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PREPARATION OF QUINONE MONOACETALS AND THEIR USE IN ORGANIC SYNTHESIS

by

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Submitted for the Degree of

MASTER OF PHILOSOPHY

University of Wales

University College of Swansea December 1994

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Especially warm thanks go to my " personal supervisor " Dominique, who always had time for my endless questions. I have also the special place in my heart for Chad and Pete, whom have shared equipments and every day life with me. Equally great thanks go to the boys, Bob, Elfyn, and Stiff, whose friendship and even teasing made my life enjoyable at home.

Thanks are also due to all those friends at the Department of Chemistry, who helped this work toward its conclusion and with whom I have pleasure of working.

Finally I would like to thank my family and friends in Finland, for their endless support and encouragement during this time abroad.

SUMMARY

The first chapter is a literature review of quinone monoacetals where is discussed their preparation and use in organic synthesis.

Phenolic oxidation by phenyliodonium diacetate is an excellent method to prepare quinone monoacetals and it is described in the following chapter.

The third chapter deals with a conversion of quinone monoacetal to the chiral spirodienone in the presence of Lewis acid and diols.

Addition and epoxidation reactions with the chiral spirodienone have been studied. This work is described in chapter four.

The experimental details are given in chapter five.

ABBREVIATIONS

The abbreviations used in this thesis are listed below:

NMR	Nuclear Magnetic Resonance
MS	Mass Spectrum
EI	Electron Impact
CI	Chemical Ionisation
UV	Ultra-violet
IR	Infra-red
HPLC	High Pressure Liquid Chromatography
m.p.	Melting point
mol	molecular
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
Glyme	1,2-Dimethoxyethanol
PIDA	Phenyliodonium diacetate
Pyrr	Pyrrole
THF	Tetrahydrofuran
Triton-B	Benzyltrimethyl ammonium hydroxide

CONTENTS

CHAPTER FOUR: ADDITION AND EPOXIDATION REACTIONS OF QUINONE MONOACETALS

CHAPTER ONE

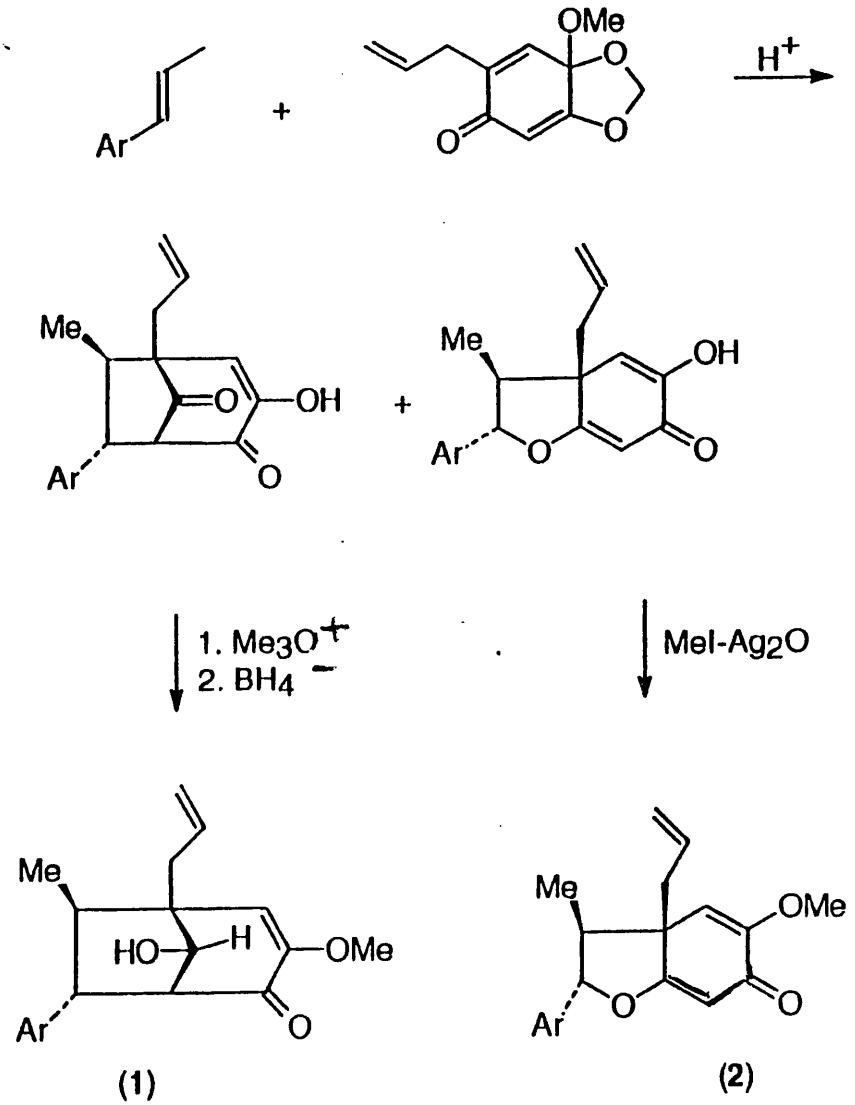
REVIEW OF QUINONE MONOACETALS

1.1 INTRODUCTION

Quinone monoacetals are potentially attractive compounds as regiospecific quinone equivalents in organic synthesis. They serve as valuable protected quinone derivatives since they are at the quinone oxidation state. Furthermore, quinone monoacetals often circumvent reactivity and regiochemical problems encountered in reactions of the unprotected quinones.

Quinone monoacetals are valuable intermediates and they serve as precursors to various types of natural products such as neolignans [1], tropolones [2], α -tocopherol [3], and anthracyclines [4].

Synthesis of guianin (**1**) and burchellin (**2**) are examples of the preparation of neolignans. Buchi has shown that those compounds can be prepared by the reaction of alkenes with substituted quinone monoacetals under acidic conditions [1] (Scheme 1).


OMe
H+
Ar
Me
OH
Ar
Me
OH
Ar
1. Me3O+
2. BH4 −
MeI-Ag2O
Me
HO
H
OMe
Ar
Me
OMe
Ar

(1) (2)

Scheme 1

1.2 PREPARATION OF QUINONE MONOACETALS

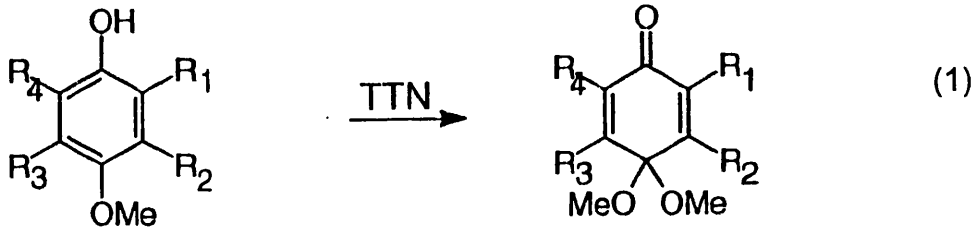
1.2.1 Chemical oxidation of phenols

Quinone monoacetals have been known for many years and prepared by oxidation of functionalized phenols. The oxidation of *p*- alkoxyphenols was first reported 1959 using ferric chloride or potassium hexacyanoferrate(III) [5]. Since that time a variety of oxidizing agents (periodic acid [6], copper(II)-pyridine complex and oxygen [7], manganese dioxide [8], lead dioxide [9], mercuric oxide with iodine [10], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [11], thallium(III)nitrate [12], phenyliodonium diacetate [13], and phenyliodonium bis(trifluoroacetate) [14]) have been used.

In most of cases, the yields of quinone monoacetals have been low, only thallium(III)nitrate, phenyliodonium diacetate and phenyliodonium bis(trifluoroacetate) have showed promise as reagents for the general oxidation of phenols to quinone monoacetals in good yields.

1.2.1.1 Thallium(III)nitrate (TTN)

Oxidation of 4-methoxyphenols with 1 equiv of TTN in methanol or a mixture of methanol and trimethyl orthoformate gives 4,4-dimethoxy-cyclohexa-2,5-dienones in high yields [12] (equation 1).

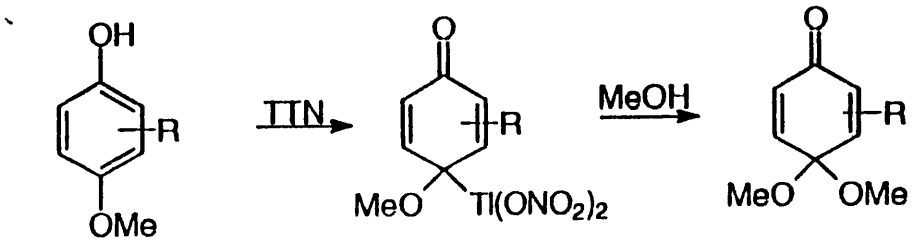


(1)

Table 1: Phenolic oxidation with TTN according to equation 1

	yield (%)
a) R_1=R_2=R_3=R_4=H	97
b) R_1=Me; R_2=R_3=R_4=H	89
c) R_1=R_4=Me; R_2=R_3=H	87
d) R_1=R_4=t-C_4H_9; R_2=R_3=H	96
e) R_1=R_4=H; R_2=R_3=H	95
f) R_1=H; R_2=R_3=OMe; R_4=COMe	92
g) R_1=Cl; R_2=R_3=R_4=H	97
h) R_1=Br; R_2=R_3=R_4=H	91

Formation of cyclohexadienones is postulated to proceed *via* intermediate (**3**), which then undergoes *ipso*-displacement of the thallium substituent by methanol (Scheme 2).

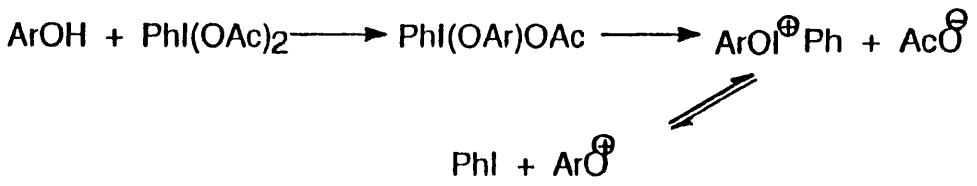


(3)

Scheme 2

1.2.1.2 Phenyliodonium diacetate (PIDA)

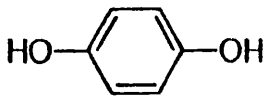
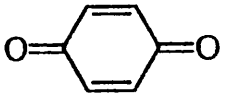
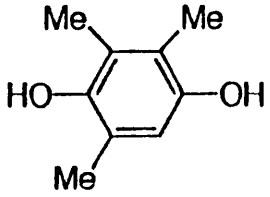
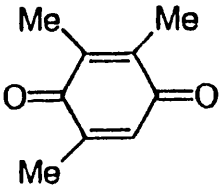
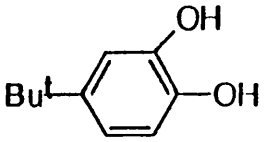
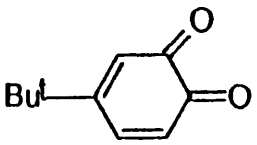
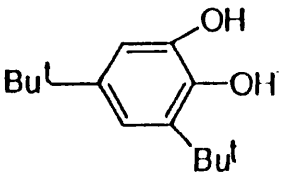
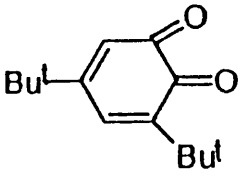
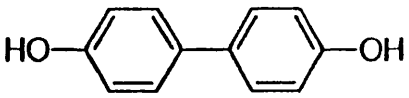
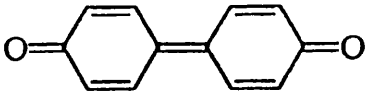
Commercially available PIDA reacts with phenols to give the intermediate, PhI(OAr)OAc which may break down *via* $ArOI^{+}Ph$, and the rather poorly nucleophilic anion, AcO^{-} (Scheme 3).



Scheme 3

Pelter and Elgendy [13] found that PIDA in methanol interacts with 1,4-and 1,2-dihydroxybenzenes to yield 1,4-and 1,2-quinones in excellent yields (Table 2, experiments 1-4). Also PIDA oxidizes 4,4'-biphenols to the corresponding extended quinones (Table 2, experiment 5).

Table 2: Oxidation of 1,4 and 1,2-dihydroxybenzenes

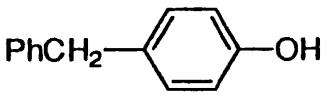
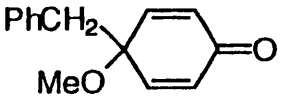
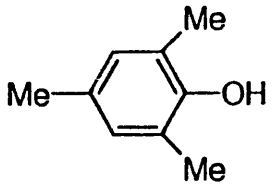
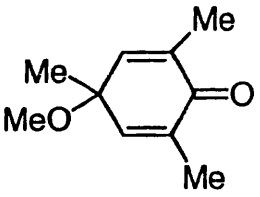
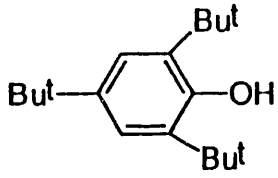
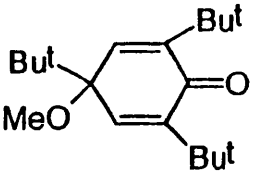
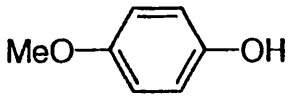
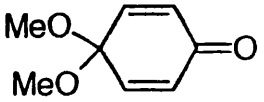
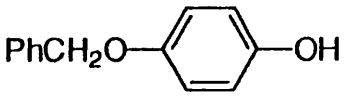
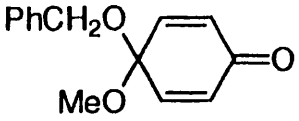
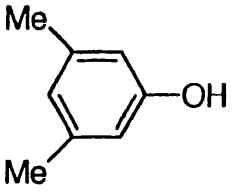
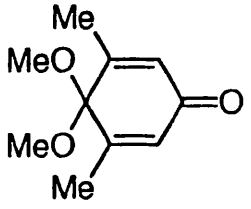
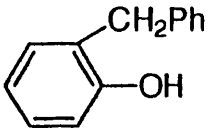
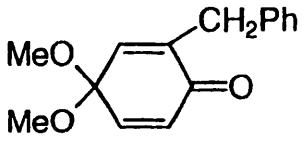
exp.	phenol	product	yield (%)
1			94
2			98
3			99
4			91
5			94*

* Hplc yield

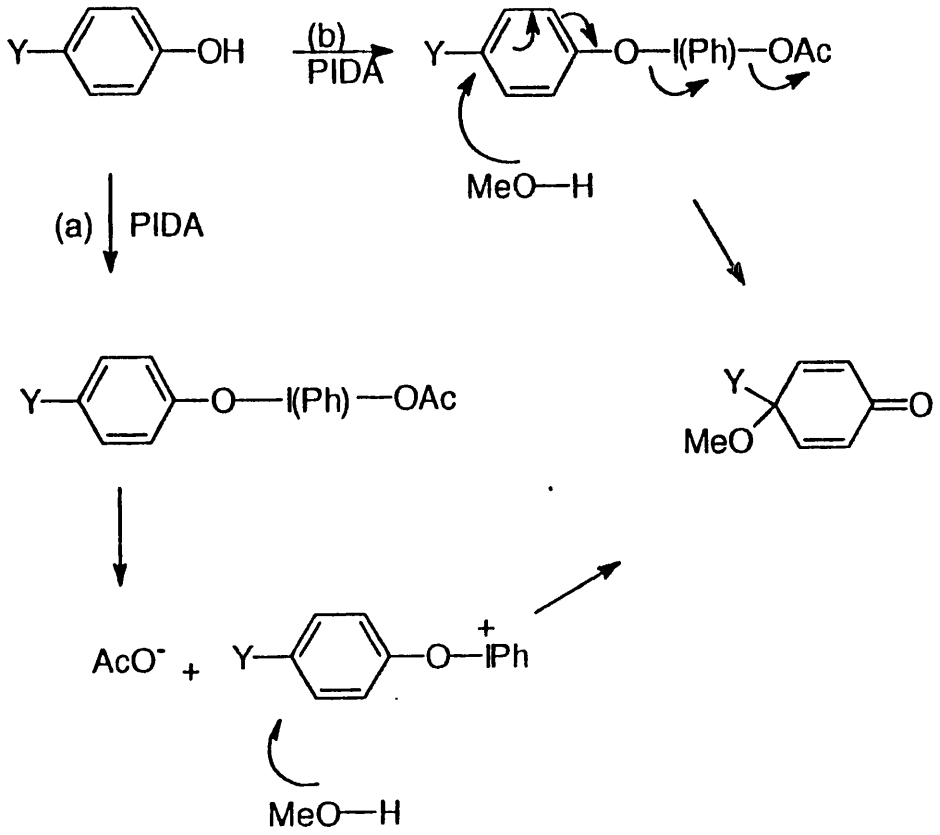
Table 3 shows that the interaction of PIDA (one equivalent) with 4-alkylphenols yields 4-alkyl-4-methoxycyclohexa-2,5-dienones (experiments 1-3). Excellent yields are obtained when the substituent on the phenol is an alkoxy group (experiments 4 and 5).

When two equivalents of PIDA are used with 4-unsubstituted phenols, it gives directly 4,4-dimethoxycyclohexa-2,5-dienones (Table 3, experiments 6 and 7).

Table 3: Oxidation of monohydric phenols

exp	phenol	product	yield (%)
1			65
2			72
3			94
4			99
5			92
6			80
7			83

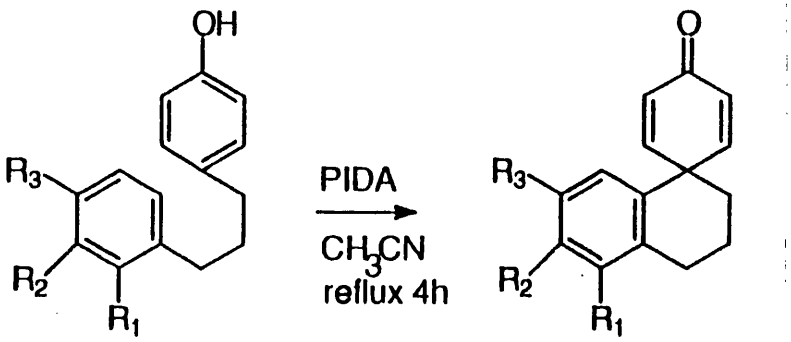
Althought the oxidation products are typical of two electron oxidations, the mechanism of PIDA-reaction is unknown. The products can proceed *via* transient aryloxeniumion ions (route a), or methanol may attack the intermediate directly (route b) (Scheme 4).



Scheme 4

In addition PIDA can be used as a phenolic oxidative coupling agent [15]. In an aprotic solvent, mixing PIDA (2 equiv.) with monophenolic 1,3-diarylpropanes at high temperature, intramolecular

coupling takes place (equation 2). The spirodienones are obtained consistently in 30% yield.



(2)

$R_1=R_2=R_3=H$ $R_1=R_2=R_3=H$

$R_1=R_2=H$; $R_3=OMe$ $R_1=R_2=H$; $R_3=OMe$

$R_1=R_3=H$; $R_2=OMe$

Most of 2'-alkenyl-substituted *p*-phenyl phenols can be oxidized by PIDA to the corresponding spiro-annulated-2,5-cyclohexadienones [16] (equation 3). This reaction is markedly dependent upon the substitution on the olefin and the aromatic ring. For example the simple vinyl system (Table 4, experiment 1) does not afford the oxidative cyclization.

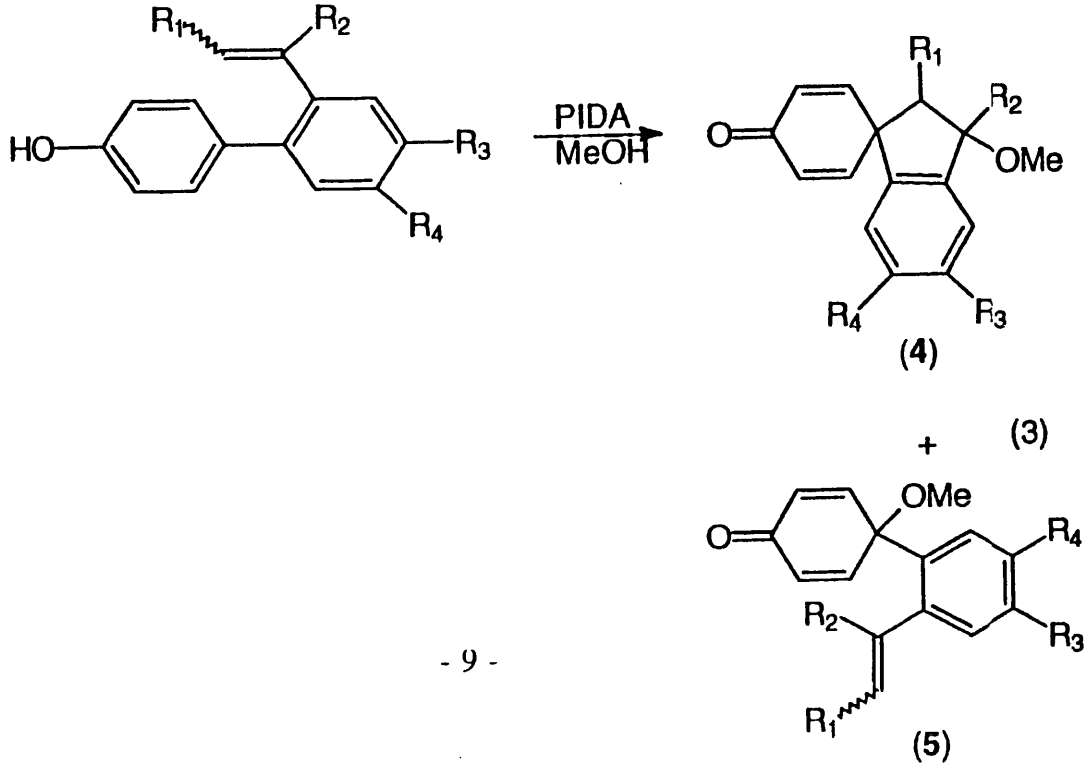
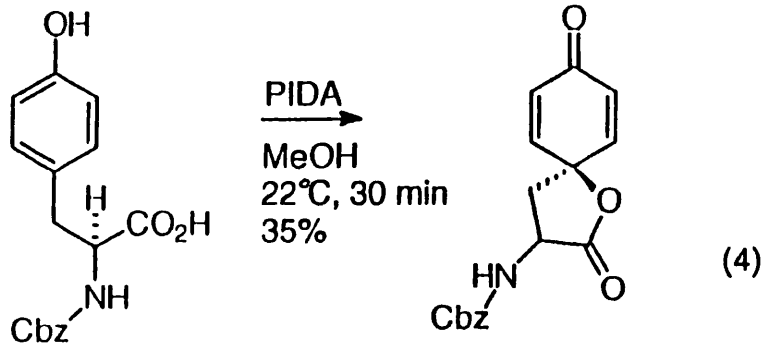


Table 4: Oxidative cyclizations of 2'-alkenyl-*p*-phenyl phenols according to equation 3

Exp.	R_1	R_2	R_3	R_4	Yield (**4**) (%)	Yield (**5**)(%)
1	H	H	H	H	-	46
2	H	CH_3	H	H	67	-
3	$-(CH_2)_3-$		H	H	50	-
4	H	H	H	CH_3	56	34
5	H	H	OCH_3	H	-	63
6	H	CH_3	OCH_3	H	48	-
7	H	CH_3	OCH_3	OCH_3	76	-
8	H	H	$-OCH_2-$		34	9
9	H	CH_3	$-OCH_2-$		79	-
10	CH_3	H	$-OCH_2-$		75	-

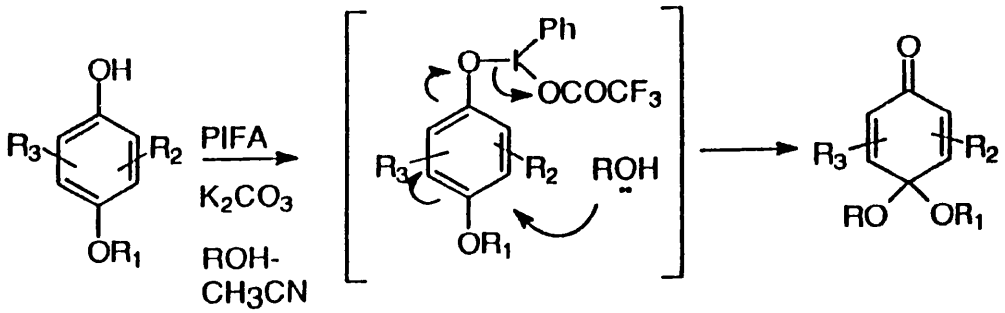
The key intermediate (**7**) for the preparation of aranorosin may be synthesised by an oxidative cyclization of tyrosine (**6**) with PIDA [17] (equation 4).



(6) (7) (4)

1.2.1.3 Phenyliodonium bis(trifluoroacetate) (PIFA)

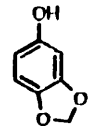
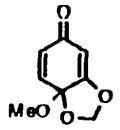
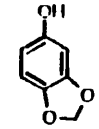
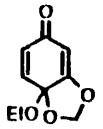
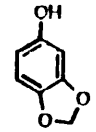
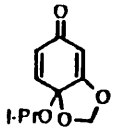
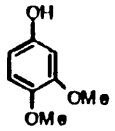
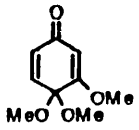
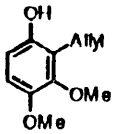
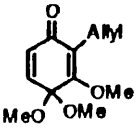
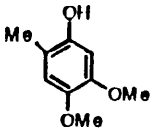
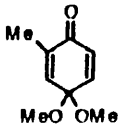
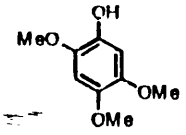
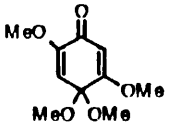
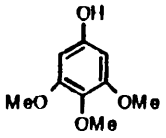
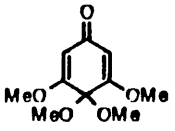
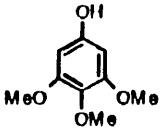
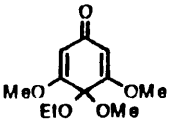
PIFA is a similar hypervalent iodine reagent to PIDA; acetyl groups having been replaced by trifluoroacetate groups. PIDA and PIFA oxidation of phenols often give the same products with similar yields. For example *p*-alkoxyphenols and their related compounds can be oxidized by PIFA in excellent yields under mild conditions [14] (Scheme 5).



Scheme 5

The results are presented in Table 5.

Table 5: Phenolic oxidation with PIFA

phenol	conditions	product	yield
	$MeOH/CH_3CN$		83 %
	$EtOH/CH_3CN$		99%
	$i\text{-}PrOH/CH_3CN$		80%
	$MeOH/CH_3CN$		90%
	$MeOH/CH_3CN$		85%
	$MeOH/CH_3CN$		85%
	$MeOH/CH_3CN$		86%
	$MeOH/CH_3CN$		quant.
	$EtOH/CH_3CN$		quant.

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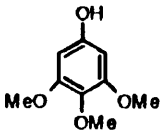
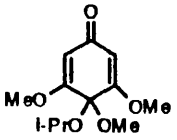
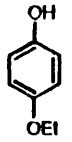
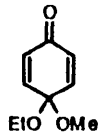
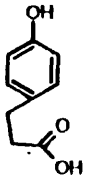
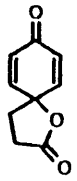
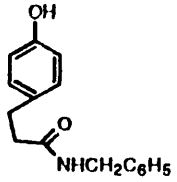
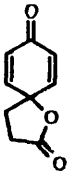
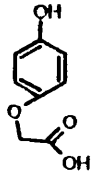
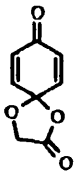
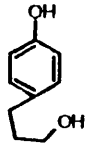
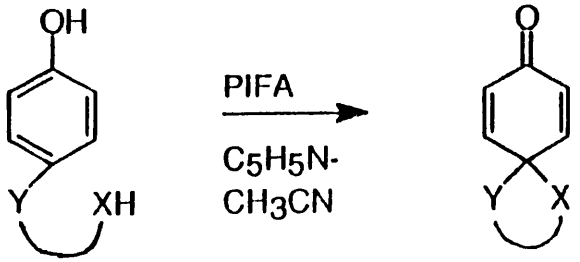
	i-PrOH/CH_3CN		97%
	MeOH/CH_3CN		90%
	CH_3CN		86%
	CH_3CN		69%
	CH_3CN		80%
	CH_3CN		59%

The corresponding spiro-compounds are also obtained via intermolecular ipso-trapping by some nucleophiles such as carboxy, amido, and hydroxy groups (equation 5).



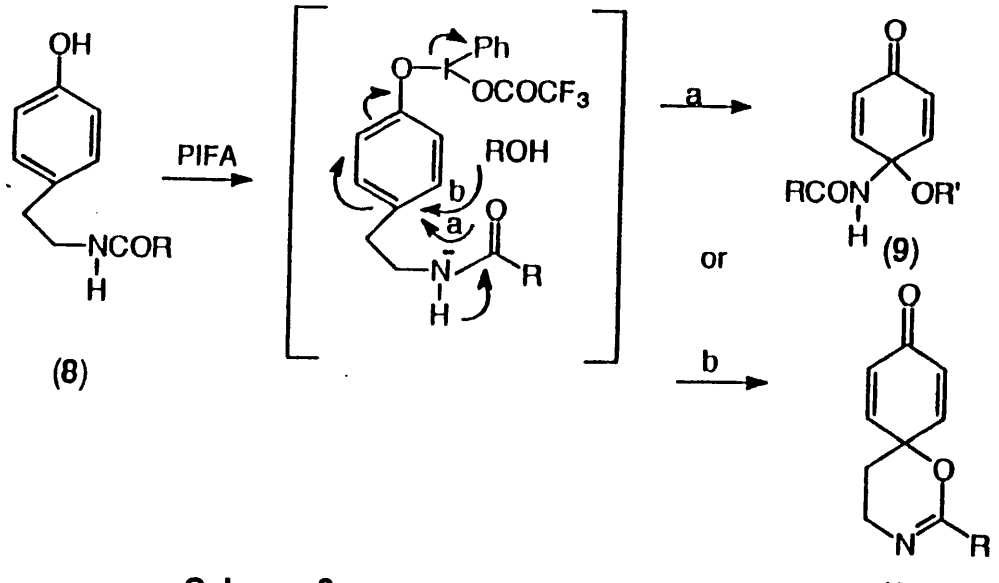
(5)

X=CO_2, CONR, O
Y=CH_2, O

Oxidation of N-acyltyramines (**8**)(Scheme 6), which have the amido group as the para substituent, with PIFA can occur in two ways, depending on the solvents which have been used [18];

(i) in a nucleophilic solvent (alcohol or acetic acid), the solvent attacks the para position of N-acyltyramines to give the corresponding quinol ether (**9**) and

(ii) in a poorly nucleophilic polar solvent (2,2,2-trifluoroethanol) cyclization occurs by the attack of the amido group to give spirocyclohexadienone (**10**).



Scheme 6

Table 6: reaction path a (Scheme 6)

N-acyltyramines (**8**)	conditions	products (**9**)	yields (%)
R		R'	
Me	MeOH	Me	76
Me	EtOH	Et	47
Me	i-PrOH	i-Pr	22
Me	$MeCO_2H$	COMe	20
t-Bu	MeOH	Me	64*
t-Bu	$MeCO_2H$	COMe	44**
Ph	MeOH	Me	61***
Ph	$MeCO_2H$	COMe	62
2,6-di-MeOPh	MeOH	Me	68
2,6-di-MeOPh	$MeCO_2H$	COMe	57

* product (**10**) was also obtained (18%)

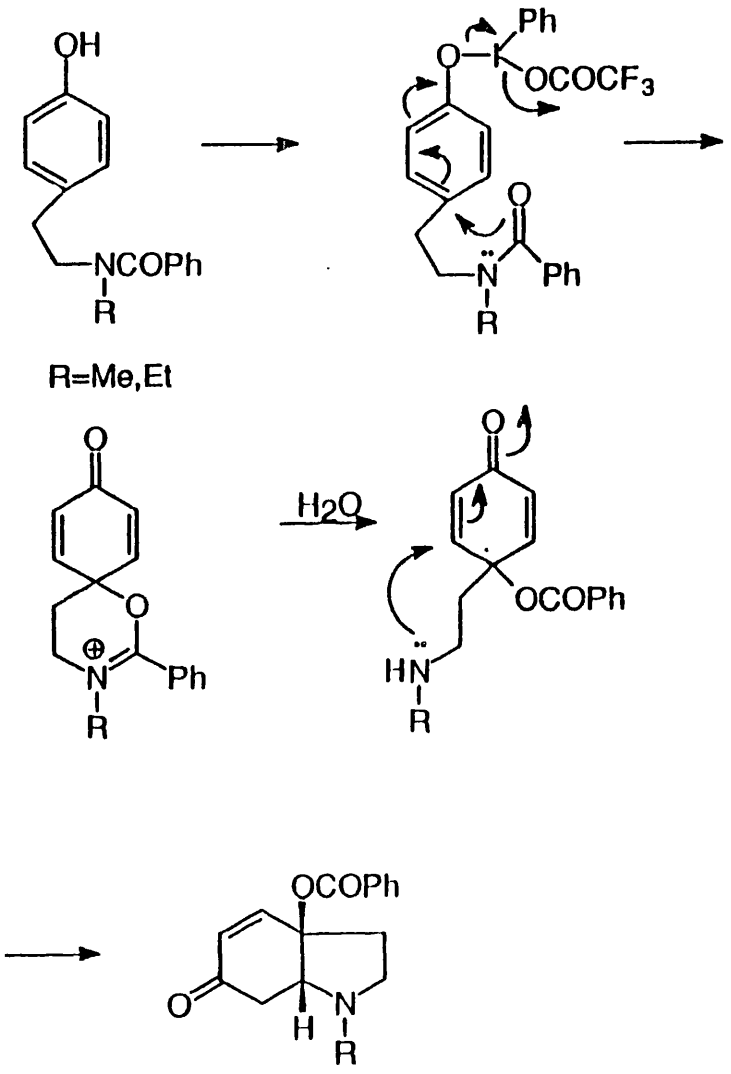
** product (**10**) was also obtained (8%)

***product (**10**) was also obtained (27%)

Table 7: reaction path b (Scheme 6)

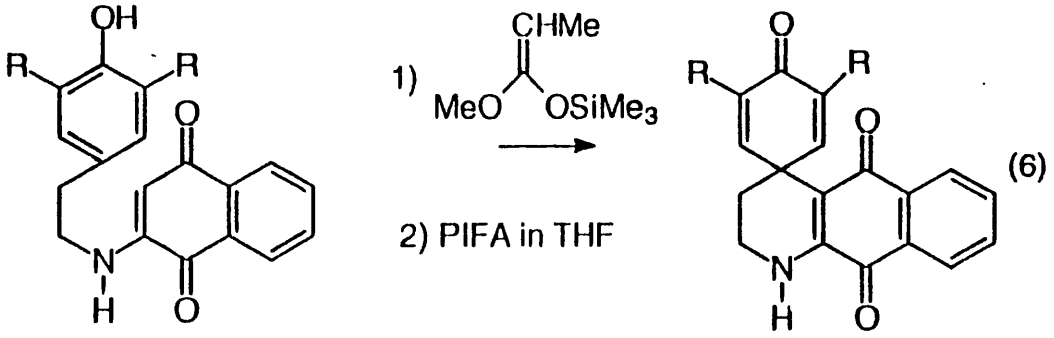
N-acyltyramines (**8**)	conditions	yields (**10**) (%)
R		
Me	CH_2Cl_2 / K_2CO_3	29
t-Bu	CF_3CH_2OH	75
t-Bu	CH_2Cl_2 / K_2CO_3	24
Ph	CF_3CH_2OH	73
Ph	CH_2Cl_2 / K_2CO_3	38
2,6-di-MeOPh	CF_3CH_2OH	74
2,6-di-MeOPh	CH_2Cl_2 / K_2CO_3	17

Treatment of N-methyl-and N-ethyl-N-benzoyltyramines with PIFA in 2,2,2-trifluoroethanol followed by aqueous workup gives the hexahydroindol-6-ones [14] (Scheme 7).



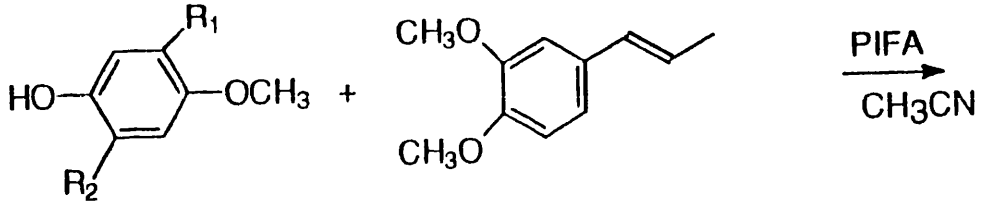
Scheme 7

The reaction of *o*-silylated *p*-substituted phenols with PIFA gives azacarbocyclic spirodienones [19] (equation 6).



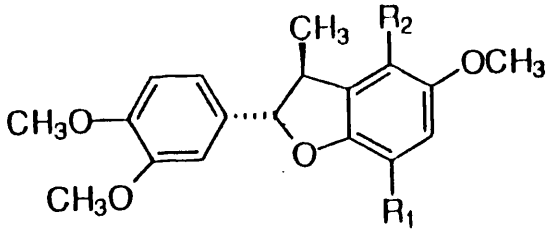
(6)

trans-Dihydrobenzofurans (**13**) can be prepared stereoselectively from oxidation of *p*-methoxysubstituted phenols (**11**) with PIFA in the presence of electron-rich styrene derivatives (**12**) [20] (equation 7).



(**11**) (**12**)

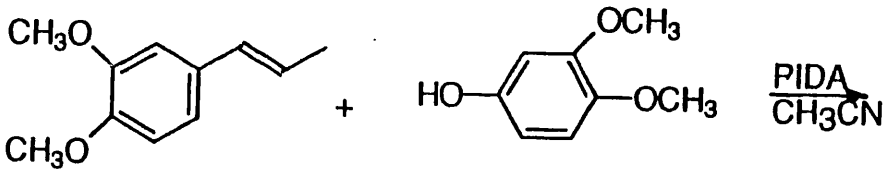
(7)



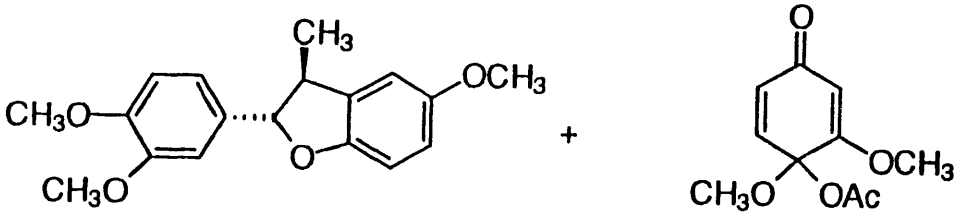
(**13**)

	Yield
(a) R_1=R_2=H	71%
(b) R_1=OCH_3, R_2=H	65%
(c) R_1=C_3H_5 , R_2=H	68%
(d) R_1=C_3H_5, R_2=Cl	40%

When PIDA is used as the oxidant, the yields are lower. One possible reason for the low yields of (**13a**) is reaction of acetic acid with the oxidized phenol intermediate leading to the monoketal derivative (**14**) (equation 8). In the case of PIFA, the generated trifluoroacetic acid is a poorer nucleophile, which explains the better yields of (**13a**).



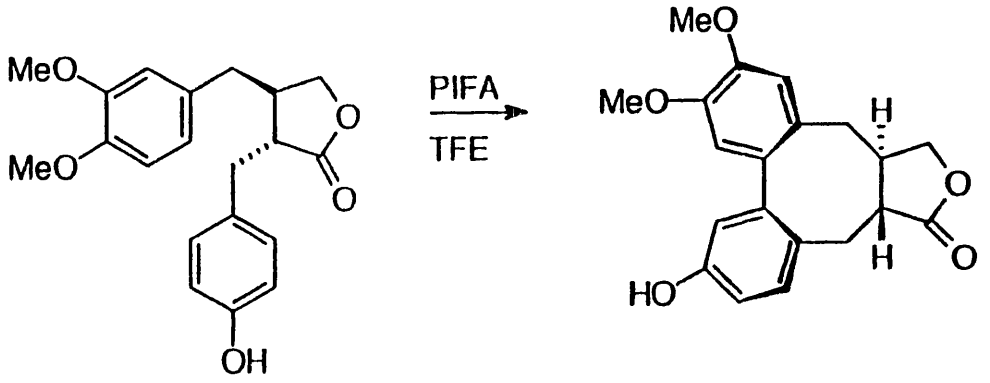
(**12**) (**11b**) (8)



(**13a**) 24% (**14**) 24%

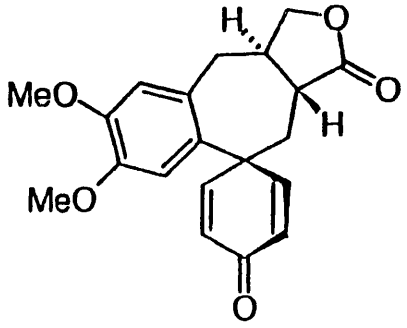
Reaction of the dibenzylbutyrolactone (**15**) with PIFA in trifluoroethanol gives as the major product either the dibenzocyclooctadiene (**16**) or the spirodienone (**17**). On standing for 2h the major product (48%) is the dibenzocyclooctadiene (**16**).

Spirodienones products such as (17) have been proposed as intermediates in the biosynthesis of dibenzocyclooctadiene lignans (equation 9) [21].



(15) (16) (9)

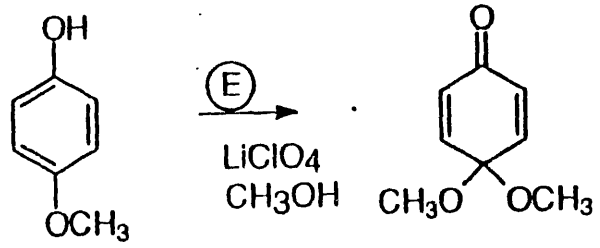
+



(17)

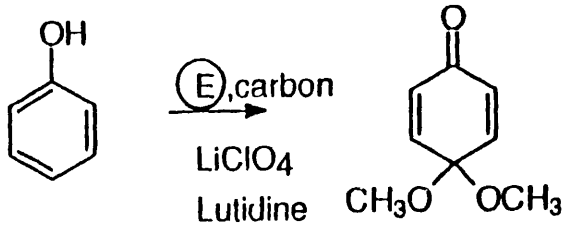
1.2.2 The electrochemical oxidation of phenols

The electrochemical oxidation of phenols is a method which allows the preparation of quinone monoacetals without the use of chemical oxidizing agents which are relatively expensive and toxic in some cases. The preparation of (**18**) *via* electrochemical oxidation of *p*-methoxyphenol [22] is an excellent alternative to chemical oxidation (equation 10).



(**18**) (10)

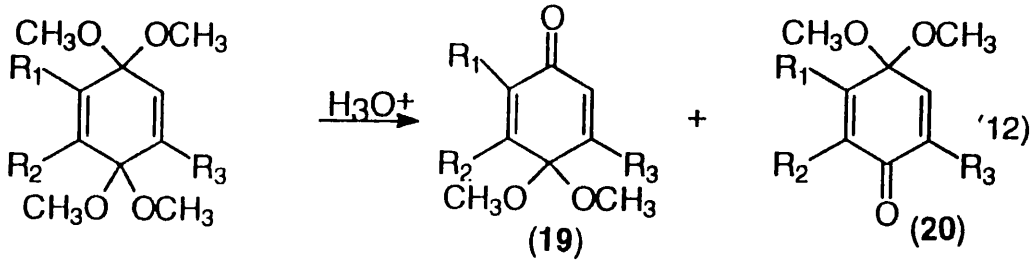
Although phenol undergoes anodic oxidation in methanol, it gives 4,4-dimethoxycyclohexa-2,5-dienone (**18**) in only modest yield [23] (equation 11).



(**18**) (11)

1.2.3 The hydrolysis of quinone *bis*ketals

Acid-catalyzed mono hydrolysis of quinone *bis*ketals [24] may afford quinone monoacetals in synthetically useful yields (equation 12).

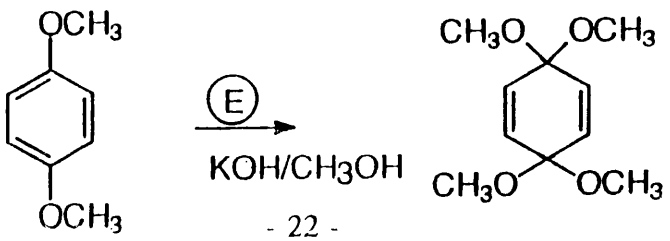


'12)

Table 8: Monohydrolysis of benzoquinone bisketals according to eq.12

R_1	R_2	R_3	yield (**19**)	yield(**20**)
H	H	Br	88%	3%
H	H	CH_3	64%	11%
H	H	$Si(CH_3)_3$	29%	38%
H	H	$CH(CH_3)(OCH_3)$	58%	19%
H	H	$NHCOCH_3$	79%	-
CH_3	CH_3	CH_3	90%	-
H	H	OCH_3	66%	-
H	H	SCH_3	60%	-
H	H	COPh	42%	-

The quinone bisketals can be prepared by anodic oxidation of 1,4-dimethoxyaryl compounds [25] (equation 13).

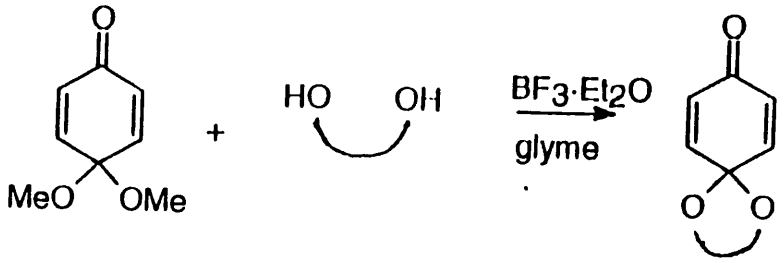


(13)

1.3 REACTIONS OF QUINONE MONOACETALS

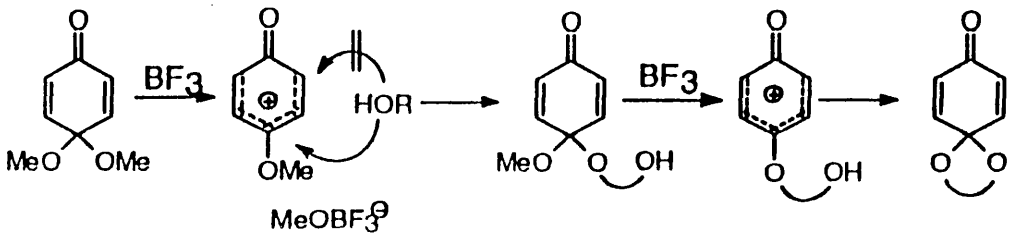
1.3.1 The exchange reaction of dimethyl ketals to give spiroketals

Pirrung and Nunn [26] have been shown that 4,4dimethoxycyclohexa-2,5-dienone undergoes acid-catalyzed exchange with diols to form spiroketals (equation 14)



(14)

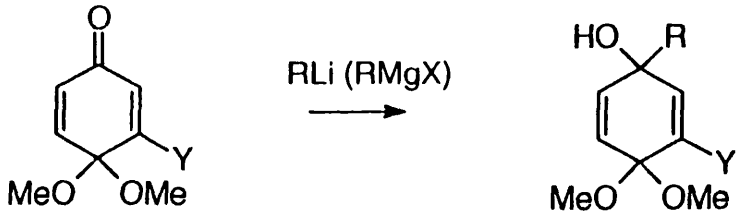
The exchange takes place under the influence of BF_3 etherate in glyme (1,2-dimethoxyethane). Spiroketals are formed in good yields (59-77%) using ethylene glycol, 2,3-butanediol, 1,3-propanediol, 2,4-pentanediol, 1,4-butanediol, and 2,5-hexanediol. In contrast the reactions with catechol, diethyl tartrate, ethanethiol, mercaptoethanol, pinacol, or 1,3-propanedithiol were unsuccessful. The mechanism of the exchange has been explained by kinetic control; attack to C-4 is shown in Scheme 8, attack at C-4 being predicted by MOPAC calculations [26].



Scheme 8

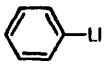
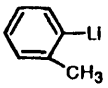
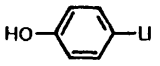
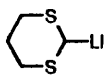
1.3.2 1,2-Additions to quinone monoacetals

An important synthetic use of quinone monoacetals is the 1,2-addition of Grignard and organolithium reagents to the carbonyl group. A number of organolithium and Grignard reagents react to give the corresponding *p*-quinol ketals in good yield [27] (equation 15).

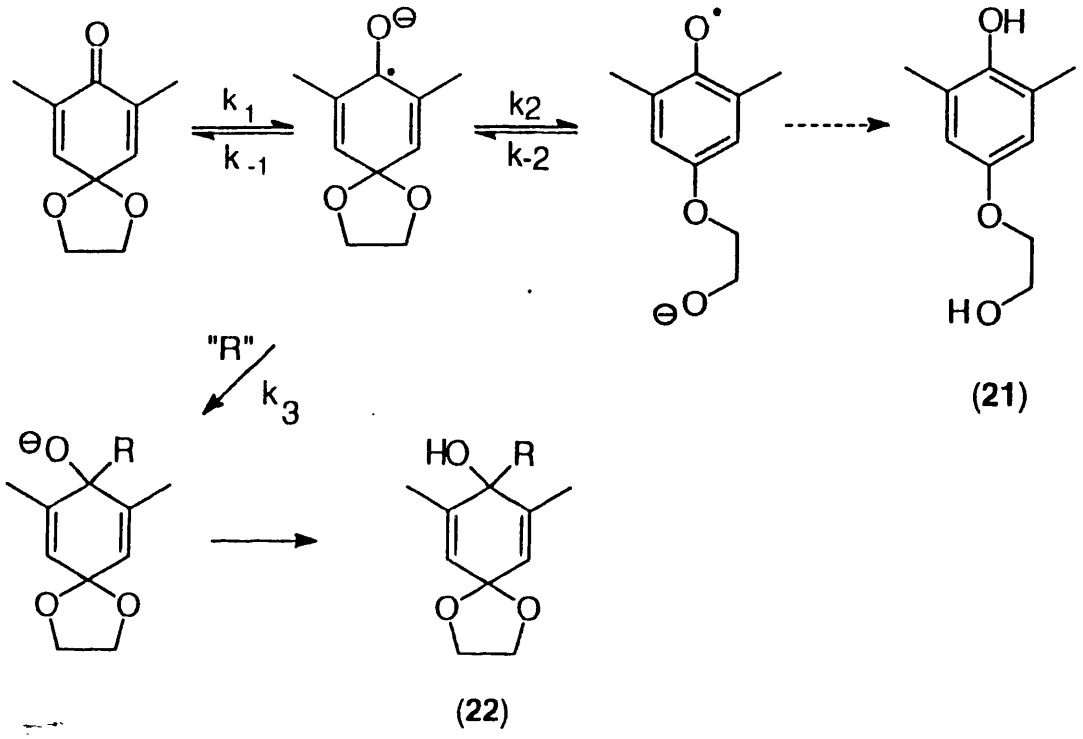


(15)

Table 9: Selected examples of *p*-quinol ketals from quinone monoketals according to eq. 15

RLi (RMgX)	Y	yield%
	H	85
	H	84
	H	90
	H	79
CH_3MgBr	Br	84
	OCH_3	90
$LiCH_2CO_2CH_3$	H	91
$PhSO_2CH_2Li$	OCH_3	86

1,2-Addition is favored, when primary and aryl organometallic reagents react with quinone monoacetals at low temperature. In the case of secondary organolithium and Grignard reagents, the quinone monoacetal is reduced to the respective phenol. This has been explained by a single-electron-transfer mechanism [28] (Scheme 9).

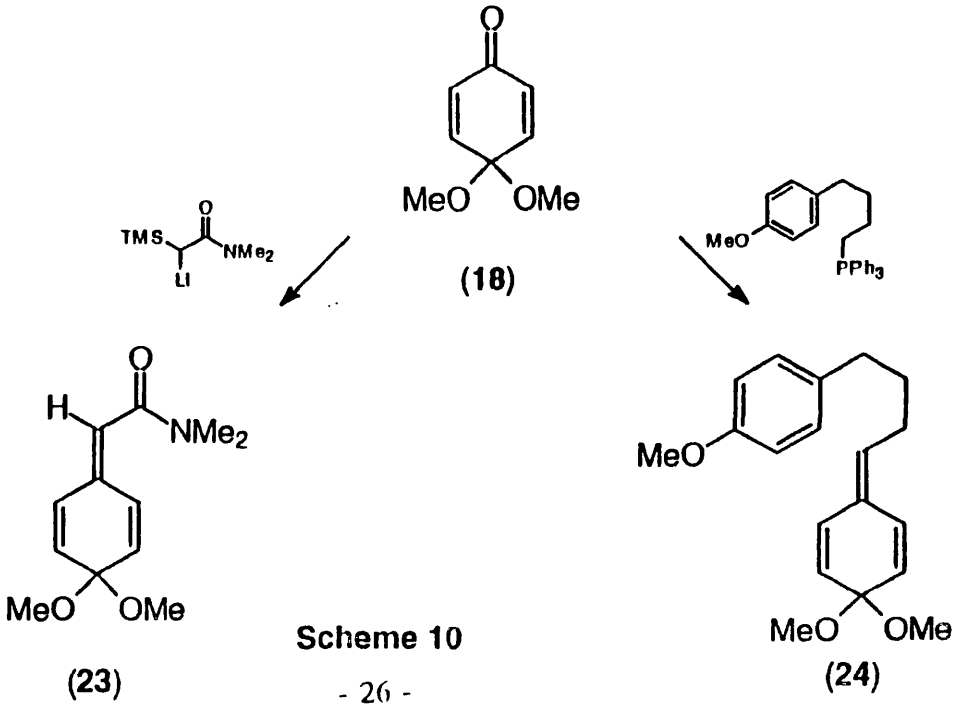


Scheme 9

Table 10: Organometallic reactions with quinone monoacetals according to Scheme 9

reagent	R	temp. C	% (21)	% (22)
Me_2CuLi	Me	-78	85	-
MeLi	Me	-78	5	95
MeMgBr	Me	-78	3	95
n-BuLi	*n*-Bu	0→25	46	46
n-BuLi	*n*-Bu	-78→25	1	95
n-BuMgBr	*n*-Bu	0	50	40
sec-BuLi	*sec*-Bu	-78→25	38	52
t-BuLi	*t*-BuLi	-78	90	-

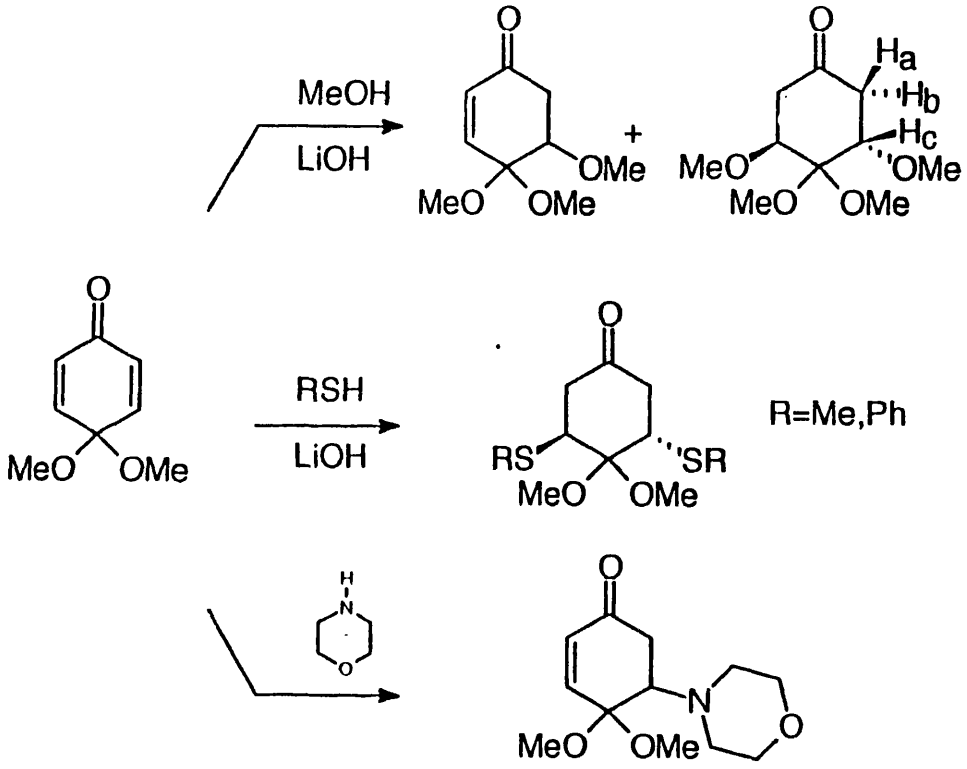
Peterson [29] (**18**→**23**) and Wittig [30] (**18**→**24**) reactions on quinone monoacetals have been also reported to yield the corresponding protected quinone methides in good yields (Scheme 10).



Scheme 10

1.3.3 Michael additions to quinone monoacetals

Quinone monoacetals are useful Michael acceptors and additions to quinone monoacetals are regiospecific. 1,4-Additions of oxygen, nitrogen and sulfur nucleophiles to 4,4-dimethoxycyclohexa-2,5-dienone are presented in Scheme 11 [31].

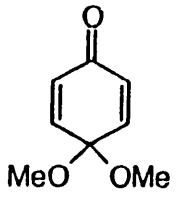
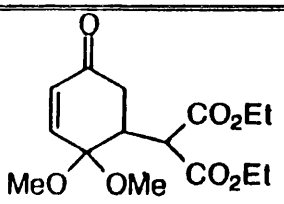
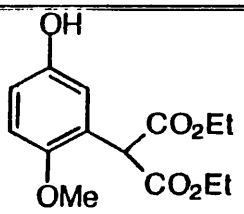
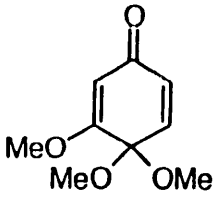
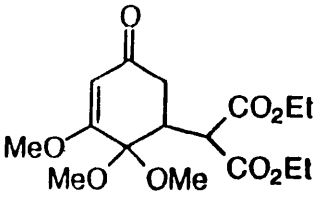
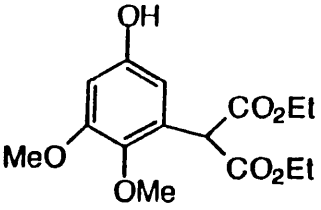
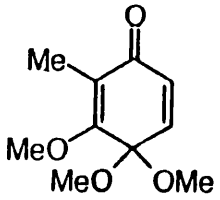
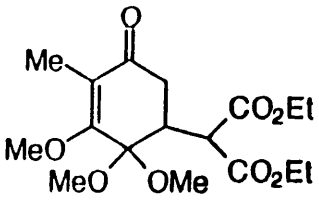
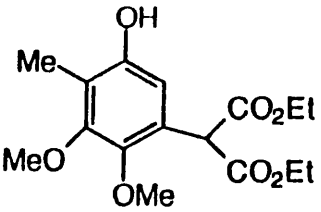
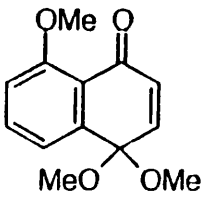
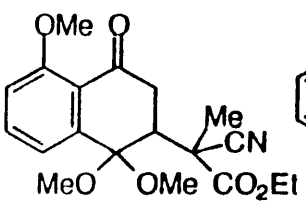
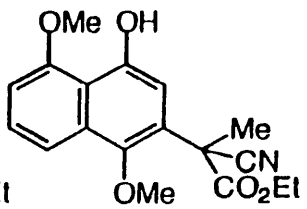


Scheme 11

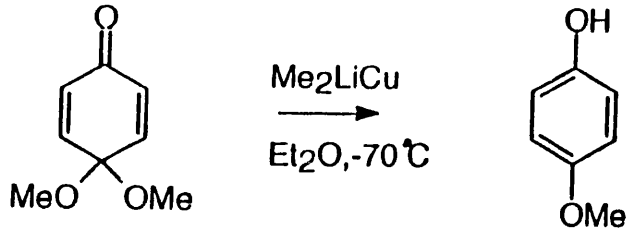
The addition of soft carbon nucleophiles such as diethyl malonate and ethyl cyanopropionate to quinone monoacetals affords 1,4-addition products in high yields [32]. These products may be aromatized by *p*-toluenesulfonic acid in refluxing benzene to give the functionalized hydroquinone ethers (Table 11). Addition of quinone monoacetal 1 or 2 to diethylmalonate and 0.1 equivalent of sodium ethoxide in ethanol at room temperature gives mono adduct in good

cyanopropionate is used (Table 11, monoacetal 4). In the case of 2-methyl-3,4,4-trimethoxy-cyclohexa-2,5-dienone , the addition is effected in tetrahydrofuran using the sodium enolate of diethyl malonate produced with sodium hydride.

Table 11: The addition of diethylmalonate and ethylcyanopropionate to quinone acetals

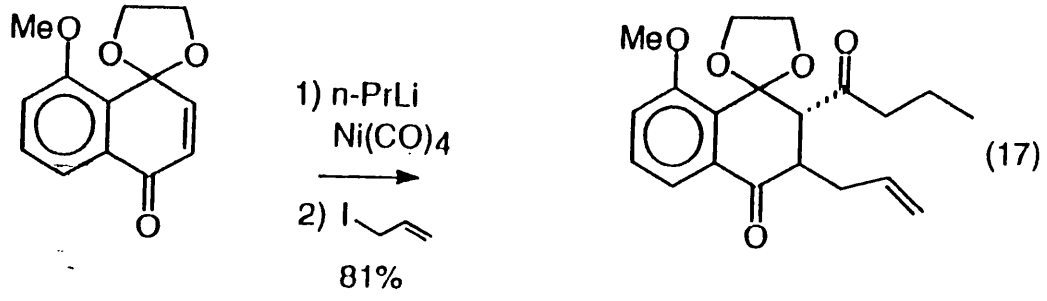
quinone monoacetal	conditions	1,4-adduct	aromatized product
 (1)	NaOEt EtOH	 (91%)	 (88%)
 (2)	NaOEt EtOH	 (83%)	
 (3)	NaH THF	 (70%)	 (86%)
 (4)	NaOEt EtOH	 (92%)	 (91%)

1,4-Additions to quinone monoacetals are not without limitation, especially when the addition involves the transfer of simple alkyl groups. Reaction of lithium dimethylcuprate with quinone monoacetal results in reduction of the quinone monoacetal to the corresponding phenol[22] (equation 16).



(16)

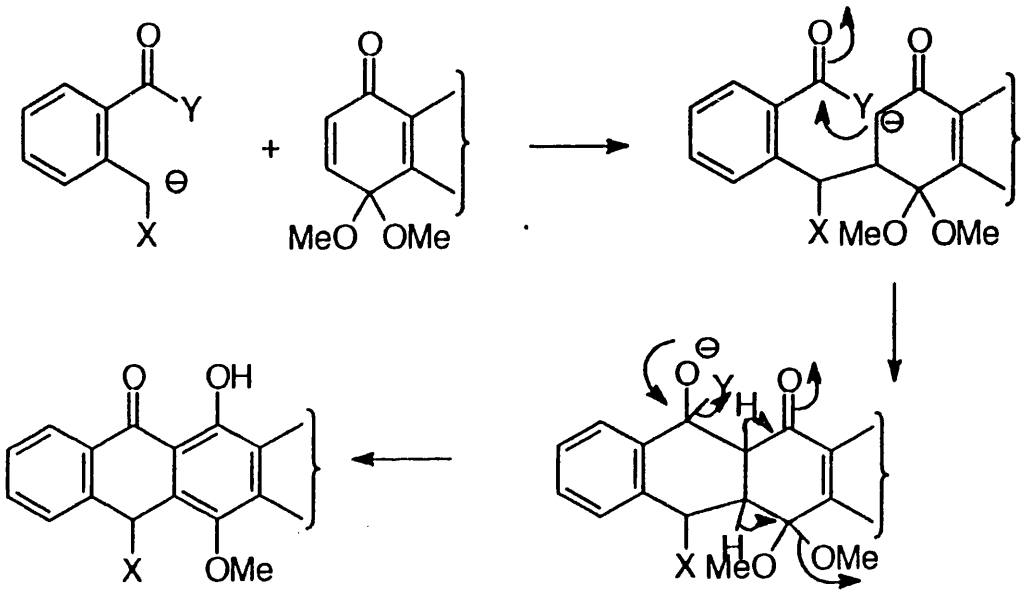
More successful 1,4-additions are addition of acyl nickel complexes of simple alkyllithium compounds to naphthoquinone monoketals [33] (equation 17).



(17)

1.3.4 Annelations of quinone monoacetals

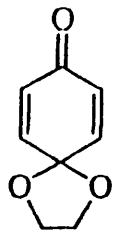
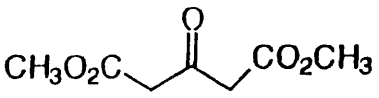
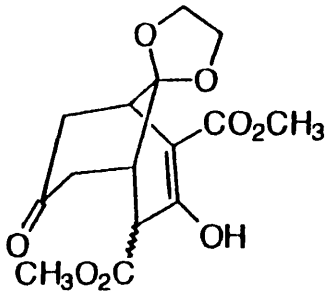
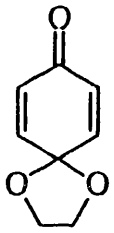
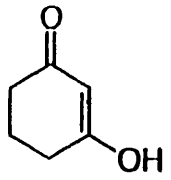
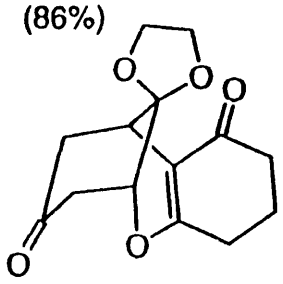
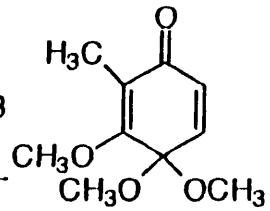
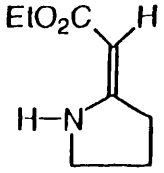
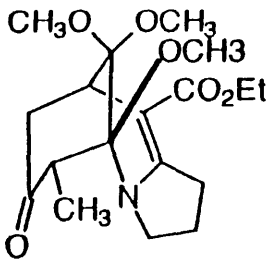
Quinone monoacetals are particularly useful for the regiospecific synthesis of polycyclic ring systems. Scheme 12 illustrates the general strategy for the utilization of quinone monoacetals in regiospecific annelation reactions.



Scheme 12

An active methylene compound may be reacted with quinone monoacetals to give β, β'-annelation products (Table 12).

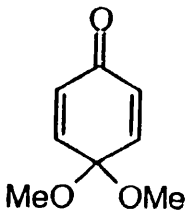
Table 12: β,β'-Annelation

exp	monoacetal	anion precursor conditions	product
1		 NaOEt ref. 34	 (86%)
2		 t-BuOK, t-BuOH ref. 35	 (85%)
3		 1) NaH 2) H_2O ref. 36	 (87%)

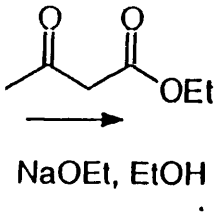
β,β'-Addition means that bimolecular nucleophilic addition to the β-carbon of the quinone monoacetal is followed by a second intramolecular addition to produce a bicyclo[3.3.1]ring system.

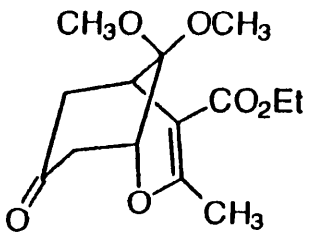
In reactions with unsymmetrically substituted quinone monoacetals, the product is formally derived from inital addition at the less hindered, more reactive β'-position (exp 3), followed by cyclization at the more substituted β -position.

An interesting dependence on reaction conditions can be noticed (Scheme 13) for the reactions of quinone monoacetals and ethyl acetoacetate [32].

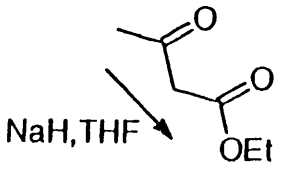


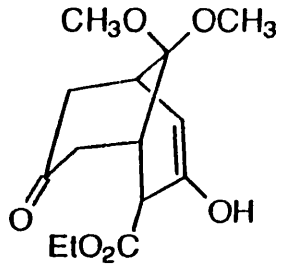
(**18**)





(**25**) (69%)





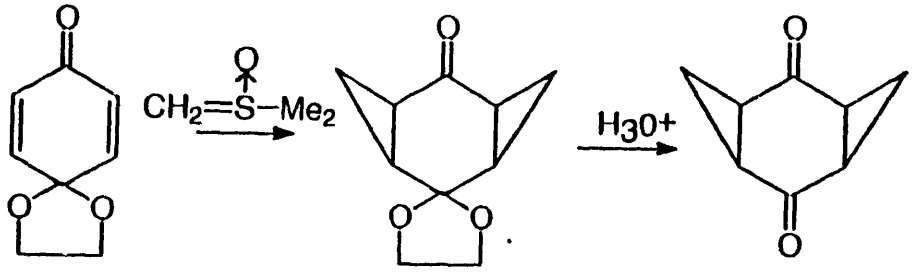
(**26**) (66%)

Scheme 13

Treatment of quinone monoacetal (**18**) with ethyl acetoacetate in ethanol containing a catalytic amount of sodium ethoxide affords product (**25**). The second step of the reaction involves bond formation between the oxygen of the ambient anion and the β'-carbon. Product (**26**) is derived from bonding of the carbon to the β'-position.

Annelation reactions can also occur *via* α,β -addition; which involves initial addition to the β -carbon, followed by intramolecular reaction of the nucleophilic center generated at the α-position with an electrophilic center.

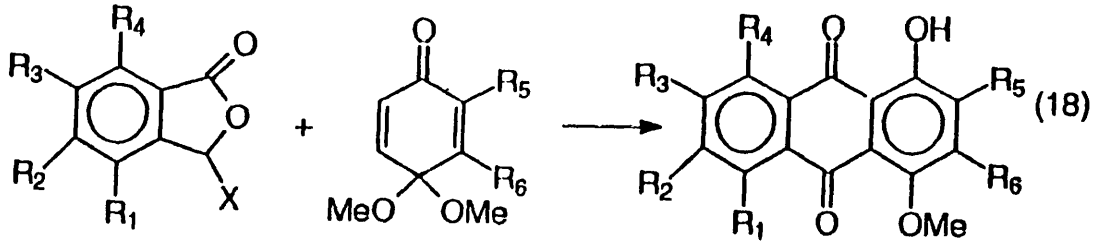
Thus (**27**) is reacted with excess of dimethylsulfoxonium methylide to give compound (**28**), which can be hydrolyzed to bishomoquinone (**29**)[37] (Scheme 14).



(**27**) (**28**) (**29**)

Scheme 14

Phthalide anion annelation of quinone monoacetals is a method for the preparation of a wide variety of anthraquinones [38] (equation 18).

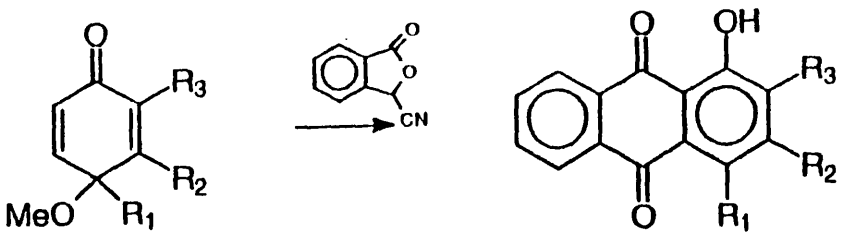


(18)

X=SO_2Ph or CN

The mild conditions and regiochemical integrity of this method makes it convenient way to prepare anthraquinones containing the 1,4-dioxygenated pattern.

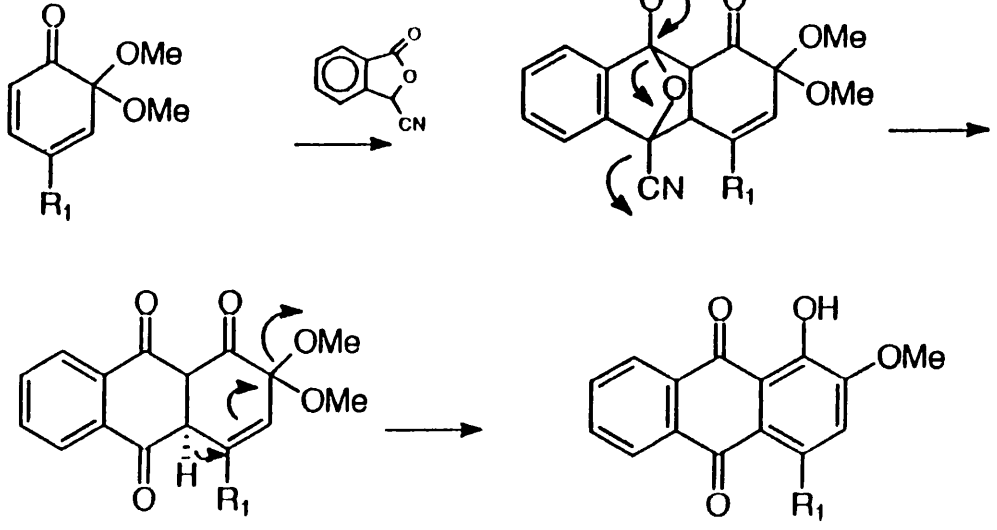
4-Alkyl or 4-aryl-4-methoxycyclohexadienones may be also annulated with the anion of 3-cyanophthalide (-78°C in THF) [39], to yield anthraquinones in high yield (equation 19).



(19)

a) R_1=Me, R_2=R_3=H
b) R_1=R_2=Me, R_3=H
c) R_1=R_3=Me, R_2=H
d) R_1=Ph, R_2=R_3=H
e) R_1=t-Bu, R_2=R_3=H

o-Quinone monoacetals also undergo annelation and presumably this involves 1,4-elimination of methanol from the intermediate (**30**) (Scheme 15).



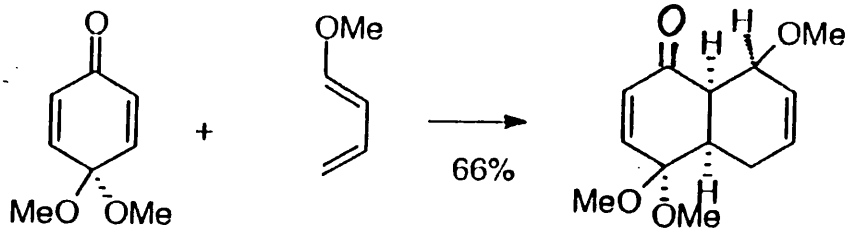
(30)

R_1=allyl, Me, t-Bu

Scheme 15

1.3.5 Diels-Alder reactions of quinone monoacetals

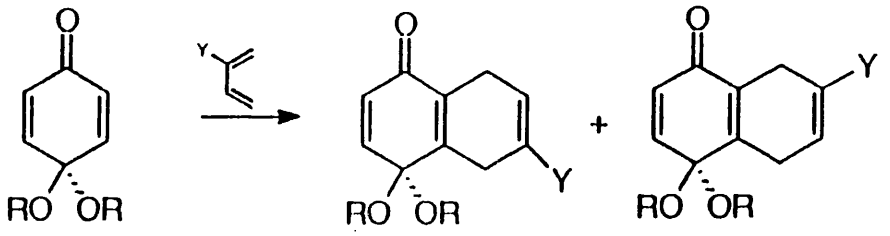
Quinone monoacetals undergo Diels-Alder reaction with 1-methoxy-butadiene, isoprene, and 2-methoxybutadiene [40]. Cycloaddition of 4,4-dimethoxycyclohexa-2,5-dienone and 1-methoxy-butadiene in benzene affords (**31**) (equation 20).



(20)

(**31**)

The reactions with 2-substituted dienes proceed more slowly than with 1-methoxybutadiene, and produce a mixture of regioisomers (equation 21).

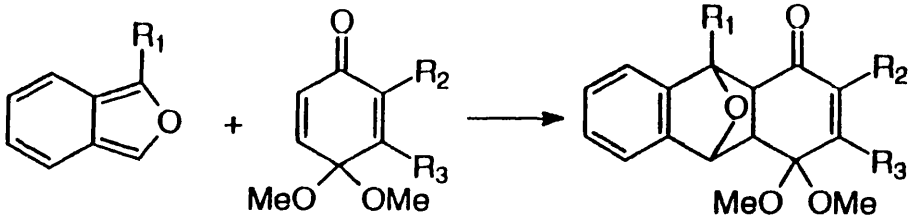


(21)

Table 13: Reactions with 2-substituted dienes according to eq. 21

	Y= OMe (T=130 °C)		Y=Me (T=140 °C)	
R	yield	isomer ratio	yield	isomer ratio
Me	55%	1:1	32%	1:1
Et	30%	1:1	36%	1:1

The cycloaddition reaction of 1-substituted isobenzofurans to quinone monoacetals is also highly regioselective and allow a facile entry into linear polycyclic ring systems [41]. In all cases the regioisomer with general structure, i.e. with the R_1-substituent of the isobenzofuran being in the same side of the molecule with the carbonyl group of the dienone, is obtained (equation 22).



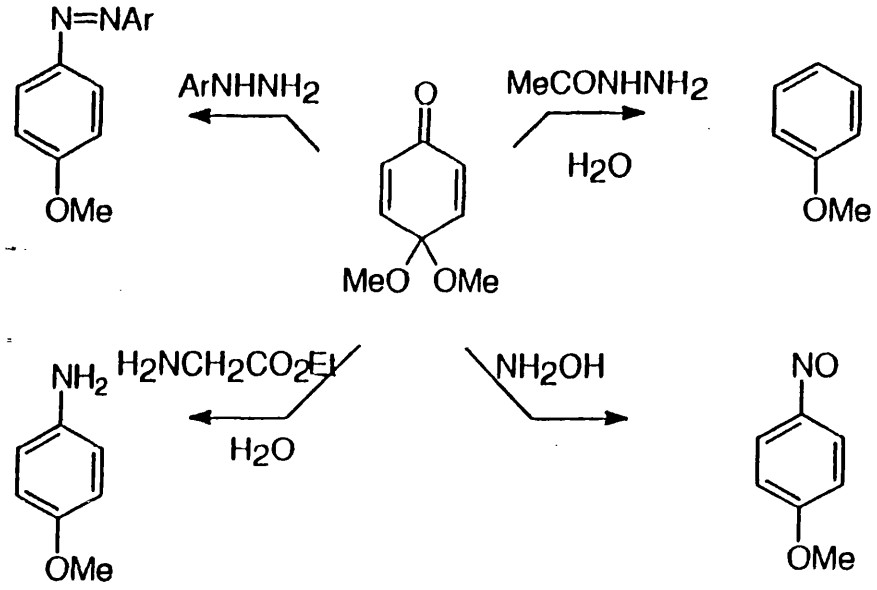
(22)

quantitive
(R_1=CH_3, R_2=R_3=H)

R_1=H,Me,OMe,$SiMe_3$,CH_2OH,CO_2Me
R_2=H,Me
R_3=H,Me,OMe

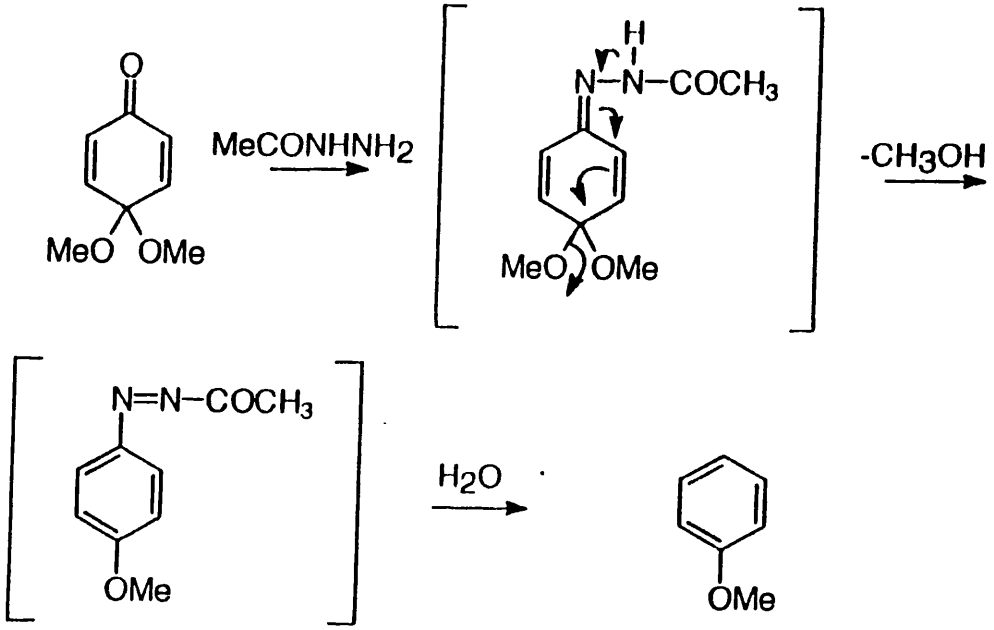
1.3.6 Reactions with ammonia derivatives

The carbonyl group of quinone monoacetal can be replaced by the nitroso, azo, amino groups, or a hydrogen atom with production of an aromatic system [42] (Scheme 16).



Scheme 16

Aryl hydrazines reacts with 4,4dimethoxycyclohexa-2,5-dienone giving 4-methoxyazobenzenes. When the aromatic group is phenyl, 4-methylphenyl or 2,4-dinitrophenyl, yields are good (90-98,5%). Reaction with acetylhydrazine followed by addition of water gives anisole, which can be isolated in 50% yield (Scheme 17).



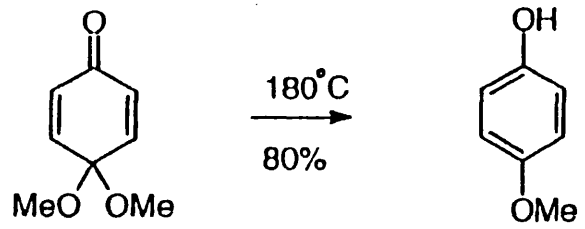
Scheme 17

The cyclohexadienone can also be converted to 4-methoxynitroso-benzene by reaction with hydroxylamine and to 4-methoxyaniline by reaction with ethyl glycinate followed by acid hydrolysis of the imine.

1.3.7 Thermal disproportionation reactions of quinone monoacetals

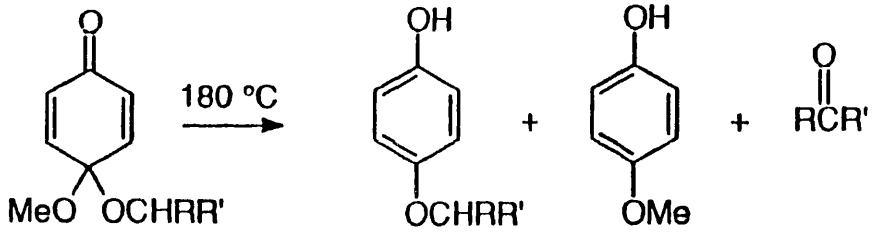
Quinone monoacetals can be easily reduced to phenols. We reported earlier electron transfer reductions by organocopper, alkyllithium and Grignard reagents. Similar results can be obtained by

thermolysis [43]. The major product isolated from thermolysis of (**18**) at 180 °C is 4-methoxyphenol (equation 23).



(18) (23)

When mixed monoacetals (**32**), are used, the reaction gives mixtures of phenols and aldehyde or ketone (equation 24).



(32) (24)

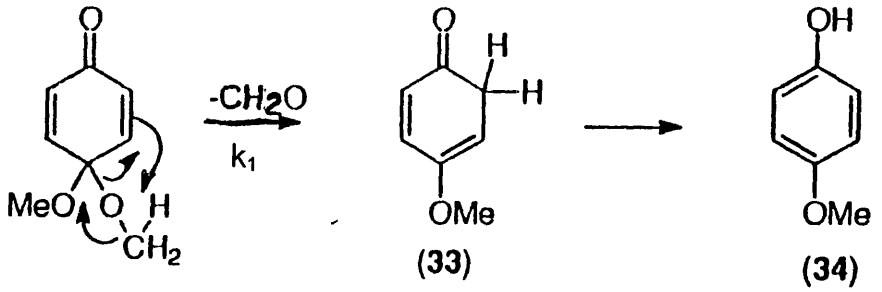
R=H, R'=Ph
R=H, R'=CH_3
R=R'=CH_3

There is two possible mechanistic pathways for the thermal disproportionation of 4,4-dimethoxycyclohexa-2,5-dienone (Scheme 18). Mechanism 1 could be viewed as an intramolecular retroheteroene reaction, which would produce (**33**) and then tautomerize to (**34**).

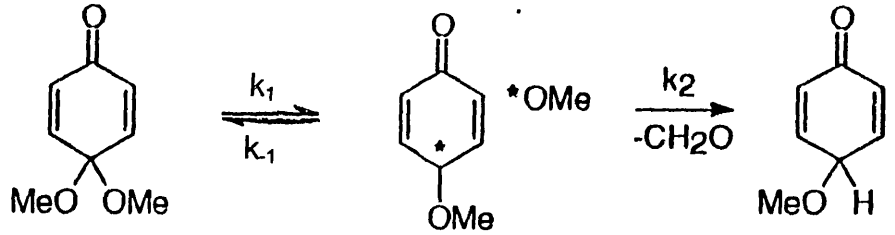
Mechanism 2 includes a stepwise process involving a dissociation and a hydrogen-transfer process. The cleavage would produce (**35**) as a charged or neutral species, which would lead to formation of (**36**) by

transfer of a hydrogen fom the methoxy moiety to the oxygen, the ortho carbon, or the para carbon of the ring (only the latter possibility is shown). Compound (**36**) would tautomerize to (**34**).

Mechanism 1:



Mechanism 2:

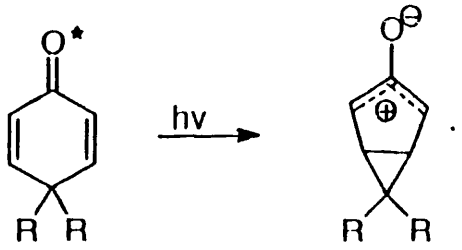


* either a radical, cation, or anion

Scheme 18

1.3.8 Photochemical rearrangements of quinone monoacetals

The rearrangement of cyclohexadienones is a classic photochemical conversion. The reactive excited state is believed to be the $n \rightarrow \pi^*$ triplet, which by β-bond formation and intersystem crossing leads to zwitterion (**37**) (equation 25)[44].

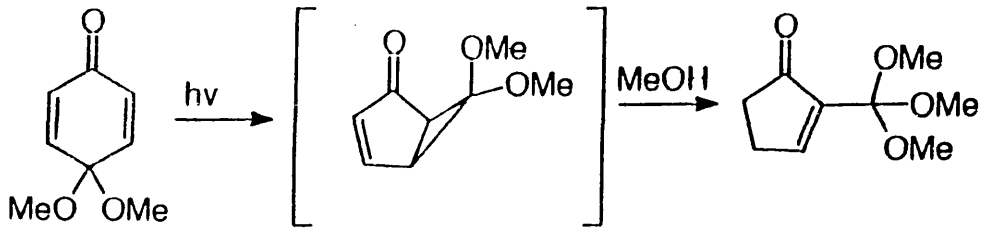


(25)

(**37**)

This intermediate may give either a bicyclo[3.1.0]hexenone or solvolysis products depending on reaction conditions.

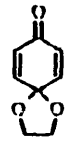
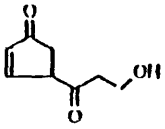
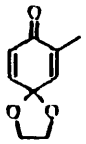
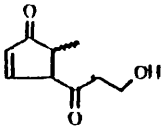
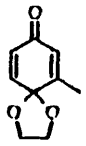
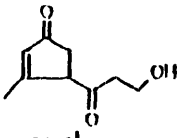
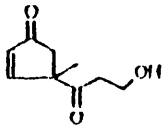
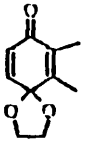
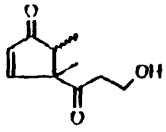
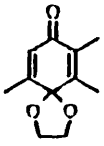
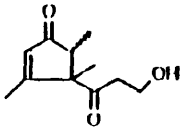
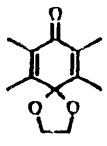
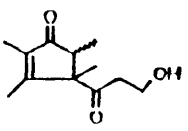
The photochemical rearrangement of 4,4-dimethoxycyclohexa-2,5-dienone (**18**) in methanol gives 2-(trimethoxymethyl)-2-cyclopentenone (**38**) in 75% yield (Scheme 19).



(**18**) **Scheme 19** (**38**)

The photorearrengements of quinone ethylene ketal are conducted at 50 mM concentration in glacial acetic acid through uranium glass with a 450 W Hanovia Source. Generally they give high yields and regioselectivity (Table 14).

Table 14: Photoarrengements of quinone ethylene ketals

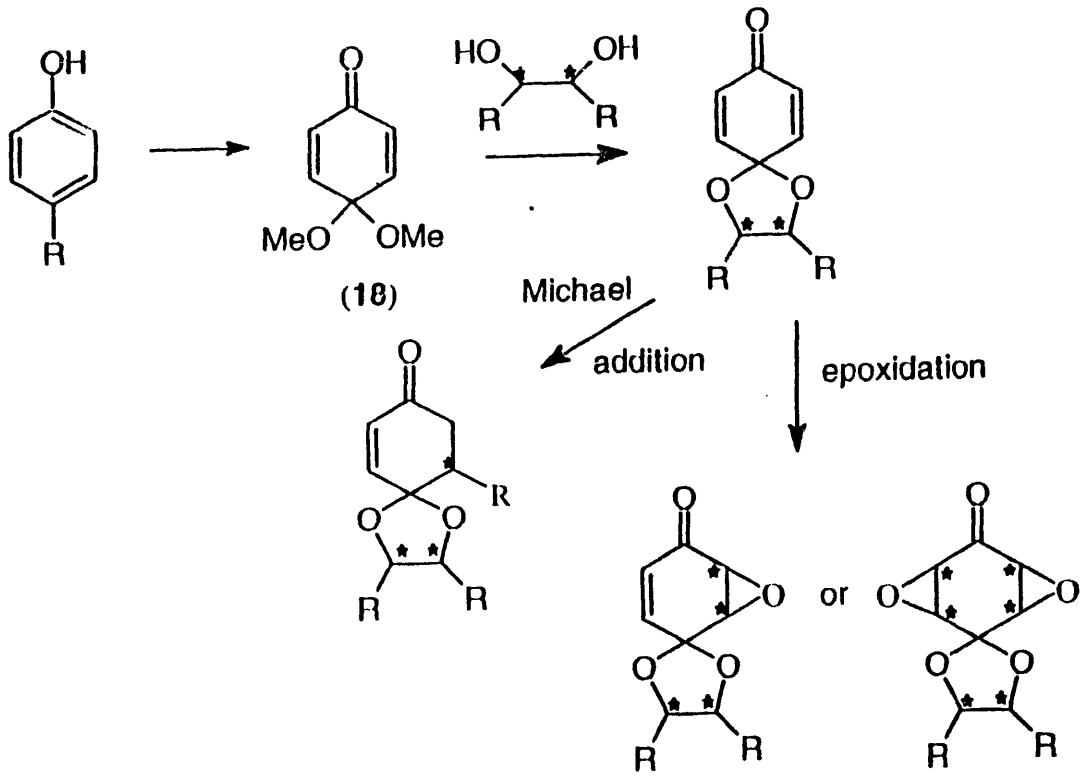
quinone ethylene ketal	product	yield
		82%
		79%
	 and	23%
		44%
		89%
		84%
		81%

The solvolysis of quinone ethylene ketal prevents the formation of a bicyclo[3.1.0]hexenone and enforces the location of the carboxyl group at the 4-position of the cyclopentenone (equation 26). Selective cleavage of bond b is contrary the precedents from bicyclic systems, where products which retain the more substituted enone double bond are favoured.

(26)

1.4 AIM OF THE PROJECT

The aim of our project was to synthesize chiral spirodienones from phenols by PIDA oxidation and then introduce two chiral centres by exchange reaction with diols. Michael additions to spirodienones were of major interest and epoxidation of double bond was an attractive method to introduce two or four extra chiral centres to the spirodienones.



Scheme 20

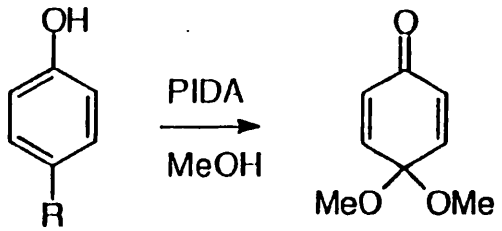
CHAPTER TWO

OXIDATION OF PHENOLS WITH PHENYLIODONIUM DIACETATE (PIDA)

2.1 INTRODUCTION

Preparation of quinone monoacetals by phenolic oxidation with PIDA is a known reaction [13], described in the first chapter.

In this chapter PIDA-oxidation of *p*-methoxyphenol, phenol, and *p*-bromophenol in methanol to give 4,4-dimethoxycyclohexa-2,5-dienone (**18**) is discussed (equation 27).



(18)

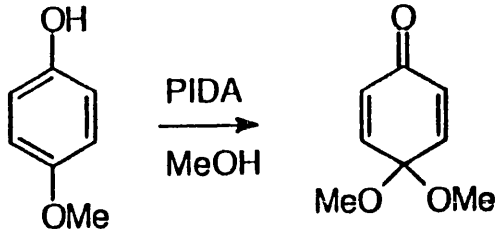
R=MeO, H, Br

(27)

At the end of the chapter attempted preparation of chiral spirodienones using PIDA in the presence of 1,2-diols are presented.

2.2 THE OXIDATION OF *p*-METHOXYPHENOL

Studies of PIDA-oxidations were started with *p*-methoxyphenol, which gave 4,4-dimethoxycyclohexa-2,5-dienone (**18**) in 99% yield (equation 28). The reaction was done in methanol using one equivalent of PIDA at room temperature.

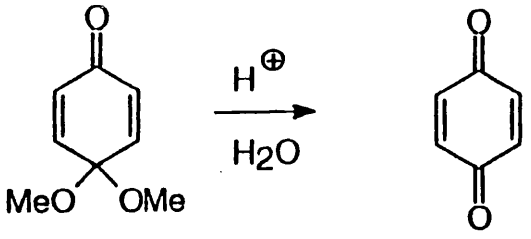


(28)

(18)

The product was isolated from the side products; iodobenzene and acetic acid, by column chromatography. It was necessary to use neutral silica gel on the column, because the use of un-neutralized silica or even neutral alumina produced *p*-benzoquinone. The neutral silica was prepared by washing with base, neutralizing with buffer solution and water, and washing with methanol and drying.

Furthermore, the isolation was done immediately after the reaction, otherwise the presence of acetic acid and air humidity produced *p*-benzoquinone (equation 29).



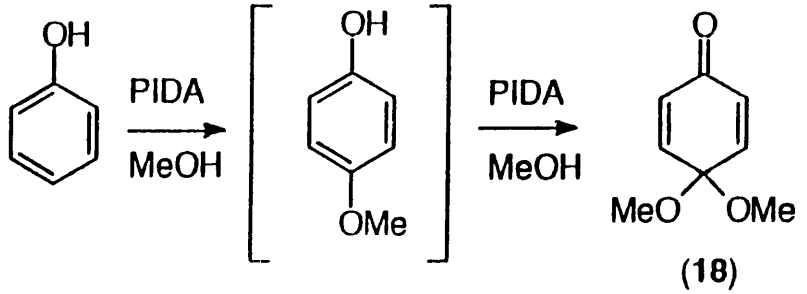
(29)

(18)

The product (**18**) is sensitive for light [44] and therefore it should be stored under nitrogen in the dark.

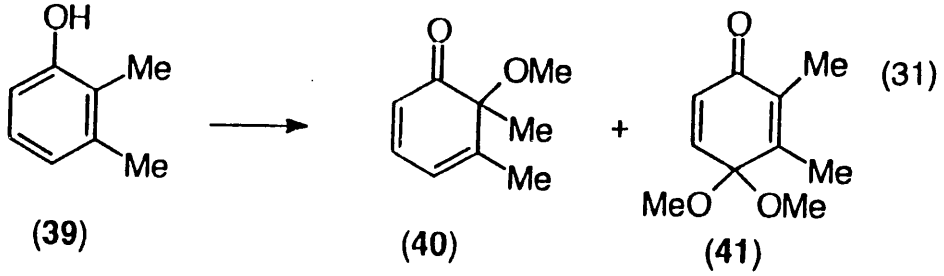
2.3 THE OXIDATION OF PHENOL

Two equivalents of PIDA were used in the oxidation of phenol to (**18**). This showed that direct conversion of *p*-unsubstituted phenols to quinone monoacetals is possible by using two equivalents of PIDA. Even that an *o*-position of phenol was unsubstituted, the reaction resulted in *p*-substitution (equation 30)



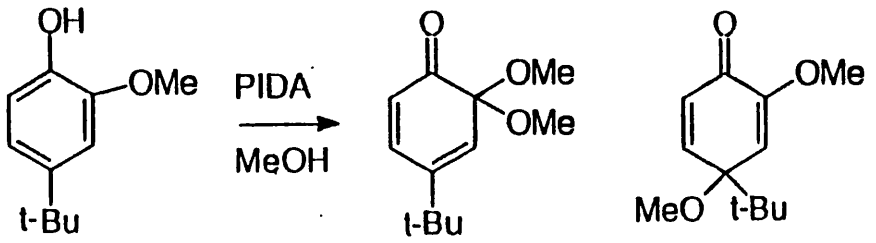
(18) (30)

Mitchell and Russell [39] reported that 2,3-dimethylphenol (**39**) oxidises with two equivalents of PIDA to afford a 1:4 mixture of dienones (**40**) and (**41**) (equation 31).



(39) (40) (41) (31)

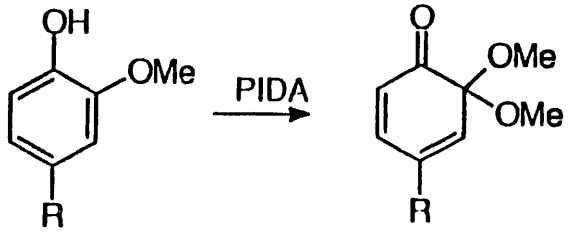
Both *o*- and *p*-substitution occurs when 1.5 equivalent of PIDA is used to oxidize *p*-t-butylphenol. Dienones (**42**) and (**43**) are obtained in 43% and 55% yield respectively (equation 32).



(32)

(42) **(43)**

Pure *o*-quinone monoacetals are afforded by oxidation of eugenol (**44**) and creosol (**45**) with one equivalent of PIDA (equation 33).



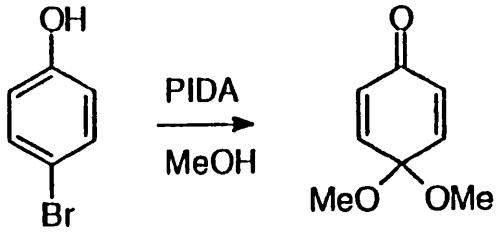
(33)

R=Allyl (**44**)

=Me (**45**)

2.4 THE OXIDATION OF *p*-BROMOPHENOL

We expected that as the bromo-group is a good leaving group, 4-bromophenol would require one equivalent of PIDA for oxidation followed by methanolysis to give 4,4-dimethoxycyclohexa-2,5-dienone (**18**). After 40 minutes reaction time HPLC showed that (**18**) was obtained in low yield (12%) (equation 34).

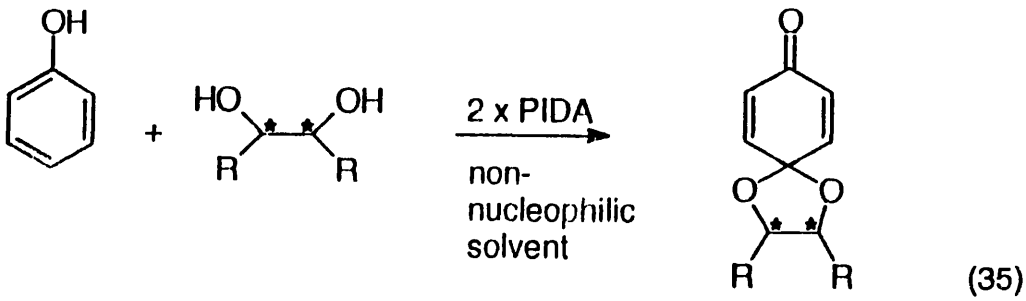


(18) (34)

When the reaction mixture was purified by column chromatography three compounds were isolated. The unreacted starting material was recovered in 52% yield. NMR spectra of two other compounds showed several peaks of methoxide group and mass specrta showed high molecular weight of compounds. This evidence support the theory that polymerization has occured.

2.5 ATTEMPTED DIRECT PREPARATION OF CHIRAL SPIRODIENONES FROM PHENOL

Chapter three describes the convertion of 4,4-dimethoxycyclohexa-2,5-dienone (**18**) into cyclic ketal using 1,2-diols. We first attempted to use one step process to produce cyclic ketals from phenol and 1,2-diol in non-nucleophilic solvent such as acetonitrile, dichloromethane, and 2,2,2-trifluoroethanol (equation 35).



(35)

The reaction was done using two equivalents of PIDA at room temperature and diethyltartrate, hydrobenzoin, and butanediol, as 1,2-diols. Unfortunately, PIDA cleaved 1,2-diols to aldehydes more rapidly than the desired reaction occured and therefore the method did not afford cyclic ketals.

2.6 CONCLUSION

Phenolic oxidation with phenyliodonium diacetate (PIDA) is an efficient way to prepare quinone monoacetals. Oxidation of *p*-methoxy-phenol and phenol under mild conditions gave 4,4-dimethoxycyclo-hexa-2,5-dienone in good to excellent yield. The reaction with *p*-bromophenol gave 4,4-dimethoxycyclohexa-2,5-dienone in lower yield (12%) and a lot of starting material (52%) was recovered.

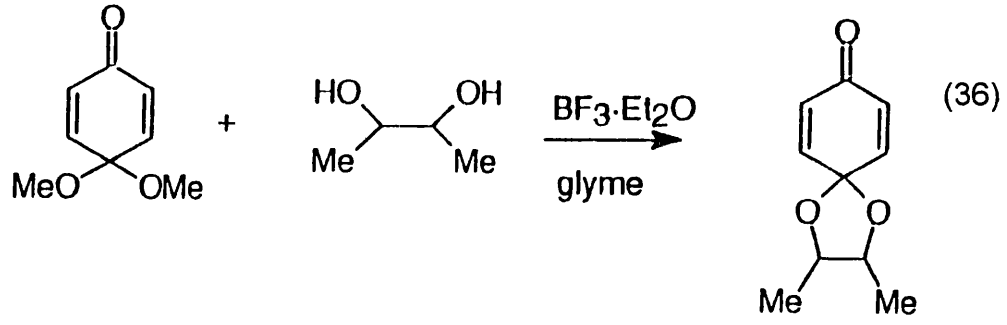
Unfortunately, direct conversion of phenol into chiral spirodienone was unsuccessful. PIDA rapidly oxidised diols to aldehydes and therefore the addition did not occur.

CHAPTER THREE

CONVERSION OF ACHIRAL TO CHIRAL SPIRODIENONES

3.1 INTRODUCTION

Exchange reactions of quinone monoacetals to chiral spirodienones were discussed in chapter one. Pirrung and Nunn's work [26] was repeated using 4,4-dimethoxycyclohexa-2,5-dienone (**18**) and 2,3-butanediol under the influence of BF_3·etherate in glyme (equation 36).



(36)

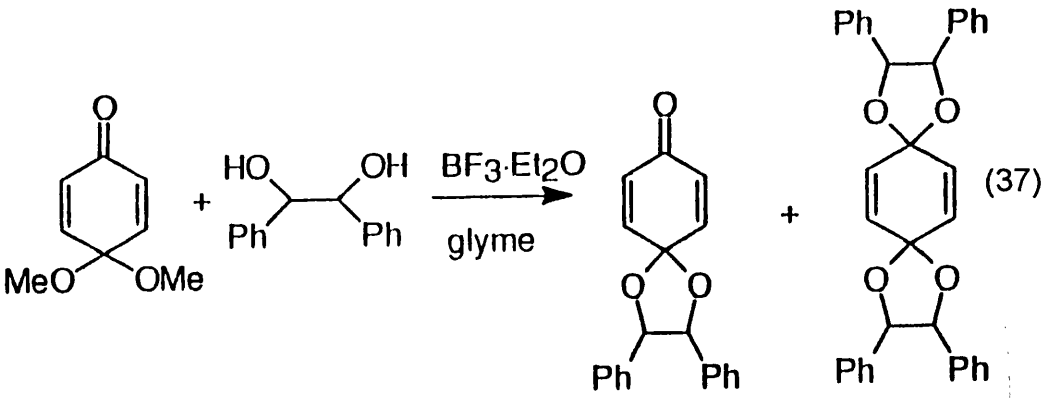
In addition, another diol, hydrobenzoin, was reacted with the quinone monoacetal. The reaction was successful under the same conditions. The exchange reaction was also tried with (±)-ephedrine and diethyl tartrate, but unfortunately exchange did not occur.

3.2 2,3-BUTANEDIOL EXCHANGE

Best results were obtained by dropwise addition of a slight excess (2.2 equiv.) of BF_3·etherate in glyme. *Meso*- and (±)-2,3-butanediol were used and the results were similar; the *meso* compound gave 43% yield and 38% yield was obtained in the case of (±)-diol.

3.3 HYDROBENZOIN EXCHANGE

The exchange reaction with hydrobenzoin had a competitive reaction; the diol also attacked the carbonyl carbon of the dienone (equation 37).



(37)

Monoketal and *bis*ketal were formed in a ratio of 2.3:1, which explains why the yields of monoketal were rather low. The yields were changing from 36% to 76% depending on the stereochemistry of hydrobenzoin (Table 15).

Table 15: hydrobenzoin exchange

hydrobenzoin	yield of monoketal
meso	43%
(±)	76%
(S,S)	36%

Both mono- and bisketal were obtained after purification by column chromatography, which gave pale yellow crystals (monoketal) and white crystals (bisketal). The bisketal is a symmetrical molecule which does not have optical rotation (Figure 1).

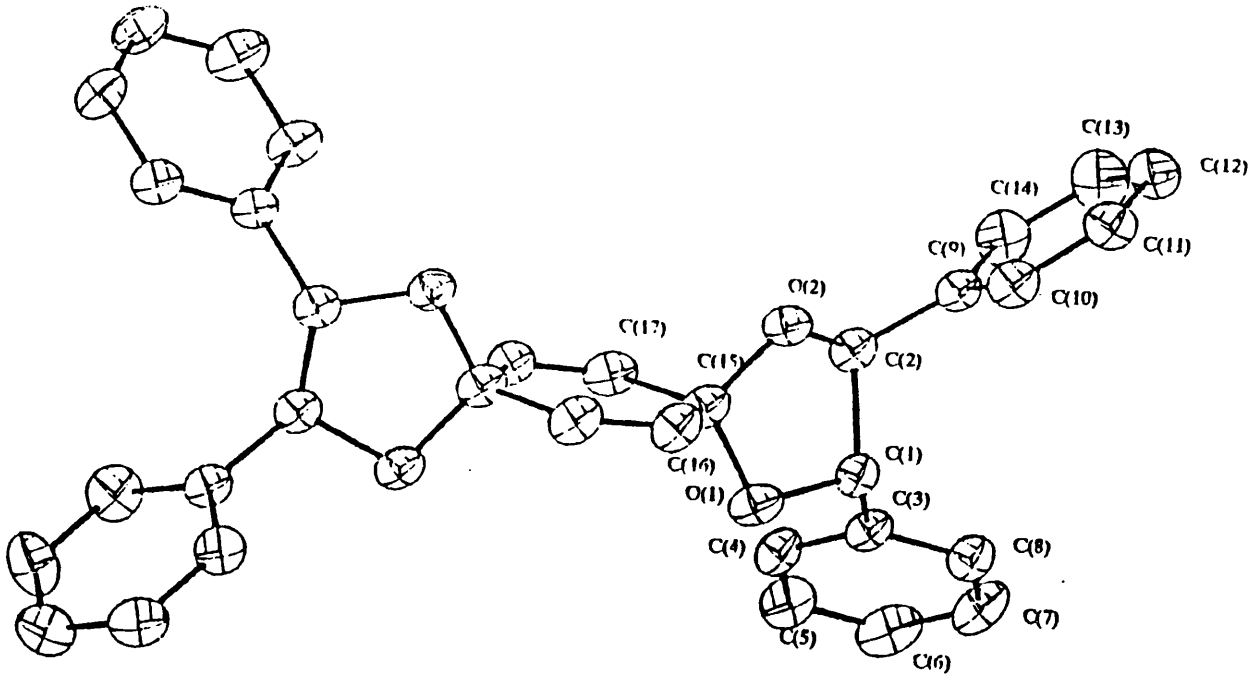


Figure 1

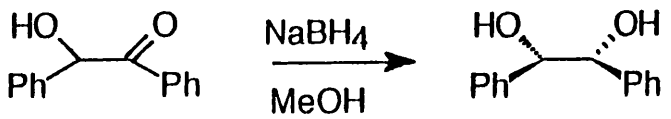
Hydrobenzoins are commercially available but rather expensive compounds, and thus we decided to prepare them ourselves. When benzoin was reduced by sodiumboro hydride, *meso*-hydrobenzoin was obtained, whereas (S,S)-hydrobenzoin was produced by oxidation of *trans*- stilbene with AD-mix-α [45].

We found that the best condition for the exchange reaction was dropwise addition of BF_3·etherate at -15 °C.

Because the bisketal was produced, milder Lewis acids than BF_3·etherate were tried. Use of zinc bromide, zinc chloride, or dimethylaluminium chloride did not produce chiral spirodienone. After one weeks' reaction time only a small amount of *p*-benzoquinone and unreacted starting material was obtained.

3.3.1 Preparation of *meso*-hydrobenzoin

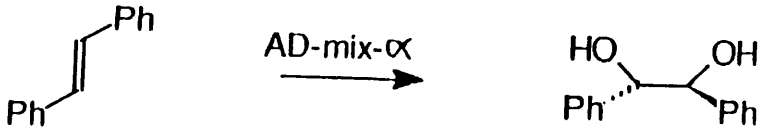
Benzoin was reduced by sodium borohydride in methanol at 0 °C to give *meso*-hydrobenzoin in good yield (70%) (equation 38).



(38)

3.3.2 Preparation of (*S,S*)-hydrobenzoin

(*S,S*)-Hydrobenzoin was prepared from *trans*-stilbene by osmium tetraoxide catalyzed asymmetric dihydroxylation [45] (equation 39).



(39)

AD-mix-α gives the *S,S*-configuration with > 99.5% ee. AD-mix-α is a commercially available mixture of potassium osmate ($K_2OsO_2(OH)_4$), $(DHQ)_2$-PHAL-ligand, $K_3Fe(CN)_6$, and K_2CO_3.

The mechanism for the oxidation [46] is explained in that first OsO_4 (or equivalently $K_2OsO_2(OH)_4$) reacts with the ligand and olefin to give (**46**) (Figure 2). This monoglycolate ester is then hydrolyzed, which releases the diol and the ligand to the organic phase while the resulting Os(VI) species finds its way into the aqueous phase as $OsO_2(OH)_4^{2-}$ (**47**). The oxidation of $OsO_2(OH)_4^{2-}$ by $Fe(CN)_6^{3-}$ regenerates OsO_4 which then migrates back to the organic phase. This transformation from $OsO_2(OH)_4^{2-}$ to OsO_4 may proceed via the Os(VIII) species $OsO_4(OH)_2^{2-}$ (**48**), which is consistent with the observed necessity of both K_2CO_3 and $K_3Fe(CN)_6$ for the second osmium migration.

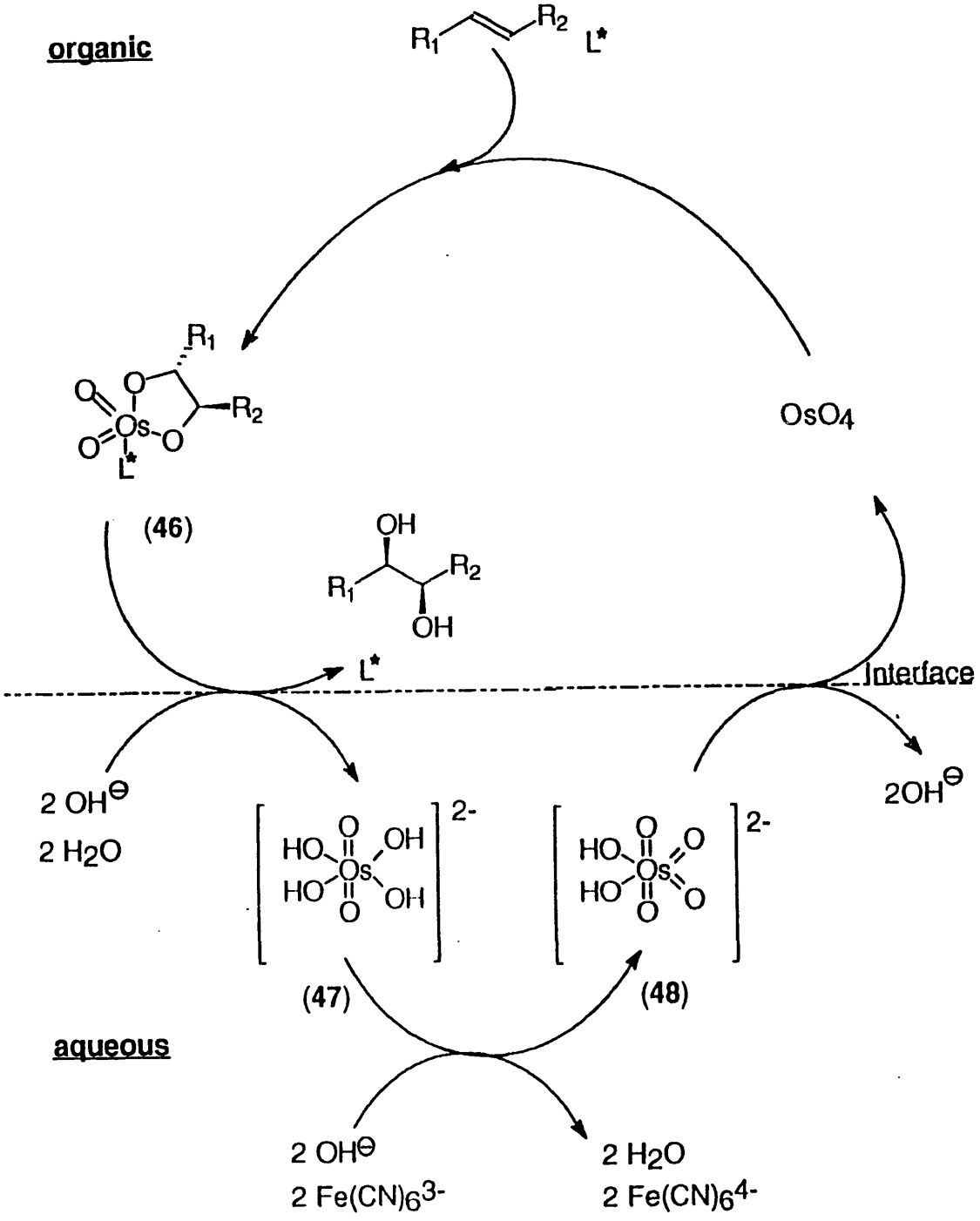

organic
R1
R2
L*
OsO4
(46)
OH
R1
R2
OH
L*
Interface
2 OH⊖
2 H2O
2OH⊖
HO
OH
Os
HO
OH
O
2-
(47)
(48)
aqueous
2 OH⊖
2 Fe(CN)6 3-
2 H2O
2 Fe(CN)6 4-

Figure 2

3.4 CONCLUSION

The conversion of quinone monoacetal to chiral spirodienone gave the best results when two equivalents of BF_3·etherate in glyme at room temperature (in the case of 2,3-butanediol) or -15 °C (in the case of hydrobenzoin) were used.

Use of hydrobenzoin gave also the *bis*-product. Milder Lewis acids such as zinc bromide, zinc chloride, and dimethyl aluminium chloride were used to try to avoid the bis product. Unfortunately, these Lewis acids did not lead the reaction to the corresponding chiral spirodienones.

CHAPTER FOUR

ADDITION AND EPOXIDATION TO QUINONE MONOACETAL

4.1 INTRODUCTION

In chapter one the reactions of quinone monoacetals were discussed and in this chapter we describe our studies with them. We were interested in Michael addition of diethyl malonate which can introduce one or two chiral centres to quinone monoacetals.

Conjugate addition using cuprates were also a part of our studies, but unfortunately the cuprates reduced quinone monoacetals to the corresponding phenols and the attempted adduct was obtained in very low yields or not at all.

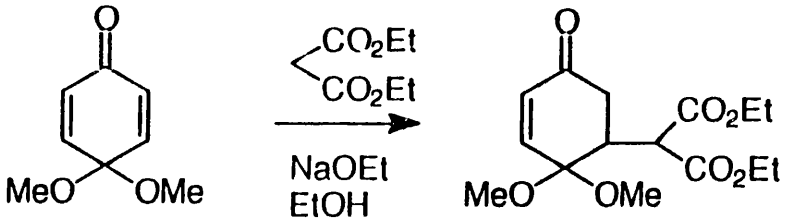
The epoxidation of quinone monoacetal is not a reported reaction in the literature. We chose to investigate the epoxidation by alkaline peroxides or dimethyldioxirane, which have been used for the epoxidation of α,β-unsaturated ketones.

4.2 ADDITION REACTION TO QUINONE MONOACETAL

4.2.1 Michael addition of diethyl malonate to quinone monoacetal

4.2.1.1 Introduction

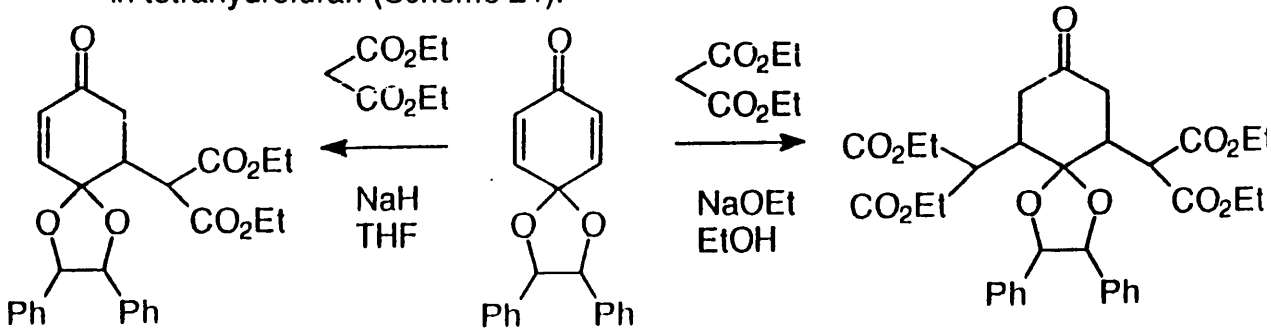
It was reported [32] that the addition of the sodium enolate of diethyl malonate to 4,4-dimethoxycyclohexa-2,5-dienone (**18**) gave monoadduct (**49**) in good yield (equation 40).



(40)

(**18**) (**49**)

However, in our hands the addition of diethyl malonate to chiral spirodienone (**51**) gave also the diadduct (**52**). We were able to control the reaction using either sodium ethoxide in ethanol or sodium hydride in tetrahydrofuran (Scheme 21).



(**50**) (major) **Scheme 21** (**51**) (**52**)

4.2.1.2 Addition of diethyl malonate to 4,4-dimethoxy-cyclohexa-2,5-dienone (18)

The addition of a catalytic amount (0.1 equiv) of sodium ethoxide and diethyl malonate in ethanol to (**18**) gave a monoadduct product (**49**) in 69% yield.

Sodium ethoxide, which was used for the preparation of the sodium enolate of diethyl malonate, was prepared from sodium and dry ethanol. It was estimated by titration with HCl, which showed that 0.076 M solution of sodium ethoxide was produced.

4.2.1.3 Addition of diethyl malonate to chiral spirodienone (51)

The addition of diethyl malonate to chiral spirodienone (**51**) was carried out using one, two, or three equiv of diethyl malonate either with sodium ethoxide in ethanol or with sodium hydride in tetrahydrofuran. The results are presented in Table 16. The treatment of chiral spirodienone with one equiv of diethyl malonate in ethanol containing 0.1 equiv of sodium ethoxide gave a mixture of mono and diadduct in ratio 1:3.4 (Table 16, experiment 1). The monoadduct (**50**) was obtained in 10% yield (50% de.)

The major product was diadduct (**52**) with 34% yield and its NMR spectrum showed four diastereoisomers.

Table 16: the addition of diethyl malonate to chiral spirodienone

Exp.	diethyl-malonate	conditions	adduct mono : di
1	1 equiv	NaOEt / EtOH	1 : 3.4
2	2 equiv	NaOEt / EtOH	0 : 100
3	1 equiv	NaH / THF	4 : 1
4	3 equiv	NaH / THF	0 : 100

When two equiv of diethyl malonate were used in the same conditions only diadduct (**52**) was obtained in 65% yield (Table 16, experiment 2). In this case NMR showed only two diastereoisomers in the ratio 1:1.7.

The monoadduct (**50**) was the major product when chiral spirodienone (**51**) was added to the diethyl malonate and one equiv of sodium hydride in anhydrous tetrahydrofuran (Table 16, experiment 3). The monoadduct was obtained in 35% yield (de>93%).

The reaction was repeated in the same conditions using three equiv of diethyl malonate which afforded only the diadduct (**52**) in 27% yield (Table 16, experiment 4).The NMR spectrum of the product showed two diastereoisomers in ratio 2.2:1.

4.2.1.4 Conclusion

Michael addition of diethyl malonate to chiral spirodienone (**51**) can be carried out in two different ways;

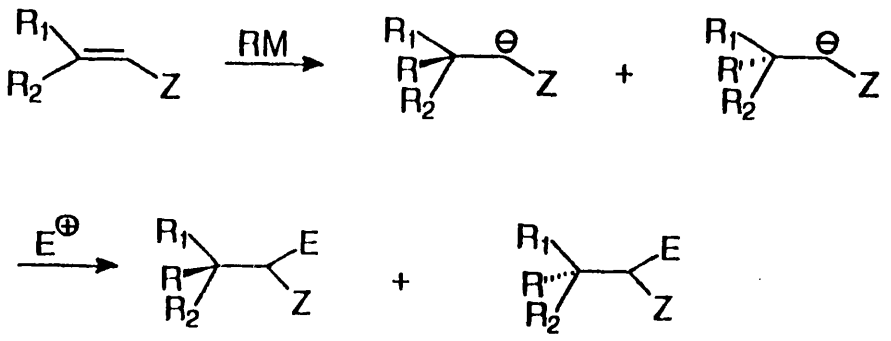
i) using sodium ethoxide in ethanol, which leads mainly to diadduct (**52**), which is the mixture of two diastereoisomers, or

ii) using sodium hydride in tetrahydrofuran which gives monoadduct (**50**) (de.>93%) when using one equiv of diethyl malonate or diadduct when excess of diethyl malonate is used

4.2.2 Conjugate addition with organocuprates

4.2.2.1 Introduction

Conjugate addition of organometallic reagents to α,β-unsaturated organic substrates is a highly useful reaction as a basic strategy for organic synthesis (Scheme 22).



Scheme 22

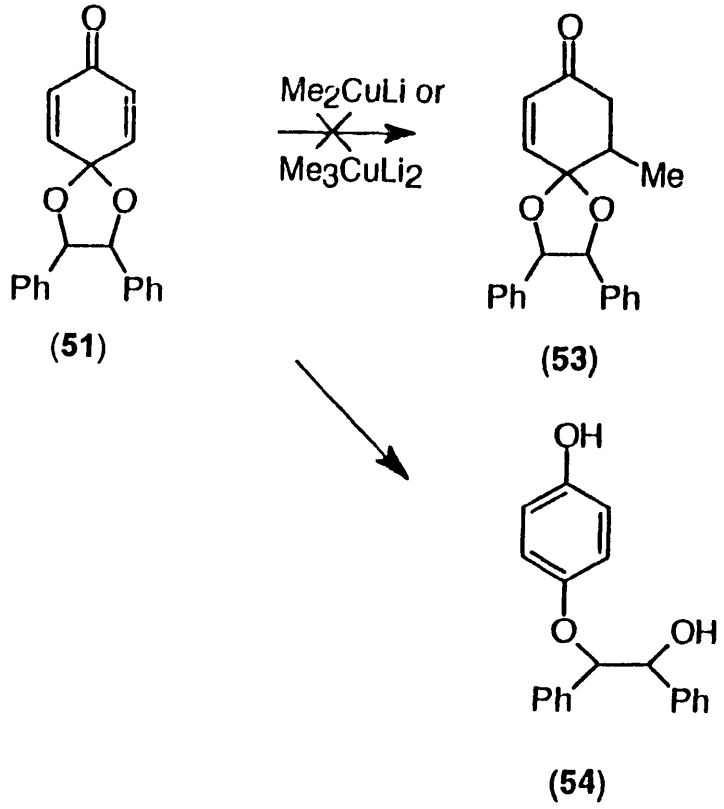
The most common organometallic reagents for conjugate additions are Grignard and cuprates.

Our studies of conjugate additions to chiral spirodienone (**51**) have been concentrated on copper reagents such as lithium organocuprates, cyanocuprates, mixed cyanocuprates, and Grignard reagents in the presence of copper salts.

4.2.2.2 Attempted conjugate addition with the Gilman reagent

Our studies of conjugate addition were started by using Gilman reagents such as lithium dimethylcuprate which undergo conjugate addition with α,β-unsaturated ketones, whereas methyl magnesium derivatives undergo 1,2-addition [47].

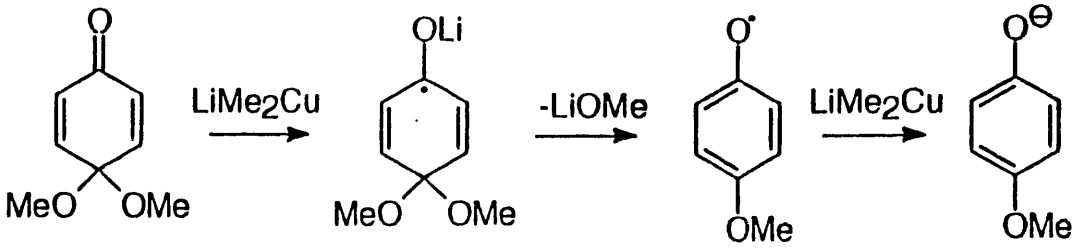
Our attempted conjugate addition with Gilman reagents (Me_2CuLi and Me_3CuLi_2) did not give desired adduct (**53**). Instead, reduction took place and the phenol (**54**) was obtained (Scheme 23).



(**51**) (**53**) (**54**)

Scheme 23

Nilsson and Ronlan [22] also reported that attempted conjugate addition with lithium dimethylcopper did not afford the expected 1,4-addition product, instead reduction occured. They suggested that the initial step in the reaction of the lithium dimethylcopper reagent with α,β-unsaturated ketones is an electron transfer to give the radical anion (**55**) of the ketone (Scheme 24). The radical anion (**55**) presumably eliminates lithium methoxide with formation of the phenoxy radical (**56**) which by further reduction affords the phenoxide ion (**57**).



(**55**) (**56**) (**57**)

Scheme 24

The Gilman reagent was prepared from methyl lithium and a solution of $Me_2S{\cdot}CuBr$-complex in dimethyl sulfide and ether [48]. $Me_2S{\cdot}CuBr$-complex was used to avoid side reactions resulting from the presence of Cu(II)compounds and the other metal salt impurities in CuBr.

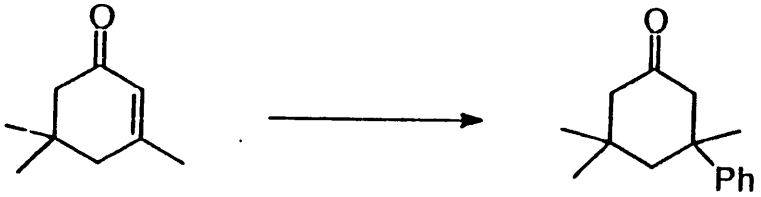
4.2.2.3 Cyanocuprate reagents

Lipshutz's [49] suggested that the addition of 3 molecular equiv of the organolithium compound to copper(I)iodide (3RLi+CuI), irrespective of solvent, affords only lower order Gilman reagents, R_2CuLi and free RLi, rather than a new higher order species, R_3CuLi_2.

Higher order cuprates, represented by the general formula $R_2Cu(CN)Li_2$, are readily prepared from copper cyanide and two equiv of an organolithium. Only one equiv of an organolithium is used for lower order cyanocuprates.

Our studies showed that both lower and higher order cyanocuprates only reduced chiral spirodienone (**51**) to the corresponding phenol (**54**) .

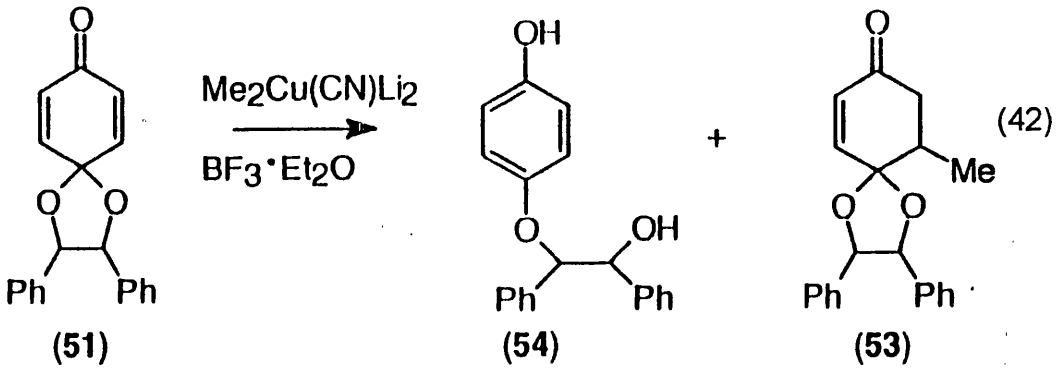
It has been reported that the effect of Lewis acid, BF_3·etherate, on higher order cyanocuprate reactions with enones is significantly positive as equation 41 shows [49]. By contrast the yields obtained with corresponding lower order cyanocuprates, $RCu(CN)Li + BF_3{\cdot}Et_2O$, tended to be 30-40% lower under otherwise identical conditions.



(41)

$PhCu(CN)Li$	0%
$Ph_2Cu(CN)Li_2$	0%
$BF_3{\cdot}Et_2O + Ph_2Cu(CN)Li_2$	>95%

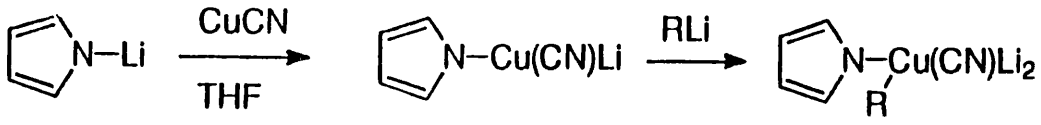
We decided to study the reaction of chiral spirodienone (**51**) with higher order cyanocuprate, $Me_2Cu(CN)Li_2$, in the presence of BF_3-etherate. The reaction gave the mainly reduced product and a small amount (6%) of the required product (**53**) (equation 42).



(51) (54) (53)

4.2.2.4 Mixed cyanocuprate from pyrrole

Treatment of N-lithiopyrrole [50] with CuCN followed by an organolithium leads to $R(Pyrr)Cu(CN)Li_2$ which shows "higher order" reactivity relative to $RCu(CN)Li$ (Scheme 25).



Scheme 25

When combined with CuCN and an RLi of one's choosing the equilibrium is established favoring the release of the pyrrolide ligand from the metal. The greater reactivity of the higher order portion of the

mixture can result in enhanced rates of reactions and improved yields of products compared to couplings based on lower order cyanocuprates RCu(CN)Li.

Unfortunately, after the reaction with $Me(Pyrr)Cu(CN)Li_2$ only reduced and unreacted starting material were obtained.

4.2.2.5 Reactions of Grignard reagents in the presence of CuBr

Grignard reagent / cuprous bromide system in THF / Me_2S has been reported by Hruby *et al.* to be an excellent method for conjugate additions [51].

This method was used for attempted conjugate addition to chiral spirodienone (**51**). Slow addition of the organocopper reagent to the chiral spirodienone at -40 °C produced four compounds as shown by TLC. After purification by column chromatography four different fractions were isolated. One was unreacted starting material (15%), another was reduced starting material (20%), and the two other fractions were unidentified. HPLC showed that both unidentified fractions were a mixture of several products, and thus the purification of those fractions was unsuccessful.

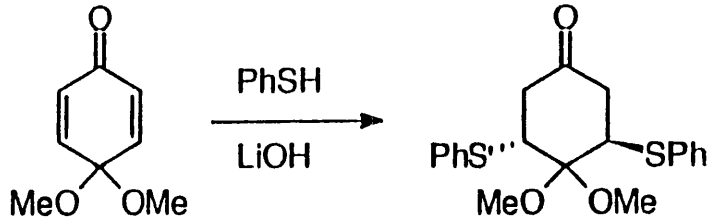
4.2.2.6 Conclusion

Attempted conjugate addition to chiral spirodienone (**51**) resulted in its reduction and the corresponding phenol (**54**) was obtained.

However, when the carbonyl group was activated by Lewis acid and "higher order" cyanocuprate was used, some 1,4-addition occured and the desired product (**53**) was isolated in low yield (6%). The main product was still the reduced phenol (**54**).

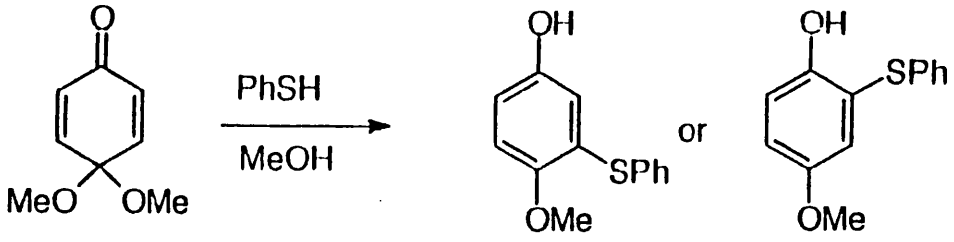
4.2.3 Addition of thiophenol

Thiophenol reacts in basic conditions with quinone monoacetal to give the *bis*-Michael adduct (equation 43) [31].



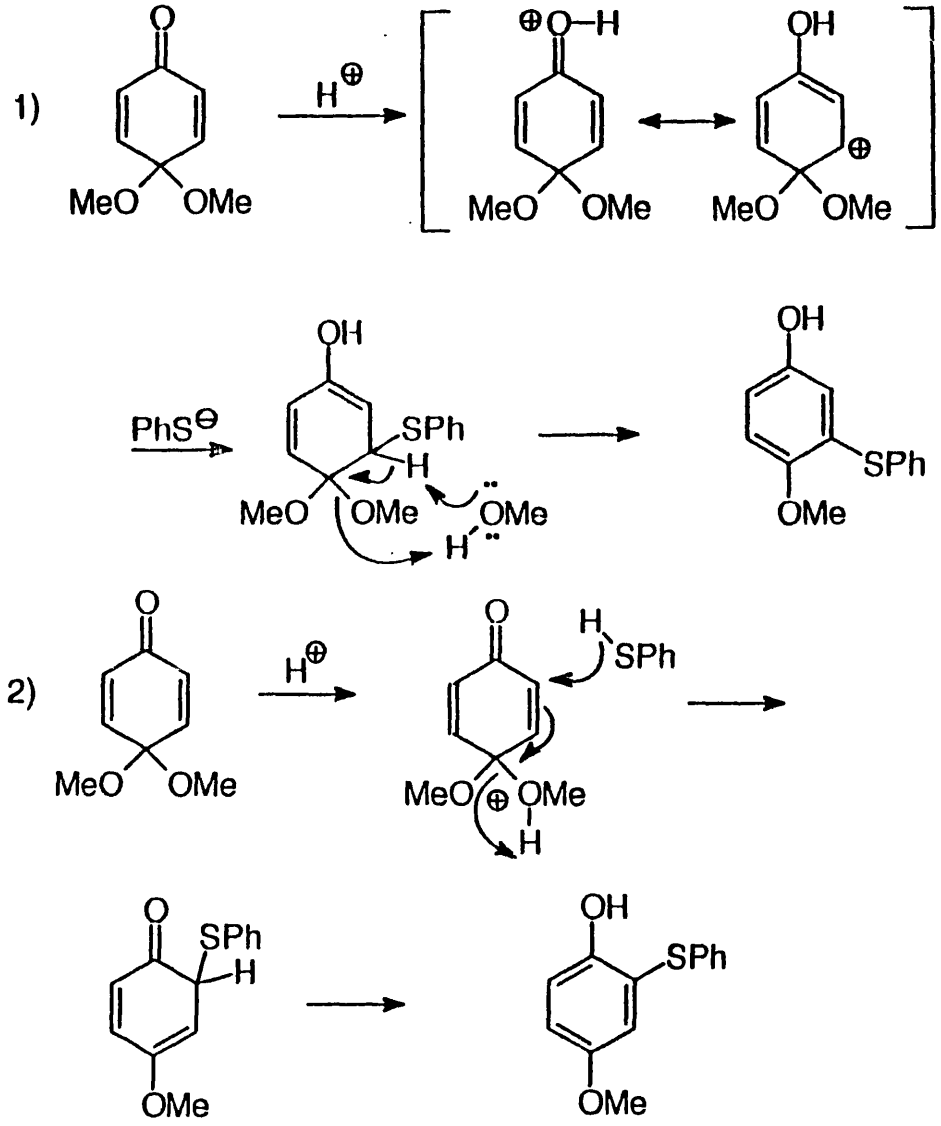
(18) (43)

When 4,4dimethoxycyclohexa-2,5-dienone (**18**) was reacted with thiophenol in methanol, the corresponding phenol was obtained in 50% yield (equation 44).



(18) (44)

Two possible products can be obtained; thiophenol can attack in the *ortho* or *meta*-position to the hydroxyl. Two different mechanisms are shown in Scheme 26.



Scheme 26

Both reaction mechanisms are based on the acidity of thiophenol (pk_a=6.50) since it has an ability to lose a proton.

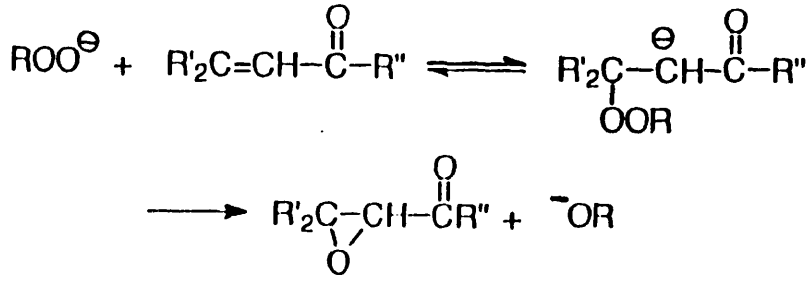
Parker and Kang [32] support the mechanism 2; acid catalyzed additions to quinone monoacetals have been shown to afford aromatic products, substituted *ortho* to the phenolic hydroxyl group.

4.3 EPOXIDATION

4.3.1 Introduction

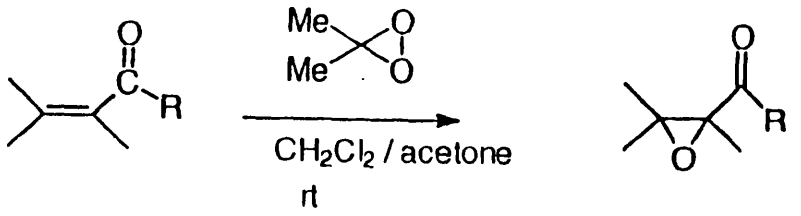
α,β-Unsaturated ketones are difficult to epoxidize by peracid or metal catalyzed methods, and therefore the epoxidation is usually carried out using alkaline hydrogen peroxide in aqueous or alcoholic solution. The use of *t*-butyl hydroperoxide offers a convenient alternative method by which the epoxidation reaction may be carried out in a non-polar medium.

The reaction mechanism of epoxidation is shown in Scheme 27.



Scheme 27

Dimethyldioxirane [52] can also be used to epoxidize α,β-unsaturated ketones with the advantage that the oxidation takes place under strictly neutral conditions (equation 45).

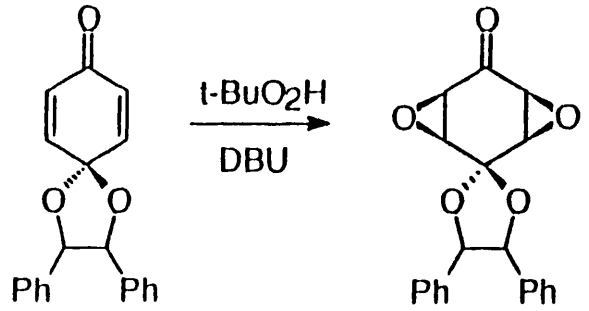


(45)

We tried the epoxidation of chiral spirodienone (**51**) in several ways; *t*-butyl hydroperoxide with DBU [53], hydrogen peroxide or *t*-butyl hydroperoxide with tetrabutylammonium fluoride [54], hydrogen peroxide and NaOH [55], *t*-butyl hydroperoxide and Triton-B [56], and dimethyldioxirane [57]. These reactions are described in the following pages.

4.3.2 Epoxidation with *t*-butyl hydroperoxide and DBU [53]

The treatment of chiral spirodienone (**51**) with *t*-butyl hydroperoxide (1 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at room temperature gave the *cis* diepoxide in 28% yield (equation 46).



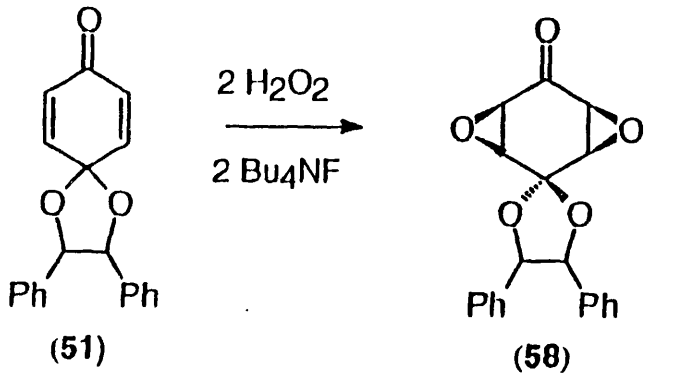
(51) (58) (46)

NMR-spectrum showed that product (**58**) was a pure diastereoisomer where both epoxides are up or down, because if the epoxide groups were *trans*, the molecule would be symmetrical and NMR should show only one peak for H-2 and H-6 and for H-3 and H-5 respectively.

4.3.3 Fluoride promoted epoxidation

Fluoride ion can promote the conjugate addition of hydroperoxides to polarized carbon-carbon double bonds and therefore the epoxidation can occur without a strong base and the need for pH control [54].

Diepoxide (**58**) was also obtained when two equiv of hydrogen peroxide and tetrabutylammonium fluoride was used to epoxidize chiral spirodienone (**51**) (equation 47).



(**51**) (**58**) (47)

After five days reaction time at room temperature the HPLC yield of diepoxide was 6%.

4.3.4 Attempted epoxidation with hydrogen peroxide in base conditions [55]

When two, three or four equiv of hydrogen peroxide with sodium hydroxide in methanol was used to epoxidize chiral spirodienone (**51**), only unreacted starting material was recovered.

The reactions were started at 0 °C and allowed to warm to room temperature. The reactions were followed two weeks by HPLC, but there was no sign of epoxide.

4.3.5 Attempted epoxidation with *t*-butyl hydroperoxide and Triton-B [56]

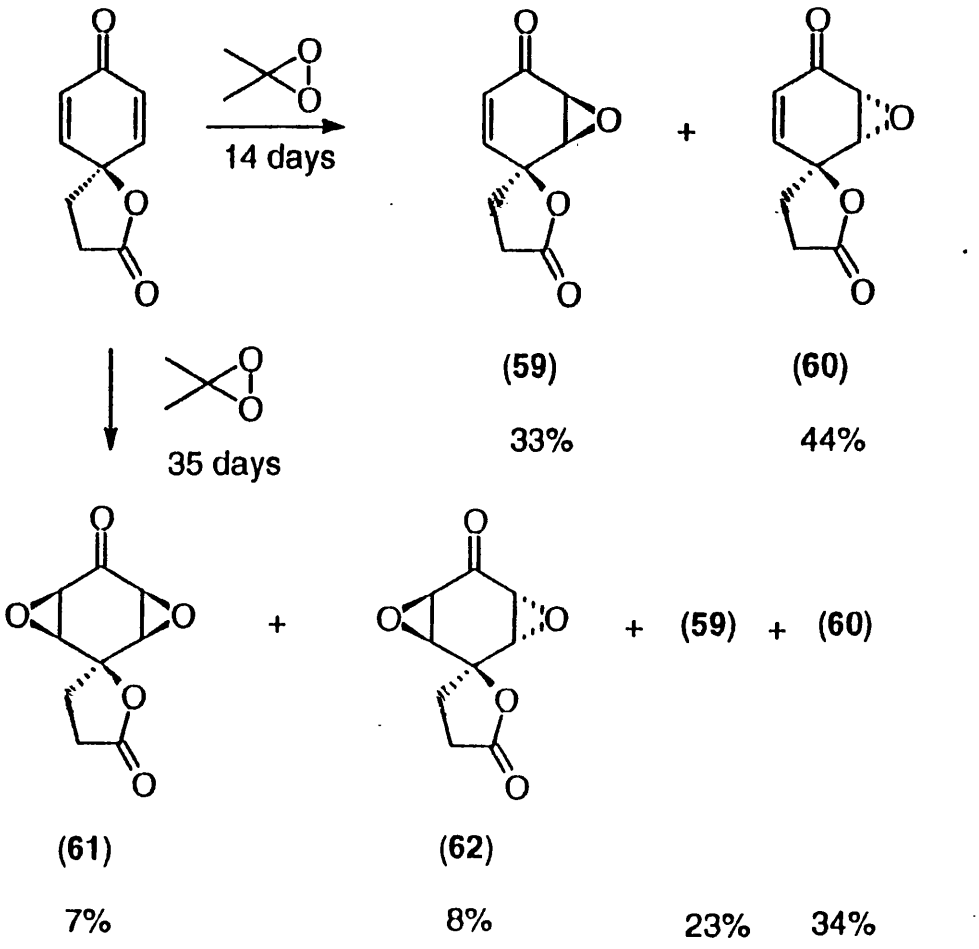
A catalytic amount of benzyltrimethylammonium hydroxide (Triton-B) was used for attempted epoxidation of chiral spirodienone (**51**) by *t*-butyl hydroperoxide.

After 6 days reaction time at room temperature only unreacted starting material was recovered.

4.3.6 Attempted epoxidation with dimethyldioxirane

Dimethyldioxirane has been successfully employed to epoxidize α,β-unsaturated ketones [52].

In addition, model studies have been carried out to investigate cyclohexadienone epoxidation [57]: dimethyldioxirane has been found to produce mono- (**59,60**) and diepoxides (**61,62**) in good overall yield (Scheme 27).



Scheme 27

Dimethyldioxirane was prepared [58] by the reaction of potassium monoperoxy sulfate with acetone under buffered conditions as a yellow solution. The acetone solution of dimethyldioxirane can be stored in the freezer for weeks, but at room temperature the dioxirane content is consumed within ca. 7h. Dimethyldioxirane in this acetone solution

consumed within ca. 7h. Dimethyldioxirane in this acetone solution was quantitatively estimated by iodometric titration [59] giving a dimethyldioxirane concentration of 0.1 M.

Chiral spirodienone (**51**) was dissolved in a solution of dimethyldioxirane in acetone and the reaction was quenched after two weeks and the residue chromatographed which gave only unreacted starting material.

4.4 Conclusion

The epoxidation with *t*-butyl hydroperoxide and DBU gave diepoxide in 28% yield. The same product was obtained but in lower yield (6%), when chiral spirodienone (**51**) was epoxidized with hydrogen peroxide and Bu_4NF.

Other reagents such as hydrogen peroxide with NaOH, *t*-butyl hydroperoxide with Triton-B, and dimethyldioxirane did not afford epoxides.

4.4 CONCLUSION

The reactions with chiral spirodienone (**51**) were successful in the case of the addition of diethyl malonate and the epoxidation of the double bond. The addition of diethyl malonate afforded either mono or bisadduct depending on conditions. The epoxidation of the chiral spirodienone gave only diepoxide which was obtained in best yield when *t*-butyl hydroperoxide was used with DBU.

Attempted conjugate additions with cuprates resulted mainly in redox reactions to give the corresponding phenol. The activation by Lewis acid with "higher order" cyanocuprate gave the desired product in low yield but reduction was still the main reaction.

CHAPTER FIVE

EXPERIMENTAL

5.1 INSTRUMENTATION

Infra-red spectra were recorded on a Pye Unicamp SP1050 infra-red spectrometer using NaCl cells with solutions and KBr disks with solids. Proton nmr were recorded on a Hitachi Perkin-Elmer R-24B spectrometer at 60mhz, a Bruker WM-250 spectrometer a 250MHz and a Bruker AC-400 spectrometer at 400MHz using $CDCl_3$ as solvent and Me_4Si as reference, except where stated. Carbon (^{13}C) nmr were recorded on Bruker WM-250 and AC-400 Fourier transform nmr spectrometers, using $CDCl_3$ as a solvent and Me_4Si as internal standard, except where stated. Low resolution mass spectra were recorded on a modified ERI MS9 or VG12-253 and accurate mass measurements were recorded on a VG ZAB-E instrument. Ultraviolet spectra were recorded on a Phillips PU 8720 UV / VIS scanning spectrophotometer with silica cells of 1 cm path length. Analytical HPLC was performed on LDC / Milton Roy apparatus consisting of a spectromonitor 3100 with constrametric pumps linked to a CI-4100 integrator and using a 25 cm x 4.9 mm column packed with APEX II ODS or Hypersil. Optical rotations were recorded on Perkin-Elmer 141 using 10 cm path length.

Melting points were recorded on a Gallenkamp hot stage apparatus and were uncorrected. Thin layer chromatography was performed on silica gel (Merck) mounted on aluminium cards with fluorescent indicator (254 nm). Flash chromatography was performed with silica gel (Merck, silica gel 230-400 mesh) neutralised using standard method [60].

5.2 REAGENTS

Solvents were treated as follows [61]. Methanol was added to cover the magnesium turnings (5.0g per 1l of methanol) and iodine (0.5g) and the mixture was warmed until the colour of iodine disappeared. The solution was allowed to reflux for 15 minutes and the rest of methanol was added through the condenser. The solution was boiled for 40 minutes under reflux. Methanol was distilled using distillation apparatus sealed from the atmosphere. THF was purified first by passing through dry, neutral alumina under nitrogen. Sodium (2g per litre) and benzophenone (8g per litre) were then added to the THF in a still and the mixture stirred under nitrogen to give a purple solution of the sodium benzophenone ketyl. The THF was then distilled from the ketyl, under argon as required. Glyme, diethyl ether and dichloromethane were passed through an alumina column, stirred for 16 hr with calcium hydride and distilled from the latter under nitrogen.

column, stirred for 16 hr with calcium hydride and distilled from the latter under nitrogen.

Dry solids were obtained by drying *in vacuo* over P_2O_5 in a pistol. Solution of *t*-butyllithium in hexane and methyllithium in ether were standardised by direct titration of the carbon-lithium bond with butan-2-ol using 1,10-phenanthroline as indicator [62]. Methylmagnesium iodine was prepared by dropwise addition of methyl iodine to a suspension of magnesium turnings in dry ether. The mixture was refluxed one hour. MeMgI was standardised by titration with butan-2-ol using N-phenyl-1-naphthylamine as indicator.

5.3 EXPERIMENTAL PROCEDURES

5.3.1 PIDA-oxidations

5.3.1.1 Preparation of 4,4-dimethoxycyclohexa-2,5-dienone (18) from *p*-methoxyphenol [13]

A dry 100 ml round-bottomed flask was charged with *p*-methoxyphenol (0.620 g, 5 mmol), dry methanol (10 ml) and a magnetic follower, sealed with a septum cap and flushed with nitrogen. A solution of phenyliodonium diacetate (PIDA) (1.610 g, 5 mmol) in methanol (40 ml) was transferred via a double-ended needle to the stirred solution of *p*-methoxyphenol at room temperature under nitrogen pressure over 40 minutes. A bright yellow colour was formed.

The removal of methanol gave a yellow oil which was purified by column chromatography on neutral silica gel using gradient elution [100% light petroleum (40-60 °C) to 100% dichloromethane]. 0.747 g of 4,4-dimethoxy-cyclohexa-2,5-dienone (yellow oil) was obtained (4.85 mmol, 97% yield).

The NMR data of (**18**) are as follows:

NMR δ_H: 3.38 (6H, s,OCH_3), 6.24 (2H, d, J=10Hz, H-2), 6.84(2H, d, J= 10Hz, H-3)

δ_C: 50.3 (OCH_3), 92.4 (C-4), 129.9 (C-2), 143.3 (C-3), 185.1 (C-1)

5.3.1.2 Preparation of 4,4-dimethoxycyclohexa-2,5-dienone (18) from phenol [13]

The method was the same as in 5.3.1.1 expect that 2 equiv of PIDA was used. The similar work-up gave 4,4-dimethoxycyclohexa-2,5-dienone (**18**) in 68% yield.

5.3.1.3 Preparation of 4,4-dimethoxycyclohexa-2,5-dienone (18) from *p*-bromophenol [13]

A solution of PIDA (1.610 g, 5 mmol) in methanol (40 ml) was added dropwise to the stirred solution of *p*-bromophenol (0.870 g, 5 mmol) and methanol (10 ml) under nitrogen pressure over 40 minutes at room temperature.

After the removal of methanol the residue was purified by column chromatography which gave three different products. One of them was unreacted starting material (0.453 g, 52%) and the others were unidentified compounds.

The data for unidentified compounds are as follows:

i) 0.097 g of red oil

NMR δ_H: 1.2 (15H,m), 3.5 (15H, m), 6.87 (1H, d, J=8.6 Hz),
7.3 (2H, m), 7.59 (1H, d, J=2.4 Hz)

δ_C: 15.1, 49.65, 49.90, 51.1, 51.2, 65.9, 97.7, 110.1, 112.2,
121.4, 124.4, 126.8, 131.8, 132.1, 134.3, 138.2, 144.8, 152

MS (EI): M, 532 (1), 517 (2), 515 (2), 330 (2), 315 (2)

(CI): M+18, 534 (2), 532 (9), 530 (10), 528 (3), 468 (4), 466 (4)

ii) 0.291 g of red oil

NMR δ_H: 3.4 (12H, m), 3.8 (3H, m), 6.0 (1H, m), 6.4 (1H, m), 6.9 (1H, m), 7.5 (1H, m)

δ_C: 44.9, 46.1, 49.3, 50.3, 50.4, 50.5, 50.6, 50.7, 56.2, 63.7, 94.1, 97.3, 112.5-151.7 (several signals), 190.8, 196.2, 197.7, 199.3

MS (EI): M, 440 (3), 438 (6), 436 (3), 334 (10), 332 (28), 330 (28), 328 (14)

(CI): M+18, 441 (1), 440 (10), 438 (20), 436 (10), 435 (1)

The yield of 4,4-dimethoxycyclohexa-2,5-dienone (12%) was obtained by HPLC, but the purification did not afford that product.

5.3.1.4 Attempted preparation of chiral spirodienones from phenol

5.3.1.4.1 From phenol and hydrobenzoin

Two equiv of PIDA (1.288 g, 4 mmol) in glyme (30 ml) was added dropwise to the solution of phenol (0.188 g, 2 mmol), hydrobenzoin (1.284 g, 6 mmol), and glyme (10 ml), under nitrogen pressure over 30 minutes at room temperature.The removal of solvent gave brown oil, which was purified by the column chromatography using gradient elution starting from 100% light petroleum (40-60 °C) to 100% dichloromethane.

0.765 g of benzaldehyde (7 mmol) was obtained.

5.3.1.4.2 From phenol and 2,3-butanediol

The reaction was carried out as in 5.3.1.4.1, expect that 1.5 equiv of 2,3-butanediol in acetonitrile was used. The desired product was not obtained.

5.3.1.4.3 From phenol and (+)-diethyltartrate

The same procedure than as above was used for the reaction with phenol and 1.2 equiv of (+)-diethyltartrate in dichloromethane. In this case the desired product was not obtained.

5.3.2 Conversion to chiral spirodienone [26]

5.3.2.1 2,3-Butanediol exchange

BF_3·Etherate (0.79 ml, 6.5 mmol) in glyme (5 ml) was added dropwise to the mixture of 4,4-dimethoxycyclohexa-2,5-dienone (0.462 g, 3 mmol) and (±)- 2,3-butanediol (1.08 g, 12 mmol) in glyme (10 ml) at room temperature. After the addition of BF_3·etherate the mixture was stirred 5 minutes. The reaction was quenched by adding dry potassium carbonate, and it was filtered off. The solvent was evaporated and the crude product was purified on the neutral silica column using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane. The thick yellow oil was obtained in 38% yield (0.205, 1.14 mmol).

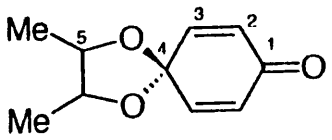
The data for (±)-product are as follows:

NMR δ_H: 1.35 (6H, d, J=5.4 Hz, CH_3), 3.8 (2H, m, H-5), 6.15 (2H, d, J=10 Hz, H-2), 6.65 (2H, d, J=10 Hz, H-3)

δ_C: 15.7 (CH_3), 78.9 (5-C), 96.4 (4-C), 127.7 (C-2),143.8 (3-C), 184.6 (1-C)

MS (EI): M, 180 (24), 136 (51)

(CI): M+18, 198 (38), 181 (100)



The reaction with *meso*-2,3-butanediol was done following the same method, except the diol was used 6-fold molar excess over (**18**) and the obtained yield of product was 43 %.

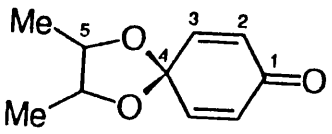
The data for *meso*-product are as follows:

NMR δ_H: 1.25 (6H, d, J=6 Hz, CH_3), 4.4 (2H, m, H-5), 6.15 (2H, m, H-2), 6.60 (1H, dd, J=3 Hz and 10 Hz, H-3), 6.75 (1H, dd, J=3 Hz and 10 Hz, H-3)

δ_C: 15.4 (CH_3), 75.6 (5-C), 97.1 (4-C), 127.5 and 129.5 (2-C), 143.5 and 146 (3-C), 185.4 (1-C)

MS (EI): M, 180 (48), 136 (49), 109 (57)

(CI): M+18, 232 (30), 198 (44), 181 (100)



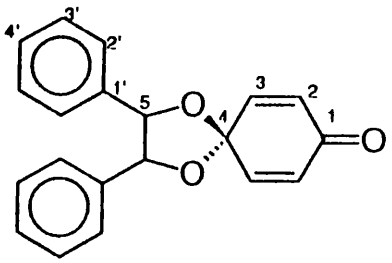
5.3.2.2 Hydrobenzoin exchange (preparation of 51)

BF_3·Etherate (3.8 ml, 31 mmol) in glyme (10 ml) was added dropwise at -15 °C to the solution of 4,4-dimethoxycyclohexa-2,5-dienone (2.314 g, 15 mmol) and *S,S*-hydrobenzoin (3.485 g, 16.3 mmol) in glyme (25 ml). The light yellow colour turned orange. The mixture was allowed to stir and warm to room temperature over 35 minutes.

The reaction was quenched by adding dry potassium carbonate. The solid potassium carbonate was filtered off. The solvent was evaporated and the crude product was purified by column chromatography using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane. The purification gave 1.642 g of monoketal (**51**) (5.4 mmol, 36%) and 1.039 g of bisketal (2 mmol, 14%).

The data for *S,S*-monoketal (**51**) are as follows:

light yellow crystals mp. 184 °C



NMR δ_H: 4.94 (2H, s, H-5), 6.28 (2H, d, J=10 Hz, 3-H), 6.9 (2H, d, J=10 Hz, 2-H), 7.3 (10H, m, Ph-H)

δ_C: 85.9 (5-C), 98.6 (4-C), 126.6 (3-C), 126.7 (4'-C), 128.7 (2'-C), 129.1 (3'-C), 143.6 (2-H), 185.2 (1-C)

MS (EI): M, 304 (13), 288 (100), 182 (94)

(CI): M+18, 322 (2), 305 (57), 214 (1)

IR: 1678, 1639, 1497, 1455, 1385, 1305, 1176, 1121, 1071

UV: λ_{max}= 244 (3.23)

Optical rotation: [α]= –59.1° (c=0.56 in chloroform)

The reaction has done following the same method but using *meso*-hydrobenzoin. The obtained yield was 43%.

The data for *meso*-monoketal are as follows:

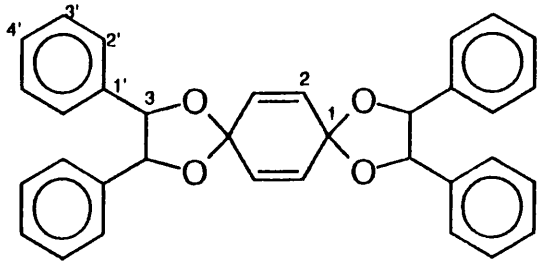
light yellow crystals mp. 163 °C

NMR δ_H: 5.80 (2H, s, H-5), 6.34 (2H, dd, J=2 Hz and 10 Hz, H-3), 6.48 (2H, dd, J=2Hz and 10 Hz), 7.2 (10H, m, H-Ph)

δ_C: 81.5 (5-C), 97.8 (4-C), 126 (3-C), 127 (2'-C), 135.3 (1'-C), 140.9 (4'-C), 143.1 (2-C), 184.4 (1-C)

The physical data and spectral properties for bis ketal are as follows:

white crystals mp. 202-4 °C



NMR δ_H: 4.88 (1H, s, H-3), 6.35 (1H, s, H-2), 7.3 (5H, m, H-Ph)

δ_C: 85.7 (3-C), 98.9 (1-C), 126.7 (2-C), 136.1 (1'-C) 127.9 (4'-C), 128 (2'-C), 131.3 (3'-C)

MS (EI): M, 288 (100), 182 (79)

(CI): M+18, 322 (5), 305 (38), 214 (100)

IR: 3066, 3042, 2902, 1605, 1497, 1455, 1413, 1375, 1361, 1309, 1246, 1216, 1125, 1011, 980, 917

Optical rotation: $[\alpha]=0$

Microanalysis: calculated: C, 81.5; H, 5.60 % found: C, 81.3; H, 5.80 %

5.3.2.3 Attempted hydrobenzoin exchange in the presence of the milder Lewis acids

5.3.2.3.1 In the presence of zinc bromide

Zinc bromide (0.226g, 1.0 mmol) in glyme (2 ml) was added dropwise at -10 °C to the mixture of 4,4-dimethoxycyclohexa-2,5-dienone (0.077g, 0.5 mmol) and *S,S*-hydrobenzoin (0.128g, 0.5 mmol) in glyme (1 ml). The mixture was allowed to warm to room temperature and stir one week. The reaction was monitored by HPLC and only the peak of *p*-benzoquinone and starting material were observed.

5.3.2.3.2 In the presence of zinc chloride

4,4-Dimethoxycyclohexa-2,6-dienone (0.128g, 0.5 mmol) and S,S-hydrobenzoin (0.128g, 0.6 mmol) in glyme (2 ml) were added dropwise at -55 °C to zinc chloride (0.150g, 1.1 mmol) in glyme (3 ml). The mixture was allowed to warm to room temperature and stir over 4 days. The

reaction was monitored by HPLC and only the peak of starting material was shown.

5.3.2.3.3 In the presence of dimethylaluminium chloride

Dimethylaluminium chloride (0.80 ml, 1.1 mmol) in glyme (3 ml) was added dropwise at -55 °C to the mixture of 4,4-dimethoxycyclo-2,5-dienone (0.077g, 0.5 mmol) and *S,S*-hydrobenzoin (0.128g, 0.6 mmol) in glyme (1 ml). The mixture was allowed to warm to room temperature and stirred over 6 days. The reaction was followed by HPLC and no peak of chiral spirodienone (**51**) was shown.

5.3.3 Preparation of hydrobenzoin

5.3.3.1 Preparation of *meso*-hydrobenzoin from benzoin

Sodium borohydride (3.57 g, 94 mmol) was added to the mixture of benzoin (20.0 g, 94 mmol) and methanol (150 ml) at 0 °C. The mixture was stirred at room temperature over 1 h. 100 ml of water was added and the mixture was extracted with ether. The ether phase was dried over magnesium sulfate. The removal of the solvent gave white crystals, which were recrystallized from chloroform. 70% yield of *meso*-hydrobenzoin (14.0 g, 65 mmol) was obtained.

The physical data and spectral properties for *meso*-hydrobenzoin are as follows:

NMR δ_H: 2.3 (2H, s, OH), 4.8 (2H, s, CH), 7.2 (10H, d, J=10 Hz, H-Ph)

δ_C: 78 (CH), 127.1 (2-C), 128.2 (4-C), 128.3 (3-C), 139 (1-C)

MS (EI): M, 197 (4), 180 (5), 107 (100)

(CI): M+18, 232 (75), 214 (100), 197 (48)

IR: 3500, 3395, 2896, 1493, 1454, 1387, 1336, 1255, 1220, 1198, 1179, 1044, 1013, 846

mp. 137-139 °C

5.3.3.2 Preparation of *S,S*-hydrobenzoin from *trans*-stilbene [45]

A 500 ml round-bottomed flask was charged with 70 ml of *t*-butyl alcohol, 70 ml of water and AD-mix-α (20.0 g). The mixture was stirred at room temperature which produced two clear phases; the lower aqueous phase appeared bright yellow.

Methanesulfonamide (1.357 g, 14.3 mmol) was added. The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. *Trans*-stilbene (2.574 g, 14.3 mmol) was added at once, and then the heterogenous slurry was stirred vigorously at 0 °C for 24 hours. Solid sodium sulphite (21.45 g, mmol) was added and the mixture was allowed to warm to room temperature and stirred 60 minutes. Ethyl acetate (150 ml) was added to the reaction mixture, and after the separation of the layers, the aqueous phase was extracted with ethyl acetate (3x50 ml). The

combined organic layers were washed with 2N KOH and dried over anhydrous magnesium sulphate. Magnesium sulphate was filtered off and the solvent was evaporated, which gave 3.542 g of crude product.

The crude product was purified by column chromatography using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% ethyl acetate. 2.983 g of *S,S*-hydrobenzoin (13.9 mmol, 97 % yield) was obtained.

The data for *S,S*-hydrobenzoin are as follows:

NMR δ_H: 4.64 (1H, s, Ph-C<u>H</u>-OH), 7.14 (5H, m, H-Ph)

δ_C: 79.7 (PH-<u>C</u>H-OH), 127.9 (4-C), 128.1 (3-C), 128.3 (2-C), 142.4 (1-C)

MS (EI): M, 197 (4), 180 (7), 167 (15), 107 (100)

(CI): M+18, 232 (100), 214 (83), 197 (25)

IR: 3499, 3394, 3029, 2895, 1493, 1453, 1402, 1386, 1335, 1298, 1255, 1219, 1198, 1044, 1013, 846

mp. 149-150 °C

optical rotation: $[\alpha]$= –104 ° (c=0.5 in toluene)

5.3.4 Addition of diethyl malonate [32]

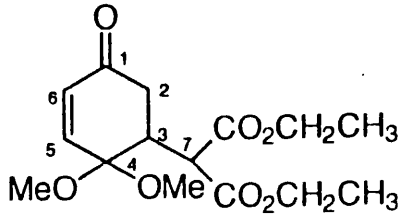
5.3.4.1 To 4,4-dimethoxycyclohexa-2,5-dienone (preparation of 49)

Sodium ethoxide (0.076 M) was prepared by adding sodium (0.200 g) to dry ethanol (90 ml). Sodium ethoxide was estimated by titration with HCl.

To a stirred solution of 4,4-dimethoxycyclohexa-2,5-dienone (0.77 g, 5.0 mmol) in 9 ml of abs ethanol was added to sodium ethoxide (6.56 ml, 0.5 mmol), followed by diethyl malonate (0.728 g, 4.55 mmol) in 9 ml of abs ethanol. The mixture was stirred at room temperature over three days. The mixture was quenched with water, and concentrated. The residue was partioned between ether and water. The ether phase was washed with water and saturated NaCl-solution and dried over $MgSO_4$. The solvent was evaporated which gave 1.225 g of crude product.

The crude product was purified by column chromatography using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane, and then to 100% ethyl acetate.

0.028 g Of 4,4-dimethoxycyclohexa-2,5-dienone was recovered and 0.149 g of the mixture of the starting material and the product. The pure product (light yellow oil) was obtained in 69 % yield (0.973 g, 3.10 mmol). The data for compound (**49**) are as follows:



NMR δ_H: 1.25 (6H, m, CH_3), 2.70 (2H, dd, J=5Hz, H-2), 3.29 (6H, d, J=4.6Hz, OCH_3), 3.38 (1H, m, H-3), 3.64 (1H, d, J=7Hz, H-7), 4.12 (2H, q, CH_2), 4.19 (2H, q, CH_2), 6.1 (1H, d, J=10 Hz, H-5), 6.8 (1H, d, J=10Hz, H-6)

δ_C: 13.9 (CH_3), 37.5 (2-C), 39.9 (3-C), 49.2 (7-C), 50.2 (OCH_3), 51.0 (OCH_3), 61.5 (CH_2), 98.1 (4-C), 131.8 (5-C), 145.5 (6-C), 168.1 (CO_2), 168.2 (CO_2), 196.7 (1-C)

MS (EI): M, 299 (4), 286 (37), 209 (100)

(CI): M+18, 332 (22), 308 (13), 283 (100),

accur. mass. calculated: 314.3368 observed: 332.1709 (M+18)

IR: 2984, 1734, 1693, 1466, 1373, 1229, 1154, 1112, 1035, 916

5.3.4.2 To chiral spirodienone (51)

5.3.4.2.1 Preparation of monoadduct (50) using NaH in THF

Diethyl malonate (0.240 g, 1.5 mmol) in dry THF (1 ml) was added dropwise at room temperature to sodium hydride (0.045g, 78.85 %, 1.5 mmol) in THF (1 ml). Chiral spirodienone (**51**) was added dropwise over 10 minutes to the mixture. The mixture was stirred at ambient temperature over 44 hours.

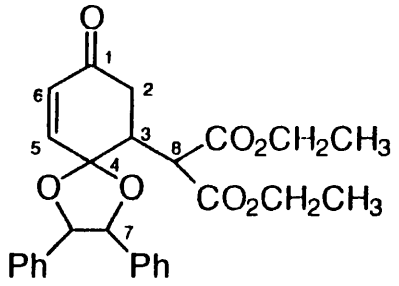
The mixture was quenched with water and concentrated. The residue was partioned between ether and water. The ether phase was washed with water and dried over $MgSO_4$. The removal of the solvent gave 0.532g

of yellow oil. The crude product was purified by column chromatography using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane, and after that to 100% ethyl acetate.

0.022 g Of unreacted chiral spirodienone (**51**) was recovered. The purification gave monoadduct (**50**) in 35% yield (yellow oil, 0.244 g, 0.53 mmol).

The diadduct (**52**) was obtained in lower yield (0.084 g, 0.13 mmol).

The data for monoadduct (**50**) are as follows:



NMR δ_H: 1.2 (6H, m, CH_3), 2.9 (1H, m, H-2), 3.1 (1H, m, H-2), 3.5 (1H, m, H-3) 4.2 (5H, m, CH_2+H-8), 4.9 (2H, m, 7-H), 6.1 (1H, d, J=10 Hz, H-5), 6.9 (1H, d, J=10 Hz, H-6), 7.3 (10H, m, H-Ph)

δ_C: 14.0 (CH_3), 37.9 (2-C), 42.6 (3-C), 50.5 (8-C), 61.6 (CH_2), 61.9 (CH_2), 84.9 (7-C), 105.4 (4-C), 126 (3'-C), 127.7 (3'-C), 128.6 (2'-C), 128.7 (2'-C), 134.5 (1'-C), 136.5 (1'-C), 145 (5-C), 167.9 (CO_2), 168 (CO_2), 197.5 (1-C)

MS (EI): M, 409 (5), 358 (35)

(CI): M+18, 528 (20), 482 (85), 286 (100)

accur. mass: calculated: 464.5168 observed: 482.2179 (M+18)

IR: 2983, 2362, 1732, 1690, 1499, 1456, 1372, 1283, 1213, 1148, 1014, 917

UV: λ_{max}= 243.2 (2.29)

microanalysis: calculated: C, 69.8; H, 6.03 % found: C, 62.7, H, 5.53 %

optical rotation: [α]=–7.89 ° (c=0.38 in chloroform)

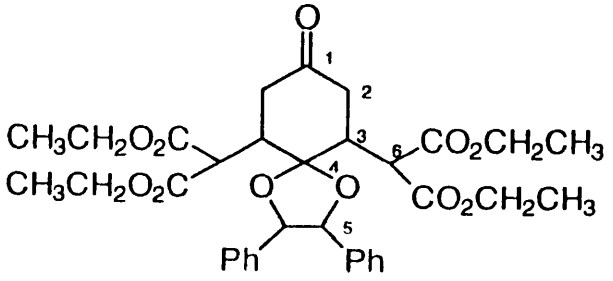
5.3.4.2.2 Preparation of diadduct (52) using NaOEt in ethanol

Sodium ethoxide (1.3 ml, 0.076M, 0.1 mmol) was added dropwise to the chiral spirodienone (**51**) in abs ethanol (5ml). Diethylmalonate (0.368 g, 2.3 mmol) in ethanol (5 ml) was added dropwise to the mixture. The mixture was stirred at room temperature over two days.

The reaction was quenched with water, and concentrated. The residue was partioned between ether and water. The ether phase was washed wuth water and brine, and dried over $MgSO_4$. The solvent was evaporated, which gave 0.483g of crude product.

The crude product was purified by column chromatography using gradient elution starting from 100% light petroleum (40-60 °C) to 100% dichloromethane. The colourless oil was obtained in 65% yield (0.405g, 0.65 mmol).

The data for diadduct (**52**) are as follows:



NMR δ_H: 1.2 (12H, m, CH_3), 1.7 (~1H, s, ?), 2.8 (4H, m,H-2), 3.5 (2H, m,H-3), 4.0 (10H, m, CH_2+H-6), 4.9 (1H, s, H-5), 5.0 (1H, s, H-5), 7.3 (10H, m, H-Ph)

δ_C: 13.78 (CH_3), 13.92 (CH_3), 13.97 (CH_3), 14.04 (CH_3), 40.93 (3-C), 41.25 (3-C), 41.65 (3-C), 41.72 (2-C), 51.44 (6-C), 51.52 (6-C), 61.49 (CH_2), 61.82 (CH_2), 61.89 (CH_2), 62.0 (CH_2), 85.23 (5-C), 85.66 (5-C), 108.65 (4-C), 109.38 (4-C), 126.51 (4'-C), 126.66 (4'-C), 126.99 (4'-C), 127.01 (4'-C), 127.62 (3'-C), 128.42 (3'-C), 128.55 (3'-C), 128.64 (3'-C), 128.69 (2'-C), 128.77 (2'-C), 128.83 (2'-C), 128.92 (2'-C), 134.99 (1'-C), 135.17 (1'-C), 135.59 (1'-C), 136.04 (1'-C), 167.80 (6-C), 167.92 (6-C), 168.05 (6-C), 168.29 (6-C), 205.78 (1-C), 206.95 (1-C)

MS (EI): M, 625 (1), 511 (5), 429 (66), 409 (30)

(CI): M+18, 642 (100), 528 (20), 446 (38)

accur. mass. calculated: 624.6874 observed: 642.2914 (M+18)

IR: 3036, 2985, 2940, 2256, 1733, 1455, 1372, 1301, 1145, 1097

UV: λ= 258.8 (0.76)

optical rotation: [α]=–4.5 ° (c=0.4 in chloroform)

microanalysis: calculated: C, 65.4; H, 6.41 % found: C, 65.5; H, 6.58 %

5.3.5 Conjugate addition with cuprates

5.3.5.1 Attempted addition with Gilman reagent [48]

5.3.5.1.1 Attempted addition with Me_2CuLi

Methyllithium (0.73 ml, 1.12 mmol) was added to the solution of $CuBr{\cdot}Me_2S$ (0.115g, 0.56 mmol) in dimethylsulfide (0.5 ml) at –78 °C. The yellow colour was formed. Lithium dimethylcuprate-solution was added to the mixture of chiral spirodienone (**51**) (0.170g, 0.56 mmol) and ether (10 ml) at –78 °C over 5 minutes. The green colour was formed. The mixture was stirred 30 minutes at –78 °C, and then it was allowed to warm to room temperature. The green colour changed to yellow. The mixture was stirred at room temperature over night and light grey colour was formed.

The resulting solution was poured into saturated aqueous ammonium chloride adjusted to pH 8-9 by the addition of aqueous NH_3. It was extracted with ether, washed with brine, and dried over $MgSO_4$. The solvent was evaporated.

The crude product was purified by column chromatography using gradient elution starting from 100% light petroleum (40-60 °C) to 100% ethyl acetate. The purification gave 0.045g of the corresponding phenol (**54**).

The data for the corresponding phenol (**54**) are as follows:

NMR (MeOD) δ_H: 4.9 (1H, d, J=7Hz, H-5), 5.1 (1H, d, J 7Hz, H-6), 6.5 (2H, d, J=9Hz, H-3), 6.7 (2H, d, J=9Hz, H-2), 7.1 (10H, m, H-Ph)

δ_C: 79.3 (5-C), 87.2 (6-C), 116.5 (3-C), 118.6 (2-C), 128.4 (C-Ph), 128.7(C-Ph), 128.8 (Ph-C), 139.7 (1'-C), 141.6 (1'-C), 152.4 (-O-C),152.7 (HO-C)

MS (EI): M, 306 (10), 289 (12), 199 (65)

(CI): M+18, 324 (100), 306 (5), 289 (18), 214 (80)

IR: no peak of ketone; 3567, 3521, 1509, 1453, 1229, 1164

5.3.5.1.2 Attempted addition with Me_3CuLi_2

The reaction was done using same method than in 5.3.5.1.1 except that 3-fold molar of methyllithium was used. The corresponding phenol (**54**) was obtained in 43 % yield. (0.261g, 0.85 mmol)

5.3.5.2 Addition of cyanocuprate reagents [49]

5.3.5.2.1 Attempted addition of MeCu(CN)Li

Methyllithium (0.35 ml, 0.5 mmol, 1.4 M) was added dropwise at –78 °C to the mixture of CuCN (0.045g, 0.5 mmol) and ether (1 ml). The mixture was allowed to warm to 0 °C. The mixture was recooled to –78 °C. The solution of chiral spirodienone (**51**) (0.152g, 0.5 mmol) in ether (10 ml) was added dropwise to the solution of MeCu(CN)Li. The mixture was allowed to stir and warm to room temperature over 2 hours.

The reaction was followed by HPLC, but only the peak of chiral spirodienone (**51**) was observed.

5.3.5.2.2 Attempted addition of $Me_2Cu(CN)Li_2$

The reaction was done following the same procedure than 5.3.5.2.1 except that 2-fold molar of methyllithium was used. Again, HPLC showed only the peak of starting material.

5.3.5.2.3 Addition of $Me_2Cu(CN)Li_2$ in the presence of BF_3·etherate

Methyllithium (2.27 ml, 3.28 mmol, 1.44M) was added dropwise at –78 °C to the solution of CuCN (0.146g, 1.64 mmol) in ether (3 ml). The mixture was allowed to warm to 0 °C when yellow participate was dissolved. The mixture was recooled to –78 °C and BF_3·etherate (0.20 ml, 1.64 mmol) was added dropwise to the mixture. The solution of chiral spirodienone (**51**) (0.500g, 1.64 mmol) in THF (6 ml) was added dropwise to $Me_2Cu(CN)Li_2$-solution. The mixture was allowed to warm to room temperature and to stir over 23 hours.

The reaction was quenched with aqueous ammonium chloride (pH=8), and ether phase was washed with water and brine, and dried over $MgSO_4$. The removal of the solvent gave 0.451g of crude product, which was purified on the column using gradien elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane, and then to 100%

ethyl acetate. The desired product (**53**) was obtained in 6% yield (0.033g, 0.10 mmol) and the corresponding phenol (**54**) in 65 % yield (0.325g, 1.06 mmol).

The data for product (**53**) are as follows:

NMR δ_H: 1.2 (3H, dd, J=6 Hz and 29 Hz, CH_3), 2.4 (1H, m, H-5), 2.7 (2H, m, H-6), 4.8 (1H, s, H-7), 6.3 (1H, d, J=10 Hz, H-3), 6.9 (1H, d, J=10 Hz, H-2), 7.3 (10H, m, H-Ph)

δ_C: 15.5 (CH_3), 15.6 (CH_3), 37.0 (5-C), 45.9 (6-C), 46.0 (6-C), 86.0 (7-C), 86.1 (7-C), 98 (4-C), 126.6 (3-C), 128.6 (Ph-C), 135.0 (1'-C), 137.0 (1'-C), 143.6 (2-C), (1-C)

MS (EI): M, 265 (38), 230 (46), 214 (10), 198 (100)

(CI): M+18, 354 (30), 337 (3), 324 (3), 305 (9), 214 (100)

IR: 3398, 2968, 2911, 2385, 1713, 1497, 1456, 1382, 1264, 1158, 1098, 1023

5.3.5.3 Attempted addition of Me(Pyrr)Cu(CN)Li_2 [50]

Butyllithium (0.39 ml, 0.5 mmol, 1.29 M) was added dropwise at room temperature to the solution of pyrrole (0.033g, 0.5 mmol) in THF (1 ml). The mixture was added to the solution of CuCN (0.044g, 0.5 mmol) in THF (1 ml). The mixture was cooled to -78 °C and methyllithium was added dropwise to the mixture. Chiral spirodienone (**51**) (0.152g, 0.5 mmol) in THF (3 ml) was added dropwise to the mixture and after the

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addition the mixture was allowed to warm to room temperature. The reaction was followed by HPLC and only the peak of chiral spirodienone was observed.

TLC showed also the spot of the corresponding phenol (**54**).

5.3.5.4 Attempted addition of Grignard reagent in the presence of CuBr [51]

Methylmagnesium iodide (1.2 ml, 3.29 mmol, 2.67M) was added dropwise at -40 °C to a solution of CuBr·Me_2S-complex (0.336g, 1.64 mmol) in dry ether (4 ml) and Me_2S. The strong yellow colour was formed. The mixture was stirred for 15 minutes. The mixture was added dropwise at -40 °C over 40 minutes to the chiral spirodienone (**51**) (0.50 g,1.64 mmol) in ether (20 ml). The mixture was allowed to warm to room temperature and stir over night.

The reaction was quenched with saturated aqueous ammonium chloride and ether was evaporated. Water (20 ml) and ethyl acetate (20 ml) were added and the resulting suspension was filtered over glass wool. The aqueous layer was separeted, and the organic solution was washed with 10% aq. NH_4OH (2x10 ml), water and brine, and dried over $MgSO_4$. The removal of the solvent gave 0.401g of crude product , which was purified on the column using gradient elution starting from 100% light petroleum (40-60 °C) to 100% ethyl acetate. Four different fractions were

isolated: chiral spirodienone (**51**) (15 %), the corresponding phenol (**54**) (0.100g, 20%), and two other fractions, which were the mixture of compounds. These two unidentified fractions were not tried to purified again.

5.3.6 Addition of thiophenol to 4,4-dimethoxycyclohexa-2,5-dienone (18) [31]

Thiophenol (0.237g, 2.16 mmol) in dry methanol (10 ml) was added dropwise under nitrogen pressure at room temperature to the solution of 4,4-dimethoxycyclohexa-2,5-dienone in methanol. The mixture was stirred over 23 hours. The solvent was evaporated which gave a yellow oil (0.296g). The crude product was purified by colum chromatography using gradient elution starting from 100% light petroleum (40-60 °C) to 100% dichloromethane. 0.127g of product was obtained (0.55 mmol, 50%).

The data for the product are as follows:

NMR δ_H: 3.8 (3H, s, OCH_3), 4.6 (1H, s, OH), 6.45 (1H, J=3.0 Hz, H-Ar), 6.6 (1H, dd, J=3.0 and 8.7Hz, H-Ar), 6.75 (1H, d, J=8.7Hz, H-Ar), 7.2-7.6 (5H, m, H-Ph)

MS (EI): M, 250 (15), 233 (100)

(CI): M+18, 232 (100), 217 (40)

accur. mass. calculated: 232.287 observed: 232.0558

IR: 3400, 1575, 1480, 1430, 1270, 1200, 1050, 1020, 900

5.3.7 Epoxidation of chiral spirodienone (51)

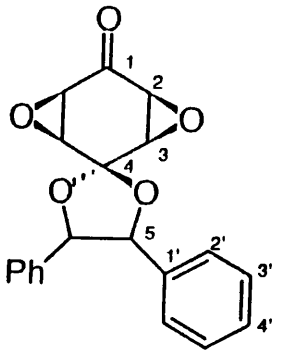
5.3.7.1 Preparation of diepoxide (58) using *t*-BuO_2H and DBU [53]

The mixture of DBU (0.167g, 1.1 mmol) and THF (2 ml) was added dropwise at room temperature to the mixture of chiral spirodienone (**51**) (0.340g, 1.10 mmol) and t-butyl hydroperoxide (0.180 ml, 1.10 mmol, 43%) in THF (4 ml). The light yellow colour changed dark red. The reaction mixture was stirred at ambient temperature over 2 days. The reaction was monitored by HPLC; after one day the diepoxide (**58**) was obtained in 28% yield.

The reaction was quenched with water and extracted with ethyl acetate. The organic phase was washed with water and brine, and dried over $MgSO_4$.

The purification of the crude product on the neutral silica gel column using gradient elution starting from 100% petroleum spirit (40-60 °C) to 100% dichloromethane , and then to 100% ethyl acetate, gave the diepoxide (**58**) (0.032g, 0.095 mmol) in 9% yield. The unreacted starting material (0.117g, 35 %) was also recovered.

The data for the diepoxide (**58**) are as follows:



NMR: δ_H: 3.5 (2H, dd, J=2.6 Hz and 3.8 Hz, H-3), 3.6 (2H, dd, J=2.6 Hz and 3.8 Hz, H-2), 4.9 (1H, d, J=8.6 Hz, H-5), 5.1 (1H, d, J=8.6 Hz, H-5), 7.3 (10H, m, H-Ph)

δ_C: 55.2 (3-C), 55.3 (3-C), 60.0 (2-C), 60.8 (2-C), 86.0 (5-C), 86.8 (5-C), 101.4 (4-C), 126-129 (Ph-C), 134.3 (1'-C), 134.4 (1'-C), 197.5 (1-C)

MS (EI): M, 324 (3), 296 (2), 180 (85)

(CI): M+18, 357 (8), 356 (30), 354 (90)

IR: 3035, 2912, 2393, 1720, 1605, 1497, 1456, 1354, 1240, 1212, 1142, 1116, 1053, 1004

5.3.7.2 Preparation of diepoxide (58) using H_2O_2 and Bu_4NF [54]

Tetrabutylammonium fluoride (2.0 ml, 2 mmol) was added dropwise at room temperature to the mixture of chiral spirodienone (**51**) (0.304g, 1.0 mmol) and hydrogen peroxide (0.252g, 2.0 mmol, 27%) in DMSO (3 ml). The mixture was stirred at room temperature and monitored by HPLC, which showed that after five days the diepoxide (**58**) was obtained in 6% yield. The purification by column chromatography did not give the diepoxide.

5.3.7.3 Attempted epoxidation of chiral spirodienone (51) with H_2O_2 and NaOH [55]

Sodium hydroxide (0.042 ml, 0.25 mmol, 6N) was added dropwise to the mixture of chiral spirodienone (**51**) (0.152g, 0.5 mmol) and hydrogen peroxide (1, 1.5, or 2 mmol) in methanol (1ml) at 0 °C. the mixture was stirred over 2.5 hours at 0 °C, and then it was allowed to warm to room temperature and stir over 2 weeks. The reactions were followed by HPLC, but only the peak of chiral spirodienone (**51**) was observed.

5.3.7.4 Attempted epoxidation of chiral spirodienone (51) with *t*-BuO_2H and Triton-B [56]

To a stirred solution of chiral spirodienone (**51**) (0.152g, 0.5 mmol) and *t*-butyl hydroperoxide (0.084 ml, 0.675 mmol, 80%) in THF (2 ml) was added at 10 °C methanolic solution of Triton-B (0.004 ml, 0.01 mmol). The mixture was stirred at room temperature over 6 days. The reaction was followed by HPLC, which showed only the peak of chiral spirodienone (**51**).

5.3.7.5 Attempted epoxidation of chiral spirodienone (51) with dimethyldioxirane [57]

5.3.7.5.1 Preparation of dimethyldioxirane [58]

A 5 l three-necked, round-bottomed reaction flask was equipped with an efficient mechanical stirrer and an addition funnel for solids, connected by means of a U tube to a two-necked receiving flask, the latter cooled at -78 °C by means of a dry ice / acetone bath.

The reaction flask was charged with a mixture of water (212 ml), acetone (160 ml), and $NaHCO_3$ (48.3g) and cooled at 5-10 °C with the help of an ice / water bath. While vigorously stirring and cooling, solid caraote (100g) was added in five portions at 3-min intervals. After 3 min of the last addition, a moderate vacuum (oil pump) was applied, the cooling bath removed from the reaction flask, and while vigorously stirring the dimethyldioxirane acetone solution distilled and collected in the cooled receiving flask. Dimethyldioxirane was obtained 120 ml and it was estimated by iodometric titration; 0.09 M.

5.3.7.5.2 Attempted epoxidation of chiral spirodienone (51)

Dimethyldioxirane in acetone (10 ml, 0.9 mmol) was added to chiral spirodienone (0.48 g, 1.58 mmol) and the mixture was stirred at room temperature over one day. The solvent was removed in vacuo. The residue was then dissolved in a fresh batch of dimethyldioxirane in

acetone (10 ml, 0.9 mmol). the reaction was stirred at room temperature over 2 weeks and the reaction was monitored by HPLC. Only the peak of chiral spirodieno (**51**) was observed.

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