Aromatic heterocycles as intermediates in natural product synthesis

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Reviewing the literature published up to the end of 1993

1 Introduction

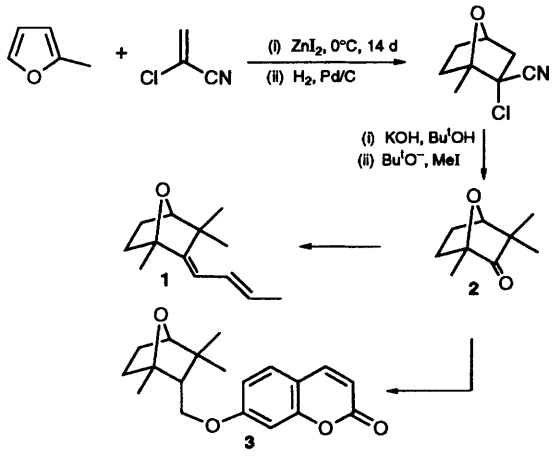
Few practitioners in organic chemistry would dispute the important role played by aromatic heterocycles in many areas of chemistry and biology. A number of essential processes for sustaining life rely upon systems derived in part from simple heteroaromatic compounds, *e.g.* the pyrrole-based porphyrins. Furthermore, many biologically active natural products and pharmaceuticals contain simple heteroaromatic residues as key components of their molecular frameworks. In the area of organic chemistry, aromatic heterocycles have emerged as extremely useful intermediates in synthesis. The aim of this article is to review the most recent advances and innovations in this area with particular reference to natural product synthesis. Readers are directed towards an excellent monograph by Meyers and several review articles for earlier accounts of work in this area.[1] The format of this article parallels that used by Lipshutz in his notable contribution to this field,[1(c)] but contains some additional new sections to reflect recent developments. This review surveys selected heteroaromatic ring systems and covers the literature up to the end of 1993. It should be noted that the synthesis of biologically active targets containing intact aromatic heterocycles are not covered in this review. Chemical applications in which no part of the heterocycle is incorporated in the reaction product are also excluded. As previous authors undertaking this task have noted, the literature of organic chemistry is not well suited for this particular type of endeavour and I apologize to all those researchers whose contributions have been inadvertently overlooked.

2 Furans

Of all the aromatic heterocycles, furan undoubtedly remains the most valuable and versatile intermediate for organic synthesis. In addition to its widespread use as a Diels–Alder diene and as a masked 1,4-dicarbonyl equivalent, many other interesting applications of furans in synthesis have been described.

2.1 Intermolecular Diels–Alder reactions

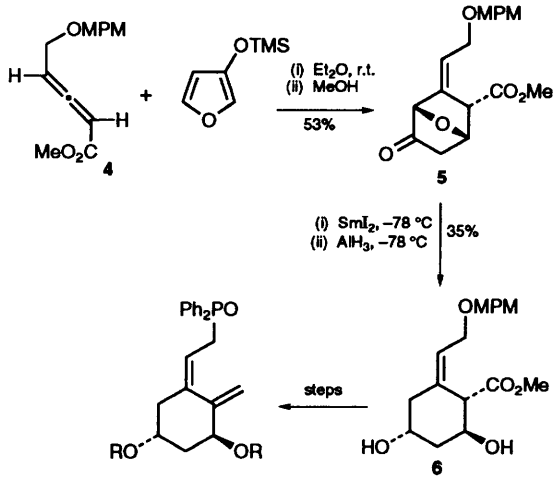
Furans have frequently been used as the diene component in Diels–Alder reactions providing entry into functionalized 7-oxabicyclo[2.2.1]hept-5-enyl systems. This ring system is contained within the skeleton of 2,5-epoxy-6(*E*),8(*E*)-megastigmadiene **1** and 3′,6′-epoxycycloaurapten **3** and a Diels–Alder approach to these compounds has recently been described.[2,3] Treatment of 2-methylfuran with 2-chloroacrylonitrile in the presence of zinc iodide facilitated the desired cycloaddition reaction (**Scheme 1**). These reaction conditions circumvented the problems normally associated with this particular diene, which shows a propensity to undergo competitive aromatic substitution reactions with



Scheme 1

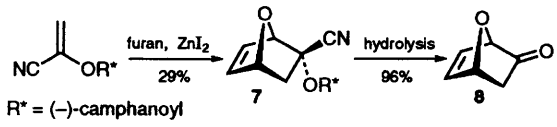
dienophiles. Removal of the double bond from the cycloadduct by hydrogenation and subsequent base-catalysed hydrolysis facilitated separation of the desired ketone from small quantities of the regioisomeric product. Dialkylation of this material provided **2** in 51% overall yield from 2-methylfuran which was subsequently taken onto both 3′,6′-epoxycycloaurapten (**3**) and 2,5-epoxy-6(*E*),8(*E*)-megastigmadiene (**1**).

Most synthetic applications of Diels–Alder derived 7-oxabicyclo[2.2.1]hept-5-enes stem from the ability of such systems to be ring-opened to highly functionalized cyclohexane derivatives.[4] For example, a furan-based Diels–Alder reaction using an allenic ester as the dienophile component has been used in an approach to the A-ring of 1α-hydroxyvitamin D (**Scheme 2**).[5] Treatment of 3-trimethylsilyloxyfuran with ester **4** at room temperature provided bicycle **5** in 53% yield after methanolic work-up. Reductive ring-opening of the oxygen bridge was accomplished with samarium(II) iodide; further stereocontrolled reduction of the ketone grouping with aluminium hydride provided cyclohexane **6** with the correct *trans* configuration of the hydroxyl groups. Synthetic manipulations of this material completed the synthesis of the A-ring fragment of 1α-hydroxyvitamin D.



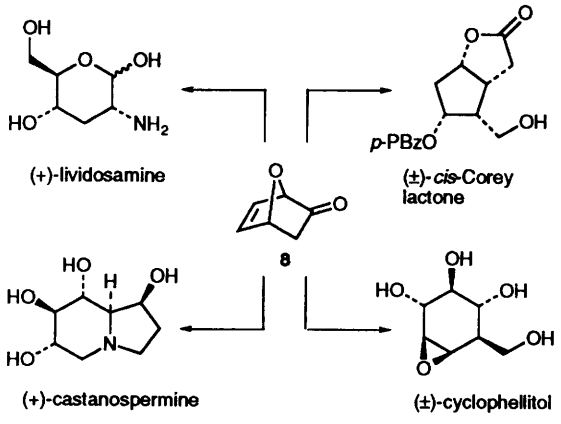
Scheme 2

Vogel and co-workers have described two routes to enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-one **8** from furan using Diels–Alder chemistry. The first approach employed a homochiral dienophile which provided bicycle **7** in enantiomerically pure form after repeated recrystallization. This material was converted into **8** by saponification and subsequent treatment with aqueous formaldehyde (**Scheme 3**).[6] Alternatively, this material can be prepared by resolution with brucine of the intermediate cyanohydrin produced by reaction of furan with achiral dienophile α-acetoxyacrylonitrile.[7] A catalytic asymmetric route to this building block has recently been described which employs a chiral Lewis acid mediated Diels–Alder reaction of furan with 2-bromoacrolein as the key step.[8]



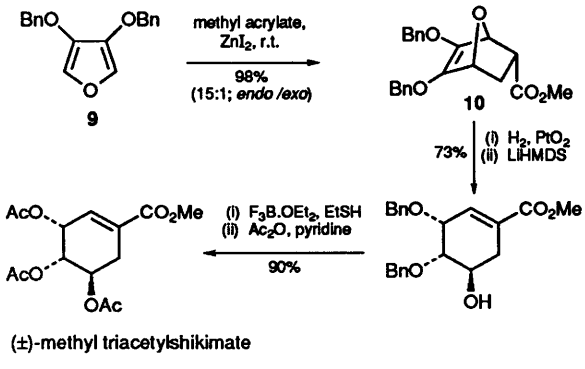
Scheme 3

Both racemic and enantiomerically pure oxabicyclo[2.2.1]hept-5-en-2-one **8** have been used for the synthesis of a diverse array of polyoxygenated systems.[9] Recent applications of this methodology include the synthesis of (+)-lividosamine,[10] (+)-castanospermine,[11] (±)-cyclophellitol[12] and potential prostaglandin precursor, all *cis* Corey lactone (**Scheme 4**).[13] Numerous other rare D- and L-sugars, *C*-nucleosides, conduritols, *C*-linked disaccharides, azasugars, and indolizidines have been prepared using this building block.[9,14] Other pseudo sugar derivatives and carbocyclic *C*-nucleosides have been synthesized using furan based Diels–Alder protocols.[15,9(c)]



Scheme 4

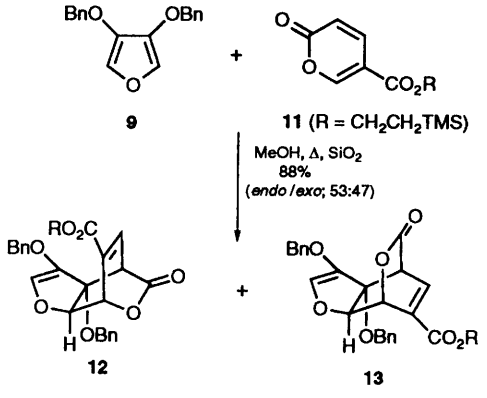
A short, efficient synthesis of (±)-methyl triacetylshikimate employed 3,4-dibenzyloxyfuran as a diene component in the key [4 + 2] cycloaddition reaction (**Scheme 5**).[16,17] The Diels–Alder reaction of **9** with excess methyl acrylate using a catalytic amount of zinc iodide proceeded smoothly furnishing oxabicycle **10** in 98% yield largely as the *endo* isomer. Catalytic hydrogenation of this isomer occurred in a stereospecific fashion from the least-hindered, *exo* face



Scheme 5

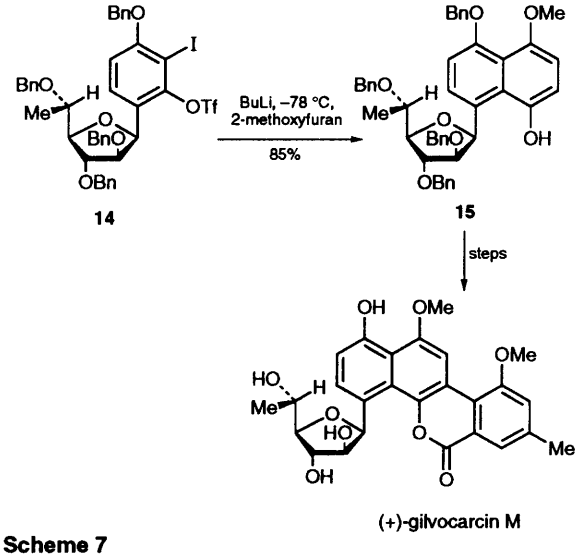
of the bicycle. Subsequent ring-opening of the ether bridge, removal of the benzyl groups, and purification of the resulting triol as the triacetate afforded (±)-methyl triacetylshikimate in 60% overall yield from 3,4-dibenzyloxyfuran.

Interestingly, 3-4-dibenzyloxyfuran has also been used as the *dienophile component* in a mild thermally-induced inverse electron demand cycloaddition.[18,19] Treatment of this furan with 2-(trimethylsilyl)ethyl coumalate **11** afforded the separable *endo* and *exo* cycloadducts **12** and **13** respectively in 88% yield (**Scheme 6**). The major *endo* adduct has been taken onto a fully functionalized southern hemisphere fragment of ivermectin.



Scheme 6

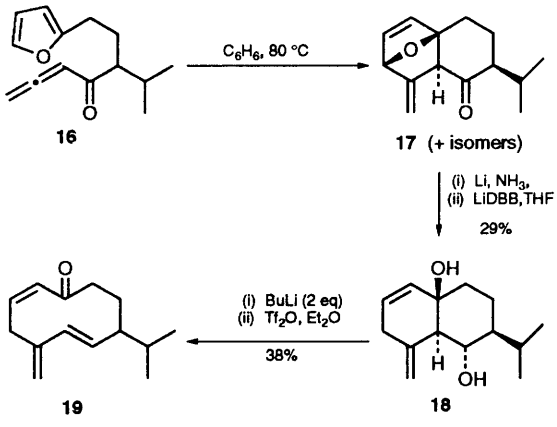
The cycloaddition of 2-methoxyfuran with a benzyne has been used to construct the antibiotic gilvocarcin M (**Scheme 7**).[20] Thus, treatment of aryl triflate **14** with butyl-lithium in the presence of this furan gave naphthalene **15** in 85% yield along with a small amount of the regioisomeric compound.[21] Sequential benzyne formation, [4 + 2] cycloaddition with the furan, and aromatization of the primary cycloadduct account for the formation of the desired naphthalene product. A number of other synthetic endeavours have used intermolecular furan Diels–Alder reactions as part of the overall strategy.[22]



Scheme 7

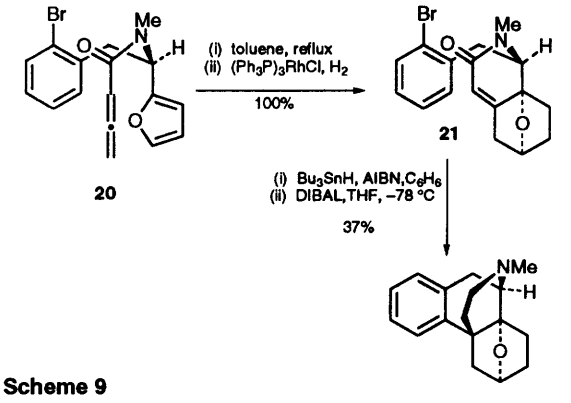
2.2 Intramolecular Diels–Alder reactions

The intramolecular furan Diels–Alder reaction (IMDAF) provides entry into a variety of functionalized ring systems and has been studied quite extensively. A formal total synthesis of periplanone has been described using an IMDAF-Grob fragmentation strategy (**Scheme 8**).[23] The electron-deficient double bond of allenic ketone **16** underwent reaction with the diene portion of the furan providing **17** along with a similar quantity of the other *exo* cycloadduct which possesses the opposite configuration at the isopropyl centre. Partial conversion of this material into more stable **17** could be accomplished by equilibration under thermodynamic conditions (mesitylene, 164°C, 24 h). Reduction of **17** to diol **18** and Grob fragmentation of the triflate derived from this material gave the ten-membered ketone **19**, which has been used previously for the synthesis of periplanone.



Scheme 8

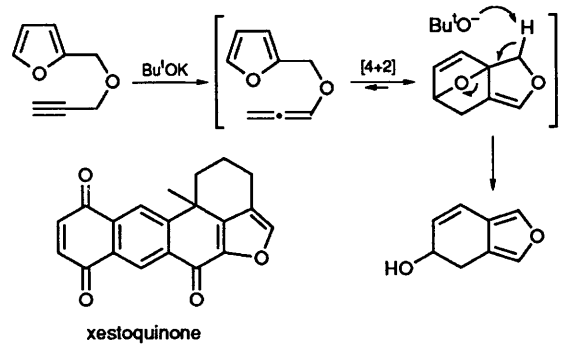
A tandem intramolecular furan Diels–Alder/radical-cyclization protocol has been described for the construction of the morphinan skeleton (**Scheme 9**).[24] Thermally-induced cyclization across the terminal double bond of allenic amide **20** and subsequent reduction of the double bond gave cycloadduct **21** in quantitative yield as a single stereoisomer. Construction of the morphinan ring system was completed by tin hydride induced radical cyclization and further reduction of the resulting amide carbonyl group using diisobutylaluminium hydride. The low



Scheme 9

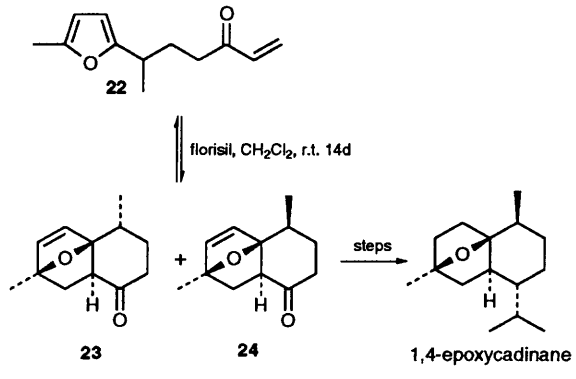
yield obtained in the final ring-forming reaction stems from the fact that the radical cyclization proceeds through the 8-*endo* as well as the desired 7-*exo* manifold.

An intermediate in the formal total synthesis of xestoquinone has been prepared using a furan ring transfer-reaction (**Scheme 10**).[25] This chemistry involves the intramolecular Diels–Alder reaction of furan with the terminal double bond of an allene generated *in situ* by isomerization of the corresponding acetylene. Under the reaction conditions, the resulting cycloadduct undergoes ring-opening, producing a new furan product. This methodology has also been applied to the synthesis of euryfuran.[26] An asymmetric variant of this reaction has been described.[27]



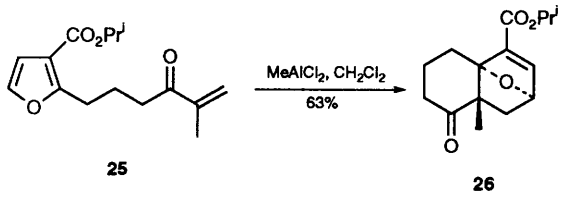
Scheme 10

Rogers and Keay have reported a route to 1,4-epoxycadinane based upon an IMDAF reaction (**Scheme 11**).[28] Cyclization of methacrolein **22** in dichloromethane in the presence of florisil produced adducts **23** and **24** (13:85 ratio). This reaction is under thermodynamic control and favours the formation of the adduct possessing the equatorial methyl substituent. Further investigations examining how other side-chain substituents effect the diastereoselectivity of these reactions were examined. A straightforward sequence of reactions was used to convert **24** into 1,4-epoxycadinane.



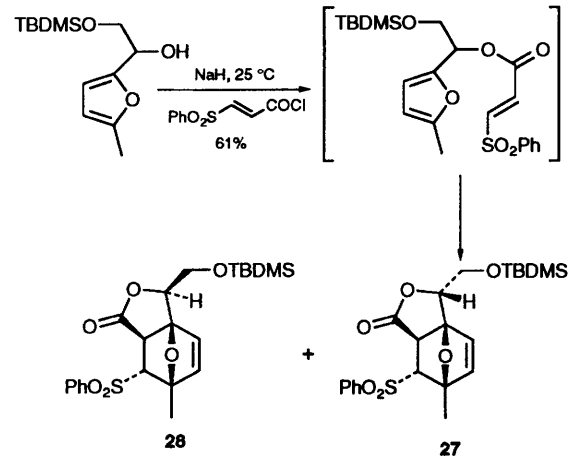
Scheme 11

It has recently been shown that an IMDAF reaction can be induced in a system in which both reaction components contain an electron-withdrawing substituent. Thus, treatment of **25** with methylaluminium dichloride provides **26**, a projected intermediate for the synthesis of the *trans*-clerodane diterpenoid avarol (**Scheme 12**).[29]



Scheme 12

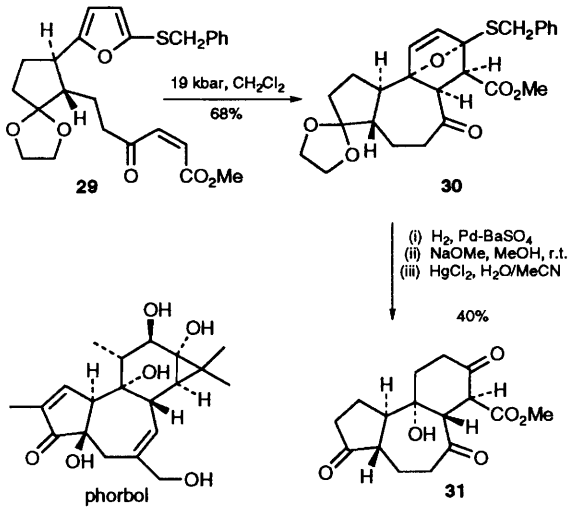
An IMDAF reaction employing a (*E*)-2-phenylsulfonyl acrylate as the dienophile component has been described (**Scheme 13**).[30] The high reactivity of this component facilitates rapid cycloaddition at room temperature, providing cycloadducts **27** and **28** in a 2:3 ratio. Unfortunately, the utilization of these products in synthesis of the bottom half of the avermectins has been unsuccessful to date, because of problems encountered in the subsequent reductive ring-opening reactions of these bridged systems.



Scheme 13

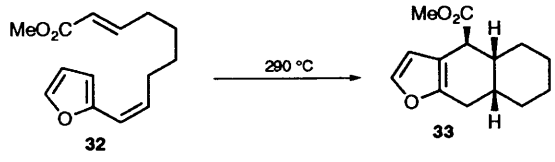
High pressure has proven useful in facilitating a number of IMDAF reactions.[31] For example, while furan **29** shows no tendency to undergo cycloaddition at ambient pressure, subjection of this material in dichloromethane to 19 kbar pressure results in stereospecific conversion into cycloadduct **30** (**Scheme 14**).[32] Reduction of the double bond, base-catalysed epimerization to the *trans* ring junction followed by hydrolytic ring-opening of the oxygen bridge provided **31**, a potential intermediate for the synthesis of phorbol.

A number of studies on the intramolecular Diels–Alder reactions of vinylfurans have been described in the literature.[33,34] Knight and co-workers have recently reported approaches to naturally occurring sesquiterpenes of the furanoeremophilane group using this chemistry (**Scheme 15**).[34] Thus, thermolysis of **32** provided furan **33** in near quantitative yield via cycloaddition and subsequent isomerization of the initially formed exocyclic double



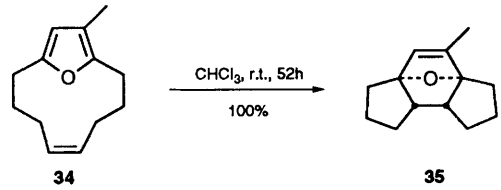
Scheme 14

bond. This reaction is highly stereoselective leading to the formation of the *cis*-fused product along with a trace (*ca.* 5%) of the *trans*-fused adduct. (*Z*)-Alkenoates were found to undergo isomerization prior to cyclization leading to mixtures of stereoisomers, and more functionalized systems often underwent competitive side-reactions limiting the synthetic scope of this methodology.



Scheme 15

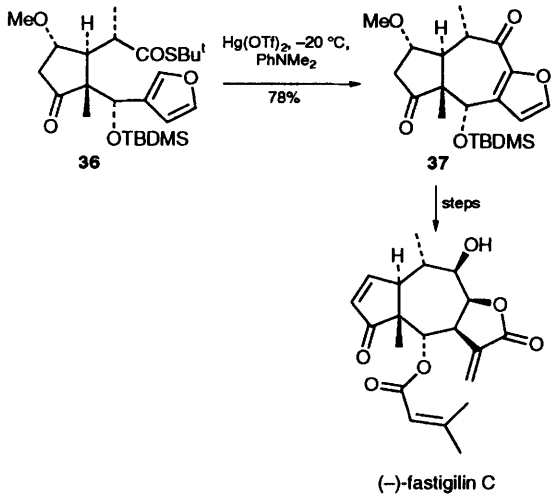
In work directed towards the synthesis of marine natural products possessing 12- and 14-membered 2,5-furanocyclic structures, Marshall and Wang observed transannular Diels–Alder reactions involving furan macrocycles.[35] For example, **34** undergoes quantitative stereospecific conversion into tetracycle **35** on standing at room temperature in chloroform solution (**Scheme 16**). The propensity of the normally unreactive furan and isolated double bond to participate in this type of Diels–Alder reaction was rationalized in terms of the strain energy associated with starting furan macrocycle **34**. Further synthetic applications of IMDAF reactions include the preparation of biflorin and several manosonones using benzynes as the dienophilic components;[36] other workers have described routes to various gibberellins using IMDAF reactions.[37]



Scheme 16

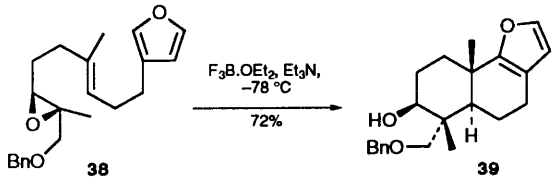
2.3 Other carbon–carbon bond-forming reactions

Tanis and co-workers have devised several protocols for the construction of natural products based upon the nucleophilic character of the furan ring system. For example, intramolecular acylation of furan **36** onto an appended t-butylthioester grouping, in the presence of mercuric(II) triflate-*N*,*N*-dimethylaniline, gave bicyclo[5.3.0]decane **37** in 78% yield. Further synthetic manipulations of this material led onto (−)-fastigilin C (**Scheme 17**).[38] A similar acylation-type cyclization reaction devised by this group has resulted in the completion of a formal total synthesis of (±)-perhydrohistrionicotoxin.[39]



Scheme 17

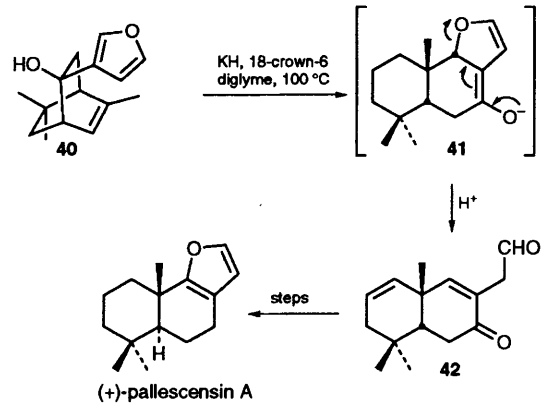
A related furan-terminated–epoxide-initiated cationic cyclization reaction has been used for a formal total synthesis of (+)-aphidicolin.[40] Lewis acid mediated cyclization of homochiral epoxide **38** furnished tricycle **39** in 72% yield (**Scheme 18**). Much experimentation was required to optimize this cyclization, which was found to be highly dependent on the exact nature of the alcohol protecting group and the Lewis acid employed.



Scheme 18

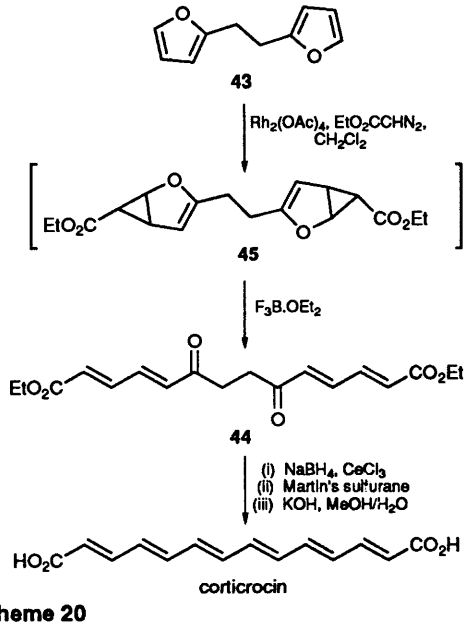
An anion-assisted oxy-Cope reaction involving a furan ring was used as the key step in the total synthesis of the furanosesquiterpene (+)-pallescensin A (**Scheme 19**).[41] Treatment of enantiomerically pure alcohol **40** with potassium hydride in diglyme at 100 °C facilitated the [3.3] sigmatropic rearrangement to **41** which underwent a subsequent retro-Michael reaction to *cis* decalin **42**. The unusually harsh reaction conditions required for this reaction were attributed, in part, to the necessity to disrupt the

aromaticity of the furan ring during this rearrangement. Annulation of the furan ring, manipulation of the decalin ring junction, and reduction of the ketone grouping completed the synthesis of the natural product.



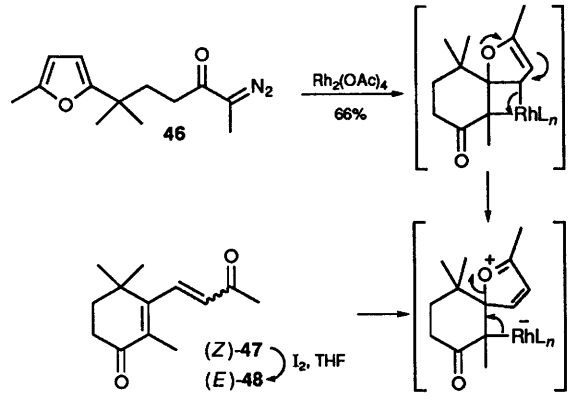
Scheme 19

Rhodium-catalysed cyclopropanations of one of the double bonds of substituted furans using diazoesters have been described.[42,43] Wenkert and co-workers have applied this chemistry to the synthesis of leukotrienes and corticrocin.[42] Reaction of difuran **43** with ethyl diazoacetate in the presence of rhodium(II) acetate and subsequent treatment with boron trifluoride etherate furnished polyene **44** in 60% yield, presumably via **45** (**Scheme 20**). Subsequent reduction, dehydration, and hydrolysis proceeded smoothly providing corticrocin in 57% yield from **44**.



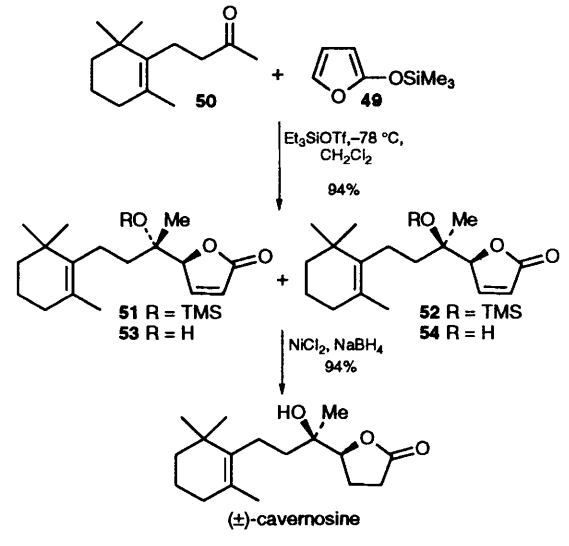
Scheme 20

Intramolecular variants of this cyclopropanation/ring-opening process have been reported.[43] Efficient syntheses of several β-ionone terpenes have been described using this chemistry.[43(d)] Diazoester **46** in the presence of rhodium(II) acetate directly produced (*Z*)-**47** which was subsequently isomerized to the *trans* isomer **48** using iodine (**Scheme 21**). A mechanistic rationale for this transformation has been proposed.



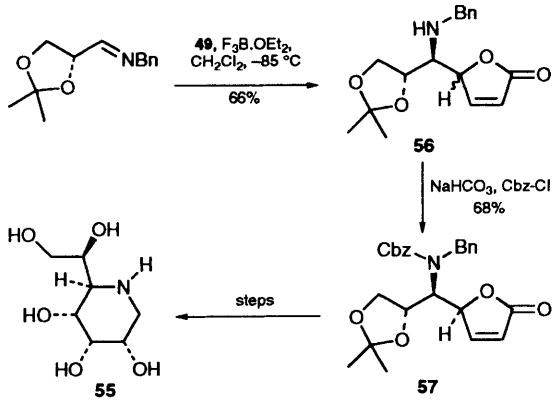
Scheme 21

2-Trimethylsilyloxyfuran (TMSOF) **49** has been shown to undergo nucleophilic addition to aldehydes in the presence of catalytic amounts of Lewis acids or fluoride ion yielding the corresponding δ-hydroxy-α,β-unsaturated-γ-lactones.[44] Lewis acids such as $F_3B.OEt_2$, $SnCl_4$, or Et_3SiOTf catalyse condensation to give mainly the *threo* diastereomer, while TBAF favours formation of the *erythro* isomer. Reaction of TMSOF with dihydro-β-ionone **50** was used in the synthesis of ichthyotoxic γ-lactone cavernosine (**Scheme 22**).[45] The desired *erythro* stereoisomer could not be produced directly in this instance using fluoride ion because this methyl ketone proved to be inert to these reaction conditions. However, condensation in the presence of triethylsilyl triflate yielded trimethylsilyl ethers **51** and **52** in 94% yield in favour of the *threo* adduct (80:20). Equilibration of this mixture (TBAF, −78 to −10°C) followed by acidic work-up provided alcohols **53** and **54** in which the *erythro* diastereomer was dominant (33:67). Separation of the isomers by chromatography followed by chemoselective reduction of **54** yielded racemic cavernosine.



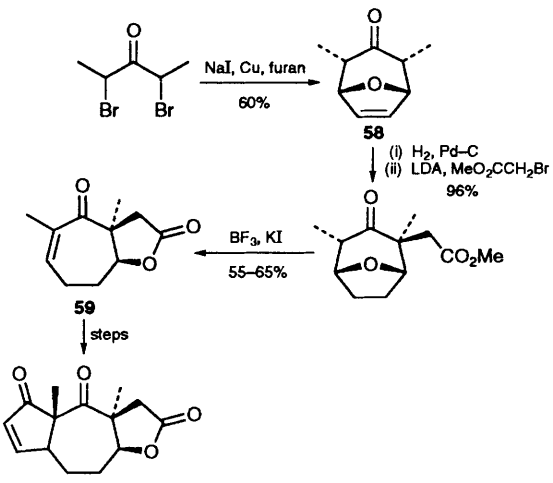
Scheme 22

Recent studies have revealed that 2-trimethylsilyloxyfuran will undergo nucleophilic addition to *N*-benzylimines, providing the corresponding δ-amino-α,β-unsaturated-γ-lactones which have been converted into iminoalditols such as **55** (**Scheme 23**).[46] Condensation of 2,3-*O*-isopropylidine-D-glyceraldehyde-*N*-benzylimine with TMSOF in the presence of boron trifluoride etherate yielded butenolide **56** as a 1:1 mixture of epimers. Subsequent protection of the amino group with the benzyloxycarbonyl group provided the *N,N*-diprotected material **57** as a single diastereomer in 68% yield. It was proposed that this isomerization results from thermodynamic equilibration of the lactone mixture under the basic reaction conditions. Dihydroxylation of the double bond, reduction to the lactol, and a series of deprotection steps led onto azasugar **55**. A variety of higher monosaccharides have been prepared by 2-trimethylsilyloxyfuran addition to *aldehydo* sugars.[47]



Scheme 23

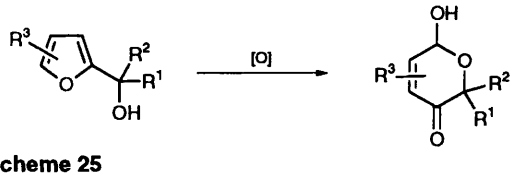
The diene portion of furan has been utilized in a number of [3 + 4] cycloadditions with oxyallyl species yielding oxabicyclo[3.2.1]oct-6-en-3-ones.[48] Such bicycles have proven useful in the synthesis of a number of polyfunctional subunits directed towards natural product synthesis.[4] A recent report describes the construction of the tricyclic skeleton of the pseudoguaianolides using such a [4 + 3] cycloaddition protocol (**Scheme 24**).[49] Generation of the oxyallyl species derived from 2,4-dibromopentan-3-one in the presence of furan produced bicycle **58** in 60% yield. Reduction of the double bond and alkylation with methyl bromoethanoate proceeded uneventfully. Lewis acid mediated opening of the oxygen bridge and subsequent lactonization provided **59**. A series of chemical manipulations to annulate on the final cyclopentenone led onto the tricyclic framework of the psuedoguaianolides. An obvious extension of this methodology has been the development of an intramolecular variant of this [4 + 3] cycloaddition reaction. Haramata, among others, has undertaken a series of studies to determine the synthetic potential of this chemistry.[50]



Scheme 24

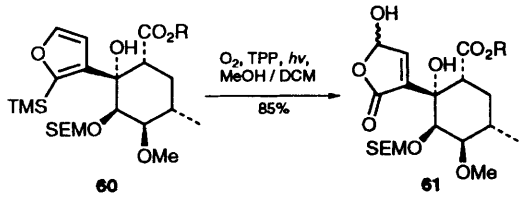
2.4 Oxidative ring cleavage reactions

Numerous oxidative methods exist for the conversion of furans into ring-opened products such as 1,4-dicarbonyl compounds and functionalized butenolides.[51] One of the most widely studied oxidative transformations of furans has been the conversion of furfuryl alcohols into the corresponding pyranones (**Scheme 25**). In 1993, two review articles on this particular transformation and its application in natural product synthesis appeared in the chemical literature.[52,53]



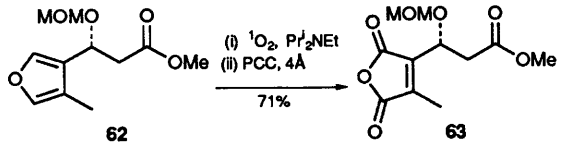
Scheme 25

Oxidative ring fission of simple furans into 1,4-dicarbonyl compounds can be facilitated by a variety of reagents.[54,55] A number of interesting products can be produced by the photo-oxidation of furans.[56] One of the most useful is the conversion of 2-trimethylsilyl-substituted furans into γ-hydroxybutenolides using singlet oxygen.[57] This transformation is performed under extremely mild reaction conditions and tolerates a wide range of functional groups. This utility of this process is well illustrated by the smooth conversion of 2-methylsilylfuran **60** into milbemycin fragment **61** (**Scheme 26**).[58] Many other examples of this transformation in natural product synthesis have been described.[59]



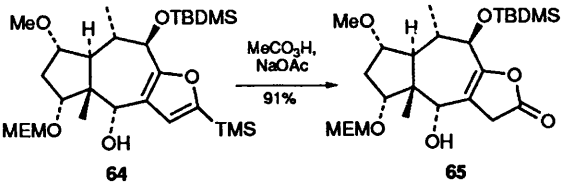
Scheme 26

Kernan and Faulkner have reported that 3-alkylfurans can be smoothly converted into 3-alkyl-4-hydroxybutenolides by treatment with singlet oxygen in the presence of a hindered base, thus circumventing the need to employ a trimethylsilyl-substituted furan.[60] This modification has been used by Isobe and co-workers to prepare the maleic anhydride portion of tautomycin (**Scheme 27**).[61,62] The key conversion of **62** into **63** involves oxidation of the 3,4-disubstituted furan with singlet oxygen followed by further oxidation of the resulting mixture of regioisomeric γ-hydroxybutenolides with PCC.



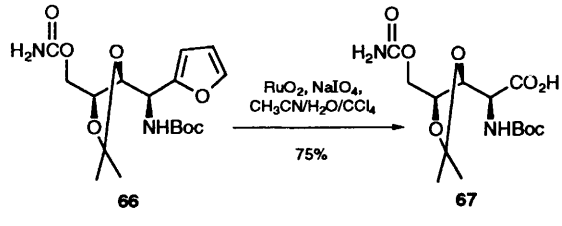
Scheme 27

2-Trimethylsilyl-substituted furans can be converted into the corresponding 3-butenolides upon oxidation with peracids.[63] An illustrative application of this chemistry is provided by the conversion of functionalized furan **64** into 3-butenolide **65**, an intermediate on route to (−)-fastigilin C (**Scheme 28**).[38] The corresponding 2-butenolides have been produced in this reaction by using acetic acid rather than chloroform as solvent.[64] An alternative oxidative procedure for the preparation of such 2-butenolides has recently been described.[65]



Scheme 28

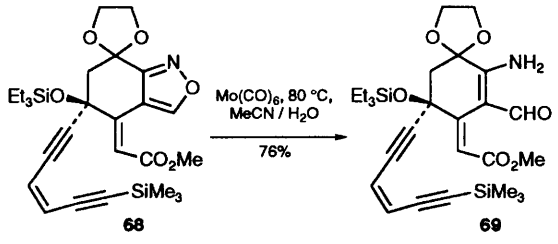
A commonly employed degradation of the furan ring to the corresponding carboxylic acid can be accomplished by treatment with ozone or ruthenium tetroxide. For example, ruthenium-based cleavage of furan **66** provides the corresponding α-amino acid **67**, which has been taken onto 5-*O*-carbamoylpolyoxamic acid (**Scheme 29**).[66] This application of furan as a protected form of the carboxyl group has been used widely in natural product synthesis.[67]



Scheme 29

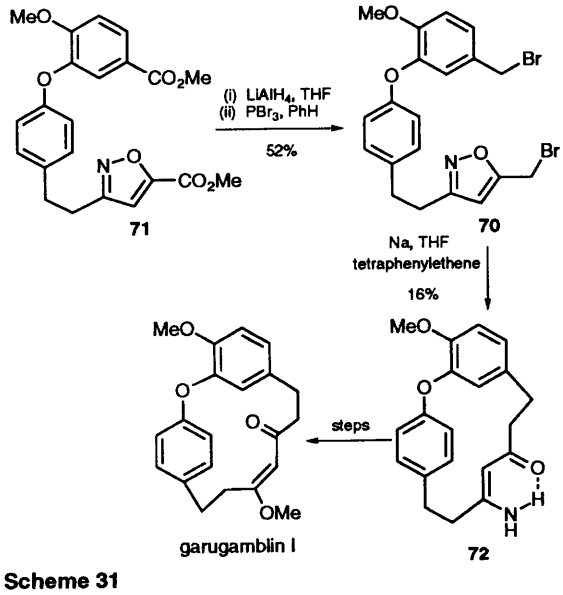
3 Isoxazoles and oxazoles

A comprehensive review detailing methods for the preparation of functionalized isoxazoles and their applications in natural product synthesis was published in 1987.[68,69] The most common use of the isoxazole ring system in organic synthesis remains its utilization as a stable masked form of the β-enaminone or β-diketone functional groups. Notably, the reductive ring-opening step required for the liberation of these functional groups can be accomplished under mild conditions with a variety of reagents.[68] The most frequently used and perhaps best procedure for facilitating this transformation employs $Mo(CO)_6$ in wet acetonitrile.[70] This protocol facilitated the smooth conversion of highly functionalized isoxazole **68** into β-enaminone **69**, an intermediate in the synthesis of (−)-calicheamicinone, the aglycone of calicheamicin γ_1 (**Scheme 30**).[71]



Scheme 30

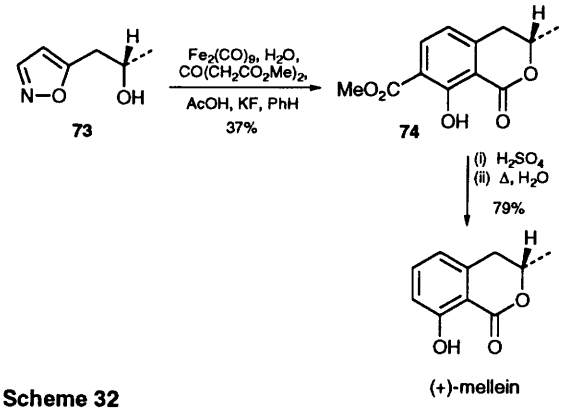
A recent synthesis of garugamblin I employed an isoxazole as a protected 1,3-dicarbonyl equivalent during a sequence of quite harsh reactions (**Scheme 31**).[72] Macrocyclization precursor **70** was prepared by reduction of diester **71** with lithium aluminium hydride followed by treatment of the resulting diol with phosphorus tribromide. Ring formation was accomplished using the radical anion generated from sodium/tetraphenylethene. Concomitant reductive cleavage of the isoxazole ring occurred under these



Scheme 31

reaction conditions, providing **72**, albeit in rather low yield. This material was subsequently converted into garugamblin I.

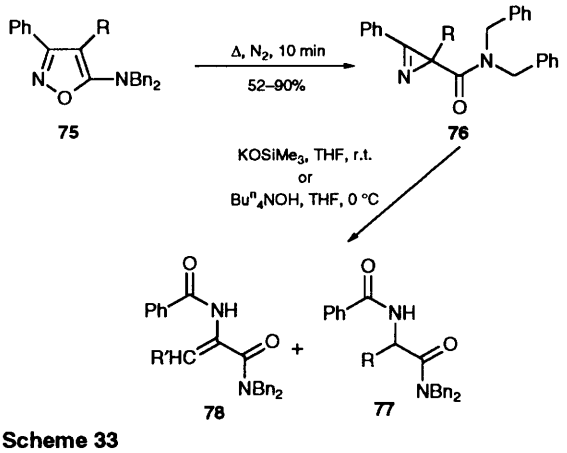
An asymmetric synthesis of dihydroisocoumarin natural product mellein has been reported.[73] Both enantiomers of key isoxazole **73** were prepared in a straightforward fashion from either (−)- or (+)-propylene oxide. Treatment of (+)-**73** with $Fe_2(CO)_9$ liberated the expected β-enaminone product which was further annulated *in situ* with dimethyl 3-oxoglutarate providing **74** (**Scheme 32**). Acidic hydrolysis and decarboxylation converted this material into (+)-mellein. An identical approach employing (−)-**73** was used to synthesize (−)-mellein.



Scheme 32

Lipshutz and Reuter have described a novel two-step procedure for the conversion of 5-aminoisoxazoles into amino acid bis-amides, a key structural subunit of the cyclopeptide alkaloids.[74] The first step in this protocol involved a thermally-induced rearrangement of isoxazole **75** into the corresponding azirine **76** (**Scheme 33**). Subsequent base-induced hydration of this azirine with either KOTMS or Bu_4NOH furnished the amino acid bis-amide 77 along with varying quantities of isomeric derivative **78**. The product ratio was found to be dependent on both the reaction conditions and the precise nature of azirine **76**. A number of other recent synthetic endeavours have employed isoxazoles as key intermediates.[75]

A review by Hassner and Fischer updating the chemistry of oxazoles was published in 1993.[76]



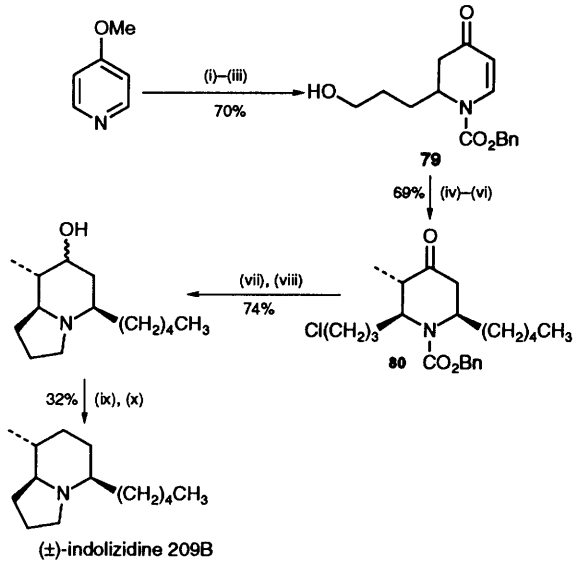
Scheme 33

Consequently, readers are directed towards this and other articles for an account of the chemistry of this ring system.[76,77]

4 Pyridines

Pyridines have been utilized as building blocks for the synthesis of a number of alkaloid natural products.[78] One of the most significant recent contributions in this area has been the development of methods for the addition of nucleophiles to pyridinium salts, allowing access to functionalized dihydropyridines and pyridines.[79]

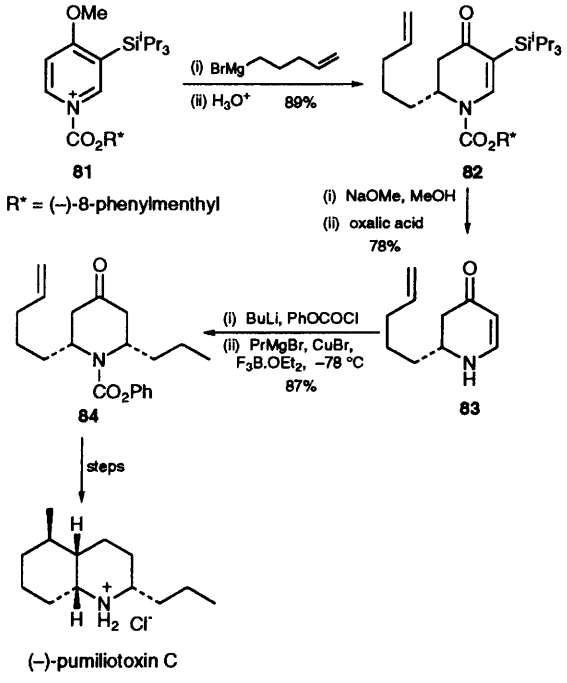
1-Acylpyridinium salts undergo regioselective nucleophilic attack at the 2-position of the pyridine ring providing entry into a variety of functionalized dihydropyridine systems. Comins and co-workers have studied the scope and limitations of this reaction and applied it to the synthesis of a number of natural products. An efficient synthesis of (±)-indolizidine 209B has been described using the nucleophilic addition of a functionalized Grignard reagent to the *N*-acyl pyridinium salt derived from 4-methoxypyridine (**Scheme 34**).[80] This reaction, after acidic hydrolysis, yielded functionalized dihydropyridinone **79** in 70% yield. Conversion of the alcohol grouping into the corresponding chloride and introduction of the methyl group proceeded uneventfully. Subsequent copper-mediated conjugate addition to this material yielded *cis*-piperidone **80** in 82% yield. Reductive removal of the benzyl carbamate facilitated intramolecular cyclization to the bicyclic skeleton which after further reduction steps provided racemic indolizine 209B in seven steps and 11% overall yield.



Reagents: (i) ClMgO⌒⌒MgCl; (ii) BnOCOCl; (iii) H_3O^+; (iv) NCS, PPh_3; (v) NaHMDS, MeI; (vi) $F_3B.OEt_2$, CuBr, $Me(CH_2)_4MgBr$; (vii) H_2, Pd–C, Li_2CO_3, MeOH; (viii) H_2, Pt–C, MeOH; (ix) $(Imid)_2CS$; (x) Bu_3SnH

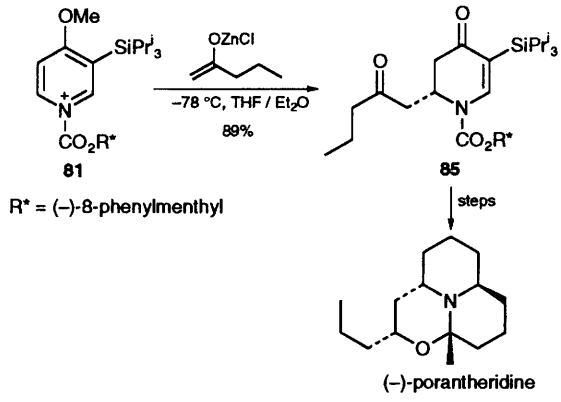
Scheme 34

An asymmetric variant of this reaction has been described by employing chiral *N*-acyl pyridinium salts. The best levels of diastereomeric induction have been accomplished using 4-methoxy-3-triisopropylsilylpyridine in conjunction with 8-phenylmenthyl chloroformate.[81] The silyl blocking group was found to be essential to achieve high levels of stereocontrol in these reactions. A number of asymmetric syntheses have exploited this chemistry, including a synthesis of (−)-pumiliotoxin C (**Scheme 35**).[82,83] Nucleophilic addition of the Grignard reagent derived from 1-bromo-4-pentene into pyridinium salt **81** gave an 89% yield of dihydropyridinone **82** as a single diastereomer. Cleavage of the carbamate and subsequent desilylation smoothly furnished **83** in good yield. Acylation of this material using phenyl chloroformate followed by diastereoselective copper-mediated conjugate addition produced *cis*-piperidone **84** which was elaborated to the natural product.



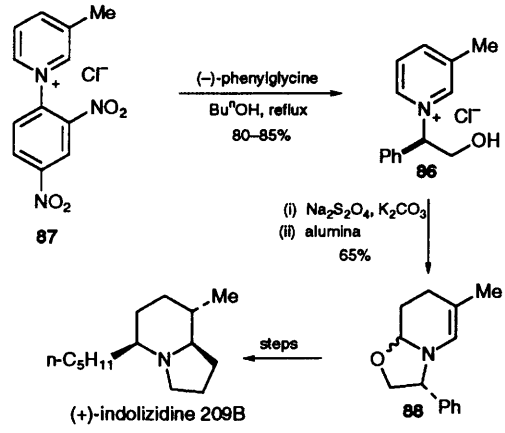
Scheme 35

While Grignard reagents have been most commonly used as the nucleophilic component in these reactions other nucleophiles can be employed. For example, an asymmetric synthesis of (−)-porantheridine employed an enolate as the nucleophilic component in this reaction (**Scheme 36**).[84] The key step in the synthesis involved regio- and stereo-controlled addition of the zinc enolate derived from pentan-2-one onto *N*-acylpyridinium salt **81** producing dihydropyridone **85** in 89% yield and 92% diastereomeric excess. Nucleophilic additions to chiral 1-acyl-4-methoxypyridinium salts employing triphenylsilylmagnesium bromide have also been described.[85] Interestingly, the opposite sense of asymmetric induction was observed with these silicon-based nucleophiles. Comins and co-workers have described the synthesis of a number of other piperidine,[86] indolizidine,[87] and quinolizidine[88] alkaloids using nucleophilic additions to *N*-acyl pyridinium salts.



Scheme 36

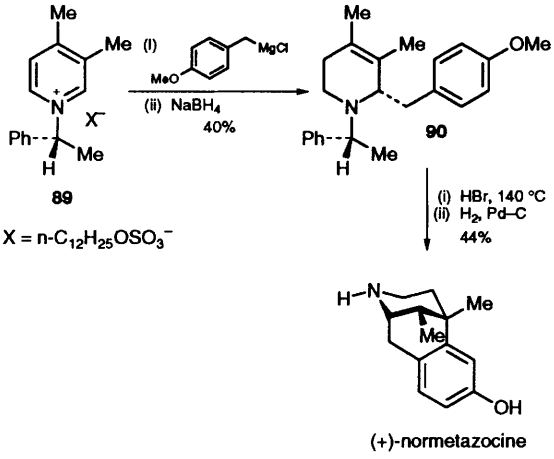
In related work, homochiral *N*-alkylpyridinium salts have been prepared by simply treating Zincke's salts with an appropriate chiral amine. In this manner, pyridinium salt **86** was synthesized from **87** and (*R*)-phenylglycinol (**Scheme 37**).[89] Regioselective reduction of this material ($Na_2S_2O_4/K_2CO_3$) produced the 1,4-dihydropyridine which cyclized to oxazolidine **88** upon filtration through alumina. This oxazolidine was used as a chiral template for further stereocontrolled nucleophilic additions at the 2- and 6-positions of the tetrahydropyridine nucleus and culminated in a synthesis of (+)-indolizidine 209B.



Scheme 37

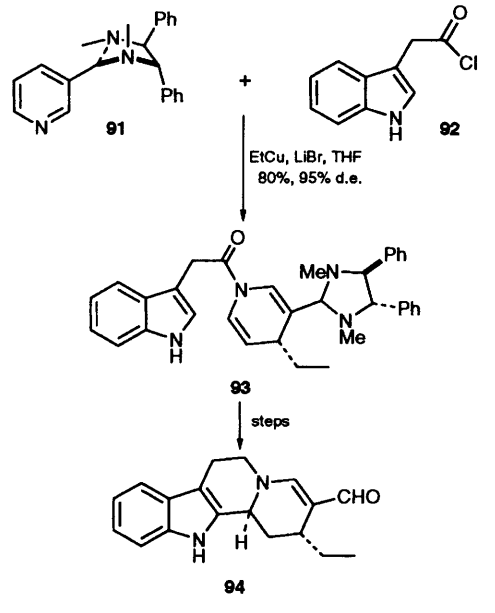
Similar chiral salts derived from α-methylbenzylamine have been used in the synthesis of (+)-normetazocine and (+)-nordextrophan.[90] Nucleophilic addition of the Grignard reagent derived from *p*-methoxybenzyl chloride onto pyridinium salt **89** and subsequent reduction of the resulting 1,2-dihydropyridine afforded **90** in 40% isolated yield (**Scheme 38**). Small quantities of other regio- and stereo-isomers were identified as side-products in this transformation. Acid-catalysed cyclization and subsequent catalytic hydrogenation afforded (+)-normetazocine in 18% overall yield from the

starting pyridinium salt. *N*-Alkylpyridinium salts have also been used to prepare a variety of fused pyridinium salts via intramolecular free radical cyclizations.[91]



Scheme 38

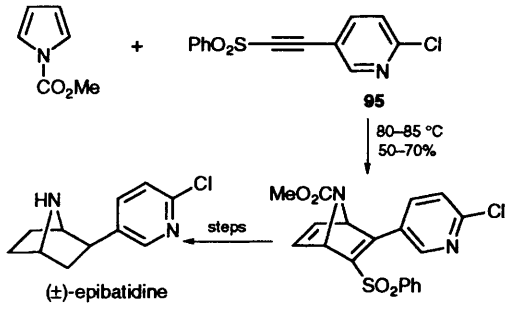
C_2-Symmetrical chiral aminals attached to the 3-position of pyridines have been used to prepare chiral 1,4-dihydropyridine-3-carboxaldehydes.[92,93] Treatment of pyridine **91** with diethyl cuprate in the presence of acid chloride **92** provided 1,4-dihydropyridine **93** in good yield and excellent diastereoselectivity (**Scheme 39**).[93] A concise sequence involving amide reduction, acid-mediated cyclization, and aminal hydrolysis furnished **94**, which is structurally related to the vallesiachotamine family of indoloquinolizidine alkaloids.



Scheme 39

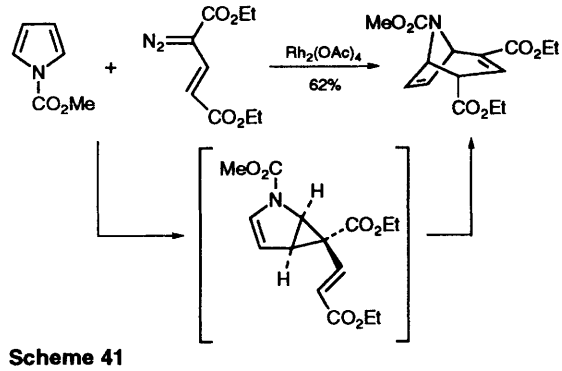
5 Pyrroles

A number of synthetic applications of the pyrrole nucleus have been described. Unlike furan, pyrrole and its derivatives show no great propensity to act as a diene component in Diels–Alder reactions.[94] Best results have been obtained using pyrroles substituted with an electron-withdrawing group on the nitrogen atom. A recent synthesis of (±)-epibatidine employed a Diels–Alder reaction between *N*-carbomethoxypyrrole and functionalized phenylsulfonyl acetylene **95** as the key step (**Scheme 40**).[95] The preparation of other 7-azabicyclo[2.2.1]hept-2-enes using pyrrole derivatives complexed to osmium(II) complexes has been reported.[96]



Scheme 40

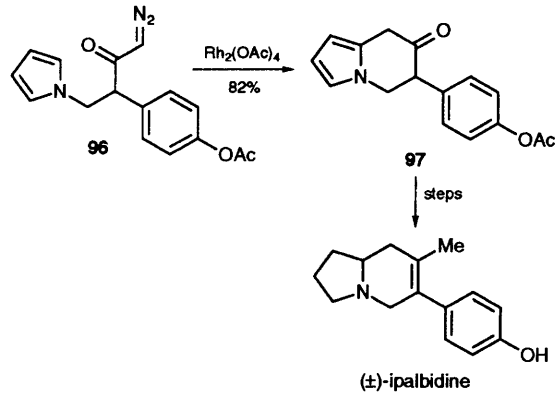
Davies and co-workers have shown that pyrroles can be utilized to access the tropane skeleton using a rhodium-catalysed cyclopropanation/sigmatropic rearrangement protocol.[97] The reaction entails treatment of a vinyl diazoester with an *N*-substituted pyrrole in the presence of a catalytic amount of a rhodium(II) catalyst (**Scheme 41**). This methodology has been used to synthesize (±)-ferruginine and (±)-anhydroecgonine methyl ester.[98] An enantioselective synthesis of the latter compound has recently been described employing a chiral vinyl diazoester derived from (*S*)-lactate.[99] Another tropane alkaloid, scopoline, has been prepared using a [4 + 3]-cycloaddition between oxyallyl and *N*-carbomethoxypyrrole as the key step.[100]



Scheme 41

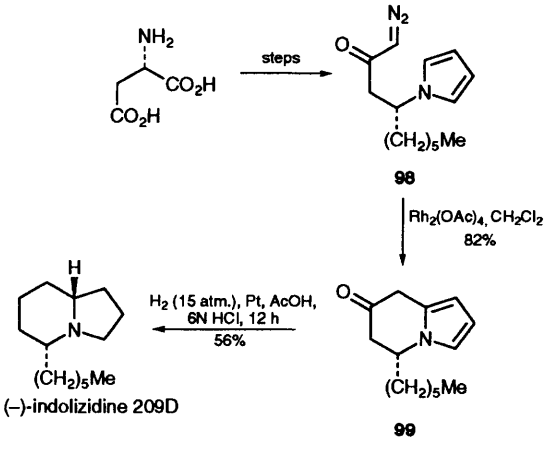
A number of natural products have been prepared using intramolecular C—H insertions of rhodium carbenoids into pyrrole systems. For example, selective insertion of the carbenoid generated by treatment of diazoketone **96** with rhodium diacetate into the 2-position of the pyrrole gave **97** in 82% yield (**Scheme 42**).[101] Detailed studies on this cyclization reaction revealed that insertion into the C—H bond of the substituted benzene ring competed with the

desired reaction pathway when the benzene ring was made more nucleophilic. A simple, four-step sequence was employed to convert **97** into (±)-ipalbidine.



Scheme 42

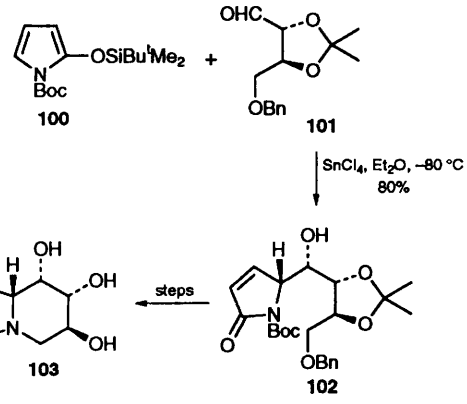
An asymmetric total synthesis of indolizidine 209D has been described using this methodology (**Scheme 43**).[102] Pyrrole **98** was prepared in a straightforward manner from L-aspartic acid in 16% overall yield. Intramolecular C—H insertion provided bicyclic pyrrole derivative **99** which was subsequently reduced to the natural product. Other indolizidines have been prepared in a similar fashion, including (±)-monomorine,[103] (+)-monomorine,[104] and (−)-indolizidine 167B.[102,104]



Scheme 43

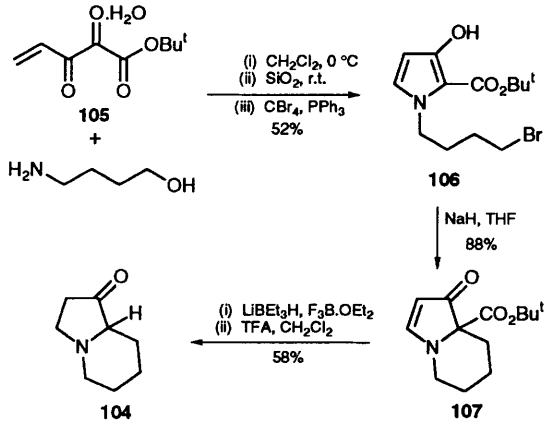
A route to indolizidine alkaloids has been developed using methodology based upon *N*-Boc-2-(t-butyldimethylsiloxy)pyrrole **100**.[105] This reagent behaves in an analogous fashion to its oxygen counterpart 2-(trimethylsiloxy)furan, undergoing nucleophilic addition to carbonyl compounds in the presence of Lewis acids.[44] Thus, reaction of **100** with L-threose derivative **101** in the presence of tin tetrachloride provided **102** in good yield as a single stereoisomer (**Scheme 44**).[106] This material was taken onto (+)-1-deoxy-8-*epi*-castanospermine **103**.

Wasserman and co-workers have prepared **104**, an intermediate in the biosynthesis of slaframine and swainsonine, using tricarbonyl chemistry (**Scheme 45**).[107] Treatment of **105** with 4-aminobutan-1-ol and



Scheme 44

subsequent treatment with triphenylphosphine and carbon tetrabromide provided functionalized pyrrole **106**. Intramolecular cyclization of this material with sodium hydride gave bicyclic **107** in 88% yield. The synthesis was completed by reduction of the carbon–carbon double bond of this material and subsequent hydrolysis/decarboxylation of the bridgehead ester group.



Scheme 45

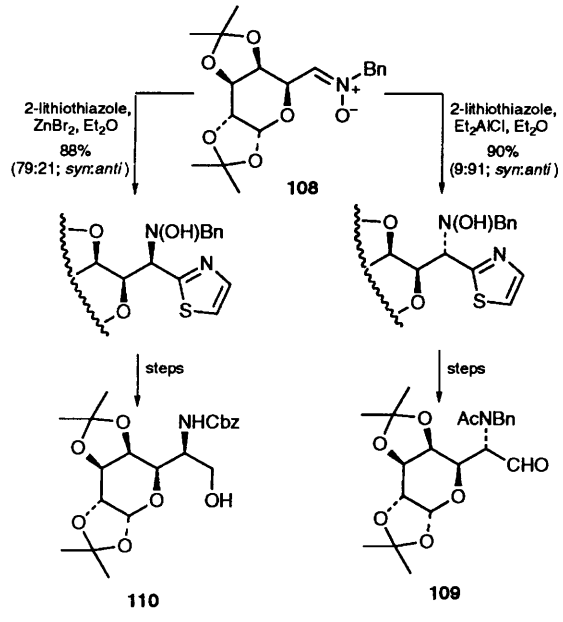
6 Thiazoles

A number of useful synthetic applications of the thiazole group have been reported which stem from the ability of it to serve as a stable formyl equivalent (**Figure 1**). Dondoni and co-workers have developed a range of chemical reagents incorporating the thiazole group, including 2-trimethylsilylthiazole (2-TST), 2-thiazolylmethylenetriphenylphosphorane (2-TMP), and 2-thiazolylcarbonitrile *N*-oxide (2-TNO) each of which provide useful building blocks for organic synthesis.[108] The value of these reagents stem in part from the stability of the thiazole group to a wide variety of reaction conditions and its ability to be unblocked to the aldehyde under relatively mild and neutral reaction conditions.[109]

Figure 1

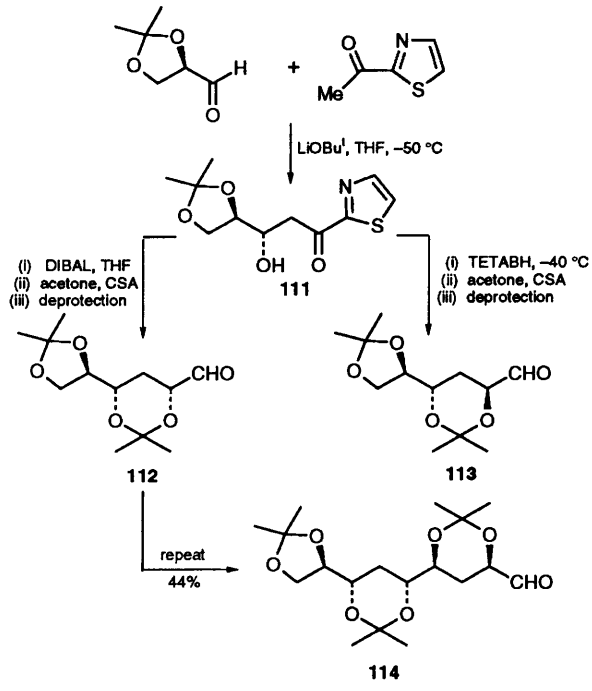
Both 2-trimethylsilylthiazole (2-TST) and 2-lithiothiazole can be employed to homologate systems by one carbon atom. Aldehydes react with 2-TST yielding the corresponding *O*-trimethylsilyl alcohols in moderate to good yields.[110] Good to excellent levels of diastereoselectivity have been accomplished in these reactions when α-alkoxy or α,β-dialkoxyaldehydes are employed as the electrophilic components.[111] The reaction of 2-TST with other electrophiles such as acid chlorides, ketenes, and azolium ions has also been described.[108,112]

The preparation of α-aminothiazole derivatives has been accomplished by nucleophilic addition of 2-lithiothiazole to *N*-benzylimine *N*-oxides (**Scheme 46**).[113,114] The stereochemical outcome of these reactions was controlled by the use of an appropriate Lewis acid additive. Thus, treatment of **108** with 2-lithiothiazole in the presence of diethyl aluminium chloride yielded the *anti* adduct as the major product, whereas use of zinc bromide favoured formation of the *syn* product. Manipulation of these materials provided **109** and **110** respectively, which represent formal total syntheses of lincosamine and destonic acid respectively.



Scheme 46

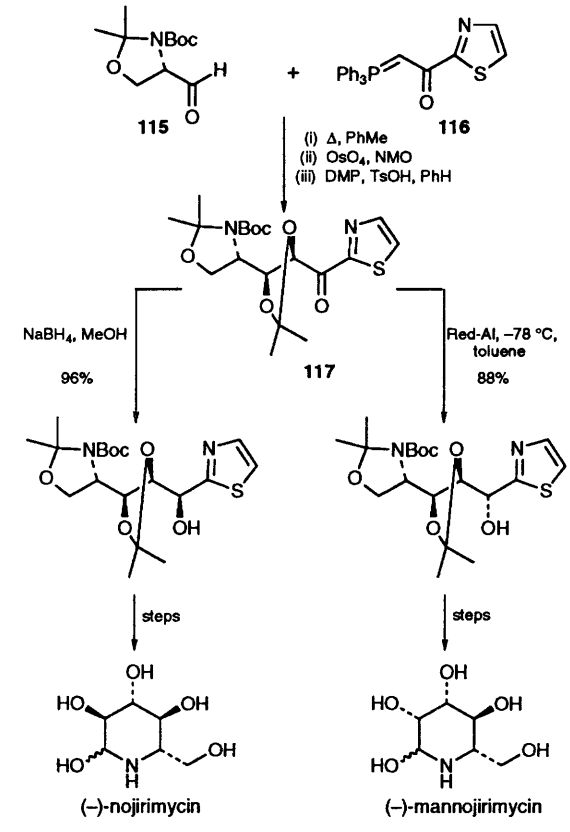
An iterative synthesis of polyols has been described in which 2-acetylthiazole is condensed with chiral α,β-dialkoxyaldehydes in a stereocontrolled fashion (**Scheme 47**).[115] Thus, aldol reaction of 2-acetylthiazole with 2,3-*O*-isopropylidene-D-glyceraldehyde in the presence of lithium t-butoxide provided **111** as a single stereoisomer. Stereocontrolled reduction of the carbonyl group using either DIBAL or tetramethylammonium triacetoxyborohydride yielded the *syn* or *anti* 1,3-diol systems respectively. Acetonide formation followed by removal of the thiazole group gave the homologated aldehydes **112** and **113**. The iterative nature of this process was established by



Scheme 47

converting **112** into **114**, by simply repeating the above protocol.

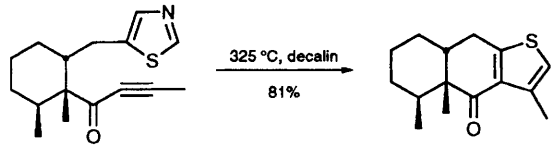
The total synthesis of the unnatural enantiomers of glucosidase and mannosidase inhibitors, nojirimycin and mannojirimycin, has recently been accomplished using thiazole-based phosphorus ylids (**Scheme 48**).[116,117] Treatment of **115** derived from L-serine with



Scheme 48

thiazole **116** provided the *trans* olefin in 90% yield. Diastereoselective dihydroxylation of this alkene (86% d.s.) and subsequent protection of the resulting diol gave **117** in 59% overall yield. Reduction of this material with sodium borohydride yielded the *anti* alcohol (≥ 95% d.s.) which was taken onto (−)-nojirimycin. Access to the *syn* alcohol was accomplished with a high degree of stereocontrol by employing Red-Al (≥ 95% d.s.) and was converted into (−)-mannojirimycin by a similar reaction sequence to that employed with (−)-nojirimycin.

Despite the low reactivity of the thiazole ring towards [4 + 2] cycloaddition reactions, Jacobi and co-workers have successfully utilized an intramolecular variant of this reaction to prepare menthane and eremophilane-type terpenes.[118] Thus, thermolysis of acetylenic ketone **118** efficiently provided tricycle thiophene **119** via intramolecular Diels–Alder cycloaddition and subsequent extrusion of hydrogen cyanide (**Scheme 49**). This material was separately converted into both 7α- and 7β-eremophilane (see Section 7).

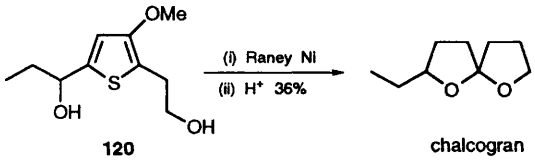


118 **119**

Scheme 49

7 Thiophenes

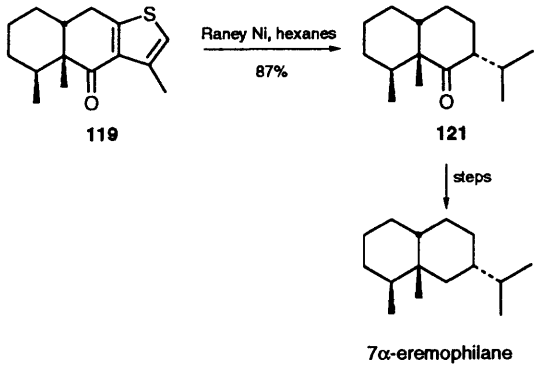
Thiophene desulfurization reactions have been utilized by several groups to prepare natural products and important synthetic building blocks.[119] Noe and co-workers have described the synthesis of the bark beetle pheromone chalcogran and a wasp anti-aggression pheromone using a strategy based upon the partial hydrogenation of substituted thiophenes.[120] Thus, reduction of **120** with Raney nickel and subsequent acid-catalysed spiroketalization gave chalcogran in modest yield (**Scheme 50**). These authors have also described a route to enantiomerically enriched secondary alcohols by desulfurization of the corresponding homochiral 2-thienylcarbinols.[121] Other routes to homochiral 2-thienylcarbinols have also been reported.[122]



120 chalcogran

Scheme 50

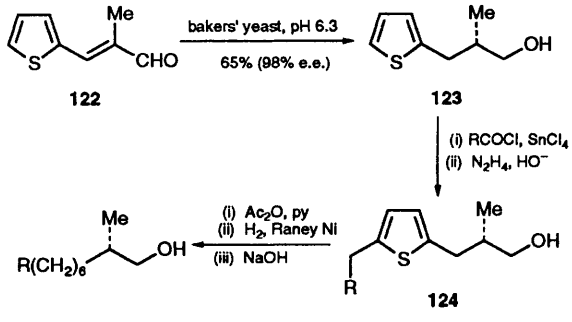
A key step in a synthesis of eremophilane-type terpenes used a reductive desulfurization step to install an isopropyl group (see Section 6). Thus, treatment of tricyclic thiophene **119** with Raney nickel provided isopropyl substituted decalin **121** as a single stereoisomer (**Scheme 51**).[118] Subsequent reductive removal of the ketone group provided 7α-eremophilane, while base-induced epimerization of **119** prior to ketone reduction afforded the isomeric compound 7β-eremophilane.



119 **121**

Scheme 51

Asymmetric reduction of α-methyl-2-thiophenepropenals with bakers' yeast provides a route to enantiomerically enriched (*S*)-2-methyl-1-alkanols.[123] Reduction of **122**, under careful pH control, provided the corresponding β-methyl-2-thiophenepropanol **123** in good yield and excellent enantiomeric excess (**Scheme 52**). Unfortunately, the higher alkyl homologues **124** (*e.g.* R = Me, n-C_3H_7) could not be efficiently prepared by direct reduction of the corresponding propenals and were best synthesized by acylation/Huang-Minlon reduction of **123**. Direct desulfurization of **123** and **124** led to partial racemization but this problem was overcome by protection of the hydroxyl group as the corresponding acetate. Other applications of thiophene desulfurization reactions include the preparation of various macrocyclic crown ethers and [n]paracyclophanes.[124]



122 **123** **124**

Scheme 52

8 Conclusion

It is obvious from the work surveyed in this article that researchers in many laboratories around the world continue to find new and innovative ways to employ aromatic heterocycles in organic synthesis. Such intermediates have proven valuable for the preparation of a diverse range of natural products

including many alkaloids, carbohydrates, and terpenes. Future work in this area will no doubt bring further exciting applications of these intermediates in synthesis.

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