Saturated and unsaturated lactones

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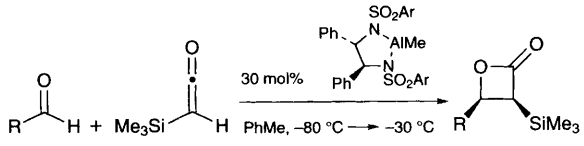
Reviewing the literature published between 1 November 1995 and 31 October 1996
Continuing the coverage in *Contemporary Organic Synthesis*, 1996 **3**, 295.

1 Introduction

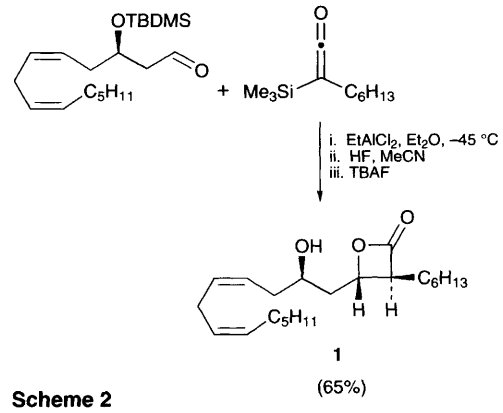
This review highlights recent advances in the synthesis of saturated and unsaturated lactones, which continue to be of importance both as synthetic intermediates and as targets, often biologically active, in their own right. The chemistry covered is classified according to the structures of the lactone products, but where general methodology is applicable across these divisions this is indicated in the text.

2 β-Lactones

Following from recent developments in the substrate controlled [2+2] cycloaddition of trimethylsilylketene to aldehydes, reviewed last year, the first catalytic, enantioselective variant of this reaction has been reported by Kocienski *et al.*[1] Achiral aldehydes and trimethylsilylketene combine in the presence of chiral aluminium bis-sulfonamide Lewis acids to give *cis*-substituted β-lactones as the major products. The optimum catalyst design is still unknown, so yields and enantioselectivity are variable and the best results are seen with aryl aldehydes (**Scheme 1**). The same group has also described in full the first total synthesis of (−)-lipstatin using a related substrate controlled cycloaddition to construct the oxetane.[2] A high level of 1,3-induction (>80% de) is observed, and sequential *O*- and *C*-desilylation gives the (−)-lipstatin skeleton **1** in good yield (**Scheme 2**).

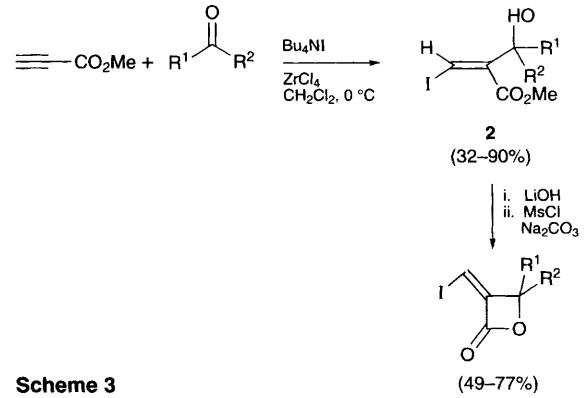


Scheme 1



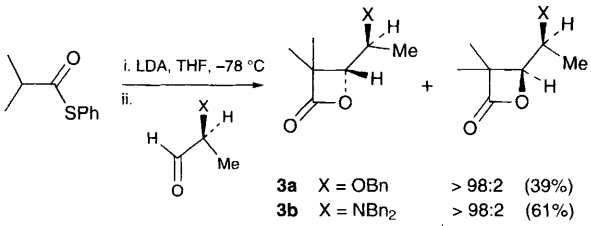
Scheme 2

A new route to α-iodomethylene-β-lactones involves the Lewis acid catalysed, tandem nucleophilic addition–aldol reactions of propynoate esters and ketones to reach the lactonisation precursors **2**.[3] Zirconium tetrachloride as catalyst gives superior yields; the lower values in the quoted ranges are associated with crowded cyclic ketones. The *Z* selectivity of the tandem reaction increases with the bulk of the carbonyl component (**Scheme 3**).



Scheme 3

An asymmetric extension of Danheiser's alkanethioate methodology uses the reaction of

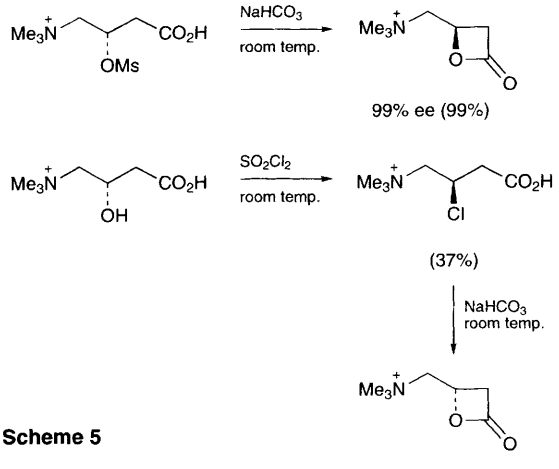


Scheme 4

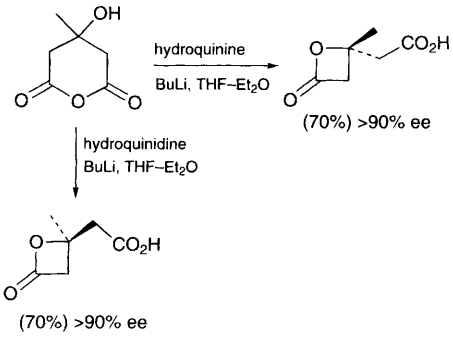
homochiral α-substituted aldehydes to give moderate yields of the β-lactone products **3**.[4] In most cases the lithium enolate attacks on the Felkin–Anh trajectory, *anti* to the heteroatom substituent, but the product of apparent chelation control is observed in the formation of the silyloxy substituted lactone **3c**. Further transformation to γ-lactones by dyotropic rearrangement is possible, and in the case of **3b** occurs spontaneously during chromatography (**Scheme 4**).

The industrial waste product (*S*)-carnitinamide can be transformed into β-lactones suitable as reagents for the incorporation of both (*R*)- and (*S*)-carnitine[5] (**Scheme 5**). The lactones are readily opened at the carbonyl with amines and alcohols, but acetate and azide react preferentially at C-3 to give O–alkyl fission with inversion. A directing effect of the quaternary ammonium group on these ambident anions is postulated. In a similar vein, β-lactones also serve as agents for the introduction of 3-hydroxy-3-methylglutarate (HMGA).[6] Here, the lactones arise from racemic HMGA anhydride by desymmetrisation with chiral lithium amide bases (**Scheme 6**). The use of ether as a co-solvent is critical for high enantioselectivity, a finding ascribed to the prevention of dissociation of the anhydride–chiral base complex.

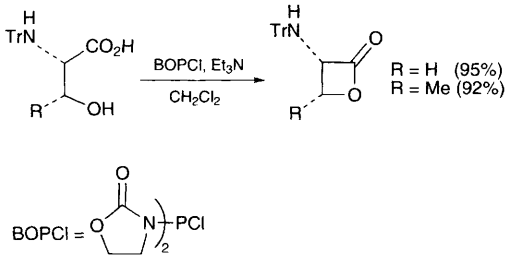
The straightforward lactonisation of 3-hydroxy acids is usually problematic but the direct cyclisation of *N*-trityl protected serine and threonine gives unexpectedly high yields of the corresponding β-lactones[7] (**Scheme 7**). This compares very favourably with the Mitsunobu and Adam cyclisation of related protected amino acids.



Scheme 5



Scheme 6

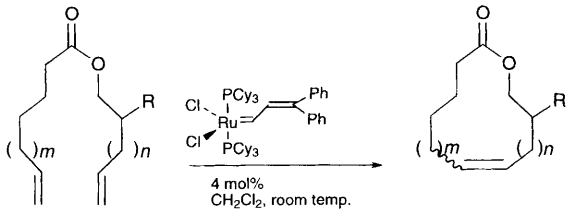


Scheme 7

3 Macrolides

Fürstner has demonstrated the general utility and efficiency of ring closing metathesis in macrolide formation[8] (**Scheme 8**). No specific conformational restraints are needed for the cyclisation of simple ω-dienes with Grubbs' ruthenium catalyst and good yields of 12- to 21-membered ring lactones are obtained. The position and steric congestion of the ring closure may be critical, as shown by the poor yield when the precursor has an allylic methyl substituent. The methodology has been applied to the asymmetric synthesis of the 12-membered ring plant growth regulator (*R*)-(+)-lasiodiplodin.[9]

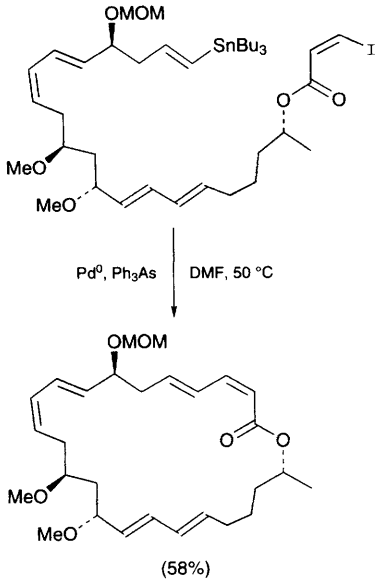
Unsaturated macrolides can also be reached by Stille coupling, as in the 24-membered precursor to macrolactin A[10] (**Scheme 9**). The acyclic material is



R	*m*	*n*	*Z*:*E*	Yield(%)
H	5	2	54:46	79
H	5	7	35:45	71
Me	5	0	0:100	10
Me	2	3	4:96	72

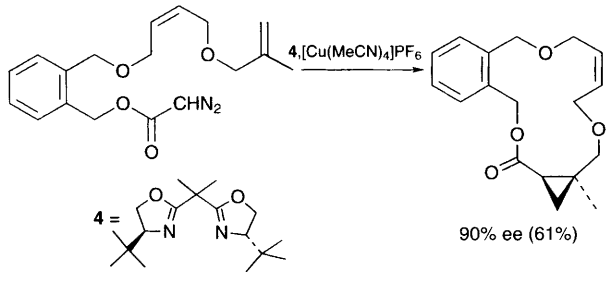
Scheme 8

in turn constructed by sequential palladium catalysed coupling reactions.



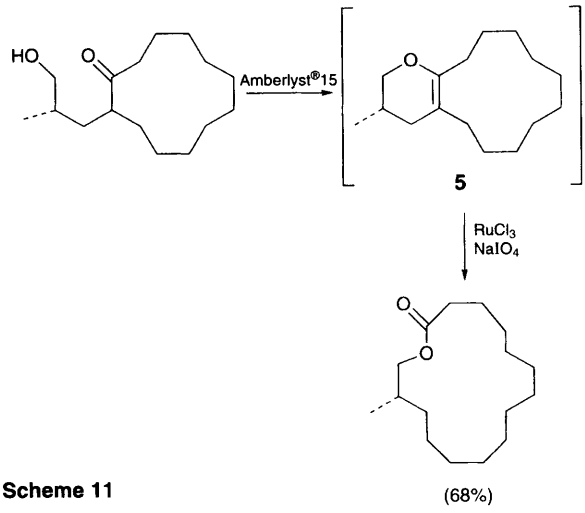
Scheme 9

Asymmetric intramolecular cyclopropanation by metal carbenoids can generate macrolides in good yield and high enantioselectivity.[11] The use of copper as the metal with Evans' bis(dihydrooxazole) ligand **4** gives superior asymmetric induction and fewer side reactions than alternative rhodium catalysts. Only the *cis*-cyclopropanes are seen and good regiocontrol between competing cyclopropanation sites is achievable (**Scheme 10**). The related intramolecular addition of rhodium carbenes to remote arenes also forms macrolides, but with less impressive regiocontrol.[12]

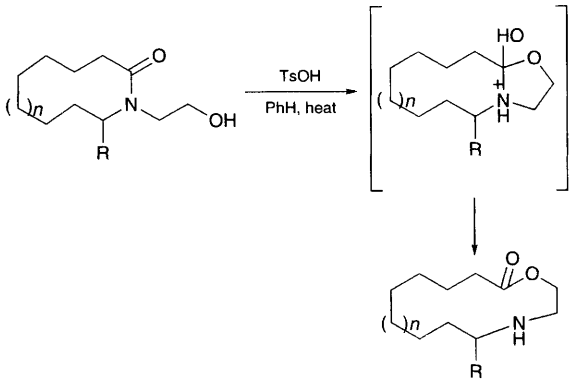


Scheme 10

Odorant macrolides and medium rings are prepared by oxidative ring expansion with ruthenium tetroxide, a method that has been refined to enable gram-scale syntheses.[13] The mechanism seems to involve direct oxidation of the enol ether **5** (**Scheme 11**), although there is evidence for the alternative oxidation of a hemiacetal intermediate in some cases. Such an intermediate is central to a novel lactam to lactone ring expansion used in the synthesis of azamacrolides.[14] The cleavage reaction is driven forward by relief of transannular strain and protonation of the basic product (**Scheme 12**). The azamacrolide **6** can also be prepared by conventional, high dilution Mukaiyama lactonisation (43%).[15]



Scheme 11

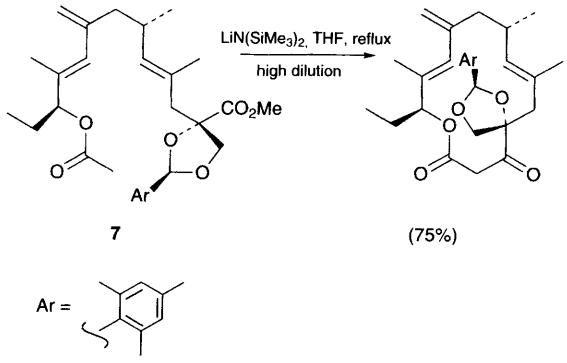


6

n	R	Yield(%)
1	Pr^n	56
4	H	83

Scheme 12

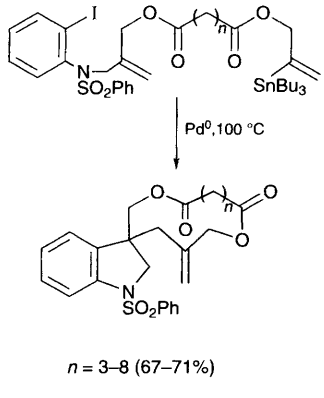
The antifungal 14-membered ring lactone galbonolide B has been made through a new macro-Dieckmann cyclisation[16] (**Scheme 13**). High dilution conditions allow cyclisation of the acetate **7** in good yield, although the corresponding propionate does not react. The C-3 methyl substituent of the natural product is installed by stereoselective alkylation of the β-keto lactone. The 2,4,6-trimethylbenzylidene acetal permits selective deprotection of the diol in the presence of the sensitive allylic lactone.



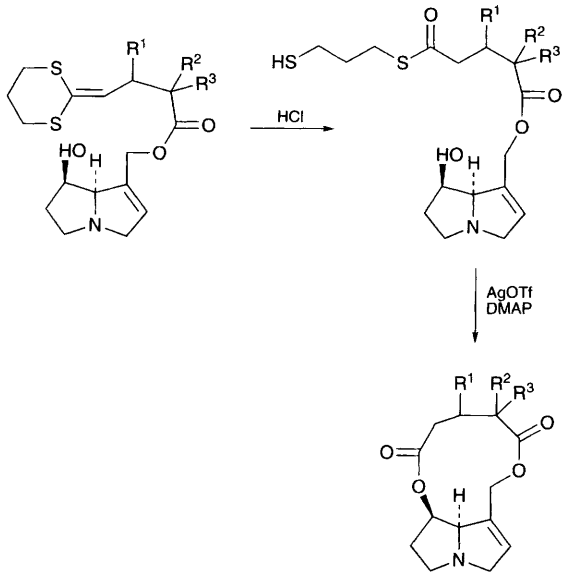
Scheme 13

Macrodiolides are accessible by application of Grigg's polycyclisation cascade.[17] Initial carbopalladation of the alkene is followed by anion capture of the alkylpalladium to generate the macrocycles (**Scheme 14**). A new strategy for the synthesis of dilactonic alkaloids uses a ketene dithioacetal as a masked carboxylic acid.[18] Mild acid hydrolysis reveals a thioester that will participate in silver(I) promoted macrolactonisation, provided that DMAP is present in the reaction mixture (**Scheme 15**). The dilactone skeleton of (*R*,*R*)-(−)-pyrenophorin has been assembled by enzymatic dimerisation of a hydroxy ester[19] (**Scheme 16**). Various lipase enzymes are competent, but the greatest synthetic utility is seen with *Candida antarctica* lipase in a reactor set up for vapour phase adsorption of methanol and water by-products.

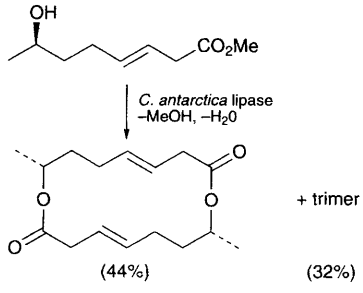
The advantages of preorganisation of seco-acids in promoting macrolactonisation are evident in Yonemitsu's computer-aided design and synthesis of the 18-membered skeleton of tedanolide.[20] By suitable rigidification with cyclic acetals, efficient cyclisation is seen (87%) without the need for high dilution conditions.



Scheme 14



Scheme 15



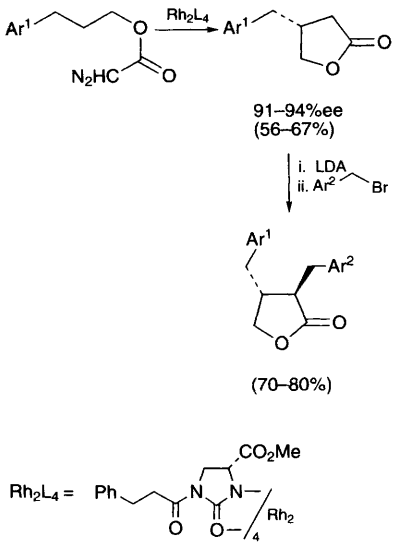
Scheme 16

4 γ-Lactones

4.1 Monocyclic γ-lactones

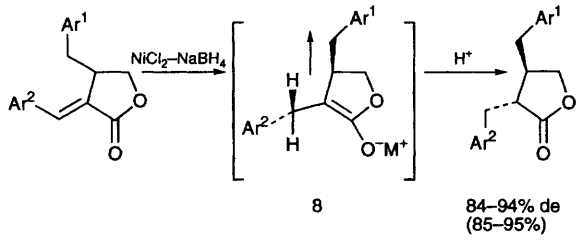
Several improved routes to simple lignans have been reported this year. Doyle *et al.* have overcome the problems of poor regio- and enantio-control in the intramolecular C–H insertion of rhodium carbenoids by using oxoimidazolidine ligands, in which the bulky *N*-acyl group is critical for high enantioselectivity[21] (**Scheme 17**).

Combined with a stereoselective alkylation, this provides a general and expedient synthesis of *trans*-butyrolactones. Another selective route to *trans*-lignans involves conjugate hydride addition to α-benzylidene-γ-lactones[22] followed by stereoselective protonation of the intermediate enolate **8** (**Scheme 18**). It is proposed that allylic 1,3-strain at the enolate double bond causes the α-substituent to shield one face of **8**. The same facial selectivity is seen in the reaction of **9** with oxygen electrophiles[23] (>95% de), leading to α-hydroxybutyrolactone lignans. The relatively unexplored *cis*-disubstituted lignans are now accessible by a straightforward

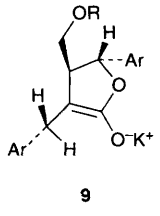


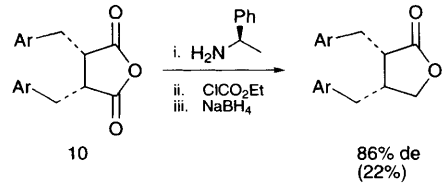
Scheme 17

desymmetrisation of the *meso*-anhydride **10** with α-methylbenzylamine[24] (**Scheme 19**). The initial acid amide is obtained in fair diastereomeric excess, which is carried through the synthesis.



Scheme 18

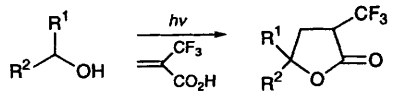




Scheme 19

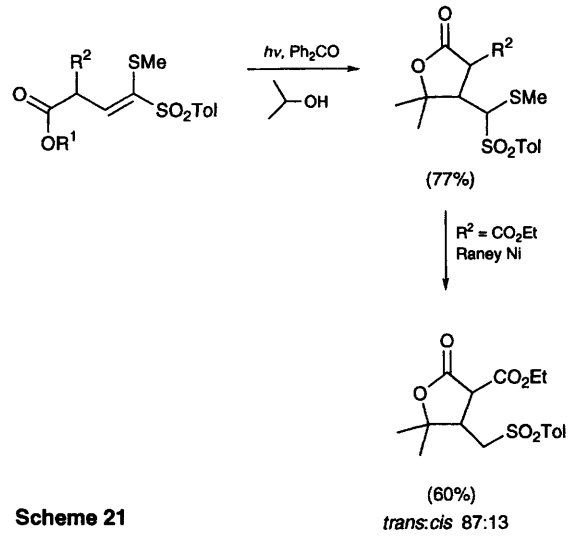
The known photocatalysed conjugate addition of 1-hydroxyalkyl radicals to butenolides has inspired a practical synthesis of α-trifluoromethyl-γ-lactones from commercially available 2-trifluoromethylacrylic acid[25] (**Scheme 20**). The addition of a photosensitiser is sometimes necessary, although not in the case $R^1 = R^2 = H$ which considerably simplifies the isolation of the product lactone. Where $R^1 \neq R^2$ there is a moderate preference for the major diastereoisomer to place the larger substituent *syn* to the trifluoromethyl group.

The same 1-hydroxyalkyl radicals will also add in conjugate fashion to vinyl sulfones[26] (**Scheme 21**). The addition–cyclisation process is very general and leads to highly functionalised products, but complex, unselective mixtures are formed from the more substituted precursors. These are simplified to some extent by reductive desulfurisation to remove a chiral centre.



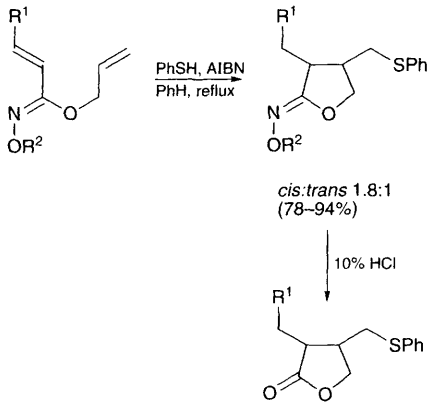
R^1	R^2	Yield(%)
H	H	(64%)
H	Me	(77%)

Scheme 20



Scheme 21

The success of intramolecular radical cyclisations can depend on the correct orientation of the donor and acceptor groups. In the case of ω-dienes tethered through hydroximates the *Z*-isomers have a conformational bias that favours reaction, contrasting with the *E*-isomers and corresponding esters which fail to cyclise.[27] The site of phenyl sulfide radical initiation is controlled by the relative degree of substitution on the two olefins. The hydroximates hydrolyse readily to the lactones (**Scheme 22**). Smooth 5-*exo*-*trig* cyclisation is also seen in the intramolecular radical addition to vinyl phosphonates, leading to the carbon analogues **11** of 2-deoxyribolactone 3-phosphate.[28]



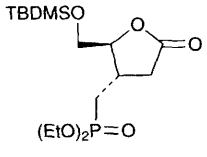
Scheme 22

Strong chelation control is exerted by α-substituents in the conjugate addition of ketyl radicals to crotonates when mediated by samarium(II) iodide[29] (**Scheme 23**). The stereochemistry of the products is rationalised by the five-membered cyclic acetal transition state **12a** for α-hydroxy groups and the seven-membered analogue **12b** for α-carbamates, resulting in a reversal of the facial reactivity of the crotonate between the two cases.

The radical cyclisation of bromoacetal **13** (**Scheme 24**) has been combined with transmetallation, alkylation and oxidation steps to give a one-pot synthesis of functionalised γ-lactones.[30] Cyclisation occurs predominantly through the all-equatorial conformation **14** leading to *trans* products (>95% de) which are isolated in pure form after the oxidation. The addition of lithium iodide is essential to promote the first step, or alternatively the iodoacetals may be used.

Conjugate addition of *tert*-butylmercury iodide to unsaturated acrylates in the dark generates organomercurials that function as radical precursors.[31] Upon photolysis in the presence of disulfides, γ-lactones are formed in moderate yields (**Scheme 25**). The methodology is much less satisfactory for δ-lactones.

The electrophilic cyclisation of pent-4-enoic acids is a direct route to γ-lactones and a novel procedure employs catalytic iodine in the presence of the free acid to generate hydrogen iodide *in situ* to promote cyclisation[32] (**Scheme 26a**). δ-Lactones are synthesised by changing the substitution on the alkene to redirect cation formation. Copper(II) bromide on alumina has been shown to be a useful reagent for the related stoichiometric bromolactonisation.[33] The selenocyclisation of pent-3-enoates and pent-



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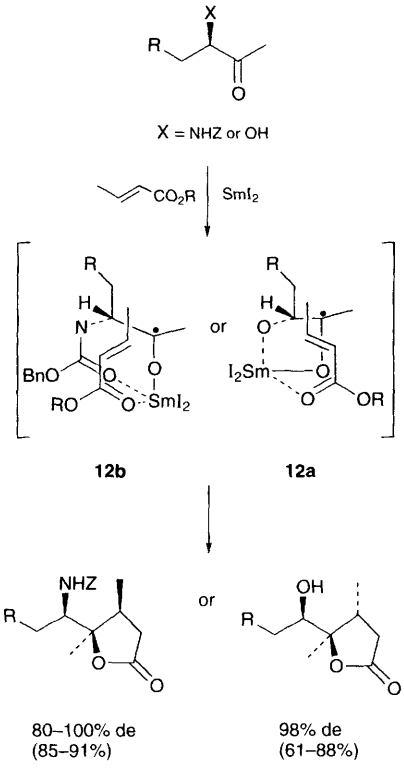
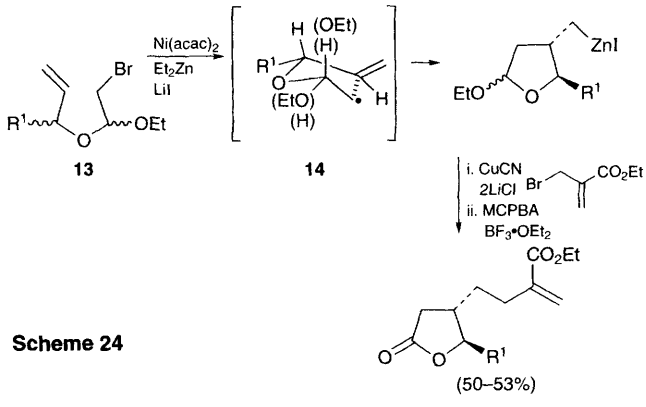


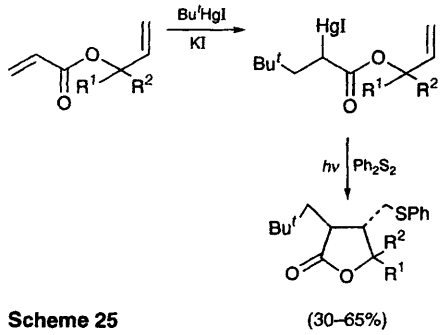
12b **12a**

Scheme 23



13 **14**

Scheme 24



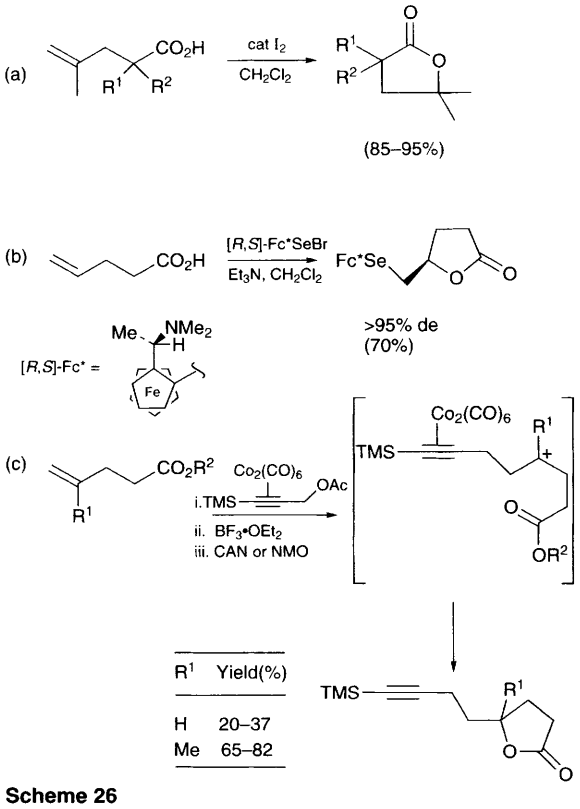
Scheme 25

4-enoates is highly enantioselective when a chiral ferroceneselenenyl electrophile is used, generated from the corresponding diselenide and bromine[34] (**Scheme 26b**). The chiral inducer is removed by radical reduction. Carbon electrophiles can also activate pent-4-enoates, as in the addition of hexacarbonyldicobalt stabilised prop-2-ynyl cations[35] (**Scheme 26c**). The greatest yields for this sequence are obtained when a stabilised tertiary cation is formed in the first addition. γ-Lactones are made more efficiently than δ-lactones.

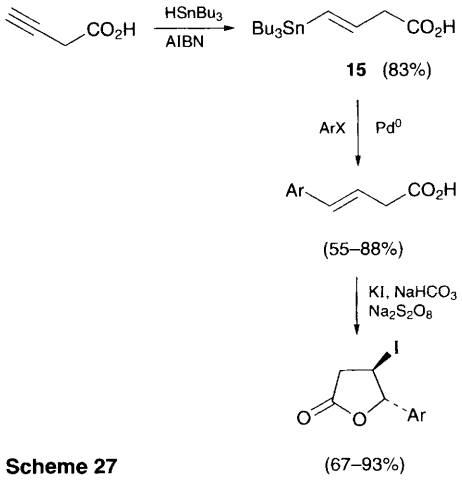
New strategies have emerged for assembling the pent-3-enoate and pent-4-enoate halolactonisation substrates. Thus, vinyltin **15** (**Scheme 27**) is easily made and undergoes palladium catalysed cross-couplings to aryl halides.[36] Pent-4-enoates have been prepared by cuprate addition to allyl acrylates, followed by Ireland–Claisen rearrangement.[37]

The ynolate **16** (**Scheme 28**) is generated by carbonylation of lithio(silyl)diazomethane and concomitant loss of dinitrogen.[38] Although **16** fails to react with most carbon electrophiles, epoxides are opened in a regioselective and stereospecific manner in the presence of trimethylaluminium, presumably *via* an ate complex. This ketenylation reaction leads to lactones after cyclisation.

The reaction of unsaturated carbonates with propenyltitanium reagents now extends to dienyl systems[39] (**Scheme 29**). The transformation is proposed to progress through the titanocycle **17** and the allyltitanium **18** which combines with aldehydes to generate *cis*-alkene products. The unusual regioselectivity towards attack at the least substituted



Scheme 26



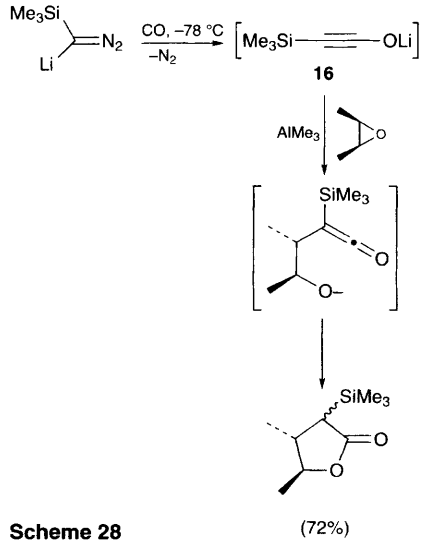
Scheme 27

carbon atom may reflect the effect of lactone coordination of the metal in stabilising one form of the allyltitanium intermediate. Full details have appeared of the application of these versatile titanium species to the synthesis of saturated γ-lactones, α-methylenebutyrolactones and butenolides.[40]

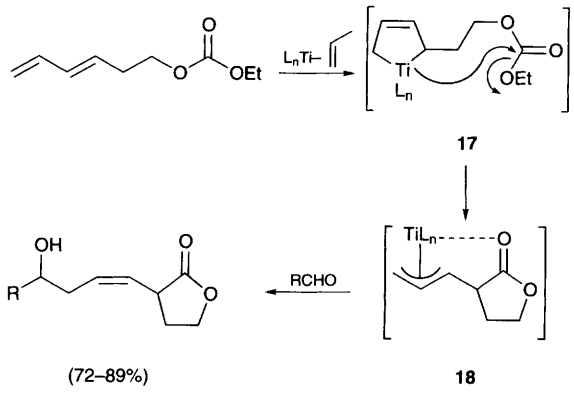
Wacker oxidation conditions convert but-3-ynyl alcohols to mono- and spiro-cyclic γ-lactones in good yields[41] (**Scheme 30**). The presence of the trimethylsilyl group is essential and extensive mechanistic studies imply that a *syn* elimination of palladium and TMS is a critical step in the catalytic pathway.

Moderate to good diastereoselectivity is achieved in the reduction of 1,4-keto esters controlled by anhydrosugar auxiliaries derived from D-glucose.[42] Chelation of the zinc cation appears to be important for good selectivities and the reaction with sodium borohydride alone is unselective. The method is also much less effective for δ-lactone formation (**Scheme 31**).

The alkylation of oxazol-5(4*H*)-ones with α-bromo ketones under phase transfer catalysis generates, very selectively, *E*-enol lactones after *in situ* trans-

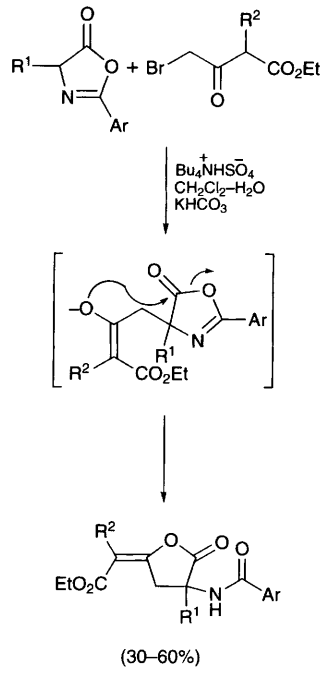


Scheme 28



Scheme 29

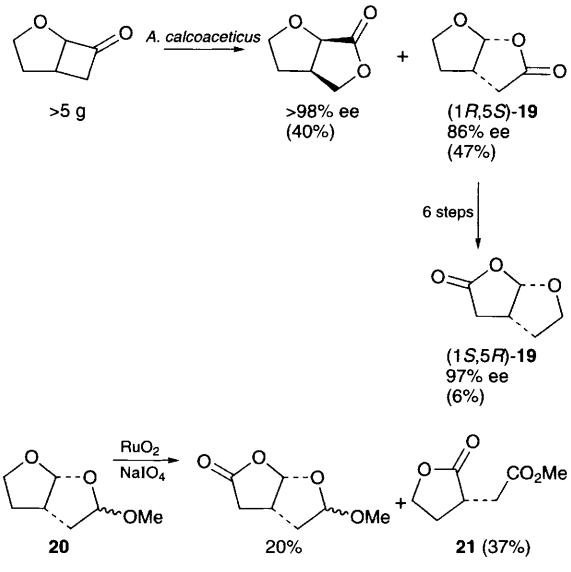
lactonisation[43] (**Scheme 32**). Although these conditions give improved yields over the homogeneous procedure, the scope is limited to 4-aryl- and 4-benzyl-oxazolones as the 4-alkyl starting materials are prone to hydrolysis in aqueous media.



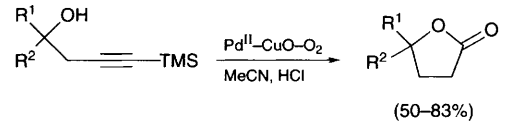
Scheme 32

4.2 Fused and bridged bicyclic γ-lactones

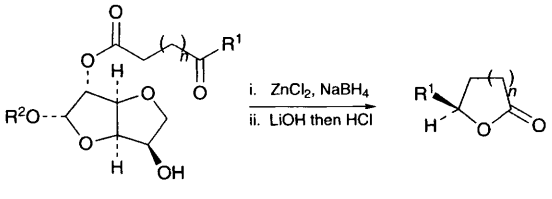
The whole-cell system containing *Acinetobacter calcoaceticus* has been used to prepare the bicyclic lactone (1*R*,5*S*)-**19** on a multigram scale[44] by a biocatalytic Baeyer–Villiger route (**Scheme 33**). A six step reduction–oxidation sequence generates the antipodal lactone (1*S*,5*R*)-**19** by carbonyl transposition, providing a route to a synthon which is not available in good enantiopurity by direct biotransformation. However, the yield of this synthesis is compromised by the competitive fission of the bicycle **20** to give lactone **21** as the major product in the key ruthenium tetroxide catalysed oxidation. A comparison of the bio-Baeyer–Villiger oxidation of a test panel of bicyclobutanones by monooxygenases from *Acinetobacter* and *Pseudomonas* species reveals an intriguing stereochemical divergence dependent on the co-factors used by the enzymes.[45] This correlates with amino acid sequence data within the two categories to suggest that there are two distinct evolutionary classes of this type of enzyme.



Scheme 33



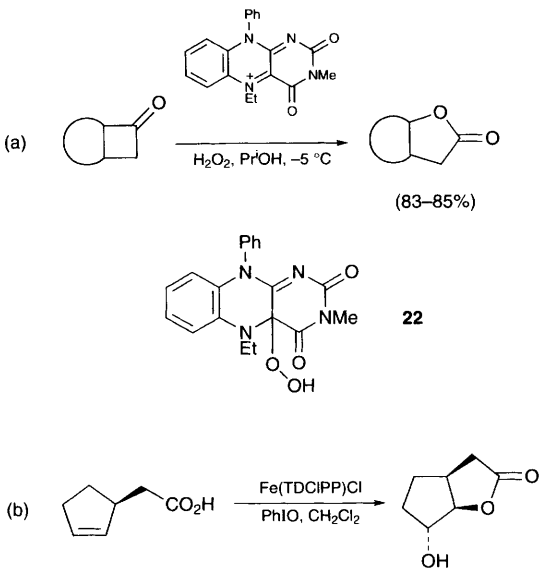
Scheme 30



n	ee(%)	Yield(%)
1	73–93	80–82
2	30–50	75–76

Scheme 31

The first example of a synthetically useful enzyme mimic for the Baeyer–Villiger oxidation of bicyclobutanones uses isoalloxazine as a flavin-related catalytic oxidant.[46] The catalyst must be alkylated for effective reaction, consistent with the hydroperoxide **22** as the oxidising species. Hydrogen peroxide in alcohol solvents is the optimum choice of oxidant (**Scheme 34a**). An iron(III) porphyrin system functions as a mimic for cytochrome P450 enzymes



TDClPP = *meso*-tetrakis(2,6-dichlorophenyl)porphyrin

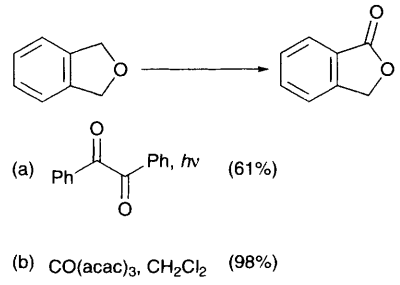
Scheme 34

in the oxidative hydroxylactonisation of pent-3-enoates and pent-4-enoates[47] (**Scheme 34b**).

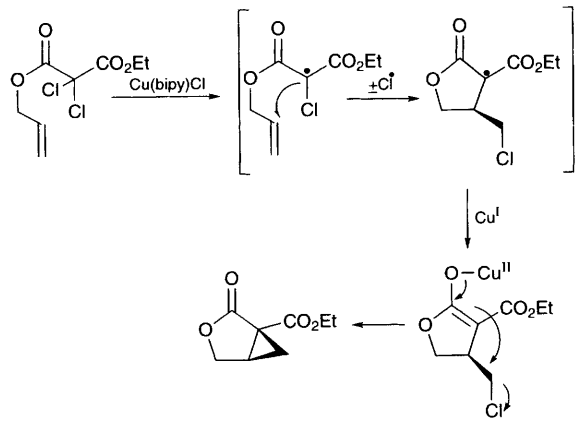
Several new oxidations of cyclic ethers to lactones have been described. Photooxidation of benzil generates benzoylperoxy radicals that will transform a range of aliphatic and aromatic ethers[48] (**Scheme 35a**). In contrast, commercially available cobalt(III) acetylacetonate is currently only satisfactory with aromatic substrates[49] (**Scheme 35b**). The related oxidation of tetrahydrofuran has been achieved with titanium silicates and hydrogen peroxide.[50]

In a parallel with Speckamp and Hiemstra's work on medium rings, ring closure to γ-lactones can be performed by copper mediated radical reactions of allylic α,α-dichloromalonates.[51] In the presence of two equivalents of the copper reagent, the radical cyclisation is complemented by a tandem intramolecular S_N2 displacement by the enolate **23** to generate a cyclopropyl ring (**Scheme 36**). The use of the malonate derivative provides a functional handle for further elaboration.

The free radical double carbonylation of alk-4-enyl iodides gives unexpected bicyclic lactones as the major products when a less reactive mediator,



Scheme 35



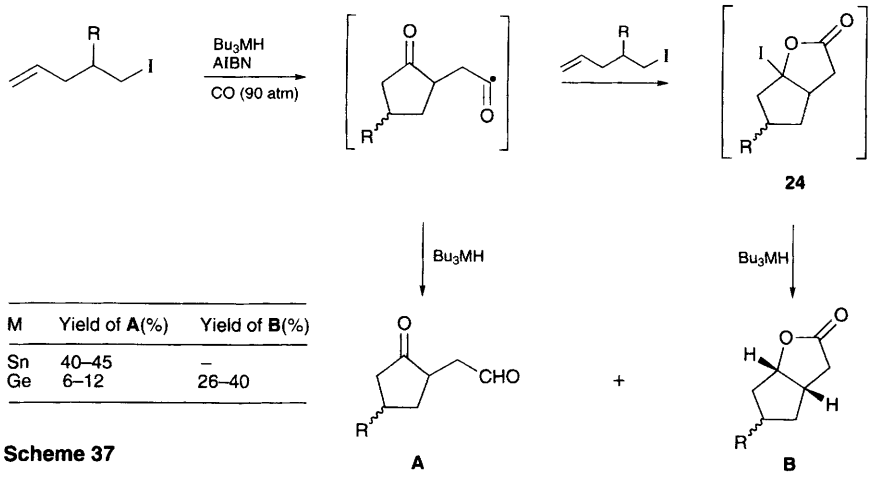
Scheme 36

such as tributylgermyl hydride, is used.[52] Although the mechanism of the second cyclisation is unclear there is some evidence to suggest iodine atom transfer from the starting material, to give intermediate **24**, is a better description than a 5-*endo-trig* radical process (**Scheme 37**).

Kocovsky *et al.* have designed and realised a catalytic system for the carbonylation and lactonisation of β-hydroxyorganomercurials, providing a general route to both *cis*- and *trans*-annulated γ-lactones[53] (**Scheme 38**). The success of the cycle lies in the choice of *p*-benzoquinone as the oxidising agent to recycle Pd^0 to Pd^{II}, although the time for complete reaction is still rather long (4 d). The precursor organomercurials **24a** and **b** are prepared by complementary cyclopropane cleavage reactions. In a separate paper[54] the authors detail how the compounds **24a** and **b** can be methylated on mercury as a method of protecting the metal–carbon bond against reduction, thus extending the range of transformations that may be carried out before cyclisation.

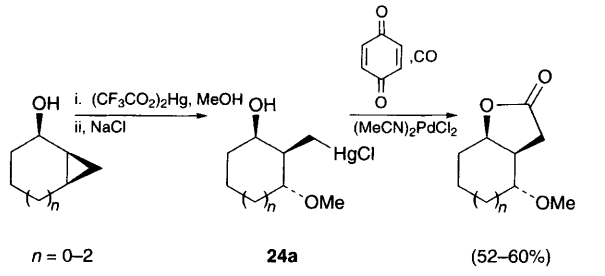
A high yielding and stereoselective lactone formation is seen in the reaction of a Fischer chromium carbene complex with ω-hydroxyalkynes.[55] The strong selectivity arises from coordination of the chromium in the vinylketene intermediate **25** (**Scheme 39**), ensuring attack of the hydroxy group and protonation from the same face as the metal. Accordingly, silylation of the alcohol reduces the selectivity as protonation now occurs in a separate, undirected step. The procedure extends to monocyclic and annulated β-, δ- and medium ring lactones.

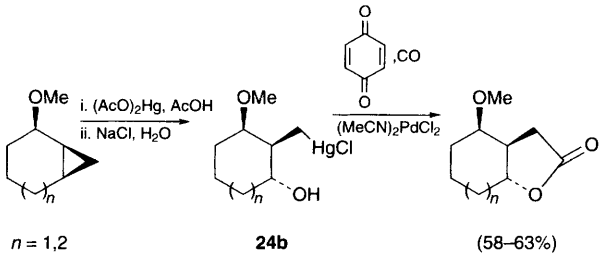
Two reports have appeared of a heteroatom variation of the intramolecular Pauson–Khand reaction. Hex-5-enals combine with stoichiometric amounts of a titanocene at room temperature to form metallocycles **26**[56] (**Scheme 40a**). In a tandem process, the C–Ti bond reacts with carbon monoxide, and this is followed by reductive elimination of the metal on exposure to air. In a parallel development,[57] thermal decomposition of the carbonylated titanocycle is found to be a cleaner, higher yielding process. The higher temperature also results in improved diastereoselection through



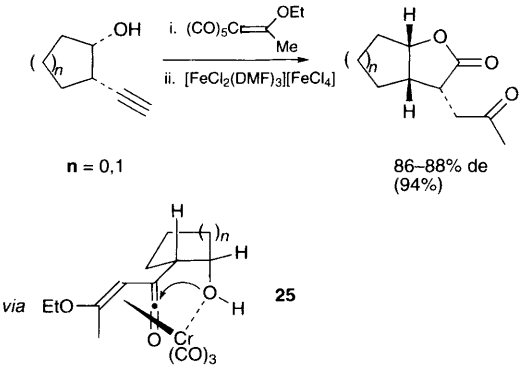
M	Yield of **A**(%)	Yield of **B**(%)
Sn	40–45	–
Ge	6–12	26–40

Scheme 37



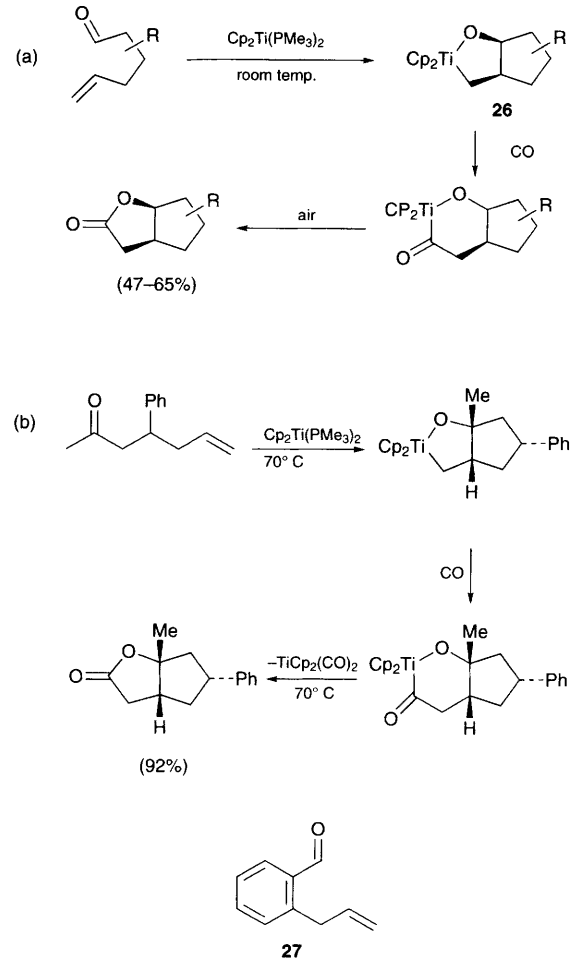


Scheme 38



Scheme 39

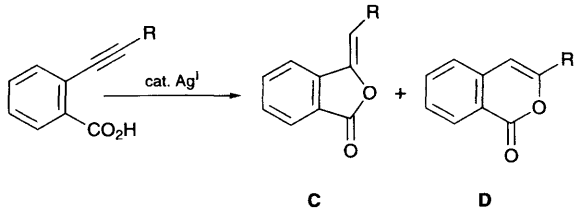
equilibration to the thermodynamic product (**Scheme 40b**). If a fused aryl ring forms part of the tether, as in **27**, cyclisation to the tricyclic γ-lactone can be achieved catalytically, presumably due to participation of the displaced $TiCp_2(CO)_2$ in the initial step.



Scheme 40

The cyclisation of 2-alkynylbenzoic acids catalysed by silver carbonate takes place predominantly in a

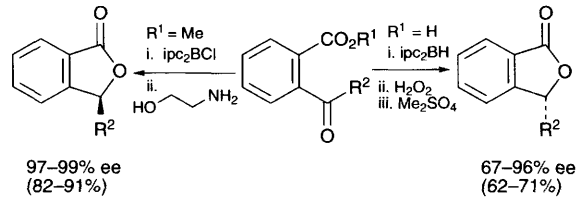
5-*endo-dig* fashion in most solvents to yield isocoumarins. In DMF, however, there is some selectivity for 5-*exo-dig* reaction and this is enhanced if silver iodide is used as the activator, leading to γ-alkylidenephthalides[58] (**Scheme 41**).



Catalyst	R	Ratio C:D	Yield(%)
Ag_2CO_3	R = Pr	16:84	85
AgI	R = Pr	84:16	90
AgI	R = Ph	100:0	92

Scheme 41

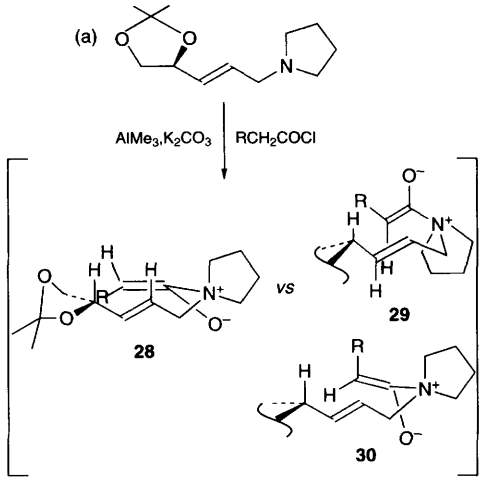
The same regioselection is seen for the formation of γ-alkylidenebutenolides and butyrolactones. Chiral 3-alkylphthalides in both enantiomeric series are available by complementary asymmetric reductions of *o*-acylbenzoates[59] (**Scheme 42**). The esters are reduced with (−)-*B*-chlorodiisopinocampheylborane (ipc_2BCl) and lactonised on heating to give (*S*)-alkylphthalides, whereas chelation controlled reduction of the free acids by diisopinocampheylborane (ipc_2BH) leads to the antipodal lactones, albeit with less reliably high enantioselectivity.

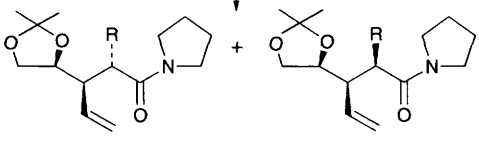


ipc = isopinocampheyl

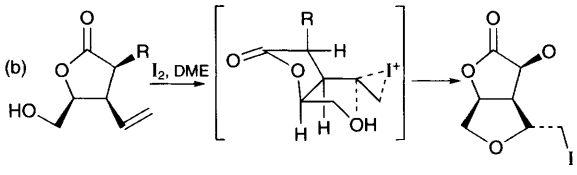
Scheme 42

A fuller exploration of the zwitterionic aza-Claisen rearrangement of *N*-allylpyrrolidines has revealed a correlation of the diastereoselectivity with the nature of the acyl substituent[60] (**Scheme 43a**). Alkyl and vinyl substituents rearrange through the expected 'chair-like' conformation of the *Z*-enolate **28**, whilst substituents with extended π-systems appear to pass through either the 'boat-like' conformer **29** or through a 'chair-like' disposition of the *E*-enolate **30**. In both cases 1,2-asymmetric induction is very high. The products can be converted into lactones by deketalisation and cyclisation. Subsequent iodoetherification is also highly diastereoselective and is driven by the minimisation of developing transannular strain in the transition state (**Scheme 43b**).



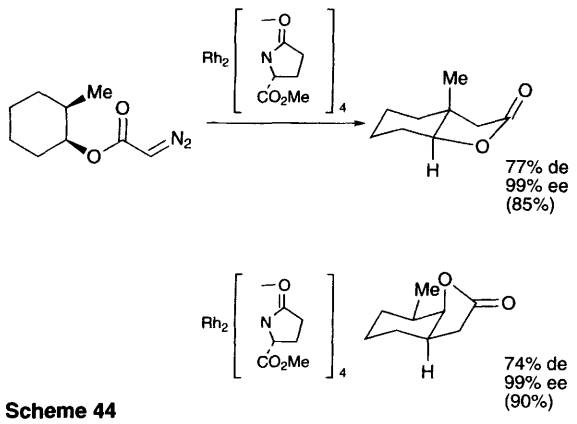


R	% de of **E**	% de of **F**	Yield(%)
Pr^i	>94		45
	>94		62
		>94	60
Ph		>94	52



Scheme 43

The factors governing the regiochemistry and enantiocontrol of rhodium(II) carboxamidate catalysed diazoinsertion reactions are complex and require optimisation for individual transformations. Nevertheless, some general controlling influences have emerged and impressive selectivities are seen in the formation of bicyclic γ-lactones[61] (**Scheme 44**). There is a preference for insertion into equatorial C–H bonds and a correlation between the enantioselectivity and the postulated orientation of the carbene with respect to the other ligands on the metal.



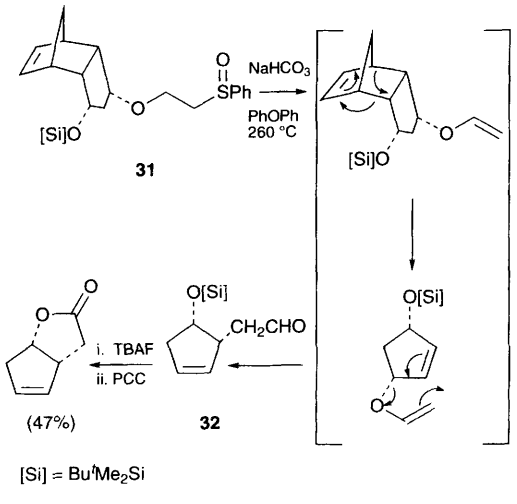
Scheme 44

An unusual threefold thermal rearrangement allows rapid progess to a bicyclic γ-lactone which is a prostanoid building block.[62] (**Scheme 45**). Elimination of the homochiral sulfoxide **31**, itself derived from a Diels–Alder adduct, is followed by a retro Diels–Alder reaction and a Claisen rearrangement to give the cyclopentene **32**. Lactol formation and oxidation complete the transformation.

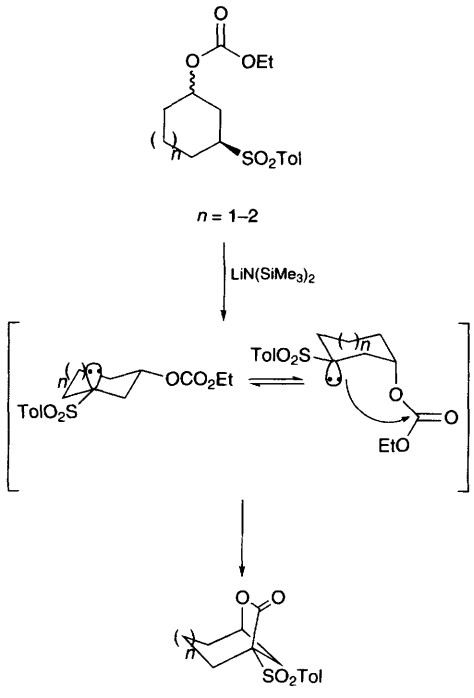
Bridged bicyclic lactones can be formed by the intramolecular cyclisation of α-sulfonyl carbanions[63] (**Scheme 46**). Rapid inversion of the anion permits smooth cyclisation of *cis* and *trans* mixtures of the cycloalkanol starting materials. However, the procedure fails for cyclopentanol derived analogues due to a combination of sluggish reaction and ring opening of the product lactones.

4.3 Polycyclic γ-lactones

Tricyclic 9-arylnaphthofuranone lignans are synthesised by the well known annulation with furan-2(5*H*)-one to give fair yields of a *ca.* 1:1 mixture of the *cis*- and *trans*-fused lactones under kinetic conditions.[64] Predominantly the thermodynamic *cis*-fused



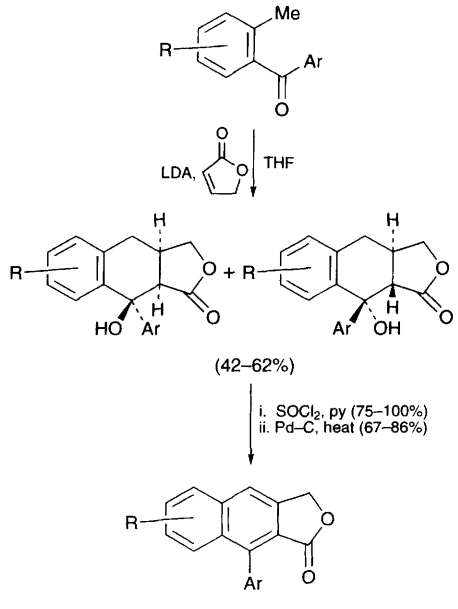
Scheme 45



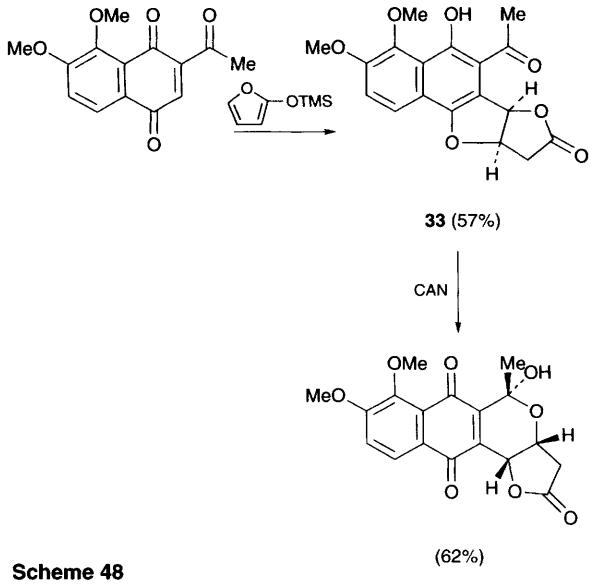
Scheme 46

product is formed if the reaction is allowed to equilibrate. Sequential dehydration and dehydrogenation generates the fully aromatised material in good yield (**Scheme 47**).

A related annulation strategy, combined with an acid catalysed epimerisation, leads to *cis*-fused lactones in the synthesis of podophyllotoxin analogues.[65] An alternative double Michael addition performs the annulation step to the tetracycle **33** (**Scheme 48**) in a synthesis of the antibiotic arizonin



Scheme 47



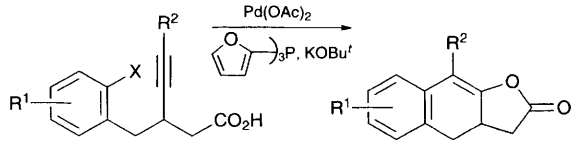
Scheme 48

C.[66] Oxidative rearrangement of **33** affords the pyranonaphthoquinone skeleton of the natural product.

A previously developed preparation of γ-alkylidene butyrolactones has been extended to a tandem carbopalladation–cyclisation process, producing tricyclic γ-lactones from pentynoic acids[67] (**Scheme 49**). The analogous cyclisation of hexynoic acids to δ-lactones has been investigated but has proved unfruitful, as have attempts to widen the scope of the reaction to include vinyl halides in place of aryl halides in the starting materials.[68]

An ambitious Diels–Alder cycloaddition is used as an efficient construction of the tricyclic core of the muscarinic receptor antagonist (+)-himbacine[69] (**Scheme 50**). The regiochemistry of cyclisation of **34** is controlled by the preferred s-*cis* conformation of the vinylcyclohexene, making this the four-electron component. Methylation of the tether forces the ester to adopt the s-*cis* conformation and minimisation of allylic 1,3-strain to this substituent also governs the facial reactivity of the dienophile. The initial *trans*-fused product is readily epimerised to the *cis*-lactone of the natural product.

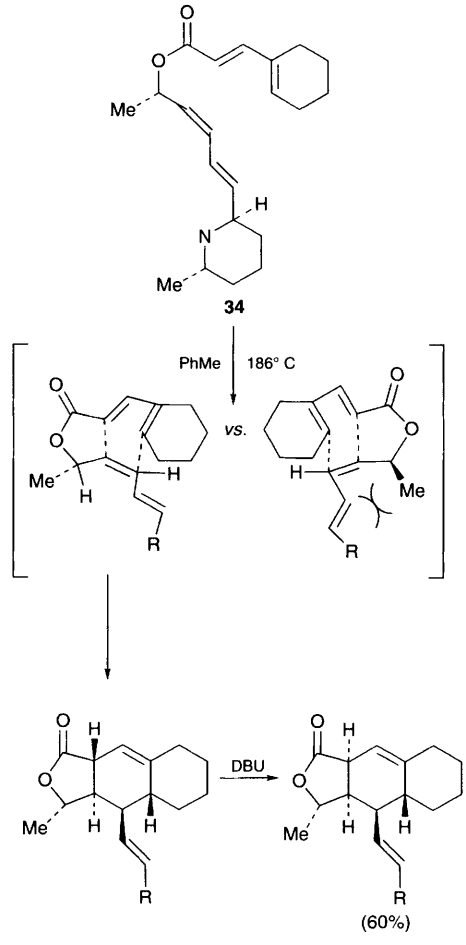
The importance of the conformational preference of tethers is also seen in the synthesis of the aristeriscanolide skeleton by intramolecular [2+2] photocycloaddition, where the conformationally mobile ether **35** (**Scheme 51**) cyclises smoothly whilst



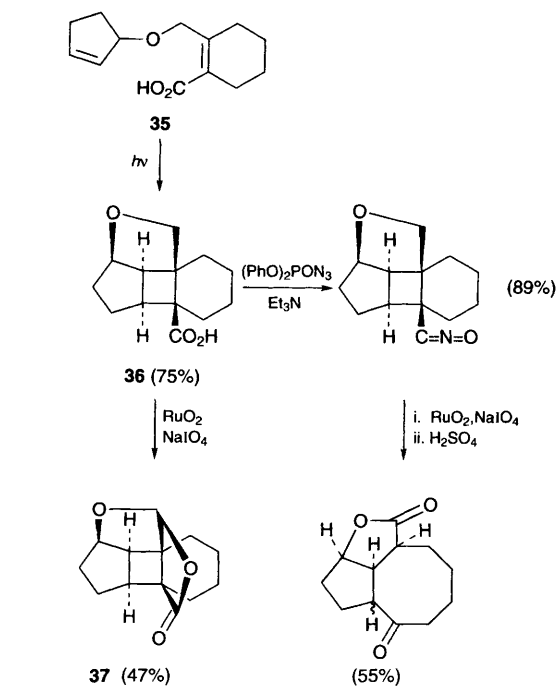
Scheme 49

related ester analogues are apparently unwilling to adopt the necessary s-*cis* conformation.[70] Curtius rearrangement and ether oxidation provide a substrate for aza de Mayo fragmentation to the required medium ring carbocycle, albeit with concomitant equilibration at one chiral centre. Direct oxidation of the acid **36** leads to the unexpected lactone **37**, which arises from interception of the carbocation oxidation intermediate by the pendant carboxylate.

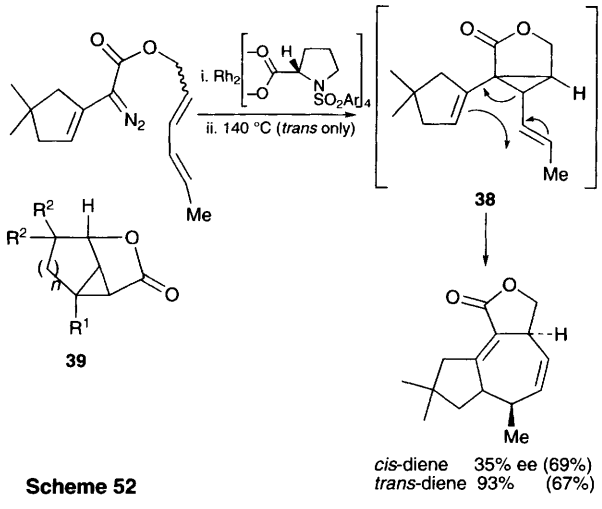
The tandem intramolecular cyclopropanation–Cope rearrangement of carbenes and dienes, catalysed by homochiral rhodium complexes, produces γ-lactones fused to 7-membered carbocycles[71] (**Scheme 52**). The cyclopropanation is found to give better asymmetric induction for *trans*-olefins than *cis*, which may reflect a more efficient side-on approach of the olefin to the carbenoid in the former case. Fortunately, for the *trans*-dienes, the intermediates **38** can be equilibrated by a thermal, diradical process to the *cis*-substituted cyclopropanes necessary for the Cope rearrangement. In a similar vein, Doyle *et al.* have reported the synthesis of the tricyclic γ-lactones **39** by intramolecular cyclopropanation of diazoacetates using their homochiral rhodium carboxamidates.[72]



Scheme 50



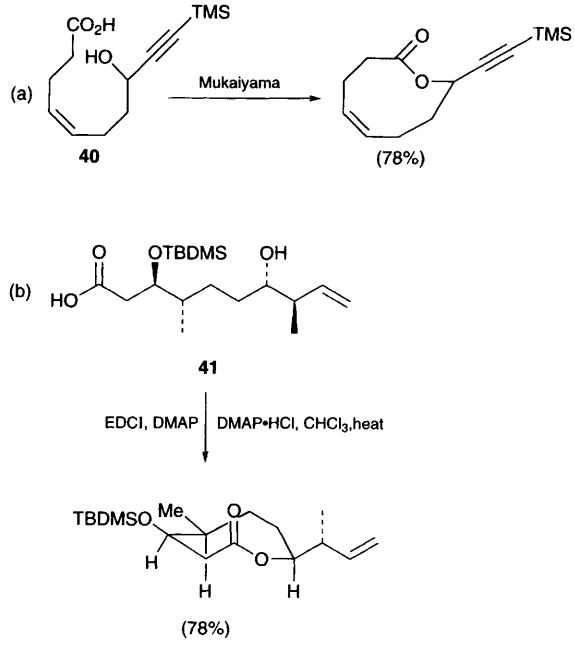
Scheme 51



Scheme 52

5 Medium ring lactones

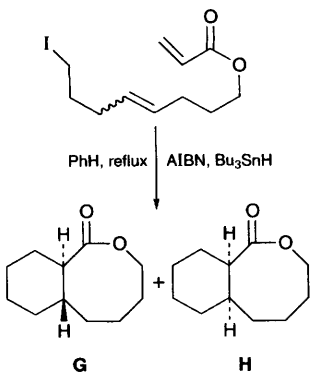
The classical lactonisation of ω-hydroxy acids to 8- and 9-membered rings is usually poor but the deleterious effect of non-bonding transannular interactions can be mitigated by a preorganising motif, such as a *Z*-alkene. Thus in a synthesis of the pseudoascidiatrienolide skeleton, Mukaiyama lactonisation of **40** (**Scheme 53a**) gives an excellent yield of the 9-membered lactone.[73] In the case of the hydroxyacid **41** (**Scheme 53b**) cyclisation to the octalactin skeleton under modified Keck conditions is presumably aided by the pseudo-equatorial disposition of two of the substituents around a chair–boat arrangement of the tether.[74] In support of this, removal of the substituents in the tether dramatically decreases the efficiency of the reaction (24%).



EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

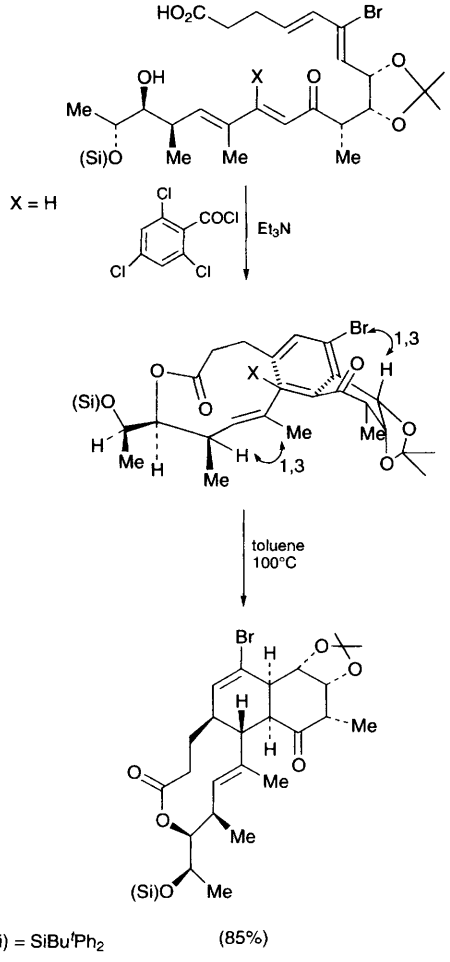
Scheme 53

Preliminary work has appeared on a tandem radical macrolactonisation–transannulation to give fused medium ring lactones.[75] There appears to be some preorganisation of the radical intermediates before cyclisation, as shown by the influence of the double bond geometry on the diastereoselectivity of the reaction (**Scheme 54**). Roush *et al.* have applied their elegant macrolactonisation–transannular cycloaddition strategy to build the skeleton of the nargenicin antibiotics, containing a 10-membered lactone[76] (**Scheme 55**). The facial reactivity of the diene component within the 18-membered macrolide is controlled by a 1,3-allylic steric interation between the bromo substituent and the neighbouring acetonide. Similarly, 1,3-allylic strain between the methyl substituent of the enone and the C-16 methyl group dictates the facial selectivity of the former. The selectivity of the Diels–Alder reaction is absolute, although some epimerisation adjacent to the ketone is observed in the tandem sequence. Regrettably, replacement of the enone by the β-diketone required for the natural products (X = OH, OR) causes the failure of the cycloaddition.

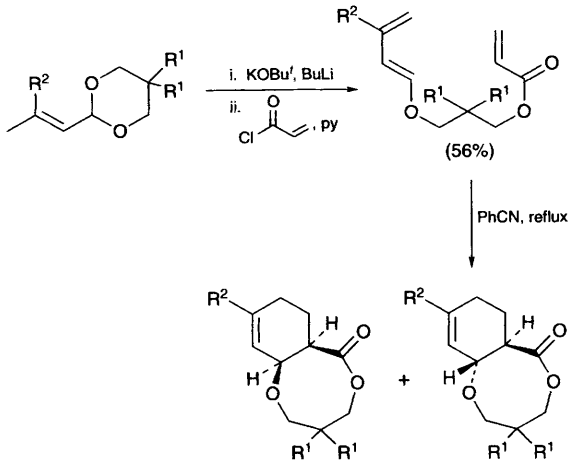


Scheme 54

Fused 8-membered lactones are prepared by tethered intramolecular Diels–Alder cyclisation of precursors derived from the opening of allylic ketals with Schlosser's Bu^{n}Li-KOBu^t combination[77] (**Scheme 56**). In all the solvents investigated the cycloaddition prefers the thermodynamic *trans*-fused



Scheme 55



R^1	R^2	Ratio J:K	Yield(%)
H	H	27:73	55
Me	Me	<5:>95	60

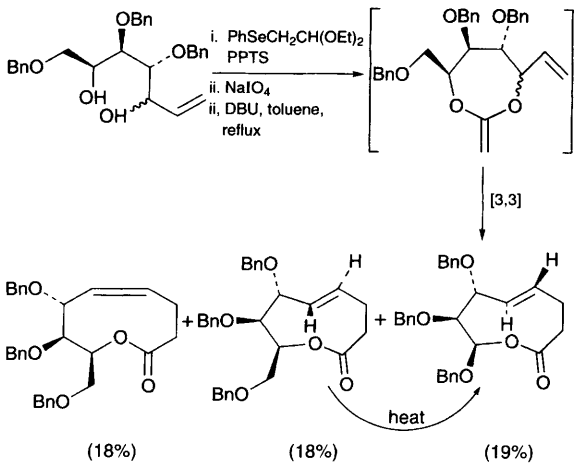
Scheme 56

products, and initial mixtures can be equilibrated to all *trans* by prolonged heating. The rate and selectivity of the reaction are enhanced by buttressing *gem*-dialkyl substituents.

In Pearson's approach to polyhydroxylated alkaloids[78] classical Claisen rearrangement is precluded by the formation of a stable orthoester resulting from the interference of an unprotected hydroxy group. However, the application of Petrzilka and Holmes' methodology allows the synthesis of the desired 9-membered lactone intermediates (**Scheme 57**). Very unexpectedly, the usually highly *Z*-selective rearrangement gives predominantly the *E*-alkene. This is not a function of the epimeric mixure of allylic alcohols, as the pure single epimers lead to a similiar outcome. Interestingly, the *E*-alkene product is observed as two thermally interconvertible atropisomers.

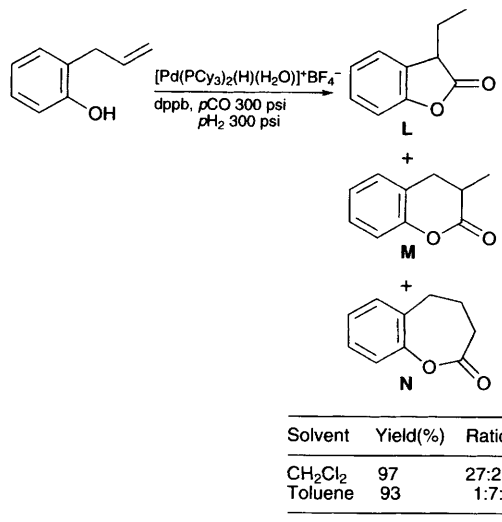
The intramolecular addition of tethered ester enolates to (η^4-1,3-diene)irontricarbonyl complexes under kinetic conditions (−78 °C) occurs exclusively at C-2 of the diene, leading to monocyclic and bridged 8-membered lactones after quenching,[79] the latter products a consequence of carbonyl insertion (**Scheme 58**). In contrast, at room temperature the reaction equilibrates to give C-1 addition and 9-membered lactones result.

Mixtures of fused 5-, 6- and 7-membered lactones are possible from the palladium catalysed cyclocarbonylation of 2-allylphenols, but the product distribution shifts to favour the 7-membered ring when toluene is the solvent[80] (**Scheme 59**). With a greater proportion of hydrogen ($CO:H_2 = 1:5$) in the hydroformylation mix, 5-membered lactones dominate, indicating that a palladium hydride catalysed double bond isomerisation is competing with carbonylation. The process is tolerant of aryl substitution and monosubstitution of the allyl group



PPTS = pyridinium toluene-*p*-sulfonate

Scheme 57

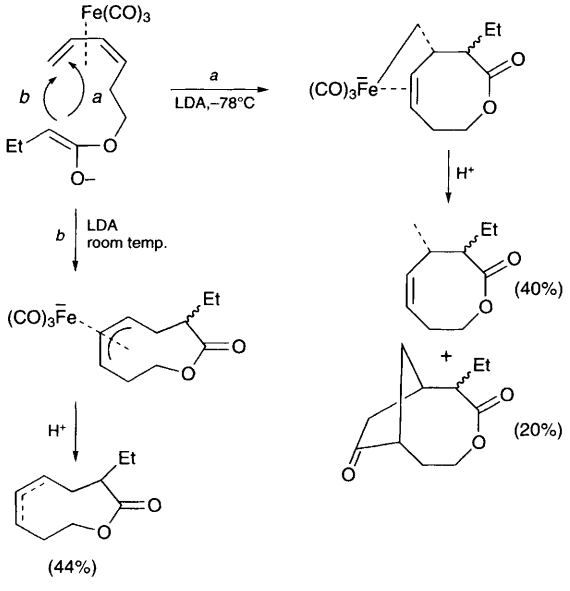


Solvent	Yield(%)	Ratio **L**:**M**:**N**
CH_2Cl_2	97	27:21:52
Toluene	93	1:7:92

Scheme 59 dppb = 1, 4-bis(diphenylphosphino)butane

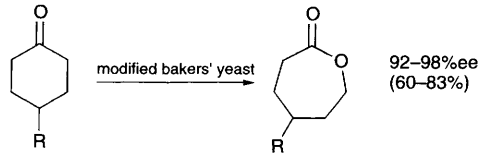
but the high gas pressures represent a barrier to general utility.

A refined model has been presented for the enantioselectivity seen in whole cell Baeyer–Villiger oxidations of cyclohexanones by *Acinetobacter* species.[81] Such transformations can be compromised by the requirements of the microorganisms for growth and the need to screen many systems for optimum suitability. This is addressed through molecular biological techniques for expressing the desired monooxygenase function in bakers' yeast, a robust, well characterised organism.[82] The modified yeast achieves high yielding and enantioselective oxidation of prochiral cyclohexanones with only small amounts (typically <3%) of ketone reduction from residual yeast activity (**Scheme 60**). The chemical Baeyer–Villiger oxidation of some bridged bicyclic ketones may be blocked by steric resistance

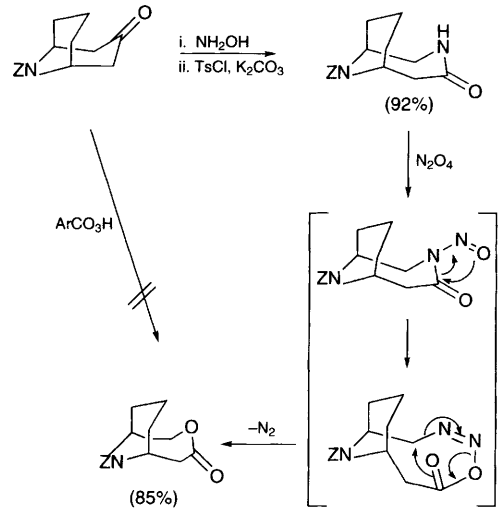


Scheme 58

to the formation of the necessary tetrahedral intermediate but this can be circumvented by sequential Beckmann and Huisgen–White rearrangements[83] (**Scheme 61**).

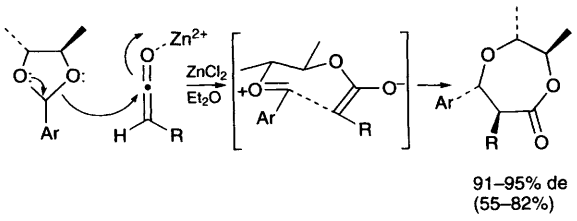


Scheme 60



Scheme 61

A highly diastereoselective synthesis of dioxepanones has been developed from the Lewis acid catalysed aldol condensation of chiral cyclic acetals with ketenes.[84] The same process extends to 8-membered rings in the achiral series. Sterically



Scheme 62

driven 'side-on' attack of the ketal to the ketene generates the *Z*-enolate which cyclises through an all-equatorial arrangement of substituents (**Scheme 62**).

In Corey's total synthesis of the rare marine antitumour agent ecteinascidin 743 the 10-membered lactone is constructed by a very efficient one-pot procedure based on a transannular thiolate Michael addition[85] (**Scheme 63**). The Swern reagent is used to activate the tertiary alcohol, followed by elimination to install the quinomethane Michael acceptor. After removal of excess reagent with *tert*-butyl alcohol, the thioether is deprotected and ring-closure occurs.

6 Spirolactones

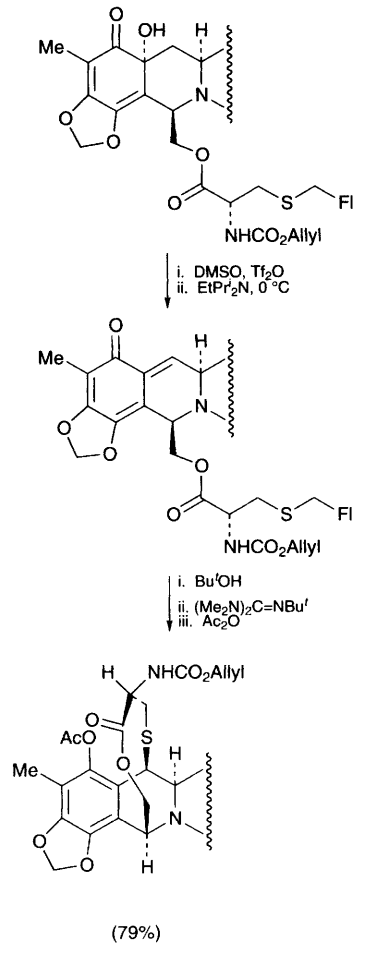
Moderate enantioselectivities are seen in the bis(alkoxycarbonylation) of homoallylic alcohols catalysed by palladium(II) and copper(I) trifluoromethanesulfonate (triflate) in the presence of bisoxazoline ligands.[86] The copper(I) triflate is essential to obtain any optical activity in the products, suggesting the formation of the cationic palladium complex **42** (**Scheme 64**) in which the facial reactivity of the olefin during insertion is determined by the minimisation of steric interactions between the bisoxazoline and the cyclic substituent.

The addition of *ortho*-lithiated diethylbenzamides to lactones and subsequent acid catalysed ketalisation provides a simple synthesis of spirolactones related to the papulacandin antifungal agents[87] (**Scheme 65a**). Substitution on the aromatic ring is not tolerated at the *meta*-position, a consequence of steric hindrance to reaction with the lactone electrophile when the anion is flanked by two groups. A similar acid catalysed spiroketalisation provides the first synthesis of the dimeric altaicadispirolactone **43**.[88] West *et al.* have demonstrated that the photochemical reaction of 2-pyrones bearing pendant alcohols also generates spirolactone ketals of this type[89] (**Scheme 65b**). Full details have appeared of the photoradical cyclisation of allyl α-phenylselenoesters to spirolactones.[90]

7 δ-Lactones

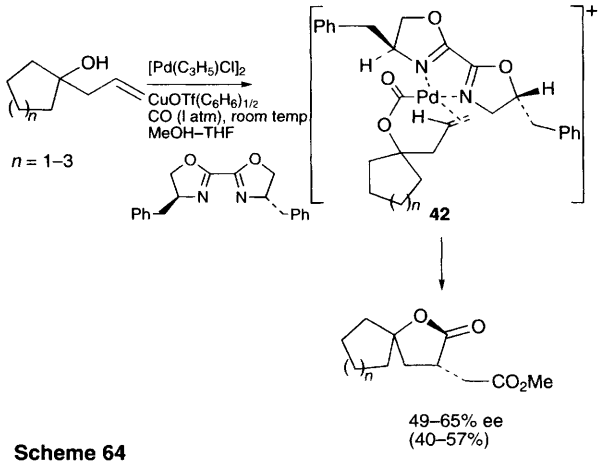
7.1 Monocyclic δ-lactones

The total synthesis of the cytotoxin (+)-goniodiol **44** (**Scheme 66**) proceeds in its closing steps by sulfone anion addition to an epoxide followed by classical lactonisation and elimination of the sulfone stabilising group.[91] A classical lactonisation also features in the recent synthesis of (+)-constanolactone E **45** where an intramolecular variant of the sulfone anion–epoxide coupling constructs the cyclopropane unit.[92] In the case of (+)-dihydrokawain **46** the strategy involves a Ru-BINAP reduction of a β-keto ester prior to lactonisation.[93]

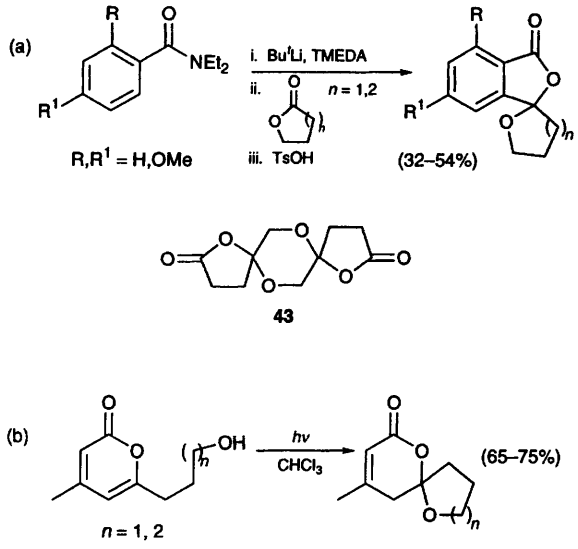


Fl = fluoren-9-yl

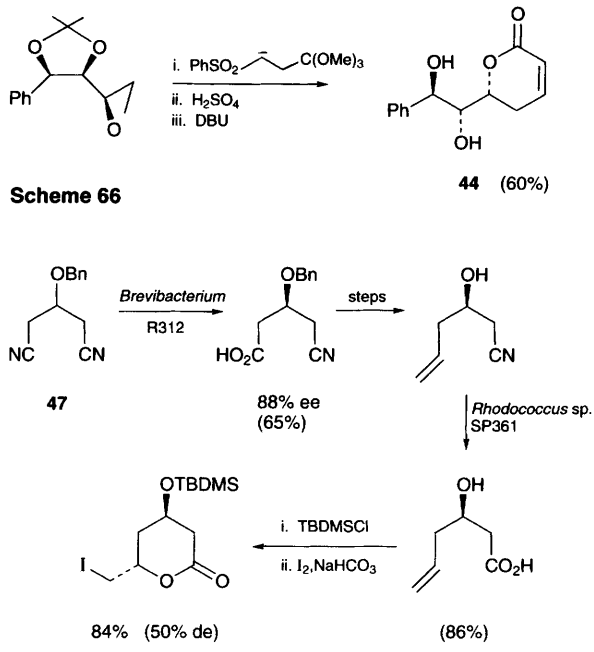
Scheme 63



Scheme 64



Scheme 65

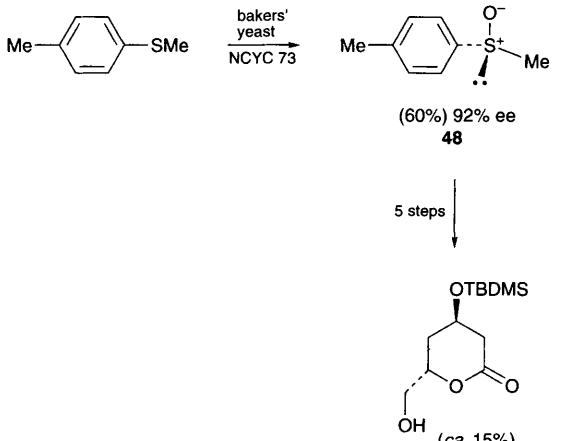


Scheme 66

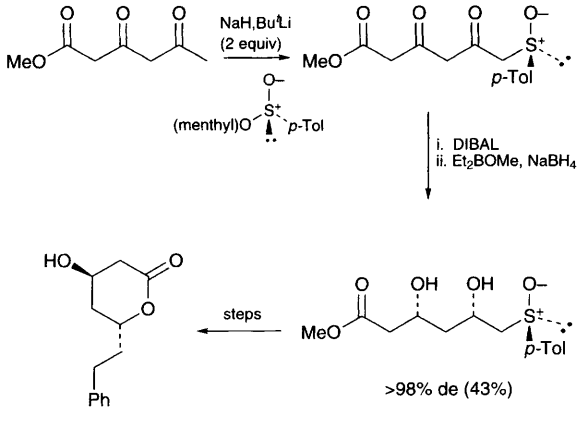
Scheme 67

A number of new approaches to the δ-lactone pharmacophore of the mevinic acids have appeared. Successive use of whole cell nitrile hydratase–amidase activity can prepare the lactonisation precursors[94] (**Scheme 67**). Treatment of the *meso*-nitrile **47** with the pro-*S* selective *Brevibacterium* R312 gives a good recovery of the monohydrolysis product in high optical purity on a multigram scale. The later, unselective biohydrolysis is also high yielding. An alternative chemo-enzymatic route applies the generation of chiral sulfoxides by bakers' yeast, again with high enantioselectivity[95] (**Scheme 68**). Semi-anaerobic cultivation conditions are needed to induce the appropriate monooxygenase, but the transformation itself takes place aerobically. The sulfoxide **48** acts as a chiral auxiliary for the diastereoselective construction of the lactone in five steps *via* an aldol condensation. A chiral sulfoxide auxiliary derived more conventionally from (−)-menthyl (*S*)-toluene-*p*-sulfinate has been used prepare the δ-lactone, this time through successive asymmetric reductions[96] (**Scheme 69**).

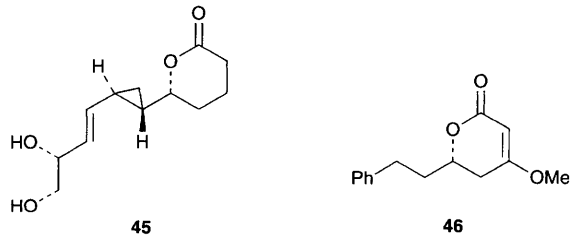
The iodolactonisation of certain mevinic lactone precursors appears to proceed through a common transition state in which the protected hydroxy substituent takes predominantly the axial position in the nascent ring.[97] In contrast, the related alkyl substituted systems adopt the expected all-equatorial conformers and this difference may reflect hydrogen bonding between the acid and the oxygen substituent (**Scheme 70**).



Scheme 68

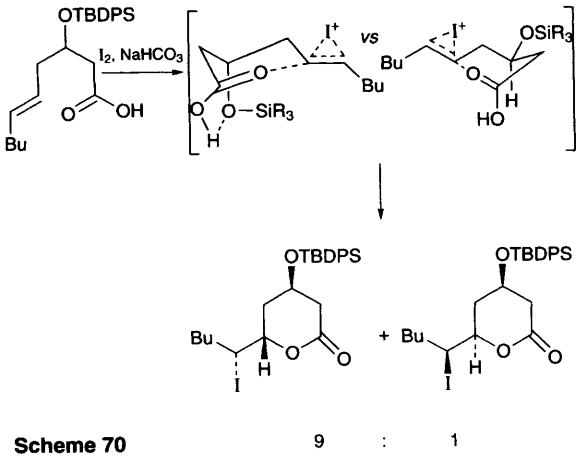


Scheme 69

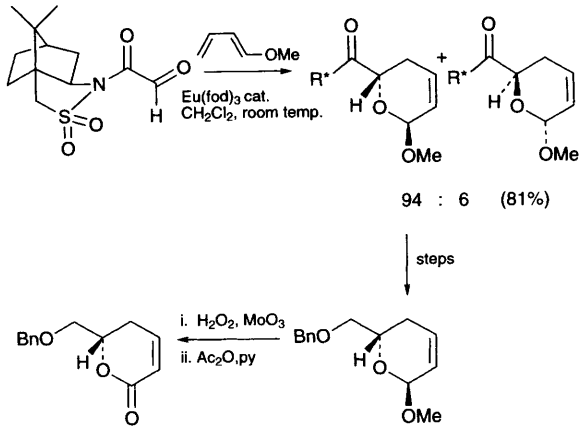


45

46



Scheme 70

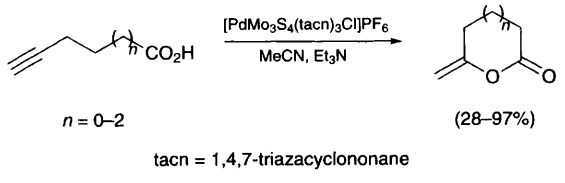


Scheme 72

A molybdenum–palladium–sulfide cluster functions as a water-soluble catalyst for the cyclisation of alkynoic acids to enol lactones.[98] The procedure is applicable to substituted alkynoic acids and will also form spirolactones (**Scheme 71**).

Oppolzer's sultam auxiliary offers a route to the mevinic δ-lactones through hetero Diels–Alder cycloaddition where inclusion of a weak lanthanide Lewis acid is critical for high diastereoselectivity.[99] After cleavage of the auxiliary the lactone is installed by anomeric oxidation with catalytic molybdenum trioxide (**Scheme 72**). A novel variation of this transformation is seen in the direct oxidation of a hydroxy acetal to a δ-lactone pheromone by aromatic peracid in the presence of a Lewis acid[100] (**Scheme 73**). In the proposed mechanism, the Lewis acid serves to activate the acetal to intramolecular attack, generating the oxonium ion **49**. This is captured by the peracid and rearranges to effect the oxidation. The straightforward Baeyer–Villiger oxidation of cyclopentanones and cyclohexanones with MCPBA is reported to be enhanced by the addition of hydrotalcites as a solid support.[101]

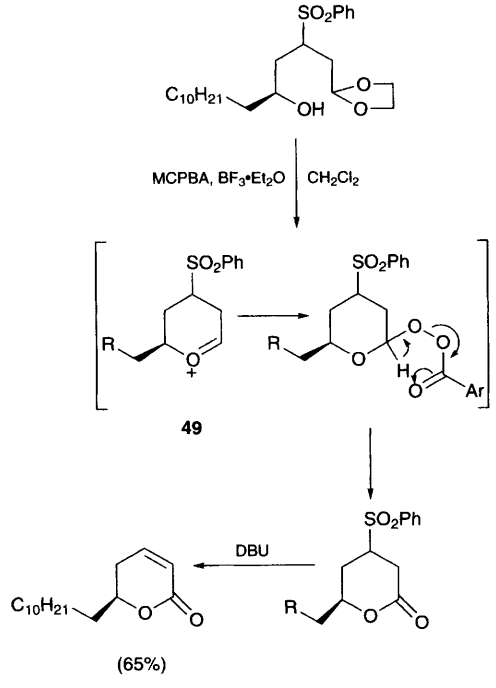
The conjugate addition of nucleophiles to dihydropyrones can be made asymmetric when chiral α-aminonitrile anions are employed as aroyl anion equivalents[102] (**Scheme 74a**). Quenching of the intermediate enolate delivers a second chiral centre onto the lactones, which can be crystallised to optical purity. Likewise, carbon nucleophiles add to the dihydropyrone **50** (**Scheme 74b**) with total control over the new ring stereocentre,[103] rationalised as the outcome of axial attack on the less hindered face of the enone. Interestingly, anions of β-diketones give only 1,2-addition products, in contrast to the behaviour of β-keto esters and



Scheme 71

malonates. Dihydropyrone starting materials of this type may be generated from pyranose sugar derivatives by a deoxygenation–oxidation sequence.[104]

Meinwald *et al.* have introduced the stannanes **51a** and **b** as reagents for the incorporation of the 2-pyrone unit, particularly into the skeleton of cardiotonic steroids.[105] The reagents are prepared from the corresponding bromides by reaction with hexamethylditin under palladium catalysis. As expected, **51a** and **b** undergo Stille couplings with aryl and vinyl halides (61–72% yield) and these reactions appear to be more efficient than the analogous couplings of the bromopyrones themselves.

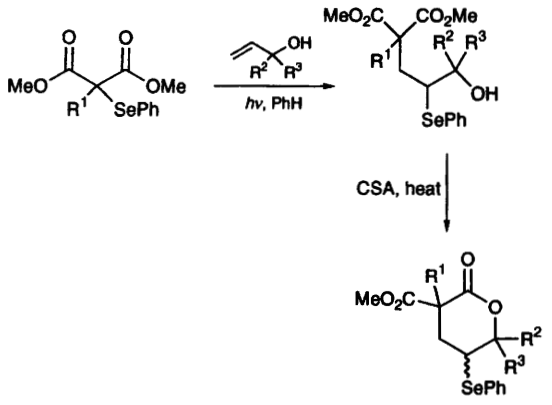


Scheme 73

A two component photoradical coupling is proposed as a synthesis of selenium functionalised δ-lactones[106] (**Scheme 75**). The 1-carbon ring contraction of lactones through radical β-(acyloxy)alkyl rearrrangements has beeen extensively probed and is found to be most efficient for the conversion of caprolactones to δ-lactones.[107]

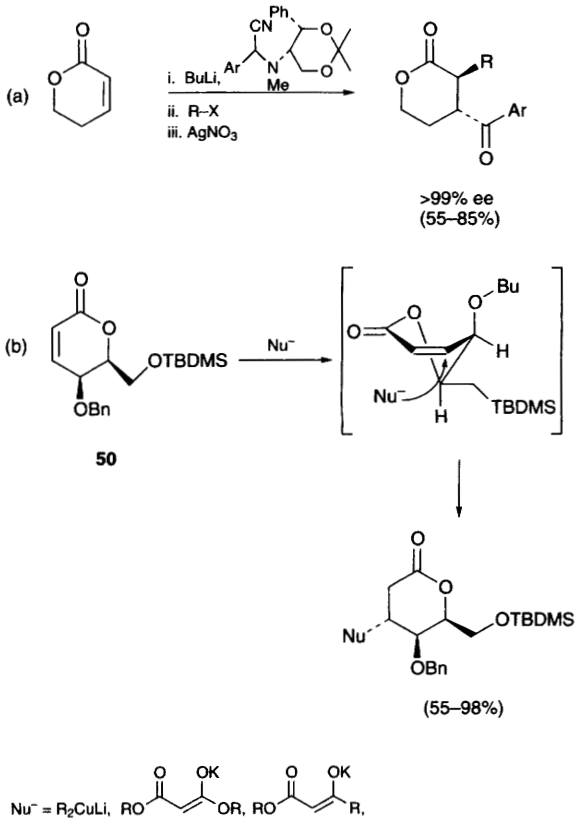
7.2 Bicyclic and polycyclic δ-lactones

The intramolecular Horner–Wadsworth–Emmons reaction is established as a strategy for the synthesis of type-I iridoid δ-lactones and the intermolecular reaction now finds favour for the construction of the type-II lactones, although the scope is limited to unsubstituted phosphonates and hence to relatively unfunctionalised targets[108] (**Scheme 76**). The initial

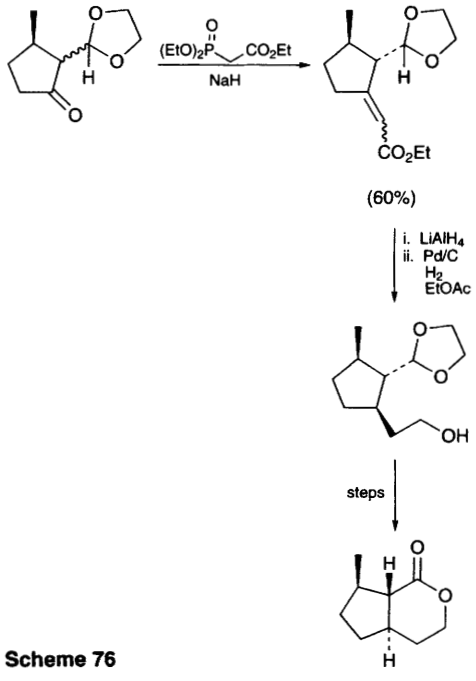


Scheme 75

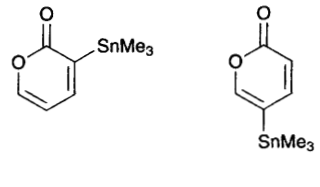
mixture of pulegone-derived ketone diastereoisomers is epimerised in the basic medium to the *trans* isomer, and catalytic hydrogenation with apparent chelation control after the condensation leads to exclusively the *trans*-fused lactones. Unfortunately, it is difficult to reverse the selectivity of the hydrogenation sufficiently to provide an efficient preparation of the *cis*-fused products.



Scheme 74

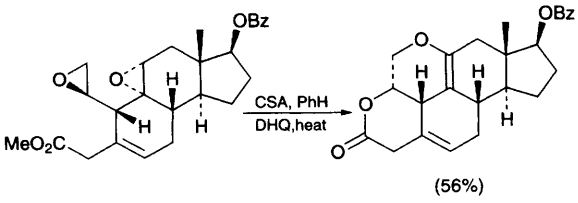


Scheme 76



51a **51b**

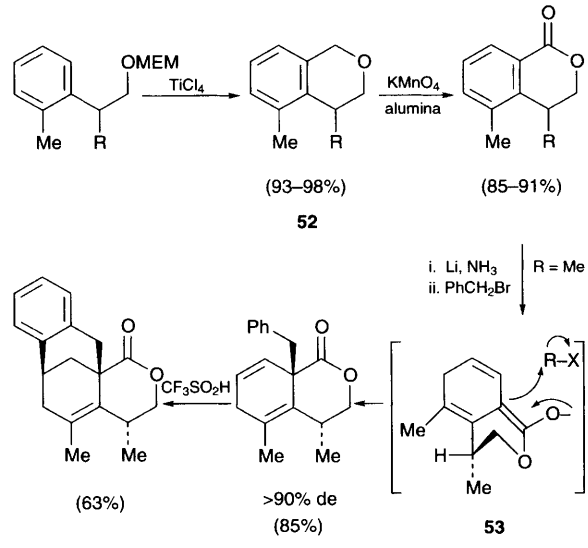
In the first chemical synthesis of the antifungal and antiinflammatory agent wortmannin the δ-lactone is closed by a double epoxide opening cascade[109] (**Scheme 77**). This transformation is necessary to establish the correct stereochemistry of the hydroxymethyl substituent on the lactone, since the equivalent iodolactonisation on a pendant olefin gives only the undesired stereoisomer.



DHQ = dihydroquinone

Scheme 77

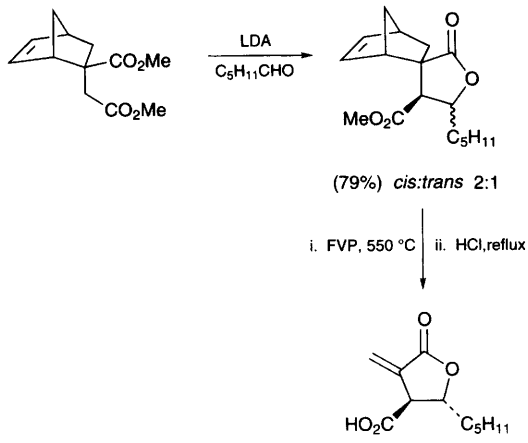
A new, general synthesis of 3,4-dihydroisocoumarins starts with the formation of the benzopyrans **52**[110] (**Scheme 78**). Of the many oxidation protocols available for such systems, potassium permanganate supported on alumina offers the greatest practical simplicity combined with high yields. The dihydroisocoumarins are excellent starting points for the synthesis of complex polycyclic lactones through functionalisation by Birch reduction–alkylation, in which the diastereoselectivity of the alkylation is ascribed to the shielding of one face of the enolate **53** by the C-4 substituent as it relieves eclipsing interactions.



Scheme 78

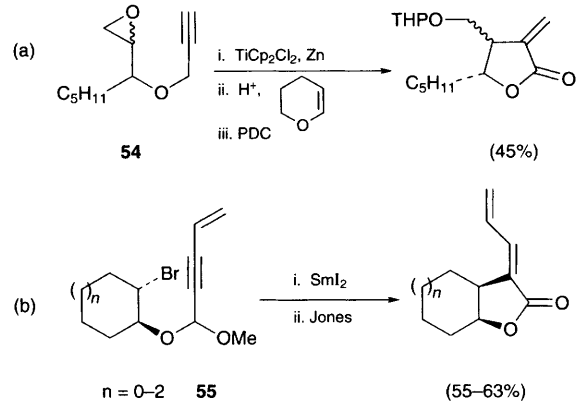
8 α-Methylenebutyrolactones

The antitumour antibiotic methylenolactocin continues to stimulate a search for new synthetic strategies, as in the direct racemic synthesis through an aldol reaction, made possible by masking the *exo* double bond as a Diels–Alder adduct[111] (**Scheme 79**). The aldol reaction is poorly selective but the desired *trans*-substitution is achieved by acid catalysed epimerisation at the close of the synthesis.



Scheme 79

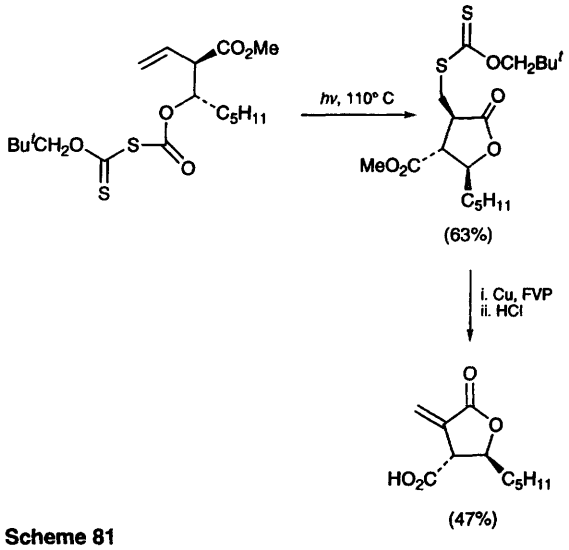
In the first of several radical-based syntheses, ring closure to an epoxide is initiated by the addition of a radical titanium species to the prop-2-ynyl ether **54**[112] (**Scheme 80a**). The oxidations of the cyclic ether and the pendant alcohol are carried out sequentially, the latter reaction again providing an opportunity for acid catalysed epimerisation of the cyclisation mixture to the *trans*-substituted lactone.



Scheme 80

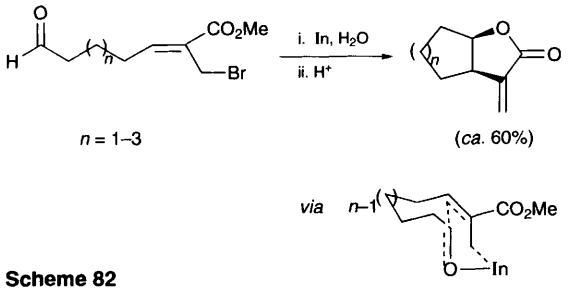
The related cyclisation of alkynyl ketals **55** (**Scheme 80b**) can be carried out with samarium(II) iodide or tributyltin hydride, although the samarium reagent offers generally higher yields, and generates exclusively the expected *cis*-fused lactones.[113] Initial mixtures of geometrical isomers of the double bond formed in the radical step are converted into the 3*E*-butadiene in the oxidation. An alternative approach uses xanthates as alkoxycarbonyl radical precursors so that cyclisation is carried out directly at the lactone oxidation level[114] (**Scheme 81**). Compared to reactions mediated by external chain-carrying reagents, this group transfer cyclisation

offers the advantage of a clean reaction at relatively high concentrations and introduces a leaving group suitably placed to generate the *exo*-methylene group.



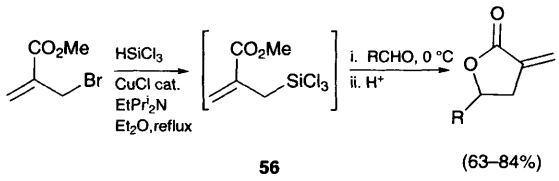
Scheme 81

The anionic allylation of carbonyl compounds with α-(halomethyl)acrylates remains a popular route to α-methylene-γ-lactones and can be carried out using several metals including lead, as recently reported.[115] An intramolecular version of this reaction uses indium as the activating metal.[116] The coupling is highly selective for the formation of the *cis*-fused lactones, presumably through a preference for the *pseudo*-chair–chair transition state over the alternative chair–boat conformation (**Scheme 82**). These processes are stoichiometric in the metal, which may be a drawback, particularly for large scale work, and can be avoided by using the corresponding allylsilane in place of the α-(halomethyl)-acrylate.[117]



Scheme 82

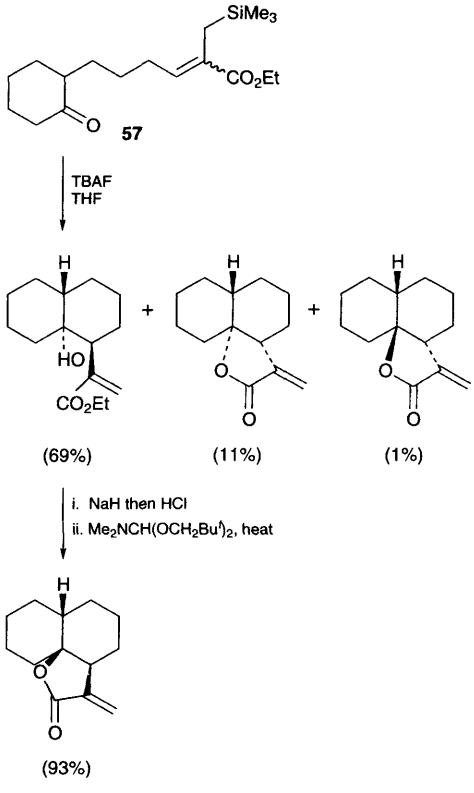
In a one-pot reaction the halide is converted under copper(I) catalysis to the allyltrichlorosilane **56** (**Scheme 83**) which then reacts with the carbonyl compound in good yield. Along similar lines the intramolecular addition of α-(trimethylsilyl)acrylates to ketones promises to be an alternative to the



Scheme 83

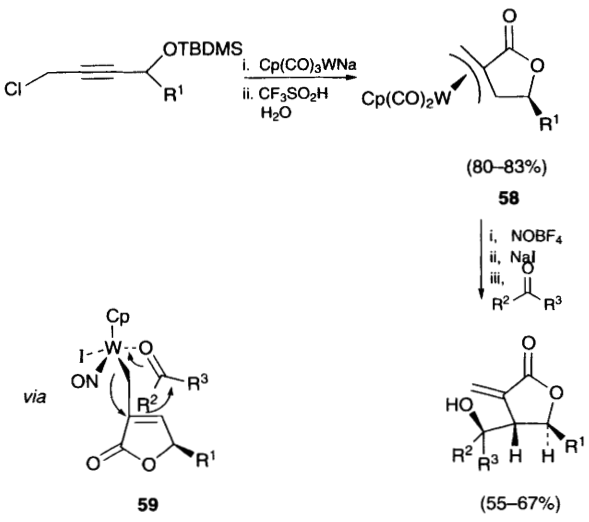
Reformatsky reaction, although the two approaches offer complementary stereochemical outcomes.[118]

Lewis acid promoted cyclisations of **57** (**Scheme 84**) are dogged by facile elimination of the product tertiary alcohol but this is overcome by fluoride ion activation of the allylsilane. The major product will not cyclise to give a *trans*-lactone fused to a *trans*-decalin but lactonisation can be achieved with inversion using Vorbruggen's methodology, amounting to a reasonably efficient synthesis of cadinanolide type lactones.



Scheme 84

Proton catalysed intramolecular alkoxycarbonylation followed by carbonyl allylation at a tungsten centre provides a remarkably stereoselective synthesis of complex α-methylene-γ-lactones from simple chloroalkynols[119] (**Scheme 85**). The silyl protecting group is critical for the selectivity of the lactonisation, which occurs by a double inversion at the siloxy bearing centre to give the *syn*-tungsten-η^3-γ-lactonyl complex **58**, whereas unprotected alkynols react by a different mechanism to give *syn* and *anti* mixtures. When activated, the π-allyl complexes **58** undergo stereoselective reaction with



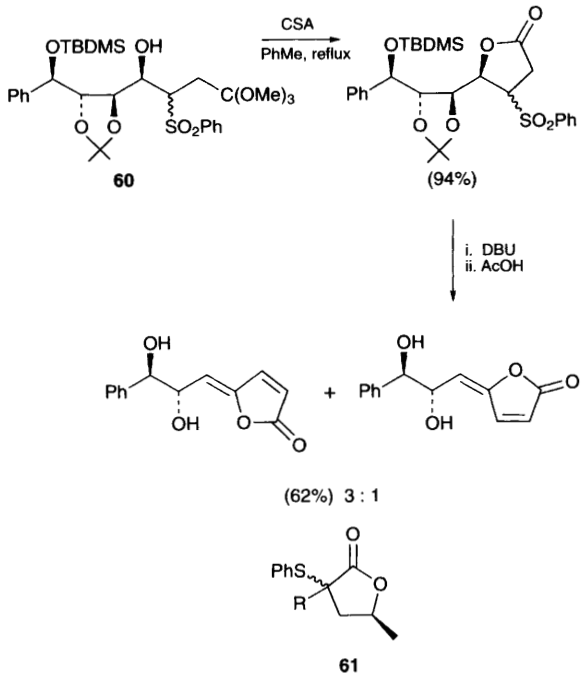
Scheme 85

aldehydes and ketones *via* the η^1-complex **59** which delivers the carbonyl compound to the less hindered face of the lactone. The methodology extends to the formation of the homologous η^3-δ- and -ε-lactonyl complexes which transesterify spontaneously on reaction with carbonyl compounds to give related α-methylene-γ-lactones.

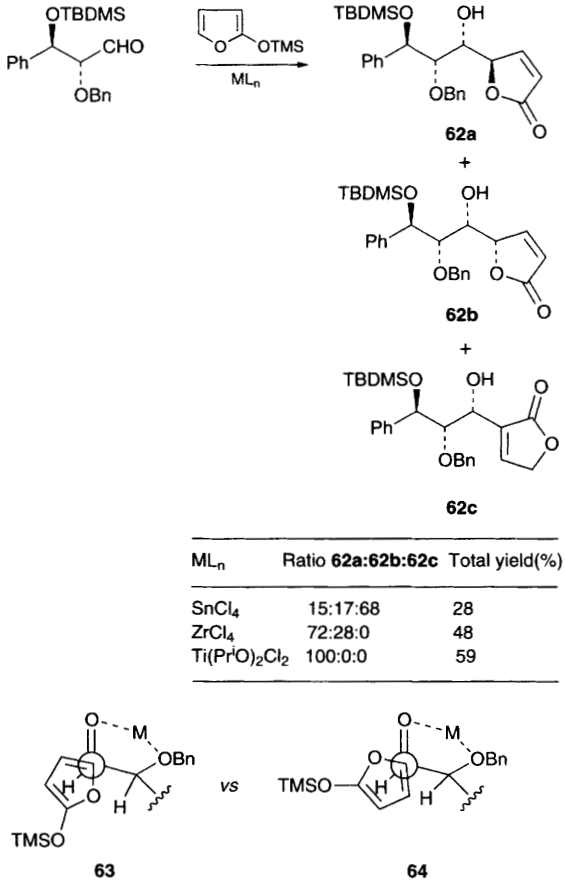
9 But-2-enolides and tetronic acids

A divergent route to the cytotoxic goniobutenolides and other *Goniothalamus* lactones has appeared, based around the lactonisation of the orthoester **60**[120] (**Scheme 86**, *cf.* **Scheme 66**). Base promoted elimination of the sulfone is accompanied by spontaneous elimination of the acetal to give, after silyl removal, a mixture of goniobutenolides A and B. Similarly, the α-phenylthiolactone **61** serves as a butenolide equivalent in which the double bond is installed by oxidation and thermal elimination.[121]

2-Trialkylsilyloxyfurans are invaluable reagents for the introduction of the butenolide moiety and their use features in several recent syntheses. In another divergent route to *Goniothalamus* lactones the regio- and stereo-selectivity of the aldol reaction of 2-trimethylsilyloxyfuran depends on the Lewis acid used.[122] Thus, tin(IV) chloride gives mainly attack from C-3 whilst C–C bond formation to C-5 is seen with other species (**Scheme 87**). The predominance of the unexpected lactone **62a** suggests that the transition state **63**, where oxygen dipole–dipole interactions are minimised, is of lower energy than the previously assumed structure **64**. The nitrogen equivalent of the aldol reaction of 2-trialkylsilyloxyfurans is a vinylogous Mannich reaction and it has been applied in Martin's synthesis of the alkaloid (+)-croomine *via* the butenolide **65**[123] (**Scheme 88**). 2-Trimethylsilyloxyfuran also adds with high diastereoselectivity to an *N*-glyoxylsultam under lanthanide Lewis acid catalysis to form the butenolide **66**[124].

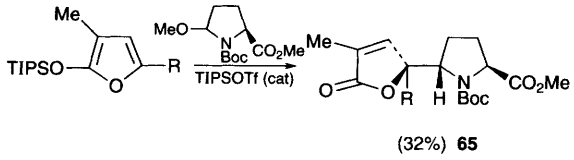


Scheme 86



ML_n	Ratio **62a:62b:62c**	Total yield(%)
$SnCl_4$	15:17:68	28
$ZrCl_4$	72:28:0	48
$Ti(Pr^iO)_2Cl_2$	100:0:0	59

Scheme 87



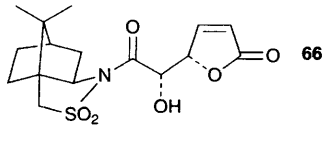
Scheme 88

Hoffman's comprehensive work on the design and application of simple butenolide building blocks has been collected in a series of papers,[125-127] concentrating particularly on the hitherto difficult functionalisation at C-4 of the butenolide ring. The bromides **67** (**Scheme 89a**) undergo Stille couplings with heteroaryl-, alkynyl- and vinyl-stannanes in good yield. The 4-vinylbutenolides **68** are versatile intermediates themselves; being oxidised to either epoxides or aldehydes, participating in Diels–Alder reactions with electron rich dienes and undergoing 1,3-dipolar cycloadditions, where strong electronic control is exerted over the regiochemistry (**Scheme 89b**). The 4-formyl derivatives will also take part in Diels–Alder reactions with electron rich dienes, completing an impressive array of transformations (**Scheme 89c**).

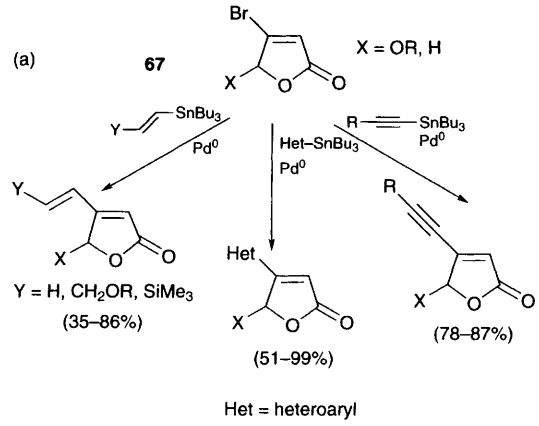
The preparation of the complementary 3- and 4-stannylated butenolides **69a** and **b** (**Scheme 90**) has also been described, involving the *ipso* radical desulfuritive stannylation of readily accessible phenylthiobutenolides.[128] Stille coupling of the stannanes with aryl iodides is successful provided fairly specific reaction conditions are adhered to, but the reagents do not appear to be suitable as precursors to the corresponding organolithiums. Another new palladium catalysed coupling available for butenolide construction is the Heck reaction of vinyl triflates and *E*-4-hydroxybut-2-enoates, where advantage is taken of the *syn* stereochemistry of the β-hydride elimination step to generate the readily lactonised *Z*-butenoate.[129] Again, the coupling conditions are quite specific but extend to vinyl and aryl iodides (**Scheme 91**).

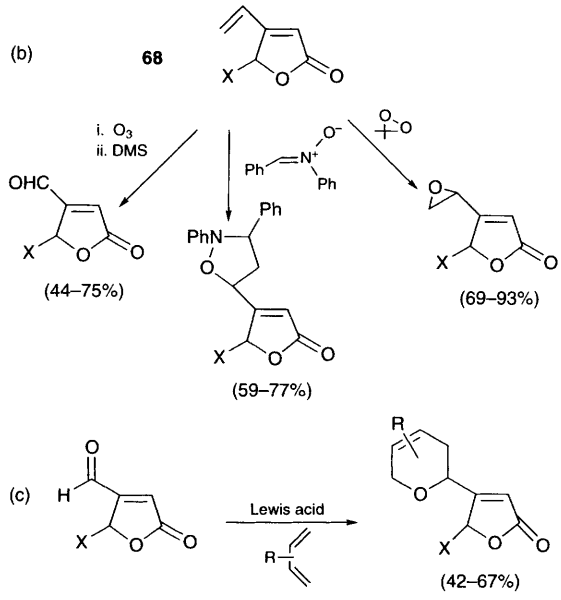
The phosphine catalysed addition of electron deficient ketones, α-keto esters and α-keto nitriles to acetylenedicarboxylate is proposed as a novel butenolide synthesis.[130] Activation of the ketones to attack by the zwitterionic intermediate **70** requires the electron withdrawing substituents, although the α-ketonitriles suffer from side reactions that reduce the yield (**Scheme 92**).

Much effort has been directed towards the asymmetric synthesis of 5-substituted butenolides and Feringa has described a general method for the substitution of 5-menthyloxybutenolides by Lewis acid catalysed nucleophilic addition to the intermediate 4-(phenylthio)lactones **71**[131] (**Scheme 93**).

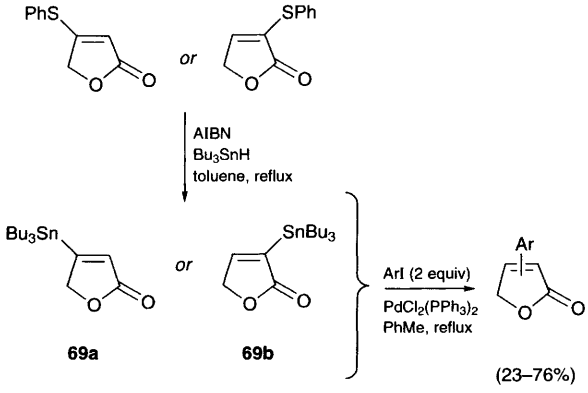


66

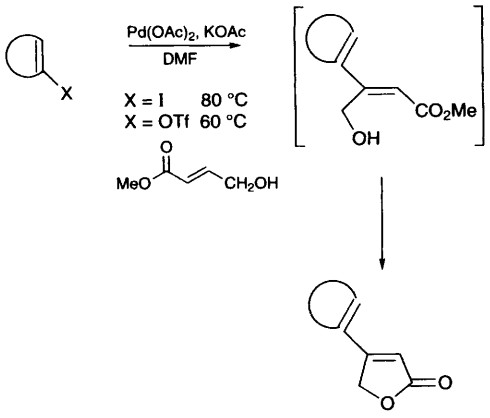




Scheme 89



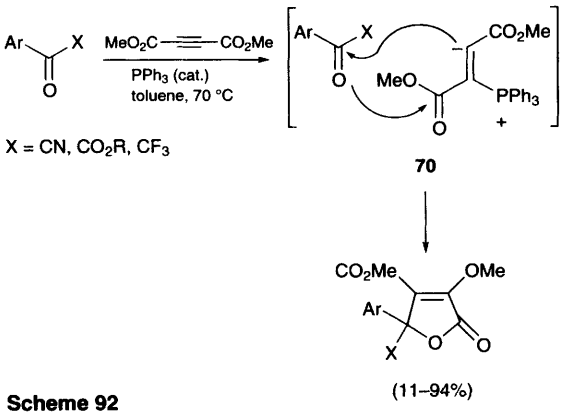
Scheme 90



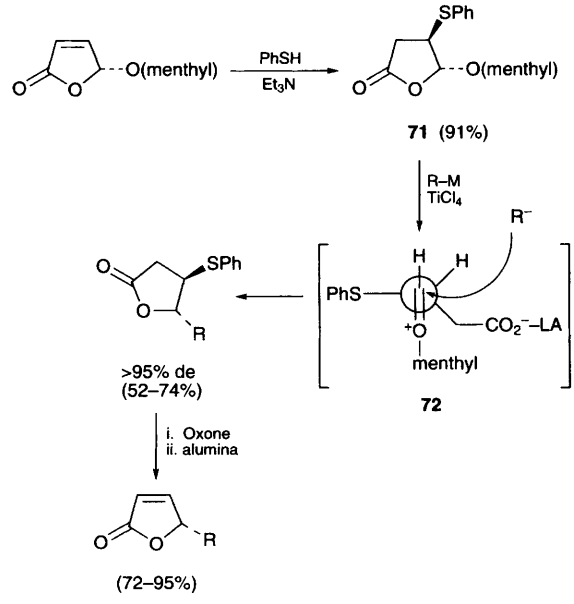
(32–89%)

Scheme 91

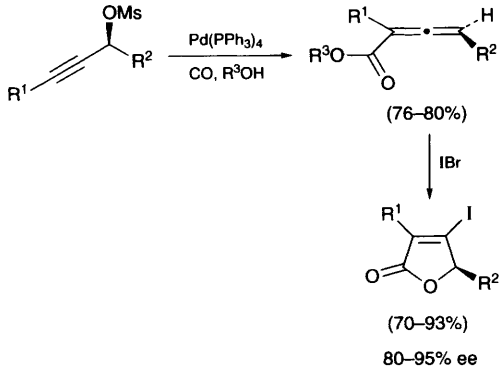
Allylsilanes, silyl enol ethers and organozincs add in Felkin–Anh fashion to the ring opened oxonium ion **72** yielding the *trans*-substituted γ-lactones.



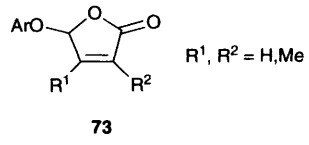
Scheme 92



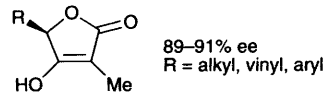
Scheme 93



Scheme 94



73



74

The phenylthio group acts to eject the alkoxide by neighbouring group participation during the relactonisation. Oxidation and elimination regenerate the substituted butenolide. Optically active butenolides are also provided by sequential palladium catalysed alkoxycarbonylation and iodolactonisation of homochiral prop-2-ynyl methanesulfonates[132] (**Scheme 94**).

Finally, two biotransformations have been applied to the preparation of single enantiomers of butenolides: the 5-acyloxybutenolides **73** come from a dynamic kinetic resolution of the corresponding 5-hydroxy compounds using Lipase PS[133] (78–86% ee at 100% conversion), while the tetronic acids **74** are produced by the Blaise reaction of optically active cyanohydrins obtained from almond flour (*R*)-nitrilase catalysed hydrocyanation of aldehydes.[134]

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