Saturated and unsaturated lactones

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Received (in Cambridge) 11th March 1999

Covering: 1 November 1997 to 31 October 1998
Previous review: 1998, 1869

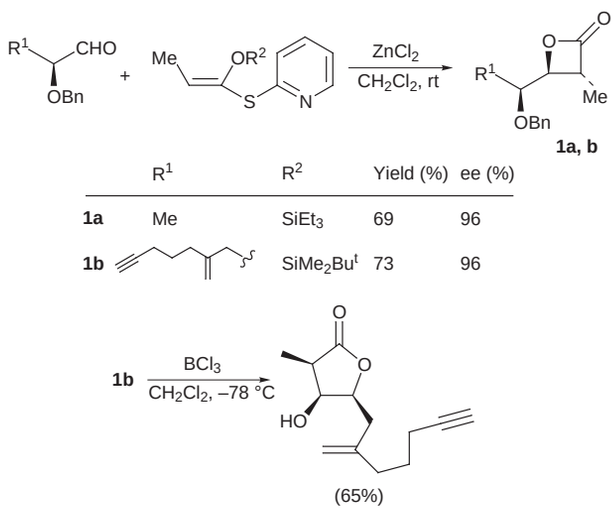
1 Introduction

This article reviews recent developments in the synthesis of lactones, concentrating on the ring-closing steps. As ever there has been much activity in this area and the selection herein, although not comprehensive, is intended as a synopsis of new methodologies and current directions of research. Full reports of previous communications that have been mentioned in prior articles in this series are not generally included except where significant new material was disclosed. The entries are classified by the ring size of the lactone products but where methodology applies across these classes this is indicated in the text.

The range of chemistry used for the preparation of lactones is broad, but a number of themes have assumed particular prominence this year. Ring-closing metathesis has been firmly established as a general method for the synthesis of macrolides and has also provided new routes to small and medium-ring lactones. Palladium catalysis remains an invaluable tool for lactone synthesis and many recent reports have focused on tandem or cascade reactions that combine the ring-closing step with further, exocyclic C–C bond formations to efficiently assemble multiply-substituted targets. Some of these methodologies may be applicable to combinatorial synthetic schemes. A few reports of more traditional multi-component syntheses of lactones both in solution and on the solid phase have also appeared. Amongst the many metal-mediated syntheses described, the compatibility of indium and bismuth reagents with aqueous media has attracted particular attention.

2 β-Lactones

The tandem Mukaiyama aldol–lactonisation recently introduced by Romo and co-workers for the synthesis of *trans*-3,4-disubstituted β-lactones has been applied to optically active α-alkoxyaldehydes[1,2] (Scheme 1). Chelation control gave high selectivity for the *syn*, *anti* aldol adducts with generally excellent optical purity, although this was compromised by epimerisation for enolisable α-aryl aldehydes (*e.g.* R^1 = Ph, 69% ee). The

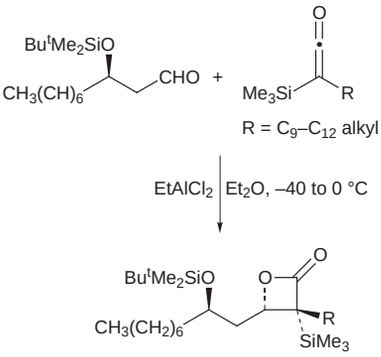


Scheme 1

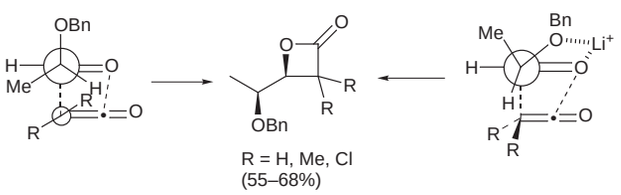
β-lactone **1b** was expanded through a tandem debenzylation–transacetylation to yield the all-*syn* γ-lactone core of the cytotoxic marine metabolite okinellin B.[2]

Further use has been made of the [2+2] cycloaddition of ketenes and aldehydes to generate β-lactones. Kocienski and co-workers achieved moderate to good 1,3-diastereocontrol in the Lewis acid catalysed addition of trimethylsilylketenes to β-alkoxyaldehydes, leading to efficient syntheses of the pancreatic lipase inhibitors panclicins A–D[3] (Scheme 2). The diastereofacial selectivity of the aldehyde was ascribed to a pseudocyclic conformation resulting from electrostatic attraction between the β-oxygen and the coordinated Lewis acid. A detailed theoretical treatment of the [2+2] cycloaddition, supported by experimental testing of the predictions, has also appeared.[4] The asynchronicity and geometry of the transition state for addition to α-alkoxyaldehydes was found to vary with the electrophilicity of the ketene, but the dominant feature in all cases was the minimisation of steric interactions between the aldehyde and the *endo* substituent of the ketene. Thus the *syn* cycloadduct was highly favoured both in the presence and absence of chelating lithium cations (Scheme 3), although high concentrations of lithium ions also enhanced the rate of reaction. Romo and co-workers have described a catalytic, asymmetric variant of this reaction using dichlorotitanium–TADDOL catalysts **2** derived from tartaric acid, but only moderate enantioselectivities (typically 20–50% ee) have been achieved thus far.[5]

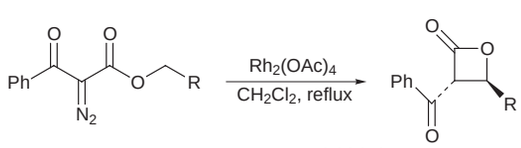
An unusually selective C–H insertion of a rhodium(II) carbenoid has been described that led exclusively to β-lactone formation from α-diazo-α-benzoyl esters[6] (Scheme 4). The selectivity appeared to be a result of steric constraints on the structure of the metallocarbene imposed by the aroyl group, since simple α-diazoacetoacetates gave only the more common γ-lactone insertion products.



Scheme 2

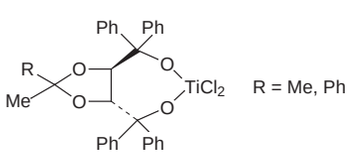


Scheme 3



R	Yield (%)
CH_2CH_2Ph	55
CH_3	58

Scheme 4



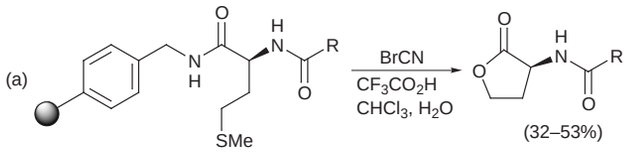
2

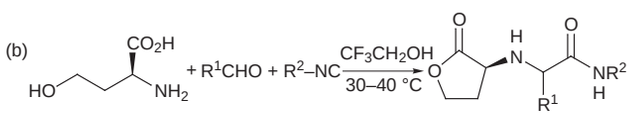
3 γ-Lactones

3.1 Monocyclic γ-lactones

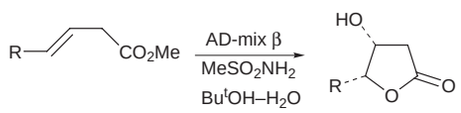
Homoserine lactones offer an attractive, simple scaffold common to several classes of biologically active small molecules and two approaches have appeared that are suitable for incorporation into a combinatorial synthetic plan. In the first, standard solid phase peptide chemistry was used to construct resin-linked methionines which were cleanly cleaved and cyclised with preservation of the L-methionine stereochemistry on treatment with cyanogen bromide[7] (Scheme 5a). In the second approach, a three-component intramolecular Ugi condensation was used to assemble homoserine lactones starting from L-homoserine itself[8] (Scheme 5b). 2,2,2-Trifluoroethanol was the optimum solvent to prevent competitive formation of ring-opened products. Although generally efficient, the wide range of yields and diastereoselectivities observed might lead to variable product distributions if the method were applied to mixture syntheses. The related readily separable diastereoisomeric lactones **3** were prepared in moderate selectivity by direct dihydroxylation of protected allylglycine.[9]

The Sharpless asymmetric dihydroxylation was employed in the synthesis of optically active γ-lactones and butenolides from β,γ-unsaturated esters[10,11] (Scheme 6). Optically pure lactones in either enantiomeric series were obtained, provided the



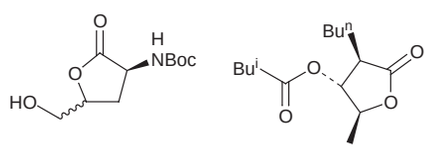


Scheme 5



R	Yield (%)	ee (%)
Bu^n	92	97
$CH_2OSiBu^tMe_2$	88	92
Me	48	80

Scheme 6



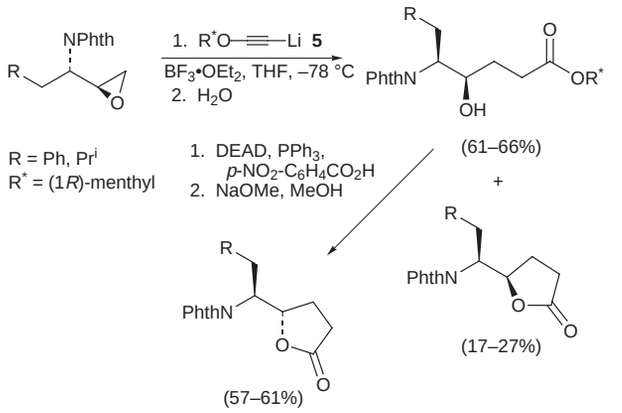
3 β:α 70:30 **4**

alkyl substituent on the *trans* olefin was sufficiently large to engender good enantiofacial discrimination in the dihydroxylation. This simple and efficient strategy was used to good effect in syntheses of several 3,4,5-*trans*,*trans*-γ-lactones, including (+)-blastmycinone **4**.

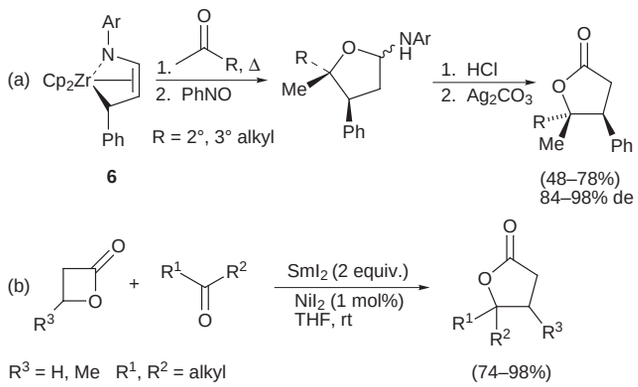
Riera and co-workers have reported two preparations of enantiomerically pure γ-alkylamino-γ-lactones, key intermediates in the synthesis of hydroxyethylene dipeptide isosteres, where both methods relied on the Sharpless asymmetric epoxidation of (*E*)-allyl alcohols to control the stereochemistry. The first[12] elaborated the epoxides by standard ring opening and Wittig homologation techniques, while the second[13] involved a novel ring opening of *N*-phthalimide protected α-amino epoxides by the lithium alkynoate **5** which served as a surrogate acetate enolate (Scheme 7). Although there was some tendency for lactonisation during hydrolysis of the ynol ether, with careful control of the conditions reasonable yields of the acyclic material were attained. Since this material was readily epimerised by Mitsunobu inversion, all diastereoisomers of the lactone scaffold were accessible.

Enders and co-workers have described readily available zirconocene-1-aza-1,3-diene complexes **6** that behave as homoenolate equivalents for the construction of γ-lactones[14] (Scheme 8a). High *trans* stereoselectivity was observed for the insertion of sterically demanding aliphatic ketones into the zirconocycle, making the process particularly attractive for the assembly of contiguous tertiary or quaternary centres. Another useful homoenolate equivalent was generated from the cleavage of β-lactones with samarium(II) iodide in the presence of catalytic nickel(II) iodide[15] (Scheme 8b), although in this case very sterically demanding carbonyl compounds did not participate in the reaction.

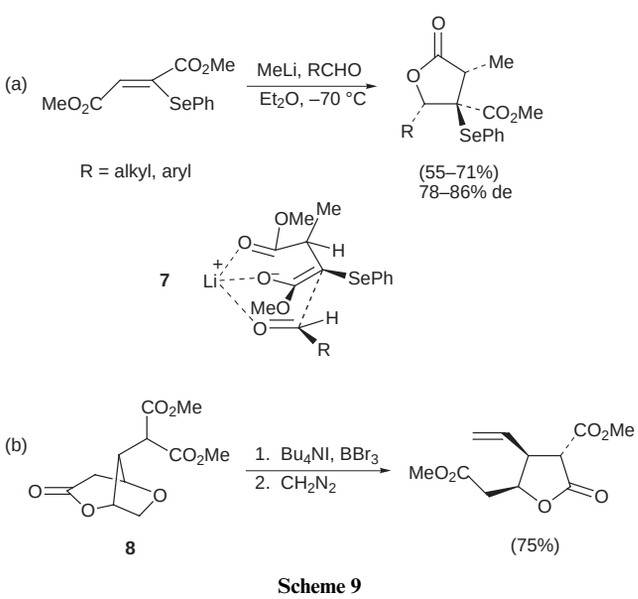
The anion formed on conjugate addition to fumarates may also be viewed as a homoenolate equivalent and a tandem Michael–aldol sequence was applied to 2-phenylselenofumarates[16] (Scheme 9a). Reasonable levels of stereo-



Scheme 7

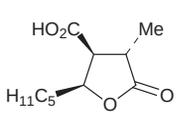


Scheme 8



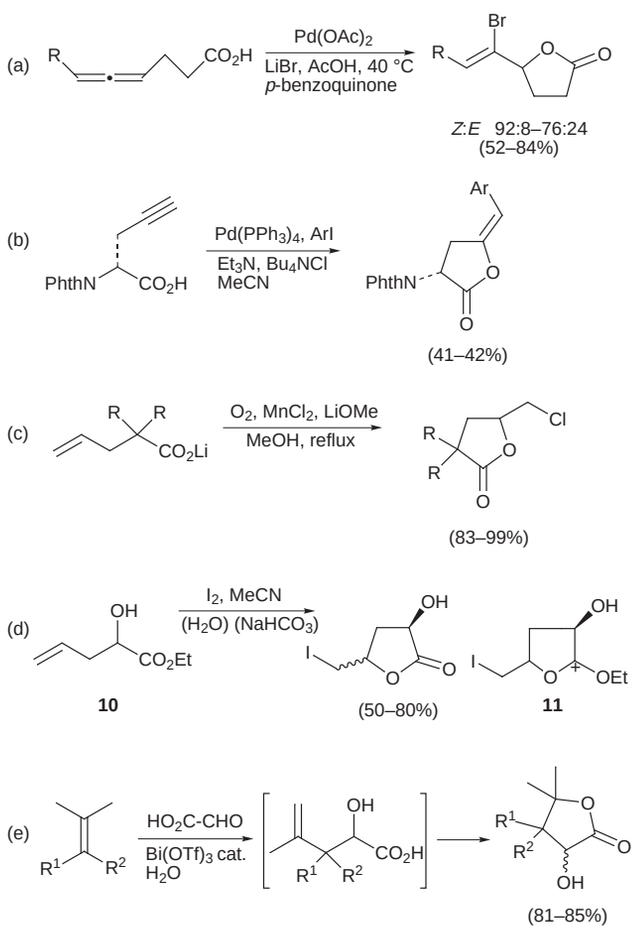
Scheme 9

control resulting from *Si* face addition to the chelated enolate **7** were observed. Elimination of the selenoxide led to butenolides, whilst radical deselenation gave intermediates for the synthesis of paraconic acids. An interesting and efficient rearrangement of the lactone **8**, triggered by dual cleavage of two C–O bonds by iodide, was observed in a synthesis of (±)-nephromopsinic acid[17] (Scheme 9b). Also in the field of paraconic acid synthesis, a chemoenzymatic approach has led to a revision of the configuration of natural (−)-phaseolinic acid **9**.[18]



9

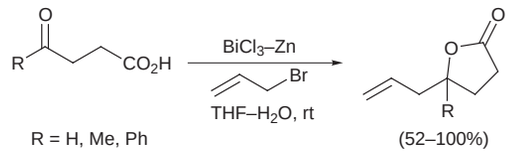
Some new variations have appeared of the well-worn path to γ-lactones through electrophilic cyclisation of unsaturated carboxylate derivatives. Bäckvall and co-workers found that γ-allenic acids cyclised in good yield upon palladium-catalysed oxidation of the allene to a π-(bromoallyl)palladium intermediate, giving mainly the (*Z*)-alkenes[19] (Scheme 10a). Palladium catalysis also effected the cyclisation of pent-4-ynoates to γ-lactones allied with tandem Heck-type coupling of aryl iodides to the intermediate vinylpalladium species[20] (Scheme 10b). Unfortunately, under the temperature and basicity needed for cyclisation, racemisation of the phthalimide protected amino acid occurred. Cyclisation of pent-4-enoates by oxidative dichlorination was also reported[21] (Scheme 10c). Willis and co-workers investigated the iodolactonisation of the simple 2-hydroxypent-4-enoate **10** by ^{18}O labelling and found the mechanistic fate of the intermediate cation **11** to vary with the presence or absence of base: S_N2 dealkylation, hydrolytic ring opening or orthoester formation of varying efficiencies were all possible pathways[22] (Scheme 10d). Similar α-hydroxy-γ-lactones resulted from the *in situ* lactonisation of pent-4-enoates formed by the carbonyl–ene reaction of alkenes and glyoxylic acid under bismuth(III) catalysis[23] in water (Scheme 10e).



Scheme 10

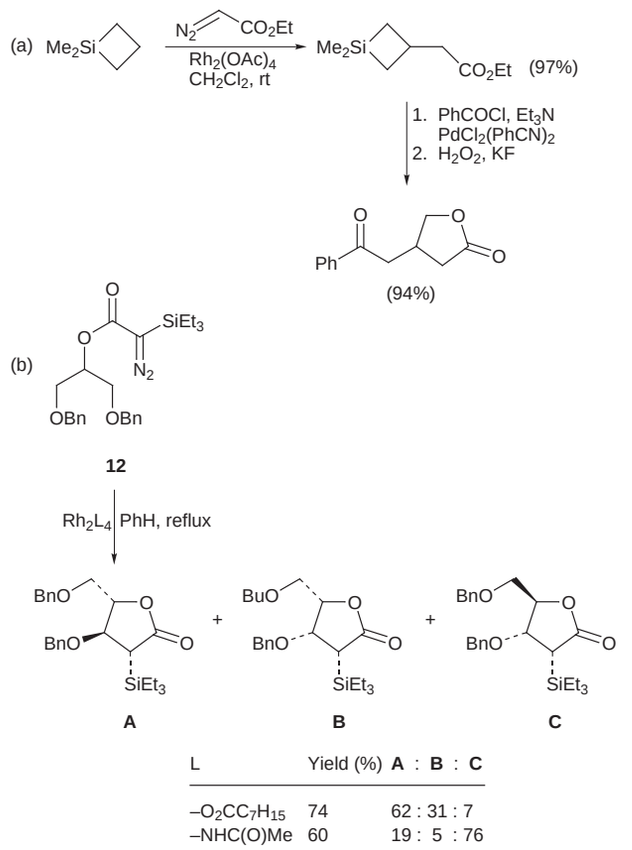
An organobismuth(III) reagent compatible with water and acidic groups was used to prepare γ-lactones by straightforward allylation of 1,4-ketoacids[24] (Scheme 11). The methodology applied equally to the synthesis of bicyclic γ-lactones and δ-lactones. A related indium-mediated Barbier allylation of γ-hydroxy-γ-lactones in water was reported by Paquette and Bernadelli.[25]

New examples have appeared of γ-lactone formation through the rhodium-catalysed C–H insertion reactions of diazoacetates. Thus the intermolecular reaction with silacyclobutanes gave exclusive and high yielding insertion into the



Scheme 11

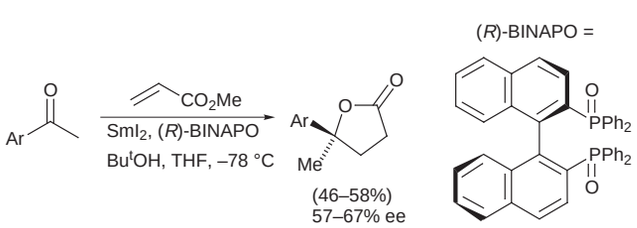
β-C–H bond, rationalised as a result of electron donation from the C–Si bond to the 3-centre, 2-electron transition state[26] (Scheme 12a). Subsequent palladium-catalysed ring opening, acyl chloride coupling and Fleming–Tamao oxidation gave γ-lactones in excellent yield. The intramolecular insertion reactions of α-silyl-α-diazoacetates such as **12** (Scheme 12b) were less selective but provided a promising entry into highly functionalised chiral γ-lactones.[27] The reversal of diastereoselectivity on changing to the carboxamide ligand reflected a shortening of the Rh–C bond lengths and a consequent increase in ligand–substrate steric interactions.



L	Yield (%)	A : B : C
$-O_2CC_7H_{15}$	74	62 : 31 : 7
–NHC(O)Me	60	19 : 5 : 76

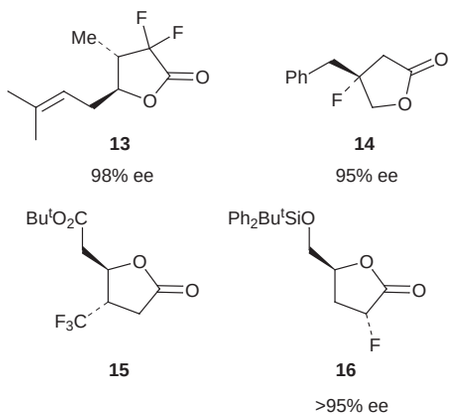
Scheme 12

In another preliminary finding on the stereoselective synthesis of γ-lactones, chiral phosphine ligands gave moderate enantiocontrol in the samarium(II) mediated addition of ketyl radicals to α,β-unsaturated esters[28] (Scheme 13). The stereochemistry was introduced in the radical Michael addition through a medium-ring chelate and was followed by protonation of the samarium(II) enolate and lactonisation.



Scheme 13

A number of articles have detailed syntheses of fluorinated γ-lactones, often with the intent of profiling the effects of fluorination on biological activity. Thus compounds **13**–**16** were prepared by, respectively, 5-*exo*-*trig* radical cyclisation of a difluorinated acetal,[29] enzymatic resolution of a fluorinated propane-1,3-diol,[30] chelation controlled Mukaiyama aldol condensation[31] and stereoselective fluorination of a 5-substituted lactone with *N*-fluorodibenzenesulfonimide.[32]

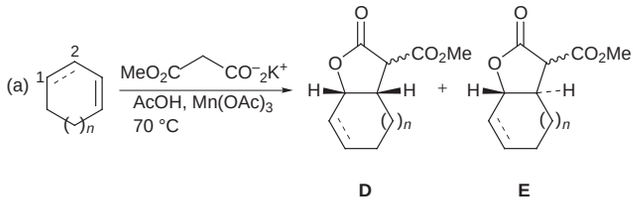


3.2 Bicyclic and polycyclic γ-lactones

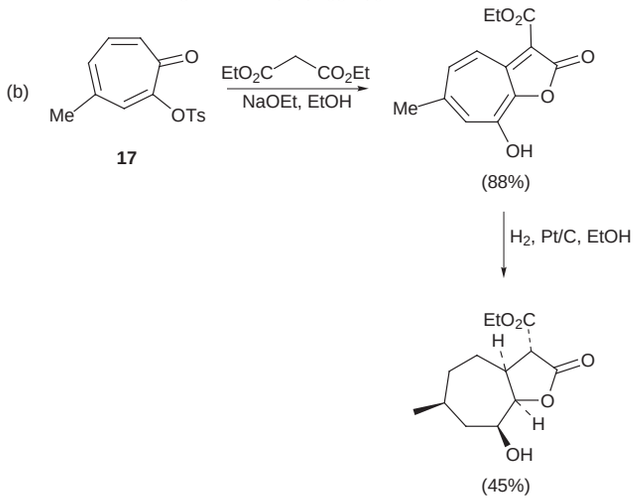
The radical annulation of olefins with acetate or malonate derivatives offers a well established direct route to γ-lactones and interesting stereoselectivity was seen in the manganese(III) mediated addition to cyclic alkenes[33] (Scheme 14a). In all cases the selectivity improved as the rigidity of the alkenes was increased by further unsaturation, but a strong preference for *cis* fusion in small systems became one for *trans* fusion with medium rings. Simple decarboxylation gave diastereomerically pure products in reasonable yields. The contrasting *cis* annulation of a γ-lactone to a medium ring was achieved by regioselective anionic condensation of a malonate enolate with 2-tosyloxytropone **17** *en route* to guaianolide and pseudoguaianolide natural products[34] (Scheme 14b). Catalytic hydrogenation of the tropolone derivative suffered from overreduction of the alcohol, but a fair overall yield of the major diastereoisomer was obtained.

Ferrocenium hexafluorophosphate **18** has been introduced as a single electron oxidant for malonate enolates, promoting intramolecular cyclisation onto alkenes[35] (Scheme 15). Competing cationic termination steps led to mixtures of bicyclic lactones and cyclopentanes depending on the substituent pattern, but this was controlled by the addition of TEMPO to give only radical termination. A separate reductive ring closure completed the lactonisation. The purely ionic cyclisation of malonates and enantiopure glycidyl nosylates led to the cyclopropanolactones **19** in good yield (41–70%) and high enantiomeric excess when caesium fluoride was used as the base.[36] Other cyclopropanolactones have been prepared by rhodium-catalysed intramolecular cyclopropanation of allylic diazoacetates.[37]

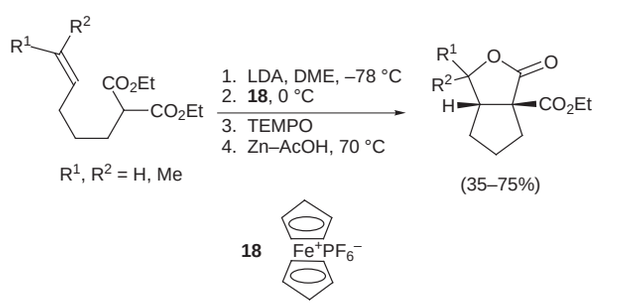
Intramolecular Diels–Alder cycloadditions of acyclic esters have been used to generate a number of polycyclic γ-lactones. During synthetic studies on the shellfish toxin gymnodimine, only *exo* cyclisation of the triene **20** was seen as a result of steric clashes between the *tert*-butyl ester and the diene methyl substituent in the alternative *endo* transition state[38] (Scheme 16). Notably, quite extreme conditions were needed and the addition of 2,6-di-*tert*-butyl-4-methylphenol as an antioxidant was essential for success. Less impressive but still synthetically useful selectivities for the expected *endo* cyclisations were seen in the formation of the bicyclic lactones **21**[39] (74%, *endo*:*exo* 6:1) and **22**[40] (54% + 22% other *endo* isomer) from an α-methylene-γ-lactone and a butenolide respectively. The γ-lactone **23** was formed in good yield (65%) from the cyclisation of a propiolate



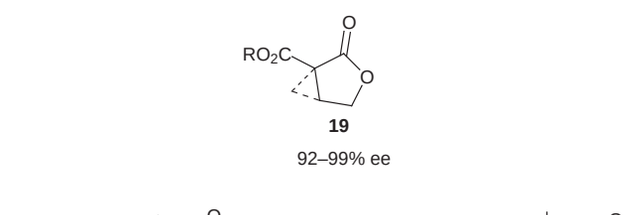
n	$\Delta_{1,2}$	D	:	E	Yield (%)
1	C—C	82	:	18	32
1	C=C	100	:	0	41
3	C=C	7	:	93	70



Scheme 14



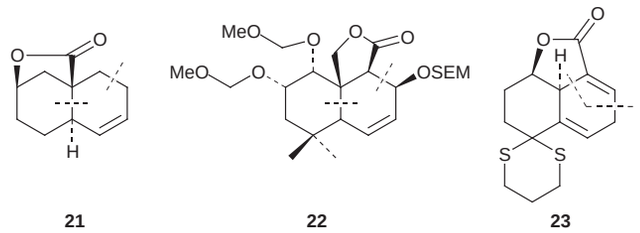
Scheme 15



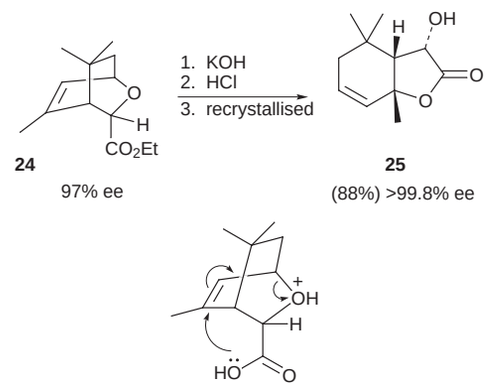
Scheme 16

ester at moderate temperature.[41] The bulky cyclic dithioacetal group was introduced specifically to enhance the population of the s-*cis* conformation of the diene precursor, since the related *gem*-dimethyl substituted material showed very poor reactivity.

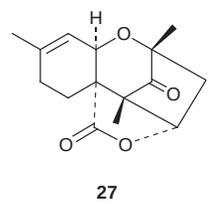
The hetero Diels–Alder adduct **24** was rearranged to give the useful bicyclic γ-lactone **25** in excellent yield and optical purity



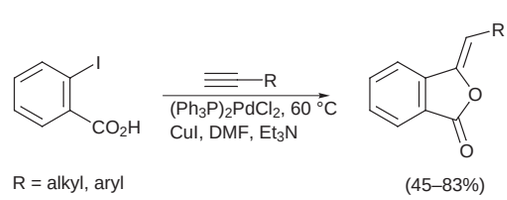
which served in turn to prepare the butenolide pheromones (*R*)-actinidiolide and (*R*)-dihydroactinidiolide[42] (Scheme 17). The rearrangement was presumed to occur through the intramolecular allylic substitution shown in **26**. White and coworkers were also able to make good use of allylic reactivity in a sequence of acid- and palladium-catalysed rearrangements leading to the lactone **27** which completed a formal synthesis of the fungal metabolite (±)-verrucarol.[43]



Scheme 17

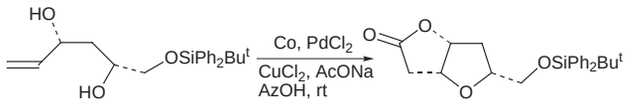


Although previous studies on the cyclisation of 2-alkynylbenzoic acids had generally produced mixtures of isocoumarins and alkylidenephthalides, the tandem palladium-catalysed coupling–cyclisation of alkynes and 2-iodobenzoic acid often gave exclusively the phthalides in good yield[44] (Scheme 18). The lactonisation was found to be catalysed by triethylamine hydrochloride through a 5-*exo-dig* pathway to give only *Z*-alkylidenephthalides.



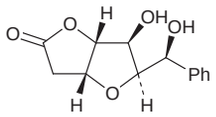
Scheme 18

Another palladium-catalysed tandem sequence was used to construct efficiently the tetrahydrofuranobutyrolactone **28** as a single diastereoisomer during a synthesis of (−)-*trans*-kumausyne[45] (Scheme 19). The related bicyclic core of (+)-goniofufurone **29** was synthesised by diastereoselective allenylation of a butyrolactone aldehyde using indium in water.[46,47] The alternative tetrahydrofuranolactone **30**, a structural motif of several lignans, was formed by highly diastereoselective



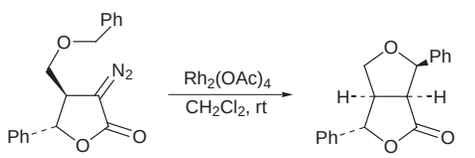
28 (93%)

Scheme 19



29

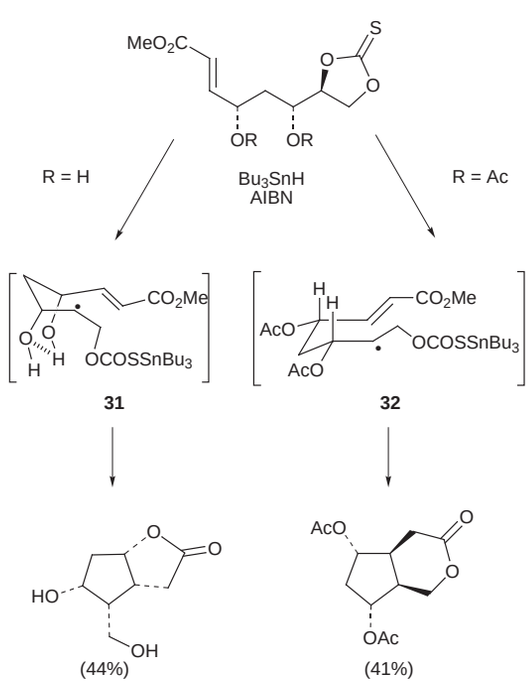
intramolecular C–H insertion of a rhodium carbenoid[48] (Scheme 20). Unfortunately, preparation of the α-diazo-γ-lactone precursor was compromised by competing azide formation in the diazo transfer to the lactone enolate (50%).



30 (90%)

Scheme 20

A detailed report has been published on the divergent synthesis of bicyclic γ- and δ-lactones from carbohydrates through 5-*exo*-*trig* radical cyclisation[49] (Scheme 21). The unprotected substrate reacted with a pseudo-axial disposition of the hydroxy groups **31**, stabilised by intramolecular hydrogen bonding, to give the all-*syn* lactone. Disruption of the hydrogen bonds by acetylation gave the equatorially substituted conformer **32** which produced the alternative δ-lactone. 5-*exo*-*trig* Radical cyclisation was also used by Nicolaou and co-workers to assemble the lactone **33** in model studies on the synthesis of the farnesyl transferase inhibitors CP-225,917 and CP-263,114.[50]

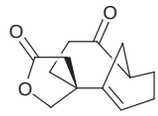


31 **32**

Scheme 21

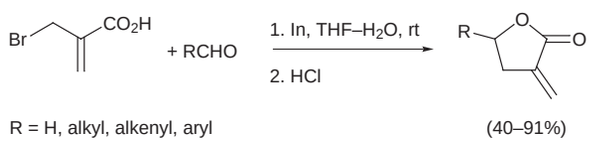
3.3 α-Alkylidene-γ-lactones

The classical intermolecular allylation of aldehydes by (α-halomethyl)acrylates has been revisited, this time using indium



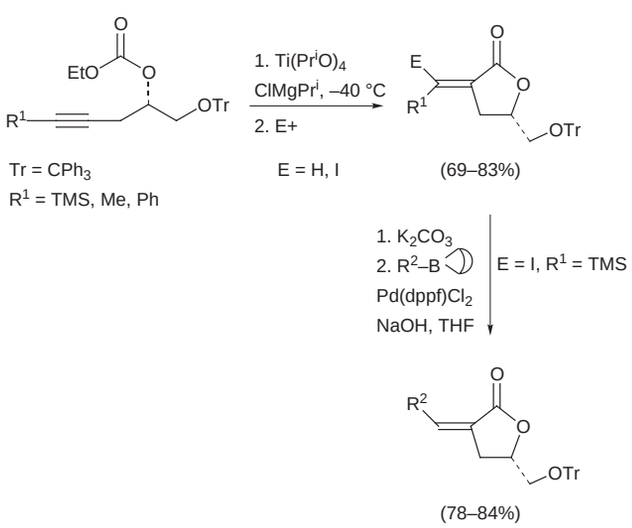
33

metal as the activating agent in aqueous media[51] (Scheme 22). Generally excellent yields were obtained for a range of saturated and unsaturated aldehydes. The zinc mediated process has also been investigated in the context of spiro-α-methylene-γ-lactone formation from steroidal ketones, where α-hydroxy substituents were found to enhance the diastereoselectivity of the addition.[52] Sato and co-workers were able to prepare isomerically pure *E*- or *Z*-α-alkylidene-γ-lactones by an extension of their work on the intramolecular nucleophilic acyl substitution of homopropargyl (but-3-ynyl) carbonates[53] (Scheme 23). The initial cyclisations gave stereoselectively the *E*-alkenes on quenching with acid. By quenching the reaction of the silyl-protected acetylene with iodine, and following this with Suzuki–Miyauma coupling, the *Z*-isomers were made instead.



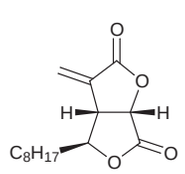
R = H, alkyl, alkenyl, aryl (40–91%)

Scheme 22



Scheme 23

Previous reviews in this series described work by Liu and co-workers on the conversion of molybdenum- and tungsten-π-allyl complexes to α-methylene-γ-lactones. This methodology has been applied to the synthesis of avenociolide **34**.[54] Additionally, an enantioselective variant of the process has been communicated[55] and a related reaction of iron alkynyl complexes was developed[56] (Scheme 24). This one-pot reaction consisted of palladium-catalysed coupling of an alkynylstannane to generate the alkynyliron complex which underwent Lewis acid promoted addition to aldehydes, presumably to give the iron oxacarbenium species **35**.



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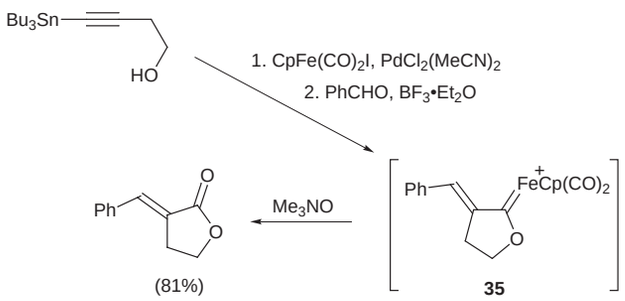
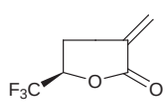


Scheme 24

Both enantiomers of the trifluoromethylated α-methylene-γ-lactone **36** and its difluoromethyl analogue were prepared in good optical purity (96–98% ee) by tandem enzymatic acylation and lactonisation from fluorinated 4-hydroxy-2-methylenepentanoates.[57] The racemic difluoromethyl derivatives **37** were reached through straightforward Reformatsky reaction of ethyl bromodifluoroacetate.[58]



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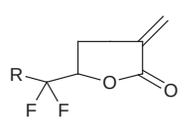
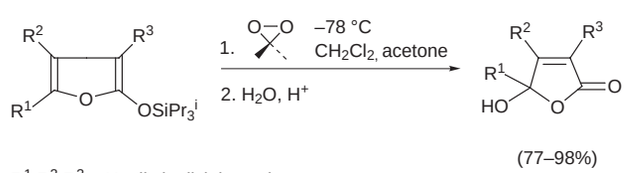


37a R = CO_2Et
37b R = CH_2OH

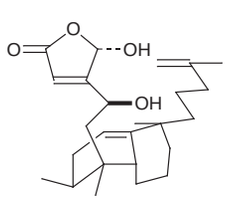
4 But-2-enolides and tetronic acids

New methodology has been reported that gave high yielding and selective oxidation of 2-trialkylsilyloxyfurans to γ-hydroxybutenolides on exposure to dimethyldioxirane[59] (Scheme 25). The chemoselectivity of this reagent was demonstrated in a synthesis of the protein phosphatase inhibitor (+)-dysidiolide **38**, where the butenolide was introduced through an aldol condensation of the (silyloxyfuranyl)titanium reagent **39** and subsequent oxidation in the presence of the alkenes and unprotected hydroxy group of the target.[60]



R^1,R^2,R^3 = H, alkyl, allyl, benzyl

Scheme 25



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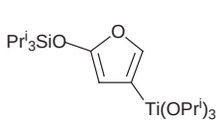
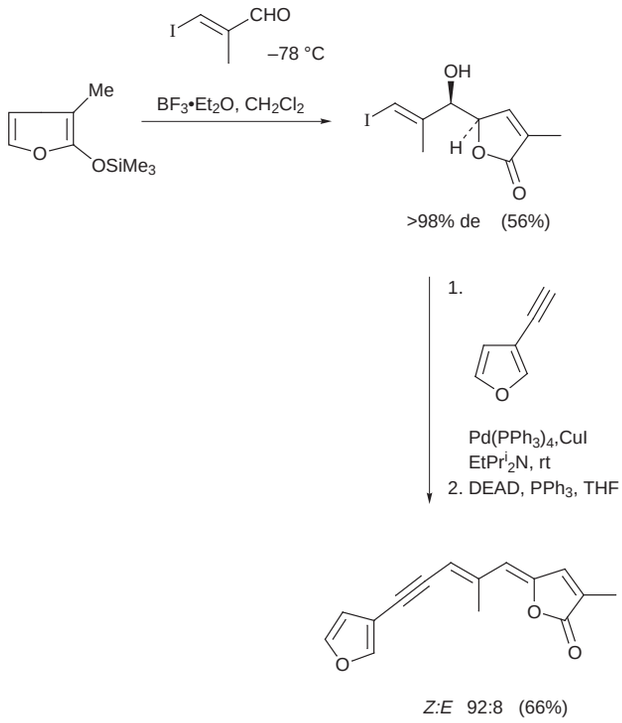
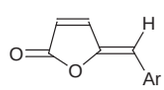


39

Brückner and co-workers have proposed a general route to γ-alkylidenebutenolides by the *anti* selective elimination of γ-(hydroxyalkyl)butenolides available from carbohydrate precursors or, as in the synthesis of (*Z*)-freelingyne, by Lewis acid catalysed aldol reactions of 2-(trialkylsilyloxy)furans[61,62] (Scheme 26). The diastereoselectivity of the Mukaiyama aldol was reversed when zinc bromide was used as the activating agent (74% de), leading to the (*E*)-alkylidenebutenolide after the elimination. Simple (*Z*)-γ-alkylidenebutenolides **40** were prepared similarly by the aldol condensation of the lithium enolate of γ-crotonolactone with aryl aldehydes followed by elimination under equilibrating conditions (57–80% yield, *ca.* 95:5 *Z*:*E*).[63] An asymmetric equivalent of this γ-enolate was used extensively in the synthesis of okadaic acid.[64–66] The vinylogous urethane lactone **41** was enolised and reacted with alkylating agents, aldehydes and acid chlorides to provide optically pure γ-substituted butenolides after removal of the auxiliary by reduction and Cope elimination (Scheme 27).



Scheme 26



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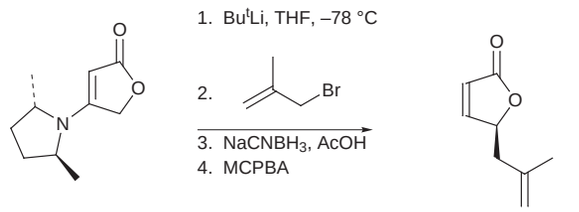


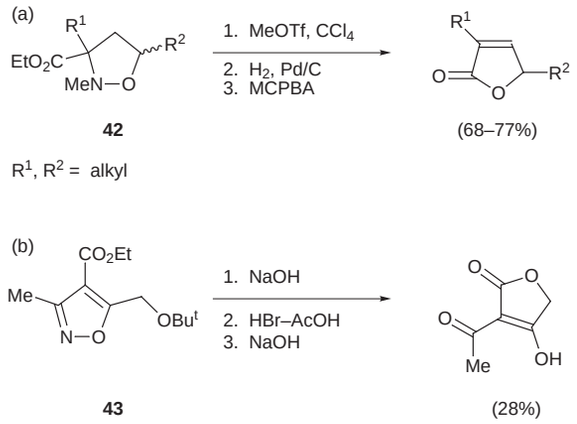
41

Scheme 27

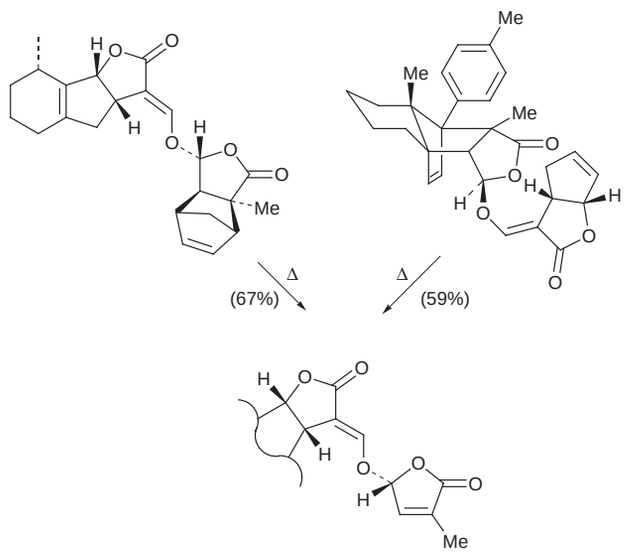
The elaboration of 1,3-dipolar cycloaddition products has given two approaches to butenolides: the isoxazolidines **42** were transformed to simple racemic butenolides in good yield by *N*-methylation, reductive ring-opening and Cope elimination[67] (Scheme 28a). Similarly, 3-acyltetronic acids were made in modest yield from the isoxazole **43**[68] (Scheme 28b). Here, hydrogen bromide in acetic acid found a novel application as the agent for reductive cleavage of the N–O bond.

Two groups have reported independent solutions to the problem of constructing strigolactones, where both used a sterically demanding template to enhance the stereoselectivity of the coupling of the butenolide moiety to the polycyclic γ-lactone. In the first case, Winterfeldt's auxiliary was appended to the butenolide,[69] whilst the second approach used cyclopentadiene.[70] Both templates were removed by thermal Diels–Alder cycloreversion with preservation of the butenolide stereochemistry and the geometry of the enol ether (Scheme 29).

The synthesis of butenolides through palladium-catalysed



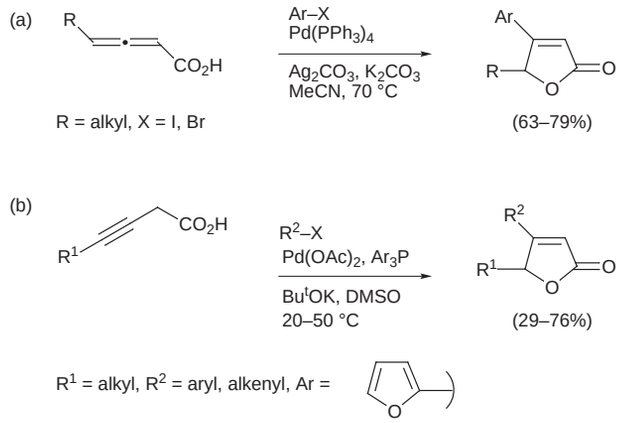
Scheme 28



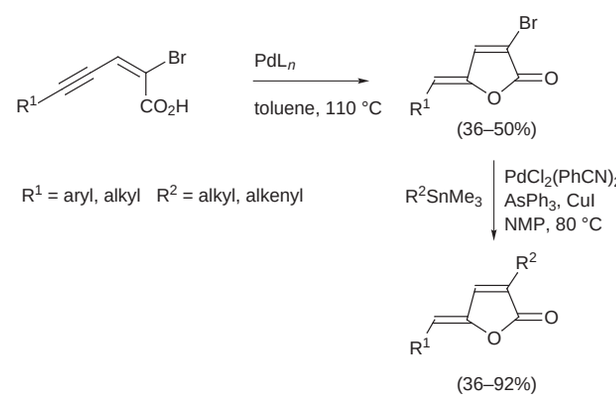
Scheme 29

couplings or lactonisations has received much attention. Marshall and co-workers have previously described the silver-catalysed lactonisation of allenic acids formed by hydrocarbonylation of allenyl palladium species, and this was exploited in syntheses of (+)-longifolicin[71] and (+)-kallolide A.[72] The related carbonylative lactonisation of propargyl alcohols can take place in the presence of diaryl dichalcogenides to generate the 4-arylthio- or 4-arylselenobutenolides **44** (14–70%).[73] A variation on this methodology was reported by Ma and Shi, where the silver-assisted lactonisation was combined with a palladium-catalysed aryl cross-coupling to give 4,5-disubstituted butenolides[74] (Scheme 30a). Low yields of butenolide were obtained using only palladium in the reaction, implying a direct carbopalladation of the allene to be possible, but the higher yields seen in the presence of silver indicated transmetalation–lactonisation to be a more favourable pathway. Rossi and co-workers have described related chemistry, starting from the 3-ynoic acids, but in this case direct carboxypalladation of the triple bond was favourable under strongly basic conditions and the addition of silver was not necessary[75] (Scheme 30b).

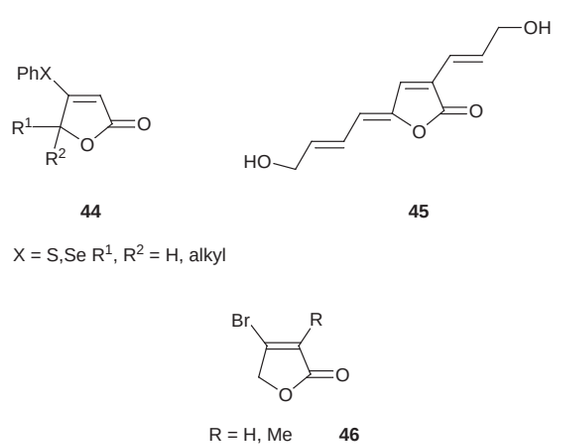
This last group have also published a new protocol for the preparation of (*Z*)-γ-alkylidenebutenolides by the palladium-catalysed lactonisation of 4-alkynyl-2-bromopropenoic acids[76] (Scheme 31). The starting materials were readily available on a mutigram scale and, when followed by Stille or Negishi coupling to the 3-bromobutenolide, this method gave rapid entry to butenolides such as lissoclinolide **45**.[77] Related targets were prepared by Boukouvalas and co-workers using the reverse of this sequence: Suzuki couplings to the 4-bromobutenolides **46**



Scheme 30

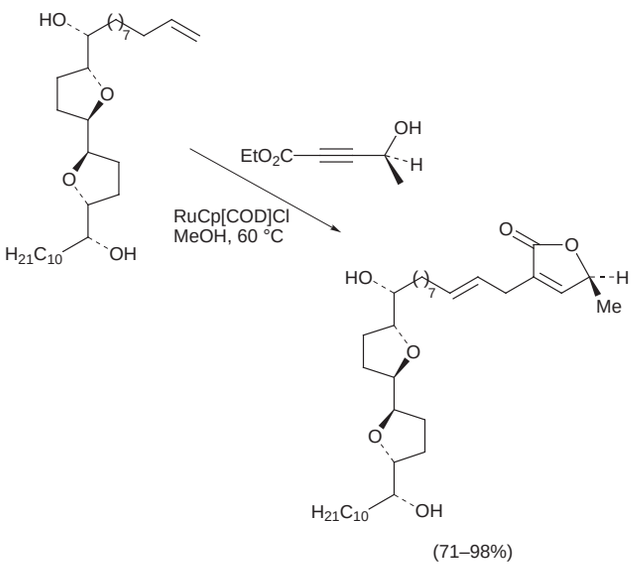


Scheme 31

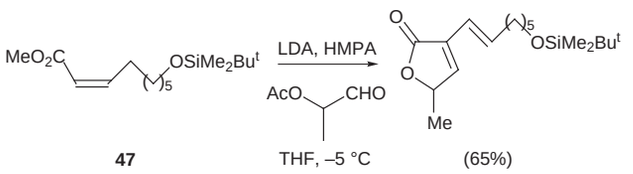


(61–85%) were followed by Mukaiyama aldol condensation to introduce the γ-alkylidene substituents.[78]

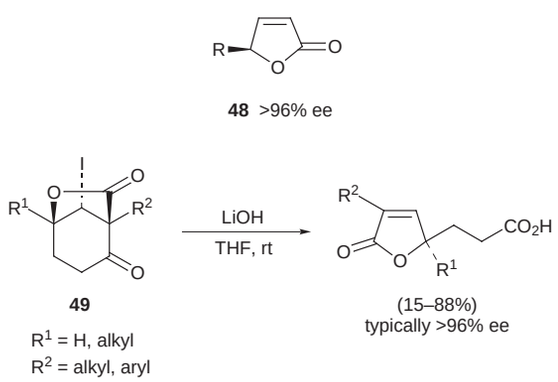
Trost and co-workers have exploited their ruthenium-catalysed Alder-ene reaction to install the chiral butenolide unit of the acetogenins (+)-squamocin K and (+)-parviflorin, without the need for protecting groups in the later stages of the synthesis[79] (Scheme 32). This process was also used by De Clercq and co-workers to construct a chiral butenolide intermediate required for an approach to (+)-hymbacine.[80] In the course of this work a novel, direct butenolide synthesis was developed comprising deconjugative enolisation of the 2-enoate **47**, aldol condensation and lactonisation after acetyl migration (Scheme 33). However, racemisation of the aldehyde component under basic conditions prevented this from being developed into an enantioselective route. Simple 5-substituted butenolides **48** were reached in high enantiomeric excess starting with bakers' yeast reduction of 3-chloro-4-oxoalkenoates[81] or by the



Scheme 32



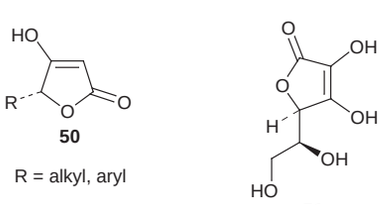
Scheme 33



Scheme 34

novel fragmentation of the bicyclic iodolactonisation products **49**[82] (Scheme 34).

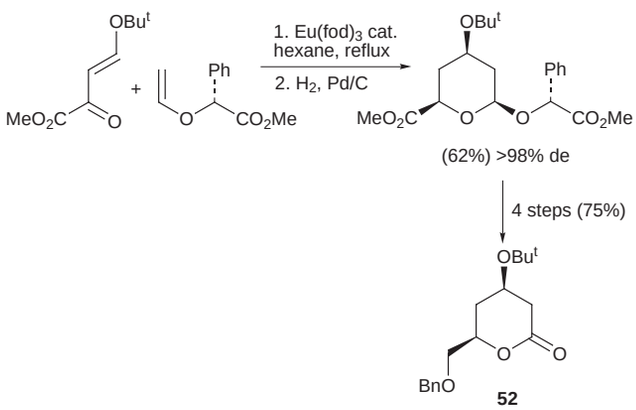
The optically active tetronic acids **50** were made from the corresponding (*R*)-*O*-trimethylsilylcyanohydrins by Blaise reaction and hydrolysis under mildly acidic conditions without racemisation.[83] The first total synthesis of L-ascorbic acid **51** from non-carbohydrate sources was achieved by sequential microbial and chemical oxidations of chlorobenzene.[84]



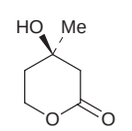
5 δ-Lactones

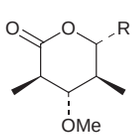
5.1 Monocyclic δ-lactones

The enantioselective synthesis of hydroxylated δ-lactones is an important goal since these motifs are widely found in compounds of biological interest, such as the antihypercholesteremic mevinic acids and the immunosuppressant discodermalide. Simple optically pure mevalonolactone derivatives were prepared starting with the lanthanide Lewis acid catalysed hetero Diels–Alder cycloaddition of *tert*-butyloxymethylenepyruvate with a vinyl ether derived from mandelic acid[85] (Scheme 35). Removal of the auxiliary and oxidation revealed the *cis*-substituted lactone which was epimerised to the *trans* isomer by ring opening and Mitsunobu inversion at C-5. (*R*)-(−)-Mevalonolactone **53** itself was prepared on a multigram scale from phenylacetone (8 steps, 55%) *via* an enantioselective enzymatic epoxide hydrolysis.[86] The stereospecific opening of chiral epoxides by trimethylaluminium was used to build the acyclic precursors of di-, tri- and tetrasubstituted hydroxylated δ-lactones,[87] including the terminal lactone fragment of discodermalide[88] (Scheme 36). Further stereoselective hydroxylation was achieved by formation of the benzylidene acetal through Evans' procedure and the final substituent was introduced by stereoselective axial alkylation of the lactone enolate. The closely similar lactones **54** were prepared by a more classical approach from the Baeyer–Villiger oxidation of substituted cyclopentanones.[89]



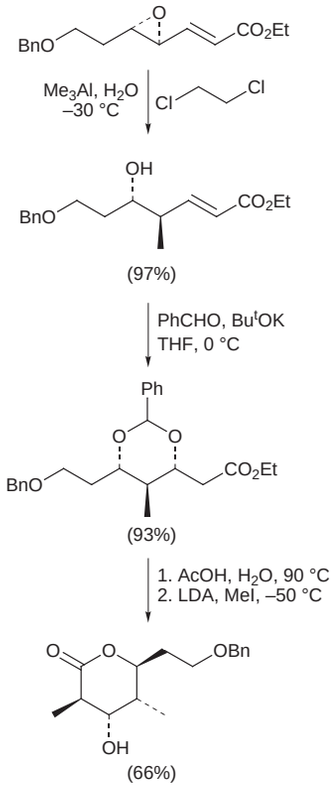
Scheme 35



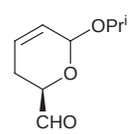


Both the enantioselectivity and yield of the oxaborolidine-catalysed reduction of simple vinyl ketones were improved by Corey and co-workers by temporary attachment of a bulky tributylstannyl group[90] (Scheme 37). Destannylation and lactonisation gave the 6-vinyl substituted lactone. Kobayashi and co-workers employed a different strategy for the construction of a 6-vinyl-5,6-dihydro-2-pyrone in the synthesis of the marine cytotoxin callystatin A.[91] The lactone was masked as the cyclic acetal **55**, where the stereochemistry was derived from (*S*)-glycidol, and was elaborated by Wittig chemistry.

Full details have appeared of the remote δ-carbonylation of saturated alcohols using lead tetraacetate for one-electron oxidation[92] (Scheme 38a). The initial alkoxy radical rearranged by 1,5-hydrogen abstraction to the carbon-centred radical **56**. Further oxidation and cyclisation of **56** to give a tetrahydrofuran was blocked provided high pressures (>40 atm) of carbon



Scheme 36

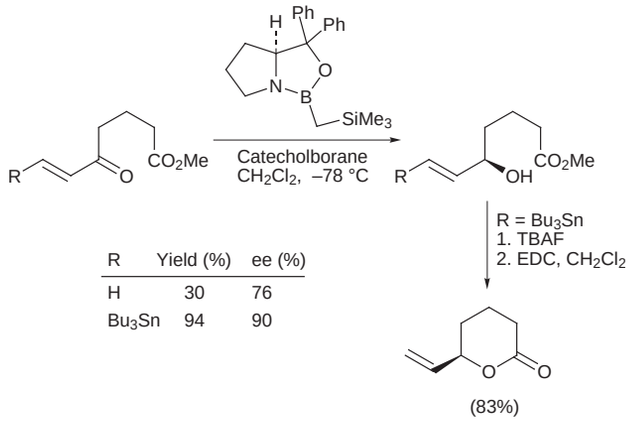


55

monoxide were used, in which case mainly the δ-lactones were produced by radical carbonylation. Higher yields were associated with secondary alcohol precursors and the method generalised to polysubstituted and polycyclic δ-lactones although little stereoselectivity was observed. The anomeric alkoxy radical **57** formed on oxidation of hexauronic acid by diacetoxyiodobenzene also underwent cleavage to a carbon-centred radical that lactonised on further oxidation[93] (Scheme 38b). Both δ- and γ-lactone derivatives of carbohydrates were accessible by this approach.

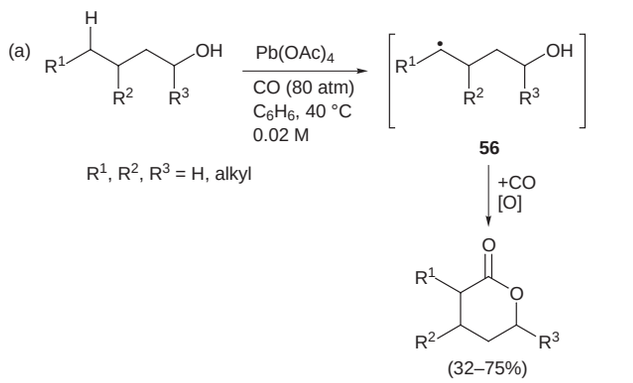
The palladium-catalysed intramolecular allylic alkylation used to construct the δ-lactone intermediate **58** (Scheme 39) in a synthesis of (+)-methyl pederate was found to be heavily solvent, temperature and catalyst dependent.[94,95] Preformed palladium(0) complexes gave very poor yields and reaction was favoured in highly polar solvents at elevated temperatures.

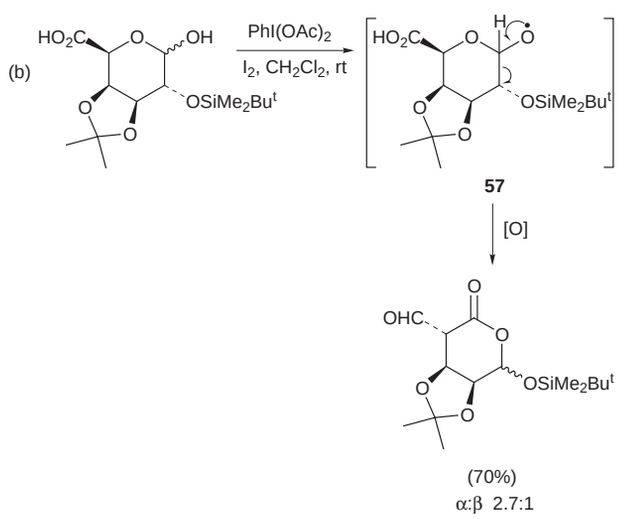
Ring-closing metathesis has featured in many recent synthetic strategies and was applied in a high yielding preparation of dihydropyrones and butenolides[96] (Scheme 40a). A wide variety of substituents were tolerated in the reaction with Grubbs' catalyst, but the addition of a Lewis acid was essential for rapid and complete conversion, presumably by disrupting unproductive chelates in the manner originally proposed by Fürstner. Monocyclic and bicyclic dihydropyrones were also efficiently prepared by Wittig olefination of hydroxyketones with phosphocumulene ylides[97] (Scheme 40b). Interestingly, the more base-sensitive ketones gave higher yields when employed as the cyclic ketals. Chiral dihydropyrones were prepared by sterically controlled hydrozirconation of homopropargyl ethers[98] (Scheme 40c). Carbonylation of the organozirconium intermediate and demetalation with iodine gave the δ-lactones in good yield (typically 50–65%). The chiral dihydropyrone **59**



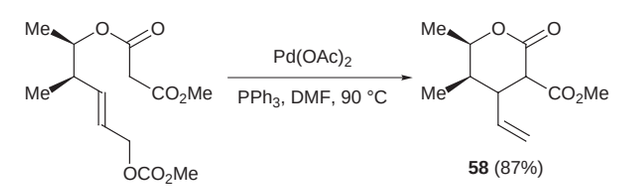
R	Yield (%)	ee (%)
H	30	76
Bu_3Sn	94	90

Scheme 37



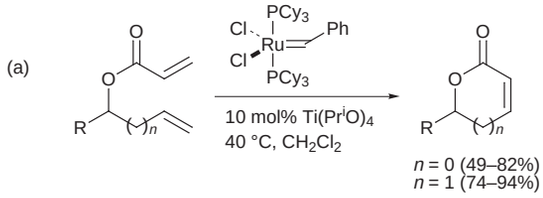


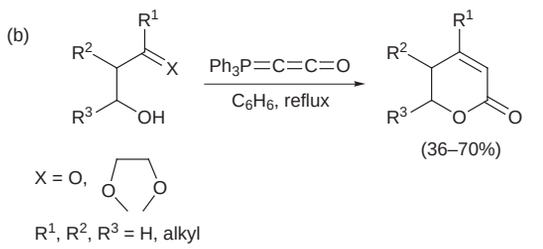
Scheme 38

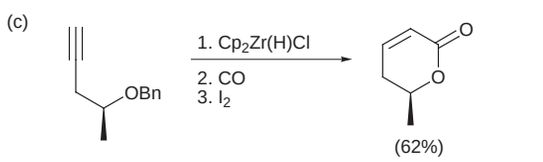


Scheme 39

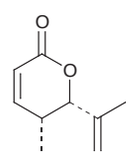
was prepared by an enantioselective aldol condensation using the vinylogous urethane chemistry developed for the synthesis of butenolides[99] (*cf.* Scheme 27). A general route to polysubstituted α-pyrones was described consisting of the palladium-catalysed coupling of internal alkynes to β-halo-(*Z*)-propenoates[100] (Scheme 41). For β-unsubstituted propenoates (R^2 = H) the selectivity of the annulation with unsymmetrical







Scheme 40



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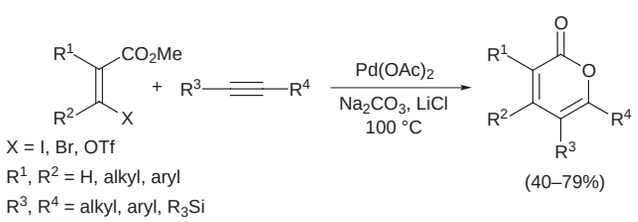
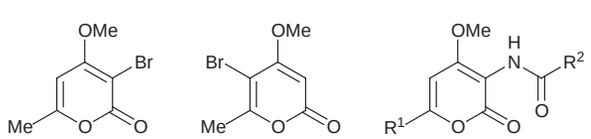


Scheme 41

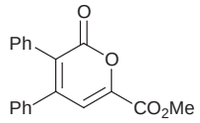
alkynes was poor (*ca.* 2 : 1) but for substituted starting materials ($R^2 \neq H$) only the sterically less demanding product ($R^3 < R^4$) was isolated. Substituted α-pyrones were also prepared by Suzuki couplings to the readily available 3- and 5-halopyrones **60** and **61**.[101] The simple 3-amino-α-pyrones **62** were made in a one-pot process (26–72% yield) from the three-component condensation of methyl ketones with dimethylacetamide dimethyl acetal and *N*-acylglycines.[102] Another one-pot reaction, the cycloaddition–bromination of alkenes and oxadiazines, gave the substituted α-pyrones exemplified by **63**.[103]



60 **61** **62** R^1 = alkyl, aryl

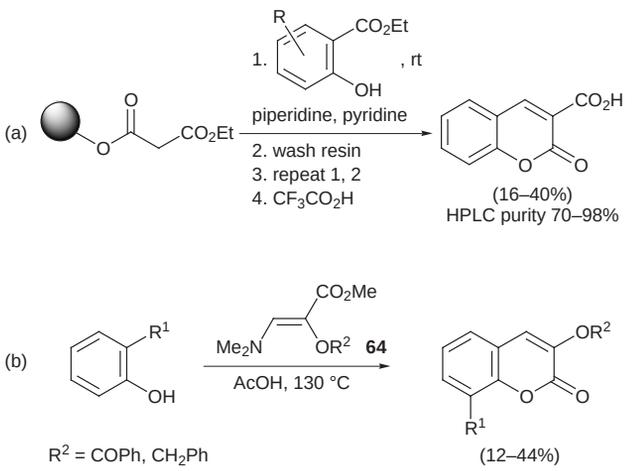
5.2 Bicyclic and polycyclic δ-lactones

The medicinally important coumarin class of bicyclic δ-lactones was prepared on solid support by a simple Knoevenagel



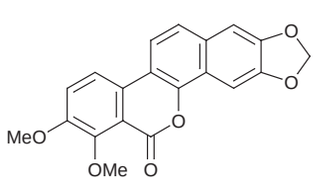
63

condensation giving fair yields and good purity of products without special purification steps[104] (Scheme 42a). Another standard coumarin synthesis, the condensation of phenols with 3-dimethylaminopropenoates, was demonstrated, albeit under harsh conditions, with the readily available 2-alkoxy derivatives **64**, leading to 3-alkoxycoumarins[105] (Scheme 42b).



Scheme 42

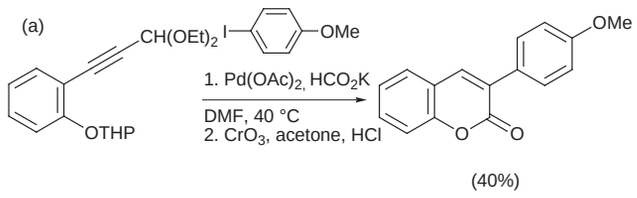
Coumarins were also made through the *syn* selective carbopalladation of aryl alkynes, a process which favoured the sterically less demanding regioisomer in the palladium-catalysed step[106] (Scheme 43a). Deprotection of the phenol, lactol formation and oxidation all took place upon treatment with chromium trioxide. A related annulation was used by Trost and co-workers to construct the tricyclic core of the calanolides[107] (Scheme 43b). High yields of isocoumarins were obtained from Stille couplings to (1,1-dibromovinyl)benzoates[108] (Scheme 43c). This cascade reaction proceeded through arylation of the (*E*)-bromide followed by oxidative insertion of palladium to the remaining (*Z*)-bromide and lactonisation. The polycyclic δ-lactone arnottin **64** was synthesised using an intramolecular palladium-catalysed aryl–aryl coupling to close the δ-lactone (71%).[109] The closely related antitumour gilvocarcin aglycones were prepared by Snieckus and co-workers using their tandem aryl–aryl coupling–directed *ortho* metalation–anionic Fries rearrangement methodology.[110]

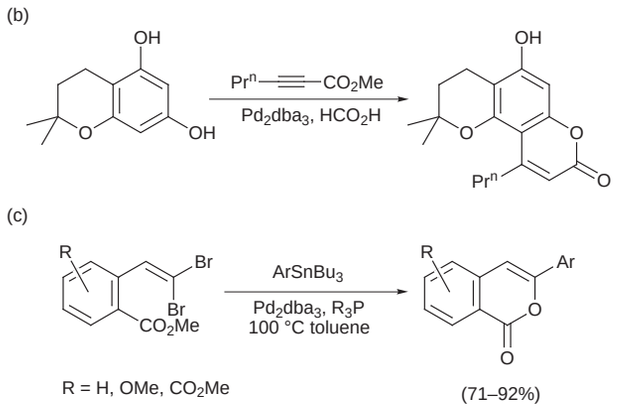


64

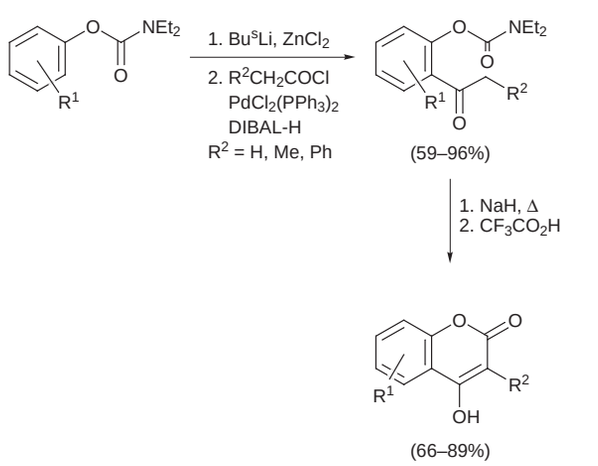
This group has also described a new variant of this sequence in which an anionic carbamoyl Bakar–Venkataraman rearrangement gave 4-hydroxycoumarins[111,112] (Scheme 44). The rearrangement of (hydroxyalkyl)phthalides under acidic conditions gave isocoumarins in good yields, presumably by eliminative ring-opening to the benzoic acid **65** and electrocyclic ring-closure[113] (Scheme 45).

4-Methoxycarbonylcoumarins were prepared under mild conditions by the electrophilic substitution of phenols with the

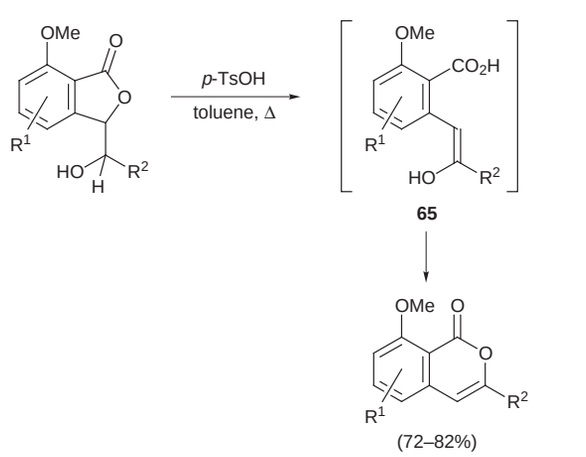




Scheme 43

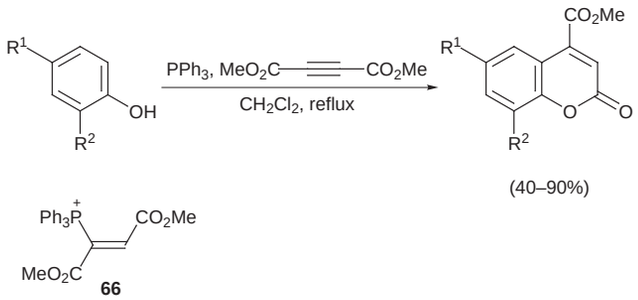


Scheme 44

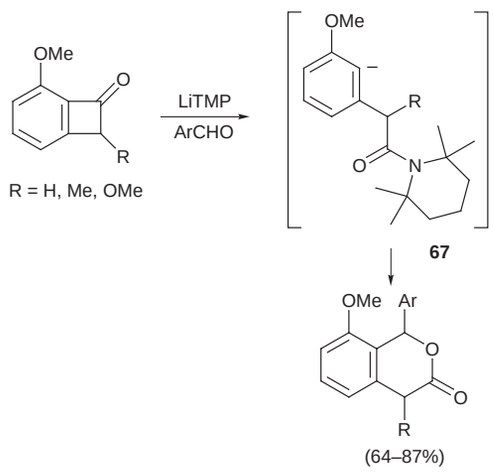


Scheme 45

adduct **66** of dimethyl acetylenedicarboxylate and triphenylphosphine[114] (Scheme 46). The lower yields in the range quoted were associated with less reactive phenols bearing electron-withdrawing substituents. An alternative to directed metalation as a means of generating aryl anions was discovered by Suzuki and co-workers when examining the aldol reactions of benzocyclobutenones[115] (Scheme 47). Addition of the base to the



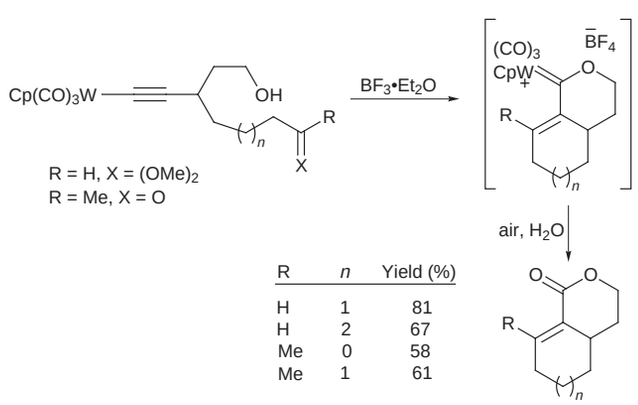
Scheme 46



Scheme 47

ketone apparently caused ring-opening to the anion **67**, which was trapped *in situ* by the aldehyde component and cyclised to give isochromanones in good yield.

The organometallic chemistry developed by Liu and co-workers for the synthesis of α-alkylidene-γ-lactones (*cf.* Scheme 24) was applied in an intramolecular sense to give bicyclic δ-lactones from alkynyltungsten complexes[116] (Scheme 48). The method was also applicable to bicyclic 7-membered lactones (40–68% yield).



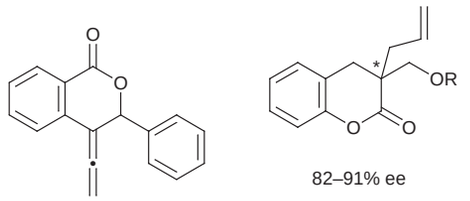
R	*n*	Yield (%)
H	1	81
H	2	67
Me	0	58
Me	1	61

Scheme 48

The allenyl δ-lactone **68** featured in preliminary studies on the synthesis of bergenin and was produced by the coupling of an *o*-carboxyphenylpropargyl bromide and benzaldehyde, mediated by indium metal in aqueous medium (71%).[117] The chiral quaternary substituted δ-lactones **69** were prepared in good optical purity by radical allylation of the corresponding α-iodolactones in the presence of an aluminium binaphthol chiral Lewis acid.[118]

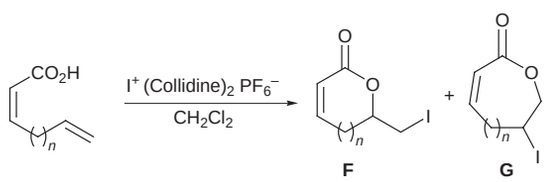
6 Medium-ring lactones

Three groups have recently illustrated the beneficial effects of appropriate conformational restriction on the synthesis of



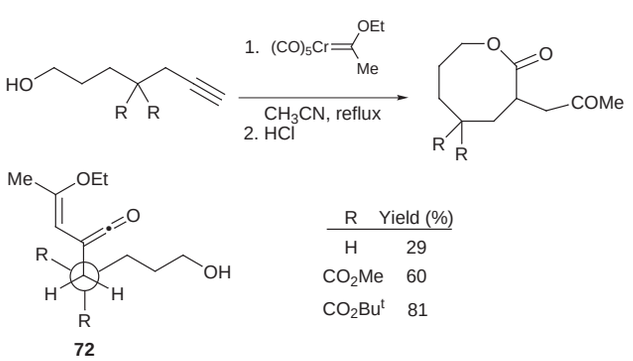
68 **69**

medium-ring lactones by classical techniques: firstly, the simple iodolactonisation of oct-7-enoic acids was found to give complete selectivity for the *exo* cyclisation product when a single *cis* alkene, or a fused aryl ring, was present in the tether [119] (Scheme 49). The effect did not extend to 9- and 10-membered rings, however, where poor yields and competing *endo* cyclisation were seen. In a second example of this effect, the Yamaguchi lactonisations that gave the 8-membered solandelactone fragment **70** [120] (63%) and the 9-membered halicholactone precursor **71** [121] (66%) were also facilitated by the *cis* alkene conformational restraint. Lastly, Mori and co-workers have investigated the effect of conformational constraint on their previously reported medium-ring synthesis from ω-hydroxyalkynes and Fischer carbene complexes [122] (Scheme 50). In this case, bulky *gem*-disubstitution in the tether dramatically improved the yield of the cyclisation, possibly through a combination of the Thorpe–Ingold effect and restriction of the acyclic intermediate **72** to the more reactive rotamer with minimised *gauche* interactions.



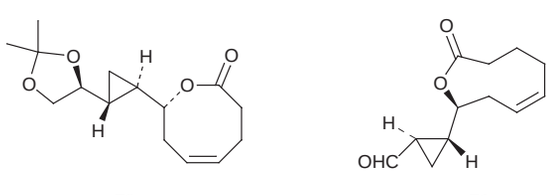
n	Yield (%)	F:G
3	80	100:0
4	30	60:40
5	20	50:50

Scheme 49



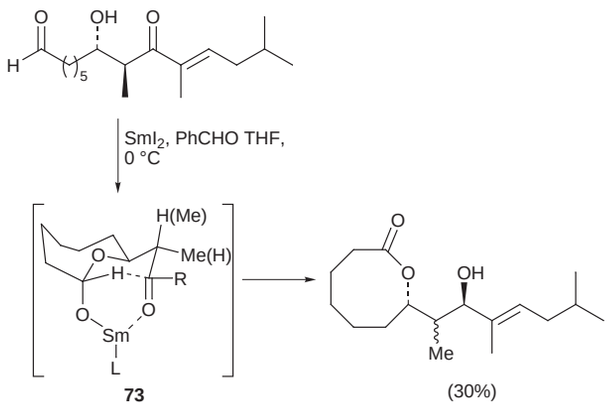
R	Yield (%)
H	29
CO_2Me	60
CO_2Bu^t	81

Scheme 50



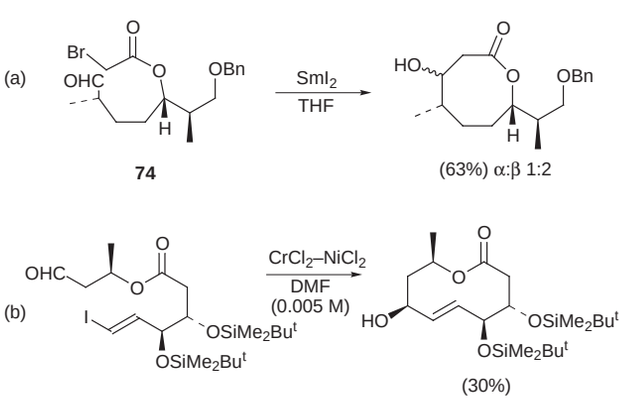
70 **71**

A novel intramolecular variation of the Evans–Tishchenko reductive acylation was developed in preliminary studies on a synthesis of octalactin A [123] (Scheme 51). The product was consistent with formation of the 8-membered cyclic hemiacetal **73** followed by intramolecular hydride transfer to the enone through a 6-membered transition state. However, the yield was disappointing and no stereoselectivity was seen, in contrast to the intermolecular reaction of related substrates under this protocol.



Scheme 51

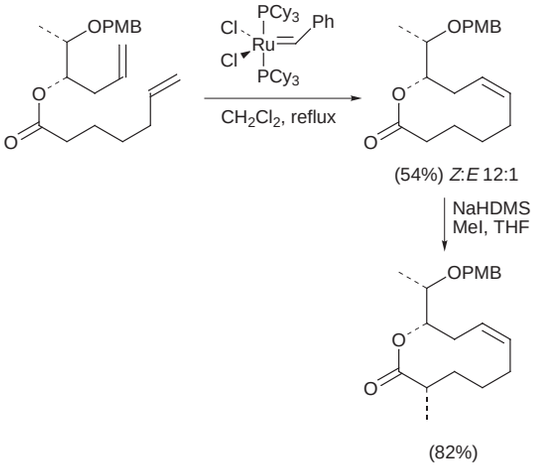
Samarium(II) iodide was used to promote the Reformatsky reaction of the δ-(bromoacetoxy)aldehyde **74** in another synthesis directed at (−)-octalactin A [124] (Scheme 52a). Although a mixture of 4-hydroxylactones was obtained, the unwanted α-epimer was readily converted to the β-isomer by oxidation and reduction (92%) where complete medium-ring stereocontrol was seen in the reduction step. Stereoselective cyclisation of an organometallic to an aldehyde was also seen in the synthesis of (−)-decarestrictin D [125] (Scheme 52b) where a Nozaki–Hiyama–Kishi coupling closed the 10-membered ring. Solvent choice was important since the stereoselectivity fell to 2:1 if the reaction was carried out in DMSO.



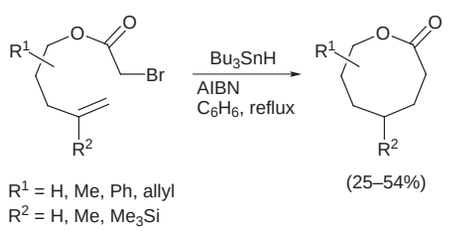
Scheme 52

Ring-closing metathesis was used extensively in the pioneering total syntheses of the cytotoxic epothilones and a recent new addition to this body of work centred on the formation of a 10-membered lactone as an intermediate for epothilone synthesis [126] (Scheme 53). This medium-ring formation was more selective for the required *cis* alkene (12:1 *Z*:*E*) than many of the earlier macrocyclic ring closures. Subsequent introduction of a methyl substituent by alkylation of the lactone enolate proceeded with complete stereoselectivity.

An unexpectedly favourable 8-*endo* radical cyclisation was found to give 8-membered lactones in moderate yield accompanied by variable proportions (16–50%) of the debrominated, uncyclised esters [127] (Scheme 54). The analogous reaction on 7- and 9-membered precursors failed to give any lactone products and, remarkably, in the presence of an alternative 5-*exo*



Scheme 53



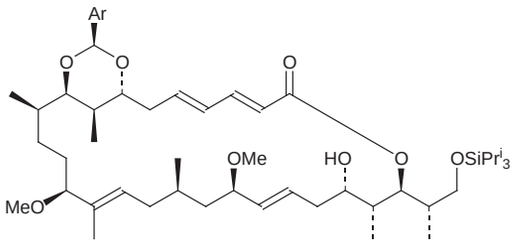
Scheme 54

cyclisation mode the 8-*endo* ring-closure was found to be faster. Molecular modelling studies were able to suggest that this preference arose from the conformational bias of the (alkoxycarbonyl)methyl radical towards the *Z* conformation, which gave a low energy 8-*endo* transition state for cyclisation. An improvement in the yield and scope of existing atom-transfer radical addition cyclisations to give medium-ring lactones was achieved with novel iron(II) and copper(I) complexes of polypyridyl ligands.[128]

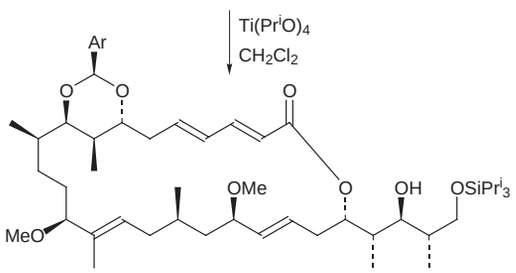
7 Macrolides

With classical macrolactonisation techniques firmly established as reliable and general procedures, the focus has mainly turned to alternative C–C bond constructions for macrocyclisation. Nevertheless, there remains the challenge of achieving macrolactonisation of partially protected *seco* acids where two or more cyclisation modes are possible. In the first of several recent examples, Evans and co-workers synthesised altohyrtin C[129] by a Yamaguchi lactonisation that was totally selective between two adjacent hydroxy groups on a six-membered ring (86%). The lactonisation of the *seco* acid precursor to aplyronine A by Paterson and co-workers was equally selective and high yielding (79%) but gave only the undesired 26-membered macrocycle **75**[130] (Scheme 55). Contraction to the 24-membered ring **76** was achieved by isomerisation with titanium tetra(isopropoxide) to a separable mixture of the two compounds (**75**:**76** 1:3, 80%). Similarly selective macrolactonisations were seen in two independent syntheses of tricolorin A.[131,132]

Several approaches to the macrolactin class of antivirals were investigated by Smith and co-workers, providing valuable insight into the requirements for efficient macrocyclisation by Stille coupling[133] (Scheme 56a). Protection of the hydroxy groups was essential and highest yields were seen when no donor ligands were added to the catalyst mixture. Even so, yields for the coupling of vinyltributylstannanes were disappointing and unreliable, and required extended reaction times (*ca.* 7 days). By reversing the positions of the reacting functionalities and switching to the more reactive trimethyltin

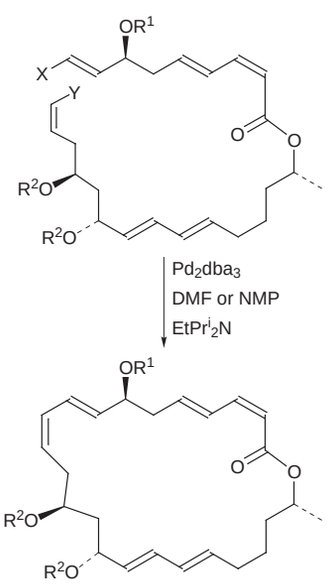


75



76 (60%)

Scheme 55



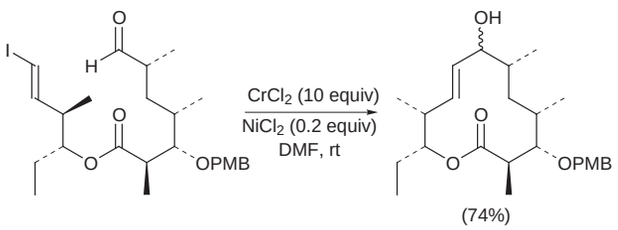
	X	Y	R^1	R^2	Yield (%)
(a)	Bu_3Sn	I	H	H	0
	Bu_3Sn	I	$SiMe_2Bu^t$	$SiMe_2Bu^t$	42
	Bu_3Sn	I	$SiEt_3$	$SiEt_3$	*ca.* 36
	I	Me_3Sn	$SiMe_2Bu^t$	$SiMe_2Bu^t$	67
	I	Me_3Sn	$SiMe_2Bu^t$	$SiEt_3$	92
(b)	Bu_3Sn	I	$SiMe_2Bu^t$		58

Scheme 56

derivative, more reliable and efficient coupling was seen in shorter time (<1 h). In another synthesis of macrolactin A, Carreira and co-workers achieved the cyclisation of a closely related intermediate[134] (Scheme 56b). The 18-membered lactone concanolide A[135] was also constructed in good yield (72%) through an intramolecular Stille coupling of a vinyl iodide and a tributylvinylstannane using the Farina catalyst [Pd_2dba_3, Ph_3As]. White and co-workers closed the 26-membered lactone of rutamycin B[136] by the Suzuki coupling of a vinyl iodide and a vinylboronate, again in high yield [$Pd(MeCN)_2Cl_2$, $AsPh_3$, Ag_2O, 70%].

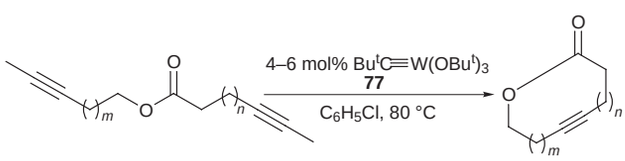
Nozaki–Hiyama–Kishi coupling served to make the 12-

membered macrolide 10-deoxymethynolide[137] (Scheme 57). The lack of stereocontrol over the alcohol was unimportant as this centre was later oxidised. Greater stereoselectivity (9:1) was encountered in the synthesis of a 16-membered spiromycin aglycone by this reaction,[138] but this example proved very demanding and a large excess of the reagents (100 equiv. $CrCl_2$, 1 equiv. $NiCl_2$, 76%) were necessary to overcome the resistance to cyclisation at high dilution.



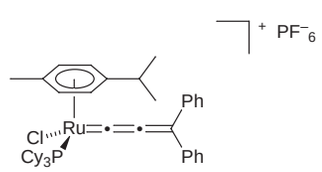
Scheme 57

Following the successful application of ring-closing metathesis to the synthesis of macrolides, particularly the epothilones, a great deal of further work has been reported in this area, including another recent synthesis of epothilone B.[139] Metathesis of simple bis-alkynes was optimised by Fürstner and co-workers with the aim of eliminating the problematic mixtures of *E* and *Z* isomers that often result from macrocyclisation by conventional olefin metathesis[140] (Scheme 58). The Shrock tungsten alkylidyne complex **77** was a highly active catalyst for the metathesis of internal alkynes to give macrolides and macrodiolides (52–97%). In some cases conversion was assisted by carrying out the reaction in 1,2,3-trichlorobenzene under reduced pressure to remove volatile alkyne by-products. The same group has also reported the readily accessible ruthenium allenylidene complex **78** as a new class of catalyst for the ring-closing metathesis of alkenes.[141] Both this new agent and Grubbs' catalyst were effective for the formation of the cytotoxic macrolide tricolorin A[141,142] (Scheme 59).



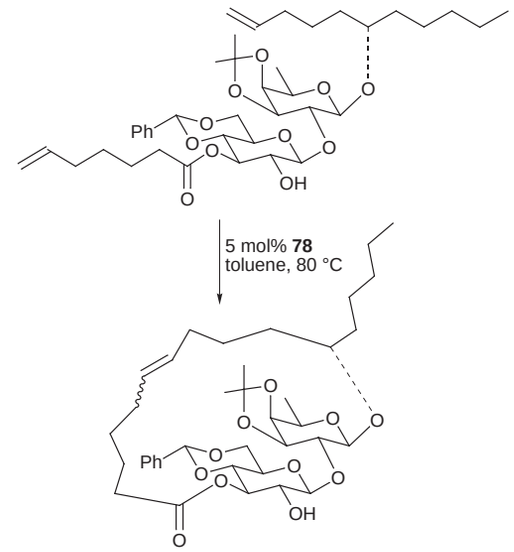
m	*n*	Yield (%)
7	1	52
7	8	52
6	7	69

Scheme 58



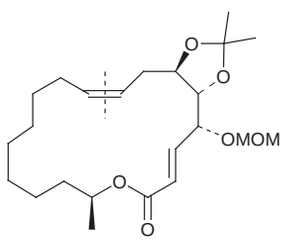
78

Grubbs' catalyst was used to prepare the 18-membered macrolide **79**, a precursor to (+)-aspicilin, where, unusually, complete selectivity for the *Z*-olefin was obtained in the metathesis (83%).[143] This target was also prepared by simple macrolactonisation of a substrate in which the γ-hydroxy-α,β-unsaturated acid moiety was derived from the oxidation of a furan.[144] The ring-closing metathesis approach described earlier for dihydropyridones (*cf.* Scheme 40) was applicable to macrolides too.[145] A systematic study of ring-closing metathesis to form 14-membered lactones and lactams underlined the importance of the position of the heteroatoms in determining the stereochemical outcome of the reaction (*Z*:*E* from 1:99 to



(85%)

Scheme 59



79

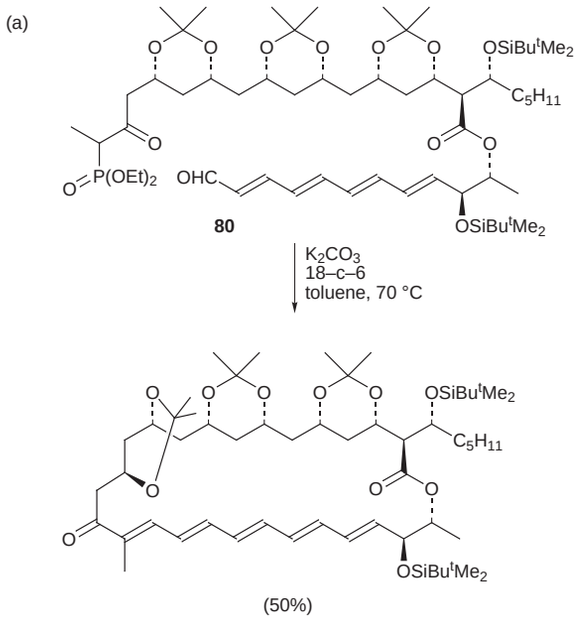
23:77).[146] There was a fair correlation between the observed product ratios and those predicted by comparison of the relative strain in the two isomeric products as estimated by molecular mechanics calculations.

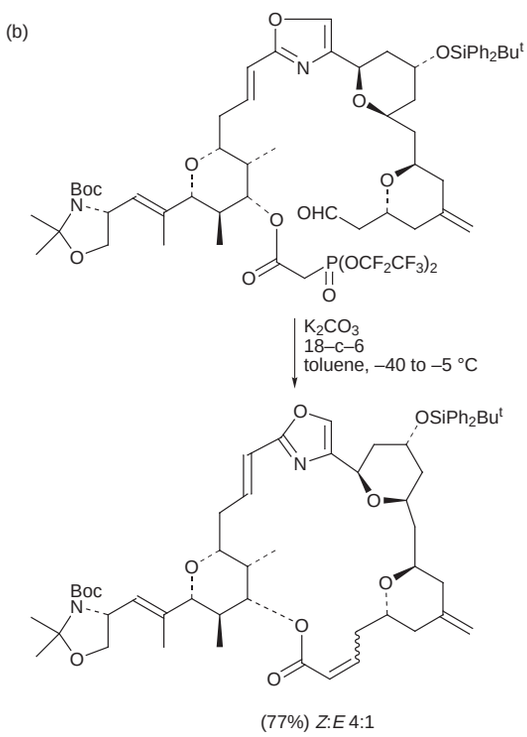
Several groups have described natural product syntheses in which intramolecular Horner–Wadsworth–Emmons reactions served to close the macrocycles. Rychnovsky and co-workers were unable to cyclise the ketophosphonate **80** under Masamune–Roush conditions [LiCl, DBU] but were successful with Still's procedure to form the trisubstituted alkene of the marine macrolide filipin III[147] (Scheme 60a). The Still conditions were also advantageous in the total synthesis of phorboxazole A, where a degree of selectivity for the desired *Z*-alkene was attained in contrast to the *E*-selectivity observed with the Masamune–Roush protocol[148] (Scheme 60b). The synthesis of the tris-oxazole containing macrolide ulapualide A also featured the Still conditions in a lower yielding ring closure (10–33%).[149]

Romo and co-workers have applied their expertise in the field of β-lactam chemistry to develop a new macrolactonisation technique based on the intramolecular alcoholysis of a β-lactam.[150] The ring-closure, which was presumed to occur through an intermediate acyl cyanide, efficiently delivered the amino-substituted macrodiolide core of the immunosuppressant pateamine (Scheme 61). Another novel macrocyclisation, this time a transacetalisation, was optimised by Wender and co-workers for the preparation of simplified analogues **81** of the protein kinase C inhibitor bryostatin (56–88%).[151]

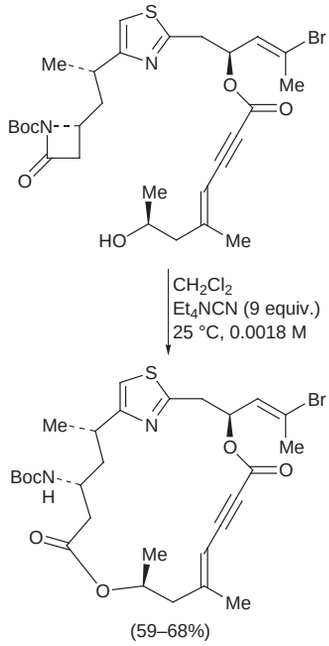
8 Spirolactones

Simple spiro-γ-lactones were delivered by a short sequence starting with the opening of spiroepoxides by aluminium ester enolates[152] (Scheme 62a). Low temperatures were necessary to avoid competing Lewis acid catalysed rearrangements of the

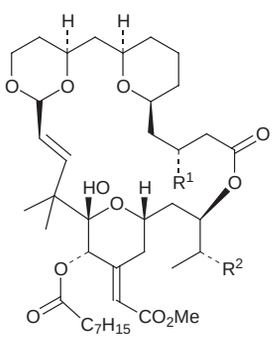




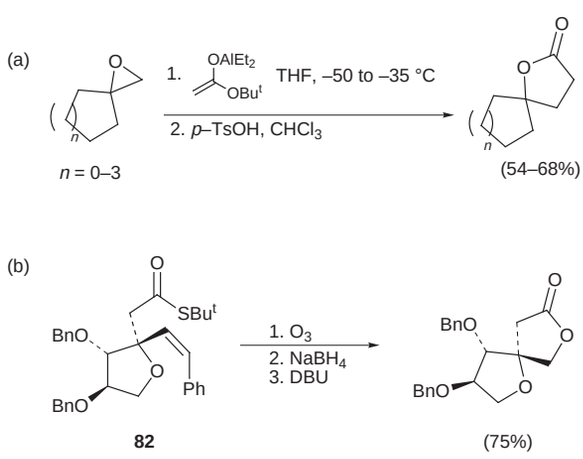
Scheme 60



Scheme 61

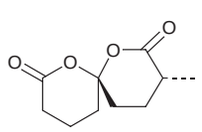


81



82

Scheme 62

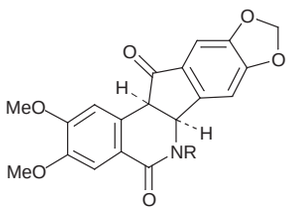


83

intermediate γ-hydroxyesters, and the process could be conveniently carried out without purification of these intermediates. Straightforward additions of lithium enolates and lithium acetylides to carbonyl compounds were used to construct the substituted tetrahydrofuran **82**. Ozonolysis and reduction of **82** gave the spirolactone skeleton of the (+)-secosyrins [153] (Scheme 62b).

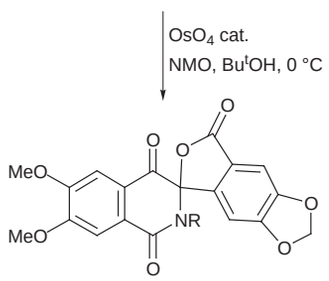
Double Baeyer–Villiger oxidation of a spirodicyclopentanone furnished the spirodilactone **83** in excellent yield (90%) and complete selectivity.[154] Studies on this and related molecules indicated that α-(acyloxy)alkyl and α-hydroxyalkyl groups generally migrated in preference to alkyl groups in the oxidation, as expected for the more electron-rich substituents. A novel and unusual oxidative rearrangement was discovered when the indenoisoquinolines **84** were exposed to the conditions for catalytic dihydroxylation, originally intended to dihydroxylate an *N*-allyl group [155] (Scheme 63). Initial attempts to elucidate the mechanism of this transformation were unsuccessful as potential intermediates, such as the α-hydroxyindanone, were found not to be converted to the products under the reaction conditions.

Spirocyclic γ-lactones were obtained as single diastereoisomers when a bulky arenechromiumtricarbonyl complex was used to control the stereochemistry of radical Michael addition to acrylates[156] (Scheme 64). Hegedus and Bueno have reported full details of the synthesis of optically active spirobutenolides *via* the photochemical addition of chromium carbenes to ene-



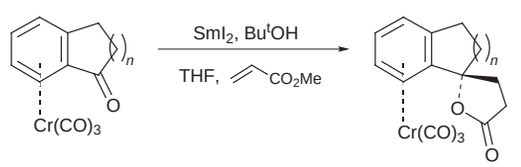
84

R = allyl, benzyl, alkyl



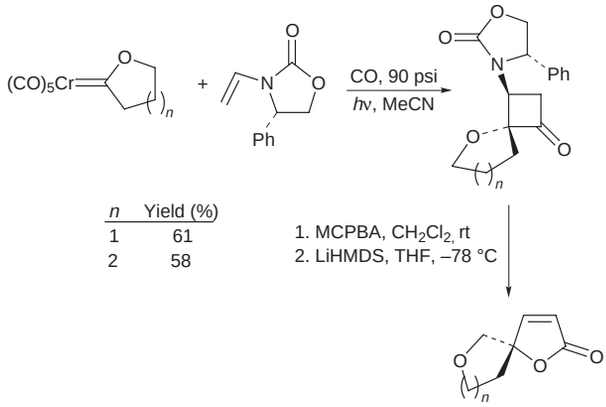
(60–92%)

Scheme 63



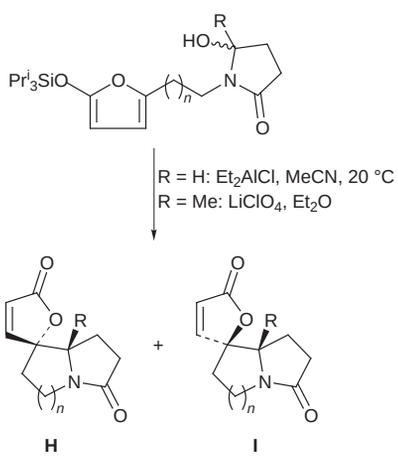
n	Yield (%)
1	71
2	65

Scheme 64



n	Yield (%)
1	61
2	58

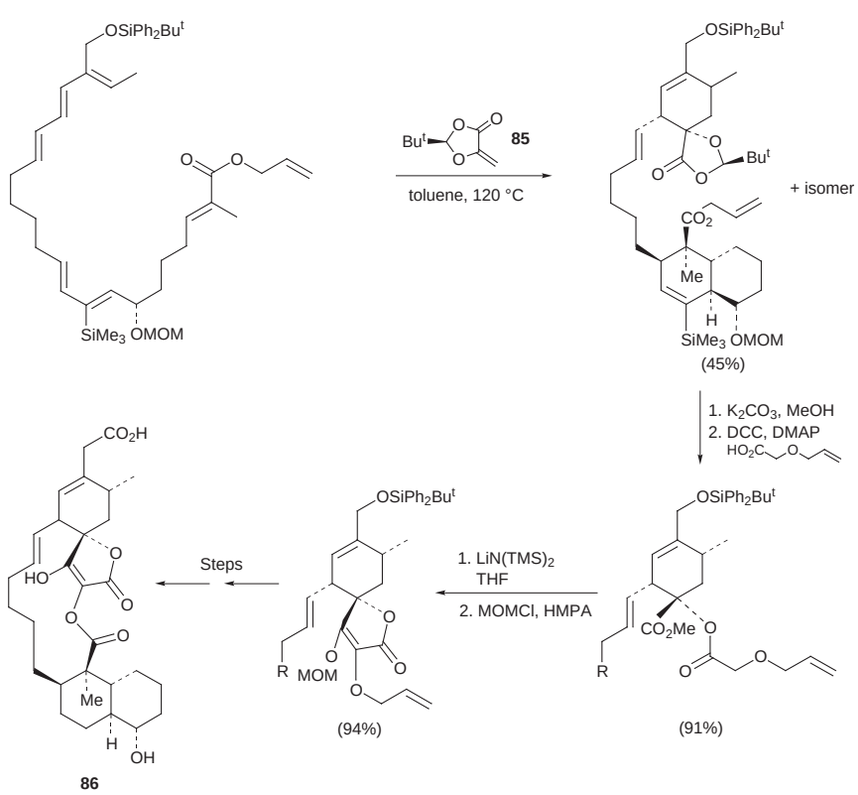
Scheme 65



n	R	**H:I**	Yield (%)
2	H	6:1	83
3	H	1.3:1	58
2	Me	20:1	58
3	Me	2:1	32

H **I**

Scheme 66



86

Scheme 67

carbamates[157] (Scheme 65). Predominantly one isomer of the spirocyclobutanone was formed in this reaction, dependent on the ring size. Subsequent Baeyer–Villiger oxidation and basic elimination to remove the auxiliary gave good yields of optically pure butenolides (>96% ee). Spirobutenolides were also made by the intramolecular vinylogous Mannich reaction of trialkylsilyloxyfurans and *N*-acyliminium ions[158] (Scheme 66). Optimum yields and selectivities for unsubstituted iminium ions (R = H) were obtained with diethylaluminium chloride in acetonitrile, but this Lewis acid was less effective for the tertiary precursors (R = Me) where lithium perchlorate was a superior reagent.

Finally, in an elegant body of work Roush and co-workers have described the preparation of spirotetronic acids by an intramolecular Dieckman cyclisation (Scheme 67). The precursor functionality could be installed through the selective Diels–Alder cycloaddition of the chiral dienophile **85**. This methodology was applied to the synthesis of the macrolide (−)-chlorothricolide **86**[159,160] where a tandem double Diels–Alder assembled the carbon skeleton, and was also used to give the related spirotetronate fragments of the antiviral quartromycins.[161,162]

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Review 8/08137I