Saturated and unsaturated lactones

T. LADUWAHETTY

Merck Sharp and Dohme, Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR

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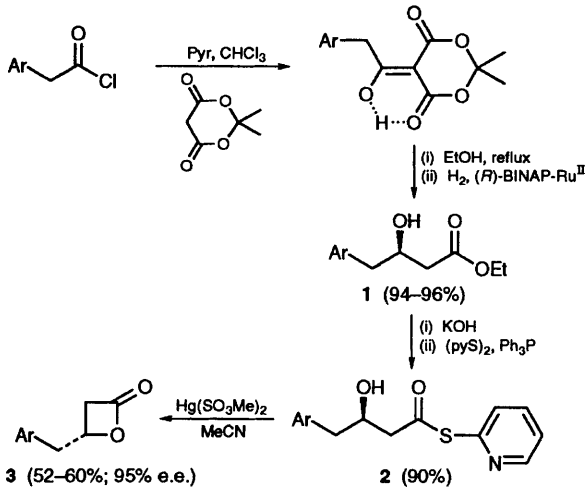


Scheme 1

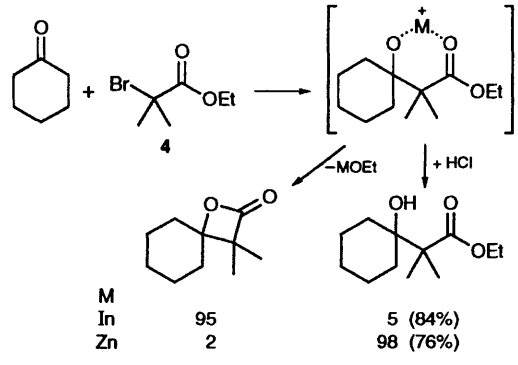
1 Introduction

This review surveys the literature relating to saturated and unsaturated lactones, and includes macrolides, tetronic acids, and α-methylene lactones. The chemistries associated with carboxylic acids and esters are covered in separate articles in *Contemporary Organic Synthesis*.

2 β-Lactones

Few lactonization methods are suitable for β-lactone formation due to the inherent lability of this moiety. In fact, hitherto, no practical methods exist for the preparation of enantiopure β-lactones. Combining Noyori's efficient protocol for the synthesis of β-hydroxy esters and a variant of the Corey/Nicolaou lactonization methodology, large-scale syntheses of β-lactones such as **3** are now possible (**Scheme 1**).[1] It was found that cyclization of the 2-pyridylthiol ester **2** is superior to the benzenethiol analogue since the latter gives the cyclized product in only 60% yield, making chromatography necessary. The use of Masamune's mercury(II) methanesulfonate catalyst together with the 2-pyridylthiol ester ensures that lactone formation occurs quickly (10 min.), without resorting to prolonged heating so that decomposition is avoided. It should be noted that only one of the six steps in the synthesis (the formation of **1**) requires chromatography, thus making it a viable synthesis on multigram-scale, to obtain β-substituted β-lactones of either absolute configuration.

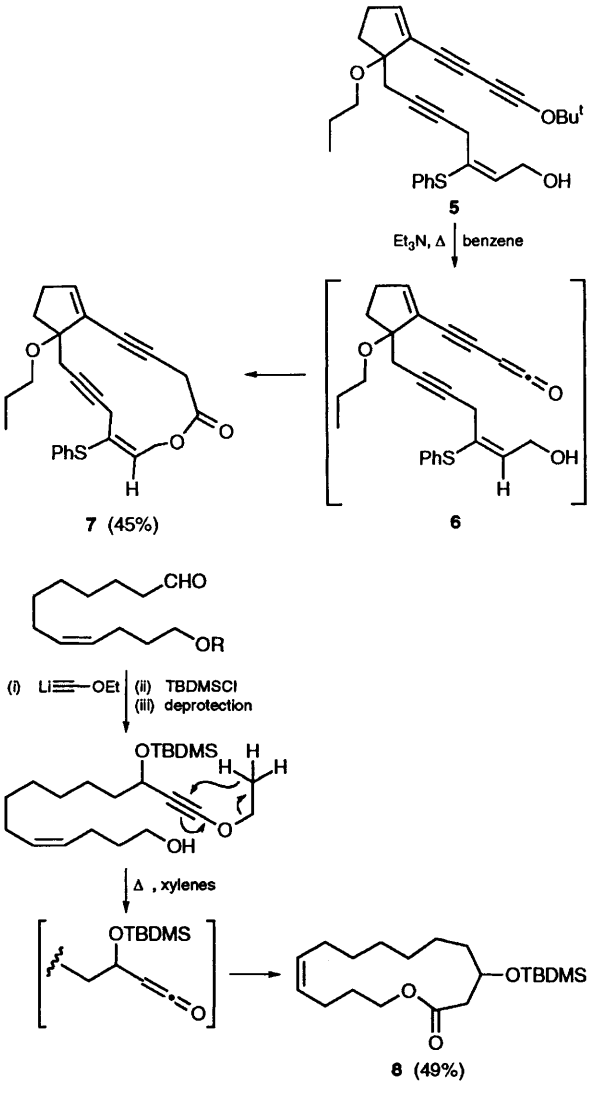
An interesting variation of the classical Reformatsky reaction involves treating the α-bromoester **4** with ketones in the presence of indium (**Scheme 2**).[2] Aliphatic ketones (with the exception of acetone) and aromatic ketones are transformed into β-lactones instead of the β-hydroxy esters. It is noteworthy that even aromatic ketones give β-lactones with zinc in DMF, instead of the traditional non-polar solvents used for the Reformatsky reaction. Formation of β-lactones using this methodology is entirely restricted to the synthesis of α,α¹,β,β¹-tetrasubstituted β-lactones, since cyclization is facilitated by the *gem*-dialkyl effect. Polar solvents such as DMF also facilitate elimination of the intermediate metal alkoxide, hence favouring β-lactone formation.



Scheme 2

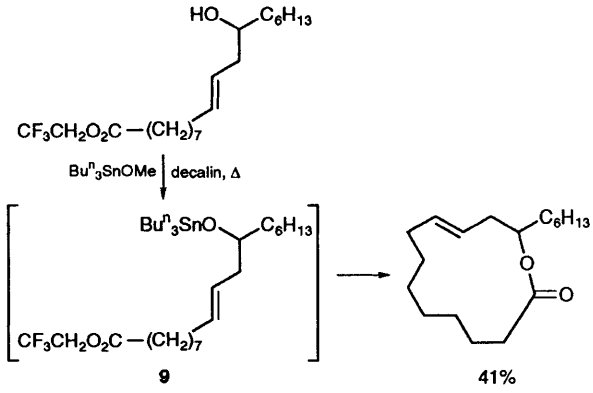
3 Macrolides

A novel macrolactonization procedure involves the *in situ* generation of a conjugated ketene, *viz.* **6**, from the 1-butoxy-1,3-diyne **5**.[3] Addition of **5** to a refluxing benzene solution of triethylamine then gives the highly functionalized lactone **7** in 45% yield. The neutral reaction conditions make this strategy ideal for acid/base sensitive compounds such as **8** (**Scheme 3**). The ethoxy alkyne intermediates, which are readily available from the corresponding aldehydes, have not only been used to construct macrolides, but also five-, six-, and seven-membered ring lactones.[4]



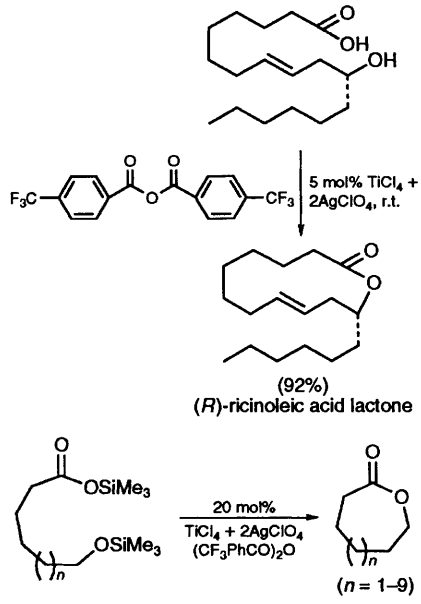
Scheme 3

1,1,1-Trifluoroethyl-ω-hydroxy-carboxylates give macrolactones (16-membered or higher) in good yields[5] under tin(IV) catalysis (**Scheme 4**). The thermodynamic impetus for the formation of the lactone is the formation of $R_3SnOCH_2CF_3$, which in turn dissociates to form the tin alkoxide **9** and trifluoroethanol which boils off under the reaction conditions. Smaller ring lactones (ten-membered and less) do not form due to competing dimerization.



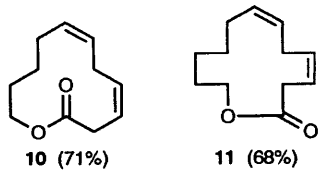
Scheme 4

Large ring lactones can be synthesized by cyclizing hydroxy acids under Lewis acidic conditions via an activated anhydride.[6,7] This method can also be used for the synthesis of seven-membered lactones (**Scheme 5**). Hydrous zirconium(IV) oxide[8] modified with TMSCl and zeolites[9] has also been used to synthesize medium to large ring lactones.

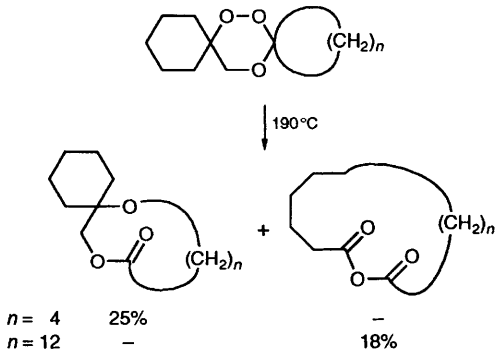


Scheme 5

Several macrolactonization methods involving acyl activation have proved to be unsuccessful for the synthesis of the macrolides **10** and **11**. The presence of the 1,4-diene and the β, γ-unsaturated ester functionality makes these pheromones unstable to heat, acid, and base. The use of the Steglich modification of the Mitsunobu cyclization, however, has enabled the efficient cyclization of the hydroxyacid precursors of **10** and **11** in very acceptable yields.[10]



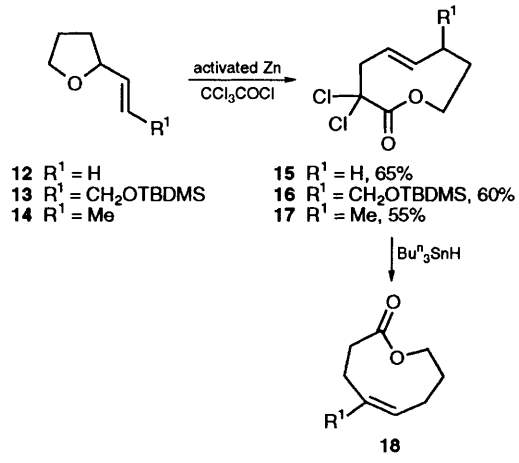
Thermolysis of 1,2,4-trioxane derivatives is an attractive possibility to access large ring systems.[11] The synthetic utility of this methodology (**Scheme 6**) is limited, however, since the rules governing ring-opening have yet to be fully understood.



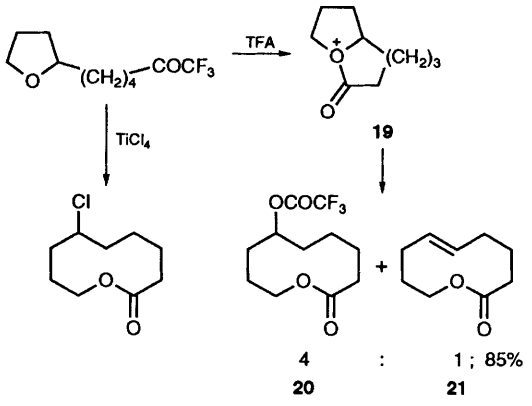
Scheme 6

4 Medium-ring lactones

A useful method for the preparation of nine-membered unsaturated lactones involves using the Malherbe–Bellus variant of the Claisen rearrangement.[12] Thus 2-vinyltetrahydrofurans (**12–14**) (**Scheme 7**) react with dichloroketene, generated *in situ*, to give the *trans*-lactones (**15–17**) in good yields. The reaction is stereospecific with regard to the stereochemistry of the initial alkene double bond. Thus a mixture of *trans/cis* (85:15) **14** gives a mixture of 2-methyl conformers of **17** (85:15). The tri-n-butyltinhydride mediated dechlorination of **14** results in the formation of the *cis*-lactone, indicating **18** to be the thermodynamically favoured product. Tetrahydrofuranyl trifluroacetic anhydrides undergo a similar ring-expansion, via an acyloxonium ion **19**,[13] to give functionalized ten-membered lactones. Attack of a nucleophile at the bridge-head carbon in **19** then gives the major product **20**, whilst regioselective elimination leads to **21** (**Scheme 8**).

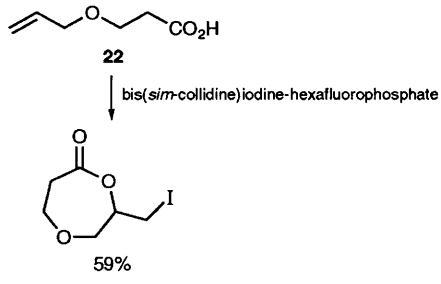


Scheme 7



Scheme 8

While iodolactonizations, to form medium-ring lactones, are not favourable processes, due to *gauche* interactions in the transition state, replacing one of the carbons with an oxygen, as in **22**, gives the seven-membered lactone product without resorting to high dilution conditions.[14]



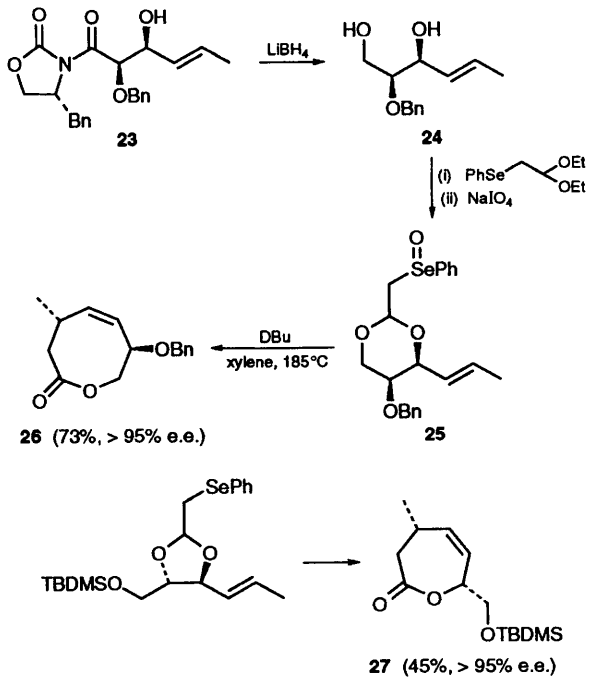
The methodology developed by Holmes *et al.* for the synthesis of medium-ring ethers has been extended to the corresponding lactones.[15] Thus the homochiral diol **24**, which is readily available from the oxazolidinone **23**, can be converted into a selenoxide **25**, which then undergoes a stereoselective Claisen rearrangement to provide the eight-membered lactone **26**. The seven-membered lactone **27** is also accessible using this methodology (**Scheme 9**).

Medium-ring and macrocyclic acetylenic lactones can be accessed by treating bicyclic tosyl-hydrazones with *N*-bromosuccinimide (**Scheme 10**).[16]

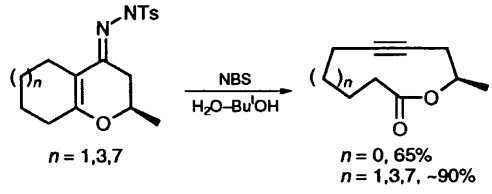
An interesting diastereoselective synthesis of medium-ring lactones **29** involves treating the trichloroacetate **28** with Cu(bpy)Cl (**Scheme 11**).[17] Although similar cyclizations of dichloroacetates have been reported previously, the dichloroacetate analogue of **28** did not cyclize. Simple alkenyl trichloroacetates (**30, 31**) do cyclize to give eight- and nine-membered rings as well, although terminal substitution of the alkene reduces the rate of the reaction. Except in the cyclization of **28**, dichloroacetates generally give higher yields than trichloroacetates in these cyclizations.

5 δ-Lactones

Radical-mediated endocyclic cleavage of the tetrahydrofuranyl hydroxy ester **32** provides the keto



Scheme 9

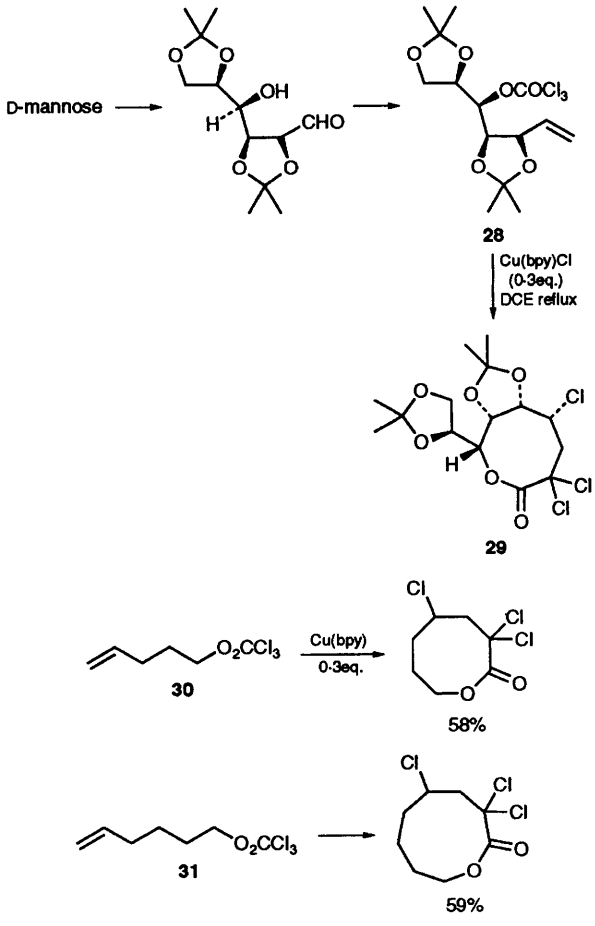


Scheme 10

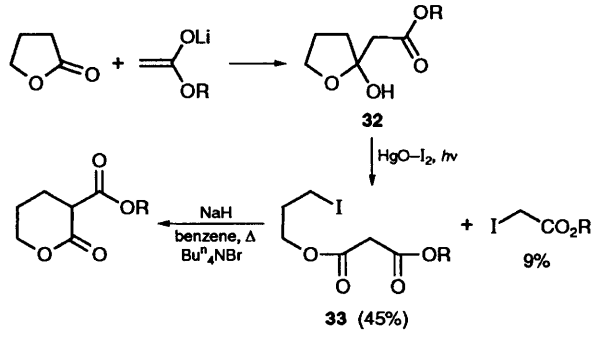
ester **33**, which then cyclizes the corresponding δ-lactone under basic conditions (**Scheme 12**).[18] The corresponding tetrahydropyranyl analogue also undergoes exclusive endocyclic cleavage although re-cyclization to the seven-membered ring only occurs when constrained in a bicyclic system (**Scheme 13**).

A diastereoselective synthesis of *cis*-4,5-disubstituted δ-lactones involves the heterolytic cleavage of vicinal donor–acceptor substituted cyclobutanes (**Scheme 14**).[19] The 1,4-zwitterionic species produced from the cyclobutane under Lewis acidic conditions forms the (*E*)-enolate intermediate **34** which then reacts with aldehydes. The resulting hydroxy esters are cyclized under acidic conditions. The chelated chair transition state explains the formation of the *cis*-lactone **35** as the major product. The reactions with methyl ketones are less selective, although dehydration of the *anti*-hydroxy ester, in preference to the *syn*, during the lactonization conditions ensures that the *cis*-lactone emerges as the major product.

The diastereoselectivity in the analogous reaction of α-monosubstituted cyclobutanes **36** with symmetrical ketones (**Scheme 15**) to provide *cis*-2,4-δ-lactones is diminished. This is attributed to the fact that the chiral centre in the zwitterionic species **37** formed from **36** is



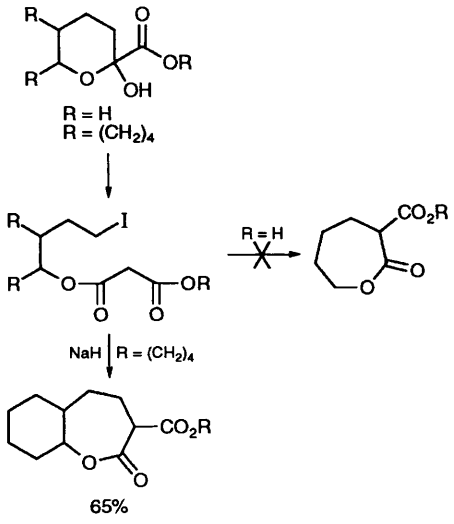
Scheme 11



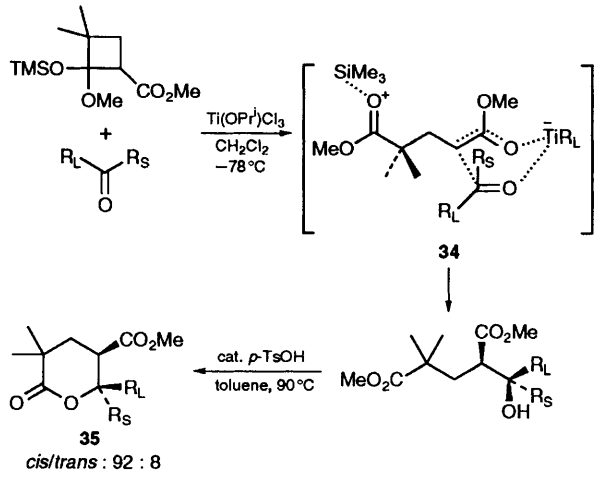
Scheme 12

β to the reaction centre and therefore less likely to influence the reaction.

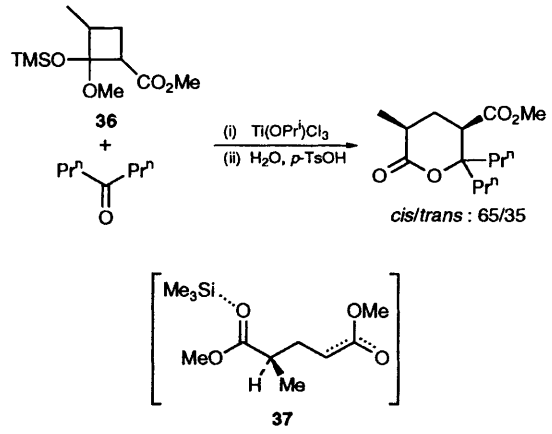
A novel cyclization strategy for the synthesis of homochiral 2,4-disubstituted β-keto-δ-lactones (**Scheme 16**) involves treating the halo diester **38** with Zn and trimethylchlorosilane.[20] Simple trituration of the crude product with hexanes then gives **39** in 70% yield. The presence of TMSCl is crucial to the reaction as the lack of it produces large amounts of the diester **40** due to protonation of the zinc enolate. Since the proton source is the product lactone, TMSCl silylates the intermediate ketal until work-up.



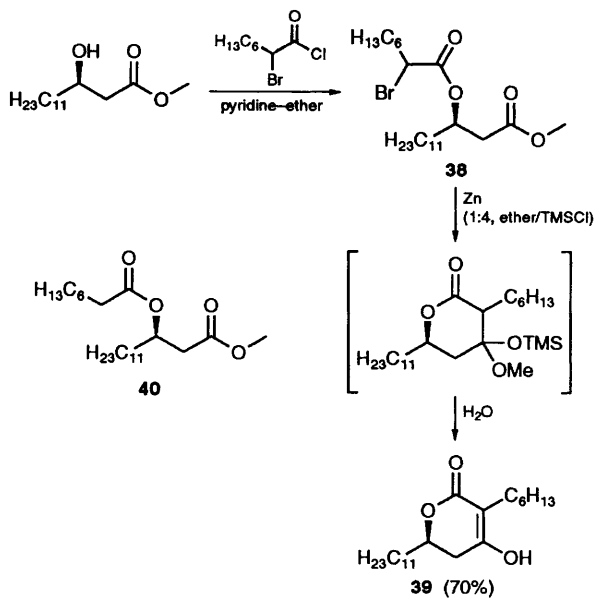
Scheme 13



Scheme 14

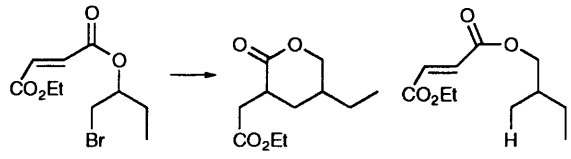


Scheme 15



Scheme 16

The radical-mediated cyclization of **41** in the presence of Bu_3SnH to produce the corresponding δ-lactone is dramatically concentration dependent (Entries **a** and **b**).[21] Under the concentrated conditions shown only the reduced product **42** is obtained. Tris(trimethylsilyl)silane, on the other hand, undergoes the desired *exo-trig* mode of cyclization to produce the δ-lactone, independent of concentration.

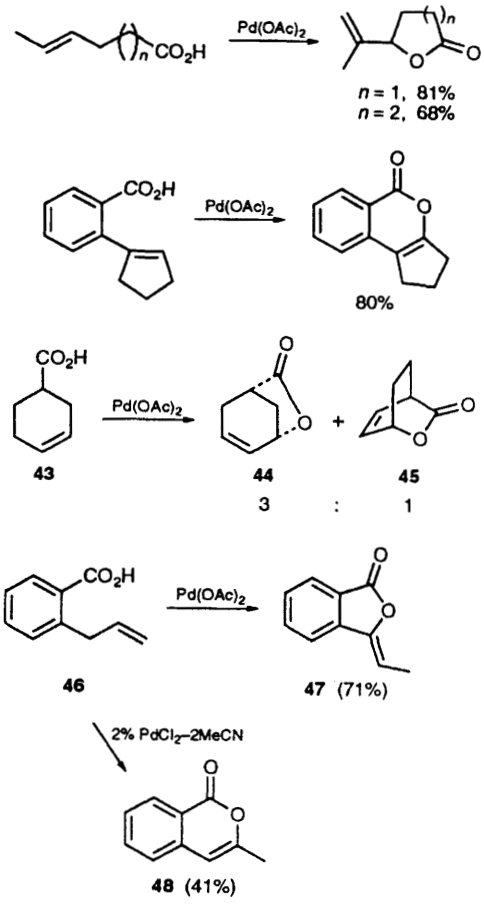


41 **42**

Concentration (ratio of volume of solvent/gram substrate)		Bu^n_3SnH	$(TMS)_3SiH$
entry **a**	x 100	0%	82%
entry **b**	x 1000	92%	90%

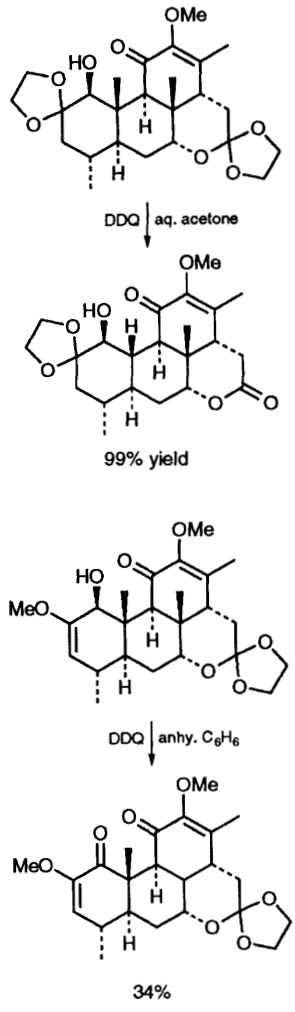
Acyloxypalladation and subsequent room temperature elimination of palladium hydride under mild conditions constitutes an efficient synthesis of bicyclic β and γ-lactones. Larock *et al.*[22] have improved upon the present methodology by employing $Pd(OAc)_2$ in DMSO. A variety of ring systems, including fused, bridged bicyclic, and spirocyclic, involving the formation of five- and six-membered rings are produced efficiently. Four-, seven- and twelve-membered rings, however, are not. The product composition in the $Pd(OAc)_2$ catalysed reaction **43** → **44**/**45** can be different from that obtained from iodolactonization or selenolactonization (**Scheme 17**). Even cyclization reactions involving different palladium catalysts can make a difference to the outcome of the reaction. Thus, Hegedus *et al.* have cyclized the alkenoic acid **46** to the 3-methyl coumarin **48** using $PdCl_2$. The (*Z*)-phthalide **47** is the only

product formed under the Larock conditions. It is likely that **47** is produced through a π-allyl intermediate which undergoes an intramolecular displacement by the carboxylate group followed by subsequent double bond isomerization.



Scheme 17

DDQ in aqueous acetone is an extremely mild method for the selective deprotection of an orthoester to a δ-lactone[23] even in the presence of an acetal (**Scheme 18**). This selectivity can be attributed to the orthoester being a more electron-rich species than the acetal, and hence forming a charge-transfer complex with the DDQ. The reaction of DDQ in benzene only effects the oxidation of the allylic hydroxyl group.

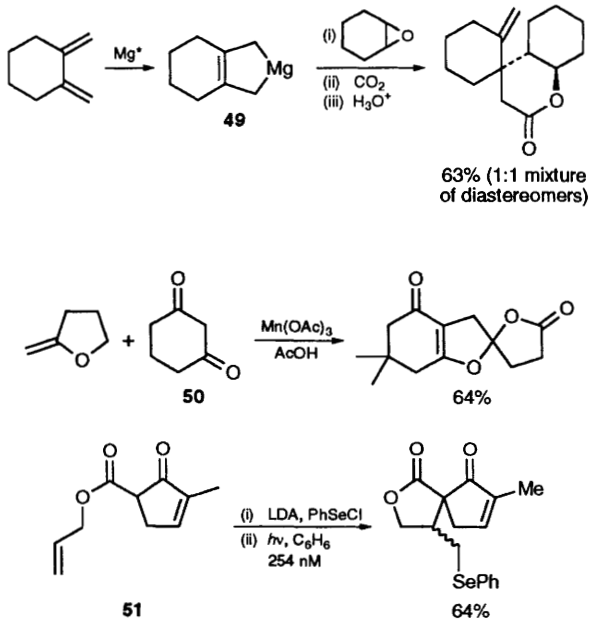


Scheme 18

6 Spirolactones

Sequential reaction of the metallocycle **49** with an epoxide and carbon dioxide provides a direct, one-step synthesis of spiro δ-lactones.[24] This approach can be used to prepare both bicyclic and tricyclic spiro-δ-lactones. Whilst good regioselectivity is observed with unsymmetrical epoxides, this methodology also provides a direct method for the synthesis of δ-lactones with a β-quaternary centre.

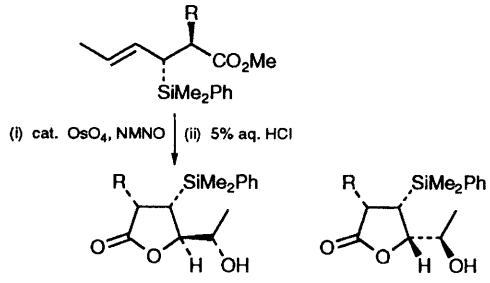
Radical cyclizations of 1,3-diones **50** or of β-keto esters **51** and alkenes either directly[25] or via a selenide[26] intermediate provide novel routes to spiro lactones (**Scheme 19**).



Scheme 19

7 γ-Lactones

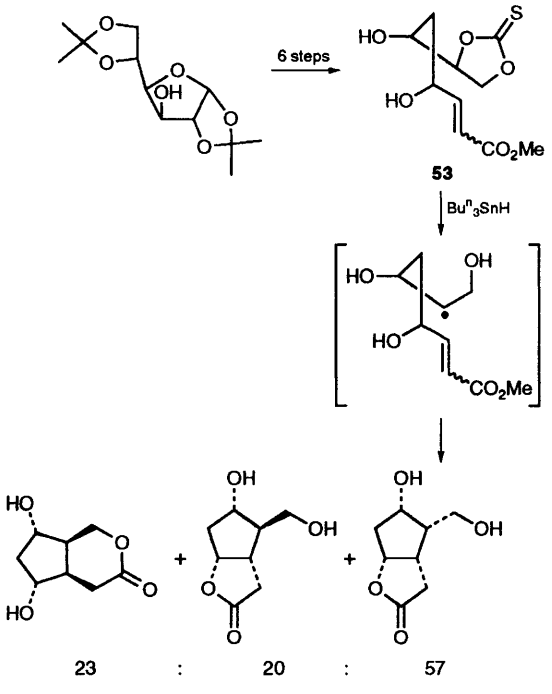
Osmium tetroxide mediated dihydroxylations of β-amino-(*E*)-crotylsilanes provide a route for the asymmetric synthesis of α-amino- γ-lactones (**Scheme 20**).[27] The diastereoselectivity arises from the approach of the osmium reagent *anti*-to the silyl group. Whereas the *anti*-diastereomer gives the 3,4-*cis*-lactone **52** in good yield and selectivity, the *syn*-diasteromer provides the 3,4-*trans*-lactone. Even basic amines are tolerated under the reaction conditions.



	trans		*cis*
$R = N_3$	15	:	1 85%
$R = NHCO_2Bu^t$	40	:	1 95%
$R = NMe_2$	23	:	1 54%

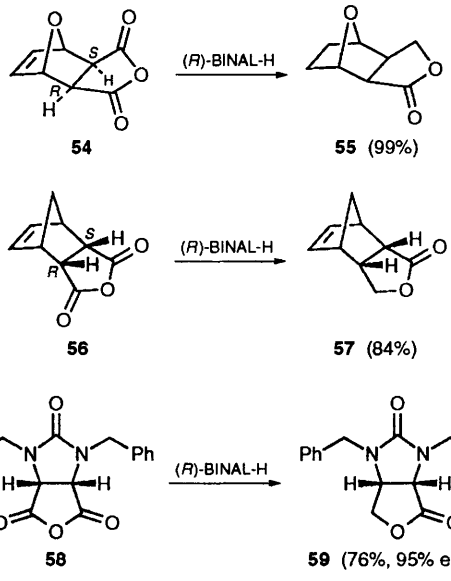
Scheme 20

The xanthate **53** derived from a sugar cyclizes in the presence of Bu_3SnH to give a mixture of bicyclic lactones in 47% yield.[28] Although there clearly needs to be an improvement in terms of selectivity, this route is a simple and elegant method of obtaining these homochiral intermediates which are precursors in prostaglandin syntheses (**Scheme 21**).



Scheme 21

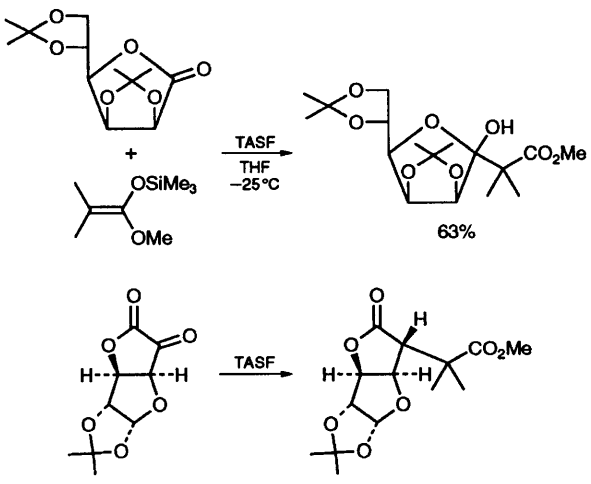
A highly enantioselective reduction of bicyclic *meso*-1,2-dicarboxylic anhydrides using Noyori's (*R*)-BINAL-H provides an efficient route into a variety of γ-lactones.[29] The lactones **55** and **57**, which are used as building blocks in the synthesis of prostanoids, are obtained in good yield with 83–89% enantiomeric excess. The fused lactone **59** which is a key intermediate in the synthesis of (+)-biotin can be obtained from **58** in 95% e.e. after one recrystallization from benzene. The reaction is governed by the steric bulk on the concave and convex faces of the bicyclic system. Thus an increase in bulk on the convex face reduces enantioselectivity, whereas an increase in bulk on the concave face improves selectivity. The chirality of the product cannot be predicted *a priori*: for instance, (*R*)-BINAL-H reduces the carbonyl attached to the group with the (*R*)-configuration in **56**, whilst reducing the carbonyl attached to the carbon with the (*S*)-configuration in **54**. But since both enantiomers of 1,1,-bi-2-naphthol are commercially available, the lactone of desired configuration can be obtained.



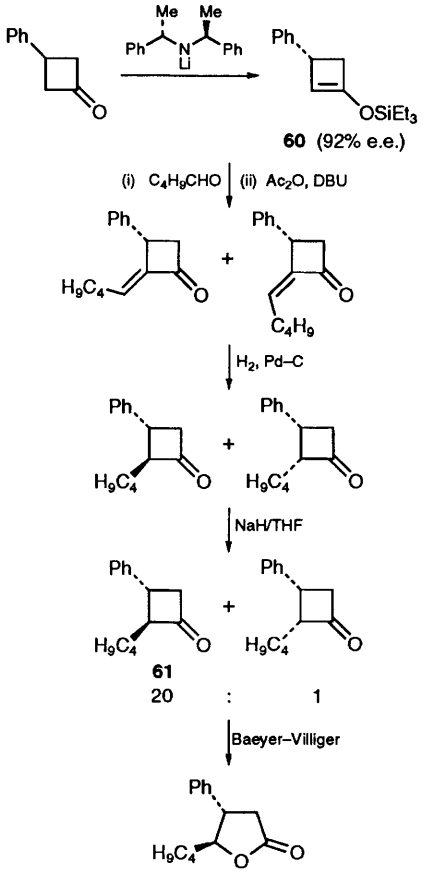
Additions of silyl ketene acetals to lactones occur only under forcing conditions. Using tris(dimethyl-amido)sulfonium trimethyl silicate (TAST) as catalyst, however, enables their smooth reaction at low temperature.[30] The greater reactivity of ketones under forcing conditions is still observed with TAST (**Scheme 22**).

Homochiral *trans*-3,4-disubstituted lactones can be synthesized from the thermodynamically stable *trans*-cyclobutanone **61**[31] which is in turn obtained by asymmetric deprotonation of 3-phenylcyclobutanone (**Scheme 23**). The direct alkylation of the enol silyl ether **60** was unsuccessful and the 2-alkylated products are obtained by sequential acylation, elimination, and hydrogenation.

Vicinal donor–acceptor substituted cyclopropanes have been used as an innovative entry to 2,3,4-trisubstituted γ-lactones. The cyclopropanes are obtained from the corresponding ketene acetal and the diazoacetic ester to give the *trans*-isomer of **62** as the

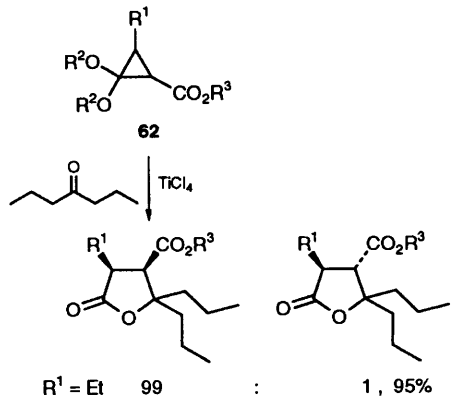


Scheme 22



Scheme 23

major product. Reactions of **62** with symmetrical ketones under Lewis acid conditions provides the *cis*-2,3-disubstituted lactones with excellent selectivity and in high yield.[32] This selectivity arises from the approach of the ketone *anti*-to the cationic substituent (**Scheme 24**). Shimada *et al.* have extended this reaction to the synthesis of *cis*-2,3-*trans*-3,4-trisubstituted γ-lactones by employing an aldehyde as the electrophile.[33] Reaction of **63** with



Scheme 24

cyclohexanaldehyde, for instance, gives the *cis-trans* product **64** with moderate selectivity (**Scheme 25**). A variety of aldehydes can be utilized, although selectivity increases with increasing bulkiness. Using $ZrCl_4$, in which the metal–oxygen bond is longer, results in a higher *trans*-3,4 selectivity (85:15).

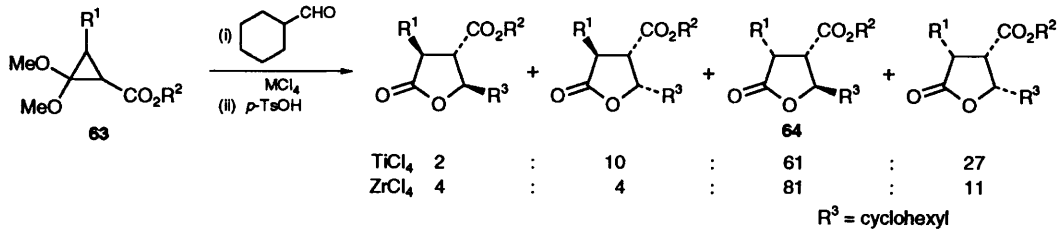
Optically active alcohols obtained by the well established reaction of chiral boron reagents with aldehydes can be converted into γ-lactones in a two step procedure (**Scheme 26**).[34] Taking advantage of the fact that aromatic esters are less likely to be reduced by borane than an alkyl ester, due to their lower basicity, the alkene **65** can be reacted with a borane reagent and oxidized *in situ* to obtain the lactone directly in good yield. The corresponding acetate protected alcohol only forms the lactone in 17% yield. For acid-sensitive lactones such as **66** thexylborane can be employed, thus avoiding the presence of HCl in the oxidizing step, since the original conditions only gives **66** in 80% e.e. (**Scheme 27**). The selectivity of disiamylborane for terminal alkenes, on the other hand, can be taken into account for the synthesis of useful intermediates such as **67**.

Enantioselective syntheses of 3,4-disubstituted butyrolactones, such as those present in (−)-*cis*-whiskey lactone, can be achieved by the samarium diodide promoted fragmentation of **68** (**Scheme 28**).[35]

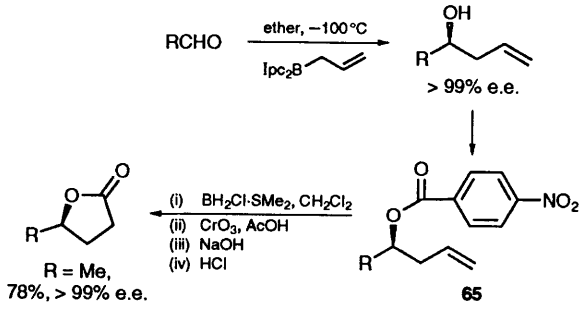
N-oxidations of β-γ-unsaturated carboxylic acids[36] followed by iodolactonizations provide a route to *trans, trans*-2,3,4-trisubstituted lactones (**Scheme 29**). The stereoselectivity of the reaction is governed by the transition state **69** and involves a 5-*endo-tet* type cyclization. The alternative transition state **70**, where the electronegative substituent allows for maximum π–σ^* interaction, leads to electron withdrawal from the olefinic system, thus making it less reactive to the electrophile.

The 4-hydroxy butenolide **71** may be readily converted into the menthyl ether **72**, which is a useful homochiral synthon for conjugate addition reactions.[37] The menthyl group can be removed later by reduction with $NaBH_4$ (**Scheme 30**).

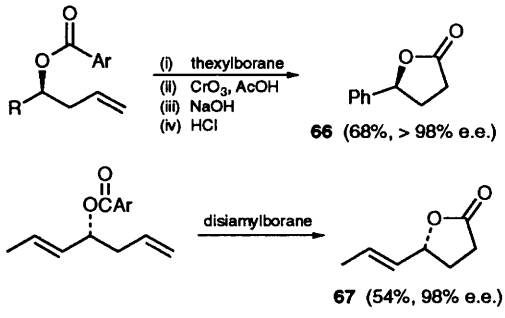
Allenol γ-lactones can be synthesized from an alkynoic acid **73** and a 2-alkynyl acetate in the



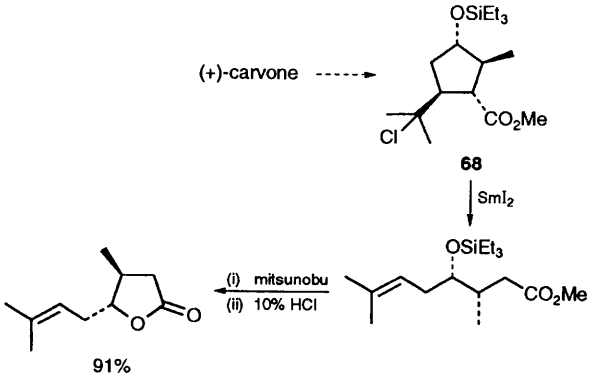
Scheme 25



Scheme 26

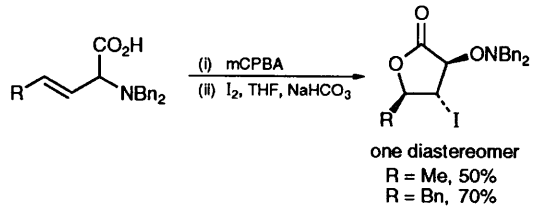


Scheme 27

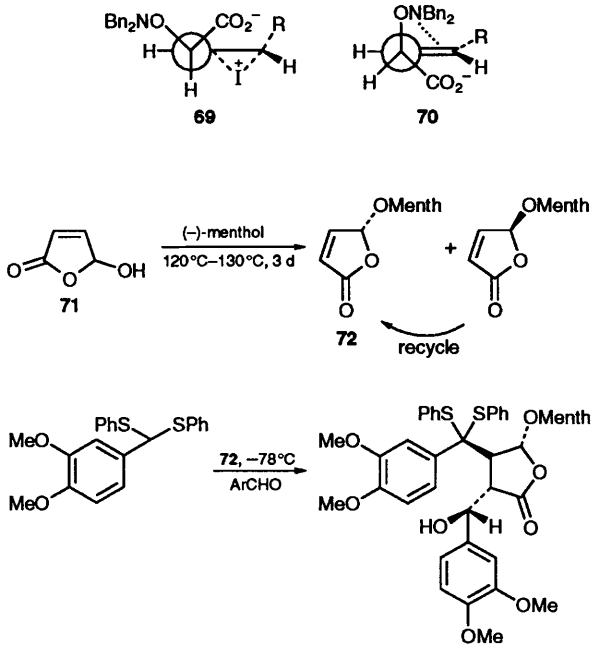


Scheme 28

presence of Pd^0.[38] This methodology is an extension of an earlier report by the same research group, involving the coupling of alkynoic acids and 1-haloalkynes. The mechanism involves the generation of a σ-allenyl palladium species which in turn activates the



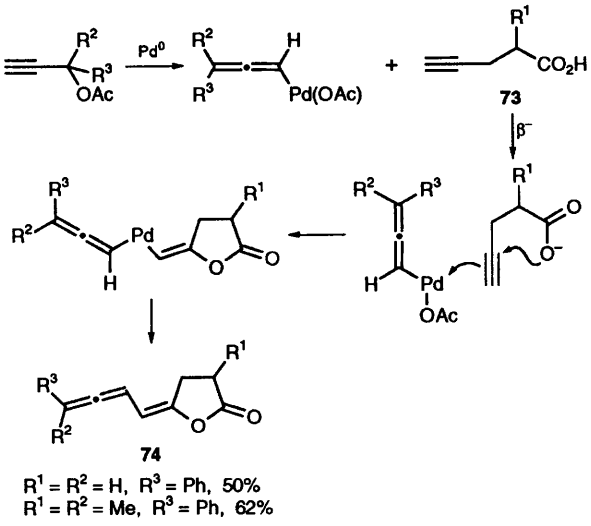
Scheme 29



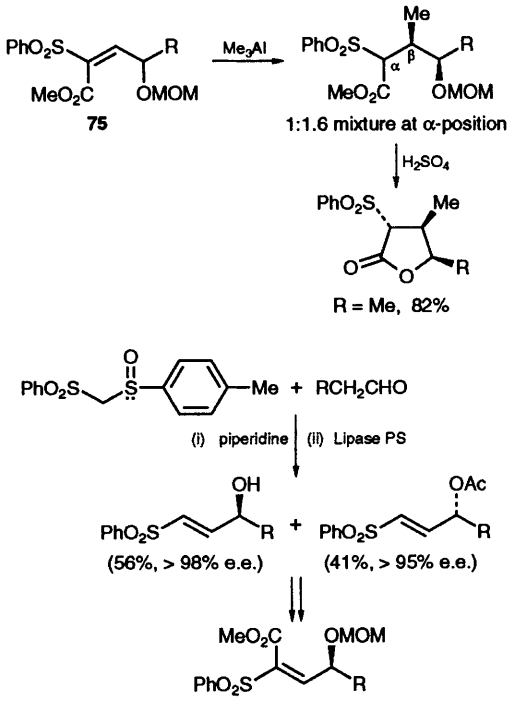
Scheme 30

intramolecular nucleophilic attack of the carboxylate anion on the triple bond to generate **74** (**Scheme 31**).

The addition of Me_3Al to α,β-unsaturated sulfone esters such as **75**, followed by acid-catalysed cyclization, provides a stereoselective route to *cis*-β-γ-substituted lactones.[39] Lithium and magnesium reagents give mixtures of 1,2- and 1,4-adducts, whilst Bu_2CuLi gives 1,4-addition without stereoselectivity. The coordination of the Me_3Al to the MOM-ether prior to addition is the origin of the diastereoselectivity in this reaction. This methodology can be used to obtain homochiral lactones by enzymatic resolution of the alcohols obtained by condensing (*S*)-(phenylsulfonyl)-*p*-tolysulfinyl methane with an aldehyde (**Scheme 32**). The sulfoxide is then



Scheme 31

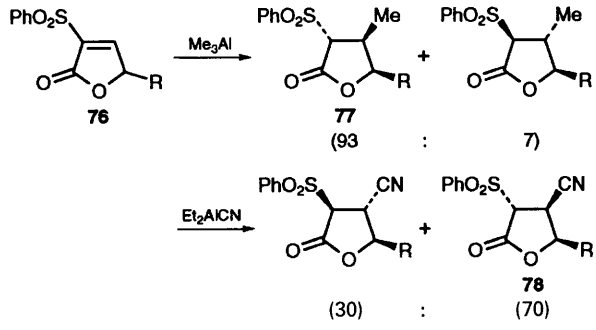


Scheme 32

eliminated and the resulting vinyl sulfone alkylated to provide the substrate for the addition of the organometallic reagent. Products with > 90% e.e. can be obtained in this manner.

The addition of Me_3Al to the butenolide **76** results directly in the *trans*-lactone **77** as the major product. Et_2AlCN, on the other hand, gives the *cis*-lactone **78** as the major product although with reduced selectivity (**Scheme 33**). This difference in stereoselectivity is attributed to the constraints imposed by the phenylsulfonyl group and its sensitivity to different reagents.

The exploitation of molecular symmetry in synthesis has been extended to the halolactonization reaction by Kurth *et al.* (**Scheme 34**).[40] The dienoic acids **79** and



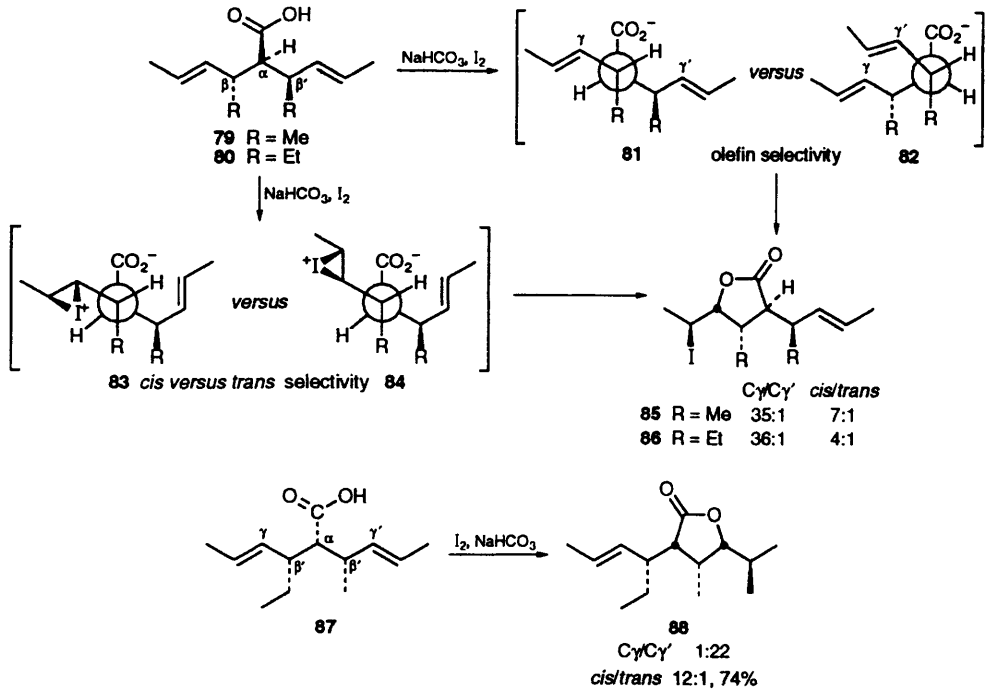
Scheme 33

80, prepared by an iterative Claisen rearrangement can be cyclized with I_2 to obtain the lactones **85** and **86** with excellent selectivity. The diastereoselectivities in the reactions of **79** and **80** arise from the fact that the nucleophilic carboxylate is confronted by two diastereoselective olefins which experience different ground-state conformations relative to the carboxylate. The conformational energy differences in the transition state favour cyclization towards the side where the carboxy and allylic substituents are *anti*; thus olefin selectivity can be anticipated when the C_α–C_β/C_α – $C_{\beta'}$ differ in stereochemistry (**81** *versus* **82**). The C_4-C_5 stereochemistry is determined by the face selectivity in the iodination (**83** *versus* **84**). The subtlety in these cyclizations can be illustrated (**Scheme 34**) by the dienoic acid **87**, where both allylic substituents are *syn* and only differ from each other by a single methylene. The acid **87** cyclizes to give the lactone **88** with $C_{\gamma}{}^{1}$ selectivity (22:1) and excellent *cis*/*trans* selectivity.

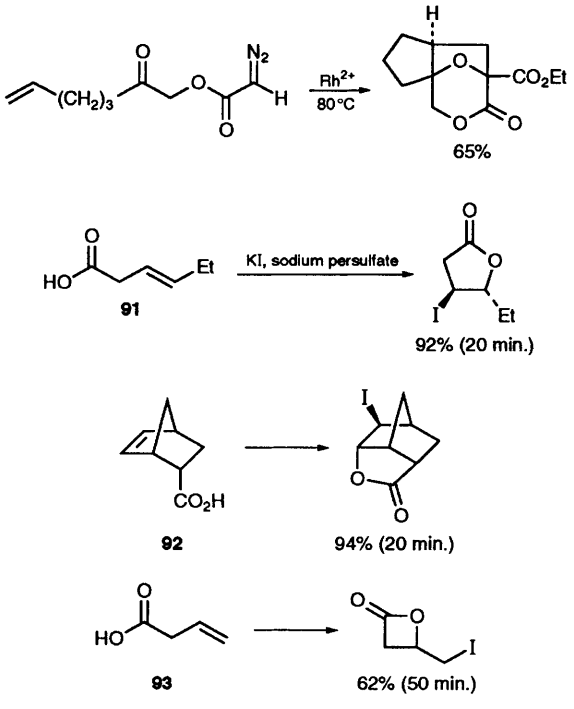
Having had success with the transition metal catalysed tandem cyclization/cycloaddition reactions of diazoketones, Padwa *et al.* have now explored the analogues reactions with diazoesters.[41] The ester **89** does not cyclize, possibly due to the reduced electrophilicity of the rhodium carbenoid. The presence of an additional stabilizing group, as in **90**, however, promotes the cyclization, providing the lactone product in good yield. Conformational differences between the mono- and di-substituted carbenoids may also govern their reactivity.

A variety of carboxylic acids afford γ-lactones in the presence of potassium iodide and sodium persulfate (**Scheme 35**). Unlike the standard iodolactonization conditions which require substantial amounts of KI and I_2, this new procedure, which is based on the *in situ* oxidation of iodide with persulfate, only requires a slight excess of KI.[42] Cyclizations of the acids **91–93** using standard iodolactonization conditions always give lower yields and need longer reaction times than the KI/persulfate method. The successful iodolactonization of but-3-enoic acid to the corresponding β-lactone is particularly noteworthy.

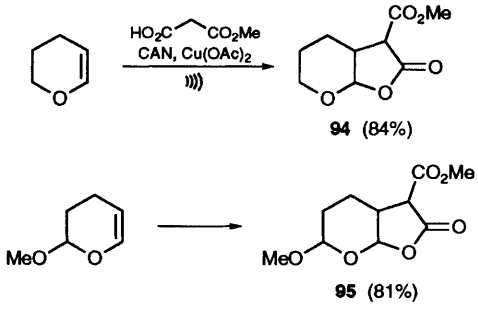
The acid-sensitive fused-ring lactones **94** and **95** can be synthesized efficiently from the cyclic enol ethers shown and the monomethyl ester of malonic acid using ceric ammonium nitrate in acetic acid.[43] Addition of $Cu(OAc)_2$ to the reaction mixtures, to oxidize any secondary radical intermediates to



Scheme 34



Scheme 35

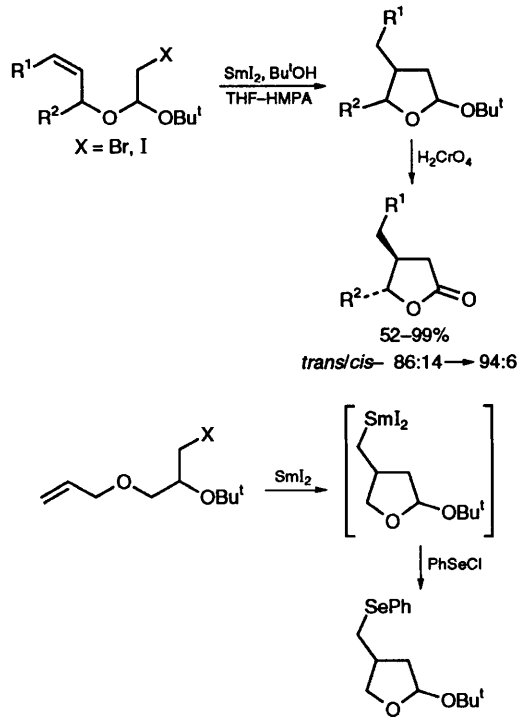


carbocations, avoids large amounts of side-products that may otherwise be formed. Ultrasound further increases the yields in the reactions by *ca.* 10%. Simple olefins give low to moderate yields of lactones, although a variety of electron-rich olefins have been shown to work very efficiently. $Mn(OAc)_3$, on the other hand, is not suitable for the synthesis of acetals such as **95**.

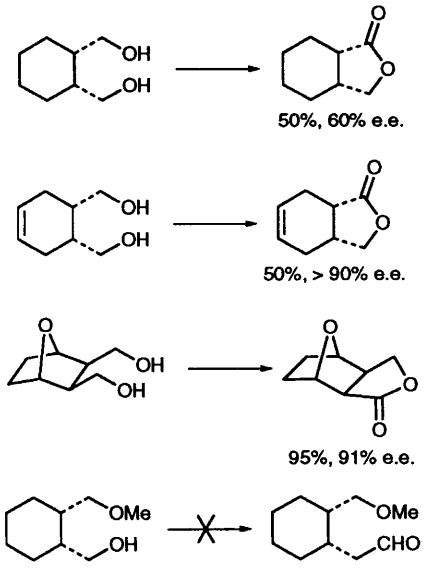
Samarium iodide promoted cyclizations of acetals provide *trans*-2,4-disubstituted γ-lactones in good yields (**Scheme 36**). Although similar to the analogous reactions with Bu_3SnH, the samarium iodide conditions are milder and avoid the troublesome removal of tin residues. This methodology also paves the way to introduce functional groups through sequential intramolecular cyclization and electrophilic trapping.

Preparations of chiral lactones from *meso*-diols can be accomplished in high yields and enantioselectivity with *Norcardia corallina* B-276.[44] Using whole cell methods such as this is more economical since it avoids the need to recycle the expensive co-factors necessary for enzyme-based methods. Analogous to *horse-liver alcohol dehydrogenase* (HLD), the initial oxidation is of the *pro*-(*S*) hydroxymethylene (**Scheme 37**). In contrast to HLD, however, the whole cell system is selective only for diols.

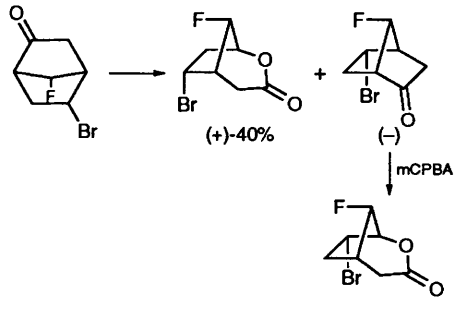
The bio-Baeyer–Villiger reaction promises to be an extremely useful method for obtaining optially pure ketones and lactones (**Scheme 38**).[45] The whole cell methodology using *Acinetobacter calcoaceticus* (NCIMB 987) or *Curvularia lunata* (NRRL 2380) has



Scheme 36

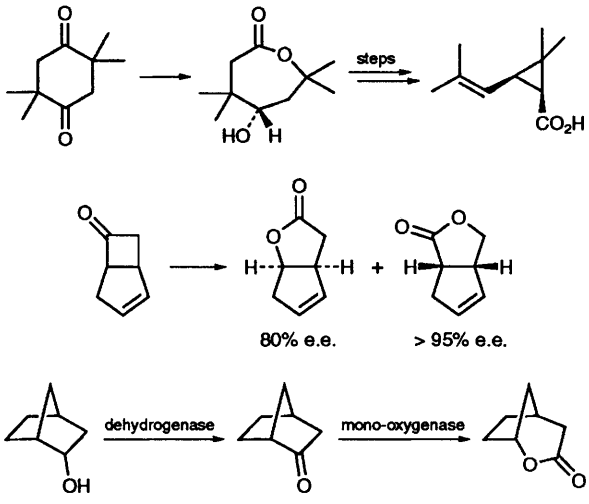


Scheme 37



Scheme 38

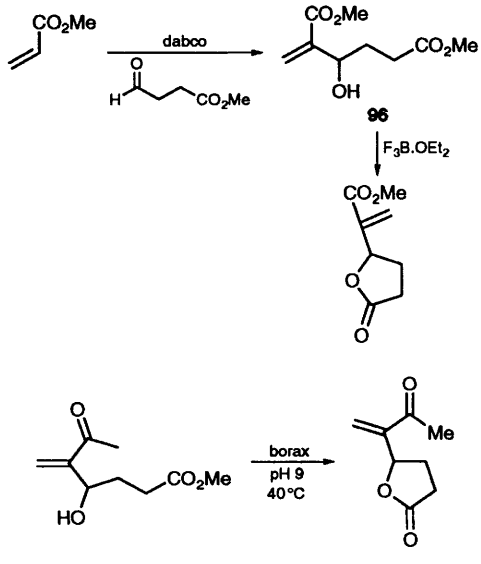
some drawbacks, as the organisms are not readily available and the yields are rarely high due to overmetabolism. A recent development in the area is the use of an enzyme-based method using a monooxygenase from the micro-organism *Pseudomonas putida*. This monoxygenase is unusual in that it utilizes NADH as its co-factor. NADH is much easier to recycle compared to the more common NADPH, which makes the whole process much more economical. This enzyme can also be used together with a dehydrogenase to convert an alcohol into a lactone directly (**Scheme 39**).



Scheme 39

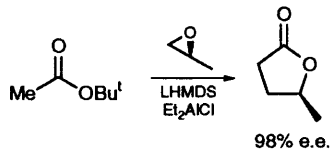
A mild method for the synthesis of 5-ethenyl-γ-lactones involves an initial Baylis–Hillman coupling to form the hydroxy ester **96**, followed by cyclization (**Scheme 40**).[46]

The enolate generated from LHMDS and t-butyl-acetate, in the presence of a Lewis acid such as



Scheme 40

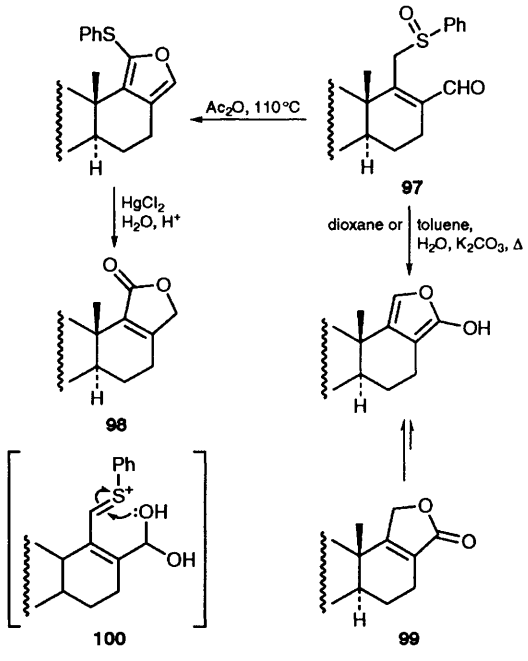
Et_2AlCl, reacts with (*R*)- or (*S*)-propylene oxide resulting in the formation of (*S*)-4-methylbutyrolactones with 98% e.e. (**Scheme 41**).[47]



Scheme 41

8 But-2-enolides and tetronic acids

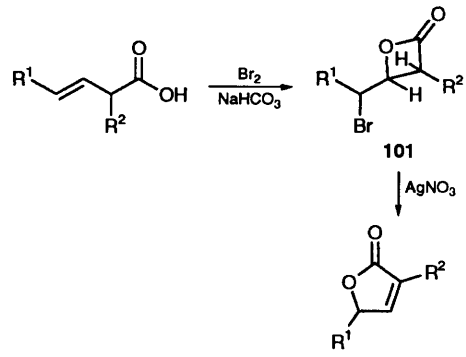
Annulated butenolides, *viz.* **98** and **99**, can be formed in a regioselective manner from the same intermediate sulfoxide **97** by generating the corresponding sulfene under different conditions.[48] Under anhydrous Pummerer conditions a vinyl sulfide is formed which upon mercury-mediated hydrolysis forms the butenolide **98** exclusively (**Scheme 42**). In the presence of H_2O, however, the thermally generated sulfene reacts via the hydrated aldehyde **100** to provide **99** as the sole product.



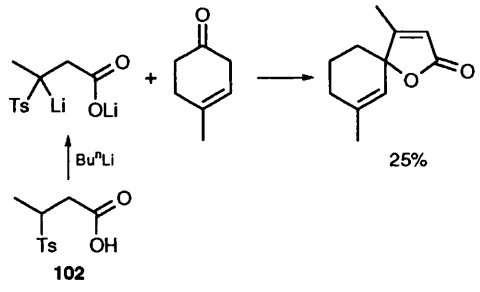
Scheme 42

Bromolactonizations of a β,γ-unsaturated carboxylic acid provides β-lactone **101** which when treated with $AgNO_3$ results in the generation of an exocyclic cation (**Scheme 43**). Ring expansions then provide α,γ-disubstituted butenolides in good yield.[49]

The addition of sodium *p*-toluenesulfinate in ethanol to α-β-unsaturated carboxylic acids provides the sulfone **102**, the dianion of which can be reacted with aldehydes and ketones.[50] The resulting



Scheme 43

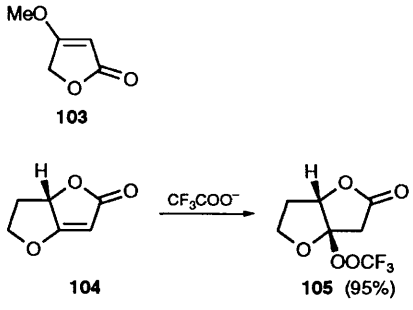


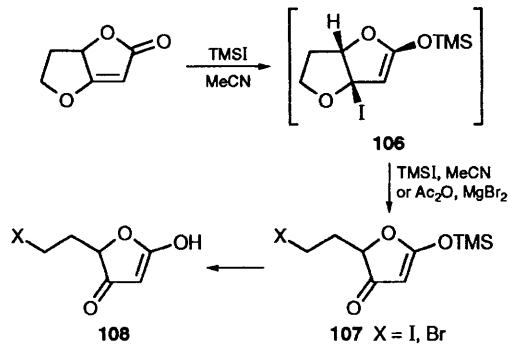
Scheme 44

hydroxyfulfone can then be converted into the butenolide in modest overall yield (**Scheme 44**).

The reactivity of bicyclic tetronates has been explored by Bertucco *et al.* and interesting differences between the monocyclic- and bicyclic-tetronates have been found.[52] Unlike the methyl tetronate **103**, which is completely inert to 1,4-addition by nucleophiles, the bicyclic tetronate **104** reacts with even poor nucleophiles such as trifluoroacetate to provide the 1,4-adduct **105** in 95% yield. Some other nucleophiles give interesting ring-opened butenolides.

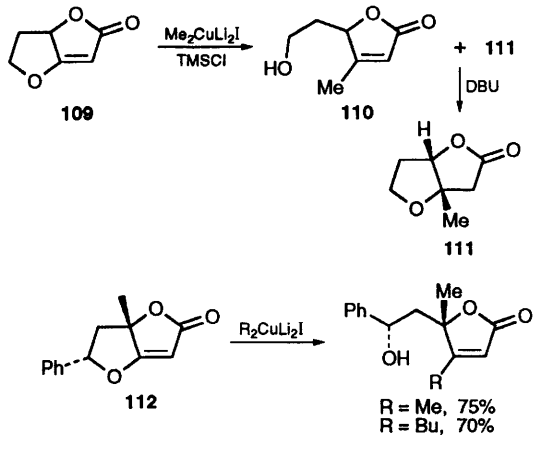
The addition of TMSI to bicyclic tetronates, a reagent previously used by Pattenden *et al.* for the de-esterification of methyl tetronates, results in rapid formation of the corresponding silyl enolate **106**. Further reaction with excess reagent then leads to the ring-opened iodide **107** which can be hydrolysed to the tetronate **108** (**Scheme 45**). The hydrolysis of the methyl tetronate itself with TMSI does not, of course, involve the initial 1,4-addition.





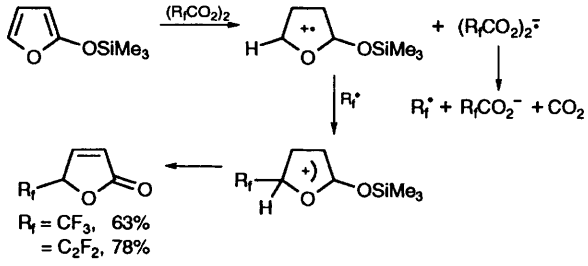
Scheme 45

The first example of a conjugate addition of a carbon nucleophile to a tetronate has also been reported by these same research workers (**Scheme 46**). The bicyclic tetronate **109** was found to react with dialkyl cuprates in the presence of TMSCI to give a mixture of the ring-opened and bicyclic products **110** and **111**, which on exposure to DBU are converted into **111** exclusively. The substituted tetronate **112** reacts with dialkylcuprates even without TMSCI, with the strain relief in the bicyclic structure being the driving force for the reaction. Methyl tetronate is, once more, inert to these conditions.

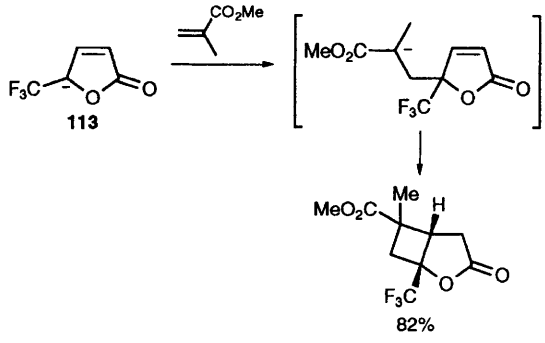


Scheme 46

4-Fluoroalkylbut-2-en-4-olides can be synthesized by reaction of 2-silyloxy furans with perfluoroalkyl peroxides (**Scheme 47**).[52] The mechanism involves the oxidation of the furan to a radical cation and the simultaneous reduction of the resulting peroxide to a radical anion which in turn dissociates to a perfluoroalkyl radical. Addition of the radical to the furan radical cation, followed by rearrangement then provides the butenolide. Due to the strong electron-withdrawing effect of the trifluoromethyl group the anion **113** can react with various acrylates under weakly basic conditions (**Scheme 48**). Defluorination, a common problem with perfluoroalkyl anions, does not occur due to delocalization into the ring.

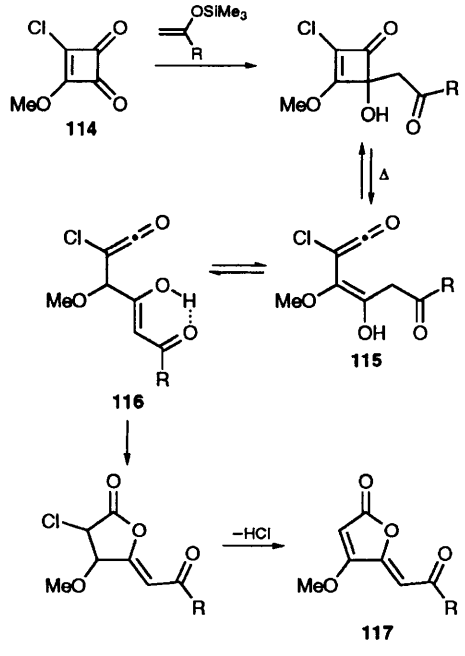


Scheme 47



Scheme 48

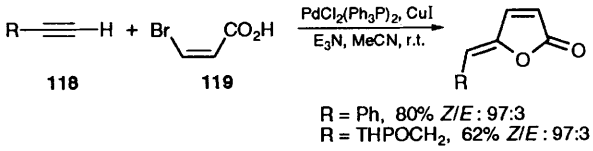
The titanium-catalysed additions of enol silanes to squaric acid **114**, and heating of the resulting α-hydroxy ketones in the presence of pyridine, results in the exclusive formation of the (*Z*)-butenolide **117** in 64% yield (**Scheme 49**).[53] The mechanism of this reaction involves a thermally allowed electrocyclic ring-opening to give **115** which recyclizes to the



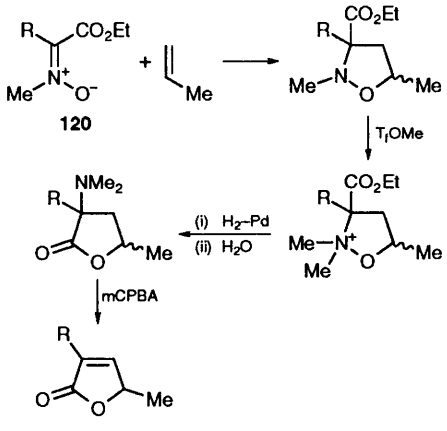
Scheme 49

butenolide. The observed (*Z*)-geometry of the methylene is due to the H-bonded enol form in the intermediate **116**.

A concise synthesis of (*Z*)-isomers of γ-alkylidenebutenolides can be achieved under mild conditions by reaction of acetylenes with bromoalkenoic acids under Pd catalysis.[54] This reaction provides an interesting interplay between the *in situ* generated Pd^0 species, which catalyses the coupling of **118** and **119**, and the Pd^{II} species which assists in the cyclization. Prolonged reaction times result in a lower *E*/*Z* ratio.



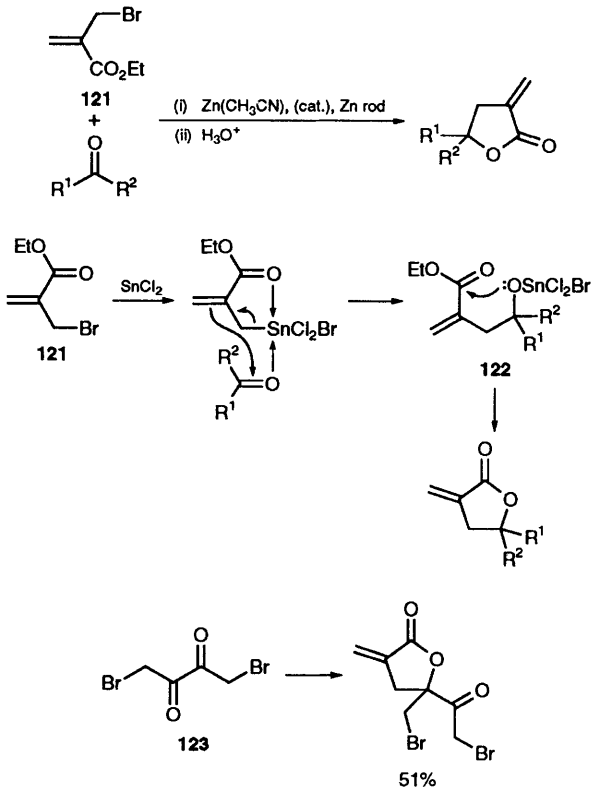
Cycloaddition reactions between the nitrile oxides **120** and propene afford mixtures of isoxazolidines (55–68% yield).[55] Conversion of the latter into their corresponding salts, followed by hydrogenolysis and elimination then provides a useful route to disubstituted butenolides (**Scheme 50**).



Scheme 50

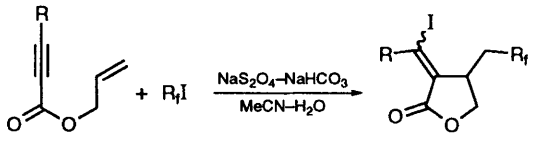
9 α-Methylene butyrolactones

The electroreduction of a catalytic amount of $ZnBr_2$ in acetonitrile provides an active Zn species which reacts with **121** and aldehydes or ketones to provide α-methylene-γ-butyrolactones in one step (**Scheme 51**).[56] The reaction is, however, sensitive to the steric hindrance around the carbonyl group. The allylic carbanion equivalent **121** also reacts with aldehydes and ketones in the presence of $SnCl_2$ to provide α-methylene-γ-butyrolactones (**Scheme 51**).[57] The allyltrihalostannane intermediate in this sequence not only enhances the nucleophilicity of the anion, but also activates the carbonyl group towards nucleophilic attack. The resulting alkoxystannane **122** is reactive enough to form the lactone *in situ*. Due to the sensitivity of the organostannane to substitution around the carbonyl, diketones such as **123** can be utilized to give only the mono-alkylated product.



Scheme 51

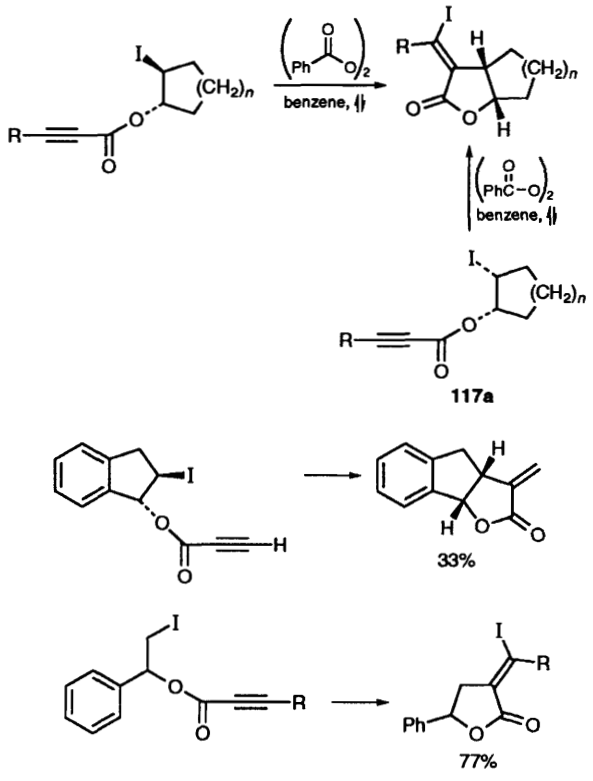
Sodium dithionite initiated cyclizations of acyclic alkynoates give fluorinated α-alkylidine γ-butyrolactones in good yield and selectivity (**Scheme 52**).[58] The reaction works best when R ≠ H, although propynoates do give modest yields (44%). The reaction is initiated by the generation of a perfluoroalkyl radical by the dithionite which, due to its electrophilic nature, adds to the more electron-rich double bond. Cyclization to the triple bond is followed by iodine transfer to the vinyl radical. Good *E*/*Z* selectivities (> 95:5) are obtained under the reaction conditions. This is due to the iodine transfer being slow, allowing the vinyl radical to invert to form the more stable (*E*) isomer.



Scheme 52

A comprehensive study of the synthesis of iodoacetylenic esters and their radical mediated cyclization to (*E*)-iodoalkylidine butyrolactones has been conducted by Weavers *et al.*[59] Whereas the *exo-dig* ring-closures of propargyl ethers and acetals have been successful, thereby making subsequent oxidation a necessity, the cyclization of the ester gives direct entry to the desired product. A variety of iodo esters have been synthesized by the iodonium ion

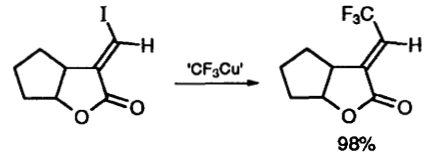
mediated addition of a carboxylic acid to an alkene. Although several radical cyclization methods were attempted [*e.g.* AIBN; Bu_3SnH; Bu_3SnCl, $NaBH_4$; cobalt(I)] only one, the heating of a benzene solution of the iodoesters with dibenzoyl peroxide, proved successful. A number of cyclic, bicyclic, and spirocyclic lactones were formed in modest (33%) to excellent yields (**Scheme 53**). With a few exceptions, the cyclizations were stereospecific giving only the (*E*)-isomer. The cyclopentyl and cyclohexyl iodo esters cyclized to give the more stable *cis*-ring junction, regardless of the stereochemistry of the initial iodo ester. As expected, larger rings give significant proportions of the *trans*-isomer.



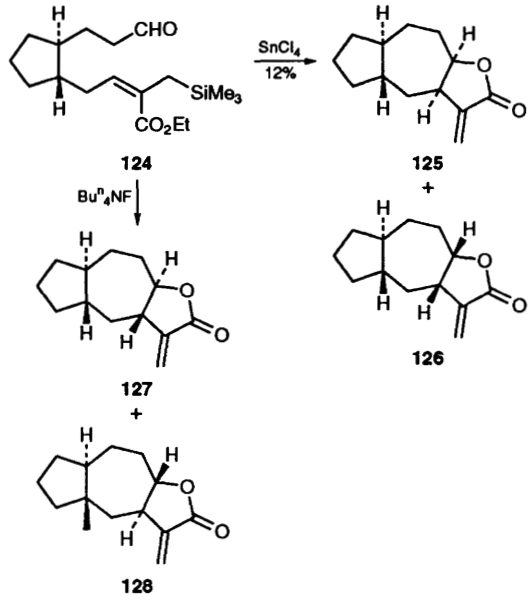
Scheme 53

Although direct photolysis of the iodoesters has proved unsuccessful, the (*E*)-alkylidine lactones can be photoisomerized to give *E*/*Z* mixtures, and the less accessible (*Z*)-isomer can then be separated by chromatography.[60] These lactones have the capacity to undergo nucleophilic displacement/elimination reactions. The degree of stereospecificity is dependent on the nucleophile.[61] An interesting difference in outcome is seen between the reaction with lithium dimethylcuprate, where a mixture of isomers are obtained, and trifluoromethylcopper (**Scheme 54**) where the geometry of the reacting double bond is conserved.[62]

Intramolecular cyclizations of ω-formyl-α-trimethylsilylmethyl α,β-unsaturated esters **124** pave the way for carbocyclization, lactonization, and α-methylenation in one step, albeit in low yield (**Scheme 55**).[63] The Lewis acid promoted cyclization of the (*Z*)-isomer **124** gives only the



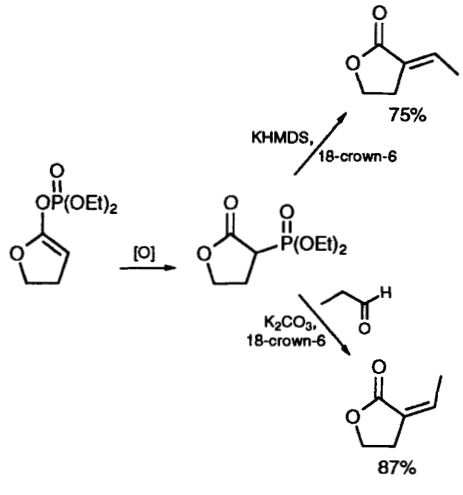
Scheme 54



Scheme 55

cis-lactones **125** and **126**, whereas fluoride promoted cyclizations provide only the *trans* isomers **127** and **128**. The five-membered ring is essential to allow for the folded conformation of **124** in order for the reaction to proceed.

α-Phosphonolactones, which are prepared by air-oxidation of vinyl phosphates, undergo Horner–Wadsworth–Emmons reactions to give (*E*)- or (*Z*)-α-methylene lactones depending on the conditions (**Scheme 56**).[64] The γ-lactone gives exclusively the



Scheme 56

(*E*)-propylidine lactone with KHMDS in the presence of 18-crown-6, whilst giving a high proportion of the (*Z*)-isomer with K_2CO_3 and 18-crown-6. A survey of the examples cited, however, reveals that the conditions for (*E*)- or (*Z*)-alkene formation vary with the structure of the starting phosphonolactone.

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