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PROGRESS IN THE CHEMISTRY OF ISOBENZOFURANS; APPLICATIONS TO THE SYNTHESIS OF NATURAL PRODUCTS AND POLYAROMATIC HYDROCARBONS

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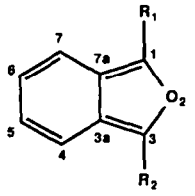
I. INTRODUCTION

The transient existence of benzo[c]furan **1**, also known as isobenzofuran (IBF) by *Chemical Abstracts*, was conclusively demonstrated[1] in 1964. It was isolated[2] in the early seventies as a crystalline solid stable only at low temperatures but easily polymerized at room temperature. Aryl substituents on the furanoid ring appear to stabilize the system, as do electron withdrawing groups. Thus 1,3-diphenyl IBF **2** was prepared[3] as long ago as 1905, and is a commercially available material; 1-phenyl-3-cyano-IBF **3** is also a stable crystalline solid[4] but isobenzofurans with a single aryl substituent do not seem to be stable enough for routine isolation. Linear and angular naphtho[c]-furans are known. The naphtho[1,2-c]furan **5** is a crystalline solid which can be melted without decomposition[5] while the linear isomer, naphtho[2,3-c]furan **4** is a transitory species[6] although its 1,3-diphenyl derivative **6** is crystalline[7] and stable in the absence of light and air.



1 (R_1=R_2=H)

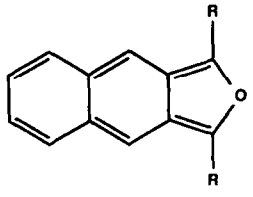
2 (R_1=R_2=Ph)

3 (R_1=Ph,R_2=CN)

16 (R_1=CH_2OH,R_2=H)

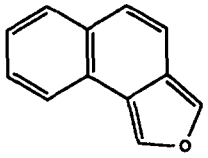
17 (R_1=$SiMe_3$,R_2=H)

18 (R_1=OAc,R_2=H)



4 (R=H)

6 (R=Ph)



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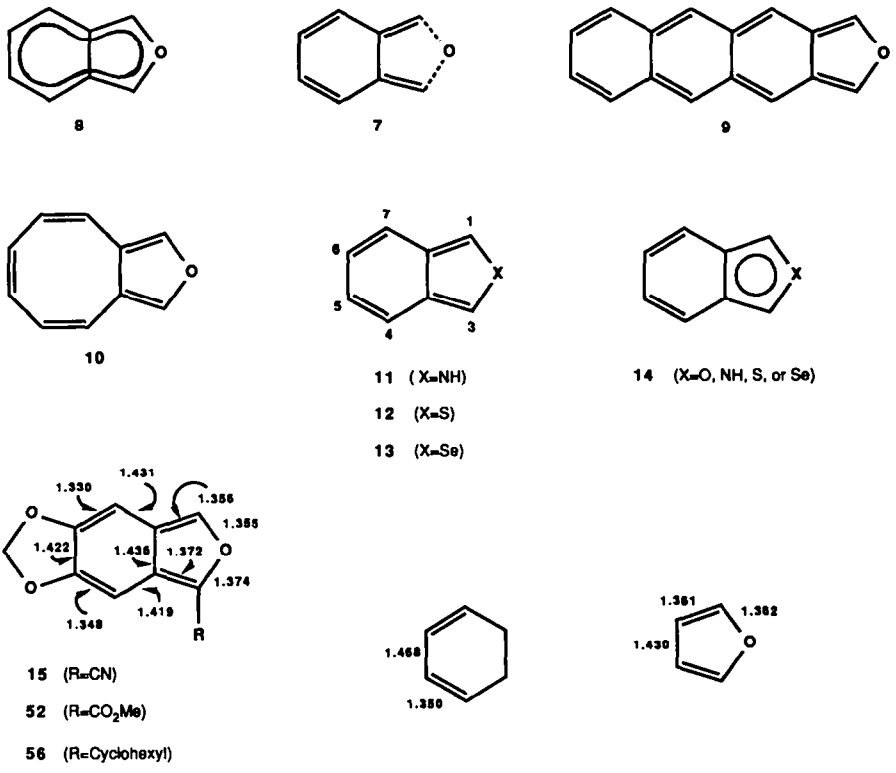
Excellent accounts of IBF chemistry have been published[8-10] with Friedrichsen's review[9] in particular being most comprehensive. Fragmented information on isobenzofurans is also found[11] as parts of chapters dealing with the benzo derivatives of furan in volume 4 of *Comprehensive Heterocyclic Chemistry*. This report will focus on the spate of activity in the 1980–87 period but some of the earlier material will be used where needed for continuity of the discussion. Although all of the important advances of these years will be cited, this is not intended as an exhaustive accounting, but rather as a subjective look at the chemistry of isobenzofurans, somewhat biased towards synthetic utility of these compounds, in accordance with the authors own proclivities.

II. STRUCTURE OF ISOBENZOFURAN

Two structural possibilities are represented diagrammatically as **7**, an oxygen-bridged *ortho*-quinodimethane and **8**, a Hückel aromatic 10-π species. Several theoretical studies, summarized in Friedrichsen's review,[9] have suggested that resonance stabilization and aromaticity is insignificant in **1** in comparison to benzo[b]furan. More recently, calculations of the topological resonance energy per electron have been completed[12] for several linear heteropolycycles and related to "percentage benzene character per π-electron". The series **1**, **4**, **9** according to these results have 25%, 31% and 35% of the aromatic character of benzene per π-electron in contrast to the corresponding nitrogen (71%, 63% and 58% respectively) and sulfur analogs (63%, 58% and 54%, respectively). These theoretical indices of aromaticity for **1** and **4** are in agreement with the instability of the heterocycles. A comparison of the furanoid proton resonances in the NMR spectra of **1** (8.40 δ) and **10** (7.20 δ) however, implied[2] the presence of a significant ring current in the former, similar to other 10-π aromatic systems. The ring current criterion of aromaticity has been questioned[13] recently and a similar contradiction pervades the discussion[14] of the aromaticity of furan.



An intriguing compromise was suggested[15] by Sardella and coworkers, based on the proposition that bond length averaging, a common criterion of aromaticity, can be estimated by measurement of the vicinal proton coupling constants. Isobenzofuran **1**, isoindole **11**, isothianaphthene **12** and benzo[c]selenophene **13** were studied. The coupling constants $^3J_{5,6}$ (single bond) and $^3J_{4,5}$ (double bond) were compared as the ratio $J_{5,6}/J_{4,5}$ (the J_{ratio}) and found to be remarkably constant at 0.72 ± 0.02 for all four heterocycles. The implication that single and double bond character in the C-4–C-7 region of these molecules is constant, correlates neither with the observed variation in chemical behavior of the heterocycles nor with the results of resonance energy calculations.[9,12] The annelation of a butadiene fragment at C-3 and C-4 of a five-membered heterocycle (i.e. in the "iso" fashion to provide **1**, **11**, **12** and **13**) proceeds with low annelation energies (1–3 kcal/mole for **1**, **11** and **12**) in contrast to the 15–19 kcal/mole for the benzo[b]isomers. The conclusion then drawn is that the butadiene fragment C-4–C-7 does not interact with the hetero-ring in any of the "iso" annelated compounds and aromaticity, if any, is confined to the five-membered heterocycle, a situation summarized in **14**. The gradations in reactivity and variations in benzene character per π-electron over the iso series are thus traceable to the differences between furan, pyrrole, thiophene and selenophene, i.e. the change in X in **14**.

Experimental values for the bond lengths and angles for any isobenzofuran were not available until 1986. An X-ray crystallographic geometry for the moderately stable IBF **15** was published in that year[16] and the results taken in comparison with the bond lengths of furan and cyclohexadiene appear to support the expression **14** for X = O at least.

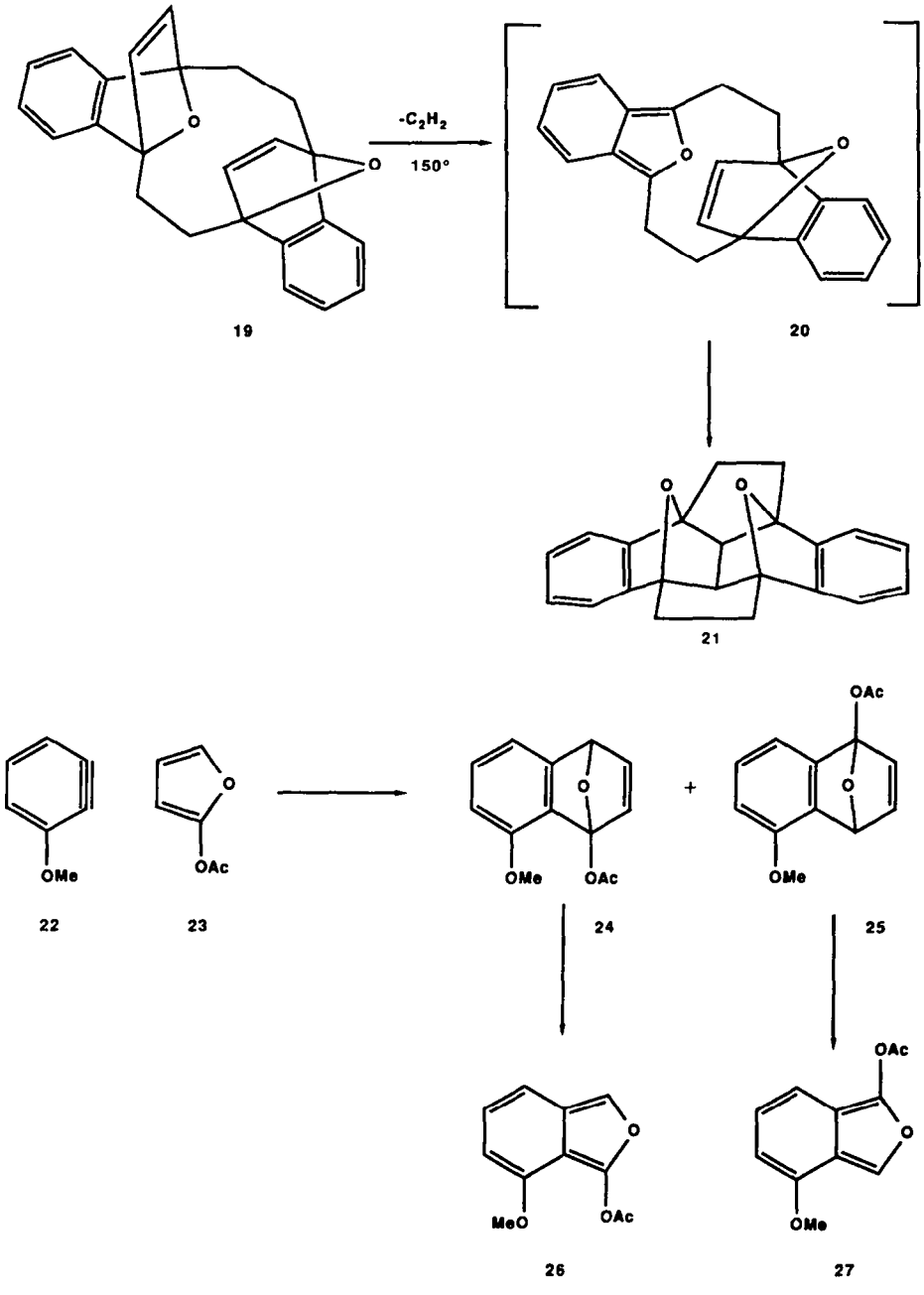
III. SYNTHESIS OF ISOBENZOFURANS

It must be emphasized that isobenzofurans, with very few exceptions, are too unstable to be isolated in the conventional sense. The following discussion of "synthetic methods" is therefore concerned with the production of transient IBF intermediates which are intercepted *in situ* by added dienophiles. The utility of any particular synthetic method in this context not only depends on the normal factors of yield, availability of starting materials, versatility and operational simplicity but also on the tolerance of the conditions used (for IBF generation) to the Diels–Alder reaction of the IBF with dienophiles.

III.1. *By retro Diels–Alder processes*

These methods are of historical importance and have been adequately reviewed.[8–10] Warrener *et al.* have further developed[17] his dipyridyl s-tetrazine technique to produce several 2-substituted isobenzofurans (**16–18**) and Wege has employed[18] Wiersum's FVT technique[10] to produce naphthol[1,2-c]furan **5** and other related oxygen heterocycles. A rather exotic application[19] of this type of Diels–Alder chemistry involves the elimination of acetylene at 150°C from **19** by a retro Diels–Alder reaction to generate IBF **20** which undergoes an immediate intramolecular Diels–Alder reaction to yield **21**.

In general these methods of generating isobenzofurans have not proven to be very useful in organic synthesis. The necessity to employ benzyne chemistry with its attendant difficulties curtails flexibility and introduces regiochemical constraints when substituents are required in specific positions of both rings of the IBF. The problem is illustrated[20] by the reaction of methoxy benzyne **22** with acetoxy furan **23** to produce regioisomers **24** and **25** which had to be separated by HPLC and individually processed *via* the tetrazine route to provide IBFs **26** and **27**. Consequently only one



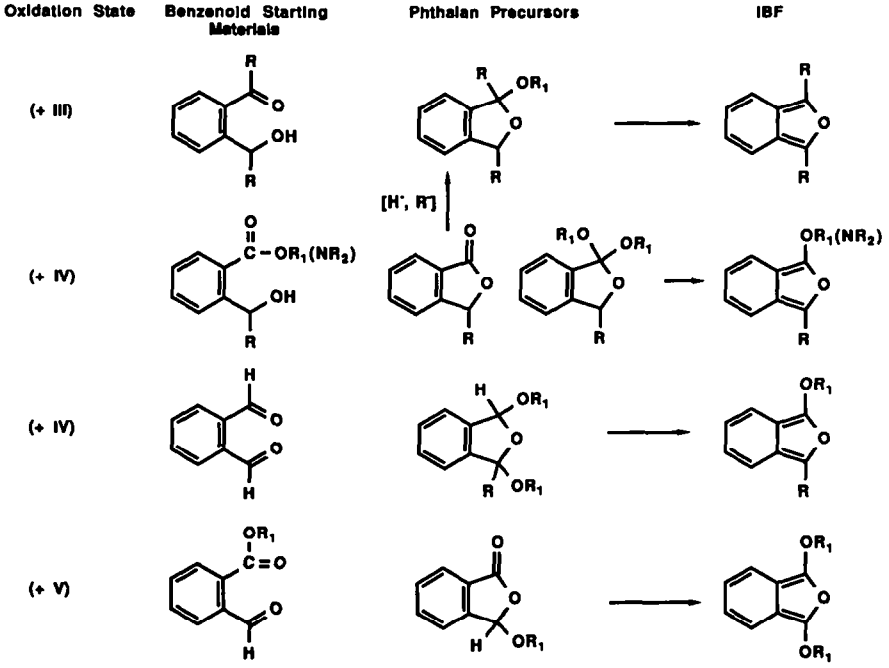
single example[21] of the application of IBF chemistry to natural product synthesis was known before 1980, and in this instance a regiochemical problem was also encountered (discussed in Section VII.1).

III.2. *From benzenoid starting materials through phthalan precursors*

These methods for the generation of isobenzofurans are the most popular and useful by far. They are conceptually and operationally simple, extremely versatile and have been employed both in the isolation of moderately stable IBFs and in the generation of diverse IBFs for natural product synthesis. Although a large variety of benzenoid starting materials have been used, all procedures in this group pass through a phthalan (or phthalide, occasionally) precursor which may or may not be isolated. To aid in the discussion and to clarify the relationship between the various synthetic processes an attempt is made to classify them by applying an oxidation state criterion to the *ortho*-disubstituted benzenoid starting material, the phthalan precursor and the resultant IBF. In Scheme 1, IBFs with three different oxidation states are recognized but only one example of a (+V) IBF is known and it was not prepared from the (+V) phthalide. The (+IV) IBF for example, may bear one oxygen or nitrogen substituent and is produced from (+IV) phthalan precursors which may arise from a (III+I) or (II+II) *ortho*-disubstituted starting material. Interconversions between the various starting materials are possible by oxidation or reduction and will be illustrated in the discussion to follow.

III.2a. *Synthesis of (+III) isobenzofurans*

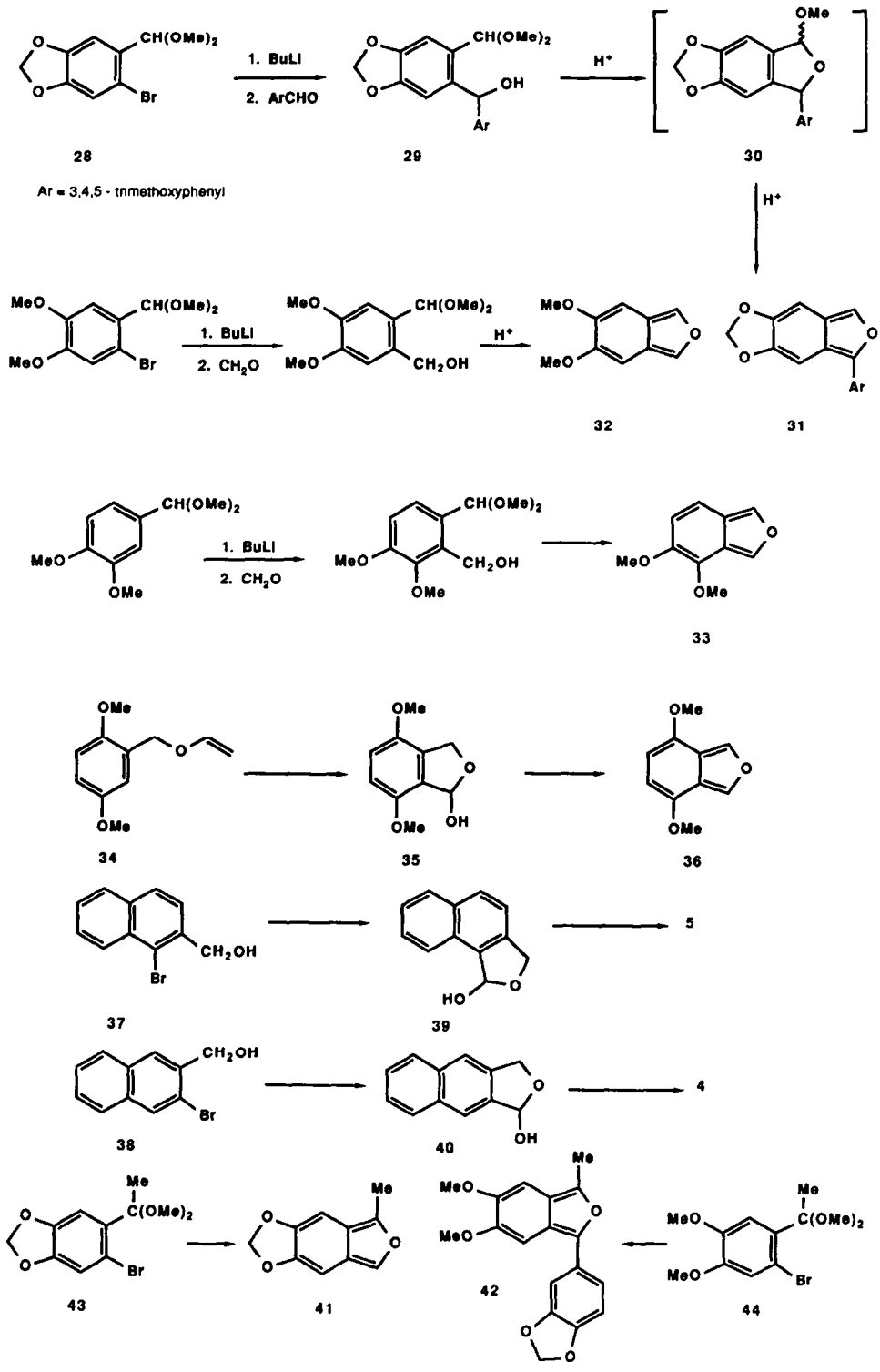
III.2a.i. *From (+III)* ortho-*disubstituted benzenoid starting materials.* These are the most direct and concise methods since no adjustment in oxidation level is required and the benzenoid starting materials are readily available or easily prepared by standard procedures. A two step generation of IBF **31**, for example from bromo acetal **28** and 3,4,5-trimethoxy benzaldehyde, was used[22] in the synthesis of several aryl naphthalide lignans. The (+III) starting material **29** and (+III) phthalan **30** may be isolated if desired but the IBF must be intercepted *in situ* by a suitable dienophile. Dry formaldehyde can be used instead[23] to provide IBF **32** from the bromoveratraldehyde acetal by the same technology. The dimethyl acetal moiety is a useful *ortho*-directing substituent[24] in aromatic lithiation and veratraldehyde acetal was directly deprotonated and quenched with formaldehyde to produce[25] the isomeric IBF **33**. Other *ortho*-directing groups may be used; the benzyl vinyl ether



Scheme 1. (R, R_1 = H, alkyl, or other carbon substituent).

34 was deprotonated,[26] quenched with dimethyl formamide and hydrolysed[25] to the (+III) phthalan **35** which is a precursor of the IBF **36** used in a synthesis of daunomycinone (discussed in Section VII.1). Naphthalenic *o*-bromo alcohols **37** and **38** were converted to (+III) naphthalans **39** and **40** by a similar sequence[27] and dehydrated to the angular and linear naphthofurans **5** and **4** respectively.

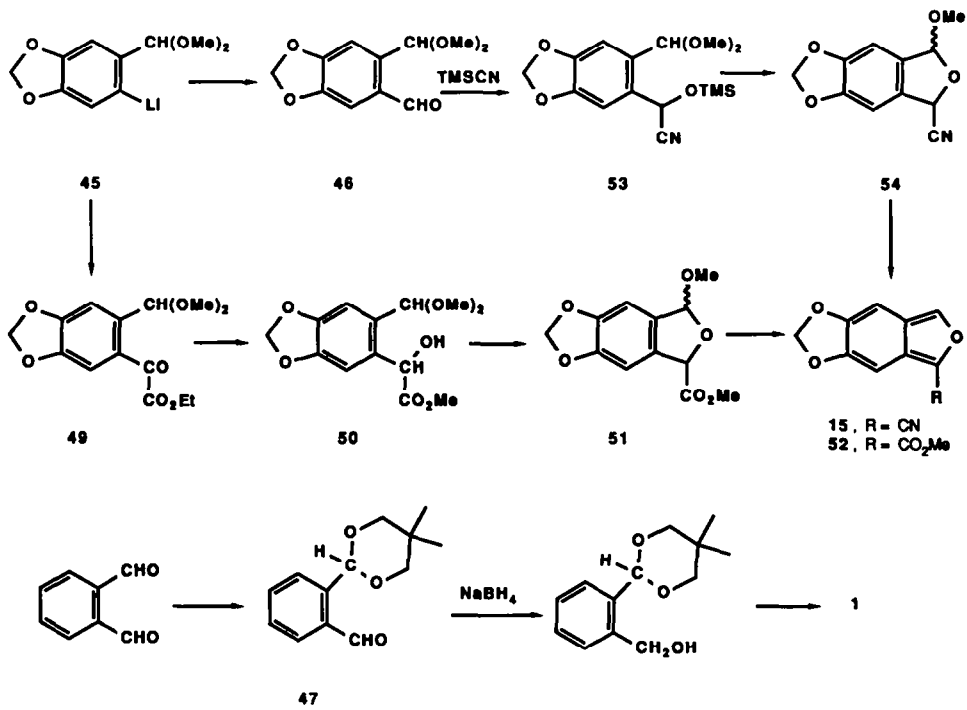
One practical limitation common to all these procedures has been the requirement that the aldehyde used for quenching the aryl lithium species should not contain an α-hydrogen atom. Thus only aryl aldehydes and formaldehyde qualify among the commonly available materials, confining



the 1-substituent of the IBF to an aryl group. Various transmetalation procedures might overcome this problem in theory but they have not been explored. The use of a bromo ketal instead of a bromo acetal has been proven[25] to be one feasible alternative route to 1-alkyl IBFs (e.g. **41** and **42** from bromo ketals **43** and **44**). Bromo ketals however are not as easily obtained as the acetals and a more versatile pathway to 1-alkyl isobenzofurans will be presented in the following section.

III.2a.ii. *From (+IV) ortho-substituted benzenoid starting materials.* Since all these processes have to pass through a (+III) phthalan precursor a reduction of some type must be carried out. This may be a hydride reduction, a hydrogenation or even a nucleophilic addition (of a carbon nucleophile) to the (+IV) material before the (+III) phthalan is reached. As envisaged in Scheme 1 two types of (+IV) starting material are possible and both have been used.

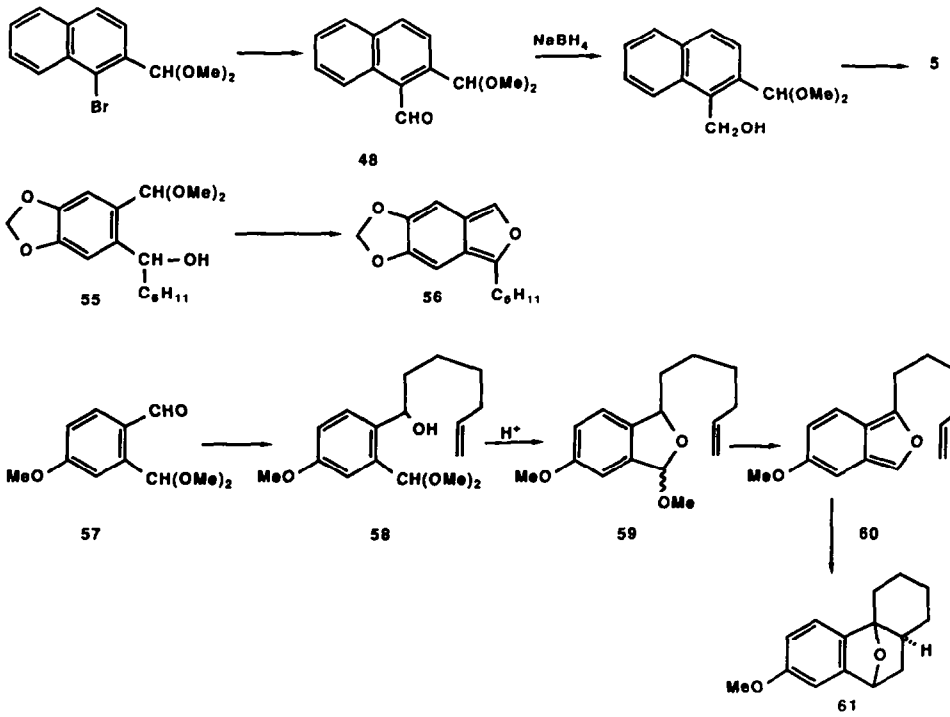
The *ortho* dicarbonyl (II+II) starting material in a protected form is often a useful starting material. Thus lithiated acetals like **45** can be quenched with dimethyl formamide and selectively hydrolysed to provide the versatile (+IV) material **46**. Such compounds may be reduced to the (+III) alcohol acetal with sodium borohydride and taken on to (+III) isobenzofurans as we have often done as a practical way of avoiding the use of dry formaldehyde required in the preparation of **32** for example. The same procedure has also been used in the preparation of **1**[28] and **5**[27] from the respective aldehyde-acetals **47** and **48**. Another illustration of the same basic idea uses diethyl oxalate instead of DMF to produce the (+IV) material **49** from **45**. Hydrogenation in alkaline methanol converts it to the (+III) material **50** which is cyclized by acid to a *cis–trans* mixture of (+III) phthalans **51** from which the crystalline, moderately stable IBF **52** is available[16] by further acid treatment.



A more valuable exploitation of the mono-protected dialdehyde **46** is to treat it with carbon nucleophiles. Thus trimethylsilyl cyanation followed by successive acid treatments leads[16] the (+IV) aldehyde **46** through the (+III) cyanohydrin **53** and the (+III) phthalans **54** to stable isobenzofuran **15**, used in the X-ray structure determination discussed earlier. This procedure is in fact a stepwise adaptation of one reported[4] much earlier when 1-phenyl-3-cyano IBF **3** was obtained in one step by reaction of the (+IV) starting material *o*-benzoyl benzaldehyde with potassium cyanide in refluxing glacial acetic acid. The same procedure applied to **46** did provide **15**, but in low and irreproducible yields probably because it lacked the stabilizing 1-phenyl substituent of **3**.

Grignard addition to **46** was also explored. Thus cyclohexyl magnesium bromide reacts to produce the (+III) alcohol **55** from which IBF **56** is generated[25] by the usual acid treatment. The potential of this technology for introducing dienophilic residues by means of the alkyl group of

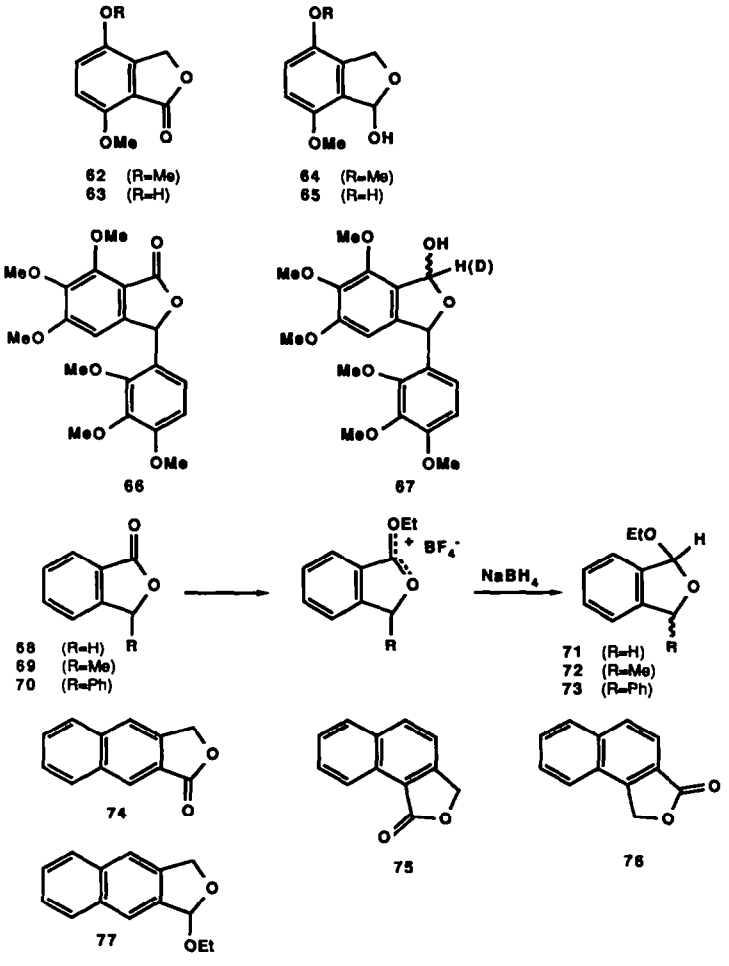
Grignard reagent in preparation for subsequent intramolecular Diels–Alder reactions was recognized[25] in 1983 and realised[29] in 1986. Thus the (+IV) aldehyde-acetal **57** prepared from *m*-anisaldehyde was treated with hexenyl magnesium bromide to form the (+III) hydroxy acetal **58** and phthalan **59**. The latter, on more vigorous acid treatment, produced the IBF **60** trapped as the *exo*-adduct **61**.



Phthalides and their equivalents are also excellent sources of (+IV) starting materials. Hydride reduction or nucleophilic attack by carbon nucleophiles provides (+III) phthalans which are the immediate precursors of the IBFs. In fact diphenyl isobenzofuran was prepared as long ago as 1905 by the reaction of phenyl phthalide with phenyl magnesium bromide.[3,9] Direct partial reduction of phthalides to hydroxy phthalans (+III) have also been possible in a limited number of examples. Thus reduction of **62**[30,31] and **63**[32] with diisobutyl aluminum hydride provides IBF precursors **64** and **65** respectively and reduction of **66**, accomplished with both diisobutyl aluminum hydride and lithium triethyl borodeuteride, provided[33,34] isobenzofuran precursor **67** with and without a deuterium label. It has been suggested[35] that a substituent "*peri*" to the phthalide carbonyl group is necessary to prevent ring opening of the phthalide and formation of tertiary alcohols with organometallic reagents, and the same reasoning may well apply to hydride reductions of the phthalide carbonyl group. Certainly, in our hands, phthalide itself (**68**) did produce a mixture of starting material, lactol and diol when partial reduction was attempted with diisobutyl aluminum hydride in toluene at −78°. Phthalyl alcohol obtained by the LAH reduction of phthalide, however, has been reoxidized[36] to the (+III) 1-methoxy phthalan precursor of **1**.

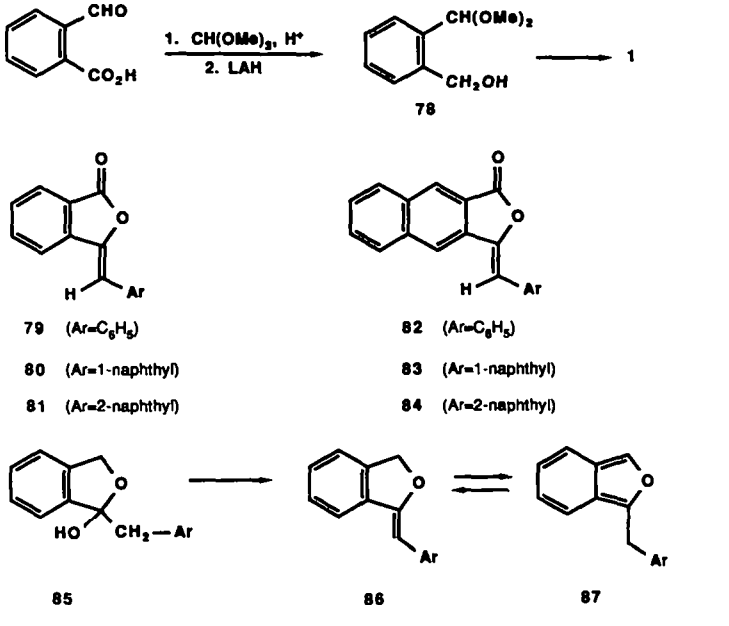
An indirect method for the (+IV) phthalide to (+III) alkoxy phthalan conversion has proven to be more general and useful. Thus phthalide,[37] methyl phthalide[38] (**69**) and phenyl phthalide[38] (**70**) all react with diethoxycarbenium fluoroborate yielding the expected Meerwein salt which is reduced with sodium borohydride in DMF to the phthalans **71**–**73**. Linear[6] and angular[5] naphthalides (**74**–**76**) behaved similarly and yielded the corresponding alkoxy naphthalans which were converted to linear and angular naphthofurans **4** and **5**. However, no report has yet appeared of the alkylation of the intermediate Meerwein salt; this should be possible in principle and if proven so in practice, access will be gained to alkyl isobenzofurans.

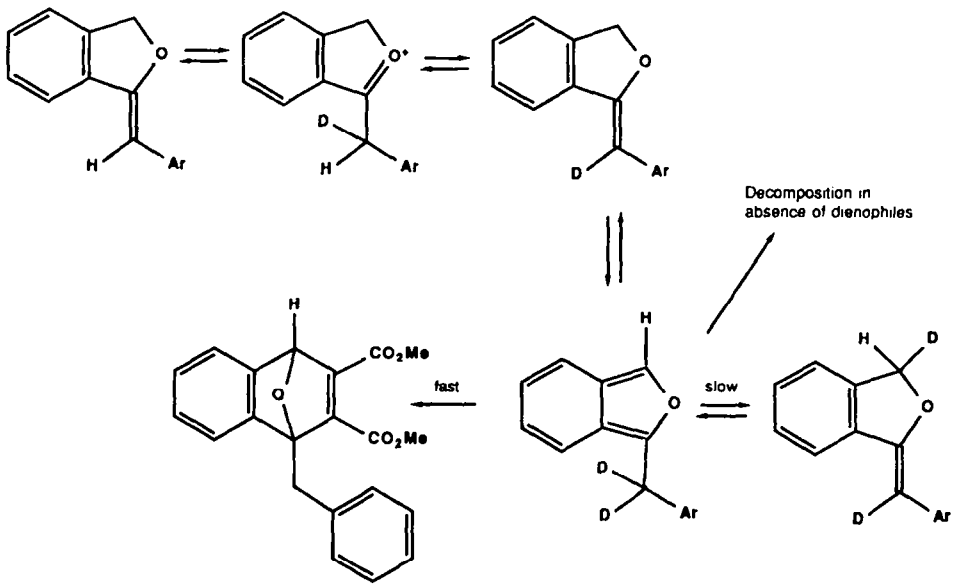
In all these cases except the linear naphthalan **77**, 1,4-elimination of alcohol was achieved by the use of lithium dialkyl amides and procedures were worked out for the isolation of etheral solutions of the IBF with reasonable shelf stability. These base/catalysed eliminations were also found[38] to be predominantly *syn* in their stereochemistry. Acid catalysed eliminations with weak acids like



acetic or mesitoic acid were proven to be reversible and deuterium incorporation was observed (i.e. R = D) in the recovered phthalan **71** when exposed to acid[6] in the presence of labelled methanol.

III.2a.iii. *From* (+ *V*) ortho-*disubstituted benzenoid starting materials.* A simple example is the preparation[39] of **1** from the commercially available 2-carboxybenzaldehyde by acetalization followed by reduction with LAH to the familiar (+III) precursor (**78**) of **1**.





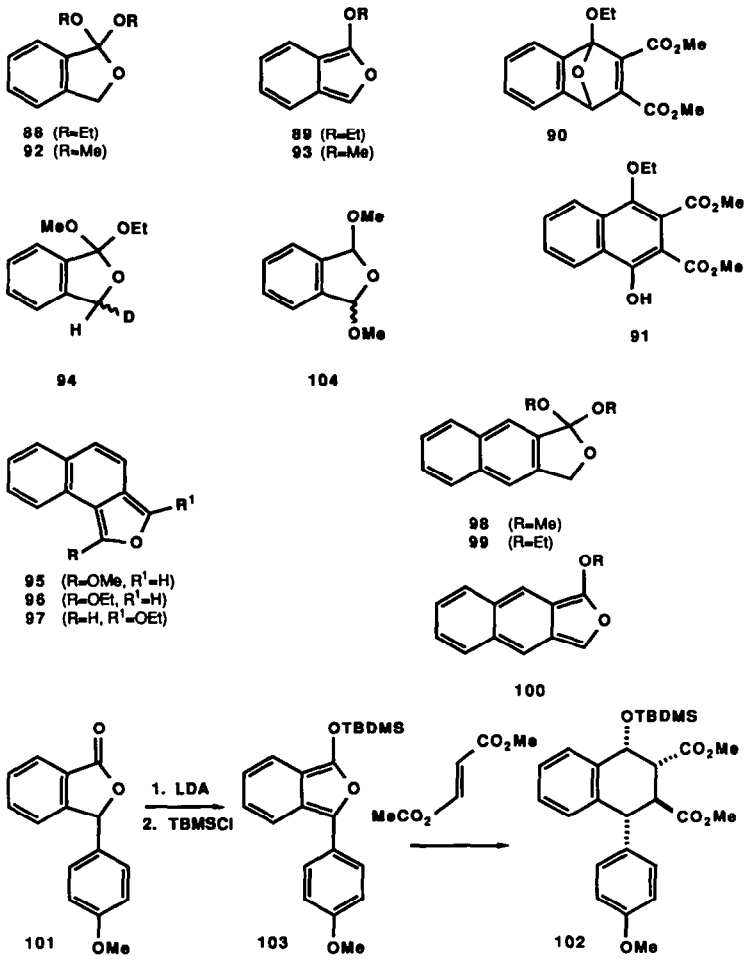
Scheme 2. Mechanism of phthalan isobenzofuran interconversion.

Benzylidene phthalide (**79**) is an interesting (+V) starting material readily available by modified Perkin reaction between phthalic anhydrides and phenyl acetic acid. Other phthalides **80** and **81**, as well as the naphthalides **82–84** are available by this general process. All these (+V) materials provide (+III) phthalans (e.g. **85**) when reduced with lithium aluminum hydride, which dehydrate to (+III) arylidene phthalans (e.g. **86**) with acid. The latter are in a tautomeric, acid/catalysed equilibrium[40,41] with the corresponding IBFs (e.g. **87**). This equilibrium was studied using CH_3CO_2D and ^1H and ^2H NMR. Deuteration at all non-aromatic carbon atoms was observed with decomposition of the IBF intervening to a greater or lesser extent depending on the system being studied. When these deuterations were run in competition with the Diels–Alder reaction (i.e. with d-acetic acid in the presence of dimethyl acetylenedicarboxylate) very little deuterium incorporation at the bridgehead position of the adduct was observed. It is therefore inferred that reprotonation of the IBF to form benzylidene phthalan is slow in comparison to its cycloaddition to the dienophile. A mechanistic proposal[41] to account for the results has been presented (Scheme 2). The same tautomeric equilibrium had been observed[42] for 1-benzylisobenzofuran (prepared by FVT) but not for 1-methyl or 1,3-dimethyl isobenzofurans.

III.2b. *Synthesis of (+IV) isobenzofurans*

III.2b.i. *From phthalides (III+I) starting materials.* The Meerwein salt obtained from phthalides (Section III.2a.ii) was first used[43] as a source of isobenzofurans 10 years ago. Upon quenching with sodium ethoxide, *ortho*-ester **88**, a (+IV) phthalan precursor of the (+IV) IBF **89**, is obtained. When heated in chloroform solution at 150° (sealed tube) in the presence of a dienophile, **88** yields **89** which is trapped by the dienophile and the adduct spontaneously aromatized. Thus with **88** and DMAD the naphthol **91** is obtained via the adduct **90**. The 1,4-elimination of methanol from **92** may also be effected by acid or base and the resultant 1-methoxy IBF **93** intercepted[44] by dienophiles. In subsequent work the 1-ethoxy IBF **89** was isolated in ethereal solution and shown to react with dienophiles to provide the expected bicyclo adducts; with d-methanol, 1,4-addition was demonstrated and the deuterated mixed *ortho*-ester **94** isolated.[45] The same basic methods have also been used[5] to prepare the (+IV) angular naphtho[c]furans **95–97** by acid catalysed elimination of the respective alcohol from the (+IV) *ortho*-ester precursors. The *ortho*-ester precursors (**98**, **99**) of the linear (+IV) naphthofuran were prepared but could not be converted[6] into the desired linear naphtho[c]furan **100** under acidic or basic conditions. This fact again reflects the greater ease of formation (stability) of the angular naphtho[c]furan over the linear isomer.

A direct access to (+IV) isobenzofurans from phthalides (see Section VI.3 also) would appear to be merely a matter of deprotonation at C-3 and quenching the enolate by O-silylation. This has

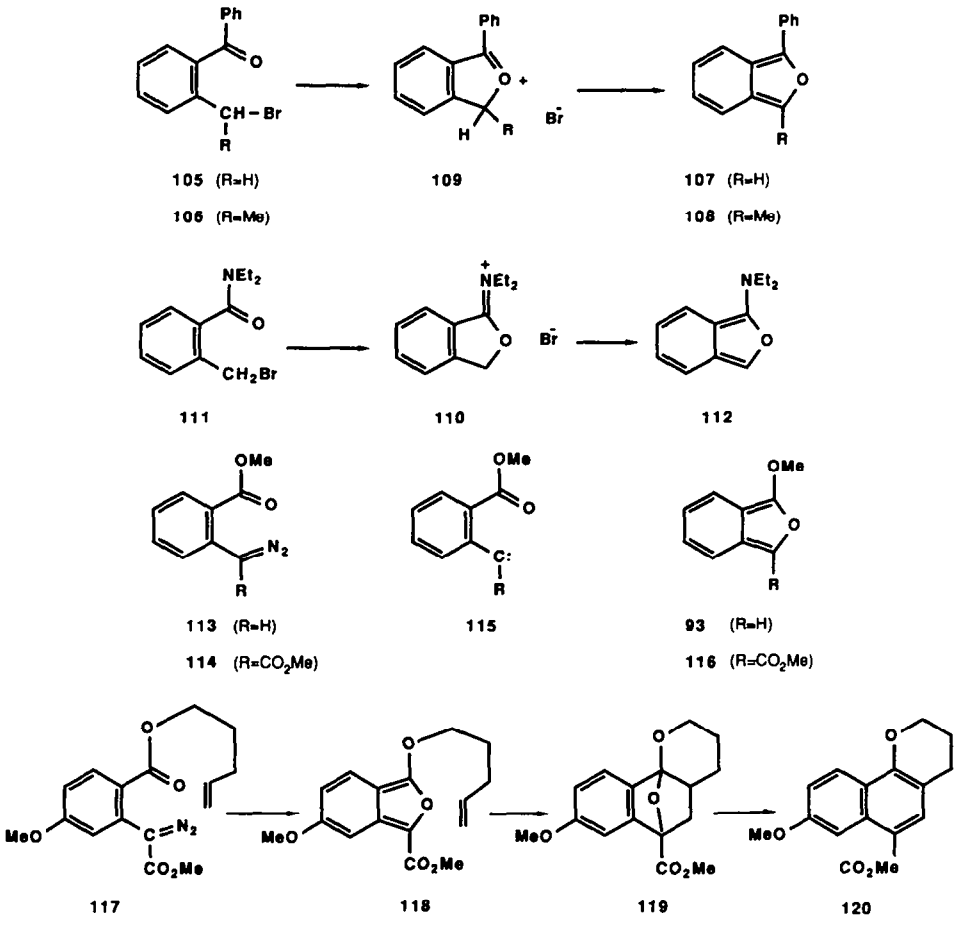


only recently been achieved[46] with a series of phenyl phthalides. The process is illustrated for the one pot conversion of phthalide **101** to the adduct **102** (major stereoisomer) via isobenzofuran **103** in 80% yield. This technique was subsequently applied to the synthesis of the lignan diphyllin (Section VII.2.a).

III.2b.ii. *From* ortho *dicarbonyl (II+II) starting materials.* The cyclic acetal of phthalaldehyde **104**, easily prepared[47] as a *cis–trans* mixture, has been exploited[48] as a (II+II) precursor of the (+IV) isobenzofuran **93**. Acid and base/catalysed elimination of methanol from both *cis* and *trans* isomers was achieved although the base catalysed process with lithium diisopropyl amide was the more efficient and proceeded best in THF to yield isolable solutions of **93**. Again it was demonstrated that **93** will add methanol to provide **92** and react with dienophiles to form the expected Diels–Alder adducts.

III.3. *Synthesis of (+III) and (+IV) isobenzofurans from other benzenoid precursors*

An early discovery of a different route to (+III) IBFs from (+III) benzenoid precursors was made in a study[49] of the side chain bromination of *ortho* alkyl benzophenones. The ready decomposition of the initially formed bromo derivatives **105** and **106**, with loss of hydrogen bromide, prompted the speculation that phenyl isobenzofurans **107** and **108** were being produced. This was easily confirmed by the formation of the usual oxabicyclo adducts when dienophiles were present in the reaction mixture. The mechanism of IBF formation was not addressed but a cationic intermediate (**109**) seems likely in view of a subsequent isolation[50] of a related salt **110** when the bromide **111** was allowed to stand at room temperature. Salt **110** corresponds to a (+IV) precursor and provides the (+IV) isobenzofuran **112** when treated with tetramethyl piperidine.

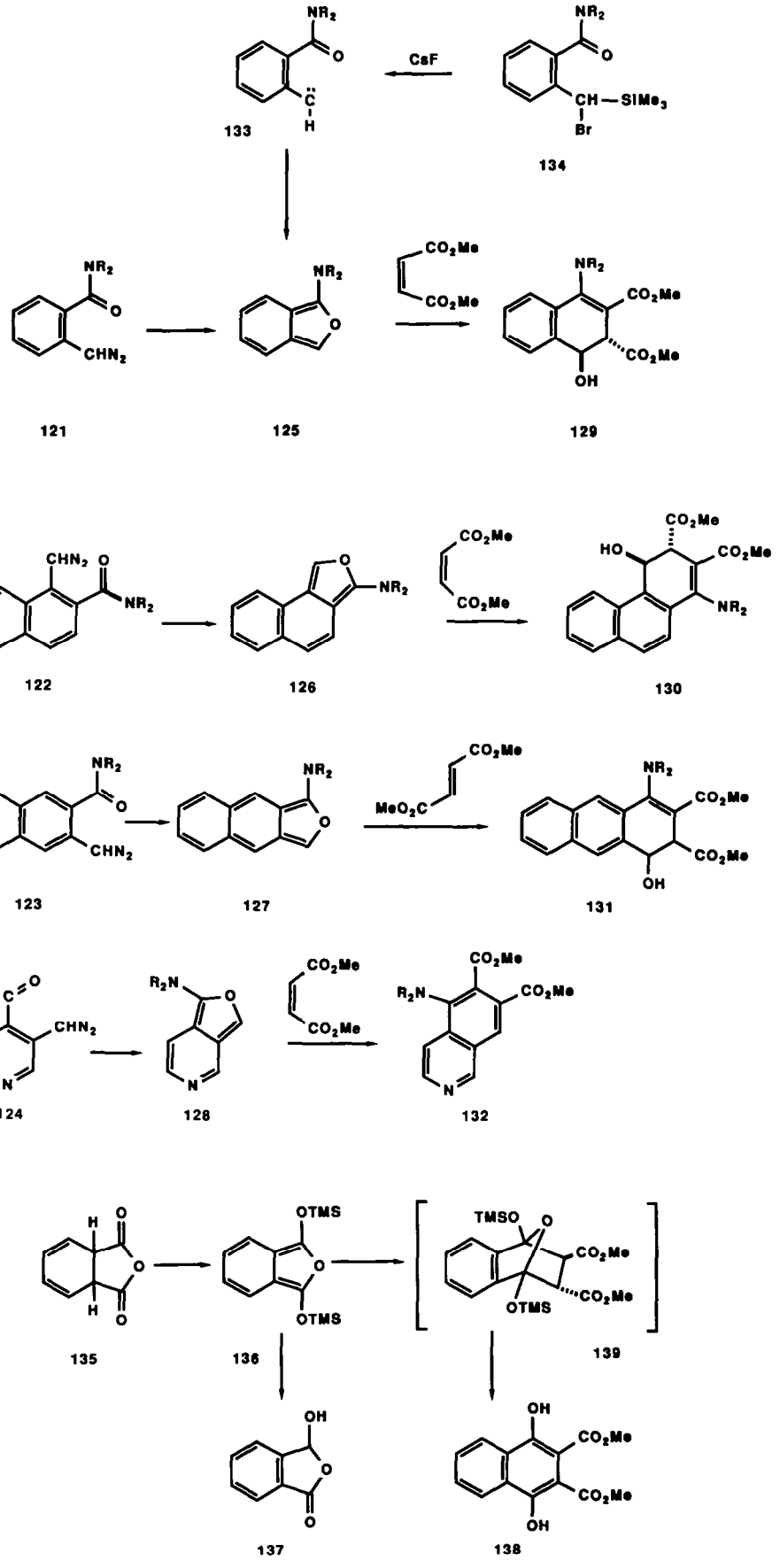


Analogous cyclizations that proceed through carbenoid intermediates have produced the (+IV) alkoxy and amino isobenzofurans. Thus the *ortho* carbomethoxy diazo compounds **113** and **114** upon treatment with $Cu(acac)_2$ cyclize via carbenes **115** with the generation of methoxyisobenzofurans **93** and **116** which may be intercepted by an added dienophile.[51] An intramolecular Diels–Alder variant of the scheme has recently been employed[29] to produce the oxaphenanthrene **120** from the diazo ester **117** through isobenzofuran **118** and adduct **119**.

Similar processes with *ortho* diazomethyl tertiary aromatic amides have been comprehensively investigated[50] and illustrated with benzene (**121**), naphthalene (**122, 123**) and pyridine (**124**) based starting materials. In all cases Diels–Alder adducts of the corresponding isobenzo (**125**), isonaphtho (**126, 127**) and azaisobenzofuran (**128**) intermediates were obtained upon treatment of the substrates with copper(II) or rhodium(II) reagents in moderate yields. In all these instances the oxabicyclo adducts were not isolated but suffered spontaneous cleavage (**129–131**) or aromatization (**132**). The presumed carbenoid intermediate **133** was also generated by α-elimination from the bromosilane **134**. The method has not been extended to the intramolecular Diels–Alder as yet, but the potential exists for preparation of interesting nitrogen heterocycles by incorporating dienophilic residues in the *N*-alkyl groups of the starting tertiary benzamide.

III.4. *Synthesis of (+V) isobenzofurans*

Phthalic anhydride, a (+VI) benzenoid starting material, upon electrochemical reduction yielded the dihydro derivative **135**, the non-benzenoid precursor of (+V) IBF **136**. This annelated succinic anhydride (**135**) was converted to its bis enolsilyl ether by standard methods (zinc chloride, triethyl amine and trimethyl silyl chloride in acetonitrile) to provide[52] a yellow solution, probably containing **136**, stable at −20°C, but rapidly transformed into hydroxy phthalide **137** at room temperature. The addition of dienophiles (dimethyl fumarate, *N*-phenyl maleiimide) produced low yields of the naphthalene 1,4-diols (e.g. **138**) formed by spontaneous aromatization of the intermediate adducts

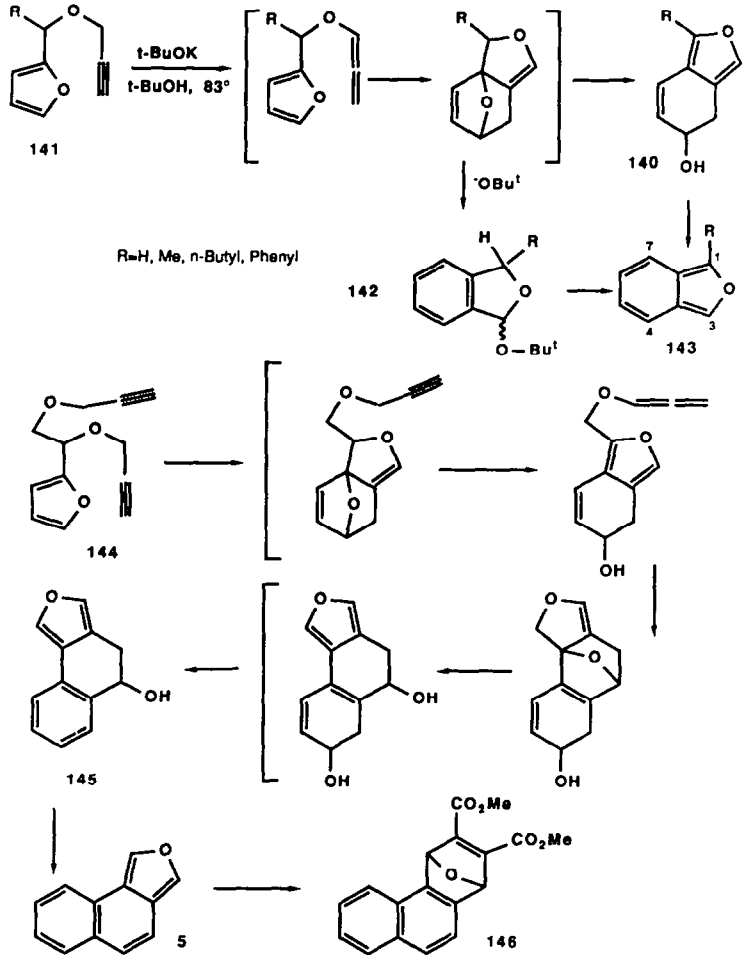

NR2
O
CsF
CH—SiMe3
Br
133
134
CHN2
121
125
CO2Me
129
122
126
130
123
127
131
R2N
124
128
132
OTMS
TMSO
135
136
139
137
138
OH

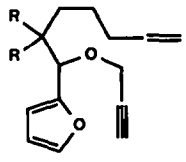
(e.g. **139**). The Diels–Alder reaction was slow at temperatures below 0°C, but above that temperature the conversion to **137** was extremely rapid. The tetraphenyl derivative of **136** (prepared from tetraphenyl phthalic anhydride) was more stable and also permitted the isolation of the oxabicyclo adducts in modest yields. These bis silyl ether adducts were aromatized by potassium fluoride in methanol.

III.5. *Isobenzofurans from non-benzenoid precursors*

A few methods in this category have been devised where the benzenoid ring is constructed from non-benzenoid precursors. Although considerable ingenuity has been displayed in some cases, the practical value of these procedures for isobenzofuran synthesis is debatable in view of the versatility of the various alternatives (Sections III.2 and III.3) and the ready availability of benzenoid starting materials.

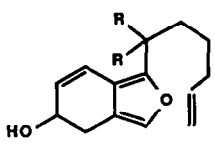
One of the more ingenious processes in this group is the so-called furan ring transfer (FRT) protocol[53] where a furanoid starting material is transformed into an annelated furanoid product by means of one or more intramolecular Diels–Alder reactions. The simplest illustration involves the production of **140** from **141** under basic conditions. A second pathway for oxygen bridge cleavage is in fact available and leads to substantial quantities of (+III) phthalans (**142**) when R is an alkyl group or a thioketal moiety. In any case, both **140** and **142** provide isobenzofurans **143** (R = H, Me, *n*-butyl, and phenyl) upon exposure to camphorsulfonic acid. The only disubstituted furanoid starting material used was a 5-methyl derivative which provided **143** bearing a 4-methyl substituent. Provision can be made in this scheme for a second intramolecular Diels–Alder reaction. Thus the furanoid material **144** undergoes a one-pot double FRT sequence to provide the angular naphtho[c]furan precursor **145**. The naphthofuran **5** is generated from the latter by acid treatment and trapped with DMAD to provide the adduct **146**. The same process carried out with furanoid





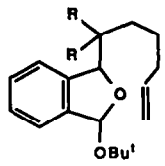
147 (R=H)

148 (R+R=-S(CH$_2$)$_3$S-)



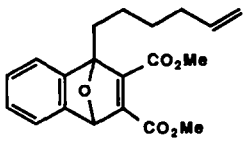
149 (R=H)

150 (R+R=-S(CH$_2$)$_3$S-)



151 (R=H)

152 (R+R=S(CH$_2$)$_3$S)



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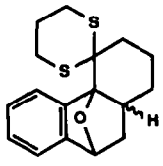

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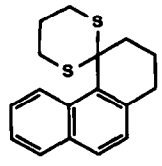

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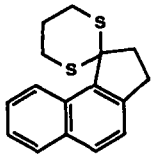


156

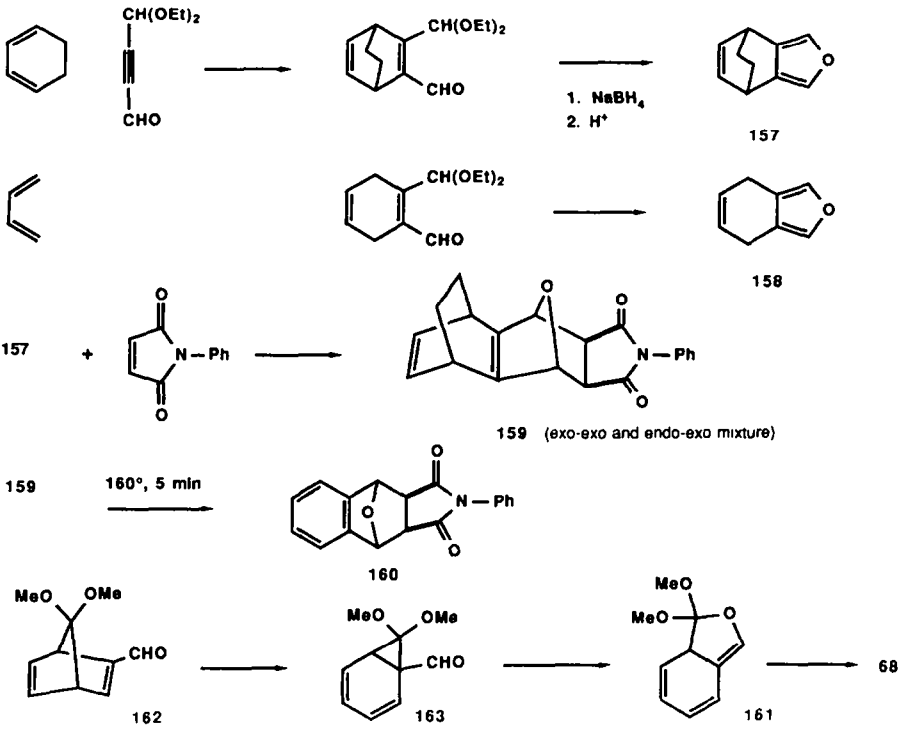
precursors bearing only one oxygen-containing substituent (e.g. **147** and **148**) produce **149**, **150** and **151**, **152** respectively after one FRT sequence. A second Diels–Alder reaction can now be effected upon acid treatment of these materials. It turns out that the **149**, **151** pair do not undergo intramolecular cycloaddition but do add intermolecularly to DMAD to provide the expected adduct **153**, while the dithianes **150**, **152** prefer to react intramolecularly even in the presence of DMAD to yield the *exo* and *endo* adducts **154** and aromatized product **155**. This difference in behavior is attributed to the dithiane substituent in **150**, **152** producing a suitable juxtaposition of diene and dienophile for the intramolecular Diels–Alder reaction. Annelation with a five-membered carbocycle (e.g. **156**) was also achieved.

A somewhat simpler approach[54] combines the alcohol-acetal technology with Diels–Alder construction of the six-membered ring to produce **157** and **158** which are masked equivalents of **1**. These furans undergo cycloaddition with dienophiles and subsequent aromatization of the adducts by thermolysis (**157**) or dehydrogenation (**158**) provides adducts of **1**. Exclusively *exo* addition is observed to take place with **157** and *N*-phenyl maleimide for example, to yield **159** (and **160** after thermolysis).

The isobenzofuranoid *ortho*-ester **161** has been reported[55] to arise from thermal rearrangement of the norbornadiene acetal **162** through norcaradiene **163**. The structure of **161** was not rigorously established but it was reported to form phthalide **68** upon treatment with trifluoroacetic acid. Methoxyisobenzofuran **93** may well be an intermediate in the latter conversion and might be intercepted by a dienophile when **161** is treated with acid or base.

IV. SPECTROSCOPIC PROPERTIES OF ISOBENZOFURANS

A brief summary of UV, ^{1}H NMR, mass and photoelectron spectra is found in one of the early reviews.[9] The isolation of some moderately stable isobenzofurans have permitted some further studies of the mass spectra and an assignment of the ^{13}C NMR spectra.[16]

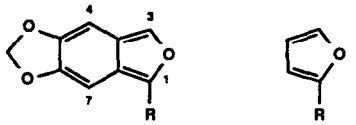


IV.1. *NMR spectra of isobenzofurans*

The ^{1}H and ^{13}C NMR spectra of **15** and **52** have been published. The proton spectra are unexceptional. Thus H-3 (the furanoid proton) is the farthest downfield at 7.85 and 7.88 ppm respectively (7.98 ppm in **1**). Signals due to H-4 and H-7 are coincident at 6.69 ppm in **15** but found at 6.65 (H-4) and 7.75 ppm (H-7) in **52**, presumably due to anisotropic deshielding of H-7 by the ester carbonyl group.

The ^{13}C NMR spectra of **15** and **52** were obtained and compared with the spectra[56] of the cyanofuran **164** and carbomethoxy furan **165**. The chemical shifts were assigned by use of broad band fully coupled spectra and by selective decoupling (H-7) of C-7 in **52** to differentiate it from C-4. Assignments of C-5 and C-6, the oxygenated carbons, are arbitrary. Although direct comparisons of the chemical shifts, **15** with **164** and **52** with **165**, are obviously not fruitful, the effect of the substituent (CN, CO_2Me) on each system, furan and isobenzofuran, can be evaluated and compared. The most convenient way of doing this is to define a differential substituent parameter $\Delta\delta$ (CO_2Me $-CN$) for the two pairs of compounds. These values, obtained by subtraction for the furanoid carbon atoms, are included in Table 1 and show by their close correspondence that the effect of these substituents on each furanoid carbon atom is similar irrespective of whether the system is a furan or isobenzofuran, i.e. in their ^{13}C shieldings the furanoid carbon atoms of an isobenzofuran are like those of a furan.

Some coupling constants were also available from the spectra and these are shown in Table 2. The furanoid carbon has a large (> 200 Hz) ^{1}J coupling with its hydrogen atom in all cases. This relates to the s-character of the bond and the observed acidity of the α-protons in these systems. Another feature of the coupling constants is the large ^{2}J value C-3a–H-3 observed in common with



15 (R=CN) **164** (R=CN)

52 (R=CO_2Me) **165** (R=CO_2Me)

Table 1. ^{13}C chemical shift assignments (δ in ppm from TMS) for **15** and **52** in $CDCl_3$

Compound	1	3	3a	7a	4	5	6	7	OCH_2O	CN	C=O	Me
15	117.6	139.5	121.9	130.9	91.2	148.7	151.5	93.1	101.8	112.5		
52	134.4	138.3	122.7	127.4	92.7	147.9	150.9	94.9	101.3	-	159.5	51.5
$\Delta\delta$ (52-15)	16.8	-1.2	0.8	-3.5								
$\Delta\delta$ (165-164) [a]	18.8	-1.6	0.3	-4.7								

[a] From Ref. 56 for corresponding carbon atoms in **164** and **165**.

Table 2. A comparison of coupling constants (Hz) for **15**, **52**, **164** and **165**

Compound	^1J C_3-H_3	C_4-H_4	C_7-H_7	OCH_2O	CH_3	^2J C_{3a}-H_3	C_{3a}-H_7	^3J C_1-H_3	C_{7a}-H_3	C_{7a}-H_4
15	208	170	169	175		13.4	5.7	7.6	6.3	5.7
52	206	169	172	175	147.3	13.4	5.7	b	5.7	5.7
164 [a]	207	-	-	-	-	13.3	-	b	6.0	-
165 [a]	205	-	-	-	-	13.5	-	b	5.8	-

[a] From Ref. 56 for corresponding carbon and hydrogen atoms.
[b] Not measurable.

the furans. In general these comparisons of the coupling constants and chemical shifts not only help to confirm the assignments of the signals in **15** and **52** but also support the expression **14** (X = O) for the structure of isobenzofuran.

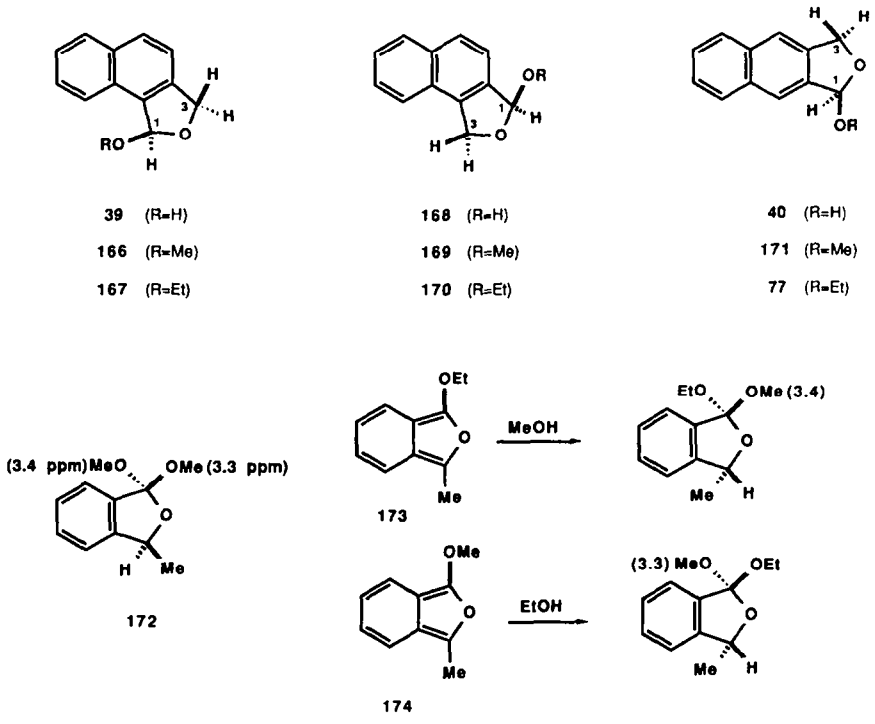
IV.2. *NMR spectra of alkoxyphthalan precursors*

The 1,3-disubstituted phthalans exist in *cis* and *trans* diastereomeric forms. The compounds bearing at least one alkoxy group show long range coupling ($J_{1,3} \approx 2.5$ Hz) between the protons H-1 and H-3 in the *trans* isomer. This has been recognized as a stereochemically diagnostic feature[25] and confirmed[38] by NOE experiments with *cis* and *trans* 1-methoxy-3-phenyl phthalans. Such long range coupling had also been observed in 2,5-dihydrofurans and ascribed[57] to a dual pathway interaction ($^4J + {}^5J$) but it is interesting that in both angular naphthalans **39**, **166–170** the signal of acetal proton H-1 is a doublet, coupled to the H-3 proton *trans* to it [$J_{1,3}$(*trans*) = 2.5–3.0 Hz] while in the linear isomers **40**, **77** and **171** the same proton is only a slightly broadened singlet.[5,27] These observations seem to suggest that the major component of the "dual pathway" interaction that produces the *trans* coupling of 2.5–3.0 Hz in these phthalans is the homobenzylic ^5J interaction. The decrease in "double bond character" of the connecting 2,3-bond of the naphthalene in **40**, **77** and **171** compared with the 1,2-bond in the six angular examples reduces homobenzylic coupling in the linear phthalans to almost zero.

A firm assignment of phthalan geometry[38] is essential for establishing the *syn* stereochemistry of both the 1,4-elimination of alcohol to produce isobenzofurans and the 1,4-addition of alcohol to the preformed IBF to regenerate the (+IV) phthalan (*ortho*-ester). Thus NOE experiments enabled the assignment of the methoxyl signals of *ortho*-ester **172** as shown. When the addition of methanol to IBF **173** and ethanol to IBF **174** was carried out the major product from **173** had a methoxyl singlet at 3.4 ppm (*cis* to H, *trans* to Me, when **172** is used as the standard) and the major product from **174** had its methoxyl singlet at 3.3 ppm, both results indicating *syn*-addition of the alcohol.[38]

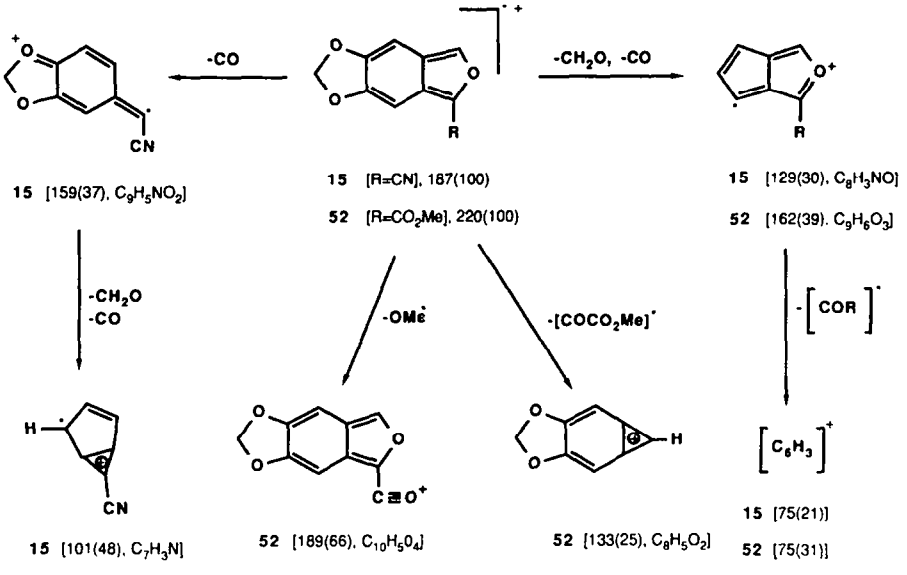
IV.3. *Mass spectra of isobenzofurans*

The mass spectrum of **1** was reported[2] to show strong peaks for the molecular ion at *m/z* 118 and for ions at *m/z* 90 and 89 resulting from its decomposition by loss of CO and subsequent loss of a hydrogen atom. The stable IBF **2** was also investigated[58] and found to produce both M^+ and M^{2+} peaks. A fragmentation scheme involving loss of the 1-substituent (C_6H_5) alone, and together with the neighboring carbon and oxygen ($M - C_6H_5CO$) was proposed.



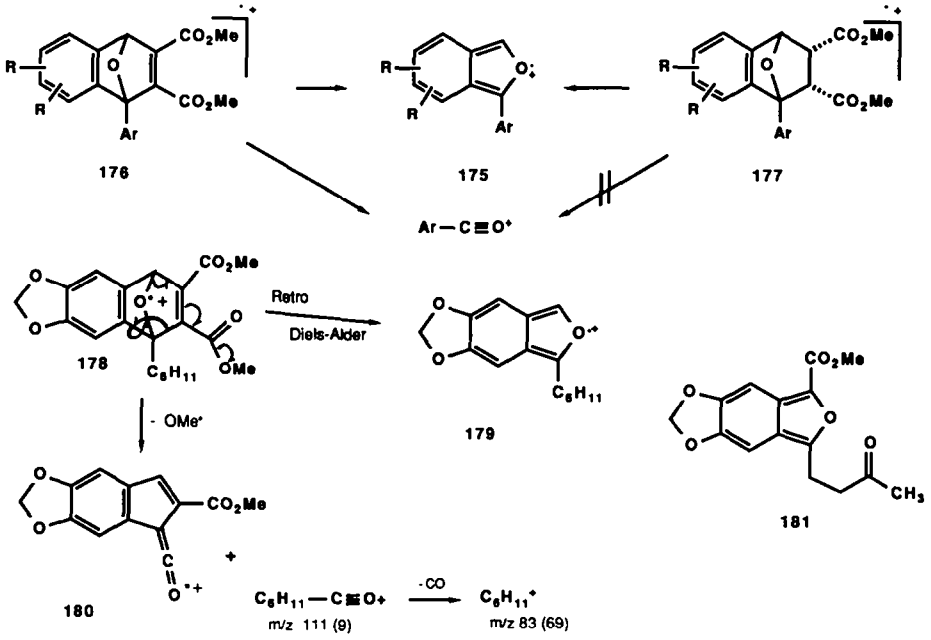
With the availability[16] of the stable isobenzofurans **15** and **52** and the report that most oxabicyclo adducts provide intense IBF ions in their mass spectra by reverse Diels–Alder cleavage, a more comprehensive study of the mass spectra of various IBFs was undertaken.[59]

A fragmentation scheme for isobenzofurans **15** and **52** with the more prominent ions shown, is found in Scheme 3. The spectra of several adducts of **15** and **52** also contained all the ions of Scheme 3 in similar abundance. Adducts of aryl isobenzofurans produced intense IBF peaks (**175**) but very little further fragmentation, except for the loss of a methyl fragment (IBF − 15) in methoxylated examples. An abundant ion found in all DMAD adducts of aryl IBFs (**176**) corresponds to the acylium ion ($ArCO^+$). The fact that this ion is not found in the hydrogenated adducts (**177**) suggests that it does not originate from the IBF ion **175** but rather by a special cleavage restricted to acetylenic adducts (**176**, **178**). In the spectrum of the cyclohexyl IBF adduct **178** for example, the base peak at



Scheme 3. The major ions in the mass spectra of isobenzofurans **15** and **52**.

m/z 244 is in fact a doublet ($C_{15}H_{16}O_3$, cyclohexyl IBF **179**, and $C_{13}H_8O_5$ **180**) whose presence is rationalized as shown. The cyclohexyl acylium cation $C_6H_{11}CO^+$ is not very prominent [*m/z* 101 (9)], unlike the $ArCO^+$ cases above (**176**), but an abundant cyclohexyl cation is observed at *m/z* 83 (69). The stable, alkyl IBF ester **181** also investigated in this study shows strong peaks at M − OMe (22), M − $COCH_3$ (100) and M − CH_2COCH_3 (84).



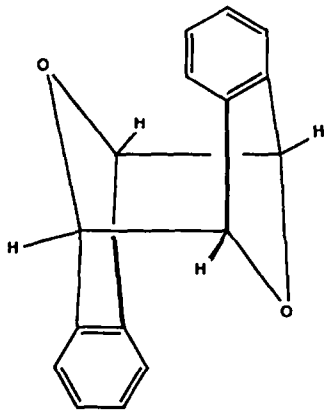
V. REACTIONS OF ISOBENZOFURANS

With one exception, all chemical reactivity of the benzo[c]furans that has been described so far is confined to the furanoid ring. The most facile and useful is the Diels–Alder reaction which has been intensively studied and will be discussed later. Reactions with singlet oxygen, photochemical reactions, lasing properties and fluorescence of IBFs have been adequately reviewed by Friedrichsen[9] and will not be considered further except for one report[60] that establishes the *anti*-stereochemistry of the [8+8] photodimer of **1** formed in acetone at −60°C as **182** by the use of lanthanide-induced shift NMR. Two other dimers were also obtained when **1** was irradiated in ether at −60°C. These were an (8+4) dimer assigned structure **183**, the only example of a reaction at the cyclohexadiene double bond termini of an IBF, and a skeletally modified product **184** whose structure was confirmed by synthesis. The former was obtained only in trace amounts and its structure is tentative.

The *syn* addition of alcohols to the furanoid moiety of IBFs has already been discussed; the 1,4-reduction of the furanoid moiety to form phthalans has also been recorded.[3,4]

V.1. *Lithiation of isobenzofurans*

The deprotonation of **1** and related IBF systems has been achieved.[61] The experimental conditions are simple, and the lithiated species easily intercepted by a variety of electrophiles. In practice the alkoxy phthalan precursor **71** in tetrahydrofuran is treated with 0.05 equivalents of diisopropylamine and 2.1 equivalents of methyl lithium at 0°C. The reaction, monitored by evolution of methane, is complete in a few minutes under these conditions. The ^1H NMR spectrum of the resulting yellow solution when determined and compared with that of **1** can also be used to monitor the formation of the lithio-IBF (**185**). Addition of D_2O and various electrophiles followed by further ^1H NMR spectra or by Diels–Alder reactions readily establish the site of lithiation as C-1 of **1**. It is believed that the lithiation is accomplished by LDA and the role of the methyl lithium is to regenerate this base. The same conditions effect the lithiation of furan but at a slow rate, and it is clear that **1** is much more acidic than furan. Sequential lithiation of **1** at both C-1 and C-3 by a



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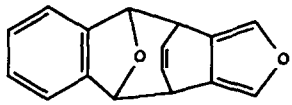

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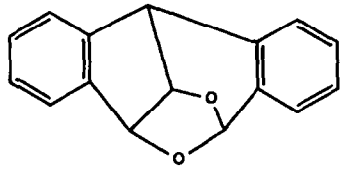
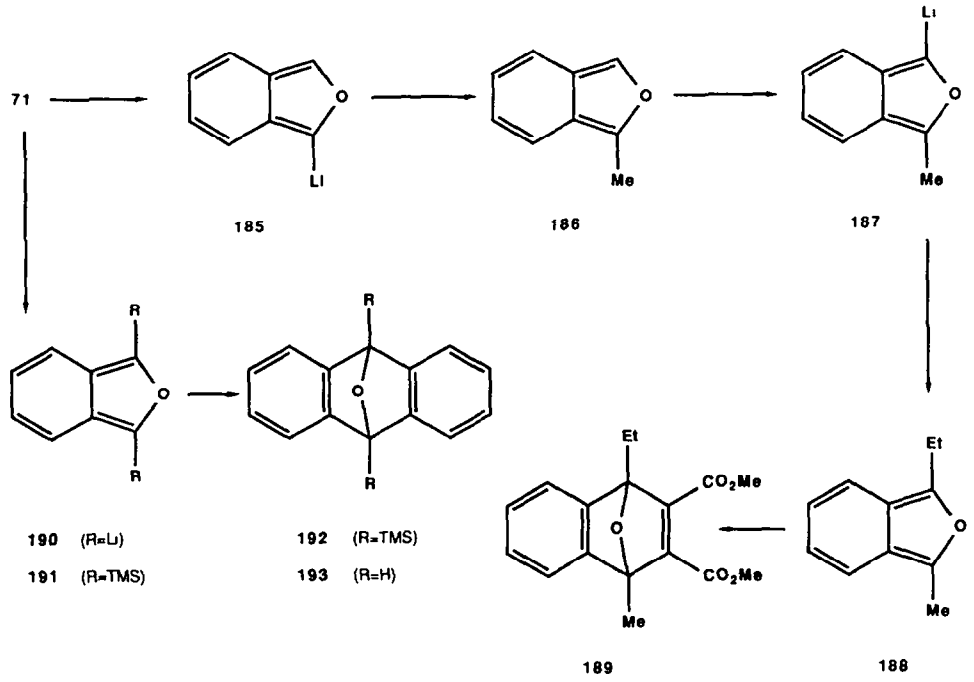


184

"one pot" procedure was also developed. Thus the alkoxy phthalan **71** was lithiated and methylated as before to produce 1-methyl IBF **186** in solution. The sequence was repeated and ethyl iodide added to quench the new lithio IBF (**187**) and provide the 1-methyl-3-ethyl IBF **188**. One equivalent of TMSCl was then added to quench the excess base and the cold solution added directly to an ethereal solution of DMAD to afford the adduct **189** in 45% yield. This versatile technique has been shown to produce a variety of adducts, substituted as desired at one or both bridgeheads by deuterium, alkyl, alkoxyl and/or silyl residues.[48,61] Benzyl IBF, however, could not be formed by these methods. The direct 1,3-dilithiation of IBF by the use of 4 equivalents of methyl lithium or butyl lithium was also possible though not as efficient as the sequential procedure. The basic conditions were also proven to be especially compatible with the generation of benzyne for Diels–Alder reactions with IBF, provided the acidic H-1 and H-3 sites were silylated. On this basis a



190 (R=Li)
191 (R=TMS)
192 (R=TMS)
193 (R=H)
185
186
187
188
189

general procedure for the use of benzyne as a dienophile was developed. The ethoxy phthalan **71** was treated with 3.1 molar proportions of *n*-butyl lithium and 0.05 moles of diisopropylamine as before at 0°C. The 1,3-dilithio species **190** generated in this manner was quenched with 2 moles of trimethylsilyl chloride and the IBF **191** formed in solution. One mole each of bromobenzene and lithium tetramethylpiperidide then produced benzyne *in situ* which afforded the adduct after 14 h. This convenient one-pot procedure from **71** to **192** (57% overall) was proven[62] to be an excellent general method for IBF–aryne cycloadditions, with the potential for rapid access to many polyaromatic hydrocarbon systems (discussed in Section VIII). Protodesilylation of the adducts (e.g. **192** → **193**) was easily achieved by fluoride or potassium hydroxide in dimethyl sulfoxide.

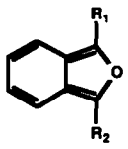
V.2. *Diels–Alder reactions of isobenzofurans*

Isobenzofurans have long been recognized as outstanding dienes (4π-components) for the Diels–Alder and other cycloaddition reactions. The commercially available 1,3-diphenyl IBF, especially, has been a popular trapping agent for transitory alkenes and alkynes.[9] The earlier work including ($\pi_4+\pi_2$) and higher cycloadditions has been comprehensively reviewed[9] and most of it involved the use of diaryl isobenzofurans. With the availability of a variety of substituted IBFs by modern synthetic techniques the scope of their Diels–Alder reactions has been greatly expanded. The rates, stereochemistry and regiochemistry have been investigated and the reaction has been used in the construction of polycyclic natural products and for PAH synthesis (discussed in Sections VII and VIII). The great reactivity of the IBF partner permits the use of dienophiles ranging from the very poor unactivated alkenes through the common carbonyl and cyanide activated alkenes to the very reactive benzynes.

Very recently, the availability of solution stable IBFs has been exploited[63] in the determination of relative rates for their Diels–Alder reactions with a common dienophile, *N*-methyl maleimide. The results shown in Table 3, while not surprising, correlate very well with substituent effects determined for the Diels–Alder reactions of butadienes even though the isobenzofurans are 10^6 more reactive than butadienes in cycloadditions. The relative rates of intramolecular Diels–Alder reactions of **196–198** were also compared. As expected the silyl IBF **198** depressed the rate about tenfold in comparison to **196** but the lithio species did not react at all, an interesting observation which suggests that lithiation can be a useful tactic to protect against Diels–Alder reactions of IBFs when required.

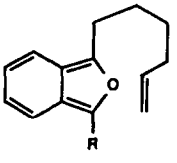
In contrast to the Diels–Alder reactions of furans, the reactions of isobenzofurans are generally not reversible under the conditions normally employed. The only exceptions are found in the cycloadditions with maleic anhydride where some examples of reversibility have been recorded.[40,64]

Table 3. The relative rates of the Diels–Alder reaction[63] with *N*-methyl maleimide

IBF 	Relative Rate
1 (R_1=R_2=H)	1
186 (R_1=H, R_2=Me)	2.2
194 (R_1=H, R_2=n-Bu)	1.8
89 (R_1=H, R_2=OEt)	3.8
3 (R_1=R_2=Ph)	0.088
191 (R_1=R_2=$SiMe_3$)	0.023
195 (R_1=OEt, R_2=$SiMe_3$)	0.25

Several reports of the regioselectivity of the Diels–Alder reactions of 1-substituted isobenzofurans (**199**) with common unsymmetrical dienophiles (**200**) have appeared. The general outcome of these investigations is that the "*ortho*" adducts (**201**) always predominate in these reactions, whether the 1-substituent in the IBF is highly electron donating[43,44,50] (R = OR, NR_2), electron withdrawing[16,17] (R = CO_2Me, CN, Br) or in between[17,40] (R = alkyl). The results have been rationalized by frontier orbital arguments. In the reactions of the stable angular naphthofuran **5** however, reversibility has been detected[5] for the addition of several dienophiles; in addition no regioselectivity at all was observed with unsymmetrical dienophiles like butenolide or α-acetoxy acrylonitrile. The 1,3-disilylated variant, isonaphthofuran **202**, was similarly devoid of regioselectivity in its reactions[65] with unsymmetrical benzynes, 3,4-pyridyne and 1,2-naphthalyne, but the replacement of one trimethyl silyl group with an ethoxy substituent (i.e. as in **203**) provoked a modest regioselectivity; the "*ortho*" adduct with 1,2-naphthalyne, **204**, was favored 2:1 over the "*meta*" regioisomer **205**, a result reinforced by the subsequent finding[66] that the isomeric naphthofuran **206** in reacting with 1,2-naphthalyne favored the "*ortho*" regioisomer (now **205**) by approximately the same ratio. Investigations with other substituted benzynes and 1-ethoxy-3-trimethylsilyl isobenzofuran (**195**) produced similar results. The low regioselectivities observed in these benzyne–IBF cycloadditions have been attributed[66] to the great reactivity of both partners. A low activation energy and an "early" transition state allow for little selectivity. Removal of the trimethylsilyl group and changing the dienophile to the less reactive α-acetoxy acrylonitrile, restores[5] complete "*ortho*" selectivity with naphthofurans **207** and **208**.

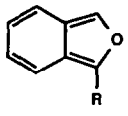
The Diels Alder additions of IBFs with olefinic dienophiles usually produce mixtures of *exo* and *endo* adducts and no general pattern is apparent. In cases where reversibility of the cycloaddition prevails the *exo* isomers gain predominance as the reaction is prolonged. The few examples[29,63] of intramolecular cycloadditions reported to date produce *exo* adducts; their formation may be rationalized by comparison of steric interactions in the *endo* and *exo* transition states of the reaction. No chiral auxiliaries have hitherto been employed in the Diels–Alder reactions of IBFs but in view of reports[67] of their use with *o*-quinodimethanes, applications to the cycloadditions of IBFs cannot be too far behind.



196 (R=H)

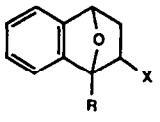
197 (R=Li)

198 ($R=SiMe_3$)

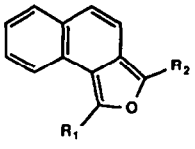


199

200



201



5 ($R_1=R_2=H$)

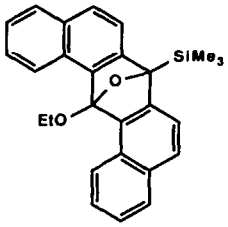
202 ($R_1=R_2=SiMe_3$)

203 ($R_1=OEt$, $R_2=SiMe_3$)

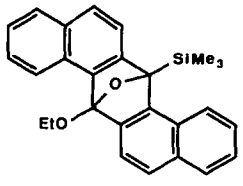
206 ($R_1=SiMe_3$, $R_2=OEt$)

207 ($R_1=H$, $R_2=OEt$)

208 ($R_1=OEt$, $R_2=H$)



204



205

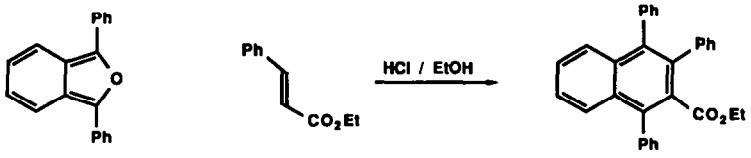
VI. CHEMICAL TRANSFORMATIONS OF OXABICYCLO ADDUCTS

The benzannelated oxabicyclo[2.2.1]heptanes and heptenes produced in the Diels–Alder reactions of IBFs with various dienophiles have proven to be a valuable source of napththalenes and hydronaphthalenes. The various methods of bridge deoxygenation that have been developed in the period under review have greatly expanded the scope of the cycloaddition as a convenient pathway to many polyaromatic hydrocarbons (PAHs) and diverse natural products as will be illustrated in later sections of this paper. At this stage however a short summary is offered of the various transformations of the adducts where carbon–carbon or carbon–oxygen bond cleavage takes place.

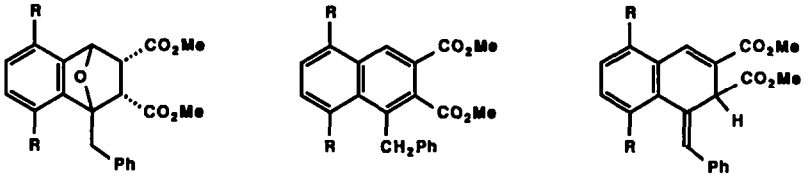
VI.1. *Reductive aromatization (dexogenation)*

Adducts of IBFs with triple bonded dienophiles (DMAD, benzyne, etc.) can be induced to extrude oxygen and produce naphthalenes (not naphthols) in variable yields by treatment of the adducts with low valent metallic reagents.[68] Another convenient procedure involving the use of an iron carbonyl[69] has also been successfully employed for IBF–aryne adducts.[62,65] The use of sodium borohydride in trifluoroacetic acid has been reported[70] to produce moderate to good yields of naphthalenes in several alkyl and halogen substituted adducts but has failed in the conversion of **209** to **210** when the iron carbonyl method alone effected the desired conversion[62] in 43% yield. Zinc and acetic acid has been used[71] with many benzyne adducts to form 9,10-disubstituted anthracenes in good yields. The subject of reductive aromatization of heteroatom bridged bicyclo heptenes has been reviewed.[72]

209 210



3 211



212 (R=H) 213 (R=H) 214 (R=H)

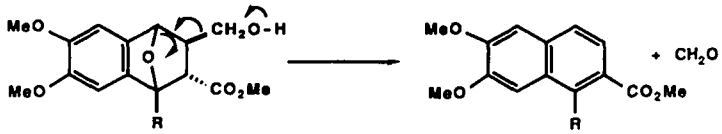
VI.2. *Aromatization without change in oxidation state*

The various methods that have been used for the conversion of oxabicyclo adducts to arenes have been reviewed.[73] Among these, the acid/catalysed process is the oldest and most commonly employed transformation of these compounds, reported[74] as long ago as 1932 (**3** to **211**). The reaction has been used many times since then, but yields range from excellent to poor and in a few instances extensive polymerization is observed and little aromatic product found.[40,75,76] Adducts of (+III) IBFs with triply bonded dienophiles (DMAD), or (+IV) IBFs with olefinic dienophiles are aromatized to naphthols; (+IV) IBFs with acetylenic dienophiles yield adducts that produce 1,4-dioxygenated naphthalenes[43] upon aromatization. Naphthalenes are formed by acid catalysed

dehydration of adducts of (+III) IBFs with olefinic dienophiles. Aromatization of adducts catalysed by various acidic reagents has been a standard procedure in PAH synthesis (Section VIII).

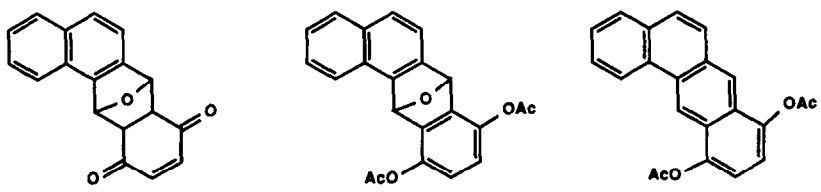
Some of the alternative pathways that lie hidden in these acid catalysed reactions have been uncovered and studied. Thus in cases where crowded, contiguously substituted arenes are produced, double bond isomerization has been observed. A typical example of such behavior is found in a study of the aromatization of adducts of some benzyl isobenzofurans. Thus, dehydration of mixtures of **212** with various acid catalysts always gave[40] mixtures of **213** and **214**, and the proportions of the non-naphthalenic product increased with increasing substitution in **212** (e.g. R = Me and R = Ph). A similar result has been observed in the acid/catalysed dehydration of crowded benzyne furan adducts.[77] Adducts substituted with a carboxyl or hydroxymethyl group in a "glycidic" relationship to the oxygen bridge also behave anomalously. Thus the benzyl IBF adduct **215** decarboxylates[40,78] upon aromatization to provide 1-benzyl naphthalene while adducts of general formulae **216** and **217** lose formaldehyde in a similar fashion to yield[79] the corresponding naphthalenes **218** and **219**. The aromatization of *p*-benzoquinone adducts by use of various acid catalysed techniques has been invariably attended by extensive decomposition[23,27,40] but in some cases the use of sodium acetate in acetic acid[21] or in methanol[40] has been successful. The aromatization of the adduct **220** was only possible by application of a two-step procedure; acetylation with acetic anhydride in pyridine was followed by *reductive* aromatization[27] of the diacetate **221** with trimethylsilyl iodide to yield the diacetoxy benzanthracene **222**. The reagent had previously been used[40] to aromatize the benzyl adduct **223** to provide a mixture of naphthol **224** and iodonaphthalene **225**

215

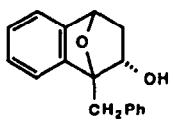


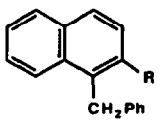
216 (R=H)
217 (R=aryl)

218 (R=H)
219 (R=aryl)



220 **221** **222**





223

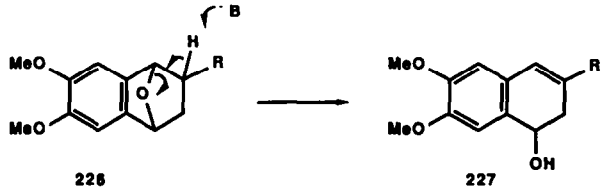
224 (R=OH)
225 (R=I)

in a non-reductive fashion. In general benzoquinone adducts, and naphthoquinone adducts to a lesser extent, are vulnerable to decomposition by anomalous pathways (discussed in Section VI.5) and aromatization by acid or base cannot be taken for granted in these cases. Adducts of (+III) IBFs with methyl vinyl ketone also undergo anomalous decomposition with acid (Section VI.5.).

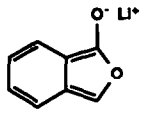
Base catalysed aromatization of simple adducts with methoxide[76] or sodium acetate[40] in methanol is believed to proceed in two steps, bridge cleavage and dehydration. The intermediate hydrated naphthalenes have been isolated and these reactions will be discussed in the next section. Other reagents used now and again for aromatization include triphenyl phosphonium dibromide[72] and phosphorus pentasulfide.[40,72]

VI.3. *Conversion to "napnthalene hydrates"*

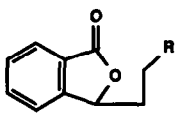
Treatment of many simple adducts with base under mild conditions effects[76] a smooth and high yield cleavage of the oxygen bridge to form 1,2-dihydro-1-hydroxy naphthalenes (naphthalene hydrates). The general reaction represented by conversion **226** to **227** (R = CHO, $COCH_3$, CO_2Me, CN) has been regarded as an anomalous "*5-endo-trig*" reverse Michael reaction whose occurrance was rationalized by qualitative frontier orbital arguments. The dihydro naphthalenes (**227**) can be isolated, the hydroxyl group may be silylated, the double bond hydrogenated, or the compounds easily dehydrated to naphthalenes with acid or base. The reaction was a key step in the synthesis of (±)-daunomycinone (Section VII.1).



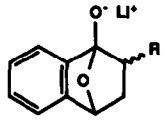
226 **227**



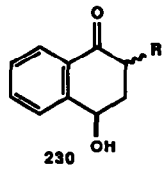
228



231



229

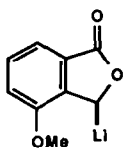


230

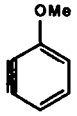
R = electron withdrawing group

This cleavage of the oxygen bridge to produce dihydronaphthalenes should be promoted by the presence of an electron-donating substituent at the bridgehead. This has indeed been shown[50] to be the case in that adducts of **125–127** which bear a dialkyl amino substituent at the bridgehead cannot be isolated but are spontaneously cleaved (*5-exo-trig*) to yield the dihydronaphthalenes **129–131**. This information, and the fact that several 1-phenyl phthalides are deprotonated and O-silylated to provide orange solutions[46] of 1-oxygenated IBFs (e.g. **103**) raises an intriguing possibility. The orange colour observed[80] in solution when phthalide is deprotonated may be an indication that the anion exists as the IBF **228**. It is then possible that the reactions of the lithio phthalide with α,β-unsaturated esters,[80] benzynes[81] and even isoquinolinium salts[82] are examples of Diels–Alder reactions of this very reactive IBF. The *exo–endo* mixtures of "*ortho*" adducts **229** (expected regioisomer) should undergo spontaneous oxygen bridge cleavage in the strongly basic medium (just like the dialkylamino adducts did) to form epimeric mixtures of hydroxy tetralones (**230**), or carbon–

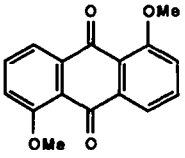
carbon bond cleavage to form substituted phthalides **231**.[80,82] In the addition[81] of the anion **232** to 3-methoxy benzyne **233** the anthraquinones **234** and **235** are formed (*ca* 20 : 1 ratio) after aerial oxidation. Similar regiochemistry is found[66] in the addition of IBF **236** to **233**. Adducts **237** and **238** are obtained in a 4 : 1 ratio.



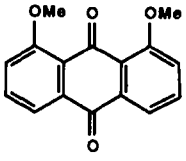
232



233



234



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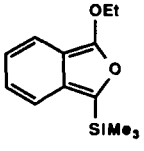
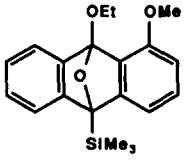
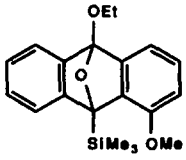


236

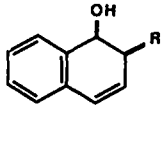


237

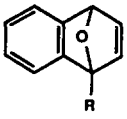


238

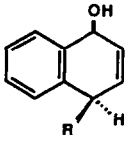
Other methods of producing "naphthalene hydrates" from oxabicyclo compounds involve hydride reduction. Two procedures have been published. Both were illustrated with the benzyne furan adduct **239** as the substrate. Application of an early procedure for the reductive cleavage of tetrahydrofuran by lithium tri-*t*-butoxyaluminohydride and triethyl borane to **239** resulted in smooth S_N2 reductive cleavage[83] to the 1.4-dihydro naphthalene **241**. By use of the bridgehead deuterated substrate **240** it was possible to establish that the reaction proceeded with inversion (**242**, > 90%) as expected for the S_N2 displacement. Similar results were observed for the IBF–cyclopentene adduct **243** which reacted very sluggishly with the deuterated reducing agent to form **244**, again with 98% inversion. In a study[84] of the hydroboration of the bicyclo substrate **239** it was observed that with



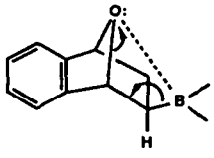
245 (R=H)
248 (R=C_4H_9)



239 (R=H)
240 (R=D)



241 (R=H)
242 (R=D)



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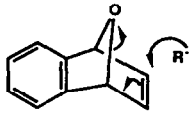
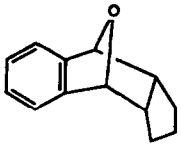
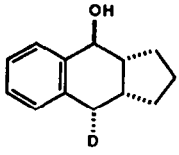


247



243



244

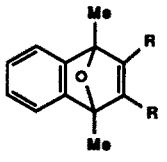
the borane methyl sulfide reagent under various conditions and with 9-BBN, the 1,2-dihydronaphthalenol **245** was the major or exclusive product. Its formation is explained by a *5-endo-trig* cleavage of the intramolecularly coordinated trialkyl borane intermediate **246**, a process akin to the reverse Michael cleavage mentioned above, and to the *exo* attack (as in **247**) of butyl lithium reagents on **239** to form[85] 2-butyl-1,2-dihydro naphthalenols **248**.

VI.4. *Conversion to tetralins*

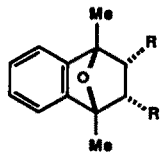
Hydrogenolysis of the benzylic oxygen bridge of the oxabicyclo adduct poses many interesting questions and possibilities. In theory, two hydrogenolysis steps are required for removal of the oxygen bridge; if the reaction is terminated after a single hydrogenolysis a 1-hydroxy tetralin will be produced. These conversions offer direct access to substituted tetralins and if the stereochemistry of the hydrogenolysis can be predictably controlled, valuable synthetic intermediates can be easily generated.

Early studies[42,86] involved the hydrogenation of benzyne–furan adducts without cleavage of the oxygen bridge. Thus the hydrogenation of **249**, for example with 10% palladium on carbon at 55 psi in ethyl acetate, proceeded to yield **250** quantitatively in 5 min. The addition of hydrogen occurs from the *exo* face of the bicyclo system as might be expected,[87] and the product is the *endo* isomer.

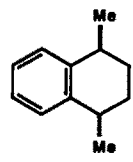
A simpler benzyne–furan adduct **251** gave conflicting results upon hydrogenation with 10% palladium/carbon at 40 psi. In ethanol after 45 min the hydrogenation of the double bond alone was observed[42] and **252** isolated in 61% yield, but in methanol after 20 min hydrogenolysis and complete deoxygenation to **253** in 97% yield was reported[88] by another research group. Inversion of stereochemistry at both benzylic carbon atoms was assumed and the *cis* stereochemistry assigned to **253**. In the course of a synthesis of the lignan lirionol (Section VII.2.c) the oxabicyclo adduct **254** was hydrogenolysed in ethyl acetate at 60 psi with 5% palladium/charcoal with retention of stereochemistry at C-1 to provide[33] the all *cis* tetralin **255** in 74% yield. Repetition of this experiment with **256** produced[34] **257** indicating retention of stereochemistry at both benzylic centers, a result



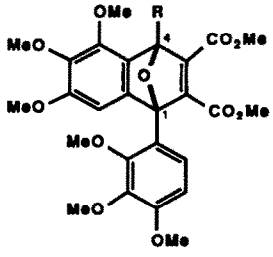
249 (R=CO_2Me)
251 (R=H)



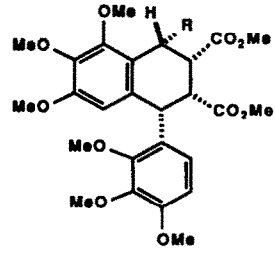
250 (R=CO_2Me)
252 (R=H)



253



254 (R=H)
256 (R=D)

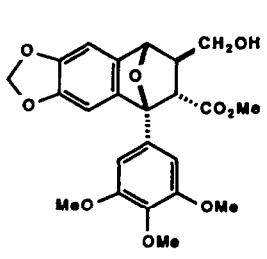


255 (R=H)
257 (R=D)

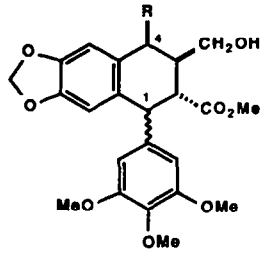
contrary to precedent in palladium catalysed benzylic hydrogenolysis. Thus in an earlier synthesis[89] of isodeoxypodophyllotoxin, the hydrogenolysis of the oxabicyclo system **258** with 10% palladium/carbon in ethyl acetate–acetic acid at 50 psi had produced a 5 : 2 mixture of C-1 epimers **259** with inversion at C-1 predominating. Again, the hydrogenolysis of the *exo* adduct **61** produces[29] a mixture of octahydrophenanthrenes **260** with the *cis* (inversion) isomer favored 9 : 1. These contradictory observations imply that the reaction is substrate and solvent dependent; no coherent

pattern is evident but a useful, though empirical route to stereochemically defined tetralins is sometimes available.

The hydrogenolysis of **258** with freshly prepared Raney nickel and hydrogen in ethanol at room temperature and pressure gave a 77% yield of the 4-hydroxy tetralin **261** with complete retention of stereochemistry at C-1. The related *endo* diester **262** can also be hydrogenolysed (reflux in ethanol for 3 h) using Raney nickel and hydrogen with similar results. The reaction is slower than the hydrogenolysis of **258** probably because **262** lacks the properly disposed haptophilic[87] β-CH_2OH group to coordinate to the catalyst surface. In addition to the chief product **263** small amounts of other compounds **264–266** have also been isolated and characterized.[90] The retention of stereochemistry at C-1 is expected[87] for hydrogenolysis with Raney nickel and the preservation of the 4-hydroxyl group with predictable stereochemistry makes this a unique and valuable means of stereocontrolled access to multisubstituted tetralin systems. The reaction has been exploited in the synthesis of many *Podophyllum* lignans (discussed in Section VII.2.b).

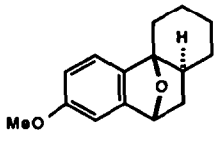


258

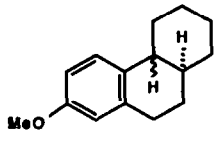


259 (R=H)

261 (R=OH)



61



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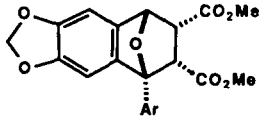

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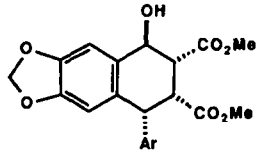

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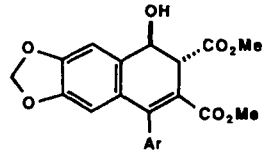

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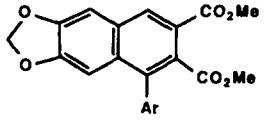

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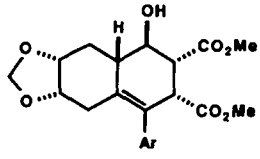
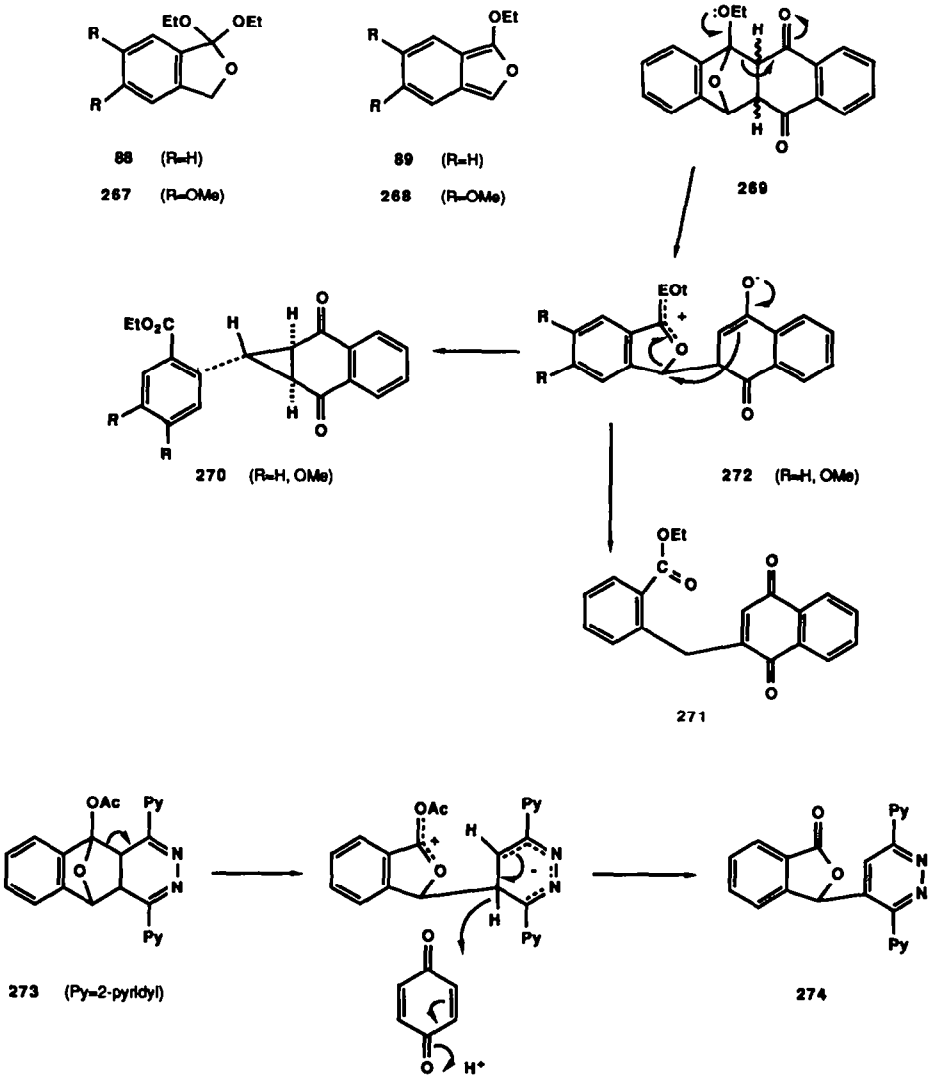


266

Ar = 3, 4, 5 - trimethoxyphenyl

VI.5. *Anomalous carbon–carbon bond cleavage*

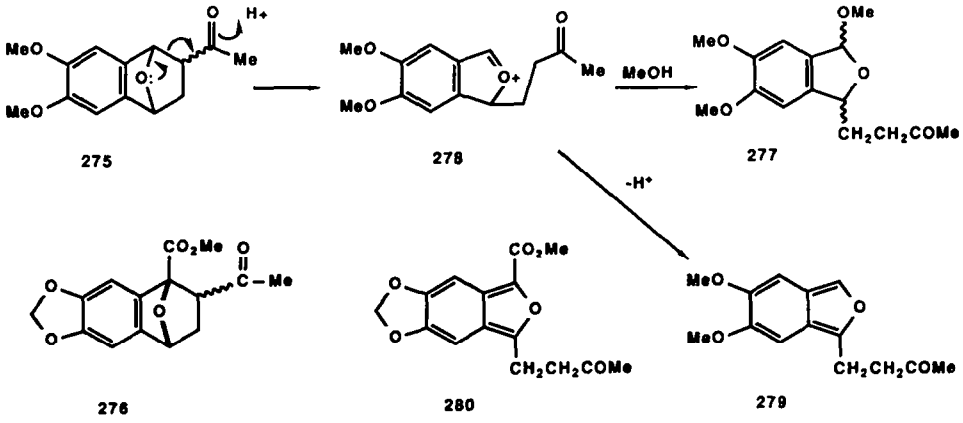
The reaction of ethoxy isobenzofurans **89** and **268**, generated from the corresponding phthalan *ortho*-esters **88** and **267**, with benzoquinone and naphthoquinone has been shown[91] to produce homoquinones by carbon–carbon cleavage of the initial oxabicyclo adducts **269**. This interpretation of the reaction requires that the *endo* adducts decompose to the *trans* cyclopropane **270** (the major isomer) while the *exo* adducts lead to the minor product of the reaction, the all *cis* homoquinone. The *trans* isomer, however, is sterically less congested than the *cis* and other possibilities have been recognized. With naphthoquinone a further product **271** was also isolated and its formation is accommodated in the general scheme by a 1,2-hydride shift in the intermediate **272**. The 1,2-bond in the s-tetrazine adduct **273** is also cleaved in a similar fashion and the intermediate subsequently oxidized by benzoquinone to produce the phthalide **274**. This anomaly in a very well researched process[2,17,20] is observed only with benzoquinone which acts as hydride acceptor here, instead of a dienophile as expected.

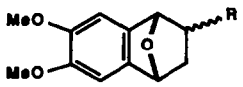


IBF adducts with methyl vinyl ketone (**275**, **276**) also undergo C-1–C-2 cleavage when treated with acid. In the presence of methanol, methoxy phthalan **277** is isolated[76] after a few minutes at room temperature. In the absence of an alcohol extensive decomposition of **275** is observed. The results have been attributed to the occurrence of a *5-endo-trig* reverse aldol ring cleavage to the oxonium ion intermediate **278** which is trapped by methanol but converted to the IBF **279** in its absence; the latter is unstable and polymerizes. This is confirmed by the isolation of stable IBF **280** when **276** is treated with concentrated sulfuric acid in methylene chloride. The facile occurrence of

5-endo-trig reactions in the [2.2.1] 7-oxabicyclo system (see also the reverse Michael reaction discussed in Section VI.3) has been given a frontier molecular orbital explanation[76] dependent on the unique geometry of these bridged compounds. Both reactions have also been found to occur in many furan adducts.

The reverse aldol reaction is not observed with ester (**281**) and nitrile (**282**) adducts but the acrolein adduct **283** does show some evidence of the reaction although most of the product is the dimethyl acetal **284** which is stable under the prevailing conditions. It is possible also that the problems experienced with the acid/catalysed aromatization of benzoquinone adducts (Section VI.2) are associated with the anomalous bond cleavages discussed in this section.





281 (R=CO_2Me)

282 (R=CN)

283 (R=CHO)

284 (R=$CH(OMe)_2$)

VII. ISOBENZOFURANS IN THE SYNTHESIS OF NATURAL PRODUCTS

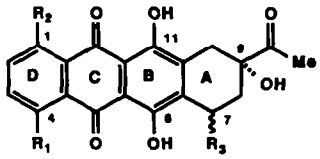
The newer methods of IBF synthesis (Section III), their Diels–Alder reactions (Section V.2) and the manifold transformation of the oxabicyclo adducts (Section VI) have created many opportunities for the synthesis of natural products containing six-membered aromatic and hydroaromatic rings. The following discussion will attempt to focus on the particular advantages of IBF usage in a synthesis and deal with those steps in which an IBF is involved rather than provide a detailed recounting of each synthesis in its entirety.

VII.1. *Anthracyclinones*

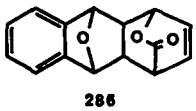
The use of isobenzofuran to construct the tetracyclic system of 7-deoxydaunomycinone **285** was reported 10 years ago. This pioneering endeavor[21] spotlighted the value of the IBF–Diels–Alder technology as a simple and efficient means of access to such compounds but at the same time exemplified the regiochemical problems associated with the reaction of remotely substituted IBFs with remotely substituted dienophiles.

Thus IBF **1**, the CD segment of the anthracyclinone molecule in this context, generated by pyrolysis[1] of α-pyrone adduct **286**, combined with the dienophile **287**, the AB segment, to produce an *exo–endo* mixture of the adducts **288** in 96% yield. Aromatization with sodium acetate in acetic acid gave the basic tetracyclic system **289** (93%) in short order. Further adjustments by standard methods eventually led to 4-demethoxy daunomycinone **290**. Regiochemical problems were encountered in adapting the scheme to the synthesis of **285**. Preparation of 4-methoxy IBF by the same procedure, and reaction with **287**, now produces a regioisomeric mixture of adducts aromatized as

before to a 1 : 1 mixture of tetracyclic quinones **291** and **292**. These were converted without separation to a 1 : 1 mixture of **285** and its regioisomer **293**.



285 (R_1=OMe, R_2=R_3=H)
290 (R_1=R_2=H, R_3= α-OH)
293 (R_1=H, R_2=OMe, R_3=H)
294 (R_1=OMe, R_2=H, R_3= α-OH)



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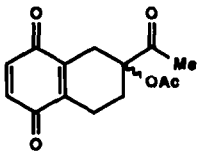

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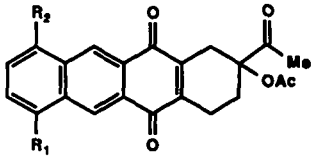
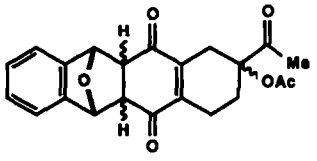


289 (R_1=R_2=H)
291 (R_1=OMe, R_2=H)
292 (R_1=H, R_2=OMe)



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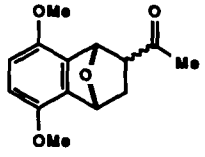

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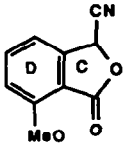

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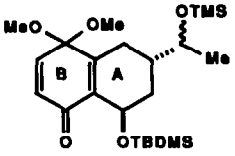

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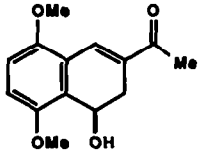


296

A more recent synthesis[31] of daunomycinone **294**, employs the Diels–Alder reaction between 4,7-dimethoxy IBF **36** and methyl vinyl ketone to assemble all the carbon atoms of the AB segment in adduct **295**. Reverse Michael cleavage (Section VI.3) gave the "naphthalene hydrate" **296** with the oxygen atom of the bridge now transformed into the "difficult" C-7 hydroxyl group of daunomycinone. This application of IBF chemistry offers rapid access to an advanced AB intermediate (**296**) which was converted to the final AB synthon **297** in 38% overall yield from the (+III) phthalan precursor **35** of IBF **36**. The synthesis of (±)-daunomycinone was then completed[31] by regiocontrolled attachment of the CD segment (the cyano phthalide **298**) and oxygenation of the tetracyclic product at C-9.

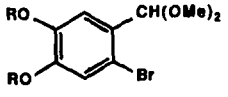
VII.2. *Lignans*

The aryl naphthalide and aryl tetralin lignans containing six-membered aromatic and hydroaromatic rings are excellent targets for synthesis by isobenzofuran–Diels–Alder techniques, and several examples are described in the following sections.

VII.2a. *Aryl naphthalide lignans*

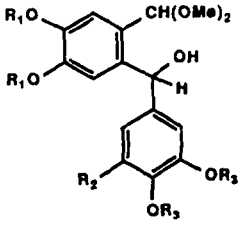
The power of the IBF route to substituted naphthols is best demonstrated in the simple three-step general synthesis[22] of several such lignans. Bromoacetals **28** and **299** were lithiated by halogen–lithium exchange and quenched with various aromatic aldehydes to produce IBF precursors **29** and **300–302** in the first step. The generation and interception of the IBF was accomplished by refluxing these hydroxy acetals in benzene with a trace of *p*-toluene sulfonic acid and excess DMAD for 2 h

to provide the naphthols **303–306** in yields of *ca* 65%. This one-pot conversion involves several intermediates [the (+ III) phthalans, the (+ III) IBF, the oxabicyclo adducts, to name some] and **30** and **307–309** have in fact been isolated. This third and final step of the synthesis involves selective reduction of that ester group proximate to the hydroxyl group of the naphthol and this was easily accomplished with borane to yield the naturally occurring lignans diphyllin **310**, taiwanin E **311**, chinensinaphthol **312** and dehydropodophyllotoxin **313** in overall yields of *ca* 35% from the respective bromo acetals **28** or **299**.



28 (R+R=CH_2)

299 (R=Me)

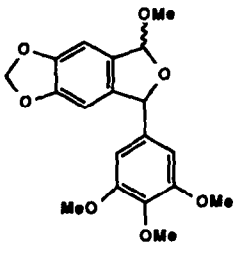


29 (R_1+R_1=CH_2, R_2=OMe, R_3=Me)

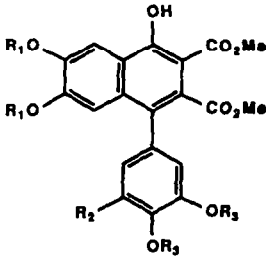
300 (R_1=Me, R_2=H, R_3+R_3=CH_2)

301 (R_1+R_1= R_3+R_3=CH_2, R_2=H)

302 (R_1+R_1=CH_2, R_2=H, R_3=Me)



30

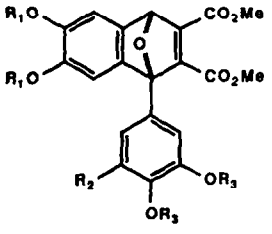


303 (R_1=Me, R_2=H, R_3+R_3=CH_2)

304 (R_1+R_1=R_3+R_3=CH_2, R_2=H)

305 (R_1+R_1=CH_2, R_2=H, R_3=Me)

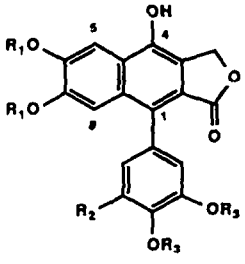
306 (R_1+R_1=CH_2, R_2=OMe, R_3=Me)



307 (R_1=Me, R_2=H, R_3+R_3=CH_2)

308 (R_1+R_1=R_3+R_3=CH_2, R_2=H)

309 (R_1+R_1=CH_2, R_2=OMe, R_3=Me)

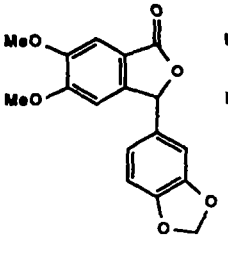


310 (R_1=Me, R_2=H, R_3+R_3=CH_2)

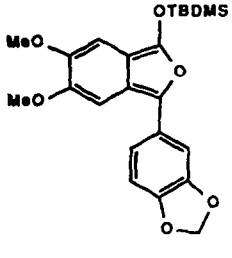
311 (R_1+R_1=R_3+R_3=CH_2, R_2=H)

312 (R_1+R_1=CH_2, R_2=H, R_3=Me)

313 (R_1+R_1=CH_2, R_2=OMe, R_3=Me)



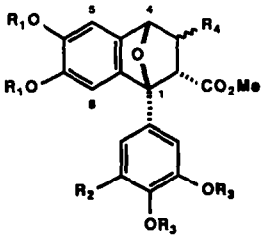
314



315

More recently[46] the phenyl phthalide **314** has been used to generate a (+IV) IBF **315**, by deprotonation and silylation, and after the unreacted LDA was destroyed by t-butanol, dimethyl fumarate was added to produce a mixture of diastereomeric adducts converted without separation to the naphthol **303** by acid treatment. Reduction of the latter with borohydride in methanol again produced the lignan diphyllin (**310**).

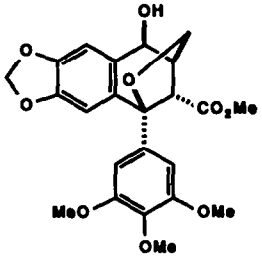
Aryl naphthalide lignans that do not carry a hydroxyl group at C-4 are found naturally as two structural variants. The *peri*-carbonyl types bear the carbonyl group of the phthalide ring at C-3 of the naphthalene while the situation is reversed in the *peri*-methylene types (e.g. **326–328**). Regiocontrolled synthesis of each type at will has always been a difficult problem and if the previous (+III) IBF route is to be applied here, a new "handle" has to be found to ensure regioselective reduction of the 3-carbomethoxy group since the 4-hydroxyl group is no longer available. When a double bonded dienophile (fumarate or maleate) reacts with a (+III) IBF, naphthalene diesters like **303–306**, lacking the C-4 hydroxyl, are produced. However, the ester groups in such compounds cannot be selectively reduced to a single phthalide. A solution to the problem[79] was found in the regioselective reduction of the C-3 ester group of an oxabicyclo intermediate prior to aromatization. The oxabicyclo adducts **307–309** were hydrogenated to the *endo* systems **316**, **317** and **262**. Epimerization at C-3 alone was achieved with sodium acetate or sodium methoxide in methanol to provide the corresponding *trans* esters **318–320** which underwent selective reduction of the C-3 *exo* ester moiety with lithium triethyl borohydride to the alcohols **321**, **322** and **258**.



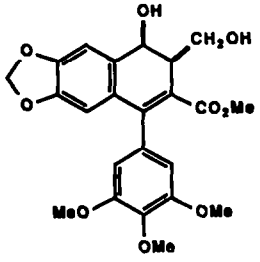
316 (R_1=Me, R_2=H, R_3=Me, R_4=α-CO_2Me) **318** (R_4=β-CO_2Me) **321** (R_4=β-CH_2OH)

317 (R_1+R_2=R_3+R_4=CH_2, R_2=H, R_4=α-CO_2Me) **319** (R_4=β-CO_2Me) **322** (R_4=β-CH_2OH)

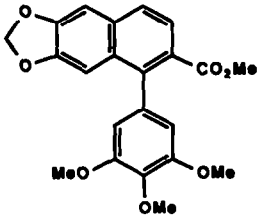
262 (R_1+R_1=CH_2, R_2=OMe, R_3=Me, R_4=α-CO_2Me) **320** (R_4=β-CO_2Me) **258** (R_4=β-CH_2OH)



323

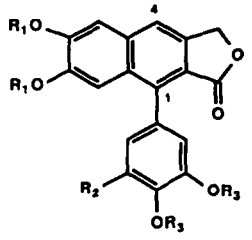


324



325

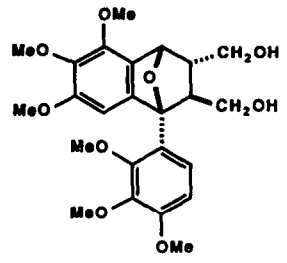
Acid catalysed aromatization of these compounds was not uneventful. The development of a new 1,3-methyleneoxy bridged product (e.g. **323** from **258**) was observed[89] and this was followed by the probable formation of the dihydronaphthalene **324** which decomposed into a 1 : 1 mixture of the desired naphthalide **328** (dehydroanhydropicropodophyllin) and the 3-nor hydroxymethyl naphthalene **325** (Section VI.2). Justicidin B **326** and Taiwanin C **327**, all *peri*-methylene lactones, were similarly prepared. The intervention of oxymethylene-bridged intermediates like **323** is not uncommon in the acid catalysed dehydration of oxabicyclo alcohols. Indeed, a doubly bridged compound **330** was isolated[34] upon treatment of the corresponding oxabicyclo diol **329** in ethanol with a few drops of acetic acid.



326 (R_1=Me, R_2=H, R_3+R_3=CH_2)

327 (R_1+R_1=R_3+R_3=CH_2, R_2=H)

328 (R_1+R_1=CH_2, R_2=OMe, R_3=Me)



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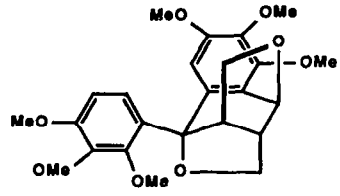
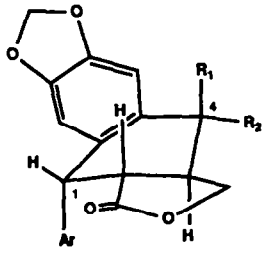


330

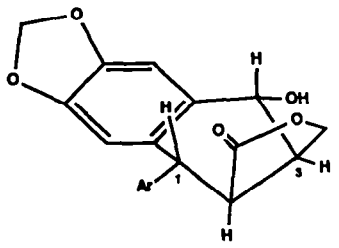
VII.2b. Podophyllum *lignans*. In addition to its structural complexity, podophyllotoxin **331** poses a formidable stereochemical challenge to the synthetic chemist. The rigidly strained *trans* lactone and the axially locked 1-aryl substituent make the molecule very prone to relaxation into the flexible *cis*-lactone picropodophyllin **332**, through the formation of a C-2 enolate with even the slightest trace of base. This fact imposes a large constraint on synthetic planning and although several elegant solutions to the problem have recently been found[92] it was a very significant issue in the choice of tactics in our synthesis of (±)-podophyllotoxin[89,90,93] and its diastereomers. The oxabicyclo system with its rigidity seemed to offer a firm framework for establishing the appropriate stereochemical relationship of the four substituents of the tetralin system. Once this had been achieved, catalytic hydrogenolysis or some equivalent thereof, was envisaged to release the structurally and stereochemically perfected tetralin requiring very minor adjustment for conversion to podophyllotoxin.

The IBF methodology was ideally suited to this plan. The oxabicyclo adduct **309**, containing all the required carbon and oxygen atoms, was rapidly accessed as already described. Catalytic hydrogenation, epimerization and reduction at C-3 all gave single stereoisomers culminating in final oxabicyclo platform **258** with correctly placed substituents in the correct stereochemical relationship for epipodophyllotoxin **333**. Raney nickel hydrogenolysis released the tetralin **334** (Section VI.4), which needed only lactonization at C-2, C-3 to produce epipodophyllotoxin. The IBF based plan had performed admirably but the last step, the lactonization, proved to be impossible to effect in a straightforward manner without extensive decomposition and/or C-2 epimerization. That problem was finally solved by other methods and **331**, **332** and **333** were eventually obtained[93] from **334**. Deoxypodophyllotoxin **335**, also a natural product, was available[89] by the palladium catalysed hydrogenolysis of **334** (at C-4) and subsequent lactonization. Other stereoisomers of podophyllotoxin were also prepared in a similar manner. The *endo* diester **262** was hydrogenolysed with Raney nickel and the resulting tetralin diester **263** reduced at the equatorial C-3 ester selectively with lithium triethyl borohydride to form **336**, which could be lactonized directly to isopicropodophyllin **337** or epimerized at C-2 to the all *trans*, all equatorial tetralin which yields isopodophyllotoxin **338** upon lactonization.[90]

VII.2c. *Lirionol*. This unusual bridged lignan assigned[94] the structure and relative stereochemistry expressed in **339** can be regarded as an aryl tetralin which has undergone intramolecular cyclization between a C-3 carboxyl group and C-6′ of the pendant aryl substituent located at C-1. On this basis a synthetic approach[33] to the molecule that passes through an all *trans* aryl tetralin like **340** can be visualized.



331 (R_1=H, R_2=OH)
333 (R_1=OH, R_2=H)
335 (R_1=R_2=H)



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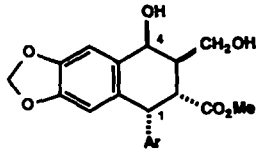

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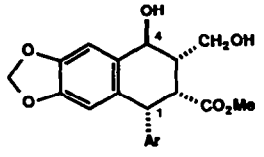

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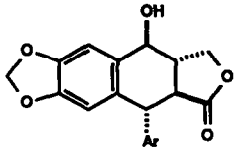

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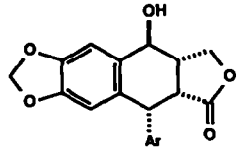
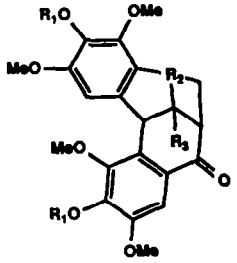


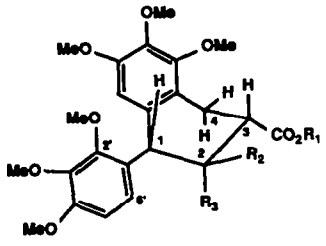
337

Ar = 3, 4, 5 - trimethoxyphenyl

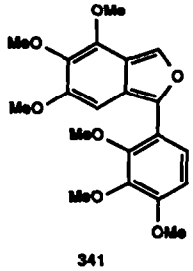
ortho-Deprotonation of 2,3,4-trimethoxy-*N*,*N*-diethyl benzamide and quenching the resultant 6-lithio species with 2,3,4-trimethoxy benzaldehyde was followed by stirring the product with acetic acid to form the phenyl phthalide **66** which was reduced with diisobutyl aluminum hydride to a mixture of diastereomeric lactols **67**. This (+III) phthalan mixture, used without purification as precursor of the (+III) IBF **341**, yielded the expected adduct **254** with DMAD. The short sequence assembles all the required carbon atoms of lirionol in 38% overall yield from the starting benzamide.



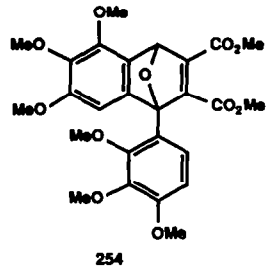
339 (R_1=R_3=H, R_2=CH_2OH)
343 (R_1=Me, R_2=H, R_3=CO_2Me)
344 (R_1=R_2=H, R_3=CH_2OH)



255 (R_1=Me, R_2=H, R_3=CO_2Me)
340 (R_1=R_3=H, R_2=CH_2OH)
342 (R_1=R_2=H, R_3=CO_2Me)
345 (R_1=R_3=H, R_2=CO_2Me)



341

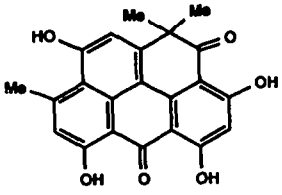


254

Hydrogenolysis of **254** with 5% palladium/charcoal in ethyl acetate at 60 psi for 12 h gave an unexpected but gratifying result. The product **255** (Section VI.4) formed in 74% yield with no trace of any C-1 epimer and was identified by 250 MHz NMR as the all *cis* tetralin with a 1,3-diequatorial, 2-axial conformation. Acid catalysed hydrolysis of the 3-equatorial ester moiety of **255** provided the acid **342** with virtually no change in the ^{1}H NMR spectrum; Friedel–Crafts cyclization proceeded to the bicylononadienone **343** whose structure and relative stereochemistry were established by X-ray crystallography thus confirming the all *cis* configurations of **255** and **342** and the stereochemical course of the palladium hydrogenolysis of **254**. The bridged intermediate **343** was subsequently converted to **344**, an epimer of **339**, the configuration assigned to lirionol. The latter was synthesized by epimerization of **342** at C-2 to provide the all *trans*, all equatorial tetralin **345** which was processed as before to yield **339**. Comparison of the ^{1}H NMR spectra of **339**, **344**, the natural lignan and their acetates established that the relative configuration of lirionol was in accord with the expression **344** and not **339** as originally assigned.

VII.3. *Resistomycin*

This pentacyclic antibiotic **346** was synthesized[95] in 1982 for the first time by means of the first recorded instance of an intramolecular Diels–Alder reaction of an IBF. The basic plan provided for the synthesis of a complex (+III) phthalan **347** (an aminal rather than an acetal) incorporating an alkyne as the dienophilic residue. This was prepared by the combination of the *ortho*-lithiated imine **348** (obtained by deprotonation of **349** with *sec*-butyl lithium–TMEDA) with the aldehyde **350**—exactly the same basic technique used in the synthesis of simpler (+III) phthalan precursors (Section III.2a.i). Treatment of **347** with various acidic reagents, but best of all with iodoacetic acid and pyridine in refluxing benzene for 8 h, gave a very acceptable yield (60%) of the crystalline oxabicyclo adduct **351**. It is probable that the iodoacetic acid alkylates the aminal nitrogen and assists the 1,4-displacement of the nitrogen residue to produce IBF **352** by quaternization of the nitrogen atom. The pyridine acts as the base to remove the phthalan proton—overall, a process akin to a 1,4-Hoffman elimination. Certainly, the yield of **351** is decreased if acetic acid is used or if the pyridine is excluded. The synthesis of resistomycin was then completed by one-pot desilylation, aromatization, demethylation and cyclization, all accomplished in 84% yield by heating **351** with pyridinium hydrochloride at 180°C for 90 min. This application of the intramolecular Diels–Alder reaction of an IBF provided the antibiotic in 20% overall yield from the commercial starting material 3,4-dimethyl phenol.



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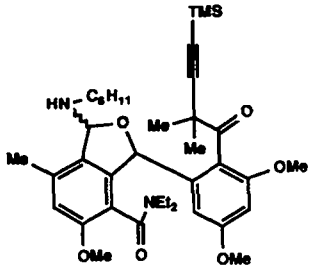
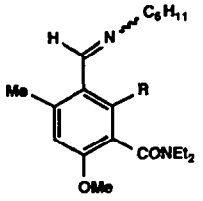
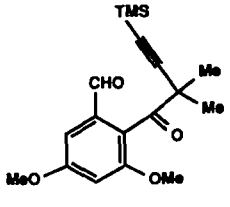


347



348 (R=Li)

349 (R=H)



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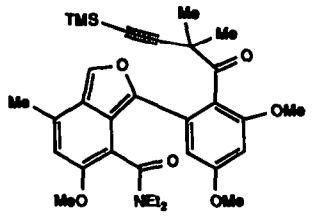

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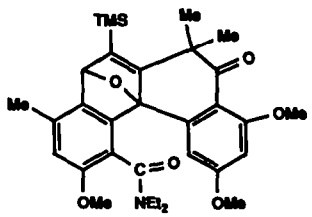
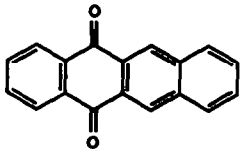


351

VIII. ISOBENZOFURANS IN THE SYNTHESIS OF POLYAROMATIC HYDROCARBONS (PAHs)

With the realization of the importance of PAHs as major environmental carcinogens, organic chemists have become increasingly concerned with the synthesis of the many and varied aromatic systems and their alkylated derivatives for assessment of carcinogenic activity and its relationship to structure. The Diels–Alder reaction has always held a prominent place among the methods employed for PAH synthesis and the great reactivity of IBFs as dienes make them prime vehicles for PAH synthesis. The first examples[10] of such applications involved the use of **1**, generated by flash vacuum thermolysis techniques, reacting with the dienophiles naphthoquinone, indene and acenaphthylene to provide **353–355** after aromatization of the intermediate adducts with acid. The synthesis of 7,12-dimethylbenzanthracene **356** employed[96] 1,3-dimethyl IBF generated by Warreners s-tetrazine method[2] in combination with methyl cinnamate as the dienophile. After aromatization and chain extension of the adduct **357**, Friedel–Crafts cyclization, reduction and dehydration produced **356**. The sterically congested 1,7,12-trimethyl analogue (**356**, R = Me) was also prepared using *ortho*-methyl methylcinnamate as the dienophile.



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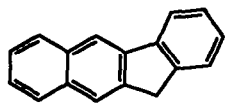

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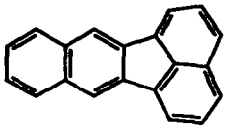

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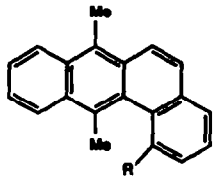
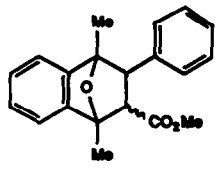
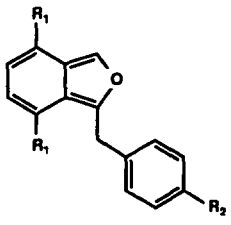


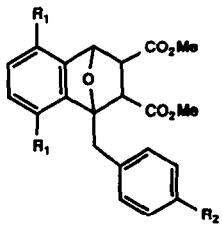
356 (R=H)

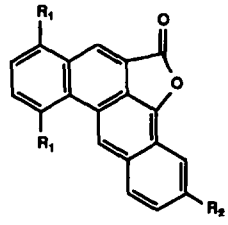


357

Other benzanthracenes were prepared by exploiting the availability of benzyl IBF **87** (Section III.2a.iii) and some of its derivatives **358–360**. The oxabicyclo adducts therefrom (of general formula **361**) were converted to the respective benzanthracene lactones **362** with polyphosphoric acid (PPA) at 90°C for 3 h. The reactions again involve aromatization and Friedel–Crafts cyclization as before, followed by lactonization of the remaining ester moiety. This reaction sequence could be repeated with the "*ortho*" adducts of similar IBFs with methyl acrylate (**363**). Aromatization with *p*-toluene sulfonic acid, saponification of the ester and cyclization with zinc chloride–acetic anhydride produced[97] the 7-acetoxy benzanthracenes represented by structure **364**. The same processes were subsequently applied[98] to other IBF analogues. Thus **365** yielded **367** when adduct **366** was treated with PPA, and **369** was produced from the β-naphthyl analogue **368** because the Friedel–Crafts acylation takes place at the more reactive α-naphthyl position. Isonaphthofurans **370** subjected to the same sequence gave the pentaphene **371** while isonaphthofurans **372** and **373** produced benzopentaphenes **374** and

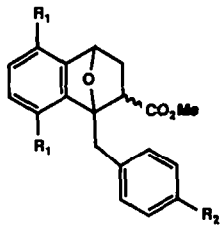


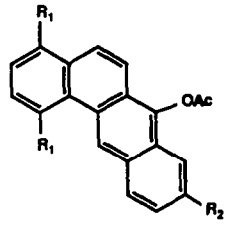




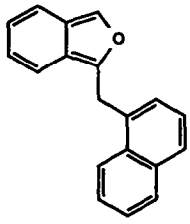
361 362

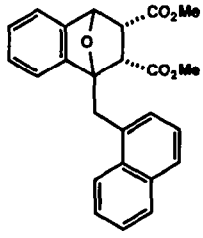
87 (R_1=R_2=H)
358 (R_1=Me, R_2=H)
359 (R_1=Ph, R_2=H)
360 (R_1=H, R_2=OMe)

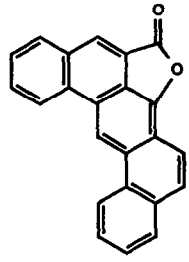




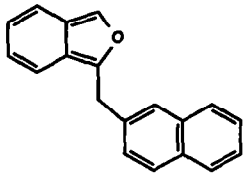
363 364

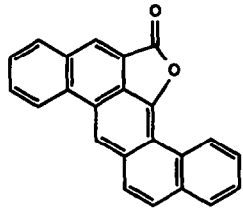






365 366 367



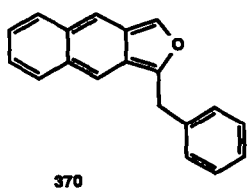


368 369

375. Much flexibility in the assembly of benzene rings for various PAH molecules is obviously available by this simple pathway.

The Diels–Alder reaction of various arynes with the 1,3-disilylated IBF **191** (Section V.I) was recently applied[99] to the synthesis of many PAHs. The benzynes **376–380** produced the adducts **381–385** respectively in fair (**383**, **385**) to excellent (**381**) yields. In all these cases the aryne was generated *in situ* by dehydrohalogenation of an aryl halide with lithium tetramethyl piperidide (LTMP). The brominated adduct **385** was also used as an aryne precursor; when treated with LTMP in the presence of **191** the bis adduct **386** is formed in moderate yield. The same compound can be obtained directly when *p*-dibromobenzene is treated with two molar proportions of **191** and excess LTMP. The regioselectivity in this reaction is noteworthy; only the linear adduct is formed. In fact, attempts to prepare an angular adduct from **384** by the same method were not successful either due to "bay region" interference of the TMS groups or lower reactivity of **384**.

Other interesting adducts **387–391** were prepared from **191** and the corresponding aryne in moderate yields. The linear tetracyclic adduct **392** was also obtained from 2-naphthalyne generated *in situ* by debromination of 2,3-dibromonaphthalene with *n*-butyl lithium.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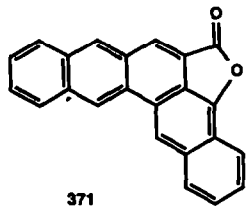
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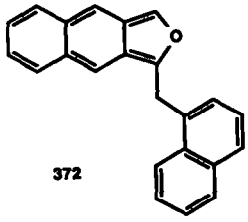
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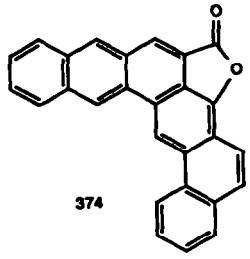
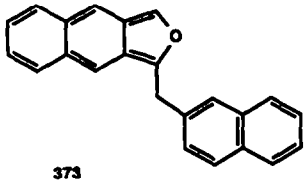
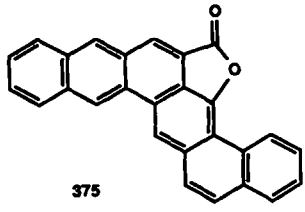
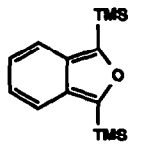

374


373


375

Bridgehead protodesilylation and aromatization of all these materials was smoothly accomplished with trifluoroacetic acid in carbon tetrachloride (or chloroform) at room temperature. These reactions displayed some interesting features. They were observed to be much faster than the aromatization of the bridgehead desilylated adducts, implying that the silicon substituent had a rate-accelerating effect, probably by stabilizing the α-carbocation formed in the initial carbon–oxygen cleavage. The phenolic materials expected in such aromatizations (Section VI.2) exist almost entirely in the keto form (in many cases) and where regioisomeric keto products were possible, one product only was formed with total or predominant regioselectivity. Thus **381**, **383** and **384** produced anthrones **393**, **395** and **396** exclusively while **382** gave a *ca* 3 : 7 mixture of regioisomeric anthrones **394** and **397**. A simple explanation advanced for this remarkable regioselectivity invokes the stabilization of the carbonium ion intermediate produced in the initial bridge cleavage by the *ortho* methyl, methoxyl, bromo substituent (leading to **393**, **395** and **396**) or *para* methyl substituent (in the preferential formation of **397** over **394**). Other unsymmetrical "anthrones" **398–401** were prepared by this method with complete regioselectivity as well as the symmetrical anthrones **402–404**.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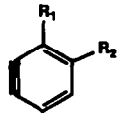
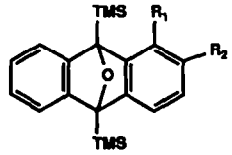
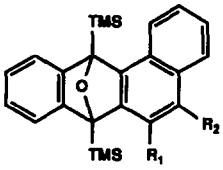
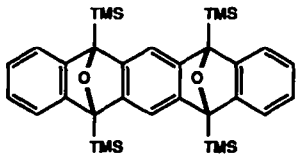

376 (R_1=Me, R_2=H)
377 (R_1=H, R_2=Me)
378 (R_1=OMe, R_2=H)
379 (R_1=Br, R_2=H)
380 (R_1=H, R_2=Br)


381 (R_1=Me, R_2=H)
382 (R_1=H, R_2=Me)
383 (R_1=OMe, R_2=H)
384 (R_1=Br, R_2=H)
385 (R_1=H, R_2=Br)



387 (R_1=H, R_2=Me)
388 (R_1=Br, R_2=H)



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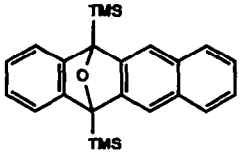
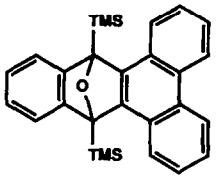


392



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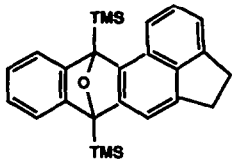

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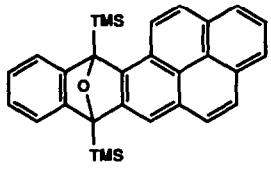

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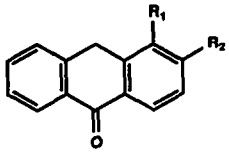
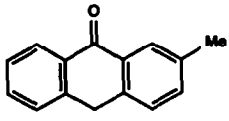
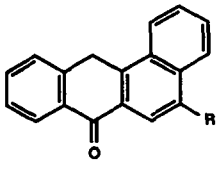


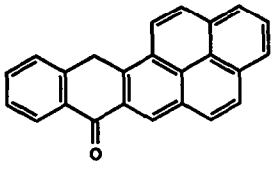
393 (R_1=Me, R_2=H)
394 (R_1=H, R_2=Me)
395 (R_1=OMe, R_2=H)
396 (R_1=Br, R_2=H)



397



398 (R=H)
399 (R=Me)



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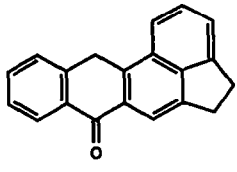
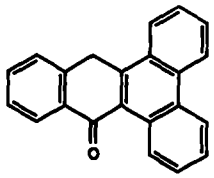
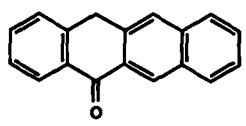


400

These compounds are readily converted to the PAH by LAH reduction and dehydration, and they may be specifically deuterated by LAD reduction or alkylated by reaction with a Grignard reagent. The linear bis adduct **386** was converted to pentacene by this sequence, specifically D-labelled benzanthracene **405** was prepared from **398** and 1,10-dimethyl anthracene **406** obtained from **393**—all good examples of the value of this IBF route to PAHs. In a subsequent publication[100] it was also observed that one-step desilylation and reductive aromatization (Section VI.1) of the anthracyne adduct **407** with zinc and acetic acid provides the angular pentacyclic hydrocarbon pentaphene **408** in good yield.



402



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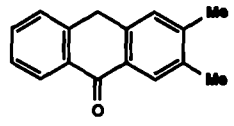

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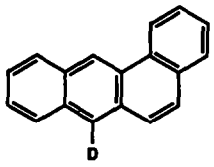

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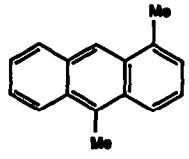

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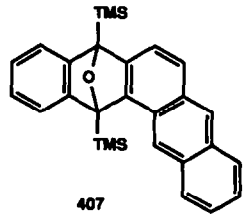

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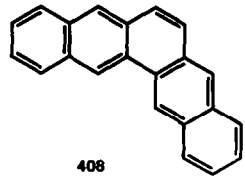

408

IX. FUTURE DIRECTIONS

The continuation of natural product synthesis with increasingly complex dienophiles as well as chiral dienophiles in both inter- and intramolecular Diels–Alder applications should be a logical next step in IBF chemistry. The preparation of metal complexes to stabilize the 4,7-diene system selectively and prevent polymerization of the less stable IBFs would be a useful advance that might allow the manipulation of substituents on the furanoid moiety. Conversely, the stabilization of the furanoid moiety by metal complexation might permit the chemistry of the diene unit to be exploited.

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