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Syntheses of Medium Sized Rings by Ring Expansion Reactions

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Contents

1. Introduction

Medium sized rings are commonly found in many groups of natural products which possess wide and diverse medicinal and biological properties. Reports on the synthesis of medium rings, published either as new methodology or as a synthesis of part of a more complex structure, occur throughout the literature. This review mainly covers the synthesis of rings containing eight- to eleven-members by ring expansion reactions, with particular emphasis on syntheses published over the last ten years Some of the older syntheses and methods of direct cyclization are, however, mentioned where appropriate. The review is broadly divided into subsections relating to ring size. Some overlap is inevitable, however, since some of the syntheses are applicable to more than one ring size. A short overview on the more classical methods for the synthesis of medium rings, particularly as applied to recent syntheses, is also covered in the appropriate sections.

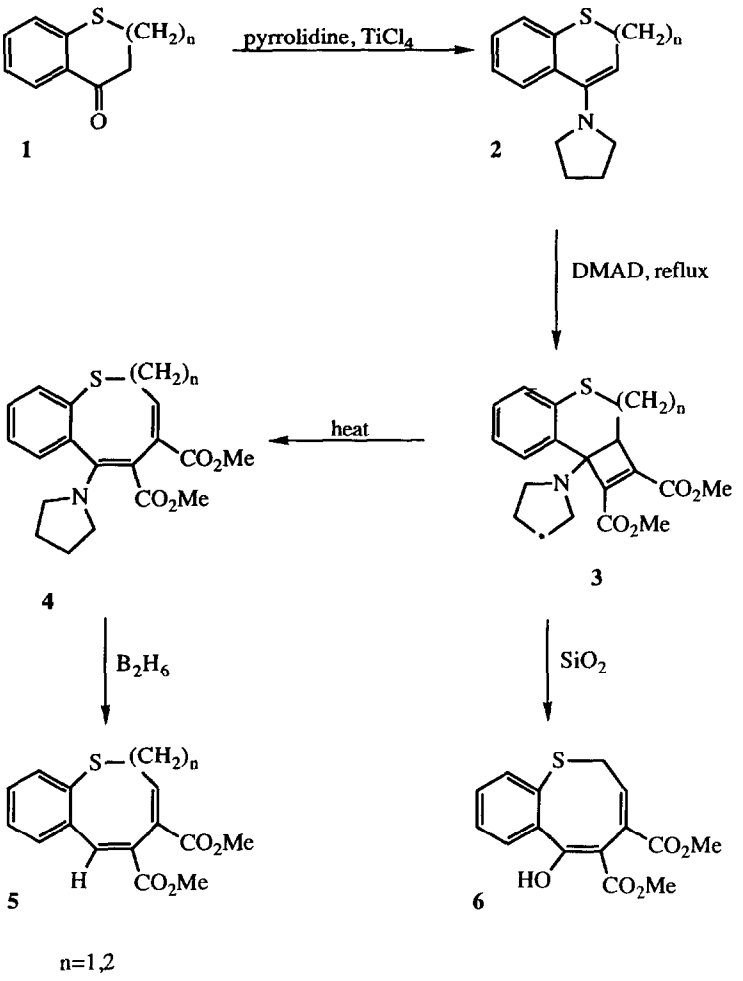
2. The synthesis of eight-membered rings.

Eight-membered rings are the smallest rings considered under the classification of medium rings. These rings are obtainable, in reasonable yield, *via* a head to tail coupling of linear α,ω-functionalized molecules. For this to be effective very dilute solutions and/ or very slow mixing of reactants (recently by the use of syringe pumps) are necessary to avoid the formation of polymers. A slight modification of this technique, where the appropriate functionality is present, has been used to produce eight-membered ring disulfides and larger.[1] The ring closure of the dithiols is effected by oxidative coupling using iodine. The concentration of iodine and dithiol are adjusted such that the colourization due to the iodine is just visible (ca 10^{-5} mol^{-1}). Yields of 73-86% are obtainable for these systems, including nine-membered ring disulfides. This compares to yields of approximately 50% for eight-membered rings under ordinary high dilution intramolecular ring cyclization conditions.[2,3]

2.1 *Sulfides. Synthesis of benzothiocins and benzothionins*

Eight- and nine-membered rings containing sulfur have been synthesised via a (2+2) cycloaddition of enamines to dimethyl acetylenedicarboxylate (DMAD) followed by electrocyclic ring opening[4] (Scheme 1) The condensation between pyrrolidine and thiochroman-4-one to give the enamine **2**, (n=1), proved to be unexpectedly difficult, but was achieved in the presence of titanium tetrachloride. Addition of DMAD to **2** occurred readily to yield the cyclobutene derivative **3**, (n=2), which formed the nine-membered ring **4**, (n=2), in one hour at room temperature. (Conversion of **3**, (n=1), to **4**, (n=1), was effected by heating at 150°C for one hour) Treatment of the cyclic enamine esters **4**, (n=1,2), with diborane gave 2*H*-1-benzothiocin (**5**, n=1) and 2,3-dihydro-1-benzothionin (**5**, n=2) in good yield. **3** (n=1) was converted into **6** *via* chromatography over silica.

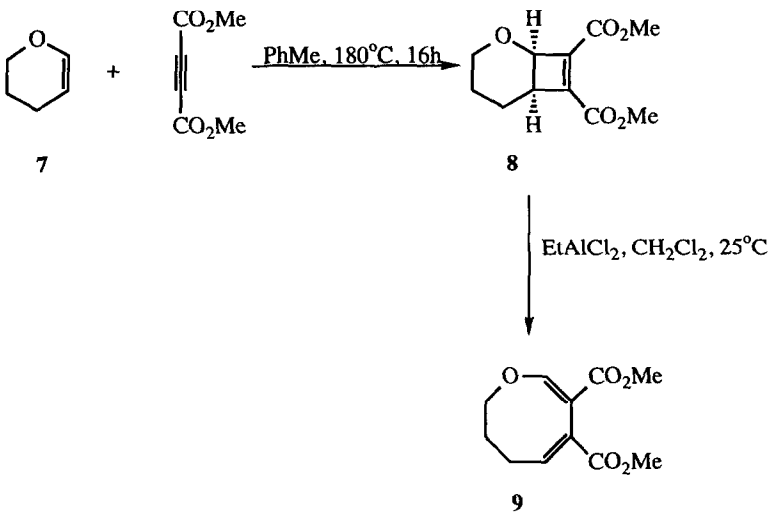
Scheme 1. Synthesis of benzothiocins and benzothionins



2 2 *Synthesis of eight-membered ring ethers*

A series of 2-substituted oxocins has been reported by Nicolaou[5] (Scheme 2). Treatment of various 2-substituted dihydropyrans at different temperatures with dimethyl acetylenedicarboxylate yielded the required oxocins. Using unsubstituted dihydropyran it was possible to isolate the intermediate **8**, which on treatment with a Lewis acid, or further heating, yielded the eight-membered ring ether. Various 2-substituted dihydropyrans were converted directly into the oxocins without formation of the four-membered ring intermediate, thus providing a convenient procedure for the synthesis of the 2-substituted oxocins.

Scheme 2. Synthesis of eight-membered ring ethers

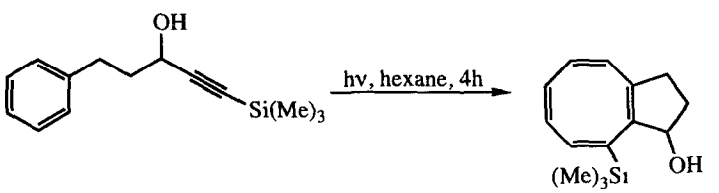


2.3 *Carbocycles via arene-alkyne photoadditions*

A route to cyclooctatetraene containing ring systems has been reported. An intramolecular insertion of alkynylsilanes to yield substituted cyclooctatetraenes has been achieved photochemically[6] (Scheme 3). By using substituents in the alkynyl side chain it was possible to achieve the syntheses of variously fused cyclooctatetraenes containing functionality in the five-membered ring of **11**.

The synthesis of carbocyclic eight-membered rings has recently been reviewed by Petasis and Patane [7]

Scheme 3. Carbocycles via arene-alkyne photocycloadditions



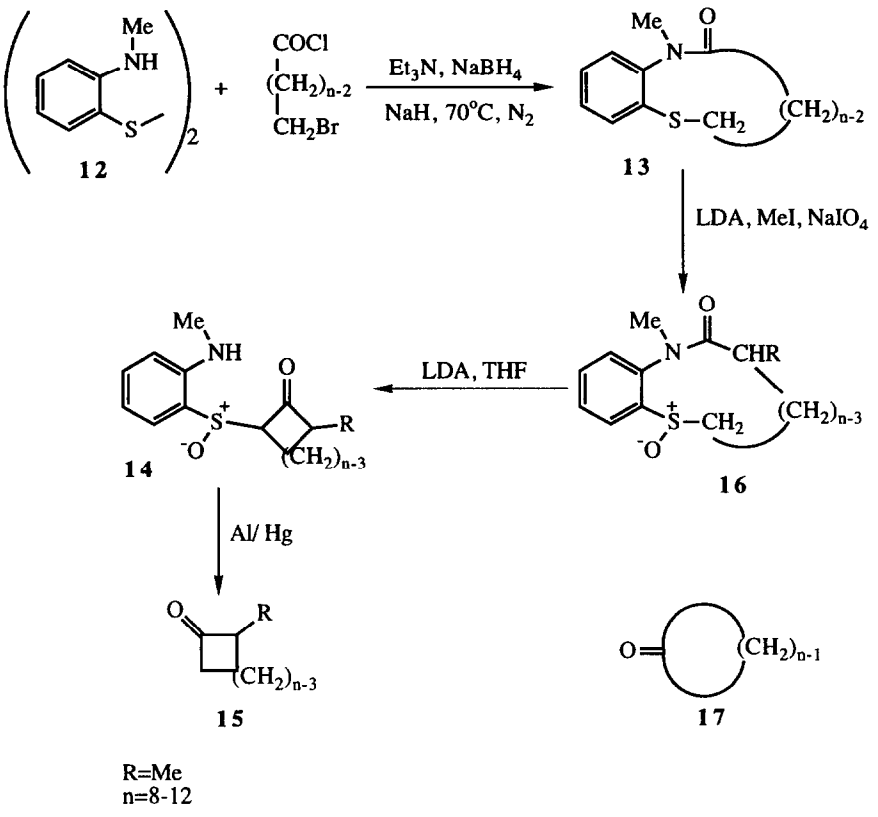
2.4 *Synthesis of ketones via intramolecular cyclization of sulfides*

Large membered ring sulfides can be prepared in high yield[8-10] *via* intramolecular cyclization reactions This has been used to produce, *via* a second intramolecular cyclization, eight- and larger-membered ring ketones[11] (Scheme 4). Medium ring ketones are difficult to synthesise due to an unfavourable entropy effect,[12] but this is minimized by the initial synthesis of the larger-membered ring sulfide **13** which forces together the two

appropriate terminal reaction sites for the formation of the ketone. Treatment of the cyclic sulfide **13** with LDA followed by iodomethane allows a methyl substituent to be introduced into the ring. Oxidation with sodium periodate yields the sulfoxide **16**. Treatment of **16** with LDA/ THF yields **14** by transacylation. Finally reductive cleavage of **14** to **15** occurs on treatment with mercury amalgam. This route enables alkyl substituents other than methyl to be introduced into the final medium-ring ketones **15**.

The unsubstituted cyclic ketones **17** were obtained by a slightly modified route. The sulfide **13** is oxidized with *meta*-chloroperbenzoic acid to the sulfone of **16** which after treatment with potassium t-butoxide in tetrahydrofuran/ dimethylsulphoxide, undergoes transacylation cleaving the tertiary amide bond to give the unsubstituted sulfone of **14** (R=H). Reductive cleavage, as for the substituted system (**14** to **15**), with Al-Hg then yields the unsubstituted ketone **17**.

Scheme 4. Synthesis of medium ring ketones

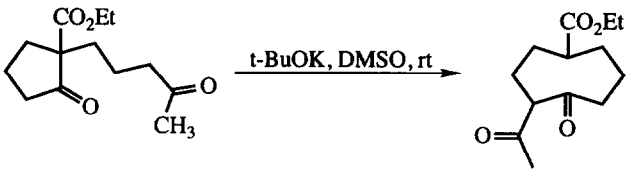


2.4.1 *Ketones by intramolecular transacylation*

Carbocyclic β-ketoesters having an α-4-ketopentyl group have been found to undergo ring cyclization/ expansion to yield eight- to ten-membered ring containing ketones **19** (Scheme 5).[13] Substrates containing groups in the α-position other than the 4-ketopentyl were also tried eg. 2-ketopropyl, but they failed to produce

the ring-expanded ketones. Variation in the size of the final ketones was thus achieved by using five- to seven-membered ring β-ketoesters.

Scheme 5. Three-carbon ring expansion of carbocyclic β-ketoesters

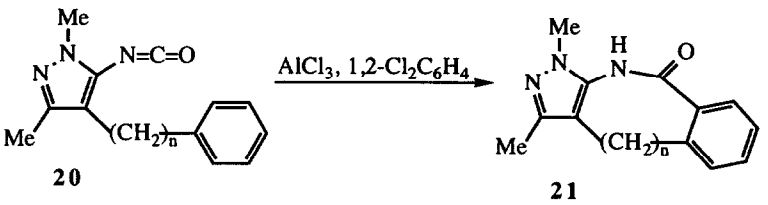


18 **19**

2.5 *Routes to lactams by isocyanate cyclization*

The intramolecular Friedel-Crafts cyclization of isocyanates **20** (Scheme 6) using a method originally developed by Butler[14] has been used to produce seven- to ten-membered ring lactams.[15] No high dilution conditions are necessary and, with the exception of the eleven-membered ring, n=5, which failed to form, all the ring systems are produced in good yield.

Scheme 6. Synthesis of medium ring lactams.



20 **21**

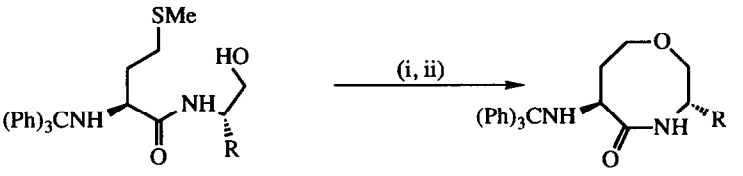
n= 1-4

2.5.1 *Optically active ether lactams from amino acids*

Use has been made of the natural amino acids to produce chiral 3-alkyl-6-tritylamino-1,4-oxazocines.[16] Treatment of the β-(N-tritylmethionyl)amino alcohols **22** (R=Me, $CHMe_2$, CH_2CHMe_2) with excess methyl iodide gave a sulfonium methiodide salt. Treatment of this resulting compound with potassium t-butoxide in ethyl acetate removes the proton from the hydroxyl group allowing intramolecular cyclization to the eight-membered ring containing chiral ether lactams **23**.

Peptides containing both an amino alcohol at the carboxy terminus of their chain and a methionyl residue are capable of undergoing this intramolecular ring cyclization (Scheme 7).

Scheme 7. Optically active ether lactams from amino acids



22 23

Reagents: (i) MeI, EtOAc, reflux 2h
(ii) t-BuOK, THF, -15°C, 20 min

3. The synthesis of nine-membered rings.

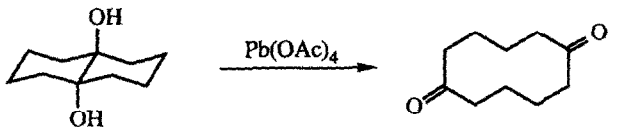
The intramolecular cyclisation of linear α,ω-functionalized molecules under high dilution conditions usually gives only poor, if any, yields of nine-membered rings. However, nine- and up to thirteen-membered rings have been synthesized via the coupling of α,ω-dibromoalkanes under concentrated and heterogeneous conditions with sodium sulfide.[17] The yields for the formation of nine- and thirteen-membered rings were 68% and 69% respectively.

For the formation of such systems special methods are employed usually involving the cleavage of a bond common to two ring systems. Some of the better known methods (Scheme 8) applied to recent syntheses of medium ring systems are (i) oxidation of *cis*- and *trans*- (illustrated) 1,2-diols **24** with lead tetraacetate to yield cyclodecanes **25**;[18] (ii) photo-oxygenation of enamines **26** as a new route to protopanes **27**;[19] (iii) cyanogen bromide or chloroformate ester induced cleavage of the 1,2-bond present in 1,2,3,4-tetrahydro-β-carboline nuclei **28**;[20] (iv) photo-solvolytic cleavage or the Hofmann degradation (illustrated) of bridgehead quaternary ammonium hydroxides **30**.[21,22]

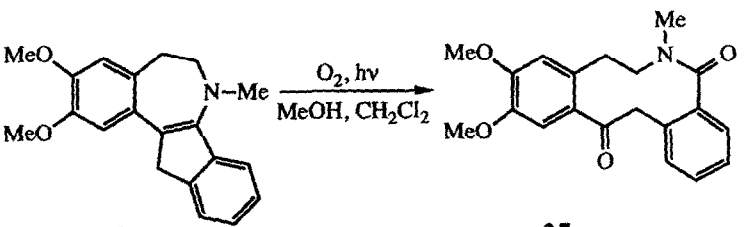
3 1 *Nine-membered ring heterocycles containing a sulfur or selenium atom*

A series of nine- and ten-membered ring heterocycles containing either a sulfur or selenium atom have been synthesised (Scheme 9).[23] The bonds to the trisubstituted bridgehead sulphonium or selenonium atoms containing either an α-cyano or ester grouping were heterolytically cleaved with either magnesium metal or sodium borohydride in ethanol to give nine- and ten-membered sulfur or selenium containing rings. It was also possible to effect this ring expansion with completely and partially saturated benzene variants of the system This thus provides a convenient and useful method for the formation of nine- and ten-membered ring heterocycles containing either sulfur or selenium atoms in yields ranging from 38% to 87% depending on the reagent used to effect the bond cleavage.

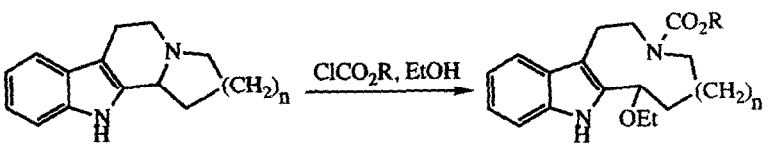
Scheme 8. General methods for the synthesis of medium rings



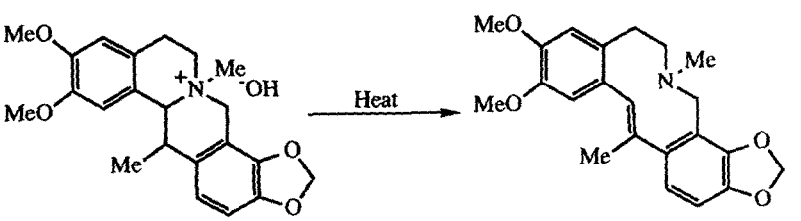
24 25



26 27

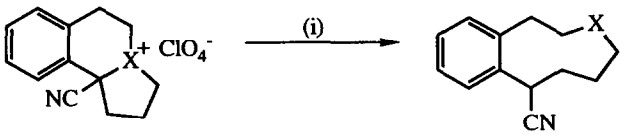


28 29



30 31

Scheme 9. Nine-membered ring heterocycles containing a sulfur or selenium atom.



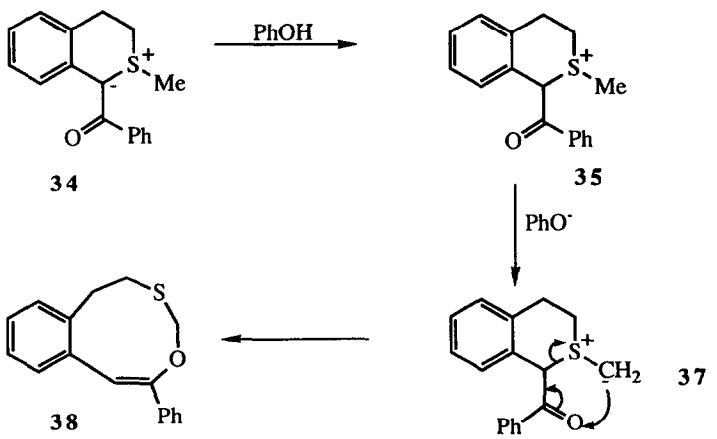
32 33

X= S or Se Reagents: (i) Mg, C_6H_6 or $NaBH_4$, EtOH

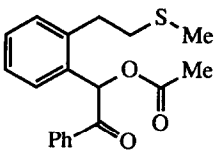
3.1.1 *Novel ring expansion of sulfur ylides*

Some rather unusual reactions, including a novel ring expansion, of sulfur ylides have been reported[24] (Scheme 10). Ylides of the type **34** are well known and treatment of this with acetic acid or thiols gave ring opened products eg **36**. The use of phenols which are less acidic than either thiols or acetic acid but more acidic than alcohols (alcohols also gave open chain systems with **34**[25]) was investigated. Treatment of the ylide **34** with two equivalents of phenol gave 6,7-dihydro-2-phenyl-3,5-benzoxathionin **38** in good yield (Scheme 10). Increasing the amount of phenol was found to decrease the yield of benzoxathionin and increase the amount of open chain compound. This was attributed to hydrogen bonding between the phenoxide anion (after proton abstraction by the ylide) and the excess phenol. This inhibits abstraction of the proton from the *S*-methyl group by the phenoxide anion and increases nucleophilic attack by phenol at the carbon atom α- to the carbonyl group. An effective way around this problem involved the use of imides such as succinimide or phthalimide. These contain an acidic proton but the conjugate base has a very low nucleophilicity, thus causing no subsequent ring opening.

Scheme 10. Novel ring expansion of sulfur ylides



34 35 37 38

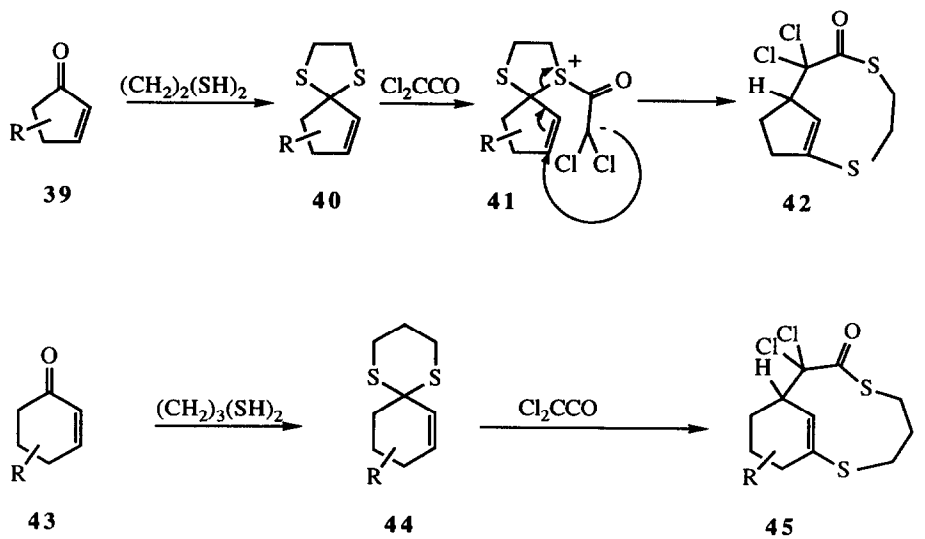


36

3.1.2 *Synthesis of rings containing two sulfur atoms, trans-1,7-dithiacyclonon-5-en-2-ones*

The formation of nine-membered sulfur containing rings is shown in Scheme 11.[26] Treatment of the thioketal **40** with dichloroketene (prepared *in situ* from dichloroacetyl chloride and triethylamine) yielded the substituted *trans*-1,7-dithiacyclonon-5-en-2-ones **42** in yields >80%. By the use of propane-1,3-dithiol the cyclohexyl ketals **44** were prepared. Treatment of these with dichloroketene yielded the corresponding *trans*-1,7-dithiacyclodec-5-en-2-ones in 78-88% yield. More recently it has been found that treatment of the thioketals of linear α,ω-unsaturated ketones with dichloroketene also yields nine-membered sulfur-containing rings.[27]

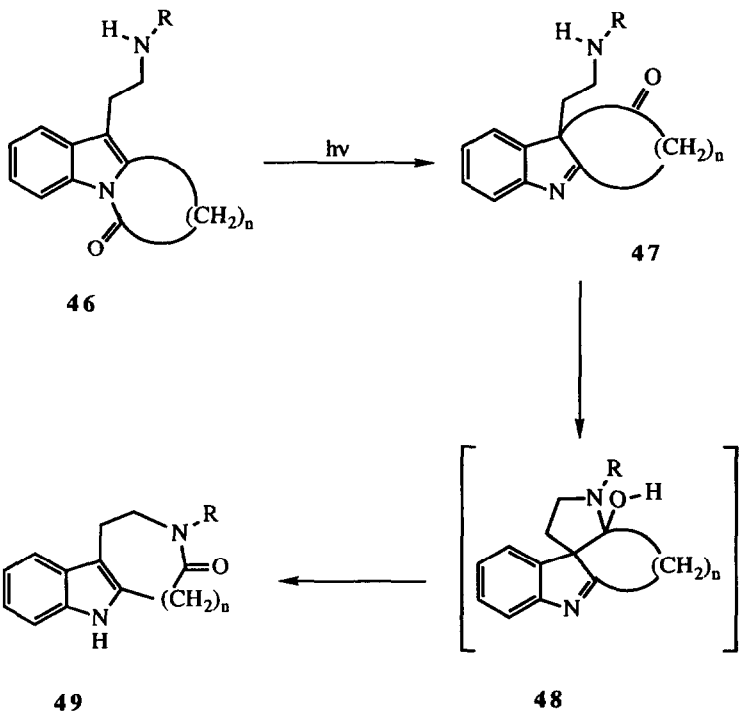
Scheme 11. Synthesis of substituted trans-1,7-dithiacyclonon-5-en-2-ones



3.2 *Lactams via a ring expansion of hemiaminals*

The ring expansion of hemiaminals (Scheme 12) to yield nine-membered ring lactams has been reported.[28] Irradiation of the enamine **46** resulted in a [1,3]acyl photo-rearrangement to the 3-acylindolenines **47**. Intramolecular formation of the hemiaminal **48** followed by cleavage results in the nine-membered ring lactam **49**, effectively an N to N'-acyl group migration overall.

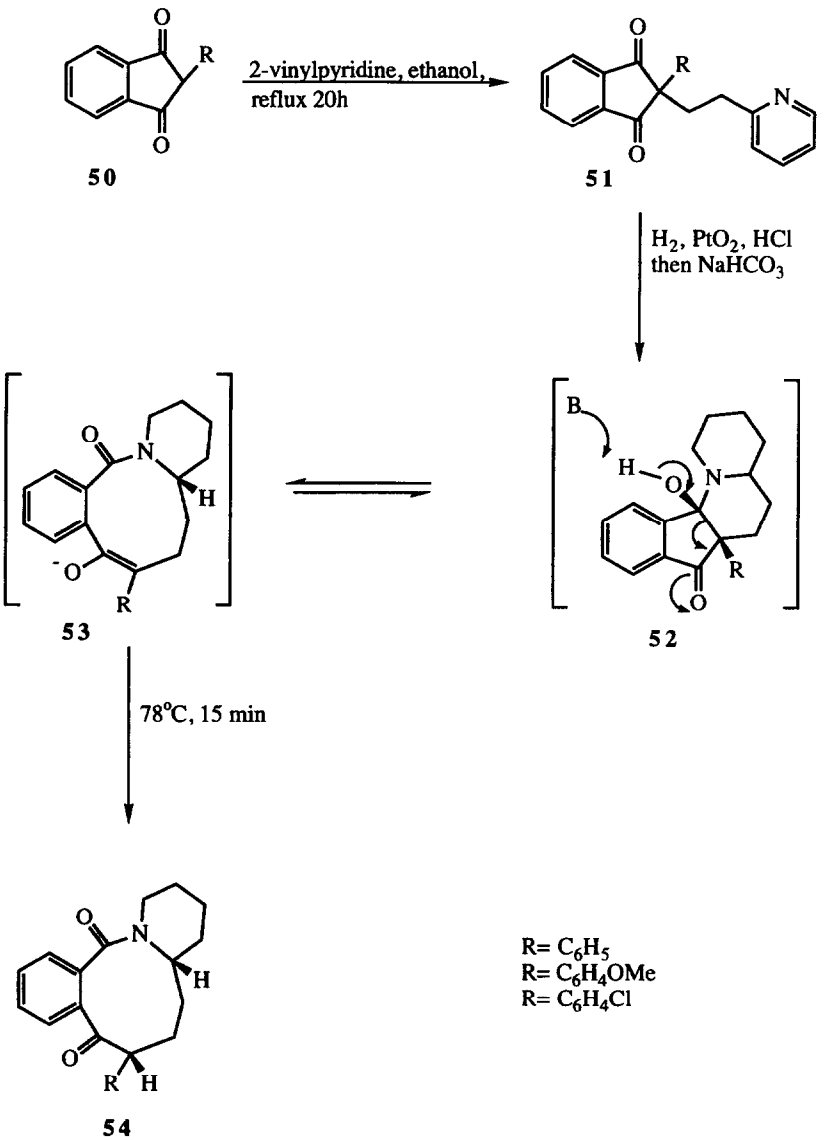
Scheme 12. Lactams *via* ring expansion of hemiaminals



3.2.1 *Ketolactams by ring expansion of 2-substituted indane-1,3-diones*

2-Phenylindane-1,3-dione **50** reacts with 2-vinylpyridine (Scheme 14) *via* a Michael addition to yield 2-phenyl-2-[2-(2-pyridyl)ethyl]-indane-1,3-dione **51**. Catalytic hydrogenation of the pyridine ring gives 2-phenyl-2-[2-(2-piperidyl)ethyl]-indane-1,3-dione. This can be isolated from a hydrogenation mixture containing hydrochloric acid, as the hydrochloride, which upon basification yields 6-phenyl-6,7,8,8a,9,10,11,12-octahydropyrido[1,2-*b*][2]benzazonine-5,14-dione **54** containing a nine-membered ring.[29] The ring expansion is not spontaneous at room temperature, however, and the 2-ethylpiperidyl compound can be isolated and stored for several weeks at -15°C. Ring expansion was investigated using ^{1}H NMR and it was found that formation of the nine-membered ring containing ketolactam occurred in 15 mins at 78°C. The carbinolamine intermediate **52** was not detected. Ring expansion of the intermediate **52** (R= *p*-methoxyphenyl), did not occur, possibly because of destabilization, whereas ring expansion of the more stabilized intermediate, **53** (R= *p*-chlorophenyl), occurred to yield the corresponding **54**.Yields of the ring expanded products were quantitative after the formation of the 2-ethylpiperidyl compound, **51**.

Scheme 14. Ketolactams by ring expansion of 2-substituted indane-1,3-diones



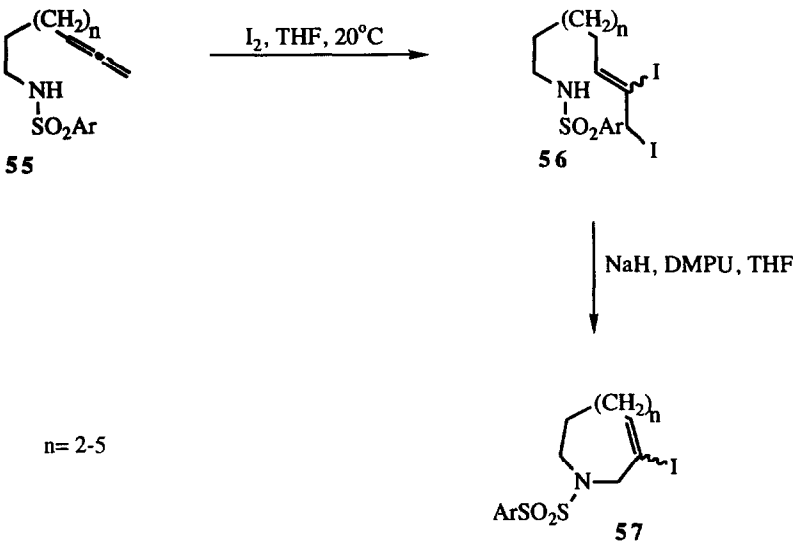
3.3 *A new route to medium-ring nitrogen-containing heterocycles*

A new route to medium-ring nitrogen containing heterocycles (Scheme 13) has been reported by Gallagher and co-workers.[30] Addition of iodine to the N-sulfonylallenic amines **55** gave the allylic iodides **56**. Treatment of these with sodium hydride in DMPU, under high dilution conditions gave the azacycles. It is interesting to

note that when n=1 an 83% yield of the 'endo' pyrrolidine product was obtained whilst only a 10% yield of **57** n=1 was obtained. Increasing n from 1 to 2 produced a 22% yield of the 'endo' piperidine compound and 35% of the azocine (n=2). Increasing n further from 2 to 3,4 and 5 yields the nine-, ten-, and eleven-membered ring endo azacycles exclusively with no detection of the smaller rings.

The synthesis of medium-ring nitrogen heterocycles has been the subject of a recent review by Evans and Holmes.[31]

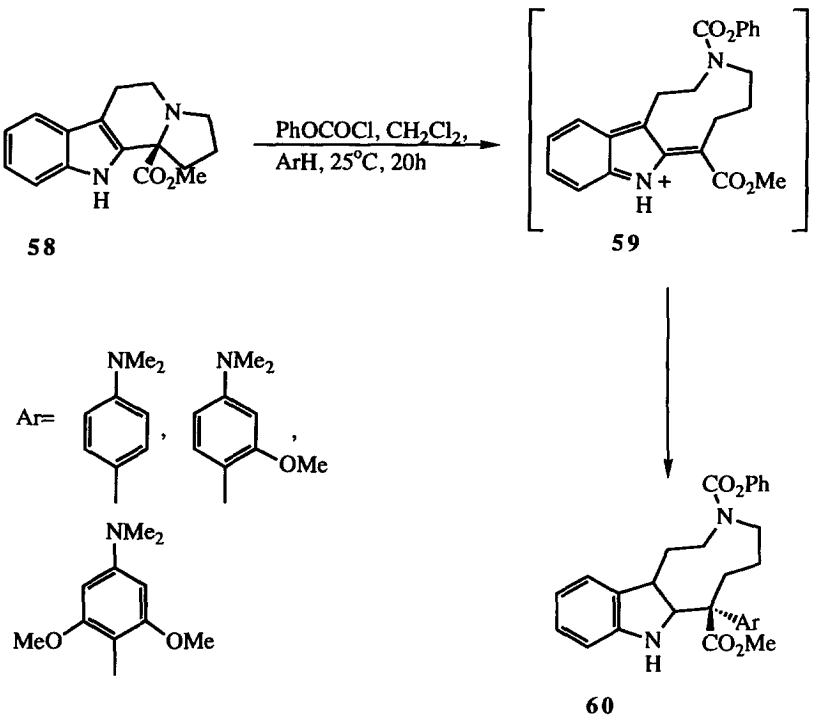
Scheme 13. A new route to medium-ring nitrogen containing heterocycles



3.4 *Non-oxidative methodology for the synthesis of vinblastine and vincristine*

Vinblastine and vincristine have aroused much synthetic interest over the years as these molecules possess clinical activity against tumours. Previous syntheses involved the use of oxidative reagents to break the C-N bond leading to nine-membered rings (Scheme 15). This could sometimes lead to the wrong stereochemistry at the C16 position This procedure involves formation of the iminium ion **59**, by treatment with phenyl chloroformate in the presence of aromatic nucleophiles, which add *in situ* to the iminium ion yielding **60**.[32] Starting with chiral **58** it was found that a 60% enantiomeric excess could be obtained when treated with phenyl chloroformate followed by 3-methoxyphenyldimethylamine. The chirality of **60** may be expected to be lost due to the formation of the planar iminium ion intermediate **59**, however due to the slow conformational processes associated with this strained ring system a 60% enantiomeric excess of **60** is retained.

Scheme 15. Non-oxidative methodology for the synthesis of vinblastine and vincristine models

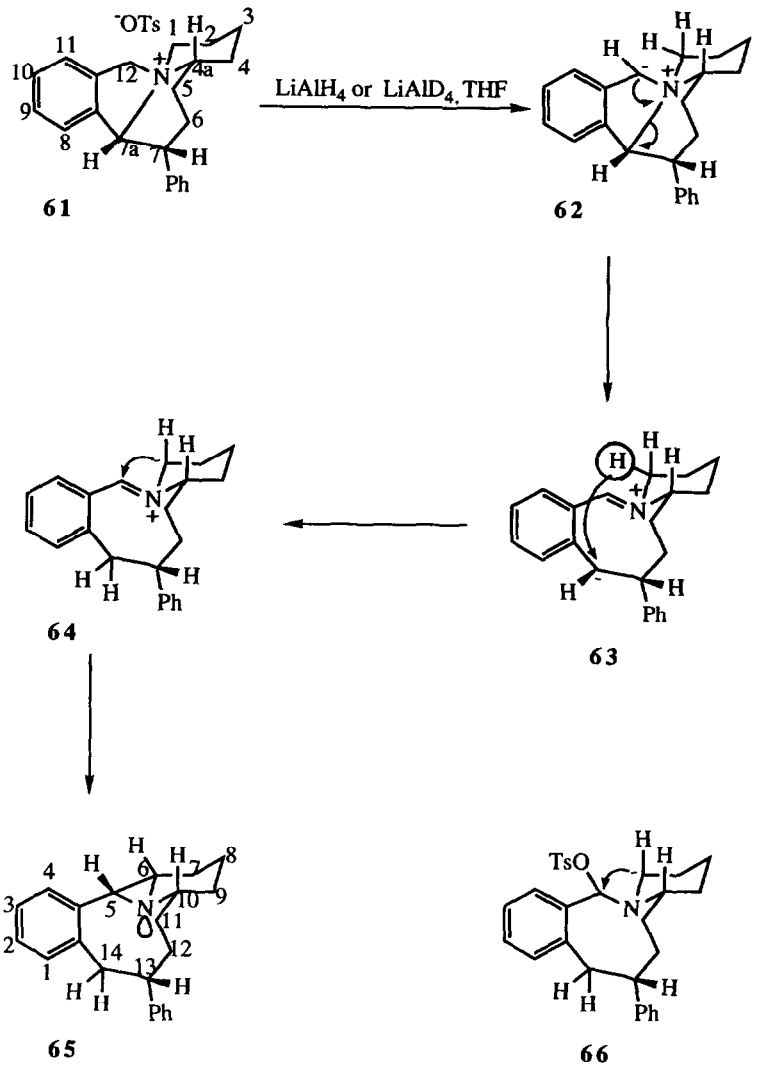


3.5 *Ring expansion of spiro-quaternary ammonium compounds*

A novel rearrangement of spiro-quaternary ammonium rel-(4a*R*,7*S*,7a*R*,13*S*) 1,2,3,4,4a,5,6,7,7a,12-decahydro-7-phenyl-isoindolo[1,2-*d*]quinolizin-13-ium tosylate **61**, when treated with lithium aluminium hydride, to a nine-membered nitrogen containing heterocycle rel-(5*S*,6*R*,10*R*,13*S*)-5,6,7,8,9,10,11,12,13,14 - decahydro-13-phenyl-5,6,10-nitrilobenzocyclododecene **65** has been uncovered.[33] The ring system is particularly unusual in containing three-, six-, and nine-membered rings common to one nitrogen atom. Treatment of **61** with lithium aluminium deuteride, even in ten fold excess, showed no incorporation of deuterium, either by ^{1}H NMR or mass spectral analysis, indicating an intramolecular process. A possible mechanism involves abstraction of a proton from the benzylic methylene of **61** followed by cleavage of the N-C(7a) bond to give **63**. Dreiding models show the C(7a) carbon atom sits close and bisects the C(1) methylene protons in **61**. Abstraction of one of the C(1) methylene protons occurs intramolecularly to yield **64** which can cyclize directly to **65** or by addition of the tosylate to the C(12) carbon atom of **64** followed by ring closure (Although the mechanism is shown in discrete steps the rearrangement probably occurs in a more concerted manner, particularly considering that no deuterium is incorporated into the final structure). In the presence of lithium aluminium hydride further reaction involving ring opening of the aziridine might be expected. However, Dreiding models indicate steric hindrance to further reduction. It is interesting to note that when the counterion of the ammonium atom is exchanged from the tosylate to mesylate, or phosphate, no rearrangement takes place

Starting materials are recovered in both cases, even after extended reaction times. This perhaps supports the latter mechanism involving participation of the tosylate anion.

Scheme 16. Ring expansion of spiro-quaternary ammonium compounds

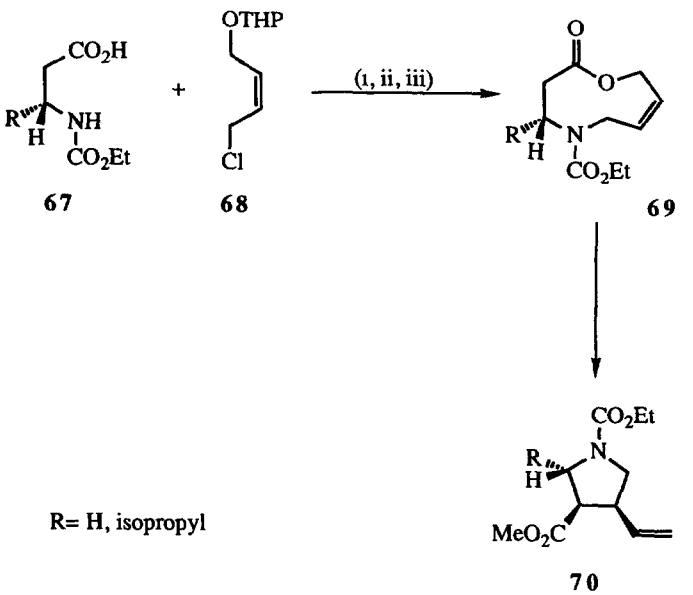


3.6 *Azalactones*

The synthesis of nine-membered ring azalactones **69** has been achieved[34] (Scheme 17) Ring closure of the α,ω-hydroxy acids was achieved using Mukaiyama's method under high dilution conditions, to give the required

azalactones, in 42% yield, after chromatography. By subjecting (*S*)-valine (R= isopropyl) to the Arndt-Eistert procedure it was possible to produce chiral derivatives of **67**. An intramolecular Claisen enolate rearrangement on the nine-membered ring azalactones **69** was later used, providing a rather neat synthesis of either chiral trisubstituted or achiral disubstituted pyrrolidines depending on the nature of **67**.

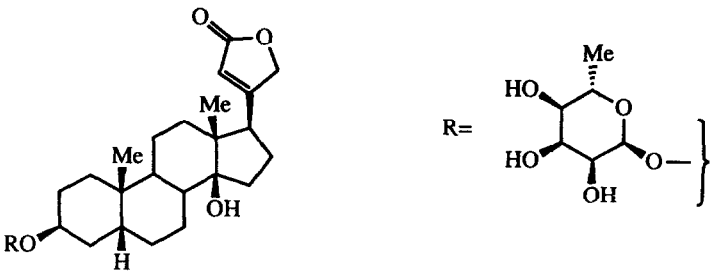
Scheme 17. Synthesis of azalactones



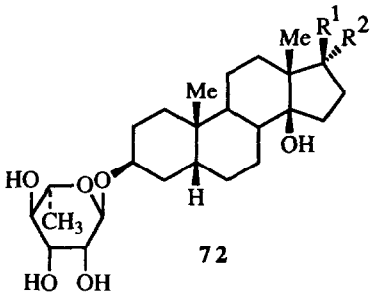
Reagents: (i) BuLi, THF, DMSO, rt, 26h
(ii) PPTS, MeOH
(iii) 2-Chloro-*N*-methylpyridinium iodide, NMe_3, MeCN, reflux, 50h

3.7 *Ring expansion of steroidal nuclei*

Recently attempts to improve and understand the therapeutic properties of cardiotonic glycosides related to digitoxigenin **71**, particularly with respect to the steroidal nucleus, have led to the synthesis of selected 3β-rhamnosyloxyandrostane derivatives **72**.[35]



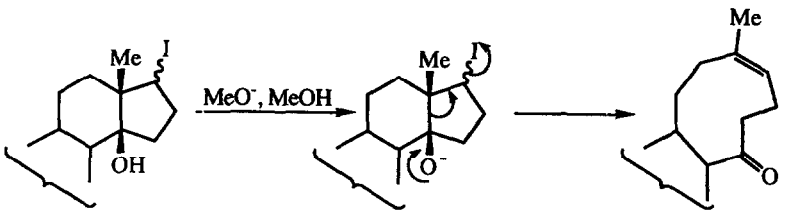
71



72

$R^1 = OAc, R^2=H$
$R^1 = OH, R^2=H$
$R^1= H, R^2=OAc$

During these syntheses modification of the groupings around the 13, 14, 15 and 16 positions led to **73**.

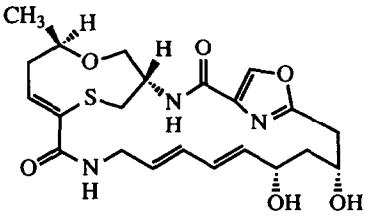


73 74 75

Treatment of this with sodium methoxide in methanol caused ring opening to produce the nine-membered ring ketone **75**.

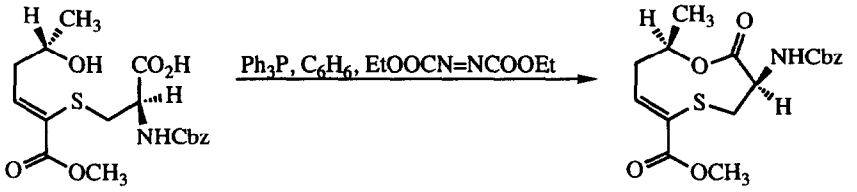
3.8 *Synthesis of the sulphidelactone of griseoviridin*

A further group of biologically active compounds containing nine-membered rings are the streptogramin antibiotics. In particular, griseoviridin **76**, has been the subject of much biological and synthetic interest.[36-39]



76

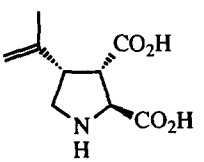
A recent synthesis of the nine-membered ring unit **78** has been achieved by the intramolecular cyclization of the hydroxy acid **77** over two days to give the **78** in 39% yield.[40]



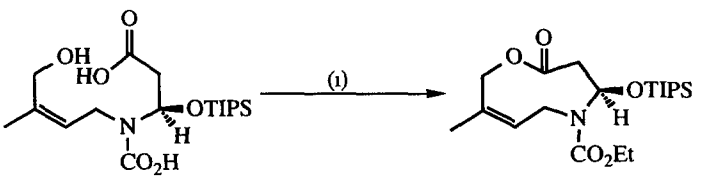
77 78

3.9 *Ring cyclizing procedures in the synthesis of (-)-α-kainic acid*

The kainoids **79**, a unique group of pyrrolidine dicarboxylic acids are of biological and chemical interest, displaying pronounced neuro-excitant properties.[41] Synthesis of (-)-α-kainic acid **79** involved, as an intermediate step, intramolecular cyclization of the hydroxy acid **80** to the nine-membered azalactone **81**, which after several synthetic stages yielded (-)-α-kainic acid **79**.



79

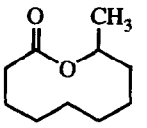


80 81

Reagents: (i) 2-Chloro-*N*-methylpyridinium iodide, methyl cyanide.

3.10 *Lactones*

Since its isolation from the eucalypt longicorn beetle, (*Phoracantha synonyma*),[42] phoracantholide I (**82**), containing a ten-membered ring lactone, has been the target for synthesis.

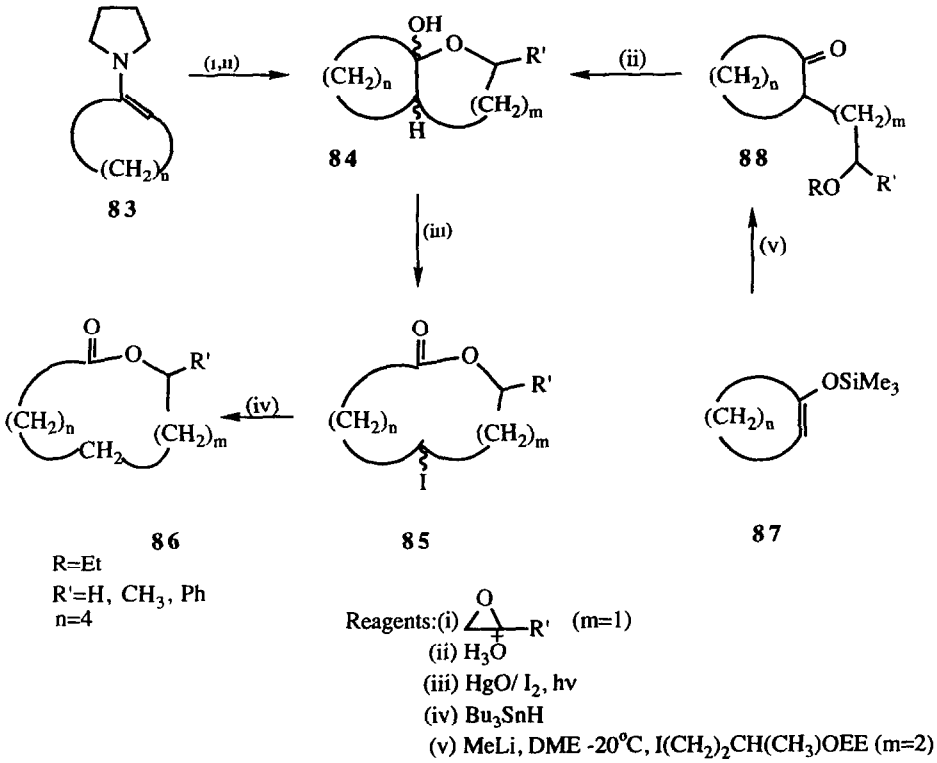


Phoracantholide I

82

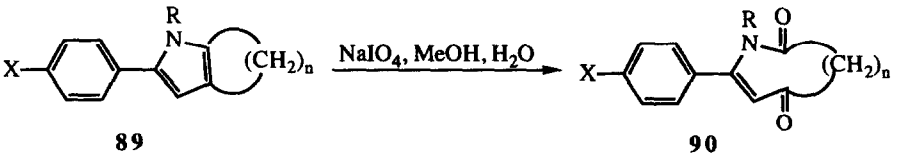
A new general method for the synthesis of nine-, ten- and eleven-membered ring lactones has been reported.[43,44] A regiospecific β-scission of the carbon-carbon bond of alkoxy radicals derived from the lactols **84** has been performed by irradiation in the presence of iodine and mercuric oxide (Scheme 19). The utility of this method was demonstrated by a short high yielding synthesis of racemic phoracantholide and may be of further use in the synthesis of other naturally occurring lactones.

Scheme 18. Synthesis of nine-membered and larger ring lactones



3.11 *Ketolactones by regioselective oxidative cleavage of enamines*

Sodium periodate has been used as a general reagent under mild conditions for oxidative cleavage of enamines **89** to produce nine-, ten-, and eleven-membered ring ketolactams **90**.[45] This synthesis involves the regioselective oxidative cleavage of the central enamine bond of bicyclic pyrroles. Yields were very good, typically 70% for the nine-membered ring ketolactam (n=4), and 57% and 37% respectively for the ten- (n=5) and eleven- (n=6) membered rings.[45]



89 **90**

n= 4,5,6
X= H, OCH_3, Cl, Br
R= H, CH_3

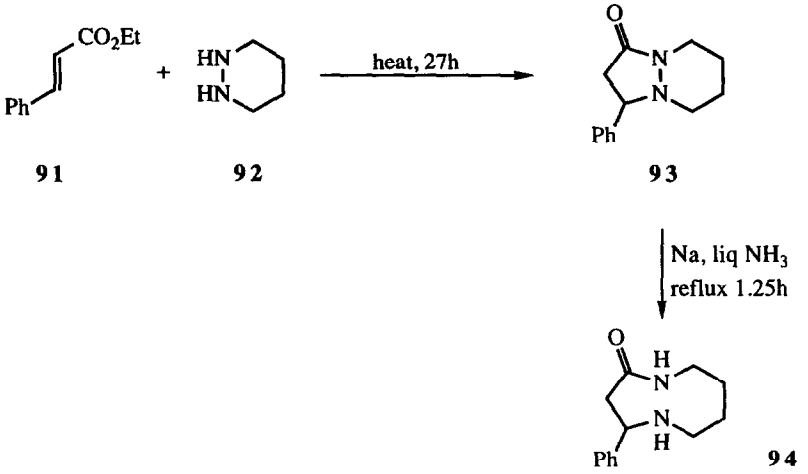
3.12 *The synthesis of aminolactams*

The synthesis of nine-membered ring amino lactams has been achieved as shown in Scheme 19. A Michael addition and condensation between piperidazine **92** and ethyl cinnamate **91** yielded 9-phenyl-1,6-diazabicyclo[4.3.0]nonan-7-one **93**. Cleavage of the central N-N bond of **93** with sodium in liquid ammonia yielded the nine-membered ring aminolactam **94**, which after several further steps gave the spermidine alkaloid celacinnine (**95**).[46]

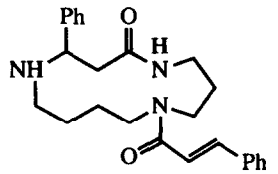
The synthesis of the polyamine alkaloid dihydroperiphylline (**96**),[47] and other eight-membered ring aminolactams,[48] has also been achieved using a ring expansion reaction analogous to that for celacinnine.

Overall, the reaction offers the possibility of being made more versatile by allowing the incorporation of substituents on the carbon atoms of the piperazine ring and/or the cinnamate moieties.

Scheme 19. The synthesis of aminolactams.

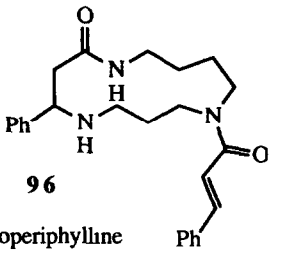


91 **92** **93** **94**



95

celacinnine



96

dihydroperiphylline

4.0 The synthesis of ten- and eleven-membered rings.

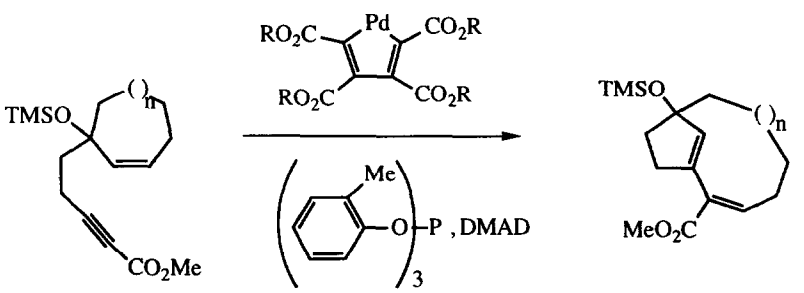
The best general method of forming ten-membered and larger (<20) ring systems is the acyloin condensation,[49,50] where a diester is heated in boiling xylene in the presence of sodium to form an α-hydroxy-ketone (acyloin). The reaction, which involves the unfavourable coupling of end groups, is presumed to take place on the surface of the sodium metal. (Although it is not known for certain, evidence suggests that RCOCOR is an intermediate,[51] as when an α, ω-di-t-butyl dialkyl diester is subjected to the conditions used in the acyloin condensation the major product is di-(t-butylketone), which presents steric hindrance to reduction to the acyloin).

Other systems in which the cyclizing end groups are held closer together, on average, than straight chains are cis-1,2-disubstituted alkenes. Ring cyclization by end group coupling of these systems has been effected to yield eleven- and twelve- membered rings in yields as high as 80%.[52,53]

4.1 *Carbocycles via an intramolecular enyne metathesis reaction*

A potentially useful crossed metathesis involving both alkynes and alkenes has been reported.[54] This is claimed to be the first example of its kind, involving both alkenes and alkynes, and offers potential use as a building block in the synthesis of natural products (e.g. taxanes and shikodomedin). The reaction (Scheme 20) involves the catalyst 2,3,4,5-tetrakis(methoxycarbonyl) palladacyclopentadiene (TCPC), which promotes ring closure of the ene-alkyne groups and coordination to the palladium. Metathesis then occurs to yield the coordinated cyclobutene compounds which rearrange to the ring expanded nine-membered ring carbocycles.

Scheme 20. Carbocycles *via* an intramolecular enyne metathesis reaction

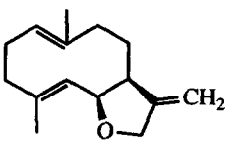


97 98

n= 1, 2, 6 DMAD= Dimethyl azodicarboxylate

4.2 *Synthesis of germacrane sesquiterpenes by the oxy-Cope reaction*

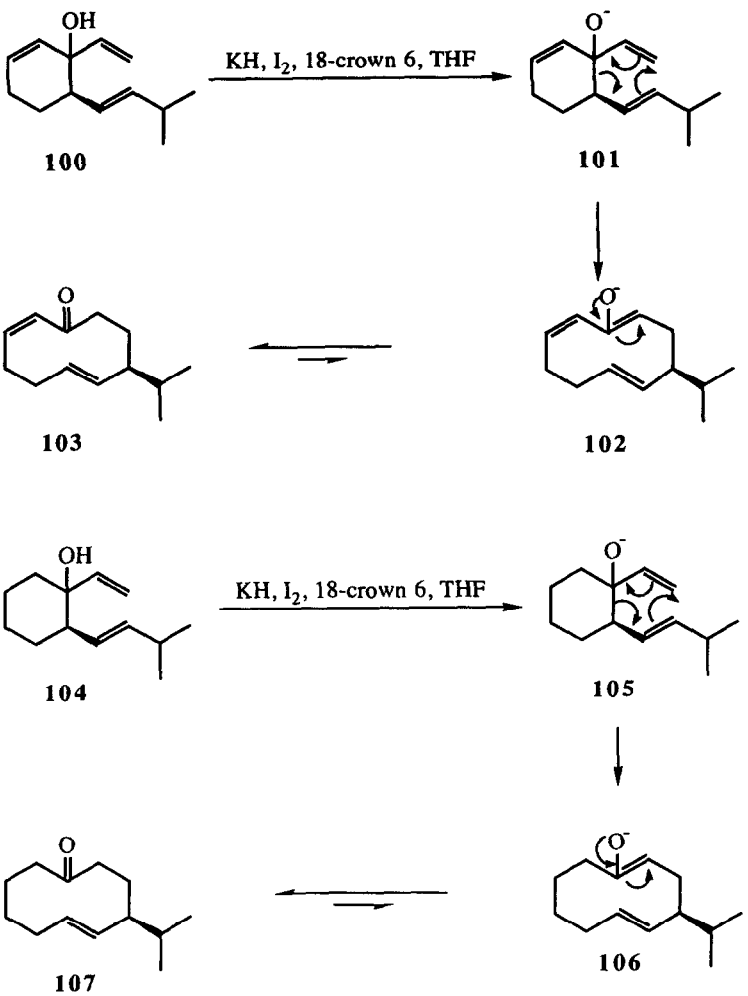
Ten-membered cyclodecadienes are found in the germacrane sesquiterpenes such as (+)-dihydrocostunolide **99**.



99

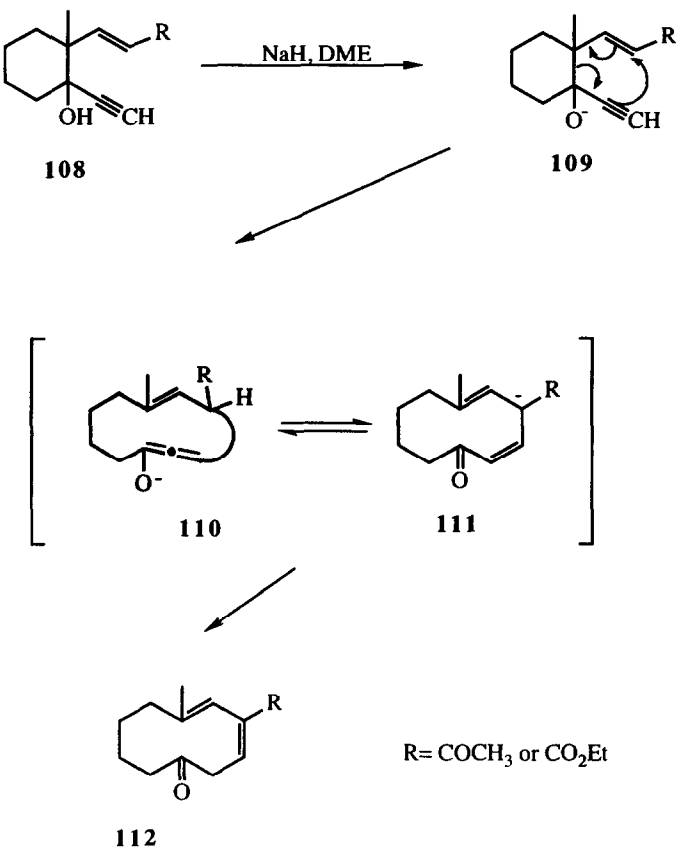
Cyclodecadienones and cyclodecenones, for possible use in the synthesis of germacrane sesquiterpenes, have been synthesised via the oxy-Cope rearrangements shown in Scheme 21.[55]

Scheme 21. Synthesis of cyclodecadienones and cyclodecenones



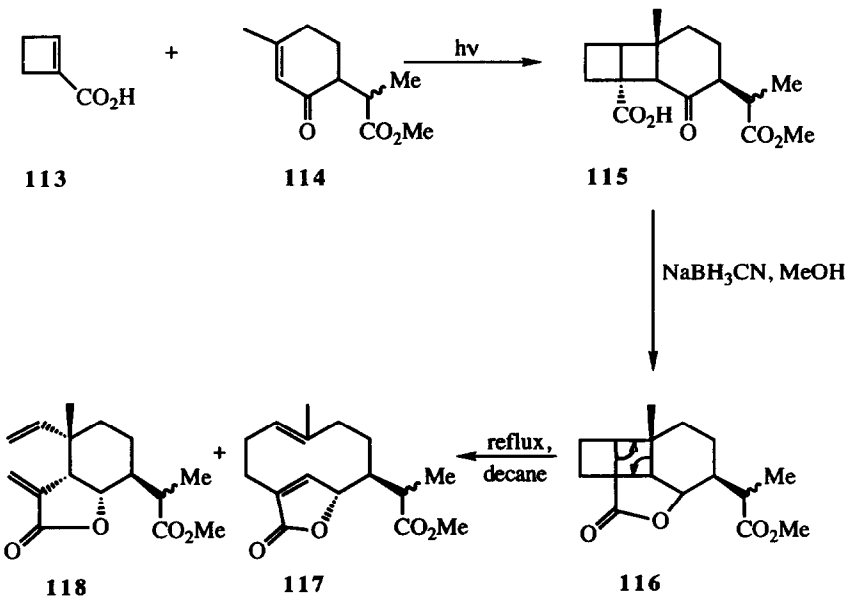
The successful application of the oxy-Cope rearrangement to the total synthesis of the germacrane sesquiterpene (+)-dihydrocostunolide[56] and the sesquiterpene aldehyde (-)-isobicyclogermacrenal[57], both containing ten-membered rings, have recently been reported. Acetylenic carbinols **108** (Scheme 22) also undergo an oxy-Cope type rearrangement to yield cyclodeca-3,5-dienones[58] **112** as possible precursors to germacrane sesquiterpenes.

Scheme 22. Synthesis of cyclodeca-3,5-dienones



A very versatile route to germacranolide, demanolide, cadinolide and guainolide sesquiterpenoid carbon skeletons has been reported[59] (Scheme 23). Photo-addition of the cyclobutene derivative **113** to the 2-cyclohexenone **114** followed by reduction of the ketone group and lactonization yielded **116**. Thermolysis of the lactone **116** gave the ten-membered ring **117** (60%) and the vinylcyclohexane derivative **118** (16%). Subsequent reactions of **117** resulted in formation of the carbon skeletons of the above-mentioned sesquiterpenoids.

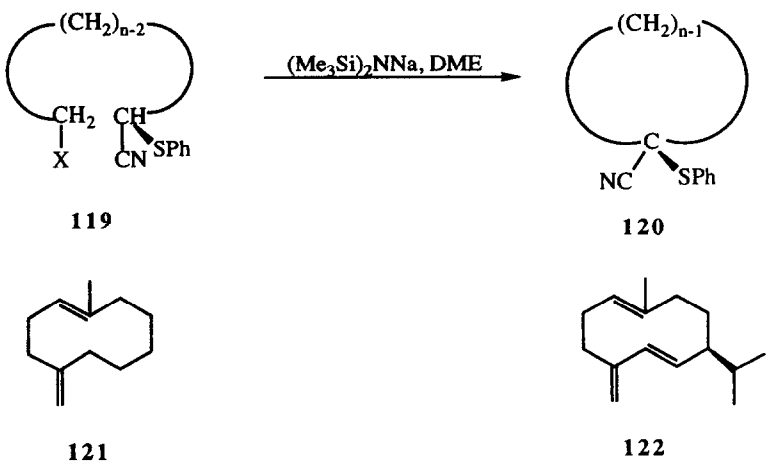
Scheme 23. Synthesis of the germacranolide sesquiterpenoid carbon skeleton



4.2.1 *Synthesis of the germacrane sesquiterpenes by direct cyclization*

A novel and useful synthesis of ten-membered and larger cycloalkenes has been developed by the use of an intramolecular cyclization of α,ω-difunctionalized molecules **119**[60] (Scheme 24).

Scheme 24. Intramolecular cyclization of α,ω-difunctionalized molecules.

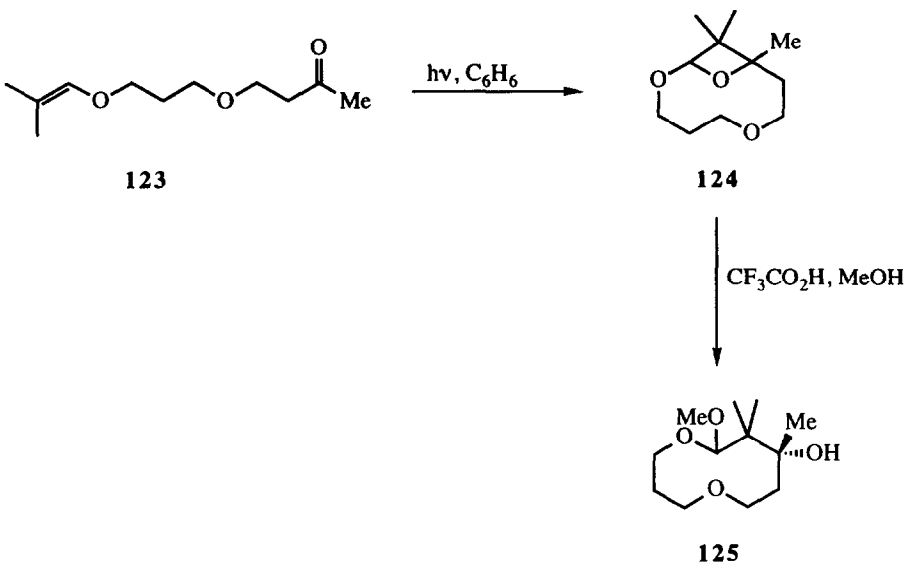


The cyclization step was not as straightforward as predicted as the use of lithium-bis(trimethylsilyl)amide in 1,2-dimethoxyethane with concentrations of the tosylate of greater than 0.05M gave the cyclic dimer of **119**. The best experimental conditions gave 80% of **120** and involved sodium-bis(trimethylsilyl)amide in 1,2-dimethoxyethane. The usefulness of this procedure was demonstrated by the synthesis of (-)-dihydrogermacrane D **121**, a possible precursor to **122** which is active as a sex pheromone mimic to the American cockroach, *Periplaneta americana*.

4.3 *Diethers. Synthesis by the Paterno-Büchi reaction*

The Paterno-Büchi reaction has been used to produce eight- to eleven-membered ring diethers.[61] A photochemically induced regioselective intramolecular cyclization of a ketone with a vinyl ether yields the cyclic acetal **124** (Scheme 25). This was then converted into the ten-membered ring diether **125** with methanol in the presence of a catalytic amount of trifluoroacetic acid. Other systems, in which the length of the alkyl chain connecting the two ether oxygen atoms was changed, were investigated. However, some loss in regioselectivity was noted although it was still possible to gain good yields (*ca.* 50%) of eight-, nine- and ten-membered ring diethers.

Scheme 25. Diethers. Synthesis by the Paterno-Büchi reaction

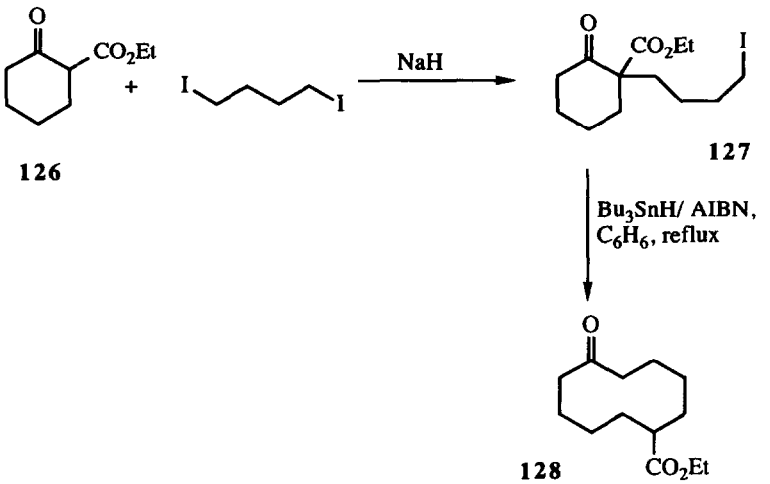


4.4 *Ketones via a free radical 3- and 4-carbon ring expansion*

Eight- to eleven-membered ring ester-substituted ketones have been synthesised by alkylating cyclic β-ketoesters with 1,3-propylene or 1,4-butylene dibromides or iodides, followed by free radical generation and cyclization[62] (Scheme 26). Treatment of the alkylated cyclic β-ketoesters with tri-n-butyltin hydride in the presence of a radical initiator (AIBN) generates the primary alkyl radical from the iodide group of **127**. This alkyl

radical adds to the ketone carbonyl group to form an oxy radical which then undergoes fragmentation-ring enlargement to the medium-ring ketone **128**. Attempts to effect the ring expansion with a 2-bromoethyl group failed, possibly due to a faster chain transfer reduction, to form a 2-ethyl β-ketoester, occurring in preference to forming the four-membered ring. The utility of the procedure was further demonstrated by starting with five- and seven-membered ring carbocyclic β-ketoesters which also underwent ring expansion to the required eight- to eleven-membered ring ester-substituted ketones.

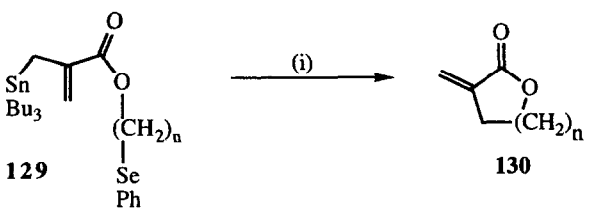
Scheme 26. Ketones *via* a free radical three- and four-carbon ring expansion



4.5 *Lactones. Synthesis via an intramolecular S_H2' radical reaction*

α-Methylene lactones containing ten- to fifteen- members have been synthesised by Baldwin *et al.*[63] (Scheme 28). The ring forming step involved a high dilution free radical S_H2' intramolecular cyclization of the ω-phenylselenoalkyl 2-(tri-n-butylstannylmethyl)propenoate esters under high dilution conditions. It is interesting to note that the six- to nine- membered ring lactones (n=2-5) failed to form. This is explained by the necessity of the ω-phenylselenoalkyl 2-(tri-n-butylstannylmethyl)propenoate esters to adopt an unfavourable s-*E* conformation, rather than the more favourable s-*Z*, allowing competing intermolecular processes to dominate.

Scheme 27. Lactones. Synthesis *via* an intramolecular S_H2' radical reaction



n= 6-11

Reagents: (i) AIBN, Bu_3SnH, C_6H_6, reflux, 48h (high dilution conditions)

4.5.1 *Lactones. A one pot synthesis by successive Michael reactions followed by ring closure*

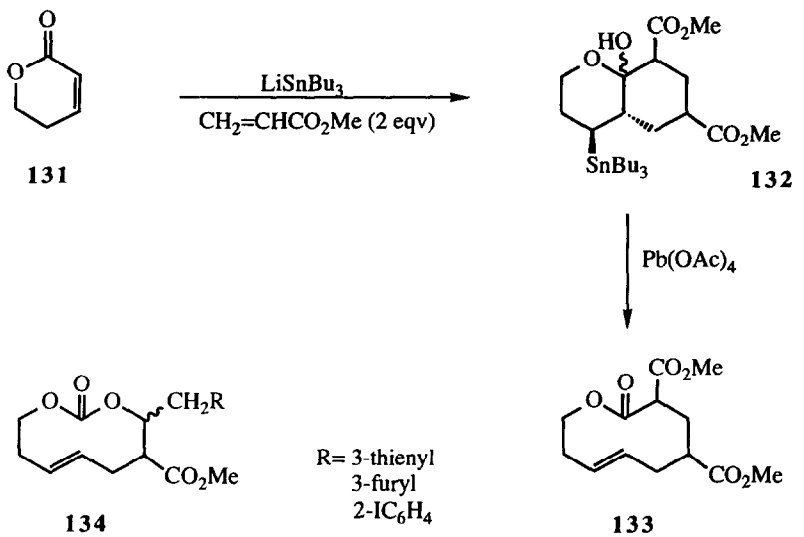
A synthetically useful one pot procedure for the synthesis of nine-, ten-, and eleven-membered ring macrolides has been reported by Posner.[64] The synthesis of the 2,4-disubstituted (*E*)-6-nonenolide containing methyl ester groups in the 2- and 4- positions is shown in Scheme 28. This sequence of reactions was characterised as a Michael-Michael-Michael-ring closure (MIMI-MIRC) product. When the first of the two methyl acrylates is replaced by ethyl vinyl ketone it is possible to substitute the 4-position of the 2,4-disubstituted (*E*)-6-nonenolide with an ethyl ketone group.

The synthesis of other macrolides containing variations in the substitution pattern of **133** were achieved under the reaction conditions described in Scheme 28. By addition of methyl acrylate to cyclohexanone followed by formaldehyde, an 8-acylated (*E*)-5-nonenolide derivative was obtained. When ethly acrylate is added to cyclohexenone followed by an aldehyde (RCH_2CHO) it was possible to obtain a substitution of R in the 9-position of the resultant nonenolides **134**. This procedure was described as a Michael-Michael-aldol-ring closure. (MIMI-ARC).

Further to the reactions previously described it was shown that similarly substituted macrolides, of different sizes (octenolides and decenolides), could be made by starting with butenolide and hexenolide, with all the substitutions mentioned for the ten-membered rings, described above, being possible.

The four variations of the MIMI-MIRC and MIMI-ARC procedures thus constitute a useful route, in both constructing nine-, ten-, and eleven-membered macrolides, and in adding substituents in predefined positions around the ring.

Scheme 28. Lactones. One-pot synthesis by successive Michael additions followed by ring closure

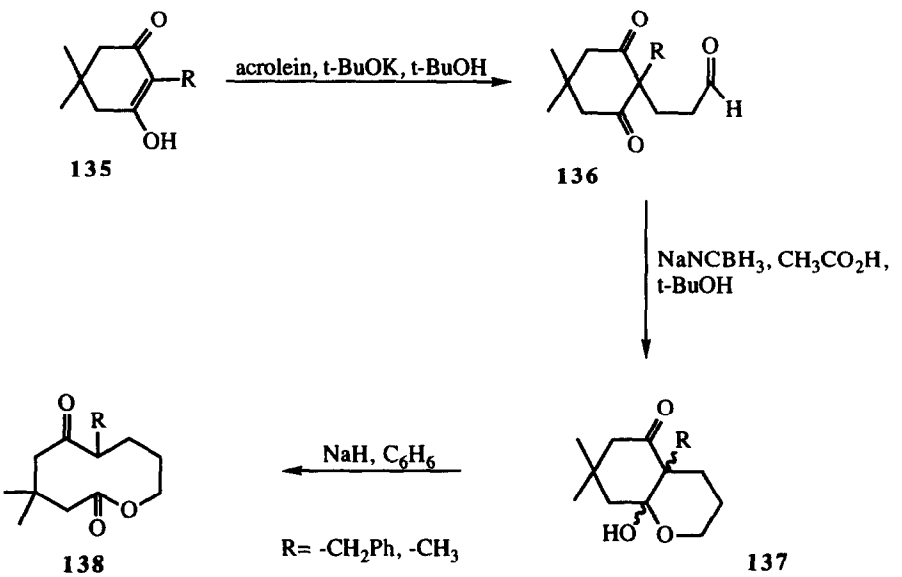


4.5.2 *Synthesis of ketolactones*

Ten- and eleven-membered ketolactones have been synthesised from various 2-substituted 1,3-diketones (Scheme 29).[65] Michael addition of 2-substituted dimedone **135** to acrolein gave the 2-substituted 2-(3-

ketopropyl)-dimedones **136**. Selective reduction of the aldehyde to give **137** was achieved using sodium cyanoborohydride in a mixture of acetic acid and t-butanol. The conversion (**137** to **138**) was effected by slow addition of **137** into refluxing benzene/sodium hydride under high dilution conditions. Yields were about 60%.

Scheme 29. Synthesis of ten-membered ring ketolactones



135 **136** **137** **138**

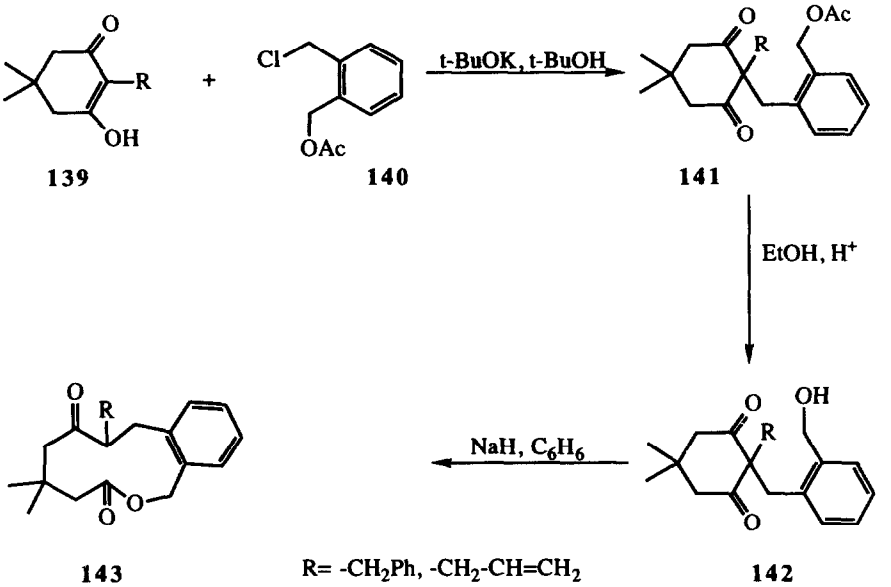
This type of cyclization reaction was also undertaken via addition of 2-(acetoxymethyl)benzyl chloride **140** to 2-alkyldimedones **139**, to yield eleven-membered ring lactones (Scheme 30).[66] Hydrolysis of the acetate **141** gave the alcohol **142** which was then treated with sodium hydride in benzene to give the eleven-membered ring lactones **143** in good yields.

Further work on these reactions (Scheme 31) involving the reaction between dimedone and *cis*-1-acetoxy-4-chloro-2-butene has been undertaken.[67] Hydrolysis of the ester and cyclization as for **141** to **143**, gave the eleven-membered ring ketolactone **147**. Many natural products including the macrolide antibiotics contain medium-ring ketolactones. This synthesis may thus offer a route to these and other natural products containing a medium-ring ketolactones.

4.5.3 *Ketolactones via the cleavage of cyclic enol ethers*

Scheme 32 presents a route to ten-, eleven-membered and larger ring containing ketolactones from cyclic enol ethers.[68] Various reagents were initially tried to cleave the vinylic bond including chromic acid/ acetic acid, chromic acid/ acetic anhydride, Jones' reagent and ozonolysis. These produced only complex mixtures of products, whereas *meta*-chloroperbenzoic acid in dichloromethane gave the ketolactones in yields ranging from 32 to 70%. More recently,[69] the cleavage of cyclic enol ethers to ketolactones has been carried out with pyridinium chlorochromate. This reagent appears to be highly selective towards the cleavage of the alkene of enol ethers and offers the advantage over other reagents mentioned above, in that enol lactones and isolated alkenes remain unaffected.

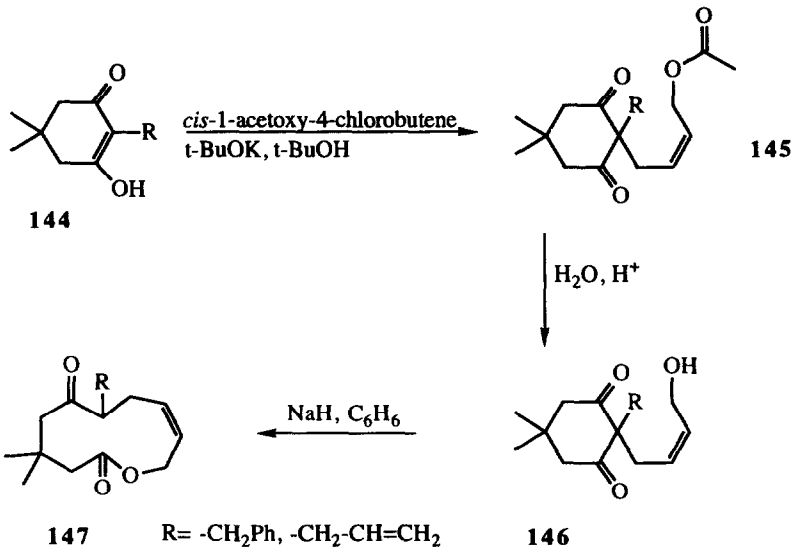
Scheme 30. Synthesis of eleven-membered ketolactones from 2-(acetoxymethyl)benzyl chloride



139 140 141 142 143

R= -CH_2Ph, -CH_2-CH=CH_2

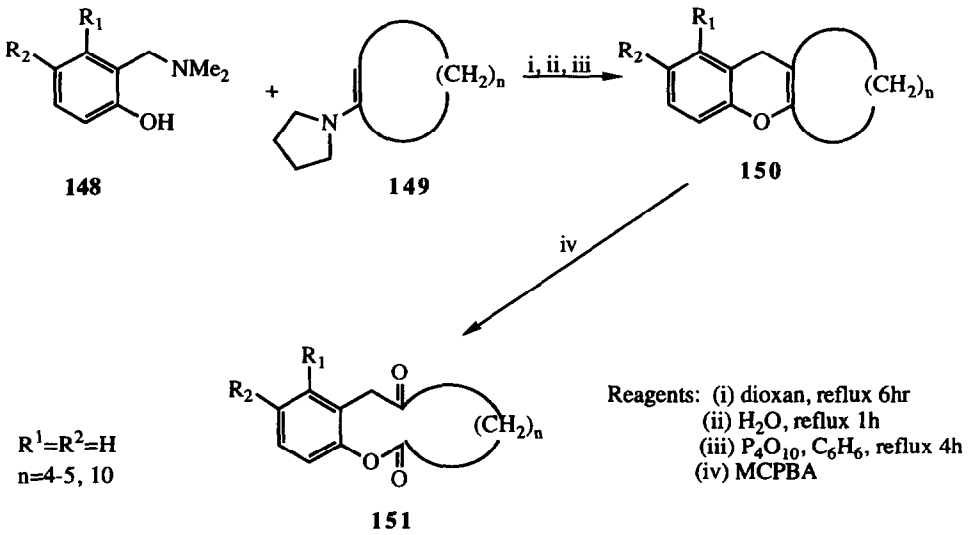
Scheme 31. Synthesis of eleven-membered ketolactones from *cis*-1-acetoxy-4-chloro-2-butene



144 145 146 147

R= -CH_2Ph, -CH_2-CH=CH_2

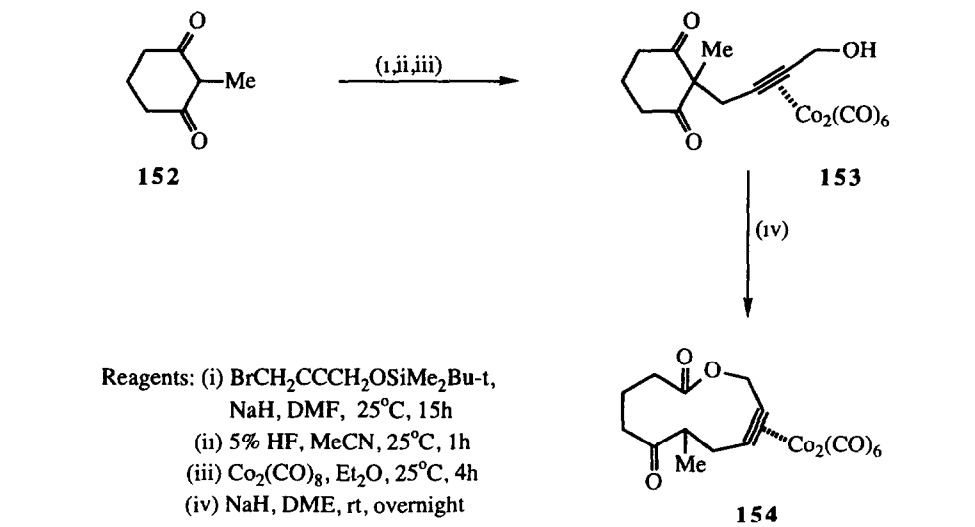
Scheme 32. Ketolactones *via* the cleavage of cyclic enolethers



4.5.4 *Eleven-membered acetylenic keto-lactones using alkyne-metal coordination*

The synthesis of medium ring lactones containing an acetylene function presents problems in that the linearity required by the acetylene group makes ring cyclization difficult. This problem is overcome by the procedure shown in Scheme 33, in which the acetylene is coordinated to a cobalt complex. This coordination allows the triple bond to 'bend', enabling ring cyclization to occur. This allowed the synthesis of eleven-membered acetylene containing lactones **154**[70] in yields between 50 and 71%.

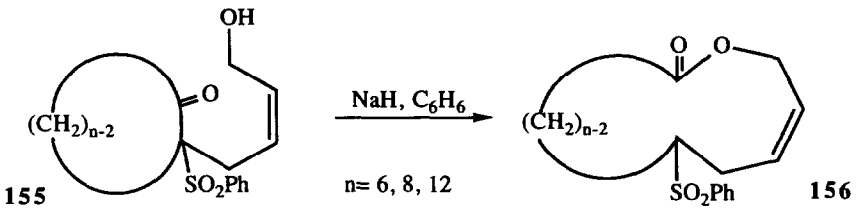
Scheme 33. Eleven-membered acetylenic ketolactones using metal promoted alkyne bonding



4.6 *Ring expansion of 2-hydroxyalkyl-2-phenylsulfonylalkanones*

Ring expansion of 2-hydroxyalkyl-2-phenylsulfonylcycloalkanones (Scheme 34) to form eleven-membered and larger lactones has been reported by Cookson and Bhat.[71] Ring expansion of **155** (n=8 and 12) was effected by boiling with sodium hydride in benzene. Ring expansion of **155** (n=6) needed the more drastic conditions provided by potassium t-butoxide in diglyme. Expansion of **155** (n=5) to the ten-membered ring lactone did not occur even under these conditions.

Scheme 34. Ring expansion of 2-hydroxyalkyl-2-phenylsulfonylcycloalkanones

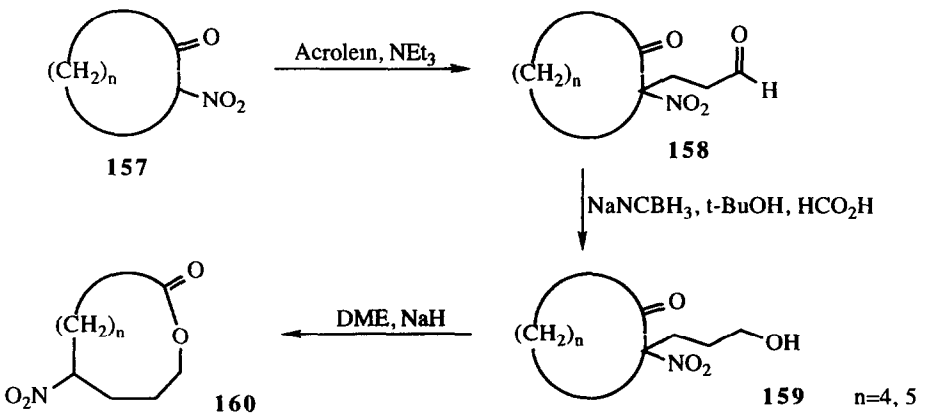


4.6.1 *Ring expansion of 2-hydroxyalkyl-2-nitroalkanones*

Since the conditions needed to effect the ring cyclization and expansion of **155** to **156** were sometimes harsh, replacement of the phenylsulfonyl group by a more strongly electron withdrawing group (nitro) was investigated[72] (Scheme 35). Ring expansion of the alcohols **159** occurred in good yield when they were refluxed in 1,2-dimethoxyethane with a catalytic amount of sodium hydride.

In the same year as the paper by Cookson and Ray, a similiar procedure involving the formation of a secondary alcohol function **163/ 164** was reported,[73] and illustrated in Scheme 36. Michael reaction between 2-nitrocyclohexanone and acrolein yielded 3-(1-nitro-2-ketocyclohexyl)propanal **162**. Selective reaction of the propyl aldehyde group over the cyclohexyl keto-group was achieved with methyl tri(2-propoxy)titanium to yield the secondary alcohol **163**, which on treatment with base gave 5-nitro-9-decanolide **165**. Later it was realized that denitration could lead to an alternative synthesis of racemic phoracantholide **82** previously discussed. This was effected using a large amount of tri-n-butyltin hydride in the presence of azobis(isobutyronitrile) (yield 20-30%).[74]

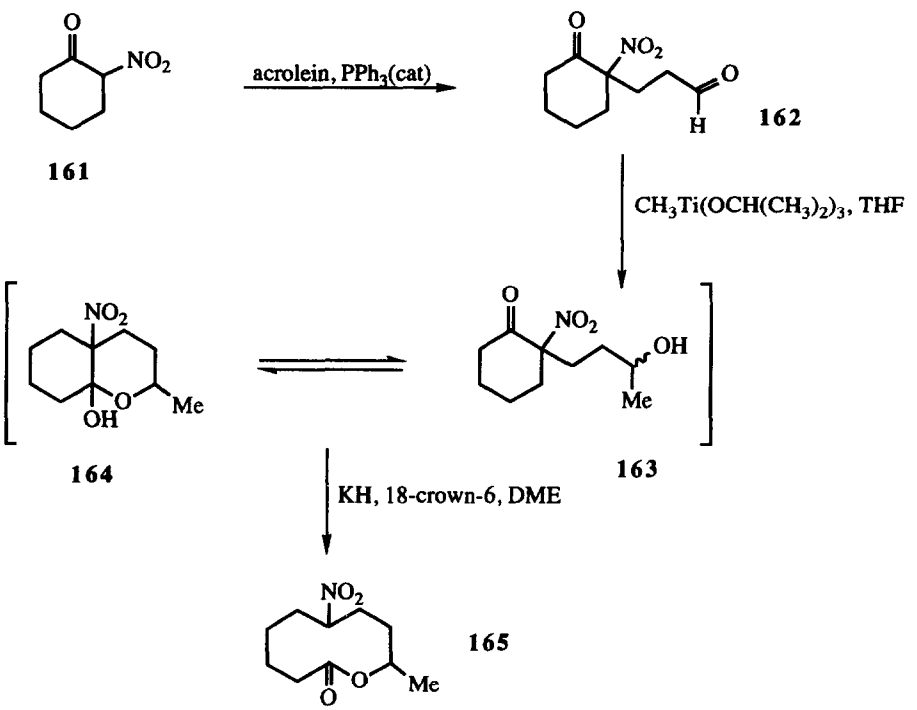
Scheme 35. Ring expansion of 2-(3-hydroxypropyl)nitrocycloalkanones



4.7 *Approach to eleven-membered ring ketolactones.*

The procedure (Scheme 37) represents a route to eleven-membered ketolactones.[75] By using α-halo ketones, which are considerably more reactive than simple alkyl halides, it was possible to produce eleven-membered ketolactones in 60% yield under relatively high concentrations (temperatures of -78°C rather than 0°C significantly increased the yield). Treatment of cyclohexanone **166** with titanium(III) chloride in the presence of hydrogen peroxide generates a free radical α- to the ketone group which subsequently undergoes a Michael type addition to acetoxymethyl vinyl ketone. Further reaction with hydrogen peroxide yields methyl 10-acetoxy-9-oxodecanoate. Dilute sulfuric acid is then used to hydrolyse the 10-acetoxy group to an alcohol which is converted into the chloride by initial formation of the mesylate ($MeSO_2Cl$, collidine) followed by displacement with lithium chloride in DMF. Finally, intramolecular cyclization occurs by nucleophilic attack of the carboxylate anion, generated from potassium carbonate in DMSO, to yield the eleven-membered ketolactones.

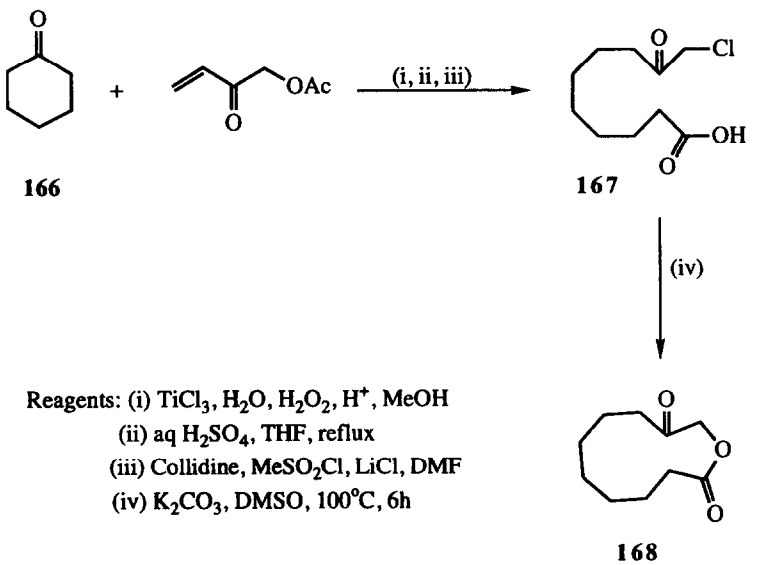
Scheme 36. Synthesis of ten-membered nitrolactones



4.8 *Ketoimides via cleavage of enamine lactams*

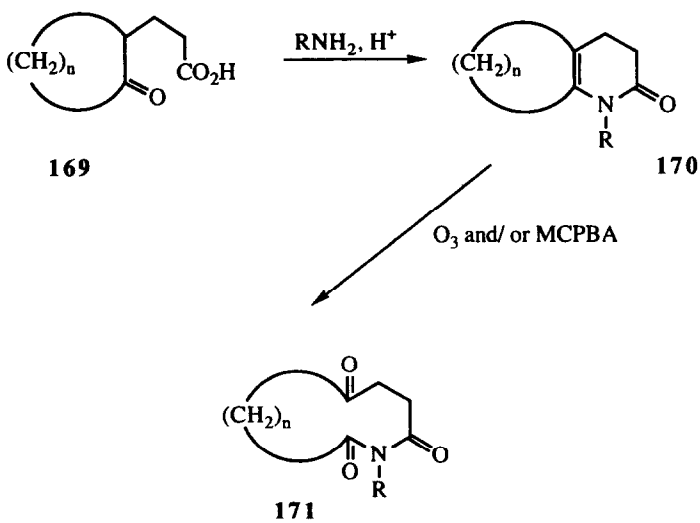
The synthesis[76] of ten-, eleven- and larger ketolactimides is summarized in Scheme 38. Oxidation of the enamine lactams **170** occurred readily with ozone and/ or metachloroperbenzoic acid; a variety of other reagents such as Jones's reagent, chromic acid in acetic acid, osmium tetroxide and periodate were not quite so effective.

Scheme 37. Approach to eleven-membered macrocyclic ketolactones



Reagents: (i) $TiCl_3$, H_2O, H_2O_2, H^+, MeOH
(ii) aq H_2SO_4, THF, reflux
(iii) Collidine, $MeSO_2Cl$, LiCl, DMF
(iv) K_2CO_3, DMSO, 100°C, 6h

Scheme 38. Synthesis of ten- to eleven-membered and larger ketoimides



R= Ph, $-CH_2Ph$
n=4-6, 10

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