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Synthesis of natural pyranonaphthoquinones and related antibiotic aza-analogues*

Jan Jacobs[1], Sven Claessens[1], Kris Huygen[2], Kourosch Abbaspour Tehrani[3], and Norbert De Kimpe[1,‡]

[1]Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium; [2]Scientific Institute of Public Health Site Ukkel, Immunology and Vaccinology Program, Engelandstraat 642, B-1180 Brussels, Belgium; [3]Organic Synthesis, Department of Chemistry, Faculty of Sciences, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

Abstract: Pentalongin, the active principle isolated from the roots of the Central East African medicinal plant *Pentas longiflora*, revealing the basic skeleton of 3,4-dehydropyranonaphthoquinones, was synthesized by ring-closing metathesis of a suitable precursor. Mollugin, together with the (+)-*cis*-dihydroxylated analogue and the tetracyclic isagarin have been isolated from *P. longiflora* as well as from other rubiaceous herbs, which are often used in Chinese folk medicine. Synthetic routes of these natural products are presented, as well as the first syntheses of the natural products 3-hydroxy- and 3-methoxymollugin. Although pyranonaphthoquinones represent a large class of natural products, reports of their naturally occurring 2-aza analogues, all of which have been isolated as 2-aza-anthraquinones, are scarce in the literature. Nevertheless, this class of compounds has been found to possess interesting antitumor, antifungal, and antibiotic properties. Therefore, several synthetic routes to new classes of 2-aza-anthraquinones were developed. In vitro testing of the obtained compounds for their activity against *Mycobacterium tuberculosis* showed promising results.

Keywords: 2-aza-anthraquinones; benz[*g*]isoquinoline-5,10-dione; benzo[*f*]isoindole-4,9-dione; pentalongin; pyranonaphthoquinones.

INTRODUCTION

Quinones are widely distributed in plants, animals, bacteria, fungi, and algae and are often associated with antitumor, antibacterial, and antiprotozoan activities [1]. Within this class of compounds, pyranonaphthoquinones consist of a large number of natural and synthetic 1*H*-naphtho[2,3-*c*]pyran-5,10-dione derivatives with some famous examples such as eleutherin (**1**), nanaomycin A (**2**), and frenolycin B (**3**) (Fig. 1), many of which were found to possess interesting antibiotic activities against Gram-positive bacteria, fungi, and mycoplasmas [2]. Furthermore, it was suggested that these pyranonaphthoquinones might also exhibit antitumor activity since Moore proposed their mechanism of action as "bioreductive alkylating agents" [3]. As a result, the development of new synthetic strategies for the synthesis of pyranonaphthoquinone derivatives is still a popular theme in organic chemistry [4]. Similarly, 2-aza-

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‡Corresponding author: Tel.: + 32 9 264 59 51; Fax: + 32 9 264 62 43.

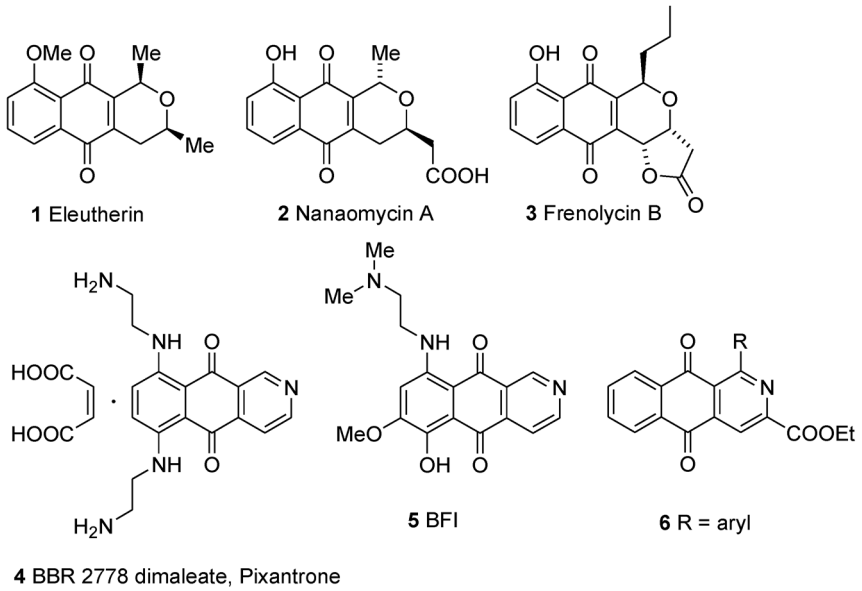
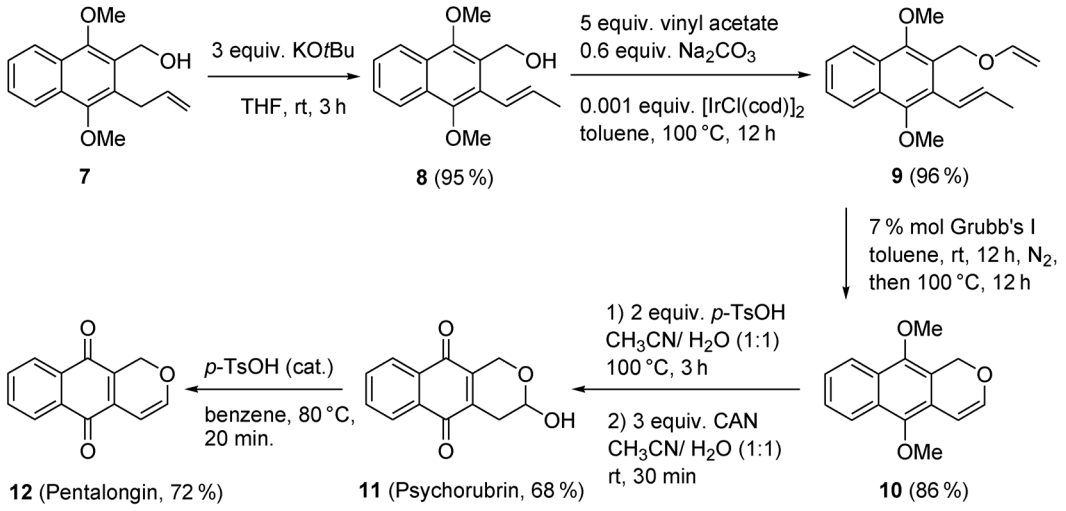


Fig. 1 Bioactive pyranonaphthoquinones and 2-aza-anthraquinones.

anthraquinones evoke much interest owing to their potent biological activities. Among others, they have been reported to show antibiotic activities [5] and they display anti-Epstein-Barr virus activities [6]. In addition, 2-aza-anthraquinone derivatives interfere with the activity of DNA topoisomerases and attract considerable attention in cancer chemotherapy as intercalating DNA binding agents [7]. In this way, potent antitumor 2-aza-anthraquinones, such as pixantrone (BBR 2778 dimaleate) **4** [8], and the benzo-fused isoquinolinedione derivative BFI **5** (Fig. 1) were discovered [9]. Moreover, pixantrone **4** has also been proposed as a very promising immunosuppressant agent for clinical use in the treatment of multiple sclerosis [10]. Finally, 1-aryl substituted 2-aza-anthraquinones **6** were evaluated as potential antitumor agents and inhibition of the proliferation of MT-4 cells at μM concentrations [11].

PYRANONAPHTHOQUINONE ANTIBIOTICS

Pentalongin **12**, which is a 3,4-dehydropyranonaphthoquinone, was first isolated as a major constituent from *Pentas longiflora* Oliver (Rubiaceae) [12]. This is an erect stemmed woody herb up to 3 m high [13], which is reputed to possess several medicinal properties. In Kenya, where it is known as nekilango or segimbe, the roots are used as a cure for tapeworm, itchy rashes, and pimples. A decoction of the roots is mixed with milk and taken as a cure for malaria, but causes acute diarrhea and acts as a purgative [14]. In Rwanda, the plant is known as isagara, and traditional healers use the powder of the roots mixed with butter as an ointment to treat scabies and the skin disease pityriasis versicolor [12b]. More recently, organic extracts of the leaves of *P. longiflora* were reported to have a very good antiplasmodial activity [15] and *Mycobacterium simiae* was found to be sensitive to plant extracts of *P. longiflora* [16]. After the isolation of the bioactive pentalongin **12**, the decision was made at our department to set up a research program, firstly to disclose new synthetic approaches for these 3,4-dehydropyranonaphthoquinones, secondly to broaden the availability of these compounds for screening, and thirdly to deliver new and interesting derivatives. In this way, intensive research was carried out in order to explore numerous synthetic pathways to the 3,4-dehydropyranonaphthoquinone pentalongin **12** and its derivatives [17]. One of the explored synthetic routes includes a ring-closing metathesis reaction using Grubbs' catalyst on an appropriate unsaturated naphthoquinone (Scheme 1). The key reaction step is



Scheme 1

the vinylation of compound **8** at the oxygen atom. This reaction was carried out with vinyl acetate in the presence of chloro-(1,5-cyclooctadiene)iridium(I) dimer ($[IrCl\text{-}(cod)]_2$) as a catalyst. Stirring at 100 °C for 12 h in toluene afforded the vinyl ether **9** in an excellent yield (96 %) as the (*E*)-isomer. This compound was converted into compound **10** using Grubbs' first-generation catalyst in toluene at 100 °C for 12 h under a nitrogen atmosphere [18]. The use of Grubbs' first-generation catalysts for the ring-closing reaction of enolic ethers is limited and known to be problematic [19]. However, recently the ring-closing reaction of vinyl ethers containing alkoxy substituents by using Grubbs' first-generation catalyst was performed succesfully by Wong [20]. Since the oxidative demethylation of compound **10** was not successful, it was necessary to make a little detour. This problematic oxidation of certain pyranonaphthalene derivatives was already observed by us [21] and by others [22]. Firstly, it was required to add water across the double bond, then it was possible to perform the oxidative demethylation to form the natural product psychorubrin **11**, a compound with antitumor activity isolated from *Psychotria rubra* [23], and in a final step water was eliminated again to get the desired pentalongin **12**.

In a continuation of the efforts made for searching new pyranonaphthoquinones, other interesting compounds were isolated (Fig. 2) from *P. longiflora* at our department together with already known compounds such as mollugin **13**, 3-hydroxymollugin **14**, 3-methoxymollugin **15**, and *trans*-3,4-dihydroxy-3,4-dihydromollugin **17** [24]. The newly isolated compounds included *cis*-3,4-dihydroxy-3,4-dihydromollugin **18** and isagarin **19** [25], the latter containing a novel structural unit in naturally occurring naphthoquinones, thus making it an important compound to synthesize. The bioactivities of the above-mentioned isolated compounds motivated organic chemists to construct novel synthetic routes to them.

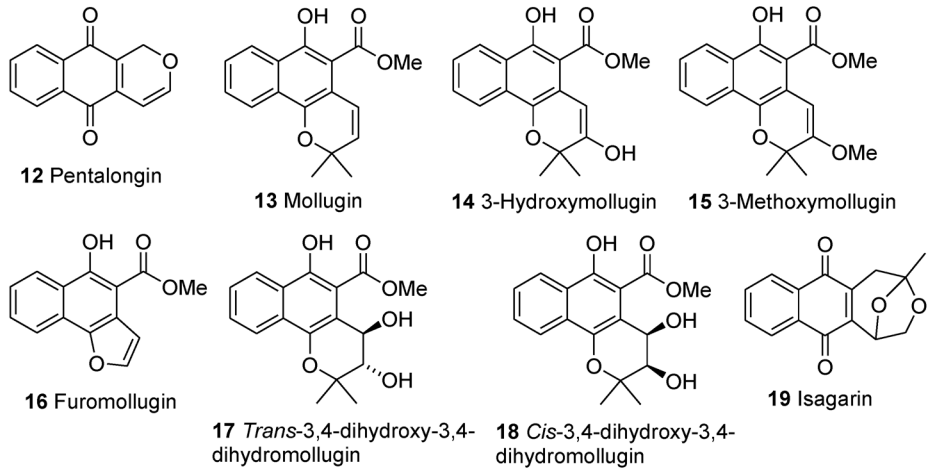
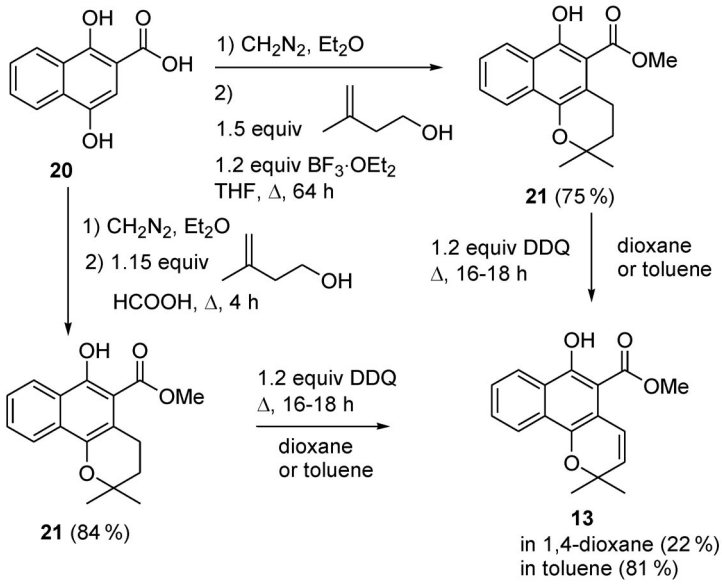


Fig. 2 Natural products isolated from *P. longiflora* and/or *R. cordifolia*.

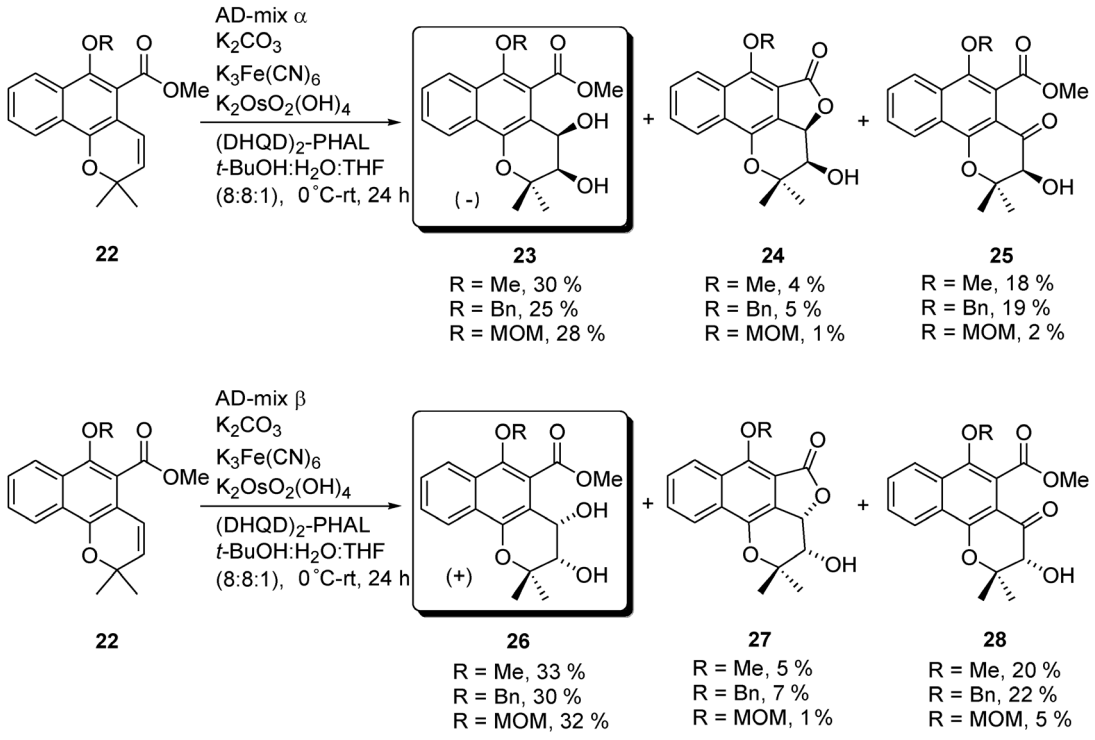
First, the synthesis of mollugin **13** was targeted. This natural product was first isolated from the rhizome of *Gallium mollugo* (Rubiaceae) and has been found in many rubiaceous herbs growing in Europe, Africa, and Asia [26]. Mollugin **13**, 3,4-dihydromollugin **21** and their analogues have shown antitumor activity [26i], antiviral activity against the hepatitis B virus [26a,g], antibacterial, and mutagenic activities [26d]. In addition, Chung et al. reported that mollugin **13** strongly inhibited collagen-induced and arachidonic acid-induced platelet aggregation [26c]. Although several synthetic routes to mollugin **13** are reported in the literature [27], continuous investigation at our department revealed the most efficient synthesis of this natural product to date (Scheme 2) [28]. First, methyl 1,4-dihydroxy-naphthalene-2-carboxylate was prepared by esterification of the carboxylic acid **20** with diazomethane. In the following step, the methyl ester was heated under reflux with 3-methyl-3-buten-1-ol in tetra-



Scheme 2 Efficient synthesis of mollugin.

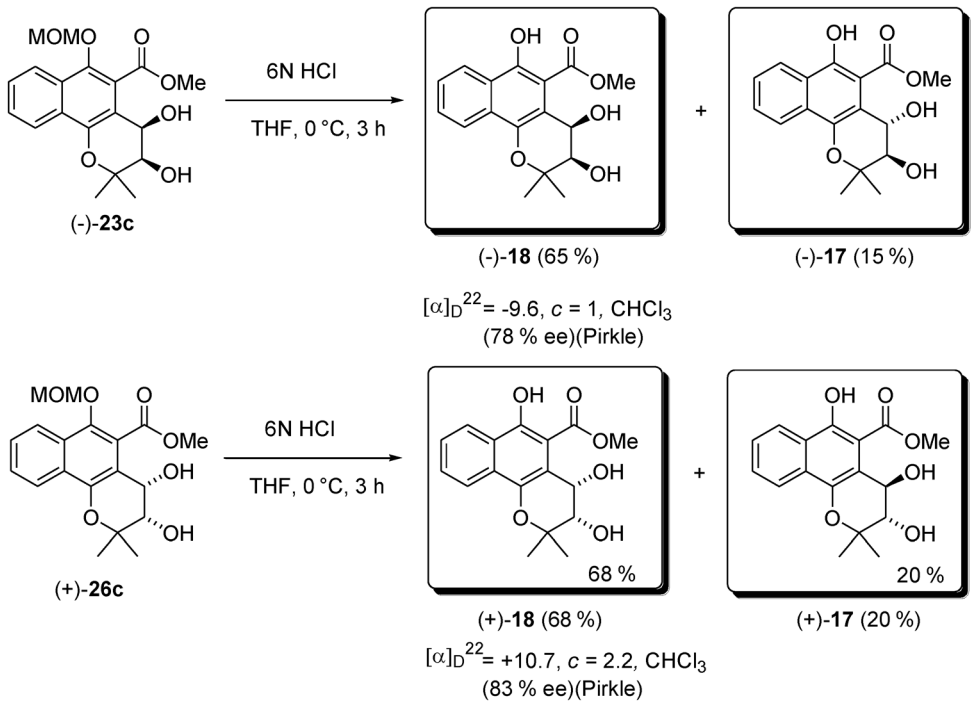
hydrofuran (THF) in the presence of $BF_3{\cdot}OEt_2$ to give rise to 3,4-dihydromollugin **21** via BF_3-activation of the alcohol moiety by borate formation and subsequent *ortho*-alkylation of the aromatic alcohol by the homoallylborate and cyclization by attack of the phenol oxygen across the proton-activated carbon–carbon double bond of the isoprenyl group. Alternatively, the yield of the isolated 3,4-dihydromollugin **21** could be increased to 84 % by using formic acid instead of $BF_3{\cdot}OEt_2$. In a next step, 3,4-dihydromollugin **21** was oxidized to the desired mollugin **13**. The literature revealed an existing method using dichlorodicyano-*p*-benzoquinone (DDQ) in dioxane resulting in mollugin **13** in 72 % yield [27b], but in our hands the yields were much lower (22 %), even after repeated attempts. Thus, this oxidation reaction was investigated thoroughly and it was found that mollugin **13** could be obtained in 81% yield by using a DDQ oxidation of dihydromollugin **21** in toluene, which is an improved oxidation procedure compared to the literature [27b].

In a following part, the synthesis of *trans*-3,4-dihydroxy-3,4-dihydromollugin **17** and *cis*-3,4-dihydroxy-3,4-dihydromollugin **18**, which have been isolated from *P. longiflora* and *Rubia cordifolia*, was investigated. Recently, the racemic syntheses of dihydroxymollugins **17** and **18** were reported by our department [29]. The *cis*-dihydroxy compound **18** was synthesized by a dihydroxylation reaction using OsO_4, and the *trans*-dihydroxy compound **17** was prepared using oxone on *O*-protected mollugin derivatives. The synthesis of racemic *trans*-3,4-dihydroxy-3,4-dihydromollugin **17** was also reported by Wang et al. by reacting dimethyldioxirane (DMD) with mollugin **13** in 62 % yield [30]. However, in our hands by employing the same reaction conditions the *trans*-3,4-dihydroxy-3,4-dihydromollugin **17** was only formed in 30 % yield along with the formation of several side products. Next, an enantioselective synthesis of *trans*-3,4-dihydroxy-3,4-dihydromollugin **17** and *cis*-3,4-dihydroxy-3,4-dihydromollugin **18** was devised by our research group with a strategy based on the Sharpless asymmetric dihydroxylation reaction using AD mixes. As encountered in the previous case, due to complex formation of the osmium species with the acidic phenolic hydroxyl moiety of mollugin **13**, only complex reaction mixtures were obtained by attempted dihydroxylation of mollugin **13** using AD-mix-α and AD-mix-β [29]. Therefore, mollugin **13** was protected as the *O*-methyl, *O*-benzyl, and *O*-methoxymethyl ether and subsequently, asymmetric dihydroxylation reactions were attempted on these *O*-protected mollugins **22** (Scheme 3) [30]. However, the original Sharpless reaction conditions failed due to solubility problems and the addition of THF as a co-solvent was found to be required. No significant improvement in the yield of the required dihydroxy compound was observed both with the *O*-benzyl and *O*-methoxymethyl protected mollugins **22** and the yields were not changed much by switching AD-mix-α to AD-mix-β. The absolute configuration of the dihydroxy compounds **26**, which are formed with AD-mix-β, were assigned as 3*S*,4*S* using the enantioselective mnemonic of the AD-reactions and by comparing analogous dihydroxylations in the literature [32]. Similarly, the absolute configuration of the dihydroxy compounds **23**, which were formed with AD-mix-α, were assigned as 3*R*,4*R*. The enantiomeric excess of the compound (+)-(3*S*,4*S*)-**26c** was determined by ^{1}H NMR experiments of the corresponding compound with Pirkle alcohol as a chiral co-solvent [33]. Thus, the highest enantioselectivity was obtained in the case of *O*-methoxymethyl-(3*S*,4*S*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **26c** using AD-mix-β and was found to be 84 % (α_D +10.9, c 1.3, $CHCl_3$). Using AD-mix-α, 78 % ee was found in the case of *O*-methoxymethyl-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **23c** (α_D –11.0, c 1.75, $CHCl_3$).



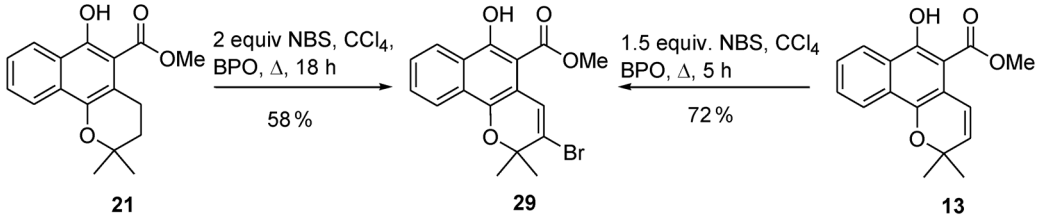
Scheme 3

Subsequently, having *O*-protected *cis*-3,4-dihydroxy-3,4-dihydromollugins in hand, research was focused on the deprotection of these compounds to obtain the targeted optically active 3,4-dihydroxy-3,4-dihydromollugins **17** and **18**. However, only the deprotection of the *O*-methoxymethyl protected *cis*-3,4-dihydroxy-3,4-dihydromollugins was successful, and in this way, the asymmetric syntheses of (–)-(3*R*,4*R*)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **18**, (–)-(3*R*,4*S*)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **17**, (+)-(3*S*,4S)-*cis*-3,4-dihydroxy-3,4-dihydromollugin **18**, and (+)-(3S,4R)-*trans*-3,4-dihydroxy-3,4-dihydromollugin **17** was achieved for the first time with good to excellent enantioselectivity (Scheme 4). This unusual formation of a *trans*-diol **17** from *cis*-diol **18** can be explained as follows. Deprotection of the methoxymethyl (MOM)-ether obviously results in a *cis*-diol. However, under excess acidic conditions the hydroxyl moiety at position 4 is protonated and easily eliminated by an electron push mechanism starting from the electron lone pair of the pyranyl-oxygen at position 1. In this way, a reactive charged *ortho*-quinomethide intermediate is formed onto which water adds and results in the formation of the more stable *trans*-isomer.



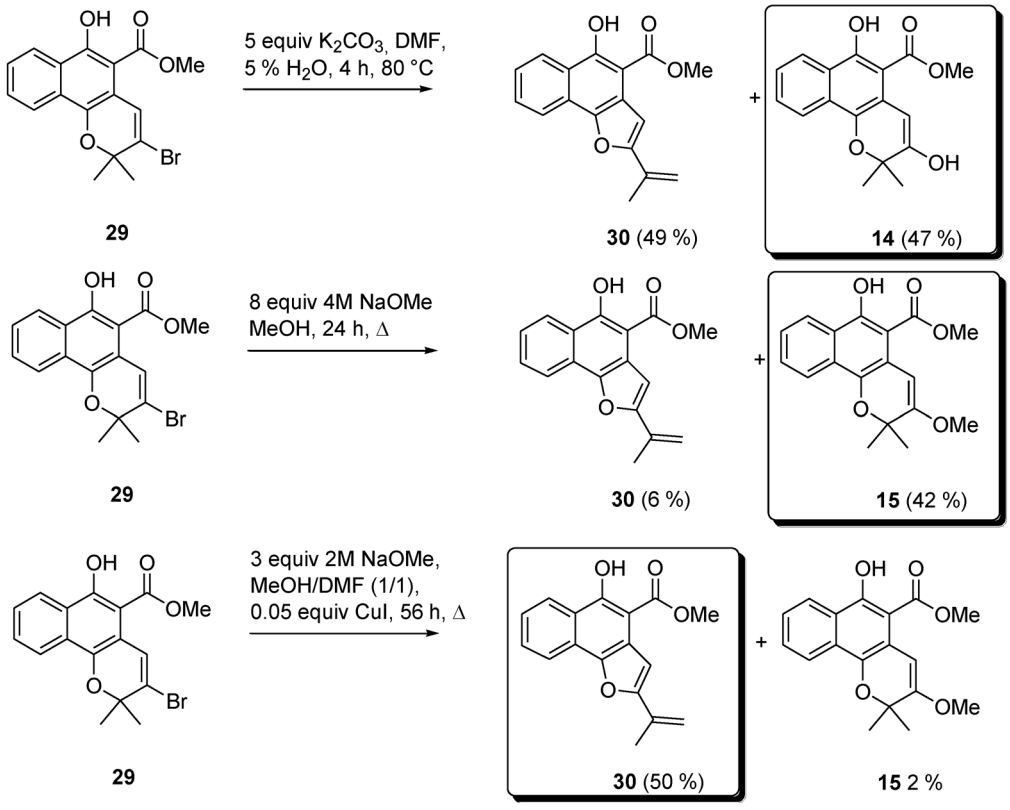
Scheme 4

3-Hydroxymollugin **14**, 3-methoxymollugin **15**, and furomollugin **16** are cytotoxic compounds isolated as minor compounds from *R. cordifolia* [24] and *P. longiflora* [34]. Syntheses of 3-hydroxymollugin **14** and 3-methoxymollugin **15** were developed starting from the easily available 3-bromomollugin **29**. It was found that 3-bromomollugin **29** can be easily formed starting from 3,4-dihydromollugin **21** by reaction with 2 equiv of *N*-bromosuccinimide in CCl_4 in the presence of benzoyl peroxide (Scheme 5) [28]. Afterwards, the synthesis of 3-bromomollugin **29** was improved from 58 to 72 % by direct bromination of mollugin **13** using *N*-bromosuccinimide in the presence of benzoyl peroxide (Scheme 5) [35].



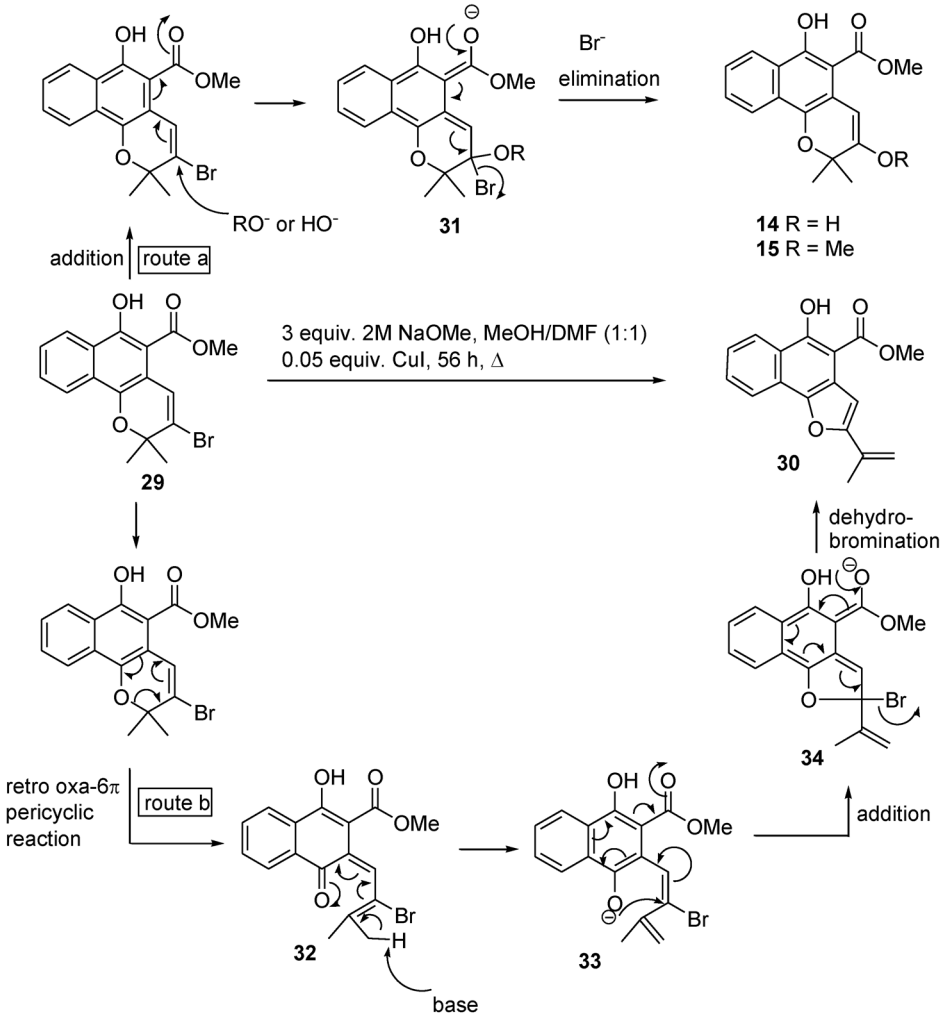
Scheme 5 Synthesis of 3-bromomollugin **29**.

Surprisingly, it was found that the reaction of 3-bromomollugin **29** with 5 equiv of potassium carbonate in dimethyl formamide (DMF), to which an addition of 5 % water was required, for 4 h at 80 °C gave rise to the natural product 3-hydroxymollugin **14** and isopropenylfuromollugin **30** in 47 and 49 % yield, respectively (Scheme 6) [35]. Analogously, sodium methoxide in methanol resulted in the formation of 3-methoxymollugin **15** and the ring-contracted methyl isopropenylfuromollugin **30** in 42 and



Scheme 6

6 % yield, respectively (Scheme 6) [35]. A mechanism for the ring contraction in the formation of isopropenylfuromollugin **30** is proposed based on a pericyclic retro oxa-6π ring-opening reaction (Scheme 7, route b). Next, the allylic hydrogen in intermediate **32** is deprotonated by the base, after which the phenolate **33** intramolecularly attacks the double bond, which is activated by the electron-withdrawing ester moiety. Then, addition-dehydrobromination results in the obtained isopropenylfuromollugin **30**. Alternatively, elimination of bromide in compound **31** occurs when sodium methoxide or hydroxide acts as a nucleophile across the conjugated vinyl bromide, leading to 3-methoxymollugin **14** or 3-hydroxymollugin **15**, respectively (Scheme 7, route a). The isolated isopropenylfuromollugin **30** is an interesting compound as it can be viewed as a structural unit of the natural products rubicordifolin **35**, rubioncolin A **36**, and rubioncolin B **37** (Fig. 3) [36]. This statement, together with the finding that these compounds are often isolated together with mollugin **13** from Rubiaceae led to the conclusion that these compounds **35**, **36**, and **37** might be biochemically related to mollugin **13** [35].



Scheme 7

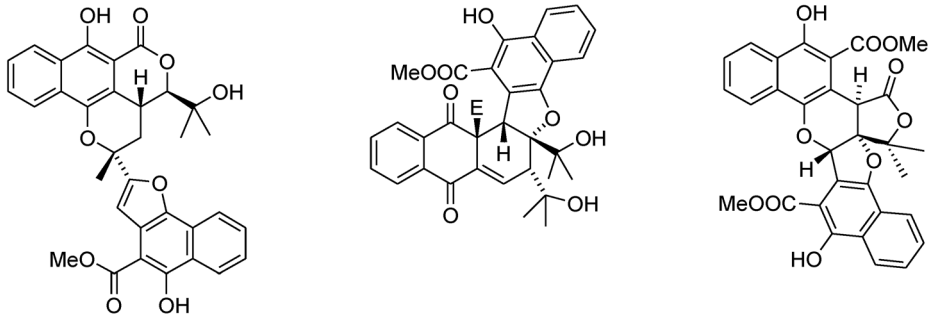
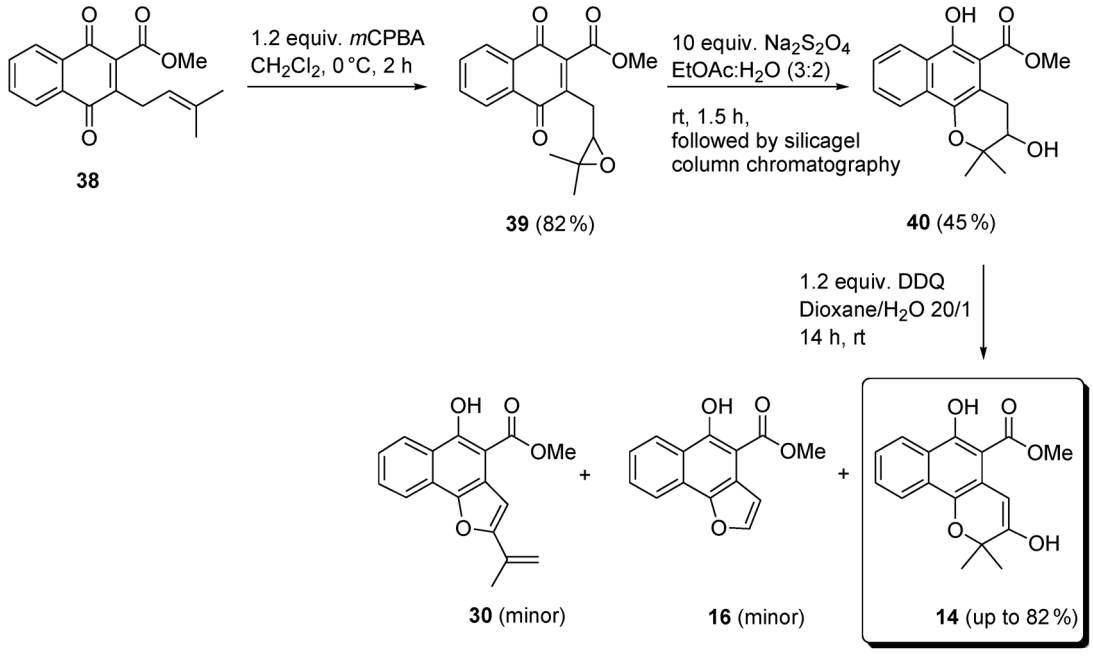
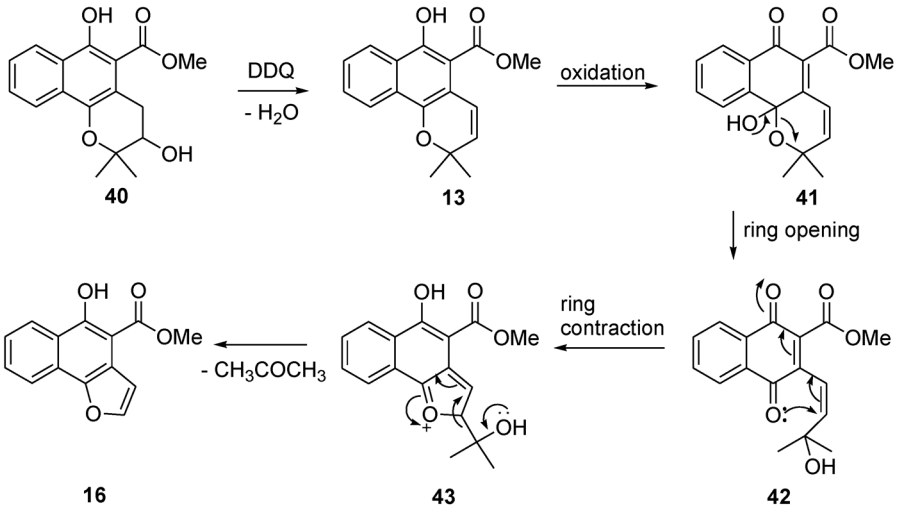


Fig. 3 Natural products isolated from Rubiaceae.

A second synthesis of 3-hydroxymollugin **14** was based on the epoxidation of methyl 3-(3-methylbut-2-enyl)-1,4-naphthoquinone-2-carboxylate **38**, which is considered to be the biochemical precursor of mollugin **13** and its analogues [35]. Subsequent reduction of the quinone moiety, ring transformation, and DDQ-oxidation resulted in 3-hydroxymollugin **14** along with the rearranged furomollugin **16**, which is a ring-contracted analogue of the natural product mollugin **13** (Scheme 8) [35]. Mechanistically, the formation of furomollugin **16** is thought to proceed via the formation of mollugin **13**, which is successfully oxidized by DDQ to compound **42** (Scheme 9). Based on the observations by



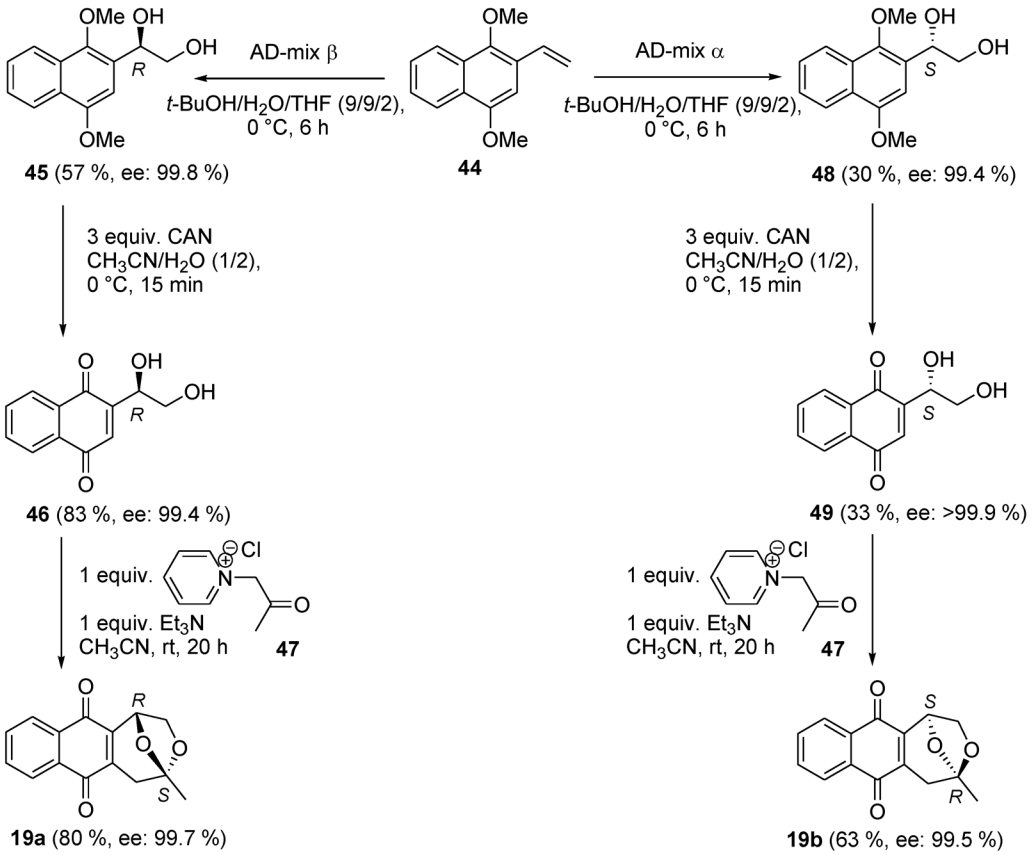
Scheme 8



Scheme 9

Trauner et al. [37], it is believed that ring contraction and elimination of acetone lead to the formation of furomollugin **16**. Having in hands a high-yielding synthesis of 3-hydroxymollugin **14**, methylation reactions were attempted in order to obtain 3-methoxymollugin **15** in high yield. Unfortunately, all attempted reaction conditions were found to be unsuccessful due to decomposition of the starting material [35].

Due to its interesting architecture, isagarin **19**, which is a minor constituent isolated from *P. longiflora* [25b], is an attractive target for synthetic chemists, which resulted in a first racemic synthesis by our department [38]. Later, a total synthesis of isagarin **19** was reported in an overall yield of 24 % using the Wacker cyclization in the key step [39]. However, isagarin **19** can exist as two different enantiomers: 1*R*,4*S*-isagarin **19a** and 1*S*,4*R*-isagarin **19b**, and since the isolated natural product was reported to be optically active [25b], it does not concern a racemic mixture. Therefore, it was decided to investigate the first enantioselective synthesis of both 1*R*,4*S*-isagarin **19a** and 1*S*,4*R*-isagarin **19b** in order to determine the configuration of the isolated natural product as its biological activity may very well reside within a single enantiomer. In this way, the Sharpless asymmetric dihydroxylation of 1,4-dimethoxy-2-vinylnaphthalene **44** and subsequent oxidative demethylation was found to give chiral 2-(1,2-dihydroxyethyl)-1,4-naphthoquinones **46** and **49**. Then, reaction of the latter naphthoquinones with acetylmethyl pyridinium ylid gave rise to the formation of a second chiral center with one possible conformation due to stereoinduction during the spontaneous intramolecular condensation reaction of the vicinal diol across the added acetonyl side chain, and accordingly, 1*R*,4*S*-isagarin **19a** and 1*S*,4*R*-isagarin **19b** were obtained smoothly (Scheme 10) [40]. Interestingly, a comparison of the opti-



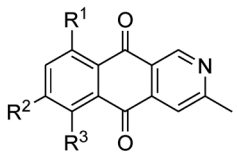
Scheme 10

cal rotation of the synthesized 1*R*,4*S*-isagarin **19a** and 1*S*,4*R*-isagarin **19b** with the reported α_D value of the naturally occurring isagarin **19** suggests that the natural product does not occur as a single enantiomer [40].

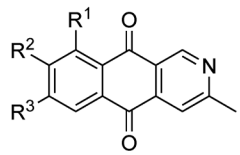
2-AZA-ANTHRAQUINONES

The various promising bioactivities of 2-aza-anthraquinones have invited many research groups to actively participate in 2-aza-anthraquinone research. However, while the first report on the synthesis of 2-aza-anthraquinones stems from the 1920s, the majority of the synthetic methodologies, which have been constructed since then, still suffer from a poor regioselectivity, low yields or a multi-step sequence. To date, various syntheses to this class of compounds have been elaborated, amongst which several contributions of our department.

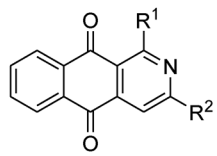
Although pyranonaphthoquinones represent a large class of natural products, their naturally occurring 2-aza analogues, all of which have been isolated as the aromatic 2-aza-anthraquinones, have rarely been found in nature. So far, only a few naturally occurring 2-aza-anthraquinones have been reported: bostrycoidin **50** [41], 9-*O*-methylbostrycoidin **51** [42], tolypocladin **52** [43], 6-deoxy-8-methylbostrycoidin **53** [44], 6-deoxybostrycoidin **54** [45], 7-*O*-demethyl-6-deoxybostrycoidin **55**, scorpinone **56** [44a,46], and benz[*g*]isoquinoline-5,10-dione **57** (Fig. 4) [47]. Nevertheless, these compounds have also been found to possess interesting biological activities. For instance, bostrycoidin **50**, a 2-aza-anthraquinone isolated from several fungi of the *Fusarium* species [41], has been shown to possess significant in vitro antibiotic activity against *Mycobacterium tuberculosis* [48]. 9-*O*-Methylbostrycoidin **51**, which is also reported as a metabolite of numerous *Fusarium* species, revealed antibiotic activity against Gram-positive bacteria [42,49]. Tolypocladin **52** was isolated from the mycelium of *Tolypocladium inflatum* and was found to display metal-chelating properties [43]. Next, benz[*g*]isoquinoline-5,10-dione **57**, isolated from *Psychotria camponutans* and *Mitracarpus scaber*, has been found active against the multidrug-resistant pathogens, such as *Plasmodium falciparum* and *Staphylococcus aureus* [47], and inhibits the glucose-dependent cellular respiration and glycerol-3-phosphate-dependent mitochondrial O_2-assimiliation of the long bloodstream forms of *Trypanosoma congolense* [50]. 6-Deoxybostrycoidin **54** and 7-*O*-demethyl-6-deoxybostrycoidin **55** 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 **50** [45,51]. Scorpinone **56** and 6-deoxy-8-methylbostrycoidin **53** have been identified in the mycelium of a Bispora-like tropical fungus and in the mycobionts of the lichen *Haematomma* sp. [44]. Recently, a genetically modified



50 $R^1 = R^3 = OH$, $R^2 = OMe$
(Bostrycoidin)
51 $R^1 = R^2 = OMe$, $R^3 = OH$
(9-*O*-Methylbostrycoidin)
52 $R^1 = R^2 = R^3 = OH$
(Tolypocladin)



53 $R^1 = OH$, $R^2 = Me$, $R^3 = OMe$
(6-Deoxy-8-methylbostrycoidin)
54 $R^1 = OH$, $R^2 = H$, $R^3 = OMe$
(6-Deoxybostrycoidin)
55 $R^1 = R^3 = OH$, $R^2 = H$
(7-*O*-demethyl-6-deoxybostrycoidin)
56 $R^1 = R^3 = OMe$, $R^2 = H$
(Scorpinone)

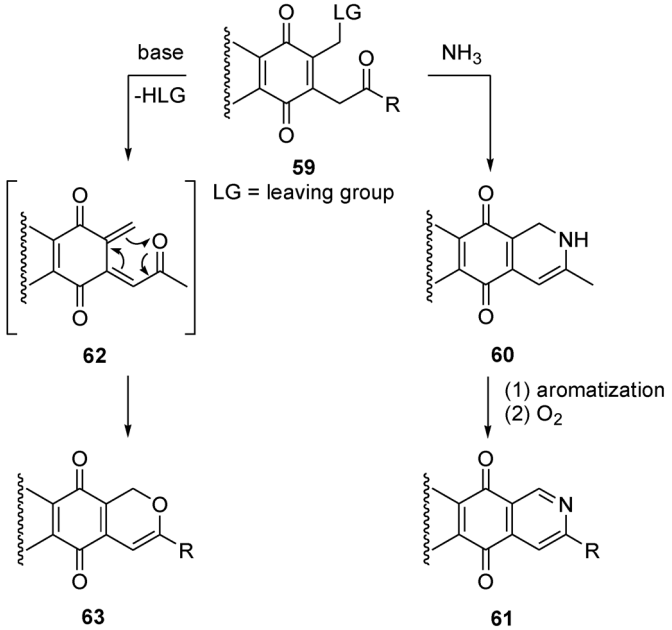


57 $R^1 = H$, $R^2 = H$
(Benz[*g*]isoquinoline-5,10-dione)
58 $R^1 = R^2 = Me$
(Utahmycin A)

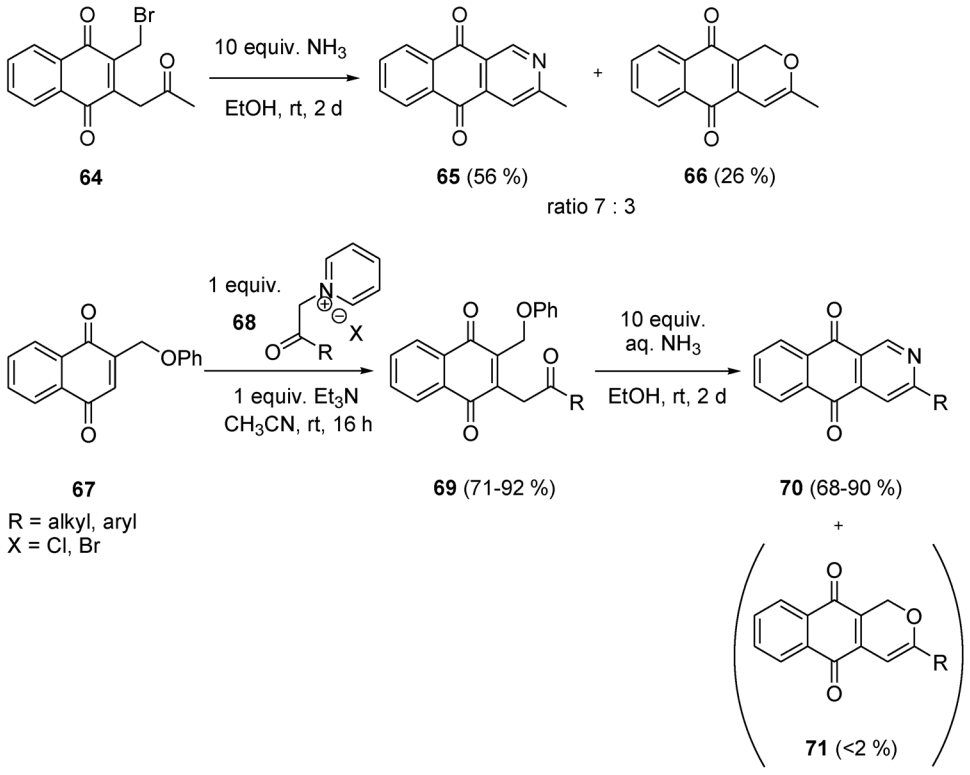
Fig. 4 Natural 2-aza-anthraquinones.

Streptomyces albus strain was reported to produce Utahmycin A **58**, which could be isolated from the ethyl acetate extract of the culture medium [52].

The hypothesis that natural 2-aza-anthraquinones originate in vivo from the incorporation of ammonia into the pyranonaphthoquinone skeleton [48] invited organic chemists to construct a biomimetic synthesis of 2-aza-anthraquinones. This strategy was elaborated at our department and relied on the synthesis of suitably substituted naphthoquinones **59** that would allow efficient syntheses of both 2-aza-anthraquinones **61** and pyranonaphthoquinones **63** (Scheme 11). The latter compounds **63** can be obtained after spontaneous electrocyclization of the intermediate *ortho*-quinomethides **62**, which are formed upon deprotonation and subsequent elimination of the leaving group in naphthoquinones **59**. 2-Aza-anthraquinones **61**, 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 **60** (Scheme 11). In order to achieve an efficient and selective synthesis of 2-aza-anthraquinones, naphthoquinones **59** were first evaluated as model substrates bearing different leaving groups at C2-methyl position. In this way, it was found that the use of 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **64** gave rise to a substantial formation of 3,4-dehydropyranonaphthoquinone **66**, while replacing the bromide by a phenoxide as a moderate leaving group afforded predominantly 2-aza-anthraquinones **70** (Scheme 12) [53]. The improved selectivity for the synthesis of 2-aza-anthraquinones 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 for the introduction of acetonyl side chains onto 2-phenoxymethyl-1,4-naphthoquinone **67** opened the way for the synthesis of 2-aza-anthraquinones **70**. Adding ammonia to adduct **69** caused aza-ring closure affording the corresponding 2-aza-anthraquinones **70** and traces of 3-alkyl and 3-aryl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones **71**, which could be removed successfully upon purification by flash chromatography on silica gel (Scheme 12).

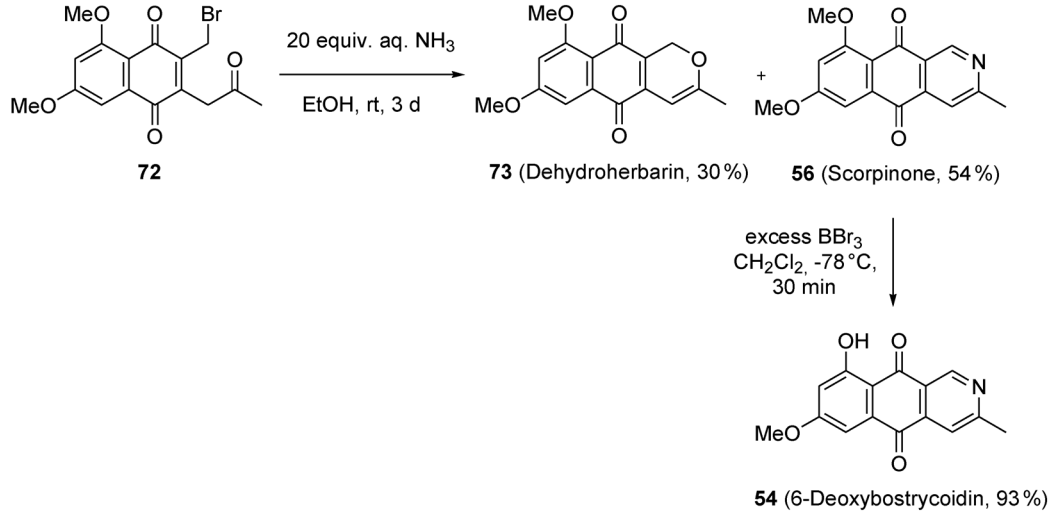


Scheme 11



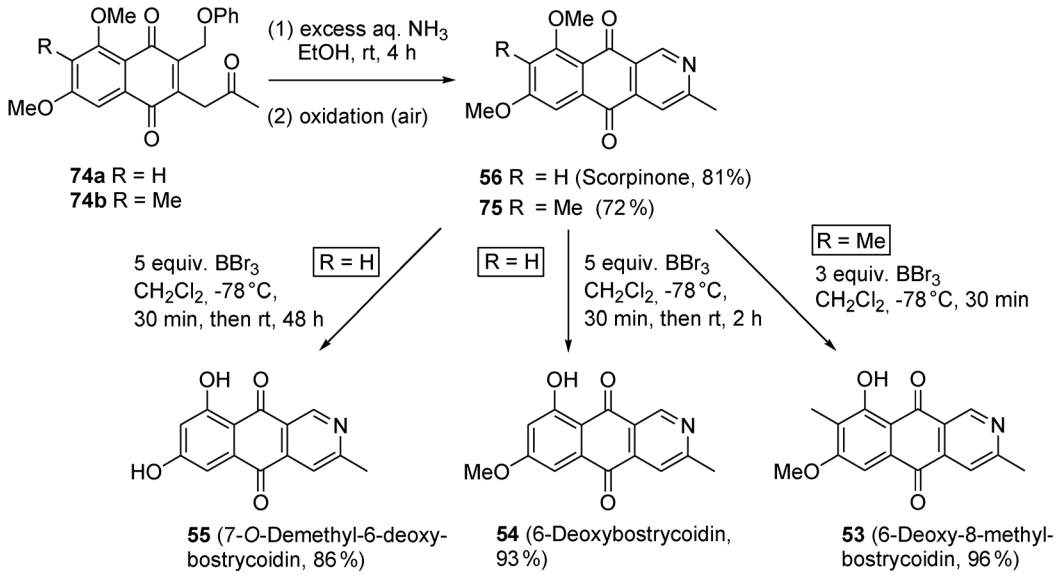
Scheme 12

This strategy enabled the construction of convenient syntheses of the natural 2-aza-anthraquinone antibiotics 6-deoxy-8-methylbostrycoidin **53**, 6-deoxybostrycoidin **54**, 7-*O*-demethyl-6-deoxybostrycoidin **55**, and scorpinone **56**. First, the reaction of 2-acetonyl-3-bromomethyl-5,7-dimethoxy-1,4-naphthoquinone **72** with aqueous ammonia resulted in a mixture of the pyranonaphthoquinone dehydroherbarin **73** and the 2-aza-anthraquinone scorpinone **56**, which could be purified by flash chromatography on silica gel in 30 and 54 % yield, respectively. Afterwards, boron(III) bromide-mediated cleavage of the ether at the C9-position afforded 6-deoxybostrycoidin **54** in 93 % yield (Scheme 13) [54].



Scheme 13

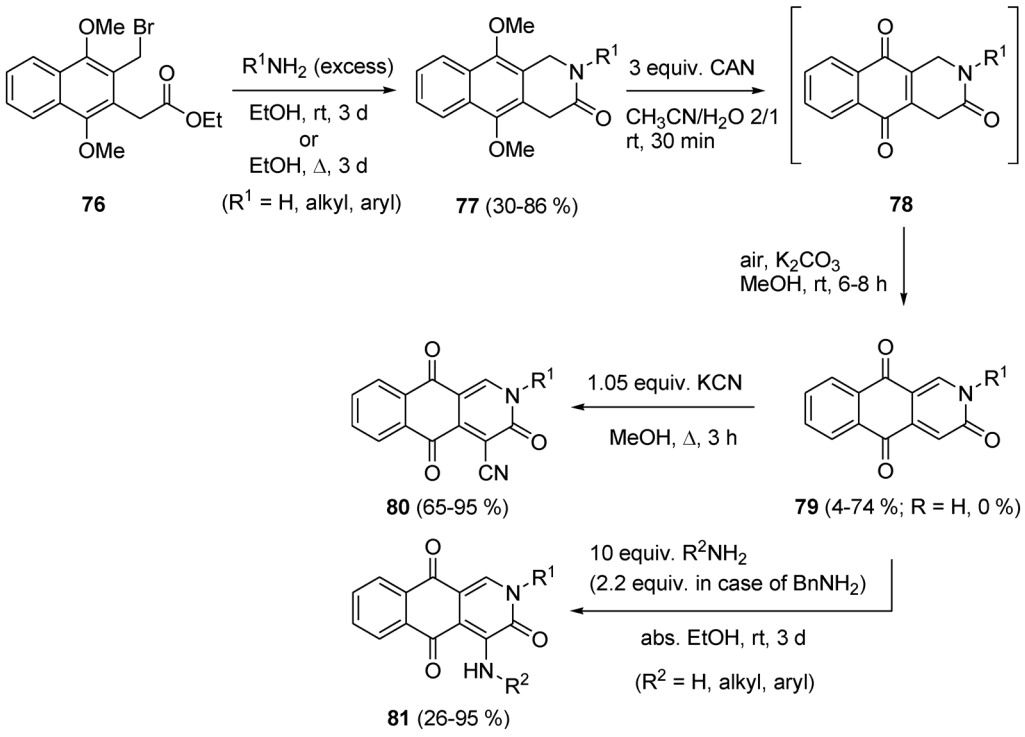
In a second report, the synthesis of scorpinone **56** and its synthetic 8-methyl analogue **75** was achieved upon treatment of suitable 3-phenoxymethyl substituted 1,4-naphthoquinones **74a** and **74b** with ammonia. Further functionalization of the synthesized 2-aza-anthraquinones **56** and **75** gave rise to an efficient and convenient synthesis of the natural antibiotics 6-deoxy-8-methylbostrycoidin **53**, 6-deoxybostrycoidin **54**, and 7-*O*-demethyl-6-deoxybostrycoidin **55** (Scheme 14) [55].



Scheme 14

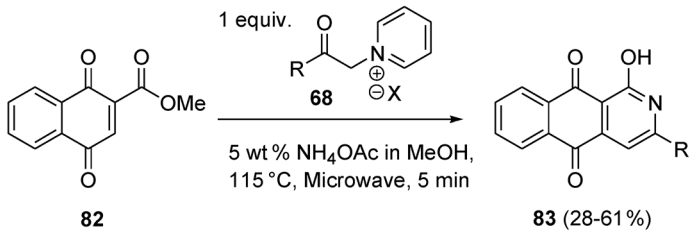
The synthesis of 2-substituted benz[*g*]isoquinoline-3,5,10(2*H*)-triones **79** was achieved after oxidation and aromatization of 5,10-dimethoxy-1,4-dihydrobenz[*g*]isoquinoline-3(2*H*)-ones **77**, which were obtained upon reaction of ethyl (3-bromomethyl-1,4-dimethoxynaphth-2-yl)acetate **76** with

ammonia or with a primary amine via substitution of the benzylic bromide and intramolecular condensation with the ester group (Scheme 15) [56]. Since the synthesized benz[*g*]isoquinoline-3,5,10(2*H*)-triones **79** possess a good Michael-acceptor unit at the C4-position, conjugate addition was evaluated in order to modify their molecular skeleton in an easy and straightforward way. 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 **80** and **81** (Scheme 15) [57].

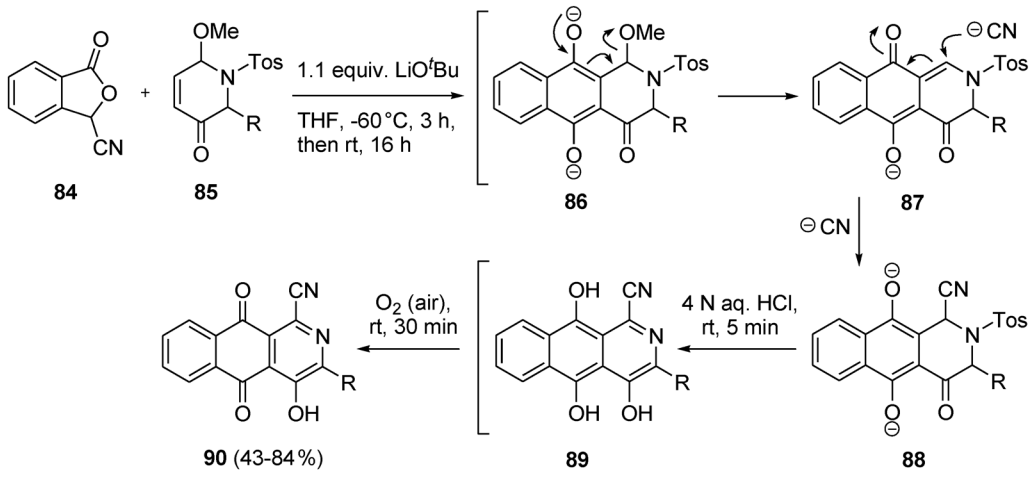


Scheme 15

Finally, a synthetic program was conducted to 1-hydroxybenz[*g*]isoquinoline-5,10-diones as a structure–activity relationship (SAR) study revealed that hydroxyl groups at the *peri*-carbonyl position enhance antibiotic activity [5]. Investigation revealed that a highly efficient synthesis of 3-substituted 1-hydroxybenz[*g*]isoquinoline-5,10-diones **83** was achieved upon reaction of activated naphthoquinone **82**, i.e., a quinone which bears an electron-withdrawing substituent at the 2-position, with different pyridinium salts **68** in a solution of ammonium acetate in methanol as an indirect source of ammonia. When this reaction mixture was introduced in a microwave reactor, the ammonia served as a base to convert the pyridinium salts to the corresponding ylids in situ and as a nitrogen source to construct the 2-aza-anthraquinone after introduction of the acetonyl side chain onto the activated naphthoquinone **82** (Scheme 16) [58]. In the same framework, a convenient synthesis of 2-aza-1-cyano-4-hydroxyanthraquinones **90** was reported by reaction of 3-cyanophthalide **84** and piperidin-3-ones **85**. Remarkably, the cyanide, which was expelled from 3-cyanophthalide **84**, added in a 1,4-fashion onto a Michael acceptor of intermediate **87**. In this way, a cyano function was introduced at the C1-position and the resulting hydroquinone **89**, which was obtained after pouring the reaction mixture in aqueous hydrochloric acid, oxidized spontaneously by air oxygen to 2-aza-anthraquinones **90** (Scheme 17) [59].



Scheme 16



Scheme 17

BENZO[*f*]ISOINDOLES

A final class of compounds, which will be discussed, concerns benzo[*f*]isoindole-4,9-diones. The heterocyclic core of these benzo[*f*]isoindole-4,9-diones is found in natural products such as *Reniera* indole **91**, which has been isolated from the blue sponge *Reniera* sp. [60]. Azamonosporascone **92** has been isolated from *Monosporascus cannonballus*, a fungus responsible for crop losses of musk melon and water melon [61]. Bhimamycin C **93** and bhimamycin D **94** were isolated from a terrestrial streptomycete [62] and display bioactivities against human ovarian cancer cell lines [63], EP_4 receptor agonists in the treatment of pain [64], and are inhibitors of HIV-1 integrase [65] (Fig. 5).

In the literature, only a limited number of synthetic pathways was developed towards compounds having a benzo[*f*]isoindole-4,9-dione core. These pathways are mainly based upon 1,3-dipolar cycloaddition of pyridinium or isoquinolinium ylids across 1,4-naphthoquinones [66], 1,3-dipolar cycloadditions of azomethine ylids generated from amino acids [67] or nitrile oxides [68], via an unusual rearrangement of 2,3-diethynyl-1,4-naphthoquinone with hydrazide [69], starting from the annelated thiophenes [70] and a photochemical addition of 2,3-diphenyl-2*H*-azirine to 1,4-naphthoquinone [71]. The synthesis of 2-methyl-2*H*-benzo[*f*]isoindole-4,9-dione is based on the formal nucleophilic displacement of both methylthio groups in 2,3-bis(methylthiomethyl)-1,4-naphthoquinone with methylamine, followed by spontaneously oxidation by oxygen from the air to afford the benzo[*f*]isoindole [72]. The rearrangement of 2-aza-anthraquinones employing 2,3-dichloro-5,6-dicyanopyrazine as the cyclization partner also resulted in the formation of benzo[*f*]isoindole-4,9-diones [73]. Drawbacks of these methods are the use of non-straightforward methods, difficult accessibility of precursors and low yields. Therefore, a short and straightforward synthesis of this interesting class of compounds is of pri-

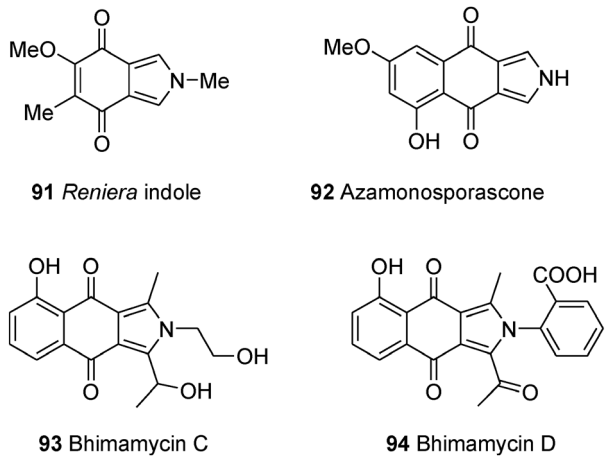
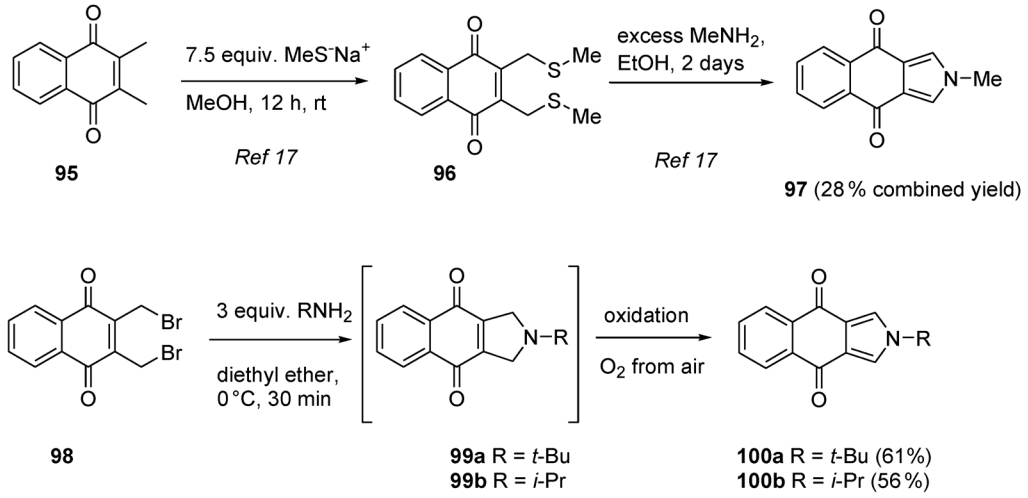


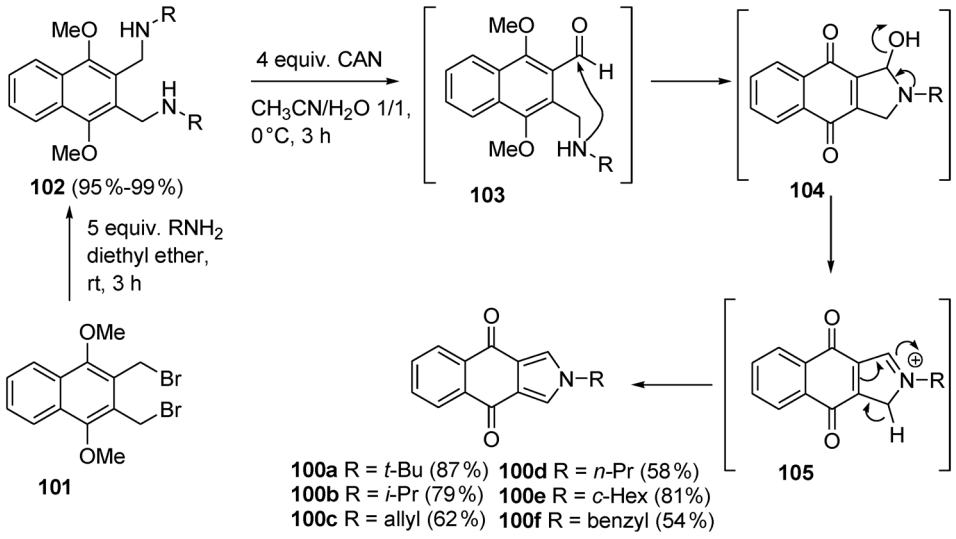
Fig. 5 Natural isoindoles.

mordial importance and was investigated at our department. Initially, we were interested in synthesizing 2-alkyl-2*H*-benzo[*f*]isoindole-4,9-diones with only substituents at nitrogen for which only one existing synthesis pathway is described by Thomson et al. [74]. According to this procedure, only the 2-methyl-substituted benzo[*f*]isoindole was prepared making use of an alkylthiolation reaction of 2,3-dimethyl-1,4-naphthoquinone **95**. Subsequent reaction of 2,3-bis(methylthiomethyl)-1,4-naphthoquinone with methylamine resulted in 2-methyl-2*H*-benzo[*f*]isoindole-4,9-dione **97** in a combined yield of 28 % (Scheme 18). In order to avoid the use of expensive 2,3-dimethyl-1,4-naphthoquinone **95**, an alternative entry was sought. Upon reaction of 2,3-bis(bromomethyl)-1,4-naphthoquinone **98**, which could be prepared by a double bromomethylation procedure from 1,4-naphthoquinone, with a primary amine a first substitution reaction is followed by a second intramolecular nucleophilic substitution to form 2,3-dihydrobenzo[*f*]isoindoles **99**. However, these intermediates **99** are not stable and are oxidized spontaneously by oxygen in the air to afford benzo[*f*]isoindole-4,9-diones **100a** and **100b** in 61 and 56 %, respectively (Scheme 18) [75].

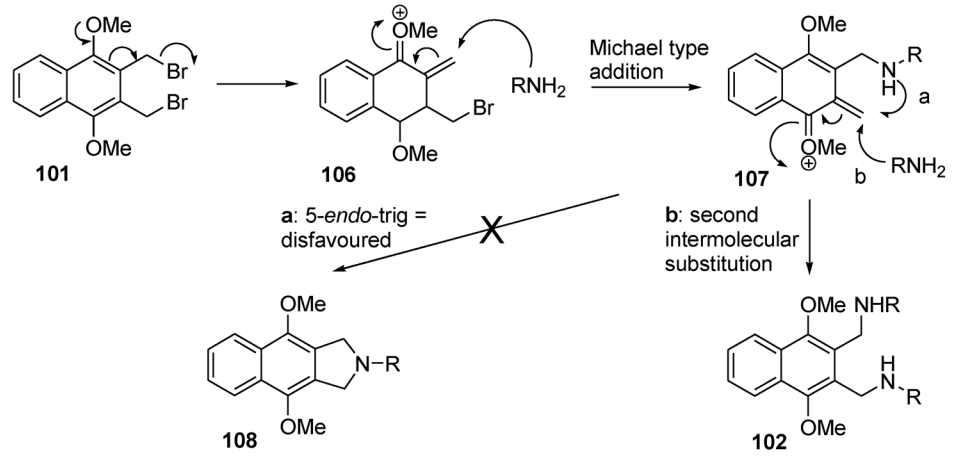


Scheme 18

Nevertheless, the obtained yields are rather moderate, and further research was carried out in order to improve the synthesis of the targeted 2-alkyl-2*H*-benzo[*f*]isoindole-4,9-diones. In this way, 2,3-bis(bromomethyl)-1,4-dimethoxynaphthalene **101**, which could easily be prepared from 1,4-dimethoxynaphthalene, was reacted with primary amines to give double substitution products **102** in excellent yield (Scheme 19) [75]. The fact that this reaction prefers to undergo twice an intermolecular substitution instead of choosing a final ring closure can be explained by the rules of Baldwin (Scheme 20). The bromide **101** is benzylic, and there is an electron-donating *ortho*-substituent present. As a consequence, this compound will easily form *ortho*-quinodimethane **106** via an electron-push mechanism, and the amine will add in a Michael-type way. A ring closure of compound **107** to 4,9-dimethoxy-2,3-dihydro-1*H*-benzo[*f*]isoindole **108** is disfavored because it would be a 5-*endo*-trig ring closure (Scheme 20). Therefore, a second intermolecular substitution reaction is occurring, giving rise to a double substitution product **102**. Next, CAN-mediated oxidative demethylation furnished the



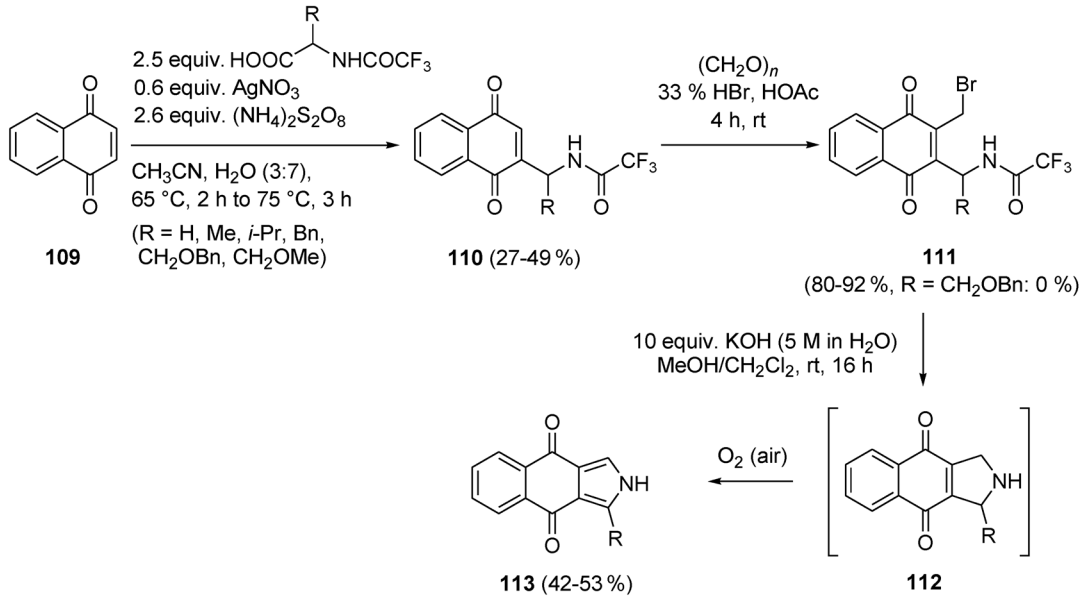
Scheme 19



Scheme 20

targeted benzo[*f*]isoindoles-4,9-diones **100** in 54–87 % yield via the mono-aldehyde **103**, which is attacked intramolecularly by the second unreacted amino moiety in a favored 5-*exo*-trig ring closure reaction resulting in hemiaminals **104**. Subsequently, hydroxide expulsion to generate an iminium ion and subsequent aromatization by loss of a proton gave the target compounds **100** (Scheme 19).

Although the *N*-substituted benzo[*f*]isoindole-4,9-diones **100** were successfully synthesized, the latter pathway did not satisfy the requirement concerning the functionalization of C1 and/or C3. Therefore, *N*-trifluoroacetyl-protected 2-(1-aminoalkyl)-1,4-naphthoquinones **110** were synthesized based on the Kochi–Anderson oxidative decarboxylation method starting from 1,4-naphthoquinone and *N*-trifluoroacetyl-α-amino acids (Scheme 21) [76]. Finally, bromomethylation and subsequent *N*-deprotection gave the target 3-substituted benzo[*f*]isoindole-4,9-diones **113**.



Scheme 21

CONCLUDING REMARKS

Questioning local healers results in a lot of information on traditional medicinal plants. Isolating the active principles from those plants is often the start of interesting research projects. The active principles serve as lead compounds in the search for new and hopefully active compounds. The results cannot be denied: 61 % of the 877 small-molecule new chemical entities introduced as drugs worldwide during 1981–2002 can be traced to or were inspired by natural products [77]. The state of work here presented is one small part in this search for new promising chemicals; hitherto, it was a satisfactory search and the synthesized compounds are currently being screened for their bioactivities. Many years of effort, hard work, exciting discoveries, and, from time to time, disappointing results emerged in a comprehensive knowledge in the field of quinone chemistry.

ACKNOWLEDGMENTS

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