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Application of Metalation Reactions for Synthesis of New Sulfur/Selenium-Containing Heterocyclic Compounds

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ABSTRACT

This thesis deals mainly with the synthesis of various sulfur/selenium-containing heterocyclic compounds, many of which include structural features present in several biologically active molecules, with particular emphasis on compounds of synthetic importance, such as indoles, as well as other heteroaromatic species.

In the first part, an efficient procedure toward synthesis of new 3-(arylthio)indoles based on reactions of aryl Grignard reagents or lithiated heteroaromatics with protected 3,3′-dithiobisindoles is described. In addition, the heterocyclic core of the marine alkaloid echinosulfone A, namely 3,3′-bis(indolyl) sulfone, was obtained by treatment of a 3-lithioindole derivative with bis(phenylsulfonyl) sulfide. These methodologies offer convenient synthetic routes toward a wide range of 3-(arylthio)indoles in good yields. In an extension, the sulfonation of 1-(phenylsulfonyl)indoles and pyrroles using chlorosulfonic acid in acetonitrile has been studied, leading to development of a simple and clean protocol for synthesis of the corresponding 1-phenylsulfonyl-1*H*-indole-3-sulfonyl chlorides and 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chlorides.

In the second part, a new practical approach is described toward the synthesis of several biologically active indolothiopyrans and related selenopyrans, as analogues of indolocarbazoles. The target compounds were accessed via treatment of C-2 metalated indoles with bis(phenylsulfonyl) sulfide or selenide, followed by cyclization of the intermediate 2,2′-di(indolyl) sulfide/selenides, involving for example triethyl orthoformate under acidic conditions.

The final section of this thesis describes a new method for synthesis of dibenzo[*b,f*]thiepins and related fused systems via ortho-metalation of aromatic acetals, followed by treatment with bis(phenylsulfonyl) sulfide, initially giving symmetrical diaryl-sulfides, which were subjected to deacetalization, and finally McMurry coupling. The method could also be extended to preparation of thiepin analogues such as 1-sila-, 1-germa- and 1-selenacyclohepta-2,4,6-trienes containing two fused aromatic or heterocyclic units.

Keywords: heterocycles, indoles, 3-(arylthio)indoles, thiopyranobisindoles, dibenzothiepins, 3,3′-dithiobisindoles, alkaloids, echinosulfone A, cyclization, ortho-metalation, McMurry coupling, sulfides, sulfones and disulfides.

LIST OF PAPERS

This thesis is based on following articles:

I. "New routes to 3-(arylthio)indoles: Application to the synthesis of the 3,3′-bis(indolyl)sulfone core of the marine alkaloid echinosulfone A"
Hamid Shirani, Birgitta Stensland, Jan Bergman and Tomasz Janosik.
Synlett **2006**, 2459-2463.

II. "Synthesis of 3-(arylthio)indoles and related compounds by reactions of metalated aromatics or heterocycles with protected 3,3′-dithiobisindoles"
Hamid Shirani and Tomasz Janosik.
Synthesis **2007**, 2690-2698.

III. "Efficient sulfonation of 1-phenylsulfonyl-1*H*-pyrroles and 1-phenylsulfonyl-1*H*-indoles using chlorosulfonic acid in acetonitrile"
Tomasz Janosik, Hamid Shirani, Niklas Wahlström, Ilham Malky, Birgitta Stensland and Jan Bergman.
Tetrahedron **2006,** *62*, 1699-1707.

IV. "Synthesis and biological evaluation of fused thio- and selenopyrans as new indolocarbazole analogues with Ahr affinity"
Emma Wincent, Hamid Shirani, Jan Bergman, Ulf Rannug, Tomasz Janosik.
Bioorg. Med. Chem. **2009**, *17*, 1648-1653.

V. "A new concise strategy for synthesis of dibenzo[*b,f*]thiepins and related fused symmetrical thiepin derivatives"
Hamid Shirani and Tomasz Janosik.
J. Org. Chem. **2007**, *72*, 8984-8986.

VI. "Synthesis of fused 1-sila-, 1-germa-, and 1-selenacyclohepta-2,4,6-trienes"
Hamid Shirani and Tomasz Janosik.
Organometallics **2008**, *27*, 3960-3963

CONTENTS

1 Background

1.1 Significance of sulfur and selenium in organic and bioorganic chemistry

1.1.1 History

The chalcogens, constituting group VI in the periodic table, include the elements oxygen (O), Sulfur (S), selenium (Se), tellurium (Te), polonium (Po) and ununhexium (Uuh). Undoubtedly, compounds incorporating the first three chalcogen elements (oxygen, sulfur and selenium) fulfill a wide range of essential chemical and biochemical functions. Several compounds in this category, e.g. the vitamins biotin (**1**), thiamine (**2**), lipoic acid (**3**) as well as the amino acids cysteine (**4**) and methionine (**6**) (both containing sulfur), selenocysteine (**5**) and selenomethionine (**7**) (both containing selenium) are essential to life and exhibit many interesting biological properties.[1,2]

4 X = SH
5 X = SeH
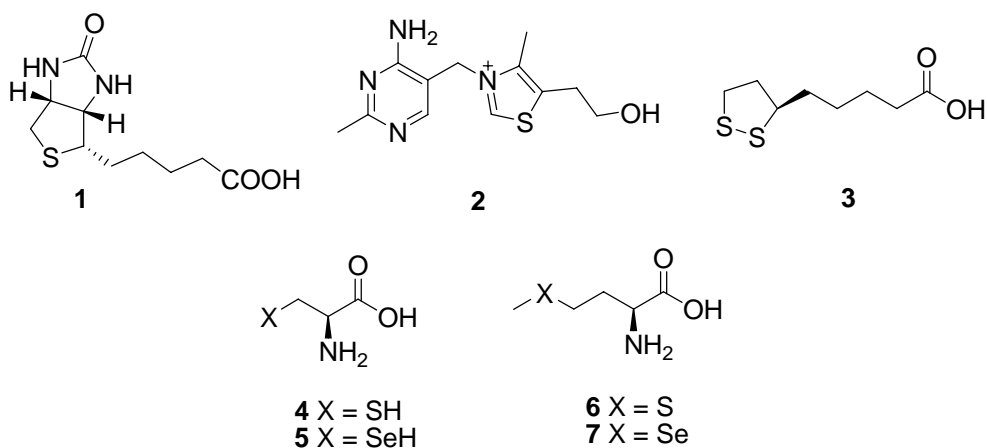
6 X = S
7 X = Se

Figure 1

The chemistry of organosulfur compounds dates from the successful synthesis of ethyl xanthate (**8**)[3] in 1822 and mercaptanes **9** in 1831 by W. C. Zeise (1789-1847). His work marks the beginning of organosulfur chemistry, with the result that most of the characteristic sulfur containing groups were known by about 1865.
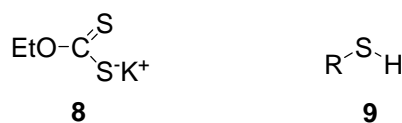

8

9

Figure 2

At an early stage, organic compounds of selenium also became known when Berzelius discovered the element selenium in 1818, and found that alkali metal selenides and tellurides resemble sulfides. The first organic Se compound, diethyl selenide, mixed with the corresponding diselenide, was prepared by Löwing in 1836, but the pure compounds were not isolated until 1869. Several other organic selenium, as well as tellurium compounds were synthesized at approximately the same time, most of them in F. Wöhler's laboratory, for example, ethaneselenol, dimethyl diselenide (1856), and others. Selenium salts were discovered in 1865, but selenoxides not until 1893. Some heterocyclic compounds containing nitrogen and Se in the same ring were synthesized in 1889-90. After this pioneering period, the development in organic selenium chemistry slowed down mostly due to complications such as sensitivity to air and light, toxicity, as well as the bad smell. However, modern methods and equipment have made it possible to prepare organic selenium compounds, in good yields and purity. The development has been catalyzed by technical and biological interest in sulfur and selenium compounds, and the study of their chemical reactions has resulted in important new methods in organic synthesis.[4,5]

1.1.2 *The special characteristics and uses of sulfur and organosulfur compounds*

Sulfur is one of the most abundant elements in universe and has been known since antiquity due to its association with volcanic eruptions. Thus, it was referred to in the past as brimstone (burning stone). It is widely distributed in nature and occurs mostly in crude oil, coal, natural gas, and in areas of high volcanic activity. Today, the recovery of subterranean deposits is accomplished by the Frasch process, in which high pressure steam is forced down to melt the sulfur and is then blown up to surface. Large amounts have also been extracted from hydrogen sulfide (H_2S) in natural gas, or by high temperature roasting of sulfide ores, such as pyrite (FeS_2). Sulfur tends to react with itself, and consequently can exist in a large number of acyclic and cyclic S_n species. All the chain and ring forms of sulfur are thermodynamically less stable than cyclooctasulfur (S_8) at 25 °C.

Most of the sulfur produced is used in manufacture in the heavy chemical industry, and one of the commercial key compounds is sulfuric acid (H_2SO_4), produced on a 100-million-ton/year scale. Sulfur is used for vulcanization of natural rubber, discovered by Goodyear and Hancock in 1847, while sulfur dioxide is employed as a preservative and

antioxidant in the food industry. Beside that, many organosulfur compounds have major industrial uses, for instance, carbon disulfide (CS_2) and DMSO are important solvents, and long chain alkane sulfonic or arensulfonic acids are important detergents. Many organosulfur compounds also show useful biological effects. The early introduction of organosulfur compounds as pharmaceuticals derived from the orange-red azo dye, one of which, prontosil (**10**) showed to inhibit the growth of *Streptococcus*. Gerhard Domagk,[6] demonstrated in 1935 that the activity was due to the formation of the metabolite sulfonamide **11** (Scheme 1), and this discovery led to the introduction of a large number of sulfa antibacterial drugs, which were later modified to give different types of activity, e.g. as diuretics and antimalarial agents. This discovery marks an important milestone in the development of medicinal chemistry, which led to the synthesis of approximately 15000 sulfonamides. Most of the sulfa drugs possess the substructure **11**, and many of the most useful compounds contain a heterocyclic nucleus. However, since the introduction of antibiotics, the use of the sulfa drugs has decreased markedly.[4]
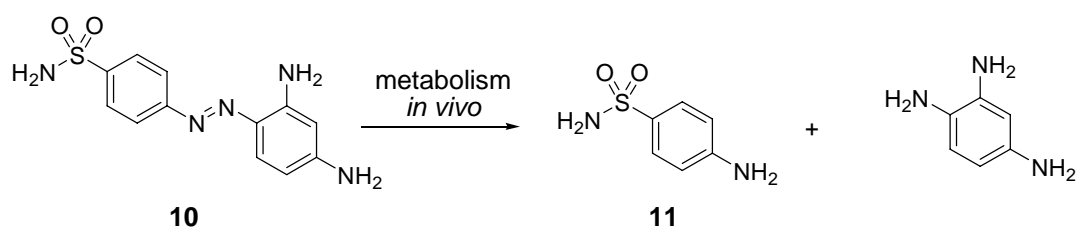
Scheme 1

1.1.3 Synthesis and reaction of organosulfur compounds

Since sulfur lies directly below oxygen in group VI of the periodic table, the chemistry of organosulfur compounds should parallel that of the oxygen analogues. Indeed, there are many similarities, e.g. between alcohols and thiols, as well as ethers and sulfides. One of the general methods for sulfuration includes the direct action of elemental sulfur (S_8) on organic compounds in the presence of a base. There is also a variety of inexpensive sulfur compounds available for sulfuration reactions, e.g. hydrogen sulfide, carbon disulfide, phosphorus pentasulfide, sodium sulfide and sulfate, sulfur dioxide/trioxide, sulfuric acid, sulfur dichloride, thionyl chloride and sulfuryl chloride.

Perhaps one of the most important organosulfur compounds is carbon disulfide, which is used primarily as a solvent for extraction of oils and waxes, but also as solvent in Friedel-Crafts reactions. Xanthates used in the manufacture of rayon and cellophane, are produced by the reaction of carbon disulfide with an alcohol in the presence of alkali. Elemental sulfur can also react with organometallics such as Grignard reagents, to provide thiols or sulfides. The reaction of Grignard reagents with other sulfur electrophiles can also lead to different products. For instance, the reactions of sulfur dioxide or trioxide with metalated species give sulfinic or sulfonic acids.[4]

1.2   Indoles

1.2.1   Historical perspective

Indole[7,8] (**12**) is the commonly used name for the benzopyrrole ring system, consisting of a benzene ring fused to the 2,3-positions of a pyrrole ring. The interest and development in indole chemistry started in mid-nineteenth century, with intensive studies of indigo (**13**), a violet-blue dye from India, originally derived from *Indigofera* species. Useful investigations of indole chemistry started when indigo was successfully oxidized to isatin (**14**), which was then reduced to oxindole (**15**).[9] Later in 1866 A. Baeyer prepared the parent substance, indole, by zinc dust reduction[10] of oxindole (**15**), and shortly thereafter he proposed the presently accepted formula in 1869.[11] Today the synthesis of indole is usually performed from non-heterocyclic precursors by cyclisation reactions of suitably substituted benzenes. Perhaps the most widely used route is the Fischer indole synthesis,[12] which also can be used on a large scale, e.g., for production of the stabilizer 2-phenylindole in manufacture of PVC.[13,14]

The studies in indole chemistry were intensified, when it was discovered that many biologically important alkaloids as well as pharmaceutical agents contain an indole unit. For instance, the essential amino acid tryptophan (**16**) in living organisms and the neurotransmitter serotonin (**17**), are two very important indole derivatives.
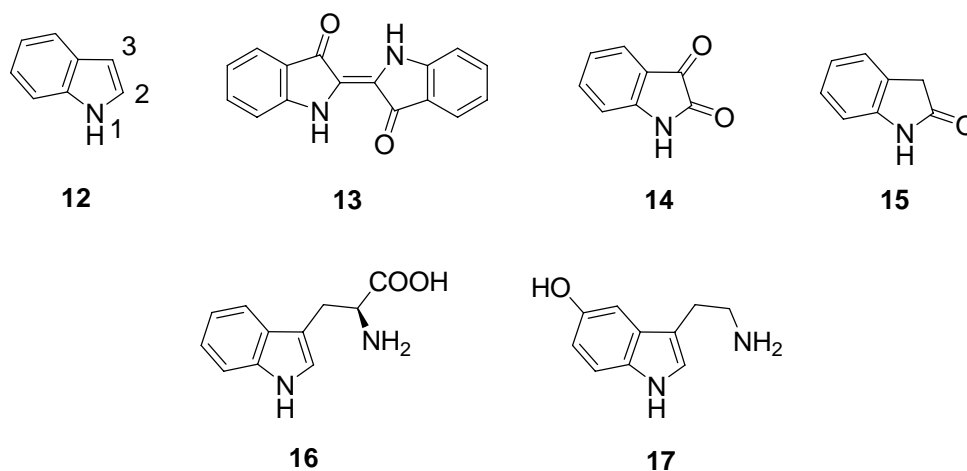
4

Figure 3

1.2.2 *Typical reactivity of indoles*

Perhaps one of the most characteristic reactions of indoles is electrophilic substitution at C-3 in the five-membered ring, which is facilitated by electron-release from the heteroatom. This preference can be rationalized by consideration of the Wheland intermediate **18** (Scheme 2), in which the enamine system in the five-membered ring does not disturb the aromaticity of the benzene ring. The positive charge in the intermediate is, of course, delocalized and the aromaticity of the six-membered ring can therefore be retained. In contrast, any attack at C-2 cannot derive assistance from the nitrogen without disrupting the aromaticity of the benzene ring. However, electrophilic substitution can occur at C-2, if for instance the C-3 is occupied by a substituent.[15]
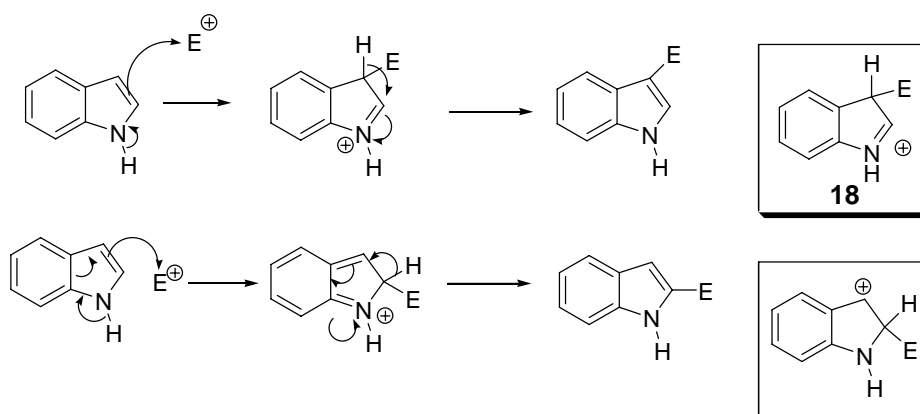
Scheme 2

1.2.3 Reactions of N- and C-metallated indoles

*N*-Metallated indole, or the indolyl anion, has two major mesomeric structures with localization of the negative charge mainly on the nitrogen and the C-3. This anion behaves as an ambident nucleophile, which reacts with electrophiles giving either N- or C- substituted products (Scheme 3). The ratio of these products depends mainly on the associated metal, the solvent polarity, and the nature of the electrophile. Generally, there is a tendency to react at nitrogen if the metal is more ionic, like sodium and potassium, whereas the more covalent magnesio-derivatives have greater tendency to react at C-3. Reactions of the indole Grignard reagent in HMPA lead to predominant attack at nitrogen, whereas less polar solvents favor attack at C-3.[16-19] However, indolyl Grignard reagents undergo reaction predominantly at C-3 with a variety of carbon electrophiles.
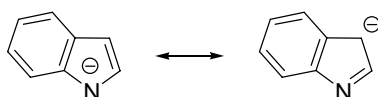
Scheme 3

Lithiation of indoles at C-2 is more complicated, and requires the absence of the acidic *N*-hydrogen, but can nevertheless be accomplished under slightly forceful condition. For instance, the presence of removable and directing protecting groups on the indole nitrogen, for example phenylsulfonyl and *t*-butoxycarbonyl (Boc), allow C-2 lithiation. This method has additional advantages not only because these *N*-substituents can assist metallation (lithiation) by chelation, but also by electron withdrawal, reinforcing the tendency for metallation to proceed at C-2.

Functionalization of indole at C-2 can also be performed according to the Katrizky protocol[20] *via* initial lithiation of indole, followed by *N*-protection with CO_2, a second lithiation with *t*-BuLi, and subsequent quenching the resulting indole dianion intermediate **19** with a suitable electrophile (Scheme 4). This route is much more convenient because the protecting group is installed *in situ*, and is removed during aqueous, slightly acidic workup.
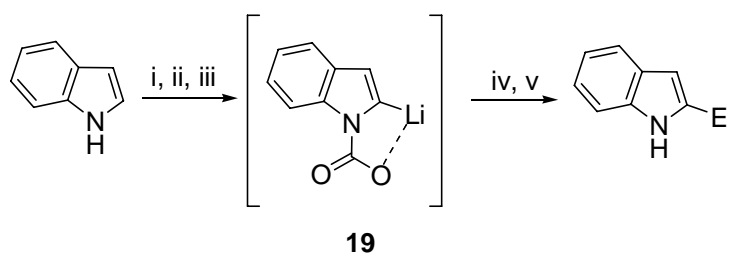
Scheme 4 *Reagents and conditions:* (i) BuLi; (ii) CO_2; (iii) *t*-BuLi; (iv) **E**$^+$, −78 °C; (v) H$^+$/H$_2$O

2   3-(Arylthio)indoles and 3-sulfonylindoles (Papers I-II)

2.1   General introduction

3-(Arylthio)indoles and related 3-sulfonylindole derivatives have recently received much attention due to their therapeutic potencial, including treatment of HIV and cancer. In particular, 3-(arylthio)indoles with the general structure **20**, and numerous related 3-sulfonylindoles, display a variety of potent biological effects. For instance, the 3-(arylthio)indole **21** has been shown to be an excellent antitubulin agent which is also capable of inhibiting growth of human breast cancer.[21,22] Moreover, the 3-sulfonylindole **22** (L-737,126) has been identified as a highly potent compound which displays significant anti-HIV properties.[23,24]
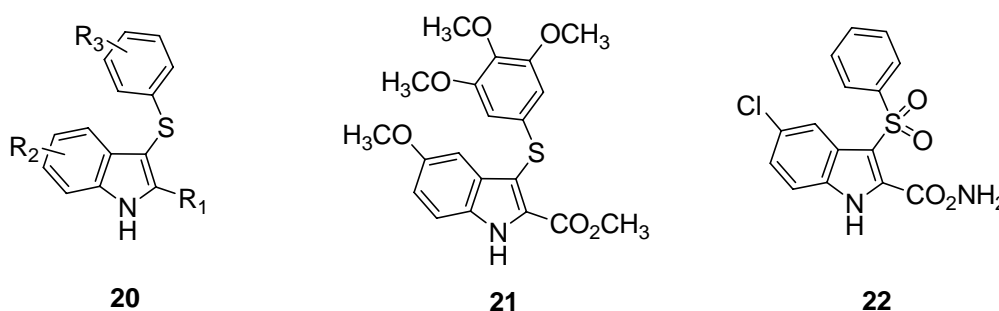

Figure 4

Apparently, good activity in this class of compounds requires some essential structural features which include: A) an ester functionality at C-2 of the indole ring, B) the sulfur bridge, C) the aryl group and D) a substituent at C-5. However, recent studies have revealed similar inhibition of tubulin despite the absence of the ester moiety at C-2 in the indole ring.[25] The biological effects of 3-(arylthio)indoles have triggered considerable interest in the synthesis and biological evaluation of new derivatives. Consequently, there are several synthetic approaches towards the 3-(arylthio)indoles or related 3-(alkylthio)indoles involving various sulfenylating reagents. Therefore, a part of the work in this thesis (papers I-III) deals with development of synthetic routes toward 3-(arylthio)indoles and sulfonylindole systems, and reactions giving rise to new related structures.

2.2   Previous synthetic efforts for synthesis of (arylthio)indoles

A crucial step in many syntheses of 3-(arylthio)indoles is the introduction of sulfur into the indole C-3 position using various sulfur sources. However, some derivatives of the parent system 3-(arylthio)indole were prepared in the early 1960s by the Fischer indole synthesis,[26,27] involving cyclization of various phenylhydrazone derivatives **23** (Scheme 5).[28]

23
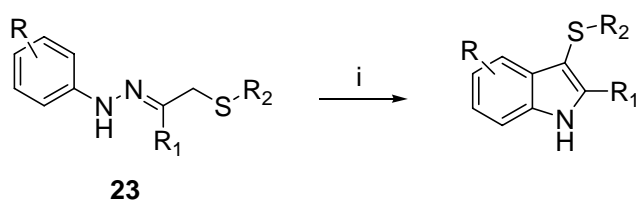
Scheme 5 *Reagents and conditions*: (i) EtOH, HCl, NH$_4$Cl, 0 °C.

Although satisfactory, this initial attempt required separate syntheses of carbonyl compounds for each 3-(arylthio)indole derivatives. Thus, in order to extend the synthetic repertoire toward such compounds, several other strategies have been reported, involving reaction of indoles with different forms of electrophilic sulfur sources (Scheme 6).
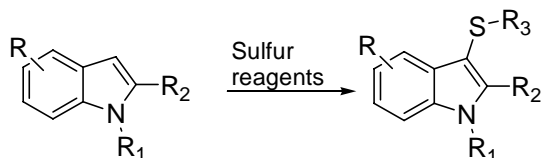
Scheme 6

Some of the used sulfenylating reagents include sulfenyl halides generated in situ, quinone mono-*O*,*S*-acetals **24**,[29] thiols in the presence of oxygen[30] or selectfluor™[31] and *N*-thiolalkyl- or *N*-thioarylphthalimides **25**.[32] Other noteworthy routes leading to 3-(arylthio)indoles derivatives, comparable to the work in this thesis, include cleavage of diaryl or dialkyl disulfides **26** by the indole anion.[33] This procedure offers a considerable advantage over the methods outlined above, due to the use of disulfides as the electrophiles. The disulfides are very stable and moderately reactive compared to the corresponding thiols or sulfenyl halides, which may cause drawbacks such as low yields, probably due to undesired side reactions.
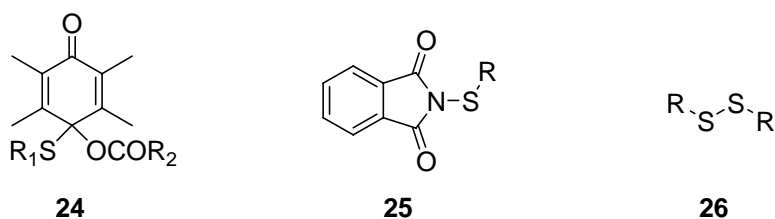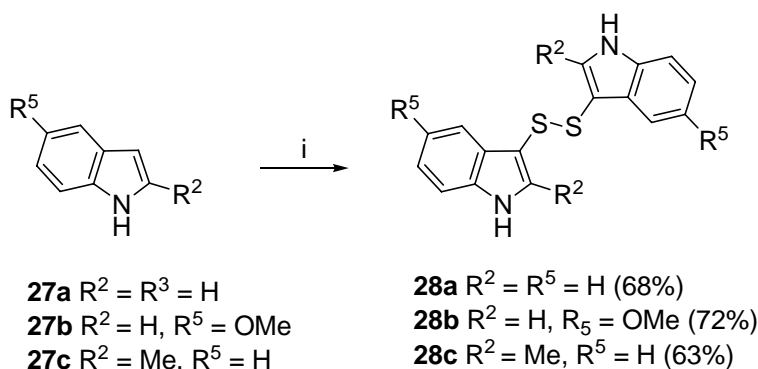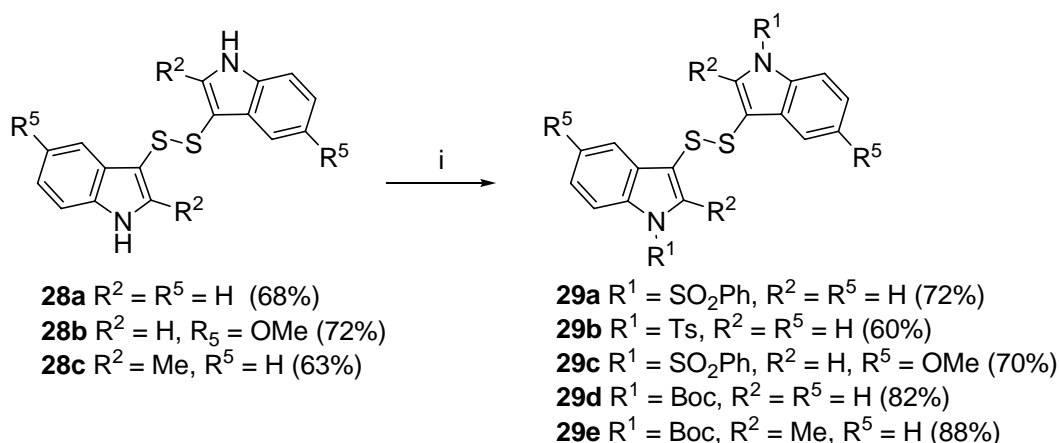
Figure 5

2.3 New approaches toward 3-(arylthio)indole derivatives (Papers I-II)

Cleavage of disulfides with organometallic reagents is a well-known method for preparation of unsymmetrical sulfides.[34] Thus, a new approach was developed involving cleavage of S-S bonds in 3,3′-dithiobisindoles by C-metallated aromatic or heteroaromatic compounds. Since this approach required access to considerable amounts of protected 3,3′-dithiobisindoles, the initial efforts were focused on preparation of the 3,3′-dithiobisindoles and their N-protection. Consequently, the 3,3′-dithiobisindoles **28a-c** were conveniently prepared according to a literature procedure by exposure of the indoles **27a-c** to thiourea in the presence of iodine in a basic medium.[35,36] It was however recognized, that a modification of the existing procedure could improve the yield of the disulfides **28a-c** significantly from 23-32% to 60-70%, simply by passing a stream of air for several hours through the reaction mixture. This outcome can be attributed to the final oxidative process which gives rise to the formation of the disulfides **28a-c**.

27a $R^2 = R^3 = H$
27b $R^2 = H$, $R^5 = OMe$
27c $R^2 = Me$, $R^5 = H$

28a $R^2 = R^5 = H$ (68%)
28b $R^2 = H$, $R_5 = OMe$ (72%)
28c $R^2 = Me$, $R^5 = H$ (63%)

Scheme 7 *Reagents and conditions*: (i) H_2NCSNH_2, I_2, NaOH, EtOH, H_2O, rt 18 h, then air, rt, 8–9 h.

Next, the conversion of the 3,3′-dithiobisindoles **28a-c** to the protected derivatives **29a-e** was explored. Despite the fact that disulfides are often readily cleaved by bases, the disulfide linkage in the 3,3′-dithiobisindoles **28a-c** proved to be stable enough under certain anhydrous basic reaction conditions. Therefore, the 3,3′-dithiobisindoles **28a-c** were treated with phenylsulfonyl chloride or *p*-toluenesulfonyl chloride in the presence of KOH and a phase transfer catalyst using CH_2Cl_2 as solvent,[37,38] providing the *N*-protected derivatives **29a-c**. In contrast, when the disulfides were treated with di-*tert*-butyl dicarbonate (Boc-anhydride) in the presence of DMAP in anhydrous THF, significant amounts of side-products were formed, probably resulting from cleavage of the disulfide linkage. Consequently, in order to introduce the Boc-group, an alternative procedure was employed, involving exposure of the disulfides **28a** and **28c** to di-*tert*-butyl dicarbonate and potassium carbonate in anhydrous DMF, giving the target compounds in good yields.

28a $R^2 = R^5 = H$ (68%)
28b $R^2 = H$, $R_5 = OMe$ (72%)
28c $R^2 = Me$, $R^5 = H$ (63%)

29a $R^1 = SO_2Ph$, $R^2 = R^5 = H$ (72%)
29b $R^1 = Ts$, $R^2 = R^5 = H$ (60%)
29c $R^1 = SO_2Ph$, $R^2 = H$, $R^5 = OMe$ (70%)
29d $R^1 = Boc$, $R^2 = R^5 = H$ (82%)
29e $R^1 = Boc$, $R^2 = Me$, $R^5 = H$ (88%)

Scheme 8 *Reagents and conditions*: (i) $PhSO_2Cl$ or TsCl, *n*-Bu_4NHSO_4, KOH, CH_2Cl_2, 0 °C, 1 h, then rt 1.5 h (for **29a–c**), or Boc_2O, K_2CO_3, DMF, rt, 18 h (for **29d–e**).

Having secured sufficient amounts of the disulfides **29a-e**, experiments involving organolithium or organomagnesium reagents could be undertaken probing their applicability in synthesis of 3-(arylthio)indole derivatives. Hence, the readily available 3,3′-dithiobisindoles **29a-e** were treated with C-metallated aromatics or heteroaromatics generated using established procedures, to produce a wide variety of 3-(arylthio)indoles. For instance, lithiation of indole at C-2 was accomplished by the Katritzky protocol[20] and subsequent quenching of the resulting indole dianion intermediate with suitably protected 3,3′-dithiobisindoles **29a** or **29e** gave the desired 2,3′-di(indolyl) sulfides **30a-b**, which could be finally deprotected in a basic medium to the parent compound **31**. Application of the Boc-protected disulfide **30b** instead of

the phenylsulfonyl protected compound **30a** in such a sequence led to an improvement of the overall yield from 30% to 80%. This outcome can be attributed to the sensitivity of benzensulfonyl group in basic media, which could cause partial removal of the protecting group.

30a R = SO$_2$Ph (38%)
30b R = Boc (81%)

31
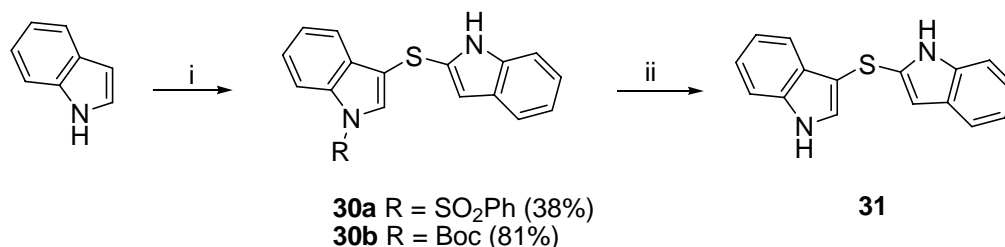
Scheme 9 *Reagents and conditions:* (i) BuLi, CO$_2$, *t*-BuLi; then **29a** or **29d**, −78 °C to rt. 16 h; (ii) KOH (1 M), EtOH, 90 °C, 30 min, 83%.

It is noteworthy, that according to the only previous example available in the literature, the 2,3'-di(indolyl) sulfide (**31**) was obtained by melting indole with elemental sulfur in a sealed vessel.[39] Now, the structure of **31** was characterized by NMR and the analytical data were compared with the literature, revealing several contradictions. In particular, the presence of a singlet peak at δ 4.77 in the literature ^{1}H NMR data (DMSO-d_6) was not consistent with the spectrum obtained for **31** in our laboratory. These observations suggest that further investigation would be needed in order to provide full insight in this reaction. However, it is known that the direct action of elemental sulfur on organic compounds can result in sulfuration, often giving complex mixtures of products. It is also known that the reaction of indole and sulfur in DMF leads predominantly to the formation of the tetrasulfide **32**.[40,41] This compound has been synthesized independently, and the structure has been confirmed by X-ray crystallography.[42]
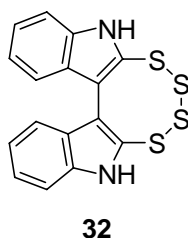

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Figure 6

In a further extension aiming to evaluate the scope of the metallation strategy, aromatics having a reactive functional group, such as ethyl 2-iodobenzoate, were converted to their Grignard reagents by exposure to *i*-PrMgCl,[43,44] followed by reactions with the appropriate disulfides **29a** and **29c**, providing 3-(arylthio)indoles

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featuring an ester unit. Representative products originating from different reagents and conditions are summarized in Table 1.

$$29a\text{-}e \longrightarrow$$

(structure with R_5, SR_3, R_2, R_1 indole core)
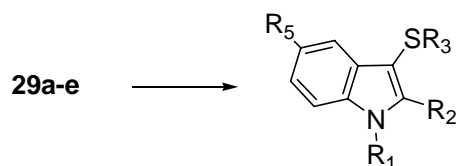
Scheme 10 *Reagents and conditions*: R^3Li, THF, $-78\ °C$, or R^3MgX, I_2 (cat), $0\ °C$, then **28a-e**.

Table 1.

Substrate	Reagents and conditions	Product	Yield%
indole (NH)	BuLi, THF, $-78\ °C$, CO_2 (g), *t*-BuLi, then **29a** or **29d**	3-(indol-2-ylthio)indole, N-R	R = SO_2Ph 39 R = Boc 81
benzofuran (O)	BuLi, THF, $-78\ °C$, then **29e**	N-Boc, 2-Me indole, S-benzofuran	82
benzothiophene (S)	BuLi, THF, $-78\ °C$, then **29b**	N-Ts indole, S-benzothiophene	70
2-iodo ethyl benzoate (CO_2Et)	*i*-PrMgCl, THF, $-20°C$ to $0°C$, then **29c**	MeO, EtO_2C, PhO_2S-N indole	75
2-iodo ethyl benzoate (CO_2Et)	*i*-PrMgCl, THF, $-20°C$ to $0°C$, then **29a**	EtO_2C, PhO_2S-N indole	69
4-bromoanisole (Br, OMe)	Mg, I_2, THF, then **29b**	N-Ts indole, S-C_6H_4-OMe	83
bromobenzene (Br)	Mg, I_2, THF, then **29d**	N-Boc indole, S-phenyl	76
1-bromonaphthalene (Br)	Mg, I_2, THF, then **29e**	N-Boc, 2-Me indole, S-naphthyl	59

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# 3 Indole- and pyrrole-3-sulfonyl chlorides (Paper III)

3.1 General introduction

Over the last few decades, the applications of sulfones in organic synthetic chemistry have increased dramatically due to their versatility in synthetic transformations.[4,45]Sulfones are easily prepared by several high-yielding routes, mainly by the oxidation of appropriate sulfides with oxidants such as m-CPBA or other suitable oxidants.[4,46,47] Moreover, sulfones may also be synthesized by alkylation of a sulfinate salt. However, as the sulfinate anion is an ambidenate nucleophile, the reaction may result in an unsatisfactory side reaction, namely alkylation of the oxygen, to yield a sulfinate ester (Scheme 11).
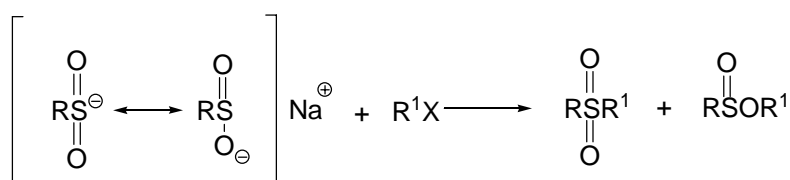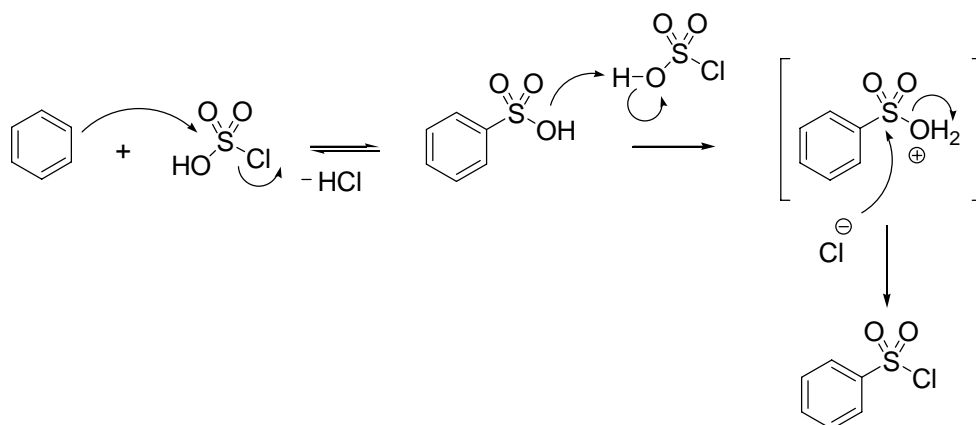

Scheme 11

Alternatively, aromatic sulfonyl chlorides are useful starting materials for preparation of sulfone derivatives. For instance, diarylsulfones are easily obtained by Friedel-Crafts reactions between arenesulfonyl chlorides and arenes (Scheme 12).[4,47]
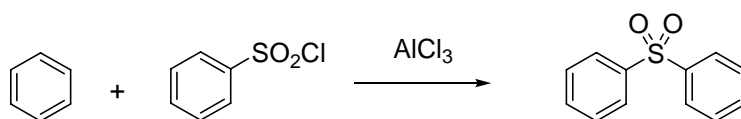
Scheme 12

Furthermore, aromatic sulfonyl derivatives can be obtained by direct sulfonation of aromatic compounds using reagents such as H_2SO_4, $ClSO_3H$, or pyridine-sulfur trioxide. The sulfonation process has a very broad scope, and many aromatic substrates can be sulfonated without damage to functional groups. For instance, a convenient route to aromatic sulfonyl chlorides involves treatment of aromatic compounds with an

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excess of chlorosulfonic acid. Since chlorosulfonation is a reversible reaction, this type of transformations often demands a large excess of reagent to avoid the formation of sulfones.[4,48] The reaction most probably involves chlorination of the initially formed sulfonic acid by an excess of chlorosulfonic acid, as shown for the reaction with benzene in Scheme 13.

Scheme 13

3.2 Sulfonation of protected indoles and pyrroles with chlorosulfonic acid

Sulfonyl chlorides are important intermediates in the synthesis of a range of sulfonyl derivatives, as the chlorine atom is easily displaced by various nucleophiles, such as amines and alcohols. Thus, sulfonyl chlorides are used as starting materials in the production of many biologically active compounds, for example the sulfonamide drugs.[4,49] As mentioned in Section 2, new studies have shown that indoles having a sulfone- or sulfonamide unit at C-3 possess interesting therapeutic properties. However, despite the fact that sulfonation procedures for a number of aromatic compounds are known, many heterocycles tend to be too sensitive for direct sulfonation, often forming mixtures of products.[4] For instance, electron rich heterocycles such as indole and pyrrole dimerize or polymerize in presence of strong acids. Sulfonation of such compounds must therefore generally be achieved by alternative methods or reagents. One such reagent is the pyridine-sulfur trioxide complex, which is a valuable for sulfonation of acid sensitive heterocycles.[50] However, there are reports describing direct sulfonation in acidic media of indole and pyrrole derivatives having strongly electron-withdrawing substituents. For instance, a series of nitroindoles and ethyl pyrrole-2-carboxylates having different substituents at the nitrogen atom have been sulfonated in neat chlorosulfonic acid (Figure 7).[51,52]
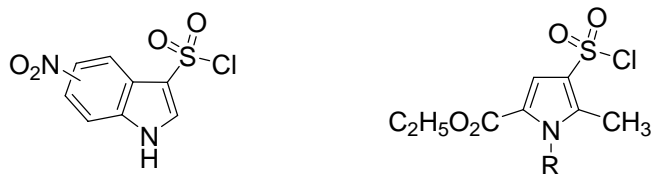
Figure 7

In our laboratory, the initial attempts were directed towards development of a simple procedure for chlorosulfonation of electron deficient indoles and pyrroles. Although the stability of both 1-phenylsulfonyl-1*H*-pyrroles and the corresponding indoles in acidic media are known, for instance in nitration at C-3,[53] the reactivity of such compounds towards sulfonating agents has never been investigated. Therefore, a series of phenylsulfonyl-protected substrates were selected in order to evaluate the scope and limitations of their reactivity *vs.* chlorosulfonic acid. Since this approach required access to substantial amounts of *N*-protected indoles and pyrroles, attention was first directed toward synthesis of such compounds. The *N*-protection of indoles was performed by a standard procedures using phenylsulfonyl chloride in the presence of a strong base and a phase transfer salt.[37,38] On the other hand, *N*-protection of pyrrole was achieved by treatment of pyrrole with BuLi in THF, followed by introduction of phenylsulfonyl chloride.

The initial experiments revealed that sulfonation of 1-phenylsulfonyl-1*H*-pyrroles **33** performed in neat chlorosulfonic acid will cause decomposition of the starting material. Consequently, the reactions were performed in the presence of acetonitrile as the solvent using an excess of chlorosulfonic acid. This combination of reagent and solvent gave clean conversion of **33** to 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chlorides **34**.
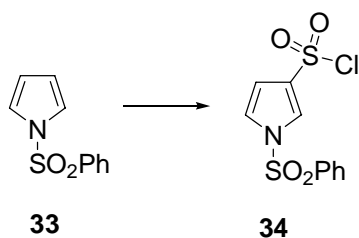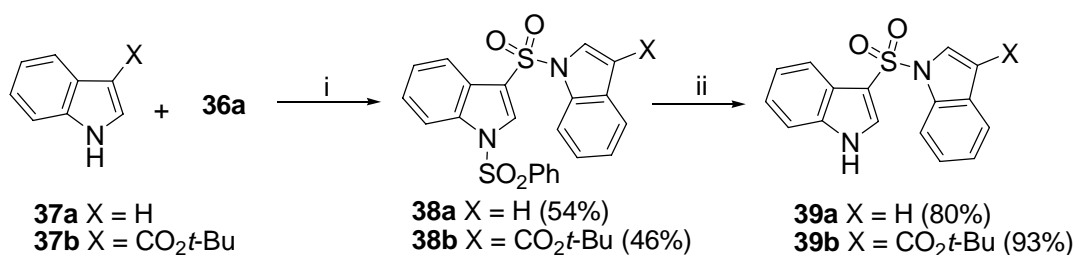

Scheme 14 *Reagents and conditions*: (i) HOSO$_2$Cl, CH$_3$CN, rt, 70–75.5 h, 46%.

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In analogy with the pyrrole, the indole derivatives **35a-b** were reacted with chlorosulfonic acid giving the desired 1-phenylsulfonyl-1*H*-indole-3-sulfonyl chlorides **36a-b**. With useful amounts of indolyl sulfonyl chlorides **35a-b** in hand, some experiments involving the reactivity and synthetic applicability of these compounds were undertaken. For example, 1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride was treated with imidazole in CH_2Cl_2, providing a clean conversion to a sulfonamide derivative.

35a R = H
35b R = 6-Br

36a R = H (79%)
36b R = 6-Br (88%)
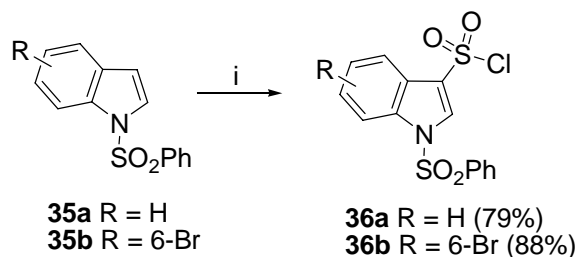
Scheme 15 *Reagents and conditions*: (i) $HOSO_2Cl$, CH_3CN, rt, 0 °C to rt, 66–75.5 h.

In a further extension, metalation of the indole derivatives **37a-b** with LDA, and subsequent treatment of the resulting lithioindoles with 1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (**36a**) gave the products **38a-b**. Removal of the protecting groups was performed under mild conditions by treatment with K_2CO_3 in order to avoid cleavage of the sulfonamide linkage between the two indole groups.

37a X = H
37b X = CO_2*t*-Bu

38a X = H (54%)
38b X = CO_2*t*-Bu (46%)

39a X = H (80%)
39b X = CO_2*t*-Bu (93%)

Scheme 16 *Reagents and conditions*: (i) LDA, THF, −78 °C to rt; (ii) K_2CO_3, MeOH, H_2O, rt, 22 h (for **39a**), or K_2CO_3, MeOH, THF, H_2O, rt, 30 min (for **39b**).

3.3 Synthetic approaches toward echinosulfone A (Papers I-III)

Indolic sulfones are also encountered in Nature, as illustrated by the isolation of the natural product echinosulfone A (**40**) from a Southern Australian marine sponge *Echinodictyum sp*.[54] The structure assigned to echinosulfone A displays several unusual

structural features, such as an unstable indole-1-carboxylic acid moiety and a sulfone bridge between the two indole units. The fact that only a few inefficient methods have been reported for the preparation of the heterocyclic core of echinosulfone A, i.e. the 3,3′-di(indolyl) sulfide (**41**), encouraged us to investigate new approaches.
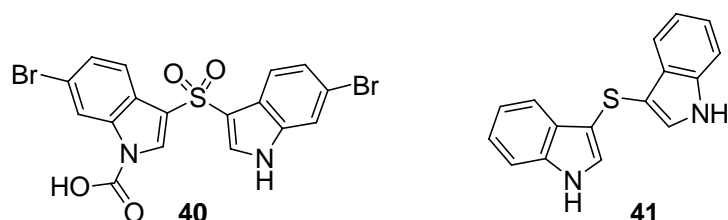

Figure 8

The first approaches toward the heterocyclic core of echinosulfone A, i.e. compounds **41** and **43**, has been reported by Madelung[55] and Oddo,[56] respectively, a long time ago. These reactions involved treatment of the indole Grignard reagent **42** with an excess of elemental sulfur or sulfuryl chloride (SO$_2$Cl$_2$). Both approaches have been reinvestigated in our laboratory, giving very low yields of the desired products after tedious work-up and purification. Furthermore, a Canadian group has investigated the reaction of indolylmagnesium bromide with ethanesulfenyl chloride, which gave a mixture of several compounds, including compound **43**.[57]
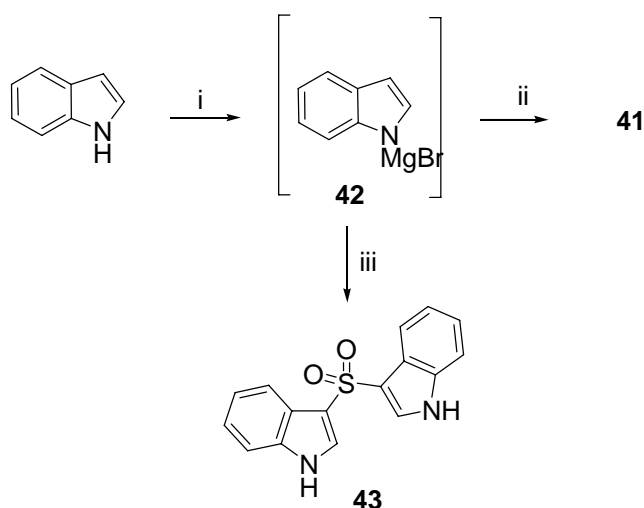
Scheme 17 *Reagents and conditions*: (i) EtMgBr, THF; (ii) S$_8$, 4 h; (iii) SO$_2$Cl$_2$, Et$_2$O, rt.

In our laboratory, the strategy for preparation of the heterocyclic core of echinosulfone A **41** involved treatment of a C-3 metalated indole with

bis(phenylsulfonyl) sulfide [$(PhSO_2)_2S$] as the sulfenylating reagent.[58-61] Hence, the readily available 3-bromo-1-(*tert*-butyldimetylsilyl)indole (**44**)[61,62] was subjected to halogen-metal exchange using *tert*-butyllithium at −78 °C, followed by treatment of the resulting 3-lithioindole derivative with 0.5 equivalents of $(SO_2Ph)_2S$. Desilylation of **45**, followed by *S*-oxidation using Oxone®, gave the target compound 3,3′-bis(indolyl) sulfone (**43**), i.e. the heterocyclic core of echinosulfone A.
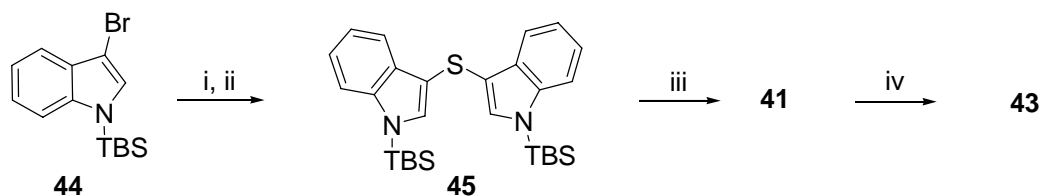
Scheme 18 *Reagents and conditions*: (i) *t*-BuLi, THF, −78 °C, 0.5 h; (ii) $(PhSO_2)_2S$, −78 °C to rt, 16 h, 57%; (iii) TBAF, THF, 0-5 °C 1 h; then rt, 20 min, 95%; (iv) Oxone®, acetone, H_2O, rt, 4 h, 70%.

Despite the fact that the method above is convenient, initial results suggested that a selective *N*-carboxylation of compound **41** is unfeasible. Therefore, an alternative route was attempted using the symmetrical disulfide **29a** as the electrophile. This provides a different approach towards selective *N*-carboxylation of compound **47** by removal of the phenylsulfonyl (SO_2Ph) group followed by carboxylation, and fluoride-induced deprotection of the *tert*-butyldimethylsilyl (TBS) group (Scheme 19). However, all attempts at *N*-carboxylation of **47** to **48** failed. This observation could be due to the fact that *N*-carboxylated indoles are sensitive and unstable,[20,63] thus also implying that the structure assigned for echinosulfone A (**40**) might be incorrect.
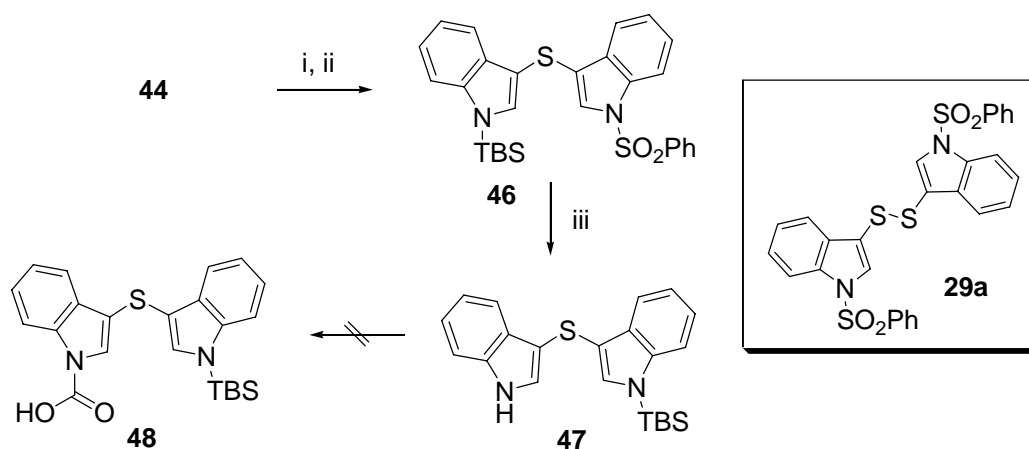
Scheme 19 *Reagents and conditions*: (i) *t*-BuLi, THF, −78 °C; (ii) **29a**, −78 °C to rt, 16 h, 47%; (iii) 1 M KOH (aq)-dioxane (1:1), 80 °C, 20 min, 46%.

Alternative interpretations of the spectral data presented in the literature suggested the isomers **49** and **50**. Hence, in order to confirm or disprove the structure given in the literature, some synthetic approaches toward these two compounds have been undertaken.
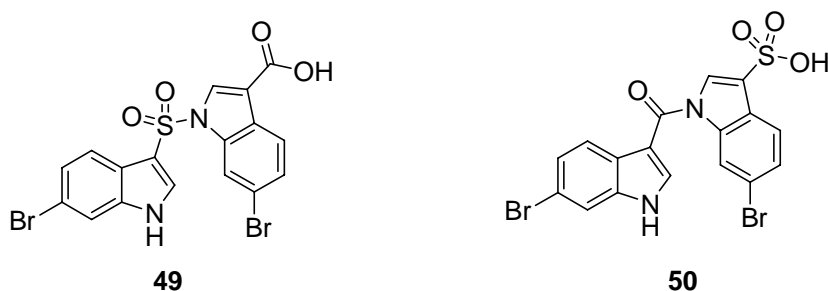

Figure 9

In principle, compound **49** can be prepared in analogy with the procedure presented in our previous work for synthesis of compounds **39a-b**. Following the same experimental procedure, *t*-butyl 6-bromoindole-3-carboxylate **51** was metalated with LDA, and thereafter treated with **36b** to provide the dimeric system **52**. Removal of the protecting group with K_2CO_3 followed by treatment with trifluoroacetic acid gave compound **53** (Scheme 20). Overall, this route proceeded in rather low yield, possibly due to a partial metalation of the indole at C-6 by a halogen-metal exchange. Therefore, aiming to improve the reaction yields, we were pleased to find that the reaction could be performed in anhydrous medium in the presence of NaOH and a phase transfer catalyst. The method proved beneficial, as the yield of **52** increased from 27% to 52% under these conditions.
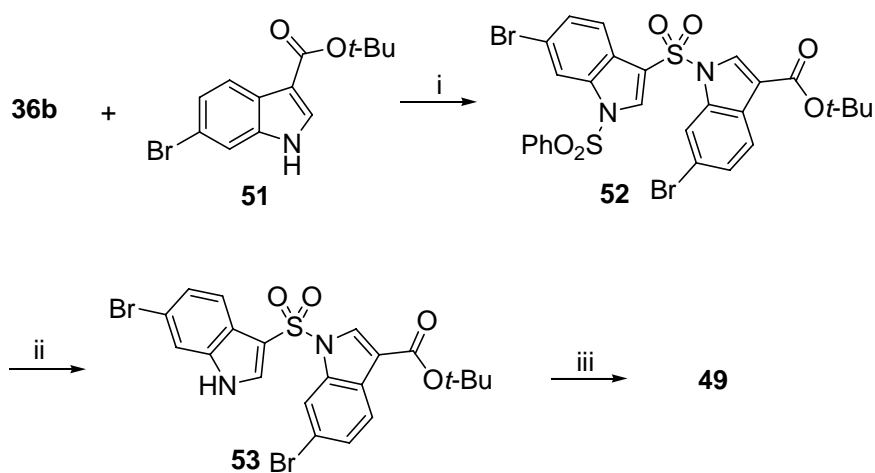
Scheme 20 *Reagents and conditions*: (i) *n*-Bu₄NHSO₄, NaOH, CH₂Cl₂, −20 °C, 45 min, 52%; (ii) K_2CO_3, MeOH, H_2O, rt, 16 h, 60%; (iii) TFA, CH₂Cl₂, rt, 48 h 73%.

Similar transformations were also used in an attempt to prepare the isomer **50**, a closely related derivative possessing a chlorosulfonyl group at the C-3 on one of the indole units. The 3-acylindole **54**[64] and 6-bromoindole were considered as precursors for the system **55**, and were connected either by metalation, or by using the phase transfer method as above. Again due to the low yield encountered during the metalation process, the phase transfer route was superior improving the yield from 31% to 62%. The sulfonation was then accomplished using chlorosulfonic acid in acetonitrile giving compound **56** in a good yield. However, attempts towards removal of the protecting group in a basic medium failed, leading only to cleavage of the carboxamide linkage of **56**.
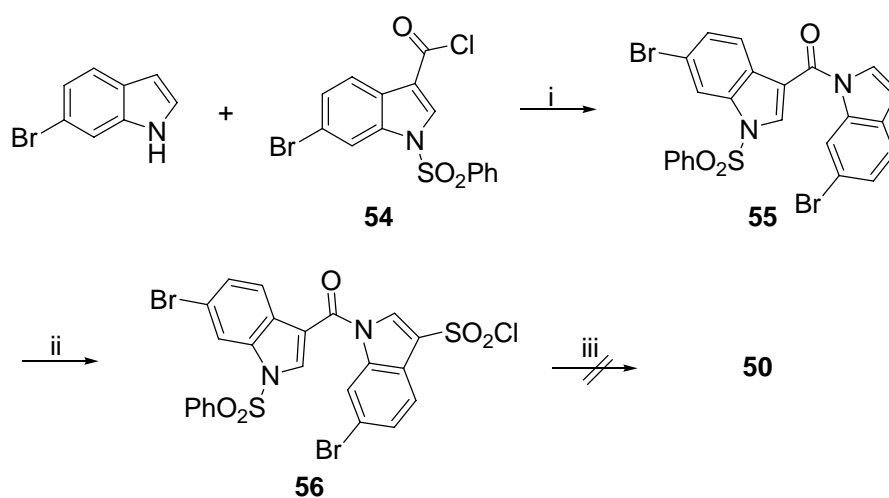
Scheme 21 *Reagents and conditions*: (i) n-Bu$_4$NHSO$_4$, NaOH, CH$_2$Cl$_2$, −20 ºC, 60 min, 62%; (ii) HOSO$_2$Cl, CH$_3$CN, rt, −20 °C to rt, 63 h, 81%; (iii) K$_2$CO$_3$, MeOH, H$_2$O, rt.

The structure of the isomer **49** was characterized by NMR and the results were compared with literature NMR data for echinosulfone A **40**.[54] The ^{13}C NMR data for echinosulfone A **40**, features a carboxylic carbon signal at δ 183.7 in DMSO-d_6, while compound **49** displayed a carbonyl resonance at δ 164.2 (See supplementary material, section 7). These results suggest that further detailed investigations will be needed to provide full insight in these reactions, and to confirm the structure of echinosulfone A.

4 Thiopyrano- and selenopyranodiindoles (Paper IV)

4.1 General introduction

There has been considerable interest in the chemistry and biology of extended fused indole systems. Among these are the indolocabazoles,[65,66] which are a class of pentacyclic aromatic systems based on an indole moiety fused with a carbazole unit. Many indolocarbazoles display interesting biological activities, and have therefore attracted considerable attention. For instance, the 6-formylindolo[3,2-*b*]carbazole (FICZ, **57**) has been demonstrated to be a powerful ligand for the aromatic hydrocarbon receptor (AhR), in fact somewhat more efficient than the environmental poison TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) (**58**).[67-69] In stark contrast to **58**, molecule **57** is quickly undergoing metabolism in biological systems. Very recently, the indolo[2,3-*b*]carbazole **59** has been shown to exhibit potent anticancer properties, demonstrating that even this type of indolocarbazoles display biological effects.[70]
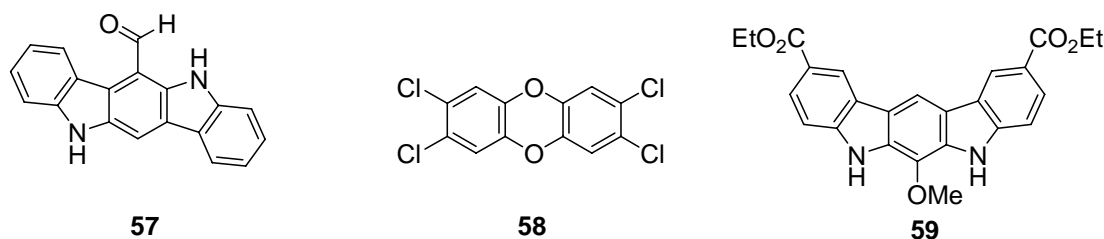

57 **58** **59**

Figure 10

Despite the tremendous amount of studies performed to date, there is relatively little known about the biological properties of indolocarbazole analogues, except for some studies devoted to indolocarbazole analogues incorporating additional heteroatoms. With this background, part of this work was focused on development of new approaches toward synthesis of sulfur analogues of several indolocarbazole isomers.

4.2 New approaches towards thiopyranodiindoles

An example of the thiopyranodiindole system has previously been observed as a product from condensation of the Vilsmeier salt with indoline-2-thione.[71,72] However, due to the need for a more general route, which would allow introduction of

substituents in the central ring, a new approach was devised based on cyclization of the precursor **60**. Consequently, compound **60** was prepared taking advantage of the Katritzky[20] protocol, followed by quenching of the resulting dianion **19** with $(PhSO_2)_2S$ for installation of a sulfur bridge between the two indole units (Scheme 22). Subsequent annulation of **60** with triethyl orthoformate, or triethyl orthoacetate in the presence of methanesulfonic acid gave the desired dark-red thiopyranodiindoles **61a-b**.

61a R = H 42%
61b R = Me 76%
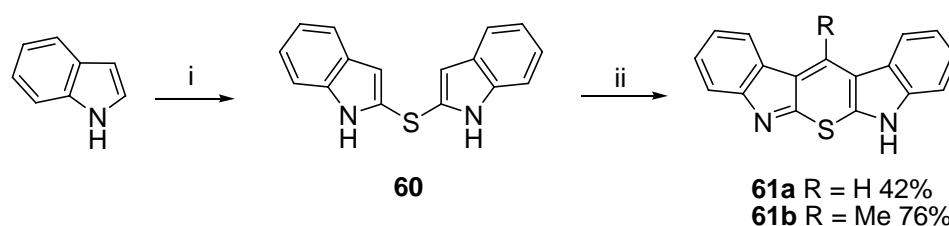
Scheme 22 *Reagents and conditions:* (i) BuLi, CO_2, *t*-BuLi, then $(SO_2Ph)_2S$, -78 °C to rt, 16 h, 63%; (ii) $HC(OEt)_3$, $MeSO_3H$, CH_3CN, rt, 4 days (for **61a**), $MeC(OEt)_3$, $MeSO_3H$, CH_3CN, rt, 4 days (for **62b**).

Furthermore, the di(indolyl) sulfide **60** proved to be a useful precursor for synthesis of additional related molecules, as treatment of **60** with acetone under acidic conditions afforded the dimethyl derivative **62**, while reaction with phosgene gave the keto derivative **63** (Scheme 23).


62

63
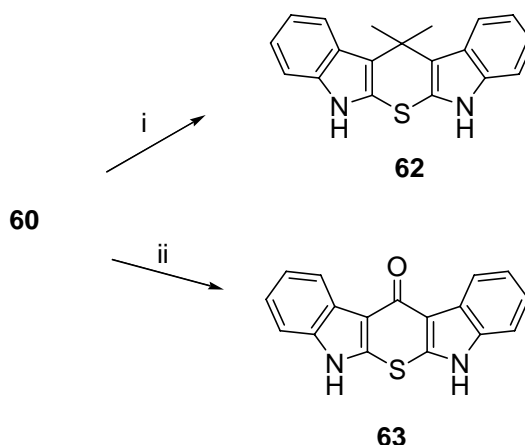
Scheme 23 *Reagents and conditions:* (i) Acetone, $MeSO_3H$, 1,4-dioxane, reflux, 2.5 h, 78%; (ii) $COCl_2$, 1,4-dioxane, rt, 24 h, 69%.

4.3 Annulation of 2,3'-di(indolyl) sulfide to thiopyranodiindole

The disulfide **29d** discussed earlier proved to be a versatile compound for related synthetic applications, as it could be used for construction of the di(indolyl) sulfide **31**, which in turn could be converted to the target system **64**. Based on previous

experiments, indole was lithiated at C-2, and reacted with the disulfide **29d** to give the mono-protected 2,3′-di(indolyl) sulfide **30b**. The protecting group was easily removed by treatment with aqueous potassium hydroxide in EtOH affording the key precursor **31**. Moreover, it was anticipated that attempted Boc-deprotection of the compound **30b** under standard conditions using TFA in CH_2Cl_2 could cause formation of a mixture of several products. Such behavior of 3-thioindoles has been noted previously.[73-75] Finally, a similar annulation reaction was performed using triethyl orthoformate, providing the thiopyranodiindole **64** in good yield. However, all attempts toward ring closure of **31** to **65** using triethyl orthoacetate failed (Scheme 24).
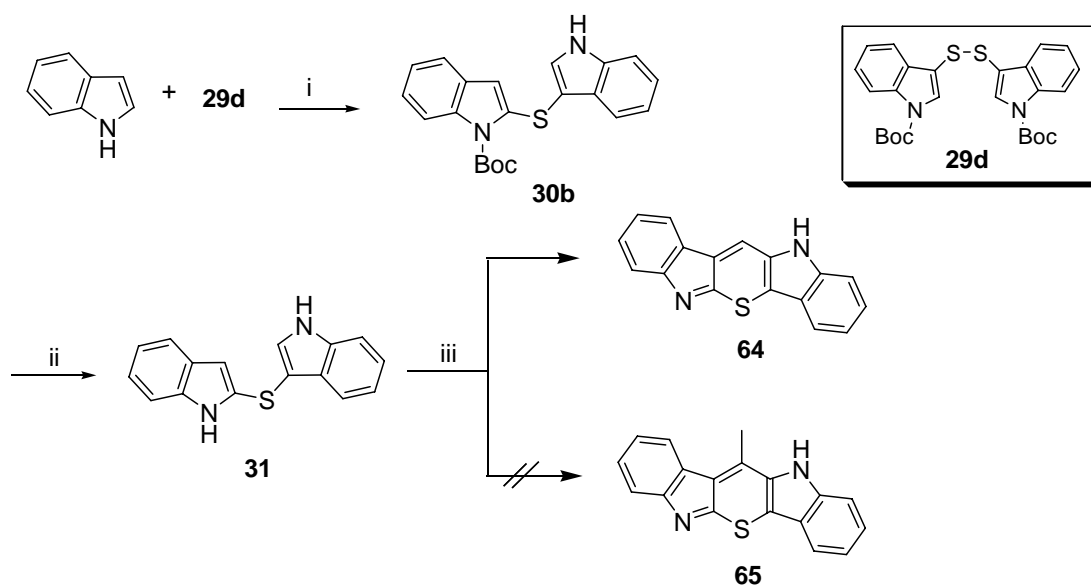
Scheme 24 *Reagents and conditions:* (i) BuLi, CO_2, *t*-BuLi, then **29d**, −78 °C to rt. 16 h, 81% (ii) KOH (1 M), EtOH, 90 °C, 30 min, 83%; (iii) HC(OEt)$_3$, MeSO$_3$H, CH$_3$CN, rt, 48 h, 66%.

4.4 Synthesis of related selenopyranodiindoles

Progressing further with our studies on thiopyranodiindoles, new attempts toward synthesis of related selenium-based ring systems were considered. Thus, in analogy with our previous approaches to thiopyronodiindoles **61-64**, the desired precursors **66a-b** were obtaied by lithiation of indole and 5-methoxyindole at C-2, and subsequent quenching with the electrophile bis(phenylsulfonyl) selenide [(SO$_2$Ph)$_2$Se] (See Section 5.3). Eventually, similar annulation reactions were performed by exposure of the selenides **66a-b** to triethyl orthoacetate or orthoformate, to produce the selenopyranodiindole derivatives **67a-d**.
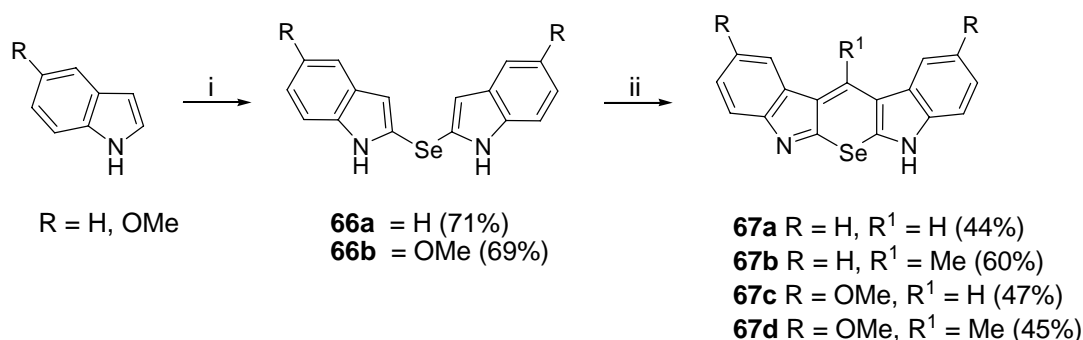
Scheme 25 *Reagents and conditions.* (i) BuLi, THF, CO$_2$, −78 °C, *t*-BuLi, then (PhSO$_2$)$_2$Se; (ii) HC(OEt)$_3$ or MeC(OEt)$_3$, MeSO$_3$H, 1,4-dioxane or CH$_3$CN.

4.5 Acylation of 2,3'-di(indolyl) sulfide

In addition, the 2,3′-di(indolyl) sulfide (**31**) was acylated by ethyl oxalyl chloride/pyridine[76] in THF or cyanoacetic acid in acetic anhydride[77] to produce the ester **68**, and the cyanoacetylated derivative **69**, respectively. However, attempts to convert these molecules to the corresponding thiopyanodiindole systems **70-71** in the presence of methanesulfonic acid in acetonitrile or 1,4-dioxane have so far been unsuccessful (Scheme 26).
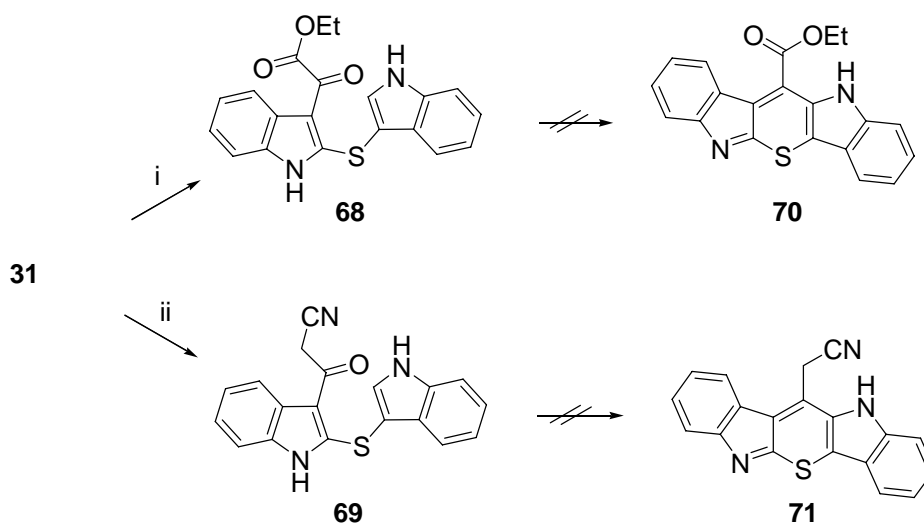
Scheme 26 *Reagents and conditions:* (i) Pyridine, ClCOCO$_2$Et, THF, 71%; (ii) Ac$_2$O, NCCH$_2$CO$_2$H, 80 °C, 5 min, 60%.

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4.6 AhR affinity of thio- and selenopyranodiindoles

Biological tests performed by Prof. Ulf Rannug's group have shown that **61a-b**, **65** and **67a-b** exhibit the highest affinity for the AhR receptor with capacities of 0.13-0.38 times compared to TCDD (**58**). Although 6-formylindolo[3,2-*b*]carbazole (FICZ, **57**) has previously been demonstrated to display much higher affinity (1.9 times),[78] these results bring forward a new and unexplored group of potent candidates displaying good qualities as AhR ligands.

5 Dibenzothiepins and related dibenzometallepins (Papers V-VII)

5.1 General introduction

The chemistry of thiepins[79-81] and related seven-membered heterocycles containing heavier elements than sulfur has received increasing attention in recent years, not only due to their pharmacological properties, but also in connection with theoretical studies. Generally, the theoretical aspects of these systems are linked with questions related to electron delocalization, and aromaticity. The fact that calculations show negative resonance energy, imply that these types of molecules are antiaromatic.[82] In this perspective, and in order to understand the nature of thiepins and related ring systems, much research has focused on synthesis and characterization of such compounds.

Many dibenzo[*b,f*]thiepins (**72**) have been found to exhibit a broad range of biological effects, mainly explored in the area of psychotropic diseases.[80] For instance, the thiepins zotepine (**73**) and isofloxythiepin (**74**)[80,83,84] have been shown to be potent neuroleptics, whereas the thiepin **75** is a prostaglandin antagonist.[85] Since the discovery of such properties, considerable efforts both regarding medicinal evaluation, as well as structural studies of these systems have emerged. Even though some of the routes have been implemented for preparation of certain target compounds, problems associated with complexity of starting materials and low overall yields still have to be overcome. Consequently, a part of this work has been focused on new synthetic approaches towards dibenzothiepins and 1-metallacycloheptatrienes (metallepins), intermediates in their syntheses, and reactions giving rise to new related systems.
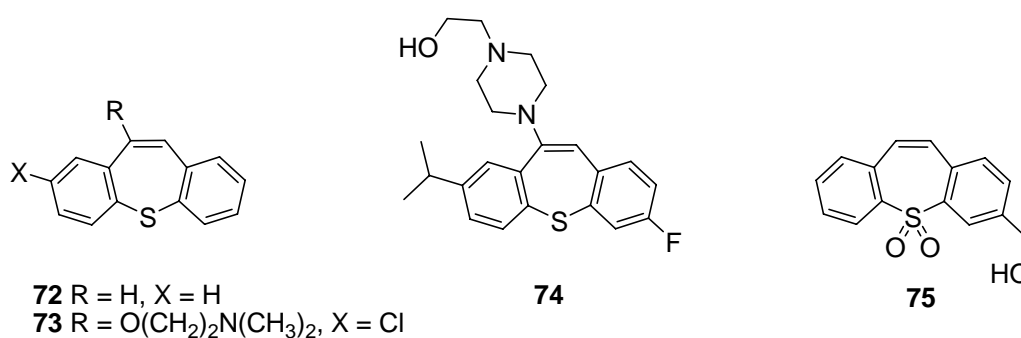

72 R = H, X = H
73 R = O(CH$_2$)$_2$N(CH$_3$)$_2$, X = Cl
74
75

**Figure 11**

5.2   Dibenzothiepins

5.2.1   Previous synthetic efforts

There are only a few synthetic approaches available toward thiepins, perhaps due to the fact that the sulfur containing seven-membered heterocycles are sensitive, and thermally unstable molecules.[79] The methods for preparation of rather stable fused thiepins, such as dibenzo[b,f]thiepins, fall into two categories, mainly based on ring expansion of 9-(hydroxymethyl)thioxanthene[86] or cyclization of substituted diaryl sulfides.[80] Accordingly, the parent system dibenzo[b,f]thiepin (**72**) was successfully obtained for the first time in late 1950s, employing a route involving an acid-induced ring expansion of 9-(hydroxymethyl)thioxanthene *p*-toluenesulfonate (**77**).[86] This alcohol was prepared by treatment of the readily available thioxanthene **76** with butyllithium, followed by condensation with formaldehyde. Finally, the *p*-toluenesulfonate of the the alcohol was reacted with boiling formic acid, resulting in formation of dibenzo[b,f]thiepin **72** *via* a rearrangement reaction (Scheme 27).
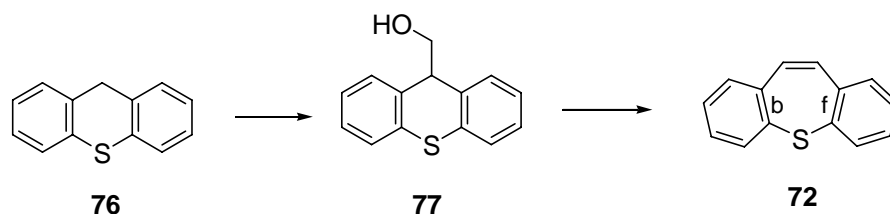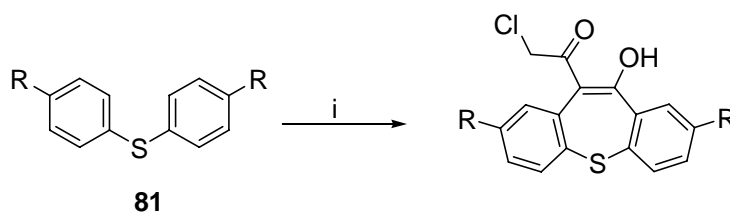

Scheme 27

There are several other synthetic protocols for construction of dibenzo[b,f]thiepin derivatives, based on Friedel-Crafts type intramolecular ring-closure of substituted diaryl disulfides.[87,88] One popular variation is acid-induced cyclization of 2-(2-arythiophenyl)acetic acids **78** and related derivatives, resulting in formation of 10,11-dihydrodibenzo[b,f]thiepin-10-one derivatives **79**.[81,89] These ketones are important intermediates for preparation of various dibenzo[b,f]thiepin derivatives, such as 10-alkoxy-, 10-amino-, and 10-thiodibenzo[b,f]thiepins **80** (Scheme 28).[80]
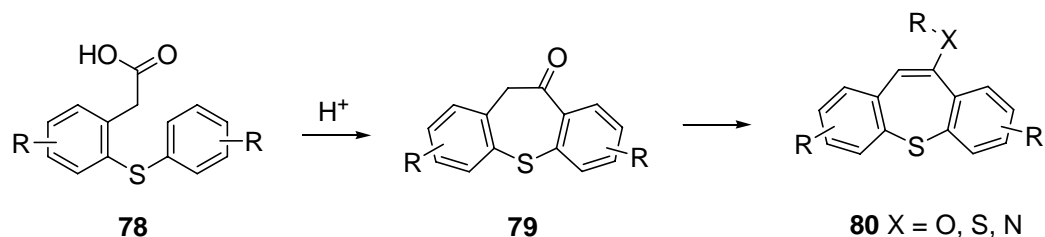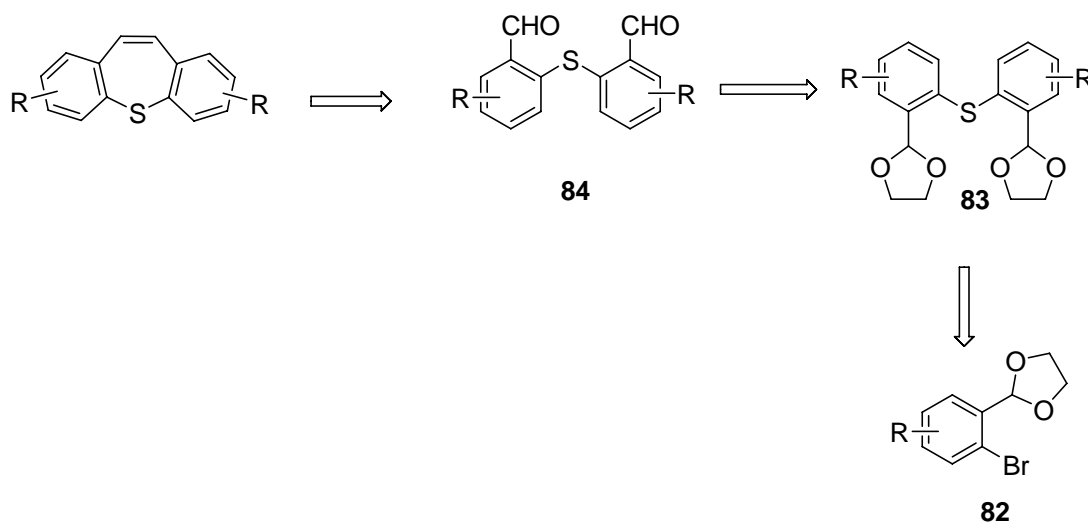

Scheme 28

28

An alternative strategy to obtain such systems, relies on the reaction of bis(4-halophenyl)sulfides **81** with chloroacetyl chloride and aluminium chloride in dichloromethane (Scheme 29).[88]

Scheme 29 *Reagents and conditions:* (i) ClCH$_2$COCl, AlCl$_3$, CH$_2$Cl$_2$.
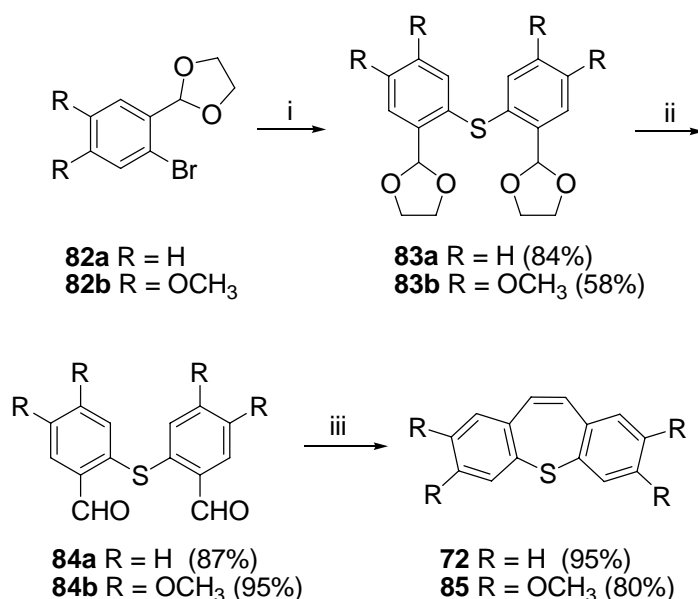
5.2.2   New approaches towards dibenzothiepins

A new approach toward the thiepin system was devised, based on intramolecular McMurry[90,91] type coupling of the intermediate bis(aryl)sulfide dialdehydes **84**, which would be available from the diacetals **83**. The potential starting materials **82** were considered as synthons for **83** (Scheme 30).

Scheme 30

It is known (Section 3.3) that reaction of metalated aromatics with bis(phenylsulfonyl) sulfide results in formation of bis(aryl) sulfides or equivalent structures.[58] Thus, it was expected that metalation[92,93] of the 2-bromobenzaldehyde acetal derivatives **82a-b**,[94,95] followed by treatment with bis(phenylsulfonyl) sulfide

[(SO$_2$Ph)$_2$S], would give the intermediates **83a-b**, which can easily be deacetalized to the dialdehydes **84a-b**. Consequently, these precursors **84a-b** were conveniently obtained *via* acetalization of the corresponding 2-bromobenzaldehydes. Thereafter, the acetals **82a**[96] and **82b**[93] were subjected to metal-halogen exchange using butyllithium, followed by treatment with bis(phenylsulfonyl) sulfide, resulting in the known dialdehyde acetals **83a-b**.[97,98] An acid-induced deacetalization of the corresponding diacetals **83a-b** resulted in the dialdehydes **84a-b**, which could serve as substrates in intramolecular McMurry coupling, yielding the parent dibenzo[*b,f*]thiepin **72** and its derivative **85**.[86]

82a R = H
82b R = OCH$_3$

83a R = H (84%)
83b R = OCH$_3$ (58%)

84a R = H (87%)
84b R = OCH$_3$ (95%)

72 R = H (95%)
85 R = OCH$_3$ (80%)

Scheme 31 *Reagents and conditions*: (i) BuLi, −78 °C, THF, 0.5 h; then (SO$_2$Ph)$_2$S, −78 °C to rt, 16 h; (ii) HClO$_4$, acetone, 1-2 h, rt; (iii) TiCl$_4$, Zn, pyridine, THF, reflux 2.5 h; then **84a-b**, rt 16 h, reflux 4 h; then K$_2$CO$_3$, rt 18 h.

The successful strategy used for synthesis of dibenzo[*b,f*]thiepins **72** and **85** encouraged us to apply this route to prepare a diindolothiepin. Hence, indole-3-carbaldehyde was protected using the phase-transfer method,[37,38] followed by acetalization under standard conditions to give 1-(phenylsulfonyl)indole-3-carbaldehyde ethylene acetal **86**.[99] Lithiation of **86** at C-2 with LDA, followed by treatment with bis(phenylsulfonyl) sulfide gave the diindolyl sulfide **87**. This intermediate was deacetalized in acidic media to the corresponding dialdehyde **88**, which was subsequently annulated by intramolecular coupling under McMurry conditions to **89**.[90] Furthermore, it was noted that attempted removal of the protecting group of **89** under basic condition resulted in degradation of the material. This could

be attributed to fact that the electron withdrawing properties of the phenylsulfonyl functionality balance the electron donating effects of the indole into the sensitive central thiepin. As mentioned above, thiepins are unstable molecules and it is known that several related derivatives can easily lose the heteroatoms even at relatively low temperatures.[79]
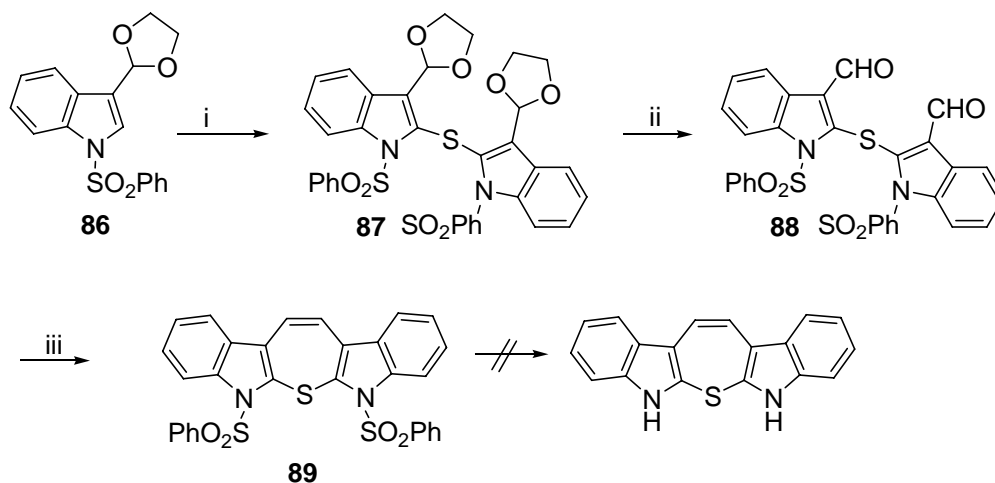
Scheme 32 *Reagents and conditions*: (i) LDA, −78 °C, THF, 0.5 h, then (SO$_2$Ph)$_2$S, −78 °C to rt, 16 h; 78%; (ii) aq. HClO$_4$, H$_2$O, 1,4-dioxane, rt, 8 h, 98%; (iii) TiCl$_4$, Zn, pyridine, THF, reflux 2.5 h; then **88**, rt 16 h, reflux 4 h; then K$_2$CO$_3$, rt 18 h, 79%.

In a further extension, 3-bromobenzo[*b*]thiophene-2-carboxaldehyde[100] was transformed to the known acetal **90**,[101] which was subjected to lithiation followed by treatment with bis(phenylsulfonyl) sulfide, giving the intermediate **91**. A similar strategy as for the other fused thiepnis **72**, **85** and **89** was applied, to provide the fused thiepin **93** (Scheme 33).
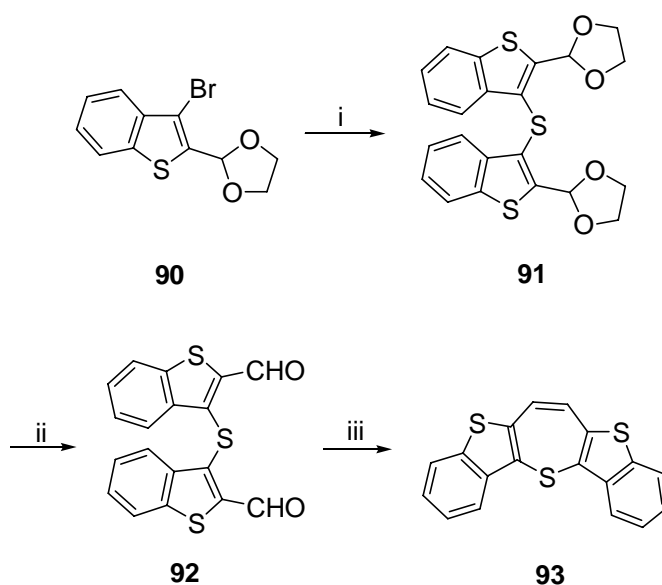
Scheme 33 *Reagents and conditions*: (i) BuLi, THF, −78 °C, 0.5 h; then (PhSO₂)₂S, −78 °C to rt, 16 h, 74%; (ii) aq. HClO₄, H₂O, acetone, rt, 24 h, 94%; (iii) TiCl₄, Zn, pyridine, THF, reflux, 2.5 h; then **92**, rt 16 h, reflux 4 h; then K₂CO₃, rt, 18 h, 86%.

5.3   1-Metallacycloheptatrienes

5.3.1   *Previous and new synthetic approaches*

Having established practical conditions for synthesis of fused thiepin systems, attention was turned to preparation of similar seven-membered heterocycles containing elements such as selenium, silicon and germanium (Figure 12). As for the thiepins, there are only a limited number of routes available to such molecules, and only a limited number of examples of such systems are known.
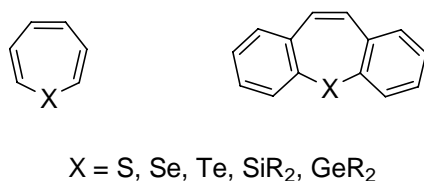

X = S, Se, Te, SiR₂, GeR₂

Figure 12

The first successful syntheses of C-unsubstituted 1-silacycloheptatriene **97a** and its analogues **97b** were described in the early 90s. This was accomplished by reaction of the silacyclohexadienyl anion **95** with CH₂Cl₂ in presence of an alkyllithium reagent, involving metal-mediated ring expansion of 1-sila- or germa-2,4-cyclohexadienes **94**

giving a bicyclic intermediate **96**, which finally isomerizes to the seven-membered heterocyclic system **97** (Scheme 34).[102,103]
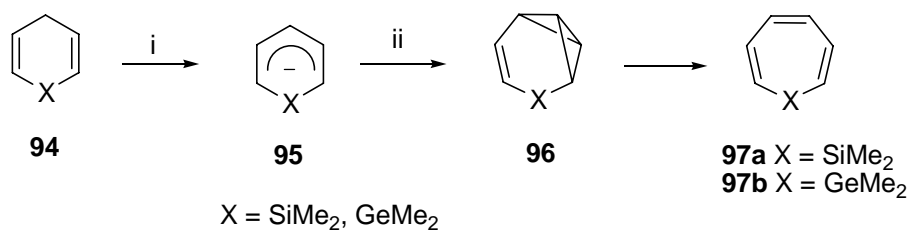
Scheme 34 *Reagents and conditions*: (i) BuLi, ether, 0 °C; (ii) BuLi, ether, −78 °C, then CH$_2$Cl$_2$.

There are several other reports describing synthesis and studies of the C-substituted cycloheptatrienes such as mono-, di- or tribenzo-metallacycloheptatriene derivatives.[104-113] A common way for construction of these systems involves treatment of the 2,2′-dilithiobibenzyl **98** with reagents such as R$_2$GeCl$_2$, R$_2$SiCl$_2$, SeCl$_4$ or TeCl$_4$, resulting in intramolecular ring closure to give dihydrometallepins **99a-b**. These can be converted to the desired dibenzometallepins **100** by various reductive processes (Scheme 35). [105-107]
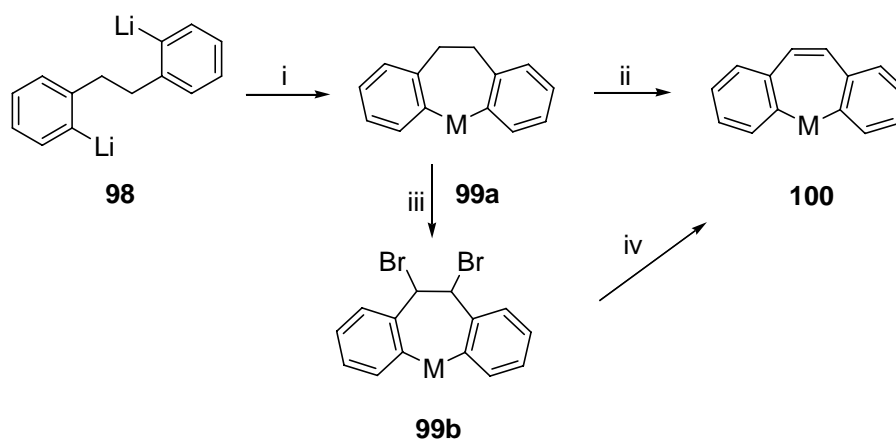
Scheme 35 *Reagents and conditions*: (i) R$_2$MCl$_2$; (ii) DDQ; (iii) NBS; (iv) Zn.

Despite all progress in synthesis of these types of compounds, there are still many aspects of their chemistry to explore. This background prompted us to initiate studies on the development of a feasible route to this type of heterocycles involving similar methodology for the dibenzo[*b,f*]thiepins (Section 5.2.2). This indicated that similar

dialdehydes, for example **101a-d** could be suitable intermediates for preparation of dibenzosilepin, and possibly an extended series of selenepin or germanepin analogues.
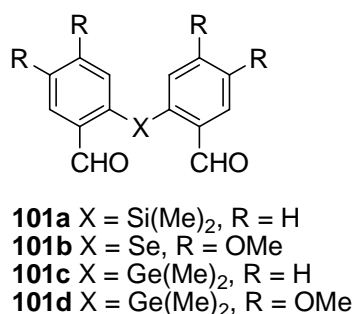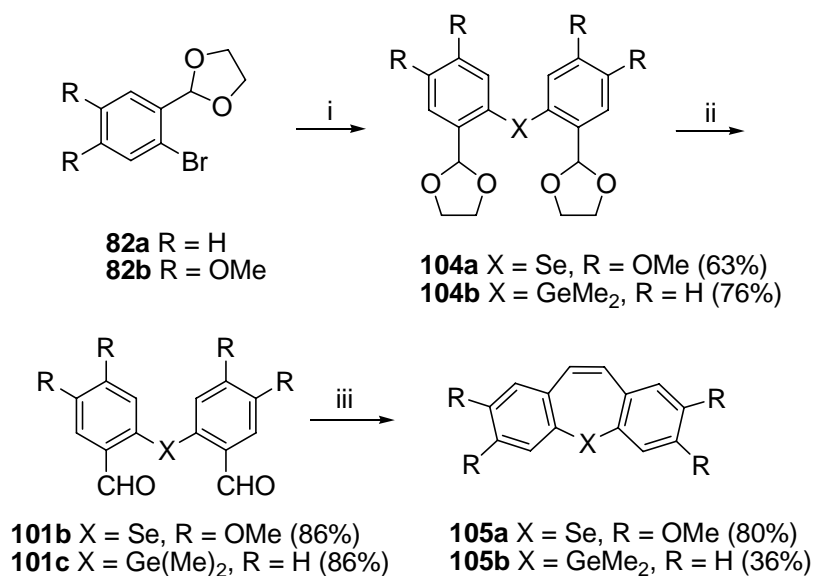

101a X = Si(Me)$_2$, R = H
101b X = Se, R = OMe
101c X = Ge(Me)$_2$, R = H
101d X = Ge(Me)$_2$, R = OMe

Figure 13

Our new approach towards synthesis of fused 1-metallacycloheptatrien-2,4,6-trienes derivatives was developed based on preparation of the dialdehydes **83a-b**. A crucial step for construction of these intermediates involves metalation of **82a-b** followed by treatment of the resulting organometallic intermediates with 0.5 equiv of reagents such as Me$_2$GeCl$_2$, Me$_2$SiCl$_2$ or bis(phenylsulfonyl) selenide [(SO$_2$Ph)$_2$Se] (**103**). Consequently, our initial approach for the synthesis of **101b** particularly, required development of a feasible procedure for preparation of (SO$_2$Ph)$_2$Se (**103**). As reported in the literature, this compound is generated by reaction of selenium oxychloride or selenium tetrachloride with sodium benzensulfinate.[114] In our laboratory we turned our attention to an alternative strategy for synthesis of (SO$_2$Ph)$_2$Se (**103**), involving treatment of sodium benzensulfinate (**102**) with selenium dichloride which can be generated by reaction of sulfuryl chloride with elemental selenium in THF (Scheme 36).[115] This route allowed the use of a more readily available, stable and inexpensive selenium source for synthesis of dialdehyde **101b**, necessary for construction of 1-selenacloheptatrien-2,4,6-trienes. The two other reagents, Me$_2$GeCl$_2$ and Me$_2$SiCl$_2$, necessary for synthesis of our planned metallepins, are commercially available.
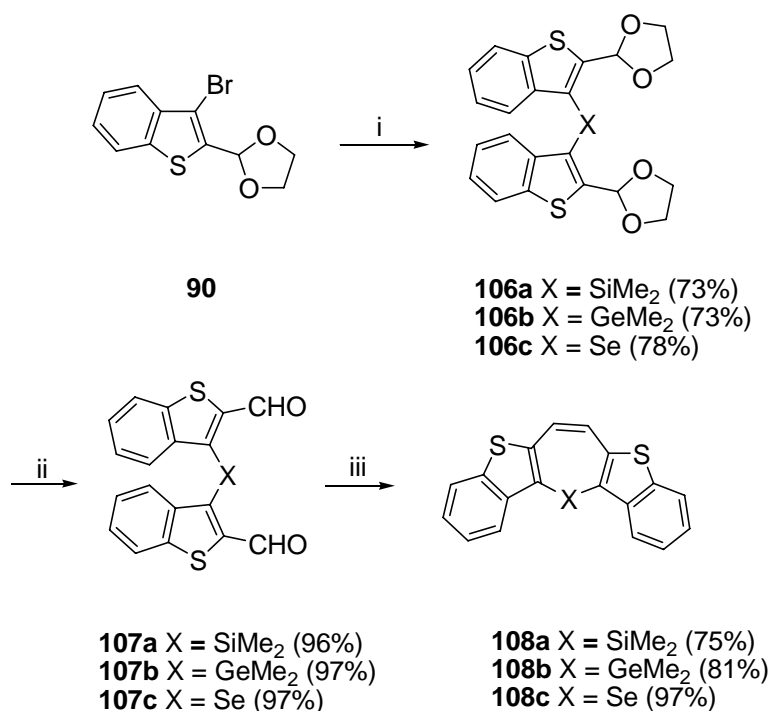

102   **103**
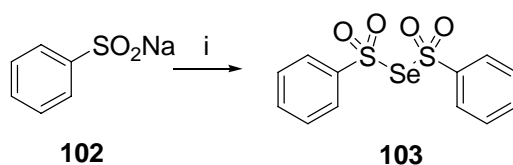
Scheme 36 *Reagents and conditions*: (i) SeCl$_2$, benzene, rt, 19 h, 54%.

Next, experiments involving preparation of new dialdehydes for their applicability as precursors in the synthesis of the planned metallepin derivatives were investigated. Hence, as described previously, the aldehydes were prepared by metalation[92] of **82a-b**, followed by treatment with appropriate reagents to give the diacetals **104a-b**. These subsequently were subjected to acid-induced deacetalization affording dialdehydes **101b-c**, which were finally annulated to the dibenzo[*b,f*]metallepins **105a-b** (Scheme 37). It was also noted that the final annulation of electron-rich aldehyde such as **101a** was not feasible, and the corresponding aldehyde **101c** gives only a modest yield of the germanepin **105b** (36%). This could be attributed to the sensitivity of these types of compounds, as it has been demonstrated that the parent system **97b** (Scheme 34) undergoes easy thermolysis at 80 °C to benzene and dimethylgermylene.[113]

82a R = H
82b R = OMe

104a X = Se, R = OMe (63%)
104b X = GeMe$_2$, R = H (76%)

101b X = Se, R = OMe (86%)
101c X = Ge(Me)$_2$, R = H (86%)

105a X = Se, R = OMe (80%)
105b X = GeMe$_2$, R = H (36%)

Scheme 37 *Reagents and conditions*: (i) BuLi, THF, −78 °C, 0.5 h; then (SO$_2$Ph)$_2$Se (for **104a**) or Me$_2$GeCl$_2$ (for **104b**), −78 °C to rt, 16 h; (ii) aq. HClO$_4$, 1,4-dioxane, 3-16 h, rt; (iii) TiCl$_4$, Zn, pyridine, THF, reflux 2.5 h; then **101b-c**, rt 16 h, reflux 4 h; then K$_2$CO$_3$, rt 18 h.

Furthermore, in an application of this strategy involving the acetal **90** (Scheme 33) a series of benzo[*b*]thiophene-fused metallacyclohepta-2,4,6-trienes **108a-c** were also prepared (Scheme 38).

90

106a X = SiMe$_2$ (73%)
106b X = GeMe$_2$ (73%)
106c X = Se (78%)

107a X = SiMe$_2$ (96%)
107b X = GeMe$_2$ (97%)
107c X = Se (97%)

108a X = SiMe$_2$ (75%)
108b X = GeMe$_2$ (81%)
108c X = Se (97%)

Scheme 38 *Reagents and conditions*: (i) BuLi, THF, −78 °C, 0.5 h; then Me$_2$GeCl$_2$/ /Me$_2$GeCl$_2$/(SO$_2$Ph)$_2$Se, −78 °C to rt, 16 h; (ii) aq. HClO$_4$, 1,4-dioxane, 3-16 h, rt; (iii) TiCl$_4$, Zn, pyridine, THF, reflux 2.5 h; then **107a-c**, rt 16 h, reflux 4 h; then K$_2$CO$_3$, rt, 18 h.

5.4   Unsymmetrical thiepins and selenepins

Earlier in this thesis, it has been shown that the S-S linkage in disulfides is a useful feature for transfer of sulfur-containing fragments. Based on the concept in our previous studies, it was anticipated that the bis(*o*-formylphenyl) diselenide/disulfide acetals **109** and **110** may also give an alternative access to new interesting scaffolds, for instance unsymmetrical thiepins or related system. These compounds can be easily cleaved by metallated species to provide unsymmetrical diacetals, which can be subjected to McMurry couplings upon deacetalization to give novel systems of unsymmetrical fused seven-membered ring heterocycles (Scheme 39).
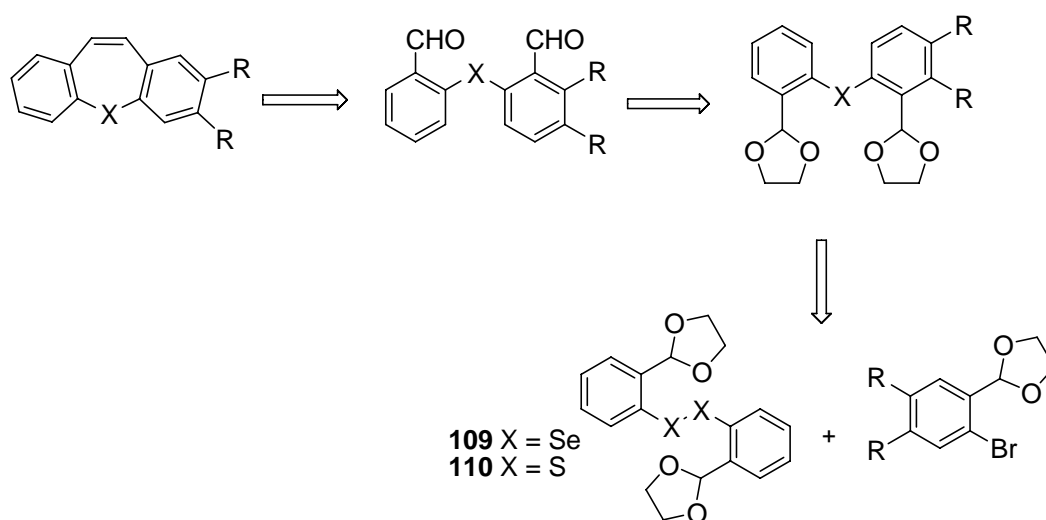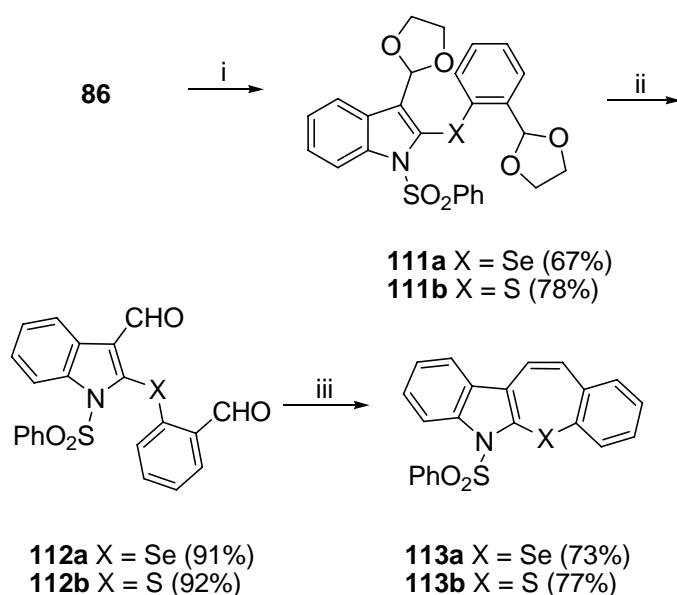
Scheme 39

The only available synthetic approach to compound **109** is based on treatment of metallated 2-bromobenzaldehyde acetal (**82a**) using BuLi, followed by introduction of elemental selenium.[116] This method gives only a low yield (20%), possibly due to the alkylation of starting material. Consequently, in order to improve the yield, compounds **109-110** were prepared by a modification of the literature procedure simply by changing the solvent from THF to ether, followed by an oxidative workup. This improved the yield to 33%, which is still rather low, but useful considering the availablity and low cost of the starting materials.
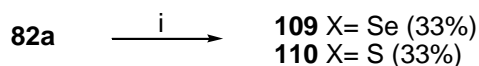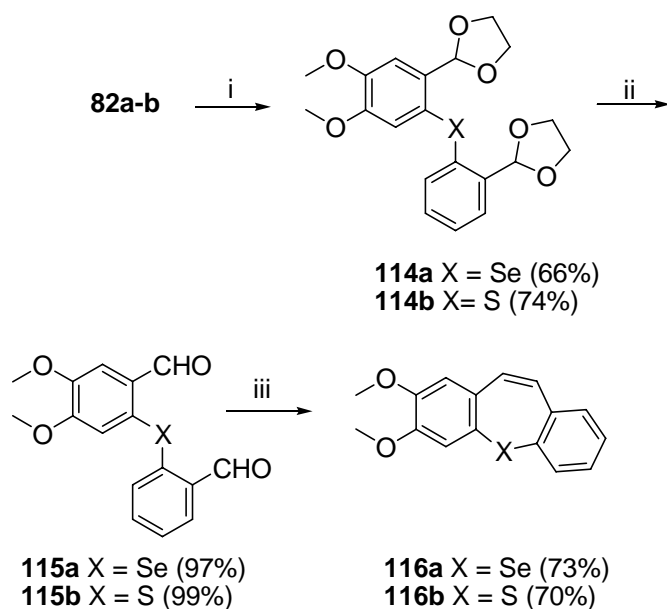

Scheme 40 *Reagents and conditions*: (i) BuLi, −78 °C, THF, 1 h, then S_8 or Se, −78 °C to rt, 16 h.

With useful amounts of the bis(*o*-formylphenyl) diselenide acetal (**109**) and the corresponding disulfide (**110**) in hand, experiments toward synthesis of new unsymmetrical thiepin and selenepin containing an indole moiety were undertaken. Thus, it was envisaged that treatment of the masked indole-3-carbaldehyde **86** with LDA, followed by the diselenide **109** or disulfide **110**, would result in the intermediates **111a-b**. As expected, these diacetals **111a-b** could be easily converted to dialdehydes **112a-b** in an acidic medium, which when finally subjected to McMurry coupling, affording the targets unsymmetrical thiepin and selenepin **113a-b**.

111a X = Se (67%)
111b X = S (78%)

112a X = Se (91%)
112b X = S (92%)

113a X = Se (73%)
113b X = S (77%)

Scheme 41 *Reagents and conditions*: (i) LDA, −78 °C, THF, 0.5 h, then **109** or **110**, −78 °C to rt, 16 h; (ii) aq. HClO₄, H₂O, acetone, 4 h, rt (iii) TiCl₄, Zn, pyridine, THF, reflux 2.5 h; then **112a-b**, rt 16 h, reflux 4 h; then K₂CO₃, rt 18 h.

Furthermore, lithiation of the acetal **82a-b** followed by treatment with the bis(*o*-formylphenyl) disulfide/diselenide acetals **109** and **110**, provided the unsymmetrical diacetals **114a-b**.[117] Likewise, these compounds were converted to the corresponding heterocycles **116a-b** in good yields.

114a X = Se (66%)
114b X= S (74%)

115a X = Se (97%)
115b X = S (99%)

116a X = Se (73%)
116b X = S (70%)

Scheme 42 *Reagents and conditions***:** (i) BuLi, −78 °C, THF, 1 h, then **109** or **110**, −78 °C to rt, 16 h; (ii) aq. HClO₄, H₂O, acetone, rt, 5 h; (iii) TiCl₄, Zn, pyridine, THF, reflux 2.5 h; then **115a** or **115b**, rt 16 h, reflux 4 h; then K₂CO₃, rt 18 h.

6 Acknowledgements

7   Supplementary material

General methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (300 MHz) using the residual solvent signal as reference. All IR spectra were performed on an Avatar 330 FT-IR instrument (Thermo Nicolet). Chemicals and solvents were obtained from commercial sources and used as received, except THF, which was distilled from sodium and benzophenone. Thin-layer chromatography (TLC) was performed with aluminum plates coated with silica gel and chromatography was performed using silica gel (40–63 μm).
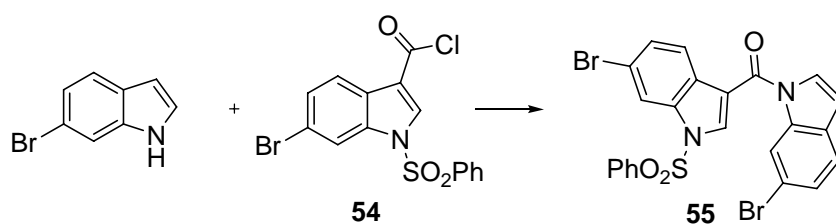
Compound 55. 3-Acylindole **54** was prepared according to literature procedure starting with 6-bromo-1-phenylsulfonyl-1*H*-indole (**36b**) (500 mg, 1.5 mmol) and used without further purification.[64] This was added as a solution in dry CH_2Cl_2 (15 mL) to a suspension of powdered NaOH (80 mg, 2 mmol), 6-bromoindole (**35b**) (1.5 mmol) and Bu$_4$NHSO$_4$ (30 mg) in dry CH_2Cl_2 (15 mL), at −20 ℃. The resulting mixture was stirred at −20 ℃ for 1 h, and H_2O (20 mL) was added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic phases were washed with water (2×20 mL), brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvents, followed by purification of the residue by silica gel column chromatography [*n*-hexane/EtOAc (6:1→3:1) gave compound **55** as white crystals; yield: 520 mg (62%). IR (neat) 1695, 1684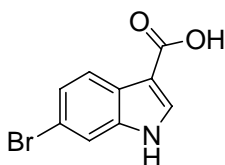, 1537, 1528, 1448, 1426, 1374, 1332, 1200, 1183, 1170, 1148, 1095, 1087, 1043, 969, 877, 844, 807, 756, 749, 719 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.57 (s, 1H), 8.49 (d, J = 1.7 Hz, 1H), 8.23-8.20 (m, 2H), 8.14 (d, J = 1.7 Hz, 1H), 7.96 (d, J = 3.8 Hz, 1H), 7.86-7.49 (m, 7H), 6.86 (d, J = 3.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 162.1, 136.2, 136.0, 135.6, 134.4, 133.0, 130.3, 129.8, 129.2, 127.9, 127.5, 127.5, 126.7, 123.4, 122.8, 118.7, 118.3, 117.1, 115.6, 114.5, 108.2.
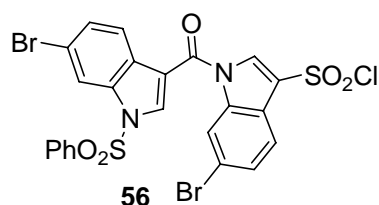
Compound 56. Chlorosulfonic acid (4.0 mmol) was added to a suspension of compound **55** (100 mg, 0.84 mmol) in dry CH_3CN (6 mL) at −20 ºC. The suspension was allowed to reach rt during 3 h and was thereafter stirred at rt for 60 h. The resulting mixture was poured into ice/water (~ 10 g) and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (2×20 mL), water (2×20 mL), brine (20 ml) and dried over $MgSO_4$. Evaporation of the solvents, followed by treatment of the residue with ether gave compound **56** as an off white solid; yield: 96 mg (81%). IR (neat) 1512, 1449, 1418, 1391, 1376, 1164, 1141, 1089, 982, 960, 851, 835, 822, 810, 730 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.58 (d, J = 1.3 Hz, 1H), 8.31 (d, J = 1.3 Hz, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 8.04-8.02 (m, 2H), 7.95 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.76-7.52 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 160.8, 136.4, 135.9, 135.0, 135.0, 131.7, 130.9, 129.8, 129.3, 128.5, 126.8, 126.1, 124.7, 122.3, 122.1, 121.0, 120.7, 120.4, 119.0, 116.5, 113.3.

6-Bromo-1H-indole-3-corboxylic Acid. TFAA (6 mmol) was added dropwise to a solution of 6-bromoindole (1.0 g, 5.1 mmol) in dry DMF (8 mL) at 0 °C and stirred for 3 h. The mixture was poured into water (10 mL) and the product was isolated by filtration and the residue was washed with water (3×20 mL). This was thereafter suspended in 20% aqueous NaOH (30 mL) and heated at reflux overnight. The mixture was cooled, washed with CH_2Cl_2 (3×20 mL), acidified (pH ~ 5) and the product was collected by filtration as light yellow solid; yield 600 mg (49%). IR (neat) 3304, 1640, 1527, 1450, 1414, 1349, 1333, 1306, 1226, 1181, 1132, 1113, 1039, 928, 894, 837, 804, 791, 773 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.92 (s, 1H), 8.02 (d, J = 2.9 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.29 (dd, J = 8.5, 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 165.5, 137.3, 133.1, 125.0, 123.9, 122.3, 114.8, 114.8, 107.6.
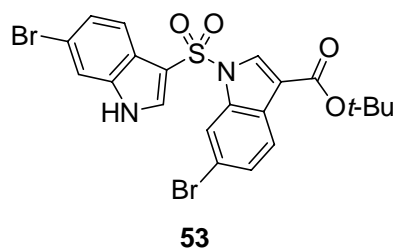
51
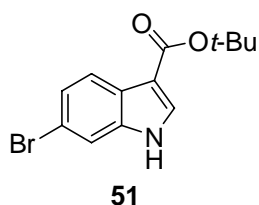
tert-Butyl 6-bromo-1*H*-indole-3-carboxylate (51). *tert*-Butyl 6-bromo-1*H*-indole-3-carboxylate (**51**) was prepared in analogy with the procedure presented in paper III, starting with 6-bromo-1*H*-indole-3-carboxylic acid (**A**) (480 g, 2.0 mmol), oxalyl chloride (6 mmol), a catalytic amount of DMF and potassium *tert*-butoxide (3.2 mmol). Purification by column chromatography using *n*-heptane/EtOAc (5:1) gave compound **51** as a white solid; yield 460 mg (78%). IR (neat) 3324, 1669, 1524, 1450, 1421, 1362, 1294, 1257, 1233, 1164, 1128, 1107, 1042, 1026, 892, 835, 793 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.51 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.57 (m, 1H), 7.36 (dd, J = 8.6, 1.7 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (CDCl$_3$) δ 163.8, 136.4, 130.6, 124.7, 124.2, 122.5, 117.0, 116.1, 113.9, 80.0, 28.1.

52
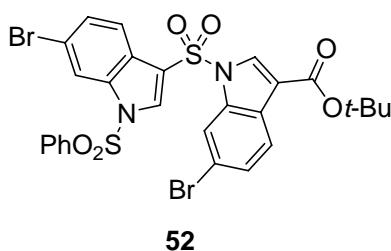
tert-Butyl-6-bromo-1-[1-(4-methyl-sulfonyl)-6-bromo-1*H*-indole-3-sulfonyl]-6-bromo-1-*H*-indole-3-carboxylate (52). Compound **52** was prepared in analogy with the procedure presented for compound **55**, starting with *t*-butyl-6-bromo-1*H*-indole-3-corboxylate (**51**) (240 mg, 0.81 mmol), 6-bromo-1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (**36b**) (350 mg, 0.81 mmol), NaOH (80 mg, 1.3 mmol), and Bu$_4$NHSO$_4$ (20 mg) at −20 ºC. The resulting mixture was stirred at −20 ºC for 45 min, and H$_2$O (20 mL) was added. The layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (15 mL). The combined organic phases were washed with water (2×20 mL), brine (20 ml) and dried over MgSO$_4$. Evaporation of the solvents, followed by purification of the residue by silica gel column chromatography [*n*-hexane/EtOAc (6:1→3:1) gave compound **52** as white crystals; yield: 29 mg (52%). IR (neat) 1708, 1383, 1188, 1166, 1157, 1133, 1119, 1089, 1066, 1051, 968, 947, 817, 794, 743, 722 cm^{-1}; ^{1}H NMR (DMSO-*d$_6$*) δ 9.63 (s, 1H), 8.52 (s, 1H), 8.33 (d, J = 1.6 Hz, 1H), 8.22-

8.19 (m, 2H), 8.12 (d, J = 1.6 Hz, 1H), 7.86-7.54 (m, 7H), 1.54 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 161.6, 135.9, 135.5, 135.2, 134.5, 134.2, 132.4, 130.2, 128.9, 127.9, 127.4, 126.1, 123.4, 122.5, 121.3, 120.0, 118.6, 116.6, 116.3, 115.7, 114.2, 81.4, 27.9.


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tert-Butyl 6-bromo-1-(1_H_-indole-3-sulfonyl)-6-bromo-1-_H_-indole-3-carboxylate (53). Compound **53** was prepared in analogy with the procedure presented in paper III, starting with compound (**52**) (100 mg, 0.15 mmol), K$_2$CO$_3$ (80 mg, 0.6 mmol). Purification by column chromatography using _n_-heptane/EtOAc (6:1→4:1) gave compound **53** as a white solid; yield 50 mg (60%). IR (neat) 1681, 1367, 1265, 1200, 1152, 1131, 1066, 1017, 964, 839, 812, 704 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 8.95 (s, 1H), 8.27 (s, 1H), 8.13-7.94 (m, 3H), 7.78-740 (m, 4H), 1.62 (s, 9H); ^{13}C NMR (CDCl$_3$) δ 162.3, 136.1, 134.7, 131.5, 130.6, 127.0, 126.5, 126.4, 123.0, 121.2, 120.1, 118.3, 118.1, 115.7, 114.9, 114.2, 113.0, 81.2, 27.9.

49
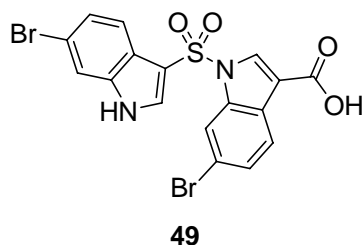
tert-Butyl 6-bromo-1-(1_H_-indole-3-sulfonyl)-6-bromo-1-_H_-indole-3-corboxylic Acid (49). TFA (0.1 mL) was added to a solution of compound **53** (63 mg, 0.11 mmol) in dry CH$_2$Cl$_2$ (10 mL) and the solution was stirred at rt for 48 h. The solvent was evaporated and the residue was subjected to column chromatography using CH$_2$Cl$_2$/MeOH (5%) giving the product as a white solid; yield (40 mg, 73%). IR (neat) 1680, 1545, 1377, 1199, 1132, 1067, 1055, 1015, 818, 801, 708 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.94 (s, 1H), 8.82 (s, 1H), 8.43 (s, 1H), 8.12 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 5.5 Hz, 1H), 7.70 (s, 1H), 7.51-7.40 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 164.2, 137.2, 135.3, 134.4, 132.2, 127.3, 126.7, 125.8, 123.5, 121.5, 119.9, 117.9, 116.6, 116.1, 115.6, 112.9, 109.4.

68
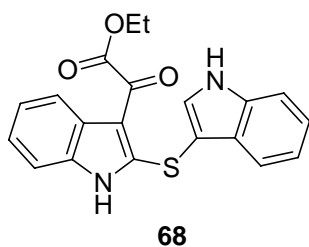
Compound 68. Compound 68 prepared according to the literature procedure[76] starting with ethyl oxalyl chloride (0.75 mmol) which was added dropwise during 10 min to a solution of 2,3′-diindolylsulfide (**31**) (130 mg; 0.5 mmol) and pyridine (0.75 mmol) in THF (5 mL) at 0 ℃. The temperature was raised to 21 ℃ and the mixture stirred for 5 h. EtOAc (10 mL) was added and the mixture was washed with 2 M HCl (5 mL), sat. NaHCO$_3$ (5 mL), then water (10 mL), brine (10 mL), and finally dried over Na$_2$CO$_3$. Evaporation under reduce pressure gave yellow solid which was crystyllized from CH$_2$Cl$_2$/heptane to give light yellow crystals. Yield (130 mg, 71%), IR (neat) 3115, 1723, 1610, 1468, 1441, 1428, 1345, 1337, 1263, 1236, 1201, 1100, 1008, 962, 758, 739 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.93 (s, 1H), 11.33 (s, 1H), 7.94 (d, J = 2.8 Hz, 1H), 7.61-7.53 (m, 2H), 7.43 (d, J = 7.8 Hz, 1H), 7.29-7.07 (m, 5H), 4.47 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 179.6, 166.0, 149.1, 136.8, 136.7, 133.6, 128.5, 126.0, 122.7, 122.3, 122.3, 120.5, 118.2, 117.8, 112.5, 112.0, 108.4, 94.8, 61.8, 13.8.

69
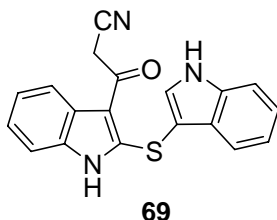
Compound 69. A mixture of 2,3′-diindolylsulfide (**31**) (200 mg; 0.75 mmol), cyanoacetic acid (1.3 mmol) and Ac$_2$O (5 mL) was heated to 80 ˚C for 5 min and allowed to cool. The product started to crystallize at 40˚C and was collected by filtration and washed with EtOH to give compound **69** as an off white solid; yield (0.15 g, 60 %). IR (neat) 3311, 1613, 1468, 1436, 1394, 1214, 943, 809, 753, 741, 732 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.81 (s, 1H), 11.45 (s, 1H), 7.79-7.76 (m, 1H), 7.62-763 (m, 1H), 7.43-7.36 (m, 2H), 7.25-7.07 (m, 4H), 6.98 (s, 1H), 4.69 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 181.9, 148.0, 137.0, 136.5, 133.6, 128.8, 125.9, 122.3, 121.8, 121.7, 120.4, 119.1, 118.0, 116.2, 112.5, 111.9, 110.8, 95.3, 32.3.

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