Saturated and unsaturated lactones

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Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 133

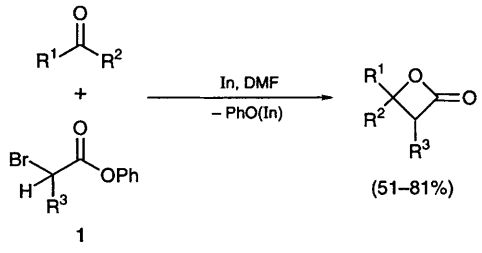
1 Introduction

This review covers the literature relating to saturated and unsaturated lactones, including macrolides, tetronic acids and α-methylenebutyrolactones. The classification of the chemistry described follows the pattern of the previous survey in *Contemporary Organic Synthesis*.[1]

2 β-Lactones

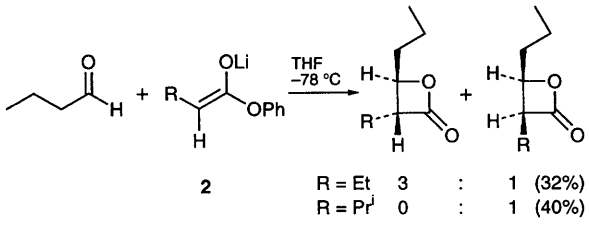
The high reactivity of the β-lactone group severely limits the number of successful lactonisation techniques available for its formation. Schick *et al.* have recently demonstrated the direct lactonisation of the β-hydroxyalkanoate intermediates formed during indium-mediated Reformatsky reactions. In its prototypical form this synthesis is restricted to α,α,β,β-tetrasubstituted β-lactones, relying on a strong *gem*-dialkyl effect to close the ring, but can be extended to less substituted systems by simply using the phenyl esters in place of the original ethyl alkanoates **Scheme 1**.[2] The more reactive phenoxide leaving group mitigates a diminution in the *gem*-dialkyl effect and good yields of simple trisubstituted β-lactones are obtained. If branched alkyl substituents are present in the ester **1**, or aldehydes are used in place of ketones, the yields of the reaction become unsatisfactory.

A more general development of this procedure uses the condensation of the lithium enolates of phenyl esters with both ketones and aldehydes, representing a convenient alternative to the



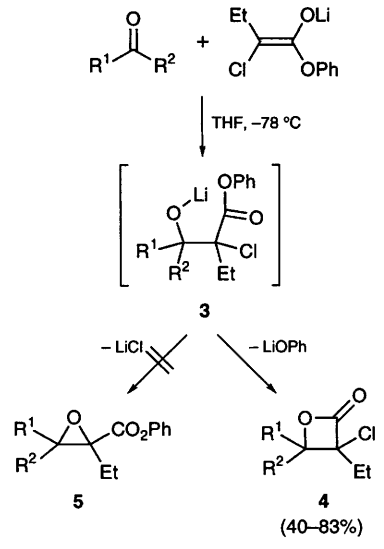
Scheme 1

Danheiser alkanthioate methodology.[3] The phenyl esters are sufficiently activated to eliminate lithium phenoxide at low temperatures to generate trisubstituted β-lactones in good yields (60–75%). In contrast to the indium-mediated reaction, this variant is successful with β-branched ester substituents. With aldehydes in place of ketones lower, but acceptable, yields are observed and α,β-disubstituted β-lactones are accessible with this procedure (**Scheme 2**). Mixtures of *cis*- and *trans*-disubstituted products are recovered, with the stereoselectivity dependent on whether a branched or a straight-chain substituent is present in the ester component **2**.



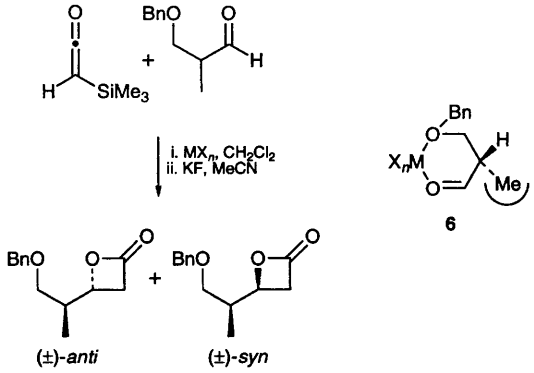
Scheme 2

The same interception of the normal pathway occurs in the Darzens reaction of phenyl 2-chloroalkanoates with carbonyl compounds (**Scheme 3**).[4] Here, lithium phenoxide eliminates more readily than lithium chloride from the intermediate β-alkoxyester **3** leading to the α-chloro β-lactone **4** instead of the usual glycidic ester **5**. The presence of the α-chloro atom contributes to a *gem*-dialkyl effect and good yields are seen with both ketones and aldehydes, although in certain cases enolisation of the aldehyde component can lead to complicated mixtures. The low diastereoselectivities in the reaction of unsymmetrical substrates parallels the poor selectivity of the Darzens reaction itself.



Scheme 3

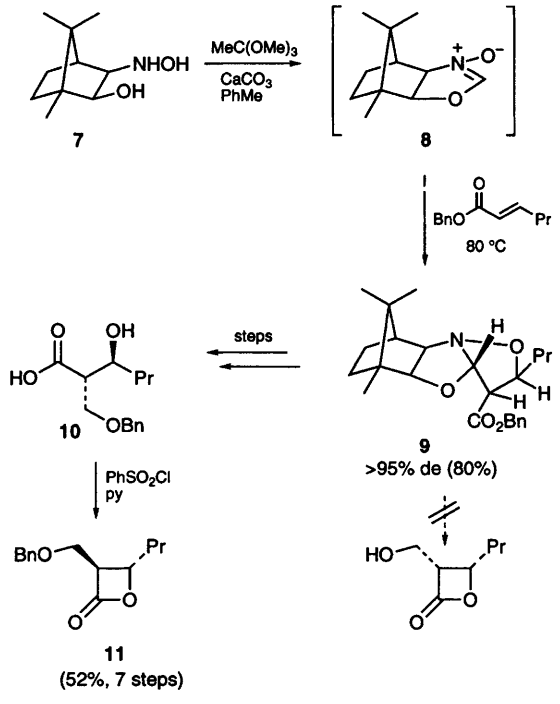
The [2+2] cycloaddition of ketenes and aldehydes is an attractive direct route to substituted β-lactones and is realised in a highly diastereoselective chelation-controlled cycloaddition of trimethylsilylketene to α- and β-alkoxy aldehydes.[5] The choice of Lewis acid is critical; monodentate species such as boron trifluoride are unselective as they do not coordinate the alkoxy group, whereas bidentate Lewis acids form rigid chelate structures such as **6** (**Scheme 4**). This leads to a high bias for attack on the π-face opposite to the α-substituent of the aldehyde. The major product has the *anti* configuration in all cases examined, consistent with the proposed chelation control. Unfortunately, optically pure aldehydes undergo partial racemisation at the α-substituent in these conditions (typically product of 88% ee is obtained), and the reaction as it stands does not lead to single enantiomers without an additional enrichment step.



(Yield)	Lewis acid	(±)-*anti*		(±)-*syn*
(83%)	$BF_3{\cdot}Et_2O$	62	:	38
(94%)	$MgBr_2{\cdot}Et_2O$	98	:	2

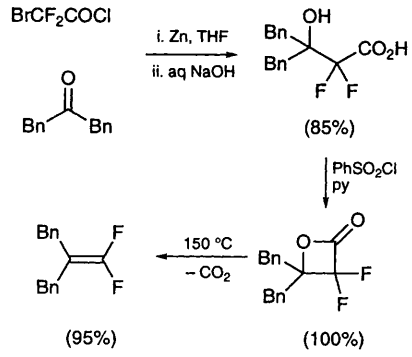
Scheme 4

Enantiomerically pure β-lactones can be synthesised *via* the classical Adam's lactonisation provided the appropriate β-hydroxy acid precursors are available. A new route to these key intermediates starts with the condensation of hydroxylaminoborneol **7** and trimethyl orthoformate to generate the oxazoline-*N*-oxide **8** (**Scheme 5**).[6] A highly regio- and stereo-selective *in situ* [2+3] cycloaddition of **8** with an α,β-unsaturated ester follows. The cycloadduct **9** contains differentiated functionality that should lead to both *cis* and *trans* α,β-disubstituted β-lactones. In practise it is not yet possible to oxidatively cleave the auxiliary in the presence of the ester group, denying access to the *cis* substituted targets. However, prior reduction of the ester and protection of the primary alcohol permits successful cleavage (and recovery) of the auxiliary. Lactonisation of the β-hydroxy acid **10** furnishes the enantiomerically pure *trans* β-lactone **11** in 42% yield over eight steps.



Scheme 5

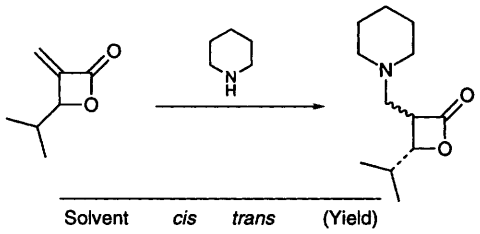
A conventional Reformatsky reaction followed by mild hydrolysis provides β-hydroxy acids which can be cyclised to give highly reactive α,α-difluoro β-lactones (**Scheme 6**).[7] Since these materials react very rapidly with water and other nucleophiles a modified non-aqueous work-up is essential after lactonisation to provide good yields of pure products. The α,α-difluoro β-lactones are decarboxylated smoothly to the corresponding 1,1-difluoroalkenes on heating in solution, a sequence that constitutes a viable alternative to ylide chemistry. This highly stereoselective decarboxylation of β-lactones underlies the use of α-methylene β-lactones as allene equivalents in organic synthesis.



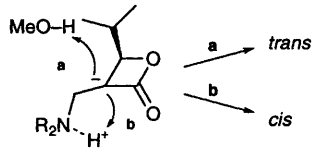
Scheme 6

Stereochemically defined allyl amines and allyl sulfides are accessible with such a strategy through recent work by Adam *et al.*[8] Conjugate additions of both amines and sulfides to α-methylene β-lactones occur under mild conditions but show a dramatic solvent dependent stereoselectivity (**Scheme 7**). Mixtures of *cis* and *trans* isomers are formed in aprotic solvents, but overwhelmingly the thermodynamically favoured *trans* isomers dominate when methanol is the reaction medium. Two competing protonation pathways are evoked to explain this observation. Proton transfer from solvent occurs preferentially on the opposite face of the β-lactone to the incoming nucleophile (path **a**), whereas in aprotic conditions the nucleophile may also serve as the proton source and the *cis* isomer is formed (path **b**). The initial mixtures of Michael adducts can be isomerised to essentially pure *trans* disubstituted β-lactones with LDA at low temperature (**Scheme 8**). Subsequent thermal decarboxylation is generally high yielding and stereoselective, provided the substituents are not too bulky, and generates the *E*-allylamines and allyl sulfides.

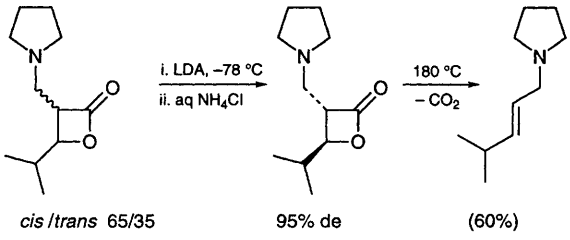
A further development of this methodology uses the addition of prochiral ester enolates to the α-methylene β-lactones to generate γ,δ-unsaturated



Solvent	*cis*	*trans*	(Yield)
THF	77	23	(69%)
MeOH	7	93	(84%)

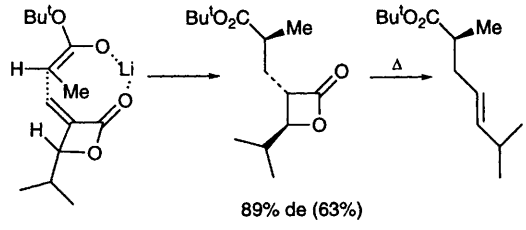


Scheme 7



Scheme 8

esters of defined geometry after decarboxylation of the intermediate β-lactones (**Scheme 9**).[9] The configurations of the Michael adducts correspond to the initial ester enolate geometry and can be seen as arising from attack of the coordinated enolate on the less hindered π-face of the α-methylene β-lactone. Good stereoselectivities are possible if enolates of well-defined geometry are used and provided the reaction is quenched at low temperature (giving the *trans* products) to avoid electrocyclic ring opening of the intermediate β-lactone enolates.

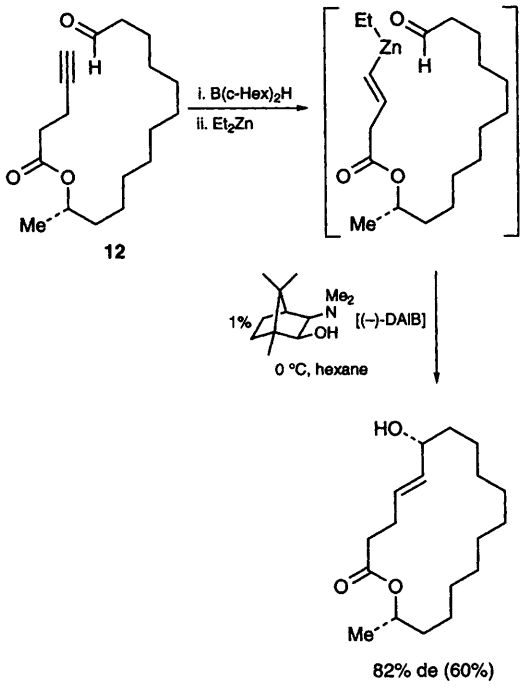


Scheme 9

3 Macrolides

An elegant and efficient asymmetric macrocyclisation introduced by Oppolzer *et al.* is the central ring closure step in a synthesis of the macrolide (+)-aspicilin (**Scheme 10**).[10] Hydroboration of the ω-alkynyl ester **12** and transmetallation with diethylzinc generates an *E*-vinylzinc species that attacks the aldehyde in the presence of catalytic amounts of (−) dimethylaminoisoborneol (DAIB) to give the *R* allylic alcohol with good diastereoselectivity. This key chiral centre is exploited further through a directed epoxidation to build up the remaining stereocentres in the target. Despite its remoteness from the forming bond, the existing chiral substituent of the substrate **12** exerts a moderate influence on the topicity of the cyclisation. The alliance of **12** and (−)-DAIB constitutes a matched pair of stereodirecting effects (82% de). The contrast is seen when the enantiomeric ligand (+)-DAIB is used to generate the *S* alcohol and the bias of the catalyst and substrate are in opposition (70% de).

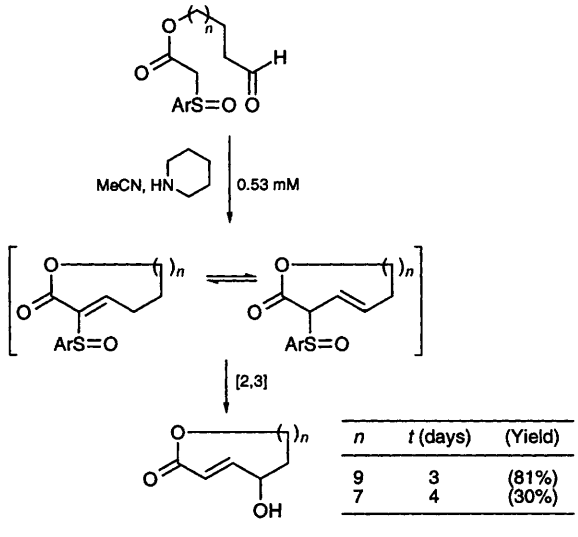
The condensation between aldehydes and sulfinyl activated methylene compounds generates γ-hydroxy α,β-unsaturated esters. As with many systems, this reaction encompasses macrolide synthesis only when



Scheme 10

high dilutions and extensive reaction times are applied.[11] A Knoevenagel condensation initiates the sequence, to be followed by a double bond shift and [2,3] sigmatropic rearrangement of the sulfinyl group. In this manner the *E* allylic alcohol is formed after hydrolysis, but as yet no control over the absolute stereochemistry of the hydroxy group has been attempted (**Scheme 11**).

Palladium catalysed carbonylation at unsaturated carbon atoms is a valuable route to esters, and preliminary investigations show that it may apply within macrolide syntheses also.[12] The cyclisation of ω-alkynyl alcohols requires two equivalents of palladium acetate with carbon monoxide at

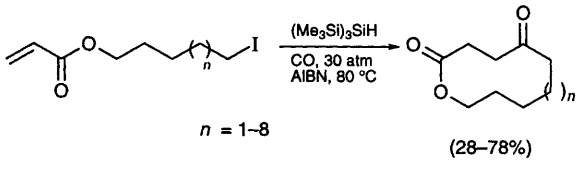


n	*t* (days)	(Yield)
9	3	(81%)
7	4	(30%)

Scheme 11

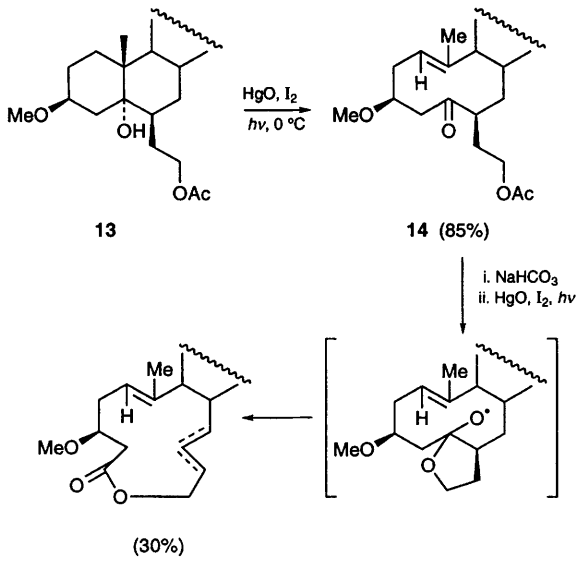
atmospheric pressure to give modest yields (11–39%) of simple, unsubstituted 15- to 20-membered lactones. The low conversion of starting material and high stoichiometry of the metal reagent are formidable barriers to the practical use of this procedure, but the mild conditions make this an attractive area for further study.

A more successful approach to the incorporation of carbon monoxide as a C1 unit in macrolactonisations uses a sequential radical annulation (**Scheme 12**).[13] A terminal alkyl radical is generated from tris(trimethylsilyl)silane and a terminal iodide, although selenides have also been used. To avoid Porter type cyclisation of the initial alkyl radical directly onto the alkenyl acceptor, high pressures (30 atmospheres) of carbon monoxide and high dilution conditions are necessary. In this way the carbon monoxide intercepts the alkyl radical and the intermediate acyl radical then cyclises. Some competitive reduction of the acyl radical by tris(trimethylsilyl)silane is observed but this does not seriously reduce the yields of the lactones. Ten-membered rings can also be formed, but yields are superior with larger systems. Of course, Porter type macrocyclisations are useful processes in their own right, and a new method of generating the primary alkyl radical involves photoirradiation of an iodoalkane in the presence of metal hydride complexes.[14] Sodium cyanoborohydride in methanol seems to be the optimal reagent for high conversion and selectivity over dimeric products.



Scheme 12

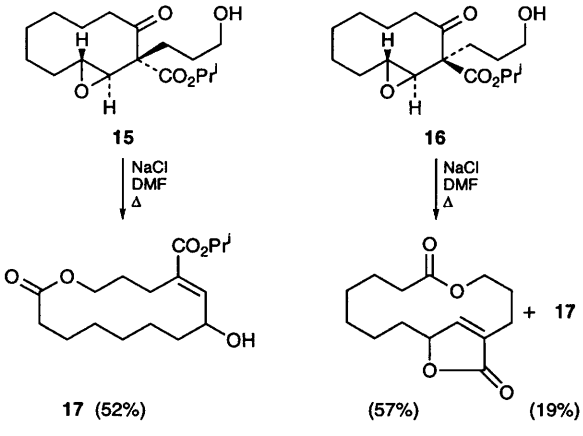
Ring expansions offer an alternative strategy to the cyclisation of linear substrates for macrolactone synthesis. In practice, though, such approaches are often dogged by a complex dependence on substituents and reaction conditions, a point illustrated in the double ring expansion by β-fragmentation of alkoxyl radicals (**Scheme 13**).[15] The alkoxyl radical generated from the tertiary alcohol **13** undergoes hydride abstraction unless the pendant primary alcohol is suitably protected, in which case the β-fragmentation product **14** is formed. The yield of the ring expansion is also very sensitive to temperature, reagent stoichiometry and choice of oxidising agent. Deprotection of the primary alcohol and a second radical fragmentation of the intermediate hemiacetal gives a low yield of the 13-membered lactone as a complicated mixture of double bond positional and geometrical isomers. In part, this is due to competing transannular cyclisations, and a better yield of the ring expanded material (63%) is achieved if the alkene **14** is reduced prior to radical generation.



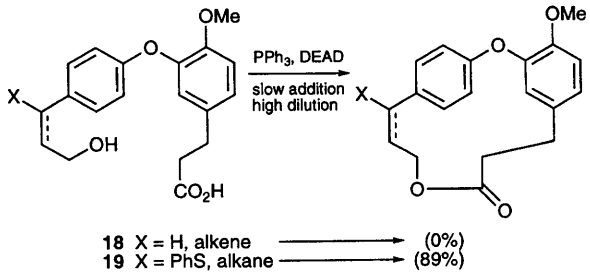
Scheme 13

In a similar vein, Grob fragmentation of medium ring ketones to macrolactones can be triggered by hemiacetal formation (**Scheme 14**).[16] Since the stereochemical outcome correlates to the relative orientations of the ester and epoxide, a concerted mechanism is implicated. However, although the *trans* oriented isomer **15** leads exclusively to the *E* alkene **17**, the unexpected formation of some of the *E* product from the substrate **16** which has the epoxide and ester in the *cis* orientation suggests that a competing two-step ionic pathway may be operating.

The exploration of natural product syntheses continues to throw new light on the substrate dependence of classical macrolactonisation techniques. The allylic alcohol **18**, an intermediate in a synthesis of the cytotoxic combrestatins,[17] does not cyclise to the strained lactone under any of the conditions tried, including Steglich's modified Mitsunobu reaction. This may be due to S_N1-initiated side-reactions in the very electron rich system. To address this problem, the double bond is



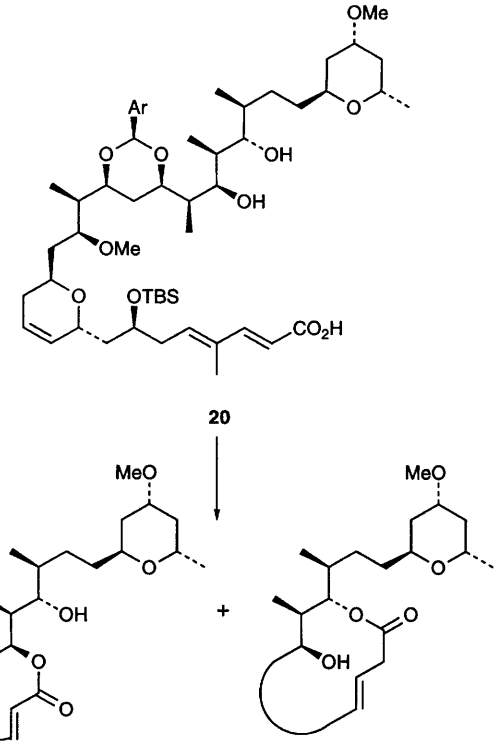
Scheme 14



Scheme 15

masked as the phenyl sulfide **19**, a change which also removes a conformational restraint from the molecule, and efficient lactonisation of **19** then proceeds (**Scheme 15**).

The synthesis of the swinholide A family of macrolides by the Paterson group exemplifies the powerful influence that the preorganisation of acyclic substrates may have in enhancing the selectivity and yield of macrocyclisations.[18] The integral tetrahydropyran of the seco acid and the cyclic acetal protecting group appear to provide conformational anchors that bring together the two ends of the chain and lead to efficient cyclisation, without the need for full hydroxy group protection (**Scheme**



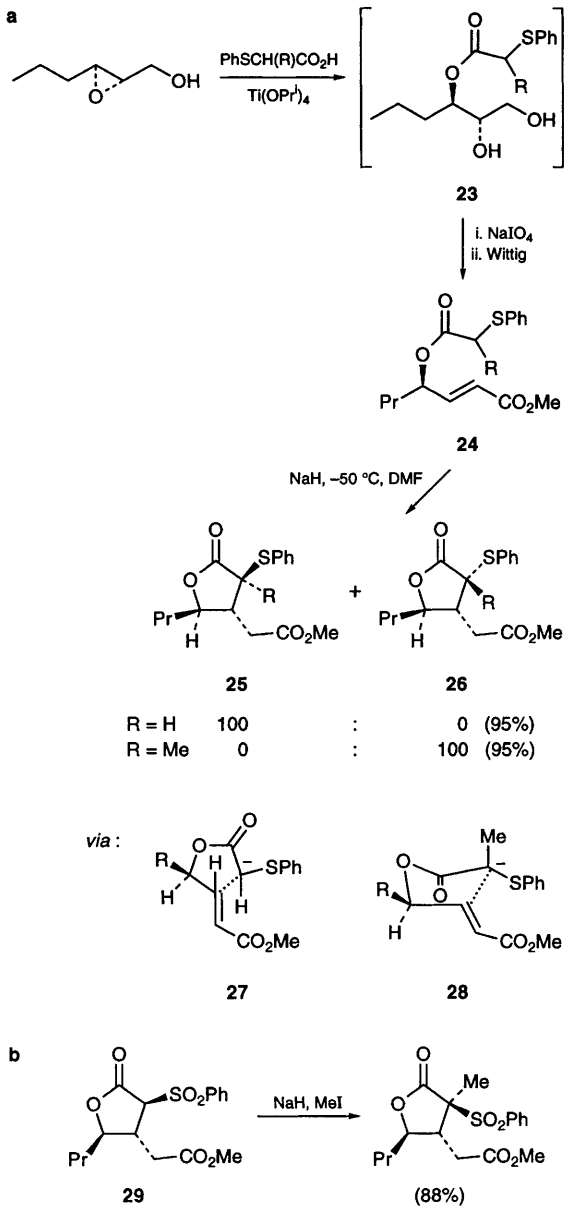
Conditions	21 : 22	(Yield)
Yamaguchi, toluene	82 : 18	(92%)
Keck, $CHCl_3$	5 : 95	(94%)
Keck, toluene	40 : 60	(73%)

Scheme 16

16). The regioselectivity of the cyclisation shows a suprising dependence on the reagents used. For example, the seco acid **20** mainly cyclises to the 22-membered lactone hemiswinholide A **21** under Yamaguchi conditions, but predominantly the 24-membered product isohemiswinholide A **22** results if Keck's reagents are employed. Intriguingly there is also a sensitivity to solvent polarity, as demonstrated by the reduction in selectivity when the Keck cyclisation is carried out in toluene instead of chloroform. This suggests that solvent polarity has a role in determining the conformational preference of the seco acid and hence the regiochemistry of the cyclisation. The same impressive degree of reagent control is exerted in the cyclisation of the dimeric seco acid precursor to the 44-membered macrodiolide swinholide A or the 46-membered isoswinholide A. Both protocols are efficient at ambient temperature and without the need for high dilution.

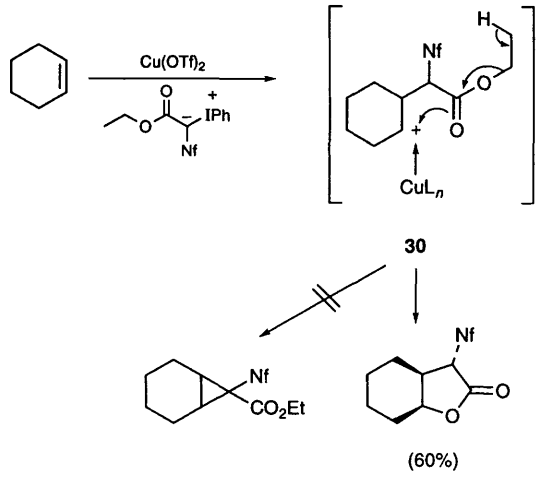
4 γ-Lactones

Intramolecular Michael addition of an α-phenylthio stabilised enolate should be a valuable method for the construction of highly functionalised, enantiomerically pure γ-lactones, offering complete control over the stereochemistry of substituents, particularly at quaternary centres (**Scheme 17a**).[19] Epoxides obtained by Sharpless oxidation are opened regioselectively with α-phenylthioacetic acid in the presence of titanium(IV) isopropoxide. The product diols **23** are susceptible to acyl migration but can be converted directly into the cyclisation precursors **24** without isolation. The choice of DMF as solvent for the intramolecular Michael reaction is critical since the esters **24** are prone to hydrolysis in most other solvents, through the elimination of 2-phenylthioketene. The cyclisation is also dependent on the temperature and base employed, with sodium hydride at −50 °C being optimal for selective formation of the major product **25** (R = H). A wide range of substituents is tolerated and neither the geometry of the double bond nor the presence of quarternary centres at the β- and γ-carbons of the nascent lactone influence the outcome. Molecular modelling suggests that the stereoselectivity is kinetic in origin and the all-*trans* product **25** is a result of *si* face attack of the *E* enolate through transition state **27**. One striking observation is that introduction of an α-substituent in the enolate completely reverses the configuration of the product lactone **26** at the α-carbon and calculations support the apparent *re* face attack of the more hindered enolate **28**. The α-phenylthio group provides a versatile handle for further transformations, and the same authors demonstrate this in a complementary route to α-quaternary γ-lactones.[20] Oxidation of the sulfide **25** (R = H) to the sulfone **29**, followed by enolisation and alkylation, goes with overall retention of configuration to generate the γ-lactone which has the opposite configuration at the α-carbon to the product **26** of the direct cyclisation (**Scheme 17b**). Models indicate that the diastereofacial bias arises from coordination of the metal counterion by a sulfone oxygen and shielding of one face of the enolate of **29** by the phenyl group. This is supported by the observation of unselective alkylation when the sulfide itself is used.



Scheme 17

γ-Lactones can be derived in one step by the radical cycloaddition of malonate derivatives and olefins. A novel parallel approach proceeds through the copper-promoted addition of a sulfonyl ylide to an alkene (**Scheme 18**).[21] Such reactions usually lead to cyclopropanation or reductive alkylation, but in this case the nonafluorobutylsulfonyl (nonaflyl, Nf) group present in the ylide stabilises the intermediate zwitterion **30** sufficiently to allow β-hydrogen elimination from the ethyl ester and closure through oxygen to the lactone. The addition



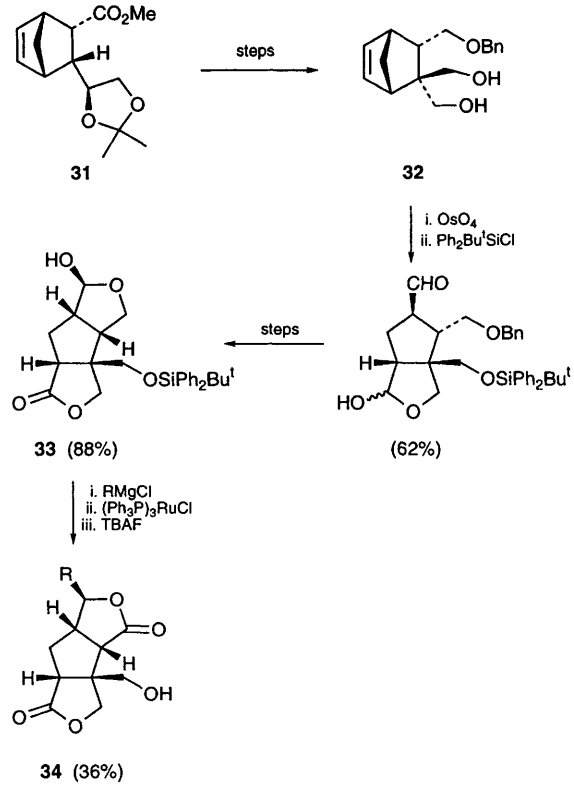
Nf = nonafluorobutylsulfonyl (nonaflyl)

Scheme 18

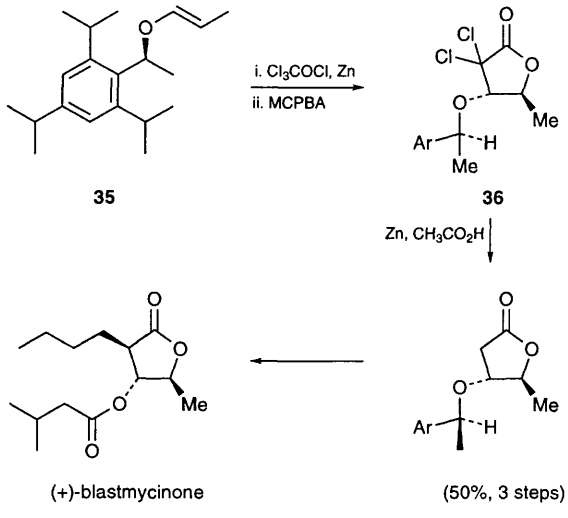
of the catalytic copper species is essential to suppress reductive alkylation, presumably by stabilising the positive charge of the zwitterion through coordination. Not suprisingly the methyl esters, which cannot undergo the β-hydrogen elimination, produce the usual cyclopropanes. A consequence of increasing the life-time of the zwitterion is to permit rotation about the C4–C5 bond with subsequent loss of the double bond stereochemistry for acyclic alkenes. The α-nonaflyl group adopts the sterically favoured *trans* relationship to the β-substituent in all the systems studied and thus this represents a rapid and stereospecific entry into fused bicyclic lactones.

Novel tricyclic bislactones originate from the conventional *syn-endo* Diels–Alder adduct **31** (**Scheme 19**).[22] Functionalisation of the cycloadduct to the diol **32** is followed by cleavage of the double bond to reveal two aldehydes, from which the two fused lactones are constructed. In the oxidation step one of the aldehydes epimerises but this is corrected in a subsequent basic cyclisation to form the highly concave lactol-lactone **33**. Treatment with Grignard reagents makes good use of the rigid scaffold to give a single diastereoisomer of the dilactone **34** after oxidation.

Previous investigations by Greene *et al.* into the cycloaddition of dichloroketene and alkenes, followed by regiospecific Baeyer–Villiger oxidation of the α,α-dichlorocyclobutanones to γ-lactones, uncovered a troublesome side reaction in the reduction of the α,α-dichlorolactones **36** (**Scheme 20**). This precluded the use of non-aryl substituents if reductive cleavage of the pendant ether auxiliary was to be successful. Now that difference in reactivity has been turned to advantage for the synthesis of β-hydroxybutyrolactones of the blastmycinone class.[23] Excellent diastereoselectivity is seen in the cycloaddition of dichloroketene with the benzylic enol ether **35**. The dichlorolactone product of subsequent Baeyer–Villiger oxidation is reduced



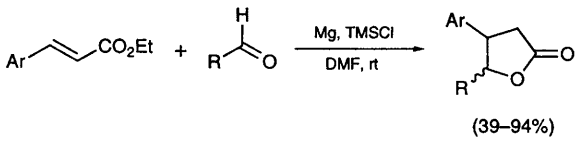
Scheme 19



Scheme 20

to the β-alkoxy lactone on treatment with zinc in acetic acid. Further manipulation gives blastmycinone and its congeners as single enantiomers.

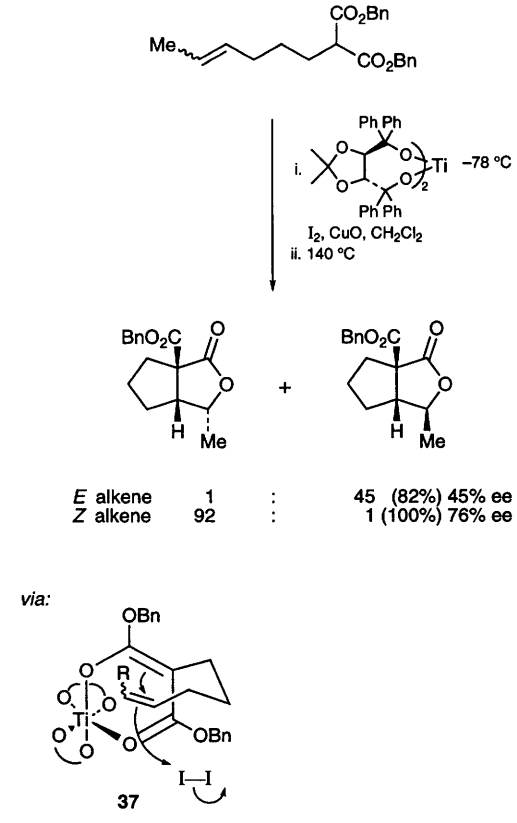
Magnesium and trimethylsilyl chloride is a new reagent combination for the reductive cross-coupling of α,β-unsaturated esters with aldehydes (**Scheme 21**).[24] Electroreduction and samarium iodide have been used in this context but the new method promises to be easier to apply and also shows complementary substrate specificity. Whereas samarium iodide is only successful with β-aliphatic



Scheme 21

α,β-unsaturated esters, the new technique is limited to the coupling of β-aryl substituted compounds. Although the *trans* β,γ-disubstituted lactone is the major isomer recovered, selectivities are generally low. Trimethylsilyl chloride is essential in the reaction and may play a dual role in activating both the metal and carbonyl substrates for single electron transfer.

Preliminary work on the asymmetric halocarbocyclisation of 4-pentenylmalonates using titanium enolates prepares fused bicyclic γ-lactones in modest to good enantiomeric purity.[25] As with the standard racemic synthesis, activation of the olefin with iodine in the presence of the enolate achieves high yields and excellent regioselectivity in the first cyclisation to the cyclopentane, followed by smooth lactonisation on heating (**Scheme 22**). The chair-like transition state **37** is postulated, where one face of the enolate is shielded by the metal ligands, and the stereospecific transformation of *Z* and *E* alkenes supports the *anti* mode of attack shown. The enantioselectivity of the reaction is currently very substrate dependent, for example *E* alkenes give consistently poorer optical purities than the *Z*



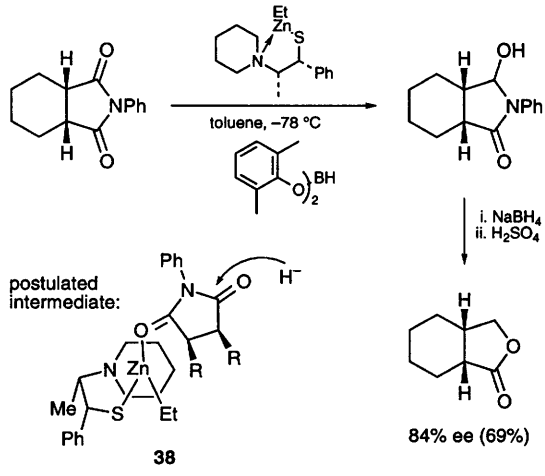
Scheme 22

isomers, indicating that the chiral ligand investigated may not be the best choice for strong reagent control.

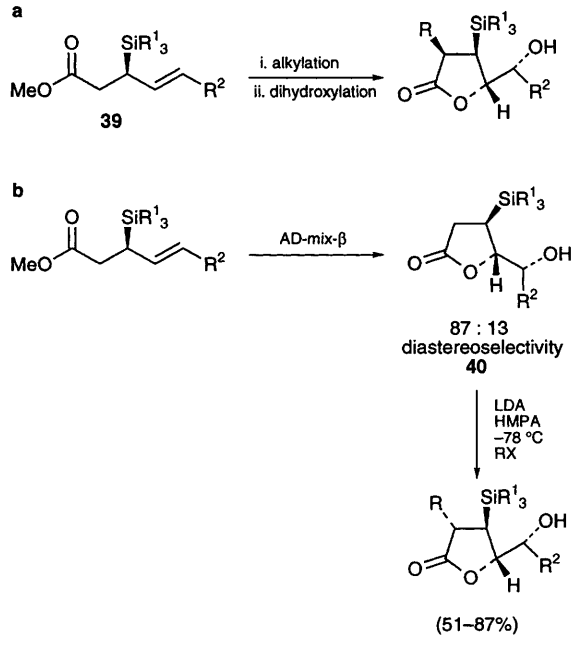
A thiazincolidine complex previously developed for the asymmetric addition of alkylzincs to aldehydes can function as a catalyst for the enantioselective reduction of cyclic *N*-phenyl *meso*-imides (**Scheme 23**).[26] The desymmetrised products are cleaved by further reduction and recyclised to the γ-lactones with good to excellent enantiomeric purity. These conditions do not yet apply efficiently to anhydrides. *N*-Phenyl substitution leads to approximately double the optical purity of other substituents such as benzyl, suggesting that an orthogonal arrangement of this substituent relative to the imide is involved in the differentiation of the two carbonyls by the catalyst. With this in mind, the extended array **38** is proposed as a model of the catalyst–substrate interaction, implying that the reducing agent attacks the indirectly activated carbonyl rather than that coordinated by zinc.

A divergent synthesis of two epimeric α-alkyl γ-lactones from the same allylsilane is created by simply reversing the order of the reaction sequence.[27] Alkylation of the allylsilane **39** gives essentially one diastereoisomer which can be lactonised after dihydroxylation of the double bond (**Scheme 24a**). If the same allylsilane is first subject to a Sharpless asymmetric dihydroxylation, the corresponding unsubstituted lactone **40** can be formed with good selectivity (**Scheme 24b**). Alkylation of the β-silyl lactone **40** takes place on the face opposite to the bulky silyl group, a reaction that is successful only when the hydroxy substituent is unprotected.

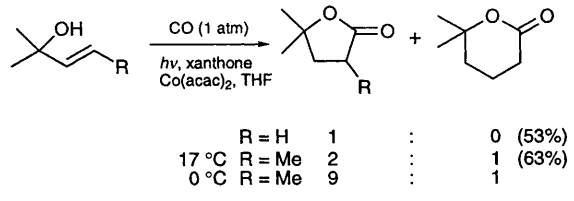
The insertion of carbon monoxide into the termini of simple allyl alcohols will generate γ-lactones (**Scheme 25**).[28] A catalytically active 16-electron species $[HCo(CO)_3]$ is generated with triplet-excited xanthone during photoirradiation under carbon monoxide. Initial metallation of the alkene, prior to carbonyl transfer, is reversible and so provides an opportunity for double bond migration. This is observed when terminally substituted



Scheme 23



Scheme 24

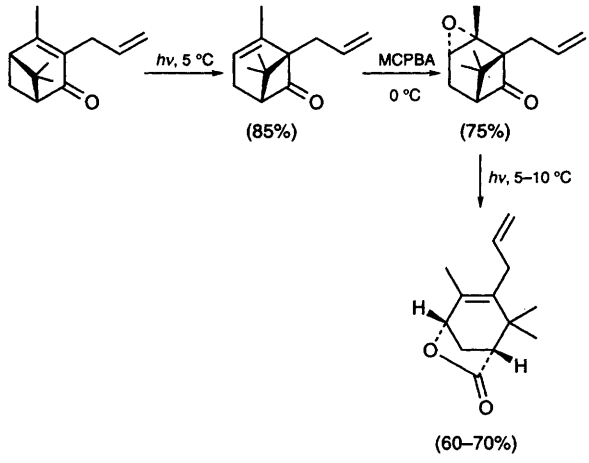


Scheme 25

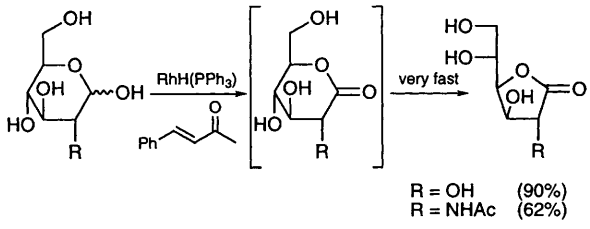
allylic alcohols undergo the process, yielding significant amounts of the δ-lactones. The isomerisation is thermal rather photochemical and is suppressed at lower temperatures. Spirolactones can also be formed with this procedure, but its use must be limited to relatively unfunctionalised materials because of the high reactivity of the triplet xanthone.

The need for efficient and practical syntheses of the Taxol® class of antitumour agents continues to stimulate research efforts in this area. Two sequential photochemical rearrangements of a readily available (*R*)-(+)-verbone derivative are used to quickly construct a highly substituted γ-lactone as an intermediate in the synthesis of the Taxol® A-ring (**Scheme 26**).[29] The first irradiation leads to a 1,3-shift of the bridging methine and is followed by a very chemo- and stereo-selective epoxidation of the *exo* face of the internal double bond. The epoxide and cyclobutanone groups fragment in the second photochemical step and rearrange to the bicyclic lactone.

A novel rhodium catalysed ring restriction is harnessed with a hydrogen transfer process in a tandem sequence for the oxidation of glucopyranoses to glycono-1,4-lactones (**Scheme 27**).[30] Under these conditions only the anomeric hydroxy group of the glucopyranose is oxidised, followed by a very



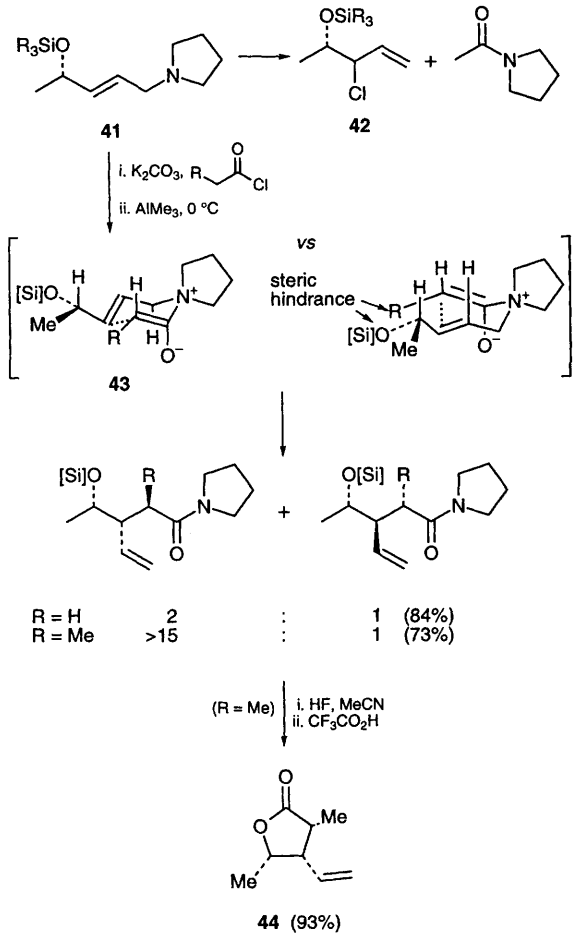
Scheme 26



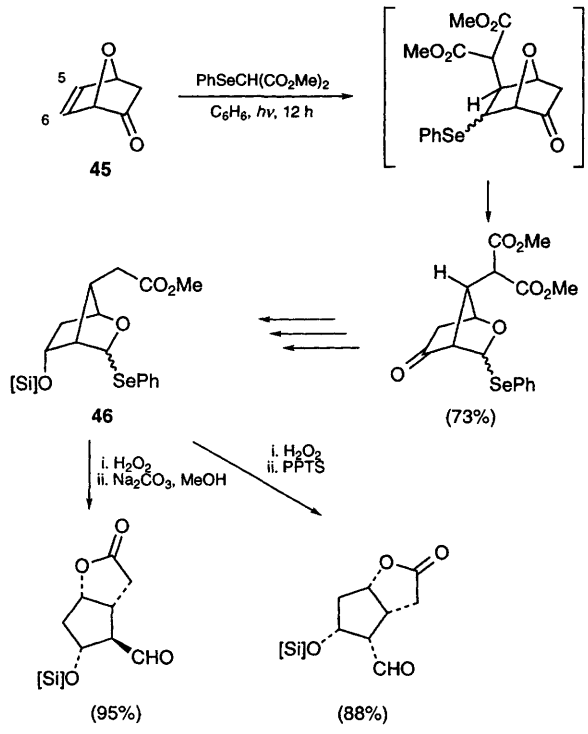
Scheme 27

rapid rearrangement to the furanone. The mechanism may involve metal coordination of the lactone and 4-hydroxy groups to promote ring opening and isomerisation to the thermodynamically favoured furanone. The system runs efficiently with either free or protected hydroxy substituents at positions other than C-4 and no influence of stereochemistry is observed. Heretofore difficult substrates, such as *N*-acetyl-D-glucosamine, are readily converted in good yield by this new procedure.

The ketene-Claisen rearrangement of acyclic allylamines has been mainly restricted to the highly activated dichloroketene and a limited scope of amines, often with disappointingly low yields. A thorough investigation of the rearrangement of the allylamine **41** shows that this is an extremely demanding reaction (**Scheme 28**).[31] Virtually all standard methods for the ketene-Claisen process fail, giving only polymeric products or the allyl chloride **42** which arises from S_N2' attack by chloride on the initial acylammonium ion. A very specific two-step process is successful in suppressing this decomposition. Following acylation of the amine in the presence of solid potassium carbonate, trimethylaluminium is added to deprotonate the acyl group. The zwitterionic intermediate rearranges preferentially through the 6-membered chair conformation **43** in which 1,3-diaxial and other steric interactions are minimised. In keeping with the outcome of other variants of the Claisen rearrangement, the zwitterion derived from acetyl chloride shows only limited diastereoselectivity. In comparison, the



Scheme 28



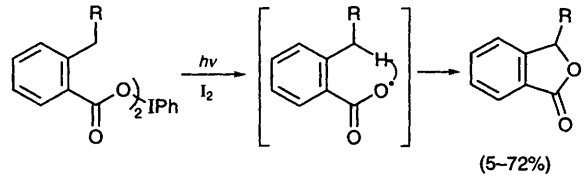
Scheme 29

bulkier methyl substituent of the *Z* amide enolate generated from propionyl chloride ensures almost complete 1,2-induction of stereochemistry. Deprotection of the silyl ether product and lactonisation with trifluoroacetic acid provides a mild and practical synthesis of a single enantiomer of the trisubstituted all-*cis* γ-lactone **44**.

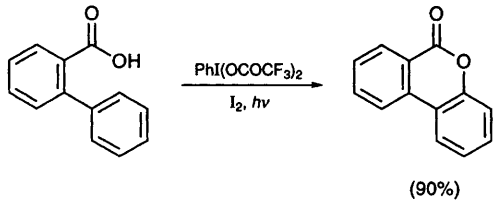
The bicyclic ketone **45** (**Scheme 29**), readily available in both enantiomeric forms, has an impressive pedigree as a starting material for natural product synthesis. In particular, radical additions to **45** proceed with complete *exo* selectivity and this is the basis of a new, divergent preparation of fused bicyclic γ-lactones related to the Corey lactone and designed for use in prostanoid syntheses.[32] The electrophilic radical generated photolytically from dimethyl α-phenylselenylmalonate adds preferentially to the more electron rich C-5 atom of the double bond. This initial adduct isomerises slowly on prolonged irradiation by a 1,3-acyl migration with concomitant phenylselenyl transfer. Functional group manipulation of the new bicycle provides an intermediate **46** that can be converted to two complementary lactones. Oxidation of the selenium acetal and lactonisation in base promotes epimerisation of the pendant formyl group to furnish a product related to the Corey lactone. In contrast, acidic lactonisation preserves the integrity of all the stereocentres in **46** to generate the all-*cis* formyl lactone.

The (diaroyloxyiodo)benzene intermediates formed *in situ* from aromatic carboxylic acids and [bis(trifluoroacetoxy)iodo]benzene dissociate to form oxygen-centred carbonyloxy radicals upon photoirradiation.[33] The fate of the radical depends on the substitution pattern of the aromatic ring. Alkyl groups in the *ortho* position undergo a 1,5-hydrogen abstraction which leads to phthalides in moderate yields (**Scheme 30**). Alternatively, if an *o*-aryl substituent is present, benzocoumarins are generated by addition of the radical to the pendant aromatic ring (**Scheme 31**). In all cases it is necessary to add iodine to the reaction mixture to re-oxidise the hydrogen iodide generated in the lactonisation step, which otherwise reduces the initial (diaroyloxyiodo)benzenes.

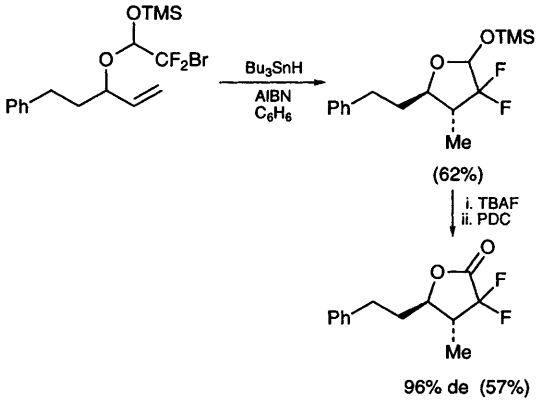
Attempts to form lactones by the cyclisation of the α-radicals generated from allyl α-bromo-α,α-difluoroacetates are thwarted by the low reactivity of these stabilised systems and only reduction products are obtained.[34] This is overcome by



Scheme 30



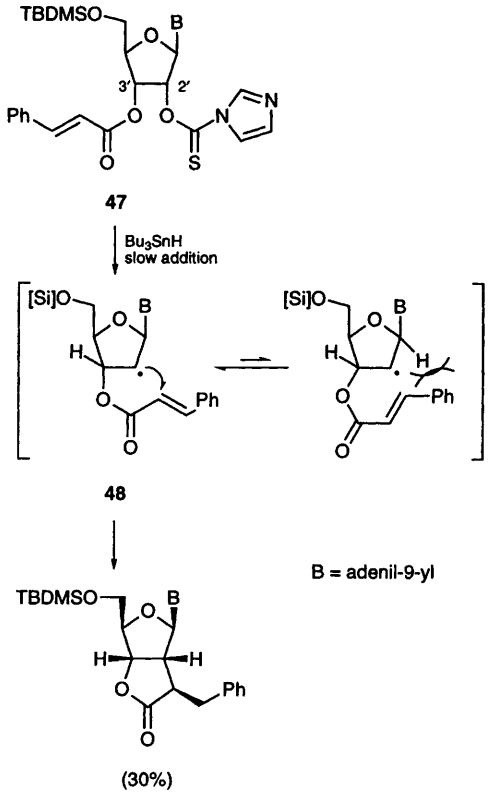
Scheme 31



Scheme 32

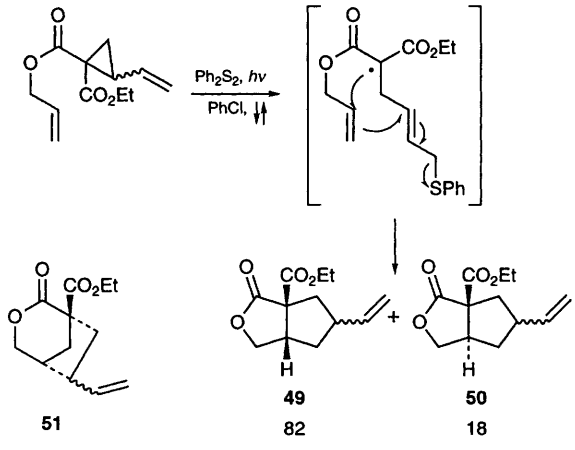
the application of a general solution first proposed by Stork and others (**Scheme 32**). Prior reduction of the ester to the corresponding silylated acetal sufficiently enhances the reactivity of the α-radical to allow smooth 5-*exo*-trig cyclisation. Exclusively the 5-membered lactols are obtained with good stereochemical control, and simple oxidation affords the α,α-difluoro-γ-lactones. The strong stereoelectronic preference for 5-*exo* ring closure is a drawback in the reaction of related homoallyl esters, where very poor yields of δ-lactols are observed. One practical problem is the volatility of the lactol cyclisation products, which can compromise the isolated yields, and might be addressed by a change in the silylating agent.

A preference for the 5-*exo*-trig mode of cyclisation is also seen when furanose radicals add intramolecularly in an 'anti-Michael' fashion to pendant α,β-unsaturated esters, making fused bicyclic lactones as intermediates for nucleoside syntheses.[35] Unfortunately, reduction of the carbon radicals competes with the cyclisation even when slow addition of tributyltin hydride is employed, and yields are only modest (**Scheme 33**). The umpolung nature of the addition is implicit in the observation that good acceptor groups (*e.g.* phenyl) at the terminus of the double bond are required for the most efficient reactions. For the 2′-deoxynucleoside radical generated from **47** only one diastereoisomeric lactone is isolated, corresponding to the approach of the radical to the ester in the less hindered s-*cis* conformation **48**. The related 3′-deoxynucleoside radical shows a reduced selectivity and products from the addition to both s-*cis* and s-*trans* conformations of the cinammate are isolated.



Scheme 33

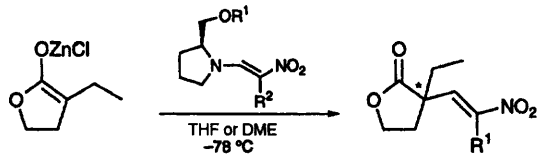
The tandem rearrangement-biscyclisation of vinylcyclopropane esters to give fused bicyclic γ-lactones also demonstrates the preeminence of 5-*exo* radical cyclisations (**Scheme 34**).[36a] Conjugate attack of phenylthio radical on the vinylcyclopropane initiates the cascade and is followed by two ring closures leading to the *cis* lactone **49** as the major product. The minor component **50** was originally reported as the bridged adduct **51** arising from equilibration of the radicals and an alternative 6-*endo* cyclisation. A subsequent erratum[36b] revises the identity of this material to the *trans* fused γ-lactone **50**, indicating that the reaction sequence is in fact under kinetic control.



Scheme 34

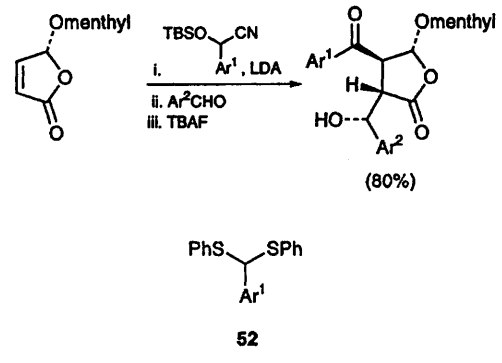
The asymmetric nitroolefination of α-alkyl δ-lactones can be extended to cover the five-membered series with an improved choice of chiral auxiliary (**Scheme 35**).[37] Substantial increases in both yields and optical purities are secured when the bulk of the oxygen substituent in the pyrrolidinol auxiliary is increased. The new silylated nitroenamines are crystalline and are therefore more readily obtained as single enantiomers. Substitution of the nitroenamine double bond also improves enantioselectivity, consistent with the key role of steric interactions between the two components in determining stereoselectivity. An interesting temperature dependent stoichiometry is observed, with three equivalents of the enolate required at −78 °C as opposed to only two equivalents at −40 °C. This is postulated to be a result of the loss of a coordinated zinc enolate at the higher temperature, raising the possibility that the oxygen substituent may also control the stereoselectivity through interference in the degree of metal coordination. Another improved methodology for α-functionalisation of γ-lactones concerns the tandem conjugate addition of silylcyanohydrin anions to chiral butenolides and reaction of the intermediate enolate with aromatic aldehydes (**Scheme 36**).[38] The cyanohydrin acyl anion equivalent is more versatile than the previously reported bis sulfide **52**.

The kinetic resolution of the racemic 4-hydroxy ester (±)-**53** (**Scheme 37**) by lactonisation with porcine pancreatic lipase (PPL) is only capable of

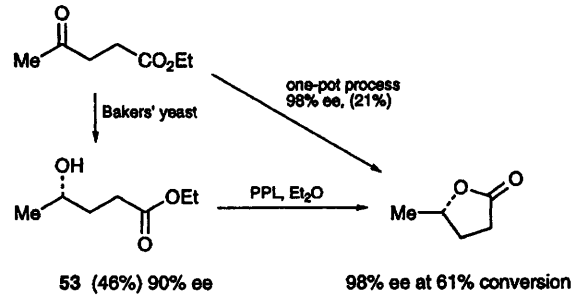


R^1	R^2	ee (%)	(Yield)
Me	H	63	(72%)
TBDMS	H	85	(99%)
TBDMS	Me	98	(99%)

Scheme 35



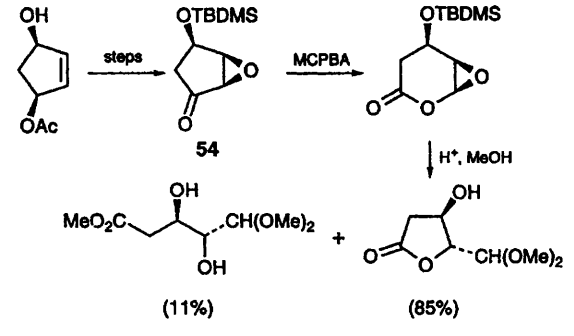
Scheme 36



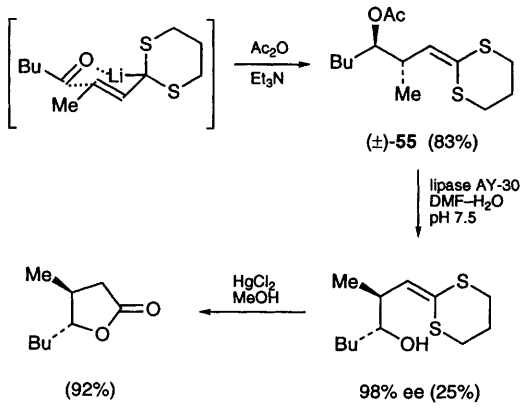
Scheme 37

giving high optical purities at low conversions (<30%) since longer reaction times allow the enzyme to convert appreciable quantities of the less reactive substrate. This common feature of biocatalytic kinetic resolutions may be circumvented by coupling with a complementary enantioselective biotransformation.[39] An initial Bakers' yeast reduction produces material enriched in one enantiomer of the alcohol (*S*)-**53**, which is the faster reacting substrate for PPL. As a consequence, the lactonisation is run to >50% conversion without loss of optical purity. The two reactions can be incorporated into a one-pot protocol to give the γ-lactone in 21% overall chemical yield and very high enantiomeric excess. Desymmetrisation of a *meso*-diol by acylation with a lipase enzyme is the starting point for the synthesis of single enantiomers of γ-lactones by a multiple oxidation strategy (**Scheme 38**).[40] Epoxidation of the olefin, directed by the free hydroxy group of the diol, is succeeded by conversion to the epoxy ketone **54** which undergoes a totally regioselective Baeyer–Villiger oxidation. The epoxy lactone product is water sensitive and this necessitates the use of a dried dichloromethane solution of the oxidant. Acidic methanolysis of the lactone opens the epoxide and promotes re-closure to the five-membered ring, although some of the acyclic material is also isolated.

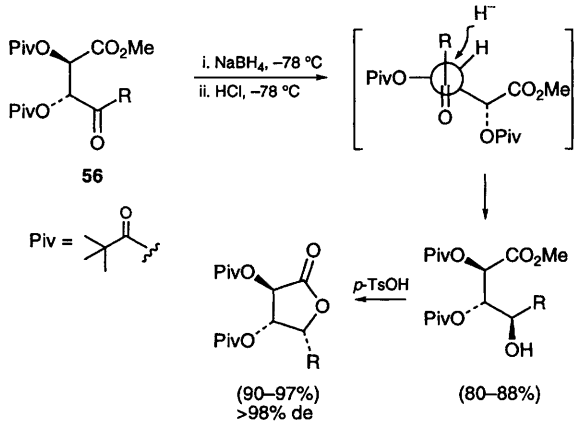
The condensation of aldehydes with the anion of prop-2-enyl-1,3-dithiane involves a six-membered, chair-like transition state that generates the *anti* relationship of the product **55** (**Scheme 39**).[41] With the relative stereochemistry thus secured a kinetic resolution of the acetate **55** catalysed by a lipase



Scheme 38

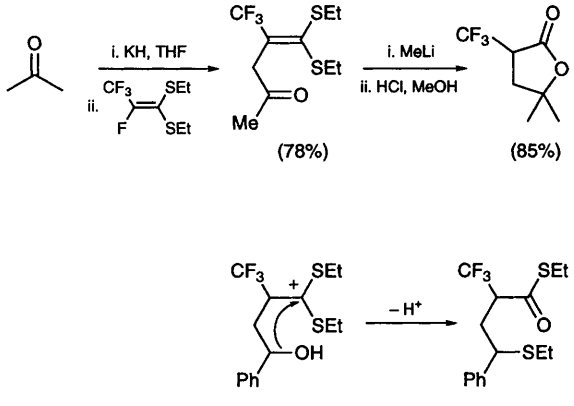


Scheme 39



Scheme 41

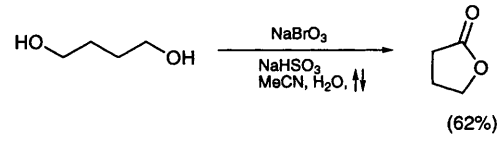
enzyme introduces absolute stereochemistry. The hydrolysis can be run in either direction but the highest optical purities are seen for the forward reaction. Changing the degree of branching in the carbon chain of the acetate can lead to a change in the configuration of the major product. The hydrolysed enantiomer is lactonised after mercury-assisted hydrolysis of the dithioketene acetal. Dithioketene-acetals also play a pivotal role in the unselective synthesis of α-trifluoromethyl γ-lactones.[42] Aliphatic enolates displace the vinylic fluoride from perfluoro-dithioketene acetals by an addition–elimination mechanism. The resulting ketones are reduced or subject to 1,2-addition by organometallics before lactonisation. These dithioketene acetals undergo acid hydrolysis without the aid of mercury salts, but this fails if an aryl substituent is introduced at C-4 since the initial carbocation adjacent to sulfur rearranges to the more stable benzylic cation (**Scheme 40**).



Scheme 40

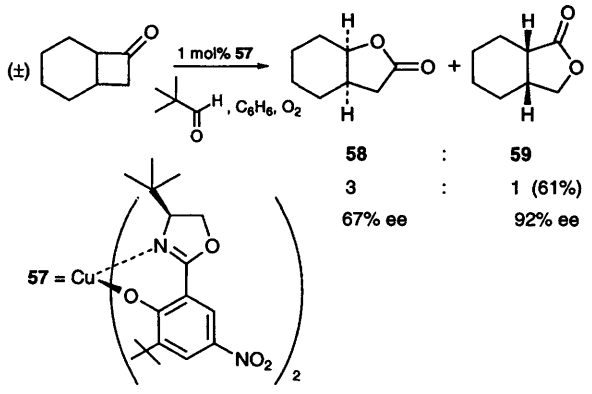
Excellent simple diastereoselection is observed in the reduction of the ketones **56** (**Scheme 41**) which are synthesised from tartaric anhydrides.[43] The sense of the addition is consistent with the non-chelated Felkin–Anh model. It is noteworthy that the pivalate protecting groups are essential to the practical success of the sequence since the analogous acetates are too water soluble to give readily isolated materials. Lactonisation is best carried out under anhydrous conditions and with careful monitoring as the highly oxygenated products appear to be sensitive to prolonged exposure to acid.

Aqueous hypobromous acid generated *in situ* from sodium perbromate and sodium hydrogen sulfite oxidises primary alcohols to esters,[44] and can also be applied to the lactonisation of simple ω-diols in moderate yield (**Scheme 42**). The mechanism, elucidated by cross-coupling experiments, is a two step oxidation *via* an intermediate lactol. The scope of the reaction is currently limited to γ- and δ-lactones, and temperature control is required to avoid over-oxidation.



Scheme 42

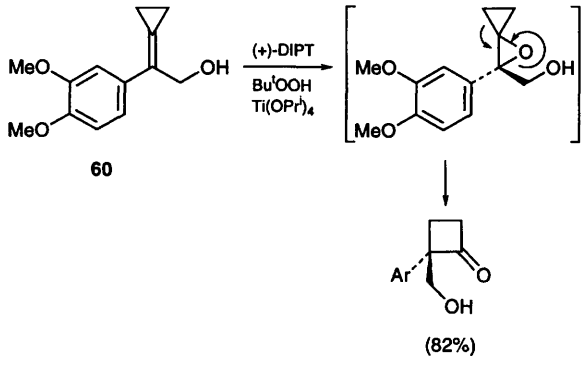
Oxygen insertion into racemic, aliphatic bicyclobutanones catalysed by the chiral copper complex **57** takes place in an enantiodivergent fashion, reminiscent of the related biocatalytic systems (**Scheme 43**).[45] One enantiomer of the cyclic ketone leads to the usual Baeyer–Villiger product **58** whilst the other forms the regioisomeric lactone **59**, where the oxygen inserts at the less substituted carbon atom. The two lactones are formed in a 1:1 ratio as evinced by GC analysis but the lactone **59** may be more susceptible to hydrolysis on work-up. The enantiodivergent nature of the transformation is revealed by the optical activity of the residual starting material (≤6% ee) which remains essentially racemic. The phenomenon is general for a range of bicyclic and bridged cyclobutanones but the optical activities of the lactones corresponding to **58** are consistently lower than those of the regioisomers, implying that a competing uncatalysed

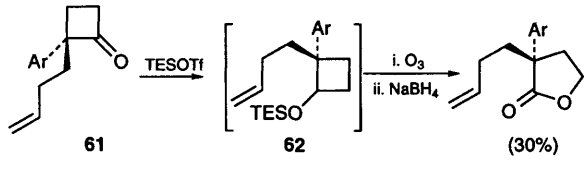


Scheme 43

pathway that converts racemic ketone to racemic lactone **58** is operating.

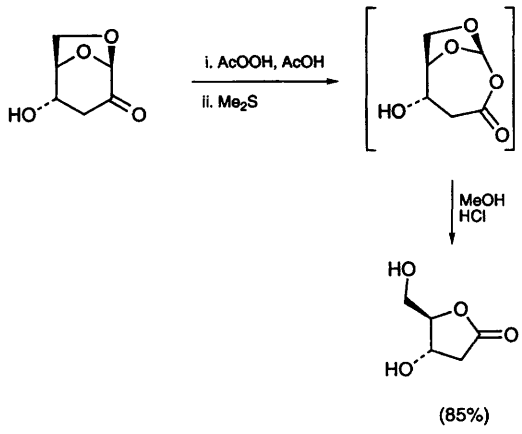
The cyclopropylidene-ethanol **60** undergoes a tandem asymmetric epoxidation and stereospecific 1,2-rearrangement when subject to Sharpless' conditions (**Scheme 44**).[46] After elaboration of the benzylic quaternary centre, conversion of the cyclobutanone **61** to the silyl enol ether **62** permits ozonolytic lactone formation in the presence of the terminal olefin. The Baeyer–Villiger oxidation of a derivative of levoglucosenone, a readily available chiral pool material prepared by the pyrolysis of cellulose, occurs regioselectively to give an orthoester which cleaves on hydrolysis to produce a hydroxylated γ-lactone (**Scheme 45**).[47]



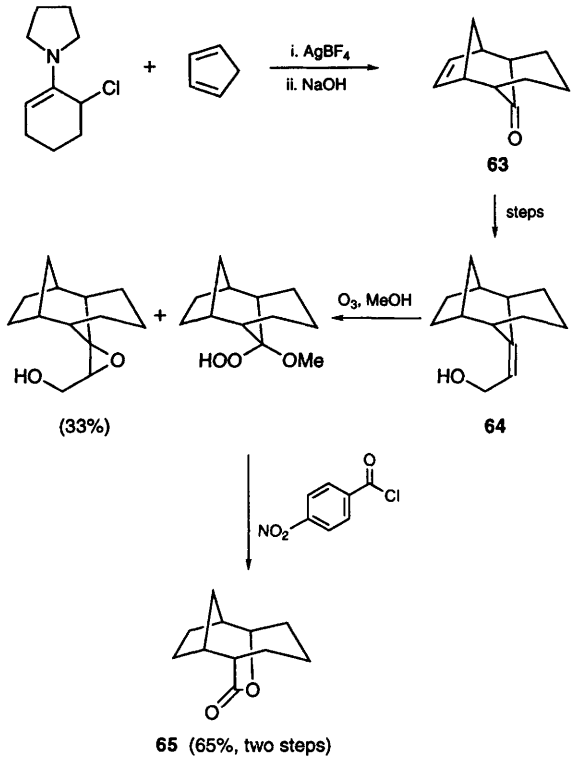


Scheme 44

The Schmid azaallyl [4+3] cycloaddition provides a possible entry into natural products containing medium ring carbocycles, but a stumbling block is the resistance of some of the product bridgehead ketones to direct oxidative cleavage, as exemplified by the ketone **63** (**Scheme 46**). Cha *et al.* circumvent

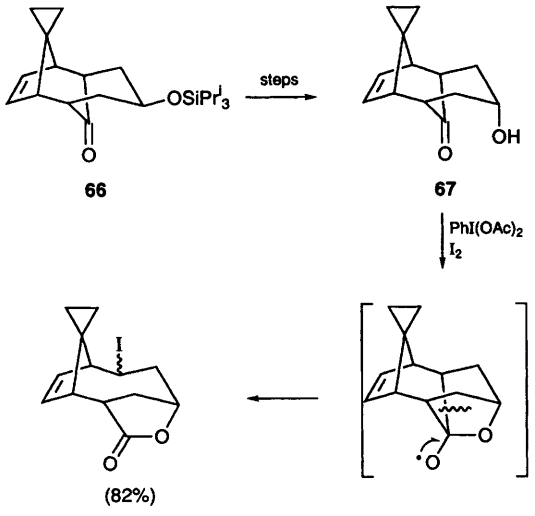


Scheme 45



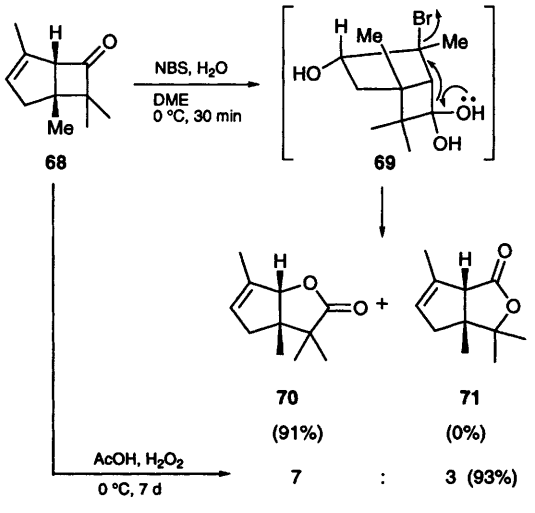
Scheme 46

this problem in two ways.[48] The bicyclic lactone **65** can be generated indirectly by Criegee rearrangement of the ozonolysis product of the homologated allyl alcohol **64**. This sequence is compromised by the formation of significant amounts of the epoxide by-product during the ozonolysis. Alternatively, the more substituted Schmid cycloadduct **66** (**Scheme 47**) is transformed by Mitsunobu inversion of the alcohol to the keto alcohol **67** which is set up for lactol formation. Although the lactol tautomer of **67** is present in only 10% abundance, generation of the oxygen centred radical is successful and smooth β-fragmentation provides the attractively functionalised bridge-opened lactone in good yield.



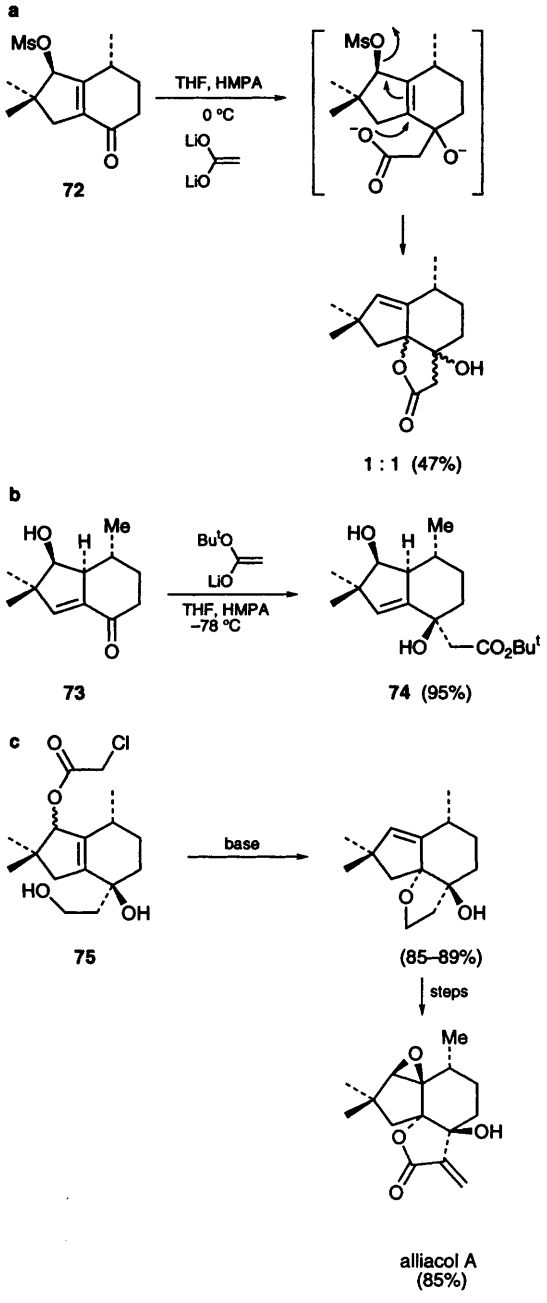
Scheme 47

A similar fragmentation is the basis for a novel replacement for the Baeyer–Villiger oxidation[49] of unsaturated bicyclobutanones typified by **68** (**Scheme 48**). Bromination of the alkene on the convex face of the bicycle dictates regioselective opening of the bromonium ion at the more accessible C-3 atom. The geometry of the resultant halohydrin **69** is ideal for *trans* coplanar fragmentation on heating, which is followed by spontaneous lactonisation to the isolated product **70**. When the alkene is unsubstituted the intermediate halohydrins can also be isolated. The reaction is notably superior to the conventional oxidation of **68** where selectivity is moderate and reaction times much longer.



Scheme 48

The tricyclic lactone core of the cytotoxin alliacol A is constructed rapidly but unselectively by the tandem aldol-S_N2'-lactonisation of dilithioacetate and the γ-mesyloxy enone **72** (**Scheme 49a**).[50] The lack of diastereofacial selectivity in the initial



Scheme 49

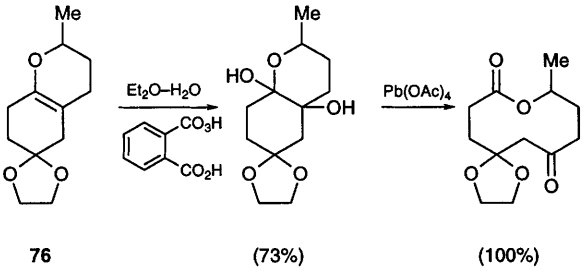
addition to the rather planar bicycle **72** is overcome if the structure **73** with a more pronounced curvature is employed (**Scheme 49b**). However, lactonisation of the product **74** after double bond migration is compromised by competing retro-Claisen fragmentation of the pendant carboxylate. This is avoided by cyclisation of the 2-chloroacetate **75** at the alcohol oxidation level, where both *syn* and *anti* modes of the S_N2' reaction occur with equal facility (**Scheme 49c**). Reoxidation of the tetrahydrofuran furnishes the desired lactone.

5 Medium ring lactones

A two step procedure is found to be the most efficient method of oxidative cleavage of the bicyclic

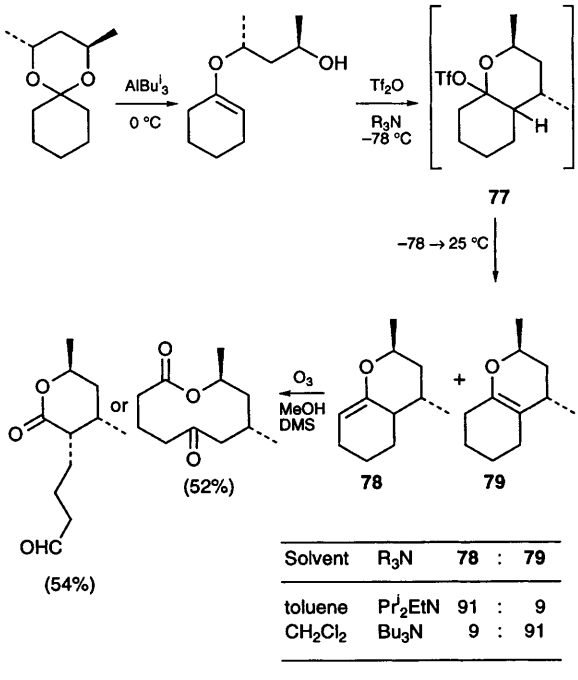
enol ether **76** to the 10-membered keto lactone product, an intermediate in the synthesis of pyrenolide B (**Scheme 50**).[51] In a related strategy, bicyclic enol ethers are assembled by the regio- and stereospecific opening of spirocyclic 1,3-dioxolanes and their subsequent reclosure through an S_N2 reaction (**Scheme 51**).[52] The regiochemistry of the elimination from the intermediate triflate **77** is base and solvent dependent, favouring the kinetic product **78** with hindered bases in toluene. The unstable enol ethers are cleaved by ozonolysis to give a reasonably controlled route to 10-membered keto lactones from the thermodynamic elimination product **79** or to δ-lactones from the other regioiosomer.

Medium ring keto lactones are also produced by the oxidation of carbocyclic homoallyl alcohols with permanganate under phase transfer catalysis (**Scheme 52**).[53] The rearrangement pathway of the metallooxetane **80**, leading to epoxides or medium ring lactones, varies with the size of the carbocycle and may be governed by the overall lipophilicity of the substrates. Improved selectivity for the formation of the keto lactones is observed when



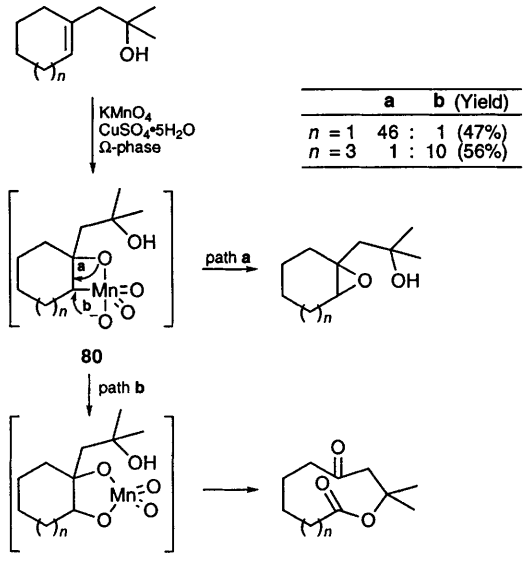
76 (73%) (100%)

Scheme 50



Solvent	R_3N	78 : 79
toluene	Pr^i_2EtN	91 : 9
CH_2Cl_2	Bu_3N	9 : 91

Scheme 51

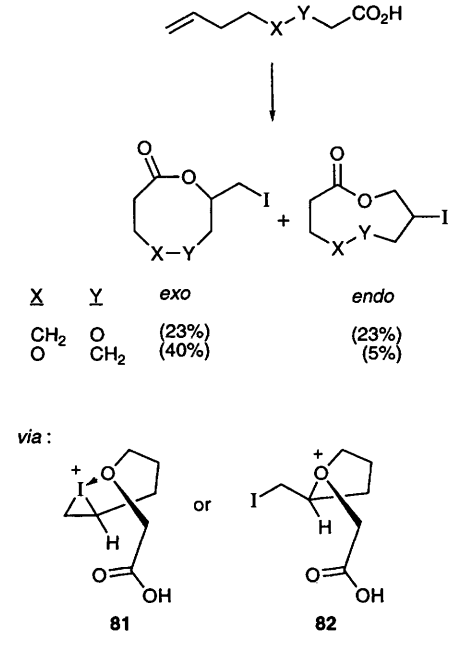


	a	b (Yield)
$n = 1$	46 :	1 (47%)
$n = 3$	1 :	10 (56%)

Scheme 52

montmorillonite clay replaces copper sulfate as the solid support.

The introduction of an oxygen atom into the chain of ω-alkenyl carboxylates facilitates iodolactonisation to seven-, eight- and nine-membered rings by reducing transannular CH···CH interactions. Rousseau[54] postulates that there may also be a favourable entropic effect resulting from neighbouring group participation by the oxygen atom in the cyclisation (**Scheme 53**). The regioselectivity of this cyclisation depends on the position of the oxygen in the tether, though *exo* ring closure is generally predominant. The pseudo-bicyclic coordinated iodonium ion **81** or the oxonium species **82**

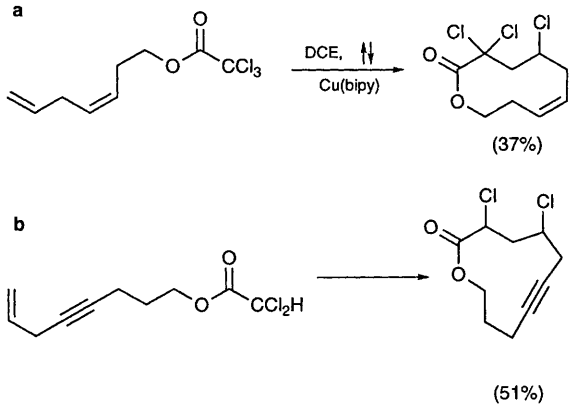


X	Y	*exo*	*endo*
CH_2	O	(23%)	(23%)
O	CH_2	(40%)	(5%)

Scheme 53

are representative of the proposed mediators of this selectivity.

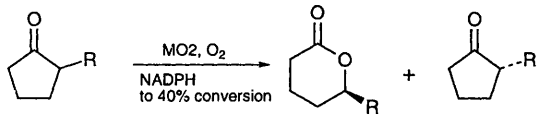
A template effect of the metal catalyst is the driving force for the exclusively *endo* radical cyclisation of alkenyl di- and tri-chloroacetates to eight and nine-membered rings developed by Speckamp *et al.*[55,56] This methodology is extended to 10- and 11-membered rings when a conformational constraint is included within the tethering chain, although forcing conditions sometimes become necessary (**Scheme 54a,b**). The sensitivity of the reaction to these constraints and to substitution within the chain reflects the close association of the radical and metal centres in this process.



Scheme 54

6 δ-Lactones

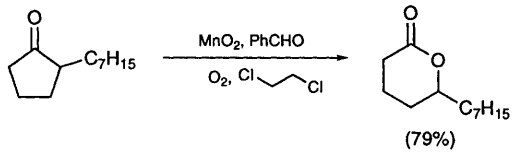
Further characterisation of the portfolio of monooxidase enzymes (MO) produced by the *Pseudomonas putida* microorganism reveals their complementary substrate specificity.[57] Whereas the NADH-dependent enzyme MO1 is efficient for the biocatalytic oxidation of bicyclic ketones, the NADPH-dependent fraction MO2 is especially suited to the production of monocyclic δ-lactones (**Scheme 55**).[58] Although excellent resolutions are seen with small, polar side chains the enzyme is intolerant of more lipophilic substituents, a limitation ascribed to its original metabolic role. The low yields are a result of competing dehydrogenase activities in the partially purified protein and better recoveries are achieved with more rigorously pure



R	ee (%) (Yield)	ee (%) (Yield)
CH_2CO_2Et	>98 (27%)	75 (37%)
$CH_2OSiBu^tMe_2$	45 (18%)	22 (25%)

Scheme 55

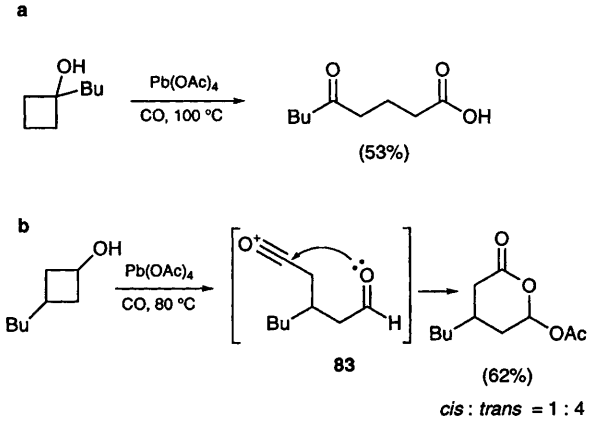
material. Preliminary experiments show that MO2 is not proficient at the oxidation of prochiral 3-substituted cyclobutanones and in this case the whole-cell *Acinetobacter calcoaceticus* system is superior.[59] The aerobic oxidation of cyclic ketones is also possible with transition metal oxides as catalysts.[60] Manganese dioxide is the best choice and a three-fold excess of an aryl aldehyde is necessary for complete conversion (**Scheme 56**). Olefins are not oxidised in these reactions, and in fact inhibit the reaction completely. Although aromatic peracid can be detected in the medium its importance to the mechanism is not clear.



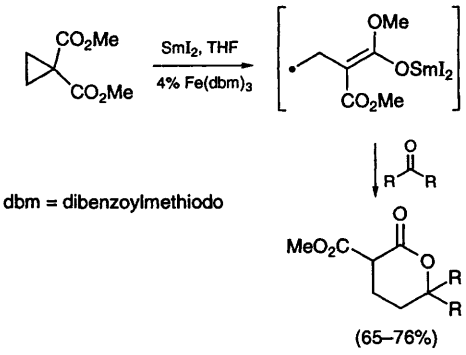
Scheme 56

The oxidative β-scission of cyclobutanols with lead tetraacetate generates alkyl radicals that can be trapped in high pressures of carbon monoxide to give 1,5-keto acids (**Scheme 57a** and **b**). Only in the case of 3-substituted cyclobutanols does the reactive intermediate oxidation product **83** cyclise to give the δ-lactones.[61] The analogous reductive ring opening of cyclopropyl ketones is promoted by samarium iodide and, with the addition of iron species to enhance the reducing power of the reagents, this chemistry is extended to cyclopropane-1,1-dicarboxylates.[62] Efficient trapping of the alkyl radicals in the presence of aliphatic ketones gives good yields of the corresponding δ-lactones (**Scheme 58**). As yet the reaction is only poorly applicable to aldehydes and aromatic ketones.

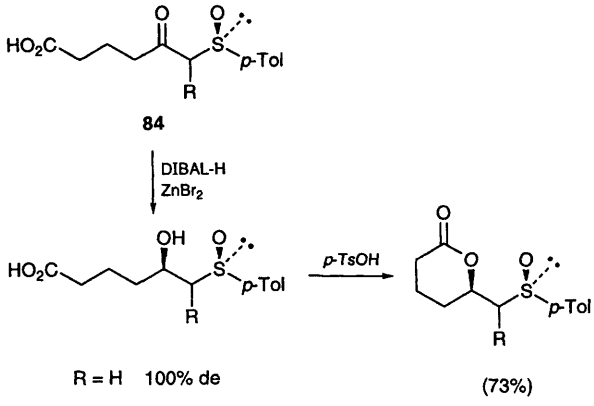
Enantiomerically pure δ-lactones are synthesised by a highly stereoselective chelation-controlled reduction of homochiral sulfinyl oxo acids (**Scheme 59**).[63] The addition of zinc bromide is required for satisfactory control over the reduction of the keto acids **84**. One drawback at present is the inseparable mixture of substituted keto acids **84** ($R \neq H$)



Scheme 57



Scheme 58

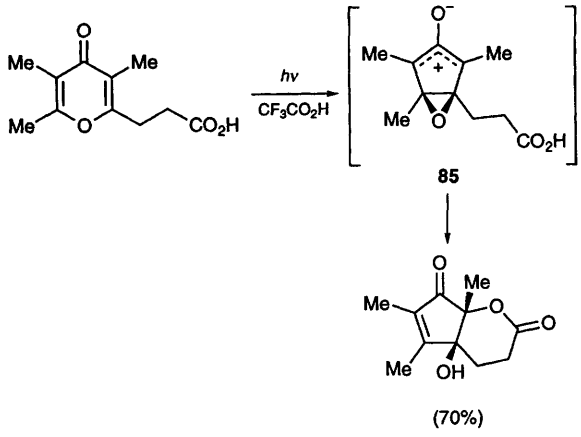


Scheme 59

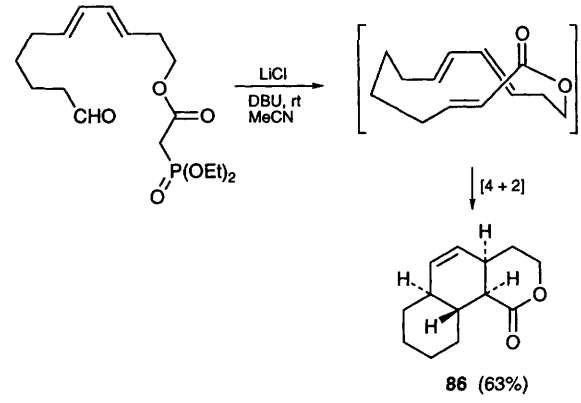
produced in the initial stages of the synthesis. However, the extra stereocentre shows only marginal influence on the selectivity of the reduction and the diastereoisomeric ratio is carried through to the product lactones.

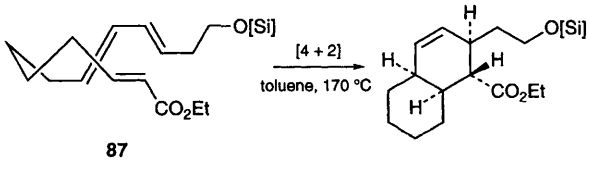
Fused bicyclic γ- and δ-lactones are obtained in good yield by the photoirradiation of pyran-4-ones bearing a pendant carboxylic acid.[64] This is a development of existing annellation processes involving the oxyallyl zwitterion **85** and is an attractive reaction for applications in natural product synthesis. Although several substitution patterns are tolerated in the reaction the highest yields are seen with peralkylated pyran-4-ones (**Scheme 60**).

Building on the work of Roush and others with macrocyclic ketones, a tandem macrolactonisation and transannular Diels–Alder cycloaddition gives rise to the tricyclic lactone **86** (**Scheme 61**) as the sole product.[65] High dilution and slow addition conditions are needed to avoid competing dimerisation during the Horner–Emmons ring closure. The *endo* selective cycloaddition goes in the opposite stereochemical sense to that of the acyclic diene **87** and under milder conditions. An efficient transannular reaction is also seen in Fraser-Reid's approach to part of the insect antifeedant azadirachtin.[66] A highly strained tricyclic lactone is formed by intramolecular conjugate radical addition to the α,β-unsaturated δ-lactone **88** (**Scheme 62**).

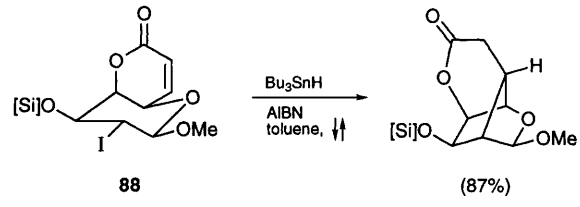


Scheme 60





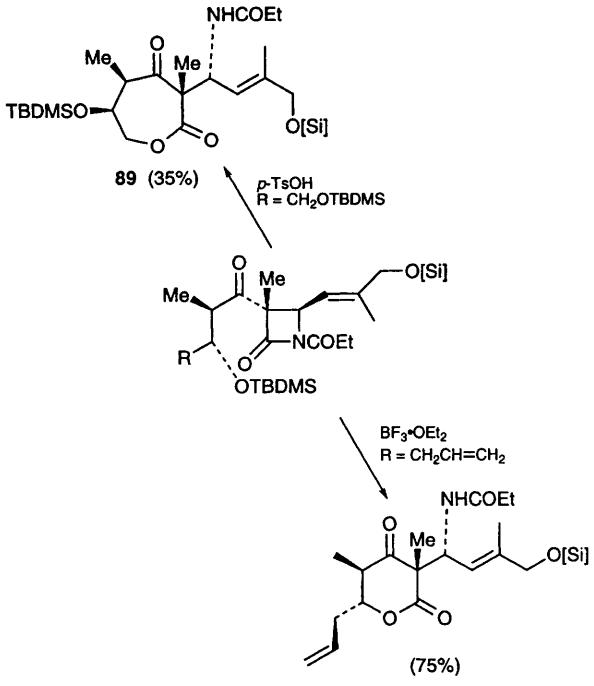
Scheme 61



Scheme 62

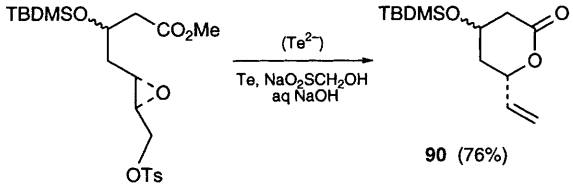
Again, slow addition and high dilution conditions are the key to the success of the reaction.

Thomas *et al.* rely on the transacylation of activated azetidinones to construct the δ-lactone portion of the macrocylic lankacidin antitumour antibiotics.[67] Careful choice of the exact substrate and protecting group array must be made to avoid side reactions, such as the formation of the seven-membered lactone **89** (**Scheme 63**). A very stereoselective acylation of an azetidinone enolate is used to put together the cyclisation precursors. The



Scheme 63

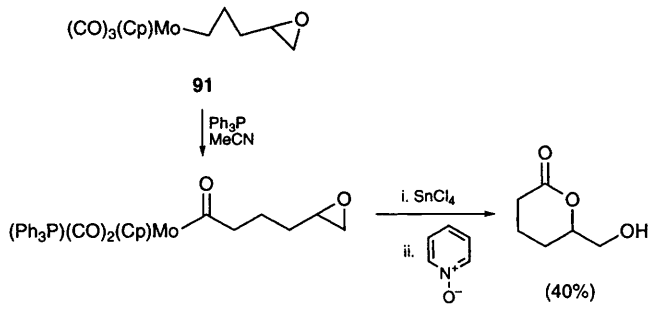
unstable δ-lactone **90**, related to a fragment of the important HMG-CoA reductase inhibitor mevinolin, is rapidly constructed by sequential Sharpless asymmetric epoxidation and a stereospecific telluride transposition (**Scheme 64**).[68] The acyclic precursor can be prepared as a single diastereoisomer from the same reagent combination on a simpler allylic alcohol.



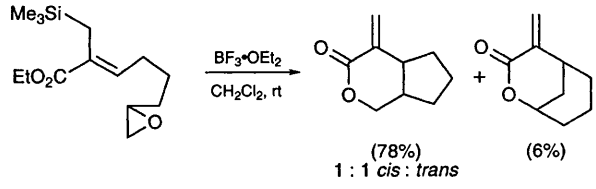
Scheme 64

The *exo* mode of cyclisation observed in the intramolecular ring closure of nucleophilic metallocarbenes onto epoxides in the presence of Lewis acids[69] is governed by the development of positive charge on the most substituted oxirane carbon (**Scheme 65**). The carbenoid is derived from the readily prepared, but unstable alkylmolybdenum **91**. Both γ- and δ-lactones are available from this reaction. A preliminary report suggests a promising new route to fused bicyclic δ-lactones through the intramolecular Sakurai–Hosomi allylation of epoxides, with 5-*exo* attack again dominant over 6-*endo* cyclisation (**Scheme 66**).[70] The presence of the deactivating ester group on the allylsilane does not interfere with the efficiency of the process.

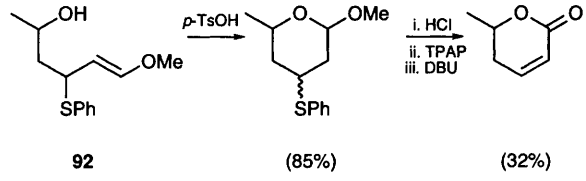
The preference for 5-*exo* cyclisation over 6-*endo* is reversed when the γ-hydroxy enol ether **92** (**Scheme 67**) is subject to acid catalysed cyclisation, since the



Scheme 65

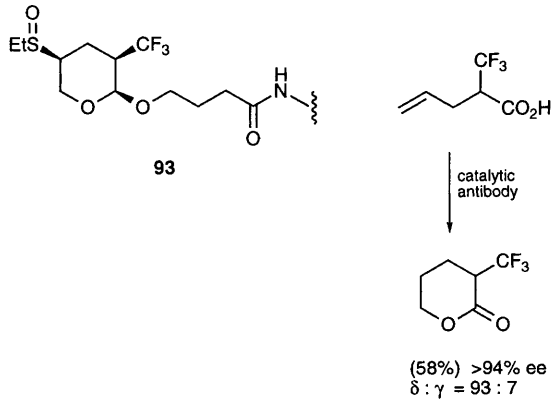


Scheme 66



Scheme 67

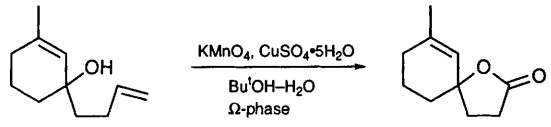
incipient positive charge is stabilised by the methoxy substituent.[71] The cyclisation precursors come from the coupling of a sulfur-stabilised anion and epoxides. Since the epoxides are readily available in enantiomerically pure form, this route is a general and rapid approach to optically active saturated and unsaturated δ-lactones. Another effective, if expensive, way of ensuring 6-*endo* cyclisation is to raise a catalytic antibody for the unfavourable process.[72] The cyclic sulfoxide hapten **93** secures an acidic residue in the antibody suitably placed to protonate only the internal carbon of the olefinic substrate (**Scheme 68**).



Scheme 68

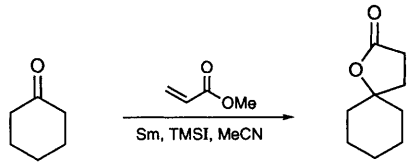
7 Spirolactones

The formation of allylic spiro-γ-lactones such as **94** (**Scheme 69**) by the direct oxidation of Barbier-type addition products is not normally feasible due to competing internal double bond oxidations and the propensity of tertiary allylic alcohols to eliminate. The use of phase transfer catalysis to modify the reactivity of permanganate[73] overcomes these restrictions and gives good yields of the spirolactones. Another direct route to these compounds involves the reductive coupling of ketones and acrylates[74] using the samarium(II) species generated from samarium metal and a trimethylsilyl halide as a convenient alternative to Kagan's method for samarium diiodide formation (**Scheme 70**).



94 (62%)

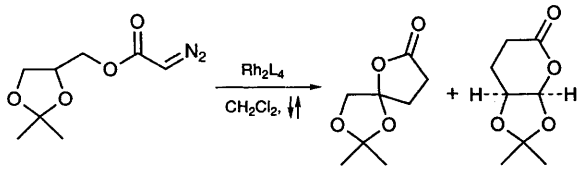
Scheme 69



(53%)

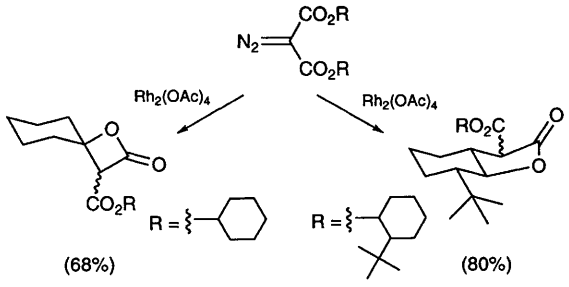
Scheme 70

The C–H insertion reactions of rhodium carbenoids show a clear general preference for five-membered ring formation, and both this selectivity and chemical yield are enhanced when rhodium(II) carboxamide catalysts are used in place of dirhodium acetate to generate the carbenes from diazoesters (**Scheme 71**).[75] The activation of C–H bonds by adjacent oxygen atoms can sometimes override the preference for five-membered ring formation, but it is also important to consider steric factors. For example, the rhodium carbenoids derived from dicyclohexyldiazomalonates exhibit two intramolecular cyclisation pathways.[76] The sterically unencumbered cyclohexyl diazoesters insert into the activated axial methine C–H bond to give spirocyclic β-lactones but introduction of a flanking substituent redirects the insertion to the less hindered methylene C–H (**Scheme 72**).



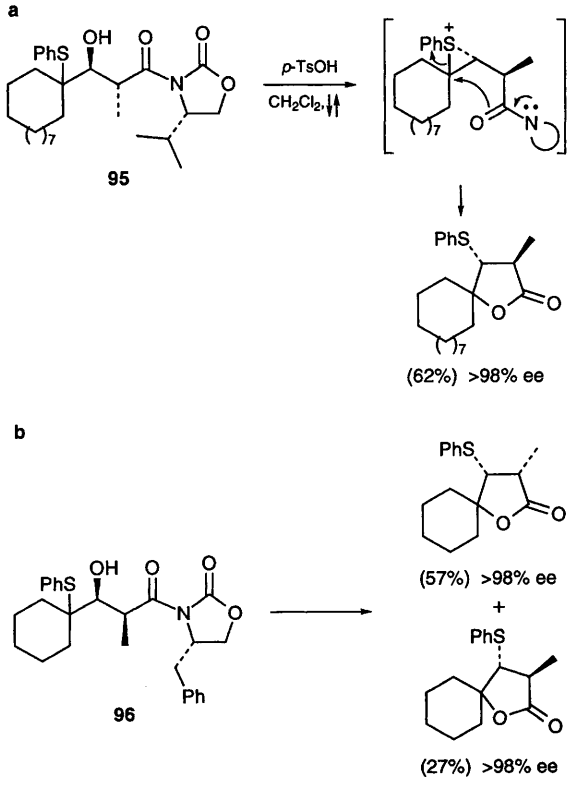
Rh_2(caprolactam)$_4$	100	:	0 (60%)
Rh_2(OAc)$_4$	50	:	50 (47%)

Scheme 71



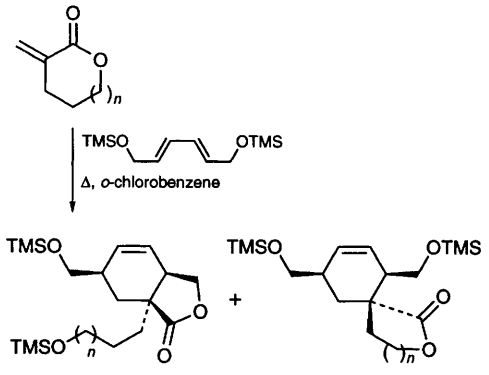
Scheme 72

Single enantiomers of spirocyclic γ-lactones are produced in good yield by coupling a diastereoselective aldol addition with Warren's stereospecific cyclisation[77] *via* an asymmetric episulfonium ion (**Scheme 73a**). The chiral auxiliaries from the aldol step are cleaved during the cyclisation and for the *anti* aldol **95** this gives a single spirocycle. Developing 1,2-strain in the nascent five-membered ring formed from the *syn* aldol **96** results in a partial epimerisation at the centre adjacent to the carbonyl group and two products are isolated (**Scheme 73b**). This epimerisation is not seen if the auxiliary is cleaved to the more nucleophilic carboxylate before cyclisation.

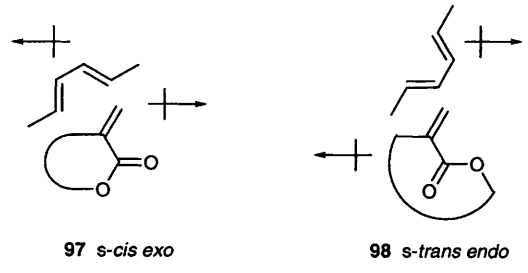


Scheme 73

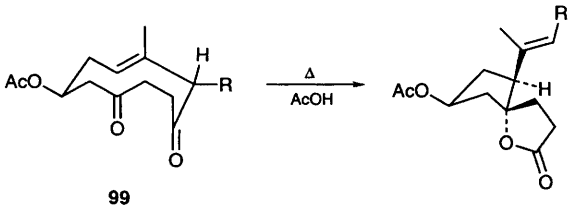
An investigation of the *exo* selectivity in Diels–Alder cycloadditions of α-methylene lactones shows that the conformation of the dienophile is the controlling factor[78] rather than secondary orbital interactions (**Scheme 74**). The *endo* cycloadducts are usually, but not exclusively, isolated as the fused bicyclic transacylation products. With small rings reasonably selective formation of the spirocyclic *exo* adducts is observed. The orientation of the two components is governed by the drive to minimise the overall dipole of the transition state. For the smaller lactones, constrained to the s-*cis* conformation, this is achieved in the *exo* addition mode **97**, but as the rings become larger the competing *endo* transition state **98** with the s-*trans* conformation is possible. An unusual stereospecific rearrangement, corresponding formally to a 'transannular ene' reaction, is seen when the 10-membered lactone **99** (**Scheme 75**) is heated in acid.[79] The precursor to this reaction comes from successive oxidative β-fragmentation of a steroid nucleus.



n	*endo* :	*exo*	(Yield)
1	18 :	82	(59%)
5	42 :	58	(77%)



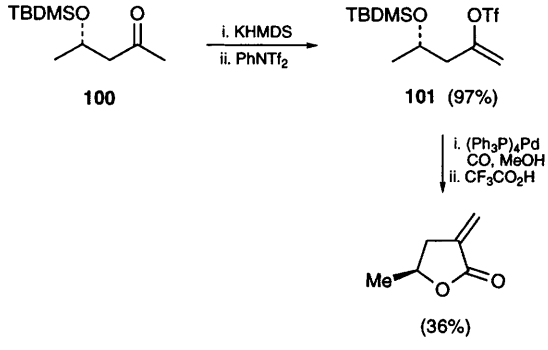
Scheme 74



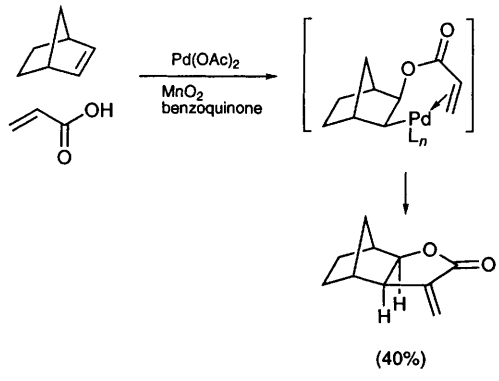
Scheme 75

8 α-Methylenebutyrolactones

Several syntheses of α-methylenebutyrolactones make use of palladium-mediated couplings to assemble the acyclic carbon skeleton. For example, carbonylation of the vinyl triflate **101** (**Scheme 76**), obtained by regioselective kinetic enolisation of the Bakers' yeast reduction product **100**, produces an ester suitable for acidic lactonisation to a homochiral lactone.[80] The carbonylation and desilylation steps have to be carried out as two separate operations as the addition of fluoride ion to the carbonylation medium completely inhibits the reaction, and also fails to remove the silyl group. A preliminary communication outlines how the synthesis of lactones can sometimes be achieved by starting with intermolecular 1,2-acryloylpalladation of olefins (**Scheme 77**).[81] This reaction is presently limited to modest yields because of polymerisation of the acrylate component. A more serious problem is the competitive formation of π-allyl palladium complexes through β-abstraction of labile allylic hydrogens, a pathway that leads to allyl acrylate esters. This currently restricts the practical application of the reaction to systems with less easily removed allylic protons. The palladium(0)–copper(I) catalysed coupling of 2-haloalk-2-enoates with vinyl stannanes generates intermediates that

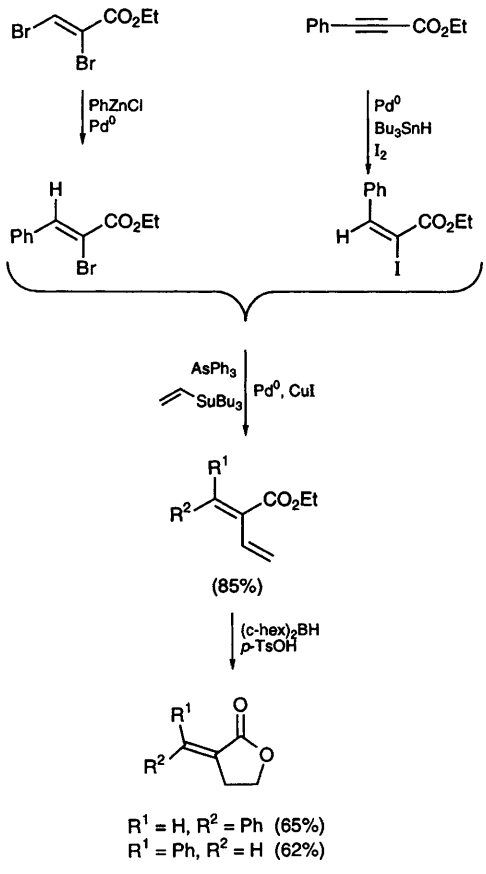


Scheme 76



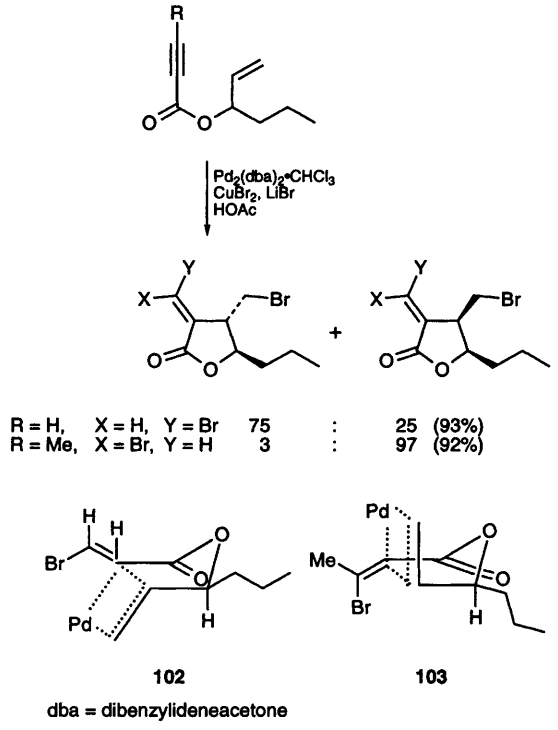
Scheme 77

can be elaborated to α-ylidenebutyrolactones.[82] Both the *E* and *Z* alkenoate coupling partners are themselves constructed with palladium chemistry, allowing complete control over the geometry of the trisubstituted exocyclic double bond of the final lactones (**Scheme 78**).



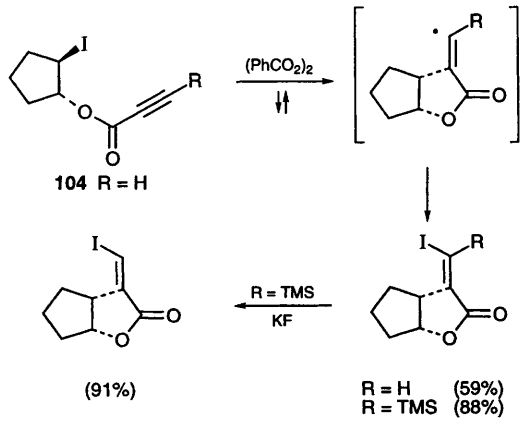
Scheme 78

The intramolecular cyclisation of allyl but-2-ynoates is also mediated by palladium.[83] Although previously reported for the production of chloromethyl substituted lactones, the procedure now extends to the more synthetically versatile bromo analogues (**Scheme 79**). The terminal substituent of the triple bond controls both the diastereoselectivity of the cyclisation and the geometry of the product double bond. The *cis* bromopalladation of unsubstituted propiolates (R = H) is followed by cyclisation through the pseudo-chair transition state **102** to give predominantly the *trans* β,γ-substituted lactone. In contrast, internal triple bonds (R = Me) undergo a *trans* bromopalladation and cyclisation *via* the pseudo-boat conformation **103** to give mainly the *cis* lactone. The greater degree of steric interactions in the latter substrates is mirrored in the higher diastereoselectivity. By starting with homochiral secondary allylic alcohols, single enantiomers of the *cis* lactones are readily obtained.[84] Thus far, attempts to incorporate the cyclisation into tandem sequences have been unsuccessful.



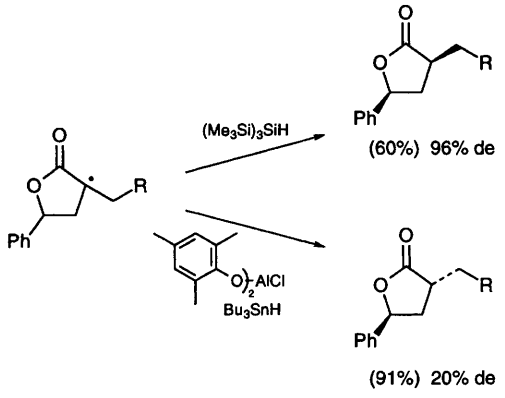
Scheme 79

In a thorough investigation, Weavers *et al.* have tracked down the inefficiency of the radical cyclisation of their unsubstituted alk-2-ynoate **104** (**Scheme 80**) to the slow transfer of iodine in the chain propagation step.[85] The vinyl radical develops appreciable electrophilic character during the transfer which can be stabilised by electron donation from alkyl substituents, but is otherwise an unfavourable process. Only limited improvements in the efficiency of the transformation are seen from changes to the solvent and initiator, or from portion-wise addition of the latter. The most practical solution is to cyclise the trimethylsilyl substituted triple bond and to remove the silicon stereospecifically to give the desired α-iodomethylenebutyrolactones in good yield. The stereochemistry of radical additions to simple α-methylenebutyrolactones is determined at



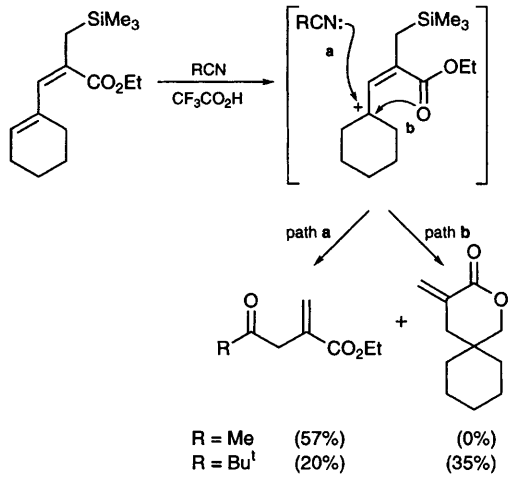
Scheme 80

the point of hydrogen transfer to the intermediate radical. Bulky reducing agents give high selectivity for approach on the less hindered face of the ring and this can be reversed to some degree by coordination of the lactone with a Lewis acid (**Scheme 81**).[86]

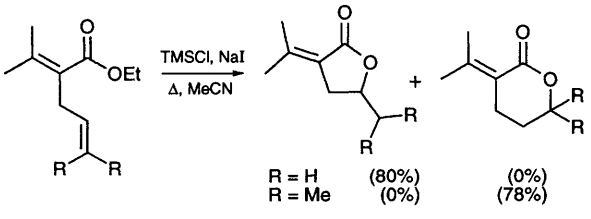


Scheme 81

A new method for the formation of spiro-α-methylenebutyrolactones has been uncovered during the investigation of the Ritter reaction of 2-(ethoxycarbonyl)penta-2,4-dienylsilanes.[87] With hindered nitriles the normal Ritter reaction (path **a**) (**Scheme 82**) is intercepted in favour of intramolecular participation of the ester group (path **b**). As yet this process is unoptimised for complete



Scheme 82

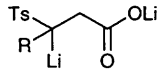


Scheme 83

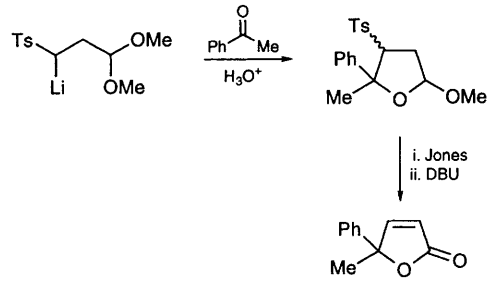
formation of the spirolactones. The related cationic cyclisation of γ,δ-unsaturated esters promoted by trimethylsilyl iodide shows the usual substituent influences on the regiochemistry of the ring closure, with formation of the initial cation directed to the most substituted olefinic carbon (**Scheme 83**).[88]

9 But-2-enolides and tetronic acids

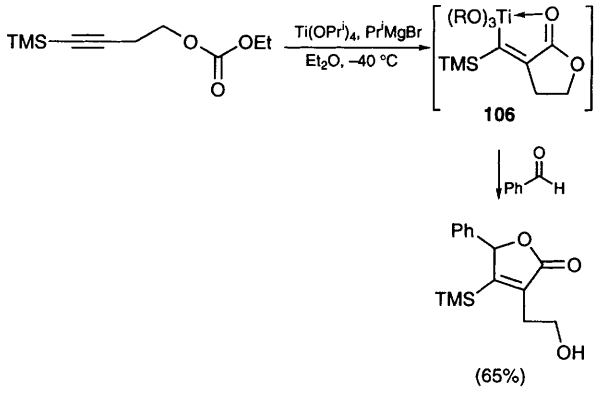
Nájera *et al.* have described previously how the dianions of 3-tosylalkanoic acids **105** function as homoenolate equivalents in the synthesis of butenolides by aldol condensations; this approach can also be applied at the aldehyde oxidation level to generate butyrolactols (**Scheme 84**).[89] Although an additional oxidation step is now required, the overall yield of the transformation is improved over the direct route.



105



Scheme 84



Scheme 85

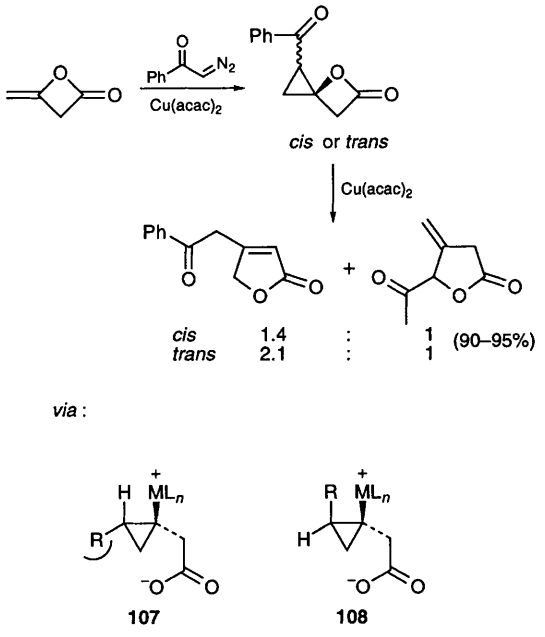
The stable vinyltitanium species **106** (**Scheme 85**) also serves as a β-acylanion equivalent.[90] Initial metallation of the homoprop-2-ynyl carbonate produces an allenyltitanium structure which cyclises by intramolecular acyl substitution to give **106**. Simple acidic quenching affords the α-methylenebutyrolactone whereas the reaction with benzalde-

hyde triggers translactonisation to yield the substituted butenolide. The transformation is general for systems with up to four carbons between the carbonate and triple bond, but only disubstituted alkynes will form the titanium reagent.

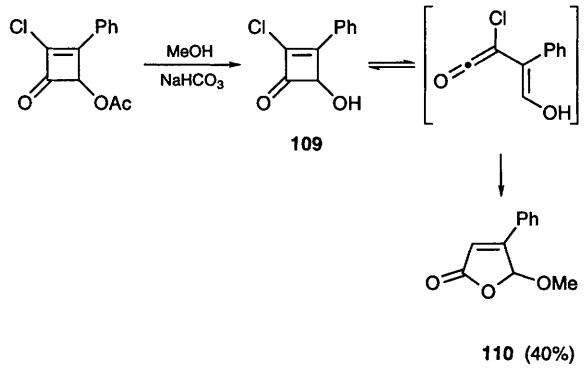
Cyclopropanation of the exocyclic double bond of diketene with metal carbenoids furnishes the expected spirocyclopropyl β-lactones. In some cases, however, progression to substituted butenolides is observed and this has now been shown to be a metal catalysed reaction that can be driven to completion (**Scheme 86**).[91] Metal insertion into and cleavage of the lactone C–O bond is proposed as the starting point for the rearrangement, followed by lactonisation with cyclopropane ring opening. The latter step is more selective when the *trans* spirolactone is used since the intermediate **107** experiences greater steric differentiation of the cyclopropane carbons than the analogous species **108** derived from the *cis* isomer.

An unexpected ring expansion is observed when the hydroxycyclobutanone **109** is prepared by methanolysis (**Scheme 87**).[92] The product **109** can be isolated in reasonable yield (51%) unless the reaction time, temperature or basicity are increased, whereupon the butenolide **110** is formed, presumably *via* electrocyclic ring opening and subsequent relactonisation with allylic substitution of the chloride, a mechanism that is precedented in the addition of enol silanes to squaric acid derivatives. Basic conditions are not essential for the rearrangement, which gives the highest yield (75%) in neutral refluxing methanol.

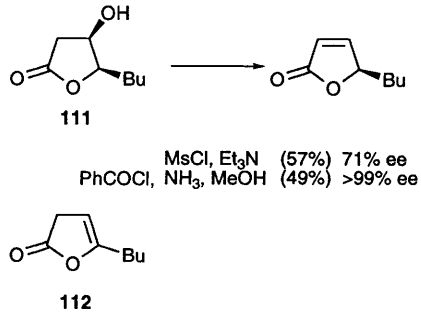
Homochiral 4-substituted butenolides are valuable synthetic precursors to functionalised γ-lactones through stereoselective reactions of the enone group. Elimination of the mesylate of alcohol **111** leads to partial racemisation due to formation of some of the intermediate enol lactone **112**.[93] This is overcome when the less reactive benzoate leaving group is used to ensure deprotonation of only the most acidic hydrogen in the elimination. Michael additions to the butenolide proceed with excellent diastereofacial selectivity on the least hindered side of the ring. The *gem*-disubstituted butenolide **113**, prepared by Hegedus *et al.* with their chromium carbene technology, shows a more varied diastereofacial bias.[94] The sterically hindered molecule does not react with cuprates but the addition of thiolates and nucleophilic epoxidation occurs *anti* to the alkoxy group, as might be expected from application of the Felkin-Anh model to this vinylogous carbonyl addition (**Scheme 89**). Nitrones also have a strong



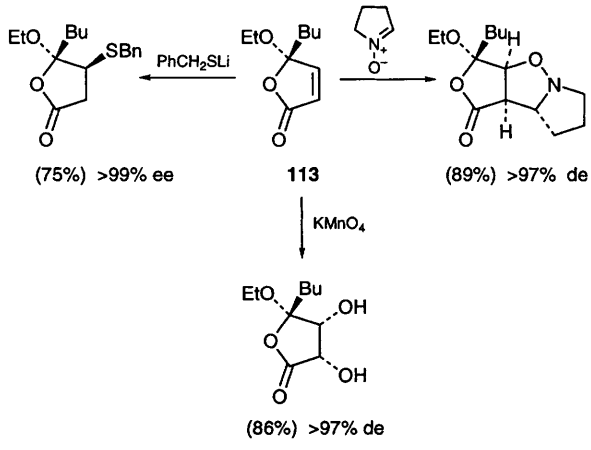
Scheme 86



Scheme 87



Scheme 88



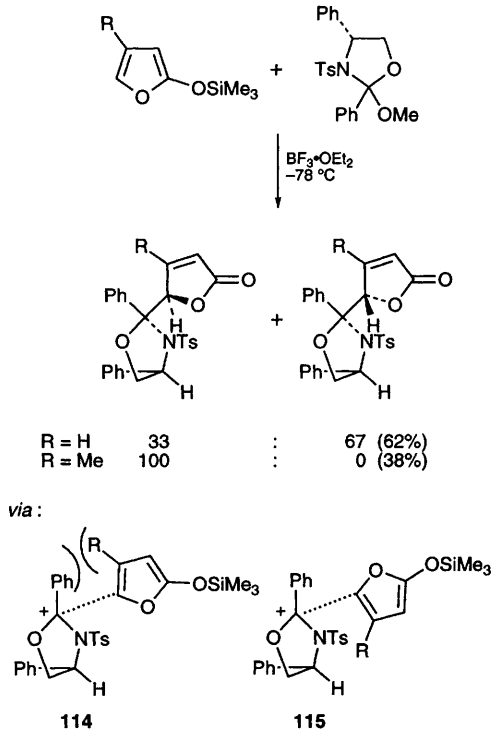
Scheme 89

preference for cycloaddition *anti* to the alkoxy group, reflecting the nucleophilic character of the nitrone in the addition to the electron-poor double bond. In contrast, azomethine ylides show a modest preference for the opposite sense of addition and permanganate dihydroxylation takes place exclusively from the same side as the alkoxy group.

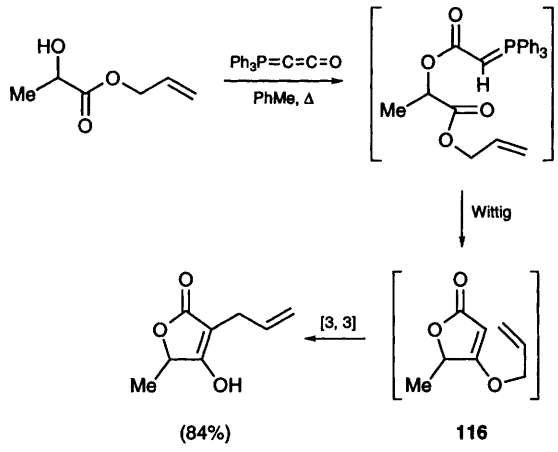
Single enantiomers of 4-substituted methyl tetronates are the product of the Lewis acid promoted addition of silyloxyfurans to chiral acyl cation equivalents (**Scheme 90**).[95] The silyloxyfuran approaches the least hindered face of the oxazolidinyl cation and the facial reactivity of the furan is determined by the level of 3-substitution. Thus the unsubstituted material shows only a modest discrimination between the two orientations **114** and **115**, whilst the 3-methoxy-2-silyoxyfuran avoids eclipsing interactions with the phenyl substituent of the oxazolidine in **114** and gives exclusively one diastereoisomer.

A novel one-pot tandem Wittig–Claisen combination permits the synthesis of α,γ-disubstituted tetronic acids from allyl α-hydroxy esters (**Scheme 91**).[96] The unrearranged product **116** can be isolated with adjustments to the reaction temperature, or by replacing allyl with simple alkyl groups. Excellent yields are obtained but attempts to apply the sequence to single enantiomers of the α-hydroxy esters presently run into problems with variable racemisation of the products.

4-Aryl-2-hydroxytetronates, which show activity as mimics of non-steroidal antiinflammatory compounds, are difficult to synthesise in optically pure form by conventional means due to the facile

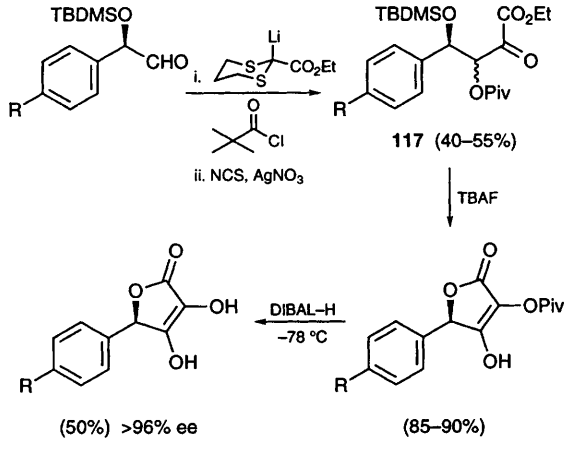


Scheme 90



Scheme 91

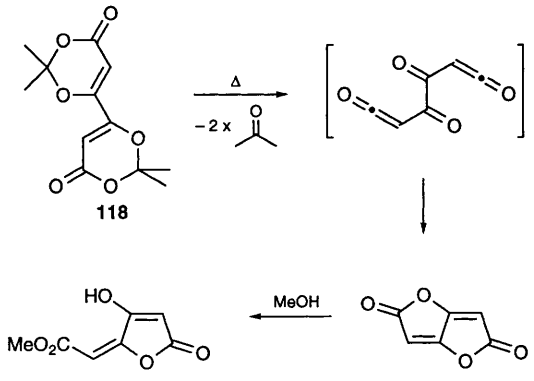
racemisation of the chiral centre. A route designed to overcome this uses pivalate protection to prevent the formation of easily racemised ketone tautomers adjacent to the stereocentre (**Scheme 92**).[97] An unexpected migration of the pivalate group is observed when the keto ester **117** is lactonised, which appears to occur post-cyclisation as other more labile protected keto esters suffer retro-aldol degradation under these conditions. The most reliable deprotection of the 2-pivaloyltetronate is by hydride reduction which again avoids the acid catalysed keto–enol tautomerism that facilitates racemisation.



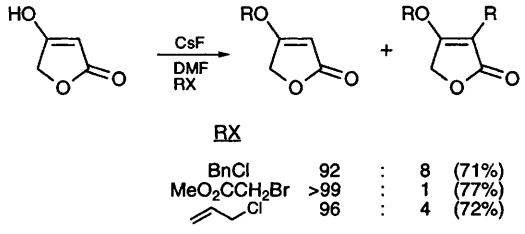
Scheme 92

The highly reactive ketipic acid dilactone[98] is formed from the pyrolysis of the masked oxalylbisketene **118** (**Scheme 93**). The dilactone is opened by nucleophiles to give the (*E*)-γ-alkylidenetetronic acids which show evidence of stabilisation by intramolecular hydrogen bonding. This nicely complements the selective synthesis of (*Z*)-γ-alkylidenetetronic acids from ketipic acid itself.

Finally, caesium fluoride in dimethylformamide is a new, mild and highly selective base for *O*-alkyl-



Scheme 93



Scheme 94

ation of tetronic acids (**Scheme 94**).[99] This system is not restricted to simple alkyl groups and is also effective for allylation, which is not possible with Mitsunobu conditions. Complete inversion of configuration is seen when a homochiral secondary mesylate is employed, although naturally the S_N2 reaction does not extend to tertiary or neopentyl halides. Both unsubstituted and substituted tetronates are converted with equal facility and the traces of *C*-alkylation products are readily removed by chromatography.

10 References

1 T. Ladduwahetty, *Contemp. Org. Synth.*, 1995, **2**, 133.
2 H. Schick, R. Ludwig, K. Kleiner and A. Kunath, *Tetrahedron*, 1995, **51**, 2939.
3 C. Wedler, A. Kunath and H. Schick, *J. Org. Chem.*, 1995, **60**, 758.
4 C. Wedler, A. Kunath and H. Schick, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2028.
5 R. Zemribo and D. Romo, *Tetrahedron Lett.*, 1995, **36**, 4159.
6 O. Dirat, T. Berranger and Y. Langlois, *Synlett*, 1995, 935.
7 W. R. Dolbier, Jr., R. Ocampo and R. Paredes, *J. Org. Chem.*, 1995, **60**, 5378.
8 W. Adam and V. O. Nava-Salgado, *J. Org. Chem.*, 1995, **60**, 578.
9 V. O. Nava-Salgado, E-M. Peters, K. Peters, H. G. von Schnering and W. Adam, *J. Org. Chem.*, 1995, **60**, 3879.
10 W. Oppolzer, R. N. Radinov and J. De Brabander, *Tetrahedron Lett.*, 1995, **36**, 2607.
11 J. Nokami, T. Taniguchi, S. Gomyo and T. Kakihara, *Chem. Lett.*, 1994, 1103.
12 M. Setoh, O. Yamada and K. Ogasawara, *Heterocycles*, 1995, **40**, 539.
13 I. Ryu, K. Nagahara, H. Yamazaki, S. Tsunoi and N. Sonoda, *Synlett*, 1994, 643.
14 M. Abe, T. Hayashikoshi and T. Kurata, *Chem. Lett.*, 1994, 1789.
15 T. Arencibia, J. A. Salazar and E. Suárez, *Tetrahedron Lett.*, 1994, **35**, 7463.
16 D. S. Stojanova and M. Hesse, *Helv. Chim. Acta*, 1995, **78**, 925.
17 S. D. Rychnovsky and K. Hwang, *J. Org. Chem.*, 1995, **59**, 5414.
18 I. Paterson, K.-S. Yeung, R. A. Ward, J. D. Smith, J. G. Cumming and S. Lamboley, *Tetrahedron*, 1995, **51**, 9467.
19 C. M. Rodriguez, T. Martin, M. A. Ramirez and V. S. Martin, *J. Org. Chem.*, 1994, **59**, 4461.
20 C. M. Rodriguez, T. Martin, M. A. Ramirez and V. S. Martin, *J. Org. Chem.*, 1994, **59**, 8081.
21 O. Menke, A. Garcia Martinez, L. R. Subramanian and M. Hanack, *Tetrahedron Lett.*, 1995, **36**, 4055.
22 J. Lee, J. J. Barchi, Jr., and V. E. Marquez, *Chem. Lett.*, 1995, 299.
23 M. B. M. de Azevedo and A. E. Greene, *J. Org. Chem.*, 1995, **60**, 4940.
24 T. Ohno, Y. Ishino, Y. Tsumagari and I. Nishiguchi, *J. Org. Chem.*, 1995, **60**, 458.
25 T. Inoue, O. Kitagawa, S. Kurumizawa, O. Ochiai and T. Taguchi, *Tetrahedron Lett.*, 1995, **36**, 1479.
26 J. Kang, J. W. Lee, J. I. Kim and C. Pyun, *Tetrahedron Lett.*, 1995, **36**, 4265.
27 M. J. Daley and G. Procter, *Tetrahedron Lett.*, 1995, **36**, 7549.
28 Y. L. Chow, Y.-J. Huang and V. Dragojlovic, *Can. J. Chem.*, 1995, **73**, 740.
29 J. D. Winkler, S. K. Bhattacharya, F. Liotta, R. A. Batey, G. D. Heffernan, D. E. Cladingboel and R. C. Kelly, *Tetrahedron Lett.*, 1995, **36**, 2211.
30 I. Isaac, I. Stasik, D. Beaupère and R. Uzan, *Tetrahedron Lett.*, 1995, **36**, 383.
31 U. Nubbemeyer, *J. Org. Chem.*, 1995, **60**, 3773.
32 J.-P. Vionnet and P. Renaud, *Helv. Chim. Acta*, 1994, **77**, 1781.
33 H. Togo, T. Muraki and M. Yokoyama, *Tetrahedron Lett.*, 1995, **36**, 7089.
34 T. Itoh, H. Ohara and S. Emoto, *Tetrahedron Lett.*, 1995, **36**, 3531.
35 S. Velaquez, M. L. Jimeno, S. Huss, J. Balzarini and M.-J. Camarasa, *J. Org. Chem.*, 1994, **59**, 7661.
36 (a) M. P. Bertrand, R. Nouguier, A. Archavlis and A. Carrière, *Synlett*, 1994, 736; (b) M. P. Bertrand, R. Nouguier, A. Archavlis and A. Carrière, *Synlett*, 1995, 216.
37 M. Node, R. Kurosaki, K. Hosomi, T. Inoue, K. Nishide, T. Ohmori and K. Fuji, *Tetrahedron Lett.*, 1995, **36**, 99.
38 A. Pelter, R. S. Ward and N. P. Storer, *Tetrahedron*, 1994, **50**, 10829.
39 S. K. Taylor, R. F. Atkinson, E. P. Almli, M. D. Carr, T. J. Van Huis and M. R. Whittaker, *Tetrahedron: Asymmetry*, 1995, **6**, 157.
40 F. Theil, *Tetrahedron: Asymmetry*, 1995, **6**, 1693.
41 Y.-C. Pai, J.-M. Fang and S.-H. Wu, *J. Org. Chem.*, 1994, **59**, 6018.
42 J.-F. Huot, M. Muzard and C. Portella, *Synlett*, 1995, 247.
43 A.-M. Fernandez, M. Jacob, J. Gralak, Y. Al-Bayati, G. Plé and L. Duhamel, *Synlett*, 1995, 431.
44 K. Takase, H. Masuda, O. Kai, Y. Nishiyama, S. Sakaguchi and Y. Ishii, *Chem. Lett.*, 1995, 871.

45 C. Bolm and G. Schlingloff, *J. Chem. Soc., Chem. Commun.*, 1995, 1247.
46 H. Nemoto, T. Tanabe and K. Fukumoto, *Tetrahedron Lett.*, 1994, **35**, 6499.
47 K. Matsumoto, T. Ebata, K. Koseki, K. Okano, H. Kawakami and H. Matsushita, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 670.
48 J. Lee, J. Oh, S. Jin, J.-R. Choi, J. L. Atwood and J. K. Cha, *J. Org. Chem.*, 1994, **59**, 6955.
49 E. Marotta, B. Piombi, P. Righi and G. Rosini, *J. Org. Chem.*, 1994, **59**, 7526.
50 J. J. La Clair, P. T. Lansbury, B. Zhi and K. Hoogsteen, *J. Org. Chem.*, 1995, **60**, 4822.
51 A. Moricz, E. Gassman, S. Bienz and M. Hesse, *Helv. Chim. Acta*, 1995, **78**, 663.
52 K. Ishihara, N. Hanaki and H. Yashimoto, *J. Chem. Soc., Chem. Commun.*, 1995, 1117.
53 J. Das and S. Chandrasekaran, *Tetrahedron*, 1994, **50**, 11709.
54 B. Simonot and G. Rousseau, *J. Org. Chem.*, 1994, **59**, 5912.
55 F. O. H. Pirrung, H. Hiemstra, W. N. Speckamp, B. Kaptein and H. E. Schoemaker, *Tetrahedron*, 1994, **50**, 12415.
56 F. O. H. Pirrung, H. Hiemstra, W. N. Speckamp, B. Kaptein and H. E. Schoemaker, *Synthesis*, 1995, 458.
57 R. Gagnon, G. Grogan, M. S. Levitt. S. M. Roberts, P. W. H. Wan and A. J. Willets, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2537.
58 B. Adger, M. T. Bes, G. Grogan, R. McCague, S. Pedragosa-Moreau, S. M. Roberts, R. Villa, P. W. H. Wan and A. J. Willets, *J. Chem. Soc., Chem. Commun.*, 1995, 1563.
59 R. Gagnon, G. Grogan, E. Groussain, S. Pedragosa-Moreau, P. F. Richardson, S. M. Roberts, A. J. Willets, V. Alphand, J. Lebreton and R. Furstoss, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2527.
60 T. Inokuchi, M. Kanazaki, T. Sugimoto and S. Torii, *Synlett*, 1994, 1037.
61 S. Tsunoi, I. Ryu, Y. Tamura, S. Yamasaki and N. Sonoda, *Synlett*, 1994, 1009.
62 T. Imamoto, T. Hatajima and T. Yoshizawa, *Tetrahedron Lett.*, 1994, **35**, 7805.
63 J. L. Garcia Ruano, A. Fuerte and M. C. Maestro, *Tetrahedron: Asymmetry*, 1994, **5**, 1443.
64 F. G. West, C. M. Amann and P. V. Fisher, *Tetrahedron Lett.*, 1994, **35**, 9653.
65 S. H. Jung, Y. S. Lee, H. Park and D.-S. Kwon, *Tetrahedron Lett.*, 1995, **36**, 1051.
66 K. J. Henry, Jr, and B. Fraser-Reid, *J. Org. Chem.*, 1994, **59**, 5128.
67 J. M. Roe and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1995, 359.
68 A. Kumar and D. C. Dittmer, *J. Org. Chem.*, 1994, **59**, 4760.
69 C. M. Marson, L. Randall and M. J. Winter, *Tetrahedron Lett.*, 1994, **35**, 6717.
70 K. Nishitani, Y. Harada, Y. Nakamura, K. Yokoo and K. Yamakawa, *Tetrahedron Lett.*, 1994, **35**, 7809.
71 R. Tiedmann, F. Narjes and E. Schaumann, *Synlett*, 1994, 594.
72 T. Kitazume and M. Takeda, *J. Chem. Soc., Chem. Commun.*, 1995, 39.
73 J. Das, P. K. Choudhury and S. Chandrasekaran, *Tetrahedron*, 1995, **51**, 3389.
74 N. Akane, T. Hatano, H. Kusui, Y. Nishiyama and Y. Ishii, *J. Org. Chem.*, 1994, **59**, 7902.
75 M. P. Doyle and A. B. Dyatkin, *J. Org. Chem.*, 1995, **60**, 3035.
76 G. Chelucci and A. Saba, *Tetrahedron Lett.*, 1995, **36**, 4673.
77 K. Chibale and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2411.
78 K. Takeda, I. Imaoka and E. Yoshii, *Tetrahedron*, 1994, **50**, 10839.
79 L. Lorenc, L. Bondarenko-Gheorghiu, N. Krstic, H. Fuhrer, J. Kalvoda and M. L. Mihailovic, *Helv. Chim. Acta*, 1995, **78**, 891.
80 G. T. Crisp and A. G. Meyer, *Tetrahedron*, 1995, **51**, 5831.
81 N. Ferret, L. Mussate-Mathieu, J.-P. Zahra and B. Waegell, *J. Chem. Soc., Chem. Commun.*, 1994, 2589.
82 F. Bellina, A. Carpita, M. De Santis and R. Rossi, *Tetrahedron*, 1994, **50**, 12029.
83 J. Ji, C. Zhang and X. Lu, *J. Org. Chem.*, 1995, **60**, 1160.
84 G. Zhu and X. Lu, *Tetrahedron: Asymmetry*, 1995, **6**, 345.
85 S. D. Mawson, A. Routledge and R. T. Weavers, *Tetrahedron*, 1995, **51**, 4665.
86 H. Urabe, K. Kobayashi and F. Sato, *J. Chem. Soc., Chem. Commun.*, 1995, 1043.
87 C. Kuroda and N. Mitsumata, *Chem. Lett.*, 1994, 1375.
88 O. Piva, *Tetrahedron*, 1994, **50**, 13687.
89 P. Bonete and C. Nájera, *Tetrahedron*, 1995, **51**, 2763.
90 A. Kasatkin, S. Okamoto and F. Sato, *Tetrahedron Lett.*, 1995, **36**, 6075.
91 N. W. A. Geraghty and P. A. Murphy, *Tetrahedron Lett.*, 1994, **35**, 6737.
92 J. L. Dillon and Q. Gao, *J. Org. Chem.*, 1994, **59**, 6868.
93 H. Takahata, Y. Uchida and T. Momose, *J. Org. Chem.*, 1995, **60**, 5628.
94 A. D. Reed and L. S. Hegedus, *J. Org. Chem.*, 1995, **60**, 3787.
95 A. Pelter, R. S. Ward and A. Sirit, *Tetrahedron: Asymmetry*, 1994, **5**, 1745.
96 R. Schobert, S. Müller and H.-J. Bestmann, *Synlett*, 1995, 425.
97 A. T. Hopper and D. T. Witiak, *J. Org. Chem.*, 1995, **60**, 3334.
98 H.-D. Stachel, M. Jungkenn, C. Koser-Gnoss, H. Poschenrieder and J. Redlin, *Liebigs Ann. Chem.*, 1994, 961.
99 T. Sato, K. Yoshimatsu and J. Otera, *Synlett*, 1995, 843.