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The Syntheses of Large-Ring Compounds

Craig J. Roxburgh

University College London, Department of Chemistry, Christopher Ingold Laboratories, 20 Gordon Street, WC1H OAJ, U.K.

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1. Introduction

A large-ring is defined as a ring containing twelve- or more atoms. There appears to be no upper limit on this number, however, the number of publications relating to ring sizes approaching twenty and beyond seems to fall off almost exponentially.

Large-rings are widely found in nature and constitute an extensive range of natural products possessing diverse biological and medicinal properties. For example, large-ring lactones, or macrolides[1] such as the erythromycins and cytochalasans possess antibiotic activity. Diarylether-containing rings such as bouvardin and deoxybouvardin possess potent antitumour antibiotic activity. Although known for some time large-rings containing the enediyne moiety such as neocarzinostatin and esperamicin have attracted considerable interest recently due to the antitumour activity known to be associated with this functionality.

The syntheses of large-rings are reported throughout the literature, however, very little has been done to concentrate the now wide range of syntheses in a single report. This report covers, albeit in a necessarily selective fashion, the syntheses of large-rings published over the last ten years and is broadly divided into sections relating to the functional groups contained within the ring structures. Some overlap is inevitable, however, as some large-rings contain more than one type of functionality. Both direct cyclization and ring-expansion methods are covered for completeness since, unlike medium-sized rings which are considerably strained, large-rings are relatively strain free and have been formed in moderate to good yields by a variety of direct cyclization procedures. This report does not include the syntheses of crown type compounds which have been reviewed elsewhere.[2]

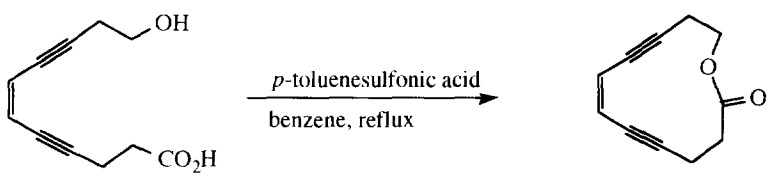
A theoretical treatment of the syntheses of carbocycles by ring-enlargement, with examples, was published some nine years ago by Hesse.[3] The synthesis of macrocycles possessing subheterocyclic rings including pyridine, furan and thiophene has been reviewed.[4]

2. The syntheses of lactones

By far the greatest number of publications on the syntheses of large-rings concerns those containing a lactone grouping. Their properties encompass antibiotic, pheromone and perfumery, as well as the complexation of a variety of metal cations.

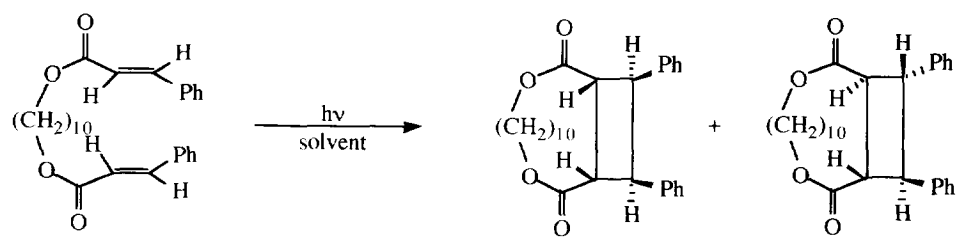
2.1 Direct cyclizations

Due to an unfavourable entropy term the direct intramolecular cyclization of large-rings is not easy, however, a number of useful methods are reported to form lactones by the intramolecular cyclization of the appropriate structures. This has been achieved in good yield when the reacting ends have, on average, been held closer together as opposed to the situation present in a straight chain. When two chains, of approximately equal length, are attached *cis*- to an alkene a ring can be formed in good yield. This has been done for the (*Z*)-enediyne system **1** to give the twelve-membered lactone **2** in 74% yield. This process should also be possible with 1,2-disubstituted aryl or heterocyclic systems.[5]



1 **2**

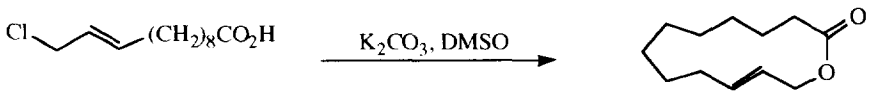
The use of hydrophobic-lipophilic forces has been exploited in the formation of the lactones **4** and **5**. The sixteen-



3 **4** **5**

membered ring dilactones were formed by photolysis of the ester **3** in a process described as hairpin-looping. The *cis*- and *trans*-fused stereoisomers **4** (β-truxinate) and **5** (δ-truxinate) were formed in combined yields of as high as 90%, when DMSO was used as the solvent.[6]

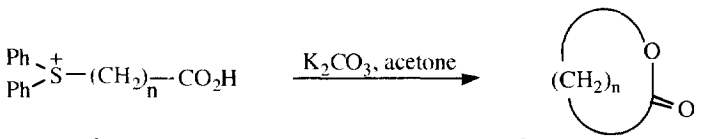
The intramolecular cyclization of the ω-chlorocarboxylic acid **6** has been reported by Knight.[7,8] Ring cyclization occurred in hot dimethyl sulfoxide in the presence of potassium carbonate. The macrolide **7** was isolated by



6 **7**

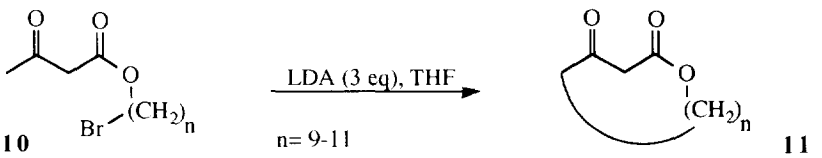
extraction with petroleum ether to avoid the losses associated with the removal of large quantities of dimethyl sulfoxide used under the high dilution conditions. The yield was 70%.

Other reagents have been used to cyclize ω-hydroxycarboxylic acids. These include the use of dicyclohexylcarbodiimide with 4-dimethylaminopyridine (DMAP) to give a hexadecanolide[9] in 95% yield, the modified Yamaguchi method (2,4,6-trichlorobenzoylchloride in xylene followed by DMAP) to yield monocillin IV dimethyl ether[10] and erythronolide A in 98% yield[11], and the use of 2-chloro-*N*-methylpyridinium iodide[12] in the synthesis of analogues of non-aromatic β-milbemycins. Similarly the direct cyclization of the (ω-carboxyalkyl)diphenylsulfonium salt **8** below, in the presence of potassium carbonate has been used to prepare twelve- to sixteen-membered lactones **9** in yields of 85-92%.[13]



8 n=10-14 **9**

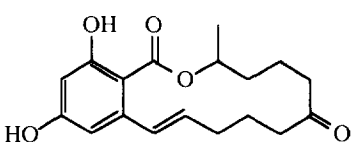
Lactones **11** have been synthesized *via* the intramolecular alkylation of dianions.[14] The synthesis involves



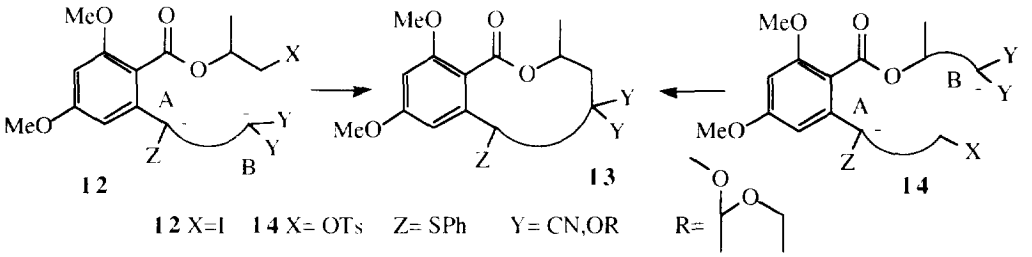
10 **11**

formation of the dianion of **10** with an excess (three equivalents) of lithium diisopropylamide (LDA) followed by intramolecular cyclization to yield the fourteen- to sixteen-membered β-ketolactones **11** in yields of 43, 45 and 49% respectively.

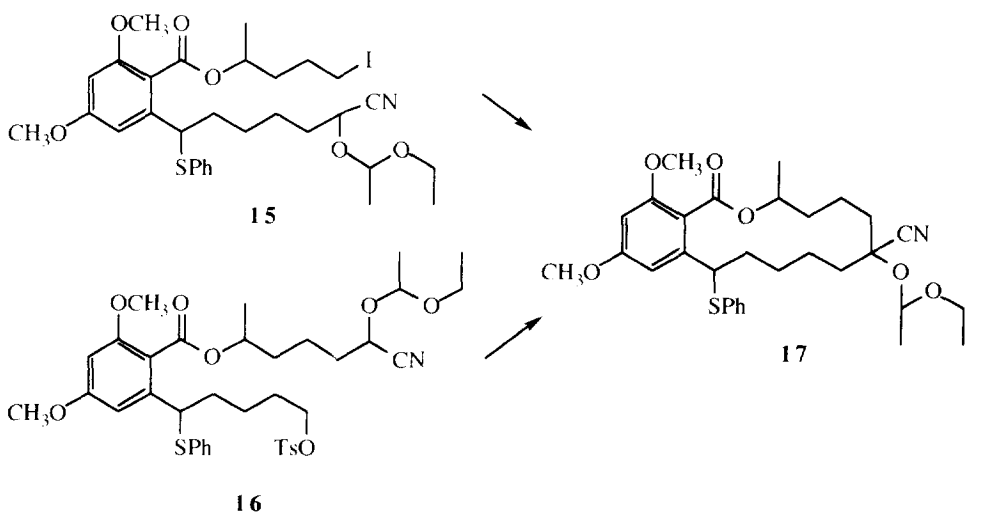
A similar intramolecular alkylation procedure involving the use of dianions has been used in the synthesis of zearalenone.[15] Here the use of dianions for cyclization is claimed to serve several purposes :1) the anion B in **12**



zearalenone



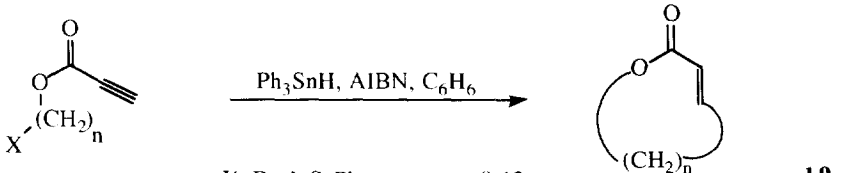
or **14** is more reactive towards alkyl halides or tosylates than anion A and is thus the anion which takes part in the intramolecular cyclization; 2) the anions A and B being contained in a single chain restricts the rotational conformations of the chain increasing the chance of the reacting centres coming together; 3) the anion A helps protect the ester group from nucleophilic attack by conjugation and also by steric effects; 4) the presence of two anions in the same molecule gives rise to larger intermolecular ionic repulsions decreasing the chances of intermolecular side reactions. Due to these factors it is not necessary to undertake the reaction using high dilution conditions. The cyclization of **15** was achieved in the presence of base to yield **17** in 95% yield after chromatography. Even with a five times excess of base the cyclized product **17** was obtained in 78% yield. The ring closure of compound **16** was also achieved in 82% yield with no indication of the potential five-membered ring being observed. The synthesis of the phenyldimethyl ether unit of zearalenone was completed from **17** in three steps in an 80% overall yield. The relatively easy and high yielding removal of the phenylthio group with sodium periodate in toluene represents future potential of this methodology in the syntheses of other naturally occurring macrolides such as lasiodiplodin, hypothmycin and curvularin.



More recently a fifteen-membered lactone has been synthesised directly from 15-hydroxypentadecanoic acid by treatment with zeolite molecular sieves at 90°C.[16]

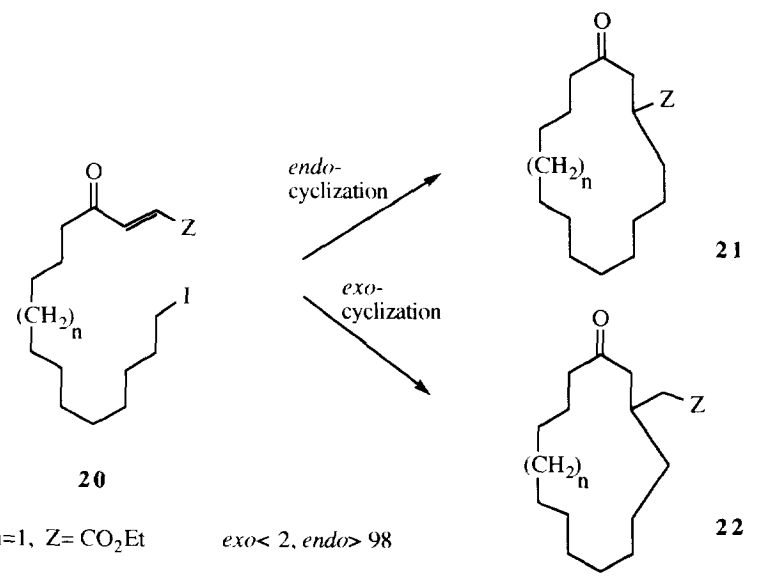
2.1.1 Radical cyclizations

A number of methods to synthesise lactones by direct free-radical methods have been reported. Carbon centred radicals tend to be nucleophilic and if generated in a chain containing a reactive electron deficient centre intramolecular cyclization may occur. This has been achieved by treatment of α,ω-iodoalkyl acrylates with tri-*n*-butyltinhydride to give twelve- to twenty-membered lactones.[17] This methodology has been extended by Baldwin, Adlington and Ramcharitar[18] to ω-iodoalkyl-propiolate esters **18**. Here the electrophilic trap is the propiolate ester, free-radical generation from the iodide giving exclusively by regio- and stereoselective cyclization the *endo-trans* α,β-unsaturated lactones **19**. The ω-iodides gave higher yields of lactones than the corresponding ω-bromides or ω-phenylselenides.



18 X=Br, I, SePh n= 9-12 **19**

Porter[19] has extended this approach to look at the regio- and diastereoselectivities of free-radical macrolactonizations. In the case of **20** A (n=1) when Z=CO_2Et there is a greater than a 98% preference for the fifteen-membered lactones **21** and less than 2% for that of the corresponding fourteen-membered ring **22** (*i.e.* 49:1). In case B (n=0) (Z=$CONEt_2$) there is a 10:1 preference for the fourteen-membered lactone **21** over the thirteen-membered ring. Thus, by choosing the appropriate groups (Z) one can to a large degree affect the regioselectivity. Diastereoselectivities were obtained where Z was a chiral pyrrolidine.



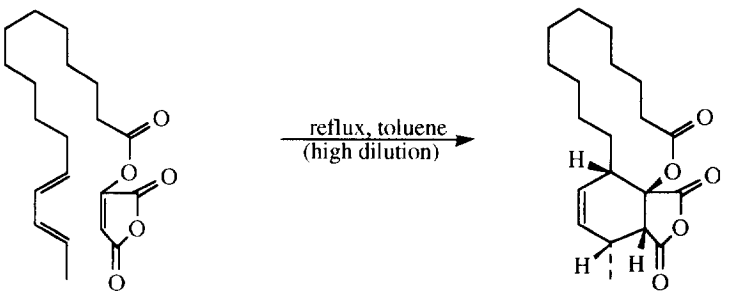
20

A n=1, Z= CO_2Et *exo*< 2, *endo*> 98

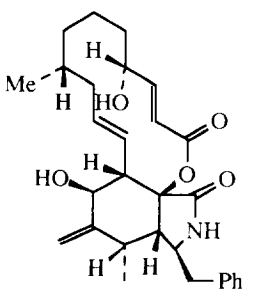
B n=0, Z= $CONEt_2$ *exo*< 1, *endo*> 10

2.1.2 Formation by intramolecular Diels-Alder reactions

Intramolecular Diels-Alder cyclizations have been used by Thomas in the formation of large-ring lactones. This procedure has found particular use in the construction of cytochalasans and their skeleton structures. The cytochalasans are a unique group of fungal metabolites and used as pharmaceutical probes on human cells. A high dilution reflux of *trans*, *trans*-hexadeca-12,14-dienoyloxymaleic anhydride **23** gave the fourteen-membered lactone **24** in 16% yield. Structure **24** contains the basic skeleton of cyctochalsan B, thus presenting the potential not only for the total synthesis of cytochalasans but also in the construction of the skeletons of other cytochalasans.[20] The synthetic procedure was extended by Thomas to the synthesis of cytochalasin H by two routes.[21,22]



23 **24**



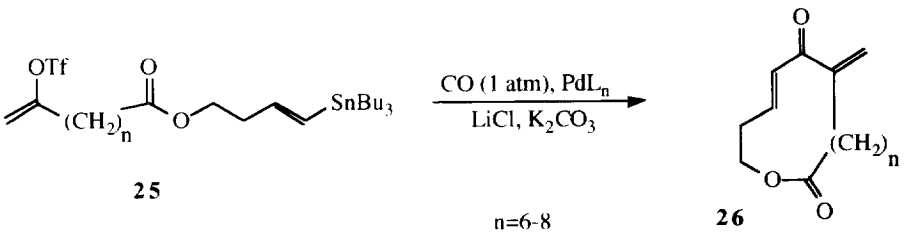
cytochalasan B

2.1.3 Cyclizations *via* polymer supports

The use of transition metals such as palladium to catalyse the formation of large-rings is well known.[23-25] However, two specific problems are often encountered with these type of intramolecular cyclizations: 1) the formation of dimers, trimers and more commonly oligomers; 2) the use of high dilution techniques involving large quantities of solvents and long reaction periods. The advantage of polymer supports is that they enable one to anchor one end of a potential ring system to a fixed polymer or resin. This can avoid unwanted side reactions. However, the anchoring sites must be the right distance apart, but not so near as to allow the free ends to undergo intermolecular reactions.

The palladium catalyst Pd(dppf)Cl_2 (dppf=1,2-bis(diphenylphosphinoferrocene)), a catalyst known to give reasonable yields (*ca* . 55%) in carbonylative couplings, was incorporated into poly(vinylpyrrolidine) together with palladium(0) (in the form of $Pd(PPh_3)_4$). Carbonylative cyclization of the substrates **25** was then achieved

giving the fourteen- to sixteen-membered rings **26** in yields of over 70%.[26] This compares to yields of approximately 20% lower when no polymer support was present using the same palladium catalyst $Pd(dppf)Cl_2$.



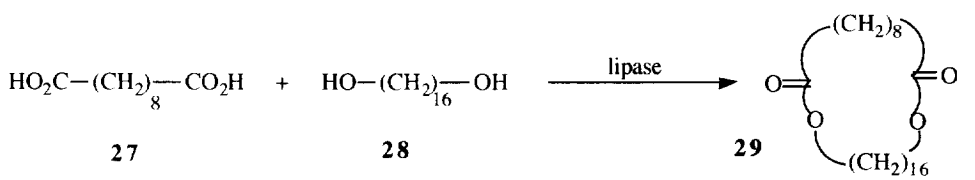
25 **26**

The use of polymer supports has been extended into what is termed a triphase catalytic cyclization.[27] The three phases are aqueous, organic and solid (polymer). A compound such as an α,ω-hydroxycarboxylic acid is transformed into its α,ω-mesylcarboxylic acid in an organic phase. This is then reacted with the solid polymer support containing for example a phosphonium mesylate group. This leaves the carboxylate end attached to the polymer support before heating causes an intramolecular displacement of the ω-mesylate group by the carboxylate to yield twelve- to sixteen-membered lactones in yields of 47 to 72%. This procedure was extended to the use of carboxylic acids containing chiral secondary alcohol groups to give the thirteen-membered lactone ricinelaidic acid in 40% yield. No loss of chirality was noticed in this reaction.[27]

This work was further extended by Regen into a practically more useful method of constructing macrocycles.[28] The potassium salts of ω-bromo carboxylic acids were used as the solid phase, which was effectively transferred to solution with tetrabutylammonium bromide. Using this in catalytic amounts offers the same effect as a sparsely populated polymer support and avoids the necessity of high dilution conditions. Using this procedure yields of over 90% were obtained for rings containing thirteen-, sixteen- and seventeen-members.

2.1.4 Enzymatic lactone syntheses

It is well known that certain enzyme lipases catalyse the hydrolysis of carboxylic esters to carboxylic acids, in aqueous media. However, these same enzymes in anhydrous organic media, such as isooctane, catalyse the reverse reaction *i.e.* esterification and hence lactonization. This enzyme mediated lactonization was first reported by Gatfield[29] using the enzyme *Mucor miehei* to give pentadecanolide from 15-hydroxypentadecanoic acid and also γ-butrolactone from 4-hydroxybutyric acid. Further work by Yamada[30] and Gutman[31] have confirmed that enzymes, in particular the enzyme porcine pancreatic lipase (PPL), in anhydrous organic solvents, catalyse the lactonization of ω-hydroxycarboxylic acids. This work has been extended by Sih[32] who has synthesised dilactones from α,ω-diacids and α,ω-diols containing sixteen- to twenty eight-members as exemplified below for the twenty eight-membered dilactone **29**.



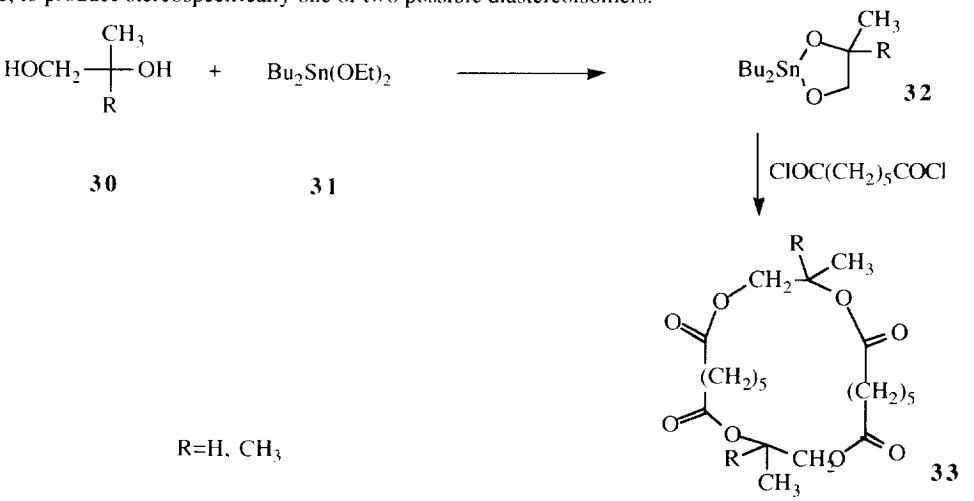
27 **28** **29**

The α,ω-diacids and α,ω-diols were incubated together with one of the lipase enzymes, porcine pancreatic lipase, *Candida cyclindracea* (OF-360) or *Pseudomonas sp* (AK and K-10) for typically two days in anhydrous isooctane at 65°C to give dilactones in yields ranging from 25 to 55%. The best yields were obtained for dilactones containing twenty four- to twenty eight-members. Some tetralactones, in some cases as much as 19%, were formed together with small traces (~4%) of hexalactones.

More recently PPL has been used to form (3*Z*, 6*Z*)-dodecanolide, one of the aggregation pheromone components of the destructive *Cucujid* beetles in the genera *Cryptolestes* and *Oryzaephilus*. By the use of enzymatic rather than chemical methods the ready and troublesome (3*Z*) double bond isomerization was avoided.[33]

2.1.5 Metal-mediated cyclizations

The use of metals in the syntheses of large-rings has been known for some time.[34] More recently the use of tin as a covalent template has been used to prepare the cyclic tetralactones **33**.[35] The method involves conversion of a diol such as **30** into the covalent tin-oxygen structure **32** before treatment of this with a diacyl halide (below) or cyclic anhydride. It was also possible to effect cyclization with diols containing a chiral centre, such as D-ethyl tartrate, to produce stereospecifically one of two possible diastereoisomers.



30 **31**

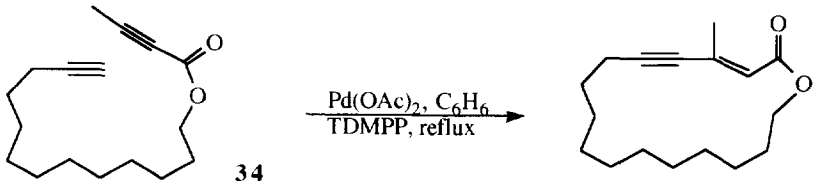
R=H, CH_3

This tin template process has also been used to synthesise chiral dilactones from 2,6-hydroxytin-difunctionalised pyridines and α,ω-diacylhalides.[36] Yields were in the region of 50 to 70%.

These neutral tin-mediated cyclizations have been extended to the lactonization of ω-hydroxycarboxylic acids.[37] Yields of the twelve-, thirteen-, sixteen- and seventeen-membered rings ranged from 47 to 85%. The usefulness of this procedure was extended to the synthesis of the lactone-containing antibiotics zearalenone, vingramycin, rodusmicin and pyrenophorin.

Another metal that mediates the synthesis of large-rings is copper, its use in the coupling of acetylene groups being well documented.[38] Trost[39] has produced a useful variation of the acetylene coupling by blocking the

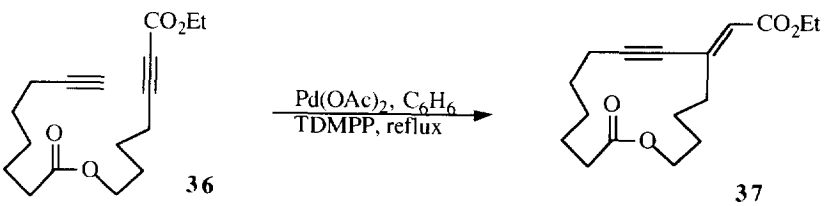
terminus of one acetylene group with a methyl group *i.e.* **34**. Coupling of this, containing an ester group, with palladium acetate in the presence of TDMPP produces the seventeen-membered acetylene-containing macrolactone **35** in 38% yield.



34 **35**

TDMPP= [tris(2,6-dimethoxyphenyl)phosphine]

This cyclization procedure was extended to the propargylic ester-containing system **36**, to yield, the fourteen-membered lactone **37**. The exocyclic grouping presents itself for further synthetic modification, adding a useful variation to this regioselective cyclization procedure.[39] Similar compounds containing fifteen-, nineteen- and twenty six-members were also synthesised using this procedure.[39]

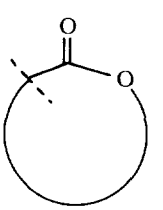


36 **37**

The regioselective synthesis of *exo*-methylene macrolides using palladium as the coupling medium has also been reported by Stille[40] to give twelve- to fifteen-membered *exo*-methylene lactones in yields of typically 55%.

The use of palladium as a coupling medium in macrolide syntheses has also been reported in the cyclization of linear molecules containing α-acylchloride and ω-(β-stannylalkenoate) groups.[41] This procedure was then utilized in the synthesis of norpatulolide B and the macrocyclic framework of the antibiotic A26771B.

All macrocyclic lactone structures to date have been formed in the last step by lactone carbon-oxygen bond-forming reactions. It was proposed by Trost[42] that the disconnection shown in **38** could in theory be feasible as the ring-forming step if the right functional groups are present. The carbonyl group of the lactone was masked as a phenylthio(acetonitrile) group, and since an addition between this group and an allylic carbonate, both present in **39**, occurs in the presence of a palladium catalyst, cyclization to **40** proceeds. Unmasking of the phenylthioacetonitrile group of **40** cleanly yielded the fourteen- and fifteen-membered lactones **41**.



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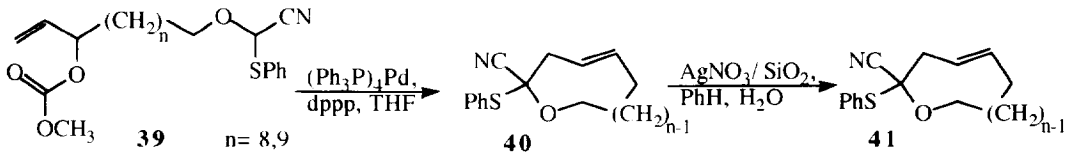
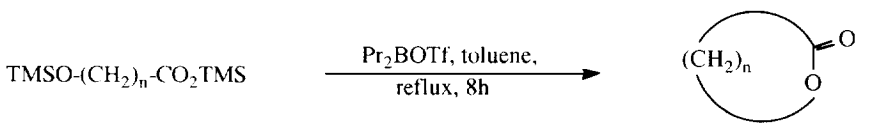
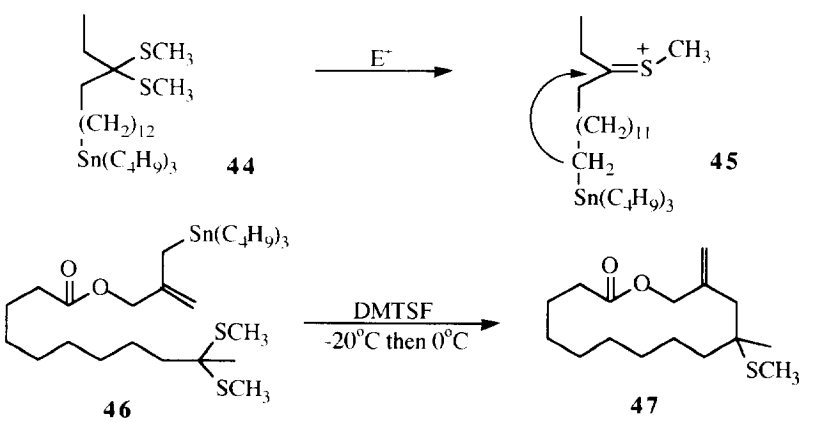


The use of boron has also been reported in the cyclization of diprotected ω-hydroxycarboxylic acids. Treatment of the trimethylsilyl ω-trimethylsilyloxycarboxylates **42** shown below with dipropylboryl triflate yields the thirteen- to sixteen-membered lactones **43** in yields of 83, 89, 94 and 85% respectively.[43]



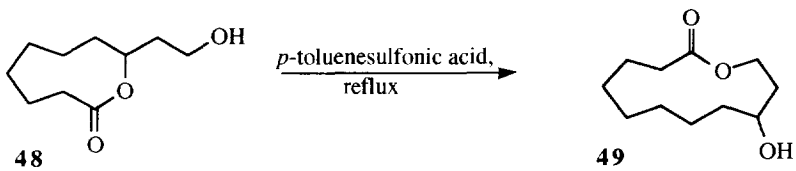
The boron reagent dimethyl(methylthiosulfonium) fluoroborate (DMTSF) has also been used in the construction of large-sized lactones. The methodology involves reaction of the thioketal group, present in **44**, with the boron electrophile, as shown below, to produce the thiocarbocation **45**, which then undergoes cyclization with the nucleophilic part of the molecule (the methallylstannane).[44] This procedure has been used in the construction of fourteen- (illustrated) **47** and fifteen-membered lactones in yields of 46 to 48%.



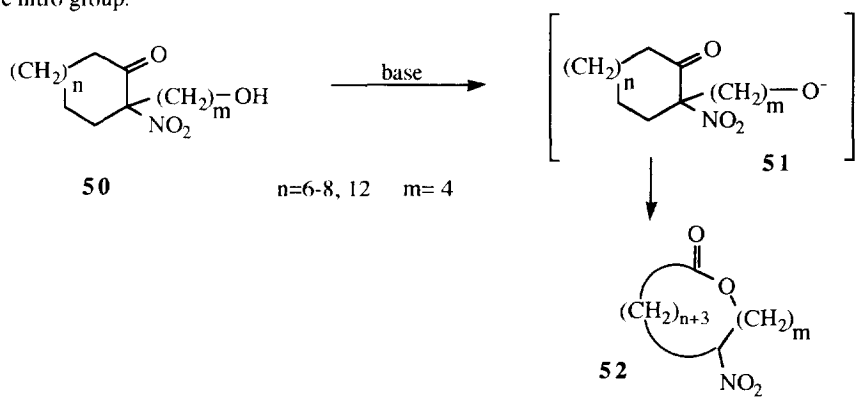
Samarium has also been reported in the synthesis of large-ring lactones.[45] The cyclization of ω-(α-bromoacyloxy)aldehydes using SmI_2 in a Reformatsky type reaction gave eleven- to fourteen-membered lactones in yields of over 80%. This method allows the inclusion of a hydroxyl group β- to the keto group thus presenting the opportunity for further synthetic modifications. However, some hydrolysis of the 13-hydroxy lactones was noted, the products therefore tended to be isolated as their acetates.

2.2 Ring-expansion methods

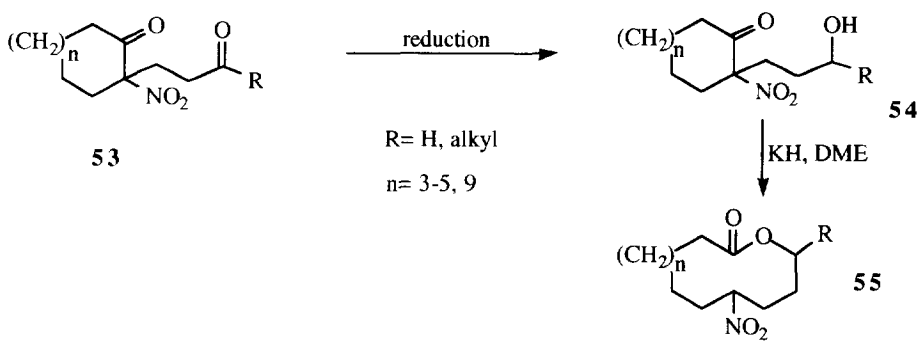
Large-ring lactones have been synthesised by the translactonization of smaller ring lactones such as **48** shown below. The thermodynamic stability of the twelve-membered lactone **49** is realised by heating the nine-membered lactone with *p*-toluenesulfonic acid for two hours to give **49** in 97% yield.[46]



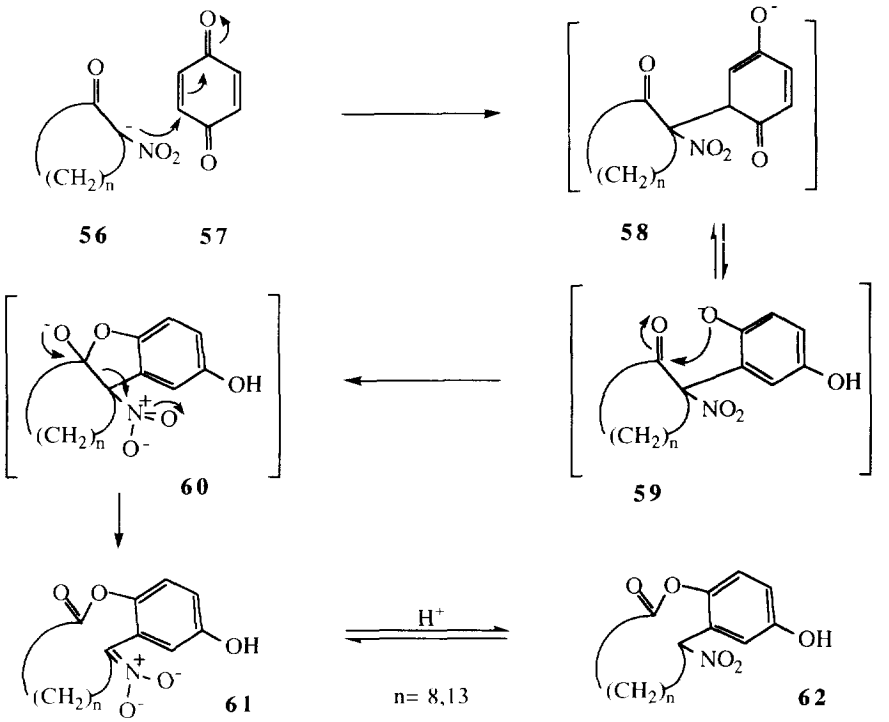
A number of lactonizations of the type below have been reported making use of the electron withdrawing nature of the nitro group. [47]



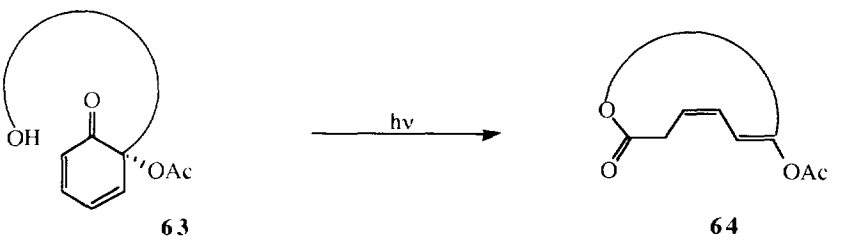
By using the systems **53** shown below[47] it is possible to obtain large-rings as for **50** to **52** but containing secondary alkyl substituents in the ring **55**.[47-50] By using a chiral reducing agent in **53** to **54** it was possible for Stanchev[51] to obtain optically active large-lactones of the type **55**. This procedure was additionally demonstrated in the synthesis of (-)-15-hexadecanolide.[52] These ring-expansion reactions have also been effected with quarternary ammonium groups in place of the nitro group.[53,54]



1,4-Benzoquinones **57**, undergo a Michael type addition with the anions of the 2-nitro substituted cycloalkanones **56**, to yield the lactones **62**, but containing, through conjugation of **58**, 1,2-disubstituted benzene rings in the final ring structures.[55]

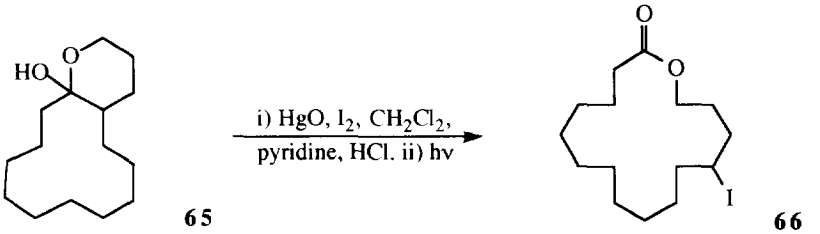


Photoirradiations have also been used to produce lactones. Wessely acetoxylation of phenols yields *O*-quinol acetates **63**. Photoirradiation of these substrates yields the large-ring lactones **64** as shown below.[56]



2.3 Radical ring-expansions

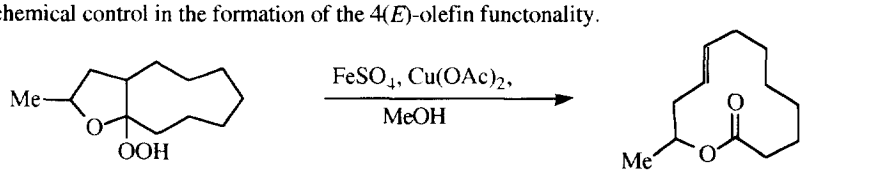
A sixteen-membered iodine-substituted lactone **66** has been formed in 30% yield by a photoirradiation of the lactol **65** in the presence of pyridine, mercury(II)oxide and iodine. The iodide was removed with tri-*n*-butyltinhydride in the presence of AIBN in *ca.* 90% yield.[57]



65 **66**

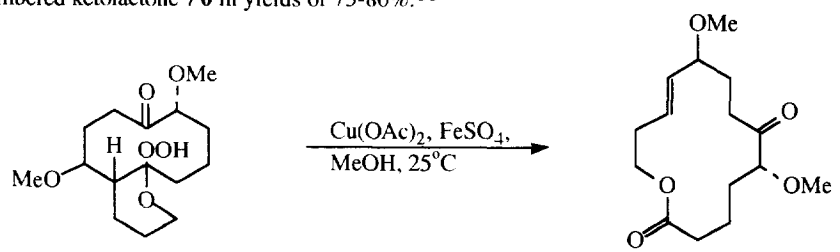
The ring-cyclization/expansion of cycloalkanones containing 2-substituted secondary alkyl radicals enables further functional groups to be introduced into the final ring structures **66**. For example treatment of a cycloheptanone containing a 2-substituted 4-bromopentyl group with a catalytic amount of tri-*n*-butyltinhydride and AIBN in benzene produces a secondary alkyl radical which after cyclization to the lactol followed by ring expansion gave an eleven-membered methyl substituted ring ketone.[58] Baeyer-Villiger oxidation of this ketone gave the corresponding twelve-membered lactone.

The use of metal ions such as iron sulphate/copper diacetate mixtures have been exploited in a homolytic fragmentation of the α-alkoxyhydroperoxide **67** to yield the olefin-containing lactone **68**.[59] The effect of an alkoxy radical adjacent to a C-C bond causes this bond to be greatly weakened. Values of 70 Kcalmol^{-1} are quite usual.[59] Yields were very high, typically 94% for the twelve-membered lactone **68**, with near complete regio- and stereochemical control in the formation of the 4(*E*)-olefin functonality.



67 **68**

Similarily an iron/copper mediated fragmentation of the α-alkoxy hydroperoxide **69** has been used to produce the fourteen-membered ketolactone **70** in yields of 75-80%.[60]



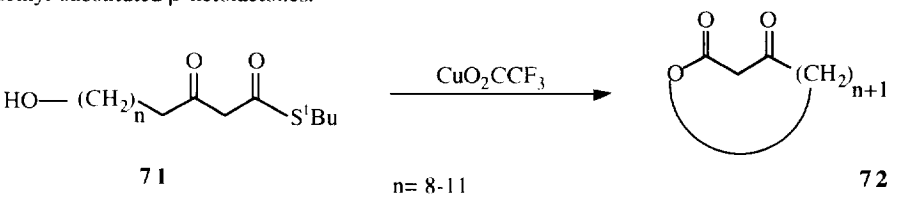
69 **70**

2.4 Ketolactones

2.4.1 Direct cyclization

Large-rings containing the β-ketolactone unit are of great importance and are found in many macrolide antibiotics. The direct cyclization to β-ketolactones to rings varying in size from thirteen- to thirty two-members

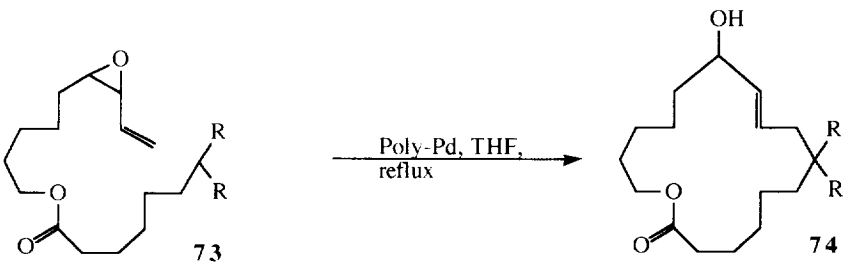
has been reported and involves a copper(I)trifluoroacetate catalysed transesterification of α-hydroxy-ω-(β-keto)thioesters.[61] By addition of a methyl group in the alkyl chain of **71** this procedure was additionally used to produce methyl-substituted β-ketolactones.[61]



71 **72**

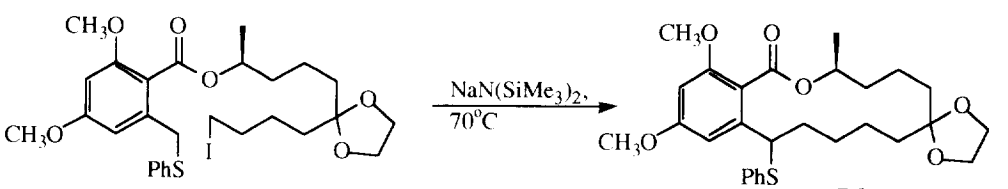
The direct transacylation of α,ω-hydroxymethyl esters has been used in the total synthesis of racemic patulolide A.[62] An intramolecular cyclization method using a β-acylketene intermediate as a trap has been used to produce a fifteen-membered β-ketolactone and the fourteen-membered β-ketolactone (-)-kromycin.[63]

A further direct macrolide cyclization has been reported by Trost.[64] Macrolides of the type **74** (R=SO_2Ph), containing seventeen- (illustrated) and twenty seven-members have been synthesised in 74 and 70% yield respectively. By using polymerically bound palladium catalysts the reacting nucleophilic and electrophilic centres are not unmasked until the substrate encounters an active site on the polymer. This avoids the necessity of the high dilution conditions often needed to avoid the formation of polymers and oligomers. Ring formation exhibited a large dependence on the cyclizing nucleophilic end-groups; when R=CO_2CH_3 no cyclized products were obtained. The easy removal of the benzenesulfonyl group from the final structures adds further versatility to this synthetic procedure.



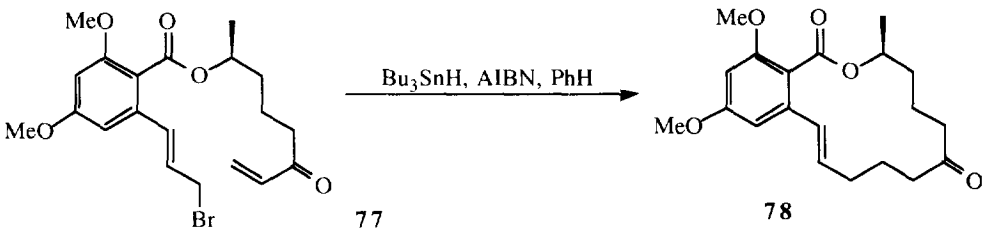
73 **74**

A direct nucleophilic displacement of the iodide of **75** by the phenylsulfide anion generated by treatment of **75** with base has been used as the key cyclization step in the synthesis of a precursor to (*S*)-(-)-zearalenone.[65] The chirality in **75** was introduced using an enzymatic (*Thermoanaerobium brockii* alcohol dehydrogenase (TBADH)) stereoselective reduction, at an earlier stage in the synthesis.



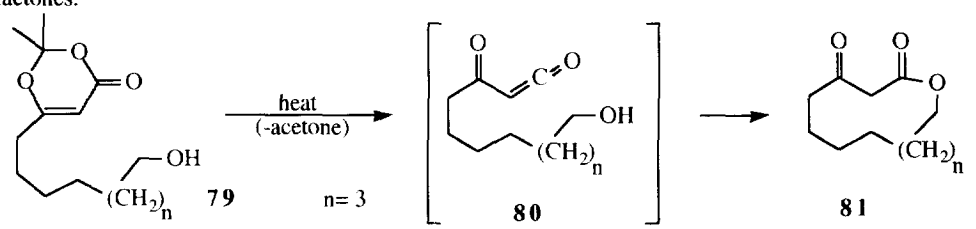
75 **76**

The synthesis of the mycotoxin (-)-zearalenone has also been achieved by Pattenden, using an intramolecular addition of a cinnamyl radical intermediate, generated from the bromide shown in **77** to the α,β-enone group. Addition of the cinnamyl radical to the α,β-enone occurred *endo*-trig to yield the fourteen-membered lactone **78** with none of the potential 11-*exo*, 12-*endo* or 13-*exo*-trig products being formed.[66,67] Conversion to (-)-zearalenone was completed by demethylation of the aromatic methoxy groups.



77 **78**

A direct route to twelve-membered β-keto lactones has been developed by an intramolecular trapping of (ω-hydroxy)acylketenes. The thermal elimination of acetone from 2,2-dimethyl-6-(ω-hydroxyalkyl)-4H-1,3-dioxin-4-ones **79** yields the intermediate (ω-hydroxy)acylketene intermediate **80** which undergoes ring cyclization to the twelve-membered β-keto lactone **81**. Ring closure to the ten- and eleven-membered β-keto lactones (n=1,2) did not occur under these conditions indicating this method is suitable for the formation of only twelve-membered β-keto lactones.[68]

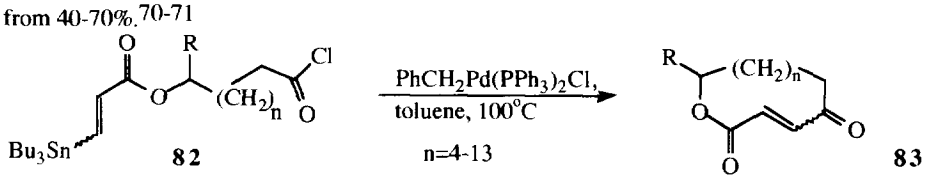


79 n= 3 **80** **81**

More recently the twenty nine-membered ketolactone-containing (-)-rapamycin has been synthesised by a direct cyclization using the Mukaiyama macrocyclization.[69]

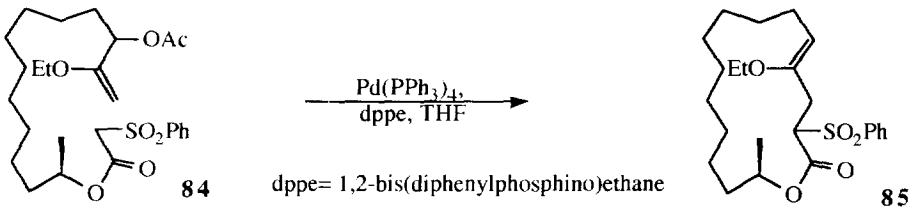
2.4.2 Metal-mediated cyclizations

Ketolactones, containing a γ-oxo-α,β-unsaturated moiety are commonly found in many macrocyclic antibiotics and fungal metabolites such as the cytochalasins. The direct palladium catalysed macrocyclization using the Stille reaction has been reported by Baldwin, Adlington and Ramcharitar. In this procedure the acid chloride and β-stannyl alkenoate end-groups of **82** are coupled using benzylchlorobis(triphenylphosphine)palladium (II) (5mol%) in toluene at 100°C to give the eleven- to twenty-membered γ-oxo-α,β-unsaturated lactones **83** in yields ranging from 40-70%.[70-71]



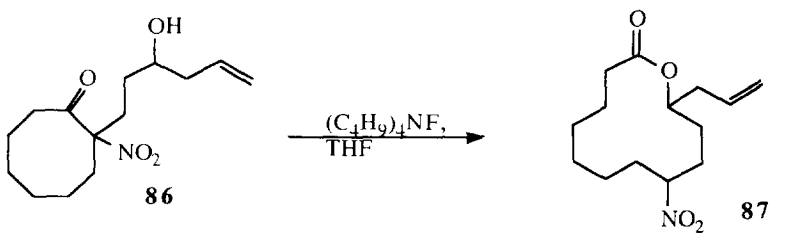
82 n=4-13 **83**

Also, the ring cyclization to ketolactones, using similar methodology has been reported by Boger.[72]
The direct cyclization of the β-ketosulfone and 2-ethoxyallyl acetate end-groups of **84** to give **85** has also been achieved using a phosphine-palladium complex. This procedure was then utilised as the key ring-forming step in the total synthesis of the antibiotic A26771B.[73]

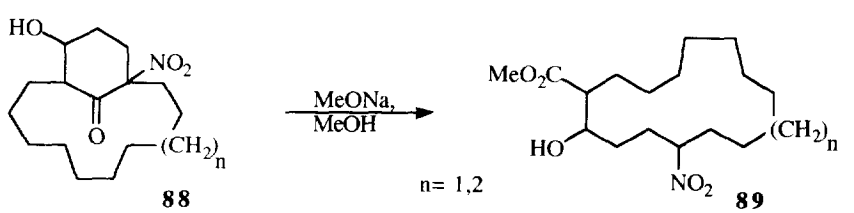


2.4.3 Ring-expansion methods

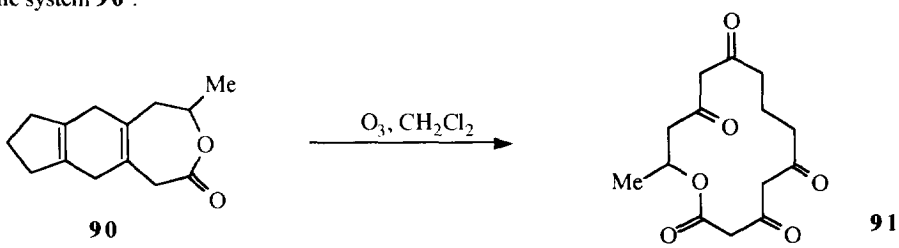
A number of eleven-, twelve- and fourteen-membered nitro-substituted ketolactones have been synthesised by Hesse[74-76] as shown below. Treatment of the secondary alcohols **86** with tetrabutylammonium fluoride gave the nitro-substituted lactones **87**. Transformation into ketolactones was achieved by a titanium trichloride catalysed Nef reaction of the nitro-group.



A methoxide catalysed ring-expansion of the bicyclic α-nitroketones **88** has been used to produce the fifteen- and sixteen-membered rings **89** as shown below. Oxidation of the hydroxyl group of **89** with chromium trioxide and a Nef type reaction on the nitro-group, previously described, gave a diketo system. Selective protection of one of the keto groups followed by a Baeyer-Villiger oxidation and deprotection yielded the required fifteen- and sixteen-membered ketolactones.[77]



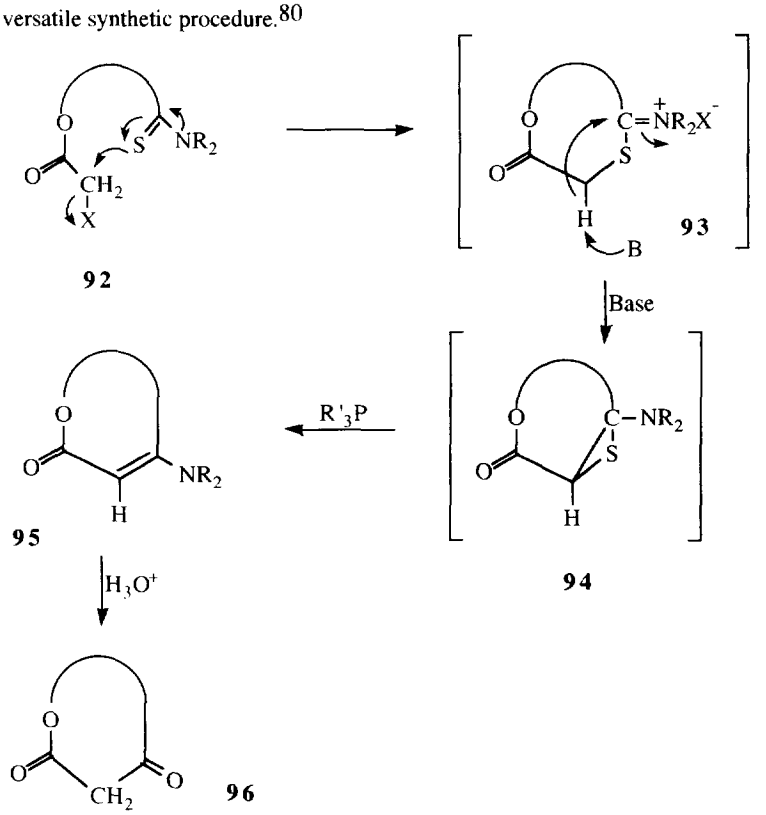
The fourteen-membered tetraketolactone **91** was synthesised in a 60% yield by an exhaustive ozonolysis of the tricyclic system **90** .[78]



90 **91**

2.4.4 Ketolactones *via* sulfide contraction

The Eschenmoser sulfide contraction[79] published in 1971 and variations, have proved useful in the construction of β-ketolactones. Generally *N,N*-dialkylthioamides **92** undergo cyclization as shown below. Treatment of the intermediate thioiminium salt **93** with an amine base (Hünig type bases are common) followed by a phosphine causes intramolecular sulfide contraction to **95**. Eschenmoser combined the amine base and phosphine steps into a single process by using $PhP[(CH_2)_3NMe_2]_2$ containing both amine and phosphine functionality. Hydrolysis of **95** gives the β-ketolactone **96**. This procedure was used to produce twelve-membered β-keto lactones containing additional ester, *cis*- and *trans*- olefins, acetylene and ketone groups making this a useful and versatile synthetic procedure.[80]

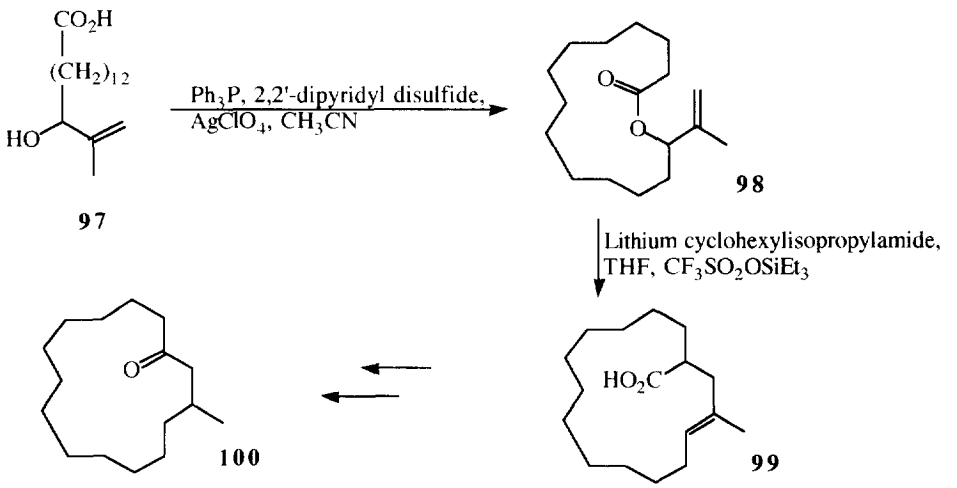


92 **93** **94** **95** **96**

3. The syntheses of ketones

3.1 The syntheses of ketones/ direct cyclizations

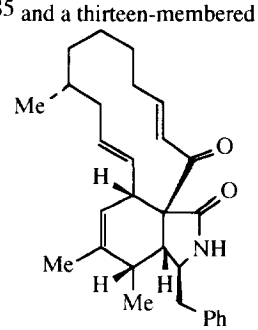
An indirect method of synthesing ketones has been used in the construction of the fifteen-membered ring ketone (±)-muscone **100**. This is initiated by direct cyclization of the allylic alcohol **97** to yield the fifteen-membered lactone **98**. Conversion of the ester grouping of **98** into its triethylsilyl enolate using a slight molar excess of lithium cyclohexylisopropylamide in THF and triethylsilyl trifluoromethylsulfonate, followed by an Ireland-Claisen rearrangement gave predominantly **99**, which after further synthetic modification yielded the fifteen-membered ring ketone **100**.[81]



97 **98** **99** **100**

Fourteen-membered ring ketones containing an allene grouping have been synthesised *via* a low temperature stannic chloride induced cyclization of keto-containing α,ω-dienes. Further modification of these allene-containing macrocyclic keto rings allowed the synthesis of the diterpenoid tobacco isolate 7,8-epoxy-4-basmen-6-one.[82]

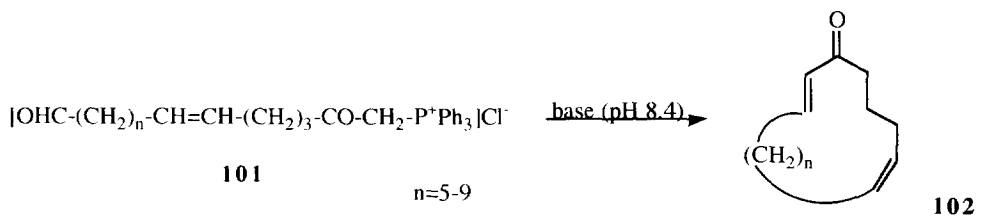
The cytochalasans, containing large-ring ketones, are an important group of fungal metabolites and have been synthesised by an intramolecular Diels-Alder cyclization, discussed previously in section 2.1.2. This Diels-Alder methodology has been extended to the syntheses of proxiphomin a naturally occurring [13]cytochalasin by two routes,[83,84] cytochalasin D,[85] and a thirteen-membered cytochalasan.[86]



proxiphomin

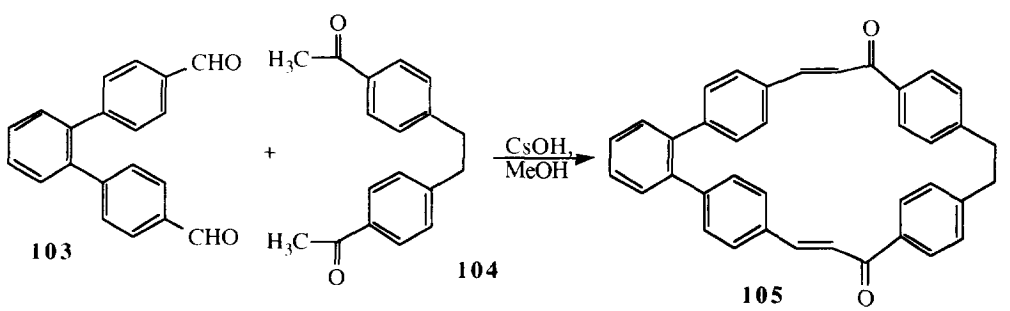
The Diels-Alder reaction has also been exploited in the construction of eleven- to nineteen-membered ring ketones containing a fused furan ring.[87]

Thirteen- to seventeen-membered ring ketones **102** have been synthesised by an intramolecular Wittig reaction of the appropriate α,ω-difunctionalised molecules **101**.[88] Treatment of the structures **101** with base to pH 8.4 yielded the thirteen- to seventeen-membered ring ketones in yields of 33 to 56%. The *cis*- geometry of the internal double bond of **101** probably has a large influence, by steric effects, on the yield of the final ring ketones **102**. Incorporation of this unit together with the *trans*- double bond introduced during the Wittig step offers the potential for further modification, adding a degree of versatility to this procedure.



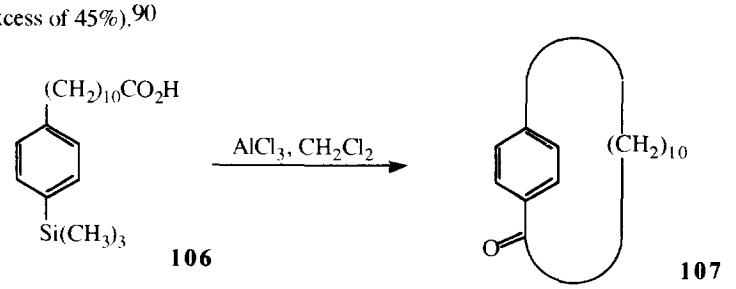
101 n=5-9 **102**

The relatively rigid structure **103**, in which the reacting end-groups are held closer together than the situation in a flexible chain, has been utilised in the synthesis of macrocyclic dichalcones such as **105**.[89] Dichalcones are important for their ability to act as non-collapsible, potentially highly functionalised, chiral cavities, capable of chelating many types of guest molecules.



103 **104** **105**

The formation of large-rings is not limited to 1,2-*cis*-disubstituted systems as the 1,3- and 1,4- (illustrated) disubstituted benzene systems **106** have been used to form fourteen- and fifteen-membered ring ketones **107** (Yields were in excess of 45%).[90]



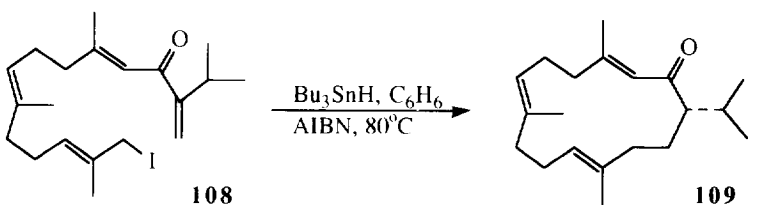
106 **107**

3.1.1 Free-radical direct cyclization

The direct free-radical cyclization of linear α,ω-disubstituted saturated chains containing twelve- or more atoms is not usually of synthetic importance due to an unfavourable entropic term, usually resulting in low yields of cyclized products.[95] However, this entropic problem is greatly lessened in at least two situations: 1) when the molecule contains functionality which holds the two cyclizing centers closer together than the situation present in a straight chain (*eg. cis*-olefins) and: 2) when, due to the electron rich nature of carbon centred radicals, there is an additional attraction between the two cyclizing centres (*eg.* enones or the propiolate esters, discussed in section 2.1.1). Making use of one or more of these factors results in higher yields of large-rings than when the corresponding unfunctionalized saturated linear chains are cyclized.[95]

This methodology, using the enone functionality, has been used by Pattenden and coworkers as a new approach in the total synthesis of (±)-mukulol,[91,92] a fourten-membered marine cembranolide found in the soft coral *Comiphora mukulo*, as shown below. The synthesis of (±)-mukulol was completed by a lithium aluminium hydride reduction of the ketone group of **109**. Also, the use of radical traps, using the enone functionality, has been used in a formal synthesis of a cembranolide isolated from the soft coral *Sinularia mayi*.[91,92] In addition Pattenden and coworkers have used enone traps to produce seventeen-membered unsaturated cyclic ketones[93] and twelve-membered unsaturated ring diketones, the latter as potential systems for tandem radical cyclizations en route to taxane alkaloid skeletons.[94]

Enones have also been used as traps by Porter to produce a saturated fourteen-membered ketone and related ketones containing acetylene and *trans*-olefin groups as well as eighteen-membered saturated ketones in yields as high as 78%.[95]



108 **109**

The use of electron-deficient centres as a radical trap has been further extended by using a 1,1-dicyano-substituted olefin as the electron acceptor to produce twenty-membered saturated carbocyclic rings.[96]

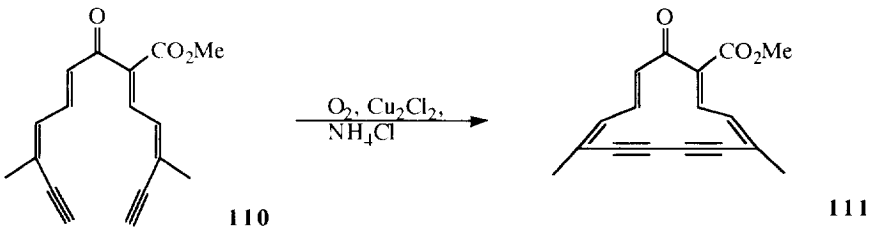
3.1.2 Metal-mediated direct cyclizations

The direct cyclization of α,ω-fuctionalized molecules does not usually give large-rings in good yields,[97] however, the direct cyclization of α-bromo-ω-oxo esters has been achieved using a samarium diiodide promoted Reformatsky reaction to give eleven-, fourteen- and fifteen-membered ring ketones in yields of 74 to 82%.[98] Although it is not known why this macrocyclization proceeds so well, it is thought that the large ionic radius, flexible coordination and high oxophilicity of the samarium play a large role.

The use of palladium has been exploited in the direct cyclization of α-4,4-bis(benzenesulfonyl)-ω-vinyl epoxides. The macrocyclization occurred at relatively high concentrations (1M) and gave fifteen-membered ring ketones in yields of 66%.[99] The use of palladium has been extended further in the direct cyclization of molecules

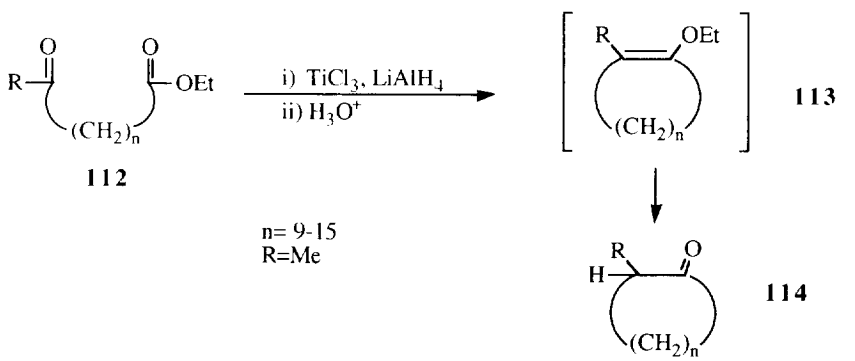
containing α-(β-keto sulfone) and ω-(ethoxyvinyl) end-groups and the synthetic versatility demonstrated by the first synthesis of the eleven-membered ring ketone (-)-aspochalasin B.[100]

Ketones containing acetylene end-groups have been synthesised by Garrett.[101] Oxidative ring closure of the diacetylene compound **110** below was affected under the Glaser conditions, which in this case was preferable to those used in the Eglinton coupling ($Cu(OAc)_2$, pyridine), to give the large-ring ketones **111**. Similarily, thirteen-membered ketones containing an additional olefin or an alkyl substituent on the side chain were also produced using one of the two oxidative coupling procedures mentioned above.



110 **111**

The use of titanium has also been exploited in the synthesis of large-rings by McMurry. Originally an activated Ti(0) reagent, prepared by the reduction of $TiCl_3$ with a Zn-Cu couple, was used to obtain cycloalkenes *via* the coupling of α,ω-diketones or α,ω-ketoaldehydes. This procedure has been demonstrated in the synthesis of the eleven-membered ring sesquiterpene humulene[102] and the fifteen-membered ring diterpene flexibilene.[103] More recently McMurry has extended this dicarbonyl coupling procedure to the keto esters **112**, synthesising eleven- to seventeen-membered ketones **114** in yields of *ca.* 58%.[104]



112 **113** **114**

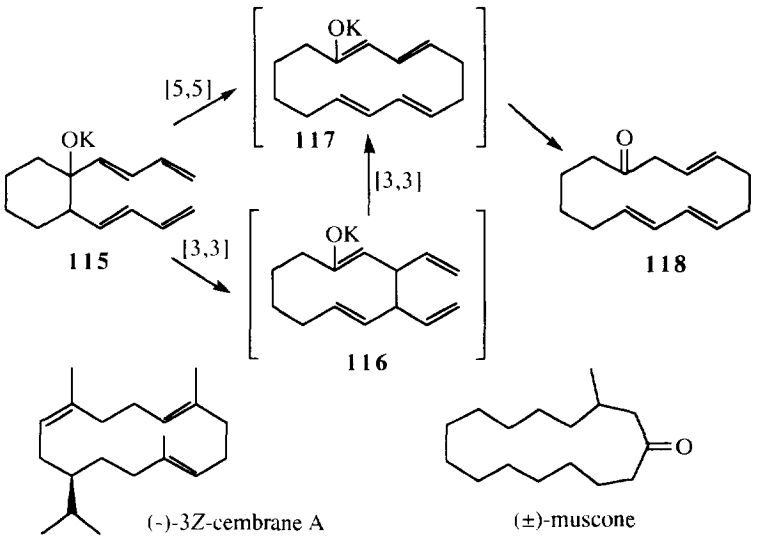
n= 9-15
R=Me

The mechanism of this reaction involves an initial pinacol-type coupling to form a carbon-carbon bond which after deoxygenation yields the enol ether intermediate **113**. Acidic hydrolysis of this intermediate gives the final ring ketones **114**.

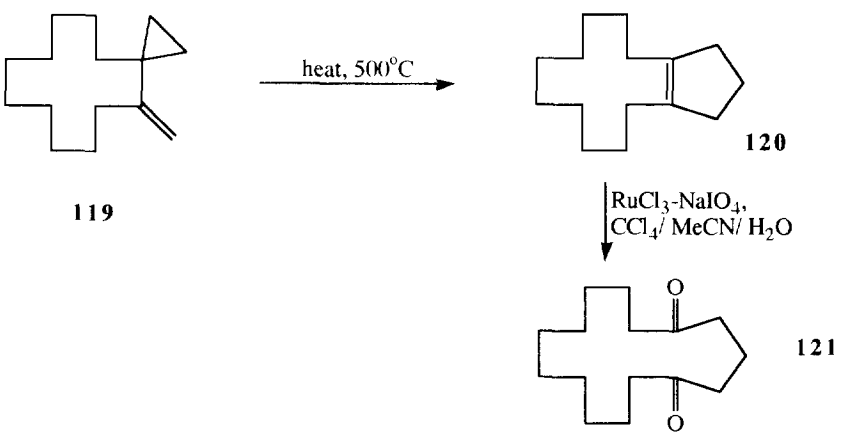
3.2 Ketones by ring-expansion reactions

The use of an enolate accelerated Cope rearrangement[105] as exemplified for **115** to **118** has been used in the synthesis of (±) muscone[106] and (-)-3*Z*-cembrane A.[107] Treatment of 5-hydroxy-deca-1,3,7,9-tetraene with

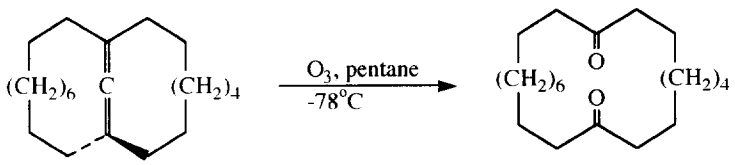
potassium yields the alkoxide **115** which can form **117**, either by a concerted [5,5] sigmatropic rearrangement or *via* two sequential [3,3] shifts. Protolysis of the potassium enolate gave the fourteen-membered ring ketone **118**. The enolate accelerated or oxy-Cope rearrangement has also been used in the synthesis of methyl-substituted and unsubstituted sixteen-membered ring ketones.[108]



Large-rings containing two ketone groups are also of interest since this extra functionality allows further synthetic modification. The vinylcylopropane-cyclopentene thermal rearrangement is well known, however, the thermal rearrangement of spirocyclic vinylcyclopropanes is relatively unexplored. Application of this rearrangement to the twelve-membered saturated system **119** yielded the [10.3.0] fused bicyclic structure **120**. This rearrangement in itself forms a useful procedure since cyclopentane rings fused with large-rings are commonly found amongst the terpenoid natural products thus providing a synthetic strategy into the framework of these molecules. Oxidative cleavage of the double bond of **120** yielded the diketone derivative **121** in 68% yield.[109]

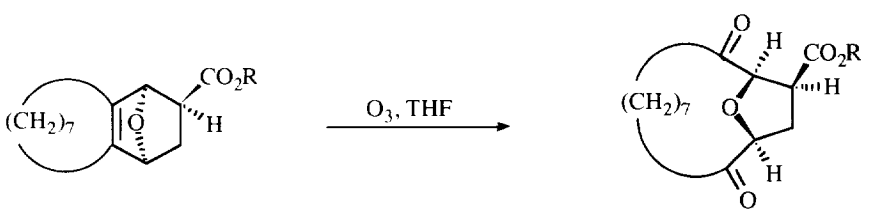


A further group of compounds containing two keto groups have also been synthesised. Precursors to these diketo-containing rings are the aptly named betweenallenes **122**. Structure **122** is an [10.8.1] betweenallene, which after ozonolysis yields the twenty-membered diketone[110] **123**.



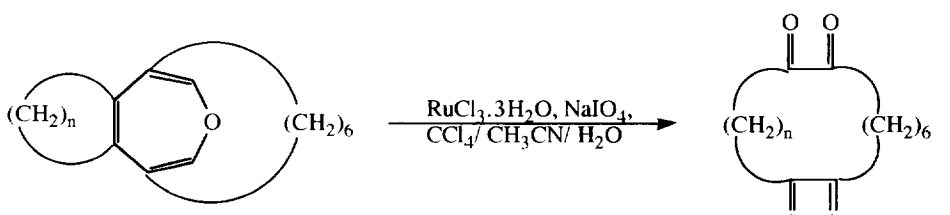
122 **123**

Diketones containing three asymmetric centres **125** have been obtained by the ozonolysis of the bridged tetrahydrofuran compounds **124**. Reduction of the keto groups with lithium tri-*tert*-butoxyaluminiumhydride (LTBAH)/triethylborane in tetrahydropyran introduced a further two asymmetric centres together with concomitant reduction of the ester group. Acetylation of this triol yielded a crystalline solid, the stereochemistry of which was confirmed by single crystal X-ray crystallography.[111]



124 R= H, CH_3 **125**

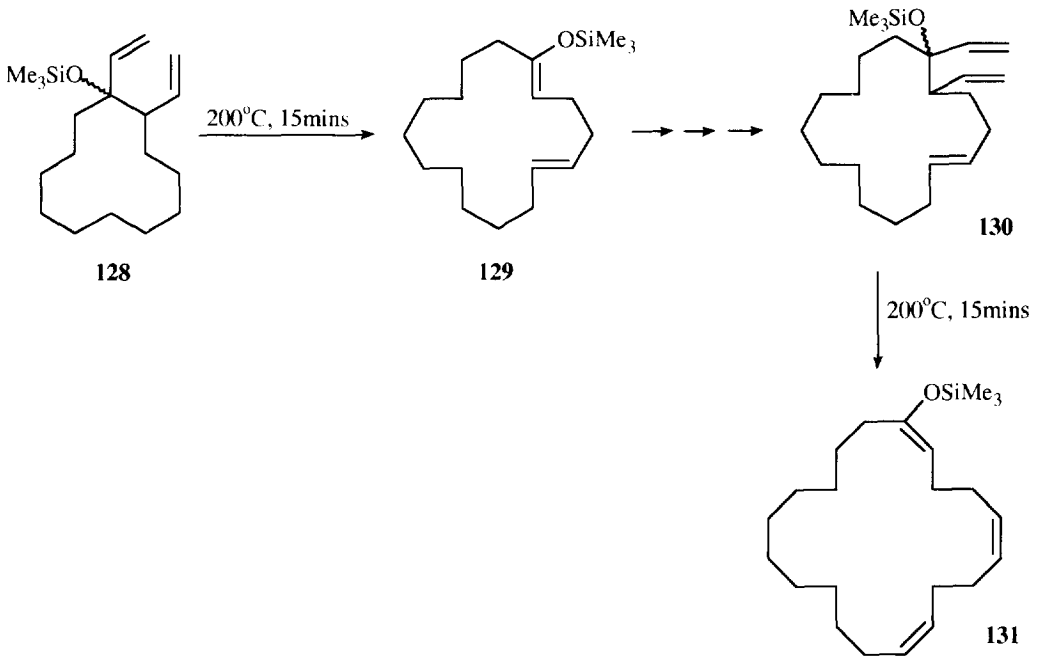
Other large-rings containing four keto groups **127** have been obtained by the ruthenium tetroxide oxidation of the oxepine-containing ring structures **126** to give sixteen- and twenty-membered rings in 40 and 33% yields respectively.[112]



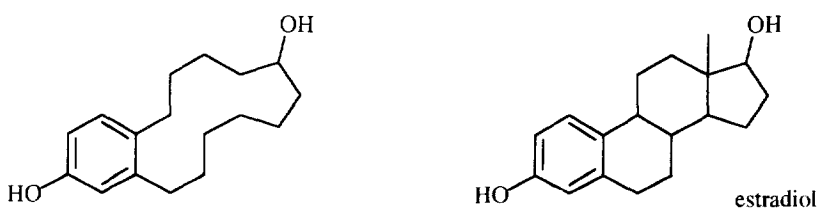
126 n=6,10 **127**

The syntheses of large-ring olefin-containing ketones with regiochemical control of the olefin groups has been reported .[113] A siloxy-Cope rearrangement of the twelve-membered ring **128** gave the sixteen-membered ring system **129** with an olefin geometry of 5*E* or 5*E* and 5*Z* depending on the stereochemistry of the

trimethylsilyl ether **128**. Three further synthetic steps yielded the triene **130** which was converted to the twenty-membered trimethylsilylether-substituted ring system **131** by thermolysis. An oxy-Cope rearrangement of the non-trimethylsilylated compound of **130** gave cycloeicosadec-5-en-1-one in 78% yield.

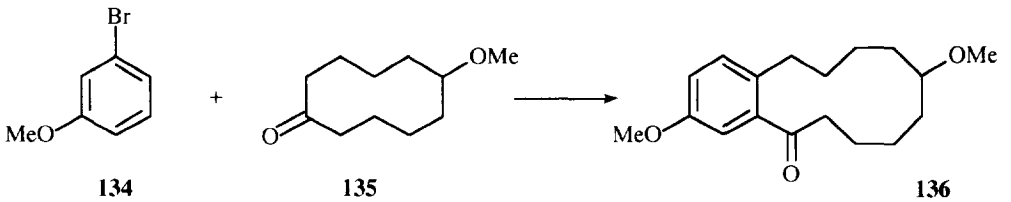


As large-ring alcohols are readily obtained by the reduction of the corresponding ketones the synthesis of the latter provides an indirect route to the potential flexible steroid systems **132**. These flexible steroid compounds mimic estradiol **133** in that the three saturated rings are replaced by a single thirteen-membered ring. These large-



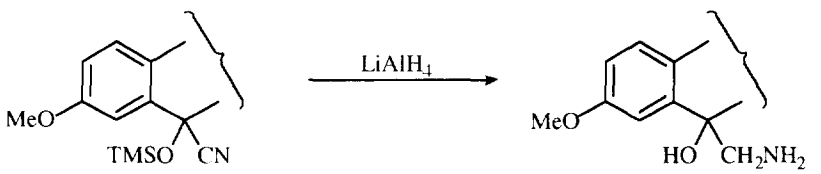
ring alcohols thus present potential for biological activity at hormone receptors. The basis for the synthesis of these large-ring alcohols comes from the known insertion reaction of benzynes (generated from bromobenzenes, such as **134**, and sodamide) into medium-ring ketones **135**. This method was used successfully to give the

twelve-membered ring[114] **136**. For the synthesis of the thirteen-membered estradiol mimic **132** one more carbon atom is needed in the lower part of ring **136**. This was achieved by treating the ketone of **136** with trimethylsilyl



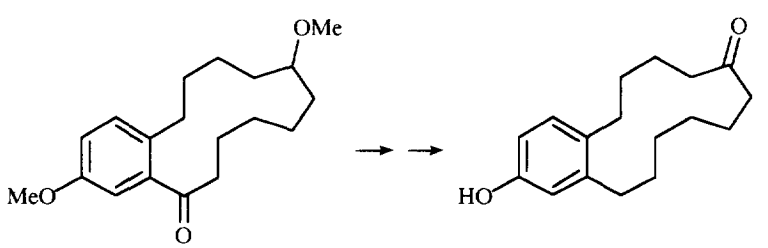
134 **135** **136**

cyanide (TMSCN) to yield **137**. Removal of the TMS group and reduction of the cyanide to an amine was achieved with lithium aluminium hydride to give **138**. Treatment of the resulting amine with nitrous acid (a



137 **138**

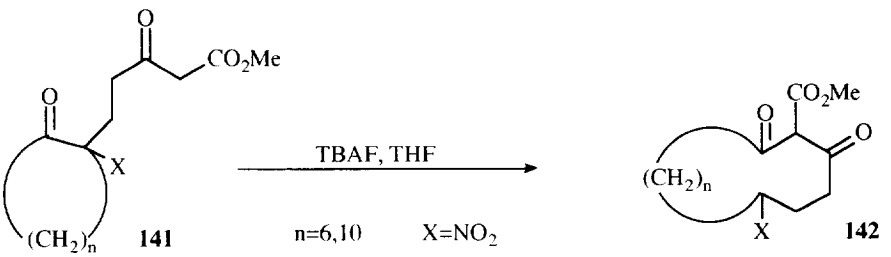
Tiffeneau-Demjanov rearrangement) gave the required thirteen-membered ketone **139** together with an equal amount of the isomer containing the carbonyl group β- to the aromatic ring. Several methods were tried to reduce the carbonyl group of **139** to a methylene. The most successful was reduction of the ketone to an alcohol with lithium aluminium hydride followed by mesylation, elimination of the mesylate and hydrogenation of the resulting olefin. Finally, the methoxy groups of **139** were cleaved to alcohols using aluminium trichloride/ethanethiol and the aliphatic alcohol group oxidized using Jones' reagent to the thirteen-membered ring ketone **140**. An alternative



139 **140**

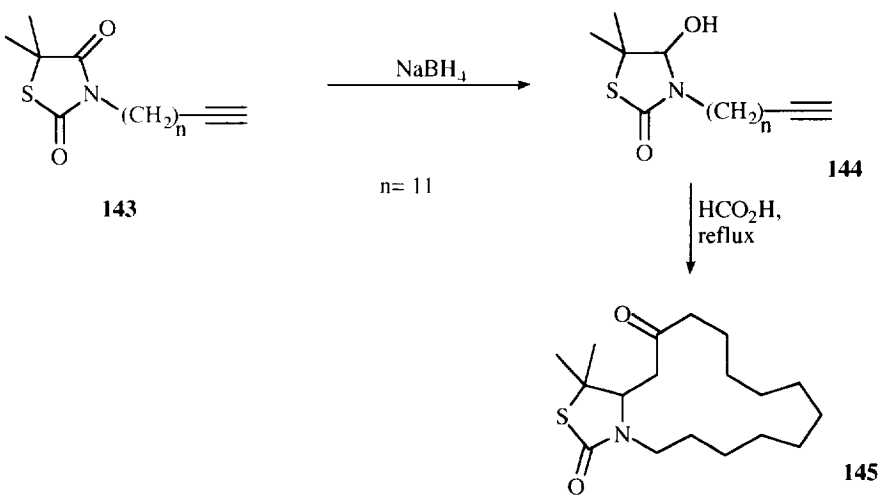
and more direct route using the Tiffeneau-Demjanov rearrangement on an 18-substituted hydroxy aminomethyl grouping (derived from an 18-keto group) also gave the thirteen-membered ring ketone **140**, however, the yields were low (<15%).[115]

The ring-expansion of the eight-, and twelve-membered rings **141**, through a six-membered intermediate, to twelve- and sixteen-membered β-keto ketones has been reported by Hesse.[116]



The replacement of X with a cyano group has also been used, with Triton B as the base, to ring-expand the twelve-membered ketones into fourteen-membered cyano-substituted ketones.[117] This type of ring-expansion process has been extended to [12.6.0] fused bicycles to yield fourteen-membered rings in yields of 60 to 70%.[118] Here the rings are fused at the 1- and 3- positions with a keto group being located in the 2-position and a nitro-group at the 1- or 3- positions. Attack of base on the keto group causes ring expansion by cleavage of the C-C bond toward the nitro group. This ring-expansion process is similar to that described in section 2.4.3 as for structure **90** to **91**.

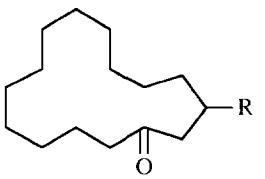
In addition to the aforementioned methods, a fifteen-membered ring containing ketone has been synthesised from the *N*-substituted hydroxyl lactam **144**, obtained by a sodium borohydride reduction of a thiazolidinedione nucleus **143**. Treatment of the hydroxy lactam **144** (n=11) with formic acid at 45°C for 45 hr



yielded the fifteen-membered ring ketone **145**. It was also possible to obtain fifteen-membered ring-containing ketones fused to five-membered lactams by starting with an imide instead of the thiazolidinedione **143**.[119]

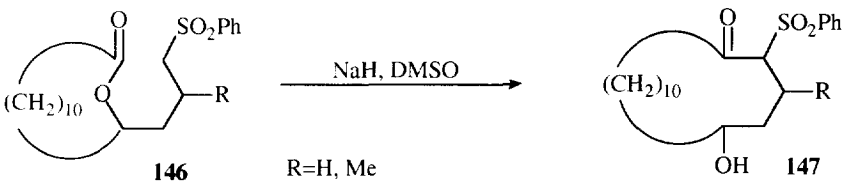
3.2.1 Routes to Exaltone® and muscone by ring-expansion reactions

The large-ring ketones Exaltone® and muscone belonging to the class of macrocyclic musk odorants have received much attention and many synthetic strategies, discussed below, have been developed towards making these molecules.



Exaltone® R=H
muscone R=Me

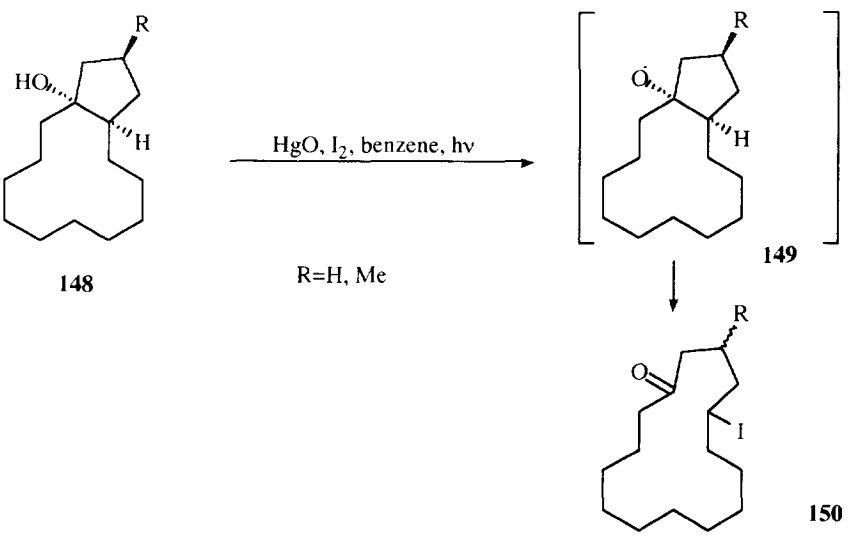
In addition the last few years has seen the publication of the synthesis of (-)-muscone. The routes to Exaltone® and muscone are thus worthy of a small section in their own right. Many examples for the syntheses of these molecules involving variants of the ring-expansion procedure shown below are known: for example the ring-expanded products **147** are converted to Exaltone® (R=H) and (±) muscone (R=Me) respectively by



146 R=H, Me **147**

removal of the phenylsulfonyl (mercury amalgam) and hydroxyl groups.[120]

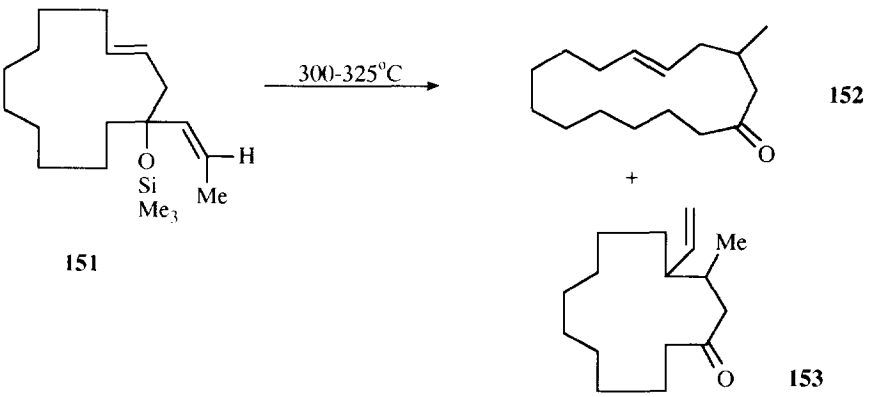
These types of ring-enlargement reactions are not limited, however, to the anionic induced ring-cyclization/expansions discussed above and have been achieved by radical means. For example both Exaltone® and (±)-muscone have been synthesised by the cleavage of the alkoxy radicals **149**, generated by photoirradiation



148 R=H, Me **149** **150**

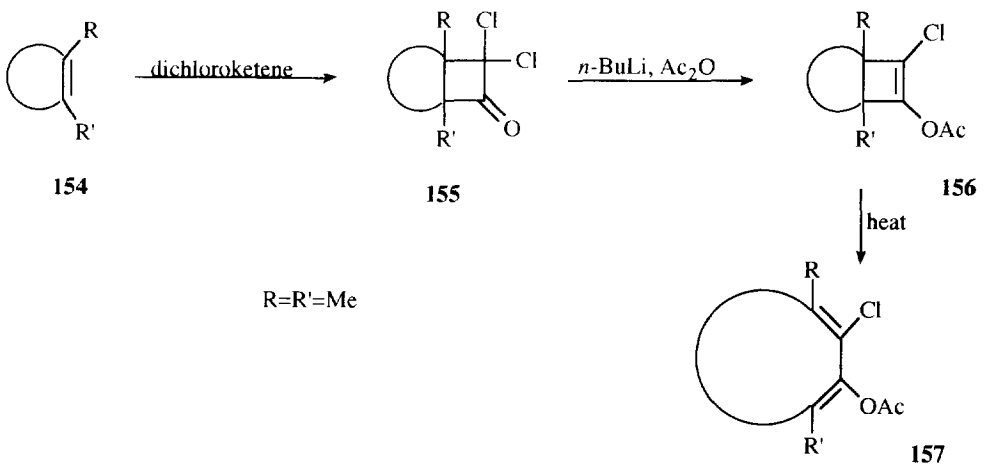
of the cyclic alcohols **148** in the presence of mercuric oxide, iodine and benzene. Photochemical removal of the iodine group was achieved in the presence of tri-*n*-butyltinhydride and AIBN in benzene to give Exaltone® (R=H) and (±)-muscone (R=Me).[121]

Intramolecular oxy-Cope type ring-expansions have been mentioned previously. A similar procedure using trimethylsilylated alcohols has been used to produce (±)-muscone in good yield. Thermal rearrangement of the trimethylsilylated alcohols **151** gave a 2:98 ratio of the 3,3-shift product **153** and the required 1,3-shift (±)-muscone precursor **152**. Compound **152** was converted into (±)-muscone by catalytic hydrogenation of the olefin group over platinum oxide.[122]



151 **152** + **153**

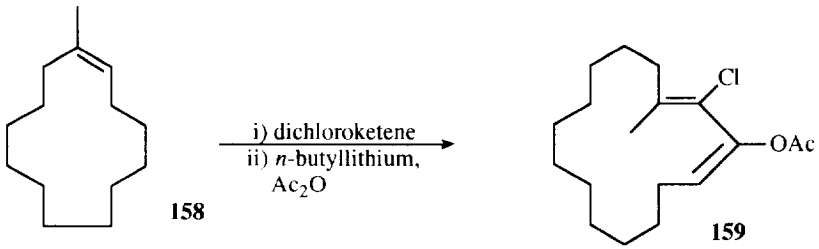
The dichloroketene has been exploited in the synthesis of (±)-muscone. Dichloroketene (prepared *in situ* from trichloroacetyl chloride and triethylamine) readily adds to olefins such as **154** forming the dichlorocyclobutanone adduct **155** as shown below. This may be treated with *n*-butyllithium and acetic anhydride to yield the



154 **155** **156** **157**

chloroacetate **156**, which after heating thermally rearrange to the ring-expanded structure **157**. This procedure has been applied to 1-methylcyclotridecene **158**, using the conditions described above, to give the ring-expanded

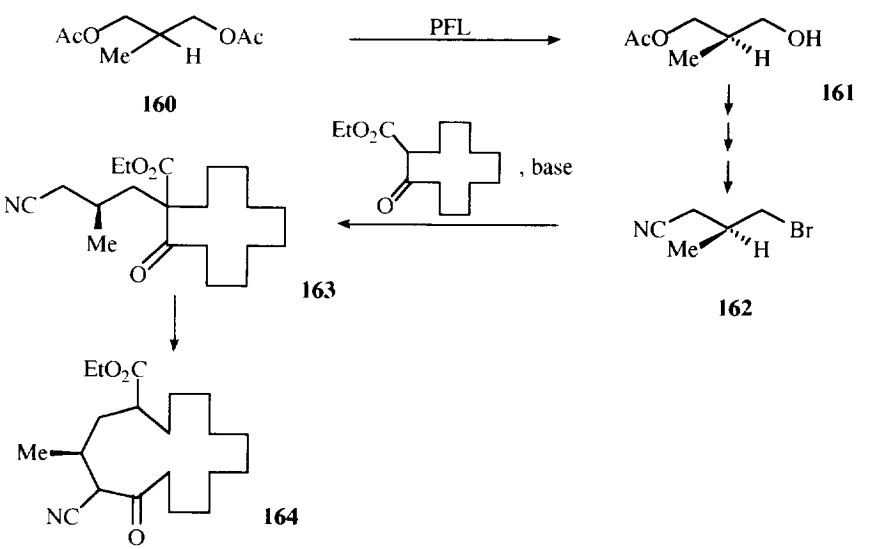
fifteen-membered compound of **159**. The synthesis of (±)-muscone was completed by acidic hydrolysis of the acetate followed by catalytic hydrogenolysis of the chloride with concomitant reduction of the olefin.[123]



158 **159**

In addition to the 3-carbon atom ring-expansion methods previously mentioned for the formation of the fifteen-membered rings Exaltone® and (±)-muscone, a mild anodic oxidative procedure has been reported for the synthesis of Exaltone®.[124] Electrolysis of α,β-unsaturated tosylhydrazones, containing the α,β-unsaturation common to a [10.3.0]bicyclic fused ring system, in solutions of methanol/acetonitrile containing a 1M concentration of a tetraalkylammonium salt (the reaction course was unaffected by the alkyl residue of the ammonium salt, however, a strong dependence on the counter ion was noted; hyperchlorite was the most efficient) yielded cyclopentadec-4-yn-1-one dimethylacetyl. This was converted into the fifteen-membered, acetylene-containing precursor to Exaltone® by acidic hydrolysis of the dimethylacetyl group.

Several reports have appeared in the literature concerned with the synthesis of (-)-muscone.[125-127] Two papers have appeared by Sakai and Xie in which an enzyme (*Pseudomonas fluoroscenslipase*, PFL) catalysed selective hydrolysis of the meso-diacetate **160** to generate a chiral residue **161**, which was incorporated into the muscone structure as follows. Protection of the alcohol **161** with a tetrahydropyran group, nucleophilic displacement of the acetoxy group with NaCN/DMSO followed by removal of the THP protecting group and



160 **161** **162** **163**

164

conversion of the resulting alcohol to a bromide (acetic acid/*N*,*N*'-carbonyldiimidazoleallyl bromide) yielded compound **162**. This was then reacted as shown above to give **163**, which after treatment with base (*t*-BuOK/DMSO) to remove the proton α- to the cyano group, allowed ring-formation/expansion to a (-)-muscone precursor. The synthesis of (-)-muscone was then completed by removal of the cyano and carboethoxy groups.[125,126]

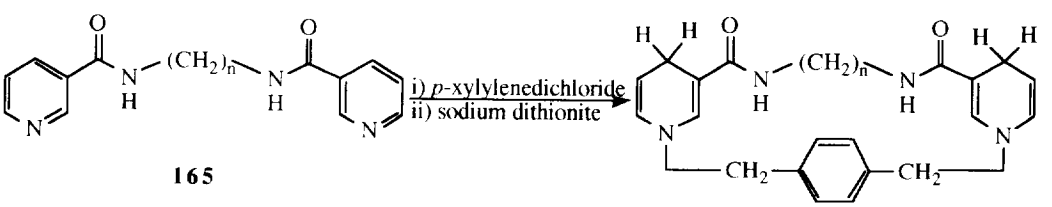
A further and shorter free radical approach to the synthesis of (-)-muscone has been reported by Dowd.[127] As above the cyano-group of **163** is replaced with an iodide, however, the ethoxycarbonyl group is absent. A free radical is generated from the iodide ($Ph_3SnCl/NaBH_3CN$/di-*t*-butylperoxide) which after cyclization/ring-expansion yields directly (-)-muscone in 15% yield.

4. The syntheses of lactams

Large-ring lactams possess a wide range of biological and physical properties. The biological properties encompass hypertensive, anti-viral and anti-tumour, whilst the physical properties include the ability to form inclusion complexes with neutral molecules and act both as redox catalysts and metalloenzymes. Consequently large-ring lactams have received considerable synthetic attention.

4.1 Direct and tin-mediated cyclizations

Several methods of synthesising lactams by direct cyclization have been reported and are described in the following section. In particular a direct base catalysed cyclization of bisnicotinamides) (n=4) **165** with *o*-, *m*- or *p*-$C_6H_4(CH_2Cl)_2$ (illustrated for *p*-xylylenedichloride) yields, after reduction of the *bis*-quaternary nicotinamide with sodium dithionite, the *bis*(1,4-dihydronicotinamides) **166**. Depending on which xylylenedihalide is used lactams containing eighteen- to twenty six-members were formed.[128] In addition to the properties mentioned earlier these ring structures find use in monolayer-bound metal complexes and semiconductors.



165

n=4,6,8,10

166

Other large-ring lactams, in which the final structure is not so rigid have also been synthesised by direct cyclization. Twelve- to fourteen-membered trilactams as potential CCK-B antagonists have been synthesised *via* a DPPA (diphenylphosphoryl azide)/$NaHCO_3$ mediated lactamization of α,ω-aminocarboxylic acids.[129]

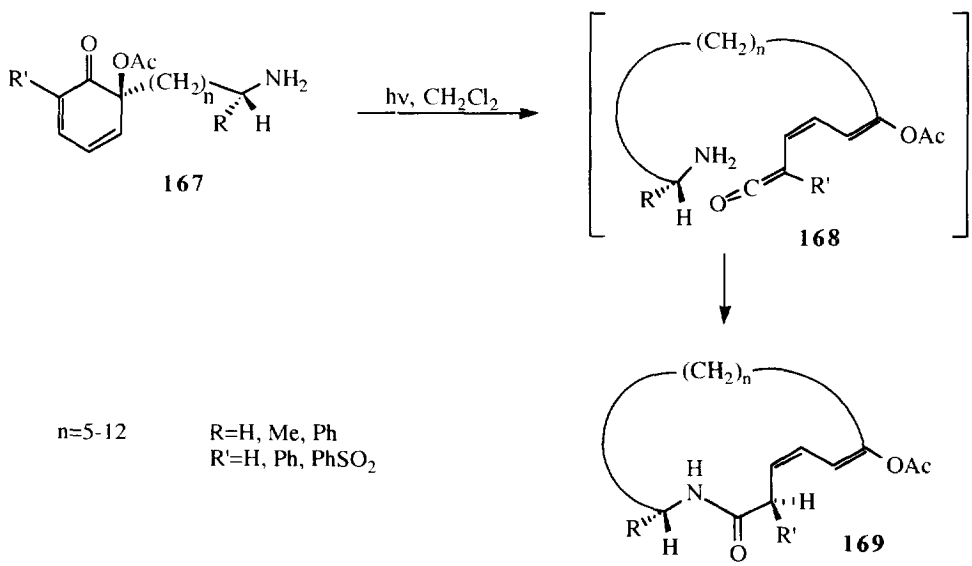
The cyclization of ω-azidocarboxylic acids has been achieved by the activation of the carboxylic acid group by a mixed anhydride method (2,4,6-trichlorobenzoyl), to give thirteen- and fourteen-membered lactams in 61 and

82% yields respectively.[130] This cyclization procedure has the additional advantage that whilst amino acids, which are often zwitterionic, are not soluble in many organic solvents the azido forms are.

Lactams containing thirty three- to thirty seven- members and four amide groups have been formed under relatively high concentrations (10^{-3}M) directly by mixing and heating the appropriate α,ω-diamines and α,ω-diacids.[131] No activation of the acid groups were required in this case.

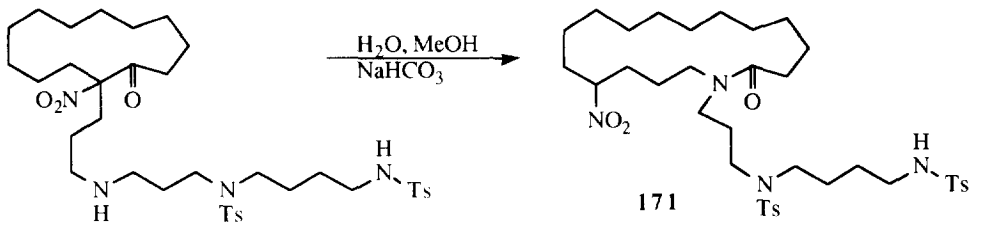
4.1.1 Photolactamization

Large-ring lactams have been synthesised by a photochemical rearrangement. Irradiation of the *ortho*-quinol acetates **167** at λ>340nm in dichloromethane yields, *via* the ring-cleaved ketene intermediate **168**, thirteen- to twenty-membered *cis*- and *trans*- olefin-containing lactams **169**.[132]



4.2 Lactams and aminolactams by ring-expansion methods

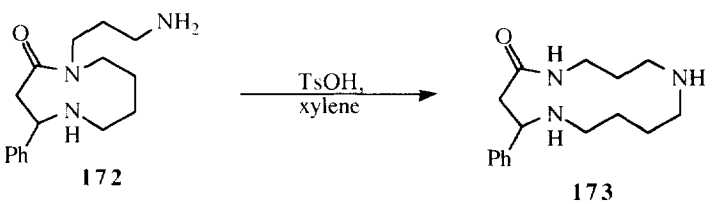
One of the most common methods of forming large-ring lactams is the ring-expansion of 2-nitro-cycloalkanones substituted in the 2-position with a nucleophilic group at the end of a short chain. This is exemplified below, where the thirteen-membered ring **170** containing a nucleophilic secondary amine group ring-expands under very mild conditions (H_2O/MeOH/$NaHCO_3$) to the seventeen-membered lactam **171**. This ring-expanded product was later converted into desoxo-indandenine, a reduction product of the main alkaloids isolated from *Onci-notis inandensis*.[133]



170 **171**

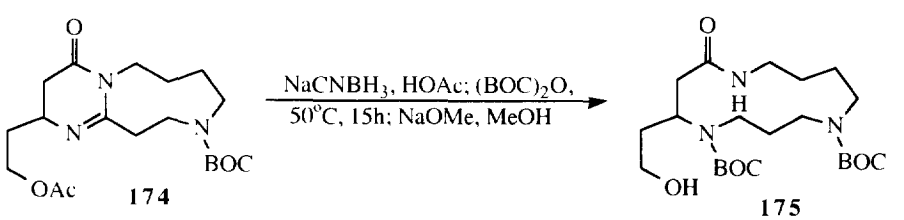
The ring-expansion of similarly substituted eight- and twelve-membered 2-nitro-cycloalkanones has also been found to give twelve- and sixteen-membered ring lactams respectively.[134,135] Similar ring-expansion strategies were used for the synthesis of the seventeen-membered spermidine alkaloid (±)-oncinotine.[136]

Further to these methods, the formation of large-ring lactams has been achieved by the translactamization of smaller sized lactams. For example, treatment of a thirteen-membered lactam, containing an *N*-3-aminopropyl chain, with tosic acid in xylene ring-expanded to a seventeen-membered amine-containing lactam.[137] Similarly, treatment of the nine-membered ring system **172** with tosic acid in xylene gave the ring-expanded thirteen-membered system **173**, which after acetylation of the *N*(1) amino-group with acetic anhydride in pyridine yielded the spermidine alkaloid (±)-*N*(1)-acetyl-*N*(1)-deoxymayfoline.[138]



172 **173**

In addition to the ring-expansion of the monocyclic systems described above the cleavage of bonds common to medium-fused-rings has been affected to yield large-ring lactams. Treatment of the [7.4.0] fused bicyclic system **174** with sodium cyanoborohydride in acetic acid cleaved the central carbon-nitrogen single bond to give



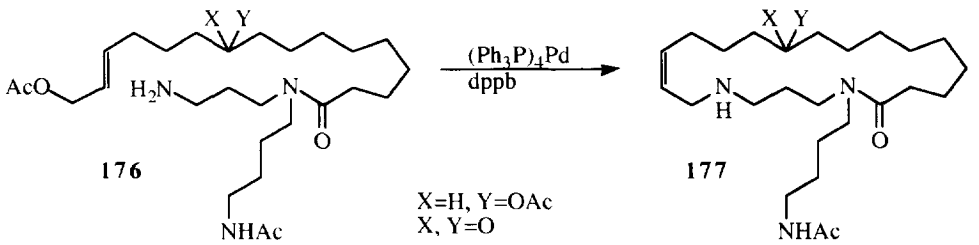
174 **175**

the thirteen-membered lactam **175**. After further synthetic modification this was converted to (±)-anhydrocannabisativine.[139] Similarly this ring-cleavage procedure has been used in the total synthesis of (±)-cannabisativine[140] and again, with further modification, (±)-anhydrocannabisativine.[141]

The synthesis and conformational behaviour of twelve-, fifteen- and sixteen-membered lactams have been extensively studied in a series of papers by Ollis, Stoddart and coworkers.[142-147]

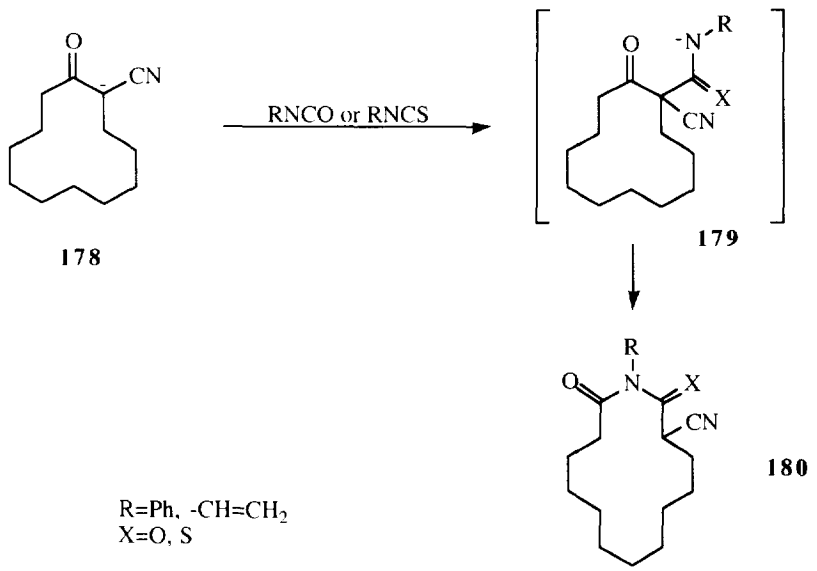
4.3 Syntheses of ketolactams

There are a few reported methods in the literature for the direct synthesis of lactams containing a keto group. However, the direct cyclization of the structures **176** (X=H, Y=OAc or X=Y=O) has been achieved in the presence of 10mol% $(Ph_3P)_4Pd$ and 12mol% of 1,4-*bis*(diphenylphosphino)butane (dppb) to give the twenty one-membered keto lactams[148] **177**.



4.4 Routes to imides

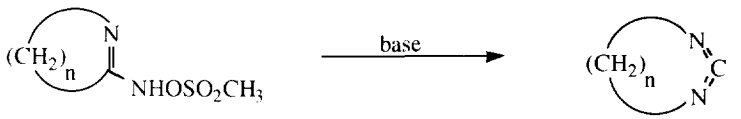
Large imide-containing rings have been synthesised by several procedures. One example involved treatment of the twelve-membered ring anion **178** with variously substituted isocyanates or isothiocyanates to give, *via* cyclization/ring-expansion of the intermediate **179**, the fourteen-membered imide or thioimide-containing rings **180**.[149]



This procedure has been extended to produce ten- and fourteen-membered unsubstituted imide-containing rings. Ring-expansion for these systems is affected as previously described but with R=allyl. The allyl group is removed in the last step of the synthesis with $Pd(PPh_3)_4/NEt_3/HCO_2H$ in dioxan, adding some versatility to these

syntheses in that the large imide-containing ring may be further modified by reaction at the nitrogen atom of the imide.[150]

The synthesis of large cyclic carbodiimides has been achieved by a Tiemann rearrangement of cyclic amidoxime *O*-methanesulfonates **181**. Treatment of the cyclic amidoxime *O*-methanesulfonates with base (potassium *t*-butoxide in 1,2-dimethoxyethane) at room temperature yielded the thirteen- and fourteen-membered ring carbodiimides **182** in 24 and 87% respectively.[151]



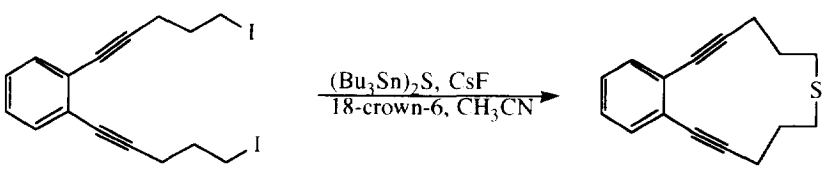
181 **182**

5. The syntheses of sulfur, oxygen, nitrogen and phosphorus-containing rings

5.1 Syntheses of sulfur-containing rings

Large sulfur-containing rings[152] are found in many human and mammalian biological systems, for example current interest is centered on the fifteen-membered thiolactone, plasma protease inhibitor α2-macroglobulin (α2M).[153,154] A review on cyclic sulfides in organic synthesis, containing a small section on large-rings, was published in 1982 by Vedejs and Kraft.[155]

A number of methods for the direct cyclization of large sulfur-containing rings have been reported.[156,157] In particular, as mentioned previously, when the two cyclizing end-groups are held close together, ring-formation can be achieved in good yields. This has been achieved for the 1,2-diacetylene substituted benzene analogue **183** to give the thirteen-membered ring **184** in 86% yield.[158]

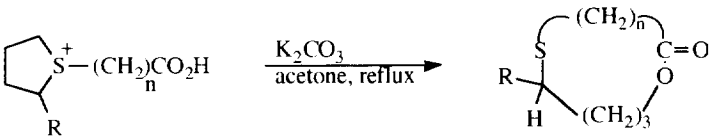


183 **184**

The direct cyclization of simple α,ω-dibromoalkanes has been achieved by treating these with hexamethyldisilathiane (HMDST) and two equivalents of methyllithium to give large-ring sulfides (a 31% yield of thiocyclotridecane was obtained from 1,12-dibromododecane using the conditions described above). This procedure was extended, by the use of HMDST/LiEt3BH as the cyclizing reagents, to the cyclization of α-bromo-

ω-acid chlorides to yield twelve- to seventeen-membered thiolactones in yields of 19 to 64%.[159] The direct cyclization of other simple α,ω-difunctionalized systems to give disulfides has been achieved, for example 1,7-dibromo-2-heptanone (2 equivalents) in the presence of sodium hydrogensulfide yields 1,9-dithia-3,15-cyclohexadecandione.[160]

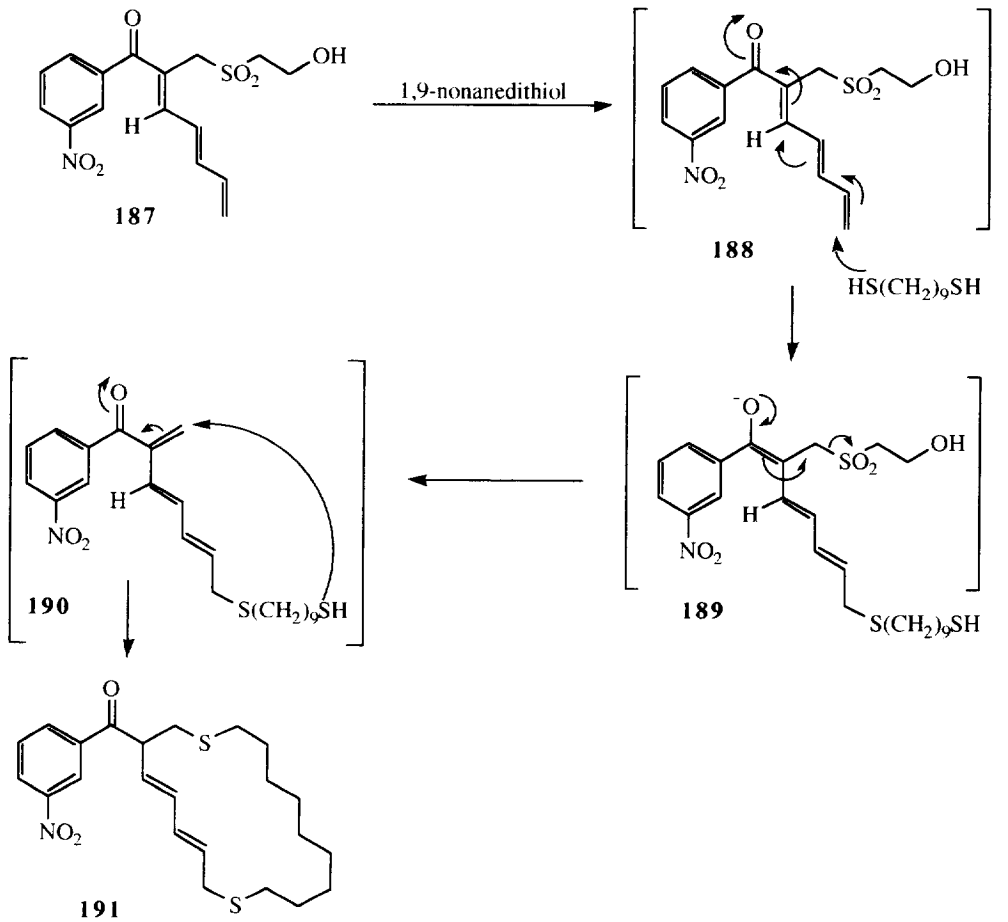
Some methods for the formation of sulfur-containing lactones are reported and described below. Treatment of the ω-carboxyalkylsulfonium salts **185** under the mildly basic conditions of potassium carbonate in acetone yielded, *via* attack of the resultant carboxylate anion on the unsubstituted α-carbon atom of the five-membered ring, seventeen- to twenty-membered sulfur-containing lactones **186** in excellent yields (72-86%).[161]



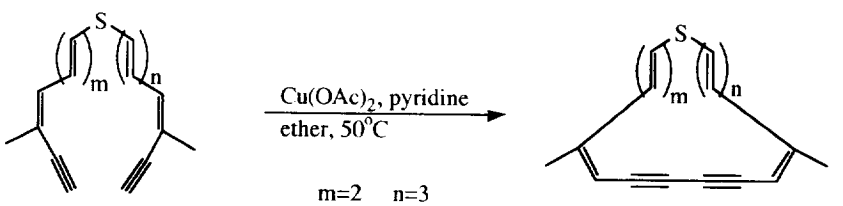
185 R=H, Me n=10-13 **186**

This procedure was extended and modified by replacing the five-membered ring with S(Ph)Et or S(Ph)(*iso*-propyl) groups, however, in these cases nucleophilic attack of the carboxylate anion α- to the sulfonate was on the alkyl chain carrying the carboxylate, thus yielding lactones. Further extension of this methodology to compounds which have a chiral carbon atom at the position mentioned above allowed the synthesis of chiral thirteen-membered rings as demonstrated for ricinelaidic acid lactone (optical purity 66%).[162]

A very elegant procedure involving a Michael addition has been used to construct large rings containing two sulfur atoms. Treatment of **187** with 1,9-nonanedithiol yields *via* a 1,8-Michael addition intermediate **188**, which after elimination of the 2-hydroxethylsulfone group and further Michael addition to the newly generated α,β-unsaturated keto structure **190** gives the eighteen-membered bis-sulfide-containing ring structure **191**. Double Michael addition of other α,ω-bis-sulfides HS-$(CH_2)_n$-SH with n=5,6 and 9 were achieved to give twelve-, thirteen- and sixteen-membered bis-sulfide-containing ring structures.[163] In addition α,ω-bis-sulfides containing -CH_2OCH_2- and -CHOH-CHOH- (*erythro* and *threo*) groups have been used in these syntheses adding some versatility to this synthetic procedure. Two consecutive Michael additions are not always observed as displacement of the sulfone (or other leaving group) sometimes occurs. The ring-forming process is dependent on the attacking nucleophile and the double bond activating and leaving groups, however, the end product remains the same. These molecules have found use as molecular 'yardsticks' being able to cross-link the sulfur atoms of protein structures.[163]



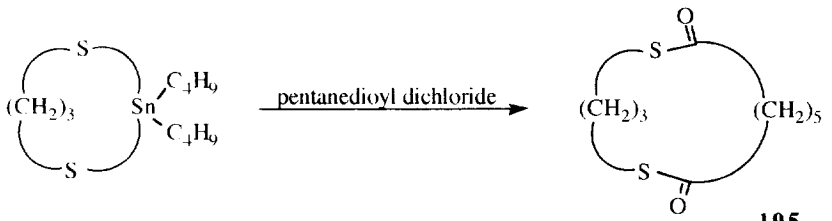
Metal ions have also found use in the construction of large sulfur-containing rings. Ring-cyclization of the terminal acetylene groups of compound **192** with anhydrous copper(II)acetate in pyridine/ether at 50°C gave the dimethyltetradehydrothia-[19]-, -[21]-, -[23]- and -[25]-annulenes **193**.[164]



192 **193**

Tin has also been exploited in the construction of large sulfur-containing rings. Reaction of dibutyltin dichloride with 1,3-propanedithiol led to the cyclic structure **194**. Treatment of this with pentanedioyl dichloride

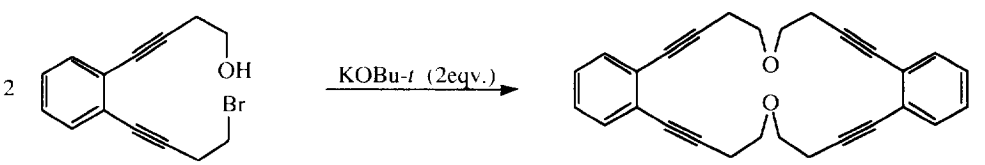
gave the twelve-membered dithiolactone **195** in 48% yield. Reasonable yields of eighteen- to twenty four-membered tetrathiolactones were also obtained under the above mentioned reaction conditions.[165]



194 **195**

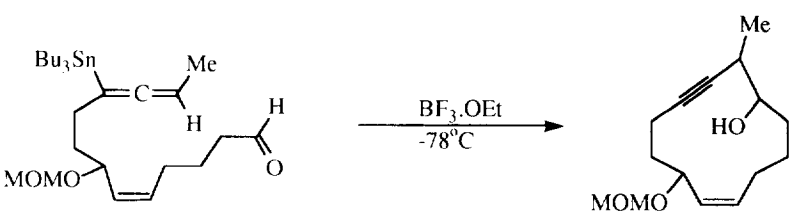
5.2 Large-ring ethers

As mentioned in the previous section on sulfur-containing rings, large-rings containing oxygen can also be made when the cyclizing end-groups are held closer together, on average, than the situation present in a straight chain. This type of conformational restriction has been used in the ring-cyclization of 2,7-difunctionalized naphthalene derivatives. The 2- and 7-hydroxyl groups of 2,7-dihydroxynaphthalene have been alkylated with 4-bromobutyrate to give the diester which after transformation of the ester groups to acid chlorides and reaction with 2,6-diaminopyridine gave twenty-membered oxygen-containing rings.[166] Similarly, the closer proximity of the cyclizing end-groups in 1,2-acetylene disubstituted benzene systems has been employed. Here, due to the linear nature of the acetylene groups, the resulting ends, for short chain lengths, are initially forced apart. Thus, treatment of the system **196** below with base not only leads to the ten-membered cyclic ether but also to the twenty-membered oxygen-containing dimeric ring **197**.[167]



196 **197**

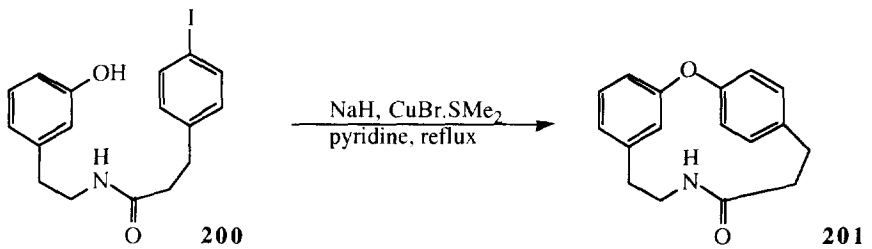
Several reports on the syntheses of twelve- and fourteen-membered 2,5-furano macrocyclic compounds which form the framework of the diterpenes pukalide, laphotoxin and the kallolides, isolated from marine natural



198 **199**

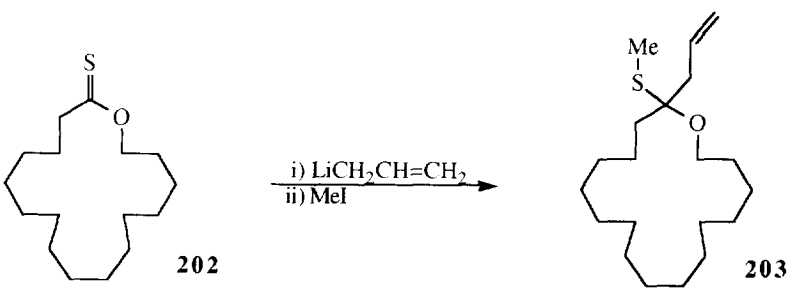
products, have appeared in the literature and are described below. The key ring-cyclizing step in the syntheses of these molecules is the boron trifluoride etherate catalysed reaction of the allenylstannyl and aldehyde end groups **198** to give the homopropargylic alcohol **199** in yields of 90%.[168] The furan ring is incorporated into the final ring structures by oxidation of the hydroxyl group to a ketone followed by treatment with $AgNO_3/CaCO_3$ and heating. This ring-cyclization procedure has been used in the construction of a number of other 2,5-furano macrocyclic compounds.[169]

Other natural products such as bouvardin, a fourteen-membered, ether-containing, potent, antitumour compound, have been synthesised by direct-cyclization. The important diarylether linkage was generated by a $CuBr.SMe_2$ catalysed intramolecular Ullmann condensation of **200** to give **201** in 58% yield.[170,171] More recently the total synthesis of bouvardin, *O*-methylbouvardin and *O*-methyl-N^9-desmethylbouvardin have been reported.[172]



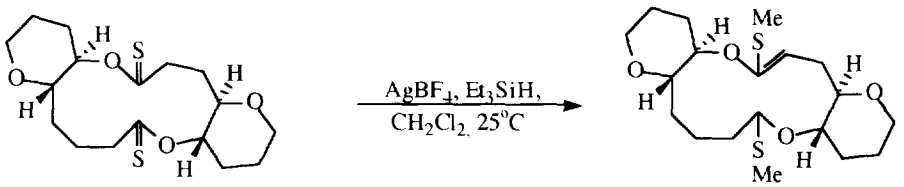
200 **201**

The syntheses of large-ring ethers has indirectly been achieved by the transformation of initially synthesised large-ring thiolactones. For example, treatment of the seventeen-membered thiolactone **202** with allyl lithium followed by iodomethane gave the compound **203** in 81% yield. Removal of the thiomethyl group with Ph_3SnH-AIBN yielded a seventeen-membered cyclic ether in 85% yield.[173]



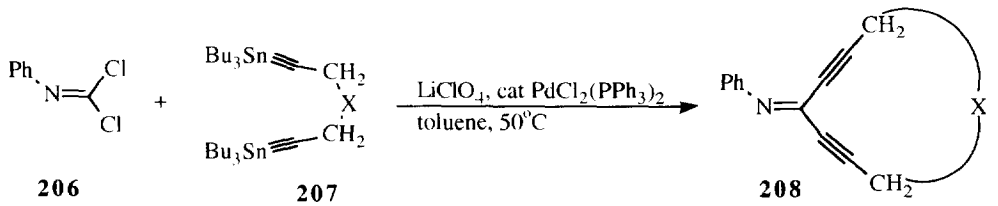
202 **203**

In addition, treatment of the fused-oxopolycyclic system **204** below, reported by Nicolaou,[174] with $AgBF_4$ gave the thirteen-membered ring structure **205**. In fact this was an undesired by-product, however, it was obtained in 44% yield. Similarly treatment of the twelve- and fourteen-membered bis-thiolactones, related to **204**, gave the corresponding twelve- and fourteen-membered structures related to **205** in 45 and 27% yield respectively. The yield for the conversion of the thirteen-membered thiolactone was only 10% and is therefore not considered to be a useful synthetic process. The thiomethyl group in **205** could then, theorectically, be removed as previously described for **203**, after reduction of the double bond.



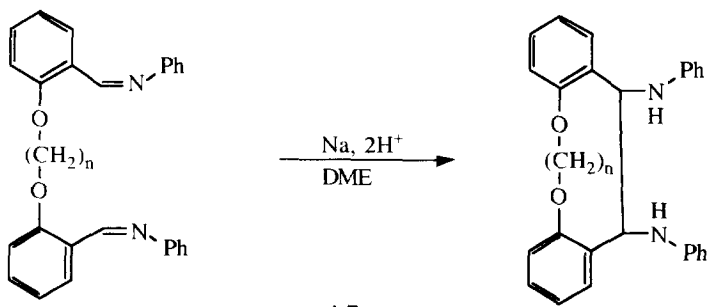
204 **205**

The use of metals, such as palladium, has also been exploited in the construction of large oxygen-containing rings. Treatment of the phenyl-substituted isocyanide dichlorides **206** with bifunctional alkyltin compounds in the presence of $PdCl_2(PPh_3)_2$ gave rings, varying in size, from twelve- to twenty- members in yields ranging from 17 to 52%. The groups X were typically $-O(CH_2)_nO-$ with n=3-6,8 and 10, and $-O(CH_2CH_2O)_m-$, with m=2 and 3 together with some 1,2-dioxyaryl moieties.[175]



206 **207** **208**

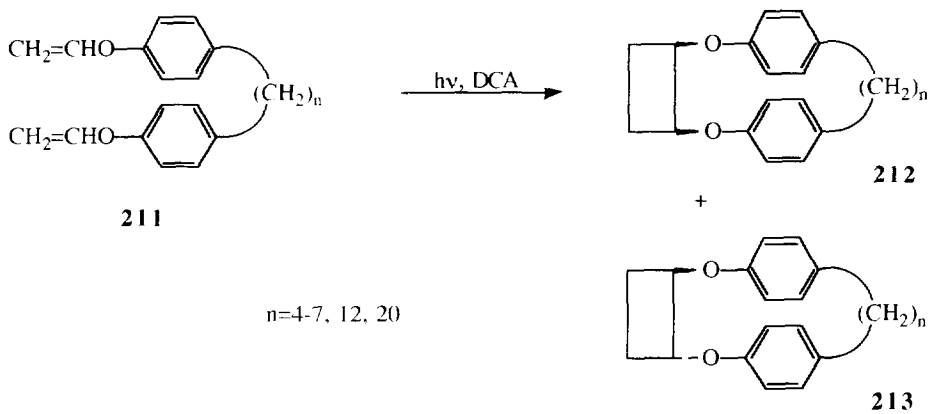
Other methods have been used to synthesise large- ether-containing rings. Reduction of the bis-Schiff's base **209** with sodium gave the twelve- to fifteen-membered rings **210**. The same procedure was used on structural variants of the below system, in which the position of the carbon and nitrogen atoms of the imine were reversed, to give twelve- to sixteen-membered ring systems additionally containing two nitrogen atoms in the ring.[176]



209 n=4-7 **210**

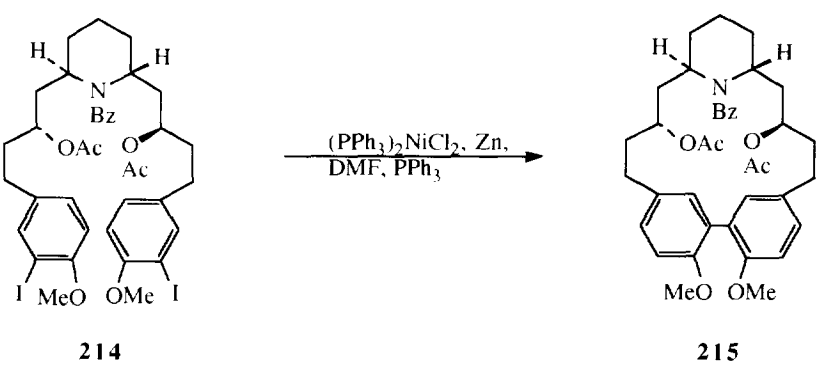
Photochemical methods have also been used. Irradiation of the α,ω-bis(4-vinyloxyphenyl)alkanes **211** for 30mins, with a high-pressure mercury lamp through a Pyrex filter, in the presence of an electron acceptor (9,10-

dicyanoanthracene (DCA)) yielded a mixture of the *cis*- and *trans*-cycloadducts **212** and **213** in combined yields of typically 60%.[177]

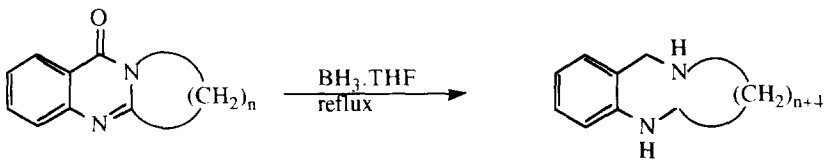


5.3 Cyclizations to amines

There are few reports in the literature, regarding methods using direct cyclization, for the syntheses of large nitrogen-containing rings. However, the use of nickel has been exploited in the ring closure of **214** to **215**, which is a precursor to the seventeen-membered ring epimer of (±)-lythranidine an alkaloid isolated from the Lythraceae family of plants.[178]

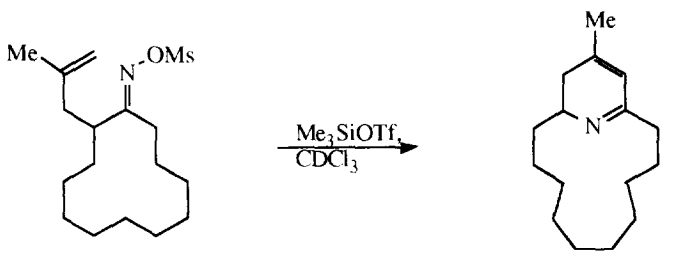


Ring systems containing more than one nitrogen atom are potentially useful because of their ability to act as ligands and in some cases mimic enzymic functions. Systems containing two nitrogen atoms have been synthesised by treatment of the structures **216** with a BH3.THF complex to give the thirteen- to nineteen-membered rings **217**.[179] Systems containing four nitrogen atoms in a seventeen-membered ring have also been synthesised using a similiar procedure.[180]



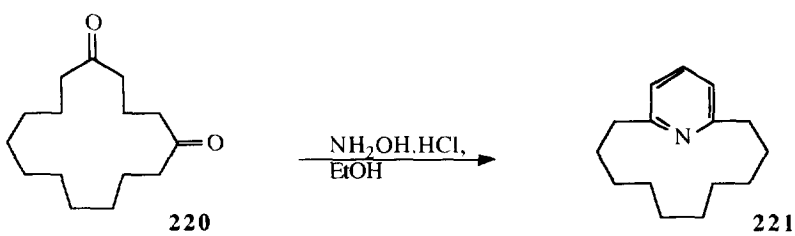
216 n=7-9, 13 **217**

The formation of the thirteen-membered nitrogen-containing rings **219** has been reported using two similar procedures. Firstly by a trimethylsilyl trifluoromethanesulfonate catalysed Beckmann rearrangement of the olefinic oxime mesylates[181] **218** to give the dihydropyridine variant **219** and secondly *via* a diethyl aluminium chloride catalysed Beckmann rearrangement of the same olefinic oxime mesylate to give, after reduction with DIBAH, the tetrahydropyridine analogue of **219**.[182]



218 **219**

Finally indirect methods have been used to construct large nitrogen-containing rings. For example treatment of the fifteen-membered 1,5-diketo-containing ring **220** with hydroxylamine hydrochloride in ethanol yields the thirteen-membered pyridine-containing structure **221**.[183]



220 **221**

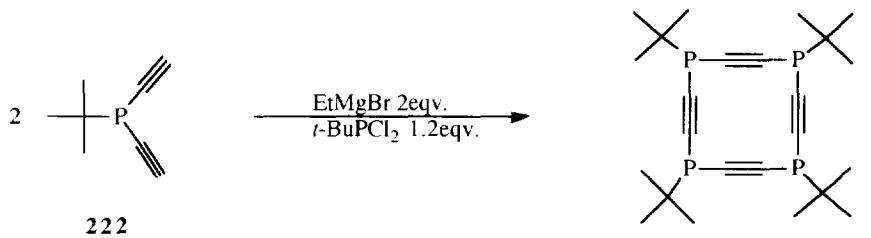
The synthesis and conformation (by single crystal X-ray analysis) of a thirteen-membered saturated quarternary nitrogen-containing ring has been reported.[184]

5.4 Routes to phosphorus-containing rings

A few methods for the preparation of large phosphorus-containing rings have been reported and are discussed here. A condensation between oxo- or thiophosphodihydrazides [RP(Y)(NCH3NH2)2 with R=Ph, C6H5O, N(CH3)2 and Y=O, S] and 1,3-dialdehydes such as 2,5-furanodicarboxaldehyde, 2,6-pyridinecarboxaldehyde or

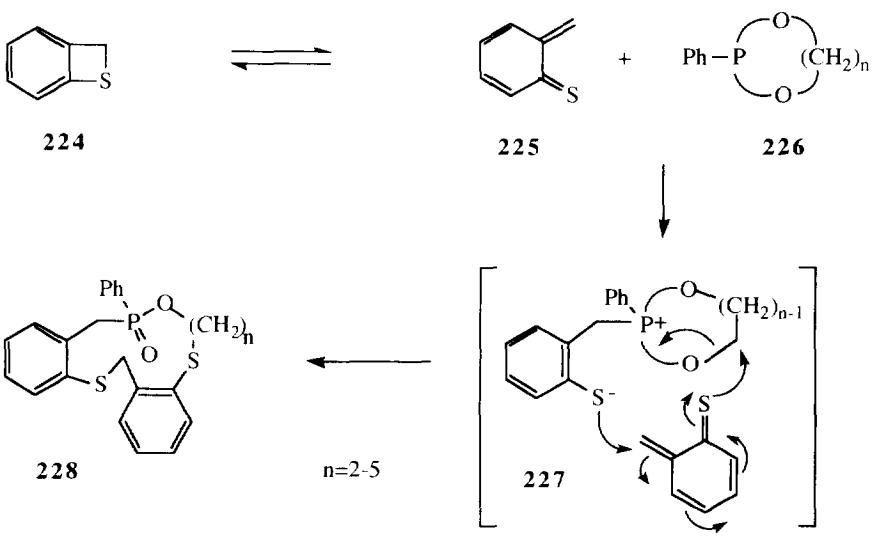
1,3-benzenedicarboxaldehyde has been used to give eighteen-, twenty-, twenty two- and thirty-membered rings in yields as high as 90%.[185]

A twelve-membered ring containing alternating phosphorus and acetylene units has been synthesised by treatment of the diacetylene system **222** in the presence of ethylmagnesium bromide (2 eqvs.) with *tert*-butylphosphorous dichloride (1.2 eqvs) to give **223** in 11% yield.[186]



222 **223**

A ring-expansion method yielding twelve- to fifteen-membered rings has been reported. Benzothiete **224** in refluxing toluene forms the open structure **225** which can undergo Michael-type additions. Nucleophilic addition of the phosphorus-containing compound **226** yields **227** which after a second Michael addition with benzothiete yields the ring structures **228**.[187]



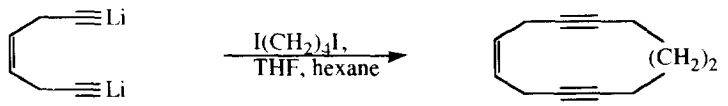
224 **225** **226**

228 **227**

6. Carbocycles

6.1 Unsaturated carbocycles by end-to-end cyclization

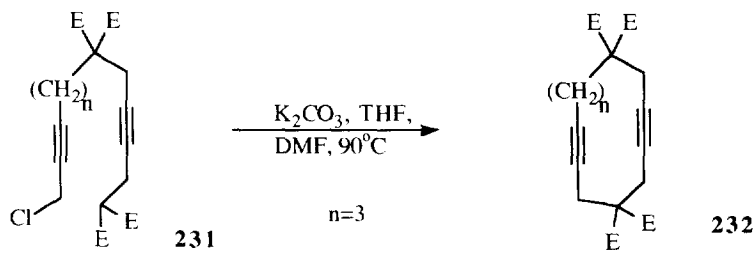
It has already been mentioned that the direct cyclization to large-rings can be achieved in good yields if conformational restrictions within the molecule hold the reacting end-groups closer together than the situation present in a simple straight chain. This has been achieved by reaction of the dianion of *Z*-4-octene-1,7-diyne **229** with 1,4-diiodobutane to give cyclododeca-4-ene-1,7-diyne **230**.[188]



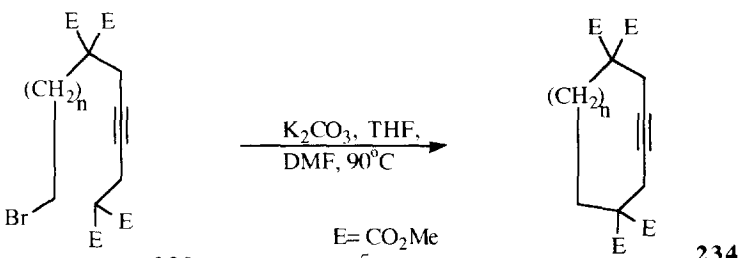
229 **230**

This cyclization reaction was also achieved with *bis*-geminal methylene alkyldiacetylides in place of the Z-alkenes above[188,189], and also with 1,2-disubstituted benzene derivatives.[189]

Similarly the conformational restrictions imposed by acetylene groups have been used in a direct cyclization to form twelve-membered mono- **234** or diacetylene-containing rings **232**.[190] This procedure was extended to include thirteen- and fourteen-membered mono- and diacetylene containing rings[191] and also to thirteen- and fourteen-membered ring systems containing *cis*- and *trans*-olefin groups in place of the acetylenes.[192]



231 **232**



233 **234**

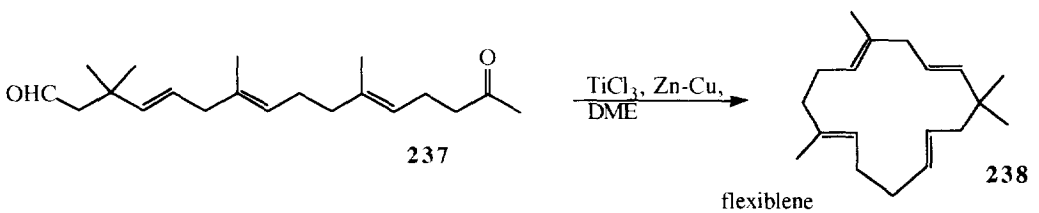
Other systems also give large-rings by direct cyclization. Treatment of **235** with *n*-butyllithium in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane) gave the twelve-membered ring system **236** which is a precursor to (±)-cubitene, a macrocyclic terpenoid compound of the defence system of termites.[193]

235 **236**

6.1.1 Metal-mediated end-to-end cyclizations

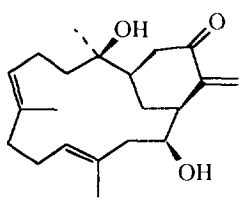
6.1.1.1 Titanium

The use of low-valent titanium in the coupling of carbonyl groups is well known and has been reviewed by McMurry.[194] Here the treatment of aldehydes, ketones or mixtures thereof with titanium trichloride and a zinc-copper couple yields alkenes in good yields. Many variations on the reagents used in conjunction with the titanium trichloride have been reported.[195] As mentioned earlier this methodology has been extended to the coupling between ketones and esters to give large-ring ketones in good yield. This coupling have been applied to the synthesis of several unsaturated carbocyclic large-ring systems. A titanium trichloride, Zn-Cu couple together with 1,14-dododecanedial or 1,14-dodecane(dimethylketone) gave respectively cyclotetradecene in 80% yield and 1,2-dimethylcyclotetradecene[196] in 82% yield. Extension of the latter system to include alkyl groups other than methyl *i.e.* dodec-11-en-1-yl has been reported.[197] The McMurry coupling has also been exploited in the intermediate steps to a number of natural products. For example flexiblene, **238** a naturally occurring fifteen-membered ring diterpene, isolated in 1976 from the soft coral *Sinularia flexibilis*, was obtained by a titanium trichloride induced coupling of the aldehydoketone **237** in good yield.[198,199] Similarly syntheses of the intermediates to the fourteen-membered antitumour cembrane lactones (±)-crassin **239** and (±)-isolobophytolide **240** have been achieved by a titanium-induced carbonyl coupling of the appropriate aldehydo ketones.[200]

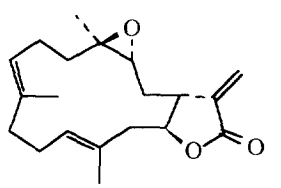


237 **238**

flexiblene



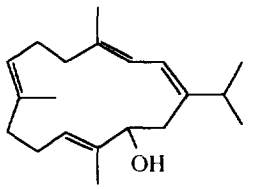
crassin



isolobophytolide

239 **240**

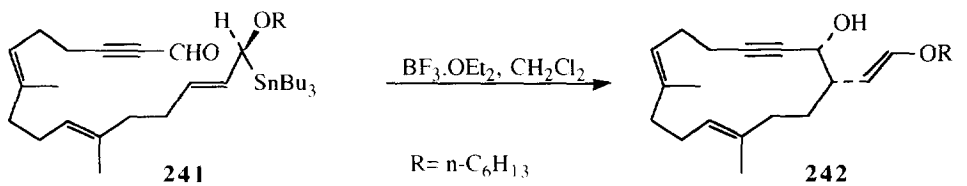
In addition to these systems the synthesis of a precursor to (±)-isosarcophytol-A below, a cembrane alcohol isolated from the Australian soft coral (*Nephthea brassica*) in 1982, has been achieved using a McMurry coupling.[201]



(±)-isosarcophytol-A

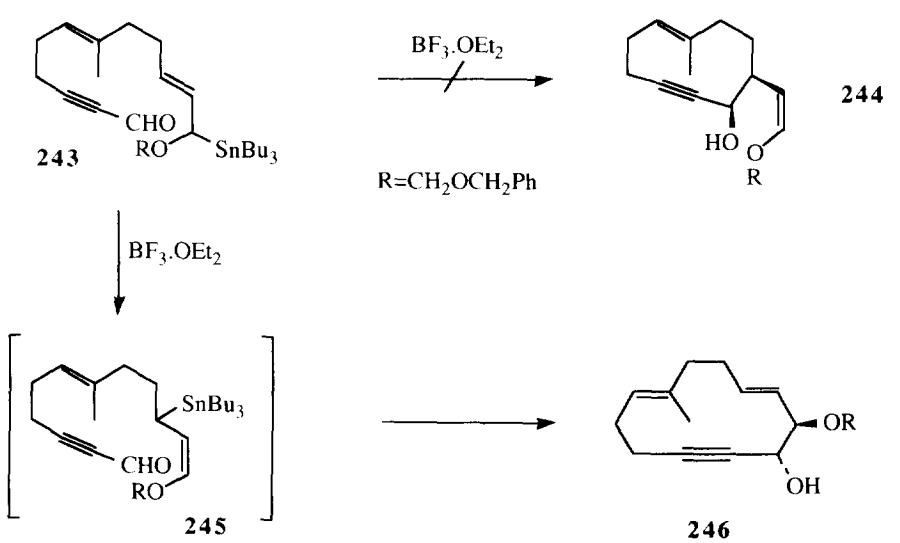
6.1.1.2 Boron

The use of boron particularly as its trifluoroetherate has been exploited in the direct-cyclization of α-aldehydo-ω-allylstannanes to large-ring containing systems. The synthesis of the fourteen-membered system **242**, as a homochiral cembranolide precursor, was achieved in 88% yield *via* treatment of **241** with boron trifluoride etherate in dichloromethane.[202]



241 **242**

Addition of the α-(alkoxy)allyl stannane and ω-acetylenic aldehyde groups of **243** does not always occur as expected. For example treatment of the system **243** with boron trifluoride etherate did not give the expected ten-membered system **244** but instead after a 1,3-shift of the tri-*n*-butyltin group to **245** gave the twelve-membered system **246**. This is explained by the fact that the alkoxy stannane **243** is not sterically disposed to undergo cyclization to **244** and thus instead undergoes a 1,3-shift to **245** before cyclization to **246**. In addition starting with non-racemic alkoxy stannane **243** allowed the isolation of optically active **246** indicating the 1,3-shift of tri-*n*-butyltin must occur stereospecifically. This methodology thus allows the synthesis of optically active large-ring systems.[203]

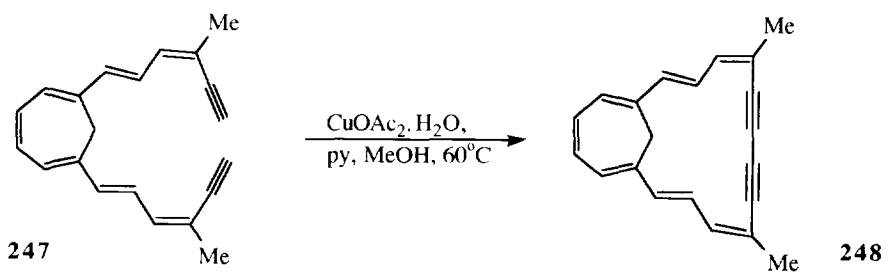


243 **245** **246**

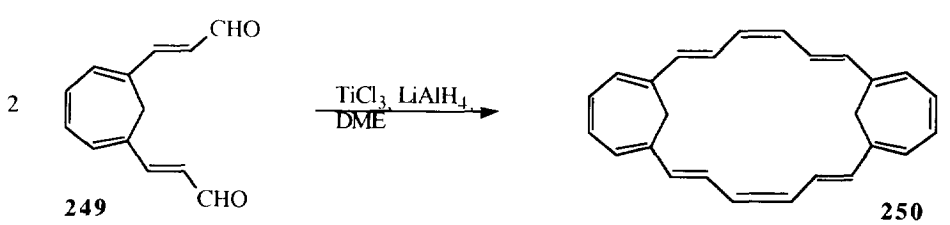
Dicyclohexylboranes have been used by Oppolzer in the cyclization of α,ω-acetylenic aldehydes to give fifteen-membered *E*-olefinic and hydroxyl-containing ring structures. By additionally performing this ring-cyclization in the presence of diethyl zinc, which acts as a transmetalating agent, and 1mol% of (-)-3-exo-(dimethylamino)*iso*borneol (DAIB), which largely controls the π-facial addition of the resulting 1-alkenyl moiety to the aldehyde the synthesis of the corresponding chiral ring structure is achieved.[204] This chiral structure was, after two further synthetic reactions, converted into (*R*)-muscone previously discussed.

6.1.1.3 Copper

The use of copper(II)acetate in the coupling of terminal acetylene groups to give large-ring sulfides has already been mentioned. Its use as a monohydrate in pyridine-methanol under high dilution conditions with diethylether as the entraining solvent has also been exploited in the ring-closure of the unsaturated diacetylene compound **247** to methano-[18]-annulene **248** and similar systems to methano-[20]-, -[22]- and -[24]-annulenes.[205] Similarly methano-bridged tetradehydro-[26]-, -[28]-, -[30]-, -[32]-, -[34]- and -[38]-annulenes have been synthesised.[206] In addition to these the syntheses of the methano-bridged tetrahydro-[36]-annulene[207] and the unusual -[20]-annuledione[208] have been synthesised by similar procedures.

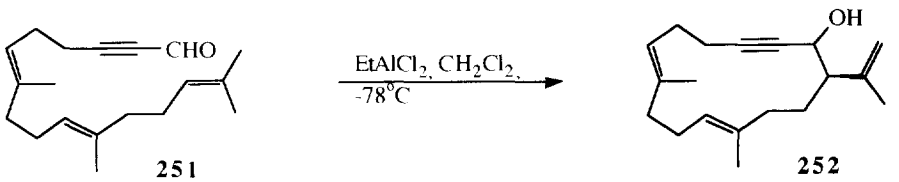


Although **250** was obtained by a McMurry-type coupling of **249** shown below it seemed appropriate to mention this ring-cyclization procedure here due to the similarity in structure to the compounds mentioned immediately prior to this. This procedure was further used to synthesise methano-[12]-, -[18]-, -[20]-, -[22]- and -[24]-annulenes as well as dimethano-[20]- and -[24]-annulenes.[209]



6.1.1.4 Aluminium, palladium and rhenium.

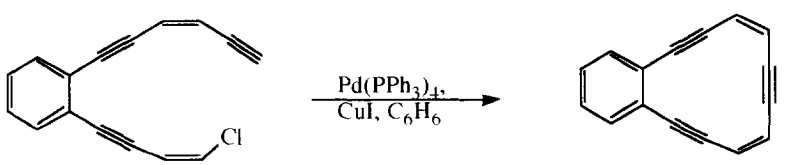
Aluminium has been employed in the formation of twelve-, fourteen- and sixteen-membered acetylene-containing ring structures. This methodology is demonstrated for the synthesis of the fourteen-membered system **252**. Treatment of the α,ω-isopropenyl acetylenic aldehyde **251** with $EtAlCl_2$ yielded the fourteen-membered unsaturated system **252**, related in structure to the cembrane natural products, in 79% yield.[210]



251 **252**

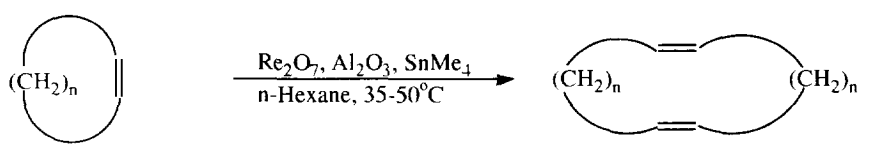
Similar ring-cyclizing conditions were used by Corey in the construction of humulene from farnesol.[211]

The use of palladium has been exploited in a short route to the construction of twelve-membered dehydro-[12]-annulenes. Treatment of **253** with tetrakis(triphenylphosphine)palladium and copper iodide gave the twelve-membered system **254** in 21% yield.[212] It was possible to produce a ring system containing the same number of atoms but with a second 1,2-disubstituted phenyl ring in place of one of the *Z*-olefins, by cyclization of the appropriate structure under identical conditions.[212]



253 **254**

The metathesis of olefins normally leads to unsaturated polymers, however, treatment of the seven- to ten-membered cycloalkanes **255** with dirheniumheptoxide on alumina activated by tintetramethyl yielded the fourteen- to twenty-membered cyclic dienes **256** in yields ranging from 30 to 74%.[213]



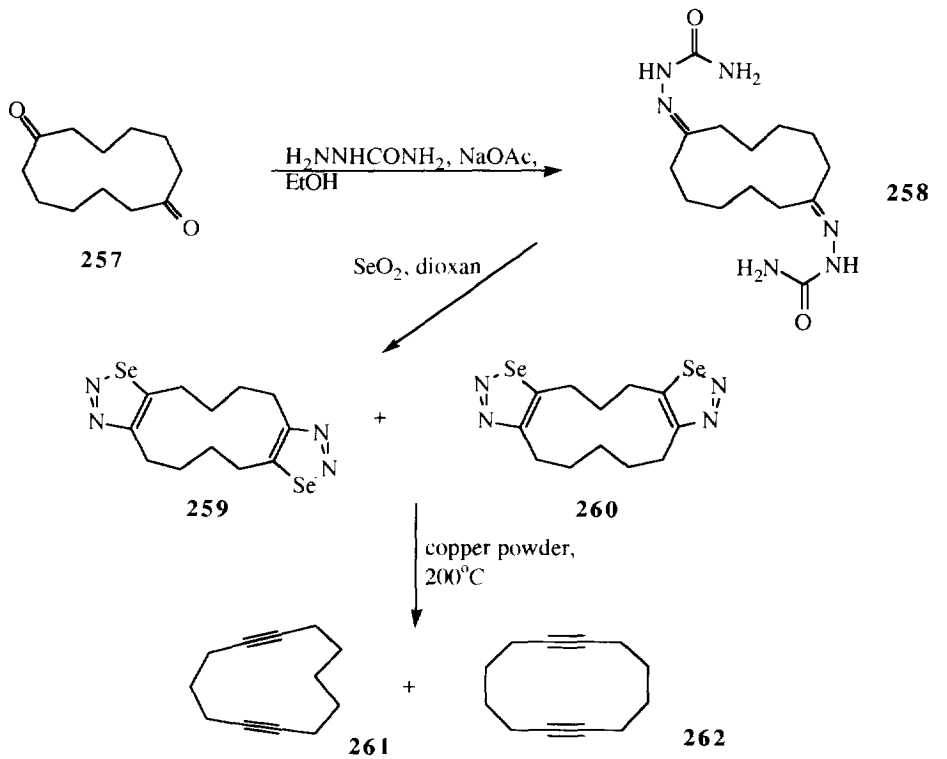
n=5-8

255 **256**

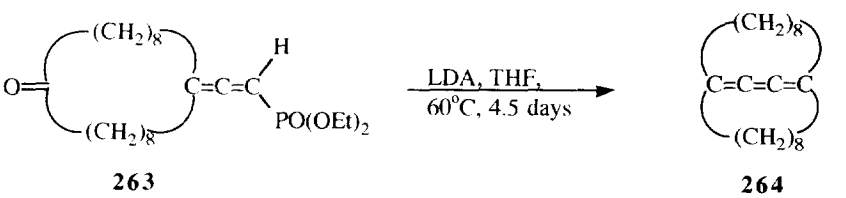
6.2 Unsaturated carbocycles: from saturated diketones, and by a ring-contraction method

Unsaturated carbocycles such as **261** and **262** are of interest for several reasons: firstly large rings containing acetylene functions are found to be the active part of the naturally occurring antitumour agents such as

calicheamycin and esperamycin. Secondly, π-units contained within large rings are interesting due to through space and through bond interactions, and thirdly, the unsaturation present in ring systems can lead to some unusual ligand effects. Synthesis of the twelve-membered diacetylene-containing rings **261** and **262** was achieved by formation of the disemicarbazone **258** from the readily available diketone **257**, conversion of this into the corresponding bisselenadiazoles **259** and **260** and thermolysis of these.[214]

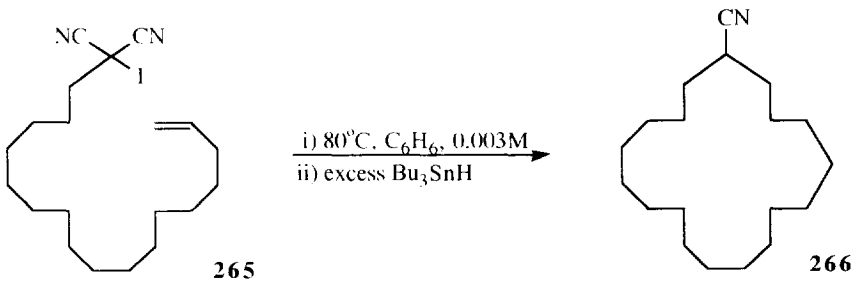


Other conformationaly restricted twelve-membered rings containing tetraene groups have been reported. Ring-contraction of the allenic phosphonate **263** by treatment with base in a variation of the Horner-Emmons-Wittig reaction yielded the twelve-membered tetraene containing system **264** in 26% yield.[215]



6.3 Saturated carbocycles

There are few reports in the literature concerning the syntheses of saturated carbocycles although these could in theory be obtained by reduction of the unsaturated systems previously mentioned. However, the synthesis of the eighteen-membered monocyano system **266** has been achieved in a surprisingly high 54% yield. Heating the



265 **266**

of the α-geminal dicyano iodide **265** at 80°C yielded a dicyanomethyl radical which underwent intramolecular *endo*-addition to the ω-olefin. Treatment of this with tri-*n*-butyltinhydride induced a radical initiated loss of one cyano group and reduction of the iodide to give monocyanocycloheptadecane **266**.[216]

Acknowledgement

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