REVIEW

Recent developments in the synthesis of furan-2(5*H*)-ones

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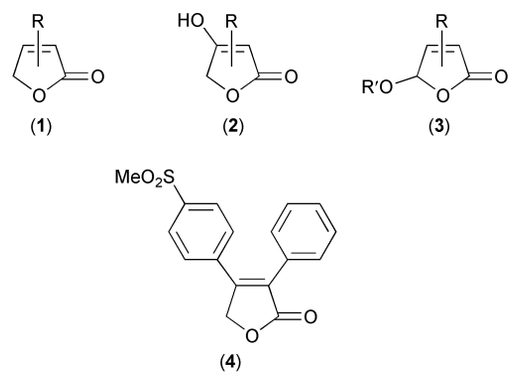
1 Introduction

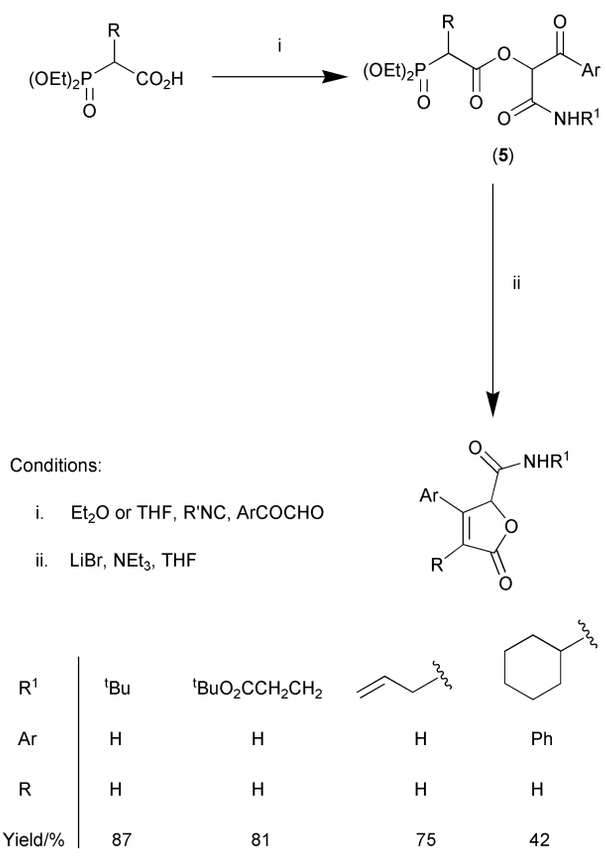
This article is concerned with recent innovations in the preparation of furan-2(5*H*)-ones (**1**, referred to hereafter as 'furanones'), compounds previously widely known as butenolides, and is divided into two main sections: *synthetic methodology* and *total synthesis*. Whereas previous reviews of the area [1] have provided broad coverage of all of the major sub-classes of this structural type, this document has concerned itself only with synthetic processes directed towards the furanone nucleus. Thus, methodology directed towards the preparation of 4-oxygenated ('tetronic acids') and 5-oxygenated (general structures **2** and **3**, respectively) has been described only when a key feature of the strategy was assembly of the actual heterocycle, or when a total synthesis was reported; the reader is, therefore, directed to the other review articles for detailed coverage of the research in those areas. The long-standing interest in the preparation of these often potently bioactive compounds has been further invigorated with the discovery and subsequent exploitation of the ability of certain 3,4-disubstituted furanones (such as VIOXX® **4**, *vide infra*) to act as highly selective inhibitors of only one of the two cyclooxygenase enzymes involved in inflammation and other pain-inducing biological processes; this allows for pain management without much of the unwanted side-effects of typical NSAIDs (**N**on-**S**teroidal **A**nti **I**nflammatory **D**rugs).



2 Synthetic methodology

2.1 *via* Olefination–cyclization

An innovative new synthetic method to furanones, *via* a Passerini-like three-component condensation, has been described.[2] Thus, the first step in the reaction sequence involves combination of an aryl glyoxal with an alkyl isonitrile and a 2-substituted 2-(diethoxyphosphoryl)acetic acid. The product of this reaction is a 2-[2-(phosphoryl)acetoxy] ketoamide (**5**), which cyclizes upon exposure to Rathke conditions [3] to give 4-aryl-5-(carboxyamido)furanone in generally good overall yields. A wide range of isonitriles and arylglyoxals undergo the reaction (Scheme 1).



Scheme 1

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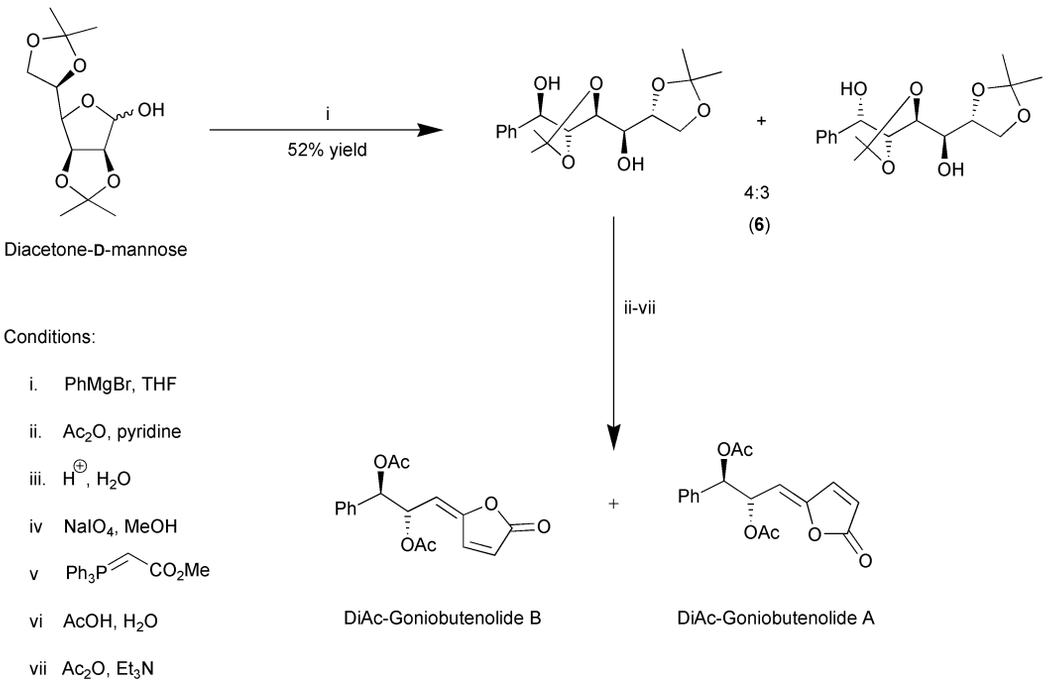
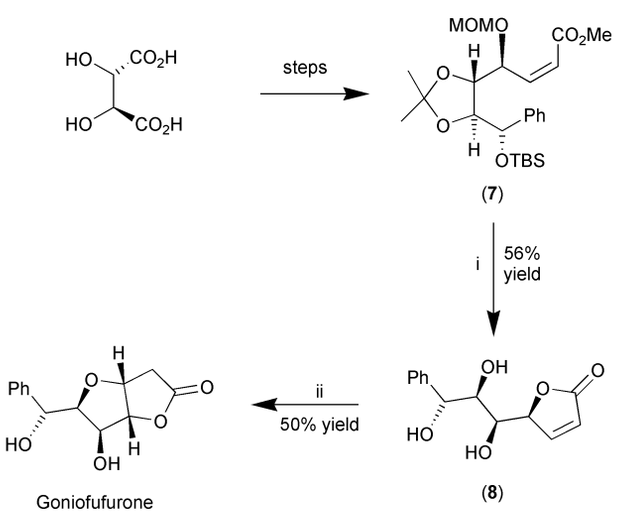


Scheme 2

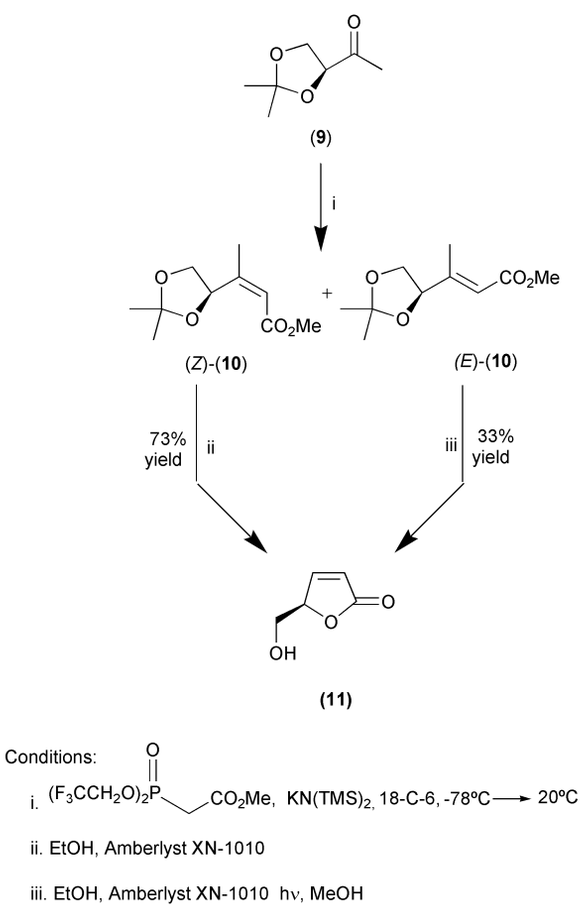
Alkylidenefuranones containing polyhydroxylated 5-substituents derived from monosaccharides have been utilized as intermediates in the preparation of Goniobutenolides.[4] The synthetic sequence commenced with the reaction of diacetone-D-mannose with phenylmagnesium bromide, giving protected hexol (**6**) as a separable mixture of diastereoisomers, obtained in a 4 : 3 ratio. The 'correct', *erythro*, isomer was then converted in six steps to acetylated Goniobutenolides A and B (Scheme 2).

The closely-related Goniofufurone has been synthesized using a similar strategy, in this case commencing with D-(−)-tartaric acid.[5] This chiral pool reagent was converted in linear fashion to differentially-protected (*Z*)-acrylate (**7**) and this key intermediate was transformed into furanone (**8**), which was itself converted into the natural products in moderate yield (Scheme 3).



Scheme 3

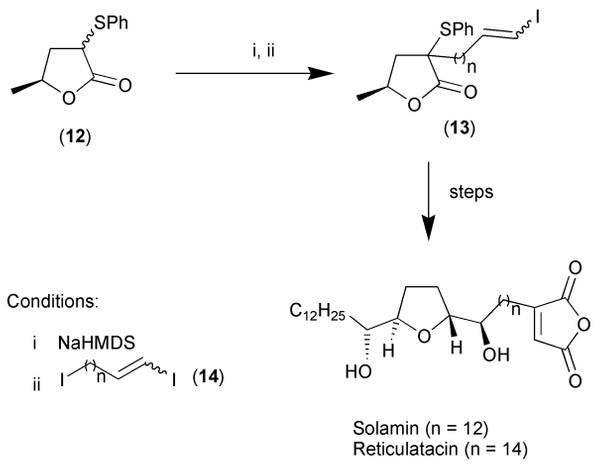
Gibson and Handa have reported that cyclization of (*E*)-acetal (**10**) to give (*R*)-(+) Umbelactone[6] (**11**) is accomplished only with difficulty, due to the reticence for isomerization shown by this acrylate. Thus, only upon photolysis using a medium-pressure mercury lamp was the alkene stereochemistry inverted, whereupon cyclization occurred spontaneously yielding the natural product, in mediocre yield (Scheme 4). By contrast, (*Z*)-acrylate (**10**) underwent deacetalization and concomitant cyclization in good yield. The need to utilize the (*E*)-isomer of the umbelactone precursor arose from the lack of selectivity observed by the authors in the preceeding Still–Gennari olefination reaction of (*S*)-ketone (**9**) (Scheme 4).



Scheme 4

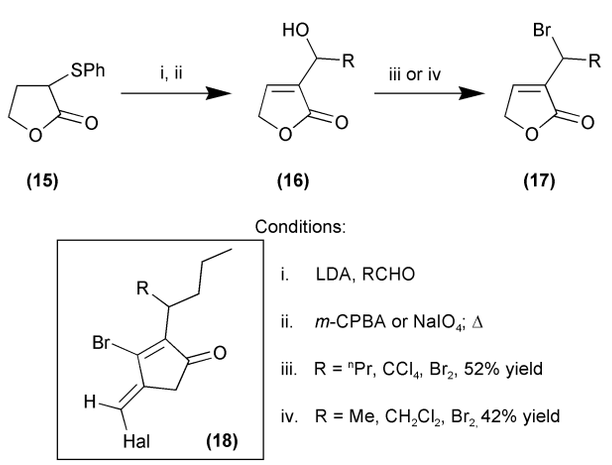
2.2 *via* Selanyl- and sulfanylbutanolides

The use of butyrolactones bearing α-thio substituents continues to offer an attractive route for synthesis of furan-2(5*H*)-ones.[7] Thus, for example, lactone (**13**), a key intermediate in the synthesis of Solamin and Reticulatacin, was prepared from sulfanylbutanolide (**12**). Firstly, (**12**) was alkylated by sequential deprotonation and treatment with diiodides (**14**). These lactones were used to assemble the core of the natural products mentioned; the final step in the synthetic sequences was pyrolytic sulfoxide elimination, thus generating the relatively fragile furanone as the synthetic 'end-game' (Scheme 5).



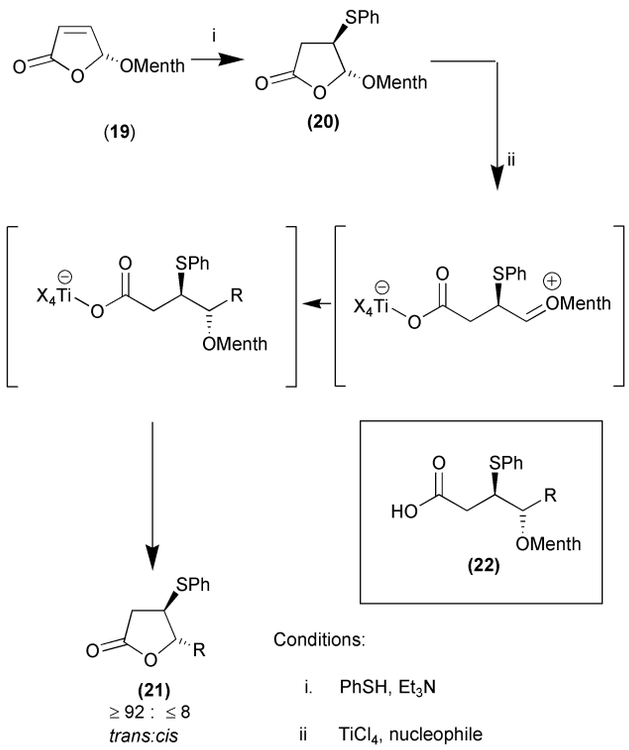
Scheme 5

En route to fimbrolides of general structure (**18**),[8] 3-hydroxyalkylfuranones (**16**) were prepared from 2-sulfanylbutanolide (**15**), by a hydroxyalkylation–oxidation–elimination sequence. Compound (**16**) then underwent reaction with molecular bromine to give 3-(1-bromoalkyl)furanones (**17**) in moderate yield; none of the expected addition product was obtained (Scheme 6).



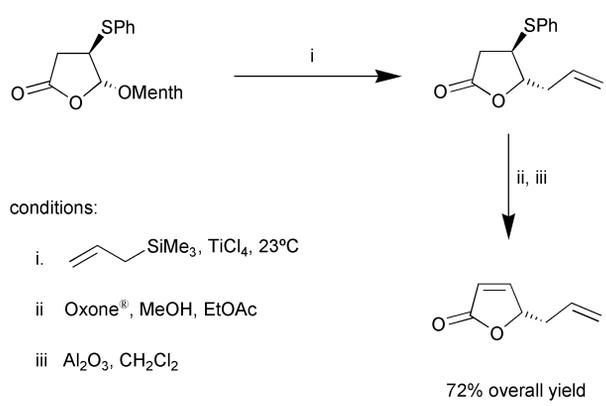
Scheme 6

Feringa and Oeveren[9] have utilized enantiomerically pure 5-menthyloxyfuranone (**19**) to gain efficient entry to 5-substituted furanones of high enantiomeric purity. Thus 5-menthyloxy-4-phenylsulfanylbutanolide (**20**, furanone numbering) reacts at room temperature with a range of carbon-centred nucleophiles to give the corresponding alkylated lactones (**21**) in moderate to good yields. That the reaction proceeds *via* initial ring-opening can be demonstrated by the isolation from the reactions of the minor product (**22**) (usually obtained in less than 10% yield); the proportion of (**22**) in the reaction mixture is drastically altered if the reaction is carried out at low temperature. Thus, when conducted at −70 °C the reaction yields (**22**) as the major product (Scheme 7).



Scheme 7

Where butanolide products are isolated, these products are produced with high levels of diastereoselectivity, favouring the *trans*-isomer. In the case of the allyl- and ethyl-substituted lactones, conversion to furanones was accomplished in good overall yield (Scheme 8).

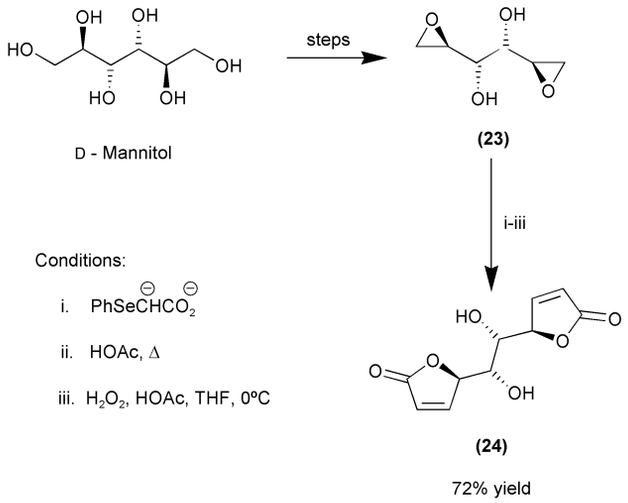


Scheme 8

Enantiomerically-pure bis(butenolides) (**24**) have been prepared from D-mannitol.[10] Thus, reaction of C_2-symmetrical diepoxide (**23**) with the dianion derived from phenylselanyl acetic acid gives a bis(butyrolactone) which yields (**24**) upon peroxidation. Compound (**24**) was wanted as a substrate to be used in a study of diastereoselective ethylene photocycloaddition processes (Scheme 9).

2.3 *via* Aldol-like strategies

When 4-alkyl substituents are present on a Feringa furanone, deprotonation is observed at the alkyl substituent upon treatment with LDA. Reaction of the resultant dienolate with



Scheme 9

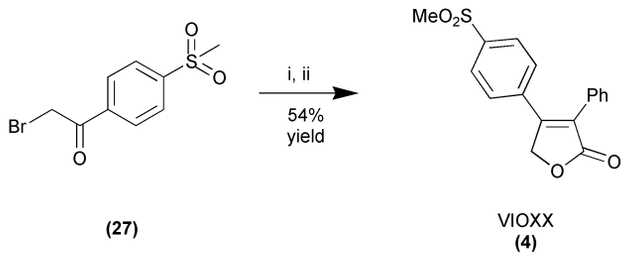
aldehydes furnishes the products of the aldol reaction at the 3-position of the furanone: 3-hydroxyalkylfuranones (**25**) are isolated from such reactions.[11] The stereochemical integrity of the 5-position seems unaffected by such reactions, meaning that the diastereomeric aldol products (obtained in an approximate 3 : 2 ratio) are easily separable by routine column chromatography. Reduction of the acetal moiety gave the naturally occurring furanone (**26**) (Scheme 10).

The Merck Frosst group have reported full details of their multi-gram synthesis of the selective COX-2 inhibitor VIOXX® (Rofecoxib, MK 966), 4-(4′-methylsulfonylphenyl)-3-phenyl-2(5*H*)-furanone (**4**).[12] The key reaction involves reaction of 2-bromomethyl-[4-(methylsulfonyl)phenyl] ketone (**27**) with phenylacetic acid, under basic conditions (Scheme 11).

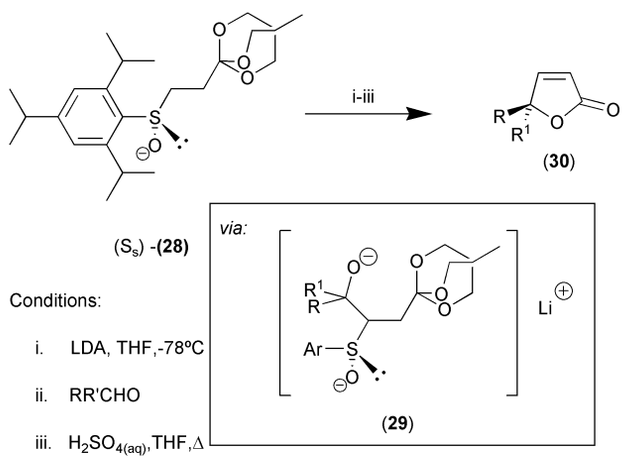
Ghosez and Renard[13] have described the use of the enantiomeric sulfoxide *ortho*-esters (R_s)-and (S_s)-(**28**) in the preparation of enantiomerically-enriched 5-substituted furanones. Thus, the aldol-like reaction of the α-lithio anions derived from (**28**) gave crude products (**29**) in good yield which were directly converted into enantiomerically-enriched furanones (**30**). Occasionally elimination of sulfinic acid was incomplete, necessitating a separate reaction in toluene to complete the synthetic cycle (Scheme 12).

The dimethylacetal of 3-tosylpropanal may be lithiated and reacted with carbonylic electrophiles to give cyclic acetals (**31**) which may be converted into furanones in a two step process.[14] The overall yields of the sequences are good (≥60%) (Scheme 13).

In a closely-related study, Craig and his co-workers[15] have

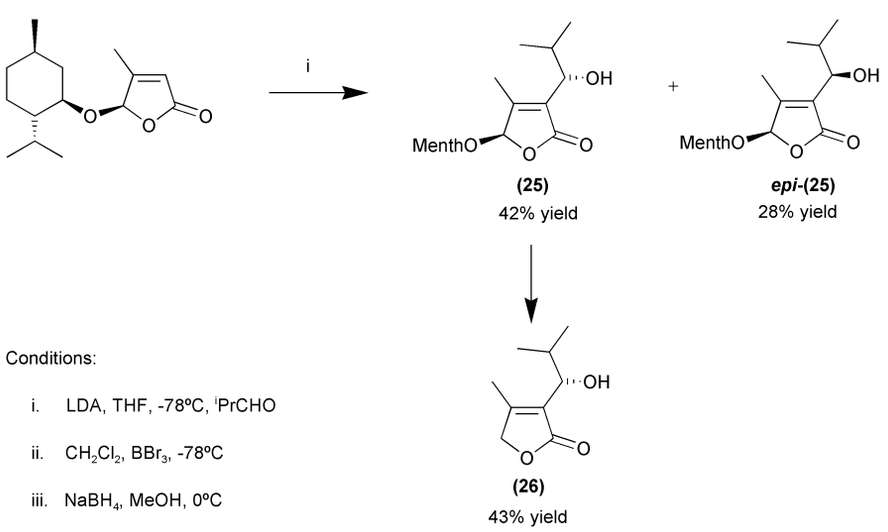


Scheme 11

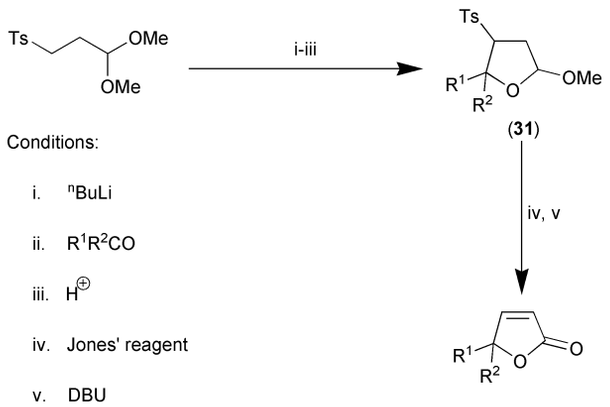


R	Ph	^{i}Pr	$^{n}C_5H_{11}$	c-Hex	Prop-2-enyl
R^1	H	H	H	H	H
Yield/%	79	78	79	82	70
e.e./%	99	90	85	89	53

Scheme 12



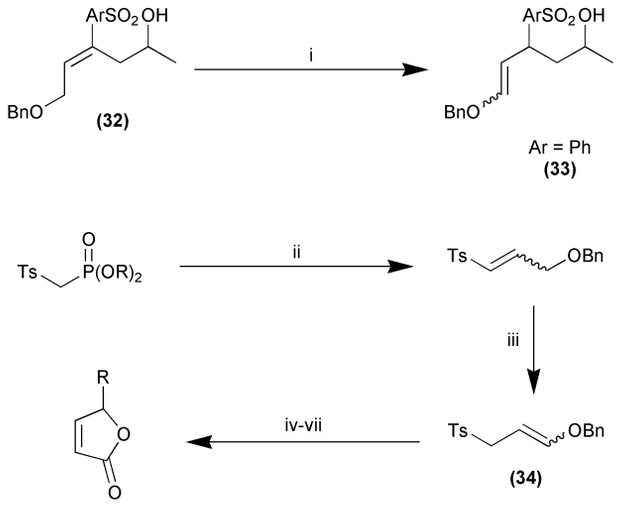
Scheme 10



R^1	^iPr	$^nC_5H_{11}$	$(CH_2)_5$	Ph
R^2	H	H	$(CH_2)_5$	Me
Yield/%	65	83	85	82

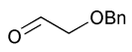
Scheme 13

reported that (alkoxyallyl)sulfones can function as synthetic equivalents of β-anions of α,β-unsaturated aldehydes or ketones. Thus, whilst pursuing possible *endo*-cyclizations of α-(hydroxyethyl)vinylsulfones (**32**), the authors chanced upon a high-yielding route to the isomeric enol ether (**33**) and extrapolated this observation to allow preparation of the structurally-simpler analogue (**34**). Compound (**34**) functions as a precursor to 5-substituted furan-2(5*H*)-ones *via* an hydroxyalkylation–cyclization–oxidation–elimination protocol; furanones are obtained in 40–60% overall yields from (**34**) (Scheme 14).



Conditions:

i. ^tBuOK, ^tBuOH, THP

ii 

iii ^tBuOK, ^tBuOH, THF

iv ^nBuLi, RCHO, THF, -78ºC

v H_2SO_4, H_2O, MeCN

vi PDC, CH_2Cl_2

vii DBU (0.6eq), CH_2Cl_2, -78ºC

Scheme 14

2.4 *via* Transition metal-catalyzed processes

Two methods have appeared describing palladium-catalyzed methods for selective cross-coupling of 3,4-difunctionalized furanones. Thus, bis(stannane) (**35**) reacts selectively with aryliodides at the 4-position, generating 4-aryl-3-tributylstannylfuranones (**36**) which can then themselves be converted to differentially-disubstituted furanones (Scheme 15).[16]

Rossi *et al.*[17] subsequently reported the use of the more readily-prepared dibromo- and dichlorofuranones (**37**) and (**38**) in regioselective Stille and Suzuki couplings; the synthesis of the antitumour compound Rubrolide M was accomplished using (**38**), whilst dibromide (**37**) was utilized in the synthesis of a range of Rubrolide analogues (Scheme 16).

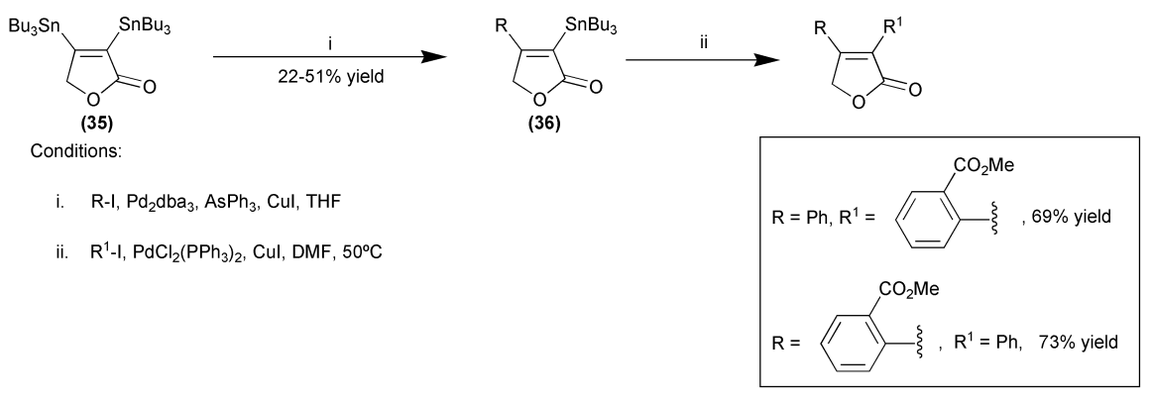
4-Bromo-2(5*H*)-furanone (*vide infra*) undergoes Pd-catalyzed cross-coupling with heteroaromatic trialkylstannanes to give 4-substituted furanones, in generally good yields.[18] 5-Alkoxyfuranones are also accessible by this methodology (Scheme 17).

Molander *et al.*[19] have reported in full, details of their group's synthetic route to Steganone. A key intermediate in this strategy is furanone (**40**), prepared in excellent yield by Stille cross-coupling of biaryl bromide (**39**) and 3-tributylstannylfuranone (**41**) (Scheme 18).[20]

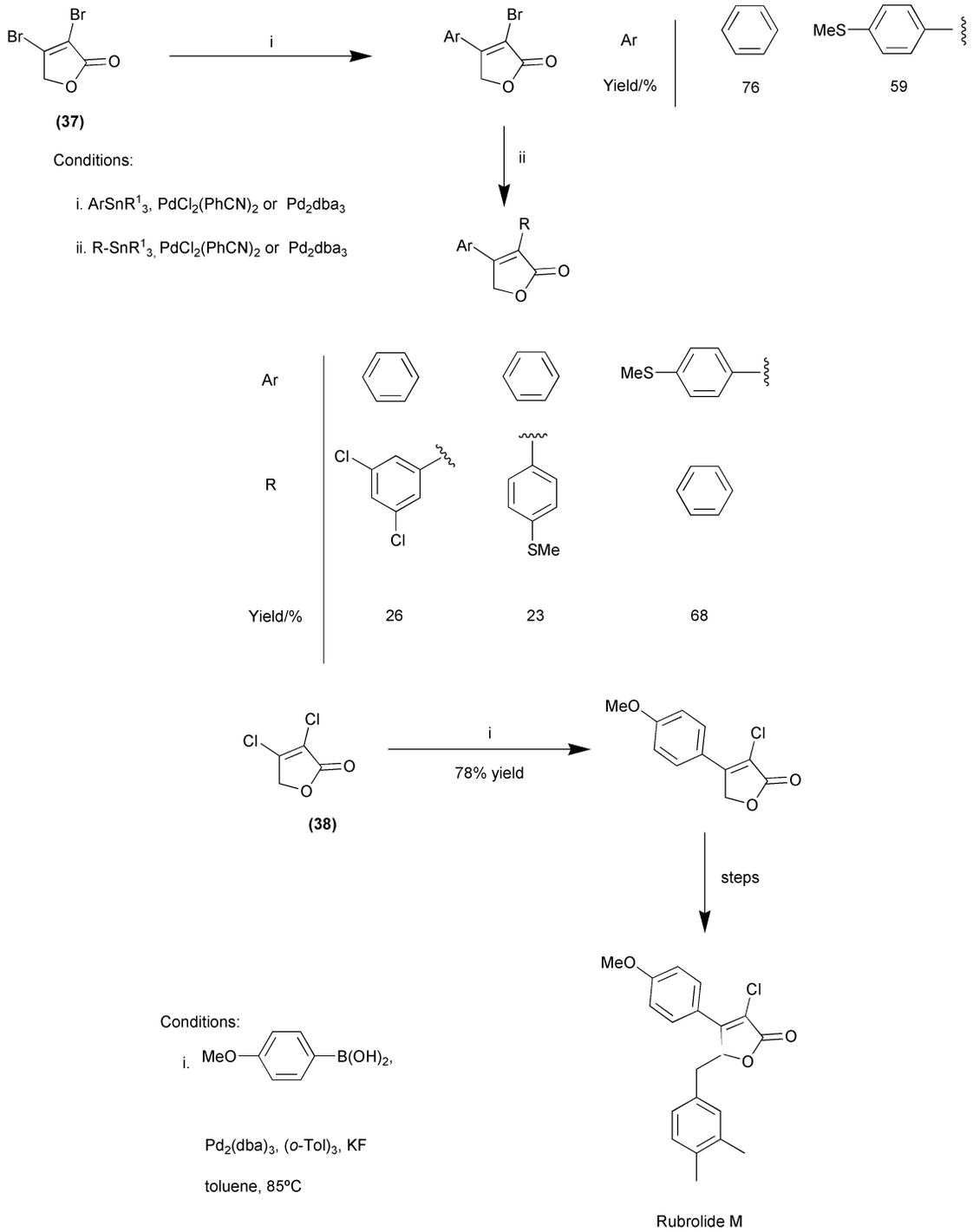
Grigg *et al.*[21] have reported the utility of tetronic acid-derived triflate† (**42**) in Suzuki couplings of functionalized 9-alkyl-9-BBNs. Thus, coupling proceeds under typical conditions to yield disubstituted furanones (**43**) and the methodology was utilized in an expedient synthesis of (−)-isoseiridine (**44**) (Scheme 19).

In a similar strategy trifluoromethylsulfonyl tetronic acids undergo efficient Suzuki coupling with cyclopropylboronic acids (as first reported by Marsden and Hildebrand[22]) furnishing 4-substituted furanones in good yields[23] (Scheme 20).

† The IUPAC name for triflate is trifluoromethanesulfonate.



Scheme 15



Scheme 16

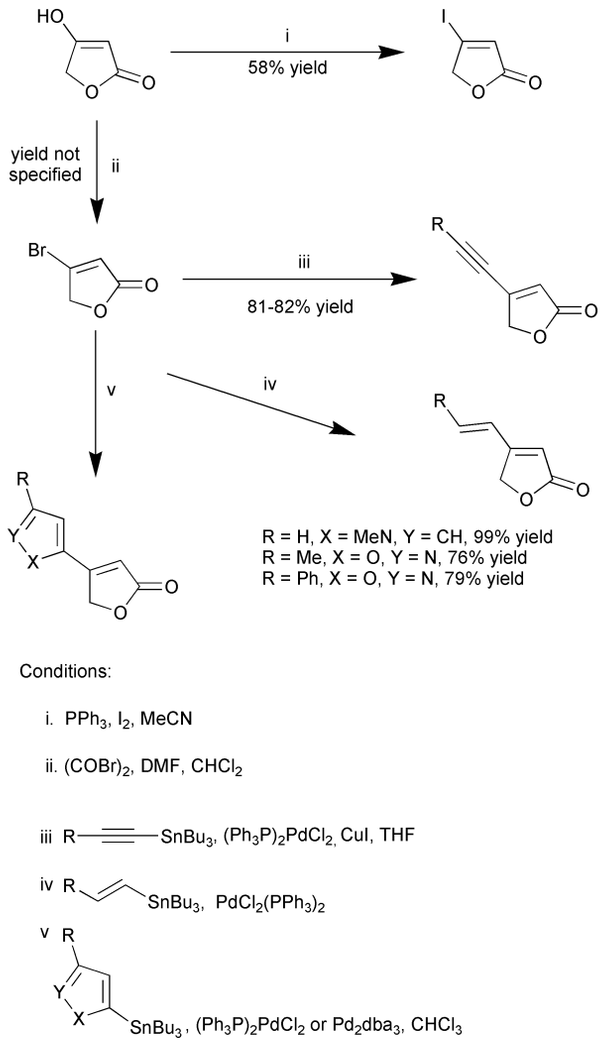
Sequential Suzuki-coupling–carbonylation reactions were used in a method which allow for stereocontrolled synthesis of polyunsaturated furanones.[24] Thus, Hanisch and Brückner have utilized a stereoselective coupling of 1,1-dibromoalkenes to give (*Z*)-congfigured 2-bromodienes, which may be converted in a three-step process to furanones (Scheme 21).

A similar process, involving carbonylation of dicyclopentadienyliron(III) reagents, has been reported by Rück-Braun *et al.* (Scheme 22).[25] Thus, in a modification to the originally-reported procedure,[26] $[Cp_2(CO)_2Fe]$-substituted unsaturated aldehydes react with main-group organometallic reagents, initially to give allylic alcohols. These intermediates then undergo cyclocarbonylation to give furanone products in moderate to good yields. The reaction is primarily useful in the preparation of 3,4-ring-fused furanones, compounds not frequently accessible by usual methods for furanone synthesis.

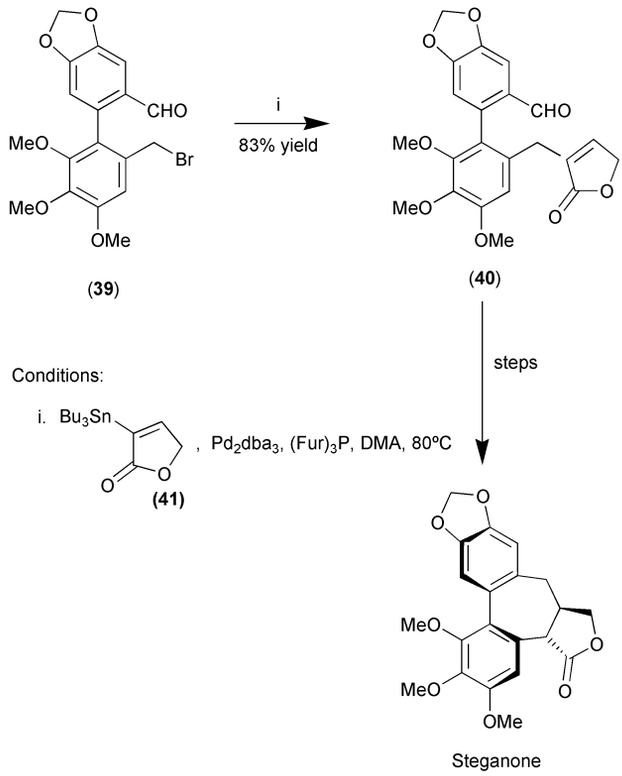
In the case of *p*-iodobenzoates, a Heck-like reaction of α-methylenebutanolide (**45**) gives a good yield of 3-benzylfuranone (**46**).[27] Where the aryl coupling partner is not so electron-deficient, however, the dominant product of the reaction is the corresponding α-benzylidene lactone (**47**) (Scheme 23).

In the presence of nickel(0) catalysts, 2(3*H*)-furanones react with aldehydes to give 4-acetyl-5-alkylfuranones in good yield, *via* a ring-opening–aldol reaction–ring-closing process (Scheme 24).[28]

(*E*)-γ-Tributylstannylmethylidenefuranones (**49**) are obtained from reaction of (*Z*)-tributylstannyl 3-iodopropenoates (**48**) and tributylstannylacetylene,[29] in good yields;



Scheme 17



Scheme 18

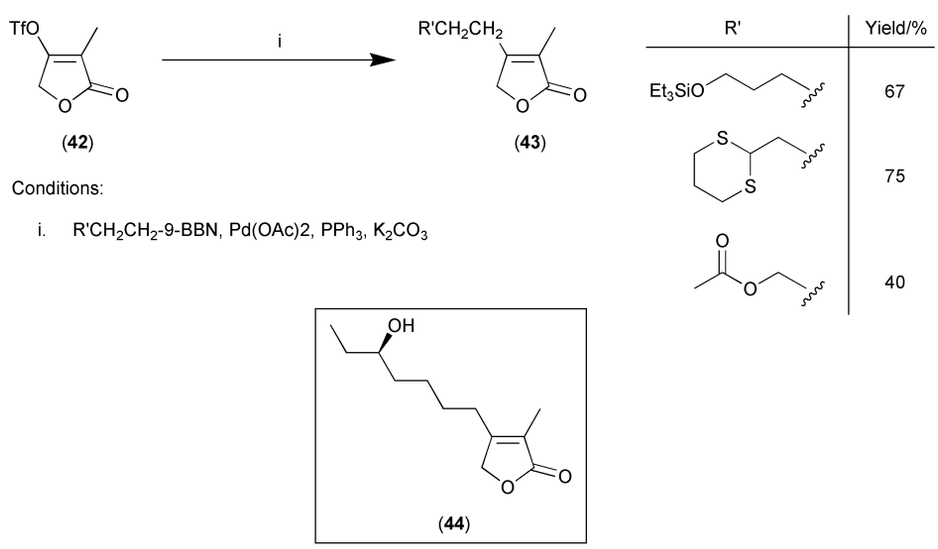
the use of the corresponding propenoic acid in the coupling reactions was very inefficient. The products of the reaction were shown to undergo successful Stille reactions (Scheme 25).

A synthesis of furanones involving cross-coupling–cyclisation protocols involving Pd(0)–Ag(I) catalyzed reactions of allenyl carboxylic acids with vinyl or aryl halides has been reported.[30] Thus, these acids react with a range of halides in the presence of $Pd(PPh_3)_4$ and Ag_2CO_3 (both present in sub-stoichiometric amounts to yield furanones directly, in good yields. The authors do not postulate whether cross-coupling (Pd(0)-catalyzed) or cyclisation (Ag(I)-catalyzed) occur first (Scheme 26).

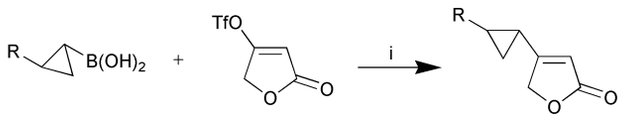
The same authors have also reported efficient cross-coupling reactions of 4-halofuranones with alkynes and organozinc reagents (Scheme 27).[31]

2.5 From furanones

3,4-difluoro-5,5-dimethylfuranone (**50**) reacts with copper(I)-modified Grignard reagents to give the products of conjugate addition–fluoride elimination, *viz*. 4-substituted 3-fluoro-5,5-dimethylfuranones (**51**).[32] Reaction of (**50**) with organolithiums, however, proceeded *via* nucleophilic attack at the C=O bond yielding 3(2*H*)-furanones (**52**) upon proteolytic work-up (Scheme 28).



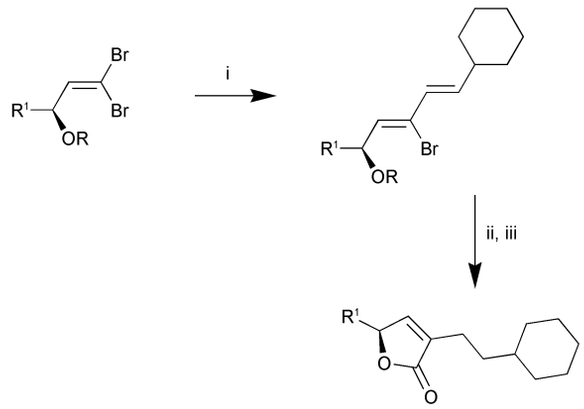
Scheme 19



Conditions:

i. $Pd(MeCN)_2Cl_2$, $AsPh_3$, Ag_2O, THF, 70°C

Scheme 20



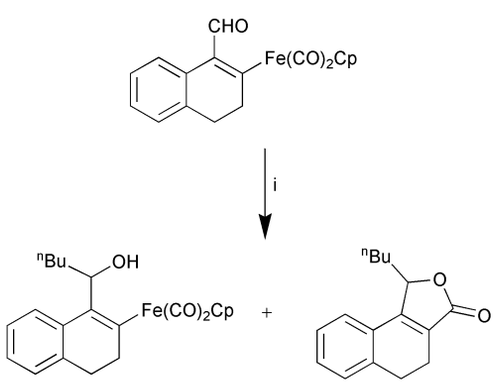
Conditions

i. $Pd(PPh_3)_4$ (3 mol%), $(HO)_2B$  , NaOH, 70°C

ii. ^tBuLi, Et_2O; $ClCO_2Et$ (100 eq), -78°C -> -5°C

iii. HCl (aq), MeOH, 50°C

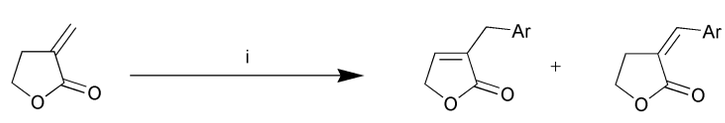
Scheme 21



Conditions:

i. ^nBuLi, -78°C -> rt; chromatography

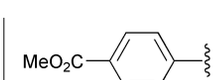
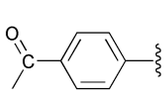
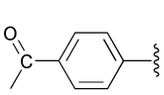
Scheme 22



(45) **(46)** : **(47)**

Conditions:

i. Ar-I, $Pd(OAc)_2$, KOAc, DMF,80°C

Ar			
Yield/%	60	64	73
Ratio (**46**):(**47**)	20:1	8:1	3:5

Scheme 23

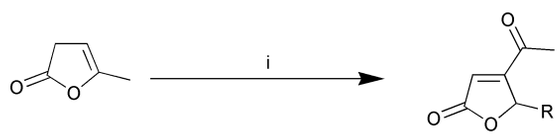
As a testament to the powerful electrophilicity of the furanone C=C bond, 5-trifluoromethylfuranone (**53**) undergoes a base-mediated dimerization *via* a Michael addition reaction to give bis(lactones) (**54**) and (**55**): the stereoselectivity of the process varies dramatically according to the nature of the basic conditions used (Scheme 29).[33]

The preparation and reactions of 5-lithiofuranone have not previously been widely investigated; this species has recently been shown to undergo regioselective aldol-like reaction with aromatic aldehydes.[34] Thus, furanone itself is deprotonated under typical conditions and reacted with such aldehydes to yield the expected adducts (**56**) in generally good yields. Moreover (and in contrast to boron triflate mediated reactions of furanones with carbonyl-containing electrophiles, *vide infra*) only the 5-hydroxyalkylated regioisomer was obtained from the reaction. These aldol products were obtained with relatively poor diastereoselectivities; they could be converted to the corresponding benzylidenefuranones (**57**) in good yields. In the latter process, predominantly (*Z*)-configured products were obtained (Scheme 30).

4-Bromo-5-(menthyloxy)furan-2(5*H*)-one (**58**) has been utilized as a precursor to a range of 4-amino- and 4-thio-functionalized enantiomerically-pure 5-menthyloxyfuranones.[35] Thus, (**58**) reacts with secondary amines and thiols to give the product (**59**) arising from an addition–elimination process (Scheme 31).

4-Vinylfuran-2(5*H*)-one (**60**) reacts with dimethyldioxirane to give epoxide (**61**), which may be converted into the analogous aziridine (**62**) by a Staudinger ring-opening–ring-closing process;[18] these reactions represent the first entry into these highly reactive furanones. Furanone (**60**) also reacts with dipoles to give furanones bearing a five-membered heterocyclic 4-substituent (Scheme 32).

Compound (**60**) also undergoes (less efficient) cycloaddition reactions with electron-rich dienes; once again, reaction occurs selectively at the exocyclic alkene of the furanone (Scheme 33).

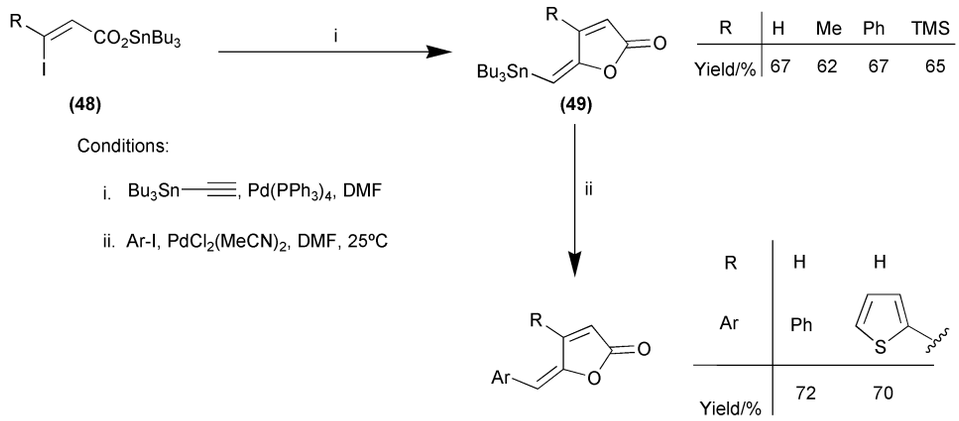


Conditions:

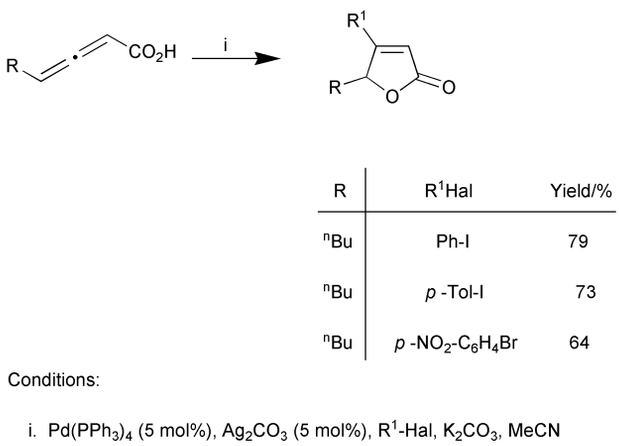
i. $Ni(cod)_2$, $4PPh_3$, Zn, RCHO, 50-60°C

R	Ph	^iPr	$^nC_6H_{13}$	$^cC_6H_{11}$
Yield/%	97	80	78	91

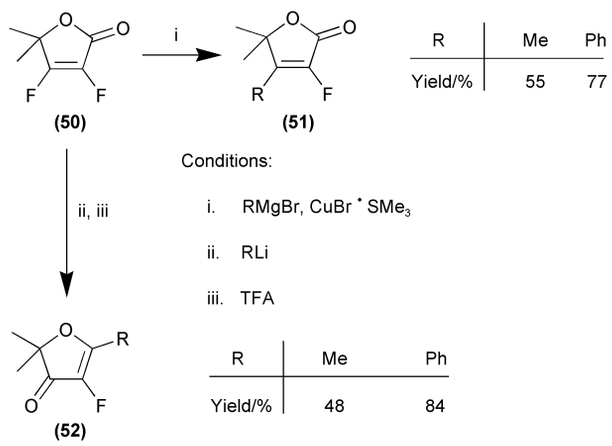
Scheme 24



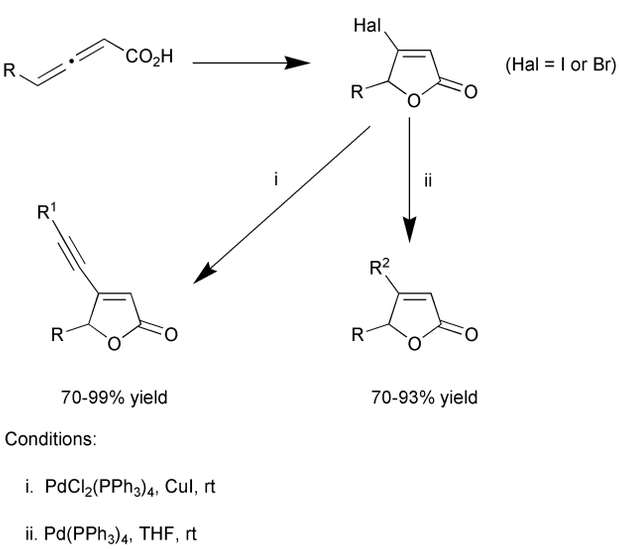
Scheme 25



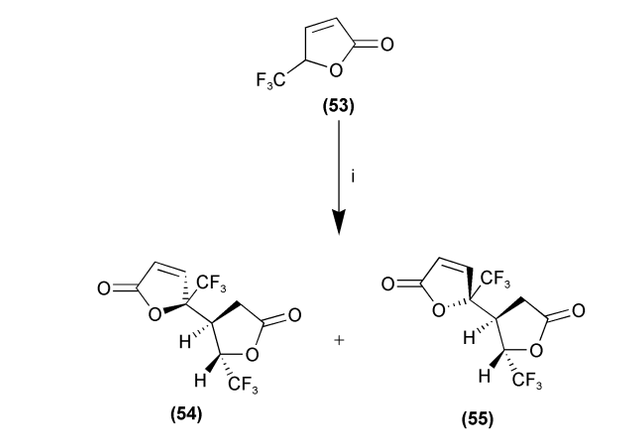
Scheme 26



Scheme 28



Scheme 27

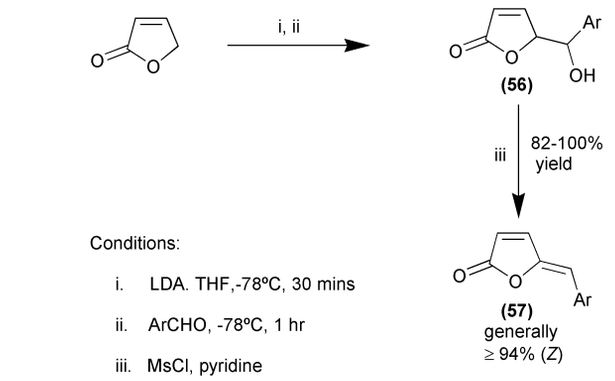


Scheme 29

2.6 From furans

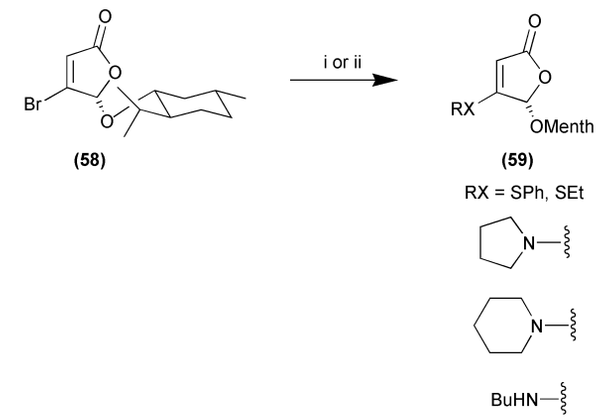
Syntheses of furanones from furan precursors continue to be widespread. Murai *et al.*[36] prepared enantiomerically pure furanone (**64**) by a sequence of acylation of 2-(triisopropyl)-oxy-4-lithiofuran by the Weinreb amide (**63**), followed by asymmetric reduction and desilylation. Furanone (**64**) was prepared in 97% ee and was utilized in the synthesis of an Azadirachtin precursor (Scheme 34).

The reactions of silyloxyfurans with enantiomerically pure tartrate-derived orthoesters (**66**) have been reported in full.[37] Thus, furans (**65**) and (**67**) undergo reaction with these ester equivalents in the presence of a range of Lewis acids in generally mediocre yields to give protected 5-acylfuran-2(5*H*)-ones

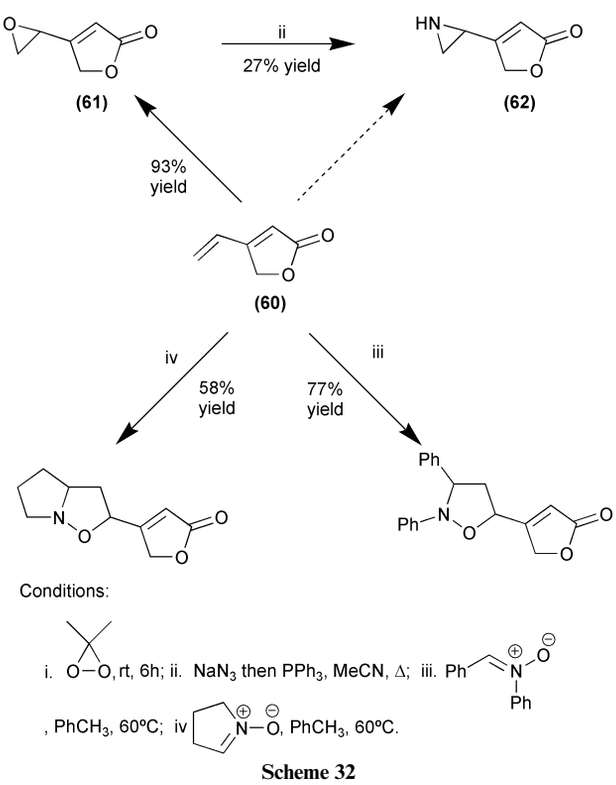


Ar		MeO	MeO OMe	
Yield/%	76	73	78	82
syn:*anti*	80:20	70:30	86:14	70:30

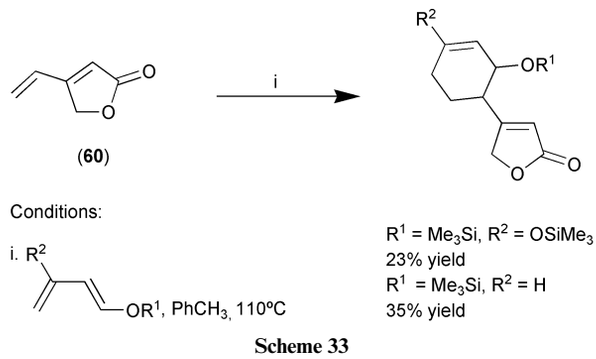
Scheme 30



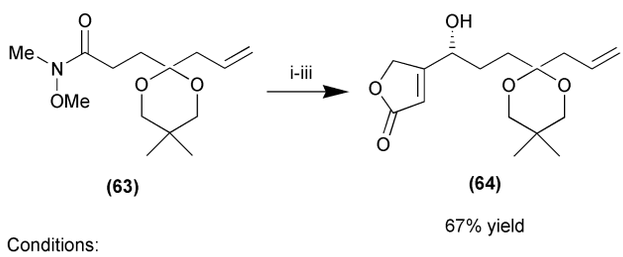
Scheme 31

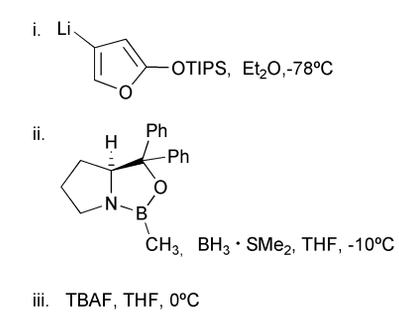


Scheme 32

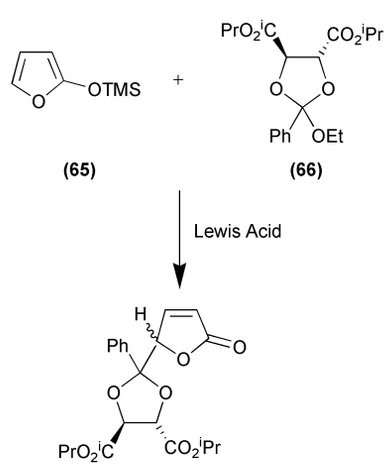


Scheme 33





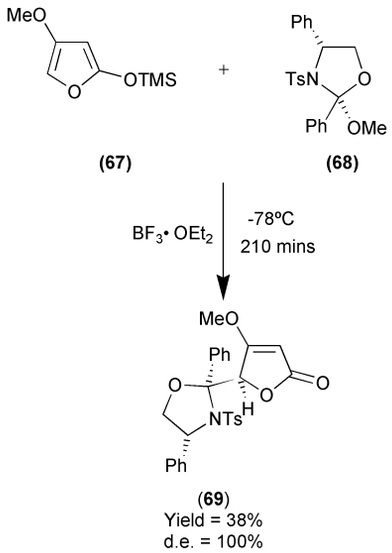
Scheme 34



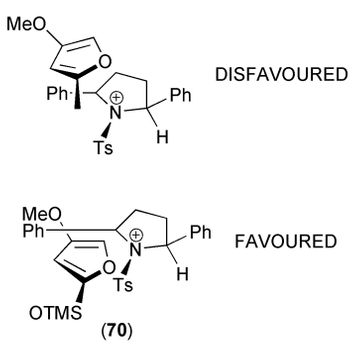
Scheme 35

with poor diastereoselectivity (Scheme 35). Higher levels of selectivity were observed when (**67**) was reacted with 2-alkoxy-oxazolidines, such as (**68**), to give protected 5-acylfuranones (**69**) (Scheme 36). The authors rationalize the face selectivity of the more selective reactions by consideration of an *endo*-like transition state (**70**).

A chemoenzymatic approach to the synthesis of the core pyranofuranone *motif* of the Manoalides has been reported.[38] Thus, racemic lactone (**71**) (prepared from furan-3-carbaldehyde) was reacted with *P. fluorescens* lipase (PFL) to give



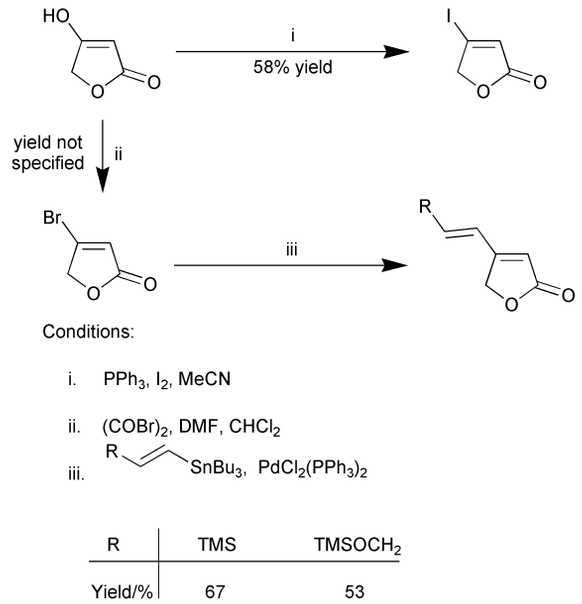
Scheme 36



alcohol (**72**) in 33% yield and 91% ee. Unreacted (4*R*,6*S*)-acetate (**73**) was contaminated with the elimination product (**74**). Using these products, the enantiomeric pyranofurans (**75**) could be prepared, whereupon it was revealed that the impure (4*R*,6*S*)-acetate had been obtained with low enantioselectivity (33% ee). Photooxygenation of (**75**) gave furanone (**76**), in poor yield (Scheme 37).

2.7 Miscellaneous methods

4-Bromo- and 4-iodofuranone have been prepared by a variety of methods: Lattman and Hoffman[39] prepared the compounds from tetronic acid. The bromide was used to prepare certain 4-vinylfuranones, in acceptable yields. The same group also prepared 4-bromomethylfuranone and 4-hydroxymethylfuranone, from 3,3-dimethylacrylic acid and dihydroxyacetone respectively (Scheme 38 and 39).

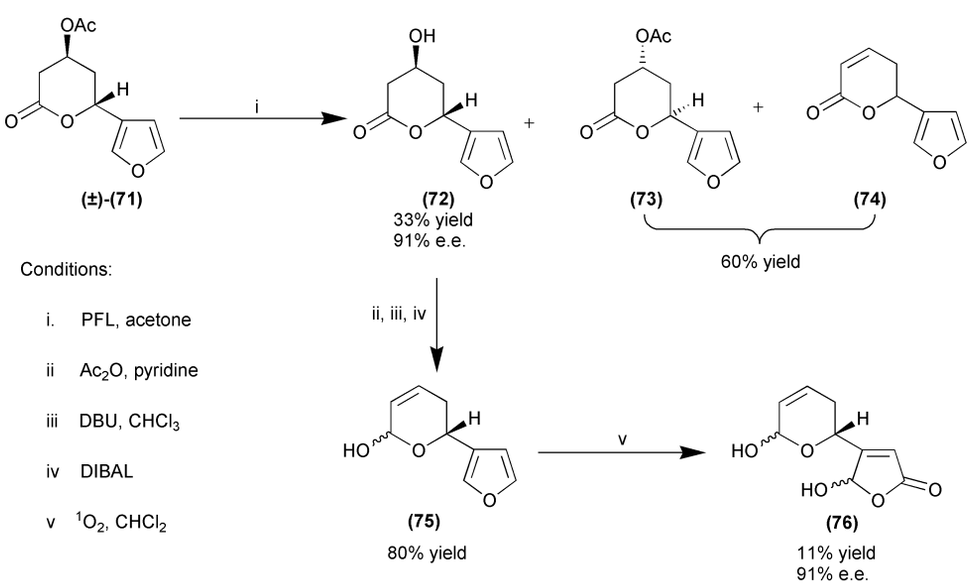


Scheme 38

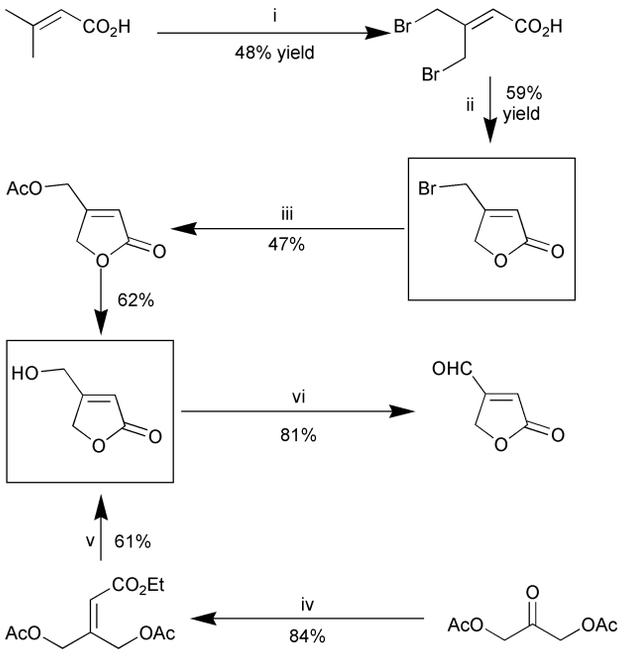
Both 3- and 4-halofuranones may be prepared from the corresponding stannanes.[40] Thus treatment of these compounds with positive halogen equivalents gives the compounds in acceptable yields (Scheme 40).

Certain 5-substituted furanones may be obtained with high ee *via* 4-hydroxy-5-iodomethylbutanolides: (**77**)[41] these lactones can function as synthetic equivalents for the cationic furanone synthon (**78**). Thus, either enantiomer of (**77**) reacts sequentially with nucleophiles and bases to give furanone products.[42] Higher enantioexcesses in the products are observed if the leaving group ability is first enhanced by benzoylation (Scheme 41).

Maleate esters (**79**) are readily accessible *via* a Baylis–Hillman reaction of dialkyl maleates with lithium amides and ketones.[43] These γ-hydroxyesters may be converted to 5,5-dialkyl-3-alkoxycarbonylfuranones by a sulfur-radical induced isomerization process.[44] Thus, these diesters react under photo-



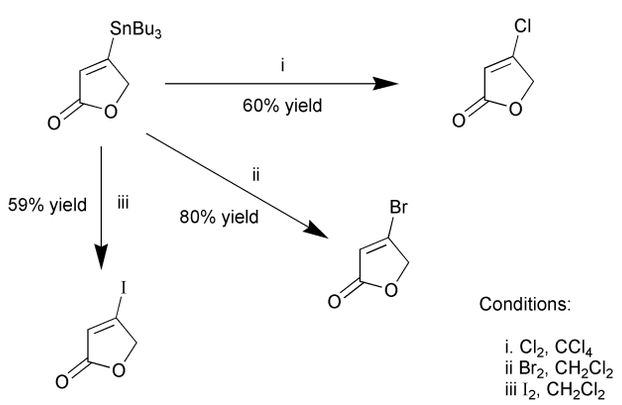
Scheme 37



Conditions:

i. NBS
ii. NaOH
iii. KOAc, 18-C-6
iv. $Et_2OCCH_2P(O)(OEt)_2$, DMAP, ^tBuOK
v. MsOH
vi. Dess-Martin

Scheme 39



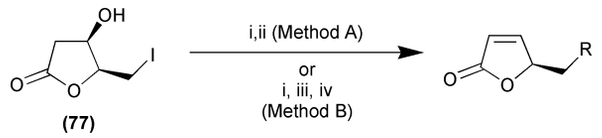
Scheme 40

thermal conditions with diphenyldisulfide in refluxing hexane to give such furanone products, in variable yields. The reaction is postulated to occur *via* an addition–cyclization–elimination process (Scheme 42).

Spirofuranone (**83**), a metabolite of a synthetic progesterone antagonist, has been prepared from ketone (**80**) *via* propargyl‡ diol (**81**).[45] Thus, the latter was obtained in virtually quantitative yield by reaction of (**80**) with propargyl alcohol in the presence of ^tBuOK; catalytic partial hydrogenation followed by oxidation using silver carbonate on Celite® gave furanone (**82**) in good overall yield. Furanone (**82**) was converted to the target molecule in short order (Scheme 43).

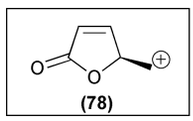
Ribbons and Sutherland[46] have extrapolated the rich chemistry of *P. putida* to allow for an expedient synthesis of (+)-muconolactone [(5*R*)-5-carboxymethyl-2(5*H*)furanone, **84**] from racemic mandelic acid. Thus, *P. putida* PR52912 converts

‡ The IUPAC name for propargyl is prop-2-ynyl.



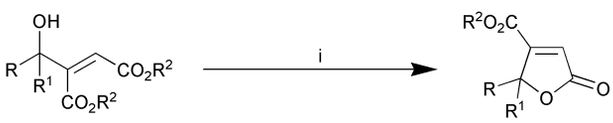
Conditions:

i. RMgBr, $CuBr \cdot SMe_2$
ii. MsCl, DMAP
iii. PhCOCl, pyridine
iv. NH_3, MeOH



R	$^nC_3H_7$		$^nC_4H_9$	
Method	A	B	A	B
Yield/%	46	40	42	40
e.e./%	71	99	81	99

Scheme 41



(**79**) Conditions:

i $(PhS)_2$, 125W Hg lamp, hexane, reflux

R	Me	Ph	Ph	Ph
R^1	Me	Me	Ph	H
R^2	Me	Et	Et	Me
Yield/%	66	77	44	46

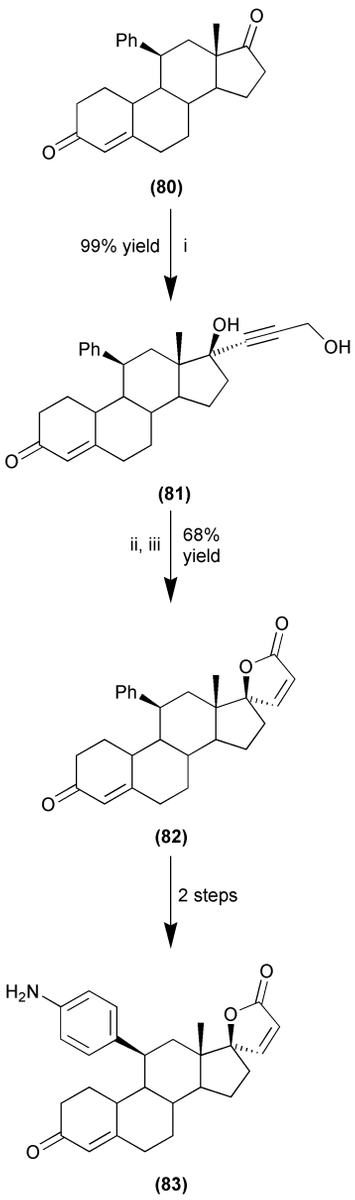
Scheme 42

this starting material to (**84**) in 97% yield *via* an eight-step biotransformation; the authors report full experimental details for preparation of (**84**) on a gram scale. As an aside, the authors demonstrate the previous stereochemical assignment of (**84**) isolated from natural sources to be incorrect; chemical correlation unambiguously assigned the (5*R*)-configuration to the dextrorotatory isomer (Scheme 44).

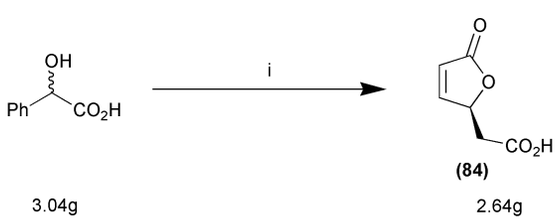
When 2-acetoxy-4-chloro-3-phenylcyclobutenone (**85**, prepared from the corresponding 2,4-dichlorocyclobutenone) is treated with methanolic sodium methoxide at room temperature, a novel rearrangement reaction occurs, yielding furanone (**87**) in moderate yield.[47] If (**85**) is simply heated in refluxing methanol, the same product is obtained in 75% yield after 8 hours. The authors suggest two possible mechanistic pathways to rationalize these observations, both involving hydroxycyclobutenone (**86**) as the fulcrum of the process (Scheme 45).

The importance of (**86**) in the transformation was shown when the compound was separately prepared and converted to (**87**); the latter transformation also occurs spontaneously when an NMR solution of pure (**86**) is left to stand for 3 days.

Squaric acid derivatives are converted, in a two-step process, to furan-2(5*H*)-ones.[48] Thus, for example, diethyl squarate (**88**) may be alkylated by reaction with organolithiums, and the products of the reaction made to undergo an oxidative ring-opening–ring-closing process upon treatment with lead tetraacetate in dry toluene at room temperature. The



Scheme 43



Scheme 44

mechanistic rationâle proposed by the authors invokes triacetoxyorganolead furanone (**89**) as a key intermediate (Scheme 46).

Alkynyl Fischer carbene complexes, such as (**90**) may be converted into ring-fused furan-2(5*H*)-ones by reaction with dihydropyridines.[49] Thus, chromiumcarbene (**90**) is transformed into a mixture of diastereomeric hexahydrobenzofuranones upon reaction with *N*-methyl-1,4-dihydropyridine. The reaction proceeds *via* anionic acyl metal complex (**91**) (Scheme 47).

3 Total syntheses

The first enantioselective synthesis of Manoalide (**94**) has been claimed.[50] The key reactions of the synthetic sequence are a Sato aldol reaction (of 3-furaldehyde) and a singlet oxygen cycloaddition process. Thus, ketoester (**93**) was prepared in 87% ee by an aldol reaction of dienol ether (**92**) with furaldehyde, followed by microwave-induced deacetylation. (**93**) was then transformed into Manoalide in six steps (Scheme 48).

Acetylmelodorinol (**95**), an anti-tumour methylenefuranone isolated from *Melodorum fruticosum* Lour, has been prepared by means of a synthetic sequence involving nucleophilic addition of 5-lithioalkoxyfurans to (*R*)-glyceraldehyde isopropylidene acetal.[51] Thus, although the addition reaction is (perhaps surprisingly) unselective, both diastereoisomers may be converted to the natural product (Scheme 49).

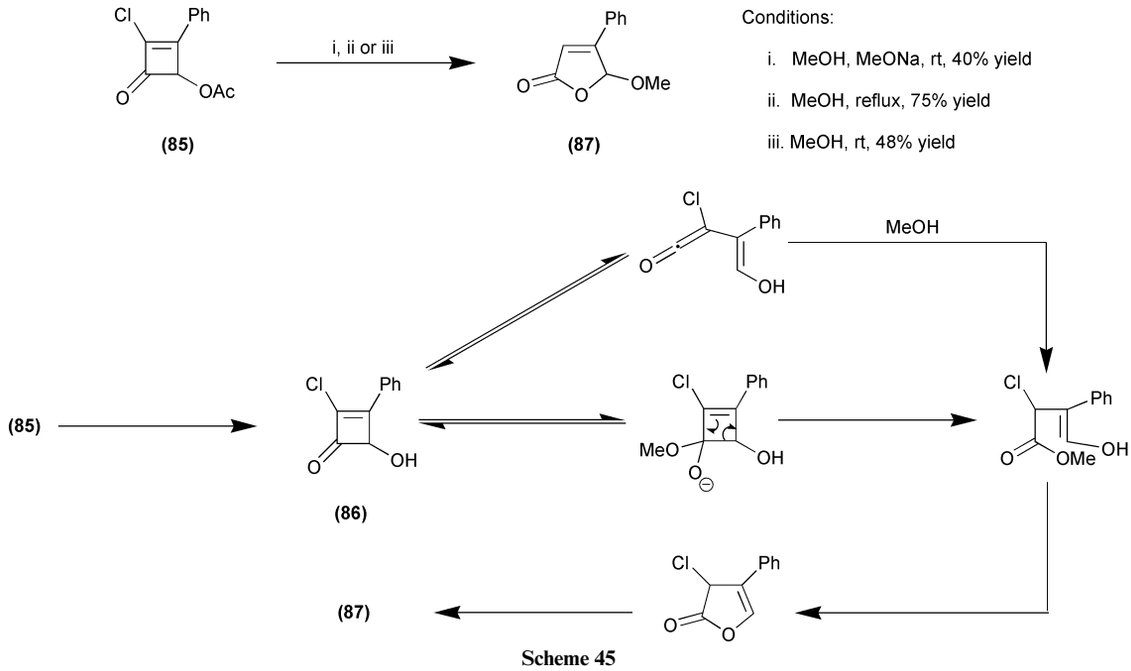
More than a hundred potent bioactive secondary metabolites have been isolated from *Annonaceae* species during the last fifteen or so years.[52] These compounds usually contain one or two tetrahydrofuran rings and often an intact furanone moiety. These so-called *Annonaceous acetogenins* have, therefore, engendered a diversity of synthetic methodology directed towards furanone synthesis. In the synthesis of Corossolone and Corossoline[53] the furanone moiety was derived from (*S*)-lactic acid, as shown below (Scheme 50).

The same group have reported the use of Jacobsen's HKR (**H**ydrolytic **K**inetic **R**esolution) in the preparation of a highly enantiomerically-enriched Corossoline intermediate.[54] Thus, epoxyfuranone (**96**) was prepared by the previously-employed synthetic pathway[55] involving aldol-like reaction of the enolate derived from methyl undec-10-enoate with protected lactaldehyde. The racemic mixture resulting was hydrolytically-resolved by reaction with a sub-stoichiometric amount of (*R*,*R*)-salen-Co(OAc). The desired epoxide (*R*)-(**96**) was obtained in 46% yield and was reacted with lithiotrimethylsilylethyne to give propargylic alcohol (**97**), which had previously been used by the authors in their synthesis of (10*R*)-corossoline. Alcohol (**97**) was shown to be virtually a single diastereoisomer (of 99% de) (Scheme 51).

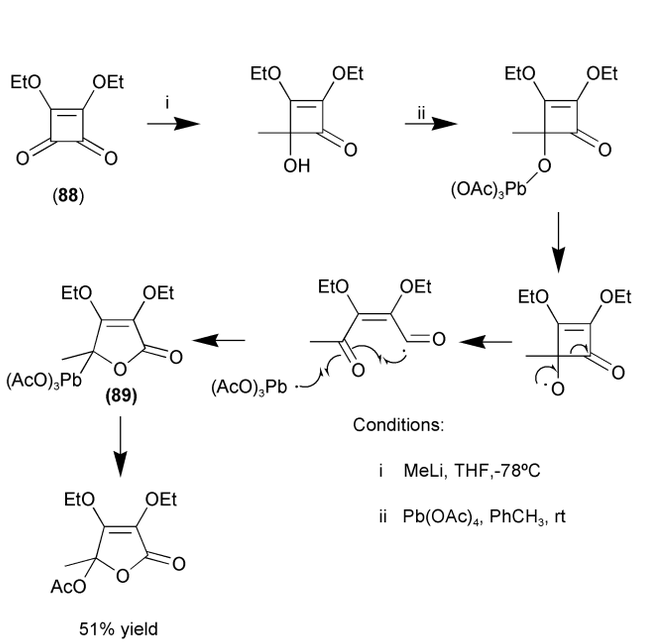
Synthetic approaches to the potent acetogenin Mucocin have littered the literature of late.[56] Koert *et al*.[57] have reported their method to this compound, in which the furanone moiety was prepared by a selanation–elimination process. Thus, butanolide (**98**) was converted to (5*R*)-furanone (**99**) in 88% yield; (**99**) was incorporated into the target molecule as shown in Scheme 52. Another approach to Mucocin involves 5-*exo*-cyclization of an acyl radical, followed by dehydration, in the key furanone-forming sequence (Scheme 53).[49b]

Ley *et al*.[58] have reported the total synthesis of another annonaceous acetogenin: Muricatetrocin C (**103**). In this synthetic sequence, the furanone moiety was introduced at an early stage *via* a similar lactaldehyde strategy. Thus acrylate (**100**) was deprotonated and treated with enantiomerically pure lactaldehyde (**101**) to give (after cyclization and elimination) (*Z*)-furanone (**102**). Compound (**102**) needed to be isomerized under photolytic conditions to the (*E*)-isomer, which was then subjected to a hetero Diels–Alder reaction as a means of introducing the required (4*R*)-hydroxy group (Scheme 54).

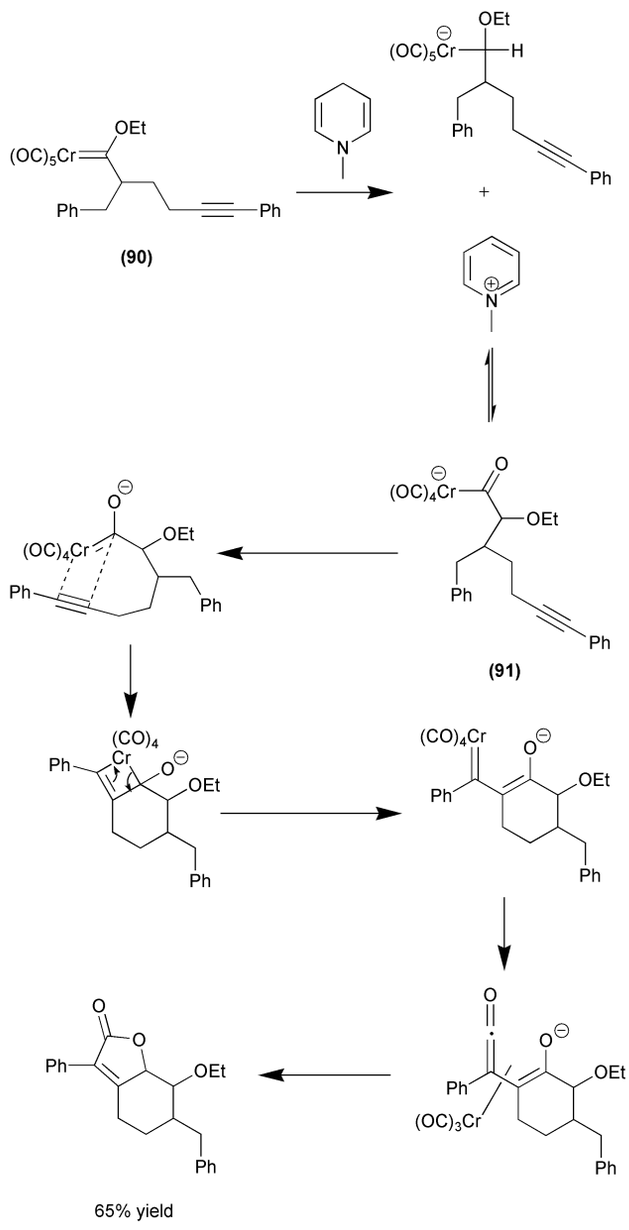
It is well-known that annonaceous acetogenins containing two tetrahydrofuran rings are approximately ten times more potent than those containing a single such heterocycle.[59] Until recently, only natural products containing non-adjacent tetrahydrofuran rings separated by not more than a four-carbon chain have been isolated. Aromin and Aromicin[60] have



Scheme 45



Scheme 46

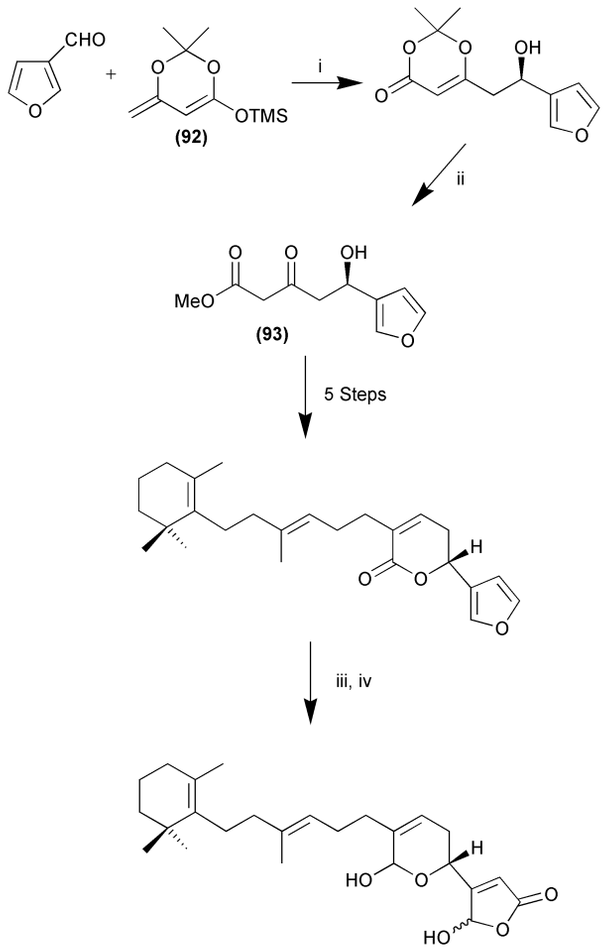


Scheme 47

been isolated from *Xylopia aromatica* and found to contain a bis(THF) core in which the saturated heterocycles are separated by a C_8 chain. Interestingly, these compounds possess activities closer to that of mono(THF) acetogenins than the bis(THF) natural products.

(+)-Hamabiwalactone B has been prepared by Stille coupling of enantiomerically-pure (5*S*)-5-methyl-3-tributylstannylfuranone with *E*-1-iodododeca-1,11-diene; the postulated absolute configuration of this natural compound was confirmed by the authors, and the enantiomeric purity of the product was confirmed by chiral HPLC, thereby revealing that the natural product had been partially racemized upon isolation (Scheme 55).[61]

Selective metal–halogen exchange reactions of derivatives of (3*S*)-1,1-dibromo-3,4-dihydroxybutene have been exploited to allow the first synthesis of the powerful antifungal agent Fugomycin (Scheme 56).[62] In this synthetic sequence,

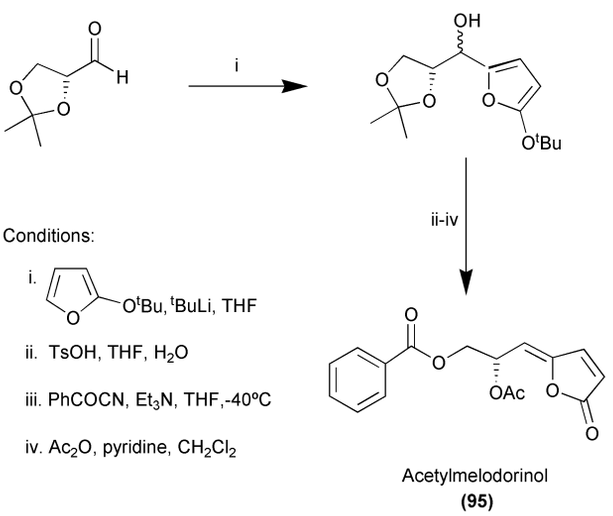


Manoalide **(94)**

Conditions:

i. $Ti(O^iPr)_4$, (*R*)-(+)-BINOL
87% e.e., 65% yield
ii MeOH, PhMe, microwave
iii DIBAL, -78ºC, PhMe
iv $^1O_2$, CH_2Cl_2, -78ºC

Scheme 48



Conditions:

i. O^{t}Bu, ^{t}BuLi, THF

ii. TsOH, THF, H_2O

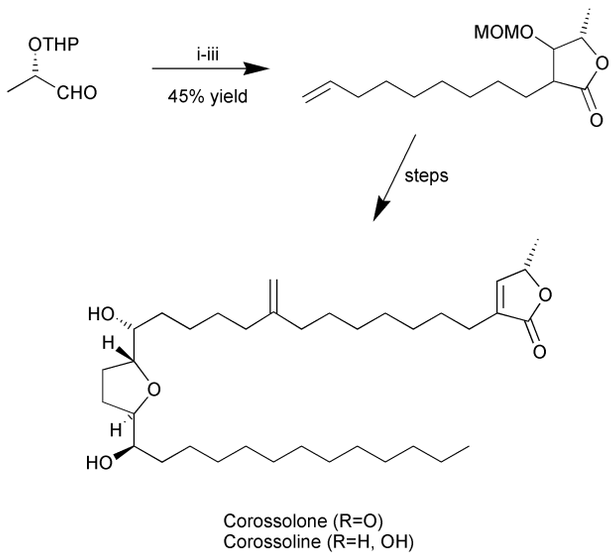
iii. PhCOCN, Et_3N, THF,-40ºC

iv. Ac_2O, pyridine, CH_2Cl_2

Acetylmelodorinol
(95)

Scheme 49

(*E*)-selective Pd(0)-catalyzed cross-coupling with hex-1-ynylmagnesium bromide yielded a mixture of bromoenynes which could be converted (*via* Br–Li exchange and carboxylation) into a direct precursor of Fugomycin. This synthesis confirmed the absolute configuration of the natural product to be (*S*).



Corossolone (R=O)
Corossoline (R=H, OH)

Conditions:

i. CO_2Me, THF-HMPA

ii. MOMCl, Hünigs base

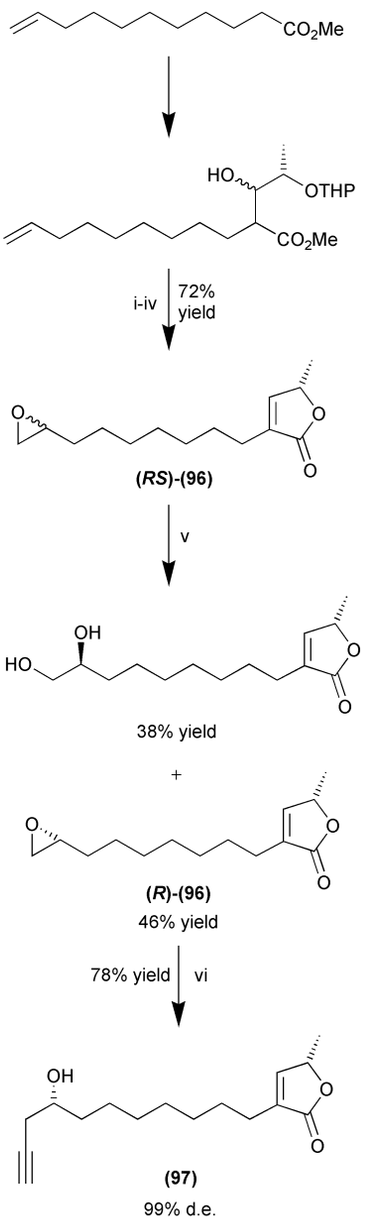
iii 10% H_2SO_4, THF

Scheme 50

The Syringolides, first isolated in 1993, have attracted the attentions of several groups. These tricyclic hemiacetals often exist in equilibrium with the ring-opened furanone (**104**) (Scheme 57). A range of synthetic strategies toward these compounds have been reported. Thus, 3-tributylstannyl- or 3-bromofuran may be converted into protected polyhydroxyfuranone (**105**) which serves as an intermediate in the synthesis of furanones (**106**) and thence the Syringolides (Scheme 58).[63]

Negishi *et al.*[64] report that Xerulin (**108**) has been prepared in an efficient and stereoselective manner using a sequential 'one-pot' Sonogashira-cyclization protocol as a key step. This reaction is between tetraenetriyne (**107**) and (*Z*)-3-iodoacrylic acid, which proceeds in good yield to give (**108**) in >96% stereopurity (Scheme 59). Two synthesis of dihydroxerulin (**109**) (a non-cytotoxic inhibitor of cholesterol biosynthesis) have been reported of late. Thus, the strategy of Rossi *et al.*[65] revolves around a disconnection of the C8–C9 alkene, whereas Siegel and Brückner[66] decided to disconnect the C6–C7 double bond: both strategies utilized Wittig olefination as the key step (Scheme 60).

Lissoclinolide (**112**) has been prepared in a stereocontrolled fashion utilizing a metal-catalyzed 5-*exo*-cyclization of 2-bromo-2-en-3-ynoates developed by the authors.[67] Thus, (*E*, *E*)-2-bromo-8-hydroxyocta-2,6-dien-4-ynoic acid (**110**) reacted with a sub-stoichiometric amount of Ag(II) to give vinylmethylidenefuranone (**111**) in good yield and as a single (*Z*,*E*)-isomer. Compound (**111**) was then cross-coupled with (*E*)-3-tributylstannylpropenol under Stille–Farina conditions to give Lissoclinolide (Scheme 61). Brückner and Görth[68] subsequently prepared Tetrenolin (**113**) and Lissoclinolide (**110**) from gulono- and mannonolactones



Conditions:

i. Ac_2O, pyridine

ii. $H_2SO_{4\ (aq)}$

iii. mCPBA, CH_2Cl_2

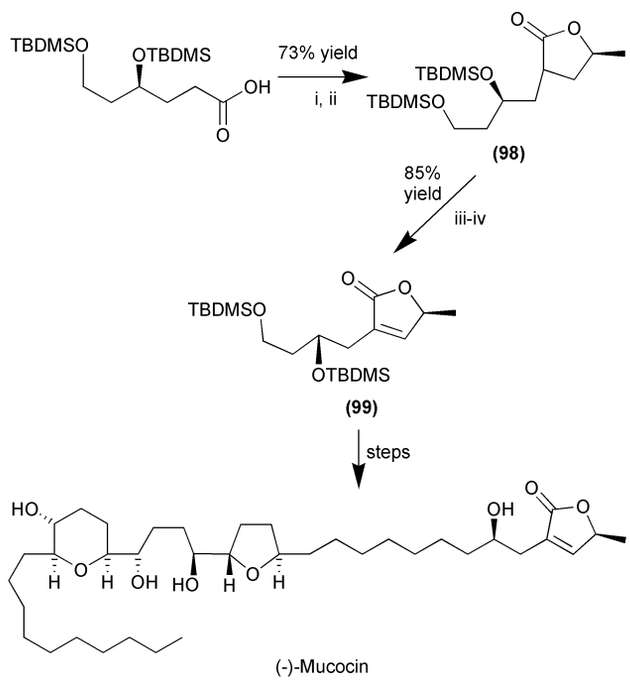
iv. DBU, THF

v. (*R*,*R*)-salen-Co(OAc) (0.5 mol%)

vi. Li—≡—TMS, $BF_3 \cdot OEt_2$

Scheme 51

(Scheme 62) and thereby confirmed that the former (postulated to be a stereoisomer of Lissoclinolide) was in fact identical to the latter. A review of the synthesis of stereodefined γ-alkylidenebutenolides has been produced from the same labs.[69]



Conditions:

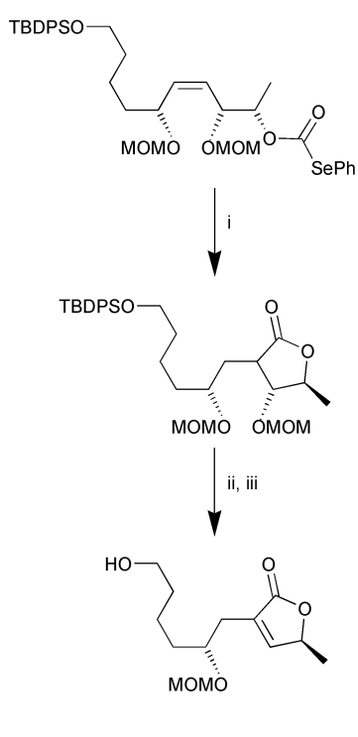
i. LDA, 0°C,

ii. ^tBuCOCl, NEt_3

iii. KHMDS, PhSeCl

iv. MMPP, THF/MeOH

Scheme 52



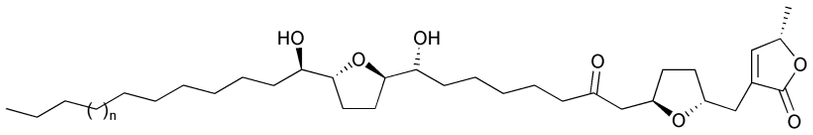
Conditions:

i. Bu_3SnH, AIBN, PhMe, 100°C

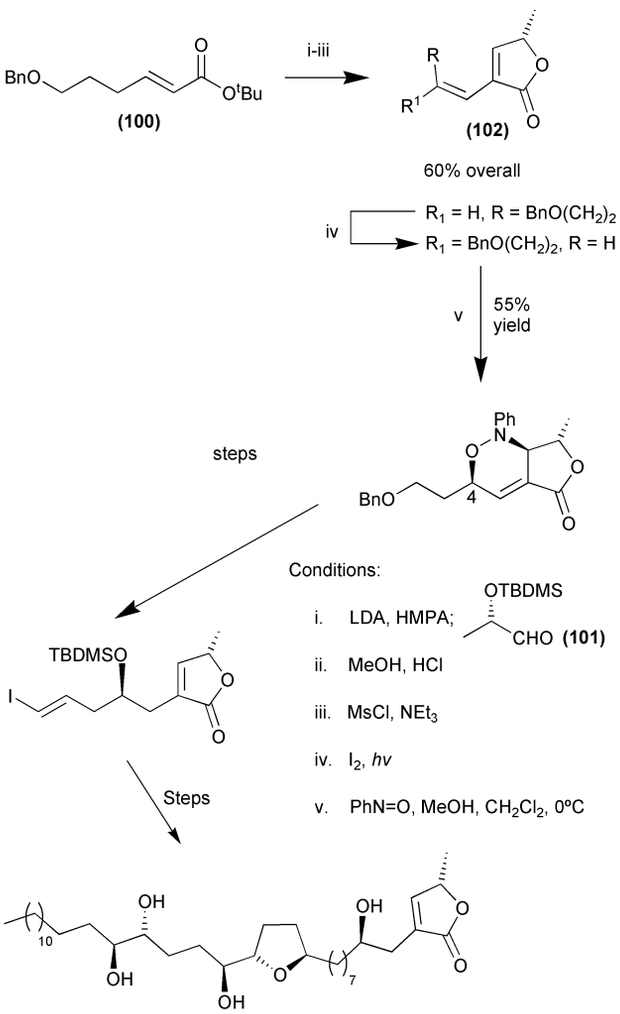
ii. TBAF, AcOH, rt

iii. DBU, MeCN, 0°C

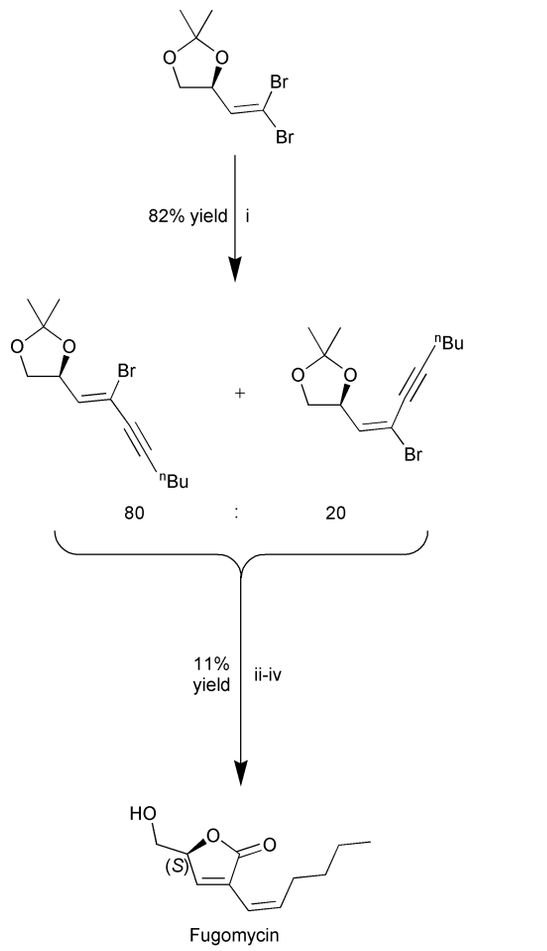
Scheme 53



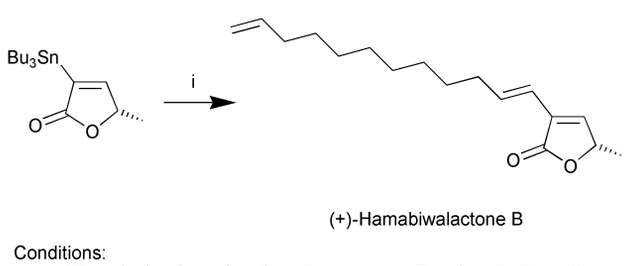
Aromin (n = 1)
Aromatic in (n = 3)



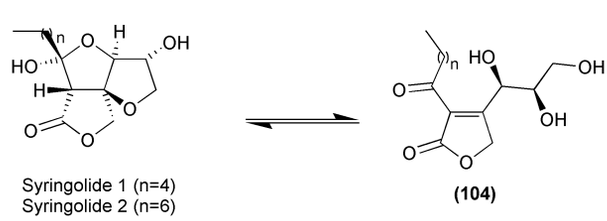
Scheme 54



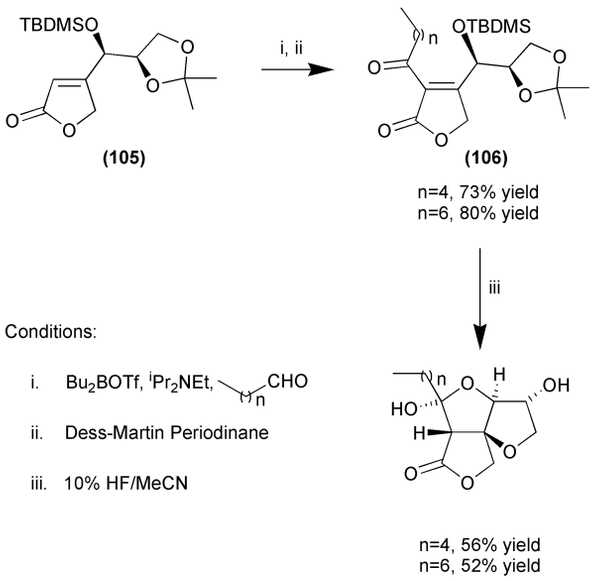
Scheme 56



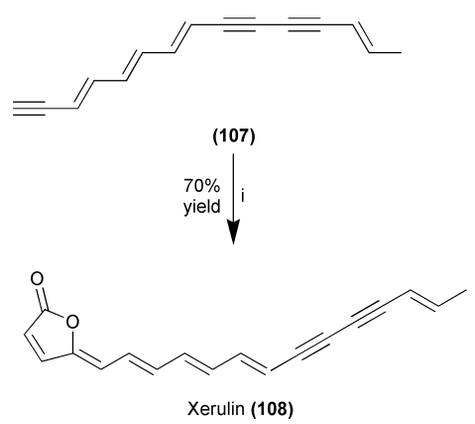
Scheme 55



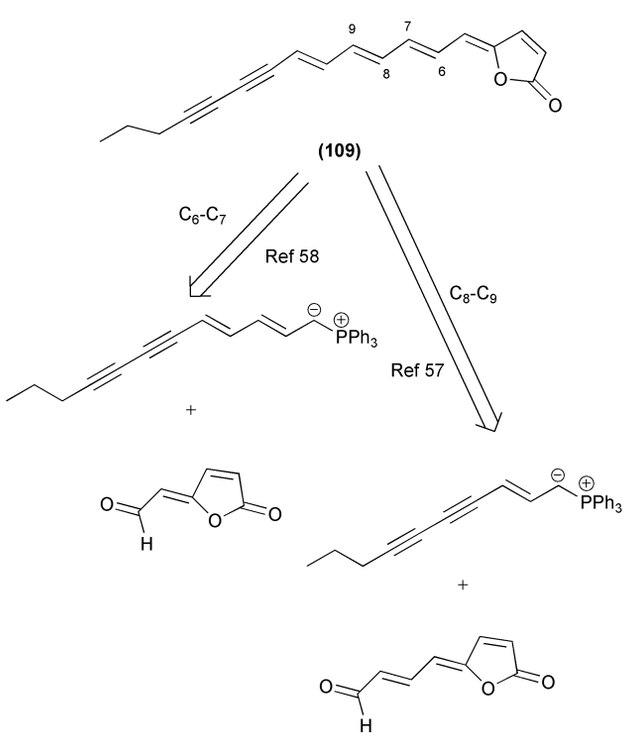
Scheme 57



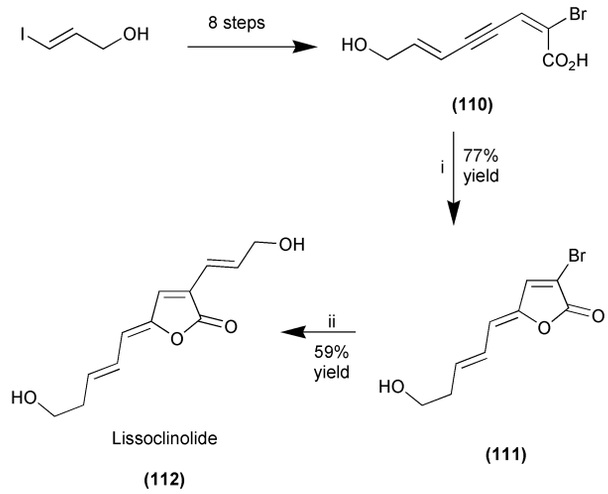
Scheme 58



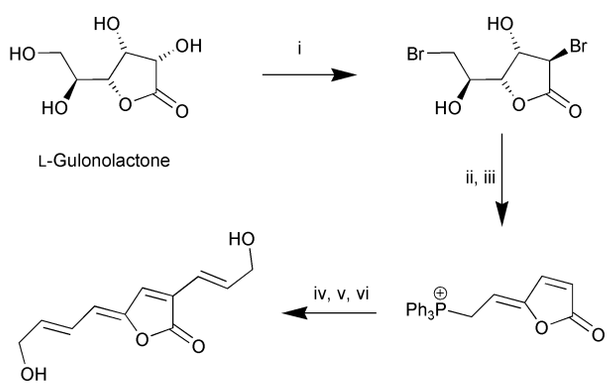
Scheme 59

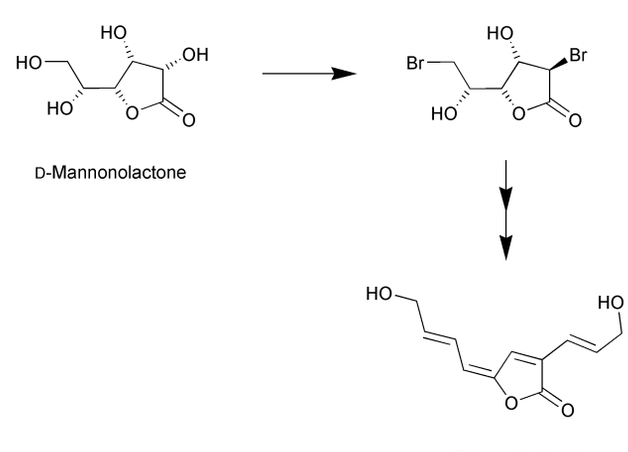


Scheme 60



Scheme 61





Scheme 62

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