DIELS-ALDER REACTIONS OF BENZO[*b*]FURAN-4,5-DIONES AND BENZO[*b*]FURAN-4,7-DIONES

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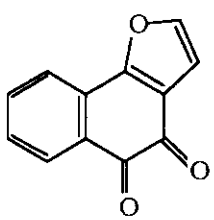
Abstract- The synthetic potentiality of benzofurandiones in Diels-Alder reactions is reported. Factors influencing the regiochemistry are discussed.

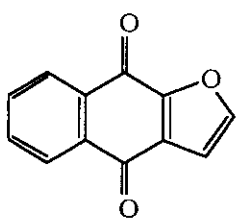
CONTENTS

I. INTRODUCTION

Hetero polycyclic quinonoid derivatives represent a very large class of naturally occurring compounds of important biological interest. Among these, some products possess a naphtho[1,2-*b*]furan-4,5-dione[1] (**I**) or a naphtho[2,3-*b*]furan-4,9-dione[2] (**II**) skeleton (Scheme 1).



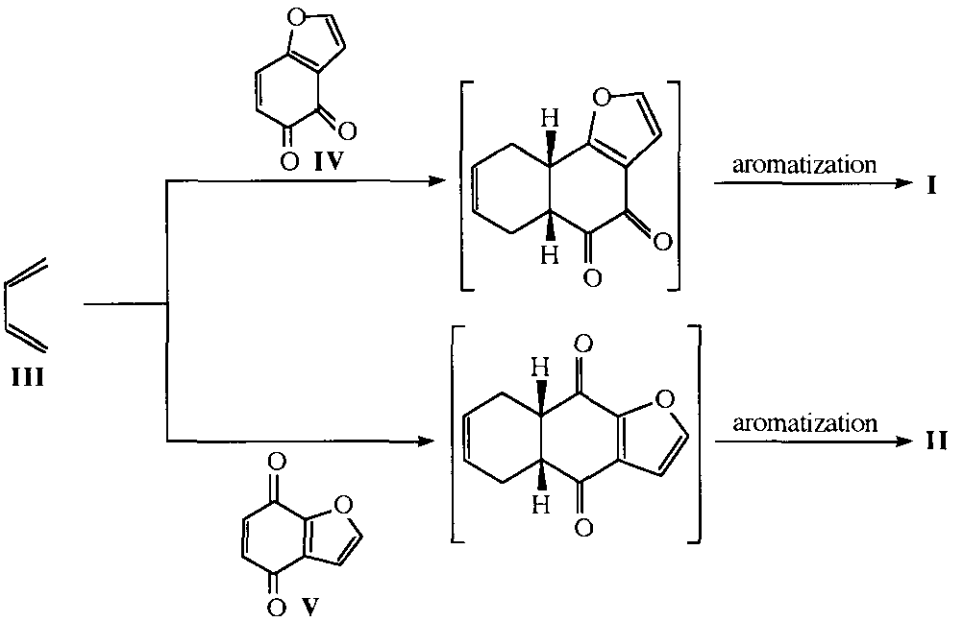
I



II

Scheme 1

The diversity of their natural origins and biological activities have both motivated considerable efforts towards their syntheses or to find pathways to structural analogues. In this idea, one of the most convenient approach was evidenced as the construction of the basic skeleton through a Diels-Alder reaction between appropriated dienes (**III**) and benzo[*b*]furan-4,5-diones (**IV**) or benzo[*b*]furan-4,7-diones (**V**) (Scheme 2).



Scheme 2

In our knowledge, none review was devoted, until now, to this research field. We wish to fill this gap by presenting the following up today report.

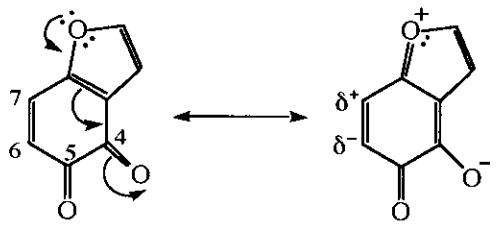
II. REGIOCHEMISTRY

Of course, according to Scheme 2, if diene (**III**) is unsymmetrically substituted, a problem of *regiochemistry* appears and mixture of regioisomers could be formed. In order to understand the regioselectivities observed, calculations of HOMO and LUMO orbital coefficients were performed but, only in few cases.

Fortunately, an easy generalized theory was proposed by Thomson *et al.*[3] It is based on the electronic resonance and further employed to explain the regiochemistry of many Diels-Alder reactions involving unsymmetrical quinones. Indeed, application of this theory allows to define electronic rich and poor sites on

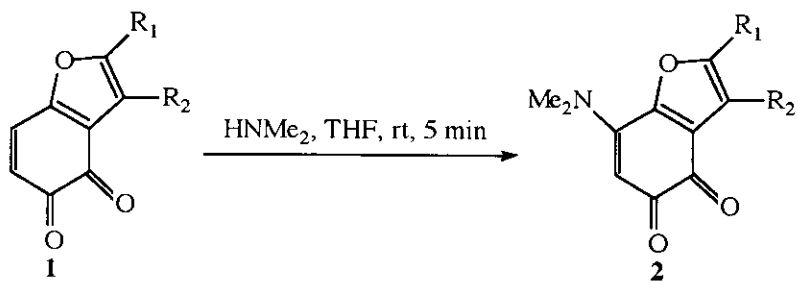
the reactive double bond of the dienophile. Afterwards, it is considered that the nucleophilic end of dienes would add preferentially to the poorer electronic site.

As an exemple, the following reasoning can be applied to benzo[*b*]furan-4,5-dione: furan oxygen, by a conjugaison phenomenon, enhances the C-4 electron density (Scheme 3).



Scheme 3

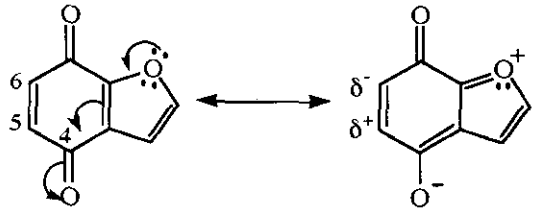
As a consequence, C-5 appears as an electrophilic site and the double bond between C-6 and C-7 is polarized as described in Scheme 3. Thus, the nucleophilic end of a diene would attack preferentially at the C-7 of that quinone. We validated besides this conclusion, with the nucleophilic addition of dimethylamine on various benzo[*b*]furan-4,5-diones (**1**) (Scheme 4).[4] Thus, the *N*,*N*-dimethylamino derivatives (**2**) were obtained as a single regioisomer. Assignement of the regiochemistry of **2** was established from their corresponding ^{1}H-NMR spectral data.



	Yield %
1a, **2a**: R_1=H, R_2=Me	80
1b, **2b**: R_1=H, R_2=Et	50
1c, **2c**: R_1, R_2=-$(CH_2)_4$-	83

Scheme 4

If we now examine the case of benzo[*b*]furan-4,7-diones, we can consider that the donor effect of the oxygen atom of furan enhances the electron density of the carbonyl at C-4 (Scheme 5).



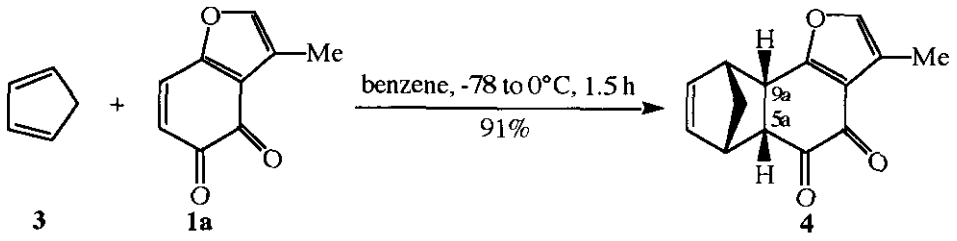
Scheme 5

In consequence, the double bond between C-5 and C-6 is polarized. Thus, the most nucleophilic end of a diene would preferentially add to C-5.

III. DIELS-ALDER REACTIONS WITH BENZO[*b*]FURAN-4,5-DIONES:

III.1. Cycloaddition of cyclopentadiene:

In view to afford naturally occurring tanshinones, Snyder *et al.* were the first whom developed a [4+2] cycloaddition strategy using a benzo[*b*]furan-4,5-dione. Their starting efforts[5] were oriented to the synthesis of quinone (**1a**), which was then submitted to react with easily available dienes. Among these, cyclopentadiene led to the isolable primary cycloadduct (**4**) in a good yield (Scheme 6).



3 **1a** **4**

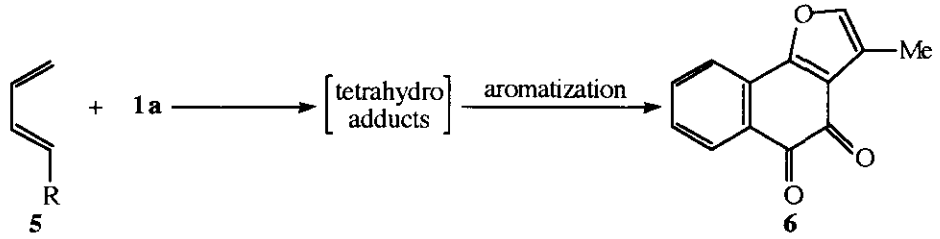
Scheme 6

The observed endo selectivity was unambigously established from ^{1}H-NMR NOE experiments. Thus, an irradiation of the bridging methylene hydrogen (*syn* to the dione ring) gave a response at H-5a and H-9a (exo protons).[1b]

III.2. Cycloadditions of buta-1,3-diene and derivatives[5]

The Diels-Alder reactions of quinone (**1a**) with the poor reactive buta-1,3-diene (**5a**) gave low yield of naphtho[1,2-*b*]furan-4,5-dione (**6**), while the use of activated dienes (**5b**) or (**5c**) afforded **6** in better

results (Scheme 7). In these examples, the primary tetrahydro adducts were only detected by ^{1}H-NMR spectroscopy, the aromatization process occurring under ambient conditions or upon silica gel.



5 **6**

	Cycloaddition conditions	Yield %
5a: R=H	neat, -78°C to rt	<10
5b: R=OTMS	benzene, reflux, 16 h	60
5c: R= OAc	benzene, reflux, 16 h	62

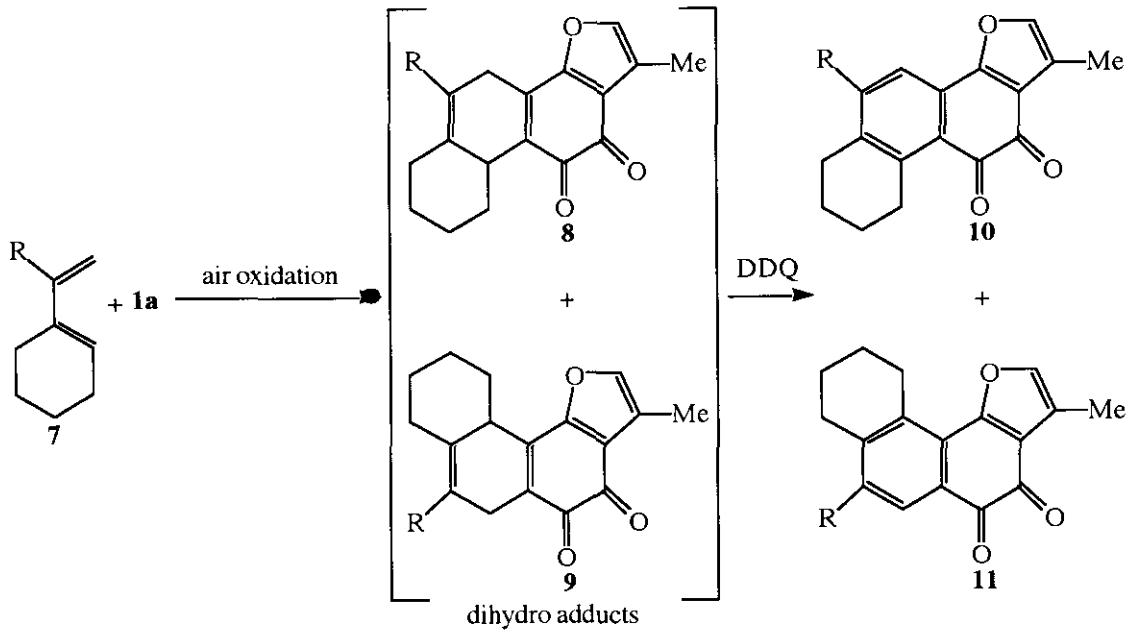
Scheme 7

Due to the directly obtained fully aromatized cycloadducts, no details were reported concerning the regiochemistry of the cycloadditions between **1a** and **5b** or **5c**.

III.3. Cycloadditions of 1-vinylcyclohexene derivatives

The above cycloadditions with simple models performed, Snyder *et al.* worked next towards the total synthesis of tanshinones. In this aim, they performed the cycloaddition reactions between quinone (**1a**) and two monosubstituted 1-vinylcyclohexenes (**7**), using different experimental conditions.[1b,5,6] The best yields were obtained under high pressure or ultrasonic irradiation (Scheme 8). In all experiments, air oxidation of the primary adducts gave the dihydro derivatives (**8**) and (**9**), which were directly aromatized to **10** and **11** with DDQ. The instability of **1a** certainly explains the poor yields observed under thermal conditions. For the same reason, the reaction carried out in the presence of the Lewis acid led to the worse result. In contrast, the use of high pressure increased strongly the yields and slightly the regiochemistry. Comparable effects were found under ultrasonic activation, in the absence of solvent. In the domain of sonochemistry, this work has besides constituted the first successfull example of sonochemical Diels-Alder reactions.[7]

In all cases, the cycloadditions were regioselective (the regioisomeric ratio were measured from ^{1}H-NMR spectra). The cycloadditions of **1a** with diene (**7a**) gave the expected regioisomer as the major product, while an inverse regiochemistry was observed with **7b**. In the latter case, the authors explained this inversion by steric factors in the endo transition state.

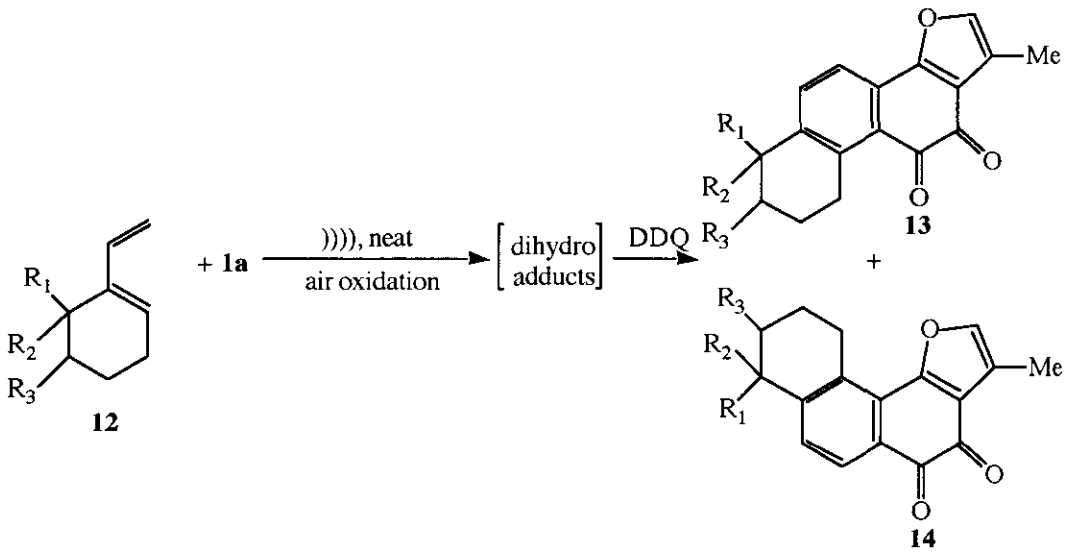


	Cycloaddition conditions	Yield %	Ratio **10/11**
7a, 8a, 9a, 10a, 11a: R=H	MeOH, reflux, 16 h	40	71/29
	11 kBar, MeOH, rt, 2 h	67	86/14
	))))), neat, 45°C, 2 h	65	78/22
	$Eu(fod)_3$ (0.08 eq.), MeOH	20	92/8
7b, 8b, 9b, 10b, 11b: R=TMS	MeOH, reflux, 4 h	28	29/71
	11 kBar, MeOH, rt, 2 h	62	22/78
	))))), neat, 45°C, 2 h	57	17/83

Scheme 8

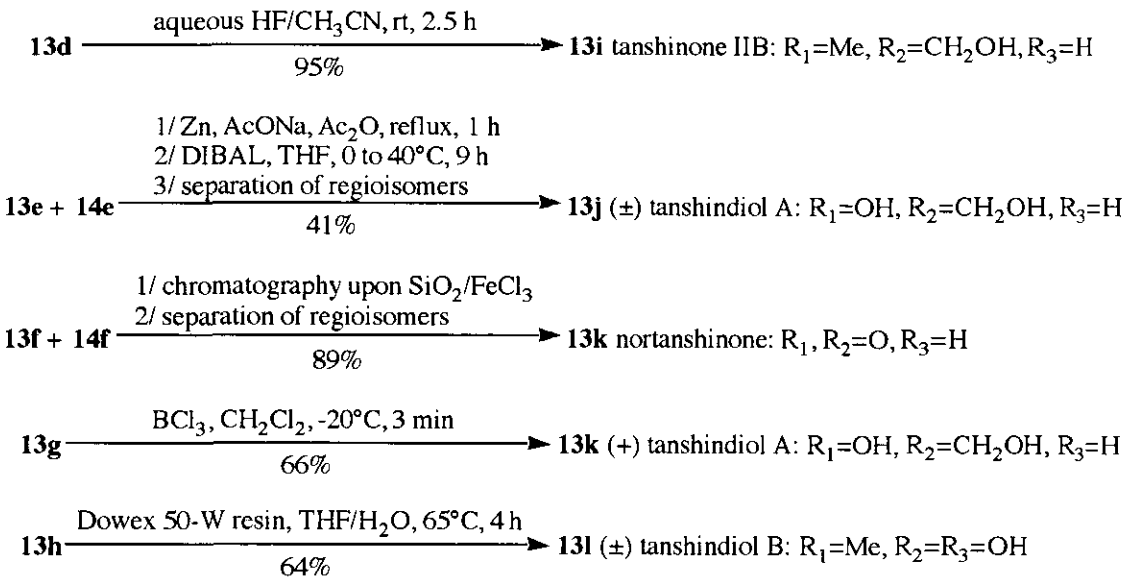
In the presence of dienes such as **12**, a similar ultrasonic activating effect was evidenced (Scheme 9).[1b,8,9] In comparison, using diene (**12a**), the thermal Diels-Alder reaction (benzene, reflux, 6 h) gave 11% of the mixture of **13a** and **14a**. On the other hand, starting with dienes (**12e**) or (**12f**), cycloadditions carried out under high pressure led to similar results comparatively with thoses obtained under ultrasonic irradiation. The regioselectivities obtained agree with the predictions of the electronic resonance theory. Indeed, it was assumed that the nucleophilic end of the dienes attacks C-7 of **1a**.

The pure naturally occurring methyl tanshinonate (**13c**) was obtained after recrystallization. The synthesis of others tanshinones was also achieved, from the aromatized cycloadducts, according to Scheme 10. Separation of the different pairs of regioisomers was performed either from the starting mixtures (**13d**, **13g** and **13h**) or in the final step of the synthesis.



	Sonochemical conditions	Yield %	Ratio **13/14**
12a, **13a**, **14a**: R_1=H, R_2=Me, R_3=H	45°C, 2 h	56	95/5
12b, **13b** (tanshinone IIA), **14b**: R_1=R_2=Me, R_3=H	45°C, 2 h	76	77/33
12c, **13c**, **14c**: R_1=Me, R_2=CO_2Me, R_3=H	45°C, 2 h	66	89/11
12d, **13d**, **14d**: R_1=Me, R_2=$CH_2OTBDMS$, R_3=H	45°C, 1.5 h	71	92/18
12e, **13e**, **14e**: R_1=CO_2Me, R_2=OBz, R_3=H	8°C, 6.5 h	76	71/29
12f, **13f**, **14f**: R_1, R_2=-$O(CH_2)_2O$-, R_3=H	45°C, 1 h	65	89/11
12g, **13g**, **14g**: R_1, R_2=-CH_2OCMe_2O-, R_3=H	rt, 2.5 h	72	80/20
12h, **13h**, **14h**: R_1=Me, R_2, R_3=-$OCMe_2O$-	45°C, 1 h	66	83/17

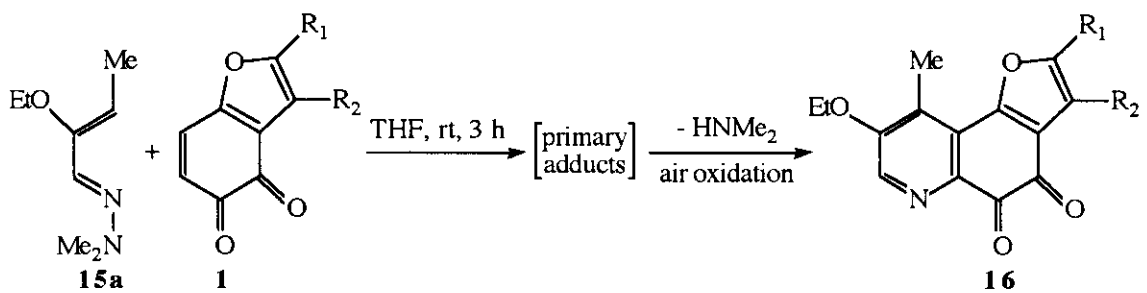
Scheme 9



Scheme 10

III.4. Cycloadditions of 2-ethoxybut-2-enal N,N-dimethylhydrazone

The ability of α,β-unsaturated *N,N*-dimethylhydrazones to undergo cycloadditions with quinones is now well established.[10] In this domain, the first examples using benzo[*b*]furan-4,5-diones (**1**) were performed in our laboratory (Scheme 11).[4]



	Yield %
1a, **16a**: R_1=H, R_2=Me	62
1b, **16b**: R_1=H, R_2=Et	40
1c, **16c**: R_1, R_2=-$(CH_2)_4$-	54

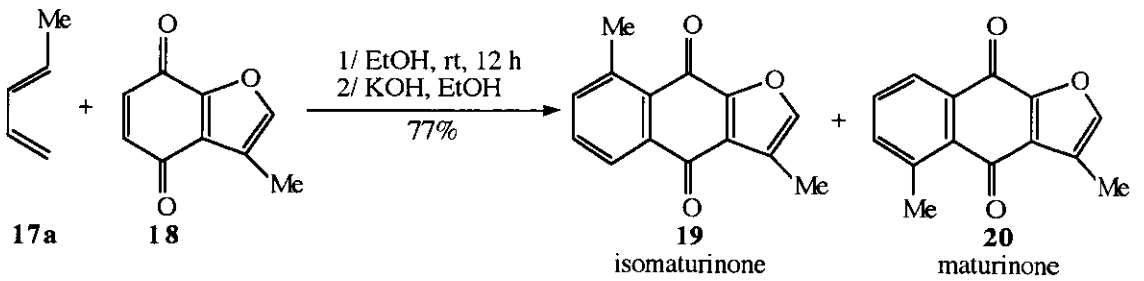
Scheme 11

Even the reaction kinetic was fast, the reaction mixture was stirred for 3 h at air atmosphere in order to achieve oxidation of the primary adducts. These cycloadditions were found to be totally regioselective, the C-4 nucleophilic end of azadiene (**15a**) adding exclusively at C-7 of quinones (**1**). Structural assignment of the furoquinolinediones (**16**) was made by ^{1}H and ^{13}C-NMR experiments. If the yields were moderate (due to the slow degradation of the starting quinones and to the nucleophilic addition of the liberated dimethylamine on these ones) they were compensated by the direct access to the fully aromatized derivatives (**16**).

IV. DIELS-ALDER REACTIONS WITH BENZO[*b*]FURAN-4,7-DIONES

IV.1. Cycloadditions of buta-1,3-diene derivatives

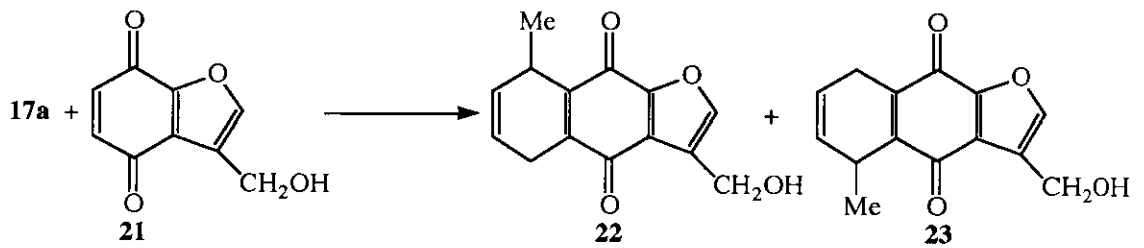
In 1969 the synthesis of maturinone, a naturally occurring naphtho[2,3-*b*]furan-4,9-dione,[11] was first envisaged through a simple cycloaddition process between penta-1,3-diene (**17a**) and *para*-quinone (**18**) (Scheme 12).[12]



Scheme 12

The initial adducts, without purification, were air-oxidized in an alkaline ethanol solution. The cycloaddition was found regioselective (87/13) but, in the favour of the undesired isomaturinone (**19**), the regiochemistry of this cycloaddition being controlled by electronic factors.

A similar cycloaddition strategy, using the same diene, was also developed in view to access to a parent compound: maturone.[13] Different experimental conditions were tried in order to increase the regioselectivity of the Diels-Alder step. Significant results of this work are given in Scheme 13.

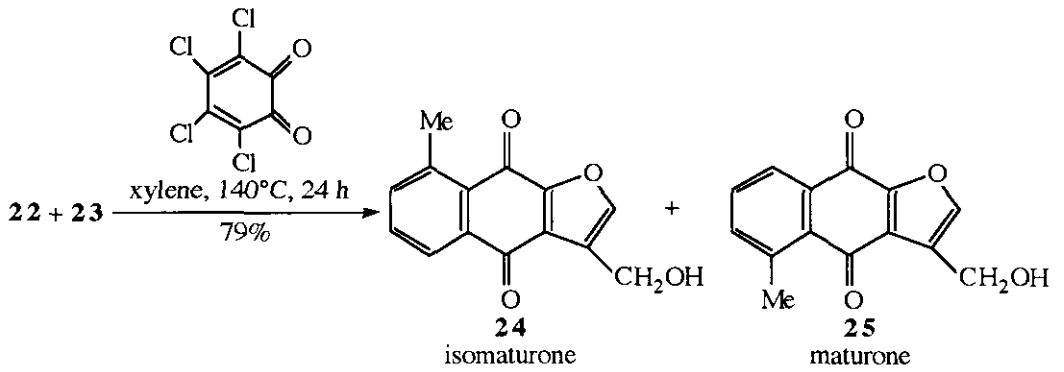


Cycloaddition conditions	Yield %	Ratio **22/23**
CH_2Cl_2, rt, 96 h	96	45/55
$BF_3.Et_2O$ (0.5 eq.), -40°C, 6 h	61	24/76
$TiCl_2(O\text{-}i\text{-}Pr)_2$ (0.5 eq.), -50°C, 17 h	66	5/95

Scheme 13

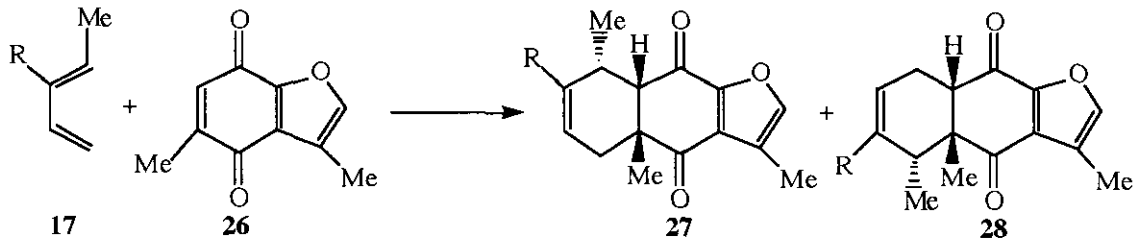
A high yield was obtained under neutral conditions, but concomitant with a very poor regioselectivity which could be attributed to the presence of the hydroxymethyl group at C-3 of the quinone. The use of Lewis acids, such as trifluoroborane or dichlorodiisopropoxytitane, resulted in an increase of the regioselectivity in favor of the maturone precursor (**23**). Such improvement of the regioselectivity was not completely explained by molecular orbital semiempirical calculation methods.[13]

Then, the mixture of regioisomers (**22**) and (**23**) was aromatized, at high temperature in the presence of chloranil (Scheme 14).



Scheme 14

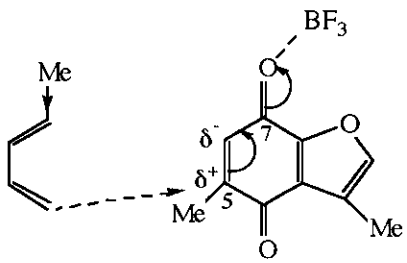
In the scope of studies devoted to the synthesis of terpenoids and related compounds, quinone (**26**) was used in Diels-Alder reactions towards penta-1,3-diene[14] (**17a**) and its 3-acetoxy[14] (**17b**) or 3-ethoxy[15] (**17c**) derivative (Scheme 15).



	Cycloaddition conditions	Yield %	Ratio **27/28**
17a, 27a, 28a: R=H	sealed tube, EtOH, 105°C, 3 h	70	0/100
	$BF_3.Et_2O$ (16 eq.), benzene, rt, 15 min	70	100/0
17b, 27b, 28b: R=OAc	sealed tube, EtOH, 105°C, 8 h	83	14/86
17c, 27c, 28c: R=OEt	benzene, reflux, 48 h	70	0/100

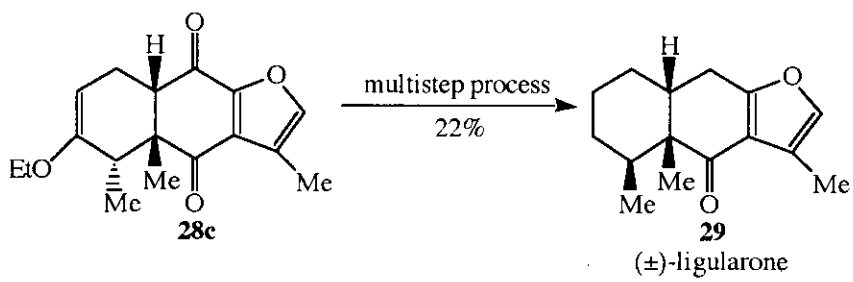
Scheme 15

The total or high regioselectivities observed under thermal conditions is in contradiction with the orientation predicted by the electronic resonance theory. These results were explained by the predominance of steric and blocking effects of the 5-methyl substituent on the electronic factors. In consequence, the nucleophilic end of the diene predominantly added at the nonsubstituted carbon (C-6) of the reactive double bond of the quinone. On the other hand, the complete inversion of the regioselectivity, in the presence of Lewis acid, was attributed to a complexation of the carbonyl at C-7 favoring the nucleophilic attack at C-5 (Scheme 16).



Scheme 16

The cycloadduct (**28c**) was used as a starting material in the total synthesis of (±)-ligularone (**29**) (Scheme 17).[15]

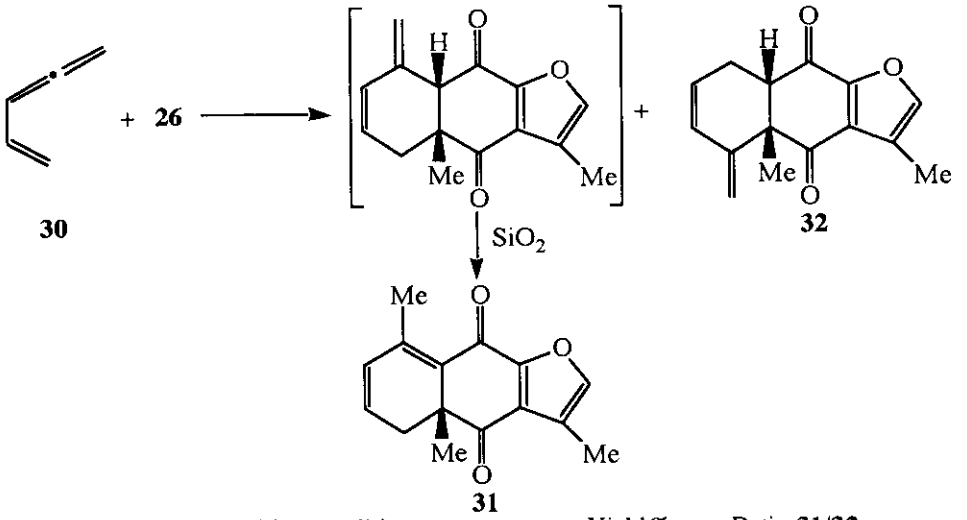


Scheme 17

With penta-1,2,4-triene (**30**), this same quinone (**26**) led, after chromatography on silica gel, to the mixture of the isomerized cycloadduct (**31**) and the unchanged primary cycloadduct (**32**) (Scheme 18).[14] Under thermal conditions, the regiochemistry was opposite to that of the former dienes, while in the presence of Lewis acid, a total regioselectivity was observed without loss in term of yield.

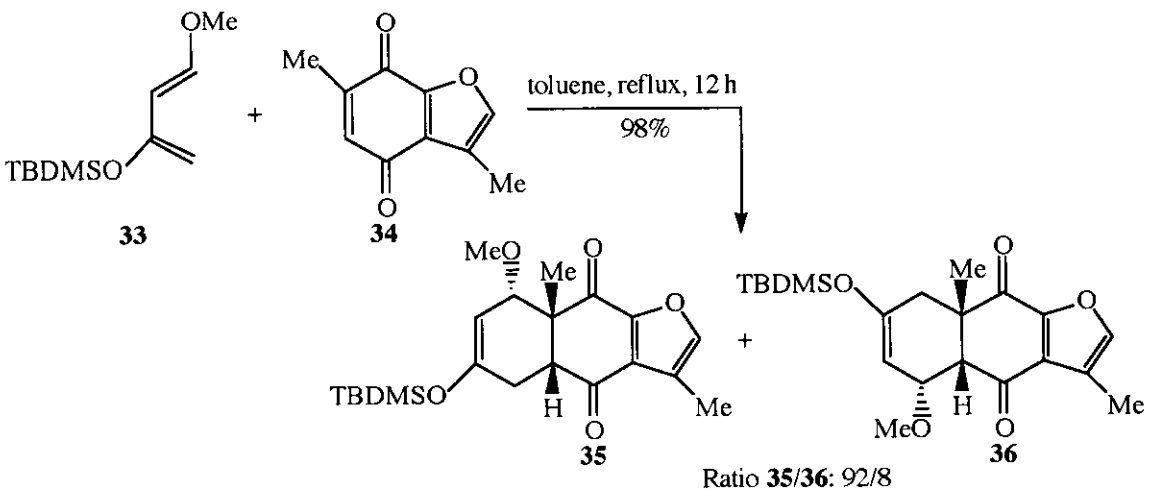
Lastly, as part of total syntheses of tubipofurans, Kanematsu *et al.* described the Diels-Alder reaction between the well polarized Danishefsky's diene (**33**) and quinone (**34**) (Scheme 19).[16] The Diels-Alder reaction appeared very efficient both in term of yield and regiochemistry. The orientation of the cycloaddition agrees with a major nucleophilic attack at C-5 of quinone (**34**), according to the blocking effect hypothesis developed above.

Total syntheses of tubipofurans were carried out (Scheme 20), from a pure sample of cycloadduct (**35**) which was easily separated from the mixture of regioisomers by recrystallization.



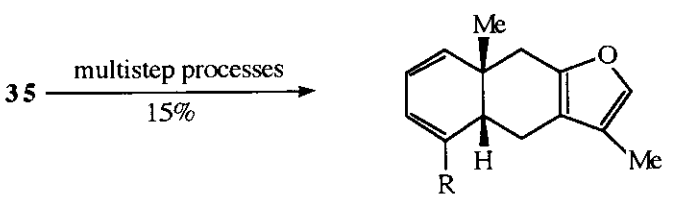
Cycloaddition conditions	Yield %	Ratio **31/32**
sealed tube, EtOH, 90°C, 7 h	75	67/33
$BF_3.EtO_2$ (1 eq.), benzene, rt, 14 h	77	100/0

Scheme 18



Ratio **35/36**: 92/8

Scheme 19

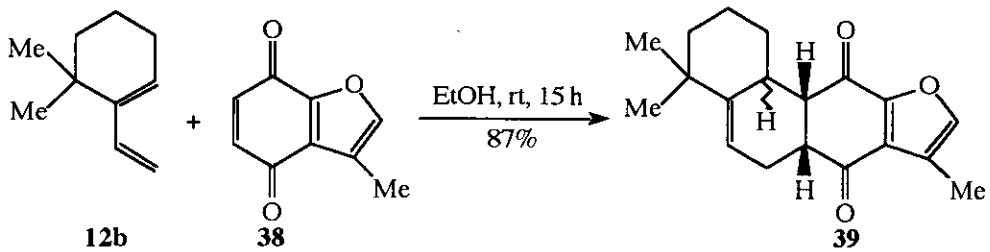


37a: R=Me (tubipofuran)
37b: R=CH_2OAc (15-acetoxytubipofuran)

Scheme 20

IV.2. Cycloaddition of 6,6-dimethyl-1-vinylcyclohexene

Another route to natural tanshinones was described through a cycloaddition key step, using diene (**12b**) and quinone (**38**) (Scheme 21).[17]

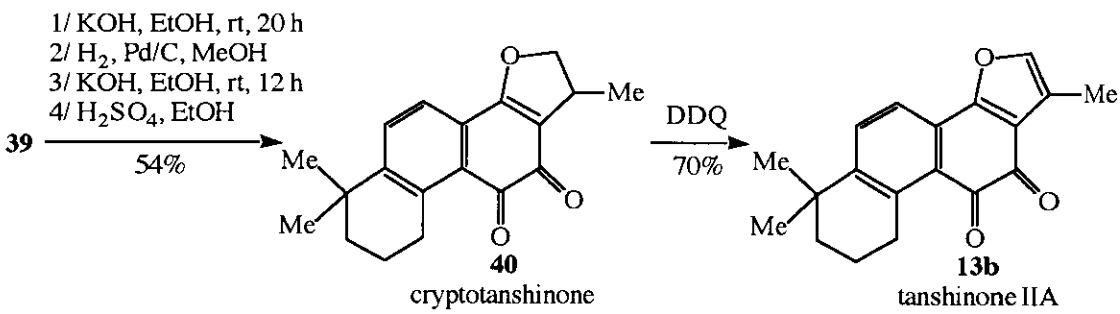


12b **38** **39**

Scheme 21

Only one primary cycloadduct was detected. The authors demonstrated that the regiocontrol of this reaction was more governed by electronic factors than by steric ones. Thus, the nucleophilic end of diene (**12b**) added to C-5 of quinone (**38**).

The naturally occurring cryptotanshinone (**40**) was afterwards synthesized in four steps from **39**. An additional oxidative step led to tanshinone IIA (**13b**) (Scheme 22).

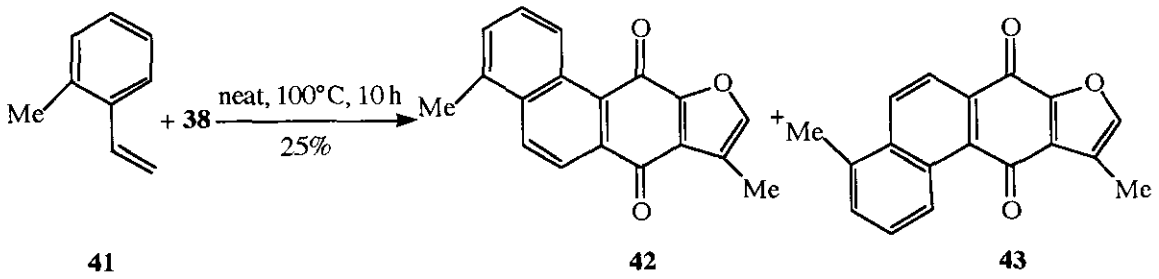


40 cryptotanshinone **13b** tanshinone IIA

Scheme 22

IV.3. Cycloaddition of 2-methylstyrene

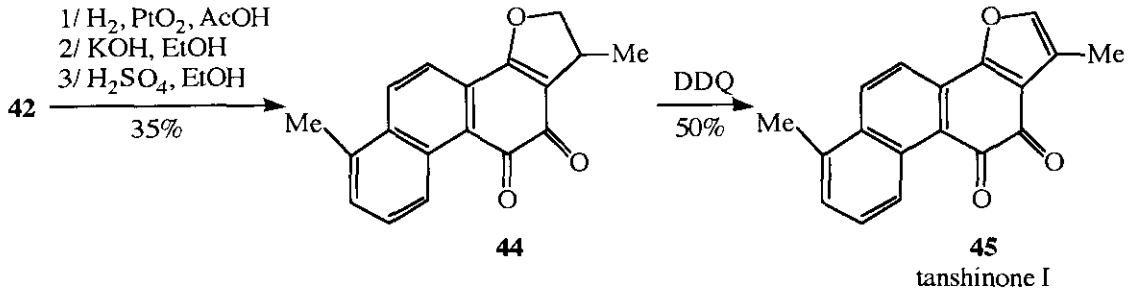
In the same work,[17] quinone (**38**) was used towards 2-methylstyrene (**41**) (Scheme 23). The aromatized cycloadducts (**42**) and (**43**) were obtained in a good regioselectivity, but in a low yield due the poor reactivity of diene (**41**). Indeed, the endocyclic double bond of the latter is implicated in the electronic resonance of the benzene ring. Nevertheless, this strategy was successfully employed for the synthesis of tanshinone I (**45**), from cycloadduct (**42**) (Scheme 24).



41 **42** **43**

Ratio **42**/**43**: 80/20

Scheme 23



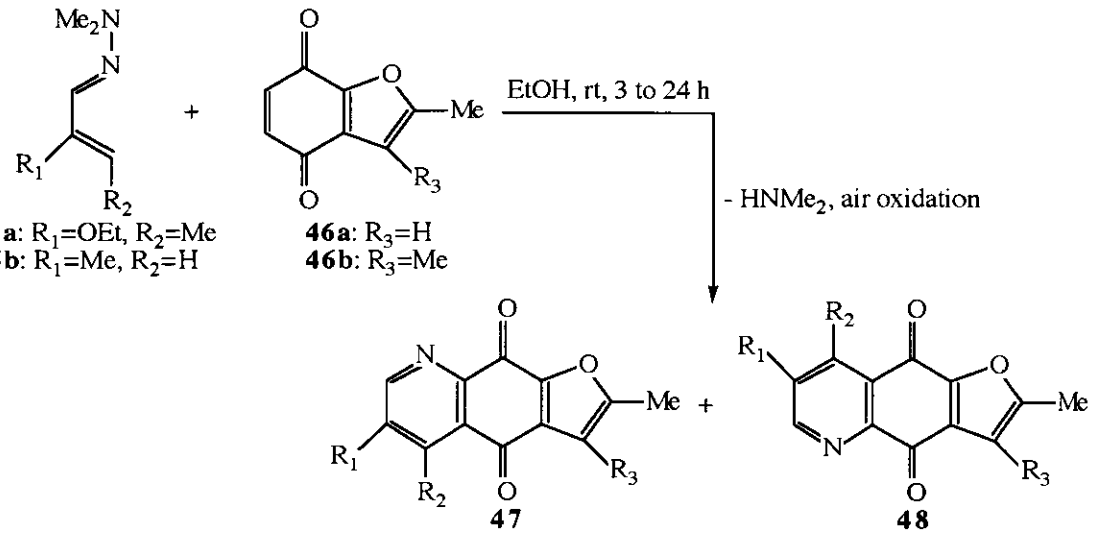
44 **45**
tanshinone I

Scheme 24

IV.4. Cycloadditions of α,β-unsaturated N,N-dimethylhydrazones

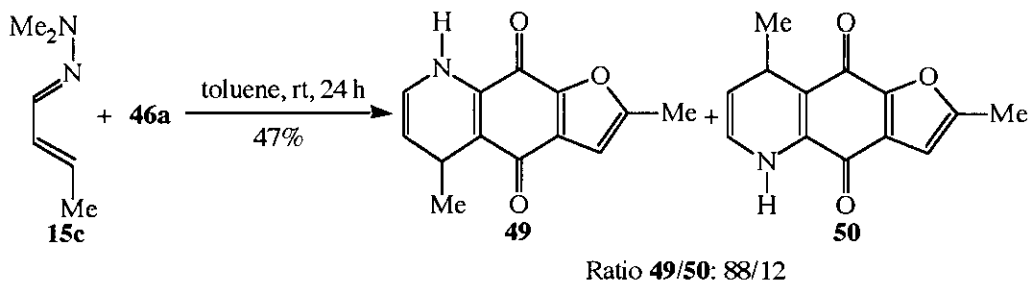
In view to obtain aza analogues of naphtho[2,3-*b*]furan-4,9-diones, we synthesized furoquinolinedione derivatives. So, we performed cycloadditions between azadienes (**15**) and quinones (**46**).[18] Starting with azadienes (**15a**) or (**15b**), we obtained directly the aromatized cycloadducts (**47**) and (**48**), after spontaneous elimination of dimethylamine and air oxidation (Scheme 25). Average to good regioselectivities were obtained, but unfortunately separation of the regioisomers failed.

On the other hand, the cycloaddition of azadiene (**15c**) with quinone (**46a**) afforded a mixture of the stable dihydro cycloadducts (**49**) and (**50**) (Scheme 26). In this case also, separation of the regioisomers from the mixture was unsuccessfull. In all these cycloadditions, the nucleophilic end of azadienes (**15**) attacked preferentially, as expected, on C-5 of quinones (**46**).



	Yield %	Ratio **47**/**48**
47aa, **48aa**: R_1=OEt, R_2=Me, R_3=H	54	55/45
47ab, **48ab**: R_1=OEt, R_2=Me, R_3=Me	67	66/34
47ba, **48ba**: R_1=Me, R_2=H, R_3=H	98	73/27
47bb, **48bb**: R_1=Me, R_2=H, R_3=Me	97	92/8

Scheme 25



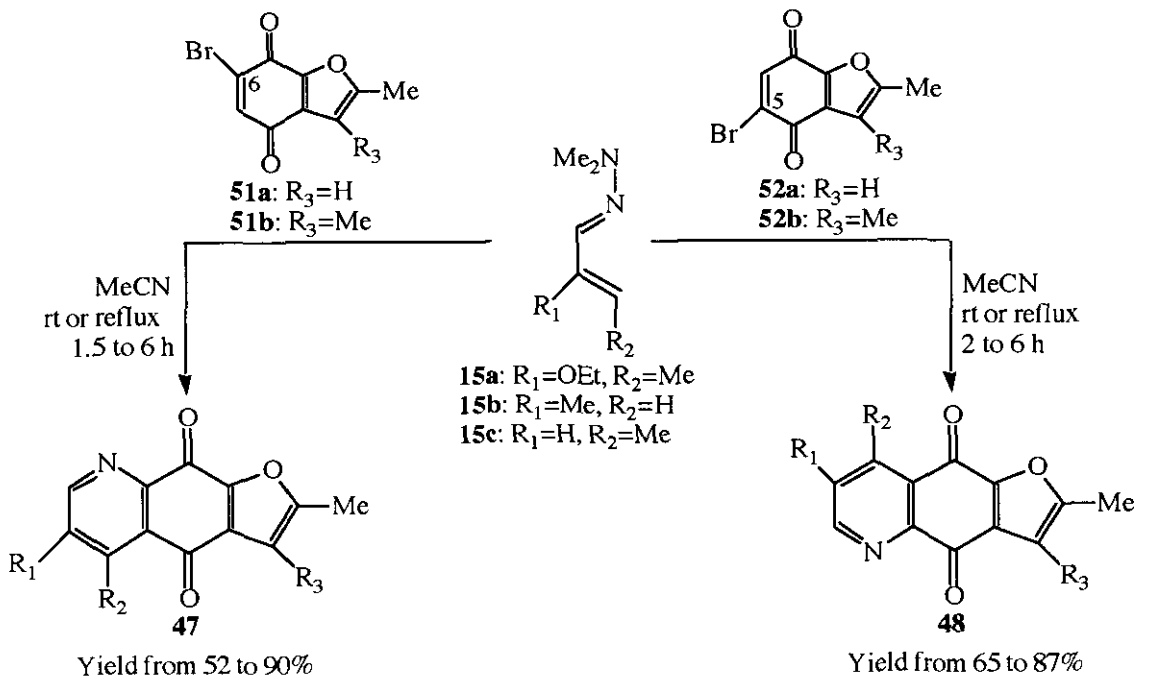
Scheme 26

V. DIELS-ALDER REACTIONS WITH 5- OR 6- BROMOBENZO[*b*]FURAN-4,7-DIONES

V.1. Cycloadditions of α,β-unsaturated N,N-dimethylhydrazones

In order to improve the above cycloadditions, at least in term of regiochemistry, we applied a strategy using brominated quinones.[19] This methodology is based on the blocking effect of the bromine atom located on the reactive double bond of the quinone. Indeed, in this case, the nucleophilic end of the diene added,

regioselectively or regiospecifically to the unbrominated carbon. Thus, starting from the brominated quinones (**51**) or (**52**), the corresponding furoquinolinediones (**47**) or (**48**) were obtained (Scheme 27).[18]

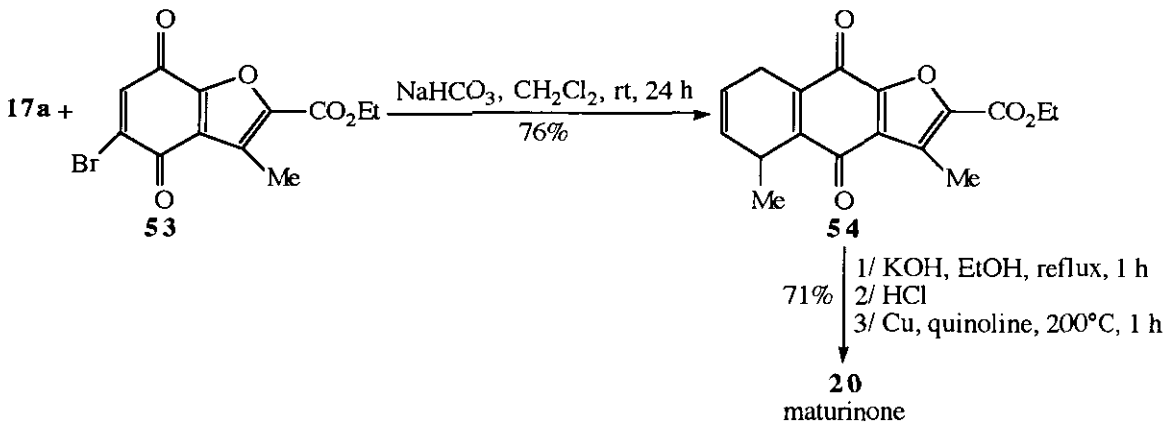


Scheme 27

The cycloaddition reactions afforded regiospecifically the fully aromatized corresponding furoquinolinediones. In most cases, a yield increase was observed by addition of triethylamine or sodium hydrogen carbonate to the reaction mixture. Such bases were used in order to trap hydrogen bromide liberated from the primary cycloadducts and thus to avoid azadienes polymerization. Moreover, it is interesting to note that the yields from these brominated quinones were significantly higher than those found from the nonbrominated ones.

V.2. Cycloaddition of penta-1,3-diene

As an illustration of the synthetic potentiality resulting from the use of brominated quinones, we described recently an efficient route to the naturally occurring maturinone.[20] Comparatively to the approach described in Scheme 12, we obtained the good regioisomer from quinone (**53**) and penta-1,3-diene (**17a**). Thus, a totally regioselective synthesis was achieved following Scheme 28.



Scheme 28

Quinone (**53**) was synthesized from commercially available starting materials with an overall yield of 30%.[20] Its cycloaddition to penta-1,3-diene (**17a**) led to the isolable dihydro adduct, which upon hydrolysis of the ester function and decarboxylation gave maturinone (**20**) in a 54% overall yield from **53**.

VI. CONCLUSION

The discovery of a large number of naturally occurring compounds from naphtho[1,2-*b*]furan-4,5-dione or naphtho[2,3-*b*]furan-4,9-dione families has initiated the emergence of a new field research. This latter was devoted to the study of the Diels-Alder reaction using dienophiles possessing an *ortho*- or *para*-benzofuran quinonoid skeleton. In this domain, although the Diels-Alder reaction from benzo[*b*]furan-4,5-diones has demonstrated their usefulness in the total synthesis of several naturally occurring tanshinones, the use of such quinones presents a drawback: their relative instability often leads to moderate yields in the cycloaddition step. Fortunately, this limitation is compensated by a high or a total regioselectivity.

Moreover, cycloaddition processes involving benzo[*b*]furan-4,7-diones were also successfully employed in the total synthesis of natural products or nitrogen structural analogues. In this case, the Diels-Alder reaction step gave generally good to excellent yields. In term of regioselectivity, the results obtained were more contrasted. If good to high regioselectivities were evidenced, in several cases the cycloaddition step afforded unseparable mixtures of regioisomers.

In an attempt to get round that problem, some solutions were tried in view to find totally regioselective pathways. Among these, the best strategy seems to be the use of quinones substituted by a leaving group

(a bromine atom in the scope of the present review) on the reactive double bond. Indeed, this strategy offers, in addition to a better regioselectivity, a precious help in the aromatization step which generally followed the Diels-Alder reaction.

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