AZANAPHTHOQUINONES: PRIVILEGED SCAFFOLDS IN NATURE. BIOLOGICAL ACTIVITIES, SYNTHESIS, AND REGIOSELECTIVE REACTIONS

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Abstract. *Quinoline-5,8-dione and isoquinoline-5,8-dione alkaloids are present in several marine and terrestrial organisms, primarily in filamentous bacteria such as actinomycetes and streptomyces, but they are also found in sponges and bryozoans. These azanaphthoquinones are usually highly cytotoxic, although some of them show good selectivity against specific organisms and are used as anticancer or antipathogenic drugs, many sharing both behaviors, such as streptonigrin. Although quinoline- and isoquinoline-5,8-diones are structurally similar, they behave differently upon nucleophilic attack to the azanaphthoquinone moiety. Due to their electronic demand, quinoline-5,8-diones show higher selectivity for the nucleophilic attack to position six and isoquinoline-5,8-dione to seven positions. Although coordination of the quinoline-5,8-dione nucleus to a Lewis acid can switch the regiochemical outcome of the nucleophilic attack, the same level of control in isoquinoline-5,8-diones is only achievable with the use of an N-oxide derivative, which changes the reaction mechanism drastically. The oxidative amination is a nucleophilic attack at a quinone scaffold followed by an oxidation step, and it is a common reaction sequence thoroughly used in the total syntheses of azanaphthoquinone alkaloids. Here, we will review this reactivity and present a few examples of newer protocols to prepare advanced intermediates with controlled substitution in all positions of azanaphthalene-5,8-diones.*

Contents

1. Introduction

No strict rules define a structure as "privileged" in the chemical-biological domain. Still, typically, they hold two to five rings, at least one electronegative atom, and a reasonable solubility in water. The resulting scaffolds from such restraints usually are rigid frameworks that show electronic densities at precise positions and can present additional functionality in a well-defined manner, enhancing molecular recognition at a specific biological target. Considering this, it is unsurprising that several heterocycles are frequently nominated as "privileged scaffolds" in medicinal chemistry. Likewise, it is also comprehensible that natural products, particularly secondary metabolites, show us a myriad of "privileged scaffolds", in this case, alkaloids. The reason for such a high number of examples is the natural selection of those structures over extensive chemical and biological evolution.[1-4]

Quinones are also outstanding examples of natural products bearing significant biological activities on diverse organisms.[5] Their polar and planar backbones, frequently bearing phenol moieties, allow strong binding to the macromolecular biological targets. The quinonoid structure can be reduced and, subsequently, protonated to furnish highly reactive semiquinone intermediates. An additional sequence of electron capture/protonation provides the final hydroquinone. This redox sequence invariantly interferes with the organism's redox homeostasis and alters the concentration of reactive oxygen species (ROS).[5]

Figure 1 depicts as examples ellipticine **1** and daunomycin **2**, which can act similarly despite their structural differences: both compounds behave as DNA intercalators with high affinity (–8.0 kcal·mol^{-1} for **1**

vs. −6.8 kcal·mol^{-1} for **2**).[6,7] Although ellipticine **1** has a 2-phenylnaphthalene pattern that mimics the pyrimidine-pyrazine base pair coordination facilitating the intercalation,[8-10] daunomycin **2** has a higher selectivity as an anticancer drug due to the minor-groove binding action of the glycone backbone that stays outside of the hydrophobic environment found between two base pairs, increasing the recognition by specific base pairs. The respective aglycone of daunomycin **2**, daunomycinone, has a little lower binding energy (5.2 kcal·mol^{-1}).[7] Similarities between compounds **1** and **2** stand not only in the planarity of a tetracyclic aromatic system. This feature is crucial since it permits both intercalators to slide into the hydrophobic environment between two flanking base pairs and establish π−π interactions. Still, they also have large polarizabilities due to conjugated rings with different electron densities, which avoid charge accumulation and facilitate the intercalation process. Both molecules also have coordination sites for metal ions (phenol and pyridinic nitrogen) which help coordinate sodium or magnesium cations in the DNA neighborhood (partially balancing the negative electron densities of phosphate oxygens), thus forming a weak electrostatic interaction with the outer surface of DNA. Finally, the increase of the charge development due to coordination/protonation reduces the ligands' LUMO energies and facilitates π−π stacking.[11,12]

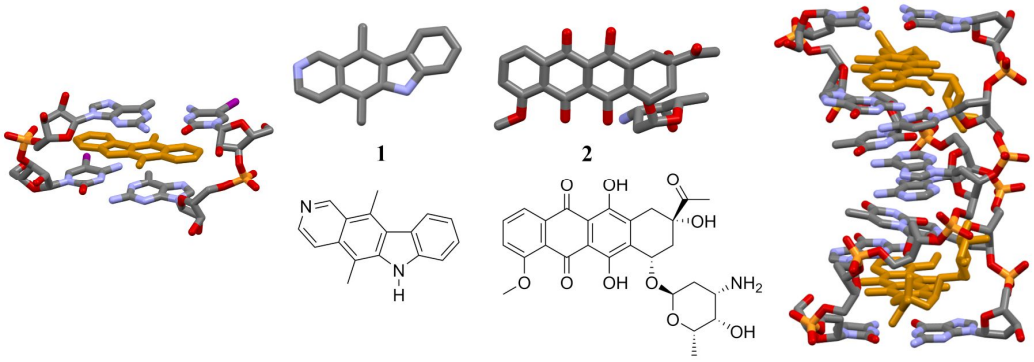


Figure 1. Ellipticine **1**, daunomycin **2**, and their intercalation adducts with nucleotides. Molecular representations in colored sticks were assembled directly from experimental XRD data acquired at references 13 and 14 for compounds **1**, **2**, and their complexes. For clarity, the atom color for intercalated ligands is dark yellow; otherwise, atoms follow CPK color assignments. Far left: Ellipticine-5-iodocytidylyl (3′-5′) guanosine complex.[13] Far right: Daunomycin-5'-d(CpGpTpApCpG)-3' complex.[14]

Ellipticine **1** and daunomycin **2** are only two illustrations of the "privileged scaffolds" based on heterocycles or quinones found in nature. Nevertheless, natural products eventually present us with examples of merged characteristics of both classes. Azanaphthoquinones (quinoline-5,8-dione, the blue fragments in Figure 2; isoquinoline-5,8-dione, the red fragments)[15,16] are present in several marine and terrestrial organisms, primarily in filamentous bacteria such as actinomycetes and streptomyces, but they were also found in sponges and bryozoans.[17-22]

Those azanaphthoquinones are usually highly cytotoxic, although some of them show good selectivity against specific organisms and are used as anticancer or antipathogenic drugs, many sharing both behaviors. Figure 2 shows some examples of these outstanding biological activities. Calothrixins A-B **3-4**, for example, are two of the most active antiplasmodial known substances,[17] and streptonigrin **5** is a currently used antibiotic.[18] Fumisoquin C **6**[19] and lavendamycin **7** are also potent antibiotics,[20] whilst mansouramycins A-D **8-11**[21] and caulibugulones A-D **12-15**[22] have high anticancer activities, although they also have low specificities to be used as a drug.

In this account, we will not address the usual syntheses of azanaphthoquinones, nor their respective precursors: alkoxy/amino/hydroxy quinolines or isoquinolines, since they are fully covered in the literature.[15-16,23-36] Instead, we will summarize the use and regiocontrol of azanaphthoquinone reactions to prepare a few selected examples of natural products of this family of highly active compounds and also

mention some representative instances of the formation of those heterocyclic nuclei containing substituents at positions 1 or 2, 3, 4, 6, and 7.

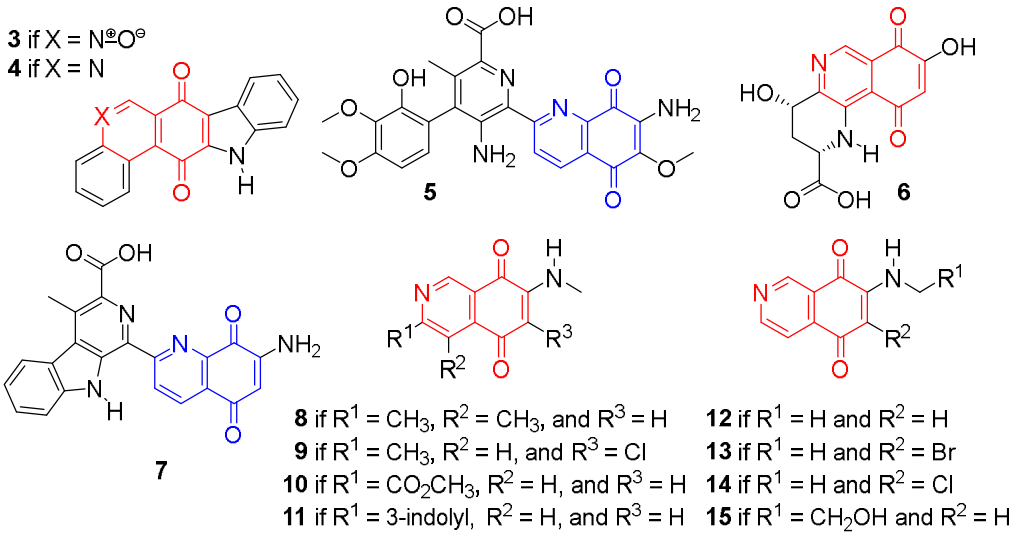


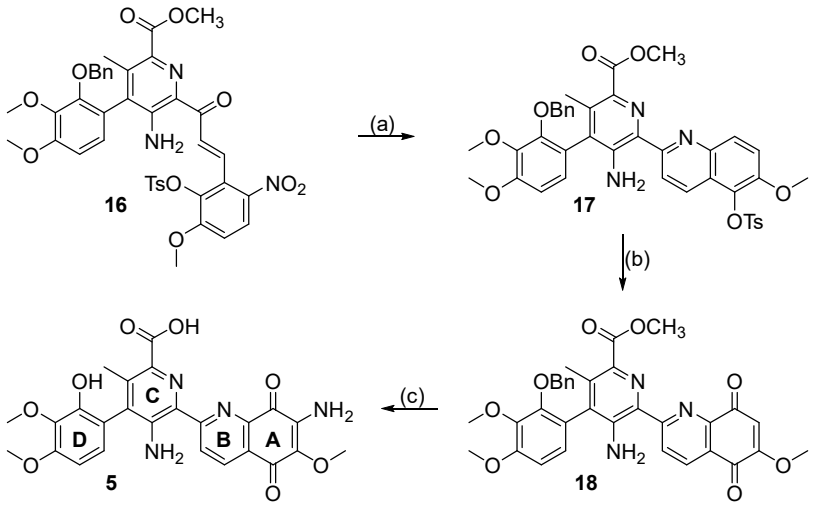
Figure 2. Selected alkaloids bearing quinoline-5,8-dione or isoquinoline-5,8-dione moieties with diverse biological activity: calothrixins A-B **3-4** (antiplasmodials),[17] streptonigrin **5** (antibiotic),[18] fumisoquin C **6** (antibiotic),[19] lavendamycin **7** (antibiotic),[20] mansouramycins A-D **8-11** (anticancers),[21] and caulibugulones A-D **12-15** (anticancers).[22]

2. Azanaphthoquinones bearing substituents at positions 1 or 2

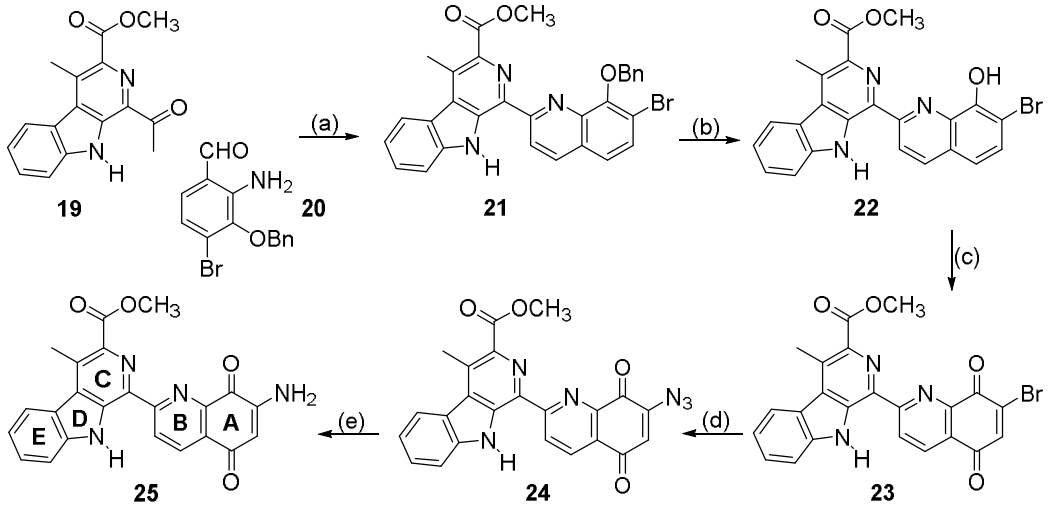
Typical examples of those patterns are streptonigrin **5** and lavendamycin **7** for the quinoline-5,8-dione ring (Schemes 1 and Figure 2); and renierol **26**, renierone **27**, and mimocin **28** for the isoquinoline-5,8-dione core (Scheme 3).

The construction of the streptonigrin **5** B ring and the amino group insertion at the correct position in ring A were the key steps of the Weinreb and coworkers' synthesis.[37,38] Reductive cyclization of **16** with sodium dithionite led to the tetracyclic compound **17** in 90% yield. Removing the sulfonate-protecting group of **17** with sodium methoxide, followed by its oxidation using Fremy's salt, yielded the quinone **18** in 90% (Scheme 1). Streptonigrin **5** was achieved through a sequence of iodination using iodine azine, iodine *ipso* displacement by sodium azide, and amine formation from the azide reduction using sodium dithionite (26% for the last three steps). The sequence strategy assures the correct regiochemistry since the electronic effect of the methoxy group at the A ring of compound **18** was exploited to control the proper positioning of the iodine at position 7 (not shown in Scheme 1). The direct oxidative amination of **18** could lead to the nucleophilic attack at the *ipso* and *cine* positions of the methoxy group.[39] Conversely, when azide anion is used as a nucleophile, only the *ipso* substitution is typically observed.[39]

The total synthesis of lavendamycin **7** B ring and the amino group insertion at the correct position in ring A by Boger and coworkers involved a similar approach, highlighting the problems concerning the regioselectivity of an oxidative amination in an azanaphthoquinone moiety (Scheme 2).[40] The Friedländer condensation of the methyl ketone **19** and amino benzaldehyde **20** furnished the quinoline **21** in 58%. The respective benzyl ether cleavage by hydrobromic acid to prepare the phenolic intermediate **22** and its subsequent oxidation using Fremy's salt provided the quinone **23** in 61% over two steps. Once again, the halogen *ipso* displacement by sodium azide forming compound **24** and its reduction using triphenylphosphine furnished lavendamycin methyl ester **25** in 42% for the last two steps. Using an azide as a nucleophile is critical to improving the *ipso* product over the *cine* substitution in a quantitative yield.[39] Boger also operated a similar strategy in their formal synthesis of streptonigrin **5**.[41]



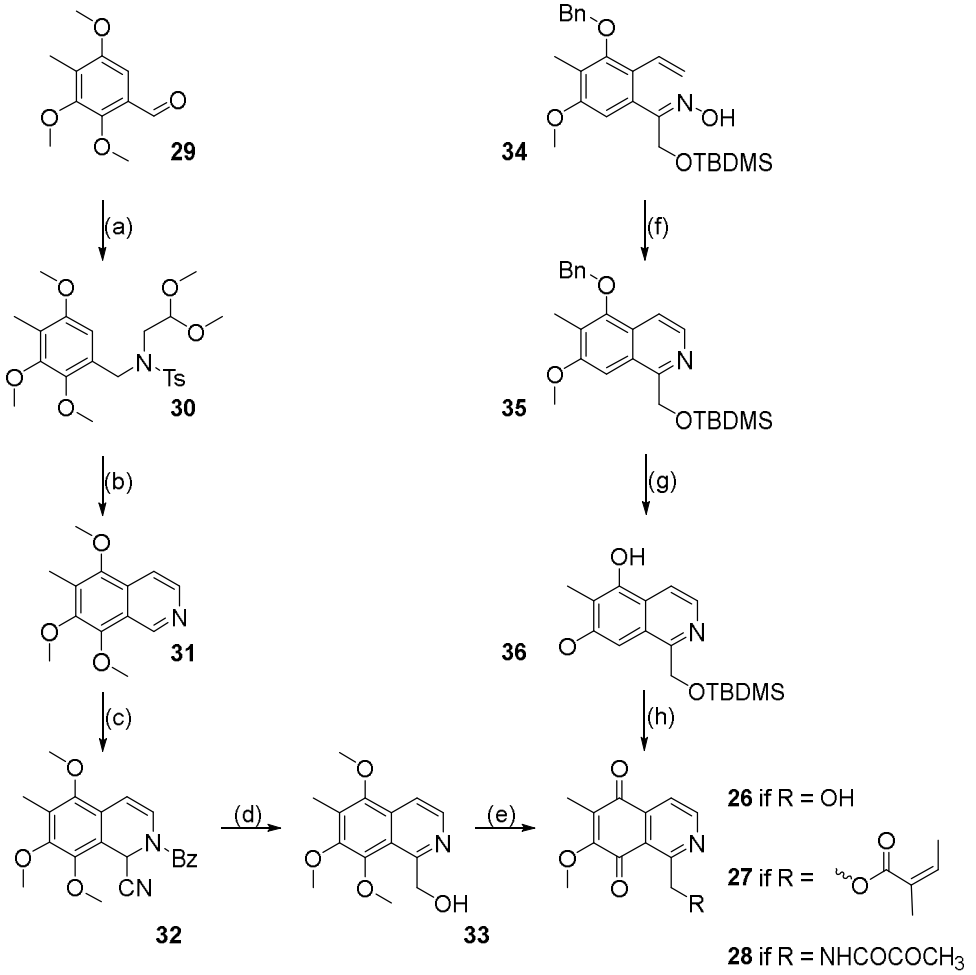
Scheme 1. Total synthesis of streptonigrin **5** by Weinreb's group: (a) $Na_2S_2O_4/CH_3OH/H_2O$, reflux, 2 h, 90%; (b) i) CH_3ONa/CH_3OH, 40 °C, 40 min, 90%; ii) $(KSO_3)_2NO/CH_3OH$, 10 min, 100%; (c) i) IN_3CH_3CN/CH_3OH, r.t., 3 h, 91%; ii) NaN_3/THF, r.t., 10 min, 58%; iii) $Na_2S_2O_4/CH_3OH/H_2O$, reflux, 5 h, 50%; iv) $K_2CO_3/CH_3OH/H_2O$, r.t., 45 h, 79%.[37,38]



Scheme 2. Total synthesis of lavendamycin methyl ester **25** by Boger's group: (a) Triton B/THF/CH_3OH, 25 °C, 18 h, 58%; (b) HBr/CH_2Cl_2, 0 °C, 20 min, 85%; (c) $(KSO_3)_2NO/CH_2Cl_2/H_2O$, NBu_4HSO_4, KH_2PO_4, 25 °C, 4.5 h, 72%; (d) NaN_3, THF, 25 °C, 21 h, 100%; (e) Ph_3P, CH_2Cl_2, 25 °C, 2 h, and then $AcOH/H_2O$, 25 °C, 3 h, 42%.[40]

Scheme 3 compares the total syntheses of renierol **26**, renierone **27**, and mimocin **28** by Kubo and Hibino groups.[42,43] Both strategies use late-stage oxidation of preformed polyfunctionalized aromatic rings.[42,43] Kubo's approach (Scheme 3 at left) used a modified Pomeranz-Fritsch isoquinoline synthesis (Jackson's modification *via* tosyl amides, in this case) **30**[44] to prepare isoquinoline **31** in five steps from aldehyde **29** in 80% global yield. The Reissert reaction of **31** furnished **32** in 73% yield, which delivered **33** in 40% upon treatment with *n*-butyllithium and formaldehyde. Oxidative demethylation of **33**, or its angelate ester, using

cerium(IV) nitrate furnished, respectively, renierol **26** and renierone **27** in a 1:2 mixture with the orthoquinone (66%).[42] Contrarily, Hibino's strategy used a 6π-azaelectrocyclization of azatrienes to build the isoquinoline moiety.[43] Heating of compound **34** in *o*-dichlorobenzene (180 °C) led to the isoquinoline **35** in 42%, which was debenzylated by catalytic hydrogenation producing the phenol **36** in 99% yield. The silyl group removal using TBAF, followed by the necessary functional group interconversion and oxidation with salcomine and molecular oxygen, gave renierol **26**, renierone **27**, and mimocin **28** in 20-95% yields.[43]

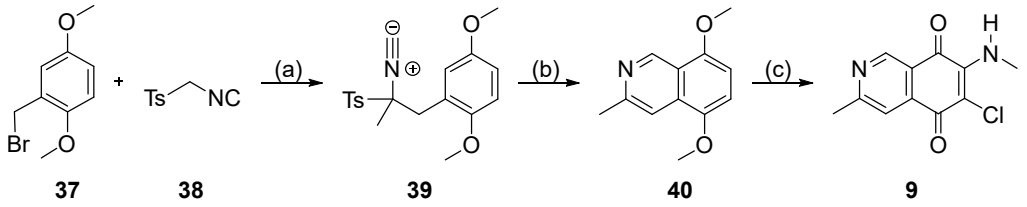


Scheme 3. Total syntheses of renierol **26**, renierone **27**, and mimocin **28** by Kubo and Hibino groups:[42,43] (a) $(CH_3O)_2CHCH_2NH_2$/ $NaBH_4$/THF, 0 °C, 18 h, and then $TsCl/H_2O$; (b) HCl/dioxane, reflux, 1 h, and then *t*-BuOK; 80% from **29**; (c) $KCN/BzCl/CH_2Cl_2$, 25 °C, 1 h, 72%; (d) *n*-BuLi/THF/CH_2O, -40 °C, 1 h, and then KOH/CH_3OH, reflux, 37%; (e) FGI, and then $CAN/H_2O/CH_3CN$, 5 °C, 15 m, up to 66%.[42] (f) *o*-Dichlorobenzene, 180 °C, 1 h, 42%; (g) H_2/Pd, 25 °C, 2 h, 42%.; (h) TBAF, then FGI, and then salcomine/O_2, up to 95%.[43]

3. Azanaphthoquinones bearing substituents at positions 3 or 4

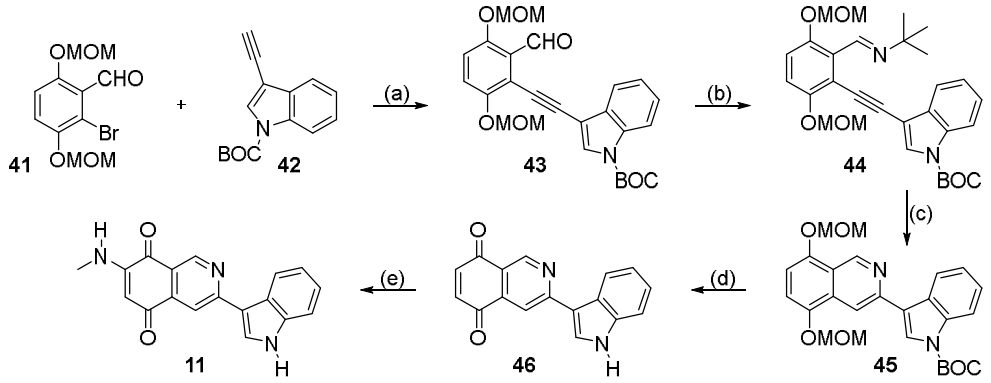
Mansouramycins A-D **8-11**[21] are representative examples of those patterns. Calothrixins A **3** and B **4**, although bearing an isoquinoline-5,8-dione moiety, are indolo[3,2-j]phenanthridine alkaloids,[17] but they will

be included here to compare and illustrate the reactivity pattern of the azanaphthoquinone framework. Vaquero's strategy to mansouramycin B (**9** at Scheme 4) used an heterocyclization of tosylmethyl isocyanide (**37**, TosMIC) derivatives to generate the isoquinoline nucleus.[45] The synthesis began with inserting the TosMIC group through an S_N2 reaction at the benzylic bromide **38** to form compound **39**. The acid-catalyzed heterocyclization of **39** using aluminum chloride (Scheme 4) furnished the isoquinoline **40** in 40% yield.[45] As with many other isoquinoline nucleus preparations, including the classical reactions such as Bischler-Napieralski,[46] Pictet-Spengler,[47] and Pomeranz-Fritsch,[48,49] the reaction efficiency depends on the correct substitution pattern of the aromatic ring to minimize steric hindrance and match the electronic requirements. In the case of the isocyanide heterocyclizations, when the methoxy groups were located at positions 3 and 4, the reaction yields varied from 67 to 88% with good regioselectivity and using trifluoroacetic acid. However, in the case of mansouramycin B (**9**), the methoxy groups were located at positions 2 and 5, so the reaction yield dropped to 40% requiring aluminum chloride as Lewis acid.[45] The oxidation of intermediate **40** used a strategy that simultaneously removed the methoxy groups by oxidation and inserting chlorine atoms at positions 6 and 7.[50] The amination of the dichlorinated intermediate furnished mansouramycin B **9** in 75% yield (23% overall yield).[45]



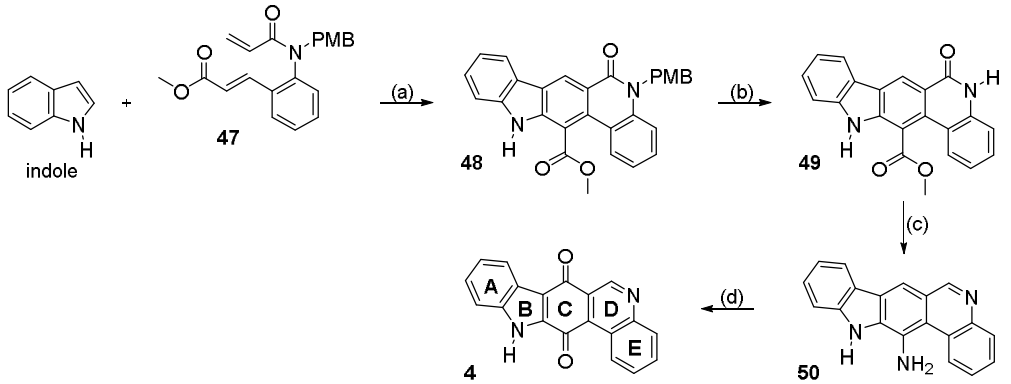
Scheme 4. Total synthesis of mansouramycin B **9** by Vaquero's group: (a) i) TBAI/CH_2Cl_2/H_2O/NaOH, r.t. ii) CH_3I, r.t., 75%; (b) CH_2Cl_2/$AlCl_3$, r.t., 40%; (c) i) TCCA/HCl/H_2O, r.t.;[50] ii) CH_3NH_2/EtOH, r.t., 75%.[45]

The Larock iminoannulation reaction is an efficient methodology to prepare isoquinolines functionalized at the third position (Scheme 5).[51,52] Nagarajan used this strategy to achieve the synthesis of mansouramycin D **11** (Scheme 5).[53] Starting from the aldehyde **41**, a Sonogashira cross-coupling with **42** permitted the preparation of the 2-alkynyl benzaldehyde **43** from which the imine **44** was prepared. The iminoannulation reaction was accomplished using copper(I) iodide in an 85% yield of **45**. Once again, the simultaneous removal of the hydroquinone diether and the *t*-butyl carbamate generated the respective hydroquinone, **46**, which was oxidated *in situ* to furnish the mansouramycin D **11** after the oxidative amination with methylamine (Scheme 5).[53]



Scheme 5. Total synthesis of mansouramycin D **11** by Nagarajan's group: (a) $PdCl_2$, PPh_3, CuI, 60 °C, 8 h, 92%.; (b) *t*-$BuNH_2$, r.t., 6 h, 75%; (c) CuI/DMF, 100 °C, 2 h, 85% from **43**; (d) i) THF/HCl/H_2O, 50 °C, 5 h; ii) O_2; (e) CH_3NH_2/EtOH/DME, 0 °C, 78% from **45**.[53]

Liu and coworkers presented a new approach to building the entire isoquinoline core in the total synthesis of calothrixin B **4**.[54] Their strategy uses a cross-coupling reaction catalyzed by palladium to construct the rings C and D of the respective indolo[3,2-j]phenanthridine alkaloid (Scheme 6).[54] This indole-to-carbazole strategy involves a tandem process containing a C3-alkenylation of indole with the acrylamide moiety of **47**.[55] This reaction triggered a cyclization cascade making the D ring, and then the C ring, in one early-stage, furnishing compound **48** in 80% yield.[54] Sequential reactions involved the *p*-methoxybenzyl cleavage of compound **48** to yield the derivative **49**, and its Curtius rearrangement to yield the amine **50**. Calothrixin B was obtained after the oxidation of the amine **50**, in 17% yield for the last four steps.[54] As mentioned above, although calothrixins A **3** and B **4** are indolo[3,2-j]phenanthridine alkaloids,[17] Liu used his strategy to achieve a very efficient synthesis of an isoquinoline-5,8-dione moiety substituted at positions 2, 3, 6, and 7 containing preformed C2 and C3 bonds from an aniline ring and newly formed bonds at positions C6 and C7 using tandem palladium-catalyzed indole C-H alkenylation/double olefin insertion.[54]



Scheme 6. Total synthesis of calothrixin B **4** by Liu's group: (a) $Pd(OAc)_2$/DMF:DMSO(9:1), O_2, 70°C, 24 h, 80%; (b) TFA/ dimethoxybenzene, 50 °C, 6 h, 74%; (c) i) Tf_2O/2-chloropyridine; ii) $Pd(OAc)_2$/TEA/HCO_2H/DPPF/DMF, 60 °C, 24 h, 60%; d) i) NaOH/dioxane, 100 °C; ii) DPPA/TEA/DMF, 80 °C, 58%; (e) NaOH/DMSO/O_2, 65%.[54]

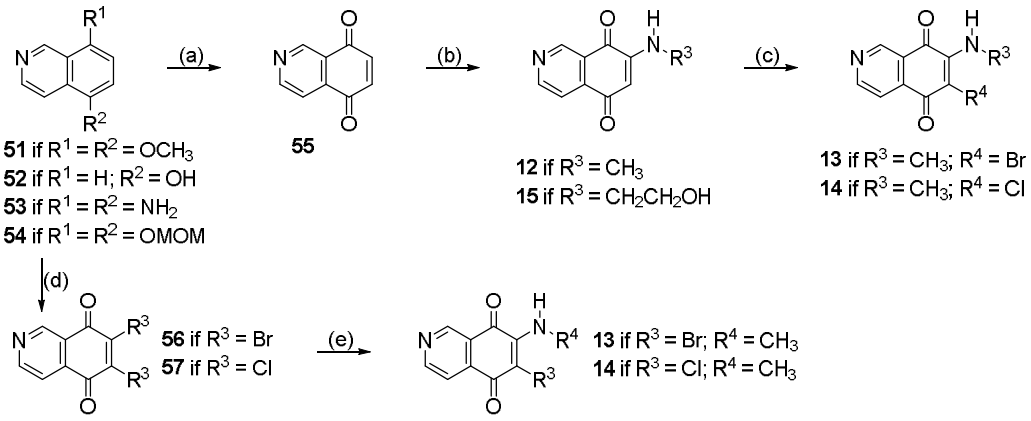
4. Azanaphthoquinones bearing substituents at positions 6 or 7

Late-stage modifications of positions 6 and 7 azanaphthoquinones are frequently used to amend complexity during the syntheses since this scaffold can be selectively prepared from mild oxidation of adequately substituted aromatics to the respective quinones (Scheme 7). This strategy was used in several alkaloid total syntheses employing diverse electron-rich-aromatic compounds.[37,38,40,41,45,50,53,56-59] Dialkylhydroquinone ethers such as **51** (Scheme 7) are more resilient to hydrolyses or oxidations and can be used in very early stages. However, they can be easily cleaved and oxidized using *N*-haloimides such as NBS, NIS, or TCCA.[50] Isoquinolines bearing hydroxy groups at positions 5 and 8 **52** or amino groups at the same positions **53** are promptly oxidized by common oxidants.[57,58] Compound **54**, for instance, can be deprotected by acid medium furnishing **52**, which are oxidized by atmospheric oxygen to yield the highly reactive quinone **55**.[59] Tunned oxidations at compound **51** can selectively furnish products with different oxidation levels. Although the use of NBS selectively gives compound **55**, the use of TBCA or TCCA also permits the oxidation of positions 6 and 7, to provide, respectively, compounds **56** or **57**.[45,50]

A usually observed drawback of such an approach is the limited regiochemical control of the reactions. Although quinoline- and isoquinoline-5,8-diones are structurally similar, they behave differently to a nucleophilic attack on the azanaphthoquinone moiety. Due to their electronic demand, the quinoline-5,8-diones show higher selectivity for the nucleophilic attack to position six and isoquinoline-5,8-dione to seven (Scheme 7).

Although a Lewis acid coordination to the quinoline-5,8-dione nucleus can switch the regiochemical outcome of the nucleophilic attack,[60-63] the same level of control in isoquinoline-5,8-diones is only

achievable with the use of an *N*-oxide derivative.[50,64-66] When the substrate has a significant preference for one specific regiochemistry, the results furnish good to excellent yields and selectivity, as in the case of quinolinequinones streptonigrin **5** (Scheme 1),[37,38,41] lavendamycin methyl ester **25** (Scheme 2),[40] as well in the isoquinolinequinones mansouramycins B **9** and D **11** (Schemes 4 and 5)[45,53,56] and caulibugulones A-D **12**-**15** (Scheme 7).[50,57-59]

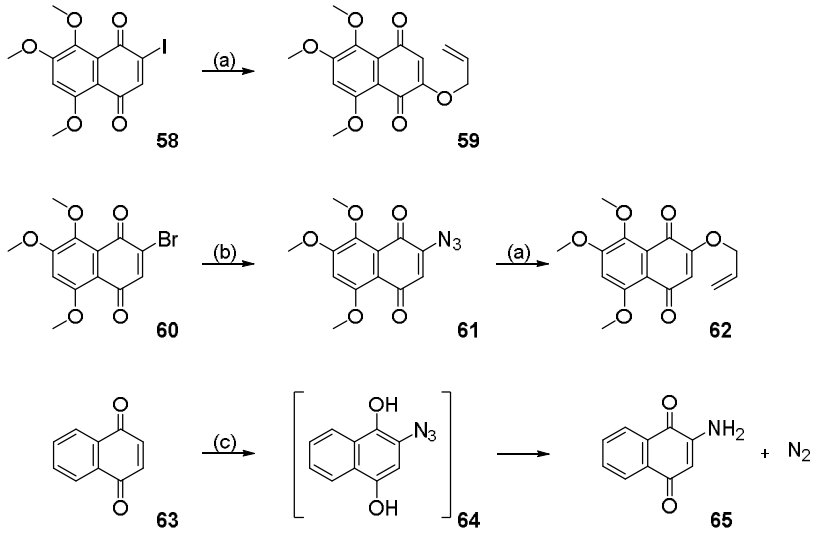


Scheme 7. Total synthesis of caulibugulones A **12**, B **13**, C **14**, and D **15**: (a) i) for **51** NBS/THF/H_2O/H_2SO_4, 25 °C, 48 h, 80%;[50] ii) for **52** PIFA/CH_3CN/H_2O/H_2SO_4, 25 °C, 2 h, 20%;[57] iii) for **53** $K_2Cr_2O_7$/H_2SO_4, 25 °C, 48 h, 67%;[58] iv) for **54** HCl/THF/H_2O, 50 °C, 1 h, 90%;[59] b) CH_3NH_2/EtOH/H_2O, CH_3NH_2/EtOH/DME/H_2O, CH_3NH_2/dioxane, or $HOCH_2CH_2NH_2$, dioxane, 25 °C, 1-24 h, 52-90%;[50,57-59] (c) i) for **13** NBS/dioxane, 25 °C, 4 h, 80-97%;[57,58] ii) for **14** NCS/CH_3OH, 25 °C, 4 h, 80-94%;[57,58] (d) i) for **56** TBCA/HBr/H_2O, 25 °C, 48 h, 60%;[50] ii) for **57** TCCA/HBr/H_2O, 25 °C, 4 h, 92%;[50] (e) CH_3NH_2/dioxane, 25 °C, 4 h, 60% for **13** and 90% for **14**.[50]

The Brimble strategy for *cine vs. ipso* nucleophilic substitution in naphthoquinones is an elegant way to control the regiochemistry of the Michael adduct (Scheme 8).[39] Typically, nucleophilic substitution proceeds with an *ipso* attack on the carbon bonded to the halogen (or a pseudo-halogen) with subsequent expulsion of the leaving group to give the expected derivate. Conversely, a similar nucleophilic attack on the adjacent carbon, the *cine* attack, gives an intermediate adduct, which after a dehydrohalogenation, affords the *cine* product. Although the leaving group has a high Mulliken electronegativity (F=10.4, Cl=8.3, N_3=7.7, Br=7.6, I=6.8 in eV),[67,68] which improves the ratio of the *ipso* attack, the reaction is also controlled by steric effects and large groups tend to direct towards to the *cine* attack (F=1.47, N_3=1.55, Cl=1.75, Br=1.83, I=1.92 in Å).[69,70] Consequently, the nature of the leaving group and the nucleophile dramatically affects the regiochemical outcome of the substitution. Compound **58** furnished a clean conversion to **59**, the *cine* substitution, as a single isomer. Oppositely, the bromoquinone **60** underwent nucleophilic substitution with low regioselectivity to beget a 3:2 ratio of isomers **59** and **62**. Interestingly, when sodium azide is used (a small and linear nucleophile), the *ipso* attack to produce **61** is observed alone.

Likewise, the nucleophilic replacement of the azide group by the allyl alcohol occurs with regiospecificity to the *ipso* position furnishing **62**. The observed regiocontrol can be attributed to a combination of steric and bond-dipole effects. Although all leaving groups have significant electronegativity and the increased C-X bond polarization facilitates the *ipso* attack, the increase of the steric hindrance at the C-X bond (N_3<Br<I) circumvents this limitation and favors the *cine* substitution.[39] Although the azide-mediated nucleophilic substitution in naphthoquinones **58** and **60** proceeds smoothly (Scheme 8), it has some applicability limitations in azanaphthoquinones. A known side reaction for such conversion is the Fieser-Hartwell redox degradation resulting in the corresponding azido hydronaphthoquinones **64** (Scheme 8) producing the corresponding aminonaphthoquinone **65** and nitrogen.[71-74] In naphthoquinones, this degradation occurs in higher temperatures or acidic media, commonly acetic acid. However, the redox

potential of the Michael adduct also plays an important role: quinones with lower redox potential also lean toward redox degradation. Azanaphthoquinones usually furnish redox degradation when reacting with inorganic azides.[72-74]



Scheme 8. First and second rows: *Cine vs. ipso* regioselection for nucleophilic substitution in naphthoquinones by Brimble's group.[39] Third row: Fieser-Hartwell redox degradation of 2-azido hydronaphthoquinones.[71] Conditions: (a) Cs_2CO_3, allyl alcohol (excess), toluene, 1h, 25 °C, then filtration; (b) NaN_3/CH_3CN, 72 h, 25 °C. Yields and regioselection: 86% for the *cine* regioisomer (first row) or 70% for the *ipso* regioisomer from compound **60** (second row).[39] In both cases, only a single regioisomer was observed; (c) $NaN_3/CH_3OH/HCl$, 15 h, 25 °C, 97%.[71-74]

5. Theoretical aspects for regioselectivity of the nucleophilic attack at azanaphthoquinones

The literature describes a slight preference for C-6 regioselectivity in nucleophilic additions at quinoline-5,8-diones, which can be significantly improved using Lewis acid catalysis.[61-63,75] Depending on the nucleophile, the regioselectivity ratio (r.r.) ranges from 1:2 up to 4:1, favoring the C6 regioisomer.[61,62] However, depending on the catalyst, the r.r. achieves values greater than 10:1 for several nucleophiles, and the yield is also improved. Cerium(III) chloride is the catalyst most commonly used in this reaction, but nickel(II), scandium(III), and zinc(II) salts are also frequently utilized.[60-63] Mancini and coworkers performed ZINDO calculations and pointed out that the r.r. increasing correlates well with the calculated charges at positions C-6 and C-7 (Δq) of the chelate **66**.[60] These results support the empirical rationale used in the literature (Figure 3). On the other hand, the direct methodology for a high-regioselective synthesis of 7-substituted quinoline-5,8-diones has seldom been mentioned.[63]

Interestingly, the same level of regiocontrol for the nucleophilic addition to isoquinoline-5,8-dione had not been reported until the work of Miranda and coworkers.[65,66] In these studies, single-point electronic energies were obtained at B3LYP-GD3(BJ)/6-311++G(3df,2p)/SMD (1,4-dioxane)) level of theory using thermal corrections to Gibbs free energies obtained at B3LYP-GD3(BJ)/6-311++G(2d,p) level, and considering the solvent effect using SMD (1,4-dioxane). All molecular geometries (minima and transition states-TS) were obtained at this last level of theory. Although the C7 selectivity is easily accomplished, even without catalysts, the switch in the regiocontrol for the attach at the C2 position is only achievable using an *N*-oxide derivative, drastically changing the reaction mechanism (Figure 4 and Scheme 9). Some suggestive results emerge from this study: (i) The electrophilicity index (ω)[76] of compounds **55** and **67** suggests that isoquinoline-5,8-dione *N*-oxide **67** is a better electrophile than **55** (ω=4.6181 eV *vs*. 4.1401 eV); (ii) there is a significant effect of a second methylamine molecule in the reaction as the plot at Figure 4 shows;[77,78] and

(iii) such effect is involved in a hydrogen transfer process and change the rate-determining step from TS3 to TS2 (Figure 4).

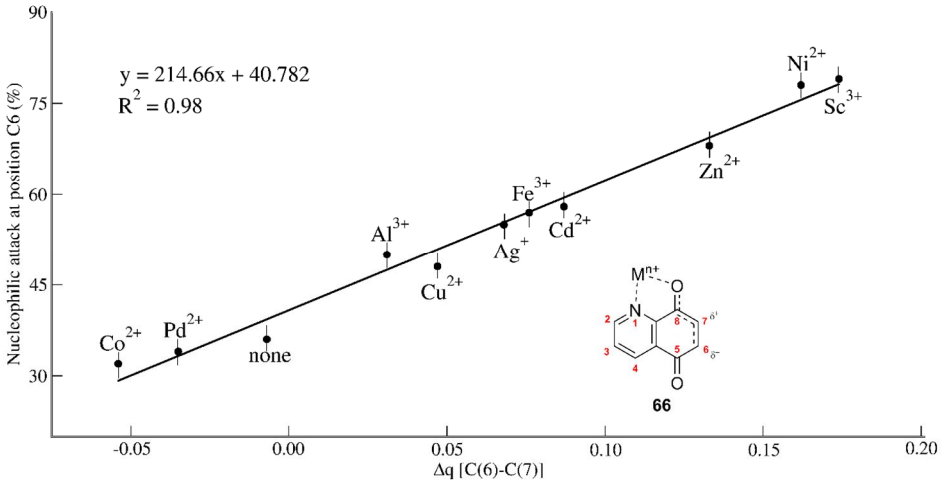


Figure 3. Linear correlation of the charge differences between positions C6 and C7 (Δq) and observed yields for the C6 regioisomer. This graphic was plotted using theoretical and experimental data from Mancini and coworkers` studies.[60]

Figure 4 shows the Gibbs free energy profiles for the nucleophilic attack of methylamine at isoquinoline-5,8-dione **55** and its *N*-oxide **67** at positions C6 and C7. Red and green lines describe the attack at position C6 in compounds **67** and **55**, respectively. Conversely, blue and yellow lines represent the attack at position C7 in compounds **67** and **55**, respectively. In both cases, a slight excess of nucleophiles considerably accelerates the reactions. This inference was observed experimentally, resulting in approximately four times higher kinetics. Also, as suggested by Figure 4, a depletion of the r.r. was noticed with large excesses of the nucleophile or a polar protic solvent. The critical issue is the assistance of the *N*-oxide moiety during the proton transfer from the ammonium group to the carbonyl at position C5 in Int 2 (Figure 4) in the rate-determining step of the reaction (TS2). The augmented basicity of the carbonyl oxygen at position C5, promoted by the extended resonance with the *N*-oxide moiety, facilitates this tautomerization.

Additionally, the acidity of the hydrogen at position C6 was also enhanced due to the vinylogous effect of the oxoammonium group at the Int3 intermediate (Scheme 9). Both phenomena stood responsible for the observed reactivity and selectivity and were used in the total syntheses of ellipticine and isocaulibugulones A-D (Scheme 10).[65,66]

5. Conclusion

Quinoline-5,8-dione and isoquinoline-5,8-dione alkaloids are usually highly cytotoxic and are found in several marine and terrestrial organisms. Despite the simplicity of their structures, some of them show good selectivity against specific metabolic pathways and are used as anticancer or antipathogenic drugs. Novel reactions to prepare advanced intermediates with controlled substitution in all positions of the azanaphthalene-5,8-dione scaffold have been developed to achieve those frameworks with a diverse substitution pattern. Frequently, azanaphthoquinones are not necessarily the target products but valuable intermediates for synthesizing other alkaloids with more fused rings. Concerning this subject, the oxidative amination at a quinone scaffold is a recursive reaction sequence thoroughly used in the total syntheses of azanaphthoquinone alkaloids, and the complete control of the regioselection outcome of this reaction is an essential tool in the alkaloid synthesis. Due to their electronic demand, the quinoline-5,8-diones show higher

selectivity for the nucleophilic attack to position six and isoquinoline-5,8-dione to seven. Although a Lewis acid coordination to the quinoline-5,8-dione nucleus can switch the regiochemical outcome of the nucleophilic attack, the same level of control in isoquinoline-5,8-diones is only achievable with the use of an *N*-oxide derivative, which changes the reaction mechanism drastically.

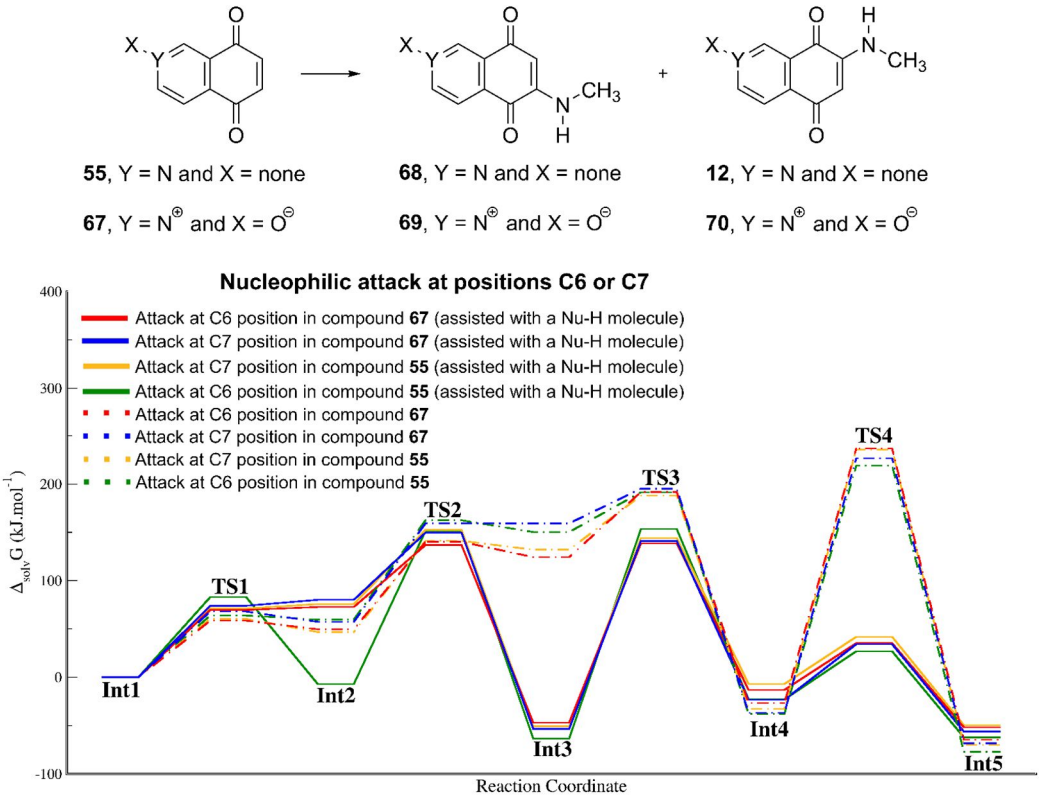


Figure 4. Gibbs free energy profiles for the nucleophilic attack of methylamine at isoquinoline-5,8-dione **55** and its *N*-oxide **67**. Dotted lines show the reaction coordinate for the non-assisted process, and solid lines show the reaction assisted by a second methylamine molecule. Regioselection: (a) green lines are related to the position 6 attack at compound **55**, and (b) yellow lines are related to the position 7 attack at compound **55**, (c) red lines are related to the position 6 attack at compound **67**, and (d) blue lines are related to the position 7 attack at compound **67**.[65,66]

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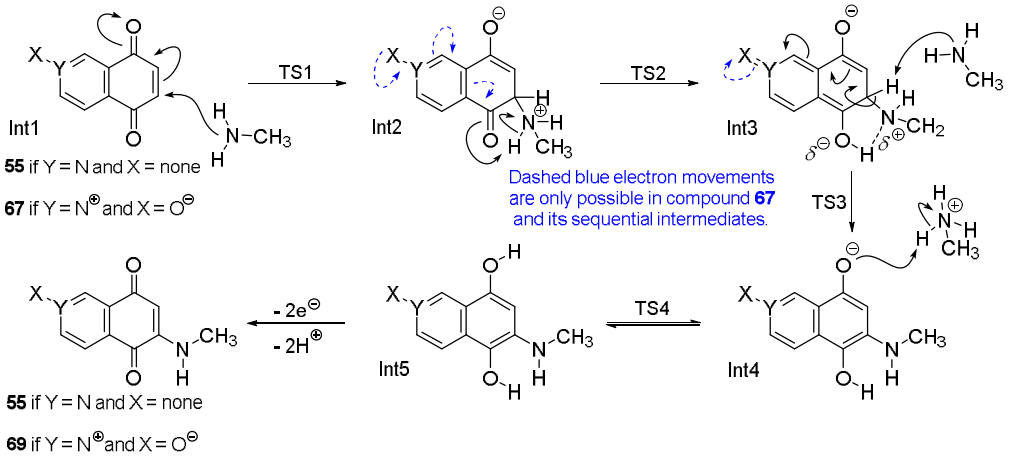
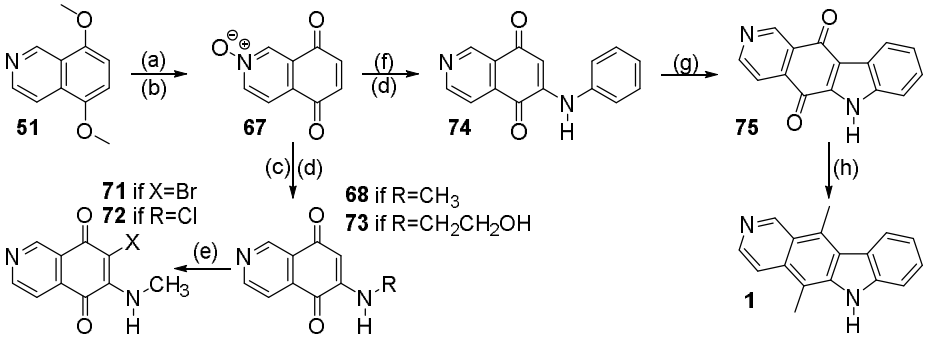


Scheme 9. Mechanism representation of the nucleophilic attack of methylamine at position 6 of isoquinoline-5,8-dione **55** and its respective *N*-oxide **67** based on the solvation Gibbs free energy profiles. Electronic energies were calculated at B3LYP-GD3(BJ)/6-311++G(3df,2p)/SMD (1,4-dioxane)) level of theory. Thermal corrections to Gibbs free energies were obtained at B3LYP-GD3(BJ)/6-311++G(2d,p)/SMD (1,4-dioxane) level. Blue dashed electron movements are possible only in compound **67** and its sequential intermediates. In both cases, TS2 is the rate-determining step (Figure 4).[65,66]



Scheme 10. Total synthesis of isocaulibugulones A **68**, B **71**, C **72**, D **73** and ellipticine **1**:[65,66] (a) *m*-CPBA/$CHCl_3$, 25 °C, 12 h, 90%; (b) NIS/CH_3CN/H_2O/H_2SO_4, 25 °C, 5 h, 85%; (c) i) for **68** CH_3NH_2/dioxane, 15 °C, 3 h, 55%; ii) for **73** $HOCH_2CH_2NH_2$/acetone, 5 °C, 3 h, 35%; (d) HCO_2H/Zn(0), 25 °C, 12 h, 43-85%; (e) for **71** HBr/DMSO, 25 °C, 3 h, 94%; ii) for **72** NCS/DMSO/$CHCl_3$, 25 °C, 12 h, 83%; (f) Aniline/dioxane, 15 °C, 5 h, 75%; (g) $Pd(OPiv)_2$, PivOH, Cs_2CO_3, $Cu(OPiv)_2$, DMA, 130 °C, 24 h, 73%; (h) MeLi, TMEDA, THF, -40 to 100 °C, 24 h; and then $NaBH_4$, EtOH, reflux, 24 h, 69%.

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