 1) LDA (2.0 equiv), **5** (1.0 equiv), THF, 1 h, 0 °C, 2) **2** (1.0 equiv), –78 → 20 °C, 14 h; *ii*: nBu$_4$NX (1.0 equiv), $BF_3{\cdot}OEt_2$ (0.5 equiv.), –78 → 20 °C, 12 h

Table 3. Products and yields

7	X	% [a]
a	Cl	64
b	Br	67
c	I	75

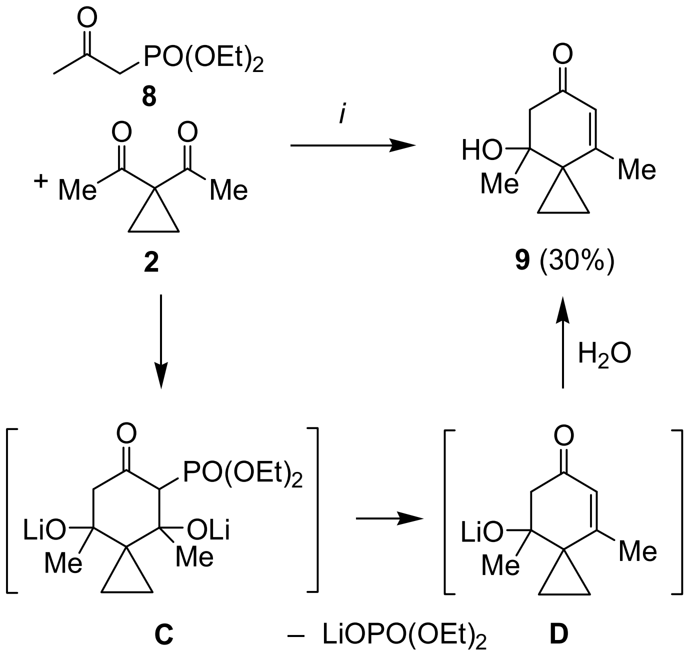
[a] Yields of isolated product



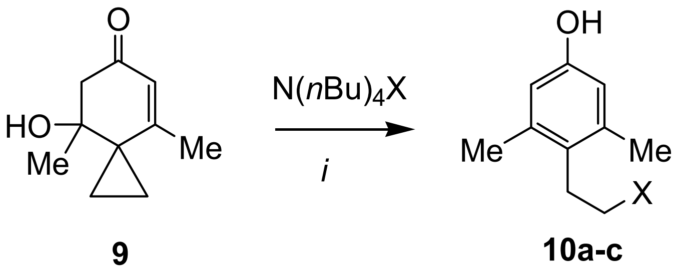
1.4. **Figure 3.** Ortep plot of **7b**

1.2.3 Diethyl 2-Oxopropylphosphonate

The cyclization of **2** with the dianion of diethyl 2-oxopropylphosphonate (**8**), generated by means of LDA, afforded the novel unsubstituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **9** (Scheme 4). The formation of **9** can be explained by cyclization (intermediate **C**), elimination of lithium diethylphosphate (intermediate **D**) and subsequent protonation upon addition of water. Alternatively, the reaction can be regarded as a domino ′aldol / Horner-Wadsworth-Emmons (HWE)′ reaction. The $BF_3{\cdot}OEt_2$-mediated reaction of **9** with tetrabutylammonium halides afforded the functionalized phenols **10a-c** (Scheme 5, Table 4).



Scheme 4. Synthesis of spirocyclopropane **9**; *i*: 1) LDA (2.0 equiv), **8** (1.0 equiv), THF, 1 h 0 °C, 2) **2** (1.0 equiv), −78 → 20 °C, 14 h



Scheme 5. Reaction of **9** with nBu$_4$NX; *ii*: nBu$_4$NX (1.0 equiv), $BF_3{\cdot}OEt_2$ (0.5 equiv.), –78 → 20 °C, 12 h

Table 4. Products and yields

10	X	% [a]
a	Cl	73
b	Br	68
c	I	63

[a] Yields of isolated product

In conclusion, 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones were prepared by cyclization of β-ketosulfone, β-ketonitrile and β-ketophosphonate dianions with 1,1-diacetylcyclopropane. These products were transformed into functionalized phenols by Lewis acid mediated reaction with tetrabutylammonium halides. The reactions reported provide a convenient two-step approach to functionalized phenols, which are not readily available by other methods.

1.3 Experimental Section

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^{1}H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60-200 mesh) was used. Melting points are uncorrected.

Typical procedure for the cyclization of 1,3-dicarbonyl dianions with 1,1 diacetylcyclopropane. A THF solution (8.5 mL) of LDA was prepared by addition of *n*BuLi (3.10 mL, 7.7 mmol, 2.5 M solution in hexane) to a THF solution of diisopropylamine (1.0 mL, 7.76 mmol) at 0 °C. After stirring for 1 h, β-ketosulfone **1** (768 mg, 3.88 mmol) was added at –78 °C and the solution was stirred for 1 h. To the solution was added 1,1-diacetylcyclopropane (**2**) (490 mg, 3.88 mmol) at –78 °C and the solution was allowed to warm to 20 °C during 14 h. To the reaction mixture was added an aqueous solution of HCl (1 M) and the organic and aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **3a** as a yellow solid (230 mg, 30%).

8-Hydroxy-4,8-dimethyl-5-(phenylsulfonyl)spiro[2.5]oct-4-en-6-one (3a): Mp = 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93–0.97 (m, 1 H, CH_2), 1.13 (s, 3 H, CH_3), 1.28–1.32 (m, 1 H, CH_2), 1.50–1.54 (m, 1 H, CH_2), 2.22 (s, 3 H, CH_3), 2.45 (d, 1 H, J = 15.8 Hz, CH_2), 2.55 (d, 1 H, J = 15.8 Hz, CH_2), 7.40–7.49 (m, 3 H, ArH), 7.83–7.87 (dd, 2 H, J = 8.4, 3.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.5, 13.6 (CH_2), 16.5, 25.8 (CH_3), 38.8 (C), 52.4 (CH_2), 69.7 (C), 128.0 (2C CH), 128.9 (2C CH), 133.3 (CH), 136.5, 149.0, 173.8, 191.4 (C); IR (KBr): $\widetilde{\nu}$ = 3407 (S), 2967 (w), 2924 (w), 1664 (m), 1544 (s), 1447 (m), 1375 (m), 1334 (s), 1301 (s), 1088 (s), 732 (s) cm^{-1}; MS (CI): m/z (%): 307 ($[M+1]^{+}$), 100), 289 (11.21), 247 (6.07), 199 (2.82); HRMS (CI): calcd. for $C_{16}H_{19}SO_4$ ($[M+1]^{+}$) 307.0996, found 307.1001.

8-Hydroxy-4,8-dimethyl-5-(4-methylphenylsulfonyl)spiro[2.5]oct-4-en-6-one (3b): Starting with n-BuLi (31mL, 78.4 mmol, 2.5 M solution in hexane), diisopropylamine (11 mL, 78.4 mmol), 1,1-diacetylcyclopropane (**2**) (5.00 g, 39.7 mmol), and p-tolylsulfonylacetone (8.41 g, 39.7 mmol) in THF (86 mL), **3b** was isolated as a colourless solid, mp = 160–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06–1.10 (m, 1 H, CH_2), 1.29 (s, 3 H, CH_3), 1.32–1.36 (m, 1 H, CH_2), 1.42–1.46 (m, 1 H, CH_2), 1.66–1.70 (m, 1 H, CH_2), 2.37 (s, 3 H, CH_3), 2.49 (s, 3 H, CH_3), 2.66 (d, 1 H, J = 13.4 Hz, CH_2), 2.72 (d, 1 H, J = 16.4 Hz, CH_2), 7.38 (d, 2 H, J = 8.0 Hz, ArH), 7.94 (d, 2 H, J = 8.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.3, 13.5 (CH_2), 16.6, 22.0, 25.8 (CH_3), 37.1 (C), 52.5 (CH_2), 71.6 (C), 128.2 (2C CH), 129.6 (2C CH), 136.8, 140.0, 144.2, 173.8, 191.5 (C); IR (KBr): $\widetilde{\nu}$ = 3489 (m), 2974 (m), 2929 (m), 1718 (m), 1679 (s), 1597 (m), 1373 (m), 1301 (s), 1186 (s), 1086 (s), 981 (s), 815 (m), 543 (s) cm^{-1}; MS (CI, 70 eV): m/z (%): 321 ($[M+1]^{+}$)100), 303 (10.21), 253 (11), 213 (9); HRMS (CI): calcd. for $C_{17}H_{21}SO_4$ ($[M+1]^{+}$): 321.11521, found: 321.11551.

Typical procedure for the reaction of 8-hydroxy-4,8-dimethyl-5-(phenylsulfonyl)spiro[2.5]oct-4-en-6-ones with tetraalkylammonium halides. To a

CH_2Cl_2 solution (12.4 mL) of **3a** (500 mg, 1.63 mmol) and of *n*-Bu_4NCl (526 mg, 1.6 mmol) was dropwise added $BF_3.OEt_2$ (0.10 mL, 0.8 mmol) at –78 °C under Argon atmosphere. The solution was allowed to warm to 20 °C over 6 h and was stirred for additional 6 h at 20 °C. The solution was filtered and the filtrate was poured into an aqueous solution of HCl (1.0 M). The organic and the aqueous layers were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **4a** as a yellow solid (435 mg, 75%).

4-(2-Chloroethyl)-3,5-dimethyl-2-(phenylsulfonyl)phenol (4a): Starting with **3a** (300 mg, 1.0 mmol), *n*-Bu_4NCl (272 mg, 1.0 mmol), CH_2Cl_2 (7.4 mL) and $BF_3{\cdot}OEt_2$ (0.06 mL, 0.5 mmol), **4a** was isolated (355 mg, 80%) as a colourless solid, mp = 192–196 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27(s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 2.89 (t, 2 H, J = 7.6 Hz, CH_2), 3.40 (t, 2 H, J = 6.9 Hz, CH_2), 6.79 (s, 1 H, CH), 7.50–7.54 (m, 2 H, ArH), 7.60–7.65 (m, 1 H, ArH), 7.83–7.87 (m, 1 H, ArH), 10.45 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.5, 20.8 (CH_3), 32.6, 41.7 (CH_2), 118.6 (C), 119.1 (CH), 126.4 (2C CH), 128.3 (C), 129.2 (2C CH), 133.5 (CH), 137.2, 142.1, 145.6, 157.1 (C); IR (KBr): $\tilde{\nu}$ = 3265 (s), 2957 (w), 2920 (w), 1601 (s), 1445 (s), 1342 (s), 1295 (m), 1109 (s), 1157 (m), 762 (m), 691 (s), 649 (s), 568 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 326 (M^+, ^{37}Cl, 10), 324 (M^+, ^{35}Cl, 22), 275 (100), 133(19), 91 (12), 77 (15); HRMS (EI): calcd.for $C_{16}H_{17}O_3ClS$ [M^+, ^{35}Cl]: 324.05814, found: 324.057851.

1.5.

1.6. **4-(2-Bromoethyl)-3,5-dimethyl-2-(phenylsulfonyl)phenol (4b):** Starting with **3a** (500 mg, 1.6 mmol), *n*-Bu_4NBr (526 mg, 1.63 mmol), CH_2Cl_2 (12.4 mL) and $BF_3{\cdot}OEt_2$ (0.1 mL, 0.8 mmol), **4b** was isolated (435 mg, 75%) as a colourless solid, mp = 144–146 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_3), 3.05 (t, 2 H, J = 7.7 Hz, CH_2), 3.23 (t, 2 H, J = 6.9 Hz, CH_2), 6.79 (s, 1 H, CH), 7.50–7.55 (m, 2 H, ArH), 7.60–7.65 (m, 1 H, ArH), 7.83–7.87 (m, 1 H, ArH), 10.62 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 21.2 (CH_3), 29.5, 33.4 (CH_2), 119.1 (C), 119.7 (CH), 127.1 (2C CH), 129.6 (2C, CH), 129.9 (C), 133.9 (CH), 137.5, 142.5, 146.1, 157.5 (C); IR (KBr): $\tilde{\nu}$ = 3264 (s), 2955 (w), 1601 (s), 1558 (s), 1445 (s), 1342 (s), 1278 (m), 1126 (s), 1083 (s), 865 (w), 761 (m), 730 (s), 642 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 370 (M^+, ^{81}Br, 21), 368 (M^+, ^{79}Br, 22), 289 (22), 275 (100), 133 (19), 91 (10), 77 (17); HRMS (EI): calcd. for $C_{16}H_{17}O_3BrS$ [M^+, ^{79}Br]: 368.00763, found: 368.007146.

4-(2-Iodoethyl)-3,5-dimethyl-2-(phenylsulfonyl)phenol (4c): Starting with **3a** (500 mg, 1.6 mmol), *n*-Bu_4NI (603 mg, 1.6 mmol), CH_2Cl_2 (12.4 mL) and $BF_3{\cdot}OEt_2$ (0.1 mL, 0.8 mmol), **4c** was isolated (425 mg, 81%) as a colourless solid, mp = 170–171 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3), 2.94–2.98 (m, 2 H, CH_2), 3.05–3.10 (m, 2 H, CH_2), 6.78 (s, 1 H, CH), 7.50–7.54 (m, 2 H, ArH), 7.58–7.62 (m, 1 H, ArH), 7.83–7.87 (m, 1 H, ArH), 10.54 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 0.0 (CH_2), 15.8, 20.0 (CH_3), 33.5 (CH_2), 117.9 (C), 118.4 (CH), 125.7 (2C CH), 128.4 (2C CH), 131.0 (C), 132.7 (CH), 136.0, 141.3, 144.5, 156.2 (C); IR (KBr): $\tilde{\nu}$ = 3262 (s), 2950 (w), 1598 (s), 1559 (s), 1445 (s), 1341 (s), 1291 (s), 1207 (m), 1125 (s), 1082 (s), 866 (m), 727 (s), 690 (s), 667 (m), 548 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 416 (M^+, 6), 289 (100), 275 (7), 196 (5), 148 (11), 91 (10), 77 (15); HRMS (EI): calcd. for $C_{16}H_{17}O_3IS$ [M^+]: 415.99376, found: 415.99368.

4-(2-Chloroethyl)-3,5-dimethyl-2-[(4-methylphenyl)sulfonyl]phenol (4d): Starting with **3b** (300 mg, 0.9 mmol), *n*-Bu_4NCl (260 mg, 0.9 mmol), CH_2Cl_2 (7.0 mL) and $BF_3{\cdot}OEt_2$ (0.06 mL, 0.5 mmol), **4d** was isolated (248 mg, 78%) as a colourless solid, mp = 118–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 2.55 (s, 3 H, CH_3), 3.11 (t, 2 H, *J* = 8.0 Hz, CH_2), 3.53 (t, 2 H, *J* = 6.6 Hz, CH_2), 6.96 (s, 1 H, CH), 7.43 (d, 2 H, *J* = 8.0 Hz, ArH), 8.37 (d, 2 H, *J* = 8.0 Hz, ArH), 10.74 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.9, 21.3, 22.0 (CH_3), 33.0, 42.1 (CH_2), 119.4

(C), 119.5 (CH), 126.5, (2C CH), 129.7 (C), 130.2 (2C CH), 137.7, 139.4, 144.9, 145.8, 157.8 (C); IR (KBr): $\tilde{\nu}$ = 3193 (m), 2960 (w), 2854 (w), 1605 (m), 1566 (m), 1463 (m), 1240 (s), 1124 (s), 1085 (s), 811 (w), 684 (s), 548 (m), 555 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 340 (M^+, ^{37}Cl, 26), 338 (M^+, ^{35}Cl, 28), 289 (100), 197 (11), 133 (23), 91 (14), 77 (10); HRMS (EI): calcd. for $C_{17}H_{19}O_3ClS$ [M^+, ^{35}Cl]: 338.07379, found: 338.07326.

4-(2-Bromoethyl)-3,5-dimethyl-2-[(4-methylphenyl)sulfonyl]phenol (4e): Starting with **3b** (500 mg, 1.5 mmol), *n*-Bu_4NBr (503 mg, 1.5 mmol), CH_2Cl_2 (11.8 mL) and $BF_3 \cdot OEt_2$ (0.10 mL, 0.8 mmol), **4e** was isolated (395 mg, 68%) as a colourless solid, mp = 135–137 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 2.51 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 3.24 (t, 2 H, *J* = 7.8 Hz, CH_2), 3.66 (t, 2 H, *J* = 6.1 Hz, CH_2), 6.97 (s, 1 H, CH), 7.49 (d, 2 H, *J* = 8.0 Hz, ArH), 8.37 (d, 2 H, *J* = 8.4 Hz, ArH), 10.76 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.5, 18.9, 20.8 (CH_3), 34.2, 41.8 (CH_2), 119.1 (C), 119.7 (CH), 126.5, (2C CH), 128.2 (C), 129.8, (2C CH), 139.2, 141.3,144.5, 145.5, 160.0 (C); IR (KBr): $\tilde{\nu}$ = 3194 (m), 2955 (w), 2853 (w), 1605 (m), 1565 (m), 1462 (m), 1239 (s), 1124 (s), 1085 (s), 811 (m), 685 (s), 548 (m), 555 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 384 (M^+, ^{81}Br, 20) 382 (M^+, ^{79}Br, 29),, 303 (25), 289 (100), 197 (12), 133(27), 91 (13), 65 (10); HRMS (EI): calcd. for $C_{17}H_{19}O_3BrS$ [M^+, ^{79}Br]: 382.02328, found: 382.02340.

4-(2-Iodoethyl)-3,5-dimethyl-2-[(4-methylphenyl)sulfonyl]phenol (4f): Starting with **3b** (400 mg, 1.3 mmol), *n*-Bu_4NI (461 mg, 1.3 mmol), CH_2Cl_2 (9.5 mL) and $BF_3 \cdot OEt_2$ (0.08 mL, 0.6 mmol), **4f** was isolated (520 mg, 84%) as a colourless solid, mp = 136–139 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.94–2.98 (m, 2H, CH_2), 3.03–3.07 (m, 2 H, CH_2), 6.75 (s, 1 H, CH), 7.30 (d, 2 H, *J* = 7.8 Hz, ArH), 7.70 (d, 2 H, *J* = 8.4 Hz, ArH), 10.47 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.0 (CH_2I), 15.6, 19.9, 20.7 (CH_3), 33.4 (CH_2), 118.1 (C), 118.4 (CH), 126.7

(2C CH), 128.9 (2C CH), 130.8, 135.9, 138.3, 143.7, 144.2. 155.0 (C); IR (KBr): $\tilde{\nu}$ = 3206 (m), 2900 (s), 1597 (s), 1562 (s), 1493 (m), 1348 (m), 1259 (m), 1166 (w), 1125 (s), 709 (s), 696 (s), 648 (w), 523 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 430 (M^+, 7), 303 (100), 289 (10), 209 (7), 133(10), 91 (18), 77 (8); HRMS (EI): calcd. for $C_{17}H_{19}O_3IS$ [M^+]: 430.00872, found 430.00864.

8-Hydroxy-4,8-dimethyl-5-cyanospiro[2.5]oct-4-en-6-one (6): Starting with *n*-BuLi (48.8 mL, 122.0 mmol, 2.5 M solution in hexane), diisopropylamine (17.2 mL, 122.0 mmol), 1,1-diacetylcyclopropane (**2**) (7.70 g, 61.4 mmol), and 5-methylisoxazole (**5**) (5.00 g, 61.4 mmol) in THF (134 mL), **6** was isolated as yellow oil (4.80 g, 41%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94–1.07 (m, 2 H, CH_2), 1.25–1.32 (m, 1 H, CH_2), 1.22 (s, 3 H, CH_3), 1.61–1.68 (m, 1 H, CH_2), 2.03 (s, 3 H, CH_2), 2.69 (d, 2 H, J = 5.7 Hz, CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.1, 13.7 (CH_2), 19.6, 25.4 (CH_3), 34.2 (C), 51.0 (CH_2), 70.1 (C), 114.1 (CN), 128.7, 171.9, 191 (C); IR (neat): $\tilde{\nu}$ = 3488 (m), 2969 (w), 2931 (w), 2228 (m), 1678 (s), 1573 (m), 1383 (s), 1295 (s), 1164 (w), 1089 (m), 965 (w), 740 (w) cm^{-1}; -MS (CI, 70 eV): *m/z* (%) 191 ($[M+1]^+$),100), 148 (11.21), 125 (7), 74 (6); HRMS (CI): calcd. for $C_{11}H_{13}O_2N$ ($[M+1]^+$): 191.09408, found: 191.093758.

4-(2-Chloroethyl)-3,5-dimethyl-2-cyanophenol (7a): Starting with **6** (300 mg, 1.6 mmol), *n*-Bu_4NCl (436 mg, 1.6 mmol), CH_2Cl_2 (11.9 mL) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol), **7a** was isolated (205 mg, 64%) as a colourless solid, mp = 124–126 °C; ^{1}H NMR (300 MHz, acetone-d_6): δ = 2.40 (s, 3 H, CH_3), 2.54 (s, 3 H, CH_3), 3.20–3.25 (m, 2 H, CH_2), 3.64–3.68 (m, 2 H, CH_2), 6.92 (s, 1 H, CH), 9.90 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 18.2, 20.7 (CH_3), 29.7, 43.1 (CH_2), 100.0 (C), 116.2 (CH), 116.6, 129.0, 142.1, 146.6, 159.3 (C); IR (KBr): $\tilde{\nu}$ = 3194 (s), 2961 (w), 1605 (s), 1566 (m), 1463 (s), 1350 (m), 1240 (m), 1224 (s), 684 (s), 555 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 211 (M^+, ^{37}Cl, 5), 209 (M^+, ^{35}Cl, 13), 160 (100), 77 (5); HRMS (EI): calcd.for $C_{11}H_{12}ONCl$ [M^+, ^{35}Cl]: 209.06019, found: 209.06040.

4-(2-Bromoethyl)-3,5-dimethyl-2-cyanophenol (7b): Starting with **6** (400 mg, 2.0 mmol), *n*-Bu_4NBr (674 mg, 2.0 mmol), CH_2Cl_2 (15.2 mL) and $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol), **7b** was isolated (142 mg, 67%) as a colourless solid; ^{1}H NMR (300 MHz, acetone-d$_6$): δ = 2.57 (s, 3 H, CH_3), 2.71 (s, 3 H, CH_3), 3.40 (t, 2 H, *J* = 7.6 Hz, CH_2), 3.72 (t, 2 H, *J* = 7.4 Hz, CH_2), 6.98 (s, 1 H, CH), 9.82 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 18.1, 20.6 (CH_2), 30.7, 33.4 (CH_3), 100.4 (C), 116.2 (CH), 116.6, 129.0, 142.0, 144.6, 159.3 (C); IR (KBr): $\tilde{\nu}$ = 2958 (m), 2928 (m), 2858 (m), 1728 (s), 1464 (m), 1286 (s), 1124 (m), 1073 (w), 742 (m), 704 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 255 (M^+, ^{81}Br, 15), 253 (M^+, ^{79}Br, 16), 174 (49), 160 (100), 77 (6); HRMS (EI): calcd. for $C_{11}H_{12}ONBr$ [M^+, ^{79}Br]: 253.00968, found: 253.00949.

4-(2-Iodoethyl)-3,5-dimethyl-2-cyanophenol (7c): Starting with **6** (400 mg, 2.0 mmol), *n*-Bu_4NI (738 mg, 2.0 mmol), CH_2Cl_2 (15.2 mL) and $BF_3{\cdot}OEt_2$ (0.13 mL, 1.0 mmol), **7c** was isolated (475 mg, 75%) as a colourless solid, mp = 185–188 °C; ^{1}H NMR (300 MHz, acetone-d$_6$): δ = 2.50 (s, 3 H, CH_3), 2.64 (s, 3 H, CH_3), 3.34–3.38 (m, 2H, CH_2), 3.43–3.47 (m, 2 H, CH_2), 6.89 (s, 1 H, CH), 9.85 (s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 2.7 (CH_2), 18.5, 20.9 (CH_3), 35.1 (CH_2), 100.0 (C), 116.6 (CH), 117.6, 131.6, 141.9, 144.5, 159.6 (C); IR (KBr): $\tilde{\nu}$ = 3223 (s), 2923 (w), 2232 (s), 1598 (s), 1443 (m), 1312 (m), 1168 (m), 1090 (w), 867 (m), 705 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 300 (M^+, 5), 174 (100), 160 (18), 77 (5); HRMS (EI): calcd. for $C_{11}H_{12}ONI$ [M^+]: 300.99581, found: 300.995296.

8-Hydroxy-4,8-dimethylspiro[2.5]oct-4-en-6-one (9): Starting with *n*-BuLi (28.6 mL, 57.2 mmol, 2.5 M solution in hexane), diisopropylamine (8.6 mL, 57.2 mmol), 1,1-diacetylcyclopropane (**2**) (7.70 g, 61.4 mmol), and diethyl 2-oxophosphonate **8** (5.55 g, 28.6 mmol) in **THF** (62ml), **9** was isolated as gummy compound (2.20 g, 29%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.76–0.80 (m, 1 H, CH_2), 0.97–1.02 (m, 2 H, CH_2), 1.22 (s, 3 H,

CH_3), 1.34–1.38 (m, 1 H, CH_2), 1.68 (s, 3 H, CH_3), 2.54 (d, 2 H, J = 15.8 Hz, CH_2), 2.65 (d, 2 H, J = 15.8 Hz, CH_2); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 9.0, 10.2 (CH_2), 19.9, 25.3 (CH_3), 32.1 (C), 51.8 (CH_2), 72.5 (C), 126.5 (CH), 161.5, 198.4 (C); IR (neat): $\tilde{\nu}$ = 3403 (s), 2975 (m), 1648 (s), 1604 (s), 1444 (m), 1387 (m), 1286 (m), 1144 (m), 1028 (m), 963 (m), 860 (m), 641 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 166 (M^+, 41), 148 (50), 138 (40), 123 (38), 107 (85), 79 (100), 43 (85); HRMS (EI): calcd. for $C_{10}H_{14}O_2$ [M^+]: 166.09883, found: 166.09916.

4-(2-Chloroethyl)-3,5-dimethylphenol (10a): Starting with **9** (334 mg, 2.0 mmol), *n*-Bu_4NCl (554 mg, 2.0 mmol), CH_2Cl_2 (16 mL) and $BF_3{\cdot}OEt_2$ (0.25 mL, 2.0 mmol), **10a** was isolated (170 mg, 68%) as a colourless solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 6 H, CH_3), 2.98–3.02 (m, 2 H, CH_2), 3.38–3.43 (m, 2 H, CH_2), 6.43 (s, 2 H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (2C, CH_3), 30.1, 42.4 (CH_2), 115.0 (2C, CH), 126.9 (C), 138.2 (2C, C), 153.8 (C); IR (KBr): $\tilde{\nu}$ = 3355 (m), 3423 (s), 2920 (m), 1712 (m), 1621 (s), 1582 (m), 1449 (s), 1315 (m), 1180 (m), 1161 (s), 1112 (w), 834 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):186 (M^+, ^{37}Cl, 17), 184 (M^+, ^{35}Cl, 13) 148 (6), 135 (100), 105 (10), 91 (14), 77 (9); HRMS (EI): calcd. for $C_{10}H_{13}OCl$ [M^+,^{35}Cl]: 184.05432, found: 184.05631.

4-(2-bromoethyl)-3,5-dimethylphenol (10b): Starting with 8-hydroxy-4,8-dimethylspiro[2.5]oct-4-en-6-one (**9**) (180 mg, 1.0 mmol), *n*-Bu_4NBr (322 mg, 1.0 mmol), CH_2Cl_2 (7.6 mL) and $BF_3{\cdot}OEt_2$ (0.074 mL, 1.0 mmol), **10b** was isolated (170 mg, 68%) as a colourless solid, mp = 76–79 °C;^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.21 (s, 6 H, CH_3), 3.12 (t, 2H, J = 6.3 Hz, CH_2), 3.34 (t, 2 H, J = 6.5 Hz, CH_2), 6.40 (s, 2 ×1 H, CH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.2 (2C, CH_3), 30.0, 32.7 (CH_2), 115.2 (2C, CH), 126.9 (C), 138.2 (2C, C), 153.8 (C); IR (KBr): $\tilde{\nu}$ = 3314 (s), 2966 (S), 2855 (w), 1596 (s), 1475 (s), 1318 (m), 1213 (w), 1191 (m), 1138 (s), 1025 (s), 852 (m), 633 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 230 (M^+, ^{81}Br, 18), 228 (M^+, ^{79}Br, 19), 149 (60), 135 (100), 105 (10), 91 (16), 77 (10); HRMS (EI): calcd. for $C_{10}H_{13}OBr$ [M^{+} ^{79}Br]: 228.01444, found: 228.01429.

4-(2-Iodoethyl)-3,5-dimethylphenol (10c): Starting with **9** (135 mg, 0.8 mmol), *n*-Bu_4NI (298 mg, 0.8 mmol), CH_2Cl_2 (6.1 mL) and $BF_3{\cdot}OEt_2$ (0.10 mL, 0.8 mmol), **10c** was isolated (170 mg, 68%) as a colourless solid, mp = 69–72 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 6 H, CH_3), 3.01 (t, 2 H, J = 4.7 Hz, CH_2), 3.06 (t, 2 H, J = 4.7 Hz, CH_2), 6.40 (s, 2 H, CH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 0.00 (CH_2) 17.7 (2C, CH_3), 32.1 (CH_2), 112.6 (2C, CH), 128,1 (C), 135.8 (2C, C), 151.1 (C); IR (KBr): $\tilde{\nu}$ = 3362 (s), 3402 (S), 2960 (w), 1705 (m), 1606 (s), 1595 (m), 1460 (s), 1312 (s), 1190 (m), 1166 (s), 1133 (s), 1024 (s), 850 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 276 (M^{+}, 8), 149 (100), 135 (21), 105 (10), 91 (13), 77 (9); HRMS (EI): calcd. for $C_{10}H_{13}OI$ [M^{+}]: 276.00056, found: 276.07548.

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Chapter 2

Synthesis and Reactions of Hydroxyspiro[5.2]cyclo-octenones based on the Cyclization of the Dianions of Acetone and of Diethyl 2-Oxopropylphosphonate with 1,1-Diacylcyclopropanes.

Tetrahedron Lett. **2008**, submitted

2.1 Introduction

Spirocyclopropanes are present in a number of pharmacologically interesting natural products, such as the cytotoxic illudins (Figure 1)[1] CC-1065 and duocarmycin SA.[2] The illudins belong to the group of alkylating anticancer agents. The reaction of a nucleophile (such as glutathione) with the unsaturated ketone moiety results in formation of a cyclohexadiene which rapidly undergoes an aromatization with concurrent ring opening of the cyclopropane moiety and alkylation of the DNA.[1] Recently, we have reported the $TiCl_4$-mediated domino ′[3+3]-cyclization-homo-Michael′ reaction of 1,3-bis(silyl enol ethers) with 1,1-diacylcyclopropanes.[3] These reactions proceed by in situ formation of a spiro[2.5]cycloocta-4,7-dien-6-one which is subsequently cleaved by the action of $TiCl_4$.

2.2 Results and Discussion

In their pioneering work, Baird and Winstein studied the synthesis of spiro[2.5]cycloocta-4,7-dien-6-ones and their reaction with various nucleophiles.[4] Padwa and coworkers reported interesting cyclization reactions of diazo compounds which allow a convenient synthesis of illudins.[5] We reported[6] the synthesis of ester-substituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones, precursors of spiro[2.5]cycloocta-4,7-dien-6-ones, based on cyclization reactions of 1,3-dicarbonyl dianions. The homo-Michael reaction of these highly activated[7] spirocyclopropanes, which exhibit a considerable antiproliferative activity against human leukemia HL60 cells, with various nucleophiles results in the formation of functionalized phenols. This transformation is related to the biosynthesis of the carcinogenic pterosins (Figure 1) which were isolated from the bracken fern *Pteridium aquilinium*.[9] It was shown earlier that the pterosins are formed from their direct biogenetic precursor, the spirocyclopropane ptaquilosin, by treatment with acid. It was proposed that the pterosins, ptaquilosin and illudin M are all formed from farnesyl phosphate *via* a common biosynthetic intermediate.[1,9] Herein, we report what are, to the best of our knowledge, the first cyclizations of the dianions of diethyl 2-oxopropylphosphonate and of acetone with 1,1-diacylopropanes. These reactions provide a convenient access to regioisomeric hydroxyspiro[5.2]cyclooctenones. Homo-Michael reactions of these products with tetrabutylammonium halides allow for a convenient synthesis of functionalized phenols which are not readily available by other methods.

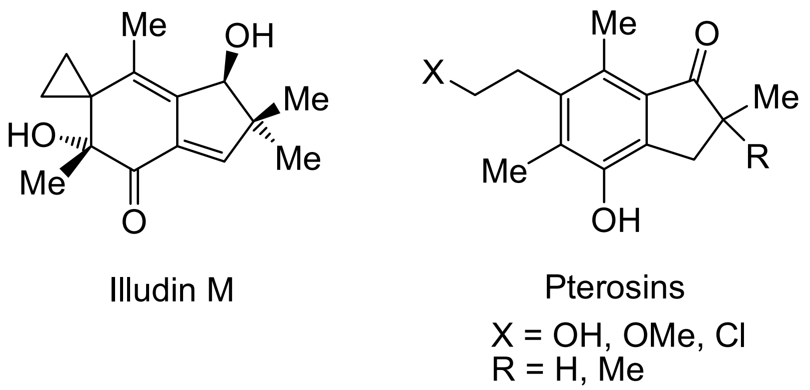
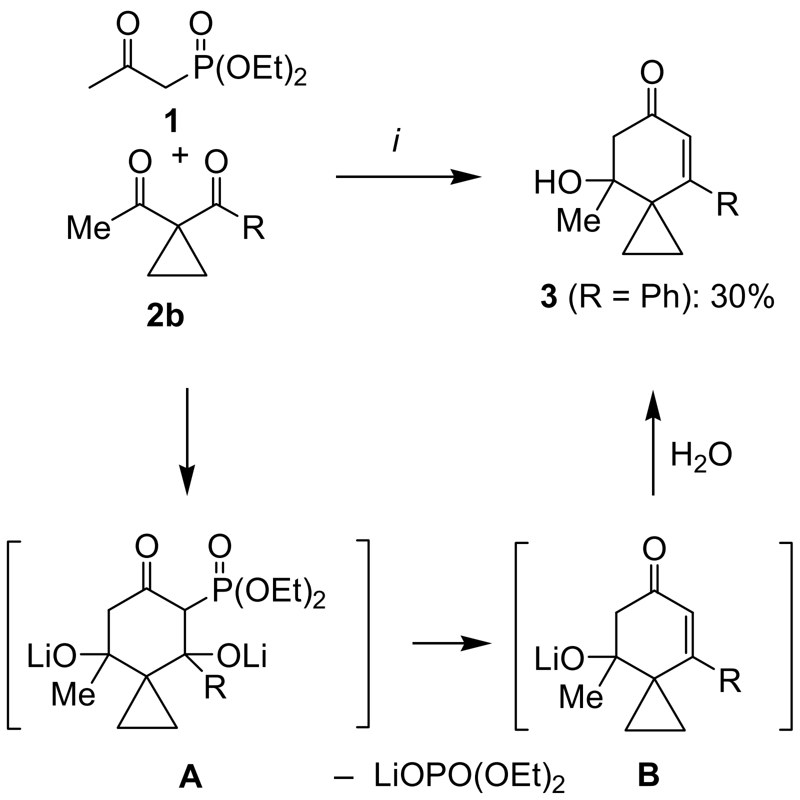


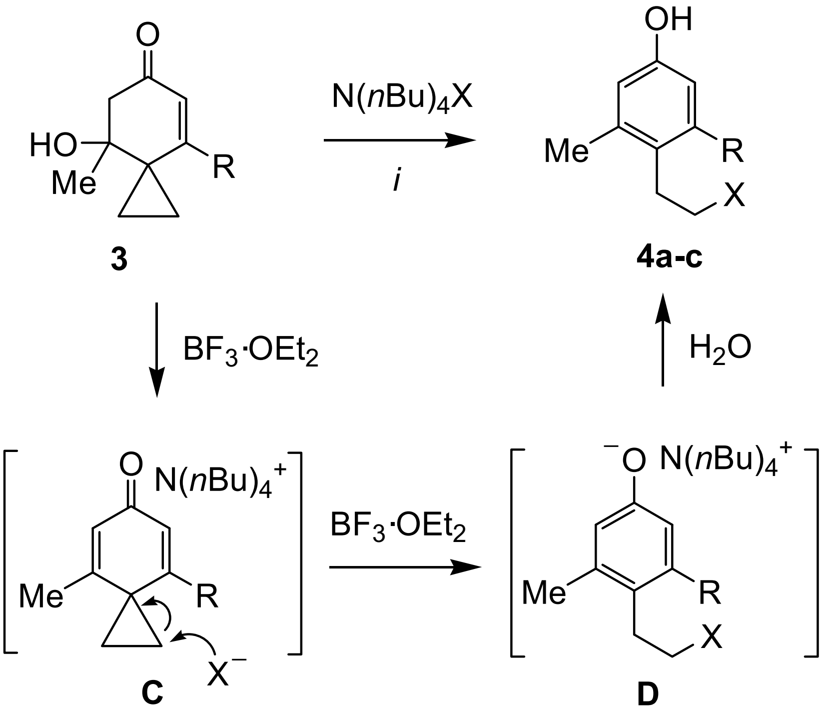
Figure 1

The cyclization of the dianion[10] of diethyl 2-oxopropylphosphonate (**1**), generated by means of LDA, with 1-acetyl-1-benzoylcyclopropane (**2b**) afforded the novel 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones and **3**, respectively (Scheme 1). The formation of **3** can be explained by cyclization (intermediate **A**), elimination of lithium diethylphosphate (intermediate **B**) and subsequent protonation upon addition of water. The reaction can be regarded as a domino ′aldol / Horner-Wadsworth-Emmons (HWE)′ reaction.



Scheme 1. Synthesis of spirocyclopropanes **3**; *i*: 1) LDA (2.0 equiv), **1** (1.0 equiv), THF, 1 h 0 °C, 2) **2,b** (1.0 equiv), −78 → 20 °C, 14 h

The $BF_3 \cdot OEt_2$-mediated reaction of **3** with tetrabutylammonium halides afforded the phenols **4a-c** containing a halogenated side chain (Scheme 2, Table 1). Products **4a-c** were presumably formed by $BF_3 \cdot OEt_2$-mediated elimination of water to give a highly reactive spiro[2.5]cycloocta-4,7-dien-6-one (intermediate **C**). The cyclopropane moiety is subsequently cleaved by $BF_3 \cdot OEt_2$-mediated attack of the halide ion to give a phenolate (intermediate **D**), which is protonated upon addition of water (aqueous work-up).



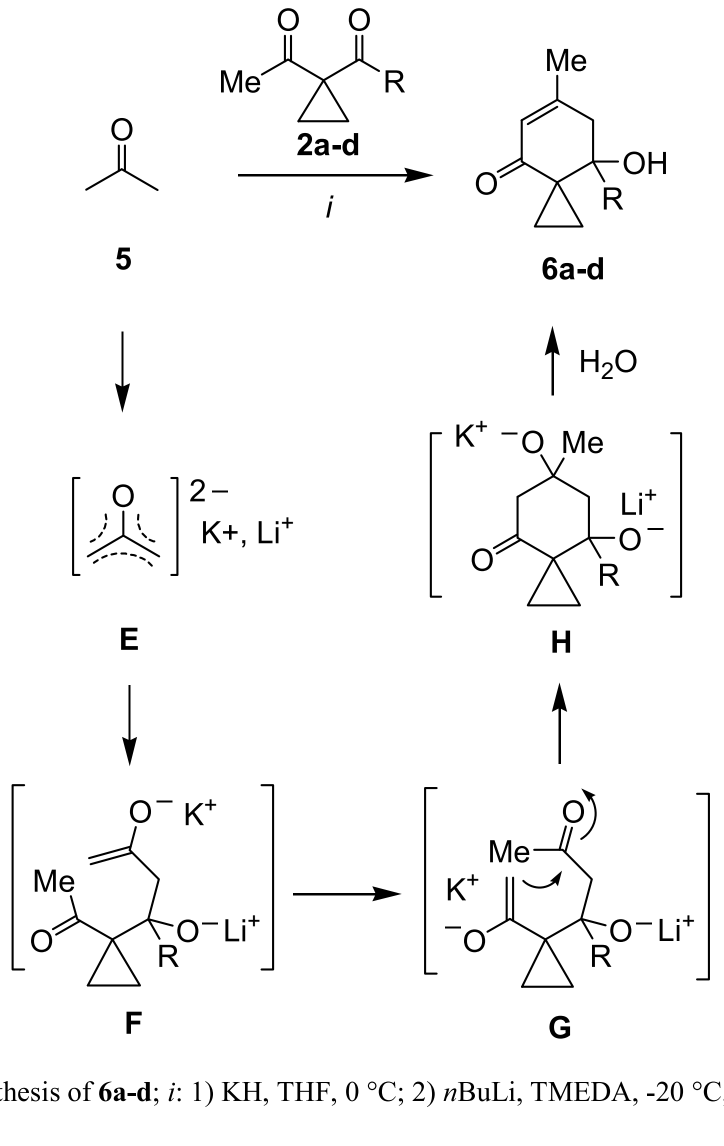
Scheme 2. Reaction of **3** with nBu$_4$NX; *i*: nBu$_4$NX (1.0 equiv), $BF_3{\cdot}OEt_2$ (0.5 equiv.), –78 → 20 °C, 12 h

Table 1. Synthesis of phenols **4a-f**

4	R	X	% [a]
a	Ph	Cl	70
b	Ph	Br	75
c	Ph	I	81

[a] Yields of isolated products

The cyclization of 1,1-diacylcyclopropanes **2a-d** with the dianion[11] of acetone (**5**), generated by addition of **5** to a THF-suspension of potassium hydride and subsequent addition of TMEDA and nBuLi, afforded the 1-hydroxyspiro[5.2]cyclooct-3-en-5-ones **6a-d** (Scheme 3).[14] The unexpected formation **6a-d**, which are regioisomers of products **3a,b**, can be explained as follows: the reaction of dianion **E** with **2a-d** afforded intermediate **F** which was transformed, by protonation and deprotonation, into intermediate **G**. The latter underwent a cyclization to give **H** which afforded **6a-d** upon aqueous work-up. Products **6b-d** were formed by regioselective attack of dianion **E** onto the aroyl rather than the acetyl group of **2b-d**.



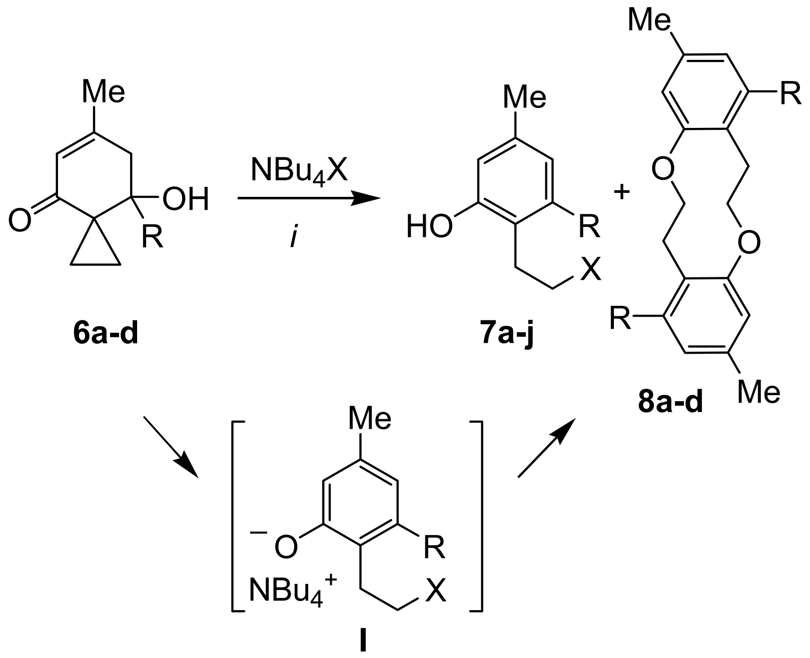
Scheme 3. Synthesis of **6a-d**; *i*: 1) KH, THF, 0 °C; 2) *n*BuLi, TMEDA, -20 °C; 3) **2a-d** –30 → 15 °C, 15

Table 2. Synthesis of spirocyclopropanes **6a-d**

6	R	% [a]
a	Me	41
b	Ph	33
c	4-ClC_6H_4	31
d	4-FC_6H_4	30

[a] Yields of isolated products

The $BF_3 \cdot OEt_2$-mediated reaction of **6a** with tetrabutylammonium halides afforded the phenols **7a-c** (Scheme 4, Table 3). [12] Their formation can be explained by a mechanism related to the one discussed for **4a-f** (*vide supra*). The structure of **7a** was independently confirmed by X-ray crystal structure analysis (Figure 2).[13] The $BF_3 \cdot OEt_2$-mediated reaction of **6b** with tetrabutylammonium chloride resulted in the formation of the halogen-free 10-membered cyclic diether **8b** in 66% yield. The employment of tetrabutylammonium bromide and iodide afforded **8b** in 63 and 79% yield, respectively. The formation of **8b** can be explained by dimerization of intermediate **I**. The reaction of spirocyclopropane **6c** with tetrabutylammonium bromide afforded a separable mixture of phenol **7g** (30%) and dimer **8c** (51%). The employment of tetrabutylammonium iodide resulted in the formation of phenol **7h** and dimer **8c** in 33 and 59% yield, respectively. The reaction of spirocyclopropane **6d** with tetrabutylammonium chloride gave exclusively dimer **8d** (50%), whereas phenol **7j** (41%) was isolated when tetrabutylammonium iodide was used. In conclusion, the product distribution seems to depend on the substituent R and on the tetraammonium halide employed.



Scheme 4. Reaction of **6a-d** with *n*Bu_4NX; *i*: *n*Bu_4NX (1.0 equiv), $BF_3{\cdot}OEt_2$ (0.5 equiv.), $-78 \rightarrow 20$ °C, 12 h

Table 3. Synthesis of phenols **7** and their dimers **8**

7	**8**	R	X	% (**7**) [a]	% (**8**) [a]
a	**a**	Me	Cl	65	0
b	**a**	Me	Br	77	0
c	**a**	Me	I	81	0
d	**b**	Ph	Cl	0	66
e	**b**	Ph	Br	0	63
f	**b**	Ph	I	0	79
g	**c**	4-ClC_6H_4	Br	30	51
h	**c**	4-ClC_6H_4	I	33	59
i	**d**	4-FC_6H_4	Cl	0	50
j	**d**	4-FC_6H_4	I	41	0

[a] Yields of isolated products

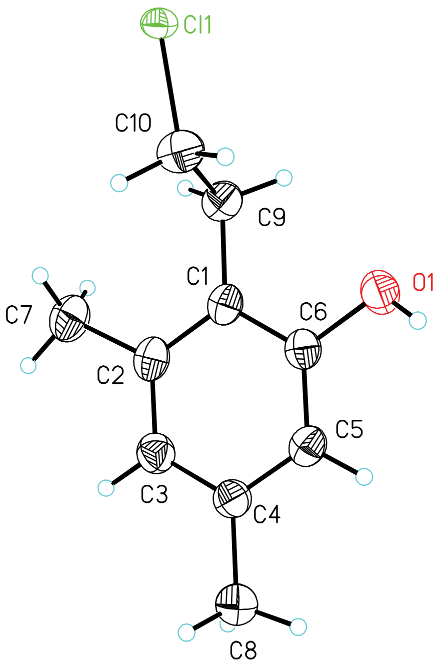


Figure 2. Ortep plot of **7a**

In conclusion, the cyclization of 1,1-diacylopropanes with the dianions of diethyl 2-oxopropylphosphonate and acetone afforded hydroxyspiro[5.2]cyclooctenones which were transformed, by homo-Michael reactions, into functionalized phenols or their dimers. The preparative scope and applications of the methodology reported is currently being studied.

2.3 Experimental Section.

Typical procedure for the cyclization of 1,3-dicarbonyl dianions with 1-acetyl-1-benzoylcyclopropane. A THF solution (27 ml) of LDA was prepared by addition of *n*BuLi (9.8 ml, 24.7 mmol, 2.5 M solution in hexane) to a THF solution of diisopropylamine (3.48 ml, 24.7 mmol) at 0 °C. After stirring for 1 h, diethyl 2-oxopropylphosphonate **1** (2.4g, 12.37mmol) was added at –78 °C and the solution was stirred for 1 h. To the solution was added 1-acetyl-1-benzoylcyclopropane**.** (**2**) (2.32g, 12.37 mmol) at –78 °C and the solution was allowed to warm to 20 °C during 14 h. To the reaction mixture was added an aqueous solution of HCl (1 M) and the organic and aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **3** as a yellow solid (850mg, 30%).

8-Hydroxy-4-methyl–8-phenylspiro[2.5]oct-4-en-6-one (3): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.79 (m, 1 H, CH_2), 0.99 (m, 1 H, CH_2), 1.13 (m, 1 H, CH_2), 1.25 (m, 1 H, CH_2), 1.34 (s, 3 H, CH_3), 2.60.(d, 1 H, J= 16.1 Hz, CH_2), 2.76.(d, 1 H, J= 15.8 Hz, CH_2), 5.88 (s, 1 H, CH), 7.0 (m, 2 H, ArH), 7.30 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 9.1, 9.4 (CH_2), 25.4 (CH_3), 35.2(C), 51.1 (CH_2), 74.3(C), 126.7 (CH), 127.5 (ArCH), 127.9 (2C, ArCH), 128.4 (2C, ArCH), 143.4, 157.2, 198.2 (C); IR (Neat): $\tilde{\nu}$ = 3395 (S), 3056 (w), 2932(w), 1643 (s), 1442 (m), 1363 (s), 1268 (s), 1118 (s), 1030 (m), 700 (s), 587 (s) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 228(M$^+$, 74), 213 (17), 145 (34), 131 (24), 115 (17), 105 (100), 83 (8), 77 (62); HRMS (CI): calcd (%) for $C_{15}H_{16}O_2$ [M$^+$] 228.11448, found 228.114140.

4-(2-Chloroethyl)-3-phenyl-5-methylphenol (4a): Starting with **3** (300 mg, 1.3 mmol), *n*-BuN_4Cl (360 mg, 1.3 mmol), CH_2Cl_2 (9.8 ml) and $BF_3.OEt_2$ (0.16 ml, 1.3 mmol), **4a** was isolated (225 mg, 70%) as a gummy compound; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2. 28 (s, 3 H, CH_3), 2.96 (t, 2H, J= 7.8 Hz, CH_2), 3.14 (t, 2 H, J= 7.7 Hz, CH_2), 4.76 (s, 1 H, OH); 6.46 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 7.16 (m, 2 H, ArH), 7.32 (m, 3 H, ArH), ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.4 (CH_3), 30.2, 33.5 (CH_2), 115.2, 116.2, (ArCH), 126.3 (C), 127.2 (ArCH), 128.2 (2C, ArCH), 128.7 (2C, ArCH), 138.6, 141.2, 144.2, 153.5 (C); IR (Neat): $\tilde{\nu}$ = 3371 (w), 2921 (m), 2851 (w), 1711 (w), 1589 (s), 1283 (s), 1176 (s), 1027 (w), 762 (s), 701 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 248 (M$^+$, ^{37}Cl, 10), 246 (M$^+$, ^{35}Cl, 29), 197 (100), 182 (31), 165 (29), 152 (9); HRMS (EI): calcd (%) for $C_{15}H_{15}OCl$ [M$^+$, ^{35}Cl] 246.08059, found 246.08046

4-(2-Bromoethyl)-3-phenyl-5-methylphenol (4b): Starting with **3** (300 mg, 1.3 mmol), *n*-BuN_4Br (418 mg, 1.3 mmol), CH_2Cl_2 (9.8 ml) and $BF_3.OEt_2$ (0.16 ml, 1.3 mmol), **4b** was isolated (288 mg, 75%) as a gummy compound; ^1H NMR (250 MHz, $CDCl_3$): δ = 2. 29 (s, 3 H, CH_3), 2.96 (t, 2H, J = 7.8 Hz, CH_2), 3.12 (t, 2 H, J = 7.6 Hz, CH_2), 4.78 (s, 1 H, OH); 6.46 (s, 1 H, ArH), 6.61 (s, 1 H, ArH), 7.17 (m, 2 H, ArH), 7.33 (m, 3 H, ArH), ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.4 (CH_3), 30.7, 33.1 (CH_2), 114.8, 116.6, 127.2 (ArCH), 127.5 (C), 128.2 (2C, ArCH), 128.9 (2C, ArCH), 138.6, 141.4, 144.3, 153.5 (C); IR (Neat): $\tilde{\nu}$ = 3418 (w), 2945 (m), 2852 (w), 1587 (s), 1317 (s), 1287 (m), 1197 (s), 1025 (m), 742 (s), 626 (m), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):292 (M^+, ^{81}Br, 26), 290 (M^+, ^{79}Br, 26), 211 (28), 197 (100), 182 (36), 165 (23), 115 (10); HRMS (EI): calcd (%) for $C_{15}H_{15}OBr$ [M^+, ^{79}Br] 290.03008, found 290.03085.

4-(2-Iodoethyl)-3-phenyl-5-methylphenol (4c): Starting with 3 (300 mg, 1.3 mmol), *n*-BuN_4I (479 mg, 1.3 mmol), CH_2Cl_2 (9.8 ml) and $BF_3.OEt_2$ (0.16 ml, 1.3 mmol), **4c** was isolated (360 mg, 81%) as a gummy compound; ^1H NMR (250 MHz, $CDCl_3$): δ = 2. 26 (s, 3 H, CH_3), 2.87 (t, 2H, J = 7.4 Hz, CH_2), 3.01 (t, 2 H, J = 7.7 Hz, CH_2), 4.79 (s, 1 H, OH); 6.43 (s, 1 H, ArH), 6.60 (s, 1 H, ArH), 7.15 (m, 2 H, ArH), 7.31 (m, 3 H, ArH), ^{13}C NMR (62 MHz, $CDCl_3$): δ = 3.1 (CH_2), 20.1 (CH_3), 34.4 (CH_2), 115.0, 116.6, 127.3 (ArCH), 128.2 (C), 128.6 (2C, ArCH), 129.9 (2C, ArCH), 138.3, 141.4, 143.3, 153.3 (C); IR (Neat): $\tilde{\nu}$ = 3441 (m), 3056 (m), 2850 (w), 1692 (w1128 (s),), 1587 (s), 1450 (s), 1312 (s), 1280 (s), 1171 (s), 1128 (s), 108 (s), 871 (s), 705 (s); cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):338 (M^+, 8), 211 (100), 196 (17), 197 (100), 181 (20), 165 (18), 115 (5); HRMS (EI): calcd (%) for $C_{15}H_{15}OI$ [M^+] 338.01621, found 338.01547.

Typical procedure for the cyclization of 1,3-dicarbonyl dianions with 1,1-diacetylcyclopropane A Diethylether (25 ml) solution of KH (2.85 g, 70 ml), To the solution was added a diethylether solution (25 ml) of acetone (4.4 ml, 60 mmol) at 0°C in 20 minutes. The temperature was allowed to rise for short period, the mixture of *n*BuLi (24 ml, 60 mmol, 2.5M solution in hexane) and TMEDA (6.96g) were added the reaction mixture at -20°C in 10 minutes. Now warmed the reaction mixture at 0°C for short period, and added the 1, 1-diacetylcyclopropane **6a** (1.89 g, 15 mmol) at -30°C. Again temperature was allowed to rise to ambient during 15h, and the solution was stirred at 15°C for 15h. The reaction mixture was poured into (10ml) acetic acid and 50 ml ice water, organic and aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **6a** as a yellow solid (1020 mg, 41%).

8-Hydroxy–6,8-dimethylspiro[2.5]oct-5-en-4-one (6a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (m, 1 H, CH_2), 0.99 (m, 1 H, CH_2), 1.10 (m, 1 H, CH_2), 1.20 (S, 3 H, CH_3), 1.24 (m, 1 H, CH_2), 1.99 (s, 3 H, CH_3), 2.42.(d, 1 H, J = 15.74 Hz, CH_2), 2.61.(d, 1 H, J = 15.83 Hz, CH_2), 5.88 (s, 1 H, CH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 11.1, 12.2 (CH_2), 24.5, 25.1 (CH_3), 35.8 (C), 41.1 (CH_2), 71.1 (C), 125.6 (CH), 155.0, 198.4 (C); IR (KBr): $\tilde{\nu}$ = 3419 (S), 2974 (w), 2932(w), 1647 (m), 1437 (s), 1381 (m), 1360 (m), 1328 (s), 1225 (s), 1197 (s), 876 (s) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 166 (M^+, 19), 151 (100), 123 (37), 111 (24), 123 (37), 83 (25), 69 (30), 43 (42); HRMS (CI): calcd (%) for $C_{10}H_{14}O_2$ [M^+] 166.09883, found 166.09862.

8-Hydroxy–6-methyl–8-phenylspiro[2.5]oct-5-en-4-one (6b): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (m, 1 H, CH_2), 1.1 (m, 1 H, CH_2), 1.25 (m, 1 H, CH_2), 1.60 (m, 1 H, CH_2), 1.70 (s, 3 H, CH_3), 2.78.(d, 1 H, J = 15.7 Hz, CH_2), 2.92.(d, 1 H, J = 15.8 Hz, CH_2), 5.88 (s, 1 H, CH), 7.2 (m, 2 H, ArH), 7.56 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.1, 12.6 (CH_2), 24.2 (CH_3), 35.2 (C), 52.3 (CH_2), 74.3(C), 126.7 (CH), 127.5 (ArCH), 127.9 (2C, ArCH), 128.3 (2C, ArCH), 143.4, 157.2, 198.2 (C); IR (Neat): $\tilde{\nu}$ = 3392 (S), 3056 (w), 2912(w), 1613 (s), 1442 (s), 1366 (s), 1262 (s), 1158 (s), 1020 (m), 701 (s), 582 (s) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 228(M^+, 74), 213 (17), 145 (32), 131 (24), 115 (13), 105 (100), 82 (8), 77 (64); HRMS (CI): calcd (%) for $C_{15}H_{16}O_2$ [M^+] 228.11448, found 228.114140.

8-4(-Chlorophenyl)-8-hydroxy–6-methylsprio[2.5]oct-5-en-4-one (6c): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.66 (m, 1 H, CH_2), 0.99 (m, 1 H, CH_2), 1.0 (m, 1 H, CH_2), 1.16 (m, 1 H, CH_2), 1.79 (s, 3 H, CH_3), 2.67.(d, 1 H, J = 16.4Hz, CH_2), 2.84.(d, 1 H, J = 15.2 Hz, CH_2), 5.74 (s, 1 H, CH), 7.13 (d, 2 H, J = 8.6 Hz, ArH), 7.28 (m, 2 H, J = 7.8 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 10.7, 11.8 (CH_2), 19.5 (CH_3), 38.3 (C), 45.5 (CH_2), 77 (C), 126.4 (CH), 128.1 (2C, ArCH), 128.9 (2C, ArCH), 133.7, 142.2, 164.3, 208.4 (C); IR (Neat): $\tilde{\nu}$ = 3380 (S), 2972 (w), 2932(w), 1643 (s), 1433 (s), 1378 (s), 1358 (m), 1186 (s), 1091 (s), 827 (s), 705 (s) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 264 (M^+, ^{37}Cl, 9), 262 (M^+, ^{35}Cl, 29), 227 (163), 180 (31), 165 (27), 145 (9), 139 (100), 111 (35), 83 (56), 39 (20); HRMS (EI): calcd (%) for $C_{15}H_{15}O_2Cl$ [M^+, ^{35}Cl] 262.05051, found 262.06056.

Typical procedure for the synthesis of functionalized phenols from spirocyclopropanes: To a CH_2Cl_2 solution (15 mL) of 8-hydroxy-6,8-dimethylspiro[2.5]oct-5-en-4-one (**6a**) (334 mg, 2.0 mmol) and of $n$$Bu_4NCl$ (554 mg, 2.0 mmol) was dropwise added $BF_3{\cdot}OEt_2$ (0.24 mL, 2.0 mmol) at –78 °C under argon atmosphere. The solution was allowed to warm to 20 °C over 6 h and was stirred for additional 6 h at 20 °C. The solution was filtered and the filtrate was poured into hydrochloric acid (1.0 M). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (silica gel, hexane/EtOAc) to give **7a** as a colourless solid (242 mg, 65%).

2-(2-Chloroethyl)-3,5-dimethylphenol (7a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.24(s, 3 H, CH_3), 2.30(s, 3 H, CH_3), 3.11 (t, 2 H, J = 8.0 Hz, CH_2), 3.67 (t, 2 H, J = 7.4 Hz, CH_2), 6.44 (s, 1 H, ArH), 6.61 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 19.4 (CH_3), 19.5 (CH_3), 30.2 (CH_2), 43.2 (CH_2), 113.8 (CH), 120.0 (C), 123.8 (CH), 137.5, 138.2, 153.8 (C). IR (KBr): $\tilde{\nu}$ = 3350 (m), 3453 (S), 2870 (m), 1716 (s), 1632 (s), 1562 (m), 1439 (s), 1325 (m), 1142 (m), 1152 (s), 1122 (w), 834 (m), cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 186 (M^+, ^{37}Cl, 9), 184 (M^+, ^{35}Cl, 21), 148 (6), 135 (100), 105 (11), 91 (13), 77 (14). HRMS (EI): calcd.for $C_{10}H_{13}OCl$ [M^+,^{35}Cl]: 184.06494, found 184.06527.

2-(2-Bromoethyl)-3,5-dimethylphenol (7b): Starting with **6a** (278 mg, 1.67 mmol), *n*-BuN_4Br (539 mg, 1.67 mmol), CH_2Cl_2 (12.6 ml) and $BF_3.OEt_2$ (0.20 ml, 1.67 mmol), **7b** was isolated (295 mg, 77%) as a gummy compound; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2. 22 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 3.18 (t, 2H, J = 7.6 Hz, CH_2), 3.48 (t, 2 H, J = 7.5 Hz, CH_2), 4.76 (s, 1 H, OH); 6.43 (s, 1 H, ArH), 6.59 (s, 1 H, ArH), 13C NMR (75 MHz, $CDCl_3$): δ = 19.4, 20.9 (CH_3), 30.2, 31.0 (CH_2), 113.8 (ArCH), 120.9 (C), 123.8 (ArCH), 137.5, 138.0, 153.7 (C); IR (Neat): $\tilde{\nu}$ = 3390 (w), 2945 (m), 2858 (w), 1674 (m), 1584 (m), 1444 (s), 1292 (w), 1128 (m), 741 (s), 704 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):230 (M^+, ^{81}Br, 22), 228 (M^+, ^{79}Br, 20), 149 (49), 135 (100), 105 (20), 91 (20), 77 (11); HRMS (EI): calcd (%) for $C_{10}H_{13}OBr$ [M^+, ^{79}Br] 228.01443, found 228.01386.

2-(2-Iodoethyl)-3,5-dimethylphenol (7c): Starting with **6a** (216 mg, 1.30 mmol), *n*-BuN_4I (479 mg, 1.30 mmol), CH_2Cl_2 (9.8 ml) and $BF_3.OEt_2$ (0.16 ml, 1.30 mmol), **7c** was isolated (295 mg, 81%) as a gummy compound; ^{1}H NMR (250 MHz $CDCl_3$,): δ = 2. 14 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 3.12 (t, 2H, J = 7.5 Hz, CH_2), 3.20(t, 2 H, J = 7.8 Hz, CH_2), 4.74 (s, 1 H, OH); 6.43 (s, 1 H, ArH), 6.58 (s, 1 H, ArH), 13C NMR (62 MHz, $CDCl_3$): δ = 3.3 (CH_2), 19.4, 20.1 (CH_3), 31.3 (CH_2), 113.8 (ArCH), 123.1 (C), 123.8 (ArCH), 136.6, 137.6, 153.4 (C); IR (Neat): $\tilde{\nu}$ = 3112 (w), 2916 (m), 1620 (m), 11442 (s), 1296 (m), 1163 (s), 1117 (m), 841 (m), 601 (m), 577 (w), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):276 (M^+, 12), 149 (100), 133 (13), 116 (8), 105 (8), 91 (16); HRMS (EI): calcd (%) for $C_{10}H_{13}OI$ [M^+] 276.00056, found 276.00076.

4-(2-Bromoethyl)-3,5-dimethyl-2-cyanophenol (7g): Starting with **6c** (288 mg, 1.1mmol), *n*-BuN_4Br (354 mg, 1.1 mmol), CH_2Cl_2 (8.3 ml) and $BF_3.OEt_2$ (0.13 ml, 1.1 mmol), 7g was isolated (110 mg, 30%) as a solid, mp = 101-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2. 29 (s, 3 H, CH_3), 2.95 (t, 2H, J = 7.7 Hz, CH_2), 3.12 (t, 2 H, J = 7.8 Hz, CH_2), 4.68 (s, 1 H, OH); 6.42 (s, 1 H, ArH), 6.62 (s, 1 H, ArH), 7.09 (d, 2 H, J = 8.5 Hz, ArH), 7.32 (d, 2 H, J = 8.4 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.1 (CH_3), 30.4, 33.0 (CH_2), 114.9, 116.9 (ArCH), 127.4 (C), 128.4 (2C, ArCH), 130.1 (2C, ArCH), 133.3, 138.8, 139.8, 143.0, 153.6 (C); IR (Neat): $\tilde{\nu}$ = 3006 (w), 2918 (m), 2852 (w), 1722 (w), 1582 (s), 1495 (s), 1386 (s), 1297 (w), 762 (s), 1001 (m), 978 (s), 824 (s), 569 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 326 (M^+, ^{37}Cl,^{81}Br, 45), 324 (M^+, ^{35}Cl, ^{79}Br, 35), 231 (100), 210 (14), 196 (65), 181 (34); HRMS (EI): calcd (%) for $C_{15}H_{14}OClBr$ [M^+, ^{35}Cl, ^{79}Br] 324.05069, found 324.05076.

4-(2-Bromoethyl)-3,5-dimethyl-2-cyanophenol (7h): Starting with **6c** (288 mg, 1.1 mmol), *n*-BuN_4I (405 mg, 1.1 mmol), CH_2Cl_2 (8.6 ml) and $BF_3.OEt_2$ (0.3 ml, 1.1 mmol), **7h** was isolated (138 mg, 33%) as a solid, mp = 105-108 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.81 (t, 2H, *J* = 7.5 Hz, CH_2), 2.95 (t, 2 H, *J* = 7.8 Hz, CH_2), 4.68 (s, 1 H, OH); 6.34 (s, 1 H, ArH), 6.61 (s, 1 H, ArH), 7.01 (d, 2 H, *J* = 8.5 Hz, ArH), 7.29 (d, 2 H, *J* = 8.4 Hz, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 2.7 (CH_2), 20.0 (CH_3), 34.0 (CH_2), 114.9, 116.9 (ArCH), 128.4 (2C, ArCH), 129.7 (C), 130.0 (2C, ArCH), 133.3, 138.5, 139.8, 142.6, 153.5 (C); IR (Neat): $\tilde{\nu}$ = 3495 (w), 2954 (w), 1698 (w), 1585 (m), 1448 (s), 1327 (m), 1287 (s), 1197 (s), 1162 (s), 1089 (s), 832 (s), 716 (m), 536 (s), cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 374 (M^+, ^{37}Cl, 7), 372 (M^+, ^{35}Cl, 16), 245 (100), 210 (50), 195 (44), 165 (24); HRMS (EI): calcd (%) for $C_{15}H_{14}OICl$ [M^+, ^{35}Cl] 372.01015, found 372.01001.

3,10-Dimethyl-1,8-diphenyl-6,7,13,14-tetrahydroibenzo[*b,g*][1,6]dioxecine (8b): Starting with **6b** (613 mg, 2.6 mmol), *n*-BuN_4Cl (744 mg, 2.6 mmol), CH_2Cl_2 (19.7 ml) and $BF_3.OEt_2$ (0.32 ml, 0.49 mmol), **8b** was isolated (750 mg, 66%) as a solid, mp = 192-196 °C; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3×2H, CH_3), 3.15 (t, 2×2H, *J* = 8.6 Hz, CH_2), 4.47 (t, 2×2H, *J* = 8.6 Hz, CH_2), 6.56 (s, 2×1H, CH), 6.68 (s, 2×1H, CH), 7.22-7.30 (m, 2×2H, ArH), 7.31-7.36 (m, 3×2H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.4 (2*C*, CH_3), 28.5 (2*C*, CH_2), 70.3 (2*C*, CH_2), 108.1 (2*C*, CH), 120.4 (2*C*, CH), 120.7 (2*C*, C), 126.0 (2*C*, ArCH), 127.0 (2×2*C*, ArCH), 127.5 (2×2*C*, ArCH), 137.3 (2*C*, C), 137.5 (2*C*, C), 139.6 (2*C*, C), 159.6 (2*C*, C); IR (Neat): $\tilde{\nu}$ = 3435 (w), 2949 (s), 2867 (m), 2556 (m), 2207 (m), 1719 (s), 1616 (s), 1450 (m), 1378 (s), 1119 (m), 1075 (m), 920 (m), 712 (w), cm^{-1};

3,10-Dimethyl-1,8-diphenyl-6,7,13,14-tetrahydrobenzo[*b,g*][1,6]dioxecine (8b): Starting with **6b** (355 mg, 1.23 mmol), *n*-BuN_4Br (395 mg, 1.23 mmol), CH_2Cl_2 (9.3 ml) and $BF_3.OEt_2$ (0.15 ml, 1.23 mmol), **8b** was isolated (415 mg, 63%) as a solid, mp = 192-196 °C.

3,10-Dimethyl-1,8-diphenyl-6,7,13,14-tetrahydroibenzo[*b,g*][1,6]dioxecine (8b): Starting with **6b** (371 mg, 1.28 mmol), *n*-BuN_4I (472 mg, 1.28 mmol), CH_2Cl_2 (9.7 ml) and $BF_3.OEt_2$ (0.16 ml, 1.28 mmol), 8b was isolated (47 5 mg, 69%) as a solid, mp = 192-196 °C.

3,10-Dimethyl-1,8-bis(dichlorophenyl)-6,7,13,14-tetrahydroibenzo[*b,g*][1,6]dioxecine (8c): Starting with **6a** (288 mg, 1.10 mmol), *n*-BuN_4Br (354 mg, 1.1 mmol), CH_2Cl_2 (8.3 ml) and $BF_3.OEt_2$ (0.13 ml, 1.10 mmol), **8c** was isolated (179 mg, 50%) as a solid, mp = 104-106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3×2H, CH_3), 3.12 (t, 2×2H, J = 7.8 Hz, CH_2), 4.47 (t, 2×2H, J = 7.9 Hz, CH_2), 6.50 (s, 2×1H, CH), 6.63 (s, 2×1H, CH), 7.99 (m, 4×2H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.4 (2*C*, CH_3), 29.5 (2*C*, CH_2), 71.1 (2*C*, CH_2), 108.1 (2*C*, CH), 121.3 (2*C*, CH), 122.2 (2*C*, C), 128.5 (2×2*C*, ArCH), 129.3 (2×2*C*, ArCH), 133.1 (2*C*, C), 137.2 (2*C*, C), 139.4 (2*C*, C), 160.0 (2*C*, C); IR (Neat): $\tilde{\nu}$ = 33350 (w), 2963 (w), 2853 (w), 1904 (w), 1703 (w), 1787 (s), 1452 (s), 1318 (m), 1378 (s), 1280 (m), 1191 (s), 1090 (m), 831 (s), cm^{-1};

3,10-Dimethyl-1,8-bis(dichlorophenyl)-6,7,13,14-tetrahydroibenzo[*b,g*][1,6]dioxecine (8c): Starting with **6c** (288 mg, 1.1 mmol), *n*-BuN_4I (405 mg, 1.1 mmol), CH_2Cl_2 (8.6 ml) and $BF_3.OEt_2$ (0.13 ml, 1.1 mmol), **8c** was isolated (23 0 mg, 59%) as a solid, mp = 103-106 °C.

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Chapter 3

Regioselective Synthesis of ω-Bromo3-ketosulfones, ω-Bromo-3-ketonitriles and 2-(ω-Bromoalkyl) benzo-furans based on a Ring-Closing / Ring-Opening′ Strategy.

Tetrahedron **2007**, *63*, 11626-11635

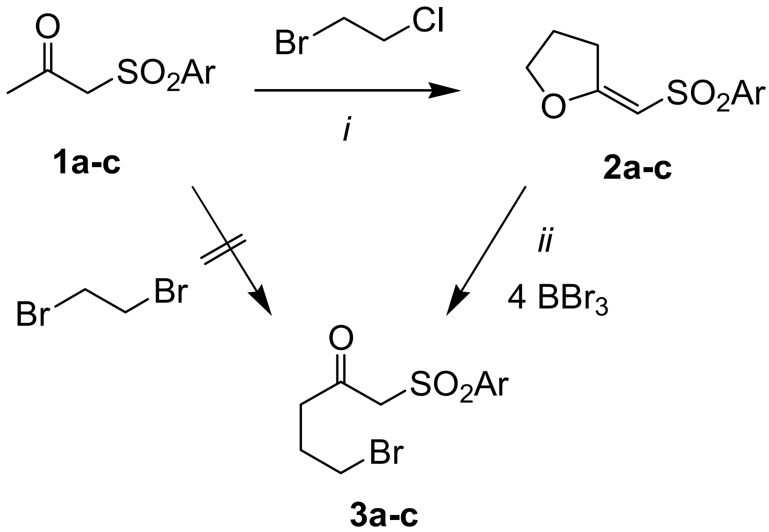
3.1 Introduction

Boron tribromide (BBr_3) represents a widely used reagent for the cleavage of methoxyarenes.[1] besides this well-known application of BBr_3, other reactions have only scarcely been reported in the literature. ω-Bromoalcohols[2] and ω-halocarboxylic acids[3] were prepared by BBr_3 mediated ring opening of cyclic ethers and lactones, respectively.[3] Recently, we reported the synthesis of 6-bromo-3-oxoalkanoates by reaction of BBr_3 with 2-alkylidenetetrahydrofurans.[4] The synthesis of benzofuran-3-carboxylic esters containing a remote bromide groups – based on a BBr_3 mediated ring transformation – has also been reported.[5] Herein, we report the 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.[6] For example; the benzofuran amiodarone is used in the clinic as a potent antiarrythmic and antianginal drug.[7] various benzofurans occur in natural products. This includes, for example, longicaudatin,[8] the sessiliflorols A and B, flemistrictin E, tovophenone C, vismiaguianone C or piperaduncin B.

3.2. Results and Discussion

3.2.1 Reactions of 3-ketosulfone dianions. 2-(2-Oxoalkylidene)tetrahydrofurans are available by cyclization[10] of 1,3-dicarbonyl dianions or 1,3-bis(silyl enol ethers) ('masked dianions') with various electrophiles, such as 1-bromo-2-chloroethane, [11] 1,4-dibromobut-2-ene, [12] or epoxides.[13] 2-(Sulfonylmethylidene)tetrahydrofurans were prepared, for example, from β-iodovinyl sulfones,[14] ω-halo and ω-hydroxy-β-ketosulfones,[15] or ω-hydroxypropargylic sulfones.[16] Another approach relies on the cyclization of 3-ketosulfone dianions with cyclic sulfates.[17] Some years ago, we 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.[12]

The cyclization of the dianions of 3-ketosulfones **1a-c**, generated by LDA (2.5 equiv.), with 1-bromo-2-chloroethane afforded the 2-(sulfonylmethylidene)-tetrahydrofurans **1a-c** (Scheme 1, Table 1). The reaction of a CH_2Cl_2 solution of **2a-c** with BBr_3 and subsequent addition of water afforded the ω-bromo-β-ketosulfones **3a-c**. The formation of **3a-c** can be explained as follows: The interaction of BBr_3 with the sulfonyl group effects a drmatic 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. Notably, products **3a-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).[18]



Scheme 1. Synthesis of ω-bromo-3-ketosulfones **3a-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

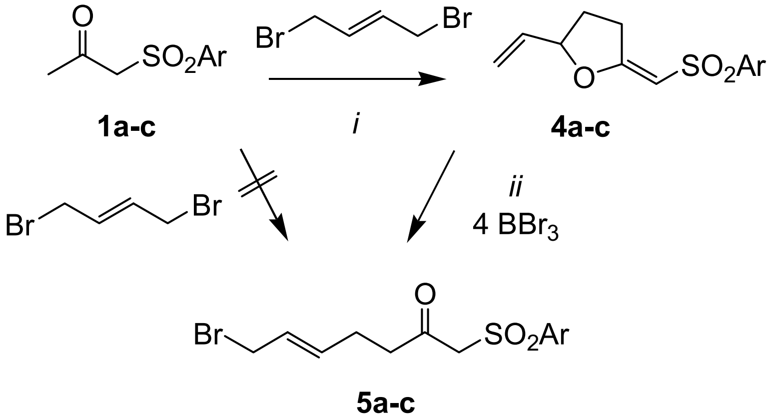
Table 1. Synthesis of **3a-c**

2,3	*Ar*	*% (2)*[a]	E/Z *(2)*[b]	*% (3)*[a]
a	Ph	45	7:3	95
b	4-MeC_6H_4	45	7:3	92
h	4-ClC_6H_4	40	6:4	65

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

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

3-Ketosulfones **7a-d** were prepared by acylation of aryl-[(2-methoxyphenyl)methyl]-sulfones **6a-c**. The cyclization of the dianions of **7a-c** with 1-bromo-2-chloroethane afforded the 2-alkylidenetetrahydrofurans **8a-d**. Treatment of **8a-d** with BBr_3 afforded the 2-(γ-bromoalkyl)-3-sulfonylbenzofurans **9a-d** (Scheme 3, Table 3). The reaction of **8a-c** with BCl_3 gave 2-(γ-hydroxypropyl)-3-sulfonylbenzofuran **9e-g**. The formation of benzofurans **9** can be explained by ring-opening of **8** 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 **9e-g**, the chloride group was hydrolyzed.



Scheme 2. *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

Table 2. Synthesis of **5a-c**

4,5	*Ar*	*% (4)*[a]	E/Z *(4)* [b]	*% (5)*[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

The structure of all products was established by spectroscopic methods. The structures of **8a** and **9a** were independently confirmed by X-ray crystal structure analyses (Figures 1 and 2).[1]

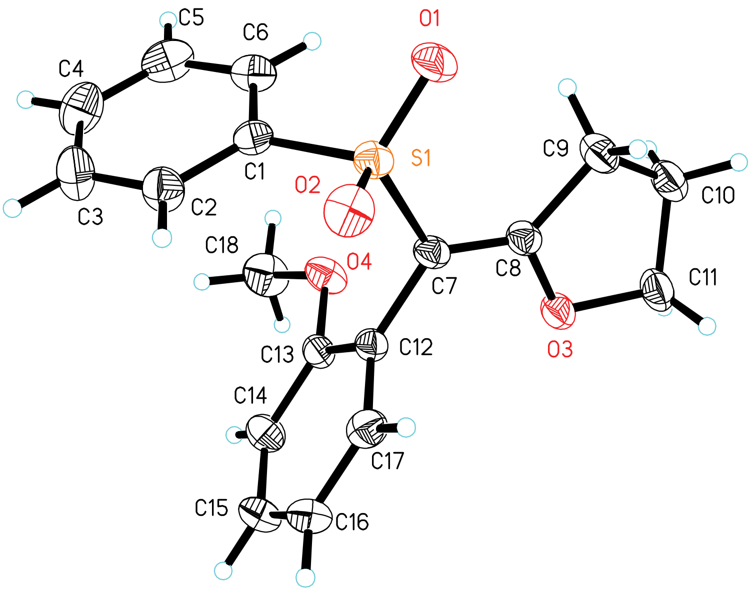
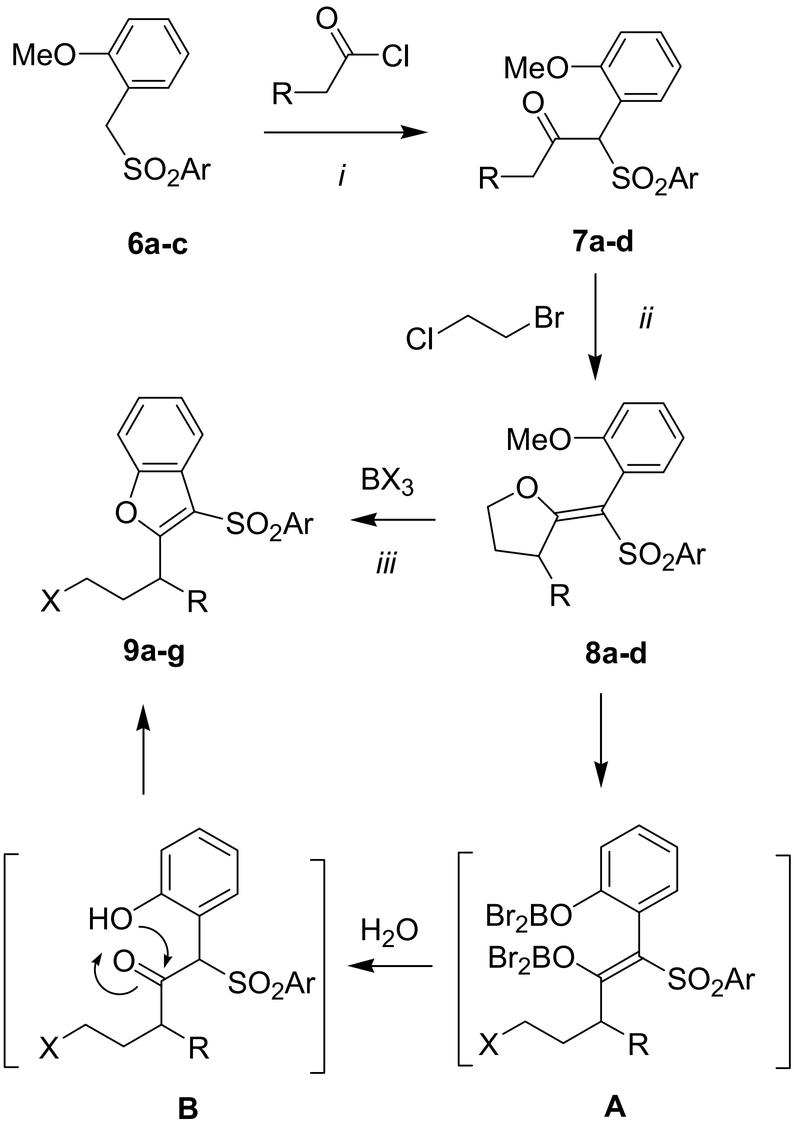


Figure 1. Ortep plot of **8a**



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Scheme 3. Synthesis of benzofurans **9a-e**, *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 3. Synthesis of benzofurans **9a-g**

7,8	*9*	*Ar*	*R*	*X*	*% (7)* [a]	*% (**8**)* [a, c]	*% (**9**)* [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.

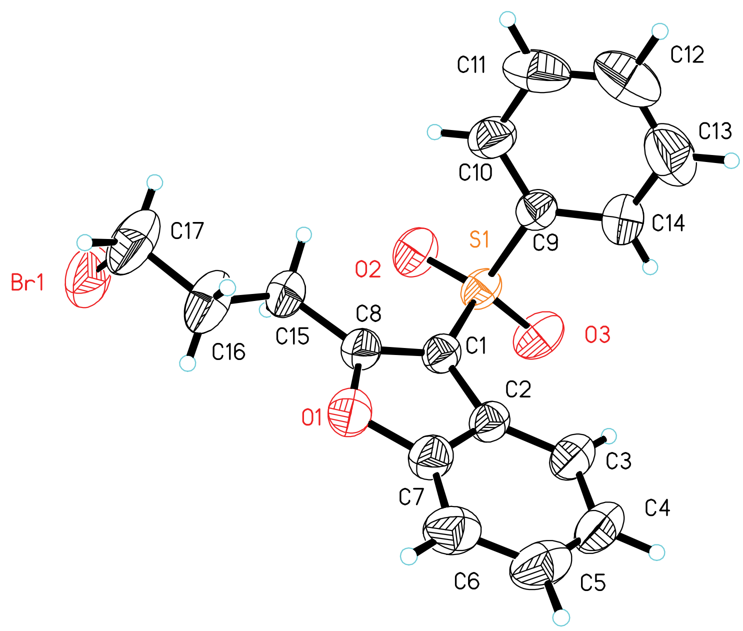
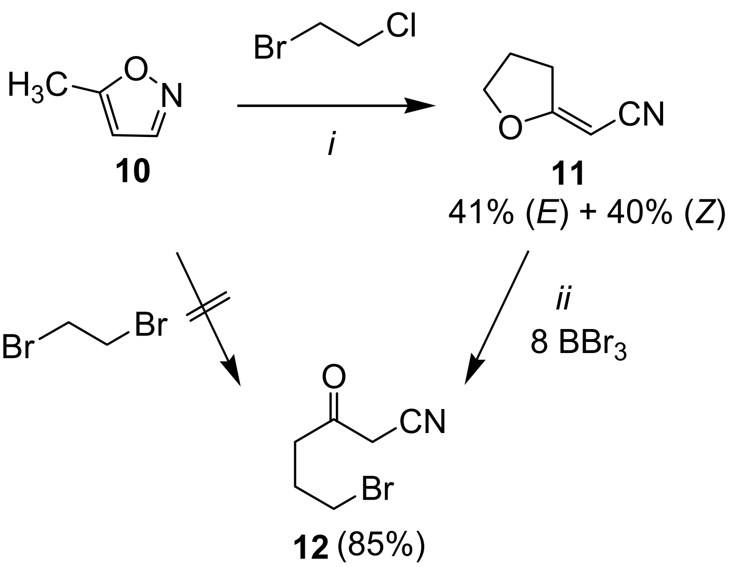


Figure 2. Ortep plot of **9a**

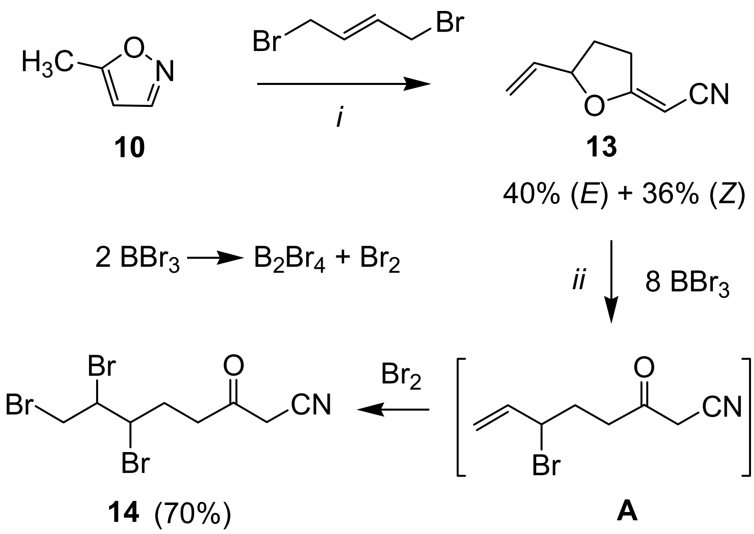
3.2.2. β-Ketonitriles

The known[11a] 2-alkylidenetetrahydrofuran **11** 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 **11** with BBr3 afforded 1-cyano-5-bromo-pentan-2-one (**12**) (Scheme 4). Despite its relatively low molecular weight, it was possible to independently confirm the structure of **12** by an X-ray crystal structure analysis (Figure 3).[19]

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[11a] 2-alkylidenetetrahydrofuran **13**. Treatment of **13** with BBr3 unexpectedtly afforded tribromide **14** (Scheme 5). Product **14** 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).

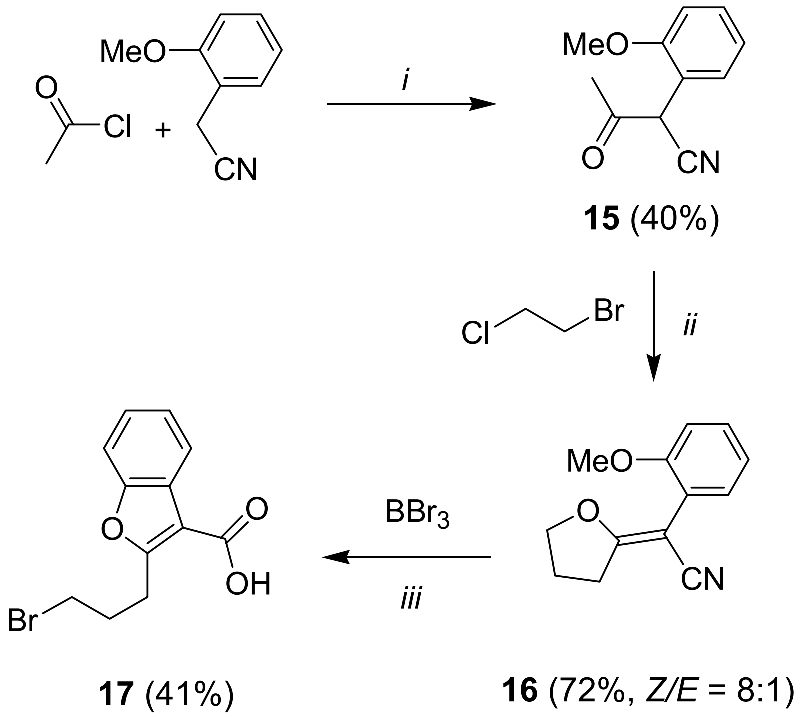


Scheme 4. Synthesis of 1-cyano-5-bromopentan-2-one (**12**). *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) $Br(CH_2)_2Cl$, −78 → 20 °C, 14 h, then reflux, 14 h; *ii*: 1) 8.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 8 h; 2) H_2O

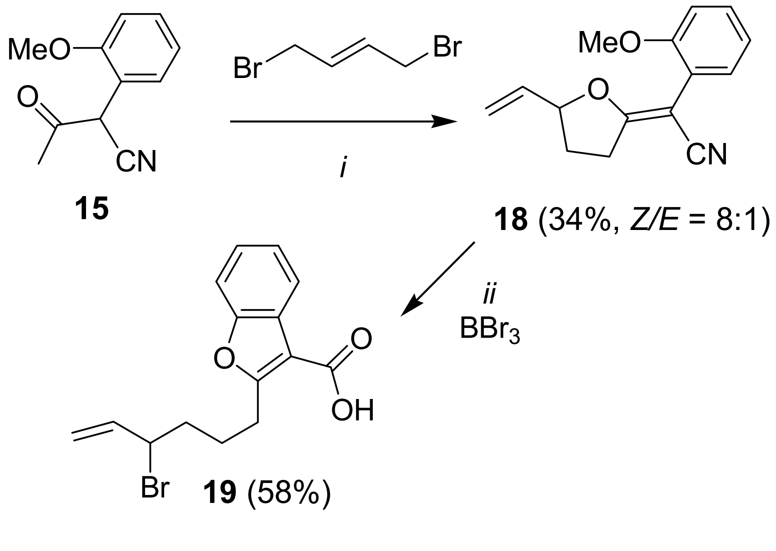


Scheme 5. *i*: 1) 2.5 equiv. LDA, THF, 0 °C, 1 h, 2) 1,4-dibromobut-2-ene, −78 → 20 °C, 20 h;; *ii*: 1) 8.0 equiv. BBr_3, CH_2Cl_2, 0 → 20 °C, 12 h, 20 °C, 6 h; 2) H_2O

The acylation of [(2-methoxyphenyl)acetonitrile with acetyl chloride afforded β-ketonitrile **15**. The cyclization of the dianion of **15** with 1-bromo-2-chloroethane gave 2-alkylidenetetrahydrofuran **16**. Treatment of the latter with BBr_3 and subsequently with HBr (62%) afforded the 2-(γ-bromoalkyl)-3-carboxybenzofuran **17** (Scheme 6). 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 15 proved to be less reactive than sulfones **8** 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 6. Synthesis of benzofuran **17**, *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



Scheme 7. Synthesis of benzofuran **19**, *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.

The cyclization of the dianion of **15** with 1,4-dibromobut-2-ene gave 2-alkylidene-5-vinyltetrahydrofuran **18**. Treatment of the latter with BBr_3 and subsequently with HBr (62%) afforded the 2-(ω-bromoalkyl)-3-carboxybenzofuran **19** (Scheme 7). The nitrile was again hydrolyzed to a carboxylic acid group upon addition of conc. hydrobromic acid.

In conclusion, we reported 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.

3.3. Experimental section

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[((4-Methyphenyl)sulfonyl)methylidene]tetrahydrofuran (2b): Starting with 1-(4-methylphenyl)sulfonyl-2-propanone **1b** (3.00 g, 14.13 mmol), 1-bromo-2-chloroethane (1.4 ml, 16.96 mmol), **2b** was isolated as a colourless solid (1.51 g, 45%, *E/Z* = 7:3), mp. 87 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98-2.09 (m, 2 ×2 H, CH_2, both isomers), 2.34 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.59 (m, 2 H, CH_2), 3.06 (dt, 2 H, J = 7.8 Hz, J = 1.7 Hz, CH_2), 4.14 (t, 2 H, J = 7.0 Hz, CH_2), 4.31 (t, 2 H, J = 6.9 Hz, CH_2), 5.39 (t, 1 H, J = 1.3

Hz, C=C*H*, *Z*-isomer), 5.67 (t, 1 H, J = 1.7 Hz, C=C*H*, *E*- isomer), .7.19-7.29 (m, 2 ×2 H, ArH, both isomers), 7.66-7.79 (m, 2 ×2 H, ArH, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.0 (CH_3), 29.7, 32.2, 36.8, 41.3, 72.7, 75.3 (CH_2), 99.2, 100.6 (CH), 128.5 (2C, CH), 128.6 (2C, CH), 130.0 (2C, CH), 130.3 (2C, CH), 136.4, 138.0, 145.0, 145.7, 169.5, 173.7 (C); IR (KBr): $\tilde{\nu}$ = 2968 (w), 2925 (w), 2886 (w), 1719 (m), 1597 (w), 1314 (s), 1142 (s), 1079 (s), 995 (m), 777 (m), 561 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 238 (M^+, 100), 174 (15), 172 (18), 132 (20), 131 (33), 118 (22), 105 (15), 91 (70), 65 (37); HRMS (ESI): calcd (%) for $C_{12}H_{14}O_3S$ ([M+1]) 238.06581, found 238.06582.

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-[(4-methylphenyl)sulfonyl]-2-pentanone (3b): Starting with **2b** (200 mg, 0.84 mmol) and BBr_3 (0.31 ml, 3.2 mmol), **3b** was isolated as a colourless solid (246 mg, 92%), mp. 48 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (quint, 2 H, J = 6.4 Hz, CH_2), 2.38 (s, 3 H, CH_3), 2.84 (t, 2 H, J = 6.8 Hz, CH_2), 3.33 (t, 2 H, J = 6.4 Hz, CH_2), 4.08 (s, 1 H, CH_2), 7.29 (d, 2 H, J = 8.0 Hz, ArH), 7.69 (d, 2 H, J = 8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3), 26.4, 32.8, 42.8, 67.6 (CH_2), 128.6 (2C, CH), 130.4 (2C, CH), 136.1, 145.9, 197.5 (C); IR (KBr): $\tilde{\nu}$ = 3043 (w), 2920 (w), 1718 (s), 1405 (m), 1317 (s), 1149 (s), 1005 (w), 817 (m), 618 (w), 514 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 320 (M^+, ^{81}Br, 0.40), 318 (M^+, ^{79}Br, 0.53), 256 (5), 254 (5), 238 (4), 212 (13), 155

(56), 151 (32), 149 (36), 148 (33), 91 (100), 65 (30), 41 (19); HRMS (ESI): calcd (%) for $C_{12}H_{15}BrO_3S$ ($[M+1]^+$, ^{81}Br) 317.99132, found 317.99198.

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-[((4-Methylphenyl)sulfonyl)methylidene]-5-vinyltetrahydrofuran (4b): Starting with 1-(4-methylphenyl)sulfonyl-2-propanone **1b** (1.00 g, 4.71 mmol), and 1,4-dibromo-2-butene (1.30 g, 5.65 mmol), **4b** was isolated as a highly viscos colourless oil (475 mg, 38%, *E/Z* = 6:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.66-1.78 (m, 2×1 H, CH–CH_2, both isomers), 2.12-2.24 (m, 2×1 H, CH–CH_2, both isomers), 2.33, 2.37 (2×s, 6H, CH_3), 2.59 (dt, 1 H, J = 7.9 Hz, J = 1.8 Hz, CH_2–C), 2.87-2.99 (m, 1 H, CH_2–C), 3.17-3.28, 3.46-3.50 (2×m, 2 H, CH_2C, *E-Z*), 4.69-4.77, 4.99-5.01 (2×m, 2 H, C*H*–CH_2), 5.10-5.26 (m, 4 H, CH_2=CH, both isomers), 5.40 (t, J = 1.4 Hz, C=C*H*, *Z* isomer), 5.68 (distorted t, J = 1.9 Hz, C=C*H*, *E* isomer), 5.71- 5.78 (m, 2 H, CH_2=C*H*, both isomers), 7.22, 7.28 (2×d, 4H, J = 8.0 Hz, J = 8.0 Hz, ArH, both isomers), 7.67, 7.78 (2×d, 4 H, J = 8.2 Hz, J = 8.3 Hz, ArH, both isomers); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 22.0 (CH_3), 29.3, 29.7, 30.0, 31.6 (CH_2), 85.0, 87.0, 99.7, 100.7 (CH), 117.7, 118.4 (CH_2), 126.8 (2C, CH), 127.7 (2C, CH), 129.5 (2C, CH), 129.9 (2C, CH), 135.3, 135.6 (CH), 141.0, 141.4, 143.5, 143.6, 169.0, 173.0 (C); IR (neat): $\tilde{\nu}$ = 3482(w), 2983 (w), 2925 (w), 2211 (w), 1719 (m), 1628 (s), 1428 (m), 1317 (s), 1151 (s), 816 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 264.1 (M^+, 27), 197 (28), 155 (23), 139.1 (8), 109.1 (50), 91.1 (100), 79.1 (20), 65.1 (23), 39.1 (11); HRMS (ESI): calcd (%) for $C_{14}H_{16}O_3S$ ([M+1]) 264.081655, found 264.08147.

7-Bromo-1-[(4-methylphenyl)sulfonyl]-5-hepten-2-one (5b): Starting with **4b** (110 mg, 0.49 mmol) and BBr_3 (0.23 ml, 2.5 mmol), **5b** was isolated as a highly viscos colourless oil (109 mg, 75%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 2.76 (t, 2 H, *J* = 7.0 Hz, CH_2), 3.84 (distorted d, 2 H, *J* = 6.4 Hz, CH_2), 4.05 (s, 2 H, CH_2), 5.63-5.66 (m, 2 H, C*H*=C*H*), 7.30 (d, 2 H, *J* = 8.1 Hz, ArH), 7.66 (d, 2 H, *J* = 8.1 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_3), 25.8, 33.1, 43.6, 67.5 (CH_2), 128.2 (CH), 128.6 (2C, CH), 130.4 (2C, CH), 133.8, (CH), 136.0, 145.9, 197.5 (C); IR (neat): $\tilde{\nu}$ = 3031 (w), 2925 (m), 2210 (w), 1720 (s), 1320 (s), 1206 (m), 1152 (s), 815 (m), 733 (w), 515 (m) cm^{-1}; GC-MS (CI): *m/z* (%): 347 ($[M+H]^+$, ^{81}Br, 7), 345 ($[M+H]^+$, ^{79}Br, 7), 267 (6), 266 (13), 265 (100), 170 (2), 139 (3), 109 (4); elemental analysis: calcd (%) for $C_{14}H_{17}BrO_3S$(345.25): C 48.70, H 4.96; found: C 48.19, H 4.98.

2-*(Z)*(3-Phenyldihydro)-2(3*H*)-furanylidene-2-(2-methoxyphenyl)-4- phenylsulfone (8a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81-1.93 (m, 2 H, CH_2), 2.27-2.432 (m, 2 H, CH_2), 3.56 (s, 3 H, OCH_3), 4.29-4.38 (m, 2 H, CH_2), 6.71-6.91 (m, 2 H, ArH), 7.12-7.24 (m, 2 H, ArH), 7.31-7.28 (m, 3 H, ArH), 7.85 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3-31.8 (CH_2), 55.6 (OCH_3), 75.1 (CH_2), 108.0 (C), 111.3, 121.0 (CH), 122.5 (C), 128..2 (2C, CH), 128.5 (2C,CH), 130.6, 132.4, 133.9 (CH), 143.8, 158.1, 167.0 (C); IR (KBr): $\tilde{\nu}$ = 3064 (w), 29641 (w), 2904 (w), 2837 (w), 1723 (w), 1634 (s), 1595 (s), 1491 (m), 1446 (s), 1302 (s), 1141 (s), 1117 (m), 1084 (m), 1025 (m), 985 (m), 756 (s), 533 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 330 (M^+, 28), 189 (27), 131 (10), 105 (9), 91 (24), 77 (26), 71 (100), 43 (25); HRMS (ESI): calcd (%) for $C_{18}H_{18}SO_4$ ([M+1]) 330.0923, found 330.09180.

2-(3-Phenyldihydro)-2(3*H*)-furanylidene-2-(2-methoxyphenyl)-(4-chlorophenyl)sulfone (8c): Starting with 1-(2-methoxyphenyl)-1-(4-chlorophenylsulfonyl)acetone (**7c**) (3.49 g, 10.32 mmol), and 1-bromo-2-chloroethane (1.0 ml, 12.38 mmol), **8c** (*E*-isomer) was isolated as a colourless oil (1.84 g, 49%) and **8c** (*Z*-isomer) was isolated as a colourless solid, mp. 144 °C. *E*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.07 (m, 2 H, CH_2), 3.28 (t, 2 H, J = 6.48 Hz, CH_2), 3.32 (s, 3 H, OCH_3), 4.07 (t, 2 H, J= 7.44 Hz, CH_2), 6.62-6.88 (m, 2 H, ArH), 7.14-7.26 (m, 4 H, ArH), 7.44-7.49 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.02, 27.4 (CH_2), 55.5 (OCH_3), 72.6 (CH_2), 110.4 (C), 111.7, 120.8 (CH), 122.9 (C), 128..6 (2C,CH), 129.5 (2C,CH), 133.8, 138.9 (CH), 140.5, 142.9, 159.1, 171.8 (C); IR (KBr): $\tilde{\nu}$ = 3095(w), 3081 (w), 2957 (w), 2902 (w), 1631 (s), 1594 (s), 1594 (m), 1490 (m), 1463 (m), 1306 (s), 1253 (s), 1239 (s), 1148 (s), 1052 (s), 899 (s), 761 (m), 616 (m), 599 (s): cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 364 (M^+, 28), 189 (28), 161 (16), 131 (10), 91 (23), 71 (100), 43 (21); HRMS (ESI): calcd (%) for $C_{18}H_{17}ClSO_4$ ([M+1]) 364.05306, found 364.052826. *Z*-Isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84-1.97 (m, 2 H, CH_2), 2.31-2.38 (m, 2 H, CH_2), 3.60 (s, 3 H, OCH_3), 4.31-4.40 (m, 2 H, CH_2), 6.68-6.93 (m, 2 H, ArH), 7.14-7.35 (m, 4 H, ArH), 7.76-7.81 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 23.3 (CH_2), 55.6 (OCH_3), 75.2 (CH_2), 108.4 (C), 111.3, 121.1 (CH), 122.2 (C), 128.6 (2C,CH), 129.9 (2C,CH), 131.3, 138.9 (CH), 138.5, 143.3, 158.3, 168.2 (C); IR (KBr): $\tilde{\nu}$ = 3080 (w), 3050 (w), 2951 (m), 2804 (m), 1631 (s), 1594 (m), 1585 (m), 1490 (s), 1463 (s), 1304 (s), 1253(m), 1232 (s), 1144 (m), 1052 (s), 899 (m), 762 (s), 616 (s), 591 (s): cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 364 (M^+, 24), 189 (28), 161 (7), 131 (10), 111 (10), 91 (23), 71 (100), 43 (22); HRMS (ESI): calcd (%) for $C_{18}H_{17}ClSO_4$ ([M+1]) 364.05306, found 364.05463.

(2-Methoxyphenyl)-[3-methyldihydo-2(*3H*)-furanylidene]methyl-phenylsulfone (8d): Starting with 1-(2-methoxyphenyl)-1-(phenylsulfonyl)-2-butanone **7d** (500 mg, 1.5 mmol), 1-bromo-2-chloroethane (0.15 ml, 1.8 mmol), **8d** was isolated as a colourless oil

(248 mg, 46%, E/Z = 8:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (t, 3 H, $J_{(Z)}$ = 5.25 Hz, CH_3), 0.79 (t, 3 H, $J_{(E)}$ = 7.25 Hz, CH_3), 1.52-1.62 (m, 2×1 H, CH_2, *Z* isomer), 1.99-2.15 (m, 2×1H, CH_2, *E* isomer), 2.25-2.67 (m, 2×1 H, CH_2, *Z* isomer), 2.70-2.81 (m, 2×1H, CH_2, *E* isomer), 3.49 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 4.24-4.39 (m, 2×2H, CH, both isomers), 6.72-7.02 (m, 5 H, ArH both isomers), 7.21-7.47 (m, 4×2 H, ArH, both isomers), 7.77-7.83 (m, 2×1 H ArH, *Z* isomer), 7.88-7.92 (m, 2×1 H ArH, *E* isomer); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 18.2 (CH_3), 31.8, 31.9 (CH_2), 38.1, 38.9 (CH), 55.6 (OCH_3), 72.6 (CH_2), 110.0 (C), 111.2, 120.6, 121.0 (CH), 122.4 (C), 128.2 (2C, CH), 128.5 (2C, CH), 130.6, 130.9, 133..4, 133.5, (CH), 143.7, 144.0, 158.0, 159.7, 170.5, 171.8, (C); IR (KBr): $\tilde{\nu}$ = 3065 (w), 2968 (m), 2907 (m), 2934 (m), 1719 (m), 1633 (m), 1491 (s), 1447 (s), 1302 (s), 1290 (s), 1253 (s), 1145 (s), 1024 (s), 975 (w), 688 (s), 529 (m): cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 340 (M^+, 27), 203 (100), 173 (15), 131 (14), 91 (42), 77 (33), 43 (27); HRMS (ESI): calcd (%) for $C_{19}H_{20}O_4S$ ([M+1]) 340.10768, found 340.10798.

2-(3-Bromopropyl)-3-(phenylsulfonyl)-benzofuran (9a): Starting with **8a** (148 mg, 0.44mmol) and BBr_3 (0.21 ml, 2.24 mmol), **9a** was isolated as a colourless solid (122 mg, 72%), mp. 92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.62 (quint, 2 H, J = 6.6 Hz, CH_2), 3.65 (t, 2 H, J = 7.4 Hz, CH_2), 3.76 (t 2H, J = 6.4 Hz, CH_2-Br), 7.60 (m, 2 H, ArH), 7.70 (m, 1 H, ArH), 7.75-7.87 (m, 3 H, ArH), 8.16 (m, 1 H, ArH), 7.89 (dd, 2 H, J = 8.17, 1.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 31.3, 32.6 (CH_2), 111.8 (CH), 118.7 (C), 120.8 (CH), 124.5 (C), 124.9 (CH), 125.9 (2C, CH), 127.1 (2C, CH), 129.7, 133.8 (CH), 142.7, 153.7, 162.7 (C); IR (KBr): $\tilde{\nu}$ = 3058 (w), 2927 (w), 1569 (s), 1451 (s), 1327 (s), 1111 (m), 1011 (w), 752 (s), 688 (s), 599 (s), 551 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 380 (M^+, ^{81}Br, 100), 78 (M^+, ^{79}Br, 93), 330 (12), 299 (26), 237 (6), 272 (34), 181 (8) 158 (17), 131 (34), 69 (30), 43 (24); HRMS (ESI): calcd (%) for $C_{!7}H_{15}BrO_3S$ ([M+1], ^{81}Br) 377.99143, found 377.99198.

2-(3-Bromopropyl)-3-[(4-chlorophenyl)sulfonyl]-benzofuran (9c): Starting with **8c** (663mg, 1.8 mmol) and BBr_3 (0.86 ml, 9.1 mmol), **9c** was isolated as a colourless solid (515 mg, 68%), mp. 116 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (quint, 2 H, *J* = 6.6 Hz, CH_2), 3.31 (t, 2 H, *J* = 7.4 Hz, CH_2), 3.43 (t 2H, *J* = 6.4 Hz, CH_2-Br), 7.26 (m, 2 H, ArH), 7.36-7.42 (m, 3 H, ArH), 7.79 (m, 1 H, ArH), 7.89 (d, 2 H, *J* = 8.17 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 31.2, 32.6 (CH_2), 111.9 (CH), 118.4 (C), 120.7 (CH), 124.3 (C), 125.0, 126.1 (CH), 128.6 (2C, CH), 130.0 (2C, CH), 140.4, 141.1, 153.7, 162.9 (C); IR (KBr): $\tilde{\nu}$ = 3083 (w), 3059 (w), 1575 (s), 1452 (s), 1157 (s), 1085 (s), 829 (m), 760(s), 658 (s), 567 (s), 479 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 414 (M^+, ^{81}Br, 100), 412 (M^+, ^{79}Br, 75), 306 (27), 305 (22), 237 (6), 205 (17), 159 (41) 131 (53), 102 (35), 75 (20); HRMS (ESI): calcd (%) for $C_{!7}H_{14}BrClO_3S$ ([M+1], ^{81}Br) 412.96127, found 412.96083.

2-(3-Bromo-1-methylpropyl)-3-(phenylsulfonyl)-benzofuran (9d): Starting with **8d** (90 mg, 0.26 mmol) and BBr_3 (0.12 ml, 1.3 mmol), **9d** was isolated as a highly viscos colourless oil (65 mg, 63%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, 3 H, *J* = 6.8 Hz, CH_3), 2.10-2.19 (m, 1 H, $\tilde{\text{CH}}CH_2$), 2.30-2.38 (m, 1 H, $\tilde{\text{CH}}CH_2$), 3.19-3.25 (m, 2H, CH_2-Br), 4.02-4.09 (m, 1 H, $C\tilde{H}_3CH$), 7.24-7.28 (m, 2 H, ArH), 7.35-7.38 (m, 1 H, ArH), 7.42-7.52 (m, 3 H, ArH), 7.86-7.90 (m, 1 H, ArH), 7.96-8.01 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5 (CH_3), 30.6 (CH_2), 31.8 (CH), 38.0 (CH_2), 111.8 (CH), 118.4 (C), 121.1 (CH), 124.5 (C), 124.9 (CH), 125.9 (2C, CH), 127.1 (2C, CH), 129.7, 133.7 (CH), 142.8, 153.6, 165.8 (C); IR (KBr): $\tilde{\nu}$ = 2974 (w), 2921 (s), 2847(w), 1567 (s), 1473 (s), 1251 (s), 1091 (s), 928 (w), 754 (s), 645 (m), 554 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 394.1 (M^+, ^{81}Br, 47), 392.1 (M^+, ^{79}Br, 45), 285 (100), 233 (4), 156 (9), 144.1 (37), 128.1 (13) 115.1 (34), 89.1 (5), 77.1 (18), 51.1 (8); HRMS (ESI): calcd (%) for $C_{!8}H_{17}BrO_3S$ ([M+1], ^{81}Br) 392.00756, found 392.00763.

2-(3-Hydroxypropyl)-3-(phenylsulfonyl)-benzofuran (9e): Starting with **8a** (227 mg, 0.68 mmol) and BCl_3 (0.53 ml, 3.4 mmol), **9e** was isolated as a higly viscos colourless oil (87 mg, 40%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (quint, 2 H, *J* = 6.4 Hz, CH_2), 3.24 (t, 2 H, *J* = 7.2 Hz, CH_2), 3.63 (t 2H, *J* = 6.0 Hz, CH_2-OH), 7.23-7.27 (m, 2 H, ArH), 7.36-7.38 (m, 1 H, ArH), 7.40-7.53 (m, 3 H, ArH), 7.81-7.84 (m, 1 H, ArH), 7.94 (dd, 2 H, *J* = 8.0, 1.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 31.2, 61.2 (CH_2), 111.7 (CH),118.7 (C),120.8 (CH),124.5 (C), 124.8, 125.8 (CH), 127.0 (2C, CH), 129.7 (2C, CH), 133.8 (CH), 142.6, 153.7, 163.9 (C); IR (KBr): $\tilde{\nu}$ = 2929 (s), 2851 (w), 1711 (w),1568 (s), 1448 (s), 1156 (s), 999 (m), 753 (s), 648 (s), 533 (s), 437 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%):316.1 (M^+, 35), 298.1 (40), 233.1 (12), 219.1 (24), 175.1 (100), 158.1 (15), 145.1 (21) 133 (48), 131.1 (64), 115.1 (50), 77.1 (48); HRMS (ESI): calcd (%) for $C_{!7}H_{16}O_4S$ ([M+1]) 316.07716, found 316.07638.

2-(3-Hydroxypropyl)-3-[(4-chlorophenyl)sulfonyl]-benzofuran (9g): Starting with **8c** (663 mg, 1.8 mmol) and BCl_3 (3.4 ml, 21.6 mmol), **9g** was isolated as a highly viscos colourless oil (300 mg, 47%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.94-2.03 (m, 2 H, *J* = 6.8 Hz, CH_2), 3.23 (t, 2 H, *J* = 7.2 Hz, CH_2), 3.63 (t 2 H, *J* = 5.9 Hz, CH_2-OH), 7.24-7.27 (m, 2 H, ArH), 7.35-7.37 (m, 1 H, ArH), 7.39 (d, 2 H, *J* = 8.7 Hz, ArH), 7.77-7.80 (m, 1 H, ArH), 7.87 (d, 2 H, *J* = 8.7 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.0, 31.1, 61.3 (CH_2), 111.8 (CH), 118.4 (C), 120.6 (CH), 124.3 (C), 125.0, 126.0 (CH), 128.5 (2C, CH), 130.0 (2C, CH), 140.4, 141.1, 153.8, 164.2 (C); IR (neat): $\tilde{\nu}$ = 3404 (w), 2932 (w), 2876 (w), 1573 (s), 1452 (s), 1155 (s), 759 (s), 619 (s), 567 (m), 480 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 350 (M^+, 13), 332 (16), 288 (5), 218 (21), 175 (100), 156 (11), 144 (26) 131 (61), 115 (42), 75 (15); HRMS (ESI): calcd (%) for $C_{17}H_{15}ClO_4S$ ([M+1]) 350.03687, found 350.03741.

2-Dihydro-2(3*H*)-furanylidene-2-(2-methoxyphenyl)acetonitrile (16): Starting with 2-(2-methoxyphenyl)-3-oxobutanenitrile **15** (1.20 g, 6.38 mmol), and 1-bromo-2-chloroethane (0.58 ml, 7.1 mmol), **16** was isolated as a colourless solid (1.00 g, 72%, *Z/E*

= 8:1), mp. 54 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15-2.21 (m, 2 H, CH_2, *Z*- isomer), 2.27-2.36 (m, 2 H, CH_2, *E*- isomer), 2.74, 3.20 (2×t, 4 H, $J_{(Z)}$ = 7.8 Hz, $J_{(E)}$ = 7.8 CH_2), 3.97 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 4.45-4.57 (m, 2×2 H, CH_2, both isomers), 7.06 (dd, 1 H, *J* = 8.9, 7.8 Hz, ArH), 7.29 (dd, 1 H, *J* = 5.91, 1.5 Hz, ArH), 7.37-7.49 (m, 2 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 24.5, 30.2, 30.8 (CH_2), 55.9, 56.0 (CH_3), 73.9, 75.0 (CH_2), 77.1, 78.9, 109.0 (C), 111.0 (CH), 116.0 (CN), 120.7, 129.6, 131.4 (CH), 154.6, 155.0, 170.8, 172.5 (C); IR (KBr): $\tilde{\nu}$ = 3441 (w), 2963 (w), 2935 (w), 2205 (s), 1628 (s), 1578 (m), 1462 (m), 1265 (s), 1184 (s), 762 (s), 656 (w) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 215 (M^+, 100), 184 (15), 158 (22), 144 (29), 115 (18), 84 (52), 75 (10); HRMS (ESI): calcd (%) for $C_{13}H_{13}NO_2$ ([M+1]) 215.09408, found 215.09436.

2-(3-Bromopropyl)-benzofuran-3-carboxlic acid (17): Starting with **16** (600 mg, 2.7 mmol), BBr_3 (1.5 ml, 16.7 mmol), and HBr (0.7 ml, 16.7 mmol), **17** was isolated as a highly viscos colourless oil (322 mg, 41%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.92-2.02 (m, 2 H, CH_2), 2.91 (t, 2 H, *J* = 8.04 Hz CH_2), 3.70 (t, 2 H, *J* = 6.98 Hz CH_2), 6.98-7.19 (m, 3 H, ArH), 7.36-7.42 (m, 4 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 37.9, 61.7 (CH_2), 93.8 (C), 190.2, 117.7, 120.8, 123.2 (CH), 125.0, 148.2, 164.2, 194.6 (C); IR (KBr): $\tilde{\nu}$ = 3385 (s), 3273 (m), 3064 (w), 2924 (s), 2854 (m), 1653 (s), 1493 (s), 1459 (m), 1243 (w), 1173 (m), 1019(m), 743 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 281 (M^+, 25), 201 (100), 175 (20), 160 (80), 103 (10), 82 (12); HRMS (ESI): calcd (%) for $C_{12}H_{11}BrO_3$ ([M+1]) 281.52341, found 281.53216.

2-(5-Vinyldihydro)-2(3*H*)-furanylidene-2-(2-methoxyphenyl)-acetonitrile (18): Starting with 2-(2-methoxyphenyl)-3-oxobutanenitrile **15** (1.30 g, 6.8 mmol), and 1,4-dibromo-2-butene (1.60 g, 7.5 mmol), **18** was isolated as a colourless oil (622 mg, 37%, *Z/E* = 8:1); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.51-2.69 (m, 2×2 H, CH_2, both isomers), 2.99 (t, 2 H, J = 7.6 Hz, CH_2), 4.18 (s, 3 H, OCH_3), 4.20 (s, 3 H, OCH_3), 5.27-5.40 (m, 1 H, CH), 5.60 (d, 2×1 H, *J* = 13.1 Hz, CH_2), 5.67 (d, 2×1 H, *J* = 17.1 Hz, CH_2), 6.18-6.33 (m, 2×1 H, CH, both isomers), 7.18-7.35 (m, 2 H, ArH), 7.51-7.81 (m, 2 H, ArH); ^{13}C

NMR (75 MHz, $CDCl_3$): δ = 30.0, 31.6 (CH_2), 56.0 (OCH_3), 81.5 (C), 86.0, 87.2 (CH), 111.0 (CH), 116.0 (CN), 118.1 (CH_2), 119.4 (C), 120.8, 121.8, 128.9, 129.6, 131.5, 135.8 (CH), 156.9, 172.3, 173.9 (C); IR (KBr): $\tilde{\nu}$ = 2936 (m), 2839 (w), 2207 (m), 1731 (m), 1635 (s), 1595 (m), 1580 (w), 1464 (s), 1262 (s), 996 (s), 757 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 241 (M^+, 100), 210 (39), 184 (15), 173 (49), 158 (21), 115 (28), 67 (23); HRMS (ESI): calcd (%) for $C_{15}H_{15}NO_2$ ([M+1]) 241.10983, found 241.10973.

2-(3-Bromo-4-pentenyl)-benzofuran-3-carboxylic acid (19): Starting with **18** (502 mg, 2.07 mmol), BBr_3 (1.17 ml, 12.44 mmol), and HBr (0.58 ml, 12.44 mmol), **19** was isolated as a colourless solid (375 mg, 58%), mp. 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84-2.09 (m, 2 H, CH_2), 287 (t, 2 H, *J* = 8.4 Hz, CH_2), 4.20 (m, 1 H, CH), 5.07 (d, 1 H, *J* = 13.4 Hz CH_2), 5.25 (d, 1 H, *J* = 17.4 Hz, CH_2), 5.77-5.92 (m, 1 H, CH), 7.11-7.49 (m, 4 H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.0,37.8 (CH_2), 72.0 (CH), 94.1 (C), 110.7 (CH), 115.0 (CH_2), 119.1, 122.1, 124.6 (CH) ,125.9 (C), 141.2 (CH), 149.1, 165.3, 195.4 (C); IR (KBr): $\tilde{\nu}$ = 3410 (m), 3252 (m), 3195 (m), 1653 (s), 1495 (s), 1479 (s), 1416 (m), 1371 (w), 1173 (m), 1017 (m), 959 (m), 729 (m): cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 309 (M^+, 19), 227 (20), 175 (33), 160 (100), 133 (17), 104 (10), 77 (15); HRMS (ESI): calcd (%) for $C_{14}H_{13}BrO_3$ ([M+1])309.23461, found 309.23156.

3.4. References

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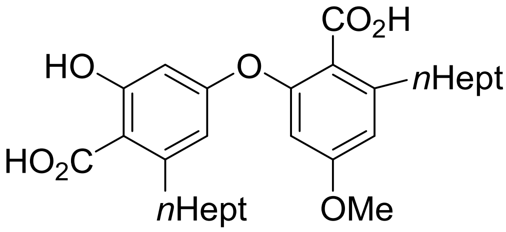
Chapter 4

Regioselective Synthesis of Diaryl Ethers based on One-Pot Cyclizations of 4-Aryloxy-1,3- bis(trimethylsilyloxy)-1,3-dienes

Tetrahedron **2008**, *64*, 529-535.

4.1. **Introduction**

Functionalized diaryl ethers are of pharmacological relevance and occur in a variety of natural products.[1] This includes, for example, geodinhydrate methylester, methyl chloroasterrate,[2a,b] 1-desgalloylsanguiin,[2c] dehydrotrigallic acid,[2d] epiphorellic acid,[2e] jolkianin,[2f] remurin A,[2g] and micareic acid (Scheme 1).[2h] The most important approach to diaryl ethers relies on the Ullmann[3] and Buchwald-Hartwig[4] reaction and on related transformations.[5] 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 often difficult or not possible at all. Some years ago, Chan *et al.* developed[6] a convenient approach to salicylates based on the cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes[7] with 3-trimethylsilyloxy-2-en-1-ones. We reported the application of this method to the synthesis of a variety of substituted benzene derivatives.[8] Recently, we reported the synthesis of 5-aryloxysalicylates[9] and 5-thioaryloxysalicylates based on reactions of 2-aryloxy- and 2-thioaryloxy-3-trimethylsilyloxy-2-en-1-ones, respectively.[10] Herein, we report, for the first time, the synthesis of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes and their application to the synthesis of diaryl ethers. Noteworthy, the reactions reported herein allow a convenient and regioselective synthesis of sterically encumbered and functionalized diaryl ethers which are not readily available by other methods.

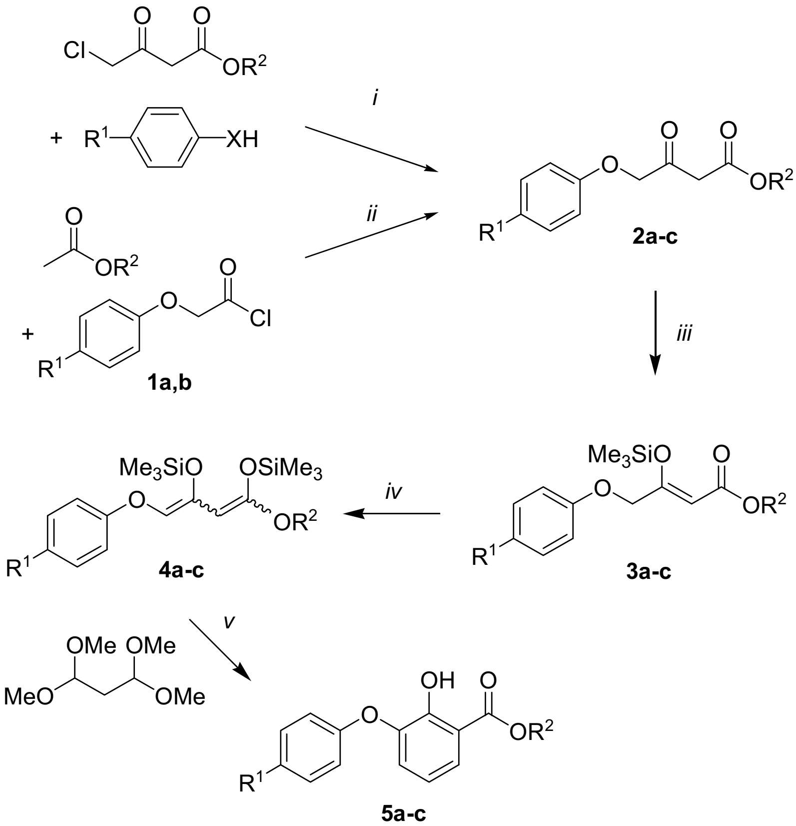


Micareic acid

Scheme 1. Micareic acid

4.2. Results and Discussion

Ethyl 4-phenoxyacetoacetate (**2a**) was prepared by base-mediated reaction of ethyl 4-chloroacetoacetate and phenol (Scheme 2, Table 1). The methyl 4-phenoxyacetoacetates **2b,c** were prepared by Claisen condensation of methyl acetate with the corresponding α-aryloxyacetic chlorides. The silylation of **2a-c** gave the 3-silyloxy-2-en-1-ones **3a-c**. The novel 4-aryloxy-1,3-bis(silyloxy)-1,3-dienes **4a-c** were prepared by deprotonation (LDA) of **3a-c** at −78 °C and subsequent addition of trimethylchlorosilane. The Me_3SiOTf-catalyzed cyclization of 4-aryloxy-1,3-bis(silyloxy)-1,3-dienes **4a-c** with 1,1,3,3-tetramethoxypropane, following our recently reported protocol,[11] afforded the 3-aryloxysalicylates **5a-c**. During the optimization of the cyclization, the concentration and the stoichiometry proved to play an important role.



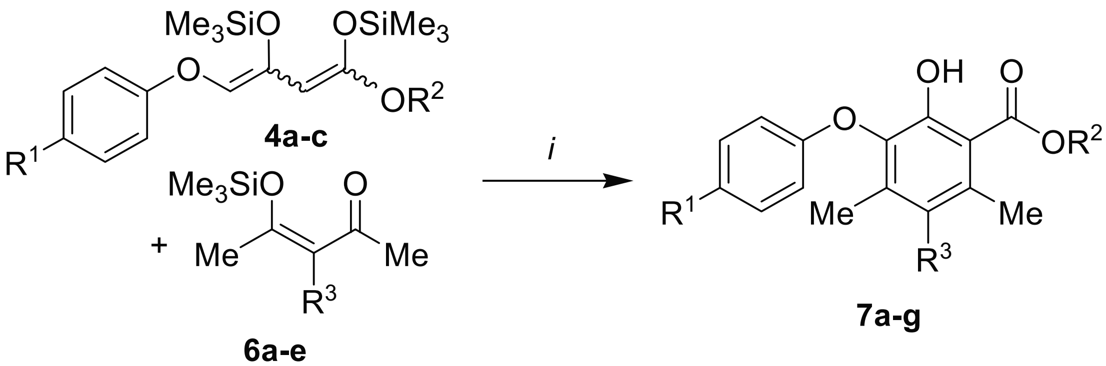
Scheme 2. Synthesis of **5a-c**; *i*: NEt_3/KOH, CH_2Cl_2/DMSO, 30 min, 0 °C/ 5 h, 20 °C; *ii*: : LDA, THF, –78 → 20 °C, 14 h; *iii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; *iv*: : LDA, THF, –78 → 20 °C; *v*: Me_3SiOTf, CH_2Cl_2, –78 → 20 °C, 20 h

Table 1. Synthesis of diaryl ethers **5a-c**

2-5	R^1	R^2	% (**2**) [a]	% (**3**) [a]	% (**4**) [a]	% (**5**) [a]
a	H	OEt	60	91	82	45
b	Cl	OMe	30	74	82	46
c	Me	OMe	40	75	84	48

Isolated yields

The $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-dienes **4a-c** with 3-silyloxy-2-en-1-ones **6a-e** afforded the 3-aryloxysalicylates **7a-g** (Scheme 3, Table 2). 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.



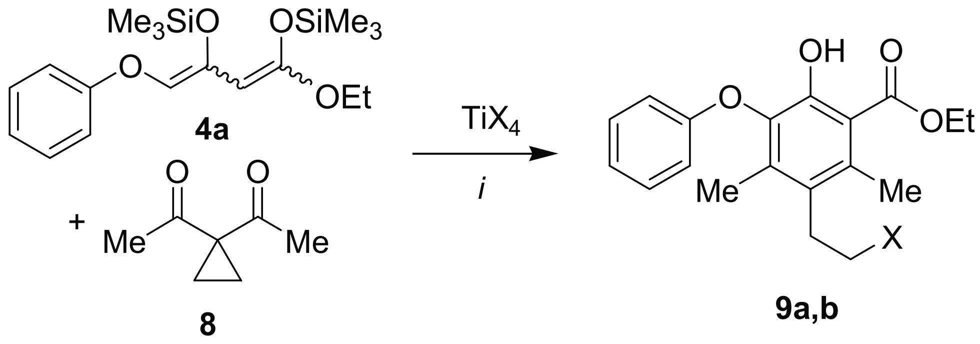
Scheme 3. Synthesis of **7a-g**; *i*: $TiCl_4$, CH_2Cl_2, $-78 \rightarrow 20$ °C, 20 h

Table 2. Synthesis of diaryl ethers 7a-g

4	6	7	R^1	R^2	R^3	% (**7**)[a]
a	**a**	**a**	H	OEt	H	37
a	**b**	**b**	H	OEt	Me	43
a	**c**	**c**	H	OEt	Cl	38
a	**d**	**d**	H	OEt	ArO [b]	30
a	**e**	**e**	H	OEt	PhS	30
b	**c**	**f**	Me	OMe	Cl	40
c	**b**	**g**	Cl	OMe	Me	40

[a] Isolated yields; [b] Ar = 3,4-$(MeO)_2C_6H_3$

The $TiCl_4$- and $TiBr_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-diene **4a** with 1,1-diacetylcyclopropane (**8**) afforded the 3-phenoxysalicylates **9a,b** containing a remote halide function (Scheme 4, Table 3). The formation of the products can be explained by means of a domino ′[3+3]-cyclization-homo-Michael′ reaction.[13] The structures of **9a** and **9b** were independently confirmed by X-ray crystal structure analyses (Figures 2 and 3).



Scheme 4. Synthesis of 9a,b; *i*: TiX_4 (X = Cl, Br), CH_2Cl_2, –78 → 20 °C, 20 h

Table 3. Synthesis of 9a,b

9	X	% (**9**) [a]
a	Cl	40
b	Br	33

a Isolated yields

The Me_3SiOTf-catalyzed reaction of 1,3-bis(silyloxy)-1,3-diene **4a** with 3-formylchromone **10** afforded the highly functionalized diaryl ether **11** (Scheme 5). The products are formed by a domino ′Michael–retro-Michael–Mukaiyama-Aldol′ reaction.[14]

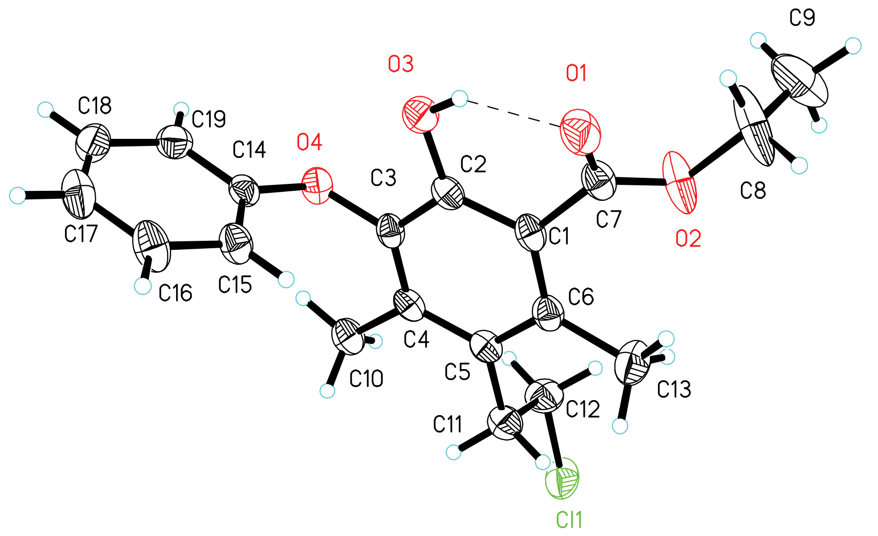


Figure 2. Ortep plot of **9a**

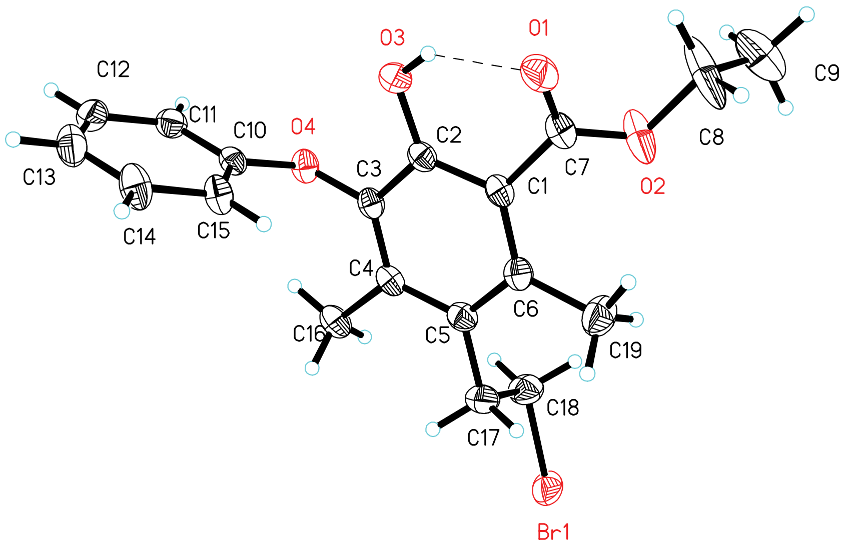
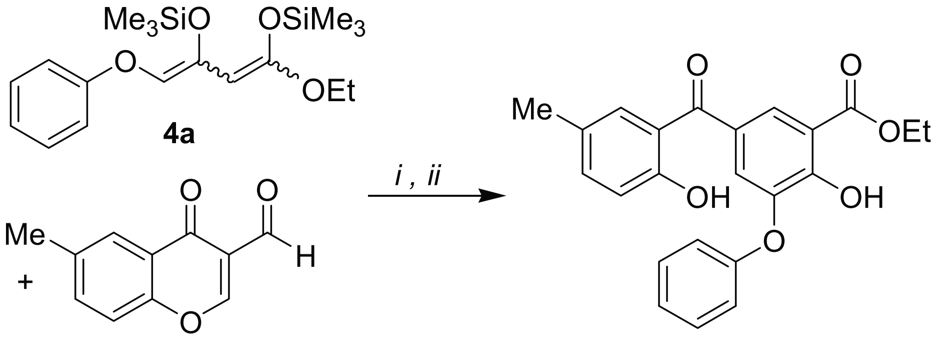


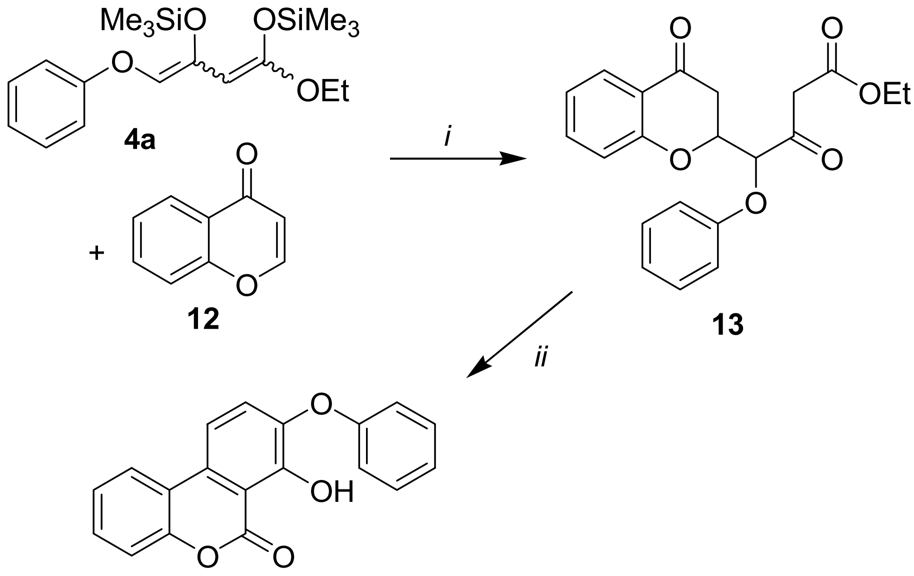
Figure 3. Ortep plot of **9**



10 **11** (35%)

Scheme 5. Synthesis of **11**; *i*: Me_3SiOTf (0.3 equiv), 20 °C, 10 min; *ii*: 1) **4a** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; 2) HCl (10%)

The Me_3SiOTf-catalyzed reaction of **4a** with chromone (**12**) afforded product **13** which was transformed (without purification) into the diaryl ether **14** (Scheme 6). The transformation of **13** into **14** proceeds by a domino ′Michael–retro-Michael–lactonization′ reaction.[15]



14 (70% from **12**)

Scheme 6. Synthesis of **14**; *i*: 1) Me_3SiOTf (0.3 equiv), 20 °C, 1 h; 2) **4a** (1.3 equiv), CH_2Cl_2, 0 → 20 °C, 12 h; 3) HCl (10%); *ii*: NEt_3 (2.0 equiv), EtOH, 20 °C, 12

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

4.3. Experimental section

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60-200 mesh) was used. Melting points are uncorrected.

General procedure for the synthesis of aryloxyacetoacetates 2a-c: ***Method A***: To a mixture of potassium hydroxide (2.0 mmol) in 2 mL of DMSO was dropwise added 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-chloroacetoacetate (1.0 mmol) was added. The mixture was stirred at room temperature overnight and then acidified by addition of hydrochloric acid (4 M). The mixture was extracted with EtOAc and the organic layer was washed with water and then with brine, and dried over Na_2SO_4. The solution was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Method B**:** A THF solution of 2.3 equiv. of LDA was prepared by addition of *n*-BuLi (0.93 mL, 2.3 mmol, 2.5 M solution in hexanes) to a THF solution (6 mL) of diisopropylamine (0.32 mL, 2.3 mmol) at 0 °C. After stirring of the solution for 30 min, methyl acetate (0.09 mL, 1.1 mmol) was added at 0 °C. After stirring for 45-60 min, to the solution was added a THF solution (4 mL) of the acid chloride (205 mg, 1.0 mmol) at −78 °C. The temperature was allowed to rise to 20 °C during 5-6 h and the solution was stirred at 20 °C for 8 h. To the solution was added a diluted aqueous solution of HCl and the mixture was 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).

General procedure for the synthesis of diaryl ethers 5a-c: To a dichloromethane solution (2 mL / mmol of **4**) of **4** (1.0 mmol) and of 1,1,3,3-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.

General procedure for the synthesis of diaryl ethers 7a-g: To a dichloromethane solution (2 mL / mmol of **4**) of **4** (1.0 mmol) and of **6** (1.0 mmol) was added $TiCl_4$ (1.0 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 $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane = 1:4).

Synthesis of ethyl-5-(2-hydroxy-3-methylbenzoyl)-3-phenoxysalicylate (11): Me_3SiOTf (0.3 equiv) was added to the 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 added. The mixture was stirred at 20 °C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine (25 mL) and dried over Na_2SO_4. The mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Synthesis of 8-phenoxy-7-hydroxy-6*H*-benzo[*c*]chromen-6-one (14): Me_3SiOTf (1.3 equiv) was added to the chromone (1.0 equiv) at 20 °C. After stirring for 1 h, 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 added. The mixture was stirred at 20 °C for 12 h and was subsequently poured into an aqueous solution of HCl (10%). The organic and the aqueous layer were separated and the latter was extracted with CH_2Cl_2 (3 x 15 mL) and dried over Na_2SO_4. The mixture was filtered and the solvent f the filtrate was removed under reduced pressure to give crude product **13**. To an EtOH solution (10 mL) of the latter was added NEt_3 (2.0 equiv) and the mixture was stirred for 12 h at 20 °C. To the solution was added hydrochloric acid (1 M) and then EtOAc. The organic and the aqueous layer were separated and the latter was extracted with EtOAc and dried over Na_2SO_4. The mixture was filtered and the solvent of the filtrate was removed under reduced pressure. The crude product was purified by chromatography (silica gel, EtOAc / *n*-heptane).

Ethyl 4,6-dimethyl-5-(2-chloroethyl)-3-phenoxysalicylate (9a): Starting 1,1-diacetylclopropane (**15**) (300 mg, 2.4 mmol) 1,3-bis(silyl enol ether) **4a** (1.200 g, 3.3 mmol), $TiCl_4$ (0.52 mL, 4.8 mmol) and CH_2Cl_2 (110 mL), **9a** was isolated as colourless crystals (328 mg, 40%), mp. 75 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, J = 7.25 Hz, CH_3), 2.14 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 3.07 (t, 2 H, J = 6.45 Hz, CH_2), 3.45 (t, 2 H, J = 7.5 Hz, CH_2), 4.37 (q, 2 H, J = 6.5 Hz, CH_2), 6.76 (m, 2 H, ArH), 6.94 (m, 1 H, ArH), 7.76 (m, 2 H, ArH), 10.41 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.4, 13.1, 17.3 (CH_3), 32.2, 41.1, 60.9 (CH_2), 112.9 (C), 113.6 (2C CH), 120.7 (CH), 126.4 (C), 128.5 (2C CH), 133.9 136.0, 138.0, 151.9, 156.7, 169.8 (C); IR (Nujol): $\tilde{\nu}$ = 3381 (w), 2981 (s), 1728 (m), 1669 (m), 1590 (m), 1491 (m), 1301 (m), 1218 (m), 1167 (m), 1036 (m), 788 (w) 750 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 450 (M^+, ^{37}Cl, 13),448 (M^+, ^{35}Cl, 41), 403 (73), 267 (83), 253 (43), 105 (100), 77 (22); HRMS (EI): calcd for $C_{19}H_{21}O_4Cl$ [M^+,^{35}Cl]: 448.11229, found 448.11180.

Ethyl 4,6-dimethyl-5-(2-bromoethyl)-3-phenoxysalicylate (9b): Starting with 1,1-diacetylcyclopropane **15** (300 mg, 2.4 mmol), 1,3-bis(silyl enol ether) **4a** (1.20 g, 3.3 mmol), $TiBr_4$ (873 mg, 2.4 mmol), and CH_2Cl_2 (110 mL), **9b** was isolated as colourless crystals (315 mg, 33%), mp. 103 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, 3 H, J = 7.1 Hz, CH_3), 2.03 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 3.05 (m, 2 H, CH_2), 3.22 (m, 2 H, CH_2), 4.27 (q, 2 H, J = 7.1 Hz, CH_2), 6.65 (m, 2 H, ArH), 6.83 (m, 1 H, ArH), 7.08 (m, 2 H, ArH), 10.23 (s, 1 H, OH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 11.4, 12.2, 16.3 (CH_3), 27.6, 31.6, 59.9 (CH_2), 111.9 (C), 112.6 (2C CH), 119.5 (CH), 126.5 (C), 127.6 (2C CH), 132.8, 134.9, 137.0, 151.0, 155.7, 168.8 (C); IR (Nujol): $\tilde{\nu}$ = 3375 (w), 2978 (s), 1734 (m), 1675 (m), 1590 (m), 1490 (m), 1319 (m), 1219 (m), 1176 (m), 1029 (m), 751 (w) 690 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 393 (M^+, ^{81}Br, 40), 391 (M^+, ^{79}Br, 40), 347 (62), 313 (26), 267 (100), 253 (33), 105 (89), 77 (34); HRMS (EI): calcd for $C_{19}H_{21}O_4Br$ ([$(M+1)^+$, ^{79}Br]: 392.06177, found 392.06199.

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Chapter 5

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′

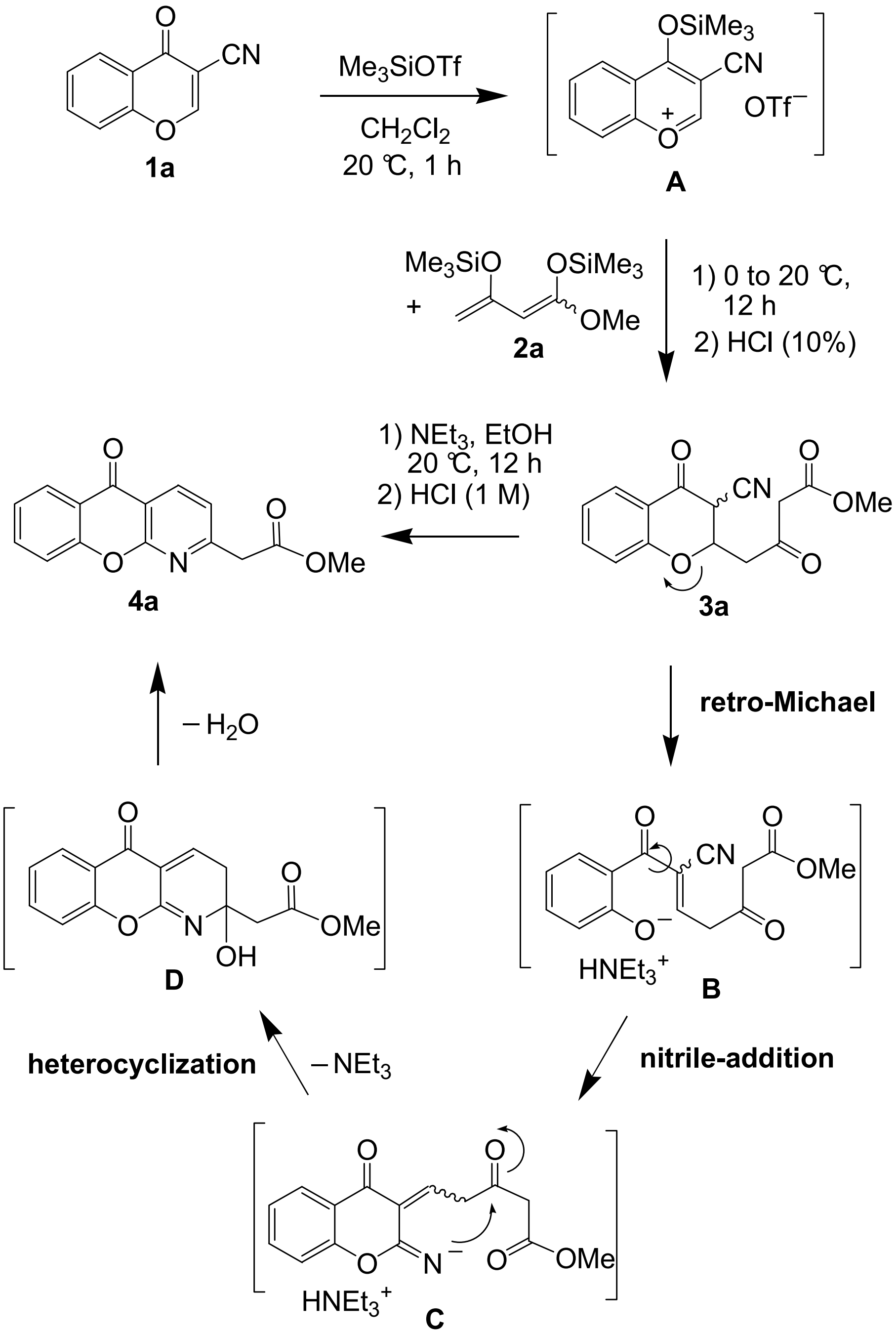
Tetrahedron **2008,** submitted

5.1. Introduction

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.[1] 1-Azaxanthones are available, based on pioneering work of Ghosh and coworkers,[2a] by base-mediated reaction of 3-cyanochromones with active methylene compounds.[2] 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.[3] Later, the TMSOTf-mediated [4+2]-cycloaddition of 1,3-butadienes with 3-cyanochromone, via its 4-(trimethylsilyloxy)benzopyrylium triflate, has been reported.[4] In the course of our interest in the development of new domino reactions[5] of 4-(silyloxy)benzopyrylium triflates,[6] we recently reported[7] the TMSOTf-mediated reaction of 3-cyanochromones with 1,3-bis(trimethylsilyloxy)-1,3-butadienes.[8] These reactions allow a convenient synthesis of functionalized 1-azaxanthones which are not readily available by other methods. Herein, full details of our methodology and a comprehensive study related to its preparative scope are reported.

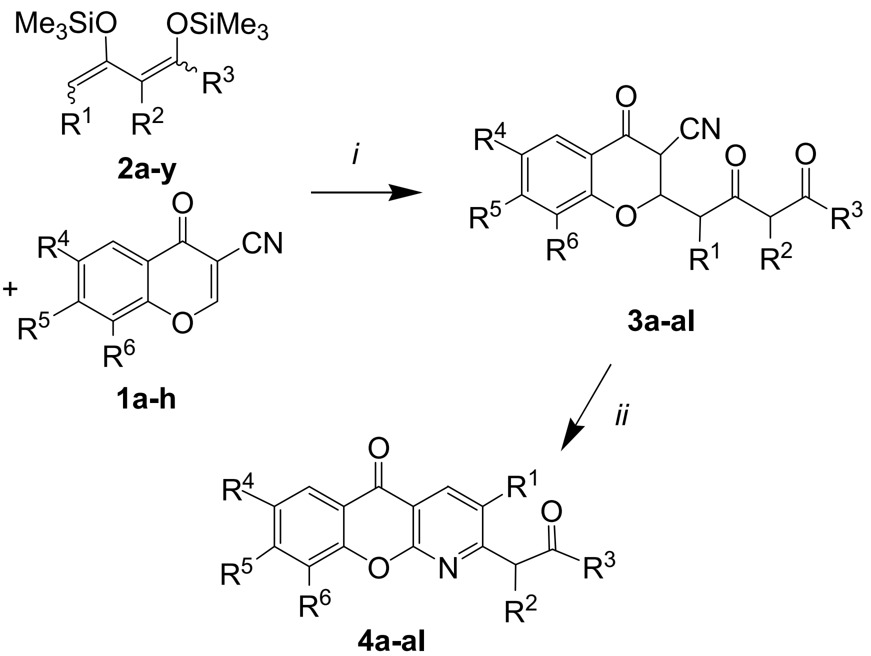
5.2. Results and Discussion

The TMSOTf-mediated reaction of **1a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **2a**, readily available in two steps from methyl acetoacetate,[9] afforded the condensation product **3a** by regioselective attack of the terminal carbon atom of **2a** onto carbon atom C-2 of **1a** and subsequent hydrolysis. Treatment of an ethanol solution of crude **3a** with triethylamine afforded 1-azaxanthone **4a** (Scheme 1). The formation of **4a** can be explained by a domino 'retro-Michael-lactonization-aldol' reaction. The base-mediated retro-Michael reaction of **3a** 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 **4a**. The transformation of **3a** into **4a** can be regarded as a domino 'retro-Michael / nitrile-addition / heterocyclization' reaction.

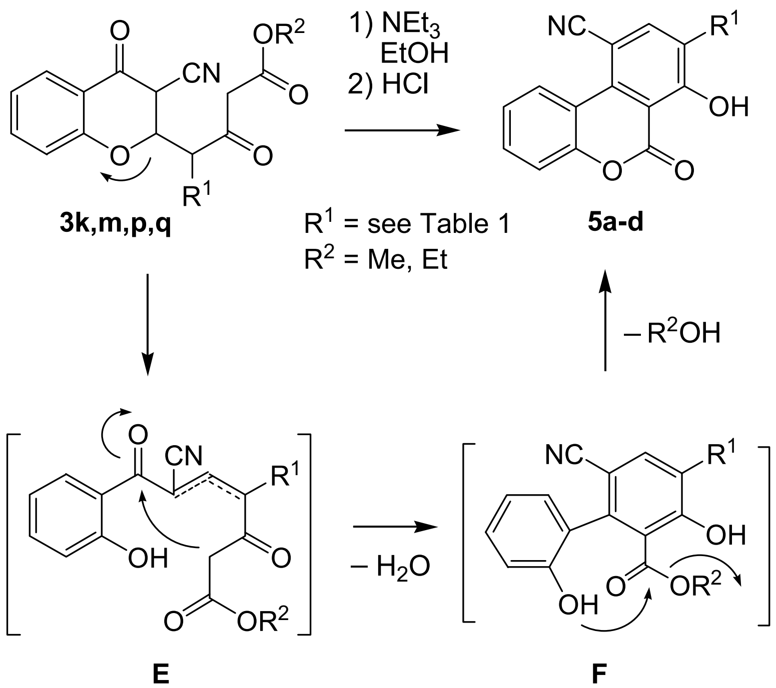


Scheme 1. Mechanism of the formation of **4a**

The reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **2a-c**, prepared from methyl, ethyl and isopropyl acetoacetate, with parent 3-cyanochromone (**1a**) and with the alkyl- and halogen-substituted 3-cyanochromones **1b-g** afforded products **3a-j** which were transformed, by reaction with NEt_3, into the 1-azaxanthones **4a-j** (Scheme 2, Table 1). The reaction of parent 3-cyanochromone **1a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **2d**, prepared from methyl 3-oxopentanoate, afforded **3a**. Treatment of **3a** with triethylamine afforded dibenzo[*b*,*d*]pyran-6-one **5a** rather than the expected methyl-substituted azaxanthone **4k**. The formation of **5a** can be explained by a competing domino ′retro-Michael-aldol-lactonization′ reaction (Scheme 3).[10] In contrast, the reaction of **2e** (derived from ethyl 3-oxopentanoate) with chlorinated 3-cyanochromone **1e** afforded azaxanthone **4l** (via **3l**). The reaction of parent cyanochromone **1a** with 1,3-bis(silyl enol ether) **2f**, prepared from ethyl 3-oxohexanoate, afforded **3m**. Treatment of the latter with base resulted in formation of a separable mixture of ethyl-substituted azaxanthone **4m** and dibenzo[*b*,*d*]pyran-6-one **5b**. In contrast, the exclusive formation of azaxanthones **4n,o** was observed when substituted cyanochromones **1e** and **1h** were employed. The propyl- and butyl-substituted dibenzo[*b*,*d*]pyran-6-ones **5c** and **5d** were isolated from the reaction of parent cyanochromone **1a** with 1,3-bis(trimethylsilyloxy)-1,3-butadienes **2g** and **2h**. The reaction of **2i** with **1a** and **1e** exclusively afforded the heptyl-substituted azaxanthones **4r** and **4s**, respectively. The allyl-substituted azaxanthones **4t** and **4u** were prepared from **2j**.



Scheme 2. Synthesis of 1-azaxanthones 4a-al a: *i*: 1) 1a-h, Me_3SiOTf, 1 h, 20 °C, 2) 2a-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 3. Mechanism of the formation of **5a-d**

Table 1. Products and yields

1	*2*	*4*	*5*	R^1	R^2	R^3	R^4	R^5	R^6	% *(4,5)*[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	O*i*Pr	H	H	H	42
b	**a**	**d**		H	H	OEt	Me	H	H	40
c	**c**	**e**		H	H	O*i*Pr	Et	H	H	31
d	**a**	**f**		H	H	OEt	*i*Pr	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	O*i*Pr	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**	*n*Pr	H	OMe	H	H	H	0 (37)[b]
a	**h**	**q**	**d**	*n*Bu	H	OMe	H	H	H	0 (42)[b]
a	**i**	**r**		*n*Hept	H	OEt	H	H	H	25
e	**i**	**s**		*n*Hept	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	**ac**	**ap**	H	H	Me	H	H	H	0

[a] Yields of isolated products **4** over two steps (based on **1**). [b] Yields in brackets refer to **5a-d** (structures see Scheme 3). [c] dr = 2:3

The reaction of 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-butadienes **2k-m** with 3-cyanochromones **1a,b,e** gave the products **3v-y** which were transformed into the 3-aryl-1-azaxanthones **4v-y**. 3-Methoxy-1-azaxanthone **4z** was prepared from 4-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **2n** which is available from methyl 4-methoxyacetoacetate. The reaction of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes **2o-q** with **1a,f,h** afforded the condensation products **3aa-ad** which were transformed into the 3-aryloxy-1-azaxanthones **4aa-ad**. Starting with 4-thioaryloxy-1,3-bis(trimethylsilyloxy)-1,3-butadienes **2r-u**, the 3-thioaryloxy-1-azaxanthones **4ae-ah** were prepared. 1-Azaxanthones **4ai** and **4aj** were prepared from **1a** and from 2-methyl- and 2-ethyl-1,3-bis(trimethylsilyloxy)-1,3-butadienes **2v** and **2w**, respectively. The reaction of **1a** with cyclohexanone-derived 1,3-bis(trimethylsilyloxy)-1,3-butadienes **2x** and **2y** gave **3ak** and **3al** which were transformed into the tetracyclic azaxanthones **4ak** and **4al**, respectively. The employment of 7- and 12-membered cyclic 1,3-bis(trimethylsilyloxy)-1,3-butadienes **2z** and **2aa** 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 (**2ab**) or 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**2ac**), resulted in the formation of complex mixtures.

The overall yields of 1-azaxanthones **4a-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 **4w-y** prepared from the phenyl- and 4-chlorophenyl-substituted dienes **2k,l**. The yields dropped for products **4x,y** which were prepared from diene **2m** (containing the sterically more demanding 2-methoxyphenyl group). The yields of 1-azaxanthones **4aa-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 1). The yields of tetracyclic products **4ak** and **4al** 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 **3ao** and **3ap** (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.

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 syntheses 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.

5.3. Experimental Section

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60-200 mesh) was used. Melting points are uncorrected.

General procedure for the synthesis of azaxanthones 4a-al and dibenzo[*b*,*d*]pyran-6-ones 5a-d: To neat 3-cyanochromone **1** (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 **3a-al**. To an ethanol solution (10 mL) of **3a-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).

Ethyl 2-(7-chloro-3-methyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (4l): Starting with 6-chlorocyanochromone (**1e**) (150 mg, 0.60 mmol), **2e** (288 mg, 0.78 mmol), Me_3SiOTf (0.14 mL, 0.78 mmol), and NEt_3 (0.16 mL, 1.20 mmol), **4l** was isolated as a colourless solid (98 mg, 41%), mp. = 190 °C. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.27$ (t, 3 H, $^3J = 7.1$ Hz, CH_3), 2.46 (s, 3 H, CH_3), 3.99 (s, 2 H, CH_2), 4.28 (q, 2 H, ^3J

= 6.9 Hz, OCH_2CH$_3$), 7.55. (d, 1 H, ^3J= 8.9, Hz, ArH), 7.71. (dd, 1 H, ^3J= 7.91, ^4J =2.5 Hz, ArH), 8.26. (d, 1 H, ^4J = 2.5 Hz, ArH), 8.46 (s, 1 H, ArH). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 14.1, 18.1 (CH$_3$), 42.3, 61.4 (CH$_2$), 115.6 (C), 120.2 (CH), 122.5 (2C, C), 125.9 (CH), 130.0 (C), 135.5, 138.1 (CH), (C), 154.0, 157.1, 159.5 (C), 169.0, 176.5 (C=O). IR (neat, cm^{-1}): $\widetilde{\nu}$ = 3092 (w), 2977 (m), 2921 (w), 1724 (s), 1667 (s), 1603 (m), 1439 (s), 1270 (s), 1180 (s), 843 (s), 788 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 333 (M$^+$, ^{37}Cl, 27), 331 (M$^+$, ^{35}Cl, 87), 285 (70), 257 (100), 230 (29), 194 (4), 126 (15), 63 (10). HRMS (ESI): calcd for $C_{18}H_{16}NO_4Cl$ (M$^+$, ^{35}Cl): 331.06059, found 331.060408.

Ethyl 2-(7-chloro-3-ethyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (4n): Starting with 6-chlorocyanochromone (**1e**) (150 mg, 0.60 mmol), 1,3-bis(silyl enol ether) **2f** (305 mg, 0.78 mmol), Me$_3$SiOTf (0.14 mL, 0.78 mmol), and NEt$_3$ (0.16 mL, 1.20 mmol), **4n** was isolated as a highly viscous yellowish oil (150 mg, 46%). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.25 (t, 3 H, ^3J = 7.3 Hz, CH$_3$), 1.33 (t, 3 H, ^3J = 7.5 Hz, CH$_3$), 2.81 (q, 2 H, ^3J = 6.9 Hz, CH_2CH$_3$), 4.00 (s, 2 H, CH$_2$), 4.20 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH$_3$), 7.55. (d, 1 H, ^3J= 8.9, Hz, ArH), 7.70 (dd, 1 H, ^3J= 7.91, ^4J =1.5 Hz, ArH), 8.28. (d, 1 H, ^4J= 2.5 Hz, ArH), 8.51 (s, 1 H, ArH). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 13.9, 14.1 (CH$_3$), 29.6, 41.7, 61.4 (CH$_2$), 115.2 (C), 120.2 (CH), 122.5 (C), 125.9 (CH), 130.0 (C), 135.5 (CH), 136.3 (C), 136.4 (CH), 154.0, 157.2, 159.0 (C), 169.2, 176.5 (C=O). IR (neat): $\widetilde{\nu}$ = 2956 (w), 2921 (m), 2935 (w), 1726 (s), 1699 (s), 1583 (m), 1428 (s), 1180 (s), 1024 (s), 789 (s), 710 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 347 (M$^+$, ^{37}Cl, 24), 345 (M$^+$, ^{35}Cl), 299 (34), 271 (100), 257 (29), 208 (4), 139 (15), 63 (10). HRMS (ESI): calcd for $C_{18}H_{16}NO_4Cl$ (M$^+$, ^{35}Cl): 345.0764, found 345.07626.

Ethyl 2-(3-ethyl-7,8-dimethyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl)acetate (4o): Starting with 6,7-dimethylcyanochromone (**1h**) (150 mg, 0.75 mmol), 1,3-bis(silyl enol ether) **2f** (302 mg, 0.97 mmol), Me$_3$SiOTf (0.17 mL, 0.97 mmol), and NEt$_3$ (0.20 mL, 1.5 mmol), **4o** was isolated as a colourless solid (100 mg, 38%), mp. = 149 °C. ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.25 (t, 3 H, ^3J = 7.1 Hz, CH$_3$), 1.34 (t, 3 H, ^3J = 7.5 Hz, CH$_3$), 2.37 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 2.79 (q, 2 H, ^3J = 7.4 Hz, C$H_2$$CH_3$), 4.0 (s, 2 H, CH_2), 4.21 (q, 2 H, ^3J = 7.2 Hz, OC$H_2$$CH_3$), 7.34 (s, 1 H, ArH), 8.00 (s, 1 H, ArH), 8.51 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.0, 14.1, 19.2, 20.6 (CH_3), 24.4, 41.7, 61.3 (CH_2), 115.6 (C), 118.5 (CH), 119.4 (C), 126.2 (CH), 133.7, 135.5 (C), 136.3 (CH), 146.2, 154.2, 157.9, 158,0 (C), 169.4, 177.4 (C=O). IR (neat): $\widetilde{\nu}$ = 2970 (w), 2921 (m), 2856 (w), 1727 (s), 1663 (s), 1607 (m), 1425 (s), 1181 (s), 1158 (s), 1026 (s), 789 (s), 739 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 339 (M^+, 96), 293 (61), 265 (100), 250 (16), 222 (7), 1194 (15), 91 (10). HRMS (ESI): calcd for $C_{20}H_{21}NO_4$ [M]: 339.14651, found 339.14641.

Ethyl 2-{3-[(4-chlorophenyl)sulfanyl]-7,8-dimethyl-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl}acetate (4af): Starting with **1h** (400 mg, 2.0 mmol), **2s** (418 mg, 2.6 mmol), Me_3SiOTf (0.46 mL, 2.6 mmol), and NEt_3 (0.55 mL, 4.0 mmol), **4af** was isolated as a colourless solid (515 mg, 56%), mp. = 147 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (t, 3 H, ^3J = 7.1 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.14 (s, 3 H, CH_3), 4.10 (q, 2 H, ^3J = 6.9 Hz, OC$H_2$$CH_3$), 4.43 (s, 2 H, CH_2), 6.92. (m, 2H, ArH), 7.05 (s, 1 H, ArH), 7.09 (m, 2H, ArH), 7.73 (s, 1 H, ArH), 8.90 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.2, 19.2, 20.7, (CH_3), 40.1, 60.9 (CH_2), 114.8 (C), 118.7 (CH), 119.4, 122.6 (C), 126.4 (CH), 129.0 (2C, CH), 132.3 (2C, CH), 133.1, 133.6, 134.6, 141.1, 147.0, 153.9, 160.0, 164.6 (C), 164.9, 176.5 (C=O). IR (neat): $\widetilde{\nu}$ = 3054 (w), 2975 (w), 2895 (w), 1703 (s), 1605 (s), 1463 (m), 1439 (s), 1240 (s), 1162 (s), 833 (s), 793 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 455 (M^+, ^{37}Cl, 17), 453 (M^+, ^{35}Cl, 46), 407 (20), 311 (30), 282 (100), 266 (23), 144 (20), 109 (15) 44 (78). HRMS (ESI): calcd for $C_{24}H_{20}NO_4ClS$ (M^+, ^{35}Cl): 453.07961, found 453.07890.

Ethyl 2-{7-methyl-3-[(4-methylphenyl)sulfanyl]-5-oxo-5*H*-chromeno[2,3-*b*]pyrid-2-yl}acetate (4ag): Starting with **1b** (400 mg, 2.16 mmol), **2t** (396 mg, 2.81 mmol), Me_3SiOTf (0.50 mL, 2.81 mmol), and NEt_3 (0.60 mL, 4.3 mmol), **4ag** was isolated as a colourless solid (572 mg, 63%), mp. = 148 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.51 (t, 3 H, ^3J = 7.2 Hz, CH_3), 2.38 (s, 3 H, CH_3), 2.58 (s, 3 H, CH_3), 4.48 (q, 2 H, ^3J = 7.1 Hz, OCH_2CH_3), 4.83 (s, 2 H, CH_2), 7.15 (d, 2 H, ^3J = 7.91, ArH), 7.37 (d, 2 H, ^3J = 7.6 Hz, ArH), 7.60 (d, 1 H, ^3J = 8.7 Hz, ArH), 7.70. (dd, 1 H, ^3J = 6.91, ^4J =2.5 Hz, ArH), 8.21 (d, 1 H, ^4J = 2.62 Hz, ArH), 9.30 (s, 1 H, ArH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.1, 20.8, 21.0 (CH_3), 40.6, 61.9 (CH_2), 114.5 (C), 118.0 (CH), 121.0, 123.2 (C), 126.1 (CH), 129.6 (2C, CH), 131.0 (C), 131.9 (2C, CH), 135.2 (C), 137.1 (CH), 137.3 (C), 140.9 (CH), 153.7, 160.1, 164.7 (C), 165.5, 176.8 (C=O). IR (neat): $\tilde{\nu}$ = 3075 (w), 2979 (w), 2810 (w), 1731 (s), 1695 (s), 1475 (m), 1339 (s), 1249 (s), 1062 (s), 803 (s), 796 (m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%) = 419 (M^+, 91), 404 (5), 373 (21), 268 (100), 240 (17), 210 (21), 105 (11). HRMS (ESI): calcd for $C_{24}H_{21}NO_4S$ (M^+): 419.11858, found 419.11936.

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Chapter 6

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

Eur. J .Org. Chem. **2008,** submitted

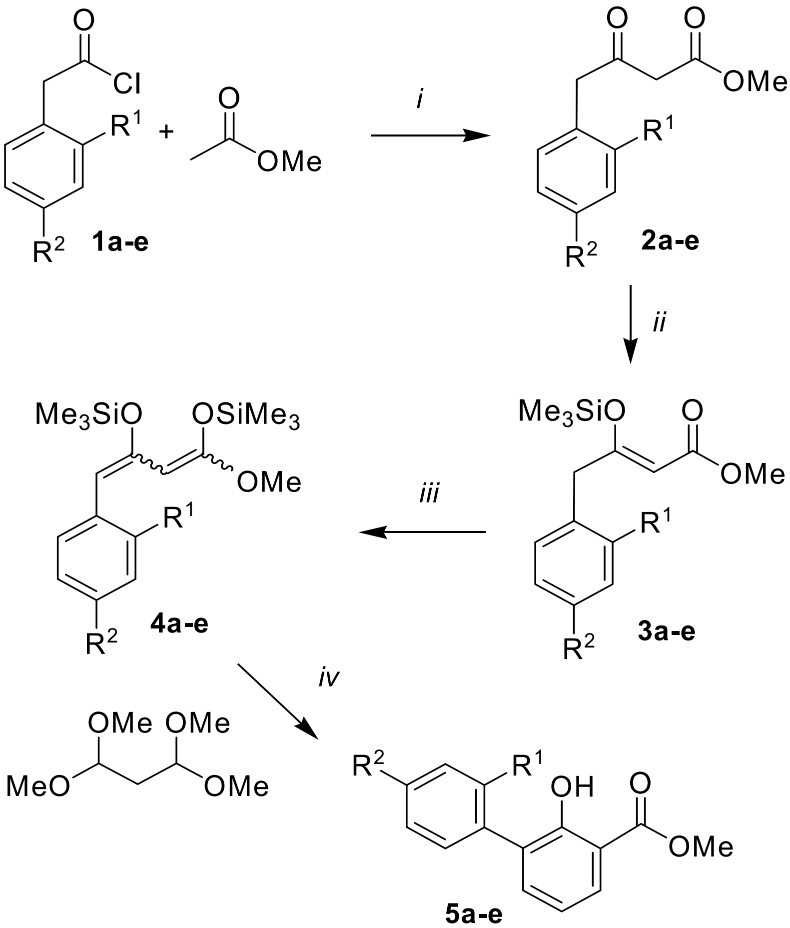
6.1. Introduction

Functionalized biaryls containing a 3-arylsalicylate substructure occur in a variety of pharmacologically relevant natural products. The simple biaryls cynandione A-C 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.[1] A number of natural products, such as knipholone, 6'-*O*-methylknipholone or (+)-asphodelin, contain an anthraquinone moiety.[2] Other compounds, e. g. secalonic acid A or globulixanthone E, contain a bixanthenyl substructure.[3] 3-Arylsalicylates are also present in many flavones (e. g. 2,3-dihydroamentoflavone,[4a] bartramiaflavone,[4b] robustaflavone,[4c] dichamanetin).[4d,e] For some derivatives, inhibition of the human liver cathepsin B and K has been reported.[4f,g] The natural product anastatin A, which contains a hydroxylated dibenzofuran moiety, shows hepatoprotective activity.[5]

The most important synthetic approach to biaryls relies on palladium(0)-catalyzed cross-coupling reactions.[6] 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[7] a convenient approach to salicylates by formal [3+3] cyclizations[8] of 1,3-bis(trimethylsilyloxy)-1,3-dienes[9] with 3-trimethylsilyloxy-2-en-1-ones. Recently, we developed a catalytic variant of this transformation.[10] Herein, we report, 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.

´6.2. Results and Discussion

The 4-arylacetoacetates **2a-e** were prepared by LDA-mediated reaction of methyl acetate with the α-arylacetyl chlorides **1a-e** (Scheme 1, Table 1). The silylation of **2a-e** afforded the 3-silyloxy-2-en-1-ones **3a-e**. The novel 4-aryl-1,3-bis(silyloxy)-1,3-dienes **4a-e** were prepared by deprotonation (LDA) of **3a-e** at −78 °C and subsequent addition of trimethylchlorosilane. The Me_3SiOTf-catalyzed cyclization of 4-aryl-1,3-bis(silyloxy)-1,3-dienes **4a-e** with 1,1,3,3-tetramethoxypropane, carried out following our recently reported procedure,[10] afforded the 3-arylsalicylates **5a-e**. The concentration and the stoichiometry proved to be important parameters during the optimization of this reaction.



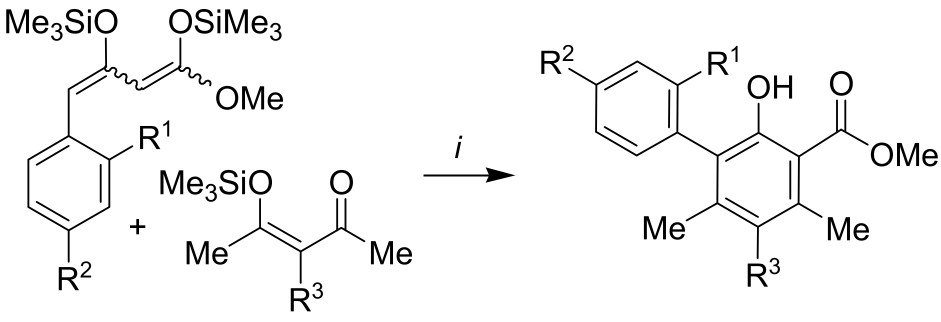
Scheme 1. Synthesis of **5a-e**; *i*: LDA, THF, –78 → 20 °C, 14 h; *ii*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; *iii*: LDA, THF, –78 → 20 °C; *iv*: Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C, 20 h

Table 1. Synthesis of biaryls **5a-e**

2-5	R^1	R^2	% (**2**)[a]	% (**3**)[a]	% (**4**)[a]	% (**5**)[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

The $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-dienes **4a-e** with 3-silyloxy-2-en-1-ones **6a-c** afforded the 3-aryloxysalicylates **7a-j** (Scheme 2, Table 2). During the optimization, it proved to be important to carry out the reactions in a highly concentrated solution.



4a-e **6a-c** **7a-j**

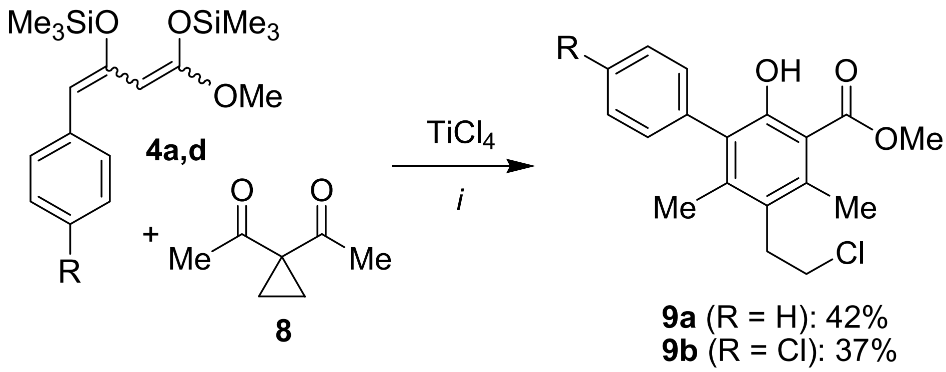
Scheme 2. Synthesis of 7a-j; *i*: $TiCl_4$, CH_2Cl_2, $-78 \rightarrow 20$ °C, 20 h

Table 1. Synthesis of biaryls **7a-j**

4	6	7	R^1	R^2	R^3	% (**7**)[a]
a	**a**	**a**	H	H	H	41
a	**b**	**b**	H	H	Cl	40
c	**a**	**c**	OMe	H	H	26
c	**b**	**d**	OMe	H	Cl	30
b	**b**	**e**	H	OMe	Cl	38
b	**a**	**f**	H	OMe	H	37
b	**c**	**g**	H	OMe	Me	38
a	**c**	**h**	H	H	Me	35
d	**b**	**i**	H	Cl	Cl	40
e	**b**	**j**	H	Me	Cl	30

[a] Isolated yields

The $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-dienes **4a** and **4d** with 1,1-diacetylcyclopropane (**8**) gave the 3-arylsalicylates **9a** and **9b**, respectively (Scheme 3). Products **9a,b** are formed by a domino ′[3+3]-cyclization-homo-Michael′ reaction.[11]



Scheme 3. Synthesis of **9a,b**; *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h

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.

6.3. Experimental section

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60-200 mesh) was used. Melting points are uncorrected.

General procedure for the synthesis of methyl 3-arylacetoacetates 2a-e: A THF solution of LDA (2.3 equiv.) was prepared by addition of *n*BuLi (0.93 mL, 2.3 mmol, 2.5 M in hexane) to a THF solution (6 mL) of diisopropylamine (0.32 mL, 2.3 mmol) at 0 °C. After the solution was stirred for 30 min, methyl acetate (0.09 mL, 1.1 mmol) was added at 0 °C. After stirring for 45-60 min, to the solution was added a THF solution (4 mL) of the acid chloride (205 mg, 1.0 mmol) at –78 °C. The temperature was allowed to rise to ambient during 5-6 h and the solution was stirred at 20 °C for 10 h. To the solution was added a diluted aqueous solution of HCl and the mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent of the filtrate was removed in vacuo and the residue was purified by chromatography (silica gel, EtOAc / *n*-heptane).

General procedure for the synthesis of biaryls 7a-j: To a dichloromethane solution (2 mL / mmol of **4**) of **4** (1.0 mmol) and of **6** (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 layers 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-(2-chloroethyl)-3-phenylsalicylate (9a): Starting with 1,1-diacetylclopropane (**8**) (252 mg, 2 mmol), 1,3-bis(silyl enol ether) **4a** (673 mg, 2.0 mmol), $TiCl_4$ (0.22 mL, 2.0 mmol) and CH_2Cl_2 (60 mL), **9a** was isolated as colourless solid (267 mg, 42%), mp. 110 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 3.09 (t, 2 H, J = 6.4 Hz, CH_2), 3.46 (t, 2 H, J = 7.4 Hz, CH_2), 3.90 (s, 3H, OCH_3), 7.12 (m, 2 H, ArH), 7.31 (m, 1 H, ArH), 7.37 (m, 2 H, ArH), 10.54 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 18.3, 18.7 (CH_3), 33.6, 42.3 (CH_2), 52.4 (OCH_3), 112.7 (C), 127.2 (CH), 127.4 (C), 128.6 (2C, CH), 128.8 (C), 130.0 (2C, CH), 137.3, 137.5, 141.8, 157.0 (C), 171.9 (C=O). IR (neat): $\tilde{\nu}$ = 3058 (w), 3023 (w), 2954 (m), 2871 (w), 1727 (w), 1650 (s), 1603 (m), 1592 (m), 1562 (w), 1437 (s), 1397 (m), 1331 (s), 1312 (s), 1210 (s), 1070 (m), 1042 (m), 957 (m), 806 (s), 733 (s), 697 (s) 530

(m) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 320 (M^+, ^{37}Cl, 16), 318 (M^+, ^{35}Cl, 46), 286 (100), 258 (8), 251 (36), 237 (75), 209 (30), 165 (40). HRMS (EI): calcd for $C_{18}H_{19}O_3Cl$ [M^+, ^{35}Cl]: 318.10172; found 318.101767.

Methyl 4,6-dimethyl-5-(2-chloroethyl)-3-(4-chlorophenyl)salicylate (9b): Starting with 1,1-diacetylclopropane (**8**) (252 mg, 2 mmol) 1,3-bis(silyl enol ether) **4d** (742 mg, 2 mmol), $TiCl_4$ (0.219 mL, 2 mmol) and CH_2Cl_2 (60 mL), **9b** was isolated as colourless solid (260 mg, 37%), mp. 112 °C; ^1H NMR (250 MHz, $CDCl_3$): δ = 2.01 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.06 (t, 2 H, J = 6.5 Hz, CH_2), 3.43 (t, 2 H, J = 7.4 Hz, CH_2), 3.89 (s, 3 H, OCH_3), 7.03 (d, 2 H, J = 8.7 Hz, ArH), 7.32 (d, 2 H, J = 8.5 Hz, ArH), 10.54 (s, 1 H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 17.3, 17.71 (CH_3), 32.4, 41.1 (CH_2), 51.3 (OCH_3), 111.3 (C), 126.2, 126.9 (C), 128.7 (2C, CH), 129.9 (CH), 131.4 (2C CH), 132.2, 134.7, 137.0, 140.8, 156.2 (C), 170.9 (C=O). IR (neat): $\tilde{\nu}$ = 3022 (w), 2998 (w), 2953 (m), 2872 (w), 1727 (w), 1650 (s), 1588 (m), 1554 (m), 1492 (m), 1436 (m), 1381 (m), 1346 (s), 1329 (s), 1309 (s), 1212 (s), 1088 (m), 1071 (m), 1040 (s), 1014 (m), 960 (m), 805(s), 759 (s), 714 (s), 541 (s) cm^{-1}. GC-MS (EI, 70 eV): *m/z* (%): 354 (M^+, ^{37}Cl, 22), 352 (M^+, ^{35}Cl, 31), 320 (100), 285 (44), 271 (68), 243 (14), 207 (16), 165 (30), 118 (20), 89 (16). HRMS (EI): calcd for $C_{18}H_{18}O_3Cl_2$ [M^+, ^{35}Cl]: 352.06275; found 352.062346.

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Chapter 7

Regioselective Synthesis of Functionalized 2-Thio-phenoxybenzoates by Formal [3+3] Cyclizations of 1-Trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 3-Silyloxy-2-en-1-ones

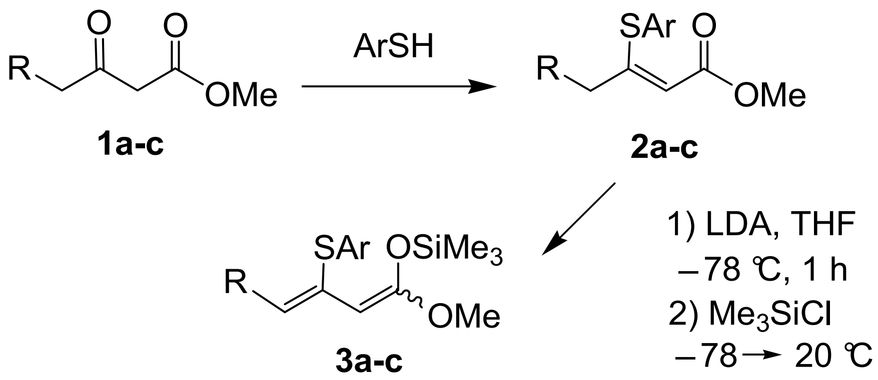
Manuscript in preparation

7.1. Introduction

Functionalized diaryl sulfides are pharmacologically important molecules which occur in various natural products. For example, they are present in dibenzothiophenes,[1] varacins (lissoclinotoxins),[2] lissoclibadins,[3] cyclic sulfides,[4] and various other natural products isolated from Streptomyces griseus.[5] Diaryl sulfides are synthetically available by reaction of arenes with sulphur[6] and sulphur dichloride,[7] by condensation of organometallic reagents with chlorophenyl-sulfide[8] and by base-mediated reaction of chloroarenes with thiophenols.[9] These reactions often suffer from their low regioselectivity and from the formation of polysulfides, due to the harsh reaction conditions. Chan and coworkers developed[10] a convenient approach to salicylates (2-hydroxybenzoates) based on formal [3+3] cyclizations[11] of 1,3-bis(silyloxy)-1,3-butadienes[12] with 3-siloxy-2-en-1-ones. Recently, we reported the application of this methodology to the synthesis of 3- and 5-thioaryloxysalicylates.[13] Herein we report, based on exploratory work of Chan *et al.*,[14] the synthesis of 2-(thioaryloxy)benzoates and thioxanthones based on formal [3+3] cyclizations of 1-methoxy-1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes with 3-silyloxy-2-en-1-ones and 1,1,3,3-tetramethoxypropane. The sterically encumbered and functionalized products reported are not readily available by other methods. In contrast to the coupling reactions outlined above, our method relies on the assembly of one of the two arene moieties

7.2. Results and Discussion

The 1-methoxy-1-trimethylsilyloxy-3-thioaryloxy-1,3-buta-dienes **3a-c** were prepared by reaction of β-ketoesters **1a-c** with thiophenol to give **2a-c** and subsequent silylation (Scheme 1, Table 1).[16]



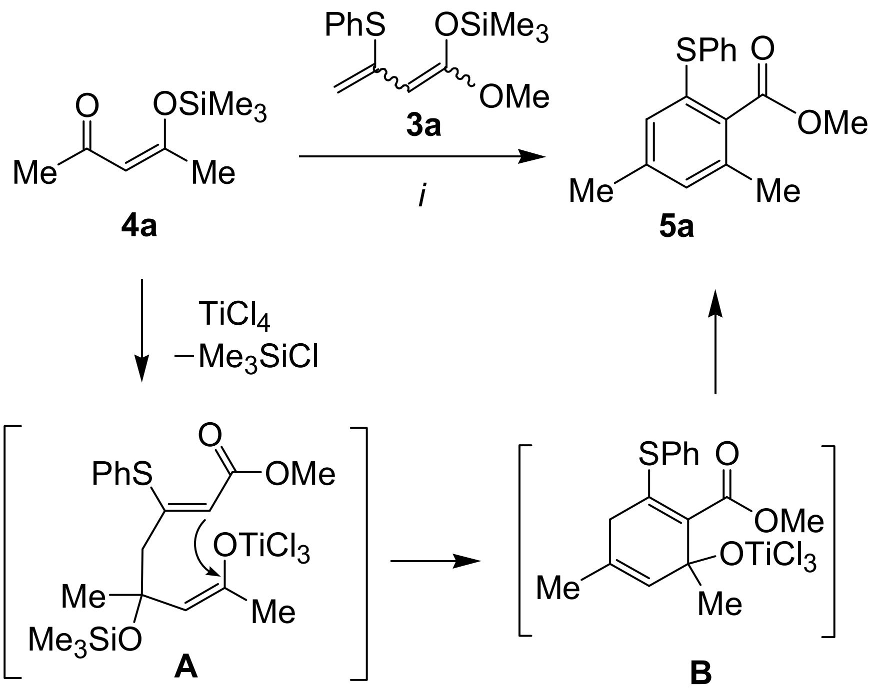
Scheme 1. Synthesis of **3a-c**

Table 1. Synthesis of 3a-e

1-3	R	Ar	% (**2**)	% (**3**)
a	H	Ph	98	98
b	Me	Ph	97	97
c	Et	Ph	96	96

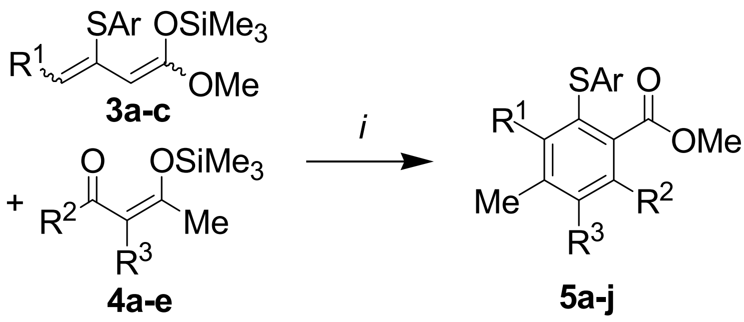
Isolated yields

The $TiCl_4$-mediated cyclization of 1-trimethylsilyloxy-3-thioaryloxy-1,3-butadiene **3a** with 3-silyloxy-2-en-1-one **4a**, prepared from methyl acetoacetate, afforded the 2-thiophenoxybenzoate **5a** (Scheme 2, Table 2). The best yields were obtained when the reaction waqs carried out in a highly concentrated solution. The formation of **3a** can be explained by $TiCl_4$-mediated attack of the terminal carbon atom of **3a** onto **4a** to give intermediate **A**, cyclization via the central carbon atom (intermediate **B**), and subsequent aromatization.



Scheme 2. Possible mechanism of the formation of **5a**

The cyclization of dienes **3a-c** with 3-silyloxy-2-en-1-ones **4a-e** afforded the 2-(thioaryloxy) benzoates **5a-j** (Scheme 3, Table 2). Noteworthy, products **5d**, **5g** and **5j** were formed with very good regioselectivity. The selectivity can be explained by selective attack of the diene onto the acetyl rather than the propionyl or benzoyl group.



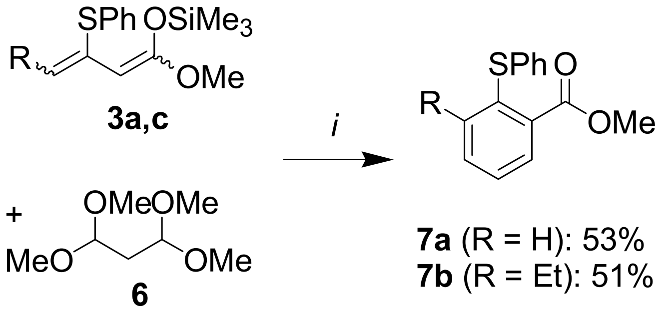
Scheme 3. Synthesis of **5a-j**

Table 1. Synthesis of 5a-j

3	4	5	Ar	R^1	R^2	R^3	% (**5**)[a]
a	**a**	**a**	Ph	H	Me	Me	57
a	**b**	**b**	Ph	H	Me	Cl	43
a	**c**	**c**	Ph	H	Me	PhS	63
a	**d**	**d**	Ph	H	*n*Pr	H	42
b	**a**	**e**	Ph	Me	Me	Me	55
b	**b**	**f**	Ph	Me	Me	Cl	49
b	**e**	**g**	Ph	Me	Ph	H	52
c	**a**	**h**	Ph	Et	Me	Me	55
c	**b**	**i**	Ph	Et	Me	Cl	51
c	**e**	**j**	Ph	Et	Ph	H	50

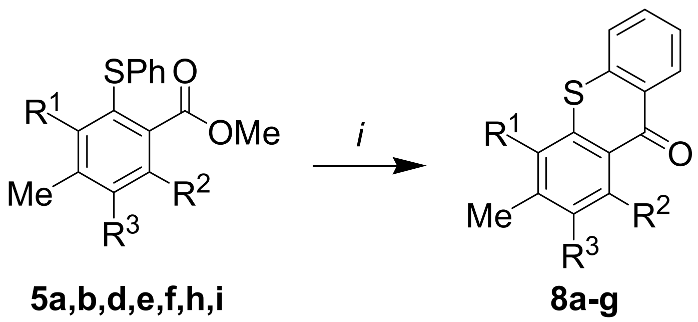
[a] Isolated yields

The cyclization of dienes **3a,c** with 1,1,3,3-tetramethoxypropane (**6**), in the presence of catalytic amounts of trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf, 0.1 equiv.), afforded the 2-(thioaryloxy)benzoates **7a,b** (Scheme 3).



Scheme 3. Synthesis of **7a,b**. *Conditions*: *i*, Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C, 20 h

Treatment of 2-(thioaryloxy)benzoates **5a,b,d,e,f,h,i** with concentrated sulfuric acid resulted in an intramolecular Friedel-Crafts cyclization to give the thioxanthones **8a-g** (Scheme 4, Table 2).



Scheme 4. Synthesis of **8a-g**. *Conditions*: *i*, Conc.H_2SO_4, → 20 °C, 2 h

Table 2. Synthesis of thioxanthones **8a-g**

5	**8**	R^1	R^2	R^3	% (**8**)
a	**a**	H	Me	Me	98
b	**b**	H	Me	Cl	97
d	**c**	H	*n*Pr	H	95
e	**d**	Me	Me	Me	97
f	**e**	Me	Me	Cl	97
h	**f**	Et	Me	Me	95
i	**g**	Et	Me	Cl	96

Isolated yields

In conclusion, we reported 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 which are not readily available by other methods. The preparative scope of the methodology is currently being studied.

7.3. Experimental Section

General procedure for the synthesis of 2-(thiophenoxy)benzoates 5a-j: To a dichloromethane solution (5 mL / mmol of **3**) of **3** (1.0 mmol) and of **4** (1.5 mmol) was added $TiCl_4$ (1.5 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 $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc / *n*-heptane = 1:4).

Methyl 2,3,4,5-tetramethyl-6-(phenylsulfanyl)benzoate (5e): Starting with 3-(siloxy)alk-2-en-1-one **4a** (450 mg, 2.41 mmol), **3b** (859 mg, 2.90 mmol), $TiCl_4$ (0.37 mL, 3.6 mmol), and CH_2Cl_2 (14 mL), **5e** was isolated as a gummy compound (400 mg, 55%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.15 (s, 3 H, CH_3), 2.17 (s, 2×3 H, CH_3), 2.24 (s, 3 H, CH_3), 3.73 (s, 3 H, OCH_3), 6.99 (m, 2 H, ArH), 7.12 (m, 3 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.5, 17.3, 17.8, 19.9 (CH_3), 51.1 (OCH_3), 124.0 (C), 125.1 (ArCH), 126.8 (2C ArCH), 128.7 (2C ArCH), 130.5, 137.5, 137.7, 138.0, 139.1, 139.6, 170.1 (C); IR (neat): $\tilde{\nu}$ = 3056 (w), 2946 (w), 1729 (s), 1598 (m), 1580 (m), 1422 (s), 1306 (m), 1232 (m), 1172 (s), 1068 (m), 737 (s) 688 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 300 (M^+, 86), 267 (100), 253 (12), 239 (10), 225 (7), 110 (89); HRMS (EI): calcd for $C_{18}H_{20}O_2S$ [M^+]: 300.11785, found 300.11812.

Methyl 3-chloro-2,4,5-trimethyl-6-(phenylsulfanyl)benzoate (5f): Starting with 3-(siloxy)alk-2-en-1-one **4b** (550 mg, 2.6 mmol), **3b** (943 mg, 3.1 mmol), $TiCl_4$ (0.42 mL, 3.9 mmol) and CH_2Cl_2 (110 mL), **5f** was isolated as a gummy compound (417 mg, 49%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.74 (s, 3 H, OCH_3), 7.00 (m, 2 H, ArH), 7.14 (m, 3 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 17.2, 17.3, 17.5 (CH_3), 51.2 (OCH_3), 123.6 (C), 125.5 (ArCH), 126 (C), 127.1 (2C ArCH), 128.9 (2C ArCH), 129.6, 136.0, 136.7, 139.4, 139.9, 166.2 (C); IR (neat): $\tilde{\nu}$ = 3010 (w), 2953 (w), 1722 (s), 1601 (m), 1580 (m), 1434 (m), 1383 (s), 1234 (s), 1151 (s), 1009 (s), 732 (s), 685 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 322 (M^+, ^{37}Cl, 28), 320 (M^+, ^{35}Cl, 74), 287 (100), 253 (17), 211 (10), 178 (20), 115; HRMS (EI): calcd for $C_{17}H_{17}O_2ClS$ [M^+, ^{35}Cl]: 320.06323, found 320.06363.

Methyl 2-phenyl-4,5-dimethyl-6-(phenylsulfanyl)benzoate (5g): Starting with 3-(siloxy)alk-2-en-1-one **4e** (500 mg, 2.0 mmol), **1b** (743 mg, 2.0 mmol), $TiCl_4$ (0.34 mL, 3.1 mmol), and CH_2Cl_2 (12.5 mL), **5g** was isolated as a gummy compound (380 mg, 52%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 3.48 (s, 3 H, OCH_3), 7.12 (m, 3 H, ArH), 7.26 (m, 3 H, ArH), 7.36 (s, 1 H, ArH), 7.42 (m, 4 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.6, 18.0 (CH_3), 50.1 (OCH_3), 124.0 (C), 125.9 (ArCH), 126.4 (2C ArCH), 126.3 (C), 127.2 (2C, ArCH), 127.4 (2C ArCH), 127.5 (2C ArCH), 127.8 (ArCH), 131.5, 132.2 (C), 136.2 (ArCH), 137.5, 138.1, 138.7, 139.9, 166.2 (C); IR (neat): $\tilde{\nu}$ = 3056 (w), 2946 (w), 1730 (s), 1580 (m), 1476 (m), 1456 (s), 1384 (w), 1246 (s), 1146 (s), 1023 (m), 697 (s) 688 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 348 (M^+, 100), 315 (89), 373 (26), 39 (9), 165 (18), 105 (7); HRMS (EI): calcd for $C_{22}H_{20}O_2S$ [M^+]: 348.11785, found 348.11834.

Methyl 5-ethyl-2,4-dimethyl-6-(phenylsulfanyl)benzoate (5h): Starting with 3-(siloxy)alk-2-en-1-one **4a** (700 mg, 3.76 mmol), **3c** (1.40 g, 4.51 mmol), $TiCl_4$ (0.61 mL, 5.64 mmol), and CH_2Cl_2 (18.8 mL), **5h** was isolated as a gummy compound (650 mg, 55%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80 (t, 3 H, *J* = 7.4 Hz, CH_3), 2.13 (s, 3 H, CH_3), 2.15 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3), 2.76 (q, 2 H, J = 7.3 Hz, CH_2), 3.67 (s, 3 H, OCH_3), 6.97 (m, 3 H, ArH), 7.10 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.5, 16.6, 16.9, 17.8 (CH_3), 24.9 (CH_2), 51.9 (OCH_3), 123.2 (C), 125.0 (ArCH), 126.6 (2C, ArCH), 128.9 (2C, ArCH), 134.2, 137.0, 138.5, 140.3, 142.7, 145.1, 170.0 (C); IR (neat): $\tilde{\nu}$ = 356 (w), 2946 (w), 1729 (s), 1580 (m), 1477 (m), 1434 (m), 1294 (m), 1224 (m), 1171 (s), 1024 (m), 736 (s) 688 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 314 (M^+, 100), 281 (56), 267 (21), 239 (16), 211 (12), 177 (23), 105 (27); HRMS (EI): calcd for $C_{19}H_{22}O_2S$ [M^+]: 314.13351, found 314.13418.

Methyl 3-chloro-2,4-dimethyl-5-ethyl-6-(phenylsulfanyl)benzoate (5i): Starting with 3-(siloxy)alk-2-en-1-one **4b** (650 mg, 3.1 mmol), **3c** (1.10 g, 3.72 mmol), $TiCl_4$ (0.51 mL, 4.65 mmol), and CH_2Cl_2 (15.5 mL), **5i** was isolated as a gummy compound (524 mg, 50%); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.74 (t, 3 H, J = 7.1 Hz, CH_3), 2.11 (s, 3 H, CH_3), 2.22 (s, 3 H, CH_3), 2.65 (q, 2 H, J = 7.4 Hz, CH_2), 3.55 (s, 3 H, OCH_3), 6.92 (m, 3 H, ArH), 7.10 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.6, 18.9, 19.7 (CH_3), 24.3 (CH_2), 52.1 (OCH_3), 126.1 (C), 126.6 (ArCH), 128.2 (2C ArCH), 131.0 (2C ArCH), 133.6, 136.9, 139.0, 139.2, 142.3, 148.1, 170.0 (C); IR (neat): $\tilde{\nu}$ = 3053 (w), 297 (w), 1727 (s), 1575 (m), 1431 (m), 1404 (m), 1280 (s), 1224 (s), 1152 (s), 1022 (s), 735 (s) 685 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 336 (M^+, ^{37}Cl, 39), 334 (M^+, ^{35}Cl, 100), 301 (52), 287 (21), 224 (10), 197 (23), 105 (34); HRMS (EI): calcd for $C_{16}H_{15}O_2ClS$ [M^+, ^{35}Cl]: 334.07888, found 334.07942.

Methyl 2-methyl-3-phenyl-5-ethyl-6-(phenylsulfanyl)benzoate (5j): Starting with 3-(siloxy)alk-2-en-1-one **4e** (717 mg, 3.0 mmol), **3c** (618 g, 2 mmol), $TiCl_4$ (0.32 mL, 3.0 mmol), and CH_2Cl_2 (10 mL), **5j** was isolated as a gummy compound (362 mg, 50%); ^1H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, J = 7.1 Hz, CH_3), 2.25 (s, 3 H, CH_3), 2.73 (q, 2 H, J = 6.4 Hz, CH_2), 3.80 (s, 3 H, OCH_3), 7.10 (m, 3 H, ArH), 7.26 (m, 5 H, ArH), 7.34 (s, 1 H, ArH), 7.67 (m, 3 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.7, (CH_3), 20.1 (CH_2), 24.4, (CH_3), 51.8 (OCH_3), 123.0 (2C ArCH), 124.4 (ArCH), 125.3 (2C ArCH), 127.7 (ArCH), 128.4 (2C ArCH), 130.3 (2C ArCH), 130.2, 133.7, 134.9 (C), 136.3 (ArCH), 137.1, 139.1, 140.6, 144.2, 148.2, 165.8 (C); IR (neat): $\tilde{\nu}$ = 3058 (w), 2947 (w), 1730 (m), 1597 (m), 1579 (m), 1453 (m), 1271 (s), 1191 (s), 739 (s), 698 (s), 618 (m) 556 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 362 (M^+, 100), 331 (19), 315 (20), 271(16), 225 (20) 178 (13); HRMS (EI): calcd for $C_{23}H_{22}O_2S$ [M^+]: 362.13350, found 362.13303. HRMS and MS different

General procedure for the synthesis of 2-(thiophenoxy)benzoates 7a,b: To a dichloromethane solution (2 mL / mmol of **3**) of **3** (1.5 mmol) and of 1,1,3,3-tetramethoxypropane (1.0 mmol) 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 diluted aqueous solution of HCl (give exact concentration, 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

Methyl 2-(phenylsulfanyl)benzoate (7a): Starting with tetramethoxypropane (0.33 mL, 2.0 mmol), **3a** (843 mg, 3.0 mmol), and TMSOTf (0.036 mL, 0.2 mmol), CH_2Cl_2 (4 mL), **7a** was isolated as a highly viscous colourless oil (275 mg, 53%); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, OCH_3), 6.75 (dd, 1 H, ^3J= 7.2, ^4J =1.87 Hz, ArH), 7.06 (ddd, 1 H, ^3J= 7.2, ^4J = 1.87, ^5J = 0.92 Hz, ArH), 7.16 (m, 2 H, ArH), 7.36 (m, 3 H, ArH), 7.48 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 52.1 (OCH_3), 124.2 (ArCH), 126.7 (C), 127.4, 129.0 (ArCH), 129.7 (2C, ArCH), 131.1, 132.2 (ArCH), 124.6 (C), 135.5 (2C, ArCH), 143.1, 166.8 (C); IR (neat): $\tilde{\nu}$ = 3056 (w), 2948 (w), 1711 (s), 1585 (m), 1562 (m), 1433 (s), 1246 (s), 1189 (m), 1056 (s), 738 (s), 688 (s) 530 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 244 (100), 213 (76), 184 (55), 152 (16), 139 (10), 108 (8); HRMS (EI): calcd for $C_{14}H_{12}O_2S$ [M^+]: 244.05525, found 244.05570.

General procedure for the synthesis of thioxanthones 8a-g: To **5** (1.0 mmol) was added concentrated sulfuric acid (98%, 12 mL / mmol of **5**) at 20 °C and the solution was stirred for 2 h. To the solution was added ice water (50 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. The residue was purified by chromatography (silica gel, heptanes / EtOAc).

1,2,3,4-Tetramethylthioxanthone (8d): Starting with **5e** (118 mg, 0.39 mmol) and conc. sulfuric acid, **8d** was isolated as a colourless solid (102 mg, 97%), mp. = 221 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.32 (s, 3 H, CH_3), 2.35 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.68 (s, 3 H, CH_3), 7.40 (m, 1 H, ArH), 7.52 (m, 2 H, ArH), 8.30 (m, 1 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.5, 16.7, 17.6, 19.4 (CH_3), 125.3, 125.8 (ArCH), 127.4, 128.4 (C), 128.9, 131.1 (ArCH), 132.2, 134.4, 134.8, 135.8, 138.0, 139.4, 184.6 (C); IR (neat): $\tilde{\nu}$ = 3064 (w), 2916 (w), 1622 (s), 1587 (s), 1433 (s), 1490 (m), 1301 (s), 1204 (m), 1093 (s), 952 (m), 743 (s) 643 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 268 (100), 253 (82), 239 (34), 184 (10), 119 (7), 69 (12); HRMS (EI): calcd for $C_{17}H_{16}O_2S$ [M^+]: 268.09164, found 268.09113.

2-Chloro-1,3,4-trimethylthioxanthone (8e): Starting with **5f** (90 mg, 0.28 mmol) and conc. sulfuric acid, **8e** was isolated as a colourless solid (78 mg, 97%), mp. = 194 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50 (s, 3 H, CH_3), 2.53 (s, 3 H, CH_3), 2.86 (s, 3 H, CH_3), 7.45 (m, 1 H, ArH), 7.57 (m, 2 H, ArH), 8.34 (m, 1 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 16.8, 18.7, 20.2 (CH_3), 125.3, 126.3, 129.0 (ArCH), 130.0 (C), 131.6 (ArCH), 131.6, 132.3, 132.7, 134.0, 134.1, 137.8, 138.7, 183.9 (C); IR (neat): $\tilde{\nu}$ = 3063 (w), 2918 (s), 1732 (m), 1624 (s), 1588 (m), 1432 (m), 1378 (m), 1229 (m), 1155 (s), 1009 (s), 741 (s) 615 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 290 (M^+, ^{37}Cl, 45), 288 (M^+, ^{35}Cl, 100), 253 (16), 225 (26), 208 (8), 119 (13), 69 (9); HRMS (EI): calcd for $C_{16}H_{13}OClS$ [M^+, ^{35}Cl]: 288.03701, found 288.03628.

1,2,3-Trimethyl-4-ethylthioxanthone (8f): Starting with **5h** (181 mg, 0.57 mmol) and conc. sulfuric acid, **8f** was isolated as a colourless solid (102 mg, 97%), mp. = 221 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.15 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.23 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 2.90 (q, 2 H, *J* = 7.4 Hz, CH_2), 7.30 (m, 1 H, ArH), 7.44 (m, 2 H, ArH), 8.22 (m, 1 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.9, 16.6, 16.8, 19.5 (CH_3), 23.7 (CH_2), 125.2, 125.8 (ArCH), 127.8 (C), 128.8 (ArCH), 131.1 (ArCH), 132.2, 133.7, 134.5, 135.3, 135.6, 136.1, 139.0, 184.9 (C); IR (neat): $\tilde{\nu}$ = 3064 (w), 2927 (s), 1624 (s), 1585 (m), 1431 (m), 1382 (s), 1366 (s), 1203 (m), 1085 (s), 1028 (m), 748 (s), 643 (m) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 282 (M^+, 89), 267 (100), 253 (21), 224 (10), 126 (9), 113 (9), 69 (16); HRMS (EI): calcd for $C_{18}H_{18}OS$ [M^+]: 282.10729, found 282.10724.

2-Chloro-1,3-dimethyl-4-ethylthioxanthone (8g): Starting with **5i** (302 mg, 0.92 mmol) and conc. sulfuric acid, **8g** was isolated as a colourless solid (270 mg, 96%), mp. = 81 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.03 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.85 (q, 2 H, *J* = 7.2 Hz, CH_2), 7.28–7.40 (m, 2 H, ArH), 7.47–7.89 (m, 2 H, ArH); ^{13}C NMR (62 MHz, $CDCl_3$): δ = 12.5, 18.0, 20.3, (CH_3), 24.1 (CH_2), 125.3 (ArCH), 126.3 (2C ArCH), 129.0 (ArCH), 130.8, 131.7, 134.4, 136.3, 136.6, 137.6, 138.4, 139.4, 184.2 (C); IR (neat): $\tilde{\nu}$ = 3045 (w), 2938 (w), 1711 (w), 1624 (s), 1587 (s), 1432 (s), 1373 (w), 1214 (s), 1174 (s), 1027 (s), 751 (m) 637 (s) cm^{-1}; GC-MS (EI, 70 eV): *m/z* (%): 304 (M^+, ^{37}Cl, 30), 302 (M^+, ^{35}Cl, 100), 267 (23), 251 (12), 221 (10), 210 (8), 97 (15), 57 (27); HRMS (EI): calcd for $C_{17}H_{15}OClS$ [M, ^{35}Cl]: 302.05268, found 302.05282.

7.4. References

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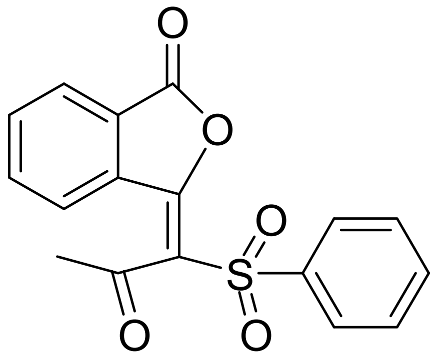
Manuscript in preparation

The following experimental data represent unpublished results from different projects.



Synthesis of 3-[2-oxo-1- (phenylsulfonyl) propylidene] -2- benzofuran -1-one: (1); Starting with phthaloyl dichloride (0.62 ml, 4.3 mmol), 2-(siloxy) -1-propenyl sulfone (1.17 g, 4.3 mmol) and $TiCl_4$ (0.47 ml, 4.3 mmol), **1** was isolated as a colourless solid (398 mg, 28%), mp. 186 °C; ^{1}H NMR (300 MHz, Acetone-d_6): δ = 2.65 (s, 3 H, CH_3), 7.65-7.83(m, 4 H, ArH), 7.96 (m, 1 H, ArH), 8.03-8.16 (m, 3 H, ArH), 8.91 (d, 1 H, J = 8.1 Hz, ArH); ^{13}C NMR (75 MHz, Acetone-d_6): δ = 33.1, (CH_3), 125.7 (C), 127.2 (CH),128.7 (2C, CH), 129.6(C), 130.6(CH), 130.7 (2C, CH),132.1 (CH), 135.4 (C), 135.6, 137.1 (CH), 142.7, 154.4, 164.6, 195.5 (C); IR (KBr): $\tilde{\nu}$ = 3098 (w), 2922 (w), 2854 (w), 1811 (s), 1711 (s), 1624 (s), 1473 (m), 1252 (s), 1001 (s), 721 (m), 618 (s), 595 (m) cm^{-1}; GC-MS (CI, 70 eV): *m/z* (%): 329 ($[M+H]^+$, 48), 287 (100), 189 (50), 173 (6), 143 (7), 73 (10); elemental analysis: calcd (%) for $C_{17}H_{12}O_5S$ (328): C 62.19, H 3.68; found: C 61.65, H 3.78.

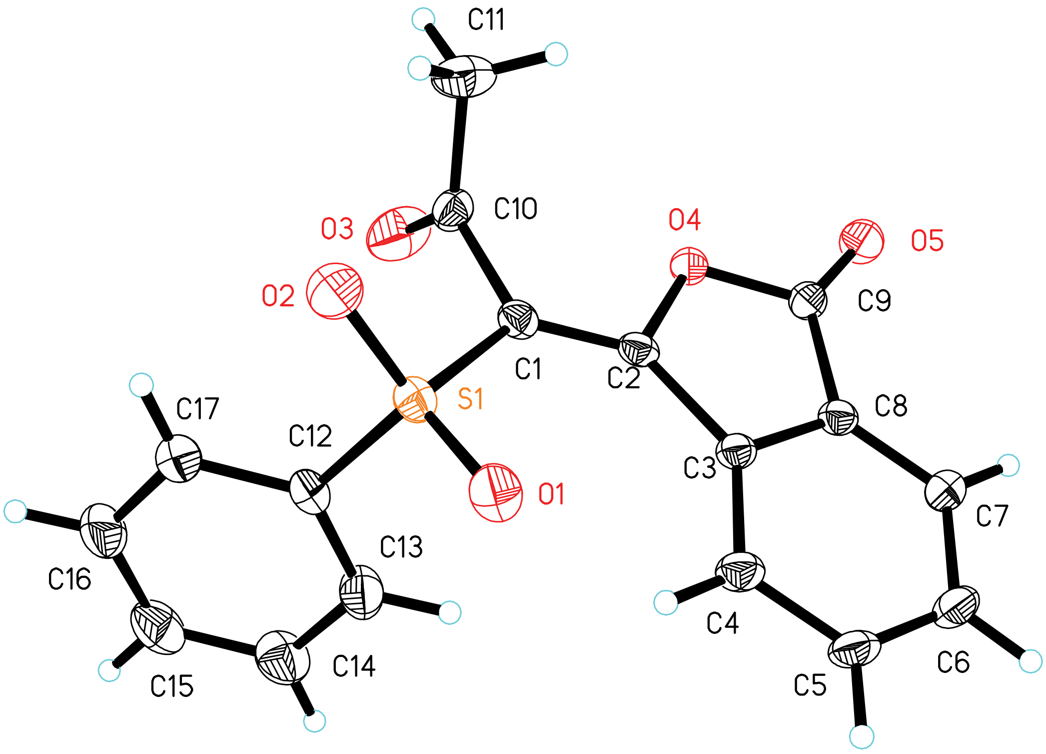
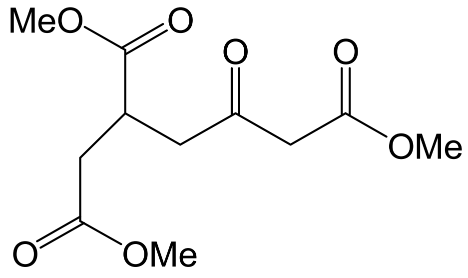


Figure 1. ORTEP plot of **1**

General procedure for synthesis 3-[2-oxo-1- (phenylsulfonyl) propylidene] -2-benzofuran -1-one: To a dichloromethane solution (13 mL) phthaloyl dichloride (0.62 ml, 4.3 mmol), 2-(siloxy) -1-propenyl sulfone **2** (1.17 g, 4.3 mmol) and TiCl4 (0.47 ml, 4.3 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 $NaHCO_3$ (15 mL). The organic and the aqueous layer were separated and the latter was extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, EtOAc / *n*-heptane = 1:4).



Synthesis of trimethyl 4-oxo-1,2,5-pentanetricarboxylate:(2);Starting dichloromethane solution (12 mL),dimethyl maleate (0.37 ml, 3 mmol), 1,3-bis (silyl enol ether), (780 mg, 3 mmol) and $TiCl_4$ (0.32 ml, 3 mmol), **3** was isolated as a colourless solid (350 mg, 44%); ^1H NMR (250 MHz, CH_2Cl_2): δ = 2.56 (m, 1 H, CH), 2.74 (d, 1 H, J = 6.9. Hz, CH_2), 2.93 (d, 1 H, J = 7.0. Hz, CH_2), 3.01 (d, 1 H, J = 6.9. Hz, CH_2), 3.18 (d, 1 H, J = 6.9. Hz, CH_2), 3.37 (s, 2H, CH_2), 3.61 (s, 3 H, OCH_3), 3:67 (s, 2×3 H, CH_3); ^{13}C NMR (62 MHz, CH_2Cl_2): δ = 27.1 (CH_2), 30.2 (CH), 44.1, 48.2 (CH_2), 53.0, 54.0, 54.2 (OCH_3), 167.0, 171.3, 173.6, 200.2 (C); IR (Neat): $\tilde{\nu}$ = 3002 (w), 2955 (w), 2850 (w), 1737 (s), 1624 (s), 1437 (m), 1367 (m), 1168 (m), 1008 (w), 848 (m), cm^{-1}; GC-MS (EI, 70 eV): m/z (%) = 260 (M^+, 18), 228 (21), 197 (25), 187 (81), 169 (42), 127 (100), 101 (29). HRMS (ESI): calcd for $C_{11}H_{16}O_7$ (M^+) 260.08905, found 260.08978.

X-Ray crystals data

Data of compound 3b (chapter 1):

Table 1. Crystal data and structure refinement for3b

Identification code	nrr76	
Empirical formula	$C_{17}H_{20}O_4S$	
Formula weight	320.39	
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 = 16.0830(3) Å	α= 90°.
	b = 7.94020(10) Å	β= 102.7740(10)°.
	c = 12.7097(2) Å	γ = 90°.
Volume	1582.89(4) $Å^3$	
Z	4	
Density (calculated)	1.344 Mg/m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	680	
Crystal size	0.42 x 0.28 x 0.25 mm^3	
Θ range for data collection	1.30 to 29.99°.	
Index ranges	$-22\leq h\leq 21$, $-11\leq k\leq 10$, $-17\leq l\leq 17$	
Reflections collected	18799	
Independent reflections	4601 [R(int) = 0.0342]	
Completeness to Θ = 29.99°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9471 and 0.9133	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4601 / 0 / 206	
Goodness-of-fit on F^2	1.048	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0466, wR2 = 0.1221	
R indices (all data)	R1 = 0.0644, wR2 = 0.1326	
Largest diff. peak and hole	0.400 and -0.334 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nrr76. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	2702(1)	8674(1)	3607(1)	31(1)
O(1)	2224(1)	9841(2)	2828(1)	44(1)
O(2)	2724(1)	9022(2)	4721(1)	45(1)
O(3)	3239(1)	5611(2)	4852(1)	44(1)
O(4)	908(1)	2054(2)	3306(1)	38(1)
C(1)	2259(1)	6625(2)	3315(1)	24(1)
C(2)	2602(1)	5352(2)	4156(1)	26(1)
C(3)	2169(1)	3665(2)	4070(1)	28(1)
C(4)	1252(1)	3714(2)	3432(1)	26(1)
C(5)	1252(1)	4545(2)	2340(1)	25(1)
C(6)	1690(1)	6196(2)	2392(1)	24(1)
C(7)	1306(1)	3411(3)	1384(1)	39(1)
C(8)	474(1)	4195(3)	1449(2)	41(1)
C(9)	682(1)	4703(2)	4020(2)	33(1)
C(10)	1477(1)	7270(3)	1394(1)	40(1)
C(11)	3748(1)	8602(2)	3403(1)	30(1)
C(12)	3885(1)	8919(3)	2382(2)	40(1)
C(13)	4708(1)	8915(3)	2230(2)	45(1)
C(14)	5396(1)	8597(3)	3074(2)	42(1)
C(15)	5245(1)	8253(3)	4084(2)	48(1)
C(16)	4423(1)	8263(3)	4259(2)	41(1)
C(17)	6297(2)	8644(4)	2903(2)	63(1)

Data of compound 4f (chapter 1):

Table 1. Crystal data and structure refinement for 4f

Identification code	nrr83	
Empirical formula	$C_{17}H_{19}IO_3S$	
Formula weight	430.28	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/n$	
Space group (Hall)	-P 2yn	
Unit cell dimensions	a = 8.95860(10) Å	= 90°.
	b = 15.7104(3) Å	= 97.7080(10)°.
	c = 12.3853(2) Å	= 90°.
Volume	1727.40(5) $Å^3$	
Z	4	
Density (calculated)	1.655 Mg/m^3	
Absorption coefficient	1.984 mm^{-1}	
F(000)	856	
Crystal size	0.38 x 0.19 x 0.14 mm^3	
Θ range for data collection	2.11 to 30.00°.	
Index ranges	$-12\leq h\leq 12$, $-22\leq k\leq 22$, $-17\leq l\leq 17$	
Reflections collected	31411	
Independent reflections	5029 [R(int) = 0.0251]	
Completeness to Θ = 30.00°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. And min. transmission	0.7687 and 0.5194	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5029 / 0 / 207	
Goodness-of-fit on F^2	1.051	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0238, wR2 = 0.0570	
R indices (all data)	R1 = 0.0296, wR2 = 0.0632	
Extinction coefficient	0.0008(2)	
Largest diff. peak and hole	1.596 and -1.041 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
For nrr83. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	9994(1)	10425(1)	8414(1)	39(1)
S(1)	5693(1)	7845(1)	3550(1)	36(1)
O(1)	5627(2)	9383(1)	1979(1)	45(1)
O(2)	5132(2)	7814(1)	2392(2)	51(1)
O(3)	4740(2)	7482(1)	4274(2)	54(1)
C(1)	6165(2)	8916(1)	3883(2)	30(1)
C(2)	6155(2)	9521(1)	3043(2)	31(1)
C(3)	6727(2)	10329(1)	3289(2)	32(1)
C(4)	7272(2)	10565(1)	4345(2)	30(1)
C(5)	7198(2)	9981(1)	5202(1)	28(1)
C(6)	6691(2)	9149(1)	4979(2)	29(1)
C(7)	7930(3)	11443(1)	4536(2)	41(1)
C(8)	7686(2)	10272(1)	6368(2)	32(1)
C(9)	9323(2)	10048(2)	6742(2)	38(1)
C(10)	6712(3)	8512(2)	5898(2)	41(1)
C(11)	7447(2)	7318(1)	3743(2)	29(1)
C(12)	8586(2)	7617(1)	3185(2)	30(1)
C(13)	9983(2)	7225(1)	3352(2)	31(1)
C(14)	10245(2)	6531(1)	4055(2)	32(1)
C(15)	9072(2)	6239(1)	4586(2)	34(1)
C(16)	7670(2)	6631(1)	4443(2)	34(1)
C(17)	11752(3)	6098(2)	4224(2)	49(1)

Data of compound 7b (chapter 1):

Table 1. Crystal data and structure refinement for 7b.

Identification code	nrr85	
Empirical formula	$C_{11}H_{12}BrNO$	
Formula weight	254.13	
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 = 4.36360(10) Å	= 90°.
	b = 9.8334(2) Å	= 93.0300(10)°.
	c = 25.0206(4) Å	= 90°.
Volume	1072.11(4) Å^3	
Z	4	
Density (calculated)	1.574 Mg/m^3	
Absorption coefficient	3.800 mm^{-1}	
F(000)	512	
Crystal size	0.30 x 0.13 x 0.08 mm^3	
Θ range for data collection	2.23 to 29.99°.	
Index ranges	$-6\leq h\leq 5$, $-13\leq k\leq 13$, $-35\leq l\leq 35$	
Reflections collected	16714	
Independent reflections	3109 [R(int) = 0.0438]	
Completeness to Θ = 29.99°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7508 and 0.3952	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3109 / 0 / 134	
Goodness-of-fit on F^2	1.043	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0309, wR2 = 0.0718	
R indices (all data)	R1 = 0.0459, wR2 = 0.0773	
Extinction coefficient	0.0029(9)	
Largest diff. peak and hole	0.413 and -0.554 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for nrr85. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	981(1)	1633(1)	4584(1)	34(1)
O(1)	9732(4)	3971(2)	7439(1)	36(1)
N(1)	8280(6)	6955(2)	6846(1)	47(1)
C(1)	7779(5)	3508(2)	7044(1)	26(1)
C(2)	6621(5)	4477(2)	6674(1)	26(1)
C(3)	4629(5)	4102(2)	6238(1)	25(1)
C(4)	3742(4)	2742(2)	6182(1)	23(1)
C(5)	4896(5)	1767(2)	6559(1)	26(1)
C(6)	6890(5)	2164(2)	6981(1)	27(1)
C(7)	7519(6)	5857(2)	6764(1)	33(1)
C(8)	3512(6)	5188(2)	5846(1)	34(1)
C(9)	1627(4)	2310(2)	5710(1)	27(1)
C(10)	3529(5)	1935(2)	5240(1)	30(1)
C(11)	3999(6)	291(2)	6512(1)	34(1)

Data of compound 8a(chapter 3):

Table 1. Crystal data and structure refinement for 8a

Identification code	nrr59a	
Empirical formula	$C_{18}H_{18}O_4S$	
Formula weight	330.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group (H.-M.)	$P2_1/n$	
Space group (Hall)	-P 2yn	
Unit cell dimensions	a = 9.0345(5) Å	= 90°.
	b = 18.1451(10) Å	= 105.293(4)°.
	c = 10.1977(6) Å	= 90°.
Volume	1612.53(16) $Å^3$	
Z	4	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	0.218 mm^{-1}	
F(000)	696	
Crystal size	0.36 x 0.23 x 0.15 mm^3	
Θ range for data collection	2.59 to 29.00°.	
Index ranges	$-12\leq h\leq 12$, $-24\leq k\leq 24$, $-13\leq l\leq 13$	
Reflections collected	14223	
Independent reflections	4236 [R(int) = 0.0510]	
Completeness to Θ = 29.00°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9680 and 0.9255	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4236 / 0 / 209	
Goodness-of-fit on F^2	1.017	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0481, wR2 = 0.1225	
R indices (all data)	R1 = 0.0701, wR2 = 0.1376	
Largest diff. peak and hole	0.435 and -0.332 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for nrr59a. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	5055(1)	1771(1)	1043(1)	25(1)
O(1)	5338(2)	1801(1)	-281(2)	37(1)
O(2)	6331(2)	1592(1)	2189(2)	33(1)
O(3)	1876(2)	222(1)	111(1)	28(1)
O(4)	936(2)	1902(1)	1204(1)	30(1)
C(1)	4341(2)	2637(1)	1408(2)	25(1)
C(2)	4732(2)	2893(1)	2733(2)	32(1)
C(3)	4133(3)	3562(1)	3015(2)	41(1)
C(4)	3170(3)	3961(1)	1980(3)	43(1)
C(5)	2802(2)	3700(1)	660(2)	39(1)
C(6)	3372(2)	3033(1)	357(2)	31(1)
C(7)	3553(2)	1159(1)	1031(2)	22(1)
C(8)	2982(2)	700(1)	-18(2)	23(1)
C(9)	3355(2)	587(1)	-1361(2)	31(1)
C(10)	2043(3)	95(1)	-2149(2)	36(1)
C(11)	1525(3)	-293(1)	-1030(2)	34(1)
C(12)	3022(2)	1159(1)	2293(2)	22(1)
C(13)	1690(2)	1544(1)	2356(2)	23(1)
C(14)	1220(2)	1543(1)	3548(2)	32(1)
C(15)	2064(3)	1163(1)	4681(2)	37(1)
C(16)	3380(3)	786(1)	4642(2)	36(1)
C(17)	3848(2)	786(1)	3448(2)	29(1)
C(18)	-263(2)	2404(1)	1306(2)	40(1)

Data of compound 9a(chapter 3):

Table 1. Crystal data and structure refinement for nrr63.

Identification code	nrr63	
Empirical formula	$C_{17}H_{15}BrO_3S$	
Formula weight	379.26	
Temperature	298(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 = 8.3485(2) Å	= 97.4920(10)°.
	b = 8.7659(2) Å	= 103.9260(10)°.
	c = 11.4679(3) Å	= 94.3050(10)°.
Volume	802.67(3) $Å^3$	
Z	2	
Density (calculated)	1.569 Mg/m^3	
Absorption coefficient	2.700 mm^{-1}	
F(000)	384	
Crystal size	0.43 x 0.25 x 0.17 mm^3	
Θ range for data collection	2.53 to 29.00°.	
Index ranges	$-11\leq h\leq 11$, $-11\leq k\leq 11$, $-15\leq l\leq 15$	
Reflections collected	17426	
Independent reflections	4206 [R(int) = 0.0204]	
Completeness to Θ = 29.00°	98.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6568 and 0.3898	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4206 / 0 / 199	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2σ(I)]	R1 = 0.0767, wR2 = 0.2342	
R indices (all data)	R1 = 0.1038, wR2 = 0.2663	
Largest diff. peak and hole	2.772 and -1.326 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for nrr63. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	7239(1)	7760(1)	14064(1)	86(1)
S(1)	6740(1)	6244(1)	8406(1)	44(1)
O(1)	7663(5)	10397(4)	10341(3)	55(1)
O(2)	6623(5)	5338(4)	9342(4)	59(1)
O(3)	7804(5)	5860(5)	7629(4)	62(1)
C(1)	7328(5)	8165(5)	9061(4)	40(1)
C(2)	7962(5)	9362(5)	8483(4)	42(1)
C(3)	8371(6)	9450(6)	7390(5)	53(1)
C(4)	8897(7)	10903(7)	7161(6)	63(1)
C(5)	9038(8)	12212(7)	8006(7)	69(2)
C(6)	8662(7)	12169(6)	9106(6)	62(1)
C(7)	8136(6)	10708(6)	9313(5)	50(1)
C(8)	7157(6)	8843(6)	10159(4)	46(1)
C(9)	4736(6)	6267(5)	7478(4)	45(1)
C(10)	3392(6)	6150(6)	7999(6)	56(1)
C(11)	1819(7)	6255(8)	7280(8)	78(2)
C(12)	1600(9)	6448(9)	6075(8)	87(2)
C(13)	2942(10)	6569(10)	5569(7)	87(2)
C(14)	4532(8)	6459(7)	6278(5)	62(1)
C(15)	6567(7)	8240(7)	11153(5)	58(1)
C(16)	6334(9)	9503(8)	12113(6)	69(2)
C(17)	5667(10)	8881(11)	13091(7)	87(2)

Data of compound 9a(chapter 4):

Table 1. Crystal data and structure refinement for 9a.

Identification code	nrr100	
Empirical formula	$C_{19}H_{21}ClO_4$	
Formula weight	348.81	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	P-1	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 9.1581(2) Å	= 73.691(2)°.
	b = 9.3847(3) Å	= 75.225(2)°.
	c = 11.4211(3) Å	= 68.448(2)°.
Volume	863.46(4) $Å^3$	
Z	2	
Density (calculated)	1.342 Mg/m^3	
Absorption coefficient	0.241 mm^{-1}	
F(000)	368	
Crystal size	0.19 x 0.15 x 0.05 mm^3	
Θ range for data collection	2.43 to 27.57°.	
Index ranges	$-11 \le h \le 11$, $-12 \le k \le 12$, $-14 \le l \le 14$	
Reflections collected	16888	
Independent reflections	3931 [R(int) = 0.0530]	
Completeness to Θ = 27.57°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9881 and 0.9557	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3931 / 0 / 224	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2σ(I)]	R1 = 0.0466, wR2 = 0.1040	
R indices (all data)	R1 = 0.0938, wR2 = 0.1260	
Largest diff. peak and hole	0.427 and -0.402 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nrr100. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	14501(1)	2012(1)	5365(1)	46(1)
O(1)	5742(2)	352(2)	8734(2)	42(1)
O(2)	7823(2)	-779(2)	7423(2)	49(1)
O(3)	6847(2)	867(2)	10496(2)	31(1)
O(4)	8901(2)	1905(2)	10992(1)	28(1)
C(1)	8068(2)	1092(2)	8315(2)	26(1)
C(2)	7913(2)	1285(2)	9517(2)	25(1)
C(3)	8947(2)	1907(2)	9759(2)	24(1)
C(4)	10077(2)	2397(2)	8842(2)	26(1)
C(5)	10170(2)	2289(3)	7620(2)	27(1)
C(6)	9170(2)	1640(2)	7343(2)	28(1)
C(7)	7081(3)	221(3)	8164(2)	30(1)
C(8)	6957(3)	-1752(4)	7290(4)	74(1)
C(9)	7970(4)	-3342(4)	7353(4)	74(1)
C(10)	11156(3)	3049(3)	9181(2)	35(1)
C(11)	11436(3)	2792(3)	6617(2)	34(1)
C(12)	12969(3)	1425(3)	6525(2)	38(1)
C(13)	9219(3)	1611(3)	6017(2)	41(1)
C(14)	7756(2)	3091(2)	11513(2)	25(1)
C(15)	6684(3)	4328(3)	10875(2)	31(1)
C(16)	5585(3)	5476(3)	11488(2)	39(1)
C(17)	5562(3)	5391(3)	12717(2)	39(1)
C(18)	6650(3)	4152(3)	13343(2)	38(1)
C(19)	7751(3)	2998(3)	12750(2)	32(1)

Data of compound 9b(chapter 4):

Table 1. Crystal data and structure refinement for 9b

Identification code	nrr101
Empirical formula	$C_{19}H_{21}BrO_4$
Formula weight	393.27
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 = 9.2053(3) Å = 72.8050(10)°.
	b = 9.4398(3) Å = 75.5310(10)°.
	c = 11.5253(3) Å = 68.299(2)°.
Volume	877.72(5) $Å^3$
Z	2
Density (calculated)	1.488 Mg/m^3
Absorption coefficient	2.361 mm^{-1}
F(000)	404
Crystal size	0.80 x 0.70 x 0.30 mm^3
Θ range for data collection	2.38 to 29.99°.
Index ranges	$-12\leq h\leq 12$, $-13\leq k\leq 13$, $-13\leq l\leq 16$
Reflections collected	23057
Independent reflections	4992 [R(int) = 0.0302]
Completeness to Θ = 29.99°	97.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.5377 and 0.2539
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4992 / 0 / 221
Goodness-of-fit on F^2	1.049
Final R indices [$I>2\sigma(I)$]	R1 = 0.0318, wR2 = 0.0871
R indices (all data)	R1 = 0.0366, wR2 = 0.0899
Largest diff. peak and hole	0.954 and -0.689 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for nrr101. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	14522(1)	7110(1)	287(1)	40(1)
O(1)	5717(2)	5376(2)	3746(1)	39(1)
O(2)	7805(2)	4192(2)	2512(2)	46(1)
O(3)	6840(1)	5865(1)	5497(1)	28(1)
O(4)	8900(1)	6881(1)	5975(1)	26(1)
C(1)	8040(2)	6098(2)	3333(1)	23(1)
C(2)	7890(2)	6285(2)	4524(1)	22(1)
C(3)	8927(2)	6896(2)	4764(1)	22(1)
C(4)	10047(2)	7388(2)	3846(1)	24(1)
C(5)	10127(2)	7289(2)	2634(1)	25(1)
C(6)	9130(2)	6643(2)	2373(1)	25(1)
C(7)	7056(2)	5228(2)	3201(2)	27(1)
C(8)	6939(3)	3213(3)	2425(4)	75(1)
C(9)	8022(4)	1677(3)	2313(3)	64(1)
C(10)	7789(2)	8079(2)	6476(1)	23(1)
C(11)	7826(2)	7987(2)	7692(2)	28(1)
C(12)	6753(2)	9162(2)	8266(2)	34(1)
C(13)	5658(2)	10407(2)	7628(2)	37(1)
C(14)	5650(2)	10489(2)	6415(2)	36(1)
C(15)	6721(2)	9330(2)	5820(2)	29(1)
C(16)	11132(2)	8027(2)	4177(2)	32(1)
C(17)	11366(2)	7809(2)	1634(2)	31(1)
C(18)	12892(2)	6443(2)	1548(2)	35(1)
C(19)	9175(2)	6599(2)	1064(2)	39(1)

Data of compound 1(manuscript in preparation):

Table 2. Crystal data and structure refinement for nso2.

Identification code	nso2
Empirical formula	$C_{17} H_{12} O_5 S$
Formula weight	328.33
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 = 5.9644(2) Å = 90°.
	b = 8.0764(2) Å = 90°.
	c = 30.6452(9) Å = 90°.
Volume	1476.21(8) $Å^3$
Z	4
Density (calculated)	1.477 Mg/m^3
Absorption coefficient	0.243 mm^{-1}
F(000)	680
Crystal size	0.61 x 0.40 x 0.17 mm^3
Θ range for data collection	2.66 to 28.99°.
Index ranges	$-7\leq h\leq 8$, $-11\leq k\leq 9$, $-41\leq l\leq 40$
Reflections collected	11922
Independent reflections	3846 [R(int) = 0.0232]
Completeness to Θ = 28.99°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9598 and 0.8658
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3846 / 0 / 209
Goodness-of-fit on F^2	1.115
Final R indices [$I>2\sigma(I)$]	R1 = 0.0313, wR2 = 0.0790
R indices (all data)	R1 = 0.0327, wR2 = 0.0800
Absolute structure parameter	0.00(6)
Largest diff. peak and hole	0.286 and -0.266 e.$Å^{-3}$

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for nso2. U (eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	4808(1)	4082(1)	8500(1)	20(1)
O(1)	4788(2)	5747(1)	8668(1)	28(1)
O(2)	6910(2)	3200(2)	8492(1)	30(1)
O(3)	2199(2)	335(2)	8434(1)	41(1)
O(4)	335(2)	2035(1)	9311(1)	19(1)
O(5)	-2243(2)	1736(1)	9839(1)	27(1)
C(1)	2966(2)	2832(2)	8805(1)	18(1)
C(2)	1396(2)	3329(2)	9088(1)	17(1)
C(3)	370(2)	4889(2)	9242(1)	18(1)
C(4)	635(3)	6550(2)	9126(1)	22(1)
C(5)	-695(3)	7708(2)	9340(1)	24(1)
C(6)	-2259(3)	7263(2)	9655(1)	26(1)
C(7)	-2560(3)	5610(2)	9765(1)	23(1)
C(8)	-1220(2)	4461(2)	9554(1)	18(1)
C(9)	-1215(2)	2655(2)	9607(1)	19(1)
C(10)	3258(2)	976(2)	8719(1)	21(1)
C(11)	4890(3)	74(2)	8998(1)	34(1)
C(12)	3670(2)	4069(2)	7970(1)	22(1)
C(13)	1632(3)	4869(2)	7893(1)	30(1)
C(14)	788(3)	4893(2)	7470(1)	35(1)
C(15)	1958(3)	4123(2)	7137(1)	36(1)
C(16)	3977(4)	3330(2)	7216(1)	36(1)
C(17)	4848(3)	3290(2)	7639(1)	29(1)

PART- B

Synthesis of tetraarylthiophenes by regioselective Suzuki cross-coupling reactions

Chapter 8

Regioselective Functionalization of Tetrabromothiophene by Suzuki-Cross-Coupling Reactions.

Tetrahedron Lett. **2007**, *48*, 845-847

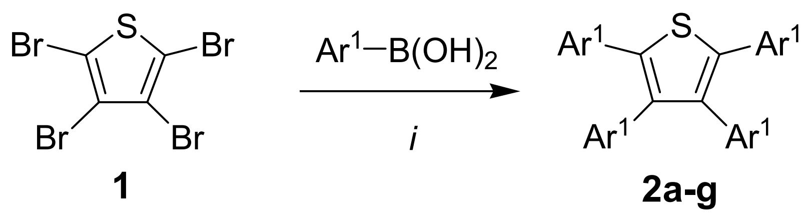
8.1. Introduction

Regioselective functionalizations of polyhalogenated heterocycles play an increasingly important role in organic synthesis.[1] These reactions rely on the higher reactivity of more electron-deficient carbon atoms while the other reactive positions remain unattacked. This concept has been applied to regioselective palladium(0) catalyzed coupling reactions which rely on the different rate of the oxidative addition of palladium(0) species to different carbon-halide bonds of the substrate. Thiophene-containing compounds constitute an important class of materials which show intrinsic electronic properties such as luminescence, redox activity, nonlinear optical chromism and electron-transport.[2] Thiophenes are also present in pharmacologically relevant natural products. This includes, for example, dibenzothiophenes,[3] [2,2';5',2"]terthiophenes,[4] and thienyl-diynes.[5]

2,3-Dibromothiophene has been functionalized by regioselective Sonogashira coupling of carbon atom C-2.[6] A very good C-2 regioselectivity was observed also for the Kumada cross coupling of 2,3- and 2,4-dibromothiophene.[7] 2,5-Disubstituted thiophenes were prepared by regioselective Sonogashira coupling reactions of tetraiodothiophene[8] and tetrabromothiophene.[9] Recently, we reported the synthesis of tetraarylthiophenes by regioselective Suzuki reactions of tetrabromothiophene.[10] Herein, we report full details of these studies. In addition, we report the regioselective functionalization of tetrabromothiophene based on metal-halide exchange reactions.we studied the preparative scope of this method and its application to the synthesis of a wide range of functionalized thiophenes.

8.2. Results and Discussion

Tetrabromothiophene (**1**) was prepared by bromination of thiophene (following a modified literature procedure).[11] The tetraarylthiophenes **2a-g**, containing four identical aryl groups, were successfully prepared by Suzuki reaction[12] of **1** (1.0 equiv.) with 5.0 equiv. of various boronic acids (Scheme 1, Table 1). The reaction of **1** (1.0 equiv.) with 2.2 equiv. of boronic acids allowed the regioselective synthesis of the 2,5-diaryl-3,4-dibromothiophenes **3a-f** (Scheme 2, Table 2). Products **3a,b** (1.0 equiv.) could be further functionalized by Suzuki-reaction with 3.0 equiv. of various arylboronic acids to give the tetraarylthiophenes **4a-f** which contain two different types of aryl groups (Scheme 2, Table 3). All reactions were carried out based on optimization studies of related Suzuki reactions carried out in our laboratory.[13] The stoichiometry of the reagents, the temperature, the solvent, and the presence of water proved to be important parameters. Oxygen-containing boronic acids showed a better solubility in 1,4-dioxane than in toluene. On the other hand, the higher boiling point of toluene proved to be advantageous in many cases. All reactions were carried out in the presence of water (solvent/water = 4:1) which proved to be very important in order to obtain good yields.[14]

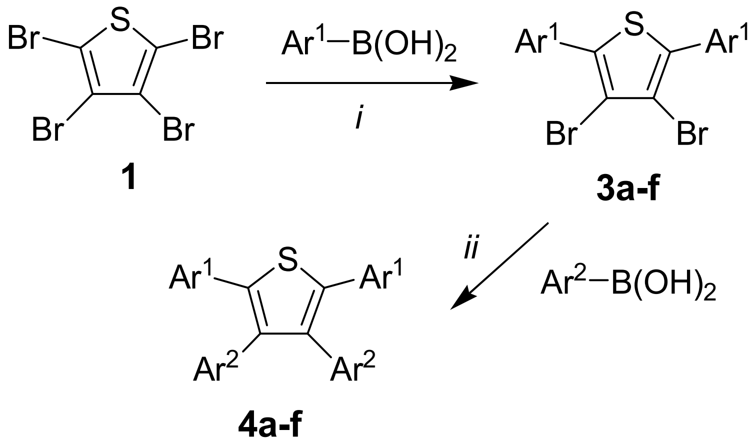


Scheme 1. Synthesis of tetraarylthiophenes **2a-g**. Conditions: *i*, **1** (1.0 equiv.), $Ar^1B(OH)_2$ (5.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (8.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 1)

Table 1. Synthesis of tetraaryl-thiophenes **2a-g**

2	Ar^1	Solvent	% (**2**)
a	Ph	Toluene	37 [a]
b	4-(MeO)C_6H_4	1,4-Dioxane	94 [b]
c	2-(MeO)C_6H_4	1,4-Dioxane	38 [b]
d	1-Naphthyl	Toluene	65 [b]
e	4-MeC_6H_4	Toluene	87 [a]
f	4-ClC_6H_4	Toluene	89 [b]
g	4-FC_6H_4	Toluene	93 [b]

[a] Isolated yields (conditions: 90 °C, 12 h); [b] isolated yields (conditions: 90 °C, 24 h)



Scheme 2. Synthesis of tetraaryl-thiophenes **4a-f**. Conditions: *i*, **1** (1.0 equiv.), $Ar^1B(OH)_2$ (2.2 equiv.), $Pd(PPh_3)_4$ (6 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 2); *ii*, **3a,b** (1.0 equiv.), $Ar^2B(OH)_2$ (3.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 3)

Table 2. Synthesis of 2,5-diaryl-3,4-dibromo-thiophenes **3a-f**

3	Ar^1	Solvent	% (**3**)
a	Ph	Toluene	32 [a]
b	$4\text{-}MeC_6H_4$	Toluene	77 [a]
c	$4\text{-}MeOC_6H_4$	1,4-Dioxane	43 [b]
d	$2\text{-}MeOC_6H_4$	1,4-Dioxane	35 [b]
e	$3,5\text{-}Me_2C_6H_3$	Toluene	54 [b]
f	2-Thienyl	Toluene	48 [b]

[a] Isolated yields (conditions: 90 °C, 12 h); [b] isolated yields (conditions: 90 °C, 24 h)

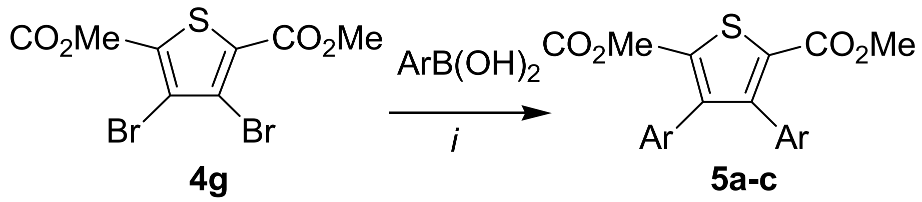
Table 3. Synthesis of tetraaryl-thiophenes **4a-f**

4	Ar^1	Ar^2	Solvent	% (**4**)
a	Ph	$4\text{-}MeC_6H_4$	Toluene	86 [a]
b	$4\text{-}MeC_6H_4$	Ph	Toluene	51 [a]
c	$4\text{-}MeC_6H_4$	$4\text{-}(MeO)C_6H_4$	Toluene+Dioxane [c]	76 [b]
d	$4\text{-}MeC_6H_4$	$4\text{-}(EtO)C_6H_4$	Toluene+Dioxane [c]	93 [b]
e	$4\text{-}MeC_6H_4$	$4\text{-}(HO)C_6H_4$	Toluene+Dioxane [c]	82 [b]
f	$4\text{-}MeC_6H_4$	$4\text{-}ClC_6H_4$	Toluene	91 [b]

[a] Isolated yields (conditions: 90 °C, 12 h); [b] isolated yields (conditions: 90 °C, 24 h); [c] toluene / dioxane = 1:1

The structures of all products were established by spectroscopic methods. The structure of **3e** was independently confirmed by an X-ray crystal structure analysis.[10] Detailed inspection of the ^{1}H and ^{13}C NMR spectra and dynamic NMR studies (variable temperature NMR etc.) of tetrakis(2-methoxyphenyl)thiophene (**2c**) show that the rotation of the aryl-groups is sterically hindered and that two (out of theoretically possible six) rotamers are present at room temperature. However, the structure of the rotamers could not be unambigiously assigned.

The double Suzuki reaction of diester **4g** with 4-chlorophenyl, 2-methoxyphenyl, and 2-hydroxyphenylboronic acid afforded the thiophenes **5a-c** (Scheme 4, Table 5).



Scheme 4. Suzuki reactions of **4g**. Conditions: *i*, **4g** (1.0 equiv.), $ArB(OH)_2$ (3.0 equiv.), $Pd(PPh_3)_4$ (5 mol-%), K_3PO_4 (4.0 equiv.), solvent/H_2O = 4:1 (solvent see Table 4)

Table 4. Synthesis of thiophenes **5a-c**

5	*Ar*	*%* [a]	Solvent
a	4-ClC_6H_4	42	Toluene
b	2-(MeO)C_6H_4	45	Toluene+Dioxane [b]
c	2-(HO)C_6H_4	49	Toluene+Dioxane [b]

[a] Isolated yields; [b] toluene / dioxane = 1:1

For 3,4-di(2-methoxyphenyl)thiophene **5b** two rotamers are present at room temperature, due to the hindered rotation of the aryl groups. In contrast, only one set of signals is observed for 3,4-di(2-hydroxyphenyl)thiophene **5c**.

8.3. Conclusions

In conclusion, tetrasubstituted thiophenes were prepared based on regioselective Suzuki reactions of tetrabromothiophene. The Suzuki reaction of tetrabromothiophene resulted in regioselective functionalization of carbon atoms C-2 and C-5 which more rapidly undergo the odidative addition with the palladium(0) catalyst. Carbon atoms C-3 and C-4 could be subsequently functionalized by Suzuki reactions. Tetraarylthiophenes containing four identical substituents could be prepared in one step from tetrabromothiophene. The yields of the Suzuki reactions are generally good, except for reactions of parent phenylboronic acid and of 2-methoxyphenylboronic acid. The yields depend also on the individual quality of the starting materials and on the handling of each individual experiment.

8.4. Experimental Section

General Comments. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60-200 mesh) was used. Melting points are uncorrected.

8.4.1.Synthesis of tetrabromothiophene (1):[12] To a chloroform solution (10 mL) of thiophene (25 mL) a chloroform solution (20 mL) of bromine (60 mL) was dropwise added within 45 minutes. The reaction mixture was warmed to room temperature and an additional amount of bromine (10 mL) was added and the reaction mixture was subsequently stirred under reflux for three hours. A saturated aqueous solution of NaOH was added and the mixture was stirred under reflux for 6 h to remove the bromine. The solvent and the excess of bromine was removed in vacuo. The product was recrystallized from a 1:1 solution of chloroform and methanol. The crude product (red to brownish crystals) was washed with cold ethyl acetate for several times to give pure **1** as colourless crystals (87%). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.3, 116.9; MS (EI, 70 eV): *m/z* (%) = 400 (M^+, 100), 321 (65), 240 (34), 161 (41).

8.3.2.General procedure for synthesis of tetraarylthiophenes 2a-g: To a toluene solution (6 mL) of **1** (0.400 g, 1.0 mmol) was added $Pd(PPh_3)_4$ (0.116 g, 10 mol-%) at 20 °C. After stirring for 30 min, the arylboronic acid (5.0 mmol), K_3PO_4 (8.0 mmol) and water (2.0 mL) were added. The mixture was stirred at 90 °C for 12 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of tetraphenylthiophene (2a). Starting with **1** (0.400 g, 1.0 mmol) and phenylboronic acid (5.0 mmol), **2a** was isolated (0.144 g, 37%) as a colourless solid; mp 168−170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.87 (m, 4×2H, Ar), 7.03 (m, 4×2H, Ar), 7.14 (m, 2×2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 126.6, 127.2, 127.8, 128.2, 129.1, 130.8 (2×10CH, Ar), 134.2, 136.4, 138.5, 139.4 (8C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3058 (w), 3022 (w), 1596 (m), 1495 (m), 1480 (m), 1444 (w), 1073 (w), 1029 (w), 793 (w), 750 (s), 695 (s), 592 (m), 518 (w). MS (EI, 70 eV): *m/z* (%) = 388 (M^+, 100), 354 (4), 310 (6), 267 (4), 178 (3), 165 (6), 121 (3), 77 (2). HRMS (EI, 70 eV): calcd for $C_{28}H_{20}S$ (M^+): 388.1280; found: 388.1274.

Synthesis of tetra(4-methoxy)thiophene (2b). Starting with **1** (0.400 g, 1.0 mmol) and 4-tolylboronic acid (5.0 mmol), **2b** was isolated (0.477 g, 94%) as a colourless solid; mp 183−185 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65, 3.72 (s, 12 H, 2×2OCH_3), 6.59, 6.69, 6.82, 7.09 (d, 4×4H, CH, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.00, 56.06 (2×2C, OCH_3), 114.8, 116.0, 130.2, 131.9 (2×8CH, Ar), 127. 0, 129.0, 137.1, 138.3, 158.0, 158.6 (2×C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3431 (w), 3031 (m), 3003 (m), 2957 (m), 2924 (m), 2840 (m), 1607 (m), 1511 (s), 1495 (s), 1286 (s), 1175 (s), 1031 (s), 834 (s), 799 (m); MS (EI, 70 eV): *m/z* (%) = 508 (M^+, 100), 255 (31), 178 (15), 172 (29), 160 (26), 96 (10). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}O_4S$ (M^+): 508.6273; found: 508.6277.

Synthesis of tetra(2-methoxy)thiophene (2c). Starting with **1** (0.400 g, 1.0 mmol) and 4-tolylboronic acid (5.0 mmol), **2c** was isolated (0.193 g, 38%) as a colourless solid; mp

171−173 °C. A doubling of some signals in the ^{1}H and ^{13}C NMR spectra is observed, due to the presence of two rotamers. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.08, 3.15, 3.26, 3.43 (4 x s, 12 H, 4 OCH_3), 6.52 (m, 4 H, Ar), 6.69 (m, 4 H, Ar), 6.90 (m, 4 H, Ar), 7.07 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.6, 54.8, 54.9, 55.1 (OCH_3), 110.1, 110.5, 110.8, 110.9, 119.8, 119.7, 120.1, 120.2, 127.4, 127.5, 128.4, 128.5, 131.3, 132.0, 132.1, 132.2 (CH, Ar), 123.7, 123.9, 134.9, 135.1, 136.9, 137.3, 156.5, 156,6, 156.7, 156.8 (C, ArC); IR (KBr, cm^{-1}) $\tilde{\nu}$ = 3432 (w), 3067 (m), 2932 (w), 2830 (w), 1597 (s), 1578 (s), 1493 (s), 1460 (s), 1240 (s), 1117 (s), 1023 (s), 752 (s), 617 (w); MS (EI, 70 eV): *m/z* (%) = 508 (M^+, 100), 387 (18), 354 (9), 294 (8), 224 (6), 178 (4), 151 (3), 91 (5). HRMS (EI, 70 eV): calcd for $C_{32}H_{28}O_4S$ (M^+): 508.1703; found: 508.1706.

Synthesis of tetra(1-naphthyl)thiophene (2d). Starting with **1** (0.400 g, 1.0 mmol) and 1-naphthylboronic acid (5.0 mmol), **2d** was isolated (0.382 g, 65%) as a colourless solid; 293–294 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (m, 4 H, Ar), 7.89 (m, 2 H, Ar), 7.06 (m, 8 H, Ar), 7.21 (m, 4 H, Ar), 7.34 (m, 4 H, Ar), 7.49 (m, 2 H, Ar), 8.21, 8,29 (d,d, ^{3}J = 7.8 Hz, 2 H, Ar), 8.58, 8,65 (d,d, ^{3}J = 7.8 Hz, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.5–129.3 (CH, Ar), 131.4, 131.6, 133.1, 133.7, 134.2, 134.6, 138.3, 140.6 (2×8C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3053 (w), 2923(w), 1592 (w), 1506 (w), 1387 (w), 1261 (w), 1016 (w), 796 (s), 772 (s), 559 (w), 427 (w); MS (EI, 70 eV): *m/z* (%) = 388 (M^+, 100), 354 (4), 310 (6), 267 (4), 178 (3), 165 (6), 121 (3), 77 (2). HRMS (EI, 70 eV): calcd for $C_{44}H_{28}S$ (M^+): 588.1906; found 588.1901.

8.3.3.General procedure for synthesis of 3,4-dibromo-2,5-diarylthiophenes (3a-f): To a toluene solution (4 mL) of **1** (0.400 g, 1.0 mmol) was added $Pd(PPh_3)_4$ (0.070 g, 6 mol-%) at 20 °C. After stirring for 30 min, the arylboronic acid (2.2 mmol), K_3PO_4 (4.0 mmol) and water (1.0 mL) were added. The mixture was stirred at 90 °C for 12 h. After cooling to ambient temperature, the mixture was diluted with EtOAc, dried (Na_2SO_4), and filtered through a short Celite pad. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography (fine flash silica gel, *n*-heptane).

Synthesis of 3,4-dibromo-2,5-diphenylthiophene (3a). Starting with **1** (0.400 g, 1.0 mmol) and phenylboronic acid (2.2 mmol), **3a** was isolated (0.125 g, 32%) as a colourless solid; mp 150–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 2×3H, Ar), 7.61 (m, 2×2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.2 (2C, CBr), 128.4, 128.7, 128.8 (2×5CH, Ar), 132.8, 138.1 (2×2C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3051 (w), 2924 (w), 2853 (w), 1477 (m), 1268 (m), 1028 (w), 749 (s), 699 (s), 628 (w), 584 (w). MS (EI, 70 eV): *m/z* (%) = 396 (M^+, [^{81}Br,^{81}Br], 55), 394 (M^+, [^{81}Br,^{79}Br], 100), 392 (M^+, [^{79}Br,^{79}Br], 53), 314 (3), 234 (48), 202 (8), 197 (7), 189 (22), 117 (12), 95 (6), 77 (5). HRMS (EI, 70 eV): calcd for $C_{16}H_{10}Br_2S$ (M^+, [^{79}Br,^{79}Br]): 391.8864; found 391.8861.

Synthesis of 3,4-dibromo-2,5-di(4-methoxy)thiophene (3c). Starting with **1** (0.400 g, 1.0 mmol) and 4-methoxyphenylboronic acid (2.2 mmol), **3c** was isolated (0.194 g, 43%) as a colourless solid; mp 171–173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 6 H, 2OCH_3), 6.93 (d, ^3J = 8.2 Hz, 4 H, Ar), 7.54 (d, ^3J = 8.2 Hz, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (2C, OCH_3), 111.4 (2C, CBr), 114.0, 129.9 (2×4CH, Ar), 126.2, 137.3, 159.9 (2×3C, ArC); IR (KBr, cm^{-1}); $\tilde{\nu}$ = 3442 (br, w), 2959 (w), 2923 (w), 2835 (w), 1598 (w), 1579 (w), 1482 (s), 1252 (s), 1179 (w), 1117 (m), 1024 (s), 796 (m), 751 (s); MS (EI, 70 eV): *m/z* (%) = 456 (M^+, [^{81}Br,^{81}Br], 48), 454 (M^+, [^{81}Br,^{79}Br], 100), 452 (M^+, [^{79}Br,^{79}Br], 43), 476 (13), 474 (12), 279 (10), 208 (12), 136 (11), 121 (19), 119 (17), 105 (16), 77 (11), 69 (3). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2O_2S$ (M^+, [^{79}Br,^{79}Br]): 451.9076; found: 451.9073.

Synthesis of 3,4-dibromo-2,5-di(2-methoxy)thiophene (3d). Starting with **1** (0.400 g, 1.0 mmol) and 2-methoxyphenylboronic acid (2.2 mmol), **3d** was isolated (0.159 g, 35%) as a colourless solid; mp 120–122 °C. A small amount of impurity could not be removed. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 6 H, 2OCH_3), 6.93 (m, 2×2 H, Ar), 7.34 (m, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.6 (2C, OCH_3), 111.2, 120.4, 130.5, 132.2 (2×4CH, Ar), 112.6, 121.7, 134.9, 157.0 (2×4C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (br, w), 2995 (w), 2961 (w), 2835 (w), 1608 (s), 1534 (s), 1491 (s), 1299 (w), 1253 (s), 1180 (s), 1040 (s), 828 (s), 805 (m), 754 (w), 578 (w), 514 (w); MS (EI, 70 eV): *m/z* (%) = 456

(M^+, [^{81}Br,^{81}Br], 47), 454 (M^+, [^{81}Br,^{79}Br], 100), 452 (M^+, [^{79}Br,^{79}Br], 43), 376 (56), 374 (53), 279 (22), 264 (37), 237 (16), 208 (9), 149 (7), 147 (7), 131 (5), 104 (6), 71 (16), 57 (25). HRMS (EI, 70 eV): calcd for $C_{18}H_{14}Br_2O_2S$ (M^+, [^{79}Br, ^{79Br}]): 451.9070; found: 451.9069.

Synthesis of 3,4-dibromo-2,5-di(3,5-dimethylphenyl)thiophene (3e). Starting with **1** (0.400 g, 1.0 mmol) and 3,5-dimethylphenylboronic acid (2.2 mmol), **3e** was isolated (0.242 g, 54%) as a colourless solid; mp 120–121 °C. A small amount of impurity could not be separated. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 12 H, 4CH_3), 6.93 (s, 2 H, Ar), 7.21 (s, 4 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (2C, CH_3), 111.8 (2C, CBr), 126.2, 129.9 (2×4CH, Ar), 123.3, 138.1, 141.4 (2×3C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3436 (br, w), 2997 (w), 2917 (m), 1598 (s), 1457 (m), 1298 (w), 1257 (w), 1039 (w), 896 (w), 852 (s), 828 (s), 707 (m), 689 (m); MS (EI, 70 eV): *m/z* (%) = 452 (M^+, [^{81}Br,^{81}Br], 50), 450 (M^+, [^{81}Br,^{79}Br], 100), 448 (M^+, [^{79}Br,^{79}Br], 45), 372 (17), 370 (16), 290 (19), 225 (5), 210 (48), 195 (15), 149 (8), 97 (7), 69 (16). HRMS (EI, 70 eV): calcd for $C_{20}H_{18}Br_2S$ (M^+, [^{79}Br,^{79}Br]): 447.9491; found: 447.9492.

Synthesis of 3,4-dibromo-2,5-di(thien-2-yl)thiophene (3f). Starting with **1** (0.400 g, 1.0 mmol) and 2-thiopheneboronic acid (0.299 g, 2.2 mmol), **3f** was isolated (0.194 g, 48%) as a colourless solid; 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (t, ^3J = 3.7 Hz, 2×1H, thiophene), 7.28 (d, ^3J = 4.1 Hz, 2×1H, thiophene), 7.41 (m, 2×1H, thiophene). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.4 (2C, CBr), 126.8, 127.1, 127.4 (2×3CH, thiophene), 132.0, 135.1 (2×2C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3094 (w), 2960 (w), 2923 (w), 1484 (w), 1418 (w), 1261 (w), 1221 (w), 1060 (w), 844 (m), 815 (m), 699 (m), 686 (s). MS (EI, 70 eV): *m/z* (%) = 408 (M^+, [^{81}Br,^{81}Br], 55), 406 (M^+, [^{81}Br,^{79}Br], 100), 404 (M^+, [^{79}Br,^{79}Br], 47), 328 (16), 326 (17), 246 (52), 202 (11), 149 (7), 127 (10), 112 (5), 95 (9), 84 (17). HRMS (EI, 70 eV): calcd for $C_{12}H_6Br_2S_3$ (M^+, [^{79}Br,^{79}Br]): 403.7993; found: 403.7986.

synthesis of 3,4-diphenyl-2,5-di(4-tolyl)thiophene (4b). Starting with **3b** (1.0 mmol) and phenylboronic acid (3.0 mmol), **4b** was isolated (0.212 g, 51%) as a colourless solid;

mp 154–155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3×2H, CH_3), 6.87 (d, ^{3}J = 8.2 Hz, 4 H, 2CH, Ar), 6.91 (d, ^{3}J = 8.2 Hz, 4 H, 2CH, Ar), 7.08 (m, 10 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (2C, CH_3), 126.3, 127.6, 128.8, 128.9, 130.7 (2×10CH, Ar), 136.7, 136.8, 138.3, 139.4 (2×4C, ArC); IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3052 (w), 2918 (w), 1544 (w), 1502 (m), 1439 (m), 1021 (w), 836 (w), 817 (m), 771 (s), 703 (s), 523 (w), 510 (w); MS (EI, 70 eV): *m/z* (%) = 416 (M^+, 100), 324 (4), 281 (6), 183 (4), 165 (6), 149 (7), 112 (13), 97 (15), 83 (19), 57 (32). HRMS (EI, 70 eV): calcd for $C_{30}H_{24}S$ (M^+): 416.1593; found: 416.1591.

8.5. References

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PART- C

Phytochemical Investigation

Of *Pulicaria undulata*

General Introduction

The medicinal plants find application in pharmaceutical, cosmetic, agricultural and food industry. The use of the medicinal herbs for curing disease has been documented in history of all civilizations. Man in the pre-historic era was probably not aware about the health hazards associated with irrational therapy. With the onset of research in medicine, it was concluded that plants contain active principles, which are responsible, for curative action of the herbs.

Before onset of synthetic era, man was completely dependent on medicinal herbs for prevention and treatment of diseases. With introduction of scientific procedures the researchers, were able to understand about toxic principles present in the green flora. The scientists isolated active constituents of the medicinal herbs and after testing some were found to be therapeutically active. Aconitine, Atisine, Lobeline, Nicotine, Strychnine, Digoxin, Atropine, Morphine are some common examples.

The efficacy of some herbal products is beyond doubt, the most recent examples being Silybum marianum (silymarin), Artemisia annua (artemesinin) and Taxus baccata (taxol). On the other hand, randomized, controlled trials have proved the efficacy of some established remedies, for instance, Ginkgo biloba for tinnitus, Hypericum perforatum is a reputed remedy for depression. In Hypericum some researchers are of the view that hypericin is the active principle of the herb and some believe that hyperforin is responsible for antidepressant action of the herb.

Recently research has supported biological activities of some medicinal herbs. Cancer is such a segment where researchers are expecting new molecules from herbs that can provide us with tools for fighting this dreaded disease. Allamanda cathratica [allamandin], Elephatopus elatus [elephantpoin], Helenium autmnale [helenalin] Vernonia hymenlepis, Heliotropium indicum [Indicine-N-oxide], Daphne mezereum (mezerien) and Stereospermum suaveolans [laphacol] are medicinal plants that have shown significant tumor inhibiting effect.

Diabetes mellitus is another area where a lot of research is going on. Ajuga reptens (the active principle is said to potentiate effects of insulin), Galagea officinalis (galagine), Bougainvillea spectabilis (pinitol), Momordica charantia (chirantin), Gymnema sylvestre (gymnemic acid) are some medicinal herbs that have shown effectiveness in non-insulin dependent diabetes. Recently extract of Tecoma stans has shown potent anti diabetic activity. Alkaloid tecomonine is considered to be active principle of the herb.Arthritis is another potential disease where no satisfactory answer is present in modern medicine. Commiphora mukul (guggulsterones), Boswellia serrata [boswellic acid], Withania somnifera (withanolides), Ruscus acueleatus (ruscogenin), Harpagophytum procumbens (harpagoside) are prominent plants with anti- arthritic activity. Harpagoside is a precious constituent as it has anti rheumatoid activity. Rest of all natural products has anti-inflammatory activityChrysanthemum parthenium traditionally known as feverfew has shown promising results in migraine, a disease that has eluded the researchers from centuries. The herb contains sesquiterpenes lactones called parthenolides, which are the active principles of the herb. Hepatoprotective action of certain botanicals deserves attention. Sedum sarmentosum [sarmentosin], Schisandra chinensis [waweizichun and schisantherin] have shown their ability to lower raised liver enzymes in viral hepatitis.

Croton sublyratus [plaunotol] has potent and wide spectrum anti peptic ulcer action. A number of plant derivatives have shown anti-Aids activity. Ancistrocladus korupensis [michellamine-b], Caulophyllum langigerum [calanolide-a], Caulophyllum teymani [costatolide-a], Homalanthus nutans [prostratin], Conospermum sp [concurvone] are the medicinal herbs from African countries that are being employed in research for finding a suitable cure for Aids.

The concept of antioxidants is fastly catching up and latest research has shown that a number of herbal derivatives have excellent antioxidant action. Bacopa monnieri contains bacosides A and B and bacoside A is a strong antioxidant, which reduces several steps of free radical damage. Coleus forskohlii [forskolin], Grape seed [proanthocyanidins], Camellia sinensis [polyphenols], Huperzia serrata [huperzine], Pinus maritima [Pycnogenol], Borago officinalis [gamma linoleic acid] and Vinca minor [Vinpocetine] are potential antioxidantsThe plant is a biosynthetic laboratory, not only for chemical compounds, but also a multitude of compounds like glycosides, alkaloids etc. These exert physiological and therapeutic effect. The compounds that are responsible for medicinal property of the drug are usually secondary metabolites. A systematic study of a crude drug embraces through consideration of primary and secondary metabolites derived as a result of plant metabolism. The plant material is subjected to phytochemical screening for the detection of various plant constituents.[12]

The genus *Pulicaria* Gaertn. of the family Compositae (Asteraceae) consists of 100 species and this genus has been the subject of several chemical investigations, giving rise to the isolation of flavonoids, sesquiterpenes, diterpenes, triterpenes, caryophyllenes and caryophyllane derivatives [13,14]. Several species of this genus have been used as insect repellents and in the treatment of dysentery [15]. The genus *Pulicaria* is placed in the tribe Inuleae s. str. [16]. Chemically this genus is not homogeneous. As pointedout previously [17] some species contain diterpenes,others caryophyllene derivatives and those now placed inthe genus *Francoeuria* contain sesquiterpene lactones. *Pulicaria undulata* L. which is a synonym of *Pulicaria crispa* Forssk. and *Francoeuria crispa* Forssk. [18] Is an annual wooly herb which can cover whole desert wadis with its bright yellow flowers and fills the air with a rich perfume. Most plants appear with only a few flower-bearing branches but, under good conditions, they can grow into a splendid bush. One of its local names "Shai-el-Gebel which gives the secret away that this plant is used as an herbal tea and as a medicinal plant. The Bedouin's or vernacular name for Pulicaria crispa is Dethdath and Desdas. The Arabic names include: Arfeg; Feliet el-Hami; El Attasa, El Eteytesa; Sabad, Gettiat, Zibl el Far, Ghobbeira and Khanouf.The Berber name are: Timetfest.This plant is used medicinally as a remedy for breathing problems. One small spoon of the herb can be boiled in a glass of water as needed. The flower branches areused for preparing a powerful sneezing powder. *Pulicaria undulate,* **C.** A. Mey. Has been studied previously, but only thymol derivatives and flavones sesquiterpenes, diterpenes [19,20] have been reported.

Botanical description of the plant *Pulicaria undulata*

Family of *Pulicaria*

“Asteraceae (compositae) is also called sunflower family Herbs, shrubs and even trees are in the Sunflower Family. What seems to be a single flower is really a group of many flowers of two kinds. The strap-shaped forms on the outer edge that look like petals are each a complete flower and are called ray florets. The tightly packed tubular forms in the centre are also complete flowers and are known as disk florets. Some members of the Sunflower Family have only ray flowers. Dandelions and chicory are examples. Other members of the family have only disk florets. Thistles are an example of this. Ray and disk flowers are connected to a structure called the receptacle and underneath the receptacle are a number of bracts known as the involucres. The largest family of vascular plants, with possibly 950 genera and 20,000 species, chiefly herbaceous and world-wide in distribution:" [Cited from ref.Munz, Flora So. Calif.95]

"The composite or aster family (Asteraceae) is one of the largest families of plants, containing about 20,000 species, distributed among more than 1,000 genera, and occurring widely on all continents, except Antarctica. This family is commonly regarded by modern botanists as the most advanced of the plant families, because of the complex, highly evolved structure of its multi-flowered, composite reproductive structures. The members of the composite family display a remarkable range of growth forms, ranging from tiny, herbaceous annual plants, to vine-like lianas, and tall, tree-like perennials. For example, some species in the genus *Senecio* are small, annual plants, such as the widespread common groundsel (*Senecio vulgaris*). In contrast, the giant senecio (*S. adnivalis*) species found on a mountain in Uganda, is a perennial plant that grows as tall as 26 ft (8 m). The most species-rich genera in the aster family are *Senecio* (about 1,500 species), *Vernonia* (900 species), *Hieracium* (800 species), and *Eupatorium* (600 species). Various members of the aster family are familiar species in natural habitats, while others are cultivated plants in gardens, and some are grown as foods. Some species in the aster family are considered to have negative values as weeds of agriculture or lawns. Members of the Asteraceae are most readily characterized by their unique floral structure. The flowers of members of this family are aggregated within a composite grouping known as an inflorescence, which in this family is known as a head. In the head, the small, individual flowers, called florets, are attached to a basal structure known as a receptacle. The latter is surrounded by one or more rows of bracts that make up the involucre Artichokes in Salinas." [Cited from ref. California. 1983 Lawrence Midgale, National Audubon Society Collection/Photo Researchers, Inc.].

Genus *Pulicaria*

Pulicaria is a genus of flowering plant in the Asteraceae family. It contains the following species:

- *Pulicaria aromatica*
- *Pulicaria dioscorides*
- *Pulicaria diversifolia*
- *Pulicaria elegans*
- *Pulicaria lanata*
- *Pulicaria stephanocarpa*
- *Pulicaria vieraeoides*

Medicinal importance of the *Pulicaria undulata*

Pulicaria undulata L. which is a synonym of *Pulicaria crispa* Forssk. and *Francoeuria crispa* Forssk. is used to treat inflammation and a potential cancer chemopreventive agent "axillarin" has also been isolated from its aerial parts [20]. It is also used as a tonic, tea substitute, and antispasmodic, hypoglycemic and for the preparation of perfumes. The essential oil obtained from its aerial parts exhibited insecticidal and antibacterial activities [21, 22].

General Experimental Conditions

Physical Constants

Optical rotations were measured on JASCO DIP-360 digital polarimeter. All the compounds were oily or gummy solids due to which their melting points were not determined.

Spectroscopy

Ultraviolet (UV) spectra were recorded in methanol on Hitachi U-3200 spectrophotometer. Infrared (IR) spectra were scanned on JASCO 302-A Infrared Spectrometer.

Proton magnetic resonance (^{1}H NMR) spectra were recorded at 300, 400 and 500 MHz on Bruker AM-300, AM-400 or AMX-500 nuclear magnetic resonance spectrometers using TMS as an internal reference. The ^{13}C NMR spectra were scanned with the same instruments at 75, 100 and 125 MHz respectively.

The heteronuclear 2D ^{1}H-^{13}C chemical shift correlation experiments were carried out at 500 MHz with a sweep width of 12820 Hz (2k data points) in $\omega 2$ and 1024 Hz (256 t_1 values zero-filled to 2K) in ω 1. In both 2D experiments, a sec. relaxation delay was used and 16 transients were performed for each t_1 value.

For NOE difference measurements, the sample was frozen under liquid nitrogen and degassed. A lower decoupler power of 0.2 watt with 35 attenuation in dbs was used. The pre-irradiation time was 11 sec; which is the sum of three delays as used in the NOE difference programme of Bruker. The impulse lengths of 100 microseconds were maintained to avoid saturation.

Low-resolution electron impact mass spectra were recorded on a Finnigan MAT 311 and MAT 311 spectrometers, coupled with PDP 11/34 computer system. Peak matching, field desorption (FD) and field ionization (FI) were performed on the Finnigan MAT 312 mass spectrometer. High resolution mass measurements and fast atom bombardment (FAB) mass measurement were carried out on Jeol JMS HX 110 mass spectrometer. FAB source using glycerol or thioglycol as the matrix and cesium iodide (CsI) as an internal standard was used for accurate mass measurements.

Chromatography

Column chromatography was performed on silica gel (Si 60, 70-230 mesh, E. Merck), vacuum liquid chromatography (VLC) was performed on silica gel (Si 60, F_{254}, E. Merck).

Flash column chromatography was performed on Eyela Flash Chromatography model EF-10, using silica gel (Si 60, 230-400 mesh, E. Merck) as an absorbent.

Precoated silica gel GF_{254} preparative plates (20×20, 0.5 mm thick) (E. Merck) were used for preparative thick layer chromatography. The purity of the samples were also checked on TLC and HPTLC plates.

Spray reagent

Ceric sulphate was used for the detection of compounds.

Ceric sulphate

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

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Chapter 9

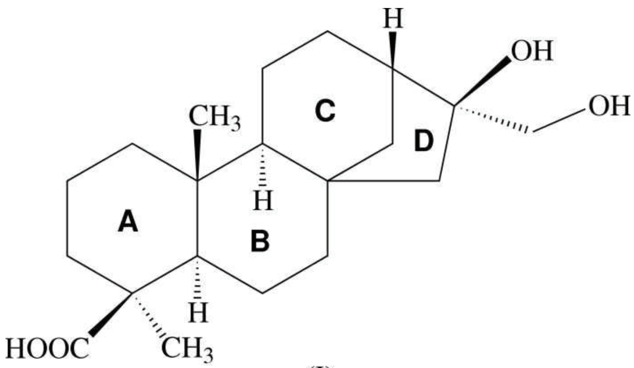
16b,17-Dihydroxy-ent-kauran-19-oic acid from *Pulicaria undulata*

Acta Cryst. (2005). E**61**, o3053–o3055

The title compound, $C_{20}H_{32}O_4$, was isolated from Pulicariaunduleta. It has an ent-kaurane diterpeniod ring system. In the crystal structure, the molecules are linked via O—H-----O hydrogen bonds into a ribbon structure.

9.1. Comment

Pulicaria unduleta is a herbaceous plant belonging to the family Asteracea (Compsitae), the largest family of the flowering plants. It comprises about 10,100 genera and 20,000species, commonly found in frigid, temperate, subtropical andtropical regions of Asia and Africa (Nasir & Ali, 1972). The genus Pulicaria has 11 species distributed in tropical and temperate regions in Pakistan (Ayoub & Elassam, 1981).Plants of this genus are known to contain flavones, alkaloids,monoterpenes, sesquiterpenes, sesquiterpene lactones (Bohlmannet al., 1979), diterpenoids, polyacetylene and thymolderivatives (Metwally et al., 1986). Ent Kauranoic acid is foundto exhibit significant activity against HIV replication in H9lymphocyte cells, with an EC50 value of 0.8 mg ml_1 with therapeutic index >5 (Wu et al., 1996). The title compound, (I),has been isolated from Helianthus petioaries (Herz & Kulanthaivel,1984) and Annona squamasa (Wu et al., 1996). We have undertaken the X-ray crystal-structure determination of(I) isolated from Pulicaria unduleta in order to establish its
Molecular conformation and relative stereochemistry.



(I)

The bond lengths in (I) show normal values (Allen et al.,1987). The C—C bond lengths lie in the range 1.514 (3)–1.574 (2) A °. All the ring junctions in the ent-kaurane diterpenoidring system are trans-fused. Rings A and B adopt chair conformations and ring C is in a distorted chair conformation,with puckering amplitude Q = 0.625 (2)_, _ = 27.3 (2)_ and ' =294.6 (4)_ (Cremer & Pople, 1975). The distortion may beattributed to the narrowing of the C13—C14—C8 bond angleto 101.95 (14)_. The five-membered ring D adopts an envelope conformation with atom C14 displaced from the C8/C15/C16/C13 plane by 0.707 (3) A ° . The C2—C3—C4—C20 torsion

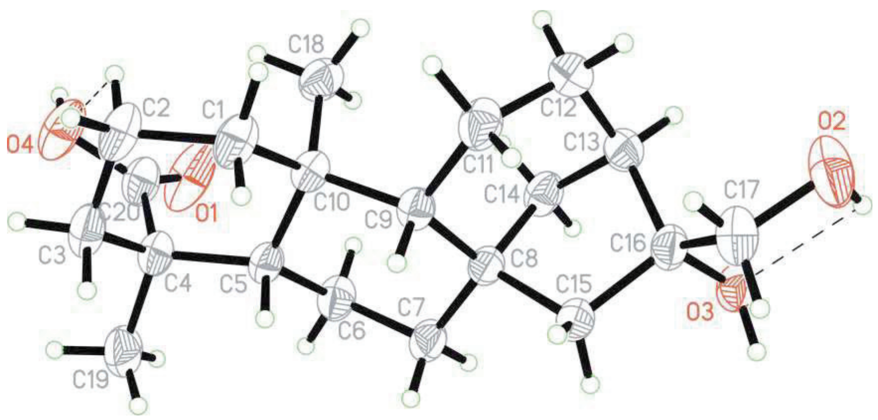


Figure 1
The molecular structure of (I), showing 50% probability displacementellipsoids and the atom-numbering scheme. Dashed lines indicate theintramolecular hydrogen bonds

angle of _71.0 (2)_ describes the _-orientation of the carboxylic acid group with respect to the ent-kaurane nucleus, whereas the hydroxymethylene group at atom C16 is _-oriented, the C15—C16—C17—O2 torsion angle being175.67 (17)_. Intermolecular O2—H1O2---O3 and C2—H2C_ _ _O4 hydrogen bonds generate rings of graph-set motifR11(5) and R11(6), respectively (Bernstein et al., 1995).The crystal structure is stabilized by O—H_ _ _O hydrogen bonds (Table 1). These hydrogen bonds link the molecules into a ribbon-like structure (Fig. 2).

9.2.Experimental

The dry plant material was chopped and soaked in methanol for a period of 30 d. The combined methanolic extract was evaporated under vacuum to yield a crude methanolic extract. The methanol extract (253 g) was then fractionated with petroleum ether (161.5g), chloroform (32.5 g), ethyl acetate (10.0 g) and butanol (50.5 g). The chloroform-soluble fraction was subjected to column chromatography using silica-gel absorbent, eluted with petroleum ether, and the polarity was gradually increased with chloroform and methanol. Various subtractions with the same constituents were combined and further purified using flash column chromatography (Si gel) and eluted with increasing polarities of petroleum ether and ethyl acetate to afford the title compound, (I). An RF value of 0.67 was noted on thin-layer chromatography (0.5% methanol–95.5% chloroform) and the compound was recrystallized from chloroform (m.p. 571–573 K).

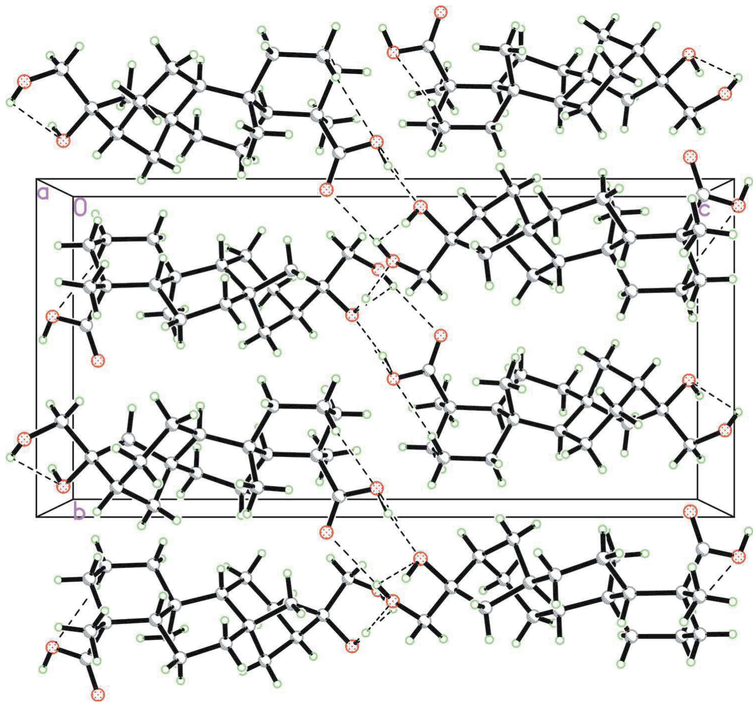


Figure 2
The crystal packing of (I), viewed down the axis. Dashed Lines indicate hydrogen bonds.

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Chapter 10

Antioxidant Flavonoids from *Pulicaria undulata*

Polish Journal of Chemistry **2006**, 745-751

10.1. Introduction:

The genus *Pulicaria* Gaertn. of the family Compositae (Asteraceae) consists of 100 species and this genus has been the subject of several chemical investigations, giving rise to the isolation of flavonoids, sesquiterpenes, diterpenes, triterpenes, caryophyllenes and caryophyllane derivatives [1,2]. Several species of this genus have been used as insect repellents and in the treatment of dysentery [2]. The constituents of *P. paludosa* Link., a Spanish endemic species, are used in an ointment for skin disorders [3]. *Pulicaria undulata* L. which is a synonym of *Pulicaria crispa* Forssk. and *Francoeuria crispa* Forssk. [4] is used to treat inflammation and a potential cancer chemopreventive agent "axillarin" has also been isolated from its aerial parts [5]. It is also used as a tonic, tea substitute, antispasmodic, hypoglycemic and for the preparation of perfumes. The essential oil obtained from its aerial parts exhibited insecticidal and antibacterial activities [6,7].

The superoxide anion, O_2^-, is formed in almost all aerobic cells and is a major agent in the mechanism of oxygen toxicity [8,9]. It is closely related to the biological course of apolexis, tumor, and inflammation etc. Compared with other oxygen radicals, superoxide anion has a longer life-time, can move to an aim at a longer distance, and thus has more dangerous. O_2^- is considered to be generated primarily by mitochondria in various cells, and by phagocytes such as granulocytes and monocytes/macrophages [10]. Under physiologic conditions, O_2^- is converted to H_2O_2 in hydrophilic solvents such as water by a disproportion reaction [11]. In addition, O_2^- can react with nitric oxide (NO) and generate highly toxic ROS including $ONOO^-$ and nitrogen oxides (NO_x) [12]. Thus, elimination of O_2^- is an important biologic need. Therefore, it is very important to study the scavenging of superoxide anion.

10.2. Results and Discussion

The ethylacetate soluble fraction of the whole plant of *Pulicaria undulata* L. (syn. *Pulicaria crispa* Forssk.) led to the isolation two new flavonoid glycosides (**1** and **6**) and their structures were deduced by a detailed analysis of their spectral data and by the comparison with the published data of the closely resembling compounds.

Pulicaroside (**1**) was isolated as an amorphous solid. Its molecular formula $C_{28}H_{32}O_7$ was established through the HRFAB-MS (+) showing a quasi-molecular ion $[M+H]^+$ peak at *m/z* 641.5447 (cald. 641.5432), which indicated 13 degrees of unsaturation. The UV spectrum of **1** with $AlCl_3$-HCl showed a 10 nm bathochromic shift in band I relative to MeOH spectrum indicating a 6-OR group in the molecule [13]. Its IR spectrum exhibited absorptions for hydroxyl groups (3418-3295 cm^{-1}), methine (2923 cm^{-1}), conjugated carbonyl group (1601 cm^{-1}), aromatic unsaturation (1506-1451 cm^{-1}), ether linkage (1285 cm^{-1}) while the broad C-O stretching bands in the region of 1137-1031 cm^{-1} suggested its glycosidic nature. Its EI-MS spectrum exhibited an ion at *m/z* 316 $[M - (2 \times \text{glucose}]^+$ and the other characteristic fragments were observed *m/z* 168 $[C_6H(OH)_3OCO]^+$ and at *m/z* 148 $[C_6H_4(OH)CCOMe]^+$ which were accounted for the trihydroxyl substituted A ring and a monohydroxyl substituted B ring respectively. Its ^{1}H-NMR spectrum revealed two *ortho*-coupled doublets at δ 8.01 (2H, *J* = 8.4) and δ 6.85 (2H, *J* = 8.4) for a para-disubstituted B ring, a singlet at δ 3.82 (3H) for a 3-*O*-methoxyl group, another singlet at δ 6.42 (1H) for H-8, similar to those of **2** [experimental part], however the presence of two anomeric doublets centered at δ 5.15 (1H, *J* = 7.4) and δ 4.92 (1H, *J* = 7.6) respectively, indicated that the structure of **1** was exactly similar to that of **2**, except for the presence of an additional *β*-glucose moiety and its presence was further confirmed by its ^{13}C-NMR spectrum which corroborated the characteristic signals for two glucose units along with the signals for a similar aglycone moiety like that of **2**. The position of the additional glucose unit was deduced through the downfield shift of C-6″ (66.8) as compared to the respective signal of **2** and HMBC correlations of H-1‴ with C-6″ and H-

6″ with C-1‴. Important HMBC correlations are shown in fig. 1. Since only D-glucose is known in nature [14], therefore, based upon the above cumulative evidences, **1** was identified as 6-hydroxykaempferol 3-methyl ether 6-*O*-[*O*-β-D-glucuronopyranosyl (1→6)] β-D-glucopyranoside.

Undulatoside (**6**) was obtained also as an amorphous solid. It was assigned a molecular formula $C_{22}H_{24}O_{12}$ on the basis of HRFAB-MS (+) (*m/z* 481.4217 $[M+H]^+$, cald. 481.4195), showing 11 degrees of unsaturation. Its UV spectrum showed absorption maxima at 324.6 nm (sh, band I) and 288.3 nm (band II) which are specific for the dihydroflavonol skeleton. Its IR spectrum revealed the absorptions for the hydroxyl groups (3540-3285 cm^{-1}) and a chelated carbonyl group (1626 cm^{-1}). Bands of aromatic ring (1578-1504 cm^{-1}) and of the glycosidic linkage (3233-1064 cm^{-1}) were also present. The EI-MS spectrum exhibited an ion at *m/z* 318 $[M – glucose]^+$ followed by the loss of a fragment with *m/z* 136 $[C_6H_4(OH)CHCHOH]^+$ and thus the methoxyl group was assigned on the ring A on the basis of a fragment ion at *m/z* 182 $[C_6H(OH)_2(OMe)OCO]^+$. Its ^{1}H-NMR spectrum revealed two sets of symmetric doublets, one at δ 7.69 (2H, J = 8.4) and δ 6.84 (2H, J = 8.4) for a para-disubstituted B ring while another at δ 5.40 (1H, J = 11.6) and δ 4.72 (1H, J = 11.6) for H-2 and H-3 respectively. It also showed two singlets at δ 6.48 (1H) and δ 3.86 (3H), for H-8 and a 6-*O*-methoxyl group respectively, similar to those of reported for (2*R*:3*R*)-dihydro-5, 7, 4′-trihydroxy-6-methoxyflavonol [15], and an additional doublet at δ 4.99 (1H, J = 7.8) was assignable to an anomeric proton, thus showing the presence of *β*-glucose moiety in this molecule. The 2*R*:3*R* configuration was assigned based on the large coupling coupling constant ($J_{2,\,3}$ = 11.6 *Hz*) and positive optical rotation sign (+ 24.8) in accordance with the literature report [15]. However, the absolute stereochemistry of the two optically active carbons could not be determined due to the small amount of the substance. The site of linkage of the glucose unit was identified through the downfield shift of C-3 (δ 77.6) and upfield shifts of C-4 (δ 196.4) and C-2 (δ 82.1) [16] as compared to those of reported for (2*R*:3*R*)-dihydro-5, 7, 4′-trihydroxy-6-methoxyflavonol [15]. The long range HMBC correlations of H-1″ with C-3 and H-3 with C-1″ further confirmed this assignment. Since only D-glucose is known in nature [14], hence on the basis of above cumulative evidences, the structure of **6** was established as (2*R*:3*R*)-dihydro-5,7,4′-trihydroxy-6-methoxyflavonol-3-*O*-*β*-D- glucopyranoside.

From our investigated source, four other known flavonones; 6-hydroxykaempferol 3-methyl ether 6-*O*-β-D-glucopyranoside (**2**) [13], 6-methoxykaempferol 3-*O*-β-D-glucopyranoside (**3**) [17], 6-methoxykaempferol (**4**) [18] and quercetagetin 3,6-dimethyl ether (axillarin) (**5**) [5] were also isolated and all these flavonoids (**1**-**6**) showed superoxide anion scavenging activity and the results are shown in table 2. As far structure-activity relationship is concerned, the presence of an additional glucose unit in **1**, in comparison with **2**, results in a slight decrease of its scavenging potential. Similarly, the mutual exchange in the positions of –OMe and –Oglc. in **3**, relative to **2**, also decreases its scavenging activity. However, when **4** was compared **3**, a free hydroxyl group at C-3 in **4** enhanced its scavenging ability as compared to that of **3**. In **5**, the presence of two adjacent hydroxyl groups in ring B unexpectedly resulted in a decrease of its scavenging activity relative to that of **4**. In **6** although the only difference with **3** was the absence of a double bond between C-2 and C-3, yet the great scavenging potential of this molecule can be rationalized for the axial and equatorial orientation of the substituents at C-2 and C-3 respectively.

10.3. Experimental Section.

General experimental procedures. 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 reagent. Purity was checked on TLC with different solvent systems using methanol, acetic acid, water and $CHCL_3$ 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. ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC and HMBC Spectra were run on Bruker spectrometers operating at 500, 400 and 300 MHz. 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.

Plant material. *The plant* Pulicaria undulata *L. (Asteraceae) was collected from Loralai, Blalochistan, and identified by Dr. Rasool Bakhsh Tareen (Taxonomist), Department of Botany, Balochistan University, Quetta, Pakistan. A voucher specimen (no. 1437a) has been deposited at the herbarium of the Botany Department of the same university.*

Extraction and purification. The shade-dried ground plant material (whole plant) (30 kg) was exhaustively extracted with methanol at room temperature. The extract was evaporated to yield the residue (753 g). The whole residue was dissolved in water and partitioned with hexane, chloroform, ethyl acetate and *n*-butanol. The ethyl acetate soluble extract (182.4 g) was subjected to CC over silica gel column using hexane with gradient of $CHCl_3$ up to 100 % and then the polarity was increased with methanol in a similar fashion. Fifteen fractions (Fr 1-15) were collected. The Fr. 5 was submitted to repeated FC (230-400 mesh) and eluted with MeOH: $CHCl_3$ (4:96) to get two sub-fractions ($Fr_{sb.}$ 5.1 and $Fr_{sb.}$5.2). The $Fr_{sb.}$5.1 was then flash choromatographed eluting with MeOH: $CHCl_3$ (3.8:96.2) to get purified **4** (25.3 mg). The $Fr_{sb.}$5.2 was then subjected to flash choromatography, eluting with MeOH: $CHCl_3$ (4:96) to purify **5** (17.6 mg). Similarly, the Fr. 9 was subjected to FC and eluted with MeOH: $CHCl_3$ (12:88) to get three sub-fractions ($Fr_{sb.}$ 9.1, $Fr_{sb.}$9.2, and $Fr_{sb.}$9.3). These three sub-fractions were again loaded on flash silica gel separately and eluted with MeOH: $CHCl_3$ (11:89, 11.5:88.5 and 12:88 respectively) to afford purified **2** (22.1 mg), **3** (17.9 mg) and **6** (10.2 mg) respecively. Likewise, the Fr. 13 was subjected to repeated FC and eluted with MeOH: $CHCl_3$ (17:83) which yielded the purified **1** (11.7 mg).

Pulicaroside (= 6-hydroxykaempferol 3-methyl ether 6-*O*-[*O*-β-D-glucuronopyr-anosyl (1→6)] β-D-glucopyranoside; **1**): Amorphous powder (11.7 mg): $C_{28}H_{32}O_7$; $[\alpha]^{23}_D + 22.3$ (c = 0.029, MeOH); UV λ_{max} nm (log ε) (MeOH): 337.1 (1.94), 286.3 (4.26); UV λ_{max} nm (log ε) ($AlCl_3$/HCl): 347.1 (2.10), 299.2 (4.29); IR ν_{max} (KBr): 3418-3295 (OH), 2923 (C-H), 1601 (C=O), 1506-1451 (C=C, Ar), 1285 (C-O-C), 1137-1031 (C-O) cm^{-1}; ^1H and ^{13}C NMR: Table 1; HRFAB-MS (+): *m/z* 641.5447 $[M+H]^+$, cald. 641.5432; FAB-MS (Pos. ion mode) *m/z* 641 $[M+H]^+$; FAB-MS (Neg. ion mode) *m/z* 639 $[M-H]^-$; EIMS: *m/z* (rel. int.): 316 $[M – (2 \text{ x glucose})]^+$ (100), 273 $[M – (2 \text{ x glucose}) - COMe]^+$ (44), 168 $[C_6H(OH)_3OCO]^+$ (41), 148 $[C_6H_4(OH)CCOMe]^+$ (32).

6-Hydroxykaempferol 3-methyl ether 6-*O*-β-D-glucopyranoside (**2**): ^{1}H-NMR (500 MHz, MeOD): 8.10 (2H, d, *J* = 8.6, H-2′, H-6′), 6.87 (2H, d, *J* = 8.6, H-3′, H-5′), 6.41 (1H, s, H-8), 5.14 (1H, d, *J* = 7.3, H-1″), 3.80 (3H, s, 3-OMe); ^{13}C-NMR (125 MHz, MeOD): 178.8 (C-4), 161.6 (C-4′), 158.6 (C-7), 158.2 (C-2), 154.9 (C-9), 153.1 (C-5), 135.0 (C-3), 134.7 (C-6), 132.1 (C-2′, 6′), 123.0 (C-1′), 116.1 (C-3′, 5′), 104.9 (C-1″), 103.8 (C-10), 96.8 (C-8), 78.3 (C-3″), 78.1 (C-5″), 75.7 (C-2″), 71.2 (C-4″), 62.6 (C-6″), 60.6 (3-OMe).

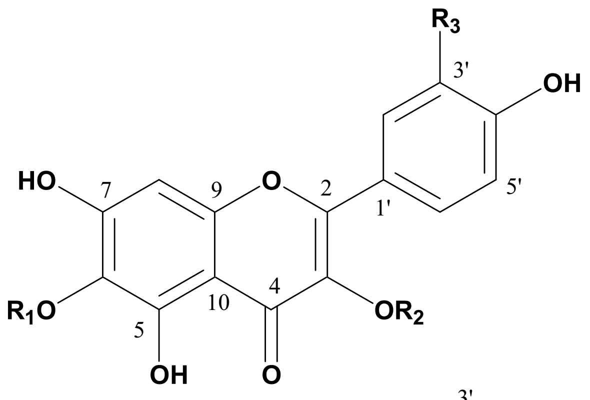
6-Methoxykaempferol 3-*O*-β-D-glucopyranoside (**3**): ^{1}H-NMR (500 MHz, MeOD): 8.04 (2H, d, *J* = 8.2, H-2′, H-6′), 6.87 (2H, d, *J* = 8.2, H-3′, H-5′), 6.51 (1H, s, H-8), 5.23 (1H, d, *J* = 6.9, H-1″), 3.87 (3H, s, 6-OMe); ^{13}C-NMR (125 MHz, MeOD): 179.8 (C-4), 161.6 (C-4′), 159.3 (C-7), 158.7 (C-2), 153.7 (C-9), 153.5 (C-5), 135.2 (C-3), 132.7 (C-6), 132.3 (C-2′, 6′), 122.8 (C-1′), 116.1 (C-3′, 5′), 106.2 (C-10), 104.3 (C-1″), 95.0 (C-8), 78.4 (C-3″), 78.0 (C-5″), 75.7 (C-2″), 71.4 (C-4″), 62.7 (C-6″), 60.9 (6-OMe).

6-Methoxykaempferol (**4**): ^{1}H-NMR (500 MHz, MeOD): 8.09 (2H, d, *J* = 8.9, H-2′, H-6′), 6.90 (2H, d, *J* = 8.2, H-3′, H-5′), 6.50 (1H, s, H-8), 3.87 (3H, s, 6-OMe); ^{13}C-NMR (125 MHz, MeOD): 175.9 (C-4), 160.5 (C-4′), 158.9 (C-2), 158.7 (C-7), 153.5 (C-9), 153.3 (C-5), 136.5 (C-3), 132.7 (C-6), 131.9 (C-2′, C-6′), 122.2 (C-1′), 116.0 (C-3′, C-5′), 105.2 (C-10), 95.0 (C-8), 60.9 (6-OMe).

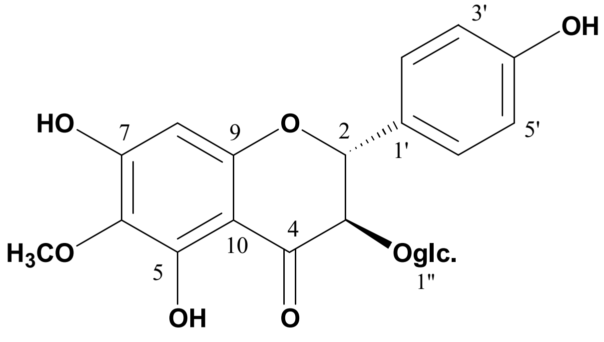
Axillarin (**= quercetagetin 3,6-dimethyl ether**; **5**): ^{1}H-NMR (500 MHz, MeOD): 7.62 (1H, d, *J* = 2.1, H-2′), 7.53 (1H, dd, *J* = 8.5, 2.1, H-6′), 6.90 (1H, d, *J* = 8.5, H-5′), 6.50 (1H, s, H-8), 3.87 (3H, s, 6-OMe), 3. 78 (3H, s, 3-OMe); ^{13}C-NMR (125 MHz, MeOD): 180.3 (C-4), 158.8 (C-7), 158.1 (C-2), 153.8 (C-9), 153.7 (C-5), 150.0 (C-4′), 146.5 (C-3′), 139.2 (C-3), 132.6 (C-6), 123.0 (C-1′), 122.3 (C-6′), 116.5 (C-2′), 116.4 (C-5′), 106.3 (C-10), 95.0 (C-8), 60.9 (6-OMe), 60.5 (3-OMe).

Undulatoside {= (2R:3R)-dihydro-5,7,4′-trihydroxy-6-methoxyflavonol-3-*O*-*β*-D- glucopyranoside; **6**}: Amorphous powder (10.2 mg): $C_{22}H_{24}O_{12}$; $[\alpha]^{23}_D$ + 24.8 (*c* = 0.01, MeOH); UV λ_{max} nm (log ε) (MeOH): 324.6 (2.6), 288.3 (3.9); UV λ_{max} nm (log ε) ($AlCl_3$/HCl): 379.1 (2.7), 308.7 (4.1); IR ν_{max} (KBr): 3450-3285 (OH), 2936 (C-H), 1626 (C=O), 1578-1504 (C=C, Ar), 1280 (C-O-C), 1156-1064 (C-O) cm^{-1}; ^{1}H and ^{13}C NMR: Table 1; HRFAB-MS (+): *m/z* 481.4217 [M+H]$^+$, cald. 481.4195; FAB-MS (Pos. ion mode) *m/z* 481 $[M+H]^+$; FAB-MS (Neg. ion mode) *m/z* 479 $[M-H]^-$; EIMS: *m/z* (rel. int.): 318 $[M - \text{glucose}]^+$ (100), 182 $[C_6H(OH)_2(OMe)OCO]^+$ (86), 136 $[C_6H_4(OH)CHCHOH]^+$ (59).

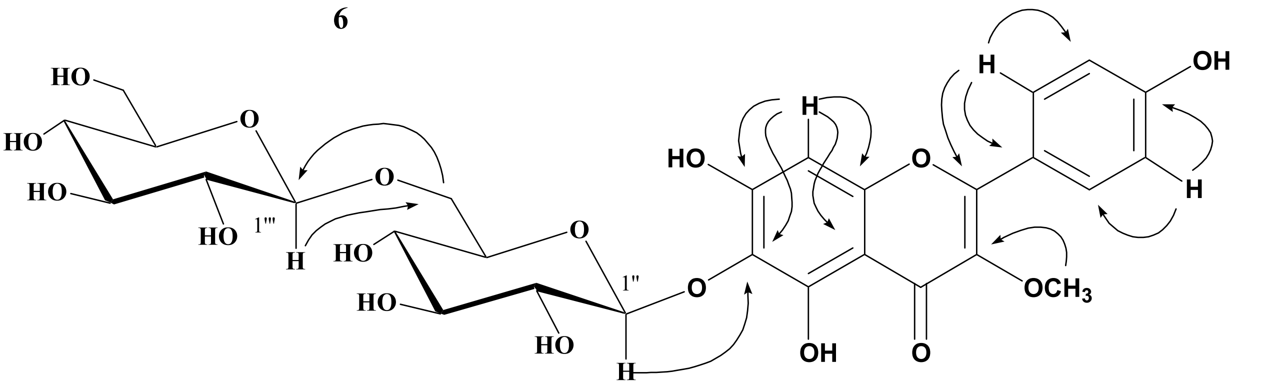
10.4.Superoxide Anion Scavenging Assay: The reaction mixture contained 280 μM β–nicotinamide adenine dinucleotide reduced form (NADH), 80 μM nitroble tetrazolium (NBT) , 8 μM phenazine methosulphate (PMS) and various concentrations of test samples in 200 μL of 0.1 M phosphate buffer (pH 7.5). The NBT, NADH and PMS were prepared in the same buffer. Test samples were dissolved in DMSO. The reaction was performed in 96-well microtitre plates (Molecular Devices, Spectramax 340) at room temperature and absorbance was measured at 560 nm [19].



Compound	R1	R2	R3
1	glc-(1''' → 6)-glc. 1''	Me	H
2	glc. 1''	Me	H
3	Me	glc. 1''	H
4	Me	H	H
5	Me	Me	OH



6



1

Fig. 1 Structures of compounds **1**-**6** and HMBC correlations of **1**

Table 1. NMR Data (MeOD) of Compounds **1** and **6**, δ in ppm, *J* in Hz

No.	**1**[a] δ (H)	**1**[a] δ(C)[b]	**6**[a] δ (H)	**6**[a] δ(C)[b]
2	-	158.3	5.40 (d, *J* = 11.6)	82.1
3	-	135.2	4.72 (d, *J* = 11.6)	77.6
4	-	178.8	-	196.4
5	-	153.4	-	157.5
6	-	134.9	-	132.2
7	-	158.8	-	159.4
8	6.42 s	154.8	6.48 s	95.5
9	-	131.3	-	156.2
10	-	104.1	-	102.1
1′	-	123.4	-	128.3
2′, 6′	8.01 (d, *J* = 8.4)	132.0	7.69 (d, *J* = 8.4)	131.4
3′, 5′	6.85 (d, *J* = 8.4)	116.2	6.84 (d, *J* = 8.4)	116.1
4′	-	161.5	-	160.9
3-OMe	3.82 s	60.6	-	-
6-OMe	-	-	3.86 s	60.9
1″	5.15 (d, *J* = 7.4)	104.2	4.99 (d, *J* = 7.8)	104.8
2″	3.45 (br t, *J* = 7.8)	75.6	3.46 (br t, *J* = 7.7)	75.5
3″	3.49 m	78.3	3.51 (br t, *J* = 7.9)	78.2
4″	3.41 m	72.0	3.42 (br t, *J* = 7.8)	71.8
5″	3.86 m	77.1	3.84 (ddd, *J* =1.9, 8.2, 11.3)	77.9
6″	4.40 (dd, *J* = 7.7, 11.6) 4.49 (dd, *J* = 1.9,	66.8	4.35 (dd, *J* = 7.4, 11.8) 4.43 (dd, *J* = 2.0, 11.8)	61.8

	11.6)			
1‴	4.92 (d, J = 7.6)	104.0	-	-
2‴	3.47 (br t, J = 7.7)	75.7	-	-
3‴	3.52 m	78.1	-	-
4‴	3.43 m	72.4	-	-
5‴	3.86 m	77.9	-	-
6‴	4.32 (dd, J = 7.8, 11.9)	62.0	-	-
	4.41 (dd, J = 1.8, 11.9)			

[a] All spectra were recorded at 500 MHz (^{1}H) and 125 MHz (^{13}C); assignment were aided by 2D-NMR
COSY, HMQC and HMBC experiments, [b] ^{13}C NMR multiplicities were determined by DEPT 135°.

Table 2. Antioxidant Activities of the Flavonoids **1-6** as Compared with the Standard Inhibitors

Substance	**Super oxide Anion Scavenging Activity (%) AT 1000 µM**
1	42.9
2	39.5
3	92.4
4	75.3
5	80.5
6	24.8
Propyl gallate [a])	92.00
3-*t*-Butyl-4-hydr-oxy anisole [a])	91.25

[a]) Standard antioxidants

10.5.References

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New ent–kaurane type Diterpene Glycoside Pulicaroside-B From *Pulicaria undulata*

Natural Product Communications, accepted

11.1. Introduction

Pulicaria undulata L. Belongs to the family Asteraceae (Compositae),one of the largest family of flowering plants, which comprises of about 1,100 genera and 20,000 species. Plants of this family are found in temperate and subtropical regions of the world [1]. The genus *Pulicaria* has eleven species, distributed in tropical and temperate regions of Pakistan [2]. The plants of this genus are used in traditional medicine as tonic, a substitute for tea, and an antispasmodic and anti-hypoglycemic drug and as ingredients of perfume [3]. Aerial parts of *Pulicaria undulata* are used for antibacterial agent [4]. Literature survey showed some reports on essential oils [5–6], terpenoids [7–8] and flavonoids [9-10] of *Pulicaria undulata*.

11.2. Results and Discussion

The *n*-butanol soluble fraction of the whole plant of *Pulicaria undulata* L. (syn. *Pulicaria crispa* Forssk.) yielded a new diterpene glycoside, pulicaroside-B (**1**), along with three known compounds paniculosides-IV (**2**) , roseoside (**3**) and corchoionol C (**4**). Their structures were deduced by detailed analysis of their spectral data and comparison of their spectral data with those of the closely related compounds [11-15]. Pulicaroside-B **1** was isolated as colourless solid. Its molecular formula ($C_{45}H_{68}O_{16}$) was established by the positive ion HRFABMS, showing a quasi-molecular ion $[M+H]^+$ peak at *m/z* 865.4480 which indicated 12 degrees of unsaturation. The absorption bands in the IR spectrum appeared at 3408 (OH), 1723 cm^{-1}, and 1653cm^{-1}. The intense IR absorption band at 1723 cm^{-1} revealed the presence of ester functionality. The intense absorption at 1653cm^{-1} indicated the presence of conjugated carbonyl functionality in the molecule. The complete hydrolysis of **1** yielded glucose as the only sugar (see experimental). This was also supported by fragment ions in the positive ion FABMS at *m/z* 703 $[M – hexose]^+$ and *m/z* 541 [M –2 hexose]$^{+}$. ^{1}H-NMR and ^{13}C-NMR data (Table 1) showed that the aglycone basic skeleton was similar to that of reported Ent-kaurene [16] and this assignment was thoroughly supported by its EIMS spectrum which exhibited an ion peak at *m/z* 334 [M –2hexose – corchoionol moiety]$^{+}$. In ^{1}H-NMR spectrum signals (H-1’’) and (H-1’’’) belonged to two sugar moieties anomeric proton doublets at δ 4.26 (*J*= 7.78 Hz) and δ 5.40 (*J*= 8.13 Hz). The evidence for the β-configuration of these sugars was drawn from the large coupling constants value of anomeric proton.

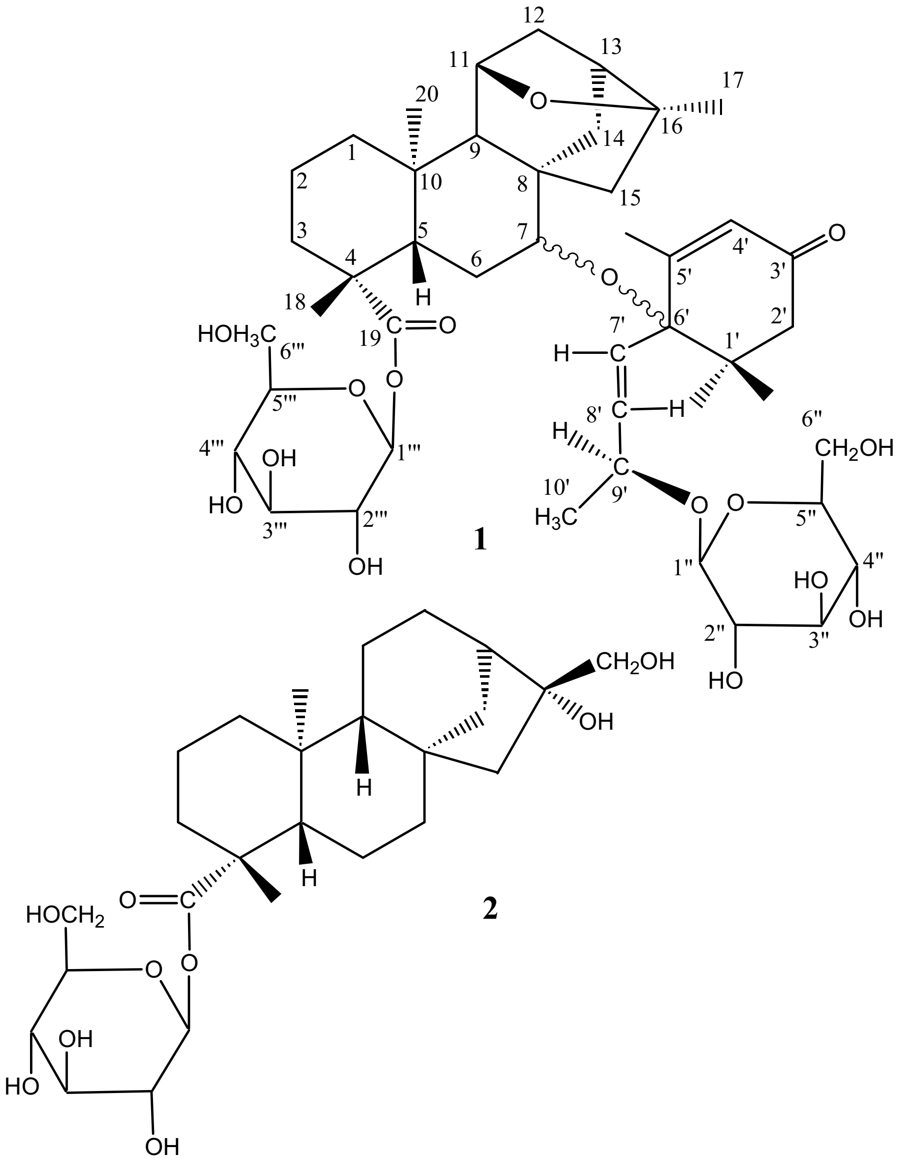
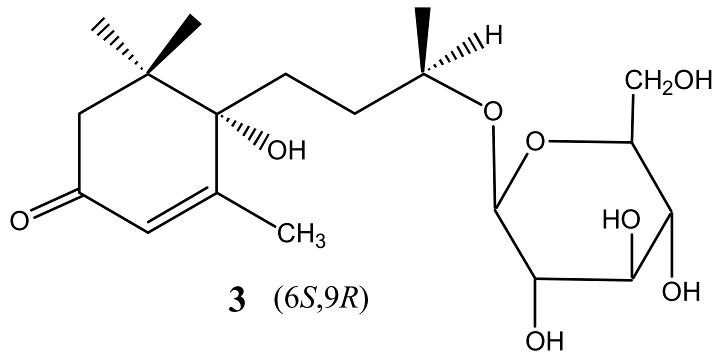
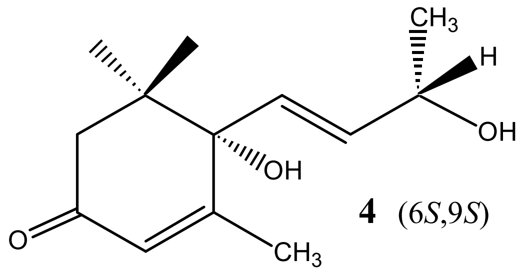


Figure-1.



3 (6*S*,9*R*)



4 (6*S*,9*S*)

The HMBC correlation between anomeric proton H-1''' (δ 5.40) and carbonyl carbon (δ 178.3) showed that one glucose was connected to aglycone through ester functionality. The HMBC correlation between anomeric proton H-1'' (δ 4.26) and carbon (δ 75.3) showed that the 2nd glucose was connected to aglycone through ether linkage. The signals for hexose were consistent with *β*–D–glucose [16]. Three singlets were present at δ 0.99, 1.20, and 1.34 in the ^{1}H–NMR spectrum for three *tert*–methyls. Their associated carbon signals in the HMQC spectrum were at δ 18.5, 29.0, and 23.4. Among other four methyl signals, three were singlets, and one narrow doublet, present at δ 1.01, 1.03, 1.28 and 1.93(d) in the ^{1}H–NMR spectrum. Their associated carbon signals in the HMQC spectrum at δ 24.7, 23.5, 22.2, and 19.6, respectively, revealed the presence of four methyls, which were related to the skeleton of corchoionol C glycoside (corchoionoside C) [14] moiety. The linkage between diterpene and the derivative of α-ionol glycoside moiety was established by ^{13}C–NMR spectrum and HMBC correlations. The downfield shift of carbon at δ 83.2, instead of 80.0, in **4** [14] indicated that C-6' of corchoionol moiety is not free. The HMBC correlation between H-7 (δ 3.45), C-7 (δ74.9) of diterpene and carbon C-6' (δ83.2) of α-ionol moiety showed that the diterpene was connected to α-ionol glycoside moiety through ether linkage between C-7 of diterpene and C-6' of α-ionol glycoside moiety. After assigning the proton and carbon chemical shifts (table 1) with the help of HMQC, HMBC, and COSY spectra (fig. 1), the structure of pulicarioside-B (**1**) was elucidated as ent-11α,16α-epoxy-16(*R*)-7-O [3-oxo-α-ionol 9-O{β-D-glucopyranosyl}]19-O[β-D-glucopyranosyl] kauranoate.

Compound **2**, **3** and **4** were isolated for the first time from this plant [11-14].

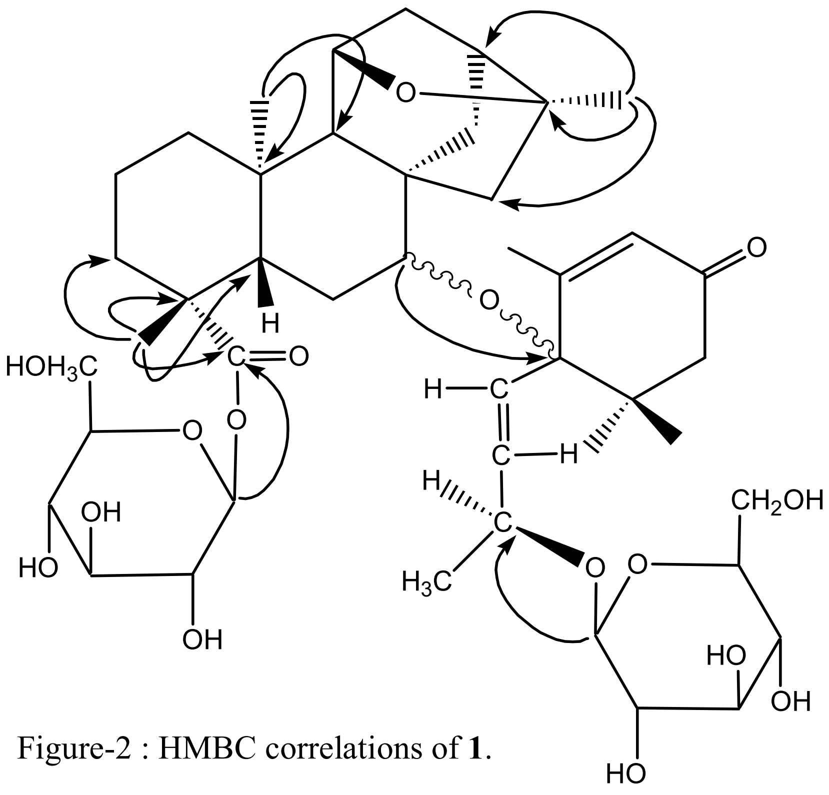


Figure-2 : HMBC correlations of **1**.

Table 1. NMR data (CD_3OD) of compound **1** δ in ppm, *J* in Hz

No.	δ (H)	δ(C)	HMBC	H^1-H^1 COSY
1	1.17,1.83	42.5		
2	1.37,1.63	20.1		
3	1.13,2.23	38.9		
4	-	44.5		
5	1.80	49.3		
6	1.94,2.16	30.2		
7	3.47	75.3	C4'	0.99, 1.80
8	-	50.5		
9	1.78	54.4		
10	-	38.1		
11	4.33bs	78.0		1.78
12	2.14	41.7		
13	2.25	46.7		1.91
14	1.91	43.7		
15	1.88	53.0		
16	-	87.0		
17	1.34s	23.4	C13, C15, C16	2.25
18	1.20s	29.0	C3, C4, C5, C19	1.80
19	-	178.0		
20	0.99s	18.5	C5, C9, C10	1.78
1′	-	42.1		
2′	2.16,2.6 (dd, *J*=16.90,16.93)	50.7		
3′	-	201.3		
4′	5.86s	127.0		
5′	-	167.1		
6′	-	83.1		
7′	5.96 (d, *J*=15.52)	133.8	C4', C8'	
8′	5.70,5.73 (dd, *J*=7.25,7.25)	133.7	C7', C9'	5.96
9′	4.56 (q, *J*=6.57)	75		
10′	1.28 (d, *J*=6.36)	22.2	C8', C9'	
11′	1.03s	23.5		
12′	1.01s	24.7		
13′	1.93 (d, *J*=1.25)	19.6		5.86
	9'-O-β-D-glucoside			
1	4.26 (d, *J*=7.78)	101.2	C9'	
2	-	74.6		
3	-	78.7		
4	-	71.1		
5	-	78.4		
6	3.65 (dd, *J*=6,11.9) 3.85 (dd, *J*=2.22,11.94)	62.4		

	19-O-β-D-glucoside ester		
1	5.4d, *J*=8.13	95.7	C19
2	-	74.1	
3	-	78.5	
4	-	71.6	
5	-	78.2	
6	3.56 (dd, *J*=5.6,11.9) 3.78 (dd, *J*=2.2,11.8)	62.3	

11.3. Experimental Section.

General: The IR spectra were recorded on Jasco-320-A spectrophotometer. The optical rotation was measured on a Jasco-DIP-360 digital polarimeter. EI-MS and FAB-MS spectra were recorded on a JMS-HX-110 spectrometer. ^{1}H-NMR, ^{13}C-NMR, COSY, NOESY, HMQC and HMBC spectra were run on Bruker spectrometers operating at 500, 400, and 300 MHz. For column chromatography, silica gel (70-230 mesh) and for flash chromatography, 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 spraying with ceric sulphate and aniline phthalate reagents. For recycling HPLC (LC 908 W) a semi-preparative (M-80) reverse phase column was used. Purity was checked on TLC with different solvent systems using methanol, acetic acid, water, and $CHCl_3$, giving single spot.

11.3.1. Plant material: The plant *Pulicaria undulata* L. (Asteraceae) was collected in August 2002 from Loralai, Balochistan, and identified by one of us (R.B.T.). A voucher specimen (no. 1437a) has been deposited at the herbarium of the Botany Department of the same University.

11.3.2.Extraction and isolation: The shade–dried ground plant material (whole plant, 30 kg) was exhaustively extracted with methanol at room temperature. The extract was evaporated to yield the residue (753 g). The whole residue was dissolved in water and partitioned with *n*-hexane, chloroform, ethyl acetate, and *n*-butanol. The *n*-butanol-soluble fraction (112 g) was subjected to column chromatography (silica gel, *n*-Hexane-$CHCl_3$ mixtures of increasing polarity, $CHCl_3$, $CHCl_3$-MeOH mixtures of increasing polarity) and fifteen fractions (1–15) were collected. Fraction 2 was subjected to repeated flash chromatography (230-400 mesh) and eluted with MeOH-$CHCl_3$ (2:98) yielding pure **4** (18.3 mg). Fraction 5 was subjected to repeated fraction chromatography (230-400 mesh) and eluted with MeOH-$CHCl_3$ (5:95) furnishing pure **3** (22.9 mg). Fraction 7 was subjected to repeated fraction chromatography (230-400 mesh) and eluted with MeOH-$CHCl_3$ (10:90) which yielded pure **2** (29.5 mg). Fraction 9 was loaded on flash silica gel and eluted with MeOH-$CHCl_3$ (15:85) to get two sub-fractions ($Fr_{sb.}$ 9.1 and $Fr_{sb.}$9.2). Fraction 9.2 was then submitted to Sephadex LH-20 and eluted with pure water, and finally purified on recycling HPLC (LC 908 W) using a reverse phase semi preparative (M-80) column. Elution was carried out at a flow rate of 4 ml/ min under isocratic conditions with MeOH-H_2O (1: 1). The peaks were detected by UV and RI detectors. The eluate of the peak at a retention time of 46 min furnished pure **1** (12.9mg).

11.3.3 Acid hydrolysis of 1 and 3: A solution of **1** and **3** separately, (3mg each) 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 obtained from the organic phase was found to be a mixture of products. . The aqueous phase was neutralized with Ag_2CO_3, filtered and evaporated under reduced pressure. The obtained residue showed the presence of glucose in **1** and **3**, when compared with the authentic sample on TLC (EtOAc-MeOH-AcOH-H_2O = 11: 2: 2: 2) . The spots were visualized by spraying with aniline phthalate reagent.

Some coupling constants are not given in table because peaks are mixed in ^{1}H-NMR spectra. The absolute configuration at C-7 and C-6’ is not defined because of the overlap of peaks in ^{1}H-NMR and NOESY spectra.

Pulicarioside-B (1) *ent*-11α,16α-epoxy-16(*R*)-7-O[6’*S*,9’*S*-3’-oxo-α-ionol 9’-O{β-D-glucopyranosyl}] 19-O[β-D-glucopyranosyl] kauranoate.

Transparent solid

$[\alpha]_D$: +26.3

IR (KBr) ν_{max}: 3408, 2928, 1723, 1653, 1280, 1071

^{1}H NMR (CD_3OD): Table 1.

^{13}C NMR (CD_3OD): Table 1.

HMBC (CD_3OD): fig. 2

HRFABMS (+) *m/z*: 865.4480 $[M+H]^+$ (calc. for $C_{45}H_{69}O_{16}$, 865.4586).

FABMS (+) *m/z*: 865 $[M+H]^+$, 703 $[M - \text{hexose}]^+$, 541 $[M -2\ \text{hexose}]^+$, 335 [M –2 hexose – (corchoionol)]$^+$

FABMS (-) *m/z*: 863 $[M-H]^-$, 701 $[M - \text{hexose}]^-$, 539 $[M -2\ \text{hexose}]^-$, 333 [M –2 hexose – (corchoionol)]$^-$;

EIMS *m/z* (rel. int.): 334 [M –2hexose – corchoionol]$^-$

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Chapter 12

A New Flavonoid from *Pulicaria undulata*

Manuscript in preparation

12.1. Result and discussion

The ethyl acetate soluble fraction of the whole plant of *Pulicaria undulata* L. (syn. *Pulicaria crispa* Forssk.) led to the isolation of a new flavonoid Undulol (**1**) and its structure was deduced by detailed analysis of spectral data and comparison of its spectral data with those of the closely related compounds [8-10].

Undulol (1) was isolated as an amorphous solid. Its molecular formula $C_{23}H_{18}O_8$ was established by the positive ion HRFAB MS showing molecular ion $[M+H]^+$ peak at *m/z* 423.0002 (cald. 423.10017), which indicated 15 degrees of unsaturation. Its IR spectrum exhibited absorption bands for hydroxyl groups (3418-3295 cm^{-1}), methyl (2923 cm^{-1}), conjugated carbonyl group (1601 cm^{-1}), and aromatic unsaturation (1506-1451 cm^{-1}). Its EI-MS spectrum exhibited an ion at *m/z* 330 $[M –(p\text{-hydoxy phenyl})]^+$. Its ^{1}H-NMR spectrum revealed two sets of *ortho*-coupled doublets for ring B and for 7-O-(p-hydroxy) phenyl ring. *Ortho*-coupled doublets at δ 7.84 (2H, *J* = 8.68) and δ 6.89 (2H, *J* = 8.86) for ortho, meta and para substituted ring B, two singlet at δ 3.87 (3H) and 3.85 (3H) for two methoxy group at C2’ and C3’ positions of ring B. *Ortho*-coupled doublets at δ 8.08 (1H, *J* = 8.78) and δ 6.93 (1H, *J* = 8.77) for para hydroxyl substituted phenyl ring. This assignment was further confirmed by its ^{13}C-NMR and HMBC spectrum. Important HMBC correlations are shown in fig. 1. Based upon the above cumulative evidences, **1** was identified as 7-O-p-hydroxy phenyl 2’, 3’-dimethoxyapigenin

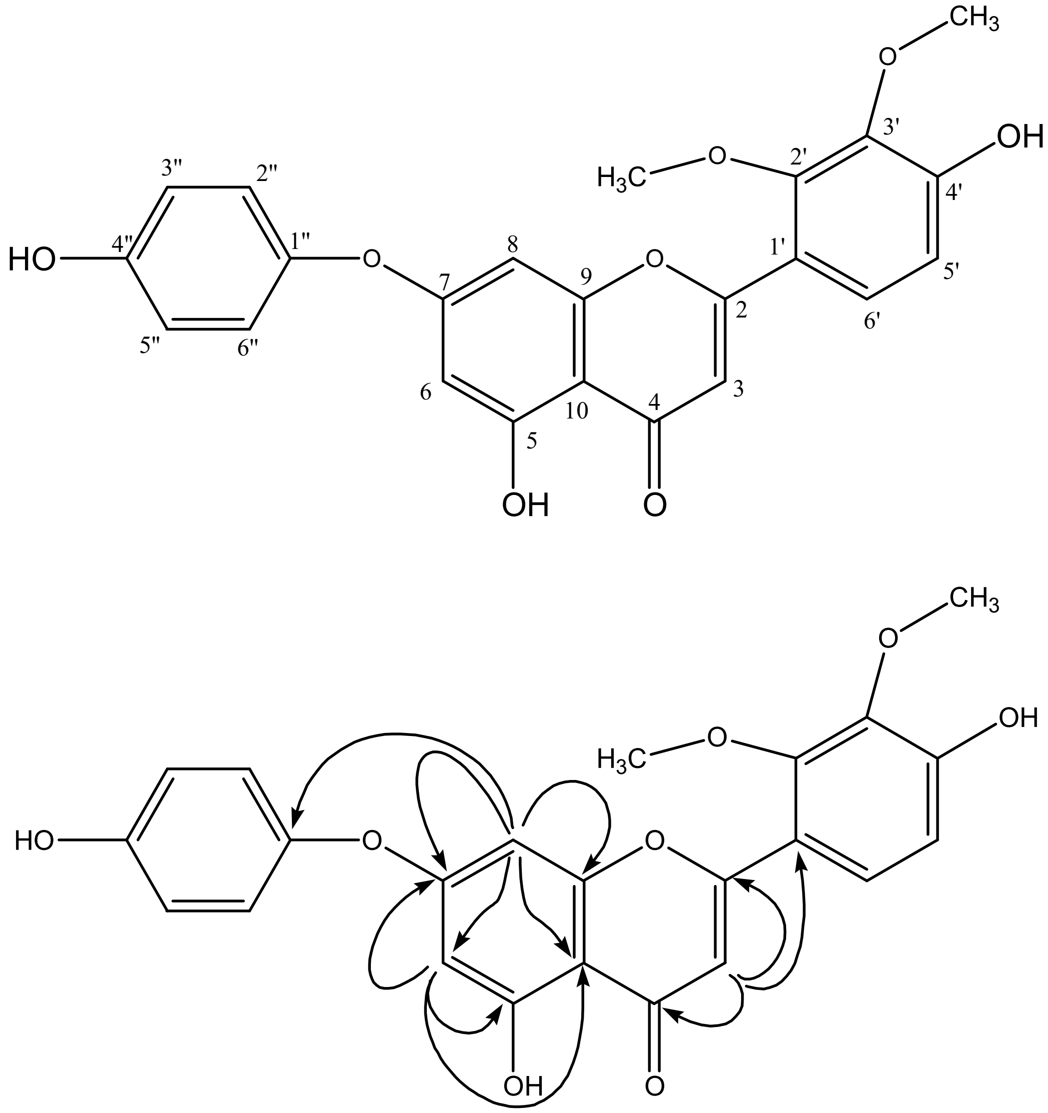

Figure 1

Structure of Compound **1** and HMBC correlations

Table 1. NMR data for compound **1** in D_3OD (δ in ppm, *J* in Hz)

No.	δ_H	δ_C[b]
2	-	166.4
3	6.59 s	103.4
4	-	184.3
5	-	154.7
6	6.55 s	95.3
7	-	177.3
8	6.49 s	94.8
9	-	158.6
10	-	112.6
1′	-	105.0
2′,	-	148.4
3′	-	136.9
4′	-	162.8
5′	6.90 (d, *J* = 8.86)	116.3
6′	7.84 (d, *J* = 8.68)	129.4
2′-OMe	3.87s	60.97
3′-OMe	3.85s	60.94
1″	-	153.7
2″,6″	8.08 (d, *J* = 8.78)	130.7
3″,5″	6.93 (d, *J* = 8.77)	117.0
4″	-	160.6

[a] All spectra were recorded at 500 MHz (^1H) and 125 MHz (^{13}C); assignment were aided by 2D-NMR
COSY, HMQC and HMBC experiments, [b] ^{13}C NMR multiplicities were determined by DEPT 135°.

12.2. General experimental procedures

The IR spectra were recorded on Hitachi-UV-3200 and JASCO-320-A spectrophotometer, respectively. ^{1}H-NMR, ^{13}C-NMR, COSY, HMQC and HMBC spectra were run on Bruker spectrometers operating at 500, 400 and 300 MHz. The chemical shifts were recorded as δ in ppm and coupling constants in Hz. EI-MS and FAB-MS spectra were recorded on a JMS-HX-110 spectrometer. For column chromatography, silica gel (70-230 mesh) and for flash chromatography, 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 reagent. Purity was checked on TLC with different solvent systems using methanol, acetic acid and $CHCl_3$ giving single spot.

12.3. Extraction and purification

The shade-dried ground plant material (whole plant) (30 kg) was exhaustively extracted with methanol at room temperature. The extract was evaporated to yield the residue (753 g). The whole residue was dissolved in water and partitioned with *n*-hexane, chloroform, ethyl acetate and *n*-butanol. The ethyl acetate soluble extract (182.4 g) was subjected to column chromatography over silica gel using *n*-hexane with gradient of $CHCl_3$ up to 100 % and then the polarity was increased with methanol in a similar fashion. Fifteen fractions were collected. The fraction 5 was submitted to repeated flash chromatography (230-400 mesh) and eluted with MeOH: $CHCl_3$ (4:96) to get two sub-fractions 5.1 and 5.2. The sub-fractions 5.1 was then flash choromatographed eluting with MeOH: $CHCl_3$ (3.8:96.2) to get purified **1** (11.7mg).

12.3.1. Undulol (1). Amorphous powder; $C_{23}H_{18}O_8$; IR(KBr) ν_{max} 3418-3295 (OH), 2923 (C-H), 1601 (C=O), 1506-1451 (C=C, Ar) cm^{-1}; ^{1}H and ^{13}C NMR, table 1; HRFAB-MS (+): *m/z* 423.00020 $[M+H]^+$, cald. 423.10017; FAB-MS (Pos. ion mode) *m/z* 423 $[M+H]^+$; FAB-MS (Neg. ion mode) *m/z* 421 $[M-H]^-$; EIMS: *m/z* (rel. int.): 330 $[M – (p\text{-hydroxy-phenyl})]^+$ (100).

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Zusammanfassung

Teil A: Spirocyclische Cyclopropane wurden durch Umsetzung von Ketosulfon- und Cyanoaceton-Dianionen hergestellt und durch Behandlung mit Tetraalkylammoniumhalogeniden in funktionaliserte Arene überführt. Durch Cyclisierung des Dianions von Aceton und eines 3-Oxophosphonates konnten regioisomere Spirocyclopropane hergestellt und durch anschließende Umsetzung mit Tetraalkylammoniumhalogeniden in funktionaliserte Arene überführt werden. Es wurden Beiträge zur Synthese von Diarylethern, Biarylen und 1-Azaxanthonen geliefert. Teil B: Weiterhin wurden Ergebnisse auf dem Gebiet der regioselektiven Synthese von Thiophenen durch Suzuki-Reaktionen von Tetrabromthiophen geliefert. Teil C: Schließlich wurden neue Naturstoffe isoliert und charakterisiert.

Part A: Spirocyclic cyclopropanes were made by reaction of ketosulfone and ketonitrile dianions. This was futher transformed to fuctionalized Arenes in the presence of tetraalkyl ammonium halides.By cyclization of the dianions from Acetone and 3-Oxophosphates it was possible to obtain regioisomeric spirocyclopropanes which were futher reacted with tetraalkyl ammoniun halides to obtain fuctionalized Arenes. Contributions were also made in the area of the Diarylether Biaryles and 1-Azaxanthones synthesis. Part B: Futher more contributions wre made in the area of regioselective synthesis of the Thiophenes by Suzuki reactions of tetrabromothiophene. Part C: Natural products were isolated and characterized.

Curriculum Vitae

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12. 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,** accepted “New ent–kaurane type diterpene glycoside pulicaorside-B”
13. Nasir Rasool, Muhammad A. Rashid, Muhammad Adeel, and Peter Langer* *Tetrahedron Lett.* **2008**, 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”

14. Muhammad A. Rashid, Nasir Rasool, Muhammad Adeel, Helmut Reinke, Christine Fischer, and Peter Langer* *Tetrahedron* **2008,** submitted “Synthesis of Functionalized Diarylsulfides based on Regioselective One-Pot Cyclizations of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes

15. Muhammad A. Rashid, Nasir Rasool, Bettina Appel, Muhammad Adeel, Vahuni 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-MichaelNitrile-Addition Heterocyclization”
16. Muhammad Adeel, Muhammad A. Rashid, Nasir Rasool, Rasheed Ahmad, Helmut Reinke, Christine Fischer, and Peter Langer* *Eur. J .Org. Chem.* **2008,** submitted “Regioselective Synthesis of Functionalized Biaryls based on Cyclizations of 4-Aryl-1,3-bis(trimethyl-silyloxy)-1,3-butadienes.”

17. Nasir Rasool, Muhammad A. Rashid, Inam Iqbal, Muhammad Imran and Peter Langer* **2008,** submitted “Regioselective Synthesis of Functionalized 2-Thio-phenoxybenzoates by Formal [3+3] Cyclizations of 1-Trimethylsilyloxy-3-thiophenoxy-1,3-butadienes with 3-Silyloxy-2-en-1-ones”

18. Muhammad.A. Rashid, V.U. Ahmad*, M.A. Abbasi, Nasir. Rasool, M.Zubair, M.A. Lodhi and M.I. Choudhary *Phytochemistry Lett.***2008,** submitted "α-Chymotrypsin Inhibiting Benzyl Derivatives from *Symplocos racemosa*"

Patents

V.U. Ahmad, N.Rasool, M.I.Choudhary, S.Nihar.Khan, Pub. No.: US 2007/ 0287674 A1 Pub. Date: Dec: 13, 2007 "New treatment of diabetes mellitus"

Abstracts in Conferences

1. Nasir Rasool, Muhammad Athar Abbasi, Asma Ejaz, M. Iqbal Chaudry and Viqar Uddin Ahmad "Antioxidant Flavonoids from Pulicaria undulata". 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-179), Abstracts, page

2. Zahid Hassan, Javid Hussain, Nasir Rasool, Aman and Viqar Uddin Ahmad "Tenacetamide C: one new Ceramide from tanacetum artimisioide". 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-071), Abstracts, page

3. Naseem Shahzad, Muhammad Athar Abbasi, Muhammad Abid Rashid, Nasir Rasool, Z Hina Siddiqui, M. Iqbal Chaudry and Viqar Uddin Ahmad "Antioxidant and α-Chymotrypsin Inhibiting Flavonoids from Clematis orientalis". 10th International Symposium on Natural Product Chemistry 2006, Poster presentation (PO-179), Abstracts, page

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.

.

Nasir rasool

Zusammenfassung entsprechend § 5 (5) der Promotionsordnung zu beiliegender Dissertation

Synthesis of Pharmacologically Relevant Arenes by [3+3] Cyclizations And Phytochemical Investigation of *pulicaria undulata*

vorgelegt von

Nasir Rasool

geboren am 02-09-1977

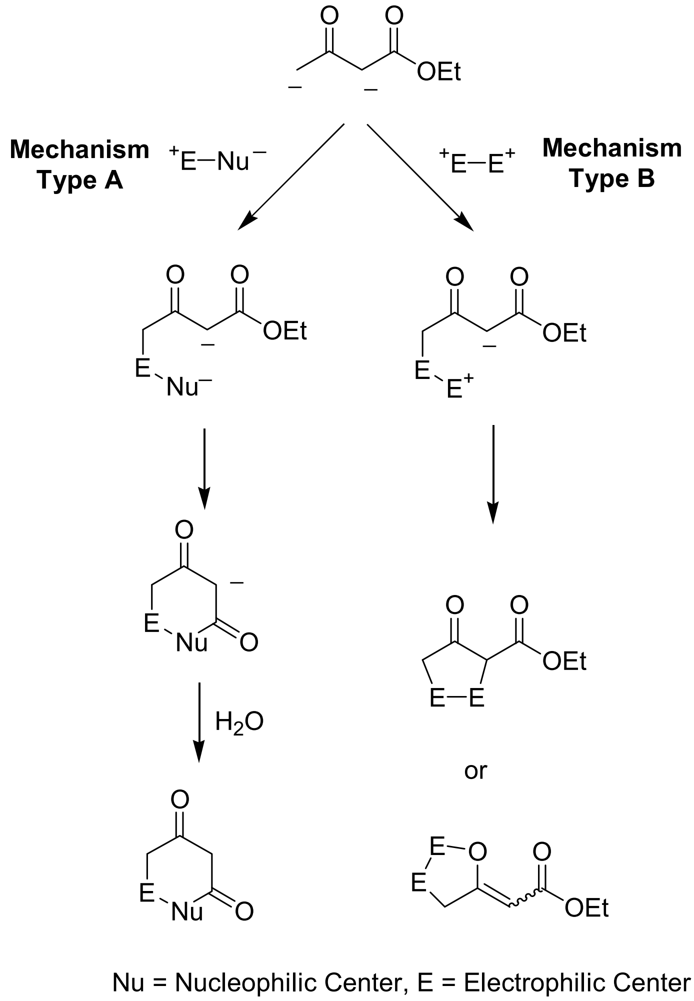
In Chichawatni, Sahiwal, Pakistan

Rostock, 29-01-2008

Ambident dianions are organic substrates containing two delocalized negative charges.[1] The generation of dianions requires strong bases such as lithium diisopropylamide (LDA) or *n*-butyllithium (*n*-BuLi). 1,3-Dicarbonyl compounds can be metallated twice by the action of two equivalents of LDA or by the use of NaH/*n*-BuLi.[2] The terminal carbon atom of the dianion can be regioselectively coupled with one equivalent of an electrophile to give a monoanion which is subsequently trapped by addition of a second electrophile. Monoanions may be alkylated twice by a double deprotonation-alkylation sequence. However, the regioselectivities of reactions of monoanions and dianions generally differ greatly. For example, 1,3-dicarbonyl monoanions are generally alkylated at the central carbon or at the oxygen atom whereas the formation of dianions allows for the functionalization of the terminal carbon atom. An exception is reactions of highly stabilized 1,3,5-tricarbonyl compounds, which contain two (rather than only one) highly C–H acidic groups. The product obtained by sequential alkylation of a stabilized carbanion can be identical to that prepared from the respective dianion.

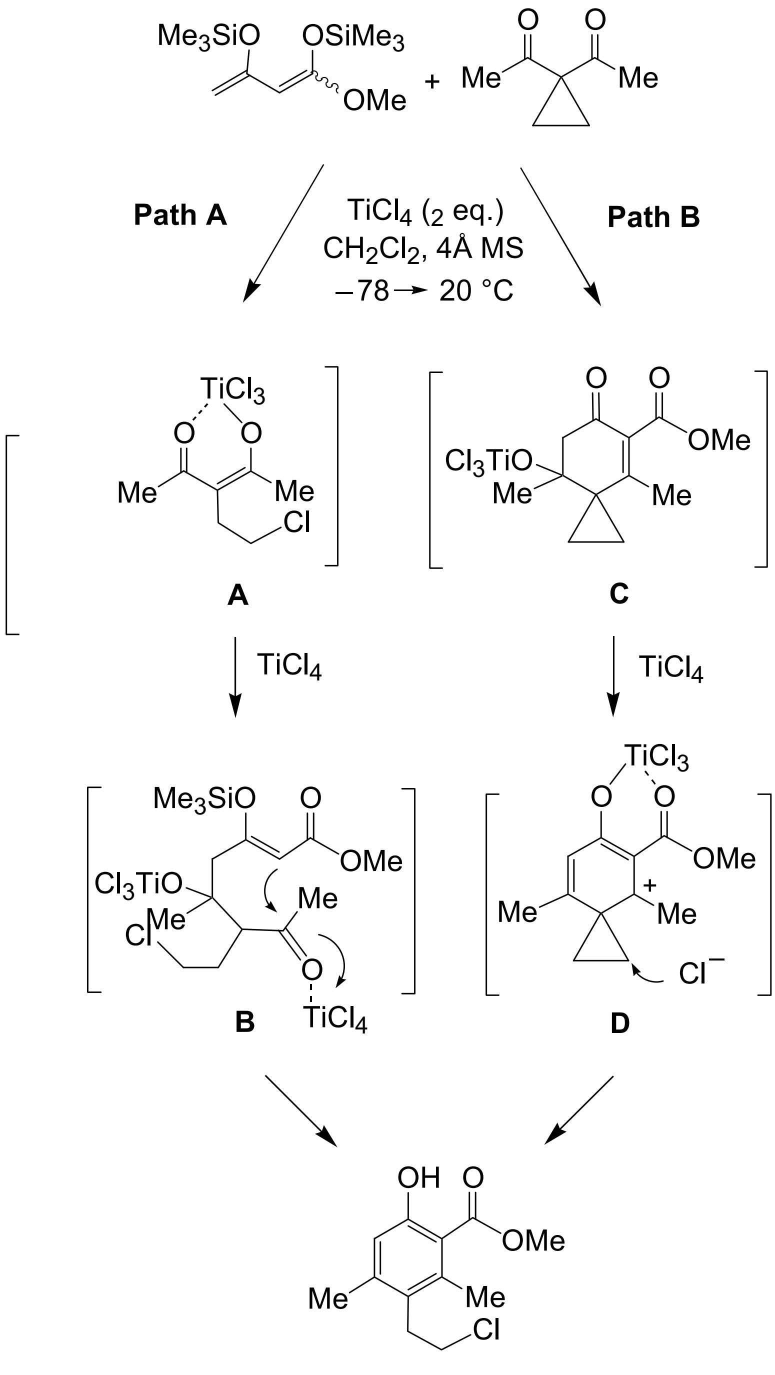
Most work in dianion chemistry has been concentrated so far on condensation reactions with monofunctional electrophiles and subsequent addition of water to give open-chained products.[2] Despite their simplicity and synthetic usefulness, cyclization reactions of dianions with dielectrophiles are relatively rare.[3-5] The use of 1,2-dielectrophiles is particularly problematic, since both dianions and 1,2-dielectrophiles represent highly reactive compounds (low reactivity matching). In addition, 1,2-dielectrophiles are often rather labile and reactions with nucleophiles can result in polymerisation, decomposition, formation of open-chained products, elimination or SET-processes. Two ways to overcome these intrinsic limitations are viable: a) a proper tuning of the reactivity of dianion and dielectrophile and b) the use of electroneutral dianion equivalents (masked dianions) in Lewis acid catalyzed reactions.

Two general mechanistic pathways can be discussed for cyclization reactions of dianions (Scheme 1): firstly, the dianion can react with a monofunctional electrophile with transposition of a negative charge from the dianion to the electrophile. This carbanion attacks an electrophilic center of the former dianion moiety (e. g. the ester group) to give a monoanion which is subsequently quenched with water (*mechanism type A*). Secondly, the dianion can react as a dinucleophile with a dielectrophile (*mechanism type B*).



Scheme 1

The Lewis acid mediated domino "[3+3]-cyclization-homo-Michael" reaction of 1,3-bis(silyl enol ethers) with 1,1-diacylcyclopropanes allows an efficient one-pot synthesis of functionalized salicylates containing a halogenated side-chain (see Scheme 2).[6] Two mechanisms can be discussed.

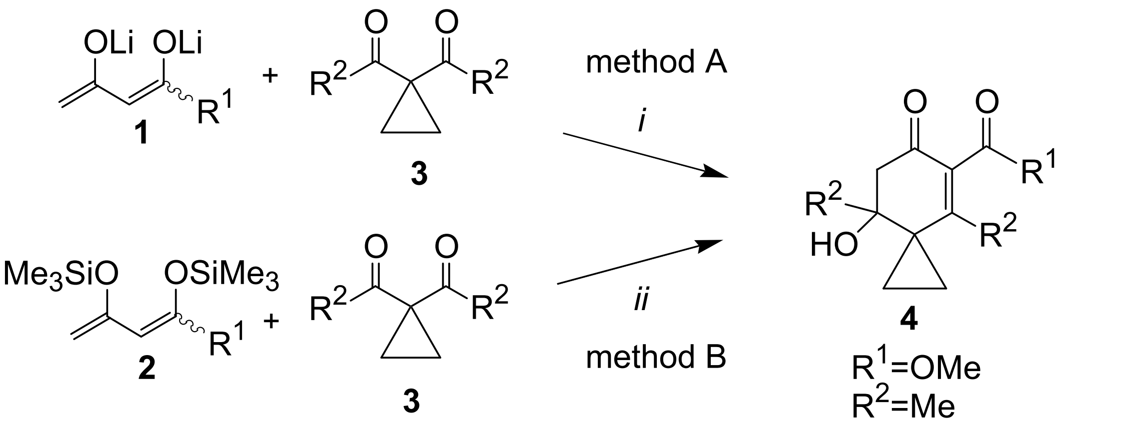


Scheme 2. Possible mechanisms of the cyclization of 1,3-bis(silyl enol ethers) with 1,1-diacetylcyclopropane

Path A: the $TiCl_4$-mediated ring-opening of 1,1-diacetylcyclopropane results in the formation of the titanium enolate **A** which subsequently undergoes a cyclization with the

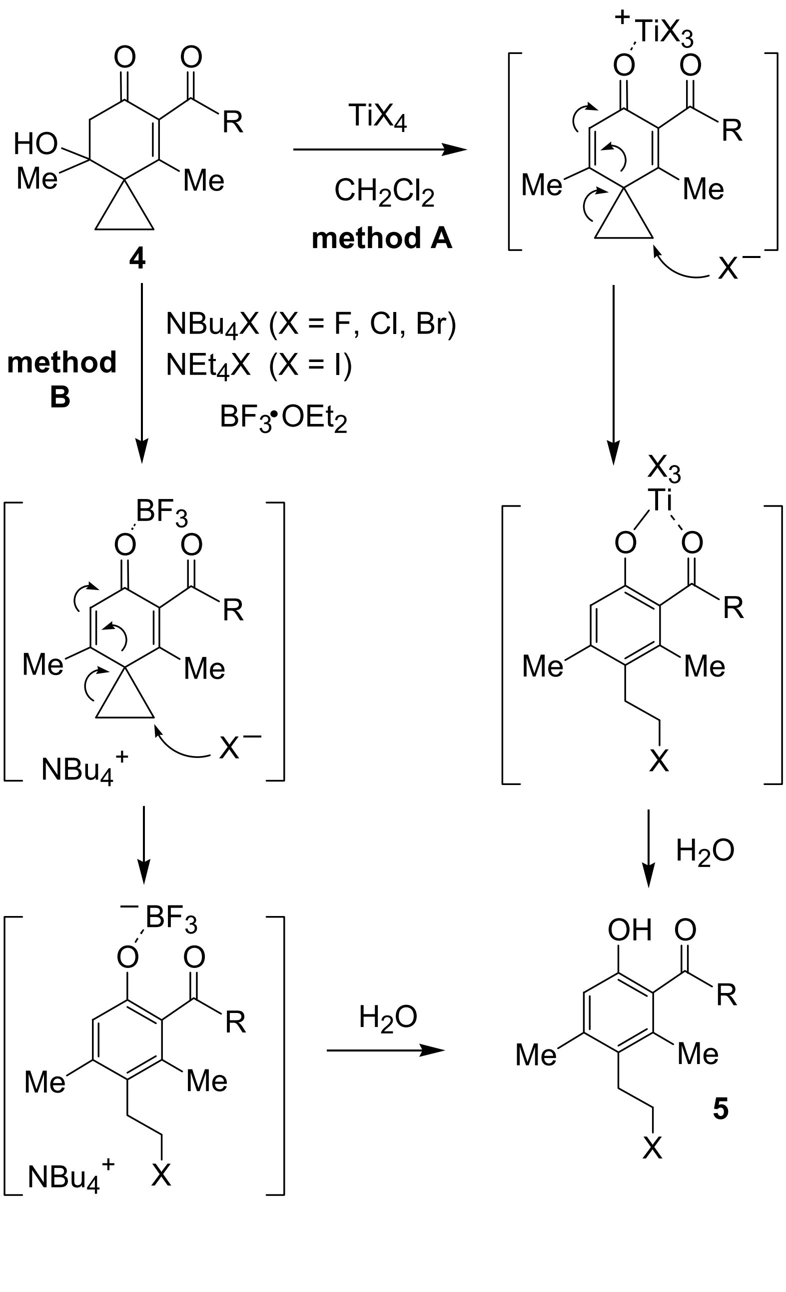
1,3-bissilyl enol ethers. Alternatively, the cyclization may precede by formation of the spirocyclic intermediate **C** and subsequent $TiCl_4$-mediated ring cleavage (homo-Michael reaction) *via* intermediate **D**. The isolation of the spirocyclopropane intermediate proved to be possible when the reaction was carried out in the presence of 0.3 equiv. of $TiCl_4$ (vide infra). Therefore, the cyclization of 1,3-bis(silyl enol ethers) with 1,1-diacylcyclopropanes presumably proceeds by mechanism type B.

The cyclization of 1,3-dicarbonyl dianions with 1,1-diacylcyclopropanes allowed the synthesis of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones in good yields (Scheme 3). The reaction of 1,3-bis(silyl enol ethers) with 1,1-diacylcyclopropanes, in the presence of 0.3 equiv. of $TiCl_4$, also afforded 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones.[7] The use of more than 0.5 equiv. of $TiCl_4$ resulted in cleavage of the cyclopropane moiety and aromatisation (Scheme 3). 1-Hydroxyspiro[5.2]cyclooct-4-en-3-ones represent analogues of the illudines.



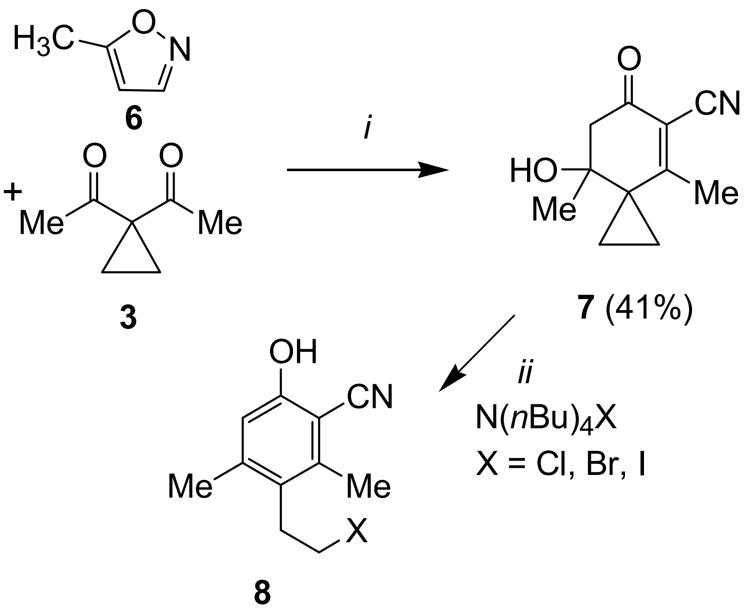
Scheme 3. Synthesis of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones (**4**); *i*, 1) LDA (2.3 equiv.), dicarbonyl compound (1.2 equiv.), THF, 1 h, 0 °C, 2) 1,1-diacetylcyclopropane (1.0 equiv.), −78 °C, 1 h, −78→20 °C, 14 h; *ii*, $TiCl_4$ (0.3 equiv.), CH_2Cl_2, −78→20 °C, 12 h.

1-Hydroxyspiro[5.2]cyclooct-4-en-3-ones **4** represent highly reactive electrophiles and strong alkylating agents.[29, 30] Treatment of 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **4** with titanium tetrahalides (method A) or tetraalkylammonium halides, in the presence of boron trifluoride (method B), resulted in the formation of 4-(2-haloethyl)salicylates **5** (Scheme 4).



Scheme 4. Reaction of 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones (**4**) with TiX_4 (method A) and NBu_4X (method B)

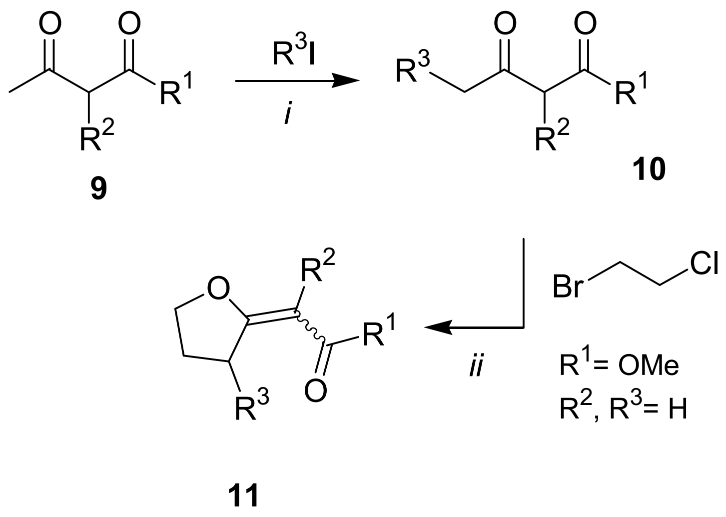
In my thesis, I adopted the above-mentioned methodology to the synthesis and reactions of novel spirocyclopropanes based on cyclizations of β-ketosulfone, β-ketonitrile **6** and β-ketophosphonate dianions with 1,1-diacetylcyclopropane. These reactions afford 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **7** which were transformed, by reaction with tetrabutylammonium halides, into functionalized phenols **8** as shown in Scheme 5.



Scheme 5. Synthesis of **8**; *i*: 1) LDA (2.0 equiv), **1** (1.0 equiv), THF, 1 h, 0 °C, 2) **2** (1.0 equiv), −78 → 20 °C, 14 h; *ii*: nBu$_4$NX (1.0 equiv), BF$_3$·OEt$_2$ (0.5 equiv.), –78 → 20 °C, 12 h

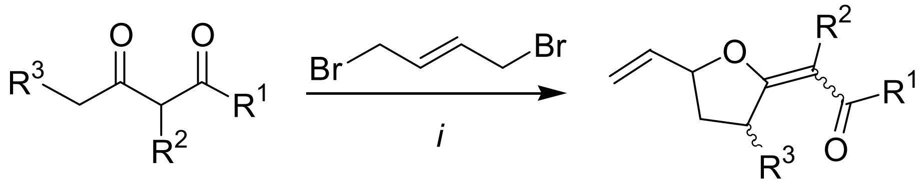
The regioselective alkylation of the dianions of simple *β*-ketoesters with alkyl iodides provides a convenient access to a variety of higher homologues[8]. These include branched, non-branched and ω-chloroalkyl-substituted derivatives. The one-pot cyclization of the dianions[9] of 1,3-dicarbonyl compounds with 1-bromo-2-chloroethane[10,11] afforded a variety of 2-alkylidenetetrahydrofurans [8,12] in good yields with very good regio- and *E/Z*-diastereoselectivity (cyclization type A, Scheme 6)[13,14]. Notably, the synthesis of 2-alkylidenetetrahydrofurans containing a remote chloro group proceeded with very good chemoselectivity. In fact, the chloro group proved to be compatible with the LDA-mediated generation of the dianions and the LDA-mediated cyclization.[8] Lindqvist *et al.*

earlier reported base-mediated intramolecular cyclizations of ω-halo-β-keto esters to give cyclic ethers or ketones[13a]. The one-pot cyclization of dilithiated ethyl 4-chloroacetoacetate with 1-bromo-2-chloroethane afforded, albeit in low yield, 3-chloro-2-alkylidenetetrahydrofuran as a separable mixture of *E*/*Z*-isomers (Scheme 6).



Scheme 6. Cyclization of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane; i: (1) LDA (2.3 equiv.), THF, 0 °C, 1 h, (2) R^3I, –78 → 20 ºC, 14 h, (3) 20 ºC, 2 h; ii: (1) LDA (2.3 equiv.), THF, 0 °C, 1 h, (2) $BrCH_2CH_2Cl$, –78 → 20 ºC, 14 h, (3) 20 ºC, 24 h or 68 °C, 9 h.

The one-pot cyclization of dilithiated 1,3-dicarbonyl compounds with 1,4-dibromo-2-butene[15] provides a convenient approach to 2-alkylidene-5-vinyltetrahydrofurans (**13**) (Scheme 7)[12]. The formation of products can be explained by a domino S_N/S_N' reaction. The products are formed as separable mixtures of *E/Z* isomers. The ratio strongly depends on the reaction time and on the substituents. The exocyclic double bond is initially formed with *Z*-configuration. By stirring of the reaction mixture at room temperature, an isomerization of the exocyclic double bond to the thermodynamically more stable *E*-configuration is observed. However, the isomerization could not be efficiently carried out after isolation of the *Z*-isomer, since the rearrangement was accompanied by decomposition. Weiler *et al.* reported that the reaction of 1,3-dicarbonyl dianions with 1,4-dichloro-2-butene (rather than 1,4-dibromo-2-butene) resulted in the formation of mixtures of open-chain products in low yields[15a]. Elegant and efficient cyclizations of 1,4-dibromo-2-butene with the stabilized carbanions of dimethyl acetone-1,3-dicarboxylate and of various other 1,3,5-tricarbonyl compounds has been reported by Rodriguez.[15c].

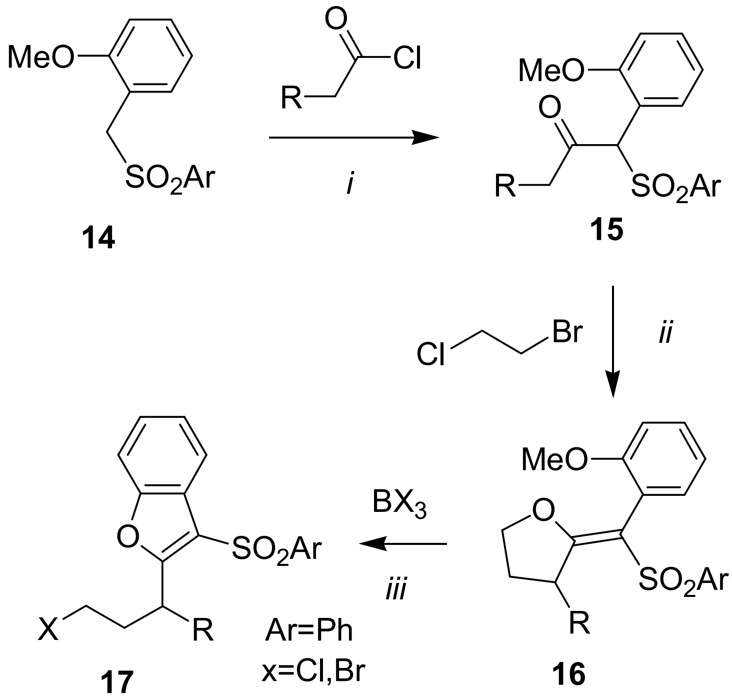


12

13 R^2,R^3=H
R^1=OEt

Scheme 7. Synthesis of 2-alkylidene-5-vinyltetrahydrofurans **13**: i: (1) LDA (2.3 equiv.), THF, 0 °C, 1 h, (2) 1,4-dibromobut-2-ene, –78 → 20 ºC, 14 h, (3) 20 ºC, 24 h.

We used the above mention methodologies to chemo- and regioselective synthesis of ω-bromo-3-ketosulfones, ω-bromo-3-ketonitriles and various functionalized 2-(ω-bromoalkyl)benzofurans by application of a ′ring-closing/ring-opening′ strategy. The cyclization of 3-ketosulfone and 3-ketonitrile dianions with 1-bromo-2-chloroethane or 1,4-dibromobut-2-ene afforded functionalized 2-alkylidenetetrahydrofurans (**16**), which were subsequently cleaved by reaction with boron tribromide or boron trichloride as shown in Scheme 8.



Scheme 8. Synthesis of benzofurans **17**, *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

In 1980, Chan and coworkers reported the first example of a new synthetic approach to salicylates based on cyclization reactions of 1,3-bis(silyl enol ethers).[16] These transformations, which can be formally regarded as [3+3] cyclizations, provide a convenient approach to a variety of functionalized arenes which are often not readily available by more classic methods. 1,3-Bis(silyl enol ethers) can be regarded as electroneutral equivalents of 1,3-dicarbonyl dianions (masked dianions) and generally attack electrophiles with their terminal carbon atom (as is the case for dianions). The chemistry of silyl enol ethers[17] and 1,3-bis(silyl enol ethers)[18] has been reviewed.

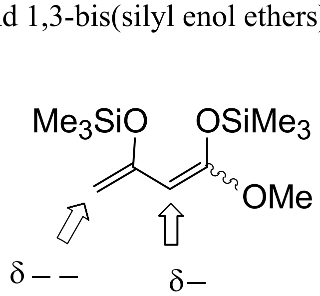
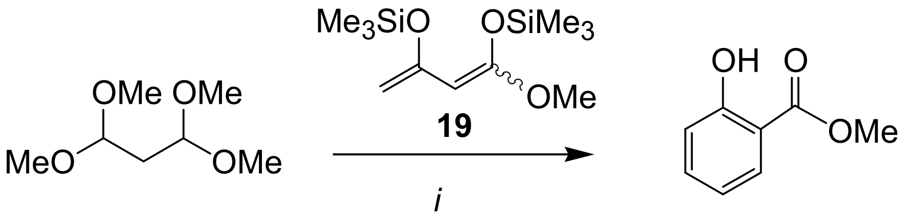


Figure 1. Reactivity of 1,3-bis(silyl enol ethers) in [3+3] cyclizations

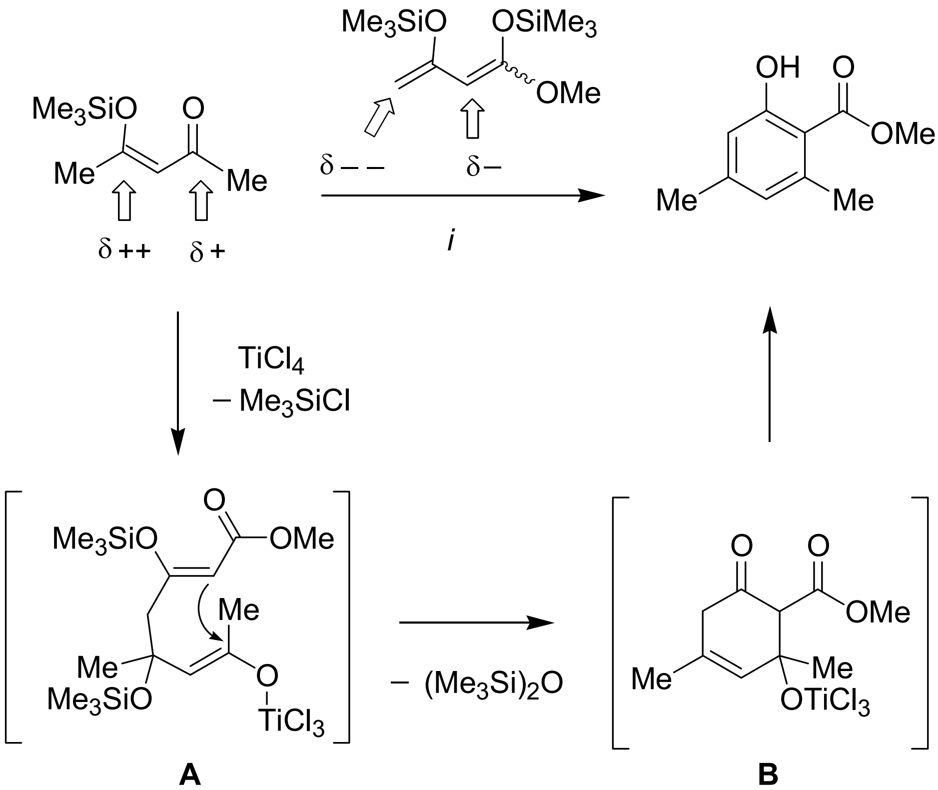
Chan and coworkers reported the $TiCl_4$ mediated synthesis of methyl salicylate by [3+3] cyclization of 1,3-bis(silyl enol ether) **19** with 1,1,3,3-tetramethoxypropane **18** (Scheme 9)[16]. This transformation proceeds by Lewis acid mediated attack of the terminal carbon atom of the 1,3-bis(silyl enol ether) onto the 1,1,3,3-tetramethoxypropane, cyclization and subsequent aromatization by double elimination of methanol.



18 20

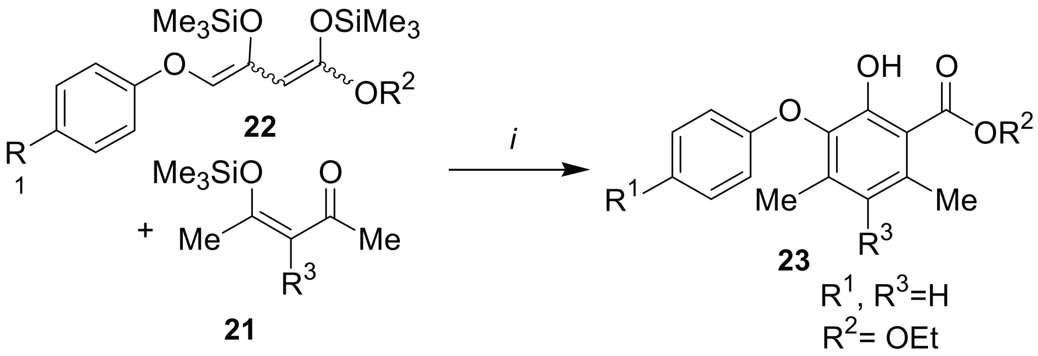
Scheme 9. Cyclization of a 1,3-bis(silyl enol ether) with 1,1,3,3-tetramethoxypropane, *i*: $TiCl_4$, CH_2Cl_2, –78 → 20 °C

Chan and coworker were the first to report the synthesis of salicylates by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-silyloxyalk-2-en-1-ones (Scheme 10)[19,20]. These cyclizations generally proceed by $TiCl_4$ mediated conjugate addition of the terminal carbon atom of the bis-silyl enol ether onto the 3-silyloxyalk-2-en-1-one, cyclization, extrusion of siloxane and aromatization.

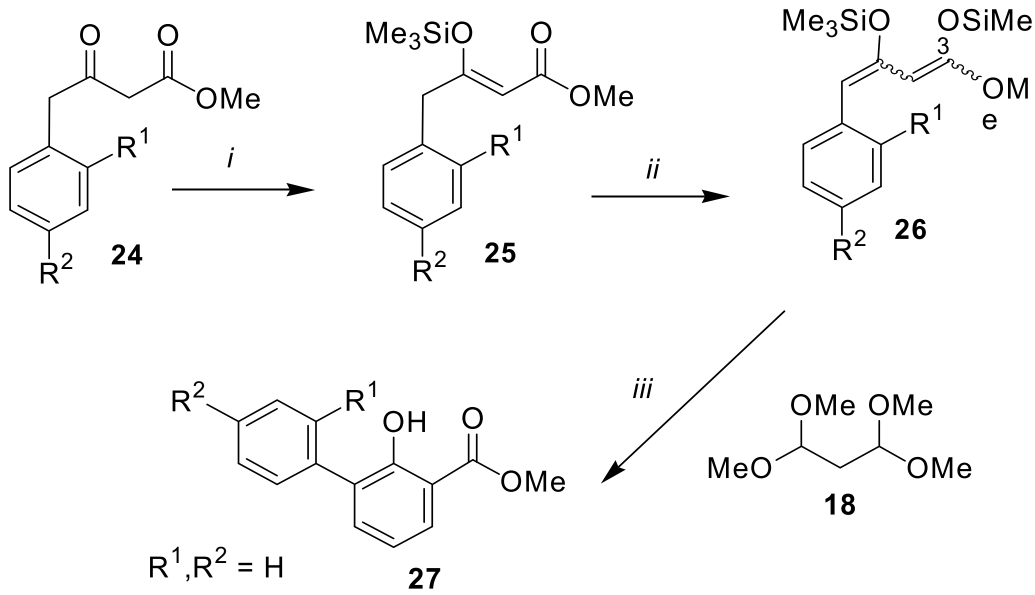


Scheme 10. Mechanism of the cyclization of 1,3-bis(silyl enol ethers) with 3-silyloxyalk-2-en-1-ones; *i*: $TiCl_4$, CH_2Cl_2, –78→20 °C

In my thesis, I have adopted this methodology of formal [3+3] cyclizations of 1,3-bis(silyl enol ethers) with 1,3-dielectrophiles, such as 1,1,3,3-tetramethoxypropane, **18** 3-(silyloxy)alk-2-en-1-ones, **21** for the synthesis of 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes **22** and 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-dienes **26** and their application to the synthesis of diaryl ethers. Noteworthy, these reactions allow a convenient and regioselective synthesis of sterically encumbered and functionalized diaryl ethers **23** and biaryls **27** (Schemes 11 and 12), which are not readily available by other methods.

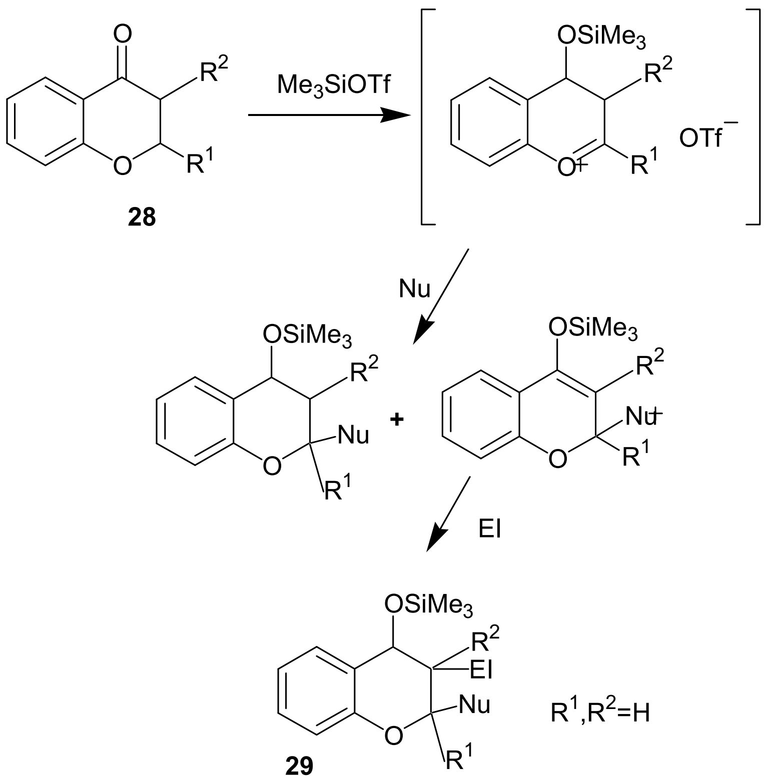


Scheme 11. Synthesis of **23**, *i***:** $TiCl_4$, CH_2Cl_2, –78 → 20 °C, 20 h.



Scheme 12. Synthesis of **27**; *i*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 72 h; *ii*: LDA, THF, –78 → 20 °C; *iii*: Me_3SiOTf (0.1 equiv.), CH_2Cl_2, –78 → 20 °C, 20 h

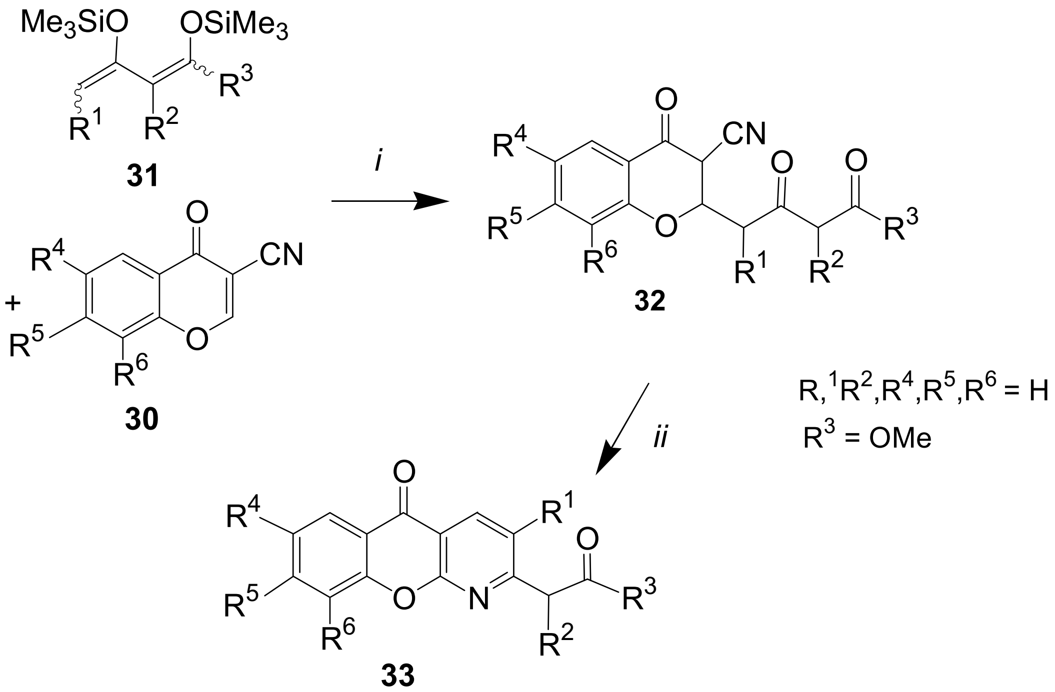
Ghosh and coworkers[21] were the first to report condensation reactions of 4-oxo-*4H*-[1] benzopyran-3-carbonitriles (henceforth called chromone-3-nitriles) with sodium azide to form 3-(1*H*-tetrazol-5-yl)chromones. They also investigated the reaction with hydrazine, phenylhydrazine, hydroxylamine, and some reactive methylene compounds, such as acetylacetone, ethyl acetoacetate,diethyl malonate, and ethyl cyanoacetate. The formal [4+2]-cycloaddition of 1,3-butadienes with 4-(trimethylsilyloxy)benzopyrylium triflates was first reported by Akiba and coworkers[22] . They have developed a facile and useful method for the regioselective introduction of carbon nucleophiles into pyrones via pyrylium cations by means of *tert*-butyldimethylsilyl triflate. It was observed that the generation of siloxypyrylium salts was one of the most effective methods for activation of the pyrone ring in the absence of other activating groups as shown in Scheme 13**.** Moreover, a synthetic advantage of this method is the tandem introduction of two kinds of substituents successively at C2 and C3 of the pyrones. These authors have further investigated reactions of chromones with various types of nucleophiles for preparation of 2-substituted chromone and xanthone derivatives.



Scheme 13

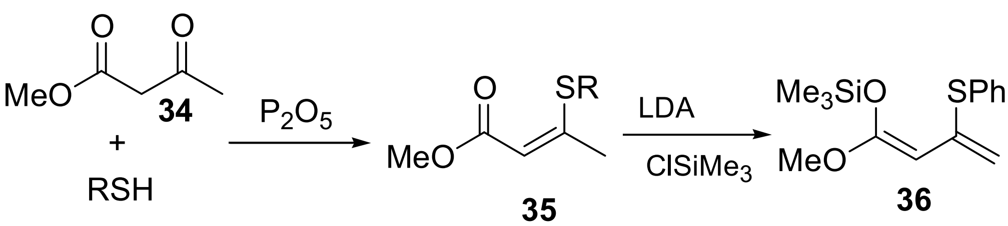
In the light of the above described methodology, the Langer group developed new domino reactions of 4-(silyloxy)benzopyryliumtriflates. For example, the TMSOTf-mediated reaction of 3-cyanochromones **30** with 1,3-bis(trimethylsilyloxy)-1,3-

butadienes **31** provides functionalized 1-azaxanthones **33** as shown in Scheme 14. The products are not readily available by other methods.

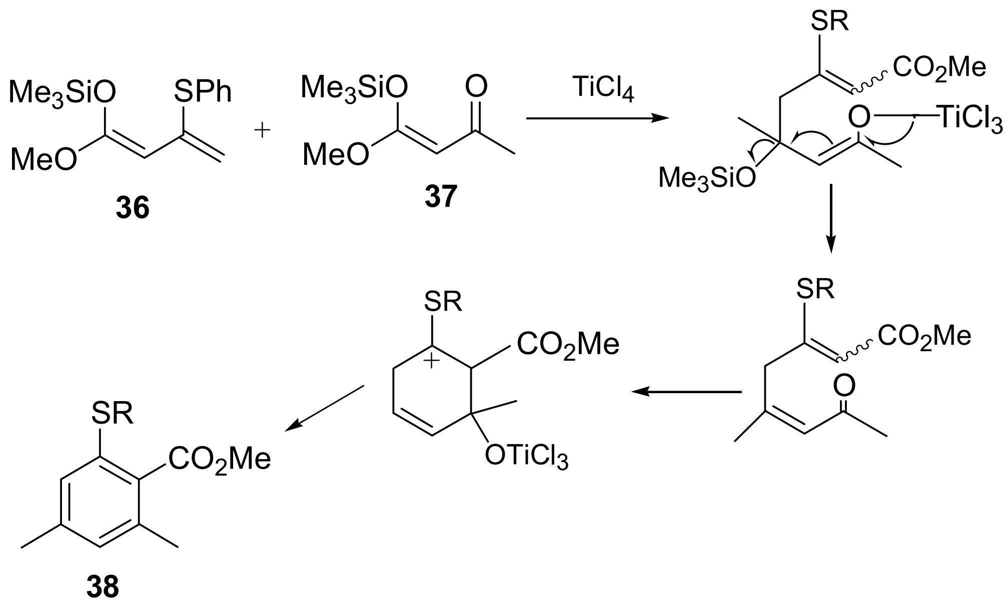


Scheme 14. Synthesis of 1-azaxanthones **33**: *i*: 1) **1**, Me_3SiOTf, 1 h, 20 °C, 2) **2**, CH_2Cl_2, 0 → 20 °C, 12 h, 3) HCl (10%); *ii*: 1) NEt_3, EtOH, 20 °C, 12 h, 2) HCl (1 M)

The chemistry of 1-silyloxy-1-methoxy-3-phenylthio-1,3-butadiene has been described by Chan and co-workers[23] in 1986. They have described the regioselectivity of the reaction of **3** with electrophiles. The reactions with unsaturated ketones and simple silyl enol ethers have been reported (Schemes 15 and 16).

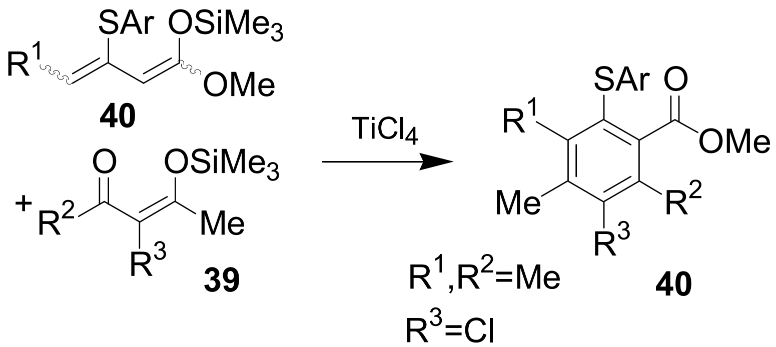


Scheme 15



Scheme 16

In my thesis, I have adopted this methodology to the synthesis of 3- and 5-thioaryloxysalicylates based on exploratory work of Chan *et al.* (Schemes 15 and 16). I synthesized 2-(thioaryloxy)benzoates and thioxanthones based on formal [3+3] cyclizations of 1-methoxy-1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes **40** with 3-silyloxy-2-en-1-ones **39** and 1,1,3,3-tetramethoxypropane. The sterically encumbered and functionalized products reported are again not readily available by other methods (Scheme 17).



Scheme 17

The palladium-catalysed Suzuki cross-coupling reaction of organoboron compounds with organic halides or pseudo-halides is a remarkably useful tool in organic synthesis. During the past decade, this reaction has been used for various carbon-carbon bond formations, which proceed under mild conditions. The reaction is largely unaffected by the presence of water, tolerates a broad range of functionalities and by-products are not toxic. The reaction has largely been employed in academic laboratories as well as in pharmaceutical and fine chemical industries to synthesise a large variety of organic molecules. For example, it has been applied industrially to the production of Losartan (**1**), which is a Merck antihypertensive drug, and has been used for the large scale synthesis of compound **2**, which is a key intermediate for the synthesis of SB-245570 (**3**), a compound useful for the treatment of depression, and as a key step in a convergent multikilogram synthesis of CI-1034 (**4**) (Figure **2**), a potent endothelian receptor antagonist[24].

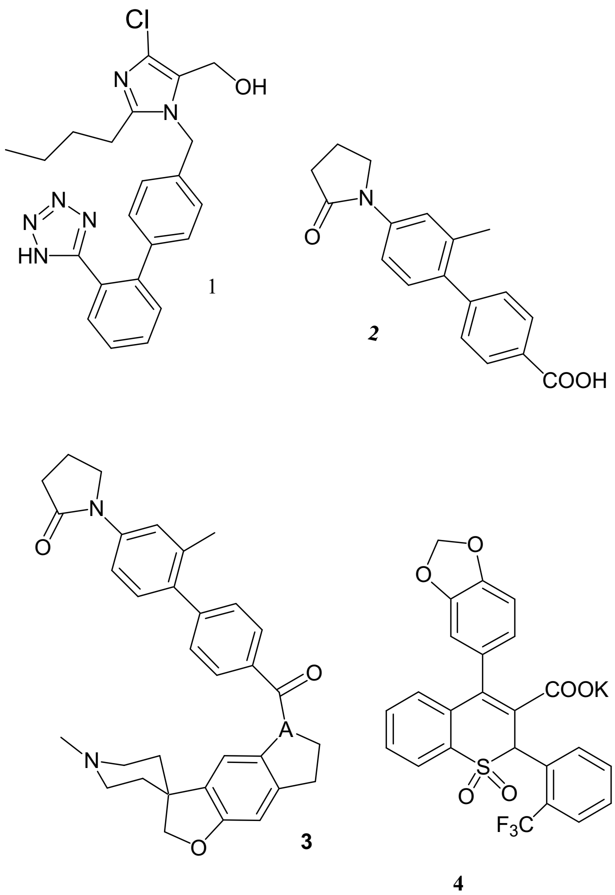
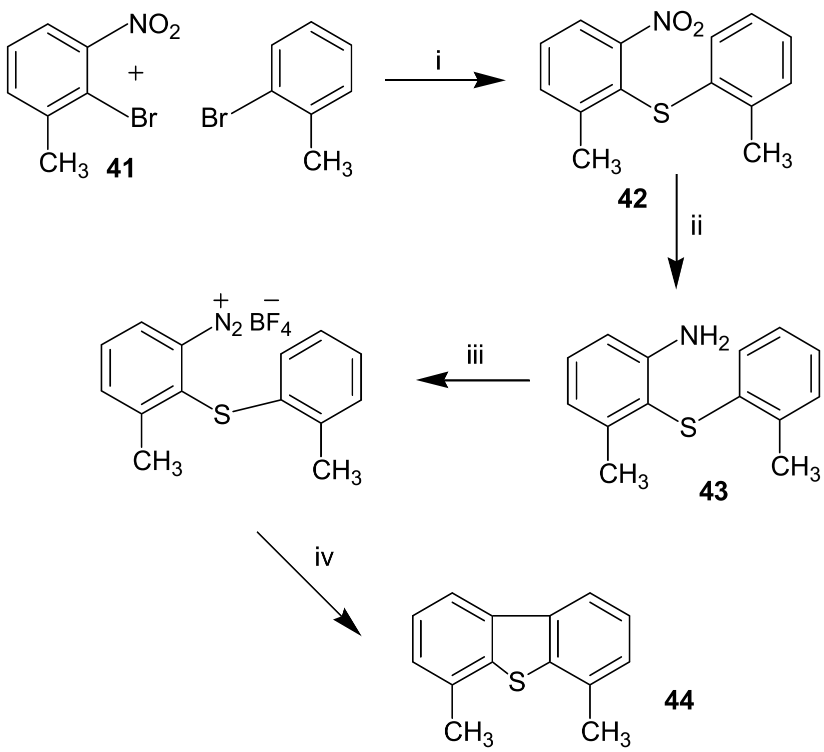
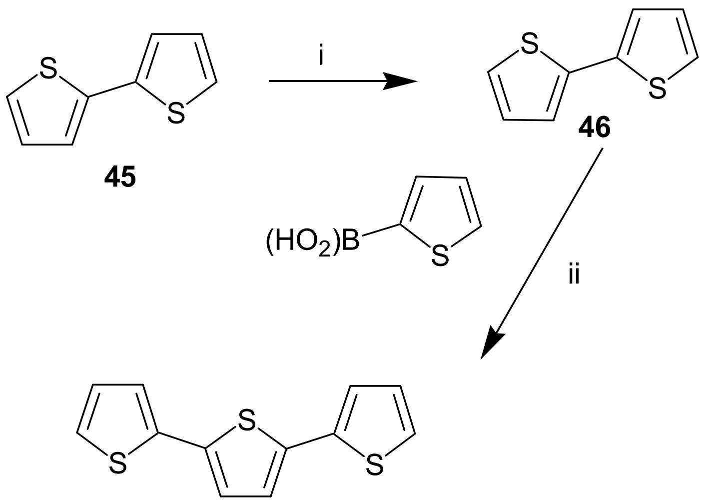


Figure 2

Thiophenes are present in pharmacologically relevant natural products. This includes, for example, dibenzothiophenes, 4,6-diethyldibenzothiophenes possessing estrogenic activity (**44**, Scheme 18),[25] [2,2';5',2"] terthiophenes,[26] (Scheme 19) and thienyl-diynes.[27] 2,3-Dibromothiophene has been functionalized by regioselective Sonogashira couplings of carbon atom C-2 (Scheme 20).[28] A very good C-2 regioselectivity was observed also for the Kumada cross coupling of 2,3- and 2,4-dibromothiophene.[29] In my thesis, I have studied the synthesis of various tetraarylthiophenes based on Suzuki reactions of tetrabromothiophenes as shown in Scheme 21.

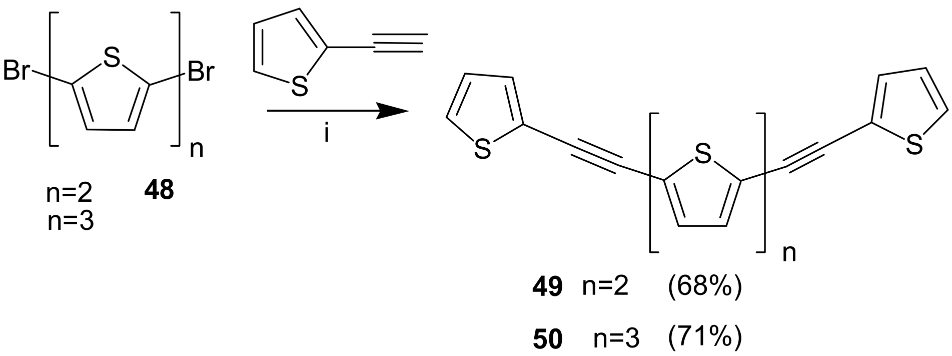


Scheme 18. Synthesis of 4,6-dimethyldibenzothiophene (**44**), i: KOH, NMP, 170 °C, 85%; ii: Pd/C, MeOH, H_2, 1 atm, RT, 90%; iii: H_2SO_4 ,$NaNO_2$, $NaBF_4$, 0° C; *iv*: Cu, DMSO, RT, 25%.

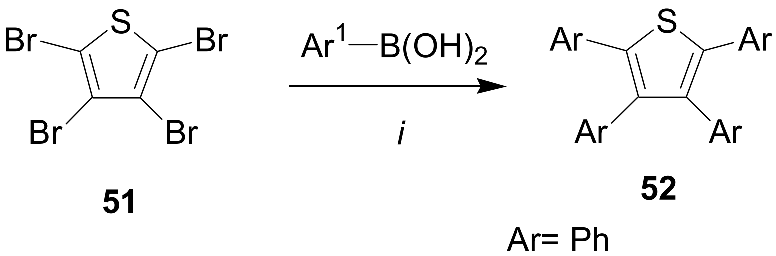


47

Scheme 19. Synthesis of of [2,2'; 5’, 2’’] terthiophenes (**47**) (*i*) NIS. DMF. Overnight**,** –20 °C, (ii) $PdCl_2$ ppf, basic alumina /KF, $\mu\nu$ 5 min, max temp 80 °C.

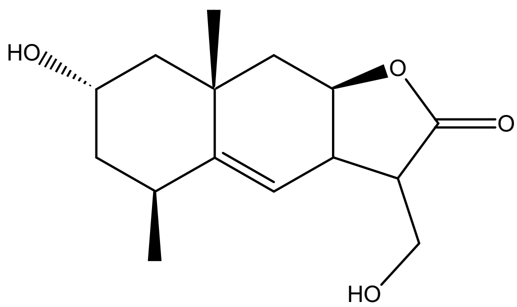


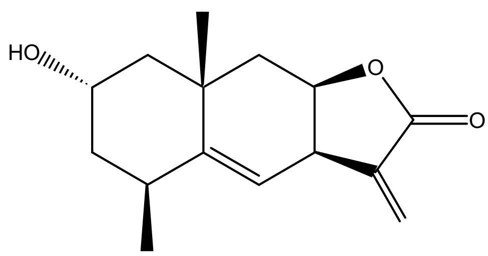
Scheme 20. Synthesis of **49, 50** (i) $Pd(PPh_3)_2Cl$, CuI, (*i*-Pr) NH, $\mu\nu$ 5 min, temp 50 °C.and $\mu\nu$ 20 min, temp 100 °C.



Scheme 21. Synthesis of tetraarylthiophene (**52)** Conditions: *i*, **1** (1.0 equiv.), $ArB(OH)_2$ (5.0 equiv.), $Pd(PPh_3)_4$ (10 mol-%), K_3PO_4 (8.0 equiv.), Toulene/H_2O = 4:1

The genus *Pulicaria Gaertn.* of the family *Compositae (Asteraceae)* consists of 100 species and this genus has been the subject of several chemical investigations, giving rise to the isolation of flavonoids, sesquiterpenes, diterpenes, triterpenes, caryophyllenes and caryophyllane derivatives[30,31] Several species of this genus have been used as insect repellents and in the treatment of dysentery[32]. The genus *Pulicaria* is placed in the tribe *Inuleae s. str.*[33] Chemically this genus is not homogeneous. As pointed out previously some species[34] contain diterpenes,others caryophyllene derivatives and those now placed inthe genus *Francoeuria* contain sesquiterpene lactones. *Pulicaria undulata* L. which is a synonym of *Pulicaria crispa* Forssk. and *Francoeuria crispa* Forssk.[35] Is an annual wooly herb which can cover whole desert wadis with its bright yellow flowers and fills the air with a rich perfume. Most plants appear with only a few flower-bearing branches but, under good conditions, they can grow into a splendid bush. One of its local names "Shai-el-Gebel which gives the secret away that this plant is used as an herbal tea and as a medicinal plant. The Bedouin's or vernacular name for Pulicaria crispa is Dethdath and Desdas. The Arabic names include: Arfeg; Feliet el-Hami; El Attasa, El Eteytesa; Sabad, Gettiat, Zibl el Far, Ghobbeira and Khanouf. This plant is used medicinally as a remedy for breathing problems. One small spoon of the herb can be boiled in a glass of water as needed. The flower branches are used for preparing a powerful sneezing powder. *Pulicaria undulata, C. A. Mey*. has been studied previously, but only thymol derivatives and flavones sesquiterpenes, diterpenes[36, 37,38] have been reported as shown in Figure 3.





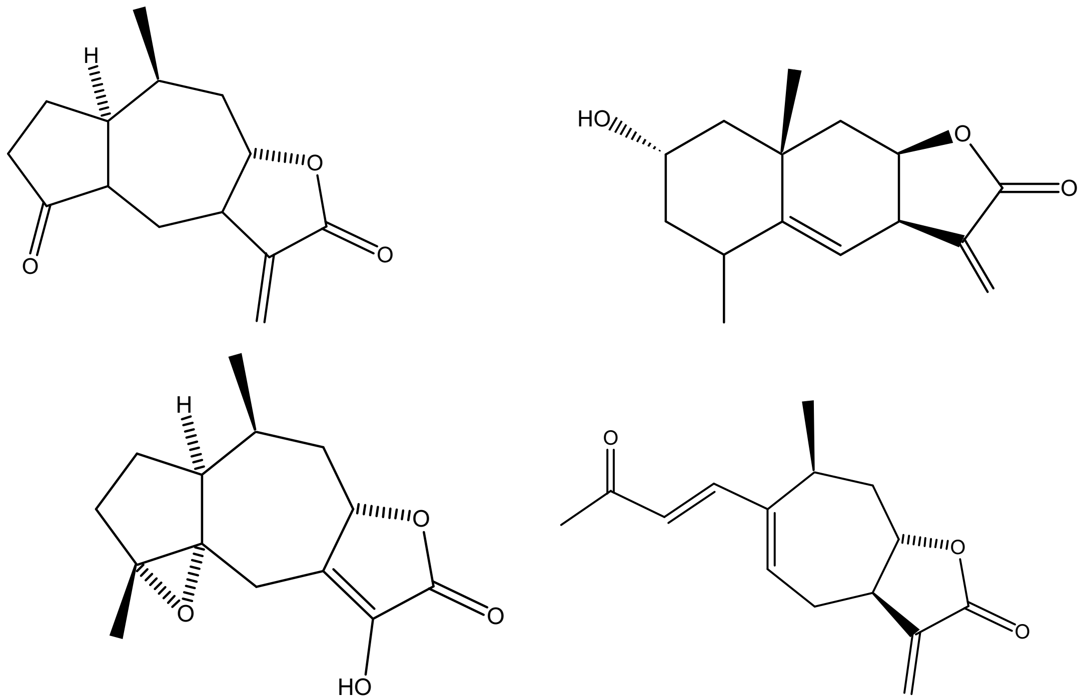


Figure 3

My own studies were focused on the isolation and characterization of new chemical constituents from *Pulicaria undulata.* This work was carried out at the H. E. J. research institute (Karachi, pakistan) under the guidance of Professor Dr. Viqar Uddin Ahmad. During these studies I have isolated and structurally elucidated different chemical constituents that belong to flavonoid and *ent*-kaurane-type diterpenes, to two new flavonoid glycosides, pulicaroside, undulatoside and one new flavonoid undulol. In addition, four known flavonones – one new *ent*-kaurane-type diterpene glycoside, pulicaroside-B together with three known compounds paniculosides-IV, roseoside and corchionol C which are derivatives of α-ionol – were isolated. The structures of the new and known compounds were elucidated by 1D- and 2D-NMR techniques, along with other spectral evidences and comparison of the spectral data with those of closely related compounds. All the flavonoids that are discussed in chapter 11 exibited superoxide anion scavenging activity.

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Description of my own contributions to the scientific publications

The coauthors of the scientific publications are given below. My own contributions to these publications can be easily recognized by the fact that I only included those compounds in the experimental section of the paper which I prepared myself. This means that the compounds given in the experimental section of my thesis are those compounds which I prepared without the help of others. In the following, my own contributions are described in great detail.

Chapter 1

The Langer group has previously reported the cyclization of the dianion of alkyl acetoacetate with 1,1-diacetylcyclopropane to give 1-hydroxyspiro[5.2]cyclooct-4-en-2-ones. I used other types of 1,3-dianions, such as β-ketosulfone, α-cyanoacetone, and diethyl 2-oxopropylphosphonate dianions and synthesized the corresponding functionalized spirocyclopropanes **3a,b** (see Scheme 1, Table 1). These products were transformed into stable aromatic phenols upon cleavage of the cyclopropane moiety by treatment with tetraalkylammonium halides in the presence of boron trifluoride to give products **4a-f** (see Scheme 2, Table 2). The novel spirocyclopropane **6** was synthesized by cyclization of 1,1-diacetylcyclopropane with the dianion of α-cyanoacetone, generated by treatment of 5-methylisoxazole with LDA (Scheme 3, Chapter 1). The $BF_3 \cdot OEt_2$-mediated reaction of **6** with tetrabutylammonium halides gave the 2-cyanophenols **7a-c** containing a remote halide group (Scheme 3, Table 3). The cyclization of 1,1-diacetylcyclopropane with the dianion of diethyl 2-oxopropylphosphonate (**8**), generated by means of LDA, afforded the novel unsubstituted 1-hydroxyspiro[5.2]cyclooct-4-en-3-one **9** (Scheme 4). The formation of **9** can be explained by cyclization (intermediate **C**), elimination of lithium diethyl phosphate (intermediate **D**) and subsequent protonation upon addition of water. Alternatively, the reaction can be regarded as a domino ′aldol / Horner-Wadsworth-Emmons (HWE)′ reaction. The $BF_3 \cdot OEt_2$-mediated reaction of **9** with tetrabutylammonium halides afforded the functionalized phenols **10a-c** (Scheme 5, Table 4). I synthesized all the above mentioned compounds myself without the help of others. The contribution of the other co-authors involves their help during chromatographic problems, spectroscopic analysis and X-ray analysis.

Chapter 2

In my thesis I studied for the first time in our group the use of acetone as a dianion in the reaction with 1,1-diacetylcyclopropane. In this chapter, my research work is mainly focussed on studies related to the dianion chemistry of acetone as well as 2-oxopropylphosphonate. I concentrated on the cyclization of the dianion of diethyl 2-oxopropylphosphonate (**1**), generated by means of LDA, with 1-acetyl-1-benzoylcyclopropane to afford the novel 1-hydroxyspiro[5.2]cyclooct-4-en-3-ones **3** (Scheme1). The $BF_3{\cdot}OEt_2$-mediated reaction of **3** with tetrabutylammonium halides afforded the phenols **4a-c** (Scheme 2, Table 1) containing a halogenated side chain. The cyclization of 1,1-diacylcyclopropanes **2a-c** with the dianion of acetone, generated by menas of a THF-suspension of potassium hydride and subsequent addition of TMEDA and *n*BuLi, afforded the 1-hydroxyspiro[5.2]cyclooct-3-en-5-ones **6a-c** (Scheme 3, Table 2). The $BF_3{\cdot}OEt_2$-mediated reaction of **6a-c** with tetrabutylammonium halides afforded the phenols **7a-h** and the halogen-free 10-membered cyclic diethers **8a-c** (Scheme 4, Table 3 in chapter). I synthesized all the above mentioned compounds myself, except for **6d**, **7i,j**, and **8d**. The other co-authors synthesized **6d**, **7i,j**, and **8d** and solved other scientific problems, such as chromatography, spectroscopic analysis and X-ray analysis.

Chapter 3

The Langer group previously reported the synthesis of 6-bromo-3-oxoalkanoates and benzofuran-3-carboxylic esters containing a remote bromide groups by reaction of BBr_3 with 2-alkylidenetetrahydrofurans. My work focussed on the synthesis of novel benzofurans based on reactions of 3-ketosulfones and 3-ketonitriles. The reaction of the dianion of 3-ketosulfone **1b** with 1-bromo-2-chloroethane gave the 2-(sulfonylmethylidene)-tetrahydrofuran **2b** (Scheme 1, Table 1). I futher synthesized the 2-(sulfonylmethylidene)-5-vinyltetrahydrofuran **4b** by cyclization of dilithiated 3-ketosulfones **1b** with 1,4-dibromobut-2-ene (Scheme 2, Table 2). The reaction of **4b** with BBr_3 afforded the ω-bromo-3-ketosulfones **5b**. In addition 3-ketosulfones **7a,b,d** were prepared by acylation of aryl-[(2-methoxyphenyl)methyl]-sulfones **6a,c**. The cyclization of the dianions of **7a,c,d** with 1-bromo-2-chloroethane afforded the 2-alkylidenetetrahydrofurans **8a,c,d**. Treatment of **8a,c,d** with BBr_3 afforded the 2-(γ-bromoalkyl)-3-sulfonylbenzofurans **9a,c,d** (Scheme 3, Table 3). The reaction of **8a,c,d** with BCl_3 gave 2-(γ-hydroxypropyl)-3-sulfonylbenzofuran **9e,g**. I studied the cyclization of the dianion of β-ketonitrile with 1-bromo-2-chloroethane and 1,4-dibromobut-2-ene to give 2-alkylidenetetrahydrofuran **16** and 2-alkylidene-5-vinyltetrahydrofuran **18**. Treatment of the latter with BBr_3 and subsequently with HBr (62%) afforded the 2-(γ-bromoalkyl)-3-carboxybenzofuran **17** (Scheme 6) and the 2-(ω-bromoalkyl)-3-carboxybenzofuran **19** (Scheme 7). I synthesized all the above mentioned compounds without the help of others. The contribution of the other co-authors is related to solve other scientific problem, such as chromatography, spectroscopic analysis and X-rays analysis.

Chapter 4

The Langer group earlier reported the synthesis of 5-aryloxysalicylates and 5-thioaryloxysalicylates based on reactions of 2-aryloxy- and 2-thioaryloxy-3-trimethylsilyloxy-2-en-1-ones, respectively. In my thesis, I synthesized for the first time 4-aryloxy-1,3-bis(trimethylsilyloxy)-1,3-dienes and studied their application to the synthesis of diaryl ethers. I focussed mainly on domino ′[3+3]-cyclization-homo-Michael′ reactions in this chapter. The $TiCl_4$- and $TiBr_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-diene **4a** with 1,1-diacetylcyclopropane (**8**) afforded the 3-phenoxysalicylates **9a,b** containing a remote halide function (Scheme 4, Table 3). I synthesized all the above mentioned compounds without the help of others. The contribution of the other co-authors is related to chromatography, spectroscopic analysis and X-ray analysis.

Chapter 5

The TMSOTf-mediated [4+2]-cycloaddition of 1,3-butadienes with 3-cyanochromone, via its 4-(trimethylsilyloxy)benzopyrylium triflate, has been previously reported by our group. In the light of this reaction, I studied the development of new applications of 4-(silyloxy)benzopyrylium triflates. The TMSOTf-mediated reaction of 3-cyanochromones with 1,3-bis(trimethylsilyloxy)-1,3-butadienes allows a convenient synthesis of functionalized 1-azaxanthones. In my thesis, I used cyanochromone, 6-chlorocyanochromone, 6-methylcyanochromone, 6,7-dimethylcyanochromone and 1,3-bis(silyl enol ethers) **2e, 2f,2s, 2t** and prepared the substituted azaxanthones **4,l,n,o,af,ag** (Scheme 2, Table 1) The other co-authors synthesized all other compounds.

Chapter 6

The Langer group has developed a convenient approach to salicylates by formal [3+3] cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes with 3-trimethylsilyloxy-2-en-1-ones. For the first time, I synthesized 4-aryl-1,3-bis(trimethylsilyloxy)-1,3-butadienes and applied them to the synthesis of functionalized biaryls. I carried out the $TiCl_4$-mediated reaction of 1,3-bis(silyloxy)-1,3-dienes **4a** and **4d** with 1,1-diacetylcyclopropane (**8**) to give the 3-arylsalicylates **9a** and **9b**, respectively (Scheme 3). The other co-authors synthesized all compounds except from the above mentioned compounds.

Chapter 7

Based on initial studies of Chan et al., I developed a new methodology for the synthesis of 2-(thioaryloxy)benzoates and thioxanthones based on formal [3+3] cyclizations of 1-methoxy-1-trimethylsilyloxy-3-thioaryloxy-1,3-butadienes with 3-silyloxy-2-en-1-ones and 1,1,3,3-tetramethoxypropane. This is related to the formal [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 3-siloxy-2-en-1-ones which has been reported in our group before. First, I synthesized the 1-methoxy-1-trimethylsilyloxy-3-thioaryloxy-1,3-

butadienes **3a-c** (Scheme 1, Table 1). Their reaction with 3-silyloxy-2-en-1-ones **4a-e** afforded the 2-(thioaryloxy) benzoates **5e,f,g,h,i,j** (Scheme 3, Table 2). The cyclization of dienes **3a,c** with 1,1,3,3-tetramethoxypropane (**6**), in the presence of catalytic amounts of trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf, 0.1 equiv.), afforded the 2-(thioaryloxy)benzoates **7a** (Scheme 3). I treated the 2-(thioaryloxy)benzoates **5,e,f,h,i** with concentrated sulfuric acid to give the thioxanthones **8d,e,f,g** (Scheme 4, Table 2). The other co-authors synthesized the remaining compounds (except from the above mentioned ones).

Chapter 8

In collaboration with another Ph.D student of the Langer group, I synthesized tetraarylthiophenes by regioselective Suzuki reactions of tetrabromothiophene. Tetrabromothiophene (**1**) was prepared by bromination of thiophene (following a modified literature procedure). The tetraarylthiophenes **2a,b,c,d,** containing four identical aryl groups, were successfully prepared by Suzuki reaction of **1** (1.0 equiv.) with 5.0 equiv. of various boronic acids (Scheme 1, Table 1 in chapter 8). The reaction of **1** (1.0 equiv.) with 2.2 equiv. of boronic acids allowed the regioselective synthesis of the 2,5-diaryl-3,4-dibromothiophenes **3a,c-f** (Scheme 2, Table 2). Product **3a** (1.0 equiv.) could be further functionalized by Suzuki-reaction using 3.0 equiv. of various arylboronic acids to give the tetraarylthiophene **4b** which contains two different types of aryl groups (Scheme 2, Table 3). I synthesized the above mentioned compounds. The contribution of the other co-authors is based on the synthesis of the other products, chromatography, spectroscopic analysis and X-ray analysis.

Chapters 9-12

Chapters 9 and 10 deal with the phytochemical investigation of *pulicaria undualta*. I selected this plant, due to the reason that it has a valuable medicinal importance. The plant *Pulicaria undulata* L. (*Asteraceae*) was collected from *Loralai*, *Blalochistan*, and identified by Dr. Rasool Bakhsh Tareen (Taxonomist), Department of Botany, Balochistan University, Quetta, Pakistan. I chopped and soaked dry plant material in methanol for a period of 30 days. The combined methanolic extract was evaporated under vacuum to yield a crude methanolic extract. The methanol extract was then fractionated with petroleum ether, chloroform, ethyl acetate and butanol. In chapter 9, the chloroform-soluble fraction was subjected to column chromatography using silica-gel, eluted with petroleum ether, and the polarity was gradually increased with chloroform and methanol to afford **16b**, 17-dihydroxy-ent-kauran-19-oic acid.

In chapter 10, the ethyl acetate soluble extract was subjected to CC over silica gel, using hexane with a gradient of $CHCl_3$ up to 100% and then the polarity was increased with methanol in a similar fashion. Fifteen fractions (Fr 1-15) were collected. The Fr 5 and Fr 9 were then subjected to flash chromatography eluting with MeOH/$CHCl_3$ to give purified compounds **1-6**: 6-hydroxykaempferol 3-methyl ether, 6-*O*-β-D-glucopyranoside (**2**), 6-methoxykaempferol 3-*O*-β-D-glucopyranoside (**3**), 6-methoxykaempferol (**4**) and quercetagetin 3,6-dimethyl ether (axillarin) (**5**) were known flavonones. Pulicaroside (**1**) and undulatoside (**6**) were isolated as new compounds in *pulicaria undulata.*

In chapter 11, the *n*-butanol soluble fraction of the whole plant of *Pulicaria undulata* L. (syn. *Pulicaria crispa* Forssk.) yielded a new diterpene glycoside, pulicaroside-B (**1**), along with three known compounds, paniculosides-IV (**2**), roseoside (**3**) and corchoionol C (**4**). Their structures were deduced by detailed analysis of their spectral data and comparison of their spectral data with those of closely related compounds. I used the recycling HPLC (LC 908 W), a semi-preparative (M-80) reverse phase column for further purification and the purity was checked by TLC with different solvent systems using methanol, acetic acid, water, and $CHCl_3$, giving a single spot**.**

In chapter 12, I used the ethyl acetate soluble fraction of the whole plant of *Pulicaria undulata* L. (syn. *Pulicaria crispa* Forssk.) which led to the isolation of the new flavonoid Undulol (**1**). Its structure was deduced by detailed analysis of the spectral data and comparison of its spectral data with those of the closely related compounds. All experimental portions of chapters 9 to 12 described above I have been done myself without the help of others. Other co-authors solved other scientific problems, such as spectroscopic analysis, X-ray analysis and the superoxide anion scavenging assay.

Chapter 1.

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

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Nasir Rasool, Muhammad A. Rashid, Muhammad Adeel, and Peter Langer* "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". *Tetrahedron Lett.* **2008**, accepted.

Chapter 3

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

Chapter 4

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

Chapter 5

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Chapter 7

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Chapter 9

Nasir Rasool, V.U. Ahmad*****, M.I. Choudary, S. Anjum, Hoong-Kun, Fun, S, Ali 16β, 17 Dihydroxy – ent-Kauran-19-oic acid from *Pulicaria undulata* ", *Acta Cryst.* **2005**, *E61*, o3053-o3055.

Chapter 10

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Signatur