Saturated and unsaturated lactones

Ian Collins

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

REVIEW PERKIN 1

Covering: 1 November 1996 to 31 October 1997
Previous review: *Contemp. Org. Synth.*, 1997, 4, 281

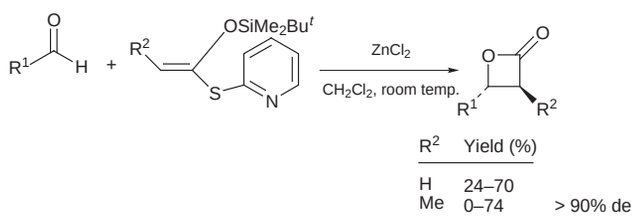
1 Introduction

This review aims to collate and summarise recent work on the synthesis of lactones, emphasising new strategies for the selective and practical construction of these molecules. Full reports following on from communications that have been mentioned in previous articles in this series are not included here unless significant new details have been disclosed. The material is classified by the structure of the lactone products, but this distinction can be somewhat arbitrary for more general methodologies and this is noted in the text.

Whilst the chemistry applied to the synthesis of lactones is very varied, there are some areas which have been especially productive: ring-closing metathesis has emerged as a general tool for macrolide construction, particularly in the elegant syntheses of the cytotoxic epothilones. Challenges remain, however, in understanding and controlling the stereoselectivity of the metathesis olefin formation and the effects of neighbouring substituents. New methods, including ring-closing metathesis, have appeared that offer alternative solutions to the problems of preparing medium-ring lactones. One such reaction, based on π-allyl palladium complex formation, illustrates the ever increasing importance of palladium catalysis in lactone synthesis, and new or improved approaches to saturated and unsaturated butyrolactones have appeared, also based on palladium chemistry. Several make use of the carbonylation reaction to incorporate carbon monoxide as the lactone carbonyl, where there is still scope for finding conditions that avoid high gas pressures. Perhaps not so generally applicable at present, but an important topic for further research, have been the cyclisations based on the insertion reactions of metal carbenoids, which have delivered routes to small, medium and large-ring lactones and may prove valuable for preparing polycyclic systems.

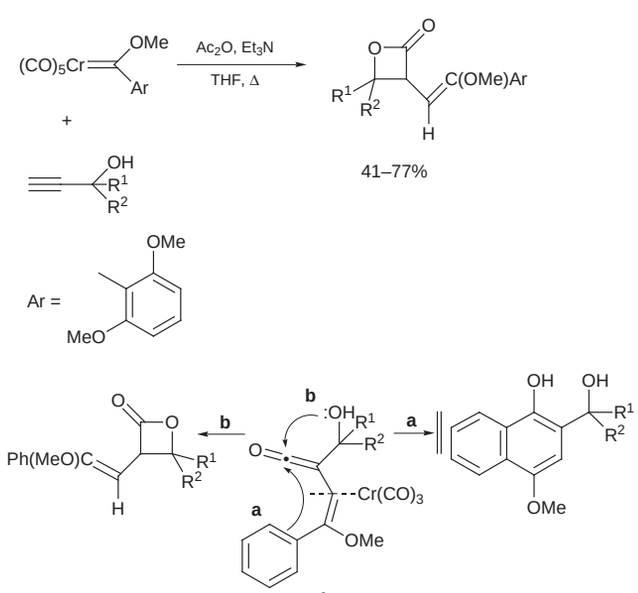
2 β-Lactones

A mild and highly diastereoselective synthesis of β-lactones by tandem aldol-lactonisation has been developed,[1] building on the recently reported work of Danheiser and Schick in this area. Terminally substituted ketene menothioacetals underwent Mukaiyama aldol condensations with aldehydes in the presence of zinc chloride at room temperature to yield almost exclusively the *trans* 3,4-disubstituted β-lactones (**Scheme 1**). The reaction was limited to sterically unencumbered saturated aldehydes since with aromatic aldehydes no β-lactones were isolated due to decomposition to olefinic products, whilst bulky aldehydes only reacted with terminally unsubstituted ketene monothioacetals. The methodology was applied to a synthesis of the pancreatic lipase inhibitor (−)-panclicin D.



Scheme 1

The observation of an unexpected side reaction in the Dötz annulation reaction led Kerr and co-workers to a new synthesis of β-lactones from propargylic alcohols, mediated by chromium carbenes[2] (**Scheme 2**). Lactone formation was postulated to arise from the diversion of the Dötz intermediate **1** from the usual electrocyclic ring closure (**path a**) towards intramolecular attack by the hydroxy group onto the ketene (**path b**). Supporting this analysis, the introduction of blocking substituents into the 2- and 6-positions of the carbene aryl substituent increased

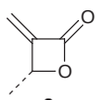


1

Scheme 2

the yield of the lactone products. A significant increase in yield was also seen with *gem*-dialkyl substitution of the alcohol, consistent with the expected Thorpe–Ingold effect.

A commercially available *Candida antarctica* lipase has been shown to give excellent optical purities in the kinetic resolution of α-methylene-β-lactones such as **2** by asymmetric transesterification.[3]



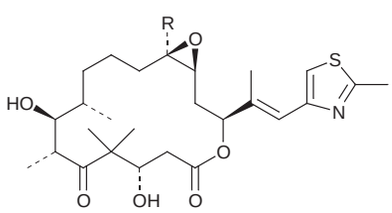
2

99% ee at 51% conversion

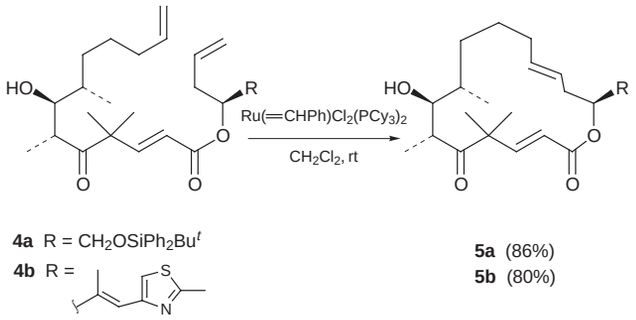
3 Macrolides

A great deal of productive synthetic effort has been expended over past months on the synthesis of the cytotoxic epothilones. This has been driven in particular by the recognition that these comparatively simple compounds exert their biological activity by the stabilisation of microtubules in a fashion similar to paclitaxel (Taxol®). Several strategies have led to successful total syntheses in this area, and have enabled the instigation of detailed studies into structure–activity relationships. Much elegant chemistry has been applied to the assembly of the epothilone skeleton, but this review will concentrate on the ring-closure techniques demonstrated.

Straightforward macrolactonisation has been applied by Nicolaou and co-workers to epothilone A **3a** and epothilone B **3b**.[4–6] In both cases, Yamaguchi conditions were employed on a protected seco-acid where the C12–C13 epoxide was masked as a (*Z*)-alkene, leading to high yields of the macrocycles (**3a**, 90%; **3b**, 77%). Importantly for later studies in this field, the analogous seco-acid containing an (*E*)-alkene also cyclised efficiently under these conditions.[5,6] Danishefsky and co-workers have applied the Keck macrolactonisation procedure in the synthesis of 8-desmethylepothilone A.[7]



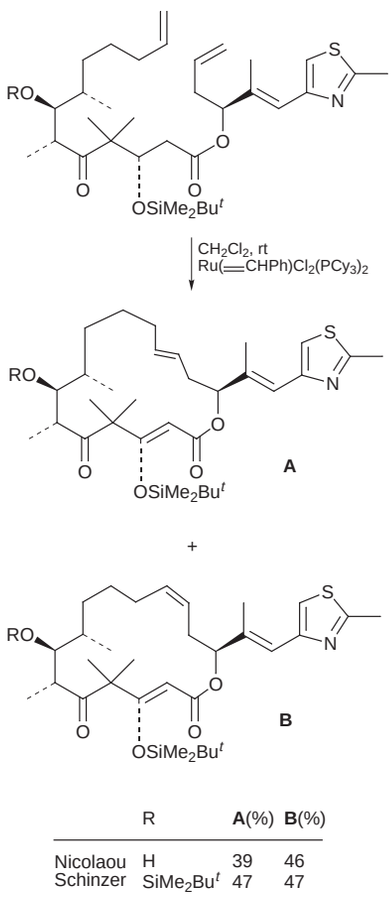
3a R = H epothilone A
3b R = Me epothilone B



4a R = $CH_2OSiPh_2Bu^t$
4b R =

5a (86%)
5b (80%)

Scheme 3



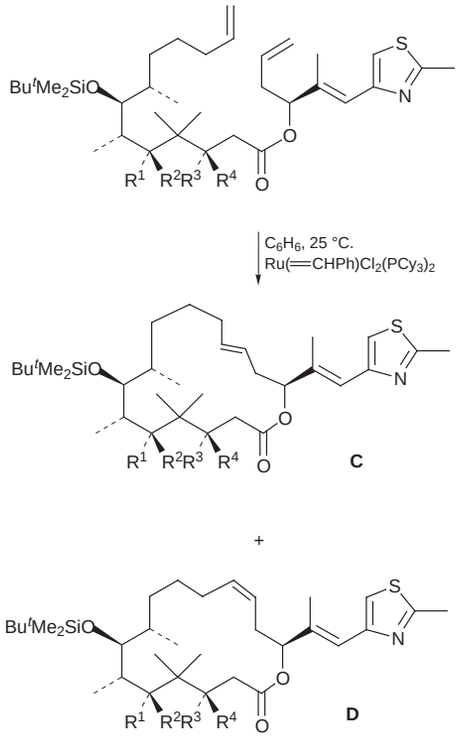
	R	A(%)	B(%)
Nicolaou	H	39	46
Schinzer	$SiMe_2Bu^t$	47	47

Scheme 4

Of perhaps more general synthetic interest have been the approaches to the macrocycles based on ring-closing metathesis. Nicolaou and co-workers have applied this strategy to the preparation of epothilone A and various analogues differing in the relative stereochemistry of the substituents.[6,8–10] Note that the equal facility of formation of the (*E*)-alkene containing macrocycles in the classical cyclisations was translated to a preference for (*E*)-alkene formation in many of the compounds studied. For example, the model systems **4a** and **4b** gave exclusively the *trans* olefins in high yield when treated with Grubbs' ruthenium catalyst (**Scheme 3**). The geometry of the olefinic product **5a** was optimistically misassigned as the desired *cis* compound in the original communication,[8] but fortunately the cyclisation of the direct precursor to epothilone A was unselective and both *cis* and *trans* products could be isolated[9,10] (**Scheme 4**). The analogous ring-closing metathesis in Schinzer *et al.*'s synthesis of epothilone A, where the substrate differed only in the protection of the C7 alcohol, also generated an unselective mixture of alkenes.[11] The investigations by Danishefsky and co-workers into related reactions have indicated a strong dependence of the geometry of the ring-closure on the functionality and stereochemistry at remote centres[12] (**Scheme 5**), although a general preference for (*E*)-alkene formation was again evident. This point was also illustrated in a recent synthesis of a simple 16-membered lactone model of the epothilones.[13]

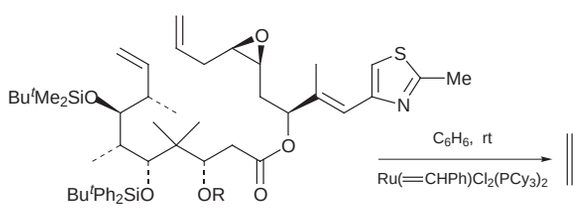
In a parallel development in the Danishefsky group, attempted ring-closure at a different point on the macrocyclic backbone was completely unsuccessful (**Scheme 6**). The failure was attributed to the presence of a large number of substituents immediately adjacent to the ring-closure site, since unfunctionalised model systems cyclised smoothly.[14] Perhaps suprisingly, in view of this tendency for substituents close to the ring-closure site to disfavour reaction, the more substituted dialkene **6** did cyclise to give both *cis* and *trans* precursors to epothilone B when treated with the Schrock molybdenum catalyst (**Scheme 7**).

Poor selectivity notwithstanding, the ring-closing metathesis approach adopted by Nicolaou and co-workers has proved very amenable to solid phase, combinatorial synthesis[6,15] (**Scheme 8**). The combinatorial fragments were loaded onto the resin by sequential Wittig, aldol and acylation reactions. Ring-closing



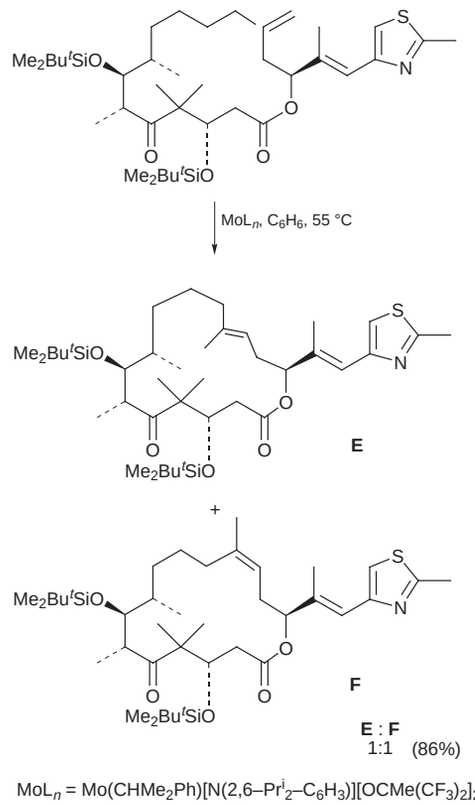
R^1	R^2	R^3	R^3	**C** : **D**	Yield(%)
$OSiPh_2Bu^t$	H	H	OH	9:1	81
$OSiPh_2Bu^t$	H	OH	H	3:1	86
–O–		H	$OSiBu^tMe_2$	2:1	88
–O–		$OSiBu^tMe_2$	H	1:1.7	86

Scheme 5



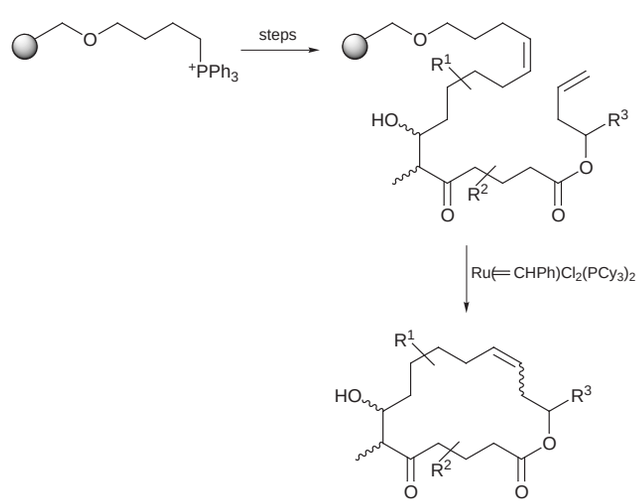
R = H or $SiMe_2Bu^t$

Scheme 6



MoL$_n$ = Mo(CHMe$_2$Ph)[N(2,6–Pr$^i_2$–C$_6$H$_3$)][OCMe(CF$_3$)$_2$]$_2$

Scheme 7



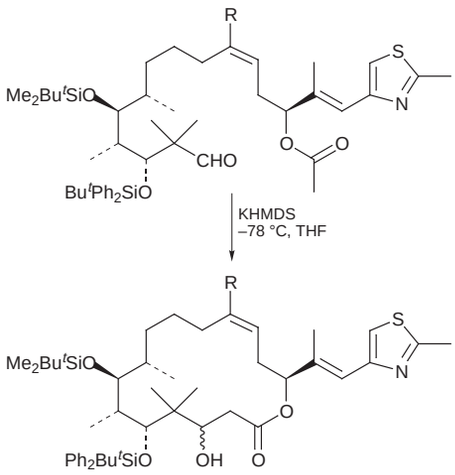
Scheme 8

metathesis formed the macrocycles and cleaved the products from the resin in a traceless manner, after which further manipulation or separation of the isomers was possible in the solution phase. Using this methodology, and the approach described below, significant insights into the structure–activity relationships of these compounds have been gained in a short time.[15,16]

Danishefsky and co-workers have also thoroughly investigated a completely different strategy for epothilone synthesis, centred on a macro-aldolisation reaction.[14,16–18] As with the macrolactonisation route, this methodology was equally applicable to both epothilones A and B (**Scheme 9**). In the former case, good stereoselectivity was seen in the cyclisation provided the reaction was quenched at high temperature (≥0 °C), suggesting that equilibration to the desired epimer may have made a significant contribution to the selectivity.

In the context of other macrocyclic chemistry, the current limitations of ring-closing metathesis as a general synthetic procedure have been pointed out by Fürstner and Langemann.[19] It appears that polar functional groups in the precursors are required for efficient reaction, implying coordination of the metal centre during metathesis. This relay process provides some explanation for the remote stereocontrol exerted by substituents in the acyclic starting materials (*cf.* Scheme 5), but as yet the model is far from predictive. In the formation of several simple 13–21-membered lactones with Grubbs' catalyst, a general preference for *trans* olefin formation was observed. The same authors have also postulated that the failure of some precursors to cyclise may be the result of stable, non-productive chelates between the metal carbenoid and polar groups in the chain. In a synthesis of (−)-gleosporone, the addition of a mild Lewis acid to disrupt the proposed chelate **8** promoted cyclisation of the recalcitrant substrate **7** which was otherwise resistant to reaction[20] (**Scheme 10**).

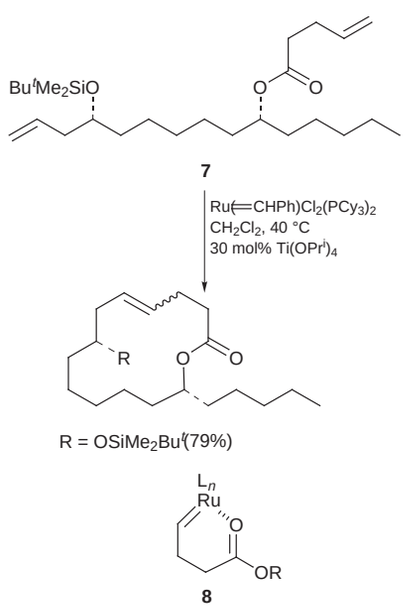
The Stille cross-coupling reaction continues to be a useful method of macrolide preparation. An ambitious example was seen in the mild, palladium-free, double Stille coupling employed by Paterson and Man in the synthesis of the core of the antibiotic elaiophylin.[21] Copper(I) thiophene-2-carboxylate, recently introduced by Liebeskind, was used to promote the coupling, giving the cyclodimerisation product in good yield



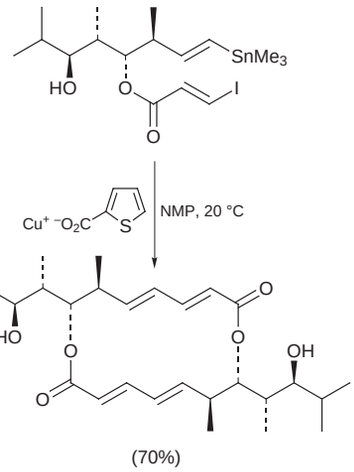
G α–OH **H** β–OH

R	**G** : **H**
H	6:1 (51%)
Me	2.1:1 (60%)

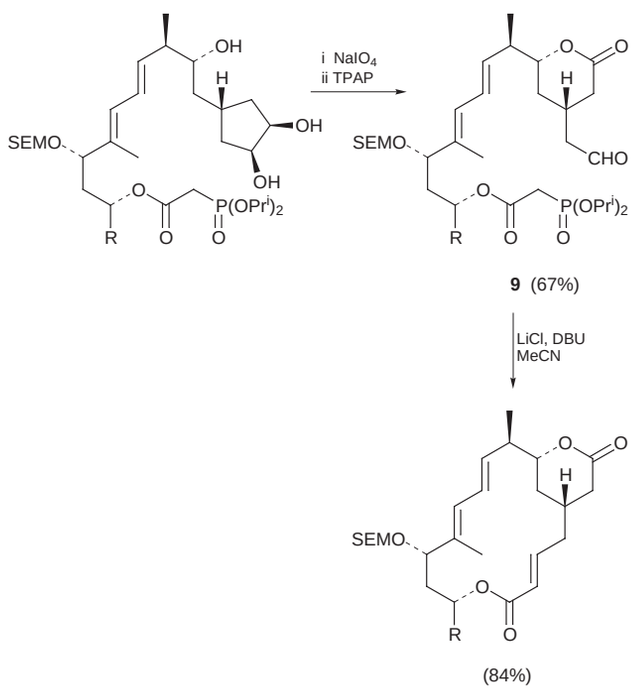
Scheme 9



Scheme 10



Scheme 11



Scheme 12

under high dilution conditions (**Scheme 11**). More conventional palladium-mediated Stille couplings have been used by Smith and co-workers in recently reported syntheses of (−)-macrolactin A[22] and (−)-rapamycin.[23] The latter cyclisation was only successful using the Farina–Scott catalyst, $[(2\text{-furyl})_3P]PdCl_2$. Farina conditions [$Pd^0$, Ph_3As] also featured in the cyclisation of the bis-lactone core of pateamine achieved by Critcher and Pattenden.[24]

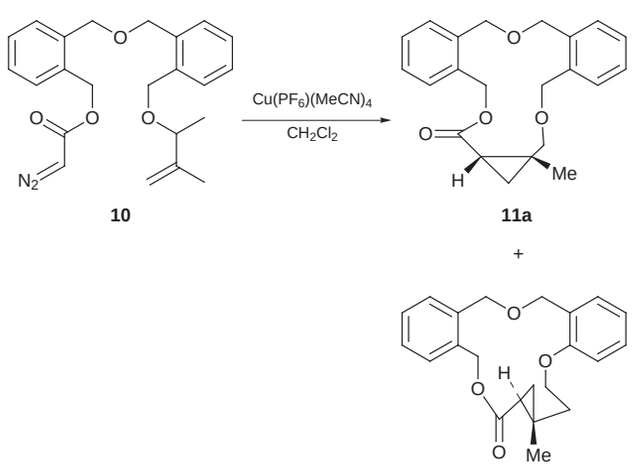
The Horner–Wadsworth–Emmons condensation has also found considerable utility in macrolide synthesis, as shown in a synthesis of the antimitotic agent rhizoxin D[25] (**Scheme 12**). Cyclisation of the phosphonate **9** at high dilution required strictly anhydrous conditions to prevent hydrolysis of the δ-lactone ring. This synthesis also featured masking of the lactone-aldehyde functionality in **9** as a cyclic vicinal diol. Cyclisation by Horner–Wadsworth–Emmons reaction formed a key part of the recent synthesis of the polyene macrolide roflamycoin.[26]

Catalytic intramolecular carbene insertions have already proved a powerful tool for small-ring lactone syntheses and are now emerging as a method for macrocycle and medium-ring formation. Doyle *et al*. have investigated the effect of catalyst and alkene substitution on the intramolecular cyclopropanation of remote olefins[27] (**Scheme 13**). Both rhodium(II) and copper(I) catalysts effected macrocyclisation of the diazoacetate **10** to the isomeric cyclopropanes **11a** and **11b**. Larger rings and 10-membered lactones were also formed by this procedure. The outcomes were consistent with initial π-complex formation between the electrophilic carbenoid and the electron-rich alkene, which offsets the intrinsic entropic barrier to macrocyclisation. As observed with the analogous ring-closing metatheses, there was only moderate stereoselectivity in the cyclopropanation in many cases, but the good yields achieved without high dilution conditions make this a promising new technique.

4 γ-Lactones

4.1 Monocyclic γ-lactones

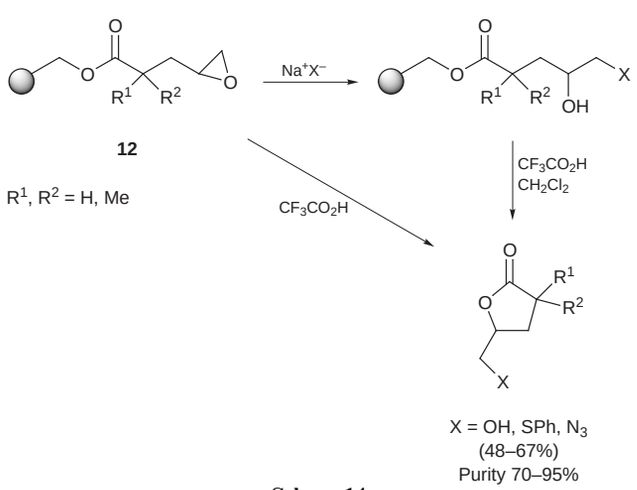
Lactones are attractive targets for solid phase synthesis, affording the opportunity to combine the cyclisation and resin cleavage steps to provide a 'traceless' synthesis. This has been exemplified in a simple preparation of substituted γ-lactones



10 **11a** + **11b**

(64%) **11a** : **11b** 4:1

Scheme 13

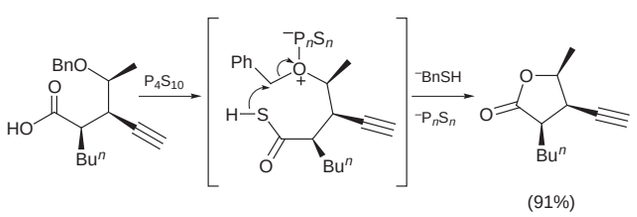


12

Scheme 14

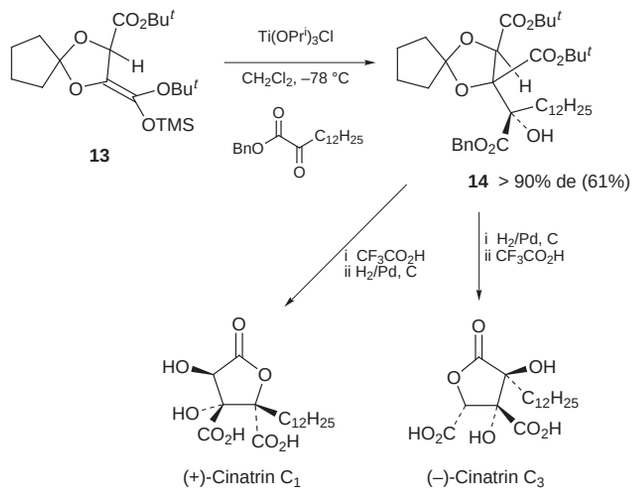
via a resin bound epoxide **12**[28] (**Scheme 14**). Azide or thiolate anions were used to open the epoxide prior to lactonisation-cleavage, giving the lactones in good yield and purity.

An interesting new deprotection-lactonisation strategy was developed for the synthesis of phaseolinic acid[29] and blastmycinolactol.[30] The deprotection of benzyl ethers with P_4S_{10} is not a general reaction, but was very efficient when a carboxylic acid was present to allow intramolecular S_N2 attack of the intermediate thioacid on the activated ether (**Scheme 15**). Other deprotection sequences proved too harsh for the sensitive alkyne in this system.



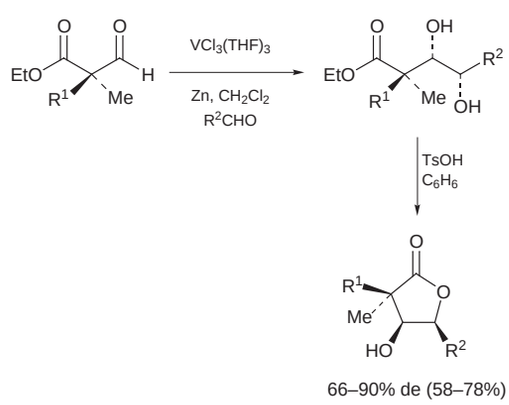
Scheme 15

Several reports have appeared dealing with the synthesis of oxygenated γ-lactones. Evans *et al.* have extended the titanium-mediated aldol chemistry used in the synthesis of zaragozic acid to give an elegant route to the phospholipase A_2 inhibitors cinatrin C_1 and C_3 from a common intermediate **14**[31] (**Scheme 16**). The stereochemical course of the aldol reaction, which was generally applicable to aldehydes, ketones and α-ketoesters, was consistent with the formation of a titanium enolate from the silylketene acetal **13** and reaction through Zimmerman–Traxler type transition states. More conventional Evans techniques have been applied to the synthesis of blastmycinone **15** and related compounds using the asymmetric boron-mediated aldol condensation of acylated oxazolidinones with homochiral α-alkoxyaldehydes.[32] Oxygenated γ-lactones have also been prepared by diastereoselective pinacol cross-coupling reactions, where chelation of the β-ester-aldehyde provided the source of the diastereofacial discrimination observed[33] (**Scheme 17**).

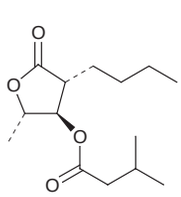


13 **14** > 90% de (61%)

Scheme 16

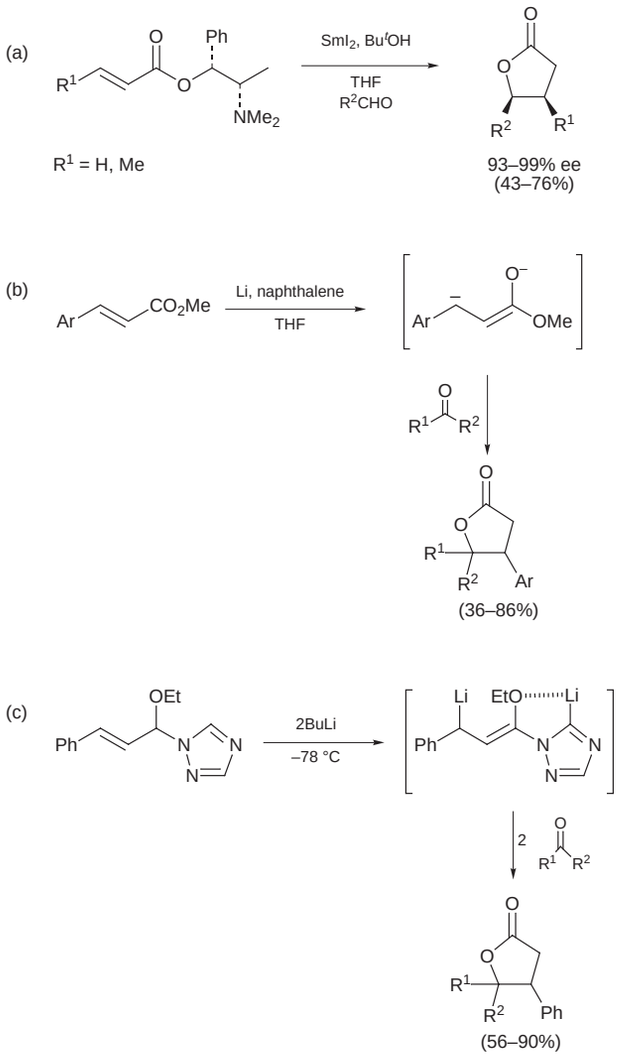


Scheme 17

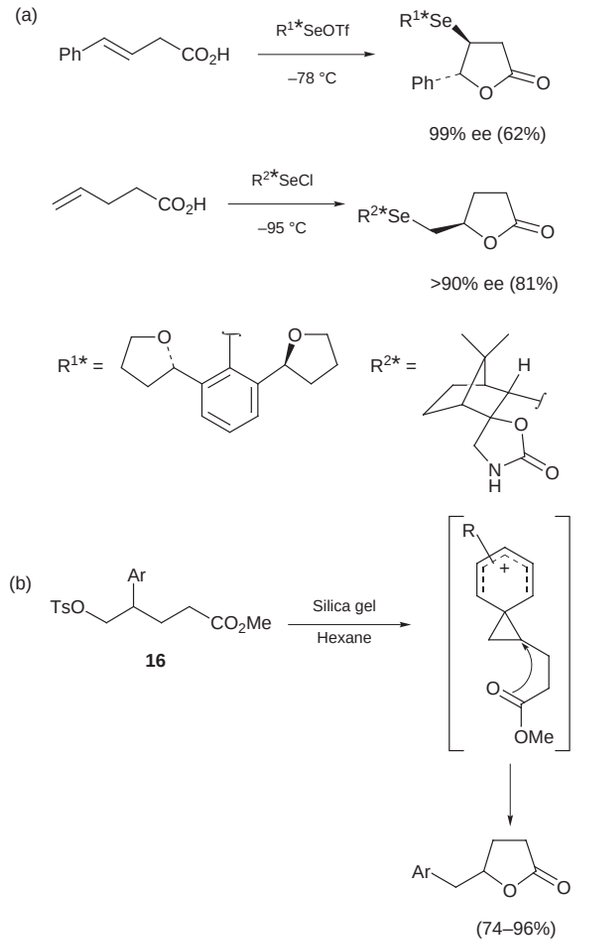


15

The coupling of α,β-unsaturated esters with aldehydes or ketones is a well established means of γ-lactone synthesis and three new variants have been reported. In the first, *N*-methylephedrine served as a chiral auxiliary in the samarium(II) mediated reaction, giving excellent asymmetric induction with moderate to good chemical yields[34] (**Scheme 18a**). In the second, stabilised homoenolate dianions were generated from β-aryl acrylates by sequential single electron transfers from lithium metal.[35] Condensation with ketones then gave the lactones (**Scheme 18b**). Thirdly, Katritzky *et al.* achieved the same construction using allylic anions stabilised by a lithiated 1,2,4-triazole as the homoenolate equivalent[36] (**Scheme 18c**). In most cases, two equivalents of the carbonyl compound were consumed since both lithiation sites of the dianion reacted. The reaction has been adapted to the synthesis of spirolactones and butenolides (*cf.* Scheme 78a).



Scheme 18



Scheme 19

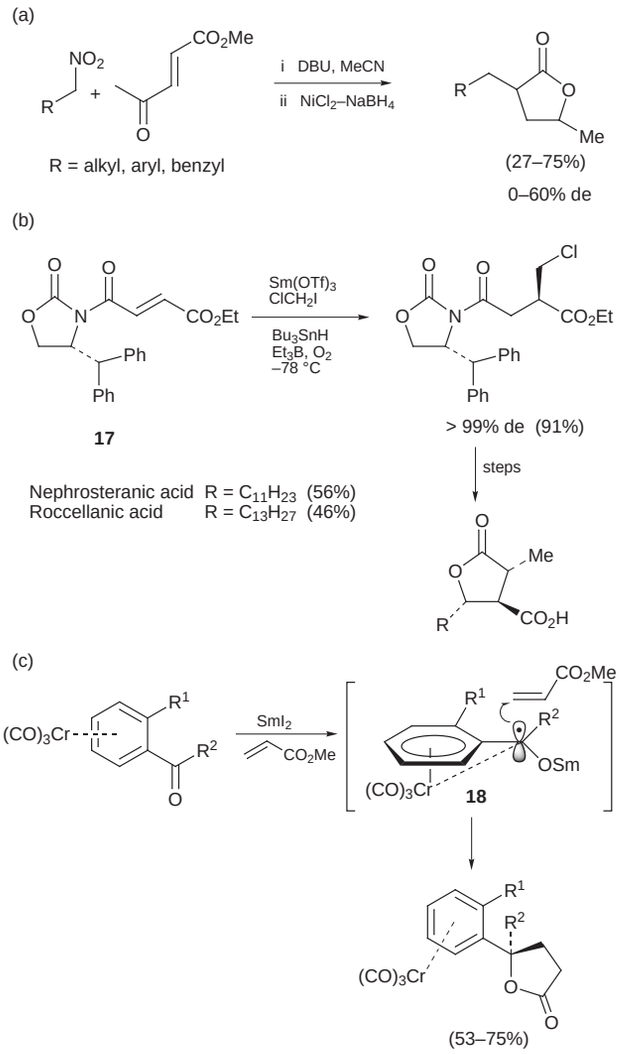
The direct electrophilic cyclisation of but-3-enoates and pent-4-enoates remains a fruitful area of research. Two reports concerning new chiral selenium electrophiles have appeared,[37,38] both of which offered high enantioselectivities (**Scheme 19a**). In a related process, phenonium ions generated by the acid promoted elimination of the tosylate **16** were found to lead to lactonisation with concomitant aryl migration[39] (**Scheme 19b**). Although high yielding, the reaction was slow (>2 days) unless the aryl group carried two activating alkoxy substituents, and did not proceed at all for the unsubstituted phenyl group.

A number of communications have dealt with the construction of the γ-lactone carbon skeleton through Michael additions. A wide range of substituted nitroalkanes were found to add regiospecifically in good yield to commercially available (*E*)-4-oxopent-2-enoate[40] (**Scheme 20a**). The resulting enones were doubly reduced at the enone olefin and the remote ketone to afford α-substituted-γ-lactones. A moderate selectivity (typically 30% de) for formation of the *trans* substituted lactones was observed. A Lewis acid mediated, asymmetric radical Michael addition formed the basis of a synthesis of (−)-nephrosteranic and (−)-roccellanic acids.[41] An Evans' oxazolidinone auxiliary served to control both the diastereofacial sense of the radical addition to the fumarate **17** and a subsequent boron-mediated aldol reaction (**Scheme 20b**). Stoichiometric amounts of chelating lanthanide Lewis acids gave optimal regio- and stereo-selectivity in the radical reaction. In the samarium(II) mediated Michael addition of ketyl radicals to acrylates, enantioselectivity was achieved by conformational stabilisation of the radical intermediate **18** by an attached arene(tricarbonyl)chromium group[42] (**Scheme 20c**). The tricarbonylchromium complexes were oxidised to the free aryl-substituted lactones with molecular iodine (87–92%).

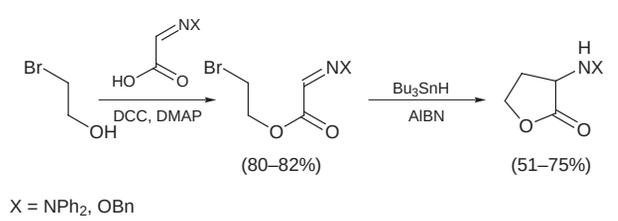
γ-Lactones bearing an α-nitrogen substituent have been rapidly assembled by radical 5-*exo*-*trig* ring closure onto diphenylhydrazones and oxime ethers[43] (**Scheme 21**). Unfortunately, the stereoselectivity of the radical reaction with more substituted alcohol components was poor, although bicyclic γ-lactones and δ-lactones were accessible in equally high yields.

Fluorination of organic compounds can lead to useful changes in physical and biological properties, and two routes to trifluoromethylated γ-lactones have appeared, the first based on sequential Ireland–Claisen rearrangement and iodolactonisation[44] (**Scheme 22**). Whereas iodolactonisation of the related α-hydroxy acid was completely unsuccessful, the protected *syn*-disubstituted acid **19** cyclised in good yield to a single product under Bartlett's conditions. Osmylation of the precursor **19** also led to a single lactone product. Interestingly, the cyclisations of the analogous *anti* material were less selective under both protocols (*ca*. 70% de). α-Fluoro-α-trifluoromethylated-γ-lactones have been prepared from an unexpected reaction of hexafluoropropene–diethylamine adduct which, instead of simply fluorinating the 3-hydroxyalk-1-enyl sulfones **20**, gave lactone products stereospecifically[45] (**Scheme 23**). A mechanism has been proposed involving initial formation of the (*E*,*E*)-enamine **21**, which can undergo intramolecular Michael attack on the vinyl sulfone.

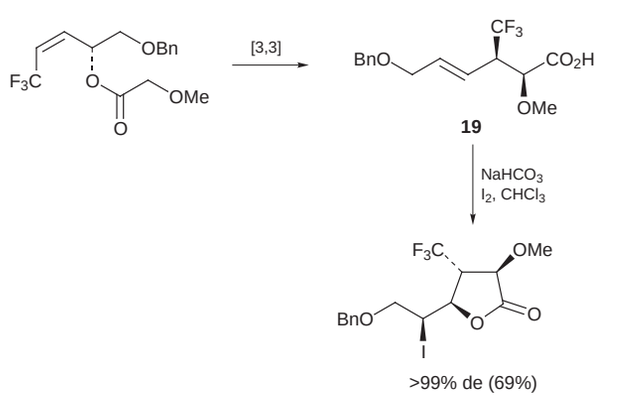
Butyrolactones have been prepared by the oxidation of 2-(tributylstannyl)tetrahydrofuran derivatives with ozone.[46] The mild conditions were compatible with free hydroxy groups, esters, ketones and acetonides (**Scheme 24a**). The hemiacetals **22**, which were obtained from the conjugate addition of cuprates to enones, have also been oxidised to γ-lactones, using



Scheme 20



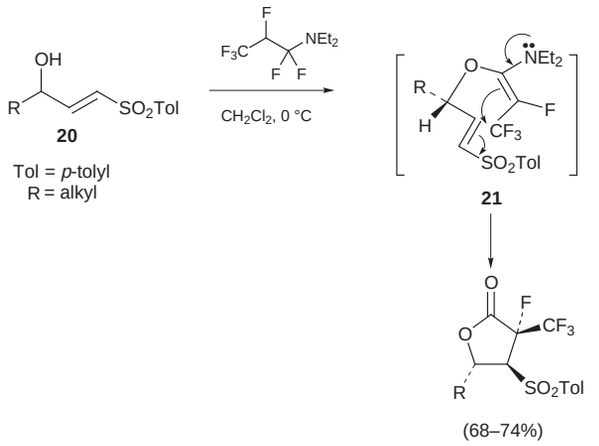
Scheme 21



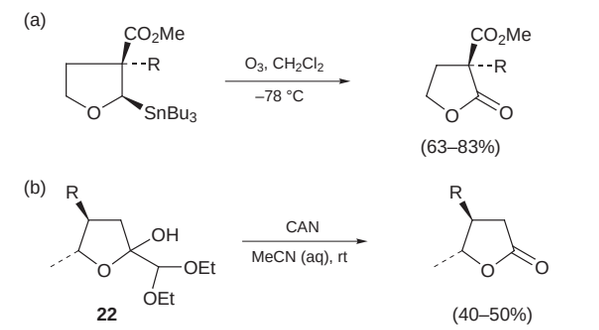
Scheme 22

cerium(IV) ammonium nitrate to effect cleavage of the pendant diethyl acetal[47] (**Scheme 24b**).

Earlier work by Brunner and Alper on the palladium

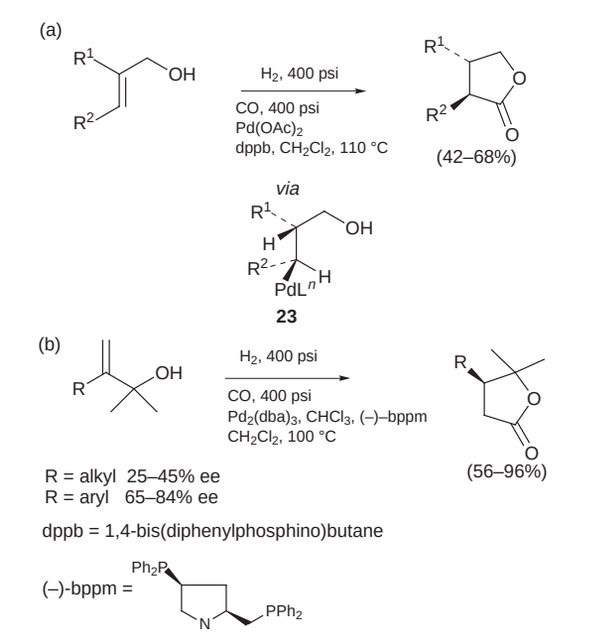


Scheme 23



Scheme 24

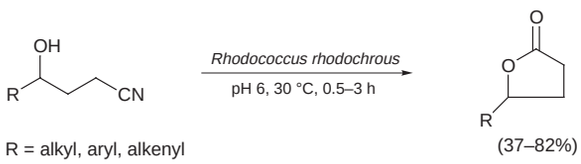
catalysed cyclocarbonylation of allylic alcohols has been followed with a highly stereoselective synthesis of *trans*-α,β-disubstituted γ-lactones[48] (**Scheme 25a**). The reaction was highly catalyst, solvent and temperature dependent and required high gas pressures. The presence of hydrogen in the reaction mixture was obligatory, suggesting a mechanism involving initial palladium hydride formation and addition to the alkene to generate **23** prior to carbonylation. By using a chiral bisphosphine ligand, an asymmetric version of the reaction was explored.[49] Again, the process was highly catalyst, solvent and temperature dependent, but good yields were obtained under optimised conditions (**Scheme 25b**). The lactones arising from aryl substituted allylic alcohols had con-



Scheme 25

sistently higher optical purities than those derived from alkyl substituted starting materials. Preliminary investigations into the mechanism suggested that the hydridopalladation was unselective and reversible, with enantioselectivity arising from the preferred ring closure of one of the diastereomeric acylpalladium species. In a similar vein, the asymmetric hydroformylation of allylic alcohols with catalytic rhodium(I) and chiral bisphosphines derived from BINAP has been described,[50] but yields and optical purities were generally lower than the palladium mediated process.

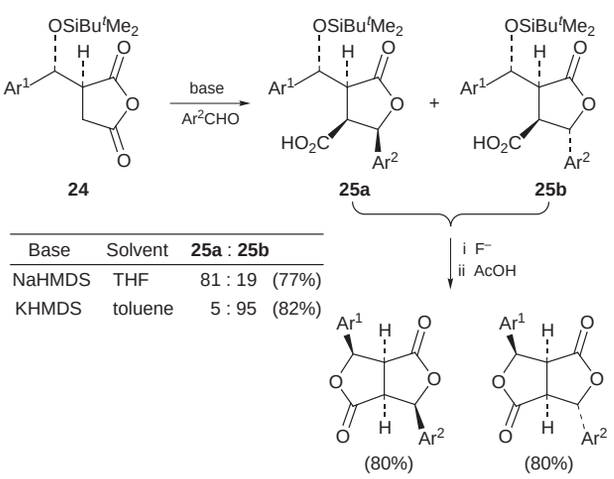
The direct synthesis of γ-lactones from γ-hydroxynitriles by a whole-cell, microbial hydrolysis has been reported[51] (**Scheme 26**). The mild and rapid conditions of the hydrolysis may make this method suitable for sensitive substrates, although the scope of the system has not yet been defined.



Scheme 26

4.2 Bicyclic and polycyclic γ-lactones

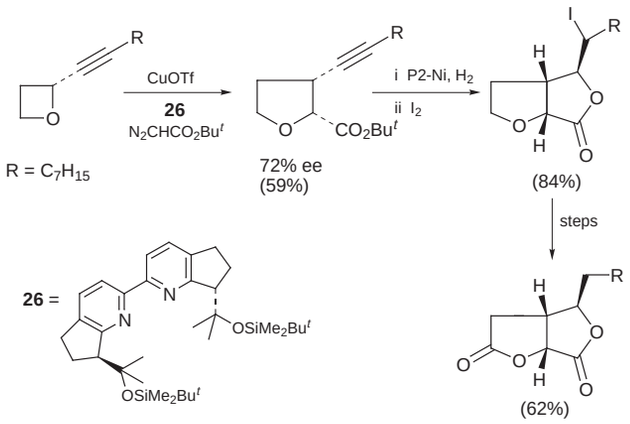
A simple and divergent route to bislactone lignans has been published, where an aldol reaction of the anhydride **24** was used to construct the carbon skeleton[52] (**Scheme 27**). Both *syn* and *anti* aldol products **25a** and **25b** could be obtained by changing the base in the condensation reaction, but the reaction was only successful when deprotonation was carried out in the presence of the aldehyde. Bislactones have also been prepared through the combination of an enantioselective oxetane ring expansion and a diastereoselective iodolactonisation[53] (**Scheme 28**). Carbene insertion into the oxetane, catalysed by the copper(I) complex of the bispyridine **26**, occurred with moderate enantioselectivity. Fortunately, the subsequent iodolactonisation was highly selective and the later intermediates could be recrystallised to greater optical purity (>90% ee).



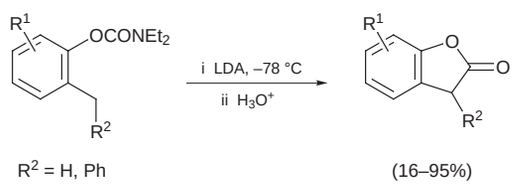
Base	Solvent	**25a** : **25b**	
NaHMDS	THF	81 : 19	(77%)
KHMDS	toluene	5 : 95	(82%)

Scheme 27

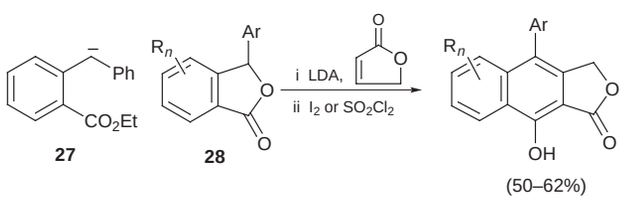
Snieckus and co-workers have developed an efficient synthesis of benzofuranones based on the homologous Fries rearrangement of laterally lithiated *O*-arylcarbamates[54] (**Scheme 29**). Regiochemically pure products were isolated from the reaction, which gave the highest yields when the *ortho* position adjacent to the carbamoyl group was blocked to prevent competitive *ortho* lithiation. Laterally lithiated arenes also featured in a synthesis of naphthofuranone lignans.[55] Although condensation of the anion **27** with furan-2(5*H*)-one was possible, the procedure failed to generalise to substituted derivatives. An



Scheme 28



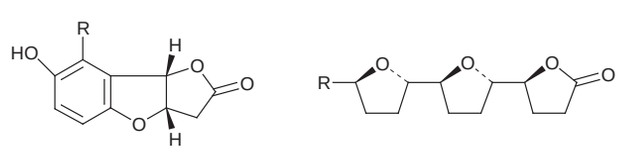
Scheme 29



Scheme 30

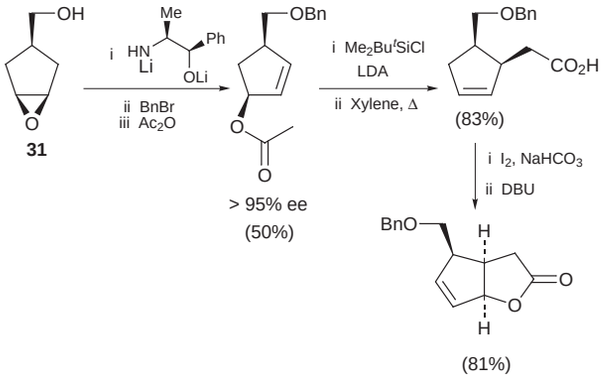
alternative approach using the lithiated lactones **28** in the tandem Michael addition–Dieckman condensation was more successful (**Scheme 30**).

Brimble has revisited earlier work on the cycloaddition of 2-(trimethylsilyloxy)furan to benzo-1,4-quinones.[56] A variety of dihydrofuro[3,2-*b*]benzofuranones **29** were prepared in good yield (43–76%). The versatile 2-(trimethylsilyloxy)furan has also been used in a replicative approach to oligo(tetrahydrofuran)lactones, such as **30**, by a sequential aldol–reduction procedure.[57]



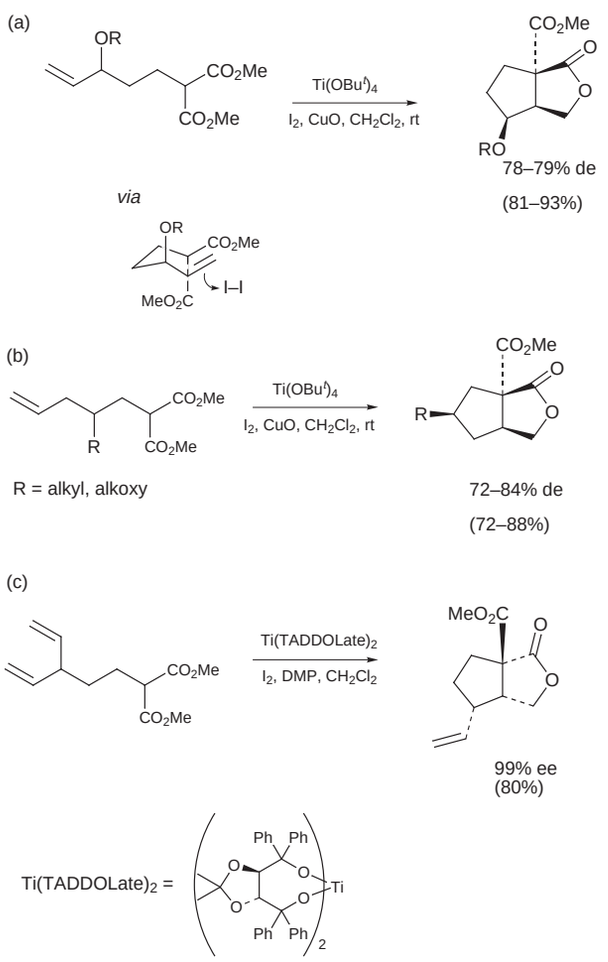
Bicyclic lactone precursors to prostaglandins and iridoid lactones have been synthesised by iodolactonisation of alkenoates derived from Ireland–Claisen rearrangement[58] (**Scheme 31**). The optically pure precursor to the [3,3]-sigmatropic rearrangement was obtained by desymmetrisation of the *meso* epoxide **31** with a chiral lithium amide. Both enantiomeric series of bislactones were accessible by this route.

A direct approach to similar bicyclic γ-lactones has been reported using the titanium promoted iodocarbocyclisation of alk-4-enylmalonates. Control of the cyclisation was possible by both 1,2- and 1,3-induction of stereochemistry through chair-like transition states, reminiscent of the analogous iodolactonisation reactions.[59] In the former case, alkoxy substituents led to high selectivities due to adoption of a pseudo-axial position to avoid destabilising electronic interactions (**Scheme 32a**). For 1,3-induction, all substituents preferred to react through the



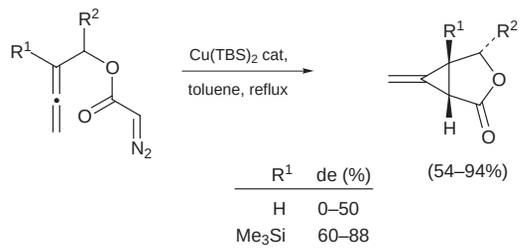
Scheme 31

equatorially arranged transition state to avoid steric repulsions (**Scheme 32b**). A very successful catalytic, enantioselective version of the reaction was developed using a titanium TADDOLate.[60] Cyclisations of simple unsubstituted alk-4-enylmalonates were achieved in good yields (60–87%) with excellent enantioselectivities (>96% ee). The chiral catalyst was also capable of enantiotopic group selectivity in the reaction of bis(alk-4-enyl)malonates (**Scheme 32c**).

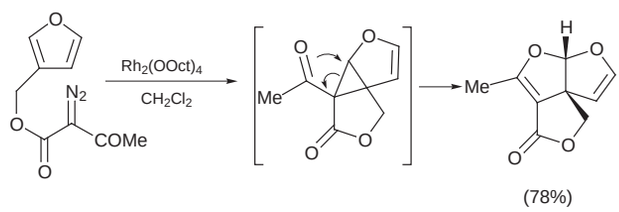


Scheme 32

Both rhodium and copper catalysts will promote the intramolecular cyclopropanation of allylic diazoacetates, although some evidence has emerged for complementary enantiocontrol between the two catalyst types.[61] In contrast, only copper catalysis was effective in cyclising allenic diazoacetates[62] (**Scheme 33**). Cyclopropanation occurred regioselectively at the more substituted double bond of the allenes, and better stereoselectivity was seen if this internal double bond was further substituted. The intramolecular cyclopropanation of furan-3-yl diazoacetates led to complex tricyclic lactone products when the intermediate cyclopropyl lactones contained a ketone suitably placed for further reaction[63] (**Scheme 34**). This sequence could offer a route to the skeleton of bilobalide and other ginkolides.

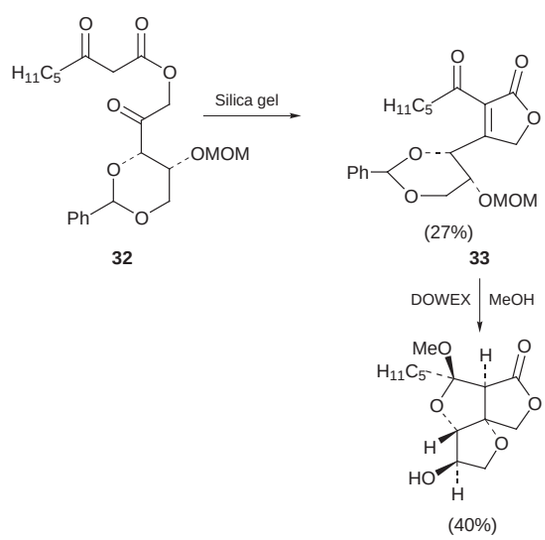


Scheme 33



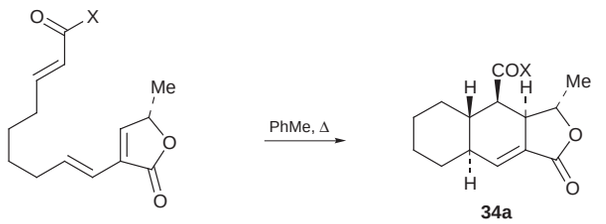
Scheme 34

The tricyclic lactone core of (−)-syringolide has been constructed by a biomimetic cascade initiated by an intramolecular Knoevenagel condensation[64] (**Scheme 35**). Oxidation of an alcohol to the unstable ketone **32** triggered the condensation under mild acid catalysis. On removal of the acetal protecting groups of **33**, intramolecular Michael addition and ketal formation gave the target molecule. Another synthesis of syringolide has been reported in which an intermediate closely allied to **33** was prepared by aldol addition to C-3 of a furan-2(5*H*)-one.[65]



Scheme 35

In a recent synthesis of the muscarinic receptor antagonist (+)-himbacine, Hart *et al*. constructed the tricyclic lactone core by a challenging Diels–Alder cycloaddition[66] (**Scheme 36**). The reactions of the ester or thioester precursors under thermal conditions were unselective, giving inseparable mixtures of **34a** and **34b**. Attempted homogeneous Lewis-acid catalysis was unsuccessful, giving either no reaction or decomposition, but the heterogeneous acid promoter formed from diethyl-



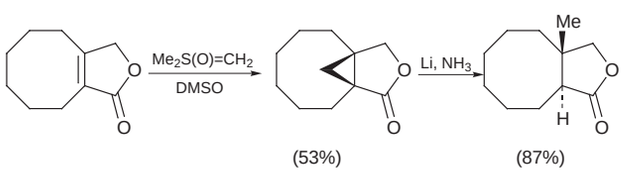
X	Conditions	Yield (%)	**34a** : **34b**
OEt	110 °C	58	1 : 1
SEt	110 °C	30	1 : 1
OEt	40 °C + acid	31	3 : 1
SEt	40 °C + acid	75	20 : 1

acid = SiO_2–Et_2AlCl

Scheme 36

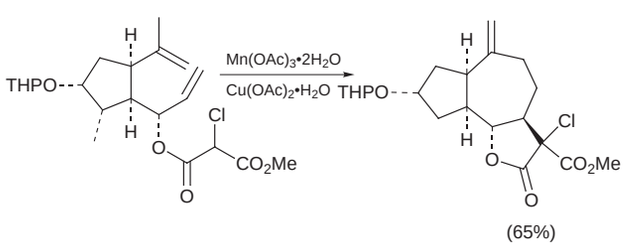
aluminium chloride on silica gave selectively the desired *endo* adducts. The larger enhancement in selectivity seen with the thioester was ascribed to preferential complexation of the Lewis acid by this group over the furanone component. A substituted furan-2(5*H*)-one has been used as the dienophile in a Diels–Alder approach to the insect antifeedant azadirachtin.[67]

The cyclopropanation–reduction of a bicyclic furan-2(5*H*)-one has been studied as a means of reaching the taxane BC ring system[68] (**Scheme 37**). Cyclopropanation of the furanone was slow and required a large excess of methylide reagent to reach completion, presumably due to competing deprotonation of the starting material. Although the cyclopropane was resistant to catalytic hydrogenolysis, dissolving metal reduction did generate the desired bicyclic lactone.



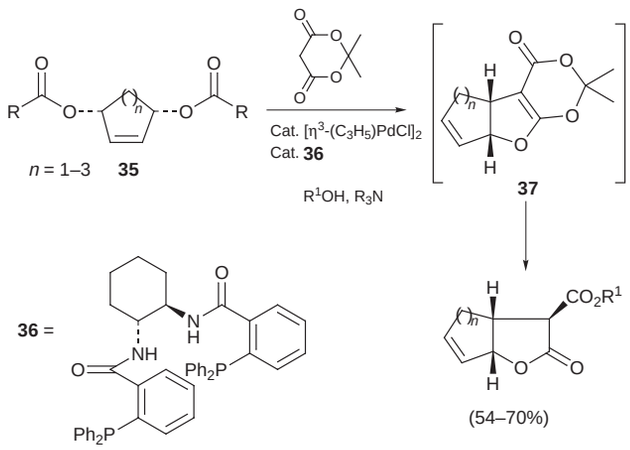
Scheme 37

The sesquiterpene lactones (−)-estafaitin and (+)-cladantholide have been synthesised by combining the well known 5-*exo*-*trig* radical cyclisations of α-haloacetals and α-chloromalonates with a 7-*endo*-*trig* cyclisation in a radical cascade[69] (**Scheme 38**). In both cases, the 5-*exo* cyclisation afforded the expected *trans* fused butyrolactones and appeared to create a scaffold that was especially suited for seven-membered ring formation in the second step.



Scheme 38

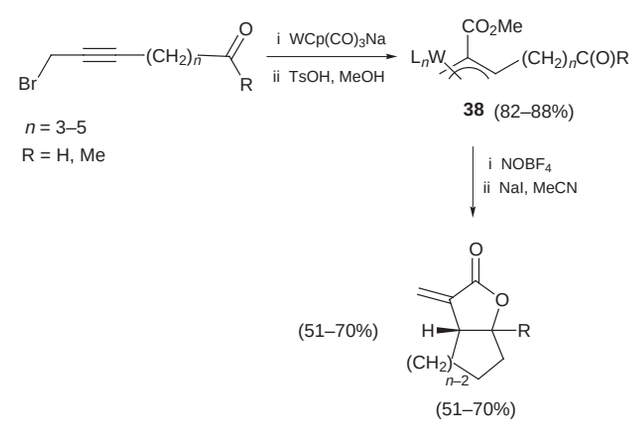
An unexpected route to optically active bicyclic γ-lactones was uncovered by Trost *et al*. during work on the asymmetric cyclopropanation of *meso* esters such as **35**[70] (**Scheme 39**). Whilst the palladium catalysed reaction with malonate esters led to cyclopropanation, using Meldrum's acid as the nucleophile gave only lactone products, presumably through the readily hydrolysed *O*-allylated intermediate **37**. Under optimised conditions, reasonable yields of lactones of high optical purity were obtained.



Scheme 39

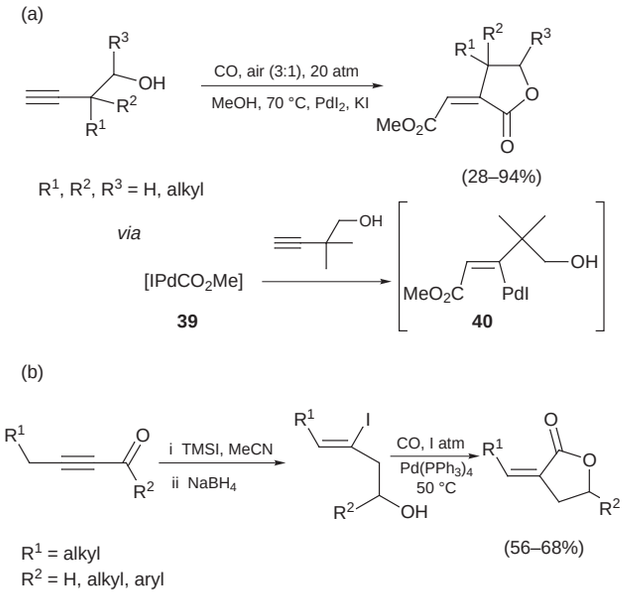
4.3 α-Methylene-γ-lactones

Liu and co-workers have previously reported a synthesis of α-methylene-γ-lactones from propargylic halides and carbonyl compounds using cyclopentenyl(tricarbonyl)tungsten complexes. This work has been applied in an intramolecular sense to propargyl halides bearing pendant aldehydes and ketones, leading to fused bicyclic α-methylene-γ-lactones[71] (**Scheme 40**). Acid promoted alkoxycarbonylation of the initial η^1-metal complex gave the η^3-metal complexes **38**. Generation of the allylic anion from these species triggered intramolecular condensation with the carbonyl and elimination of the metal to form the exocyclic double bond. The stereochemistry of the ring fusion varied with the length of the tether. The same chemistry was also demonstrated for the analogous molybdenum species.[72]



Scheme 40

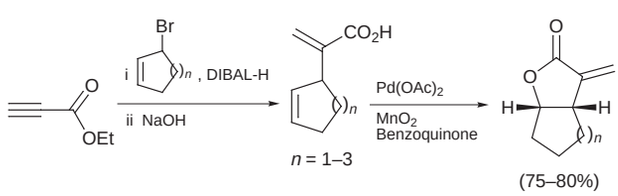
Palladium catalysed oxidative carbonylation of but-3-yn-1-ols is an attractive method of preparing α-methylene-γ-lactones and has been achieved under mild, moderate pressure conditions using a catalytic system based on the PdI_4^{2-} ion[73] (**Scheme 41a**). The reaction has been rationalised by formation of the alkoxycarbonylpalladium species **39** which would undergo *syn* addition to the alkyne. Subsequent carbon monoxide insertion into the alkenylpalladium intermediate **40** and ring closure would generate the lactones. The reaction was applicable to propargyl alcohols to produce β-lactones, but only when α,α-disubstitution was present to give the necessary Thorpe–Ingold effect for ring closure. In a similar vein, conjugated ynones have been shown to lead to α-methylene-γ-lactones through a sequence consisting of deconjugative hydridoiodination, carbonyl reduction and palladium catalysed carbonylation[74] (**Scheme 41b**). The last step was carried out at atmospheric pressure and was presumed to involve an alkenylpalladium species similar to **40**. Although a wide range of substituents



Scheme 41

were tolerated at C-5 of the lactone products, only alkyl substituted alkynes would undergo the initial deconjugation reaction.

Acryloxypalladation of alkenes avoids the use of carbon monoxide and can generate α-methylene-γ-lactones in a single step, but has been limited to olefins without labile allylic hydrogens since these can lead to competitive π-allylpalladium complex formation and diversion of the reaction towards allylic acrylates. An alternative solution to this problem has been found by breaking the reaction down into separate C–C and C–O bond forming steps.[75] Thus, allylation of the enolate derived from conjugate reduction of ethyl propynoate provided a substrate that readily closed to give the α-methylene-γ-lactones on generation of π-allylpalladium intermediates (**Scheme 42**).



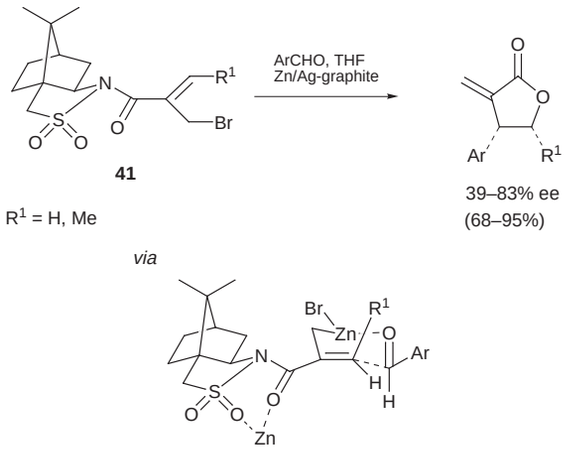
Scheme 42

Oppolzer's sultam chiral auxiliary has been used in the anionic allylation of aldehydes with (α-halomethyl)acrylates, an enduring route to α-methylene-γ-lactones[76] (**Scheme 43**). Moderate to good enantioselectivities were seen in the Dreiding–Schmidt reaction of the sultamamides **41** with aryl aldehydes, where the proposed favoured transition state involved chelation of the auxiliary to give s-*cis* orientation of the acrylate component and pseudo-equatorial disposition of the aldehyde substituent in a chair-like six-membered ring.

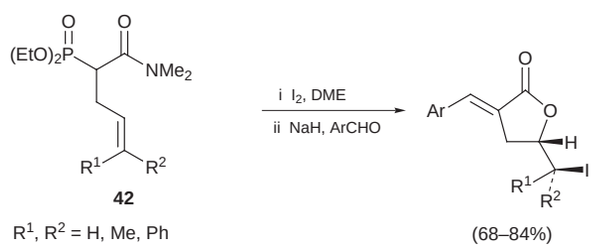
Classical halolactonisation of 2-(diethylphosphono)pent-4-enamides was used to form precursors to α-methylene-γ-lactones, in which the phosphonate group served to introduce the exocyclic double bond by Wadsworth–Emmons reaction after ring closure[77] (**Scheme 44**). Despite starting with diastereomeric mixtures of the α-phosphonates **42**, the stereospecific *trans* iodolactonisation and subsequent (*E*)-selective alkylidenation led to single isomers of the targets in excellent yields.

5 Medium-ring lactones

An elegant and potentially very competitive new method for medium ring lactonisation, using 1,2-bis(dimethylsilyl)benzene

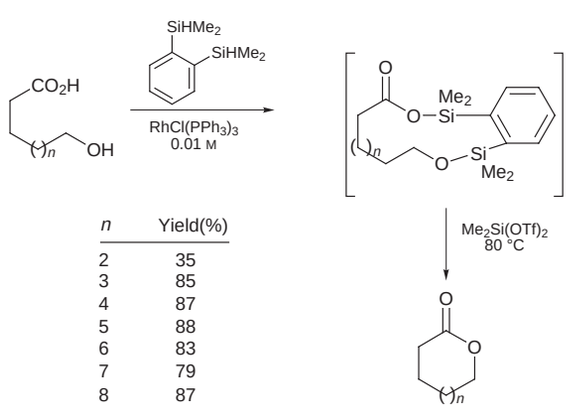


Scheme 43



Scheme 44

as a template for cyclisation, has been designed and brought to fruition by Mukaiyama *et al.*[78] Rhodium catalysed bis-silylation of ω-hydroxycarboxylic acids gave intermediate macrocyclic silyl siloxycarboxylates which rearranged upon treatment with dimethylsilyl bis(trifluoromethanesulfonate) to afford the desired medium ring lactones in excellent yields (**Scheme 45**). Only small quantities (<10%) of diolide by-products were observed in the reaction, which was particularly effective for the difficult eight- and nine-membered rings.

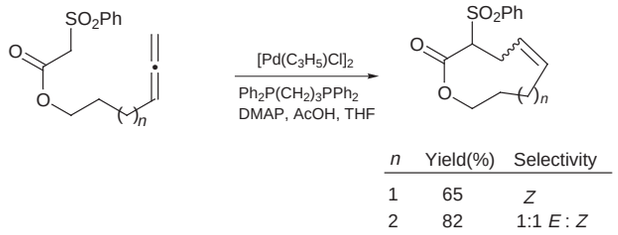


n	Yield(%)
2	35
3	85
4	87
5	88
6	83
7	79
8	87

Scheme 45

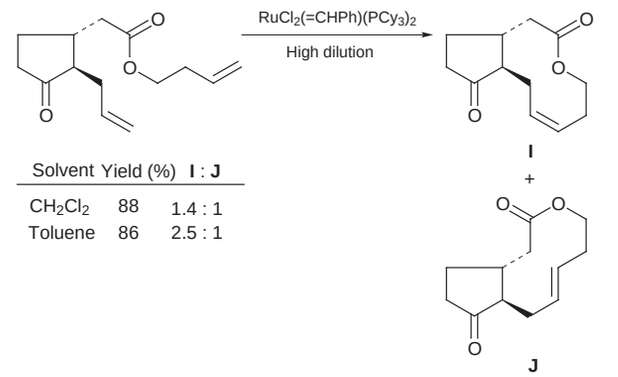
Another new method for medium ring lactonisation was reported by Trost *et al.*[79] The intramolecular cyclisation of active methylene compounds onto allene-derived cationic π-allylpalladium complexes showed an unexpected preference for the usually very disfavoured nine-membered ring formation (**Scheme 46**). 4-Dimethylaminopyridine was found to be the optimum base for the cyclisation, prompting speculation that bifunctional catalysis may be involved in the process. The method was equally applicable to macrolide synthesis (57–67% yields).

Ring closing metathesis has been shown to apply to the formation of 10-membered lactones in a synthesis of Jasmine ketolactone by Fürstner and Müller[80] (**Scheme 47**). As with



n	Yield(%)	Selectivity
1	65	*Z*
2	82	1:1 *E* : *Z*

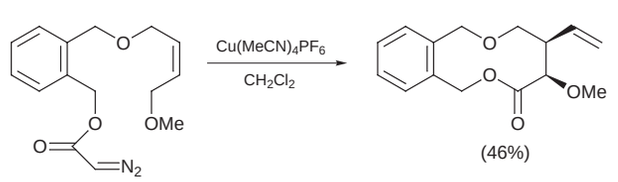
Scheme 46



Solvent	Yield (%)	**I** : **J**
CH_2Cl_2	88	1.4 : 1
Toluene	86	2.5 : 1

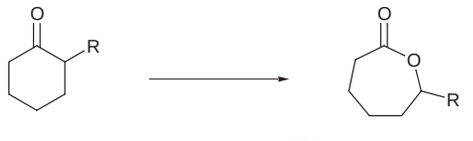
Scheme 47

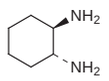
related studies in the macrolide series, only limited control over double bond geometry was possible (*cf.* Schemes 4, 5, 7, 8 and 10). Oxygen-containing 10-membered lactones have also been prepared by sequential macrocyclic oxonium ylide formation and [2,3]-sigmatropic rearrangement mediated by metal carbenoids[81] (**Scheme 48**). The isolated yields in this preliminary work were compromised by the formation of intramolecular cyclopropanation by-products (*cf.* Scheme 13), which were minimised by the use of copper in preference to rhodium as the metal centre.



Scheme 48

Several reports have dealt with new variants of the Baeyer–Villiger oxidation of ketones, particularly for the formation of seven-membered lactones from cyclohexanones. Oxidation of ketones with bis(trimethylsilyl) peroxide was catalysed by the Lewis acid prepared from tin(IV) chloride and *trans*-1,2-diaminocyclohexane[82] (**Scheme 49a**). Molecular sieves were found to be essential to prevent deactivation of the catalyst by hexamethyldisiloxane formed in the reaction. For substituted cyclohexanones, regioselectivity was high (>17 : 1) and the yields were generally improved over previous procedures using bis-(trimethylsilyl) peroxide as the oxidant. This method may prove an interesting platform from which to build an enantioselective procedure. Magnesium monoperoxyphthalate hexahydrate, the more stable alternative to *m*-chloroperbenzoic acid, has been used successfully for Baeyer–Villiger oxidations both in aqueous methanol[83] and dry acetonitrile[84] (**Scheme 49b,c**). A previously described 'designer yeast' expressing the cyclohexane monooxygenase from *Acinetobacter sp.* has achieved the oxidative kinetic resolution of 2-alkylcyclohexanones, giving excellent optical purities in both the lactone products and recovered ketones[85] (**Scheme 49d**). In purified form, the same enzyme was coupled with a protein-engineered formate dehydrogenase to provide a cell-free system for the preparative bio-oxidation of 4-alkylcyclohexanones.[86]



(a)	$(TMSO)_2$, 25 mol% $SnCl_4$, 	(78–91%)
(b)	MMPP, $NaHCO_3$, MeOH(aq)	(92%)
(c)	MMPP, MeCN	(56–94%)
(d)	'Designer yeast'	(41–79%)
	NCIB 9871 monooxygenase	95–98% ee

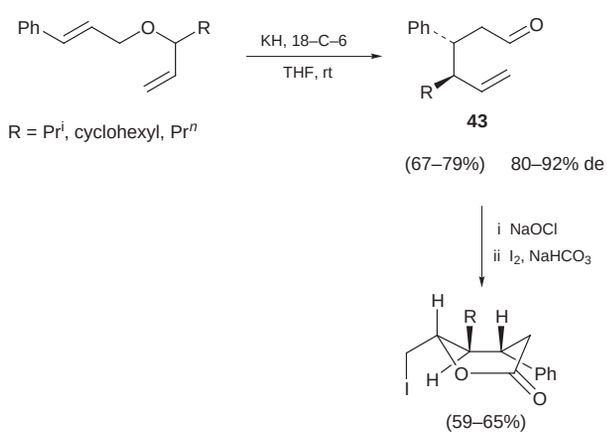
MMPP = magnesium monoperoxyphthalate hexahydrate

Scheme 49

6 δ-Lactones

6.1 Monocyclic δ-lactones

Pent-5-enoate lactone precursors have been constructed by tandem [2,3]-Wittig and anionic oxy-Cope rearrangements[87] (**Scheme 50**). The second of these two reactions went predominantly through a chair-like transition state to yield the *syn* substituted aldehydes **43**. After oxidation, subsequent iodolactonisation was highly selective for the formation of δ-lactones in a boat conformation, as determined by X-ray crystallography and NMR spectroscopy, when bulky substituents were present. Only with the less bulky *n*-propyl substituent was the alternative chair conformation observed, giving a mixture of products.

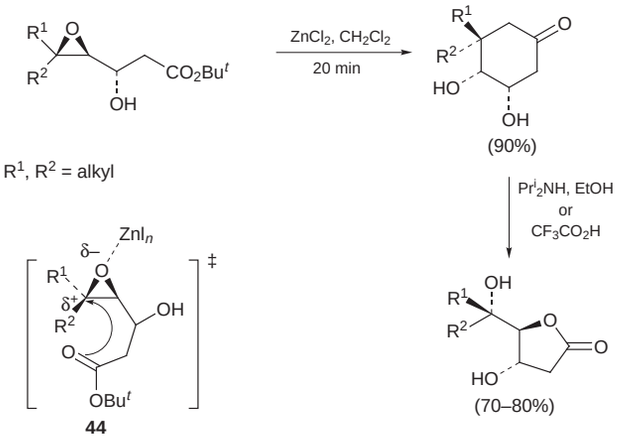


Scheme 50

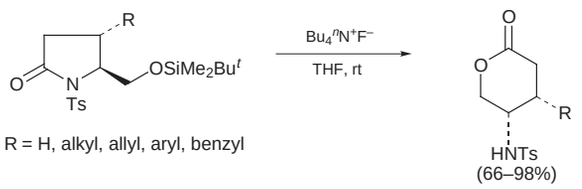
δ-Lactones were the kinetic product of Lewis acid assisted cyclisation of 3-hydroxy-4,5-epoxypentanoates, although equilibration with acid or base led to the more stable γ-lactones[88] (**Scheme 51**). Interestingly, when the 3-hydroxy group was silylated before cyclisation, only the γ-lactones were formed, which suggested stabilisation by hydrogen bonding in the unprotected δ-lactone diol may have been important. The kinetic preference for 6-*endo-tet* opening of the epoxide was consistent with a transition state **44** where developing cationic character at C-5 was stabilised by electron donation from the dialkyl substitution.

A simple and general one-step protocol for the preparation of 5-amino-δ-lactones from pyrrolidinones has been reported, improving upon earlier multi-step approaches to the same transformation[89] (**Scheme 52**). The fluoride induced deprotection and lactam ring-opening was only successful with *N*-tosyl protection, to provide a good leaving group, and *tert*-butyldimethylsilyl protection of the pendant alcohol.

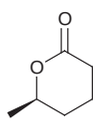
An efficient and highly enantioselective preparation of the simple δ-lactone **45** from commercially available 5-oxohexanoic acid has been developed, using a bio-reduction followed by a



Scheme 51



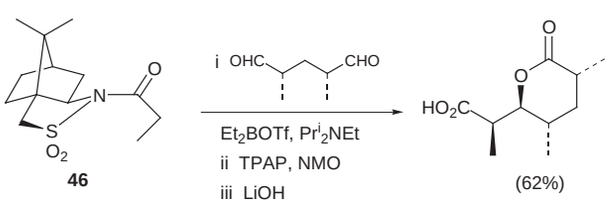
Scheme 52



45

lipase catalysed kinetic resolution.[90] The process was applied on a gram-scale to give **45** in 62% yield with 99.7% ee.

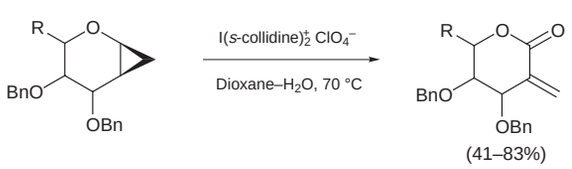
The *N*-propionyl derivative of Oppolzer's bornanesultam **46** has been used to desymmetrise a *meso*-dialdehyde through an aldol reaction, giving a very rapid enantioselective synthesis of the Prelog–Djerassi lactonic acid[91] (**Scheme 53**). The stereoselectivity of the aldol was determined as typically 80% de, the unwanted diastereoisomer being removed chromatographically after the oxidation step.



TPAP = tetrapropylammonium perruthenate

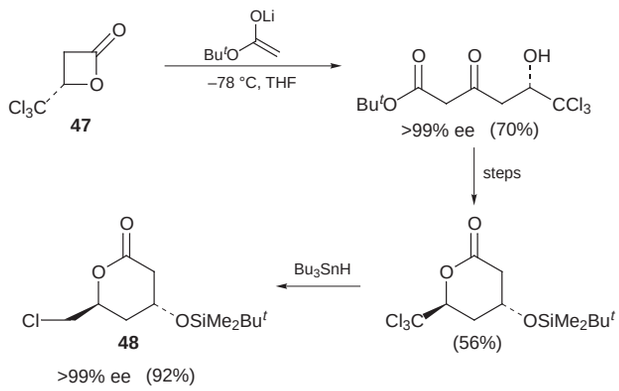
Scheme 53

1,2-Cyclopropanated sugars were transformed directly into α-methylene-δ-lactones by treatment with iodonium di(*s*-collidine)perchlorate, which effected a tandem sequence of ring opening, oxidation and elimination in one pot[92] (**Scheme 54**).

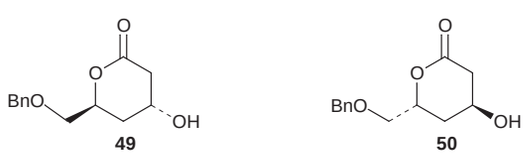


Scheme 54

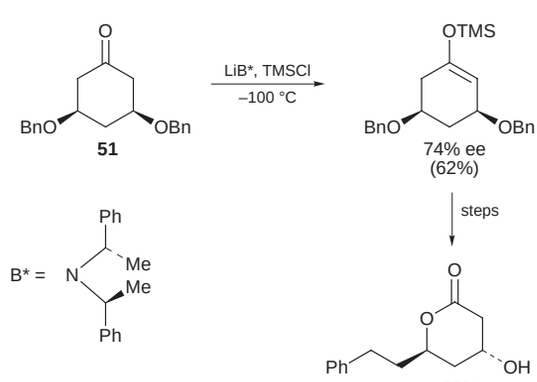
The assembly of the 4-hydroxy-δ-lactone component of the mevinic acid class of HMG CoA reductase inhibitors has been an area of continuing synthetic interest. Enantiomerically pure β-trichloromethyl-β-lactones served as the starting point for one asymmetric approach to this pharmacophore.[93] The β-lactone **47** reacted with a large excess of lithio-*tert*-butylacetate to give only the product arising from oxygen–acyl bond fission (**Scheme 55**). After *syn* reduction and lactonisation, the pendant trichloromethyl group was reduced cleanly with tri-*n*-butyltin hydride to provide the useful, optically pure synthetic intermediate **48**. The enantiomeric pair of lactones **49** and **50** have been prepared from (*R*)- and (*S*)-epichlorohydrin respectively by similarly straightforward chemistry.[94]



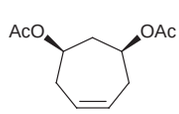
Scheme 55



Desymmetrisation of the *meso* cyclohexanone **51** by enantioselective deprotonation in the presence of a chiral base formed the basis of an asymmetric synthesis of the mevinic lactone[95] (**Scheme 56**). Ozonolysis of the silyl enol ether product revealed the carbon skeleton of the eventual lactone product. Although the enantioselectivity of the deprotonation was not complete, later intermediates were suited to enhancement of optical purity by recrystallisation. Desymmetrisation of the *meso* diacetate **52** by enzymic hydrolysis has been proposed as an entry into the mevinic lactones.[96] As with the above synthesis, the lactone carbonyl and 6-substituent were unmasked by ozonolysis of the alkene.

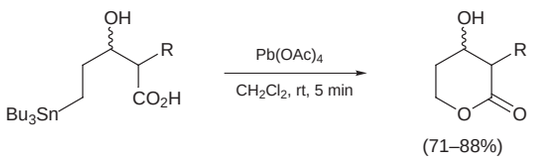


Scheme 56



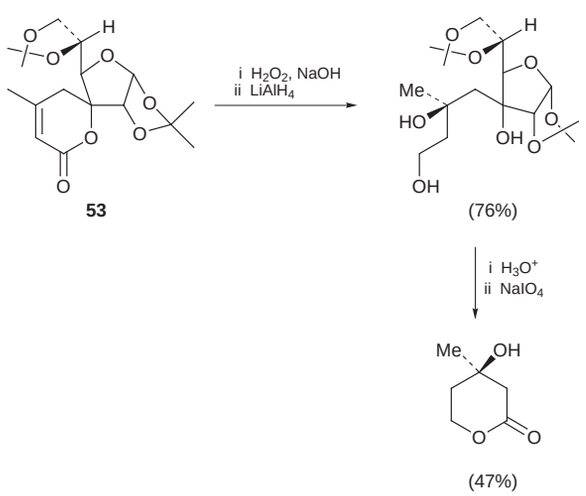
52

A novel, high yielding and rapid oxidative cyclisation with lead tetraacetate has been developed for the synthesis of 4-hydroxy-δ-lactones from alkylstannanes[97] (**Scheme 57**). In the proposed mechanism, the presence of the free hydroxy group in the carbon chain was essential to coordinate the metal and deliver cyclisation as opposed to oxidative elimination to give an alkene.

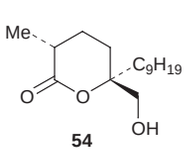


Scheme 57

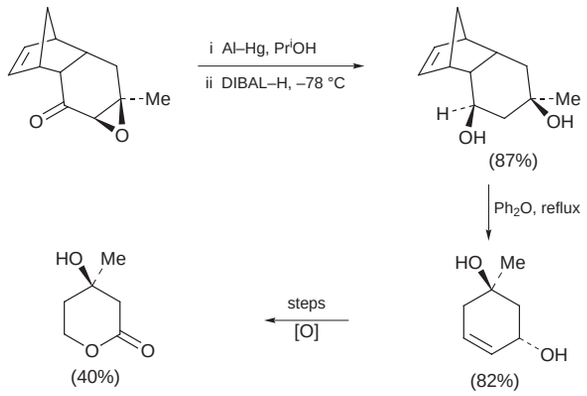
Two approaches to (*R*)-mevalonolactone have appeared that use template-directed synthesis. In the first, the lactone was constructed while spiro-fused to diacetone-D-glucose[98] (**Scheme 58**). Epoxidation of the spirolactone **53** was selective (>90% de) for the less hindered face of the double bond. The carbon skeleton was cleaved from the template by exhaustive oxidation after acetal deprotection. The sequence was amenable to modification to give, for the first time, a synthesis of the fully deuterated lactone. In a second approach, another stereoselective epoxidation was used to introduce the functionality of the lactone, which was this time asssembled on a tricyclic template generated in optically pure form by an enzymatic desymmetrisation[99] (**Scheme 59**). The template also served to direct reduction of the carbonyl group, and the lactone skeleton was freed from the template by retro-Diels–Alder reaction. Again, an exhaustive oxidation sequence was employed in the final stages of the synthesis. This template chemistry has found application in the synthesis of (−)-malyngolide **54**.[100]



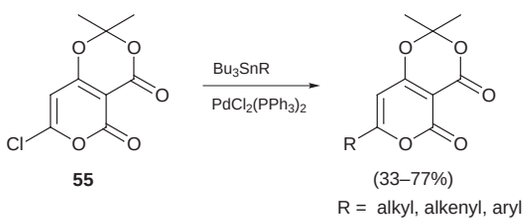
Scheme 58



The rapid analogue approach to the synthesis of biologically active compounds has become *de rigueur* in many medicinal chemistry laboratories, creating a need for new syntheses that are suited to this purpose, especially in the area of heterocyclic compounds. One such route has been developed for the synthesis of 6-substituted-2-pyrones, based on the Stille coupling of organostannanes to the known 6-chloro-2-pyrone **55**[101] (**Scheme 60**). Subsequent reaction of the products with amines



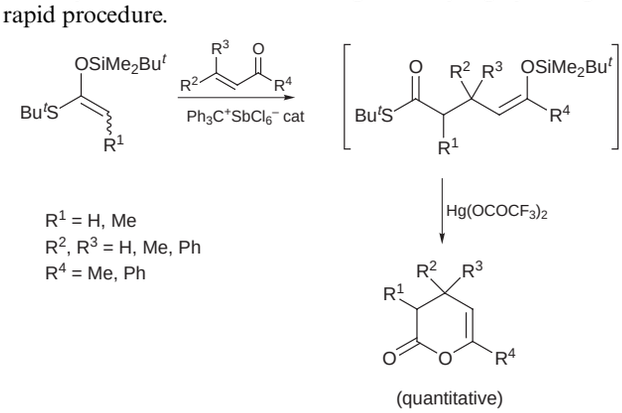
Scheme 59



Scheme 60

or alcohols was found to cleave the dioxinone ring to yield the 4-hydroxy-3-carboxamides and esters.

Modern reagent combinations have been used to update a well-established path to 3,4-dihydro-2-pyrones from enones[102] (**Scheme 61**). The trityl cation served as the catalyst for Michael addition of silyl enol thioethers to the enones, followed by a mercury mediated lactonisation to give a very high yielding and rapid procedure.



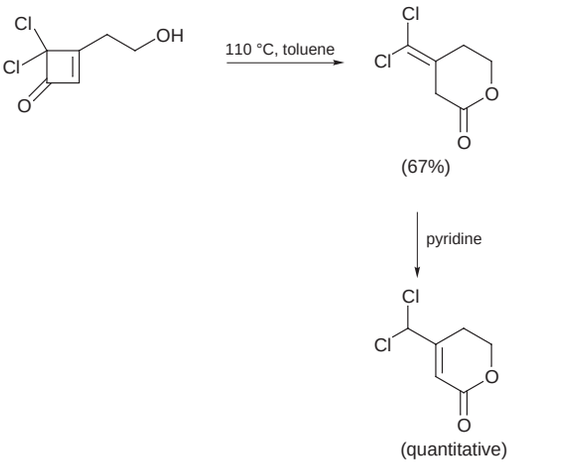
Scheme 61

Preliminary work on a new synthesis of 5,6-dihydro-2-pyrones has been reported[103] (**Scheme 62**). Electrocyclic ring opening of a 4,4-dichlorocyclobutenone bearing a pendant hydroxyethyl side chain resulted in δ-lactone formation through intramolecular entrapment of the ketene intermediate. The initial product was stable but could be isomerised in base to the dihydropyrone.

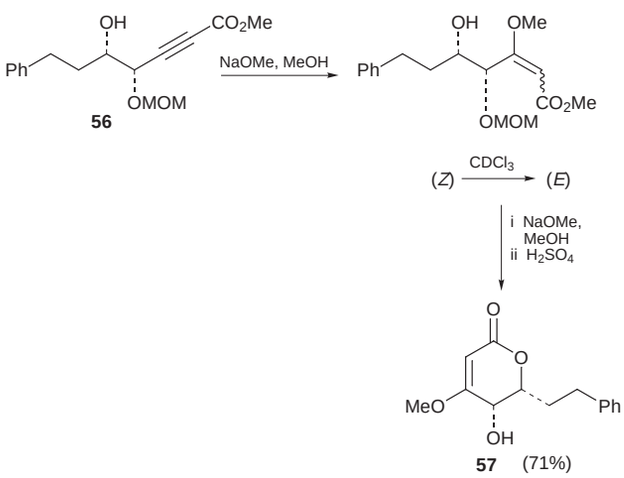
The fortuitous observation of the rearrangement of an NMR sample was carried through to the preparative scale in the synthesis of dihydrokawain-5-ol **57**, a constituent of kava extract[104] (**Scheme 63**). Conjugate addition of methoxide to the alkynoate **56** gave mainly the unproductive (*Z*)-alkenoate. However, the mild acidity offered by untreated deuterated chloroform provided a suitable medium for isomerisation to the (*E*)-isomer, leading to a good yield of the natural product after cyclisation.

6.2 Bicyclic and polycyclic δ-lactones

Marko *et al*. have reported that an unexpected improvement



Scheme 62

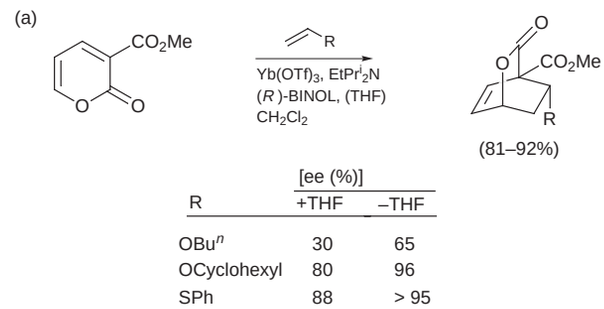


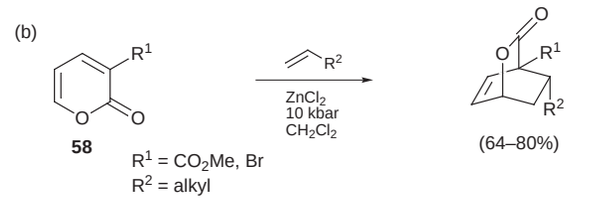
Scheme 63

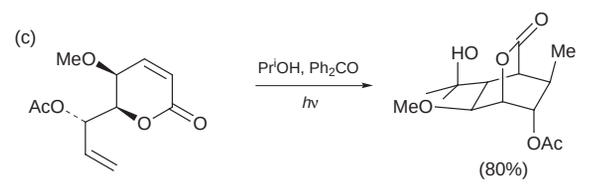
in the enantioselectivity of inverse electron demand Diels–Alder reactions of 3-carboxymethyl-2-pyrone occurred when coordinating ligands, such as alcohols, water or THF, were added to the chiral lanthanide catalyst[105] (**Scheme 64a**). Although the exact structure of the catalyst remains obscure, it is possible that the additives displace triflate ligands from the metal, provoking reaction through more tightly coordinated cationic complexes. In related work, Posner *et al*. have shown that the application of both Lewis acid catalysis and high pressure was necessary to coax unactivated alkenes to react with the 2-pyrones **58**, although reaction times remained long (3–5 days)[106] (**Scheme 64b**). Good yields of *syn* addition products were isolated with high selectivity for the *endo* cycloadducts. A photochemical radical addition–cyclisation has been shown to form related saturated bicyclic δ-lactones from 3,4-dihydro-2-pyrones and propan-2-ol[107] (**Scheme 64c**). The conjugate addition of the ketyl radical to 3,4-dihydro-2-pyrones has been exploited before, but translactonisation usually interferes to generate butyrolactones. With a suitably placed internal alkene trap, bicyclic products were isolated in good yield.

Tricyclic 2-pyrones have been prepared from the Michael addition–aldol condensation of 4-hydroxy-2-pyrones and cyclohex-1-enecarbaldehyde catalysed by L-proline[108] (**Scheme 65**). Excellent transfer of stereochemistry (>99% de) was seen when a substituent was present at C-4 of the cyclohexene, leading to *trans* substitution in the saturated ring, but the diastereoselectivities associated with other substitution patterns in the aldehyde were more modest.

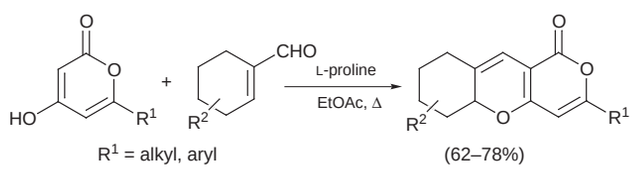
3,4-Dihydroisocoumarins were prepared directly from *o*-toluates using tellurium–lithium exchange to generate a benzylic anion in the presence of the electrophilic ester group[109]





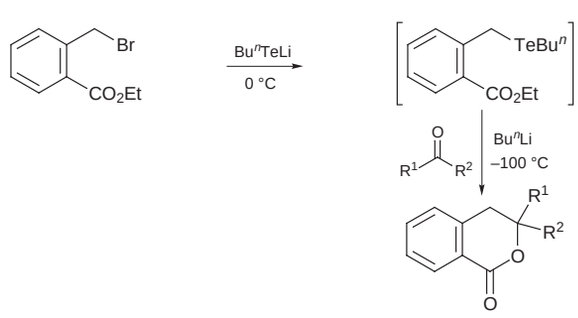


Scheme 64



Scheme 65

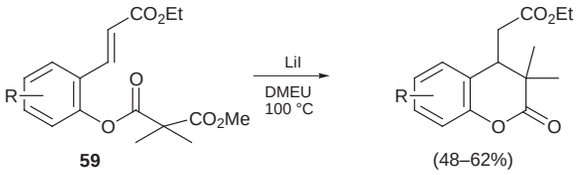
(**Scheme 66**). Even under these mild conditions, intermolecular self-condensation of the lithiated toluate was problematic unless the transmetallation was carried out in the presence of the carbonyl compound. The isomeric 3,4-dihydrocoumarins have been prepared by 6-*exo*-*trig* cyclisation of the enolate generated by S_N2 dealkylation–decarboxylation of the methyl dimethylmalonates **59**[110] (**Scheme 67**). The reaction was limited to substrates that gave tertiary enolates, and yields were compromised somewhat by competitive dissociation to phenolic decomposition products.



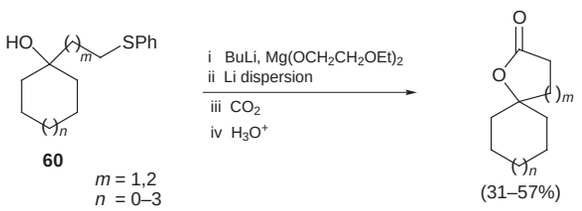
Scheme 66

7 Spirolactones

A versatile direct synthesis of five- and six-membered spirolactones has been described using (lithioalkoxy)lithiums stabilised in solution by magnesium 2-ethoxyethoxide, which dramatically reduces the propensity of the metallated species to react with ethereal solvents[111] (**Scheme 68**). The intermediate sulfides



Scheme 67

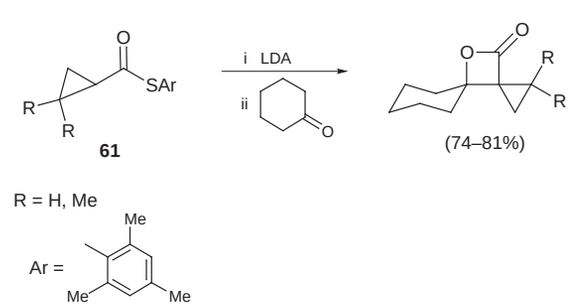


Scheme 68

60 were readily prepared from the addition of vinyl and allyl Grignards to cyclic ketones, followed by radical addition of thiophenol to the terminal alkenes.

Corey and Zheng have improved upon established conditions for the direct samarium(II) mediated annulation of ketones with acrylates.[112] By including zinc amalgam, trimethylsilyl triflate and lithium iodide in the reaction mixture, samarium(II) was regenerated *in situ*, reducing the samarium(II) iodide requirement to catalytic levels (10 mol%). Careful titration of the reagents during the reaction was necessary, however, to reduce side-reactions attributed to the presence of excess trimethylsilyl triflate.

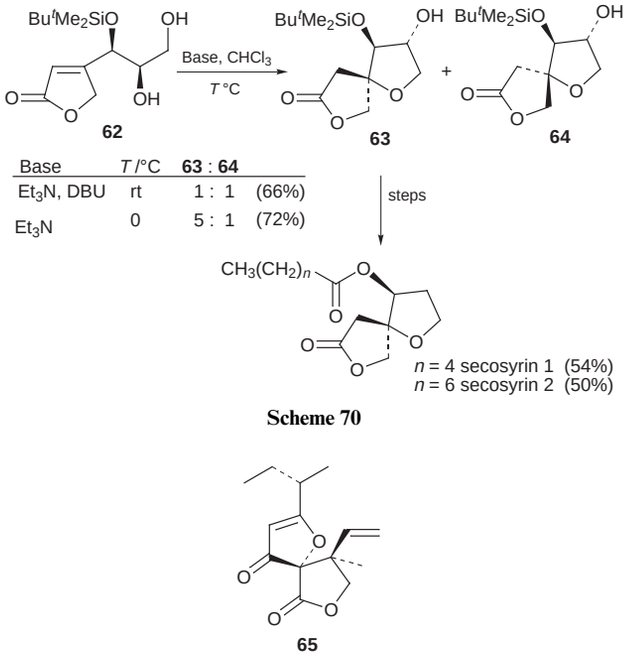
The β-lactone synthesis devised by Danheiser *et al*. has been adapted for the preparation of α,β-bis(spirocyclic)-β-lactones as intermediates *en route* to alkylidenecyclopropanes[113] (**Scheme 69**). The choice of the bulky mesityl thioester was critical in limiting side-reactions arising from self-condensation of the thioester **61** in the enolisation step. When aldehydes were used in place of ketones in the aldol reaction, no cyclisation to the β-lactones was observed, despite successful condensation.



Scheme 69

The intramolecular Michael addition of the primary alcohol in the butenolide **62** was found to have a surprising base and temperature dependent diastereofacial selectivity[114] (**Scheme 70**). The major isomer **63** from the most selective conditions tried was converted by simple protecting group manipulation into secosyrins 1 and 2. These natural products are structurally closely related to the tricyclic syringolides, and this approach may prove adaptable to these targets too. Straightforward chemistry was also used in the first synthesis of the plant natural product (±)-hyperolactone **65**.[115]

The marine sponge isolate (−)-ircinianin has been made through an intramolecular Diels–Alder cycloaddition of the triene **66**[116] (**Scheme 71**). The assembly of **66** by Nozaki–Hiyama coupling was only poorly selective (20% de) but the major, desired isomer underwent cycloaddition spontaneously at room temperature to give the spirobutenolide product in



Scheme 70

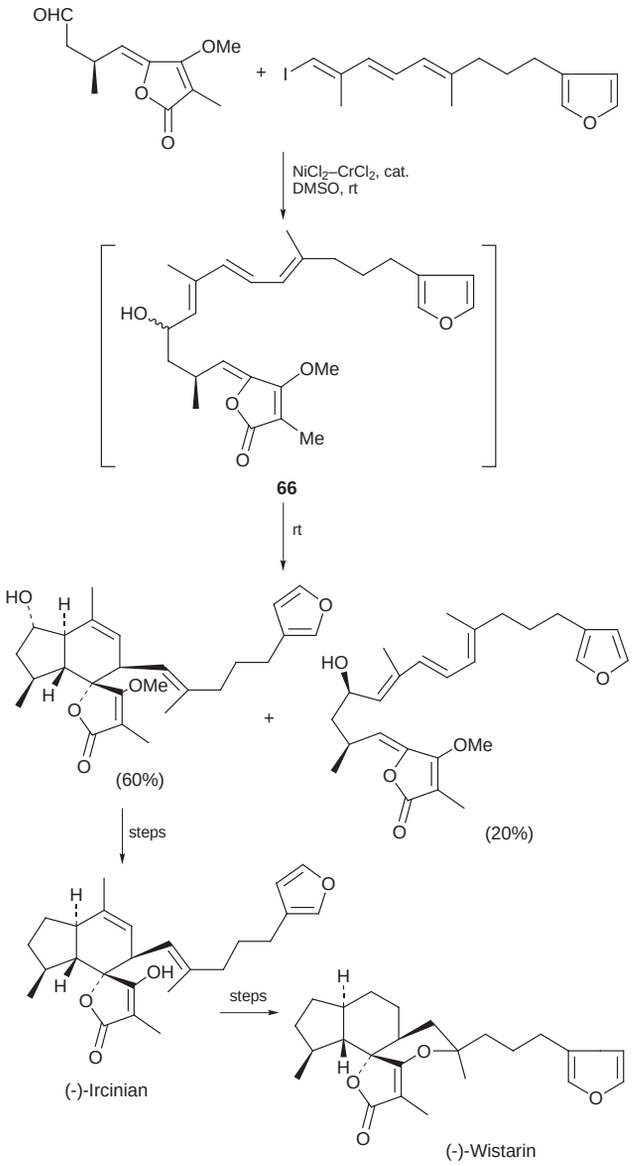
good isolated yield. Under more forcing conditions (xylene, 150 °C) the minor isomer of the triene **66** also cyclised, but to an unselective mixture of three diastereoisomeric products. (−)-Ircinianin was converted to (+)-wistarin by iodoetherification in the first total synthesis of this molecule, revealing a minor error in the structure previously proposed for this material.

8 But-2-enolides and tetronic acids

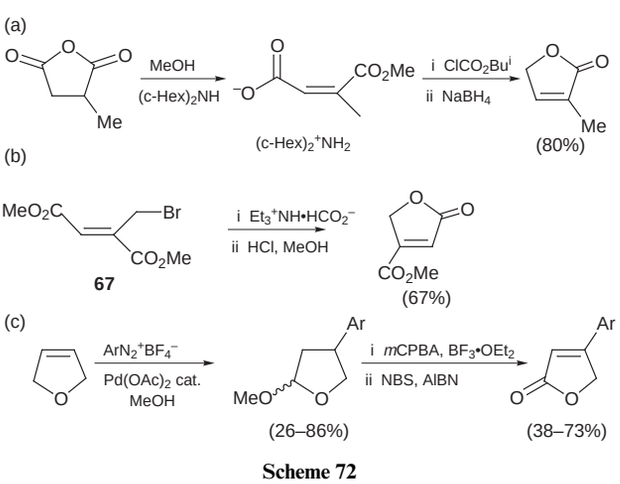
There has been a continuing interest in practical, large scale syntheses of low molecular weight butenolides as building blocks for incorporation into larger targets. For example, simple 3-methylfuran-2(5*H*)-one was prepared in three steps from citraconic anhydride, making use of a frontier-orbital controlled alcoholysis of the anhydride to differentiate the two carbonyls[117] (**Scheme 72a**). 4-Methoxycarbonylfuran-2(5*H*)-one was obtained in good yield on a large scale by the displacement of the allylic bromide of fumarate **67** with formate anion and subsequent alcoholysis[118] (**Scheme 72b**). Simple 4-arylbutenolides and tetronates were quickly assembled *via* the Heck reaction of 2,5-dihydrofuran and subsequent oxidations[119] (**Scheme 72c**).

2-(Trimethylsilyloxy)furan and other metallated derivatives of furan-2(5*H*)-one have maintained their high profile as butenolide precursors. Mannich products of the former reagent were made when hexahydro-1,3,5-triazines provided the *N*-methyleneamine equivalents under Lewis acid catalysis[120] (**Scheme 73a**). The optimum choice of Lewis acid was sensitive to the *N*-substituents on the triazines. Chiral Lewis acids have been shown to catalyse the enantioselective conjugate addition of 2-(trimethylsilyloxy)furan to chelating acrylamides[121] (**Scheme 73b**). A combination of copper(II) triflate and a bis(oxazoline) ligand **68** gave excellent yields and enantioselectivities, with acceptable *anti* selectivity in the generation of the two new chiral centres (>8.5:1). When the catalyst was changed to scandium(III) triflate and a BINOL-derived ligand, improved *anti* selectivity was observed (>50:1) but at the expense of the optical purity of the products (<70% ee).

The conjugate addition of 2-(trimethylsilyloxy)furan to the substituted cyclopentenone **69** catalysed by tin(IV) chloride gave a poorly selective mixture dominated by the *cis* disubstituted adducts.[122] In contrast, the reaction of lithiated furan-2(5*H*)-one was very selective for *trans* disubstituted product formation, presumably through a preferred chelated transition state (**Scheme 74**). The material thus prepared was carried through in



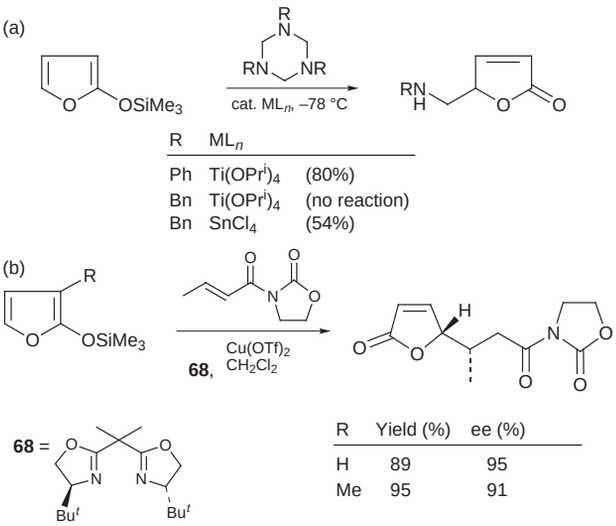
Scheme 71



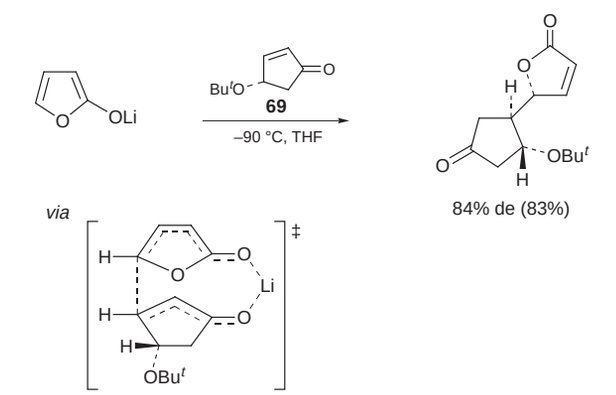
Scheme 72

a synthesis of the macrolide (+)-brefeldin A. Along the same lines, in a recent synthesis of the cytotoxins melodorinol **70a** and acetylmelodorinol **70b**, 5-lithio-2-(*tert*-butyloxy)furan proved superior in the addition to a simple glyceraldehyde than the alternative Lewis acid mediated addition of 2-(trimethylsilyloxy)furan.[123]

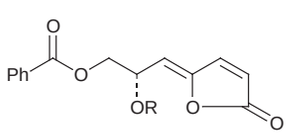
Much material has been published dealing with the construc-



Scheme 73



Scheme 74

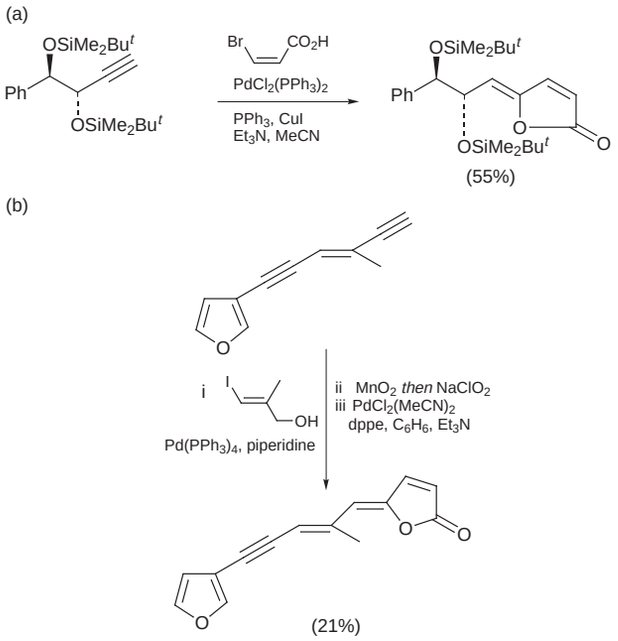


70a R = H
70b R = Ac

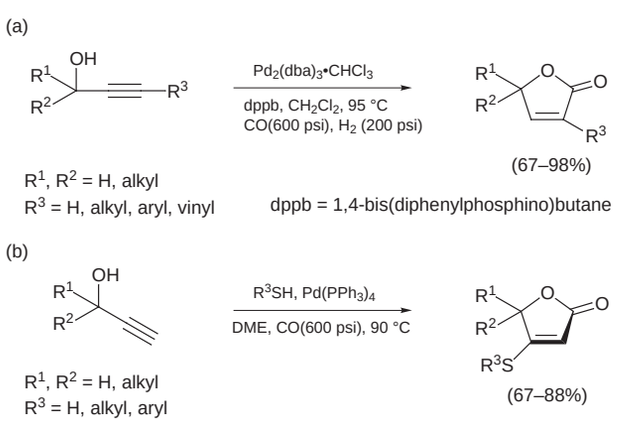
tion of butenolides through palladium catalysed carbonylation or lactonisation of unsaturated substrates. Kotora and Negishi have worked extensively on the tandem cross-coupling and lactonisation of alkynes and (*Z*)-β-haloacrylates. This led to syntheses of the antibiotic rubrolides,[124] and also featured in a synthesis of (+)-goniobutenolide A[125] (**Scheme 75a**). Another group followed a similar approach to freelingyne, except that the enyne cross-coupling and lactonisation steps were conducted separately[126] (**Scheme 75b**).

Conditions developed by Alper and co-workers for the cyclocarbonylation of allylic alcohols (*cf.* **Scheme 25**) were also applied to give butenolides from both terminal and internal alkynols[127] (**Scheme 76a**). Although yields were excellent and a range of substitution patterns was produced, the reaction required very high gas pressures, which may be a practical limitation. A further modification of the conditions led to the first demonstration of synthetically useful palladium catalysed thiocarbonylation of propargylic alcohols[128] (**Scheme 76b**).

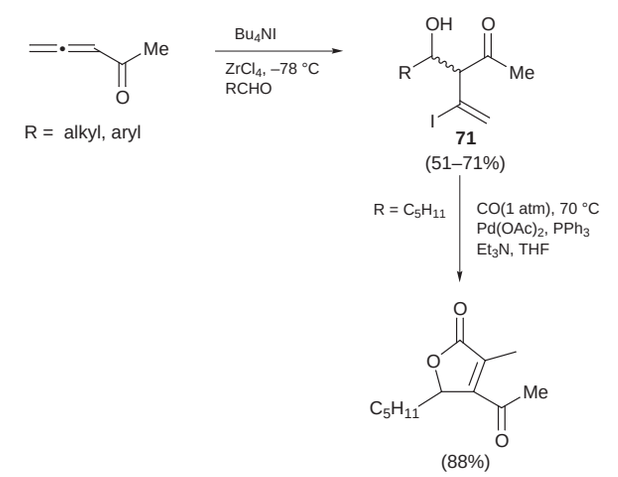
The cyclocarbonylation of the vinyl iodide **71** occurred smoothly under mild conditions to give the butenolide[129] (**Scheme 77**). Compound **71** and analogues were readily prepared by tandem nucleophilic addition–aldol reactions of an electron deficient allene with iodide and aldehydes respectively.



Scheme 75

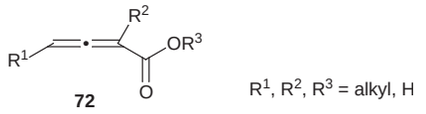


Scheme 76

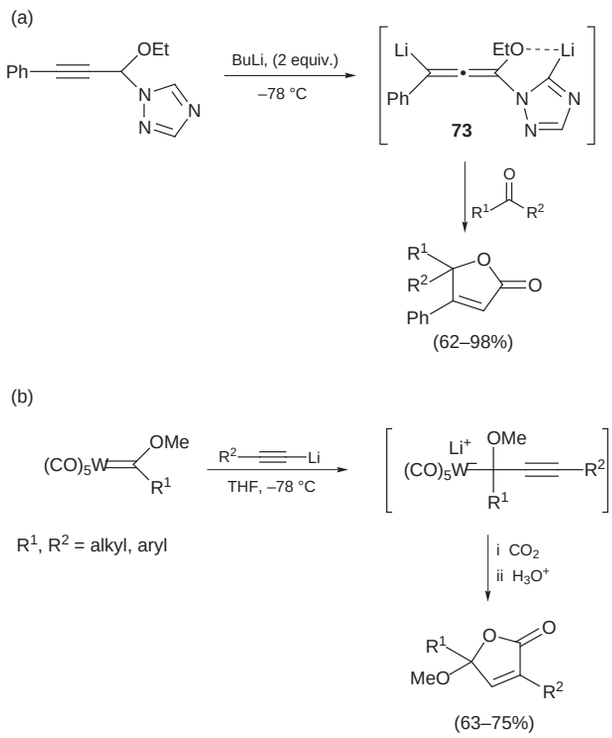


Scheme 77

Marshall *et al.* have previously described the preparation of butenolides by carboxylation of propargylic mesylates and subsequent electrophilic cyclisation of the intermediate allenic acids or esters **72**.[130] This sequence was applied to the synthesis of the butenolide moiety in various cytotoxic annonaceous acetogenins.[131,132] Katritzky *et al.* have explored the use of 1,2,4-triazole stabilised allenic anions **73** in preparing butenolides,[133]

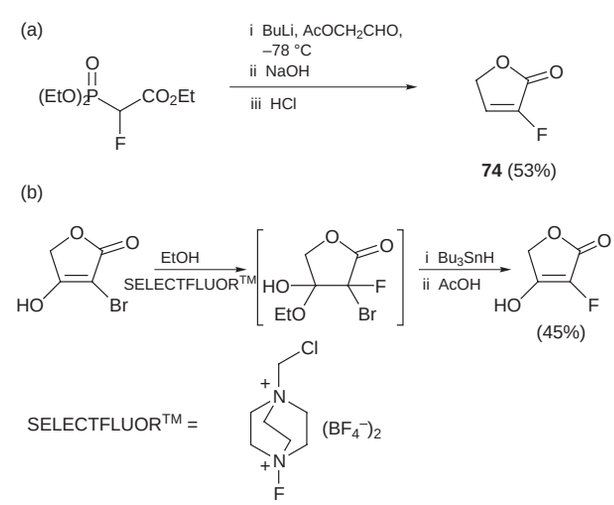


methodology that parallels the synthesis of saturated γ-lactones (**Scheme 78a**, *cf.* Scheme 18c). The addition of alkynyllithiums to Fischer-type carbene complexes has also been found to generate allene anion equivalents, leading to butenolides after carboxylation and lactonisation[134] (**Scheme 78b**).



Scheme 78

Finally, several reports detailing routes to fluorinated butenolides have appeared: 2-fluorobut-2-enolide **74** was initially reached from D-erythronolide *via* a low-yielding S_N2 reaction of fluoride ion.[135] An improved procedure used the Wadsworth–Emmons reaction of an α-fluorophosphonate to build the carbon skeleton (**Scheme 79a**). Whilst hard carbon nucleophiles were found to open the ring of **74** through 1,2-addition, soft carbon nucleophiles underwent 1,4-addition and the intermediate enolates could be further elaborated to fluorinated analogues of simple lignans. An equally efficient approach was used by Ge and Kirk to prepare 2-fluorotetronic



Scheme 79

acid by electrophilic fluorination of 2-bromotetronic acid in ethanol[136] (**Scheme 79b**). The alcohol solvent was important, suggesting activation of C-2 to fluorination by initial ethanol addition at C-3 to give a hemiacetal. This synthesis complemented the author's work on derivatives of 2-deoxy-2-ascorbic acid.[137,138]

9 References

1 H. W. Yang and D. Romo, *J. Org. Chem.*, 1997, **62**, 4.
2 J. P. A. Harrity, N. M. Heron, W. J. Kerr, S. McKendry, D. Middlemiss and J. S. Scott, *Synlett*, 1996, 1184.
3 W. Adam, P. Groer and C. R. Saha-Möller, *Tetrahedron: Asymmetry*, 1997, **8**, 833.
4 K. C. Nicolaou, F. Sarabia, S. Ninkovic and Z. Yang, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 525.
5 K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay and Z. Yang, *J. Am. Chem. Soc.*, 1997, **119**, 7974.
6 K. C Nicolaou, N. Wissinger, J. Pastor, S. Ninkovic, F. Sarabia, Y. He, D. Vourloumis, Z. Yang, T. Li, P. Giannakakou and E. Hamel, *Nature*, 1997, **387**, 268.
7 A. Balog, P. Bertinato, D.-S. Su, D. Meng, E. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *Tetrahedron Lett.*, 1997, **38**, 4529.
8 K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg and Z. Yang, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2399.
9 Z. Yang, Y. He, D. Vourloumis, H. Vallberg and K. C. Nicolaou, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 166.
10 K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, F. Roschangar, F. Sarabia, S. Ninkovic, Z. Yang and J. I. Trujillo, *J. Am. Chem. Soc.*, 1997, **119**, 7960.
11 D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm and M. Cordes, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 523.
12 D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *J. Am. Chem. Soc.*, 1997, **119**, 2733.
13 R. E. Taylor and J. D. Haley, *Tetrahedron Lett.*, 1997, **38**, 2061.
14 D. Meng, P. Bertinato, A. Balog, D.-S. Su, T. Kamenecka, E. J. Sorensen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1997, **119**, 10 073.
15 K. C. Nicolaou, D. Vourloumis, T. Li, J. Pastor, N. Winssinger, Y. He, S. Ninkovic, F. Sarabia, H. Vallberg, F. Roschangar, N. P. King, M. R. V. Finlay, P. Giannakakou, P. Verdier-Pinard and E. Hamel, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2097.
16 D.-S. Su, A. Balog, D. Meng, P. Bertinato, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2093.
17 A. Balog, D. Meng, T. Kamenecka. P. Bertinato, D.-S. Su, E. J. Sorensen and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2801.
18 D.-S. Su, D. Meng, P. Bertinato, A. Balog, E. J. Sorensen, S. J. Danishefsky, Y.-H. Zheng, T.-C. Chou, L. He and S. B. Horwitz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 757.
19 A. Fürstner and K. Langemann, *Synthesis*, 1997, 792.
20 A. Fürstner and K. Langemann, *J. Am. Chem. Soc.*, 1997, **119**, 9130.
21 I. Paterson and J. Man, *Tetrahedron Lett.*, 1997, **38**, 695.
22 A. B. Smith, III, and G. R. Ott, *J. Am. Chem. Soc.*, 1996, **118**, 13 095.
23 A. B. Smith, III, S. M. Condon, J. A. McCauley, J. L. Leazer, Jr., J. W. Leahy and R. E. Maleczka, Jr., *J. Am. Chem. Soc.*, 1997, **119**, 962.
24 D. J. Critcher and G. Pattenden, *Tetrahedron Lett.*, 1996, **37**, 9107.
25 D. R. Williams, K. M. Werner and B. Feng, *Tetrahedron Lett.*, 1997, **38**, 6825.
26 S. D. Rychnovsky, U. D. Khire and G. Yuang, *J. Am. Chem. Soc.*, 1997, **119**, 2058.
27 M. P. Doyle, C. S. Peterson, M. N. Protopopova, A. B. Marnett, D. L. Parker, Jr., D. G. Ene and V. Lynch, *J. Am. Chem. Soc.*, 1997, **119**, 8826.
28 C. Le Hetet, M. David, F. Carreaux, B. Carboni and A. Sauleau, *Tetrahedron Lett.*, 1997, **38**, 5153.
29 P. A. Jacobi and P. Herradura, *Tetrahedron Lett.*, 1996, **37**, 8297.
30 P. A. Jacobi and P. Herradura, *Tetrahedron Lett.*, 1997, **38**, 6621.
31 D. A. Evans, B. W. Trotter and J. C. Barrow, *Tetrahedron*, 1997, **53**, 8779.
32 M. P. Sibi, J. Lu and C. L. Talbacka, *J. Org. Chem.*, 1996, **61**, 7848.
33 M. Kang, J. Park and S. F. Pedersen, *Synlett*, 1997, 41.
34 S. Fukuzawa, K. Seki, M. Tatsuzawa and K. Mutoh, *J. Am. Chem. Soc.*, 1997, **119**, 1482.
35 E. Alonso, D. J. Ramón and M. Yus, *Tetrahedron*, 1997, **53**, 2641.
36 A. R. Katritzky, G. Feng and H. Lang, *J. Org. Chem.*, 1997, **62**, 706.
37 R. Déziel, E. Malenfant, C. Thibault, S. Frechétte and M. Gravel, *Tetrahedron Lett.*, 1997, **38**, 4753.
38 T. G. Back and B. P. Dyck, *Chem. Commun.*, 1996, 2567.
39 S. Nagumo, T. Furukawa, M. Ono and H. Akita, *Tetrahedron Lett.*, 1997, **38**, 2849.
40 R. Ballini and G. Bosica, *Synlett*, 1996, 1115.
41 M. P. Sibi and J. Ji, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 274.
42 N. Taniguchi and M. Uemura, *Tetrahedron Lett.*, 1997, **38**, 7199.
43 D. L. J. Clive and J. Zhang, *Chem. Commun.*, 1997, 549.
44 T. Konno and T. Kitazume, *Tetrahedron: Asymmetry*, 1997, **8**, 223.
45 K. Ogura, K. Ogu, T. Ayabe, J. Sonehara and M. Akazome, *Tetrahedron Lett.*, 1997, **38**, 5173.
46 P. Gilbert, M. L. Lewis, P. Quayle, Y. Zhao and K. Mills, *Tetrahedron Lett.*, 1996, **37**, 9115.
47 S. Amigoni, J. Schulz, L. Martin and Y. Le Floc'h, *Tetrahedron: Asymmetry*, 1997, **8**, 1515.
48 M. Brunner and H. Alper, *J. Org. Chem.*, 1997, **62**, 7565.
49 W.-Y. Yu, C. Bensimon and H. Alper, *Chem. Eur. J.*, 1997, **3**, 417.
50 K. Nozaki, W. Li, T. Horiuchi and H. Takaya, *Tetrahedron Lett.*, 1997, **38**, 4611.
51 S. K. Taylor, N. H. Chmiel, L. J. Simons and J. R. Vyvyan, *J. Org. Chem.*, 1996, **61**, 9084.
52 S. Yoshida, T. Ogiku, H. Ohmizu and T. Iwasaki, *J. Org. Chem.*, 1997, **62**, 1310.
53 K. Ito, T. Fukuda and T. Katsuki, *Synlett*, 1997, 387.
54 A. V. Kalinin, M. A. J. Miah, S. Chattopadhyay, M. Tsukazaki, M. Wicki, T. Nguen, A. L. Coelho, M. Kerr and V. Snieckus, *Synlett*, 1997, 839.
55 K. Kobayashi, K. Maeda, T. Uneda, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans. 1*, 1997, 443.
56 M. A. Brimble and R. J. R. Elliott, *Tetrahedron*, 1997, **53**, 7715.
57 B. Figadere, J.-F. Peyrat and A. Cavé, *J. Org. Chem.*, 1997, **62**, 3428.
58 D. M. Hodgson and A. R. Gibbs, *Synlett*, 1997, 657.
59 T. Inoue, O. Kitagawa, Y. Oda and T. Taguchi, *J. Org. Chem.*, 1996, **61**, 8256.
60 T. Inoue, O. Kitagawa, A. Saito and T. Taguchi, *J. Org. Chem.*, 1997, **62**, 7384.
61 M. P. Doyle, C. S. Peterson, Q.-L. Zhou and H. Nishiyama, *Chem. Commun.*, 1997, 211.
62 M. Lautens, C. Meyer and A. van Oeveren, *Tetrahedron Lett.*, 1997, **38**, 3833.
63 H. M. L. Davies and R. L. Calvo, *Tetrahedron Lett.*, 1997, **38**, 5623.
64 H. Yoda, M. Kawauchi, K. Takabe and K. Hosoya, *Heterocycles*, 1997, **45**, 1895.
65 T. Honda, H. Mizutani and K. Kanai, *J. Org. Chem.*, 1996, **61**, 9374.
66 D. J. Hart, J. Li, W.-L. Wu and A. P. Kozikowski, *J. Org. Chem.*, 1997, **62**, 5023.
67 N. Kanoh, J. Ishihara and A. Murai, *Synlett*, 1997, 737.
68 T. E. Janini and P. Sampson, *J. Org. Chem.*, 1997, **62**, 5069.
69 E. Lee, J. W. Lim, C. H. Yoon, Y. Sung, Y. K. Kim, M. Yun and S. Kim, *J. Am. Chem. Soc.*, 1997, **119**, 8391.
70 B. M. Trost, S. Tanimori and P. T. Dunn, *J. Am. Chem. Soc.*, 1997, **119**, 2735.
71 S.-J. Shieh, C.-C. Chen and R.-S. Liu, *J. Org. Chem.*, 1997, **62**, 1986.
72 S.-J. Shieh and R.-S. Liu, *Tetrahedron Lett.*, 1997, **38**, 5209.
73 B. Gabriele, G. Salerno, F. De Pascali, M. Costa and G. P. Chiusoli, *J. Chem. Soc., Perkin Trans. 1*, 1997, 147.
74 F.-T. Luo, M.-W. Wang and Y.-S. Liu, *Heterocycles*, 1996, **43**, 2725.
75 S. Jabre-Truffert and B. Waegell, *Tetrahedron Lett.*, 1997, **38**, 835.
76 R. Csuk, C. Schröder, S. Hutter and K. Mohr, *Tetrahedron: Asymmetry*, 1997, **8**, 1411.
77 C.-W. Lee, J. M. Gil and D. Y. Oh, *Heterocycles*, 1997, **45**, 943.
78 T. Mukaiyama, J. Izumi and I. Shiina, *Chem. Lett.*, 1997, 187.
79 B. M. Trost, P.-Y. Michellys and V. J. Gerusz, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1750.
80 A. Fürstner and T. Müller, *Synlett*, 1997, 1010.
81 M. P. Doyle and C. S. Peterson, *Tetrahedron Lett.*, 1997, **38**, 5265.
82 R. Göttlich, K. Yamakoshi, H. Sasai and M. Shibasaki, *Synlett*, 1997, 971.
83 T. Mino, S. Matsuda, M. Nishio and M. Yamashita, *J. Org. Chem.*, 1997, **62**, 2633.
84 M. Hirano, S. Yakabe, A. Satoh, J. H. Clark and T. Morimoto, *Synth. Commun.*, 1996, **26**, 4591.
85 J. D. Stewart, K. W. Reed, J. Zhu, G. Chen and M. M. Kayser, *J. Org. Chem.*, 1996, **61**, 7652.
86 S. Rissom, U. Schwarz-Linek, M. Vogel, V. I. Tishkov and U. Kragl, *Tetrahedron: Asymmetry*, 1997, **8**, 2523.
87 N. Greeves, W.-M. Lee and J. V. Barkley, *Tetrahedron Lett.*, 1997, **38**, 6453.

88 K. Nacro, M. Baltas, J.-M. Escudier and L. Gorrichon, *Tetrahedron*, 1997, **53**, 659.
89 J. Cossy, M. Cases and D. G. Pardo, *Tetrahedron Lett.*, 1996, **37**, 8173.
90 T. Sugai, K. Hamada, T. Akeboshi, H. Ikeda and H. Ohta, *Synlett*, 1997, 983.
91 W. Oppolzer, E. Walther, C. P. Balado and J. De Brabander, *Tetrahedron Lett.*, 1997, **38**, 809.
92 C. V. Ramana and M. Nagarajan, *Synlett*, 1997, 763.
93 M. Shimizu, K. Ishi and T. Fujisawa, *Chem. Lett.*, 1997, 765.
94 M. Oizumi, M. Takahashi and K. Ogasawara, *Synlett*, 1997, 1111.
95 T. Honda, S. Ono, H. Mizutani and K. O. Hallinan, *Tetrahedron: Asymmetry*, 1997, **8**, 181.
96 H. Kaku, M. Tanaka, Y. Norimine, Y. Miyashita, H. Suemune and K. Sakai, *Tetrahedron: Asymmetry*, 1997, **8**, 195.
97 M. Yamamoto, M. Hirota, K. Kishikawa, S. Kohmoto and K. Yamada, *Synthesis*, 1997, 937.
98 M. Kishida, N. Yamauchi, K. Sawada, Y. Ohashi, T. Eguchi and K. Kakinuma, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 891.
99 M. Shimizu, T. Kamikubo and K. Ogasawara, *Tetrahedron: Asymmetry*, 1997, **8**, 2519.
100 H. Konno, K. Hiroya and K. Ogasawara, *Tetrahedron Lett.*, 1997, **38**, 6023.
101 P. D. May and S. D. Larsen, *Synlett*, 1997, 895.
102 S. Kobayashi and M. Moriwaki, *Synlett*, 1997, 551.
103 J. L. Dillon, Q. Gao, E. A. Dillon and N. Adams, *Tetrahedron Lett.*, 1997, **38**, 2231.
104 R. W. Friesen and C. Vanderwal, *J. Org. Chem.*, 1996, **61**, 9103.
105 I. E. Marko, I. Chellé-Regnaut, B. Leroy and S. L. Warriner, *Tetrahedron Lett.*, 1997, **38**, 4269.
106 G. H. Posner, R. H. Hutchings and B. T. Woodward, *Synlett*, 1997, 432.
107 A. M. Gómez, S. Mantecón, S. Valverde and J. López, *J. Org. Chem.*, 1997, **62**, 6612.
108 D. H. Hua, Y. Chen, H.-S. Sin, M. J. Maroto, P. D. Robinson, S. W. Newell, E. M. Perchellet, J. B. Ladesich, J. A. Freedman, J.-P. Perchellet and P. K. Chiang, *J. Org. Chem.*, 1997, **62**, 6888.
109 L. Ollero, L. Castedo and D. Dominguez, *Synlett*, 1997, 1047.
110 R. A. Bunce and C. L. Schilling, III, *Tetrahedron*, 1997, **53**, 9477.
111 I. D. Kostas and C. G. Screttas, *J. Org. Chem.*, 1997, **62**, 5575.
112 E. J. Corey and G. Z. Zheng, *Tetrahedron Lett.*, 1997, **38**, 2045.
113 R. L. Danheiser, T. W. Lee, M. Menichincheri, S. Brunelli and M. Nishiuchi, *Synlett*, 1997, 469.
114 P. Yu, Y. Yang, Z. Y. Zhang, T. C. W. Mak and H. N. C. Wong, *J. Org. Chem.*, 1997, **62**, 6359.
115 D. Ichinari, T. Ueki, K. Yoshihara and T. Kinoshita, *Chem. Commun.*, 1997, 1743.
116 J. Uenishi, R. Kawahama and O. Yonemitsu, *J. Org. Chem.*, 1997, **62**, 1691.
117 G. H. L. Nefkens, J. W. J. F. Thuring and B. Zwannenburg, *Synthesis*, 1997, 291.
118 I. Beltaïef, R. Besbes, H. Amri and J. Villiéras, *Tetrahedron Lett.*, 1997, **38**, 813.
119 G. Mehta and S. Sengupta, *Tetrahedron Lett.*, 1996, **37**, 8625.
120 H.-J. Ya, K.-H. Kang, Y.-G. Ahn and S.-J. Oh, *Heterocycles*, 1997, **45**, 277.
121 H. Kitajima and T. Katsuki, *Synlett*, 1997, 568.
122 R. K. Haynes, W. W.-L. Lam, L.-L. Yeung, I. D. Williams, A. C. Idley, S. M. Starling, S. C. Vonwiller, T. W. Hambley and P. Lelandais, *J. Org. Chem.*, 1997, **62**, 4552.
123 C.-C. Shen, S.-C. Chou, C.-J. Chou and L.-K. Ho, *Tetrahedron: Asymmetry*, 1996, **7**, 3141.
124 M. Kotora and E. Negishi, *Synthesis*, 1997, 121.
125 M. Kotora and E. Negishi, *Tetrahedron Lett.*, 1996, **37**, 9041.
126 H. Mori, H. Kubo, H. Hara and S. Katsumura, *Tetrahedron Lett.*, 1997, **38**, 5311.
127 W.-Y. Yu and H. Alper, *J. Org. Chem.*, 1997, **62**, 5684.
128 W.-J. Xiao and H. Alper, *J. Org. Chem.*, 1997, **62**, 3422.
129 C. Zhang and X. Lu, *Tetrahedron Lett.*, 1997, **38**, 4831.
130 J. A. Marshall, M. A. Wolf and E. M. Wallace, *J. Org. Chem.*, 1997, **62**, 367.
131 J. A. Marshall and K. W. Hinkle, *J. Org. Chem.*, 1997, **62**, 5989.
132 J. A. Marshall and M. Chen, *J. Org. Chem.*, 1997, **62**, 5996.
133 A. R. Katritzky, D. Feng and H. Lang, *J. Org. Chem.*, 1997, **62**, 715.
134 N. Iwasawa, K. Maeyama and M. Saitou, *J. Am. Chem. Soc.*, 1997, **119**, 1486.
135 J. Kvicala, J. Plocar, R. Vlasáková, O. Paleta and A. Pelter, *Synlett*, 1997, 986.
136 P. Ge and K. L. Kirk, *J. Fluorine Chem.*, 1997, **84**, 45.
137 P. Ge and K. L. Kirk, *J. Org. Chem.*, 1996, **61**, 8671.
138 P. Ge and K. L. Kirk, *J. Org. Chem.*, 1997, **62**, 3340.