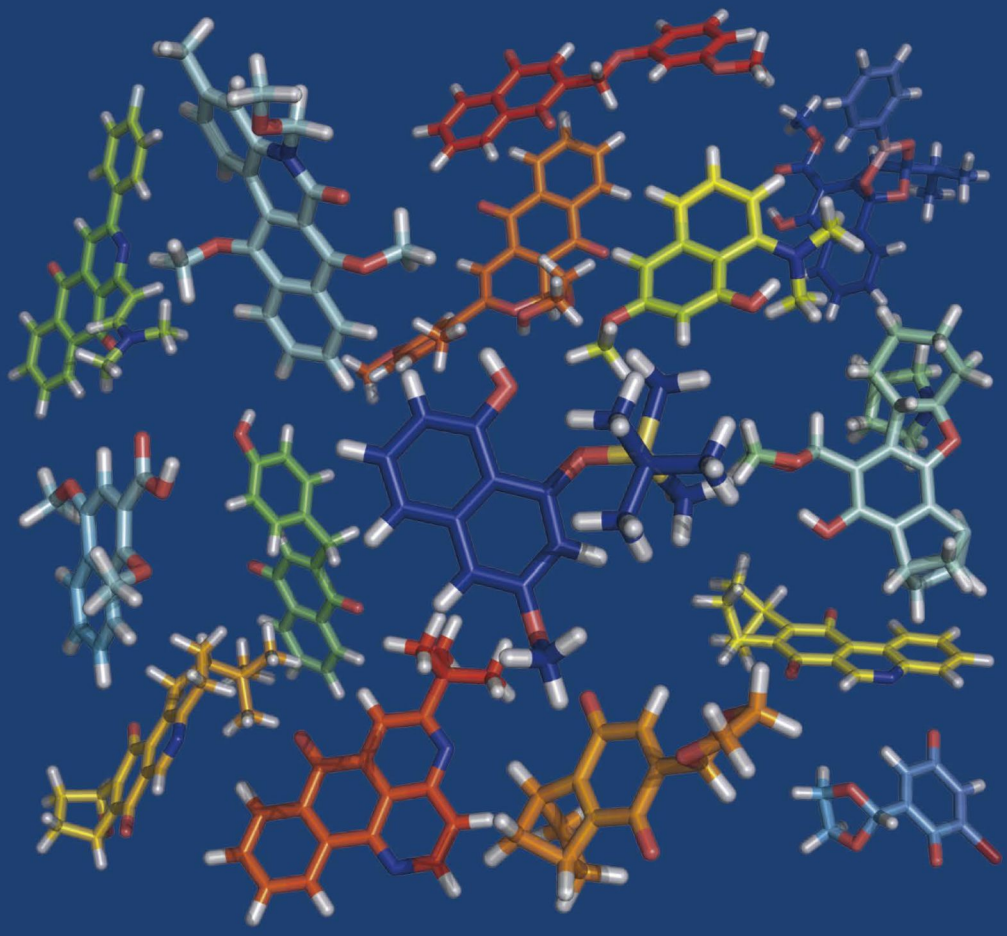

Synthesis of heterocyclic annulated quinones and quinoid compounds

Pieter Claes

UNIVERSITEIT GENT

FACULTEIT BIO-INGENIEURSWETENSCHAPPEN

Generalists know less and less about more and more until eventually they know nothing about everything. Specialists know more and more about less and less until eventually they know everything about nothing.

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Synthesis of heterocyclic annulated quinones and quinoid compounds

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The author,

ir. Pieter Claes

The promoter,

Prof. Dr. ir. Norbert De Kimpe

Woord vooraf

Met het de verdediging van dit doctoraat komt een einde aan negen jaar van mijn leven waar ik steeds met heimwee naar zal terugkijken. De faculteit bio-ingenieurwetenschappen is zonder enige twijfel de tofste van de hele wereld en ik heb hier altijd graag gewerkt en gestudeerd. De weg naar het doctoraat was zelden recht en de afgelopen vier jaar werden de nodige obstakels omzeild of beklommen. Ik stond er gelukkig niet alleen voor en ik ben iedereen die me in raad en of daad heeft bijgestaan zeer dankbaar. Ik wil dan ook al mijn (voormalige) collega doctoraatsstudenten en ATP'ers bedanken, het is altijd vree plezant geweest op de bureau, binnen en buiten het labo en alle plaatsten daartussen. Natuurlijk verdienen ook vrienden en (schoon)familie een eervolle vermelding. Iedereen bij naam noemen zou mensen onrecht aandoen maar de volgende mensen verdienen toch een bijzondere vermelding. Eerst en vooral prof. De Kimpe, om me de kans te bieden dit doctoraal onderzoek te verwezenlijken en me te vormen tot de wetenschapper die ik vandaag ben. Sven en Jan om me gedurende mijn thesis reeds te begeleiden en me te lanceren in mijn doctoraat alvorens ze ons verlieten richting industrie. Gert, Nils, Stijn, zijn opvolger Koen en wisselende stand-ins voor de doorgaans ontspannende rondjes whist tijdens de pauze. Francis, mijn thesisstudent voor zijn bijdrage aan dit onderzoek. Bart, voor zijn hulp bij het creëren van deze cover en om me nog enigszins normaal te doen voelen. Davy en de mensen van het WIV, het was steeds aangenaam samenwerken en we hebben samen zeker mooie resultaten geboekt. Cedric, mijn zwem- en klimmaatje, ik hoop dat je er snel terug bovenop bent en dat we er nog lang samen een lap tegen kunnen geven. Last but not least wil ik Sophie bedanken: jij bent er altijd voor mij geweest en bent zonder enige twijfel het beste dat me ooit overkomen is.

Pieter

Augustus 2013

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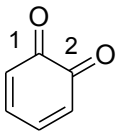
List of abbreviations

9-BBN	9-Borabicyclo[3.3.1]nonane
AHBA	3-Amino-5-hydroxybenzoic acid
ATR	Attenuated total reflectance
Boc	*tert*-Butoxycarbonyl
BPO	Benzoyl peroxide
CAN	Cerium ammonium nitrate
CRM	Complex reaction mixture
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCP	3,5-Dichloropyridine
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
DMSO	Dimethyl sulfoxide
DMF	*N*,*N*-Dimethylformamide
DMF-DMA	*N*,*N*-Dimethylformamide dimethyl acetal
HIV	Human Immunodeficiency Virus
IC	Inhibitory Concentration
LDA	Lithium *N*,*N*-diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
MIC	Minimum Inhibitory Concentration
MOM	Methoxymethyl
MS	Multiple Sclerosis
Ms	Methanesulfonyl
MTBE	Methyl *tert*-butyl ether
NBS	*N*-Bromosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NRP	Nonribosomal Peptide Synthetase
NMP	*N*-Methyl-2-pyrrolidone
OTf	Trifluoromethanesulfonate
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PKS	Polyketide synthase
PPTS	Pyridinium *p*-toluenesulfonate
selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
TB	Tuberculosis
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TOSMic	Tosylmethylisocyanide
TPCD	Tetrakis(Pyridine)Cobalt(II) Dichromate
Ts	*para*-Toluenesulfonyl
WHO	World Health Organisation
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XDR-TB	Extensively drug resistant tuberculosis

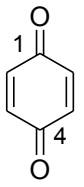
1 Introduction and Goals

1.1 General background

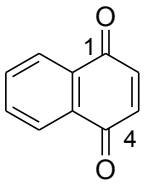
The subject of this PhD thesis concerns the field of quinones, which are a class of cyclic conjugated diketones in which the carbon atoms of the carbonyl groups are part of the ring structure. Quinones can be subdivided in *ortho*-quinones, such as *ortho*-benzoquinone **1**, and *para*-quinones such as *para*-benzoquinone **2**. Even though *ortho*-quinones constitute an important class of compounds, the current research deals with *para*-quinones. Depending on the number of annulated rings, quinones can be divided in three main groups: benzoquinones **1** and **2**, naphthoquinones **3** and anthraquinones **4**. As the title of the thesis reveals, the current research deals with quinones that contain a heterocyclic ring. Anthraquinones bearing an oxygen atom at the 2 position are called pyranonaphthoquinones **5**, when the heteroatom is nitrogen, they are called 2-aza-anthraquinones **6**.



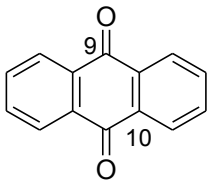
1 1,2-benzoquinone



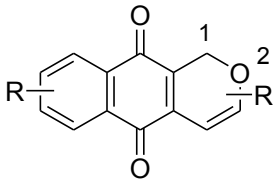
2 1,4-benzoquinone



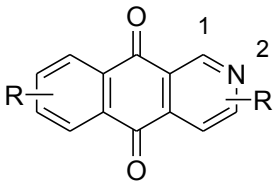
3 1,4-naphthoquinone



4 9,10-anthraquinone



5 pyranonaphthoquinones



6 2-aza-anthraquinones

The first time quinones emerged in the literature dates back to the early 1800's when 1,4-benzoquinone **2** was obtained by the oxidation of quinic acid,[1] which was isolated from a *Cinchona* species (Rubiaceae), a genus of medicinal plants native to tropical South America. In this respect, the word 'quinone' is etymologically traced to the Quechua word 'kina-kina', which means holy bark.

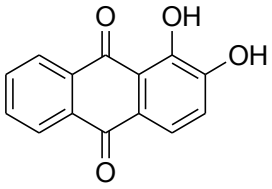
1.2 Quinones in nature

Quinones are widely distributed in plants, fungi and bacteria, arthropods and echinoderms.[2] Their appearance in other phyla is rare apart from the widely distributed 'bioquinones' such as ubiquinone ('ubique' is Latin for everywhere), which are involved in cellular respiration and photosynthesis. These secondary metabolites enhance the survival chances of the producing organism by enhancing inter- and intraspecies communication and competition, facilitation of reproduction, deterrence of predators and chemical defence against parasites and diseases. A striking example of quinones in

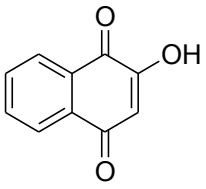
higher animals are the bombardier beetles (Carabidae) which, when physically assaulted, eject a hot quinoid spray from the tip of their abdomen.[3] A beautiful example of intraspecies communication is *Leucosceptrum canum* (Lamiaceae), 'the bird's coca cola tree' in which a proline-benzoquinone adduct acts as a colour attractant to bird pollinators.[4] Secondary metabolites represent a large source of biologically and pharmacologically active compounds and often serve as leads for drug development.[5] Moreover, the use of medicinal plants in traditional medicine is still very popular in many developing countries.[6] Quinones constitute a major and important group within bioactive natural products, as they have been shown to possess antitumour, antibacterial, antiviral, antifungal and antiprotozoal activities, of which many examples can be found throughout this thesis. Therefore, they are a popular subject amongst synthetic organic chemists.[7] Even to date, new quinones continue to be isolated from various sources.[8] However, quinone chemistry is not limited to the synthesis of potential bioactive compounds. Recently, it was discovered that mussels 'glue' themselves to their wet substrate using quinone chemistry, which inspired researchers to create a new type of medical adhesive for use in pancreatic islet transplantation, an experimental procedure for patients with type 1 diabetes.[9]

1.3 Quinones in industry

The first industrial synthesis of quinones dates back from 1868 when the natural dye alizarin **7** was synthesised.[10] This was the first time that a natural pigment was duplicated synthetically. As this process replaced the expensive and labour intensive extraction process of the roots of Madder plants (*Rubia sp.*), the synthetic alizarin **7** could be produced for a fraction of the cost of the natural product. This boosted the use of quinones in organic synthesis even though quinone dyes are mostly replaced by more stable pigments such as azo dyes. Lawsone **8**, isolated from leaves of the Henna plant (*Lawsonia inermis*, Lythraceaea), is used as a dye for the skin, fingernails, hair, cloth and leather.[11]

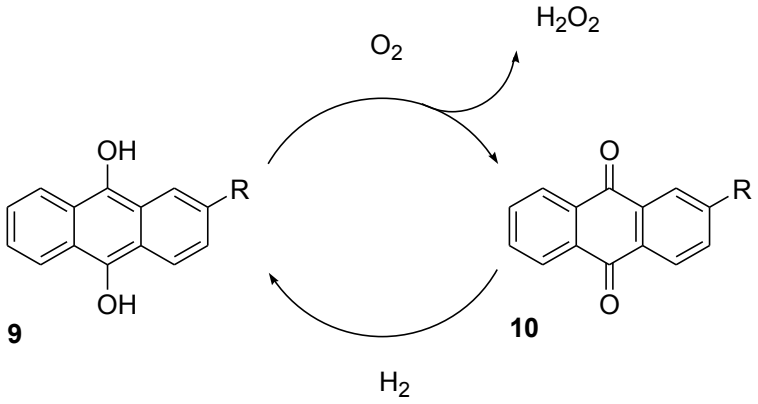


7 Alizarin



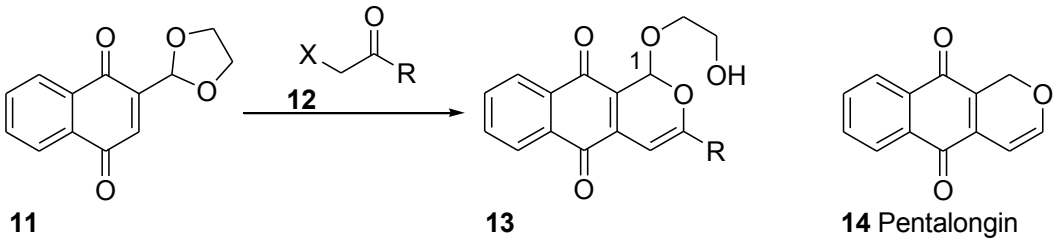
8 Lawsone

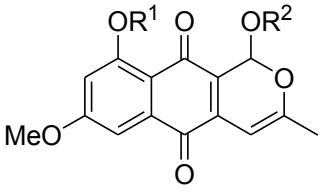
The most important application of quinones in industry is the production of hydrogen peroxide.[12] Hydrogen peroxide is manufactured almost exclusively by the Riedl-Pfleiderer process, in which an anthraquinone is circulated between its reduced and oxidised form by means of reduction with H_2 followed by oxidation with air and liberation of hydrogen peroxide.



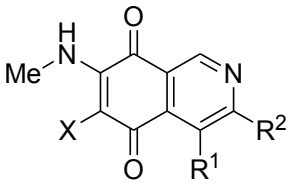
1.4 Goals of the research

(1) As stated above, natural products are an important source of lead compounds towards drug discovery.[5] For instance, anticancer drugs such as daunorubicin, doxorubicin, mitomycin and mitoxantrone are all quinones derived from natural products or are natural products themselves. Pentalongin **14** was isolated from the roots of the African woody herb *Pentas longiflora* Oliv.[13] The roots of this herb are used in the traditional Kenyan medicine as a cure against tapeworm, itchy rash and acne. A decoction of the roots is mixed with milk and used as a cure for malaria, but causes acute diarrhoea and acts as a purgative. In Rwanda the plant is known as Isagara and it is mixed with butter as an ointment to treat scabies and the skin disease Pityriasis versicolor.[14] A first goal of this thesis was a search for a catalytic method to synthesise 1-(2-hydroxyethoxy)pyranonaphthoquinones **13** starting from 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **11**, which is a substitute for the corresponding unstable 2-formyl-1,4-naphthoquinone. As these compounds **13** bear and acetal function at C-1, they are versatile synthetic intermediates, which not only allow functionalisation at this position but also easy conversion into the corresponding 2-aza-anthraquinones. These properties would allow the total synthesis of natural products such as 1-hydroxydehydroherbarin **15a**, the ascomycones A **15b** and B **15c** and the mansouramycins **16**. Even though a non-catalytic version of this reaction is widely used in quinone chemistry, catalysis would reduce the number of reaction steps, reduce the use of toxic pyridine and allow for a wider substrate scope.



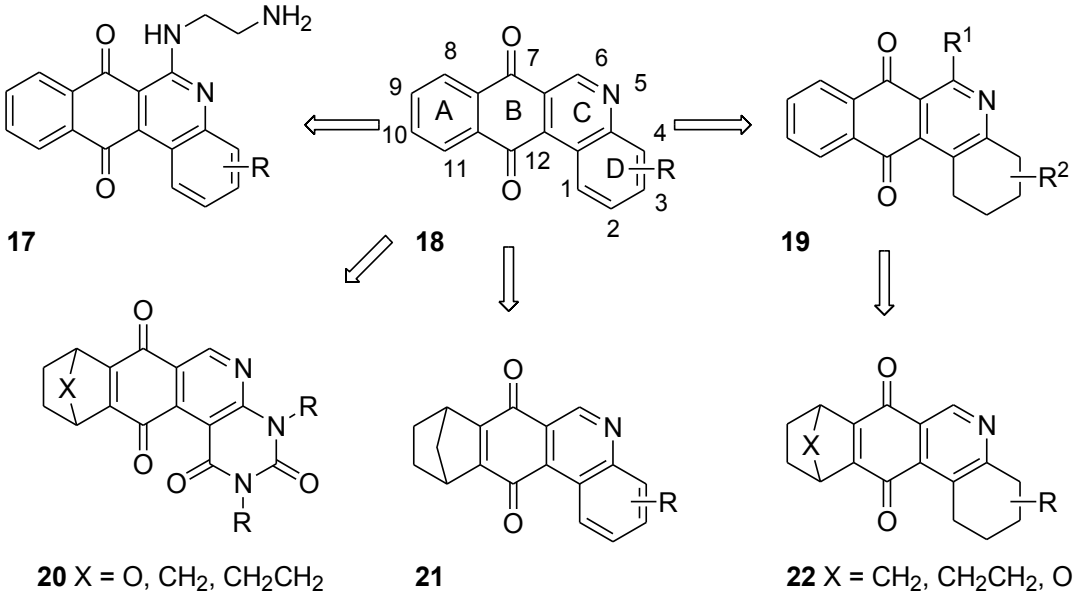


15a 1-Hydroxydehydroherbarin
15b & c Ascomycone A & B



16 Mansouramycin A - D

(2) At our research department, substantial research has been devoted towards the synthesis of new bio-active pyranonaphthoquinones and 2-aza-anthraquinones.[15,16,17] The current efforts focus on the synthesis of a library of benzo[*j*]phenanthridine-7-12-dione **18** derivatives, which will be tested in collaboration with the Scientific Institute of Public Health (Uccle, Brussels) against *Mycobacterium tuberculosis* and some related Mycobacteria such as *M. bovis*, *M. avium* subspecies and *M. ulcerans*. During previous research, various benzo[*j*]phenantridine-7-12-diones **18** were tested against *Mycobacterium tuberculosis*.[18] It was found that these 2-aza-anthraquinones **18** showed promising antimycobacterial activity even though this activity was accompanied by a relatively high cytotoxicity. Therefore, the synthesis of variations of the benzo[*j*]phenanthridinedione scaffold **18** was envisaged focusing on the design of more 'out of plain' derivatives and further functionalisation of the benzo[*j*]phenanthridinedione scaffold at C-6. Thus, the synthesis of C-6 substituted benzo[*j*]phenanthridinediones **17**, 1,2,3,4-tetrahydrobenzo[*j*]phenanthridinediones **19**, 8,9,10,11-tetrahydrobenzo[*j*]phenanthridinediones **21**, 1,2,3,4,8,9,10,11-octahydrobenzo[*j*]phenanthridinediones **22** and dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **20** was envisaged.

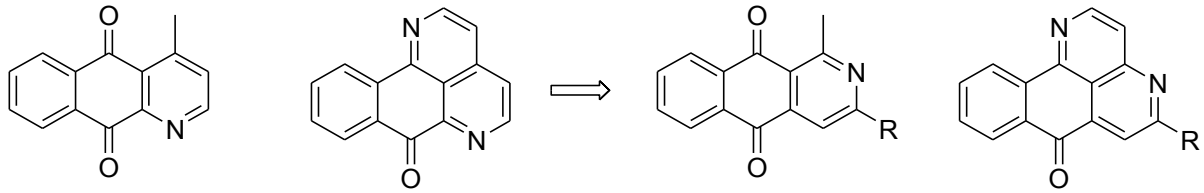


17 **18** **19**

20 X = O, CH_2, CH_2CH_2 **21** **22** X = CH_2, CH_2CH_2, O

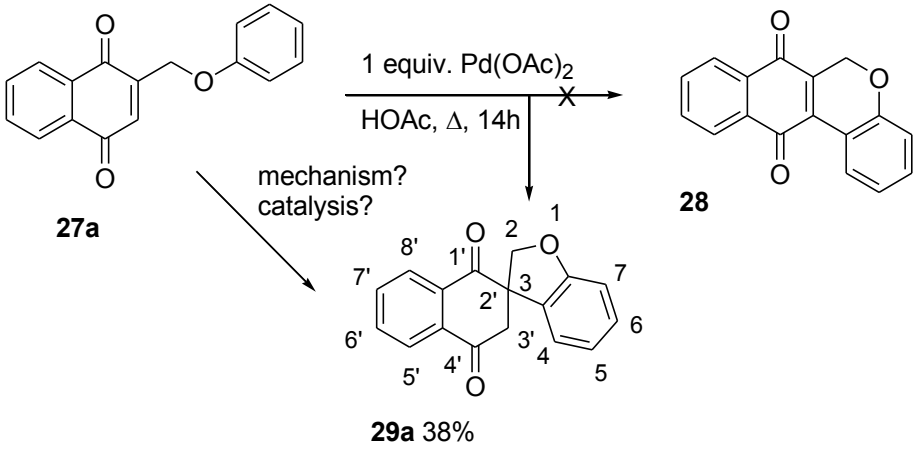
(3) Cleistopholine **23** and sampangine **24** are two strongly related polycyclic aromatic alkaloids isolated from different plants belonging to the Annonaceae family with a wide range of interesting biological activities.[19] As they are reported to have antimycobacterial activity and as it is postulated

that 2-aza-anthraquinones are more bioactive than their corresponding 1-aza-analogues, a short and efficient synthesis of analogues **25** and **26** of cleistopholine **23** and sampangine **24** was envisaged.



23 Cleistopholine **24** Sampangine **25** **26**

(4) During previous research, it was found that the reaction of 2-phenoxymethyl-1,4-naphthoquinone **27a** with palladium(II) acetate did not yield the expected benzopyranonaphthoquinone **28** but led to spirocyclisation product **29a**. In the present study, this surprising reaction was thoroughly investigated in order to propose a mechanism, to develop catalytic conditions, to synthesise derivatives and to explore the scope and limitations. The 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthoquinone] structural motif has never been prepared before. Even though several methods to synthesise structurally similar spiroheterocyclic compounds exist in the literature,[20] the oxygen atom is always directly connected to the spiro carbon.



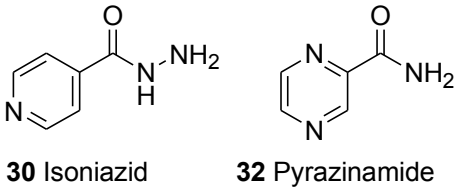
27a **28**

29a 38%

1.5 Tuberculosis

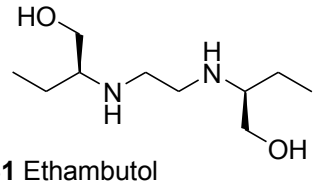
Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). The disease is spread in the air when sick people with pulmonary TB expel bacteria, for example by coughing. In general, a relatively small proportion of people infected with *Mycobacterium tuberculosis* will develop TB disease; however, the probability of developing TB is much higher among immunosuppressed and human immunodeficiency virus (HIV) positive people.[21] Without treatment, mortality rates are high. Treatment for new cases of drug-susceptible TB consists of a 6-

month regimen of 4 first-line drugs: isoniazid **30**, ethambutol **31**, pyrazinamide **32**, and rifampicin **33**.[21]

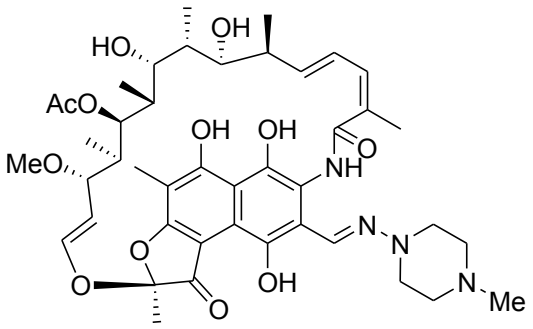


30 Isoniazid

32 Pyrazinamide



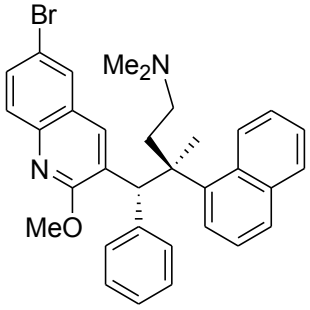
31 Ethambutol



33 Rifampicin

Treatment for multidrugresistant TB (MDR-TB), defined as resistance to isoniazid **30** and rifampicin **33**, the two most powerful anti-TB drugs, is longer and requires more expensive and toxic drugs. For most patients with MDR-TB, the current regimens recommended by WHO last 20 months. TB is an enormous healthcare challenge, especially in immunosuppressed and HIV-positive patients. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.43 million people died from TB, including almost one million deaths among HIV-negative individuals and 430 000 among people who were HIV-positive. TB is one of the top killers of women, with 300 000 deaths among HIV-negative women and 200 000 deaths among HIV-positive women in 2011.[21] In addition to its high prevalence, drug-resistant isolates have emerged in most parts of the world. Research efforts have centred on the development of new chemical entities with improved antimicrobial coverage of *Mycobacterium tuberculosis* and a simpler dosing schedule. Advantages of such an agent may be greater efficacy, improved patient compliance, less resistance and decreased healthcare costs.[21] Given the high rate of attrition, a steady supply of new chemical entities is crucial.[22]

By the end of 2012, bedaquiline **34** (brand name Sirturo®, manufactured by Johnson & Johnson) was approved by the US Food and Drug Administration. It is a diarylquinoline anti-TB drug and the first new medicine to fight TB in more than 40 years. It is specifically approved to treat multidrugresistant TB.[23]



34 Bedaquiline

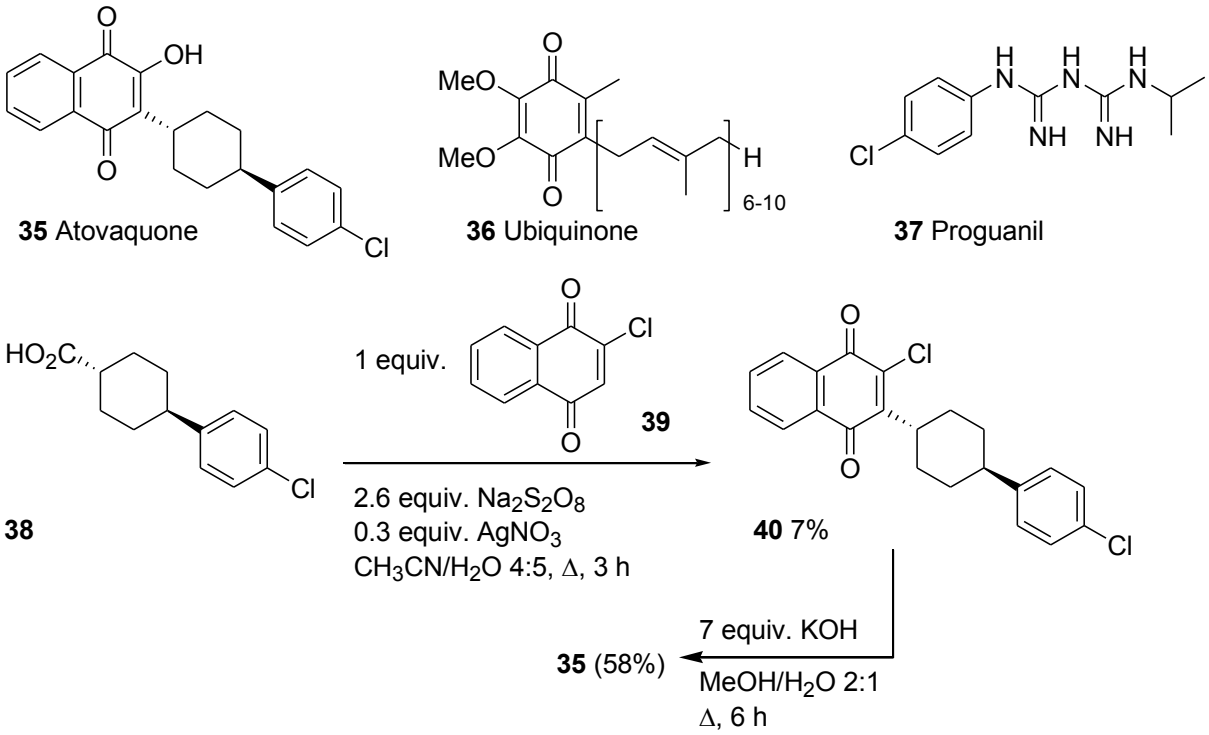
2 Literature overview: 1,4-quinones in modern day drugs: (bio)synthesis and mechanism of action

This literature overview aims at giving an overview of 1,4-quinones that are currently in use in modern medicine or are in phase I-III clinical studies.

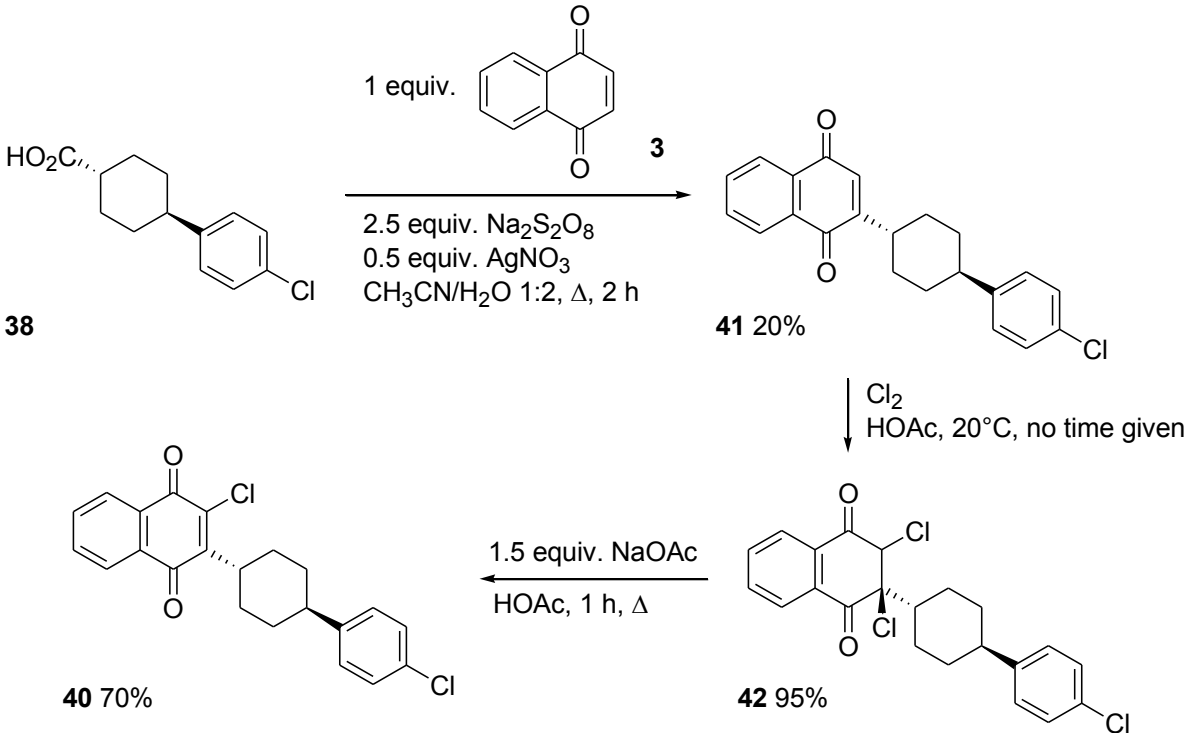
2.1 1,4-Naphthoquinones

2.1.1 Atovaquone 35

Atovaquone **35**[24] has broad-spectrum activity against *Plasmodium spp*., *P. carinii*, *Babesia spp*., and *Toxoplasma gondii*. It is a highly lipophilic compound with very low aqueous solubility. Currently, atovaquone **35** is marketed as Mepron (GlaxoSmithKline). Atovaquone **35** is used to treat or prevent pneumocystis pneumonia in AIDS patients,[25] in combination with azithromycin for the treatment of babesiosis, it is active against *Toxoplasma gondii* and used for patients with toxoplasmosis that are intolerant to standard therapies or multiple drug intolerance.[26] Atovaquone **35** is available as a combination preparation with proguanil **37** under the brand name Malarone (GlaxoSmithKline) for the treatment and prevention of malaria.[27] The drug is structurally similar to ubiquinone **36** (coenzyme Q), which is an integral component of the electron transport system in aerobic respiration. Ubiquinone **36** accepts electrons from dehydrogenase enzymes and passes them to electron transport cytochromes. Atovaquone **35** inhibits the binding of ubiquinone **36** to the protozoal cytochrome complex. The consequence of this inhibition is the collapse of the mitochondrial membrane potential. Atovaquone **35** is prepared by means of radical alkylation of 2-chloro-1,4-naphthoquinone **39** with 4-(4-chlorophenyl)cyclohexanecarboxylic acid **38** in low yield followed by alkaline hydrolysis of the vinylic chloride **40**.[28]

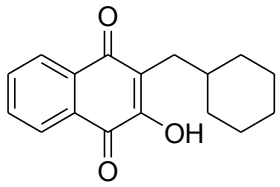


The low yield of the radical alkylation step has been subject of intense research. However, few higher yielding processes were discovered. In 2009 a patent was filed in which Atovaquone **35** was prepared by means of a radical alkylation of 4-(4-chlorophenyl)cyclohexanecarboxylic acid **38** and 1,4-naphthoquinone **3**. The obtained quinone **41** was chlorinated and subsequently dehydrochlorinated to yield intermediate **40**, which was then treated identical as above.[29]

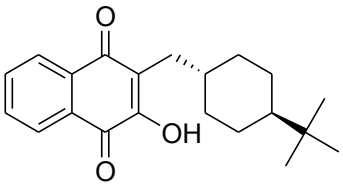


2.1.2 Parvaquone 43 and buparvaquone 44

Parvaquone **43** and buparvaquone **44** are 2-hydroxy-1,4-naphthoquinone antiprotozoal drugs related to atovaquone **35**. These compounds are used in the treatment of East Coast fever, a lympho-destructive disease of cattle, caused by the protozoan parasite *Theileria parva*.[30] They are synthesised using the same radical alkylation-hydrolysis procedure as atovaquone **35**.[31] Parvaquone **43** and other cyclohexyl substituted quinones are metabolised in mammals via hydroxylation at the 4-position of the cyclohexyl ring. Therefore, this position was blocked in buparvaquone **44** with a *tert*-butyl group resulting in a compound which is approximately eight times more active *in vivo* than parvaquone **43**.[30a]



43 Parvaquone



44 Buparvaquone

2.2 Anthraquinones

Anthraquinones constitute the largest group of quinones in medicinal use. Given their flat nature, they are excellent intercalating agents and are therefore mainly applied as antitumour drugs. They are all very lipophilic and have thus to be administered intravenous.

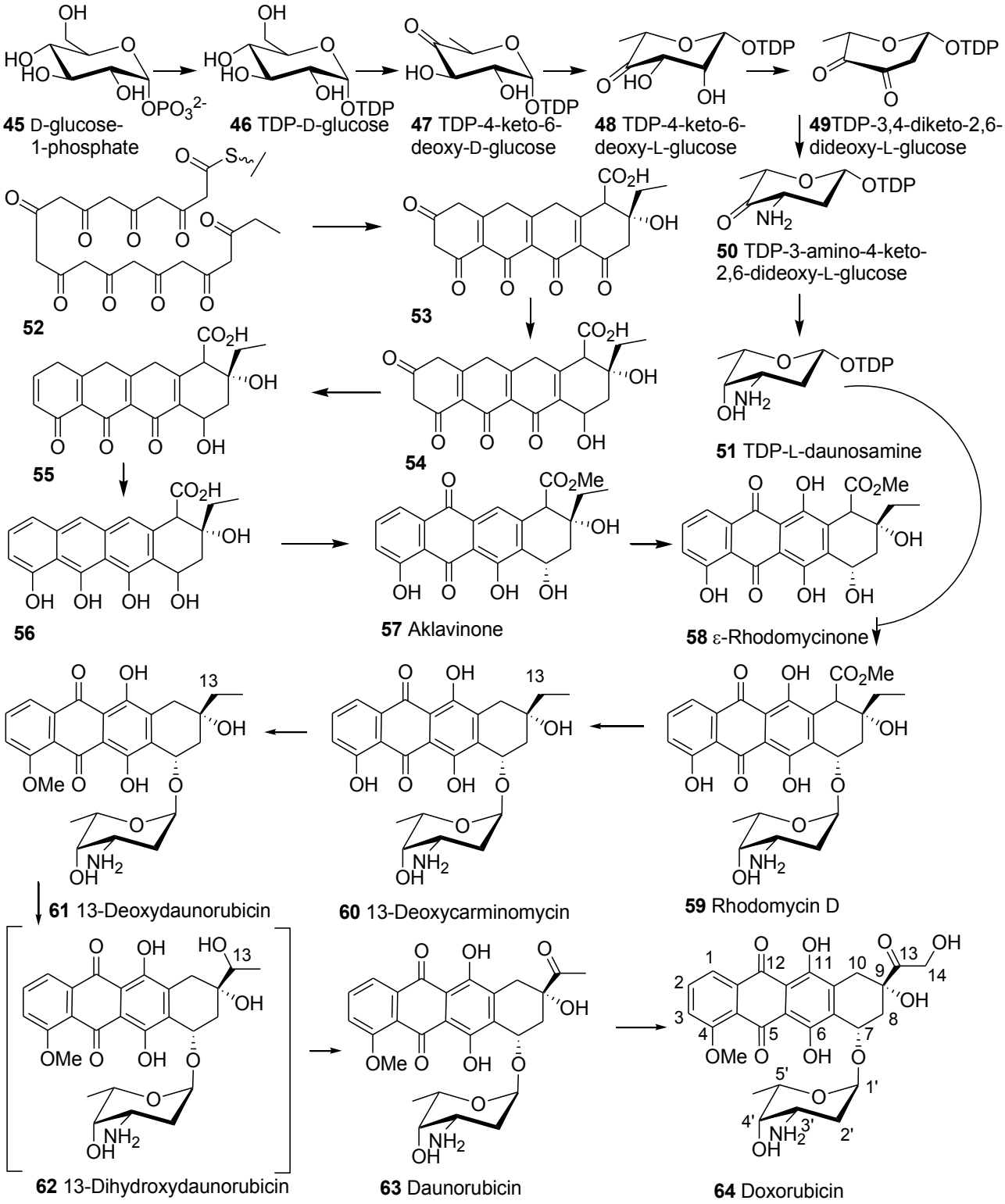
2.2.1 Anthracyclines

Anthracyclines are anthraquinones coupled with an amino-sugar used in cancer chemotherapy. Their corresponding aglycons are called anthracyclinones. Anthracyclines are amongst the most important drugs in the treatment of many neoplastic diseases, such as leukaemias, lymphomas, lung, ovarian, breast and uterine cancers. They have the widest spectrum of activity in human cancers and only a few cancers (e.g. colon cancer) are unresponsive to them.[39] Unfortunately, chronic administration of anthracyclines induces cardiomyopathy leading to heart failure.[32]

Anthracyclines have three mechanisms of action: (a) Intercalation between the base pairs of the DNA or RNA strands, thus preventing replication.[33] (b) Inhibition of topoisomerase II thus blocking DNA transcription and replication by preventing the relaxation of the supercoiled DNA. (c) Creation of free oxygen radicals that damage DNA and cell membranes. This is the main cause of the cardiotoxicity of anthracyclines, which is thought to be caused by the formation of semiquinone free radicals. These radicals can lead to tissue damage through mechanisms such as membrane lipid peroxidation. The heart is more susceptible to this process owing to a relative lack of free radical detoxifying enzymes.

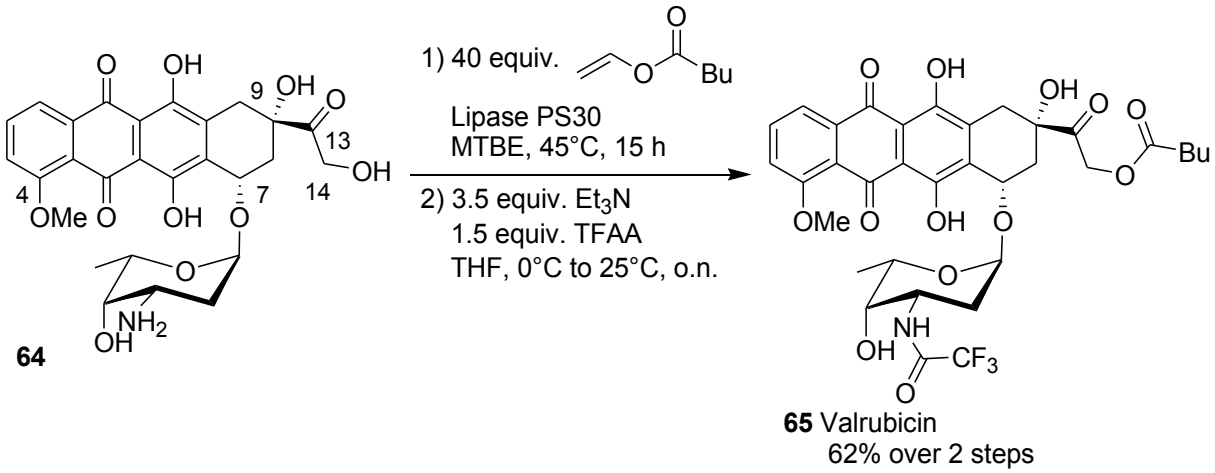
The two most prominent anthracyclines are daunorubicin (daunomycin) **63** and doxorubicin (doxomycin) **64**. They were developed as anticancer agents in the 1960's. Daunorubicin **63** was

isolated from *Streptomyces peucetius var. caesius*. Doxorubicin **64** (brand name Adriamycin) is closely related to daunorubicin **63** and was isolated by mutating the *Streptomyces* strain from which daunorubicin **63** was isolated.[34] Doxorubicin **64** is more potent than daunorubicin **63**, and one of the most widely prescribed and effective cytotoxic anticancer agents.[35] The most serious clinical limitations are dose-dependent cardiotoxicity and susceptibility to multi-drug resistance.[36] The main mode of action of doxorubicin **64** is DNA intercalation: when doxorubicin **64** is intercalated, the C-9 ketone and the daunosamine sugar moiety coordinate in the minor groove and stabilise the DNA complex by hydrogen bounding and interaction with topoisomerase II. Biosynthetically, daunorubicinone is derived from 9 acetate units and 1 propionate unit, which accounts for the ethyl group. The biosynthesis of doxorubicin **64** is completed in three stages: (a) formation of ε-rhodomycinone **58** via a polyketide synthase pathway, (b) formation of thymidine diphosphate (TDP)-L-daunosamine **51** starting from D-glucose-1-phosphate and (c) glycosylation followed by post-modifications (methylation, decarboxylation, and hydroxylation). As with many complex natural products, the chemical synthesis of doxorubicin **64** is challenging e.g. the introduction of the labile 7,9-dihydroxy functionality.[37] Doxorubicin **64** and daunorubicin **63** are produced via genetically engineered *Streptomyces* strains. Although a number of organisms (including *S. peucetius* ATCC 29050) produce daunorubicin **63**, *S. peucetius* ATCC 27952 is the only organism reported to produce doxorubicin **64**.[38]

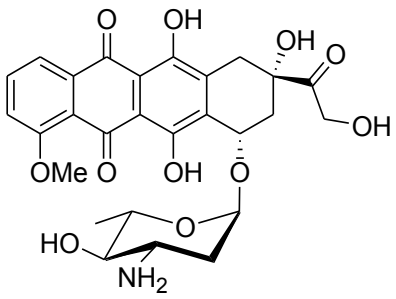


A large number of semi-synthetic anthracyclines exist but none of them is significantly better than the original doxorubicin **64**.[39] Promising doxorubicin **64** derivatives involve mainly alteration of the sugar structure[40] or alterations at C-9.[41] As doxorubicin **64** is hard to synthesise chemically,[37] most derivatisation approaches start from the complete molecule, which is complicated due to the present polyfunctionality and sensitivity to heat, pH, metal ions and light. Therefore, selective microbial

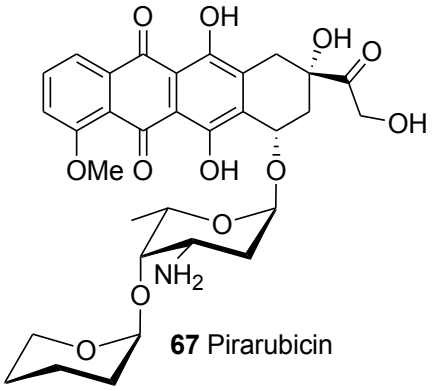
transformations are often deployed.[42] For instance valrubicin **65**, which is used to treat bladder cancer,[43] is synthesised chemo-enzymatically from doxorubicin **64** by means of a *Pseudomonas cepacia* lipase catalysed esterification followed by *N*-trifluoroacetylation with trifluoroacetic anhydride (TFAA).[44]



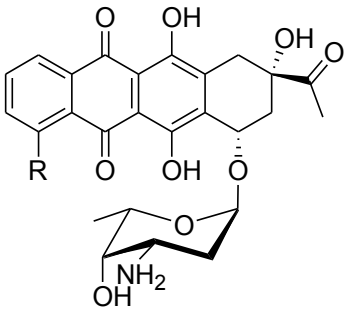
Epirubicin **66** has the opposite chirality as doxorubicin **64** at the 4'-position. It is prepared from daunorubicin **63** by oxidation of the 4'-OH followed by stereoselective reduction of the ketone and bromination of C-14 followed by hydrolysis of the 14-CH_2Br fragment.[45] It is used for the treatment of carcinomas, lymphomas and sarcomas. Other clinically relevant anthracyclines include pirarubicin **67** (carcinomas, lymphomas, sarcoma), idarubicin **68a** (acute leukaemias), carminomycin **68b**, aclarubicin **69** (acute leukaemias and non-Hodgkin's lymphomas) and zorubicin **70** (acute leukaemias).



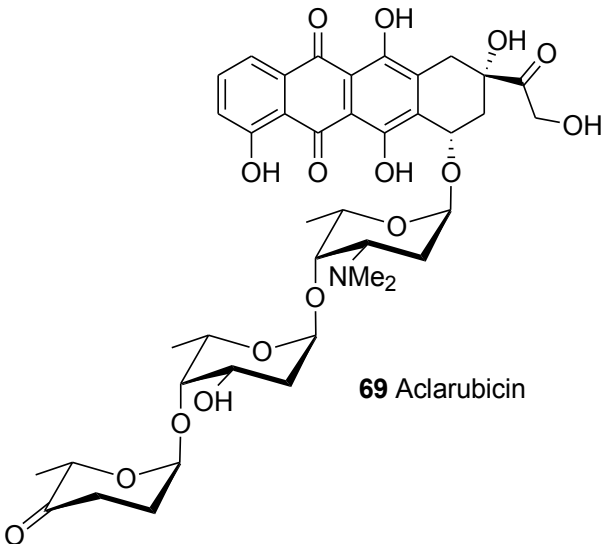
66 Epirubicin



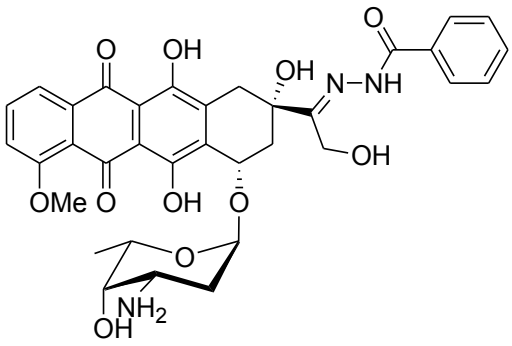
67 Pirarubicin



68a Idarubicin R = H
68b Carminomycin R = OH



69 Aclarubicin



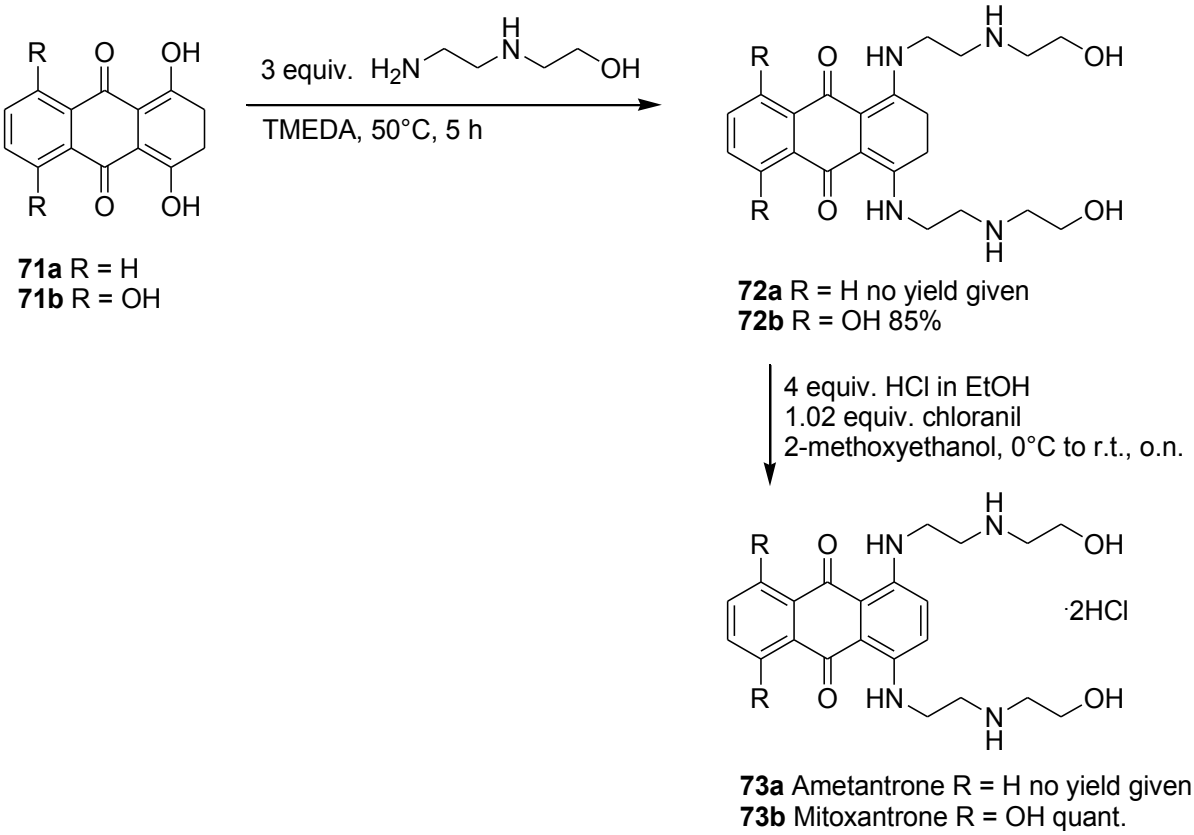
70 Zorubicin

As so far no better alternative for doxorubicin **64** is found, some methods focus on 'mechanical' modification of doxorubicin **64**. Such methods include using prodrugs, encasing doxorubicin **64** in liposomes or changing the drug administration method to retard the height of peak plasma levels. High peak plasma levels are thought to be related to the cardiotoxicity of doxorubicin **64**.[39] Alternatively, doxorubicin **64** can be administered together with a substance that mitigates cardiotoxicity, such as dexrazoxane or amifostine.[46]

2.2.2 Ametantrone 73a and mitoxantrone 73b

The anthraquinone ametantrone **73a** was identified as an antitumour compound by means of random screening. Mitoxantrone **73b** (brand name Novantrone®) was prepared in an attempt to design structurally less complex analogues of doxorubicin **64**, focusing on the anthraquinone and amino moieties as most important sites for intercalative binding.[47] On a molar base, mitoxantrone **73b** is ten to 100 times more potent than ametantrone **73a**[48] and it is active against both solid tumours and leukaemias.[47] Intravenous mitoxantrone **73b** treatment improved neurological disability and delayed progression in multiple sclerosis (MS) patients. Its presumed mechanism of action in patients with MS is via immunomodulatory mechanisms, although these remain to be fully elucidated.[49] Ametantrone

73a and mitoxantrone **73b** are synthesised by means of the addition of 2-(2-aminoethylamino)ethanol to 2,3-dihydro-1,4-dihydroxyanthraquinones **71a** and **71b** in tetramethylethyleendiamine (TMEDA) followed by oxidation with chloranil and HCl salt formation.[50] As with all anthraquinone anticancer drugs, cardiotoxicity is a major side effect. The cardiotoxicity of mitoxantrone **73b** and doxorubicin **64** has been associated with the metal chelating ability of the adjacent hydroxyl and quinone groups. Formation of drug-metal complexes could enhance redox cycling by a metal catalysed type reaction. The lower cardiotoxicity associated with mitoxantrone **73b** than with doxorubicin **64** is ascribed to the diminished rate of superoxide radical formation.

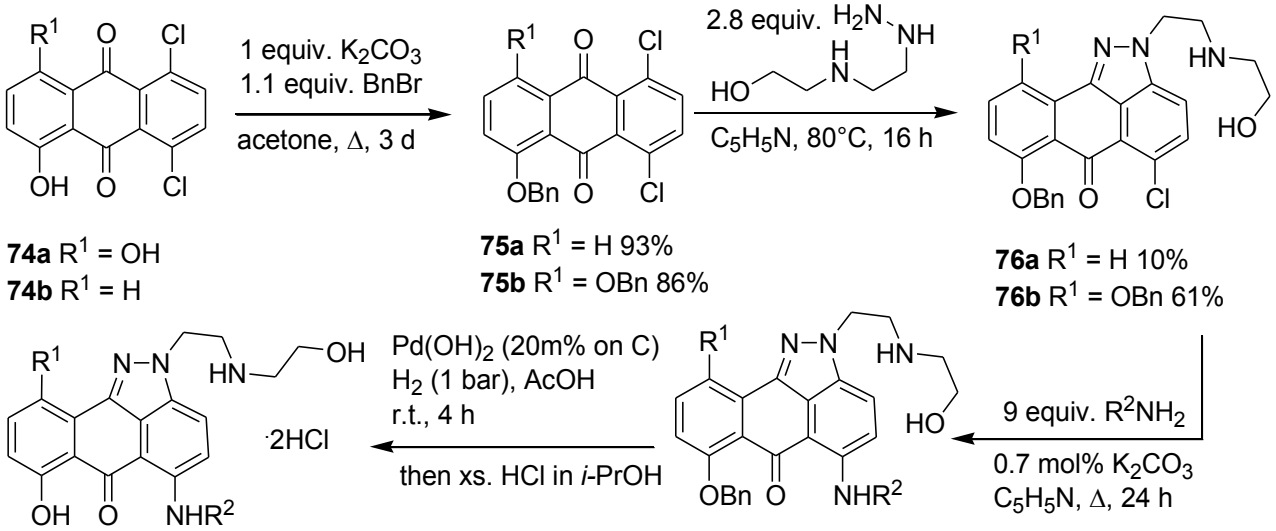


2.2.3 Anthrapyrazoles 78

A strategy to reduce cardiotoxicity is to modify the quinone chromophore so that the reduction of the quinone is more difficult. This can be achieved by rendering the redox potential of the quinone more negative, thus rendering more difficult the electron addition. Chromophore modified synthetic analogues are designed to be more resistant to enzymatic reduction while retaining the planarity of the parent quinone scaffolds.[51] Another important factor responsible for the cardiotoxic side effects is the affinity displayed by the quinones for their oxidoreductases as they stimulate oxygen free radical production.[51]

The quinone chromophore is turned more resistant to enzymatic reduction by replacing a carbonyl group in the B ring with an imine moiety. This substitution decreases redox cycling and the generation

of semiquinone free radicals.[56] Based on the abovementioned considerations, a new class of DNA complexers, the anthra[1,9-*cd*]pyrazol-6(2*H*)-ones (anthrapyrazoles) **78** were synthesised.[52] The anthrapyrazoles **78** inhibit DNA, RNA and protein synthesis but they are much more potent inhibitors of DNA synthesis than RNA. This is in contrast to doxorubicin **64** and mitoxantrone **73b** which have equivalent activity in both processes. Reaction of anthraquinones **75** with a monoalkylhydrazine gave chloroanthrapyrazoles **76**, whose subsequent condensation with primary or secondary alkylamines provided the target 'two-armed' anthrapyrazoles **78**.[53] Losoxantrone **78a**[54], pyroxanthone **78b**[55] and teloxantrone **78c** are the three most studied anthrapyrazoles and were evaluated against various types of cancer.[56,57]



74a R^1 = OH
74b R^1 = H

75a R^1 = H 93%
75b R^1 = OBn 86%

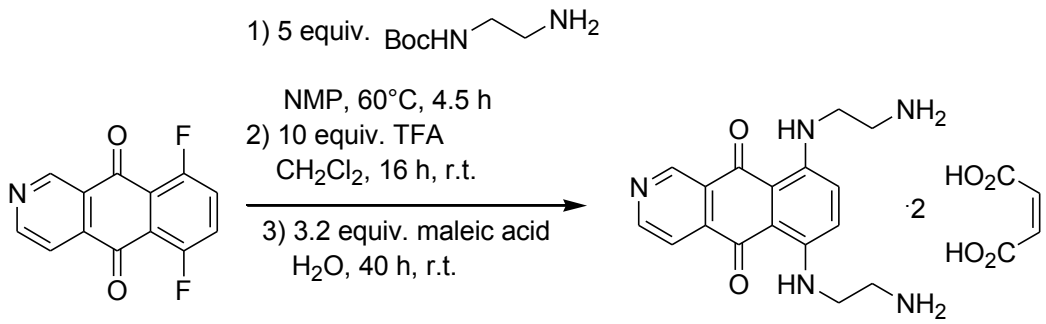
76a R^1 = H 10%
76b R^1 = OBn 61%

78a Losoxantrone R^1 = H, R^2 = $(CH_2)_2NH(CH_2)_2NH_2$ 97%
78b Teloxantrone R^1 = OH, R^2 = $(CH_2)_2NHCH_3$ 52%
78c Pyroxantrone R^1 = OH, R^2 = $(CH_2)_3NH_2$ 48%

77a R^1 = H, R^2 = $(CH_2)_2NH(CH_2)_2NH_2$ 50%
77b R^1 = OBn, R^2 = $(CH_2)_2NHCH_3$ 68%
77c R^1 = OBn, R^2 = $(CH_2)_3NH_2$ 72%

2.2.4 Pixantrone 80

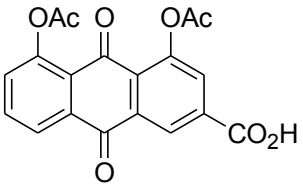
Pixantrone dimaleate[58] **80** is significantly less cardiotoxic than mitoxantrone **73b** and in phase III clinical studies for the treatment of patients with non-Hodgkin's lymphoma.[59] It is prepared by reaction of difluoro-2-aza-anthraquinone **79** with *N*-Boc-protected ethylenediamine followed by Boc deprotection and maleate salt formation. Pixantrone dimaleate **80** is approved by the United States Food and Drug Administration and the European Medicines Agency. It is marketed by Cell Therapeutics Incorporated under the brand name Pixuvri®.[60]



79 **80** Pixantrone 67% overall

2.2.5 Diacerein 81

Unlike other anthraquinones, diacerein (diacetylrhein) **81** is not an intercalating drug but is used to treat osteoarthritis.[61] Diacerein is a slow-acting drug taken as a pill that may slow down the breakdown of cartilage and relieve pain and swelling. Its use is disputed as it not clear whether diacerein **81** works and whether it is safer than other drugs used to treat osteoarthritis.[62]



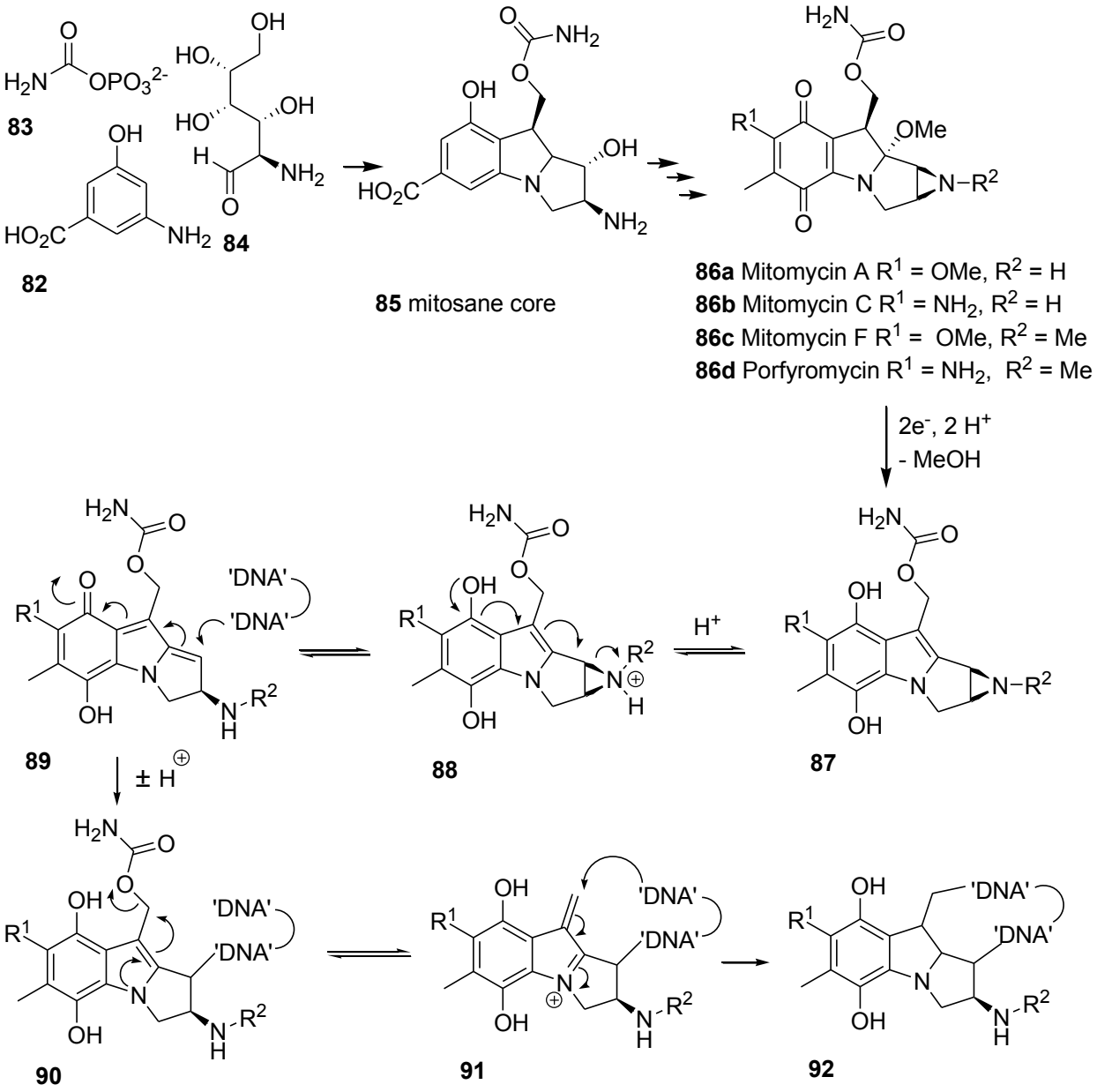
81 Diacerein

2.3 Benzoquinones

2.3.1 Mitomycins 86

Mitomycins **86** were isolated from various *Streptomyces sp.* and are used as anticancer compounds against a wide range of tumours.[63] They have a complex aza-heterocyclic basic skeleton consisting of an aziridine fused to a pyrroloindolodione.[64] Mitomycins **86** act as prodrugs by *in vivo* transformation to the active metabolite giving irreversible bis-alkylation of DNA. Mitomycin C **86b** is the most studied mitomycin and was isolated from the bacterium *Streptomyces lavendulae*. It has become one of the most effective drugs against non-small-cell lung carcinoma, as well as other tumours.[65] The mitosane core **85** is derived from a combination of 3-amino-5-hydroxybenzoic acid (AHBA) **82**, carbamoyl phosphate **83** and D-glucosamine **84**.[66] AHBA **82** is also a common precursor to other anticancer drugs, such as the rifamycins **110-113** and geldanamycin **104**. The use of mitomycin C **86b** in cancer treatment relies on the cytotoxic selectivity for hypoxic cells characteristic of solid tumours.[67] Even though mitomycin C **86b** is relatively unreactive toward DNA, it becomes a reactive alkylating agent upon reduction.[68] Reduction of the quinone moiety followed by ring opening of the aziridine creates a 1,6-Michael acceptor to which initial DNA attack occurs. Next, the carbamoyl moiety is expelled, thus forming a second site of addition for the DNA molecule. To date, little

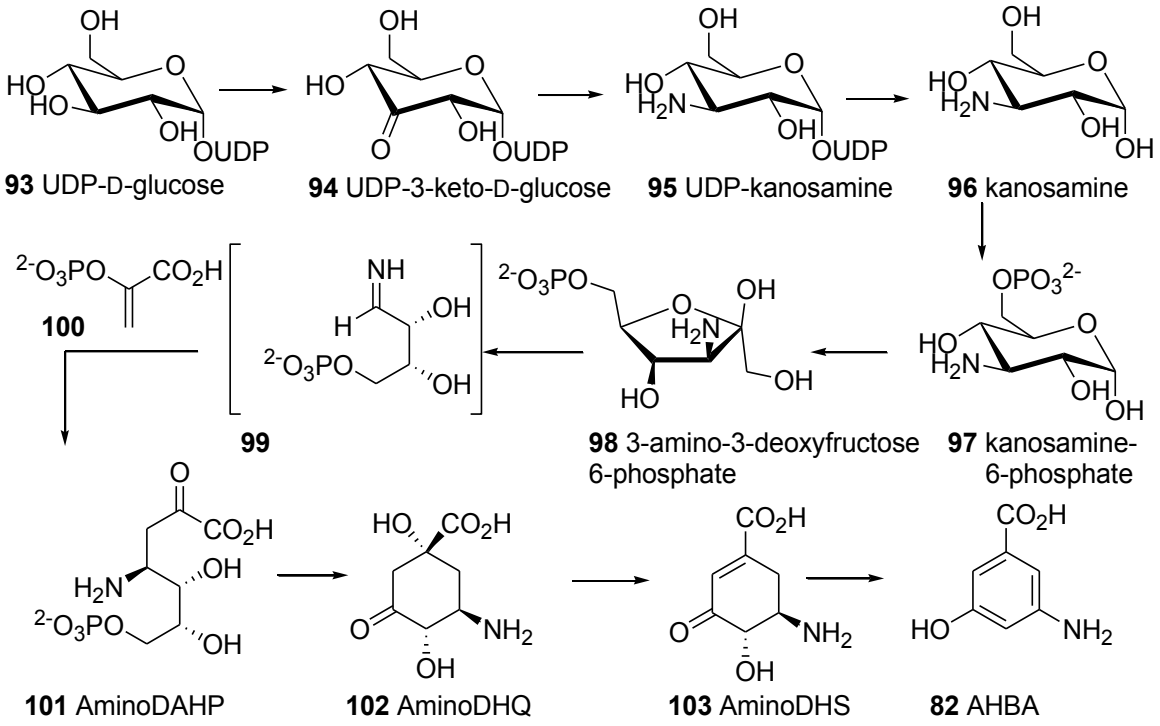
synthetic modified mitomycins have been prepared and it is known to be a notoriously difficult synthetic target.[69]



2.4 Ansamycins

Ansamycins ('ansa' is Latin for handle) consist of an aromatic moiety which is bridged at nonadjacent positions by an aliphatic polyketide chain. The aromatic moiety can be either a naphthalene or a naphthoquinone ring system as in the naphthalenic ansamycins naphthomycin, tolypomycin, halomycin, the rifamycins or the streptovaricins or it can be a benzene or a benzoquinone ring system as in the benzenic ansamycins geldanamycin, herbimycin or ansamitocin.[70] The biosynthesis of this class of antibiotics involves the assembly of AHBA **82**, followed by sequential addition of the polyketide chain, which then undergoes further tailoring processes. The origin of AHBA **82** is related

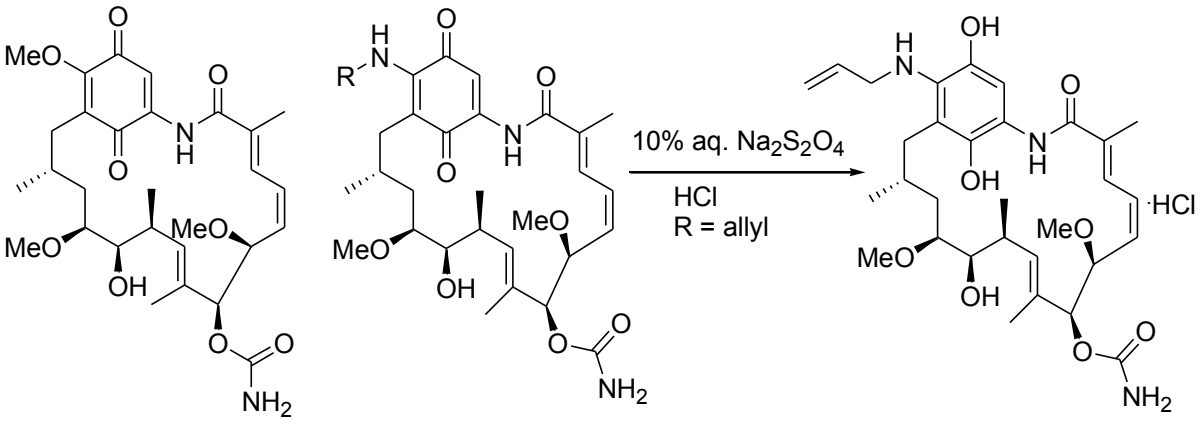
to the shikimate pathway. Reductive amination of uridine diphosphate (UDP) 3-ketoglucose **94** followed by isomerisation and transketolisation leads to aldimine **99**, which is condensed with phosphoenolpyruvate **100** towards 3,4-dideoxy-4-amino-D-arabinoheptulosonic acid 7-phospate (aminoDAHP) **101**. AminoDAHP **101** is cyclised towards 5-deoxy-5-amino-3-dehydroquinic acid (aminoDHQ) **102**, which dehydrates to 5-deoxy-5amino-3-dehydroquinic acid (aminoDHS) **103** which further dehydrates to AHBA **82**.[70]



2.4.1 Geldanamycin 104

Geldanamycin **104** is a benzoquinone ansamycin that binds to the ATP binding site of the heat shock protein of 90 kDa (Hsp90) and inhibits its function. It was originally discovered in the Actinobacterium *Streptomyces hygroscopicus*.[71] Hsp90 serves a chaperone role to properly fold and deliver client proteins to appropriate intracellular locations and is transcriptionally upregulated by heat and other stressors. Thus, compounds that inhibit Hsp90 could affect tumours by blocking the synthesis of molecules on which tumours depend for their development. Geldanamycin **104** induces Hsp90 mediated degradation of proteins that are mutated in tumours preferentially over their normal cellular counterparts. Despite the powerful antitumour qualities of geldanamycin **104**, hepatotoxicity limits its uses as an anticancer drug. It was found that derivatisation of geldanamycin at position 17 led to a reduction of the hepatotoxic properties, and improved solubility. 17-Allylamino-17-demethoxygeldanamycin (17-AAG, tanespimycin)[72] **105a** underwent various phase II clinical studies and a phase III clinical trial but its use proves to be limited as the bioavailability is modest, the compound is instable and it has a low therapeutic index.[73,74] 17-(Dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG, alvespimycin) **105b** is a more water-soluble analogue of

geldanamycin **104** and is administered as the HCl salt. It has been evaluated for the treatment of solid tumours[75] and leukaemia.[76] IPI-493 **105c** is another orally available derivative, currently in phase I studies.[74] A drawback of these drugs is that the benzoquinone moiety must undergo reductive metabolism and detoxification by quinone oxidoreductase NQ1 before they can act against Hsp90.[74] Less prone to oxidative stress and more water soluble than tanespimycin **105a** or alvespimycin **105b** is IPI-504 (retaspimycin hydrochloride) **106**, which has been evaluated in phase II and phase III clinical trials.[74]

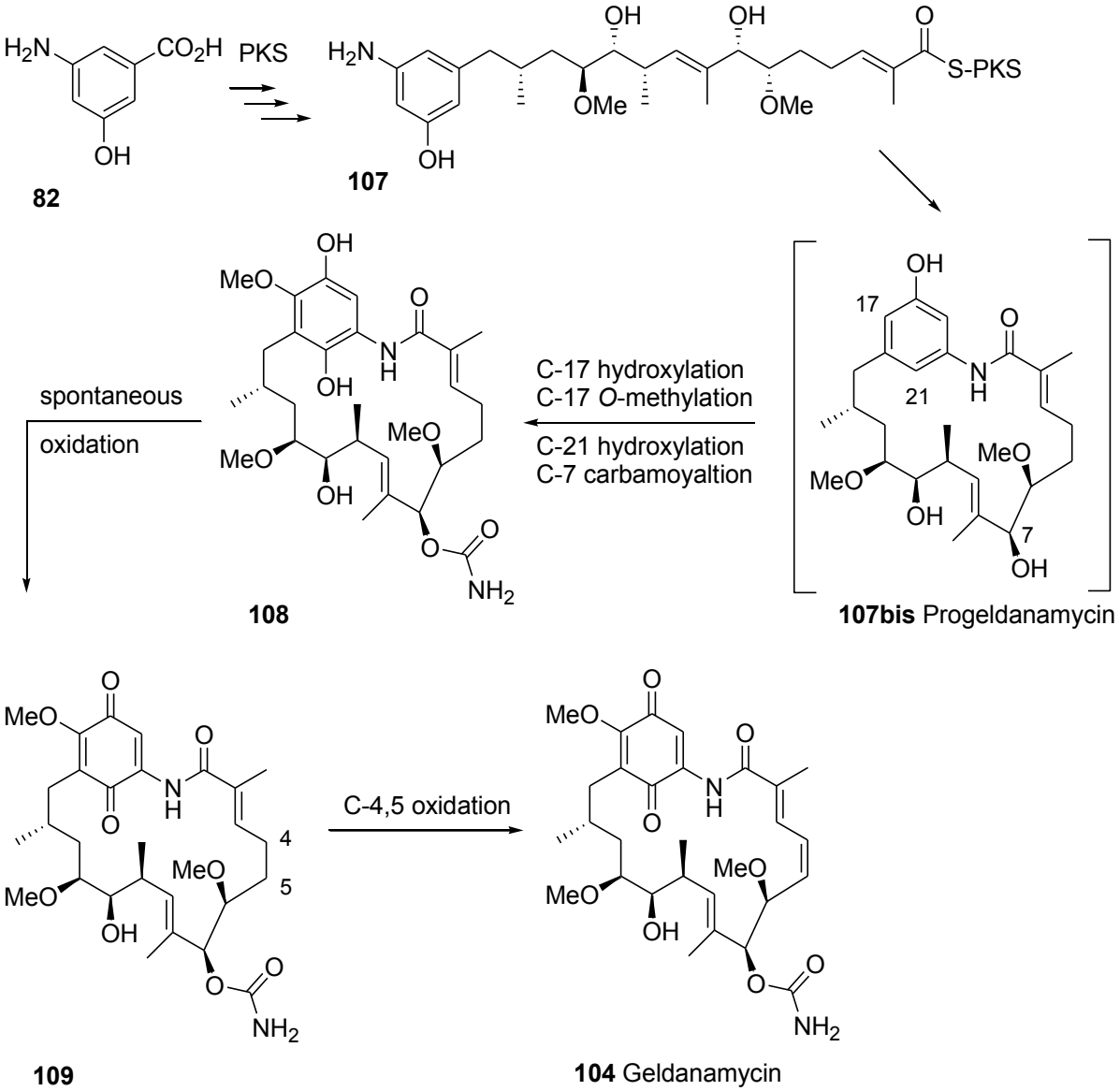


104 Geldanamycin

105a Tanespimycin R = Allyl
105b Alvespimycin
R = $Me_2NHCH_2CH_2$.HCl
105c IPI-493 R = H

106 Retaspimycin

As all ansamycins, geldanamycin **104** originates from AHBA **82**, which is elaborated with a polyketide chain followed by macrocyclic lactam formation. The initial PKS product, progeladanamycin **107bis**, is converted in geldanamycin by post-PKS modification steps, which include C-17 hydroxylation, C-17 *O*-methylation, C-21 oxidation, C-7 carbamoylation and C-4,5 oxidation.[77] Even though most chemical functionalisation is done at the benzoquinone moiety, it is possible to introduce variations in the polyketide structure by genetic engineering of the ketoreductase, dehydratase or enoylreductase domains of PKS.[78]

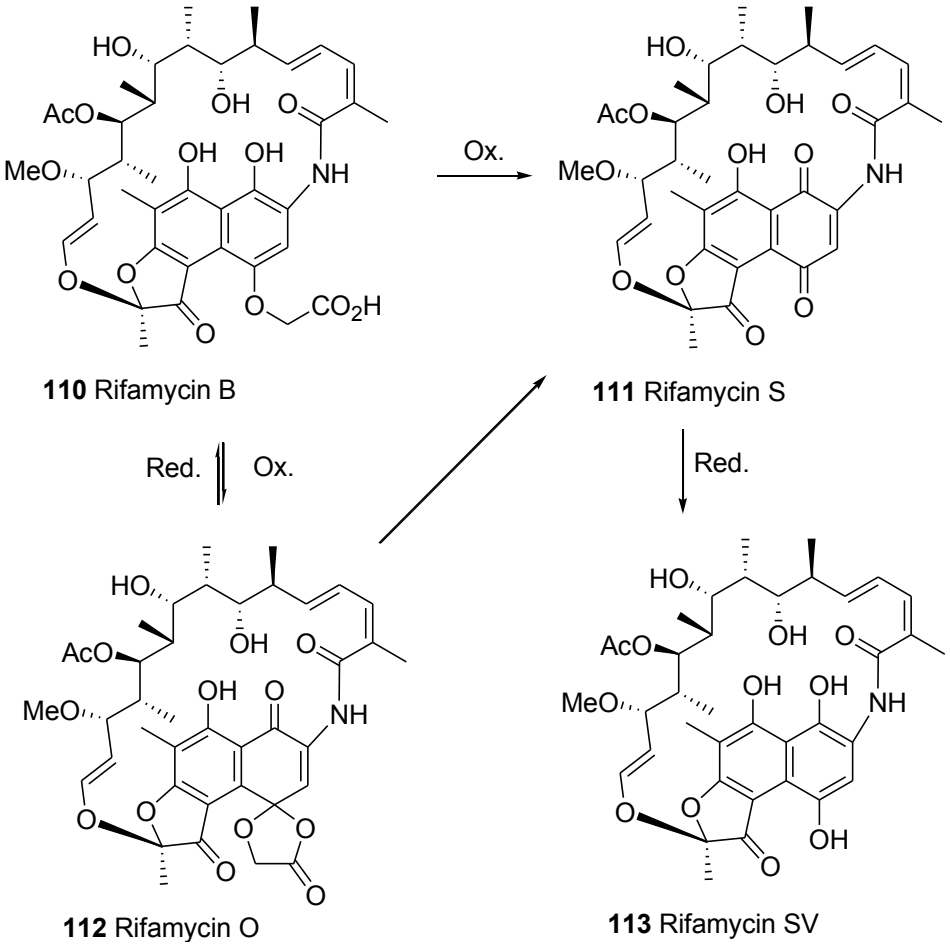


2.4.2 Rifamycins

The rifamycin antibiotics are fermentation products of *Streptomyces mediterranei* sp. One of the substances originally isolated by *S. mediterranei* sp. n. was rifamycin B **110**. Even though rifamycin B **110** has no antibacterial activity, it is not stable and readily degrades to the very active derivative rifamycin S **111**, even in buffered neutrals solutions and air as the oxidant. Rifamycin S **111** inhibits the growth of Gram-positive bacteria at concentrations as low as 0.0025 μg of antibiotic per ml. The sodium salt of rifamycin SV **113** was the first commercial available rifamycin under the brand name Rifacin®.[81] Clinically, the rifamycins proved to be a very valuable class of antibiotics, especially for the treatment of TB, but the naturally occurring compounds had the disadvantage of not being orally active.[79]

The antibacterial activity of rifamycins relies on the inhibition of bacterial RNA synthesis. This inhibition is not due to interaction with the template but to the high affinity of rifamycins to

prokaryotic DNA dependent RNA polymerase.[80] Since this inhibition is highly specific, the rifamycins are an important tool in the study of RNA biosynthesis and metabolism.[79]



110 Rifamycin B **111** Rifamycin S

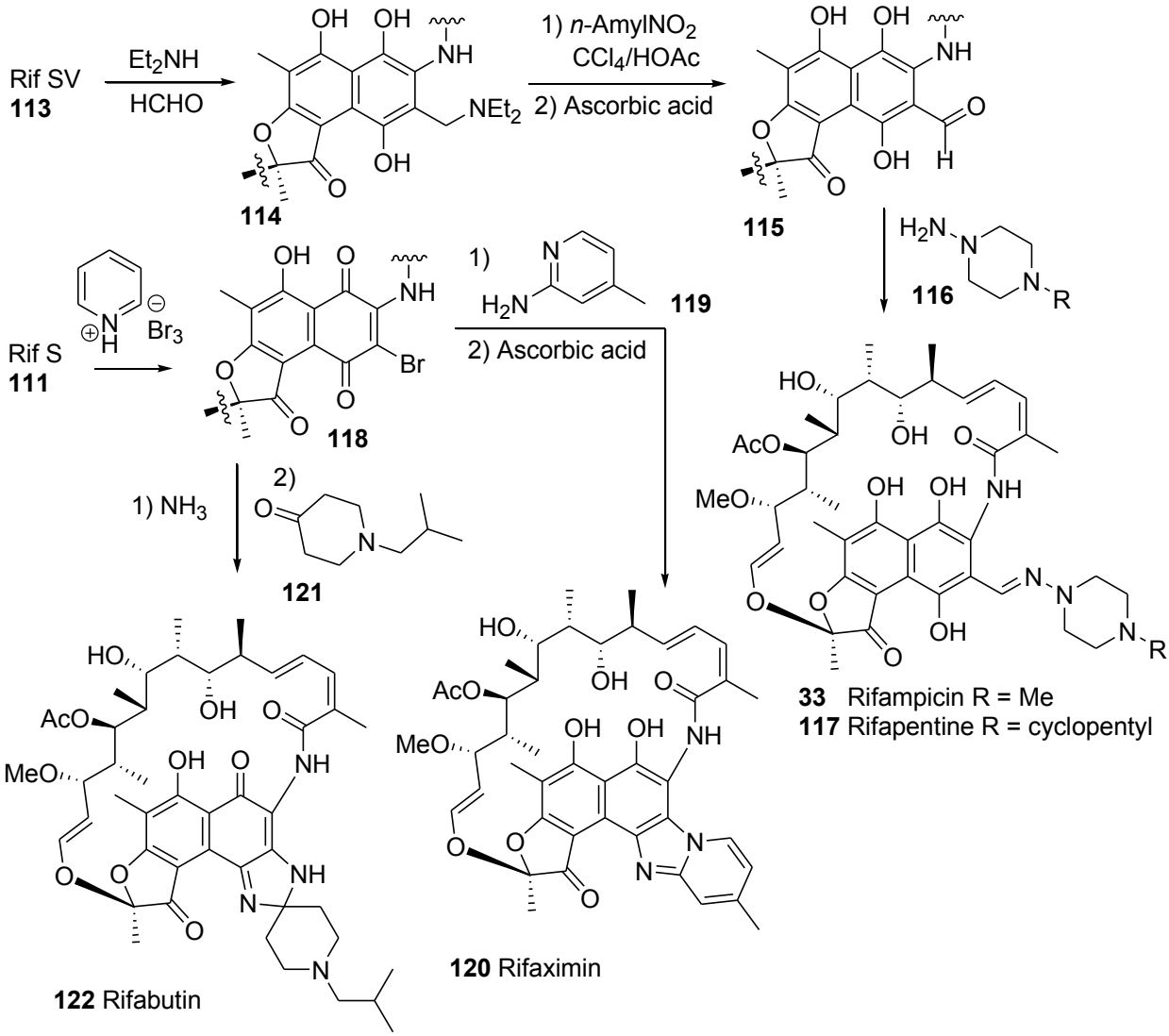
112 Rifamycin O **113** Rifamycin SV

When the structure of the natural rifamycins was elucidated,[81] various semisynthetic derivatives were prepared. In many cases, rifamycin S **111** or SV **113** were modified by the introduction of substituents in position three, which contains the only aromatic hydrogen. Chemical modifications are mostly done on the quinone chromophore as these modifications do not alter the antimicrobial properties. It was found that *N*,*N*-disubstituted hydrazones showed very high activity against gram positive bacteria and *Mycobacterium tuberculosis*.

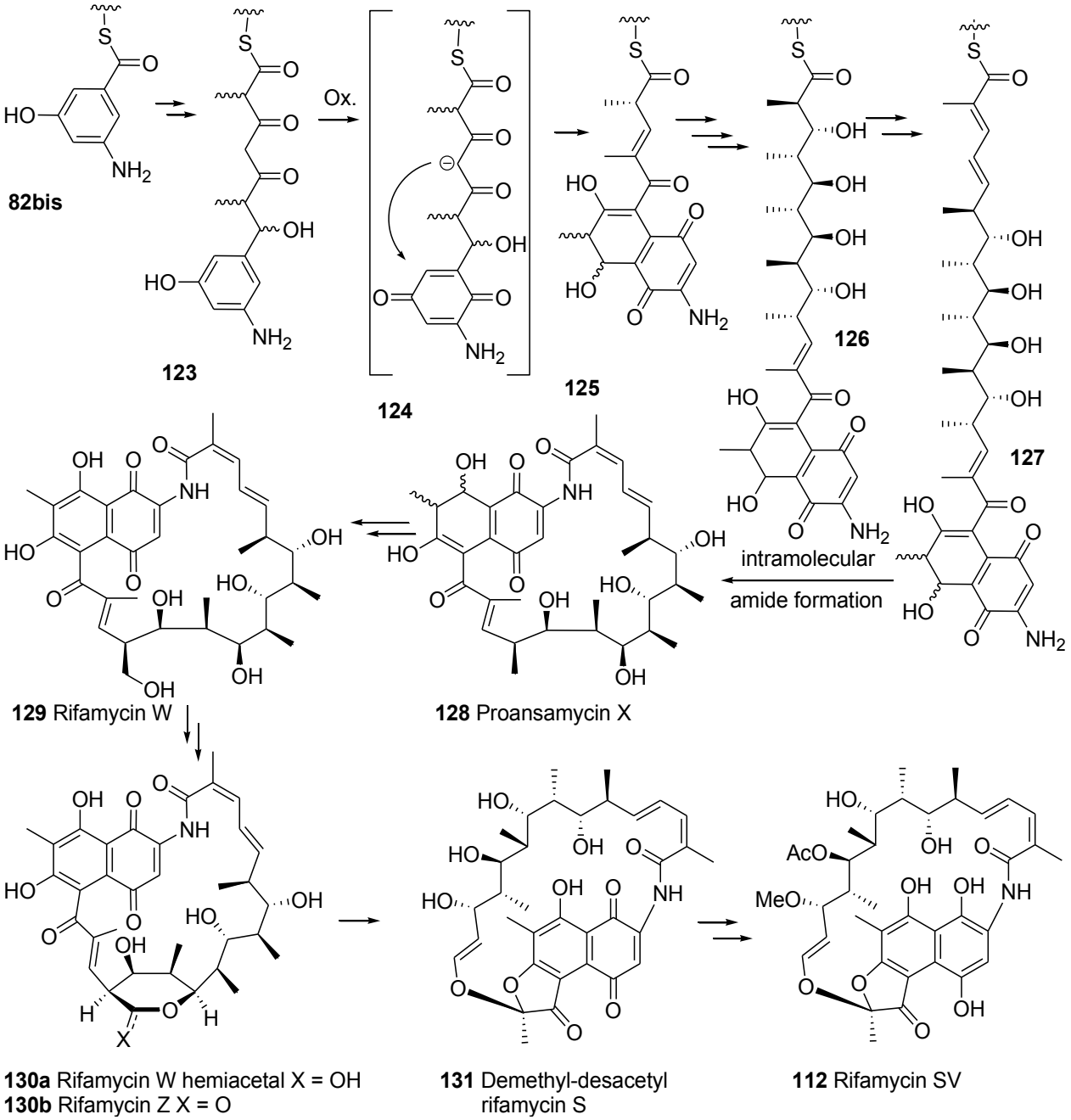
Rifampicin (US: rifampin) **33**, the compound most widely used for both clinical an biochemical purposes, is an orally available 3-*N*-(4-methylpiperazinyl)formimidoyl derivative of rifamycin SV **113**.[79] Eukaryotic enzymes are at least 10^4 times less sensitive to inhibition by rifampicin **33**. It is one of the most potent and broad spectrum antibiotics against bacterial pathogens and is a key component of anti-TB therapy. Rifampicin **33** diffuses freely into tissues, living cells and bacteria making it extremely effective against intracellular pathogens like *Mycobacterium tuberculosis*.[82] As bacteria quickly develop resistance against rifampicin **33**, the drug is typically used in combination with other antimycobacterial agents, especially isoniazid **30**.[70]

Like rifampicin **33**, rifaximin **120** binds to the β-subunit of bacterial DNA-dependent RNA polymerase and inhibits bacterial RNA synthesis. Rifaximin **120** is a nonabsorbable oral antibiotic that acts locally in the gastrointestinal tract and is used to treat traveller's diarrhoea and for the treatment of hepatic encephalopathy.[83] Rifapentine **117** differs in structure from rifampicin **33** by the presence of a cyclopentyl ring instead of a methyl substituent on the piperazinyl moiety. Both rifapentine **117** and its active metabolite, 25-desacetylrifapentine, localise within monocyte derived macrophages, thus allowing for intracellular inhibition of *Mycobacterium tuberculosis* as compared with that of the parent or metabolite alone.[84] Spiropiperidyl substituted rifamycin derivative rifabutin **122**[85] is a first-line oral agent recommended by the WHO for the treatment of MDR-TBC.[86] It is active against a number of rifampicin **33** resistant clinical pathogens.

Rifampicin **33** and rifapentine **117** are prepared starting from 3-formylrifamicin SV **115** and the appropriate hydrazine **116**.[87] 3-Formylrifamycin SV **115** is prepared by oxidation-reduction[88] of 3-(diethylaminomethyl)rifamicin SV **114**, which in turn is prepared by means of a Mannich reaction starting from rifamycin SV **113**.[89] Rifaximin **120** is prepared by reaction of 3-bromorifamycin S **118**[90] and 2-amino-4-picoline **119** followed by reduction with ascorbic acid. Rifabutin **122** is prepared by reaction of 3-bromorifamycin S **118** with ammonia followed by condensation with *N*-isobutylpiperidin-4-one **121**.



Biosynthetically, the rifamycins are synthesised starting from AHBA **82**, via a type I polyketide pathway (PKS I) in which chain extension is performed using 2 acetate and 8 propionate units. An oxidative cyclisation step forms the naphthoquinone subunit, which after further polyketide chain extension ring-closes to the macrocyclic lactam. Further post-modification steps, which include oxidation, methylation and acetylation steps, lead to the rifamycins.



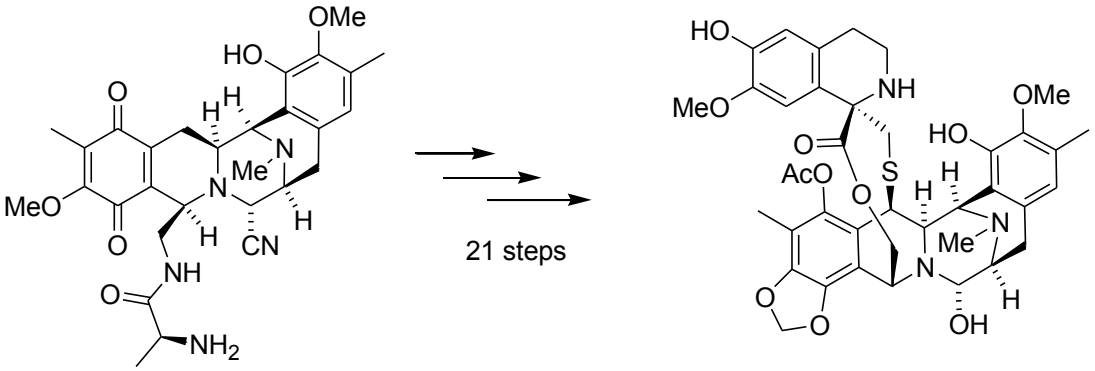
2.5 1,4-Quinone derived drugs

2.5.1 Trabectedin 133

Trabectedin (ecteinascidin 743, ET743) **133** is an alkaloid consisting of three fused tetrahydroisoquinoline rings isolated from the marine tunicate *Ecteinascidia turbinata*,[91] it is marketed under the brand name Yondelis® for the treatment of various cancers. Trabectedin **133** is the only novel DNA interactive small molecule to have gained market approval in the last few years.[92] The mechanism of action of trabectedin **133** is different from that of other anticancer drugs. Two of the tetrahydroisoquinoline rings form a covalent interaction with the minor groove of DNA, while the

third ring protrudes from the DNA molecule, thus allowing interactions with other macromolecules.[93] In contrast to standard antineoplastic alkylating agents such as cyclophosphamide that bind guanine at the *N*-7 or *O*-6 position in the DNA major groove, trabectedin **133** binds to the exocyclic *N*-2 amino group of guanines in the DNA minor groove through an iminium intermediate generated *in situ* by dehydration of the hemi-aminal. The hemi-aminal moiety is imperative for the pharmacological activity of trabectedin **133**, as related compounds without this reactive group were 100 times less active than trabectedin.[94]

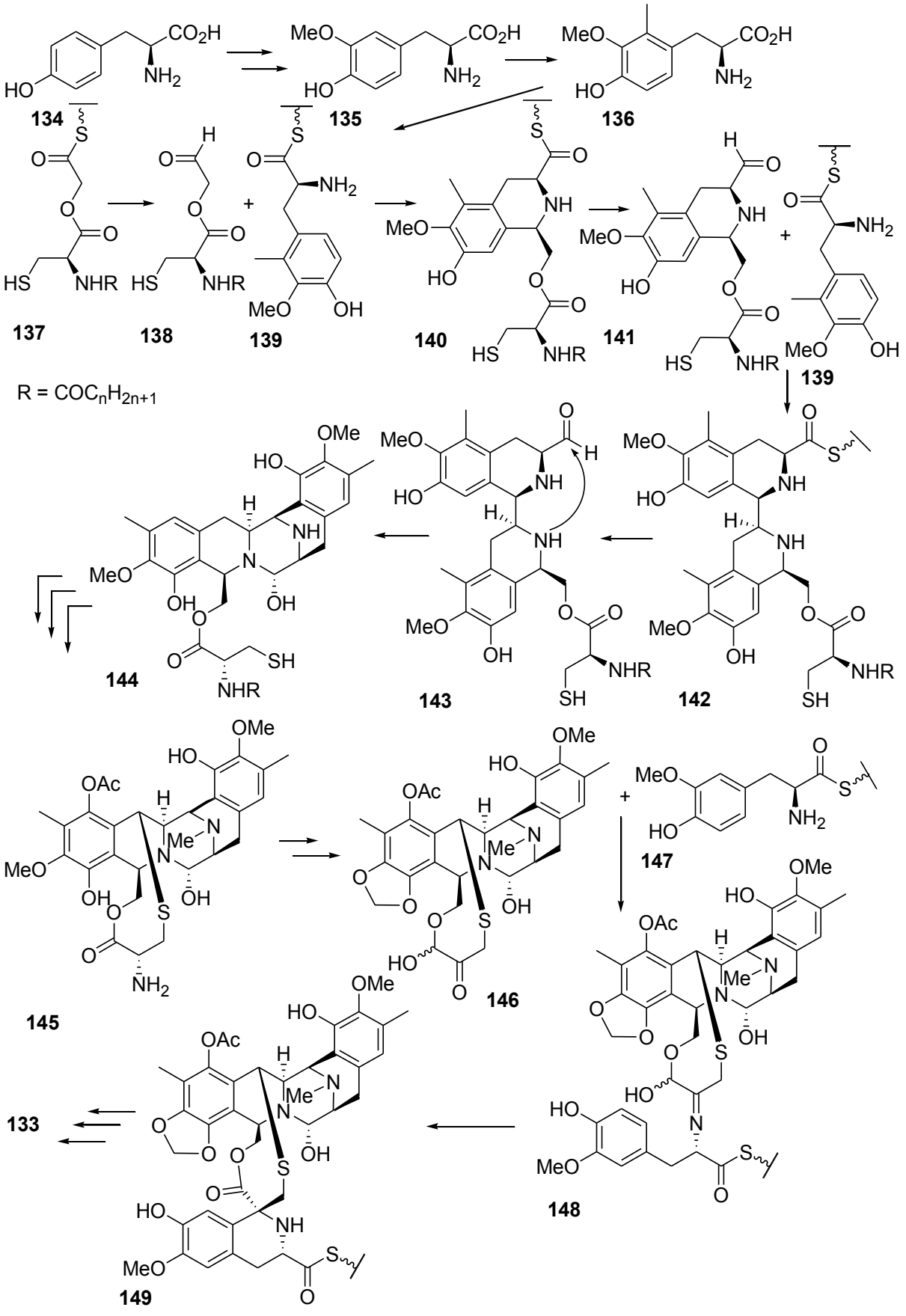
Trabectedin **133** is currently produced semi-synthetically in 21 steps starting from Cyanosafracin B **132**, which is produced via fermentation on a kilogram scale from the wild-type producer *Pseudomonas fluorescens*.[95]



132 Cyanosafracin B **133** Trabectedin

The similarity of trabectedin **133** to other bacterial derived natural products such as safracin and the saframycins is an indication that trabectedin **133** is of prokaryotic origin, likely from a bacterium that is closely associated to *E. turbinata*.[96] Trabectedin **133** is synthesised by nonribosomal peptide synthetases[97] (NRP) starting from three tyrosines, a methionine and a glycolic acid unit. Initially, tyrosine is hydroxylated and methylated towards building blocks **134** and **135**. A double Pictet-Spengler-like condensation of fragment **138** with two modified tyrosines leads to dimeric tetrahydroisoquinoline **143**, which then intramoleculary cyclises to form the bridged A-B ring fragment **144**. The C ring is then formed by oxidative cyclisation of the thiol group, followed by multiple tailoring steps leading to macrocycle **146** which is condensed with a third modified tyrosine **147**, thus forming spirocyclic tetrahydroisoquinoline fragment **149**, which is further converted in trabectedin **133**.[98,99]

Using metagenomic sequencing of total DNA from the tunicate/microbial consortium, it was found that *Candidatus endoecteinascidia frumentensis* produces trabectedin **133**. As with many symbiotic bacteria, it is not possible to cultivate it in the lab. Significant efforts have been made to identify the NRP genes to allow direct production of the drug through metabolic engineering.[100]


134
135
136
137
138
139
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141
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R = COCnH2n+1
144
143
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146
147
148
133
149

2.6 Conclusion

Medicinal chemists often distrust the quinone scaffold due to the common prejudice that their multitude of mode of action turns them into non-selective compounds 'that are active against everything'. However, this literature overview clearly demonstrates that quinones play a key role in modern medicine. Apart from the well-known anthracyclines and other DNA-damaging agent such as mitomycin C **86b** and pixantrone **81**, which are all widely used in the treatment of cancer, other quinones are in medicinal use which are highly selective for a certain group of organisms. For instance atovaquone **35** selectively kills protozoa while the rifamycins selectively kill Gram-positive bacteria with rifampicin **33** being one of the first-line antibiotics in the battle against tuberculosis. The high selectivity that can be obtained with these compounds is a strong incentive to develop new antimycobacterial quinones and to develop new strategies towards the synthesis of heterocyclic annulated quinones.

3 Results and discussion

3.1 Introduction

The experiments performed in this PhD thesis aim at the development of new entries into the synthesis of heterocyclic quinones and the development of new quinone leads active against *Mycobacterium tuberculosis*.

Pyridinium ylids are a very important tool in quinone chemistry and probably the best way of introducing acetonyl side chains on the quinone scaffold. Therefore, a catalytic version of this chemistry would make a valuable contribution to the tools available for the quinone chemist. For instance, some pyridinium salt are very hard to prepare due to their high hygroscopicity so it would be interesting to have a method that departs directly from the corresponding α-haloketones.

An important goal is the development of new synthetic strategies for both the elaboration as well as further derivatisation of the benzo[*j*]phenanthridine scaffold, a lead compound from previous research, towards new antimycobacterial compounds possessing higher activity and greater selectivity. In this respect, also the synthesis of C-4 fluorinated pyranonaphthoquinones was envisaged as potential new leads against *M. tb*.

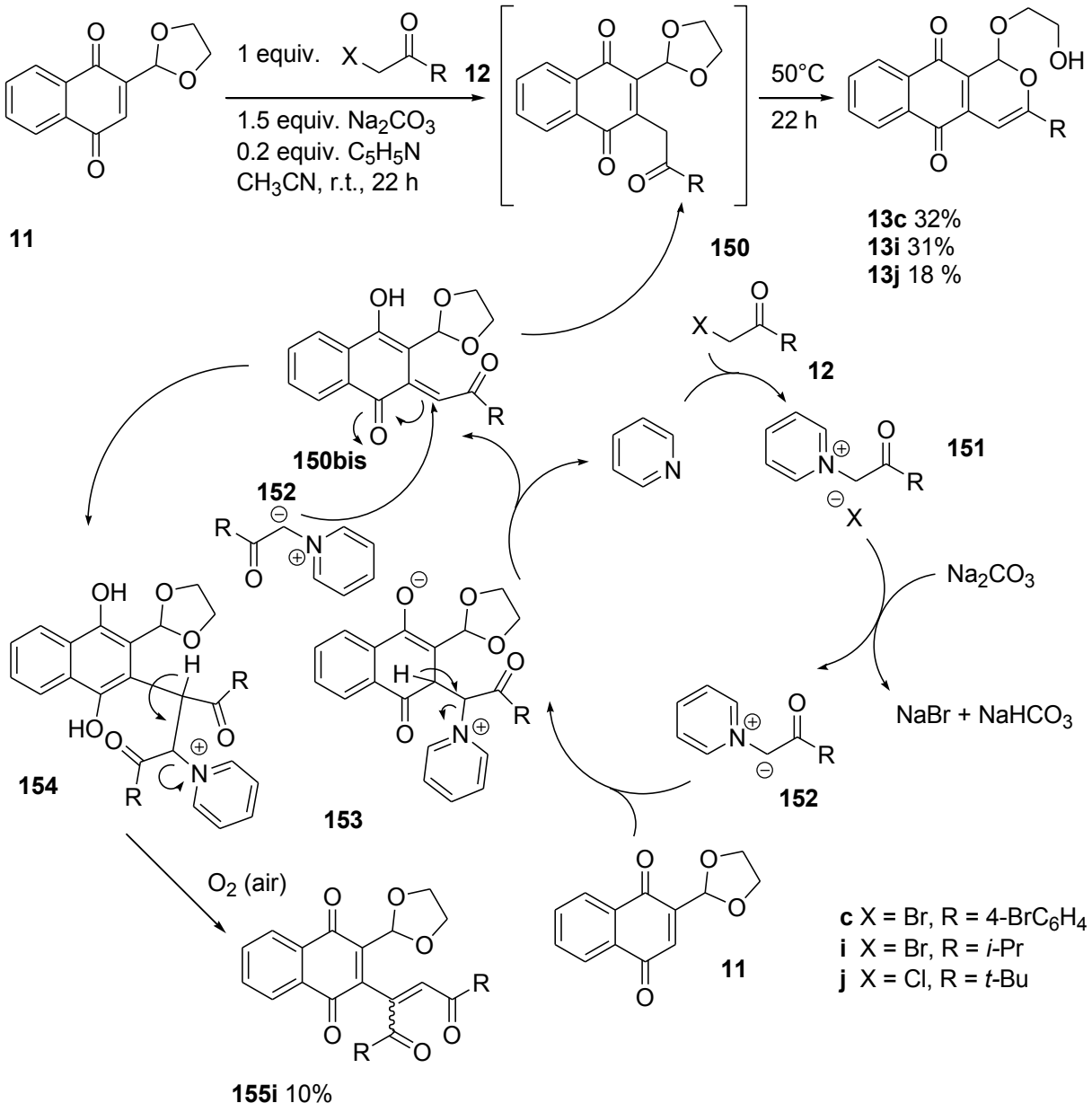
When unexpected reactions were encounter, they were further investigated in detail. In this respect, a new entry in the synthesis of aminonaphtholes and a catalytic synthesis of spironaphthoquinones, a scaffold previously unknown in the literature, is discussed.

3.2 Catalytic addition of pyridinium ylids to form C-1 functionalised pentalongin derivatives 13

Pyridinium ylids are versatile tools in organic synthesis, giving rise to different heterocycles, for instance pyridines, furans, azepines, etc.[101] More specifically, in quinone chemistry, pyridinium ylids proved to be very useful to introduce acetonyl side chains onto quinone moieties. After introduction of the acetonyl side chain, further elaboration towards the natural product isagarin,[102] anthraquinones, pyranonaphthoquinones,[103] 2-aza-anthraquinones[104] and indolizines[105] has been reported.

During previous research, 3-aryl-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-diones **13** were obtained by means of the reaction of a pyridinium salt and 2-(1,3-dioxolan-2-yl)naphthoquinone **11** in the presence of triethylamine.[106] Recently, catalytic versions of this ammonium ylid chemistry emerged to synthesise cyclopropanes[107] and aziridines[108] as well as an enantioselective cyclopropanation using a synthetic modified quinine as the chirality inducing agent. Benefits of this

method are the catalytic use of organic base and the *in situ* preparation of ammonium salts as well as the corresponding ylids. Even though most papers use DABCO (1,4-diazabicyclo[2.2.2]octane) as the catalytic tertiary amine, no reaction was observed when these reaction conditions were applied to 1-bromo-3-methylbutan-2-one **12i** and 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **11**.[109] Repeating the same reaction with a catalytic amount of pyridine instead of DABCO yielded 1-(2-hydroxyethoxy)-3-isopropyl-*1H*-benzo[*g*]isochromene-5,10-dione **13i** in 31% yield. A side product **155i** was formed due to addition of a second pyridinium ylid **152** onto the enone moiety of intermediate **150bis** followed by elimination of pyridine and aerobic oxidation. It was isolated in 10% yield and was also found in the other reaction mixtures but only in trace amounts. In the optimal reaction conditions, 1.5 equivalents Na_2CO_3, one equivalent α-halogenated ketone **12**, one equivalent 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **11** and 0.2 equivalents pyridine are reacted overnight at room temperature to form the acylmethyl substituted quinone **150**. Subsequently, heating at 60°C for 20 hours induced cyclisation towards 1-(2-hydroxyethoxy)pyranonaphthoquinones **13**.



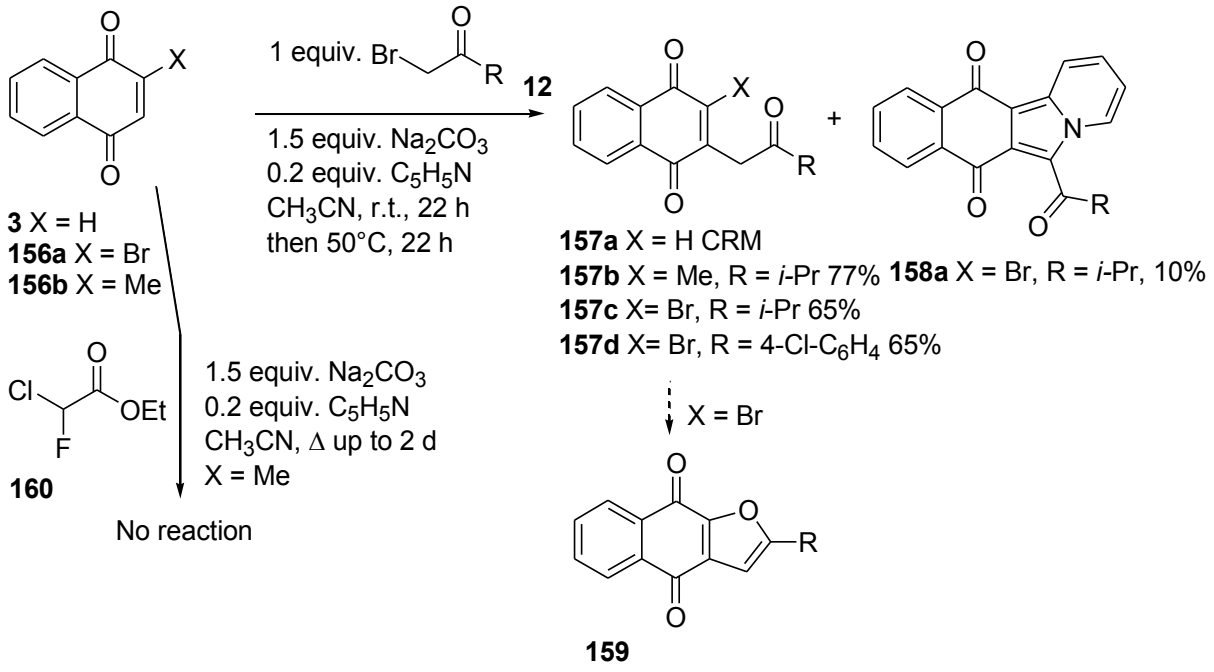
The catalytic version of the reaction proved to give similar results in the synthesis of 1-(2-hydroxyethoxy)pyranonaphthoquinones **13** in comparison to the equimolar method (Table 1). It has however the advantage that there is no need to preform the pyridinium salt and only a catalytic amount of pyridine is needed.

Table 1. Comparison between the equimolar and catalytical synthesis of 1-(2-hydroxyethoxy)pyranonaphthoquinones **13**.

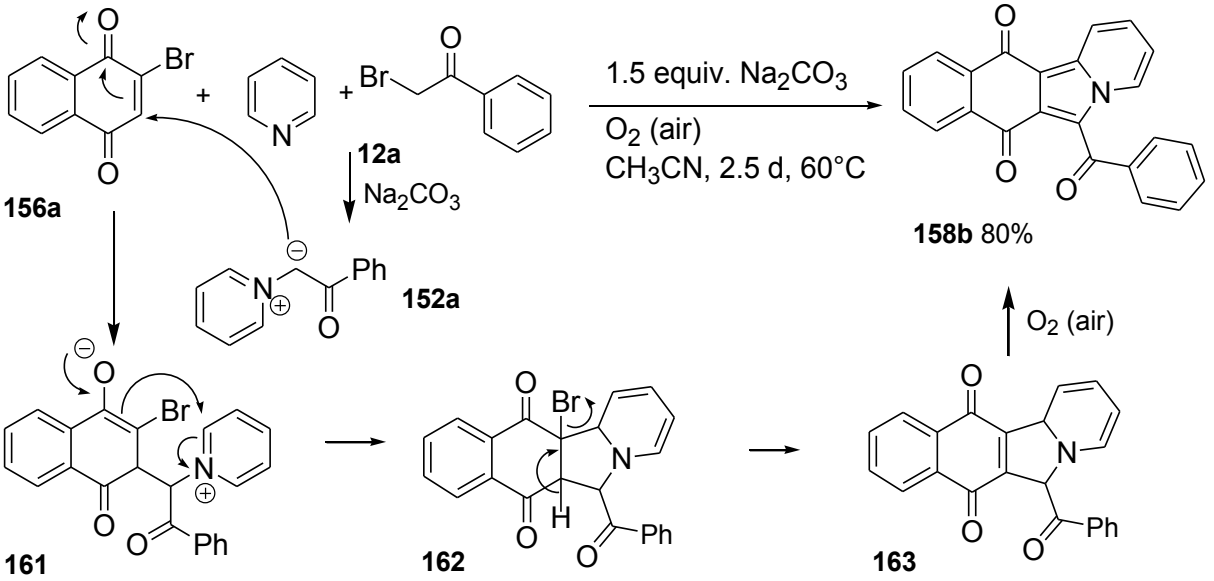
Compound	X	R	Equimolar method (%)		Catalytic method (%)	
			Crude[c]	Isolated Yield	Crude[c]	Isolated Yield
13a	Br	C_6H_5	57	52	24	-
13b	Br	4-$MeOC_6H_4$	47	43	72	-
13c	Br	4-BrC_6H_4	55	52	53	32
13d	Br	4-FC_6H_4	44	41	77	-
13e	Br	4-ClC_6H_4	68	65	57	-
13f	Br	4-MeC_6H_4	70[b]	69	52	-
13g	Br	2,5-$(MeO)_2C_6H_3$	72[b]	48	57	-
13h	Cl	Me	64	42	70[a]	-
13i	Br	*i*-Pr	51	27	60	31
13j	Cl	*t*-Bu	81	74	42[a]	18

Notes: (a) for X = Cl, the reaction only occurred upon the addition of 10 mol% of KI and heating for 2 d at 60°C. (b) reaction under the given reaction conditions yielded a mixture of **150** and **13** and the reaction mixture was heated at 50°C for 12 h in the presence of 5 equiv. Na_2CO_3 to obtain complete conversion. (c) Occurrence in the crude reaction mixture after workup determined by means of LC.

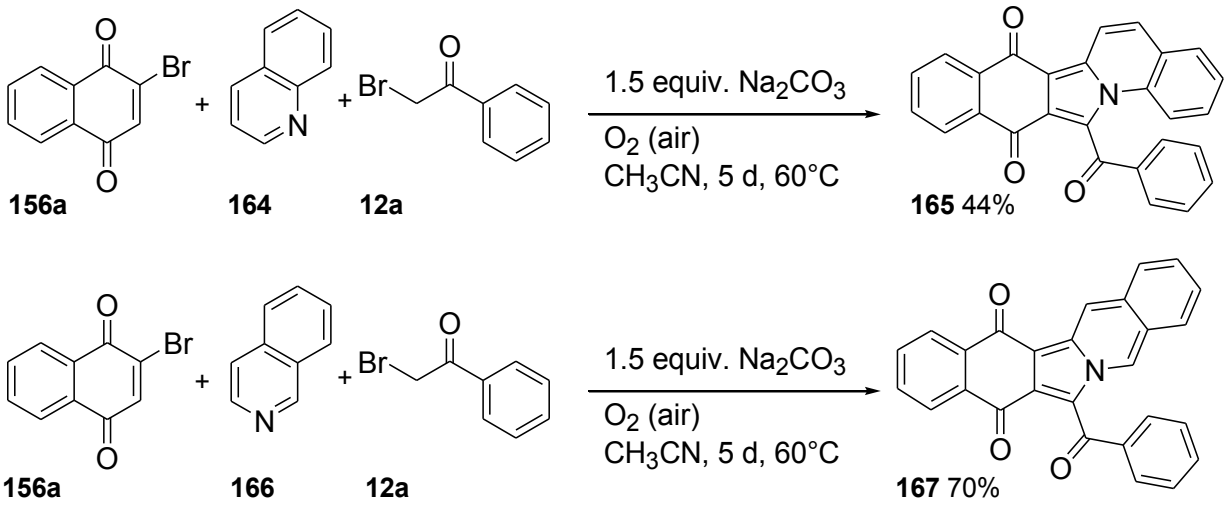
When the above developed reaction was applied to alternative substrates such as 2-bromo-1,4-naphthoquinone **156a**, or menadione **156b** and 2-bromo-4'-chloroacetophenone **12e** or bromomethyl isopropyl ketone **12i**, the corresponding acetonylnaphthoquinones **157** were obtained and no further cyclisation was observed towards naphtho[2,3-*b*]furan-4,9-diones **159** for the bromine substituted compounds. In case of the reaction of 2-bromo-1,4-naphthoquinone **156a** and bromomethyl isopropyl ketone **12i**, a trace amount of 6-isobutyrylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione **158a** was obtained. In case of 1,4-naphthoquinone **3**, a complex reaction mixture was obtained. No reaction was observed when menadione **156b** was reacted with ethyl chlorofluoroacetate **160** in the presence of 0.2 equiv. pyridine and 1.5 equiv. of Na_2CO_3 in boiling acetonitrile.



Repeating the reaction with a full equivalent of pyridine, 2-bromo-1,4-naphthoquinone **156a** and 2-bromoacetophenone **12a**, resulted in the formation of 6-benzoyl-benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione **158b** in 80% yield after 2.5 days heating in acetonitrile. Addition of pyridinium ylid **152a** to 2-bromo-1,4-naphthoquinone **156b** results in pyridinium intermediate **161**, which then undergoes intermolecular cyclisation towards compound **162**. After elimination of the bromide atom, intermediate **163** is oxidised by air oxygen towards benzoisoindole **158b**, which might explain the sluggishness of the reaction.

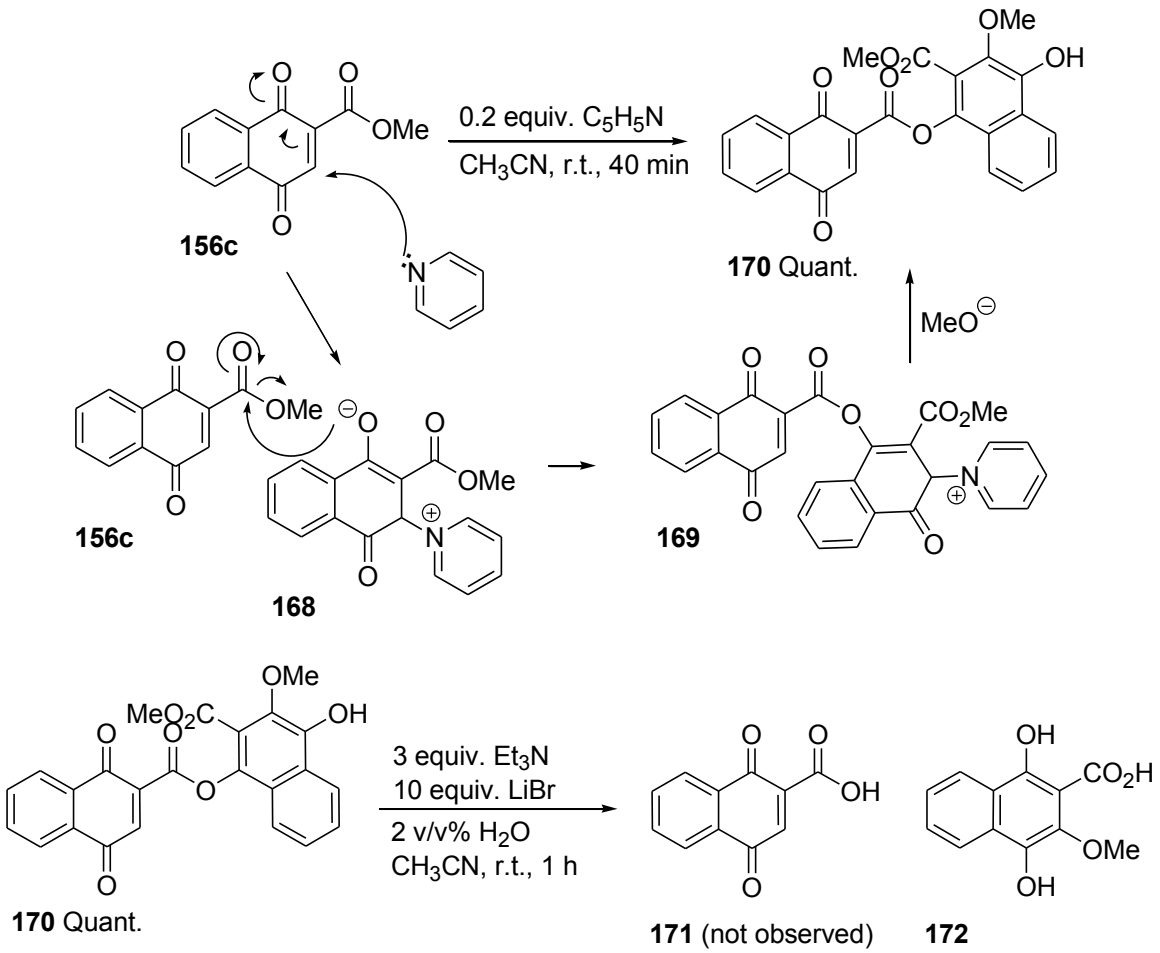


Repeating the reaction with quinoline **164** and isoquinoline **166** gave the corresponding 13-benzoylbenzo[5,6]isoindolo[2,1-*a*]quinoline-7,12-dione **165** and 8-benzoylbenzo[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione, **167** in 44% and 70% yield, respectively.



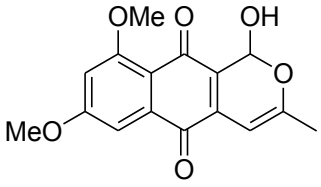
An alternative method to prepare these benzoisoindoles is known in the literature in which 1,4-naphthoquinone is reacted with a pyridinium salt in the presence of tetrakis(pyridine)cobalt(II) dichromate (TPCD) as the stoichiometric oxidant.[110] The yields are similar as compared to the reaction discussed above but the reaction times are significantly shorter. This type of reactions with pyridinium ylids in which the heterocyclic base is incorporated in the end product have recently received considerable attention to synthesise indolizines, imidazo[1,2-*a*]pyridines and pyrrolo[2,1-a]isoquinolines.[111,112]

When 2-methoxycarbonyl-1,4-naphthoquinone **156c** was reacted with a bromomethyl ketone, pyridine and K_2CO_3, a dimerisation-like reaction of the starting material occurred and no acetonylated product was observed. When the reaction was repeated at -45°C, this dimerisation-like reaction still occurred. Executing the reaction with only a catalytic amount of pyridine, gave pseudo-dimer with putative structure **170** in quantitative yield. A plausible mechanism is proposed: 1,4-addition of pyridine across the quinone chromophore leads to zwitterion **168** which then attacks across the ester function of a second quinone to form adduct **169**. This quinone **169** is then converted in the end product **170** through substitution of pyridine by methoxide. In an attempt to gain additional structural evidence for this putative structure **170**, a mild basic hydrolysis[113] was performed. This resulted in the formation of a highly polar, insoluble yellow solid from which 1,4-dihydroxy-3-methoxynaphthalene-2-carboxylic acid **172** was identified. 1,4-Naphthoquinone-2carboxylic acid **171** was not observed and it is very likely that this compound is not stable under the present conditions. Additional evidence should be collected to establish the structure of compound **170** with certainty.

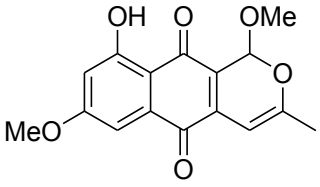


3.2.1 Attempted synthesis of ascomycone A, B and 1-hydroxydehydro-herbarin 15a-c

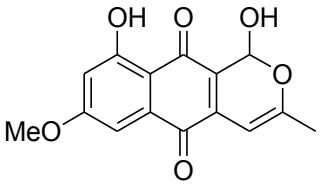
Benzo[*g*]chromenediones with an acetal function at C-1, such as pentalongin analogues **15**, are found in nature. 1-Hydroxydehydroherbarin **15a** was isolated from a *Corynespora* species occurring in the cavern beard lichen *Usnea cavernosa*.[114] Ascomycone A **15b** and B **15c** were isolated from an unidentified Ascomycete and exhibit activity against the phytopathogens *Magnaporthe grisea* (rice blast fungus) and *Fusarium graminearum* (wheat head blight fungus).[115] Their corresponding dihydro analogues thysanone **173** and astropaquinones B **174a** and C **174b**[116] have pronounced biological properties, such as inhibition of HRV-3C protease. The interesting biological activities of **173** and **173** have raised considerable interest among synthetic chemists.[117,127]



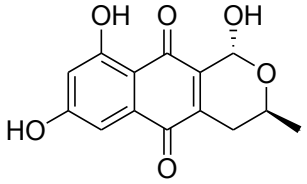
15a 1-Hydroxydehydroherbarin



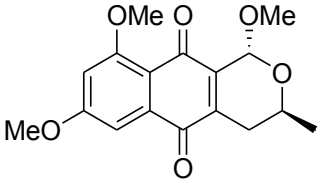
15b Ascomycone A



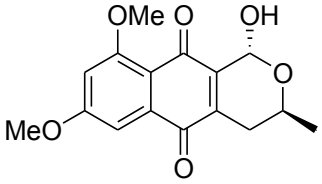
15c Ascomycone B



173 thysanone

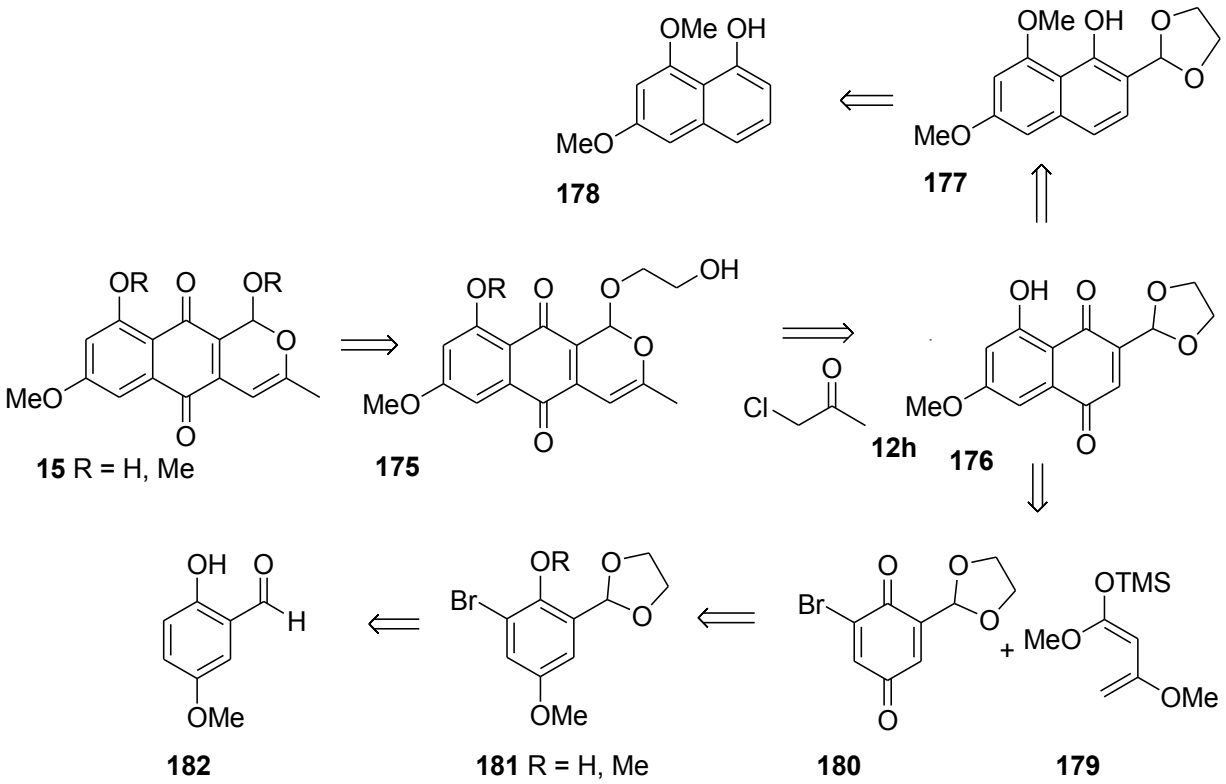


174a Astropaquinone B



174b Astropaquinone C

It was envisaged to synthesise 1-hydroxydehydroherbarin **15a** and ascomycone A **15b** and B **15c** by means of the abovementioned catalytic pyridinium ylid methodology. Retrosynthetically, reaction of (1,3-dioxolan-2-yl)-1,4-naphthoquinone **176** with chloroacetone **12h** followed by hydrolysis or methanolysis of the acetal function would lead to the desired 1-hydroxyherbarin **15a** or ascomycones **15b** and **15c**. Dioxolanylnaphthoquinone **176** would be synthesised by means of a regioselective Diels-Alder reaction between Brassard diene **179**, which is readily available from methyl 3-oxobutanoate, and 2-bromo-6-(1,3-dioxolan-2-yl)-1,4-benzoquinone **180**. The latter quinone **180** could be prepared starting from 2-hydroxy-5-methoxybenzaldehyde **182**. It should be noted that one cannot simply brominate 2,5-dimethoxybenzaldehyde as this would result in formation of the wrong isomer. Alternatively, dioxolanylnaphthoquinone **176** could be prepared starting from 6,8-dimethoxynaphth-1-ol **178** by means of formylation and acetalisation followed by Cu(I) mediated air oxidation[118] of the naphthol towards quinone **176**.



Thus, 2-hydroxy-5-methoxybenzaldehyde **182** was brominated with bromine in glacial acetic acid[119] followed by acetalisation of aldehyde **183a** resulting in 2-bromo-6-(1,3-dioxolan-2-yl)-4-methoxyphenol **181a** in 93% yield. 2-Bromo-6-(1,3-dioxolan-2-yl)-1,4-dimethoxybenzene **181b** was prepared analogously in 95% yield. Attempts to oxidise these substrates by means of cerium ammonium nitrate (CAN) resulted in a complex mixture due to hydrolysis of the dioxolanyl function. No reaction was observed upon attempted oxidation of dimethoxybenzene **181b** with four equivalents of CoF_3.[120] By means of [bis(trifluoroacetoxy)iodo]benzene (PIFA), it was possible to oxidise phenol **181a** towards 2-bromo-6-(1,3-dioxolan-2-yl)-1,4-benzoquinone **180**, in 53% yield, which only had a limited stability. Unfortunately, this quinone **180** failed to undergo the desired Diels-Alder reaction with Brassard diene **179**, even though this reaction has been successfully applied in quinone chemistry on similar substrates.[121] It appeared that no matter which conditions were used, no product was formed and the starting benzoquinone **180** simply decomposed while the Brassard diene remained intact (Table 2). As the quinone-2-carboxadehydes that would result from the hydrolysis of the dioxolanyl group are not stable, entries 2-9 focus on the addition of a base to trap the HBr that would be formed during the restoring of the aromaticity after the initial Diels-Alder reaction. In entry 10, the TMS-group of Brassard diene **179** was *in situ* deprotected with MeLi in an attempt create a more reactive diene.

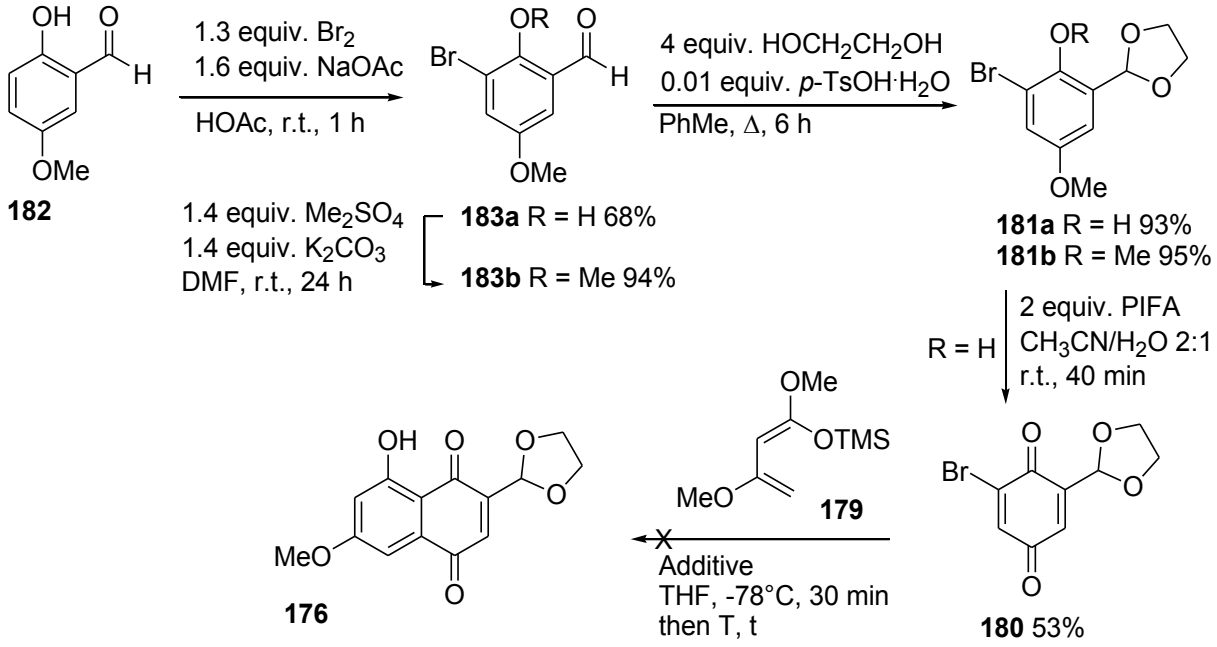
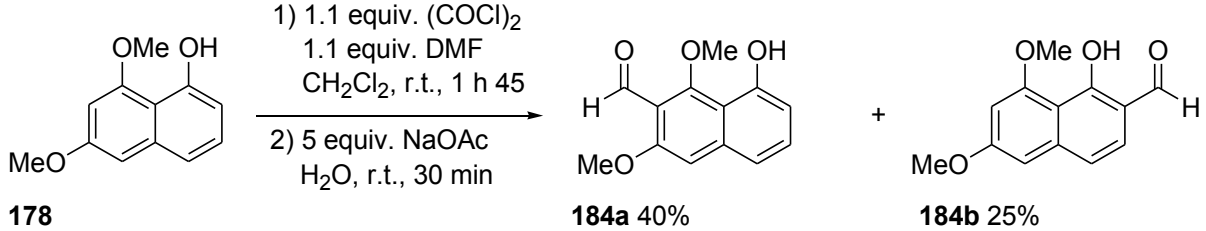


Table 2. Attempted reaction conditions for the Diels-Alder reaction of benzoquinone **180** with Brassard diene **179**.

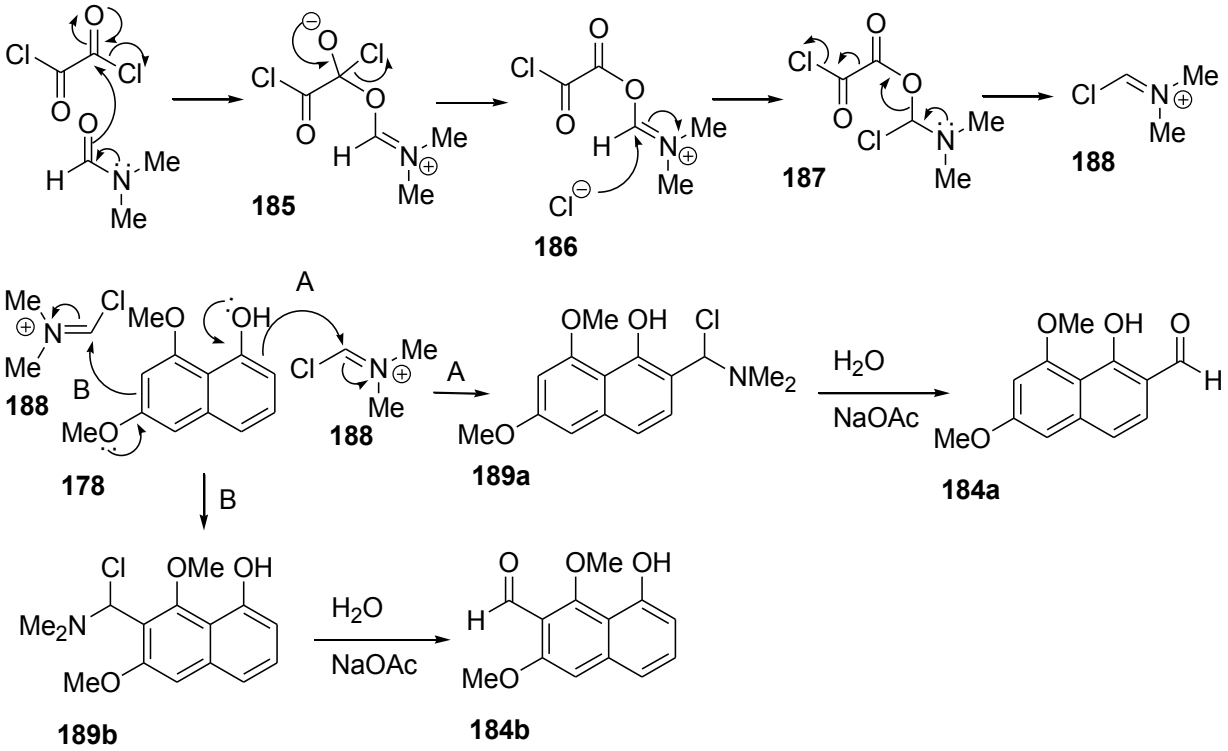
Entry	Additive	T	t (h)	Result	Entry	Additive	T	t (h)	Result
1	none	0	0	-	6	2 equiv. pyridine	0	0	-
2	2 equiv. Na_2CO_3	0	0	-	7	2 equiv. pyridine	r.t.	15	-
3	2 equiv. Na_2CO_3	r.t.	15	-	8	2 equiv. pyridine	50°C	7	-
4	2 equiv. Na_2CO_3	50°C	7	-	9	2 equiv. pyridine	Δ	36	-
5	2 equiv. Na_2CO_3	Δ	36	-	10	1 equiv. MeLi then **180**	-	-	crm[a]

(a) Complex reaction mixture

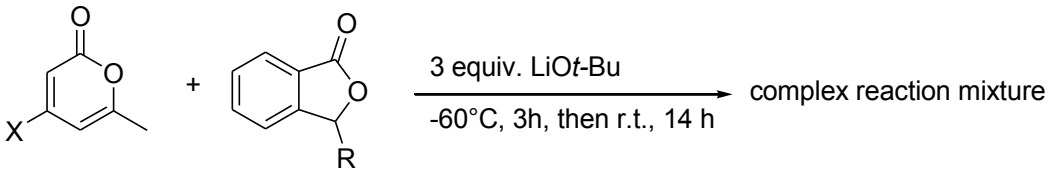
Giving the difficulties with the Diels-Alder reaction, alternative pathways were investigated. It was envisaged to synthesise 2-(1,3-dioxolan-2-yl)-8-hydroxy-6-methoxy-1,4-naphthoquinone **176** starting from 6,8-dimethoxynaphth-1-ol **178**.[122] A modified Vislmeier-Haack formylation with DMF and oxalyl chloride[123] yielded a mixture of 2-formyl-8-hydroxy-1,3-dimethoxynaphthalene **184a** and 2-formyl-1-hydroxy-6,8-dimethoxynaphthalene **184b**. Unfortunately, the undesired regioisomer **184a** was the major product due to the strong directing effect of the two methoxy groups. Repeating the reaction at 0°C only slowed down the reaction and an identical ratio of regioisomers was obtained. When the reaction was performed at -78°C, no reaction was observed. Regioselectivity is often an issue in the functionalisation of oxygenated naphthalenes.[124]



The reaction mechanism is depicted below: initial reaction of oxalyl chloride with DMF leads to the formation of reactive intermediate **188**, which then reacts with naphthol **178** towards chloroaminals **189**. Hydrolysis then leads to the formation of aldehydes **184a** and **184b**.



Alternatively, a phthalide annulation strategy[125] could be deployed with model substrates 4-bromo-6-methyl-pyran-2-one **190a**[126] or 4-methoxy-6-methyl-pyran-2-one **190b** as the Michael acceptors and 3-cyanophthalide **191a** or 3-tosylphthalide **191b** as the phthalides. When the reaction was performed under the standard phthalide annulation conditions, complex mixtures were obtained is all cases.



190a X = Br
190b X = OMe
191a R = CN
191b R = Ts

However, when the reaction was performed using only one equivalent of LiO*t*-Bu at -90°C with 4-bromo-6-methyl-pyran-2-one **190a** and 3-cyanophthalide **191a**, 3-cyano-3-(6-methyl-2-oxo-2*H*-pyran-4-yl)-phthalide **192** was isolated in 77% yield. No reaction was observed with the less reactive 4-methoxy-6-methyl-pyran-2-one **190b** and the reaction could not be performed with 3-tosylphthalide **191b** as it was insoluble at -90°C in THF. 3-Cyano-3-(6-methyl-2-oxo-2*H*-pyran-4-yl)-phthalide **192** appeared to be relatively stable and could not be converted into the corresponding

pyranonaphthoquinone **193** (Table 3). A similar strategy towards the ascomycones **15**, deploying a Staunton–Weinreb annulation, was attempted unsuccessfully by Brimble *et al*.[127]

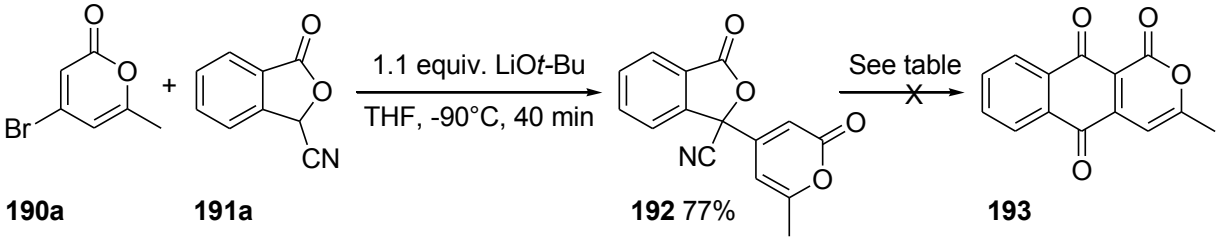
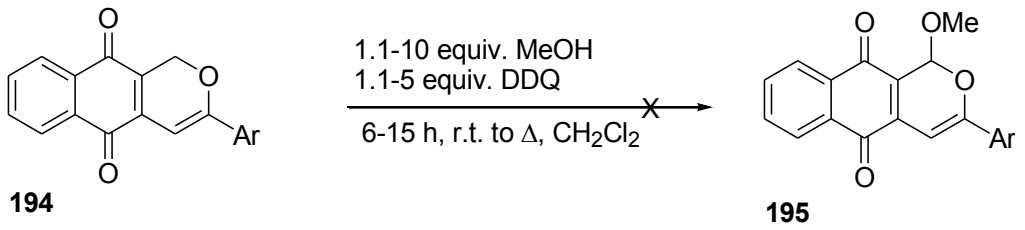


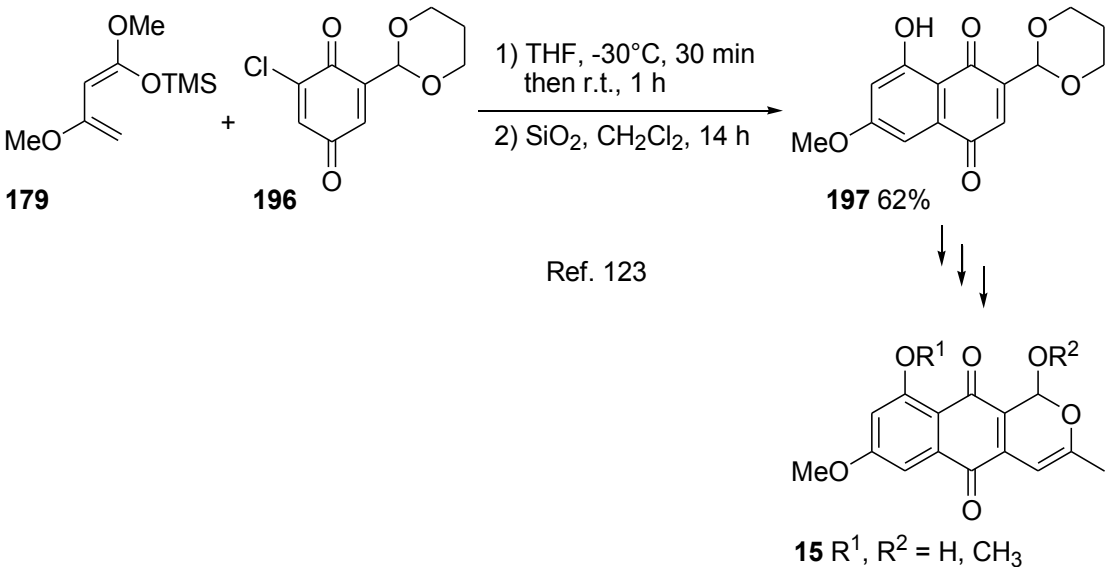
Table 3. Attempted reaction conditions to convert 3-cyano-3-(6-methyl-2-oxo-2*H*-pyran-4-yl)-phthalide **192** into pyranonaphthoquinone **193**.

Entry	Reagents	conditions
1	0.1 to 1 equiv. $BF_3 \cdot OEt_2$	CH_2Cl_2, 0°C to Δ, 2 d
2	0.1 to 1 equiv. *p*-TsOH·H_2O	PhMe or CH_2Cl_2, r.t. to Δ, 4 d
3	0.2 equiv. DABCO	THF, r.t. to Δ, 3 d

It was also investigated whether it would be possible to oxidise the readily available pyranonaphthoquinones **194**[263] towards 1-methoxypyranonaphthoquinones **195**.[128] However, no results were obtained. Other authors also failed to perform this transformation in their quest for ascomycones **15**.[127]

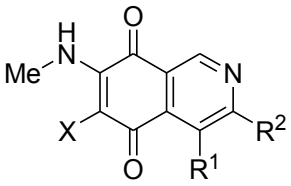


While these trials were performed, a total synthesis of 1-hydroxydehydroherbarin **15a**, ascomycones A **15b** and B **15c** was published using the pyridinium ylid methodology discussed above. The authors also attempted a Diels-Alder reaction to construct quinone intermediate **176** and experienced the same problem. After thorough investigation of the reaction, it was found that the problems could be overcome by replacement of the 1,3-dioxolanyl group by a 1,3-dioxanyl group.[129]

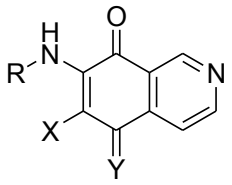


3.2.2 Attempted synthesis of mansouramycins A-D 16

Mansouramycins A-D **16** are cytotoxic isoquinolinediones isolated from a marine-derived *Streptomyces sp*. isolate Mei37.[130] They are closely related to the cytotoxic caulibugulones A-F **198** from the marine bryozoan *Caulibugula intermis*.[131] Caulibugulones A-F **198** were synthesised by oxidation of 5-aminoisoquinoline followed by functionalisation of the quinone moiety.[132]

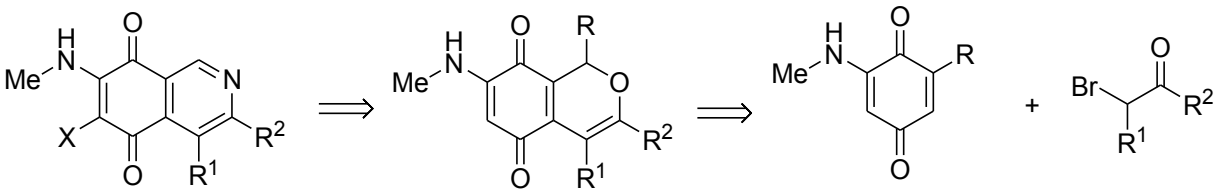


16a Mansouramycin A X = H, $R^1 = R^2$ = Me
16b Mansouramycin B X = Cl, R^1 = H, R^2 = Me
16c Mansouramycin C X = H, R^1 = H, R^2 = CO_2Me
16d Mansouramycin D X = H, R^1 = H, R^2 = indol-3-yl



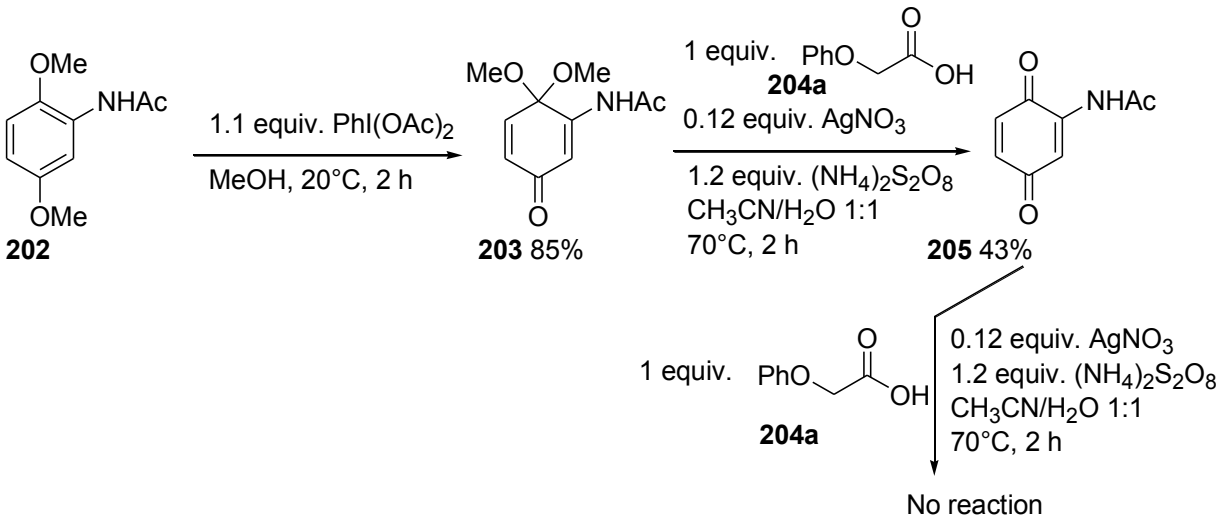
198a Caulibugulone A X = H, Y = O, R = Me
198b Caulibugulone B X = Br, Y = O, R = Me
198c Caulibugulone C X = Cl, Y = O, R = Me
198d Caulibugulone D X = H, Y = O, R = $(CH_2)_2OH$
198e Caulibugulone E X = H, Y = NH, R = Me
198f Caulubigilone F X = H, Y = $N(CH_2)_2OH$, R = Me

As the C-1 alkoxy substituted pyranonaphthoquinones **13** can readily be converted into the corresponding 2-aza-anthraquinones by means of NH_4OAc in acetic acid[106] or NH_4OH,[104a,133] it was attempted to apply the abovementioned pyridinium ylid methodology to the synthesis of mansouramycins A-D **16**. Thus, it was envisaged to react 2-(1,3-dioxolan-2-yl)-6-methylamino-1,4-benzoquinone **200a** or 2-phenoxymethyl-6-methylamino-1,4-benzoquinone **200b** and a bromomethyl ketone **201** to form pyranobenzoquinone **199a** or **199b**. This quinone would then be converted in the mansouramycins **16** using an appropriate nitrogen source.



16 **199a** R = H **200a** R = 1,3-dioxolan-2-yl **201**
199b R = OCH_2CH_2OH **200b** R = CH_2OPh

Thus, the synthesis of benzoquinone **200b** by means of a radical alkylation reaction of an amino substituted quinone was envisaged. The quinone was protected as the dimethyl acetal in order to introduce the phenoxymethyl side chain regioselectively. As a methylamino group is not tolerated by most oxidative reagents, the nitrogen atom was acetylated and an oxidative dearomatisation in anhydrous methanol with PIDA[134] was effectuated towards *N*-(6,6-dimethoxy-3-oxocyclohexa-1,4-dienyl)-acetamide **203**. When the radical alkylation reaction was performed, the phenoxyacetic acid **204a** hydrolysed the acetal and no alkylated product could be retrieved. When the reaction was repeated using quinone **205**, no alkylated product could be obtained either. Alternatively, an anilide could be directly oxidised to the quinone with Dess-Martin periodinane, however this has been so far only demonstrated on *para*-substituted anilides.[135]



Attempts to directly add NaN_3, amines,[136] amides[137] or benzylhydroxylamine[138] to benzoquinone intermediate **180** all led to decomposition of the starting material. Attempts to prepare a brominated phenoxymethylbenzoquinone as a more robust alternative for 2-bromo-6-(1,3-dioxolan-2-yl)-1,4-benzoquinone **180** by bromination of phenoxymethyl-1,4-benzoquinone **207a**, led to the formation of 5,6-dibromo-2-(4-bromophenoxymethyl)-cyclohex-2-ene-1,4-dione **208**. Also attempts to perform Buchwald-Hartwig coupling reactions with dioxolanylbromobenzenes **181** using either Pd(0)[139] or Cu(I)[140] as a catalyst did not yield any coupling product either (Table 4). An alternative entry into this

building block would be nitration followed by reduction and functionalisation of 2-hydroxy-5-methoxybenzaldehyde **182**. Unfortunately, this route could not be completed due to time constraints.

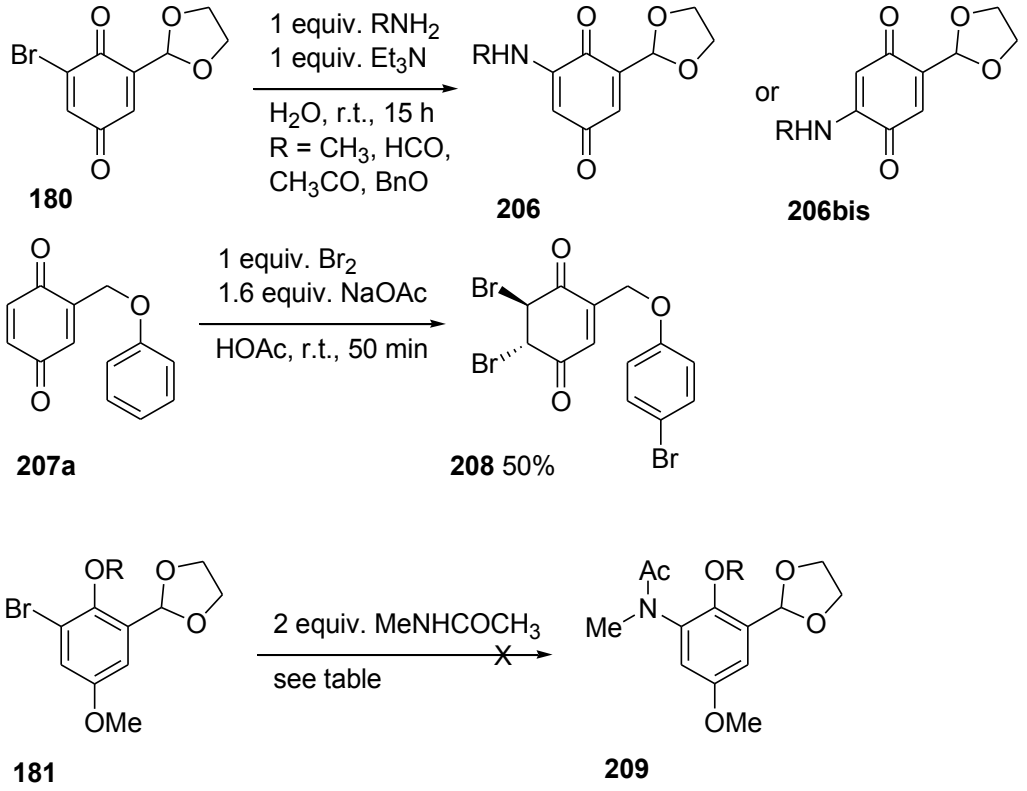
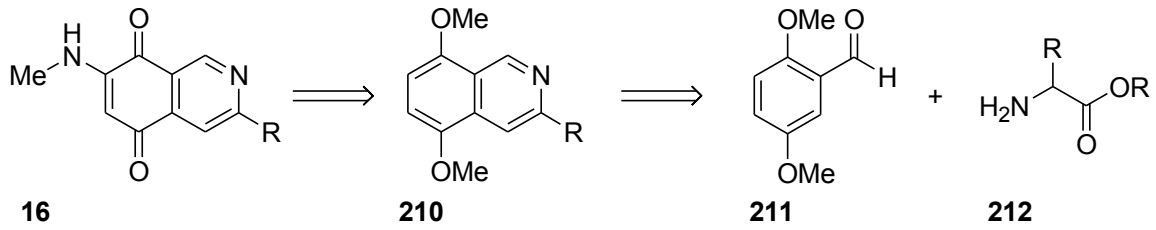


Table 4. Attempted reaction conditions for the Buchwald-Hartwig amination of bromobenzenes **181**.

Entry	R	Catalyst	Base	Ligand	Solvent, t, T
1	Me	5 mol% Cu_2O	2 equiv. NaO*t*-Bu	None	NMP, 100°C, 10 h
2	H	5 mol% Cu_2O	2 equiv. NaO*t*-Bu	None	NMP, 100°C, 10 h
3	Me	3 mol% $Pd(OAc)_2$	2 equiv. NaO*t*-Bu	9 mol% xantphos	PhMe, 100°C, 18 h
4	Me	2.5 mol% $Pd(dba)_2$	2 equiv. NaO*t*-Bu	5 mol% *t*-Bu_3P	PhMe, 100°C, up to 3 d
5	Me or H	5 mol% $Pd(dba)_2$	2 equiv. NaOPh	5 mol% xantphos	PhMe or 1,4-dioxane 100°C, up to 3 d
6	Ac or Bz	2.5 mol% $Pd(dba)_2$	2 equiv. NaO*t*-Bu	5 mol% *t*-Bu_3P	PhMe, 100°C, up to 3 d

An alternative strategy would be to synthesise the isoquinoline skeleton **210** via a Pomeranz-Fritsch reaction starting from 2,5-dimethoxybenzaldehyde **211** and amino acid ester **212**. All these amino acid esters **212** are either commercially available or can be made in one step from readily available starting materials.[141]



Reductive amination of alanine methyl ester **212a**[142] with 2,5-dimethoxybenzaldehyde **211** followed by acid base extraction proved to be a very useful method to prepare amine **213** in good yield and without flash chromatography. This in contrast to the reaction of alanine methyl ester **212a** with 2-bromomethyl-1,4-dimethoxybenzene **214**, which leads predominantly to dialkylated product **215**. After testing several *N*-sulfonylation conditions, it was found that *N*-tosyl or *N*-mesyl protection could be most efficiently effectuated by means of reaction of 1.3 equivalents of *p*-tosyl or mesyl chloride in pure pyridine, yielding sulfonamides **216a** and **216b** in 76% and 79% yield, respectively, without the need for flash chromatography. Initially, DIBAL was used to convert this intermediate into the corresponding aldehyde **217** but, as mixtures of the aldehyde and alcohol were obtained, it was found more convenient to completely reduce the ester to the alcohol with $LiAlH_4$ followed by a Swern oxidation.[143] When aldehyde **217** was heated in HCl/1,4-dioxane, tetrahydroisoquinoline **218** was formed instead of the desired dihydroisoquinoline.[144] Attempts to aromatise this compound **218** by mesylating the alcohol in boiling acetonitrile only gave trace amounts of isoquinoline **210a** even after two days of reflux. Also no aromatisation occurred when the compound was oxidised with CAN. After some experimentation it was found that aldehyde **217** could be converted into isoquinoline **210a** by means of reaction in neat chlorosulfonic acid[145] in low yield (Table 5). Subsequent oxidative demethylation with CAN gave quinone **220** in good yield.

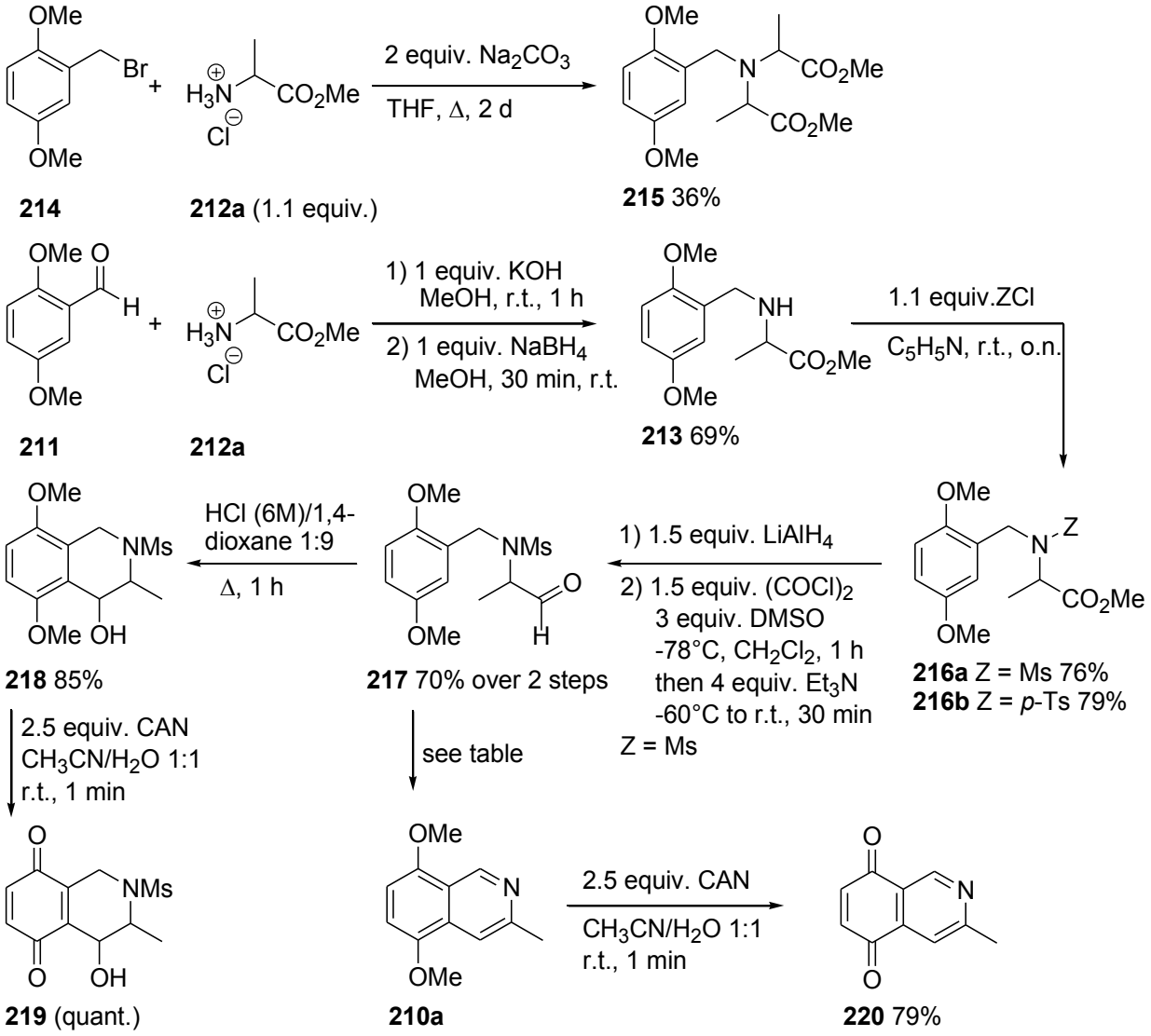


Table 5. Attempted reaction conditions to convert aminoaldehyde **217** in isoquinoline **210a**.

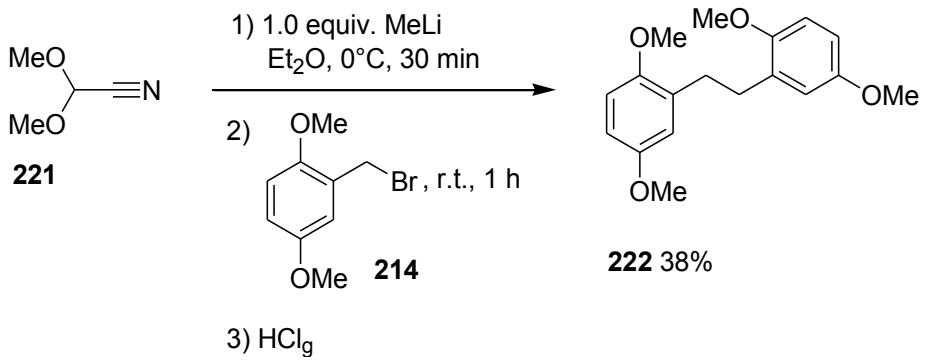
Entry	reagent	Solvent	Time	Temp	Result
1	1 mol% *p*-TsOH·H_2O	PhMe	o.n.	Δ	Complex reaction mixture
2	3 equiv. *p*-TsOH·H_2O	PhH	3 h	Δ	5% **210a**
3	3 equiv. $POCl_3$	$CHCl_3$	15 h	r.t.	No reaction
4	3 equiv. $POCl_3$	$CHCl_3$	15 h	Δ	Complex reaction mixture
5	10 equiv. $ClSO_3H$	-	5 min then 15 min	-20°C r.t.	44% **210a**

Even though this procedure presents a way of synthesising the mansouramycin quinone building block, the sequence is long, the yields are low and the cyclisation step harsh and low-yielding. Moreover, it is not a demonstration of the developed methodology and the steps that would complete this synthesis have already been demonstrated in the synthesis of related natural products. After the establishment of this synthetic route it was found that in 2008 a German PhD student completed the synthesis of three Mansouramycins **16**. However, this synthesis was overlooked as it was never

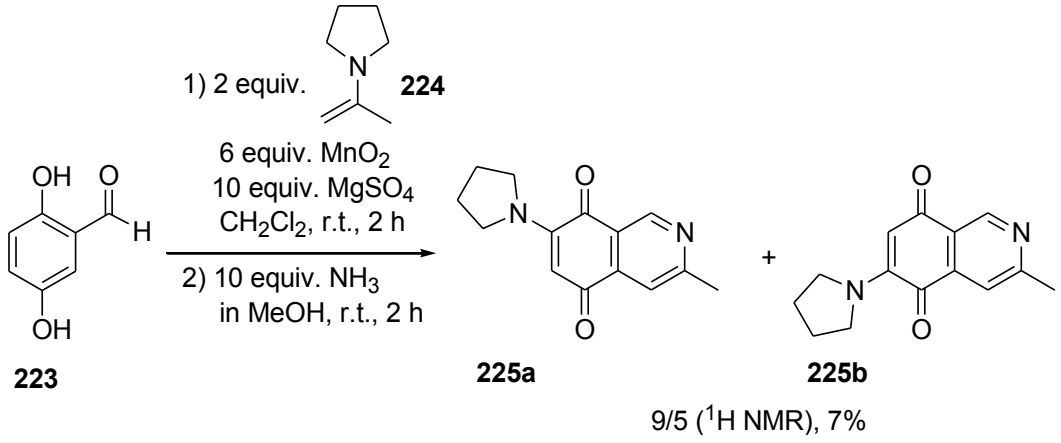
published and was only discovered by obtaining his PhD thesis. The methodology is very similar: the isoquinoline skeleton is synthesised by means of a Pictet-Spengler reaction followed by dehydrogenation of the tetrahydroisoquinoline.[146]

Even though many mild and elegant methods exist in the literature to synthesise the isoquinoline or pyridine[147] skeleton, they are almost invariably substituted by aromatic substituents[148] and most are unsuited to synthesise simple alkyl substituted isoquinolines.

An attempt to prepare isoquinoline **210a** in a 'one pot' protocol by means of addition of MeLi onto dimethoxyacetonitrile **221**[149] followed by reaction with 2-bromomethyl-1,4-dimethoxybenzene **214** only led to homocoupled product **222** probably due to failure of MeLi to add across dimethoxyacetonitrile **221** under the presented conditions.



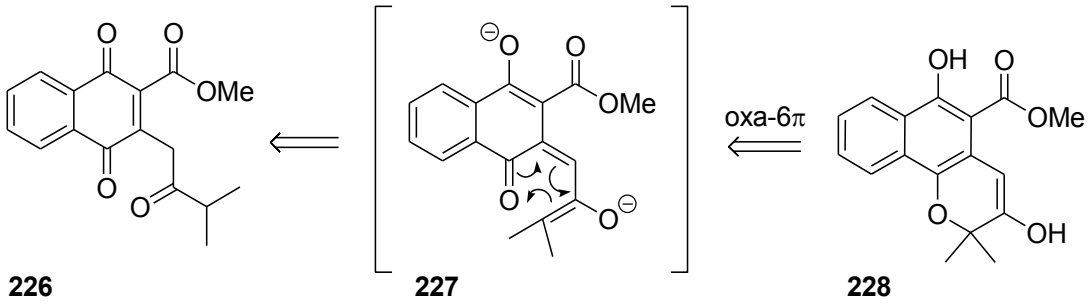
Another attempt to perform a one pot oxidative addition of enamine **224**[150] onto 2,5-dihydroxybenzaldehyde **223** followed by ammonia mediated ring-closure and addition across the quinone moiety lead to pyrrolidin-1-yl-isoquinoline-5,8-diones **225** in low yield.



3.2.3 Attempted synthesis of 3-hydroxymollugin 228

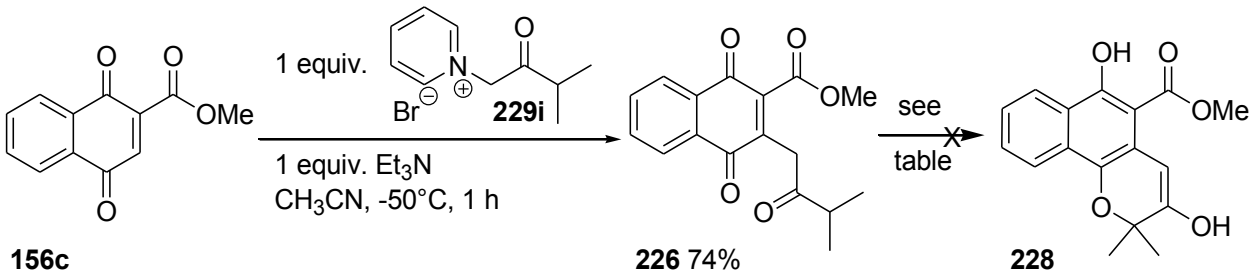
3-Hydroxymollugin **228** is a cytotoxic compound which has been isolated from *Rubia cordifolia*[151] and *Pentas longiflora*.[152] It was recently synthesised in our research group in two steps from mollugin by means of a bromination followed by hydrolysis.[153] A short and efficient synthesis of

hydroxymollugin was envisaged by means of an oxa-6-π electrocyclisation of acetonylnaphthoquinone **226**, analogous to a synthesis of mollugin.[154]



226 **227** **228**

Methyl-3-(3-methyl-2-oxobutyl)-1,4-naphthoquinone-2-carboxylate **226** was prepared by means of reaction of pyridinium salt **229** at low temperature with methoxycarbonyl-1,4-naphthoquinone **156c** in good yield.[15] It was imperative to use no more than one equivalent of Et_3N as the use of even a slight excess lead to significant formation of methyl-9*b*-hydroxy-2-isopropyl-5-oxo-5,9b-dihydronaphtho[1,2-*b*]furan-4-carboxylate **230**. Unfortunately, none of the tested conditions lead to the desired 3-hydroxymollugin **228**. Interestingly, when acetonylnaphthoquinone **226** was heated in the presence of phenylboronic acid, as in the key step of the synthesis of rubicordifolin,[155] one compound was formed with five additional aromatic protons, suggesting the incorporation of phenylboronic acid. Recording of a ^{11}B NMR spectrum revealed a shift of 28.38 ppm, consistent with a phenylboronic ester. Thus, phenylboronic acid ester **231** was obtained in almost quantitative yield.

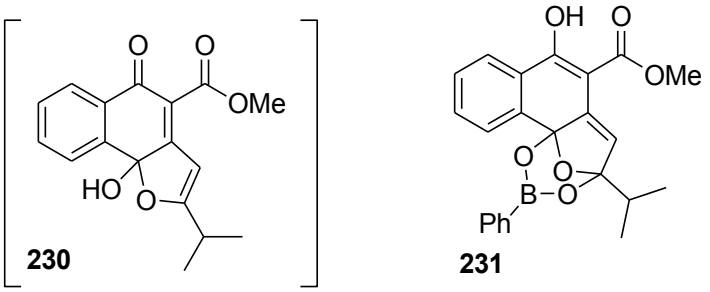


156c **226** 74% **228**

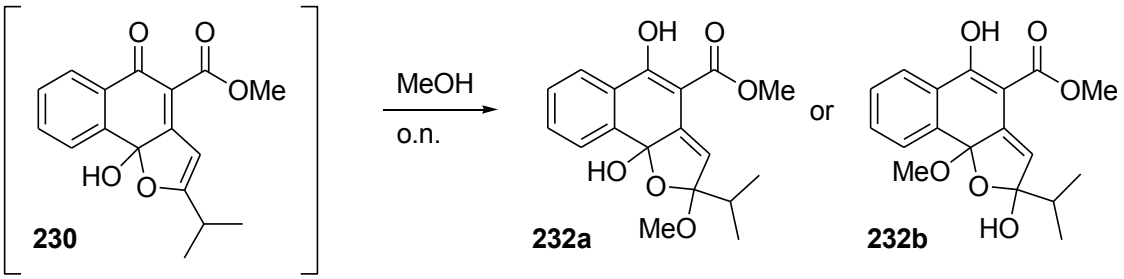
Table 6. Attempted reaction conditions for the cyclisation of acetonylnaphthoquinone **226** towards 2-hydroxymollugin **228**.

Entry	Base	Additive	Solvent	Temperature	Time	Result
1	2.5 equiv. Et_3N	None	PhMe	110°C	17 h	No reaction
2	none	2 equiv. $ZnCl_2$	PhMe	110°C	4 h	No reaction
3	5 equiv. Li*O*t-Bu	None	*t*-BuOH/THF 1:1	r.t.	16 h	Complex reaction mixture
4	2 equiv. K*O*t-Bu	None	THF	r.t.	2 h	**230**
5	2 equiv. LiHMDS	None	THF	-78°C to 0°C	4 h then 10 h	Complex reaction mixture
6	2 equiv. Li*O*t-Bu	None	THF	-78°C to 0°C	4 h then 10 h	Complex reaction mixture
7	-	1 equiv.	PhMe	110°C	3 h	**231** 94%

$PhB(OH)_2$



Compound **230** could not be purified and upon attempted recrystallisation from methanol, methanol adduct **232** was formed. Even though from a mechanistically point of view, the formation of **232a** is more likely, it was not possible to unambiguously assign the structure using HSQC and HMBC spectra.



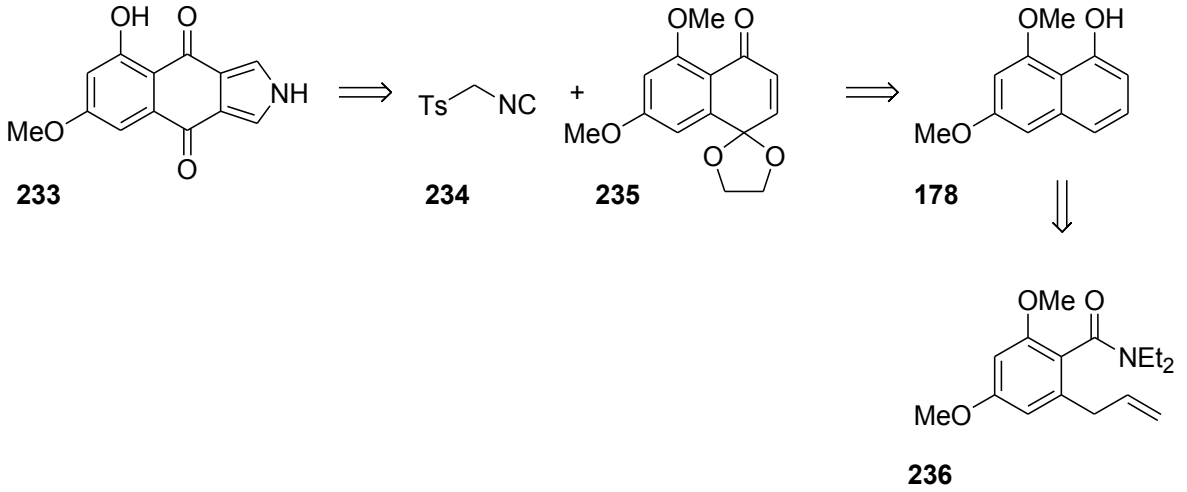
3.2.4 Conclusion and discussion

A catalytic version of pyridinium ylid chemistry was developed and applied on the synthesis of C-1 substituted pyranonaphthoquinones **13**. The method works equally well as the corresponding stoichiometric reaction but has advantages such as the reduction of the necessary amount of pyridine, the elimination of the need to prepare the corresponding pyridinium salts. When this method is applied on 2-bromo-1,4-naphthoquinone **156a**, the aromatic base is incorporated in the product resulting in the formation of benzo[*f*]isoindolediones. It was attempted to apply the catalytic methodology on the total synthesis of some naturally occurring quinones. Unfortunately, no synthesis could be completed due to failure to synthesise the appropriate starting material. Nevertheless, this is a work in progress and the total synthesis of the Mansouramycins **16** should be completed following the pyridinium ylid route highlighted above rather than via the Pomeranz-Fritsch route.

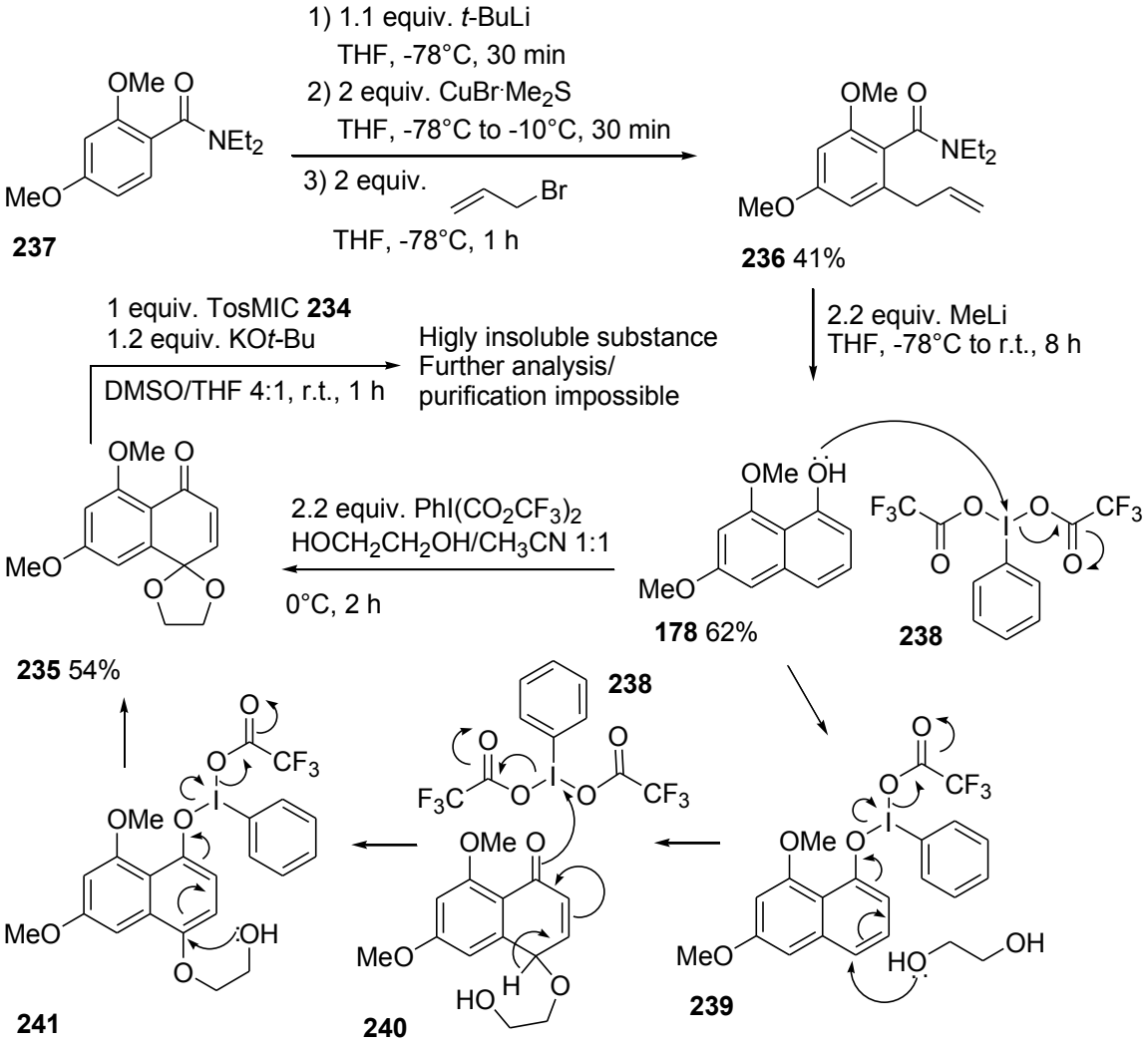
3.3 Unexpected aminonaphthol synthesis

Azamonosporascone **233** is a isoindoloquinone isolated from the fungus *Monosporascus cannonballus*, a plant pathogen that causes severe production losses to muskmelon and watermelon.[156] Its synthesis was envisaged from the reaction of quinone monoketal **235** and *p*-tosylmethyl isocyanate **234** (TosMIC). The quinone moiety is protected as its monoketal as addition of TosMIC to the

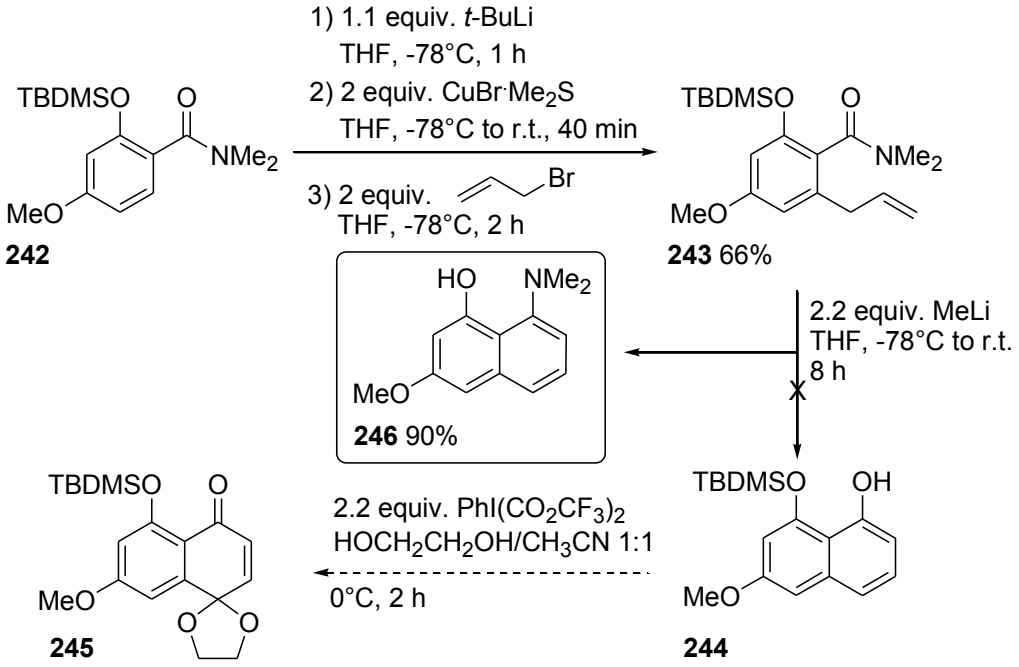
corresponding quinone would lead to aromatisation, thus preventing cyclisation to the pyrrole ring.[157] Selective cleavage of the methoxy ether *ortho* of the carbonyl function would then lead to azamonosporascone **233**.[158] Quinone monoketal **235** can be prepared from naphthol **178**, which is prepared by MeLi mediated cyclisation of *N*,*N*-diethylallylbenzamide **236**.[159]



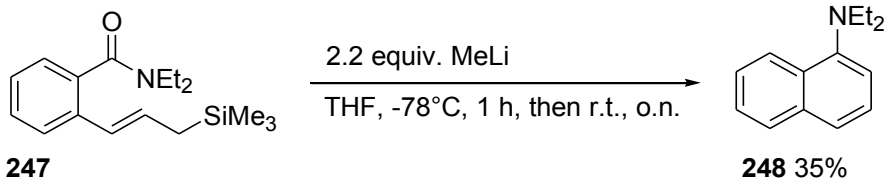
Thus, 2,4-dimethoxy-*N*,*N*-diethylbenzamide **237** was *ortho*-lithiated with *t*-BuLi, followed by Li-Cu(I) exchange using $CuBr_2 \cdot Me_2S$ and subsequently reacted with allyl bromide to 2-allyl-*N*,*N*-diethyl-4,6-dimethoxybenzamide **236** in 41% yield. Even though procedures exist that convert the organolithium in a Grignard reagent using $MgBr_2 \cdot OEt_2$, followed by reaction with allyl bromide, no reaction was observed following these protocols.[159]Allylated amide **236** was then cyclised with MeLi towards naphthol **178** which was oxidatively dearomatised using PIFA in anhydrous CH_3CN and ethylene glycol.[160] Initial attack of naphthol **178** on a first molecule of PIFA **238**, leads to activated intermediate **239**, on which ethylene glycol attacks in a 1,4-fashion followed by elimination of the trifluoroacetoxyiodobenzene residue. After aromatisation and attack on a second molecule of PIFA **238**, intramolecular cyclisation and elimination leads to quinone monoketal **235**. When quinone monoketal **235** was reacted with TosMIC,[161] a highly insoluble substance was obtained that could not be purified nor characterised.



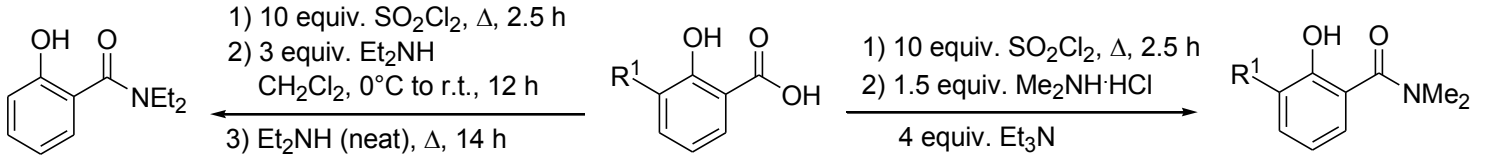
In order to tackle this problem, it was decided to synthesise a range of alternative substrates for this reaction. Initially, the synthesis of *tert*-butyldimethylsilanoxy substituted quinone monoketal **245** was envisaged starting from *ortho*-silanoxy functionalised naphthol **244**. Thus, 2-(*tert*-butyldimethylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide **242** was reacted with allyl bromide as described above towards allylbenzamide **243** in good yield. Surprisingly, the subsequent reaction with MeLi did not result in the expected naphthol **244** but 8-dimethylamino-3-methoxynaphthalen-1-ol **246** was formed in 90% yield as the sole reaction product. It was isolated as a white solid which turned purple upon standing. Even though the structure bears close resemblance to proton sponges, reports on this aminonaphthol structure are quite rare in the literature. 5-Amidonaphthols have been deployed as substrates for a dye sensitised oxidation towards the corresponding 5-amido-1,4-naphthoquinones.[162]



One precedent of this surprising reactivity was found in the literature, in which *N*,*N*-diethyl-2-(3-trimethylsilanylpropenyl)-benzamide **247** was converted into *N*,*N*-diethyl-1-aminonaphthalene **248** in 35% yield under the presented conditions via a Peterson olefination-like reaction.[122]



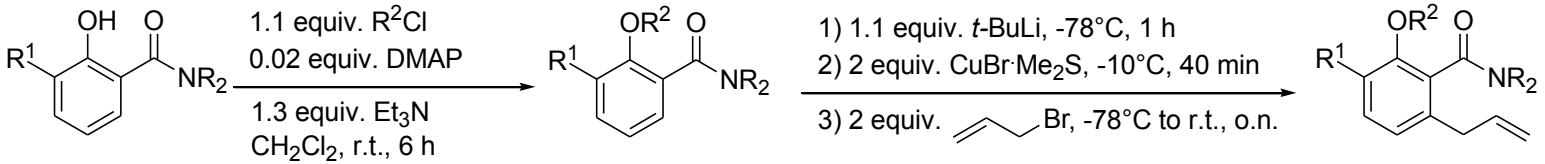
Confronted with this surprising reaction, it was decided to investigate its scope and limitations in depth. Starting from salicylic acids **249**, *N*,*N*-diethyl[163] **250** and *N*,*N*-dimethyl **251** benzamides were synthesised, protected with a TBDMS, a TIPS[164] or a TBDPS[165] group and subsequently allylated towards 2-allyl-6-silanyloxy-*N*,*N*-dialkylbenzamide **253** and **256** in good to excellent yield with exception of the TBDPS group, which seemed to interfere with the allylation step. In case of 3-methylbenzamide **253e**, a complex reaction mixture was retrieved from the allylation reaction probably due to concomitant deprotonation of the benzylic hydrogens. In case of other substituted dimethylbenzamides such as 3-methoxy-, 5-methoxy- and 4-trifluoromethyl-2-(*tert*-butyldimethyl-silanyloxy)-*N*,*N*-dimethylbenzamide, the allylation reaction gave mixtures of unreacted starting material, mono- and double allylated products probably due to a combination of coordinating and inductive effects. In case of 2,4-bis-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide, deprotection of the TBDMS group ortho of the amide function occurs probably due to a combination of sterical hindrance and the strong electron donating effect of the TBDMS groups.



250 quant.

249a R^1 = H
249b R^1 = Me

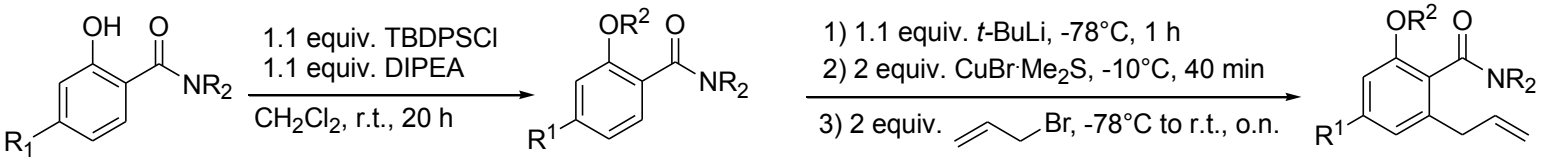
251a R^1 = H 72 %
251b R^1 = Me 71%



250 R = Et, R^1 = H
251a R = Me, R^1 = H
251b R = R^1 = Me

252a R = Et, R^1 = H, R^2 = TBDMS 95%
252b R = Et, R^1 = H, R^2 = TIPS 93%
252c R = Me, R^1 = H, R^2 = TBDMS 89%
252d R = Me, R^1 = H, R^2 = TIPS 84%
252e R = Me, R^1 = Me, R^2 = TBDMS 36%

253a R = Et, R^1 = H, R^2 = TBDMS 88%
253b R = Et, R^1 = H, R^2 = TIPS 91%
253c R = Me, R^1 = H, R^2 = TBDMS 65%
253d R = Me, R^1 = H, R^2 = TIPS 98%
253e R = Me, R^1 = Me, R^2 = TIPS CRM

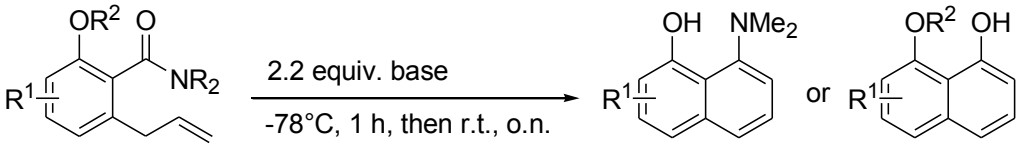


250 R = Et, R^1 = H
254 R = Me, R^1 = OMe

255a R = Et, R^1 = H, R^2 = TBDPS 95%
255b R = Me, R^1 = OMe, R^2 = TBDPS 64%

256a R = Et, R^1 = H, R^2 = TBDPS trace
256b R = Me R^1 = OMe, R^2 = TBDPS 29%

Next, the allylated compounds **253** and **256b** were reacted with MeLi or LDA. Only the compound bearing a TBDMS protective group and a *N*,*N*-dimethylamide gave the desired aminonaphthol **257** in 47 and 57% yield, respectively. All other combinations gave complex mixtures and neither the aminonaphthol **257** nor the corresponding hydroxynaphthol **258** were observed (Table 7).



253, **256b** **257** R^1 = H **258**
246 R^1 = 3-OMe

Table 7. Reaction of 2-allylbenzamides **253** and **256a** with MeLi or LDA.

Base	R^1	H		H		OMe
	R^2	TBDMS		TIPS		TBDPS
	R	Me	Et	Me	Et	Me
MeLi		**257** 47%	Complex reaction mixture	Complex reaction mixture	Complex reaction mixture	Complex reaction mixture
LDA		**257** 57%	Complex reaction mixture	Complex reaction mixture	Complex reaction mixture	Complex reaction mixture

It was hypothesised that no reaction was observed due to the extra sterical hindrance induced by the TIPS, TBDPS or diethylamidogroup. Therefore, *N*-(2-hydroxybenzoyl)pyrrolidine **259a** and *N*-(2-hydroxybenzoyl)morpholine **259b** were synthesised as the 'tied back' alkyl chains would result in less sterical hindrance. As LDA was found to give the best yield in the above trail, allylated benzamides **261** were reacted with 2.2 equiv. of LDA, unfortunately none of them yielded the desired aminonaptholes. No results were obtained either with only 1 equivalent of LDA or with the much weaker base LiO*t*-Bu.

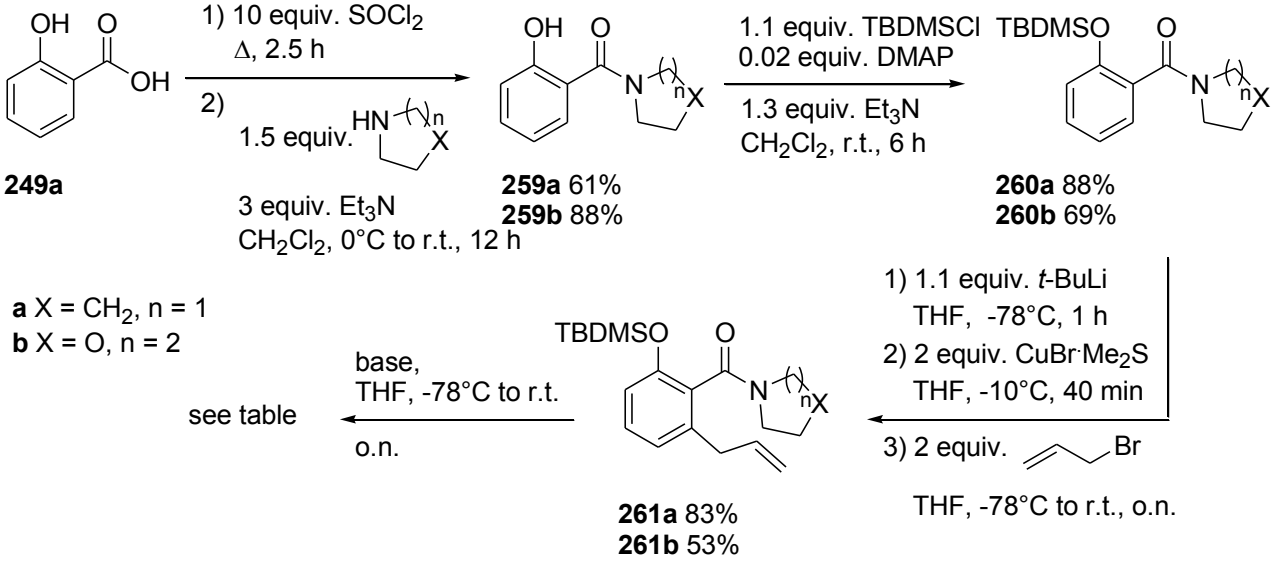
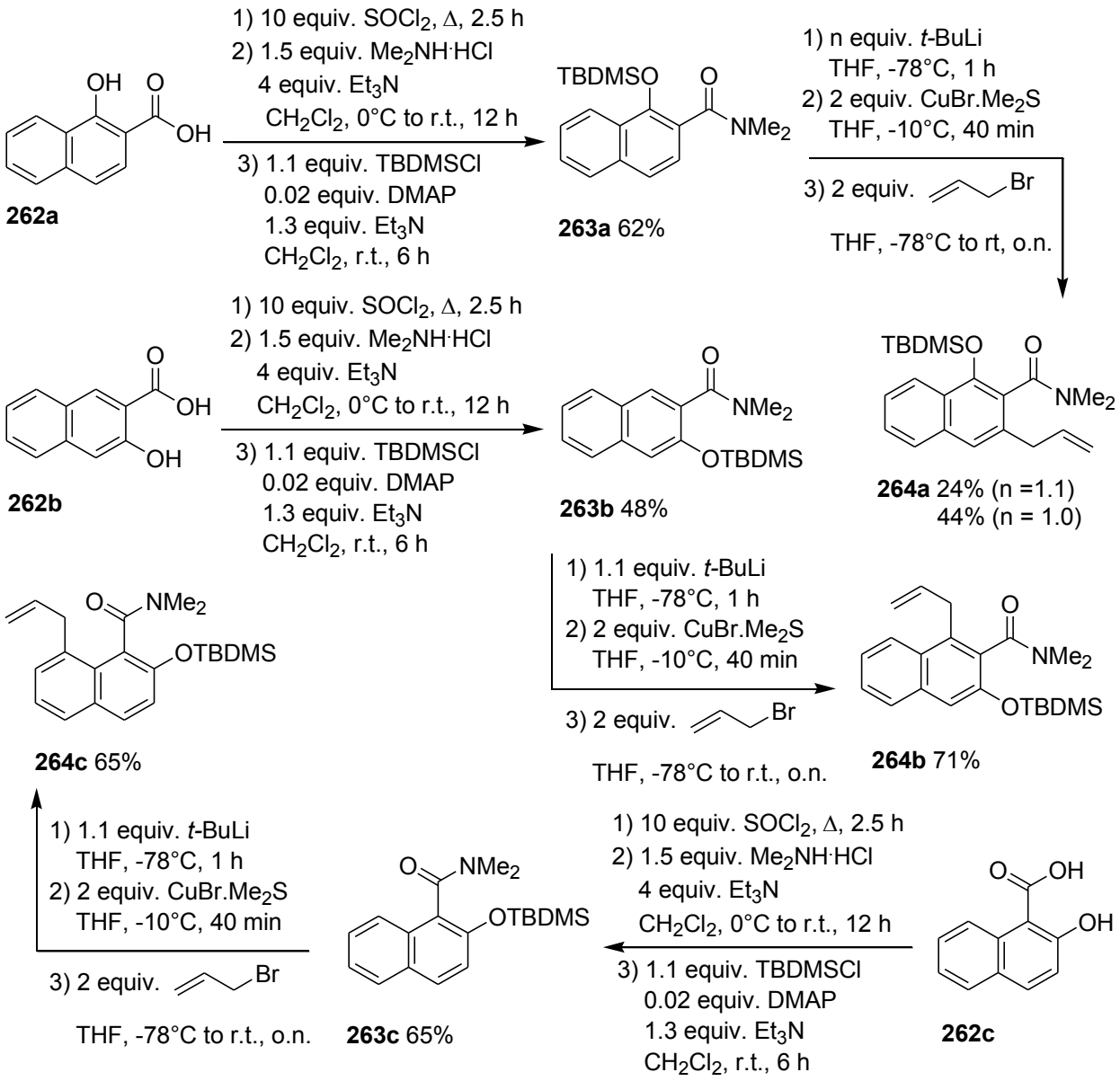


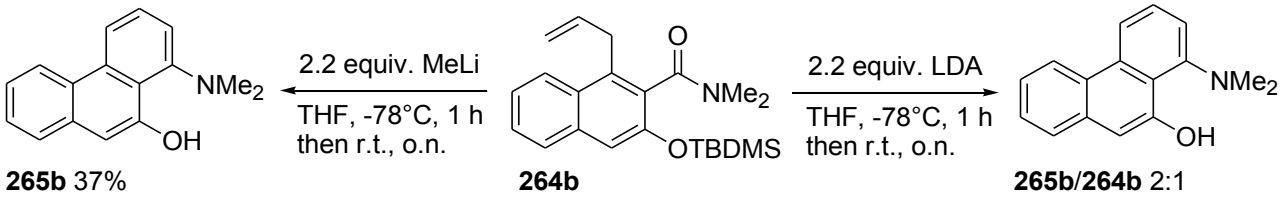
Table 8. Reaction of 2-allylbenzamides **261** with LDA or LiO*t*-Bu.

X	n	Base	Result	X	n	Base	Result
CH_2	1	2.2 equiv. LDA	Complex reaction mixture	CH_2	1	1.0 equiv. LDA	Complex reaction mixture
O	2	2.2 equiv. LDA	Complex reaction mixture	CH_2	1	2.2 equiv. LiO*t*-Bu	No reaction

Having established that the cyclisation reaction only occurred when the protective group is a TBDMS group and the amide a *N*,*N*-dimethylamide, the reactivity of allyl-*tert*-butyldimethylsilanyloxy-*N*,*N*-dimethylnaphthalenecarboxamides **264** was investigated. Starting from the three possible *ortho*-hydroxynaphthoic acids **262**, allyl-*tert*-butyldimethylsilanyloxy-*N*,*N*-dimethylnaphthalene-carboxamides **264** were synthesised as described above. In case of 3-allyl-1-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-2-carboxamide **264a**, a low isolated yield was obtained as various side products were formed, reducing the amount of *t*-BuLi to 1.1 equiv. gave an isolated yield of 44%.

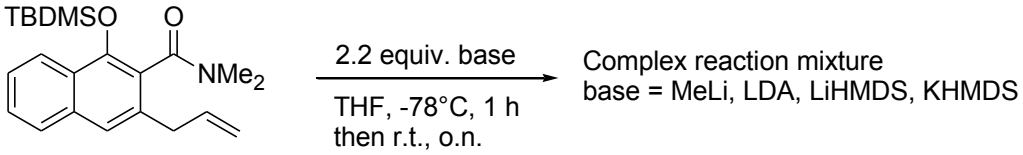


When 1-allyl-3-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-2-carboxamide **264b** was reacted with LDA, a 2:1 mixture of naphthol **265b** and starting material **264b** was obtained. When the reaction was repeated with MeLi, 8-dimethylaminophenanthren-9-ol **265b** was isolated in low yield.

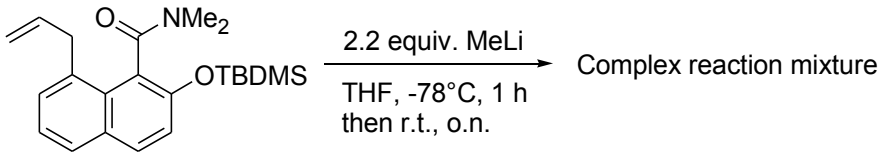


In case of *N*,*N*-dimethyl-8-allyl-2-(*tert*-butyldimethylsilanyloxy)-naphthalene-1-carboxamide **264c**, a complex reaction mixture was obtained, as could be expected since ring closure would form a non-aromatic seven-membered ring. Contrary to what was expected, a complex mixture was retrieved as

well in case of *N*,*N*-dimethyl-3-allyl-1-(*tert*-butyldimethylsilanyloxy)-naphthalene-2-carboxamide **264a**. Other bases such as LDA, LiHMDS of KHMDS also gave complex mixtures.

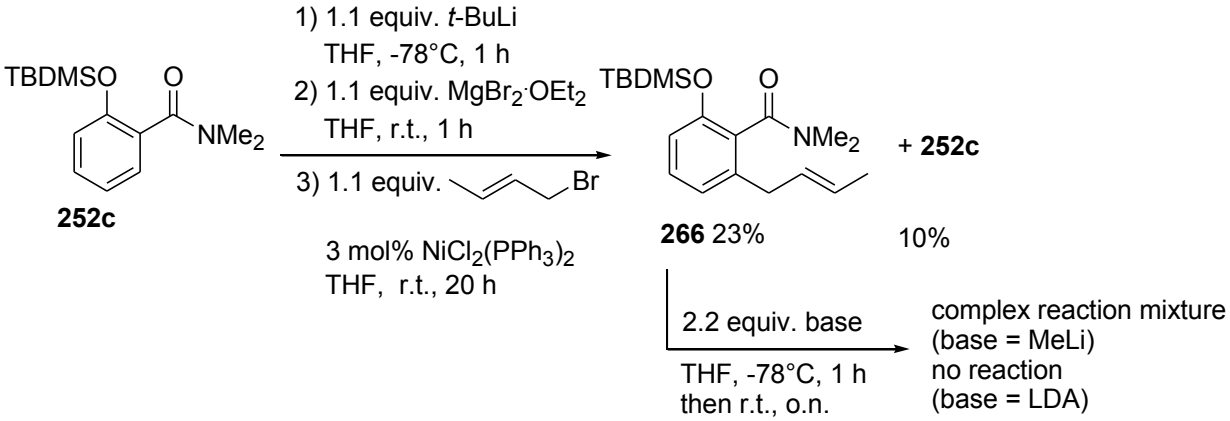


264a



264c

Next, a butenyl side chain was introduced by means of a Kumada coupling.[166] Thus was the arylmagnesium species resulting from ortholithiation and transmetalation of *N*,*N*-dimethylbenzamide **252c** reacted with crotyl bromide and bis(triphenylphosphine)nickel(II) dichloride as a catalyst. Even though a low yield of crotylated amide **266** was obtained as the reaction was only performed once and no optimisation was attempted. When amide **266** was reacted with a lithiated base, either no reaction (LDA) or a complex mixture (MeLi) was obtained. Apparently the additional sterical hindrance introduced by the methyl group impedes allyl anion from attacking the amide.

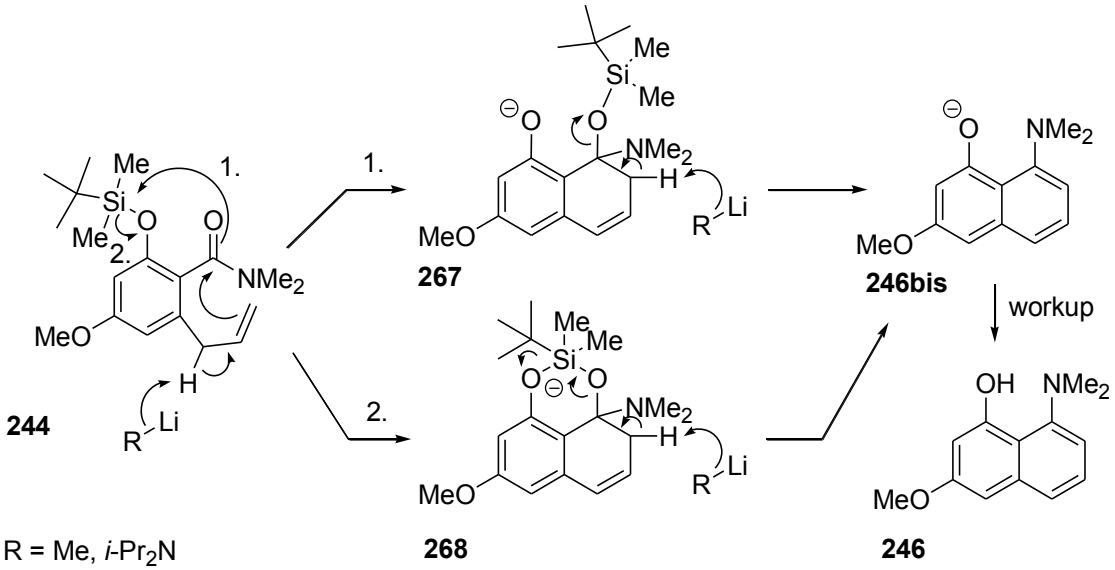


252c

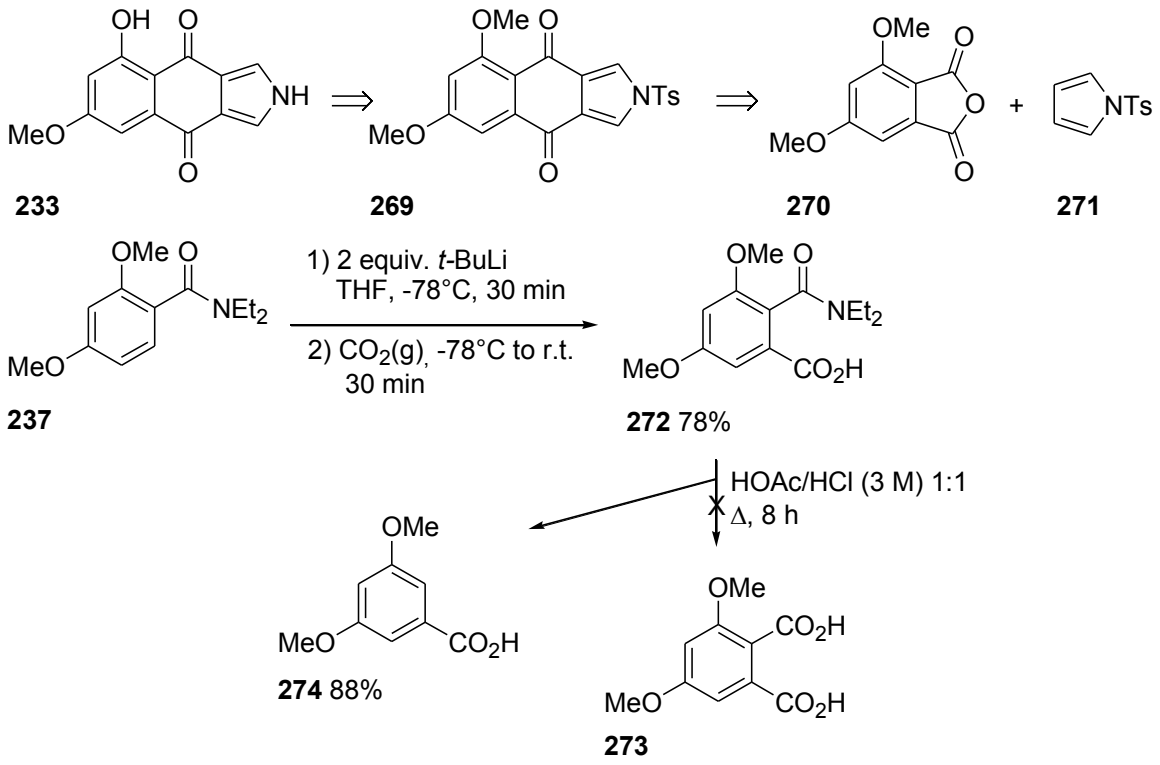
As it was observed that the aminonaphtholes turned purple when exposed to air, it was attempted to oxidise 8-dimethylaminonaphthalen-1-ol **257** with PIFA. However, this reaction led to immediate decomposition of the starting aminonaphthol **257**.

Based on the abovementioned observations, a mechanism was proposed. As an alkyllithium reagent or LDA is not capable to deprotect a TBDMS-group, this should happen via an intramolecular reaction. Initial deprotonation of the allyl side chain gives a mesomeric stabilised anion that can attack the TBDMS group which is then transferred to the amide oxygen either via a S_N2-type reaction either via

a hypervalent silicium intermediate **268** as a pentavalent silicon centre is permitted due to hybridisation with the vacant d-orbitals of silicon. Subsequent deprotonation followed by elimination of the *tert*-butyldimethylsilyloxy group leads to aminonaphthol **246**. This mechanism explains why two equivalents of base are needed and why more sterical hindered groups do not give any reaction. Related *tert*-butyldimethylsilyl transfer reactions are known in the literature in which a carbon nucleophile reacts with an *ortho*-silanoxybenzaldehyde or an *ortho*-silanoxyacetophenone followed by trapping of the resulting oxyanion by the neighbouring silyl group.[167] *O*,*O*-TBDMS and TBDPS migrations have been observed in polyols.[168]



In an alternative trial, it was attempted to form azamonosporascone **233** from anhydride **270**[169] and *N*-tosylpyrrole **271** based on the literature precedent that 1-(benzenesulfonyl)pyrrole reacts smoothly with 2,5-dimethoxybenzoyl chloride to give a good yield of the corresponding 3-benzoylpyrrole.[170] To do so, *N*,*N*-diethylbenzamide **237** was *ortho*-lithiated followed by quenching with dry carbon dioxide gas to form *N*,*N*-diethyl-3,5-dimethoxyphthalamic acid **272**.[171] However, when it was attempted to hydrolyse this compound towards the desired dicarboxylic acid **273**, decarboxylation occurred and 3,5-dimethoxybenzoic acid **274** was obtained.

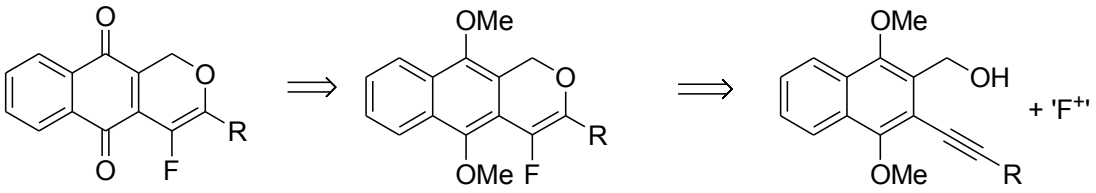


3.3.1 Conclusion and discussion

During an attempted synthesis of the natural product azamonosporascone **233**, an unexpected aminonaphthol synthesis was discovered upon reaction of 2-allyl-6-(*tert*-butyldimethylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide **243** with methyllithium. The scope and limitations of this reaction were investigated in debt and it was found that reaction only occurred when the amide was and *N*,*N*-dimethylbenzamide and the silanoxy group was a *tert*-butyldimethylsilanyloxy group. The base should be methyllithium or LDA. Moreover, the reaction seems to work better for benzamides than for naphthamides. As an extension of this work, it might be interesting to investigate the reactivity of *N*-monoalkylated 2-allyl-6-silanoxybenzamides under the presented conditions.

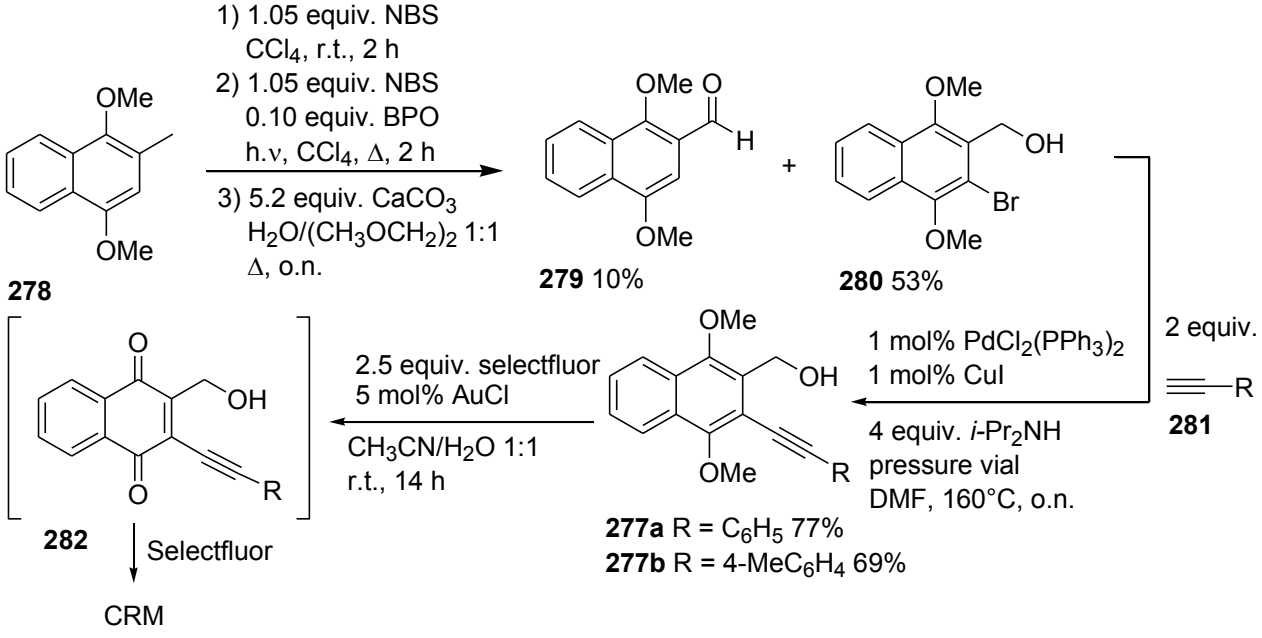
3.4 Attempted synthesis of C-4 fluorinated pyranonaphthoquinones 275

Very few compounds or strategies exist towards heterocyclic quinones bearing a fluorine atom in the heterocyclic moiety. During previous research at our department, fluorinated pentalongin analogues **275** were prepared by means of a late stage fluorination of the pyran moiety followed by acid catalysed double bound regeneration in low yield.[172] An alternative strategy was envisaged in which both the pyran ring and the fluorine substituent are constructed in one step starting from alkyne **277** and an electrophilic fluorine source by means of a gold catalysed 6-endo-dig cyclisation.[173,174]

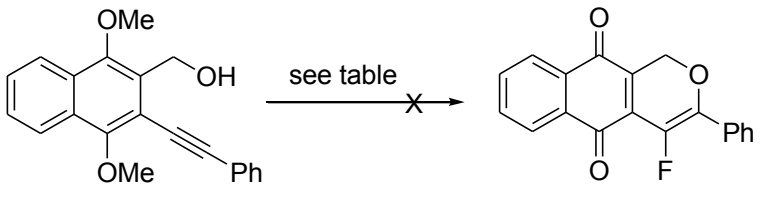


275 **276** **277**

Thus, 3-bromo-1,4-dimethoxy-2-hydroxymethylnaphthalene **280** was prepared by means of ionic and radical bromination[175] of naphthalene **278** followed by hydrolysis of the benzylic bromide[176] and isolated in 53% yield together with 10% of aldehyde **279** resulting from overbromination. 3-Bromo-1,4-dimethoxy-2-hydroxymethylnaphthalene **280** was then coupled with an arylacetylene **281** to form 1,4-dimethoxy-2-hydroxymethyl-3-arylethynylnaphthalenes **277**. When these alkynes **277** were brought into reaction with selectfluor and AuCl, a complex reaction mixture was retrieved. From spectral analysis it was observed that selectfluor, which is besides a source of electrophilic fluorine also a strong oxidant, oxidised dimethoxynaphthalenes **277** towards the corresponding quinones **282** and further decomposed it.



Further attempts to perform the proposed cyclisation such as shortening of the reaction time, augmenting the catalyst loading, addition of a base, use of another fluorinating agent, all gave either no reaction or stranded on the abovementioned problem (Table 9).



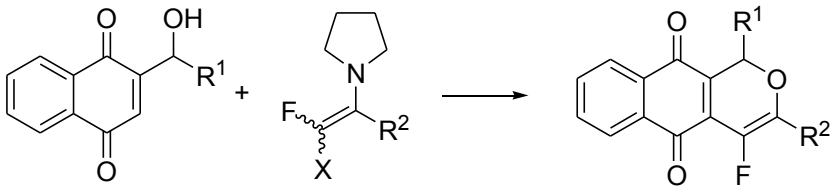
277a **275a**

Table 9. Attempts towards the cyclisation-fluorination of alkyne **277a**.

Fluorinating agent	Additive	Catalyst	Solvent	T	t	Result
5 equiv. selectfluor	-	10 mol% AuCl	CH_3CN/H_2O 1:1	r.t.	2 h	Complex reaction mixture
2.5 equiv. selectfluor	5 equiv. Na_2CO_3	5 mol% AuCl	CH_3CN/H_2O 1:1	r.t.	4 d	No reaction
2.5 equiv. NFSI	-	5 mol% AuCl	CH_3CN	r.t. to 50°C	1 d	No reaction
2.5 equiv. NFSI	-	5 mol% AuCl	CH_3CN	Δ	o.n.	Complex reaction mixture

3.4.1 Conclusion and discussion

It was attempted to synthesise C-4 fluorinated pyranonaphthoquinones **275** as these compounds are of interest from both a synthetic as a biological point of view. Unfortunately, the proposed strategy did not work as the electrophilic fluorine source preferentially reacts with the hydroquinone moiety rather than effectuate the desired gold catalysed 6-endo-dig cyclisation. An alternative entry into this interesting scaffold could be the addition of a fluorinated enamine **284** onto 2-hydroxymethyl-1,4-naphthoquinone **283**.



283 **284** X = H, halogen **275**

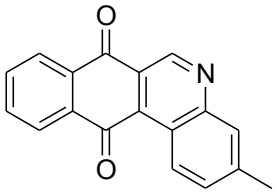
3.5 Synthesis of benzo[*j*]phenanthridinediones, tetrahydrobenzo[*j*]-phenanthridinediones, octahydrobenzo[*j*]phenanthridinediones and dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetra-ones as new leads against *Mycobacterium tuberculosis*

3.5.1 Introduction

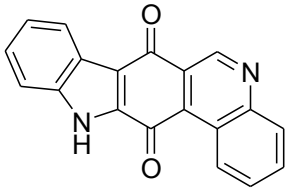
At our research department, substantial research has been devoted towards the synthesis of new 2-aza-anthraquinones having antimycobacterial activity.[16,17] In collaboration with the Scientific Institute of Public Health (Uccle, Brussels), where a PhD student, Davie Cappoen, performs his doctoral research on the testing of the antimycobacterial activity, cytotoxicity, genotoxicity etc., various sets of compounds were prepared and tested and based on the results, new sets of compounds were developed. Apart from *Mycobacterium tuberculosis*, other clinically relevant mycobacteria were

tested. *M. bovis*, closely related to *Mycobacterium tuberculosis*, causes tuberculosis in ruminants but can also infect humans.[177] *M. avium* subsp. *avium* is a bird pathogen birds but can cause opportunistic infections in AIDS patients. *M. avium* subsp. *paratuberculosis* causes Johne's disease or paratuberculosis in ruminants which may be linked to Crohn's disease in humans.[178] *M. ulcerans* ultimately causes Buruli ulcer, a necrotizing skin disease.[179] No biotesting results will be discussed as this is part of a separate PhD. During this research, various interesting leads were identified that deserve further research.

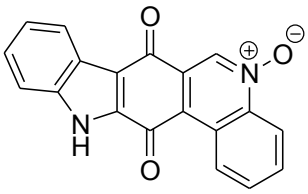
During previous research, various benzo[*j*]phenantridine-7-12-diones **18** were tested against *Mycobacterium tuberculosis*.[18] It was found that 3-methylbenzo[*j*]phenanthridine-7,12-dione **18a** showed promising antimycobacterial activity even though this activity was accompanied by a relatively high cytotoxicity. Also benzophenanthridines, although mostly benzo[*c*]phenanthridines, occur in nature and some of them show potent antibacterial activities.[180] Calotrixin A **285a** and B **285b**, isolated from two cyanobacteria,[181] are structurally very similar to the proposed structures and have been shown to possess antimalarial and anticancer activities. Various total syntheses of both compounds have been reported.[182]



18a MIC_{50} = 0.21 μM
IC_{50} = 3.21 μM

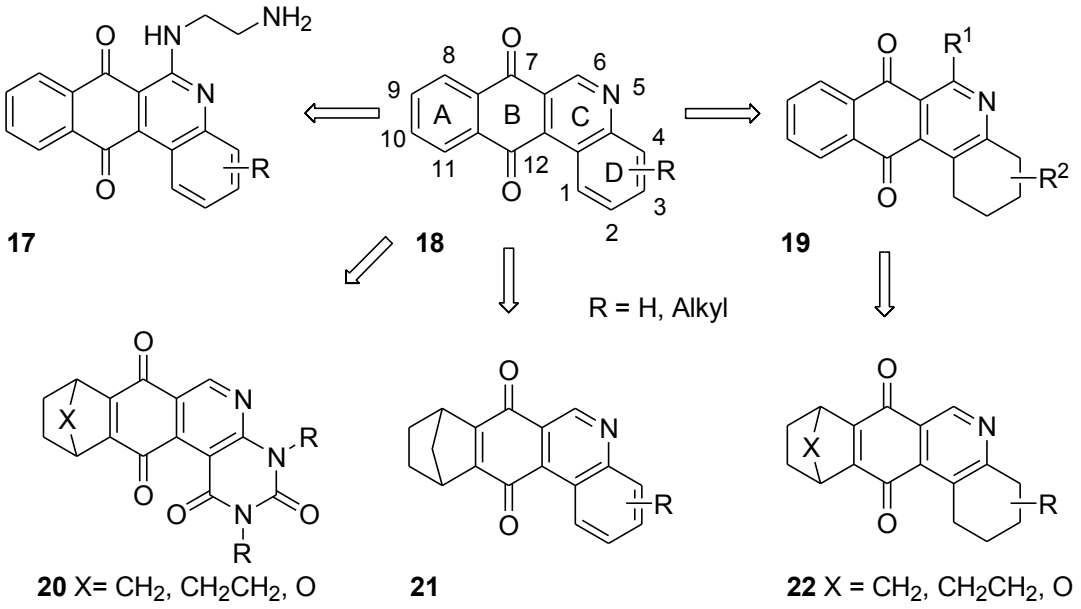


285a Calotrixin A



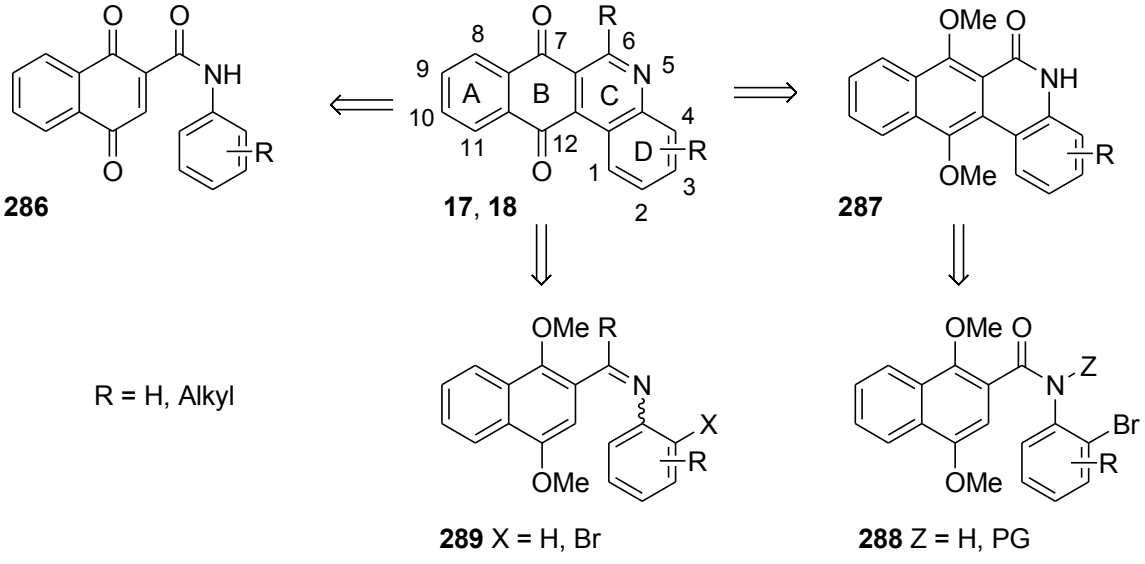
285b Calotrixin B

Therefore, the synthesis of variations of the benzo[*j*]phenanthridinedione scaffold **18** were envisaged. It was attempted to introduce an aminoalkylamino side chain on the benzo[*j*]phenanthridinedione scaffold as in the anticancer drugs mitoxantrone **73b** and pixantrone **80** and derivatives thereof (see section 2.2). In order to synthesise more 'out of plane' derivatives to counter potential intercalation, the synthesis derivatives in which one or two of the ring are turned aliphatic was envisaged. This would result in the synthesis of 1,2,3,4-tetrahydrobenzo[*j*]phenanthridinediones **19** with an aliphatic D-ring, 8,9,10,11-tetrahydrobenzo[*j*]phenanthridinediones **21** with an aliphatic A-ring and octahydrobenzo[*j*]phenanthridinediones **22** with both an aliphatic A and D-ring. As a further expansion of the tetrahydrobenzo[*j*]phenanthridinedione skeleton, the synthesis of dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **20** was envisaged.

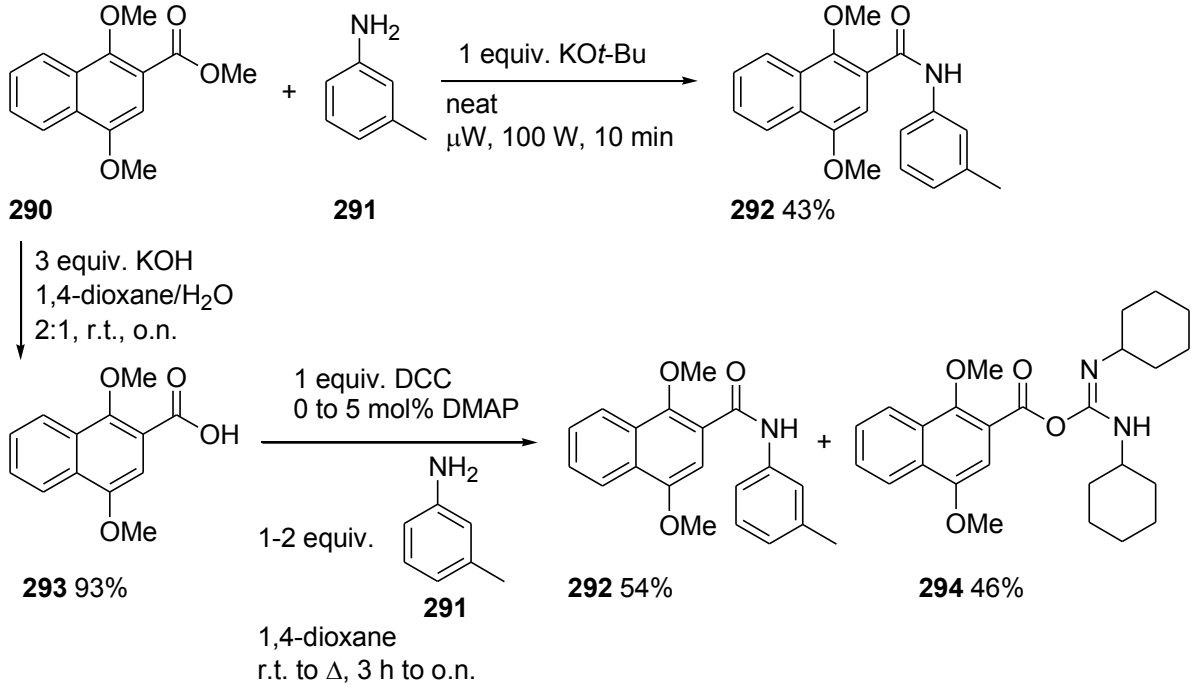


3.5.2 New entries towards the benzo[*j*]phenanthridinedione scaffold

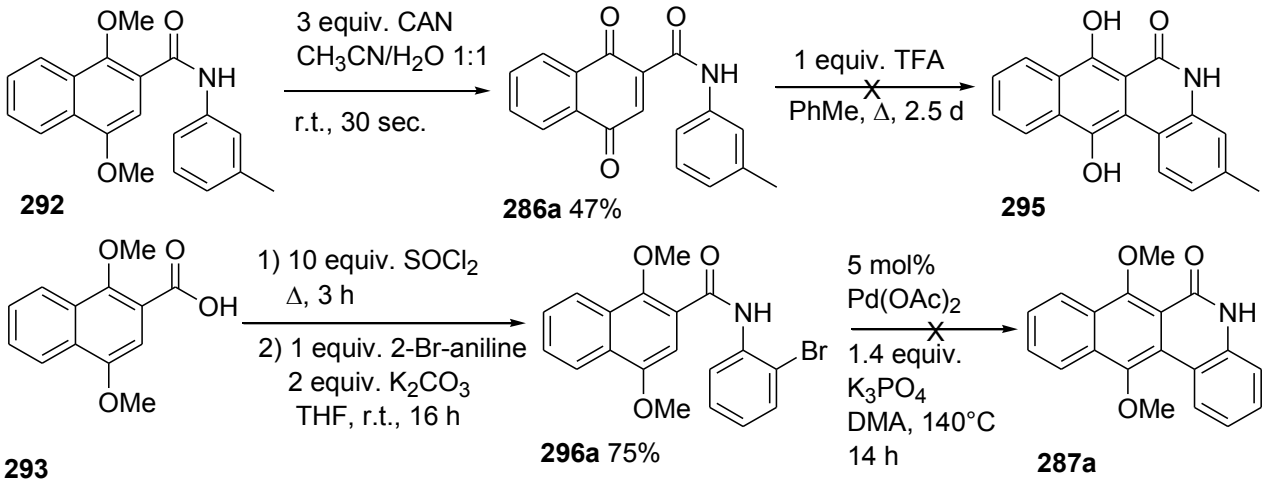
Benzo[*j*]phenanthridinediones **18** have been synthesised at our research department using a palladium(II) acetate mediated intramolecular Heck reaction.[18] However, a relatively complex starting material is required, a large amount of palladium(II) acetate is needed to effectuate the cyclisation step and the overall yield is moderate. Therefore, alternative, shorter or more versatile pathways to this promising leads were investigated. From a synthetic strategic point of view, it was preferred to introduce the C-ring as a lactam, thus allowing further functionalisation of C-6. The direct or acid-catalysed ring closure of naphthoquinone amides **286** and the organometal-catalysed ring closure of halogenated amides **288** were investigated. Also a direct or an organometal-catalysed ring closure of an appropriate imine **289** was considered.



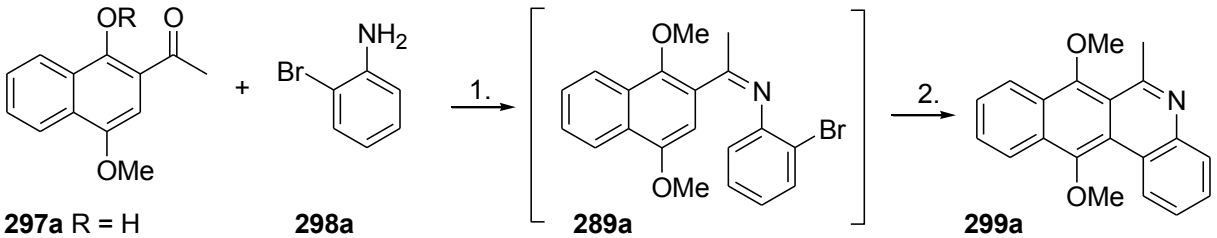
Initially, it was investigated whether quinone amides **286** could be directly converted into the corresponding lactams as can be done with the corresponding esters.[183] Direct formation of an amide starting from 1,4-dihydroxynaphthoic acid did not result in any favourable results due to autoxidation and 1,4-addition of 3-methylaniline **291**. It was then attempted to convert methyl-1,4-dimethoxynaphthalene-2-carboxylate **290**[16] into the corresponding amide **292** using microwave irradiation in the presence of KO*t*-Bu.[184] Despite testing several conditions, the maximum isolated yield was 43%. Next, methyl-1,4-dimethoxy-naphthalene-2-carboxylate **290** was saponified towards the corresponding carboxylic acid **293** and reacted with DCC and 3-methylaniline **291**. However, in all cases, approximately 1:1 mixtures of the desired amide **292** and DCC adduct **294** were obtained.



Subsequently, *N*-*meta*-tolyl-1,4-dimethoxynaphthalene-2-carboxamide **292** was oxidatively demethylated towards 2-*meta*-tolylaminocarbonyl-1,4-naphthoquinone **286a** in 47% yield. However this quinone did not cyclise in the presence of TFA even after 2.5 days of boiling under reflux in toluene. Also, the palladium-catalysed intramolecular arylation of *N*-(2-bromophenyl)amide **296a** did not work out and resulted in a mixture of unidentified high-molecular weight compounds.



Direct imination followed by an intramolecular Heck reaction would be a very elegant way of constructing the benzo[*j*]phenanthridine skeleton. Thus, it was attempted to form the imine derived from 2-acetyl-1-hydroxy-4-methoxynaphthalene **297a** with 2-bromoaniline **298a**. However, no imination was observed using Deans Stark conditions, $Ti(OEt)_4$ or molecular sieves. As it was suspected that the *peri*-hydroxyl function interfered in the imination process, it was methylated and the product was reacted again with 2-bromoaniline **298a** and molecular sieves. Even though some imine **289a** was formed, no further conversion was observed after heating for 15 h and isolation was not attempted. When palladium(II) acetate was added to this mixture, the formation of benzophenanthridine **299a** was observed but only in trace amounts (Table 10). No further attempts were performed as the palladium catalysed ring closure of amides followed by functionalisation seemed to be a more viable route. Direct oxidative coupling of an aniline with 2-acetyl-1,4-dihydroxynaphthalene has been described in the literature to synthesise these compounds but this resulted in a mixture of various addition products amongst which the desired benzo[*j*]phenanthridine-7,12-diones **18**.[185]

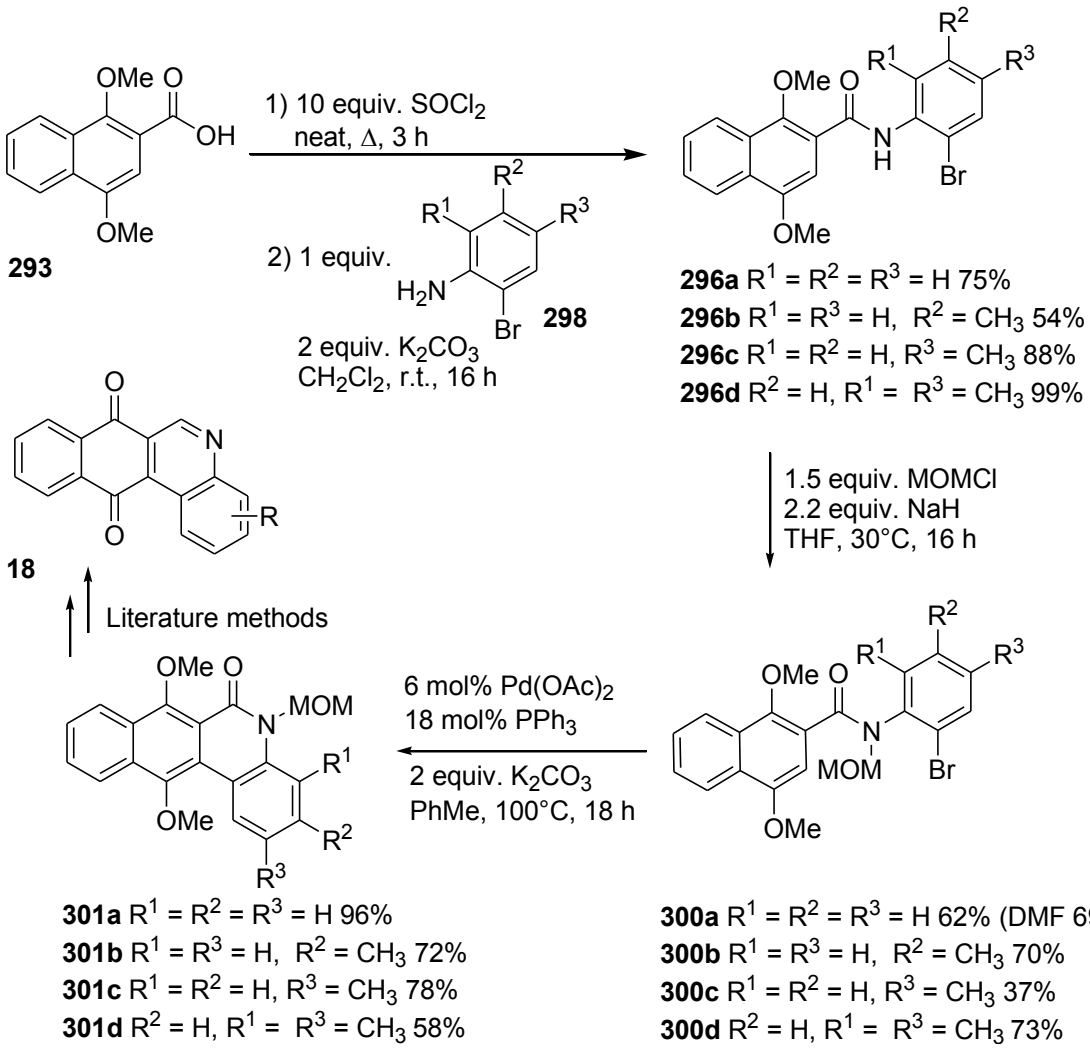


297a R = H **298a** **289a** **299a**
297b R = Me

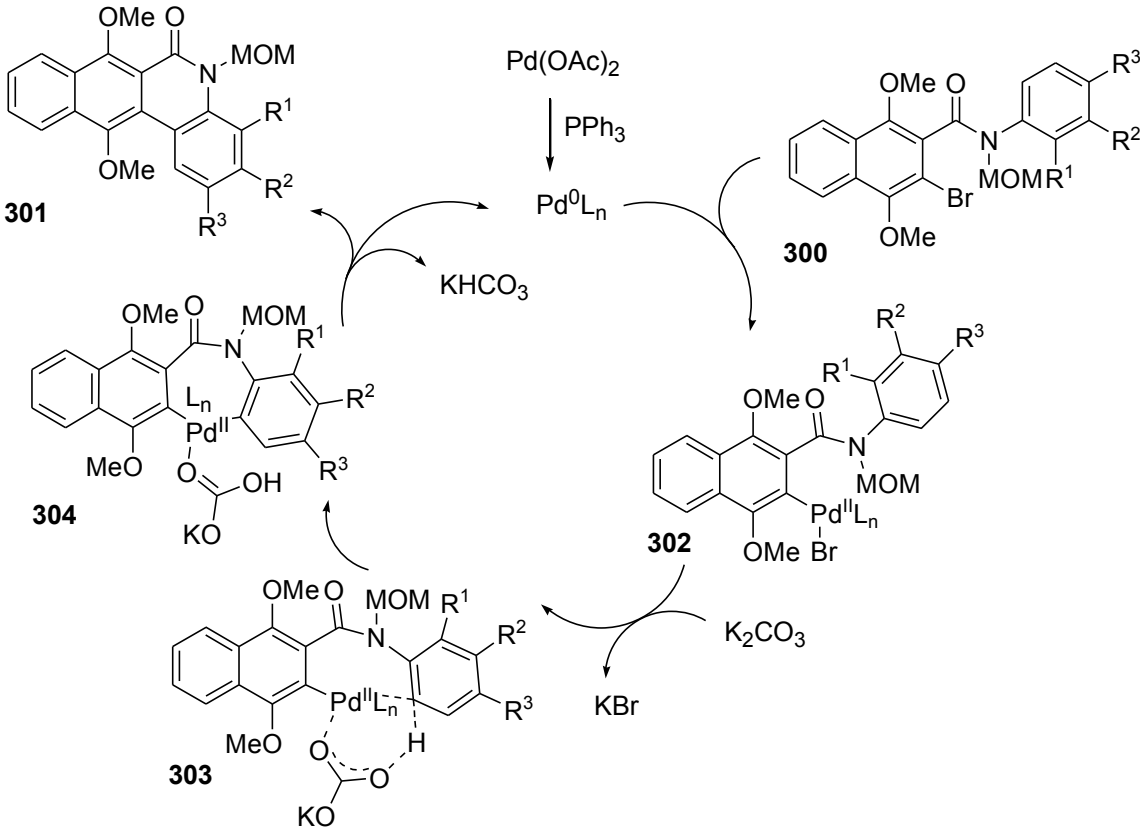
Table 10. Attempted synthesis of benzophenanthridine **299a** via imination followed by a Heck reaction.

Entry	R	Step 1	Result	Step 2	Result
1	H	1 mol% *p*-TsOH·H_2O PhMe, Δ, 24 h	No reaction	-	-
2	H	3 equiv. $Ti(OEt)_4$ CH_2Cl_2, r.t., 2 d	No reaction	-	-
3	H	4 Å MS, PhMe, Δ, 15 h	Complex reaction mixture	-	-
4	H	4 Å MS, 5 equiv. $NaHCO_3$, PhMe, Δ, 15 h	Complex reaction mixture	-	-
5	Me	4 Å MS, PhMe, 70°C, 15 h	**289a** + **297b**	10 mol% $Pd(OAc)_2$ 30 mol% PPh_3 2 equiv. K_2CO_3 PhMe, Δ, 100°C, 18 h	**299a** (trace) +**297b**

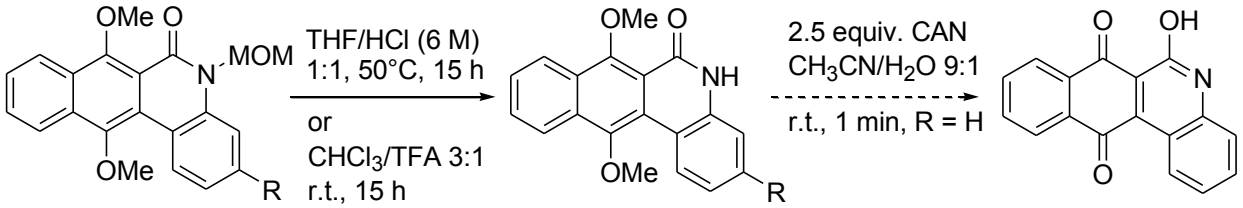
A literature search revealed that in order to perform palladium-catalysed intramolecular arylation on *N*-arylbenzamides, they have to be tertiary.[186] Thus, *N*-2-bromophenyl-1,4-dimethoxynaphthalene-2-carboxamides **296** were prepared by means of reaction of the acid chloride of 1,4-dimethoxynaphthalene-2-carboxylic acid **293** and the appropriate bromoaniline **298** in the presence of 2 equiv. of K_2CO_3. The corresponding MOM protected amides **300** were prepared in moderate to good yields by reaction with MOMCl and NaH in anhydrous THF and occurred as a mixture of two rotamers. A slight increase in yield was observed when the reaction was performed in DMF. Alternative MOM-protection procedures such as the use of MOMBr or the reaction of dimethoxymethane in the presence of P_2O_5 did not give better yields.[186b] *N*-MOM protected amides **300** then underwent a palladium-catalysed intramolecular arylation in good to excellent yields towards lactams **301**. These lactams could be converted into the previously prepared benzo[*j*]phenanthridinediones **18** using literature methods.[182,187]



The mechanism of the intramolecular Heck reaction is clarified in the scheme below. Contrary to a normal Heck reaction, palladacycle formation does not occur via an S_EAr mechanism but via a proton abstraction mechanism.[188] Thus, initial oxidative addition leads to organopalladium intermediate **302**, which then undergoes ligand exchange towards **303** as bromine is to weakly basic to effectuate the deprotonation step.[189] Next, Pd participates in an agnostic interaction with the C-H bound, followed by deprotonation via the carbonate ligand and formation of the palladacycle **304**. Reductive elimination leads to the desired benzo[*j*]phenanthridinediones **301** and restores the Pd catalyst for a next cycle.



7,12-Dimethoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **301** were deprotected with concentrated HCl towards lactams **287**. Alternatively, this deprotection step could be performed with TFA[190] in a similar yield but an easier purification. Lactam **287a** was oxidised with CAN towards 6-hydroxybenzo[*j*]phenanthridinedione **305**. However, a highly insoluble compound was formed which could not be characterised by NMR or LC-MS. As this would not make a good biotesting candidate, no further attempts were made to synthesise analogues of this compound.

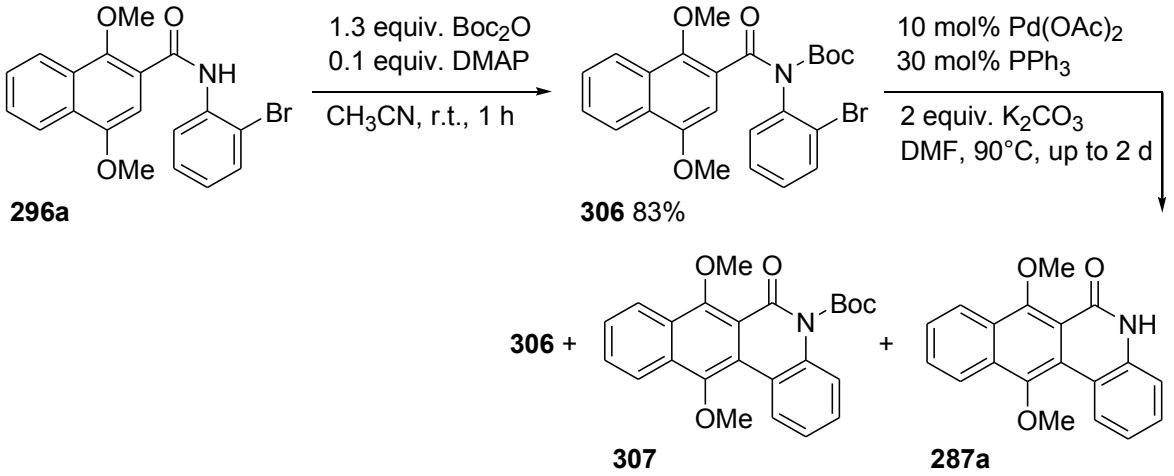


301a R = H
301b R = Me

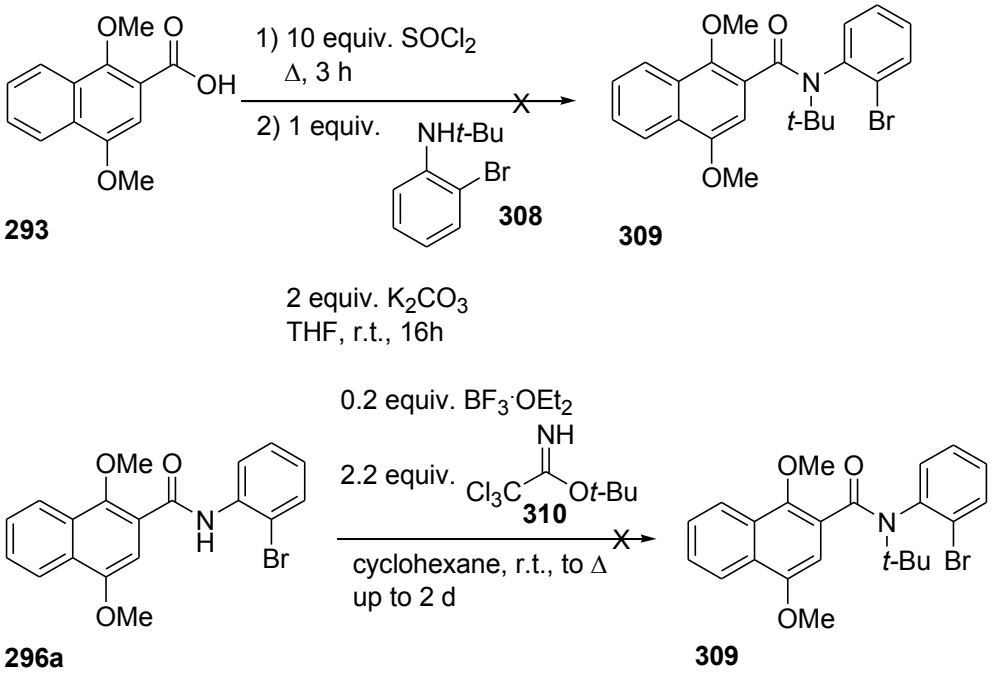
287a R = H 84% (HCl)
287b R = Me 67% (HCl)

305

Other *N*-protective groups were evaluated but none of them gave results that were as good as the MOM group. While *N*-(2-bromophenyl)-1,4-dimethoxynaphthalene-2-carboxamide **296a** smoothly reacted with Boc anhydride, the corresponding Heck reaction with intermediate **306** was a failure and even after two days of reflux, no full conversion was obtained.

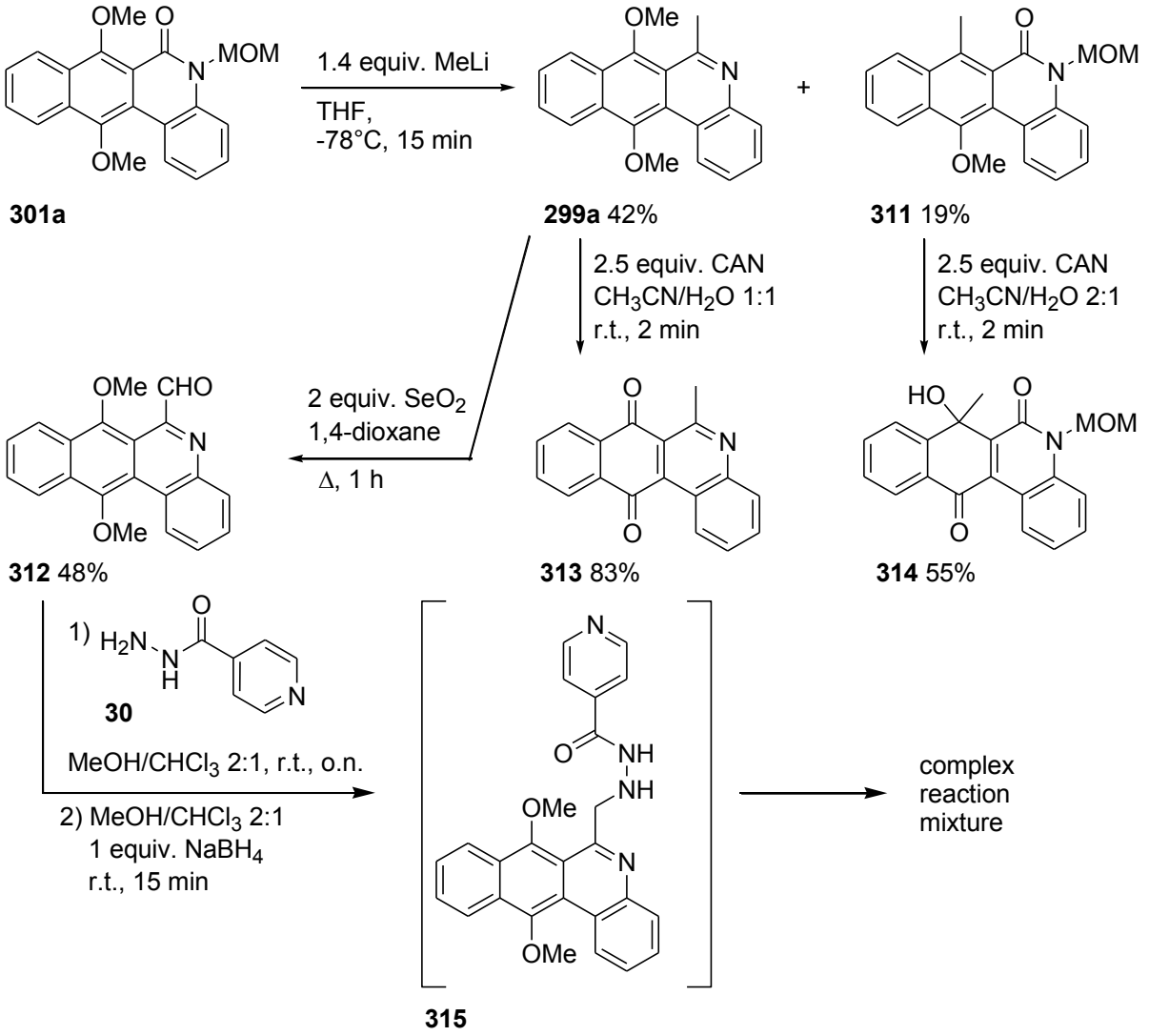


Attempts to prepare a *N-tert*-butyl protected amide **309** either by reaction of *N-tert*-butylaniline **308**[191] with carboxylic acid **293** or by direct reaction of amide **296a** with *tert*-butyl 2,2,2-trichloroacetimidate **310** were unsuccessful, probably due to sterical hindrance.

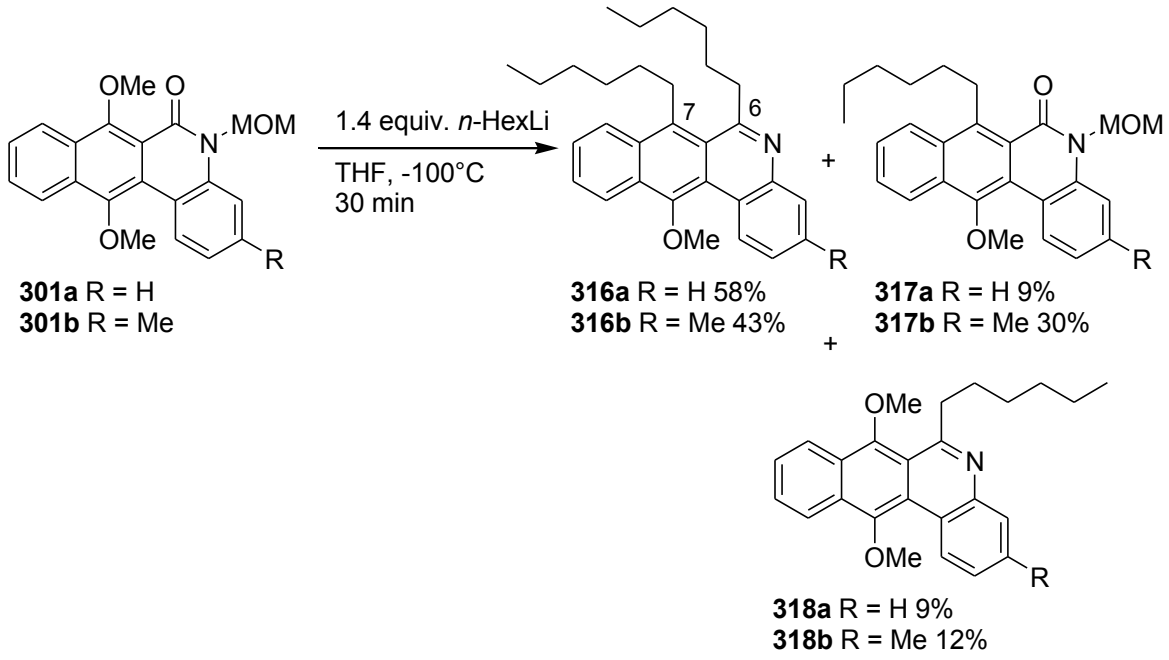


Next, the synthesis of 6-alkyl substituted benzo[*j*]phenanthridine derivatives was envisaged. Thus, MeLi was added[192] to MOM-protected benzo[*j*]phenanthridine **301a**. Apart from the expected 6-methylbenzo[*j*]phenanthridine **299a**, a 1,4-adduct **311** was isolated. This is rather remarkable as organolithium reagents are very hard reagents and tend to react in a 1,2-fashion and examples of this reactivity in the literature are rather rare.[193] Oxidation of the obtained reaction products with CAN yielded the desired 6-methylbenzo[*j*]phenanthridine-7,12-dione **313** and 7-hydroxy-5-methoxymethyl-7-methyl-5,7-dihydrobenzo[*j*]phenanthridine-6,12-dione **314**. As a check whether the quinone function is really primordial for biological activity, both compounds were tested against *Mycobacterium tuberculosis*. While quinone **313** showed an activity comparable to the previously

tested benzo[*j*]phenanthridinediones **18**, no activity was observed for compound **314**. As the methyl function could serve as an attachment point for the synthesis of bifunctional molecules, it was oxidised with SeO_2 in 1,4-dioxane towards the corresponding aldehyde **312**. This aldehyde **312** was then reductively aminated with the first-line anti-TBC drug isoniazid **30**. Even though the imine was formed and appeared to be stable in solution, the corresponding amine **315** readily decomposed and could not be isolated.



When the intriguing organolithium addition was repeated with *n*-hexyllithium, a third reaction product **316**, which was formed by double addition, was the major product. Even though the reaction temperature was further lowered to -100°C, no increase of 1,2-addition was observed. This confirms that the reaction is under sterical control and that initial attack preferentially occurs at C-7. The desired C-6 alkylated compounds **318** were only minor products and the amounts were too small to be further oxidised towards the targeted quinones.



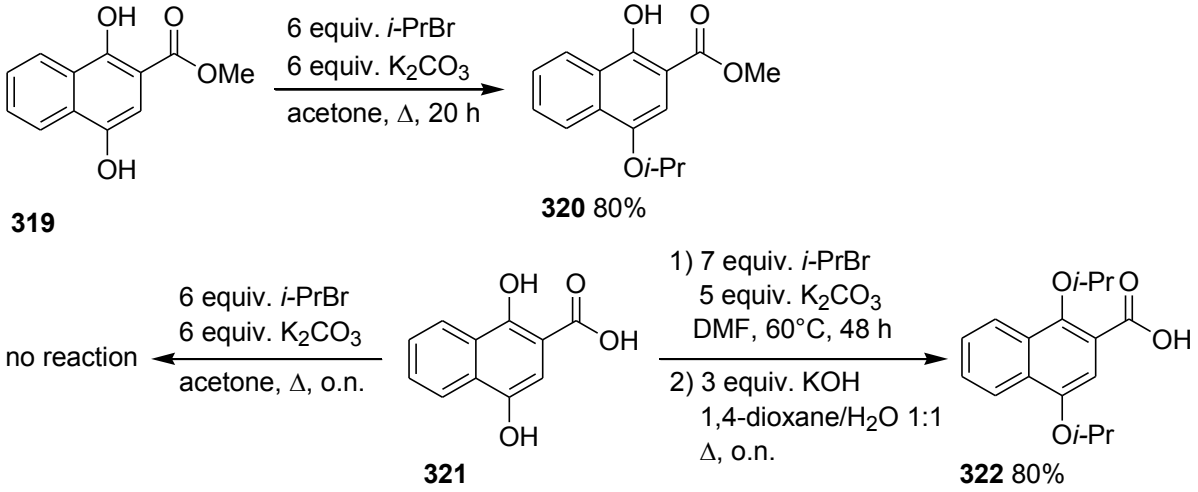
301a R = H
301b R = Me

316a R = H 58%
316b R = Me 43%

317a R = H 9%
317b R = Me 30%

318a R = H 9%
318b R = Me 12%

In order to tackle this problem, the methyl group was replaced by an *iso*-propyl group to augment sterical hindrance at this position. Therefore, the synthesis of di-*iso*-propoxynaphthalene carboxylic acid **322** was envisaged. However, due to the additional sterical hindrance either no reaction occurred or only one hydroxy group was alkylated resulting in the formation of methyl 1-hydroxy-4-isopropoxynaphthalene-2-carboxylate **320**. It was then found that by using a large excess of *iso*-propyl bromide in DMF followed by saponification the desired carboxylic acid **322** could be synthesised in good yield.[194]



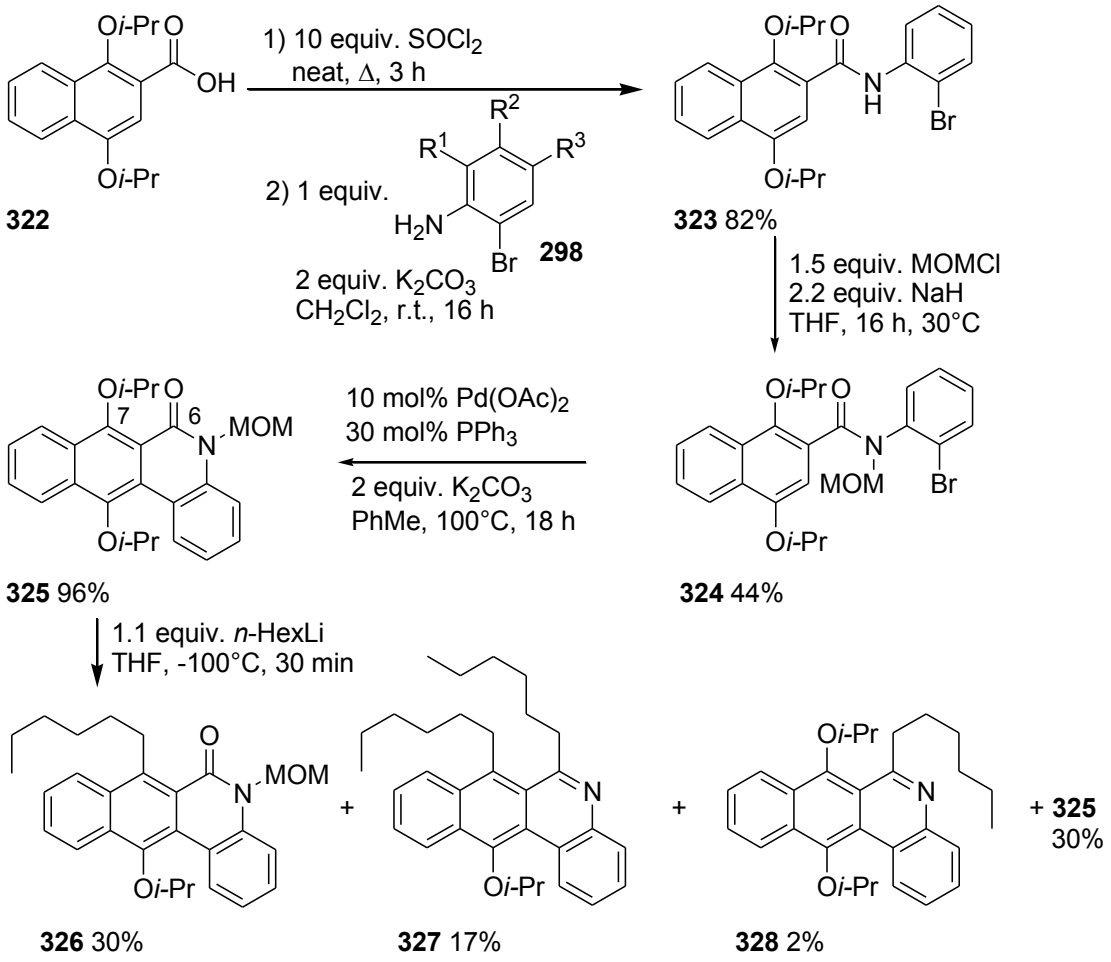
319

320 80%

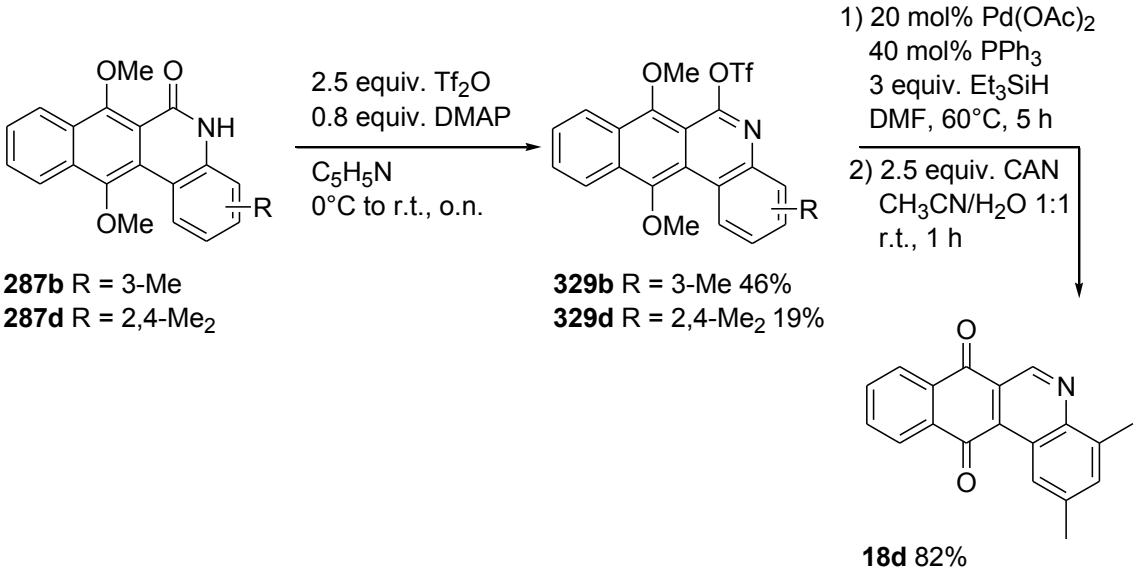
321

322 80%

Having in hand carboxylic acid **322**, the abovementioned synthesis sequence was repeated to form 5-methoxymethyl-7,12-di-*iso*-propoxy-5*H*-benzo[*j*]phenanthridin-6-one **325**. However, when *n*-hexyllithium was added to this compound, a mixture consisting mainly of unreacted starting material (30%), 1,4-addition product **326** (30%) and 17% of double addition product **327** containing only a trace amount of the desired 1,2-adduct **328** was formed.



An alternative would be to convert lactams **287** in the corresponding triflates **329** with triflic anhydride and to perform the addition reaction on these substrates. However these reactions were found to be low yielding and the products **329** hard to isolate. Even though reaction was observed with Tf_2O catalysed by DMAP in pyridine,[195] the yield was rather low. No reaction was observed when triflation was attempted with an alternative triflating agent such as $PhNTf_2$.[196] Moreover, alternatives in the modern literature exist to perform this conversion in a one-pot fashion.[197] The triflate group of 7,12-dimethoxy-2,4-dimethylbenzo[*j*]phenanthridin-6-yl trifluoromethanesulfonate **329d** was removed by means of Et_3SiH under Pd(0)-catalysis followed by oxidative demethylation to yield 2,4-dimethyl-benzo[*j*]phenanthridine-7,12-dione **18d**, which was not prepared during previous studies. The palladium catalysed reduction is a mild alternative to direct reduction of the lactam function with $LiAlH_4$ followed by acid hydrolysis, which is known to be low yielding for this specific type of compounds.[182,187] However, as the triflation step is low yielding, there is little advantage in this specific case.

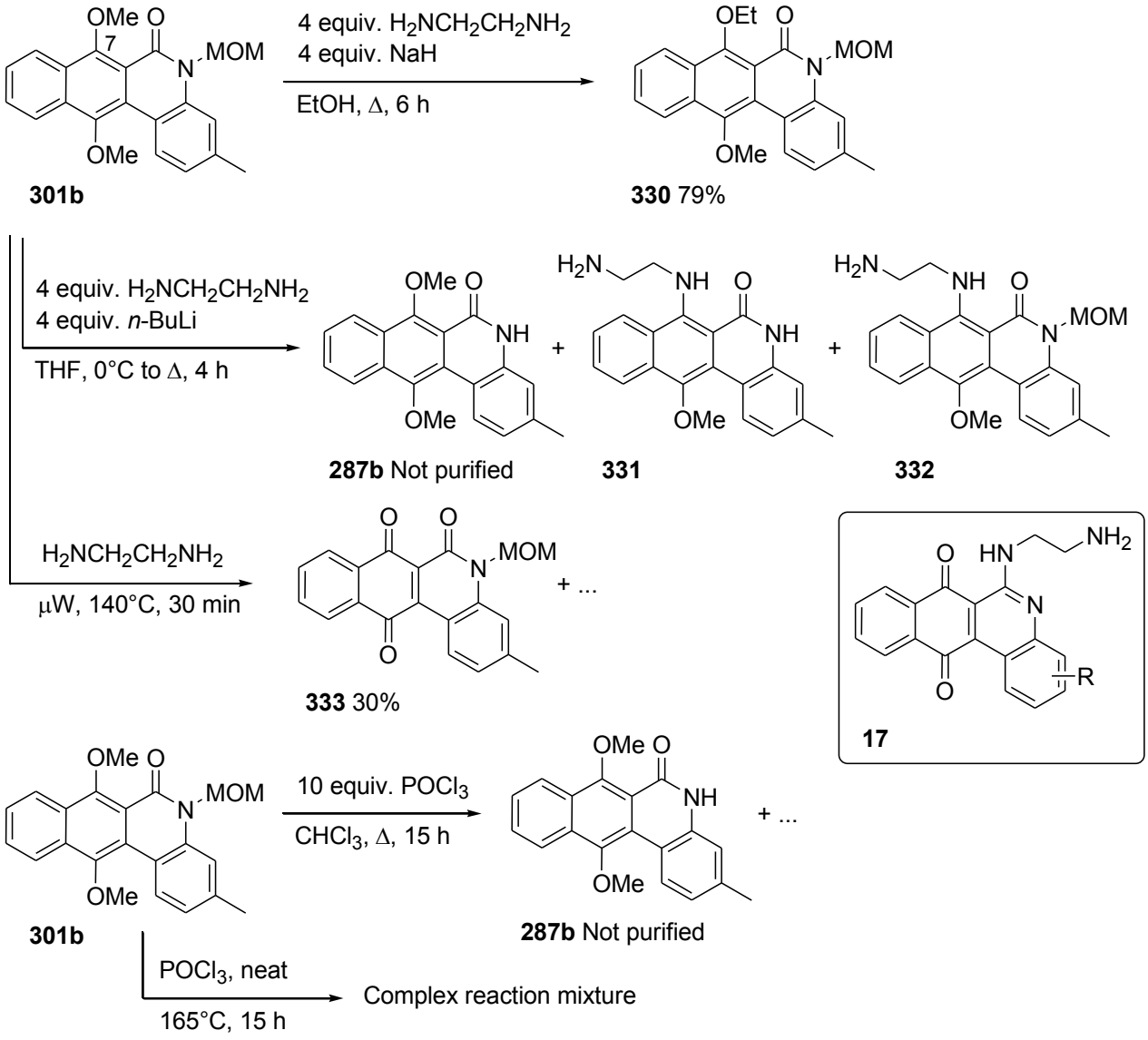


287b R = 3-Me
287d R = 2,4-Me_2

329b R = 3-Me 46%
329d R = 2,4-Me_2 19%

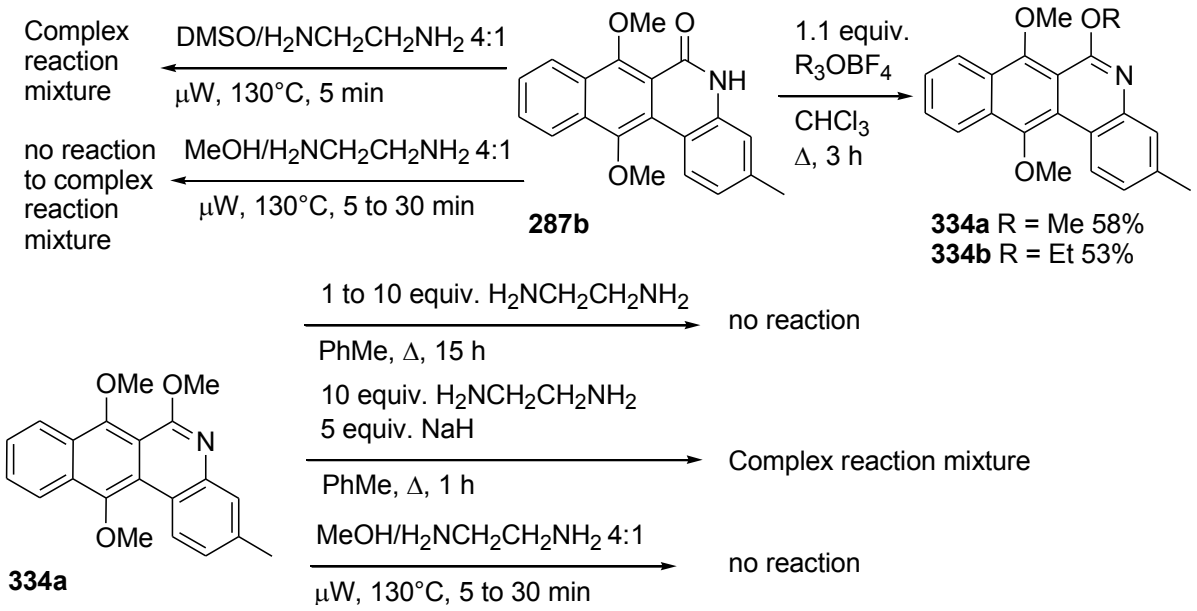
18d 82%

Next, the synthesis of 6-aminoethylamino substituted benzophenanthridines **17** was investigated by studying the reaction of MOM-protected lactam **301b** with ethylenediamine as it is known that an amidine can be synthesised directly from a pyridinone and an amine.[203] This would result in compounds similar to the anticancer drugs mitoxantrone **73b** and pixantrone **80**. Moreover, this would allow the preparation of salts thus improving aqueous solubility and hence bioavailability, a major problem with this class of compounds.[198] When lactam **301b** was brought into reaction in boiling ethanol and NaH as a base, the 7-methoxy group was substituted by an ethoxy group leading to 7-ethoxyphenanthridine **330**. Even though surprising, this is conform the abovementioned observations regarding 1,4-alkyllithium addition. When the reaction was repeated in THF, a mixture of compounds was obtained including 7,12-dimethoxy-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **287b**, 7-(2-aminoethylamino)-12-methoxy-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **331** and 7-(2-aminoethylamino)-12-methoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **332**. Strangely, when MOM-protected lactam **301b** was heated in neat ethylenediamine, various products were formed, amongst which quinone **333** which could be isolated in 30% yield from the mixture. It was then attempted to convert lactam **301b** into the corresponding chloropyridine with $POCl_3$ as 2-chloropyridine derivatives are known to react regioselectively with amines. A chloropyridine could also serve as a point of attachment for a coupling reaction.[199] However, only deprotection product **287b** was observed when the reaction was performed in boiling chloroform and a complex mixture was retrieved when the reaction was performed neat.[200] An alternative would be the use of PCl_3.[201]



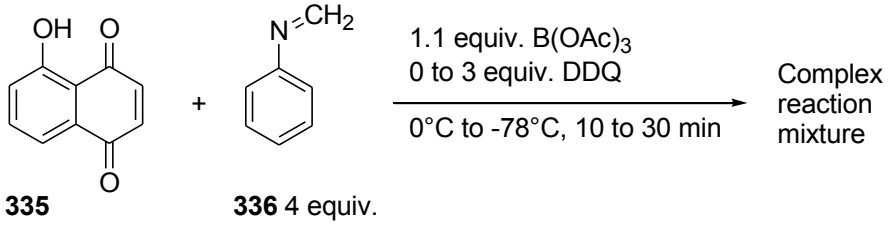
Next, 7,12-dimethoxy-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **287b** was converted in the corresponding alkoxypyridines **334** using trialkyloxonium tetrafluoroborate salts[202] in boiling chloroform in moderate yield. When the thus obtained trimethoxybenzophenanthridine **334a** was reacted with ethylenediamine, no reaction was observed either in batch or the microwave or a complex mixture was retrieved when NaH was used. When lactam **287b** was reacted in the microwave in a mixture of ethylenediamine and MeOH or DMSO,[203] complex mixtures were retrieved as well. Other authors have reported similar issues in pursuing this alkylamino substitution of a lactam and its

derivatives.[204]

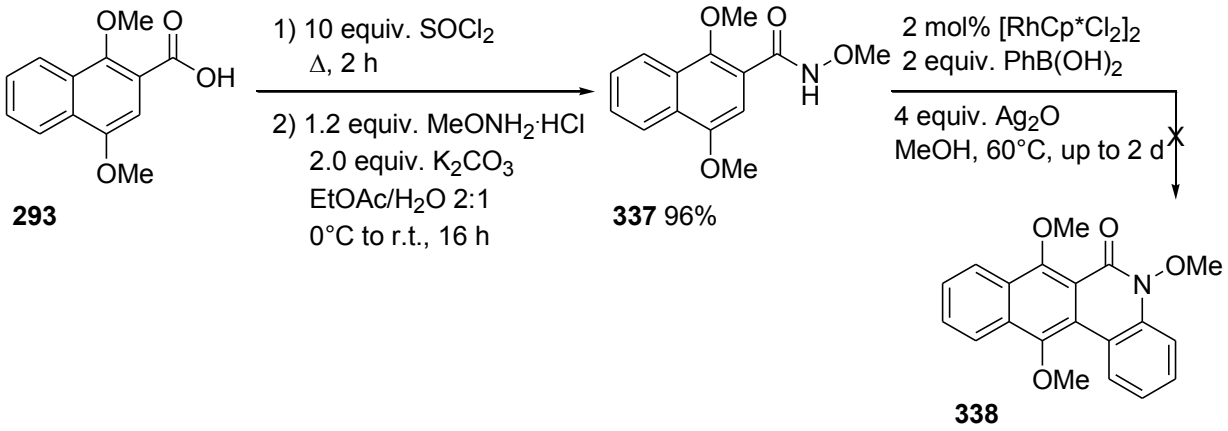


3.5.3 Alternative entries towards the benzo[*j*]phenanthridinedione scaffold

Recently, a synthesis of the angucyclinone skeleton by means of a $B(OAc)_3$ promoted Diels-Alder reaction between juglone **335** and various styrenes in the presence of DDQ was reported.[205] Attempts to create an aza-analogue of this reaction with methylenephenylamine **336**[206] as the diene were not successful.



In another paper, the phenanthridine skeleton was synthesised by means of a rhodium(III)-catalysed oxidative CH coupling of *N*-methoxybenzamides with arylboronic acids.[207] However, no formation of 5,7,12-trimethoxy-5*H*-benzo[*j*]phenanthridin-6-one **338** was observed when the reaction was performed with *N*-methoxynaphthalenecarboxamide **337**, $PhB(OH)_2$, Ag_2O and 2 mol% of $\{RhCp^*Cl_2\}_2$ ($Cp^* = Me_5C_5$).



3.5.4 Synthesis of 1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-diones 19

Next, the synthesis of tetrahydrobenzophenanthridinediones **19** was envisaged via an enamine addition strategy. Pyranonaphthoquinones **341** can be synthesised by means of the addition of a pyrrolidine enamine **340a** to 2-(hydroxymethyl)-1,4-naphthoquinone **339** followed by aerobic oxidation.[208] Thus, it was attempted to convert pyranonaphthoquinone **341**[208] into the corresponding 2-aza-anthraquinone **19a** using ammonium acetate. However, no satisfying reaction conditions could be found using either microwave or batch conditions. Interestingly, when pyranonaphthoquinone **341** was boiled in acetic acid, aromatisation of the D-ring occurred leading to benzo[*c*]pyranonaphthoquinone **28** (Table 11). Formation of this compound is believed to proceed via sequential keto-enol tautomerisation towards the hydroquinone and aerobic oxidation towards the quinone. This type of oxidative aromatisation reactions are known to hamper the synthesis of 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones.[209]

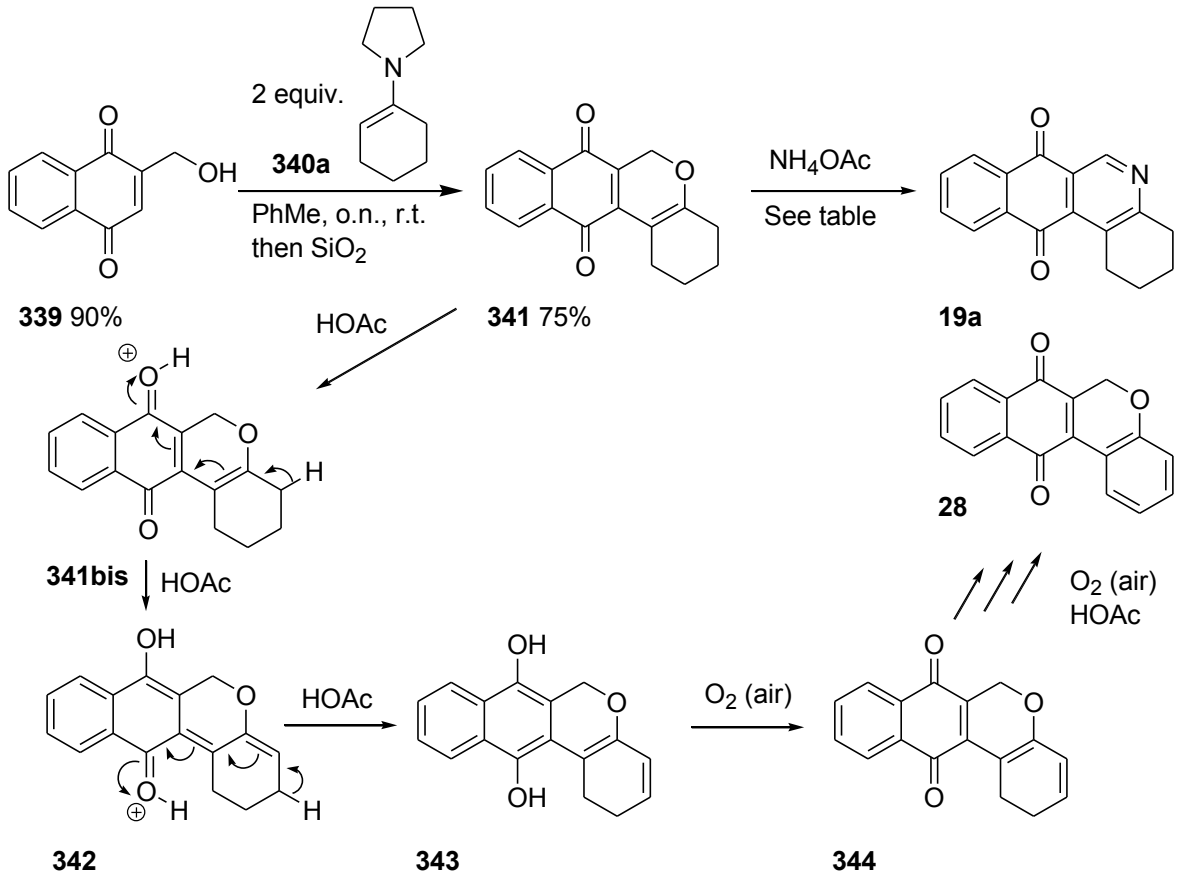
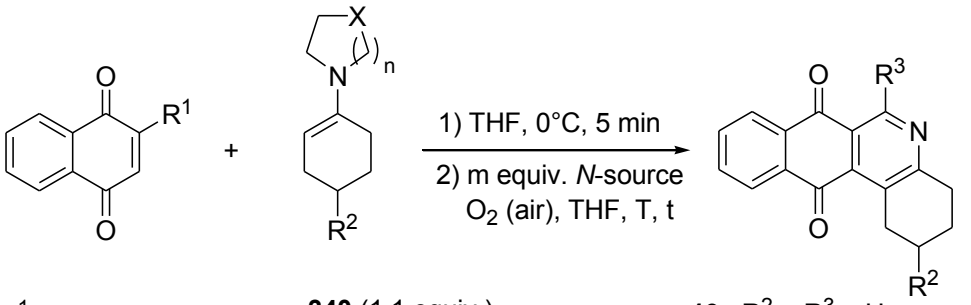


Table 11. Attempted reaction conditions for the conversion of pyranonaphthoquinone **341** into 2-aza-anthraquinone **19a**.

Entry	Reagents	Time	T/Power	Reaction mode	Result	Yield (%)
1	5 m/v% NH_4OAc in MeOH	120 min	115°C	microwave	**19a**	20
2	5 m/v% NH_4OAc in MeOH	10 min	140 W	microwave	**19a**	16
3	10 m/v% NH_4OAc in HOAc	4 h	Δ	batch	**28**	30

Therefore, and alternative procedure was deployed in which the enamine adduct is converted in a one-pot protocol to the corresponding 2-aza-anthraquinone **19**.[210] Thus, the synthesis of tetrahydrobenzophenanthridinediones **19** was envisaged starting from the addition of Stork enamines **340** to 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **11**[109] and 2-acetyl-1,4-naphthoquinone **345** followed ammonia-mediated conversion of the enamine adduct and aerobic oxidation towards the corresponding 2-aza-anthraquinones **19**.[210] Even though a precedent of this methodology exists in the literature[210] (Table 12, entry 3), this could not be reproduced in good yield even upon several replications. Therefore, several enamines and conditions for the ammonia-mediated ring opening-ring closure sequence were investigated but no satisfying conditions were found. Best results were obtained using ten equivalents of 7 M NH_3 in MeOH as the nitrogen source (Table 12, entry 4).



11 R^1 = 1,3-dioxolan-2-yl
345 R^1 = acetyl

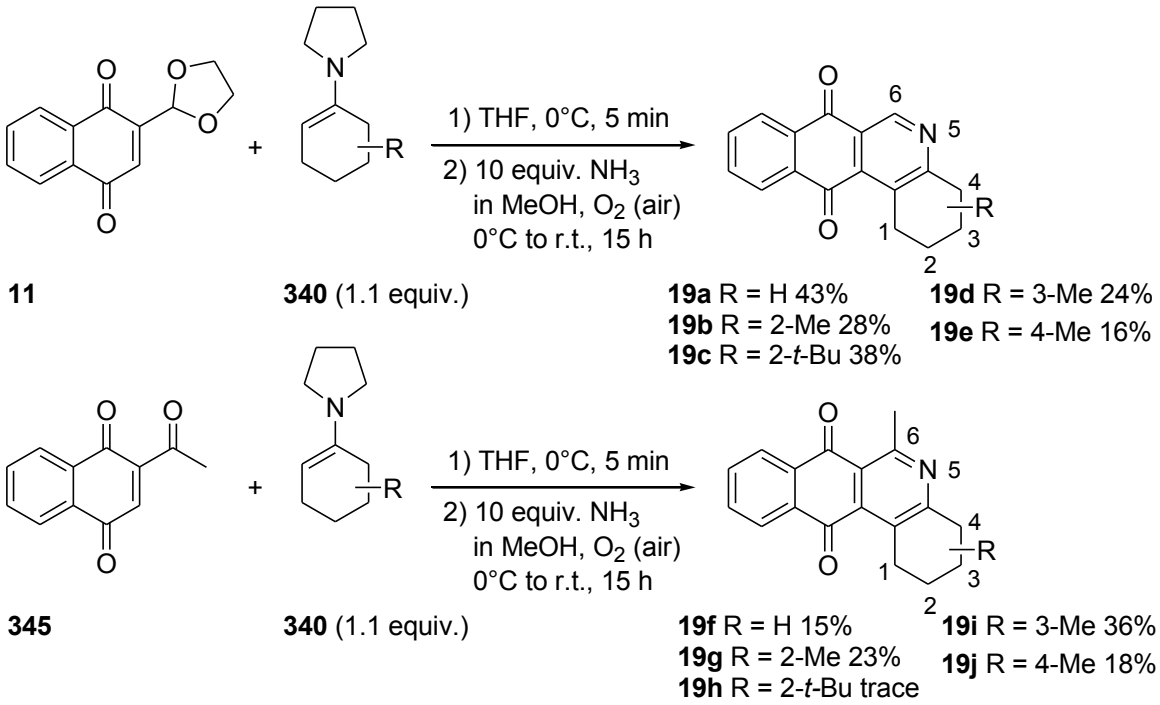
340 (1.1 equiv.)

19a $R^2 = R^3 = H$
19f $R^2 = H$, $R^3 = Me$
19h $R^2 = t$-Bu, $R^3 = Me$

Table 12. Attempted reaction conditions for the conversion of naphthoquinones **11** and **327** in 2-aza-anthraquinones **19**.

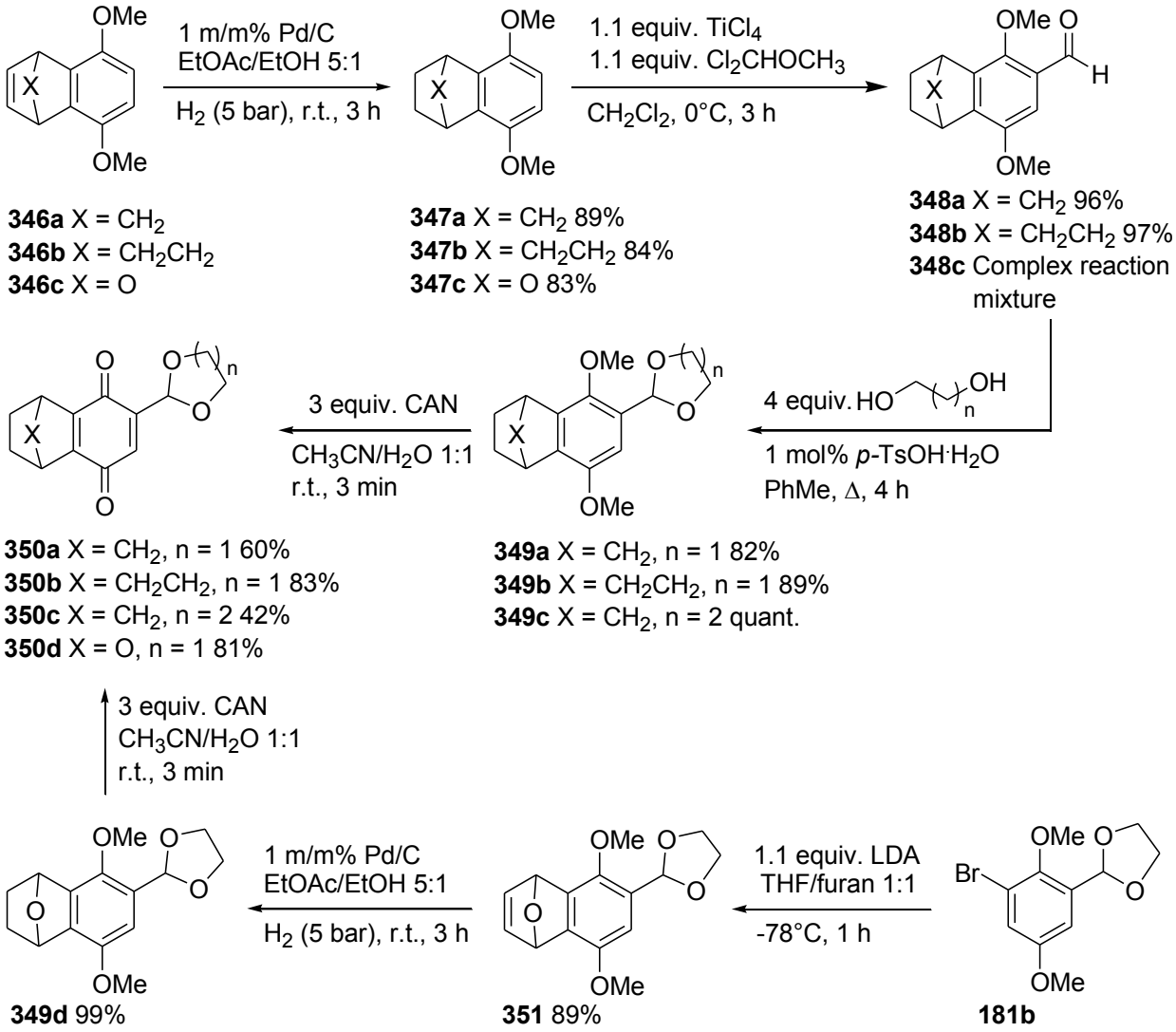
Entry	X	n	R^1	R^2	R^3	m	*N*-source	T	t	Result
1	CH_2	1	1,3-Dioxolan-2-yl	H	H	10	$NH_{3,aq}$ in MeOH	0°C to r.t.	15 h	**19a** 12%
2	CH_2	1	1,3-Dioxolan-2-yl	H	H	10	7 M NH_3 in MeOH	0°C to r.t.	15 h	**19a** 43%
3	CH_2	1	Acetyl	H	Me	10	$NH_{3,aq}$ in MeOH	0°C to r.t.	15 h	**19a** 5%
4	CH_2	1	Acetyl	H	Me	10	7 M NH_3 in MeOH	0°C to r.t.	15 h	**19f** 15%
5	CH_2	1	Acetyl	*t*-Bu	Me	1.5	7 M NH_3 in MeOH	0°C to r.t.	15 h	**19h** trace
6	O	2	Acetyl	*t*-Bu	Me	1.5	7 M NH_3 in MeOH	0°C to r.t.	15 h	**19h** trace
7	O	2	Acetyl	*t*-Bu	Me	10	NH_4OAc	0°C to r.t.	15 h	**19h** trace
8	CH_2	2	Acetyl	*t*-Bu	Me	1.5	7 M NH_3 in MeOH	0°C	30 min	**19h** trace
9	CH_2	2	Acetyl	*t*-Bu	Me	1.5	NH_4OAc	0°C to r.t.	15 h	**19h** trace
10	CH_2	2	Acetyl	*t*-Bu	Me	1	NH_4OAc	0°C	Up to 1 h	No reaction
11	CH_2	2	Acetyl	*t*-Bu	Me	2	NH_4OAc	0°C	30 min	**19h** trace
12	CH_2	2	Acetyl	*t*-Bu	Me	3	NH_4OAc	0°C	Up to 1 h	**19h** trace
13	O	2	Acetyl	*t*-Bu	Me	2	7 M NH_3 in MeOH	0°C	30 min	**19h** trace

Using these conditions, a set of D-ring substituted derivatives **19**, bearing either a methyl or no substituent of no substituent at C-6 were synthesised in low yields. When these compounds were tested against *Mycobacterium tuberculosis*, no significant activity was observed. However, it was found that compounds **19a-e**, with no substitution at C-6 were more active than the corresponding methyl-substituted derivatives **19f-j**. Therefore, the synthesis of 2-aza-anthraquinones with an aliphatic A-ring and no substitution at C-6 was envisaged.



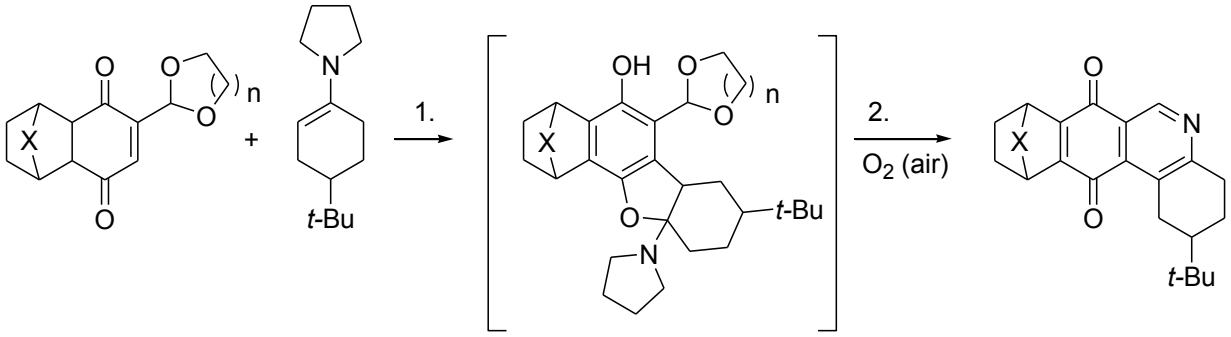
3.5.5 Synthesis of 8,11-bridged 1,2,3,4,8,9,10,11-octahydrobenzo[*j*]-phenanthridine-7,12-diones 22

The synthesis of methano-, ethano- and epoxy-bridged octahydrobenzo[*j*]phenanthridinediones **22** was envisaged using the abovementioned methodology. The starting dioxolanylnaphthoquinones **350a** and **350b** were synthesised starting from 5,8-dimethoxy-1,4-dihydronaphthalenes **346**[211], which were hydrogenated over palladium on carbon and subsequently subjected to a Rieche formylation[212] using dichloromethyl methyl ether and titanium(IV) chloride. These aldehydes **348** were then reacted with ethylene glycol followed by oxidative demethylation with cerium(IV) ammonium nitrate (CAN) to afford 6-**(**1,3-dioxolan-2-yl)-1,2,3,4-tetrahydronaphthalene-5,8-diones **350a** and **350b**. As these compounds only had a very limited stability, they had to be used immediately in the next step. An additional more stable dioxanyl derivative **350c** was prepared in a similar way. Attempts to formylate 1,2,3,4-tetrahydro-1,4-epoxynaphthalene **347c** gave complex mixtures. Attempts to acetylate this compound using acetyl chloride and $AlCl_3$ failed as well, indicating that the epoxy-bridge is to labile for this kind of transformations. Therefore, 2-(5,8-dimethoxy-1,4-dihydro-1,4-epoxynaphthalen-6-yl)-1,3-dioxolane **351** was prepared by means of a Diels-Alder reaction with furan and the benzyn derived from 2-(3-bromo-2,5-dimethoxyphenyl)-1,3-dioxolane **181b**. Hydrogenation of the isolated double bound followed by oxidative demethylation with CAN yielded the desired quinone **350d** in 81% yield.



No reaction was observed when enamine **340c** was added to 6-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione **350a** under the abovementioned conditions (Table 13, entries 1 and 2). Upon the addition of 10 mol% of $BF_3 \cdot OEt_2$, the desired octahydrobenzo[*j*]phenanthridinedione **22a** was formed in 48 % yield (Table 13, entry 3). Use of larger amounts of $BF_3 \cdot OEt_2$ or alternative nitrogen sources did not improve the yield (Table 13, entries 4 and 5). When the reaction was performed in toluene with various amounts of $BF_3 \cdot OEt_2$, no reaction was observed due to precipitation of the enamine adduct **352a** (Table 13, entry 6). Also the use of oxidative conditions did not yield any favourable results. The use of CAN led to a complex mixture and both Ag_2O and MnO_2 were not able to oxidise the enamine adduct (Table 13, entries 7-9). When the reaction was performed with the more stable dioxanylnaphthoquinone **350c**, enamine adduct **352c** was formed in 70% yield (Table 13, entry 10). This adduct proved to be very stable and the desired octahydrobenzophenanthridinedione **22a** could not be formed as this intermediate either did not react or decomposed (Table 13, entries 11-14). Upon the use of 6-(1,3-dioxan-2-yl)-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-5,8-dione **350b**, enamine adduct **352b** was formed in 34% yield (Table 13, entry 15). This intermediate did not convert

to the desired 2-aza-anthraquinone **22b** upon the use of NH_3 in MeOH, possibly due to the additional sterical hindrance of the ethano bridge (Table 13, entry 16). Upon treatment with ammonium acetate in HOAc, the desired octahydrobenzophenanthridinedione **22b** was formed in 33% yield (Table 13, entry 17).



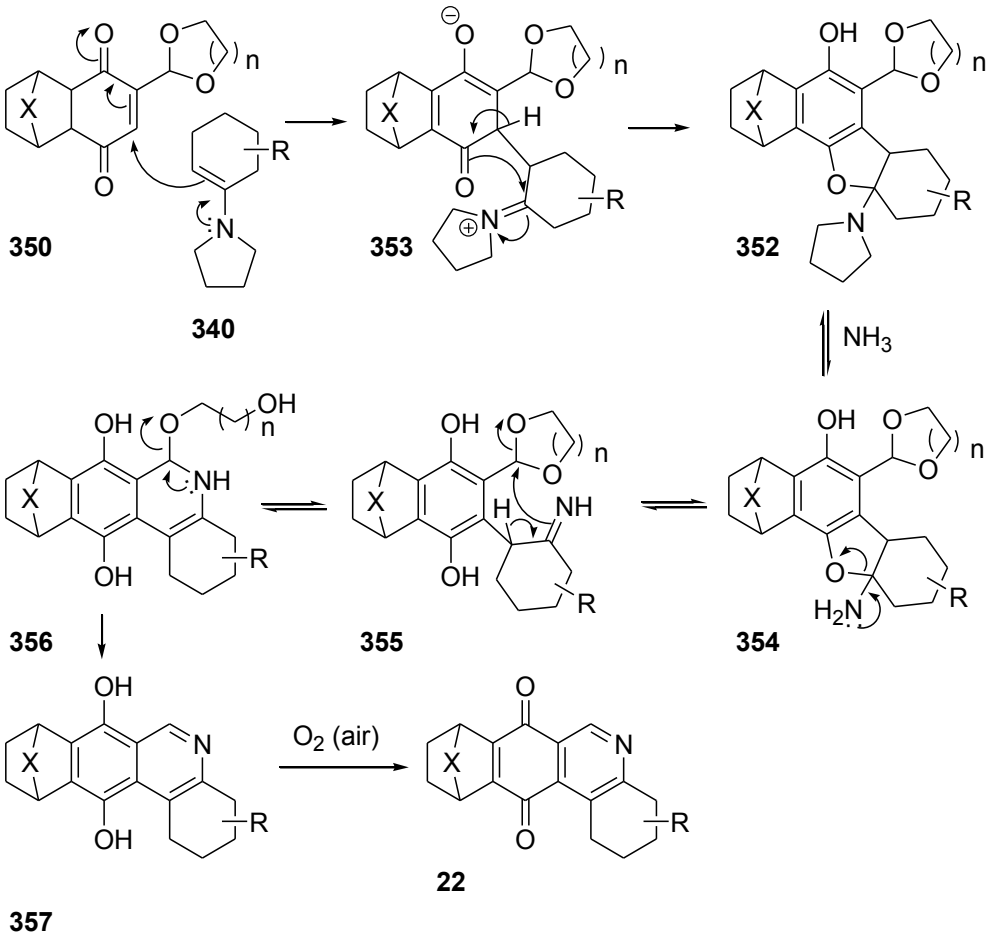
350a X = CH_2, n = 1 **340c** (1.1 equiv.) **352a, b, c** **22a** X = CH_2
350b X = CH_2CH_2, n = 1 **22b** X = CH_2CH_2
350c X = CH_2, n = 2

Table 13. Attempted reaction conditions for the conversion of 6-(1,3-dioxan-2-yl)-1,2,3,4-tetrahydronaphthalene-5,8-diones **350** in the corresponding 2-aza-anthraquinones **22**.

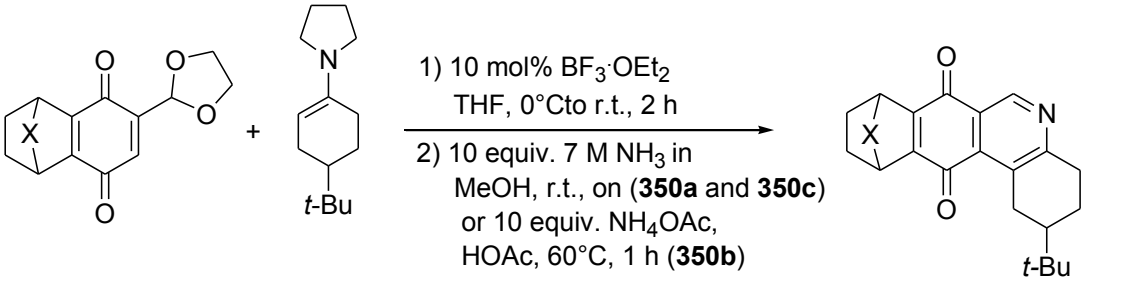
Entry	n	X	1	2	Result
1	1	CH_2	THF, 0°C, 5 min	10 equiv. 7 M NH_3 in MeOH, THF, 0°C to r.t., 2 h	No reaction
2	1	CH_2	THF, 0°C to r.t., on	10 equiv. 7 M NH_3 in MeOH, THF, 0°C to r.t., 2 h	No reaction
3	**1**	**CH_2**	**10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h**	**10 equiv. 7 M NH_3 in MeOH, THF, r.t., o.n.**	**22a 48%**
4	1	CH_2	1,1 equiv. $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. 7 M NH_3 in MeOH, THF, r.t., o.n.	**22a** 28%
5	1	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. NH_4OAc in HOAc, 50°C, 2 h	**22a** 23%
6	1	CH_2	0, 10 or 100 mol% $BF_3{\cdot}OEt_2$, PhMe, 0°C to r.t., 3 h	10 equiv. 7 M NH_3 in MeOH, PhMe, r.t., o.n.	**352c** (not isolated)
7	1	CH_2	2.1 equiv. CAN, THF, 0°C, 2 h	-	Complex mixture
8	1	CH_2	4 equiv. MnO_2, 5 equiv. $MgSO_4$, THF, 0°C to r.t., 2 h	-	**352c** (not isolated)
9	1	CH_2	2.1 equiv. Ag_2O, 5 equiv. $MgSO_4$, THF, 0°C to r.t., 2 h	-	**352c** (not isolated)
10	2	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	-	**352c** 70%
11	2	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. 7 M NH_3 in MeOH, THF, r.t., 2 h to o.n.	No reaction towards **22a**
12	2	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF,	10 equiv. NH_4OAc in	No reaction towards

			0°C to r.t., 3 h	MeOH, Δ, 2 h to on	**22a**
13	2	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. NH_4OAc in HOAc, 50°C, 2 h to o.n.	No reaction towards **22a**
14	2	CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. NH_4OAc in HOAc, 100°C (pressure vial)	Slow decomposition of intermediate **352c**
15	1	CH_2CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	-	**22b** (34%)
16	1	CH_2CH_2	10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h	10 equiv. 7 M NH_3 in MeOH, r.t., o.n.	No reaction towards **22b**
17	**1**	**CH_2CH_2**	**10 mol% $BF_3{\cdot}OEt_2$, THF, 0°C to r.t., 3 h**	**10 equiv. NH_4OAc in HOAc, 60°C, 1 h**	**22b (33%)**

The reaction mechanism of the abovementioned reaction is illustrated below. Initial attack of Stork enamine **340** on quinone **350** leads to iminium species **353**, which is trapped intramoleculary leading to the formation of adduct **352**. Conversion of hemiaminal function of **352** towards hemiaminal **354** leads to ring opening and subsequent ring closure by intramolecular attack of the thus formed imine on the acetal function. Expulsion of the glycol followed by aerobic oxidation yields the desired octahydrobenzophenanthridinediones **22**.



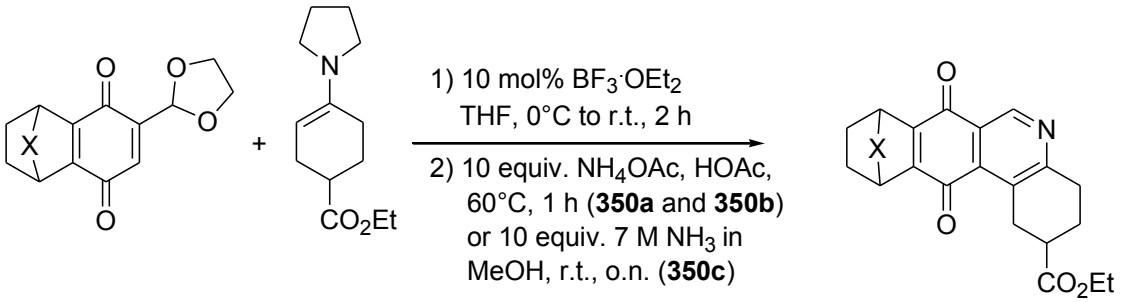
Using the abovementioned reaction conditions, one additional *O*-bridged *tert*-butyl substituted derivative **22c** was synthesised. The second step was performed with NH_3 in MeOH as the acetic acid conditions led to ring opening of the epoxy-bridge. Starting from ethyl-4-pyrrolidin-1-ylcyclohex-3-enecarboxylate **358**, two ester substituted derivatives **22d** and **22e** were synthesised. The reaction with 6-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-5,8-dione **350d** resulted in a complex mixture. Next, substitution of a carbon by nitrogen was envisaged. When the enamine addition was performed with 1-methyl-4-pyrrolidin-1-yl-1,2,3,6-tetrahydropyridine **359a**, a complex reaction mixture was obtained for both quinones **350a** and **350b**. Upon treatment of quinone **350a** with 1-*tert*-butoxycarbonyl-4-pyrrolidin-1-yl-1,2,3,6-tetrahydropyridine **359b**, 2-*tert*-butoxycarbonyl-1,2,3,4,8,9,10,11-octahydro-2-aza-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **22g** was isolated in 17% yield. Even though promising antimycobacterial activity accompanied with a relative low cytotoxicity and no genotoxicity was observed for 2-aza-anthraquinones **22**, no further derivatisation of the obtained compounds was attempted due to the low yields of the addition reactions.



350a X = CH_2
350b X = CH_2CH_2
350d X = O

340c

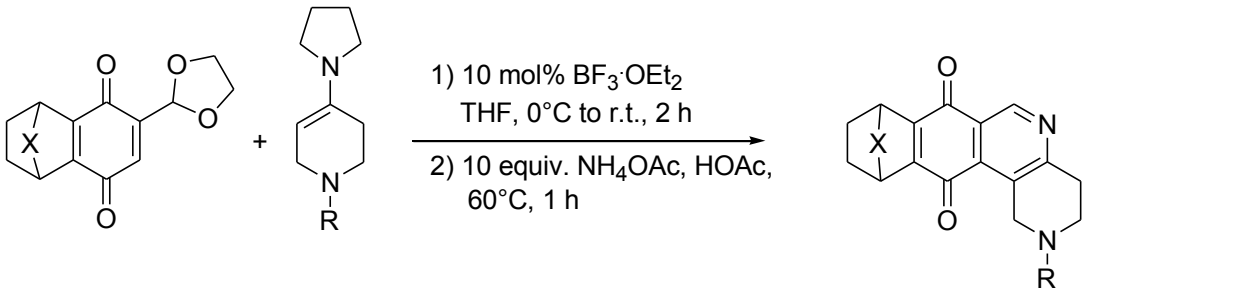
22a X = CH_2 48%
22b X = CH_2CH_2 33%
22c X = O 14%



350a X = CH_2
350b X = CH_2CH_2
350d X = O

358

22d X = CH_2 18%
22e X = CH_2CH_2 10%
22f X = O CRM



350a X = CH_2
350b X = CH_2CH_2

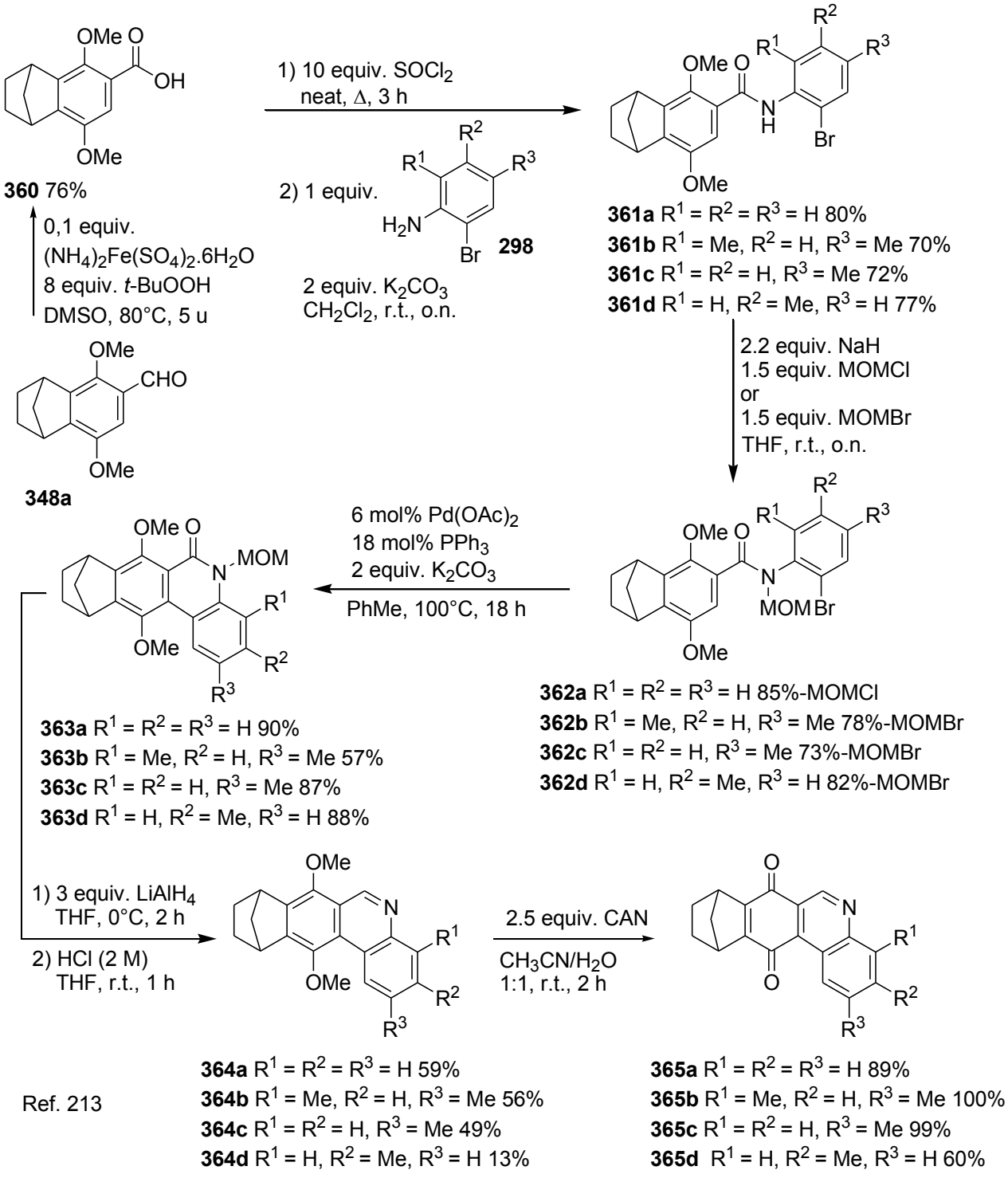
359a R = Me
359b R = Boc

22g X = CH_2, R = Boc 17%

All octahydrobenzophenanthridines **22** showed good activity against *Mycobacterium tuberculosis*. For instance 2-*tert*-butyl-1,2,3,4,8,9,10,11-octahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **22a** has a MIC_{50} of 0.14 μg/mL, accompanied with a cytotoxicity (IC_{50}) of 33.3 μg/mL, which results in a selectivity index of 237.9.

3.5.6 Synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones 365

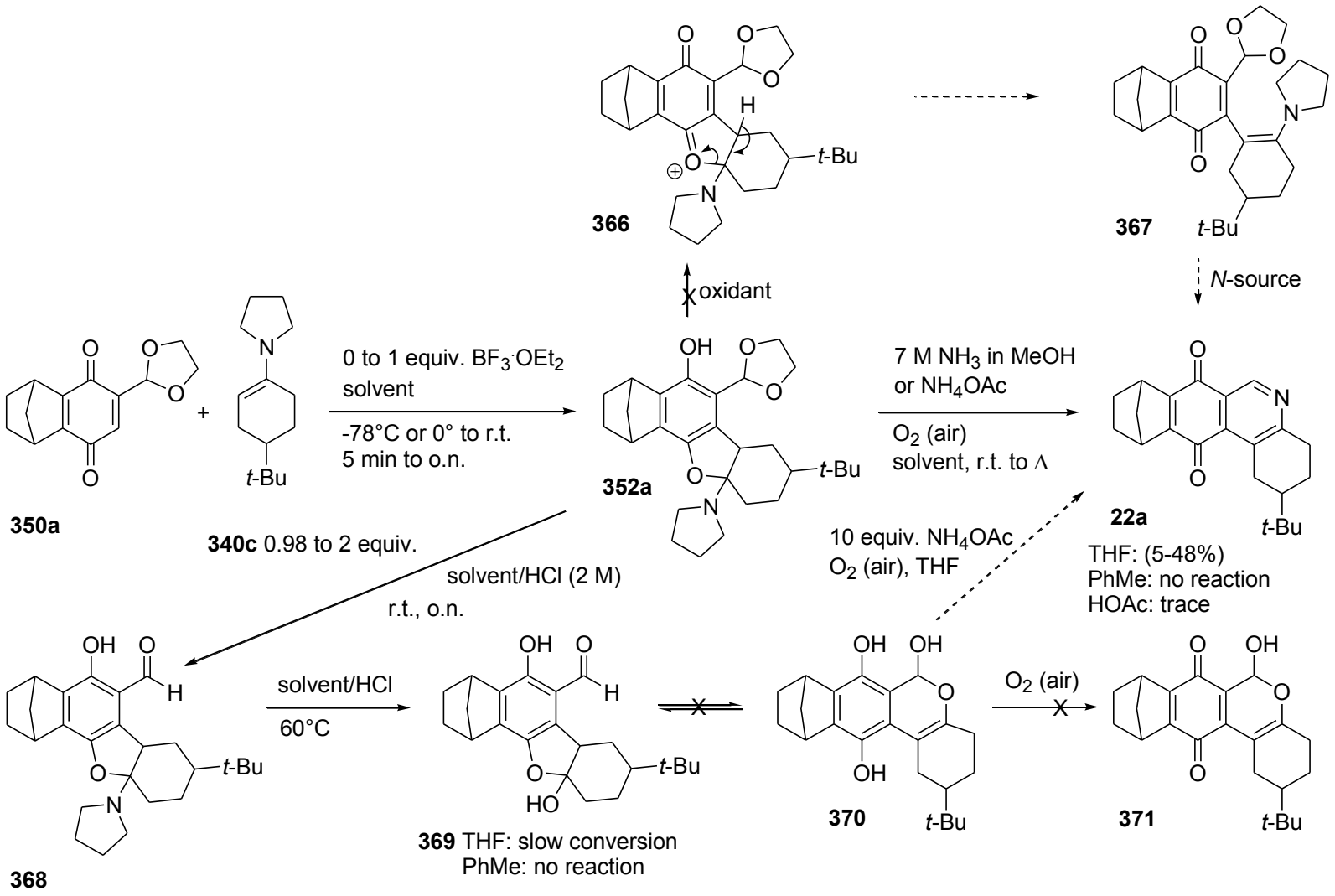
Having in hand an efficient methodology to synthesise 7,12-dimethoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **301** (see section 3.5.2), it was applied to the synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **365**. These reactions were the subject of a master thesis.[213] The starting carboxylic acid **360** was prepared by means of an iron-catalysed oxidation of 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxaldehyde **348a**. Next, four lactams **363** were synthesised using the methodology described above and were subsequently reduced with $LiAlH_4$ followed by treatment with HCl to convert the intermediate hemi-aminals into the corresponding pyridines **364**.These compounds **364** were then oxidatively demethylated towards 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **365**, which were tested against *Mycobacterium tuberculosis*. It was found that especially phenanthridine-7,12-dione **365a** possessed good antimycobacterial activity with a MIC_{50} lower than 0.1 μg/mL. In contrast to the 8,11-bridged 1,2,3,4,8,9,10,11-octahydrobenzo[*j*]phenanthridine-7,12-diones **22**, which are highly active but have a low yielding synthesis (see section 3.5.5), 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **365a** is easy to synthesise and possesses a good activity. Therefore, this compound **365a** was synthesised on a gram scale in order further biological testing towards pharmacokinetics and the potential target of these molecules.



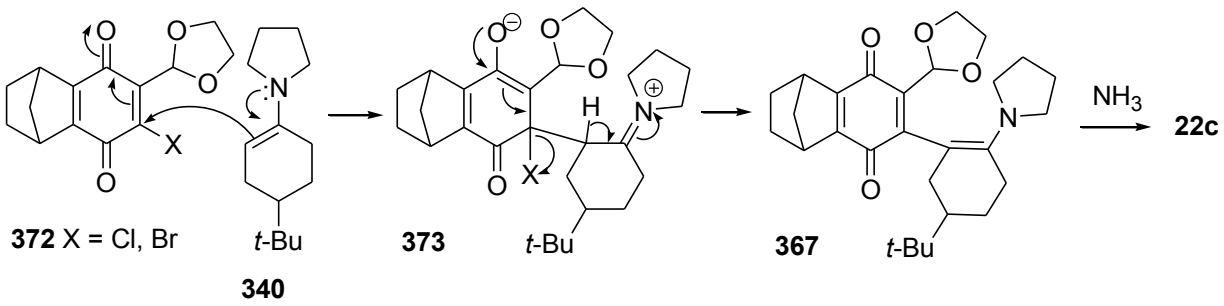
3.5.7 Alternative entries towards the tetra/octahydrobenzo-phenanthridinedione scaffold

As stated above, the enamine strategy towards the tetra/octahydrobenzophenanthridinedione scaffold is problematic. The problems with this reaction are summarized in the following scheme. The main problem is not the enamine addition but the formed adduct: as in this adduct the iminium ion is

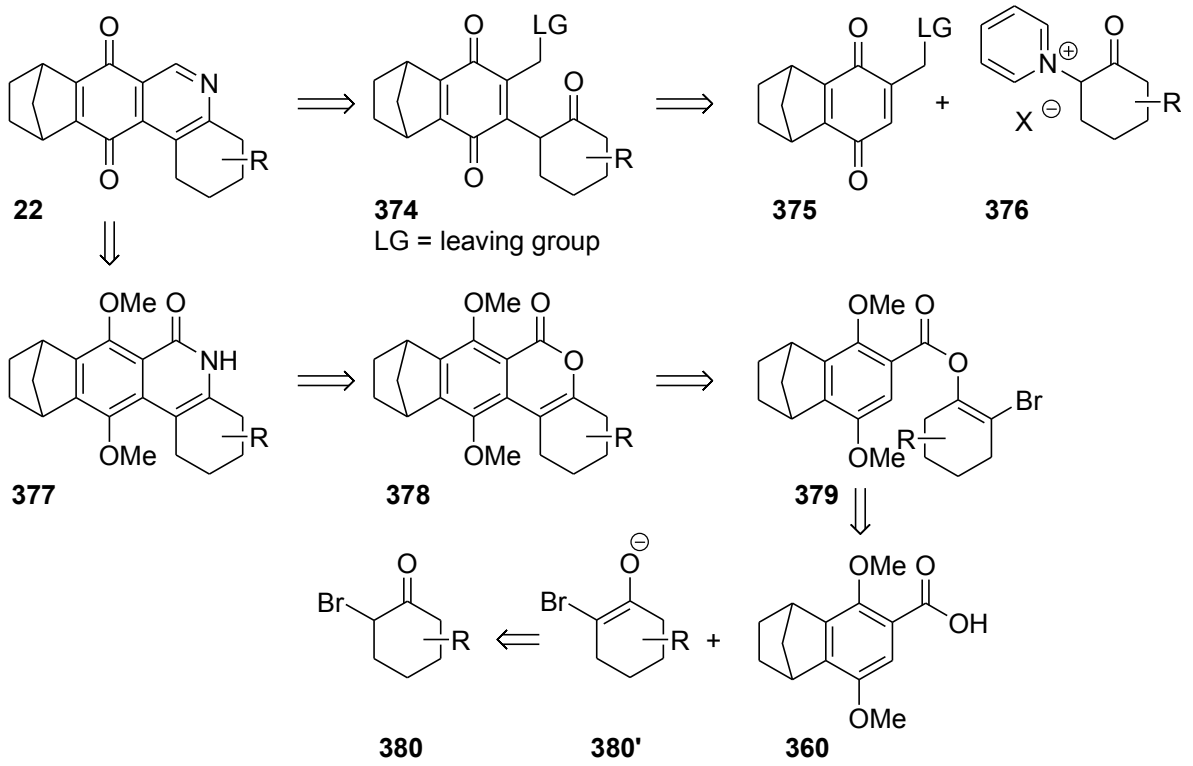
trapped by a naphthalenic OH, a stable adduct **352a** is formed, which hardly further converts to the desired 2-aza-anthraquinone **22**. This result is in contrast with the enamine reaction with hydroxymethylnaphthoquinone **339**, in which the hydroxymethyl group traps the iminium ion, thus avoiding the hydroquinone chromophore and allowing aerobic oxidation towards the quinone. Adduct **352a** even does not oxidise towards cyclohexenylquinone **367** when an external oxidant such as MnO_2 or Ag_2O is added. Even though the dioxolanyl function can be relatively easily hydrolysed twards aldehyde **368**, the hydrolysis of the hemi-aminal appears to be much harder and there seems to be no equilibration between hemiacetal **369** and its corresponding hydroquinone **370** as this compound would be readily converted in the desired 2-aza-anthraquinone **22a** in the presence of ammonium acetate and air.


366
367
t-Bu
N-source
oxidant
0 to 1 equiv. BF3·OEt2
solvent
-78°C or 0° to r.t.
5 min to o.n.
350a
352a
7 M NH3 in MeOH
or NH4OAc
O2 (air)
solvent, r.t. to Δ
22a
THF: (5-48%)
PhMe: no reaction
HOAc: trace
340c 0.98 to 2 equiv.
solvent/HCl (2 M)
r.t., o.n.
10 equiv. NH4OAc
O2 (air), THF
solvent/HCl
60°C
O2 (air)
368
369 THF: slow conversion
PhMe: no reaction
370
371

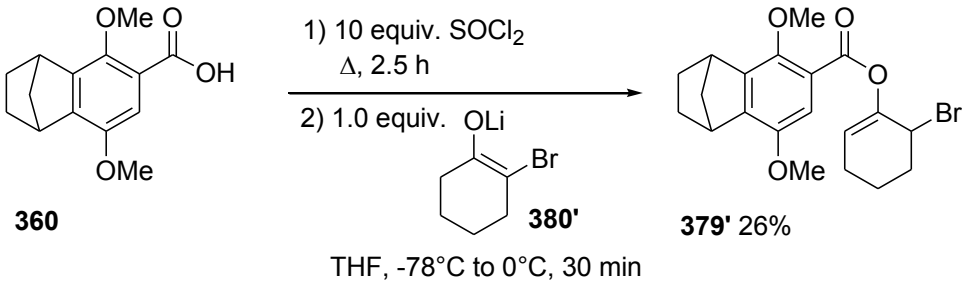
A potential alternative to make the enamine addition work would be to introduce a halogen on the quinone moiety. Initial enamine addition would then be followed by elimination of the halogen atom thus restoring the quinone chromophore and avoiding the formation of adduct **352a**. The resulting cyclohexenylquinone **367** should be readily convertible into the desired octahydrobenzophenanthridine **22c**.



Some alternative entries towards the octahydrobenzophenanthridine skeleton were briefly investigated. One of the major problems in quinone chemistry is that quinones are notoriously difficult substrates to add carbon nucleophiles onto due to potential aromatisation. One of the best ways to do so is the addition of pyridinium ylids. Therefore, reaction of pyridinium salt **376** with quinone **375** towards cyclohexylquinone **374** would make a valuable alternative. However, even though one procedure exists to make the pyridinium salt of 2-bromo-α-tetralone by stirring it in pyridine for two weeks,[214] this is problematic for cyclohexanone derivatives due to the presence of two enolisable positions. Exploratory experiments using this procedure or a Ortholeva-King reaction[215] towards pyridinium salts **376** only gave complex mixtures. Alternatively, octahydrobenzo[*j*]phenanthridinediones **22** could be synthesised by means of a Heck reaction of 2-bromocyclohex-1-enyl naphthalene-6-carboxylate **379** followed by conversion of lactone **378** in lactam **377**, reduction towards the pyridine and oxidative demethylation towards the targeted benzophenanthridines **22**.



In a test experiment in which the corresponding acid chloride of 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxylic acid **360** was reacted with lithium 2-bromocyclohex-1-enolate **380'**, which was preformed from 2-bromocyclohexanone **380** and 1.1 equiv. of LiHMDS, the wrong isomer **379'** was obtained in low yield. Apparently, the 0.1 excess of LiHMDS led to isomerisation of the double bound.



Alternatively, 2-acetylnaphthoquinone **345** was added to oxime **381a** but no reaction was observed even after the addition of $BF_3 \cdot OEt_2$ and refluxing (Table 14, entry 1). Similarly, cyclohexanone **381b** was reacted with 2-acetyl-1,4-naphthoquinone **345** in the presence of ammonium acetate under microwave irradiation but only trace amounts of 2-aza-anthraquinone **19f** could be isolated (entry 2). When an oxidant was added, a complex mixture was immediately obtained (entry 3). When the imine was preformed starting from the hydroquinone followed by oxidation with MnO_2, a complex mixture was retrieved as well.

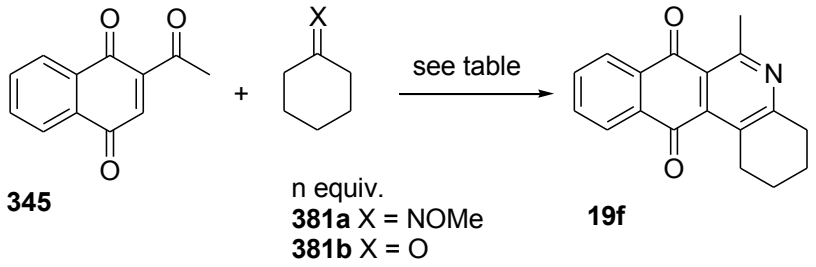


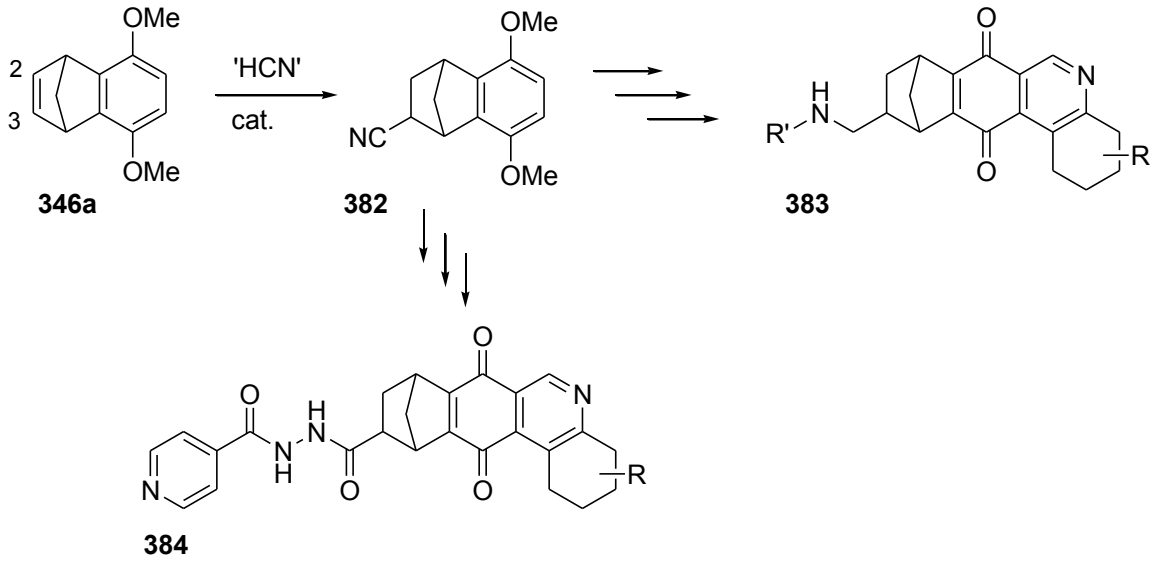
Table 14. Attempted reaction conditions for the formation of tetrahydrobenzo[*j*]phenanthridinedione **19f**.

Entry	X	n	Reagents	Conditions	Result
1	NOMe	1	0 to 10 mol% $BF_3 \cdot OEt_2$	THF, r.t. to Δ, 4 h to 2 d	No reaction
2	O	3	5% (m/v) NH_4OAc	MeOH, μW, 6 min	**19f** trace
3	O	3	5% (m/v) NH_4OAc, 5 equiv. MnO_2 5 equiv. $MgSO_4$	MeOH, 0°C to r.t., 24 h	Complex reaction mixture

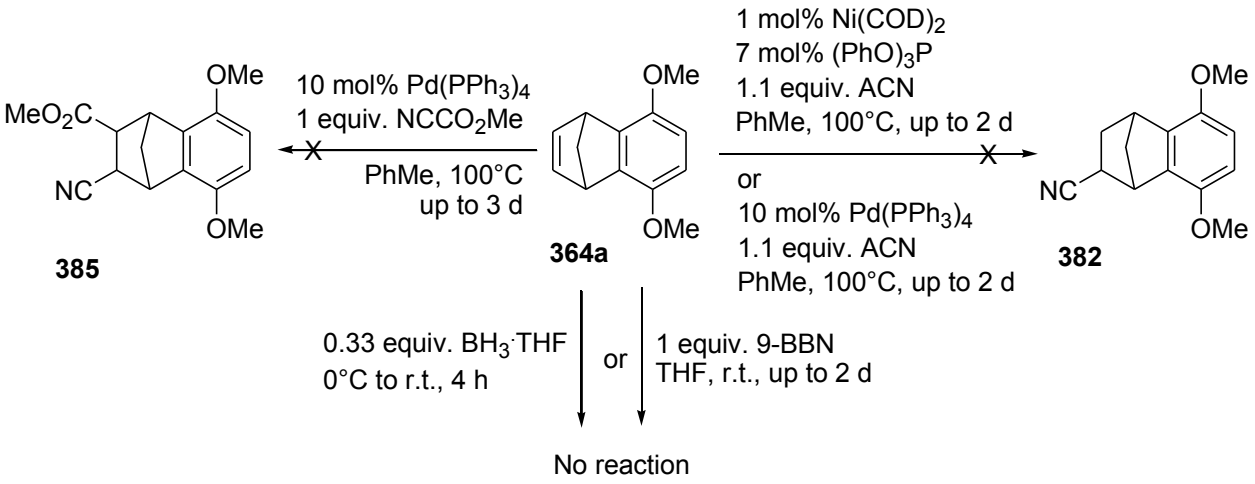
Another alternative would be the conversion of the quinone into a quinone monoketal to mask the quinone moiety and thus prevent cyclisation after addition of the enamine. However these compounds were found to be extremely unstable and therefore not suitable starting materials.

3.5.8 Attempted further derivatisation of the octahydrobenzo-[*j*]phenanthridine scaffold

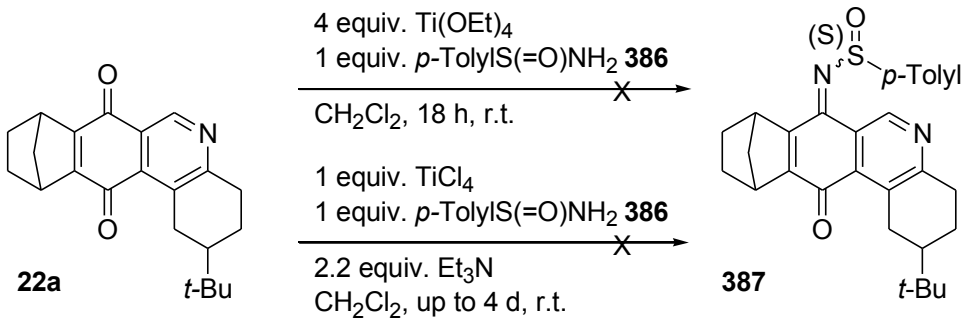
Instead of hydrogenating the C-2,C-3 double bound of 1,4-dihydro-5,8-dimethoxynaphthalene **346a**, it could be used as a point of further functionalisation e.g. to attach a polar side chain or to form bifunctional molecules such as **383** and **384**. Therefore, the possibility of hydrocyanating this double bound was investigated towards 2-cyanonaphthalene **382**. This could be done by organometal-catalysed addition of HCN or by hydroboration followed by cleavage with KCN and $Pb(OAc)_4$.[216]



Even though the double bound is readily hydrogenated due to the strain liberation of the five-membered ring, all attempts to hydrocyanate **364a** towards nitrile **382** using acetone cyanohydrin (ACH) under Pd(0)- or Ni(0)-catalysis[217] failed and so did attempts to cyanocarboxylate towards ester **385** with methylcyanoformate under Pd(0) catalysis or hydroborate with 9-BBN or $BH_3 \cdot THF$.[218] Hydroformylation would be a good alternative for these reactions.



As octahydrobenzophenanthridinedione **22a** is potentially a mixture of four diastereoisomers (two are observed in ^1H NMR but as the yields are very low, it cannot be excluded that more isomers are formed), it would be interesting to separate them. Two exploratory reactions using (*S*)-*p*-toluenesulfinamide **386** as the chiral derivatisation agent towards quinone imine **387** were performed unsuccessfully.



3.5.9 Synthesis of dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-tetraones 20

In order to further explore the tetrahydrobenzo[*j*]phenanthridinedione skeleton towards a structure-activity relationship, dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **20** were synthesised. The synthesis of these 2-aza-anthraquinones **20** was effectuated by means of an oxidative

addition[219] of 6-amino-1,3-dialkyluracils **389**[220] onto 1,4-dihydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehydes **388**. The synthesis of the latter ones proceeded via boron(III) bromide mediated demethylation of the corresponding 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-6-carboxaldehydes **348a** and **348b**. The synthesis of a third derivative, bearing a 1,4-epoxy-bridge failed due to ring opening. 6-Amino-1,3-dialkyluracils **389** were synthesised from triphosgene, a primary amine and cyanoacetic acid following literature protocols.[220] All demethylation conditions[221] attempted on 5,8-dihydroxy-6-formyl-1,2,3,4-1,4-epoxytetrahydronaphthalene **348c** failed to perform this transformation. In general, the yields of the oxidative addition were lower for the short chained derivatives and higher for the longer chains. No significant differences in yields were observed between the methano- and the ethano-bridged series (Table 15). In case of 6-aminouracil **389a**, no reaction was observed even after 24 h of reaction. Dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **20** were only moderate active against *Mycobacterium tuberculosis* with MIC_{50}'s around 1-2 µg/mL but showed only modest cytotoxicity with IC_{50}'s around 15-20 µg/mL.

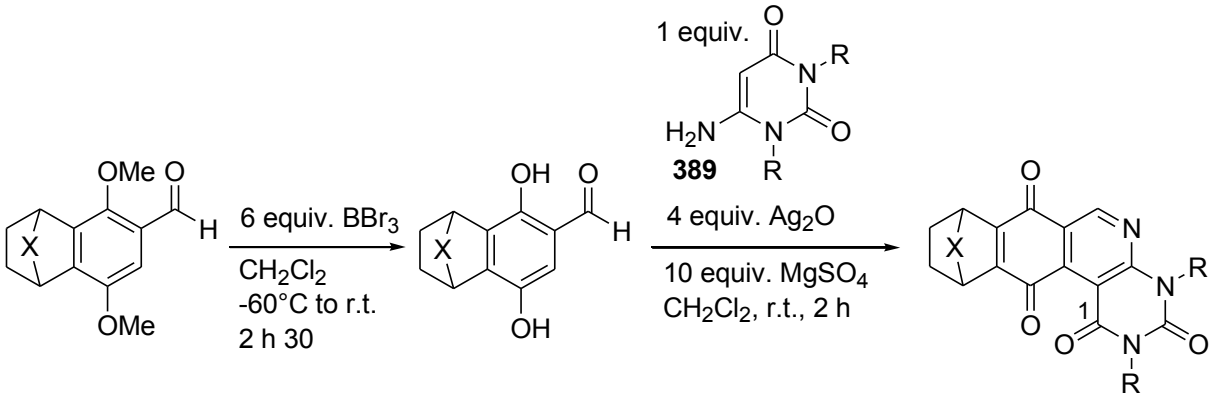
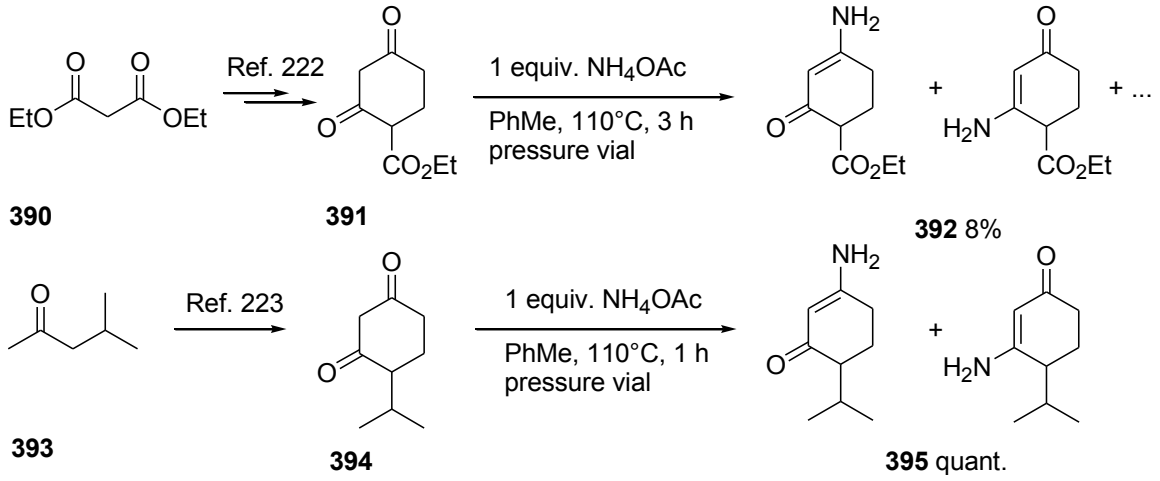


Table 15. Isolated yields for the synthesis of dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-tetraones **20**.

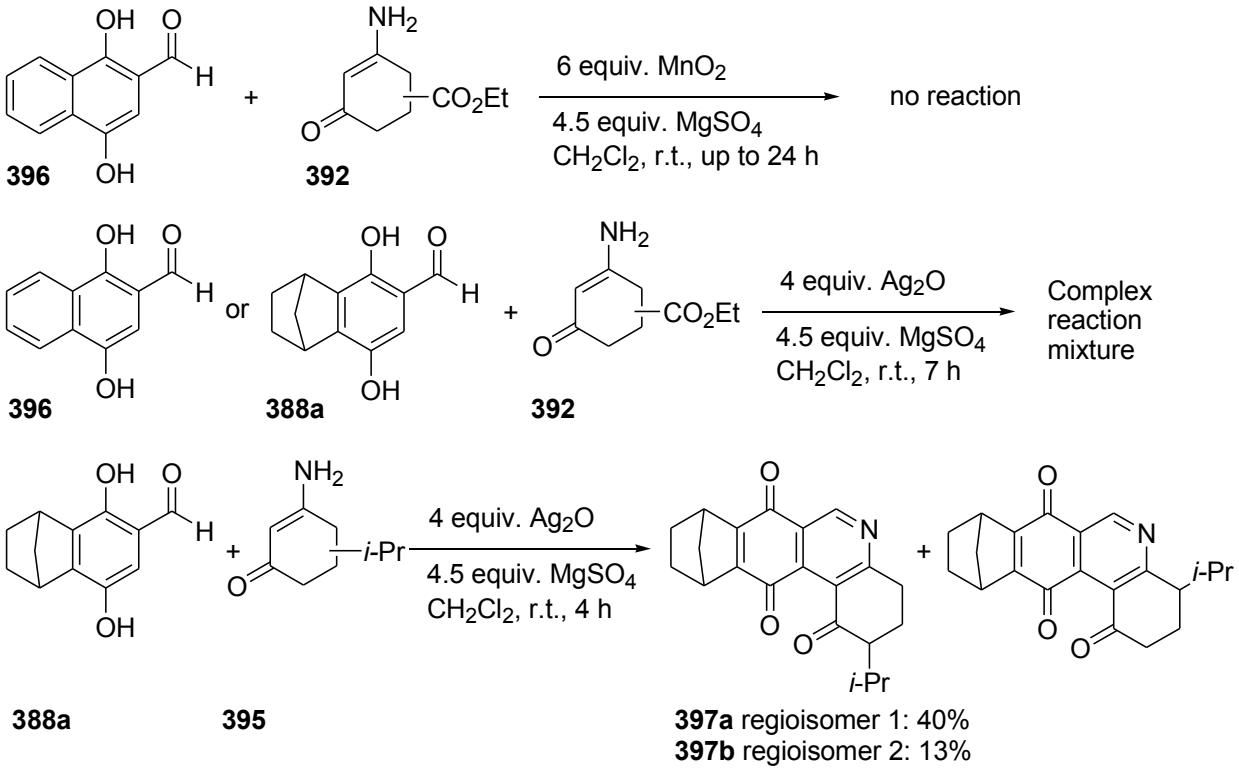
R	X			
	CH_2		CH_2CH_2	
	Compound	Yield (%)	Compound	Yield (%)
H	**20a**	-	**20l**	-
Me	**20b**	54	**20m**	48
Et	**20c**	86	**20n**	89
n-Pr	**20d**	85	**20o**	83
i-Pr	**20e**	33	**20p**	48
n-Bu	**20f**	57	**20q**	90
i-Bu	**20g**	67	**20r**	89
n-Pentyl	**20h**	71	**20s**	64
i-Pentyl	**20i**	93	**20t**	90
n-Hexyl	**20j**	93	**20u**	90
n-Heptyl	**20k**	88	**20v**	78

Next, the synthesis of alkyl and ethoxycarbonyl substituted derivatives was envisaged, mimicking the substitution pattern of lead compound **22a**. As an ester functionality in the D-ring gave a good antimycobacterial activity combined with a good therapeutic index, an ester substituted derivative was envisaged as well. Enaminones **392** and **395** were prepared from the corresponding diketones **391**[222] and **394**[223] and ammonium acetate. They were obtained as inseparable mixtures of both regioisomers. It was not possible to determine the isomeric ration by means of LC, GC or NMR.



When enaminones **392** were reacted with 1,4-dihydroxynaphthalene-2-carboxaldehyde **396** using MnO_2 as the oxidant, no reaction was observed. When the reaction was repeated with Ag_2O, a complex mixture was obtained for both 1,4-dihydroxynaphthalene-2-carboxaldehyde **396** and 5,8-dihydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxaldehyde **388a**. Oxidative addition of enaminones **395** to dihydroxynaphthalene **388a** under the conditions mentioned above yielded a mixture regioisomers **397**, which were separated by means of preparative HPLC. It was not possible to unambiguously assign the regioisomers based on 2D-NMR techniques. As the activity of compounds **397** was only moderate and no differences were observed between both regioisomers, no further derivatives were synthesised.

It should be noted that this methodology could present an alternative entry into the octahydrobenzophenanthridine core upon reduction of the C-1 carbonyl. Of course, this would only be true for symmetric diketones given the regioselectivity issue discussed above.



3.5.10 Conclusion and discussion

Benzo[*j*]phenanthridinediones **18** were identified as promising antimycobacterial leads during previous research at our research department. Starting from this lead scaffold, a wide variety of derivatives were synthesised in order to find new leads and to establish a structure-activity relation. Initially, a new and efficient synthesis of this basic scaffold was developed, which uses a intramolecular Heck reaction as the key transformation. Even though this synthetic route was designed to further decorate the benzo[*j*]phenanthridine scaffold at C-6 via the lactam function, no efficient conditions were found to do so. A major obstacle is the adjacent methoxy substituent, which does not only introduces sterical hindrance but also terns the structure more electron-rich. During this experiments, it was found that alkyllithium reagent are able to add in a 1,4 fashion across MOM-protected benzo[*j*]phenanthridines **301**. Having established this synthesis, it was applied on the synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **365**.

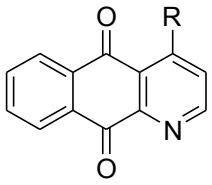
In a second part, 1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-diones **19** were synthesised by means of the reaction of a Stork enamine **340** with naphthoquinone **11** or **345** followed by ammonia mediated ring closure. As these compounds had little antimycobacterial activity, 1,2,3,4,8,9,10,11-octahydro-benzo[*j*]phenanthridine-7,12-diones **22** were synthesised by means of the same methodology. Much of these compounds showed promising antimycobacterial activity accompanied by a low cytotoxicity. The enamine methodology is not an efficient way of synthesising these compounds as the yields are in general low and there is an urgent need for an efficient synthesis of these compounds.

In a third part, 20 dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **20** were synthesised by means of an oxidative addition methodology. Even though their cytotoxicity is low, their antimycobacterial activity is only moderate.

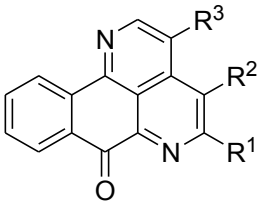
It is interesting to note that both 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **365** and 1,2,3,4,8,9,10,11-octahydrobenzo[*j*]phenanthridine-7,12-diones **22** display good antimycobacterial activity as compared to 1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-diones **19**. This is an indication that modification of the A-ring can boost activity while the D-ring appears to be less important.

3.6 Synthesis of analogues of the bioactive natural products cleistopholine 23 and sampangine 24

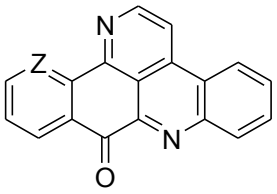
Cleistopholine **23** and sampangine **24** are two strongly related polycyclic aromatic alkaloids isolated from different plants belonging to the Annonaceae family with a wide range of interesting biological activities.[19] Cleistopholine **23** is a tricyclic 1-aza-anthraquinone alkaloid isolated from the root bark of *Cleistopholis patens*.[224a] Sampangine **24** is a tetracyclic naphthyridine alkaloid isolated from the stem bark of *Cananga odoranta*.[224b] Cleistopholine **23** showed fungitoxic activity against *Candida albicans* and *Cryptococcus neoformans,* which are opportunistic fungi in AIDS patients.[19e] In addition to exhibiting a powerful activity against *Mycobacterium intracellulare* with a minimum inhibitory concentration (MIC = 0.78 μg/ml) which is lower than the MIC for current anti-TB drugs as rifampicin **33** (MIC = 0.5-0.9 μg/ml) and streptomycin (MIC = 2-8 μg/ml),[225] sampangine **24** is known to possess strong antifungal activity.[19d] Synthetic analogues **398**, **399** and **400a** showed strong activity against *M. intracellulare*. Ascididemin **400b**, a metabolite from the marine tunicate *Didemnum sp*. is very active against the rapidly growing *M. aurum* A+ strain.[225] In the literature, a straightforward synthesis of sampangine **24** starting from cleistopholine **23** has been reported.[226]



23 R = Me
Cleistopholine
MIC = 12.5 µg/ml
398 R = Et
MIC = 12.5 µg/ml



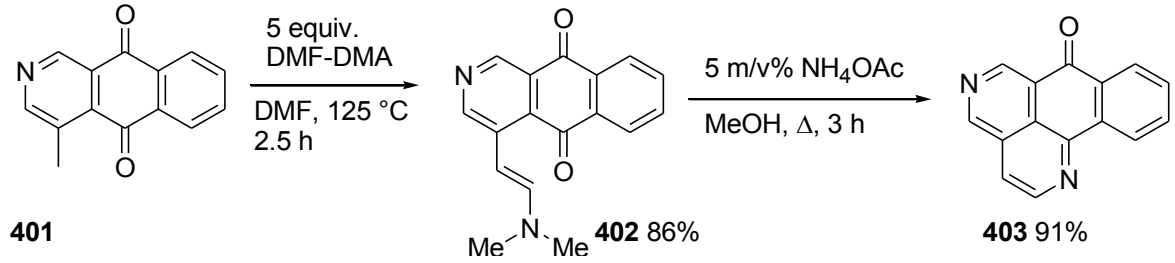
24 Sampangine: $R^1 = R^2 = R^3 = H$, MIC = 0.78 µg/ml
399a $R^1 = R^3$, R^2 = Br, MIC = 3.12 µg/ml
399b R^1 = OEt, R^2 = Br, R^3 = Br, MIC = 25 µg/ml
399c $R^1 = R^3$, R^2 = Cl, MIC = 3.12 µg/ml
399d $R^1 = R^3$, $R^2 = OCH_3$, MIC = 3.12 µg/ml
399d $R^1 = R^2$, $R^3 = OCH_3$, MIC = 1.56 µg/ml
399e $R^1 = R^2$, $R^3 = CH_3$, MIC = 0.39 µg/ml



400a Z = CH
MIC = 0.39 µg/ml
400b Ascididemin: Z = N
MIC = 0.25 µg/ml

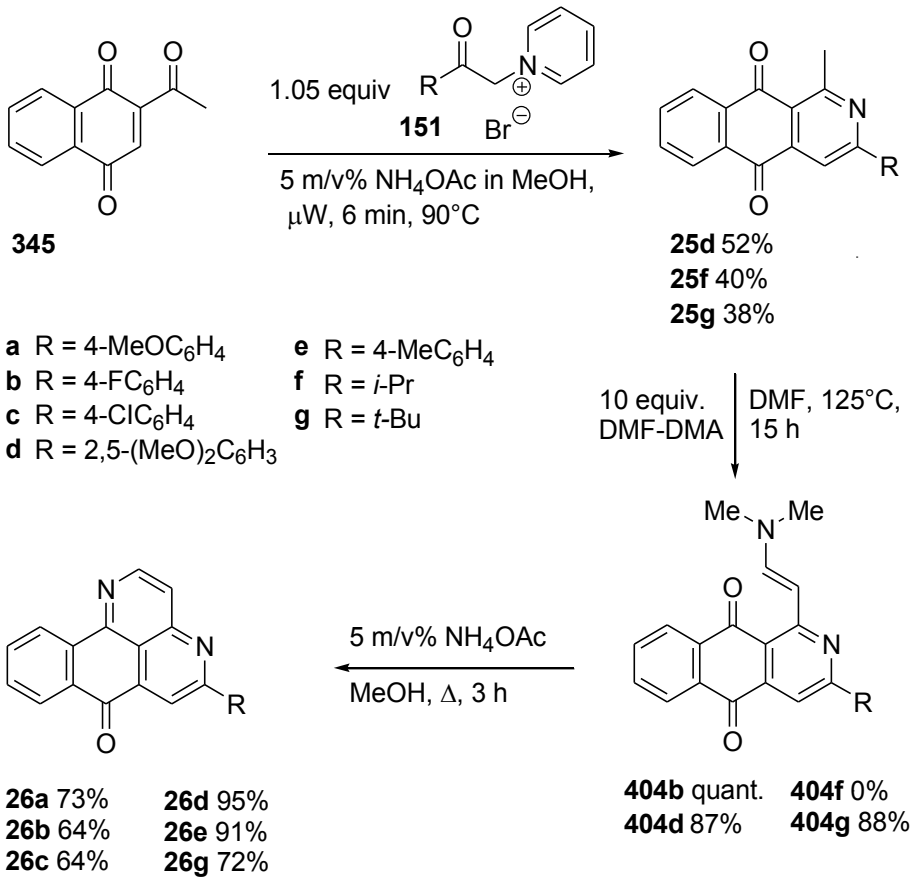
Since it is postulated that 2-aza-anthraquinones are potentially more bioactive than their corresponding 1-aza-analogues, a short and efficient synthesis of regioisomeric analogues of cleistopholine **23** and sampangine **24** was performed. Even though numerous analogues have been synthesised with the nitrogen atom at the 1-position,[19d,227] these analogues with the nitrogen atom at the 2-position have not been reported yet in the literature.

Initially, the synthesis of an unsubstituted aza-analogue of sampangine **24** was envisaged, starting from (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **402**, which was previously prepared at our research department.[228] This enamine **402** was reacted with an excess of ammonium chloride in boiling acetic acid as described in the synthesis of sampangine **24**.[226] However, a complex reaction mixture was obtained. After testing several reaction conditions, (*E*)-4-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **402** was converted in excellent yield towards unsubstituted sampangine analogue **403,** i.e. 7*H*-naphtho[3,2,1-*i,j*]-2,6-naphthiridin-6-one, by heating with ammonium acetate in methanol.



Next, the synthesis of substituted sampangine analogues **26** was envisaged starting from 3-substituted-1-methylbenzo[*g*]isoquinoline-5,10-diones **25**. The latter were prepared by applying a microwave protocol previously developed at our research department for the synthesis of 1-hydroxybenzo[*g*]isoquinoline-5,10-diones.[229] This reaction involved the Michael addition of the appropriate pyridinium ylids across the enone moiety followed by elimination of pyridine to generate

the intermediate 3-acylmethylquinones which underwent cyclisation with ammonia to provide 2-aza-anthraquinones **25**. Thus, 2-acetyl-1,4-naphthoquinone **345** and different pyridinium salts **151** were irradiated for 6 minutes in a 5 m/v% solution of ammonium acetate in methanol forming 1-methylbenzo[*g*]isoquinoline-5,10-diones **25** in 38-52% yield. Subsequently, these 2-aza-anthraquinones **25** were reacted with an excess of *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in DMF at 125°C for 15 hours to yield 3-substituted1-[2-(dimethylamino)-vinyl]benzo[*g*]isoquinoline-5,10-diones **404** in good to excellent yields with the exception of 3-isopropyl-1-methyl-2-aza-anthraquinone **25f** which was not accessible due to the formation of complex reaction mixture. Boiling under reflux of 1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **404** in a 5 m/v% solution of NH_4OAc in methanol afforded 5-substituted-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-ones **26** in 64-95% yield. As 3-substituted 1-[2-(dimethylamino)-vinyl]benzo[*g*]isoquinoline-5,10-diones **404** showed promising antimycobacterial activities, it was attempted to synthesise the corresponding 3-substituted 1-[2-(dimethylamino)-ethyl]benzo[*g*]isoquinoline-5,10-diones. However, hydrogenation of the dimethylaminovinyl group gave complex mixtures and attempts to perform Mannich type reactions starting from 1-methylbenzo[*g*]isoquinoline-5,10-diones **25** gave no reaction in all cases.[230]



During spectroscopic analysis of 1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **404**, an interesting phenomenon was observed. In ^{13}C NMR, the signals of the dimethylamino group were not

observed at 75 MHz and 25°C in none of the derivatives due to coalescence. When the system was driven to fast exchange (75 MHz, 50°C), a broad peak of low intensity was observed. No higher temperature could be applied due to decomposition of compounds **404**. When the system was driven to slow exchange and subjected to a higher field (125 MHz, -50°C), a clear resolution of both methyl peaks was observed as exemplified by 2,5-dimethoxyphenyldimethylaminovinyl-benzoisoquinolinedione **404d** and *tert*-butyldimethylaminovinylbenzoisoquinolinedione **404g**.

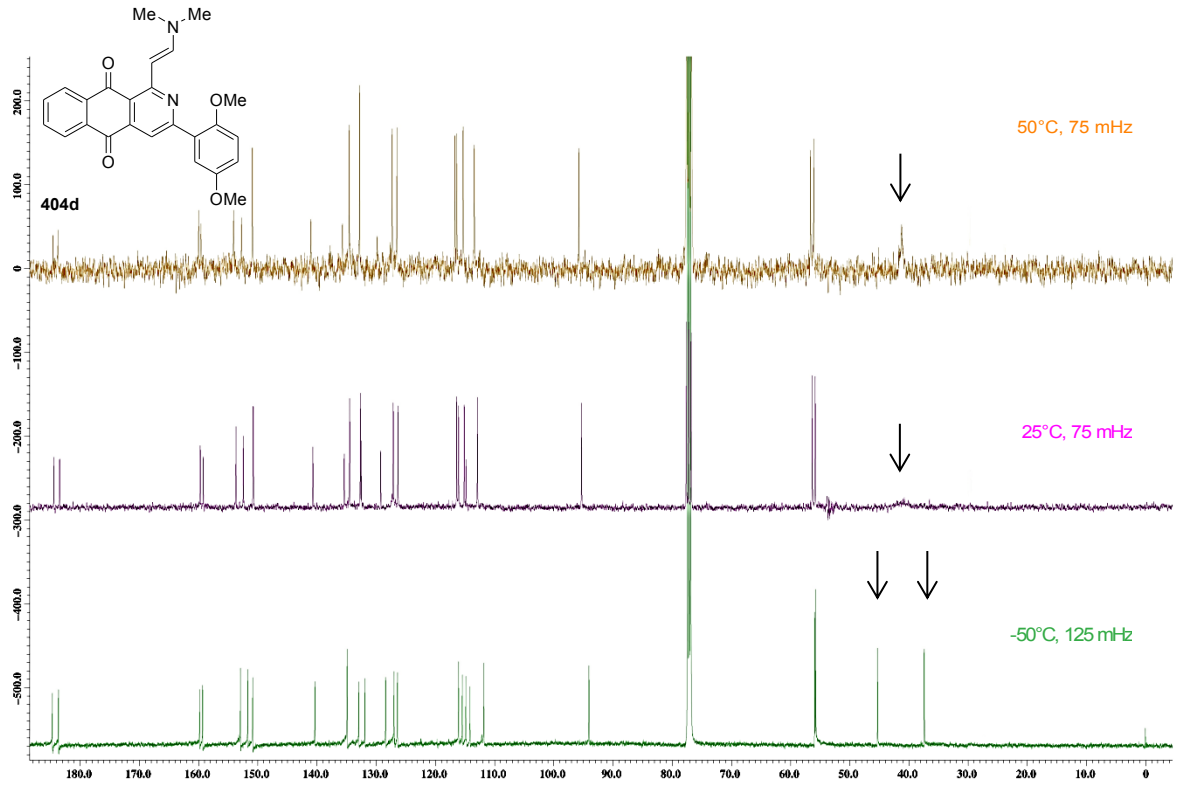


Figure 1. ^{13}C NMR spectra of 2,5-dimethoxyphenyldimethylaminovinylbenzoisoquinolinedione **404d** at 50°C, 25°C and -50°C.

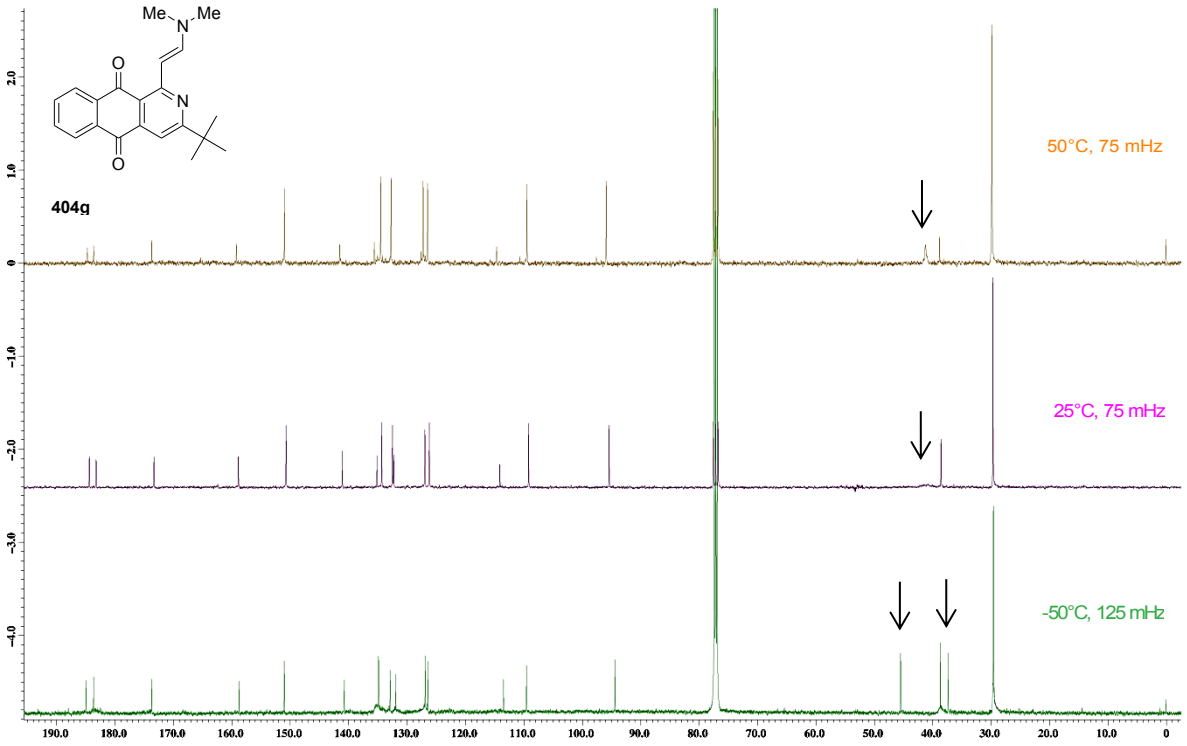


Figure 2. ^{13}C NMR spectra of *tert*-butyldimethylaminovinylbenzoisoquinolinedione **404g** at 50°C, 25°C and -50°C.

In ^{1}H NMR, a clear split-up of the methyl signal is observed as well. The low temperature spectra were recorded at the Laboratory for NMR and Structure Analysis of the Department of Organic Chemistry, Ghent University (Prof. José Martins).

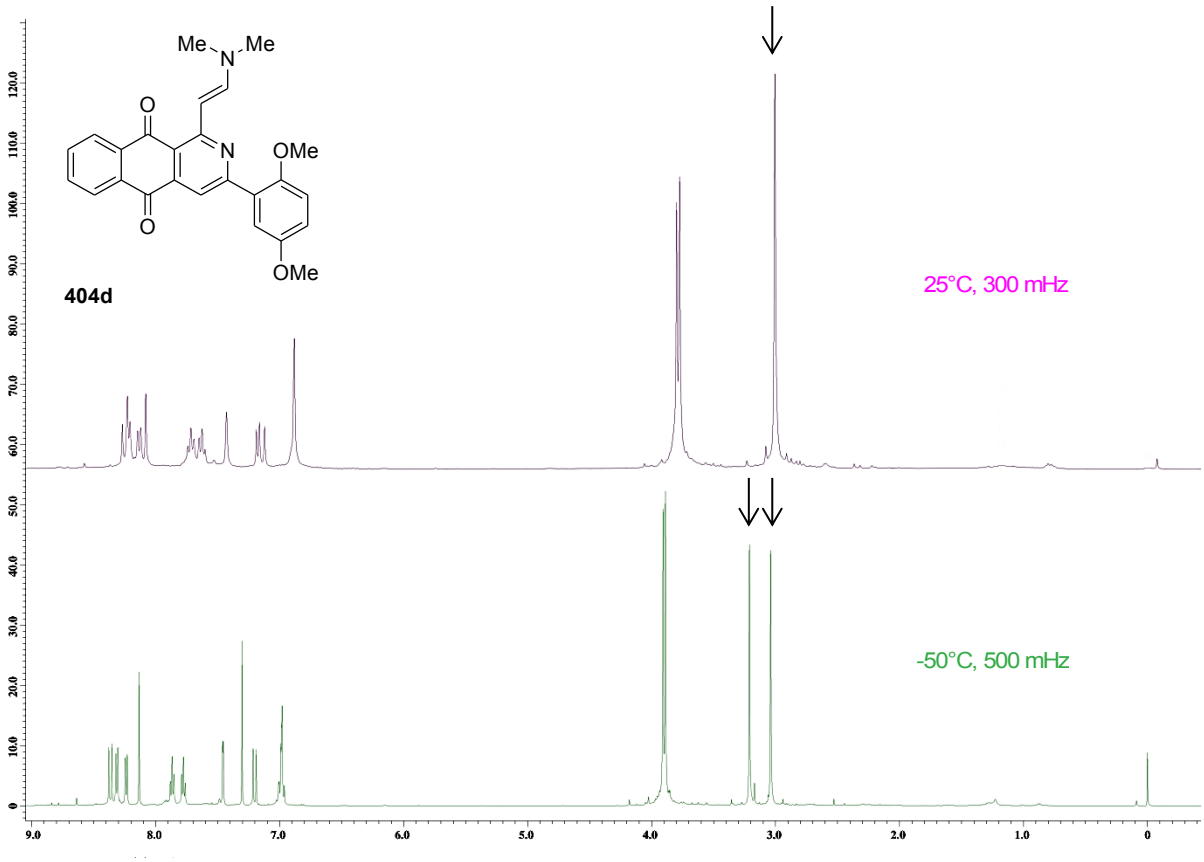


Figure 3. ^{1}H NMR spectra of 2,5-dimethoxyphenyldimethylaminovinylbenzoisoquinolinedione **404d** at 25°C and -50°C.

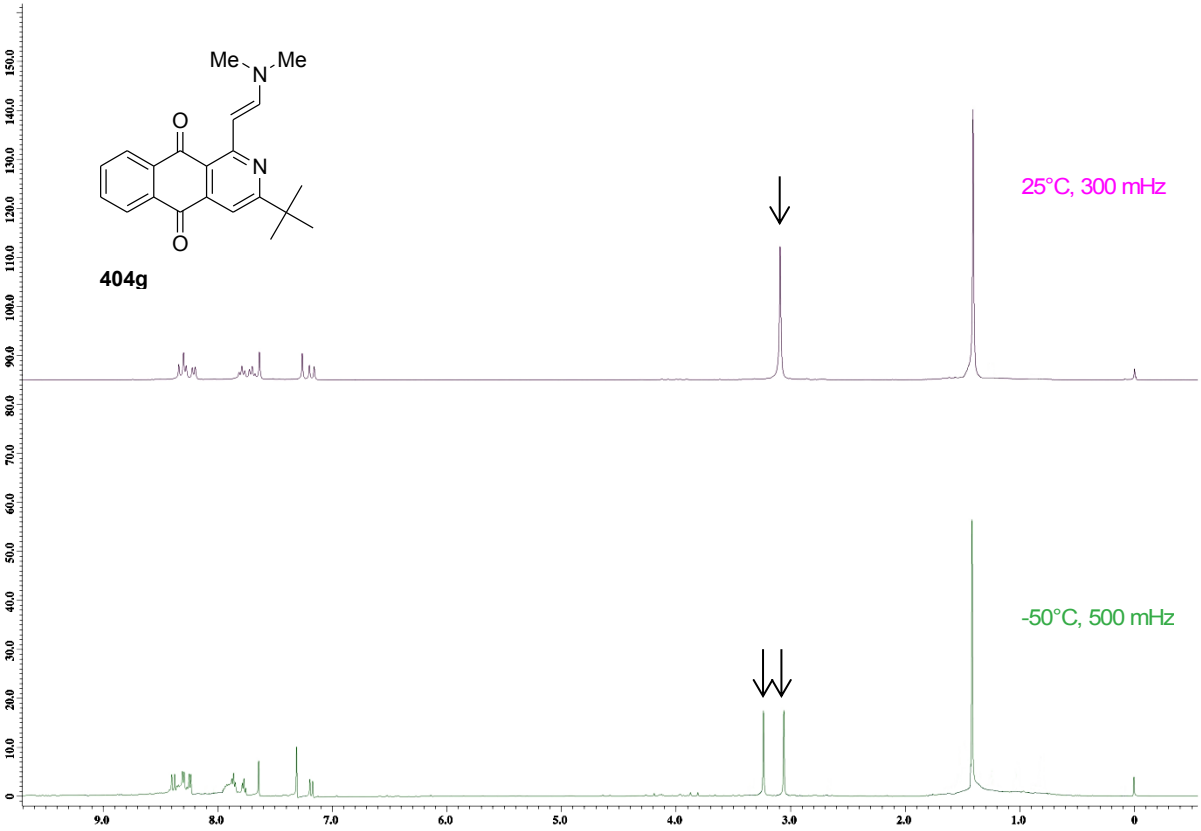
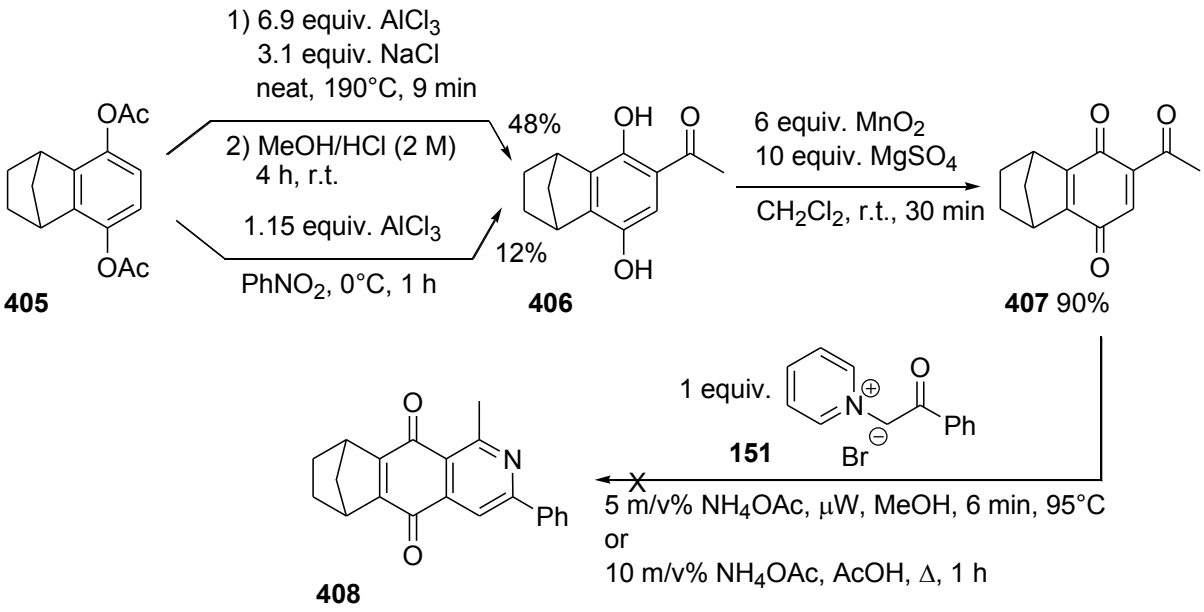


Figure 4. ^{1}H NMR spectra of *tert*-butyldimethylaminovinylbenzoisoquinolinedione **404g** at 25°C and -50°C.

Attempts to expand this methodology towards the synthesis of bridged cleistopholine analogues **408** failed for unknown reasons. A Fries rearrangement was performed on 5,8-diacetoxy-1,2,3,4-tetrahydro-1,4-methano-naphthalene **405** resulting in the corresponding 6-acetyl-1,2,3,4-tetrahydro-1,4-methano-5,8-dihydroxynaphthalenene **406** in low ($PhNO_2$) to moderate yield ($AlCl_3$/NaCl smelt). This hydroquinone **406** was oxidised with MnO_2 towards quinone **407**, which was reacted with pyridinium salt **151h** under both batch and microwave Kröhnke conditions but in both cases a complex mixture was retrieved.



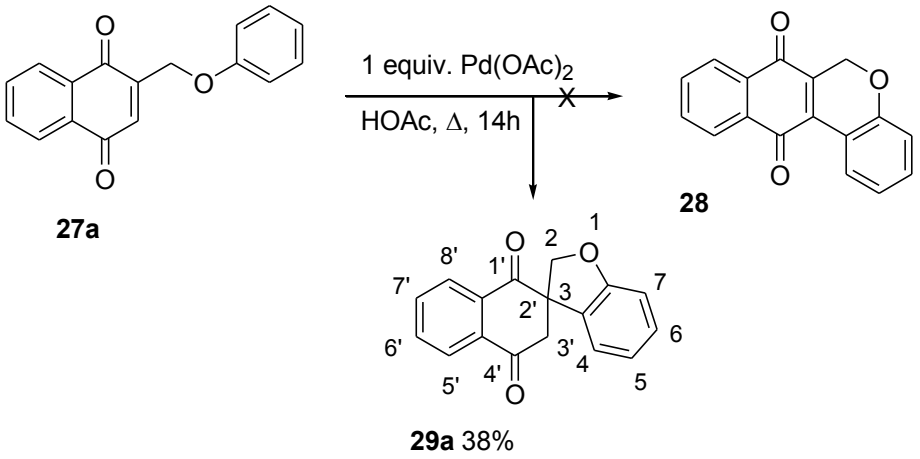
3.6.1 Conclusion

One unsubstituted and various substituted analogues of the natural products cleistopholine **23** and sampangine **24** were synthesised using pyridinium ylid and enamine chemistry. Interestingly, the intermediate enamines **371** were found to be very active with MIC_{50}'s around one micromolar and cytotoxicities around 20-40 μM and no genotoxicity (vitotox and comet assay).[231] Some reports on analogous compounds containing a 2-(dimethylamino)vinyl substituent suggested that their activity could be attributed to *in vivo* hydrolysis of the dimethylaminovinyl substituent to the aldehyde.[232] These finding pose an incentive to synthesise further derivatives of these enamines. Initial attempts to do so were unsuccessful.

3.7 Palladium(II)-catalysed synthesis of 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthoquinones] 29: novel spirocyclisation reaction of quinones.

Our research group has been involved substantially in the synthesis of bioactive heterocyclic quinones and related natural products.[102,104a,233] During a study of tetracyclic benzopyranonaphthoquinone **28**, its synthesis was envisaged by means of a palladium(II)-catalysed intramolecular oxidative coupling.[234] Thus, 2-phenoxymethyl-1,4-naphthoquinone **27a** was reacted with one equivalent of palladium(II) acetate in boiling acetic acid for 14 hours, yielding a single compound. Surprisingly, the obtained compound contained two aliphatic CH_2's and had the same mass as 2-phenoxymethyl-1,4-naphthoquinone **27a**. Moreover, a trisubstituted olefinic carbon was present at 58 ppm (^{13}C-NMR, $CDCl_3$), indicative of an aliphatic trisubstituted olefinic centre next to an electron withdrawing group

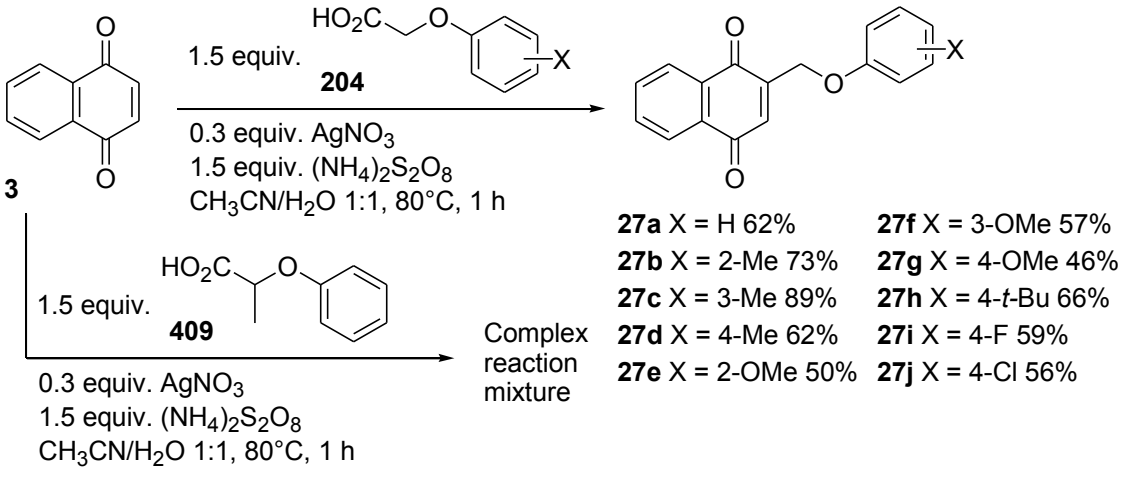
or atom. Thus, the molecular skeleton of spirocyclisation product 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthalene]-1',4'-dione **29a**, which was isolated in 38% yield, was proposed.



In the present study, this surprising reaction was thoroughly investigated. To the best of our knowledge, the 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthoquinone] structural motif concerns a novel heterocyclic skeleton. Even though several methods to synthesise structurally similar spiroheterocyclic compounds exist in the literature, the oxygen atom is always directly connected to the spirocyclic carbon.[235]

3.7.1 Synthesis of the starting 2-aryloxymethyl-1,4-naphthoquinones 27

The starting 2-aryloxymethyl-1,4-naphthoquinones **27** were synthesised by means of a radical aryloxymethylation of naphthoquinone **3** using phenoxyacetic acids **204** in water with ammonium persulfate as a radical initiator and a catalytic amount of $AgNO_3$ as a radical transfer agent.[236] In order to assure full solubility of the starting phenoxyacetic acids **204**, acetonitrile had to be added as a cosolvent. Thus, 2-aryloxymethyl-1,4-naphthoquinones **27a-j** were synthesised in 46-73% yield. In case of naphthalen-2-yloxyacetic acid, naphthalen-1-yloxyacetic acid, 2,3-dimethylphenoxyacetic acid and 2-phenoxypropionic acid **409**, a complex mixture was retrieved. Phenoxyacetic acids **204** were either commercially available or synthesised from chloroacetic acid and the appropriate phenol.



It was attempted to apply this radical alkylation reaction on the synthesis of 2-phenylaminomethyl-1,4-naphthoquinone **412**. An initial attempt with anilinoacetic acid **410a** led to a complex mixture. When *N*-acetylanilinoacetic acid **410b** was deployed, overalkylation occurred, as the monoalkylated product was soluble in the reaction medium.

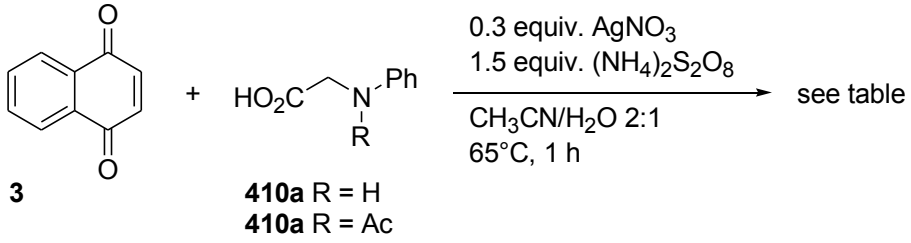
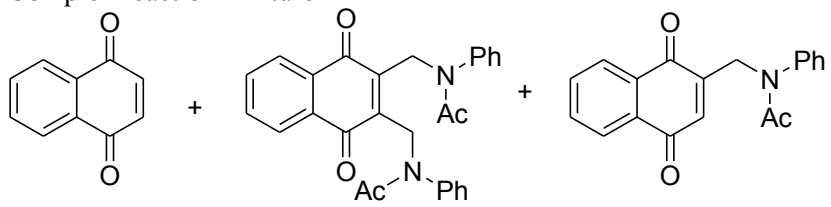


Table 16. Attempted radical alkylation of 1,4-naphthoquinone **3** with anilinoacetic acids **410**.

R	Result
H	Complex reaction mixture
Ac	
	3 22% **411** 10% **412a** 11%

3.7.2 Investigation and optimisation of the reaction conditions

From a mechanistic point of view, it must be noted that contrary to the oxidative coupling of quinones with arenes, the spirocyclisation product **29a** is no oxidation product and, as a consequence, there should be no need for a reduction of the palladium catalyst.

Initially, it was investigated whether or not the spirocyclisation could be a Friedel-Crafts type reaction by reacting a myriad of hard and soft metal salts with 2-phenoxymethyl-1,4-naphthoquinone **27a** in glacial acetic acid. None of the tested metal salts, *i.e.* LiCl, $MgBr_2$, $TiCl_4$, $(NH_4)_2Ce(NO_3)_6$, $FeCl_3$, $AgNO_3$, $AlCl_3$, $NiCl_3$, $Co_2(SO_4)_3$, $SnCl_4$ and $Cu(OTf)_2$, yielded the desired spiroquinone **29a** (Table 17). Strong acids, such as CF_3COOH, *p*-TsOH, H_2SO_4 or TfOH did not effectuate the desired conversion either. However, in some cases (entries 3, 5, 7 and 10) the rearranged 2-(4-hydroxybenzyl)-1,4-naphthoquinone **413a** was formed in a low to good yield by means of a Claisen type rearrangement. Interestingly, only the *para*-substituted product could be isolated without any trace of the *ortho*-substituted compound. Even though some examples of Claisen rearrangements of allyloxybenzene derivatives are known in literature,[237] none of them is uniquely *para*-selective. When titanium(IV) chloride was deployed, 2-chloromethyl-1,4-naphthoquinone **414** was found to be the major reaction product.

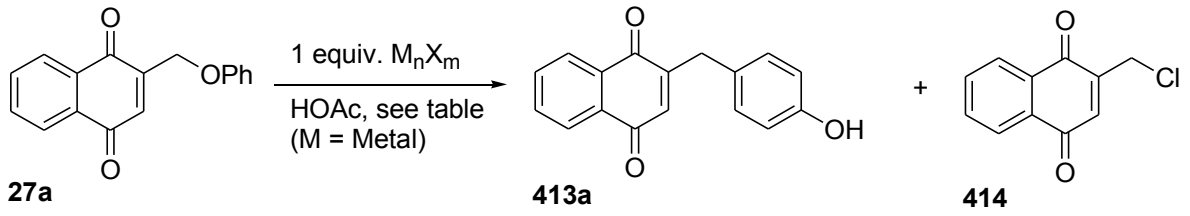
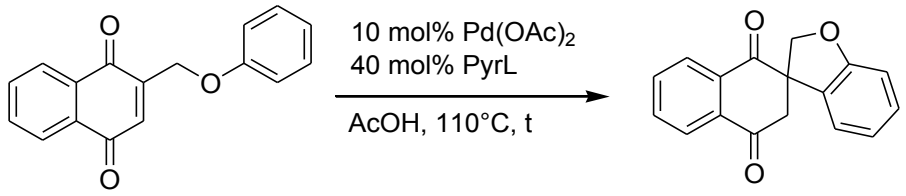


Table 17. Reaction of metal salts with 2-phenoxymethyl-1,4-naphthoquinone **27a** in acetic acid. The reaction conditions were gradually increased in strength until conversion or a complex reaction mixture was obtained. When no conversion was observed after two days of boiling under reflux, the reaction was stopped.

Entry	M_nX_m	Reaction conditions	Result	Entry	M_nX_m	Reaction conditions	Result
1	LiCl	Δ, 15 h	Complex reaction mixture	6	$AgNO_3$	Δ, 15 h	No conversion
2	$MgBr_2$	Δ, 15 h	Complex reaction mixture	7	$AlCl_3$	Δ, 5 h	**413a** 12%
3	$TiCl_4$	r.t., 6 h	**413a** 14% + **414** 68%	8	$NiCl_3 \cdot 6H_2O$	Δ, 2 d	No conversion
4	CAN	Δ, 15 h	Complex reaction mixture	9	$Co_2(SO_4)_3 \cdot 7H_2O$	Δ, 2 d	No conversion
5	$FeCl_3$	Δ, 5 h	**413a** 12%	10	$SnCl_4$	r.t., 15 h	**413a** 80%
				11	$Cu(OTf)_2$	Δ, 1 h	Complex reaction mixture

As quinones oxidise Pd(0) to Pd(II), palladium-catalysed reactions in quinone chemistry are limited to Pd(II)-catalysis.[238] Therefore, it was attempted to optimise the conversion following the reaction conditions reported by Stolz *et al*.[239], *i.e.* 40 mol% of ethyl nicotinate and 10 mol% of $Pd(OAc)_2$ in *tert*-amyl alcohol/AcOH 4:1. Disappointingly, no conversion of **27a** was observed (Table 18, entry 1). It appeared that no matter which ligand was used, the palladium complex only remained stable in pure acetic acid and decomposed in all other solvents or combinations thereof (*tert*-amyl alcohol/AcOH 4:1, DMF, DMA or pinacolone). Together with the fact that addition of one equivalent of NaOAc leads to a complex mixture (entry 2), it can be concluded that a protic acid should play a crucial role in the reaction mechanism. It is clear that the more electron poor the ligand, the faster the initial reaction. However, most reactions end prematurely due to decomposition of the palladium complex (entries 5-8) and a compromise has to be made between catalyst stability and reactivity. Only 3,5-dichloropyridine (entry 4) lead to full conversion but the reaction was very sluggish and took 12 days to attain completion. When ligands were introduced bearing 2 coordinating nitrogen atoms such as 2,2'-bipyridines or phenanthrolines, little (entry 9) or no conversion (entries 10-13) towards spiroquinone **29a** was observed. Also the conditions recently reported by Li *et al*.,[240] in which 20

mol% of *N*-acetyl glycine is used as the ligand and hexafluoroisopropanol as the solvent, were tested but no significant conversion was observed even when the solvent was changed to acetic acid.



27a **29a**

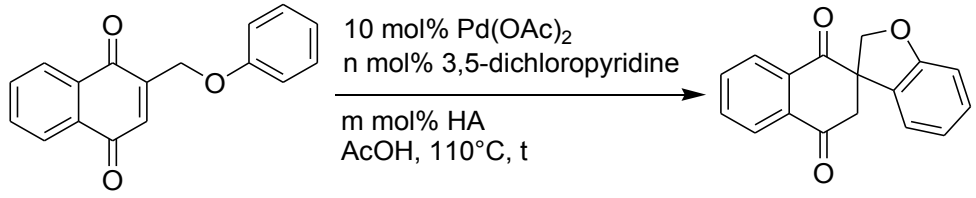
Table 18. Ligand screening for the spirocyclisation reaction using 40 mol% pyridine ligand in acetic acid.

Entry	PyrL	pK_a ($PyrLH^+$)[241]	$PyrlH^+$ (%)*	t	Result**
1	ethyl nicotinate	3.35	88,7	20 h	No conversion to **29a**
2	ethyl nicotinate + 1 equiv. NaOAc	3.35	88,7	20 h	Complex reaction mixture
3	pyridine-3-carbonitrile	1.39	24,1	23 h	No reaction
4	3,5-dichloropyridine	0.90	14,5	12 d	**29a** (53%)
5	5-bromo-2-chloropyridine	-0.61	2,7	20 h	29% conversion to **29a**
6	2,5-dichloropyridine	-0.79	2,2	7 h	26% conversion to **29a**
7	2,6-dibromopyridine	-2.22	0,4	18 h	15% conversion to **29a**
8	2-chloro-3-nitropyridine	-2.35	0,4	23 h	<10% conversion to **29a**
9	2,2'-bipyridinyl	4.34, 0.70	98,6	15 h	<10% conversion to **29a**
10	4,4'-dibromo-2,2'-bipyridinyl	2.20, -0.44	49,7	15 h	No conversion to **29a**
11	2,2'-bipyridinyl-3,3'-dicarboxylic acid	1.40, -1.24	24,3	15 h	No conversion to **29a**
12	1,10-phenanthroline-5,6-dione	1.45, -1.17	25,5	15 h	No conversion to **29a**
13	5-chloro-1,10-phenanthroline	3.91, -0.48	96,3	15 h	No conversion to **29a**

* Calculated at 25°C assuming that [AcOH] >> [AcO^-], for the dibasic species only pK_{a1} was taken into account.
** All reactions were monitored by LC-MS and stopped when no further conversion was observed.

When the amount of ligand was varied between 10 and 40 mol%, the reaction time could be reduced to seven days using 15 or 30 mol% of ligand (Table 19, entries 2 and 5) without lowering the yield. For further experiments, it was decided to work with 15 mol% of ligand, which corresponds with a calculated 23% protonation at 25°C. When 5 to 15 mol% of trifluoroacetic acid (TFA) were added, the reaction time could be reduced to four days. When 5 mol% of TFA was used, compound **29a**, was obtained in 62% yield (entry 7), while more TFA led to lower yields (entries 8 and 9). The addition of stronger acids (*p*-toluenesulfonic acid, methanesulfonic acid or trifluoromethanesulfonic acid) led to significant decomposition of the palladium complex and no full conversion was observed after four

days. Replacement of TFA by the higher boiling heptafluorobutyric acid (HFBA) did not result in an increased yield (entry 10).



27a **29a**

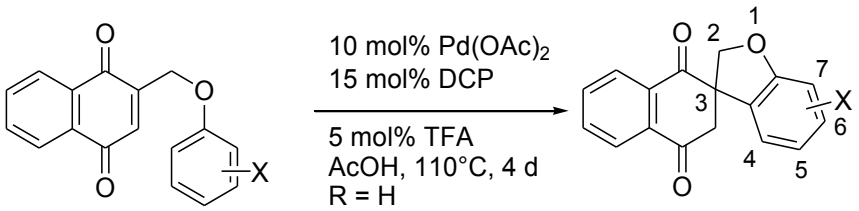
Table 19. Fine-tuning of the catalytic cycle for the spirocyclisation reaction towards spironaphthoquinone **29a**.

Entry	n	m	HA	t (d)	Yield (%)	Entry	n	m	HA	t (d)	Yield (%)
1	10	-	-	7	38	6	40	-	-	12	53
2	15	-	-	7	53	**7**	**15**	**5**	**TFA**	**4**	**62**
3	20	-	-	9	30	8	15	10	TFA	4	42
4	25	-	-	8	38	9	15	15	TFA	4	35
5	30	-	-	7	52	10	15	5	HFBA	4	49

HFBA = $CF_3(CF_2)_2COOH$

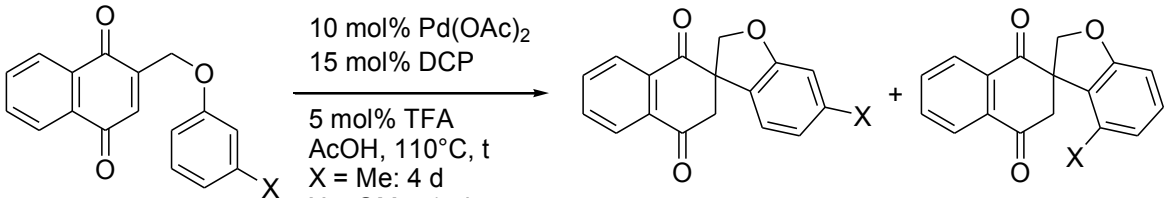
3.7.3 Synthesis of further derivatives and proposed reaction mechanism

The yield of the spirocyclisation reaction was strongly dependent on the substitution pattern of the aryloxy group of the starting 2-(aryloxymethyl)-1,4-naphthoquinones **27**. While *meta*- and *para*-substituted aryloxy groups gave spiroquinones **29** in good yields, little (**27b**) or no (**27e**) conversion was observed in the case of *ortho*-substituted aryloxy groups. Replacement of acetic acid by hexafluoroisopropanol did not give any reaction either. Apart from the fact that only one reactive position is available for cyclisation, there is no satisfying explanation so far for this observation. In case of *meta*-substituted compounds, regioisomers were formed in a ratio of about 5:1. Interestingly, in case of naphthoquinone **27f**, the reaction was finished after only 15 h. This is attributed to the electron donating properties combined with the sterically favoured position of the methoxy group. Solubility might also play a key role as 2-aryloxymethyl-1,4-naphthoquinones have a low to very low solubility in acetic acid and solubilisation often only occurs at 90-100°C. For instance 2-(2,4-dichlorophenoxymethyl)-1,4-naphthoquinone fails to react under the presented conditions as it does not dissolve in boiling acetic acid. When tetrachloroethene is added as a cosolvent to obtain full dissolution, no reaction is observed. This highlight the importance to perform the reaction in pure acetic acid. Other apparent differences in yield based on the electronic nature of the substituents were not observed.



27

29a X = H 62%
29b X = 7-Me 21%
29d X = 5-Me 68%
29e X = 7-OMe (no reaction)
29g X = 5-OMe 59%
29h X = 5-*t*-Bu 71%
29i X = 5-F 53%
29j X = 5-Cl 69%

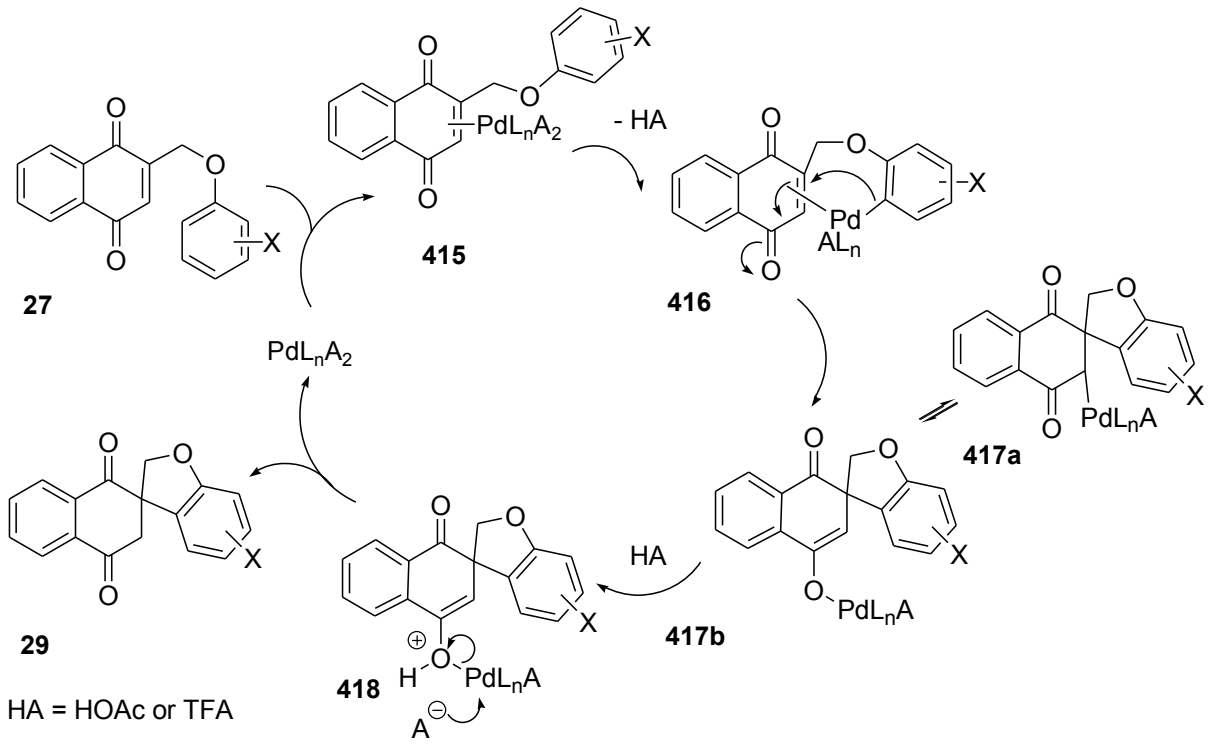


27c X = Me
27f X = OMe

29ca X = Me 51%
29fa X = OMe 61%

29cb X = Me 11%
29fb X = OMe 13%

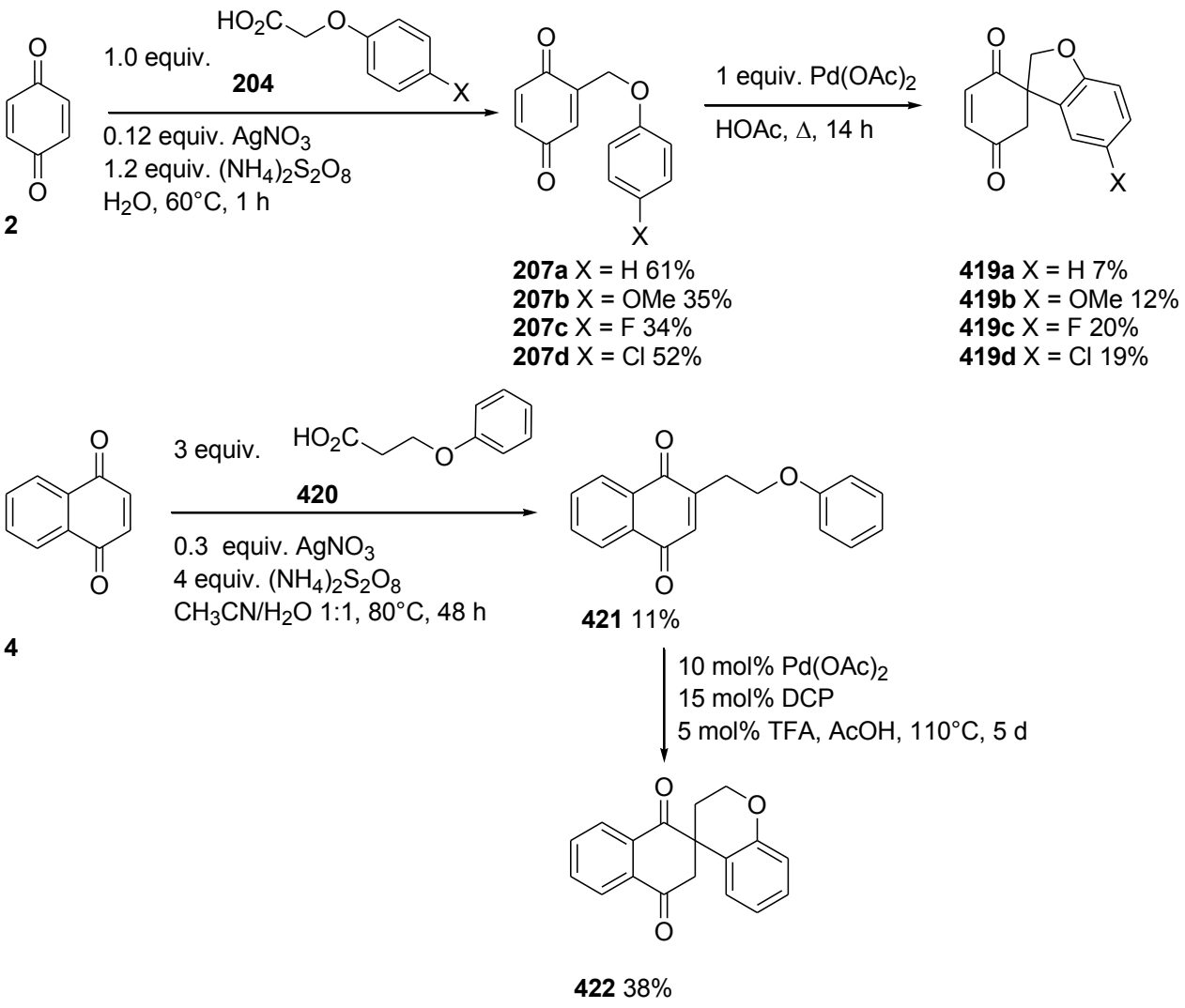
Based on the abovementioned observations, a reaction mechanism is proposed. Initial coordination of the palladium catalyst with the naphthoquinone moiety, which behaves as a π-acid ligand, increases the electron deficiency of the palladium centre.[242] Arene palladation of naphthoquinone-Pd(II)-complex **415** leads to organopalladium intermediate **416**. This intermediate **416** will undergo an intramolecular Michael addition leading to palladium enolate **417a**.[238c,243,244] Acid-mediated regeneration of the palladium complex followed by tautomerisation finally leads to spiroquinone **27**. It is believed that the addition of TFA accelerates the hydrolysis of palladium enolate **417b**, thus giving rise to shorter reaction times. It should be noted that the reaction is a cyclo-isomerisation and does not need a co-oxidant as most other palladium(II) catalysed reactions.[238,245]



3.7.4 Alternative substrates for the spirocyclisation reaction

3.7.4.1 2-aryloxymethyl-1,4-benzoquinones 207 and 2-(2-phenoxyethyl)-1,4-naphthoquinone 421

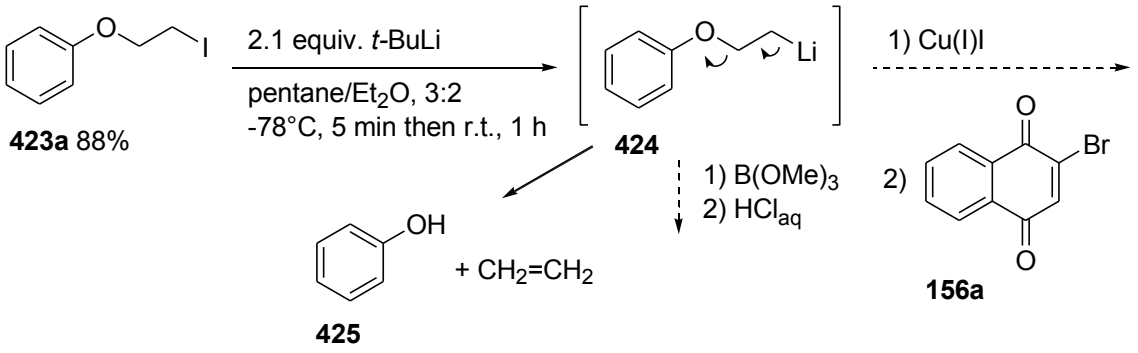
Application of the optimised spirocyclisation conditions to 2-aryloxymethyl-1,4-benzoquinones **207** lead to complex reaction mixtures. 2*H*,3'*H*-Spiro[benzofuran-3,2'-benzoquinones] **419** could only be synthesised using a full equivalent of palladium(II) acetate in boiling acetic acid in low yields. This is attributed to the high reactivity of the benzoquinone moiety, which also explains the lower yields of the radical alkylation reaction as compared to 2-aryloxymethyl-1,4-naphthoquinones **27**. The spirocyclisation reaction of 2-(2-phenoxyethyl)-1,4-naphthoquinone **421** was found to be significantly slower than the one of phenoxymethyl-1,4-naphthoquinone **27a** and was stopped after five days. From this reaction, 3'*H*-spiro[chroman-3,2'-naphthalene]-1',4'-dione **422** was isolated in 38% yield, together with 22% of starting material **421**.



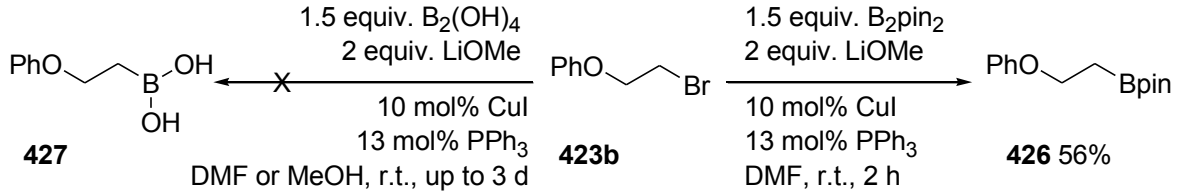
3.7.4.2 Attempted alternative syntheses towards 2-(2-phenoxyethyl)-1,4-naphthoquinone 421

The synthesis of phenoxyethyl-1,4-naphthoquinone **421** was previously described at our research department[15] but is low yielding as the intermediate radical is not stabilised. Alternatives were sought to find a one- or two-step synthesis with an acceptable yield. Both organocuprate addition across 2-bromo-1,4-naphthoquinone and various Suzuki-coupling reaction conditions were investigated.

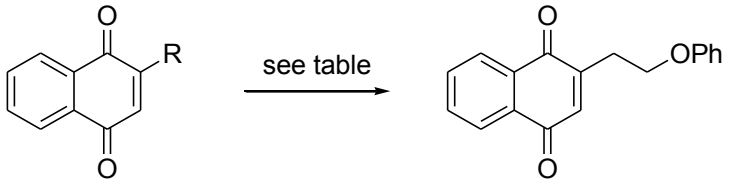
When lithium-iodine exchange[246] was performed on 2-iodoethyl phenyl ether **423a**, the corresponding alkyllithium readily decomposed by the formation of phenol and ethylene, making the formation of organocuprates or borates in this way impossible.



By means of Cu(I) catalysis, 4,4,5,5-tetramethyl-2-(2-phenoxyethyl)-1,3,2-dioxaborolane **426** was prepared starting from 2-bromoethyl phenyl ether **423b**.[247] Using the same procedure, it was not possible to prepare boronic acid **427**.



However, under standard Suzuki coupling conditions, both decomposition of boronic ester **426** and addition of water onto 2-bromo-1,4-naphthoquinone 1**56a** were observed (Table 20, entries 1 and 2). Therefore, reactions should be conducted at room temperature in the presence of a minimal amount of H_2O. An initial attempt at room temperature using tricyclohexylphosphine did not yield any product (entry 3). Also the reaction between 1,4-naphthoquinone-2-boronic acid **428**[248] and 2-bromoethyl phenyl ether **423b** did not give any result (entries 4-6).



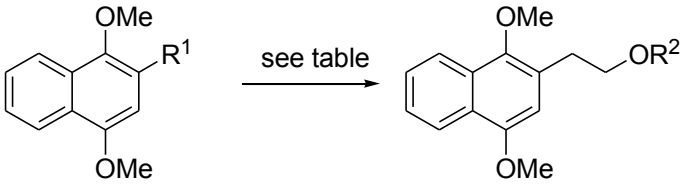
156a R = Br
428 R = $B(OH)_2$

421

Table 20. Attempted reaction conditions for the conversion of quinones **156a** and **428** into phenoxyethoxynaphthoquinone **421**.

Entry	R	Reagents	Conditions	Result
1	Br	1.25 equiv. $BpinCH_2CH_2OPh$ 3.5 equiv. K_2CO_3 5 mol% $Pd(OAc)_2$ 10 mol% PPh_3	PhMe/H_2O 20:1, 110°C, 3 h	No reaction
2	Br	1.25 equiv. $BpinCH_2CH_2OPh$ 3.5 equiv. K_3PO_4 5 mol% $Pd(OAc)_2$ 10 mol% PPh_3	PhMe/H_2O 20:1, 110°C, 3 h	No reaction
3	Br	1.25 equiv. $BpinCH_2CH_2OPh$ 1.3 equiv. $K_3PO_4 \cdot H_2O$ 4 mol% $Pd(OAc)_2$ 8 mol% PCy_3	THF, r.t., up to 4 d	No reaction
4	$B(OH)_2$	0.66 equiv. $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu 5 mol% $Pd(OAc)_2$ 10 mol% PCy_3	1,4-dioxane, r.t., 24 h	No reaction
5	$B(OH)_2$	0.66 equiv. $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu 5 mol% $Pd(OAc)_2$ 10 mol% PCy_3	*t*-AmylOH, r.t., 24 h	No reaction
6	$B(OH)_2$	0.66 equiv. $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu 5 mol% $Pd(OAc)_2$ 10 mol% $PCy_3 \cdot HBF_4$	*t*-AmylOH, r.t., 24 h	No reaction

Alternatively, no reaction was observed upon Pd(0)- or Cu(I)-catalysed reaction of 1,4-dimethoxynaphthalene-2-boronic acid **429a** with 2-bromoethyl phenyl ether **423b** using room temperature Suzuki reaction protocols (Table 21, entries 1-4).[249] Also ortholithiation of 1,4 dimethoxynaphthalene **429b** was attempted. As direct reaction of the corresponding aryllithium with 2-bromoethyl phenyl ether **423b** would result in various side reactions such as lithium-halogen exchange and elimination, the use of the corresponding cuprates or zincates was envisaged. Unfortunately, ortholithiation followed by Li-Cu or Li-Zn[250] exchange and reaction with 2-bromoethyl phenyl ether **423b** was unsuccessful (entries 5-6) and only elimination products could be retrieved. In case of a chain extension with 1,2-ethylene sulfate (1,3,2-dioxathiolane-2,2-dioxide) as a C-2 building block,[251] a trace amount of the desired product could be observed in both cases (entries 7-8).



429a R^1 = $B(OH)_2$ **430a** R^2 = Ph
429b R^1 = H **430b** R^2 = OH

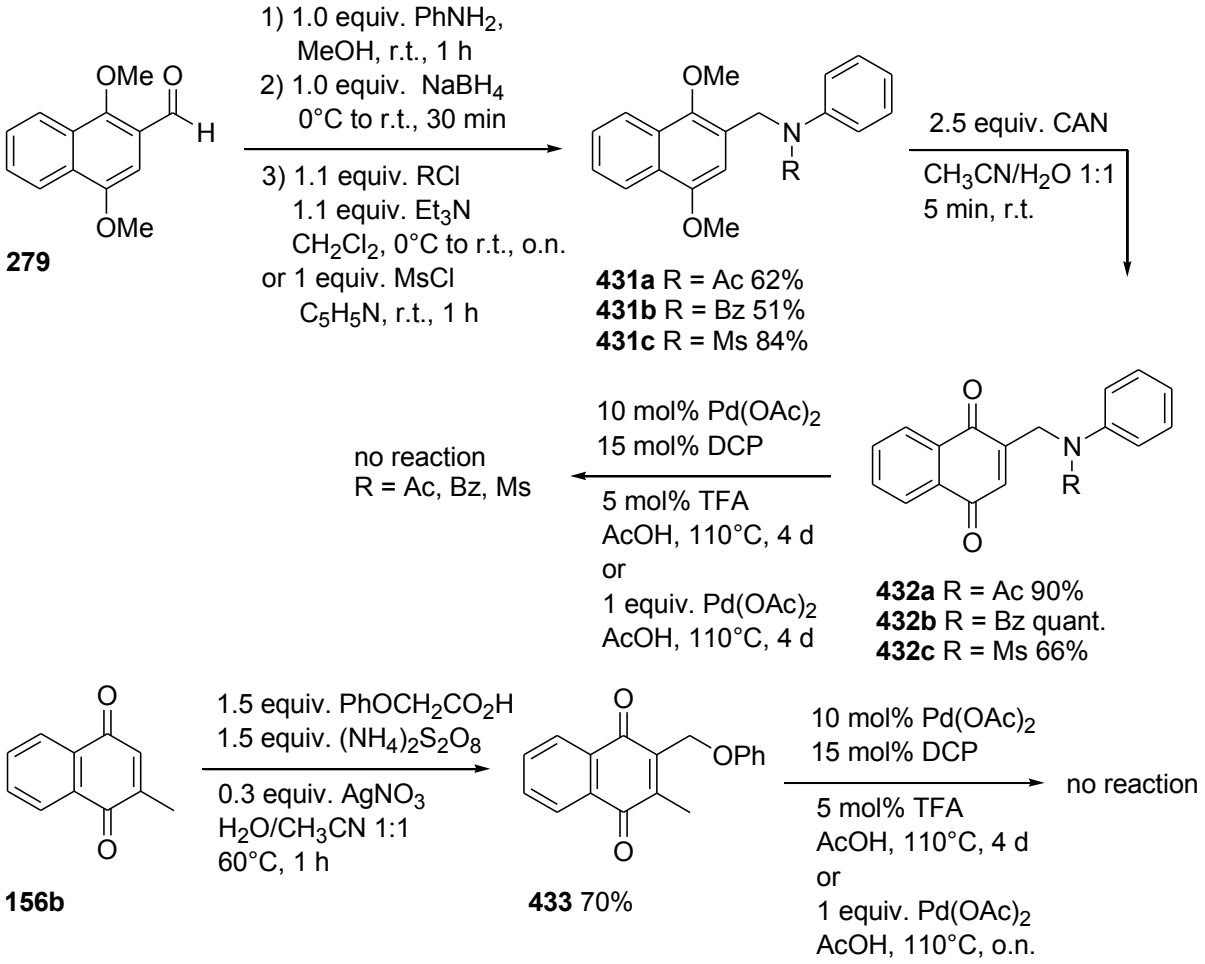
Table 21. Attempted conversion of naphthalenes **429** in phenoxy- or hydroxyethylnaphthalenes **430**.

Entry	R^1	Reagents	Conditions	R^2	result
1	$B(OH)_2$	5 mol% $Pd(OAc)_2$ 10 mol% $PCy_3 \cdot HBF_4$ 0.66 or 3 equiv. $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu	1,4-dioxane, r.t., o.n.	Ph	No reaction
2	$B(OH)_2$	5 mol% $Pd(OAc)_2$ 10 mol% PCy_3 0.66 equiv. $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu	*t*-AmylOH, r.t., 24 h	Ph	No reaction
3	$B(OH)_2$	5 mol% $Pd(OAc)_2$ 10 mol% $PCy_3 \cdot HBF_4$ 0.66 $BrCH_2CH_2OPh$ 3 equiv. KO*t*-Bu	*t*-AmylOH, r.t., 24 h	Ph	No reaction
4	$B(OH)_2$	10 mol% CuI 13 mol% PPh_3 1 equiv. $BrCH_2CH_2OPh$ 2 equiv. LiOMe	DMF, r.t., o.n.	Ph	No reaction
5	H	1) 1.5 equiv. *n*-BuLi 2) 2 equiv. CuX 3) 2 equiv. XCH_2CH_2OPh X = Br, I	0°C, 4 h, THF 0°C, 1 h, THF -78°C to r.t., o.n., THF	Ph	No reaction
6	H	1) 1.5 equiv. *n*-BuLi 2) 1.05 equiv. $ZnCl_2$ 3) 1 equiv. $BrCH_2CH_2OPh$	0°C, 4 h, THF 0°C, 1 h, THF -78°C to r.t., o.n., THF	Ph	No reaction
7	H	1) 1.5 equiv. *n*-BuLi 2) 1.2 equiv. ethylene sulfate 3) H_2SO_4 (3.4 M)	0°C, 4 h, THF -78°C to r.t., 1 h, THF Δ, 2 d	OH	trace
8	H	1) 1.5 equiv. *n*-BuLi 2) 1.2 equiv. ethylene sulfate 3) 2 equiv. PhOH	0°C, 4 h, THF -78°C to r.t., 1 h, THF PhMe, Δ, 2 d	Ph	trace

3.7.4.3 2-Anilinomethylnaphthoquinones 432 and 2-methyl-3-phenoxymethyl-1,4-naphthoquinone 433

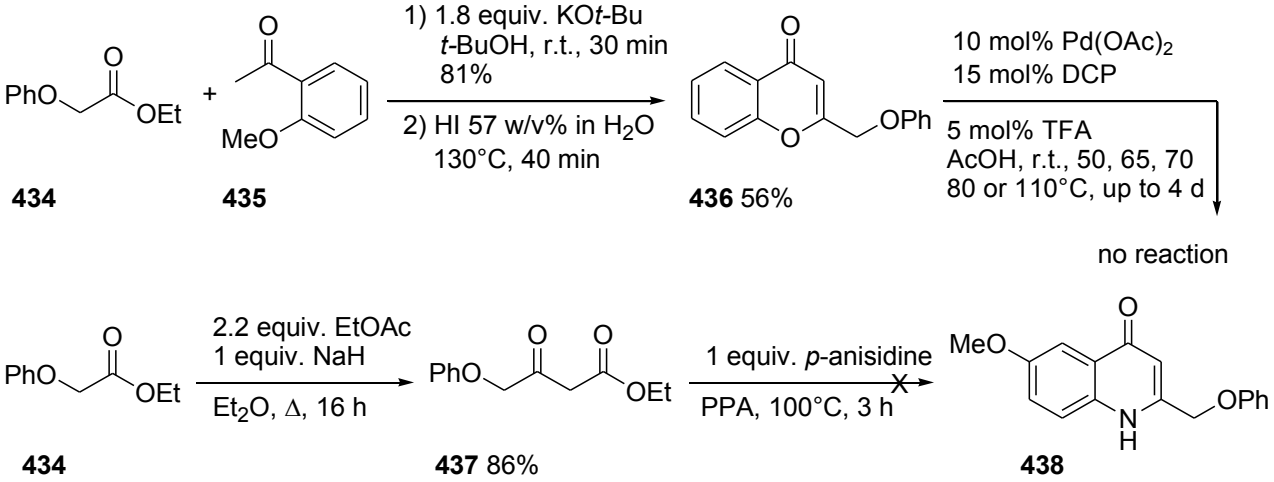
N-Mesyl-, *N*-acetyl- and *N*-benzyl-protected anilinomethylnaphthoquinones **432** were prepared via oxidative demethylation of anilinomethyldimethoxynaphthalenes **431**. These compounds **431** were prepared by means of a reductive amination of naphthaldehyde **279** with aniline followed by *N*-protection with an acyl chloride or mesyl chloride. 2-Methyl-3-phenoxymethyl-1,4-naphthoquinone **433** was prepared using the radical alkylation conditions as described above. None of these substrate

gave rise to a spirocyclisation reaction neither under the catalytical conditions nor using a full equivalent of $Pd(OAc)_2$.



3.7.4.4 Non-quinoid substrate: 2-phenoxymethylchromen-4-one 436

Further alternative substrates for the spirocyclisation reaction were evaluated. Starting from ethyl phenoxyacetate **434** and 2-methoxyacetophenone **435**, 2-phenoxymethylchromen-4-one **436** was synthesised in two steps following a literature protocol.[264] Attempts to make the corresponding *N*-analogue **438** by means of a condensation reaction of *para*-anisidine and β-ketoester **437**[252] resulted in a complex mixture.

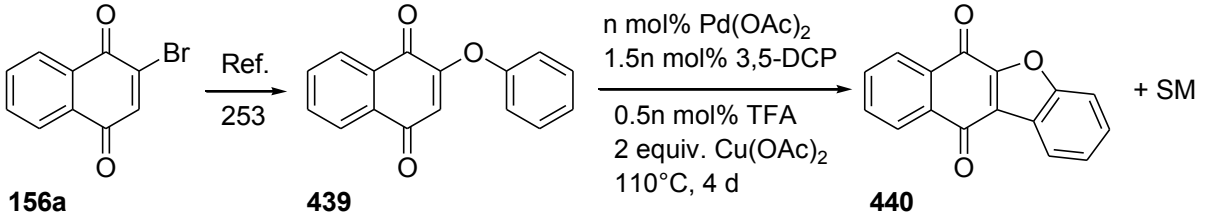


434 **435** **436** 56% **437** 86% **438**

3.7.4.5 2-phenoxynaphthoquinone 439

When 2-phenoxynaphthoquinone[253] 439 **was subjected to the spirocyclisation conditions, a small amount of benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione** 440 **was formed. Even though this compound is known in the literature, the synthesis is a long multistep sequence having a low overall yield.[254] It was attempted to raise the amount of product formed by adding a co-oxidant. When 1,4-benzoquinone** 2 **was used as a co-oxidant, a complex mixture was obtained, while using $Cu(OAc)_2$, a 3:1 mixture of starting material/product was obtained and this did not change even upon refluxing for 12 days (**

Table 22, entry 1). Systematically raising the amount of catalyst (and thus ligand and additive) resulted in full conversion and isolation of benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440** in 67% yield upon the use of 40 mol% $Pd(OAc)_2$ (entry 4).

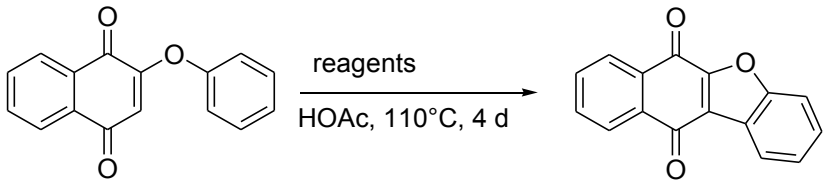


156a **439** **440**

Table 22. Conversion of 2-phenoxynaphthoquinone **439** in benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440** by increasing the reagent loading.

Entry	n	Result	Entry	n	Result
1	10	**439**/**440** 3:1, isolated yield **440** <10%	3	30	**439**/**440** 3:1
2	20	**439**/**440** 3:1	4	40	**439**, 67% isolated yield

Control experiments were performed to check whether all reagents are necessary. From Table 23, it can be deduced that $Cu(OAc)_2$ is not an adequate co-oxidant as addition of this reagent only results in a 5% increase of the conversion. Also no significant change in conversion was observed upon omission of the pyridine ligand.



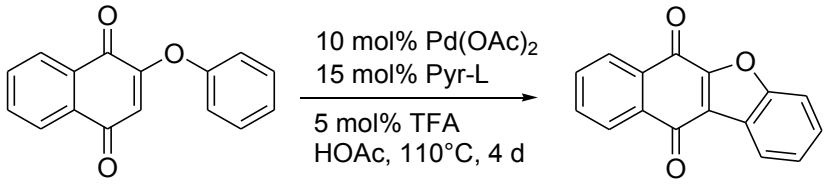
439 **440**

Table 23. Control experiments for the palladium mediated conversion of 2-phenoxynaphthoquinone **439** in benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440**.

Entry	Reagents	Conversion[1]	Entry	Reagents	Conversion[1]
1	40 mol% $Pd(OAc)_2$	23%	4	40 mol% $Pd(OAc)_2$ 2 equiv. $Cu(OAc)_2$	11%
2	60 mol% DCP	0	5	40 mol% $Pd(OAc)_2$, 60 mol% DCP 2 equiv. $Cu(OAc)_2$	24%
3	40 mol% $Pd(OAc)_2$ 60 mol% DCP	19%			

[1] Monitored by ^{1}H NMR

In order to find better conditions, pyridine ligands were screened as described above but none could match the initial 3,5-dichloropyridine (Table 24).

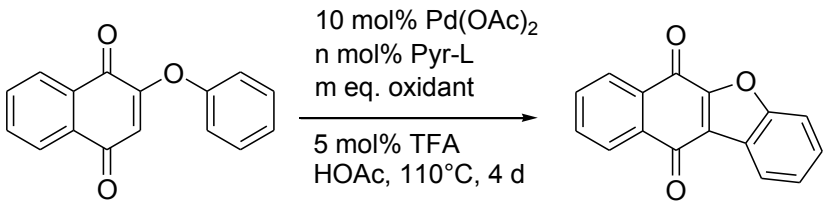


439 **440**

Table 24. Ligand screening for the conversion of 2-phenoxynaphthoquinone **439** in benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440**.

Entry	Pyr-L	Result	Entry	Pyr-L	Result
1	Ethyl nicotinate	No reaction	4	Pyridine	No reaction
2	3-Cyanopyridine	Trace	5	Ethyl isonicotinate	Trace
3	5-Bromo-2-fluoropyridine	Trace	6	2-Acetylpyridine	Trace

Next to alternative ligands, alternative co-oxidants were evaluated. Apart from the traditional metal derived oxidants (Table 25, entries 1, 3, 5), also pyridine-*N*-oxides[255] (entries 2 and 4) were evaluated. None of them yielded favourable results.



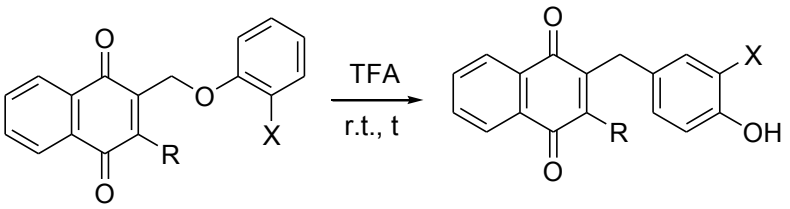
439 **440**

Table 25. Screening for alternative co-oxidants for the conversion of 2-phenoxynaphthoquinone **439** in benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440**

Entry	n	Pyr-L	m	Oxidant	Result
1	15	Pyridine-2,6-dicarboxylic acid	2	$Cu(OAc)_2$	Trace
2	-	-	2,15	Pyridine-*N*-oxide	No reaction, Pd mirror
3	15	3,5-dichloropyridine	4	MnO_2	21% conversion
4	15	3,5-dichloropyridine	2	DCP-*N*-oxide	22% conversion
5	15	3,5-dichloropyridine	2	CAN	Trace

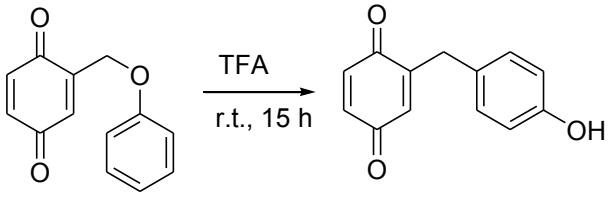
3.7.5 Unexpected Claisen-type rearrangement of 2-aryloxymethyl-1,4-quinones 27 and 207a

During the reaction optimisation it was found that when 2-phenoxymethyl-1,4-naphthoquinone **27a** was stirred overnight at room temperature in pure TFA, 2-(4-hydroxybenzyl)-1,4-naphthoquinone **413a** was formed in 74% yield as the sole reaction product. All attempts to execute this Claisen type rearrangement on aryloxymethylnaphthoquinones **27** bearing a *meta*- and *para*-substituted aryloxy group gave complex mixtures. Aryloxymethylnaphthoquinones **27b** and **27e** bearing an *ortho*-substituted aryloxy group did react via this Claisen rearrangement pathway to provide the corresponding phenols **413b** and **413c** but in case of 2-(2-methoxyphenoxymethyl)-1,4-naphthoquinone **27e** the yield was low due to formation of several side products. For 3-methyl-2-phenoxymethyl-1,4-naphthoquinone **433**, the Claisen rearrangement did occur but only after three days and resulted in the formation of 2-(4-hydroxybenzyl)-3-methyl-1,4-naphthoquinone **413d** in 60% yield. Claisen rearrangement of 2-phenoxymethyl-1,4-benzoquinone **207a** afforded 2-(4-hydroxybenzyl)-1,4-benzoquinone **441a** in 64% yield. No reaction was observed upon treatment of *N*-mesyl-, *N*-acyl- or *N*-benzoyl-2-phenylaminomethyl-1,4-naphthoquinones **432** or 2-phenoxymethylchromen-4-one **436** with TFA.



27a R = H, X = H
27b R = H, X = Me
27e R = H, X = OMe
433 R = Me, X = H

413a R = H, X = H, t = 15 h 74%
413b R = H, X = Me, t = 15 h 73%
413c R = H, X = OMe, t = 15 h 42%
413d R = Me, X = H, t = 3 d 60%



207a **441a** 64%

3.7.6 Conclusion and discussion

A new spiroheterocyclic molecular skeleton was synthesized starting from 2-aryloxymethyl-1,4-naphthoquinones **27** and 2-(2-phenoxyethyl)-1,4-naphthoquinone **421** using palladium(II)-catalysis. Under optimal conditions, 10 mol% of palladium(II) acetate, 15 mol% of 3,5-dichloropyridine and 5 mol% of trifluoroacetic acid in acetic acid at 110°C were used. Good yields were obtained for *meta*- and *para*- substituted aryloxymethyl-1,4-naphthoquinones **27**. Alternative substrates were evaluated for this novel reaction. Where 2-(2-phenoxyethyl)-1,4-naphthoquinone **421** cyclised under the presented conditions, 2-aryloxymethyl-1,4-benzoquinones **207** only cyclised using a full equivalent of palladium(II) acetate. No reaction was observed for 2-anilinomethylnaphthoquinones **432**, 2-methyl-3-phenoxymethyl-1,4-naphthoquinone **433** or 2-phenoxymethylchromen-4-one **436**. When 2-phenoxynaphthoquinone **439** was subjected to the spirocyclisation conditions, a small amount of benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **440** was formed. This reaction could not be optimised.

From a mechanistic point of view, it is interesting to note that the reaction of 2-(3-methoxyphenoxymethyl)-1,4-naphthoquinone **27f** is more than six times faster than the other 2-aryloxy-1,4-naphthoquinones **27**. This might be an indication that some mechanistic details are still poorly understood and that there are still alternative substrates that would be a better match for this reaction.

Unsubstituted or *ortho*-substituted 2-aryloxymethyl-1,4-quinones **27**, **207a**, **433** were found to rearrange towards the corresponding 2-(4-hydroxyaryl)-1,4-quinones **413** and **441a** upon treatment with trifluoroacetic acid.

4 Perspectives

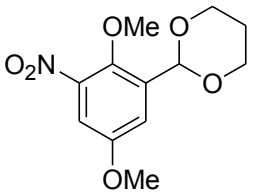
During this doctoral research, very divergent topics from the realm of quinone chemistry were discussed, of which many are work in progress.

The catalytic version of the pyridinium ylid chemistry developed in this thesis provides a valuable tool for the quinone chemist. It should allow the synthesis of the Mansouramycins **16** starting from building block **442**, which is readily accessible starting from 4-methoxysalicaldehyde.

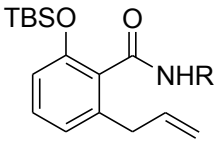
The methyllithium or LDA mediated ring-closure of 2-allyl-6-*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamides towards 8-dimethylamino-1-naphtholes provides a new entry into this class of compounds. The scope of this reaction should be further explored. For instance, it would be interesting to investigate the reactivity of 2-allyl-6-*tert*-butyldimethylsilanyloxy-*N*-alkylbenzamides **443**.

Amongst the results discussed, especially octahydrobenzo[*j*]phenanthridinediones **22** deserve further attention from biochemists and synthetic chemists. Even though these compounds **22** display highly promising antimycobacterial activities, the synthesis currently presented is low yielding, whereas a high yielding synthesis is a prerequisite to obtain sufficient amounts of material to further explore biological properties such as mode of action and pharmacokinetics. A more efficient synthesis of octahydrobenzo[*j*]phenanthridinediones **22** will very likely involve enamine chemistry, for instance by reaction of a hydroxymethyl-1,4-naphthoquinone with an enamine. Enamines are favoured reagents as they are readily accessible, react regioselectively with the quinone chromophore and allow for easy derivatisation of the lead structure. Furthermore, the 8,11-bridge in the A-ring seems to play an important role in boosting activity while cytotoxicity is reduced. In order to investigate this, the synthesis of non-bridged octahydrobenzo[*j*]phenanthridinedione derivatives should be performed. Apart from varying the substituents, it would also be interesting to synthesise derivatives with an expanded or reduced D-ring **444** in order to identify the prerequisite elements for activity and thus the pharmacophore. It is also very important to note that only pharmacodynamics were under investigation while pharmacokinetics are of course equally important. Quinones are highly lipophilic and notoriously insoluble compounds. It will therefore be necessary to add a polar carrier to the molecule and for instance the synthesis of quinone-lysine conjugates would be an interesting future goal.

The palladium(II) catalysed spirocyclisation of 2-aryloxymethyl-1,4-naphthoquinones leads to the synthesis of a spiroheterocyclic skeleton which was previously unknown in the literature. In order to explore the full scope of this reaction, further substrates should be evaluated that would be a better match for this reaction. For instance 3-aryloxymethyl-2-cyclopentenone or 3-aryloxymethyl-2-cyclohexenones **445** would be interesting substrates for further investigation.



442



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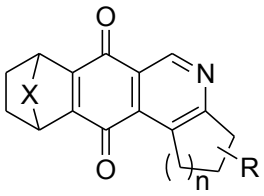
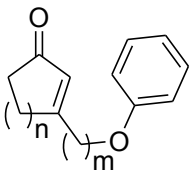


444



445

5 Experimental section

5.1 General experimental methods

Column chromatography was carried out using a glass column with silica gel (Aldrich, particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Preparative TLC was performed on uniplate™ silica plates (F_{254}, 20x20 cm, coating 2 mm). Automated flash chromatography was performed on a Reveleris® X2 Flash Chromatography System. Solvent systems were determined via initial TLC analysis on silica gel (Merck, Kieselgel 60F_{254}, precoated 0.25 mm). Compounds were revealed by UV light or $KMnO_4$ oxidation. ^1H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{19}F NMR (282 MHz) spectra were recorded with a Jeol JNM-EX 300 NMR spectrometer. Peak assignments were performed with the aid of the DEPT, 2D COSY, HSQC, HMBC techniques. The NMR samples were prepared with commercially available deuterated solvents with $SiMe_4$ (^1H and ^{13}C NMR), $BF_3{\cdot}OEt_2$ (^{11}B NMR) or $CFCl_3$ (^{19}F NMR) as an internal standard. Low resolution mass spectra were recorded using an Agilent 1100 series VS (ESI, 4000 V) mass spectrometer via a direct inlet or via LC-MS coupling [Phenomenex luna column; 250x3 mm length, 5 µm particle size, 100 A pore size with 5 mM NH_4OAc in H_2O and acetonitrile as eluents]. High resolution mass spectra were recorded on a Finnigan MAT 95 XPAPI-GC-Trap tandem mass spectrometer or a tandem spectrometer Agilent 6220 TOF-LC/MS. Infrared spectra were recorded with a Perkin Elmer BX FT-IR spectrometer. Melting points were recorded on a Buchi Melting point B-540 apparatus or a Wagner & Munz Hot bench, Kofler system and are uncorrected. Microwave reactions were performed in a CEM Discover® microwave. CH_2Cl_2, DMF, EtOAc, *tert*-AmylOH and CH_3CN were distilled over CaH_2, PhMe, Et_2O and THF were distilled from sodium benzophenone ketyl and methanol was dried by distillation over magnesium/iodine. All reagent were used without further purification and all glassware was oven-dried prior to use. All alkyllithium reagents used were titrated prior to use with *N*-benzylbenzamide in anhydrous THF.[256] Reaction progress was monitored by means of LC-MS of GC-FID.

5.2 Catalytic addition of pyridinium ylids

5.2.1 Synthesis of 1-(2-hydroxyethoxy)pyranonaphthoquinones 13

Pyridine (0.174 mmol, 19 µL, 0.2 equiv.) was added dropwise to a solution of 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **11** (0.2 g, 0.873 mmol), the desired halomethylketone **12** (0.873 mmol, 1.0 equiv.) and Na_2CO_3 (1.31 mmol, 129 mg, 1.5 equiv.) in CH_3CN (3.5 ml). The reaction mixture was stirred at room temperature for 22 h and subsequently heated at 60 °C for 22 h, shielded from light by means of aluminium foil. It was then poured in brine (8 ml) and the aqueous phase was extracted with chloroform (3x4 ml). Evaporation of the solvent *in vacuo* yielded the product which was further

purified by means of column chromatography on silica gel (petroleum ether/ethyl acetate). For chloromethylketones **12h** and **12j**, KI was added (0.087 mmol, 14.4 mg, 0.1 equiv.) and the reaction mixture was heated for two days at 60 °C. 1-Bromo-3-methyl-2-butanone **12i** was not commercially available and was prepared according to a literature procedure.[257] Most compounds have been described during previous research,[258] with the exception of the following compounds:

3-(4-Bromophenyl)-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-dione 13c

32%, mp 187.5°C, red crystals. ^{1}H NMR ($CDCl_3$): δ 3.09 (1H, br s, $CH_2O\underline{H}$), 3.67-3.81 (2H, m, CH_2O), 3.99-4.06 (1H, m, $C\underline{H}_aCH_bO$), 4.10-4.17 (1H, m, $CH_aC\underline{H}_bO$), 6.68 (1H, s, CH-1), 6.89 (1H, s, CH-4), 7.59 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.71 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.71-7.83 (2H, m, 2xCH_{Ar}), 8.10-8.18 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 62.20 (CH_2O), 70.85 (CH_2O), 93. 31 (CH-4), 95.25 (CH-1), 122.26 (C_{quat}), 125.68 (C_{quat}), 126.38 (CH_{Ar}), 126.89 (CH_{Ar}), 127.64 (2xCH_{Ar}), 131.82 (C_{quat}), 132.02 (C_{quat}), 132.15 (2xCH_{Ar}), 132.69 (C_{quat}), 133.77 (CH_{Ar}), 134.49 (CH_{Ar}), 136.90 (C_{quat}), 157.97 (C_{quat}), 182.81 (2xC=O). IR (ATR): ν 3472 (OH), 1673 (C=O), 1649, 1543, 1484, 1270 (C-O), 1306 cm^{-1}. MS (ES$^-$) *m/z* (%): 425/427 ([M-H]$^-$, 100/98).

3-(2,5-Dimethoxyphenyl)-1-(2-hydroxyethoxy)-1*H*-benzo[*g*]isochromene-5,10-dione 13f

52% (LC), mp 152.2°C, dark red crystals. ^{1}H NMR ($CDCl_3$): δ 3.15 (1H, t, J = 6.9 Hz, $CH_2O\underline{H}$), 3.80 (2H + 3H, m + s, CH_2O + CH_3O), 3.93 (3H, s, CH_3O), 3.95-4.07 (1H, m, $C\underline{H}_aCH_bO$), 4.10-4.17 (1H, m, $CH_aC\underline{H}_bO$), 6.67 (1H, s, CH-1), 6.93 (1H, d, J = 9.4 Hz, CH-3'), 6.98 (dd, J = 9.4 Hz, 2.8 Hz, CH-4'), 7.35 (1H, s, CH-4), 7.41 (1H, d, J = 2.8 Hz, CH-6'), 7.70-7.80 (2H, m, 2xCH_{Ar}), 8.12-8.16 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.91 (CH_3O), 56.23 (CH_3O), 62.27 (CH_2O), 70.72 (CH_2O), 94.81 (CH-1), 98.47 (CH-4), 112.76 (CH-3'), 114.02 (CH-6'), 117.18 (CH-4'), 121.78 (C_{quat}), 122.58 (C_{quat}), 126.25 (CH_{Ar}), 126.78 (CH_{Ar}), 132.03 (C_{quat}), 132.81 (C_{quat}), 133.59 (CH_{Ar}), 134.28 (CH_{Ar}), 137.32 (C_{quat}), 152.92 (C_{quat}), 153.45 (C_{quat}), 156.11 (C_{quat}), 182.92 (C=O), 183.18 (C=O). IR (ATR): ν 3423 (OH), 1670 (C=O), 1643, 1531, 1497, 1298 cm^{-1}. MS (ES$^-$) *m/z* (%): 407 ([M-H]$^-$, 100).

1-(2-Hydroxyethoxy)-3-(4-methylphenyl)-1*H*-benzo[*g*]isochromene-5,10-dione 13g

57% (LC), mp 153.5°C, red crystals. ^{1}H NMR ($CDCl_3$): δ 2.46 (3H, s, CH_3), 3.10 (1H, t, J = 7.0 Hz, $CH_2O\underline{H}$), 3.68-3.81 (2H, m, CH_2O), 3.99-4.06 (1H, m, $C\underline{H}_aCH_bO$), 4.10-4.17 (1H, m, $CH_aC\underline{H}_bO$), 6.71 (1H, s, CH-1), 6.89 (1H, s, CH-4), 7.27 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.71-7.81 (2H, m, 2xCH_{Ar}), 7.77 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 8.10-8.18 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.64 (CH_3), 62.20 (CH_2O), 70.67 (CH_2O), 92.37 (CH-4), 95.21 (CH-1), 121.45 (C_{quat}), 126.26 (3xCH_{Ar}), 126.78 (CH_{Ar}), 129.64 (2xCH_{Ar}), 130.34 (C_{quat}), 131.88 (C_{quat}), 132.78 (C_{quat}), 133.53 (CH_{Ar}), 134.34 (CH_{Ar}), 137.30 (C_{quat}), 141.76 (C_{quat}), 182.69 (C=O), 183.03 (C=O). IR (ATR): ν 3447 (OH), 1674, 1646, 1540, 1507, 1270 cm^{-1}. MS (ES$^+$) *m/z* (%): 301 ([M-$HOCH_2CH_2O$]$^+$, 100).

1-(2-Hydroxyethoxy)-3-methyl-1*H*-benzo[*g*]isochromene-5,10-dione 13h

70% (LC), mp 108.6°C, brown crystals. ^{1}H NMR ($CDCl_3$): δ 2.17 (3H, s, CH_3), 3.17 (1H, br s, OH), 3.68-3.83 (2H, m, C$\underline{H}_2$OH), 3.93-4.06 (2H, m, C$\underline{H}_2$CH$_2$OH), 6.13 (1H, s, CH-1), 6.50 (1H, s, CH-4), 7.68-7.77 (2H, m, CH-7 & CH-8), 8.07-8.11 (2H, m, CH-6 & CH-9). ^{13}C NMR ($CDCl_3$): δ 21.05 (CH_3), 62.13 (CH_2O), 70.65 (CH_2O), 94.10 (CH-4), 95.04 (CH-1), 120.83 (C_{quat}), 126.16 (CH-6 or CH-9), 126.62 (CH-6 or CH-9), 131.69 (C_{quat}), 132.48 (C_{quat}), 133.52 (CH-7 or CH-8), 134.22 (CH-7 or CH-8), 136.90 (C_{quat}), 162.60 (C_{quat}); 182.91 (C=O), 182.96 (C=O). IR (ATR): *v* 3461 (OH), 1671, 1656, 1556 cm^{-1}. MS (ES$^+$) *m/z* (%): 309 ([M+Na]$^+$, 100).

1-(2-Hydroxyethoxy)-3-isopropyl-1*H*-benzo[*g*]isochromene-5,10-dione 13i

31%, mp 89.6°C, brown crystals. ^{1}H NMR ($CDCl_3$): δ 1.24 (6H, d, J = 7.2 Hz, CH(C$\underline{H}_3$)$_2$), 2.67 (1H, septet, J = 7.2 Hz, C$\underline{H}$(CH$_3$)$_2$), 3.10 (1H, m, CH$_2$O$\underline{H}$), 3.80 (2H, m, CH$_2$O), 3.92-3.99 (1H, m, C$\underline{H}_a$CH$_b$O), 4.02-4.14 (1H, m, CH$_a$C$\underline{H}_b$O), 6.17 (1H, s, CH-4), 6.53 (1H, s, CH-1), 7.70-7.89 (2H, m, 2xCH$_{Ar}$), 8.10-8.14 (2H, m, 2xCH$_{Ar}$). ^{13}C NMR ($CDCl_3$): δ 19.96 (CH(C$\underline{H}_3$)$_2$), 20.21 (CH(C$\underline{H}_3$)$_2$), 33.71 (C$\underline{H}$(CH$_3$)$_2$), 62.17 (CH$_2$O), 70.61 (CH$_2$O), 91.40 (CH-4), 94.82 (CH-1), 121.22 (C_{quat}), 126.20 (CH$_{Ar}$), 126.69 (CH$_{Ar}$), 131.82 (C_{quat}), 132.55 (C_{quat}), 133.56 (CH$_{Ar}$), 134.26 (CH$_{Ar}$), 137.13 (C_{quat}), 170.65 (C_{quat}), 183.01 (C=O), 183.15 (C=O). IR (ATR): *v* 3542 (OH), 1669 (C=O), 1652, 1582, 1560, 1297 (C-O) cm^{-1}. MS (ES$^-$) *m/z* (%): 313 ([M-H]$^-$, 100).

2-(1,3-Dioxolan-2-yl)-3-(1-isobutyryl-4-methyl-3-oxo-pent-1-enyl)-1,4-naphthoquinone 155i

This compound was isolated as a side product from the reaction that leads to compound **13i.**

10%, orange crystals, mp 132.8°C. Mixture of E/Z isomers, only major isomer resolved. ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, d, J = 6.6 Hz, CH_3), 1.09 (6H, d, J = 6.6 Hz, 2xCH_3), 1.13 (3H, d, J = 6.6 Hz, CH_3), 2.75 (1H, septet, J = 6.6 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.94 (1H, septet, J = 6.6 Hz, C$\underline{H}$(CH$_3$)$_2$), 3.76-3.90 (4H, m, OCH$_2$CH$_2$O), 6.10 (1H, s, C$\underline{H}$(OCH$_2$CH$_2$O)), 7.17 (1H, s, CH-2'), 7.73-7.82 (2H, m, 2xCH$_{Ar}$), 8.09-8.18 (2H, m, 2xCH$_{Ar}$). ^{13}C NMR ($CDCl_3$): δ 17.52 (CH_3), 17.77 (CH_3), 18.62 (CH_3), 19.34 (CH_3), 37.31 (C$\underline{H}$(CH$_3$)$_2$), 41.94 (C$\underline{H}$(CH$_3$)$_2$), 64.43 (OCH$_2$), 64.40 (OCH$_2$), 98.14 (C$\underline{H}$(OCH$_2$CH$_2$O)), 126.64 (CH$_{Ar}$), 127.01 (CH$_{Ar}$), 129.97 (CH-2'), 132.09 (C_{quat}), 132.25 (C_{quat}), 134.06 (CH$_{Ar}$), 134.20 (CH$_{Ar}$), 138.43 (C_{quat}), 144.06 (C_{quat}), 146.96 (C_{quat}), 182.88 (C=O), 183.59 (C=O), 201.44 (C=O), 203.37 (C=O). IR (ATR): ν 1667, 1657, 1284, 1079, 965, 731, 720 cm^{-1}. MS (ES$^+$) *m/z* (%): 397 ([M+H]$^+$, 100).

5.2.2 Synthesis of acetonylated 1,4-naphthoquinones 157

Pyridine (2 mmol, 0.16 mL, 0.2 equiv.) was added dropwise to a solution of 2-bromo-1,4-naphthoquinone **156a** or menadione **156b** (10 mmol), the desired halomethylketone **12** (10 mmol, 1.0

equiv.) and Na_2CO_3 (15 mmol, 1.6 g, 1.5 equiv.) in CH_3CN (30 ml). The reaction mixture was stirred at room temperature for 22 h and subsequently heated at 60 °C for 22 h. The acetonitrile was evaporated, the residue was redissolved in EtOAc (30 mL) and water (30 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (3x10 ml). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded the crude product which was further purified by means of column chromatography on silica gel (petroleum ether/ethyl acetate). From the reaction of 2-bromo-1,4-naphthoquinone **156a** with bromomethyl isopropyl ketone **12i**, 6-isobutyrylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione **158a** was isolated as a side product in 10% yield.

2-Methyl-3-[2-isopropyl-2-oxo-ethyl]-1,4-naphthoquinone 157b

77%, yellow needles, mp 75.8°C. ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, d, *J* = 7.2 Hz, CH(C<u>H</u>$_3$)$_2$), 2.13 (3H, s, CH_3), 2.84 (1H, septet, *J* = 7.2 Hz, C<u>H</u>(CH$_3$)$_2$), 3.86 (2H, s, CH_2), 7.66-7.75 (2H, m, CH_{Ar}), 8.02-8.07 (1H, m, CH_{Ar}), 8.08-8.13 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 13.26 (CH_3), 18.45 (2xCH_3), 38.74 (CH_2), 41.42 (<u>C</u>H(CH$_3$)$_2$), 126.37 (CH_{Ar}), 126.43 (CH_{Ar}), 131.83 (C_{quat}), 132.20 (C_{quat}), 133.53 (CH_{Ar}), 133.62 (CH_{Ar}), 141.03 (C_{quat}), 145.77 (C_{quat}), 184.11 (C=O), 184.71 (C=O), 209.43 (C=O). IR (ATR): ν 1702; 1656, 1291, 1044, 706 cm^{-1}. MS (ES$^+$) *m/z* (%): 257 ([M+H]$^+$, 100).

2-Bromo-3-[2-isopropyl-2-oxo-ethyl]-1,4-naphthoquinone 157c

65%, yellow needles, mp 84.3°C. ^{1}H NMR ($CDCl_3$): δ 1.24 (6H, d, *J* = 7.2 Hz, CH(C<u>H</u>$_3$)$_2$), 2.82 (1H, septet, *J* = 7.2 Hz, C<u>H</u>(CH$_3$)$_2$), 4.10 (2H, s, CH_2), 7.73-7.80 (2H, m, CH_{Ar}), 8.07-8.13 (1H, m, CH_{Ar}), 8.15-8.21 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 18.42 (2xCH_3), 41.63 (CH_2), 43.29 (<u>C</u>H(CH$_3$)$_2$), 127.31 (CH_{Ar}), 127.74 (CH_{Ar}), 131.28 (C_{quat}), 131.33 (C_{quat}), 134.17 (CH_{Ar}), 134.34 (CH_{Ar}), 141.13 (C_{quat}), 146.29 (C_{quat}), 177.44 (C=O), 181.33 (C=O), 207.95 (C=O). IR (ATR): ν 1698, 1676, 1658, 1271, 1044, 781, 705 cm^{-1}. MS (ES$^+$) *m/z* (%): 321/323 ([M+H]$^+$, 100/97).

2-Bromo-3-[2-(4-chlorophenyl)-2-oxo-ethyl]-1,4-naphthoquinone 157d

67%, orange solid, mp 155°C. ^{1}H NMR ($CDCl_3$): δ 4.59 (2H, s, CH_2), 7.51 (2H, d, *J* = 8.8 Hz, 2xCH_{Ar}), 7.75-7.83 (2H, m, CH_{Ar}), 8.00 (2H, d, *J* = 8.8 Hz, 2xCH_{Ar}), 8.10-8.15 (1H, m, CH_{Ar}), 8.19-8.24 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 41.80 (CH_2), 127.39 (CH_{Ar}), 127.80 (CH_{Ar}), 129.25 (2xCH_{Ar}), 129.83 (2xCH_{Ar}), 131.33 (C_{quat}), 131.34 (C_{quat}), 134.29 (CH_{Ar}), 134.43 (CH_{Ar}), 134.60 (C_{quat}), 140.34 (C_{quat}), 141.65 (C_{quat}), 146.16 (C_{quat}), 177.38 (C=O), 181.30 (C=O), 192.68 (C=O). IR (ATR): ν 1671, 1660, 1588, 1313, 1274, 1210, 990, 812 cm^{-1}. MS (ES$^-$) *m/z* (%): 387/385 ([M-H]$^-$, 100/57).

6-Isobutyrylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione 158a

10%, orange needles, mp 186.3°C. ^{1}H NMR ($CDCl_3$): δ 1.24 (6H, d, *J* = 7.2 Hz, CH($C\underline{H}_3$)$_2$), 2.96 (1H, septet, *J* = 7.2 Hz, C$\underline{H}$(CH_3)$_2$), 7.18 (1H, dt, *J* = 1.1, 6.9 Hz, CH_{Ar}), 7.41 (1H, ddd, *J* = 1.1, 6.9, 9.1 Hz, CH_{Ar}), 7.73 (1H, dt, *J* = 1.1, 7.4 Hz, CH_{Ar}), 7.75 (1H, dt, *J* = 1.1, 7.4 Hz, CH_{Ar}), 8.16-8.27 (3H, m, 3xCH_{Ar}), 9.83 (1H, d, *J* = 7.4 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 19.16 (2xCH_3), 40.06 ($\underline{C}$H(CH_3)$_2$), 114.91 (C_{quat}), 117.94 (CH_{Ar}), 121.16 (CH_{Ar}), 121.57 (C_{quat}), 126.32 (CH_{Ar}), 127.28 (CH_{Ar}), 128.12 (CH_{Ar}), 128.22 (CH_{Ar}), 133.22 (CH_{Ar}), 133.82 (C_{quat}), 133.97 (CH_{Ar}), 134.19 (C_{quat}), 134.37 (C_{quat}), 139.38 (C_{quat}), 175.00 (C=O), 182.19 (C=O), 204.97 (C=O). IR (ATR): ν 1665, 1490, 1226, 1044, 935, 753, 709 cm^{-1}. MS (ES$^+$) *m/z* (%): 318 ([M+H]$^+$, 100).

5.2.3 Synthesis of isoindolodiones 163, 165 and 167

A flask was loaded with 2-bromo-1,4-naphthoquinone **156a** (1 g, 4.22 mmol), 2-bromoacetophenone **12a** (840 mg, 4.22 mmol), the appropriate *N*-heterocyclic base (4.22 mmol) and Na_2CO_3 (671 mg, 6.33 mmol) and CH_3CN (20 ml). The mixture was allowed to stir open to the air for 2.5 days at 60°C. Next, the solvent was evaporated *in vacuo* and the residue redissolved in EtOAc (10 mL) and water (10 mL) and the organic phase was separated and washed with water (2x10 mL). The organic phase was dried over $MgSO_4$, evaporated *in vacuo* and purified by means of flash chromatography.

6-Benzoylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione 163

80%, ^{1}H NMR ($CDCl_3$): δ 7.20 (1H, dt, 1.1, 7.4 Hz, CH_{Ar}), 7.37-7.48 (3H, m, 3xCH_{Ar}), 7.57-7.61 (1H, m, CH_{Ar}), 7.66 (1H, dt, *J* = 1.1, 7.4 Hz, CH_{Ar}), 7.73 (1H, dt, *J* = 1.1, 7.4 Hz, CH_{Ar}), 7.89-7.97 (3H, m, 3xCH_{Ar}), 8.01 (1H, dd, *J* = 1.1, 7.4, CH_{Ar}), 8.26 (1H, dd, *J* = 1.1, 7.4, CH_{Ar}), 9.81 (1H, d, *J* = 7.4 Hz, CH_{Ar}). Spectral data in accordance with the literature data.[110]

13-Benzoylbenzo[5,6]isoindolo[2,1-*a*]quinoline-7,12-dione 165

70%, ^{1}H NMR ($CDCl_3$): δ 7.40-7.56 (6H, m, 6xCH_{Ar}), 7.61-7.83 (5H, m, 5xCH_{Ar}), 8.09 (2H, m, 2xCH_{Ar}), 8.32 (1H, d, *J* = 8.0 Hz, CH_{Ar}), 8.50 (1H, d, *J* = 8.0 Hz, CH_{Ar}). Spectral data in accordance with the literature data.[110]

7-Benzoylbenzo[5,6]isoindolo[2,1-*b*]isoquinoline-8,13-dione 167

44%, ^{1}H NMR ($CDCl_3$): δ 7.40-7.56 (4H, m, 4xCH_{Ar}), 7.63-7.79 (5H, m, 5xCH_{Ar}), 7.82 (1H, dd, *J* = 1.1, 7.7 Hz, CH_{Ar}), 8.08-8.13 (3H, m, 3xCH_{Ar}), 8.32 (1H, dd, *J* = 1.1, 7.7, CH_{Ar}), 8.50 (1H, d, *J* = 9.4 Hz, CH_{Ar}). Spectral data in accordance with the literature data.[110]

5.2.4 Methyl 1-(naphthalene-1,4-dione-2-carbonyloxy)-4-hydroxy-3-methoxynaphthalene-2-carboxylate 170

To a stirred solution of 2-methoxycarbonyl-1,4-naphthoquinone[259] **156c** (400 mg, 1.84 mmol) in acetonitrile (20 mL) was added pyridine (30 µL, 0.4 mmol, 0.2 equiv.) using a syringe. The reaction mixture was allowed to stir for 40 min and subsequently evaporated *in vacuo*. The residue was redissolved in EtOAc (10 mL) and water (10 mL), and the organic phase was separated and washed with brine (2x10 mL). The organic phase was dried over $MgSO_4$, evaporated *in vacuo* and purified by means of flash chromatography to yield dimer **170** (100 mg) as an orange solid.

Note: as the starting 2-methoxycarbonyl-1,4-naphthoquinone **156c** is only moderately soluble in CH_3CN, the reaction length is strongly dependent on the concentration. It is possible to perform the reaction more concentrated but then the reaction will be significantly longer.

Quantitative yield, brown solid, mp 119°C. ^{1}H NMR ($CDCl_3$): δ 3.58 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.32 (1H, s, CH-3'), 7.63 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.69-7.83 (3H, m, 3xCH_{Ar}), 8.03 (1H, dd, J = 1.1, 7.7 Hz, CH_{Ar}), 8.11-8.17 (2H, m, 2xCH_{Ar}), 8.44 (1H, d, J = 7.7 Hz, CH_{Ar}), 11.91 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 52.59 (OCH_3), 52.82 (OCH_3), 104.20 (C_{quat}), 111.28 (CH-3), 121.86 (CH_{Ar}), 124.23 (CH_{Ar}), 125.65 (C_{quat}), 126.81 (CH_{Ar}), 127.04 (CH_{Ar}), 127.12 (CH_{Ar}), 130.06 (C_{quat}), 130.29 (CH_{Ar}), 130.81 (C_{quat}), 131.22 (C_{quat}), 134.69 (CH_{Ar}), 134.96 (CH_{Ar}), 143.99 (C_{quat}), 154.17 (C_{quat}), 158.75 (2xC_{quat}), 162.69 (C=O), 170.74 (C=O), 179.65 (C=O), 181.99 (C=O). IR (ATR): ν 3074, 2969, 1661, 1346, 1235, 958, 765, 728 cm^{-1}. MS (ES^+) *m/z* (%): 433 ($[M+H]^+$, 100).

5.3 Attempted synthesis of ascomycone A, B and 1-hydroxydehydro-herbarin 15

5.3.1 Synthesis of 2-bromo-6-(1,3-dioxolan-2-yl)-4-methoxybenzenes 181

A solution of 3-bromo-2-hydroxy-5-methoxybenzaldehyde **183a** or 3-bromo-2,5-dimethoxybenzaldehyde[119] **183b** (20 mmol), ethylene glycol (4.5 mL, 80 mmol, 4 equiv.) and *p*-TsOH·H_2O (0.2 mmol, 38 mg) in PhMe (40 mL) was equipped with a Dean-Stark apparatus and boiled under reflux for 4 hours. Next, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (40 mL), washed with aqueous saturated $NaHCO_3$ (40 mL) and brine (3x40 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded pure 2-bromo-6-(1,3-dioxolan-2-yl)-1,4-dimethoxybenzene **181a** or 2-bromo-6-(1,3-dioxolan-2-yl)-4-methoxyphenol **181b**. Both compounds had only a limited stability, so (HR)MS recording was not possible.

2-Bromo-6-(1,3-dioxolan-2-yl)-4-methoxyphenol 181a

93%, yellow crystals, mp 56.7°C. ^{1}H NMR ($CDCl_3$): δ 3.72 (3H, s, OCH_3), 4.01-4.06 (2H, m, CH_2O), 4.08-4.13 (2H, m, CH_2O), 5.95 (1H, s, $CH(OCH_2)_2$), 6.85 (1H, d, *J* = 2.8 Hz, CH-5), 7.05 (1H, d, *J* = 2.8 Hz, CH-3), OH not observed. ^{13}C NMR ($CDCl_3$): δ 56.01 (OCH_3), 65.13 (OCH_2CH_2O), 102.27 ($\underline{C}H(OCH_2)_2$), 111.01 (C_{quat}), 112.81 (CH_{Ar}), 118.98 (CH_{Ar}), 123.68 (C_{quat}), 145.61 (C_{quat}), 153.16 (C_{quat}). IR (ATR): ν 3306 (OH), 1495 (CH_{Ar}), 1477, 1230, 1122, 1040, 853, 778 cm^{-1}. MS (ES+) *m/z* (%): 433/434 ($[M+H]^+$, 100/97). Due to fragmentation of the dioxolanyl ring, no HRMS could be recorded.

2-Bromo-6-(1,3-dioxolan-2-yl)-1,4-dimethoxybenzene 181b

95%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.01-4.05 (2H, m, CH_2O), 4.06-4.15 (2H, m, CH_2O), 6.06 (1H, s, $CH(OCH_2)_2$), 7.03 (1H, d, *J* = 2.9 Hz, CH-5), 7.10 (1H, d, *J* = 2.9 Hz, CH-3). ^{13}C NMR ($CDCl_3$): δ 55.86 (OCH_3), 62.34 (OCH_3), 65.43 (OCH_2CH_2O), 99.39 ($\underline{C}H(OCH_2)_2$), 115.59 (CH_{Ar}), 117.58 (C_{quat}), 119.61 (CH_{Ar}), 133.32 (C_{quat}), 149.55 (C_{quat}), 156.22 (C_{quat}). IR (ATR): ν 2940, 2888, 1475, 1426, 1219, 1130, 1046, 995, 733 cm^{-1}. Due to fragmentation of the dioxolanyl ring, no (HR)MS could be recorded.

5.3.2 2-Bromo-6-(1,3-dioxolan-2-yl)-1,4-benzoquinone 180

2-Bromo-6-(1,3-dioxolan-2-yl)-4-methoxyphenol **181a** (1 g, 3.64 mmol) was dissolved in a 2:1 mixture of acetonitrile/water (15 mL). To this solution, a solution of PIFA (3.13 g, 6.26 mmol, 2 equiv.) in a 2:1 mixture of acetonitrile/water (30 mL) was added dropwise at room temperature. The reaction was allowed to stir for 30 min at room temperature and quenched by the addition of H_2O (30 mL). The mixture was extracted with EtOAc (50 ml) and washed with H_2O (40 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The crude was recrystallised from EtOH overnight at -20°C to obtain 2-bromo-6-(1,3-dioxolan-2-yl)-1,4-benzoquinone **180** as yellow needles in 53% yield.

53%, yellow crystals, mp 122°C (decomp). ^{1}H NMR ($CDCl_3$): δ 4.05 (4H, s, OCH_2CH_2O), 5.93 (1H, d, *J* = 1.1 Hz, $CH(OCH_2)_2$), 6.92 (1H, dd, *J* = 1.1, 2.8 Hz, CH-5), 7.30 (1H, d, *J* = 2.8 Hz, CH-3). ^{13}C NMR ($CDCl_3$): δ 65.69 (OCH_2CH_2O), 98.28 ($\underline{C}H(OCH_2)_2$), 132.28 (CH_{Ar}), 138.11 (CH_{Ar}), 143.18 (C_{quat}), 178.72 (C_{quat}), 185.03 (2xC=O). IR (ATR): ν 1798, 1590, 1388, 1275, 1178, 1070, 767 cm^{-1}. Due to fragmentation of the dioxolanyl ring, no (HR)MS could be recorded.

5.3.3 Formylation of 6,8-dimethoxynaphth-1-ol 178

Oxalyl chloride (68 mg, 0.54 mmol) was added dropwise to DMF (39 mg, 0.54 mmol) at 10°C. The solution was allowed to stir for 15 min without cooling. Then CH_2Cl_2 (1 mL) was added and 6,8-dimethoxynaphth-1-ol **178** (100 mg, 0.49 mmol) was added dropwise in CH_2Cl_2 (1.5 mmol). The reaction mixture was allowed to stir at room temperature an followed up by means of TLC. After

1 h 45, the reaction was quenched by the addition of NaOAc (201 mg, 2.45 mmol) in H_2O (5 mL) and allowed to stir for an additional 30 min. The reaction was extracted with CH_2Cl_2 (10 mL) and washed with brine (2x5 mL). Drying of the organic phase over $MgSO_4$, evaporation of the solvent *in vacuo* and separation of the regioisomers by means of preparative TLC (petroleum ether/ethyl acetate), yielded 8-hydroxy-1,3-dimethoxynaphthalene-2-carboxaldehyde **184a** 1-hydroxy-6,8-dimethoxy-naphthalene-2-carboxaldehyde **184b** as pale white solids.

8-Hydroxy-1,3-dimethoxynaphthalene-2-carboxaldehyde 184a

40%, pale white solid, mp 153°C. ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 6.36 (1H, s, CH-4), 6.82 (1H, dd, *J* = 1.1, 8.3 Hz, CH-5 or CH-7), 7.48 (1H, t, *J* = 8.3 Hz, CH-6), 8.81 (1H, dd, *J* = 8.3, 1.1 Hz, CH-5 or CH-7), 8.97 (1H, s, OH), 10.67 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 56.43 (OCH_3), 56.52 (OCH_3), 91.21 (CH_{Ar}), 110.12 (C_{quat}), 110.42 (CH_{Ar}), 111.25 (C_{quat}), 116.14 (CH_{Ar}), 131.82 (CH_{Ar}), 134.80 (C_{quat}), 154.87 (C_{quat}), 163.20 (C_{quat}), 165.74 (C_{quat}), 190.02 (C=O). IR (ATR): ν 3390, 1648, 1597, 1415, 1208, 1219, 811, 715 cm^{-1}. MS (ES^+) *m/z* (%): 233 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{13}O_4]^+$: 233.0814, found 233.0809.

1-Hydroxy-6,8-dimethoxynaphthalene-2-carboxaldehyde 184b

25%, pale white solid, mp 101°C. ^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.51 (1H, d, *J* = 2.2 Hz, CH_{Ar}), 6.69 (1H, d, *J* = 2.2 Hz, CH_{Ar}), 7.14 (1H, d, *J* = 9.1 Hz, CH_{Ar}), 7.57 (1H, d, *J* = 9.1 Hz, CH_{Ar}), 10.21 (1H, s, CHO), 11.58 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 55.66 (OCH_3), 56.47 (OCH_3), 98.72 (CH_{Ar}), 100.12 (CH_{Ar}), 110.61 (C_{quat}), 115.68 (C_{quat}), 118.64 (2xCH_{Ar}), 126.72 (C_{quat}), 141.67 (C_{quat}), 161.45 (C_{quat}), 162.66 (C_{quat}), 191.85 (C=O). IR (ATR): ν 3323, 2981, 1652, 1621, 1600, 1381, 1368, 799 cm^{-1}. MS (ES^+) *m/z* (%): 233 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{13}O_4]^+$: 233.0814, found 233.0817.

5.3.4 3-Cyano-3-(6-methyl-2-oxo-2*H*-pyran-4-yl)phthalide 192

A solution of 3-cyanophthalide **191a** (570 mg, 2.64 mmol) in THF (10 mL) was cooled to -90°C and Li*Ot*-Bu (2.91 mL, 1 M in THF, 1.1 equiv.) was added dropwise. The mixture was allowed to stir for 15 minutes and subsequently 4-bromo-6-methyl-pyran-2-one **190a** (499 mg, 2.64 mmol, 1 equiv.) in THF (5 mL) was added dropwise. After 40 min, the reaction mixture was quenched by the addition of H_2O (4 mL) and was allowed to warm to room temperature. The reaction mixture was partitioned between H_2O (10 mL) and EtOAc (20 mL). The organic phase was washed with brine (2x10 mL) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* yielded pure 3-cyano-3-(6-methyl-2-oxo-2*H*-pyran-4-yl)-phthalide **192** (543 mg, 2.03 mmol, 77%).

77%, pale white solid, mp 143°C. ^{1}H NMR ($CDCl_3$): δ 2.26 (3H, s, CH_3), 5.84 (1H, s, CH-5'), 6.54 (1H, s, CH-3'), 7.65 (1H, d, *J* = 7.7 Hz, CH-4 or CH-7), 7.80 (1H, dt, *J* = 1.1, 7.7 Hz, CH-5 or CH-6),

7.91 (1H, dt, *J* = 1.1, 7.7 Hz, CH-5 or CH-6), 8.06 (1H, dd, *J* = 1.1, 7.7 Hz, CH-4 or CH-7). ^{13}C NMR ($CDCl_3$): δ 20.44 (CH_3), 76.98 (C-3), 99.24 (CH-5'), 110.35 (CH-3'), 113.88 (C≡N), 123.01 (CH-4 or CH-7), 123.74 (C_{quat}), 127.28 (CH-4 or CH-7), 132.54 and 136.58 (CH-5 and CH-6), 144.03 (C_{quat}), 150.02 (C_{quat}), 161.03 (C_{quat}), 165.03 (C=O), 166.32 (C=O). IR (ATR): ν 1785, 1746, 1239, 954, 749, 686 cm^{-1}. MS (ES^+) *m/z* (%): 268 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{15}H_{10}NO_3]^+$: 268.0610, found 268.0606.

5.4 Attempted synthesis of mansouramycins A-D 16

5.4.1 5,6-Dibromo-2-(4-bromophenoxymethyl)cyclohex-2-ene-1,4-dione 208

Bromine (52 µL, 1 equiv.) was added dropwise to a solution of phenoxymethylbenzoquinone **207a** (200 mg, 1 mmol) and NaOAc (82 mg, 1.6 mmol) in glacial acetic acid (6 mL). After 50 min, the reaction mixture was evaporated in vacuo, redissolved in CH_2Cl_2 (15 mL) and washed with water (2x 10 mL). The organic phase was dried over $MgSO_4$, evaporated in vacuo and purified by means of column chromatography to yield 5,6-dibromo-2-(4-bromophenoxymethyl)cyclohex-2-ene-1,4-dione **208**.

50%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.81 (1H, dd, *J* = 2.2, 17.6 Hz, C$\underline{H}_A$H$_B$O), 4.81 (1H, dd, *J* = 2.8, 1.7 Hz, CH-5), 4.86 (1H, d, *J* = 2.8 Hz, CH-6), 4.97 (1H, dd, *J* = 2.2, 17.6 Hz, CH$_A\underline{H}_B$O), 6.83 (2H, td, *J* = 2.8, 8.8 Hz, 2xCH$_{Ar}$), 6.90 (1H, dd, J = 1.7, 2.2 Hz, CH-3), 7.42 (2H, td, *J* = 2.8, 8.8 Hz, 2xCH$_{Ar}$). ^{13}C NMR ($CDCl_3$): δ 45.17 (CH-5), 45.42 (CH-6), 63.63 (CH_2O), 114.42 (C_{quat}), 116.52 (2xCH$_{Ar}$), 131.67 (CH-3), 132.72 (2xCH$_{Ar}$), 144.20 (C_{quat}), 156.55 (C_{quat}), 186.98 (C=O), 187.20 (C=O). IR (ATR): ν 1690 (C=O), 1681 (C=O), 1486, 1236, 1165, 1000, 818 cm^{-1}. MS: no ionisation observed.

5.4.2 Synthesis of 5,8-dimethoxy-3-methylisoquinoline 210a via a Pomeranz-Fritsch sequence

Methyl 2-(2,5-dimethoxybenzylamino)propionate 213

A solution of methyl alaninate HCl salt **212a** (6.98 g, 50 mmol) and KOH (2.8 g, 50 mmol) in MeOH (500 mL) was boiled under reflux until full dissolution occurred. The solution was cooled to room temperature and 2,5-dimethoxybenzaldehyde **211** (8.56 g, 51.5 mmol, 1.03 equiv.) was added. The reaction mixture was allowed to stir for 1 hour and subsequently $NaBH_4$ was added (1.89 g, 50 mmol, 1 equiv.) and stirring was continued for 30 min. Next, the reaction mixture was evaporated *in vacuo* and the residue was partitioned between H_2O (100 mL) and EtOAc (100 mL). The organic phase was extracted with aqueous HCl (2 M, 3x50 mL) and discarded. The aqueous extract was neutralised using solid NaOH and extracted with EtOAc (3x50 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to yield pure amine **213** as a yellow oil.

69%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, d, *J* = 6.6 Hz, CH_3), 2.07 (1H, br s, NH), 3.39 (1H, q, *J* = 6.6 Hz, CH-2), 3.69 (3H, s, OCH_3), 3.69 (1H, d, *J* = 12.9 Hz, $NC\underline{H}_AH_B$), 3.77 (3H, s, OCH_3), 4.66 (1H, d, *J* = 18.2 Hz, $NCH_A\underline{H}_B$), 3.79 (3H, s, OCH_3), 6.76-6.84 (2H, m, CH-3'and CH-4'), 6.87 (1H, d, *J* = 2.2 Hz, CH-6'). ^{13}C NMR ($CDCl_3$): δ 19.96 (CH_3), 47.08 (NCH_2), 51.57 ($COO\underline{C}H_3$), 55.56 (OCH_3), 55.69 (OCH_3), 55.85 (CH-2), 111.07 (CH_{Ar}), 112.29 (CH_{Ar}), 115.74 (CH_{Ar}), 128.86 (C_{quat}), 151.71 (C_{quat}), 153.39 (C_{quat}), 175.91 (C=O). IR (ATR): ν 2906, 2833, 1732, 1497, 1214, 1064, 1047 cm^{-1}. MS (ES^+) *m/z* (%): 349 ($[M+NH_4]^+$, 100).

Methyl 2-[bis(2,5-dimethoxybenzyl)amino]propionate 215

A solution of 2-bromomethyl-1,4-dimethoxybenzene **214** (1.65 g, 7.14 mmol), methyl alaninate HCl salt **212a** (1 g, 7.16 mmol, 1.1 equiv.) and Na_2CO_3 (1.52 g, 14.32 mmol, 2 equiv.) in anhydrous THF (20 mL) was boiled under reflux for two days. The solution was cooled to room temperature and partitioned between H_2O (20 mL) and EtOAc (20 mL). The organic phase was extracted with aqueous HCl (2 M, 3x10 mL) and discarded. The aqueous extract was neutralised using solid NaOH and extracted with EtOAc (3x10 mL). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to yield pure methyl 2-[bis(2,5-dimethoxybenzyl)amino]propionate **215** as a yellow oil.

36%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, d, *J* = 7.2 Hz, CH_3), 3.61 (1H, q, *J* = 7.2 Hz, CH-2), 3.72 (3H, s, OCH_3), 3.73 (6H, s, 2xOCH_3), 4.66 3.74 (6H, s, 2xOCH_3), 3.82 (4H, d, *J* = 3.3 Hz, 2xNCH_2), 6.69-6.75 (4H, m, 2xCH-3'and 2xCH-4'), 7.22 (2H, d, *J* = 3.0 Hz, 2xCH-6'). ^{13}C NMR ($CDCl_3$): δ 14.84 (CH_3), 48.84 (2xNCH_2), 51.33 ($COO\underline{C}H_3$), 55.62 (2xOCH_3), 55.91 (2xOCH_3), 57.42 (CH-2), 111.21 (2xCH_{Ar}), 111.97 (2xCH_{Ar}), 115.41 (2xCH_{Ar}), 129.62 (2xC_{quat}), 151.99 (2xC_{quat}), 153.72 (2xC_{quat}), 174.74 (C=O). MS (ES^+) *m/z* (%): 404 ($[M+H]^+$, 100).

Methyl 2-(2,5-dimethoxybenzylamino)propionate **213** (3 g, 11.84 mmol) was dissolved in pyridine (20 mL) and cooled to 0°C. Next, mesyl chloride or tosyl chloride (15.4 mmol, 1.3 equiv.) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. Afterwards, the mixture was poured in ice water and extracted with Et_2O (3x100 mL). The organic phases were washed with aqueous HCl (2 M, 2x50 mL), dried over $MgSO_4$ and evaporated *in vacuo* to yield pure sulfonamides **216a** and **216b**.

Methyl 2-[(2,5-dimethoxybenzyl)methanesulfonylamino]propionate 216a

76%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, d, *J* = 7.2 Hz, CH_3), 2.99 (3H, s, CH_3SO_2), 3.70 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.48 (2H, s, NCH_2), 4.61 (1H, q, *J* = 7.2 Hz, CH-2), 6.76-6.77 (2H, m, CH-3'and CH-4'), 7.13 (1H, s, CH-6'). ^{13}C NMR ($CDCl_3$): δ 16.71 (CH_3), 40.10 (CH_3SO_2), 44.33 (NCH_2), 52.41 ($COO\underline{C}H_3$), 55.74 (OCH_3), 55.80 (OCH_3), 56.36 (CH-2), 111.05 (CH_{Ar}), 113.30 (CH_{Ar}), 115.53 (CH_{Ar}), 126.58 (C_{quat}), 150.98 (C_{quat}), 153.67 (C_{quat}), 172.29 (C=O). IR

(ATR): ν 2949, 1740, 1499, 1329, 1218, 1145, 1042, 766 cm^{-1}. MS (ES^+) *m/z* (%): 348 ($[M+NH_4]^+$, 100).

Methyl 2-[(2,5-dimethoxybenzyl)-(toluene-4-sulfonyl)amino]propionate 216b

79%, yellow oil. ^1H NMR ($CDCl_3$): δ 1.32 (3H, d, *J* = 7.2 Hz, CH_3), 2.41 (3H, s, CH_3Ar), 3.45 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.49 (2H, s, NCH_2), 4.60 (1H, q, *J* = 7.2 Hz, CH-2), 6.72 (2H, s, CH-3'and CH-4'), 7.08 (1H, s, CH-6'), 7.28 (2H, d, *J* = 7.7 Hz), 7.73 (2H, d, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$): δ 16.04 (CH_3), 21.51 (CH_3Ar), 43.57 (NCH_2), 51.95 ($COO\underline{C}H_3$), 55.42 (CH-2), 55.65 ($2xOCH_3$), 110.99 (CH_{Ar}), 113.33 (CH_{Ar}), 115.19 (CH_{Ar}), 126.58 (C_{quat}), 127.51 ($2xCH_{Ar}$), 129.45 ($2xCH_{Ar}$), 137.19 (C_{quat}), 143.36 (C_{quat}), 150.87 (C_{quat}), 153.58 (C_{quat}), 171.70 (C=O). IR (ATR): ν 2949, 1741, 1498, 1339, 1217, 1154, 1044, 658 cm^{-1}. MS (ES^+) *m/z* (%): 151 ([M-$C_{11}H_{14}NO_4S]^+$, 100), 430 ($[M+Na]^+$, 17).

2-[(2,5-Dimethoxybenzyl)methanesulfonylamino]propan-1-ol

$LiAlH_4$ pellets (1.75 g, 46.17 mmol, 1.5 equiv.) were added to a solution of methyl-2-[(2,5-dimethoxybenzyl)methanesulfonylamino]propionate **216a** (200 mg, 30.78 mmol) in anhydrous Et_2O (10 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated solution of potassium sodium tartrate (15 mL) and extracted with Et_2O (3x 10 mL). The organic phases were dried over $MgSO_4$, evaporated *in vacuo* and purified by means of flash chromatography to yield pure 2-[(2,5-dimethoxybenzyl)methanesulfonylamino]-propan-1-ol as a pale white solid.

74%, pale white solid, mp 71°C. ^1H NMR ($CDCl_3$): δ 1.18 (3H, d, *J* = 7.2 Hz, CH_3), 2.20-2.28 (1H, m, OH), 2.83 (3H, s, CH_3SO_2), 3.44-3.62 (2H, m, OCH_2), 3.78 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.04-4.14 (1H, m, CH-2), 4.39 (2H, s, NCH_2), 6.81 (2H, s, CH-3'and CH-4'), 7.16 (1H, s, CH-6'). ^{13}C NMR ($CDCl_3$): δ 15.43 (CH_3), 40.61 (CH_3SO_2), 42.00 (NCH_2), 55.75 (OCH_3), 56.00 (OCH_3), 56.55 (CH-2), 64.08 (OCH_2), 111.66 (CH_{Ar}), 113.73 (CH_{Ar}), 116.17 (CH_{Ar}), 126.74 (C_{quat}), 150.91 (C_{quat}), 153.79 (C_{quat}). IR (ATR): ν 3362, 1498, 1323, 1471, 1323, 1218, 1140, 1036 cm^{-1}. MS (ES^+) *m/z* (%): 361 ($[M-H+OAc]^-$, 100). HRMS (ES^+) calcd. for $[C_{15}H_{24}NO_7S]^+$: 362.1274, found 362.1284.

2-[(2,5-Dimethoxybenzyl)methanesulfonylamino]propanal 217

To a solution of $(COCl)_2$ (2.9 mL, 22.9 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (160 mL) was added dropwise a solution of DMSO (4.9 mL, 45.8 mmol, 3 equiv.) in anhydrous CH_2Cl_2 (30 mL) at -78°C. After 30 min, 2-[(2,5-dimethoxybenzyl)methanesulfonylamino]propan-1-ol (6.95 g, 22.9 mmol) was added in anhydrous CH_2Cl_2 (30 mL) and the reaction was stirred for 1 h at -78°C. The reaction temperature was raised to -60°C and Et_3N (12.8 mL, 91.6 mmol, 4 equiv.) was added dropwise. The reaction was then allowed to warm to room temperature and stirred for an additional 30 minutes. Next,

the reaction mixture was poured in water (250 mL) and extracted with CH_2Cl_2 (2x80 mL). The combined organic fractions were washed with water (3x80 mL) and brine (1x80 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded pure aldehyde **217** as pale white crystals.

95%, pale white crystals, mp 70.9°C. ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, d, J = 7.2 Hz, CH_3), 2.96 (3H, s, CH_3SO_2), 3.75 (6H, s, 2xOCH_3), 4.10 (1H, q, J = 7.2 Hz, CH-2), 4.40 (1H, d, J_{AB} = 15.4 Hz, NC$\underline{H}_A H_B$), 4.44 (1H, d, J_{AB} = 15.4 Hz, NC$H_A\underline{H}_B$), 6.754-6.83 (2H, m, CH-3'and CH-4'), 7.04 (1H, d, J = 2.8 Hz, CH-6'), 9.42 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 12.38 (CH_3), 41.08 (CH_3SO_2), 44.74 (NCH_2), 55.71 (OCH_3), 55.83 (OCH_3), 62.59 (CH-2), 111.62 (CH_{Ar}), 114.34 (CH_{Ar}), 116.49 (CH_{Ar}), 124.93 (C_{quat}), 151.48 (C_{quat}), 153.79 (C_{quat}), 199.32 (C=O). IR (ATR): ν 3008, 2838, 1725, 1500, 1324, 1223, 1139, 970, 715 cm^{-1}. MS (ES^+) *m/z* (%): 319 ($[M+HH_4]^+$, 100).

2-Methanesulfonyl-5,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol 218

2-[(2,5-Dimethoxybenzyl)methanesulfonylamino]propanal **217** (800 mg, 2.65 mmol) was dissolved in 1,4-dioxane (12 mL) and aqueous HCl (6 M, 2 mL) and boiled under reflux during 1 h. The mixture was allowed to warm to room temperature, neutralised with aqueous saturated $NaHCO_3$ and extracted with Et_2O (3x15 mL). The combined organic fractions were dried over $MgSO_4$ and evaporation of the solvent followed by flash chromatography yielded pure 2-methanesulfonyl-5,8-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinolin-4-ol **218** as white needles.

85%, pale white needles, mp 167.9°C. ^{1}H NMR ($CDCl_3$): δ 1.21 (3H, d, J = 6.6 Hz, CH_3), 3.06 (3H, s, CH_3SO_2), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.30 (1H, d, J = 18.2 Hz, C$\underline{H}_A H_B$-1), 4.56 (1H, dq, J = 1.7, 6.6 Hz, CH-3), 4.66 (1H, d, J = 18.2 Hz, C$H_A\underline{H}_B$-1), 5.25 (1H, d, J = 1.7 Hz, CH-4), 6.76-6.84 (2H, m, CH-6 or CH-7), OH not observed. ^{13}C NMR ($CDCl_3$): δ 17.48 (CH_3), 38.53 (CH_2-1), 39.91 (CH_3SO_2), 54.59 (CH-4), 54.89 (CH-3), 55.62 (OCH_3), 56.15 (OCH_3), 109.33 (CH_{Ar}), 110.40 (CH_{Ar}), 121.38 (C_{quat}), 121.51 (C_{quat}), 149.52 (C_{quat}), 151.36 (C_{quat}). IR (ATR): ν 2977, 1487, 1474, 1318, 1262, 1159, 1127, 1071, 1038, 963, 795 cm^{-1}. MS (ES^+) *m/z* (%): 284 ($[M-OH]^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{18}NO_4S]^+$: 284.0957, found 284.0957.

5,8-Dimethoxy-3-methylisoquinoline 210a

$ClSO_3H$ (1.55 mL, 23.3 mmol, 10 equiv.) was cooled to -20°C and 2-[(2,5-dimethoxybenzyl)methanesulfonylamino]propanal **217** (670 mg, 2.33 mmol) was added. The reaction mixture was stirred for 5 minutes at this temperature and subsequently for 15 min at room temperature. Then, the reaction mixture was neutralised with aqueous NaOH (2 N) and extracted with CH_2Cl_2 (2x10 mL). The combined organic fractions were dried over $MgSO_4$, evaporated *in vacuo* and purified by means of flash chromatography to yield pure 5,8-dimethoxy-3-methyl isoquinoline **210a** (210 mg, 1.03 mmol, 44%).

44%, yellow gum, mp 61°C. ^{1}H NMR ($CDCl_3$): δ 2.71 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 6.68 (1H, d, *J* = 8.3 Hz, CH-6 or CH-7), 6.85 (1H, d, *J* = 8.3 Hz, CH-6 or CH-7), 7.79 (1H, s, CH-4), 9.49 (1H, s, CH-1). ^{13}C NMR ($CDCl_3$): δ 24.53 (CH_3), 55.75 (OCH_3), 55.89 (OCH_3), 103.33 and 107.60 (CH-6 and CH-7), 112.78 (CH-4), 119.47 (C_{quat}), 130.13 (C_{quat}), 146.84 (CH-1), 147.99 (C_{quat}), 150.40 (C_{quat}), 152.32 (C_{quat}). IR (ATR): ν 1629, 1582, 1424, 1328, 1258, 1096 cm^{-1}. MS (ES^+) *m/z* (%): 204 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{12}H_{14}O_2]^+$: 204.1025, found 204.1019.

3-Methylisoquinoline-5,8-dione 220

To a solution of 5,8-dimethoxy-3-methylisoquinoline **210a** (210 mg, 1.03 mmol) in CH_3CN (5 mL) was added a solution of CAN (1.42 g, 2.58 mmol, 2.5 equiv.) in H_2O (5 mL) in one portion. The reaction mixture was allowed to stir for 60 sec and poured in a 1:1 mixture EtOAc/H_2O (15 mL). The H_2O phase was discarded and the organic phase was washed with water (5 mL).The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to yield the crude quinone, which was recrystallised from EtOH to yield pure 5,8-dimethoxy-3-methylisoquinoline (140 mg, 0.81 mmol, 79%) as a yellow solid.

79%, yellow solid, mp 113.6°C. ^{1}H NMR ($CDCl_3$): δ 2.74 (3H, s, CH_3), 7.01 (1H, d, *J* = 10.3 Hz, CH-6 or CH-7), 7.05 (1H, d, *J* = 10.3 Hz, CH-6 or CH-7), 7.73 (1H, s, CH-4), 9.22 (1H, s, CH-1). ^{13}C NMR ($CDCl_3$): δ 25.48 (CH_3), 117.93 (CH-4), 122.74 (C_{quat}), 137.04 (C_{quat}), 138.46 and 139.18 (CH-6 and CH-7), 148.51 (CH-1), 166.07 (C_{quat}), 184.37 (C=O), 184.75 (C=O). IR (ATR): ν 1664, 1582, 1591, 1314, 1048, 861 cm^{-1}. MS (ES^+) *m/z* (%): 174 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{10}H_8NO_2]^+$: 174.0555, found 174.0550.

5.5 Attempted synthesis of 3-hydroxymollugin 228

Methyl 3-(3-methyl-2-oxobutyl)-1,4-naphthoquinone-2-carboxylate 226

A solution of 2-(methoxycarbonyl)naphthoquinone **156c** (1.36 g, 6.3 mmol) and 1-isobutyrylpyridiniumbromide **229i** (1.53 g, 2.31 mmol) in CH_3CN (20 mL) was cooled to -50°C and Et_3N (0.876 mL, 2.31 mmol, 1 equiv.) was added dropwise. After 1 h at -50°C, the reaction was quenched by the addition of aqueous HCl (2 M, 20 mL) and extracted with EtOAc (2x20 mL). The combined organic extracts were dried over $MgSO_4$, evaporated *in vacuo* and purified by means of column chromatography (petroleum ether/ethyl acetate 4/1) to yield methyl 3-(3-methyl-2-oxobutyl)-1,4-naphthoquinone-2-carboxylate **226** as a brown solid.

74%, brown solid, mp 56.7°C. ^{1}H NMR ($CDCl_3$): δ 1.20 (6H, d, *J* = 7.2 Hz, 2xCH_3), 2.77 (1H, septet, *J* = 7.2 Hz, C<u>H</u>$(CH_3)_2$), 3.85 (2H, s, CH_2), 3.93 (3H, s, $CO_2C\underline{H}_3$), 7.73-7.81 (2H, m, 2xCH_{Ar}), 8.05-8.13 (2H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 18.27 (2xCH_3), 39.11 (CH_2), 41.48 (<u>C</u>H$(CH_3)_2$), 52.96 ($CO_2\underline{C}H_3$), 126.60 (CH_{Ar}), 126.84 (CH_{Ar}), 131.36 (C_{quat}), 131.47 (C_{quat}), 134.25 (CH_{Ar}), 134.42 (CH_{Ar}),

140.48 (C_{quat}), 142.52 (C_{quat}), 164.80 (C_{quat}), 181.30 (C=O), 183.79 (C=O), 208.42 (C=O). IR (ATR): ν 1726, 1668, 1287, 1240, 1043, 714 cm^{-1}. MS (ES^+) *m/z* (%): 300 ($[M+H]^+$, 100).

Methyl 5-hydroxy-8-isopropyl-10-phenyl-8,11a-epoxy-8,11a-dihydro-9,11-dioxa-10-bora-cyclohepta[*a*]naphthalene-6-carboxylate 231

A solution of methyl-3-(3-methyl-2-oxobutyl)-1,4-naphthoquinone-2-carboxylate **226** (100 mg, 0.33 mmol) and $PhB(OH)_2$ (40 mg, 0.33 mmol) in PhMe (3 mL) was boiled under reflux for 3 h. The reaction mixture was evaporated *in vacuo* and redissolved in CH_2Cl_2 (10 mL) and H_2O (10 mL). The organic phase was separated, dried over $MgSO_4$, evaporated *in vacuo* and purified by means of preparative TLC (petroleum ether/ethyl acetate 98/2) to yield boronic acid ester **231** (126 mg, 0.312 mmol, 94%).

94%, pale yellow crystals, 163.1°C. ^1H NMR ($CDCl_3$): δ 1.16 (6H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)_2$), 2.41 (1H, septet, *J* = 6.6 Hz, $C\underline{H}(CH_3)_2$), 4.14 (3H, s, OCH_3), 6.13 (1H, s, CH-7), 7.33-7.38 (2H, m, $2xCH_{Ar}$), 7.43-7.48 (1H, m, CH_{Ar}), 7.57 (1H, dt, *J* = 1.1, 7.7 Hz, CH-13 or CH-14), 7.65 (1H, dt, *J* = 1.1, 7.2 Hz, CH-13 or CH-14), 7.85 (2H, dd, *J* = 1.1, 7.2 Hz, CH-12 and CH-15), 8.04 (1H, d, *J* = 8.0 Hz, CH_{Ar}), 8.41 (1H, d, *J* = 8.0 Hz, CH_{Ar}), 11.99 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 16.16 (CH_3), 16.19 (CH_3), 34.84 ($\underline{C}H(CH_3)_2$), 52.62 (OCH_3), 84.70 (CH-7), 102.17 (C_{quat}), 114.34 (C_{quat}), 120.35 (C_{quat}), 122.37 (CH_{Ar}), 124.37 (C_{quat}), 124.69 (CH_{Ar}), 126.75 (C_{quat}), 127.39 (CH_{Ar}), 127.88 ($2xCH_{Ar}$), 129.71 (CH_{Ar}), 131.96 (CH_{Ar}), 135.30 ($2xCH_{Ar}$), 147.84 (C_{quat}), 157.16 ($2xC_{quat}$), 171.29 (C=O). ^{11}B NMR ($CDCl_3$): δ 31.07 (1H, s, $ArB(OR)_2$). IR (ATR): ν 2976, 1661, 1440, 1335, 1233, 767, 699 cm^{-1}. MS (ES^+) *m/z* (%): 301 ($M–PhBO+H]^+$), 405 ($[M+H]^+$, 30). HRMS (ES^+) calcd. for $[C_{23}H_{22}BO_6]^+$: 405.1510, found 405.1504.

Methyl 5,9*b*-dihydroxy-2-isopropyl-2-methoxy-2,9*b*-dihydronaphtho[1,2-*b*]furan-4-carboxylate or 232a methyl 2,5-dihydroxy-2-isopropyl-9*b*-methoxy-2,9b-dihydro-naphtho[1,2-*b*]furan-4-carboxylate 232b

Methyl 9*b*-hydroxy-2-isopropyl-5-oxo-5,9b-dihydronaphtho[1,2-*b*]furan-4-carboxylate **230** was heated in MeOH and allowed to stand overnight upon which crystallisation occurred. Filtration yielded the title compound as white crystals.

23% from 2-(methoxycarbonyl)naphthoquinone **156c**, pale white crystals, mp 142.6°C. ^1H NMR ($CDCl_3$): δ 1.08 (3H, d, *J* = 6.6 Hz, CH_3), 1.12 (3H, d, *J* = 6.6 Hz, CH_3), 2.17 (1H, septet, *J* = 6.6 Hz, $C\underline{H}(CH_3)_2$), 3.59 (3H, s, OCH_3), 4.08 (3H, s, $CO_2C\underline{H}_3$), 4.74 (1H, br s, OH), 4.89 (1H, s, CH-3), 7.56 (1H, dt, *J* = 1.1, 7.7 Hz, CH-7 or CH-8), 7.63 (1H, dt, *J* = 1.1, 7.7 Hz, CH-7 or CH-8), 8.00 (1H, d, *J* = 7.7 Hz, CH-6 or CH-9), 8.38 (1H, d, *J* = 7.7 Hz, CH-6 or CH-9), 11.93 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 16.47 (CH_3), 16.53 (CH_3), 35.43 ($\underline{C}H(CH_3)_2$), 52.67 (OCH_3), 60.10 ($\underline{C}O_2CH_3$), 83.39 (CH-

3), 102.08 (C_{quat}), 110.92 (C-2), 112.81 (C_{quat}), 122.37 (CH_{Ar}), 124.31 (C_{quat}), 124.58 (CH_{Ar}), 126.64 (C_{quat}), 127.25 (CH_{Ar}), 129.57 (CH_{Ar}), 147.67 (C_{quat}), 156.83 (C_{quat}), 171.20 (C=O). IR (ATR): ν 3396, 1658, 1644, 1434, 1238, 1227, 768 cm^{-1}. MS (ES^+) *m/z* (%): 301 ($[M\text{-}OMe]^+$, 100).

5.6 Unexpected aminonaphthol synthesis

6',8'-Dimethoxyspiro[1,3-dioxolane-2,1'-naphthalen]-4'-one 235

A solution of 6,8-dimethoxynaphthalen-1-ol **178** (800 mg, 3.9 mmol) in anhydrous CH_3CN (15 mL) was added dropwise to a solution of PIFA (3.7 g, 8.58 mmol, 2.2 equiv.) in anhydrous ethylene glycol (25 mL) and anhydrous CH_3CN (15 mL) at 0°C over a 2 h period. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, extracted with Et_2O and washed with brine. Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* followed by purification by means of column chromatography (petroleum ether/ethyl acetate 1:1) yielded 6',8'-dimethoxyspiro[1,3-dioxolane-2,1'-naphthalen]-4'-one **235** (552 mg, 54%) as a white solid.

54%, pale white powder, mp 178.1°C. ^1H NMR ($CDCl_3$): δ 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.22-4.29 (2H, m, CH_2O), 4.30-4.37 (2H, m, CH_2O), 6.22 (1H, d, *J* = 10.2 Hz, CH-3'), 6.52 (1H, d, *J* = 2.2 Hz, CH_{Ar}), 6.66 (1H, d, *J* = 10.2 Hz, CH-2'), 6.72 (1H, d, *J* = 2.2 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.62 (OCH_3), 56.37 (OCH_3), 65.78 (OCH_2CH_2O), 99.59 (CH-2'), 100.46 (C_{quat}), 103.85 (CH-3'), 114.17 (C_{quat}), 131.09 (CH_{Ar}), 138.58 (CH_{Ar}), 145.41 (C_{quat}), 162.11 (C_{quat}), 164.28 (C_{quat}), 182.68 (C=O). IR (ATR): ν 1665, 1596, 1573, 1321, 1215, 1161, 1047, 1025, 950 cm^{-1}. MS (ES^+) *m/z* (%): 263 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{14}H_{15}NO_5]^+$: 263.0920, found 263.0926.

5.6.1 General procedures for the synthesis of *N*,*N*-dialkylbenzamides

***N*,*N*-Dimethylbenzamides 251 and 254[260]**

The appropriate benzoic acid derivative (72.4 mmol) was added to $SOCl_2$ (53 mL, 724 mmol, 10 equiv.) and boiled under reflux for 2.5 h. Next, the solvent was evaporated *in vacuo*, the residue redissolved in a small portion of benzene and evaporated again. The residue was taken up in anhydrous CH_2Cl_2 (50 mL) and added dropwise to a solution of Me_2NH_4Cl (8.86 g, 109 mmol, 1.5 equiv.) and Et_3N (40.4 mL, 290 mmol, 4 equiv.) in CH_2Cl_2 (100 mL) at 0°C. The reaction mixture was allowed to stir overnight at room temperature. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and the organic phase was washed with HCl (1 M, 100 mL), H_2O (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield pure *N*,*N*-dimethylbenzamides.

The same procedure was applied to the synthesis of *N*-(2-hydroxybenzoyl)pyrrolidine **259a** and *N*-(2-hydroxybenzoyl)morpholine **259b** using 1.5 equiv. of pyrrolidine or morpholine and 3 equiv. of Et_3N.

***N*,*N*-Diethylbenzamides 250[163]**

The appropriate benzoic acid derivative (72.4 mmol) was added to $SOCl_2$ (53 mL, 724 mmol, 10 equiv.) and boiled under reflux for 2.5 h. Next, the solvent was evaporated *in vacuo*, the residue redissolved in a small portion of benzene and evaporated again. The residue was taken up in anhydrous CH_2Cl_2 (50 mL) and added dropwise to a solution of diethylamine (22.5 mL, 217 mmol, 3 equiv.) in CH_2Cl_2 (100 mL) at 0°C. The reaction mixture was allowed to stir overnight at room temperature. The excess diethylamine and CH_2Cl_2 were removed *in vacuo* and the residue taken up in neat Et_2NH (20 mL) and boiled under reflux for 18 h. Excess Et_2NH was removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (300 mL). The organic phase was washed with aqueous HCl (1 M, 100 mL), H_2O (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to yield pure *N*,*N*-diethylbenzamides.

5.6.2 General procedure for TBDMS or TIPS protection[164]

To a solution of the appropriate benzamide (30 mmol) in CH_2Cl_2 (100mL) under a nitrogen atmosphere was added DMAP (73 mg, 0.60 mmol, 0.02 equiv.), Et_3N (5.4 mL, 39.0 mmol, 1.3 equiv.) and TBDMSCl or TIPSCl (33.0 mmol, 1.1 equiv.). The reaction was stirred at ambient temperature for 12 h. NH_4Cl (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3x100mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated. Flash chromatography (petroleum ether/ethyl acetate) yielded the appropriate silanoxybenzamides.

2-(*tert*-Butyldimethylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide 242

^{1}H NMR ($CDCl_3$): δ 0.17 (6H, s, 2xCH_3), 0.94 (9H, s, $C(CH_3)_3$), 2.86 (3H, s, NCH_3), 3.04 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 6.33 (1H, d, *J* = 2.5 Hz, CH-3), 6.54 (1H, dd, *J* = 8.5, 2.5 Hz, 1H, CH-5), 7.18 (1H, d, *J* = 8.5 Hz, CH-6). Spectral data in accordance with the literature.[260]

6-(*tert*-Butyldimethylsilanyloxy)-*N*,*N*-diethylbenzamide 252a

93%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.21 (3H, s, CH_3Si), 0.23 (3H, s, CH_3Si), 0.97 (9H, s, $C(CH_3)_3$), 1.01 (3H, t, *J* = 7.2 Hz, CH_3), 1.25 (3H, t, *J* = 7.2 Hz, CH_3), 3.11 (1H, dq, *J* = 14.3, 7.2 Hz, $C\underline{H}_AH_BN$), 3.24 (1H, dq, *J* = 14.3, 7.2 Hz, $CH_A\underline{H}_BN$), 3.45 (1H, dq, *J* = 13.5, 7.2 Hz, $C\underline{H}_CH_DN$), 3.64 (1H, dq, *J* = 13.5, 7.2 Hz, $CH_C\underline{H}_DN$), 6.82 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 6.97 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.18-7.25 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -5.01 (CH_3Si), -4.60 (CH_3Si), 12.73 (CH_3), 13.60 (CH_3), 17.58 ($\underline{C}(CH_3)_3$), 25.16 ($C(\underline{C}H_3)_3$), 38.65 (CH_2N), 42.30 (CH_2N), 118.78 (CH_{Ar}), 120.86 (CH_{Ar}), 127.27 (CH_{Ar}), 129.07 (CH_{Ar}), 129.32 (C_{quat}), 150.55 (C_{quat}), 168.34 (C=O). IR (ATR): ν 2956 (CH), 2931 (CH), 1635, 1249, 915, 758 cm^{-1}. MS (ES^+) *m/z* (%): 308 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{17}H_{30}NO_2Si]^+$: 308.2046, found 308.2041.

***N*,*N*-Diethyl-2-tri-*iso*-propylsilanyloxybenzamide 252b**

93%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 1.02 (3H, t, *J* = 7.2 Hz, CH_3), 1.08 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 1.10 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 1.24 (3H, t, *J* = 7.2 Hz, CH_3), 1.27 (3H, septet, *J* = 7.7 Hz, 3xC$\underline{H}(CH_3)_2$), 3.12 (1H, dq, *J* = 14.4, 7.2 Hz, C$\underline{H}_A$H$_B$N), 3.25 (1H, dq, *J* = 14.4, 7.2 Hz, CH$_A\underline{H}_B$N), 3.49 (1H, dq, *J* = 13.6, 7.2 Hz, C$\underline{H}_C$H$_D$N), 3.58 (1H, dq, *J* = 13.6, 7.2 Hz, CH$_C\underline{H}_D$N), 6.83 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 6.94 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.16-7.23 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 12.45 (3x$\underline{C}H(CH_3)_2$), 12.68 (CH_3), 13.65 (CH_3), 17.51 (3xCH($\underline{C}H_3)_2$, 38.75 (CH_2N), 42.44 (CH_2N), 118.20 (CH_{Ar}), 120.46 (CH_{Ar}), 127.22 (CH_{Ar}), 128.90 (C_{quat}), 129.36 (CH_{Ar}), 151.00 (C_{quat}), 168.43 (C=O). IR (ATR): ν 2966 (CH), 2943 (CH), 2867 (CH), 1636, 1273, 917, 754, 678 cm^{-1}. MS (ES$^+$) *m/z* (%): 350 ([M+H]$^+$, 100).

6-(*tert*-Butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide 252c

89%, white solid, mp 68.8°C. ^{1}H NMR ($CDCl_3$): δ 0.17 (3H, s, CH_3Si), 0.22 (3H, s, CH_3Si), 0.97 (9H, s, $C(CH_3)_3$), 2.88 (3H, s, NCH_3), 3.09 (3H, s, NCH_3), 6.81 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 6.99 (1H, dt, *J* = 1.1, 8.3 Hz, CH_{Ar}), 7.22-7.28 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -4.97 (CH_3Si), -4.51 (CH_3Si), 17.61 ($\underline{C}(CH_3)_3$), 25.20 (C($\underline{C}H_3)_3$), 34.27 (CH_3N), 37.72 (CH_3N), 119.01 (CH_{Ar}), 121.36 (CH_{Ar}), 127.87 (CH_{Ar}), 128.92 (C_{quat}), 129.73 (CH_{Ar}), 150.81 (C_{quat}), 169.14 (C=O). IR (ATR): ν 2941 (CH), 2865 (CH), 1628, 1479, 1280, 1257, 908, 882 cm^{-1}. MS (ES$^+$) *m/z* (%): 280 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{15}H_{26}NO_2Si]^+$: 280.1733, found 280.1735.

***N*,*N*-Dimethyl-2-tri-*iso*-propylsilanyloxybenzamide 252d**

84%, white crystals, mp 66.7°C. ^{1}H NMR ($CDCl_3$): δ 1.07 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 1.10 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 1.29 (3H, septet, *J* = 7.2 Hz, 3xC$\underline{H}(CH_3)_2$), 2.88 (3H, s, CH_3N), 3.08 (3H, CH_3N), 6.83 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 6.96 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.19-7.25 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 12.48 (3x$\underline{C}H(CH_3)_2$), 17.64 (3xCH($\underline{C}H_3)_2$), 34.29 (CH_3N), 37.80 (CH_3N), 118.31 (CH_{Ar}), 120.93 (CH_{Ar}), 127.79 (CH_{Ar}), 128.58 (C_{quat}), 129.59 (CH_{Ar}), 151.21 (C_{quat}), 169.26 (C=O). IR (ATR): ν 2941 (CH), 2864 (CH), 1628, 1280, 1257, 882 cm^{-1}. MS (ES$^+$) *m/z* (%): 322 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{32}NO_2Si]^+$: 322.2202, found 322.2212.

2-(*tert*-Butyldimethylsilanyloxy)-3,*N*,*N*-trimethylbenzamide 252e

36%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.10 (3H, s, CH_3Si), 0.12 (3H, s, CH_3Si), 1.02 (9H, s, $C(CH_3)_3$), 2.24 (3H, s, CH_3), 2.87 (3H, s, NCH_3), 3.06 (3H, s, NCH_3), 6.93 (1H, t, *J* = 7.4 Hz, CH_{Ar}), 7.13-7.18 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -4.10 (CH_3Si), -3.66 (CH_3Si), 17.74 (CH_3), 18.45 ($\underline{C}(CH_3)_3$), 26.04 (C($\underline{C}H_3)_3$), 34.84 (CH_3N), 38.13 (CH_3N), 122.08 (CH_{Ar}), 126.70 (CH_{Ar}), 129.16 (C_{quat}), 129.50 (C_{quat}), 132.25 (CH_{Ar}), 149.32 (C_{quat}), 170.05 (C=O). IR (ATR): ν 2930 (CH), 2858 (CH), 1635 (C=O), 1460, 1262, 1224, 909, 759 cm^{-1}. MS (ES$^+$) *m/z* (%): 294 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{16}H_{28}NO_2Si]^+$: 294.1889, found 294.1886.

_N_-[2-(_tert_-Butyldimethylsilanyloxy)benzoyl]pyrrolidine 260a

88%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.20 (6H, s, 2xCH_3Si), 0.97 (9H, s, $C(CH_3)_3$), 1.82-1.97 (4H, m, 2xCH_2), 3.29 (2H, br s, NCH_2), 3.61 (2H, t, J = 6.6 Hz, NCH_2), 6.82 (1H, d, J = 7.7 Hz, CH_{Ar}), 6.99 (1H, t, J = 7.7 Hz, CH_{Ar}), 7.01-7.30 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -4.56 (CH_3Si), -4.22 (CH_3Si), 18.00 ($\underline{C}(CH_3)_3$), 25.57 ($C(\underline{C}H_3)_3$), 41.75 (CH_2), 46.93 (CH_2), 66.61 (NCH_2), 66.79 (NCH_2), 119.50 (CH_{Ar}), 121.73 (CH_{Ar}), 128.11 (C_{quat}), 128.17 (CH_{Ar}), 130.23 (CH_{Ar}), 151.21 (C_{quat}), 168.08 (C=O). IR (ATR): ν 2930 (CH), 1634, 1453, 1251, 750 cm^{-1}. MS (ES$^+$) *m/z* (%): 306 ([M+H]$^+$, 100).

_N_-[2-(_tert_-Butyldimethylsilanyloxy)benzoyl]morpholine 260b

69%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.18 (3H, s, CH_3Si), 0.22 (3H, s, CH_3Si), 0.98 (9H, s, $C(CH_3)_3$), 3.21-3.38 (2H, m, CH_2), 3.44-3.55 (2H, m, CH_2), 3.65-3.72 (2H, m, CH_2), 3.82 (1H, td, J = 3.9, 12.4 Hz, $C\underline{H}_AH_B$), 4.06 (1H, td, J = 3.9, 12.4 Hz, $C\underline{H}_AH_B$), 6.82 (1H, d, J = 7.7 Hz, CH_{Ar}), 7.00 (1H, t, J = 7.7 Hz, CH_{Ar}), 7.24-7.29 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -4.56 (CH_3Si), -4.22 (CH_3Si), 18.00 ($\underline{C}(CH_3)_3$), 25.57 ($C(\underline{C}H_3)_3$), 41.75 (CH_2), 46.93 (CH_2), 66.61 (NCH_2), 66.79 (NCH_2), 119.50 (CH_{Ar}), 121.73 (CH_{Ar}), 128.11 (C_{quat}), 128.17 (CH_{Ar}), 130.23 (CH_{Ar}), 151.21 (C_{quat}), 168.08 (C=O). IR (ATR): ν 2929 (CH), 2857, 1637, 1459, 1252, 756 cm^{-1}. MS (ES$^+$) *m/z* (%): 206 ([M+H]$^+$, 100).

1-(_tert_-Butyldimethylsilanyloxy)-_N_,_N_-dimethylnaphthalene-2-carboxamide 263a

62% over 2 steps, pink crystals, mp 75°C. ^{1}H NMR ($CDCl_3$): δ 0.05 (3H, s, CH_3Si), 0.16 (3H, s, CH_3Si), 1.12 (9H, s, $C(CH_3)_3$), 2.94 (3H, s, NCH_3), 3.12 (3H, s, NCH_3), 7.42 (1H, d, J = 8.3 Hz, CH-3 or CH-4), 7.48-7.53 (2H, m, 2xCH_{Ar}), 7.55 (1H, d, J = 8.3 Hz, CH-3 or CH-4), 7.80-7.83 (1H, m, CH_{Ar}), 8.14-8.17 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -4.13 (2xCH_3Si), 18.22 ($\underline{C}(CH_3)_3$), 25.84 ($C(\underline{C}H_3)_3$), 34.67 (CH_3N), 37.87 (CH_3N), 122.17 (CH_{Ar}), 122.98 (C_{quat}), 123.06 (CH_{Ar}), 125.27 (CH_{Ar}), 125.57 (CH_{Ar}), 126.58 (CHAr), 127.57 (CH_{Ar}), 135.04 (2xC_{quat}), 146.80 (C_{quat}), 169.68 (C=O). IR (ATR): ν 2928 (CH), 2857 (CH), 1629 (C=O), 1386, 1113, 826, 763 cm^{-1}. MS (ES$^+$) *m/z* (%): 330 ([M+H]$^+$, 100).

3-(_tert_-Butyldimethylsilanyloxy)-_N_,_N_-dimethylnaphthalene-2-carboxamide 263b

48% over 2 steps, pale white solid, mp 77°C. ^{1}H NMR ($CDCl_3$): δ 0.23 (3H, s, CH_3Si), 0.31 (3H, s, CH_3Si), 1.00 (9H, s, $C(CH_3)_3$), 2.88 (3H, s, NCH_3), 3.13 (3H, s, NCH_3), 7.15 (1H, s, CH-4), 7.36 (1H, dt, J = 1.4, 7.8 Hz, CH-6 or CH-7), 7.45 (1H, dt, J = 1.4, 7.8 Hz, CH-6 or CH-7), 7.69 (1H, d, J = 7.8 Hz, CH-5 or CH-8), 7.77 (1H, d, J = 7.8 Hz, CH-5 or CH-8), 7.77 (1H, s, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.94 (CH_3Si), -4.34 (CH_3Si), 17.74 ($\underline{C}(CH_3)_3$), 25.31 ($C(\underline{C}H_3)_3$), 34.41 (CH_3N), 37.86 (CH_3N), 113.94 (CH_{Ar}), 124.15 (CH_{Ar}), 126.19 (CH_{Ar}), 126.57 (CH_{Ar}), 127.45 (CH_{Ar}), 127.64 (CH_{Ar}), 128.61 (C_{quat}),

130.63 (C_{quat}), 134.28 (C_{quat}), 149.09 (C_{quat}), 168.94 (C=O). IR (ATR): ν 2927 (CH), 2857 (CH), 1630 (C=O), 1451, 1259, 1178, 931, 751 cm^{-1}. MS (ES^+) *m/z* (%): 330 ($[M+H]^+$, 100).

2-(*tert*-Butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-1-carboxamide 263c

65% over 2 steps, pale white solid, mp 135°C. ^1H NMR ($CDCl_3$): δ 0.23 (3H, s, CH_3Si), 0.28 (3H, s, CH_3Si), 1.01 (9H, s, $C(CH_3)_3$), 2.84 (3H, s, NCH_3), 3.21 (3H, s, NCH_3), 7.05 (1H, d, *J* = 9.4 Hz, CH-3), 7.35 (1H, dt, *J* = 1.1, 7.7 Hz, CH-6 or CH-7), 7.45 (1H, dt, *J* = 1.1, 7.7 Hz, CH-6 or CH-7), 7.67 (1H, d, *J* = 7.7 Hz, CH-5 or CH-8), 7.73 (1H, d, *J* = 9.4 Hz, CH-4), 7.77 (1H, d, J = 7.7 Hz, CH-5 or CH-8). ^{13}C NMR ($CDCl_3$): δ -4.19 (CH_3Si), -3.78 (CH_3Si), 18.15 ($\underline{C}(CH_3)_3$), 25.68 ($C(\underline{C}H_3)_3$), 34.65 (CH_3N), 37.87 (CH_3N), 120.40 (CH_{Ar}), 122.84 (C_{quat}), 124.29 (CH_{Ar}), 124.38 (CH_{Ar}), 127.24 (CH_{Ar}), 128.02 (CH_{Ar}), 129.29 (C_{quat}), 130.05 (CH_{Ar}), 131.41 (C_{quat}), 148.86 (C_{quat}), 168.75 (C=O). IR (ATR): ν 2958 (CH), 2929 (CH), 1634 (C=O), 1465, 1244, 830, 786 cm^{-1}. MS (ES^+) *m/z* (%): 330 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{28}NO_2Si]^+$: 330.1889, found 330.1891.

5.6.3 General procedure for TBDPS protection[165]

DIPEA (2.79 mL, 16 mmol) and *tert*-butyldiphenylsilyl chloride (4.16 mL, 16 mmol) were added to a solution of the appropriate benzamide (14.5 mmol) in dichloromethane (40 mL) under a N_2 atmosphere. The reaction mixture was stirred for 20 h at room temperature. Afterwards, H_2O (40 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2x40 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate).

2-(*tert*-Butyldiphenylsilanyloxy)-*N*,*N*-diethylbenzamide 255a

95%, colourless crystals, mp 90-92°C. ^1H NMR ($CDCl_3$): δ 1.04 (9H, s, $C(CH_3)_3$), 1.09 (3H, t, *J* = 7.2 Hz, CH_3), 1.32 (3H, t, *J* = 7.2 Hz, CH_3), 3.26 (1H, dq, *J* = 14.4, 7.2 Hz, $C\underline{H}_AH_BN$), 3.39 (1H, dq, *J* = 14.4, 7.2 Hz, $CH_A\underline{H}_BN$), 3.55 (1H, dq, *J* = 13.6, 7.2 Hz, $C\underline{H}_CH_DN$), 3.72 (1H, dq, *J* = 13.6, 7.2 Hz, $CH_C\underline{H}_DN$), 6.39-6.45 (1H, m, CH_{Ar}), 6.83-6.92 (2H, m, 2xCH_{Ar}), 7.17-7.21 (1H, m, CH_{Ar}), 7.31-7.48 (5H, m, 5xCH_{Ar}), 7.70-7.77 (5H, m, 5xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.43 (CH_3), 14.27 (CH_3), 19.43 ($\underline{C}(CH_3)_3$), 26.29 ($C(\underline{C}H_3)_3$), 39.34 (CH_2N), 43.02 (CH_2N), 119.28 (CH_{Ar}), 121.09 (CH_{Ar}), 127.44 (CH_{Ar}), 127.53 (CH_{Ar}), 127.85 (2xCH_{Ar}), 127.93 (2xCH_{Ar}), 129.01 (C_{quat}), 129.18 (CH_{Ar}), 129.30 (CH_{Ar}), 130.00 (CH_{Ar}), 131.39 (C_{quat}), 133.01 (C_{quat}), 134.89 (CH_{Ar}), 135.26 (CH_{Ar}), 135.64 (CH_{Ar}), 150.92 (C_{quat}), 169.15 (C=O). IR (ATR): ν 2931 (CH), 1635, 1427, 1112, 921, 700 cm^{-1}. MS (ES^+) *m/z* (%): 432 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{27}H_{34}NO_2Si]^+$: 432.2359, found 432.2363.

2-(*tert*-Butyldiphenylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide 255b

64%, white crystals, mp 105.2. ^{1}H NMR ($CDCl_3$): δ 1.07 (9H, s, $C(CH_3)_3$), 3.99 (3H, s, NCH_3), 3.16 (3H, s, NCH_3), 3.33 (3H, s, OCH_3), 5.97 (1H, d, *J* = 2.2 Hz, CH-3), 6.46 (1H, dd, *J* = 2.2, 8.3 Hz, CH-5), 7.18 (1H, d, *J* = 8.3 Hz,), 7.39 (6H, br s, 6xCH_{Ar}), 7.72 (4H, m, 4xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 19.48 ($\underline{C}(CH_3)_3$), 26.41 ($C(\underline{C}H_3)_3$), 36.84 (CH_2N), 38.47 (CH_2N), 54.96 (OCH_3), 105.08 (CH_{Ar}), 107.44 (CH_{Ar}), 121.21 (C_{quat}), 127.96 (6xCH_{Ar}), 128.63 (CH_{Ar}), 130.14 (4xCH_{Ar}), 135.48 (2xC_{quat}), 152.25 (C_{quat}), 160.54 (C_{quat}), 169.75 (C=O). IR (ATR): ν 2933 (CH), 1624, 1605, 1204, 1111, 986, 700 cm^{-1}. MS (ES^+) *m/z* (%): 434 ($[M+H]^+$, 100).

5.6.4 General procedure for the preparation of 2-allyl-6-silanyloxy-*N*,*N*-dialkylbenzamide derivatives

A solution of the appropriate 2-silanyloxy-*N*,*N*-dialkylbenzamide (12.9 mmol) in anhydrous THF (35 mL) was cooled to -78°C and freshly titrated *t*-BuLi in hexanes (16.96 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred for 1h at -78°C and subsequently $CuBr{\cdot}Me_2S$ (5.30 g, 25.8 mmol, 2 equiv.) was added and the mixture was allowed to warm to -10°C and stirred for 40 min. Next, the mixture was cooled to -78°C and allyl bromide (2.33 mL, 25.8 mmol, 2 equiv.) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The salts were filtered off over Celite® and the filtrate was extracted with EtOAc (100 mL) and washed with H_2O (3x50 mL). Drying over $MgSO_4$ and evaporation of the solvent in vacuo followed by flash chromatography gave the corresponding 2-allyl-6-silanyloxy-*N*,*N*-dialkylbenzamide derivatives.

2-Allyl-6-(*tert*-butyldimethylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide 243

66%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.24 (3H, s, CH_3Si), 0.95 (9H, s, $C(CH_3)_3$), 2.78 (3H, s, CH_3N), 3.05 (3H, s, CH_3N), 3.27-3.37 (2H, m, CH_2-1'), 3.78 (3H, s, OCH_3), 5.02-5.08 (2H, m, $=CH_2$-3'), 5.83-5.89 (1H, m, CH-2'), 6.22 (1H, d, *J* = 2.2 Hz, CH-5), 6.39 (1H, d, *J* = 2.2 Hz, CH-3). ^{13}C NMR ($CDCl_3$): δ -4.80 (CH_3Si), -4.24 (CH_3Si), 17.78 ($\underline{C}(CH_3)_3$), 25.37 ($C(\underline{C}H_3)_3$), 34.16 (CH_2-1'), 37.66 ($N(CH_3)_2$), 54.97 (OCH_3), 102.92 (CH-5), 107.47 (CH-3), 115.77 ($=CH_2$-3'), 121.54 (C_{quat}), 136.38 (CH-2'), 139.30 (C_{quat}), 152.29 (C_{quat}), 160.20 (C_{quat}), 168.74 (C=O). IR (ATR): ν 2954, 2929, 1602, 1332, 1154, 834, 779 cm^{-1}. MS (ES^+) *m/z* (%): 350 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{32}NO_3Si]^+$: 350.2152, found 350.2158.

2-Allyl-6-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-diethylbenzamide 253a

88%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.23 (3H, s, CH_3Si), 0.96 (9H, s, $C(CH_3)_3$), 1.04 (3H, t, *J* = 7.2 Hz, CH_3), 1.25 (3H, t, *J* = 7.2 Hz, CH_3), 3.13 (2H, q, *J* = 7.2 Hz, CH_2N), 3.21-3.32 (2H, m, CH_2-1'), 3.32 (1H, dq, *J* = 13.6, 7.2 Hz, $C\underline{H}_CH_DN$), 3.76 (1H, dq, *J* = 13.6, 7.2 Hz, $CH_C\underline{H}_DN$), 5.04-5.12 (2H, m, $=CH_2$-3'), 5.86-6.00 (1H, m, CH-2'), 6.67 (1H, d, *J* = 7.7 Hz, CH-5), 6.83 (1H, d, *J* = 7.7 Hz, CH-3), 7.13 (1H, t, *J* = 7.7 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.56 (CH_3Si), -

3.93 (CH_3Si), 12.94 (CH_3), 14.01 (CH_3), 18.18 ($\underline{C}(CH_3)_3$), 25.69 ($C(\underline{C}H_3)_3$), 37.23 (CH_2-1'), 38.97 (CH_2N), 43.11 (CH_2N), 116.31 (=CH_2-3'), 116.70 (CH-5), 121.99 (CH-3), 128.93 (CH-4), 129.21 (C_{quat}), 136.64 (CH-2'), 138.26 (C_{quat}), 151.42 (C_{quat}), 168.13 (C=O). IR (ATR): ν 2956 (CH), 2931 (CH), 1635, 1249, 915, 758 cm^{-1}. MS (ES^+) *m/z* (%): 348 ($[M+H]^+$, 100).

6-Allyl-*N*,*N*-diethyl-2-tri-*iso*-propylsilanyloxybenzamide 253b

91%, colourless oil. ^1H NMR ($CDCl_3$): δ 1.05 (3H, t, *J* = 7.2 Hz, CH_3), 1.08 (9H, d, *J* = 7.7 Hz, 3xCHC$\underline{H}_3$), 1.10 (9H, d, *J* = 7.7 Hz, 3xCHC$\underline{H}_3$), 1.25 (3H, t, *J* = 7.2 Hz, CH_3), 1.28 (3H, septet, *J* = 7.7 Hz, 3xC$\underline{H}(CH_3)_2$), 3.13 (1H, q, *J* = 7.2 Hz, C$\underline{H}_A$$H_B$N), 3.14 (1H, q, *J* = 7.2 Hz, $CH_A\underline{H}_B$N), 3.21-3.39 (3H, m, C$\underline{H}_C$$H_D$N and CH_2-1'), 3.84 (1H, dq, *J* = 13.8, 7.2 Hz, $CH_C\underline{H}_D$N), 5.04-5.12 (2H, m, CH_2-3'), 5.87-6.00 (1H, m, CH-2'), 6.69 (1H, d, *J* = 7.7 Hz, CH-5), 6.81 (1H, d, *J* = 7.7 Hz, CH-3), 7.11 (1H, t, *J* = 7.7 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ 12.85 (3x$\underline{C}$H$(CH_3)_2$), 12.97 (CH_3), 13.92 (CH_3), 17.97 (3xCH($\underline{C}H_3)_2$, 37.08 (CH_2-1'), 38.91 (CH_2N), 40.05 (CH_2N), 116.19 (=CH_2-3' and CH-5), 121.50 (CH-3), 128.71 (CH-4), 136.55 (CH-2'), 138.08 (C_{quat}), 151.62 (C_{quat}), 167.99 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): ν 2942 (CH), 2943 (CH), 2867 (CH), 1635, 1461, 1278, 1023, 682 cm^{-1}. MS (ES^+) *m/z* (%): 390 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{23}H_{40}NO_2Si]^+$: 390.2828, found 390.2839.

2-Allyl-6-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide 253c

65%, colourless oil. ^1H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.24 (3H, s, CH_3Si), 0.96 (9H, s, $C(CH_3)_3$), 2.80 (3H, s, CH_3N), 3.06 (3H, s, CH_3N), 3.29 (1H, dd, *J* = 6.9, 15.1 Hz, C$\underline{H}_A$$H_B$-1'), 3.39 (1H, dd, *J* = 6.9, 15.1 Hz, $CH_A\underline{H}_B$-1'), 4.99-5.08 (2H, m, =CH_2-3'), 5.82-5.96 (1H, m, CH-2'), 6.66 (1H, d, *J* = 8.0 Hz, CH-5), 6.83 (1H, d, *J* = 8.0 Hz, CH-3), 7.14 (1H, t, *J* = 8.0 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.56 (CH_3Si), -3.99 (CH_3Si), 18.03 ($\underline{C}(CH_3)_3$), 25.57 ($C(\underline{C}H_3)_3$), 34.36 (CH_3N), 37.58 (CH_2-1'), 37.87 (CH_3N), 115.88 (=CH_2-3'), 116.49 (CH-5), 122.41 (CH-3), 128.86 (C_{quat}), 129.25 (CH-4), 136.77 (CH-2'), 138.60 (C_{quat}), 151.44 (C_{quat}), 168.94 (C=O). IR (ATR): ν 2930 (CH), 1620 (C=O), 1600, 1252, 781 cm^{-1}. MS (ES^+) *m/z* (%): 320 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{30}NO_2Si]^+$: 320.2046, found 320.2053.

6-Allyl-*N*,*N*-dimethyl-2-tri-*iso*-propylsilanyloxybenzamide 253d

98%, colourless oil. ^1H NMR ($CDCl_3$): δ 0.89 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 0.91 (9H, d, *J* = 7.2 Hz, 3xCHC$\underline{H}_3$), 1.10 (3H, septet, *J* = 7.2 Hz, 3xC$\underline{H}(CH_3)_2$), 2.62 (3H, s, CH_3N), 2.88 (3H, s, CH_3N), 3.10 (1H, ddd, *J* = 1.7, 6.7, 15.3, C$\underline{H}_A$$H_B$-1'), 3.19 (1H, dd, *J* = 6.7, 15.3, $CH_A\underline{H}_B$-1'), 4.79-4.90 (2H, m, CH_2-3'), 5.63-5.77 (1H, m, CH-2'), 6.50 (1H, d, *J* = 8.0 Hz, CH-5), 6.61 (1H, d, *J* = 8.0 Hz, CH-3), 6.93 (1H, dt, *J* = 1.7, 8.0 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ 12.67 (3x$\underline{C}$H$(CH_3)_2$), 17.83 (3xCH($\underline{C}H_3)_2$), 34.04 (CH_2N), 37.39 (CH_2-1'), 37.66 (CH_2N), 115.62 (=CH_2-3'), 115.77 (CH-5), 121.74 (CH-3),

128.25 (C_{quat}), 128.89 (CH-4), 136.52 (CH-2'), 138.22 (C_{quat}), 151.49 (C_{quat}), 168.66 (C=O). IR (ATR): ν 2943 (CH), 2866 (CH), 1639 (C=O), 1461, 1277, 1026, 682 cm^{-1}. MS (ES^+) *m/z* (%): 362 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{36}NO_2Si]^+$: 362.2515, found 362.2514.

2-Allyl-6-(*tert*-butyldiphenylsilanyloxy)-4-methoxy-*N*,*N*-dimethylbenzamide 256b

29%, pale white crystals, mp 97°C. ^1H NMR ($CDCl_3$): δ 1.05 (9H, s, $C(CH_3)_3$), 2.92 (3H, s, CH_3N), 3.14 (3H, s, CH_3N), 3.28 (1H, dd, *J* = 7.2, 15.7 Hz, $C\underline{H}_AH_B$-1'), 3.32 (3H, s, OCH_3), 3.39 (1H, dd, *J* = 7.2, 15.7 Hz, $CH_A\underline{H}_B$-1'), 5.02-5.10 (2H, m, $=CH_2$-3'), 5.81 (1H, d, *J* = 2.2 Hz, CH-5), 5.82-5.96 (1H, m, CH-2'), 6.31 (1H, d, *J* = 2.2 Hz, CH-3), 7.32-7.47 (6H, m, $6xCH_{Ar}$), 7.68-7.75 (4H, m, $4xCH_{Ar}$). ^{13}C NMR ($CDCl_3$): δ 19.52 ($\underline{C}(CH_3)_3$), 26.38 ($C(\underline{C}H_3)_3$), 34.55 (NCH_3), 37.78 (CH_2-1'), 38.21 (NCH_3), 54.96 (OCH_3), 102.81 (CH-5), 108.20 (CH-3), 116.15 (CH_2-3'), 121.01 (C_{quat}), 127.96 ($2xCH_{Ar}$), 128.00 ($2xCH_{Ar}$), 130.14 ($2xCH_{Ar}$), 131.62 (C_{quat}), 133.03 (C_{quat}), 135.36 ($2xCH_{Ar}$), 135.74 ($2xCH_{Ar}$), 136.55 (=CH-2'), 139.22 (C_{quat}), 152.26 (C_{quat}), 159.84 (C_{quat}), 169.12 (C=O). IR (ATR): ν 2932, 1626, 1601, 1156, 701 cm^{-1}. MS (ES^+) *m/z* (%): 474 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{29}H_{36}NO_3Si]^+$: 474.2465, found 474.2478.

***N*-[2-Allyl-6-(*tert*-butyldimethylsilanyloxy)benzoyl]pyrrolidine 261a**

83%, yellowish oil. ^1H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.24 (3H, s, CH_3Si), 0.95 (9H, s, $C(CH_3)_3$), 1.74-1.95 (4H, m, $2xCH_2$), 3.01-3.09 (1H, m, $C\underline{H}_AH_B$-1'), 3.25-3.34 (2H, m, NCH_2), 3.41-3.49 (1H, m, $CH_A\underline{H}_B$-1'), 3.57-3.62 (2H, t, *J* = 6.9 Hz, NCH_2), 4.98-5.09 (2H, m, CH_2-3'), 5.81-5.95 (1H, m, CH-2'), 6.67 (1H, d, *J* = 8.0 Hz, CH-5), 6.83 (1H, d, *J* = 8.0 Hz, CH-3), 7.14 (1H, t, *J* = 8.0 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.89 (CH_3Si), -4.20 (CH_3Si), 17.71 ($\underline{C}(CH_3)_3$), 24.45 (CH_2), 25.33 ($C(\underline{C}H_3)_3$), 25.60 (CH_2), 37.40 (CH_2-1'), 45.05 (NCH_2), 48.84 (NCH_2), 115.48 (CH_2-3'), 116.51 (CH-5), 122.17 (CH-3), 129.01 (CH-4), 129.80 (C_{quat}), 136.51 (CH-2'), 137.90 (C_{quat}), 151.00 (C_{quat}), 166.91 (C=O). IR (ATR): ν 2929 (CH), 1630, 1460, 1420, 1252, 837 cm^{-1}. MS (ES^+) *m/z* (%): 346 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{20}H_{32}NO_2Si]^+$: 346.2202, found 346.2209.

***N*-[2-Allyl-6-(*tert*-butyldimethylsilanyloxy)benzoyl]morpholine 261b**

53%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.23 (3H, s, CH_3Si), 0.98 (9H, s, $C(CH_3)_3$), 3.14-3.31 (2H, m, CH_2), 3.34-3.38 (2H, m, CH_2), 3.46-3.59 (2H, m, CH_2), 3.62-3.70 (2H, m, CH_2), 3.78-3.85 (1H, m, $C\underline{H}_AH_B$-1'), 3.96-4.03 (1H, m, $CH_A\underline{H}_B$-1'), 5.02-5.08 (2H, m, CH_2-3'), 5.84-5.98 (1H, m, CH-2'), 6.68 (1H, d, *J* = 8.0 Hz, CH-5), 6.85 (1H, d, *J* = 8.0 Hz, CH-3), 7.16 (1H, t, *J* = 8.0 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.46 (CH_3Si), -3.96 (CH_3Si), 18.15 ($\underline{C}(CH_3)_3$), 25.75 ($C(\underline{C}H_3)_3$), 37.39 (CH_2-1'), 41.52 (CH_2), 46.61 (CH_2), 66.72 (CH_2), 66.85 (CH_2), 116.28 (CH_2-3'), 116.82 (CH-5), 122.63 (CH-3), 127.83 (C_{quat}), 129.50 (CH-4), 136.71 (CH-2'), 138.61 (C_{quat}), 151.65 (C_{quat}), 167.53

(C=O). IR (ATR): ν 2857 (CH), 1638, 1460, 1426, 1276, 836 cm^{-1}. MS (ES^+) *m/z* (%): 362 ($[M+H]^+$, 100).

3-Allyl-1-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-2-carboxamide 264a

18%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.13 (3H, s, CH_3Si), 0.20 (3H, s, CH_3Si), 1.09 (9H, s, $C(CH_3)_3$), 2.81 (3H, s, CH_3N), 3.08 (3H, s, CH_3N), 3.47 (1H, dd, *J* = 5.5, 15.3 Hz, $C\underline{H}_AH_B$-1'), 3.65 (1H, dd, *J* = 8.0, 15.3 Hz, $CH_A\underline{H}_B$-1'), 5.03-5.10 (2H, m, $=CH_2$-3'), 5.86-5.99 (1H, m, CH-2'), 7.37 (1H, s, CH-4), 7.42 (1H, dt, *J* = 1.1, 7.8 Hz, CH-6 or CH-7), 7.47 (1H, dt, *J* = 1.1, 7.8 Hz, CH-6 or CH-7), 7.75 (1H, d, *J* = 7.8 Hz, CH-5 or CH-8), 8.06 (1H, d, *J* = 7.8 Hz, CH-5 or CH-8). ^{13}C NMR ($CDCl_3$): δ -3.41 (CH_3Si), -3.24 (CH_3Si), 18.71 ($\underline{C}(CH_3)_3$), 26.24 ($C(\underline{C}H_3)_3$), 34.59 (CH_3N), 37.94 (CH_2-1'), 38.15 (CH_3N), 116.06 ($=CH_2$-3'), 122.38 (CH_{Ar}), 123.27 (CH_{Ar}), 124.34 (C_{quat}), 124.87 (CH_{Ar}), 126.46 (C_{quat}), 126.77 (CH_{Ar}), 127.51 (CH_{Ar}), 134.75 (C_{quat}), 135.84 (C_{quat}), 136.92 (CH-2'), 147.27 (C_{quat}), 168.89 (C=O). IR (ATR): ν 2929 (CH), 1630 (C=O), 1384, 829 cm^{-1}. MS (ES^+) *m/z* (%): 370 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{32}NO_2Si]^+$: 370.2202, found 370.2210.

1-Allyl-3-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-2-carboxamide 264b

71%, yellow solid, mp 92°C. ^1H NMR ($CDCl_3$): δ 0.27 (3H, s, CH_3Si), 0.33 (3H, s, CH_3Si), 0.99 (9H, s, $C(CH_3)_3$), 2.79 (3H, s, CH_3N), 3.13 (3H, s, CH_3N), 3.80 (2H d, *J* = 6.6 Hz, , CH_2-1'), 4.98-5.04 (2H, m, $=CH_2$-3'), 5.94-6.07 (1H, m, CH-2'), 7.05 (1H, s, CH-4), 7.37 (1H, dt, *J* = 1.1, 7.7 Hz, CH-6 or CH-7), 7.44 (1H, dt, *J* = 1.1, 7.7 Hz, CH-6 or CH-7), 7.68 (1H, d, *J* = 7.7 Hz, CH-5 or CH-8), 7.97 (1H, d, *J* = 7.7 Hz, CH-5 or CH-8). ^{13}C NMR ($CDCl_3$): δ -4.59 (CH_3Si), -3.97 (CH_3Si), 18.06 ($\underline{C}(CH_3)_3$), 25.60 ($C(\underline{C}H_3)_3$), 34.23 (CH_3N), 34.42 (CH_3N), 38.00 (CH_2-1'), 112.40 (CH-4), 115.99 ($=CH_2$-3'), 124.28 (CH_{Ar}), 124.72 (CH_{Ar}), 126.44 (CH_{Ar}), 127.35 (CH_{Ar}), 127.87 (C_{quat}), 130.74 (C_{quat}), 134.26 (C_{quat}), 134.67 (C_{quat}), 136.17 (CH-2'), 149.29 (C_{quat}), 169.06 (C=O). IR (ATR): ν 2929 (CH), 1624 (C=O), 1392, 840 cm^{-1}. MS (ES^+) *m/z* (%): 370 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{32}NO_2Si]^+$: 370.2202, found 370.2210.

8-Allyl-2-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylnaphthalene-1-carboxamide 264c

65%, gummy yellow solid, mp < 50 °C. ^1H NMR ($CDCl_3$): δ 0.13 (3H, s, CH_3Si), 0.15 (3H, s, CH_3Si), 1.03 (9H, s, $C(CH_3)_3$), 2.37-2.54 (2H, dd, *J* = 5.5, 15.3 Hz, CH_2-1'), 2.69 (3H, s, CH_3N), 2.77 (3H, s, CH_3N), 5.18-5.32 (2H, m, $=CH_2$-3'), 5.95-6.11 (1H, m, CH-2'), 7.11 (1H, d, *J* = 8.8 Hz, CH_{Ar}), 7.28-7.47 (2H, m, 2xCH_{Ar}), 7.65-7.81 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ -3.05 (2xCH_3Si), 17.05 ($\underline{C}(CH_3)_3$), 25.72 (CH_3N), 27.02 ($C(\underline{C}H_3)_3$), 33.97 (CH_3N), 40.47 (CH_2-1'), 116.95 ($=CH_2$-3'), 116.95 (CH_{Ar}), 118.98 (CH_{Ar}), 122.93 (CH_{Ar}), 124.38 (CH_{Ar}), 126.52 (C_{quat}), 128.00 (C_{quat}), 128.08 (CH_{Ar}), 130.29 (CH_{Ar}), 130.73 (C_{quat}), 137.93 (CH-2'), 152.97 (C_{quat}), 170.43 (C=O). IR (ATR): ν 2926, 2854, 1573, 1249, 819, 747 cm^{-1}. MS (ES^+) *m/z* (%): 370 ($[M+H]^+$, 100).

5.6.5 2-But-2-enyl-6-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide 266

A solution of 2-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide **252c** (3.58 mmol) in anhydrous THF (15 mL) was cooled to -78°C and freshly titrated *t*-BuLi in hexanes (7.17 mmol, 2 equiv.) was added dropwise. The reaction mixture was stirred for 1h at -78°C and subsequently $MgBr_2 \cdot Et_2O$ (1.01 g, 3.94 mmol, 1.1 equiv.) was added and the mixture was allowed to warm to room temperature and stirred for 1 h. Next, the Grignard was added dropwise to a solution of crotyl bromide (0.48 mL, 3.94 mmol, 1.1 equiv.) and $NiCl_2(PPh_3)_2$ (70 mg, 0.11 mmol, 3 mol%) in THF (10 mL) at room temperature and stirred for 20 h. The salts were filtered off over Celite® and the filtrate was extracted with EtOAc (20 mL) and washed with H_2O (3x10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* followed by flash chromatography gave 2-but-2-enyl-6-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamide **266** (223 mg, 0.84 mmol, 23%) together with 10% of starting material **252c**.

23%, colourless oil. ^{1}H NMR ($CDCl_3$): δ 0.19 (3H, s, CH_3Si), 0.23 (3H, s, CH_3Si), 0.96 (9H, s, $C(CH_3)_3$), 1.64-1.68 (3H, m, CH_3-4'), 2.79 (3H, s, CH_3N), 3.07 (3H, s, CH_3N), 3.17-3.36 (2H, m, CH_2-1'), 5.46-5.51 (2H, m, CH-2' and CH-3'), 6.65 (1H, d, *J* = 7.7 Hz, CH-5), 6.82 (1H, d, *J* = 8.0 Hz, CH-3), 7.13 (1H, t, *J* = 8.0 Hz, CH-4). ^{13}C NMR ($CDCl_3$): δ -4.66 (CH_3Si), -4.13 (CH_3Si), 17.90 (CH_3-4'), 25.71 ($\underline{C}(CH_3)_3$), 25.46 ($C(\underline{C}H_3)_3$), 34.24 (CH_2-1'), 36.36 (CH_3N), 37.69 (CH_3N), 116.15 (CH-5), 122.22 (CH-3), 126.32 (CH-4), 129.09 and 129.13 (CH-2' and CH-3'), 139.29 (C_{quat}), 151.24 (C_{quat}), 168.88 (C=O) one trisubstituted olefinic carbon is not observed. IR (ATR): ν 2930 (CH), 1620 (C=O), 1600, 1252, 781 cm^{-1}. MS (ES$^+$) *m/z* (%): 334 ([M+H]$^+$, 100).

5.6.6 Organolithium mediated ring-closure

A solution of the appropriate allylsilanoxybenzamide (2.86 mmol) in THF (20 mL) was cooled to -78°C and freshly prepared LDA or titrated MeLi (5.72 mmol, 2.2 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction was quenched with aqueous saturated NH_4Cl (20 mL) and extracted with EtOAc (30 mL). Drying over $MgSO_4$ and evaporation *in vacuo* of the solvent followed by flash chromatography (petroleum ether/ethyl acetate) yielded the corresponding aminonaphthol.

8-Dimethylamino-3-methoxynaphthalen-1-ol 246

90% (base = MeLi), pale white solid, mp 87°C. ^{1}H NMR ($CDCl_3$): δ 2.80 (6H, s, $N(CH_3)_2$), 3.88 (3H, s, OCH_3), 6.54 (1H, d, *J* = 2.2 Hz, CH-2), 6.65 (1H, d, *J* = 2.2 Hz, CH-3), 7.19 (1H, dd, *J* = 1.1, 8.0 Hz, CH-7), 7.34 (1H, t, *J* = 8.0 Hz, CH-6), 7.54 (1H, dd, *J* = 1.1, 8.0 Hz, CH-5), OH not observed. ^{13}C NMR ($CDCl_3$): δ 45.88 ($N(CH_3)_2$), 54.88 (OCH_3), 97.09 (CH-2), 101.32 (CH-4), 114.38 (CH-7), 114.72 (C_{quat}), 125.39 (CH-5), 126.09 (CH-6), 136.89 (C_{quat}), 149.81 (C_{quat}), 157.97 (C_{quat}), 158.98

(C_{quat}). IR (ATR): ν 3089, 2988, 2855, 1619, 1581, 1330, 1157, 1148, 1017 cm^{-1}. MS (ES^+) *m/z* (%): 218 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{16}NO_2]^+$: 218.1181, found 218.1176.

8-Dimethylaminonaphthalen-1-ol 257

57% (base = LDA), pale white solid, mp 57°C. ^1H NMR ($CDCl_3$): δ 2.84 (6H, s, $N(CH_3)_2$), 6.85 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.28 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.34 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.36 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.39 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.66 (1H, d, *J* = 7.7 Hz, CH_{Ar}), OH not observed. ^{13}C NMR ($CDCl_3$): δ 46.42 ($N(CH_3)_2$), 110.00 (CH_{Ar}), 116.86 (CH_{Ar}), 118.02 (CH_{Ar}), 119.01 (C_{quat}), 125.67 (CH_{Ar}), 126.77 (CH_{Ar}), 127.71 (CH_{Ar}), 136.34 (C_{quat}), 150.03 (C_{quat}), 156.87 (C_{quat}). IR (ATR): ν 3050, 2951, 1279, 1016, 825, 761 cm^{-1}. MS (ES^+) *m/z* (%): 188 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{12}H_{14}NO]^+$: 188.1075, found 188.1077.

8-Dimethylaminophenanthren-9-ol 265b

37% (base = MeLi), yellow solid, mp 133°C (decomp). ^1H NMR ($CDCl_3$): δ 2.88 (6H, s, $N(CH_3)_2$), 7.06 (1H, s, CH-10), 7.42 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.52 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.58 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.64 (1H, t, *J* = 7.7 Hz), 7.70 (1H, d, *J* = 7.7 Hz), 8.52 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 8.60 (1H, d, *J* = 7.7 Hz, CH_{Ar}), OH not observed. ^{13}C NMR ($CDCl_3$): δ 46.55 ($N(CH_3)_2$), 107.15 (CH_{Ar}), 112.90 (C_{quat}), 119.13 (CH_{Ar}), 120.40 (C_{quat}), 121.90 (CH_{Ar}), 122.89 (CH_{Ar}), 123.41 (CH_{Ar}), 126.63 (CH_{Ar}), 126.74 (CH_{Ar}), 127.38 (CH_{Ar}), 133.39 (C_{quat}), 134.17 (C_{quat}), 150.08 (C_{quat}), 154.39 (C_{quat}). IR (ATR): ν 3053, 2857, 1627, 1442, 1324, 1110, 758 cm^{-1}. MS (ES^+) *m/z* (%): 238 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{16}H_{16}NO]^+$: 238.1232, found 238.1234.

2-Carbamoyl-3,5-dimethoxybenzoic acid 272

A solution of *N*,*N*-diethyl-2,4-dimethoxybenzamide **237** (3 g, 12.64 mmol) in anhydrous THF (35 mL) was cooled to -78°C and freshly titrated *t*-BuLi in hexanes (16.96 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was stirred for 30 min and subsequently dry CO_2 gas was bubbled through the solution at -78°C. After 5 min the reaction was allowed to warm to room temperature and acidified with HCl (2 M) to pH = 1. The mixture was cooled to 0°C and the precipitate was filtered of. Recrystallisation from H_2O, yielded pure 2-carbamoyl-3,5-dimethoxybenzoic acid **272** (3.13 g, 11.12 mmol, 88%) as a pale white solid.

88%, pale white solid, mp 163.2°C. ^1H NMR (DMSO-d_6): δ 0.92 (3H, t, *J* = 7.2 Hz, CH_3), 1.08 (3H, t, *J* = 7.2 Hz, CH_3), 2.99 (2H, q, *J* = 7.2 Hz, NCH_2), 3.20 (1H, dq, *J* = 13.6, 7.2 Hz, $NC\underline{H}_AH_B$), 3.55 (1H, dq, *J* = 13.6, 7.2 Hz, $NC\underline{H}_AH_B$), 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 6.81 (1H, d, *J* = 2.2 Hz, CH_{Ar}), 6.96 (1H, d, *J* = 2.2 Hz, CH_{Ar}), OH not observed. ^{13}C NMR (DMSO-d_6): δ 12.45 (CH_3), 13.81 (CH_3), 38.36 (NCH_2), 42.56 (NCH_2), 55.03 (OCH_3), 56.44 (OCH_3), 102.86 (CH_{Ar}), 106.41 (CH_{Ar}), 121.53 (C_{quat}), 130.41 (C_{quat}), 157.10 (C_{quat}), 160.24 (C_{quat}), 166.58 (C=O), 167.36 (C=O). IR (ATR): ν

2978, 1712, 1593, 1459, 1315, 1213, 1056 cm^{-1}. MS (ES^-) *m/z* (%): 280 ($[M-H]^-$, 100). HRMS (ES^+) calcd. for $[C_{14}H_{20}NO_5]^+$: 282.1342, found 282.1342.

5.7 Attempted synthesis of C-4 fluorinated pyranonaphthoquinones 275

5.7.1 1,4-Dimethoxy-2-hydroxymethyl-3-arylethynylnaphthalenes 277

A pressure vial was loaded with 3-bromo-1,4-dimethoxy-2-hydroxymethylnaphthalene **280** (1g, 3.4 mmol), $PdCl_2(PPh_3)_2$ (24 mg, 0.034 mmol, 1 mol%), CuI (6.4 mg, 0.034 mmol, 1 mol%), *i*-Pr_2NH (1.9 ml, 13.6 mmol, 4 equiv.) and anhydrous, degassed DMF (10 mL). The mixture was purged with N_2 and allowed to stir for 5 min. Then, a solution of the appropriate arylacetylene (4.08 mmol, 1.2 equiv.) in anhydrous degassed DMF (2 mL) was added dropwise under a N_2 atmosphere. The pressure vial was sealed and heated overnight at 160°C. The reaction mixture was filtered over Celite®, dissolved in EtOAc (50 mL) and washed with H_2O (3x20 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* followed by flash chromatography (petroleum ether/ethyl acetate) yielded the corresponding 1,4-dimethoxy-2-hydroxymethyl-3-arylethynylnaphthalenes **277a** and **277b**.

1,4-Dimethoxy-2-hydroxymethyl-3-phenylethynylnaphthalene 277a

77%, pale white crystals, mp 70.9°C. ^1H NMR ($CDCl_3$): δ 2.69 (1H, br s, OH), 4.00 (3H, s, OCH_3), 4.16 (3H, s, OCH_3), 5.09 (2H, s, CH_2O), 7.37-7.41 (3H, m, 3xCH_{Ar}), 7.54-7.64 (4H, m, 4xCH_{Ar}), 8.08-8.12 (1H, m, CH_{Ar}), 8.14-8.20 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 59.05 (CH_2), 62.11 (OCH_3), 63.57 (OCH_3), 83.86 (≡C_{quat}), 98.60 (≡C_{quat}), 112.22 (C_{quat}), 122.78 (CH_{Ar}), 122.89 (CH_{Ar}), 123.06 (C_{quat}), 127.01 (CH_{Ar}), 127.59 (CH_{Ar}), 128.64 (2xCH_{Ar}), 128.78 (C_{quat}), 128.86 (CH_{Ar}), 129.01 (C_{quat}), 129.97 (C_{quat}), 131.62 (2xCH_{Ar}), 150.72 (C_{quat}), 155.67 (C_{quat}). IR (ATR): ν 3435, 1351, 1046, 995, 759, 691 cm^{-1}. MS (ES^+) *m/z* (%): 301 ($[M-OH]^+$, 100), 319 ($[M+H]^+$, 5).

1,4-Dimethoxy-2-hydroxymethyl-3-(4-methylphenyl)ethynylnaphthalene 277b

69%, yellow crystals, mp 94.3°C. ^1H NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 2.63 (1H, t, *J* = 6.6 Hz, OH), 4.01 (3H, s, OCH_3), 4.16 (3H, s, OCH_3), 5.09 (2H, d, *J* = 6.6 Hz, CH_2O), 7.20 (2H, d, *J* = 7.7 Hz, 2xCH_{Ar}), 7.50 (2H, d, *J* = 7.7 Hz, 2xCH_{Ar}), 7.54-7.59 (2H, m, 2xCH_{Ar}), 8.08-8.13 (1H, m, CH_{Ar}), 8.15-8.18 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.52 (CH_3), 58.81 (CH_2), 62.81 (OCH_3), 63.39 (OCH_3), 83.21 (≡C_{quat}), 98.73 (≡C_{quat}), 112.37 (C_{quat}), 119.88 (C_{quat}), 122.61 (CH_{Ar}), 122.69 (CH_{Ar}), 126.80 (CH_{Ar}), 127.30 (CH_{Ar}), 128.64 (C_{quat}), 128.77 (C_{quat}), 129.24 (2xCH_{Ar}), 129.88 (C_{quat}), 131.36 (2xCH_{Ar}), 138.89 (C_{quat}), 150.57 (C_{quat}), 155.32 (C_{quat}). IR (ATR): ν 3505, 1350, 1039, 820, 772 cm^{-1}. MS (ES^+) *m/z* (%): 315 ($[M-OH^-]^+$, 100), 333 ($[M+H]^+$, 5).

5.8 New entries towards the benzo[*j*]phenanthridinedione scaffold

2-*m*-Tolylaminocarbonyl-3-*m*-tolylamino-1,4-naphthoquinone

A solution of 1,4-dihydroxynaphthalene-2-carboxylic acid (2 g, 9.8 mmol), *meta*-toluidine **291** (1.05 g, 9.8 mmol, 1 equiv.) and DCC (2.02 g, 9.8 mmol, 1 equiv.) in anhydrous 1,4-dioxane was stirred overnight under a nitrogen atmosphere. Then, MnO_2 (5.11 g, 58.8 mmol, 6 equiv.) and $MgSO_4$ (11.80 g, 98 mmol, 10 equiv.) were added and the mixture was stirred for 30 min. The solids were filtered off and the filtrate was evaporated *in vacuo* to yield a mixture that consisted mainly of 2-*m*-tolylaminocarbonyl-3-*m*-tolylamino-1,4-naphthoquinone was obtained, which was further purified by means of flash chromatography.

Red solid, mp 186°C. ^{1}H NMR ($CDCl_3$): δ 2.37 (3H, s, CH_3), 2.38 (3H, s, CH_3), 6.91-6.97 (3H, m, 3xCH_{Ar}), 7.11 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.23-7.29 (2H, m, 2xCH_{Ar}), 7.50 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.51 (1H, s, CH_{Ar}), 7.65 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.80 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.89 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 8.22 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 12.25 (1H, br s, NH), 13.96 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.49 (CH_3), 21.66 (CH_3), 103.63 (C_{quat}), 118.37 (CH_{Ar}), 121.59 (CH_{Ar}), 121.88 (CH_{Ar}), 125.04 (CH_{Ar}), 125.35 (CH_{Ar}), 126.38 (CH_{Ar}), 126.86 (CH_{Ar}), 127.62 (CH_{Ar}), 128.90 (CH_{Ar}), 129.04 (CH_{Ar}), 131.30 (C_{quat}), 132.87 (CH_{Ar}), 133.61 (C_{quat}), 135.27 (CH_{Ar}), 138.02 (C_{quat}), 138.92 (C_{quat}), 139.30 (C_{quat}), 139.85 (C_{quat}), 154.84 (C_{quat}), 167.62 (NC=O), 181.55 (C=O), 182.34 (C=O). IR (ATR): ν 3026 (NH), 1690, 1528, 1288, 780 cm^{-1}. MS (ES$^-$) *m/z* (%): 395 ([M-H]$^-$, 15). HRMS (ES$^+$) calcd. for $[C_{25}H_{21}N_2O_3]^+$: 397.1552, found 397.1546.

5.8.1 1,4-Dimethoxynaphthalene-2-carboxylic acid 293

To a solution of methyl-1,4-dimethoxynaphthalene-2-carboxylate **290** (50 g, 203 mmol) in 1,4-dioxane (160 mL) was added a solution of KOH (3.41 g, 609 mmol, 3 equiv.) in H_2O (320 mL) and stirred overnight. Then EtOAc (100 mL) was added and the mixture was extracted with aqueous saturated $NaHCO_3$ (3x100 mL). The aqueous phase was acidified using concentrated HCl to pH = 1 and cooled to 0°C. The thus formed precipitation was filtered of and washed with H_2O (10 mL). Further freeze drying yielded 1,4-dimethoxynaphthalene-2-carboxylic acid **293** (43.8 g, 189 mmol, 93%) as a white solid.

93%, white solid, mp 172.5°C. ^{1}H NMR ($CDCl_3$): δ 4.04 (3H, s, OCH_3), 4.11 (3H, s, OCH_3), 7.36 (1H, s, CH-3), 7.62-7.68 (2H, m, 2xCH_{Ar}), 8.08-8.13 (1H, m, CH_{Ar}), 8.29-8.33 (1H, m, CH_{Ar}), 11.41 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 56.00 (OCH_3), 64.30 (OCH_3), 103.34 (CH-3), 117.59 (C_{quat}), 122.90 (CH_{Ar}), 122.98 (CH_{Ar}), 127.65 (CH_{Ar}), 128.44 (CH_{Ar}), 129.60 (C_{quat}), 151.47 (C_{quat}), 152.43 (C_{quat}), 167.15 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): ν 2923 (OH), 1689, 1672, 1595, 1367, 1112, 1091, 60, 736 cm^{-1}. MS (ES$^+$) *m/z* (%): 233 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{13}H_{13}O_4]^+$: 233.0814, found 233.0813.

N-meta-Tolyl-1,4-dimethoxynaphthalene-2-carboxamide 292

A microwave vial was loaded with methyl-1,4-dimethoxynaphthalene-2-carboxylate **290** (250 mg, 1.01 mmol), *meta*-toluidine **291** (109 mg, 1.01 mmol, 1 equiv.) and KO*t*-Bu (113 mg, 1.01 mmol, 1 equiv.). The vial was flushed with nitrogen and irradiated in the microwave during 10 min at 100 W. The resulting mixture was partitioned between EtOAc (10 mL) and H_2O (10 mL) and the organic phase was dried over $MgSO_4$, evaporated *in vacuo* and purified by means of flash chromatography to yield *N-meta*-tolyl-1,4-dimethoxynaphthalene-2-carboxamide **292** (140 mg, 0.43 mmol, 43%)

43%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 4.01 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.98 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.28 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.50 (1H, s, CH_{Ar}), 7.52-7.63 (4H, m, 4xCH_{Ar}), 8.11-8.15 (1H, m, CH_{Ar}), 8.25-8.31 (1H, m, CH_{Ar}), 10.06 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.69 (CH_3), 55.94 (OCH_3), 63.49 (OCH_3), 130.51 (CH-3), 117.21 (CH_{Ar}), 120.80 (CH_{Ar}), 121.99 (C_{quat}), 122.72 (CH_{Ar}), 122.81 (CH_{Ar}), 125.22 (CH_{Ar}), 127.39 (CH_{Ar}), 127.62 (CH_{Ar}), 128.26 (C_{quat}), 128.72 (C_{quat}), 129.07 (CH_{Ar}), 138.52 (C_{quat}), 139.16 (C_{quat}), 148.94 (C_{quat}), 152.42 (C_{quat}), 163.65 (C=O). IR (ATR): ν 2931 (CH), 1635, 1427, 1112, 921, 700 cm^{-1}. MS (ES$^+$) *m/z* (%): 322 ([M+H]$^+$, 100).

2-*meta*-Tolylaminocarbonyl-1,4-naphthoquinone 286a

To a solution of *N-meta*-tolyl-1,4-dimethoxynaphthalene-2-carboxamide **292** (140 mg, 0.44 mmol) in CH_3CN (5 mL) was added a solution of CAN (717 mg, 1.31 mmol, 2.5 equiv.) in H_2O (5 mL) in one portion. The reaction mixture was allowed to stir for 30 sec and poured in a 1:1 mixture EtOAc/H_2O (10 mL). The H_2O phase was discarded and the organic phase was washed with water (5 mL).The organic phase was dried over $MgSO_4$ and evaporated in vacuo to yield the crude quinone, which was recrystallised from EtOH to yield pure 2-*meta*-tolylaminocarbonyl-1,4-naphthoquinone **286a** (60 mg, 0.21 mmol, 47%) as a yellow solid.

47%, yellow solid. ^{1}H NMR ($CDCl_3$): δ 2.38 (3H, s, CH_3), 7.00 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.27 (1H, t, *J* = 7.7 Hz, CH-5'), 7.54 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.59 (1H, s, CH-2'), 7.80-7.88 (2H, m, 2xCH_{Ar}), 8.01 (1H, s, CH-3), 8.10-8.15 (1H, m, CH_{Ar}), 8.17-8.23 (1H, m, CH_{Ar}), 10.73 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.65 (CH_3), 117.88 (CH_{Ar}), 121.38 (CH-2'), 126.20 (CH_{Ar}), 126.20 (CH_{Ar}), 126.60 (CH_{Ar}), 125.22 (CH_{Ar}), 127.44 (CH_{Ar}), 129.10 (CH-5'), 132.22 (C_{quat}), 134.75 (CH_{Ar}), 135.06 (CH_{Ar}), 136.66 (C_{quat}), 137.55 (C_{quat}), 148.94 (C_{quat}), 139.24 (C_{quat}), 142.55 (CH-3), 159.17 (NC=O), 184.85 (C=O), 186.74 (C=O). IR (ATR): ν 2931 (CH), 1635, 1427, 1112, 921, 700 cm^{-1}. MS (ES$^+$) *m/z* (%): 292 ([M+H]$^+$, 100).

5.8.2 General procedure for the preparation of *N*-2-bromophenyl-1,4-dialkoxynaphthalene-2-carboxamides 296 and 323

The appropriate 1,4-dialkoxynaphthalene-2-carboxylic acid **293** or **322** (21.53 mmol) was dissolved in $SOCl_2$ (15.5 mL, 215.3 mmol, 10 equiv.) and refluxed for 2.5 h under a nitrogen atmosphere. The reaction mixture was evaporated *in vacuo* and redissolved in anhydrous CH_2Cl_2 (20 mL) and added dropwise to a solution of the appropriate 2-bromoaniline (21.53 mmol, 1 equiv.) and K_2CO_3 (5.95 g, 43.06 mmol, 2 equiv.) in CH_2Cl_2 (40 mL) at 0°C. Next, the salts were filtered off and the filtrate was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (2x50 mL) and aqueous HCl (2 M, 2x50 mL). Drying over $MgSO_4$, evaporation of the solvent *in vacuo* and recrystallisation from EtOH or flash chromatography yielded pure *N*-2-bromophenyl-1,4-dialkoxynaphthalene-2-carboxamides **296** and **323**.

N-2-Bromophenyl-1,4-dimethoxynaphthalene-2-carboxamide 296a

75%, yellow powder, mp 142°C. ^{1}H NMR ($CDCl_3$): δ 4.02 (6H, s, 2xOCH_3), 6.95 (1H, dt, *J* = 1.1, 7.2 Hz, CH_{Ar}), 7.35 (1H, t, *J* = 7.2 Hz, CH_{Ar}), 7.49 (1H, s, CH-3), 7.52-7.58 (3H, m, 3xCH_{Ar}), 8.07-8.14 (1H, m, CH_{Ar}), 8.21-8.26 (1H, m, CH_{Ar}), 8.74 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}), 10.75 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 55.79 (OCH_3), 63.82 (OCH_3), 103.27 (CH-3), 113.25 (C_{quat}), 121.38 (C_{quat}), 122.08 (CH_{Ar}), 122.64 (CH_{Ar}), 122.90 (CH_{Ar}), 124.89 (CH_{Ar}), 127.21 (CH_{Ar}), 127.62 (CH_{Ar}), 128.26 (C_{quat}), 128.31 (CH_{Ar}), 128.77 (C_{quat}), 132.52 (CH_{Ar}), 137.03 (C_{quat}), 149.26 (C_{quat}), 152.16 (C_{quat}), 163.72 (C=O). IR (ATR): ν 3292 (NH), 2969, 1665, 1532, 1372, 1106, 755 cm^{-1}. MS (ES$^+$) *m/z* (%): 386/388 ([M+H]$^+$, 100/97). HRMS (ES$^+$) calcd. for [$C_{19}H_{17}{}^{81}BrNO_3$]$^+$: 386.0392, found 386.0398.

N-(2-Bromo-5-methylphenyl)-1,4-dimethoxynaphthalene-2-carboxamide 296b

54%, pale white solid, mp 166.0°C. ^{1}H NMR ($CDCl_3$): δ 2.35 (3H, s, CH_3), 4.03 (6H, s, 2xOCH_3), 6.78 (1H, d, *J* = 8.3 Hz, CH-4'), 7.43 (1H, d, *J* = 8.3 Hz, CH-3'), 7.50 (1H, s, CH-3), 7.53-7.69 (2H, m, 2xCH_{Ar}), 8.11-8.14 (1H, m, CH_{Ar}), 8.23-8.26 (1H, m, CH_{Ar}), 8.59 (1H, s, CH-6'), 10.71 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.48 (CH_3), 55.80 (OCH_3), 63.85 (OCH_3), 103.25 (CH-3), 110.03 (C_{quat}), 121.42 (C_{quat}), 122.66 (CH_{Ar}), 122.75 (CH_{Ar}), 122.95 (CH_{Ar}), 125.88 (CH_{Ar}), 127.24 (CH_{Ar}), 127.65 (CH_{Ar}), 128.11 (C_{quat}), 128.80 (C_{quat}), 132.09 (CH_{Ar}), 136.61 (C_{quat}), 138.51 (C_{quat}), 149.29 (C_{quat}), 152.19 (C_{quat}), 163.81 (C=O). IR (ATR): ν 3291 (NH), 1671 (C=O), 1587, 1539, 1410, 1370, 1107 cm^{-1}. MS (ES$^+$) *m/z* (%): 400/402 ([M+H]$^+$, 100/97). HRMS (ES$^+$) calcd. for [$C_{20}H_{19}{}^{81}BrNO_3$]$^+$: 400.0548, found 400.0552.

N-(2-Bromo-4-methylphenyl)-1,4-dimethoxynaphthalene-2-carboxamide 296c

88%, pale white solid, mp 144.4°C. ^{1}H NMR ($CDCl_3$): δ 2.34 (3H, s, CH_3), 4.07 (6H, s, 2xOCH_3), 7.19 (1H, d, *J* = 8.0 Hz, CH-5'), 7.44 (1H, d, *J* = 1.1 Hz, CH-3'), 7.53 (1H, s, CH-3), 7.58-7.65 (2H,

m, 2xCH_{Ar}), 8.16-8.20 (1H, m, CH_{Ar}), 8.27-8.31 (1H, m, CH_{Ar}), 8.59 (1H, d, *J* = 8.0 Hz, CH-6'), 10.70 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 20.53 (CH_3), 55.78 (OCH_3), 63.80 (OCH_3), 103.31 (CH-3), 113.16 (C_{quat}), 121.45 (C_{quat}), 121.93 (CH_{Ar}), 122.63 (CH_{Ar}), 122.90 (CH_{Ar}), 127.19 (CH_{Ar}), 127.56 (CH_{Ar}), 128.09 (C_{quat}), 128.72 (C_{quat}), 128.93 (CH_{Ar}), 132.77 (CH_{Ar}), 134.43 (C_{quat}), 134.95 (C_{quat}), 149.19 (C_{quat}), 152.14 (C_{quat}), 163.61 (C=O). IR (ATR): ν 3314 (NH), 1665, 1519, 1370, 1296, 1104, 991 cm^{-1}. MS (ES^+) *m/z* (%): 400/402 ($[M+H]^+$, 100/97).

***N*-(2-Bromo-4,6-dimethylphenyl)-1,4-dimethoxynaphthalene-2-carboxamide 296d**

99%, pale white solid, mp 138.9°C. ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, s, CH_3), 2.32 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.03 (1H, s, CH-5'), 7.32 (1H, s, CH-3'), 7.55 (1H, s, CH-3), 7.56-7.62 (2H, m, 2xCH_{Ar}), 8.09-8.15 (1H, m, CH_{Ar}), 8.26-8.30 (1H, m, CH_{Ar}), 9.66 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 19.42 (CH_3), 20.71 (CH_3), 55.83 (OCH_3), 64.04 (OCH_3), 103.63 (CH-3), 120.90 (C_{quat}), 122.22 (C_{quat}), 122.72 (CH_{Ar}), 122.83 (CH_{Ar}), 127.19 (CH_{Ar}), 127.50 (CH_{Ar}), 128.09 (C_{quat}), 128.78 (C_{quat}), 130.74 (CH_{Ar}), 130.83 (CH_{Ar}), 131.82 (C_{quat}), 137.84 (C_{quat}), 138.51 (C_{quat}), 149.64 (C_{quat}), 152.13 (C_{quat}), 164.02 (C=O). IR (ATR): ν 3339 (NH), 1656, 1591, 1489, 1368, 1220, 1104, 765 cm^{-1}. MS (ES^+) *m/z* (%): 414/416 ($[M+H]^+$, 100/97).

***N*-2-Bromophenyl-1,4-di-*iso*-propoxynaphthalene-2-carboxamide 323**

82%, orange oil. ^{1}H NMR ($CDCl_3$): δ 1.41 (6H, d, *J* = 6.1 Hz, CH($C\underline{H}_3$)$_2$), 1.47 (6H, d, *J* = 6.1 Hz, CH($C\underline{H}_3$)$_2$), 4.46 (1H, septet, *J* = 6.1 Hz, C$\underline{H}$(CH_3)$_2$), 4.86 (1H, septet, *J* = 6.1 Hz, C$\underline{H}$(CH_3)$_2$), 7.00 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.37 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.46 (1H, s, CH-3), 7.55-7.62 (3H, m, 3xCH_{Ar}), 8.11-8.14 (1H, m, CH_{Ar}), 8.30-8.33 (1H, m, CH_{Ar}), 8.75 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 10.34 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.95 (CH($\underline{C}H_3$)$_2$), 22.00 (CH($\underline{C}H_3$)$_2$), 70.34 ($\underline{C}$H(CH_3)$_2$), 79.21 ($\underline{C}$H(CH_3)$_2$), 105.16 (CH-3), 112.73 (C_{quat}), 121.57 (CH_{Ar}), 122.78 (CH_{Ar}), 123.24 (CH_{Ar}), 123.61(C_{quat}), 124.66 (CH_{Ar}), 126.66 (CH_{Ar}), 127.07 (CH_{Ar}), 128.17 (CH_{Ar}), 129.13 (C_{quat}), 129.44 (C_{quat}), 132.42 (CH_{Ar}), 136.58 (C_{quat}), 145.84 (C_{quat}), 149.91 (C_{quat}), 164.72 (C=O). IR (ATR): ν 3312, 2976, 1672, 1525, 1380, 1101, 1087, 751 cm^{-1}. MS (ES^+) *m/z* (%): 442/444 ($[M+H]^+$, 60/58).

5.8.3 General procedure for the preparation of *N*-2-bromophenyl-*N*-methoxymethyl-1,4-dialkoxynaphthalene-2-carboxamides 300 or 324

A solution of the appropriate *N*-2-bromophenyl-1,4-dialkoxynaphthalene-2-carboxamide **296** or **323** (6.4 mmol) in anhydrous THF (30 ml) was cooled to 0°C and under a N_2 atmosphere, washed NaH (563 mg, 14.08 mmol, 1.5 mmol) was added. After the addition, the reaction mixture was allowed to stir for 30 min and subsequently MOMCl (0.73 mL, 9.6 mmol, 1.5 equiv.) was added dropwise. The reaction mixture was warmed to 30°C and stirred for 16 h. The reaction was quenched with H_2O (40 mL) and extracted with EtOAc (2x40 mL). The organic phases were dried over $MgSO_4$, evaporated *in*

vacuo and purified by means of flash chromatography (petroleum ether/ethyl acetate) to yield pure *N*-2-bromophenyl-*N*-methoxymethyl-1,4-dialkoxynaphthalene-2-carboxamides **300** or **324**.

_N_-2-Bromophenyl-_N_-methoxymethyl-1,4-dimethoxynaphthalene-2-carboxamide 300a

62%, colourless oil. ^{1}H NMR ($CDCl_3$): major rotamer δ 3.66 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.68 (1H, d, *J* = 10.2 Hz, $NC\underline{H}_AH_B$), 5.91 (1H, d, *J* = 10.2 Hz, $NCH_A\underline{H}_B$), 6.69 (1H, s, CH-3), 6.93 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.02 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.38-7.51 (4H, m, 4xCH_{Ar}), 7.95 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 8.09 (1H, d, *J* = 8.3 Hz, CH_{Ar}). Minor rotamer δ 3.66 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.77 (1H, d, *J* = 10.2 Hz, $NC\underline{H}_AH_B$), 4.94 (1H, d, *J* = 10.2 Hz, $NCH_A\underline{H}_B$), 6.88 (1H, s, CH-3), 7.28-7.31 (1H, m, CH_{Ar}), 7.38-7.51 (2H, m, CH_{Ar}), 7.54-7.64 (2H, m, 2xCH_{Ar}), 7.73-7.76 (1H, m, CH_{Ar}), 8.14 (1H, d, *J* = 8.3 Hz), 8.29 (1H, d, *J* = 8.3 Hz). Major/minor = 5/1. ^{13}C NMR ($CDCl_3$): major rotamer δ 55.62 (OCH_3), 56.98 (OCH_3), 63.63 (OCH_3), 77.56 (NCH_2), 100.78 (CH-3), 122.12 (CH_{Ar}), 122.37 (CH_{Ar}), 122.66 (C_{quat}), 126.14 (CH_{Ar}), 126.75 (CH_{Ar}), 126.81 (C_{quat}), 127.24 (C_{quat}), 127.91 (CH_{Ar}), 127.99 (C_{quat}), 129.71 (CH_{Ar}), 131.99 (CH_{Ar}), 132.84 (CH_{Ar}), 139.42 (C_{quat}), 145.50 (C_{quat}), 151.38 (C_{quat}), 170.30 (C=O). Minor rotamer δ 55.83 (OCH_3), 56.98 (OCH_3), 63.91 (OCH_3), 82.32 (NCH_2), 102.29 (CH-3), 122.37 (CH_{Ar}), 122.60 (CH_{Ar}), 124.23 (C_{quat}), 125.86 (CH_{Ar}), 126.81 (CH_{Ar}), 127.24 (C_{quat}), 127.99 (CH_{Ar}), 128.45 (C_{quat}), 129.71 (CH_{Ar}), 131.99 (CH_{Ar}), 132.84 (CH_{Ar}), 133.63 (C_{quat}), 139.22 (C_{quat}), 146.25 (C_{quat}), 152.08 (C_{quat}), 170.30 (C=O). IR (ATR): ν 3350, 2937, 2838, 2570, 1669, 1612, 1516, 1251, 1180, 1029 cm^{-1}. MS (ES$^+$) *m/z* (%): 215 ([M-C_8H_9BrNO]$^+$, 100), 430/432 ([M+H]$^+$, 10/9.7).

_N_-(2-Bromo-5-methylphenyl)-_N_-methoxymethyl-1,4-dimethoxynaphthalene-2-carboxamide 300b

70%, colourless oil. ^{1}H NMR ($CDCl_3$): major rotamer δ 2.03 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 4.67 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 5.89 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.67 (1H, s, CH-3), 6.71 (1H, dd, *J* = 1.7, 8.3 Hz, CH-4'), 7.20 (1H, d, *J* = 1.7 Hz, CH-6'), 7.26 (1H, d, *J* = 8.3 Hz, CH-3'), 7.42 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 7.48 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 7.97 (1H, dd, *J* = 1.1, 7.7 Hz, CH-5 or CH-8), 8.09 (1H, dd, *J* = 1.1, 7.7 Hz, CH-5 or CH-8). Minor rotamer δ 2.38 (3H, s, CH_3), 3.14 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.75 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 4.92 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.88 (1H, s, CH-3), 7.08 (1H, dd, *J* = 1.7, 8.3 Hz, CH-3'), 7.30 (1H, d, *J* = 1.7 Hz, CH-6'), 7.56 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 7.60 (1H, d, *J* = 8.3 Hz,), 7.61 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 8.14 (1H, dd, *J* = 1.1, 7.7 Hz, CH-5 or CH-8), 8.29 (1H, dd, *J* = 1.1, 7.7 Hz, CH-5 or CH-8). Major/minor = 4/1. ^{13}C NMR ($CDCl_3$): major rotamer δ 20.29 (CH_3), 55.39 (OCH_3), 56.81 (OCH_3), 63.42 (OCH_3), 77.38 (NCH_2), 100.58 (CH-3), 118.92 (C_{quat}), 121.88 (CH_{Ar}), 122.22 (CH_{Ar}), 125.77 (C_{quat}), 125.91 (CH_{Ar}), 126.57 (CH_{Ar}), 127.06 (C_{quat}), 127.87 (C_{quat}), 130.45 (CH_{Ar}), 132.16 (CH_{Ar}), 132.37 (CH_{Ar}), 137.88 (C_{quat}), 138.92 (C_{quat}), 145.45 (C_{quat}), 151.15 (C_{quat}), 170.10 (C=O). Minor rotamer 20.74 (CH_3), 55.60

(OCH_3), 55.94 (OCH_3), 63.69 (OCH_3), 82.21 (NCH_2), 102.08 (CH-3), 118.92 (C_{quat}), 122.43 (CH_{Ar}), 124.17 (CH_{Ar}), 125.77 (C_{quat}), 125.91 (CH_{Ar}), 126.57 (CH_{Ar}), 127.06 (C_{quat}), 128.31 (C_{quat}), 130.45 (CH_{Ar}), 132.16 (CH_{Ar}), 133.03 (CH_{Ar}), 138.39 (C_{quat}), 138.72 (C_{quat}), 146.07 (C_{quat}), 151.87 (C_{quat}), 170.10 (C=O). IR (ATR): ν 2935 (CH), 1664 (C=O), 1460, 1366, 1102, 1061, 770, 730 cm^{-1}. MS (ES^+) *m/z* (%): 215 ($[M-C_8H_9BrNO]^+$, 100), 444/446 ($[M+H]^+$, 15/14).

_N_-(2-Bromo-4-methylphenyl)-_N_-methoxymethyl-1,4-dimethoxynaphthalene-2-carboxamide 300c

37%, yellow viscous oil. ^1H NMR ($CDCl_3$): major rotamer δ 1.94 (3H, s, CH_3), 3.64 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.65 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 5.91 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.71 (1H, s, CH-3), 7.16 (1H, s, CH-3'), 7.28 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 7.31-7.44 (2H, m, 2xCH_{Ar}), 7.47-7.58 (1H, m, CH_{Ar}), 7.95 (1H, d, *J* = 7.7 Hz), 8.06 (1H, d, *J* = 7.7 Hz). Minor rotamer δ 2.29 (3H, s, CH_3), 3.40 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.74 (1H, d, *J* = 9.9 Hz, $NC\underline{H}_AH_B$), 6.06 (1H, d, *J* = 9.9 Hz, $NCH_A\underline{H}_B$), 6.70 (1H, s, CH-3), 6.87 (1H, s, CH-3'), 7.24-7.58 (4H, m, 4xCH_{Ar}), 8.12 (1H, d, *J* = 7.7 Hz), 8.26 (1H, d, *J* = 7.7 Hz). Major/minor = 5/1. ^{13}C NMR ($CDCl_3$): major rotamer δ 20.32 (CH_3), 55.43 (OCH_3), 56.75 (OCH_3), 63.40 (OCH_3), 77.51 (NCH_2), 100.69 (CH-3), 121.99 (CH_{Ar}), 122.03 (CH_{Ar}), 122.19 (CH_{Ar}), 125.86 (C_{quat}), 125.93 (CH_{Ar}), 126.57 (CH_{Ar}), 126.62 (C_{quat}), 127.06 (C_{quat}), 127.85 (C_{quat}), 128.57 (CH_{Ar}), 133.07 (CH_{Ar}), 136.55 (C_{quat}), 139.90 (C_{quat}), 145.27 (C_{quat}), 151.19 (C_{quat}), 170.33 (C=O). Minor rotamer not resolved. IR (ATR): ν 2930 (CH), 1667 (C=O), 1595, 1459, 1367, 1290, 1104, 1083, 1044, 770 cm^{-1}. MS (ES^+) *m/z* (%): 215 ($[M-C_8H_9BrNO]^+$, 100), 430/432 ($[M+H]^+$, 10/9.7).

_N_-(2-Bromo-4,6-dimethylphenyl)-_N_-methoxymethyl-1,4-dimethoxynaphthalene-2-carboxamide 300d

73%, colourless oil. ^1H NMR ($CDCl_3$): major rotamer δ 2.33 (3H, s, CH_3), 2.49 (3H, s, CH_3), 3.06 (3H, s, OCH_3), 4.00 (6H, s, 2xOCH_3), 4.72 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 5.77 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.87 (1H, s, CH_{Ar}), 7.10 (1H, s, CH_{Ar}), 7.38 (1H, s, CH_{Ar}), 7.43 (1H, t, *J* = 8.3 Hz, CH-6 or CH-7), 7.49 (1H, t, *J* = 8.3 Hz, CH-6 or CH-7), 8.02 (1H, d, *J* = 8.3 Hz, CH-5 or CH-8), 8.13 (1H, dd, *J* = 8.3 Hz, CH-5 or CH-8). Minor rotamer δ 2.12 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.61 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.98 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 4.07 (3H, s, OCH_3), 4.88 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.68 (1H, s, CH_{Ar}), 6.72 (1H, s, CH_{Ar}), 7.18 (1H, s, CH_{Ar}), 7.54 (1H, t, *J* = 7.7 Hz, CH-6 or CH-7), 7.59 (1H, t, *J* = 7.7 Hz, CH-6 or CH-7), 8.09 (1H, d, *J* = 7.7 Hz, CH-5 or CH-8), 8.28 (1H, dd, *J* = 7.7 Hz, CH-5 or CH-8). Major/minor = 6/5. ^{13}C NMR ($CDCl_3$): rotamers not distinguishable, all peaks given δ 18.90 (CH_3), 18.94 (CH_3), 20.51 (CH_3), 20.76 (CH_3), 55.72 (OCH_3), 55.92 (OCH_3), 56.97 (OCH_3), 58.17 (OCH_3), 63.78 (OCH_3), 64.17 (OCH_3), 80.24 (NCH_2), 83.53 (NCH_2), 102.03 (CH_{Ar}), 102.37 (CH_{Ar}), 122.41 (CH_{Ar}), 122.46 (CH_{Ar}), 122.67 (CH_{Ar}), 124.05 (C_{quat}), 124.98 (C_{quat}), 125.62 (C_{quat}), 126.26 (CH_{Ar}), 126.52 (CH_{Ar}), 126.63 (CH_{Ar}), 127.15 (CH_{Ar}), 127.35 (C_{quat}), 128.78

(C_{quat}), 128.72 (C_{quat}), 131.18 (CH_{Ar}), 131.44 (CH_{Ar}), 131.68 (CH_{Ar}), 136.08 (C_{quat}), 137.18 (C_{quat}), 139.36 (C_{quat}), 139.59 (C_{quat}), 139.73 (C_{quat}), 140.93 (C_{quat}), 146.49 (C_{quat}), 147.51 (C_{quat}), 150.89 (C_{quat}), 152.11 (C_{quat}), 169.29 (C=O), 169.96 (C=O). IR (ATR): ν 2935 (CH), 1664 (C=O), 1595, 1460, 1366, 1102, 1061, 770, 730 cm^{-1}. MS (ES^+) *m/z* (%): 458/460 ($[M+H]^+$, 100/97). HRMS (ES^+) calcd. for $[C_{23}H_{25}BrNO_4]^+$: 458.0967, found 488.0952.

_N_-2-Bromophenyl-_N_-methoxymethyl-1,4-di-*iso*-propoxynaphthalene-2-carboxamide 324

44%, pale white solid, mp 100°C. ^1H NMR ($CDCl_3$): δ 1.30 (3H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_A(CH_3)_B$), 1.31 (3H, d, *J* = 6.1 Hz, $CH(CH_3)_A(C\underline{H}_3)_B$), 1.41 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.64 (3H, s, OCH_3), 4.62 (2H, septet, *J* = 6.1 Hz, $2xC\underline{H}(CH_3)_2$), 4.69 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 5.83 (1H, d, *J* = 10.5 Hz, $NCH_A\underline{H}_B$), 6.75 (1H, s, CH-3), 6.89 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 7.03 (1H, dt, *J* = 1.7, 7.7 Hz, CH-6 or CH-7), 7.34 (1H, dd, *J* = 1.7, 7.7 Hz, CH-5 or CH-8), 7.37-7.42 (2H, m, $2xCH_{Ar}$), 7.54 (1H, dd, *J* = 1.7, 7.7 Hz, CH-5 or CH-8), 7.91-7.95 (1H, m, CH_{Ar}), 8.08-8.11 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.89 (CH_3), 22.26 (CH_3), 22.71 (CH_3), 22.79 (CH_3), 57.11 (OCH_3), 70.46 ($\underline{C}H(CH_3)_2$), 77.53 ($\underline{C}H(CH_3)_2$), 78.17 (NCH_2), 103.94 (CH-3), 122.26 (CH_{Ar}), 122.60 (C_{quat}), 122.92 (CH_{Ar}), 125.67 ($2xC_{quat}$), 125.94 (CH_{Ar}), 127.47 (CH_{Ar}), 127.62 (C_{quat}), 129.47 ($2xCH_{Ar}$), 131.68 (CH_{Ar}), 132.44 (CH_{Ar}), 139.44 (C_{quat}), 142.55 (C_{quat}), 149.00 (C_{quat}), 170.69 (C=O). IR (ATR): ν 2976, 1665, 1380, 1372, 1104, 1080, 751, 729 cm^{-1}. MS (ES^+) *m/z* (%): 486/488 ($[M+H]^+$, 7/7).

5.8.4 General procedure for the preparation of 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones 301 or 325

A Schlenk tube was loaded with the appropriate *N*-2-bromophenyl-*N*-methoxymethyl-1,4-dialkoxynaphthalene-2-carboxamide **301** or **324** (1 mmol), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol, 6 mol%), PPh_3 (47.2 mg, 0.18 mmol, 18 mol%), oven-dried K_2CO_3 (276 mg, 2 mmol, 2 equiv.) and anhydrous, degassed PhMe (15 mL). The Schlenk tube was evacuated and back-filled with Ar three times and placed in an oil bath preheated to 100°C. After 18 h, the reaction mixture was filtered over a pad of Celite® and washed with EtOAc. The filtrate was evaporated *in vacuo* and purified by means of flash chromatography (petroleum ether/ethyl acetate) to yield pure 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **301** or **325**.

7,12-Dimethoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-one 301a

96%, pale white needles mp 101.7°C. ^1H NMR ($CDCl_3$): δ 3.56 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.13 (3H, s, OCH_3), 5.76 (2H, s, NCH_2), 7.30 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.47 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.57 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.60 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.70 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 8.31 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 8.44 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 9.22 (1H, d, *J* = 7.7 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 56.84 (OCH_3), 60.93 (OCH_3), 63.34 (OCH_3), 74.30 (NCH_2), 115.19 (C_{quat}), 115.49 (CH_{Ar}), 118.89 (C_{quat}), 122.15 (C_{quat}), 122.66 (CH_{Ar}), 123.25 (CH_{Ar}), 124.34 (CH_{Ar}), 126.95 (CH_{Ar}), 128.16

(CH_{Ar}), 128.99 (C_{quat}), 129.18 (CH_{Ar}), 129.29 (CH_{Ar}), 131.85 (C_{quat}), 136.78 (C_{quat}), 149.42 (C_{quat}), 156.97 (C_{quat}), 160.95 (C=O). IR (ATR): ν 1649 (C=O), 1451, 1357, 1063, 750 cm^{-1}. MS (ES^+) *m/z* (%): 350 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{20}NO_4]^+$: 350.1392, found 350.1394.

7,12-Dimethoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one 301b

72%, pale white solid, mp 124.0°C. ^1H NMR ($CDCl_3$): δ 2.49 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 5.77 (2H, br s, NCH_2), 7.14 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}), 7.37 (1H, s, CH-4), 7.58-7.63 (1H, m, CH-9 or 10), 7.68-7.73 (1H, m, CH-9 or 10), 8.30 (1H, d, *J* = 8.3 Hz, CH-8 or 11), 8.44 (1H, d, *J* = 8.3 Hz, CH-8 or 11), 9.11 (1H, d, *J* = 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.75 (CH_3), 56.76 (OCH_3), 60.64 (OCH_3), 63.16 (OCH_3), 74.12 (NCH_2), 114.96 (C_{quat}), 115.65 (CH_{Ar}), 116.14 (C_{quat}), 122.22 (C_{quat}), 122.41 (CH_{Ar}), 124.17 (CH_{Ar}), 124.25 (CH_{Ar}), 126.58 (CH_{Ar}), 127.91 (CH_{Ar}), 128.57 (C_{quat}), 128.96 (CH_{Ar}), 131.70 (C_{quat}), 136.69 (C_{quat}), 139.44 (C_{quat}), 148.89 (C_{quat}), 156.78 (C_{quat}), 160.97 (C=O). IR (ATR): ν 2925 (CH), 1656 (C=O), 1613, 1353, 1259, 1088, 1066, 964 cm^{-1}. MS (ES^+) *m/z* (%): 364 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{22}NO_4]^+$: 364.1549, found 364.1542.

7,12-Dimethoxy-5-methoxymethyl-2-methyl-5*H*-benzo[*j*]phenanthridin-6-one 301c

78%, pale white solid, mp 113.6°C. ^1H NMR ($CDCl_3$): δ 2.47 (3H, s, CH_3), 3.54 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 5.75 (2H, br s, NCH_2), 7.28 (1H, dd, *J* = 1.1, 8.8 Hz, CH-3), 7.46 (1H, d, *J* = 8.8 Hz, CH-4), 7.58-7.63 (1H, m, CH-9 or 10), 7.67-7.73 (1H, m, CH-9 or 10), 8.31 (1H, d, *J* = 8.8 Hz, CH-8 or 11), 8.44 (1H, d, *J* = 8.8 Hz, CH-8 or 11), 9.05 (1H, d, *J* = 1.1 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 21.23 (CH_3), 56.65 (OCH_3), 60.70 (OCH_3), 63.20 (OCH_3), 74.12 (NCH_2), 115.24 (CH_{Ar}), 118.63 (C_{quat}), 122.11 (C_{quat}), 122.49 (CH_{Ar}), 124.23 (CH_{Ar}), 126.78 (CH_{Ar}), 128.22 (CH_{Ar}), 128.83 (C_{quat}), 129.03 (CH_{Ar}), 130.00 (CH_{Ar}), 131.73 (C_{quat}), 132.40 (C_{quat}), 134.46 (C_{quat}), 149.21 (C_{quat}), 156.84 (C_{quat}), 160.75 (C=O), one trisubstituted olefinic carbon not observed. IR (ATR): ν 2932 (CH), 1659 (C=O), 1450, 1354, 1263, 1062, 1034, 766 cm^{-1}. MS (ES^+) *m/z* (%): 364 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{22}NO_4]^+$: 364.1549, found 364.1539.

7,12-Dimethoxy-5-methoxymethyl-2,4-dimethyl-5*H*-benzo[*j*]phenanthridin-6-one 301d

58%, yellow oil. ^1H NMR ($CDCl_3$): δ 2.40 (3H, s, CH_3), 2.58 (3H, s, CH_3), 3.22 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 5.50 (2H, s, NCH_2), 7.09 (1H, d, *J* = 1.1, Hz, CH-3), 7.55-7.61 (1H, m, CH-9 or CH-10), 7.66-7.71 (1H, m, CH-9 or CH-10), 8.29 (1H, d, *J* = 8.3 Hz, CH-8 or CH-11), 8.45 (1H, d, *J* = 8.3 Hz, CH-8 or CH-11), 8.66 (1H, d, *J* = 1.1 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 20.95 (CH_3), 21.45 (CH_3), 56.52 (OCH_3), 61.24 (OCH_3), 63.46 (OCH_3), 78.84 (NCH_2), 113.91 (C_{quat}), 121.77 (C_{quat}), 122.23 (CH_{Ar}), 123.24 (C_{quat}), 124.11 (CH_{Ar}), 125.21 (CH_{Ar}), 126.63 (CH_{Ar}), 127.38 (C_{quat}), 128.48 (C_{quat}), 129.01 (CH_{Ar}), 131.82 (C_{quat}), 133.21 (C_{quat}), 133.42 (C_{quat}), 133.70 (CH_{Ar}),

148.14 (C_{quat}), 157.27 (C_{quat}), 163.84 (C=O). IR (ATR): ν 2930 (CH), 1655 (C=O), 1450, 1348, 1092, 1062, 765 cm^{-1}. MS (ES^+) *m/z* (%): 378 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{22}NO_4]^+$: 378.1705, found 378.1704.

7,12-Di-*iso*-propoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-one 325

96%, yellow oil. ^1H NMR ($CDCl_3$): δ 1.23 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.38 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.52 (3H, s, OCH_3), 4.37 (1H, septet, *J* = 6.1 Hz, $C\underline{H}(CH_3)_2$), 4.73 (1H, septet, *J* = 6.1 Hz, $C\underline{H}(CH_3)_2$), 3.74 (2H, br s, NCH_2), 7.21-7.27 (1H, m, CH_{Ar}), 7.39-7.44 (1H, m, CH_{Ar}), 7.51-7.56 (2H, m, CH_{Ar}), 7.60-7.66 (1H, m, CH_{Ar}), 8.33 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 8.49 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 9.11 (1H, dd, *J* = 1.7, 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 22.39 ($CH(\underline{C}H_3)_2$), 22.70 ($CH(\underline{C}H_3)_2$), 56.62 (OCH_3), 74.20 ($\underline{C}H(CH_3)_2$), 76.17 ($\underline{C}H(CH_3)_2$), 78.99 (NCH_2), 114.34 (C_{quat}), 115.39 (CH_{Ar}), 119.94 (C_{quat}), 122.41 (C_{quat}), 122.60 (CH_{Ar}), 123.15 (CH_{Ar}), 125.07 (CH_{Ar}), 126.34 (CH_{Ar}), 128.22 (CH_{Ar}), 128.61 (CH_{Ar}), 128.92 (CH_{Ar}), 130.34 (C_{quat}), 133.22 (C_{quat}), 136.28 (C_{quat}), 146.02 (C_{quat}), 154.46 (C_{quat}), 161.46 (C=O). IR (ATR): ν 2973, 1660, 1252, 1101, 1060, 752 cm^{-1}. MS (ES^+) *m/z* (%): 406 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{25}H_{28}NO_4]^+$: 406.2018, found 406.2007.

5.8.5 General procedure for the preparation of 7,12-dimethoxy-5*H*-benzo[*j*]phenanthridin-6-ones 287

A solution of the appropriate 7,12-dimethoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-one **301** (0.31 mmol) in 1,4-dioxane (2 mL) and aqueous HCl (6 M, 2 mL) was heated to 50°C and stirred overnight. It was then extracted with EtOAc (10 mL) and H_2O (10 mL) and the organic phase was dried over $MgSO_4$, evaporated *in vacuo* and purified by means of column chromatography ($CHCl_3$) to yield pure 7,12-dimethoxy-5*H*-benzo[*j*]phenanthridin-6-ones **287**.

7,12-Dimethoxy-5*H*-benzo[*j*]phenanthridin-6-one 287a

84%, pink needles, mp 260.0. ^1H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 4.21 (3H, s, OCH_3), 7.31 (2H, d, *J* = 7.7 Hz, 2xCH_{Ar}), 7.47 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.66 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.75 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 8.35 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 8.49 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 9.21 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 10.36 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 61.02 (OCH_3), 63.71 (OCH_3), 115.77 (CH_{Ar}), 115.90 (C_{quat}), 118.02 (C_{quat}), 122.78 (CH_{Ar}), 123.10 (C_{quat}), 124.35 (CH_{Ar}), 127.04 (CH_{Ar}), 128.35 (CH_{Ar}), 128.90 (C_{quat}), 129.19 (CH_{Ar}), 129.24 (CH_{Ar}), 129.27 (CH_{Ar}), 131.74 (C_{quat}), 135.90 (C_{quat}), 150.14 (C_{quat}), 152.65 (C_{quat}), 161.82 (C=O). IR (ATR): ν 2924, 1666, 1593, 1354, 1262, 1067, 999, 838, 750 cm^{-1}. MS (ES^+) *m/z* (%): 306 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{16}NO_3]^+$: 306.1130, found 306.1130.

7,12-Dimethoxy-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one 287b

67%, yellow solid, mp 273.3°C. ^{1}H NMR ($CDCl_3$): δ 2.48 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 4.20 (3H, s, OCH_3), 7.10-7.13 (2H, m, 2xCH_{Ar}), 7.61-7.66 (1H, m, CH-9 or CH-10), 7.70-7.76 (1H, m, CH-9 or CH-10), 8.33 (1H, d, J = 8.3 Hz, CH_{Ar}), 8.47 (1H, d, J = 8.3 Hz, CH_{Ar}), 9.07 (1H, d, J = 8.3 Hz, CH_{Ar}), 10.17 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 21.49 (CH_3), 60.91 (OCH_3), 63.60 (OCH_3), 115.45 (C_{quat}), 115.86 (CH_{Ar}), 122.67 (CH_{Ar}), 123.27 (C_{quat}), 124.35 (CH_{Ar}), 124.43 (CH_{Ar}), 126.81 (CH_{Ar}), 128.28 (CH_{Ar}), 128.64 (C_{quat}), 129.16 (CH_{Ar}), 131.73 (C_{quat}), 135.91 (C_{quat}), 139.67 (C_{quat}), 149.73 (C_{quat}), 156.60 (C_{quat}), 161.70 (C=O), one trisubstituted olefinic carbon not observed. IR (ATR): ν 2916, 1657, 1444, 1352, 1260, 1067, 999, 771, 762 cm^{-1}. MS (ES$^+$) *m/z* (%): 320 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{20}H_{18}NO_3]^+$: 320.1287, found 320.1286.

5.8.6 *N*-2-Bromophenyl-*N*-*tert*-butoxycarbonyl-1,4-dimethoxynaphthalene-2-carboxamide 306

A solution of *N*-2-bromophenyl-1,4-dimethoxynaphthalene-2-carboxamide **296a** (1 g, 2.59 mmol), DMAP (32 mg, 0.26 mmol, 0.1 equiv.) and Boc_2O (735 mg, 3.37 mmol, 1.3 equiv.) in anhydrous CH_3CN (10 mL) was stirred at room temperature for 1 h. The reaction mixture was evaporated *in vacuo*, redissolved in CH_2Cl_2 and washed with brine. Drying over $MgSO_4$, evaporation of the solvent *in vacuo* and flash chromatography gave pure *N*-2-bromophenyl-*N*-*tert*-butoxycarbonyl-1,4-dimethoxynaphthalene-2-carboxamide **306** (1.05 g, 2.16 mmol, 83%) as white crystals.

83%, white crystals, mp 157.5°C. ^{1}H NMR ($CDCl_3$): δ 1.12 (9H, s, $C(CH_3)_3$), 3.97 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 6.93 (1H, s, CH-3), 7.22 (1H, dt, J = 1.1, 7.7 Hz, CH_{Ar}), 7.38 (1H, dt, J = 1.1, 7.7 Hz, CH_{Ar}), 7.43 (1H, dt, J = 1.1, 7.7 Hz, CH_{Ar}), 7.50-7.59 (2H, m, 2xCH_{Ar}), 7.67 (1H, dd, J = 1.1, 8.0 Hz, CH_{Ar}), 8.09-8.15 (1H, m, CH_{Ar}), 8.23-8.29 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 27.28 ($C(\underline{C}H_3)_3$), 55.77 (OCH_3), 63.68 (OCH_3), 83.62 ($\underline{C}(CH_3)_3$), 102.20 (CH-3), 122.49 (CH_{Ar}), 122.54 (CH_{Ar}), 123.61 (C_{quat}), 125.68 (C_{quat}), 126.80 (CH_{Ar}), 127.09 (CH_{Ar}), 127.48 (C_{quat}), 128.23 (C_{quat}), 128.43 (CH_{Ar}), 129.82 (CH_{Ar}), 130.42 (CH_{Ar}), 133.27 (CH_{Ar}), 138.03 (C_{quat}), 147.15 (C_{quat}), 151.44 (C_{quat}), 151.71 (C_{quat}), 169.35 (C=O). IR (ATR): ν 2970, 1731 (C=O), 1671 (C=O), 1474, 1370, 1238, 1153, 1071, 750, 744 cm^{-1}. MS (ES$^+$) *m/z* (%): 387/388 ([M-Boc+H]$^+$, 100/97). MS (ES$^+$) calcd. for $[C_{19}H_{17}{}^{81}BrNO_3]^+$: 386.0392, found 386.0387.

5.8.7 Organolithium addition to 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones 301 or 325

To a solution of the appropriate 7,12-dialkoxy-6-methylbenzo[*j*]phenanthridine **301** or **325** (1.25 mmol) in anhydrous THF (8 mL) was added freshly titrated organolithium (1.75 mmol, 1.4 equiv. in Et_2O or hexanes) at -78°C (MeLi) or -100°C (*n*-HexLi). The reaction mixture was allowed to stir for 15 min (MeLi) or 30 min (*n*-HexLi), quenched with a saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2x10 mL). Purification by means of flash chromatography yielded the corresponding 1,2-adducts **299a**, **318** and **328**, 1,4-adducts **311**, **317** and **326** and double adducts **316** and **327**.

7,12-Dimethoxy-6-methylbenzo[*j*]phenanthridine 299a

42%, yellow needles, mp < 50°C. ^{1}H NMR ($CDCl_3$): δ 3.23 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 7.52-7.67 (4H, m, 4xCH_{Ar}), 8.01 (1H, dd, *J* = 1.7, 8.0 Hz, CH_{Ar}), 8.32 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 8.37 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 9.42 (1H, dd, *J* = 1.7, 8.0 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 28.76 (CH_3), 60.93 (OCH_3), 64.09 (OCH_3), 118.34 (C_{quat}), 121.82 (C_{quat}), 122.32 (C_{quat}), 122.81 (CH_{Ar}), 123.45 (CH_{Ar}), 126.51 (CH_{Ar}), 126.89 (CH_{Ar}), 127.01 (CH_{Ar}), 127.35 (C_{quat}), 127.90 (CH_{Ar}), 128.52 (CH_{Ar}), 128.77 (CH_{Ar}), 129.77 (C_{quat}), 143.03 (C_{quat}), 150.37 (C_{quat}), 152.58 (C_{quat}), 158.46 (C=O). IR (ATR): ν 1448, 1377, 1358, 1066, 989, 756 cm^{-1}. MS (ES$^+$) *m/z* (%): 304 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{20}H_{18}NO_2]^+$: 304.1338, found 304.1326.

12-Methoxy-5-methoxymethyl-7-methyl-5*H*-benzo[*j*]phenanthridin-6-one 311

19%, brown prisms, mp 108.3°C. ^{1}H NMR ($CDCl_3$): δ 3.28 (3H, s, CH_3), 3.56 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.74 (2H, s, NCH_2), 7.29 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.47 (1H, dt, *J* = 1.1, 7.7 Hz, CH_{Ar}), 7.55-7.72 (3H, m, 3xCH_{Ar}), 8.38 (2H, dd, *J* = 1.7, 8.3 Hz, 2xCH_{Ar}), 9.21 (1H, dd, *J* = 1.7, 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 18.04 (CH_3), 56.79 (OCH_3), 61.08 (OCH_3), 74.66 (NCH_2), 115.37 (CH_{Ar}), 119.30 (C_{quat}), 121.85 (C_{quat}), 123.01 (CH_{Ar}), 123.28 (CH_{Ar}), 125.94 (CH_{Ar}), 126.96 (CH_{Ar}), 128.17 (CH_{Ar}), 128.22 (CH_{Ar}), 129.06 (CH_{Ar}), 130.34 (C_{quat}), 133.68 (C_{quat}), 136.67 (C_{quat}), 137.73 (C_{quat}), 151.77 (C_{quat}), 163.76 (C=O), one trisubstituted olefinic carbon not observed. IR (ATR): ν 2929, 1653, 1649, 1259, 1078, 1057, 751 cm^{-1}. MS (ES$^+$) *m/z* (%): 302 ([M-OMe]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{20}H_{16}NO_2]^+$: 302.1181, found 302.1181.

6-*n*-Hexyl-7,12-dimethoxybenzo[*j*]phenanthridine 318a

9%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$), 1.25-1.37 (4H, m, 2xCH_2), 1.43-1.52 (2H, m, CH_2), 1.74-1.84 (2H, m, CH_2), 3.54-3.59 (2H, m, C-6-CH_2), 3.96 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 7.57-7.74 (4H, m, CH-8 to CH-11), 8.03 (1H, dd, *J* = 1.7, 7.6 Hz, CH_{Ar}), 8.43 (2H, dt, *J* = 1.7, 7.6 Hz, 2xCH_{Ar}), 9.45 (1H, dd, *J* = 1.7, 7.6 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.21 (CH$_2$$\underline{C}H_3$), 22.76 ($CH_2$), 29.61 ($CH_2$), 29.92 ($CH_2$), 31.92 ($CH_2$), 41.17 ($CH_2$Ar), 61.14 ($OCH_3$), 64.38 ($OCH_3$), 117.34 ($C_{quat}$), 122.28 ($C_{quat}$), 122.46 ($C_{quat}$), 122.93 ($CH_{Ar}$), 123.70 ($CH_{Ar}$), 126.60 ($CH_{Ar}$), 126.93 ($CH_{Ar}$), 127.04 ($CH_{Ar}$), 127.53 ($C_{quat}$), 127.94 ($CH_{Ar}$), 128.60 ($CH_{Ar}$), 129.07 ($CH_{Ar}$), 129.83 ($C_{quat}$), 143.12 ($C_{quat}$), 150.58 ($C_{quat}$), 152.37 ($C_{quat}$), 162.39 ($C_{quat}$). IR (ATR): ν 2952, 2926, 1729, 1281, 1269, 757 cm^{-1}. MS (ES$^+$) *m/z* (%): 374 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{25}H_{28}NO_2]^+$: 374.2120, found 374.2118.

7-*n*-Hexyl-12-methoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-one 317a

9%, pale white solid, mp <50°C. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$), 1.30-1.47 (4H, m, 2xCH_2), 1.58-1.69 (2H, m, CH_2), 1.77-1.88 (2H, m, CH_2), 3.55 (3H, s, OCH_3), 3.71-3.88 (2H,

m, C-6-CH_2), 3.88 (3H, s, OCH_3), 5.74 (2H, br s, NCH_2), 7.25-7.31 (1H, m, CH_{Ar}), 7.42-7.48 (1H, m, CH_{Ar}), 7.51-7.57 (1H, m, CH_{Ar}), 7.60-7.70 (2H, m, CH_{Ar}), 8.33-8.40 (2H, m, 2xCH_{Ar}), 9.20 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.33 ($CH_2\underline{C}H_3$), 22.99 (CH_2), 30.41 (CH_2), 30.55 (CH_2), 31.75 (CH_2), 31.95 (CH_2), 56.62 (OCH_3), 56.90 (OCH_3), 74.64 (NCH_2), 104.12 (C_{quat}), 115.45 (CH_{Ar}), 122.78 (C_{quat}), 123.15 (2xCH_{Ar}), 126.00 (CH_{Ar}), 127.01 (CH_{Ar}), 128.19 (CH_{Ar}), 129.07 (C_{quat}), 130.69 (C_{quat}), 133.10 (CH_{Ar}), 136.72 (CH_{Ar}), 142.49 (C_{quat}), 142.81 (C_{quat}), 151.90 (C_{quat}), 153.53 (C_{quat}), 163.26 (C=O). IR (ATR): ν 2952, 2925, 2855, 1729, 1283, 1263, 756 cm^{-1}. MS (ES^+) *m/z* (%): 372 ($[M\text{-}OMe]^+$, 100).

6,7-Di-*n*-hexyl-12-methoxybenzo[*j*]phenanthridine 316a

58%, yellow gum, mp < 50°C. ^{1}H NMR ($CDCl_3$): δ 0.83-0.90 (6H, m, 2x$C\underline{H}_3CH_2$), 1.25-1.38 (8H, m, 4xCH_2), 1.38-1.53 (4H, m, 2xCH_2), 1.73-1.90 (4H, m, 2xCH_2), 3.32-3.38 (2H, m, CH_2), 3.60-3.65 (2H, m, CH_2), 3.98 (3H, s, OCH_3), 7.51-7.57 (1H, m, CH_{Ar}), 7.60-7.71 (3H, m, 3xCH_{Ar}), 7.95 (1H, dd, *J* = 1.7, 8.2 Hz, CH_{Ar}), 8.32-8.36 (1H, m, CH_{Ar}), 8.47-8.50 (1H, m, CH_{Ar}), 9.34 (1H, dd, *J* = 1.7, 8.2 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.13 (2x$CH_2\underline{C}H_3$), 22.71 (2xCH_2), 29.65 (CH_2), 29.98 (CH_2), 30.16 (CH_2), 31.63 (CH_2), 31.71 (CH_2), 31.86 (CH_2), 32.74 (CH_2), 41.54 (CH_2), 61.34 (OCH_3), 121.61 (C_{quat}), 122.46 (C_{quat}), 123.10 (CH_{Ar}), 124.90 (C_{quat}), 125.47 (CH_{Ar}), 126.51 (CH_{Ar}), 126.57 (CH_{Ar}), 126.67 (CH_{Ar}), 126.93 (CH_{Ar}), 128.06 (CH_{Ar}), 128.31 (CH_{Ar}), 128.64 (C_{quat}), 132.45 (C_{quat}), 135.04 (C_{quat}), 142.26 (C_{quat}), 152.29 (C_{quat}), 163.42 (C=O). IR (ATR): ν 2952, 2924, 1458, 1270, 751, 726 cm^{-1}. MS (ES^+) *m/z* (%): 460 ($[M+O_2+H]^+$, 100).

6-*n*-Hexyl-7,12-dimethoxy-3-methylbenzo[*j*]phenanthridine 318b

12%, yellow oil. ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.28-1.38 (4H, m, 2xCH_2), 1.42-1.84 (2H, m, CH_2), 1.73-1.84 (2H, m, CH_2), 2.57 (3H, s, CH_3), 3.55 (2H, t, *J* = 7.2 Hz, C-6-CH_2), 3.95 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 7.44 (1H, dd, *J* = 1.7, 8.8 Hz, CH-2), 7.61-7.74 (2H, m, CH-9 and CH-10), 7.84 (1H, d, *J* = 1.7, CH-4), 8.39-8.44 (2H, m, CH-8 and CH-11), 9.33 (1H, d, *J* = 8.8 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 14.26 ($CH_2\underline{C}H_3$), 21.43 (CH_2), 22.79 (CH_3), 29.65 (CH_2), 29.97 (CH_2), 31.97 (CH_2), 41.19 (CH_2Ar), 61.05 (OCH_3), 64.38 (OCH_3), 117.31(C_{quat}), 119.91 (C_{quat}), 122.48 (C_{quat}), 122.86 (CH_{Ar}), 123.73 (CH_{Ar}), 126.40 (CH_{Ar}), 126.90 (CH_{Ar}), 127.27 (C_{quat}), 127.90 (CH_{Ar}), 128.40 (CH_{Ar}), 129.03 (CH_{Ar}), 129.83 (C_{quat}), 138.75 (C_{quat}), 143.24 (C_{quat}), 150.23 (C_{quat}), 152.42 (C_{quat}), 162.43 (C_{quat}). IR (ATR): ν 2952, 2925, 2855, 1729, 1283, 1263, 756 cm^{-1}. MS (ES^+) *m/z* (%): 388 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{26}H_{30}NO_2]^+$: 388.2277, found 388.2283.

7-*n*-Hexyl-12-methoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one 317b

30%, yellow solid, mp < 50 °C. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.31-1.47 (4H, m, 2xCH_2), 1.59-1.68 (2H, m, CH_2), 1.77-1.88 (2H, m, CH_2), 2.48 (3H, s, CH_3), 3.55 (3H, s, OCH_3),

3.66-3.82 (2H, m, C-6-CH_2), 3.84 (3H, s, OCH_3), 5.74 (2H, br s, NCH_2), 7.10 (1H, dd, J = 1.1, 8.8 Hz, CH-2), 7.33 (1H, d, J = 1.1, CH-4), 7.57-7.68 (2H, m, CH-9 and CH-10), 8.32-8.38 (2H, m, CH-8 and CH-11), 9.07 (1H, d, J = 8.8 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 14.32 ($CH_2\underline{C}H_3$), 21.90 (CH_2), 22.96 (CH_3), 30.38 (CH_2), 30.51 (CH_2), 31.72 (CH_2), 31.98 (CH_2), 56.62 (OCH_3), 60.88 (OCH_3), 74.55 (NCH_2), 115.54 (CH_{Ar}), 116.60 (C_{quat}), 122.14 (C_{quat}), 123.01 (CH_{Ar}), 124.23 (CH_{Ar}), 125.94 (CH_{Ar}), 126.73 (CH_{Ar}), 128.02 (CH_{Ar}), 128.11 (CH_{Ar}), 130.63 (C_{quat}), 132.81 (C_{quat}), 136.74 (C_{quat}), 139.28 (C_{quat}), 142.38 (C_{quat}), 150.23 (C_{quat}), 151.45 (C_{quat}), 163.36 (C=O). IR (ATR): ν 2954, 2926, 1652, 1614, 1455, 1273, 1087, 763 cm^{-1}. MS (ES$^+$) *m/z* (%): 450 ([M+O_2+H]$^+$, 100). HRMS (ES$^+$) calcd. for [$C_{27}H_{32}NO_5$]$^+$: 450.2281, found 450.2285.

6,7-Di-*n*-hexyl-12-methoxy-3-methylbenzo[*j*]phenanthridine 316b

43%, yellow gummy solid, mp < 50°C. ^{1}H NMR ($CDCl_3$): δ 0.78-0.99 (6H, m, 2x$C\underline{H}_3CH_2$), 1.31-1.43 (4H, m, 2xCH_2), 1.43-1.48 (8H, m, 4xCH_2), 1.79-1.88 (4H, m, 2xCH_2), 2.55 (3H, s, CH_3), 3.34-3.38 (2H, m, CH_2), 3.59-3.64 (2H, m, CH_2), 3.96 (3H, s, OCH_3), 7.38 (1H, d, J = 8.3 Hz, CH-1), 7.60-7.67 (2H, m, CH-9 and CH-10), 7.80 (1H, s, CH-4), 8.32 (1H, d, J = 7.7 Hz, CH-8 or CH-11), 8.46 (1H, d, J = 7.7 Hz, CH-8 or CH-11), 9.24 (1H, dd, J = 1.1, 8.3 Hz, CH-2). ^{13}C NMR ($CDCl_3$): δ 14.16 (2x$CH_2\underline{C}H_3$), 21.43 (CH_3), 22.76 (2xCH_2), 29.71 (CH_2), 30.03 (CH_2), 30.27 (CH_2), 31.66 (CH_2), 31.77 (CH_2), 31.90 (CH_2), 32.81 (CH_2), 41.56 (CH_2), 61.26 (OCH_3), 119.94 (C_{quat}), 121.86 (C_{quat}), 123.05 (CH_{Ar}), 124.92 (C_{quat}), 125.54 (CH_{Ar}), 126.35 (CH_{Ar}), 126.58 (CH_{Ar}), 126.93 (CH_{Ar}), 128.02 (CH_{Ar}), 128.06 (CH_{Ar}), 128.67 (C_{quat}), 132.23 (C_{quat}), 135.13 (C_{quat}), 138.44 (C_{quat}), 142.34 (C_{quat}), 152.00 (C_{quat}), 163.59 (C=O). IR (ATR): ν 2952, 2922, 2850, 1458, 1262, 750 cm^{-1}. MS *m/z* (%): 474 ([M+O_2+H]$^+$, 100). HRMS (ES$^+$) calcd. for [$C_{31}H_{40}NO_3$]$^+$: 474.3008, found 474.3017.

7-*n*-Hexyl-12-*iso*-propoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-one 326

30%, pale white solid, mp 105.2. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, t, J = 7.2 Hz, $C\underline{H}_3CH_2$), 1.25 (6H, d, J = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.35-1.47 (4H, m, 2xCH_2), 1.59-1.68 (2H, m, CH_2), 1.78-1.88 (2H, m, CH_2), 3.55 (3H, s, OCH_3), 3.65-3.87 (2H, m, C-6-CH_2), 4.37 (1H, septet, J = 6.1 Hz, $C\underline{H}(CH_3)_2$), 5.73 (2H, br s, NCH_2), 7.21 (1H, d, J = 7.7 Hz, CH_{Ar}), 7.42 (1H, t, J = 7.7 Hz, CH_{Ar}), 7.52 (1H, d, J = 7.7 Hz, CH_{Ar}), 7.57-7.65 (2H, m, 2xCH_{Ar}), 8.28-8.33 (1H, m, CH_{Ar}), 8.41-8.46 (1H, m, CH_{Ar}), 9.14 (1H, d, J = 7.7 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.32 ($CH_2\underline{C}H_3$), 22.58 ($CH(\underline{C}H_3)_2$), 22.96 (CH_2), 30.39 (2xCH_2), 31.77 (CH_2), 32.01 (CH_2), 56.62 (OCH_3), 74.67 (NCH_2), 76.53 ($\underline{C}H(CH_3)_2$), 115.25 (CH_{Ar}), 119.96 (C_{quat}), 122.11 (C_{quat}), 122.38 (C_{quat}), 122.58 (CH_{Ar}), 124.00 (CH_{Ar}), 125.73 (CH_{Ar}), 126.83 (CH_{Ar}), 127.62 (CH_{Ar}), 128.32 (CH_{Ar}), 128.87 (CH_{Ar}), 132.29 (C_{quat}), 132.83 (C_{quat}), 136.37 (C_{quat}), 141.67 (C_{quat}), 149.09 (C_{quat}), 163.47 (C=O). IR (ATR): ν 2960, 2925, 1662, 1370, 1330, 1081, 761 cm^{-1}. MS (ES$^+$) *m/z* (%): 432 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for [$C_{28}H_{34}NO_3$]$^+$: 432.2538, found 432.2530.

6,7-Di-*n*-hexyl-12-*iso*-propoxybenzo[*j*]phenanthridine 327

17%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.77-0.93 (6H, m, 2x$C\underline{H}_3CH_2$), 1.17-1.41 (8H, m, 4xCH_2), 1.28 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.48-1.60 (4H, m, 2xCH_2), 1.75-1.86 (4H, m, 2xCH_2), 3.30-3.36 (2H, m, CH_2), 3.55-3.60 (2H, m, CH_2), 4.52 (1H, septet, *J* = 6.1 Hz, $C\underline{H}(CH_3)_2$), 7.43-7.50 (1H, m, CH_{Ar}), 7.55-7.65 (3H, m, 3xCH_{Ar}), 7.90 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}), 8.26-8.30 (1H, m, CH_{Ar}), 8.51-8.55 (1H, m, CH_{Ar}), 9.29 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 14.18 (2x$CH_2\underline{C}H_3$), 22.64 ($CH(\underline{C}H_3)_2$), 22.76 (2xCH_2), 29.61 (CH_2), 30.10 (CH_2), 30.26 (CH_2), 31.55 (CH_2), 31.78 (CH_2), 31.90 (CH_2), 32.71 (CH_2), 41.36 (CH_2), 76.50 ($\underline{C}H(CH_3)_2$), 122.08 (C_{quat}), 123.12 (C_{quat}), 124.11 (CH_{Ar}), 124.64 (C_{quat}), 125.33 (CH_{Ar}), 126.51 (3xCH_{Ar}), 126.58 (CH_{Ar}), 127.51(CH_{Ar}), 128.23 (CH_{Ar}), 130.35 (C_{quat}), 132.28 (C_{quat}), 134.28 (C_{quat}), 141.80 (C_{quat}), 149.24 (C_{quat}), 163.99 (C=O). IR (ATR): ν 2955, 2926, 2855, 1458, 1272, 1109, 934, 751 cm^{-1}. MS (ES$^+$) *m/z* (%): 488 ([M+O_2+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{32}H_{42}NO_3]^+$: 488.3165, found 488.3170.

5.8.8 Oxidative demethylation of MeLi adducts 299a and 311

To a solution of MeLi adduct **299a** or **311** (0.44 mmol) in CH_3CN (5 mL) was added a solution of CAN (717 mg, 1.31 mmol, 2.5 equiv.) in H_2O (5 mL) in one portion. The reaction mixture was allowed to stir for two min and poured in a 1:1 mixture EtOAc/H_2O (10 mL). The H_2O phase was discarded and the organic phase was washed with aqueous NaOH (2 M, 5 mL).The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to yield the crude oxidation products which were further purified by means of preparative TLC.

6-Methylbenzo[*j*]phenanthridine-7,12-dione 313

83%, bright yellow solid, mp 153.2°C. ^{1}H NMR ($CDCl_3$): δ 3.21 (3H, s, CH_3), 7.68-7.74 (1H, m, CH_{Ar}), 7.79-7.81 (3H, m, 3xCH_{Ar}), 8.07 (1H, dd, *J* = 1.1, 9.1 Hz, CH_{Ar}), 8.20-8.23 (2H, m, 2xCH_{Ar}), 9.38 (1H, d, *J* = 9.1 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 27.94 (CH_3), 122.19 (C_{quat}), 124.95 (C_{quat}), 126.70 (2xCH_{Ar}), 128.14 (CH_{Ar}), 129.38 (CH_{Ar}), 129.45 (CH_{Ar}), 132.20 (CH_{Ar}), 133.19 (C_{quat}), 133.71 (C_{quat}), 134.05 (CH_{Ar}), 134.48 (CH_{Ar}), 134.64 (C_{quat}), 150.49 (C_{quat}), 158.89 (C_{quat}), 184.97 (C=O), 186.91 (C=O). IR (ATR): ν 1667 (C=O), 1590, 1326, 1274, 1025, 762 cm^{-1}. MS (ES$^+$) *m/z* (%): 274 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{12}NO_2]^+$: 274.0868, found 274.0869.

7-Hydroxy-5-methoxymethyl-7-methyl-5,7-dihydrobenzo[*j*]phenanthridine-6,12-dione 314

55%, yellow solid, mp 117.4°C. ^{1}H NMR ($CDCl_3$): δ 1.85 (3H, s, CH_3), 3.49 (3H, s, OCH_3), 5.81 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 5.92 (1H, d, *J* = 10.5 Hz, $NC\underline{H}_AH_B$), 6.75 (1H, s, OH), 7.36-7.42 (1H, m, CH_{Ar}), 7.48-7.54 (1H, m, CH_{Ar}), 7.58-7.76 (3H, m, 3xCH_{Ar}), 8.00 (1H, dd, *J* = 1.1, 7.7 Hz, CH_{Ar}), 8.11 (1H, dd, *J* = 1.1, 7.7 Hz, CH_{Ar}), 9.05 (1H, dd, *J* = 1.1, 9.1 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 34.15 (CH_3), 57.20 (OCH_3), 70.17 (C-7), 74.08 (NCH_2), 115.50 (CH_{Ar}), 117.16 (C_{quat}), 124.29 (CH_{Ar}), 125.47 (CH_{Ar}), 126.74 (CH_{Ar}), 128.14 (CH_{Ar}), 129.00 (CH_{Ar}), 130.25 (C_{quat}), 131.19 (CH_{Ar}), 134.20

(CH_{Ar}), 134.95 (C_{quat}), 138.26 (C_{quat}), 138.42 (C_{quat}), 147.36 (C_{quat}), 162.95 (NC=O), 185.52 (C=O). IR (ATR): ν 3404 (OH), 2967 (CH), 1664 (C=O), 1636 (C=O), 1352, 1185, 1129, 1085, 1056, 760 cm^{-1}. MS (ES^+) *m/z* (%): 318 ($[M-OH]^+$, 100), 336 ($[M+H]^+$, 60). HRMS (ES^+) calcd. for $[C_{20}H_{16}NO_3]^+$: 318.1130, found 318.1118.

5.8.9 7,12-Dimethoxy-6-formylbenzo[*j*]phenanthridine 312

A solution of 7,12-dimethoxy-6-methylbenzo[*j*]phenanthridine **313a** (100 mg, 0.33 mmol) and Se_2O (73 mg, 0.66 mmol, 2 equiv.) in 1,4-dioxane (5 mL) was boiled under reflux for 1 h. The reaction mixture was filtered over a pad of Celite® and evaporated *in vacuo*, redissolved in EtOAc (10 mL) and washed with H_2O (2x10 mL). Purification by means of preparative TLC yielded pure aldehyde **312** (50 mg, 0.16 mmol, 48 %) as a yellow oil.

48%, yellow oil. ^1H NMR ($CDCl_3$): δ 3.96 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 7.68-7.80 (4H, m, 4xCH_{Ar}), 8.23-8.26 (1H, m, CH_{Ar}), 8.36 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 8.49 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 9.45-9.51 (1H, m, CH_{Ar}), 10.67 (1H, s, CHO). MS *m/z* (%): 318 ($[M+H]^+$, 100).

5.8.10 Methyl 1-hydroxy-4-*iso*-propoxynaphthalene-2-carboxylate 320

A solution of methyl 1,4-dihydroxynaphthalene-2-carboxylate **319** (1 g, 4.58 mmol), K_2CO_3 (3.8 g, 27.50 mmol, 6 equiv.) and 2-bromopropane (2.6 mL, 27.50 mmol, 6 equiv.) in anhydrous acetone (20 mL) was boiled under reflux for 20 h. The solids were filtered off and the filtrate was evaporated *in vacuo*. The thus obtained residue was recrystallised from EtOH to yield methyl 1-hydroxy-4-*iso*-propoxynaphthalene-2-carboxylate **320** (0.95 g, 4.49 mmol, 80%) as yellow needles.

80%, yellow needles, mp 55.0-56.2°C. ^1H NMR ($CDCl_3$): δ 1.43 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.99 (3H, s, OCH_3), 4.66 (1H, septet, *J* = 6.1 Hz, $C\underline{H}(CH_3)_2$), 7.10 (1H, s, CH-3), 7.52-7.57 (1H, m, CH-6 or CH-7), 7.59-7.65 (1H, m, CH-6 or CH-7), 8.20 (1H, dd, *J* = 1.1, 8.4 Hz, CH-5 or CH-8), 8.38 (1H, dd, *J* = 1.1, 8.4 Hz, CH-5 or CH-8), 11.61 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 22.18 ($CH(\underline{C}H_3)_2$), 52.29 (OCH_3), 71.07 ($\underline{C}H(CH_3)_2$), 104.08 (CH-3), 104.49 (C_{quat}), 122.34 (CH_{Ar}), 122.79 (CH_{Ar}), 125.70 (C_{quat}), 126.26 (CH_{Ar}), 128.90 (CH_{Ar}), 131.21 (C_{quat}), 145.74 (C_{quat}), 155.49 (C_{quat}), 171.38 (C=O). IR (ATR): ν 2878, 1659, 1599, 1437, 1332, 1233, 1084, 766 cm^{-1}. MS (ES^-) *m/z* (%): 259 ($[M-H]^-$, 100). HRMS (ES^+) calcd. for $[C_{15}H_{17}O_4]^+$: 261.1127, found 261.1120.

5.8.11 1,4-Di-*iso*-propoxynaphthalene-2-carboxylic acid 322

A solution of 1,4-dihydroxynaphthalene-2-carboxylic acid **321** (1 g, 4.9 mmol), K_2CO_3 (3.38 g, 24.5 mmol, 5 equiv.) and 2-bromopropane (3.2 mL, 33.8 mmol, 7 equiv.) in anhydrous DMF (10 mL) was heated at 60°C during 48 h. After cooling to room temperature, H_2O (20 mL) was added and the mixture was extracted with EtOAc (3x5 mL). The combined organic extracts were evaporated *in vacuo* and redissolved in 1,4-dioxane (5 mL) to which was added a solution of KOH (823 mg, 14.7

mmol, 3 equiv.) in H_2O (10 mL) and stirred overnight. The mixture was acidified to pH = 1 and extracted with EtOAc (3x10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded pure 1,4-di-*iso*-propoxynaphthalene-2-carboxylic acid **322** (1.13 g, 3.90 mmol, 80%) as an amber solid.

80%, amber solid, mp 95.2°C. ^{1}H NMR ($CDCl_3$): δ 1.46 (12H, d, J = 6.1 Hz, 2xCH(C$\underline{H}_3$)$_2$), 4.70 (1H, septet, J = 6.1 Hz, C$\underline{H}$(CH$_3$)$_2$), 4.85 (1H, septet, J = 6.1 Hz, C$\underline{H}$(CH$_3$)$_2$), 7.40 (1H, s, CH-3), 7.56-7.65 (2H, m, CH-6 and CH-7), 7.99-8.05 (1H, m, CH-5 or CH-8), 8.31-8.36 (1H, m, CH-5 or CH-8), 11.66 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 21.71 (CH(C$\underline{H}_3$)$_2$), 21.77 (CH(C$\underline{H}_3$)$_2$), 70.41 (C$\underline{H}$(CH$_3$)$_2$), 79.92 (C$\underline{H}$(CH$_3$)$_2$), 104.95 (CH-3), 118.83 (C_{quat}), 122.86 (CH_{Ar}), 122.95 (CH_{Ar}), 126.89 (CH_{Ar}), 127.76 (CH_{Ar}), 128.26 (C_{quat}), 130.03 (C_{quat}), 147.62 (C_{quat}), 149.94 (C_{quat}), 167.29 (C=O). IR (ATR): ν 3074, 2975, 1736, 1677, 1401, 1380, 1103, 1085, 932, 764 cm^{-1}. MS (ES$^-$) *m/z* (%): 287 ([M-H]$^-$, 100).

5.8.12 Triflation of 7,12-dimethoxy-5*H*-benzo[*j*]phenanthridin-6-ones 287

A solution of the appropriate 7,12-dimethoxy-5*H*-benzo[*j*]phenanthridin-6-one **287** (0.31 mmol) and DMAP (30.5 mg, 0.25 mmol, 0.8 equiv.) in pyridine (5 mL) was cooled to 0°C and Tf_2O (0.13 mL, 0.78 mmol, 2.5 equiv.) was added dropwise under a N_2 atmosphere. The reaction mixture was stirred for 24 h and quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3x10 mL). Drying over $MgSO_4$, evaporation of the solvent *in vacuo* followed by preparative TLC (petroleum ether/ethyl acetate) yielded pure 7,12-dimethoxybenzo[*j*]phenanthridin-6-yl trifluoromethanesulfonates **329**.

7,12-Dimethoxy-3-methylbenzo[*j*]phenanthridin-6-yl trifluoromethanesulfonate 329b

46%, red oil. ^{1}H NMR ($CDCl_3$): δ 2.50 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 7.24-7.32 (1H, m, CH_{Ar}), 7.48 (1H, dd, J = 1.7, 8.3 Hz, CH-3), 7.61-7.74 (2H, m, CH_{Ar}), 8.35-8.40 (1H, m, CH-8 or CH-11), 8.50-8.65 (1H, m, CH-8 or CH-11), 9.28 (1H, d, J = 8.3 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 21.36 (CH_3), 61.27 (OCH_3), 64.73 (OCH_3), 110.81 (C_{quat}), 121.41 (C_{quat}), 123.06 (CH_{Ar}), 123.51 (q, J_{CF} = 68.8 Hz, CF_3), 124.08 (CH_{Ar}), 127.24 (CH_{Ar}), 127.33 (CH_{Ar}), 127.84 (C_{quat}), 129.21 (CH_{Ar}),129.29 (CH_{Ar}), 130.32 (CH_{Ar}), 131.04 (C_{quat}), 139.79 (C_{quat}), 140.32 (C_{quat}), 150.51 (C_{quat}), 151.52 (C_{quat}), 2 trisubstituted olefinic carbons not observed. ^{19}F NMR ($CDCl_3$): δ -72.83- -72.21. IR (ATR): ν 2920, 1635, 1277, 1205, 1135, 1028 cm^{-1}. MS (ES$^+$) *m/z* (%): 452 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{21}H_{17}F_3NO_5S]^+$: 452.0780, found 452.0780.

7,12-Dimethoxy-2,4-dimethylbenzo[*j*]phenanthridin-6-yl trifluoromethanesulfonate 329d

19%, orange crystals, mp 126.4°C-127.9°C. ^{1}H NMR ($CDCl_3$): δ 2.59 (3H, s, CH_3), 2.71 (3H, s, CH_3), 3.94 (3H, s, OCH_3), 4.15 (3H, s, OCH_3), 7.43 (1H, s, CH-3), 7.66-7.80 (2H, m, CH-9 and CH-10), 8.41-8.46 (2H, m, CH-8 and CH-11), 9.17 (1H, s, CH-1). ^{13}C NMR ($CDCl_3$): δ 18.22 (CH_3), 22.45 (CH_3), 61.20 (OCH_3), 64.70 (OCH_3), 111.09 (C_{quat}), 123.13 (CH_{Ar}), 123.96 (2xCH_{Ar}), 124.32 (C_{quat}),

125.19 (CH_{Ar}), 127.36 (CH_{Ar}), 127.99 (C_{quat}), 129.13 (CH_{Ar}), 130.92 (C_{quat}), 131.34 (q, J_{CF} = 68.8 Hz, CF_3), 131.85 (CH_{Ar}), 136.87 (C_{quat}), 137.06 (C_{quat}), 138.43 (C_{quat}), 148.55 (C_{quat}), 150.87 (C_{quat}), 151.23 (C_{quat}). IR (ATR): ν 1413, 1362, 1214, 1196, 1133, 908 cm^{-1}. ^{19}F NMR ($CDCl_3$): δ -72.86- -72.71. MS (ES^+) *m/z* (%): 466 ($[M+H]^+$, 35). HRMS (ES^+) calcd. for $[C_{22}H_{19}F_3NO_5S]^+$: 466.0936, found 466.0935.

2,4-Dimethylbenzo[*j*]phenanthridine-7,12-dione 18d

A solution of 7,12-dimethoxy-2,4-dimethylbenzo[*j*]phenanthridin-6-yl trifluoromethanesulfonate **329d** (25 mg, 0.054 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 20 mol%) and PPh_3 (5.2 mg, 0.02 mmol, 40 mol%) in anhydrous DMF (0.5 mL) under a nitrogen atmosphere was heated for 10 min at 60°C. Then Et_3SiH (30 µL, 0.16 mmol, 3 equiv.) was added dropwise and the reaction mixture was stirred for 5 h at 60°C and subsequently diluted with $CHCl_3$ (5 mL). The organic solution was washed with water, a saturated $NaHCO_3$ solution, brine, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified by preparative TLC (petroleum ether/ethyl acetate 1/1) to yield 7,12-dimethoxy-2,4-dimethylbenzo[*j*]phenanthridine (14 mg, 0.044 mmol, 82%) as a yellow solid. This compound was dissolved in CH_3CN (2 mL) and a solution of CAN (28 mg, 0.11 mmol, 2.5 equiv.) in H_2O (2 mL) was added in one portion. The reaction was allowed to stir for 1 h at room temperature and subsequently partitioned between $CHCl_3$ (10 mL) and H_2O (10 mL). The aqueous phase was discarded and the organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to quantitatively yield 2,4-dimethylbenzo[*j*]phenanthridine-7,12-dione **18d** as a bright yellow solid.

82%, bright yellow solid, mp 205°C. ^1H NMR ($CDCl_3$): δ 2.54 (3H, s, CH_3), 2.76 (3H, s, CH_3), 7.50 (1H, s, CH-3), 7.81-7.83 (2H, m, CH-9 and CH-10), 8.24-8.25 (2H, m, CH-8 and CH-11), 9.12 (1H, s, CH-1), 9.68 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 18.65 (CH_3), 22.42 (CH_3), 122.93 (C_{quat}), 124.25 (C_{quat}), 124.87 (CH-1), 126.54 and 127.36 (CH-8 and CH-11), 132.03 (C_{quat}), 133.13 (C_{quat}), 134.35 and 134.60 (CH-9 and CH-10), 134.72 (CH-3), 137.64 (C_{quat}), 140.75 (C_{quat}), 146.11 (CH-6), 149.99 (C_{quat}), 183.64 (2xC=O), one trisubstituted olefinic carbon not observed. IR (ATR): ν 2620, 1665, 1273, 717 cm^{-1}. MS (ES^+) *m/z* (%): 288 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{14}NO_2]^+$: 288.1025, found 288.1029.

5.8.13 7-Ethoxy-12-methoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one 330

A solution of 7,12-dimethoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **301b** (113 mg, 0.33 mmol), ethylenediamine (75 mg, 1.24 mmol, 4 equiv.) and washed NaH (30 mg, 1.24 mmol, 4 equiv.) in EtOH (5 mL) was boiled under reflux for 6 h. The solvent was evaporated *in vacuo* and the residue redissolved in EtOAc (10 mL) and washed with H_2O (3x10 mL). The organic phase was dried over $MgSO_4$, evaporated *in vacuo* and recrystallised from EtOH to yield 7-ethoxy-12-methoxy-

5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **330** (93 mg, 0.26 mmol, 79%) as yellow needles.

79%, yellow needles, mp 129-130°C. ^{1}H NMR ($CDCl_3$): δ 1.59 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 2.46 (3H, s, CH_3), 3.55 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.26 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 5.75 (2H, br s, NCH_2), 7.13 (1H, dd, *J* = 1.1, 8.3 Hz, CH_{Ar}), 7.36 (1H, s, CH-4), 7.56-7.62 (1H, m, CH-9 or 10), 7.69-7.73 (1H, m, CH-9 or 10), 8.29 (1H, d, *J* = 8.3 Hz, CH-8 or 11), 8.45 (1H, d, *J* = 8.3 Hz, CH-8 or 11), 9.10 (1H, d, *J* = 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 16.00 ($C\underline{H}_3CH_2$), 21.90 (CH_3), 56.81 (OCH_3), 60.81 (OCH_3), 71.98 (OCH_2), 74.18 (NCH_2), 115.03 (C_{quat}), 115.77 (CH_{Ar}), 116.35 (C_{quat}), 122.34 (C_{quat}), 122.45 (CH_{Ar}), 124.34 (CH_{Ar}), 124.57 (CH_{Ar}), 126.61 (CH_{Ar}), 128.05 (CH_{Ar}), 129.10 (CH_{Ar}), 131.77 (C_{quat}), 136.80 (C_{quat}), 139.55 (2xC_{quat}), 148.80 (C_{quat}), 156.05 (C_{quat}), 161.20 (C=O). IR (ATR): ν 2923, 1667, 1352, 1082, 1062, 763 cm^{-1}. MS (ES$^+$) *m/z* (%): 378 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{23}H_{24}NO_4]^+$: 378.1705, found 378.1712.

5.8.14 Synthesis of 6-alkoxy-7,12-dimethoxy-3-methylbenzo[*j*]phenanthridines 334

To a solution of 7,12-dimethoxy-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **287b** (100 mg, 0.31 mmol) in anhydrous $CHCl_3$ (5 mL) was added the appropriate trialkyloxonium tetrafluoroborate (0.34 mmol, 1.1 equiv.) under a N_2 atmosphere. The solution was boiled under reflux for 3 h, quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (3x5 mL). The organic phase was dried over $MgSO_4$, evaporated in vacuo and purified by means of preparative TLC to yield 6-alkoxy-7,12-dimethoxy-3-methylbenzo[*j*]phenanthridines **334** as oils that crystallised slowly.

6,7,12-Trimethoxy-3-methylbenzo[*j*]phenanthridine 334a

58%, pale white solid, mp 110.2°C. ^{1}H NMR ($CDCl_3$): δ 2.53 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 4.28 (3H, s, OCH_3), 7.30 (1H, dd, *J* = 1.7, 8.3 Hz, CH-3), 7.57-7.71 (2H, m, CH-9 and CH-10), 7.64 (1H, s, CH-4), 8.37 (1H, d, *J* = 8.3 Hz, CH-8 or CH-11), 8.43 (1H, d, *J* = 8.3 Hz, CH-8 or CH-11), 9.24 (1H, d, *J* = 8.3 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 21.40 (CH_3), 54.04 (OCH_3), 60.90 (OCH_3), 63.97 (OCH_3), 112.11 (C_{quat}), 119.10 (C_{quat}), 122.64 (CH_{Ar}), 123.91 (CH_{Ar}), 124.02 (C_{quat}), 126.38 (CH_{Ar}), 126.45 (CH_{Ar}), 127.21 (2xCH_{Ar}), 128.02 (C_{quat}), 128.16 (CH_{Ar}), 130.13 (C_{quat}), 138.93 (C_{quat}), 142.80 (C_{quat}), 149.84 (C_{quat}), 152.11 (C_{quat}), 159.01 (C_{quat}). IR (ATR): ν 2940, 1596, 1374, 1358, 1220, 1065, 754, 740 cm^{-1}. MS (ES$^+$) *m/z* (%): 334 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{21}H_{20}NO_3]^+$: 334.1443, found 334.1446.

6-Ethoxy-7,12-dimethoxy-3-methylbenzo[*j*]phenanthridine 334b

53%, pale white solid, mp 101.2°C. ^{1}H NMR ($CDCl_3$): δ 1.62 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 2.52 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 4.07 (3H, s, OCH_3), 4.73 (2H, q, *J* = 7.2 Hz, OCH_2), 7.29 (1H, dd, *J* = 1.7, 8.3 Hz, CH-3), 7.57-7.69 (3H, m, CH-4, CH-9 and CH-10), 8.36 (1H, d, *J* = 8.3 Hz, CH-8 or CH-

11), 8.43 (1H, d, *J* = 8.3 Hz, CH-8 or CH-11), 9.23 (1H, d, *J* = 8.3 Hz, CH-1). ^{13}C NMR ($CDCl_3$): δ 14.70 ($\underline{C}H_3CH_2$), 21.39 (CH_3), 60.88 (OCH_3), 62.30 (OCH_2), 63.91 (OCH_3), 112.34 (C_{quat}), 119.01 (C_{quat}), 122.63 (CH_{Ar}), 123.93 (CH_{Ar}), 124.09 (C_{quat}), 126.29 (2xCH_{Ar}), 127.16 (CH_{Ar}), 127.19 (CH_{Ar}), 128.09 (CH_{Ar}), 130.09 (C_{quat}), 138.86 (2xC_{quat}), 142.95 (C_{quat}), 149.82 (C_{quat}), 152.11 (C_{quat}), 158.65 (C_{quat}). IR (ATR): ν 2978, 2930, 1594, 1356, 1065, 740 cm^{-1}. MS (ES^+) *m/z* (%): 348 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{22}NO_3]^+$: 348.1600, found 348.1601.

5.8.15 5-Methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridine-6,7,12-trione 333

A solution of 7,12-dimethoxy-5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridin-6-one **301b** (100 mg, 0.31 mmol) in ethylenediamine (1 mL) was heated under microwave irradiation at 140°C for 30 min. the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (3x10 mL). The organic phase was dried over $MgSO_4$, evaporated *in vacuo* and purified by means of preparative TLC to yield 5-methoxymethyl-3-methyl-5*H*-benzo[*j*]phenanthridine-6,7,12-trione **333** (31 mg, 0.093 mmol, 30%) as a bright red solid.

30%, red solid, mp 168-169°C. ^{1}H NMR ($CDCl_3$): δ 2.53 (3H, s, CH_3), 3.54 (3H, s, OCH_3), 5.82 (2H, s, NCH_2), 7.23 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 7.44 (1H, s, CH-4), 7.77 (1H, dt, *J* = 1.7, 7.2 Hz, CH-9 or CH-10), 7.68-7.81 (1H, dt, *J* = 1.7, 7.2 Hz, CH-9 or CH-10), 8.12 (1H, dd, *J* = 1.7, 7.2 Hz, CH-8 or CH-11), 8.20 (1H, dd, *J* = 1.7, 7.2 Hz, CH-8 or CH-11), 8.88 (1H, d, *J* = 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 22.52 (CH_3), 57.51 (OCH_3), 74.12 (NCH_2), 113.53 (C_{quat}), 115.68 (CH_{Ar}), 122.44 (C_{quat}), 125.93 (CH_{Ar}), 126.45 (CH_{Ar}), 126.72 (CH_{Ar}), 130.40 (CH_{Ar}), 133.27 (C_{quat}), 133.56 (CH_{Ar}), 134.67 (CH_{Ar}), 142.03 (C_{quat}), 142.13 (C_{quat}), 145.61 (C_{quat}), 159.04 (NC=O), 181.64 (C=O), 186.85 (C=O), one trisubstituted olefinic carbon not observed. IR (ATR): ν 2981 (CH), 1686 (C=O), 1677, 1522, 1278, 1084, 950, 751 cm^{-1}. MS *m/z* (%): 334 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{20}H_{16}NO_4]^+$: 334.1079, found 334.1085.

5.8.16 *N*-Methoxy-1,4-dimethoxynaphthalene-2-carboxamide 337

1,4-Dimethoxynaphthalene-2-carboxylic acid **293** (5 g, 21.5 mmol) was added to $SOCl_2$ (15.5 mL, 215 mmol, 10 equiv.) and boiled under reflux for 2.5 h. The reaction mixture was evaporated *in vacuo* and redissolved in EtOAc (50 mL). $MeONH_2 \cdot HCl$ (2.16 g, 25.6 mmol, 1.2 equiv.) was added to a biphasic mixture of K_2CO_3 (5.95 g, 43 mmol, 2 equiv.) in a 2:1 mixture of EtOAc (125 mL) and H_2O (62.5 mL). The resulting solution was cooled to 0 °C followed by dropwise addition of the acid chloride. The reaction was allowed to stir at r.t. for 16h. Afterwards the phases were extracted with EtOAc (3x60 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give the desired product **337** without any further purification (5.4 g, 20.6 mmol, 96%).

96%, brown solid, 95°C. ^{1}H NMR ($CDCl_3$): δ 3.95 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.39 (1H, s, CH-3), 7.56-7.64 (2H, m, 2xCH_{Ar}), 8.05-8.11 (1H, m, CH_{Ar}), 8.26-8.29 (1H, m,

CH_{Ar}), 10.44 (1H, br s, NH). ^{13}C NMR ($CDCl_3$): δ 55.42 (OCH_3), 62.79 (OCH_3), 64.06 (OCH_3), 102.54 (CH-3), 119.45 (C_{quat}), 122.31 (2xCH_{Ar}), 126.86 (CH_{Ar}), 127.10 (CH_{Ar}), 127.54 (C_{quat}), 128.06 (C_{quat}), 148.32 (C_{quat}), 151.88 (C_{quat}), 164.07 (C=O). IR (ATR): ν 3186 (NH), 1644 (C=O), 1369, 1092, 767 cm^{-1}. MS (ES^+) *m/z* (%): 262 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{14}H_{16}NO_4]^+$: 262.1079, found 262.1072.

5.9 Synthesis of 1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-diones 19

A stirred solution of dioxolanylnaphthoquinone **11** (1.5 mmol) or acetylnaphthoquinone **345** (1.5 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was cooled to 0°C. Freshly distilled enamine **340** (1.65 mmol) was added dropwise in 2 mL of anhydrous THF. Then, 7 M NH_3 in MeOH (1.4 mL, 10 equiv.) was added dropwise and the reaction was allowed to warm to room temperature and stirred open to the air overnight. After careful evaporation of the solvents, the reaction mixture was redissolved in EtOAc (15 mL) an washed with brine (2x10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* gave a crude mixture which was purified by means of preparative TLC (hexane/ethyl acetate) and subsequent recrystallisation from EtOH to yield the desired 1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-diones **19**.

1,2,3,4-Tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19a

43%, yellow needles, mp 149.2°C. ^1H NMR ($CDCl_3$): δ 1.86-2.00 (4H, m, 2xCH_2), 3.14 (2H, t, *J* = 6.1 Hz, CH_2), 3.42 (2H, t, *J* = 6.1 Hz, CH_2), 7.79-7.85 (2H, m, CH-9 and 10), 8.21-8.29 (2H, m, CH-8 and 11), 9.37 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 21.98 (CH_2), 22.68 (CH_2), 28.21 (CH_2), 34.73 (CH_2), 125.13 (C_{quat}), 126.58 and 127.33 (CH-8 and 11), 132.41 (C_{quat}), 133.19 (C_{quat}), 134.28 and 134.45 (CH-9 and 10), 133.91 (C_{quat}), 135.42 (C_{quat}), 146.86 (CH-6), 166.33 (C_{quat}), 183.20 (C=O), 185.47 (C=O). IR (ATR): ν 2941 (CH), 2867 (CH), 1674 (C=O), 1660 (C=O), 1557 (CH_{Ar}), 1297, 1288, 712 cm^{-1}. MS (ES^+) *m/z* (%): 264 ($[M+H]^+$, 100).

2-Methyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19b

28%, yellow crystals, mp 125.9°C. ^1H NMR ($CDCl_3$): δ 1.20 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 1.50-1.64 (1H, m, CH), 1.84-1.96 (1H, m, CH), 2.00-2.09 (1H, m, CH), 2.88 (1H, dd, *J* = 10.7, 19.0 Hz, CH), 3.06-3.27 (2H, m, CH_2), 3.66 (1H, ddd, *J* = 1.7, 4.8, 19.1 Hz, CH), 7.79-7.85 (2H, m, CH-9 and 10), 8.21-8.30 (2H, m, CH-8 and 11), 9.37 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 21.94 (CH_3), 28.96 (CH_2), 30.06 (CH_2), 34.39 (CH_2), 36.53 (CH), 125.13 (C_{quat}), 126.63 and 127.33 (CH-8 and 11), 132.48 (C_{quat}), 132.75 (C_{quat}), 134.31 and 134.49 (CH-9 and 10), 135.42 (C_{quat}), 146.93 (CH-3), 166.16 (C_{quat}), 183.24 (C=O), 185.59 (C=O). IR (ATR): ν 2948 (CH), 2873 (CH), 1672(C=O), 1557 (CH_{Ar}), 1288, 716 cm^{-1}. MS (ES^+) *m/z* (%): 278 ($[M+H]^+$, 100).

2-*tert*-Butyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19c

38%, amber crystals, mp 194.1°C. ^{1}H NMR ($CDCl_3$): δ 1.06 (9H, s, $C(CH_3)_3$), 1.45-1.54 (2H, m, CH_2), 2.11-2.19 (1H, m, CH), 2.92-3.13 (2H, m, CH_2), 3.25 (1H, dd, *J* = 3.2, 19.1 Hz, CH), 3.64 (1H, dd, *J* = 3.2, 19.1 Hz, CH), 7.79-7.84 (2H, m, CH-9 and 10), 8.21-8.29 (2H, m, CH-8 and 11), 9.34 (1H, CH-6). ^{13}C NMR ($CDCl_3$): δ 23.35 (CH_2), 27.40 ($C(\underline{C}H_3)_3$), 29.98 (CH_2), 32.71 ($\underline{C}(CH_3)_3$), 35.54 (CH_2), 44.44 (CH-2), 125.18 (C_{quat}), 126.63 and 127.35 (CH-8 and 11), 132.46 (C_{quat}), 133.61 (C_{quat}), 134.28 and 134.49 (CH-9 and 10), 134.55 (C_{quat}), 146.87 (CH-6), 158.22 (C_{quat}), 166.43 (C_{quat}), 183.27 (C=O), 185.58 (C=O). IR (ATR): ν 2948 (CH), 2868 (CH), 1675 (C=O), 1660 (C=O), 1595 (CH_{Ar}), 1298, 709 cm^{-1}. MS (ES^+) *m/z* (%): 320 ($[M+H]^+$, 100).

3-Methyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19d

24%, yellow solid, mp 168°C. ^{1}H NMR ($CDCl_3$): δ 1.15 (3H, d, *J* = 6.1 Hz, $CHC\underline{H}_3$), 1.36-1.50 (1H, m, CH), 1.94-2.01 (2H, m, CH_2), 2.71 (1H, dd, *J* = 10.3, 18.4 Hz), 3.17-3.32 (2H, m, CH_2), 3.58-3.66 (1H, m, CH), 7.79-7.84 (2H, m, CH-9 and 10), 8.20-8.28 (2H, m, CH-8 and 11), 9.36 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 21.57 (CH_3), 27.86 (CH_2), 28.18 (CH_2), 30.82 (CH_2), 43.00 (CH), 125.24 (C_{quat}), 126.66 and 127.39 (CH-8 and 11), 132.51 (C_{quat}), 132.95 (C_{quat}), 132.75 (C_{quat}), 134.34 and 134.51 (CH-9 and 10), 135.41 (C_{quat}), 147.09 (CH-6), 166.26 (C_{quat}), 183.35 (C=O), 185.62 (C=O). IR (ATR): ν 2952 (CH), 2925 (CH), 1672 (C=O), 1559 (CH_{Ar}), 1299, 1277, 710 cm^{-1}. MS (ES^+) *m/z* (%): 278 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{16}NO_2]^+$: 278.1181, found 278.1181.

4-Methyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19e

16%, yellow solid, mp 123°C. ^{1}H NMR ($CDCl_3$): δ 1.44 (3H, d, *J* = 7.2 Hz, $CHC\underline{H}_3$), 1.67-2.13 (4H, m, 2xCH_2), 3.19 (1H, sextet, *J* = 6.6 Hz, CH-4), 3.35 (1H, td, *J* = 6.6, 19.3 Hz, CH), 3.46 (1H, td, *J* = 6.6, 19.3 Hz, CH), 7.79-7.84 (2H, m, CH-9 and 10), 8.21-8.29 (2H, m, CH-8 and 11), 9.41 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 19.84 (CH_2), 21.57 (CH_3), 28.70 (CH_2), 29.94 (CH_2), 37.57 (CH-4), 124.92 (C_{quat}), 126.52 and 127.32 (CH-8 and 11), 132.41 (C_{quat}), 132.95 (C_{quat}), 134.29 and 134.41 (CH-9 and 10), 134.55 (C_{quat}), 135.45 (C_{quat}), 146.86 (CH-6), 170.17 (C_{quat}), 183.26 (C=O), 185.52 (C=O). IR (ATR): ν 2944 (CH), 2874 (CH), 1672 (C=O), 1588 (CH_{Ar}), 1559 (CH_{Ar}), 1298, 1281, 720 cm^{-1}. MS (ES^+) *m/z* (%): 278 ($[M+H]^+$, 100).

6-Methyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19f

15%, orange needles, mp 180.7°C. ^{1}H NMR ($CDCl_3$): δ 1.83-1.98 (4H, m, 2xCH_2), 3.02 (3H, s, CH_3), 3.06 (2H, t, *J* = 6.3 Hz, CH_2), 3.34 (2H, t, *J* = 6.3 Hz, CH_2), 7.74-7.83 (2H, m, CH-9 and 10), 8.14-8.22 (2H, m, CH-8 and 11). ^{13}C NMR ($CDCl_3$): δ 22.13 (CH_2), 22.99 (CH_2), 26.81 (CH_2), 28.41 (CH_2), 34.73 (CH_3), 123.97 (C_{quat}), 126.66 (CH-8 and 11), 131.51 (C_{quat}), 133.73 (C_{quat}), 133.79 (CH-9 or 10), 133.94 (C_{quat}), 134.23 (CH-9 or 10), 135.42 (C_{quat}), 158.17 (C_{quat}), 164.45 (C_{quat}), 185.03 (C=O),

186.46 (C=O). IR (ATR): ν 2942 (CH), 2868 (CH), 1670 (C=O), 1589 (CH_{Ar}), 1537 (CH_{Ar}), 1288, 722, 713 cm^{-1}. MS (ES^+) *m/z* (%): 278 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{16}NO_2]^+$: 278.1181, found 278.0819.

2,6-Dimethyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19g

23%, orange crystals, mp 164.2°C. ^1H NMR ($CDCl_3$): δ 1.18 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 1.48-1.61 (1H, m, CH), 1.79-1.91 (1H, m, CH), 1.97-2.06 (1H, m, CH), 2.84 (1H, dd, *J* = 11.0, 18.7 Hz, CH), 3.00 (1H, s, CH_3), 3.04-3.12 (2H, m, CH_2), 3.50 (1H, ddd, *J* = 1.7, 4.5, 18.7 Hz, CH), 7.72-7.81 (2H, m, CH-9 and 10), 8.12-8.20 (2H, m, CH-8 and 11). ^{13}C NMR ($CDCl_3$): δ 21.97 (CH_3), 26.81 (CH_3), 29.20 (CH), 30.16 (CH_2), 34.39 (CH_2), 36.76 (CH_2), 123.88 (C_{quat}), 126.64 (CH-8 and 11), 131.01 (C_{quat}), 133.71 (C_{quat}), 133.80 (CH-9 or 10), 133.91 (C_{quat}), 134.23 (CH-9 or 10), 137.71 (C_{quat}), 158.22 (C_{quat}), 164.23 (C_{quat}), 184.97 (C=O), 188.48 (C=O). IR (ATR): ν 2933 (CH), 2869 (CH), 1667 (C=O), 1590 (CH_{Ar}), 1289, 724 cm^{-1}. MS (ES^+) *m/z* (%): 292 ($[M+H]^+$, 100).

3,6-Dimethyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19i

36%, yellow needles, mp 168°C. ^1H NMR ($CDCl_3$): δ 1.14 (3H, d, *J* = 6.6 Hz, CHC$\underline{H}_3$), 1.33-1.47 (1H, m, CH), 1.95-2.07 (2H, m, CH_2), 2.65 (1H, dd, *J* = 10.5, 18.2 Hz), 3.02 (3H, s, CH_3), 3.10-3.30 (2H, m, CH_2), 3.46-3.55 (1H, m, CH), 7.73-7.82 (2H, m, CH-9 and 10), 8.12-8.24 (2H, m, CH-8 and 11). ^{13}C NMR ($CDCl_3$): δ 21.58 (CH_3), 26.79 (CH_3), 27.95 (CH_2), 28.23 (CH_2), 31.05 (CH_2), 43.02 (CH), 123.88 (C_{quat}), 126.61 and 126.64 (CH-8 and 11), 130.92 (C_{quat}), 133.64 (C_{quat}), 133.74 (CH-9 or 10), 133.83 (C_{quat}), 134.19 (CH-9 or 10), 137.48 (C_{quat}), 158.31 (C_{quat}), 164.28 (C_{quat}), 184.86 (C=O), 186.30 (C=O). IR (ATR): ν 2948 (CH), 2928 (CH), 1667 (C=O), 1591 (CH_{Ar}), 1294, 1264, 724 cm^{-1}. MS (ES^+) *m/z* (%): 292 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{18}NO_2]^+$: 292.1338, found 292.0978.

4,6-Dimethyl-1,2,3,4-tetrahydrobenzo[*j*]phenanthridine-7,12-dione 19j

18%, orange needles, mp 161.5°C. ^1H NMR ($CDCl_3$): δ 1.42 (3H, d, *J* = 7.2 Hz, CHC$\underline{H}_3$), 1.64-1.81 (2H, m, CH_2), 1.87-1.99 (1H, m, CH), 2.02-2.11 (1H, m, CH), 3.01 (3H, s, CH_3), 3.11 (1H, sextet, *J* = 6.6 Hz, CH-4), 3.25 (1H, td, *J* = 6.6, 19.3 Hz, CH), 3.35 (1H, td, *J* = 6.6, 19.3 Hz, CH), 7.71-7.80 (2H, m, CH-9 and 10), 8.11-8.19 (2H, m, CH-8 and 11), 9.41 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 20.19 (CH_3), 21.66 (CH_2), 26.90 (CH_3), 28.91 (CH_2), 30.10 (CH_2), 37.49 (CH-4), 123.71 (C_{quat}), 126.58 and 126.64 (CH-8 and 11), 131.12 (C_{quat}), 132.95 (C_{quat}), 133.73 (CH-9 or 10), 134.00 (C_{quat}), 134.14 (CH-9 or 10), 137.76 (C_{quat}), 158.11 (C_{quat}), 168.25 (C_{quat}), 185.09 (C=O), 185.52 (C=O). IR (ATR): ν 2981 (CH), 2935 (CH), 1666 (C=O), 1590 (CH_{Ar}), 1280, 725 cm^{-1}. MS (ES^+) *m/z* (%): 292 ($[M+H]^+$, 100). HRMS (ES^-) calcd. for $[C_{19}H_{16}NO_2]^-$: 290.1181, found 290.1336.

5.10 Synthesis of octahydrobenzophenanthridinediones 22

5.10.1 Synthesis of 6-(1,3-dioxolan-2-yl)-1,2,3,4-tetrahydronaphthalene-5,8-diones 350a, 350b and 6-(1,3-dioxan-2-yl)-1,2,3,4-tetrahydronaphthalene-5,8-dione 350c

To a Parr bottle were added 1,4-dihydro-5,8-dimethoxynaphthalene **346a** or **346b**[211] (35 mmol), Pd/C (1 m/m%), EtOH (25 mL) and EtOAc (125 mL). The reaction was stirred for 3 h at room temperature under a hydrogen atmosphere of 5 bar. Next, the reaction mixture was filtered over a pad of Celite® and evaporated *in vacuo* to afford pure 1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene **347a** or **347b**. These compounds **347** (30 mmol) were dissolved in anhydrous CH_2Cl_2 (100 mL), cooled to 0°C and under a nitrogen atmosphere, $TiCl_4$ (33 mmol, 3.62 mL) was slowly added dropwise. Next, Cl_2CHOMe (33 mmol, 2.99 mL) was slowly added dropwise. When the addition was complete, the reaction was stirred for 3 hours at 0°C and cautiously quenched with ice-cold water (50 mL). The reaction mixture was washed with brine (2x50 mL), dried over $MgSO_4$ and evaporated *in vacuo*. Purification by means of column chromatography yielded 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-6-carboxaldehydes **348a** and **348b** as pale white solids.

5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxaldehyde 348a

96%, pale white solid, mp 89°C. ^{1}H NMR ($CDCl_3$): δ 1.18-1.30 (2H, m, CH_2), 1.52-1.55 (1H, m, $C\underline{H}_AH_B$), 1.73-1.78 (1H, m, $C\underline{H}_AH_B$), 2.91-2.05 (2H, m, CH_2), 3.63 (1H, br d, J = 1.1 Hz, CH-1 or CH-4), 3.69 (1H, br d, J = 1.1 Hz, CH-1 or CH-4), 3.84 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 7.13 (1H, s, CH-5), 10.32 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 25.97 (CH_2), 26.73 (CH_2), 40.23 (CH), 41.19 (CH), 49.02 (CH_2), 55.78 (OCH_3), 62.81 (OCH_3), 106.96 (CH_{Ar}), 126.87 (C_{quat}), 140.93 (C_{quat}), 145.80 (C_{quat}), 149.58 (C_{quat}), 151.93 (C_{quat}), 189.81 (C=O). IR (ATR): ν 2949 (CH), 2868 (CH), 1677 (C=O), 1589, 1475, 1387, 1309, 1212, 1021 cm^{-1}. MS (ES$^+$) *m/z* (%): 233 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{14}H_{17}O_3]^+$: 233.1178, found 233.1179.

5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-6-carboxaldehyde 348b

97%, pale white solid, mp 85°C. ^{1}H NMR ($CDCl_3$): δ 1.28-1.41 (4H, m, 2xCH_2), 1.75-1.86 (4H, m, 2xCH_2), 3.44 (1H, br s, CH), 3.54 (1H, br s, CH), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 7.19 (1H, s, CH-5), 10.37 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 25.20 (2xCH_2), 25.46 (2xCH_2), 26.59 (CH), 27.17 (CH), 55.66 (OCH_3), 64.55 (OCH_3), 105.13 (CH_{Ar}), 126.41 (C_{quat}), 138.69 (C_{quat}), 142.03 (C_{quat}), 150.93 (C_{quat}), 153.13 (C_{quat}), 189.70 (C=O). IR (ATR): ν 2943 (CHO), 2863 (CH), 1675 (CH_{Ar}), 1391, 1114 cm^{-1}. MS (ES$^+$) *m/z* (%): 247 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{19}H_{19}O_3]^+$: 247.1334, found 247.1338.

A solution of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-6-carboxaldehydes **348a** or **348b**, ethylene glycol or propylene glycol (80 mmol) and *p*-TsOH·H_2O (0.2 mmol, 38 mg) in PhMe (40 mL) was

equipped with a Dean-Stark piece and boiled under reflux for 4 hours. Next, the reaction mixture was allowed to cool to room temperature, diluted with EtOAc (40 mL), washed with aqueous saturated $NaHCO_3$ (40 mL) and brine (3x40 mL). Drying over $MgSO_4$ and evaporation of the solvent yielded pure 2-(5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-6-yl)-1,3-dioxolanes **349a** or **349b**, 2-(5,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-6-yl)-1,3-dioxane **349c**. Dioxolanes **349a** and **349b** had only a limited stability so no (HR)MS could be recorded.

2-(5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1,3-dioxolane 349a

82%, pale white solid, mp 106.4°C. ^{1}H NMR ($CDCl_3$): δ 1.14-1.27 (2H, m, CH_2), 1.48 (1H, d, J = 8.8 Hz, C$\underline{H}_A$H$_B$), 1.70 (1H, d, J = 8.8 Hz, CH$_A$$\underline{H}_B$), 1.84-1.98 (2H, m, CH_2), 3.57 (1H, br s, CH-1 or CH-4), 3.61 (1H, br s, CH-1 or CH-4), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.01-4.09 (2H, m, CH_2O), 4.10-4.21 (2H, m, CH_2O), 6.05 ($CH(OCH_2)_2$), 6.84 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 26.42 (CH_2), 26.90 (CH_2), 39.84 (CH), 41.19 (CH), 49.14 (CH_2), 55.92 (OCH_3), 62.15 (OCH_3), 65.37 (OCH_2), 65.40 (OCH_2), 99.88 ($\underline{C}H(OCH_2)_2$), 106.93 (CH_{Ar}), 127.45 (C_{quat}), 138.45 (C_{quat}), 140.77 (C_{quat}), 146.71 (C_{quat}), 149.22 (C_{quat}). IR (ATR): ν 2951 (CH), 2868 (CH), 1489, 1458, 1387, 1218, 1110, 1054, 1021 cm^{-1}.

2-(5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-ethanonaphthalen-6-yl)-1,3-dioxolane 349b

89%, pale white crystals, mp 113°C. ^{1}H NMR ($CDCl_3$): δ 1.26-1.38 (4H, m, 2xCH_2), 1.69-1.81 (4H, m, 2xCH_2), 3.36-3.37 (1H, m, CH), 3.45-3.46 (1H, m, CH), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.03-4.11 (2H, m, CH_2O), 4.13-4.21 (2H, m, CH_2O), 6.11 (1H, s, C$\underline{H}(OCH_2)_2$), 6.92 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 25.61 (2xCH_2), 25.74 (2xCH_2), 26.10 (CH), 27.46 (CH), 55.88 (OCH_3), 63.28 (OCH_3), 65.42 (OCH_2CH_2O), 99.92 ($\underline{C}H(OCH_2)_2$), 105.62 (CH_{Ar}), 127.09 (C_{quat}), 134.86 (C_{quat}), 137.97 (C_{quat}), 147.88 (C_{quat}), 154.54 (C_{quat}). IR (ATR): ν 2939 (CH), 1487, 1383, 1217, 1114 cm^{-1}.

2-(5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)-1,3-dioxane 349c

Quantitative yield, yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.11-1.23 (2H, m, CH_2), 1.46 (1H, d, J = 8.3 Hz, C$\underline{H}_A$H$_B$), 1.43 (1H, d, J = 10.5 Hz, OCH$_2$C$\underline{H}_A$H$_B$), 1.68 (1H, d, J = 8.8 Hz, CH$_A$$\underline{H}_B$), 1.84-1.94 (2H, m, CH_2), 2.18-2.32 (1H, m, OCH$_2$CH$_A$$\underline{H}_B$), 3.56 (1H, s, CH-1 or CH-4), 3.58 (1H, s, CH-1 or CH-4), 3.81 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.02 (2H, dd, J = 11.8, 11.6, 2xC$\underline{H}_{AX}$H$_{EQ}$O), 4.02 (2H, dd, J = 4.1, 11.6, 2xCH$_{AX}$$\underline{H}_{EQ}$O), 5.79 (1H, s, C$\underline{H}$(OCH$_2CH_2CH_2$O)), 6.91 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 25.68 (CH_2), 26.17 (CH_2), 26.65 (CH_2), 39.57 (CH), 40.87 (CH), 48.82 (CH_2), 55.54 (OCH_3), 61.85 (OCH_3), 67.37 (2xOCH_2), 97.45 ($\underline{C}$H(OCH$_2$CH$_2$CH$_2$O)), 106.70 (CH_{Ar}), 128.83 (C_{quat}), 137.59 (C_{quat}), 140.26 (C_{quat}), 145.06 (C_{quat}), 149.15 (C_{quat}). IR (ATR): ν 2954 (CH), 2867 (CH), 1388, 1220, 1111, 1096 cm^{-1}. MS (ES$^+$) *m/z* (%): 291 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{17}H_{23}O_4]^+$: 291.1596, found 291.1595.

2-(5,8-Dimethoxy-1,4-dihydro-1,4-epoxynaphthalen-6-yl)-1,3-dioxolane 351

A solution of freshly prepared LDA (2 equiv., 17.5 mmol) in anhydrous THF (10 ml) was cooled to -78°C and furan (10 mL) was added dropwise. Next, 2-(3-bromo-2,5-dimethoxyphenyl)-1,3-dioxolane **181b** (2.5 g, 8.65 mmol) dissolved in 2.5 mL THF was slowly added dropwise. The reaction mixture was allowed to stir for 1 h at -78°C and quenched with 10 mL H_2O. The reaction mixture was diluted with 20 mL of EtOAc and washed twice with brine (10 mL). Drying over $MgSO_4$, evaporation of the solvent *in vacuo* followed by recrystallisation from Et_2O gave pure 2-(5,8-dimethoxy-1,4-dihydro-1,4-epoxynaphthalen-6-yl)-1,3-dioxolane **351**.

89%, pale white solid, mp 131°C. ^{1}H NMR ($CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.98-4.07 (2H, m, CH_2O), 4.08-4.18 (2H, m, CH_2O), 5.90 (1H, d, *J* = 1.7 Hz, CH-1 or 8), 6.05 ($CH(OCH_2)_2$), 6.02 (1H, d, *J* = 1.7 Hz, CH-1 or 8), 6.83 (1H, s, CH-5), 7.03 (1H, dd, *J* = 1.7, 5.5 Hz, CH-9 or CH-10), 7.03 (1H, dd, *J* = 1.7, 5.5 Hz, CH-9 or CH-10). ^{13}C NMR ($CDCl_3$): δ 56.14 (OCH_3), 61.46 (OCH_3), 65.17 (OCH_2CH_2O), 79.76 and 81.30 (CH-1 and CH-8), 99.39 ($\underline{C}H(OCH_2)_2$), 109.54 (CH-5), 128.20 (C_{quat}), 138.03 (C_{quat}), 139.09 (C_{quat}), 142.29 and 142.97 (CH-9 and CH-10), 146.66 (C_{quat}), 148.36 (C_{quat}). IR (ATR): ν 2897 (CH), 1478, 1392, 1222, 1055 cm^{-1}. MS (ES$^+$) *m/z* (%): 277 ($[M+H]^+$, 100). HRMS (ES$^+$) calcd. for $[C_{15}H_{17}O_5]^+$: 277.1076, found 277.1072.

2-(5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-6-yl)-1,3-dioxolane 349d

2-(5,8-Dimethoxy-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-6-yl)-1,3-dioxolane **349d** was prepared using the same procedure as 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalenes **347**.

99%, white crystals, mp 81-82.5°C. ^{1}H NMR ($CDCl_3$): δ 1.35-1.51 (2H, m, CH_2), 1.99-2.13 (2H, m, CH_2), 3.82 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.01-4.07 (2H, m, CH_2O), 4.08-4.18 (2H, m, CH_2O), 5.56 (1H, d, *J* = 4.4 Hz, CH-1 or 8), 5.66 (1H, d, *J* = 4.4 Hz, CH-1 or 4), 6.04 ($CH(OCH_2)_2$), 6.93 (1H, s, CH-7). ^{13}C NMR ($CDCl_3$): δ 26.09 (CH_2), 26.71 (CH_2), 55.97 (OCH_3), 61.40 (OCH_3), 65.34 (OCH_2CH_2O), 76.47 and 77.72 (CH-1 and CH-8), 99.45 ($\underline{C}H(OCH_2)_2$), 108.89 (CH-5), 128.60 (C_{quat}), 136.02 (C_{quat}), 136.92 (C_{quat}), 145.16 (C_{quat}), 147.47 (C_{quat}). IR (ATR): ν 2954 (CH), 1482, 1394, 1069 cm^{-1}. MS (ES$^+$) *m/z* (%) 279 ($[M+H]^+$, 100). HRMS (ES$^+$) calcd. for $[C_{15}H_{19}O_5]^+$: 279.1233, found 279.1231.

To a stirred solution of dioxolanes **349a**, **349b** or **349d** or dioxane **349c** (1.81 mmol) in CH_3CN (10 mL) was added a solution of CAN (5.43 mmol, 2.98 g) in H_2O (10 mL) in one portion at room temperature. After 3 minutes, the reaction mixture was diluted with EtOAc (20 ml) and washed twice with brine (10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded the crude quinones **350** which were used as such. All dioxolanylnaphthoquinones **350** were unstable and had to

be used directly in the next step. 6-(1,3-Dioxan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione **350c** was purified by means of preparative TLC.

6-(1,3-Dioxolan-2-yl)-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione 350a

60%, orange solid, mp 68.4°C. ^{1}H NMR ($CDCl_3$): δ 1.05-1.15 (2H, m, CH_2), 1.32-1.36 (1H, m, CH), 1.54-1.59 (1H, m, CH), 1.81-1.90 (2H, m, CH_2), 3.39 (1H, d, *J* = 1.4 Hz, CH-1 or CH-4), 3.42 (1H, d, *J* = 1.4 Hz, CH-1 or CH-4), 3.93-3.98 (4H, m, OCH_2CH_2O), 5.79 ($C\underline{H}(OCH_2)_2$), 6.60 (1H, s, CH-7). ^{13}C NMR ($CDCl_3$): δ 24.88 (CH_2), 24.93 (CH_2), 40.47 (CH), 40.53 (CH), 47.83 (CH_2), 65.31 (OCH_2), 65.45 (OCH_2), 98.00 ($\underline{C}H(OCH_2)_2$), 131.64 (CH_{Ar}), 142.26 (C_{quat}), 151.67 (C_{quat}), 151.93 (C_{quat}), 183.46 (C=O), 184.65 (C=O). IR (ATR): ν 2953 (CH), 2878 (CH), 1645 (C=O), 1337, 1088, 943 cm^{-1}.

6-1,3-Dioxolan-2-yl-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-5,8-dione 350b

83%, red oil. ^{1}H NMR ($CDCl_3$): δ 1.29 (4H, br d, *J* = 8.0 Hz, 2xCH_2), 1.73 (4H, br d, *J* = 8.0 Hz, 2xCH_2), 3.33 (1H, s, CH), 3.37 (1H, m, CH), 4.05 (2H, s, CH_2O), 4.05 (2H, s, CH_2O), 5.93 (1H, s, $C\underline{H}(OCH_2)_2$), 6.80 (1H, s, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 24.79 (4xCH_2), 26.00 (2xCH), 65.06 (OCH_2CH_2O), 97.75 ($\underline{C}H(OCH_2)_2$), 131.08 (CH_{Ar}), 141.82 (C_{quat}), 147.70 (C_{quat}), 147.90 (C_{quat}), 182.91 (C=O), 184.10 (C=O). IR (ATR): ν 2949 (CH), 2868 (CH), 1648 (C=O), 751 cm^{-1}.

6-1,3-Dioxan-2-yl-1,2,3,4-tetrahydro-1,4-methanonaphthalene-5,8-dione 350c

42%, orange solid, mp 101°C. ^{1}H NMR ($CDCl_3$): δ 1.15 (2H, d, *J* = 8.8 Hz, CH_2), 1.39 (1H, d, *J* = 9.1 Hz, $C\underline{H}_AH_B$), 1.43 (1H, d, J = 13.4 Hz, $OCH_2C\underline{H}_AH_B$), 1.62 (1H, d, *J* = 9.1 Hz, $CH_A\underline{H}_B$), 1.90 (2H, d, *J* = 8.8 Hz, CH_2), 2.09-2.25 (1H, m, $OCH_2CH_A\underline{H}_B$), 3.47 (2H, s, CH-1 and CH-4), 3.96 (2H, dd, *J* = 13.4, 10.5, 2x$C\underline{H}_{AX}H_{EQ}O$), 4.20 (2H, d, *J* = 10.5, 2x$CH_{AX}\underline{H}_{EQ}O$), 5.55 (1H, s, $C\underline{H}(OCH_2CH_2CH_2O)$), 6.80 (1H, s, CH-7). ^{13}C NMR ($CDCl_3$): δ 24.90 (CH_2), 24.96 (CH_2), 25.64 (CH_2), 40.49 (CH-1 or CH-4), 40.59 (CH-1 or CH-4), 47.75 (CH_2-9), 67.42 (OCH_2), 67.49 (OCH_2), 94.64 ($\underline{C}H(OCH_2CH_2CH_2O)$), 132.70 ($CH_{Ar}$), 142.51 ($C_{quat}$), 151.44 ($C_{quat}$), 151.53 ($C_{quat}$), 182.63 (C=O), 184.66 (C=O). IR (ATR): ν 2955 (CH), 1645 (C=O), 1097 (C-O) cm^{-1}. MS (ES$^+$) *m/z* (%): 261 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{15}H_{17}O_4]^+$: 261.1127, found 261.1121.

6-1,3-Dioxolan-2-yl-1,2,3,4-tetrahydro-1,4-epoxynaphthalene-5,8-dione 350d

81%, red solid, mp 79°C (decomp.). ^{1}H NMR ($CDCl_3$): δ 1.30-1.45 (2H, m, CH_2), 2.02-2.12 (2H, m, CH_2), 4.04 (4H, s, OCH_2CH_2O), 5.46 (2H, t, *J* = 5.0 Hz, CH-1 and CH-4), 5.87 ($C\underline{H}(OCH_2)_2$), 6.73 (1H, s, CH-5). ^{13}C NMR ($CDCl_3$): δ 23.77 (CH_2), 23.83 (CH_2), 64.93 (OCH_2), 65.11 (OCH_2), 76.27 and 76.34 (CH-1 and CH-4), 97.38 ($\underline{C}H(OCH_2)_2$), 131.30 (CH_{Ar}), 142.26 (C_{quat}), 149.78 (C_{quat}), 150.00 (C_{quat}), 181.90 (C=O), 182.92 (C=O). IR (ATR): ν 2980 (CH), 2885 (CH), 1655 (C=O), 1305, 1286, 875 cm^{-1}.

5.10.2 Synthesis of octahydrobenzophenanthridinediones 22a-22g

Method A

A stirred solution of dioxolanylnaphthoquinones **350** (1.5 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was cooled to 0°C and $BF_3 \cdot OEt_2$ was added dropwise (19 µL, 0.1 equiv.). Next, freshly distilled enamine **340c**, **358**, or **359b** (1.65 mmol) was added dropwise in anhydrous THF (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Then, NH_3 7 M in MeOH (1.4 mL, 10 equiv.) was added dropwise and the reaction was allowed to stir open to the air for 15 h. After careful evaporation of the solvents, the reaction mixture was redissolved in EtOAc (15 mL) an washed with brine (2x10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* gave a crude mixture which was purified by means of preparative TLC (hexane/ethyl acetate). Recrystallisation from EtOH yielded the desired 1,2,3,4-octahydrobenzo[*j*]phenanthridine-7,12-diones **22**.

Method B

After the enamine addition, the reaction mixture was evaporated *in vacuo* and subsequently redissolved in 10 mL of HOAc. After the addition of NH_4OAc (15 mmol, 1.16 g) the reaction mixture was stirred at 60°C for 1 hour open to the air. Next, the reaction mixture was evaporated *in vacuo*, redissolved in 15 mL of EtOAc, washed with an aqueous saturated $NaHCO_3$ solution (2x10 mL) and brine (10 mL). Further purification proceeded as in method A.

2-*tert*-Butyl-1,2,3,4,8,9,10,11-octahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 22a

48%, yellow solid, mp 140.0°C. ^{1}H NMR ($CDCl_3$): δ 1.02 (9H, s, $C(CH_3)_3$), 1.22-1.31 (2H, m, CH_2), 1.38-1.49 (3H, m, CH_2 and CH), 1.66-1.72 (1H, m, CH), 1.95-2.05 (2H, m, CH_2), 2.08-2.13 (1H, m, CH), 2.75 (1H, dd, J = 11.0, 18.7 Hz, CH), 2.91-3.06 (1H, m, CH), 3.15-3.22 (1H, m, CH), 3.61 (2H, s, 2xCH), 3.73 (1H, d, J = 18.7 Hz), 9.06 (1H, CH-6). ^{13}C NMR ($CDCl_3$): major isomer δ 23.28 (CH_2), 25.20 (CH_2), 25.26 (CH_2), 27.31 ($C(\underline{C}H_3)_3$), 29.04 (CH_2), 32.70 ($\underline{C}(CH_3)_3$), 35.51 (CH_2), 40.81 (CH), 41.19 (CH), 44.33 (CH_2), 47.72 (CH-2), 124.80 (C_{quat}), 133.09 (C_{quat}), 134.75 (C_{quat}), 145.33 (CH-6), 152.43 (C_{quat}), 155.33 (C_{quat}), 182.05 (C=O), 184.89 (C=O). Minor isomer δ 23.51 (CH_2), 25.26 (CH_2), 25.46 (CH_2), 27.31 ($C(\underline{C}H_3)_3$), 29.71 (CH_2), 32.64 ($\underline{C}(CH_3)_3$), 35.34 (CH_2), 40.91 (CH), 41.45 (CH), 44.33 (CH_2), 46.93 (CH-2), 124.86 (C_{quat}), 133.02 (C_{quat}), 135.32 (C_{quat}), 145.33 (CH-6), 152.51 (C_{quat}), 155.41 (C_{quat}), 182.16 (C=O), 185.07 (C=O). Major/minor 3.7/1. IR (ATR): ν 2954 (CH), 2872 (CH), 1656 (C=O), 1321 cm^{-1}. MS (ES$^+$) *m/z* (%): 336 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{22}H_{26}NO_2]^+$: 336.1964, found 336.1957.

2-*tert*-Butyl-1,2,3,4,8,9,10,11-octahydro-8,11-ethanobenzo[*j*]phenanthridine-7,12-dione 22b

33%, yellow solid, mp 154.0°C. ^{1}H NMR ($CDCl_3$): δ 1.03 (9H, s, $C(CH_3)_3$), 1.23-1.34 (4H, m, 2xCH_2), 1.40-1.49 (2H, m, CH_2), 1.73-1.85 (4H, m, 2xCH_2), 2.09-2.16 (1H, m, CH), 2.86 (1H, dd, *J* = 11.0, 18.6 Hz, CH), 2.96-3.08 (1H, m, CH), 3.16-3.24 (1H, m, CH), 3.51 (2H, s, 2xCH), 3.60 (1H, dd, *J* = 18.6, 3.6 Hz), 9.14 (1H, CH-6). ^{13}C NMR ($CDCl_3$): δ 23.46 (CH_2), 25.20 (CH_2), 25.25 (CH_2), 25.40 (CH_2), 25.48 (CH_2), 26.52 (CH-8 or CH-11), 26.87 (CH-8 or CH-11), 27.39 ($C(\underline{C}H_3)_3$), 29.65 (CH_2), 32.72 ($\underline{C}(CH_3)_3$), 35.52 (CH_2), 44.47 (CH-2), 124.34 (C_{quat}), 133.10 (C_{quat}), 134.61 (C_{quat}), 145.71 (CH-6), 149.18 (C_{quat}), 151.84 (C_{quat}), 181.96 (C=O), 184.45 (C=O). IR (ATR): ν 2944 (CH), 2867 (CH), 1660 (C=O), 1618 (CH_{Ar}), 1566 (CH_{Ar}), 1297 cm^{-1}. MS (ES^+) *m/z* (%): 350 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{23}H_{28}NO_2]^+$: 350.2120, found 350.2119.

2-*tert*-Butyl-1,2,3,4,8,9,10,11-octahydro-8,11-epoxybenzo[*j*]phenanthridine-7,12-dione 22c

14%, yellow solid, mp 128.5°C. ^{1}H NMR ($CDCl_3$): major isomer δ 1.02 (9H, s, $C(CH_3)_3$), 1.37-1.51 (4H, m, 2xCH_2), 2.06-2.17 (3H, m, CH_2 and CH), 2.73 (1H, dd, J = 19.1, 10.9, CH), 3.02-3.08 (1H, m, CH), 3.16-3.19 (1H, m, CH), 3.72 (1H, dd, *J* = 3.9, 17.6 Hz, CH), 5.57 (2H, dd, *J* = 4.4, 11.0, CH-8 and CH-10), 9.08 (1H, CH-6). Minor isomer δ 1.02 (9H, s, $C(CH_3)_3$), 1.37-1.51 (4H, m, 2xCH_2), 2.06-2.17 (3H, m, CH_2 and CH), 2.87 (1H, dd, J = 19.1, 10.9, CH), 2.96-3.00 (1H, m, CH), 3.23-3.25 (1H, m, CH), 3.40 (1H, dd, *J* = 3.9, 17.6 Hz, CH), 5.57 (2H, dd, *J* = 4.4, 11.0, CH-8 and CH-10), 9.07 (1H, CH-6). Major/minor 3/1. ^{13}C NMR ($CDCl_3$): major isomer δ 23.19 (CH_2), 24.47 (CH_2), 24.61 (CH_2), 27.31 ($C(\underline{C}H_3)_3$), 29.94 (CH_2), 32.73 ($\underline{C}(CH_3)_3$), 35.54 (CH_2), 35.54 (2xCH), 44.27 (CH-2), 124.76 (C_{quat}), 133.61 (C_{quat}), 145.48 (CH-6), 150.66 (C_{quat}), 153.51 (C_{quat}), 167.19 (C_{quat}), 182.92 (C=O), 183.87 (C=O). Minor isomer δ 23.46 (CH_2), 24.55 (CH_2), 24.76 (CH_2), 27.31 ($C(\underline{C}H_3)_3$), 29.17 (CH_2), 32.65 ($\underline{C}(CH_3)_3$), 35.37 (2xCH), 42.76 (CH-2), 125.06 (C_{quat}), 134.54 (C_{quat}), 145.48 (CH-6), 158.00 (C_{quat}), 159.44 (C_{quat}), 167.07 (C_{quat}), 180.92 (C=O), 183.87 (C=O). IR (ATR): ν 2958 (CH), 2869 (CH), 1661 (C=O), 1561 (CH_{Ar}), 1320 cm^{-1}. MS (ES^+) *m/z* (%): 338 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{24}NO_3]^+$: 338.1756, found 338.1755.

2-ethoxycarbonyl-1,2,3,4,8,9,10,11-octahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 22d

18%, light brown solid, mp 61.5°C. ^{1}H NMR ($CDCl_3$): Isomer I δ 1.10-1.14 (2H, m, CH_2), 1.18 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.37 (1H, d, J = 1.5 Hz, $C\underline{H}_AH_B$), 1.58-1.60 (1H, m, $CH_A\underline{H}_B$), 1.85-1.90 (2H, m, CH_2), 1.95-1.97 (1H, m, $C\underline{H}_CH_D$), 2.07-2.13 (1H, m, $CH_C\underline{H}_D$), 2.61-2.71 (1H, m, CH-2), 2.91-3.00 (2H, m, CH_2), 3.29 (1H, dd, *J* = 8.8, 19.1 Hz, $C\underline{H}_EH_F$), 3.47 (1H, dd, *J* = 5.0, 19.1 Hz, $CH_E\underline{H}_F$), 3.52 (2H, br s, 2xCH), 4.09 (2H, q, *J* = 7.2 Hz, $C\underline{H}_2CH_3$), 8.93 (1H, CH-6). Isomer II δ 1.13-1.72 (2H, m, CH_2), 1.22 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.40 (1H, d, J = 1.5 Hz, $C\underline{H}_AH_B$), 1.60-1.63 (1H, m, $CH_A\underline{H}_B$), 1.90-1.92 (2H, m, CH_2), 1.98-2.07(1H, m, $C\underline{H}_CH_D$), 2.13-2.22 (1H, m, $CH_C\underline{H}_D$), 2.72-2.81 (1H, m, CH-2), 3.00-3.12 (2H, m, CH_2), 3.33 (1H, dd, *J* = 10.7, 19.1 Hz, $C\underline{H}_EH_F$), 3.52 (2H, br s, 2xCH), 3.62

(1H, dd, *J* = 5.8, 19.1 Hz, $CH_E\underline{H}_F$), 4.12 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 8.93 (1H, CH-6). Isomer I/II 1/1. ^{13}C NMR ($CDCl_3$): isomer I δ 14.26 (CH_3), 24.27 (CH_2), 25.16 (CH_2), 25.25 (CH_2), 29.27 (CH_2), 32.46 (CH_2), 38.82 (CH-2), 40.79 (CH), 41.25 (CH), 47.10 (CH_2), 124.93 (C_{quat}), 130.31 (C_{quat}), 134.98 (C_{quat}), 145.53 (CH-6), 152.49 (C_{quat}), 155.33 (C_{quat}), 164.42 (C_{quat}), 174.54 (C=O), 181.71 (C=O), 184.37 (C=O). Isomer II δ 14.26 (CH_3), 24.55 (CH_2), 25.16 (CH_2), 25.30 (CH_2), 29.92 (CH_2), 32.91 (CH_2), 39.34 (CH-2), 40.84 (CH), 41.33 (CH), 47.37 (CH_2), 124.93 (C_{quat}), 130.37 (C_{quat}), 135.20 (C_{quat}), 145.61 (CH-6), 152.55 (C_{quat}), 155.36 (C_{quat}), 164.42 (C_{quat}), 174.59 (C=O), 181.72 (C=O), 184.43 (C=O). IR (ATR): ν 2956 (CH), 2875 (CH), 1728 (C=O), 1655 (C=O), 1566 (CH_{Ar}), 1179 cm^{-1}. MS (ES$^+$) *m/z* (%): 352 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{21}H_{22}NO_4]^+$: 352.1549, found 352.1527.

2-ethoxycarbonyl-1,2,3,4,8,9,10,11-octahydro-8,11-ethanobenzo[*j*]phenanthridine-7,12-dione 22e

10%, light brown solid, mp 118-120°C. ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 1.35 (4H, br d, *J* = 8.3 Hz, 2xCH_2), 1.79 (4H, m, br d, *J* = 8.3 Hz, 2xCH_2), 2.02-2.15 (1H, m, CH), 2.22-2.32 (1H, m, CH), 2.77-2.87 (1H, m, CH), 3.04-3.21 (2H, m, CH_2), 3.45 (1H, dd, *J* = 18.6, 8.1 Hz, CH), 3.51 (2H, br s, CH_2), 3.70 (1H, dd, *J* = 18.6, 5.5 Hz), 4.20 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 9.17 (1H, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.35 ($\underline{C}H_3CH_2$), 24.56 (CH_2), 25.22 (CH_2), 25.25 (CH_2), 25.29 (2xCH_2), 25.34 (CH_2), 26.53 and 27.06 (CH-8 and CH-11), 29.89 (CH_2), 32.91 (CH_2), 39.29 (CH-2), 124.48 (C_{quat}), 130.37 (C_{quat}), 134.64 (C_{quat}), 146.11 (CH-6), 149.29 (C_{quat}), 151.87 (C_{quat}), 164.34 (C_{quat}), 174.69 (C=O), 181.68 (C=O), 184.02 (C=O). IR (ATR): ν 2980 (CH), 1725 (C=O), 1654 (C=O), 1301, 1240, 1180 cm^{-1}. MS (ES$^+$) *m/z* (%): 366 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{22}H_{24}NO_4]^+$: 366.1705, found 366.1692.

2-*tert*-Butoxycarbonyl-1,2,3,4,8,9,10,11-octahydro-2-aza-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 22g

17%, orange solid, mp 98°C. ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 1.23-1.26 (2H, m, CH_2), 1.02 (10H, s+m, $C(CH_3)_3$ and $C\underline{H}_AH_B$), 1.69-1.72 (1H, m, $CH_A\underline{H}_B$), 2.00 (2H, dd, *J* = 2.5, 6.9, CH_2), 3.15 (2H, t, *J* = 6.1 Hz,CH_2-4), 3.63 (2H, s, CH-8 and CH-11), 3.73 (1H, dt, *J* = 12.9, 6.1 Hz, $C\underline{H}_AH_B$-3), 3.87 (1H, dt, *J* = 12.9, 6.1 Hz, $C\underline{H}_AH_B$-3), 9.15 (1H, CH-6). ^{13}C NMR ($CDCl_3$): δ 25.23 (CH_2), 25.28 (CH_2), 28.40 ($C(\underline{C}H_3)_3$), 33.77 (CH_2-4), 40.89 (CH_2-3), 41.31 (CH-8 and CH-9), 45.11 (CH_2-1), 47.45 (CH_2-13), 80.52 ($\underline{C}(CH_3)_3$), 124.86 (C_{quat}), 124.86 (C_{quat}), 129.19 (C_{quat}), 134.11 (C_{quat}), 146.25 (CH-6), 152.98 (C_{quat}), 154.66 (C_{quat}), 155.21 (C_{quat}), 162.84 (C=O), 181.58 (2xC=O). IR (ATR): ν 2980 (CH), 1697 (C=O), 1659 (C=O), 1160, 1150, cm^{-1}. MS (ES$^+$) *m/z* (%): 381 ([M+H]$^+$, 70). HRMS (ES$^+$) calcd. for $[C_{22}H_{25}N_2O_4]^+$: 381.1814, found 381.1806.

5.10.3 Synthesis of enamine adduct 352c

A stirred solution of dioxolanylnaphthoquinone **350c** (1.5 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was cooled to 0°C and $BF_3 \cdot OEt_2$ was added dropwise (19 µL, 0.1 equiv.). Next, freshly distilled enamine **340c** (1.65 mmol) was added dropwise in 2 mL of anhydrous THF. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. After careful evaporation of the solvents, the reaction mixture was redissolved in EtOAc (15 mL) an washed with brine (2x10 mL). Drying over $MgSO_4$, evaporation of the solvent *in vacuo* and purification by means of preparative TLC (hexane/ethyl acetate) gave enamine adduct **352c** as a white solid in 70% yield.

8-*tert*-Butyl-6-(1,3-dioxan-2-yl)-10a-pyrrolidin-1-yl-1,2,3,4,6b,7,8,9,10,10a-decahydro-1,4-methanobenzo[*b*]naphtho[2,1-*d*]furan-5-ol 352c

70%, white solid, mp 180.5°C. ^{1}H NMR ($CDCl_3$): δ 0.85 (9H, s, $C(CH_3)_3$), 1.09-1.31 (7H, m, CH-8, $C\underline{H}_AH_B$, $C\underline{H}_CH_D$, 2xCH_2), 1.40-1.52 (2H, m, $C\underline{H}_EH_F$, $C\underline{H}_GH_H$), 1.56-1.71 (4H, m, $CH_C\underline{H}_D$, $CH_E\underline{H}_F$, CH_2), 1.82-1.84 (2H, m, CH_2), 1.96-2.01 (1H, m, $CH_A\underline{H}_B$), 2.05-2.13 (2H, m, CH_2), 2.22-2.30 (1H, m, $CH_G\underline{H}_H$), 2.53-2.62 (2H, m, CH_2), 2.74-2.84 (2H, m, CH_2), 3.12-3.21 (1H, m, CH-6b), 3.43 (1H, br s, CH-1 or CH-4), 3.57 (1H, br s, CH-1 or CH-4), 3.90-4.02 (2H, m, CH_2O), 4.26-4.35 (2H, m, CH_2O), 5.62 (1H, s, $C\underline{H}(O(CH_2)_3O)$, 7.35 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 21.48 (CH_2), 23.83 (2xCH_2), 25.78 (CH_2), 26.27 (CH_2), 26.79 (CH_2), 27.16 ($C(\underline{C}H_3)_3$), 31.63 (CH_2), 32.41 (CH_2), 32.91 ($\underline{C}(CH_3)_3$), 39.85 and 40.29 (CH-1 and CH-4), 43.06 (CH-8), 45.52 (2xCH_2), 46.56 (CH-6b), 49.43 (CH_2), 67.45 (CH_2O), 67.97 (CH_2O), 102.04 ($\underline{C}H(O(CH_2)_3O)$, 103.15 (C10a), 112.29 (C_{quat}), 115.04 (C_{quat}), 127.68 (C_{quat}), 128.51 (C_{quat}), 129.54 (C_{quat}), 132.77 (C_{quat}), 134.95 (C_{quat}), 142.19 (C_{quat}), 145.16 (C_{quat}). IR (ATR): ν 3420 (OH), 2957 (CH), 2866 (CH), 1090 (C-O), 746 cm^{-1}. MS (ES$^+$) *m/z* (%): 468 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{29}H_{42}NO_4]^+$: 468.3114, found 468.3113.

5.10.4 6-Bromo-4-*tert*-butylcyclohex-1-enyl-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxylate 379'

1,4-Dimethoxy-5,6,7,8-tetrahydro-5,8-methanonaphthalene-2-carboxylic acid **360** (253 mg, 1.02 mmol) was added to $SOCl_2$ (0.74 mL, 10.2 mmol, 10 equiv.) and boiled under reflux for 2.5 h. The reaction mixture was evaporated *in vacuo* and redissolved in anhydrous THF (5 mL). A solution of 2-bromocyclohexanone **380** (1.02 mmol, 181 mg) in anhydrous THF (5 mL) was cooled to -78°C and LiHMDS (1.12 mL 1 M in THF, 1.12 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was allowed to stir for 15 min at that temperature and subsequently the acid chloride was added dropwise. The temperature was allowed to warm to 0°C and the reaction was stirred for an additional 30 min. Then H_2O (10 mL) and EtOAc (10 mL) was added and the mixture was extracted with aqueous HCl (2 N, 10 mL) and aqueous saturated $NaHCO_3$ (10 mL). The organic phase was dried

($MgSO_4$), evaporated in vacuo and purified by means of column chromatography to yield the title compound **379'** as a colourless oil (120 mg, 0.27 mmol, 26%).

26%, colourless oil. ^{1}H NMR ($CDCl_3$): δ mixture of major and minor isomer, minor not resolved 0.94 (9H, s, $C(CH_3)_3$), 1.16-1.28 (2H, m, 2x$C\underline{H}_N H_X$), 1.50-1.54 (2H, m, 2x$CH_N\underline{H}_X$), 1.71-1.74 (1H, m, CH), 1.92-2.01 (2H, m, 2xCH), 2.18-2.38 (4H, m, 2xCH_2), 3.62 (1H, br s, CH-1 or CH-4), 3.66 (1H, br s, CH-1 or CH-4), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.03-2.05 (1H, m, CH), 5.73-5.76 (1H, m, CH), 7.24 (1H, s, CH-7). ^{13}C NMR ($CDCl_3$): δ 25.68 (CH_2), 26.12 (CH_2), 26.71 (CH_2), 27.34 ($C(\underline{C}H_3)_3$), 31.74 ($\underline{C}(CH_3)_3$), 34.07 (CH_2), 38.38 (CH_2), 40.35 and 40.88 (CH-1 and CH-4), 48.99 and 49.11 (CH-*t*-Bu and CH-Br), 55.97 (OCH_3), 62.43 (OCH_3), 112.11 (CH-2'), 112.31 (C_{quat}), 120.05 (CH-7), 120.81 (C_{quat}), 143.00 (C_{quat}), 143.21 (C_{quat}), 146.94 (C_{quat}), 149.01 (C_{quat}), 164.77 (C=O). IR (ATR): ν 2957, 1736, 1481, 1317, 1224, 1158, 1022 cm^{-1}. MS (ES$^+$) *m/z* (%): 231 ([M-$C_{10}H_{16}BrO$]$^+$, 100), 463/465 ([M+H]$^+$, 45/40).

5.11 Synthesis of dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones 20

5.11.1 Synthesis of 6-amino-1,3-dialkyluracils 389

6-Aminouracil **389a** and 6-amino-1,3-dimethyluracil **389b** are commercially available. All other 6-amino-1,3-dialkyluracils **389** were synthesised from triphosgene, a primary amine and cyanoacetic acid following literature protocols.[220] The following 6-amino-1,3-dialkyluracils were not reported previously in the literature:

6-Amino-1,3-di-*n*-pentyluracil 389h

71%, white solid, mp <50°C. ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, *J* = 6.6 Hz, CH_3), 0.89 (3H, t, *J* = 6.6 Hz, CH_3), 1.24-1.36 (8H, m, 4xCH_2), 1.53-1.57 (2H, m, $NCH_2C\underline{H}_2$), 1.66-1.71 (2H, m, $NCH_2C\underline{H}_2$), 3.81-3.90 (4H, m, 2xNCH_2), 4.97 (1H, s, CH-5), 5.89 (2H, s, NH_2). ^{13}C NMR ($CDCl_3$): δ 13.92 (CH_3), 13.98 (CH_3), 22.35 (CH_2), 22.44 (CH_2), 27.71 (CH_2), 27.77 (CH_2), 28.82 (CH_2), 29.13 (CH_2), 41.14 (NCH_2), 42.76 (NCH_2), 77.47 (CH-5), 151.58 (C_{quat}), 154.32 (C_{quat}), 163.26 (C_{quat}). IR (ATR): ν 3347 (NH), 3204 (NH), 2956 (CH), 2931 (CH), 1607 (C=O), 1492 cm^{-1}. MS (ES$^+$) *m/z* (%): 268 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{14}H_{26}N_3O_2]^+$: 268.2025, found 268.2027.

6-Amino-1,3-di-*iso*-pentyluracil 389i

64%, white solid, mp 142-143°C. ^{1}H NMR ($CDCl_3$): δ 0.94 (6H, d, *J* = 6.6 Hz, 2xCH_3), 0.98 (6H, d, *J* = 6.6 Hz, 2xCH_3), 1.44-1.73 (6H, m, 2xCH_2, 2xCH), 3.84-3.92 (4H, m, 2xNCH_2), 4.69-4.81 (2H, m, NH_2), 4.97 (1H, s, CH-5). ^{13}C NMR ($CDCl_3$): δ 22.52 (CH_3), 22.64 (CH_3), 26.41 (CH), 26.49 (CH), 36.76 (CH_2), 36.93 (CH_2), 39.95 (NCH_2), 41.51 (NCH_2), 77.57 (CH-5), 151.55 (C_{quat}), 154.03 (C_{quat}),

163.29 (C_{quat}). IR (ATR): ν 3351 (NH), 3216 (NH), 2957 (CH), 1608 (C=O), 1583, 1495 cm^{-1}. MS (ES^+) *m/z* (%): 268 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{14}H_{26}N_3O_2]^+$: 268.2025, found 268.2021.

6-Amino-1,3-di-*n*-heptyluracil 389k

Quantitative yield, white solid, mp <50°C. ^1H NMR ($CDCl_3$): δ 0.82-0.91 (6H,m, 2xCH_3), 1.17-1.38 (16H, m, 8xCH_2), 1.53-1.71 (4H, m, 2x$NCH_2C\underline{H}_2$), 3.81-3.90 (4H, m, 2xNCH_2), 4.99 (1H, s, CH-5), 5.28 (2H, br s, NH_2). ^{13}C NMR ($CDCl_3$): δ 14.13 (CH_3), 14.16 (CH_3), 22.64 (CH_2), 22.70 (CH_2), 26.97 (CH_2), 27.08 (CH_2), 28.10 (CH_2), 28.26 (CH_2), 29.03 (CH_2), 29.17 (CH_2), 41.34 (NCH_2), 42.87 (NCH_2), 78.03 (CH-5), 151.61 (C_{quat}), 153.79 (C_{quat}), 163.38 (C_{quat}). IR (ATR): ν 3347 (NH), 2923 (CH), 1698 (C=O), 1511, 1411 cm^{-1}. MS (ES^+) *m/z* (%): 324 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{34}N_3O_2]^+$: 324.2651, found 324.2648.

5.11.2 Synthesis of amino-*iso*-propylcyclohexenones 395

A pressure vial was loaded with 4-*iso*-propylcyclohexane-1,3-dione **394**[223] (1.17 g, 7.59 mmol), ammonium acetate (585 mg, 7.59 mmol) and toluene (6 mL). The vial was sealed and the reaction was heated at 110°C for 1 hour. After cooling, the solvent was evaporated *in vacuo* to yield crude amino-*iso*-propylcyclohexenones **395**, which were recrystallised from EtOH as colourless prisms. Attempts to separate both regioisomers by means of column chromatography were unsuccessful.

Quantitative yield, colourless prisms, mp < 50°C. ^1H NMR ($CDCl_3$): δ 0.83 (3H, d, *J* = 6.9 Hz, CH_3), 0.96 (3H, d, *J* = 6.9 Hz, CH_3), 1.74-1.87 (1H, m, CH), 1.91-2.50 (2H, m, CH_2), 2.31-2.50 (3H, m, CH and CH_2), 4.92 (2H, br s, NH_2), 5.23 (1H, s, CH-2). ^{13}C NMR ($CDCl_3$): δ 18.53 (CH_3), 20.94 (CH_3), 21.80 (CH_2), 26.48 (CH_2), 27.87 (CH), 50.07 (CH), 100.02 (CH-2), 166.36 (C_{quat}-NH_2), 199.70 (C=O). IR (ATR): ν 3354 (NH), 3157 (NH), 2954 (CH), 1538, 1531, 1207, 1189 cm^{-1}. MS (ES^+) *m/z* (%): 154 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_9H_{16}NO]^+$: 154.1232, found 154.1232.

5.11.3 Synthesis of 1,4-dihydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehydes 388

A solution of 1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehyde **348a** or **348b** (20 mmol) in anhydrous CH_2Cl_2 (100 mL) under a nitrogen atmosphere was cooled to -60°C. Next, BBr_3 (120 mmol, 11.6 mL) was added dropwise and the reaction was allowed to room temperature. After 2.5 h, the reaction was cautiously quenched with water (80 mL) and extracted with CH_2Cl_2 (2x50 mL). The combined organic extracts were dried over $MgSO_4$, evaporated *in vacuo* and purified by means of column chromatography (petroleum ether/ethyl acetate 4/1) to yield the desired 1,4-dihydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehydes **388a** or **388b**.

1,4-dihydroxy-5,6,7,8-tetrahydro-5,8-methanonaphthalene-2-carboxaldehyde 388a

81%, yellow solid, mp 140°C. ^{1}H NMR ($CDCl_3$): δ 1.20-1.24 (2H, m, 2x$CH_x\underline{H_n}$), 1.55-1.58 (1H, m, $CH_s\underline{H_a}$), 1.73-1.79 (1H, m, $C\underline{H_s}H_a$), 1.93-1.98 (2H, d, *J* = 9.4 Hz, 2x$C\underline{H_x}H_n$), 3.56 (1H, d, *J* = 1.4 Hz, CH-1 or CH-4), 3.71 (1H, d, J = 1.4 Hz, CH-1 or CH-4), 4.60-4.62 (1H, m, OH), 6.79 (1H, s, CH-7), 9.73 (1H, s, OH), 10.60 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 25.92 and 26.01 (CH_2-2 and CH_2-3), 39.54 and 40.58 (CH-1 and CH-4), 49.13 (CH_2-9), 117.68 (CH-7), 119.56 (C_{quat}), 136.52 (C_{quat}), 142.69 (C_{quat}), 146.03 (C_{quat}), 149.45 (C_{quat}), 196.11 (C=O). IR (ATR): ν 3331 (OH), 2960 (CH), 1629, 1477 (CH_{Ar}), 1309, 1243 cm^{-1}. MS (ES^+) *m/z* (%): 205 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{12}H_{13}O_3]^+$: 205.0865, found 205.0861.

1,4-dihydroxy-5,6,7,8-tetrahydro-5,8-ethanonaphthalene-2-carboxaldehyde 388b

61%, green solid, mp 181°C. ^{1}H NMR ($CDCl_3$): δ 1.29-1.41 (4H, m, 2xCH_2), 1.75-1.87 (4H, m, 2xCH_2), 3.39 (1H, s, CH-1 or CH-4), 3.58 (1H, s, CH-1 or CH-4), 4.79 (1H, s, OH), 6.85 (1H, s, CH-7), 9.76 (1H, s, OH), 10.80 (1H, s, CHO). ^{13}C NMR ($CDCl_3$): δ 25.17 (2xCH_2), 25.39 (2xCH_2), 25.86 and 27.69 (CH-1 and CH-4), 115.28 (CH-7), 117.99 (C_{quat}), 133.25 (C_{quat}), 142.31 (C_{quat}), 143.41 (C_{quat}), 150.81 (C_{quat}), 196.20 (C=O). IR (ATR): ν 3309 (OH), 2980 (CH), 1626, 1328, 1188, 670 cm^{-1}. MS (ES^+) *m/z* (%): 219 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{15}O_3]^+$: 219.1021, found 219.1015.

5.11.4 Synthesis of 2,4-dialkyl-8,9,10,11-tetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraones 20

To a stirred solution of 1,4-dihydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehyde **388a** or **388b** (0.5 mmol), a 6-amino-1,3-dialkyluracil **389** (0.5 mmol) and $MgSO_4$ (2.5 mmol, 302 mg) in anhydrous dichloromethane (5 mL) was added freshly prepared Ag_2O (2 mmol, 464 mg). The reaction was allowed to stir at room temperature for 2 hours and subsequently filtered over a pad of Celite® and evaporated *in vacuo*. The residue was purified by means of preparative TLC (CH_2Cl_2) to yield pure 2,4-dialkyl-8,9,10,11-tetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraones **20**.

2,4-dimethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20b

54%, yellow needles, mp 227°C. ^{1}H NMR ($CDCl_3$): δ 1.25 (2H, d, *J* = 9.4 Hz, 2x$CH_x\underline{H_n}$), 1.48 (1H, dd, *J* = 1.1, 9.4 Hz, $CH_s\underline{H_a}$), 1.71 (1H, d, 9.4 Hz, $C\underline{H_s}H_a$), 2.02 (2H, d, *J* = 9.4 Hz, 2x$C\underline{H_x}H_n$), 3.48 (3H, s, NCH_3), 3.62 (1H, br s, CH-8 or CH-11), 3.68 (1H, br s, CH-8 or CH-11), 3.75 (3H, s, NCH_3), 9.22 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 25.61 and 25.89 (CH_2-9 and CH_2-10), 29.17 (NCH_3), 30.59 (NCH_3), 41.26 and 42.87 (CH-8 and CH-11), 45.98 (CH_2-13), 106.93 (C_{quat}), 123.93 (C_{quat}), 144.71 (C_{quat}), 150.87 (C_{quat}), 152.23 (CH-6), 152.63 (C_{quat}), 154.52 (C_{quat}), 157.33 (NC=O), 158.54 (NC=O), 179.21 (C=O), 181.44 (C=O). IR (ATR): ν 2978 (CH), 1720 (C=O), 1670 (C=O), 1658 (C=O), 1574

(CH_{Ar}), 1546, 1316, 1287 (C-N), 1273 (C-N), 742 cm^{-1}. MS (ES^+) *m/z* (%): 338 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{16}N_3O_4]^+$: 338.1141, found 338.1148.

2,4-diethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20c

86%, yellow needles, mp 97-98°C. ^1H NMR ($CDCl_3$): δ 1.18 (2H, d, *J* = 9.1 Hz, 2x$CH_x\underline{H_n}$), 1.23-1.28 (6H, m, 2xCH_3), 1.41 (1H, d, *J* = 9.1 Hz, $CH_s\underline{H_a}$), 1.64 (1H, d, *J* = 9.1 Hz, $C\underline{H_s}H_a$), 1.95 (2H, d, *J* = 9.1 Hz, 2x$C\underline{H_x}H_n$), 3.56 (1H, br s, CH-8 or CH-11), 3.62 (1H, br s, CH-8 or CH-11), 3.99-4.17 (2H, m, NCH_2), 4.30-4.50 (2H, m, NCH_2), 9.19 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 12.90 (CH_3), 13.20 (CH_3), 25.58 and 25.86 (CH_2-9 and CH_2-10), 37.85 (NCH_2), 38.88 (NCH_2), 41.20 and 42.81 (CH-8 and CH-11), 45.89 (CH_2-13), 107.21 (C_{quat}), 123.85 (C_{quat}), 144.92 (C_{quat}), 149.90 (C_{quat}), 152.31 (CH-6), 152.55 (C_{quat}), 154.04 (C_{quat}), 157.24 (NC=O), 158.25 (NC=O), 179.24 (C=O), 181.66 (C=O). IR (ATR): ν 2982 (CH), 1715 (C=O), 1663 (C=O), 1655 (C=O), 1574 (CH_{Ar}), 1545 (CH_{Ar}), 1316, 1289 (C-N), 1270 (C-N), 740 cm^{-1}. MS (ES^+) *m/z* (%): 366 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{20}H_{20}N_3O_4]^+$: 366.1454, found 366.1459.

2,4-Di-*n*-propyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20d

85%, yellow crystals, mp 125°C. ^1H NMR ($CDCl_3$): δ 0.90 (6H, t, *J* = 7.4 Hz, 2xCH_3), 1.16 (2H, d, *J* = 8.8 Hz, 2x$CH_x\underline{H_n}$), 1.39 (1H, d, *J* = 9.9 Hz, $CH_s\underline{H_a}$), 1.61-1.70 (5H, m, $C\underline{H_s}H_a$ and 2x$C\underline{H_2}CH_3$), 1.93 (2H, d, *J* = 8.8 Hz, 2x$C\underline{H_x}H_n$), 3.53 (1H, br s, CH-8 or CH-11), 3.60 (1H, br s, CH-8 or CH-11), 3.87-4.04 (2H, m, NCH_2), 4.17-4.35 (2H, m, NCH_2), 9.13 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 11.13 (CH_3), 11.29 (CH_3), 20.96 ($\underline{C}H_2CH_3$), 21.14 ($\underline{C}H_2CH_3$), 25.52 and 25.80 (CH_2-9 and CH_2-10), 41.16 and 42.73 (CH-8 and CH-11), 44.04 (NCH_2), 44.93 (NCH_2), 45.86 (CH_2-13), 107.01 (C_{quat}), 123.79 (C_{quat}), 144.83 (C_{quat}), 150.26 (C_{quat}), 152.16 (CH-6), 152.49 (C_{quat}), 154.17 (C_{quat}), 157.13 (NC=O), 158.36 (NC=O), 179.15 (C=O), 181.59 (C=O). IR (ATR): ν 2964 (CH), 2877 (CH), 1720 (C=O), 1660 (C=O), 1575 (CH_{Ar}), 1547 (CH_{Ar}), 1315, 1285 (C-N), 1273 (C-N), 752, 740 cm^{-1}. MS (ES^+) *m/z* (%): 394 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{24}N_3O_4]^+$: 394.1767, found 394.1779.

2,4-Di-*iso*-propyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20e

33%, yellow viscous oil. ^1H NMR ($CDCl_3$): δ 1.19 (2H, d, *J* = 9.6 Hz, 2x$CH_x\underline{H_n}$), 1.43 (1H, d, *J* = 9.1 Hz, $CH_s\underline{H_a}$), 1.51-1.56 (12H, m, 4xCH_3), 1.66 (1H, d, *J* = 9.1 Hz, $C\underline{H_s}H_a$), 1.97 (2H, d, *J* = 9.6 Hz, 2x$C\underline{H_x}H_n$), 3.59 (1H, br s, CH-8 or CH-11), 3.66 (1H, br s, CH-8 or CH-11), 5.14 (1H, septet, *J* = 6.8 Hz, NCH), 5.70 (1H, septet, *J* = 6.8 Hz, NCH), 9.16 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 18.81 (CH_3), 19.66 (CH_3), 19.82 (CH_3), 20.03 (CH_3), 25.54 and 25.83 (CH_2-9 and CH_2-10), 41.18 and 42.70 (CH-8

and CH-11), 45.93 (CH_2-13), 47.76 (NCH), 48.48 (NCH), 108.24 (C_{quat}), 123.53 (C_{quat}), 144.34 (C_{quat}), 149.89 (C_{quat}), 151.34 (CH-6), 152.68 (C_{quat}), 154.30 (C_{quat}), 157.00 (NC=O), 159.31 (NC=O), 179.38 (C=O), 181.74 (C=O). IR (ATR): ν 2971 (CH), 1721 (C=O), 1657, 1575 (CH_{Ar}), 1548 (CH_{Ar}), 1285 (C-N), 1273 (C-N), 756, 740 cm^{-1}. MS (ES^+) *m/z* (%): 394 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{24}N_3O_4]^+$: 394.1767, found 394.1774.

2,4-Di-*n*-butyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20f

57%, amber viscous oil. ^1H NMR ($CDCl_3$): δ 0.93 (6H, t, *J* = 7.2 Hz, 2xCH_3), 1.21 (2H, d, *J* = 8.8 Hz, 2x$CH_x\underline{H_n}$), 1.35-1.45 (5H, m, 2x$C\underline{H_2}CH_3$ and $CH_s\underline{H_a}$), 1.61-1.71 (5H, m, 2x$C\underline{H_2}CH_3$ and $CH_s\underline{H_a}$), 1.97 (2H, d, *J* = 8.8 Hz, 2x$C\underline{H_x}H_n$), 3.59 (1H, br s, CH-8 or CH-11), 3.66 (1H, br s, CH-8 or CH-11), 3.96-4.13 (2H, m, NCH_2), 4.26-4.44 (2H, m, NCH_2), 9.21 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 13.86 (2xCH_3), 20.12 ($\underline{C}H_2CH_3$), 20.32 ($\underline{C}H_2CH_3$), 25.64 and 25.92 (CH_2-9 and CH_2-10), 29.78 (CH_2), 30.04 (CH_2), 41.26 (CH-8 or CH-11), 42.56 (NCH_2), 42.85 (CH-8 or CH-11), 43.46 (NCH_2), 45.97 (CH_2-13), 107.15 (C_{quat}), 123.91 (C_{quat}), 145.00 (C_{quat}), 150.37 (C_{quat}), 152.35 (CH-6), 152.64 (C_{quat}), 154.28 (C_{quat}), 157.30 (NC=O), 158.51 (NC=O), 179.35 (C=O), 181.82 (C=O). IR (ATR): ν 2959 (CH), 2874 (CH), 1720 (C=O), 1668 (C=O), 1657 (C=O), 1575 (CH_{Ar}), 1547 (CH_{Ar}), 1285 (C-N), 1273 (C-N), 755, 740 cm^{-1}. MS (ES^+) *m/z* (%): 422 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{24}H_{28}N_3O_4]^+$: 422.2080, found 422.2085.

2,4-Di-*iso*-butyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20g

67%, yellow viscous oil, mp 135°C. ^1H NMR ($CDCl_3$): δ 0.88-0.95 (12H, m, 4xCH_3), 1.19 (2H, d, *J* = 9.6 Hz, 2x$CH_x\underline{H_n}$), 1.42 (1H, d, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.65 (1H, d, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.96 (2H, d, *J* = 9.6 Hz, 2x$C\underline{H_x}H_n$), 2.10-2.25 (2H, m, 2x$C\underline{H}(CH_3)_2$), 3.57 (1H, br s, CH-8 or CH-11), 3.64 (1H, br s, CH-8 or CH-11), 3.83-3.99 (2H, m, NCH_2), 4.15-4.27 (2H, m, NCH_2), 9.18 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 19.98 (2xCH_3), 20.13 (CH_3), 20.24 (CH_3), 25.63 and 25.89 (CH_2-9 and CH_2-10), 27.28 ($\underline{C}H(CH_3)_2$), 27.34 ($\underline{C}H(CH_3)_2$), 41.25 and 42.82 (CH-8 and CH-11), 45.97 (CH_2-13), 49.28 (NCH_2), 50.00 (NCH_2), 107.01 (C_{quat}), 123.93 (C_{quat}), 144.96 (C_{quat}), 151.01 (C_{quat}), 152.17 (CH-6), 152.64 (C_{quat}), 154.58 (C_{quat}), 157.24 (NC=O), 158.78 (NC=O), 179.32 (C=O), 181.79 (C=O). IR (ATR): ν 2959 (CH), 2874 (CH), 1721 (C=O), 1657 (C=O), 1575 (CH_{Ar}), 1548 (CH_{Ar}), 1286 (C-N), 1272 (C-N), 753, 740 cm^{-1}. MS (ES^+) *m/z* (%): 422 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{24}H_{28}N_3O_4]^+$: 422.2080, found 422.2083.

2,4-Di-*n*-pentyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20h

71%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.81-0.89 (6H, m, 2xCH_3), 1.18 (2H, d, *J* = 9.4 Hz, 2x$CH_x\underline{H_n}$), 1.27-1.36 (8H, m, 4xCH_2), 1.41 (1H, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.63-1.69 (5H, m, 2xCH_2 and $CH_s\underline{H_a}$), 1.95 (2H, d, *J* = 9.4 Hz, 2x$C\underline{H_x}H_n$), 3.56 (1H, br s, CH-8 or CH-11), 3.62 (1H, br s, CH-8 or CH-11), 3.92-4.09 (2H, m, NCH_2), 4.22-4.40 (2H, m, NCH_2), 9.17 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.00 (2xCH_3), 22.36 (4xCH_2), 25.58 and 25.84 (CH_2-9 and CH_2-10), 28.87 (CH_2), 29.06 (CH_2), 41.20 (CH-8 or CH-11), 42.68 (NCH_2), 42.79 (CH-8 or CH-11), 43.54 (NCH_2), 45.91 (CH_2-13), 107.08 (C_{quat}), 123.82 (C_{quat}), 144.90 (C_{quat}), 150.26 (C_{quat}), 152.25 (CH-6), 152.54 (C_{quat}), 154.20 (C_{quat}), 157.21 (NC=O), 158.40 (NC=O), 179.24 (C=O), 181.70 (C=O). IR (ATR): ν 2956 (CH), 2631 (CH), 1721 (C=O), 1668 (C=O), 1578 (CH_{Ar}), 1547 (CH_{Ar}), 1285 (C-N), 1272 (C-N), 754, 740 cm^{-1}. MS (ES^+) *m/z* (%): 450 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{26}H_{32}N_3O_4]^+$: 450.2393, found 450.2398.

2,4-Di-*iso*-pentyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20i

93%, yellow crystals, mp 146-147°C. ^{1}H NMR ($CDCl_3$): δ 0.91-0.94 (12H, m, 4xCH_3), 1.17 (2H, d, *J* = 9.6 Hz, 2x$CH_x\underline{H_n}$), 1.40 (1H, d, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.46-1.57 (4H, m, 2xCH_2), 1.58-1.67 (3H, 2x$C\underline{H}(CH_3)_2$ and $C\underline{H_s}H_a$), 1.94 (2H, d, *J* = 9.6 Hz, 2x$C\underline{H_x}H_n$), 3.54 (1H, br s, CH-8 or CH-11), 3.62 (1H, br s, CH-8 or CH-11), 3.94-34.09 (2H, m, NCH_2), 4.23-4.41 (2H, m, NCH_2), 9.16 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 22.41 (CH_3), 22.50 (3xCH_3), 25.54 and 25.81 (CH_2-9 and CH_2-10), 26.24 ($\underline{C}H(CH_3)_2$), 26.38 ($\underline{C}H(CH_3)_2$), 36.21 (CH_2), 36.52 (CH_2), 41.16 (CH-8 or CH-11), 41.31 (NCH_2), 42.23 (CH-8 or CH-11), 42.76 (NCH_2), 45.85 (CH_2-13), 107.06 (C_{quat}), 123.76 (C_{quat}), 144.81 (C_{quat}), 150.11 (C_{quat}), 152.22 (CH-6), 152.51 (C_{quat}), 154.10 (C_{quat}), 157.15 (NC=O), 158.28 (NC=O), 179.17 (C=O), 181.64 (C=O). IR (ATR): ν 2956 (CH), 2931 (CH), 2872 (CH), 1717 (C=O), 1656 (C=O), 1670 (C=O), 1576 (CH_{Ar}), 1548 (CH_{Ar}), 1317 (C-N), 1286 (C-N) cm^{-1}. MS (ES^+) *m/z* (%): 450 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{26}H_{32}N_3O_4]^+$: 450.2393, found 450.2397.

2,4-Di-*n*-hexyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20j

93%, amber viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.82-0.91 (6H, m, 2xCH_3), 1.21 (2H, d, *J* = 9.6 Hz, 2x$CH_x\underline{H_n}$), 1.26-1.39 (12H, m, 6xCH_2), 1.43 (1H, d, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.61-1.72 (5H, m, 2xCH_2 and $CH_s\underline{H_a}$), 1.97 (2H, d, *J* = 9.6 Hz, 2x$C\underline{H_x}H_n$), 3.59 (1H, br s, CH-8 or CH-11), 3.65 (1H, br s, CH-8 or CH-11), 3.95-4.11 (2H, m, NCH_2), 4.25-4.43 (2H, m, NCH_2), 9.21 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.12 (2xCH_3), 22.64 (2xCH_2), 25.66 and 25.94 (CH_2-9 and CH_2-10), 26.52 (CH_2), 29.71 (CH_2), 27.68 (CH_2), 27.91 (CH_2), 31.54 (2xCH_2), 41.28 (CH-8 or CH-11), 42.84 (NCH_2), 42.87 (CH-8 or CH-11), 43.68 (NCH_2), 46.00 (CH_2-13), 107.18 (C_{quat}), 123.91 (C_{quat}), 145.01 (C_{quat}), 150.36 (C_{quat}), 152.37 (CH-6), 152.65 (C_{quat}), 154.29 (C_{quat}), 157.32 (NC=O), 158.51 (NC=O), 179.38 (C=O), 181.82

(C=O). IR (ATR): ν 2956 (CH), 2928 (CH), 1721 (C=O), 1669 (C=O), 1657 (C=O), 1576 (CH_{Ar}), 1285 (C-N), 1273 (C-N) cm^{-1}. MS (ES^+) *m/z* (%): 478 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{28}H_{36}N_3O_4]^+$: 478.2706, found 478.2714.

2,4-Di-*n*-heptyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20k

88%, yellow oil. ^1H NMR ($CDCl_3$): δ 0.76-0.85 (6H, m, 2xCH_3), 1.11-1.35 (22H, m, 2x$CH_x\underline{H_n}$, 10xCH_2), 1.38 (1H, d, *J* = 9.4 Hz, $CH_s\underline{H_a}$), 1.55-1.69 (5H, m, 2xCH_2 and $CH_s\underline{H_a}$), 1.94 (2H, d, *J* = 8.0 Hz, 2x$C\underline{H_x}H_n$), 3.54 (1H, br s, CH-8 or CH-11), 3.61 (1H, br s, CH-8 or CH-11), 3.91-4.07 (2H, m, NCH_2), 4.21-4.38 (2H, m, NCH_2), 9.15 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.06 (2xCH_3), 22.56 (2xCH_2), 25.55 and 25.81 (CH_2-9 and CH_2-10), 26.71 (CH_2), 26.91 (CH_2), 27.62 (CH_2), 27.84 (CH_2), 28.93 (2xCH_2), 31.71 (2xCH_2), 41.17 (CH-8 or CH-11), 42.70 (NCH_2), 42.76 (CH-8 or CH-11), 43.54 (NCH_2), 45.86 (CH_2-13), 107.05 (C_{quat}), 123.77 (C_{quat}), 144.86 (C_{quat}), 150.22 (C_{quat}), 152.19 (CH-6), 152.49 (C_{quat}), 154.17 (C_{quat}), 157.16 (NC=O), 158.32 (NC=O), 179.17 (C=O), 181.62 (C=O). IR (ATR): ν 2955 (CH), 2926 (CH), 2856 (CH), 1721 (C=O), 1670 (C=O), 1658 (C=O), 1576 (CH_{Ar}), 1285 (C-N), 1273 (C-N) cm^{-1}. MS (ES^+) *m/z* (%): 506 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{30}H_{40}N_3O_4]^+$: 506.3019, found 506.3015.

2,4-Dimethyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20m

48%, yellow needles, mp 266°C. ^1H NMR ($CDCl_3$): δ 1.34-1.47 (4H, m, 2xCH_2), 1.75-1.87 (4H, m, 2xCH_2), 3.50 (5H, s, NCH_3 and CH-8 and CH-11), 3.77 (3H, s, NCH_3), 9.33 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 25.28 (2xCH_2), 25.35 (2xCH_2), 26.75 and 28.44 (CH-8 and CH-11), 29.15 (NCH_3), 30.54 (NCH_3), 106.63 (C_{quat}), 123.26 (C_{quat}), 144.07 (C_{quat}), 148.94 (C_{quat}), 150.88 (C_{quat}), 152.77 (CH-6), 153.95 (C_{quat}), 154.28 (NC=O), 158.59 (NC=O), 178.91 (C=O), 180.85 (C=O). IR (ATR): ν 2952 (CH), 1717 (C=O), 1688 (C=O), 1668 (C=O), 1652 (C=O), 1573 (CH_{Ar}), 1486, 1292 (C-N), 1274 (C-N), 838 cm^{-1}. MS (ES^+) *m/z* (%): 352 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{18}N_3O_4]^+$: 352.1297, found 352.1303.

2,4-Diethyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20n

89%, yellow needles, mp 192°C. ^1H NMR ($CDCl_3$): δ 1.28-1.33 (6H, m, 2xCH_3), 1.34-1.41 (4H, m, 2xCH_2), 1.75-1.83 (4H, m, 2xCH_2), 3.47 (1H, s, CH-8 or CH-11), 3.49 (1H, s, CH-8 or CH-11), 4.13 (2H, q, *J* = 7.0 Hz, NCH_2), 4.45 (2H, q, *J* = 7.0 Hz, NCH_2), 9.30 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 12.89 (CH_3), 13.21 (CH_3), 25.28 (2xCH_2), 25.34 (2xCH_2), 26.72 and 28.43 (CH-8 and CH-11), 37.84 (NCH_2), 38.84 (NCH_2), 106.89 (C_{quat}), 123.17 (C_{quat}), 144.27 (C_{quat}), 148.82 (C_{quat}), 149.89 (C_{quat}),

152.76 (CH-6), 153.84 (C_{quat}), 153.93 (NC=O), 158.27 (NC=O), 178.91 (C=O), 180.02 (C=O). IR (ATR): ν 2956 (CH), 2938 (CH), 1719 (C=O), 1682 (C=O), 1667 (C=O), 1574 (CH_{Ar}), 1552, 1291 (C-N), 753 cm^{-1}. MS (ES^+) *m/z* (%): 380 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{22}N_3O_4]^+$: 380.1610, found 380.1614.

2,4-Di-*n*-propyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20o

83%, yellow crystals, mp 153°C. ^1H NMR ($CDCl_3$): δ 0.98 (6H, t, *J* = 7.2 Hz, 2xCH_3), 1.31-1.45 (4H, m, 2xCH_2), 1.64-1.81 (8H, m, 2xCH_2, 2xC$\underline{H}_2CH_3$), 3.47 (1H, s, CH-8 or CH-11), 3.50 (1H, s, CH-8 or CH-11), 4.03 (2H, t, *J* = 7.7 Hz, NCH_2), 4.34 (2H, t, *J* = 7.7 Hz, NCH_2), 9.30 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 11.18 (CH_3), 11.34 (CH_3), 20.99 ($\underline{C}H_2CH_3$), 21.21 ($\underline{C}H_2CH_3$), 25.28 (2xCH_2), 25.33 (2xCH_2), 26.72 and 28.41 (CH-8 and CH-11), 44.12 (NCH_2), 44.95 (NCH_2), 106.77 (C_{quat}), 123.17 (C_{quat}), 144.24 (C_{quat}), 148.85 (C_{quat}), 150.33 (C_{quat}), 152.71 (CH-6), 153.81 (C_{quat}), 154.12 (NC=O), 158.47 (NC=O), 178.91 (C=O), 180.06 (C=O). IR (ATR): ν 2960 (CH), 2871 (CH), 1720 (C=O), 1668 (C=O), 1656 (C=O), 1578 (CH_{Ar}), 1288 (C-N), 751, 741 cm^{-1}. MS (ES^+) *m/z* (%): 408 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{23}H_{26}N_3O_4]^+$: 408.1923, found 408.1928.

2,4-Di-*iso*-propyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20p

48%, yellow crystals, mp 89°C. ^1H NMR ($CDCl_3$): δ 1.31-1.43 (4H, m, 2xCH_2), 1.55 (6H, d, *J* = 6.8 Hz, 2xCH_3), 1.57 (6H, d, *J* = 6.8 Hz, 2xCH_3), 1.74-1.85 (4H, m, 2xCH_2), 3.48 (1H, s, CH-8 or CH-11), 3.50 (1H, s, CH-8 or CH-11), 5.16 (1H, septet, *J* = 6.8 Hz, NCH), 5.72 (1H, septet, *J* = 6.8 Hz, NCH), 9.25 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 19.42 (2xCH_3), 19.76 (2xCH_3), 25.28 (2xCH_2), 25.33 (2xCH_2), 26.72 and 28.32 (CH-8 and CH-11), 47.73 (NCH), 48.43 (NCH), 107.91 (C_{quat}), 122.85 (C_{quat}), 143.61 (C_{quat}), 148.97 (C_{quat}), 149.89 (C_{quat}), 151.78 (CH-6), 153.62 (C_{quat}), 154.18 (NC=O), 159.35 (NC=O), 179.06 (C=O), 181.05 (C=O). IR (ATR): ν 2947 (CH), 1722 (C=O), 1667 (C=O), 1659 (C=O), 1578 (CH_{Ar}), 1287 (C-N), 753, 740 cm^{-1}. MS (ES^+) *m/z* (%): 408 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{23}H_{26}N_3O_4]^+$: 408.1923, found 408.1927.

2,4-Di-*n*-butyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20q

90%, yellow viscous oil. ^1H NMR ($CDCl_3$): δ 0.93 (3H, t, *J* = 7.2 Hz, CH_3), 0.94 (3H, t, *J* = 7.2 Hz, CH_3), 1.30-1.45 (8H, m, 2xCH_2, 2xCH_2CH_3), 1.66 (4H, pentet, *J* = 7.4 Hz, 2x$NCH_2C\underline{H}_2$), 1.74-1.82 (4H, m, 2xCH_2), 3.44 (1H, s, CH-8 or CH-11), 3.48 (1H, s, CH-8 or CH-11), 4.04 (2H, t, *J* = 7.4 Hz, NCH_2), 4.35 (2H, t, *J* = 7.4 Hz, NCH_2), 9.28 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 13.86 (2xCH_3), 20.12 ($\underline{C}H_2CH_3$), 21.32 ($\underline{C}H_2CH_3$), 25.35 (2xCH_2), 25.42 (2xCH_2), 26.80 and 28.50 (CH-8 and CH-

11), 29.78 ($NCH_2C\underline{H}_2$), 30.04 ($NCH_2C\underline{H}_2$), 42.59 (NCH_2), 43.43 (NCH_2), 106.87 (C_{quat}), 123.23 (C_{quat}), 144.34 (C_{quat}), 148.92 (C_{quat}), 150.37 (C_{quat}), 152.83 (CH-6), 153.93 (C_{quat}), 154.19 (NC=O), 158.52 (NC=O), 179.03 (C=O), 181.17 (C=O). IR (ATR): ν 2958 (CH), 2870 (CH), 1720 (C=O), 1668 (C=O), 1657 (C=O), 1578 (CH_{Ar}), 1289 (C-N), 753, 734 cm^{-1}. MS (ES^+) *m/z* (%): 436 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{25}H_{30}N_3O_4]^+$: 436.2236, found 436.2243.

2,4-Di-*iso*-butyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20r

89%, yellow crystals, mp 71°C. ^1H NMR ($CDCl_3$): δ 0.91 (6H, d, *J* = 7.2 Hz, 2xCH_3), 0.94 (6H, d, *J* = 7.2 Hz, 2xCH_3), 1.29-1.41 (4H, m, 2xCH_2), 1.76-1.78 (4H, m, 2xCH_2), 2.19 (2H, nonuplet, *J* = 7.1 Hz, 2x$C\underline{H}(CH_3)_2$), 3.45 (1H, s, CH-8 or CH-11), 3.49 (1H, s, CH-8 or CH-11), 3.92 (2H, t, *J* = 7.2 Hz, NCH_2), 4.23 (2H, t, *J* = 7.2 Hz, NCH_2), 9.26 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 20.00 (2xCH_3), 20.19 (2xCH_3), 25.35 (2xCH_2), 25.40 (2xCH_2), 26.79 (CH-8 or CH-11), 27.28 ($\underline{C}H(CH_3)_2$), 27.37 ($\underline{C}H(CH_3)_2$), 28.45 (CH-8 or CH-11), 49.31 (NCH_2), 49.94 (NCH_2), 106.75 (C_{quat}), 123.27 (C_{quat}), 144.31 (C_{quat}), 148.95 (C_{quat}), 151.04 (C_{quat}), 152.66 (CH-6), 153.85 (C_{quat}), 154.49 (NC=O), 158.83 (NC=O), 179.01 (C=O), 181.15 (C=O). IR (ATR): ν 2958 (CH), 2871 (CH), 1721 (C=O), 1676 (C=O), 1657 (C=O), 1579 (CH_{Ar}), 1290 (C-N), 752, 734 cm^{-1}. MS (ES^+) *m/z* (%): 436 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{25}H_{30}N_3O_4]^+$: 436.2236, found 436.2240.

2,4-Di-*n*-pentyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20s

64%, amber viscous oil. ^1H NMR ($CDCl_3$): δ 0.84-0.92 (6H, m, 2xCH_3), 1.30-1.45 (12H, m, 6xCH_2), 1.62-1.73 (4H, m, 2x$NCH_2C\underline{H}_2$), 1.77-1.80 (4H, m, 2xCH_2), 3.46 (1H, s, CH-8 or CH-11), 3.49 (1H, s, CH-8 or CH-11), 4.04 (2H, t, *J* = 7.7 Hz, NCH_2), 4.35 (2H, t, *J* = 7.7 Hz, NCH_2), 9.28 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.07 (2xCH_3), 22.44 (2x$\underline{C}H_2CH_3$), 25.37 (2xCH_2), 25.44 (2xCH_2), 26.80 (CH-8 or CH-11), 27.38 (CH_2), 27.64 (CH_2), 28.50 (CH-8 or CH-11), 28.94 ($NCH_2C\underline{H}_2$), 29.16 ($NCH_2C\underline{H}_2$), 42.81 (NCH_2), 43.60 (NCH_2), 106.89 (C_{quat}), 123.24 (C_{quat}), 144.35 (C_{quat}), 148.93 (C_{quat}), 150.37 (C_{quat}), 152.84 (CH-6), 153.93 (C_{quat}), 154.19 (NC=O), 158.54 (NC=O), 179.04 (C=O), 181.18 (C=O). IR (ATR): ν 2956 (CH), 2870 (CH), 1721 (C=O), 1669 (C=O), 1657 (C=O), 1578 (CH_{Ar}), 1289 (C-N), 754 cm^{-1}. MS (ES^+) *m/z* (%): 464 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{27}H_{34}N_3O_4]^+$: 464.2549, found 464.2552.

2,4-Di-*iso*-pentyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20t

90%, yellow crystals, mp 132-133°C. ^1H NMR ($CDCl_3$): δ 0.94 (6H, d, *J* = 5.5 Hz, 2xCH_3), 0.96 (6H, d, *J* = 5.5 Hz, 2xCH_3), 1.29-1.42 (4H, m, 2xCH_2), 1.51-1.58 (4H, m, 2x$NCH_2C\underline{H}_2$), 1.61-1.70 (2H, m,

2xC<u>H</u>$(CH_3)_2$), 1.76-1.78 (4H, m, 2xCH_2), 3.44 (1H, s, CH-8 or CH-11), 3.47 (1H, s, CH-8 or CH-11), 4.04 (2H, t, *J* = 7.7 Hz, NCH_2), 4.36 (2H, t, *J* = 7.7 Hz, NCH_2), 9.27 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 22.53 (4xCH_3), 25.34 (2xCH_3), 25.39 (2xCH_2), 26.33 (<u>C</u>H$(CH_3)_2$), 26.50 (<u>C</u>H$(CH_3)_2$), 26.78 and 28.47 (CH-8 and CH-11), 36.27 (CH_2), 36.61 (CH_2) 41.46 (NCH_2), 42.30 (NCH_2), 106.87 (C_{quat}), 123.19 (C_{quat}), 144.25 (C_{quat}), 148.89 (C_{quat}), 150.22 (C_{quat}), 152.81 (CH-6), 153.88 (C_{quat}), 154.10 (NC=O), 158.42 (NC=O), 178.98 (C=O), 181.11 (C=O). IR (ATR): ν 2956 (CH), 2870 (CH), 1720 (C=O), 1668 (C=O), 1579 (CH_{Ar}), 1290 (C-N), 753 cm^{-1}. MS (ES^+) *m/z* (%): 464 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{27}H_{34}N_3O_4]^+$: 464.2549, found 464.2551.

2,4-Di-*n*-hexyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20u

90%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.79-0.88 (6H, m, 2xCH_3), 1.19-1.42 (16H, m, 8xCH_2), 1.60-1.71 (4H, m, 2x$NCH_2C\underline{H}_2$), 1.75-1.82 (4H, m, 2xCH_2), 3.43 (1H, s, CH-8 or CH-11), 3.46 (1H, s, CH-8 or CH-11), 4.01 (2H, t, *J* = 7.7 Hz, NCH_2), 4.33 (2H, t, *J* = 7.7 Hz, NCH_2), 9.25 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.04 (2xCH_3), 22.56 (2x<u>C</u>H_2CH_3), 25.29 (2xCH_2), 25.36 (2xCH_2), 26.44 (CH_2), 26.64 (CH_2), 26.73 (CH-8 or CH-11), 27.60 (CH_2), 27.84 (CH_2), 28.42 (CH-8 or CH-11), 31.46 (2xCH_2), 42.76 (NCH_2), 43.56 (NCH_2), 106.81 (C_{quat}), 123.16 (C_{quat}), 144.25 (C_{quat}), 148.83 (C_{quat}), 150.28 (C_{quat}), 152.72 (CH-6), 153.84 (C_{quat}), 154.11 (NC=O), 158.42 (NC=O), 178.92 (C=O), 181.06 (C=O). IR (ATR): ν 2955 (CH), 2928 (CH), 2868 (CH), 1721 (C=O), 1670 (C=O), 1657 (C=O), 1578 (CH_{Ar}), 1289 (C-N), 754 cm^{-1}. MS (ES^+) *m/z* (%): 492 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{29}H_{38}N_3O_4]^+$: 492.2862, found 492.2869.

2,4-Di-*n*-heptyl-8,9,10,11-tetrahydro-8,11-ethanobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraone 20v

78%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 0.78-0.88 (6H, m, 2xCH_3), 1.20-1.27 (10H, m, 5xCH_2), 1.28-1.41 (10H, m, 5xCH_2), 1.60-1.70 (4H, m, 2x$NCH_2C\underline{H}_2$), 1.73-1.81 (4H, m, 2xCH_2), 3.43 (1H, s, CH-8 or CH-11), 3.47 (1H, s, CH-8 or CH-11), 4.01 (2H, t, *J* = 7.7 Hz, NCH_2), 4.33 (2H, t, *J* = 7.7 Hz, NCH_2), 9.25 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 14.10 (2xCH_3), 22.61 (2x<u>C</u>H_2CH_3), 25.32 (2xCH_2), 25.37 (2xCH_2), 26.76 (2xCH_2), 26.97 (CH-8 or CH-11), 27.69 (CH_2), 27.92 (CH_2), 28.45 (CH-8 or CH-11), 28.99 (2xCH_2), 31.77 (2xCH_2), 42.81 (NCH_2), 43.57 (NCH_2), 106.83 (C_{quat}), 123.18 (C_{quat}), 144.28 (C_{quat}), 148.84 (C_{quat}), 150.29 (C_{quat}), 152.75 (CH-6), 153.85 (C_{quat}), 154.14 (NC=O), 158.45 (NC=O), 178.95 (C=O), 181.09 (C=O). IR (ATR): ν 2955 (CH), 2926 (CH), 2857 (CH), 1721 (C=O), 1670 (C=O), 1579 (CH_{Ar}), 1289 (C-N), 754 cm^{-1}. MS (ES^+) *m/z* (%): 520 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{31}H_{42}N_3O_4]^+$: 520.3175, found 520.3180.

5.11.5 Synthesis of 3,4,8,9,10,11-hexahydro-2*H*-8,11-methano-benzo[*j*]phenanthridine-1,7,12-triones 397

To a stirred solution of 1,4-dihydroxy-5,6,7,8-tetrahydro-5,8-methanonaphthalene-2-carboxaldehyde **388a** (204 mg, 1 mmol), amino-*iso*-propylcyclohexenones **395** (153 mg, 1 mmol) and $MgSO_4$ (5 mmol, 604 mg) in anhydrous dichloromethane (10 mL) was added freshly prepared Ag_2O (4 mmol, 927 mg). The reaction was allowed to stir at room temperature for 4 hours and subsequently filtered over a pad of Celite® and evaporated *in vacuo*. The residue was purified by means of column chromatography (petroleum ether/ethyl acetate) followed by preparative HPLC (CH_3CN/H_2O) to yield 3,4,8,9,10,11-hexahydro-2*H*-8,11-methanobenzo[*j*]phenanthridine-1,7,12-triones **397a** and **397b**.

Regioisomer 397a

40%, yellow solid, mp 63°C. ^{1}H NMR ($CDCl_3$): δ 1.10 (3H, d, *J* = 6.6 Hz, CH_3), 1.18 (3H, d, *J* = 6.6 Hz, CH_3), 1.22 (1H, m, CH), 1.50 (1H, d, *J* = 9.4 Hz, CH), 1.70 (1H, d, *J* = 9.4 Hz, CH), 1.93-2.13 (3H, m, CH and CH_2), 2.20-2.32 (2H, m, CH_2), 2.50-2.57 (1H, m, CH), 3.01 (1H, ddd, *J* = 17.6, 9.1, 5.0 Hz, CH), 3.23 (1H, ddd, *J* = 17.6, 6.6, 5.0 Hz, CH), 3.64 (2H, br s, CH-8 and CH-11), 9.22 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 19.35 (CH_3), 20.99 (CH_3), 23.58 (CH_2), 25.37 (CH_2), 25.68 (CH_2), 29.17 (CH_2), 31.37 (CH), 41.14 and 42.18 (CH-8 and CH-11), 46.32 (CH_2-13), 55.63 (CH), 126.51 (C_{quat}), 128.91 (C_{quat}), 140.16 (C_{quat}), 149.81 (CH-6), 152.98 (C_{quat}), 156.14 (C_{quat}), 168.37 (C_{quat}), 180.56 (C=O), 181.69 (C=O), 201.66 (C=O). IR (ATR): ν 2958, 2874, 1697, 1657, 1567, 1318, 1273, 739 cm^{-1}. MS (ES^+) *m/z* (%): 336 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{22}NO_3]^+$: 336.1600, found 336.1596.

Regioisomer 397b

13%, yellow solid, mp 95°C. ^{1}H NMR ($CDCl_3$): δ 1.03 (3H, d, *J* = 6.6 Hz, CH_3), 1.15 (3H, d, *J* = 6.6 Hz, CH_3), 1.22-1.26 (1H, m, CH), 1.45-1.49 (1H, m, CH), 1.69-1.73 (1H, m, CH), 1.68-2.01 (3H, m, CH and CH_2), 2.00-2.31 (1H, m, CH), 2.34-2.44 (1H, m, CH), 2.66-2.44 (1H, m, CH), 3.15 (1H, ddd, *J* = 18.3, 10.6, 6.1 Hz, CH), 3.28 (1H, ddd, *J* = 17.6, 3.5, 5.0 Hz, CH), 3.63 (2H, br s, CH-8 and CH-11), 9.22 (1H, s, CH-6). ^{13}C NMR ($CDCl_3$): δ 19.13 (CH_3), 21.28 (CH_3), 25.03 (CH_2), 25.29 (CH_2), 25.49 (CH_2), 27.60 (CH_2), 32.52 (CH), 41.10 and 41.92 (CH-8 and CH-11), 47.30 (CH_2-13), 55.34 (CH), 126.02 (C_{quat}), 127.25 (C_{quat}), 139.44 (C_{quat}), 149.87 (CH-6), 153.26 (C_{quat}), 155.94 (C_{quat}), 167.96 (C_{quat}), 180.66 (C=O), 181.30 (C=O), 201.69 (C=O). IR (ATR): ν 2961, 2874, 1703, 1657, 1569, 1323, 1291 cm^{-1}. MS (ES^+) *m/z* (%): 336 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{22}NO_3]^+$: 336.1600, found 336.1596.

5.12 Synthesis of analogues of the bioactive natural products sampangine 24 and cleistopholine 23

5.12.1 Synthesis of 7*H*-naphtho[3,2,1-*i,j*]-2,6-naphthiridin-6-one 403

(*E*)-4-[2-(Dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-dione **402** (133 mg, 0.48 mmol) was mixed with 10 ml of a 5 m/v% solution of ammonium acetate in anhydrous methanol under a nitrogen atmosphere and boiled under reflux for three hours. Then the solvent was evaporated *in vacuo.* The residue was dissolved in dichloromethane (15 ml) and washed with a saturated sodium bicarbonate solution (25 ml) and brine (25 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography (petroleum ether/ ethyl acetate) to afford 7*H*-naphtho[3,2,1-*i,j*]-2,6-naphthiridin-6-one **403** (80 mg, 91%).

91%, yellow solid, mp 201.4°C. ^{1}H NMR ($CDCl_3$): δ 7.68 (1H, td, *J* = 7.7 and 1.1 Hz, H-8), 7.82 (2H, s and td, *J* = 7.7 and 1.1 Hz, H-5 and H-9), 8,25 (2H, m, H-6 and H-9), 8.39 (1H, dd, *J* = 7.7 and 1.1 Hz, H-7), 8.78 (1H, dd, *J* = 7.7 and 1.1 Hz, H-10), 8.91 (1H, d, *J* = 6.1 Hz, H-2), 9.56 (2H, br. d, J = 6.1 Hz H-1 and H-3). ^{13}C NMR ($CDCl_3$): 119.02 (CH_{Ar}), 121.22 (C_{quat}), 124.58 (CH_{Ar}), 125.24 (CH_{Ar}), 127.70 (CH_{Ar}), 129.06 (C_{quat}), 131.24 (CH_{Ar}), 132.35 (C_{quat}), 134.55 (CH_{Ar}), 135.86 (C_{quat}), 145.90 (CH_{Ar}), 146.43 (CH_{Ar}), 149.27 (C_{quat}), 157.09 (CH_{Ar}), 183.29 (C=O). IR (ATR): ν_{max}1666, 1655, 1591, 1289 cm^{-1}. MS (ES^+) m/z (%): 233 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{15}H_9N_2O]^+$: 233.0715, found 233.0711.

5.12.2 Synthesis of 3-substituted-1-methylbenzo[*g*]isoquinoline-5,10-diones 25

2-Acetyl-1,4-naphthoquinone **345** (0.35 g, 1.75 mmol) and pyridinium salts **151**[261] (1.83 mmol) were added to a previously prepared 5 m/v% solution of ammonium acetate in anhydrous methanol (6 ml). The sealed reaction vessel was heated for 6 min. at 90°C in a CEM Discover® microwave apparatus (ramp time 5 min, p_{max} 10.0 psi). Subsequently, the reaction mixture was cooled in ice water and filtered. The solid was washed with 20 ml of cold methanol and redissolved in chloroform. This solution was filtered over Celite® and evaporated *in vacuo* to yield 3-aryl-1-methylbenz[*g*]isoquinoline-5,10-diones **25**. 3-Alkyl-1-methylbenz[*g*]isoquinoline-5,10-diones **25f** and **25g** did not precipitate upon cooling and were extracted with ethyl acetate (10 ml) and brine (2x10 ml) and subsequently purified by means of column chromatography.

3-(2,5-Dimethoxyphenyl)-1-methylbenzo[*g*]isoquinoline-5,10-dione 25d

52%, orange solid, mp 213.1°C. ^{1}H NMR ($CDCl_3$): δ 3.17 (3H, s, CH_3), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.98 (1H, dd, *J* = 1.1, 8.3 Hz, CH-3'), 7.02 (1H, dd, *J* = 1.1, 8.3 Hz, CH-4'), 7.61 (1H, dd, *J* = 2.2, 1.1 Hz, CH-6'), 7.80 (1H, dt, *J* = 1.7, 7.5 Hz, CH-7 or CH-8), 7.86 (1H, dt, *J* = 1.7, 7.5 Hz, CH-7 or CH-8), 8.29 (1H, dd, *J* = 1.7, 7.5 Hz, CH-6 or CH-9), 8.32 (1H, dd, *J* = 1.7, 7.5 Hz, CH-6 or CH-

9), 8.67 (1H, s, CH-4). ^{13}C NMR ($CDCl_3$): δ 26.82 (CH_3), 55.97 (OCH_3), 56.36 (OCH_3), 113.05 (CH-4), 116.00 (CH_{Ar}), 117.25 (CH_{Ar}), 119.59 (CH_{Ar}) 122.78 (C_{quat}), 126.90 (CH_{Ar}), 127.45 (CH_{Ar}), 128.02 (C_{quat}), 132.72 (C_{quat}), 133.85 (CH_{Ar}), 134.58 (C_{quat}), 134.96 (CH_{Ar}), 140.20 (C_{quat}), 152.34 (C_{quat}), 153.99 (C_{quat}), 159.61 (C_{quat}), 161.55 (C_{quat}), 183.61 (C=O), 183.99 (C=O). IR (ATR): ν_{max} 1677, 1660, 1571, 1282, 1261 cm^{-1}. MS (ES$^+$) *m/z* (%): 360 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{22}H_{18}NO_4]^+$: 360.1236, found 360.1220.

1-Methyl-3-isopropylbenzo[*g*]isoquinoline-5,10-dione 25f

40%, yellow solid, mp 137.1°C. ^{1}H NMR ($CDCl_3$): δ 1.38 (6H, d, *J* = 6.8 Hz, $CH(C\underline{H}_3)_2$), 3.09 (3H, s, CH_3), 3.21 (1H, septet, *J* = 6.8 Hz), 7.79 (1H, dt, *J* = 1.7, 7.6 Hz, CH-7 or CH-8), 7.85 (1H, dt, *J* = 1.7, 7.6 Hz, CH-7 or CH-8), 7.90 (1H, s, CH-4), 8.27 (1H, dd, *J* = 1.7, 7.6 Hz, CH-6 or CH-9), 8.30 (1H, dd, *J* = 1.7, 7.6 Hz, CH-6 or CH-9). ^{13}C NMR ($CDCl_3$): δ 22.25 ($CH(\underline{C}H_3)_2$), 26.56 (CH_3), 37.10 ($\underline{C}H(CH_3)_2$), 114.57 (CH-4), 122.60 (C_{quat}), 126.72 (CH_{Ar}), 127.32 (CH_{Ar}), 132.41 (C_{quat}), 133.67 (CH_{Ar}), 134.71 (C_{quat}), 134.84 (CH_{Ar}), 140.57 (C_{quat}), 161.44 (C_{quat}), 172.60 (C_{quat}), 183.35 (C=O), 183.67 (C=O). IR (ATR): ν_{max} 2928, 1676, 1666, 1573, 1336, 1279, 715 cm.$^{-1}$ MS (ES$^-$) *m/z* (%): 266 ([M-H]$^-$, 100). HRMS (ES$^+$) calcd. for $[C_{17}H_{16}NO_2]^+$: 266.1181, found 266.1175.

1-Methyl-3-*tert*-butylbenzo[*g*]isoquinoline-5,10-dione 25g

38%, orange solid, mp 90.7°C. ^{1}H NMR ($CDCl_3$): δ 1.44 (9H, s, $C(CH_3)_3$), 3.08 (3H, s, CH_3), 7.77 (1H, dt, *J* = 1.7, 7.4 Hz, CH-7 or CH-8), 7.83 (1H, dt, *J* = 1.7, 7.4 Hz, CH-7 or CH-8), 8.03 (1H, s, CH-4), 8.25 (1H, dd, *J* = 1.7, 7.4 Hz, CH-6 or CH-9), 8.28 (1H, dd, *J* = 1.7, 7.4 Hz, CH-6 or CH-9). ^{13}C NMR ($CDCl_3$): δ 26.77 (CH_3), 29.90 ($C(\underline{C}H_3)_3$), 38.55 ($\underline{C}(CH_3)_3$), 113.29 (CH-4), 122.23 (C_{quat}), 126.86 (CH_{Ar}), 127.39 (CH_{Ar}), 132.64 (C_{quat}), 133.76 (CH_{Ar}), 134.46 (C_{quat}), 134.90 (CH_{Ar}), 140.54 (C_{quat}), 160.95 (C_{quat}), 174.69 (C_{quat}), 183.82 (C=O), 184.04 (C=O). IR (ATR): ν_{max} 2958, 2925, 1676, 1575, 1276, 711 cm.$^{-1}$ MS (ES$^+$) *m/z* (%): 280 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{18}NO_2]^+$: 280.1338, found 280.1340.

5.12.3 Synthesis of 3-substituted-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones 404

To a solution of 3-substituted-1-methylbenzo[*g*]isoquinoline-5,10-diones **25** (0.55 mmol) in anhydrous DMF (5 ml), DMF-DMA (0.73 mL, 5.5 mmol, 10 equiv.) was added under a nitrogen atmosphere and the reaction mixture was heated for 15 hours in an oil bath at 125°C. Next, the reaction mixture was poured in 30 ml of water, and extracted with CH_2Cl_2 (3x10 mL). The organic phase was washed three times with brine, dried over $MgSO_4$, evaporated and concentrated under high vacuum to remove residual traces of DMF, thus affording 3-substitited-1-[2-(dimethylamino)vinyl]benzo[*g*]isoquinoline-5,10-diones **404** in high purity. Due to coalescence of the 2-(dimethylamino)vinyl system, the

dimethylamino group is not visible in ^{13}C NMR at 25°C. In order to view this peak, ^{13}C spectra were recorded at 50°C ($CDCl_3$).

3-(4-Fluorophenyl)-1-[2-(dimethylamino)viny]lbenzo[*g*]isoquinoline-5,10-dione 404b

Quantitative yield, deep blue solid, mp 224.5°C. ^1H NMR ($CDCl_3$): δ 3.11 (6H, s, $N(CH_3)_2$), 7.18 (2H, dd, J_{HF} = 8.5, J_{HH} = 8.8 Hz, H-3' and H-5'), 7.21 (1H, d, J = 12.7 Hz, C<u>H</u>=CHN$(CH_3)_2$), 7.70 (1H, t, J = 7.7 Hz, H-7 or H-8), 7.80 (1H, t, J = 7.7 Hz, H-7 or H-8), 7.94 (1H, s, H-4), 8.16 (2H, dd, J_{HF} = 5.5, J_{HH} = 8.8 Hz, H-2' and H-6'), 8.21 (1H, d, J = 7.7 Hz, H-6 or H-9), 8.29 (1H, d, J = 7.7 Hz, H-6 or H-9), 8.35 (1H, d, J = 12.7 Hz, C<u>H</u>=CHN$(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 40.24 ($N(CH_3)_2$), 95.31 (=CH), 109.48 (CH-4), 115.16 (C_{quat}), 115.73 (2xCH_{Ar}, J_{CF} = 21.9 Hz), 126.86 (2xCH_{Ar}, J_{CF} = 56.5 Hz), 129.39 (CH_{Ar}), 129.50 (CH_{Ar}), 132.35 (C_{quat}), 132.83 (CH_{Ar}), 134.73 (CH_{Ar}), 134.92 (C_{quat}, J_{CF} = 2.3 Hz), 135.41 (C_{quat}), 141.94 (C_{quat}), 151.03 (=CH), 158.92 (C_{quat}), 160.08 (C_{quat}), 164.26 (C_{quat}, J_{CF} = 250.4 Hz), 183.38 (C=O), 184.26 (C=O). ^{19}F NMR ($CDCl_3$): δ -111.55 (1F, s, C_{quat}-F). IR (ATR): ν_{max} 2925, 1668, 1599, 1537, 1506, 1361 cm.$^{-1}$ MS (ES^+) *m/z* (%): 373 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{24}H_{21}N_2O_3]^+$: 373.1352, found 373.1353.

1-[2-(Dimethylamino)vinyl]-3-(2,5-dimethoxyphenyl)benzo[*g*]isoquinoline-5,10-dione 404d

87%, dark blue solid, mp 193.3°C. ^1H NMR ($CDCl_3$): δ 3.01 (6H, s, $N(CH_3)_2$), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 6.90 (2H, d, J = 1.7 Hz, CH-3' and CH-4'), 7.13 (1H, d, J = 12.7 Hz, C<u>H</u>=CHN$(CH_3)_2$), 7.84 (1H, t, J = 1.7 Hz, CH-6'), 7.64 (1H, dt, J = 1.1, 7.7 Hz, H-7 or H-8), 7.73 (1H, dt, J = 1.1, 7.7 Hz, H-7 or H-8), 8.11 (1H, s, H-4), 8.15 (1H, d, J = 7.7 Hz, H-6 or H-9), 8.22 (1H, d, J = 7.7 Hz, H-6 or H-9), 8.24 (1H, d, J = 12.7 Hz, CH=C<u>H</u>N$(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 41.07 ($N(CH_3)_2$), 55.85 (OCH_3), 56.33 (OCH_3), 95.31 (=CH), 112.90 (CH-4), 112.90 (CH_{Ar}), 114.84 (C_{quat}), 115.15 (CH_{Ar}), 116.09 (CH_{Ar}), 116.41 (CH_{Ar}), 126.32 (CH_{Ar}), 127.13 (CH_{Ar}), 129.24 (C_{quat}), 132.49 (C_{quat}), 132.69 (CH_{Ar}), 134.49 (CH_{Ar}), 135.41 (C_{quat}), 140.7s0 (C_{quat}), 150.77 (=CH), 152.46 (C_{quat}), 153.68 (C_{quat}), 159.19 (C_{quat}), 159.73 (C_{quat}), 183.49 (C=O), 184.45 (C=O). IR (ATR): ν_{max} 1669, 1604, 1554, 1215, 1100, 715. MS (ES^+) *m/z* (%): 415 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{25}H_{23}N_2O_4]^+$: 415.1658, found 415.1663.

1-[2-(Dimethylamino)vinyl]-3-*tert*-butylbenzo[*g*]isoquinoline-5,10-dione 404g

88%, dark blue solid, mp 189.5°C. ^1H NMR ($CDCl_3$): δ1.41 (9H, s, $C(CH_3)_3$), 3.08 (6H, s, $N(CH_3)_2$), 7.16 (1H, d, J = 12.4 Hz, C<u>H</u>=CHN$(CH_3)_2$), 7.62 (1H, s, H-4), 7.66 (1H, dt, J = 1.3, 7.6 Hz, H-7 or H-8), 7.76 (1H, dt, J = 1.3, 7.6 Hz, H-7 or H-8), 8.17 (1H, dd, J = 1.3, 7.6 Hz, H-6 or H-9), 8.26 (1H, dd, J = 1.3, 7.6 Hz, H-6 or H-9), 8.29 (1H, d, J = 12.4 Hz, CH=C<u>H</u>N$(CH_3)_2$). ^{13}C NMR ($CDCl_3$): δ 29.81 (C(<u>C</u>$H_3)_3$), 29.81 (<u>C</u>$(CH_3)_3$), 41.16 ($N(CH_3)_2$), 95.53 (=CH), 109.30 (CH-4), 114.23 (C_{quat}), 126.31 (CH_{Ar}), 127.06 (CH_{Ar}), 132.41 (C_{quat}), 132.61 (CH_{Ar}), 134.45 (CH_{Ar}), 135.27 (C_{quat}), 141.19 (C_{quat}),

150.84 (=CH), 160.00 (C_{quat}), 173.46 (C_{quat}), 183.35 (C=O), 184.52 (C=O). IR (ATR): ν_{max} 1660, 1608, 1566, 1307, 1245, 1096, 715 cm^{-1}. MS (ES^+) *m/z* (%): 335 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{23}N_2O_2]^+$: 335.1760, found 335.1763.

5.12.4 Synthesis of 5-substituted-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-ones 26

3-Substituted 1-[2-(dimethylamino)vinyl]-benzo[*g*]isoquinoline-5,10-diones **404** (0.45 mmol) were mixed with 10 ml of a 5 m/v% solution of ammonium acetate in anhydrous methanol and boiled under reflux for three hours. After completion of the reaction, the solvent was evaporated and the residue was redissolved in dichloromethane (15 ml). Then, the reaction mixture was washed with saturated sodium bicarbonate solution (25 ml) and brine (25 ml). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*. The resulting residue was purified by column chromatography using dichloromethane as eluent to afford 5-substituted 7*H*-naphtho[3,2,1-*de*]naphthyridine-7-ones **26**. Due to their high insolubility, no ^{13}C-NMR could be recorded for compounds **26b** and **26c**. Recording was attempted with up to 10.000 scans and a relaxation delay of 3 sec. in $CDCl_3$, acetone-d_6, DMSO-d_6, CS_2 and CF_3CO_2D.

5-(3-Methoxyphenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26a

73%, yellow solid, mp 214.9°C. ^{1}H NMR ($CDCl_3$): δ 3.92 (3H, s, OCH_3), 7.08 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 7.66 (1H, dt, *J* = 1.1, 7.6 Hz, H-9 or H-10), 7.82 (1H, dt, *J* = 1.1, 7.6 Hz, H-9 or H-10), 7.94 (1H, d, *J* = 7.6 Hz, H-8 or H-11), 8.28 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 8.38 (1H, d, *J* = 6.9 Hz, H-3), 8.72 (1H, s, CH-6), 8.83 (1H, d, *J* = 7.6 Hz, H-8 or H-11), 8.89 (1H, d, *J* = 6.9 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ55.56 (OCH_3) 114.57 (2xCH_{Ar}), 116.37 (C_{quat}), 118.03 (CH_{Ar}), 122.11 (CH_{Ar}), 125.41 (CH_{Ar}), 127.92 (CH_{Ar}), 129.56 (2xCH_{Ar}), 130.57 (C_{quat}), 130.66 (CH_{Ar}), 131.84 (C_{quat}), 135.04 (CH_{Ar}), 136.45 (C_{quat}), 147.91 (CH_{Ar}),149.58 (C_{quat}), 150.92 (C_{quat}), 161.99 (C_{quat}), 162.14 (C_{quat}), 183.52 (C=O). IR (ATR): ν_{max} 1668, 1590, 1381, 1255, 1174, 708 cm^{-1}. MS (ES^+) *m/z* (%): 339 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{15}N_2O_2]^+$: 339.1134, found 339.1133.

5-(4-Fluorophenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26b

64%, yellow solid, mp 250.0°C. ^{1}H NMR (DMSO-d_6): δ 7.50 (2H, dd, J_{HH} = 9.0, J_{HF} = 9.1, H-3' and H-5'), 7.83 (1H, dt, *J* = 1.1, 7.7 Hz, H-9 or H-10), 8.01 (1H, dt, *J* = 1.1, 7.7 Hz, H-9 or H-10), 8.12 (1H, d, *J* = 7.2 Hz, H-3), 8.34 (1H, dd, *J* = 1.1, 7.7 Hz, H-8 or H-11), 8.49-8.56 (2H, dd, J_{HH} = 9.0, J_{HF} = 5.5, H-2' and H-6'), 8.80 (1H, s, H-6), 8.83 (1H, dd, *J* = 1.1, 7.7 Hz, H-8 or H-11), 9.03 (1H, d, *J* = 7.2 Hz, H-2). Due to the high insolubility of this compound, no ^{13}C NMR could be recorded. ^{19}F NMR ($CDCl_3$): δ -109.95 (1F, s, C_{quat}-F). IR (ATR): ν_{max} 1667, 1591, 1340, 1226, 759 cm^{-1}.MS (ES^+) *m/z* (%): 327 ($[M+H]^+$, 100). No satisfactory HRMS could be obtained.

5-(4-Chlorophenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26c

64%, yellow solid, mp 279.2-280.9°C. ^{1}H NMR ($CDCl_3$): δ 7.57 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 7.69 (1H, t, *J* = 7.5 Hz, H-9 or H-10), 7.88 (1H, t, *J* = 7.5 Hz, H-9 or H-10), 8.05 (1H, d, *J* = 5.5 Hz, H-3), 8.28 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 8.41 (1H, d, *J* = 7.5 Hz, H-8 or H-11), 8.77 (1H, s, H-6), 8.87 (1H, d, *J* = 7.5 Hz, H-8 or H-11), 8.96 (1H, d, 5.5 Hz, H-2). Due to the high insolubility of this compound, no ^{13}C NMR could be recorded. IR (ATR): ν_{max} 1668, 1590, 1446, 1380, 1367, 1338, 1280, 1231, 1091, 1012, 836, 758, 704 cm^{-1}. MS (ES^+) *m/z* (%): 343 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{11}ClN_2O]^+$: 343.0560, found 343.0626.

5-(2,5-Dimethoxyphenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26d

95%, yellow solid, mp 225.4°C. ^{1}H NMR ($CDCl_3$): δ3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 7.00 (1H, d, *J* = 8.1 Hz, H-3'), 7.03 (1H, dd, *J* = 2.8, 8.1 Hz, H-4'), 7.53 (1H, d, *J* = 2.8 Hz, H-6'), 7.64 (1H, dt, *J* = 1.1, 7.7 Hz, H-9 or H-10), 7.83 (1H, dt, *J* = 1.1, 7.7 Hz, H-9 or H-10), 7.99 (1H, d, *J* = 5.5 Hz, H-3), 8.36 (1H, dd, *J* = 1.1, 7.7 Hz, H-8 or H-11), 8.85 (1H, dd, *J* = 1.1, 7.7 Hz, H-8 or H-11), 8.85 (1H, s, H-6), 8.90 (1H, d, *J* = 5.5 Hz, H-3). ^{13}C NMR ($CDCl_3$): δ 56.00 (OCH_3), 56.35 (OCH_3), 113.02 (CH_{Ar}), 116.12 (CH_{Ar}), 116.55 (C_{quat}), 117.67 (CH_{Ar}), 122.23 (CH_{Ar}), 123.73 (CH_{Ar}), 125.39 (CH_{Ar}), 127.88 (CH_{Ar}), 128.58 (C_{quat}), 130.72 (CH_{Ar}), 132.02 (C_{quat}), 133.82 (C_{quat}), 134.98 (CH_{Ar}), 136.43 (C_{quat}), 147.62 (CH_{Ar}), 149.74 (C_{quat}), 150.77 (C_{quat}), 152.06 (C_{quat}), 154.12 (C_{quat}), 162.65 (C_{quat}), 183.67 (C=O). IR (ATR): ν_{max} 1664, 1593, 1499, 1416, 1226, 1035 cm^{-1}. MS: *m/z* (%) 369 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{23}H_{17}N_2O_3]^+$: 369.1239, found 369.1244.

5-(3-Methylphenyl)-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26e

91%, yellow solid, mp 229.3-230.4°C. ^{1}H NMR ($CDCl_3$): δ 2.56 (3H, s, CH_3), 7.39 (2H, d, *J* = 8.0 Hz, H-3' and H-5'), 7.66 (1H, t, *J* = 7.7 Hz, H-9 or H-10), 7.82 (1H, t, *J* = 7.7 Hz, H-9 or H-10), 7.99 (1H, d, *J* = 5.8 Hz, H-3), 8.21 (2H, d, *J* = 8.0 Hz, H-2' and H-6'), 8.40 (1H, d, *J* = 7.7 Hz, H-8 or H-11), 8.76 (1H, s, H-6), 8.85 (1H, d, *J* = 7.7 Hz, H-8 or H-11), 8.92 (1H, d, 5.8 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ 21.58 (CH_3) 116.59 (C_{quat}), 118.41 (CH), 122.23 (CH), 125.44 (CH), 127.92 (2xCH), 129.97 (2xCH), 130.73 (CH), 131.90 (C_{quat}), 135.09 (CH), 135.16 (CH),135.31 (C_{quat}), 136.46 (C_{quat}), 141.48 (C_{quat}), 147.94 (CH), 149.73 (C_{quat}), 150.93 (C_{quat}), 162.58 (C_{quat}), 183.52 (C=O). IR (ATR): ν_{max} 1665, 1591, 1442, 1377, 1365, 1339, 1285, 1234, 1073, 817, 760, 706 cm^{-1}. MS (ES^+) *m/z* (%): 323 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{22}H_{14}N_2O]^+$: 323.1106, found 323.1176.

5-*tert*-Butyl-7*H*-naphtho[3,2,1-*de*]naphthyridine-7-one 26g

72%, yellow solid, mp 168.0°C. ^{1}H NMR ($CDCl_3$): δ1.54 (9H, s, $C(CH_3)_3$), 7.61 (1H, dt, *J* = 1.1, 7.6 Hz, H-9 or H-10), 7.81 (1H, dt, *J* = 1.1, 7.6 Hz, H-9 or H-10), 7.91 (1H, d, *J* = 5.8 Hz, H-3), 8.35 (1H, dd, *J* = 1.1, 7.6 Hz, H-8 or H-11), 8.43 (1H, s, CH-6), 8.81 (1H, dd, *J* = 1.1, 7.6 Hz, H-8 or H-11), 8.88 (1H, d, *J* = 5.6 Hz, H-3). ^{13}C NMR ($CDCl_3$): δ 30.00 ($C(\underline{C}H_3)_3$), 39.42 ($\underline{C}(CH_3)_3$), 116.11 (C_{quat}),

118.15 (CH_{Ar}), 122.18 (CH_{Ar}), 125.25 (CH_{Ar}), 127.79 (CH_{Ar}), 128.58 (C_{quat}), 130.54 (CH_{Ar}), 131.82 (C_{quat}), 133.82 (C_{quat}), 134.52(C_{quat}), 134.86 (CH_{Ar}), 136.29 (C_{quat}), 147.48 (CH_{Ar}), 149.38 (C_{quat}), 149.99 (C_{quat}), 175.84 (C_{quat}), 183.58 (C=O). IR (ATR): ν_{max}1729, 1661, 1592, 1270, 1227, 705 cm^{-1}. MS (ES^+) *m/z* (%): 289 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{17}N_2O]^+$: 289.1341, found 289.1339.

5.12.5 6-Acetyl-1,2,3,4-tetrahydro-1,4-methano-5,8-naphthoquinone 407

6-Acetyl-5,8-dihydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene 406

Under a N_2 atmosphere, $AlCl_3$ (1.77 g, 13.26 mmol, 6.9 equiv.) and NaCl (344 mg, 5.89 mmol, 3.1 equiv.) were molten at 140°C. Then the temperature was raised to 195°C and 5,8-diacetoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene **405** (500 mg, 1.9 mmol) was added. The mixture was stirred for 9 min and quenched with aqueous HCl (2 M, 20 mL), the solids were filtered of and washed with H_2O. The solids were then redissolved in MeOH (4 mL) and conc. HCl (12 M, 0.2 mL) and stirred for 4 h at room temperature. Next, the mixture was poured in icewater and the solids were filtered off and further purified by means of column chromatography to yield 6-acetyl-5,8-dihydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene **406** (200 mg, 0.91 mmol, 48%) as a yellow solid.

48%, yellow solid, mp 155.7°C. ^{1}H NMR ($CDCl_3$): δ 1.20 (2H, br d, *J* = 11.0 Hz, $C\underline{H}_N H_X$), 1.53 (1H, d, *J* = 9.4 Hz, $C\underline{H}_A H_S$), 1.73 (1H, d, *J* = 9.4 Hz, $CH_A\underline{H}_S$), 1.93 (2H, br d, *J* = 11.0 Hz, $CH_N\underline{H}_X$), 2.54 (3H, s, CH_3), 3.54 (1H, s, CH-1 or CH-4), 3.70 (1H, s, CH-1 or CH-4), 4.99 (1H, br s, OH), 7.01 (1H, s, CH-7), 11.90 (1H, s, OH). ^{13}C NMR ($CDCl_3$): δ 26.01 (CH_2), 26.15 (CH_2), 26.96 (CH_3), 39.74 and 40.61 (CH-1 and CH-4), 49.17 (CH-9), 114.70 (CH-7), 118.42 (C_{quat}), 136.80 (C_{quat}), 141.45 (C_{quat}), 144.77 (C_{quat}), 150.46 (C_{quat}), 204.24 (C=O). IR (ATR): ν 3286, 2868, 1641, 1573, 1483, 1311, 1201, 740, 728 cm^{-1}. MS (ES^+) *m/z* (%): 219 ($[M+H]^+$, 100).

6-Acetyl-1,2,3,4-tetrahydro-1,4-methano-5,8-naphthoquinone 407

A solution of 6-acetyl-5,8-dihydroxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene **406** (100 mg, 0.46 mmol), $MgSO_4$ (552 mg, 4.6 mmol, 10 equiv.) and MnO_2 (240 mg, 2.8 mmol, equiv.) in anhydrous CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min. Filtration of the solids and evaporation of the solvent *in vacuo* (bath temperature ≤ 30°C) yielded 6-acetyl-1,2,3,4-tetrahydro-1,4-methano-5,8-naphthoquinone **407** (90 mg, 0.42 mmol, 90%) as a brown oil.

90%, brown oil. ^{1}H NMR ($CDCl_3$): δ 1.95 (2H, br d, *J* = 8.3 Hz, $C\underline{H}_N H_X$), 1.44 (1H, d, *J* = 8.8 Hz, $C\underline{H}_A H_S$), 1.68 (1H, d, *J* = 8.8 Hz, $CH_A\underline{H}_S$), 1.96 (2H, br d, *J* = 8.3 Hz, $CH_N\underline{H}_X$), 2.55 (3H, s, CH_3), 3.51 (2H, s, CH-1 and CH-4), 6.82 (1H, s, CH-7). ^{13}C NMR ($CDCl_3$): δ 25.03 (2xCH_2), 30.99 (CH_3), 40.70 and 40.84 (CH-1 and CH-4), 47.84 (CH-9), 135.74 (CH-7), 142.74 (C_{quat}), 151.91 (2xC_{quat}), 182.72

(C=O), 184.14 (C=O), 197.76 (C=O). IR (ATR): ν 2953, 1697, 1648, 1332, 1237 cm^{-1}. MS (ES^+) *m/z* (%): 217 ($[M+H]^+$, 100).

5.13 Palladium(II)-catalysed synthesis of 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthoquinones] 29

5.13.1 Synthesis of 2-aryloxymethyl-1,4-naphthoquinones 27 and 433

To a solution of 37.5 mmol of phenoxyacetic acid **204** in distilled water (80 mL) and acetonitrile (80 mL), were successively added 1,4-naphthoquinone **3** (3.95 g, 25 mmol, 1.5 equiv.) and $AgNO_3$ (1.27 g, 7.5 mmol, 0.3 equiv.). The mixture was heated to 80°C until dissolution was complete. The resulting solution was stirred vigorously while a solution of ammonium peroxydisulfate (8.56 g, 37.5 mmol, 1.5 equiv.) in distilled water (80 mL) was added dropwise. Throughout the addition, the reaction mixture was maintained at 80°C. After the addition was complete, the mixture was stirred for 5 minutes at 80°C and was then cooled to 5-10°C in an ice-bath. The precipitated solid was collected by suction filtration, washed with cold water (50 mL) and pressed to remove most of the liquid. Inorganic contaminants, usually present in small amounts, were removed by dissolving the solid in boiling acetone (350 mL) and filtering the hot solution. Concentration of the filtrate *in vacuo* gave a dark red crude product, which was recrystallised from ethanol. In case of 3-methyl-2-phenoxymethyl-1,4-naphthoquinone **433**, 2-methyl-1,4-naphthoquinone **156b** was used as a starting material.

2-Phenoxymethyl-1,4-naphthoquinone 27a

62%, Yellow needles, mp 163°C (Lit.[262] 163-164°C). ^1H NMR ($CDCl_3$): δ 5.05 (2H, d, J = 2.0 Hz, CH_2O), 6.98-7.02 (3H, m, 3xCH_{Ar}), 7.17 (1H, t, J = 2.0 Hz, CH-3), 7.29-7.34 (2H, m, 2xCH_{Ar}), 7.72-7.78 (2H, m, CH-6 and CH-7), 8.07-8.13 (2H, m, CH-5 and CH-8). ^{13}C NMR ($CDCl_3$): δ 63.54 (CH_2O), 114.76 (2xCH_{Ar}), 121.77 (CH_{Ar}), 126.44 and 126.47 (CH-5 and CH-8), 129.80 (2xCH_{Ar}), 132.08 (C_{quat}), 133.91 and 134.03 (CH-6 and CH-7), 134.23 (CH-3), 146.25 (C_{quat}), 157.85 (C_{quat}), 184.66 (C=O), 184.75 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1659 (C=O), 1586, 1299, 1240 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 265 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{17}H_{11}O_3]^-$: 263.0708, found 263.0716.

2-(2-Methylphenoxymethyl)-1,4-naphthoquinone 27b

73%, yellow crystals, mp 160.0°C. ^1H NMR ($CDCl_3$): δ 2.34 (3H, s, CH_3), 5.09 (2H, d, J = 2.2 Hz, CH_2O), 6.89-6.95 (2H, m, 2xCH_{Ar}), 7.16-7.22 (3H, m, 2xCH_{Ar} and CH-3), 7.74-7.81 (2H, m, 2xCH_{Ar}), 8.09-8.16 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 16.53 (CH_3), 63.49 (CH_2O), 111.12 (CH_{Ar}), 121.39 (CH_{Ar}), 126.44 (CH_{Ar}), 126.51 (CH_{Ar}), 126.96 (C_{quat}), 127.07 (CH_{Ar}), 131.13 (CH_{Ar}), 132.00 (C_{quat}), 132.03 (C_{quat}), 133.79 (CH-3), 133.91 (CH_{Ar}), 134.23 (CH_{Ar}), 146.61 (C_{quat}), 155.90 (C_{quat}), 184.65

(C=O), 184.80 (C=O). IR (ATR): *v* 1657 (C=O), 1588, 1296, 1245 (C-O), 748 cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1008.

2-(3-Methylphenoxymethyl)-1,4-naphthoquinone 27c

89%, yellow solid, mp 166.5°C. ^1H NMR ($CDCl_3$): δ 2.35 (3H, s, CH_3), 5.07 (2H, d, J = 2.2 Hz, CH_2O), 6.78-6.84 (3H, m, 3xCH_{Ar}), 7.17-7.23 (2H, m, CH_{Ar} and CH-3), 7.74-7.80 (2H, m, 2xCH_{Ar}), 8.08-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.61 (CH_3), 63.52 (CH_2O), 111.63 (CH_{Ar}), 115.59 (CH_{Ar}), 122.60 (CH_{Ar}), 126.44 (CH_{Ar}), 126.47 (CH_{Ar}), 129.51 (CH_{Ar}), 132.02 (C_{quat}), 132.03 (C_{quat}), 133.87 (CH_{Ar}), 134.02 (CH_{Ar}), 134.20 (CH_{Ar}), 139.93 (C_{quat}), 146.39 (C_{quat}), 157.90 (C_{quat}), 184.71 (C=O), 184.77 (C=O). IR (ATR): *v* 1660 (C=O), 1583, 1296 (C-O), 1250 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1025.

2-(4-Methylphenoxymethyl)-1,4-naphthoquinone 27d

62%, yellow needles, mp 145.5°C. ^1H NMR ($CDCl_3$): δ 2.30 (3H, s, CH_3), 5.05 (2H, d, J = 2.2 Hz, CH_2O), 6.89 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.11 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.18 (1H, t, J = 2.2 Hz, CH-3), 7.73-7.80 (2H, m, 2xCH_{Ar}), 8.07-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 20.57 (CH_3), 63.66 (CH_2O), 114.58 (2xCH_{Ar}), 126.41 (2xCH_{Ar}), 130.22 (2xCH_{Ar}), 130.98 (C_{quat}), 132.06 (C_{quat}), 133.90 (2xCH_{Ar}), 134.15 (C_{quat}), 146.37 (C_{quat}), 155.77 (C_{quat}), 184.62 (C=O), 184.69 (C=O). IR (ATR): *v* 1659 (C=O), 1628, 1509, 1296, 1244 (C-O), 1232 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1015.

2-(2-Methoxyphenoxymethyl)-1,4-naphthoquinone 27e

50%, yellow solid, mp 193°C. ^1H NMR ($CDCl_3$): δ 3.91 (3H, s, CH_3O), 5.16 (2H, d, J = 1.8 Hz, CH_2O), 6.87-7.02 (4H, m, 4xCH_{Ar}), 7.23 (1 H, t, J = 1.8 Hz, CH-3), 7.74-7.80 (2H, m, 2xCH_{Ar}), 8.08-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.97 (CH_3O), 64.98 (CH_2O), 112.17 (CH_{Ar}), 114.18 (CH_{Ar}), 120.95 (CH_{Ar}), 122.46 (CH_{Ar}), 126.43 (CH_{Ar}), 126.49 (CH_{Ar}), 132.04 (C_{quat}), 132.07 (C_{quat}), 133.87 (CH-3), 134.02 (2xCH_{Ar}), 146.38 (C_{quat}), 147.32 (C_{quat}), 149.84 (C_{quat}), 184.78 (2xC=O). IR (ATR): *v* 1659 (C=O), 1589, 1505, 1253, 1230 (C-O), 739 cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0964.

2-(3-Methoxyphenoxymethyl)-1,4-naphthoquinone 27f

57%, yellow solid, mp 130.0°C. ^1H NMR ($CDCl_3$): δ 3.81 (3H, s, CH_3O), 5.07 (2H, d, J = 2.2 Hz, CH_2O), 6.55-6.61 (3H, m, 3xCH_{Ar}), 7.17-7.24 (2H, m, CH-3 and CH_{Ar}), 7.74-7.80 (2H, m, 2xCH_{Ar}), 8.07-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.40 (CH_3O), 63.62 (CH_2O), 101.34 (CH_{Ar}), 106.78 (CH_{Ar}), 107.34 (CH_{Ar}), 126.43 (2xCH_{Ar}), 130.23 (CH_{Ar}), 132.06 (C_{quat}), 133.90 (CH_{Ar}), 133.99 (CH_{Ar}), 134.20 (CH_{Ar}), 138.72 (C_{quat}), 146.16 (C_{quat}), 159.07 (C_{quat}), 161.04 (C_{quat}), 184.60 (C=O), 184.72

(C=O). IR (ATR): *v* 1657 (C=O), 1588, 1298, 1249 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0969.

2-(4-Methoxyphenoxymethyl)-1,4-naphthoquinone 27g

46%, yellow crystals, mp 136.1-137.1°C. ^1H NMR ($CDCl_3$): δ 3.77 (3H, s, CH_3O), 5.02 (2H, d, J = 2.2 Hz, CH_2O), 6.82-6.96 (4H, m, 4xCH_{Ar}), 7.18 (1 H, t, J = 2.2 Hz, CH-3), 7.19-7.80 (2H, m, 2xCH_{Ar}), 8.07-8.14 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.80 (CH_3O), 64.30 (CH_2O), 114.90 (2xCH_{Ar}), 115.74 (2xCH_{Ar}), 126.43 (CH_{Ar}), 126.46 (CH_{Ar}), 132.09 (C_{quat}), 133.90 (CH-3), 134.02 (CH_{Ar}), 134.20 (CH_{Ar}), 146.51 (C_{quat}), 152.03 (C_{quat}), 154.52 (C_{quat}), 184.71 (C=O), 184.80 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1659, 1508, 1234 cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^-) calcd. for $[C_{18}H_{13}O_4]^-$: 293.0814, found 293.0822.

2-(4-*tert*-Butylphenoxymethyl)-1,4-naphthoquinone 27h

66%, yellow solid, mp 139.0°C. ^1H NMR ($CDCl_3$): δ 1.31 (9H, s, $(CH_3)_3C$), 5.07 (2H, d, J = 2.2 Hz, CH_2O), 6.93 (2H, d, J = 9.1 Hz, 2xCH_{Ar}), 7.19 (1 H, t, J = 2.2 Hz, CH-3), 7.34 (2H, d, J = 9.1 Hz, 2xCH_{Ar}), 7.74-7.80 (2H, m, 2xCH_{Ar}), 8.07-8.16 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 31.60 (($\underline{C}H_3)_3C$), 34.24 ($(CH_3)_3\underline{C}$), 63.65 (CH_2O), 114.26 (2xCH_{Ar}), 126.43 (CH_{Ar}), 126.46 (CH_{Ar}), 126.57 (2xCH_{Ar}), 132.11 (C_{quat}), 133.88 (CH_{Ar}), 134.03 (CH_{Ar}), 134.20 (CH_{Ar}), 144.49 (C_{quat}), 146.48 (C_{quat}), 155.64 (C_{quat}), 184.69 (C=O), 184.77 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1661 (C=O), 1591, 1512, 1297, 1245 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 321 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{21}O_3]^+$: 321.1491, found 321.1479.

2-(4-Fluorophenoxymethyl)-1,4-naphthoquinone 27i

59%, yellow crystals, mp 158.6-159.0°C. ^1H NMR ($CDCl_3$): δ 5.04 (2H, d, J = 2.0 Hz, CH_2O), 6.91-7.05 (4H, m, 4xCH_{Ar}), 7.17 (1H, s, CH-3), 7.75-7.81 (2H, m, 2xCH_{Ar}), 8.09-8.13 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 64.26 (CH_2O), 115.83 (J_{CF} = 6.9 Hz, 2xCH_{Ar}), 116.20 (J_{CF} = 23.2 Hz, 2xCH_{Ar}), 126.46 (CH_{Ar}), 126.51 (CH_{Ar}), 132.06 (C_{quat}), 133.96 (CH_{Ar}), 134.05 (CH_{Ar}), 134.28 (CH-3), 146.03 (C_{quat}), 153.99 (C_{quat}), 153.99 (C_{quat}) 157.81 (J_{CF} = 238.8 Hz, C_{quat}), 184.60 (C=O), 184.71 (C=O). ^{19}F NMR ($CDCl_3$): δ -125.03 - -122.60 (1F, m). IR (ATR): *v* 1655, 1506, 1206 cm^{-1}. MS (ES^-) *m/z* (%): 281 ($[M-H]^-$, 70). HRMS (ES^-) calcd. for $[C_{17}H_{10}FO_3]^-$: 281.0614, found 281.0628.

2-(4-Chlorophenoxymethyl)-1,4-naphthoquinone 27j

20%, yellow needles, mp 165.9-166.0°C (Lit.[263] 167-169.5°C). ^1H NMR ($CDCl_3$): δ 5.21 (2H, s, CH_2O), 6.84 (2H, d, J = 8.5 Hz, 2xCH_{Ar}), 7.21 (1H, s, CH-3), 7.24 (2H, d, J = 8.5 Hz, 2xCH_{Ar}), 7.78-7.81 (2H, m, 2xCH_{Ar}), 8.14-8.19 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 63.91 (CH_2O), 116.05 (2xCH_{Ar}), 126.47 (CH_{Ar}), 126.51 (CH_{Ar}), 126.72 (C_{quat}), 129.68 (2xCH_{Ar}), 131.99 (C_{quat}), 132.03 (C_{quat}), 133.97 (CH_{Ar}), 134.06 (CH_{Ar}), 134.31 (CH-3), 145.77 (C_{quat}), 156.45 (C_{quat}), 184.55 (C=O),

184.65 (C=O). IR (ATR): *v* 1655, 1596, 1221 cm^{-1}. MS (ES^+) *m/z* (%): 299 ($[M+H]^+$, 93). HRMS (ES^-) calcd. for $[C_{17}H_{10}ClO_3]^-$: 297.0319, found 297.0314.

3-Methyl-2-phenoxymethyl-1,4-naphthoquinone 433

70%, yellow crystals, mp 110.4°C. ^1H NMR ($CDCl_3$): δ 2.33 (3H, s, CH_3), 5.13 (2H, s, CH_2O), 6.96-7.00 (3H, m, 3xCH_{Ar}), 7.23-7.34 (2H, m, 2xCH_{Ar}), 7.67-7.77 (2H, m, 2xCH_{Ar}), 8.09-8.17 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 13.25 (CH_3), 60.73 (OCH_2), 114.83 (2xCH_{Ar}), 121.47 (CH_{Ar}), 126.52 (CH_{Ar}), 126.67 (CH_{Ar}), 129.67 (2xCH_{Ar}), 131.93 (C_{quat}), 132.19 (C_{quat}), 133.77 (CH_{Ar}), 133.90 (CH_{Ar}), 140.11 (C_{quat}), 148.37 (C_{quat}), 158.49 (C_{quat}), 183.72 (C=O), 185.30 (C=O). IR (ATR): *v* 1664, 1589, 1294 cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 25). HRMS (ES^-) calcd. for $[C_{18}H_{13}O_3]^-$: 277.0865, found 277.0873.

5.13.2 Synthesis of 2'*H*,3*H*-spiro[benzofuran-3,2'-naphthoquinones] 29

To a 10 mL vial were added 3,5-dichloropyridine (0.15 mmol, 22 mg), trifluoroacetic acid (0.05 mmol, 6 mg), palladium(II) acetate (0.10 mmol, 22 mg), 2-aryloxymethyl-1,4-naphthoquinones **27** (1 mmol) and acetic acid (4 mL). The flask was sealed and stirred at 110°C for 4 days. The reaction mixture was then diluted with chloroform (10 mL), filtered over a pad of Celite®, washed with water (10 mL) and aqueous saturated sodium hydrogen carbonate (2x10 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Flash chromatography on silica gel with ethyl acetate : hexane (1:9) yielded 2'*H*,3*H*-spiro[benzofuran-3,2'-naphthoquinones] **29**. Upon (LC-)MS analysis most spiroquinones were found to give very poor mass spectrometric ionisations. Regioisomeric spironaphthoquinones **29c** and **29f** were further separated by means of preparative HPLC.

2*H*,3'*H*-Spiro[benzofuran-3,2'-naphthalene]-1',4'-dione 29a

62%, yellow crystals, mp 88.0°C. ^1H NMR ($CDCl_3$): δ 3.30 (1H, d, J_{ab} = 16.8 Hz, C$\underline{H}_a$$H_b$-C=O), 3.32 (1H, d, J_{ab} = 16.8 Hz, $CH_a\underline{H}_b$-C=O), 4.31 (1H, d, J_{ab} = 8.8 Hz, C$\underline{H}_a$$H_b$O), 5.43 (1H, d, J_{ab} = 8.8 Hz, $CH_a\underline{H}_b$O), 6.64-6.73 (2H, m, 2xCH_{Ar}), 6.86 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 7.17 (1H, dt, *J* = 1.6 and 7.2 Hz, CH_{Ar}), 7.78-7.87 (2H, m, 2xCH_{Ar}), 8.12-8.22 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.76 ($\underline{C}H_2$-C=O), 58.41 (C_{spiro}), 77.62 (CH_2O), 110.93 (CH_{Ar}), 120.98 (CH_{Ar}), 123.82 (CH_{Ar}), 126.80 (CH_{Ar}), 127.50 (C_{quat}), 128.48 (CH_{Ar}), 130.28 (CH_{Ar}), 134.61 (C_{quat}), 134.89 (CH_{Ar}), 134.93 (CH_{Ar}), 135.61 (C_{quat}), 159.93 (C_{quat}), 193.85 (C=O), 193.98 (C=O). IR (ATR): *v* 1694, 1590 cm^{-1}. MS (ES^-) *m/z* (%): 263 ($[M-H]^-$, 100). HRMS (ES^+) calcd. for $[C_{17}H_{13}O_3]^+$: 265.0865, found 265.0856.

2*H*,3'*H*-Spiro[7-methylbenzofuran-3,2'-naphthalene]-1',4'-dione 29b

21%, yellow solid, mp 160.0°C. ^1H NMR ($CDCl_3$): δ 2.21 (3H, s, CH_3), 3.28 (1H, d, J_{ab} = 16.2 Hz, C$\underline{H}_a$$H_b$-C=O), 3.30 (1H, d, J_{ab} = 16.2 Hz, $CH_a\underline{H}_b$-C=O), 4.29 (1H, d, J_{ab} = 9.1 Hz, C$\underline{H}_a$$H_b$O), 5.42 (1H, d, J_{ab} = 9.1 Hz, $CH_a\underline{H}_b$O), 6.46 (1H, d, *J* = 7.7 Hz, CH-6), 6.59 (1H, t, *J* = 7.7 Hz, CH-5), 6.97 (1H, d,

J = 7.7 Hz, CH-4), 7.76-7.85 (2H, m, 2xCH_{Ar}), 8.09-8.19 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 15.25 (CH_3), 48.79 ($\underline{C}H_2$-C=O), 58.70 (C_{spiro}), 76.73 (CH_2O), 120.86 (CH-5), 121.16 (CH-6), 121.24 (C_{quat}), 126.73 (CH_{Ar}), 128.43 (CH_{Ar}), 131.41 (CH-4), 134.66 (C_{quat}), 134.80 (CH_{Ar}), 134.87 (CH_{Ar}), 135.62 (C_{quat}), 158.32 (C_{quat}), 193.95 (C=O), 194.14 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1689 (C=O), 1592, 1247 (C-O), 753 cm^{-1}. MS (ES$^+$) *m/z* (%): 279 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1005.

2*H*,3'*H*-Spiro[6-methylbenzofuran-3,2'-naphthalene]-1',4'-dione 29ca

51%, yellow solid, mp 108.5°C. ^{1}H NMR ($CDCl_3$): δ 2.25 (3H, s, CH_3), 3.29 (2H, s, CH_2-C=O), 4.29 (1H, d, J_{ab} = 9.3 Hz, C$\underline{H}_a$H$_b$O), 5.42 (1H, d, J_{ab} = 9.3 Hz, CH$_a\underline{H}_b$O), 6.50 (2H, s, 2xCH_{Ar}), 6.68 (1H, s, CH_{Ar}), 7.76-7.89 (2H, m, 2xCH_{Ar}), 8.10-8.20 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 21.57 (CH_3), 48.78 ($\underline{C}H_2$-C=O), 58.15 (C_{spiro}), 77.77 (CH_2O), 111.54 (CH_{Ar}), 121.74 (CH_{Ar}), 123.38 (CH_{Ar}), 124.66 (C_{quat}), 126.75 (CH_{Ar}), 128.43 (CH_{Ar}), 134.66 (C_{quat}), 134.80 (CH_{Ar}), 134.87 (CH_{Ar}), 135.60 (C_{quat}), 140.83 (C_{quat}), 160.17 (C_{quat}), 194.01 (C=O), 194.07 (C=O). IR (ATR): *v* 1687 (C=O), 1591, 1253 (C-O), 1245 (C-O), 759 cm^{-1}. MS (ES$^+$) *m/z* (%): 279 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1012.

2*H*,3'*H*-Spiro[4-methylbenzofuran-3,2'-naphthalene]-1',4'-dione 29cb

11%, white solid. mp 179.5°C ^{1}H NMR ($CDCl_3$): δ 2.20 (3H, s, CH_3), 3.23 (1H, d, J_{ab} = 16.2 Hz, CH$_a\underline{H}_b$-C=O), 3.53 (1H, d, J_{ab} = 16.2 Hz, CH$_a\underline{H}_b$-C=O), 4.43 (1H, d, J_{ab} = 8.8 Hz, C$\underline{H}_a$H$_b$O), 4.48 (1H, d, J_{ab} = 8.8 Hz, C$\underline{H}_a$H$_b$O), 6.74 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 6.78 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.17 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.80-7.85 (2H, m, 2xCH_{Ar}), 8.09-8.14 (1H, m, CH_{Ar}), 8.18-8.22 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 19.46 (CH_3), 47.49 ($\underline{C}H_2$-C=O), 60.03 (C_{spiro}), 79.68 (CH_2O), 108.07 (CH_{Ar}), 123.70 (CH_{Ar}), 126.40 (C_{quat}), 126.96 (CH_{Ar}), 128.20 (CH_{Ar}), 130.11 (CH_{Ar}), 134.83 (CH_{Ar}), 134.98 (CH_{Ar}), 135.27 (C_{quat}), 135.45 (C_{quat}), 160.29 (C_{quat}), 194.42 (C=O), 195.41 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1691 (C=O), 1682 (C=O), 1591, 1463, 1288 (C-O), 985 cm^{-1}. MS (ES$^+$) *m/z* (%): 279 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1011.

2*H*,3'*H*-Spiro[5-methylbenzofuran-3,2'-naphthalene]-1',4'-dione 29d

68%, bright orange solid, mp 108.5°C. ^{1}H NMR ($CDCl_3$): δ 2.09 (3H, s, CH_3), 3.28 (1H, d, J_{ab} = 16.2 Hz, C$\underline{H}_a$H$_b$-C=O), 3.31 (1H, d, J_{ab} = 16.2 Hz, CH$_a\underline{H}_b$-C=O), 4.28 (1H, d, J_{ab} = 9.3 Hz, C$\underline{H}_a$H$_b$O), 5.36 (1H, d, J_{ab} = 9.3 Hz, CH$_a\underline{H}_b$O), 6.44 (1H, d, *J* = 1.7 Hz, CH-4), 6.75 (1H, d, *J* = 8.5 Hz, CH-7), 6.95 (1H, dd, *J* = 8.5 and 1.7 Hz, CH-6), 7.78-7.88 (2H, m, 2xCH_{Ar}), 8.12-8.20 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 20.84 (CH_3), 48.70 ($\underline{C}H_2$-C=O), 58.44 (C_{spiro}), 77.91 (CH_2O), 110.46 (CH_{Ar}), 124.11 (CH_{Ar}), 126.75 (CH_{Ar}), 127.62 (C_{quat}), 128.41 (CH_{Ar}), 130.35 (C_{quat}), 130.77 (CH_{Ar}), 134.58 (C_{quat}), 134.84 (CH_{Ar}), 134.89 (CH_{Ar}), 135.59 (C_{quat}), 157.91 (C_{quat}), 194.01 (C=O), 194.17 (C=O). IR (ATR):

v 1692 (C=O), 1591, 1490, 1246 (C-O), 759 cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1016.

2*H*,3'*H*-Spiro[6-methoxybenzofuran-3,2'-naphthalene]-1',4'-dione 29fa

61%, yellow solid, mp 129°C. ^1H NMR ($CDCl_3$): δ 3.29 (2H, s, CH_2-C=O), 3.71 (3H, s, OCH_3), 4.30 (1H, d, J_{ab} = 8.8 Hz, $C\underline{H}_aH_bO$), 5.44 (1H, d, J_{ab} = 8.8 Hz, $CH_a\underline{H}_bO$), 6.23 (1H, dd, *J* = 8.4 and 2.2 Hz, CH-5), 6.42 (1H, d, *J* = 2.2 Hz, CH-7), 6.50 (1H, d, *J* = 8.4 Hz, CH-4), 7.77-7.87 (2H, m, 2xCH_{Ar}), 8.11-8.20 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.82 ($\underline{C}H_2$-C=O), 55.59 (OCH_3), 57.77 (C_{spiro}), 78.27 (CH_2O), 97.10 (CH_{Ar}), 106.92 (CH_{Ar}), 119.60 (C_{quat}), 124.03 (CH_{Ar}), 126.75 (CH_{Ar}), 128.43 (CH_{Ar}), 134.64 (C_{quat}), 134.78 (CH_{Ar}), 134.89 (CH_{Ar}), 135.56 (C_{quat}), 161.41 (C_{quat}), 161.91 (C_{quat}), 193.99 (C=O), 194.04 (C=O). IR (ATR): *v* 1687 (C=O), 1595, 1498, 1281 (C-O), 1147 (C-O) cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0969.

2*H*,3'*H*-Spiro[4-methoxybenzofuran-3,2'-naphthalene]-1',4'-dione 29fb

13%, pale white solid, mp 156.5°C. ^1H NMR ($CDCl_3$): δ 3.17 (1H, d, J_{ab} = 16.5 Hz, $C\underline{H}_aH_b$-C=O), 3.49 (3H, s, OCH_3), 3.58 (1H, d, J_{ab} = 16.5 Hz, $CH_a\underline{H}_b$-C=O), 4.35 (1H, d, J_{ab} = 9.1 Hz, $C\underline{H}_aH_bO$), 5.00 (1H, d, J_{ab} = 9.1 Hz, $CH_a\underline{H}_bO$), 6.36 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 6.52 (1H, d, *J* = 8.3 Hz, CH_{Ar}), 7.16 (1H, t, *J* = 8.3 Hz, CH_{Ar}), 7.72-7.82 (2H, m, 2xCH_{Ar}), 8.10-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 47.33 ($\underline{C}H_2$-C=O), 58.84 (OCH_3), 58.13 (C_{spiro}), 79.95 (CH_2O), 103.77 (CH_{Ar}), 115.47 (C_{quat}), 126.05 (CH_{Ar}), 128.08 (CH_{Ar}), 131.44 (CH_{Ar}), 134.05 (CH_{Ar}), 134.38 (2xCH_{Ar}), 134.44 (C_{quat}), 136.31 (C_{quat}), 156.54 (C_{quat}), 161.59 (C_{quat}), 194.13 (C=O), 195.20 (C=O). IR (ATR): *v* 1687 (C=O), 1594, 1464, 1248 (C-O), 1093 (C-O), 753 cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0964.

2*H*,3'*H*-Spiro[5-methoxybenzofuran-3,2'-naphthalene]-1',4'-dione 29g

59%, orange crystals, mp 133.4°C. ^1H NMR ($CDCl_3$): δ 3.28 (1H, d, J_{ab} = 16.5 Hz, $C\underline{H}_aH_b$-C=O), 3.32 (1H, d, J_{ab} = 16.5 Hz, $CH_a\underline{H}_b$-C=O), 3.57 (3H, s, OCH_3), 4.29 (1H, d, J_{ab} = 9.1 Hz, $C\underline{H}_aH_bO$), 5.34 (1H, d, J_{ab} = 9.1 Hz, $CH_a\underline{H}_bO$), 6.23 (1H, d, *J* = 2.8 Hz, CH-4), 6.69 (1H, dd, *J* = 2.8 Hz and 8.8 Hz, CH-6), 6.77 (1H, d, *J* = 8.8 Hz, CH-7), 7.77-7.86 (2H, m, 2xCH_{Ar}), 8.08-8.20 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.59 ($\underline{C}H_2$-C=O), 55.98 (OCH_3), 58.79 (C_{spiro}), 78.01 (CH_2O), 110.57 (CH-4), 110.79 (CH-7), 114.70 (CH-6), 126.80 (CH_{Ar}), 128.41 (CH_{Ar}), 134.61 (C_{quat}), 134.82 (CH_{Ar}), 134.86 (CH_{Ar}), 135.53 (C_{quat}), 154.05 (C_{quat}), 154.16 (C_{quat}), 193.67 (C=O), 194.01 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): *v* 1686, 1483 cm^{-1}. MS (ES^-) *m/z* (%): 293 ($[M-H]^-$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_4]^+$: 295.0970, found 295.0964.

2*H*,3'*H*-Spiro[5-*tert*-butylbenzofuran-3,2'-naphthalene]-1',4'-dione 29h

71%, orange solid, mp 145.0°C. ^{1}H NMR ($CDCl_3$): δ 1.06 (9H, s, $(CH_3)_3C$), 3.29 (1H, d, J_{ab} = 16.2 Hz, $C\underline{H}_aH_b$-C=O), 3.33 (1H, d, J_{ab} = 16.2 Hz, $CH_a\underline{H}_b$-C=O), 4.30 (1H, d, J_{ab} = 9.3 Hz, $C\underline{H}_aH_bO$), 5.38 (1H, d, J_{ab} = 9.3 Hz, $CH_a\underline{H}_bO$), 6.64 (1H, d, J = 2.2 Hz, CH-4), 6.77 (1H, d, J = 8.5 Hz, CH-7), 7.18 (1H, dd, J = 2.2 8.5 Hz, CH-6), 7.77-7.88 (2H, m, 2xCH_{Ar}), 8.09-8.14 (1H, m, CH_{Ar}), 8.19-8.22 (1H, m, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 31.46 ($(\underline{C}H_3)_3C$), 34.26 ($(CH_3)_3\underline{C}$), 48.64 ($\underline{C}H_2$-C=O), 58.67 (C_{spiro}), 77.71 (CH_2O), 110.08 (CH_{Ar}), 120.60 (CH_{Ar}), 126.52 (CH_{Ar}), 127.04 (C_{quat}), 127.21 (CH_{Ar}), 128.37 (CH_{Ar}), 134.80 (2xCH_{Ar}), 135.68 (C_{quat}), 144.00 (C_{quat}), 157.73 (C_{quat}), 193.98 (C=O), 194.16 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): ν 1690 (C=O), 1497 (C-O), 1263 (C-O), 1342, 820 cm^{-1}. MS (ES$^+$) *m/z* (%): 338 ($[M+NH_4]^+$, 100). HRMS (ES$^+$) calcd. for $[C_{21}H_{24}NO_3]^+$: 338.1756, found 338.1749.

2*H*,3'*H*-Spiro[5-fluorobenzofuran-3,2'-naphthalene]-1',4'-dione 29i

53%, yellow crystals, mp 154.6-155.1°C. ^{1}H NMR ($CDCl_3$): δ 3.29 (1H, d, J_{ab} = 16.2 Hz, $C\underline{H}_aH_b$-C=O), 3.32 (1H, d, J_{ab} = 16.2 Hz, $CH_a\underline{H}_b$-C=O), 4.34 (1H, d, J = 8.8 Hz, $C\underline{H}_aH_bO$), 5.38 (1H, d, J = 8.8 Hz, $CH_a\underline{H}_bO$), 6.37 (1H, dd, J_{HF} = 2.8 Hz, J_{HF} = 8.3 Hz, CH-4), 6.77 (1H, dd, J_{HH} = 8.8 Hz, J_{HF} = 4.4 Hz, CH-7), 6.86 (1H, ddd, J_{HH} = 2.8 Hz and 8.8 Hz, J_{HF} = 8.3 Hz, CH-6), 7.79-7.89 (2H, m, 2xCH_{Ar}), 8.09-8.22 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.55 ($\underline{C}H_2$-C=O), 58.68 (C_{spiro}), 78.83 (CH_2O), 110.02 (J_{CF} = 19.6 Hz, CH-4), 111.25 (J_{CF} = 3.5 Hz, CH-7), 116.73 (J_{CF} = 24.2 Hz, CH-6), 126.95 (CH_{Ar}), 128.48 (CH_{Ar}), 128.60 (C_{quat}), 134.37 (C_{quat}), 135.12 (2xCH_{Ar}), 135.39 (C_{quat}), 155.97 (C_{quat}), 157.22 (J_{CF} = 238.8 Hz, C_{quat}), 193.35 (C=O), 195.59 (C=O). ^{19}F NMR ($CDCl_3$): -122.20- -122.58 (1F, m). IR (ATR): ν 1686, 1482 cm^{-1}. MS (ES$^-$) *m/z* (%): 281 ($[M-H]^-$, 100). HRMS (ES$^-$) calcd. for $[C_{17}H_{10}FO_3]^-$: 281.0614, found 281.0612.

2*H*,3'*H*-Spiro[5-chlorobenzofuran-3,2'-naphthalene]-1',4'-dione 29j

69%, brown oil. ^{1}H NMR ($CDCl_3$): δ 3.29 (1H, d, J_{ab} = 16.2 Hz, $C\underline{H}_aH_b$-C=O), 3.31 (1H, d, J_{ab} = 16.2 Hz, $CH_a\underline{H}_b$-C=O), 4.33 (1H, d, J = 9.1 Hz, $C\underline{H}_aH_bO$), 5.36 (1H, d, J = 9.1 Hz, $CH_a\underline{H}_bO$), 6.61 (1H, d, J = 2.2 Hz, CH_{Ar}), 6.74-6.81 (1H, m, CH_{Ar}), 7.07-7.18 (1H, m, CH_{Ar}), 7.78-7.89 (2H, m, 2xCH_{Ar}), 8.11-8.19 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.50 ($\underline{C}H_2$-C=O), 58.46 (C_{spiro}), 78.44 (CH_2O), 111.91 (CH_{Ar}), 116.76 (C_{quat}), 123.89 (CH_{Ar}), 125.65 (C_{quat}), 127.01 (CH_{Ar}), 128.54 (CH_{Ar}), 129.53 (C_{quat}), 130.31 (CH_{Ar}), 135.22 (2xCH_{Ar}), 135.35 (C_{quat}), 158.68 (C_{quat}), 193.46 (C=O), 193.58 (C=O). IR (ATR): ν 1693, 1474 cm^{-1}. MS (ES$^-$) *m/z* (%): 297 ($[M-H]^-$, 100). HRMS (ES$^-$) calcd. for $[C_{17}H_{10}ClO_3]^-$: 297.0319, found 297.0314.

5.13.3 Synthesis of 2-aryloxymethyl-1,4-benzoquinones 207

To 125 mL of distilled water, the appropriate phenoxyacetic acid **204** (50 mmol), 1,4-benzoquinone **2** (5.40 g, 50 mmol) and $AgNO_3$ (1 g, 6 mmol, 0.12 equiv.) were added successively. The mixture was then heated to 60-65°C until dissolution was complete. The resulting solution was stirred vigorously

while a solution of ammonium peroxydisulfate (13.7 g , 60 mmol, 1.2 equiv.) in distilled water (25 mL) was added at a rate of 0.5 mL per minute for the first 40 minutes and then at a rate of 0.25 mL per minute for the last 20 minutes. Throughout the addition, the reaction mixture was maintained at 60-65°C. After the addition was complete, the mixture was stirred for 5 minutes at 65°C and was then cooled to 5-10°C using an ice-bath. The precipitated solid was collected by suction filtration, washed with 50 mL of cold water and pressed to remove most of the liquid. Inorganic contaminants, usually present in small amounts, were removed by dissolving the solid in 350 mL of boiling acetone and filtering the hot solution. Concentration of the filtrate *in vacuo* gave a dark red crude product, which was recrystallised from ethanol. For the aryloxymethyl-1,4-benzoquinone derivatives **207b-d** full dissolution of the starting materials did not occur at 65°C and small amounts of acetonitrile were added until full dissolution occurred.

2-Phenoxymethyl-1,4-benzoquinone 207a

61%, mp 138°C (Lit.[236] 137-138°C), ^{1}H NMR ($CDCl_3$): δ 4.92 (2H, d, OCH_2, J = 1.7 Hz), 6.74-6.85 (2H, m, 2x=CH), 6.94-7.03 (4H, m, 4x=CH), 7.28-7.36 (2H, m, 2x=CH). ^{13}C NMR ($CDCl_3$): δ 63.13 (OCH_2), 114.72 (2x=CH), 121.85 (=CH), 129.80 (2x=CH), 131.88 (=CH), 136.52 (=CH), 136.81 (=CH), 144.22 (C_{quat}), 157.76 (C_{quat}), 186.86 (C=O), 187.29 (C=O). IR (ATR): ν 1651 (C=O), 1600, 1496, 1247 (C-O) cm^{-1}. MS (ES$^-$) *m/z* (%): 213 ([M-H]$^-$, 35). HRMS (ES$^-$) calcd. for $[C_{13}H_9O_3]^-$: 213.0552, found 213.0561.

2-(4-Methoxyphenoxymethyl)-1,4-benzoquinone 207b

35%, red powder, mp 146.0°C. ^{1}H NMR ($CDCl_3$): δ 3.78 (3H, s, OCH_3), 4.87 (2H, d, CH_2O, J = 1.7 Hz), 6.78-6.98 (7H, m, CH-3,5,6 and 4xCH_{Ar}), ^{13}C NMR ($CDCl_3$): δ 55.78 (OCH_3), 63.91 (OCH_2), 114.90 (2xCH_{Ar}), 115.74 (2xCH_{Ar}), 131.82 (=CH), 136.49 (=CH), 136.77 (=CH), 144.43 (C_{quat}), 151.94 (C_{quat}), 154.58 (C_{quat}), 186.88 (C=O), 187.30 (C=O). IR (ATR): ν 1646, 1231 cm^{-1}. MS (ES$^-$) *m/z* (%): 244 ([M]$^-$, 100). HRMS (ES$^-$) calcd. for $[C_{14}H_{11}O_4]^-$: 243.0657, found 243.0664.

2-(4-Fluorophenoxymethyl)-1,4-benzoquinone 207c

34%, brown needles, mp 158.9°C. ^{1}H NMR ($CDCl_3$): δ 4.91 (2H, d, CH_2O, J = 1.7 Hz), 6.74-7.23 (7H, m, CH-3,5,6 and 4xCH_{Ar}), ^{13}C NMR ($CDCl_3$): δ 63.85 (OCH_2), 115.83 (2xCH_{Ar}, J_{CF} = 8.1 Hz), 116.21 (2xCH_{Ar}, J_{CF} = 23.1 Hz), 131.86 (=CH), 136.49 (=CH), 136.83 (=CH), 144.00 (C_{quat}), 153.91 (C_{quat}), 157.85 (C_{quat}, J_{CF} = 240.0 Hz), 186.75 (C=O), 187.21 (C=O). ^{19}F NMR ($CDCl_3$): δ -122.37- -122.46 (1F, m). IR (ATR): ν 1649, 1506, 1219 cm^{-1}. MS (ES$^-$) *m/z* (%): 231 ([M-H]$^-$, 100). HRMS (ES$^-$) calcd. for $[C_{13}H_8FO_3]^-$: 231.0458, found 231.0467.

2-(4-Chlorophenoxymethyl)-1,4-benzoquinone 207d

52%, yellow needles, mp 155.8°C. ^{1}H NMR ($CDCl_3$): δ 4.89 (2H, dd, CH_2O, J = 1.1 and 2.5 Hz), 6.77-6.95 and 7.25-7.30 (7H, m, CH-3,5,6 and 4xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 63.48 (OCH_2), 116.02 (2xCH_{Ar}), 126.81 (C_{quat}), 129.70 (2xCH_{Ar}), 131.86 (=CH), 136.48 (=CH), 136.83 (=CH), 143.73 (C_{quat}), 156.37 (C_{quat}), 186.68 (C=O), 187.12 (C=O). IR (ATR): ν 1648, 1626, 1491, 1249 cm^{-1}. MS (ES^-) *m/z* (%): 247 and 249 ([M-H]$^-$, 100 and 32). HRMS (ES^-) calcd. for $[C_{13}H_8O_3]^-$: 247.0162, found 247.0172.

5.13.4 Synthesis of 2'*H*,3*H*-spiro[benzofuran-3,2'-benzoquinones] 419

A solution of 2-aryloxymethyl-1,4-benzoquinones **207** (1.5 mmol) and palladium(II) acetate (1.5 mmol, 0.37 g) in acetic acid (30 mL) was heated under reflux for 14 h. The reaction mixture was poured in water and extracted with dichloromethane (3x10 mL). The combined organic extracts were washed with water and with a saturated solution of sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Flash chromatography on silica gel or preparative TLC with ethyl acetate / hexane (1:4) yielded 2'*H*,3*H*-spiro[benzofuran-3,2'-benzoquinones] **419**. Upon (LC)-MS analysis most spiroquinones were found to give very poor mass spectrometric ionisations.

2*H*,3'*H*-Spiro[benzofuran-3,2'-benzene]-1',4'-dione 419a

7%, pale white crystals, mp 114.5°C. ^{1}H NMR ($CDCl_3$): δ 3.09 (1H, d, J_{ab} = 16.5 Hz, C$\underline{H}_a$H$_b$-C=O), 3.14 (1H, d, J_{ab} = 16.5 Hz, CH$_a$$\underline{H}_b$-C=O), 4.21 (1H, d, J = 9.9 Hz, C$\underline{H}_a$H$_b$O), 5.24 (1H, d, J = 9.9 Hz, CH$_a$$\underline{H}_b$O), 6.81 (2H, m, 2x$CH_{Ar}$), 6.94 (2H, s, 2x =CH), 7.00-7.05 (1H, m, CH_{Ar}), 7.18-7.88 (1H, m CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.24 ($\underline{C}H_2$-C=O), 58.01 (C_{spiro}), 77.46 (CH_2O), 111.12 (CH_{Ar}), 121.07 (CH_{Ar}), 123.54 (CH_{Ar}), 127.04 (C_{quat}), 130.55 (CH_{Ar}), 141.19 (=CH), 141.73 (=CH), 159.82 (C_{quat}), 194.94 (C=O), 195.55 (C=O). IR (ATR): ν 1682, 1478 cm^{-1}. MS no ionisation observed. HRMS (ES^+) calcd. for $[C_{13}H_{11}O_3]^+$: 215.0708, found 215.0704.

2*H*,3'*H*-Spiro[5-methoxybenzofuran-3,2'-benzene]-1',4'-dione 419b

12%, yellow crystals, mp 129.7°C. ^{1}H NMR ($CDCl_3$): δ 3.08 (1H, d, J_{ab} = 16.5 Hz, C$\underline{H}_a$H$_b$-C=O), 3.15 (1H, d, J_{ab} = 16.5 Hz, CH$_a$$\underline{H}_b$-C=O), 3.71 (3H, s, OCH_3), 4.20 (1H, d, J = 9.1 Hz, C$\underline{H}_a$H$_b$O), 5.19 (1H, d, J = 9.1 Hz, CH$_a$$\underline{H}_b$O), 6.57-6.63 (1H, m, CH_{Ar}), 6.73-6.80 (2H, m, 2xCH_{Ar}), 6.95 (2H, br s, 2x=CH). ^{13}C NMR ($CDCl_3$): δ 48.09 ($\underline{C}H_2$-C=O), 56.15 (OCH_3), 58.41 (C_{spiro}), 77.86 (CH_2O), 110.11 (CH_{Ar}), 111.07 (CH_{Ar}), 115.15 (CH_{Ar}), 127.91 (C_{quat}), 141.24 (=CH), 141.73 (=CH), 153.88 (C_{quat}), 154.28 (C_{quat}), 195.03 (C=O), 195.43 (C=O). IR (ATR): ν 1678, 1482, 1470 cm^{-1}. MS (ES^-) *m/z* (%): 243 ([M-H]$^-$, 100). HRMS (ES^-) calcd. for $[C_{14}H_{12}O_4]^-$: 244.0741, found 244.0717.

2*H*,3'*H*-Spiro[5-fluorobenzofuran-3,2'-benzene]-1',4'-dione 419c

20%, yellow viscous oil. ^{1}H NMR ($CDCl_3$): δ 3.10 (1H, d, J_{ab} = 16.5 Hz, C$\underline{H}_a$H$_b$-C=O), 3.15 (1H, d, J_{ab} = 16.5 Hz, CH$_a$$\underline{H}_b$-C=O), 4.26 (1H, d, J = 9.4 Hz, C$\underline{H}_a$H$_b$O), 5.22 (1H, d, J = 9.4 Hz, CH$_a$$\underline{H}_b$O),

6.71-6.95 (3H, m, 3xCH_{Ar}), 6.96 (2H, s, 2x =CH). ^{13}C NMR ($CDCl_3$): δ 48.07 ($\underline{C}H_2$-C=O), 58.32 (C_{spiro}), 78.20 (CH_2O), 110.81 (J_{CF} = 25.4 Hz, CH_{Ar}), 111.46 (J_{CF} = 8.1 Hz, CH_{Ar}), 117.03 (J_{CF} = 24.2 Hz, CH_{Ar}), 128.02 (J_{CF} = 8.1 Hz, C_{quat}), 141.07 (=CH), 141.85 (=CH), 150.92 (C_{quat}), 157.29 (J_{CF} = 238.8 Hz, C_{quat}), 194.56 (C=O), 195.03 (C=O). ^{19}F NMR ($CDCl_3$): -122.82- -122.89 (1F, m). IR (ATR): ν 1684, 1482 cm^{-1}. MS (ES^-) *m/z* (%): 231 ($M-H^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{10}FO_3]^+$: 233.0609, found 233.0614.

2*H*,3'*H*-Spiro[5-chlorobenzofuran-3,2'-benzene]-1',4'-dione 419d

19%, yellow crystals, mp 129.7°C. ^{1}H NMR ($CDCl_3$): δ 3.09 (1H, d, J_{ab} = 16.5 Hz, C$\underline{H}_a$H$_b$-C=O), 3.15 (1H, d, J_{ab} = 16.5 Hz, CH$_a\underline{H}_b$-C=O), 4.23 (1H, d, J = 9.9 Hz, C$\underline{H}_a$H$_b$O), 5.23 (1H, d, J = 9.9 Hz, CH$_a\underline{H}_b$O), 6.79 (1H, d, J = 8.3 Hz, CH_{Ar}), 6.96 (3H, br s, 2x =CH and CH_{Ar}), 7.17 (1H, dd, J = 2.2 and 8.3 Hz, CH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 48.03 ($\underline{C}H_2$-C=O), 58.04 (C_{spiro}), 78.18 (CH_2O), 112.09 (CH_{Ar}), 123.70 (CH_{Ar}), 128.79 (C_{quat}), 125.79 (C_{quat}), 130.55 (CH_{Ar}), 141.04 (=CH), 141.91 (=CH), 158.54 (C_{quat}), 194.39 (C=O), 194.92 (C=O). IR (ATR): ν 1686, 1474 cm^{-1}. MS (ES^-) *m/z* (%): 247/249 ([M-H]$^-$, 100/35). HRMS (ES^-) calcd. for $[C_{13}H_8ClO_3]^-$: 247.0168, found 247.0161.

5.13.5 Synthesis of 3'*H*-spiro[chroman-3,2'-naphthalene]-1',4'-dione 422

To a 10 mL vial were added 3,5-dichloropyridine (0.15 mmol, 22 mg), trifluoroacetic acid (0.05 mmol, 6 mg), palladium(II) acetate (0.10 mmol, 22 mg), 2-(2-phenoxyethyl)-1,4-naphthoquinone **421** (1.0 mmol, 278 mg) and acetic acid (4 mL). The vial was sealed with a septum and stirred at 110°C for 4 days. The reaction mixture was then diluted with chloroform, washed water (10 mL) and saturated sodium hydrogen carbonate (2x10 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. Flash chromatography on silica gel with ethyl acetate/hexane (1:9) yielded 3'*H*-spiro[chroman-3,2'-naphthalene]-1',4'-dione **422**.

36%, white needles, mp 94.2-94.8°C. ^{1}H NMR ($CDCl_3$): δ 2.12 (1H, ddd, J = 14.2, 7.6 and 5.0 Hz, C$\underline{H}_a$CH$_b$CH$_2$O), 2.30 (1H, ddd, J = 14.2, 5.3 and 3.3 Hz, CH$_a$C$\underline{H}_b$CH$_2$O), 3.13 (1H, d, J = 16.2 Hz, C$\underline{H}_a$H$_b$-C=O), 3.64 (1H, d, J = 16.2 Hz, C$\underline{H}_a$H$_b$-C=O), 4.11-4.25 (2H, m, CH_2O), 6.88-6.94 (2H, m, 2xCH_{Ar}), 7.04-7.08 (1H, m, CH_{Ar}), 7.17-7.26 (1H, m, CH_{Ar}), 7.78-7.81 (2H, m, 2xCH_{Ar}), 8.05-8.15 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 33.10 ($\underline{C}H_2CH_2O$), 49.34 (C_{spiro}), 51.25 ($\underline{C}H_2$-C=O), 61.81 (CH_2O), 117.84 (CH_{Ar}), 120.91 (CH_{Ar}), 122.28 (C_{quat}), 126.25 (CH_{Ar}), 128.28 (CH_{Ar}), 128.34 (CH_{Ar}), 129.02 (CH_{Ar}), 133.33 (C_{quat}), 134.43 (CH_{Ar}), 134.82 (CH_{Ar}), 154.91 (C_{quat}), 195.18 (C=O), 198.33 (C=O), one trisubstituted olefinic carbon is not observed. IR (ATR): ν 1691, 1595, 1492 cm^{-1}. MS (ES^+) *m/z* (%): 278 ($[M+H]^+$, 3), 86 (39), 84 (64), 49 (100). HRMS (ES^+) calcd. for $[C_{18}H_{15}O_3]^+$: 279.1021, found 279.1014.

5.13.6 Synthesis of 2-(4-hydroxybenzyl)-1,4-quinones 413 and 441a

A solution of 2-phenoxymethyl-1,4-quinones (1.5 mmol) in trifluoroacetic acid (6 mL) was stirred for 15 h (for 2-phenoxymethyl-1,4-quinones **27a, 27b, 27e** and **207a**) or three days (for 3-methyl-2-phenoxymethyl-1,4-naphthoquinone **433**) at room temperature. Subsequently, trifluoroacetic acid was evaporated *in vacuo* and the residue was dissolved in chloroform (20 mL). This solution was washed with water, saturated aqueous $NaHCO_3$ and brine (3x10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* gave the crude product, which was purified further by means of column chromatography on silica gel (petroleum ether/ethyl acetate). 2-(4-Hydroxybenzyl)-1,4-benzoquinone **441a** was found to be prone to polymerisation.

2-(4-Hydroxybenzyl)-1,4-naphthoquinone 413a

74%, brown crystals, mp 159.6-160.2°C. ^{1}H NMR ($CDCl_3$): δ 3.83 (2H, s, CH_2Ar), 5.08 (1H, br s, ArOH), 6.61 (1H, s, CH-3), 6.80 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.11 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.70-7.76 (2H, m, 2xCH_{Ar}), 8.02-8.13 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 35.02 (CH_2Ar), 115.80 (2xCH_{Ar}), 126.20 (CH_{Ar}), 126.75 (CH_{Ar}), 128.84 (C_{quat}), 130.77 (2xCH_{Ar}), 132.19 (C_{quat}), 132.29 (C_{quat}), 133.83 (CH_{Ar}), 133.88 (CH_{Ar}), 135.56 (CH-3), 151.30 (C_{quat}), 154.64 (C_{quat}), 185.23 (C=O), 185.38 (C=O). IR (ATR): ν 3395, 1650, 1510 cm^{-1}. MS (ES$^+$) *m/z* (%): 265 ([M+H]$^+$, 100). HRMS (ES$^-$) calcd. for $[C_{17}H_{11}O_3]^-$: 263.0708, found 263.0704.

2-(4-Hydroxy-3-methylbenzyl)-1,4-naphthoquinone 413b

73%, green solid, mp 151.0°C. ^{1}H NMR ($CDCl_3$): δ 2.23 (3H, s, CH_3), 3.79 (2H, s, CH_2Ar), 5.10 (1H, br s, ArOH), 6.61 (1H, s, CH-3), 6.73 (1H, d, J = 7.9 Hz, CH-5' or CH-6'), 6.94 (1H, d, J = 7.9 Hz, CH-5' or -6'), 6.98 (1H, s, CH-2'), 7.71-7.74 (2H, m, CH-6 and CH-7), 8.02-8.11 (2H, m, CH-5 and -8). ^{13}C NMR ($CDCl_3$): δ 15.90 (CH_3), 35.00 (CH_2Ar), 115.34 (CH-5' or CH-6'), 124.41 (C_{quat}), 126.20 and 126.77 (CH-5 and CH-8), 128.09 (CH-5' or CH-6'), 128.61 (C_{quat}), 132.11 (CH-2'), 132.17 (C_{quat}), 132.31 (C_{quat}) 133.85 and 133.88 (CH-6 and CH-7), 135.56 (CH-3), 151.51 (C_{quat}), 153.00 (C_{quat}), 185.30 (C=O), 185.55 (C=O). IR (ATR): ν 3380 (OH), 1652 (C=O), 1595, 1336, 1267 cm^{-1}. MS (ES$^+$) *m/z* (%): 279 ([M+H]$^+$, 100). HRMS (ES$^+$) calcd. for $[C_{18}H_{13}O_3]^+$: 277.0865, found 277.0862.

2-(4-Hydroxy-3-methoxybenzyl)-1,4-naphthoquinone 413c

42%, yellow crystals, mp 169.0°C. ^{1}H NMR ($CDCl_3$): δ 3.83 (2H, s, CH_2Ar), 3.88 (3H, s, OCH_3), 5.55 (1H, br s, ArOH), 6.61 (1H, s, CH-3), 6.74-6.75 (2H, m, 2xCH_{Ar}), 6.88 (1H, d, J = 8.8 Hz, CH-5' or -6'), 7.72-7.75 (2H, m, CH-6 and CH-7), 8.03-8.13 (2H, m, CH-5 and -8). ^{13}C NMR ($CDCl_3$): δ 35.54 (CH_2Ar), 56.01 (OCH_3), 111.92 (CH_{Ar}), 114.75 (CH_{Ar}), 122.37 (CH_{Ar}), 126.20 and 126.75 (CH-5 and CH-8), 128.44 (C_{quat}), 132.19 (C_{quat}), 132.28 (C_{quat}) 133.82 and 133.88 (CH-6 and CH-7), 135.56 (CH-3), 144.71 (C_{quat}), 146.80 (C_{quat}), 151.27 (C_{quat}), 185.26 (C=O), 185.36 (C=O). IR (ATR): ν 3355 (OH),

1652, 1590, 1517, 1274, 1234 cm^{-1}. MS (ES^+) *m/z* (%): 295 ($[M+H]^+$, 100). HRMS (ES^-) calcd. for $[C_{18}H_{13}O_4]^-$: 293.0814, found 293.0809.

2-(4-Hydroxybenzyl)-3-methyl-1,4-naphthoquinone 413d

60%, orange crystals, mp 50.5°C. ^1H NMR ($CDCl_3$): δ 2.25 (3H, s, CH_3), 3.94 (2H, s, CH_2Ar), 5.43 (1H, br s, ArOH), 6.73 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.09 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.66-7.72 (2H, m, 2xCH_{Ar}), 8.04-8.10 (2H, m, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 13.34 (CH_3), 31.66 (CH_2Ar), 115.62 (2xCH_{Ar}), 126.37 (CH_{Ar}), 126.55 (CH_{Ar}), 129.86 (2xCH_{Ar}), 130.03 (C_{quat}), 132.11 (C_{quat}), 132.17 (C_{quat}), 133.61 (CH_{Ar}), 133.64 (CH_{Ar}), 144.25 (C_{quat}), 145.74 (C_{quat}), 154.35 (C_{quat}), 184.95 (C=O), 185.67 (C=O). IR (ATR): *v* 3481, 1653, 1514 cm^{-1}. MS (ES^+) *m/z* (%): 279 ($[M+H]^+$, 65). HRMS (ES^-) calcd. for $[C_{18}H_{13}O_3]^-$: 277.0870, found 277.0825.

2-(4-Hydroxybenzyl)-1,4-benzoquinone 441a

64%, red viscous oil. ^1H NMR ($CDCl_3$): δ 3.66 (2H, d, J = 1.4 Hz, CH_2Ar), 6.06 (1H, br s, ArOH), 6.37 (1H, dd, J = 1.6 and 3.9 Hz, CH-3), 6.72-6.79 (2H, m, CH-5 and CH-6), 6.80 (2H, d, J = 8.3 Hz, 2xCH_{Ar}), 7.04 (2H, d, J = 8.3 Hz, 2xCH_{Ar}). ^{13}C NMR ($CDCl_3$): δ 34.50 (CH_2Ar), 115.88 (2xCH_{Ar}), 128.15 (C_{quat}), 130.69 (2xCH_{Ar}), 133.19 (=CH), 136.46 (=CH), 136.86 (=CH), 149.29 (C_{quat}), 154.87 (C_{quat}), 187.58 (C=O), 188.20 (C=O). IR (ATR): *v* 3372, 1651, 1513 cm^{-1}. MS (ES^-) *m/z* (%): 213 ($[M-H]^-$, 100). Due to the instability of this compound, no HRMS or elementary analysis could be performed.

5.13.7 Synthesis of *N*-protected 2-phenylaminomethyl-1,4-naphthoquinones 432

1,4-dimethoxynapthalene-2-carboxaldehyde **279** (1 g, 4.62 mmol) and aniline (426 mg, 4.62 mmol, 1 equiv.) were dissolved in anhydrous methanol (10 mL) and stirred at room temperature for 1 h in a dry flask fitted with a $CaCl_2$ tube. Next, the reaction mixture was cooled to 0°C and $NaBH_4$ (175 mg, 4.62 mmol, 1 equiv.) was added portionwise and the reaction mixture was allowed to warm to room temperature. After 30 minutes, the solvent was evaporated *in vacuo* and the residue dissolved in EtOAc (10 mL) which was washed with brine (2 x 10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded 1.26 g (94%) of pure 1,4-dimethoxy-2-phenylaminomethylnapthalene as a yellow oil which solidified upon standing.

1,4-Dimethoxy-2-phenylaminomethylnapthalene

94%, orange solid, mp 96.5°C. ^1H NMR ($CDCl_3$): δ 3.94 (6H, s, 2xOCH_3), 4.51 (2H, s, CH_2O), 6.71-6.76 (3H, m, 3xCH_{Ar}), 6.82 (1H, s, CH-3), 7.20 (2H, td, J = 2.2 and 6.9 Hz, 2xCH_{Ar}),7.45-7.58 (2H, m, CH-6 and 7), 8.07 (1H, dd, J = 1.1 and 8.3 Hz, CH-5 or 8), 8.23 (1H, dd, J = 1.1 and 8.3 Hz, CH-5

or 8). ^{13}C NMR ($CDCl_3$): δ 43.48 (CH_2N), 55.81 (OCH_3), 62.61 (OCH_3), 104.35 (CH-3), 113.22 ($2XCH_{Ar}$), 117.86 (CH_{Ar}), 122.03 (CH_{Ar}), 122.64 (CH_{Ar}), 125.60 (CH_{Ar}), 126.32 (C_{quat}), 126.92 (CH_{Ar}), 127.35 (C_{quat}), 128.84 (C_{quat}), 129.50 ($2xCH_{Ar}$), 147.38 (C_{quat}), 148.66 (C_{quat}), 152.39 (C_{quat}). IR (ATR): ν 3377 (NH), 1600 (CH_{Ar}), 1505, 1374, 1091 (C-N), 752 cm^{-1}. MS (ES^+) *m/z* (%): 294 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{20}NO_2]^+$: 294.1494, found 294.1484.

1,4-dimethoxy-2-phenylaminomethylnapthalene (635 mg, 2.16 mmol) and Et_3N (0.33 mL, 1.1 equiv.) were dissolved in 4 mL of anhydrous dichloromethane. The mixture was cooled to 0°C and acetyl chloride or benzoyl chloride (1.1 equiv.) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. Next, Et_3NHCl was filtered off and the filtrate was extracted once with brine (5 mL). Purification by column chromatography on silica gel (petroleum ether/ethyl acetate) gave the corresponding *N*-protected 1,4-dimethoxy-2-phenylaminomethylnapthalenes **431a** and **431b**.

***N*-Acetyl-1,4-dimethoxy-2-phenylaminomethylnapthalene 431a**

62%, yellow crystals, mp 80°C. ^{1}H NMR ($CDCl_3$): δ 1.94 (3H, CH_3C=O), 3.44 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 5.18 (2H, s, CH_2O), 6.84 (1H, s, CH-3), 7.0.1-7.06 (2H, m, $2xCH_{Ar}$), 7.20-7.33 (3H, m, $3xCH_{Ar}$), 7.43-7.52 (2H, m, CH-6 and 7), 7.88-7.93 (1H, m, CH-5 or 8), 8.19-8.23 (1H, m, CH-5 or 8). ^{13}C NMR ($CDCl_3$): δ 22.91 ($\underline{C}H_3CO$), 46.65 (CH_2N), 55.78 (OCH_3), 62.23 (OCH_3), 104.55 (CH-3), 122.11 (CH_{Ar}), 122.46 (CH_{Ar}), 125.51 (CH_{Ar}), 125.60 (C_{quat}), 126.35 (C_{quat}), 126.41 (C_{quat}), 126.64 (CH_{Ar}), 128.14 (CH_{Ar}), 128.37 ($2xCH_{Ar}$), 129.65 ($2XCH_{Ar}$), 142.89 (C_{quat}), 147.76 (C_{quat}), 152.13 (C_{quat}), 170.95 (C=O). IR (ATR): ν 1645 (C=O), 1631, 1594 (CH_{Ar}), 1494, 1369, 1228 (C-N), 670 cm^{-1}. MS (ES^+) m/z (%): 336 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{21}H_{22}NO_3]^+$: 336.1600, found 336.1593.

***N*-Benzoyl-1,4-dimethoxy-2-phenylaminomethylnapthalene 431b**

51%, white solid, mp 143.0°C. ^{1}H NMR ($CDCl_3$): δ 3.62 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 5.43 (2H, s, CH_2O), 6.91-7.06 (5H, m, $5xCH_{Ar}$), 7.12-7.22 (4H, m, $4xCH_{Ar}$), 7.36-7.50 (4H, m, $4xCH_{Ar}$), 7.96 (1H, d, *J* = 7.7 Hz, CH-5 or 8), 8.22 (1H, d, *J* = 7.7 Hz, CH-5 or 8). ^{13}C NMR ($CDCl_3$): δ 47.86 (CH_2N), 55.80 (OCH_3), 62.39 (OCH_3), 104.05 (CH-3), 122.14 (CH_{Ar}), 122.51 (CH_{Ar}), 125.59 (CH_{Ar}), 125.86 (C_{quat}), 126.35 (C_{quat}), 126.76 (CH_{Ar}), 126.96 (CH_{Ar}), 127.91 ($2xCH_{Ar}$), 127.97 ($2xCH_{Ar}$), 128.54 (C_{quat}), 128.73 ($2xCH_{Ar}$), 129.10 ($2xCH_{Ar}$), 129.79 (CH_{Ar}), 136.32 (C_{quat}), 143.53 (C_{quat}), 147.59 (C_{quat}), 152.31 (C_{quat}), 171.30 (C=O). IR (ATR): ν 1637 (C=O), 1594, 1366, 1090 (C-O) cm^{-1}. MS (ES^+) m/z (%): 398 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{26}H_{24}NO_3]^+$: 398.1756, found 398.1757.

1,4-dimethoxy-2-phenylaminomethylnapthalene was dissolved in 10 mL of pyridine, cooled to 0°C and mesyl chloride (0.35 mL, 5.67 mmol, 1.3 equiv.) was added dropwise. The reaction was then allowed to warm to room temperature and stirred for one hour. Next, the reaction mixture was poured

in icewater (20 mL) and extracted with EtOAc (3x10 mL). The combined organic fractions where washed with aqueous HCl (2 N, 3 x 10 mL) and brine (10 mL). Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded 1.36 g (84%) of pure 1,4-dimethoxy-*N*-mesyl-2-phenylaminomethylnapthalene **431c**.

1,4-Dimethoxy-*N*-mesyl-2-phenylaminomethylnapthalene 431c

84%, pale white solid, mp 131.5°C. ^{1}H NMR ($CDCl_3$): δ 3.04 (3H, CH_3SO_2), 3.67 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.10 (2H, s, CH_2O), 6.85 (1H, s, CH-3), 7.18-7.34 (3H, m, 3xCH_{Ar}), 7.42-7.52 (2H, m, 5xCH_{Ar}),7.42-7.52 (2H, m, CH-6 and 7), 7.92-7.95 (1H, m, CH-5 or 8), 8.16-8.20 (1H, m, CH-5 or 8). ^{13}C NMR ($CDCl_3$): δ 37.78 (CH_3SO_2), 48.99 (CH_2N), 55.81 (OCH_3), 62.72 (OCH_3), 104.35 (CH-3), 122.09 (CH_{Ar}), 122.57 (CH_{Ar}), 124.14 (C_{quat}), 125.80 (CH_{Ar}), 126.52 (C_{quat}), 126.80 (CH_{Ar}), 128.28 (CH_{Ar}), 128.34 (C_{quat}), 128.86 (2xCH_{Ar}), 129.48 (2xCH_{Ar}), 139.29 (C_{quat}), 147.76 (C_{quat}), 152.11 (C_{quat}). IR (ATR): 1597 (CH_{Ar}), 1338 (S=O), 1154 (S=O), 771 cm^{-1}. MS (ES^+) *m/z* (%): 201 ([M-PhNMs]$^+$, 100). HRMS (ES^+) calcd. for $[C_{13}H_{13}O_2]^+$: 201.0916, found 201.0915.

To a stirred solution of a *N*-protected 1,4-dimethoxy-2-phenylaminomethylnapthalene **431** (2 mmol) in CH_3CN (8 mL) was added a solution of cerium ammonium nitrate (2.74 g, 5 mmol, 2.5 equiv.) in water (8 mL). The reaction was stirred for 10 minutes at room temperature. Next, the reaction mixture was poured out in 20 mL of CH_2Cl_2 and washed two times with brine. Drying over $MgSO_4$ and evaporation of the solvent *in vacuo* yielded pure *N*-protected-2-phenylaminomethyl-1,4-naphthoquinones **432**.

***N*-Acetyl-2-phenylaminomethyl-1,4-naphthoquinone 432a**

90%, amber solid, mp 164.0°C. ^{1}H NMR ($CDCl_3$): δ 2.00 (3H, CH_3CO), 4.89 (2H, d, J = 1.7 Hz, CH_2O), 6.92 (1H, t, J = 1.7 Hz, CH-3), 7.24-7.51 (5H, m, 5xCH_{Ar}), 7.70-7.77 (2H, m, CH-6 and 7), 8.03-8.10 (2H, m, CH-5 and 8). ^{13}C NMR ($CDCl_3$): δ 22.59 (CH_3C=O), 48.61 (CH_2N), 126.22 (CH_{Ar}), 126.43 (CH_{Ar}), 127.61 (2xCH_{Ar}), 128.37 (CH_{Ar}), 130.03 (2xCH_{Ar}), 131.96 (C_{quat}), 132.05 (C_{quat}), 133.88 (CH_{Ar}), 133.93 (CH_{Ar}), 134.02 (CH_{Ar}), 143.07 (C_{quat}), 145.76 (C_{quat}), 171.12 (NC=O), 184.74 (2xC=O). IR (ATR): ν 1658 (C=O), 1299, 782 cm^{-1}. MS (ES^+) m/z (%): 306 ([M+H]$^+$, 100). HRMS (ES^+) calcd. for $[C_{19}H_{16}NO_3]^+$: 306.1130, found 306.1123.

***N*-Benzoyl-2-phenylaminomethyl-1,4-naphthoquinone 432b**

Quantitative yield, yellow solid, mp 180.5°C. ^{1}H NMR ($CDCl_3$): δ 5.04 (2H, d, J = 1.7 Hz, CH_2O), 6.90 (1H, t, J = 1.7 Hz, CH-3), 6.99-7.22 (9H, m, 9xCH_{Ar}), 7.27-7.30 (2H, m, 2xCH_{Ar}), 7.59-7.65 (2H, m, CH-6 and 7), 7.92-8.01 (2H, m, CH-5 and 8). ^{13}C NMR ($CDCl_3$): δ 49.40 (CH_2N), 126.32 (CH_{Ar}), 126.52 (CH_{Ar}), 127.07 (2xCH_{Ar}), 128.02 (2xCH_{Ar}), 129.07 (2xCH_{Ar}), 129.48 (2xCH_{Ar}), 130.37 (CH_{Ar}), 132.06 (C_{quat}), 132.14 (C_{quat}), 133.91 (CH_{Ar}), 133.96 (CH_{Ar}), 134.08 (CH_{Ar}), 143.95 (C_{quat}), 143.58

(C_{quat}), 145.88 (C_{quat}), 170.69 (NC=O), 184.75 (C=O), 184.88 (C=O). IR (ATR): ν 1644 (C=O), 1632 (C=O), 1365, 1299, 700 cm^{-1}. MS (ES^+) m/z (%): 368 ($M+H^+$, 100). HRMS (ES^+) calcd. for $[C_{24}H_{18}NO_3]^+$: 368.1287, found 368.1289.

***N*-Mesyl-2-phenylaminomethyl-1,4-naphthoquinone 432c**

66%, yellow solid, mp 220.5°C. ^1H NMR ($CDCl_3$): δ 3.00 (3H, CH_3SO_2), 4.92 (2H, d, *J* = 1.7 Hz, CH_2O), 7.14 (1H, t, *J* = 1.7 Hz, CH-3), 7.30-7.35 (2H, m, 2xCH_{Ar}), 7.38-7.47 (4H, m, 4xCH_{Ar}), 7.69-7.77 (2H, m, CH-6 and 7), 8.01-8.08 (2H, m, CH-5 and 8). ^{13}C NMR ($CDCl_3$): δ 37.28 (CH_3SO_2), 49.36 (CH_2N), 126.47 (CH_{Ar}), 128.02 (2xCH_{Ar}), 128.51 (CH_{Ar}), 129.94 (2xCH_{Ar}), 131.96 (C_{quat}), 132.08 (C_{quat}), 133.93 (CH_{Ar}), 134.25 (CH_{Ar}), 135.51 (CH_{Ar}), 139.35 (C_{quat}), 145.62 (C_{quat}), 184.54 (C=O), 184.89 (C=O). IR (ATR): ν 1659 (C=O), 1595 (CH_{Ar}), 1338 (S=O), 1306, 1160 (S=O), 1093 (C-N), 774 cm^{-1}. MS (ES^+) m/z (%): 342 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{18}H_{16}NO_4S]^+$: 342.0800, found 342.0802.

5.13.8 Synthesis of 2-phenoxymethylchromen-4-one 436

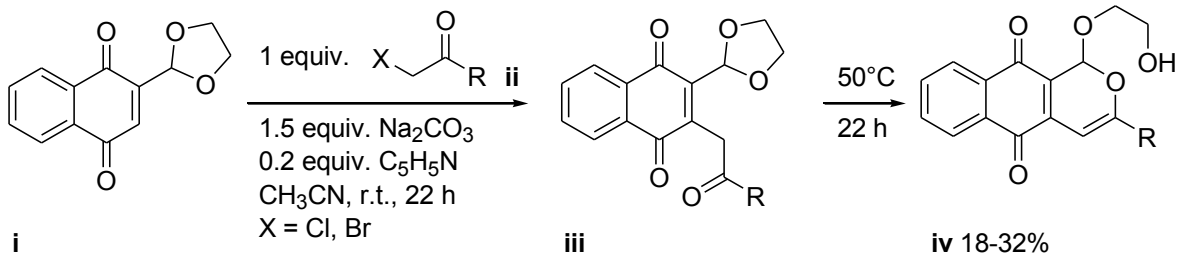
2-Phenoxymethylchromen-4-one **436** was synthesised following a literature procedure describing the synthesis of 2-(4-chlorophenoxy)methylchromen-4-one.[264]

56%, white crystals, mp 96.5°C. ^1H NMR ($CDCl_3$): *δ* 4.98 (2H, d, *J* = 1.2 Hz, CH_2O), 6.54 (1H, s, CH-3), 6.96-7.05 (3H, m, 3xCH_{Ar}), 7.29-7.36 (2H, m, 2xCH_{Ar}), 7.38-7.48 (2H, m, 2xCH_{Ar}), 7.65-7.68 (1H, m, CH_{Ar}), 8.19 (1H, dd, *J* = 1.4 and 8.0 Hz). ^{13}C NMR ($CDCl_3$): *δ* 65.74 (CH_2O), 109.63 (CH-3), 114.75 (2xCH_{Ar}), 118.02 (CH_{Ar}), 122.00 (2xCH_{Ar}), 123.97 (C_{quat}), 125.28 (CH_{Ar}), 125.62 (CH_{Ar}), 129.74 (2xCH_{Ar}), 133.86 (CH_{Ar}), 156.10 (C_{quat}), 157.59 (C_{quat}), 163.88 (C_{quat}), 177.68 (C=O). IR (ATR): *ν* 1647 (C=O), 1466, 1355, 1243 (C-O), 1220 (C-O), 751 cm^{-1}. MS (ES^+) *m/z* (%): 253 ($[M+H]^+$, 100). HRMS (ES^+) calcd. for $[C_{16}H_{13}O_3]^+$: 253.0865, found 253.0859.

6 Summary

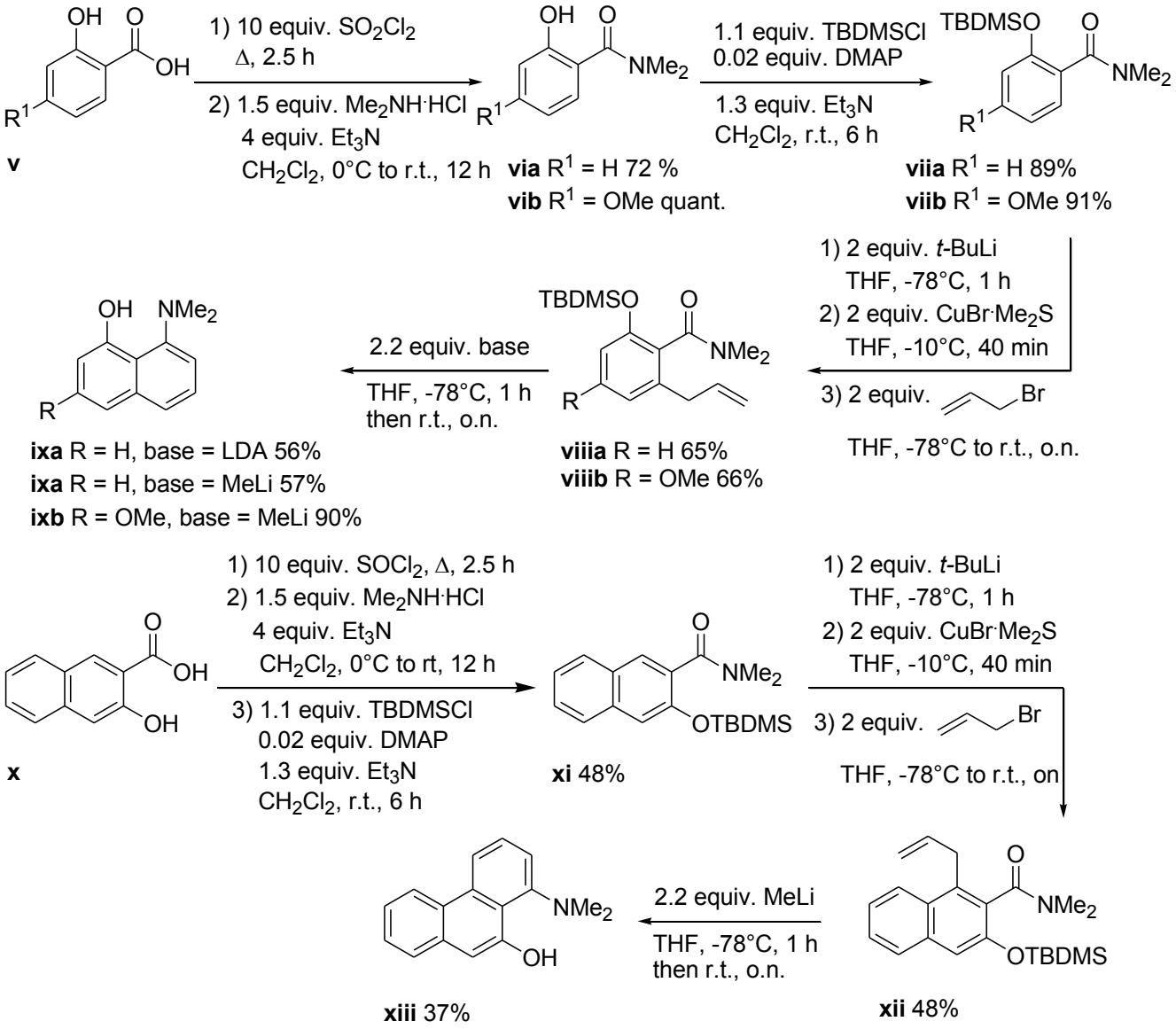
The present doctoral thesis concerns the chemistry of heterocyclic annelated quinones. More specifically, pyranonaphthoquinones, spironaphthoquinones and a wide range of benzophenanthridinedione derivatives were prepared. These benzophenanthridinedione series were synthesised as a part of a screening program against *Mycobacterium tuberculosis* in cooperation with the Scientific Institute of Public Health (Uccle, Brussels).

(1) Catalytic reaction conditions were developed in order to prepare 1-(2-hydroxyethoxy)pyranonaphthoquinones **iv** starting from 2-(1,3-dioxolan-2-yl)-1,4-naphthoquinone **i**. Even though these conditions performed equally well as the corresponding stoichiometric version, there is no need to prepare the corresponding pyridinium salts and only a catalytic amount of pyridine is needed.



It was envisaged to apply this methodology to the synthesis of various natural products such as the pyranonaphthoquinones ascomycone A and B, 1-hydroxydehydroherbarin and the mansouramycins, which are isoquinolinediones. Unfortunately, none could be prepared as it was not possible to synthesise the appropriate starting material for both classes.

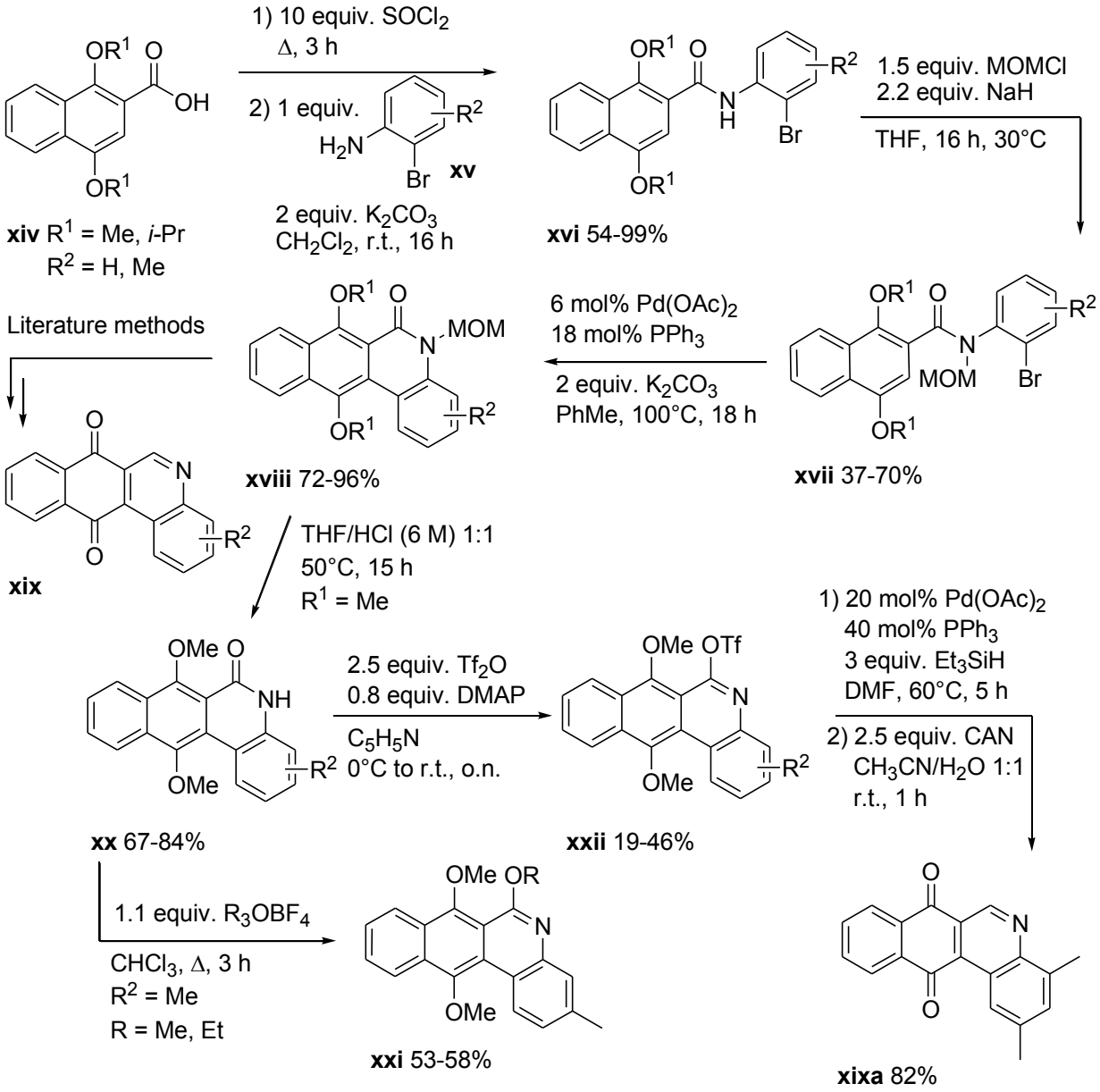
(2) An unexpected synthesis of aminonaphtholes was found. This reaction proceeded via a MeLi- or LDA-mediated cyclisation of a 2-allyl-6-*tert*-butyldimethylsilanyloxy-*N*,*N*-dimethylbenzamide derivative **viii** or **xii**. The reaction was investigated in depth and various protective group (TBDMS, TIPS, TBDPS) and amide (dimethyl, diethyl, pyrrolidinyl, morpholinyl) combinations were evaluated. It appeared that the reaction only occurred when the amide is a *N*,*N*-dimethylamide and the protective group a TBDMS group, as all other combinations resulted in complex mixtures. When these allyl-(*tert*-butyldimethylsilanyloxy)-*N*,*N*-dimethylbenzamides were reacted with MeLi or LDA, various aminonaphtholes **ix** and one aminophenanthrenol **xiii** were prepared in 37-90% yield.



It was attempted to synthesise fluorinated pyranonaphthoquinones by means of a gold catalysed 6-endo-dig cyclisation but no favourable results were obtained.

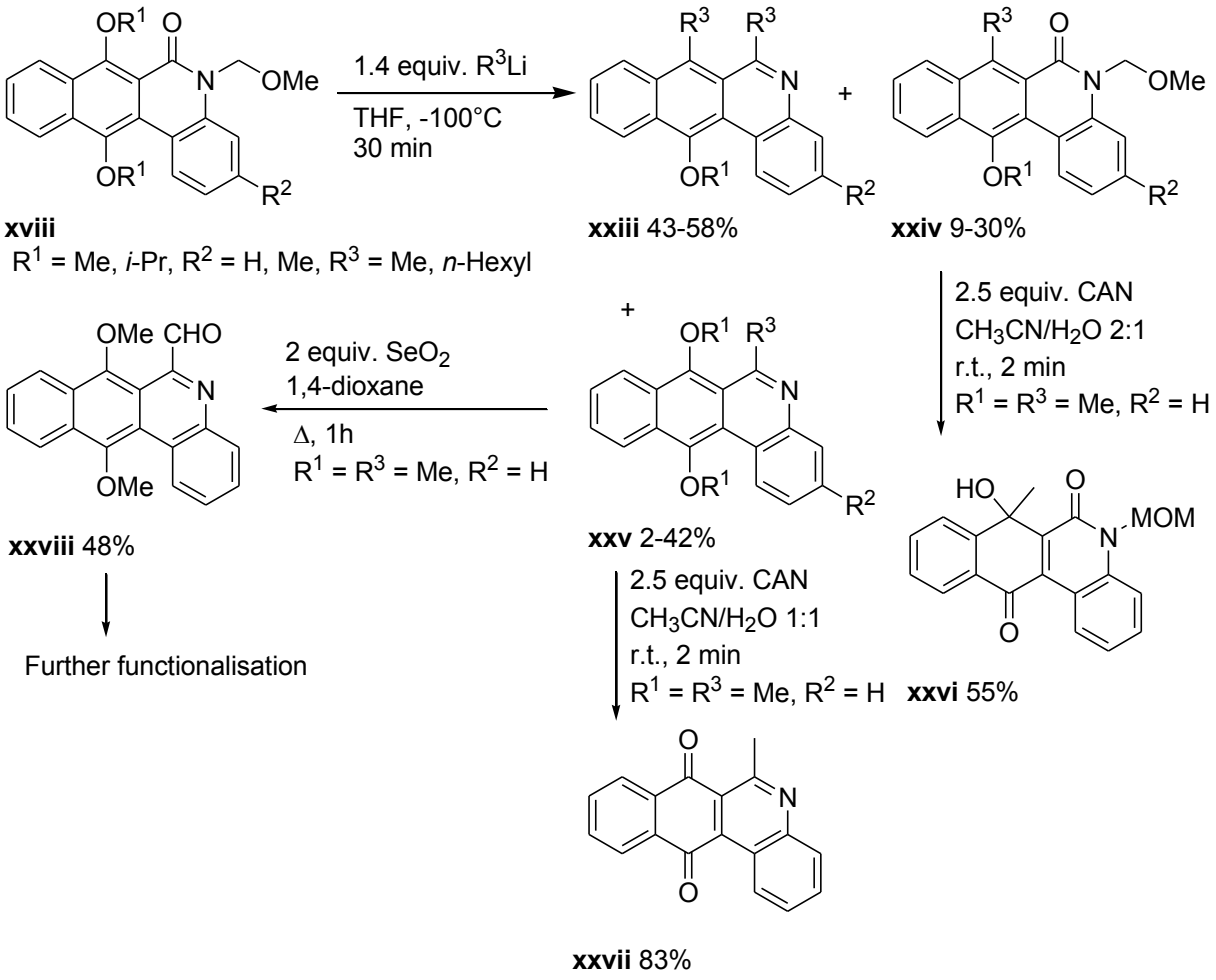
(3) Various benzo[*j*]phenanthridinedione analogues were prepared as a part of our screening program against *Mycobacterium tuberculosis* and related mycobacteria such as *M. bovis*, *M. avium* subspecies and *M. ulcerans*. Initially, an alternative synthesis was developed towards the known benzo[*j*]phenanthridinediones **xix** that allows more flexibility and could be deployed in the synthesis of our library of antimycobacterial compounds. Thus, amides **xvi** were prepared in good yields starting from dialkoxynaphthalene carboxylic acids **xiv** and bromoanilines **xv**. The amide nitrogen was MOM-protected and subsequent cyclisation by means of a palladium-catalysed intramolecular arylation afforded 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **xviii**. These key intermediates **xviii** can be converted into the previously prepared benzo[*j*]phenanthridinediones **xix** by means of literature procedures. 7,12-Dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones

xviii were deprotected by means of HCl and further converted towards alkoxypyridines **xxi** and triflates **xxii**. One triflate was defunctionalised by means of Pd(0)-catalysis and oxidised to 2,4-dimethylbenzo[*j*]phenanthridine-7,12-dione **xixa**, which was not prepared previously. Analogous to anticancer drugs such as mitoxantrone and pixantrone, it was attempted to synthesise 6-aminoalkyl-aminobenzo[*j*]phenanthridine-7,12-diones. However, no adequate conditions could be found when ethylenediamine was reacted with 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **xviii**, 7,12-dimethoxy-5*H*-benzo[*j*]phenanthridin-6-ones **xx** or 6-alkoxy-7,12-dimethoxy-3-methylbenzo[*j*]phenanthridines **xxi**.

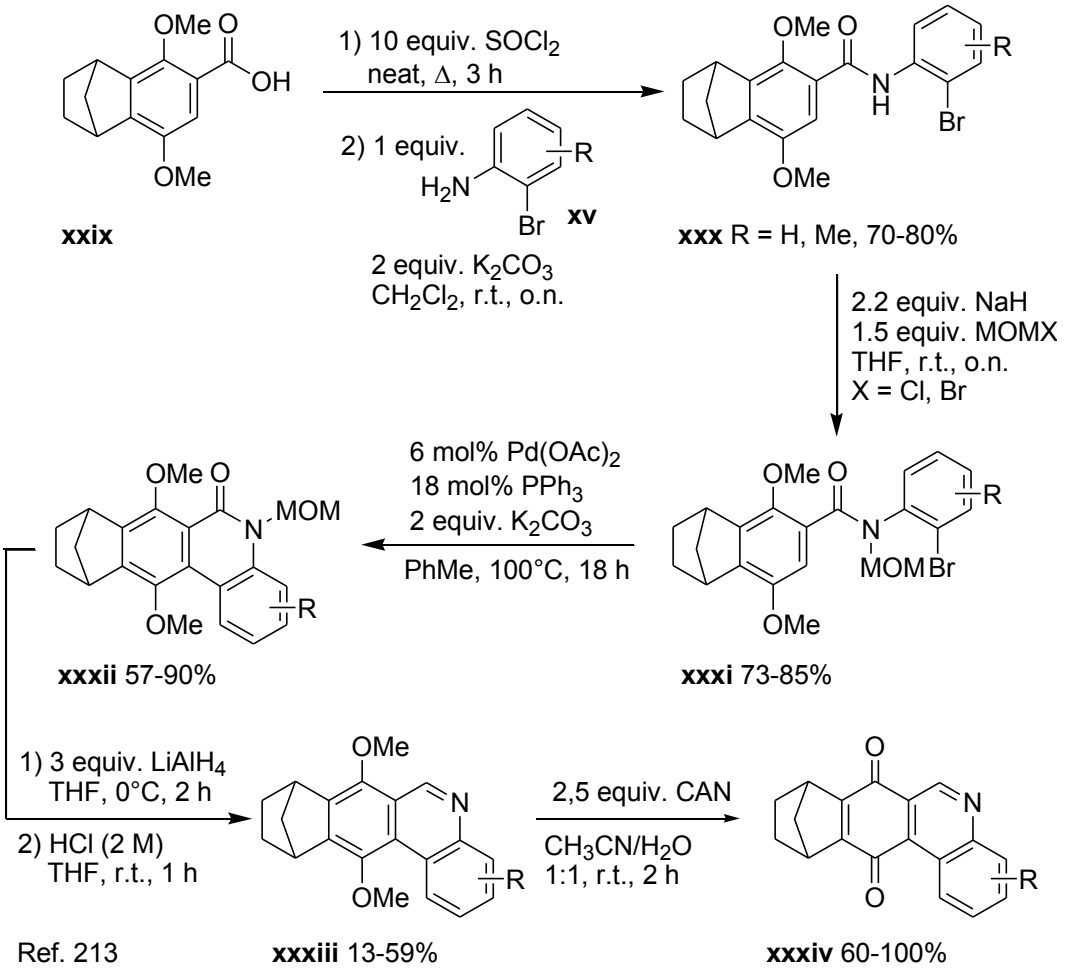


When 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]phenanthridin-6-ones **xviii** were reacted with alkyllithium reagents at low temperature, an interesting reactivity was observed. Instead of giving exclusively the desired 1,2-adducts **xxv**, a mixture of 1,2-adducts **xxv**; 1,4-adducts **xxiv** and double

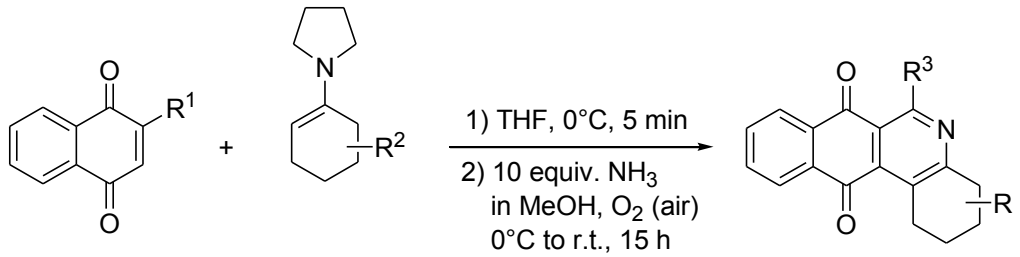
addition products **xxiii** was obtained. The proportion of 1,4-addition and double addition increased as the sterical hindrance of the reactants increased. The MeLi adducts were oxidised with CAN towards quinone **xxvii** and quinoid compound **xxvi**. The benzylic methyl of 7,12-dimethoxy-6-methylbenzo[*j*]phenanthridine **xxv** was oxidised with SeO_2 towards aldehyde **xxviii**, which could serve as an attachment point for further functionalisation.



The abovementioned methodology was applied to the synthesis of 8,9,10,11-tetrahydro-8,11-methano-benzo[*j*]phenanthridine-7,12-diones **xxxiv**. Lactam **xxxii** was prepared as described above, reduced by means of $LiAlH_4$ and the resulting hemi-aminal hydrolysed to the corresponding pyridine **xxxiii** with aqueous HCl followed by oxidative demethylation with CAN resulting in the target 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **xxxiv** in good yields. This synthesis was the subject of a master thesis.[213]



Next, the synthesis of 1,2,3,4-tetrahydrobenzophenanthridinediones **xxxvii** was envisaged. These compounds were prepared by means of the addition of enamine **xxxvi** across 2-(1,3-dioxolan-2-yl)-1,4 naphthoquinones **i** or 2-acetyl-1,4-naphthoquinone **xxxv** followed by ammonia-mediated cyclisation of the intermediate benzonaphthofurans. Despite extensive optimisation, no reaction conditions could be found that gave good yields.



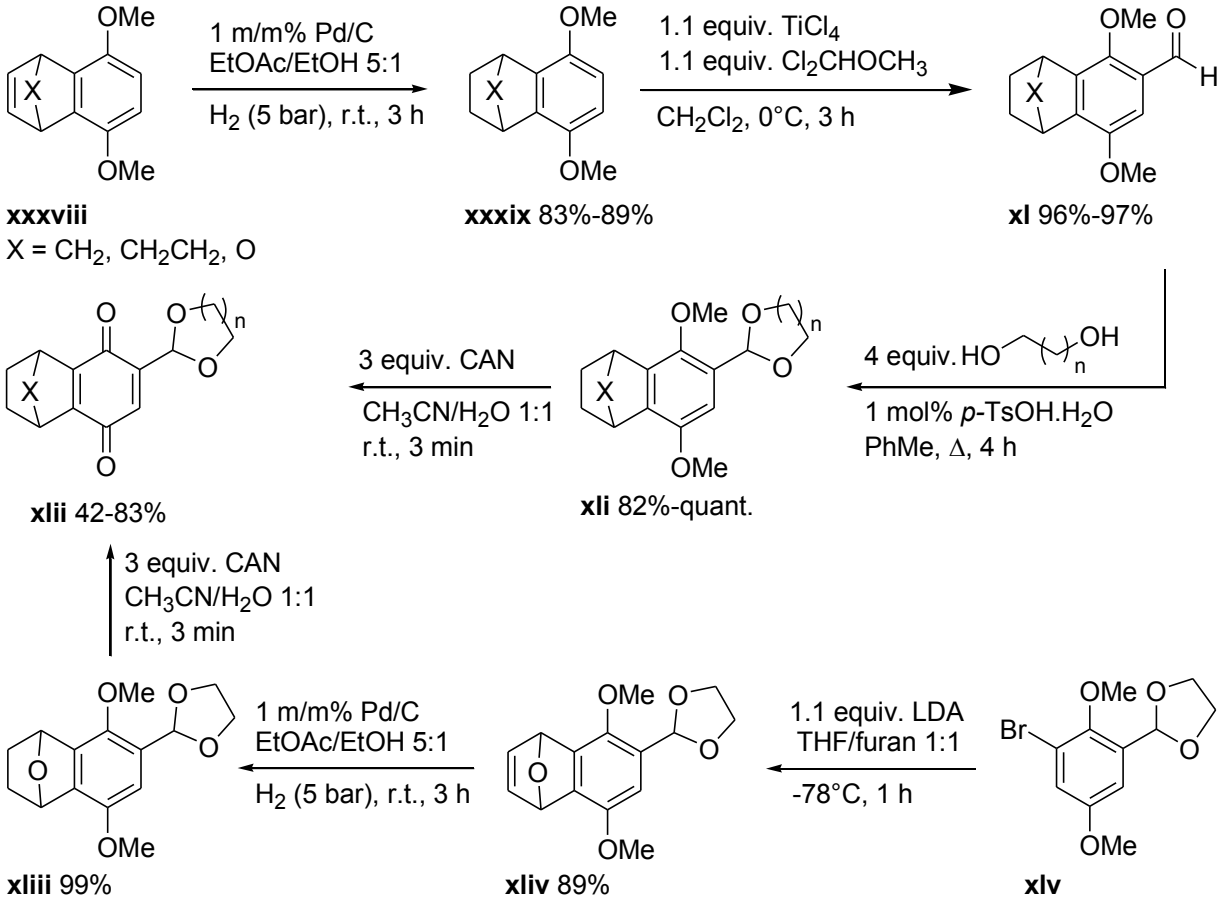
i R^1 = 1,3-dioxolan-2-yl **xxxv** R^1 = acetyl

xxxvi (1.1 equiv.) R^2 = H, Me, *t*-Bu

xxxvii trace-38% R^3 = H, Me

As these 1,2,3,4-tetrahydrobenzophenanthridinediones **xxxvii** were found to only give moderate activity against *Mycobacterium tuberculosis*, 8,11-bridged 1,2,3,4,8,9,10,11-octahydrobenzophenanthridinediones **xlviii** were prepared. It was assumed that the introduction of a 8,11-bridge would counter potential intercalation. The starting 5,6,7,8-tetrahydro-2-(1,3-dioxolan-2-

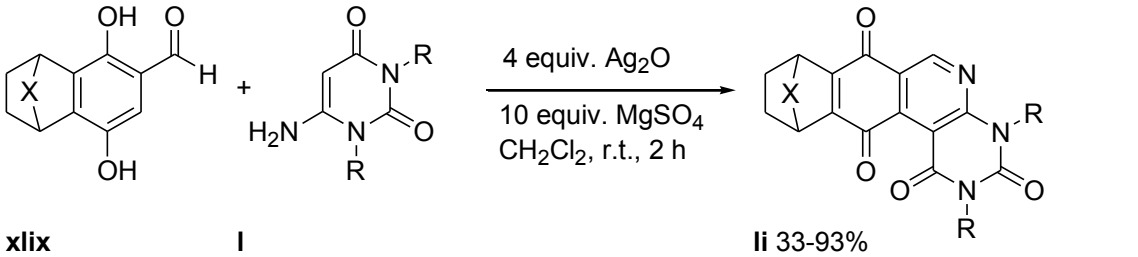
yl)-1,4-naphthoquinones **xlii** were prepared via a Diels-Alder methodology, with a minor modification for the *O*-bridged derivatives as they did not tolerate the formylation step.



Again, no optimised reaction conditions could be found despite extensive optimisation. However, various compounds showed a good activity against *Mycobacterium tuberculosis* and related Mycobacteria accompanied with an acceptable cytotoxicity and no genotoxicity.

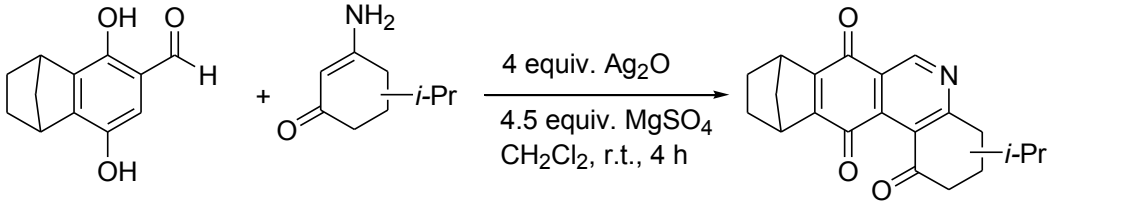
A fourth series of benzophenanthridinedione derivatives prepared were dialkyl-tetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinolinetetraones **li** and 3,4,8,9,10,11-hexahydro-2*H*-8,11-methanobenzo[j]phenanthridine-1,7,12-triones **liii**. They were prepared by means of an oxidative

addition of dialkylaminouracils **l** or 3-aminocyclohex-2-enones **lii** onto 1,4-dihydroxy-5,6,7,8-tetrahydronaphthalene-2-carboxaldehydes **xlix**. However, their antimycobacterial activity was only modest.



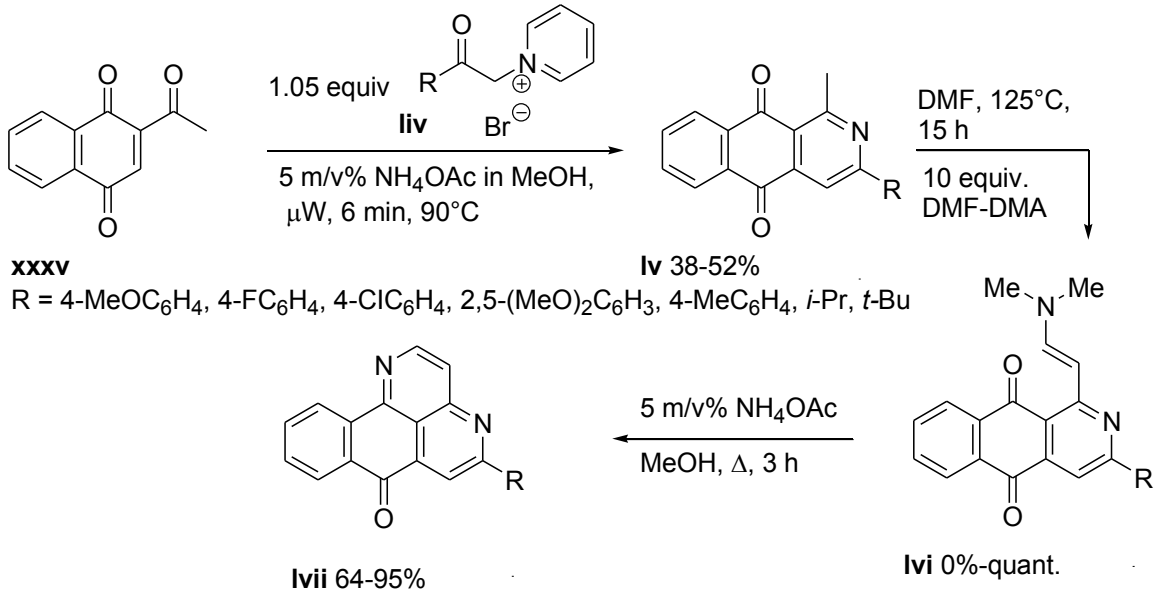
xlix **l** **li** 33-93%

X = CH_2, CH_2CH_2 R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *s*-Bu, *n*-Pentyl, *i*-Pentyl, *n*-Hexyl, *n*-Heptyl



xlixa **lii** **liii** 40 + 13%

(4) A series of cleistopholine and sampangine analogues were prepared as a part of our program to find new leads against *Mycobacterium tuberculosis*. The cleistopholine analogues were prepared by means of reaction of pyridinium salts **liv** with 2-acetyl-1,4-naphthoquinone **xxxv** under Kröhnke conditions. The dimethylaminovinyl function was installed by means of reaction with DMF-DMA followed by ring closure with ammonium acetate towards the corresponding sampangin analogues **lvii**. 1-(2-Dimethylaminovinyl)-benzo[*g*]isoquinoline-5,10-diones **lvi** were found to be promising leads against Mycobacteria.

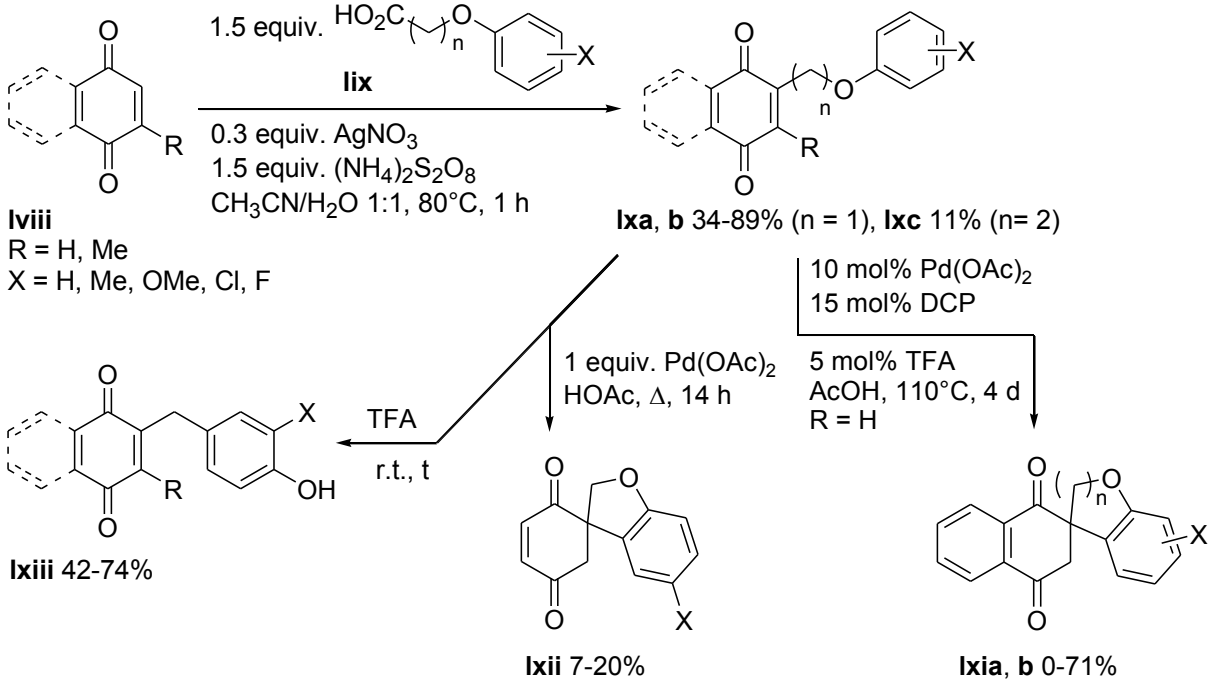


xxxv **lv** 38-52%

R = 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2,5-$(MeO)_2C_6H_3$, 4-MeC_6H_4, *i*-Pr, *t*-Bu

lvii 64-95% **lvi** 0%-quant.

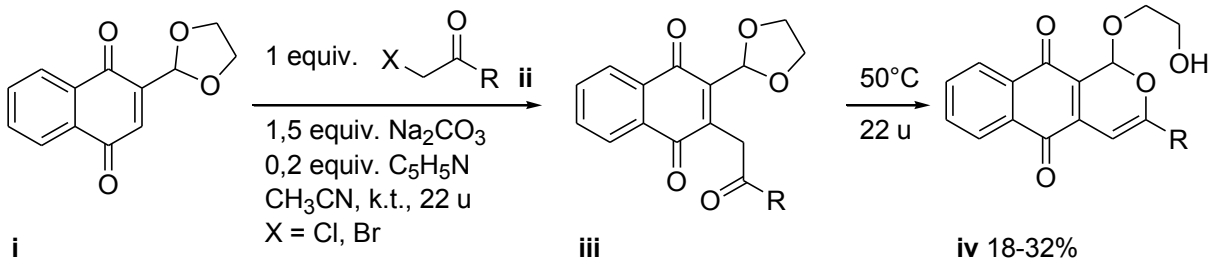
(5) The palladium(II)-catalysed synthesis of 2*H*,3'*H*-spiro[benzofuran-3,2'-quinones] **lxi**, was studied. The starting 2-aryloxymethyl-1,4-naphthoquinones **lxa**, 2-aryloxymethyl-1,4-benzoquinones **lxb** or 2-phenoxyethyl-1,4-naphthoquinone **lxc** were prepared by means of a radical alkylation reaction. After optimisation of the reaction conditions, 2*H*,3'*H*-spiro[benzofuran-3,2'-quinones] **lxi** were obtained in modest to good yields when reacted with 10 mol% $Pd(OAc)_2$, 15 mol% 3,5-dichloropyridine and 5 mol% TFA in acetic acid at 110°C for four days. Application of the optimised spirocyclisation conditions to aryloxymethyl-1,4-benzoquinones **lxb** lead to complex reaction mixtures. 2*H*,3'*H*-Spiro[benzofuran-3,2'-benzoquinones] **lxii** could only be synthesised using a full equivalent of palladium(II) acetate in boiling acetic acid in low yields. A six-membered ring spiroquinone **lxib** was synthesised starting from 2-(2-phenoxyethyl)-1,4-naphthoquinone **lxc** in 38% yield. As 2-(2-phenoxyethyl)-1,4-naphthoquinone **lxc** could only be prepared in low yield, attempts were made to find a more efficient synthesis. Unfortunately, none were found. No reaction was observed when substrates structurally related to aryloxymethyl-1,4-naphthoquinones **lxa** such as 3-methyl-2-phenoxymethyl-1,4-naphthoquinone, *N*-mesyl-, *N*-acyl- or *N*-benzoyl-2-phenylaminomethyl-1,4-naphthoquinones or 2-phenoxymethylchromen-4-one were subjected to the optimised spirocyclisation conditions or when the reaction was performed with a full equivalent of palladium(II) acetate. An interesting side reaction that was observed was the rearrangement of 2-aryloxymethyl-1,4-quinones **lx** towards the corresponding 2-(4-hydroxybenzyl)-1,4-quinones **lxiii** when stirred at room temperature in pure TFA. The presented spirocyclisation is a novel transformation leading to a heterocyclic skeleton previously unknown in the literature.



7 Samenvatting

Het voorgestelde doctoraatsonderzoek handelt over de chemie van heterocyclisch geanneleerde chinonen. Meer specifiek, pyranonaftochinonen, spironaftochinonen en een brede waaier aan benzo[*j*]fenantridinedionderivaten werden bereid. Deze series van benzofenantridinedionanaloga werden bereid als een deel van een screeningsprogramma tegen *Mycobacterium tuberculosis* in samenwerking met het Wetenschappelijk Instituut voor Volksgezondheid (Ukkel).

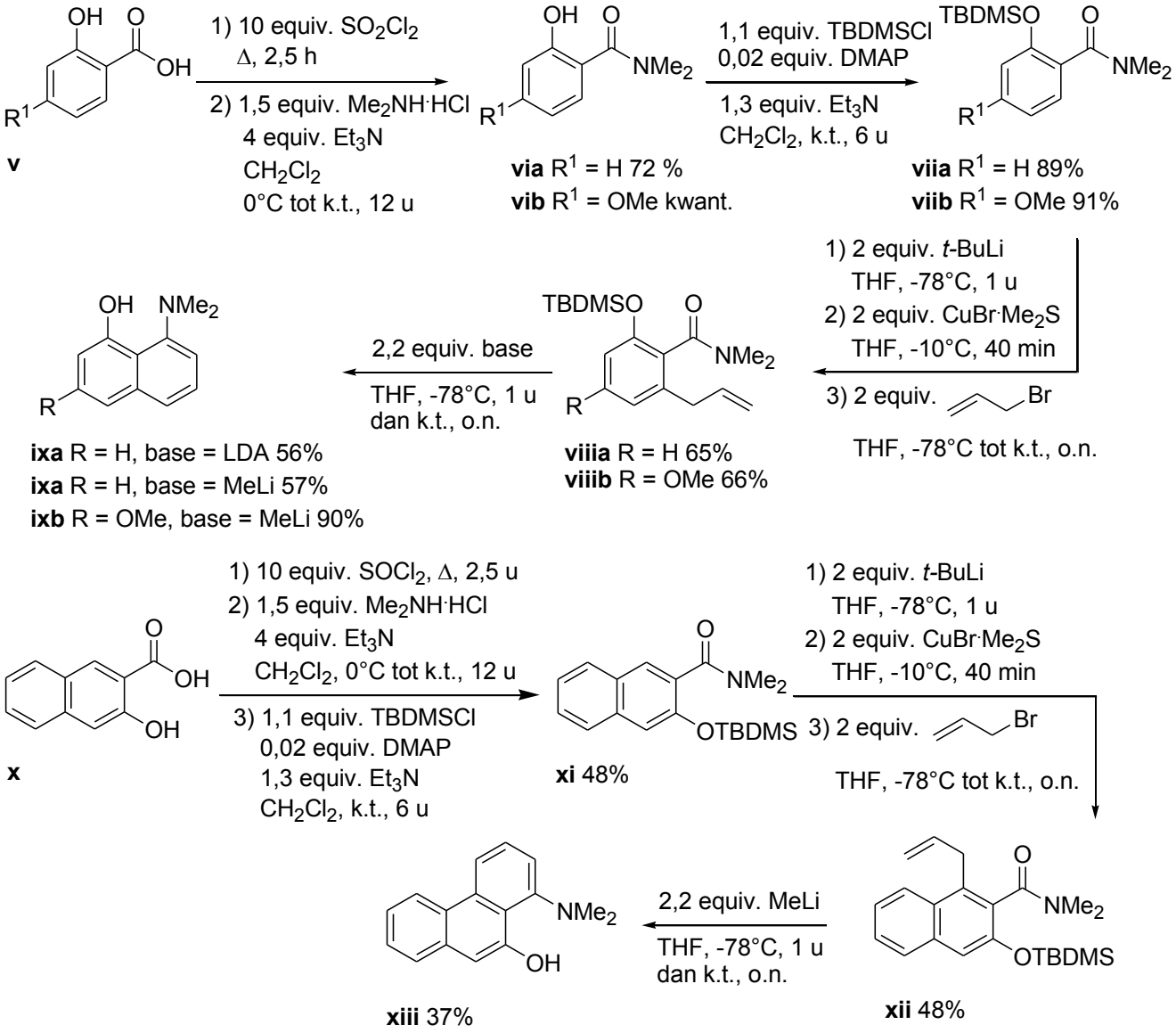
(1) Katalytische reactieomstandigheden werden ontwikkeld om 1-(2-hydroxyethoxy)pyranonaftochinonen **iv** te bereiden startende van 2-(1,3-dioxolan-2-yl)-1,4-naftochinon **i**. Hoewel deze reactieomstandigheden gelijkaardige resultaten geven als de overeenkomstige stoichiometrische versie, dient het overeenkomstige pyridiniumzout niet op voorhand bereid te worden en is enkel een katalytische hoeveelheid pyridine nodig.



R = 4-BrC_6H_4, *i*-Pr, *i*-Bu

Het was vooropgesteld om deze methodologie toe te passen op de synthese van verscheidene natuurproducten zoals de pyranonaftochinonen ascomycone A en B, 1-hydroxydehydroherbarin en de mansouramycins, dewelke isochinolinedionen zijn. Helaas kon geen enkel van deze natuurproducten bereid worden, gezien het niet mogelijk was de gepaste startmaterialen te synthetiseren in beide gevallen.

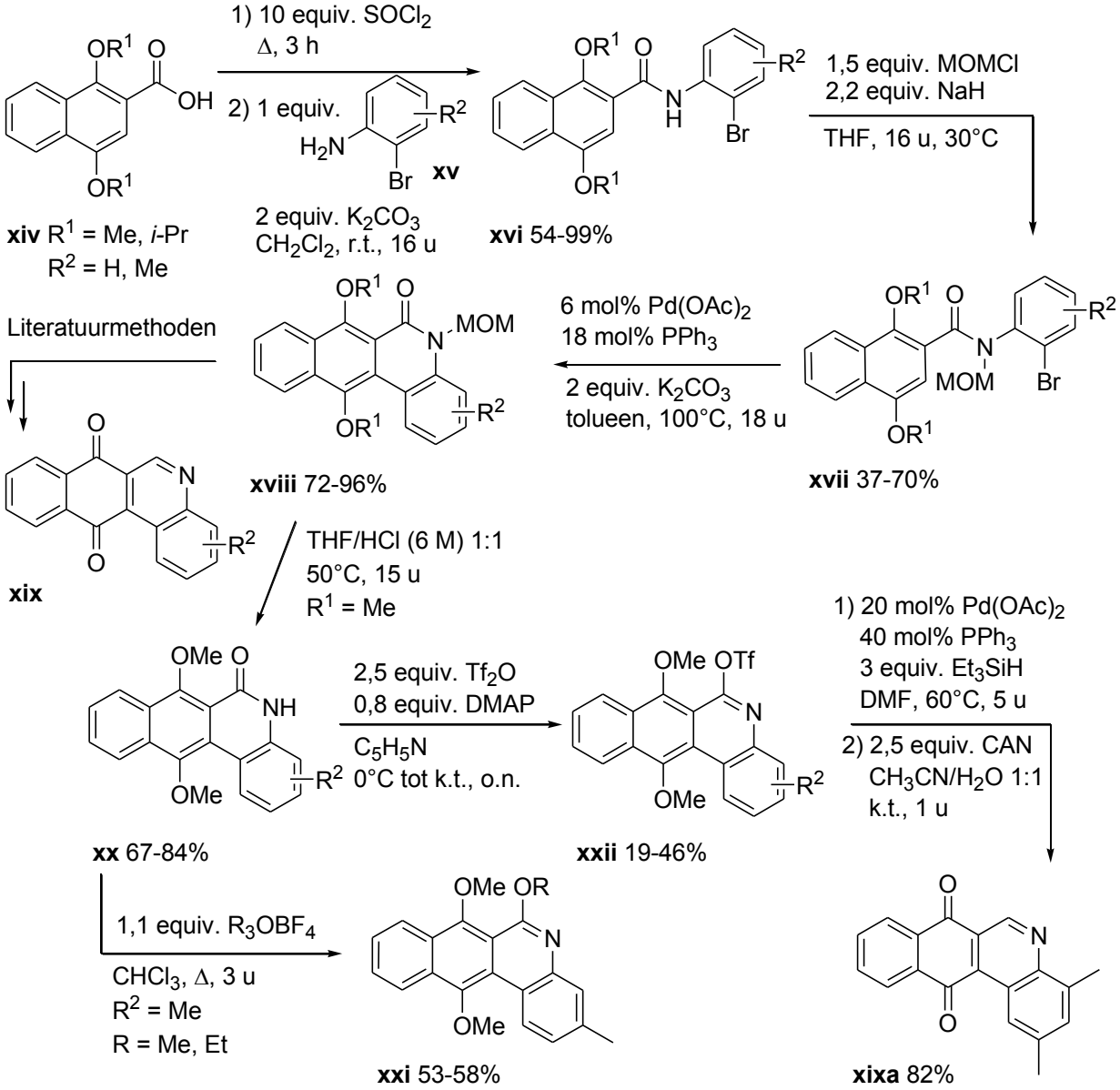
(2) Een onverwachte synthese van aminonaftolen werd ontdekt. Deze reactie geschiedde via MeLi- of LDA-gemedieerde ringsluiting van een 2-allyl-6-*tert*-butyldimethylsilanyloxy-*N*,*N*-dimethylbenzamidederivaat **viii** of **xii**. De reactie werd grondig onderzocht en verscheidene beschermende groep (TBDMS, TIPS, TBDPS) en amide (dimethyl, diethyl, pyrrolidinyl, morfolinyl) combinaties werden geëvalueerd. Het bleek dat de reactie enkel doorging wanneer het amide een *N*,*N*-dimethylamide is en de beschermende groep een TBDMS groep, terwijl alle andere combinaties resulteerden in complexe mengsels. Aldus werden aminonaftolen **ix** en aminofenantrenol **xiii** gesynthetiseerd in 37-90% rendement.



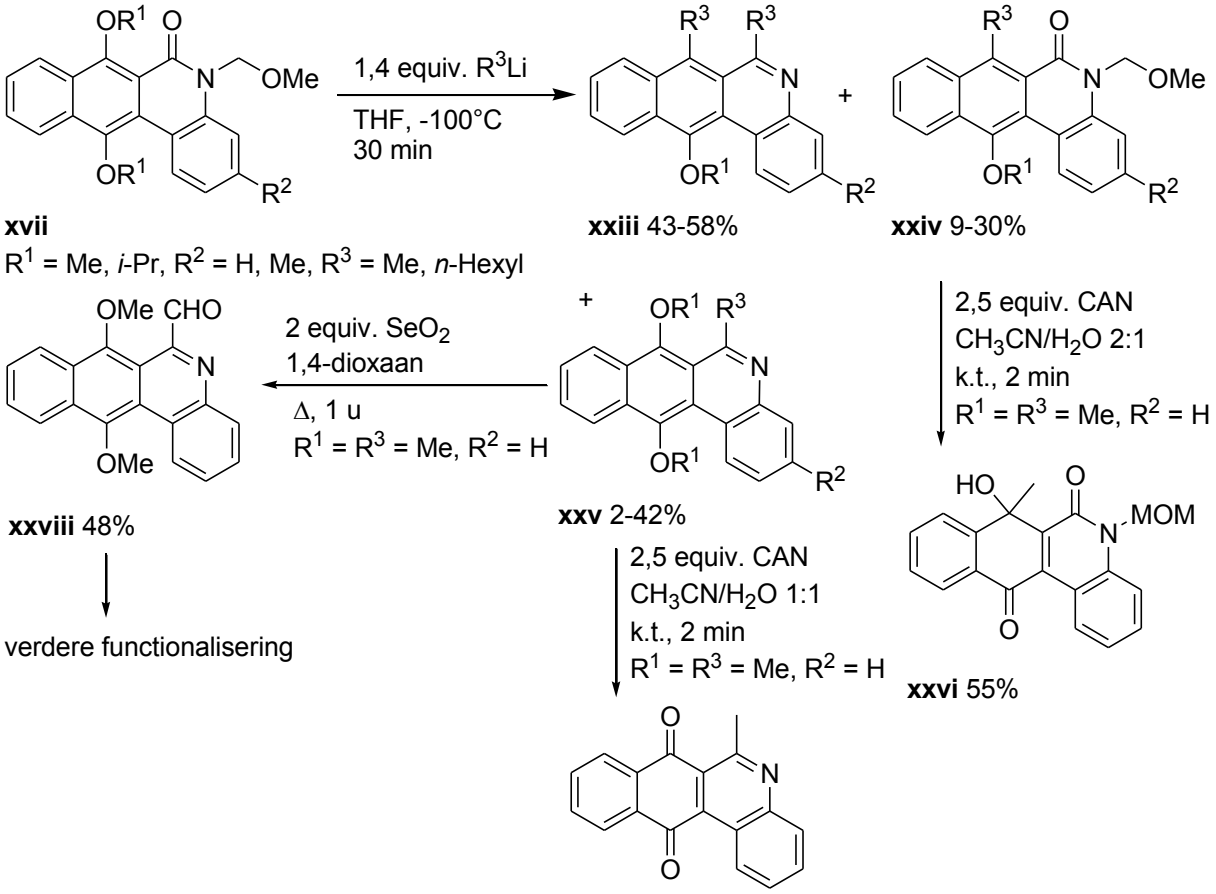
Er werd gepoogd om gefluoreerde pyranonaftochinonen te synthetiseren waarbij in één stap het gefluoreerde pyraanskelet werd geconstrueerd door middel van een goud-gekatalyseerde 6-endo-dig ringsluiting, maar geen bevredigende resultaten werden behaald.

(3) Verscheidene benzo[*j*]fenantridinedion analoga werden bereid als deel van een screeningsprogramma tegen *Mycobacterium tuberculosis* en aanverwante mycobacteria zoals *M. bovis*, *M. avium* ssp. en *M. ulcerans*. Initieel werd een alternatieve synthese ontwikkeld voor de gekende benzo[*j*]fenantridinedionen **xix** die meer flexibiliteit toelaat en toegepast kon worden in de synthese van een bibliotheek van antimycobacteriële verbindingen. Aldus werden amiden **xvi** bereid startende van dialkoxynaftaleencarbonzuren **xiv** en 2-broomanilines **xv**. De amidestikstof werd MOM-beschermd en vervolgens werd het amide gecycliseerd door middel van een palladium-gekatalyseerde intramoleculaire arylering tot 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]fenantridin-6-onen **xviii**. Deze sleutelintermediairen **xviii** kunnen omgezet worden in de voorheen bereidde

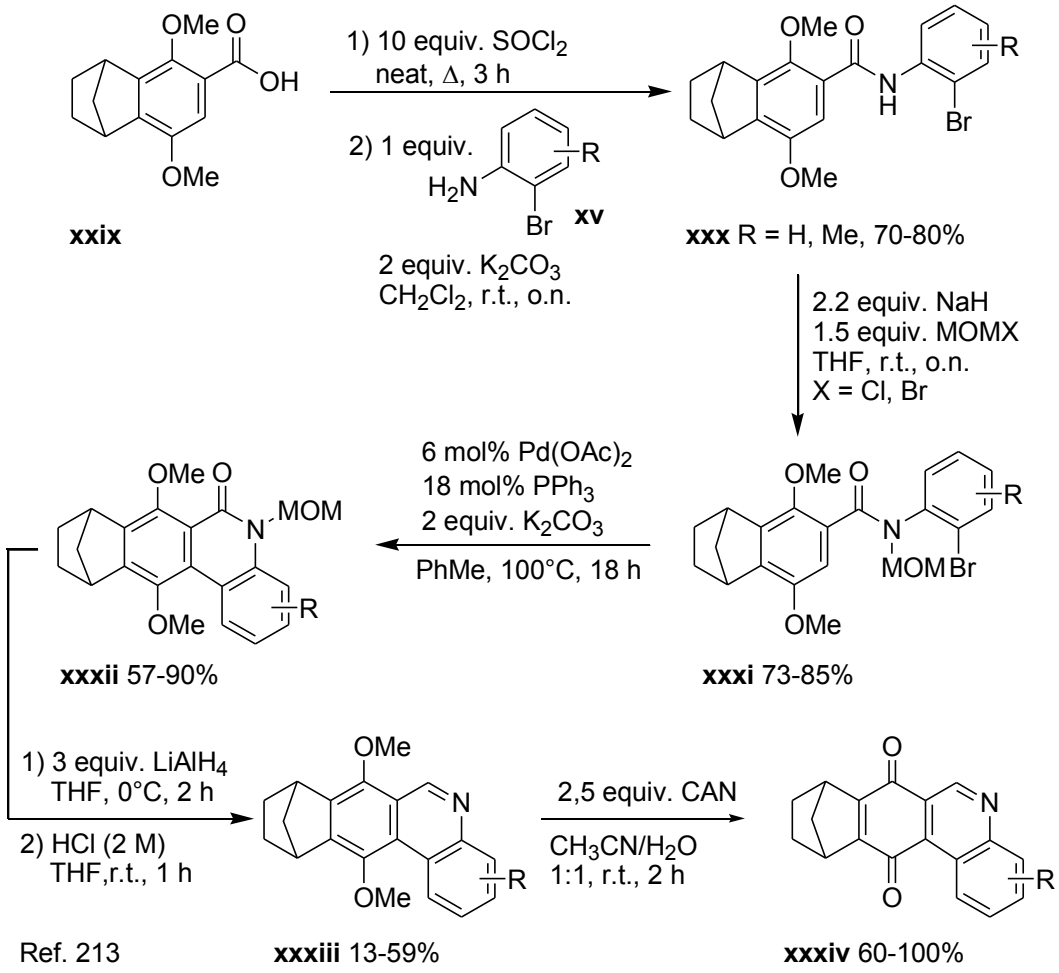
benzo[*j*]fenantridinedionen **xix** door middel van literatuurprocedures. 7,12-Dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]fenantridin-6-onen **xviii** werden ontschermd door middel van zoutzuur en verder omgezet tot alkoxypyridinen **xxi** en triflaten **xxii**. Triflaat **xxiia** werd gedefunctionaliseerd door middel van Pd(0)-katalyse en geoxideerd tot 2,4-dimethylbenzo[*j*]fenantridine-7,12-dion **xixa**, hetwelke nog nooit eerder bereid was. Analoog aan antikankergeneesmiddelen zoals mitoxantrone en pixantrone, werd gepoogd om 6-aminoalkylaminobenzo[*j*]fenantridine-7,12-dionen te synthetiseren. Er konden echter geen adequate reactieomstandigheden gevonden worden wanneer ethyleendiamine in reactie gebracht werd met 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]fenantridin-6-onen **xviii**, 7,12-dimethoxy-5*H*-benzo[*j*]fenantridin-6-onen **xx** of 6-alkoxy-7,12-dimethoxy-3-methylbenzo-[*j*]fenantridinen **xxi**.



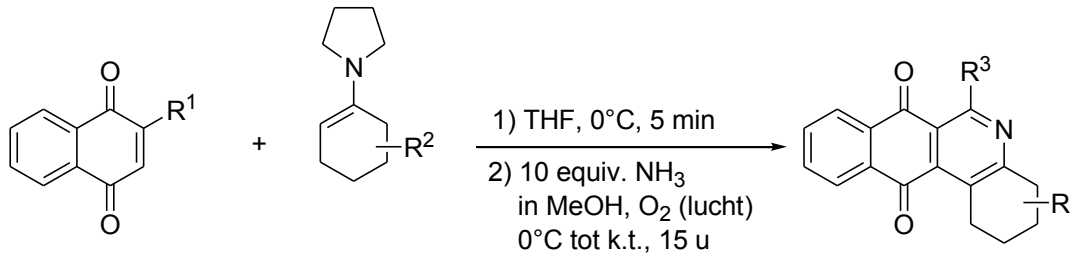
Wanneer alkyllithium reagentia werden toegevoegd aan 7,12-dialkoxy-5-methoxymethyl-5*H*-benzo[*j*]fenantridin-6-onen **xvii** bij lage temperatuur werd een interessante reactiviteit vastgesteld. In plaats van uitsluitend het verwachte 1,2-adduct **xxv** te geven, werd een mengsel van 1,2-adduct **xxv**, 1,4-adduct **xxiv** en dubbele additieproducten **xxiii** verkregen. Het aandeel van 1,4-additie- en dubbel additieproduct nam toe als de sterische hindering toenam. De MeLi adducten werden geoxideerd met CAN tot chinon **xxvii** en chinonoide verbinding **xxvi**. De benzylische methylgroep van 7,12-dimethoxy-6-methylbenzo[*j*]fenantridine **xxv** werd geoxideerd met SeO_2 tot aldehyde **xxviii** dat zou kunnen dienen als een aanhechtingspunt voor verdere functionalisering.



De bovenvermelde methodologie werd toegepast op de synthese van 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]fenanthridine-7,12-dionen **xxxiv**. Lactam **xxxii** werd gesynthetiseerd zoals hierboven beschreven, gereduceerd door middel van $LiAlH_4$ en het resulterend hemi-aminal werd gehydrolyseerd door middel van waterig HCl tot pyridine **xxxiii**. Oxidatieve demethylering met CAN resulteerde in de beoogde 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]fenanthridine-7,12-dionen **xxxiv** in goede rendementen. Deze synthese was het onderwerp van een masterthesis.[213]



Vervolgens werd de synthese van 1,2,3,4-tetrahydrobenzofenantridinedionen **xxxvii** aangevat. Deze verbindingen werden gesynthetiseerd door middel van de additie van enamine **xxxvi** aan 2-(1,3-dioxolan-2-yl)-1,4-naftochinon **i** of 2-acetyl-1,4-naftochinon **xxxv** gevolgd door ammoniak gemedieerde ringsluiting van de intermediaire benzonaftofuranen. Ongeacht intensieve optimalisatie, konden geen reactieomstandigheden gevonden worden die goede rendementen gaven.



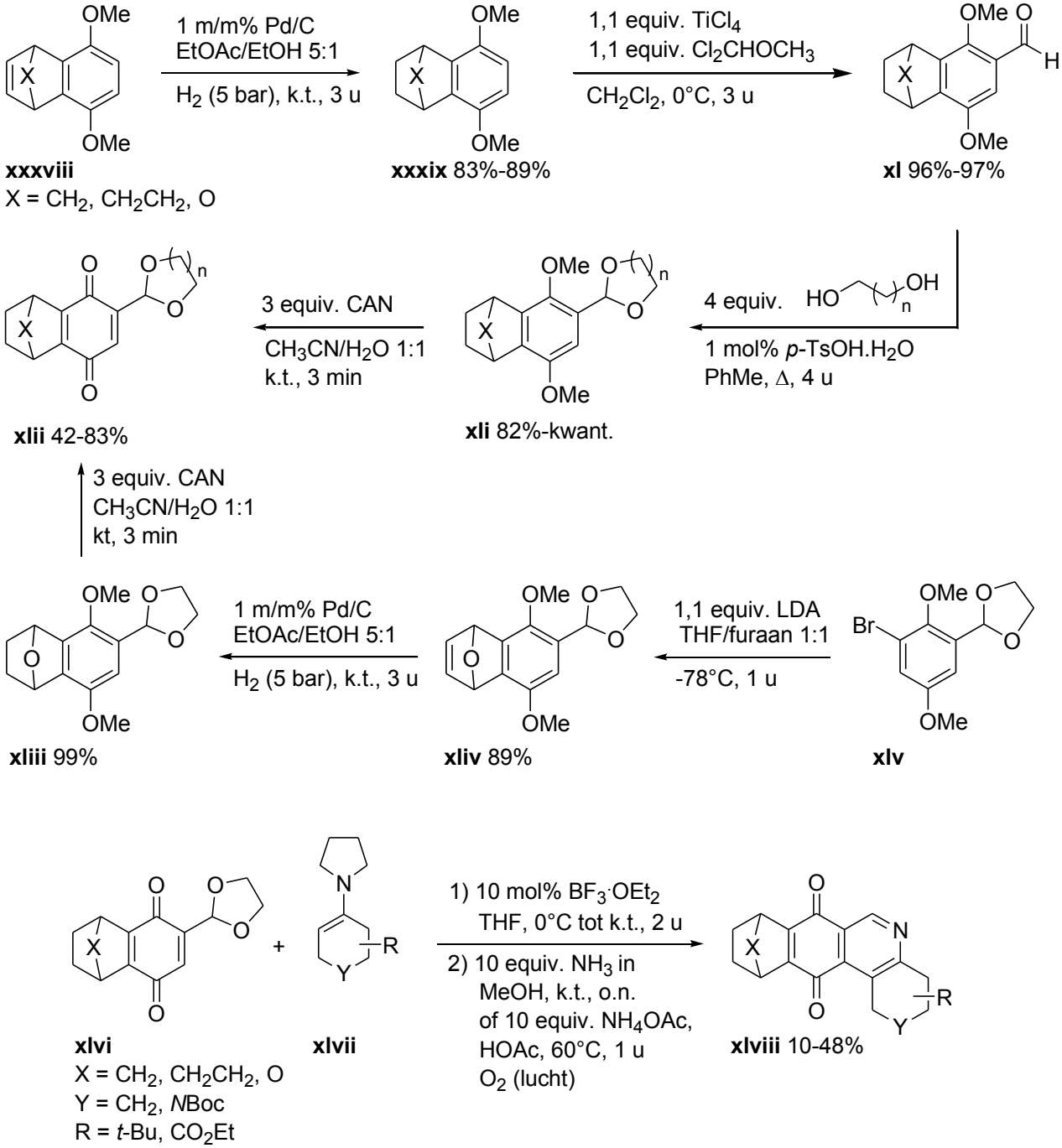
i R^1 = 1,3-dioxolan-2-yl
xxxv R^1 = acetyl

xxxvi(1,1 equiv.)
R^2 = H, Me, *t*-Bu

xxxvii spoor-38%
R^3 = H, Me

Gezien deze 1,2,3,4-tetrahydrobenzo[*j*]fenantridinedionen **xxxvii** slechts een matige activiteit vertoonden tegen *Mycobacterium tuberculosis*, werden 8,11-gebrugde 1,2,3,4,8,9,10,11-octahydrobenzo[*j*]fenantridinedionen **xlviii** bereid. Het werd vooropgesteld dat de introductie van de 8,11-brug potentiele intercalatie zou kunnen tegengaan. De startmaterialen, 5,6,7,8-tetrahydro-2-(1,3-

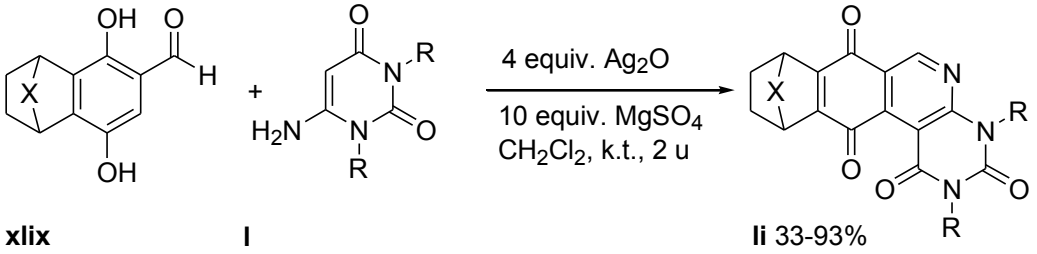
dioxolan-2-yl)-1,4-naftochinonen **xxxlii** werden bereid via een Diels-Alder methodologie, met een kleine aanpassing voor de *O*-gebrugde derivaten gezien deze de formyleringsstap niet tolereerden.



Opnieuw konden geen optimale reactieomstandigheden gevonden worden ongeacht uitgebreide pogingen tot optimalisatie. Desalniettemin vertoonden verscheidene verbindingen een goede activiteit tegen *Mycobacterium tuberculosis* en aanverwante Mycobacteria vergezeld van een aanvaardbare cytotoxiciteit en geen genotoxiciteit (komeettest en vitotox assay).

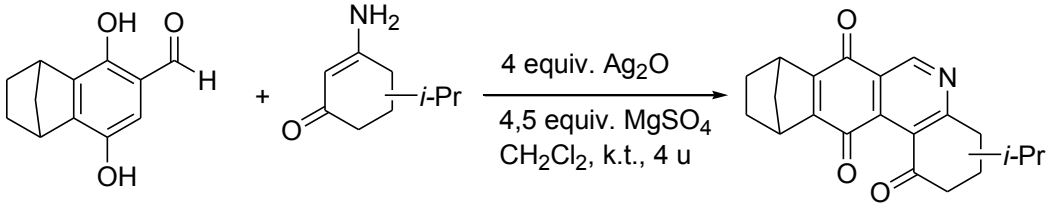
Een vierde serie van benzofenantridinedionderivaten waren dialkyltetrahydrobenzo[*g*]pyrimido[4,5-*c*]isochinolinetetraonen **li** en 3,4,8,9,10,11-hexahydro-2*H*-8,11-methanobenzo[*j*]fenantridine-1,7,12-

trionen **liii**. Deze werden bereid door middel van een oxidatieve additie van dialkylaminouracilderviaten **l** of 3-aminocyclohex-2-enonen **lii** aan 1,4-dihydroxy-5,6,7,8-tetrahydronaftaleen-2-carboxaldehydes **xlix**. Hun antimycobacteriële activiteit was echter slechts matig.



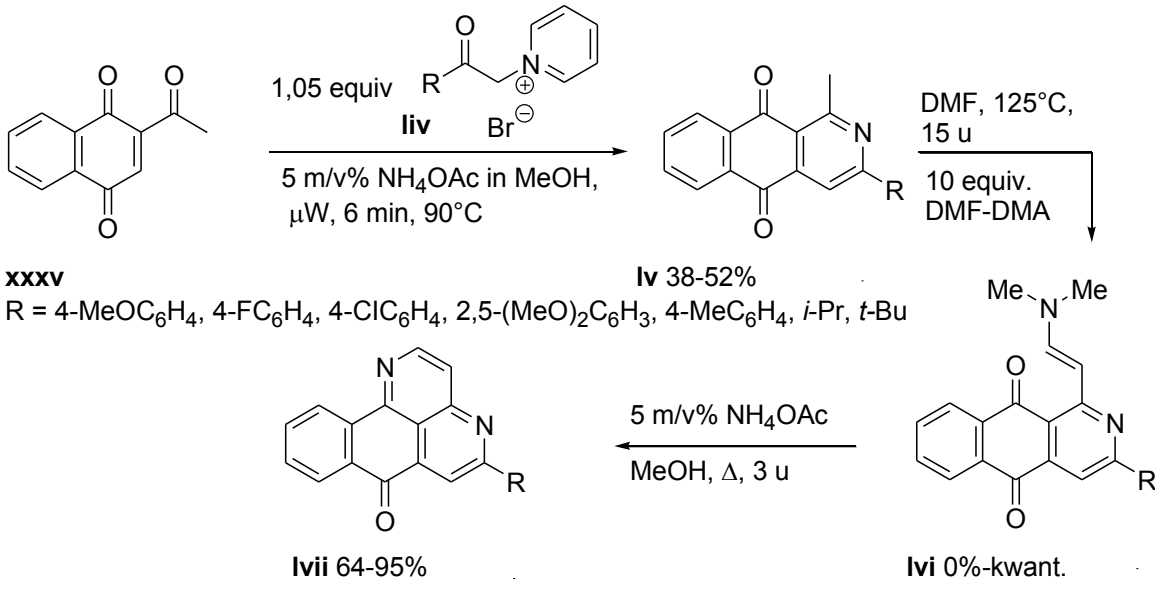
xlix **l** **li** 33-93%

X = CH_2, CH_2CH_2 R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *s*-Bu, *n*-Pentyl, *i*-Pentyl, *n*-Hexyl, *n*-Heptyl



xlixa **liii** **liii** 40 + 13%

(4) Een serie van cleistofoline en sampangine analoga werd bereid als deel van het lopend onderzoeksprogramma om nieuwe leads te vinden met activiteit tegen *Mycobacterium tuberculosis*. De cleistofoline analoga werden bereid door middel van reactie van pyridiniumzouten **liv** met 2-acetyl-1,4-naftochinon **xxxv** onder Kröhnke omstandigheden. De dimethylaminovinylfunctie werd geïnstalleerd gebruik makend van DMF-DMA gevolgd door ringsluiting met ammoniumacetaat tot de overeenkomstige sampangin analoga **lvii**. 1-(2-Dimethylaminovinyl)benzo[*g*]isochinoline-5,10-dionen **lvi** bleken een veelbelovende antimycobacteriële activiteit te bezitten.

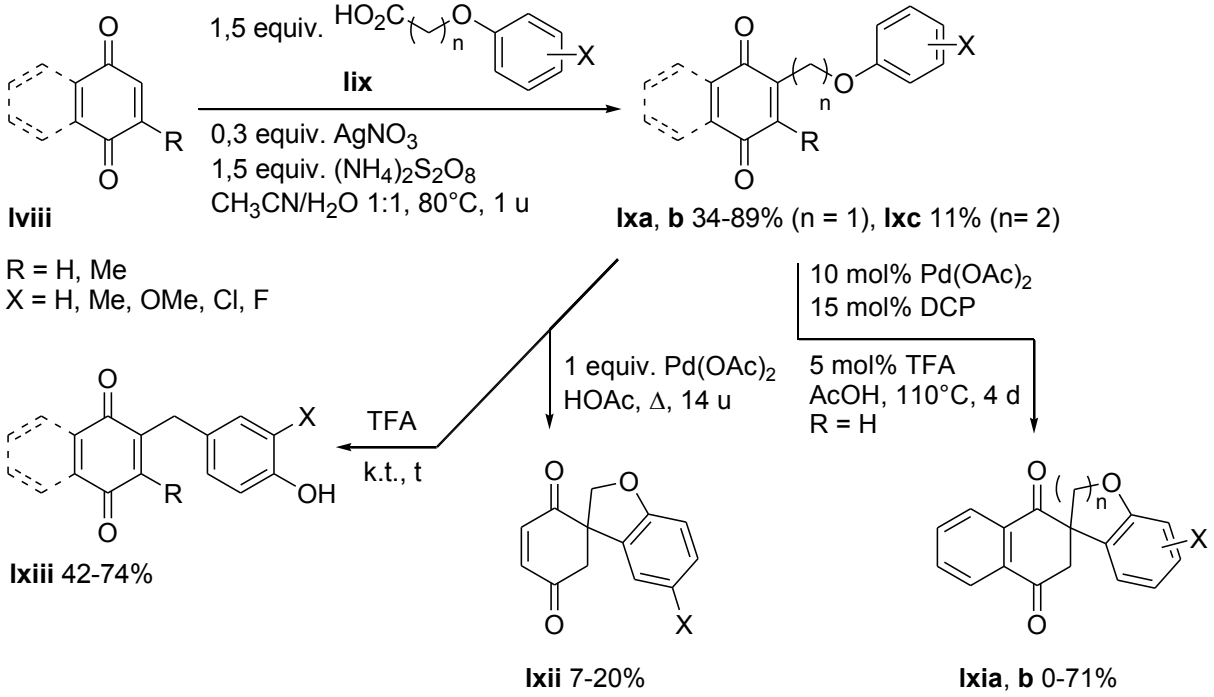


xxxv **lv** 38-52%

R = 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 2,5-$(MeO)_2C_6H_3$, 4-MeC_6H_4, *i*-Pr, *t*-Bu

lvii 64-95% **lvi** 0%-kwant.

(5) De palladium(II)-gekatalyseerde synthese van 2*H*,3'*H*-spiro[benzofuraan-3,2'-chinonen] **lxi** werd diepgaand bestudeerd. De startmaterialen, 2-aryloxymethyl-1,4-naftochinonen **lxa**, 2-aryloxymethyl-1,4-benzochinonen **lxb** of 2-phenoxyethyl-1,4-naftochinon **lxc** werden bereid door middel van een radicale alkyleringsreactie. Na optimalisatie van de reactieomstandigheden werden 2*H*,3'*H*-spiro[benzofuraan-3,2'-naftochinonen] **lxi** bekomen in matig tot goed rendement wanneer ze in reactie gebracht werden met 10 mol% $Pd(OAc)_2$, 15 mol% 3,5-dichloorpyridine en 5 mol% TFA in azijnzuur bij 110°C gedurende vier dagen. De geoptimaliseerde reactieomstandigheden faalden voor aryloxymethyl-1,4-benzochinonen **lxb**. 2*H*,3'*H*-Spiro[benzofuraan-3,2'-benzochinonen] **lxii** konden enkel gesynthetiseerd worden door middel van reactie met een volledig equivalent palladium(II) acetaat in kokend azijnzuur in lage rendementen. 3'*H*-Spiro[chromaan-3,2'-naftaleen]-1',4'-dion **lxib** werd bereid startende van 2-(2-phenoxyethyl)-1,4-naftochinon **lxc** in 38% rendement. Geen reactie werd geobserveerd wanneer substraten structureel verwant aan de aryloxymethyl-1,4-naftochinonen **lxa** zoals 3-methyl-2-fenoxymethyl-1,4-naftochinon, *N*-mesyl-, *N*-acyl- of *N*-benzoyl-2-fenylaminomethyl-1,4-naftochinonen of 2-fenoxymethylchromeen-4-on werden onderworpen aan de geoptimaliseerd spirocyclisatiereactieomstandigheden of reactie met een volledig equivalent palladium(II) acetaat. Een interessante zijreactie was de omlegging van 2-aryloxymethyl-1,4-chinonen **lx** naar de overeenkomstige 2-(4-hydroxybenzyl)-1,4-chinonen **lxiii** wanneer ze bij kamertemperatuur in puur trifluorazijnzuur geroerd werden. De gepresenteerde spirocyclisatie is een nieuwe transformatie en leidt tot een heterocyclisch skelet, voorheen ongekend in de literatuur.



8 References

[1] Lautemann, E. *Ann. Chem. Pharm.*, **1863**, *125*, 9.

[2] (a) Thomson, R.H. *Naturally Occurring Quinones*, second edition, Academic Press, London and New York, **1971**, p. 725. (b) Thomson, R.H. *Naturally Occurring Quinones III: Recent Advances*, third edition, Chapman and Hall, London and New York, **1987**, pp. 719.

[3] Eisner, T.; Aneshansley, D. J. *Proc. Natl. Acad. Sci. USA*, **1999**, *96,* 9705-9709.

[4] Luo, S-H.; Liu, Y.; Niu, J. H.; Jing, S-X.; Zhao, X.; Schneider, B.; Gershenzon, J.; Li, S-H. *Org. Lett.*, **2012**, *16*, 4146-4149.

[5] (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.*, **2007,** *70,* 461-477. (b) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.*, **2012**, *75*, 311–335.

[6] (a) Kokwaro, J.O. *Medicinal Plants of East Africa*, East African Literature Bureau: Kampala, Nairobi, Dar es Salaam, **1976,** pp. 190. (b) Troupin, C.G., Ed. *Flore du Rwanda, Spermatophytes*, Institut National de Recherche Scientifique: Butare (Rwanda), **1985**, Vol. 3, pp. 196. (c) Vandebroek, I., Calewaert, J. B., De Jonckheere, S., Sanca, S., Semo, L., Van Damme, P., Van Puyvelde, L., De Kimpe, N. *Bulletin of the World Health Organisation*, **2004**, *82*, 243-250.

[7] (a) Thomson, R.H., In *The Chemistry of the Quinoid Compounds*, Part 1, S. Patai (Ed.), John Wiley and Sons, New York, **1974**, 111-161. (b) Methoden der Organischen Chemie (Houben-Weyl), vierte Auflage, Band VII/3a, Chinone, Teil 1, E. Müller (Ed.), Georg Thieme Verlag, Stuttgart, **1977**, pp. 732. (c) Naruta, Y., Maruyama, K. In *The Chemistry of Quinoid Compounds*, volume 2, S. Patai and Z. Rappoport (Eds.), John Wiley and Sons, New York, **1988**, 241-402. (d) Finley, K.T. In *The Chemistry of Quinoid Compounds*, volume 2, S. Patai and Z. Rappoport (Eds.), John Wiley and Sons, New York, **1988**, p. 537-716.

[8] (a) Zhanga, G.; Hagera, A.; Moosa, M.; Irmera, A.; Bargoub, R.; Chatterjeeb, M. *Eur. J. Med. Chem*., **2011**, *46*, 5778-5789. (b) Carr, G.; Derbyshire, E. R.; Caldera, E.; Currie, C. R.; Clardy, J. *J. Nat. Prod.*, **2012**, *75*, 1806−1809. (c) Ding, Z-G.; Zhao, J-Y.; Li, M-G.; Huang, R.; Li, Qi-M.; Cui, X-L.; Zhu, H-J.; Wen, M-L. *J. Nat. Prod.*, **2012**, *75*, 1994−1998. (d) Olaoluwa, O. O.; Aiyelaagbe, O. O.; Reid, I. D. *Tetrahedron*, **2013**, in press. (e) Menna, M.; Aiello, A.; D'Aniello, F.; Imperatore, C.; Luciano, P.; Vitalone, R.; Irace, C.; Santamaria, R. *Eur. J. Org. Chem*., **2013**, *16*, 3241–3246. (f) Cheng, Y-B.; Jensen, P. R.; Fenical, W. *Eur. J. Org. Chem.*, **2013**, *18*, 3751–3757. (g) Wang, X.; Shaaban, K. A.; Elshahawi, S. I.; Ponomareva, L. V.; Sunkara, M.; Zhang, Y.; Copley, G. C.; Hower, J. C.; Morris, A. J.; Kharel, M. K.; Thorson, J. S. *J. Nat. Prod*. **2013**, *76*, 1441−1447.

[9] Brubaker, C. E.; Kissler, H.; Wang, L-J.; Kaufman, D. B.; Messersmith, P. B. *Biomaterials*, **2010**, *31*, 420-427.

[10] (a) Graebe, C., Liebermann, C. *Ber.*, **1869**, *2*, 14. (b) *Encyclopaedia Britannica*, 1911 edition, http://www.1911encyclopedia.org/Sir_William_Henry_Perkin

[11] Roy, P. K., Singh, M., Tewari, P. Composition of Henna Powder, Quality Parameters and Changing Trends in its Usage. Henna, Cultivation, Improvement and Trade, **2005**, 39–40. Jodhpur, India, Central Arid Zone Research Institute.

[12] Hage, R., Lienke, A. *Angew. Chem. Int. Ed.*, **2005**, *42*, 206-222.

[13] (a) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry*, **1991**, *30*, 1726-1727. (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, J.; Verpoorte, R. *Magn. Res. Chem.*, **1993**, *31*, 329-330.

[14] *Medicinal Plants of East-Africa*; Kowaro, J. O., Ed; East African Literature Bureau: Dar Es Salaam, **1976**, 190.

[15] Kesteleyn, B. 'Synthesis of pyranonaphthoquinones and related naturally occurring heteroanthraquinones', PhD thesis, Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, **1999**.

[16] Claesens, S. 'Development of new methods for the synthesis of annulated quinones and quinoid compounds' *PhD thesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, **2007**.

[17] Jacobs, J. 'New entries to pyranonaphthoquinone and 2-azaanthraquinone antibiotics', *PhD thesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University **2009**.

[18] Cappoen, D.; Jacobs, J. Nguyen Van, T.; Claessens, S.; Diels, G. Anthonissen, R. Einarsdottir, T. Fauville, M.; Verschaeve, L. Huygen, K; De Kimpe, N. *Eur. J. Med. Chem*., **2012**, *48*, 57-68.

[19] (a) Orabi, K.Y.; Li, E.; Clark, A.M.; Hufford, C.D. *J. Nat. Prod.*, **1999**, *62*, 988-992. (b) Muhammad, I.; Dunbar, D.C.; Takamatsu, S.; Walker, L.A.; Clark, A.M. *J. Nat. Prod.*, **2001**, *64*, 559-562. (c) Lago, J.H.G.; Chaves, M.H.; Ayres, M.C.C.; Agripino, D.G.; Young, M.C.M. *Planta Med.*, **2007**, *73*, 292 -295. (d) Peterson, J.R.; Zjawiony, J.K.; Liu, S.; Hufford, C.D.; Clark, A.M.; Rogers, R.D. *J. Med. Chem.*, **1992**, *35*, 4069-4077.

[20] (a) Huang, C.; Liu, B. *Chem. Commun.*, **2010**, *46*, 5280-5282. (b) Takenaga, N.; Uchiyama, T.; Kato, D.; Fujioka, H.; Dohi, T.; Kita, Y. *Heterocycles*, **2011**, *82*, 1327-1336.

[21] WHO Global tuberculosis report **2012**.

[22] Dover, L. G.; Coxon, G. D. *J. Med. Chem.*, **2011**, *54*, 6157–6165.

[23] Diacon, A. H.; Pym, A.; Grobusch, M.; Patientia, R.; Rustomjee, R.; Page-Shipp, L.; Pistorius, C.; Krause, R.. Bogoshi, M.; Churchyardn, G.; Venter, A.; Allen, J.; Palomino, J. C.; De Marez, T.; van Heeswijk, R. P.; Lounis, N.; Meyvisch, P.; Verbeeck, J.; Parys, W.; de Beule, K.; Andries, K.; Mc Neeley, D. F. *N. Engl. J. Med.*, **2009**, *360*, 2397–2405.

[24] For reviews on atovaquone, see: (a) Haile, L.G.; Flaherty, J. F. *Ann. Pharmacother.*, **1993** *27*, 1488-94. (b) Baggish, A. L.; Hill, D. R. *Antimicrob.Agents Chem.*, **2002**, *46*, 1163–1173

[25] Hughes, W.; Leoung, G.; Kramer, F.; Bozette, S. A.; Safrin, S.; Frame, P.; Clumeck, N.; Masur, H.; Lancaster, D.; Chan, C.; Lavell, J.; Rosenstock, J.; Falloon, J.; Feinber, J.; Lafon, S.; Rogers, M.; Sattler, F. *N. Engl. J. Med.*, **1993**, *328*, 1521–1527.

[26] (a) Kovacs, J. & the NIAID Clinical Centre Intramural AIDS Program *Lancet*, **1992**, *340*, 637–638. (b) Katlama, C.; Mouthon, B.; Gourdon, D.; Lapierre, D.; Rousseau, F. *AIDS*, **1996**, *10*, 1107-1112. (c) Torres, R. A.; Weinberg, W.; Stansell, J.; Leoung, G.; Kovacs, J.; Rogers, M.; Scott, J. *Clin. Infect Dis.*, **1997**, *24*, 422–429.

[27] Malarone prescribing information http://us.gsk.com/products/assets/us_malarone.pdf

[28] (a) Hudson, A. T.; Randal, A. W. *Eur. Pat. Appl.*, 123238, **14 Apr 1984**. (b) Hudson, A. T. *PCT Int. Appl.,* 9104021, **26 Oct 1989**.

[29] Kumar, A.; Dike, S. Y.; Mathur, P.; Nellithanath, B. T.; Sharma, B.; Kore, S. .; Buchude, V. S. *PCT Int. Appl*., 2009007991, **15 Jan 2009**.

[30] (a) McHardy, N.; Wekesa, L. S.; Hudson, A.T.; Randall, A. W. *Res Vet Sci.*, **1985**, *39*, 29-33. (b) Muraguri, G.R.; Kiara, H. K.; McHardy, N. *Vet. Parasitol.*, **1999**, *87*, 25-37.

[31] Hudson, A. T.; Randall, A. W. *Eur. Pat. Appl.*, 77551, **27 Apr 1983**.

[32] (a) Minotti, G.; Menna, P.; Salvatorelli, E.; Cairo, G.; Gianni, L. *Pharmacol Rev.*, **2004**, *56*, 185–229. (b) Peng, X;. Chen, B.; Lim, C. C.; Sawyer, D. B. *Mol. Interv.*, **2005**, *5*, 163–71.

[33] Momparler, R. L.; Karon, M.; Siegel, S. E.; Avila, F. *Cancer Res.*, **1976**, *36*, 2891–2895.

[34] (a) Tan, C.; Tasaka, H.; Yu, K-P.; Murphy, L.; Karnofsky, D. *Cancer*, **1967**, *20*, 333–53. (b) Di Marco, A.; Gaetani, M.; Scarpinato, B. *Cancer Chemother. Rep.*, **1969**, *53*, 33-7.

[35] Lown, J. W. *Pharmacol. Therapeut*., **1993**, *60*, 185–214.

[36] (a) Hortobágyi, G. N. *Drugs*, **1997**, *54,* 1-7. (b) Gewirtz, D. A. *Biochem. Pharmacol*., **1999**, *57*, 727 –741.

[37] Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Tetrahedron*, **1984**, *40*, 4649-4656.

[38] Niraula, N. P.; Kim, S-H.; Sohng, J. K.; Kim, E-S. *Appl Microbiol Biotechnol*, **2010**, *87*, 1187–1194.

[39] Weiss, R. B. *Semin. Oncol*., **1992**, *19*, 670-86.

[40] Farquhar, D.; Cherif, A.; Bakina, E.; Nelson, J. A. *J. Med. Chem.*, **1998,** *41,* 965-972.

[41] Adams, N.; Blake, C.; Broadhurst, M. J.; Bushnell, D. J.; Hassall, C. H.; Hartmann, H. R. Keech, E.; Stratton, A. R.; Thomas, G. J. *J. Med. Chem.*, **1990**, *33*, 2380–2384.

[42] (a) Marshall, V. P.; Reisender, E. A.; Reineke, L. M.; Johnson, J. H.; Wiley, P. F. *Biochemistry*, **1976**, 15, 4139–4145. (b) Johdo, O.; Yoshioka, T.; Naganawa, H.; Takeuchi, T.; Yoshimoto, A. *J. Antibiot.*, **1996**, *49*, 669-675.

[43] Onrust, S. V.; Lamb, H. M. *Drugs Aging,* **1999**, *15*, 69-75.

[44] Altreuter, T. H.; Clark, D. S.; Michels, P. C.; Rich, J. O.; Meckler, H.; Dordick, J. S. *PCT Int. Appl.*, 2003057896, **17 Jul 2003**.

[45] Zabudkin, A. F.; Matvienko, V.; Itkin, A. M.; Matveev, A. *U.S. Pat. Appl. Publ.*, US 20070142309 A1 20070621, **2007**.

[46] Bjelogrlic S. K.; Radic, J.; Radulovic, S.; Jokanovic, M.; Jovic, V. *Exp. Biol. Med.* **2007**, *232*, 1414 -1424.

[47] Murdock, K. C.; Child, R. G.; Fabio, P. F.; Angier, R. B. *J. Med. Chem.*, **1979**, *22*, 1024-30.

[48] Kapuscinski, J.; Darzynkiewicz, Z. *Proc. Natl. Acad. Sci. USA*, **1986**, 83, 6302-6306.

[49] Scott, L. J.; Figgitt, D. P. *CNS Drugs*, **2004**, *18*, 379-396.

[50] Durr, F. E.; Murdock, K. C. *U.S.Pat Apl*, 4197249, **08 Apr 1980**.

[51] Stefanska, B.; Dzieduszycka, M.; Martelli, S.; Tarasiuk, J.; Bontemps-Gracz , M.; Borowski, E. *J. Med. Chem*., **1993**, 36, 38-41.

[52] (a) Fry, D. W.; Boritzki, T. J.; Besserer, J. A.; Jackson, R. C. *Biochem. Pharmacol*., **1985**, *34*, 3499 -3508. (b) Judson, I. R. *Semin. Oncol.*, **1992**, *19*, 687-694.

[53] Showalter, H. D. H.; Johnson, J. L.; Hoftiezer, J. M.; Turner, W. R.; Werbel, L. M.; Leopold, W. R.; Shillis, J. L.; Jackson, R. C.; Elslager, E. F. *J. Med. Chem*., **1987**, *30*, 121-131.

[54] Beylin, V. G.; Goel, O. P.; Showalter, H. D. H. *U.S. Pat.* 4672129, **06 Jun 1987**.

[55] Showalter, H. D. H.; Arbor, A.; Johnson, J. L.; Leslie, M. Y.; Werbel, E. F. *U. S. Pat. Apl*. 4556654, **03 Dec 1985**.

[56] Gogas, H.; Mansi, J. L. *Cancer Treat. Rev.*, **1996**, *21*, 541-52.

[57] Albain, K. S.; Liu P. Y.; Hantel, A.; Poplin, E. A.; O'Toole, R. V; Wade, J. L. 3rd; Maddox, A. M.; Alberts, D. S.; *Gynecol. Oncol*., **1995**, 57, 407-11.

[58] (a) Spinelli, S.; Didomenico, R. *PCT Int. Appl*., 9526189, **05 Oct 1995**. (b) Krapcho, A. P.; Petry, M. E.; Getahun, Z.; Landi, J. J. Jr.; Stallman, J.; Polsenberg, J. F.; Gallagher, C. E.; Maresch, M. J.; Hacker, M. P. *J. Med. Chem.*, **1994**, *37*0, 828-37.

[59] (a) El-Helw, L.M.; Hancock, B.W. *Future Oncol.*, **2009**, *5*, 445-53. (b) Papadatos-Pastos, D.; Pettengell, R. *Expert Rev. Hematol*., **2013**, *6*, 25-33.

[60] http://www.celltherapeutics.com/pixantrone

[61] http://www.evapharma.com/products/Diacerein-Cap/

[62] Fidelix, T.S.; Soares, B.; Trevisani V., F. M. Diacerein for osteoarthritis. *Cochrane Database of Systematic Reviews*, **2006**, *1*. Art. No.: CD005117.

[63] Mao, Y.; Varoglu, M.; Sherman, D. H. J. *Bacteriol*., **1999**, *181*, 2199-2208.

[64] (a) Webb, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidacks, C. *J. Am. Chem. Soc*., **1962**, *84*, 3185-3187. (b) Webb, J. S.; Cosulich, D. B.; Mowat, J. H.; Patrick, J. B.; Broschard, R. W.; Meyer, W. E.; Williams, R. P.; Wolf, C. F.; Fulmor, W.; Pidacks, C. *J. Am. Chem. Soc*., **1962**, *84*, 3187-3188.

[65] Bradner, W. T. *Cancer Treat. Rev.*, **2001**, *27*, 35–50.

[66] (a) Hornemann, Y.; Kehrer, J. P.; Nunez, C. S.; Ranieri, R. L. *J. Am. Chem. Soc.*, **1974**, *96*, 320–322. (b) Anderson, G. M.; Kibby, J. J.; Rickards, R. W.; Rotschild, J. M. *J. Chem. Soc., Chem. Commun*., **1980**, *24*, 1277–1278. (c) Varoglu, M.; Mao, Y.; Sherman, D. H. *J. Am. Chem. Soc*. **2001**, *123*, 6712 –6713.

[67] Kennedy, K. A.; Rockwell, S.; Sartorelli, A. C. *Cancer Res*., **1980**, *40*, 2356–2360.

[68] (a) Hornemann, U.; Ho, Y-K.; Mackey Jr., J. K.; Srivastava, S. C. *J. Am. Chem. Soc.*, **1976**, *98*, 7069 -7074. (b) Keyes, S. R.; Fracasso, P. M.; Heimbrook, D. C.; Rockwell, S.; Sligar, S. G.; Sartorelli, A. C. *Cancer Res.*, **1984**, *44*, 5638–5643.

[69] Andrez, J-C. *Beilstein J. Org. Chem.*, **2009,** *5,* No. 33.

[70] Floss, H. G.; Yu, T-W. *Chem. Rev*., **2005**, 105, 621-635.

[71] (a) DeBoer, C.; Meulman, P.A.; Wnuk, R.J.; Peterson, D.H. *J. Antibiot*., **1970**, *23*, 442-447.

[72] Schulte, T. W.; Neckers, L. M. *Cancer Chemother. Pharmacol*., **1998**, *42*, 273-279.

[73] Pacey, S.; Gore, M;; Chao, D.; Banerji, U.; Larkin, J.; Sarker, S.; Owen, K.; Asad, Y.; Raynaud, F.; Walton, M.; Judson, I.; Workman, P.; Eisen, T. *Invest. New Drugs*, **2012**, *30*, 341-349.

[74] Hong, D. S.; Banerji, U.; Tavana, B.; George, G. C.; Aaron, J.; Kurzrock, R. *Cancer Treat. Rev*., **2013**, *39*, 375-387.

[75] Pacey, S.; Wilson, R.H.; Walton, M.; Eatock, M. M.; Hardcastle, A.; Zetterlund, A.; Arkenau, H. T.; Moreno-Farre, J.; Banerji, U.; Roels, B.; Peachey, H.; Aherne, W.; de Bono, J. S.; Raynaud, F.; Workman, P.; Judson, I. *Clin Cancer Res.*, **2011**, *15*, 1561-70.

[76] Lancet J. E.; Gojo, I.; Burton, M.; Quinn, M.; Tighe, S. M.; Kersey, K.; Zhong, Z.; Albitar, M. X.; Bhalla, K.; Hannah, A. L.; Baer, M. R. *Leukemia*, **2010**, *24*, 699-705.

[77] Lee, D.; Lee, K.; Cai, X. F.; Dat, N. T.; Boovanahalli, S. K.; Lee, M.; Shin, J. C.; Kim, W.; Jeong, J. K.; Lee, J. S.; Lee, C-H.; Lee, J-H.; Hong, Y-S.; Lee, J. J. *ChemBioChem*., **2006**, *7*, 246-248.

[78] Kilm, W.; Lee, D.; Hong, S. S.; Na, Z.; Shin, J. C.; Roh, S. H.; Wu, C-Z.; Choi, O.; Lee, K.; Shen, Y -M.; Paik, S-G.; Lee, J. J.; Hong, Y-S. *ChemBioChem*., **2009**, *10*, 1243-1251.

[79] Wehrli, W.; Staehelin, M. *Bacteriol. Rev*., **1971**, *35*, 290-309.

[80] Floss H. G.. Yu T. W. *Chem Rev*., **2005**, *105*, 621-632.

[81] Prelog, V. *Pure Appl. Chem*., **1963**, *7*, 551-564.

[82] Campbell, E. A.; Korzheva, N.; Mustaev, A.; Murakami, K.; Nair, S.; Goldfarb, A.; Darst, S.A. *Cell,* **2001**, *104*, 901–12.

[83] Rivkin, A.; Gim, S. *Clin. Ther. 33*, **2011**, 812-827.

[84] Temple, M. E.; Nahata, M. C. *Ann. Pharmacother*., **1999**, *33*, 1203-1210.

[85] (a) Sanfilippo, A.; Della Bruna, C.; Marsili, L.; Morvillo, E.; Pasqualucci, C. R.; Schioppacasi, G.; Ungheri, D. *J. Antibiot*., **1980**, *33*, 1193-1198.

[86] Guidelines for treatment of tuberculosis, fourth edition, WHO, **2010**, ISBN: 9789241547833.

[87] Maggi, N.; Pasqualucci, C. R.; Ballotta, R.; Sensi, P. *Chemother*., **1966**, *11*, 285-292.

[88] Maggi, N.; Gallo, G. G.; Sensi, P. *Farmaco-Ed. Sci.*, **1967***, 22,* 316-322.

[89] Maggi, N.; Arioli, V.; Sensi, P. *J. Med. Chem*., **1965**, *8*, 790-793.

[90] Dampier, M. F.; Chen, C-W.; Whitlock Jr., H. W. *J. Am. Chem. Soc*., **1976**, *98*, 7064-7069.

[91] Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J., Jr.; Sakai, R.; Thompson, A. G.; Sthroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. J. *J. Nat. Prod.*, **1990**, *53*, 771.

[92] Hartley, J. A.; Hochhauser, D. *Curr. Opin. Pharmacol.*, **2012**, *12*, 398–402.

[93] [No authors listed] *Drugs R. D*., **2006**, 7, 317-328.

[94] D' Incalci, M.; Galmarini, C. M. *Mol. Cancer Ther.*, **2010**, *9*, 2157-2163.

[95] Cuevas, C.; Perez, M.; Martin ,M. J.; Chicharro, J. L.; Fernandez-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de La Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett*., **2000**, *2*, 2545-8.

[96] Piel, J. *Curr. Med. Chem.*, **2006**, *13,* 39-50.

[97] Fishbach, M. A.; Walsh, C. T. *Chem. Rev.*, **2006**, *106*, 3468-3496.

[98] Sherman, D. H.; Ehrlich, G. D.; Janto, B.; Williams, R. M.; Rath, C. M. *PCT Int. Appl.*, WO 2011130719 A2, **02 Nov 2011**.

[99] (a) Pospiech, A.; Cluzel, B.; Bietenhader, J.; Schupp, T. *Microbiology*, **1995**, *141*, 1793-1803. (b) Velasco, A.; Acebo, P.; Gomez, A.; Schleissner, C.; Rodríguez, P.; Aparicio, T.; Conde, S.; Muñoz, R.; de la Calle, F.; Garcia, J. L.; Sánchez-Puelles, J. M. *Mol. Microbiol*., **2005**, *56*, 144-154. (c) Li, L.;

Deng, W.; Song, J.; Ding, W.; Zhao, Q. F.; Peng, C.; Song, W. W.; Tang, G. L.; Liu, W. *J. Bacteriol*., **2008**, *190*, 251-263.

[100] Rath, C. M.; Janto, B.; Earl, J.; Ahmed, A.; Hu, F. Z.; Hiller, L.; Dahlgren, M.; Kreft, R.; Yu, F.; Wolff, J. J.; Kweon, H. K.; Christiansen, M. A.; Håkansson, K.; Williams, R. M.; Ehrlich, G. D.; Sherman, D. H. *ACS Chem Biol.*, **2011**, *6*, 1244-1256.

[101] (a) Johnson, A.W. Ylid Chemistry, Department of Chemistry, University of Saskatchewan, Regina, Saskatchewan, Canada, Academic Press, New York, **1966**, pp. 388. (b) Kröhnke, F. *Synthesis*, **1976**, 1-24.

[102] (a) Kesteleyn, B.; Van Puyvelde, L.; De Kimpe, N. *J. Org. Chem.*, **1999**, *64*, 438-440. (b) Jacobs, J.; Claessens, S.; De Mol, E.; El Hady, S.; Minguillon, C.; Alvarez, M.; De Kimpe, N. *Tetrahedron*, **2010**, *66*, 5158-5160.

[103] (a) King, L.C.; Ostrum, G. K. *J. Org. Chem.*, **1964**, *29*, 3459-3461. (b) Aldersley, M.F.; Dean, F.M.; Hamzah, A.S. *Tetrahedron Lett*., **1986**, *27*, 255-258.

[104] (a) Kesteleyn, B.; Nguyen Van, T.; De Kimpe, N. *Tetrahedron*, **1999**, *55*, 2091-2102. (b) Nguyen Van, T.; Verniest, G.; Claessens, S.; De Kimpe N. *Tetrahedron*, **2005**, *61*, 2295-2300. (c) Jacobs, J.; Claessens, S.; Mbala, B. M.; Huygen, K.; De Kimpe, N. *Tetrahedron*, **2009**, *65,* 1193-1199

[105] (a) Zhao, S.; Neves, M.G.P.M.S.; Tome, A.C.; Silva, A.M.S.; Cavaleiro, J.A.S. *Tetrahedron Lett*., **2005**, *46*, 5487-5490. (b) Liu, Y.; Hu, H.-Y.; Liu, Q.-J.; Hu, H.-W.; Xu, J.-H. *Tetrahedron*, **2007**, *63*, 2024-2033.

[106] Claes, P. 'Nieuwe toetredingen tot heterocyclisch geanneleerde Chinonen', *Master thesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, **2008-2009**.

[107] Del Villar, I. S.; Gradillas, A.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett*., **2010**, *51*, 3095-3098.

[108] Yadav, L.D.S.; Garima, R.K. *Synlett*, **2009**, *19*, 3123-3126.

[109] Claes, P.; Jacobs, J.; Claessens, S.; De Kimpe, N. *Tetrahedron*, **2010**, *66*, 7088-7096.

[110] Wang, B-X.; He, T.; Hu, H-W. *Huaxue Xuebao*, **2003**, *61*, 889-892, 2003.

[111] Hu, H.; Shi, K.; Hou, R.; Zhang, Z.; Zhu, Y.; Zhou, J. *Synthesis*, **2010**, *23*, 4007-4014.

[112] (a) Adib, M.; Mohamadi, A.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. R. *Synlett*, **2010**, *11*, 1606-1608 (b) Proença, M. F.; Costa, M. *Tetrahedron*, **2010**, 66, 4542-4550. (c) Lee, H. S.; Lee, S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.*, **2011**, *52*, 5039–5042. (d) Naskar, S.; Banerjee, M.; Hazra, A.; Mondal, S.; Maity, A.; Paira, R.; Sahu, K. B.; Saha, P.; Banerjee, S.; Mondal, N. B. *Tetrahedron Lett*., **2011**, *52*, 1527–1531.

[113] Mattsson, S.; Dahlström, M.; Karlsson, S. *Tetrahedron Lett*., **2007**, *48*, 2497-2499.

[114] Paranagama, P. A.; Wijeratne, E. M. K.; Burns, A. M.; Marron, M. T.; Gunatilaka, M. K.; Arnold, A. E.; Gunatilaka, A. A. L. *J. Nat. Prod.*, **2007**, *70,* 1700–1705.

[115] Opatz, T.; Kolshorn, H.; Eckhard, T.; Anke, H. *J. Nat. Prod.*, **2008**, *71*, 1973-1976.

[116] (a) Wang, L.; Dong, J. Y.; Song, H. C.; Shen, K. Z.; Wang, L. M.; Sun, R.; Wang, C. R.; Gao, Y. X.; Li, G. H.; Li, L.; Zhang, K. Q.; *Planta Med.*, **2009**, *75*, 1339-1343. (b) Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A.; *Tetrahedron Lett.*, **1991**, *32*, 5279.

[117] (a) Sperry, J.; Yuen, T. Y.; Brimble, M. A.; *Synthesis*, **2009**, 2561-2569. (b) Sperry, J.; Brimble, M. A.; *Synlett*, **2008**, 1910-1912. (c) Brimble, M. A.; Houghton, S. I.; Woodgate, P. D.; *Tetrahedron*, **2007**, *63*, 880-887. (d) Bulbule, V. J.; Koranne, P. S.; Deshpandeb, V. H.; Borate, H. B.; *Tetrahedron*, **2007**, *63*, 166-170. (e) Sawant, R. T.; Waghmode, S. B.; *Tetrahedron*, **2009**, *65*, 1599-1602. (f) Donner, C. D.; Gill, M.; *Tetrahedron Lett.*, **1999**, *40*, 3921-3924.

[118] Bringmann, G.; Zhang, G;; Hager, A.; Moos, M.; Irmer, A.; Bargou, R.; Chatterjee, M. *Eur. J. Med. Chem*., **2001**, *46*, 5778-5789.

[119] McGarrigle, E. M.; Murphy, D. M.; Gilheany, D. G. *Tetrahedron-Asymmetr*., **2004**, *15*, 1343-1354.

[120] Tomatsu, A.; Takemura S.; Hashimoto, K.; Nakata, M. *Synlett*, **1999**, *9*, 1474-1476.

[121] Nguyen Van, T.; Verniest, G.; Claessens, S.; De Kimpe, N. *Tetrahedron*, **2005**, *61*, 2295-2300.

[122] Sibi, M. P.; Dankwardt, J. W.; Snieckus, V. *J. Org. Chem*., **1986**, *51*, 271-273.

[123] Mikhaleva, A. I.; Ivanov, A. V.; Skital'tseva, E. V.; Ushakov, I. A.; Vasil'tsov, A. M.;. Trofimov, B. A. *Synthesis*, **2009**, *4*, 587-590.

[124] Sörgel, S.; Azap, C.; Reißig, H-U. *Eur. J. Org. Chem.*, **2006**, 4405–4418.

[125] (a) Mal, D.; Pahari, P. *Chem. Rev.*, **2007**, *107*, 1892-1918. (b) Rathwell, K.; Brimble, M. A. *Synthesis*, **2007**, *5*, 643-662.

[126] Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lua, F-J.; Schmidt, J. P. *Bioorg. Med. Chem*., **2004**, *12*, 4285–4299.

[127] Wadsworth, A. D.; Sperry, J. Brimble, M. A. *Synthesis*, **2010**, *15*, 2604–2608.

[128] Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett.*, **1998**, *8*, 1579-l 584.

[129] Dong, W-K.; Huang, X.; Xu, D-C.; Lia, X-S.; Xie, J-W. *J. Braz. Chem. Soc*., **2012**, *23*, 280-284.

[130] Hawas, U. W.; Shaaban, M.; Shaaban, K. A.; Speitling, M.; Maier, A.; Kelter, G.;Fiebig, H. H.; Meiners, M.; Helmke, E.; Laatsch, H. *J. Nat. Prod.*, **2009,** *72,* 2120–2124.

[131] Milanowski, D. J.; Gustafson, K. R.; Kelley, J. A.;McMahon, J. B. *J. Nat. Prod*., **2004**, *67*, 7 0–73.

[132] Alagille, D.; Baldwina, R. M.; Tamagnan, G. D. *Tetrahedron Lett*., **2004**, *45*, 6179–6181.

[133] Nguyen Van, T.; Verniest, G.; Claessens, S. De Kimpe, N. *Tetrahedron*, **2005**, *61*, 2295–2300.

[134] (a) Mal, D.; Ray, S. *Eur. J. Org. Chem.* **2008**, *17*, 3014–3020. (b) Wipf, P.; Kim, Y.; Jahn, H. *Synthesis*, **1995**, *12*, 1549-1561.

[135] (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.*, **2001**, *124*, 2212-2220. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Sugita, K. *J. Am. Chem. Soc.*, **2001**, *124*, 2221-2232.

[136] Tandon, V. K.; Maurya, H. K. *Tetrahedron. Lett*., **2009**, *50*, 5896-5902.

[137] Ott, R.; Pinter, E.; Kajtna, P. *Monatsh. Chem*., **1979**, *110*, 51-62.

[138] Bittner, S.; Lempert, D. *Synthesis*, **1994**, *9*, 917-919.

[139] (a) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.*, **1999,** *64,* 5575-5580. (b) Qin, L.; Cui, H.; Zou, D.; Li, J.; Wua, Y.; Zhu, Z.; Wub, Y. *Tetrahedron Lett*., **2010**, *51*, 4445–4448.

[140] Xu, H.; Wolf, C. *Chem. Commun*., **2009**, *13*, 1715–1717.

[141] (a) Jiang, B.; Huang, Z-G. *Synthesis*, **2005**, *13*, 2198–2204. (b) Zhao, J-L.; Liu, L.; Zhang, H-B. Wu, Y-C.; Wang, D.; Chen, Y-J. *Synlett*, **2006**, *1*, 96–100. (c) Sakai, N.; Asano, J.; Shimano, Y.;

Konakahara, T. *Tetrahedron*, **2008**, *64*, 9208–9215. (d) Kang, Q.; Zhao, Z-A.; You, S-L. *Tetrahedron*, **2009**, *65* 1603–1607.

142 Zhou, Y.; Zhao, M.; Wub, Y.; Li, C.; Wub, J.; Zheng, M.; Peng, L.; Peng, S. *Bioorg. Med. Chem*., **2010**, *18*, 2165–2172.

143 Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles*, **1987**, *26*, 2805-2809.

144 (a) Kubo, A.; Nakahara, S. Inaba, K.; Kithara, Y. *Chem. Pharm. Bull.,* **1986**, *34*, 4056-4068. (b) Bracca, A. B. J.; Kaufman, T. S. *Eur. J. Org. Chem*., **2007**, *31*, 5284–5293.

145 Kido, K.; Watanabe, Y. *Chem. Pharm. Bull*., **1987**, *35*, 4964-4966.

146 Beerlink, J. 'Totalsynthese der Mansouramycine AE aus Streptomyces sp. und Rhodiumkatalysierte 1,2 -Additionen an cyclische Enone', *PhD thesis,* Institute for Organic and Biomolecular Chemistry, Göttingen University, **2008**.

147 Suzuki, H.; Sakai, N.; Iwahara, R.; Fujiwaka, T. Satoh, M.; Kakehi, A.; Konakahara, T. *J. Org. Chem.*, **2007**, *72*, 5878-5881.

148 (a) Todorovic, N. Awuah, E.; Albu, S.; Ozimok, C.; Capretta, A. *Org. Lett*., **2011**, *13*, 6180-6183. (b) Yang, F.; Zhang, J.; Wu, Y. *Tetrahedron*, **2011**, *67*, 2969-2973. (c) Villuendas, P.; Urriolabeitia, E. P. *J. Org. Chem.*, **2013**, *78*, 5254–5263.

149 Kirchmeyer, S.; Mertens, A.; Arvanaghi, M.; Olah G. A. *Synthesis*, **1983**, *6*, 498-500.

150 Ahlbrecht, H.; Raab, W. *Synthesis*, **1980**, *4*, 320-322.

151 Itokawa, H.; Ibraheim, Z. Z.; Qiao, Y. F.; Takeya, K. *Chem. Pharm. Bull*., **1993**, *41*, 1869–72.

152 El-Hady, S.; Bukuru, J.; Kesteleyn, B.; Van Puyvelde, L.; Nguyen, V. T.; De Kimpe, N. *J. Nat. Prod*., **2002**, *65*, 1377–1379.

153 Sastry, M. N. V.; Claessens, S.; Habonimana, P.; De Kimpe, N. *J. Org. Chem*., **2010**, *75*, 2274–2280.

154 Habonimana, P.; Claessens, S.; De Kimpe, N. *Synlett*, **2006**, *15*, 2472–2475.

155 Lumb, J-P.; Trauner, D. *J. Am. Chem. Soc.*, **2005**, *127*, 2870-2871.

156 Stipanovic, R. D.; Zhang, J.; Bruton, B. D.; Wheeler, M. H. *J. Agric. Food Chem*., **2004**, *52*, 4109-4112.

157 (a) Spreitzer, H.; Holzer, W.; Pushmann, C.; Pichler, A.; Kogard, A.; Tschetschkowitsch, K.; Heinze, T.; Bauer, S.; Shabaz, N. *Heterocycles*, **1997**, *45*, 1989-1997. (b) Spreitzer, H.; Pichler, A.; Holzer, W.; Kratzel, M.; Slanz, R.; Koulouri, A.; Krenn, P.; Parrer, U.; Szieber, P. *Heterocycles*, **1998**, *54*, 111-121.

158 Adogla, E. A.; Janser, R. F. J.; Fairbanks, S. S.; Vortolomei, C. M.; Meka, R. K.; Janser, I. *Tetrahedron Lett*., **2012**, *53*, 11-14.

159 Sibi, M. P.; Miah, M. A. J.; Snieckus, V. *J. Org. Chem*., **1984**, *49*, 737-742.

160 Lalic, G.; Corey, E. J. *Org. Lett.*, **2007**, *9*, 4921-4923.

161 Shanab, K.; Pongprom, N.; Wulz, E.; Holzer, W. Spreitzer, H.; Schmidt, P.; Aicher, B.; Müller, G. Günther, E. *Bioorg. Med. Chem. Lett*., **2007**, *17*, 6091–6095.

162 Haggiage, E.; Coyle, E. E.; Joyce, K.; Oelgemöller, M. *Green Chem*., **2009**, *11*, 318-321.

163 Ripper, J.; Janssen, C.; Jenkins, I.; Le, P. V.; Quin, R. *WO2005061484A1*, **7 Jul 2005**.

164 Clayden, J.; Stimson, C. C.; Helliwell, M.; Keenan, M. *Synlett*, **2006**, 6, 873–876.

165 Hartmann, C. E.; Groß, P. J.; Niegerb, M.; Bräsea, S. *Org. Biomol. Chem*., **2009**, *7*, 5059–5062.

166 Minato, A.; Tamao, K.; Hayashi, T.; Suzuki, K.; Kumada, M. *Tetrahedron Lett.*, **1981**, *22*, 5319-5322.

[167] (a) Markwalder, J. A.; Mutlib, D. D. C. A.; Cordova, B. C.; Klabe, R. M.; Seitz, S. P. *Bioorg. Med. Chem. Lett.*, **2011**, *11*, 619-622. (b) Couladouros, E. A.; Strongilos, A. T.; Papageorgiou, V. P.; Plyta, Z. F. *Chem. Eur. J.*, **2002**, *8*, 1795-1803. (c) Nicolaou, K. C.; Xu, H.; Wartmann, M. *Angew. Chem. Int. Ed.*, **2005**, *44*, 756 –761.

[168] (a) Jones, S. S.; Reese, C. B. *J. Chem. Soc. Perkin. Trans. I*, **1979**, 2762-2764. (c) Mulzer, J.; Schöllhorn, B. *Angew. Chem. Int. Ed*., **1990**, *29*, 431-432.

[169] Dos Santos, E. d. A.; Beatriz, A.; Pires de Lima, D.; Marques, M. R.; Leite, C. B. *Quim. Nova*, **2009**, *32*, 1856-1859.

[170] Aquino-Binag, C.; Kumar, N.; Pigram, P. *Org. Prep. Proced. Int.*, **1995**, *27*, 700-703.

[171] De Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron,* **1992**, *48*, 4863-4869.

[172] Van Hende, E. 'Synthesis of fluorinated azaheterocyclic compounds', *PhD thesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering*, Ghent University* **2009**.

[173] Schuler, M.; Silva, F.; Bobbio, C.; Tessier, A.; Gouverneur, V. *Angew. Chem. Int. Ed*., **2008**, *47*, 7927 -7930

[174] Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. *J. Org. Chem.*, **2010**, *75*, 897–901.

[175] Nguyen Van, T.; Kesteleyn, B.; De Kimpe, N. *Tetrahedron*, **2002**, *58*, 121-127.

[176] Kelley, M. R.; Borch, R. F.; Nyland, R. L. *WO2009042544A1*, **2 Apr. 2009**.

[177] Hotter, G. S.; Collins, D. M. *Vet. Microbiol*., **2012**, *151*, 91-98.

[178] (a) Cortez-Escalante, J. J.; Santos, A. M.; Garnica, G. C.; Sarmento, A. L.; Castro, C.N.;Romero, G.A. *Rev. Soc. Bras. Med. Trop*. **2012**, *45*, 407-409. (b) Chiodini, R.J.; Chamberlin, W.M.; Sarosiek, J.; McCallum, R.W. *Crit. Rev. Microbiol*. **2012**, *38*, 52-93.

[179] Einarsdottir, T.; Huygen, K. *Hum. Vaccin*. **2012**, *7*, 1198-1203.

[180] Luo, X.; Pedro, L.; Milic, V.; Mulhovo, S.; Duarte, A.; Duarte, N.; Ferreira, M-J. U. *Planta Med*., **2012**, *78*, 148–153.

[181] Rickards, R. W.; Rothschild, J. M.; Willis, A. C.; de Chazal, N. M.; Kirk, J.; Kirk, K.; Saliba, K. J.; Smith, G. D. *Tetrahedron*, **1999**, *55*, 13513.

[182] Bernardo, P. H.; Fitriyano, W.; Chai, C. L. L. *Synlett*, **2007**, *12*, 1935-1939. (b) Matsumoto, K.; Choshi, T.; Hourai, M.; Zamami, Y.; Sasaki, K.; Abe, T.; Ishikura, M.; Hatae, N.; Iwamura, T.; Tohyama, S.; Nobuhiro, J.; Hibino, S. *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 4762–4764.

[183] Müller, P.; Venakis, T.; Uegster, C. H. *Helv. Chim. Acta*, **1979**, *62*, 2833-2840.

[184] Sirisha, K.; Bikshapathi, D.; Achaiah, G.; Reddy, V. M. *Eur. J. Med. Chem.*, **2011**, *46,* 1564-157.

[185] Pardo, M.; Joos, K.; Schäfer, W. *Liebigs Ann. Chem*., **1979**, 503-521.

[186] (a) Harayama, T.; Akiyama, T.; Kawano, K. *Chem. Pharm. Bull*., **1996**, *44*, 1634-1636. (b) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc*., *Perkin Trans. 1*, **2001**, *5*, 523–528. (c) Bernardo, P. H.; Khanijou, J. K..; Lam, T. H.; Tong, j. C.; Chai, C. L. L. *Tetrahedron Lett*. **2011**, *52*, 92–94.

[187] Bernardo, P. H.; Khanijou, J. K.; Lam, T. H.; Tong, J. C.; Chai, C. L. L. *Tetrahedron Lett*., **2011**, *52*, 92-94.

[188] Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.*, **2005**, *127*, 13754-13755.

[189] García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.*, **2006**, *128*, 1066-1067.

[190] Iino, T.; Asai, M.; Ohno, A.; Inamura, S.; Ishikawa, M.; Ohtake, N. *WO2010024110A1*, 4 Mar **2010**.

[191] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, N. *Org. Lett*., **2008**, *10*, 1759-1762.

[192] (a) Kawanaka, Y.; Kobayashi, K.; Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.; Fujii, A.; Hirai, K.; Naka, M.; Komeno, M.; Nakai, H.; Toda, M. *Eur. J. Med. Chem.*, **2003**, *38*, 277 -288. (b) Szostak, M.; Yao, L.; Aubé, J. *J. Am. Chem. Soc*., **2010**, *132*, 2078-2084.

[193] Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tatsuzawa, T.; Tokuda, M.; Suginome, H. *J. Org. Chem.*, **2000**, *65,* 7495-7500.

[194] Pasturel, J. Y.; Solladie, G.; Maignan, J. *Fr. Demande*, FR 2833259 A1 20030613, **2003**.

[195] Guillier, F.; Nivoliers, F.; Godart, A.; Marsais, F.; Quéguiner, C.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem*., **1995**, *60*, 292-296.

[196] (a) Hendrickson, J. B.; Bergeron, R. *Tet. Lett*., **1973**, *46*, 4607-4610. (b) Rudyanto, M.; Yuichiro T., Morita, H.; Honda, T. *Org. Lett.*, **2008**, *10*, 1921–1922.

[197] (a) Xiao, K-J.; Luo, J-M.; Ye, K-Y.; Wang, Y.; Huang, P-Q. *Angew. Chem. Int. Ed*., **2010**, *49*, 3037 –3040. (b) Xiao, K-J.; Wang, Y.; Ye, K-Y.; Huang, P-Q. *Chem. Eur. J*., **2010**, *16*, 12792 – 12796. (c) Xiao, K-J.; Wang, A-E.; Huang, P-Q. *Angew. Chem. Int. Ed*., **2012**, *51*, 8314 –8317.

[198] Krapcho, P. A. *Eur. Pat. Appl.*, EP 503537 A1 19920916, **1992**.

[199] (a) Cheng, D.; Han, D.; Gao, W.; Jiang, J.; Pan, S.; Wan, Y.; Jin, Q. *PCT Int. Appl*., 2008014291, 31 Jan **2008**. (b) Baroni, M.; Bono, F.; Delbary-Gossart, S.; Vercesi, V. *PCT Int. Appl*., 2011080445, 07 Jul **2011**.

[200] (a) Bredereck, H.; Bredereck, K. *Chem. Ber.*, **1961**, *94*, 2278-2295. (b) Kelley, C.; Zhang, Y.; Parhi, A.; Kaul, M.; Pilch, D. S.; LaVoie, E. J. *Bioorg. Med. Chem*., **2012**, *20*, 7012-7029.

[201] Verniest, G.; Wang, X.; De Kimpe, N.; Padwa, A. *J. Org. Chem.*, **2010**, *75* 424–433.

[202] O'Connor, S. J.; Newcom, J. S.; Ralbovsky, J. L.; Gustafson, G. R.; Beckett, R. P.; Luo, R. X. *PCT Int. Appl*., 2010068520, 17 Jun **2010**.

[203] Sun, G.; Slassi, M.; Isaac, M.; Quach, T.; Xin, T.; He, Z. *PCT Int. Appl*., 2008009125, 24 Jan **2008**.

[204] Croisy-Delcey, M.; Carrez, D.; Bisagni, E. *Eur. J. Med. Chem.,* **1988**, *23*, 101-103.

[205] Hsu, D-S.; Huang, J-Y. *J. Org. Chem.*, **2012**, *77*, 2659–2666.

[206] Yongzhi, L.; Binke, N.; Mingjiu, L.; Lieping, W.; Zongying, L.; Chao, X.; Cheng X.; Yuemei, W.; Kangyun, L.; Qiaonan, S.; Jianping, Z. *Faming Zhuanli Shenqing*, 101863859, 20 Oct **2010**.

[207] Karthikeyan, J.; Haridharan, R.; Cheng, C-H. *Angew. Chem. Int. Ed.*, **2012**, *51*, 12343 –12347.

[208] (a) Kobayashi, K.; Uchida, M.; Uneda, T.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Tetrahedron Lett*., **1998**, 7725-7728. (b) Kobayashi, K.; Uchida, M.; Uneda, T.; Yoneda, K.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans 1*, **2001**, 2977-2982.

[209] (a) Jacobs, J.; Kesteleyn, B.; De Kimpe, N. Tetrahedron, **2008**, *64*, 4985–4992. (b) (b) Jacobs, J.; Kesteleyn, B.; Mbala, B. M.; Diels, G.; De Kimpe, N. *Tetrahedron*, **2008**, *64*, 6364-6371.

[210] Kobayashi, K.; Takanohashi, A.; Watanabe, T.; Morikawa, O.; Konishi, H. *Tetrahedron Lett*., **2000**, 7657-7660.

[211] Schmid, G. H.; Rabai, J. *Synthesis*, **1998**, 332-33.

[212] Nyland II, R. L.; Luo, M.; Kelley, M. R.; Borch, R. F. *J. Med. Chem.*, **2010**, *53*, 1200-1210.

[213] Holvoet, F. 'Synthese van nieuwe 8,9,10,11-tetrahydrobenzo[*j*]fenantridine derivaten', *Masterthesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University **2013**.

[214] Enzensperger, C.; Lehmann, J. *J. Med. Chem.*, **2006,** *49,* 6408-6411.

[215] (a) Ortoleva, G. *Gazz. Chim. Ital*., **1899**, *29*, 503. (b) King, L. C. *J. Am. Chem. Soc.*, **1944**, *66*, 894-895.

[216] (a) Masuda, Y.; Hoshi, M.; Yamada, T.; Arase, A. *Chem. Commun*., **1984**, 398-399. (b) Burden, P. M.; Allan, R. D.; Hambley, T.; Johnston, G. A. R. *J. Chem. Soc., Perkin Trans 1*, **1998**, 3163-3169.

[217] (a) RajianBabu, T. V. (B.); Casalnuovo, A. L. *Pure Appl. Chem.*, **1994**, *66*, 1535-1542. (b) Yan, M.; Xu, Q-Y.; Chan, A. S. C. *Tetrahedron-Asymmetr*., **2000**, *11*, 845–849. (c) Falk, A.; Göderz, A-L.; Schmalz, H-G. *Angew. Chem. Int. Ed*., **2013**, *52*, 1576 –1580.

[218] (a) Brown, H. C.; Joshi, N. N.; Pyun, C.; Singaram, B. *J. Am. Chem. Soc*., **1989**, *111*, 1754-1758. (b) Clay, J. M.; Vedejs, E. *J. Am. Chem. Soc.*, **2005**, *127*, 5766-5767.

[219] (a) Valderrama, J. A.; Araya-Maturana, R.; Gonzáles, F.; Tapia, R.; Fariña, F.; Paredes, M. C. *J. Chem. Soc. Perkin Trans 1*, **1991**, 555-559. (b) Valderrama, Jaime A.; González, M. Florencia; Colonelli, Pamela; Vásquez, David *Synlett*, **2006**, *17*, 2777-2780. (c) Valderrama, J. A.; Colonelli, P.; Vásquez, D.; Florencia González, M.; Rodríguez, J. A.; Theoduloz, C. *Bioorg. Med. Chem.*, **2008**, *16*, 10172 -10181. (d) Iribarra, J.; Vásquez, D.; Theoduloz, C.; Benites, J.; Ríos, D.; Valderrama, J. *Molecules*, **2012**, *17*, 11616-11629.

[220] (a) Du, H.; Zhao, B.; Shi, Y. *Org. Synth.*, **2009**, *86*, 315-324. (b) Matsievitch, R.; Tworowski, D. *PCT Int. Appl.*, 2007110868, 04 Oct **2007**.

[221] (a) Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett*., **1997**, *38*, 8749-8752 (b) Chakraborti, A. K.; Sharma, L.; Nayak, M. K. *J. Org. Chem.*, **2002**, *67*, 6406-6414. (c) Mazzini, F.; Galli, F.; Salvadori, P. *Eur. J. Org. Chem.*, **2006**, *24*, 5588–5593.

[222] Sparrow, K.; Barker, D.; Brimble, M. A. *Tetrahedron*, **2012**, *68*, 1017-1028.

[223] Pralay, D.; Dharminder, S.; Bikram, S. *PCT Int. Appl*., 2011117881, 29 Sep **2011**.

[224] (a) Waterman, P.G.; Muhammad, I. *Phytochemistry* **1985**, *24*, 523-527. (b) Rao, J.U.M.; Giri, G.S.; Hanumaiah, T.; Rao, K.V.J. *J. Nat. Prod.*, **1986**, *49*, 346-347.

[225] Okunade, A.L.; Elvin-Lewis, M.P.R., Lewis, W.H. *Phytochemistry*, **2004**, *65*, 1017-1032.

[226] Bracher, F. *Liebigs Ann. Chem*., **1989**, 87-88.

[227] Yin, H.; Kong, F.; Wang, S.; Yao, Z-J *Tetrahedron Lett*., **2012**, *53*, 7078-7082.

[228] Mbala, B. M. 'Synthesis of quinoid natural products and their analogues', *PhD thesis,* Department of Sustainable Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, **2011**.

[229] Jacobs, J.; Claessens, S.; Mbala, B. M.; Huygen, K. H.; De Kimpe, N. *Tetrahedron*, **2009**, *65*, 1193 -1199.

[230] Finkelstein, J.; Linder, S. M. *J. Am. Chem. Soc.*, **1951**, *73*, 302–304.

[231] Claes, P.; Cappoen, D.; Mbala, B. M.; Jacobs, J.; Mertens B.; Mathys, V.; Verschaeve, L.; Huygen, K.; De Kimpe, N. *Eur. J. Med. Chem*. **2013**, *67*, 98-110.

[232] Copp, B. R.; Christiansen, H. C.; Lindsaya, B. G.; Franzblaub, S. G. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 4097–4099

[233] (a) Kesteleyn, B.; Van Puyvelde, L.; De Kimpe N. *J. Org. Chem.*, **1999**, *64*, 1173-1179. (b) Kesteleyn, B.; De Kimpe N. *J. Org. Chem.*, **2000**, *65*, 635-639. (c) Kesteleyn, B.; De Kimpe N. *J. Org. Chem.*, **2000**, *65*, 640-644. (d) Nguyen Van, T.; De Kimpe, N. *Tetrahedron*, **2003**, *59*, 5941-5946. (e) Claessens, S.; Jacobs, J.; Van Aeken, S.; Abbaspour Tehrani, K.; De Kimpe, N. *J. Org. Chem.*, **2008**, *73*, 7555-7559.

[234] (a) Itahara, T. *J. Org. Chem.*, **1985**, *50*, 5546-5550. (b) Singh, P. K.; Rohtagi, B. K.; Khanna, R. N. *Synth. Commun*., **1992**, *22*, 987-993. (c) Yogo, M.; Ito, C. Furukawa, H. *Chem. Pharm. Bull.*, **1991**, *39*, 328-334.

[235] (a) Huang, C.; Liu, B. *Chem. Commun.*, **2010**, *46*, 5280-5282. (b) Takenaga, N.; Uchiyama, T.; Kato, D.; Fujioka, H.; Dohi, T.; Kita, Y. *Heterocycles*, **2011**, *82*, 1327-1336.

[236] Jacobsen, N.; De Franco, R. J.; Benson, R. E. *Org. Synth*., **1977**, *56*, 68-71.

[237] (a) Goto, M.; Hayashi, T.; Goda, K.; Okada, Y. *Nippon Kagaku Kaishi*, **1986**, *8*, 1096-1101. (b) Kuntz, E.; Amgoune, A.; Lucas, C.; Godard, G. *J. Mol. Cat. A. Chem*., **2006**, *244*, 124-138. (c) Pincock, A. L.; Pincock, J. A.; Stefanova, R. *J. Am. Chem. Soc.*, **2002**, *124*, 9768-9778.

[238] (a) Rao, M. L. N.; Giri, S. *RSC Advances*, **2012**, *2*, 12739-12750. (b) Moon, Y.; Hong, S. *Chem. Commun.*, **2012**, *48*, 7191-7193. (c) Zhao, Y.; Zhang, Y.; Wang, J.; Li, H.; Wu, L.; Liu, Z. *Synlett*, **2010**, *15*, 2352-2356. (c) Molina, M. T.; Navarro, C.; Moreno, A.; Csákÿ, A. G. *Org. Lett*., **2009**, *11*, 4938-4941. (d) Knölker, H.-J.; Reddy, K. R. *Heterocycles*, **2003**, *60*, 1049-1052.

[239] (a) Ferreira, E. M.; Stolz, B. M. *J. Am. Chem. Soc.*, **2003**, *125*, 9578-9578. (b) Zhang, H.; Ferreira, E. M.; Stolz, B. M. *Angew. Chem. Int. Ed.*, **2004**, *43*, 6144-6148.

[240] Li, G.; Leow, D.; Wan, L.; Yu, J-Q. *Angew. Chem. Int. Ed*., **2013**, *52*, 1245-1247.

[241] (a) Perrin, D. D. Dissociation Constants of Organic Bases in Aqueous Solution; Butterworths: London, **1965**, 141-183. (b) Rogne, O. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 489-492. (c) Ramsey, B. G.; Walker, F. A. *J. Am. Chem. Soc.*, **1974**, *96*, 3314-3316. When no pKa reference could be found, a value was calculated using MarvinSketch 6.0.

[242] (a) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc*., **2010**, *132*, 11978-11987. (b) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*., **2007**, *129*, 11904-11905. (c) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. Eur. J.*, **2001**, *7*, 2481-2489. (d) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem*., **1984**, *49*, 4619-4631.

[243] (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc*., **2001**, *123*, 5816-5817. (b) Albéniz, C. A.; Catalina, M. M.; Espinet, P.; Redón, R. *Organometallics*, **1999**, *18*, 5571.

[244] Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*., **2011**, *133*, 4455-4464.

[245] (a) Izawa, Y.; Zheng, Z.; Stahl, S. S. *Angew. Chem. Int. Ed*., **2013**, *52*, 3672-3675. (b) Jana, R.; Pathak, T. P.; Jensen, K. H.; Sigman, M. S. *Org. Lett*., **2012**, *14*, 4074-4077. (c) Zheng, C.; Wang, D.; Stahl, S. S. *J. Am. Chem. Soc.*, **2012**, *134*, 16496-16499. (d) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc*., **2010**, *132*, 7870-7871. (e) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun*., **2004**, *2*, 218-219.

[246] Bailey, W. F.; Punzalan, E. R. *J. Org. Chem*., **1990**, *55*, 5404-5406.

[247] Yang, C-T.; Zhang, Z-Q.; Tajuddin, H.; Wu, C-C.; Liang, J.; Liu, J-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed*., **2012**, *51*, 528-532.

[248] Veguillas, M.; Redondo, M. C.; García, I.; Ribagorda, M.; Carreño, M. C. *Chem. Eur. J*., **2010,** *16*, 3707-3719.

[249] (a) Netherton, M. R;; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.*, **2001**, *123*, 10099-10100. (b) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.*, **2002**, *124*, 13662-13663. (c) Sato, B.; Fu, G. C. *J. Am. Chem. Soc*., **2007**, *129*, 9602-9603.

[250] Kim, J. G.; Walsh, P. J. *Angew. Chem. Int. Ed*., **2006**, *45*, 4175-4178.

[251] Schläger, T.; Oberdorf, C.; Tewes, B.; Wünsch, B. *Synthesis*, **2008**, *11*, 1788-1792.

[252] (a) Solodukhin, S. Y.; Peregudov, A. S.; Vorontsov, E. V.; Chkanikov, N. D. *Molecules*, **2004**, *9*, 164 -169. (b) Nadaraj, V.; Selvi, S. T. *Indian J. Chem*., **2007**, *46B*, 1203-1207.

[253] Bolognesi, M. L.; Lizzi, F.; Perozzo, R.; Brunc, R.; Cavalli, A. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 2272–2276.

[254] Martínez, A.; Fernándeze, M.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron*, **2005**, *61*, 1353 -1362.

[255] (a) Copéret, C.; Adolfsson, H.; Chiang, J. P.; Yudin, A. K.; Sharpless, K. B. *Tetrahedron Lett*., **1998**, *39*, 761-764. (b) Copéret, C;; Adolfsson, H.; Tinh-Alfredo, V. K.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem*., **1998**, *63*, 1740-1741.

[256] Burchat, A. F.; Chong, M. J.; Nielsen, N. *J. Organometal. Chem*., **1997**, *542*, 281-238.

[257] Gaudry, M.; Marquet, A. *Org. Synth., Coll. Vol. 6*, **1988**, *55, 193.*

[258] Claes, P.; Jacobs, J.; Claessens, S.; De Kimpe, N. *Tetrahedron*, **2010**, *66*, 7088-7096.

[259] Barker, D.; Brimble, M. A.; Do, P.; Turner, P. *Tetrahedron*, **2003**, *59*, 2441-2449.

[260] Nicolaou, K. C.; Lim, Y. W.; Piper, J. L.; Papageorgiou, C. D. *J. Am. Chem. Soc*., **2007**, *129*, 4001 -4013.

[261] Jacobs, J.; Van Hende, E.; Claessens, S.; De Kimpe, N. *Curr. Org. Chem.*, **2011**, *15*, 1340-1362.

[262] Jacobsen, N.; Torssell,K. *Liebigs Ann. Chem.*, **1972**, *763*, 135-147.

[263] Aldersly, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. F.; Ennis, D. S. *J. Chem. Soc. Perkin Trans. 1*, **1990**, *8*, 2163-2174.

[264] Guryar, M. K.; Bagavant, G. *Curr. Sci. India*, **1978**, *47*, 683-4.

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2 Education

September 2004 – June 2009 Master in bioscience engineering: chemistry and bioprocess technology (great distinction), Ghent University.

July 2008 - June 2009 Master thesis: 'Nieuwe toetredingen tot pyranonaftochinonen en 2-aza-antrachinonen.' Promoter: Prof. Dr. ir. Norbert De Kimpe.

February 2008 - July 2008 Erasmus: Ingénieur chimiste, option Chimie Organique Fine, Ecole Nationale Supérieure de Chimie de Montpellier, France.

3 Experience

August 2009 –September 2013 Doctoral research: 'Synthesis of heterocyclic annulated quinones and quinoid compounds'. Ghent University. Promoter: Prof. Dr. ir. Norbert De Kimpe.

2011-2013 Tutoring of a master thesis and a PhD student.

Januari 2012 General Information cycle: overall picture of the international cooperation, Belgian Technical Cooperation (BTC), Brussels.

June 2008 - July 2008 Internship at the Institut Européen des Membranes (IEM), Montpellier.

August - September 2008 Internship at Belgomilk Kallo.

4 Scientific activities

Courses and passive conference participations

3-4 December 2009 13th Sigma-Aldrich Organic Synthesis Meeting, Spa, Belgium.

January 2010 - April 2010 Course 'Medicinal Chemistry Course and Introduction to the European Patent System', Dr. Lieven Meerpoel, Head of Medicinal Chemistry, Oncology (Janssen Research & Development) and Prof. Wim De Borggraeve (KUL), Leuven, Belgium.

2-3 December 2010 14th Sigma-Aldrich Organic Synthesis Meeting, Spa, Belgium.

12-14 September 2011 Summer school 'Homogeneous catalysis and Fine Chemicals', Antwerp University, Belgium.

6-7 December 2012 16th Sigma-Aldrich Organic Synthesis Meeting, Spa, Belgium.

Poster presentations

11-16 July 2010 Claes, P.; Jacobs, J.; Claessens, S.; De Kimpe, N. 'Short synthesis of functionalized pentalongin derivatives using pyridinium ylid chemistry', 12th Belgium Organic Synthesis Symposium, Namur, Belgium.

1-2 December 2011 Claes, P.; Jacobs, J.; Kesteleyn, B.; Nguyen Van, T.; De Kimpe, N. 'Palladium catalysed synthesis of 2'*H*,3*H*-spiro[benzofuran-3,2'-quinones]', 15th Sigma-Aldrich Organic Synthesis Meeting, Spa, Belgium.

20-22 February 2012 Claes, P.; Mbala, B. M.; Jacobs, J.; Cappoen, D.; Huygen, K.; Verschaeve, L.; Nguyen Van, T.; De Kimpe, N. 'Synthesis and biological evaluation of benzo[*j*]phenantridine-7,12-diones as anti-tuberculosis agents', 2nd International Conference on Pharmaceutics & Novel Drug Delivery Systems, San Francisco, U.S.

15-20 July 2012 Claes, P.; Cappoen, D.; Jacobs, J.; Huygen, K. Verschaeve, L.; Nguyen Van, T.; De Kimpe, N. 'Synthesis and biological evaluation of new 2-azaanthraquinone derivatives as anti-tuberculosis agents', 13th Belgium Organic Synthesis Symposium, Namur, Belgium.

Peer-reviewed SCI-papers

Claes, P.; Jacobs, J.; Claessens, S.; De Kimpe, N. 'Short synthesis of functionalized pentalongin derivatives using pyridinium ylid chemistry', *Tetrahedron*, **2010**, *66*, 7088-7096. (IF 2012 2.80)

Mbala, B. M.; Jacobs, J.; Claes, P.; Mudogo, V.; De Kimpe, N. 'Investigation towards an efficient synthesis of benzo[*g*]isoquinoline-1,5,10(2*H*)-triones', *Tetrahedron*, **2011**, *67*, 8747-8756. (IF 2012 2.80)

Nguyen Van, T.; Claes, P.; De Kimpe, N. 'Synthesis of functionalized diketopiperazines as cyclotryprostatin and tryprostatin analogues', *Synlett*, **2013**, *24*, 1006-1010. (IF 2012 2.66)

Claes, P.; Cappoen, D.; Mbala, B. M. Jacobs, J.; Mertens, B.; Mathys, V.; Verschaeve, L.; Huygen, K.; De Kimpe, N. 'Synthesis and anti-mycobacterial activity of analogues of the bio-active natural products sampangine and cleistopholine' *Eur. J. Med. Chem*., **2013**, *67*, 98-110. (IF 2012 3.50)

Claes, P.; Jacobs, J.; Kesteleyn, B.; Nguyen Van, T.; De Kimpe, N. 'Palladium(II)-catalyzed synthesis of 2*H*,3'*H*-spiro[benzofuran-3,2'-naphthoquinones]' *J. Org. Chem.*, **2013**, *78*, 8330−8339. (IF 2012 4.56)

Nguyen Van, T.; Claes, P.; De Kimpe, N. 'Synthesis of hexahydropyrazino[1,2-b]isoquinolines as simplified saframycin analogues', *Synlett*, accepted for publication. (IF 2012 2.66)

Submitted papers

Claes, P.; Cappoen, D.; Uythethofken, C.; Jacobs, J.; Mertens, B.; Mathys, V.; Verschaeve, L.; Huygen, K.; De Kimpe, N. '2,4-dialkyl-8,9,10,11-tetrahydrobenzo[*g*]pyrimido[4,5-*c*]isoquinoline-1,3,7,12(2*H*,4*H*)-tetraones as new leads against *Mycobacterium tuberculosis*.' Submitted to *Eur. J. Med. Chem.* (IF 2012 3.50)

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