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Synthetic Applications of Furan Diels-Alder Chemistry

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1. INTRODUCTION

Few reactions can compete with the Diels-Alder cycloaddition with respect to the degree of structural complexity that can be achieved in a single synthetic step. Well-known and extensively studied for many decades, the Diels-Alder reaction remains as one of the most frequently employed synthetic methods for the construction of six-membered ring systems.[1] The high regio- and stereoselectivity typically displayed by this pericyclic process and the ease of execution have contributed toward its popularity.[1] In recent years, various chiral auxiliaries and catalysts for asymmetric Diels-Alder chemistry have been developed that allow the cycloaddition to proceed with very high levels of selectivity.[1,2] The use of chiral Lewis acid catalysts and high pressure to enhance the selectivity and rate of these [4π + 2π]-cycloadditions have further extended the scope of this remarkable reaction.[3]

Diels-Alder cycloadditions using furans as the 4π diene component were amongst the first reactions studied by Diels and Alder almost seventy years ago.[4] Today, the addition of maleic anhydride to furan is a classic textbook example of this prominent organic name reaction. The proclivity of furans to undergo [4+2]-cycloadditions with various π-bonds is well established and has attracted the attention of many research groups, as it allows for the rapid construction of valuable synthetic intermediates. The initial cycloaddition gives rise to a substituted 7-oxabicyclo[2.2.1]hept-5-ene (7-oxanorbornene) that can be manipulated with impressive selectivity leading to a variety of interesting target molecules.

The chemistry of furans has been systematically reviewed from time to time.[5,6] Although individual chapters within these monographs or review articles often deal with the Diels-Alder chemistry of furans,[5,6] no treatise specifically dedicated to this important aspect of furan chemistry has appeared. The present review is intended to provide a selective, rather than exhaustive, survey of the bimolecular and intramolecular Diels-Alder cycloaddition chemistry of furans. Emphasis is given to papers of recent origin, most of them between 1985 and 1996, that were not covered in previous review articles on this subject.[5,6]

2. BIMOLECULAR DIELS-ALDER REACTIONS OF FURANS

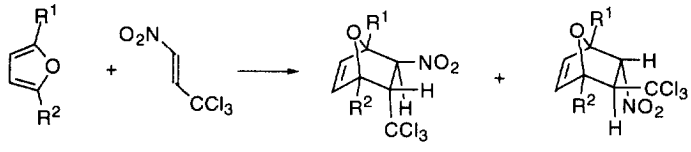
2.1. *Scope and Limitations*

2.1.1. *Alkenes*

It is well-known that aromatic heterocycles, such as furans, thiophenes, and pyrroles, can undergo Diels-Alder reactions as 4π diene components despite their aromaticity and hence expected decreased reactivity. In general, furans undergo [4+2]-cycloadditions with a variety of dienophiles, such as activated

alkenes, alkynes, or allenes. However, many researchers observe distinct differences with respect to yields, reaction times, required experimental conditions, and stereoselectivities, depending on the substitution pattern on the furan ring and the nature of the dienophile. In many cases, the retro-Diels-Alder reaction becomes a problem from a synthetic point of view.[5,6] For example, Cook showed that the reaction of 2,5-disubstituted furans with fumaronitrile depends on the reaction temperature, the concentration of the substrates, and the solvent employed.[7] Using chloroform as the solvent at low temperatures (-20 °C) resulted in a shift in the equilibrium, giving the highest concentration of cycloadduct. The presence of the alkyl substituents on the furan ring also affected the Diels-Alder equilibrium. For example, there was a greater proportion of cycloadduct derived from 2,5-dimethylfuran as compared with reaction using furan. The reaction temperature also had an effect on the equilibrium of the Diels-Alder reaction when α-chloroacrylonitrile was used as the dienophile.[8] In these studies, the reaction temperature also affected the *exo/endo* stereoselectivity of the cycloaddition, with higher amounts of *endo* adducts being observed at lower reaction temperatures.

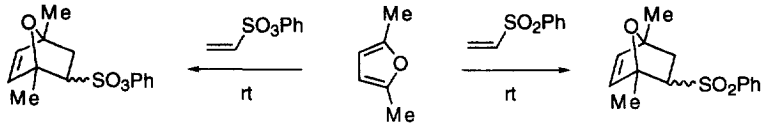
The influence of the furan ring substituents on *exo/endo* selectivity was also noted in the reaction of 2,5-disubstituted furans with 1,1,1-trichloro-3-nitro-propene.[9] Here, the trichloromethyl group preferred to be *endo* with increasing substitution on the furan ring. Interestingly, 2-methylfuran reacted much faster than furan or dimethylfuran (83% conversion after 4h for **1c/2c** as opposed to 90% conversion after 14 days for **1a/2a**).



1	**2**
a; $R^1 = R^2 = H$	45:41
b; $R^1 = R^2 = Me$	100:0
c; $R^1 = Me$, $R^2 = H$	75:25

Phenyl vinylsulfonate, a particularly reactive dienophile, added to furans in excellent yields even at room temperature without Lewis acid catalysis.[10] The room temperature cycloaddition reaction displayed a typical preference for the *endo* isomer (*i.e.* **3**), whereas cycloaddition at 70 °C showed a preference for the *exo* adduct. The mild conditions, high yields, and potential of the sulfonate group for further functionalization provides this method with many advantages. Importantly, the related cycloaddition with phenyl vinyl sulfone gave significantly lower yields of the corresponding cycloadduct (*e.g.* **4**).

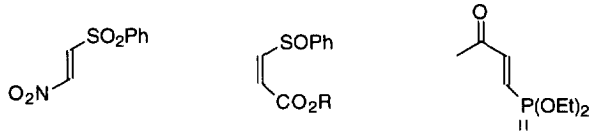
In a similar fashion, furan added to the doubly activated vinyl sulfone **5** at room temperature to furnish a 63:37 mixture of *endo/exo* adducts.[11] In a related study, Picker reported the use of racemic vinyl sulfoxides **6** in



3 (95%)
endo/exo 5.4:1

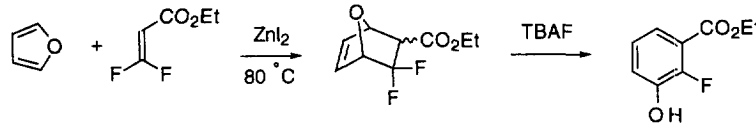
4 (50%)

the cycloaddition to furan.[12] Preadsorption of the sulfoxides onto silica gel gave a mixture of all four possible diastereoisomers after 84 days at room temperature. Keto vinylphosphonate **7** was also shown to be a suitable candidate for furan cycloadditions.[13] Best results were achieved using Et_2AlCl as the Lewis acid at -25 °C, which led to an 86% yield of an *endo/exo* mixture of labile cycloadducts.



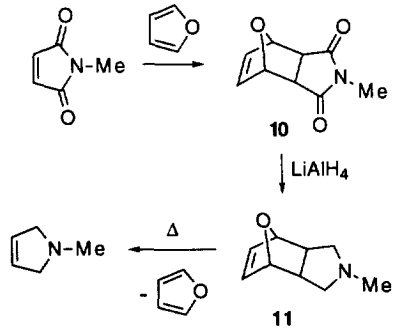
5 **6a**; R = H **6b**; R = Me **7**

Ethyl 3,3-difluoroacrylate was yet another successful dienophile utilized in Diels-Alder chemistry.[14] Cycloaddition of the acrylate to furan in the presence of zinc iodide at 80 °C gave a 40% yield of **8** as a 4:1 mixture of *endo/exo* isomers. Treatment of **8** with tetrabutylammonium fluoride as a strong base gave phenol **9**, thus representing a synthetically useful approach to fluoro-substituted phenols.



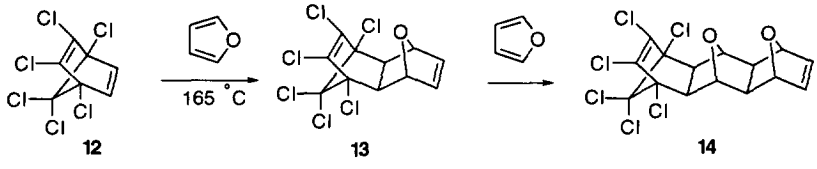
8 **9**

[4+2]-Cycloaddition chemistry has frequently been used as a method for the protection of reactive double bonds or other functional groups. In the furan series, cycloaddition to *N*-methylmaleimide provided the expected cycloadduct **10** (96%), which could then be reduced by $LiAlH_4$ to the tricycle **11** (89%). Pyrolysis of

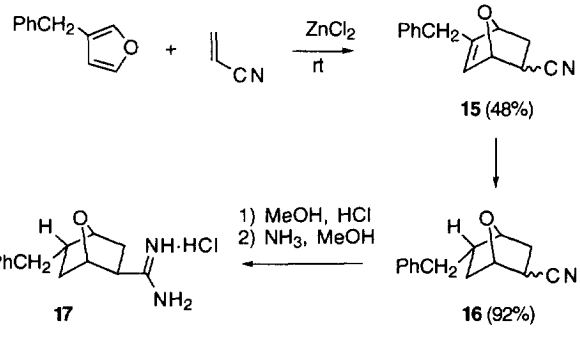


11 in a solution of silicon oil at 250-300 °C gave *N*-methyl-3-pyrroline in 60% yield, previously unattainable in pure form.[15]

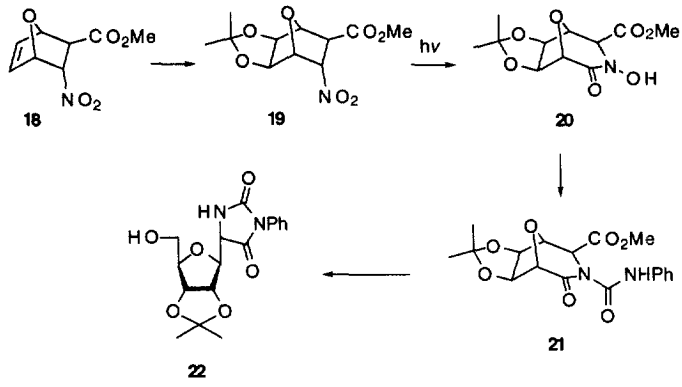
Hexachloronorbornadiene (**12**) underwent cycloaddition with furan at 165 °C to provide cycloadduct **13** as the major product, together with the *bis*-cycloadduct **14**.[16] X-ray structure analysis of a dibromo derivative of cycloadduct of **13** established the *endo-exo* structure shown.



Examples of Diels-Alder cycloadditions using simple 3-alkylfurans are relatively rare. One case involves the cycloaddition of acrylonitrile to 3-benzylfuran which gave a 2:1 mixture of *endo/exo* isomers **15** that could be separated and independently reduced to the corresponding bicycle **16**.[17] Treatment of both isomers of **16** with methanolic HCl and subsequently with ammonia furnished the *exo*-amidine **17**, a rigid bicycle of interest as a small molecule mimetic of the binding region of the cellular receptor CD4.[17]

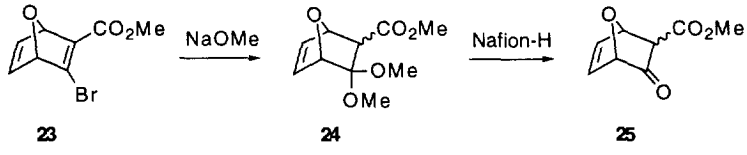


Sera reported an application of a [4+2]-cycloaddition involving methyl 3-nitroacrylate towards the synthesis of C-nucleosides.[18] Transformation of the *endo* cycloadduct **18** into the corresponding reduced diol followed by isopropylidenation gave dioxolane **19**. Photoisomerization of **19** led to the bicyclic hydroxamic acid **20**, which was converted into urea **21** by standard methods. Reduction with $NaBH_4$ afforded the hydantoin C-riboside **22** in good overall yield.[18]

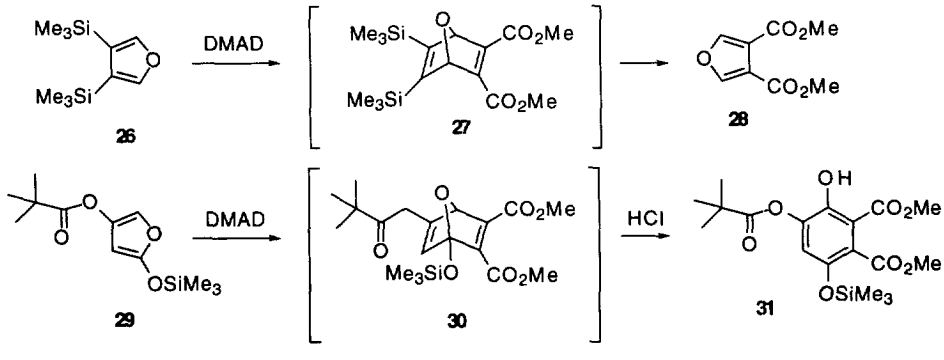


2.1.2. *Alkynes*

Methyl 3-bromopropionate reacted with furan at 80 °C to afford the stable cycloadduct **23**, which was converted to a 9:1 *endo/exo* mixture of epimeric acetals **24** by treatment with sodium methoxide in methanol. Hydrolysis of the acetals **24** using Nafion-H led to the bicyclic ß-ketoesters **25** without noticeable epimerization.[19] In effect, methyl 3-bromopropionate acts as a methoxycarbonylketene equivalent, allowing the preparation of both epimers of **25** in three steps and good overall yield.



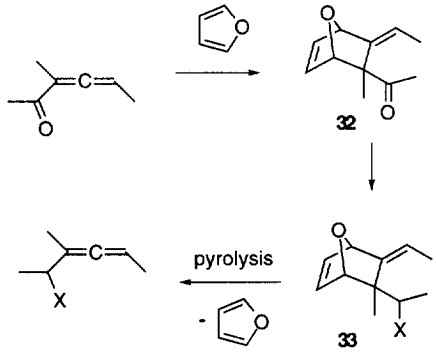
An example of an acetylenic furan cycloaddition reaction was reported by Wong.[20] Addition of 3,4-*bis*(trimethylsilyl)furan to dimethyl acetylenedicarboxylate (DMAD) at 75 °C gave furan-3,4-dicarboxylate **28**, presumably by extrusion of *bis*(trimethylsilyl)acetylene from the initially formed cycloadduct **27**. In contrast, the addition of DMAD to silyloxy-substituted furan **29** (available in two steps from tetronic acid) at room



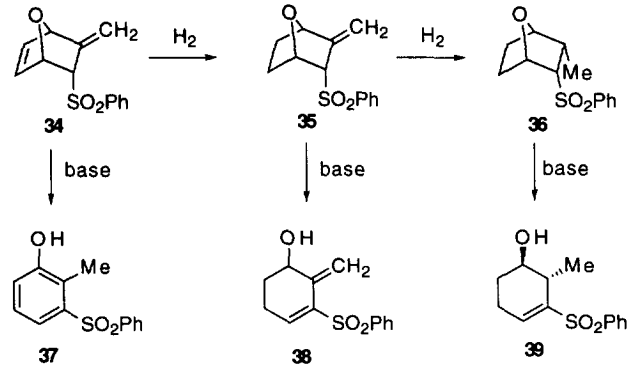
temperature gave a stable cycloadduct **30** that could be further transformed into hydroquinone **31** (70%) by treatment with catalytic amounts of HCl.[21] Stable [4π + 2π]-furan cycloadducts were also obtained using the highly reactive *bis*(*tert*-butylsulfonyl)acetylene,[22] as well as nitro(trimethylsilyl)acetylene.[23] In 1984, Wong reviewed the conversion of various furan-acetylene adducts into arenes by subsequent aromatization.[24]

2.1.3. *Allenes*

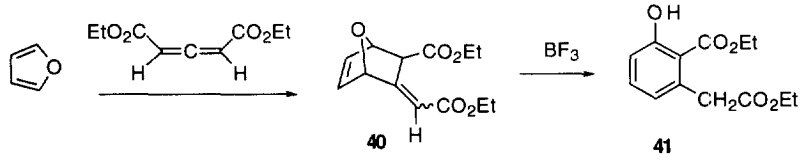
Another class of dienophiles that undergoes smooth Diels-Alder cycloaddition to furans are allenes that possess at least one electron-withdrawing group at the terminal carbon. This reaction provides a route to easily functionalizable cyclic systems containing an alkylidene moiety which can serve as important building blocks for the synthesis of natural products. For example, allenic ketones cycloadd to furan with relative ease and in high yield.[25] Further manipulation of the resulting cycloadduct **32** (*i.e.* by reduction of the carbonyl group, or oxime-formation with subsequent reduction) gave bicycles of type **33**. Cycloreversion of these modified cycloadducts regenerates the "*masked*" allenic functionality and thus allows for the preparation of a variety of functionalized allenes.



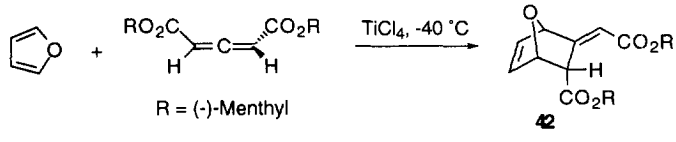
In a similar fashion, phenylsulfonyl allene cycloadds with furan at 100 °C to give a 58% yield of the *endo* cycloadduct **34** (together with a 3% yield of the corresponding *exo* adduct).[26] Whereas partial hydrogenation selectively reduced the ring double-bond to produce the *exo* methylene compound **35**, exhaustive hydrogenation resulted in the formation of the di-*endo* structure **36**. The base-catalyzed rearrangement (*n*-butyl lithium at -70 °C, then water) of bicycles **34-36** provided an easy entry into an array of interesting substituted cyclohexenols **37-39**. Recently, Braverman showed that the dienophilic character of allenyl sulfones drastically increased with the introduction of a trichlorosulfonyl group.[27] Indeed, addition of trichlorosulfonyl allene to furan proceeded even at room temperature, producing the [4+2]-cycloadducts (*endo/exo* 9:1) in quantitative yield.



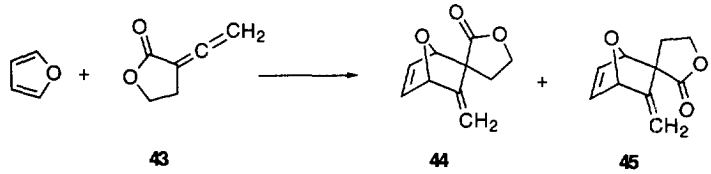
Allenic esters have also been shown to add to furans in a highly regio- and stereospecific fashion.[28] Lewis acids such as $Eu(fod)_3$ and $Pr(fod)_3$ were found to catalyze these cycloadditions. Several mol-% significantly enhanced the selectivities and yields of these reactions without adversely affecting fragile functionalities. Particularly reactive *bis*-ester allenes such as 1,3-dicarboethoxyallene underwent rapid smooth cycloaddition with furan and 2,5-dimethylfuran at 40 °C.[29] The resulting adducts (*e.g.* **40**) were easily transformed into phenol **41** using boron trifluoride in methylene chloride.



An interesting variation of the above process involved the addition of optically active (*R*)-di-(-)-menthyl allene-1,3-dicarboxylate onto furan in an asymmetric Diels-Alder reaction.[30] Three equivalents of titanium tetrachloride at -40 °C gave the highest diastereofacial selectivity and afforded a 53% isolated yield of the optically active adduct **42**, which represents a very useful chiral intermediate for synthetic applications.



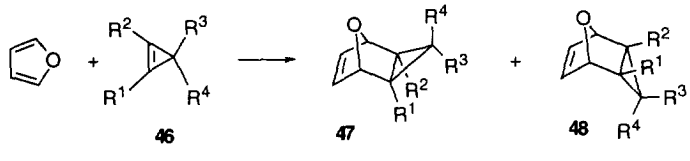
Cycloaddition of α-vinylidene-γ-butyrolactone **43** with furan produced a 9:1 mixture of the expected spiroadducts **44** and **45** in 86% combined yield.[31]

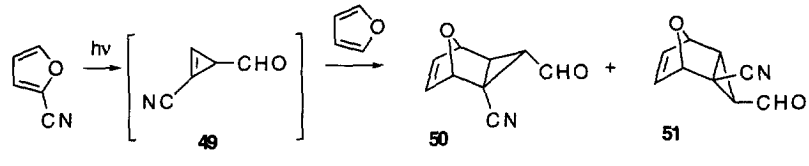


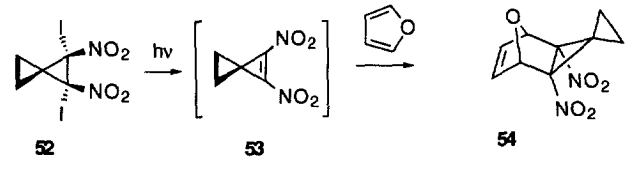
2.2. *Reactive π-Bonds*

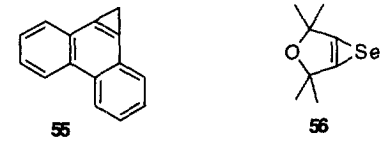
Aside from the important synthetic potential of Diels-Alder reactions of furans, these cycloadditions have also been used to trap unstable intermediates containing highly reactive (*e.g.*, strained) π-bonds. The resulting bimolecular cycloadducts are stable and fully characterizable materials that provided valuable information about the nature of the reactive π-system.

Considering their high strain energy, cyclopropenes are expected to function as active dienophiles with furans; indeed, many examples of cyclopropene-furan cycloadditions have been reported.[32-36] In general, these reactions afford mixtures of *exo* and *endo* isomers. Their ratio is markedly dependent on the nature of the substituents present on the cyclopropene ring, in particular the R^3 and R^4 (gem) substituents. According to Apeloig,[32] "*the parent cyclopropene and 1,2-disubstituted cyclopropenes are expected to yield endo-adducts, exclusively or predominantly. 3,3-Gem-disubstituted cyclopropenes are predicted to yield exo-adducts.*" In the case of cyclopropenes where $R^3 \neq R^4$, the cycloaddition may not only be *exo* or *endo*, but for each of these modes the reaction can also take place on either of the two diastereotopic faces of the cyclopropene.[33] For example, cycloaddition of 1,2,3-trichloro-3-fluorocyclopropene to furan led to the *exo*-adduct **47** as the major product with the fluorine atom *syn* to the oxygen bridge (R^4 = F). The facial selectivity was attributed to electrostatic interactions between the fluorine atom and the bridgehead Cl substituents in the transition state.[33]

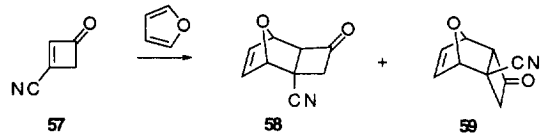






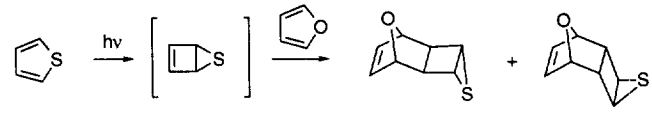


Trapping of the highly reactive cyclopropene **49** (generated by *in situ* irradiation of 2-cyanofuran) with furan provided a mixture of *exo/endo* adducts **50** and **51**.[37] Similarly, irradiation of diiodospiropentane **52** in the presence of furan resulted in the formation of cycloadduct **54**, providing firm evidence for the existence of dinitrospiropentene **53** as a reactive intermediate.[38] Other reactive "*cyclopropene*" derivatives that have been trapped with furan include 1*H*-cyclopropa[*l*]phenanthrene (**55**)[39,40] and selenirene **56**.[41] Compared to cyclopropenes, cyclobutenes showed a significantly lower dienophilicity, undoubtedly as a result of the reduced ring strain. However, the activated ß-cyanocyclobutenone **57** readily underwent Diels-Alder cycloaddition with furan at room temperature to furnish a 10:1 mixture of the *exo/endo* cycloadducts **58** and **59** in 95% combined yield.[42] The homologous ß-cyanocyclopentenone showed no reactivity towards furan under identical reaction conditions.[42]



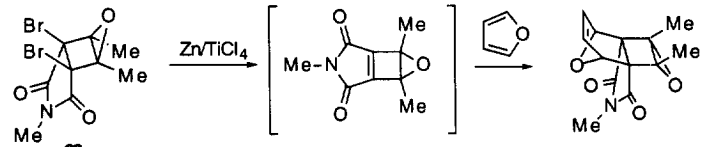
57 **58** **59**

In 1985 Strausz generated the elusive Dewar thiophene **60** by irradiating a solution of thiophene in furan at 229 nm.[43] The resulting Dewar thiophene **60** was immediately trapped by furan at room temperature to afford a mixture of the stable Diels-Alder cycloadducts **61** and **62** in a 5:3 ratio. Matrix-photolysis experiments with thiophene at -170 °C and subsequent trapping of **60** with furan also produced **61** and **62**, thereby confirming that the trapped species was indeed an intermediate and not a short-lived excited state of thiophene.[43]



60 **61** **62**

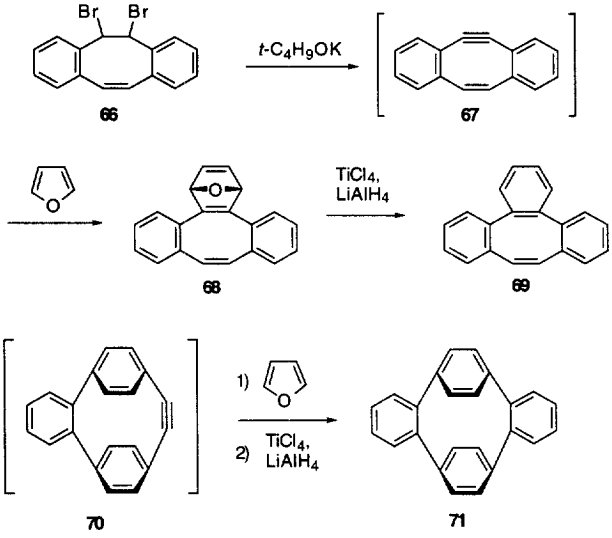
In a somewhat related manner, Dewar furan derivative **64** was generated from **63** and underwent [4+2]-cycloaddition with furan to provide the expected cycloadduct **65**.[44]



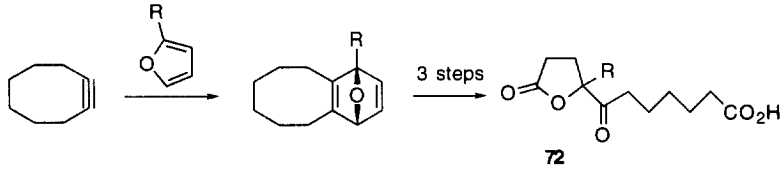
63 **64** **65**

Strained cycloalkynes are another class of reactive π-systems that have been conveniently trapped with furans. Wong reported the generation of 5,6-didehydrodibenzo[*a*,*e*]cyclooctene (**67**) by dehydrobromination of dibromide **66** with *tert*-butoxide.[45] The reactive cyclooctyne underwent rapid cycloaddition with furan at room

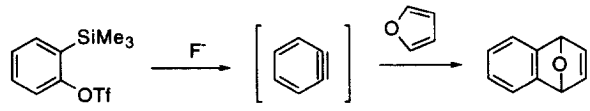
temperature. Deoxygenation of cycloadduct **68** with low valent titanium produced tribenzo[*a,c,e*]cyclooctene **69**. Following a similar sequence of reactions, Wong synthesized dibenzo[2.2]paracyclophane **71** *via* cyclophyne intermediate **70**.[46]



A [4+2]-cycloaddition reaction of cyclooctyne with substituted furans was used by Tochtermann for the preparation of γ,γ-disubstituted γ-lactones of type **72**. The initial cycloadducts were subjected to a sequence of reduction/oxidation to arrive at the desired lactone **72**.[47]

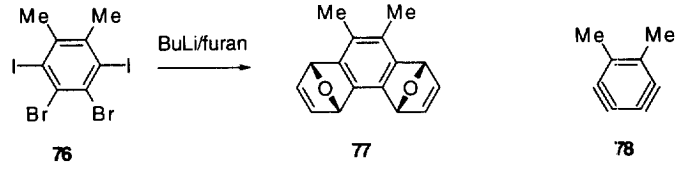


Benzyne (**74**) can be considered a special example of a highly strained cycloalkyne, and its trapping with furan is well-known. Kobayashi reported a mild method for benzyne generation involving a fluoride-induced 1,2-elimination of *ortho*-trimethylsilylphenyl triflate (**73**).[48] Treatment of **73** with tetramethyl-ammonium fluoride in HMPT at room temperature gave cycloadduct **75** in 96% yield. The classic thermal decomposition of benzenediazonium-2-carboxylate at 60 °C in the presence of furan and catalytic triethylammonium chloride resulted in an 85% yield of **75**.[49] *meta*-Alkoxyaryl bromides underwent efficient deprotonation with LDA and subsequent bromide elimination to afford the corresponding benzynes, which were trapped with furan in a Diels-Alder manner.[50] The acid catalyzed ring-opening of the oxo-bridge in 1,4-dihydro-1,4-epoxynaphthalenes of type **75** resulted in the formation of 1-hydroxynaphthalenes in high yield.[51]

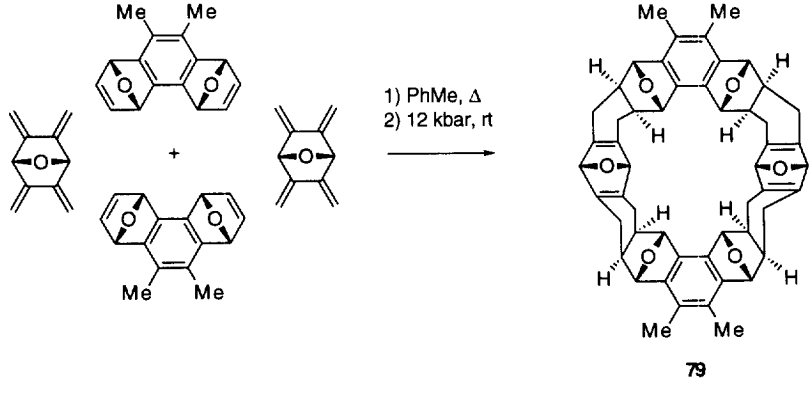


73 **74** **75**

Stoddart has extensively exploited the principle of repetitive arene and *bis*-arene cycloaddition to furans for the design and synthesis of novel macropolycyclic structures.[52,53] For example, *bis*-dienophile **77** obtained from *ortho*-xylene **76** with butyllithium followed by trapping of the resulting *bis*-arene equivalent **78** with two equivalents of furan represents a suitable building block for the construction of the macropolycylic belt-like molecule **79**. Diels-Alder reaction of **77** with an appropriate *bis*-diene under alternate thermal and high-pressure conditions afforded macrocycle **79** in good yield, together with an acyclic isomer.[52,53]

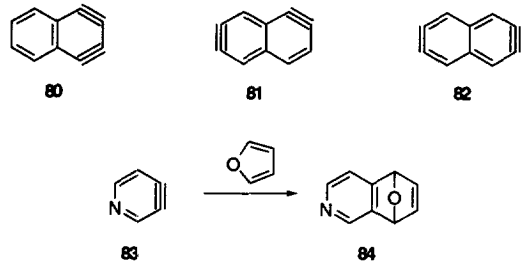


76 **77** **78**



79

Using similar methodology, the "*twin-benzannulation*" of naphthalene *via* formal Diels-Alder cycloaddition of furan to 1,3-, 1,6-, and 2,6-naphthodiynes **80-82** was reported by Gribble to furnish the corresponding polyaromatic hydrocarbons triphenylene, benzo[*a*]anthracene, and naphthacene.[54] 3,4-Pyridyne (**83**) is one of the better known heteroarynes, and various trapping reactions with furans have been reported.[55-57]

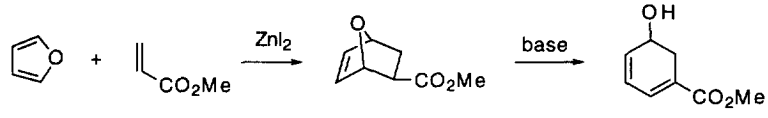


80 81 82

83 84

2.3. *Catalysts and High Pressure*

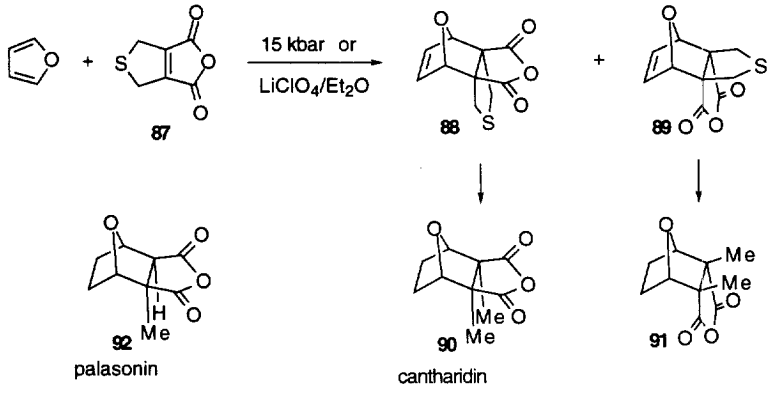
Furan itself is a relatively poor diene in Diels-Alder cycloadditions and reacts only with very reactive dienophiles to form respectable yields of [4+2]-cycloadducts.[5,6] Numerous attempts have been made to improve the yields in such cycloaddition reactions by the use of Lewis acid catalysts or high-pressure protocols. For example, catalytic quantities of zinc iodide greatly accelerate the rate and improve the yield of the cycloaddition of methyl acrylate or acrylonitrile to furan.[58] The resulting 7-oxabicyclo[2.2.1] heptenes (**85**), obtained as mixtures of *exo/endo* isomers, serve as valuable intermediates for the preparation of cyclohexenol derivatives **86** through base-catalyzed β-elimination of the heteroatom bridge.[58] For sensitive dienes and dienophiles, Danishefsky employed $Yb(fod)_3$ as a mild cycloaddition catalyst.[59] Addition of acrolein to furan in the presence of 10 mol-% of $Yb(fod)_3$ at room temperature led to a 40% yield of a 4.5:1 mixture of *exo/endo* cycloadducts.[59] Similar yields and selectivities were obtained using hexafluoroisopropanol, which acts as a mild Lewis acidic solvent in this reaction.[60] Recently, cation-exchanged clay minerals such as Cr^{3+}-Tonsil 13 were found to significantly enhance the rate of the furan/MVK Diels-Alder reaction.[61]



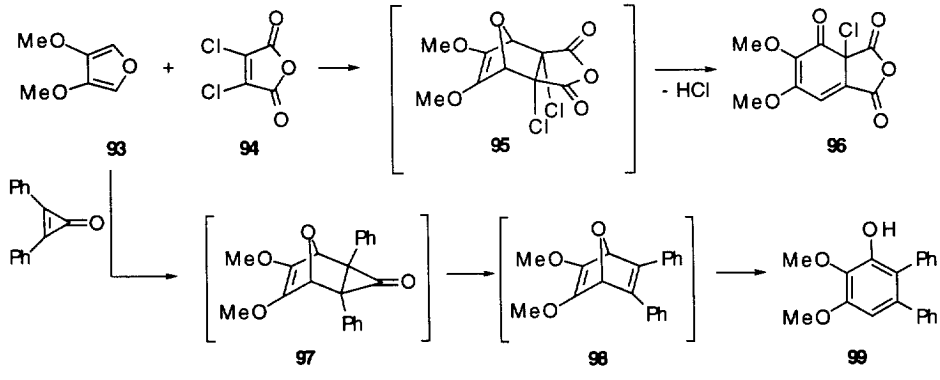
85 86

One of the most noted reactions of furan involves its cycloaddition with substituted maleic anhydrides in the context of the synthesis of cantharidin. Dauben synthesized cantharidin (**90**), a natural product and potent vesicant, from 2,5-dihydothiophene-3,4-dicarboxylic anhydride (**87**) and furan.[62] The high-pressure induced Diels-Alder cycloaddition proceeded at 15 kbar and provided a 85:15 mixture of cycloadducts **88** and **89**. Hydrogenation and desulfurization (Raney-Ni) of the isomeric mixture followed by fractional recrystallization afforded cantharidin **90**.[62] In a later study, Grieco demonstrated that the same cycloaddition could occur at atmospheric pressure employing 5.0M lithium perchlorate/ether as the reaction medium (Grieco reagent) (70% yield, **88**:**89** = 85:15).[63] In a subsequent investigation involving the cycloaddition of 3-methylmaleic anhydride to furan, Dauben found that Grieco's conditions were unsuccessful, giving only 10% of the cycloaddition product. This was attributed to the fact that lithium perchlorate/ether not only enhanced the cycloaddition

process, but also accelerated the cycloreversion reaction.[64] However, the high-pressure induced reaction gave an 82% yield of the desired [4+2]-cycloadduct.[64] Hydrogenation of this cycloadduct over Pd/C led to (±)-palasonin **92** in 97% yield.[64]

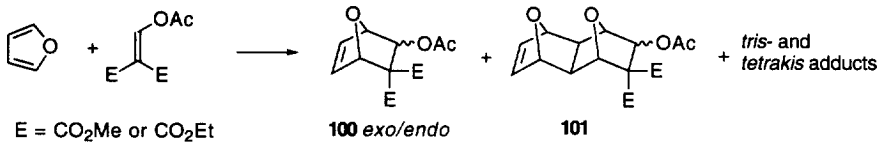


In a related example, the somewhat more reactive 3,4-dimethoxyfuran (**93**) underwent Diels-Alder addition with dichloromaleic anhydride (**94**) at 10 kbar to give anhydride **96**.[65] This product probably arose through an acid-catalyzed rearrangement of cycloadduct **95**. The reaction of **93** with diphenylcyclopropenone (10 kbar) resulted in the formation of phenol **99** in 24% yield.[65] Cycloaddition to give **97** followed by decarbonylation and rearrangement nicely accounts for the formation of **99**. 3,4-Dimethoxyfuran (**93**) formed isolable Diels-Alder adducts with cyclohexene- and cyclopentene-1,2-dicarboxylic anhydrides at 8 kbar. The yields were moderate, and the Diels-Alder cycloadducts readily reverted to the starting materials under normal pressure.[66] Kinetic measurements of the cycloreversion reaction of the 3,4-dimethoxyfuran/1,4-benzoquinone cycloadduct demonstrated that the stabilization of such adducts depended mainly on the substituents present on the furan ring.[67]



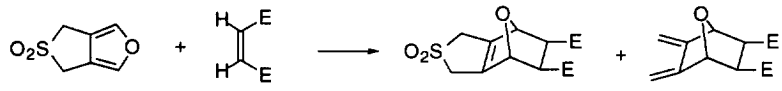
Dialkyl (acetoxymethylene)malonates also underwent high-pressure mediated Diels-Alder cycloadditions with furan.[68] Apart from the expected 1:1 adducts, the reaction produced considerable amounts of *bis*-, *tris*-,

and *tetrakis* adducts. With this system, Lewis acid catalysis (*i.e.*, zinc iodide) combined with high pressure did not afford cycloaddition products, but rather products resulting from Michael-type addition.[68]



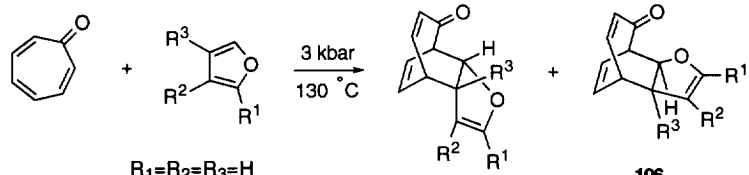
E = CO_2Me or CO_2Et **100** *exo/endo* **101**

Thienofuran dioxide **102** is an interesting building block that under thermal conditions (120 °C) gave addition products of type **104,** together with other cycloadducts derived from the addition of excess dienophile to the exocyclic diene moiety present in **104**.[69] Under high-pressure conditions (12 kbar), however, dienophiles added selectively to the furan moiety in **102** to produce tricycles such as **103**.[69]



102 E = CO_2Me **103** **104**

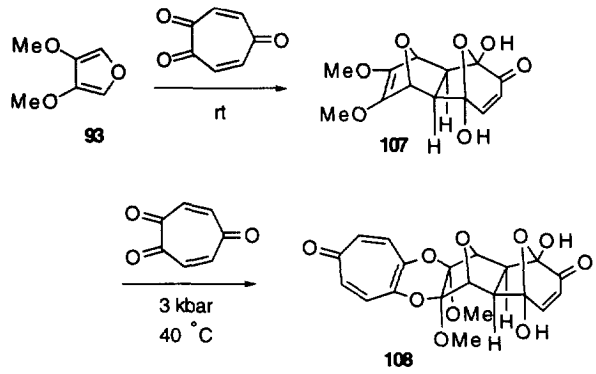
Using high pressure, furans can be forced to participate in [4π + 2π] cycloadditions as the 2π component (*i.e.*, as a dienophile). Thus, treatment of furan, 2-methoxyfuran, or 3,4-dimethoxyfuran with tropone at 3 kbar and 130 °C produced a 1:1-mixture of cycloadducts **105** and **106**, as well as various other cycloaddition products.[70,71] Analysis of the FMO interactions suggested that these [4π + 2π] cycloadditions were $LUMO_{tropone}$- $HOMO_{furan}$ controlled.[70]



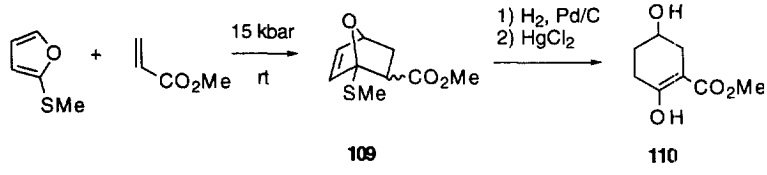
R_1=R_2=R_3=H
R_1=R_2=H; R_3=OMe
R_1=H; R_2=R_3=OMe

105 **106**

With *p*-tropoquinone, 3,4-dimethoxyfuran (**93**) acts as a 4π component and under normal pressure gave the expected 1:1-cycloadduct **107** in 49% yield *via* intramolecular hemiacetalization.[72] At 3 kbar, the same reaction yielded an additional product (**108**) that resulted from the 4π cycloaddition of the α-dioxo group in *p*-tropoquinone to the electron-rich double bond in **107**.[72]



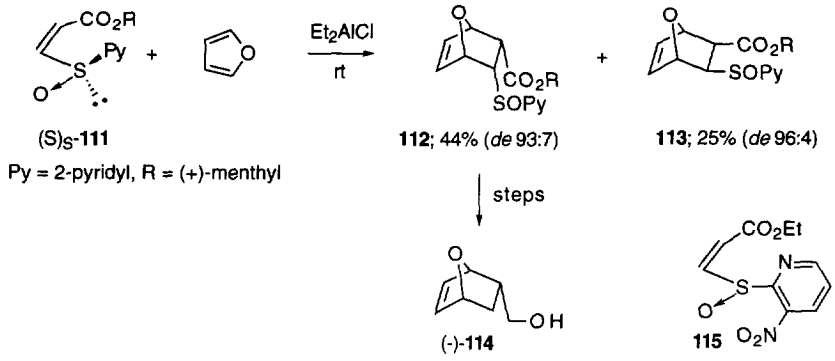
Kotsuki reported on the high-pressure cycloadditions of 2-methylthio- and 2-acetoxyfuran.[73] For example, cycloaddition of methyl acrylate to 2-methylthiofuran led to a 2:1 *endo/exo* mixture of oxabicycloheptanes **109** (64%). Hydrogenation, followed by treatment with mercuric chloride, gave 4-hydroxycyclohexanone **110** in quantitative yield.[73]



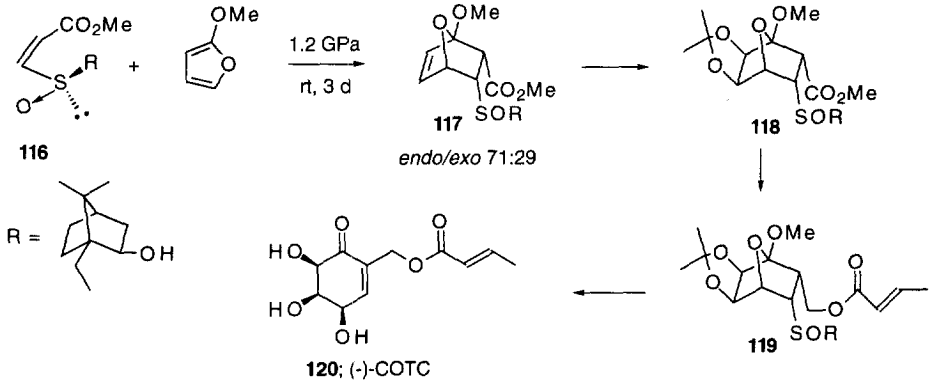
The Diels-Alder reaction of furan was used to study the rate acceleration in an ultracentrifuge experiment.[74] In the reaction of furan with maleic anhydride, the reaction rate increased significantly as a function of the centrifugal pressure.[74] Furthermore, Jenner showed that water can alter the kinetics and the chemo- and *endo*-selectivity of furan high-pressure reactions, presumably through polarity and hydrophobic effects.[75]

2.4. *Asymmetric Diels-Alder Reactions*

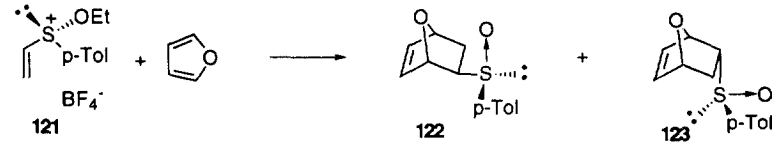
The first efficient asymmetric synthesis of 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate by a highly diastereoselective furan Diels-Alder reaction was reported in 1986 by Koizumi.[76] When the optically active 3-(2-pyridylsulfinyl)acrylate $(S)_S$-**111** was used as the chiral dienophile, a mixture of *endo* and *exo* cycloadducts **112** and **113** was obtained in 69% combined isolated yield. With both isomers, high diastereoselectivities were encountered. The major (*endo*) isomer could be readily transformed into the enantiomerically pure alcohol **114**. Even higher diastereoselectivities (*de* > 98:2) were found for the nitro-substituted analog (*i.e.*, **115**).[77] Due to the enhanced reactivity of this dienophile, this [4+2]-cycloaddition proceeded without Lewis acid catalysis.



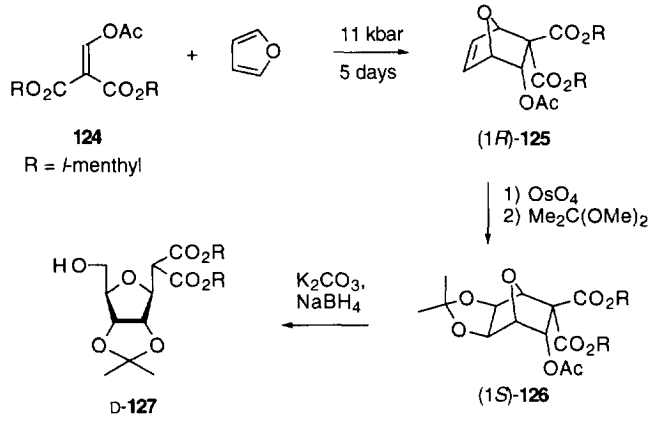
In a similar fashion, chiral dienophile **116** underwent cycloaddition with 2-methoxyfuran under high-pressure conditions.[78] The resulting mixture of *endo/exo* adducts (*de* for both > 98:2) was dihydroxylated and subsequently transformed into acetonide **118**. Conversion of **118** into crotonate ester **119** followed by acid hydrolysis gave the antibiotic (-)-COTC **120**.[78]



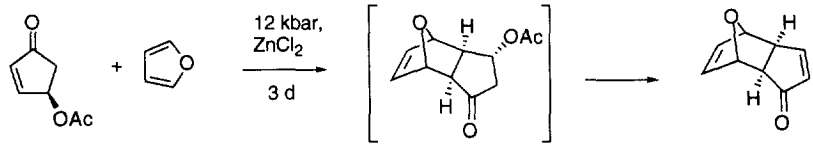
Kagan described a method to enhance the Diels-Alder reactivity of vinyl sulfoxides.[79] Activation of chiral *p*-tolyl vinyl sulfoxides by transformation into their corresponding sulfonium salts (*i.e.* by *O*-alkylation with Meerwein reagent) or by addition of catalytic or stoichiometric quantities of TMSOTf dramatically affected reaction rates and diastereoselectivities. For example, extremely high diastereoselectivities (*de* > 98%) were obtained from sulfonium salt **121** and furan at -20 °C (**122** *exo*/**123** *endo* = 59:41). The TMSOTf-promoted cycloaddition gave somewhat lower selectivities.[79] It is interesting to note that the two activation methods afforded sulfoxides that were epimeric at the sulfur atom, as the configuration was inverted when the sulfonium cycloadducts were converted to the corresponding sulfoxides.[79]



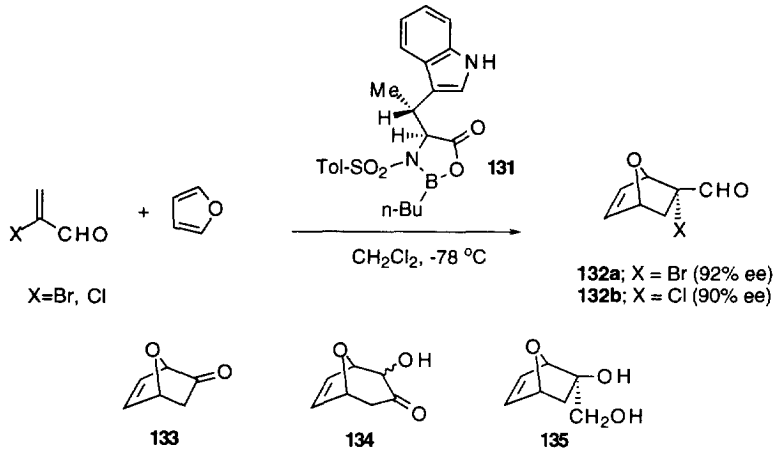
Di-*l*-menthyl acetoxymethylenemalonate (**124**) is another chiral dienophile that has been utilized in asymmetric Diels-Alder reactions.[80] High-pressure mediated addition of **124** to furan produced a mixture of labile *endo* and *exo* cycloadducts (*i.e.* **125**) that were immediately converted into the corresponding acetonides **126**. The reductive retrograde aldol reaction of the *endo* product **126** resulted in the formation of β-D-ribofuranosylmalonate **127**. Analogous manipulation of the *exo* product gave the corresponding non-natural L-analog.[80]



Zwanenburg examined 4-hydroxycyclopent-2-enone derivatives as chiral synthetic equivalents of cyclopentadienone in asymmetric Diels-Alder reactions.[81] The high-pressure mediated cycloaddition of (*R*)-(+)-**128** to furan, followed by treatment of the crude cycloadduct with base, afforded tricyclodecadienone **130** in 35% yield and 53% *ee*. The moderate diastereoselectivity enountered in this asymmetric cycloaddition was attributed to opposing steric and electronic effects.[81]

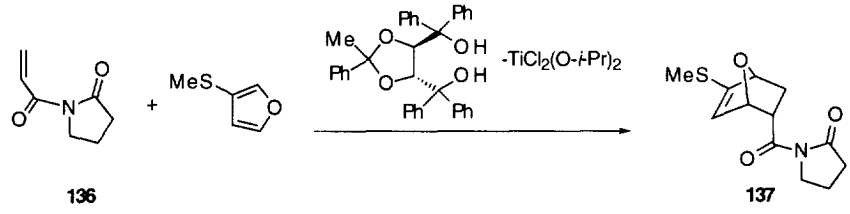


In 1993 Corey first reported the application of a catalytic enantioselective cycloaddition to furan.[82] In the presence of 10 mol-% of the oxazaborolidine-derived chiral catalyst **131**, 2-bromo- and 2-chloroacrolein smoothly underwent cycloaddition (-78 °C, 5 h) with furan to give the cycloadducts **132a,b** in > 98% chemical



yield (*exo/endo* 99:1) with 96:4 and 95:5 enantioselectivity, respectively. The *N*-tosylcarboxylic acid precursor of the chiral catalyst could be efficiently recovered for reuse in each case. Bromo derivative **132a** served as a valuable precursor for the preparation of a variety of interesting oxabicycles, such as **133-135,** in enantiomerically pure form.

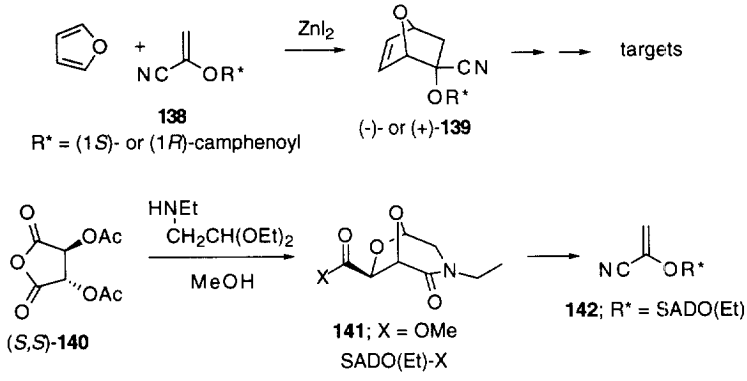
Narasaka reported another example of a catalytic enantioselective furan cycloaddition reaction.[83] Reaction of 3-methylthiofuran with acrylamide **136** in the presence of 10 mol-% of a chiral titanium catalyst at -10 °C led to cycloadduct **137** (*endo/exo* = 85:15) in 97% combined yield. The enantiomeric excess of the *endo* product **137** was 87%.



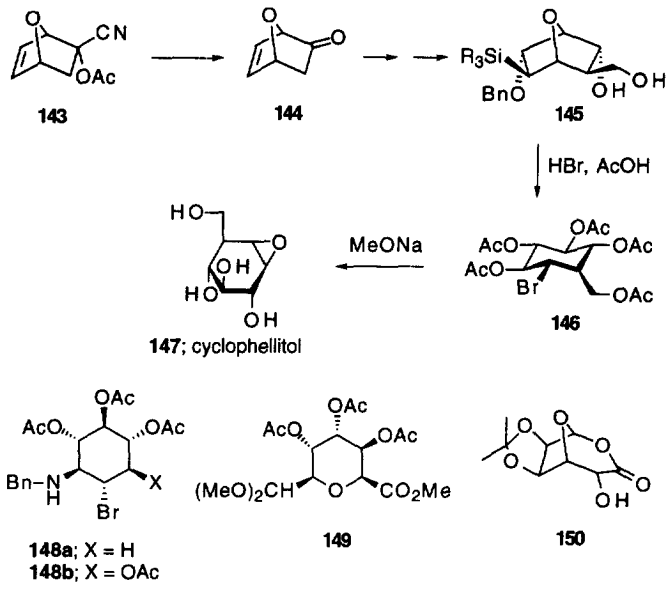
2.5. *Total Synthesis*

The use of furans as the starting point for the total synthesis of natural products has flourished within the last decade.[84] The initial cycloadducts can be manipulated with impressive versatility, leading to a number of naturally occurring targets. The use of chiral dienophiles in these [4π + 2π]-cycloadditions affords enantiomerically pure intermediates that serve as extremely useful chirons (chiral synthons) for the total synthesis of carbohydrates and related target molecules. Work in this area was pioneered by Vogel, and the

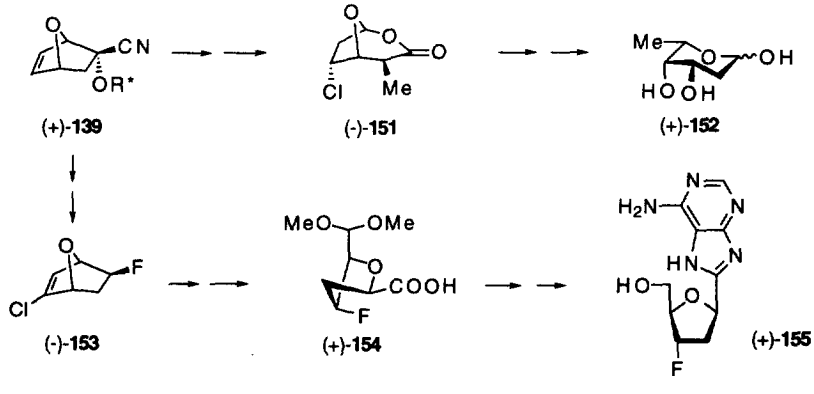
literature up to 1990 has been reviewed.[85] The key step involves cycloaddition of furan with a chiral dienophile, leading to a 7-oxabicyclo[2.2.1]hept-5-en-2-yl (7-oxanorbornenyl) derivative in optically pure form.[85] One of the chiral dienophiles that was developed for this purpose is 1-cyanovinyl (1*R*)- or (1*S*)-camphonate (**138**). Reaction with furan under zinc iodide catalysis produces the corresponding cycloadducts (-)- or (+)-**139** in high yield and optical purity.[85] Another chiral auxiliary developed by Vogel is SADO(Et)-X **141**, obtained from di-*O*-acetyl (*S,S*)-tartaric anhydride with *N*-ethylaminoacetaldehyde diethylacetal.[86] Bicycle **141** was readily converted to the corresponding 1-cyanovinyl ester **142**, which underwent cycloaddition with furan to give optically pure Diels-Alder cycloadduct **139** (R* = SADO(Et)). 7-Oxanorbornenyl derivatives, such as **139**, possess three unsubstituted carbon centers and therefore have been coined "*naked sugars*". Substitution of these centers proceeded with high stereoselectivity, leading to polysubstituted 7-oxanorbornane derivatives that have the same density of stereochemical information as hexoses.[85]

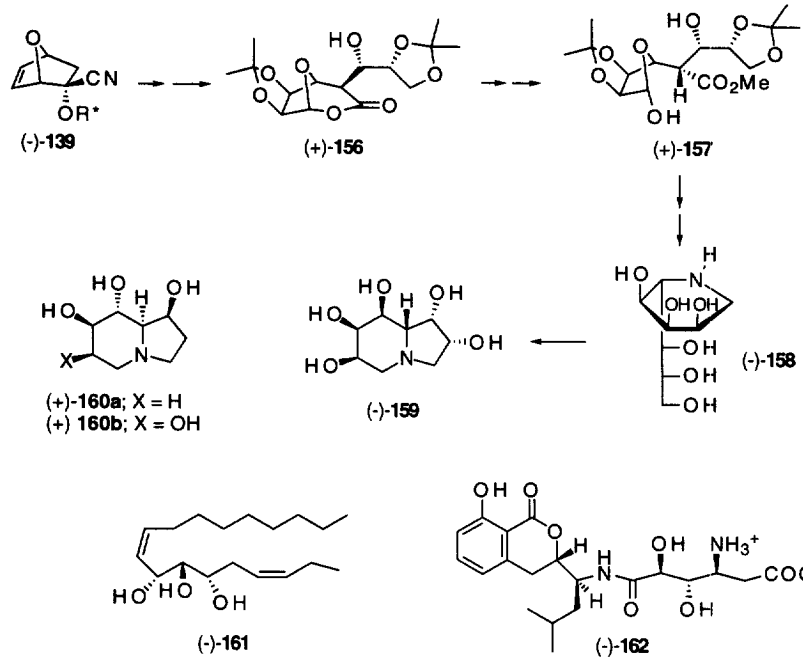


The application of "*naked sugar*" methodology towards the synthesis of various kinds of natural products has attracted some attention in recent years. In many instances, racemic model studies were first conducted using cycloadduct **143** derived from furan and 1-cyanovinyl acetate. For example, **143** was converted into 7-oxanorbornenone **144** and subsequently transformed into the polyfunctionalized oxanorbornane **145** in 6 steps. Treatment with HBr/AcOH, followed by MeONa, led to the carbasugar (±)-cyclophellitol (**147**), a potential drug used against HIV and metastasis.[87] In related work, the syntheses of (±)-aminobromocyclitols **148**,[88] ß-C-hexopyranosyl derivative **149**,[89] and dioxabicyclo[3.2.1]-octan-3-one **150**,[90] from **143** were reported.

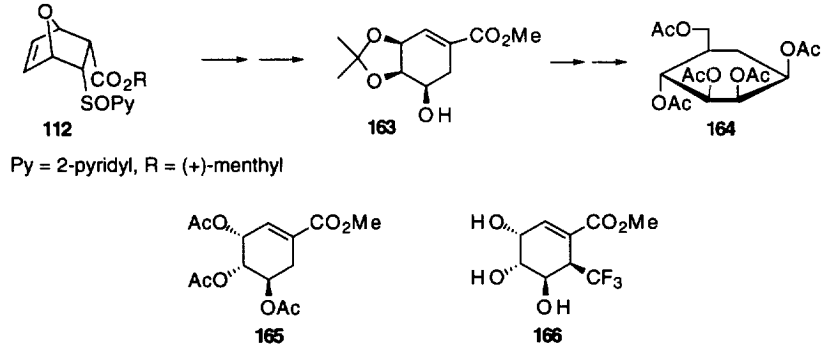


Starting from the enantiomerically pure adduct (+)-**139**, Vogel reported a concise 8-step synthesis of 2-deoxy-L-fucose (+)-**152** *via* urono-6,1-lactone (-)-**151**.[91] From the same precursor, the potential antiviral agent (+)-**155** was obtained in 9 steps and 12% overall yield.[92] Starting from enantiomeric (-)-**139**, a route to 1,5-dideoxy-1,5-imino-D-*erythro*-L-allo-octitol (-)-**158** and pentahydroxyindolizidine (-)-**159** was developed,[93] nicely demonstrating the potential of these chirons for the asymmetric synthesis of complicated azasugars and alkaloids. Similar methodology gave (+)-6-deoxycastanospermine (**160a**), a close analog of the promising anti-cancer and anti-HIV alkaloid castanospermine (**160b**).[94] The use of "*naked sugar*" methodology is not limited to complex carbohydrate synthesis,[95] but has also been applied to the asymmetric synthesis of the C_{18}-fatty acid **161**,[96] and the gastroprotective agent AI-77-B (**162**).[97]

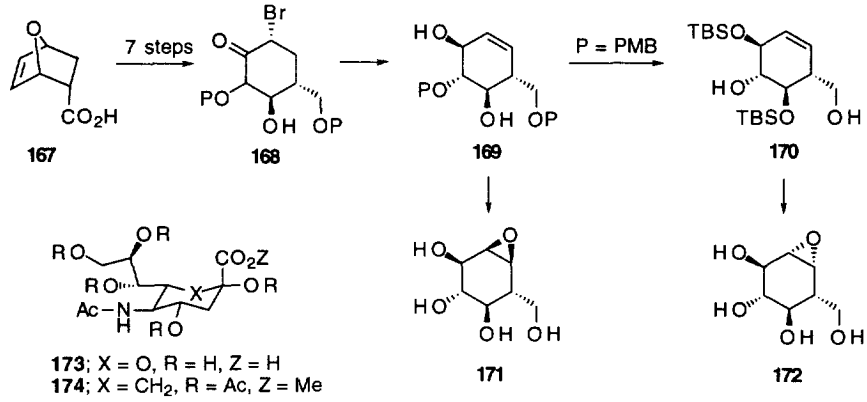




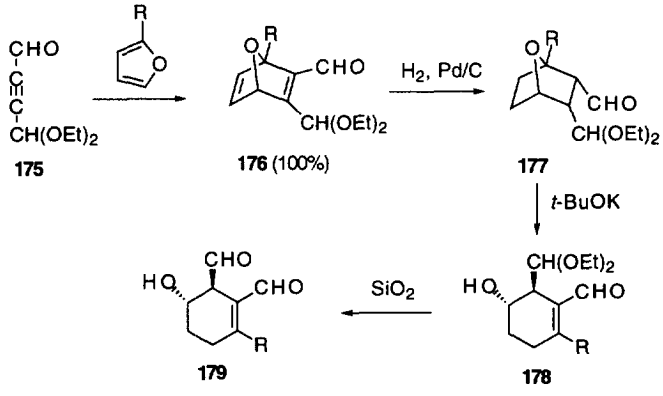
In 1990 Koizumi reported the first chiral synthesis of a pseudo sugar.[98] The asymmetric cycloaddition reaction of $(S)_S$-3-(2-pyridylsulfinyl)acrylate **111** with furan furnished the enantiomerically pure adduct **112** (see below), that was subsequently converted into the protected *epi*-shikimate derivative **163**. Further transformation (6 steps) provided pseudo-ß-D-mannopyranose **164** in fair overall yield and high optical purity.[98] Alternative approaches to racemic methyl triacetylshikimate **165** from 3,4-dibenzyloxyfuran/methyl acrylate adducts,[99] and to 6-trifluoromethylshikimic acid **166** from furan/trifluoromethylbutenoic acid adducts[100] have been described in the literature.



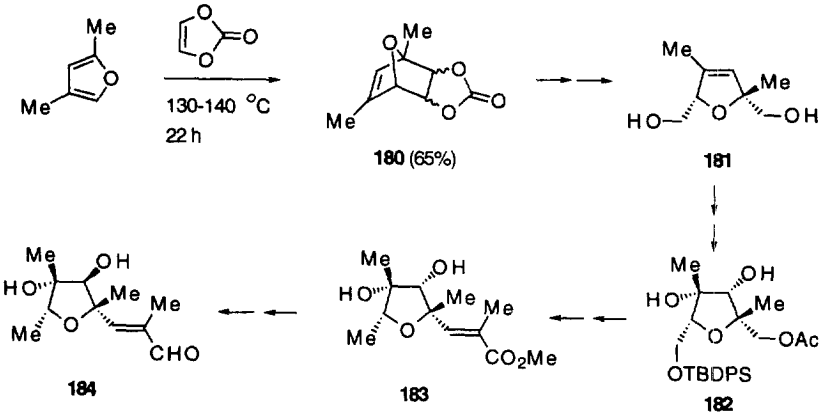
A concise, stereodivergent synthesis of (±)-cyclophellitol (**172**) and its unnatural diastereomer (1*R**,1*S**)-cyclophellitol (**171**) starting from the furan/acrylic acid cycloadduct **167** was reported recently.[101] The key intermediate was the protected diol **169**. For P = benzyl, the epoxidation with MCPBA is controlled by the free allylic hydroxyl group and led, after debenzylation, to (1*R**,1*S**)-cyclophellitol (**171**). A protection (TBSOTf)/debenzylation sequence converted cyclohexenol **169** (P = PMB) into the silyl-protected diol **170**. Selective epoxidation of this diol afforded (±)-cyclophellitol **172** after deprotection.[101] Diels-Alder adduct **167** has also been employed for the synthesis (21 steps) of a carbocyclic analog of *N*-acetylneuraminic acid **173**, *i.e.* the peracetylated derivative **174**.[102]



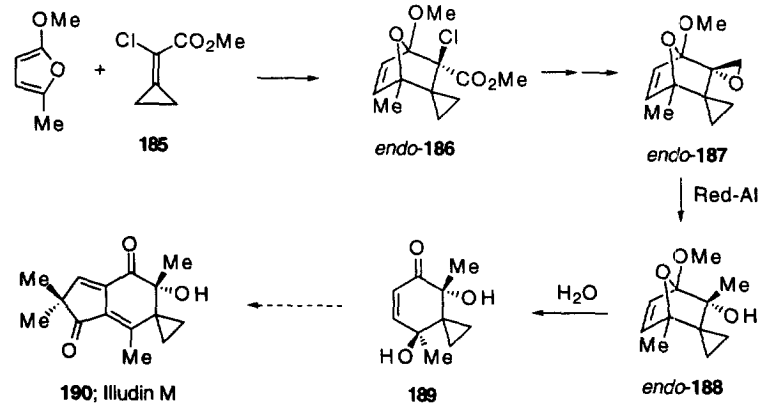
A considerable number of terpenoid natural products that contain an unsaturated 1,4-dialdehyde functionality are known, and many of these compounds possess potent biological activity.[103] Using 4,4-diethoxybut-2-ynal (**175**) as an acetylene dicarbaldehyde synthon, Sterner developed an expeditious 4-step sequence to cyclohex-1-ene-1,6-dicarbaldehydes of type **179**.[103] The key step involved the Diels-Alder reaction of **175** with substituted furans. This reaction proceeded smoothly with complete regioselectivity and in quantitative yield.



A total synthesis of (±)-citreoviral (**184**), a metabolite of *Penicillium citreoviride* B, starting from 2,4-dimethylfuran and vinylene carbonate was reported by Yamamura.[104] The reaction produced a 7:5 mixture of the *exo/endo* cycloadducts **180** in 65% combined yield. From **180**, the synthesis of (±)-citreoviral **184** required 19 steps.

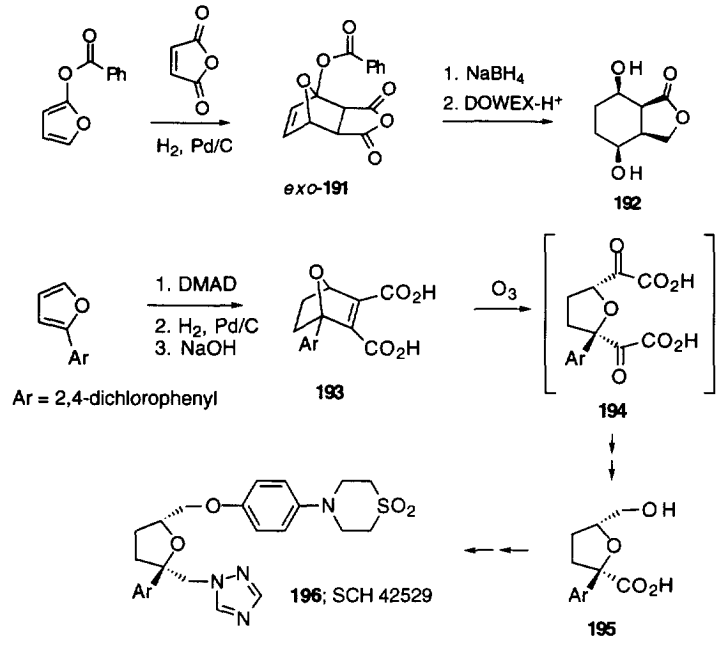


Using 2-chloro-2-cyclopropylideneacetate **185** as a cyclopropyl building block, deMeijere proposed a synthetic approach towards the antibacterial and cytotoxic sesquiterpene illudin M (**190**).[105] Initial Diels-Alder reaction of **185** with the appropriately substituted furan gave the *endo* cycloadduct **186** as the major product. The α-chloroester functionality in **186** was converted into the spiroexpoxide group of **187**, which proved to be a suitable precursor for the desired tertiary alcohol grouping present in illudin M. Thus, reduction of epoxide **187** with Red-Al® followed by cleavage of the oxo-bridge in **188** with wet silica gel gave cyclohexenone **189** in 23% overall yield from **185**. Application of an appropriate cyclopentenone annulation method to **189** should eventually lead to illudin M (**190**).

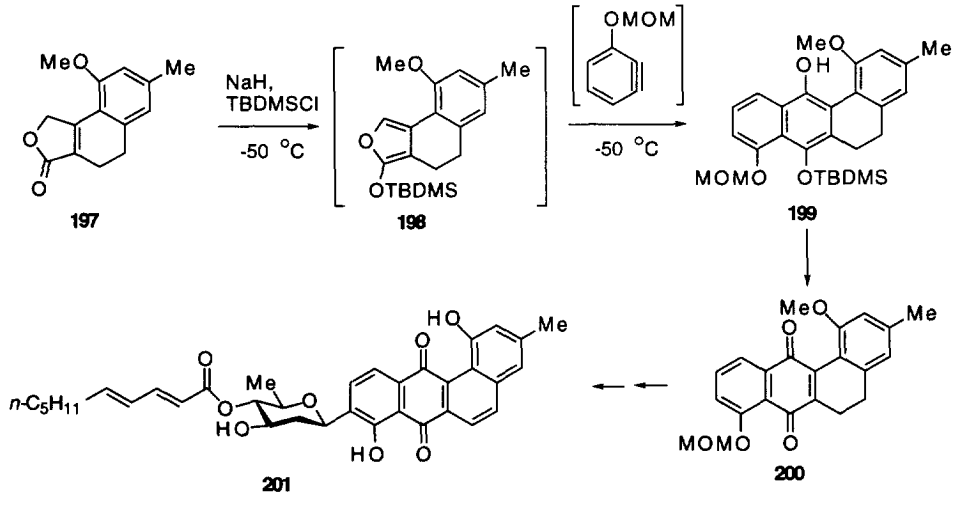


The [4+2]-cycloaddition of 2-(benzoyloxy)furan with maleic anhydride was used as the first step in a short synthesis of dihydroxyperhydroisobenzofuranone **192**, a natural product found in garlic.[106] An aqueous

Diels-Alder reaction of a halogenated 2-arylfuran with DMAD was employed in a multi-step synthesis of the orally active azole antifungal **196**, (*i.e.* SCH 42529).[107]

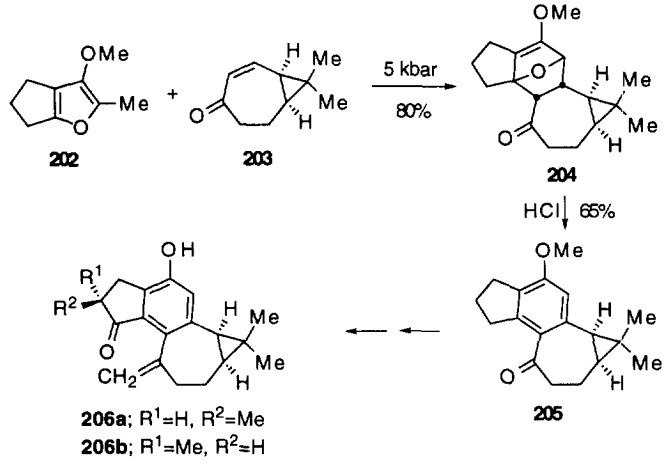


The first total synthesis of the angucycline-class antibiotic C104 (**201**) was recently accomplished using a benzyne-furan cycloaddition as the key step.[108] Angularly fused α-siloxyfuran **198**, generated *in situ* by treatment of butenolide **197** with NaH-TBDMSCl, was subjected to a cycloaddition reaction with an α-alkoxybenzyne, also generated *in situ* from the corresponding α-iodotriflate and butyllithium. Oxidative work-



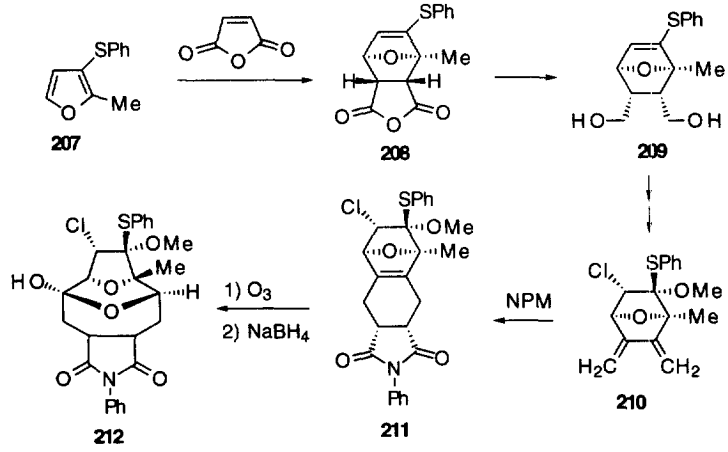
up of the [4π + 2π]-cycloaddition provided the hydroquinone **199**, which was oxidized to the tetracyclic quinone **200**. Subsequent glycosidation and further elaboration (6 steps) led to the desired antibiotic target C104 (**201**).[108]

A short and elegant synthesis of jatropholones A (**206a**) and B (**206b**) using Diels-Alder methodology was reported by the Smith group.[109,110] The high-pressure induced cycloaddition of the fused furan **202** with the homochiral enone **203** at 5 kbar provided cycloadduct **204** in 80% yield. Subsequent aromatization (**205**),



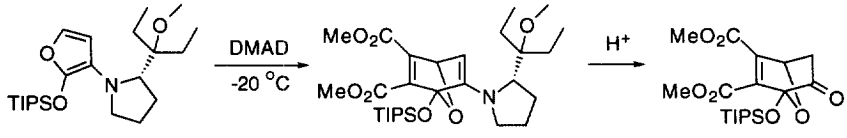
introduction of the *exo* methylene group, regioselective oxidation, and methylation afforded a separable mixture of jatropholones A and B (**206**) in 6% overall yield (12 steps).[109,110]

An interesting approach to the furanoheliangolide ring skeleton, found in many sesquiterpenoid natural products, was reported by McDougal.[111] Cycloaddition of maleic anhydride to furan **207** gave cycloadduct **208**, which was reduced to diol **209** and subsequently converted to diene **210**. The Diels-Alder reaction of



N-phenylmaleimide with **210** gave the polycycle **211**. Ozonolysis of the oxa-bridged Δ^9-octalin furnished the corresponding dione, which was selectively reduced by sodium borohydride to give hemiketal **212** possessing the furanoheliangolide skeleton.[111]

Recently, Schlessinger found that furans bearing a proline-derived chiral auxiliary in the 3-position (*e.g.* **213**) function as chiral 4π–synthons in Diels-Alder chemistry.[112,113] These chiral dienes underwent a variety of Diels-Alder cycloadditions with olefinic and acetylenic dienophiles, showing excellent facial- and *endo/exo*-selectivities. For example, cycloaddition of DMAD with furan **213** at -20 °C gave, after hydrolysis of the enamine residue present in cycloadduct **214**, the optically pure bicyclic ketone **215** in 71% yield .[113] No trace of its enantiomer was detected. This sequence of reactions made this family of chiral furans available for further natural product synthesis.



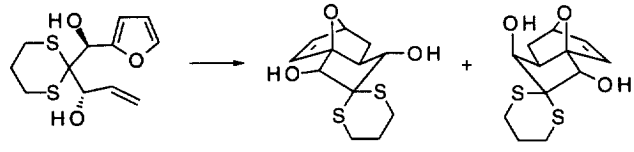
213 **214** **215**

3. INTRAMOLECULAR DIELS-ALDER REACTIONS OF FURANS

3.1. *Scope and Limitations*

3.1.1. *Nature of the Diene*

The intramolecular Diels-Alder reaction (*IMDA*) is amenable to the use of furans as dienes and is frequently designated as the *IMDAF*. The scope of the reaction is quite broad with respect to the diene (furan), dienophile, and the tether linking the two. An example of the IMDAF is the cyclization of alkenyl furan **216**, which involves the intramolecular cycloaddition of a terminal olefin onto a 2-alkyl furan, the simplest possible diene for this type of reaction.[114-115] The high degree of substitution on the tether is important not only for functionalizing the adduct, but also for enhancing the rate of the reaction (*cf.* Section 3.2.1.).

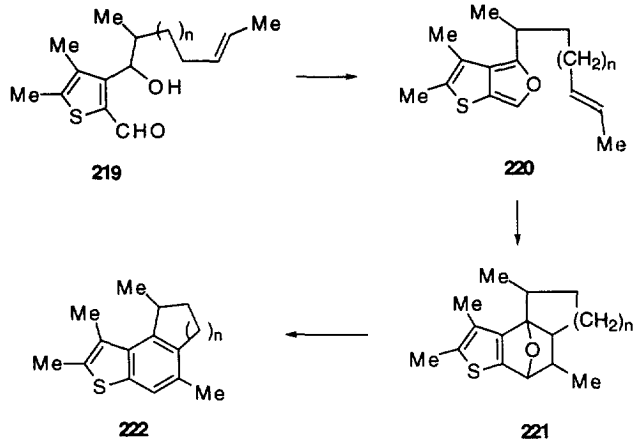


216 **217** **218**

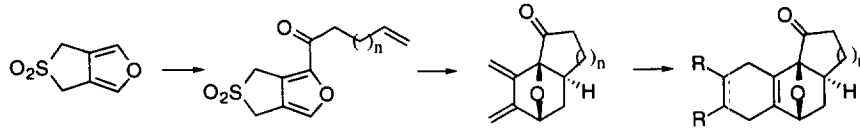
3.1.1.1 *Fused Furans*

In addition to the presence of various substituents, the furan ring can also be part of a fused system, whereby polycyclic adducts are obtained. For example, Schöning and Friedrichsen[116] took advantage of a

latent 3,4-fused furan in their synthesis of racemic thiamarmelerin (**222**), a thiophene analog of a naturally occurring furanosesquiterpene. Thus, thiophene **219** was converted to **222** in 71% yield using acid-catalyzed thermolysis. The reaction presumably proceeds *via* the fused alkenyl furan intermediate **220** and the corresponding cycloadduct **221**, which undergoes subsequent C-O scission and elimination of water to give the observed product.



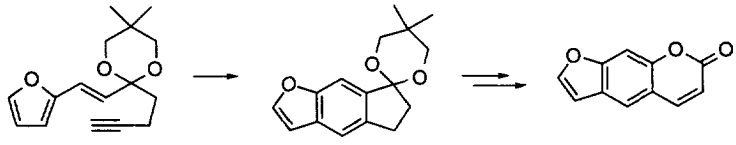
The fused ring on the furan moiety also can be used as a handle for further transformations. Thienofuran dioxide **223** was selectively acylated at the 2-position, setting the stage for the *IMDAF* reaction.[117-119] The resulting adduct underwent spontaneous chelotropic elimination to furnish the oxadimethylene-norbornane derivatives **225**. These compounds have been further elaborated with a variety of dienophiles to give functionalized polycyclic compounds (*i.e.* **226**) in high yield. The regioselectivity of the final step was found to be highly dependent on the nature of the dienophile. Use of cyclic 2-π donors (*e.g.*, benzoquinone) afforded tetracyclic products.



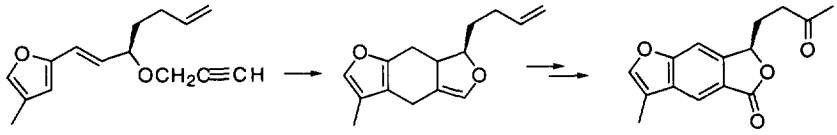
3.1.1.2. *Vinyl Furans*

When the furan ring contains a vinyl group in the 2-position, the cycloaddition can occur across this π-system. The dienophile is usually (but not always) located at the terminal position of the tether. Kanematsu and coworkers used this strategy for the construction of psoralen (**229**)[120] as well as the naturally occurring benzofuran lactone **232**,[121] where the vinyl/furan diene was trapped by a transient allenyl π-bond (*cf.* Section

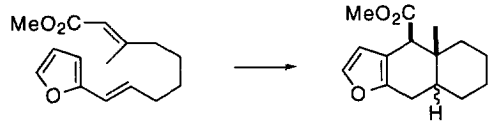
3.1.2.3.). Analogous reactions have been reported for systems containing electron-deficient[122-123] as well as unsubstituted[124] olefins as dienophiles (*e.g.*, **233** → **234** and **235** → **236**).



227 **228** **229**



230 **231** **232**



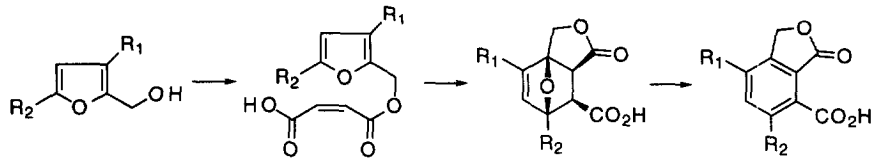
233 **234**

235 **236**

3.1.2. *Nature of the Dienophile*

3.1.2.1. *Alkenes*

As described above, the π-system of the dienophile can contain many types of functionality. The simplest possible case is a non-functionalized olefin as demonstrated by the cycloaddition of alkenyl furan **216**. The Diels-Alder reaction usually occurs more rapidly, however, if the alkene contains electron-withdrawing groups. For example, treatment of furfuryl alcohol with maleic anhydride in chloroform at room temperature led to the *IMDAF* adduct **239** *via* the acid-ester **238**.[125] A study of solvent effects on the analogous diester systems suggests a polar transition state for the cycloaddition.[126]

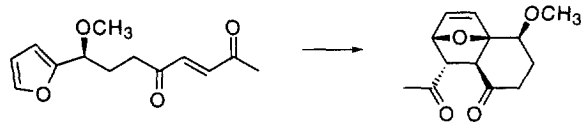


237 **238** **239** **240**

Jung and co-workers[127] utilized the *IMDAF* cycloaddition of *N*-furfurylacrylamide **241**, where the alkene is flanked by amide and chloro functionalities, in their approach to ivermectin. The reaction proceeded in high yield to form the tricyclic cycloadduct **242**, where the chloro substituent showed a preference for the *endo* orientation.

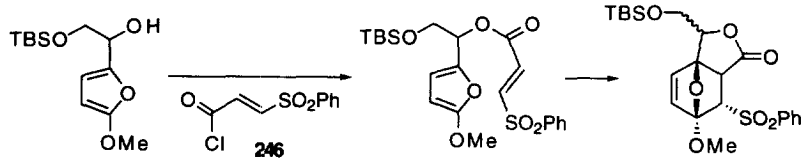
241 **242**

The enedione system **243** underwent a Lewis acid-catalyzed *IMDAF* at room temperature to afford cycloadduct **244** in 67% yield as a single diastereomer. In this case, the high diastereoselectivity was attributed to a favorable pseudoequatorial orientation of the methoxy substituent in the transition state.[128]

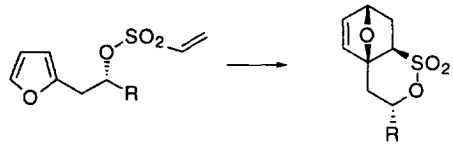


243 **244**

Reaction of furfuryl alcohol **245** with *E*-2-(phenylsulfonyl)acryloyl chloride (**246**) at room temperature led to the facile formation of oxanorbornene **248** *via* the intermediate adduct **247**. The system is activated by the 5-methoxy group on the furan ring, which provides electron density to the diene. In addition, the cycloaddition reaction is enhanced by the strong electron-withdrawing ability of the phenylsulfonyl group on the acrylate system, which is otherwise sluggish or unreactive in such intramolecular cycloadditions.[129] So powerful are such sulfur-based dienophiles that monoactivated vinylsufonic acid esters (*i.e.*, **249**) undergo smooth cycloaddition to form the *exo*-adducts exclusively. MNDO and MMPMI calculations suggest thermodynamic control of the stereochemistry.[130]

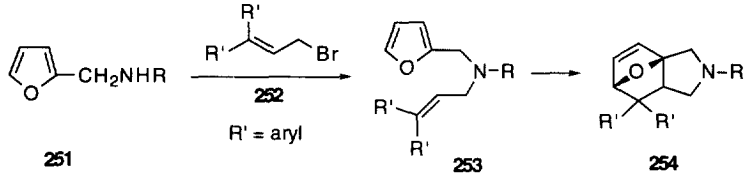


245 247 248



249 250

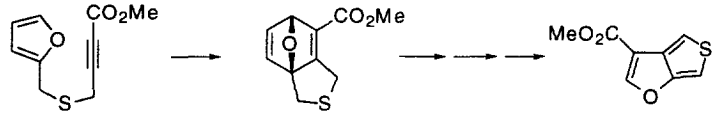
The successful use of aryl substituted alkenes as dienophiles has also been reported. Thus, heating furfuryl amine **251** with allyl bromide **252** in benzene at reflux under phase-transfer conditions led to the formation of adduct **254** in high yield.[131]



251 253 254

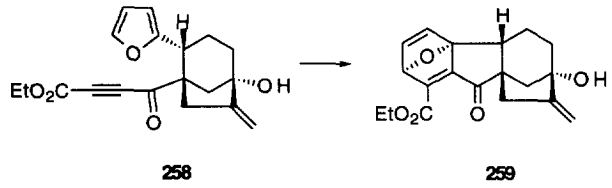
3.1.2.2. *Alkynes*

When the dienophile presents itself as an alkyne, the actual reactive species can be either the triple bond or the isomeric allene (*cf.* Section 3.1.2.3.). In the former case, the alkynyl group is typically activated in the terminal position. For example, Wege and coworkers[132,133] have used the methyl propiolate derivative **255** to furnish the key intermediate **256** (99% yield) for their synthesis of thieno[3,4-b]furan (**257**).

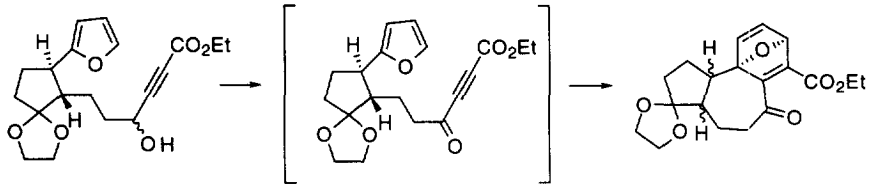


255 256 257

The alkynyl functionality may also be diactivated, as seen in Grootaert and DeClercq's approach to functionalized gibbanes.[134] In this protocol, the A-B ring juncture was constructed by the *IMDAF* reaction of ester **258**, which furnished cycloadduct **259** as a 3:1 mixture of diastereomers. Harwood and co-workers have observed a similar cycloaddition (*i.e.*, **260** → **262**) in their attempt to synthesize phorbol.[135]



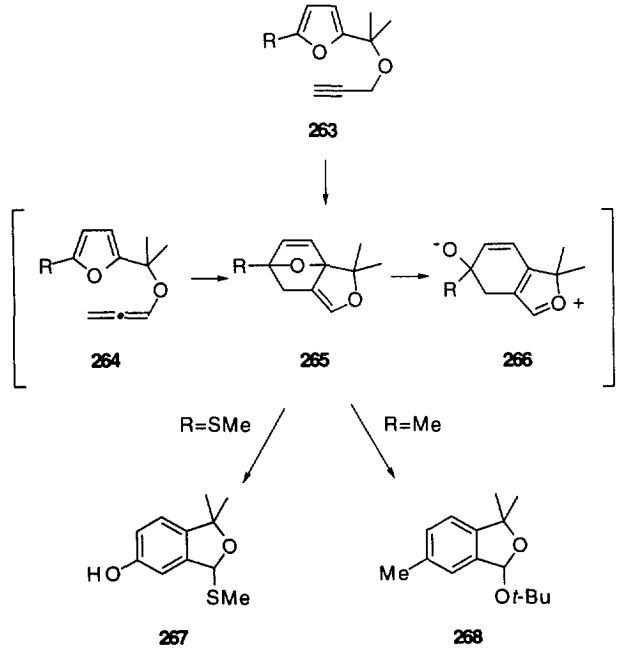
258 259



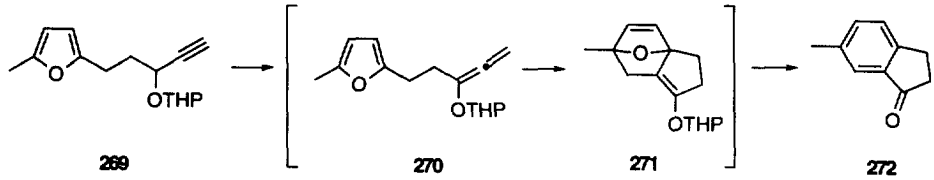
260 261 262

3.1.2.3. *Allenes*

When non-activated terminal alkynes are employed in the *IMDAF* reaction, these substrates usually undergo intramolecular cycloaddition *via* an isomeric allene species. For example, Wu and co-workers[136-137] have studied the *IMDAF* reaction of the furfuryl propargyl ether system **263**. In the presence of base, the



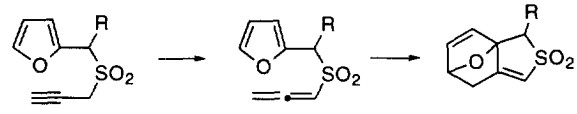
263 264 265 266 267 268



269 270 271 272

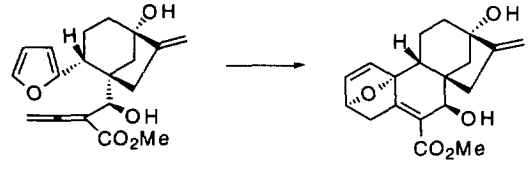
triple bond isomerized to form the rearranged allenyl ether **264**. Cycloaddition then took place across the terminal allene bond to provide the intermediate cycloadduct **265**, which is believed to undergo subsequent fragmentation *via* the zwitterionic structure **266**. In the case where the furan contained a 5-methylthio group, anovel rearrangement was observed to occur affording **267**, presumably by an elimination/addition sequence. This rearrangement is not possible when the 5-substituent on the furan ring is a methyl group. Instead, the initially generated oxonium ion is captured by solvent to give the corresponding *t*-butoxy derivative **268**. A similar protocol was used to form indanones of type **272**.[138]

The intermolecular variant of the Diels-Alder reaction with allenyl sulfones is well-known, and its application to the *IMDAF* has also been reported. For example, treatment of furfuryl propynyl sulfone **273** with a catalytic amount of aluminum oxide resulted in the rearrangement to allenyl sulfone **274.** Further heating gave cycloadduct **275** in 89% yield.[139]



273 274 275

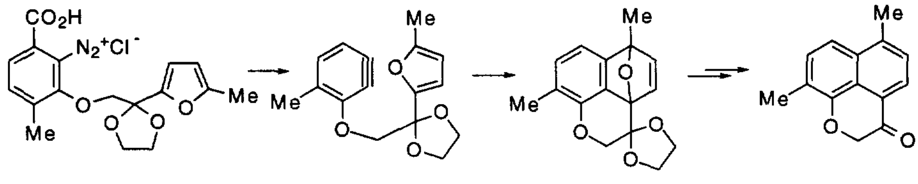
In a similar fashion, the complex carbomethoxy allene **276** underwent an *IMDAF* reaction to form the tetracyclic adduct **277**. Several points are worth noting here, not least of which is the exceptional reactivity of the allene as a dienophile. The isomeric alkynyl system reacted only sluggishly, whereas cyclization of **276** occurred spontaneously at room temperature. The regioselectivity is also interesting, as frontier molecular orbital theory predicts a greater reactivity of the double bond α to the ester functionality. Repulsive non-bonded interactions were invoked to rationalize the observed results. Intriguingly, adduct **277** was formed as a single diastereomer.[140]



276 277

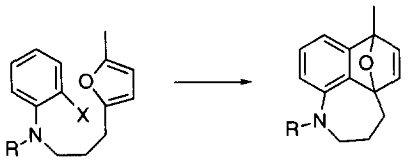
3.1.2.4. *Benzynes*

Compared to other types of dienophiles, the benzyne functionality has been encountered infrequently in the *IMDAF* reaction. Best and Wege[141-142] have used this approach, however, to prepare tricyclic ketone **281**, a key intermediate used for the synthesis of biflorin and mansonone E, I, and F. The requisite benzyne intermediate was synthesized by the thermal decomposition of diazotized anthranilic acid derivative **278**. The subsequent cycloaddition proceeded in good yield.

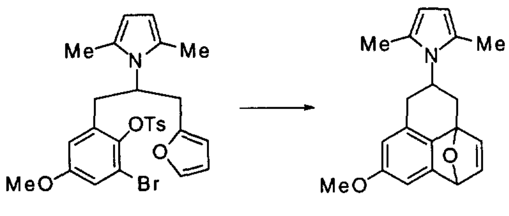


278 **279** **280** **281**

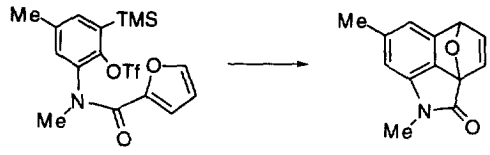
Of course, the crucial aspect of such benzyne *IMDAF* reactions involves the generation of the benzyne moiety itself. Most conventional methods for generating such reactive intermediates tend to be harsh. Other examples of benzyne formation and subsequent cycloaddition include: treatment of an aryl halide with strong base (**282** → **283**),[143] the reaction of a tosyl aryl bromide with phenyllithium (**284** → **285**),[144] and the treatment of a trimethylsilyl aryl triflate with TBAF (**286** → **287**).[145]



282 **283**



284 **285**

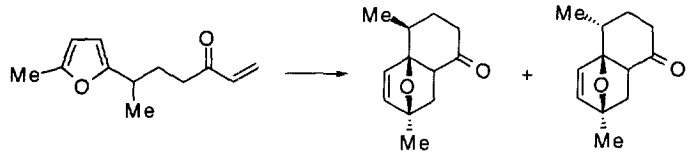


286 287

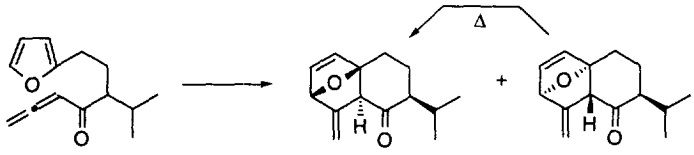
3.2. *Mechanistic Considerations*

3.2.1. *Substituent/Structural Effects*

The course of the *IMDAF* cycloaddition (*i.e.*, rate, stereochemistry) can be greatly affected by substitution at various sites in the substrate. When a single bulky substituent is present on the tether, the most stable cycloadduct will be formed in such a way as to minimize non-bonded interactions, with the sterically demanding group typically assuming an equatorial orientation. These products are the result of thermodynamic control and may not be the major isomer formed in the initial reaction mixture. For example, storage of furanoenone **288** at room temperature for 12 h initially gave an equimolar mixture of cycloadducts **289** and **290**, but after 14 days the proportion of the former isomer, in which the methyl group is situated in an equatorial position, reached 86%.[146] Similarly, the *IMDAF* of furanoketoallene **291** in benzene at reflux afforded a 5:4-mixture of **292** and **293**. At higher temperature (165 °C), the relative abundance of **292** increased to 2:1.[147]

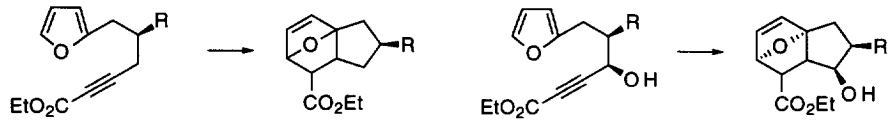


288 289 290

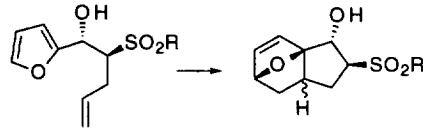


291 292 293

Substitution on the tether also has the added effect of accelerating the [4+2]-cycloaddition, the origin of which is the subject of much debate. For example, a 60-fold increase in the rate of reaction was observed when the furyl alkynoate **294a** (R=H) was substituted with a bulky substituent on the tether (*i.e.*, **294b**, R=*t*-Bu). Interestingly, when an α-hydroxy group was present on the tether (*i.e.*, **296**), the rate increased again by the same order of magnitude.[148-149] The rate enhancement was found to be proportional to steric bulk. This was



294; R=H or *t*-Bu **295** **296** **297**

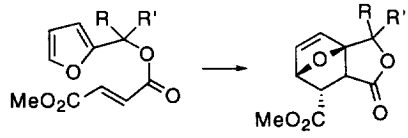


298; R=Me, Ph or *t*-Bu **299**

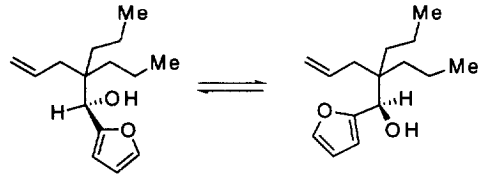
demonstrated with sulfonyl furan **298**, where changing from a methylsulfonyl substituent to the *t*-butyl analog resulted in a 7-fold increase in relative rate.[150] A similar effect was encountered when the substituent was located at another site on the tether.[151]

This rate acceleration is generally referred to as the *t-butyl effect*, for obvious reasons. A related phenomenon is the *gem-dialkyl effect*, which refers to the rate acceleration observed in substrates with *gem*-disubstitution on the tether (*i.e.*, **300**). Various explanations have been put forth to reconcile these results. Of course, the classic rationale for the *gem-dialkyl acceleration* is the *Thorpe-Ingold effect*, which is based on angle compression derived from steric repulsion. Recently, Jung and Gervay have studied this angle compression aspect in detail *via* spiro substrates (*e.g.*, **300**, R, R'=$(CH_2)_2$) and have reached the conclusion that such perturbations are outweighed by the reactive rotamer effect, that is, an enrichment of "*productive*" rotamers in the ground state as a result of the substitution pattern.[151] Work by Sternbach and co-workers[152] supports this hypothesis, as these workers also observed that a propyl group exhibited a larger effect on rotamer population than did a methyl group (*i.e.* **302** *vs* **303**).

Dolata and co-workers, on the other hand, developed an axiomatic model of the *IMDAF* reaction.[153] Reactive rotamers were determined using MM2 calculations, followed by ground state and transition state conformational analysis with the WIZARD and MOPAC software packages. The calculations suggest that the



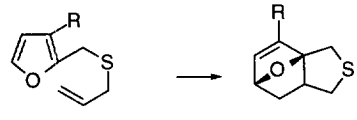
300 **301**



302 303

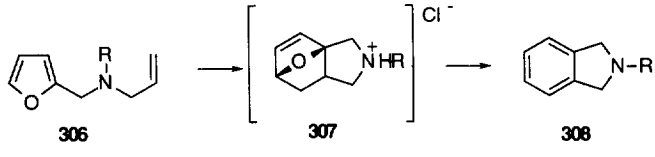
gem-dialkyl effect is not due to a change in the rotamer population, but to an overall reduction in the $\Delta G^{\ddagger}$ of the reaction.[154]

Substitution on the furan ring itself can also dramatically influence the course of the reaction. For example, introduction of a 3-methyl substituent on the furan ring increased the yield of cycloadduct **305** from 23% (for the unsubstituted analog) to 77%. A steric argument was invoked, as the 3-bromo derivative behaved in a manner similar to the methyl analog.[155]



304 305

Other more subtle aspects of the tether group were found to be important. For example, the furfurylamine derivative **306** did not undergo *IMDAF* reaction until protonated, possibly due to alterations in



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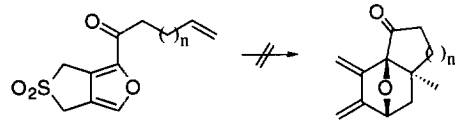

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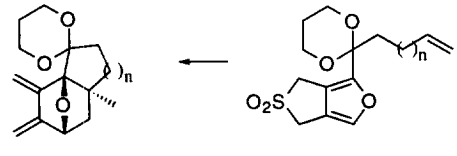
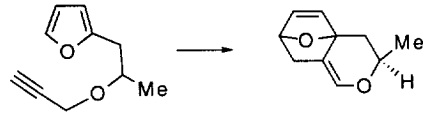


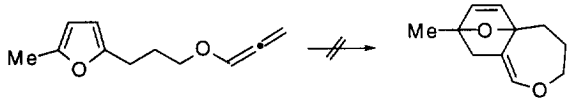
311b 310

the tether geometry.[156] Likewise, ketofuran **309** was reticent to react until the carbonyl group was protected. Here, two factors facilitated the reaction[157]: (1) a change from sp^2 to sp^3 hybridization, and (2) the *gem-dialkoxy effect (vide supra)*[151] which is known to be larger than the *gem-dialkyl effect*.

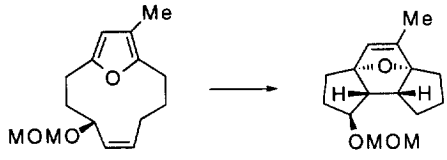
The chain length also has a significant impact on the facility of the reaction. For example, whereas propargyl ether **312** underwent ready cyclization in high yield, the homolog **314** provided no detectable cycloadduct under similar conditions.[158] This was also demonstrated with *IMDAF* substrates **316** and **318**. In these cases, the dienophile was tethered on both sides, thus locking the system into an ideal conformation for cycloaddition. Indeed, **316** was quantitatively converted to the tetracyclic product **317** at room temperature.[159] However, the ring system present in **319** was thermally labile, resulting in retro-cyclization at room temperature to furnish **318**.[160]



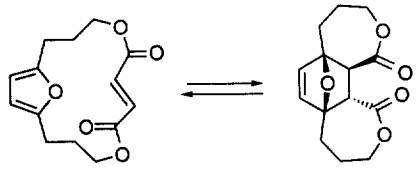
312 **313**



314 **315**

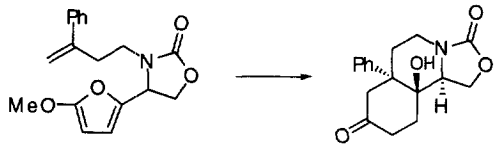


316 **317**



318 **319**

Many *IMDAF* reactions are fraught not so much with kinetic barriers, as with thermodynamic disadvantages (*i.e.*, cycloreversion). One way to drive such reactions is to follow the initial cycloaddition with a subsequent irreversible step. For example, the methoxy substituent on the furan ring of **320** allows for the isolation of the highly functionalized isoquinoline analog **321**, as the conformationally demanding cycloadduct can suffer cleavage of the hemiacetal functionality and thereby avoid cycloreversion.[161]



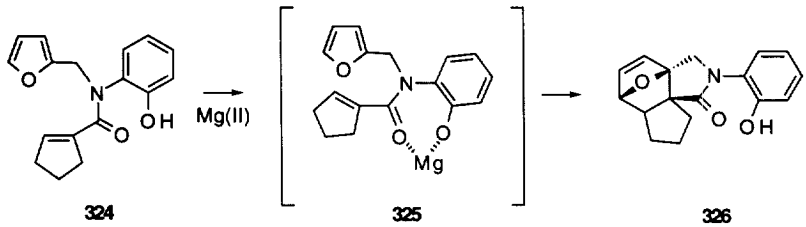
320 **321**

3.2.2. *Catalysts*

There are a variety of reagents and techniques which have been utilized to catalytically accelerate the *IMDAF*. The amount of "*catalyst*" required usually depends upon the substrate used. Certain Lewis acids are known to promote the *IMDAF* reaction, most notable of which is methylaluminum dichloride. For alkenyl furans, in which the dienophile is activated by a carbonyl group (*i.e.*, **322**), catalytic quantities of $MeAlCl_2$ are often quite effective in facilitating the cycloaddition.[162] This has also been extended to systems in which the furan ring is substituted with electron withdrawing groups.[163] Interestingly, with enone type dienophiles, the yields are generally higher using catalytic amounts of Lewis acid than with a molar excess. This was rationalized on the basis that decomplexation of the Lewis acid from the adduct becomes faster than cycloreversion, thus driving the reaction forward.[164] For acetylenic systems, or ester-activated alkenes, however, a stoichiometric amount of Lewis acid was required.[165-166]

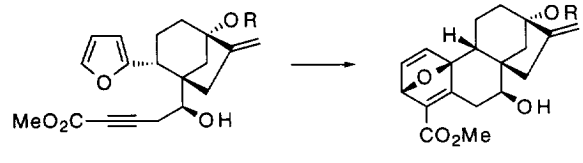
322 **323**

Some catalysts operate on a template principle, coordinating both the diene and dienophile moieties of the substrate and bringing the two together in close proximity. Certain molybdenum and tungsten complexes have shown such activity in the *IMDAF* reaction.[167] If the substrate is suitably functionalized, the optimized conformation can be facilitated by divalent metal ions. For example, the highly substituted amide **324** underwent only modest cycloaddition under normal thermal conditions. Addition of a magnesium salt resulted in a dramatic increase in efficiency, providing a 65% yield of adduct **326**.[168] Presumably, the metal serves to create the highly structured intermediate **325** with concomitant acceleration, somewhat reminiscent of the *t*-butyl effect.



324 **325** **326**

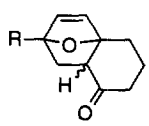
Other noteworthy reagents that have been used to increase reaction rates or improve equilibrium ratios are: lithium and calcium chloride,[169] florisil,[170] silica gel saturated with water,[171] and ß-cyclodextrins.[172] The last example is particularly interesting, as its application seems to be fairly general even though the mode of action is not entirely understood. One possibile explanation is derived from a kinetic argument, where the cavity of the cyclodextrin provides a complexation site for the two reactive sites of the substrate. It is also possible that the "*catalyst*" binds to the adduct thereby preventing cycloreversion. In any event, the applicability of this protocol is nicely illustrated in the synthesis of giberellins GA_1 and GA_3, where the key *IMDAF* reaction (**327** → **328**), which is quite demanding with respect to substrate structure and functionality, is facilitated by ß-cyclodextrin.[173]



327 **328**

3.2.3. *High-pressure Reactions*

Another useful technique for activating otherwise recalcitrant systems is through the use of high pressure. This is particularly applicable to systems containing a 4-carbon tether without substitution.[174] High pressure is a convenient alternative to heat, as it minimizes thermal decomposition and kinetic products are often obtained.[175] Harwood and coworkers have studied high-pressure furan cycloadditions using monoactivated and diactivated dienophiles, and have made the following observations: 6,6-fused ring systems (*i.e.*, **329**) are readily prepared using high pressure, the favored products having *exo*-stereochemistry at the ring junction. 7,6-Fused ring systems (*i.e.*, **330**) can also be prepared, although not as easily, with a mixture of *endo*- and *exo*-products being formed. In addition, "*internally*" activated precursors such as **331** are more reactive than "*externally*" activated analogs (*i.e.*, **332** and **333**). Within the latter grouping, the *E*-alkene geometry is more prone to undergo cycloaddition.[176] In the case of diactivated dienophiles (*i.e.*, **334**), the external activating group tends to adopt an *endo*-orientation.[177]



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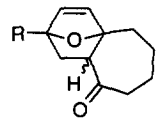

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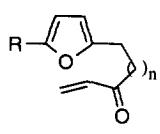

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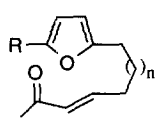

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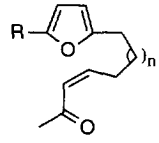

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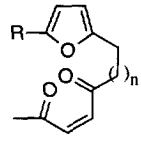
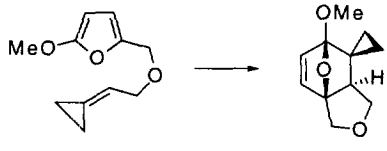


334

The relative mildness of these conditions was nicely illustrated in the high pressure mediated *IMDAF* reaction using an unactivated methylenecyclopropane terminator on the dienophile, in which the very labile cycloadduct **336** was obtained in > 95% yield.[178]

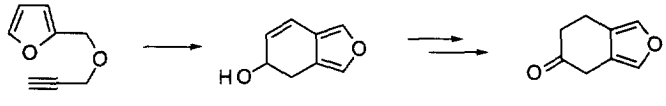


335 336

3.3. *Applications*

3.3.1. *Methodology*

The *IMDAF* has been used as the cornerstone in certain useful synthetic methods. For example, Kanematsu and co-workers have elaborated a furan ring transfer protocol (FRT) using substrates containing an ether linkage on the tether. The principle is best demonstrated for the synthesis of isobenzofuranone **339**.[179] The method has also been extended into a double furan transfer reaction, as demonstrated in the sequential cycloaddition of **340** to **343**,[180-181] or by an annulative technique, as shown in the fusion of a furan ring onto the furanocyclohexanone **344**.[182] This type of chemistry was applied to the synthesis of euryfuran,[183] and xestoquinone,[184] as well as the ring systems of several spongiaditerpenoids.[185]



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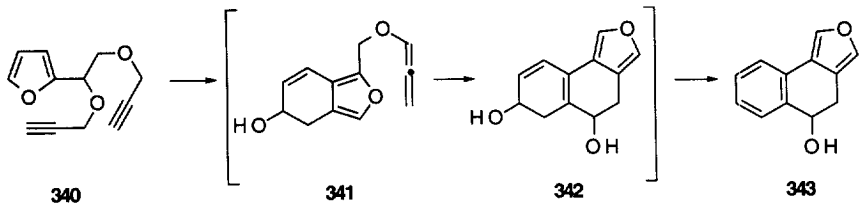

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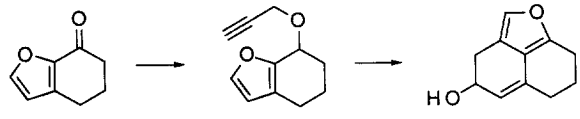
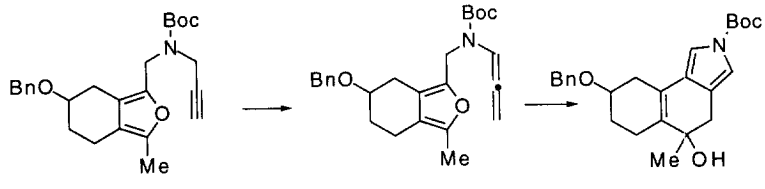


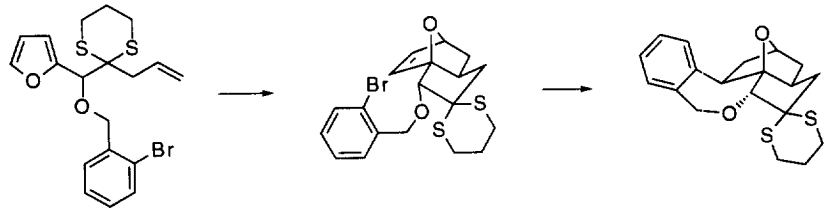
344 345 346

If a nitrogen atom is present on the tether instead of an oxygen, the same type of sequence becomes a furan-pyrrole exchange reaction. Thus, furfuryl propargylamine **347** underwent cyclization at 40°C in basic medium to give the hydroisoindole **349**.[185]



347 348 349

Another very useful synthetic method is the tandem *IMDAF*/radical cyclization sequence, through which three fused rings can be rapidly assembled with a high degree of stereoselectivity. For example, heating furan **350** in benzene at reflux resulted in the formation of cycloadduct **351** and its *O*-epimer in a 10:1 ratio. Subsequent treatment of **351** with *n*-butyl tin hydride gave **352** as a single isomer, in which the benzoxepin ring was formed with complete stereocontrol in the radical cyclization.[186] While the double bond derived from the Diels-Alder diene is usually involved in such protocols, other sites of unsaturation can also be used as the radical acceptor. One example involves the construction of the morphinan derivative **356** by an initial *IMDAF* reaction of furan **353**, followed by protection of the endocyclic double bond as the epoxide and then treatment



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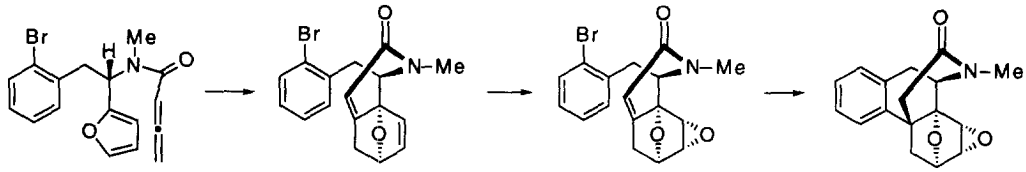
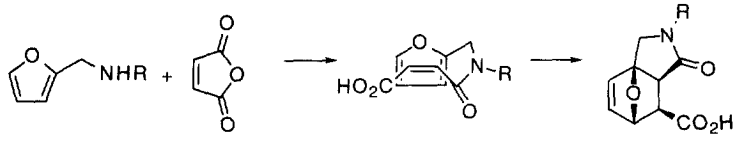


353 354 355 356

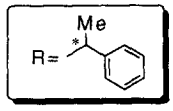
with tributyltin hydride to give **356**, along with the isomer derived from radical attack α to the carbonyl group.[187-188]

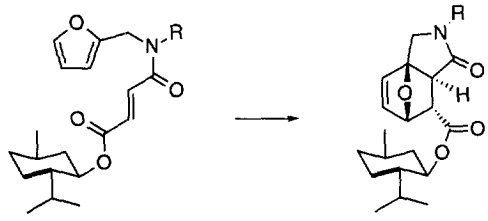
3.3.2. *Asymmetric Synthesis*

Of course, application to the synthesis of optically pure compounds is a desirable goal for most methodologies. In the case of the *IMDAF* reaction, this can be approached from various angles. In cases where an amine is present on the tether, a chiral auxiliary can be attached at this site. For example, when the *N*-substituted furfuryl amine **357** was treated with maleic anhydride, an *IMDAF* reaction ensued *via* **359**. The course of the cycloaddition was determined by the pendant α-methyl benzyl group.[189] A similar approach using (-)-phenylglycinol to confer chirality was applied to the asymmetric total synthesis of (+)-farnesiferol C.[190] Chiral auxiliaries can also be attached in an external fashion, as in the menthyl ester **360**.[191]



357 358 359

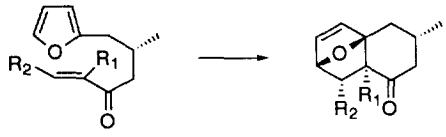




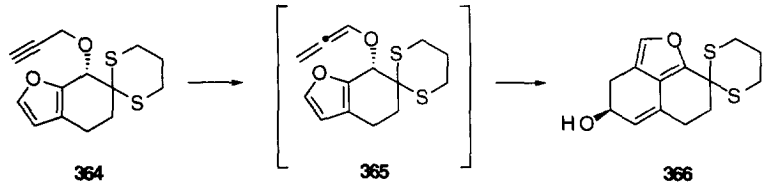
360 361

The directing chiral center can also be an integral part of the substrate, as in the furyl enone **362**. In this case, thermodynamic control is quite effective in providing cycloadduct **363** as the sole product, where the

methyl group has assumed an equatorial position.[192] Kanematsu and co-workers have demonstrated that chirality can also be transferred in their furan ring transfer reaction (*vide supra*). For example, optically pure **364** undergoes smooth *FRT* under basic conditions to give **366** in 98% yield.[193]



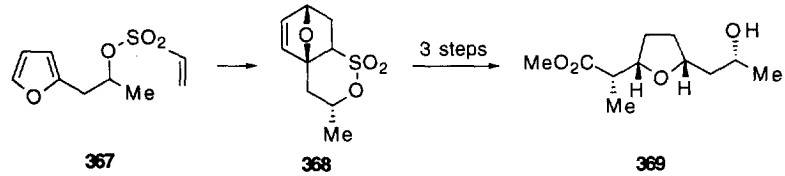
362 **363**



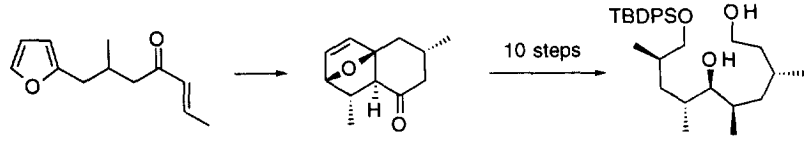
364 **365** **366**

3.3.3. *Synthetic Targets*

The *IMDAF* reaction has also found utility in the total synthesis of a broad spectrum of natural products, particularly the more highly oxygenated ones. For example, a succinct route to methyl nonactate, a precursor used for the synthesis of actins, involved the [4+2]-cycloaddition of furyl sulfonic acid derivative **367** as the key step.[194] Similarly, the (±)-C_{15}-C_{23} segment of the venturicidins (**372**) was prepared stereoselectively in 17 steps from 2-furaldehyde in an overall yield of 7%, in which the foundation for all the relative stereochemistry was set down by the *IMDAF* reaction of furan **370**.[195]



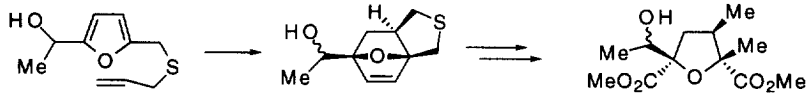
367 **368** **369**



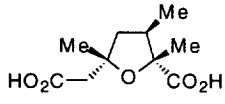
370 **371** **372**

The ability to set the configuration of many centers at once makes this protocol particularly attractive

for very compact, highly substituted targets. Klein and Shanklin have used this method for the preparation of jaconecate ester **375** in their total synthesis of (±)-dimethyl jaconate.[196] A similar approach was utilized in the synthesis of (±)-nemorensic acid (**376**), the diacid portion of retroisosenine.[197]

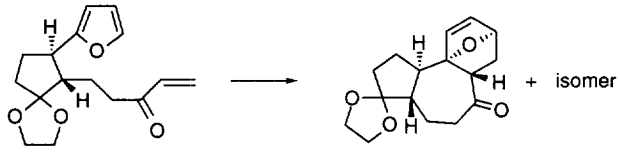


373 **374** **375**

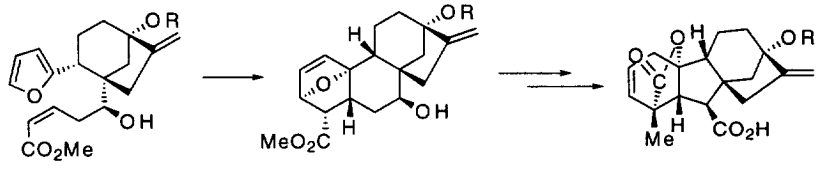


376

The *IMDAF* reaction creates many rings in a single step and therefore, it also has found application in the preparation of polycyclic targets. For example, the phorbol analog **378** was constructed *via* the *IMDAF* process at low temperature and ambient pressure, with control of the relative stereochemistry between the *trans*-fused A-B ring junction and the existing stereocenters.[198] DeClercq and coworkers have reported on a novel route to (+)-gibberellin A_5 (**381**) which involves the *IMDAF* reaction of the complex furan **379** as the key step.[199] An *IMDAF*-based route to construct the A-D ring system of batrachotoxin was also reported by Kishi and Grinsteiner.[200]



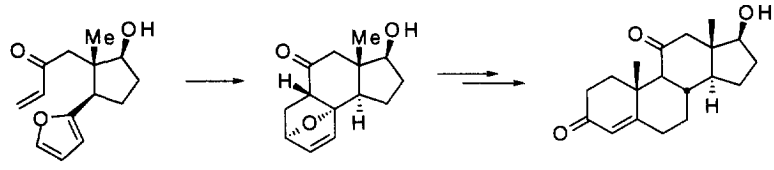
377 **378**



379 **380** **381**

DeClercq and coworkers have found that under controlled conditions, appropriately substituted alkenyl furans can undergo the *IMDAF* reaction to give products with the necessary functionality and relative stereochemistry for eventual transformation into corticosteroids.[201-202] This has been applied to a novel *D* →

BCD → *ABCD* route to 11-ketosteroids, hinging upon the stereoselective *IMDAF* reaction of furyl enone **382** to cycloadduct **383**, which is stable in aqueous medium but undergoes cycloreversion in organic media. This intermediate is then converted into 11-ketotestosterone (**384**) over several steps.[203]



382 **383** **384**

The many structurally diverse and highly successful examples cited above clearly indicate that the Diels-Alder reaction of furans continues to be of value for the synthesis of carbocycles as well as heterocycles. It is a reasonable expectation that future years will see a continued evolution of the [4+2]-cycloaddition chemistry of furans in organic synthesis.

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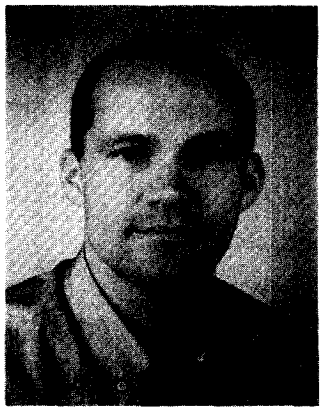
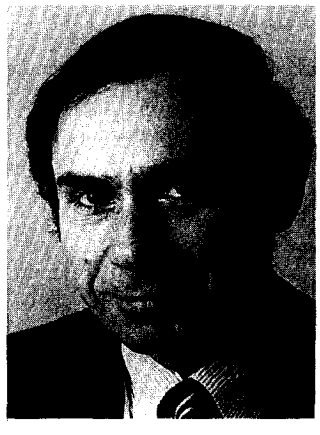
Biographical Sketch



C. Oliver Kappe

S. Shaun Murphree



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C. Oliver Kappe was born in Graz, Austria in 1965. He received his diploma degree (1989) and doctoral degree (1992) from the Karl-Franzens-University in Graz where he worked with Gert Kollenz on cycloaddition and rearrangement reactions of acylketenes. After periods of postdoctoral research work with Curt Wentrup at the University of Queensland in Brisbane, Australia (1993-1994), and with Albert Padwa at Emory University in Atlanta (1994-1996), he moved back to the University of Graz in 1996 to start his independent academic career. He received the Dissertation Award of the Austrian Chemical Society in 1993, the Erwin-Schrödinger Fellowship of the Austrian Science Foundation in 1994 and the APART Fellowship of the Austrian Academy of Sciences in 1996. His current research interests include dihydropyrimidine chemistry, design and synthesis of calcium channel modulators, and the enantioselective synthesis of guanidinium alkaloids.

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Albert Padwa was born in New York City. He received both his B. A. and Ph. D. degrees (Cheves Walling) from Columbia University. After a NSF postdoctoral position with Howard Zimmerman at The University of Wisconsin, he was appointed Assistant Professor of Chemistry at The Ohio State University in 1963. He moved to SUNY Buffalo in 1966 as Associate Professor and was promoted to Professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. He has held visiting positions at University Claude Bernard, France (1978), University of California at Berkeley (1982), The University of Wurzburg, Germany (1985), and Imperial College of Science and Technology, U. K. (1991). Professor Padwa has been the recipient of an Alfred P. Sloan Fellowship (1968-1970), John S. Guggenheim Fellowship (1981-1982), Alexander von Humboldt Senior Scientist Award (1983-1985), and a Fullbright Hays Scholarship (1991) and is the co-author of more than 500 publications. His research interests include heterocyclic chemistry, dipolar cycloadditions, alkaloid synthesis, tandem transformations, organometallic chemistry, and organic photochemistry.

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