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MEDIUM RING LACTONES.

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1. Introduction

1.1 Medium ring compounds in general

Medium ring compounds (those having a ring size in the range 8 to 11)[1] are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. Hydrocarbons, as well as heterocyclic compounds (ethers, lactones, amines, amides) have been isolated, and a number of reviews have already been published.[2]

These compounds have specific characteristics which had been recognised by at the beginning of this century,[3] and it was soon observed that they were much more difficult to synthesise by cyclisation methods than other cyclic compounds including macrocyclic compounds (ring sizes ≥ 12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavoured by entropy as well as enthalpy [3] (vide infra). The entropic factor is disfavoured by the carbon chain becoming too long, and thus the probability of a reaction taking place between the two chain termini decreases. The enthalpic factor is mainly created by steric interactions. There are three different interactions:

- torsional effects in single bonds (Pitzer strain)
- deformation of bond angles from their optimal values (Baeyer strain)
- transannular strain, particularly important in medium ring compounds.

A stereoelectronic factor can also pertain in the case of heterocyclic compounds. Strong repulsions between non-bonded atoms have been reported in compounds like cyclodecane. In this compound, Dunitz has calculated that the transannular H ····· H distances are on average 1.85 Å (instead of 1.95 - 2.00 Å to avoid interactions), while the distance between carbons 1 and 5 is 3.29 Å.[4]

The strain of medium ring hydrocarbons is also evidenced by their heat of formation [5a] and their relative (to cyclohexane) strain energy (Table 1).[5b]

ring size	$\Delta H°f$ kcal/mole	strain energy kcal/mole
6	-29.5	0
7	-28.2	6.2
8	-29.7	9.6
9	-31.7	12.5
10	-36.3	12.9
11	-42.9	11.2
12	-55.0	4.0

Table 1: Heats of formation and relative strain energies in cycloalkanes (from ref 5).

The negative entropy necessary for cyclisations which give medium ring compounds disfavours the reaction, and in fact favours intermolecular reaction. This phenomenon can be counteracted by utilising high-dilution conditions, as was first suggested by Ruggli.[6] Two different techniques can be used:

1) the compound to be cyclised is introduced in one portion at the beginning of the reaction into a large volume of solvent,

2) the compound is introduced slowly in a small volume of solvent to maintain its concentration at a very low level (influxion procedure). This second technique, first introduced by Ziegler,[7] is generally more convenient. A kinetic treatment of these intra-, intermolecular reactions has been reported which showed that if k_r (rate constant for the formation of the cyclic monomer) and k_p (rate constant for the formation of the dimer) are known optimal concentration conditions can be determined.[8]

$$\text{linear monomer} \xrightarrow{k_r} \text{cyclic monomer}$$

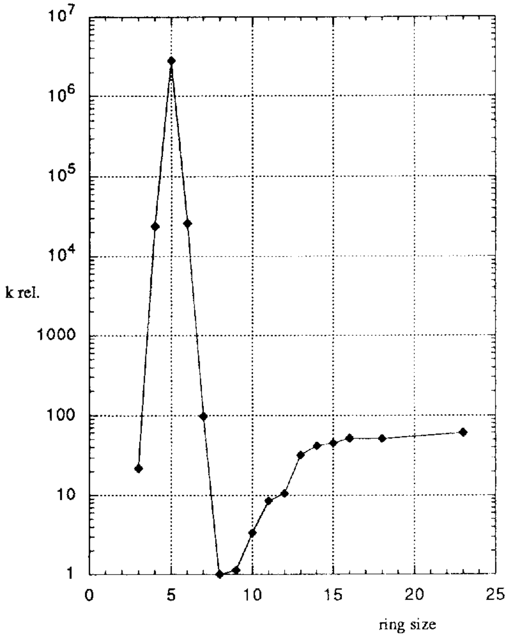
$$\text{2 linear monomers} \xrightarrow{k_p} \text{dimer}$$

Even under these conditions, medium ring formation remains difficult, and numerous methods have been developed to improve or avoid the cyclisation step. These methods are reported in this review.

1.2 Medium ring lactones in general

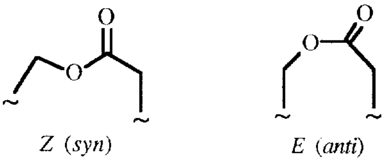
The pioneering work of Hunsdiecker and Erlbach reported the yields obtained in the reaction of ω-bromo alkanoic acids with potassium carbonate to give the corresponding lactones.[9] Good yields were observed in the preparation of five- to eight- and twelve- to eighteen-membered ring lactones. The yield of the nine-membered ring lactone was almost zero. This work was subsequently reinvestigated and developed by the Illuminati group.[10] They measured with great precision the rate of lactone formation in the ring sizes 3 to 23 by reaction of ω-bromoalkanoic acids with a base (KOH or diisopropylethylamine) in 21% aqueous DMSO.

In Scheme 1, the relative rate constants obtained in this work are given. A maximum rate of cyclisation was observed for the formation of γ-butyrolactone and then the rate decreased dramatically to the 8-membered ring lactone, which was formed more than 10^6 times less rapidly than the 5-membered ring lactone. A slow increase of the cyclisation rate was then observed, the cyclisation rate constant of the 18-membered ring lactone being close to that of the intermolecular reaction rate constant (formation of esters). From a synthetic point of view, these constant rate values mean that good yields (intramolecular reactions) should be obtained for the formation of 3- to 7- and 13- to 18-membered ring lactones, while polymerisation (intermolecular reactions) should be the major pathway for 8- to 12-atom chains[11] (but see, however, chapter 3.1.1).



Scheme 1: Reactivity plot for the formation of lactones from ω-bromoalkanoic acids (from ref 10b*)*

In medium ring lactones, stereoelectronic factors can, however decrease the strain energy slightly. Lactones can exist in *Z* (or *syn*) and *E* (or *anti*) forms (Scheme 2).



Scheme 2: Conformations of lactone functions

The *syn* form is in general more stable than the *anti* form (2-8 kcal/mole). For lactones with a ring sizes of at least 7 the rings are forced into the disfavoured *anti* conformation. In 8- and 9-membered ring lactones, an equilibrium *syn anti* conformation was observed, while in 10- and 11-membered ring lactones (and macrolactones), the *syn* form is normal.[12,13]

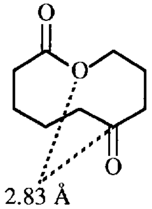
In Table 2, the strain energies for the 5- to 13-membered ring lactones as calculated by Wiberg and Waldron [14] from enthalpies of reduction are given.

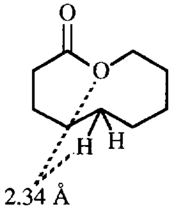
Comparison of these strain energies with the values of the corresponding hydrocarbons (see Table 1) show the influence of this factor.

Compound	strain energy kcal/mole
butyrolactone	8.8 ± 0.9
valerolactone	11.2 ± 0.9
caprolactone	10.7 ± 0.7
heptanolactone	12.4 ± 0.8
octanolactone	11.6 ± 0.8
nonanolactone	8.2 ± 0.8
decanolactone	7.3 ± 0.7
undecanolactone	7.1 ± 0.9
dodecanolactone	6.7 ± 0.8
tridecanolactone	4.5 ± 0.8

Table 2: Strain energies for 5- to 13-membered ring lactones (from ref 14*).*

In the presence of additional carbonyl functions on the lactone framework, attractive electrostatic interactions were observed. For example, in the keto lactone below, the transannular C-O distance was 2.83 Å, whilst the sum of the van der Waal radii is 3.1 Å.[15]





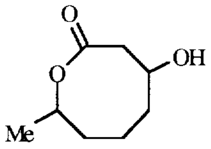
Similarly, Wiberg considered the possibility of an attractive interaction between the transannular hydrogens and the ether oxygen in nonalactone. The distance was found to be 2.34 Å, whilst the minimum H-O intermolecular non-bonded distance calculated is 2.58 Å.[13]

2. Naturally occurring medium ring lactones

Natural products containing a medium ring lactone framework are found in plants, insects (pheromones) and bacteria (antibiotics); they can have a terrestrial or a marine origin.

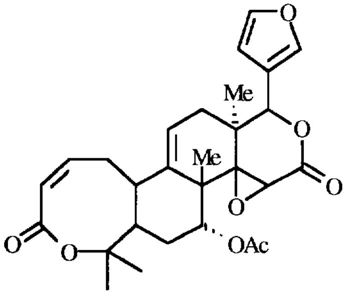
2.1 Eight-membered ring lactones (2-oxocanones)

A very simple octanolide, cephalosporolide D, was found to be a metabolite of the fungus *Cephalosporium aphidicola*.[16]

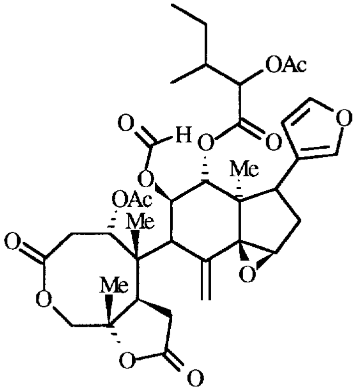


cephalosphorolide D

Recently, more complex lactones have been isolated. For example 1-(10-19) abeo-obacun-9(11)-en-7α-yl acetate was extracted from the seeds and the fruits of a variety of grapefruit (Poncirus trifoliata).[17]

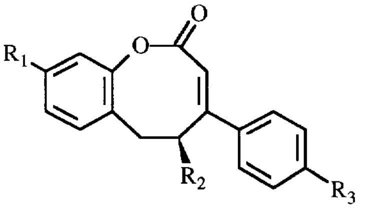


1-(10-19)abeo-obacun-9(11)-en-7 α-yl acetate



dregeanin

Another limonoid triterpene with a similar structure, dregeanin, structure was isolated from the timber of a small West Africa tree of, *Trichilia dreageora* [18] (and also *T. heudelotti*).[19] The aromatic glycosides, puerosides A and B, were recently isolated from the roots of *Pueraria lobata* Ohwi; these constitute one of the most important oriental drugs.[20] Three products with the same skeleton were isolated from a vegetable (Leguminosae) *Ononis speciosa* which grows in the south of Spain (Andalucia).[21]



a: pueroside A: R_1=OH; R_2=α-L-rhamnopyranosyl-(1-6)-β-D-glycopyranosyl; R_3=OH

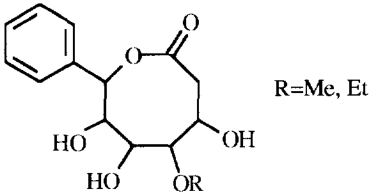
b: pueroside B: R_1=OMe; R_2=R_3=β-D-glycopyranosyl

c: specionin: R_1= R_2=R_3= OH

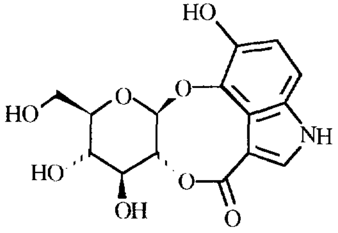
d: specioside A: R_1= OH; R_2=β-D-glycopyranosyl; R_3=OH

e: specioside B: R_1=β-D-glycopyranosyl; R_2= R_3=OH

Two eight-membered ring lactones have been isolated from *Goniothalamus giganteus* (Annonaceae), and show murine toxicity in the 3PS lymphocytic leukemia system.[22]

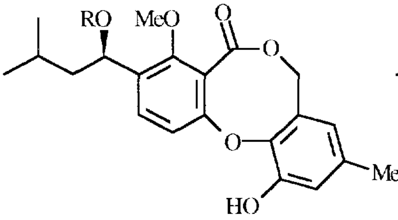


Ovatolide has also reported and synthesised recently.[23] This compound is found in the leaves of a Thai medicinal plant with laxative, febrifuge and astringent properties, *Bridelia* sp. (Euphorbiaceae).



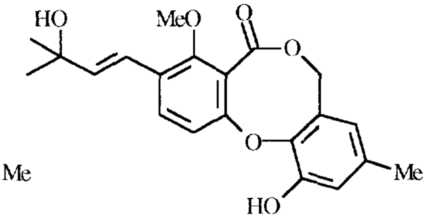
ovatolide

Penicillide, a metabolite of the fungus *Penicillium species* was found to be a root-growth stimulant.[24] A closely related compound, dehydroisopenicillide was isolated from another fungus, *Talaromyces derxi*, cultivated on rice.[25] Penicillide was also isolated from the mycelium of *Penicillium vermiculatum* and given the alternative name vermixocin A.[26] Another metabolite, vermixocin B was also formed during this culture. We suggested that this compound should be named penicillide B.



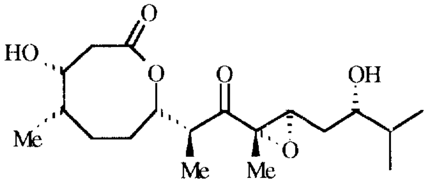
penicillide A or vermixocin A (R=H)

penicillide B or vermixocin B (R=Ac)

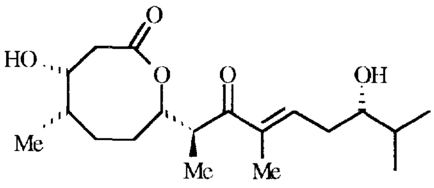


dehydroisopenicillide

Octalactins A and B are metabolites of a marine bacterium, *Streptomyces sp.* collected from the surface of a gorgonian, *Pacifigorgia sp.*, found in the Sea of Cortez, Mexico. Octalactin A shows cytotoxic activity against murine and human cancer cell lines.[27] Total syntheses of these compounds were recently reported.[28]

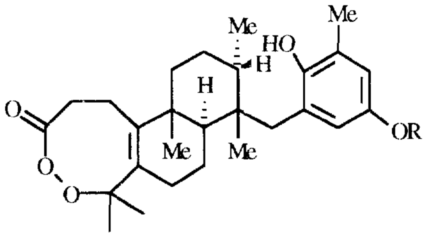


octalactin A

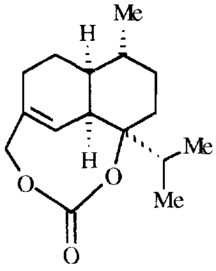


octalactin B

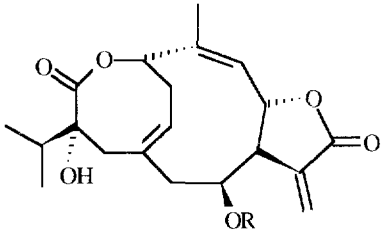
Two unusual peroxylactones were isolated from the brown seaweed *Taonia atomaria*, [29] and recently a cyclic carbonate was found in the aerial parts of a herb, *Fabiana imbricata*, native to central Chile.[30]



R=Me, Ac

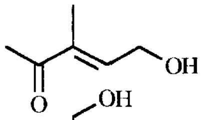


The sesquiterpene lactones, schkuhripinnatolides A-C, were found in the aerial part of *Schkuhria pinnata*, which grows principally in the tropical areas of Central and South America [31].

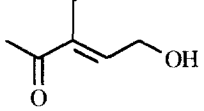


schkuhripinnatolide A: R = H

schkuhripinnatolide B: R =

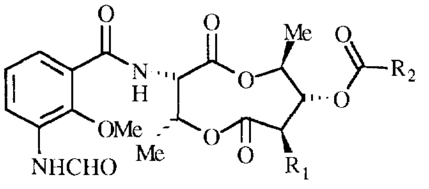


schkuhripinnatolide C: R =



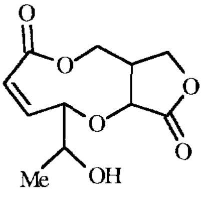
2.2 Nine-membered ring lactones (2-oxonanones)

Antimycin A is a mixture of *streptomyces* fermentation products which shows very interesting antibiotic activity.[32] Thus far, five families of antimycin A have been well characterised, namely A_1, A_2, A_3, A_4 and A_5. In each family, different esters possessing three or four carbons can exist.[33]

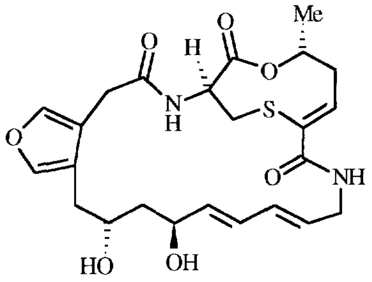


A_1: R_1= hexyl
A_2: R_1= hexyl
A_3: R_1= butyl
A_4: R_1= butyl
A_5: R_1= ethyl

Two other antibiotics, zhijangjunsu [34] and griseoviridin [35] have a 2-oxonanone skeleton. Zhijangjunsu was obtained from a culture of *Streptomyces roseflavus*, and griseoviridin whose structure was determined by X-ray analysis, was isolated from *Streptomyces griseus*.

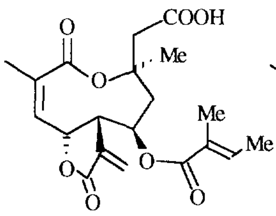


zhijangjunsu

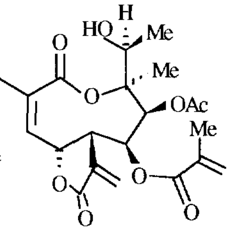


griseoviridin

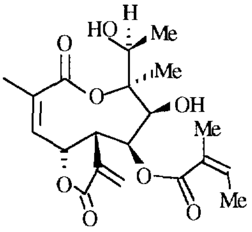
Numerous products have been found in the aerial parts of *Trichogonia* species collected in Arizona. One of these was a secoheliangolide (compound A).[36a] Similarly, the aerial parts of Trichogonia species which grow in Brazil yield three lactones (compounds B, C, D) of similar structure.[36]



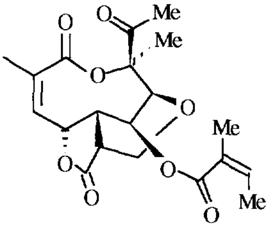
A



B

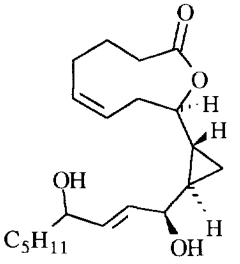


C

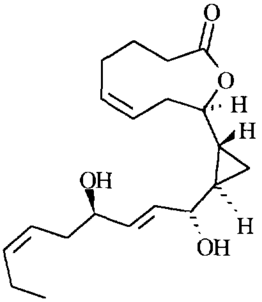


D

Interesting lactones, halicholactone [37] and neohalicholactone,[38] have also been found in marine organisms. These fatty acid metabolites were found in the sponge *Halichondria okadai* collected off the coast of Japan.

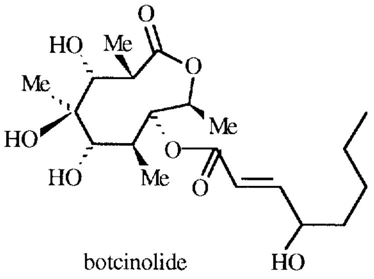


halicholactone



neohalicholactone

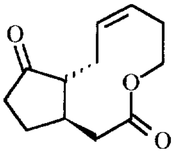
Very recently, a strain of *Botrytis cinerea* isolated from raspberry fruit (*Rubus ideaus*) growing in Georgia (USA) was reported to produce botcinolide which possesses herbicide properties.[39]



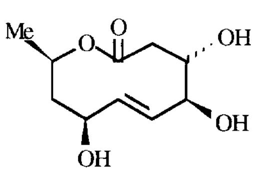
botcinolide

2.3 Ten-membered ring lactones (2-oxecanones)

The oldest natural product possessing an oxecan-2-one framework would appear to be the jasmine ketolactone, a component of the essential oil of *Jasminum grandiflorium* isolated in 1942,[40] whose structure was confirmed twenty years later.[41] More recently, tuckolide was isolated as metabolite of the Canadian tuckahoe, the sclerotium of *Polyporus tuberaster*, a subterranean fungus.[42]

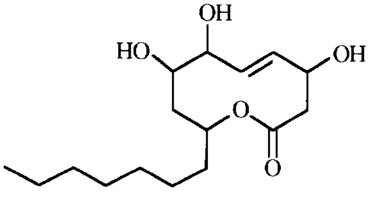


jasmine lactone

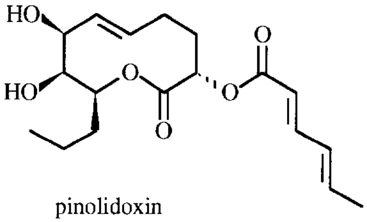


tuckolide

Achaetolide, a compound with a very similar structure, was also isolated from the fungus, *Achaetomium cristalliferum*.[43]

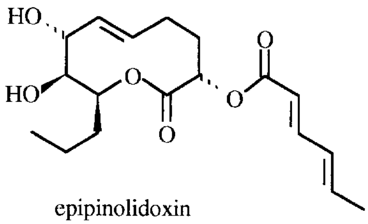


achaetolide

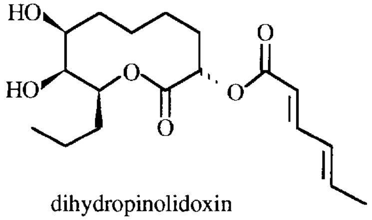


pinolidoxin

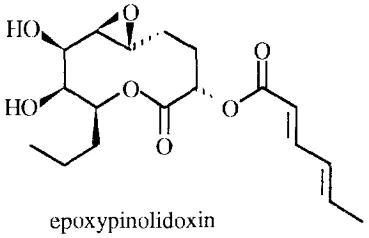
Pinolidoxin, a phytotoxin (anthraenose of pea) was produced by the fungus *Aschochyta pinodes*.[44] Subsequently, three new metabolites of this fungus were found: epi-, dihydro, and epoxypinolidoxins.[45]



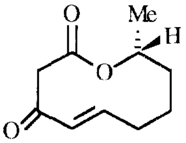
epipinolidoxin

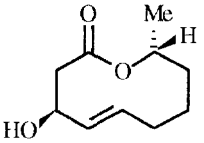


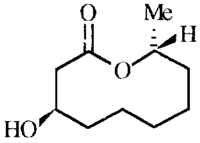
dihydropinolidoxin

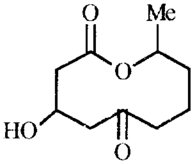

epoxypinolidoxin

Diplodialides A, B, C and D, the metabolites of the phytopathogenic fungus *Diplodia pinea*, have more simple structures than pinolidoxine derivatives.[46] Diplodialide A has been reported to be a steroid hydroxylase inhibitor.

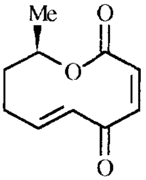

diplodialide A

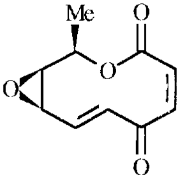

diplodialide B

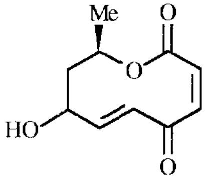

diplodialide C


diplodialide D

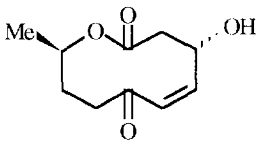
Another phytopathogenic fungus, *Pyrenophora teres*, produces metabolites, pyrenolides A, B and C, which have similar structures to the diplodialides.[47] These compounds show inhibitory activity against fungi.[48]

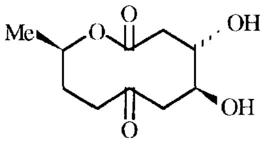

pyrenolide A


pyrenolide B

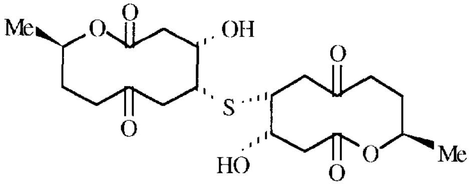

pyrenolide C

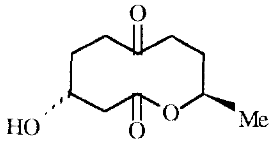
Two other similar structures, cephalosporolides B and C, are metabolites of the fungus *Cephalosporium aphidicola*.[16]


cephalosporolide B


cephalosporolide C

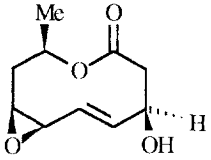
Another interesting metabolite, thiobiscephalosporolide A, was isolated during the fermentation of *Cephalosporium a.* and found to be a dimeric 10-membered ring lactone.[49] On degradation, it led to a compound which is a regioisomer of diplodialide D. The biogenesis of these different compounds has been discussed recently.[50]



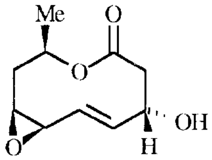


thiobiscephalosporolide A

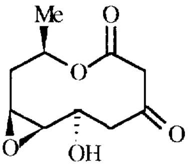
Various oxygenated oxecan-2-ones, decarestrictines A-K, were formed during the fermentation of *Penicillium simplicissimum*.[51] These compounds show important inhibitory effects on cholesterol biosynthesis.[52]



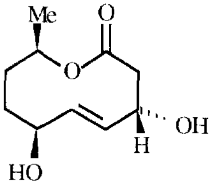
decarestrictine A_1



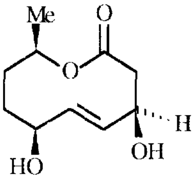
decarestrictine A_2



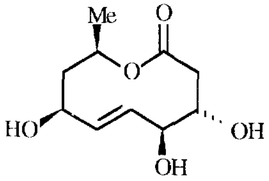
decarestrictine B



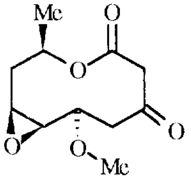
decarestrictine C_1



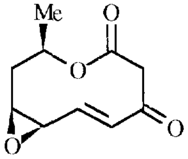
decarestrictine C_2



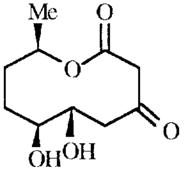
decarestrictine D



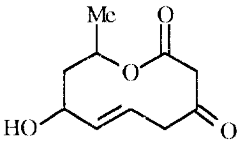
decarestrictine E



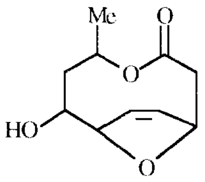
decarestrictine F



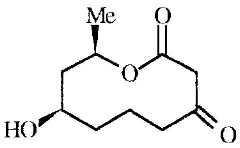
decarestrictine G



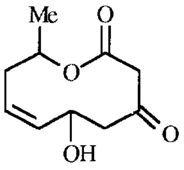
decarestrictine H



decarestrictine I



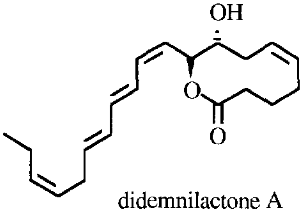
decarestrictine J



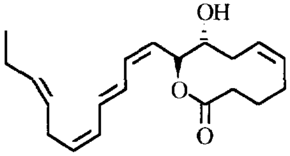
decarestrictine K

Decarestritine D is identical to tuckolide, and its isolation was published simultaneously.[42]

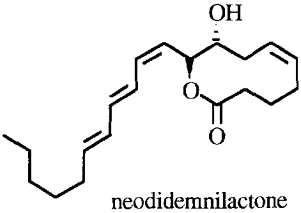
Metabolites of *Didemnum moseleyi* (Herdman), a tunicate living in the sea in Japan, didemnilactones A and B, and neodidemnilactone, were also found to be 10-membered ring lactones.[53] These compounds exhibit weak binding activity to leukotriene B_4 receptors in human polymorphonuclear leukocyte membrane fractions.



didemnilactone A

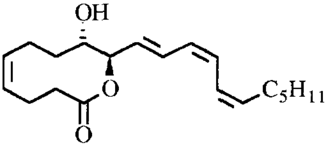


didemnilactone B

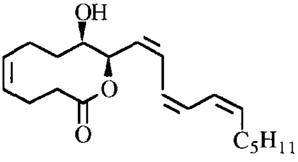


neodidemnilactone

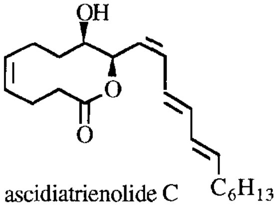
Ascidiatrienolides A, B, and C,[54a] whose structures were recently reinvestigated,[54b] were found in marine ascidian (*Didemnum candidum*) and corresponded to oxidation products of C_{20} fatty acid.



ascidiatrienolide A

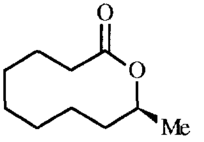


ascidiatrienolide B

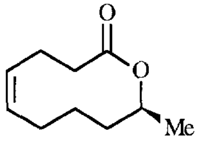


ascidiatrienolide C

The metasternal gland secretion of the common eucalypt longicorn, *Phoracantha semipunctata* contains two lactones as major components, phoracantholide I and phoracantholide J.[55]

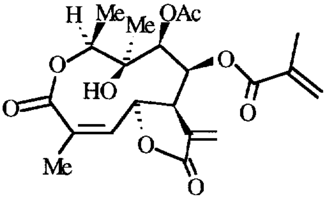


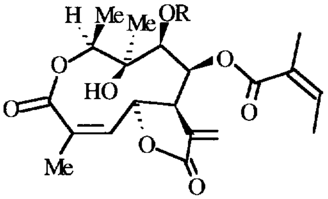
phoracantholide I



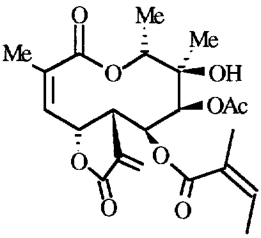
phoracantholide J

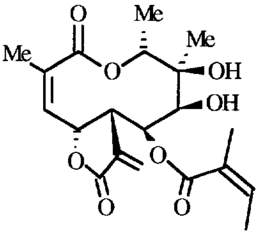
Much more complex lactones have been also isolated. Trichlogoniolide lactones were also observed among the metabolites isolated in the aerial parts of *Trichogonia* species (*vide supra*).[36]



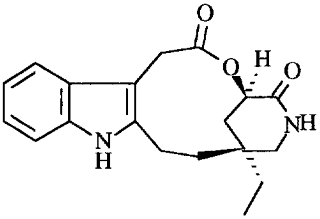


R = H, Ac



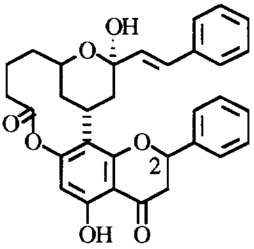


A new alkaloid, aspidochibine, was isolated from the bark of the tree, *Aspidosperma quebracho blanco* Schlecht, which is used for the treatment of bronchial asthma and dyspnoe in South America.[56]

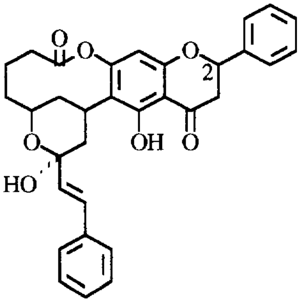


aspidochibine

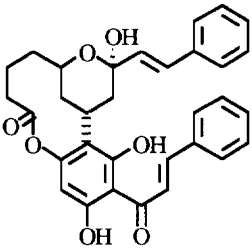
Four flavanones, kurziflavolactones A, B, C and D, and a chalcone, kurzichalcolactone, have been found recently in the leaves of a Malaysian plant, *Cryptocarya kurzeii* (Lauracae) and have a weak cytotoxicity against KB cells.[57]



2R: kurziflavolactone A
2S: kurziflavolactone B

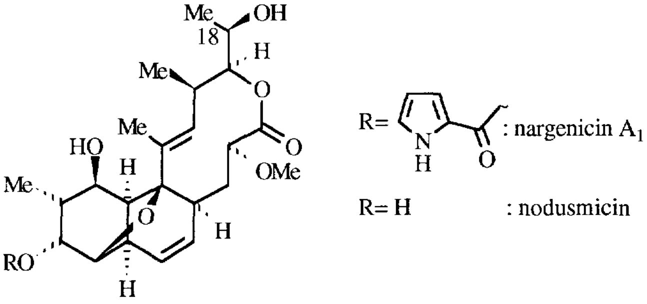


2S: kurziflavolactone C
2R: kurziflavolactone D



kurzichalcolactone

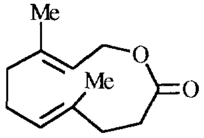
Nargenicin A_1 [58] and nodusmicin [59] are antibiotics produced by *Nocardia argentinensis* and *Saccharopolyspora hirsuta* respectively. Their biosynthesis was recently investigated.[60]



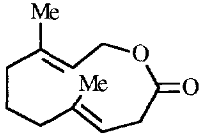
18-Deoxynargenicin A_1 was prepared, and showed more potent activity against *streptococci* than nargenicin A_1.[61]

2.4 Eleven-membered ring lactones (oxacycloundecan-2-ones)

Other than crotalan derivatives, only a limited number of natural products with this size of lactone are known. Ferrulactone I was isolated from the volatile components of *Cryptolestes ferrugineus* frass, the rusty grain beetle which infests stored grain.[62]



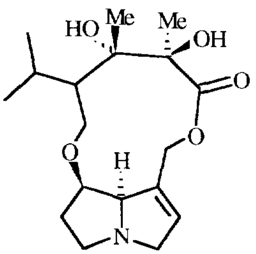
ferrulactone I



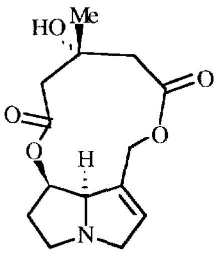
suspensolide

The sex pheromone suspensolide was isolated from the male Carribbean fruitfly, *Anastrepha suspensa* Loew, a major pest of fruit in Central and North America.[63]

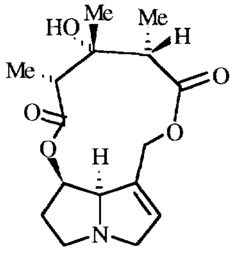
Numerous pyrroliridine alkaloids have been isolated from *Crotalacia* species. These plants (Leguminosae) are usually known to have in general high toxicities (hepatotoxicity and carcinogenicity) and are responsible for death in livestock as well as in humans. About 30 of these compounds are actually known to possess an eleven-membered ring dilactone skeleton (crotalanan).[64] The total syntheses of some of them (dicrotaline,[65] fulvine,[66] crispatine,[66] monocrotaline,[67] and crobarbatine [68]) have been reported.



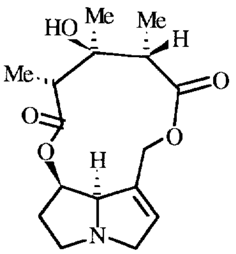
crotalanan



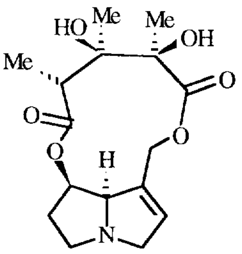
dicrotaline



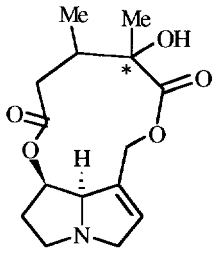
fulvine



crispatine



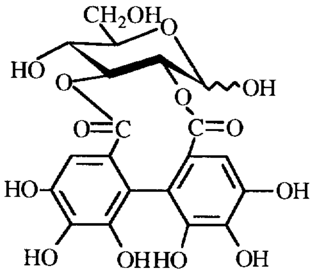
monocrotaline



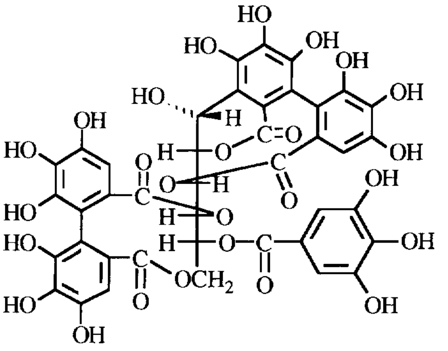
crobarbatine

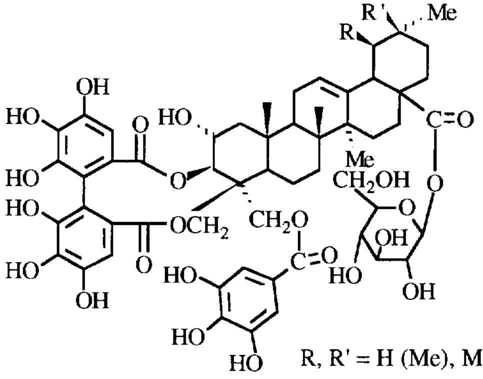
*(stereochemistry unknown)

Hydrolysable tannins have been isolated from the leaves of Fagaceae such as *Quercus aliena* Blume, *Castanopsis hystrix*, and *Castanopsis cuspidata*.[69] A large number these complex compounds has nine- or ten-membered diolide structures. Representative examples are shown below.



2,3-(S)-HHDP- D-glucose





R, R' = H (Me), Me (H)

castanopsinin I

3. Preparation of medium ring lactones

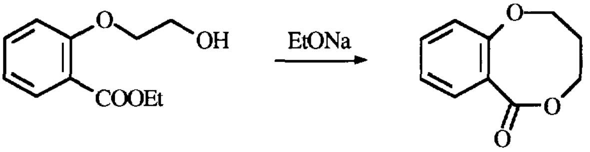
3.1 Lactonisation of ω-hydroxyalkanoic acids

3.1.1 Direct cyclisation

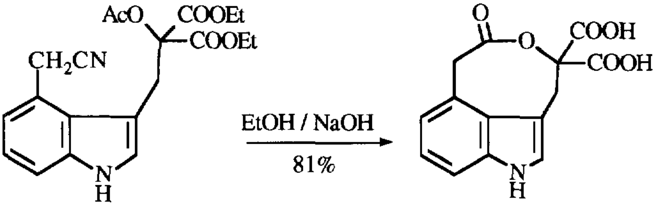
A number of reviews have been published on the subject of cyclisation methods and the synthesis of macrolides. However, only a few containing information about medium ring lactones are available.[70] The most complete is probably that of Vilarrasa and coworkers.[70d]

The first attempt to prepare medium ring lactones by cyclisation of ω-hydroxyalkanoic acids was reported by Stoll and Rouvé.[71] They showed that of oligomer was the major product and the yields of monolide were very low (for example 1% for the formation of nonanolide). An attempts to improve the yield by using boron trifluoride etherate in the presence of unfunctionnalized polystyrene beads as catalyst was not successful.[72] Stoll and Rouvé's procedure was, however applied successfully to the synthesis of phoracantholide I (60% yield).[73]

Lactonisation of a hydroxy ester with sodium ethanoate has also been reported to work; however, the yield was not reported.[74]

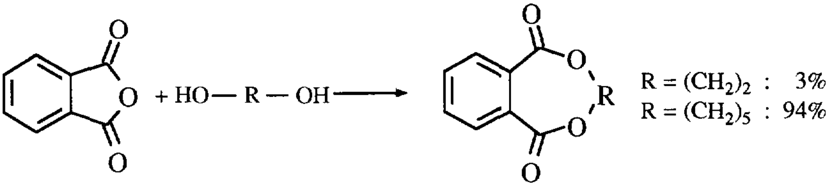


The intramolecular reaction of an alcoholate with a nitrile was also reported to lead to an eight-membered ring lactone.[75]

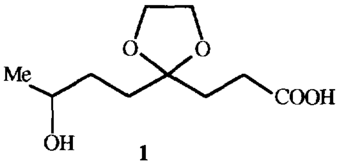


The lactonisation of ω-hydroxyalkanoates, carried out in a flow reactor charged with zirconium(IV) oxide at 275°C in a toluene solution, was reported to give moderate yields of 7-heptanolide (48%) and 8-octanolide (35%).[76] It was subsequently found that zirconium(IV) chloride modified by trimethylsilyl chloride was superior, and 8- and 9-membered ring lactones were obtained in improved yields (67-77%).[77] Depolymerisation at 270°C of linear polyesters in the presence of $MgCl_2$ was also studied. In the range 8-11-membered ring lactones, diolides were the major product.[78]

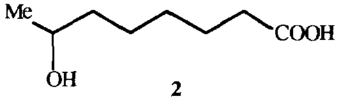
Cyclic diesters were formed by thermolysis at 220-270°C of phthalic anhydride with diols in the presence of tetrabutyltitanate.[79]



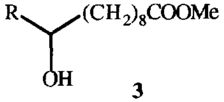
The cyclisation of ω-hydroxyalkanoic acids and alkanoates by means of enzyme-catalysed lactonisations has also been studied. No reaction was observed between hydroxy acid **1** and the lipase of *Pseudomonas sp.*, while hydroxy acid **2** led to a mixture of two diastereoisomeric diolides.[80] Similarly, lactonisation of ω-hydroxydecanoic acid was studied with different lipases, and only a mixture of di-, tri-, tetra- and pentanolides was obtained, and macrolactones could also be formed.[81]



1



2



3

Lactonisation of racemic methyl 10-hydroxyundecanoate (**3**: R = CH_3) with the lipase of *Pseudomonas* sp was reported to give a mixture of mono- and diolide.[82] Recently, this study was reinvestigated with PPL as lipase. With methyl 10-hydroxydecanoate (**3**: R = H), di- and triolides were the major products, while with methyl 10-hydroxyundecanoate (**3**: R = Me) the monolide was the major product. With 10-hydroxydodecanoate (**3**: R = Et), the tendency to favour of the monolide becomes more marked (the ratio was 81:19 in favour of the monolide), although the reactivity of the substrate was very low.[83] Using vinyl esters did not give much better results. With vinyl 10-hydroxyundecanoate, only 11% of the corresponding (*R*)-8-membered ring lactone was formed. For the other ring sizes, no monolides were seen.[84]

3.1.2 Activation methods

The activation methods of ω-hydroxy acids that have been developed to synthesise macrolactones have already been reviewed.[70] This section will focus on results obtained in the lactonisation of 8-hydroxyoctanoic acid (as an example) using some of these methods (see Table 3).

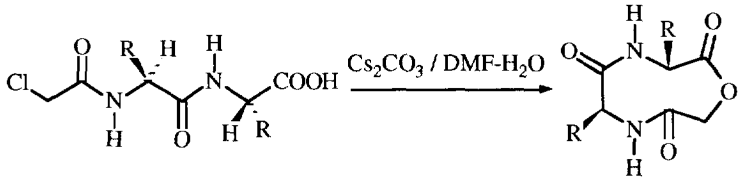
Table 3: Lactonisation of 8-hydroxyoctanoic acid

Method	Ref.	Yield in nonalactone (diolide) (%)
Corey	85	8[a] (41)
Mitsunobu	86	0.8 (70)
Mukaiyama	87	13 (34)
Steliou	88	0[b] (36)
Vorbrüggen	89	0 (14)
Yamaguchi	90	18 (41)

[a]) 25% yield in glc ; [b]) 8-methylnonanolide

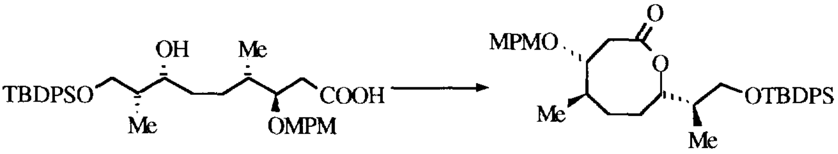
In all cases, unsatisfactory yields of nonanolide were observed; comparable results should be obtained for other medium-ring lactone sizes. In a recent study, Bartra and Vilarrasa [91] have reinvestigated different activation methods for the cyclisation of 9-hydroxydecanoic acid to give phoracantholide I using the same reaction conditions. The best results were observed using the method developed by Gerlach [92] (50% yield), while very low yields were obtained using some of the methods reported in Table 3. However, in their review, Batra and Vilarrasa [70d] have collected examples which show that the cyclisation leading to natural products can occur if a double bond is present in the carbon chain (see, in particular the appendix to their review), sometimes with satisfactory yields. Additional examples are shown below

Kellog and coworkers found that formation of a nine-membered ring ring lactone could sometimes be favourable. Lactonisation of $(Gly)_2$ (R = H) and $(Leu)_2$ (R = i-Bu) led to the corresponding monolide, while $(Val)_2$ (R = i-Pr) led to the diolide.[93]

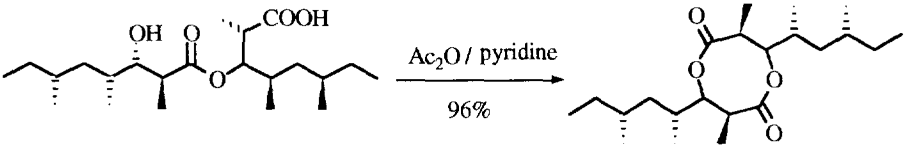


R= H (85%)
R= *i* Bu (88%)

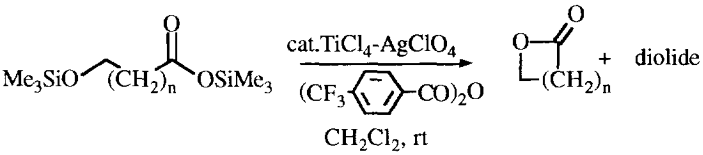
A similar observation was made by Buszek during the synthesis of octalactins A and B.[28a] The key lactonisation step, leading to the 8-membered ring lactone, occurred in high yield (73%) using the Corey method.



An 8-membered ring diolide was also reported to be readily formed by the cyclisation of the corresponding hydroxyacid.[94]

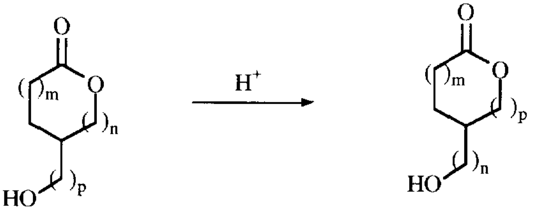


Recently, Mukaiyama and coworkers [95] have reported a new activation method based on the lactonisation of silyl ω-siloxyalkanoate using *p*-trifluoromethylbenzoic anhydride and a catalytic amount of a mixture of $TiCl_4$ and $AgClO_4$. In the specific case of medium ring lactones, low yields were obtained (0% for the 8 and 9-membered ring lactones; 33% for the decanolide) except for the formation of the undecanolide (70%).

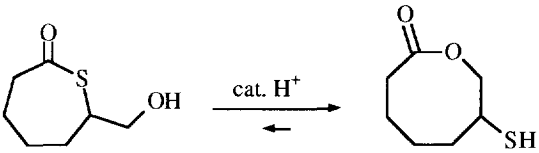


3.1.3 Translactonisation method

In this method, first introduced by Corey and coworkers,[96] a hydroxy lactone is subjected to the action of a catalytic amount of acid to give a thermodynamically more stable hydroxylactone.



Since medium ring lactones are less stable than other lactones, it should be, *a priori*, difficult to obtain medium ring lactones by this technique. Corey showed that an 8-membered ring lactone can be transformed to a 11-membered ring lactone. In a subsequent work, Vedejs and coworkers [97] have shown that, starting with thiolactones, such an isomerisation can indeed take place. For example, a seven-membered ring thiolactone was transformed in good yield to a 8-membered ring lactone (70% yield) even though equilibrium between these two lactones was observed.

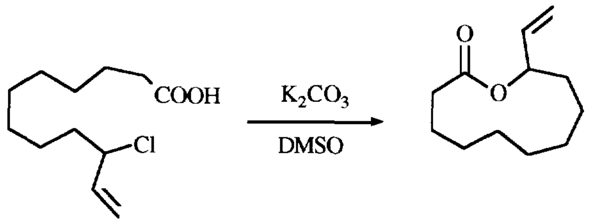


The transformation 6 → 8 was much less favourable (20% yield) and diolide was obtained (30%). The transformations 9 → 10 and 10 → 11 were accomplished in high yields (70 - 91%). The former reaction was applied to the preparation of phoracantholide I.[97]

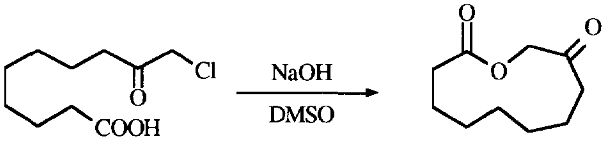
Isomerisation of 7-membered ring lactone to a 10-membered ring lactone was observed by Corey during the synthesis of erythronolides,[98] and transformation of macrolides to 10 and 11-membered ring lactones were also described.[99] These examples are, however specific, and can probably be explained by strain relief favoured by the conformations of the resulting medium ring lactones.

3.2 Cyclisation of ω-haloalkanoic acids and related compounds

The cyclisation of ω-haloalkanoic acids induced by a base such as K_2CO_3 or NaOH is one of the oldest methods available for the preparation of medium ring lactones. Hunsdiecker reported the formation 10- and 11-membered ring lactones in good yields by the reaction of the corresponding bromoalkanoic acids with potassium carbonate.[9] The kinetic study of Illuminati and coworkers showed the limitation of this method and the necessity of high dilution conditions if medium ring lactones are to be formed in satisfactory yields (*vide supra*).[10b] These chemists also examined the kinetic influence on the cyclisation of a *gem*-dimethyl substituent fixed in the 3-position of the carbon chain. Formation of 3,3-dimethyl nonanolactone occurred 6.6 times faster than nonanolactone; however, in the other ring sizes examined (10 and 11), no such effect was observed.[100] Using the optimal cyclisation conditions necessary for the synthesis of 11-undecanolide described by Galli and Mandolini [101] (reaction at 100°C in DMSO in the presence of K_2CO_3), Cameron and Knight obtained an 11-membered ring lactone in 60% yield.[102]



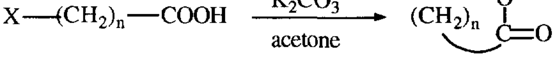
With NaOH in DMSO, Karin and Sampson achieved the cyclisation of 10-chloro-9-oxodecanoic acid in high yield.[103] This cyclisation occurred 70 times faster than that of 10-bromodecanoic acid. The activation induced by the α-keto function is very important.[103b]



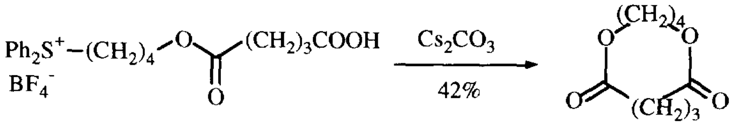
Regen reported the formation of lactones by treatment of ω-bromoalkanoic acids under solid-liquid phase transfer conditions, which simulated high dilution conditions.[104] However, the 9-membered ring lactone was obtained in only 26% yield by reaction of the potassium salt of the bromoacid with tetrabutylammonium bromide in toluene. Closure of ω-methanesulfonyloxyalkanoic acids using a three-phase system (aq. $NaHCO_3$/toluene/phosphonium salt cross-linked polymer) gave lower yields.[105]

Kellog reported that ω-halo acids led, when treated with caesium carbonate, to macrolides in good yields.[106] For 8- to 10-membered ring lactones, this cyclisation did not work as diolides were formed and only the undecalactone was obtained in 23% yield. However employing O-methanesulfonyl derivatives in this cyclisation was found to be favourable, and 10- and 11-membered ring lactones were obtained in approximately 50% yields.[107] The superiority of O-methanesulfonyl derivatives was also recognised by Vedejs in the syntheses of fulvine,[66] crispatine,[66] and monocrotaline.[67a]

Another possible improvement was proposed by Matsuyama and coworkers [108] who studied the cyclisation of sulfonium salts. For macrolides, the replacement of bromide (X = Br) by a sulfonium salt (X = $^+SPh_2$, BF_4^-) led to improved yields.

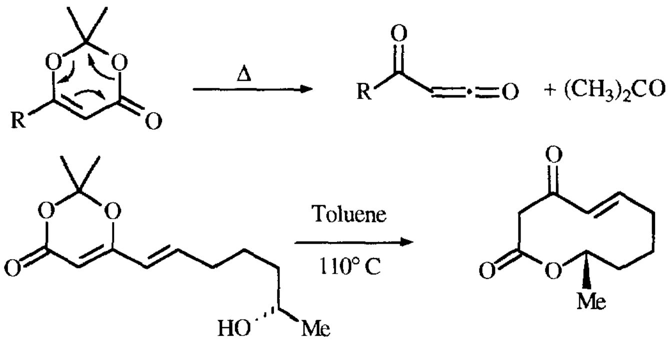


For medium ring lactones, however, the yields in these cyclisations were still low (18 and 33% respectively for the 8- and 9-membered ring lactones). The reaction was subsequently improved slightly by using caesium carbonate as base.[109] This new technique has allowed the preparation of a 11-membered ring dilactone, and was applied to the synthesis of 13,13-dimethyl-1,2-didehydrocrotalanine (70% yield). This method gave comparable results to those reported by Vedejs.[66, 67a]

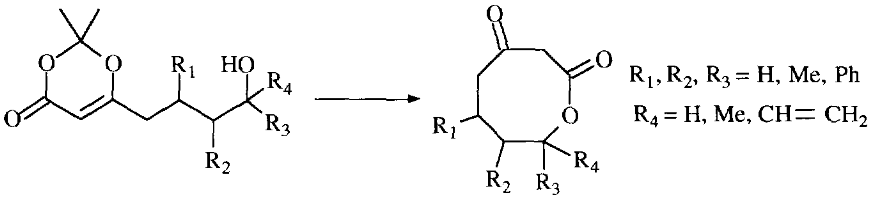


3.3 Intramolecular alcohol-ketene reactions

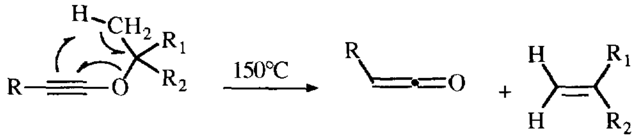
It would appear that the activation of an acid generates under some conditions, a ketene which then reacts intramolecularly with a free alcohol to give the lactone. This was demonstrated in the Mukaiyama method by Funk and coworkers.[110] However as has already been shown, the efficiency of this approach is not obvious for the preparation of medium ring lactones. Two research groups have shown independently that the thermal generation of ketenes from dioxolenones is much more efficient. Boeckman obtained (+)-diplodialide A in 68% yield using this method.[111]

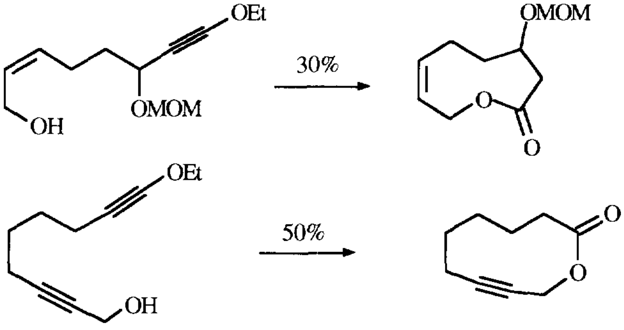


Petasis prepared β-keto-8-membered ring lactones in yields above 90% in the same way.[112] These yields were attributed in part to the presence of the keto group which lowered the strain energy in the lactones.

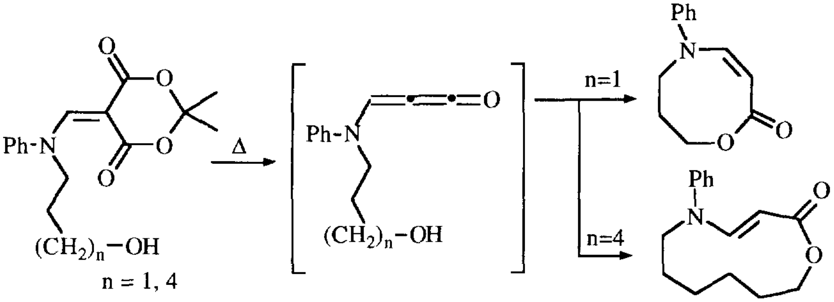

R_1, R_2, R_3 = H, Me, Ph
R_4 = H, Me, CH= CH_2

Recently, it has been reported that heating ethyl alkynyl ethers at 150°C in the presence of tributylamine also lead to ketenes, which can be trapped intramolecularly by alcohols to give medium ring lactones in modest yields.[113]

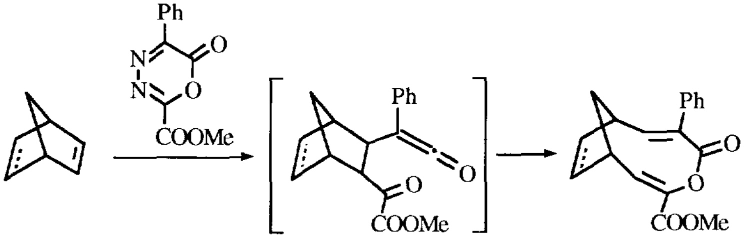




Intramolecular trapping of methyleneketene (generated at 400-500°C using flow conditions) was also reported to lead in low yields (22-35%) to the formation of β-amino-α,β-unsaturated medium ring lactones.[114] The geometry of the carbon-carbon double bond depends on ring size.

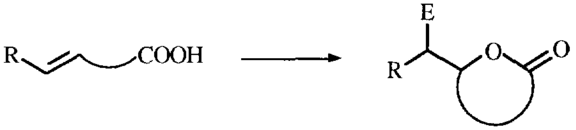


Reaction of oxadiazinones with norbornene and norbornadiene led, *via* the γ-oxoketene and subsequent intramolecular trapping of the enol, to unsaturated nine-membered ring lactones. A similar reaction was observed with bicyclo[2.1.1]hexene. This reaction appears to be limited to strained cyclopentene derivatives.[115]

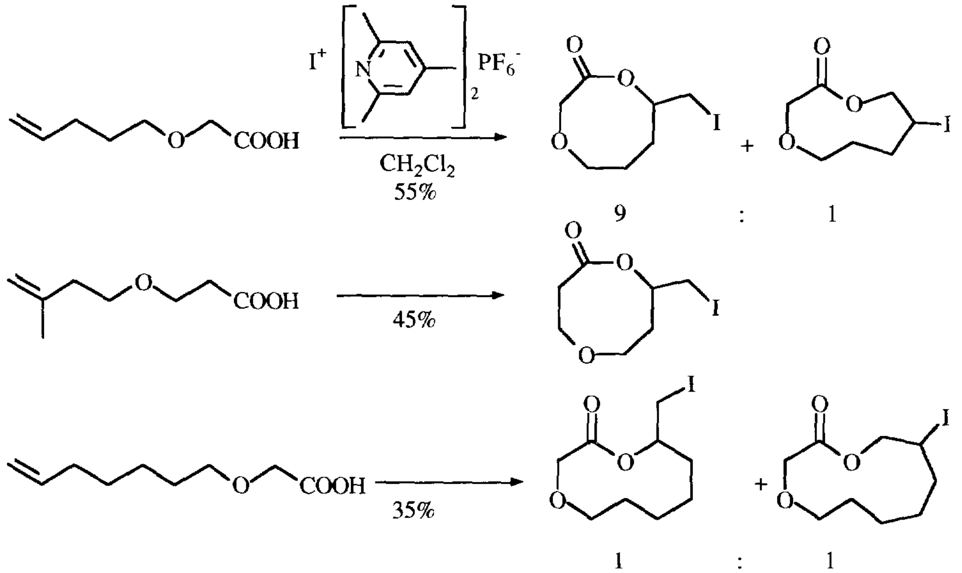


3.4 Electrophilic heteroatom cyclisations

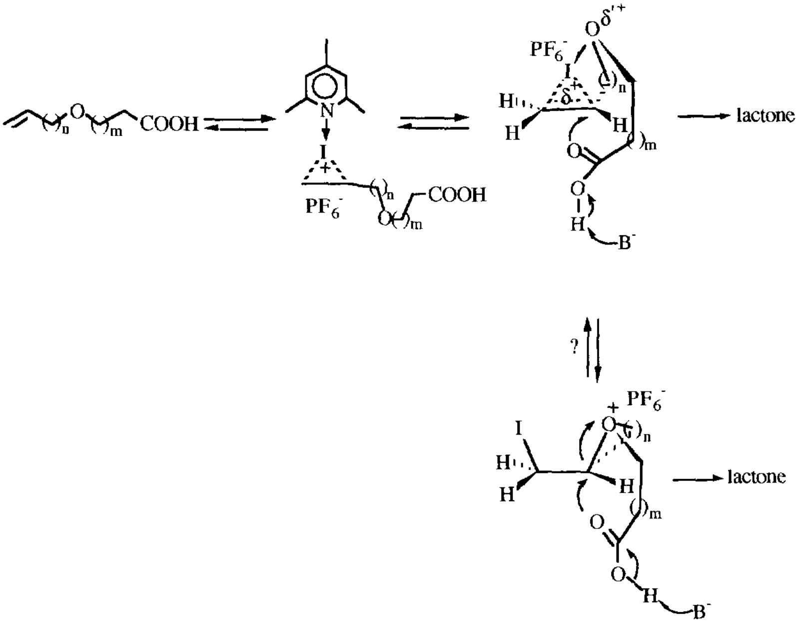
Electrophilic heteroatom cyclisations have been widely used in organic synthesis, in particular for the preparation of 4- to 6-membered ring lactones.[116] The most common electrophilic reagents are I_2, Br_2, PhSeCl, $Hg(OAc)_2$, $Pd(OAc)_2$, and $AgNO_3$.



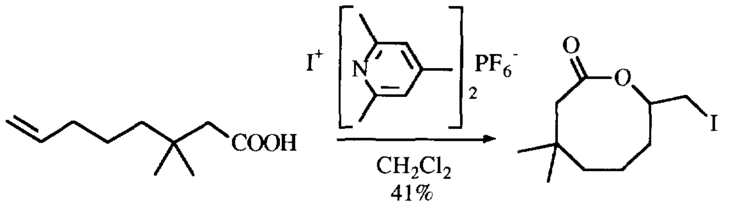
Until recently, this approach was found to be unsuccessful for the preparation of medium ring lactones. Rousseau and coworkers studied iodolactonisation using bis(*sym*-collidine)iodine(I) hexafluorophosphate as reagent.[117] With ω-alkenoic acids, low yields (4%) of 8- and 11-membered ring lactones were seen. However, introduction of an oxygen atom in the chain[118] favoured the cyclisation.

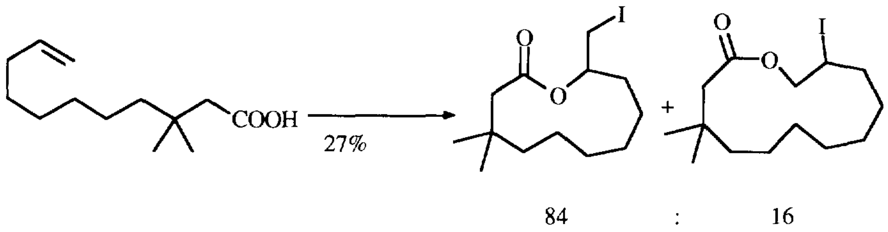


In these ring sizes, in general, a competitive endo-exo cyclisation was observed. The influence of the oxygen atom was explained by its participation in the stabilisation of the intermediate.[117b]

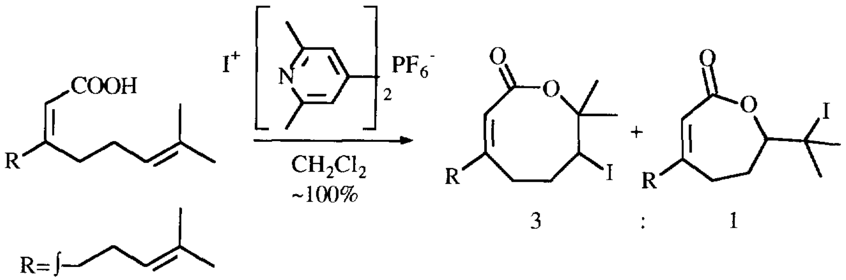


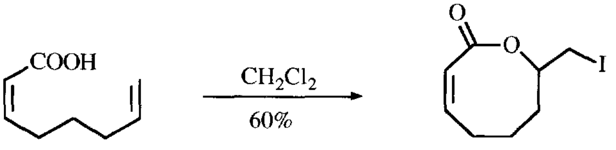
Introduction of a *gem*-dimethyl group on one of the carbons in the chain also had a beneficial effect.[119] Eight- to eleven-membered ring lactones were obtained in moderate yields.





A third factor was found to favour the cyclisation, the presence of a *cis* double bond. For example, reaction of bis(*sym*-collidine)iodine(I) hexafluorophosphate with 10-sesquigeranic acid led in quantitative yield to a mixture of 7- and 8-membered ring lactones.[120a] The major octanolide was formed by an endo-mode cyclisation. Eight-membered ring lactones could also be formed by an exo-mode cyclisation.[120b]

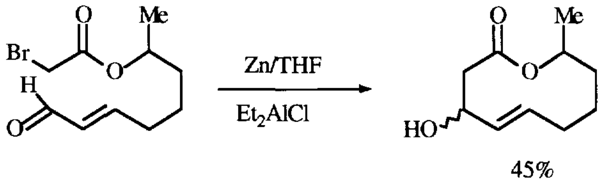




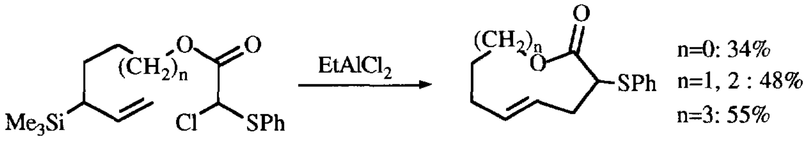
3.5 Cyclisation *via* carbon-carbon formation

3.5.1 Electrophile-induced cyclisation

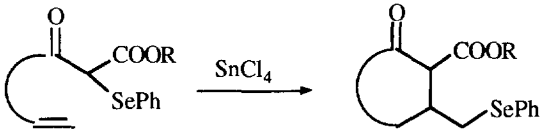
Intramolecular Reformatsky reaction promoted by Et_2AlCl was found to induce the ring closure and give an unsaturated 10-membered ring lactone, of which one diastereoisomer was diplodialide A.[121]



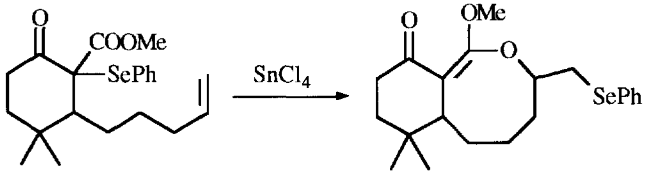
Intramolecular additions of allylsilanes to α-chlorosulfides promoted by $EtAlCl_2$ furnished, in moderate yields, 8- to 11-membered ring lactones.[122] A formal synthesis of phoracantholide I was also reported (42% yield for the cyclisation step).



Ley reported that alkenyl α-phenylseleno β-keto esters could be cyclised in the presence of $SnCl_4$.[123]



For keto ester **4**, a sensitive ketene acetal corresponding to the eight-membered ring lactone could be isolated (84%). This reaction does not appear to have been exploited.



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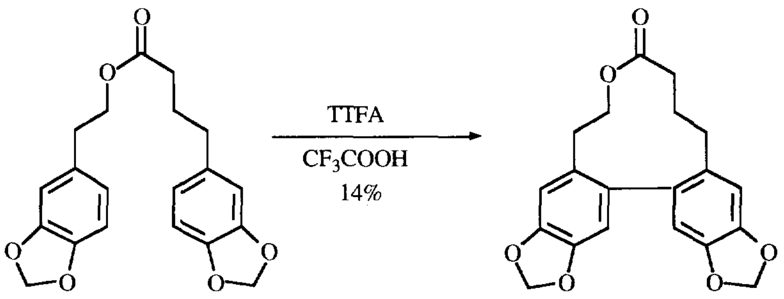
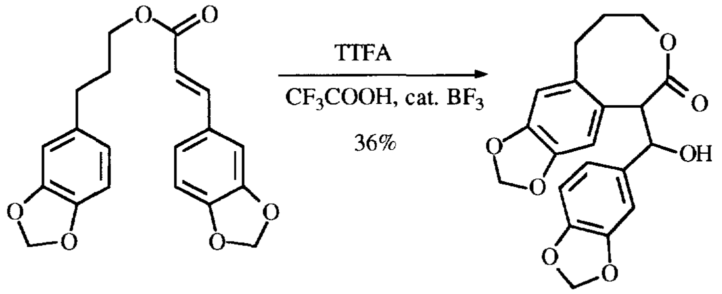
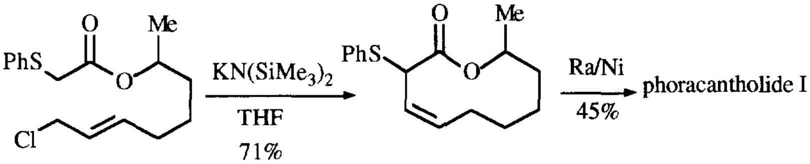
An interesting, if not very efficient, synthesis of 8- and 11-membered ring lactones was accomplished using thallium(III) trifluoroacetate (TTFA) as oxidizing agent for aryl groups and carbon-carbon double bonds.[124]



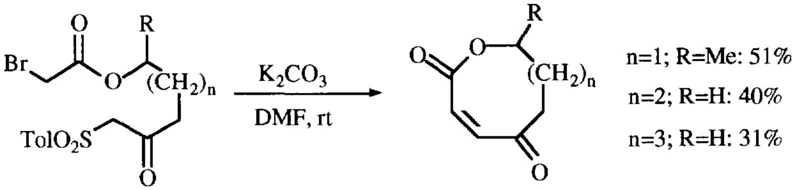


3.5.2 Nucleophile-induced cyclisation

Tsuji and coworkers have shown that lactone formation could take place by carbon-carbon bond formation via the intramolecular alkylation of a carbanion generated from phenylthioacetate.[125] This strategy was applied to the preparation of a ten-membered ring lactone, which could be transformed into phoracantholide I.



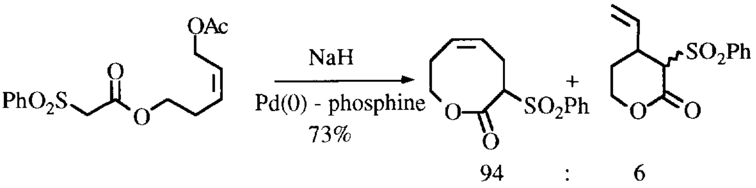
A very similar method was employed by Lygo and O'Connor who studied the intramolecular cyclisation of β-ketosulphone anions with bromoacetates. Moderate yields were obtained for 8-10-membered ring lactones.[126]

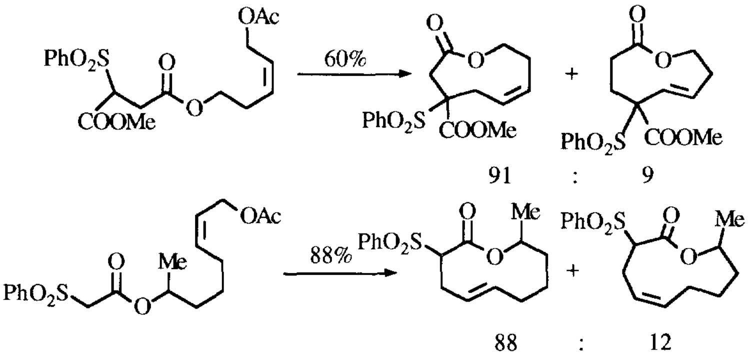


3.5.3 Metal-induced coupling reactions

3.5.3.1 Palladium-induced reactions

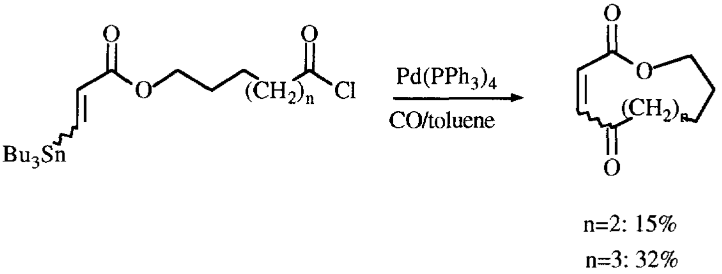
Work in this field was pioneered by Trost who observed that stabilised anions react intramolecularly with allylic acetates in the presence of Pd(PPh$_3$)$_4$ and 1,2-diphenylphosphinoethane to give medium ring lactones.[127] Examples are given below. Interestingly, the higher ring size lactones were always the only or major products.





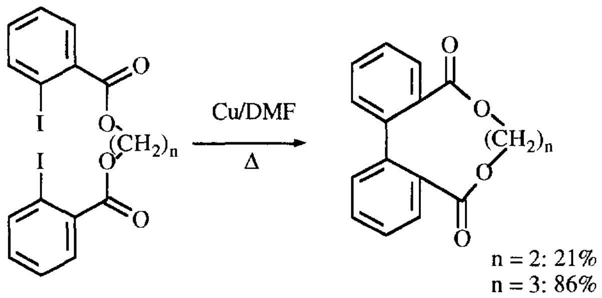
In cases where either a *cis* or *trans* double bond could be formed, the *trans* (*E*) was always the major. Cyclisation of ethyl carbonates instead of acetates was reported to give improved yields.[128]

Recently, Baldwin and coworkers reported the intramolecular Pd(0)-catalysed coupling of acid chloride and β-stannylalkenoate in the presence of CO as a new route to 10-20-membered ring lactones. For the medium lactones, low yields were observed.[129]

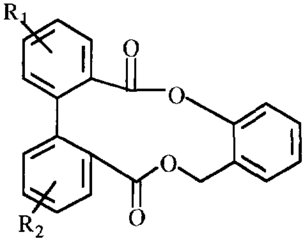


3.5.3.2 Copper-induced reaction

The Ullman reaction was found to be a useful method for the synthesis of 11-membered ring lactones (80-90%). The corresponding 10-membered ring compound was formed in only 21% yield.[130]

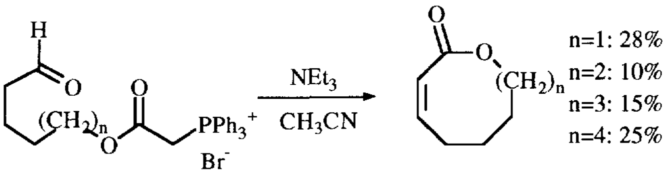


Introduction of an aryl group between the two esters functions also appears to favour reaction (82-88%).

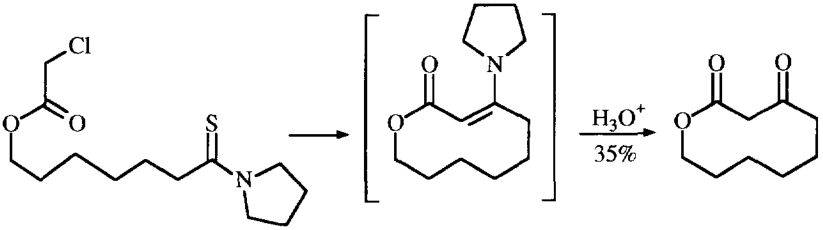


3.5.4 Intramolecular double bond formation

While numerous applications of the Wittig or Wittig-Horner reactions to the formation of macrolides have been reported (see reference 70d), almost nothing was known about the formation of medium ring lactones by this approach. Recently, Le Floc'h and coworkers have examined the reaction of ω-aldehydophosphoranes generated under high dilution conditions.[131] Medium ring lactones were obtained in low yields; diolides were the major products.



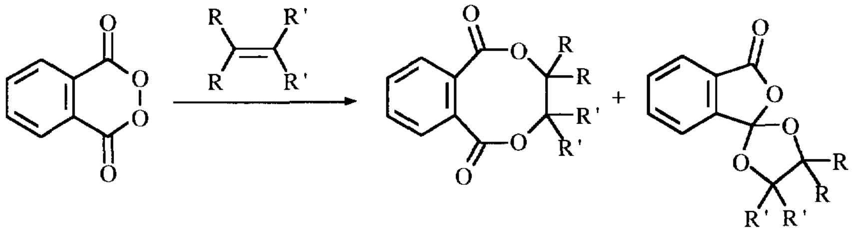
Thioamides are known to react with bromoacetate to give β-amino-α,β-ethylenic esters. The intramolecular version of this reaction was used by Ireland for the preparation of 10-membered ring lactones. This reaction was applied to a synthesis of diplodialide A.[132]



3.5.5 Radical-induced cyclisations

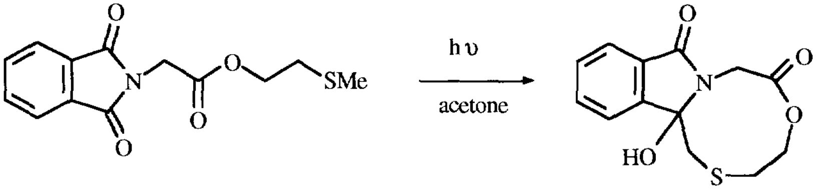
3.5.5.1 Thermal generation

Thirty years ago, Greene showed that heating of perphthalic anhydride in tetrachloromethane in the presence of olefins led to the formation of the corresponding diesters in modest yields.[133]

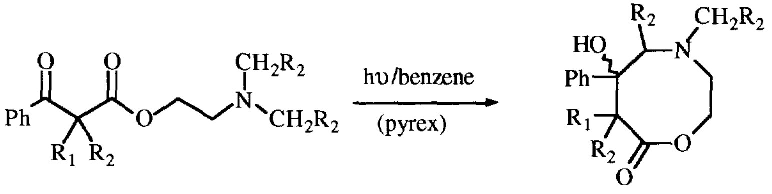


3.5.5.2 Photochemical generation

Irradiation of a phthalimide derivative possessing a terminal sulfide group on a side chain was found to lead, *via* a Norrish type II process (1,10-hydrogen abstraction), to a 9-membered ring lactone in high yield (80%).[134] This reaction was mainly used in the formation of macrocyclic compounds.

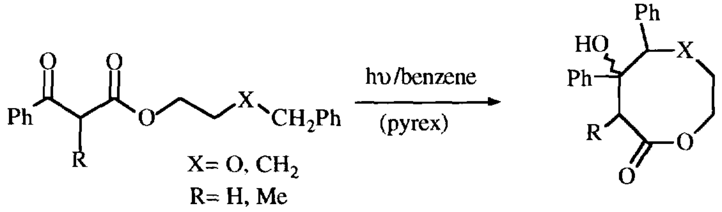


Formation of 8-membered lactones was subsequently reported using this photochemical reaction. Irradiation of amino β-keto esters gave eight-membered ring lactones (1,9-hydrogen abstraction) in 33-63% yields. This reaction was less successful for the synthesis of larger lactones.[135]



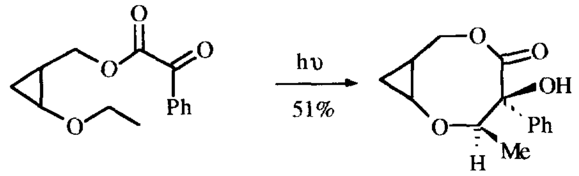
R_1, R_2 = H, Me, Ph

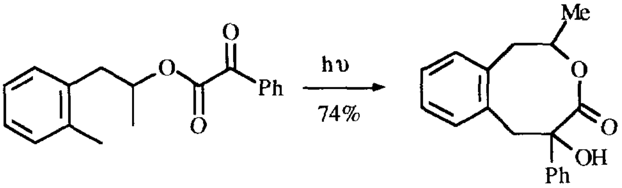
Subsequently, the researchers found that the nitrogen atom was not necessary and cyclisation occurred with ω-phenylalkyl-β-oxo esters (48-76%). γ-Butyro- and δ-valerolactones could not be formed using this reaction.[136]



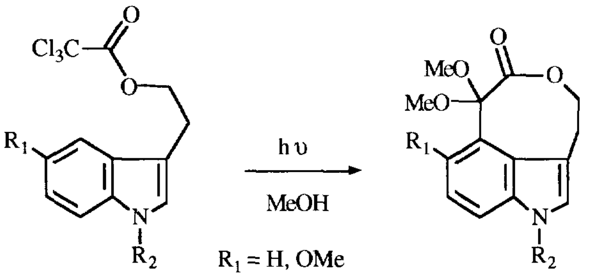
X= O, CH_2
R= H, Me

A comparable 1,9-hydrogen abstraction was reported by Kraus and Wu during the irradiation of α-keto esters. In this case also, eight-membered ring lactones were obtained in good yields.[137]



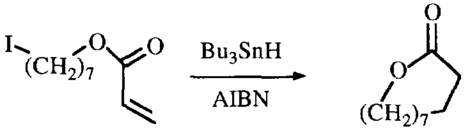


Irradiation of trichloroacetyl tryptophols in a mixture acetonitrile-methanol (98:2) also gave 8-membered ring lactones in good yields (36-77%).[138] The corresponding dichloroacetates were found to react much less efficiently.

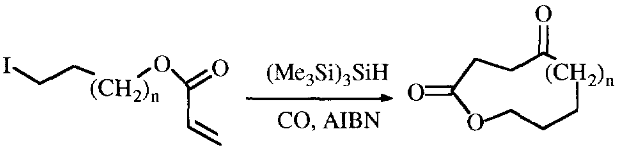


3.5.5.3 Chemical generation

Porter reported that treatment of ω-iodoalkyl acrylate with tributyltin hydride and AIBN in benzene led to the formation of a 11-membered ring lactone in low yield (15-25%).[139]

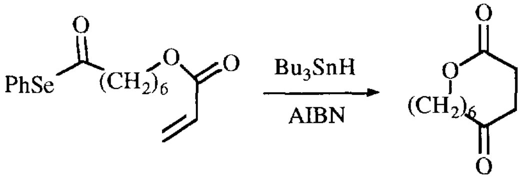


The yields of this cyclisation was subsequently improved (77-95%) and extended to the 10-membered ring lactone, by modification of the reaction procedure.[140] However, the corresponding propiolate could not be used.[141a] When these substrates were treated with tris(trimethylsilyl)silane and AIBN under 30 atmospheres of CO γ-ketolactones were formed. This reaction was applied to the preparation of 10- to 17-membered ring lactones.[141b]

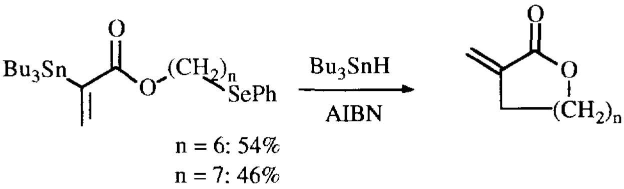


n=1; 0 %
n=2; 28 %
n=3; 68 %

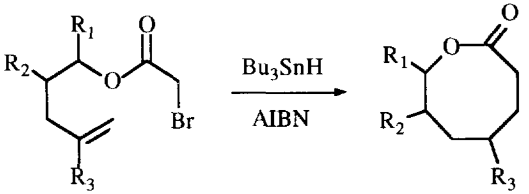
Boger showed that [ω-phenylselenocarbonyl]alkyl acrylates could led to the same radical cyclisation. The 11-membered ring lactone was formed in 47% yield under high dilution conditions.[142]



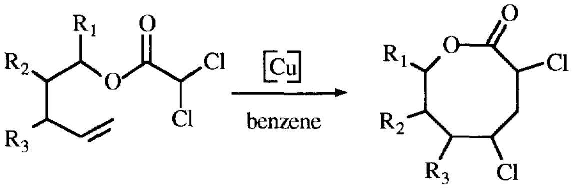
Baldwin showed that ω-phenylselenoalkyl α-tributyltinacrylates also lead to 10- and 11-membered ring lactones when treated with tributyltin hydride and AIBN. This cyclisation did not work for the smaller medium ring lactones.[143]



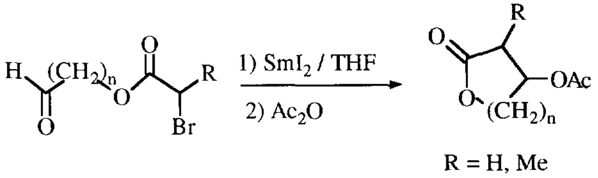
Very recently it has been shown that ω-alkenyl haloacetates can also led intramolecularly to lactones. Interestingly, this approach appears complementary to the previous reaction since 8- (and sometimes 9-) membered ring lactones were formed preferentially. Lee and coworkers reported that 8-membered ring lactones are formed (25-53%) when ω-alkenyl bromoacetates are treated with tributyltin hydride in benzene.[144] When this 8-endo cyclisation was in competition with a 5-exo process, the latter was *not* observed.



Speckamp and coworkers have studied the cyclisation of ω-alkenyl dichloroacetates, and found that they give 8-membered ring lactones in high yields (50-92%). However, the radical reaction was not induced as in the precedent cases by $HSnBu_3$, but by the apparently more efficient Cu(I) chloride-2,2'-bipyridine complex.[145] A 9-membered ring lactone was also formed in good yield. ω-Alkenyltrichloroacetates have more or less the same reactivity in the formation of 8 and 9-membered ring lactones.[146]

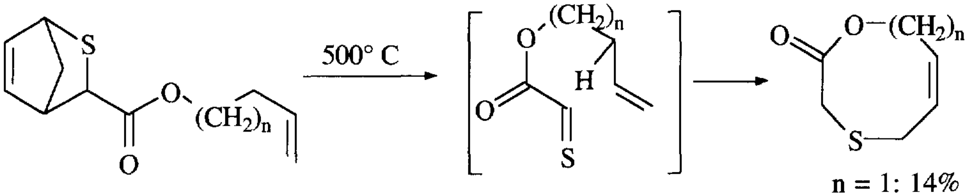


Finally, the cyclisation of ω-oxoalkenyl α-bromoalkanoates induced by SmI_2 has been reported to lead in high yields (76-92%) to 9-11-membered ring lactones.[147] Macrolides were also formed with the same efficiency. This method was applied to the preparation of ferrulactone I.[148]



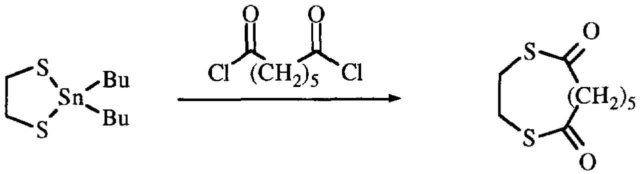
3.6 Other cyclisation methods

Alkenyl thiooxoacetates, generated at 500°C by flash vacuum pyrolysis gave by intramolecular ene reaction, 8- to 11-membered ring β-thialactones.[149] The ene reaction seems to be the rate-limiting step.

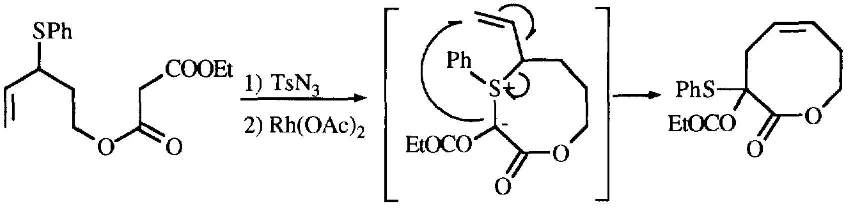


n = 1: 14%
n = 2: 57%
n = 3: 63%
n = 4: 66%

Mandolini and coworkers have studied the ring closure of bifunctionalised reagents, and have applied this procedure to the preparation of dithialactones.[150] By a two component influx procedure, 67% of the cyclised product was obtained.



Yoshikoshi and coworkers have found that allylsulfonium ylides, generated from 2-phenylthio-4-pentenol diazomalonate using a catalytic amount of rhodium acetate, afforded in low yield (19%) an eight-membered ring lactone. This reaction was much more efficient for the formation of ε-caprolactones.[151]



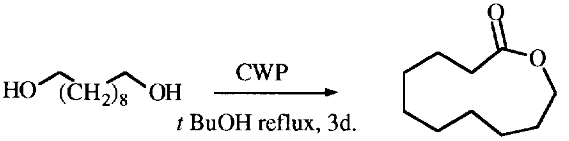
3.7 Oxidation procedures

3.7.1 Baeyer-Villiger reactions

If the corresponding cyclanones are available, Baeyer-Villiger oxidation is a good way of accessing medium-ring lactones. Peracetic acid in acetone was reported to give the eight-membered ring lactone in good yield (85%), while for larger rings, large amounts of acyclic hydroxy acids were obtained.[152] Mixtures of hydrogen peroxide and acetic anhydride was also used for the formation of heptanolactones.[153] Other Baeyer-Villiger agents such as H_2O_2-arsenate polystyrene resins,[154] oxone,[155] oxygen in the presence of a nickel complex and benzaldehyde [156] have been tested on cycloheptanone, without a great deal of success. Indeed, Friess observed a very low reactivity of cyclooctanone when compared to cyclohexanone, during the reaction with perbenzoic acid.[157] White found also a low reactivity of cyclooctanone with permaleic acid,[158] compared to other ketones. *meta*-Chloroperbenzoic acid was also used, but if the yields were good the reaction times were in general very long (several days).[159] One of the choice reagents appears to be trifluoroperacetic acid prepared *in situ* from concentrated H_2O_2 (70%,[14] 85%,[160] or 90% [161]). Excellent yields were obtained for all the medium ring ketones. The main drawback of this method is however the fact that concentrated hydrogen peroxide is not widely available. A promising new reagent was recently reported using the stable and commercially available urea-hydrogen peroxide adduct. In the presence of trifluoroacetic anhydride, the reagent transformed cycloheptanone into heptanolide rapidly (30 min) in 85% yield.[162] The reaction of the urea-hydrogen peroxide adduct in the presence of maleic anhydride was also studied, but appeared less successful (64% of heptanolide after 10 h).[163] Bis(trimethylsilyl)peroxide was also reported to be of no use for the preparation of medium ring lactones.[164]

3.7.2 Diol oxidation

Oxidative dehydrogenation of 1,10-decanediol by 35% H_2O_2 catalysed with tris(acetylpyridinium) 12-tungstophosphate $[\pi\text{-}C_6H_5N^+(CH_2)_{15}CH_3]_3(PW_{12}O_{40})^{3-}$ was reported to give the 11-membered ring lactone in 40% yield.[165]

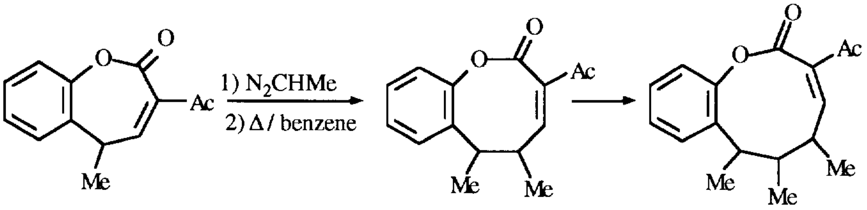


3.8 Ring expansion methods

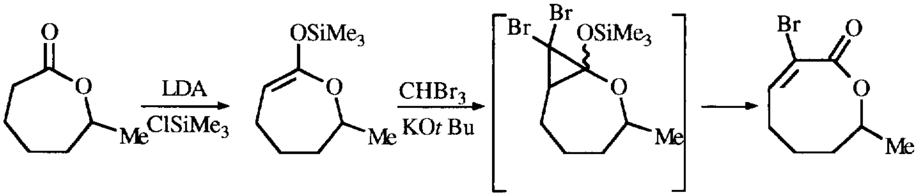
3.8.1 Lactone-ring expansion

3.8.1.1 One-carbon ring expansion

Dean and coworkers showed that reaction of benzooxepinone with diazoethane led to an 8-membered ring lactone by a one carbon ring expansion (50% yield). An iterative reaction was possible and three successive ring expansions could be made.[166] The presence of the aromatic ring was not essential.[167]

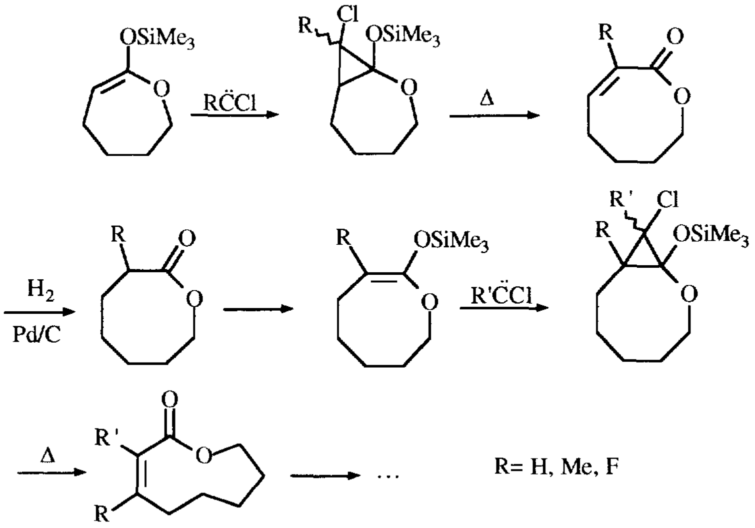


Another interesting approach, introduced by Ohshiro and coworkers, consists of the addition of dibromocarbene to the trimethylsilylenol ether derived from 6-heptanolide.[168]



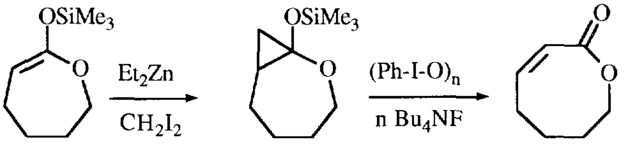
The 8-membered ring lactone, isolated in 46% yield, was subsequently treated with a mixture of diethylphosphonate-triethylamine to give the β,γ-unsaturated lactone.

This strategy was developed by Rousseau and coworkers who showed that this ring expansion is fairly general.[169] The formation of 8-, 9- and 10-membered ring lactones was reported in good yields.



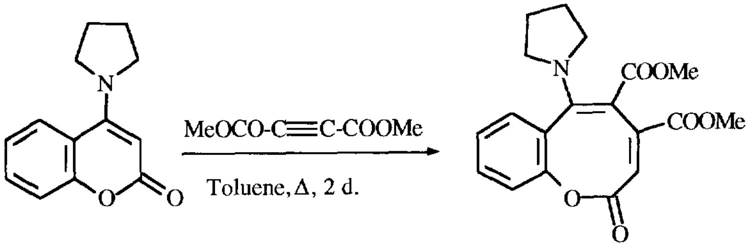
Chloro, chloromethyl and chlorofluorocarbenes were used for this transformation. 9- and 10-membered ring lactones were obtained as *E*/*Z* mixtures. The *E* isomers were isomerised in the presence of iodine into the Z isomers, or transformed under acidic conditions into diolides. This method was applied to the synthesis of phoracantholide I.[170]

In a similar reaction, Moriarty and coworkers reported that the reaction of iodosobenzene with 1-trimethylsilyloxy-2-oxabicyclo[6.1.0]nonane led to the corresponding α,β-unsaturated lactone (73% yield).[171] This method should be applicable to other medium ring sizes.

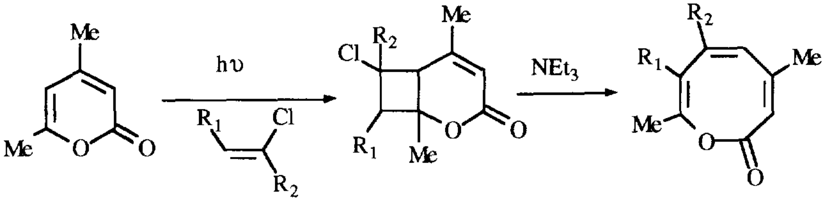


3.8.1.2 Two-carbon ring expansion

Addition of dimethyl acetylenedicarboxylate to 4-(pyrrolidin-1-yl)coumarin was reported to furnish the 8-membered ring lactone (43%).[172] The intermediate bicyclic adduct was not isolated.



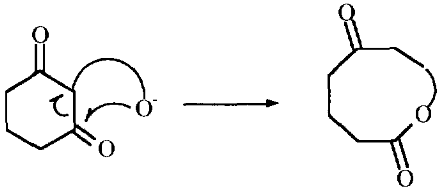
A second approach, limited to pyrones has also been published. When the photoadduct of dimethylpyrone and a chloro olefin was treated with triethylamine, the corresponding oxacyclooctatrienone is formed in good yield.[173]



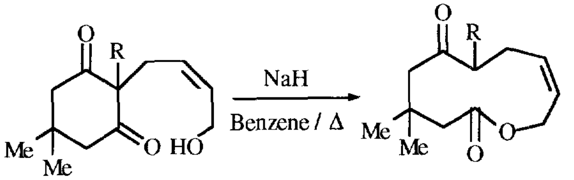
3.8.2 *Cyclanone-ring expansion*

3.8.2.1 Mahajan approach

In this approach first developed by Mahajan,[174] a cyclohexane-1,3-dione undergoes an intramolecular reverse Dieckmann reaction and leads to ketolactones.

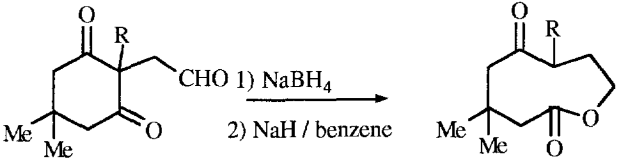


Mahajan obtained (60-72%) 11-membered ring lactones in good yields.[174]

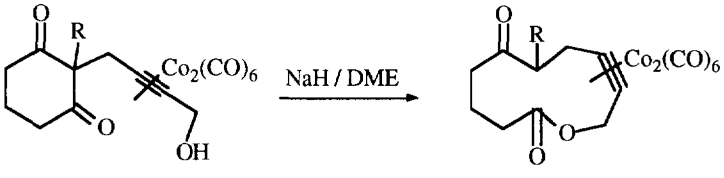


R= $PhCH_2$, allyl, Me

Further examples have also been reported for this ring size.[175] This method has also been extended to the preparation of nine-membered ring lactones.[176]

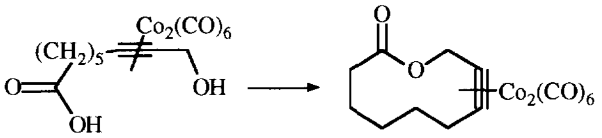


The Mahajan method has been used by Schore and coworkers for the synthesis of acetylenic 11-membered ring lactones, (50-71%) which were found to be stable if there was a complexation of the carbon-carbon triple bond by a cobalt complex.[177]



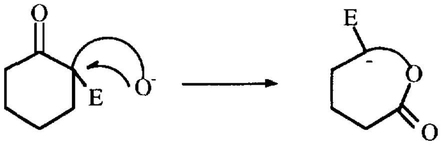
R = Me, allyl, Ac

This method was found to be inadequate for the preparation of smaller lactones. However, the Mukaiyama activation method has allowed the synthesis of a ten-membered ring lactone (20%).

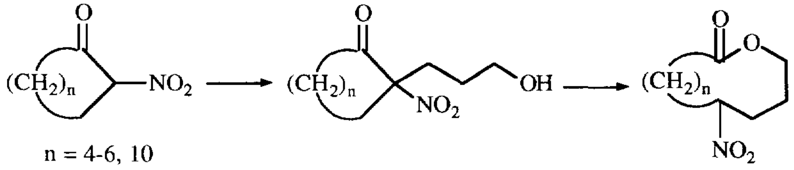


3.8.2.2 Hesse-Cookson approach

In this strategy, the chain bearing the alcohol is on the same carbon as the electron withdrawing group.



It was soon determined [178] that the best electron withdrawing group for this reaction was NO_2. Cookson [178b] and Hesse [179] reported their results simultaneously. Cookson showed that this method could be applied to the preparation of 10- and 11-membered ring lactones with excellent yields (76-78%), while Hesse applied this approach to the synthesis of phoracantholide I. (See also reference 180).

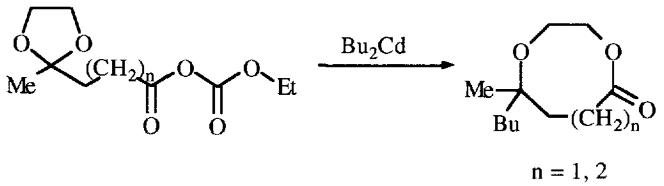


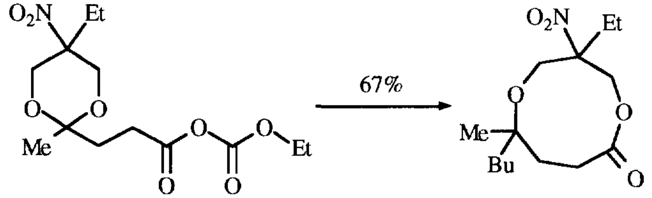
n = 4-6, 10

3.8.3 Heterocycle-ring expansion

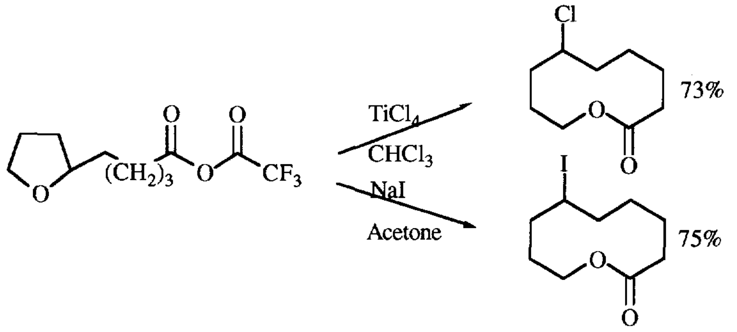
3.8.3.1 Oxa compound rearrangement

Le Mahieu found that the reaction of functionalised 1,3-dioxolane with dialkylcadmium leads in good yields (47-70%) to eight- and nine-membered ring lactones.[181] Participation of the cadmium and magnesium chloride seems necessary in the mechanism of this isomerisation.



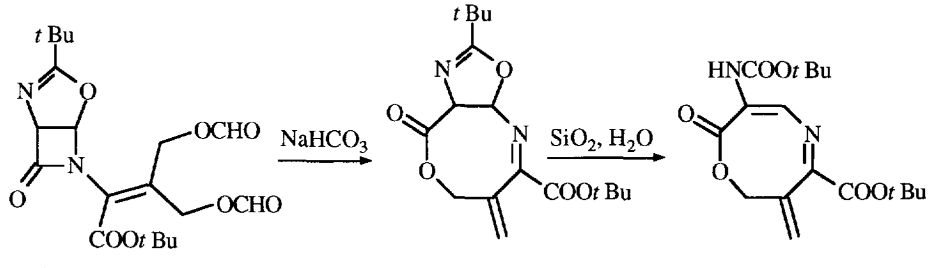


Recently, Grayson and Roycroft reported that reaction of 5-(tetrahydro-2-fury)pentanoic trifluoroacetic anhydride with a Lewis acid ($TiCl_4$) or NaI in acetone leads to the formation of halolactones.[182]

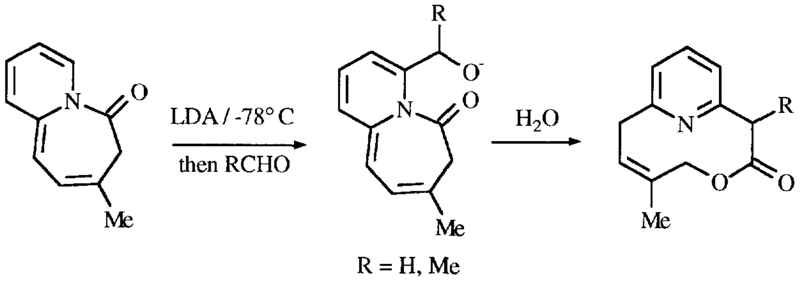


3.8.3.2 Lactam rearrangement

Transformation in low yield (18%) of a β-lactam into an aza-8-membered ring lactone has been reported. The structure of the hydrolysis product was determined by X ray crystallography.[183]

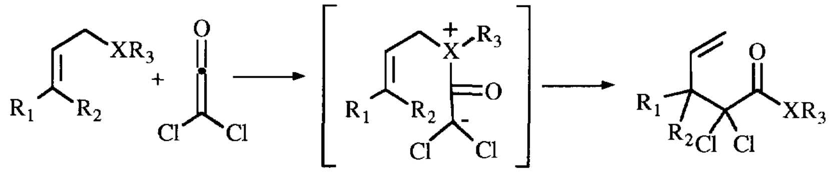


Eberbach and coworkers found that the carbanion formed from pyrido[1,2a] azepinone reacts with aldehydes and gives by ring expansion, 10-membered ring lactones.[184]

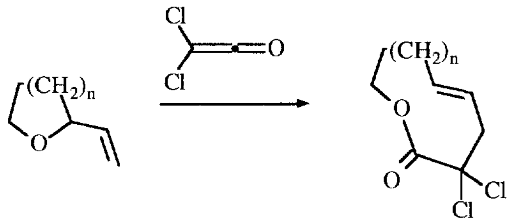


3.9 Cycloaddition of allylic ethers with dichloroketene

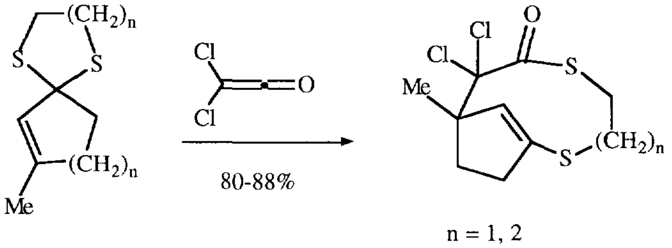
Malherbe and Bellus reported that the reaction of dichloroketene (and chloro(trichloroethyl)ketene) with allyl ethers, thioethers and selenoethers leads, *via* a polar rearrangement of the intermediate, to γ,δ-unsaturated esters (30-50% yields).[185]



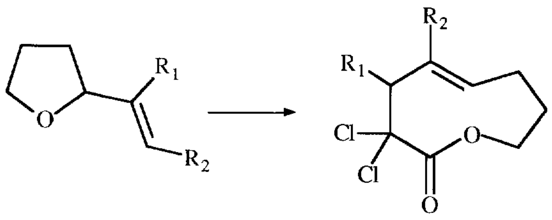
When the reaction was carried out with cyclic ethers, the lactones formed corresponded to a 4 carbon chain expansion. This reaction was applied to the synthesis of phoracantholide I. Addition of DME to the reaction mixture was found to give improved yields.[186]



Vedejs reported moderate yields in the case of allylthioethers.[97b] Rossini and coworkers found that the rearrangement also occurred with cyclic α,β-unsaturated thioacetals.[187]



Further examples of the preparation of 9-membered ring lactones were reported recently.[188]

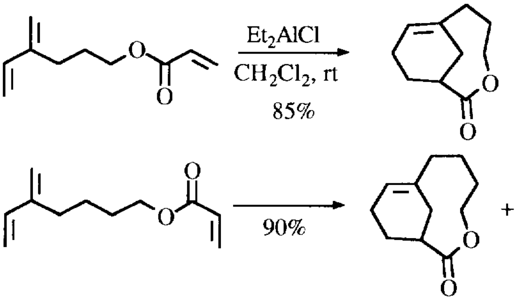


R_1 = H, CH_2OSiPh_2t Bu
R_2 = H, Me, $SiMe_3$

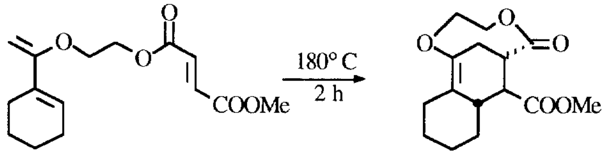
3.10 Thermal reactions

3.10.1 Diels-Alder reactions

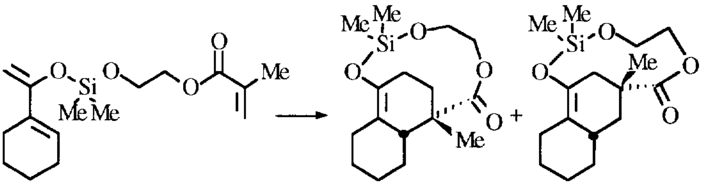
Shea, during his study of the intramolecular Diels-Alder reaction, showed that it could be applied to the synthesis of bicyclic medium ring lactones.[189]



Introduction of an oxygen atom in the 2 position of the diene allowed the regio- and stereochemistries to be controlled in some cases.[190,191]

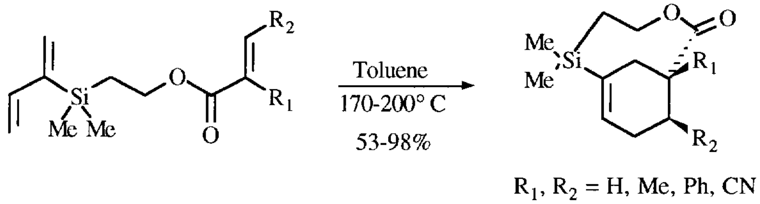


25-45%



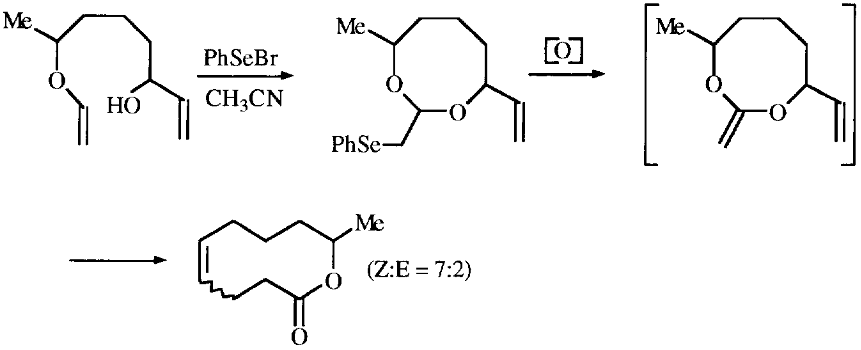
70 : 30

It was also reported that with 1,3-butadiene-2-silyl compounds could also give excellent regioselectivity.[191]

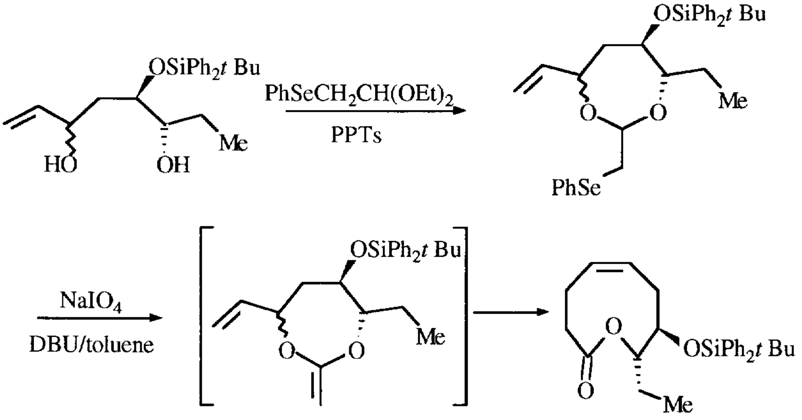


3.10.2 [3.3] Sigmatropic rearrangement

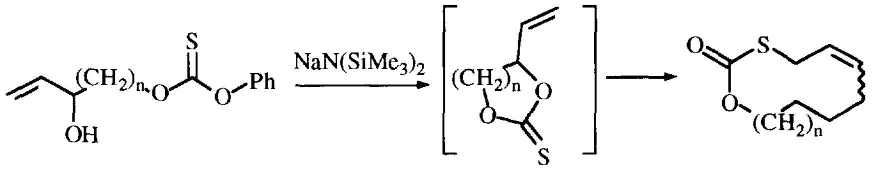
An interesting 10-membered ring lactone synthesis was reported by Petrzilka, based on a Claisen rearrangement.[192] The desired cyclic intermediate was formed by an unusual phenylselenoetherification.



This strategy was further developed by Holmes for the preparation of 7-,[193] 8-,[193] and 9-[54b,194] membered lactones, which are useful intermediates for the preparation of complex marine natural products.



The [3.3] sigmatropic rearrangement of allylic thiocarbonate to medium ring thiocarbonate has been studied extensively by Kurihara and coworkers. Highly stereoselective formation of medium ring compounds was observed, leading to an *E* or *Z* carbon-carbon double bond, depending on the ring size.[195]

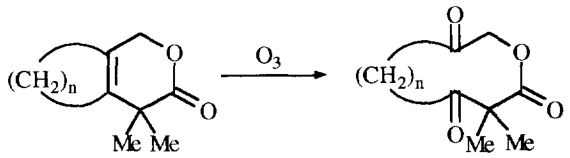


n = 2 : 65%; *Z* double bond
n = 3 : 25%; *E* double bond
n = 4 : 78%; *Z* double bond
n = 5 : 55%; *E* double bond

3.11 Cleavage of unsaturated bicyclic compounds

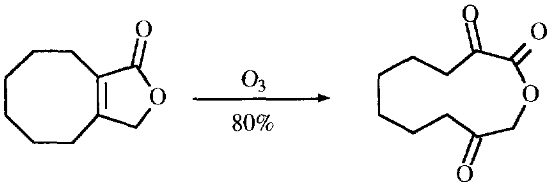
3.11.1 Unactivated carbon-carbon double bond

Thirty years ago, Falbe and Korte reported the synthesis of medium ring lactones using for the first time, to the best of our knowledge, cleavage of bicyclic compounds.[196] Different cleavage conditions were tested, but the reaction with ozone led to the best yields.

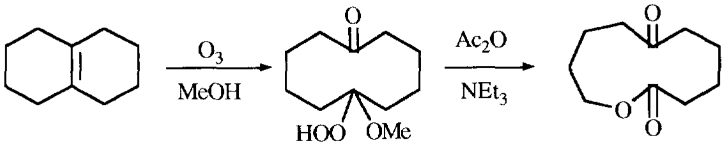


n = 3 ; 62%
n = 4 ; 51%
n = 5 ; 50%

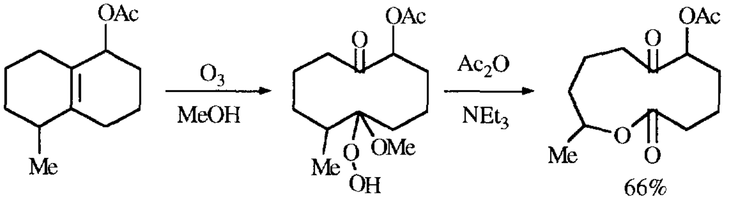
The same cleavage of an inactivated carbon-carbon double bond was used recently for the preparation of an eleven-membered ring lactone.[197]



In another approach Schreiber and Liew studied the ozonolysis of a bicyclic olefin. This reaction gave a perhemiacetal which after a Griegee rearrangement, gave the desired lactone.[198] Excellent regiochemical specificity was observed if an acetoxy group was present in the α position to the carbon-carbon double bond.[198]



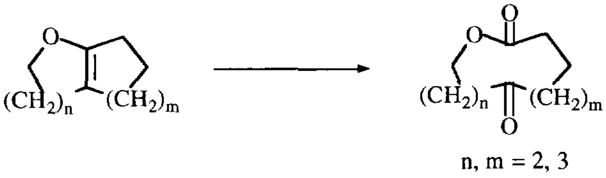
74%



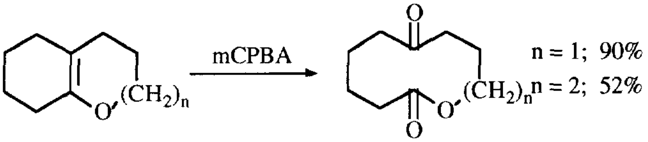
3.11.2 Activated carbon-carbon double bond

3.11.2.1 Oxidative cleavage

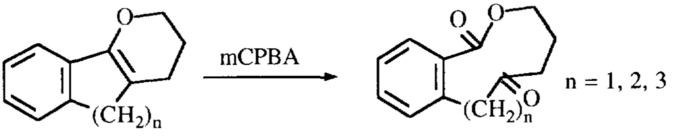
In this approach, a bicyclic enol ether was treated with an oxidant to give a ketolactone.



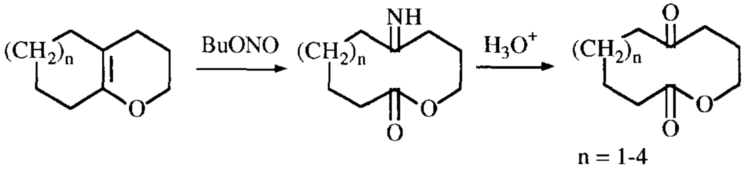
This reaction was first investigated by Borowitz, who showed that it is general for the formation of 10- and 11-membered ring lactones.[199]



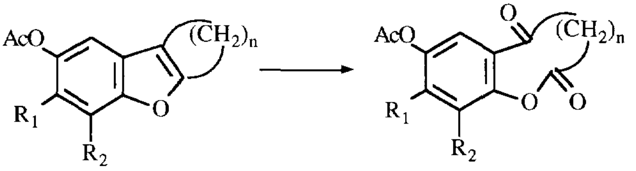
meta-Chloroperbenzoic acid was the reagent of choice for this cleavage, although ozone could be also used.[193d] Benzo-medium ring lactones have been prepared in good yields using this procedure.[200]



Mahajan showed some years later that n-butylnitrite was an excellent alternative reagent for this cleavage.[201]

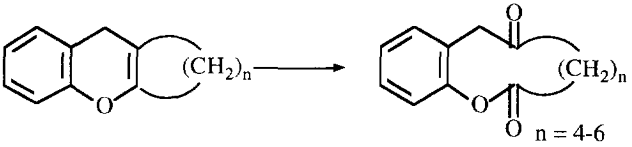


Much less reactive benzo and naphthofurans can be also cleaved; however, ozone or CrO_3 are necessary.[202]



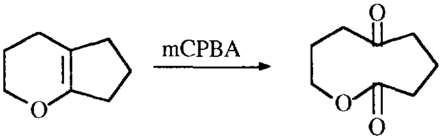
$R_1, R_2 = H, -CH=CH-CH=CH-$
n = 4-6

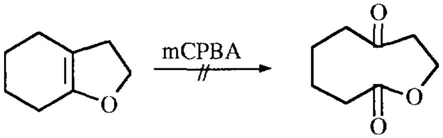
In the case of benzo- and naphthopyrans, mCPBA was found to be the best oxidant.[203]



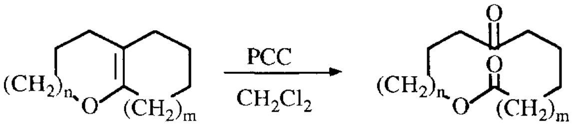
More recently, Jennings and coworkers showed that oxidation of 3,4,5-trisubstituted furans with *m*CPBA also gives medium ring-lactones.[204] The Borowitz procedure was used as key step in synthesis of biotin.[205]

Maitte and coworkers have showed that, with *m*CPBA, cleavage of 5-membered ring cyclic enol ethers did not occur and extensive degradation of products was seen instead.[206]





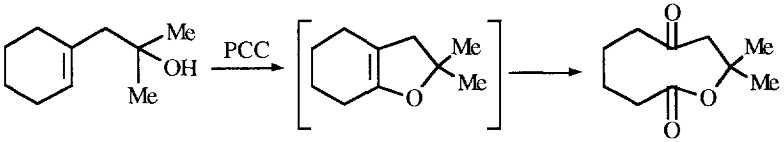
The mixture of ruthenium tetraoxide-sodium metaperiodate [207] and Corey's reagents, PCC, and PDC,[208] were also found to be effective for this oxidative cleavage; Corey's reagents seem, however, to give better yields.



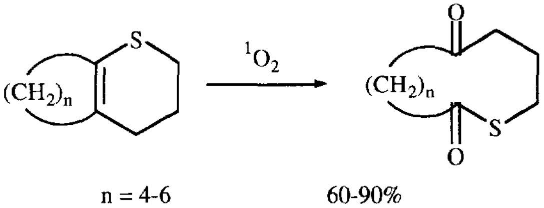
n, m = 0, 1, 2

63-85%

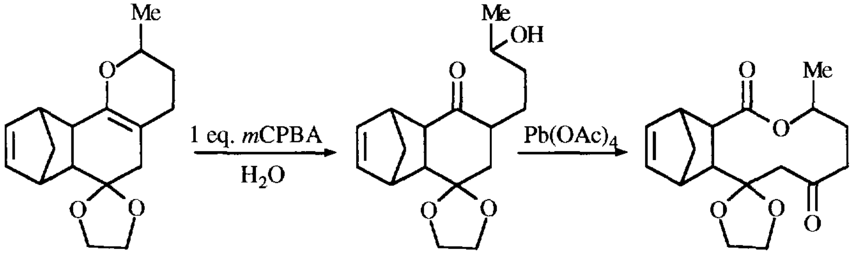
An interesting result was also reported by the Chandrasekaran group. Oxidation of a tertiary homoallylic alcohol led in 42% yield to the nine-membered ring ring lactone, *via* the *in situ* formation of the enol ether.[209]



This oxidative cleavage is not limited to ethers; Mahajan showed that an enol thioether could be cleaved using singlet oxygen.[210]

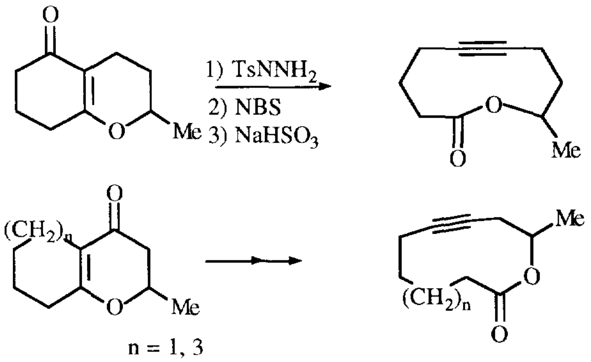


In their synthesis of pyrenolide B, a Japanese group found that it was not possible to cleave a bicyclic enol ether in satisfactory yield. Instead it was opened to give an α-hydroxyketone which, after reaction with lead tetraacetate, gave the desired 10-membered ring lactone in 65% yield.[211]



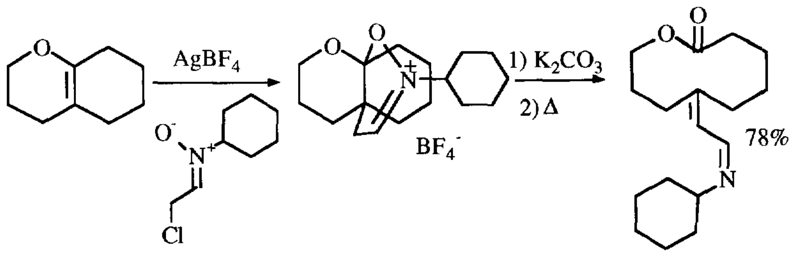
3.11.2.2 Fragmentation reactions

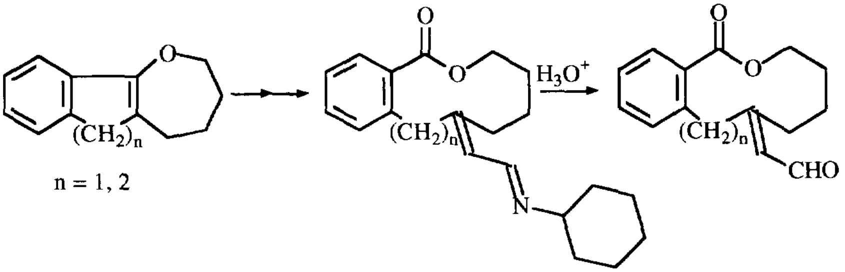
Mahajan reported recently that the fragmentation of keto enol ethers leads to 9- and 10-membered ring acetylenic lactones.[212]



3.11.2.3 1,2-Oxazine cleavage

Shatzmiller and coworkers reported that cyclic enol ethers react with α-chloronitrone to give an adduct which, after reaction with potassium carbonate and heating, give to medium ring lactones in excellent yields.[213]

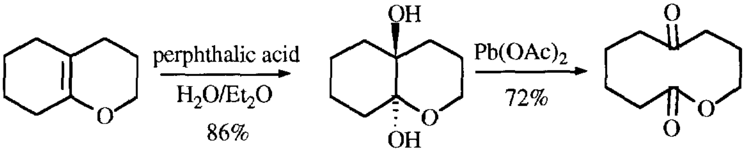




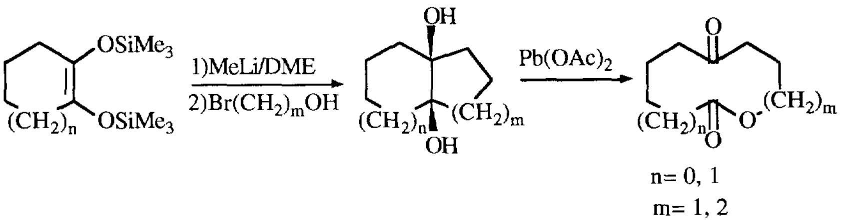
3.12 Cleavage of saturated bicyclic compounds

3.12.1 Ionic cleavage of bicyclic hemiketals

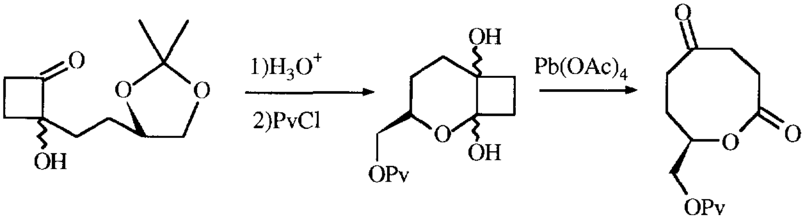
The first approach using this method was published by Borowitz, who reported the cleavage of a bicyclic *trans* 1,2-diol with lead tetraacetate[214]



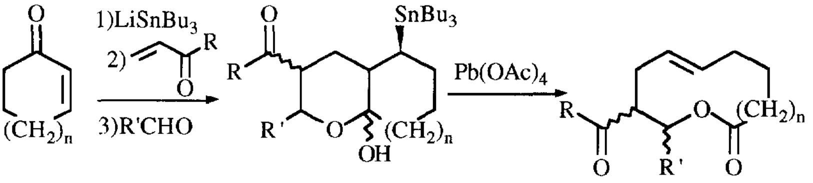
Wakamatsu and coworkers showed that bicyclic *cis* 1,2-diols, formed by alkylation of 1,2-enediolates with m-bromo-1-alkanols, can also undergo to the same fragmentation.[215] The application of this to the synthesis of diplodialides A and C was reported.[216]



This method was subsequently used by Murai in a efficient preparation of a key intermediate lactone for his synthesis of (+) laurencin.[217]

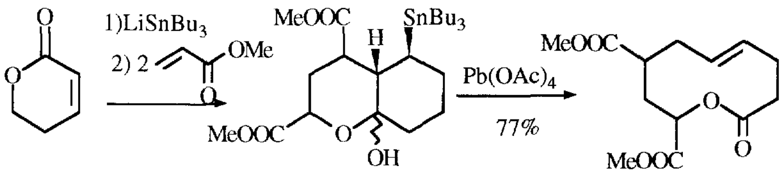


Posner used the same strategy to cleave bicyclic hemiketals, which were formed by sequential Michael reaction of enals or enones. Application of the reaction to the preparation of phoracantholide was reported.[218]

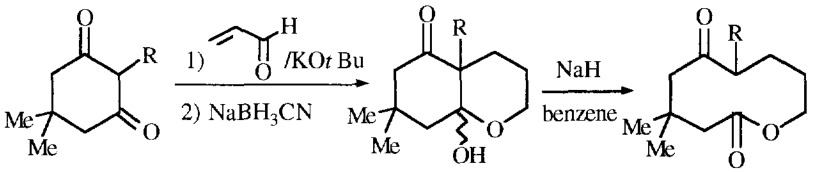


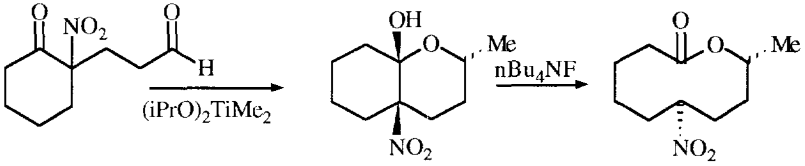
n = 0, 1, 2 R, R' = alkyl, aryl 30-47%

The same sequential Michael addition and cleavage were also performed using methyl acrylate.[219]



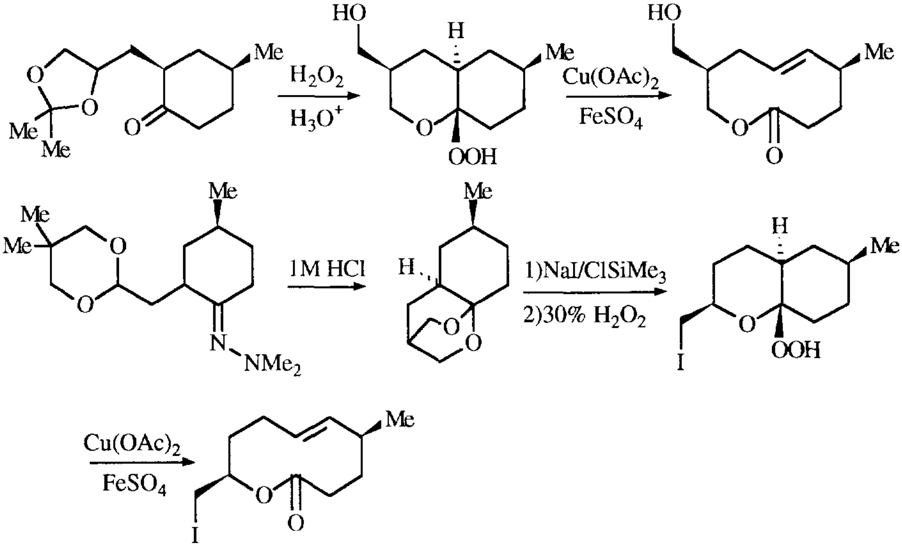
The anionic cleavage of hemiketals was also successfully investigated; however, the presence of an anion-stabilising group appears to be necessary. Mahajan used a keto group,[220] and Hess a nitro group.[221]



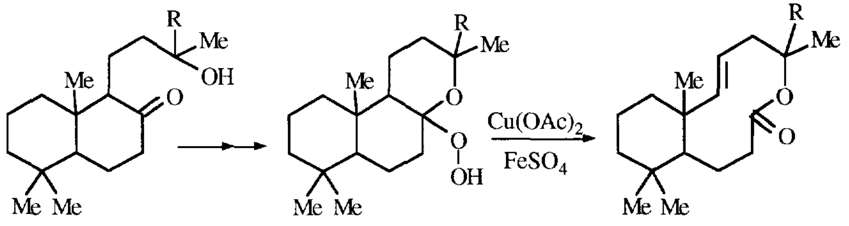


3.12.2 Radical cleavage of bicyclic hemiketals

Schreiber and coworkers have reported the preparation of perhemiacetals which, when treated with a mixture of $FeSO_4$ and $Cu(OAc)_2$, give the corresponding lactones.[222]

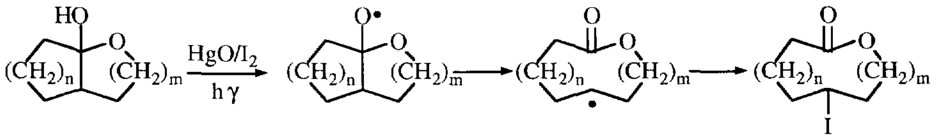


When this cleavage was applied to manool derivatives, bicyclic 10-membered ring lactones resulted.[223]



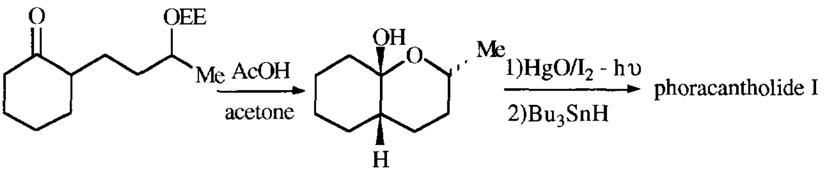
R = H, Me

Treating a hemiketal with a mixture of HgO and I_2 generates hypoiodites, which undergo a photolysis-inducted regioselective homolytic cleavage of the transannular carbon-carbon bonds to give ring-enlarged lactones.

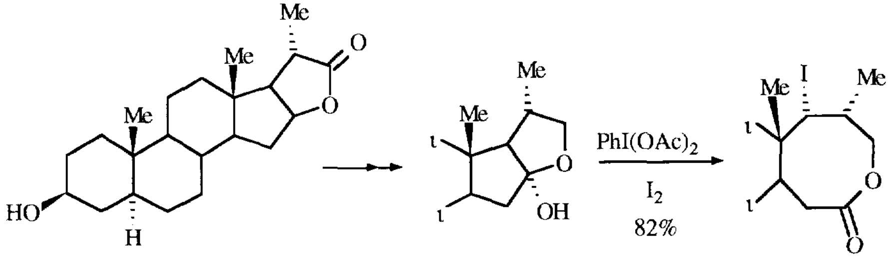


50-80%

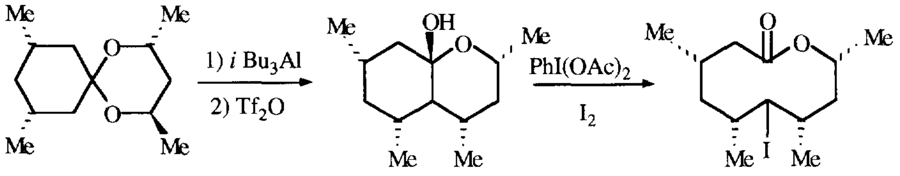
This method was applied to give a high yield preparation of 9- to 11-membered ring ring lactones.[224]



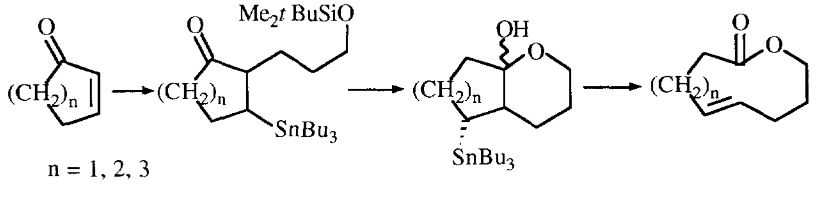
Suarez and coworkers found that a mixture of diacetoxyiodobenzene and I_2 could also be used for the fragmentation of these bicyclic hemiketals.[225]



Using this procedure, Yamamoto has reported the preparation of a ten-membered ring lactone which is a key intermediate for the synthesis of (-)-lardoline.[226]



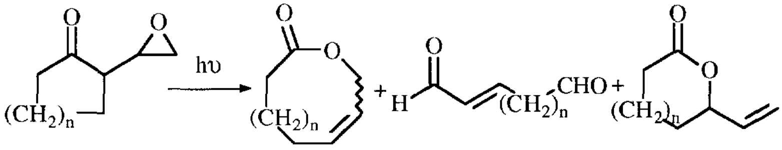
Nagao found that this reagent was also very useful for the cleavage of tributylstannyl lactols, and unsaturated lactones could be obtained in good yields.[227]



3.13 Other approaches

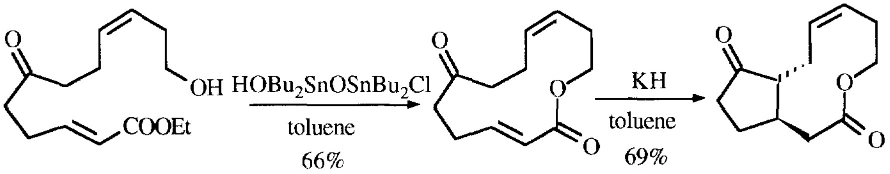
3.13.1 Photolysis of β,γ-epoxycyclanones

The photolysis of β,γ-epoxy-cycloheptanone and -cyclooctanone in hexane has been reported to give 10- and 11-membered ring unsaturated lactones (*E*/*Z* mixture) in moderate yields (~ 40%). However, cyclohexanone and cyclopentanone derivatives gave low yields, because of the increased proportion of side products.[228]



3.13.2 *Transannular Michael reaction*

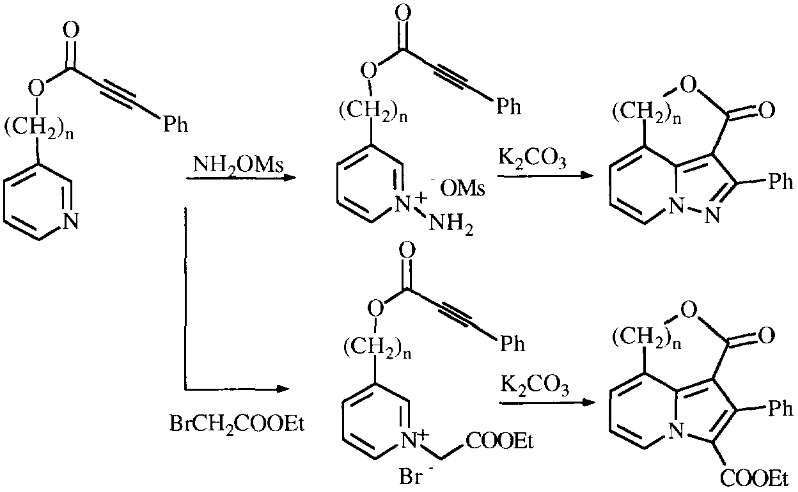
In their studies directed towards the synthesis of (±)-jasmine lactone, Shimizu and Nakayawa showed that a 13-membered ring lactone could be made first, and then the 10-membered ring lactone could be obtained by an intramolecular Michael reaction.[229]



Since, it is in general easier to prepare macrolactones than medium ring lactones by lactonisation, transannular reactions could prove to be an useful method for the preparation of bicyclic medium ring lactones.

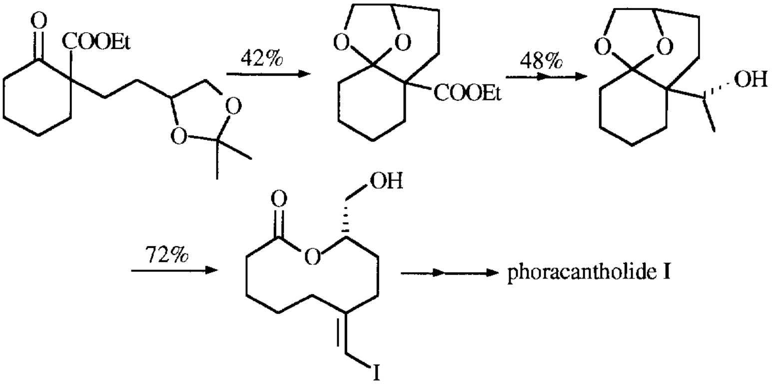
3.13.3 *Intramolecular 1,3-dipolar reactions*

Miki and coworkers found that esters formed from phenylpropiolates and 4-(3-pyridyl)alkanols led, after N-quaternisation and basic treatment of the resulting salts, to 7-9-membered ring lactones, (25-35%) via 1,3-dipolar cycloadditions.[230] No of δ-lactones were formed.

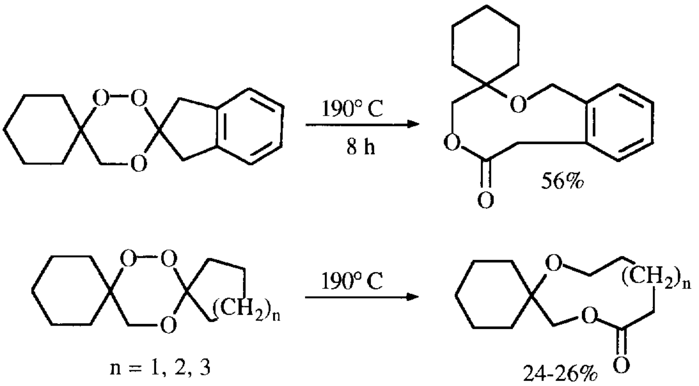


3.13.4 Fragmentation reactions

Sakai and coworkers have explored the possibility of preparing medium ring lactones by a Grob fragmentation of tricyclic acetals.[231] This strategy was applied to a fairly lengthy synthesis of phoracantholide.

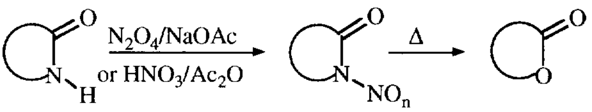


Thermal cleavage of an indan spiro-1', 2', 4'-trioxane derivative has been reported to lead, by a radical ring expansion to a 9-membered ring lactone.[232] Recently, it was reported that this rearrangement could be applied more generally to different dispirocompounds.[233]



3.13.5 Lactam → lactone transformation

Vilarrasa has studied the transformation of lactams into lactones. The reaction occurs in high yields for all ring sizes, including medium ring. Nitration takes place with nitric acid, or alternatively nitrosation with N_2O_4 is used (60-70%).[234]

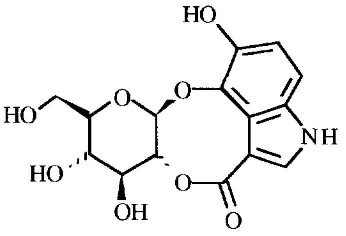


4. Synthesis of medium ring lactones

Following on form the chemistry reported by Vilarrasa and Bartra in their review [70d], and since all the synthetic methods for the preparation of medium ring lactones have been reported in the previous chapter, the following is a summary of the preparation of natural products containing such lactones. The different columns show :

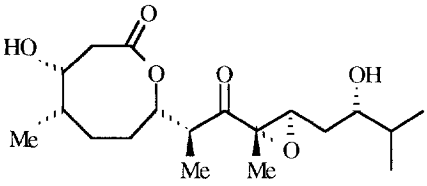
- the structural formula and the name of the natural product prepared
- the senior author involved in the synthesis
- the chapter of this review where the synthesis of the lactone framework is described
- the yield reported for this step
- the reference of the synthesis

8-membered ring lactone:



ovatolide

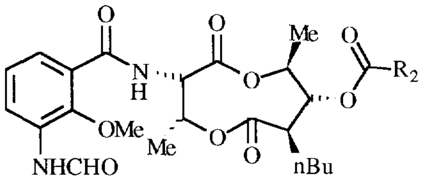
Delgado	3.1.2	72%	23



octalactin A (and B)

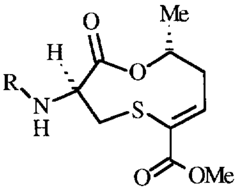
Buszek	3.1.2	73%	28a
Clardy	3.7.1	83%	28b

9-membered ring lactones:



antimycin A_3

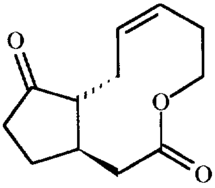
Kinoshita	3.1.2	13%	235
Nakata	3.1.2	-	236
Inghardt	3.1.2	-	237
Wasserman	3.1.2	20%	238



griseoviridin

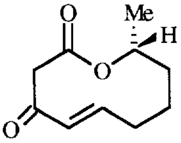
Meyers	3.1.2	47%	239
Helquist	3.1.2	20%	240
Miller	3.1.2	39%	241

10-membered ring lactones:



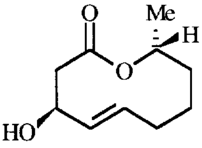
jasmine lactone

Gerlach	3.1.2	71%	242
Mori	3.1.2	77%	243
Shimizu	3.13.2	69%	229



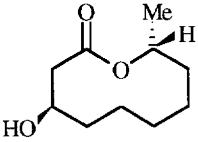
diplodialide A

Wada	3.1.2	38%	244
Gerlach	3.1.2	67%	245
Tsuji	3.5.1	45%	121
Ireland	3.5.4	25%	132
Boeckman	3.3	68%	111
Wakamatsu	3.12.1	100%	216



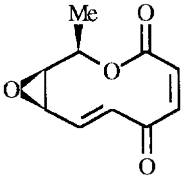
diplodialide B

Gerlach	3.1.2	67%	245
Tsuji	3.5.1	45%	121



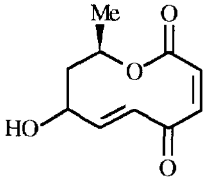
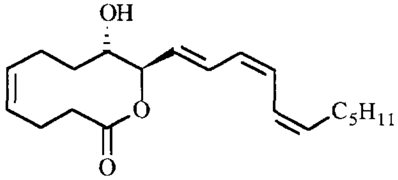
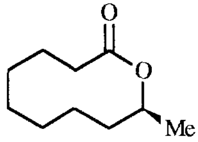
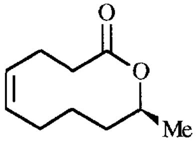
diplodialide C

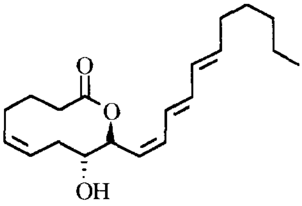
Wakamatsu	3.12.1	100%	216
Tsuji	3.5.1	71%	125



pyrenolide B

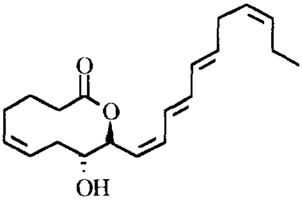
Asaoka	3.11.2	65%	211
Tanaka	3.7.1	63%	246

 pyrenolide C	Wasserman	3.1.2	47%	247
 ascidiatrienolide A	Holmes	3.1.2	96%	54b
 phoracantholide I	Gerlach	3.1.2	71%	248
	Petrzilka	3.10.2	81%	192
	Bellus	3.9	55%	185
	Wakamatsu	3.12.1	100%	216
	Tsuji	3.5.2	71%	125
	Nicolaou	3.4	NR	249
	Trost	3.5.3.1	80%	127
	Vedejs	3.1.3	91%	97a
	Barbier	3.2	45%	107
	Mori	3.1.2	67%	250
	Akiba	3.5.1	42%	122
	Wasserman	3.1.2	25%	251
	Cossy	3.1.1	60%	73
	Cossy	3.1.2	55%	252
	Hesse	3.12.1	97%	221
	Rousseau	3.8.1.1	65%	170
	Ono	3.12.1	81%	253
	Suginome	3.12.2	76%	224
	Posner	3.12.1	28%	218
	Mahajan	3.11.2	65%	201b
	Naoshima	3.1.2	44%	254
	Ban	3.7.1	79%	255
	Sakai	3.13.4	72%	231
	Batra-Vilarrasa	3.1.2	0-55%	91
	Mahajan	3.11.2.1	65%	212
 phoracantholide J	Gerlach	3.1.2	71%	248
	Trost	3.1.2	30%	127
	Mori	3.1.2	67%	250
	Bellus	3.9	55%	185



neodidemnilactone

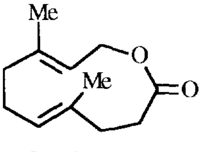
Niwa, Yamada	3.1.2	53%	53b



didemnilactone A

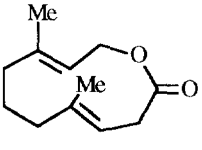
Niwa, Yamada	3.1.2	42%	53b

11-membered ring lactones:



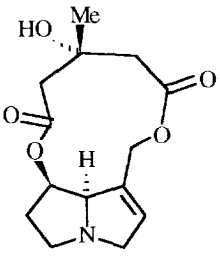
ferrulactone I

Oehlschalger	3.5.2	52%	256
	3.1.2	37%	256
Mori	3.1.2	33%	257
Inanaga	3.5.5.1	47%	148
Cheski	3.1.2	42%	258



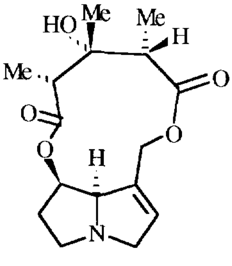
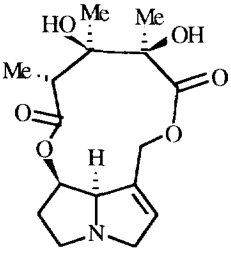
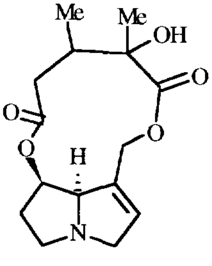
suspensolide

Mori	3.1.2	9%	259
Battiste	3.1.2	19%	260a
Oehlschalger	3.1.2	30%	260b



dicrotaline

Robins	3.1.2	32%	65a, b
Niwa	3.1.2	10%	65c
Vedejs	3.1.2	60%	66

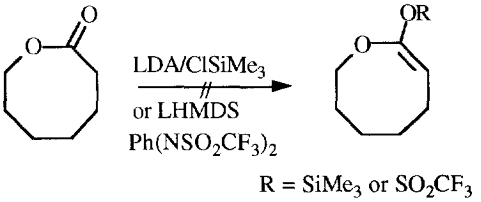
 fulvine	Vedejs (similar results with crispatine)	3.1.2	80%	66
 monocrotaline	Vedejs	3.1.2	71%	67a
	Niwa	3.1.2	37%	67b
	Yamada	3.1.2	64%	67c
 crobarbatine	Meinwald	3.1.2	62%	68

5 Reactivity and application of medium ring lactones

5.1 Reactivity of medium ring lactones

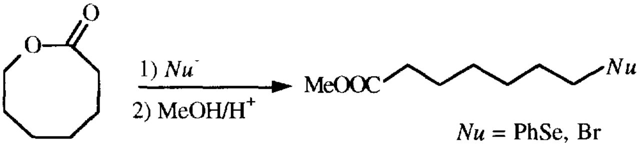
5.1.1 Chemical reactions

It is well known that the trimethylsilylenol ethers of γ-butyrolactones and δ-valerolactones can be obtained in good yields from the corresponding lactones using lithiated bases.[261] When this reaction was performed on medium ring lactones, it was observed that the ketene acetal was not obtained with heptanolide. It this case, the major product was the α-silylated lactone.[169] Attempts to circumvent this C-silylation were unsuccessful. A comparable result was observed by Murai during his attempts to obtain the corresponding enol triflate.[262]



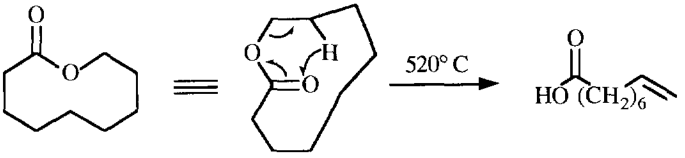
It was shown that this problem could be prevented if a substituent was present α- to the carbonyl group,[169] or if the keteneacetal was generated with *t*-butyldimethylsilyltrifluoromethane sulfonate.[262b] (See also reference 263).

As in 5- and 6-membered ring ring lactones, the heptanolide underwent cleavage of its alkyl-oxygen bond when treated with nucleophilic reagents such as sodium phenylselenate [264] and triphenylphosphine-bromine complex.[265] These reactions seem to be applicable to other medium ring sizes.



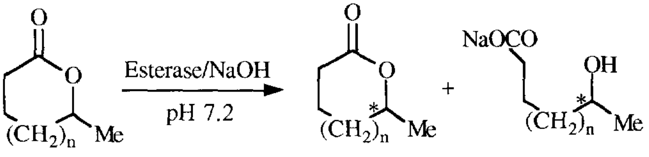
5.1.2 Thermal reaction

Bailey and Bird have studied the pyrolysis of lactones at 520°C. At this temperature ε-caprolactone was recovered almost unchanged, while the 10-membered ring lactone gave the ω-unsaturated acid (92% yield).[266] For this ring size (and higher-membered ring lactones) the steric strain in the transition state is lower and thus a 1,5-hydrogen transfer is allowed.



5.1.3 Enzymatic resolution

Enzymatic hydrolysis of 6- to 11-membered ring ring ketones using pig liver esterase (PLE) and horse liver esterase (HLE) at pH 7.2 was reported to afford optically active lactones with good to excellent enantiomeric excesses (ee s: 70-100%).[170]



n= 1-4

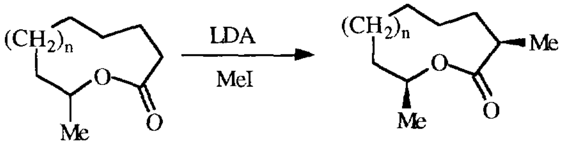
In these hydrolyses, an improvement in ee was observed when the ring size was increased. This method appears to be useful for the preparation of optically active medium ring lactones.[267]

5.2 Applications of medium ring lactones

5.2.1 Applications of lactone conformations

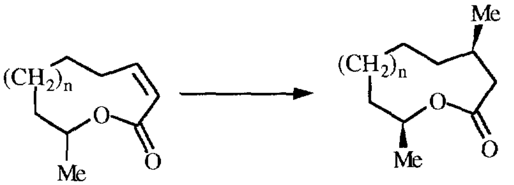
In a fundamental paper, Still and Galynker reported that, contrary to some of the ideas that have been put forward, the structures of medium (and large) ring molecules such as lactones exist in only a few stable conformations.[161] These conformations can be used to control the alkylation of enolates, or the catalytic hydrogenation of a carbon-carbon double bond.

Still showed, for example that α-alkylation of ω-substituted medium ring lactones leads exclusively to the introduction of the substituent in the *cis* arrangement.



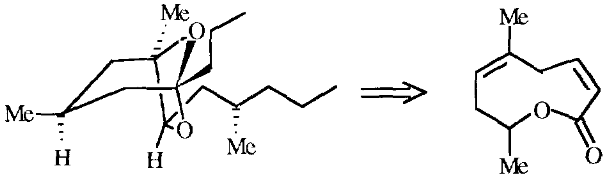
n = 1, 2, 3 *cis/trans*>98/2

In the same way, 1,4-addition of dimethylcuprate to the double bond of α,β-unsaturated lactones leads mainly to *cis* -dimethyl products.

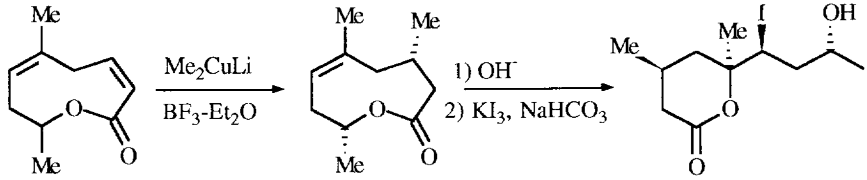


n = 1, 2, 3 *cis/trans*>80/20

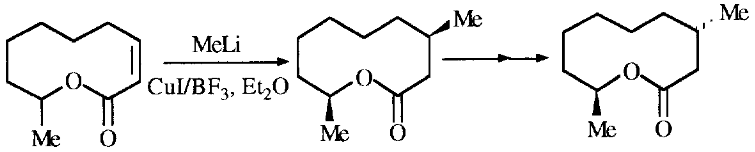
Still and Galynker used this strategy for a stereospecific synthesis of the C30-C43 segment of palytoxin, a marine toxin, starting with an unsaturated 9-membered ring lactone.[268]



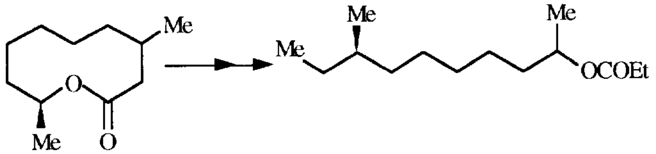
1,4-Addition of dimethylcuprate to the conjugated double bond of this lactone led exclusively to the introduction of the methyl in the *cis* position which after saponification and iodolactonisation, gave only one diastereoisomer. The iodolactone was then transformed into the desired bicyclic acetal.



This strategy was also used by Ferreira for a diastereoselective preparation of 8-methyl-2-decanol, which is a sex pheromone secreted by a female western corn rootworm.[269] The starting ten-membered ring lactone was prepared following the Wakamatsu method (see chapter 3.12.1), and after the 1,4-addition of methyl cuprate, gave exclusively the *cis* -dimethyl product.

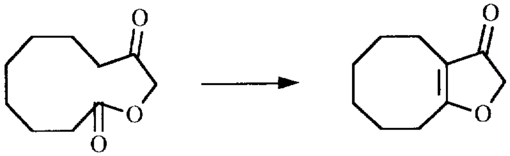


The transformation of the *cis* lactone into the *trans* lactone was then accomplished by catalytic hydrogenation of the intermediate unsaturated lactone (*cis/trans*: 23/77). Hydrolysis of these two lactones and reduction of the acidic functions gave the two diastereoisomers of the pheromone.

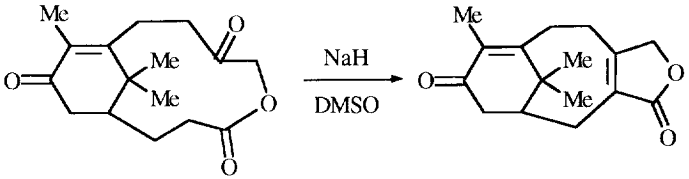


5.2.2 Transannular reactions

Sampson found that treating 11-membered ring ketolactones (see chapter 3.2) with sodium hydride in DMSO forms to bicyclic compounds by means of a transannular condensation.[103a]

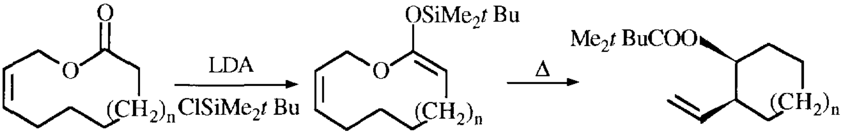


A similar condensation was used for the synthesis of the A and B rings of taxane derivatives.[103b]

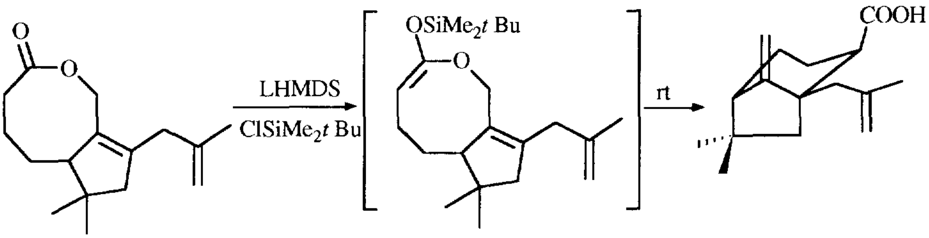


5.2.3 Carbo- and heterocycle ring formation

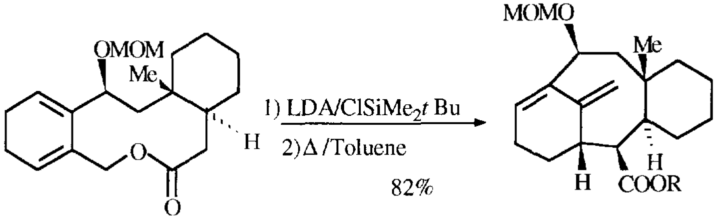
Funk and coworkers studied an Ireland-Claisen rearrangement in which all the atoms participating in the sigmatropic rearrangement are incorporated into a lactone ring.[270]



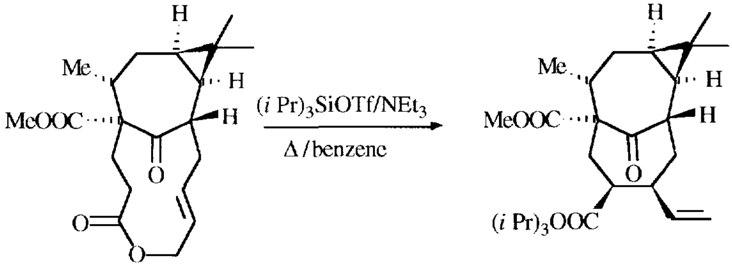
This rearrangement was shown to occur in excellent yields for 8-11 membered ring lactones (70-91%). If the carbon-carbon double bond in the starting lactone was *cis*, a stereospecific rearrangement was observed, leading to *cis* products.[270,271] Funk used this approach in the preparation of a key intermediate for a quadrone synthesis.[263]



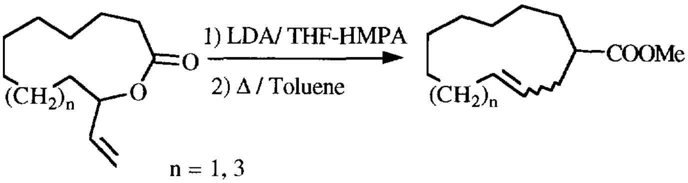
Similar efficiency was observed in the synthesis of the taxane ring system.[272]



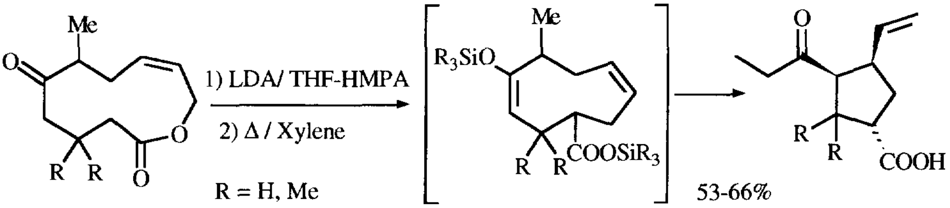
Funk also applied this Claisen rearrangement to the synthesis of the BCD ring system of engerol.[273]



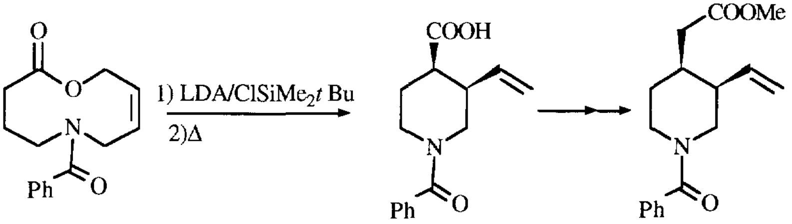
Knight and coworkers simultaneously studied the same rearrangement in large ring lactones (13 and 15-membered ring) and in medium rings possessing a vinyl group. In this latter case, medium ring carbocycles were obtained (63-80%).[274]



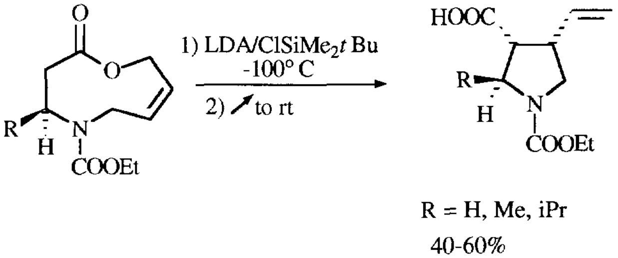
With 11-membered ring lactones, the Z ester exclusively was isolated. With enol ethers formed from 5-keto lactones, instead of the Claisen rearrangement, a 1,3 rearrangement was first observed followed by a 3,3 rearrangement.[275]



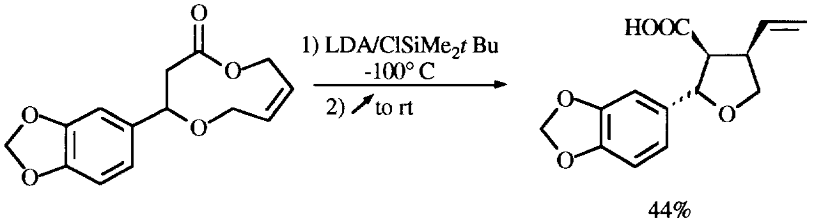
Applications of the Claisen rearrangement to the formation of heterocycles have also been reported. Funk used it for the synthesis of N-benzylmeroquinene methyl ester, a key intermediate in the synthesis of alkaloids such as quinine.[276]



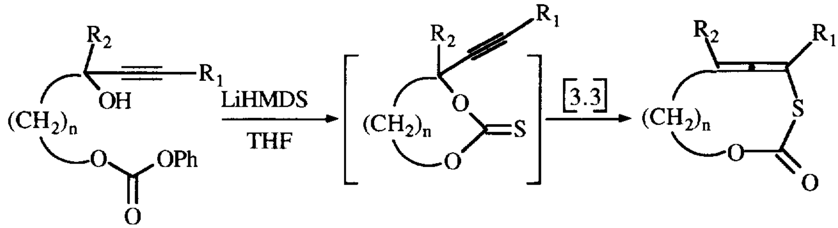
Knight obtained di- and trisubstituted pyrrolidines starting from 9-membered ring lactones.[277]



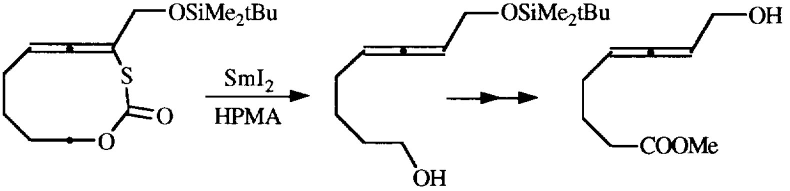
Similarly, he showed that trisubstituted tetrahydrofurans could be obtained with high diastereoselectivity.[278]



Kurihara and coworkers used the 3,3 sigmatropic rearrangement of thionocarbonates in the preparation of medium ring allenothiocarbonates.[279]



A ten-membered ring carbonate ($R_1 = CH_2OSiR_3$, $R_2 = H$) was then transformed to racemic methyl 8-hydroxy-5,6-octadienoate, an antifungal constituent of *Sapium japonicum* (Euphorbiacae).



6. Conclusion

Medium ring compounds, and particularly lactones, have become an important class of compounds in organic chemistry, and now their chemistry cannot be considered as marginal. As has been shown, an ever-increasing number of natural products possessing this framework has been isolated. Efficient methods for the synthesis of these compounds have appeared in the last few years, although lactonisation methods remain a weak point. The efficiency of some of these methods, allows medium ring lactones to be planned as intermediates for more complex syntheses. Further advances can be anticipated in the near future.

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