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A survey of synthetic routes towards 2-azaanthraquinones

Jan Jacobs [a], Kourosch Abbaspour Tehrani [b], Norbert De Kimpe [a,*]

[a] Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium
[b] Organic Synthesis, Department of Chemistry, Faculty of Sciences, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

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1. Introduction

2-Azaanthraquinones evoke much interest owing to their potent biological activities. Among others, they have been reported to show antimicrobial activities[1] and they display anti-Epstein-Barr virus activities.[2] In addition, 2-azaanthraquinone derivatives interfere with the activity of DNA topoisomerases and attract considerable attention in cancer chemotherapy as intercalating DNA binding agents.[3] DNA intercalation occurs when the DNA helix locally unwinds, which causes the base pairs to separate, and compounds of an appropriate size slide in between base pairs of the DNA helix.[4] Intercalating agents may then interact with DNA and form hydrogen, covalent or ionic bonds. In this way, structural distortions are induced as the two DNA strands cannot return to their normal helical structure, which leads to inhibition of DNA topoisomerases I and II. As a result, transcription and replication of DNA as well as DNA repair processes are stopped, which makes intercalating agent very potent mutagens.[5] Studying intercalating compounds, the presence of polycyclic aromatic rings, which make the compound planar, can be identified to be an essential structural feature. It has also been stated that compounds with three to four coplanar rings would give optimum intercalation and that the presence of an *N*-heterocyclic moiety improves the intercalating properties due to additional hydrogen bonding.[6] In this way, 2-azaanthraquinones have always attracted considerable attention in cancer chemotherapy, which led to the discovery of potent antitumour agents, such as pixantrone (BBR 2778 dimaleate) **1**,[7] and the benzo-fused isoquinolinedione derivative BFI **2** (Fig. 1).[8]

* Corresponding author. Tel.: +32 9 264 59 51; fax: +32 9 264 62 21; e-mail address: norbert.dekimpe@ugent.be (N. De Kimpe).

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Moreover, pixantrone **1** has also been proposed as a very promising immunosuppressant agent for clinical use in the treatment of multiple sclerosis.[9] Finally, 1-aryl-substituted 2-azaanthraquinones **3** were evaluated as potential antitumour agents and showed inhibition of the proliferation of MT-4 cells at μM concentrations.[10]

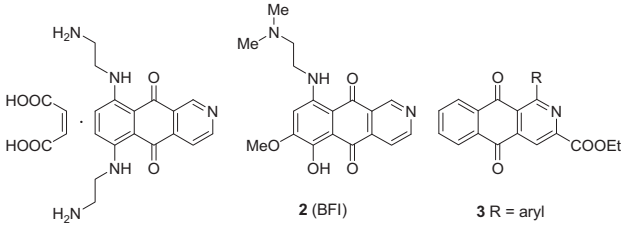
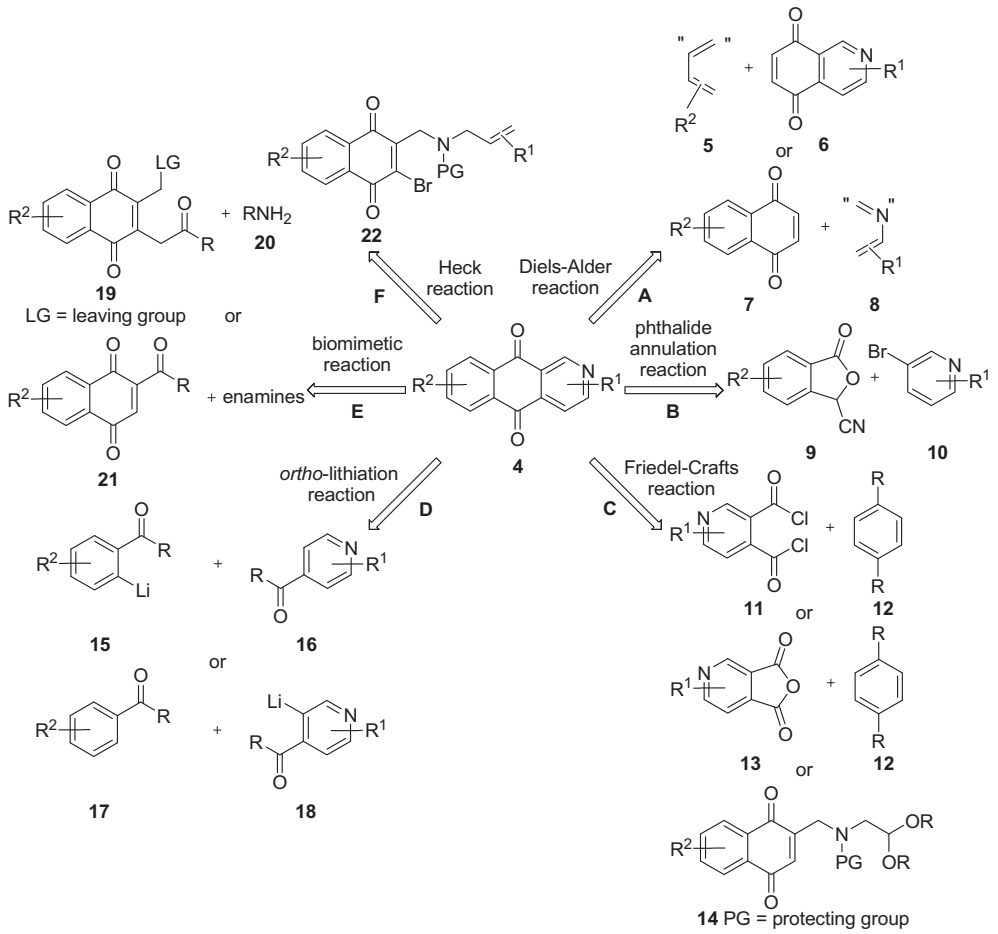


Fig. 1. 2-Azaanthraquinones with highly promising bioactivities.

The various interesting bioactivities of 2-azaanthraquinones have invited many research groups to actively participate in 2-azaanthraquinone research. To date, various syntheses to provide this class of compounds have been elaborated, amongst which several contributions have originated from our department. In this respect, this review aims to give a comprehensive overview of the different synthetic efforts to 2-azaanthraquinones, i.e., benz[*g*]isoquinoline-5,10-diones *sensu stricto* and benz[*g*]isoquinoline-3,5,10(2*H*)-triones as their structural analogues, in the literature. In short, six different strategies were reported to give access to 2-azaanthraquinones **4** (Scheme 1) and these include: (**A**) Diels–Alder reaction of isoquinoline-5,8-diones **6** or 1,4-naphthoquinones **7** with suitable 1,3-dienes **5** and 2-aza-1,3-dienes **8**, respectively, (**B**) phthalide-annulation reaction of cyanophthalide **9** and 3-bromopyridines **10**, (**C**) Friedel–Crafts reaction of acid chloride **11** or acid anhydride **13** with 1,4-disubstituted benzenes **12** and Friedel–Crafts-type intramolecular cyclization of a suitable functionalized 1,4-naphthoquinone **14**, (**D**) *ortho*-lithiation approach by reaction of lithiated aromatic amides **15** and pyridines **18** with suitable electrophiles **16** and **17**, (**E**) biomimetic approach, which refers to the addition of ammonia, primary amines **20** and enamines to functionalized naphthoquinones **19** and **21** and subsequent intramolecular ring closure, and (**F**) intramolecular Heck reaction of functionalized 1,4-naphthoquinones **22**.

2. Naturally occurring 2-azaanthraquinones

Although pyranonaphthoquinones represent a large class of natural products, their naturally occurring 2-aza analogues, all of which have been isolated as the aromatic 2-azaanthraquinones, have rarely been found in nature. So far, only a few naturally occurring 2-azaanthraquinones have been reported: bostrycoidin **23**,[11] 9-*O*-methylbostrycoidin **24**,[12] tolypocladin **25**,[13] 6-deoxy-8-methylbostrycoidin **26**,[14] 6-deoxybostrycoidin **27**,[15] 7-*O*-demethyl-6-deoxybostrycoidin **28**, scorpinone **29**[14a,16] and benz[*g*]isoquinoline-5,10-dione **30**[17] (Fig. 2). Nevertheless, these compounds have also been found to possess interesting biological activities. For instance, bostrycoidin **23**, a 2-azaanthraquinone isolated from several fungi of the *Fusarium* species,[11] has been shown to possess significant in vitro antibiotic activity against



Scheme 1. Overview of synthetic approaches towards 2-azaanthraquinones.

Mycobacterium tuberculosis.[18] 9-*O*-Methylbostrycoidin **24**, which is also reported as a metabolite of numerous *Fusarium* species, revealed antibiotic activity against Gram-positive bacteria.[12,19] Tolypocladin **25** was isolated from the mycelium of *Tolypocladium inflatum* and was found to display metal-chelating properties.[13] Next, benz[*g*]isoquinoline-5,10-dione **30**, isolated from *Psychotria camponutans* and *Mitracarpus scaber*, has been found to be active against multidrug resistant pathogens, such as *Plasmodium falciparum* and *Staphylococcus aureus*,[17] and inhibits the glucose-dependent cellular respiration and glycerol-3-phosphate-dependent mitochondrial O_2-assimiliation of the long bloodstream forms of *Trypanosoma congolense*.[20] 6-Deoxybostrycoidin **27** and 7-*O*-demethyl-6-deoxybostrycoidin **28** were isolated from a yellow strain mutant of *Nectria haematococca*, which was grown in an asparagin-enriched medium, as intermediates in the biosynthesis of bostrycoidin **23**.[15,21] Scorpinone **29** and 6-deoxy-8-methylbostrycoidin **26** have been identified in the mycelium of a Bispora-like tropical fungus and in the mycobionts of the lichen *Haematomma* species.[14] Recently, a genetically modified *Streptomyces albus* strain was reported to produce utahmycin A **31**, which could be isolated from the ethyl acetate extract of the culture medium.[22]

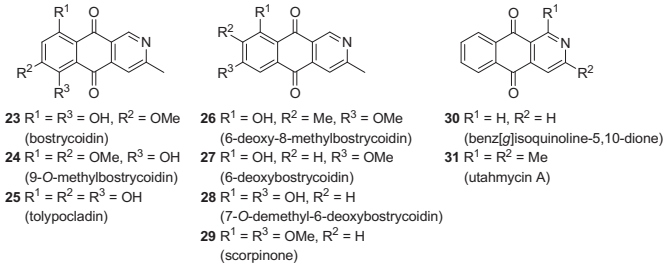
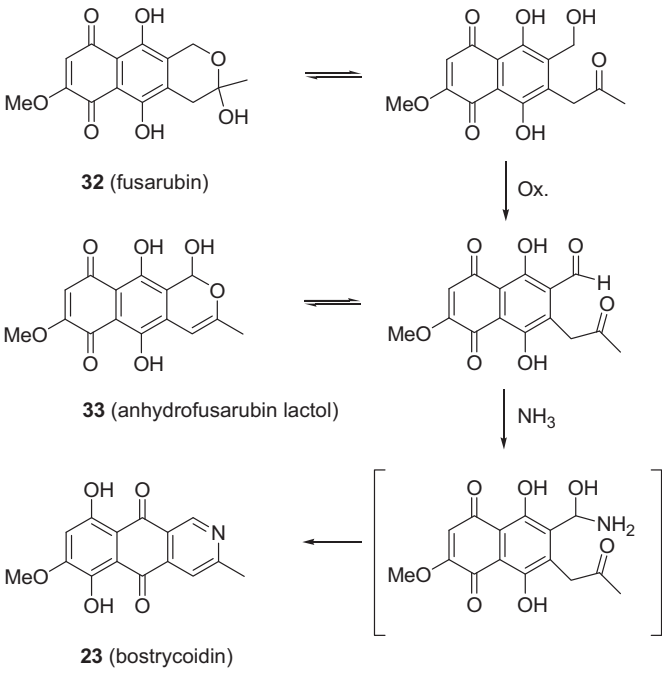


Fig. 2. Natural 2-azaanthraquinones.

3. Biosynthesis

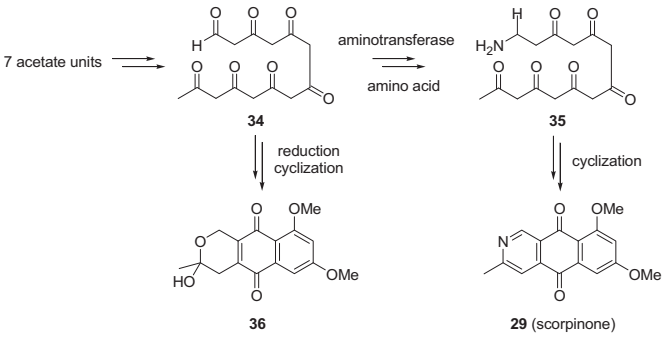
One of the remarkable features of quinone biosynthesis in nature is that they are derived from a variety of different precursors and by different pathways. However, one of the most common biosynthetic pathways leading to quinones is the polyacetate or acetate–polymalonate pathway.[23] In this pathway, compounds with a polyketomethylene backbone are formed, starting from acetyl-coenzyme A and malonyl-coenzyme A. These polyketomethylenes are then modified specifically in enzymatic processes like cyclization, dehydration, oxidation and reduction, rearrangement and group transfer to yield anthraquinones and pyranonaphthoquinones.[23] These pyranonaphthoquinones have been suggested to form the corresponding 2-aza analogues by incorporation of ammonia into their skeleton.[18] According to this hypothesis, it was postulated that bostrycoidin **23** might originate from fusarubin **32**, first by oxidation to the intermediate anhydrofusarubin lactol **33** and then by reaction with ammonia. In another study, the synthesis of compounds **33** and **23** has been found to be similarly sensitive to the carbon-to-nitrogen ratio and pH of the culture conditions, suggesting that these compounds share a common biosynthetic precursor (Scheme 2).[24]

In this way, the biosynthesis of 2-azaanthraquinones like bostrycoidin **23** has been related to an in vivo detoxifying process for high ammonia concentrations. However, the possibility that 2-azaanthraquinone **23** is an artefact, which is formed in the culture media of the *Fusarium* fungi, could not be excluded in this study.[18] Alternatively, the pyranonaphthoquinone skeleton of compound **36** was demonstrated to originate from heptaketide **34**.[25] A recent study showed a possible biosynthesis of scorpinone



Scheme 2. Biosynthetic pathway of 2-azaanthraquinones by ammonia incorporation.

29 by nitrogen incorporation into the intermediate heptaketide **34**, which is mediated by an aminotransferase that utilizes an amino acid as the nitrogen source (Scheme 3).[16] Finally, 2-azaanthraquinones have been described as detoxifying agents for high heavy-metal concentrations after the discovery of the siderophoric activity of tolypocladin **25**.[13]



Scheme 3. Biosynthetic pathway of 2-azaanthraquinones by enzymatic nitrogen incorporation.

4. Diels–Alder approach

In the past decade, the successful use of doxorubicin **37** and mitoxantrone **38** (Fig. 3)[26] and of pixantrone **1** and BFI **2** (Fig. 1) in the treatment of several leukaemias, lymphomas and solid tumours invited organic chemists to explore the synthesis of 2-azaanthraquinones in the search for new antitumour drugs that retain the core quinone moiety and exhibit different spectra of potency, together with a reduced toxicity. In this way, an impetus was given to explore the possibilities in the synthesis of 2-azaanthraquinones.

To date, the Diels–Alder reaction has been proven to be valuable, as it is the most popular method for the synthesis of these compounds. However, for substituted 1,4-naphthoquinones, these cycloadditions are generally unsatisfactory in terms of yields and separation of the different regioisomers. This can be demonstrated

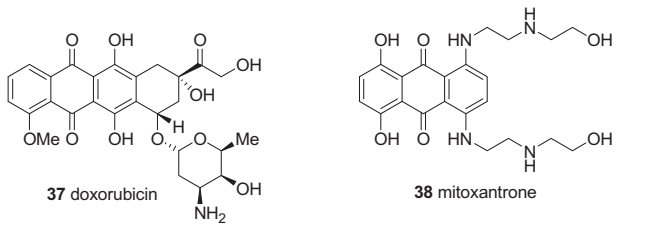
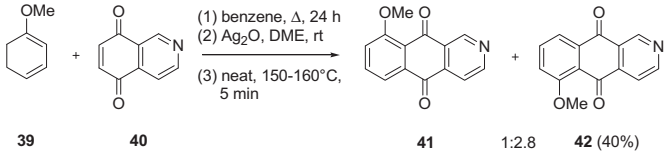
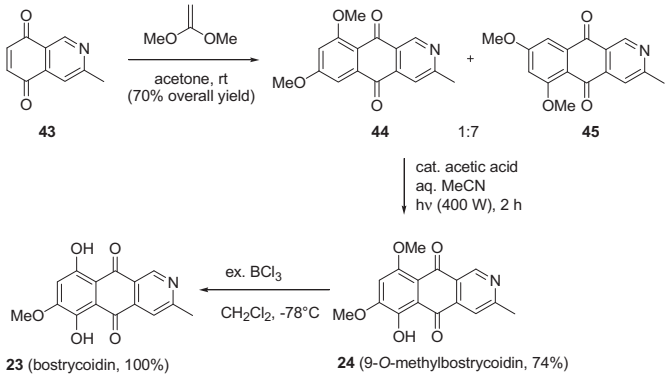


Fig. 3. Clinically useful quinones in cancer treatment.

by the reported cycloaddition of 1-methoxycyclohexa-1,3-diene **39** and isoquinoline-5,8-dione **40**, which afforded a 1:2.8 mixture of the regioisomers **41** and **42** after silver(I) oxidation and thermal elimination of ethylene (Scheme 4).[27] The observed regioselectivity is consistent with the presence of a more electron-deficient carbonyl group in the γ-position of the *N*-atom in the pyridine ring.[28] According to the same synthetic plan, the natural antibiotic bostrycoidin **23** and its 9-*O*-methyl derivative **24** have been synthesized from 3-methylisoquinoline-5,8-dione **43** by 1,2-addition with ketene dimethyl acetal to give the isomeric 2-azaanthraquinones **44** and **45** in a ratio of 1:7 and in an overall yield of 70%. Ultraviolet-light irradiation of the minor regioisomers **44** afforded 9-*O*-methylbostrycoidin **24**, which gave bostrycoidin **23** upon treatment with excess boron(III) chloride (Scheme 5).[29] Later, the sample principle was used to synthesize 1-substituted benz[*g*]isoquinoline-5,10-diones in 39–54% yield by cycloaddition of 1,4-diacetoxy-1,3-butadiene to different 1-substituted isoquinoline-5,8-diones.[30]

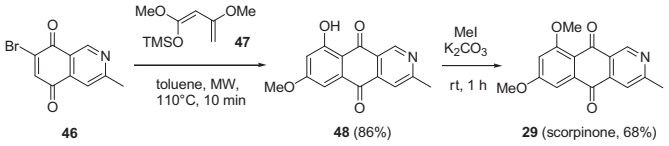


Scheme 4.



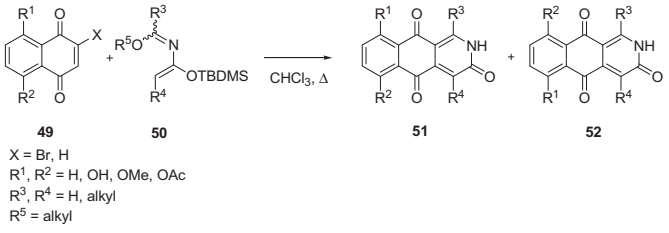
Scheme 5.

To enhance the regioselectivity, the use of Lewis acids[31] and of 5-hydroxy- and 5-methoxy-1,4-naphthoquinones has been reported, due to the known directing effect of these substituents.[31b,32] Another possibility is the use of 2- or 3-bromo-1,4-naphthoquinones in the Diels–Alder reaction.[32b,33] As these compounds are more electron deficient than 1,4-naphthoquinones, they are more reactive towards 2-aza-1,3-butadienes. Furthermore, the bromine atom in bromonaphthoquinones exerts a stronger regiochemical control in these cycloadditions than the 5-substituent of 1,4-naphthoquinones (e.g., OH, OMe), since the electron-rich end of a diene is known to add exclusively at the unsubstituted carbon of bromonaphthoquinones.[32b,34] However, the poor regioselectivity of this reaction upon the use of substituted dienes or dienophiles is still a major drawback. Nevertheless, in a recent report, a microwave-assisted Diels–Alder reaction of 7-bromo-3-methylisoquinoline-5,8-dione **46** with oxygenated diene **47** allowed a regioselective synthesis of the natural antibiotic, scorpinone **29** (via **48**) (Scheme 6).[35]

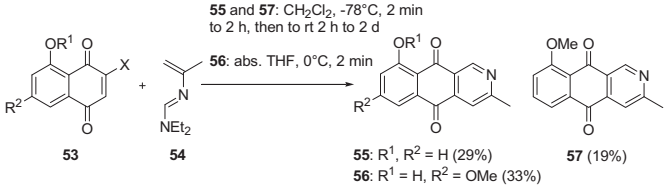


Scheme 6.

A second mode of the Diels–Alder-mediated synthesis of 2-azaanthraquinones can be demonstrated by the synthesis of a series of benz[*g*]isoquinoline-3,5,10(2*H*)-triones **51** and **52** by a Diels–Alder reaction between substituted 1,4-naphthoquinones **49** and disilyloxylated 2-aza-1,3-butadienes **50** (Scheme 7).[33,36] More recently, a multicomponent reaction, which relied on an intramolecular Diels–Alder reaction, was reported to give rise to a 1,4-disubstituted benz[*g*]isoquinoline-3,5,10(2*H*)-trione after ozonolysis and subsequent aromatization.[37] The structure of the synthesized benz[*g*]isoquinoline-3,5,10(2*H*)-triones hinted at a potential antitumour activity, but, unfortunately, the in vitro cytotoxicity tests against murine leukaemia cells (L-1210) and a tumour cell line showed only weak activity.[33b] The drawbacks of this method are the separation of the different regioisomers and the unsatisfactory yields of the target compounds. Finally, a similar methodology, which relied on a hetero-Diels–Alder reaction of substituted 1,4-naphthoquinones **53** and *N*-(*N*,*N*-diethylaminomethylidene)-propene-2-amine **54**, was reported for the synthesis of 2-azaanthraquinones **55**–**57** (Scheme 8).[38] However, the advantage of the short synthetic route was counteracted by the low isolated yields of the target compounds.



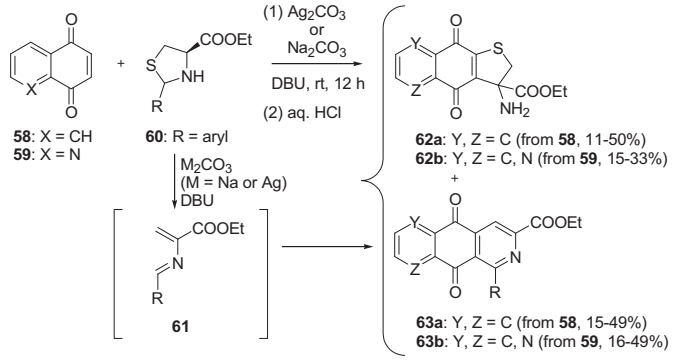
Scheme 7.



Scheme 8.

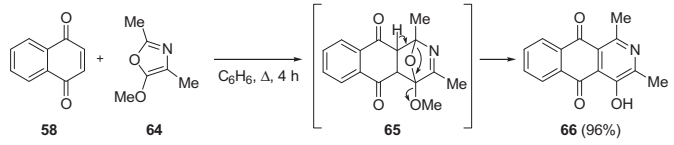
A special type of Diels–Alder reaction was reported, which relied on the in situ formation of azadienes **61**. In this one-step reaction, naphthoquinone **58** or quinoline-5,8-dione **59** are reacted with different 2-arylthiazolidine derivatives **60** in the presence of base.

After acidic workup, 2-azaanthraquinones **62a**,**b** and dihydrothieno [2,3-*b*]naphtho-4,9-diones **63a**,**b** were retrieved, which have been shown to be potent antitumour compounds (Scheme 9).[10,39]



Scheme 9.

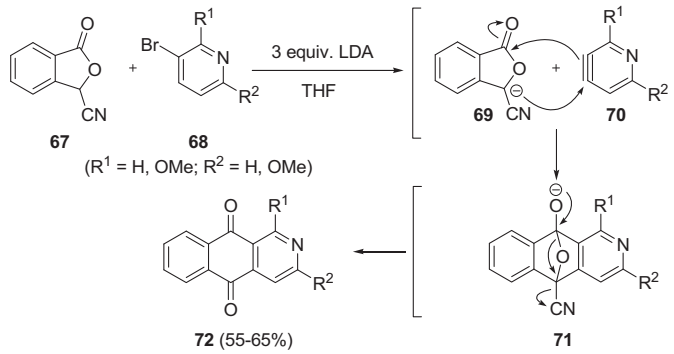
Finally, the reaction of 2,4-dimethyl-5-methoxyoxazole **64** with naphthoquinone **58** as dienophile has been reported as an efficient synthesis of 2-azaanthraquinone **66** (via **65**) (Scheme 10).[40]



Scheme 10.

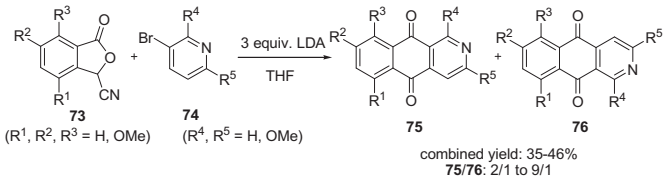
5. Phthalide annulation approach

The phthalide annulation reaction is a tandem Michael addition–Dieckmann condensation reaction between a stabilized phthalide anion and a suitable Michael acceptor. After its discovery by Schmid in 1965,[41] this reaction was developed further simultaneously by Kraus[42] and by Hauser[43] in the late 1970s.[44] Although numerous anthraquinones and pyranonaphthoquinones have been synthesized using the phthalide annulation reaction, the application of this reaction to the synthesis of 2-azaanthraquinones has been very limited. The first phthalide annulation-mediated synthesis of 2-azaanthraquinones **72** stems from 1988, when the reaction of phthalide anions **69** with heteroaryne intermediates **70**, generated from bromopyridines **68**, 3-cyanophthalide **67** and lithium diisopropylamide (LDA), was reported (Scheme 11).[3a] Later, this strategy was successfully applied to the synthesis of fluorinated 2-azaanthraquinones.[45]



Scheme 11.

However, upon the introduction of substituted phthalides **73** and bromopyridines **74** in the phthalide annulation reaction, the formation of different regioisomers **75** and **76**, which could be separated by column or thin-layer chromatography, could be witnessed (Scheme 12).[3a] Later, the same tendency was reported in the synthesis of substituted indoloquinones.[46]



Scheme 12.

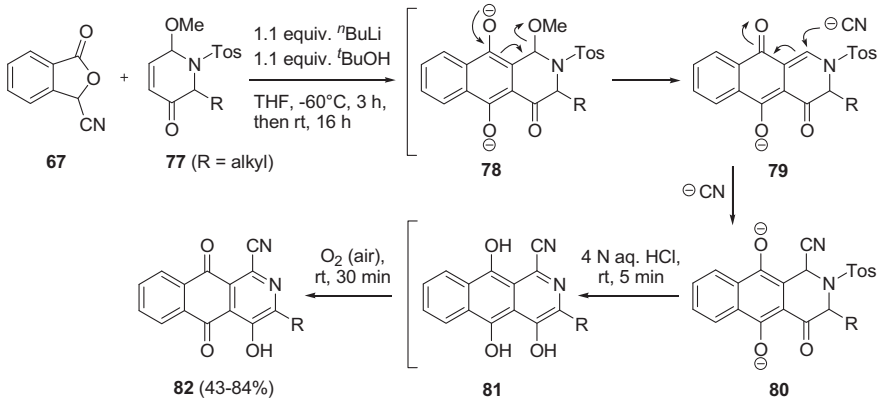
Finally, a convenient synthesis of 2-aza-1-cyano-4-hydroxyanthraquinones **82** was reported by reaction of 3-cyanophthalide **67** and piperidin-3-ones **77** (Scheme 13).[47] Remarkably, the cyanide, which was expelled from 3-cyanophthalide **67**, added in a 1,4-fashion onto a Michael acceptor of intermediate **79**. In this way, a cyano function was introduced at the C1 position and the resulting hydroquinone **81**, which was obtained after pouring intermediate **80** into aqueous hydrochloric acid, was oxidized spontaneously by aerial oxygen to 2-azaanthraquinones **82** (Scheme 13).

6. Friedel–Crafts approach

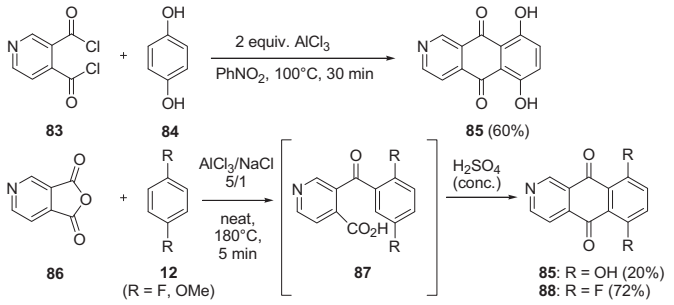
Successful Friedel–Crafts syntheses of simple 2-azaanthraquinones **85** and **88** have been reported by the reaction of acid chloride **83**,[48] or anhydride **86**,[49] with 1,4-disubstituted benzenes **84** and **12** (Scheme 14). Other (non Friedel–Crafts) approaches towards intermediates similar to compounds **87** have been reported in the literature.[38,50] However, the use of asymmetrically trisubstituted benzenes in the reaction with anhydride **86** results in the formation of different regioisomers, which limits the use of the Friedel–Crafts reaction for the synthesis of specific substituted 2-azaanthraquinones. This is demonstrated by the synthesis of the natural product, tolypocladin **25**, by condensation of 1,2,4-trimethoxybenzene **89** and 2-methylpyridine-4,5-dicarboxylic anhydride **90** under Friedel–Crafts conditions, affording regioisomers **91** and **92**, which could be separated by crystallization (Scheme 15).[51] Final cyclization and demethylation of the minor isomer **91** with concentrated sulfuric acid gave tolypocladin **25** in 48% yield. Analogously, the major regioisomer **92** was converted to isotolypocladin in 55% yield.

Another drawback of the classical Friedel–Crafts approach towards 2-azaanthraquinones is the lack of reactivity of pyridine derivatives in electrophilic acylation processes. Therefore, the use of the Houben–Hoesch reaction has been reported for the construction of the 2-azaanthraquinone skeleton. In this approach, benzaldehydes **94** and 3-cyanopyridines **95** are introduced in a radical acylation, which gives rise to the intermediates **96**, since it had been shown that radicals generated from aldehydes by the addition of iron(II) sulfate and *tert*-butyl hydroperoxide act as nucleophilic species affecting acylation of pyridines in the α- and γ-positions.[52] The intramolecular Houben–Hoesch reaction, which involves an acid-catalyzed electrophilic substitution across the nitrile moiety followed by hydrolysis, then gives rise to the formation of 2-azaanthraquinones **97** (Scheme 16). However, the lack of selectivity in the radical pyridine acylation in the first step is still a major drawback for the use of this method.

Recently, the use of an acid-mediated intramolecular cyclization of different *N*-protected 2-(((2,2-dimethoxyethyl)amino)methyl)-1,4-naphthoquinones **98** was described for the synthesis of 1,2-

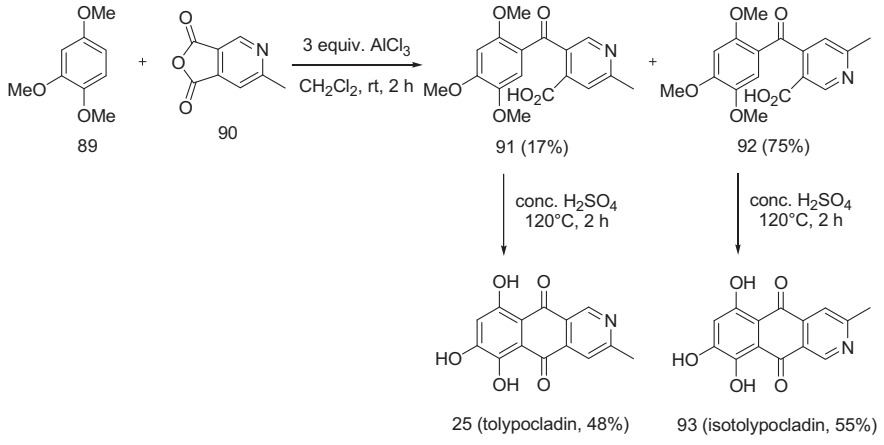


Scheme 13.

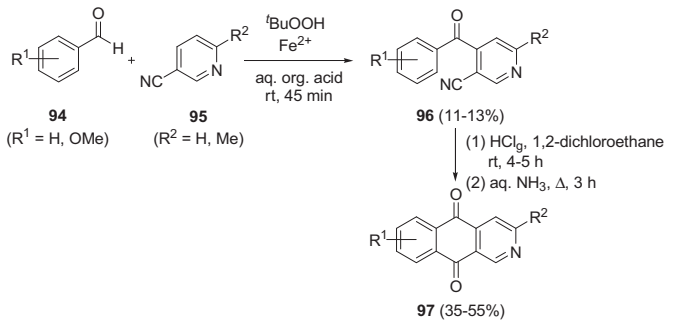


Scheme 14.

dihydrobenz[*g*]isoquinoline-5,10-diones **100**[53] as part of research on structural modifications of pentalongin, the active principle of *Pentas longiflora* Oliv.[54] However, the severe reaction conditions, which were required to synthesize the targeted 1,2-dihydrobenz[*g*]isoquinoline-5,10-diones **100** were often incompatible with the use of *N*-protecting groups and, as a consequence, benz[*g*]isoquinoline-5,10-dione **30** was obtained (Scheme 17). The acid-catalyzed intramolecular cyclization of the *N*-*tert*-Boc-protected 1,4-naphthoquinone acetal **98** was found only to proceed upon treatment with a saturated solution of dry hydrogen chloride in diethyl ether at room temperature for 16 h (Scheme 17). In a first step, the acetal function of compound **98** was protonated and, after elimination of methanol from intermediate **101**, the corresponding stabilized carbenium ion was formed, which gave rise to compound

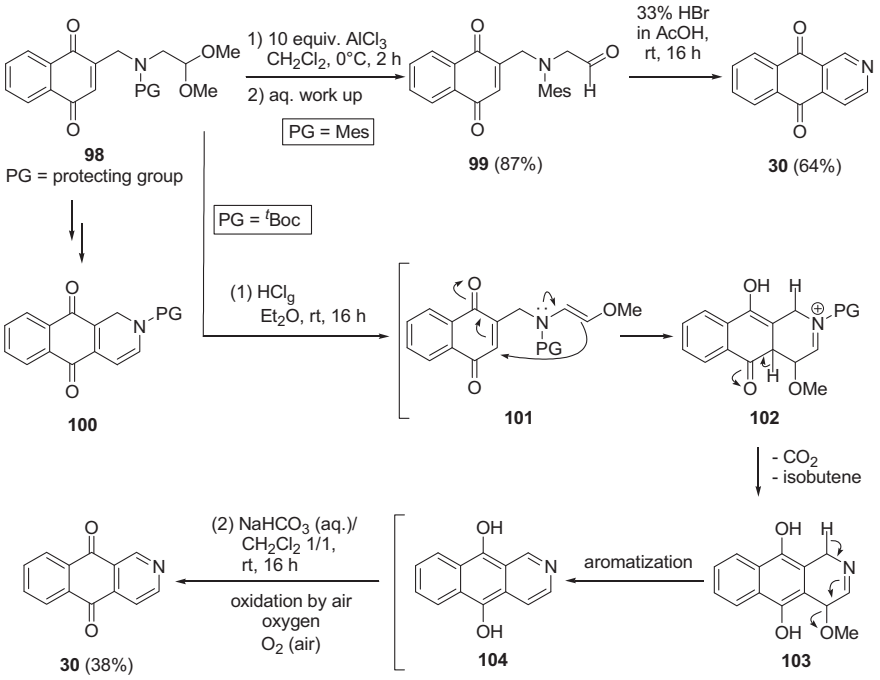


Scheme 15.



Scheme 16.

102 via an intramolecular 6-*endo*-*trig* ring closure. Then, deprotection of the *N*-*tert*-Boc group and elimination of methanol from intermediate **103**, followed by spontaneous oxidation in air of hydroquinone **104**, gave rise to the formation of benz[*g*]isoquinoline-5,10-dione **30**. Similarly, using *N*-methanesulfonyl-protected 1,4-naphthoquinone acetal **98** as a substrate for the Lewis acid-catalyzed intramolecular cyclization, treatment with excess aluminium(III) chloride in dichloromethane afforded aldehyde **99**, which was subsequently treated with 33% HBr in acetic acid in order to obtain intramolecular cyclization. Unfortunately, the hydrolysis of the *N*-methanesulfonyl group could not be avoided, even upon using less concentrated solutions of hydrobromic acid and a shorter reaction time, and, as a result, benz[*g*]isoquinoline-5,10-dione **30** was obtained in 64% yield.



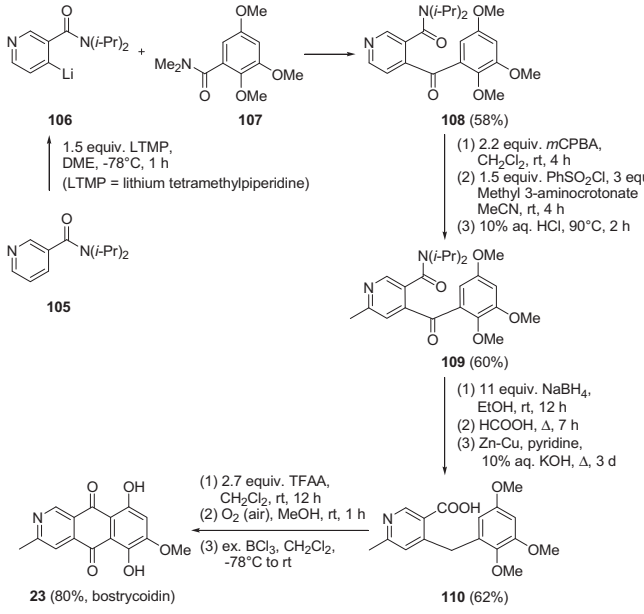
Scheme 17.

7. *Ortho*-lithiation approach

In 1987, Watanabe and co-workers demonstrated the usefulness of the *ortho*-lithiation reaction in the synthesis of 2-azaanthraquinones by describing a synthesis of bostrycoidin **23** based on a regiospecific lithiation of substituted pyridine **105** and subsequent reaction of the lithiated pyridine **106** with benzamide **107**.[55] Then, the methyl group at the 3-position of bostrycoidin **23** was introduced upon *m*-CPBA-mediated oxidation of pyridine **108** to the corresponding *N*-oxide, which was converted into the *N*-sulfonate in the next step. Simultaneous nucleophilic addition of methyl 3-aminocrotonate to the intermediate iminium function, followed by hydrolysis of the ester function to the carboxylic acid and subsequent decarboxylation, afforded compound **109**. Reductive cleavage by zinc-copper of the lactone, which was formed after treatment of compound **109** with sodium borohydride and formic acid, resulted in the synthesis of carboxylic acid **110**. Finally, intramolecular electrophilic substitution, subsequent oxidation with oxygen in air and boron(III) chloride-mediated demethylation afforded bostrycoidin **23** (Scheme 18).

Since the heteroatom-directed tandem lithiation does not suffer from the disadvantages of poor regioselectivity and low yields, in comparison with the above-presented methods, this methodology has also been applied successfully for the synthesis of other 2-azaanthraquinones.[56] In this way, anilides **111** were *ortho*-lithiated regioselectively with *n*-butyllithium and subsequent condensation of the intermediate lithium salts with methyl isonicotinate afforded the pyridoylated compounds **112**, which cyclized spontaneously to 3-hydroxyisoindolin-1-ones **113** upon hydrolytic workup. The latter compounds were treated with sulfuric acid and the resulting carboxylic acids were converted into the corresponding methyl esters **114**. Finally, regiospecific lithiation of the pyridine ring at the C-3 carbon atom of the *ortho*-pyridoylated methyl benzoate **115** and subsequent cyclization via an intramolecular addition–elimination sequence of the generated lithiated species across the ester function afforded 2-azaanthraquin-ones **116** (Scheme 19).

Later, the same principle was used for the synthesis of benz[*g*]isoquinoline-5,10-dione **30** and benzo[*j*]phenanthridine-7,12-dione **120** via intermediates **119** by the reaction of dimethyl phthalate or

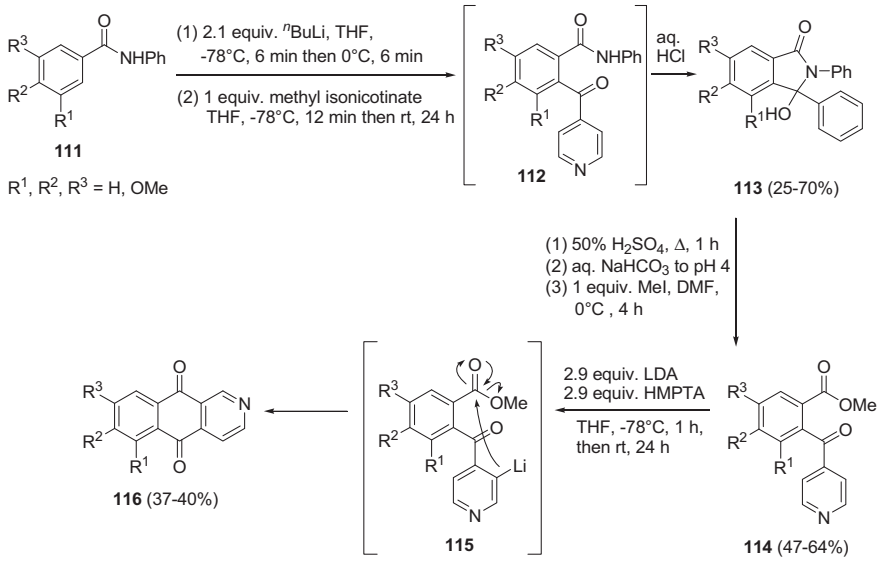


Scheme 18.

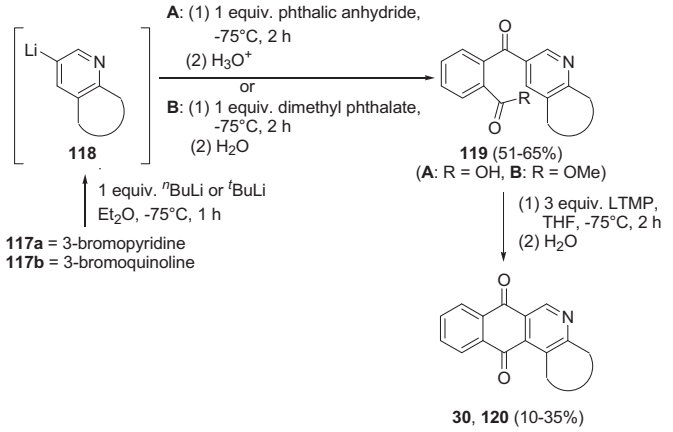
phthalic anhydride with 3-lithiopyridine and 3-lithioisoquinoline **118**, which were generated in situ by reaction of *n*-butyl- or *tert*-butyllithium with 3-bromopyridine **117a** and 3-bromoquinoline **117b**, respectively (Scheme 20).[57]

8. Ammonia-induced cyclization

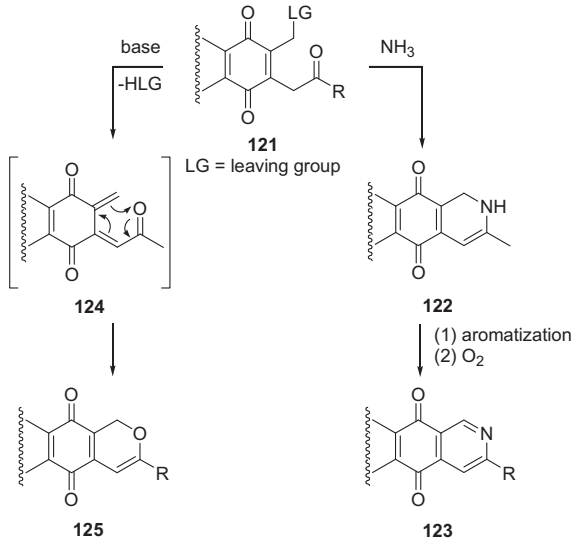
The hypothesis that natural 2-azaanthraquinones originate in vivo from the incorporation of ammonia into the pyranonaphthoquinone skeleton (see Section 3)[18] invited organic chemists to construct a biomimetic synthesis of 2-azaanthraquinones. This biomimetic strategy was elaborated at our department and relied on the synthesis of suitably substituted naphthoquinones **121** that would allow



Scheme 19.



Scheme 20.

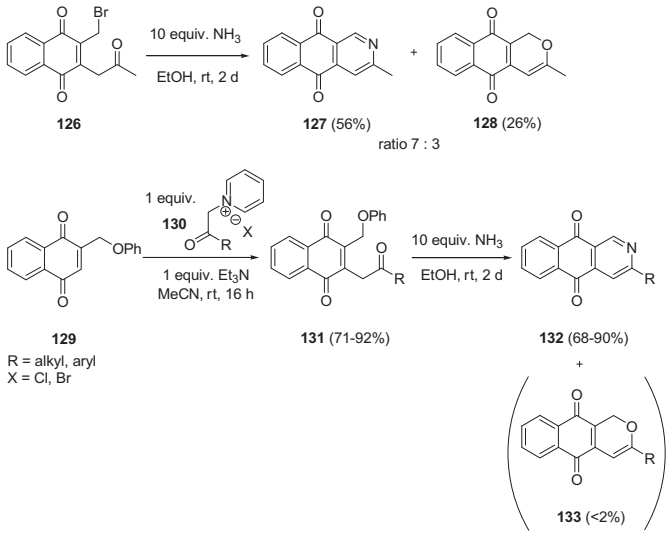


Scheme 21.

efficient syntheses of both 2-azaanthraquinones **123** and pyranonaphthoquinones **125** (Scheme 21). The latter compounds **125** can be obtained after spontaneous electrocyclization of the intermediate *ortho*-quinomethides **124**, which are formed upon deprotonation and subsequent elimination of the leaving group in naphthoquinones **121**. 2-Azaanthraquinones **123**, on the other hand, can be synthesized upon substitution of the leaving group with ammonia and subsequent addition–elimination reaction of the aminomethyl group across the carbonyl function of the adjacent acetonyl side chain and spontaneous aromatization and oxidation of intermediate **122**.

In order to achieve an efficient and selective synthesis of 2-azaanthraquinones, naphthoquinones **121** were first evaluated as model substrates bearing different leaving groups at the C2-methyl position. In this way, it was found that the use of 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **126** gave rise to substantial formation of 3,4-dehydropyranonaphthoquinone **128** in comparison with the targeted 2-azaanthraquinone **127**, while replacing the bromide by a phenoxide as a moderate leaving group afforded predominantly 2-azaanthraquinones **132** (Scheme 22).[58] The improved selectivity for the synthesis of 2-azaanthraquinones can be explained by the poorer leaving group capacity of phenoxide, which slows down the formation of the pyranonaphthoquinone side-product, since it depends on the elimination rate of phenol. As a result, the use of pyridinium ylids, which were generated in situ from the corresponding pyridinium salts **130**,[59] for the introduction of acetonyl side chains onto 2-phenoxymethyl-1,4-naphthoquinone **129** opened up the way for the synthesis of 2-azaanthraquinones **132**. Adding ammonia to adduct **131** caused aza-ring closure, affording the corresponding 2-azaanthraquinones **132** and traces of 3-alkyl- and 3-aryl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones **133**, which could be removed successfully upon purification by flash chromatography on silica gel (Scheme 22).

This strategy enabled the construction of convenient syntheses of the natural 2-azaanthraquinone antibiotics, 6-deoxy-8-methylbostrycoidin **26**, 6-deoxybostrycoidin **27**, 7-*O*-demethyl-6-deoxybostrycoidin **28** and scorpinone **29**. First, the reaction of 2-acetonyl-3-bromomethyl-5,7-dimethoxy-1,4-naphthoquinone **134** with aqueous ammonia resulted in a mixture of the pyranonaphthoquinone, dehydroherbarin **135** and the 2-azaanthraquinone, scorpinone **29**, which could be purified by flash chromatography on silica gel in 30 and 54% yield, respectively (Scheme 23).[54c] Afterwards, boron(III) bromide mediated cleavage of the ether at the C9position afforded 6-deoxybostrycoidin **27**, which could be functionalized further to 2-azaanthraquinone **136**. In a second report,

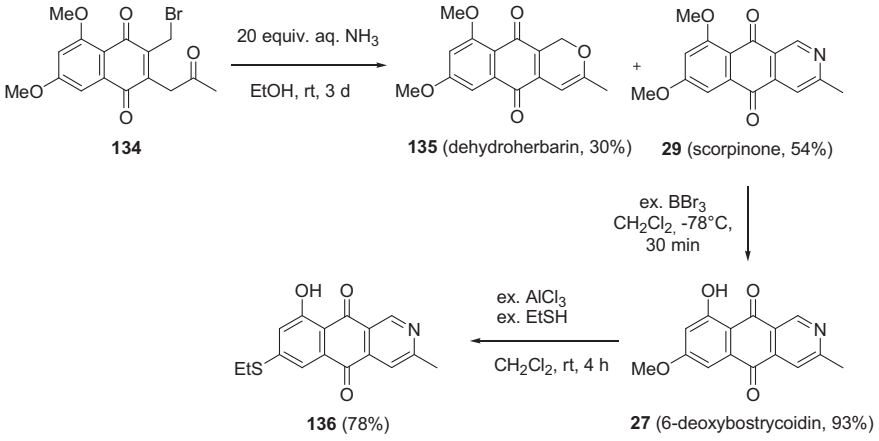


Scheme 22.

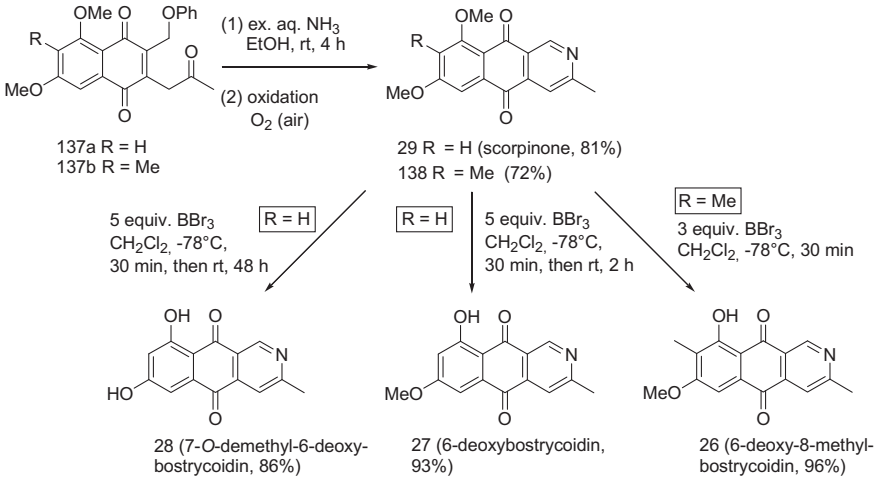
29 and **138** gave rise to an efficient and convenient synthesis of the natural antibiotics, 6-deoxy-8-methylbostrycoidin **26**, 6-deoxybostrycoidin **27** and 7-*O*-demethyl-6-deoxybostrycoidin **28** (Scheme 24).[60]

The synthesis of 2-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **142** was achieved after oxidation and aromatization of 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **140**, which were obtained upon reaction of ethyl (3-bromomethyl-1,4-dimethoxynaphth-2-yl)acetate **139** with ammonia or with a primary amine via substitution of the benzylic bromide and intramolecular condensation with the ester group (Scheme 25).[61] Since the synthesized benz[*g*]isoquinoline-3,5,10(2*H*)-triones **142** possess a good Michael acceptor at the C4position, conjugate addition was evaluated in order to modify their molecular skeleton in an easy and straightforward manner. In this way, addition of a proper nucleophile, e.g., potassium cyanide or a primary amine, followed by aromatization by tautomerization and spontaneous oxidation by air, yielded 2,4-disubstituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **143** and **144** (Scheme 25).[62]

Kobayashi and co-workers developed a method using only mild reaction conditions for the synthesis of 2-azaanthraquinones in

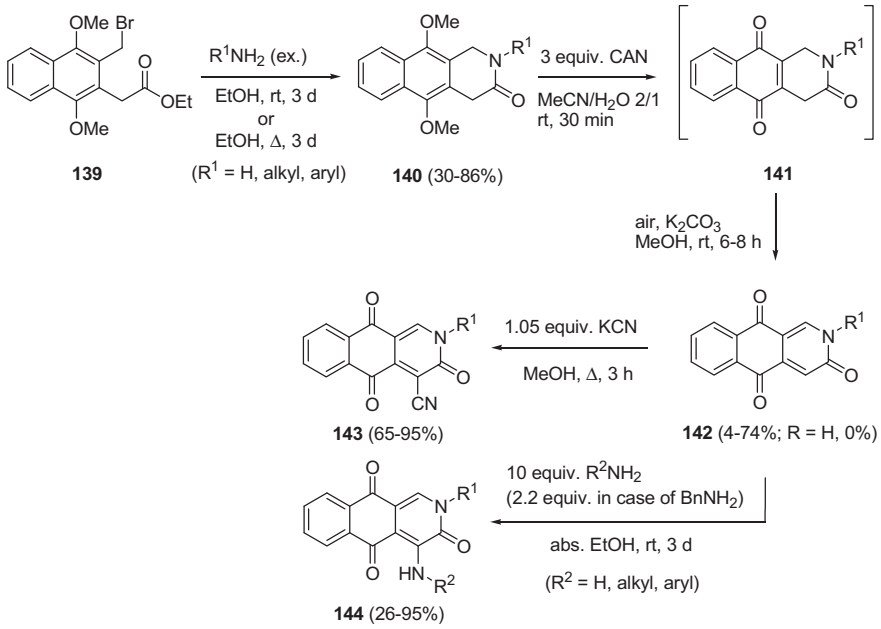


Scheme 23.



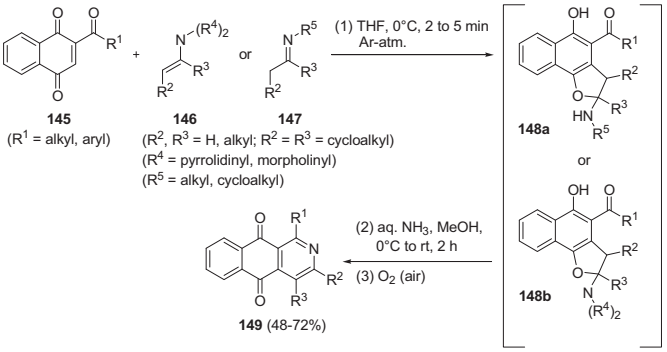
Scheme 24.

the synthesis of scorpinone **29** and its synthetic 8-methyl analogue **138** was achieved upon treatment of suitable 3-phenoxymethyl-substituted 1,4-naphthoquinones **137a** and **137b** with ammonia. Further functionalization of the synthesized 2-azaanthraquinones which an activated naphthoquinone **145**, i.e., quinone, which bears an electron-withdrawing substituent at the 2-position, was reacted with a suitable enamine. Such activated quinones are very reactive towards nucleophiles because the LUMO at position 3 is



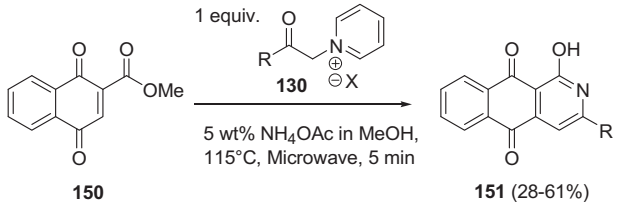
Scheme 25.

substantially lowered. Thus, nucleophilic addition of an enamine (e.g., enamines **146** or the corresponding enamines of ketimines **147** via keto–enol tautomerism) onto the activated naphthoquinone **145** afforded the corresponding intermediate hydroxybenzofuran derivatives **148a**,**b**, which could be efficiently converted into 2-azaanthraquinones **149** upon treatment with aqueous ammonia and spontaneous oxidation in air (Scheme 26).[63]



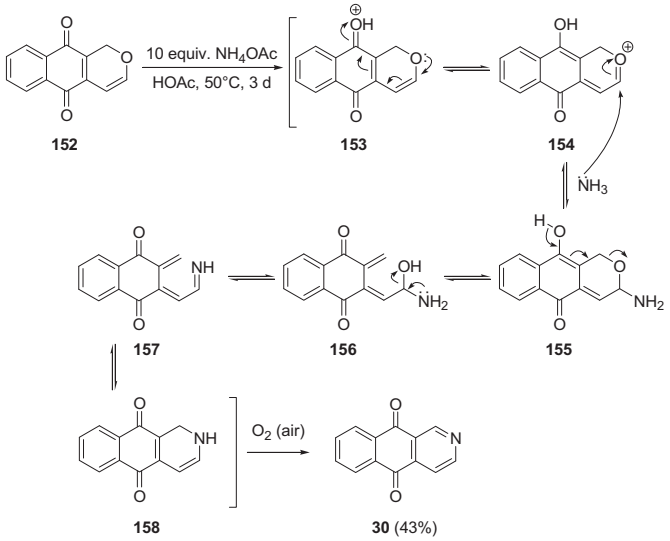
Scheme 26.

Within this framework, a synthetic program to 1-hydroxy-benz[*g*]isoquinoline-5,10-diones was conducted as an SAR study revealed that hydroxyl groups at the *peri*-carbonyl position enhance antibiotic activity.[1] Investigations revealed that a highly efficient synthesis of 3-substituted 1-hydroxy-benz[*g*]isoquinoline-5,10-diones **151** was achieved upon reaction of activated naphthoquinone **150** with different pyridinium salts **130** in a solution of ammonium acetate in methanol as an indirect source of ammonia (Scheme 27).[64] When this reaction mixture was introduced in a microwave reactor, the ammonia served as a base to convert the pyridinium salts into the corresponding ylids in situ and as a nitrogen source to construct the 2-azaanthraquinone after introduction of the acetonyl side chain onto the activated naphthoquinone **150**.

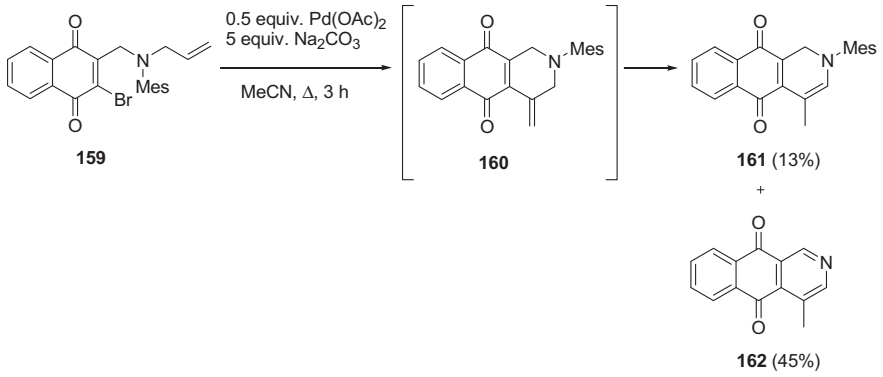


Scheme 27.

More recently, the biosynthesis of 2-azaanthraquinones has inspired an exploration of the biomimetic transformation of the natural product, pentalongin **152**, into benz[*g*]isoquinoline-5,10-dione **30** by means of ammonia. Reacting 3,4-dehydropyrano-naphthoquinone **152** under Kröhnke conditions, which refers to the use of ammonium acetate in acetic acid as an indirect source of ammonia,[65] resulted in the formation of the natural 2-azaanthraquinone **30** in 43% yield by acid catalyzed tautomerization of intermediate **153**, addition of ammonia onto **154**, formation of an *ortho*-quinomethide **156**, elimination of water, cyclization of **157** to **158** and final oxidation (Scheme 28).[66]



Scheme 28.



Scheme 29.

9. Heck reaction

Related to our research on structural modifications of pentalongin, the active principle of the medicinal plant *P. longiflora* Oliv.,[54] a new synthesis of *N*-protected 1,2-dihydro-benz[*g*]isoquinoline-5,10-diones **161** was envisaged by means of an intramolecular Heck reaction in the key step. The Heck reaction, which is not disturbed by heteroatoms, such as nitrogen and oxygen,[67] allowed a smooth construction of the benz[*g*]isoquinoline skeleton, starting from *N*-methanesulfonyl 2-((allylamino)methyl)-3-bromo-1,4-naphthoquinone **159**. In this way, the Heck-cyclization product **160** could be easily formed, which spontaneously isomerized to the more conjugated and, thus, more stable isomer **161**. However, 4-methylbenz[*g*]isoquinoline-5,10-dione **162** was obtained as the major reaction product after conducting the Heck reaction and it was isolated in 45% yield together with 13% of the desired 2-methanesulfonyl-4-methyl-1,2-dihydrobenz[*g*]*iso*-quinoline-5,10-dione **161** (Scheme 29).[68] Probably, the synthesized 1,2-dihydrobenz[*g*]isoquinoline-5,10-dione **161** oxidizes spontaneously to the more stable 4-methylbenz[*g*]isoquinoline-5,10-dione **162**, which has been recently established as an antibiotic compound.[1] In vitro testing revealed compound **162** to have a good bioactivity against representative strains of Gram-positive bacteria (*S. aureus*, *Bacillus subtilis*), Gram-negative bacteria (*Proteus vulgaris*, *Pseudomonas aeruginosa*), yeasts (*Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Candida utilis*, *Rhodotorula rubra*) and filamentous fungi (*Aspergillus niger*, *Penicillium chrysogenum*, *Mucor mucedo*).[1]

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Biographical sketch

Jan Jacobs obtained his engineering degree in chemistry in 2005 at Ghent University. He completed his Ph.D. research in 2009 under the supervision of Prof. N. De Kimpe at Ghent University, where his research involved the synthesis of new pyranonaphthoquinone and 2-aza-anthraquinone antibiotics. Currently, he is working as a Postdoctoral fellow of the Research Foundation—Flanders (FWO) in the research group of Prof. N. De Kimpe at the Department of Sustainable Organic Chemistry and Technology at Ghent University.

Kourosch Abbaspour Tehrani was born in Ghent, Belgium, in 1970. He received the diploma of chemical agricultural engineer in 1993 and obtained the Ph.D. degree in 1997, both from Ghent University (Belgium) under the supervision of Prof. N. De Kimpe, studying the synthesis of functionalized pyrroles. Subsequently he performed a postdoctoral stay at Loker Hydrocarbon Research Institute, University of Southern California, under the supervision of Prof. N. Petasis (Los Angeles) and from 1999 to 2001 he was a Postdoctoral fellow of the Research Foundation—Flanders (FWO) under the supervision of Prof. N. De Kimpe. In December 2001 he became Assistant Professor at the Faculty of Science and Bioengineering Sciences of the Vrije Universiteit Brussel and in February 2010 he took up the position of Associate Professor at the Department of Chemistry, Faculty of Science at the University of Antwerp. He is the author of 63 papers in international peer-reviewed journals. His research interests are focused on synthetic heterocyclic chemistry related to medicinal and agrochemical applications and the development of new synthetic methodologies using organoboron compounds.

Norbert De Kimpe obtained the diploma of chemical agricultural engineer in 1971, the Ph.D. degree in 1975, and the habilitation degree in 1985, all from Ghent University, Ghent (Belgium). He performed postdoctoral research work at the University of Massachusetts, Harbour Campus, at Boston (USA) (1979) and at the Centre National de Recherche Scientifique (CNRS) in Thiais, Paris (France) (1983), where he worked on unstable nitrogen-substituted sulfenyl derivatives and electron-deficient carbenium ions, respectively. He made his scientific career at the Belgian National Fund for Scientific Research, where he went through all stages up to the position of Research Director. During this career, he was affiliated with the Department of Organic Chemistry, Faculty of Bioscience Engineering at Ghent University, where he took up teaching positions since 1987. He is now full professor in organic chemistry at the latter institution. He was a guest professor at the Centre Universitaire de Recherche sur la Pharmacopée et la Médecine Traditionelle in Butare (Rwanda, Central Africa), and at the Universities of Perpignan (France), Helsinki (Finland), Leuven (Belgium), Siena (Italy), Barcelona (Spain), Sofia (Bulgaria), Buenos Aires (Argentina) and Pretoria (South Africa). He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (Russia) in 1998 and from the University of Szeged (Szeged, Hungary) in 2007. He obtained the Medal of Honour of Sofia University (Bulgaria) in 2006 and was awarded the A. N. Kost medal of the Mendeleev Russian Chemical Society in 2010. He is Member of the Royal Flemish Academy of Belgium, Section Natural Sciences and the Academia Scientiarum et Artium Europea (European Academy of Sciences and Arts), Salzburg (Austria). He is Fellow of the Royal Society of Chemistry (UK) and IUPAC Fellow. He is the author of 560 articles in international peer-reviewed journals. His research interests include (1) the synthesis of heterocyclic compounds, with focus on agrochemicals, pharmaceuticals and natural products, (2) flavour chemistry and (3) the bioassay-guided isolation of bioactive natural products from medicinal plants.