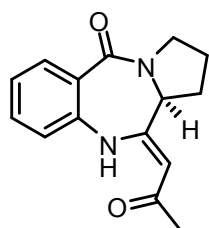


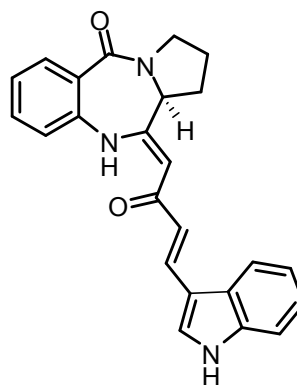


Synthetic studies towards 7- and 8-membered *N*-heterocycles, particularly 1,4-Pyrrolobenzodiazepines

Total synthesis of Fuligocandin A and B



Fuligocandin A



Fuligocandin B

Karolinska Institutet, Stockholm, Sweden

**Synthetic studies towards
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Total synthesis of Fuligocandin A and B



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ABTRACT

This dissertation is concerned with the synthesis of 7- and 8-membered *N*-heterocycles, particularly 1,4-pyrrolobenzodiazepines. A non-chromatographic method for conversion of carbonyl-functionalities to the corresponding thiocarbonyls is described.

A formal total synthesis of the pyrrolobenzodiazepine natural product DC-81 was developed starting from vanillin. The tricyclic core structure was successfully obtained in 6 steps and several approaches for transformation of this key diamide to obtain the target molecule DC-81 was investigated.

A convergent and concise synthesis of the pyrrolobenzodiazepine natural products fuligocandin A and B was developed employing Eschenmoser sulfide contraction as a key step. Fuligocandin B could be obtained in optically active form and the method was applied to obtain a number of vinyllogous amides.

The thionating power of a reagent obtained from P₄S₁₀ and pyridine was investigated and the actual structure of the crystalline reagent could for the first time be conclusively determined and confirmed by X-ray crystallography. A range of carbonyl compounds have been converted to the corresponding thiocarbonyl derivatives without the need for chromatographic purification.

The final part of this thesis features synthetic studies towards 7- and 8-membered heterocycles starting from anthranilnitrile. Accordingly, addition of Grignard reagents to *N*-acylderivatives of anthranilnitrile resulted in the formation of 1,4-benzodiazepin-3-ones and the method was also applied to obtain the higher homologue 1,5-benzodiazocin-4-one. Furthermore, the imino-intermediates initially formed by reaction of anthranilnitrile and Grignard reagents could be transformed to dibenzo-1,5-diazocines. Thus, an unusual bridged *N*-heterocycle was isolated and its structure was confirmed by X-ray crystallography.

Keywords: 1,4-Pyrrolobenzodiazepines, DC-81, 1,4-benzodiazepin-3-one, 1,5-benzodiazepin-4-one, dibenzo[b,f][1,5]-diazocine, fuligocandin, Eschenmoser sulfide contraction, alkaloid, total synthesis, vinyllogous amides, TRAIL, thionation reagent, Lawesson's reagent, thioamide.

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LIST OF PAPERS

This thesis is based on the following publications (I-VI):

- I. “Practical, high-yielding formal synthesis of the DNA-binding antitumor agent pyrrolo(2,1-c)[1,4]benzodiazepine-5-one, DC-81, starting from vanillin”
Birgitta Pettersson, Vedran Hasimbegovic, Jan Bergman.
Manuscript
- II. “Total synthesis of fuligocandines A and B”
Birgitta Pettersson, Vedran Hasimbegovic, Jan Bergman
Tetrahedron Letters, **2010**, 51, 238-239.
- III. “One-pot Eschenmoser episulfide contractions in DMSO: Applications to the synthesis of fuligocandins A and B and a number of vinylogous amides”
Birgitta Pettersson, Vedran Hasimbegovic, Jan Bergman
Journal of Organic Chemistry, **2011**, 76, 1554-1561.
- IV. “Thionations using a P₄S₁₀-pyridine complex in solvents such as acetonitrile and dimethyl sulfone”
Jan Bergman, Birgitta Pettersson, Vedran Hasimbegovic, Per H. Svensson.
Journal of Organic Chemistry, **2011**, 76, 1546-1553.
- V. “Synthetic studies towards 1,5-benzodiazocines”
Birgitta Pettersson, Jan Bergman, Per H. Svensson.
Manuscript
- VI. “Synthesis of 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones by addition of Grignard reagents to derivatives of *o*-aminobenzonitrile”
Birgitta Pettersson, Anna Rydbeck, Jan Bergman.
Organic & Biomolecular Chemistry, **2009**, 7, 1184-1191.

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1. Introduction

1.1. *Natural Products and Organic Synthesis*

Nature is full of organic compounds known as natural products, that is, secondary metabolites that are produced by a plant, animal or organism but not essential for its growth or development in contrast to primary metabolites. *Alkaloids* constitute a subgroup of natural products which usually contain cyclic structures with basic nitrogen atoms and several of the compounds discussed in this thesis belong to this particular class. So, why does the plant, animal or organism spend valuable energy on producing these substances? At first, natural products were considered to be mere waste products but later they were found to possess a variety of valuable properties. Many alkaloids are neuro- or cyto-toxins which are primarily part of a chemical defence strategy against other organisms such as microbes, herbivores and in some cases even against competing plants, functioning as herbicides.¹ Nevertheless, many alkaloids contain several functional groups and thus are able to interact with various biological targets. The chemical structures of natural compounds and alkaloids display an enormous structural diversity and one may wonder why some structures are rather symmetrical and simple (e.g. urea, **1**) whereas others have wacky and complex architecture (e.g. manzamine, **2**) (Figure 1.1). One could argue that this could be a result of evolution and more complex substances could have evolved as a result of their beneficial increase in potency. Accordingly, the plant (or organism) may have to put more effort into constructing the more complex substance, but only in small amounts since it interacts more efficiently with its biological target. Some of these complex compounds display extreme potency as in the case of brevetoxin (**3**); a neurotoxin produced by algae and associated with the so called red tide catastrophes which have been responsible for massive killings of fish and other marine life forms.² Digitalis (Digoxin) is another deadly poison, nevertheless when consumed in an appropriate amount it possesses useful cardiotoxic properties. In fact, if you consume some sort of pharmaceutical substance, it is a fair chance that it contains an alkaloid, or derivative thereof, since a vast number of natural products are used as medicinal drugs. Thus, natural products attain powerful properties which can be both healing and perilous, or as Paracelsus wrote in the sixteenth century “*In all things there is a poison and there is nothing without a poison. It depends only upon the dose if something is toxic or not*”.³

Complex molecules have been produced by nature for a long period of time, whereas it was only in the beginning of the nineteenth century that humans began to synthesize organic (carbon containing) molecules.⁴ Thus the birth of organic chemistry is often associated with Wöhler’s synthesis of urea (**1**). This was a milestone in chemical and biological science which proved that a product of biological metabolism could be produced from the mineral world without involvement of a biological process. Ever since, a myriad of methods and reagents have been developed as tools for the synthetic chemist. This dissertation is about synthesis of natural products and development of synthetic methods which can be used to obtain both natural products and designed molecules.

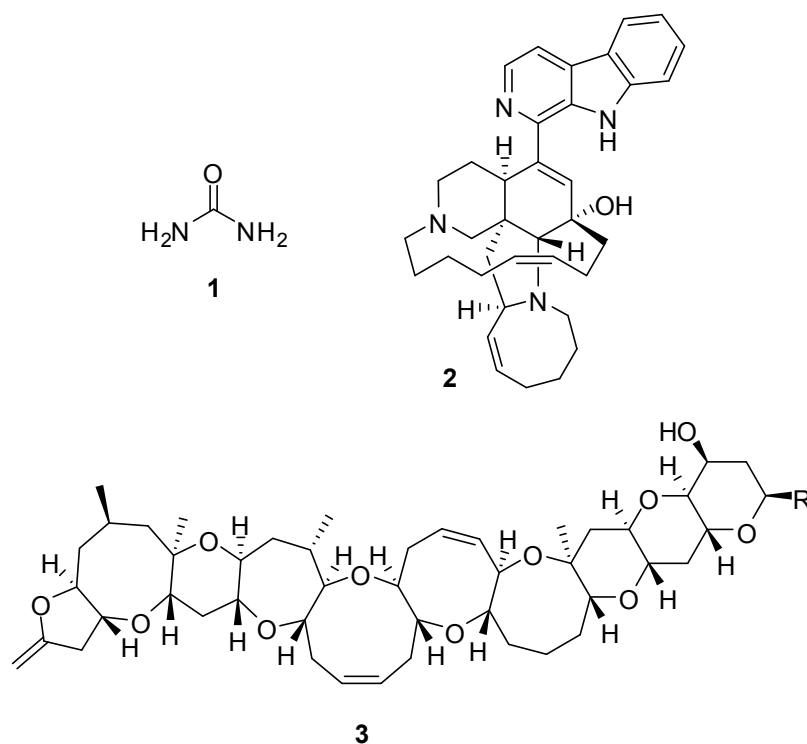


Figure 1.1. Urea, manzamine and brevetoxin 1; R = $-\text{CH}_2\text{C}(=\text{CH}_2)\text{CHO}$

1.2. 1,4-Benzodiazepines

1.2.1. Discovery and Historical Perspective

Compounds containing the 1,4-benzodiazepine (Bzp) core (**4**) have been known for their anxiety-relieving and sedative properties for a long period of time (Figure 1.2).⁵ Valium (diazepam) (**5**) is perhaps the most renowned example but other variants, such as Xanax (**6**) (alprazolam) and Ativan (**7**) (lorazepam) are more commonly prescribed today.⁶

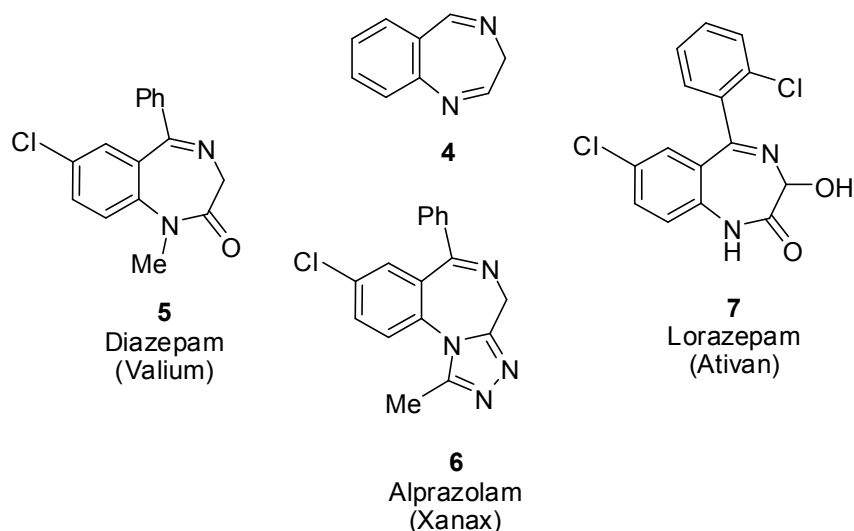
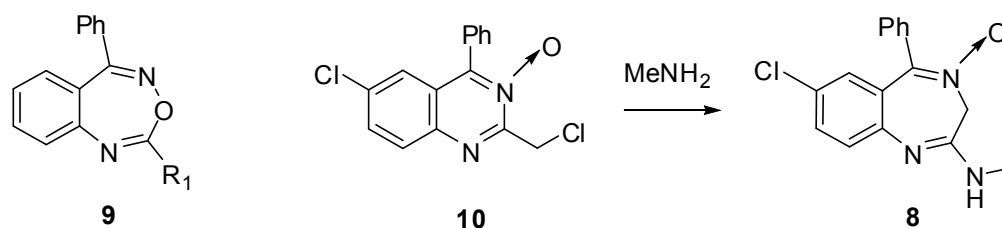


Figure 1.2.

The first synthetic benzodiazepine, chlorodiazepoxide (**8**), was serendipitously discovered in the mid 1950's by researchers at Hoffman LaRoche searching for new tranquilizers (Scheme 1.1).⁷ Their target compound, containing a benzoxadiazepine ring system (**9**), was never obtained and the actual products isolated from the reactions were in fact quinazoline-3-oxides (e.g. **10**). Upon treatment with base, **10** underwent an unexpected rearrangement to form the biologically active chlorodiazepoxide **8**, which later was marketed as Librium.⁸ The anxiety-relieving effects of benzodiazepines have been widely exploited in clinical practice although the uses have declined due to risk of addiction after long-term use.⁹ The use of serotonin re-uptake inhibitors (SSRI) and other drugs have currently come to replace the use of benzodiazepines to some extent.⁶



Scheme 1.1.

It was discovered in 1975 that benzodiazepines act by potentiating the inhibitory effects of the GABA neurotransmitter.¹⁰ GABA is the most abundant neurotransmitter in the brain and it mediates most inhibitory responses in the vertebrate brain.¹¹ Bzp bind to and modulate the GABA_A subreceptor, thereby enhancing the action of GABA. This leads to a wide variety of pharmacological responses in addition to the well-known tranquilizing and muscle relaxing effects. For example, compound **11** has recently been investigated as a clinical candidate for treating respiratory syncytial viral (RSV) infections whereas Bzp **12** has shown antiprotozoal activities (Figure 1.3).¹² In addition, bzp are found useful in the field of peptidomimetics. The nitrogen atoms in the seven-membered ring are perfectly spaced to mimic endogenous peptides, hence some Bzp have found applications as non-peptide peptidomimetics.¹³

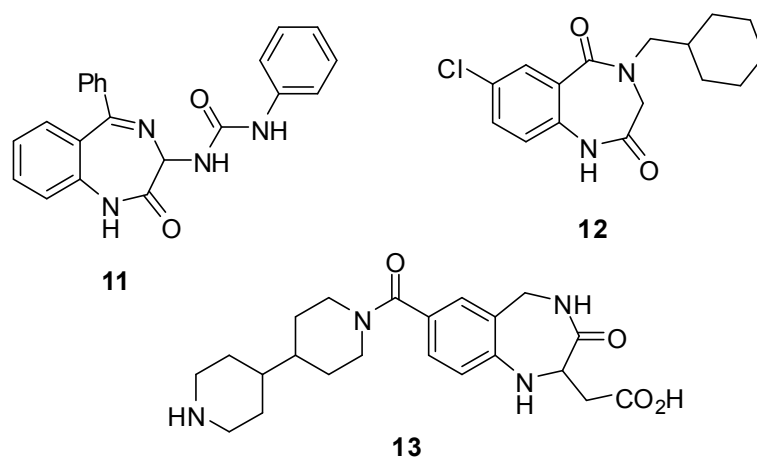


Figure 1.3.

In spite of the remarkable variety of 1,4-benzodiazepine-2-one derivatives investigated to date, reports on 1,4-benzodiazepin-3-ones are limited. However, recent years have seen an intensified interest in these compounds.¹⁴ For example, Lotrifiban (**13**) has been used as an antithrombotic agent in clinical trials.¹⁵

1.2.2. Naturally Occurring 1,4-Benzodiazepines

Benzodiazepine alkaloids constitute a group of secondary metabolites derived from anthranilic acid. One of the earliest benzodiazepine alkaloids to be isolated was cyclopenin (**14**), produced by the fungus *Penicillium cyclopium* (Figure 1.4).¹⁶ Later on, a number of benzodiazepine alkaloids have been isolated e.g. anacine (**15**), asperlicin (**16**), benzomalvin A (**17**) and sclerotigenin (**18**).¹⁷ The CNS activities associated with synthetic benzodiazepines have not been found among the natural benzodiazepines,¹⁸ however many of them show a number of other useful biological properties; cyclopenin-type alkaloids exhibit antibiotic and phytotoxic properties whereas asperlicin has proved to be a potent cholecystokinin (CCK) antagonist.^{17c, 18-19}

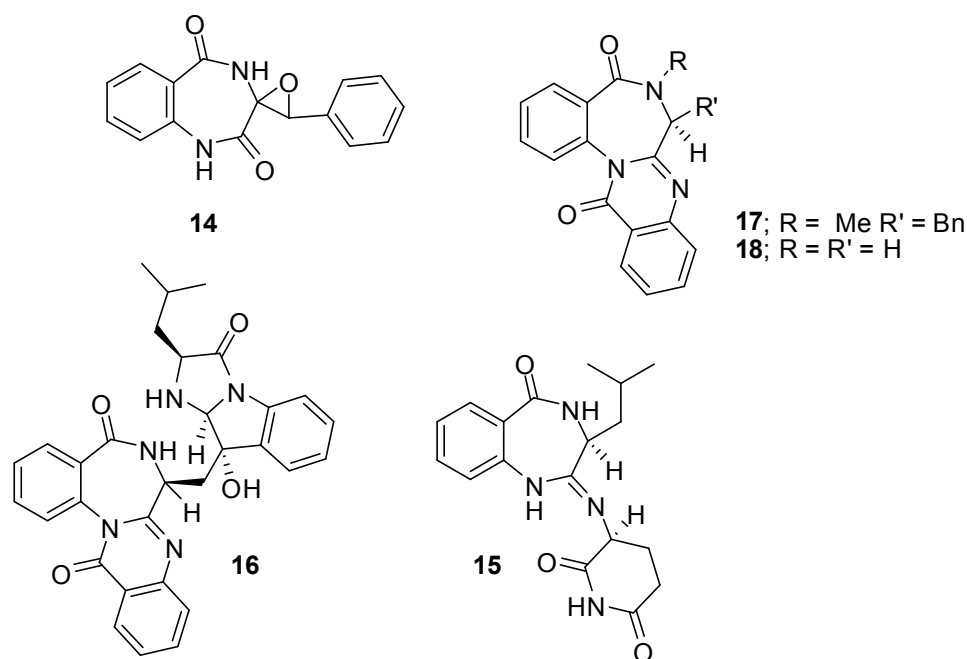


Figure 1.4. 1,4-Benzodiazepine alkaloids.

1.2.3. 1,4-Pyrrolobenzodiazepines

1.2.3.1. Structure and Biological Activity

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) scaffold (**19**) (Figure 1.5) is present in a number of naturally occurring, anti-tumor antibiotics produced by *Streptomyces* and *Micrococci* species.²⁰ In 1963, Leimgruber and co-workers isolated the first natural PDB containing the amino-carbinol function and named it anthramycin (**20**) due to its structural similarity to anthranilic acid.²¹ Later on, these workers also achieved the total synthesis of this tricyclic compound whose structure also has been confirmed by X-ray crystallography.²²

Hitherto, eighteen "anthramycins" have been isolated from natural sources and all but three are biologically active.²³ Among the most thoroughly investigated monomeric members of this family are anthramycin (**20**), DC-81 (**21**), tomaymycin (**22**) and sibiromycin (**23**). Sibiromycin was first discovered in Siberia and represents one of the most potent natural PBD discovered to date. A number of reviews concerning the biological activity and total syntheses of natural and synthetic PDBs are available in the literature.^{20, 23-24}

The tricyclic core (**19**) of these compounds consists of the aromatic ring A, the 7-membered 1,4-diazepine ring B and the pyrrolidine C. The N10-C11 imine functional group is rather unstable, for example in aqueous solution the imine function establishes equilibrium with its carbinolamine (Figure 1.6). Another important feature of the PBD core is the stereocenter at C11a. All natural PDB derivatives possess the *S* form, which allow them to adopt a right handed twist, tailor-made for interaction with α -helical (B-form) DNA. In fact, racemization at this stereocenter significantly reduces the biological activity.²⁵ Thus, the unique structure

of the PBD scaffold makes them a valuable source for development of DNA interacting agents.

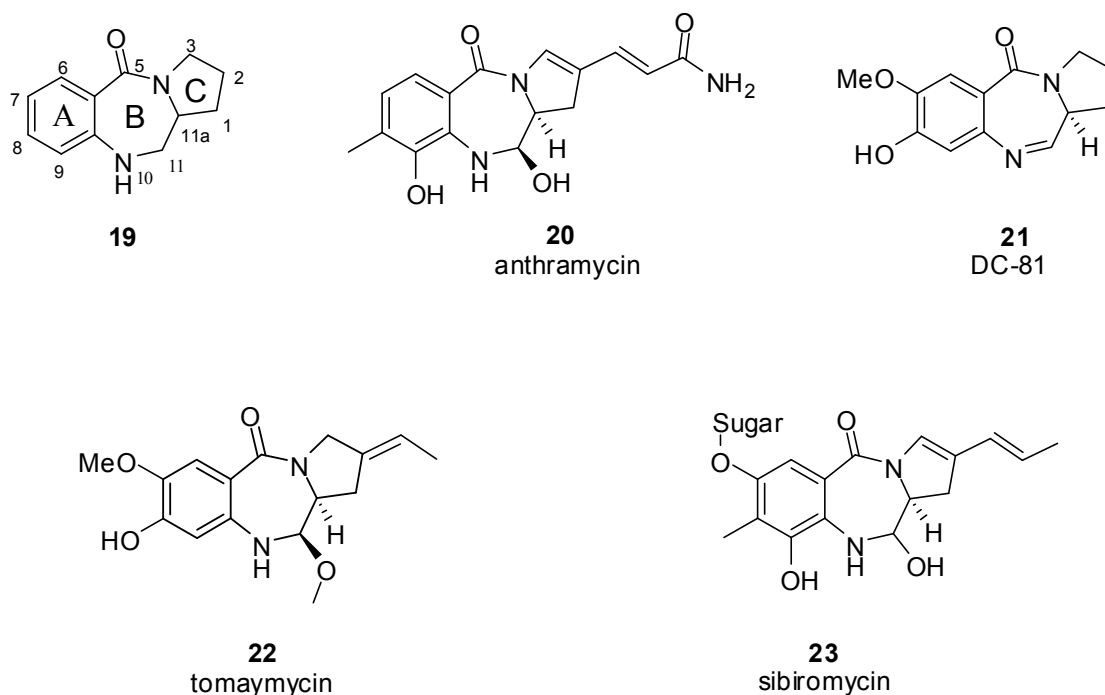


Figure 1.5. *1,4-Pyrrolobenzodiazepine alkaloids.*

More recently a number of new PBDs, namely circumdatines A-J, were found in *Aspergillus* fungi from both terrestrial and marine sources. Notably, the previously reported structures of circumdatines A and B have recently been revised from betaine- (**24**) to the unique oxepin framework (**25** and **26**) (Figure 1.6).²⁶ Another interesting member of PBD family is the natural alkaloid tilivalline (**27**) which have demonstrated cytotoxic properties toward mouse leukaemia.²⁷ In addition to the cytotoxic and anti-tumour properties, some PBD derivatives also exhibit CNS-activity. Particularly, PBDs methylated at N10 (e.g. **28**) have shown promise as anxiolytic drug candidates.²⁸ Furthermore, recent studies have shown that some PBDs (e.g. **29**) act as selective GABA(A) modulators and anti-viral agents.²⁹

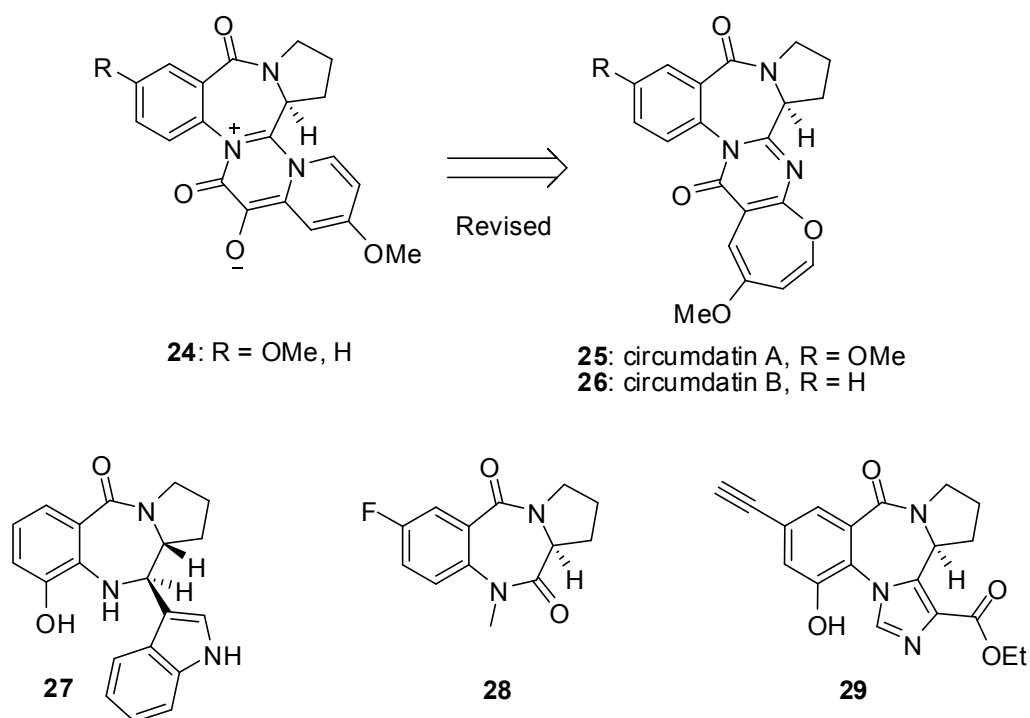
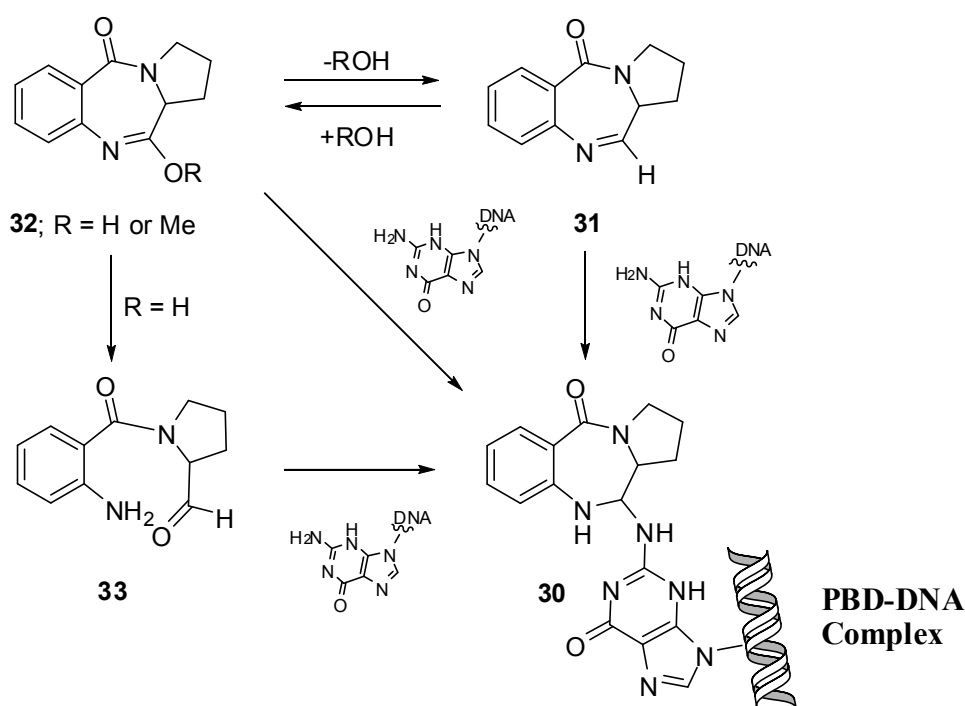


Figure 1.6.

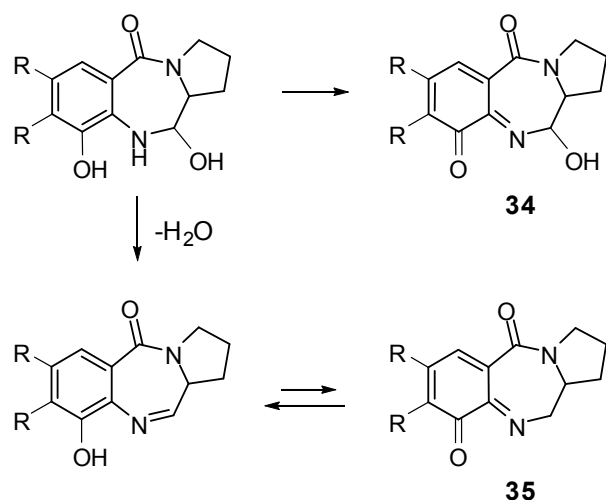
As has been already mentioned, all members of the PBD family are biologically active, demonstrating antibiotic, anti-viral and anti-tumour properties. However, further pharmacological investigations have shown that the anti-tumour activity is probably most clinically significant.^{24b} As discussed in 2.2.1., selectivity poses one of the major challenges in chemotherapy and one strategy to overcome this problem involves design of compounds that recognize and bind to specific DNA sequences of oncogenic DNA. The PDBs act as DNA minor groove binders and exert high sequence specificity in combination with extremely potent anti-tumour activity. The mechanism of action is based on alkylation of specific DNA sequences leading to disruption of vital functions such as transcription or replication.^{24b} As a result of these events the cell is destined for apoptosis. Extensive studies of DNA-PBD adducts have revealed an amidine linkage between the C10 of PDB and guanine-NH₂ of DNA (**30**, Scheme 1.2.). However, the details of the alkylation mechanism are presently unknown. The fact that PDB N10-C11 imine-carbinolamine bond is in equilibrium complicates the situation. Actually, three electrophilic species have been proposed; imine **31**, carbinol amine **32** (or corresponding methyl ether) and the ring-opened compound **33**. A mechanism involving a direct attack of guanine on imine **31** (Scheme 1.2) is most probable.^{23, 30} Two additional mechanisms have, however, been proposed. One of them involves an attack of guanine on carbinolamine **32** (or its 11-methyl ether) eliminating water via an S_N2- type reaction.³¹ Alternatively, the diazepane ring is fragmented to afford aldehyde **33** which upon imine formation with guanine subsequently cyclizes to give the DNA-PBD adduct **30**.³²



Scheme 1.2.

1.2.3.2. Synthetic Analogues of PBDs

Clinical studies have shown that PBDs lack toxicities that are often associated with cancer therapeutic agents, for example bone marrow depression or hepatic toxicity.³³ Nevertheless, dose-limiting cardio-toxicity and some other undesired effects have precluded their continued clinical applications.³⁴ The cardio toxicity of PBDs has been associated with the oxidative dearomatization, or more precisely, the formation of quinone-imine intermediates (**34** and **35**) (Scheme 1.3.),^{24a} thus efforts have been made to synthesize analogues nonconvertible to these harmful compounds.



Scheme 1.3.

One approach involves replacement of the anthranilate ring (ring A) with a 5 or 6-membered heterocycle such as **36** (Figure 1.7).^{24a} The cardio-toxicity was successfully reduced but unfortunately this approach also reduced the anticancer activity. In recent years novel PBD analogues have been developed by an approach which involves linking a PBD with another known DNA-interacting agent e.g. hybrid **37** consisting of DC-81 linked to an indolecarbonyl moiety.³⁵

Finally, a promising development is the use of dimeric DNA-crosslinking agents consisting of two monomeric PBDs linked together by means of a spacer. Activity studies of these dimeric derivatives have demonstrated a remarkable increase of both cytotoxicity and sequence selectivity. One of the best candidates, SJG-136 (**38**), is currently under phase II clinical evaluation.³⁶

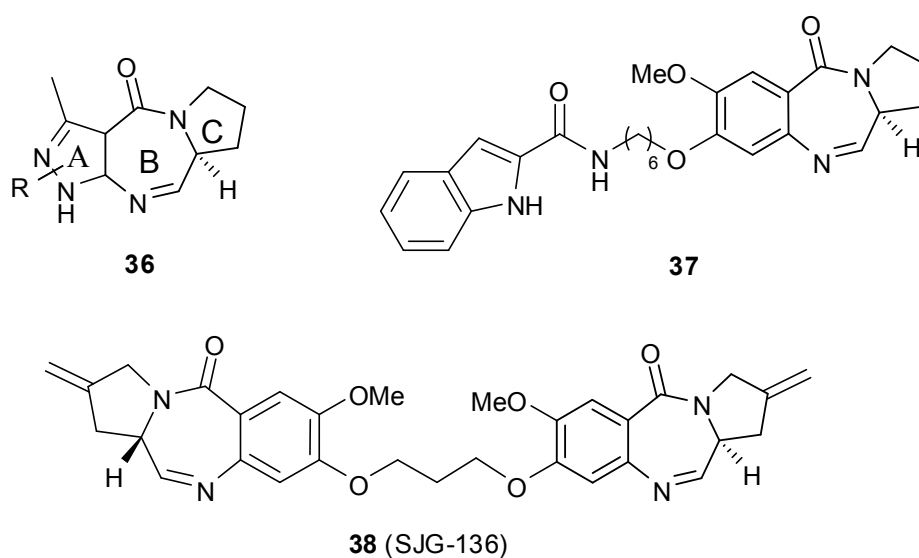


Figure 1.7.

1.2.3.3. Biogenesis of 1,4-Pyrrolobenzodiazepine Alkaloids

Hurley et al. have studied the biosynthesis of a number of PBDs through isotopic feeding experiments with focus on anthramycin (**20**), tomaymycin (**22**) and sibiromycin (**23**) (Figure 1.8).³⁷ Studies have shown that all three compounds arise from a common biogenetic origin, the amino acid tryptophan. Hence, it is proposed that tryptophan (**39**) is transformed, through the kynurenine pathway, to 3-hydroxy anthranilic acid (**40**) which constitutes the PBD A-ring. The pyrrolidine, C-ring, is derived from tyrosine (**41**) through an L-dopa intermediate that is transformed to pyrrolidine intermediate **42**. Furthermore, methionine (**43**) acts as a methylating agent. In the case of sibiromycin, the sugar unit is proposed to be derived from D-glucose (**44**).

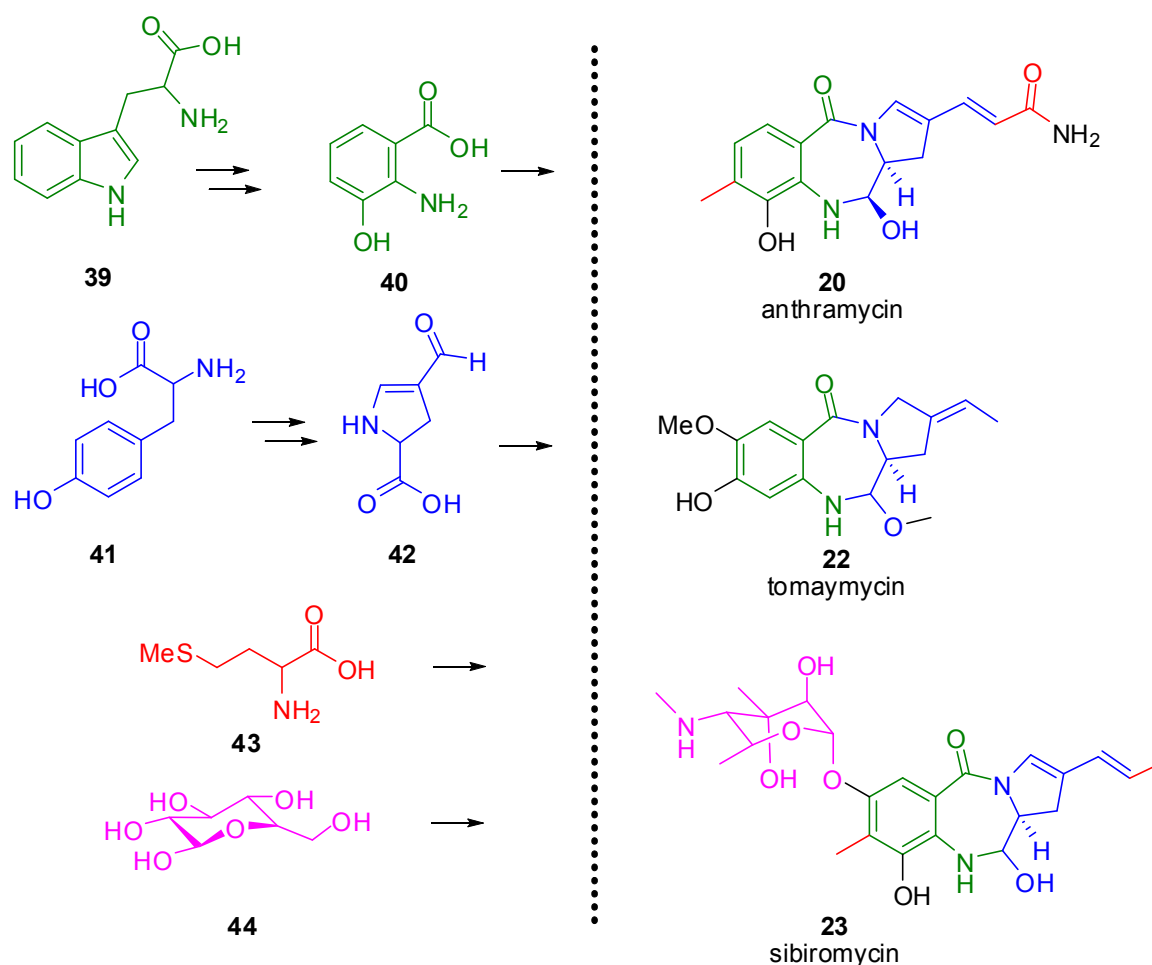


Figure 1.8.

1.3. Synthetic studies towards DC-81, a PBD Alkaloid (Manuscript I)

1.3.1. Isolation and Background

Continuous interest in pyrrolobenzodiazepine alkaloids attracted our attention toward the anthramycin natural product DC-81 (**21**, Figure 1.9). DC-81 was isolated for the first time in 1983 by Japanese researchers investigating extracts from the actinomycete *Streptomyces roseiscleroticus*.³⁸ Like most of the members of the anthramycin family, DC-81 is a potent anti-tumour antibiotic (*vide supra*).

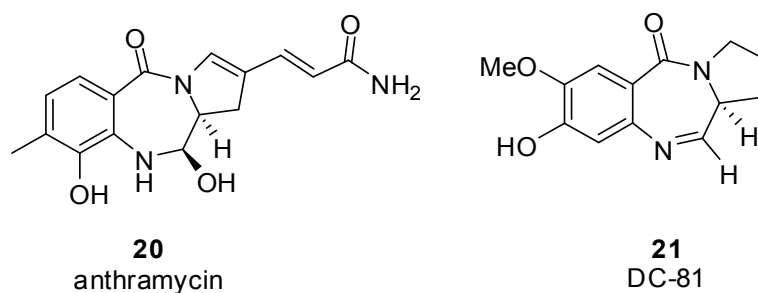
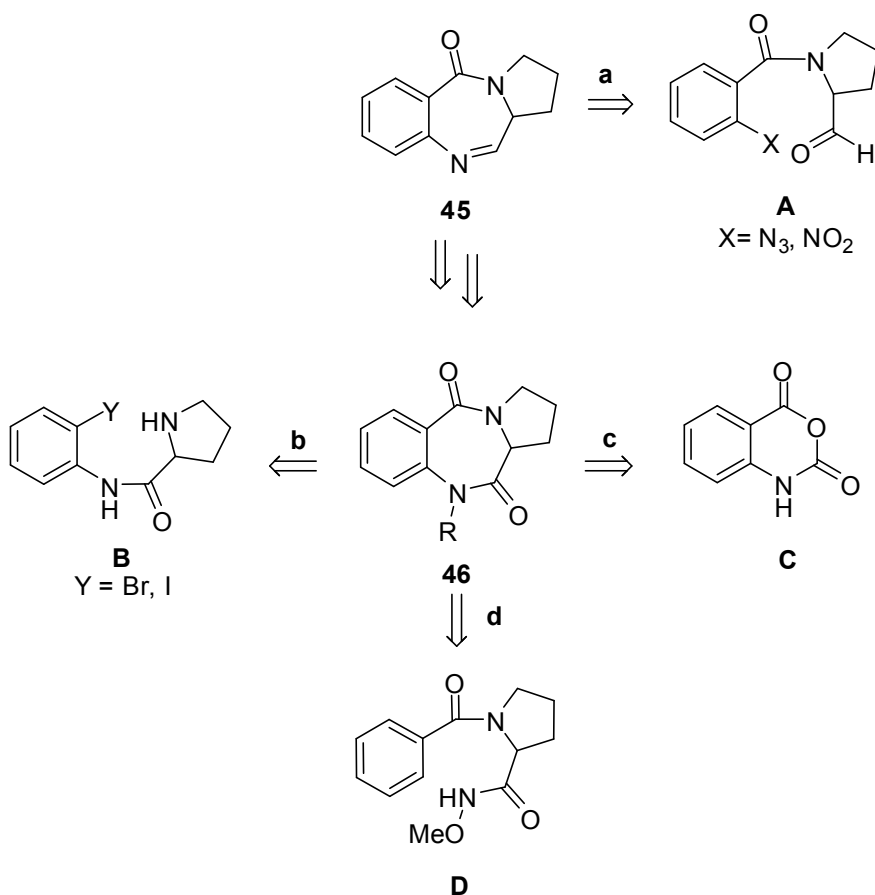


Figure 1.9.

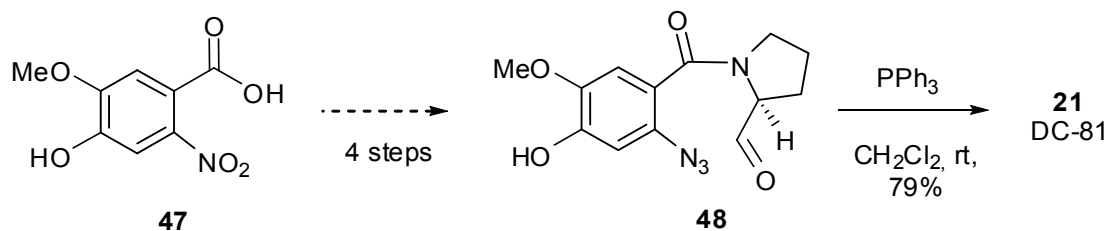
1.3.2. Previous Synthetic Efforts towards DC-81

Various strategies have been proposed and implemented for the synthesis of DC-81 (**21**). It has been found that the formation and reactivity of the imine function (N10-C11) is a frequently encountered problem, the imine formation is therefore preferably introduced late in the synthesis using mild methods. In addition, the hydrogenolysis of the *O*-benzyl ether protecting group is problematic in some cases.³⁹ Another point to consider in the synthesis of DC-81, is that racemization of C-11a must be avoided. The synthetic routes toward 1,4-pyrrolobenzodiazepines have previously been reviewed e.g. by Thurston et al.^{20, 24c} and scheme 1.4 provides a short overview of the four main conceptual approaches; route a, b, c and d. The overview comprises 1,4-pyrrolobenzodiazepines as a group with emphasis on DC-81 syntheses.



Scheme 1.4. Compound **46**; R = OMe, H.

A literature survey shows that **route a**, notable for giving direct access to imines of type **45**, represent the most widely employed method. This route is in turn divided into two different approaches; intermolecular cyclization *via* either aza-Wittig⁴⁰ or reductive cyclization reactions of azido- or nitro aldehydes **A** (Scheme 1.4).⁴¹ Molina et al. achieved an elegant synthesis of DC-81 starting from **47** employing aza-Wittig methodology which does not require the protection of the phenolic hydroxy group (**48**) (Scheme 1.5).^{40a} More recent developments of the aza-Wittig route have involved the use of solid support techniques.⁴²

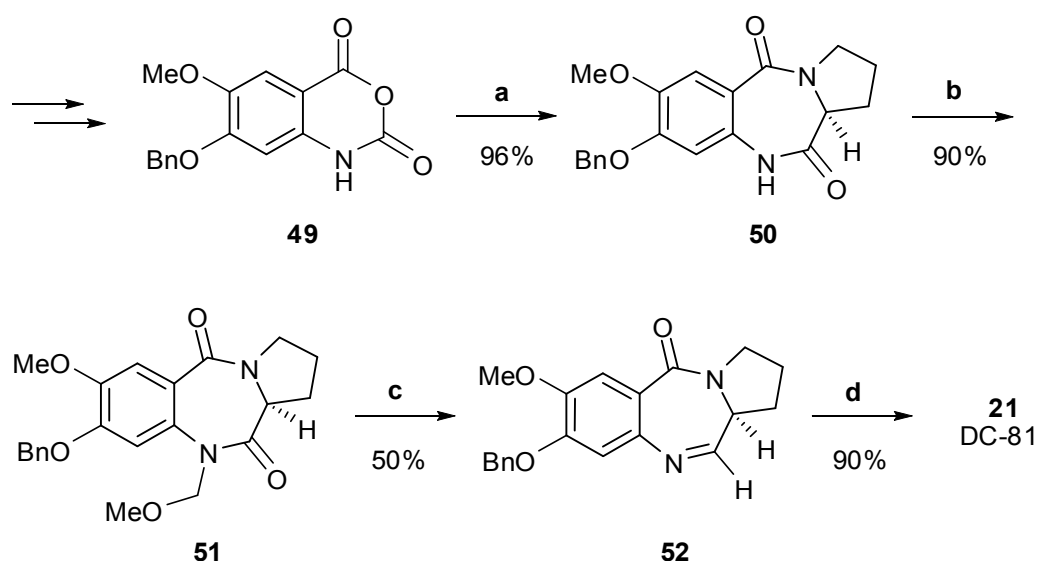


Scheme 1.5.

Routes b, c, and d proceed *via* common the diamide precursor **46** which is transformed to the imine **45** using chemo-selective hydride-based reduction. However, this procedure is hampered by the over-reduction of the imine function as well as azepane ring cleavage.³⁹

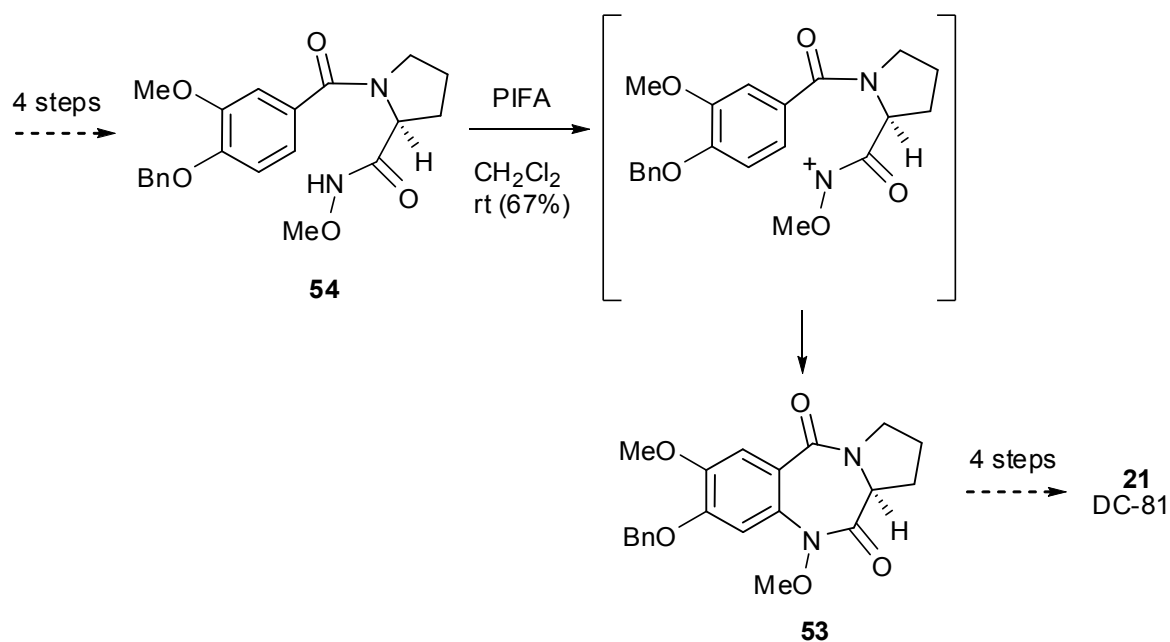
Route b, developed by Mori et al, is based on palladium catalyzed carbonylation of 2-halo anilides (**B**) (Figure 1.4)⁴³ For example, tomaymycin (**22**) has been synthesised using this route which often is hampered by low yields and complex mixtures of products.

Heating isatoic anhydride (**C**) (Figure 1.4, **route c**) together with L-proline in a suitable solvent (DMF or DMSO), represents an extremely facile entry to the PDB skeleton.⁴⁴ This approach, *via* isatoic anhydride **49**, initially developed by Wright and Brabander, represents the key step in Wang's total synthesis of DC-81.⁴⁵ Alkylation of the diamide (**50**), with methyl chloromethyl ether followed by reduction of **51** using LiBH₄ gave imine **52** (Scheme 1.6). Nevertheless, this method is hampered by over-reduction, resulting in a moderate isolated yield of imine **52** (50% isolated, 95% based on recovery of starting material). In an alternative route employing radical chemistry, diamide **50** has been constructed via isatoic anhydride.⁴⁶



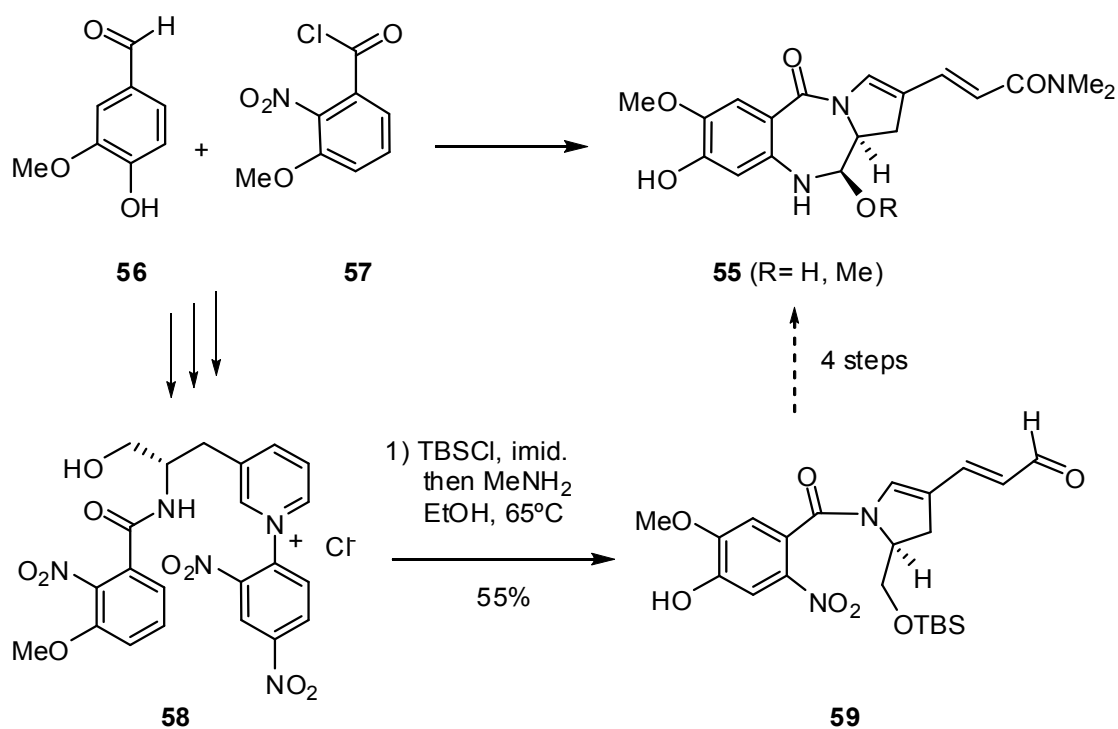
Scheme 1.6. Reagents and Conditions: (a) L-proline, DMSO, 120°C (b) NaH, MOMCl, THF, 90°C (c) LiBH₃, THF, -10°C (d) Pd/C, 1,4-cyclohexadiene, EtOH, rt

A more recent approach (**route d**, Figure 1.4), utilizes a PIFA mediated nitrene insertion as a key cyclization step providing diamide **53** from **54** (Figure 1.7).⁴⁷ The idea of C-H insertion is appealing since it does not require the acyclic substrates to possess an *ortho*-substituent. This approach is particularly useful for the preparation of analogues with densely substituted aryl nuclei, analogues possessing a difficult substitution pattern and especially for the synthesis of heteroaromatic analogues of PBDs. However, for the preparation of DC-81 (**21**) by this route is, in my opinion, less convenient since nitration of *O*-benzylated vanillin easily introduces the required *ortho*-substituent. The crucial imine function was installed by dehydrogenation of the corresponding amine using NMO/TPAP in acetonitrile. This reagent mixture is frequently used to attain C10-N11 amine dehydrogenation.



Scheme 1.7.

Notably, Vanderwal et al.⁴⁸ very recently reported a original approach toward porothramycins **55** (starting from vanillin **56** and the nitro compound **57**), via a Zincke pyridinium ring-opening/ring-closing cascade of **58** to key precursor **59**, which thereafter can further be elaborated to **55** according to a published method (Scheme 1.8).⁴⁹

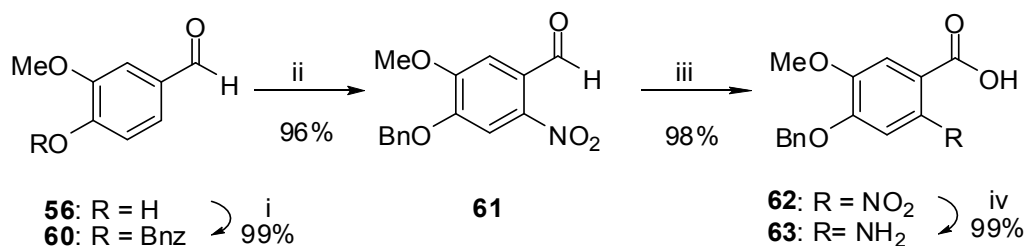


Scheme 1.8. Vanderwal's formal total synthesis of porothramycins.

1.3.3. Results and Discussion

1.3.3.1. Synthesis of the PDB Core Structure

The aim of our studies was to develop a practical and readily scalable total synthesis of DC-81 (**21**) using route **c** (Scheme 1.4) starting from vanillin (**56**). Thus, initial *O*-benzylation (**60**) and nitration gave nitro-benzaldehyde **61** which could be recrystallized from acetone with minimal loss of the desired product (Scheme 1.9).

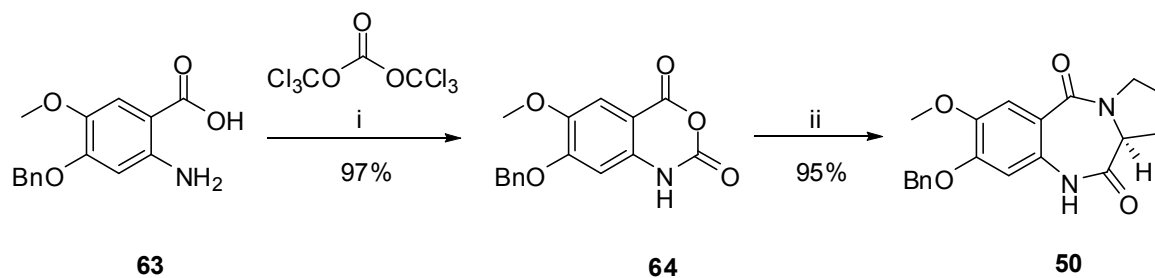


Scheme 1.9. Reagents and conditions: (i) Benzyl bromide, K₂CO₃, DMF, rt; (ii) HNO₃/AcOH, ~10°C → rt; (iii) AgO₂, NaOH (aq), 70 °C → reflux; (iv) Pt/C (5%), H₂, EtOH, rt.

Next, aldehyde **61** was treated with KMnO₄ according to a literature procedure, in our hands the reaction turned out to be messy and low-yielding (< 50% yield).⁵⁰ However, a lesser-known method, Delépine aldehyde oxidation (not to be confused with Delépine reaction which is an amine synthesis) gave the *o*-nitrobenzoic acid derivative **62** in nearly quantitative yield (98%).⁵¹

Reduction of the nitro group of **62** posed two problems: 1.) the presence of hydrogenolysis-sensitive *O*-benzyl ether and 2.) the presence of both acidic and basic functions in the anthranilic acid derivative **63**, a factor which complicates the work-up. According to literature, **62** has been transformed to **63** using sodium borohydride-nickel(II) chloride system or tin(II) chloride in methanol.^{45, 52} However, with tin(II) chloride reduction only small amounts of **63** were obtained after a tedious workup. Consequently, a more general method was developed for the reduction of aromatic nitro groups in the presence of hydrogenolysis-sensitive functionalities (e.g. *O*-benzyl, *N*-benzyl and halo aryl groups) using 1 atm catalytic hydrogenation over platinum on carbon (5%).⁵³ Hence, hydrogenation of **62** gave **63** in quantitative yield, after a simple workup.

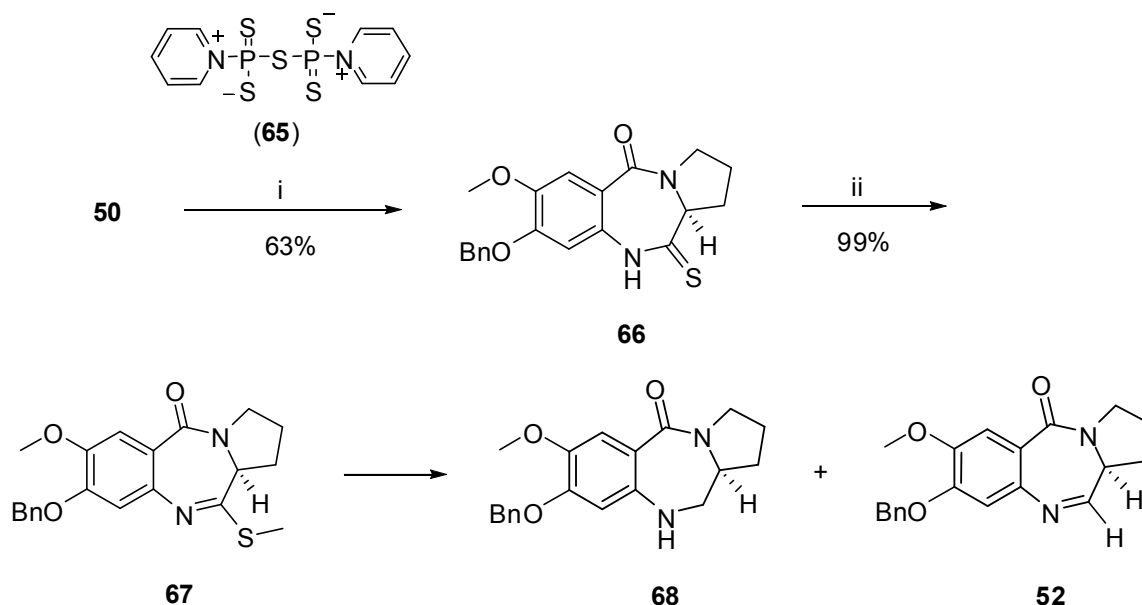
Conversion of the substituted anthranilic acid **63** into the anhydride **64** was accomplished employing triphosgene (bis(trichloromethyl) carbonate) in THF (Scheme 1.10). The crude product was conveniently purified by titration in acetone, giving pure **64** in 97% yield. Alternative methods using ethyl chloroformate instead of the rather unpleasant triphosgene gave unsatisfactory results.⁵⁴ Subsequent heating of the isatoic anhydride derivative **64** with L-proline in DMSO gave the desired PBD **50**.



Scheme 1.10. Reagents and conditions: (i) triphosgene, THF, rt; (ii) L-proline, DMSO, 100°C.

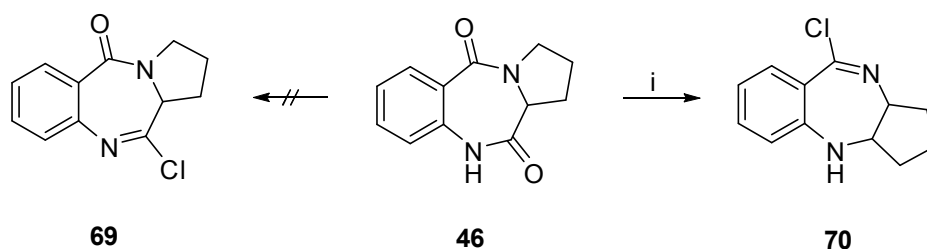
1.3.3.2. Attempts to Attain the Imine Function of DC-81

With the newly developed selective thionation reagent (P_2S_5 -Py₂) (**65**) in hand (further discussed in 3.2.), we chose to pursue the elusive imine **22** via monothione **66**. Thus, treating diamide **50** with P_2S_5 -Py₂ in hot acetonitrile gave monothione **66** in 85% yield (Scheme 1.10). Desulfuration of the methylated monothione **67**, using Raney Ni gave inconsistent results. In most cases, amine **68** was the only product isolated from the reaction. Desulfuration of the methylated monothione **67** had previously been accomplished using Al-Hg or HgCl₂/MeOH in a very low yield.⁵⁵



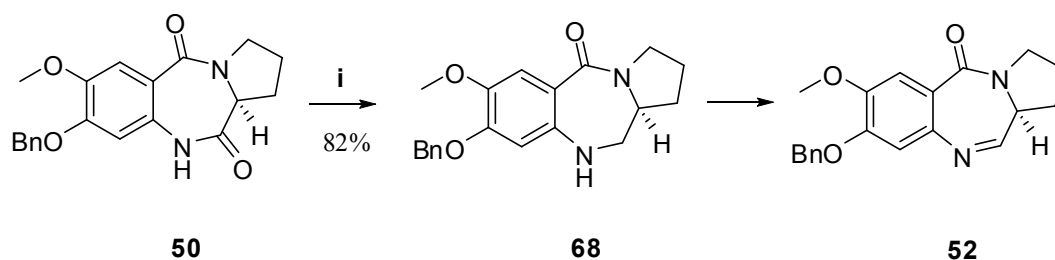
Scheme 1.11. Reagents and conditions: (i) MeCN, 60°C, 4h; (ii) MeI, rt, THF, 30 min.

Chlorination of diamide **46** to **69** is difficult to accomplish,⁵⁶ thus refluxing diamide **46** in POCl₃ with catalytic amount of pyridine or phosphorus pentachloride gave no reaction, whereas microwave heating of an identical mixture induced an interesting rearrangement, giving the chloroimine **70** (Scheme 1.12).⁵⁷



Scheme 1.12. Reagents and conditions: (i) $POCl_3$, pyridine, μw (700W) (60%).

At this point the attention was turned to an alternative pathway, proceeding *via* amine **68**. A Japanese group has developed a useful method for the selective reduction of primary and secondary amides using $NaBH_4/AcOH$ system in dioxan.⁵⁸ Thus following this procedure, the secondary amide function of compound **50** was selectively reduced to afford amine **68** (Scheme 1.13).



Scheme 1.13. Reagents and conditions: (i) $NaBH_4$, $AcOH$, dioxane, $15^\circ C \rightarrow reflux$.

The dehydrogenation of the amine **68** to the imine **52** proved to be the most challenging step, particularly since we wanted to avoid the use of ruthenium based methods. Attempted one-pot *N*-chlorination of **68** using NCS followed by base-induced elimination using DBU gave a complex mixture of products. Next, the transformation was attempted using the Parikh-Doering reaction used for the oxidations of alcohols to aldehydes.⁵⁹ In this Swern-based procedure, DMSO is activated by sulfur trioxide-pyridine complex in presence of triethylamine and in this manner acts as an oxidising agent. This method was appealing since it is conducted at room temperature and uses inexpensive chemicals as well as having a convenient work-up. After running the reaction overnight TLC showed that all starting material was consumed, however the NMR spectrum of the crude product was not in the agreement with the structure **52**. A number of additional methods were attempted, such as dehydrogenation using MnO_2 , DDQ, TCCA, various hypervalent iodine reagents, selective Raney nickel desulfurization of thioimidates etc., however none of these methods provided the desired imine in satisfying amounts.

1.4. 1,5-Benzodiazocines

1,5-Benzodiazocines (**71**) are higher homologues of the well-known 1,4-benzodiazepines **4** and members of this family possess a broad spectrum of pharmacologically useful activities. Some derivatives exhibit similar psychoactive properties to benzodiazepines and thus have been used as benzodiazepine drugs.⁶⁰ In addition, properties such as cholesterol-lowering and hormone-like activities have been reported.⁶¹ In recent times, material chemists have explored

the electrochemical properties of diaryldibenzo[b,f][1,5]-diazocines (**72**) which were found useful as a basis for molecular machines and artificial muscles.⁶² In general, eight membered rings are difficult to prepare since their formation is usually hampered by unfavourable entropic factors and transannular interactions.⁶³ Synthetic routes toward 1,5-benzodiazocines have been reviewed.⁶⁴ The crucial cyclization step has been affected using various strategies e.g. aza-Wittig cyclization,⁶⁵ intramolecular dehydration,⁶⁶ and ring expansion reactions,⁶⁷ however special conformational restrictions are usually required in order to obtain reasonable yields from direct cyclization of acyclic precursors.^{63, 68} For example, Banfi and later also Buchwald et al. provided efficient approaches toward medium-sized *N*-heterocycles (**73**) employing ring expansion of an β -lactam **74** with an neighbouring nitrogen nucleophile (Scheme 1.14).⁶⁹ In recent years, ring closing metathesis has provided a useful entrance to medium and large sized rings.⁷⁰

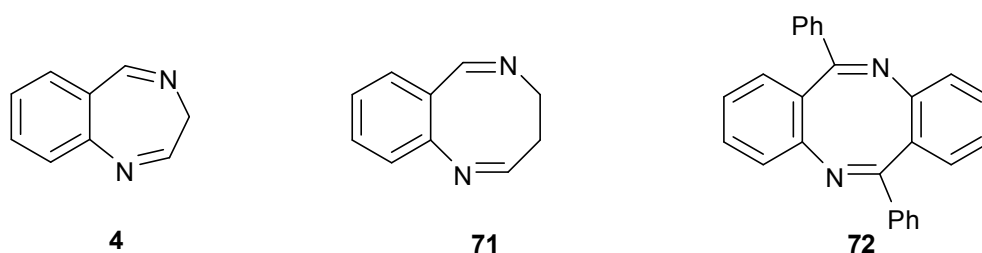
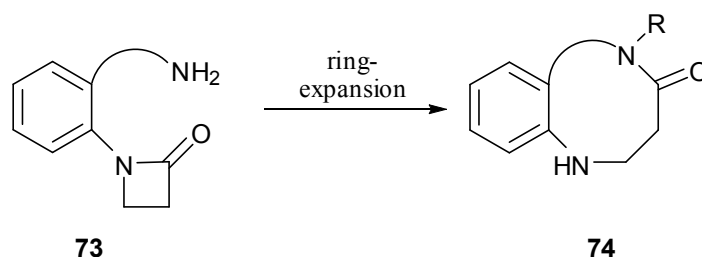


Figure 1.10.



Scheme 1.14. Buchwald's approach toward medium sized *N*-heterocycles.

Tröger's base (**75**), a bridged variant of a dibenzo[b,f][1,5]diazocine, has a chiral aromatic cleft structure with a unique ability to host guests and as a result act as a supramolecular receptor (Figure 1.11).⁷¹ Although most applications of Tröger's base are within the field of supramolecular chemistry, pharmacological applications have also been reported.⁷² More recently, the interest in Tröger's bases has extended to the bridged structure **76**, containing an additional nitrogen available for further interactions and modifications.⁷³ Synthetic studies towards analogues of compound **76** are discussed in 4.2.

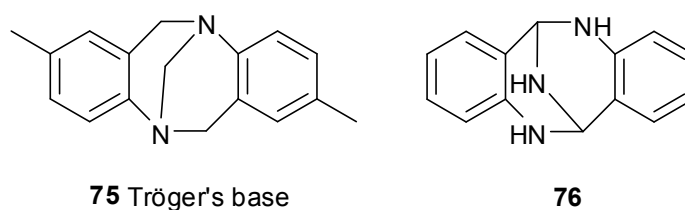


Figure 1.11.

2. Fuligocandin A and B (Papers II-III)

2.1. Isolation and Background

Myxomycetes, true slime molds, belong to the lowest classes of eukaryotes and are using spores for reproduction. Despite their simplicity, these organisms are able to synthesize complex secondary metabolites for example pyrroloiminoquinones (**77**), bisindolylmaleimides (**78**) and molecules of terpenoid types e.g. **79** (Figure 2.1).⁷⁴

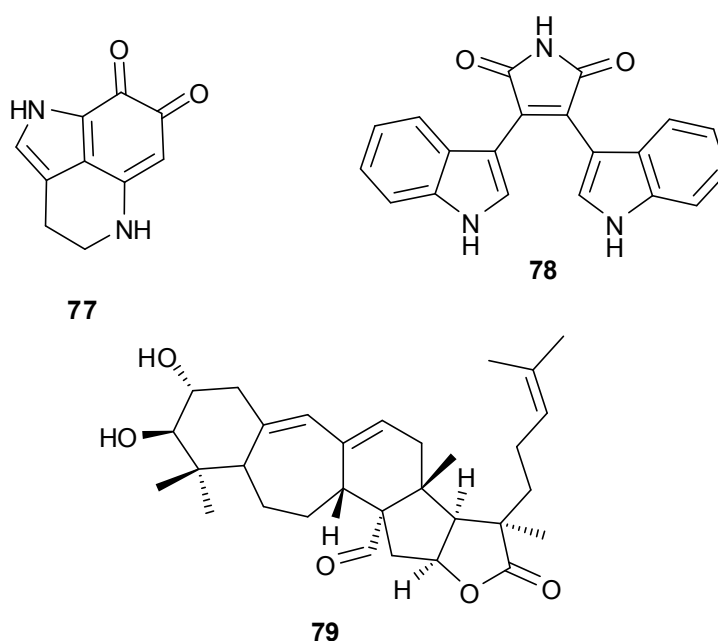


Figure 2.1.

In 2004, Ishibashi et al. collected the fruit bodies of the myxomycete *Fuligo candida* in Kochi prefecture, Japan.⁷⁵ Upon detailed investigation these workers isolated several new interesting compounds, namely, cycloanthranilyl-proline (**46**) and three previously unknown derivatives (**80-82**) thereof (Figure 2.2). Interestingly, cycloanthranilyl-proline **46** was synthesized prior to isolation from natural sources (see 2.4.1).⁴⁴ Compounds **80**, **81** and **82** were named fuligocandin A, B and C, respectively.⁷⁶ The organic phase of the extract contained fuligocandin A as the major constituent, which could be isolated as colourless plates whereas fuligocandin B appeared as a yellow pigment. Fuligocandin C is a water soluble, unstable compound which readily undergoes conversion to fuligocandin A (**80**) *via* decarboxylation.⁷⁵

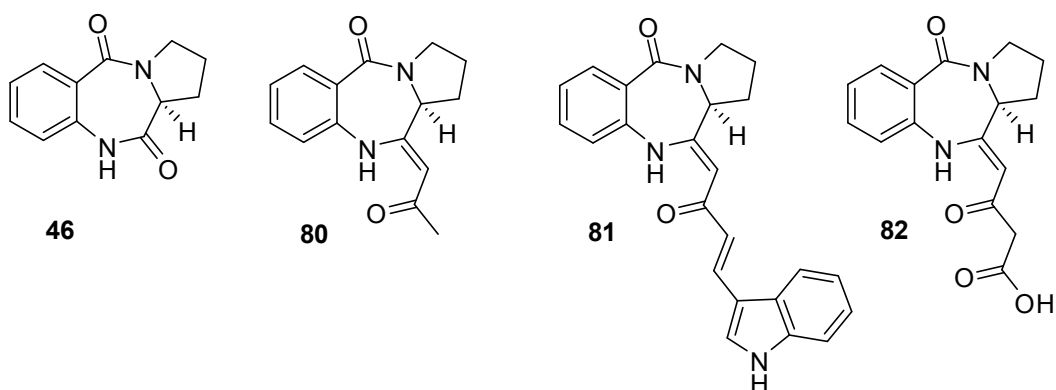


Figure 2.2. Structures of cycloanthranilyl proline (**46**) and fuligocandines A-C (**80-82**).

Curiously, a new chlorine-containing myxomycete natural product, namely dehydrofuligoic acid (**83**), has recently been isolated from the *Fuligo septica* f. *flava* (Figure 2.3).⁷⁷

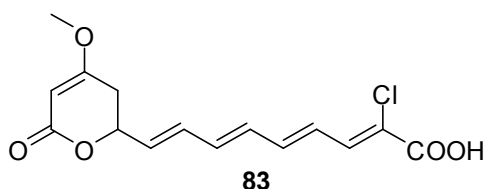


Figure 2.3.

2.2. Biological Activity of Fuligocandin B

2.2.1. Cancer Therapy Targeting TRAIL

An ideal cancer therapy should be able to induce apoptosis in cancer cells with no negative effect on normal cells. A potentially useful method for achieving this goal is to target signalling pathways related to tumor-cell-selective apoptosis. Consequently, the so-called tumor necrosis factor related apoptosis inducing ligand (TRAIL) signalling pathway is of great current interest since it induces apoptosis in tumor cells but not in normal cells.⁷⁸ The TRAIL mechanism is not fully understood, but it is suggested that initially TRAIL binds to specific death receptors, which are mainly expressed in cancer cells, hence triggering a cascade of reactions that eventually lead to apoptosis (Figure 2.4)⁷⁹ However, a growing problem in cancer therapy is that a considerable variety of cancer cells, especially some highly malignant tumors, have developed resistance to apoptosis induction by TRAIL. Successful use of TRAIL for cancer therapy is dependant on overcoming this resistance. Chemotherapy in combination with irradiation poses one method commonly used to combat resistance, albeit it suffers from serious drawbacks due to lack of selectivity.^{78, 80}

2.2.2. Fuligocandin B and TRAIL

As described in the previous section, tumor-selective strategies for overcoming resistance to TRAIL-induced apoptosis are of great potential in cancer therapy. This prompted Hasegawa and co-workers to initiate a screening program aimed at finding natural compounds that have strong synergism with TRAIL but low toxicity to normal cells.^{76, 80b} Indeed, upon investigation of an extract of *Fuligo Candida* they found a compound that exhibits anti-tumor activity toward TRAIL-resistant leukaemia cells *via* a novel p53- independent mechanism. The exact mechanism is so far unknown but the study indicates that fuligocandin B (**81**) initially up-regulates Cox-2 expression which catalyzes the transformation of arachidonic acid (PG's) to prostaglandins PGH₂ which in turn increase the production of 15d-PGJ₂ that enhance sensitivity to TRAIL and eventually will lead to apoptosis (Figure 2.4).⁷⁶

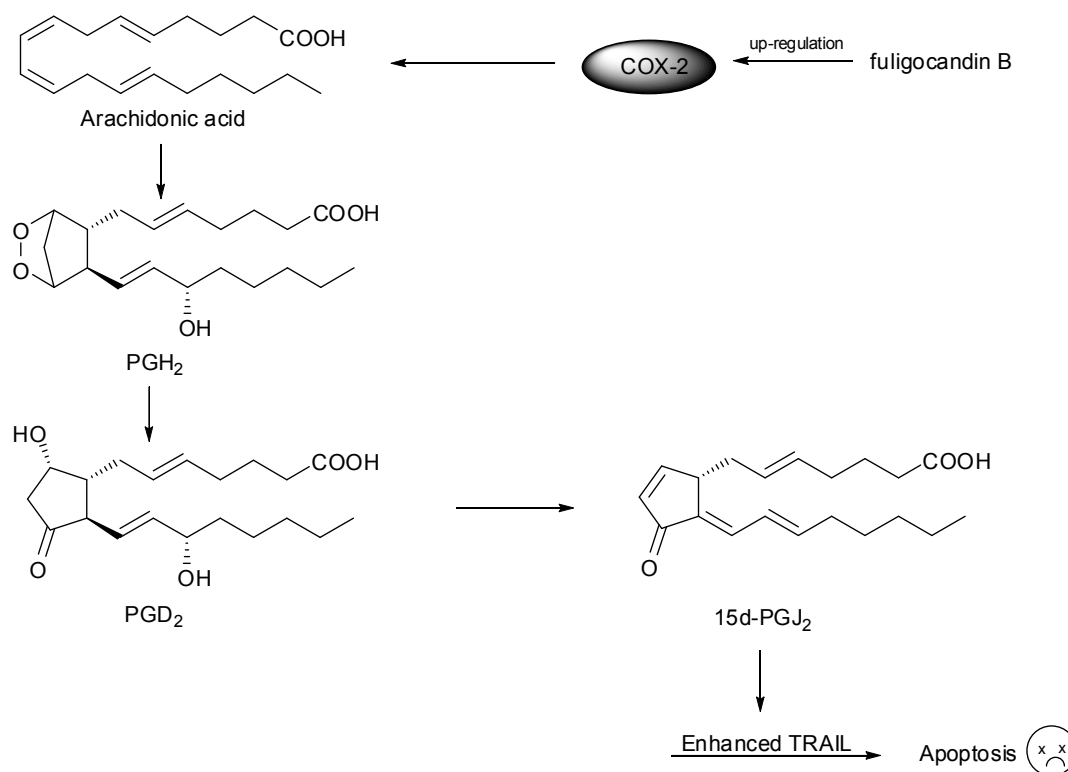
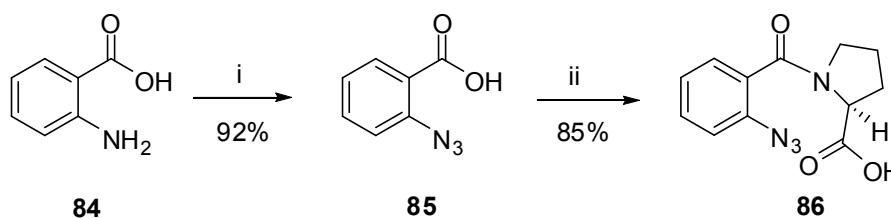


Figure 2.4. Mechanism of action proposed for fuligocandin B via TRAIL.

2.3. Previous Synthetic Efforts towards Fuligocandin A and B

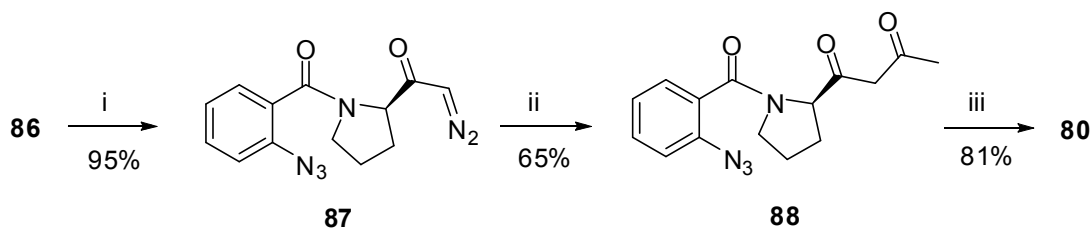
2.3.1. More's Approach

In 2009, during the course of our own investigations, More et al. reported on the first synthesis of fuligocandin A, which was prepared in 6 steps.⁸¹ Diazotization of anthranilic acid (**84**) followed by treatment with sodium azide afforded the azide derivative **85** which upon subsequent amidation gave compound **86**.



Scheme 2.1. Reagents and conditions: (i) NaNO_2 , HCl , NaN_3 , MeCOONa (ii) a) SOCl_2 b) *L*-proline, NEt_3 .

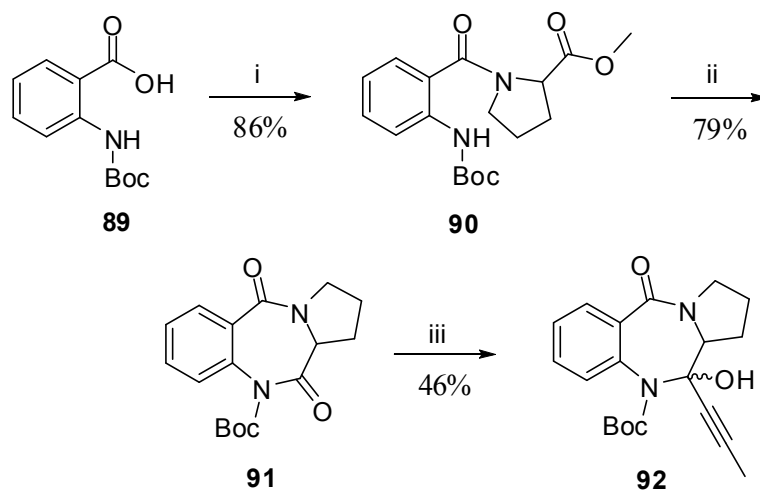
Activation of compound **86** with ethyl chloroformate followed by homologation with diazomethane gave α -diazo ketone **87** which could be isolated as both *syn* and *anti* rotamers (5.2:1) (Scheme 2.2). Next, using an interesting carbene insertion protocol, previously developed by Padwa, the diketo compound **88** was obtained. The crude azidoketone was treated with triphenylphosphine and cyclized via aza-Wittig reaction to fuligocandin A (**80**). Synthesis of other fuligocandines has not yet been reported using this method.



Scheme 2.2. Reagents and conditions: (i) ethyl chloroformate, NEt_3 , CH_2N_2 (ii) MeCHO , SnCl_2 (iii) PPh_3 .

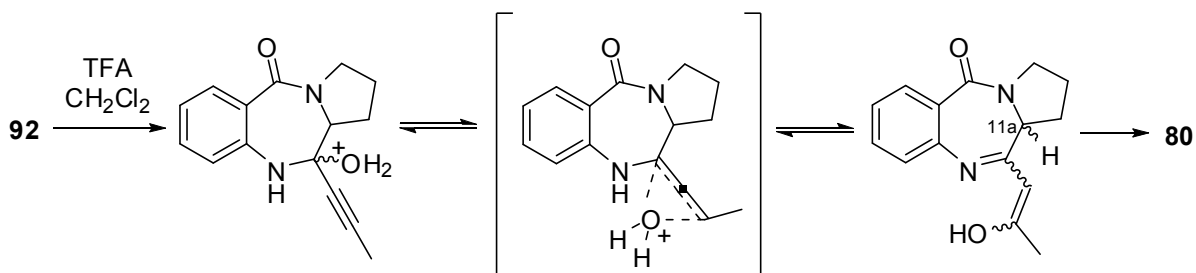
2.3.2. Arai's Approach

In 2010, Arai and co-workers reported a successful strategy toward both fuligocandin A (5 steps) and B (6 steps), using Meyer-Schuster rearrangement as the key step.⁸² First, *N*-protected anthranilic acid (**89**) was reacted with *L*-proline methyl ester to give **90** (Scheme 2.3.). Hydrolysis of the methylester and subsequent cyclization, induced by the peptide coupling agent PyBOP and Hünig's base (DIPEA), afforded PBD **91**. Elaboration using propynyl lithium gave the alkynyl-substituted PBD **92** in 46 % yield.



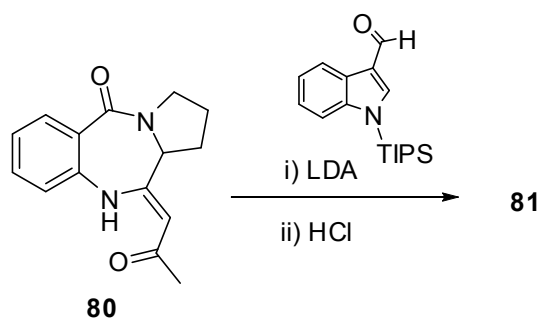
Scheme 2.3. Reagents and conditions: (i) *L*-proline methyl ester hydrochloride (ii) a) LiOH
b) PyBOP, DIPEA (iii) propynyl lithium

Cleavage of the *N*-Boc protecting group under standard conditions (TFA) simultaneously induced Meyer-Schuster rearrangement giving fuligocandin A (**80**) as the required *Z*-isomer (Scheme 2.4.). However, the enantiomeric excess was only 40 % due to racemization at C11a. Performing the reaction at lower temperature (-20 °C) somewhat reduced this undesirable reaction and ultimately 70 % *ee* could be achieved.



Scheme 2.4. Meyer-Schuster rearrangement.

Finally, aldol condensation between **80** and TIPS-protected indole-3-carbaldehyde furnished fuligocandin B (**81**) (61% *ee*) in 63% yield (Scheme 2.5).

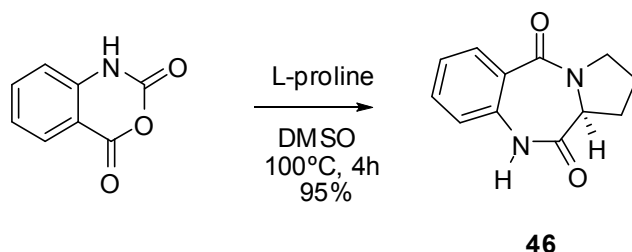


Scheme 2.5.

2.4. Results and Discussion

2.4.1. The PDB Core

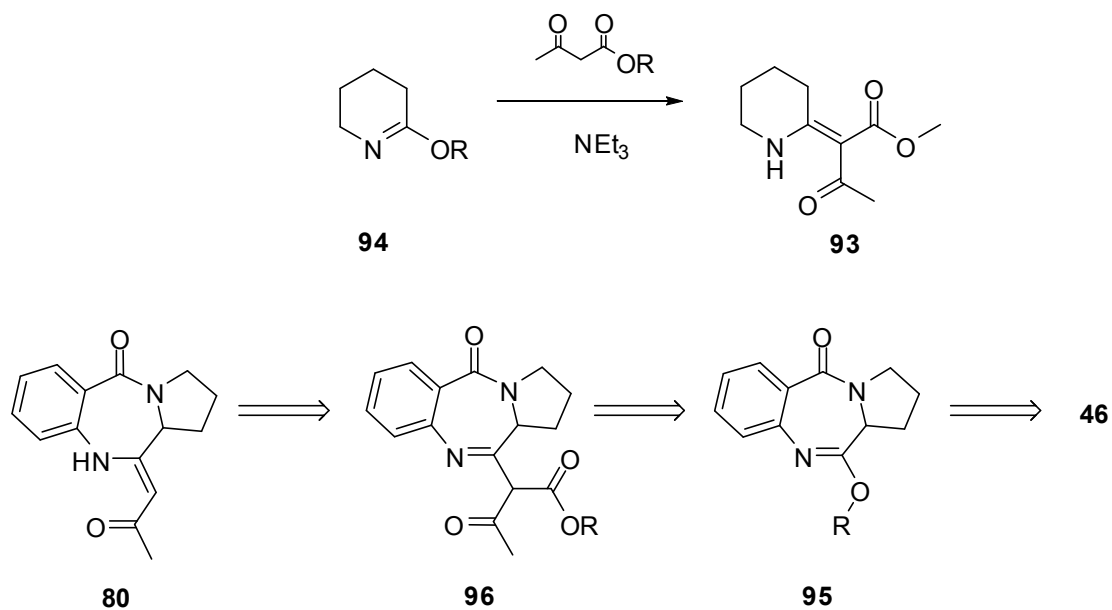
In planning the synthesis of fuligocandin A and B, the method toward PDB **46** developed by Wright and Brabander (Scheme 2.6.) was viewed as the most straightforward and thus became our starting point.⁴⁴ Thus, isatoic anhydride was heated with L-proline in DMSO and the desired *S*-enantiomer of PDB **46** could be isolated in an excellent yield.



Scheme 2.6.

2.4.2. Initial Efforts towards Fuligocandin A

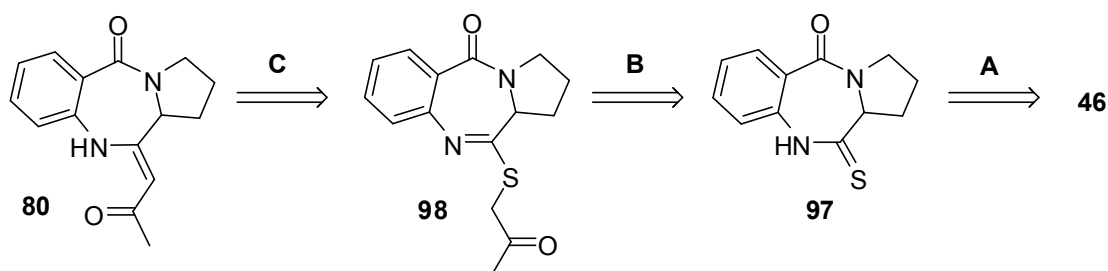
With PDB **46** in hand, attempts were made to prepare fuligocandin A (**80**) by manipulating the carbonyl of the secondary amide in order to attain coupling with an active methylene compound, essentially using a variation of Claisen condensation. Thus, inspired by Yamazaki et al. who obtained compound **93** by heating tetrahydro-2-methoxy pyridine **94** with methyl acetoacetate in presence of base, we set out to prepare compound **95** (Scheme 2.7).⁸³ The plan was to further elaborate imidate **95** with methyl acetoacetate in the presence of a base to give **96**, followed by Krapcho decarboxylation in hope to obtain fuligocandin A (**80**). However, failures in advancing diamide **46** to the imidate **95** by attempted alkylation using both Meerwein's salt and dimethyl sulfate forced us to abandon this approach.



Scheme 2.7.

2.4.3. Second Approach towards Fuligocandin A

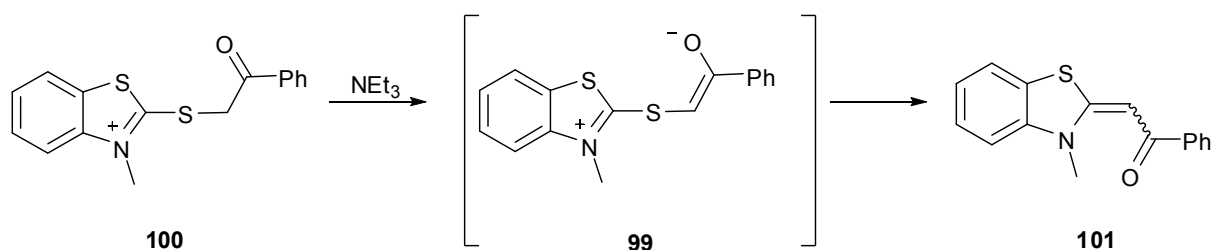
Next, focus was aimed at an alternative strategy, namely Eschenmoser sulfide contraction – a reaction which would constitute a key coupling step. This approach involved initial regioselective thionation of PDB **46** (A) giving thioamide **97** followed by alkylation using chloroacetone to compound **98** (B) and subsequent extrusion of sulfur, resulting in a new carbon-carbon bond (C) and thereby fuligocandin A (**80**) (Scheme 2.8.).



Scheme 2.8.

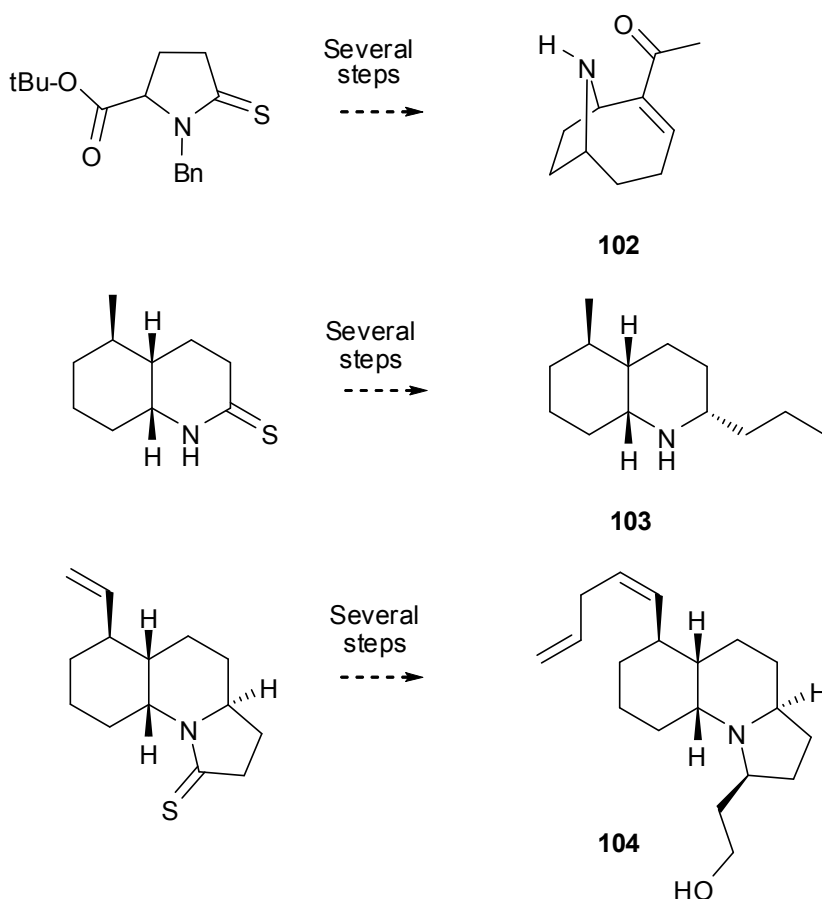
2.4.3.1. Eschenmoser Sulfide Contraction

The observation that alkylated thioamides form new carbon-carbon bonds *via* extrusion of sulfur in presence of base was first described by Knott in 1955.⁸⁴ During his seminal studies, Knott intended to prepare **99** from **100**, but failed to isolate the desired zwitterionic intermediate **99** as it was readily converted into vinylogous amide **101** via extrusion of sulfur (Scheme 2.9).



Scheme 2.9.

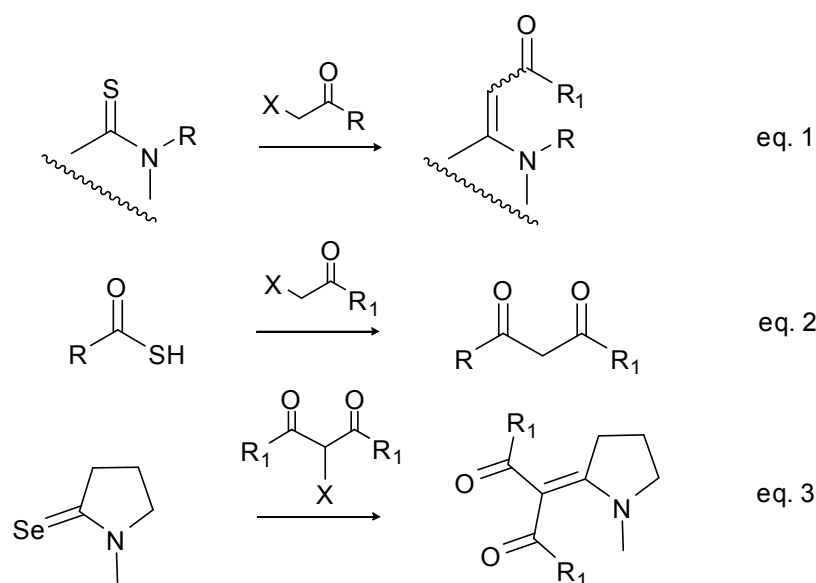
The method remained unexplored until it was used by R. B. Woodward and A. Eschenmoser as a key coupling reaction in their synthesis Vitamin B12.⁸⁵ A few years later, Eschenmoser further developed the general utility of this method by transforming a number of thioamides to vinylogous amides and urethanes.⁸⁶ Since then, the Eschenmoser sulfide contraction has emerged as an important synthetic tool and has been used in the synthesis of a number of natural products, some of which are shown in scheme 2.10.⁸⁷ Anatoxin (**102**) is one of the most potent agonist known for the nicotinic acetylcholine receptor.⁸⁸ Pumilotoxin C (**103**) and gephyrotoxin (**104**) are amphibian alkaloids, known for their use as highly toxic dart poisons.^{87, 89}



Scheme 2.10. Synthesis of selected alkaloids using Eschenmoser sulfide contraction.

This reaction usually requires the use of both base and thiophile and it is strongly dependant on the structural features of the reactants. Reaction involving secondary thioamides

requires forcing conditions, e.g. elevated temperatures, long reaction times, the use of strong bases (such as *t*-BuOK) and triphenylphosphine as thiophile. In contrast, tertiary amides undergo contraction readily under mild conditions (eq. 1) (Scheme 2.11).⁹⁰

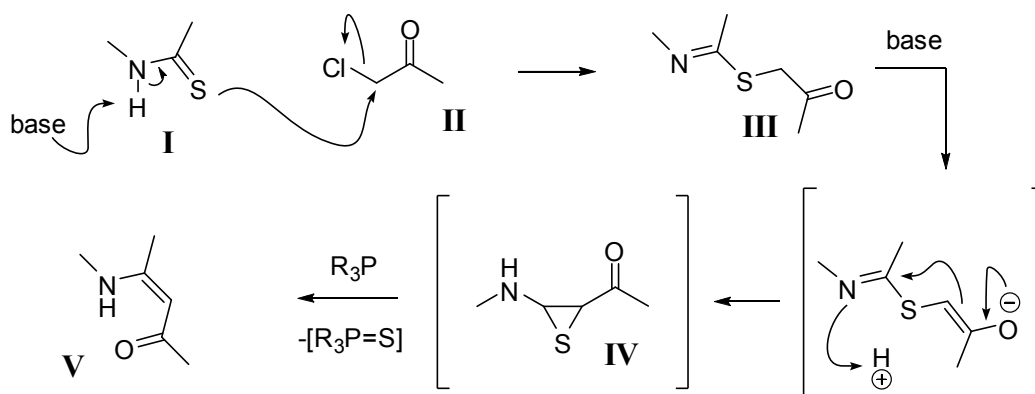


Scheme 2.11.

In addition, thiocarboxylic acids have also been used in Eschenmoser coupling reactions, resulting in 1,3-dicarbonyl compounds (eq. 2).⁸⁷ Interestingly, Hussain et al. recently reported the use of selenoamides in place of thioamides (eq. 3).⁹¹

2.4.3.2. Mechanistic Considerations

The Eschenmoser sulfide contraction can proceed via either oxidative or alkylative precoupling.^{2b} The latter variant begins by alkylation of thioamides (**I**) with enolisable α -halocarbonyl compounds (**II**), followed by cyclization of the thiocarbonyl ylide (**III**) to the epi-sulfide (**IV**) which upon thiophile promoted extrusion of sulfur gives vinylogous amides (**V**) (Scheme 2.12).

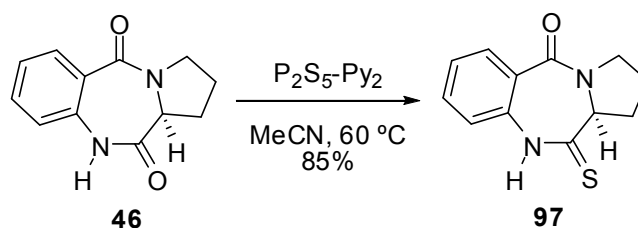


Scheme 2.12. *R* = phenyl or alkoxy.

Reversibility of the thioamide alkylation is a frequently encountered problem when the electrophile (**II**) bears a nucleophilic leaving group.⁹² It is nevertheless possible to avoid retro-alkylation by employing a non-nucleophilic leaving group, such as triflate.⁸⁷

2.4.3.3. Regioselective Thionation

The Eschenmoser-strategy required synthesis of monothione **97**, a compound previously obtained by treating diamide **46** with Lawesson's reagent. However, by using literature methods, based on Lawesson's reagent, we experienced lack of selectivity and difficulties during the workup.⁹³ In fact, these drawbacks prompted us to explore the potential of an alternative thionating agent, namely the crystalline P_2S_5 - Py_2 complex which, as it happened, was under development in our lab (See 3.2). Our efforts turned out fruitful and the monothione **97** was attained in an excellent yield as a bright yellow solid without the need of chromatographic purification (Scheme 2.13).

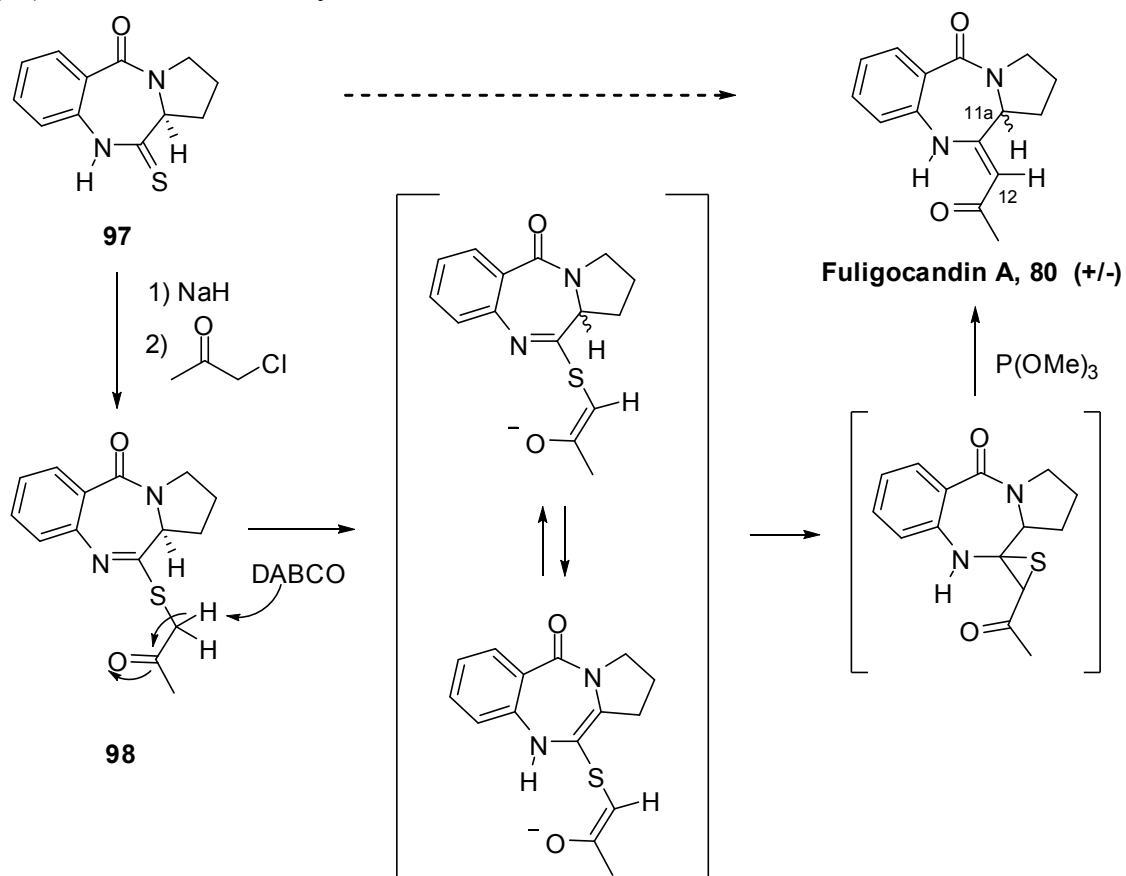


Scheme 2.13.

2.4.3.4. Preparation of Fuligocandin A

Initial alkylation of **97** with chloroacetone gave **98** which was isolated in quantitative yield (Scheme 2.14). Thereafter, a plethora of Eschenmoser coupling conditions described in the literature was screened but fuligocandin A (**80**) remained elusive.

At this point we envisioned that the use of DMSO as reaction solvent could enhance the prospects of the reaction by exposing the carbanion in the coupling step. The use of DMSO would also facilitate the S_N2 alkylation step, enabling a facile one-pot protocol. Preliminary experiment was conducted in DMSO using DBU as a base and triethyl phosphite as sulfur scavenger. Indeed, analysis of the crude mixture indicated the characteristic NMR signals of the desired vinylogous amide (¹H at 5.29 ppm and ¹³C at 91.0 ppm). However, the yield was rather low (40%) and purification was complicated by difficult-to-remove triethyl phosphite and its sulfur analogue (triethyl thiophosphonate). Interestingly, substituting DBU to DABCO resulted in a cleaner reaction. At this point it is worth mentioning that a frequently encountered problem with Eschenmoser sulfide contraction is removal of the sulfur scavenger and its sulfur analogues which often require resort to chromatography. This even prompted A. Eschenmoser to develop a dual reagent containing both amine base and thiophile which has the advantage that it can be separated from the product by aqueous wash.^{86b} More recently, the use of solid-supported triphenylphosphine has been reported.⁹⁴ However, we could solve this problem by using trimethyl phosphite in place of triethyl phosphite, this measure simplified the workup considerably as trimethyl phosphite as well as the by-product trimethyl thiophosphonate could be removed by co-evaporation with ethanol. As a result, fuligocandin A (**80**) was isolated in 98% yield.



Scheme 2.14. Proposed mechanism of the formation of fuligocandin A from **97**.

Unfortunately, the stereocenter at C11a was lost under the conditions employed, and fuligocandin A was isolated as a racemate. This is in agreement with the observations of Arai et al. and also More et al., who reported that racemization readily occurs at this center under basic or acidic conditions (See 2.3.2.).⁸¹⁻⁸²

2.4.3.5. Convergent Synthesis of Fuligocandin B

The synthesis of a target compound can be planned and executed *via* either linear or convergent routes (Figure 2.5). The convergent strategy has several advantages i.e. higher overall yield due to the use of shorter routes and better supply of starting materials.

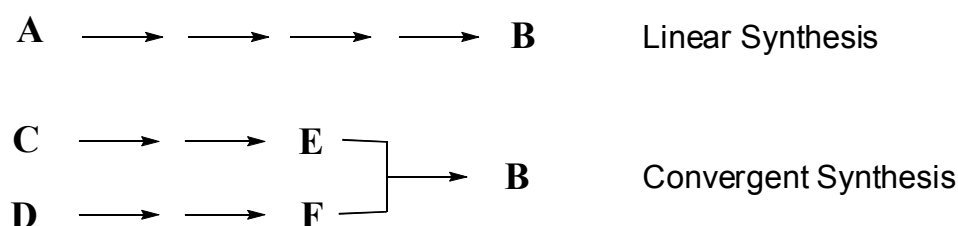
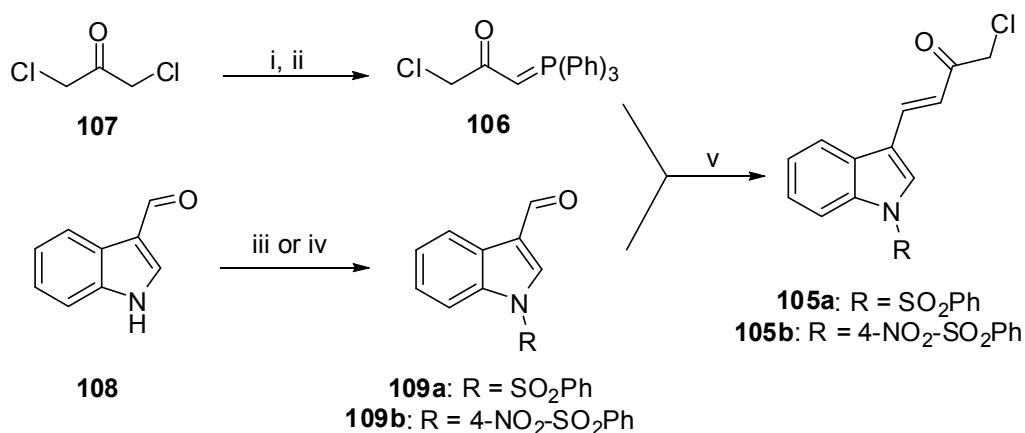


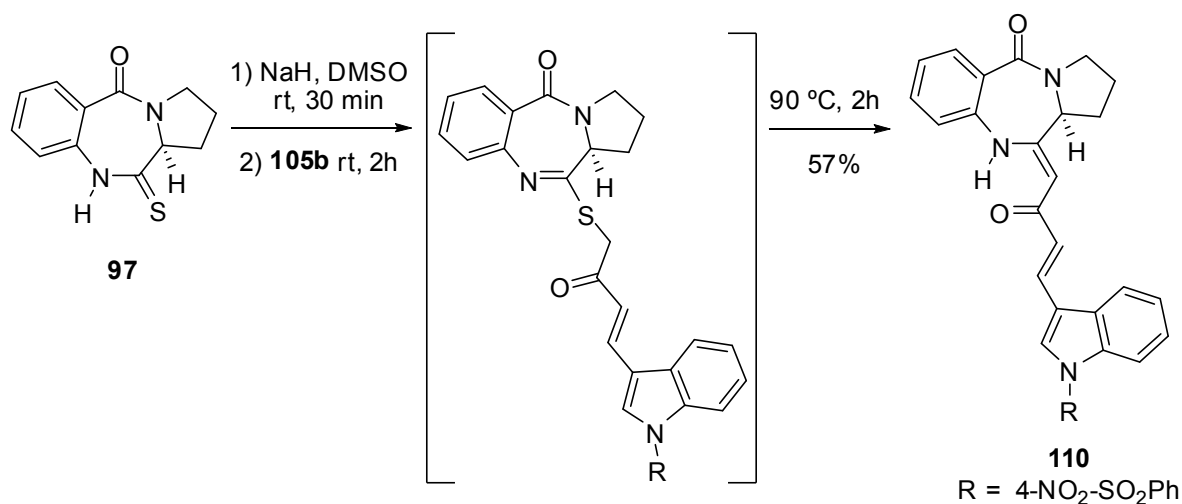
Figure 2.5.

With the synthesis of fuligocandin A (**80**) completed the aim was to prepare fuligocandin B (**81**) by coupling the halide **105** with thione **97** under previously established conditions. The ylide⁹⁵ **106** was readily made from 1,3-dichloroacetone (**107**) but all attempts to couple this ylide via a Wittig reaction with 3-formylindole failed (Scheme 2.16). However, attachment of an electron withdrawing protecting group enabled the Wittig reaction (Scheme 2.15). Accordingly, aldehyde **108** was protected with benzenesulfonyl chloride or *p*-nitrobenzenesulfonyl chloride (NsCl) to give **109a** and **109b**, respectively. Both aldehydes (**109a** and **109b**) underwent a smooth Wittig reaction with the phosphorus ylide **106** at gentle reflux in methanol. Interestingly, conducting the experiment in other solvents, for example benzene, DMSO, H₂O and DMF gave no reaction or poor yields of the required indole derivatives **105**. An attempt using *N*-Boc-protected indole-3-carbaldehyde failed due to the rapid cleavage of the *N*-Boc protecting group.



Scheme 2.15. Reagents and conditions: (i) PPh_3 , THF, rx, 24h (89%) (ii) Na_2CO_3 , H₂O/MeOH, rt, 12h (98%) (iii) 109a: $PhSO_2Cl$, NaOH, TBAHS, rt, 10h (89%) (iv) 109b: NsCl, Et_3N , DMAP, rt, 12h (98%) (v) MeOH, rx, 48h (105a: 69%, 105b: 80%).

Coupling of the monothione **97** and the indole-fragment **105** according to the procedure described in the previous section to obtain fuligocandin A (DABCO, P(OMe₃)) gave the deprotected fuligocandin B, albeit in low yield (<20 %) (Scheme 2.16). In the event, TLC analysis indicated that consumption of the starting materials was incomplete, but it also revealed that the desired coupled product **110** appeared in the absence of both DABCO and P(OMe)₃. Guided by this observation, the sulfide contraction was conducted under purely thermal conditions resulting in the formation of the protected fuligocandin B **110**. Fortunately, the optical activity was preserved under these thermal conditions and the optical rotation of **110** was determined to be +611°.



Scheme 2.16.

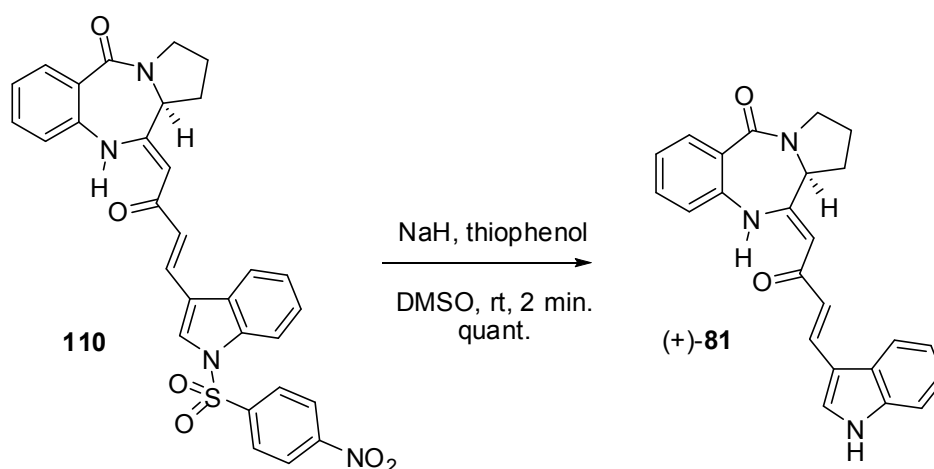
The reversibility of the alkylation step was a problem and the reaction did not proceed to completion. NaI has been reported to shift the equilibrium toward the alkylated product but in this case it did not improve the outcome of the reaction. The Eschenmoser sulfide contraction and also the Wittig reaction was more successful with the use of the nosyl-protecting group instead of the less electron withdrawing phenylsulfonyl-group.

2.4.3.6. Fukuyama's Deprotection Method

At this stage, removal of the nosyl protecting group was all that remained for the completion of the synthesis. This step was complicated by the risk of losing the optical activity due to racemization at C11 as well as the possibility of Michael addition. Attempts using Cs₂CO₃ and MeOH effectively removed the protecting group but, unfortunately, these conditions also lead to racemization of the final product.

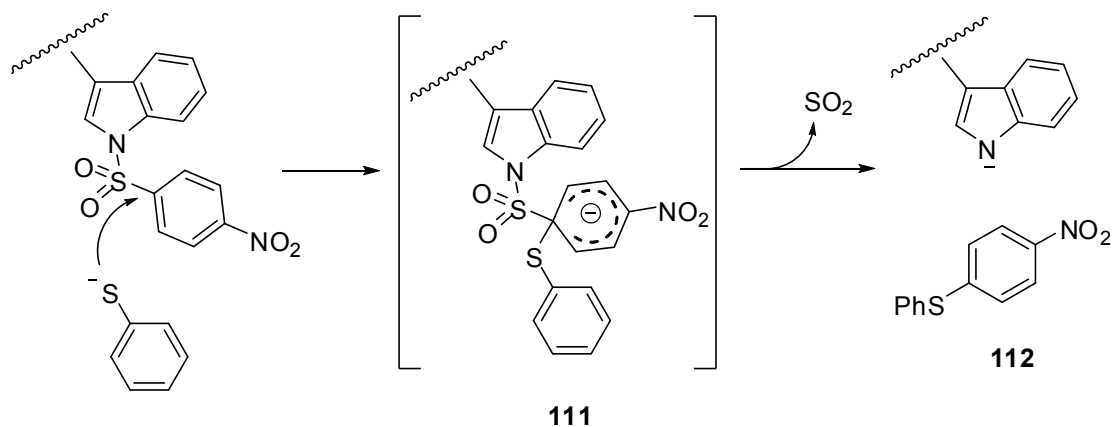
In 1995 Fukuyama and co-workers reported on an exceptionally mild and high yielding deprotection strategy for 2- and 4-nitrobenzenesulfonamides using thiolates in DMF.⁹⁶ Accordingly, sodium phenylthiolate (1 eq.) was added to a solution of the protected fuligocandin B (**110**) in DMSO, whereupon fuligocandin B (**81**) was obtained in racemic form (Scheme 2.17). Undesired racemization was avoided by the use of excess (2 eq.) thiophenol in relation to sodium hydride. Supposedly, racemization is prevented by excess thiophenol, acting as a Brønsted acid and neutralizing the basic species formed as a result of the

deprotection. Experiments using thiolate of the less malodorous reagent mercaptopyridine gave unsatisfactory results. Thus, the optical rotation of **3** was determined (+140°) and is in agreement with data previously reported by Nakatani et al. (+149°).⁷⁵



Scheme 2.17.

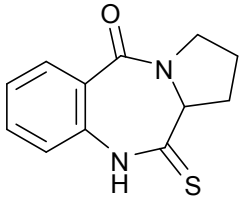
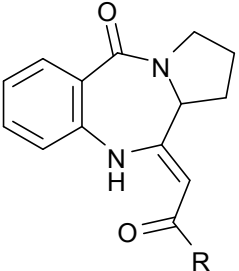
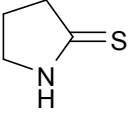
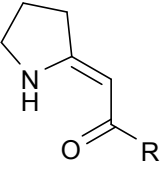
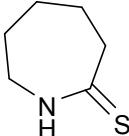
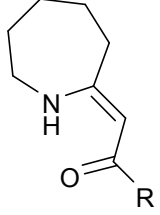
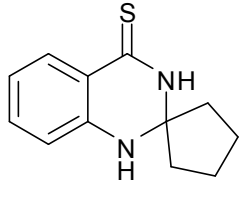
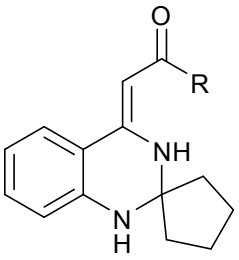
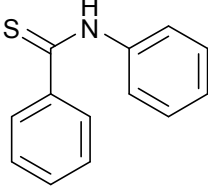
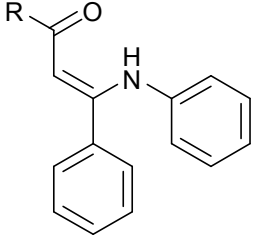
The mechanism proposed for Fukuyama's deprotection involves initial thiolate attack on *ipso* carbon, which proceeds via the Meisenheimer complex **111** (Scheme 2.18). Accordingly, extrusion of SO₂ results in formation of the deprotected amine and (4-nitrophenyl)(phenyl)sulfane **112**.⁹⁷



Scheme 2.18.

2.5. Generalisation of the One-pot Eschenmoser Protocol

After obtaining fuligocandin A and B using the modified Eschenmoser sulfide contraction procedure, we were prompted to further study the scope of this one-pot protocol. A number of vinylogous amides were prepared in good yield and the position of the double bond was determined by NOE studies in selected cases.

Entry	Thione	Vinylogous amide	R =	Yield ^a (%)
1	 97		85 (R=Me)	98
			80b	93
			80c	89
2	 113		114a	83
			114b	87
			114c	85
3	 115		116a	77
			116b	89
			116c	-
4	 117		118a	82
			118b	80
			118c	81
5	 119		120a	84
			120b	85
			120c	87

^aYields of isolated, pure vinylogous amides
a = R = -CH₃; **b** = R = -C₆H₅; **c** = R = -*p*-biphenyl

TABLE 1. Vinylogous amides via Eschenmoser sulfide contraction.

3. Thionation of Carbonyl Compounds Using the P_2S_5 - Py_2 Complex (Paper IV)

3.1. Thiocarbonyl Compounds

Thiocarbonyl compounds and particularly thioamides are present in several biologically active and pharmacologically useful compounds. For example, the anti-tuberculosis drug ethionamide (**121**) is presently the most proscribed drug for treating drug-resistant tuberculosis (Figure 3.1).⁹⁸ Furthermore, a number of well-known drugs containing amide moieties have been thionated in the past e.g. diazepam (**5**, Valium), sildenafil (**122**, Viagra) and acyclovir (**123**).⁹⁹ Thiosildenafil was recently found as an additive in “natural” supplements, marketed as aphrodisiac for treating erectile dysfunction.¹⁰⁰

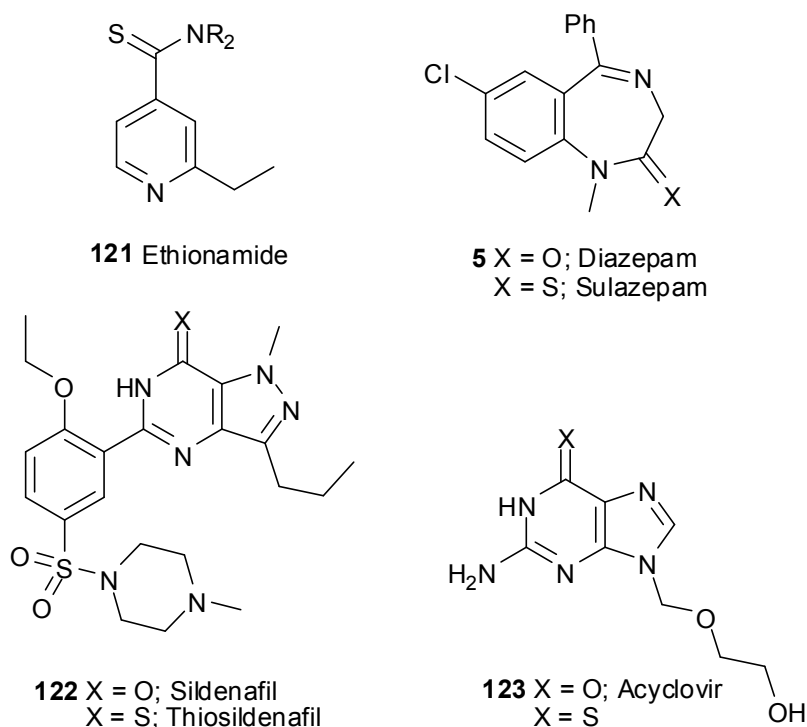


Figure 3.1.

Recent findings suggest that the noxious gas H_2S is an endogenous ligand that appears to be involved in several biological processes including neuromodulation, inflammation and pain perception.¹⁰¹ These findings have increased the interest in H_2S releasing drugs containing sulfur moieties such as thioamides. The naproxen (**124**) derivative ATB-346 (**125**) represents one of the H_2S releasing drug candidates in development (Figure 3.2).¹⁰²

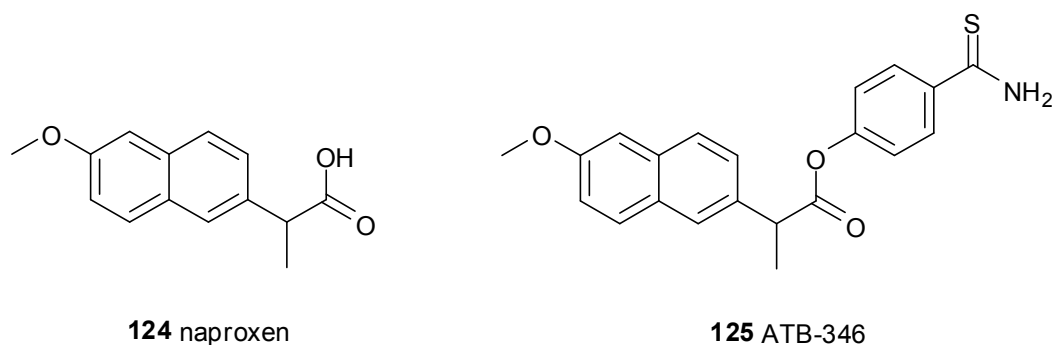


Figure 3.2.

In addition to the pharmacologically useful activities, thioamides are versatile synthetic intermediates, particularly as synthons for preparation of sulfur-nitrogen heterocycles (see 3.1.2.).

3.1.1. Structure and Reactivity of Thioamides



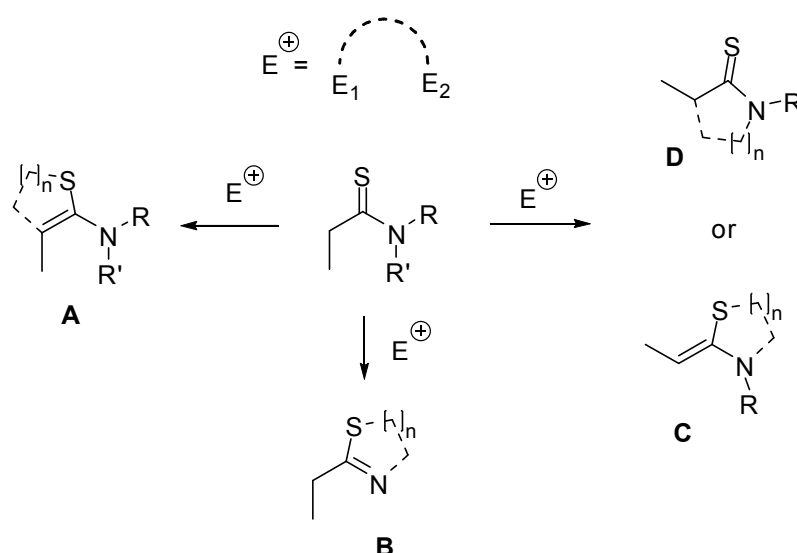
Figure 3.3. *Amide and thioamide.*

Replacing the oxygen of an ordinary amide with sulfur introduces a number of new properties. Sulfur is not nearly as electronegative as oxygen, in fact, it has more or less equal electronegativity as carbon. Furthermore, the larger covalent radius of sulfur, compared to oxygen, results in less efficient overlap in $S_{3p}-C_{2p}$ π -bond, thus the $C=S$ bond is weaker than the $C=O$ bond.¹⁰³ Thioaldehydes and thioketones are usually very unstable and must be prepared *in situ*, however thioamides and thioesters are stabilized by the extra conjugation from the nitrogen or oxygen lone pair and are therefore easier to handle.¹⁰⁴

Thioamides are more reactive than amides, for example they are readily reduced to amines using Raney nickel. On the other hand, thioamides are more resistant to hydrolysis than ordinary amides. Thioamides react with electrophiles either at sulfur or at nitrogen, however *N*-alkylation is rare and likely to proceed via kinetically controlled S-alkylation followed by rearrangement under appropriate conditions.¹⁰³ In the presence of acid, thioamides are protonated at sulfur in a similar manner as amides.

3.1.2. Synthetic Applications of Thioamides

The stability of thioamides relative to other thiocarbonyl compounds combined with their diverse reactivity makes them valuable synthons. Their reactivity, as ambident electrophiles and nucleophiles, in rearrangements and pericyclic reactions as well as in radical chemistry, has been widely used to solve synthetic problems.¹⁰⁵ Recent developments involve a variant of Liebeskind-Srogl coupling that use palladium catalyzed coupling of thioamides with arylboronic acids.¹⁰⁶ Thus, e.g. pyridine-2(1H)-thione will undergo carbon-carbon cross coupling with phenylboronic acid to give 2-phenylpyridine in high yield. Similarly, 2-thiouracil has been coupled with e.g. 2-furyltributylstannane to 2-furyl-2-pyrimidine-4-one. Moreover, thioamides are widely used as starting materials for the preparation of heterocycles, thiazoles in particular.^{105b} Perhaps the most reliable route to thiazoles is the Hantzsch reaction (not to be confused with the Hantzsch pyridine synthesis) discovered in 1887.¹⁰⁷ Versatility of the key thioamide function allows for an unusual variation during the heterocyclization step (compounds A-D, Scheme 3.1). The useful Hantzsch thiazole synthesis belongs to the category B reaction.



Scheme 3.1. Various heterocyclizations by reactions of a common thioamide precursor with dielectrophiles

3.1.3. Conventional Methods towards Thiocarbonyl Compounds

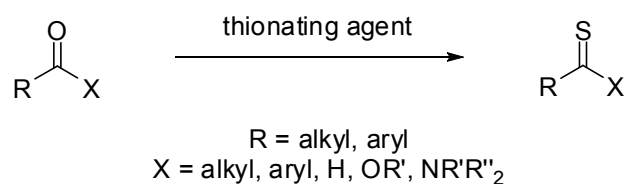


Figure 3.4.

The generally most applied synthetic route toward thiocarbonyl compounds is thionation of the corresponding carbonyl compound (Figure 3.4.). This transformation proceeds particularly well with amides and thus a number of reagents have been developed for this purpose. Heating of the corresponding amide with P_4S_{10} (**126**) in an appropriate solvent, such as toluene or xylene, represents one of the most widely used methods.¹⁰⁸ More recently, Lawesson's reagent (**127a**) have to a great extent come to replace the use of P_4S_{10} .¹⁰⁹ The thionating properties of the reagent **127a** was first studied by Schumacher in the late 1960's.¹¹⁰ However, the scope and limitations of the reagent was largely unknown for a decade when the work of a Danish group brought widespread attention to the general utility of the reagent.¹¹¹

Lawesson's reagent is usually more selective than P_4S_{10} and in case of primary amides, less hampered by nitrile formation. However, the drawbacks associated with these methods have resulted in the development of a large number of modified reagents (e.g. **127b** and **127c**, Figure 3.5.) and procedures which are further discussed in 3.2.2.

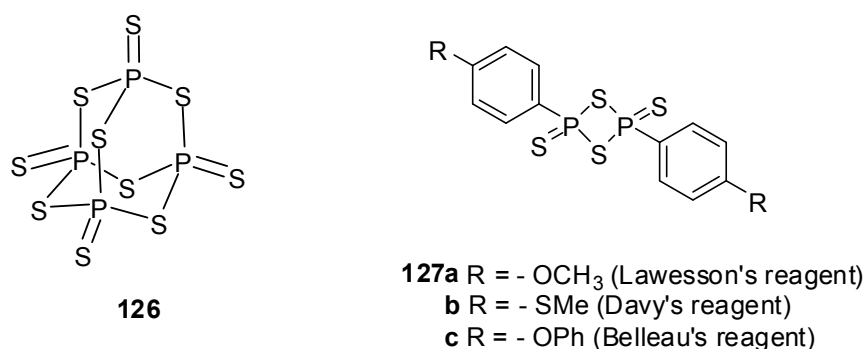
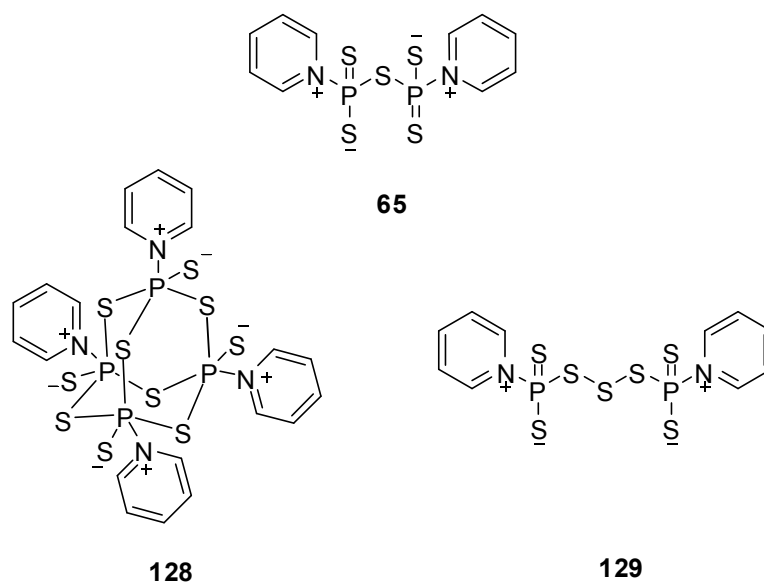


Figure 3.5.

3.2 The P_2S_5 -Py₂ Complex

3.2.1. Structure and Reactivity

P_4S_{10} react readily with refluxing pyridine to form the zwitterionic reagent **65**. In spite of the fact that P_4S_{10} in pyridine has been utilized to thionate carbonyl compounds for a long period of time, the structure of this reagent has been determined only recently (paper 3). Previously, Meisel et al. suggested the structure **65** after analyzing ³¹P NMR data and comparing it to the known derivatives.¹¹² Weintraub proposed another structure (**128**) this was later also retained by Söder and Stratman.¹¹³ The structure **65** has now been unequivocally confirmed by X-ray crystallography (Paper 3) (Figure 3.7). Interestingly, the related structure **129** was also determined by X-ray crystallography in a recently reported paper. The thionating power of this reagent, prepared by heating elemental sulphur (S₈) together with P_4S_{10} in pyridine, is still unknown.¹¹⁴



Scheme 3.6.

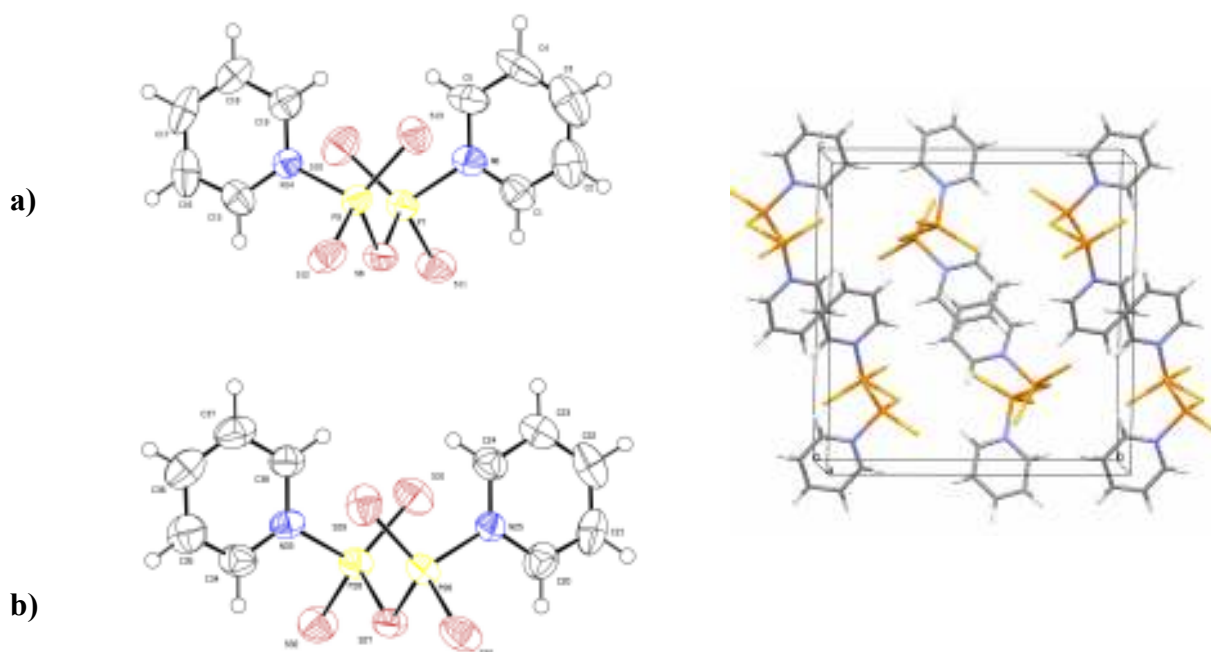


Figure 3.7. The molecular *a)* and crystal structure *b)* of **65**. The crystal structure contains two symmetry independent molecules *a)*.

The results reported in paper 3 illustrate the reactivity profile of reagent **65** towards a wide range of amides and electron rich carbonyl compounds (e.g. **130**) (Figure 3.8). The ratio is usually 1.1 eq. reagent to 4 eq. carbonyl compound, thus the central sulfur atom is supposed to be devoid of thionating power. In cases when two amide functions are present, selectivity could be attained by fine-tuning the conditions (e.g. **131** and **97**). Ester carbonyl groups

remain generally unreactive towards the reagent **65** and this is also true for most ketones, however particularly electron-rich ketones could be thionated in some cases (e.g. **132**). Thioaldehydes are usually very sensitive toward di- tri- and oligo-merization and therefore difficult to isolate as monomers. Hence, the trimer **133** was obtained when **65** was reacted with benzaldehyde **134**, in accordance with previously reported results from thionating **134**.^{104b-g}

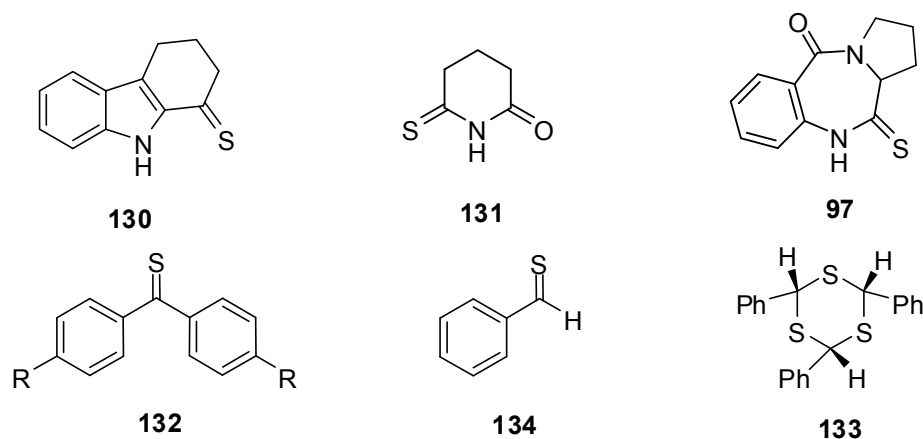


Figure 3.8.

The P_2S_5 -Py₂ reagent (**65**) is moisture-sensitive and the degradation-product **135** was isolated after dissolving/suspending **65** in acetonitrile and adding a small amount of water. Big beautiful crystals were deposited and the structure **135** was confirmed by X-ray crystallography (Figure 3.9).

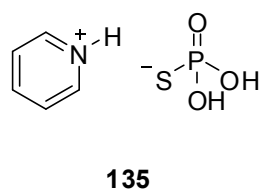


Figure 3.9.

3.2.2. The P_2S_5 -Py₂ Reagent versus Conventional Methods

The utility of reagent **65** as a thionating agent is reported in Paper 3. A variety of amides were thionated in acetonitrile or pyridine, or in some cases even as a melt in dimethylsulfone. The thermal stability of this reagent may be one of its most striking features. This allows reactions to occur at temperatures in the range 165-175 °C (i.e. in dimethylsulfone), whereas LR have been reported to decompose at temperatures above 110 °C.^{109b, c} Moreover, the reagent **65** has fair solubility in hot acetonitrile and good solubility in hot pyridine.

Conventional methods involving P_4S_{10} or Lawesson's reagent are usually heterogeneous reactions.^{105a} This has prompted the development of more soluble variants of LR (**127a**) e.g. Davey's reagent (**127b**) and Belleau's reagent (**127c**) (Figure 3.5), as well as flourous

variants.^{105a, 115} P_4S_{10} have also been modified in the past, thus methods involving addition of various bases e.g. Na_2CO_3 (Brillon's reagent), $NaHCO_3$ (Scheeren's reagent), $R-Li$, $(TMS)_2O$ or even silicon oil have been reported, although some of these are difficult to reproduce.^{104a, 115a, 116} Furthermore, the low solubility of LR have induced several research groups to use LR in combination with microwaves or ultrasound.^{104a}

Using the reagent **65**, selectivity could be attained in several cases when two carbonyl functions were present in the starting material. For example, **131** and **97** were formed in good yield when performing the reaction in hot acetonitrile. Compound **97** have been thionated several times in the past using LR. In our hands, tedious chromatographic purification was always required to separate the dithionated by-product or remains of starting material. Using the reagent **65** in hot acetonitrile, the monothionated product could be isolated by filtration in 85% yield. The fully thionated species **136** and **137** could be isolated by adding an additional amount (0.25 eq) of the reagent.

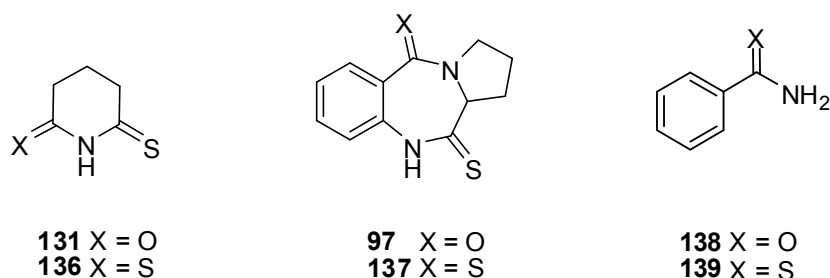


Figure 3.10.

Nitrile formation is a problem often encountered when thionating primary amides using P_4S_{10} , but sometimes also with LR.^{111b, 117} With the reagent **65**, this was never a problem e.g. amide **138** was thionated to **139** in 85% yield.

The purification of products from the reactions with Lawesson's reagent are often tedious and associated with painful chromatographic separation to remove spent reagent and foul-smelling by-products.^{105b} Actually, the drawbacks associated with LR have prompted Ley et al. to develop a solid-phase supported thionating agent.¹¹⁷ A recent example of the difficulties associated with conventional methods is provided by researchers attempting to thionate derivatives of the alkaloid luotonin A (**140a**, Figure 3.11).¹¹⁸

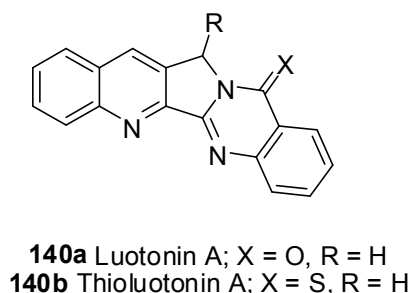


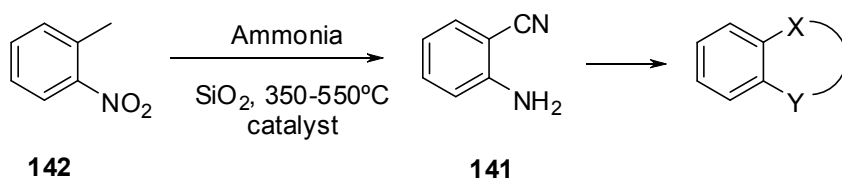
Figure 3.11.

Finally, it should be stressed that chromatographic purification was not required after any of the thionations using reagent **65**. Degradation products of reagent **65** are water-soluble and therefore aqueous work-up gave sufficiently pure products.

4. 1,4-Benzodiazepines and 1,5-Benzodiazocines from Anthranilonitrile (Manuscript V and Paper VI)

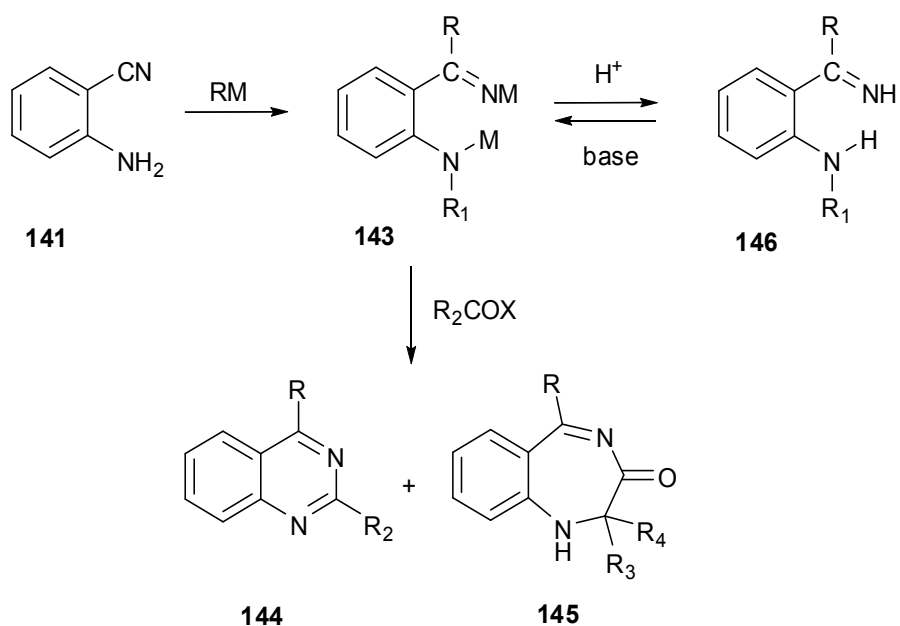
4.1. Addition of Organometallics to Anthranilonitrile

Anthranilonitrile (**141**), produced industrially from 2-nitrotoluene (**142**) by gas phase reaction with ammonia and dehydration catalyst,¹¹⁹ is relatively non-toxic and thus a useful starting-material for the preparation of benzo-fused nitrogen heterocycles.¹²⁰ The two nitrogen-containing functional groups are readily transformed into moieties that cyclize under appropriate conditions, forming e.g. quinazolines or 1,4-benzodiazepines.¹²¹



Scheme 4.1.

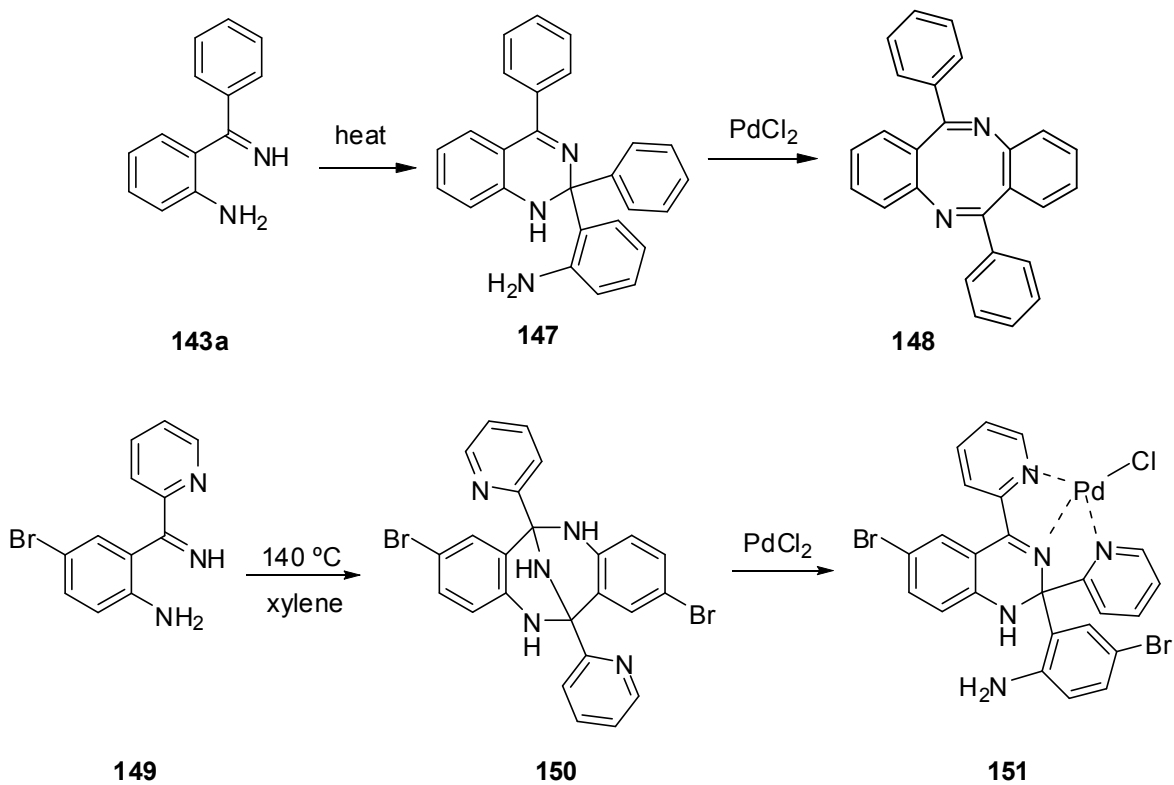
Reactions involving addition of organometallic reagents to anthranilonitrile (**141**) has been a subject of continuous interest in our group. We have previously shown that treating anthranilonitrile with two equivalents of an organometallic reagent (e.g. Grignard or lithium reagent), leads to the formation of an dianion **143**, that readily reacts with various electrophiles to afford *N*-heterocycles e.g. quinazolines (**144**) and 1,4-benzodiazepines (**145**) (Scheme 4.2).¹²¹⁻¹²² The protonated imine **146** is surprisingly stable and could be isolated in crystalline form.



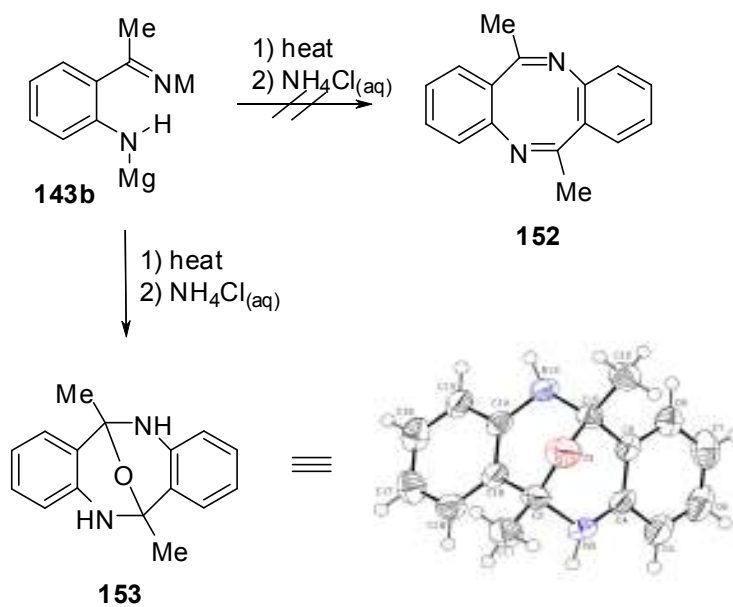
Scheme 4.2. ($R = \text{aryl}$; $R_1 = \text{H or Me}$; $R_2 = \text{alkyl}$; $R_3 = \text{H or alkyl}$; $R_4 = \text{alkyl}$)

4.2. 1,5-Benzodiazocines from Addition of Grignard Reagents to Anthranilonitrile (Manuscript V)

During the course of the work toward quinazolines and benzodiazepines it was found that prolonged heating of dianion **143a** resulted in the formation of **147** (Scheme 4.3.). Exposed to PdCl_2 , dimer **147** gave the well-known dibenzo[b,f][1,5]-diazocine **148**.^{64b, 123} Similar transformations have been studied by Leganza et al. (Scheme 4), thus anion **149** gave the dimer **150** which could be transformed to an analogue of compound of **147**, namely **151**.¹²⁴ Interestingly, X-ray studies revealed the presence of palladium, still coordinated to the nitrogens of the molecule.

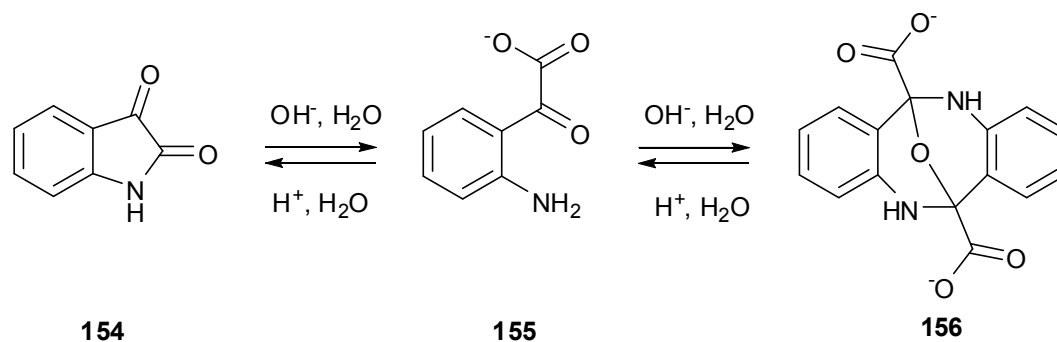


Scheme 4.3.



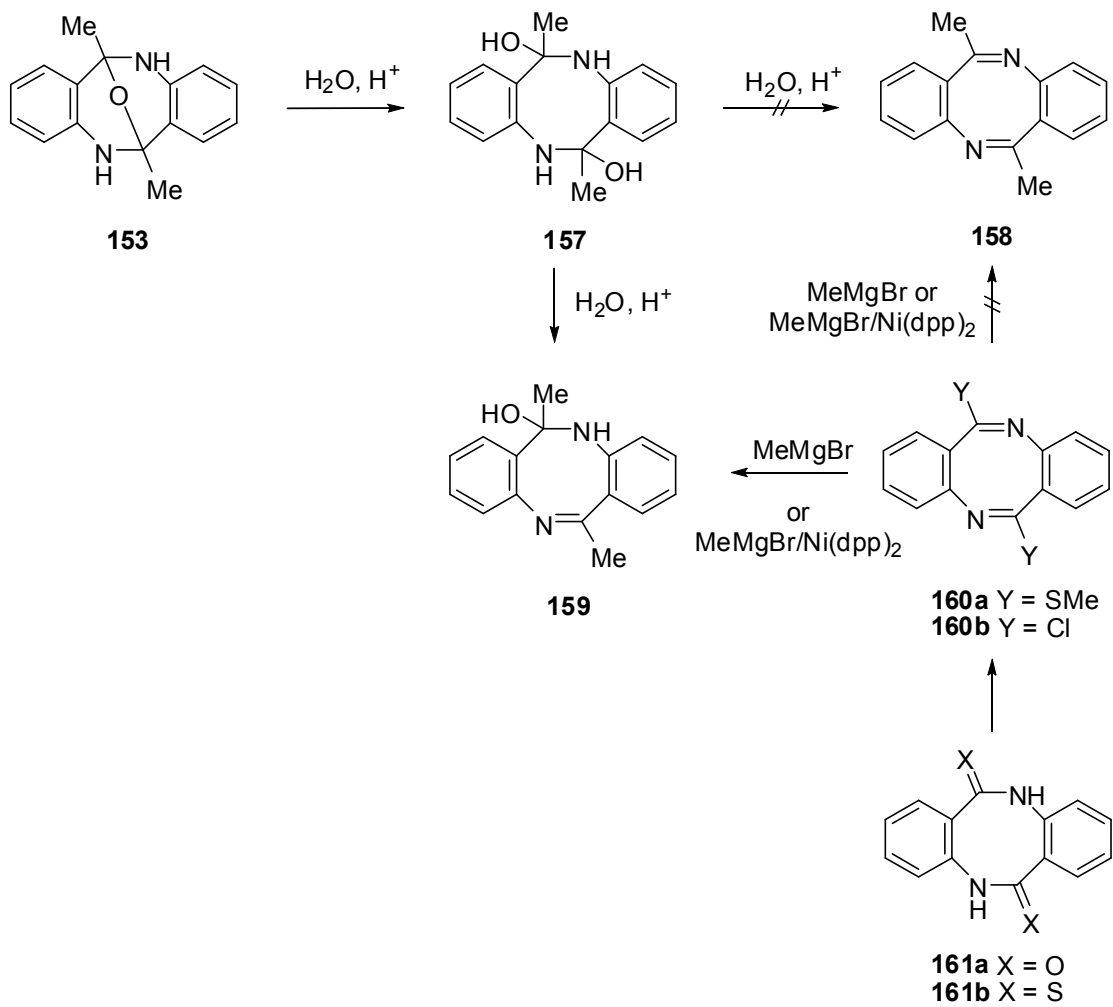
Scheme 4.4.

Heating of dianion **143b**, prepared from anthranilonitrile and methylmagnesium bromide, did not result in the formation of dimer **152** (Scheme 4.4.). However, the bridged compound **153** (the structure was confirmed by X-ray crystallography) was isolated after refluxing **143b** in THF. This type of transannular ether *N*-heterocyclic system is rare and there are only scattered reports of similar benzodiazocines in literature.¹²⁵ In an interesting study by Stefanovic et al. a base-induced ring-opening of isatin (**154**) gave intermediate **155** which condensed to the 1,5-benzodiazocine **156** - an unstable molecule that converts back to isatin readily under acidic conditions (Scheme 4.5.).^{125a}



Scheme 4.5.

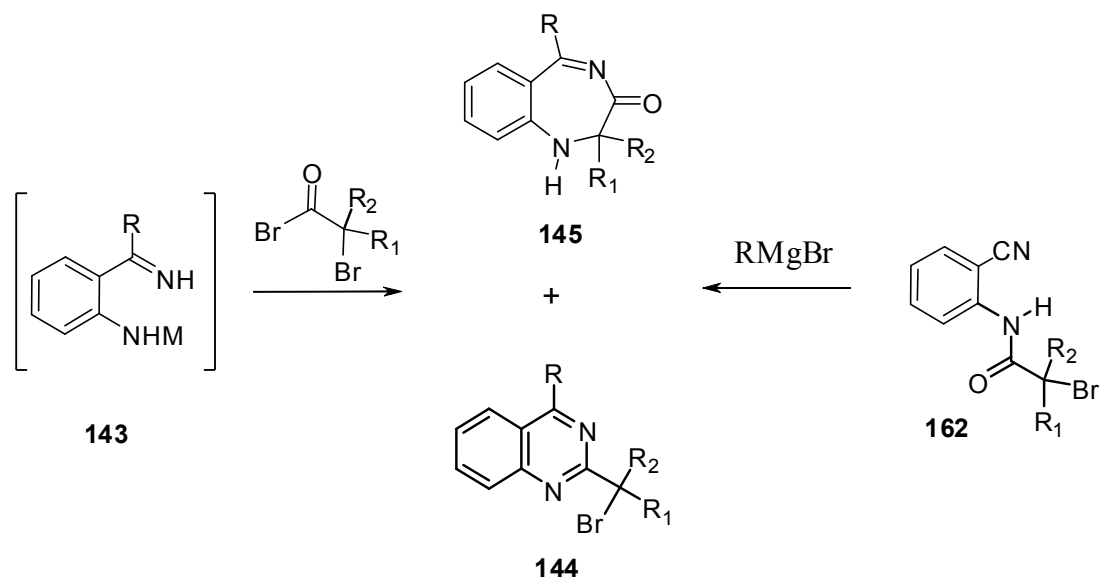
Further investigation of the diazocine **153** showed that addition of acetic acid induced ring-opening to give the symmetrical dihydroxy derivative **157** (Scheme 4.6.). There is no general procedure for preparation of 2,6-dialkyldibenzo[*b,f*][1,5]diazocines, e.g. **158**, and attempts to obtain this compound from **153** failed. However, NMR analysis indicated the formation of a partially dehydrated compound, namely **159**, which rapidly decomposed at room temperature. At this point we investigated the nickel-catalysed addition of MeMgBr to *S*-methyl compound **160a** according to the method originally developed by Wenkert.¹²⁶ The isolated product was identical to the unstable compound **159** previously obtained from **153**. According to literature, treating **160b** with various nucleophiles have resulted in 2,6-disubstituted dibenzo[1,5]diazocines.¹²⁷ Consequently, dichloride **160b**, prepared from diamide **161** and PCl₅, was treated with MeMgBr. Nevertheless, once again, dibenzo[1,5]diazocine **159** was isolated from the reaction, instead of the desired compound **158**.



Scheme 4.6.

4.3. Synthesis of 1,4-benzodiazepin-3-ones and 1,5-benzodiazocin-4-ones (Paper VI)

5.3.1. Background



Scheme 4.7. ($R = \text{aryl}$; $R_1 = \text{alkyl or H}$; $R_2 = \text{alkyl}$)

It has previously been shown that the dianion **143** is a suitable starting material for 1,4-benzodiazepine-3-ones **145** (Scheme 4.7).^{122, 128} For example, addition of 2-bromoisobutyryl bromide to dianion **143** ($R = \text{Ph}$) gave 1,4-benzodiazepine **145** ($R = \text{Ph}$) which could be separated into two separate conformers (Figure 4.1).^{128b} Benzodiazepine **145** could alternatively be obtained by treatment *N*-acyl anthranilonitrile (**162**) with Grignard reagents (Scheme 4.7).^{128c} Quinazolines **144** were obtained as by-products in both cases.

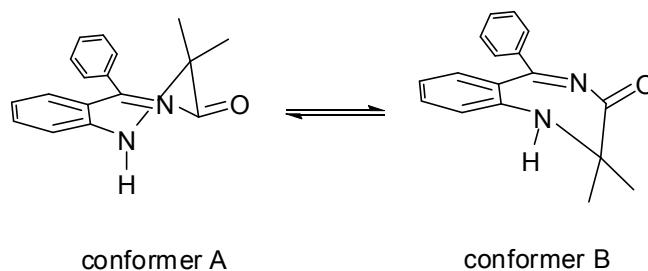
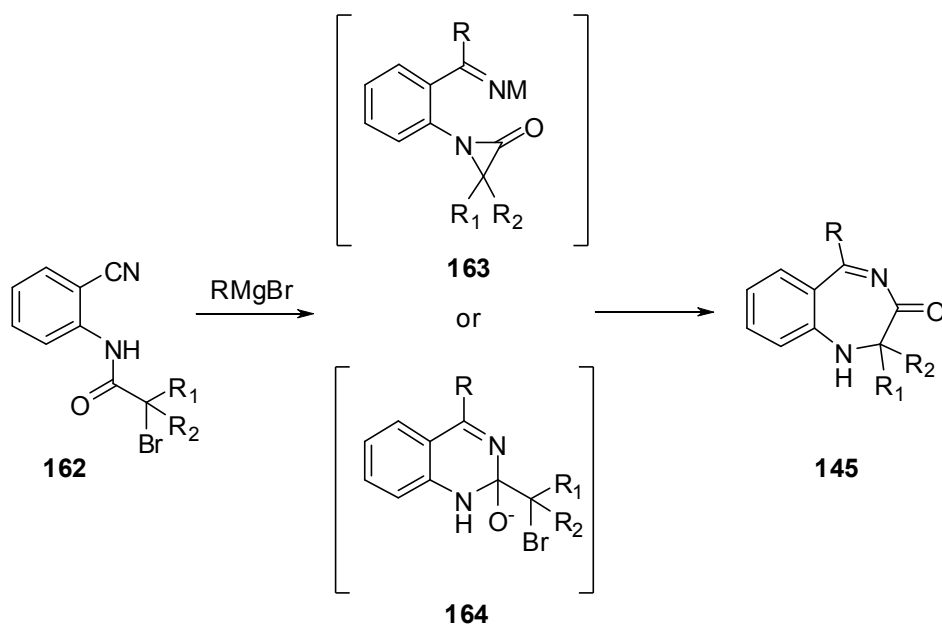


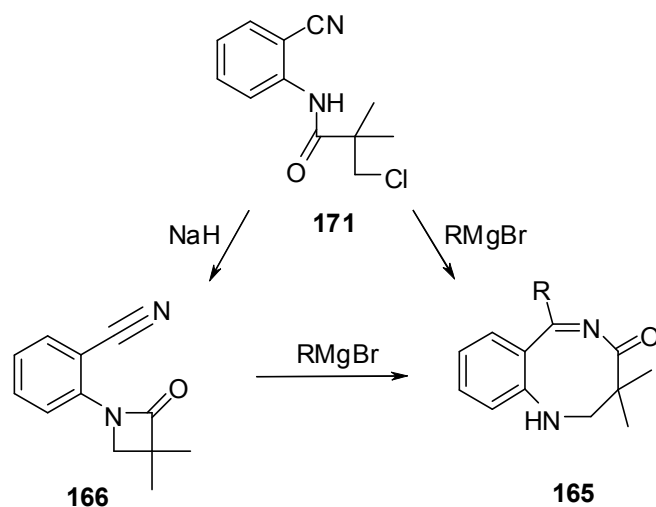
Figure 4.1. The two isolable conformers (A and B) of 1,2-dihydro-2,2-dimethyl-5-phenyl-3H-1,4-benzodiazepin-3-one (**145**).^{128b}

4.3.2. Mechanistic Aspects



Scheme 4.8. ($R = \text{aryl}$; $R_1 = \text{alkyl or H}$; $R_2 = \text{alkyl}$)

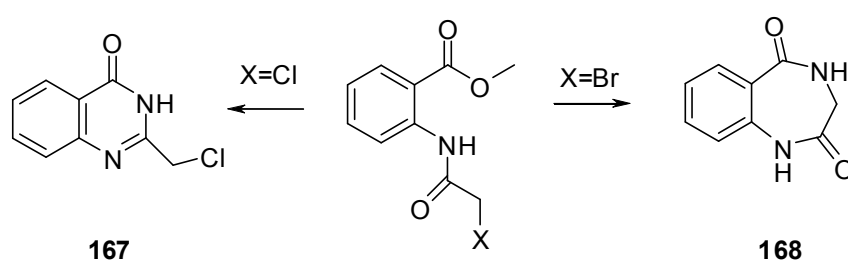
The mechanism leading to these rare 1,4-benzodiazepin-3-ones (**145**) obviously proceeds *via* a rearrangement (Scheme 4.8.). Mechanistic considerations involving intramolecular ring opening of a α -lactam intermediate (**163**) appeared to be supported by the formation of 1,5-benzodiazocine **165** from β -lactam **166** (Scheme 4.9). However, evidence for the existence of α -lactam **163** was never obtained. Moreover, the fact that *N*-methyl anthranilonitrile could be converted to an *N*-methylated derivative of **145** ($R = \text{Ph}$) is in strong disagreement with the α -lactam proposal.¹²² To this end, proposed ring-expansion of a 6-membered intermediate **164** appears more appealing since this suggestion would also provide a common intermediate for the simultaneous formation of quinazoline by-products (**144**).



Scheme 4.9.

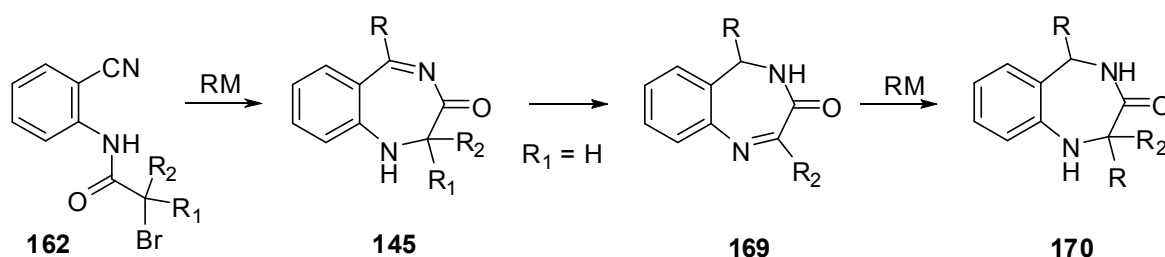
4.3.3. Current Work

1,4-benzodiazocin-3-ones are relatively rare compared to 1,4-benzodiazepin-2-ones and in paper IV we further investigated these intriguing products by addition of Grignard reagents to the *N*-acylated anthranilonitrile derivative **162**. A few factors were determined to affect the outcome of the reaction of **162** and organometallic reagents; the nature of α -halide X, the organometallic reagent (RM) and the substituents (R_1 and R_2) at the α -position. The nature of the halide was found to influence the size of the ring, thus in some cases ($Y=Cl$) quinazolines was obtained via intramolecular attack on the amide anion. This is in agreement with the findings of Párkányi who found that methyl *N*-chloroacetyl anthranilate cyclized to *N*-chloromethyl-4-quinazolinone (**167**) when treated with ammonia, while methyl *N*-bromoacetyl anthranilate gave 1,4-benzodiazepin-2,5-dione (**168**) under the same reaction conditions (Scheme 4.10.).¹²⁹



Scheme 4.10.

Addition of alkyl Grignard reagents and lithium reagents (*n*-BuLi, PhLi) to **162** gave 4-amino-2-quinolinones via halogen-metal exchange at α -carbon as previously reported by Bergman et al.^{128a} Thus, in order to favour the formation of the desired benzodiazepine **145**, bromo-substituted starting material **162** was treated with aryl-Grignard reagents (RM = PhMgBr or thienylMgBr).



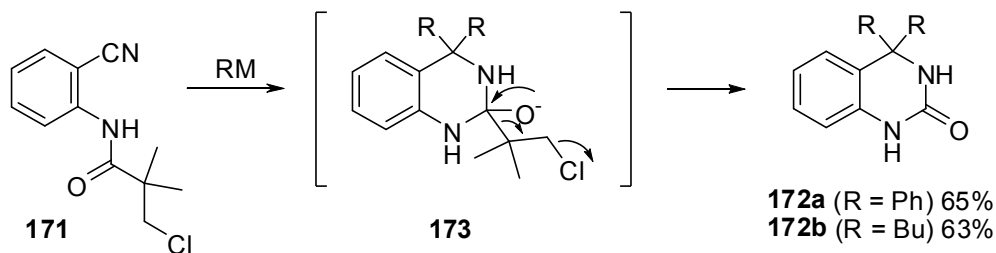
Scheme 4.11. $R = \text{phenyl or thienyl}$, $R_1 = H \text{ or alkyl}$, $R_2 = \text{alkyl}$.

A number of 1,4-benzodiazepines was obtained and it was found that in cases when α -protons were present ($R^1=H$), the isomer of **145**, namely **169** was the major isolated product (Scheme 4.11). It is plausible that **169** is formed *via* a hydride transfer of the initially formed compound **145**. Hence, in one case **145** ($R = \text{Ph}$, $R_2 = \text{Et}$) was isolated and transformed to **169** by addition of another equivalent of phenylmagnesium bromide. The imine bond of **169** is

susceptible to nucleophiles and the addition of a second Grignard reagent, resulting in compound **170**, which was observed in some cases (R = Ph, R₂=Et).

The methodology was also applied to synthesize the higher homologue of **145**, namely **165** which could be obtained by addition of Grignard reagents to *N*-β-haloacyl derivative **171** or alternatively by initial cyclization of **171** to β-lactam **166** (Scheme 4.9).

It is known that lithium reagents and cerium reagents may add twice to nitriles.¹³¹ However, somewhat surprisingly addition of lithium reagents to **171** resulted in quinazolinones **172a** and **172b** (Scheme 4.12). According to a proposed mechanism isobutene and chlorine is lost via Grob fragmentation of intermediate **173**.

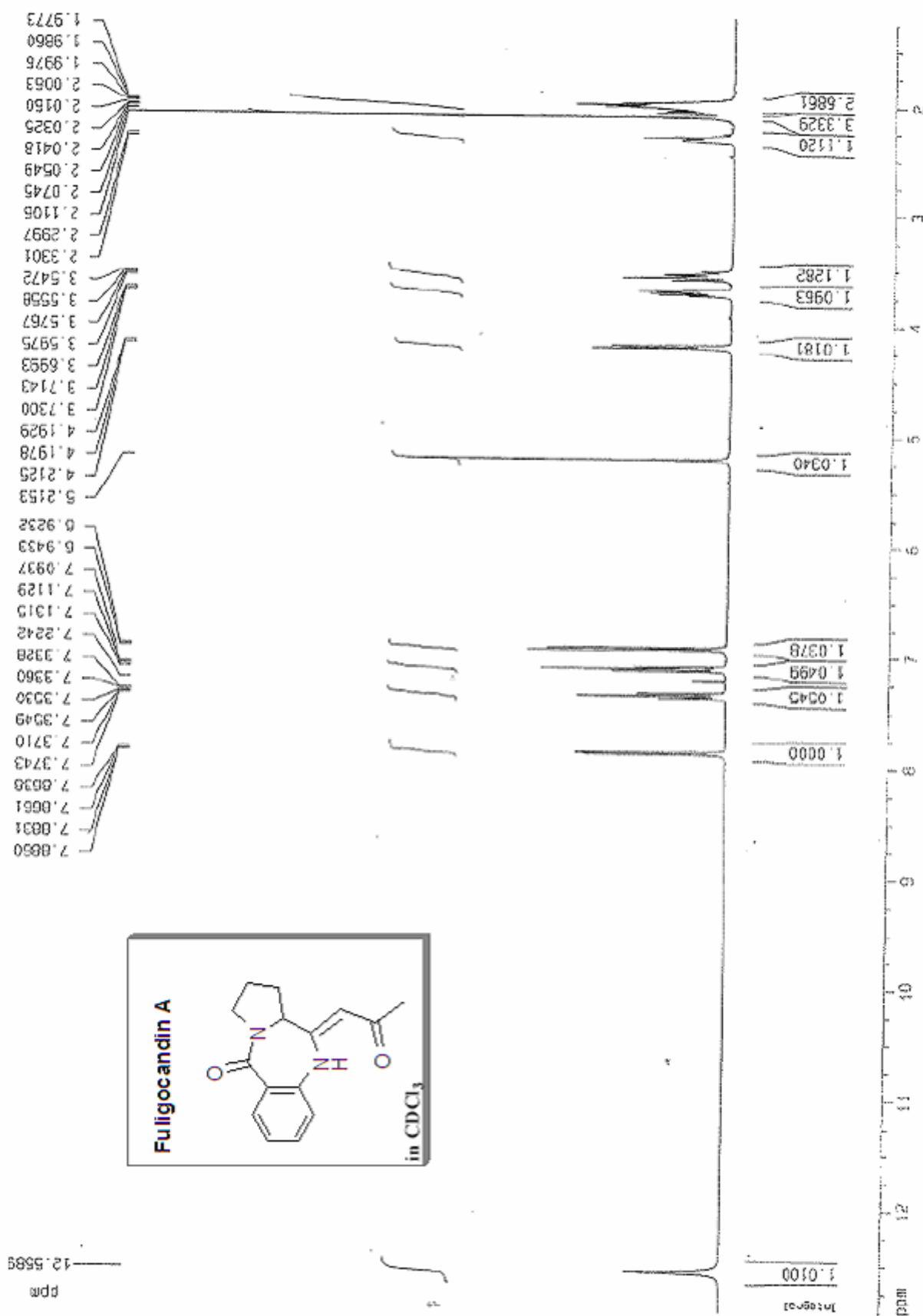


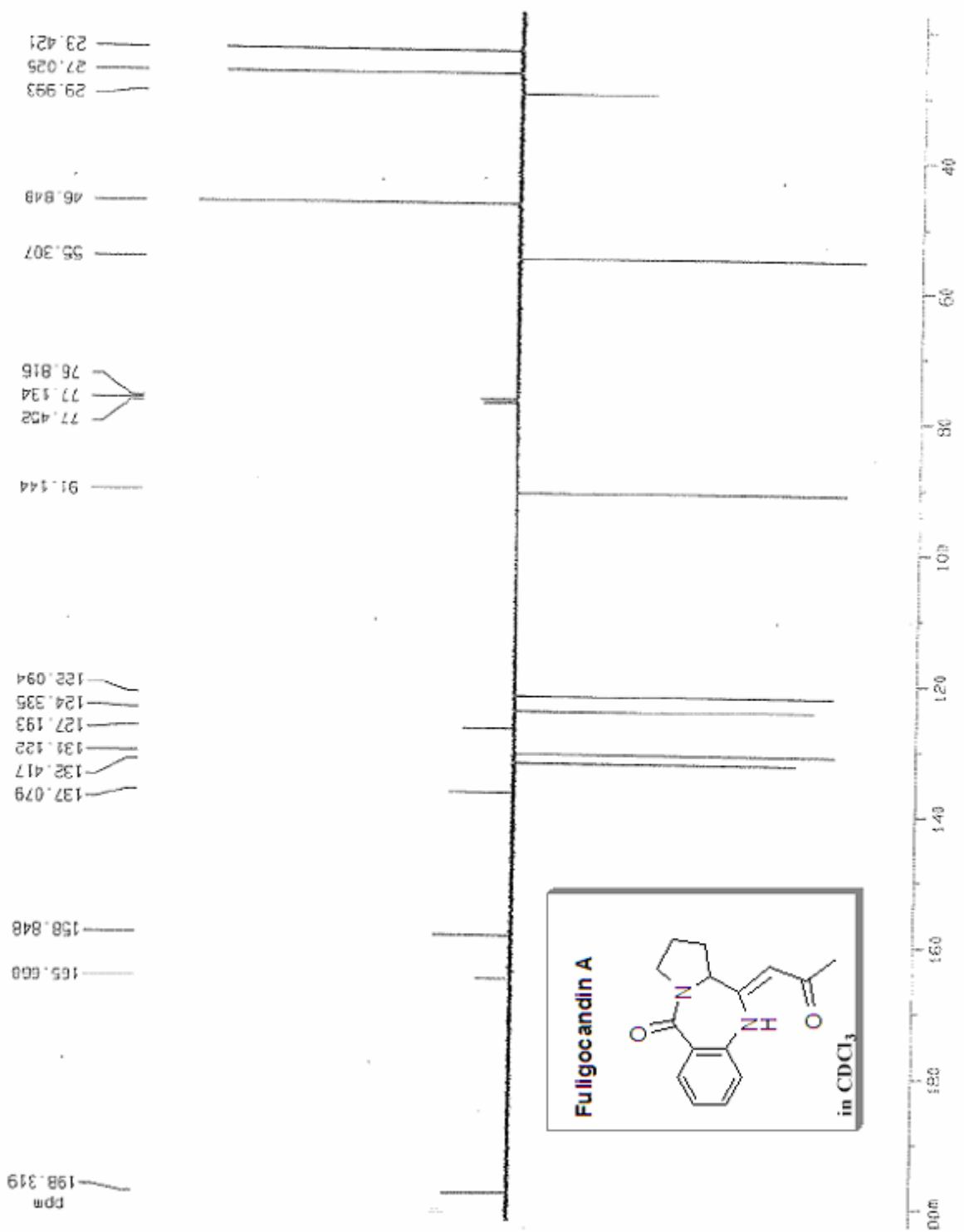
Scheme 4.12. *Grob fragmentation.*

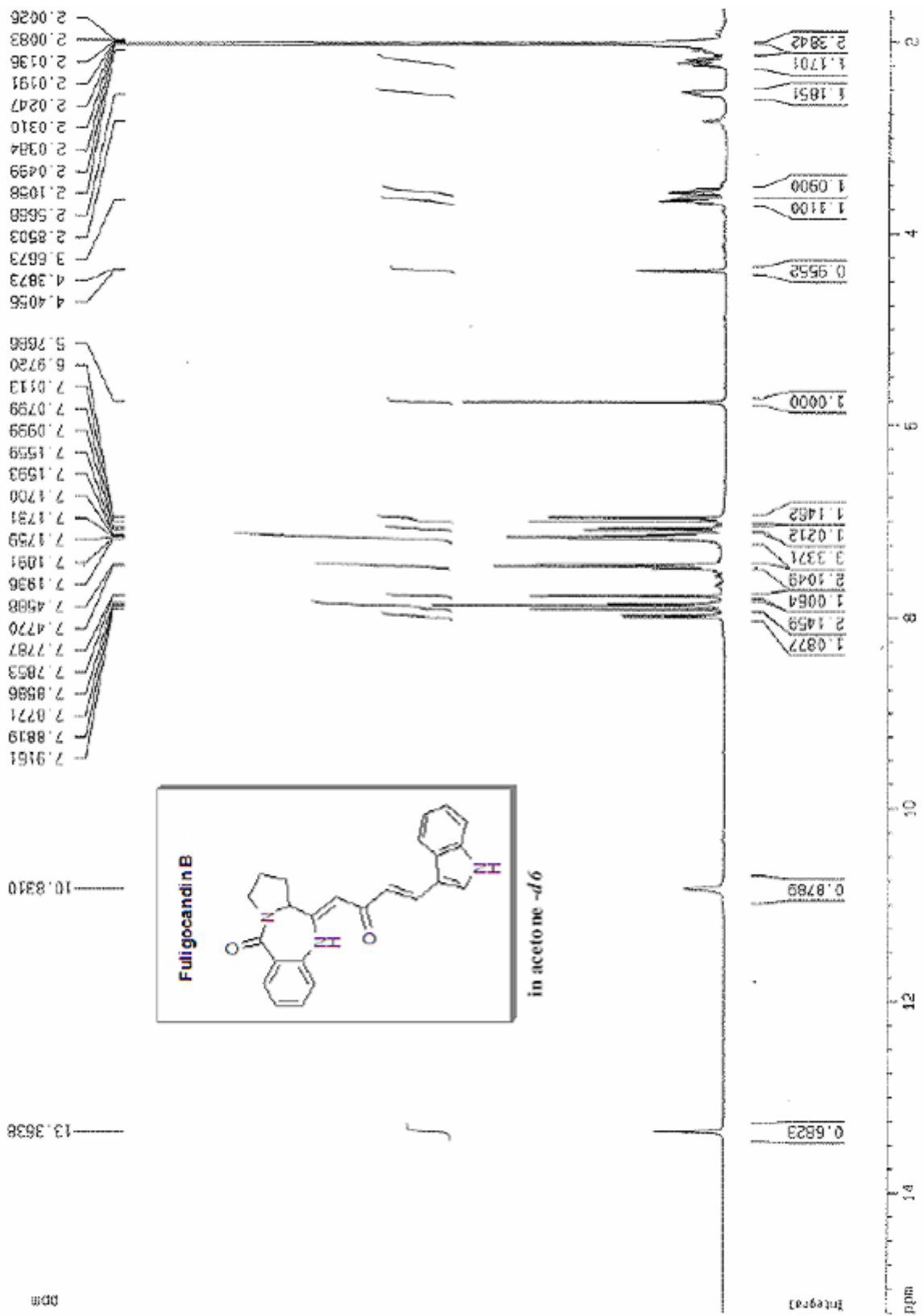
List of abbreviations

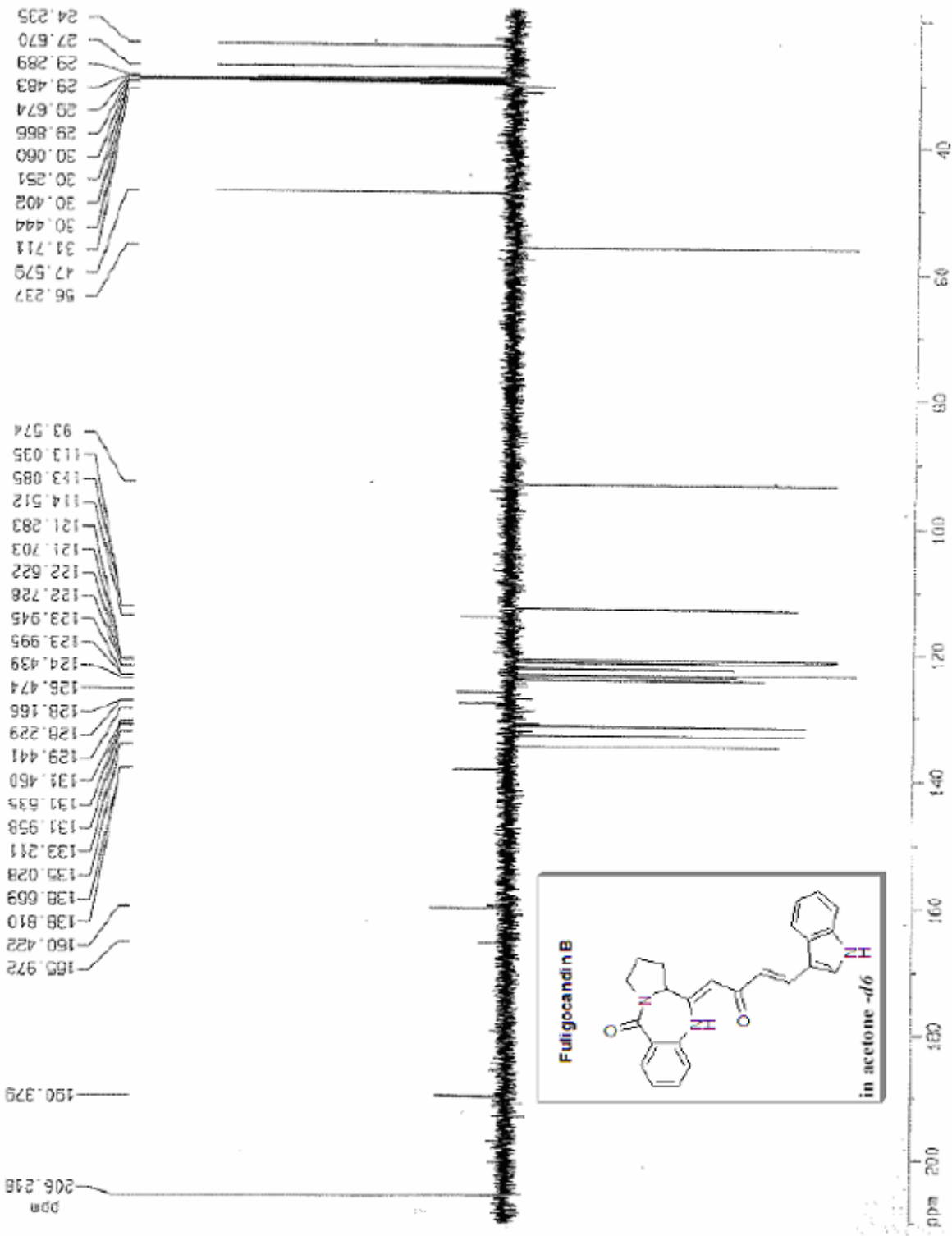
Ac	Acetyl
AcOH	Acetic acid
Bn	Benzyl
Bzp	Benzodiazepine
Boc	<i>tert</i> - Butyloxycarbonyl
n-BuLi	<i>n</i> - Butyl lithium
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	Dichlorodicyanobenzoquinone
DIBAL	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> - diisopropylethylamine (Hünig's base)
DMAP	4-(<i>N,N</i>-Dimethylamino)pyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EI	Electron ionization
ESI	Electrospray ionization
Et ₃ N	Triethyl amine
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast Atom Bombardment
GABA	Gamma-aminobutyric acid
HMPA	Hexamethyl phosphorousamide
IR	Infrared (analysis)
LAH	Lithium aluminium hydride
M	Molar
<i>m</i> -CPBA	<i>meta</i> - Chloroperbenzoic acid
MeI	Methyl iodide
MeOH	Methanol
MnO ₂	Manganese dioxide
mp	melting point
MS	mass spectroscopy
NaH	sodium hydride
NCS	<i>N</i> - chlorosuccimide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
PBD	Pyrrolobenzodiazepine
Ph	Phenyl
PhMgBr	Phenylmagnesium bromide
PIFA	Phenyl iodine bis(trifluoroacetate)
PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RaNi	Raney nickel
rt	room temperature
TCCA	Trichloroisocyanuric acid
TEA	Triethylamine
THF	Tetrahydrofuran
SO ₂	sulfur dioxide

Appendix: ^1H NMR and ^{13}C NMR spectra for Fuligocandin A and B









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