Five-Membered Heteroaromatic Rings as Intermediates in Organic Synthesis†

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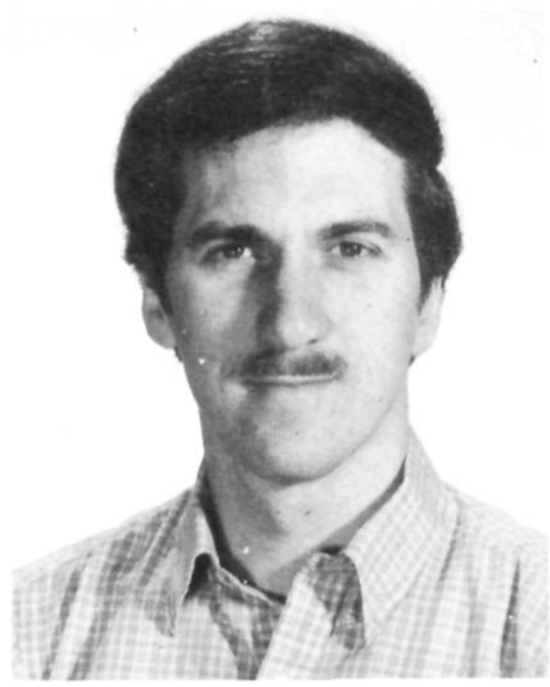

Bruce H. Lipshutz hails originally from the Washington Heights section of New York City. Following receipt of a B.A. degree in chemistry at S.U.N.Y. Binghamton in 1973 with Howard Alper, he did graduate work at Yale under the direction of Harry Wasserman. Upon completion of his Ph.D. in 1977, he went north on I-95 to Harvard University for a two-year stint as an American Cancer Society Postdoctoral Fellow in the laboratories of E. J. Corey. In 1979, he moved cross-country to join the faculty at the University of California, Santa Barbara. Thanks to the efforts of his co-workers, he has been named an American Cancer Society Junior Faculty Research Awardee (1981–1983), an A.P. Sloan Fellow (1984–1988), a Dreyfus Teacher–Scholar (1984–1989), and a UCSB Plous Memorial Teaching Awardee (1984). He has also had the quite unexpected good fortune to be cited in *Esquire* magazine's first "National Register" (1984). His research interests center around the development of new reagents and methods in synthetic chemistry, including such areas as organocopper, silicon, and palladium chemistry and the use of heterocycles as masked functional group equivalents, along with applications of these processes to natural products synthesis.

I. Introductory Comments

There is an interesting psychology associated with heterocyclic chemistry which persists to this day. It is commonly accepted that a majority of the published work in organic chemistry involves at least one heterocyclic ring. Moreover, in providing us with a wealth of fascinating molecular arrays over half of which possess heterocyclic constitution, nature presents a most cogent argument for developing an appreciation for this area. And yet, while numerous synthetic practitioners devote their entire careers to the laboratory-based construction of heterocycle-containing natural products, rarely does one consider himself, let alone admit to being, a heterocyclic chemist. This state of mind endures, made more inveterate by the constant short shrift which undergraduate textbooks notoriously afford this topic. Even invited lecturers, e.g., at Gordon Conferences on this area, are oftentimes quick to amusingly comment when a particular target or intermediate constitutes a "real" heterocycle.

How the synthetic community perceives heterocyclic chemistry is probably not a critical issue. More important is the recognition that heterocycles can play a pivotal role not only as goals in synthesis, but as mediators of synthetic transformations. It is now over a decade since the appearance of the benchmark monograph by Meyers,[1] which formally legitimized the use of heterocycles as a viable and occasionally superior means of arriving at functionalized materials. Just as synthetic chemistry has blossomed since that time, so has the use of heterocycles in synthesis. Such growth in popularity necessitates that this review concentrate on the synthetic utility of one specific subdivision, namely, *selected* heteroaromatic systems consisting of five-membered rings. Highlighted are papers of quite recent extraction, most between 1982 and 1985, which were not covered in a related chapter,[2] yet which likewise relate mainly to efforts in natural products synthesis. It is intended that this contribution supply further testimony to the potential of heteroaromatics, and heterocycles in general, to serve as latent functional group equivalents, thereby stimulating further developments in this field.

Surely there are a number of papers which have been inadvertently overlooked in the course of writing this review. Unfortunately, as was noted over a decade ago,[1] the chemical literature is still not conducive to identifying heterocycles as a source of masked functionality.

† Dedicated to Professor Harry H. Wasserman on the occasion of his 65th birthday.

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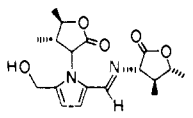
II. Five-Membered Heteroaromatics

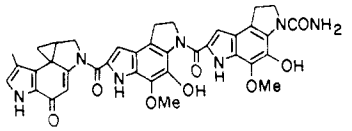
A. Heterocycles Containing One Heteroatom

1. Pyrroles

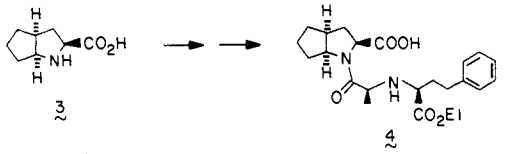
Although the pyrrole nucleus continues to find expression in many naturally occurring compounds, two interesting examples of which include the pyrrole alkaloid funebrine (1),[3] and the potent antitumor agent



Funebrine, 1

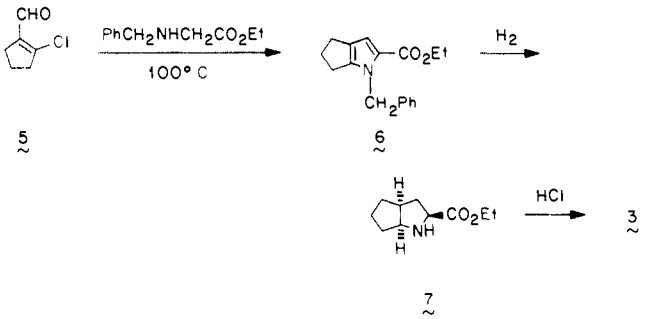


CC-1065, 2



3 4

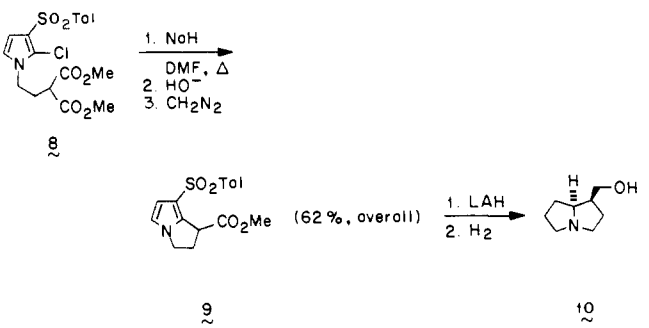
CC-1065 (2),[4] relatively few applications to non-pyrrole-containing systems have been reported in the recent past. The pyrrole ring as a latent pyrrolidine has been used to advantage in a synthesis of 2-azabicyclo-[3.3.0]octane-3-carboxylic acid (3), a key procursor to Hoe 498 (4), a highly active angiotensin converting enzyme inhibitor.[5] Following conversion of aldehyde 5 to pyrrole 6, hydrogenation with 10% Pd/C in EtOH



5 6 7 3

containing 3% concentrated H_2SO_4 under 50 bars of hydrogen at 30 °C for 24 h reduced both the pyrrole ring and the benzyl group to afford 7 (58%). Subsequent hydrolysis with hot 5 N HCl afforded the desired acid 3.

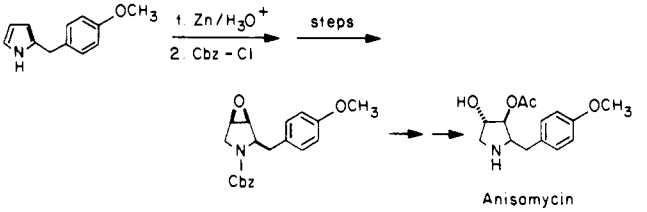
(±)-Isoretronecanol (10) was constructed from pyrrole via an annulation sequence which effects a Michael addition–elimination via the chloro malonate 8 to give 9.[6] Reduction of the tosyl moiety sets the stage for hydrogenation over rhodium on alumina at one atmosphere to afford 10. The presence of the tosyl group



8 9 10

is essential for carrying out what is otherwise a very difficult and rare example of a nucleophilic displacement on a pyrrole (not assisted by copper).

Reduction of a 2-benzylpyrrole with Zn in HCl (67%) has been used to ultimately arrive at (±)-anisomycin.[7]

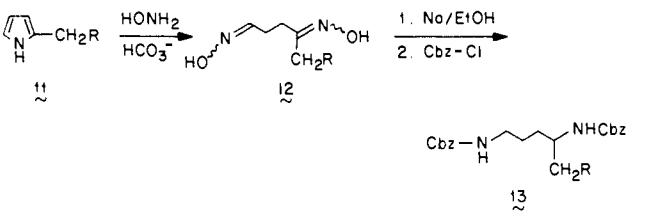


Anisomycin

The 3-pyrroline so generated is ideally situated for halohydrin formation and subsequent epoxidation. The required functionality bearing the appropriate stereochemical relationships in the natural antibiotic follows from a sequence which involved ring opening (TFA/CF_3CO_2Na, Δ), nitrogen protection (Cbz–Cl), selective C-3 hydroxyl protection (TCE–Cl), acetylation, and deprotection (Zn/HOAc, then H_2, Pd/C). The overall yield from the syn epoxide was an impressive 75%.

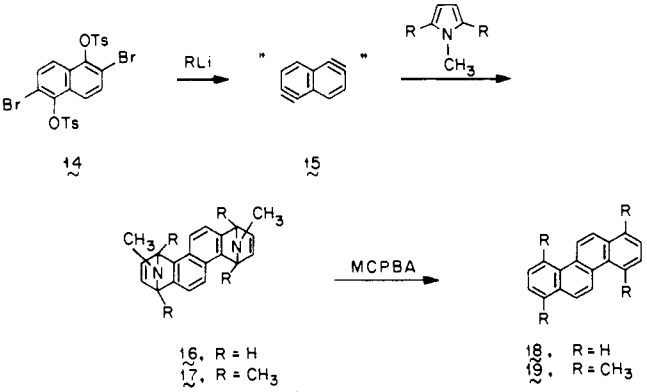
Pyrrole itself, as in the case of 10, has also served as the starting material for the preparation of substituted putrescines. These 1,4-diaminobutanes, along with derivatives spermine and spermidine, are presently well-recognized to be intimately involved in protein synthesis and cell proliferation.[8]

In recognition of some earlier chemistry involving the conversion of pyrrole to bis(oximes) with hydroxylamine,[9a] Argentinian workers prepared 2-alkylated derivatives 11 which likewise underwent ring opening to 12, formed as a mixture of syn and anti isomers (45–50%).[9b] Reduction with Na/EtOH led to the diamines which were isolated (50–60%) and stored as their bis(Cbz) derivaties, 13.



11 12 13

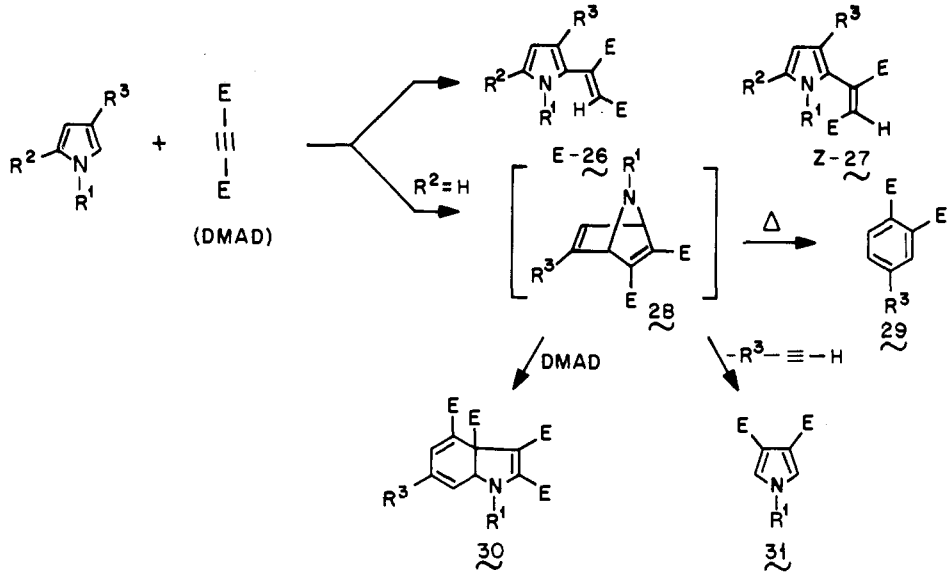
Several reports have appeared which utilize the pyrrole ring for its butadiene component in Diels–Alder constructions. En route to various carcinogenic polycyclic aromatic hydrocarbons, Gribble employed both *N*-methyl- and 1,2,5-trimethylpyrrole in twin Diels–Alder cycloadditions, formally, with 1,5-dinaphthodiyne.[10] The bis(aryne) is arrived at via organolithium-induced double elimination of bromo tosylate 14 in the presence of the pyrrole. Adducts 16



14 15 16, R = H 17, R = CH_3 18, R = H 19, R = CH_3

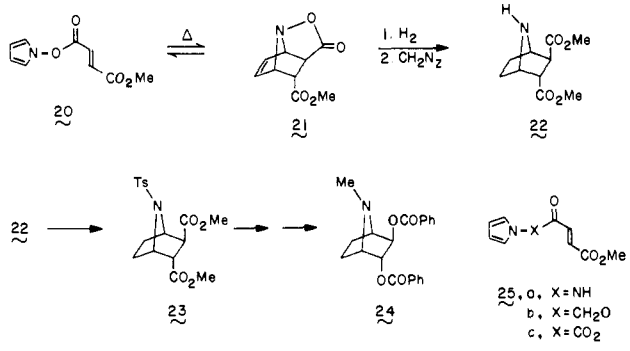
(40%) and 17 (56%) could be oxidatively deaminated

SCHEME I



using MCPBA in $CHCl_3$ to form chrysene **18** (R = H, 33% overall from **14**) and the novel chrysene analogue **19** (R = CH_3, 49% overall).

The first example of an intramolecular Diels–Alder reaction involving a pyrrole has recently been published.[11] Acylated 1-hydroxypyrrole **20** upon heating in toluene (0.05 M, 20 min) afforded a 2.5 to 1 equilibrium mixture of **20** to **21**. Decreasing the reaction temperature to 39 °C over time (21 days) shifted the equilibrium toward **21**, thereby permitting a 68% yield of adduct to be realized (86% based on recovered **20**).

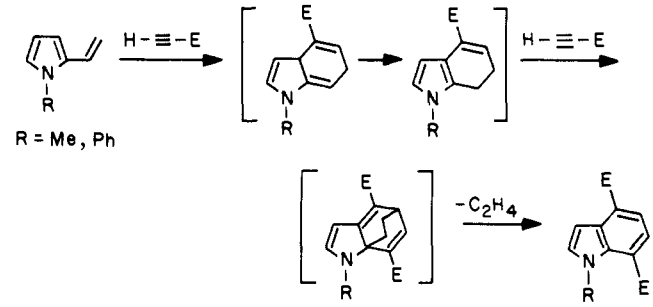


Hydrogenation with 5% Pd/C with subsequent esterification (CH_2N_2) gave the 2-*endo*-3-*exo*-dicarboxylate **22** (70%). Further manipulation of **22** led to sulfonamide **23**, a precursor to pseudo-4-norcocaine **24**. All efforts to extend this chemistry to other N-substituted acylated pyrroles, e.g., **25** a,b,c, were unsuccessful even under forcing conditions (T = 35–210 °C) or attempted Lewis acid catalysis (with Et_2AlCl or $BF_3{\cdot}Et_2O$).

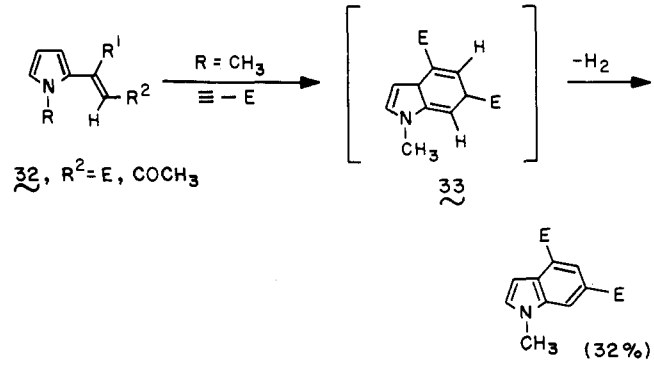
The Noland group has continued their studies on reactions of dimethyl acetylenedicarboxylate (DMAD) with pyrroles[12] and 2-vinylpyrroles.[13] The former substrates tend to undergo Diels–Alder additions with DMAD giving different product mixes depending upon conditions. With the 2-position free and (usually) in the presence of added HOAc in refluxing Et_2O, 1:1 Michael adducts **26** and **27** predominate (*E* and *Z* isomers). The initially formed cycloadducts **28** are unstable and were found, depending upon conditions, to either (a) revert to **26** and **27**, (b) undergo retro-Diels–Alder with loss of a terminal acetylene to **31**, (c) eliminate the bridging nitrogen to afford phthalates **29**, or (d) react with a second equivalent of DMAD giving products **30** (Scheme I).

Interestingly, when similar reactions are conducted under high pressure (15 kbar) as described by Kotsuki et al., the reaction course may be altered significantly.[14] For example, upon treatment of pyrrole itself with DMAD, none of the 1:2 adduct **30** (R^1, R^3 = H) is observed.

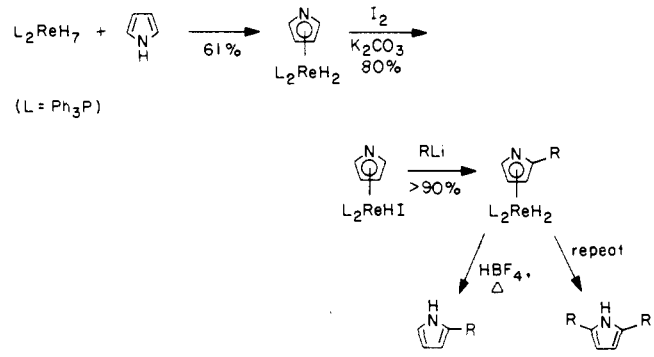
2-Vinylpyrroles provide a somewhat atypical starting point for the preparation of indoles.[13,15] These educts



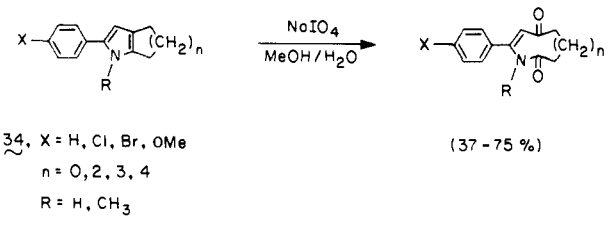
react in a [4π + 2π] sense with various dienophiles to yield dihydro- or tetrahydroindoles, rather than undergoing cycloaddition across the 2,5-positions of the ring. Steric and electronic effects associated with both partners exert considerable influence on the relative rates of reactions, as well as the tendency of the adducts to undergo oxidation to indole derivatives. Unlike their furan and thiophene analogues, vinylpyrroles containing an electron-withdrawwing group (**32**) still possess sufficient reactivity to give, albeit in modest yields (2–35%), the corresponding indoles, presumably via **33**.



The starting unsaturated pyrroles can be obtained via Wittig processes on pyrrole aldehydes, or by way of the excellent route recently described by Felkin using rhenium complexes.[16]

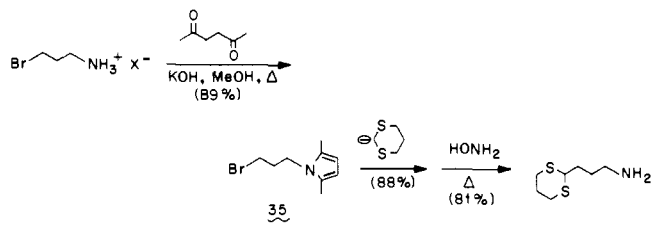


Medium-ring keto lactams are formed in good yields from bicyclic pyrroles **34**.[17] Regiospecific oxidation of



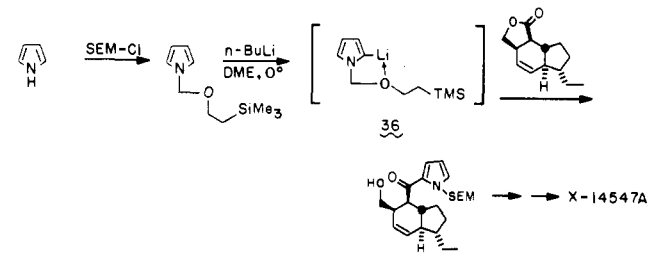
the central double bond occurs under the influence of $NaIO_4$ at −5 °C to afford 8–11-membered ring systems. The method is limited, however, as 2-carbethoxy-4,5,6,7-tetrahydroindole is unreactive, and the 2-protio analogue (R = H, n = 2) leads to a complex mixture of products.

Protecting-group chemistry has also benefited from a potentially valuable procedure wherein primary amines are converted, upon exposure to hexane-2,5-dione, to 2,5-dimethylpyrroles, e.g., **35**. Such deriva-



tives withstand the actions of strong bases (RLi, RMgX, 5 M KOH) and brief treatment with mineral acids (2 M HCl, room temperature, 1 h). Unmasking of the free amine follows from $HONH_2$-induced openiing (vide supra). The method applies best to aryl, pyridyl, and alkyl systems with yields for each step ≥ 80%.[18]

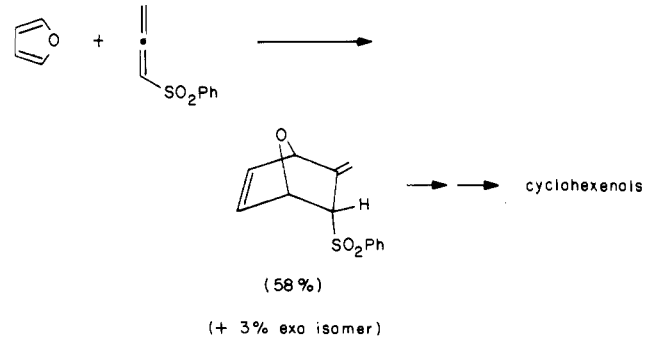
Protection of a pyrrole nitrogen as its [β-(trimethylsilyl)ethoxy]methyl (i.e., SEM) derivative, among others,[19a-f] has been accomplished utilizing its sodium salt in DMF along with commercially available SEM–Cl,[19g] reported originally from our laboratories in 1980.[19h] The location of oxygen may assist in a metalation/alkylation or acylation scheme, e.g., in the formation of **36** en route to the ionophoric antibiotic X14547A.[20] Deprotection can be accomplished using $BF_3{\cdot}Et_2O$ and then Triton B, or n-Bu_4NF/DMF at 45 °C.



2. Furans

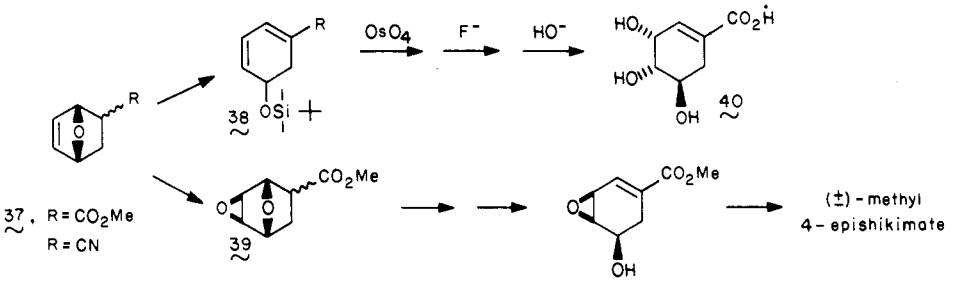
A. Intermolecular Diels–Alder Reactions. By far the most heavily exploited of the monocyclic heteroaromatic systems is the furan ring. The proclivity of substituted furans to undergo Diels–Alder cycloadditions presents an invitation for rapid construction of valuable intermediates which many research groups have accepted. Notwithstanding Dewar's conclusions regarding the general mechanism of Diels–Alder reactions, arrived at in fact from furan–maleic anhydride cycloreversion kinetic data,[21] the synthetic value of this intermolecular process is widely recognized as a means of carbon–carbon bond construction ultimately leading to a variety of target molecules or sections thereof. For example, in order to arrive at some 3,4,5-trihydroxycyclohexenes, which include shikimic acid **40** and related metabolites,[22] the furan cycloadduct **37** could be either parlayed into diene **38** or epoxidized to **39** (Scheme II). Osmylation of silyl ether **38** followed by desilylation and hydrolysis leads to (±)-shikimic acid, while manipulation of **39** affords the 4-epi derivative (methyl ester).

Related work in this area by Campbell and Sainsbury has also been reported,[23] wherein the initial [4 + 2] cycloaddition of furan with an acrylate is greatly enhanced by the use of catalytic quantities of ZnI_2, as originally described by Brion.[24] Cyclohexenol derivatives have likewise been prepared using (phenylsulfonyl)propadiene as the dienophile in hot toluene without Lewis acid catalysis.[25]

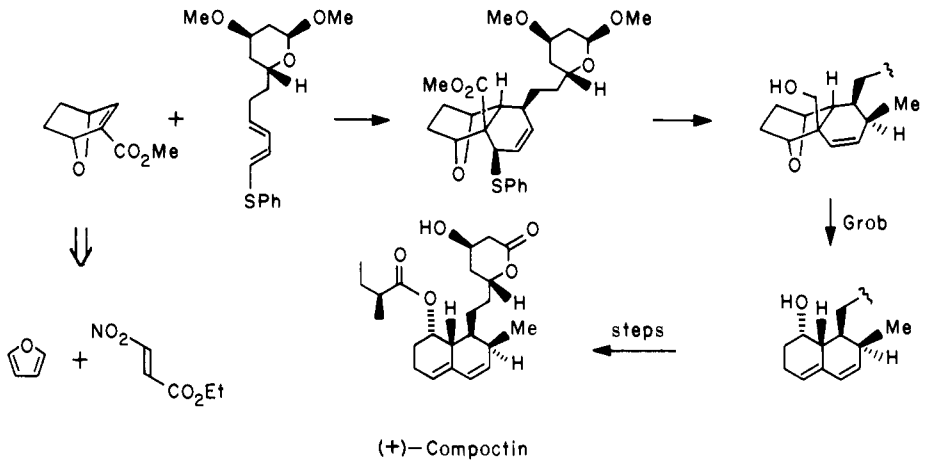


Several other groups have described the beneficial effects of various Lewis acids on Diels–Alder reactions of furans. Kotzuki found that $BF_3{\cdot}OEt_2$ encourages the addition of acryloyl chloride and methyl acrylate to furan in good yields (ca. 76%).[26] Interestingly, the former gives a 7:3 mixture of exo:endo adducts, while the enoate gives the completely inverted ratio of 3:7 exo:endo products. Both Cu(I) and Cu(II) have been found to catalyze the addition of α-acetoxy- and α-chloroacrylonitrile to furan, reactions which proceed at atmospheric pressure between 20–35 °C.[27] At slightly higher temperatures, solvated triorganotin cations, e.g.,

SCHEME II

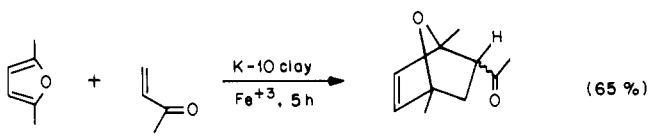


SCHEME III



(+)-Compoctin

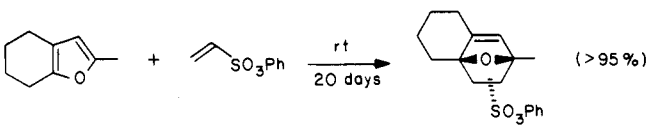
$(C_6H_{11})_3Sn(CH_3CN)_2^+$ SbF_6^-, are also effective catalysts.[28] When K-10 bentonite clay is doped with ferric



exo : endo = 0.6 : 1

salts or $AlCl_3$, furan and 2,5-dimethylfuran have been shown to cycloadd to acrolein and MVK at −43 °C in good yields.[29]

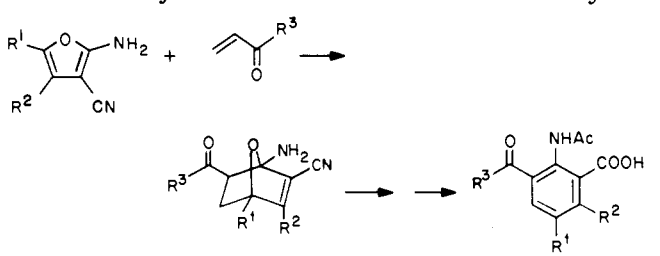
Without Lewis acid catalysis, the potentially critical role of temperature in controlling the extent of furan cycloaddition has been noted by Schuda.[30] Use of a highly reactive dienophile, such as phenyl vinylsulfonate, allows high yields of adducts to be formed under quite mild conditions (see below).[31] Similar



endo only

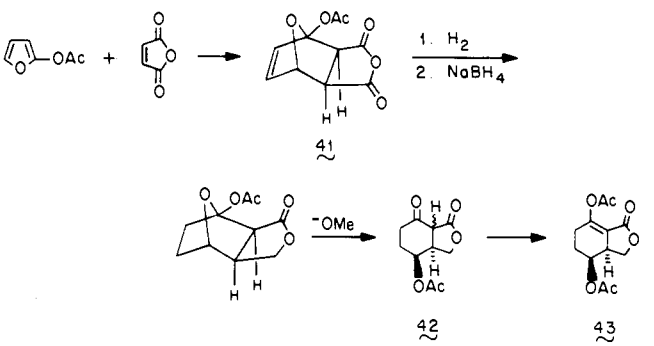
reaction parameters have been noted using 1,1,1-trichloro-3-nitro-2-propene.[32]

As a route to anthranilate derivatives, 4,5-disubstituted 2-amino-3-cyanofurans can be used as Diels–Alder dienes in conjunction with activated olefins.[33] Cycloaddition occurs readily in refluxing acetone over a 24-h period. Given the established chemical, biological, and medicinal properties of anthranilic acids, as well as their value as precursors to heterocycles, this combination offers a quick entry into this aromatic series.

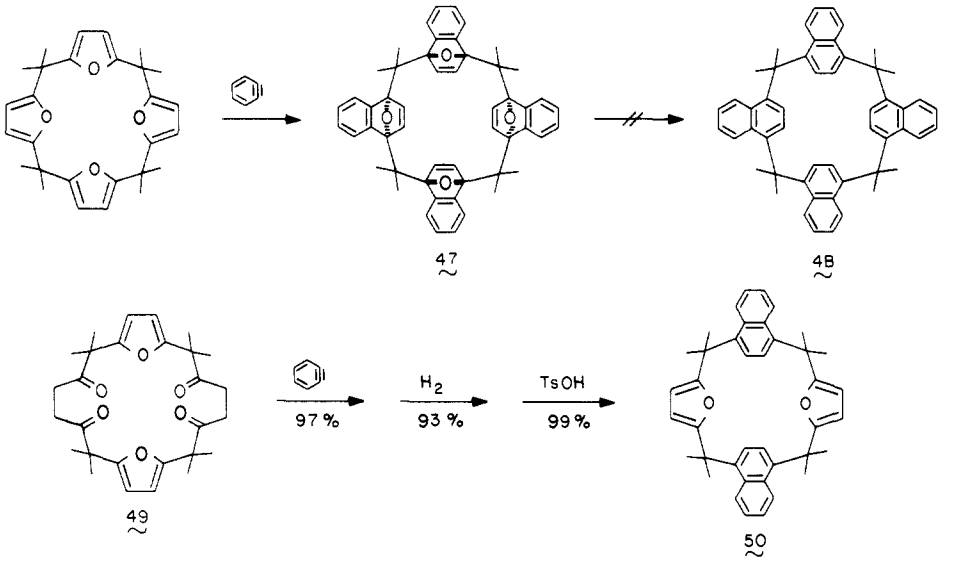


An intermolecular cyclization between two chiral components has expeditiously led to the entire carbon framework of the fungal metabolite compactin (Scheme III)[34]. The resolved dienophile, itself prepared from manipulation of the cycloadduct formed from furan and ethyl β-nitroacrylate, readily reacts with the (*E*)-vinyl sulfide partner (1 equiv, $PhCH_3$, 125 °C, 14 h) to afford the cycloadduct in 70% yield. Further handling set the stage for Grob fragmentation (KH, $PhCH_3$, Δ), which upon acylation (~quantitative), hydrolysis, and oxidation to the lactone (71%) and demethylation (31%) afforded synthetic compactin.

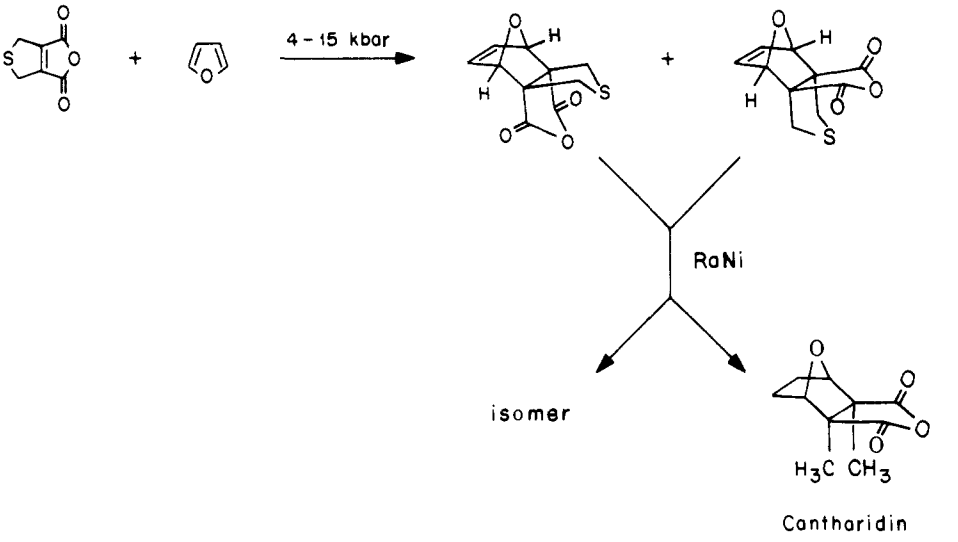
Cyclohexanone derivatives, potentially useful synthetic intermediates, can be arrived at by way of Diels–Alder additions using 2-acetoxyfuran.[35] Initial treatment with maleic anhydride leads to **41**, which upon hydrogenation, selective reduction with $NaBH_4$, and methoxide cleavage affords **42**. Acetylation to **43** conclusively demonstrated the regiospecific nature of the hydride reduction.



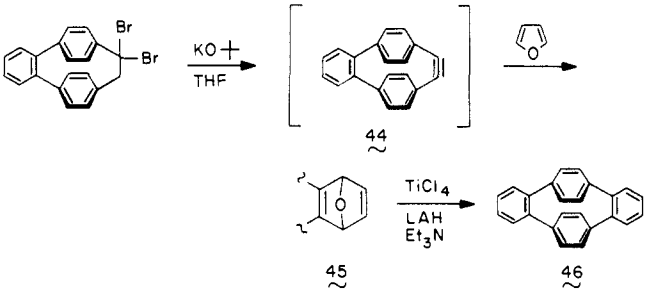
SCHEME IV



SCHEME V



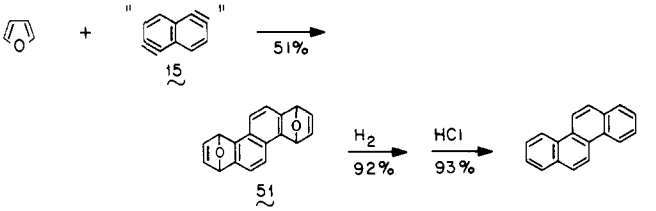
Furan has been employed in a Diels–Alder sense as a means of constructing the previously unknown, theoretically interesting dibenzo[2.2]paracyclophane **46**.

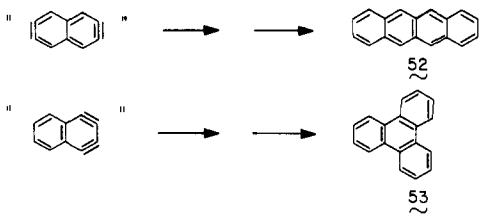


Base-induced formation of acetylene **44** followed by [4 + 2] cycloaddition leads to **45**, which is deoxygenated by a low-valent titanium species generated in situ.[36a]

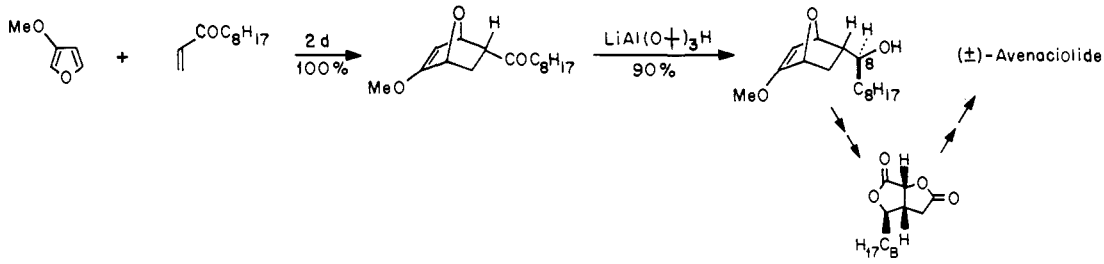
Benzyne(s) react with furans to afford, for example, the novel macrocycles **47** and **50**. All attempts to deoxygenate **47** to produce the [1.1.1.1] paranaphthalenophane **48** were unsuccessful, although **49** could be converted stepwise to **50** (Scheme IV).[36b]

As in the case of pyrroles (vide supra), furan adds to the equivalent of 1,5-naphthodiyne (i.e., **14** + PhLi) at 10 °C to yield the bis(adduct) **51** (51%). Hydrogenation and thence dehydration with HCl in EtOH led to the desired hydrocarbon, chrysene. This approach to polycyclic aromatics may also be extended to linear systems (e.g., substituted naphthacenes **52**), as well as to angularly fused rings (e.g., triphenylenes, **53**).[10]

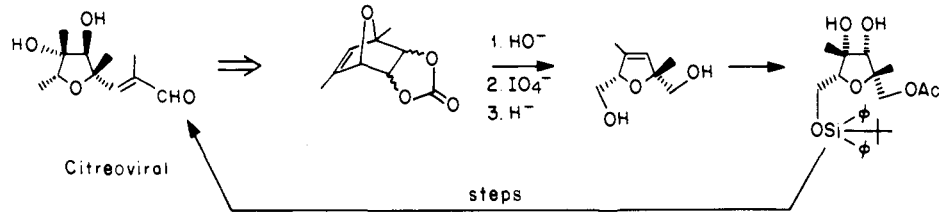




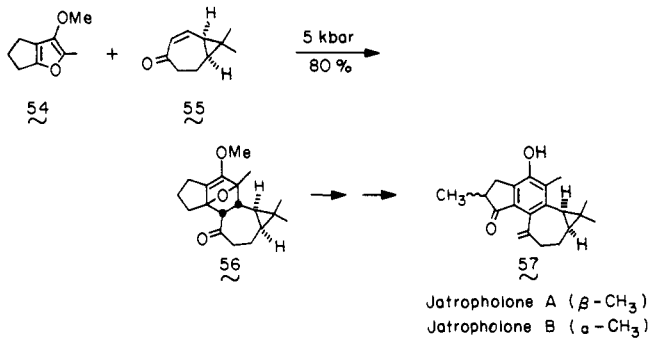
SCHEME VI



SCHEME VII

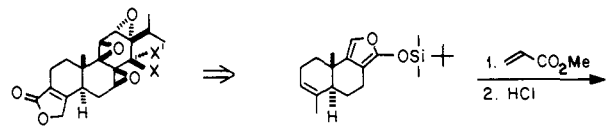


As an alternative to Lewis acid accelerated cycloadditions between furan(s) and less activated dienophiles, high-pressure conditions (1–20 kbar) have not only enabled many reactant combinations to proceed at reasonable rates and lower temperatures but have allowed otherwise inert substrates to participate in cycloaddition schemes (Scheme V). In addition to the Dauben contribution describing the synthesis of the potent vesicant cantharidin from 2,5-dihydrothiophene-3,4-dicarboxylic anhydride and furan,[37a-c] which has been recently performed on a preparative scale,[37d] total syntheses of (+)-jatropholone A and B have been realized which relied heavily on high-pressure Diels–Alder additions of methoxyfuran **54** to chiral enone **55**.[37e] The initial adduct **56**, isolated in 80% yield, was then parlayed into **57**.



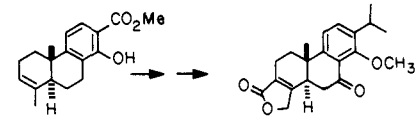
Another example, wherein a 3-methoxyfuran participates in a [4 + 2] sense with, e.g., an unsaturated ketone, illustrated below, concerns a route to the avenaciolides (Scheme VI.)[37f] The initial endo adduct reduces stereoselectively to the 2*RS*,8*RS* alcohol based on steric considerations. Ozonolysis (with an oxidative workup), saponification, $Pb(OAc)_4$ oxidation, hydrolysis and finally Jones oxidation afforded the intermediate bis(lactone), a well-known precursor to these natural products.

A formal total synthesis of the promising antitumor agent triptolide employed an intermolecular Diels–Alder reaction of a (silyloxy)furan with methyl acrylate (5 equiv, PhH, 65–70 °C, 2 days) which ultimately provided the required salicyclic ester. Several additional transformations gave the 7-oxo butenolide, a known precursor to triptonide, and thence triptolide.[38]

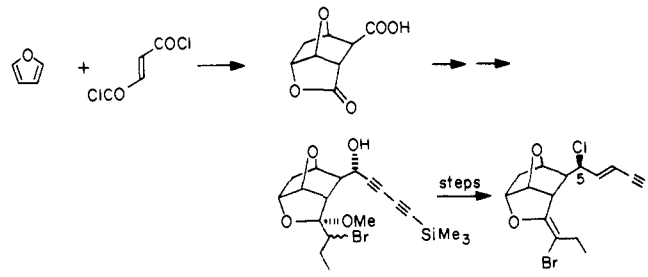


X=OH, X'=H (Triptolide)

X = X' = O (Triptonide)



Furan has been converted, *via* its cycloadduct with fumaroyl chloride, to a tricyclic lactone, which following a five-step protocol afforded a mixture of four bromo bis(acetylenes), two of which are shown. Acetylenic

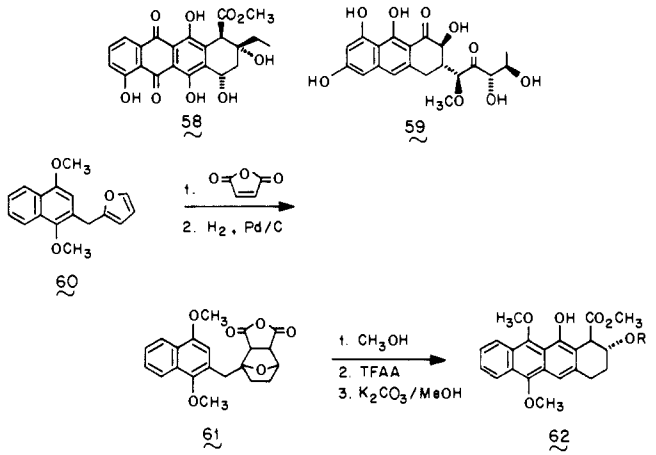


reduction of this mixture, together with pyrolytic loss of MeOH, chlorination, and desilylation gave the product, which by comparison of ^{13}C NMR data with literature values served to establish the relative stereochemistry at C-5 for the halogenated cyclic ether, (±)-*trans*-maneonene-B.[39a]

A new metabolite of *Penicillium citreoviride B*, citreoviral, which is related to cotreoviridin, the potent inhibitor of enzyme-catalyzed ATP synthesis and ATP hydrolysis, has been synthesized utilizing 2,4-dimethylfuran as educt (Scheme VII). Cycloaddition with vinylene carbonate (130–140 °C, 22 h) gave two adducts, both convertible to the diol shown below. Protecting group chemistry and osmylation gave the

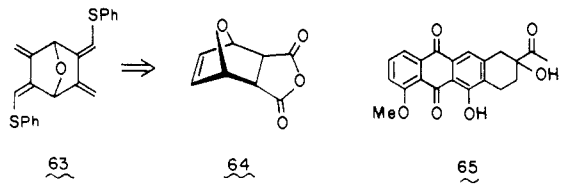
silyl ether diol, which by a series of conventional reactions ultimately produced a compound identical with natural material.[39b]

A tandem Diels–Alder/Friedel–Crafts acylation sequence has been applied to the synthesis of intermediates potentially useful for preparing the anthraquinone antitumor agents rhodomycinone (**58**) and olivin (**59**).[40a] A five-step protocol was developed in-

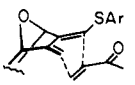


volving the addition of maleic anhydride to furan **60** producing an unstable adduct, which readily hydrogenated to **61**. Methanolysis of **61** afforded a keto ester which cyclized under the influence of trifluoroacetic anhydride (TFAA) at 25 °C to trifluoroacetate **62** (R = $COCF_3$). Saponification of **62** lead to the key tetracyclic intermediate **62** (R = H) in 51% overall yield. Subsequent work relying upon the same strategy has provided an entry to 6-deoxyanthracycline analogues containing a δ-lactone moiety.[40b]

Intermediates **63** and related tetraenes,[41a] arrived at by further handling (4 steps) of an initial furan–maleic anhydride adduct **64**,[41b,c] have proven useful in strategies leading to, e.g., **65**, a known precursor of the an-

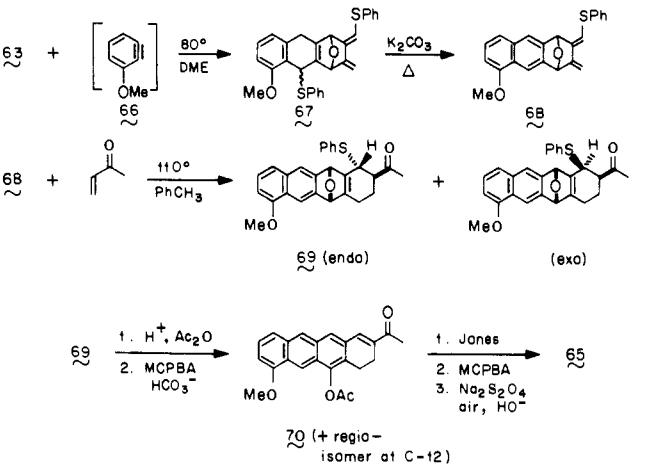


thraquinone antitumor agent aglycone (±)-11-deoxydaunomycinone.[41d] This bis(dienyl sulfide) **63**, envisioned as the B ring in the tetracyclic array, undergoes regio- and stereoselective tandem Diels–Alder reactions utilizing successively different dienophiles. Hence, initial addition of benzyne **66** to **63** affords **68** via **67**, thereby effecting annulation. Subsequent cycloaddition with MVK in hot toluene gives rise to two stereoisomers **69** (+ isomer) in 77% yield favoring the product **69** (9:1) of *endo*-face attack, proceeding predominantly via the transition state shown. Treatment of separated **69** with

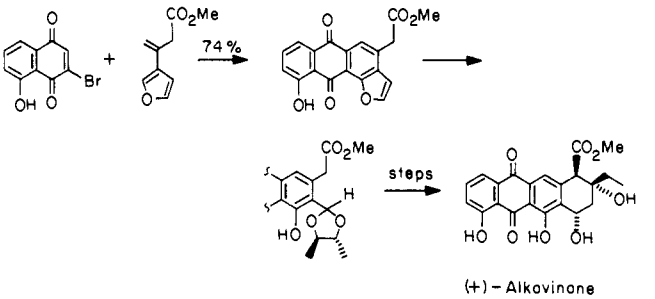


acetic anhydride containing catalytic TFA at 80 °C and then with MCPBA/$NaHCO_3$ to effect elimination leads to **70**, which is ultimately converted to **65**, a known precursor to 11-deoxydaunomycinone.

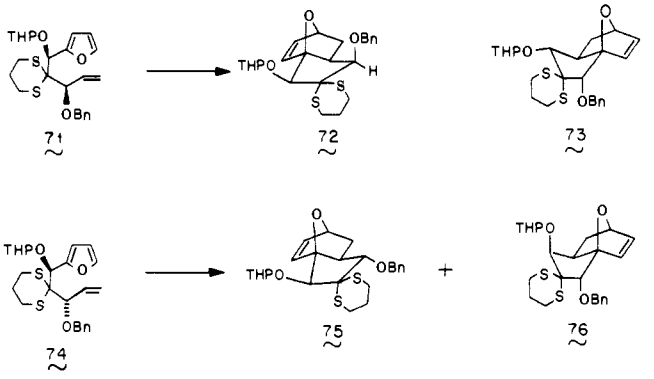
The highly sought aglycone of the antitumor agent aclacinomycin A, aklavinone, has been synthesized in



optically pure form via a key quinone plus vinylfuran cyclization. Bromojuglone efficiently added to the furan regiospecifically to give the benzofuran product following autoxidation of the initial adduct. Ozonolysis/Me_2S cleaved the furan to the phenol aldehyde, which was converted to the chiral acetal with D-(−)-2,3-butanediol/PPTS. Aldol chemistry under the influence of $SnCl_4$ (3 h, −25 °C), base-induced cyclization, and ether hydrolysis to remove the chiral auxiliary lead to (+)-aklavinone.[42]



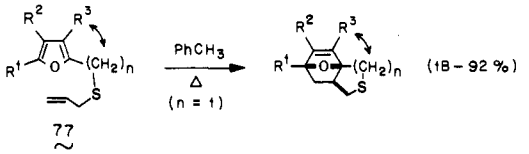
B. Intramolecular Diels–Alder Reactions (IMDA). The power of an intramolecular [4 + 2] cycloaddition strategy has been applied to a variety of furan-containing substrates.[43] Insight concerning the subtle factors which control not only the rates of cyclization but also the stereochemical consequences has begun to accrue. Experimental data on systems wherein the furan and dienophile is tethered by three carbon atoms suggest that the nature and orientation of the substitutents on the chain may be important issues.[44] For example, while the protected *syn*-1,3-diol **71** leads exclusively to product **73** (<1% **72**), the anti isomer **74** affords a mildly selective, albeit inverted 9:1 ratio of **75**:**76**.[44a] Solvent effects are surprisingly minimal.[44b]



More recent work suggests, on the basis of careful ^1H

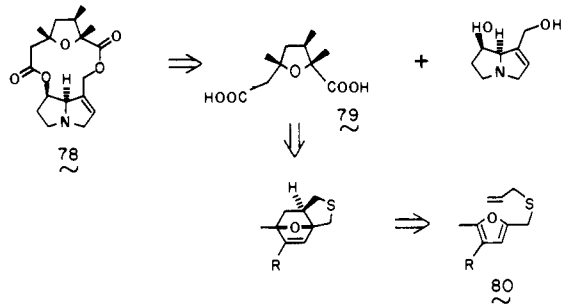
NMR studies with supporting X-ray crystallographic data, that in cases where geminal substitution on the tether exists, factors such as bond lengths, bond angles, and nonbonding interactions which are not disfavored are of prime importance.[44c]

The proposal that steric, rather than electronic factors, dictate the likelihood of a furan intramolecular cycloaddition is further supported in the case of allylic sulfides **77**.[45a] The more extensive the substitution pattern on the furan nucleus the higher the yield of adduct. Experimental evidence would indicate that an eclipsing interaction between a group at C-2 and the methylene unit of the side-chain, alleviated in the product, is responsible for the success of this process. A 3-bromo derivative **77**, $R^1 = R^2 = H$, $R^3 = Br$, which might be expected to deactivate the furan if electronic effects are significant, cycloadds quite efficiently (83%).



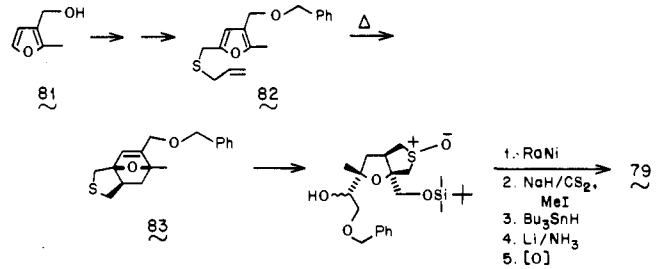
77

Although allylic sulfides such as **77** wherein the diene and dienophile are separated by more than one methylene unit (i.e., $n > 1$) are essentially unreactive, substituted furfuryl allyl sulfides of type **80** have been used to arrive at (±)-nemorensic acid **79**, the diacid segment of retroisosenine **78**.[45b] Starting from known precursor



78 **79** **80**

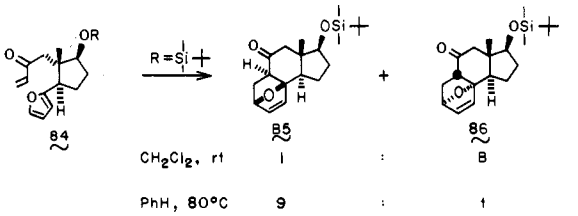
81, **82** is produced which undergoes [4 + 2] closure in the anticipated[46] exo sense to **83** in hot toluene in 48% yield (plus 40–45% recovered furan). Following ozo-



81 **82** **83** **79**

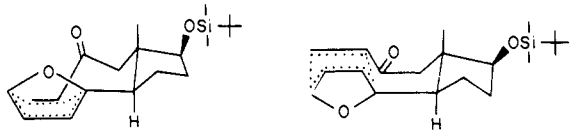
nolysis and silyation, the latent cis vicinal dimethyl unit is formed upon Raney nickel reduction. Barton deoxygenation, deprotection, and Jones oxidation afforded **79**.

De Clerq has utilized this intramolecular process to devise entries to both 11-keto steroids and functionalized gibbane skeletons. The former targets were envisioned as arising via addition of enone **84** to the monosubstituted furan.[47] Not surprisingly, exo products **85** and **86** are formed, the ratio of which is dependent upon conditions.[47c] Interestingly, **86** predominates at lower temperatures, presumably due to the preferred



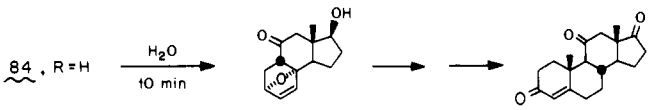
84 **85** **86**

boat-chair-boat-like transition state **88** (rather than the boat-chair-chair, **87**) in the cyclodecane system. When



87, BCC **88**, BCB

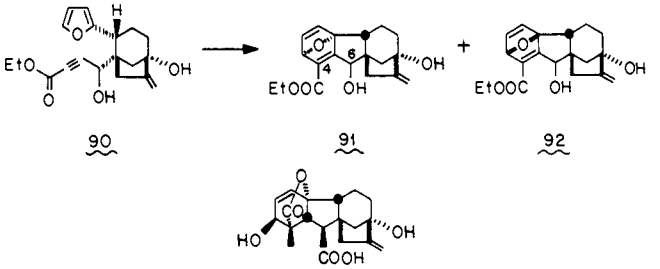
the same reaction was attempted in the absence of the TBDMS protecting group, little of the corresponding product was produced. However, by simply shaking a reaction vessel containing **84**, R = H, for 10 min in cold H_2O, a 75% yield of adduct **89** was realized isomer free!



89 (>75%)

Further manipulation of this intermediate led to (±)-11-ketotestosterone.[47b]

The conversion of *m*-methoxybenzoic acid to ynoate **90** sets up an opportunity for intramolecular cycloaddition which, upon heating in benzene for 24 h, forms two products **91** and **92** (3:1). Both bear an obvious

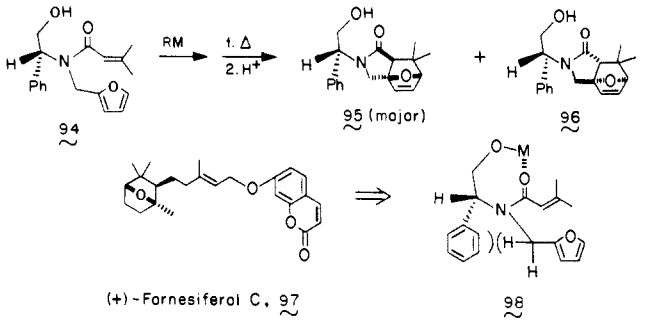


90 **91** **92** **93**, GA_3

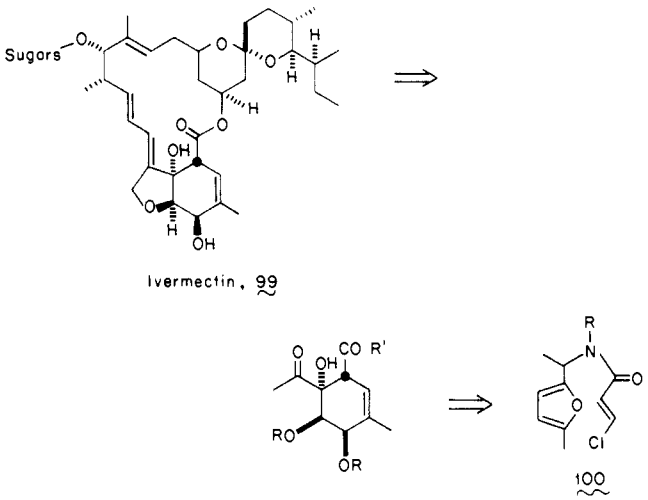
relationship to gibberellic acid (GA_3, **93**) and contain functionality at both C-4 and C-6 needed for eventual introduction of additional carbons and for completion of the A-ring.[48]

A synthesis of sesquiterpene (+)-farnesiferol C, **97**, proceeds via an intramolecular asymmetric Diels–Alder coupling of **94** using (*S*)-(−)-phenylglycinol as a chiral auxiliary.[49a] Introduction of magnesium salts encourages chelation controlled addition of the furan moiety for steric reasons (see **98**) from the face opposite the aromatic ring, leading to **95** and **96** in an 88:12 ratio (77%). Further handling of the major, desired isomer results in **97**, the antipode of the natural material.

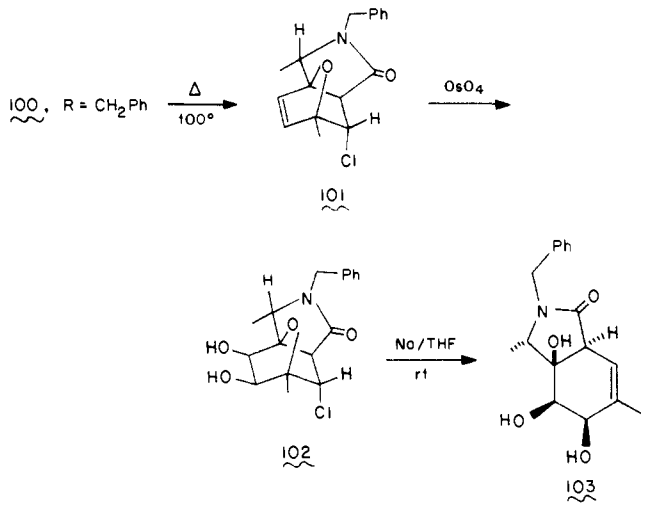
The "southern" zone of the avermectins, e.g., in ivermectin, **99**, a dihydroxyhexahydrobenzofuran, is being approached via an intramolecular cycloaddition of an acrylamide with a furan.[50] Early model studies[50a] have demonstrated that cyclizations proceed quite readily in refluxing toluene in excellent yields especially when a tertiary amide is involved, as noted in the literature



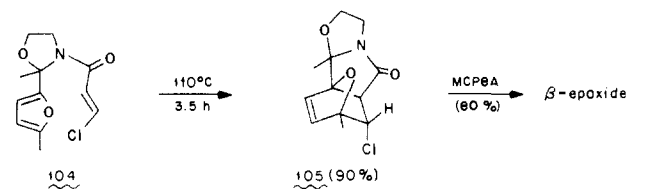
previously.[46,51] The presence of a methyl group on the connecting chain in **100** also significantly enhances the



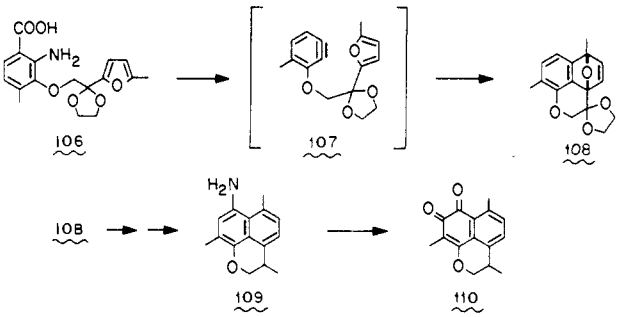
rate of adduct formation. Following cis hydroxylation (97%) from the undesired exo face of adduct **101**, reductive opening of the endo-oriented furan cycloadduct **102** with sodium in THF at ambient temperature affords the bicyclic lactam **103**. Owing to the fact that



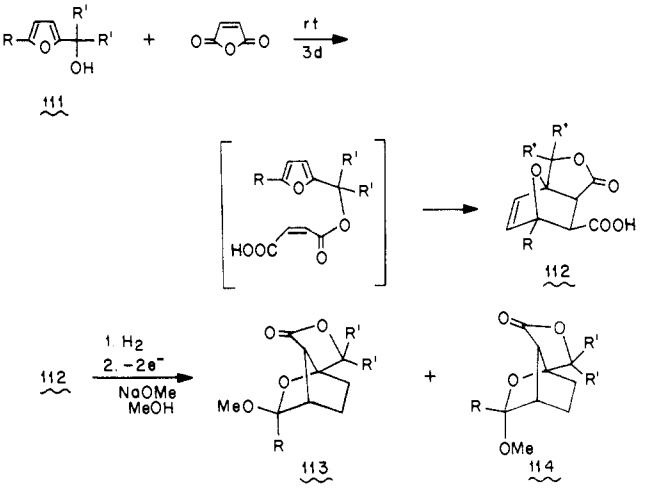
both the stereochemistry of the tertiary alcohol and the oxidation state at the adjacent carbon are incorrect, the cycloaddition with aminal **104** was performed giving **105** to the extent of 90%. While this adduct nicely addresses the need for an acetyl side chain, future work concentrating on the derived β-epoxide may solve the stereochemical issue at the ring junction bearing the hydroxyl group.[50b]



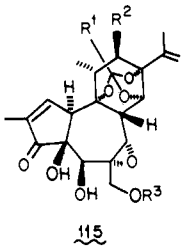
A synthesis of the naturally occurring naphthoquinone mansonone E, **110**, isolated from the wood of *Mansonia altissima*, makes use of an intramolecular [benzyne + furan] cycloaddition.[52] Treatment of anthranilic acid **106** with isoamyl nitrite/HCl followed by thermolysis in dichloroethane proceeds through **107** to adduct **108** in 86% yield. Subsequent aromatization and eventual oxidation of the derived amine **109** with Fremy's salt afforded the desired material.



In model studies directed toward highly oxygenated iridoid monoterpenes, a sequence involving intramolecular furan cycloaddition, hydrogenation, and anodic oxidative decarboxylation, starting with **111** and maleic anhydride, lead ultimately via **112** to produce **113** and **114** (2.3->13:1) in excellent yields. Such a scheme obviates the regiochemical issues associated with methanolysis of the initial substituted furan–maleic anhydride adduct.[53]



The first example of a seven-membered carbocycle fused to a cyclohexene, generated through the IMDA reaction of a furan, has very recently been reported.[54] As a preliminary study with overtones relating to the daphnane diterpenes of general structure **115**, intramolecular closure of enone furan **116** was envisioned. While all attempts to promote this cycloaddition using either thermal or Lewis acid based conditions were unsuccessful, subjecting **116** to 14 kbars of pressure at room temperature in CH_2Cl_2 afforded *endo*-**117** and *exo*-**118**. Interestingly, **117** was the more stable isomer, reverting back to **116** with a half-life of 1100 min at 40 °C, while **118** has $t_{1/2}$ = 90 min at 40 °C. Moreover, these observations are contrary to earlier reports where *inter*molecular cycloadditions at elevated pressures were



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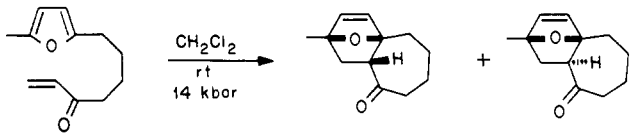
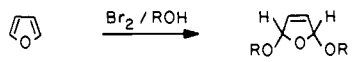


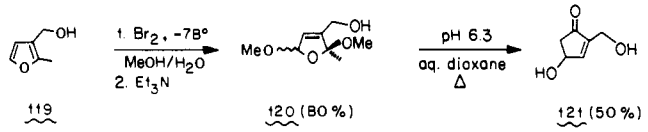
116 117 118

shown to be irreversible. The explanation may be due to intramolecularity, or other factors such as ring size and/or relative volumes of activation of the transition states involved.[55]

C. Furan Oxidation Reactions. The oxidation of a furan ring has oftentimes been used to express the latent functionality present within this heterocyclic framework. While halogenation in, e.g., CCl_4, leads to halogenated furans, in hydroxylic solvents bromination or chlorination at low temperatures is well-known to efficiently afford 2,5-dialkoxy-2,5-dihydro derivatives.[56] Related reactions in aqueous media continue to attract attention from the mechanistic perspective.[57]

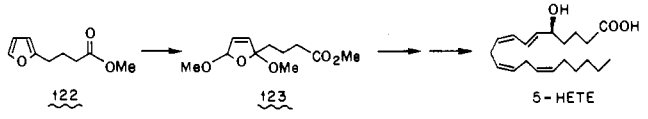


In recognition of the numerous biologically active compounds which contain relatively simple cyclopentanone rings, furan **119** was called on as starting material for **120**, readily arrived at via treatment of **119** with Br_2 in wet methanol. Refluxing **120** in aqueous dioxane at pH 6.3 afforded the desired cyclopentenone **121**.[58]



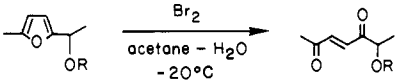
119 120 (80%) 121 (50%)

The innate masked 1,4-dicarbonyl moiety in furan ester **122** was similarly converted to **123** (Br_2/MeOH, Na_2CO_3, −30 °C) in 79% yield. Ring opening (H_2O, 45 °C, 73%) to the *cis*-keto aldehyde followed by isomerization (I_2, Et_2O, room temperature) and standard Wittig elongation ultimately gave (±)-5-HETE.[59]

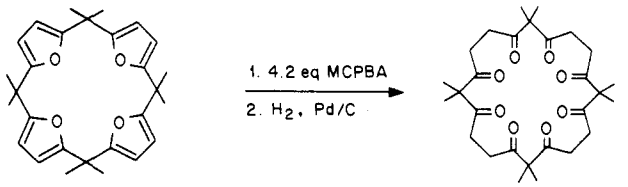


122 123 5-HETE

A most recent report describing modified conditions for the Br_2/MeOH-based oxidation (i.e., the Clauson–Kaas reaction) has appeared.[60] Carrying out this reaction in acetone–water (85:15) with 1 equiv Br_2 initially at −20 °C to room temperature affords directly the *E* isomers in very good yields. The process may be conducted in the presence of excess pyridine should acid sensitive functionality be present.

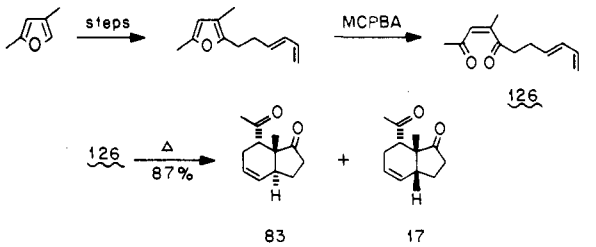


As an alternative to the classical oxidative ring openings of furans via X_2/ROH (vide supra), methods which rely on peracids have been developed. While there are a few scattered earlier reports on such a process,[61] Williams and LeGoff found that MCPBA may be the reagent of choice for effecting this transformation of furan to *cis*-enedione.[62a] Sufficiently mild conditions prevail such that acid-catalyzed isomerization is usually not observed.[63] By varying the stoichiometry, e.g., polyfuran macrocycle **124** has been converted to octaketone **125** in excellent yield (87%).



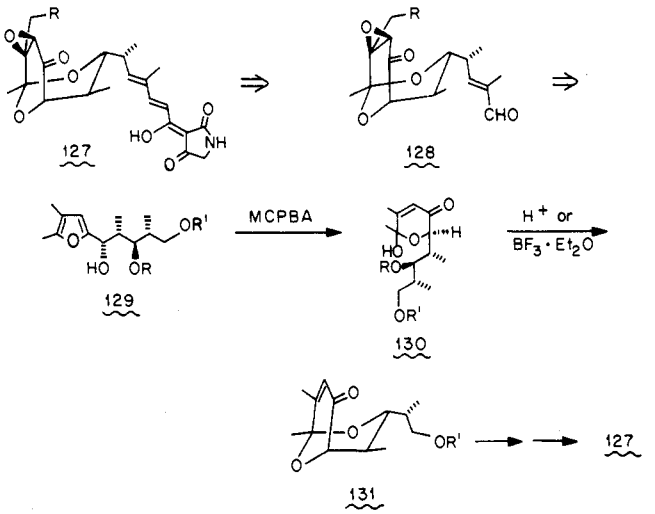
124 125

More recently, these same authors have applied this valuable procedure to a dimethylfuran, the product **126** from which (even at room temperature) cyclized to a mixture of hydrindenones in high yield.[62b] As in the case of halogen-based oxidations, mechanistic information on the MCPBA-induced oxidation has recently appeared.[64]



83 17

Due to the array of biological activities associated with the tetramic acid family of antibiotics, several groups have directed their attention toward the synthesis of, in particular, tirandamycin A, **127** (R = H).[65]



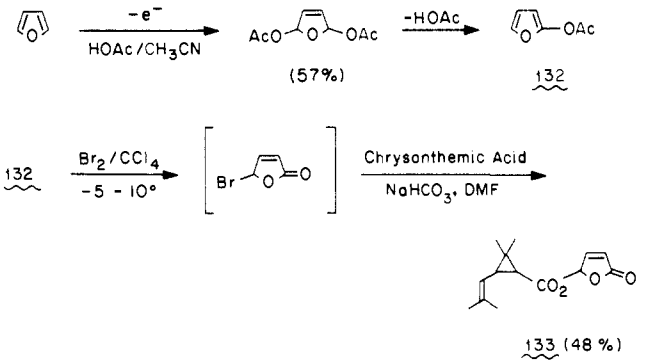
127 128 129 130 131

It is perhaps not surprising that the functionalized pyranone **128** was equated with trisubstituted furan **129**, a strategy which serves as the focal point of a number of ongoing approaches. Key intermediate **129** is highly susceptible to MCPBA oxidation at subambient temperatures giving a hydroxy-3-pyrone system, **130** (vide infra), which upon exposure to Lewis or protic

acid closes to bicyclic enone **131**. A subsequent series of transformations common to most routes results in either a formal[65a] or total synthesis[65b] of **127** (R = H).[65c]

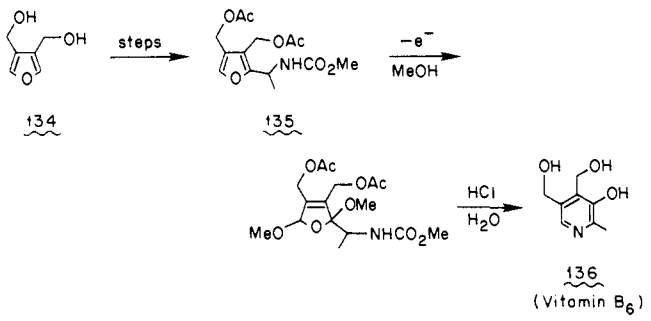
Pyridinium chlorochromate (PCC) has also been shown to effectively oxidize furans.[66] Although less frequently utilized then halogen or peracid (vide supra), PCC in refluxing CH_2Cl_2 usually affords good yields of α,β-unsaturated-δ-dicarbonyl compounds of the *E* configuration. The double bond geometry reflects the mildly acidic character of PCC which catalyzes the conversion of the initially formed *Z* isomer, isomerization also being aided by the heating required for this oxidative cleavage.

Electrochemical procedures have also been applied to furan oxidations.[67] Product formation is a function of both the substitution pattern on the ring, as well as the medium employed in the anodic oxidation. Hence, Shono and co-workers found that 2-acetoxyfuran, **132**,

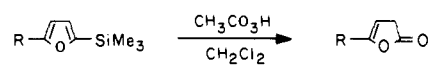


a useful precursor to 4-substituted butenolides, is easily arrived at via anodic oxidation of furan in HOAc/CH_3CN/NaOAc, followed by HOAc elimination.[68a] Furan **132** may be further manipulated as illustrated to the pyrethroid analogue **133**.

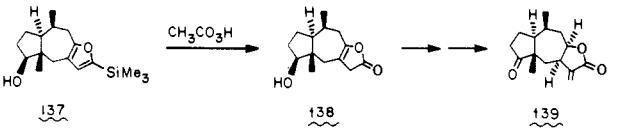
The conversion of furan diol **134** to urethane **135** likewise provides a system amenable to electrochemical oxidation, in this case in methanol solution.[68b] The bis(adduct) is subsequently cyclized following hydrolysis, to pyridoxine hydrochloride, **136** (31% from **135**).



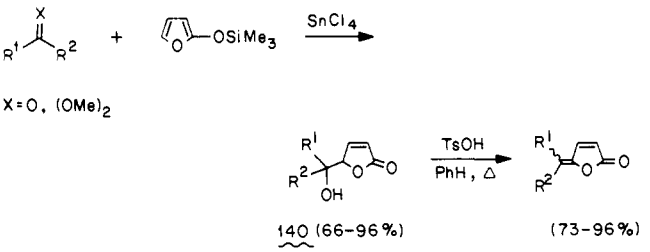
The facile oxidation of the furan nucleus has spawned numerous syntheses of butenolides of varying substitution patterns depending upon the aromatic precursor. Thus, Δ^3-butenolides may be realized from 5-alkyl-2-(trimethylsilyl)furans under the influence of buffered 40% peracetic acid (4 equiv) at 0 → 7 °C.[69] In a similar way, Δ^2-butenolides are formed from 3- or 4-substituted 2-(trimethylsilyl)furans.[70]



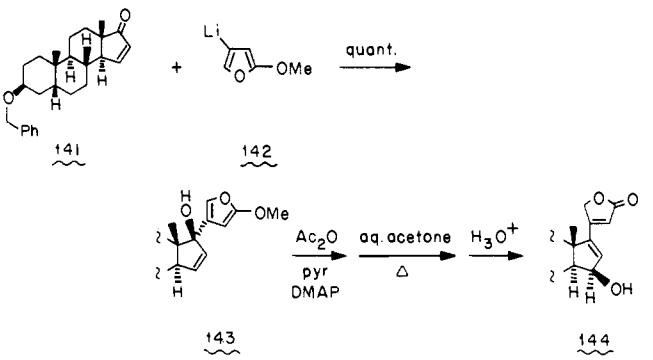
Schultz et al. have successfully applied this original Kuwajima[69] procedure to synthetic goals in the pseudoguaianolide sesquiterpene area.[71] In their recently described total synthesis of *dl*-confertin, **139**, furan **137** is converted to the enol lactone **138** without contamination due to the Δ^2-isomer.



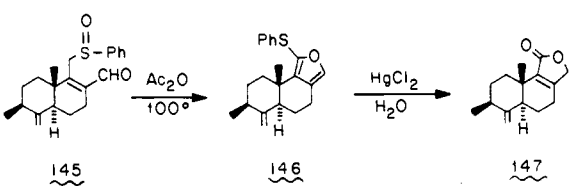
2-[(Trimethylsilyl)*oxy*]furan condenses with various acetals, aldehydes, and ketones in the presence of $SnCl_4$ to afford butenolides **140**. Treatment of adducts **140** in hot benzene with catalytic TsOH or HBr leads to dehydration thereby forming 4-ylidenebutenolides in good overall yields.[72]



While 2-Me_3SiO-substituted furans have been used in Lewis acid mediated condensations, related 2-alkoxy derivatives are valuable in that they undergo rapid hydrolysis in aqueous acid. Methoxyfuran **143**, constructed from steroid ketone **141** and the novel organometallic **142**, taken together serve as a straightforward entry into the cardioactive steroids (e.g., digitoxigenine) via intermediate butenolide **144**.[73]

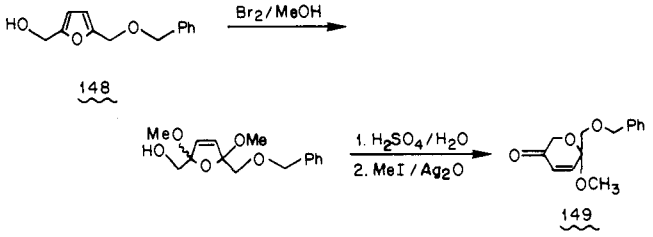


A new procedure for butenolide formation en route to colorata-4(13),8-dienolide (**147**), one of only a few sesquiterpenes containing a rearranged drimane framework, relies on the hydrolysis of a 2-thiophenoxy-substituted furan **146**, derived from sulfoxide **145**.[74] Mercuric ion induced hydrolysis, performed at ambient temperatures, minimized double-bond isomerization affording **147** in 60% yield.



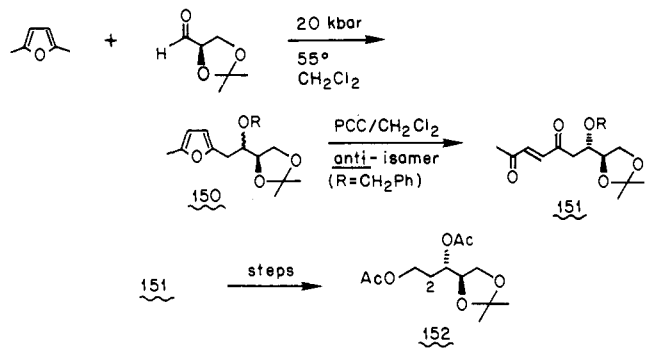
Efforts in carbohydrate-related research have also benefited from the masked functionality contained within furans.[75a] 4-Ketohexoses, e.g., **149** and derivatives, have been secured from monoprotected 2,5-bis-

(hydroxymethyl)furan **148** via the usual Br_2/MeOH



oxidation (86%) followed by hydrolysis (quant) and glycosidation (85%).[75b] Subsequent experimentation on diulose **149** involving reductions, hydroxylations, or epoxidations with ultimate ring opening lead to products of the *α-tagato-*, *α-sorbo-*, *α-psico-*, and *β-fructo-* configurations.

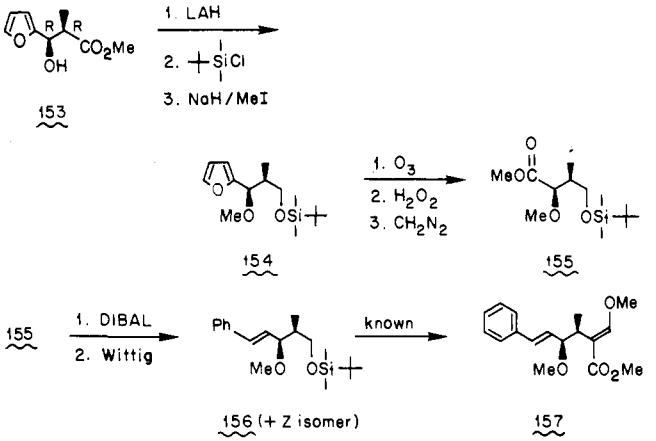
Under high pressure conditions (20 kbar), 2,5-dimethylfuran reacts with the acetonide of D-glyceraldehyde to afford diastereomeric adducts **150** (R = H) in a ratio of 4:1.[76] In order to determine the direction of asymmetric induction, a chemical method was chosen which also serves as a route to 2-deoxypentitols and relies upon initial oxidation of the furan ring in the major isomer of **150** (R = CH_2Ph) to **151**. A series of



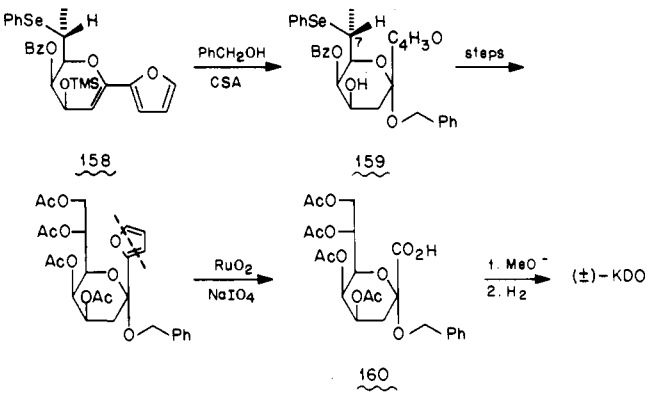
straightforward steps ((1) DIBAL; (2) $OsO_4/NaIO_4$; (3) $NaBH_4$; (4) H_2; (5) Ac_2O/pyr) affords 1,3-di-*O*-acetyl-4,5-*O*-isopropylidene-2-deoxy-D-ribitol, **152**, with an $[\alpha]_D$ = −21° (lit. $[\alpha]_D$ = −23.2°) thereby establishing the absolute configuration at the newly created chiral center as that shown.

An increasingly popular use of the furan ring derives from its ability to function as a latent carboxylic acid. Under dry ice–acetone cooling, ozonolysis of **154**, arrived at via microbiological reduction of the corresponding keto ester precursor of **153**, followed by oxidative workup and esterfication gives **155** (29% overall).[77] Reduction and thence Wittig olefination afforded a 43:57 mixture of *E* to *Z* isomers (94%). Separation of the optically active desired *E* isomer **156** constitutes a formal total synthesis of (−)-oudemansin **157**, an antibiotic obtained from mycelial cultures of *Oudemansiella mucida*.

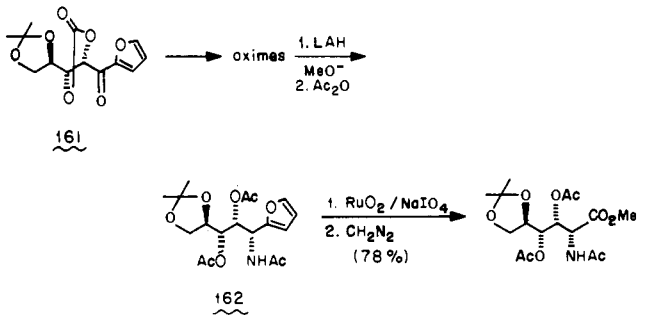
More recently, Danishefsky[78] and Mukaiyama[79] have employed the furan-to-acid conversion in syntheses of (±)-3-deoxy-D-*manno*-2-octulopyranosate (KDO) and methyl D-glucosaminate, respectively. Both rely on the ruthenium tetraoxide catalyzed oxidation of a 2-substituted furan, the procedure for which has been significantly improved upon (and generalized for the oxidation of several functional groups) by Sharpless.[80] Following a series of carbohydrate-building reactions, the strategy for which relied heavily on a modified, yet vintage, Danishefsky diene–aldehyde cycloaddition,[81]



furan glycal **158** was in hand. Glycoside formation with concomitant silyl ether cleavage afforded a single diastereomer **159** as shown, proven by X-ray analysis on a related derivative, which also established the configuration at C-7 as "*R*". Ultimately, selective oxidation of the furan nucleus led to the desired acid (86%), whereupon final methanolysis and catalytic hydrogenation of **160** gave (±)-KDO.



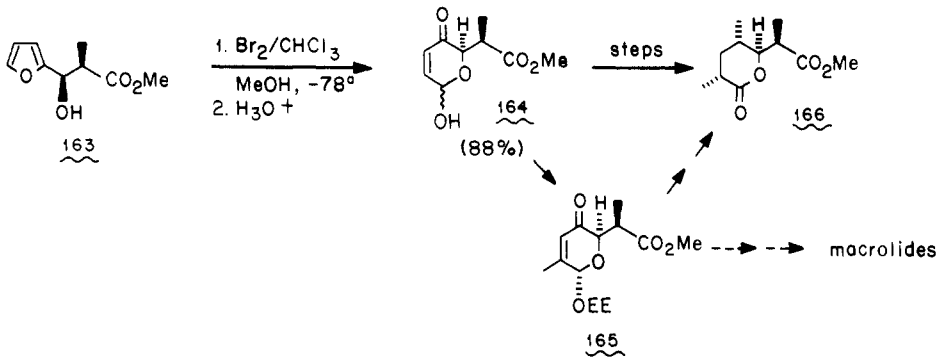
The Japanese group, as part of their exploratory work on developing new routes to sugars, have given further extension[79] to their cross-aldol chemistry which proceeds via Sn(II) enediolates.[82] Hence, from furylglyoxal, D-glyceraldehyde, and metallic tin at 0 °C, polyol **161** (in protected form) is obtained as the predominant isomer. *O*-Benzyloxime formation (mixture of isomers, 86%), reduction and acetylation gave amide **162** (75%), along with 8% of its diastereomer. Oxidative cleavage



to the acid lead after diazomethane esterification to the target sugar (78%), whose stereochemical integrity was assured by conversion to 2-acetamido-2-deoxy-D-glucitol pentaacetate in four steps (LAH, Ac_2O, H_3O^+, Ac_2O).

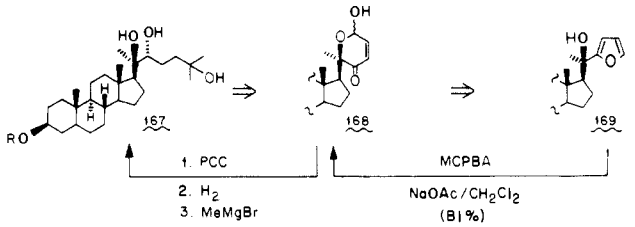
Although oxidations of furans afford 1,4-dicarbonyl compounds or their equivalents (vide supra), the proximity of a free hydroxyl group, as in furfuryl al-

SCHEME VIII

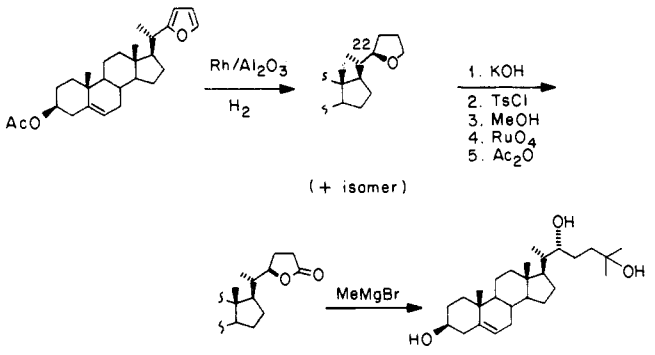


cohols, leads instead under acid catalysis to hydroxy-3-pyrones.[83] Such an oxidation–hydrolysis sequence has been applied to a chiral synthesis of the Prelog–Djerassi lactone **166** (methyl ester).[84] Thus, enantiomerically pure furan ester **163**, realized from furfural employing the Evans aldol protocol,[85] upon treatment with molecular bromine at low temperature for 30 min followed by exposure of the initially formed dimethoxyfurans to 10% aqueous H_2SO_4–THF (1:1, room temperature, 24 h) afforded **164**. Lactol **164** could be carried on to **166**, which proceeds through intermediate **165**, the latter compound being potentially useful for gaining entry to the macrolide antibiotics (e.g., aglycones tylonolide and erythronolide) (Scheme VIII).

Tetrol **167** (R = H), possessing a 20-hydroxyecdysone-type side chain, has been prepared stereoselectively by Kametani via pyrone **168**.[86] Furfuryl alcohol **169** served as the precursor to **168**, formed by 1,2-addition of 2-lithiofuran to the THP ether of pregnanolone.

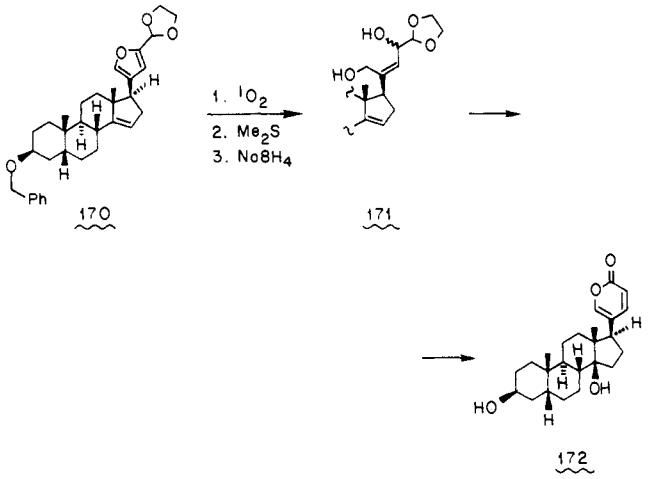


A follow-up paper by this group describing a related approach to the same end has also recently appeared.[87] In this work, however, the furanyl steroid is *reduced* to a mixture of tetrahydrofurans, and subsequently converted to their lactones with RuO_4. Grignard opening afforded the expected two products, epimeric at C-22.



The facility and efficiency with which singlet molecular oxygen ($^1O_2$) cycloadds to furans has generated considerable interest on the mechanistic[88] as well as synthetic fronts. Reports dealing with the subsequent chemistry of furan endoperoxides, including their thermal rearrangements,[89] Baeyer–Villager[90] and silicon[91] rearrangements, potential for chemiluminescent processes,[92] and sensitivity to solvent effects,[93] have all appeared in the past few years.

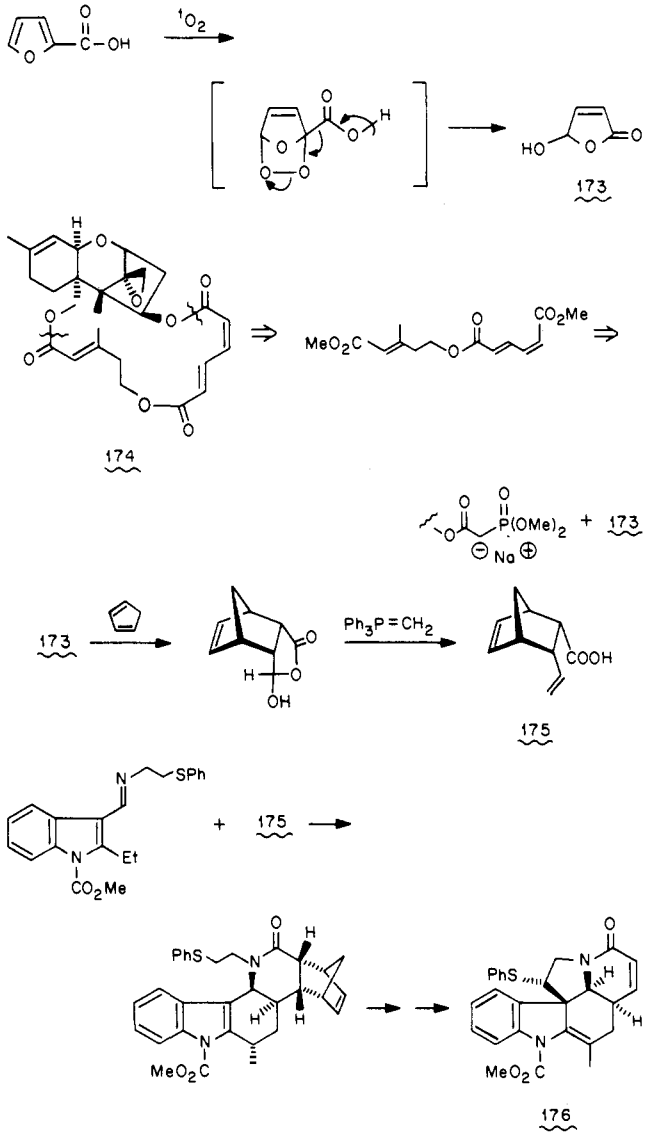
From the synthetic perspective, another furan-to-pyrone transformation was developed using $^1O_2$ for purposes of converting acetal **170**, itself derived from digitoxigenin, to bufalin, **172**.[94] Exposure of **170** to light and oxygen at −70 °C in CH_2Cl_2 in the presence of mesotetraphenylporphine (0.4%) led to an endoperoxide which was treated with excess Me_2S. After workup, the residue was reduced to diol **171** in aqueous THF/NaOH with $NaBH_4$. Isolation by preparative TLC afforded an 82% yield of **171**. Five additional



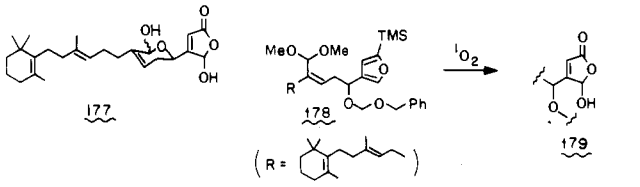
steps, including acetal hydrolysis (3 N HCl, 95%) oxidation (Ag_2CO_3/Celite, 75%), mesylation–elimination (MsCl/DBN, 85%), hydration (aq NBS, RaNi, 70%), and debenzylation (H_2, $Pd(OH)_2$, 70%) resulted in the desired natural product, **172**.

Photooxidation of 2-furoic acid, devised in response to difficulties faced in reproducing a literature route to malaldehydic acid (**173**), leads essentially quantitatively to this key substance.[95] Subsequent Horner–Emmons chemistry employing **173** allows for the stereoselective preparation of the macrocyclic component of verrucarin J, **174**,[95] as well as the precursor to dienophile **175**, a pivotal partner en route to *Aspidosperma*-type alkaloids (e.g., **176**).[96]

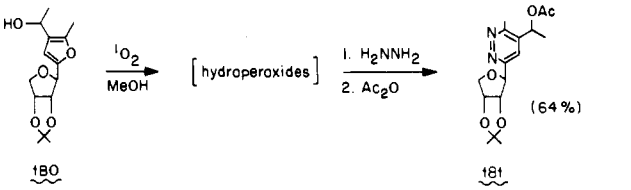
Substituted γ-hydroxybutenolides as targets rather than as intermediates, as in the cases of manoalide **177** and strigol, may be formed in excellent yields via photooxidation of silylated furans.[97] Thus, for example,



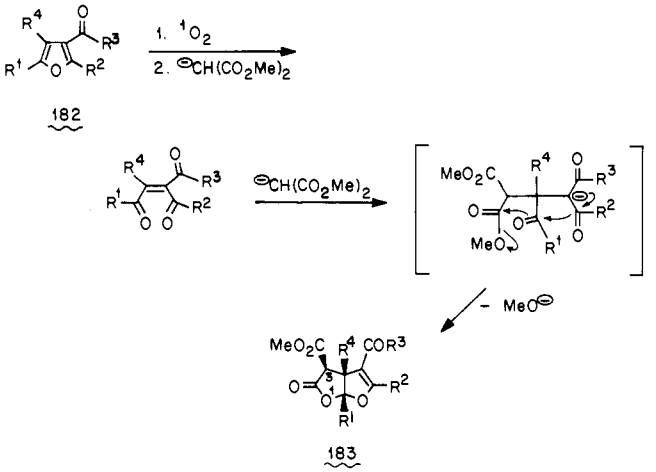
178, an intermediate along the pathway to **177**, reacts in 5 min with $^1O_2$ at −78 °C to afford **179** in 89% yield. This reaction takes advantage of a rapid intramolecular silatropic shift studied earlier by Adam.[91] It is noteworthy that the silyl moiety in **178** not only enhances the rate of endoperoxide formation, but also controls the regiochemical outcome of second-stage endoperoxide breakdown. These concepts have been successfully applied to the total syntheses of both manoalide and *seco*-manoalide.[98]



C-Glycosylpyridazines **181**, analogues of C-nucleosides, are easily constructed from *C*-furanosylfurans **180** by way of singlet oxygenation in MeOH.[99] Introduction of excess hydrazine serves to both reduce the initially formed mixture of hydroperoxides and to induce cyclization to **181**.

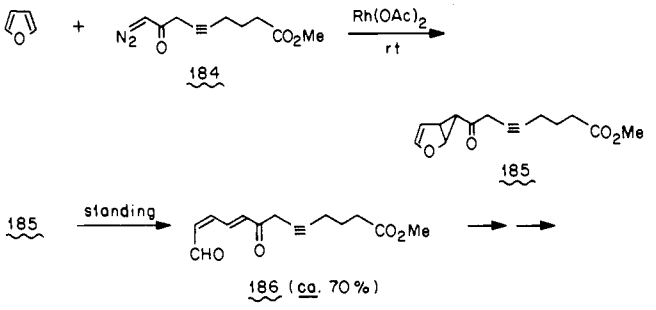


A one-pot procedure for the conversion of highly substituted furans to furofurans **183** involves sequential treatment of **182** with $^1O_2$ in THF at −15 °C, followed by inverse addition of the endoperoxide generated to a suspension of dimethyl malonate anion (2.5 equiv). Workup affords bicyclic systems of general formula **183** in 45–63% overall yields, compounds which are structurally similar to those of known antifeedant activity.[100]



D. Other Reactions of Furans in Synthesis. In addition to the reactions outlined above involving Diels–Alder additions or direct oxidations of furans, there are several other ways in which this heteroaromatic nucleus has been modified,[101] e.g., photochemically,[102] via organometallics[103] or by conversion into wanted functionality.[104]

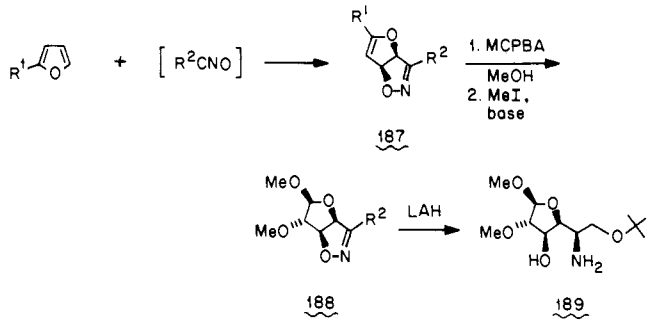
Continuing a strategy originally reported in 1980,[105a] a contingent from Merck Frosst has successfully synthesized both (±)-8- and (±)-9-HETE.[105b] Although these substances have attracted considerably less attention than the well-established 5-, 11-, 12-, and 15-congeners, both display chemotactic activity. Further biological testing has been stymied, however, owing to the lack of available material. Their route relies on the rhodium acetate catalyzed addition of a diazocarbonyl compound (e.g., **184**) to furan thereby generating cyclpropyl derivative **185**, which slowly converts to **186**



(±)-HETE'S

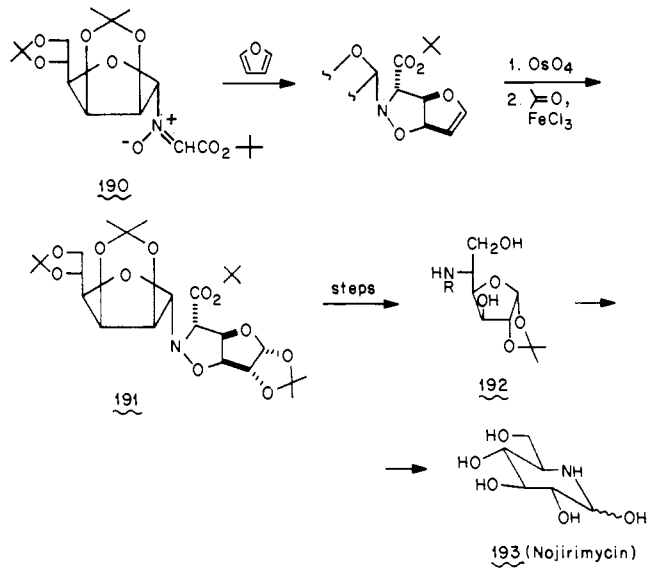
upon standing (ca. 70%). *cis,trans*-Dienes of this type represent the key substructure from which all of the HETE's may be synthesized.

Jager has made extensive use of substituted isoxazolines **187** as amino sugar precursors. [3 + 2]-Cycloaddition of furan to in situ liberated nitrile oxides under high dilution conditions leads to adducts **187**. With R^1 = H and R^2 = CH_2O-*t*-Bu, treatment of **187** with

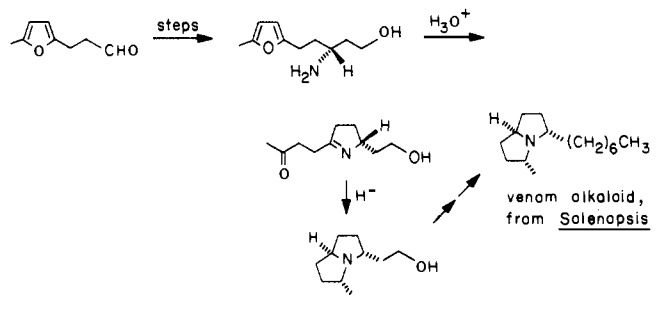


MCPBA in MeOH followed by methylation gave **188**, the LAH reduction of which afforded predominantly (≥ 95:5) **189**, recognized as a protected form a 5-epi-nojirimycin.[106a] A more recent contribution highlights **187** as an important synthetic intermediate for amino-deoxypentose construction of the *xylo* or *arabino* variety.[106b]

Nojirimycin itself (i.e., **193**) has been synthesized via a related cycloaddition scheme invoking furan and nitrone **190**.[107] The highly functionalized glycoside **191**, obtained from these educts after sequential osmylation and isopropylidenation, could be manipulated in six efficient steps to **192**, a known precursor to **193**.

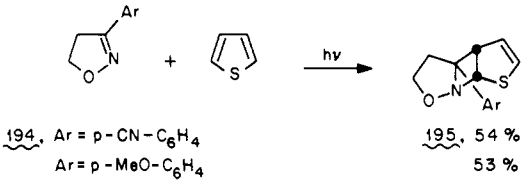


An enantioselective synthesis of a pyrrolizidine ant venom alkaloid[108a] makes use of the aqueous acid ($HClO_4$, H_2O, 90 °C) hydrolysis of furans, the original procedure for which was described by Buchi.[108b] The pyrroline so formed could be reduced ($NaCNBH_3$, pH 4) to the required bicyclic, which upon standard treatment (oxidation, Wittig, H_2) afforded the natural product.



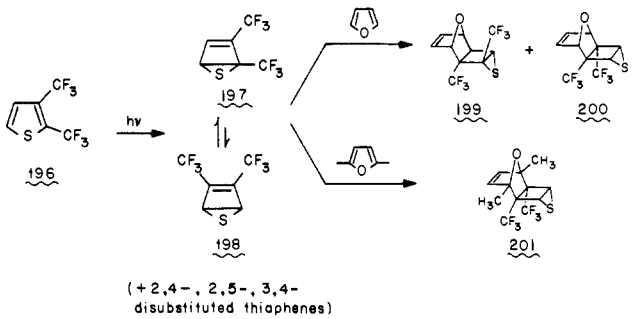
3. Thiophenes

An excellent, comprehensive review by Iddon on the applications of thiophenes to synthesis appeared in 1983 and deals, in particular, with their ring opening and cycloaddition reactions.[109] More recently, a number of photocycloadditions have been reported, each of which features a distinguishing mode of thiophene reactivity. For example, irradiation of 3-aryl-2-isoxazolines **194** in thiophene leads to [2 + 2] adducts **195** resulting from a head-to-head combination, as established by NMR.



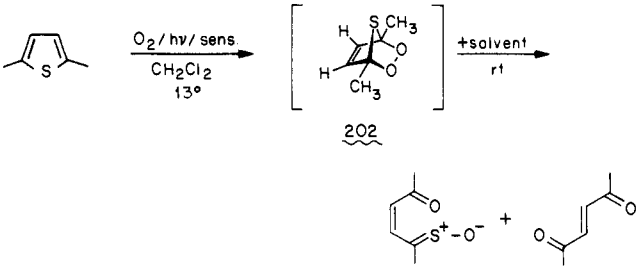
To account for the regiospecificity of the coupling, an exciplex was invoked as an intermediate, although attempts to detect exciplex emission were not successful.[110]

Placement of two trifluoromethyl groups on thiophene adds sufficient stability for isolation of the Dewar thiophenes formed from gas-phase irradiation of **196** with a low-pressure Hg lamp.[111] The mixture of **197** and **198** (8:1) reacts with furan to afford both **199** and **200**, while 2,5-dimethylfuran leads to only one product **201**.



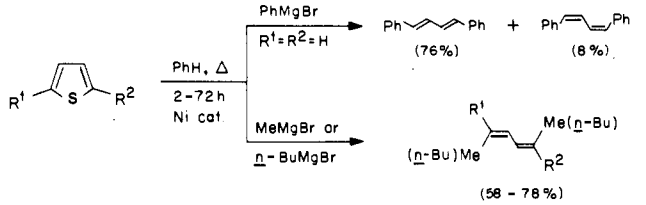
Using ^{19}F NMR, it was deduced that steric and electronic effects are responsible for both the equilibrium ratio and the preferences noted for their subsequent Diels–Alder chemistry.

While the singlet oxygenation of thiophene itself does not occur, 2,5-dimethylthiophene is sufficiently reactive to produce two products via **202**.[112] Evidence of a spectroscopic nature (^1H, ^{13}C NMR) has recently been offered to support the exclusive intermediacy of the thermally explosive thiaozonide **202**.

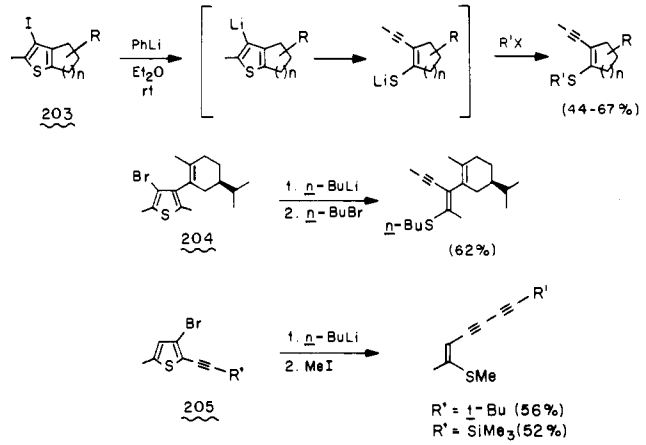


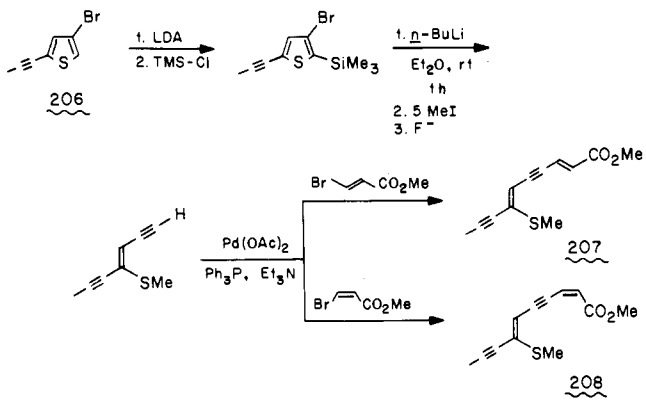
Thiophenes which are not fused to benzene or naphthalene rings have been found to react, as do their fused analogues, with Grignard reagents in the presence of a low valent nickel species affording good yields of conjugated dienes. Both alkyl and arylmagnesium

bromides were examined, the former effecting heterocycle unmasking to *Z,Z* isomers stereospecifically, while PhMgBr showed a preference for generation of the all-trans network.[113]

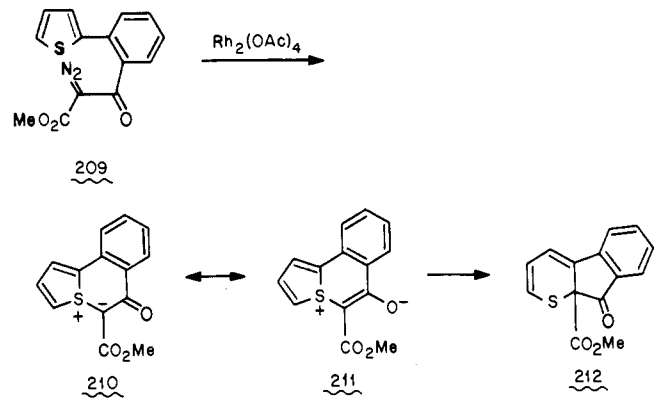


Extensive studies by a Swedish group on the ring opening reactions of 3-lithiothiophenes have been conducted over the past few years.[114] Metal–halogen exchange with *n*-BuLi or PhLi in Et_2O at ambient temperatures leads to acetylenic thioenol ethers wherein the double bond is solely of the *Z* configuration. The reaction works equally well with a variety of substituents at the remaining 2,4, and/or 5-positions, including fused rings (e.g., **203**),[114a] chiral appendages (e.g., **204**),[114b] and acetylenic moieties (e.g., **205**).[114c] From this latter class of substituted thiophenes, e.g., **206**, two naturally occurring substances **207** and **208** from the plant genus *Anthemis* were successfully synthesized, each in three steps.

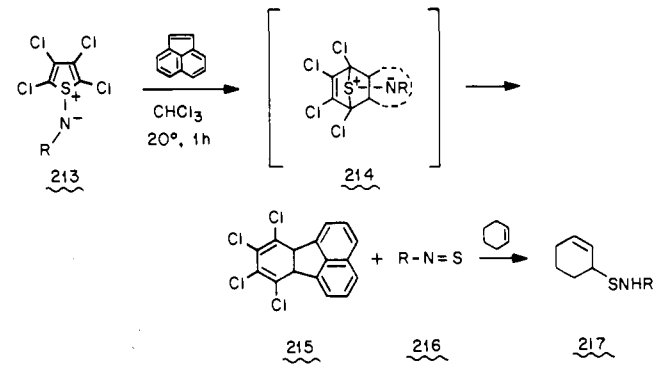




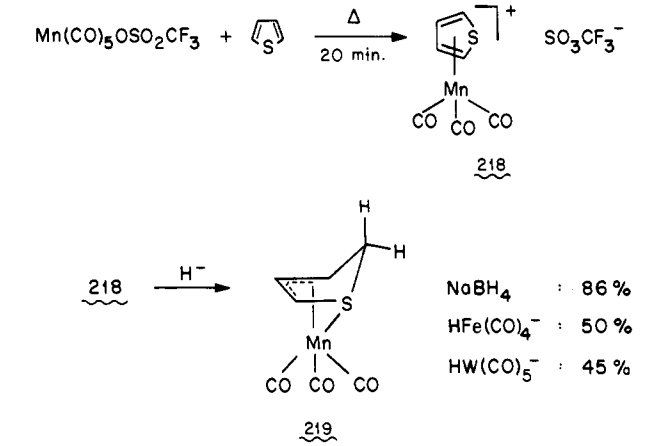
A rare example of a sulfur ylide involving a substituted thiophene has been formed which results in heteroaromatic ring expansion to a thiopyran derivative **212**.[115] Rhodium(II) catalyzed decomposition of diazo keto ester **209** leads to ylide **210** stabilized by the potentially aromatic (14π-electron) resonance tautomer **211**. Product **212** was confirmed unequivocally by spectral and X-ray diffraction data, and can be accounted for by a Stevens rearrangement.



The cycloadditions of thiophene *S–N* ylides have recently led to a novel route to thionitroso compounds **216**.[116] These materials are of limited stability yet can be conveniently handled as either their ene or Diels–Alder adducts. Hence, when the tetrachlorothiophene *S–N* ylide **213** is treated with an olefin, best exemplified in the case of added acenaphthalene (1 equiv) and an equimolar amount of cyclohexene as a trapping agent, adducts **215** and **217** are formed via **214** in quantitative yields.



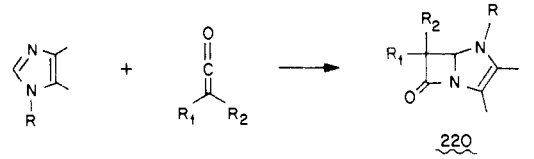
An interesting manganese tricarbonyl π-complex of thiophene (**218**) has been prepared so as to evaluate species of this type as potential intermediates in the heterogeneous, catalyzed hydrodesulfurization (HDS) of this heterocycle.[117] Salts **218** react with a variety of nucleophiles under mild conditions thereby destroying the rings aromaticity, which may be the key barrier to its HDS. Importantly, complexes **218** also readily react with metal hydrides (e.g., $NaBH_4$, $HW(CO)_5^-$, $HFe(CO)_4^-$, etc.), nucleophiles which are likely to be present on the surface of the HDS catalyst, further supporting the hypothesis that π-bonded thiophene may be involved.

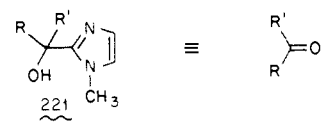


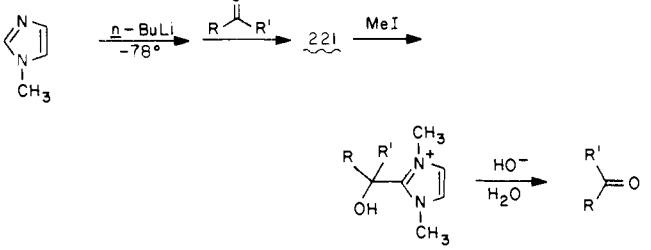
B. Heterocycles Containing Two Heteroatoms

1. Imidazoles

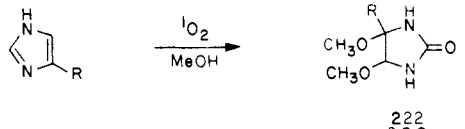
Imidazoles as masked functional group equivalents have attracted, at best, scant attention in natural products related endeavors. Only scattered reports which are primarily physical organic in nature have appeared,[118] although some interesting analogues of bioactive compounds were noted, e.g., **220**.[118a] In addition, the recently described use of an imidazole as a protecting group for the carbonyl function represents a novel sequence, as shown.[119] Regeneration of the carbonyl group follows from exposure of **221** to MeI and ultimately aqueous base.



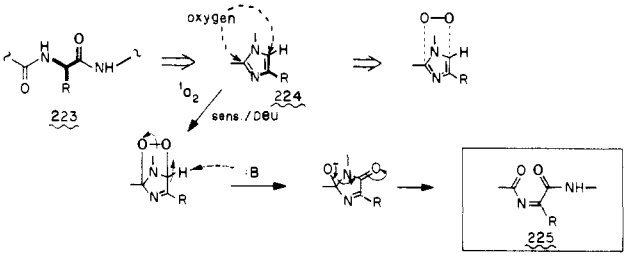


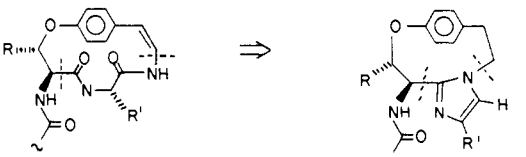


Insofar as directing imidazole chemistry toward compounds of natural origin, a report from these laboratories in 1984 dealing with their oxidative conversion to optically active amino acid derivatives, to our knowledge, was the first of its kind.[120] While the singlet oxygenation of imidazoles has been extensively studied by Wasserman[121a] and Foote,[121b] these reactions in MeOH solution oftentimes afford products of solvent inclusion, typified by **222**. Through the exercise of reviewing the reactions of electrophilic $^1O_2$ with electron-rich heteroaromatic systems,[122] it seemed reasonable to question the fate of a presumed imidazole endoperoxide in aprotic media. Recognizing that any Diels–Alder-like process involving $^1O_2$ places two oxygen atoms in a 1,6-relationship, and given the two nitrogen atoms present in imidazole, arrow pushing suggested that an acylimine **225**, the immediate procursor to an amino acid bis(amide) **223**, might be the logical outcome. Gratifyingly, nature posed few obstacles to the execution of this analysis, and after having arrived at the essential 1,2,4-trisubstitution pattern in **224**[123,124] high yields (≥90%) of adducts **225** could be isolated.[120]



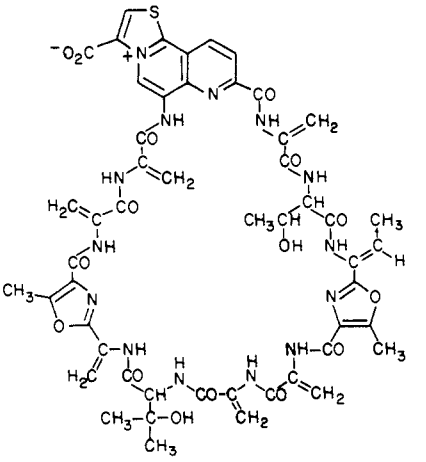
Although $NaBH_4$ reductions of **225** were usually quantitative, racemic materials obviously result. Chiral, nonracemic amino acid derivatives could be prepared via base-catalyzed isomerization to the dehydro bis(amides) **226**, which nicely hydrogenate at room temperature in the presence of premixed Rh(NBD)Cl dimer (0.05 equiv)/(*R*,*R*)-DIPAMP (0.025 equiv) to afford excellent ee's of products.[120] More recently, the oxidation level of **225** has permitted the introduction of carbon appendages thereby giving rise to α-alkylated amino acids **227** in protected form (Scheme IX).[125] These latter substances are known to be important constitutents of enzyme inhibitors. Ultimately, it is our goal to extend this methodology to a synthesis of the cyclopeptide alkaloids[123] through the agency of para-, or more likely, metaimidazolophanes.

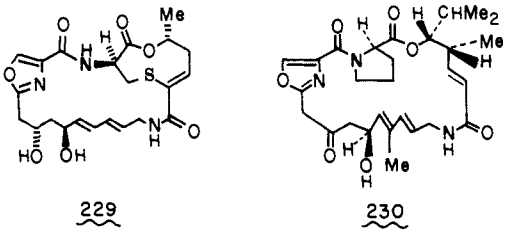




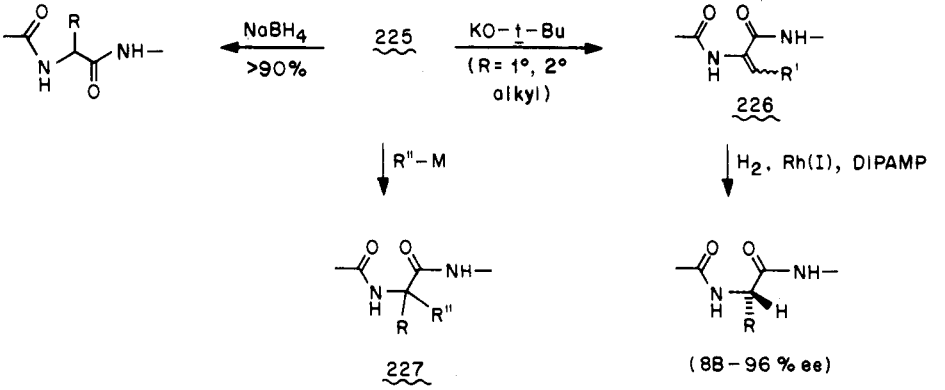
2. Oxazoles

Natural products related chemistry featuring use of the oxazole ring has advanced considerably in the recent past. Nature continues to occasionally incorporate this nucleus into some architectually fascinating specimens, as with the antibiotics berninamycin A, **228**,[126] griseoviridin, **229**,[127] and virginiamycin M_2, **230**.[128] Even far simpler substitution patterns (e.g., 5-butyloxazole) have been noted for their distinctive aroma properties.[129]

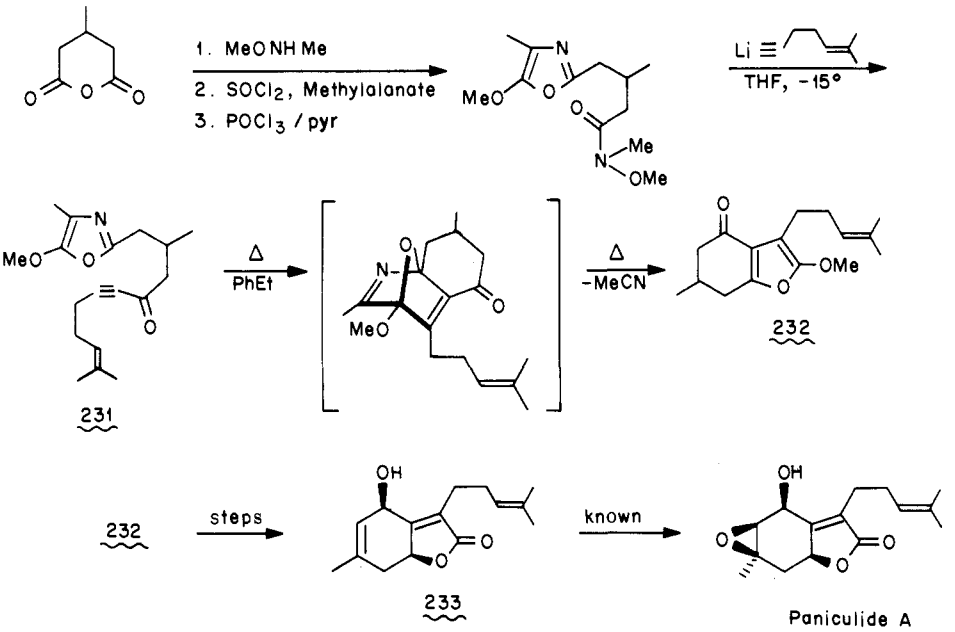




SCHEME IX

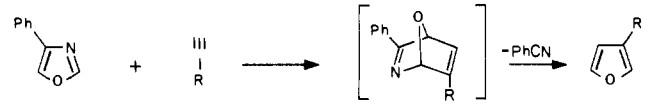


SCHEME X



Much of the enthusiasm for oxazole chemistry is masterfully portrayed in reviews by Turchi,[130] which accent both the syntheses and reactions of this heterocycle.

Many uses of oxazoles stem from the facile and usually efficient Diels–Alder additions which can be effected under relatively mild conditions. Thus, in addition to the in-depth studies by Wasserman and coworkers which concentrate on the functionalization[131] and subsequent singlet oxygenations–rearrangements of trisubstituted systems (which form the basis of a separate review in this issue), most approaches to natural products involve carbon–carbon multiple bonds as dienophiles. Liotta has shown that 3-substituted furans can be realized, usually in very good yields, in one step using acetylenes and 4-phenyloxazole.[132]

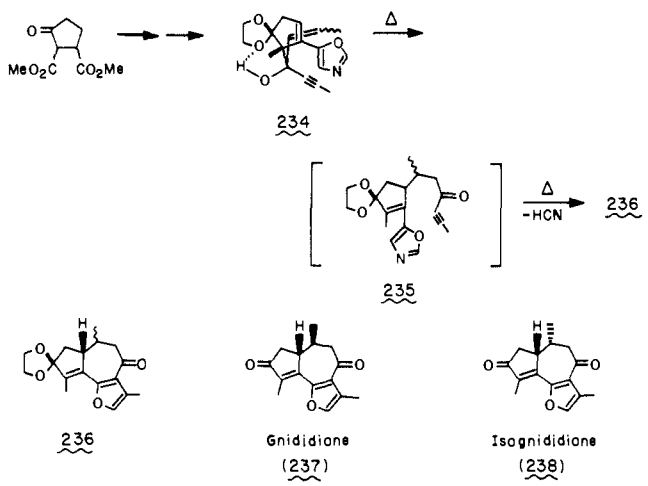


Jacobi et al., have utilized the intramolecular variation with terrific success in their conquests of several furanosesquiterpenes (Scheme X).[133] Beginning with 3-methylglutaric anhydride, acetylenic ketone oxazole **231** was constructed, thermolysis of which at 136 °C for 11 h yielded **232** to the extent of 94%, representing a 61% overall yield. The newly generated alkoxyfuran **232** can be readily converted to butenolide **233**, and ultimately to (±)-paniculide A.[133a]

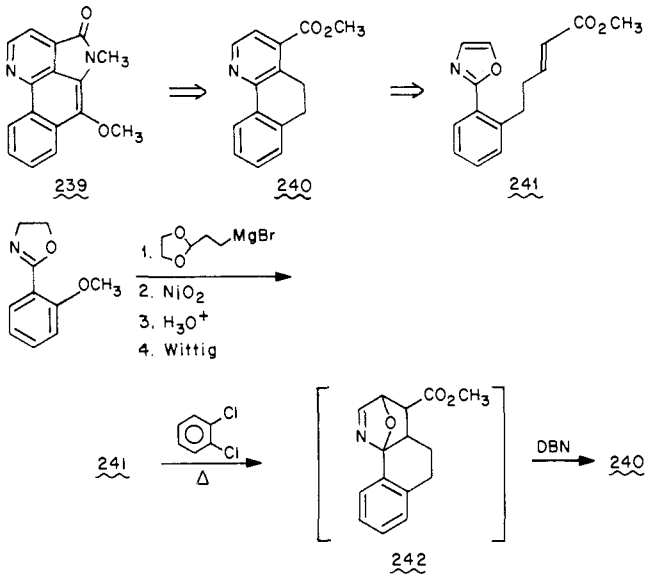
The promise of this approach was further manifested by the same group en route to petasalbine and ligularone,[133b] as well as gnididione and isognididione.[133c]

Gnididione is a plant-based tumor inhibitor isolated by Kupchan from *Gnidia latifolia*, and is the first known example of a furan-containing guiane sesquiterpene. Their concept of "bis heteroannulation"[134] was applied to this series wherein Cope rearrangement of **234** at 110 °C in mesitylene led to acetylenic oxazole **235**, isolable if desired in 87% yield. At ca. 160 °C, however, **235** was converted directly with loss of HCN to **236**, the hydrolysis of which afforded **237** and **238**. Such a tandem (oxy-Cope)–(Diels–Alder)–(retro-Diels–Alder) sequence is the first of its kind, the culmination of which firmly established the structure of gnididione as that in **237**.

Oxazole–olefin cycloadducts[135a] have been known since 1957 to decompose to substituted pyridines.[135b] Evaluation of an intramolecular version of this scheme

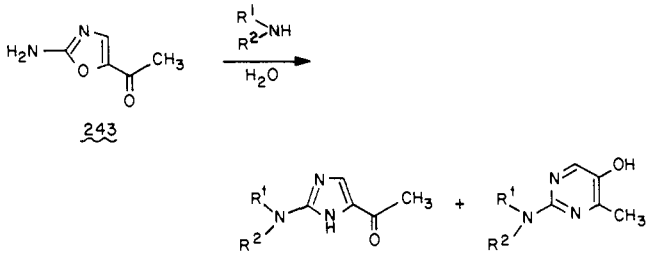


toward the azaphenanthrene alkaloid eupolauramine **239** rested on the thermal cyclization of **241** to **240** in 76% yield. The presence of DBN (0.75 equiv) was



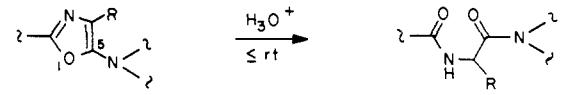
critical in controlling the destiny of the initial adduct **242**, perhaps the amidine acting to prevent acid-catalyzed decomposition. Subsequent handling of **240**, for which two routes were developed, led to eupolauramine.[136]

Rearrangements of variously configured oxazoles have also been of interest of late. Padwa has looked at, e.g., thermal [3,3]-sigmatropic shifts of 2-allyloxy-4,5-disubstituted oxazoles, as well as their photochemically induced reorganizations.[137] A Pfizer group, by virtue of an interest in histamine and histidine pharmacology, has devised a route to 1*H*-5-acetyl-2-aminoimidazoles starting with 5-acetyl-2-aminooxazoles. The procedure calls for refluxing a mixture of **243** in H_2O containing

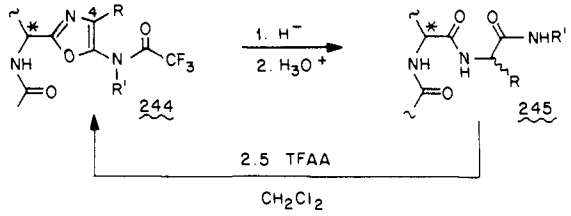


excess primary or secondary amine. Although yields are moderate (32–62%) the procedure is straightforward, with the byproduct being the corresponding 5-hydroxy-4-methyl-2-substituted aminopyrimidines.[138]

Concurrent with our ongoing efforts in imidazole chemistry (vide supra),[120,123,124] we have developed the use of appropriately substituted oxazoles as masked dipeptide equivalents. Literature reports had shown that placement of a free amino residue at the 5-position on the ring imparts ketene acetal-like behavior, and hence upon exposure to dilute H_3O^+ at subambient temperatures the amino acid bis(amide) is formed.[139]

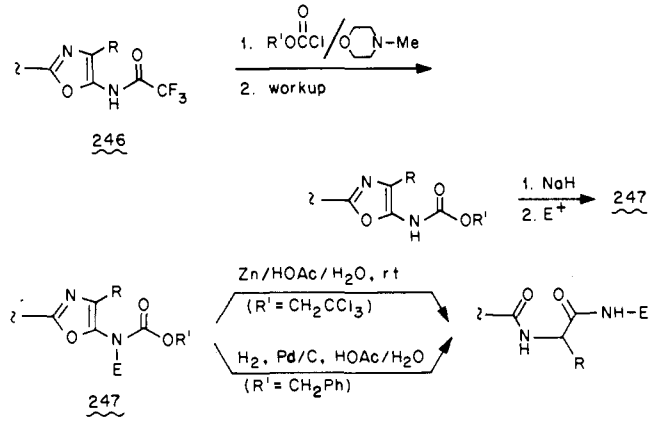


Based on this pioneering work of Fleury, which also demonstrated that 5-aminooxazoles could be formed from bis(amides) in neat trifluoroacetic anhydride (TFAA),[139] we have examined this oxazole/amino acid equivalence with respect to masked dipeptides.[140] That is, a mixture of diastereomeric dipeptides **245** can be



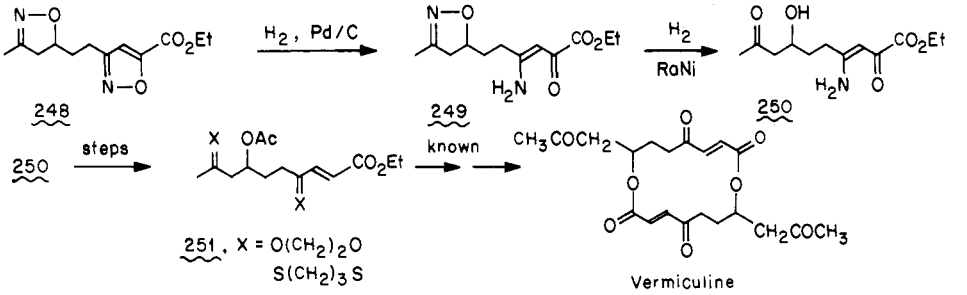
cyclized using controlled quantities of TFAA in CH_2Cl_2 to afford optically pure, protected 5-aminooxazole derivatives **244**. Although hydride removal of the acyl moiety as well as ring opening do not induce racemization, the resultant dipeptides containing the newly formed chiral centers (originally C-4 of the oxazoles) unfortunately show little more than "chicken soup"[142a] de's.[142b]

More importantly for cyclopeptide alkaloid total synthesis, it is necessary for the amide nitrogen to undergo ready alkylation, clearly representing, in one retrosynthetic sense (see below), the key macrocycle-forming step. Surprisingly, trifluoroacetamides of this

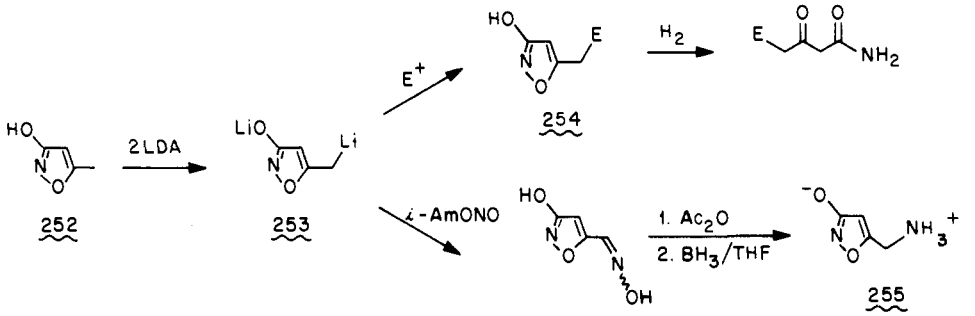


type (i.e., **246**) are essentially inert to alkylating agents (e.g., MeI) in the presence of NaH or KH.[140] Hence, an exchange process was developed which permits, in one operation and in high yields (>80%), the conversion of trifluoroacetamides to various other amides or urethanes, which may then be alkylated efficiently.[140] Both the benzyloxycarbonyl- and the β,β,β-trichloroethoxycarbonyl-derivatives **247** are attractive intermediates,

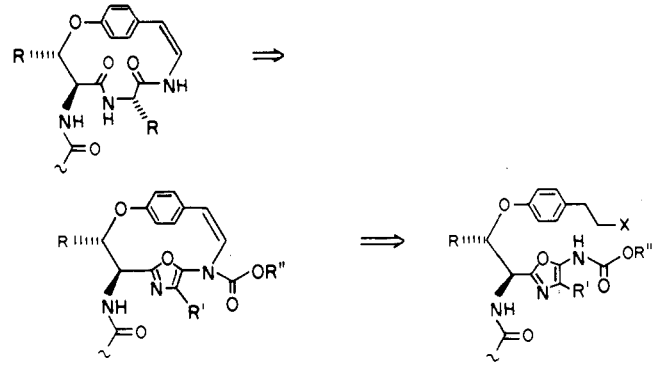
SCHEME XI



SCHEME XII



as each is ultimately amenable to selective deprotection to the free amine with concommitant oxazole unraveling under very mild conditions.[141] The successful gathering of these results and others has provided the impetus for further studies which address the critical issue of cyclophane formation from heterocyclophane seco oxazoles.

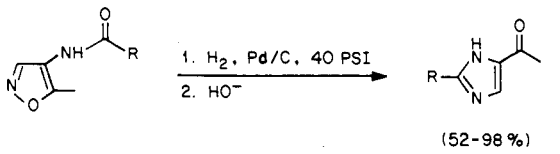


3. Isoxazoles

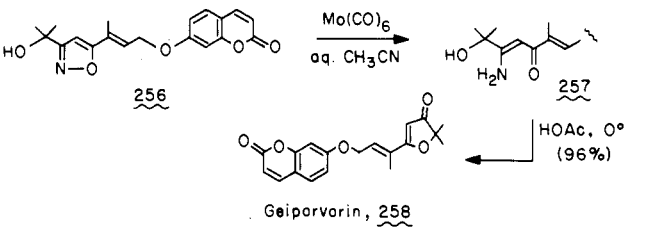
Essentially all of the recent uses of isoxazoles in synthesis stem from the facility with which N–O bond cleavage (i.e., reduction) can be effected. Many rely on catalytic hydrogenation to unmask the vinylogous amide moiety. Thus, reductive scission of isoxazole **248** to **249** takes place rapidly in the presence of 10% Pd/C, with uptake of only 1 equiv of hydrogen.[143] To effect N–O cleavage of the nonaromatic isoxazoline ring, Raney nickel in MeOH containing HOAc was called for, thereby giving **250**. A subsequent series of steps led to **251**, known precursors of vermiculine (Scheme XI).

The dianion of 3-hydroxy-5-methylisoxazole (**253**), formed from **252** with 2 equiv LDA in THF at −10 °C, readily reacts with electrophiles to afford products **254** (Scheme XII). Hydrogenation with Pd/C or PtO_2 catalyst gives excellent yields of β-keto amides. Dianion **253** also serves as the point of departure for a short synthesis of muscimol, **255**, found in *Amanita muscaria*. This interesting zwitterionic isoxazole is a GABA agonist, as well as the agent responsible for this mushroom's hallucinogenic effects.[144]

An appealing conversion of 4-aminoisoxazoles to acylimidazoles likewise passes through an initial hydrogenation in EtOH over ca. 1 h.[145] Exposure of the filtered solution containing the crude product to NaOH at reflux (1 h) followed by cooling and addition of solid NH_4Cl affords the imidazoles in good to excellent yields.

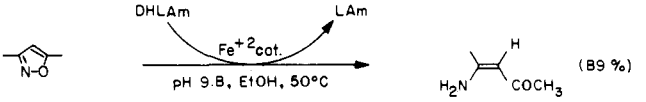


Reductive procedures other than catalytic hydrogenation have also appeared quite recently, in some cases owing to the obvious limitations imposed by schemes which include hydrogenation. For example,

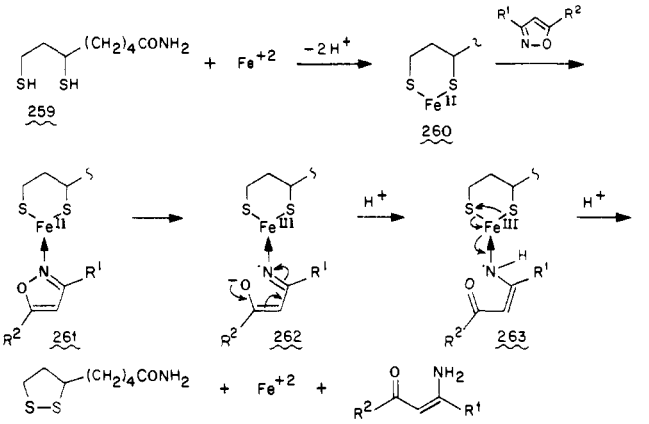


an Italian group[146] has found that isoxazole **256**, clearly not amenable to hydrogenation due to the trisubstituted olefin present, could be quantitatively cleaved to **257** using Nitta's method ($Mo(CO)_6$ in moist CH_3CN).[147] Cyclodehydration completed the synthesis of the antitumor agent geiparvarin **258**.[146]

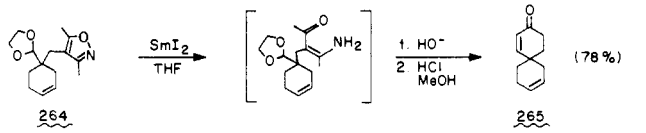
The redox reaction involving lipoamide (LAm), a coenzyme which assists acyl transfer in vivo, and dihydrolipoamide (DHLAm, **259**) has found useful extension to organic synthesis.[148] The combination of



DHLAm with an Fe(II) salt ($Fe(NH_4)_2(SO_4)_2$) is very effective at isoxazole ring scission under conditions which hold promise for future use in the presence of other functionality. Mechanistically, this process is proposed to proceed via initial complexation of the isoxazole nitrogen to **260** giving **261**. Such a hypothesis

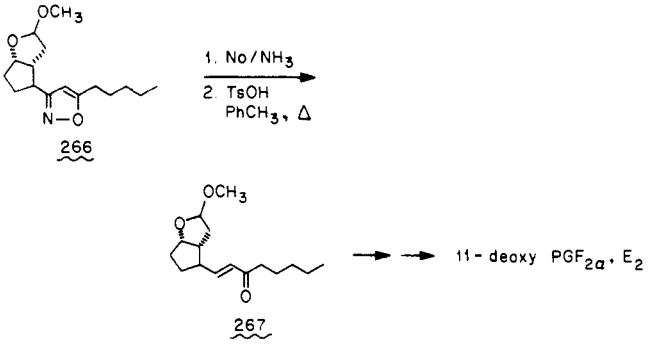


is reasonable, being similar to that proposed in isoxazole reductions with $Mo(CO)_6$ (vide supra),[147] and is also most likely involved with isoxazole reductions via samarium iodide (e.g., see the conversion of **264** to **265**).[149]



One-electron reduction by DHLAm–Fe(II) would give **262**, and thence **263** by tautomerization. Another one-electron reduction of **263** by DHLAm–Fe(II) gives the enone, LAm, and Fe(II) ion.

The ω-chain of 11-deoxyprostaglandins has been constructed via a 3,5-disubstituted isoxazole intermediate, **266**, the heteroaromatic ring of which was formed by way of a cycloaddition of an in situ generated nitrile oxide with 1-heptyne (70%). Metal/ammonia reduction (3 equiv) followed by acid treatment of the crude β-amino ketone (to effect loss of ammonia) gave **267** in 66% overall yield.[150]



III. Concluding Remarks

The five-membered heterocycles discussed herein were chosen as a representative sampling of the many heteroaromatic ring systems which have been used in synthetic situations. By concentrating on a select, yet commonly employed subgroup, this opus strives to manifest through literature examples the abundance of valuable albeit latent functionality innate to these deceivingly simple molecules. Based on these contributions, it would seem appropriate to pronounce the state of "heteroaromatics in synthesis" to be one of excellent health. Future synthetic applications of both existing and newly evolving reactions within this domain may well be limited only by the extent to which one has developed an appreciation for, and recognizes the potential of, heterocyclic chemistry.

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