Saturated and partially unsaturated carbocycles

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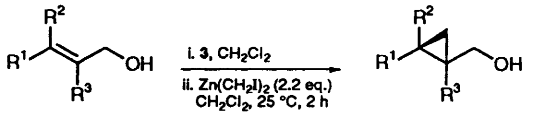
Reviewing the literature published between January 1994 and April 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1994, 1, 433

1 Three-membered rings

1.1 Metal carbenoid-based methods

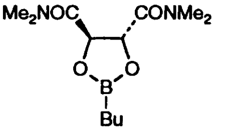
1.1.1 From dihaloalkanes

The familiar zinc carbenoid-based Simmons–Smith cyclopropanation remains a popular method for the formation of three-membered rings, allowing as it does the induction of chirality through transition state interactions with chelating heteroatoms (usually oxygen). Allylic alcohols such as **1** are the most commonly used starting materials, and a number of new chiral auxiliaries and/or catalysts have been developed to facilitate their asymmetric cyclopropanation. The most notable examples are the tartrate-derived dioxaborolane ligands **3** and **4** reported by Charette *et al.*[1,2] which, when added to **1** prior to treatment with the conventional Simmons–Smith reagent (Zn/CH_2I_2), give the corresponding cyclopropyl methanols **2** with excellent yields and enantiomeric excesses. Care is, however, required for the safe use of this method.[2] The method has also been used by Zercher *et al.*[3] and by Barrett *et al.*[4] for the preparation of vicinal cyclopropanes; for example the conversion of the diene **5** into either **6** or **7**, in which it was found to be markedly superior to other methods.[4]



1

2
≥80% yield
91–94% ee



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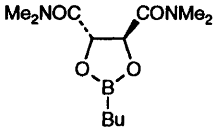

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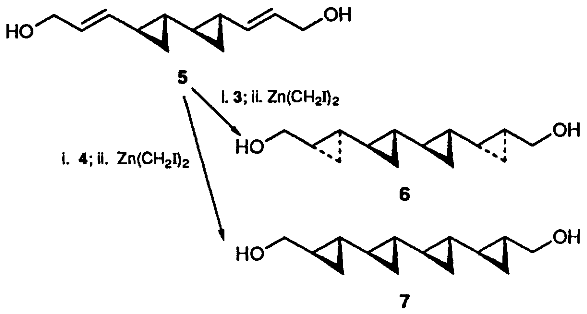
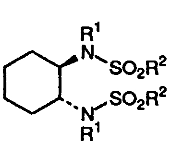


A more conventional approach to such vicinal cyclopropanes (which form part of the natural product FR-900848) has been reported by Armstrong *et al.*[5] In a similar vein Denmark *et al.* have studied the use of auxiliaries derived from the chiral diamines **8** and **9**,[6,7] obtaining moderate to



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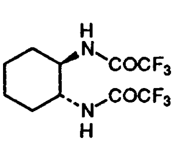

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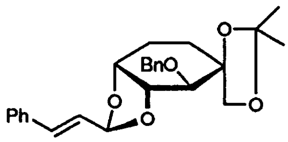
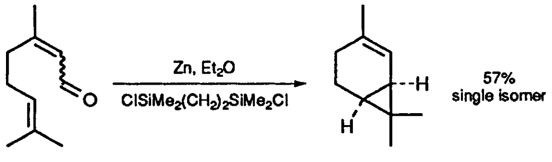


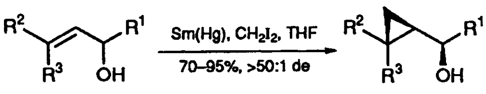
10

good enantiomeric excesses. The new acetal-type auxiliary **10** derived from fructose has been described for the cyclopropanation of 2-alkenals.[8]

An unusual route into terpenoid-derived bicyclo[4.1.0] systems such as carene **12** from acyclic terpenoid enals, *e.g.* citral **11**, has been described by Motherwell *et al.*[9] The outcome appears to be independent of the alkene geometry in the substrate. Lautens has studied the samarium-based cyclopropanation of a range of mono- and bi-metallic alkenols **13**, with the *syn* cyclopropanes **14** being obtained in very good yields and with high diastereoselectivity.[10] The same procedure was also applied[11] to the regioselective cyclopropanation of α-allenyl alcohols **15**, giving the synthetically useful cyclopropylmethylenes **16**. It is noteworthy that in the latter case conventional zinc carbenoid methods completely failed to give the required chemoselectivity.

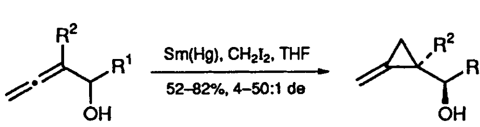


11 **12**



13 **14**

R^1 = alkyl; R^2, R^3 = H, alkyl, TMS, Bu_3Sn



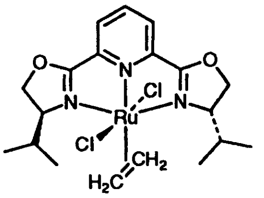
15 **16**

R^1 = alkyl; R^2 = H, alkyl, MeO

1.1.2 From diazocarbonyl compounds

The other classical method for effecting metal-carbenoid mediated cyclopropanations – treatment of alkenes with diazocarbonyl compounds in the presence of a metal catalyst – has also received considerable attention recently. Nishiyama has reported the use of the chiral ruthenium bis(oxazolinyl)pyridine catalyst **17** for the asymmetric cyclopropanation of terminal alkenes.[12] In a similar vein, Kanemasa *et al.* have described a 1,2-diamine–Cu(II) triflate complex derived from **18**, which is applicable to the cyclopropanation of disubstituted alkenes as well;[13] diastereoisomeric and enantiomeric excesses are only moderate however.

Finally, Martin and co-workers have studied the intramolecular cyclopropanation reactions of secondary allylic diazoacetates **20** using the rhodium catalyst **19**; good to excellent degrees of *endo*-selectivity were achieved.[14]



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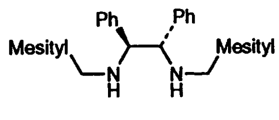

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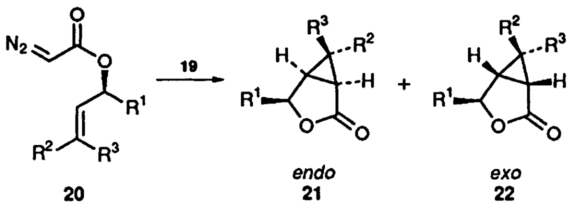
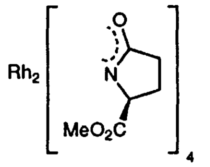


20 **21** **22**



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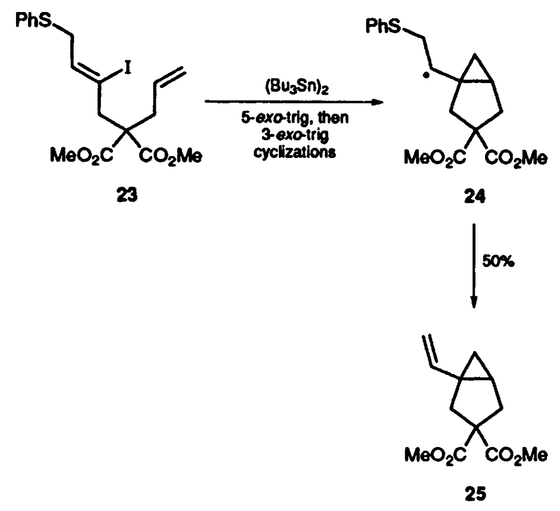
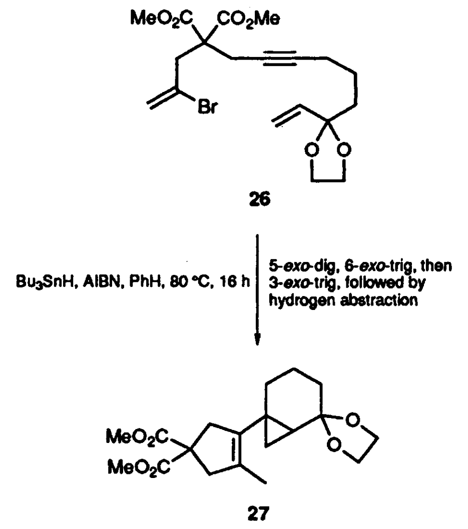
1.2 Free radical methods

Free radical methods are not commonly used for cyclopropane ring synthesis, since 3-*exo*-trig closures to give cyclopropylmethyl radicals are readily reversible, with the equilibrium favouring the open-chain form. However, if the product radical is either trapped out, or is sufficiently stable to allow reduction to be competitive with ring opening, cyclopropane products *can* be obtained. An example of the former has been reported by Gravel, where dienes such as **23** may be cyclised to give the intermediate **24**, which immediately eliminates phenylthiyl radical to give the bicyclo[3.1.0]hexane **25**.[15]

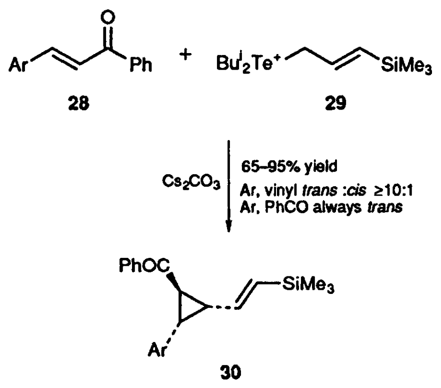
A more unusual example has been described by Malacria, where the enyne **26** undergoes sequential 5-*exo*-dig, 6-*exo*-trig and 3-*exo*-trig cyclisations to give an allylic radical, which proves to be *more* stable than the open chain form resulting from the first two cyclisations.[16] Final hydrogen abstraction from the tin hydride then leads to the tricycle **27**.





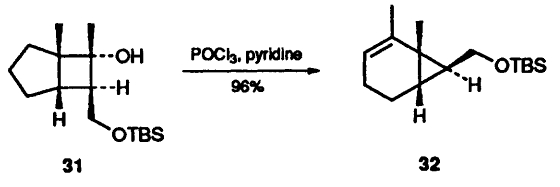
1.3 Ylide-based methods

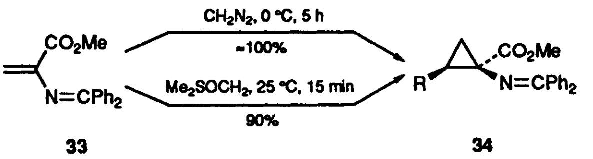
An unusual method for the synthesis of cyclopropanes, based on organotellurium chemistry, has been described by Huang *et al.*, wherein chalcones **28** are reacted with the reagent **29** in the presence of an inorganic base, giving the cyclopropanes **30**.[17] Also, the familiar dimethylsulfoxonium methylide cyclopropanation of chalcone has now been carried out in the solid state.[18]

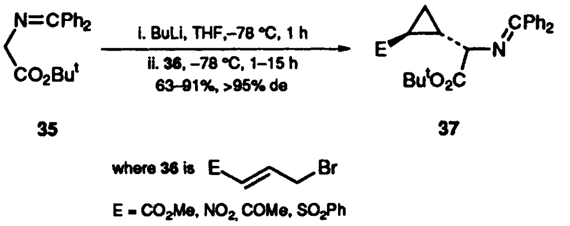


1.4 Other routes to three-membered rings

Fused cyclobutane ring systems such as **31** have been transformed cleanly and efficiently into the fused cyclopropanes **32**.[19] Two research groups have reported new approaches to various cyclopropyl amino acids. Cativiela *et al.* have followed the most straightforward of these, by treating α,β-didehydroamino acid derivatives such as **33** with either diazoalkanes or sulfonium ylides, to give the protected amino acids **34**.[20] In contrast, de Meijere and co-worker have reported the use of three carbon synthons such as **36** as Michael acceptors in a synthesis of the cyclopropyl-substituted protected amino acids **37**.[21]



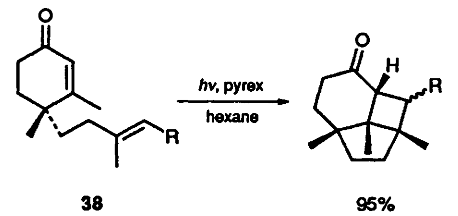




2 Four-membered rings

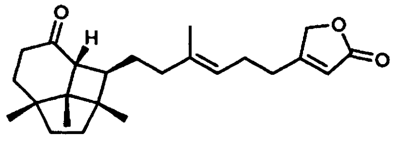
2.1 Photochemical methods

The elaboration of cyclobutanes by photocycloadditions between alkene bonds remains one of the most engaging and enduring reactions in modern synthesis. Houk *et al.*[22] have used *ab initio* theory to study the regioselectivity of intermolecular photocycloadditions of triplet cyclohexenones to alkenes; and Becker *et al.*[23,24] have provided further results of their extensive studies of the regio- and stereochemical outcomes of intramolecular [2+2] photocycloadditions involving various alkene substituted cyclo-2-alkenones. A silicon-tethered variant of the intramolecular [2+2] photocycloaddition process has been described.[25] Meyers *et al.*,[26] together with Koga *et al.*,[27] have demonstrated the power of intramolecular [2+2] photocycloadditions involving chiral starting materials (**38** and **40**) in the target synthesis of natural products, *viz* lintenone A **39** and stoechospermol B **41** respectively.



38

95%



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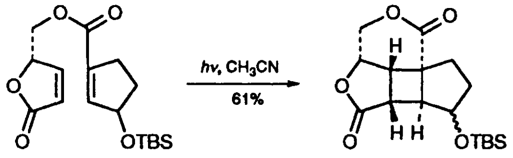

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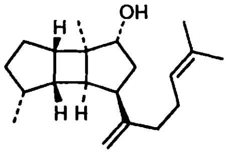

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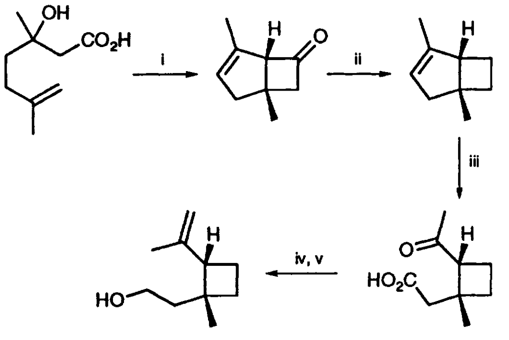
2.2 Other routes to four-membered rings

The procedure whereby cyclobutanones can be prepared through an intramolecular [2 + 2] cycloaddition between an *in situ* generated α,β-unsaturated ketene and a C=C bond, has now been utilised[28,29] in a stereoselective synthesis of the pheromone grandisol **42** (**Scheme 1**).[30]



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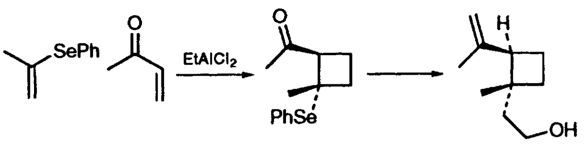
Reagents: i. Ac$_2$O, CH$_3$CO$_2$K, Δ; ii. NH$_2$NH$_2$, then (EtOCH$_2$CH$_2$)$_2$O, KOH, Δ; iii. RuCl$_3$–NaIO$_4$; iv. Me$_3$SiCH$_2$MgCl, then SOCl$_2$; v. LiAlH$_4$–Et$_2$O

Scheme 1

In a demonstration of the scope for the reported selenium-directed, stereoselective [2 + 2] cycloaddition of silyl vinyl selenides to enones, Yamazaki *et al.*[31] have described a concise synthesis of fragenol **43**, which is a constituent of *Artemisia fragrans willd.*



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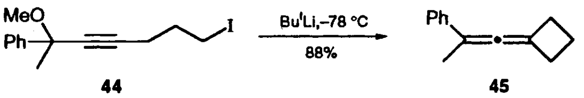
Some interesting alkenylidene cyclobutanes have been synthesised by cyclisations of acetylenic alkyllithiums (formed by lithium–iodine exchange) bearing a prop-2-ynylic leaving group, *viz* **44**→**45**,[32] and Ihara *et al.*[33] have described a neat synthesis of fused four-membered rings from cyclopropyl ketones on treatment with TMS-iodide, *i.e.* **46**→**47**.



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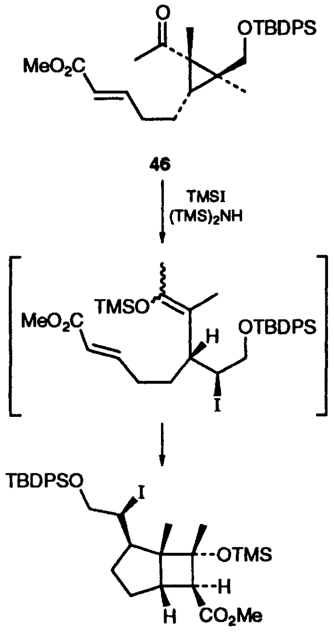

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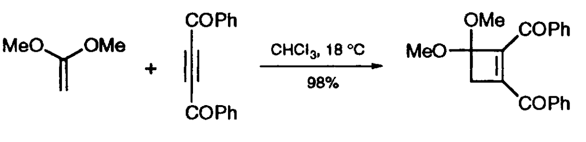
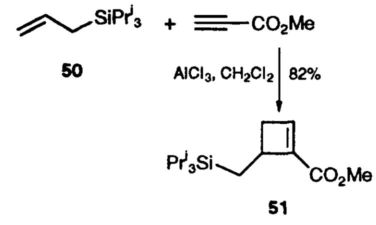
2.3 Cyclobutenes

Cyclobutenes are useful intermediates in synthesis; for example, they undergo facile electrocyclic ring opening to functionalised 1,3-dienes. 3,3-Dimethoxycyclobutenes **49** are now easily prepared from the [2 + 2] cycloaddition of 1,1-dimethoxyalkenes **48** to electron-poor alkynes in anhydrous chloroform at low temperature, *e.g.* 18 °C.[34] Other substituted cyclobutenes, *e.g.* **51** can be produced from Lewis acid catalysed reactions between allylsilanes and acetylenes, *viz* **50**→**51**.[35]



48 49

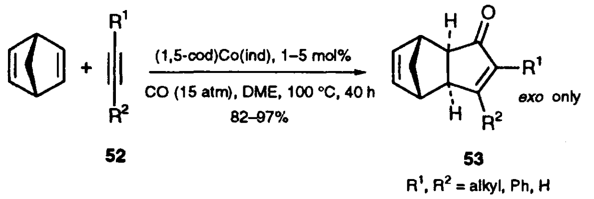


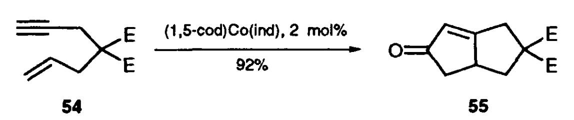
3 Five-membered rings

3.1 Transition metal-based methods

3.1.1 Cobalt

The familiar Pauson–Khand reaction (henceforth ‘PKR’) has once again been the subject of considerable interest. Perhaps the most notable achievement has been the discovery by Jeong, Chung and co-workers of the first reasonably general *catalytic* version of the reaction.[36] The method is effective for both the *inter*molecular (**52**→**53**) and the *intra*molecular (**54**→**55**) reaction; the same authors have reported an alternative method for the latter based on the use of phosphite co-ligands.[37]

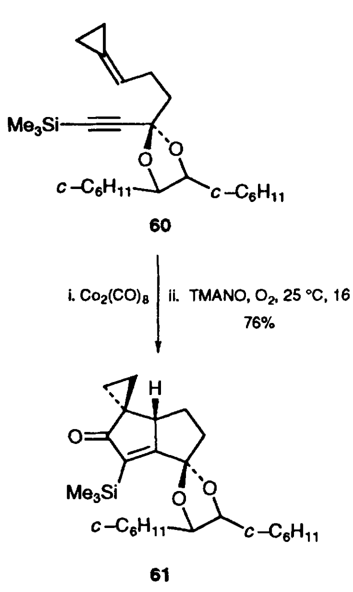


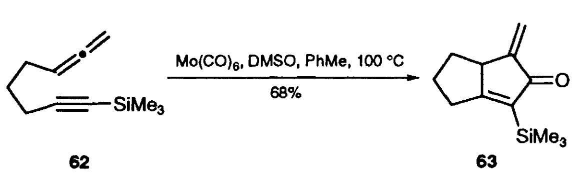


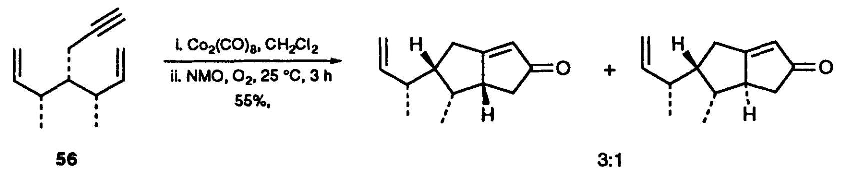
Another interesting development has been the observation by Schore *et al.* of reversed (*endo*) selectivity in the PKR of the dienyne **56**;[38] this clearly indicates that the normal *exo* preference of the intramolecular reaction can be reversed in certain situations. Progress has also been made in the field of chiral auxiliaries, with Greene and Pericàs describing the use of a camphor-derived auxiliary to control diastereoselectivity in the PKR of **57**; the conversion of the product **58** into the useful chiral cyclopentenone **59** is also described.[39]

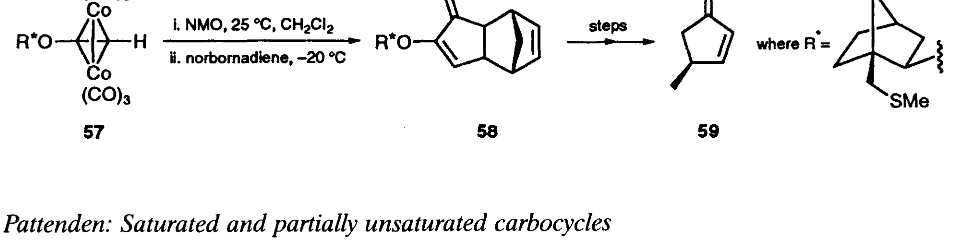
De Meijere *et al.* have synthesised a range of spiro(cyclopropyl)cyclopentenones such as **61** by using methylenecyclopropanes **60** as the alkene component[40,41] – a reasonable (6.5:1) ratio of diastereoisomers was obtained by the use of the appropriate chiral dioxolane auxiliary. In a similar vein α-methylene cyclopentenones **63** have been prepared by carrying out the PKR with allene intermediates such as **62**.[42] In this case the substitution of molybdenum for cobalt was required in order to effect reaction. Finally, syntheses of (+)-kainic acid,[43] (+)-taylorione[44] and a model for xestobergsterol[45] have been published using the PKR in key steps.

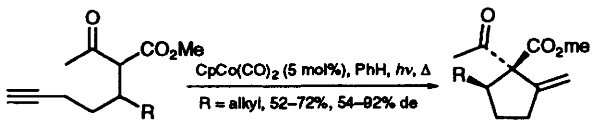
One other novel use of cobalt catalysis is in the cycloisomerisation of ε′-acetylenic β′-alkyl β-ketoesters such as **64** to methylenecyclopentanes **65**.[46]







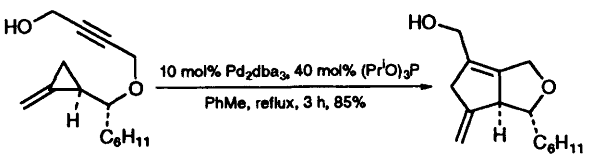




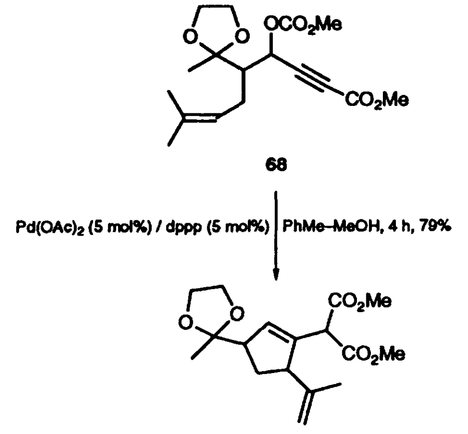
64 **65**

3.1.2 Palladium and nickel

The use of methylenecyclopropanes in Pd-catalysed [3 + 2] cycloadditions to alkynes has been explored by Motherwell *et al.*[47] and by Lautens *et al.*[48] Lautens *et al.* have also shown that the process (*e.g.* **66**→**67**) proceeds with overall *retention* of stereochemistry at the cyclopropane chiral centre. Mandai and co-workers have devised an interesting route from β-alkynyl carbonates such as **68** to the cyclic products **69**; the reaction is believed to proceed via a 1,1-dicarboethoxyallene intermediate, which undergoes an intramolecular ene reaction to give the observed product.[49]



66 **67**



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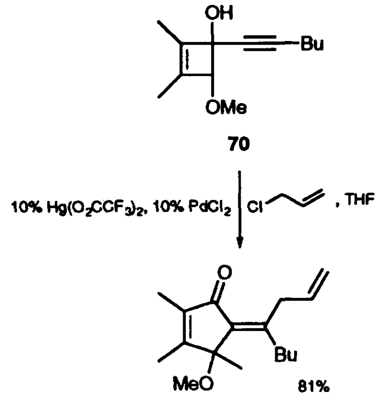
69

Liebeskind *et al.* have reported a convenient approach to cyclopentenones such as **71** by the Pd–Hg mediated ring expansion of alkynyl cyclobutenols such as **70**.[50] The method can also be used to make cyclopent-4-ene-1,3-diones, as can the treatment of 1-hydroxy-1-alkynyl cyclobutenols with Fischer carbenes.[51] In another related use of ring expansion Fukumoto *et al.* have developed a novel approach to tetrahydro-indanones **73** by treating vinylcyclobutanols such as **72** with catalytic Pd(II); the alkyl palladium species formed by ring expansion inserts *in situ* into the pendant alkene.[52,53]

The work of Trost *et al.* towards 'atom economical' cyclisations continues; a Pd catalyst for the cycloisomerisation of 1,6- or 1,7-enynes to dialkylidene cyclopentanes or cyclohexanes (which can then be used as dienes in similarly economical Diels–Alder cycloadditions) has been reported.[54] De Meijere and co-workers have reported a similar method, whereby the cycloisomerisation step is replaced with a Heck reaction.[55]



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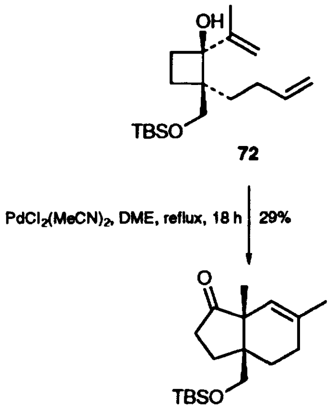
71



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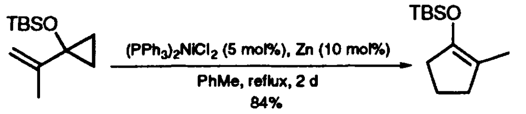
73

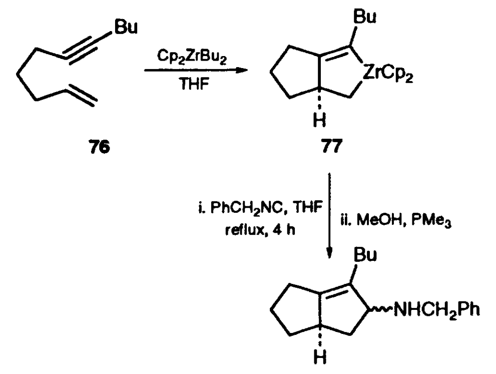
Finally, two interesting uses of nickel catalysis have been reported. In the first of these Ryu, Sonoda and others have described a relatively mild method for carrying out a vinylcyclopropyl ether to cyclopentanone enol ether rearrangement, *viz* **74**→**75**, based on the use of a Zn–Ni catalyst.[56] In the second, Mori *et al.* have published details of a novel cyclisation of π-allyl nickel complexes, derived from 1,3-dienes, onto pendant carbonyl groups; the method is also applicable to six- and seven-membered rings.[57]



74 **75**

3.1.3 Zirconium

The Zr-mediated intramolecular cyclisation of 1,6-dienes or enynes **76** is a well-established method of forming cyclopentanes, and proceeds by way of intermediate zirconabicycles **77**. Whitby *et al.* have shown that the conversion of **77** into amino bicyclo[3.3.0]octanes **78** is possible by treatment with

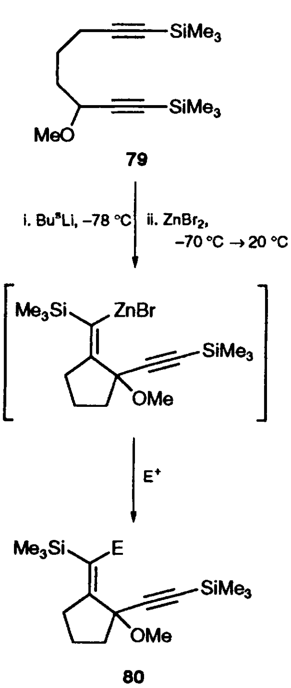


76 **77** **78**

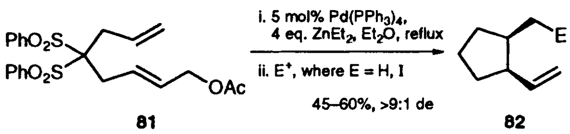
isonitriles, followed by heating and then quenching, either with methanol or an alkyne (the latter giving a vinyl amine product).[58] A number of researchers have published studies of regio- and stereo-control in the initial cyclisation step,[59–61] of which Negishi's is perhaps the most interesting.[62] Finally, the method has been used as the key step in a formal total synthesis of (−)-dendrobine.[63,64]

3.1.4 Other transition metals

Normant and Marek have published a general study of intramolecular carbometallations of organozinc reagents derived from 6-halo-1-alkenes, and observed exclusively 5-*exo*-trig cyclisation in all cases studied.[65] This is a potentially powerful method, in that it tolerates quite reactive functional groups (*e.g.* esters). The RZn species is also easily prepared and, unlike in radical reactions, the product can be trapped *inter*molecularly using a wide range of electrophiles. The same authors have also published a novel route to alkynyl *exo*-methylene cyclopentanes **80**, based on the 3-metallation of 3-methoxy-1,7-diynes **79**.[66] In related work the equivalent metallo-ene reaction has also been performed, by carrying out the metallation–transmetallation procedure on a 1,6-enyne.[67] Oppolzer *et al.* have described a similar reaction, using a Pd–Zn system to effect the conversion of **81** into **82**, as predominantly the *cis* isomer.[68]

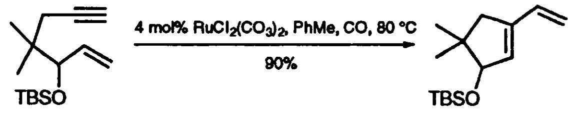


79 **80**



81 **82**

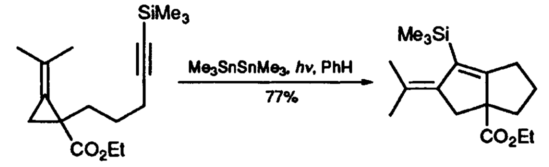
In another variation on metal-catalysed enyne cyclisation, Murai *et al.* have demonstrated that the isomerisation of 1,6-enynes **83** to vinyl cyclopentenes **84** (usually achieved using Pd catalysis – see Section 3.6 for examples) can be effected using a ruthenium catalyst.[69] This approach has the advantage over Pd-based methods in that terminal alkynes can be used without formation of undesirable isomers; it can also be applied to 1,7-enynes. Finally, a new variant on the cyclisation of 1,6-diynes has been reported by Ojima *et al.*, based on silylformylation.[70]



83 **84**

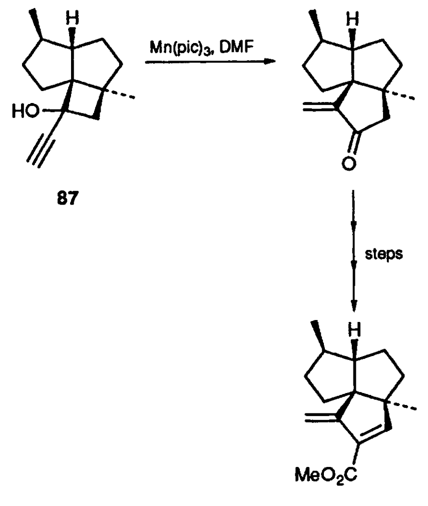
3.2 Free radical-based methods

Work by Singleton and collaborators has shown that the synthesis of methylenecyclopentanes, starting from methylenecyclopropanes, can be carried out by using a radical-mediated [3 + 2] cyclisation strategy.[71] The method is illustrated by the conversion of **85** into the diquinane **86**,[72] and can also be applied to intermolecular cycloadditions.[73]



85 **86**

Snider has utilised the Mn-based oxidative radical fragmentation of alkynyl cyclobutanols **87** (*cf.* the Pd/Hg method in Section 3.1.2) in a total synthesis of (−)-methyl cantabradienate **88**.[74] Shirahama and Matsuda have described a completely diastereoselective route to 2-vinylcyclopentaols **90**, based on the trapping of ketyl radicals formed by samarium(II) iodide reduction of carbonyl compounds such as **89**.[75] Molander *et al.* have published a related study on the 5-*exo* and 6-*exo* cyclisations of similarly-obtained ketyl radicals,[76] and Fallis *et al.* have studied the intramolecular trapping of samarium-generated radicals with hydrazone acceptors.[77]



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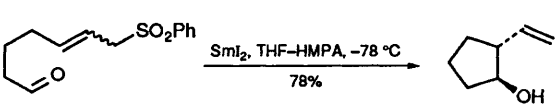

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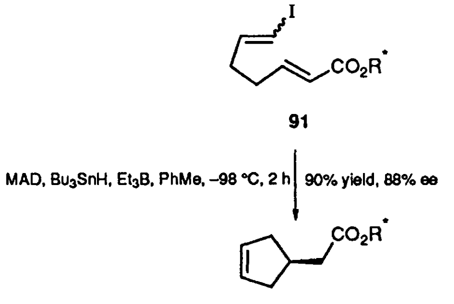
90

The concurrent use of radical methods and Lewis acid chelation of chiral ester auxiliaries has been deployed by Nishida *et al.* for the asymmetric synthesis of 3-alkylcyclopentenes **92** starting from ω-haloalkenyl acrylates **91**.[78] The reaction gives good enantiomeric excesses and can also be used with dibromoolefins.

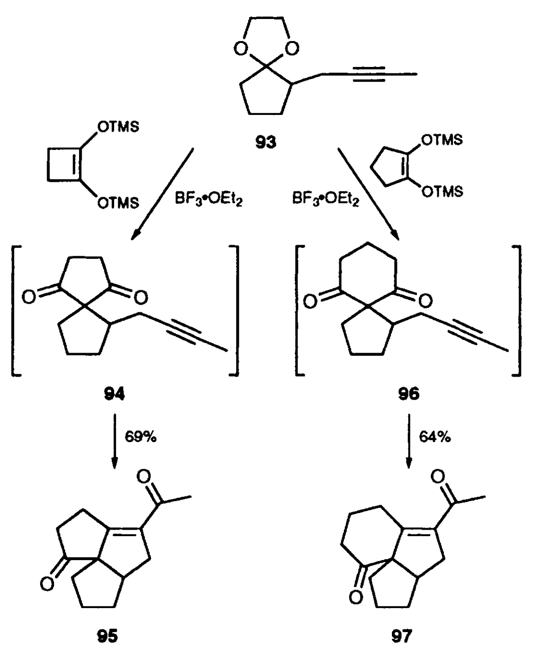


92

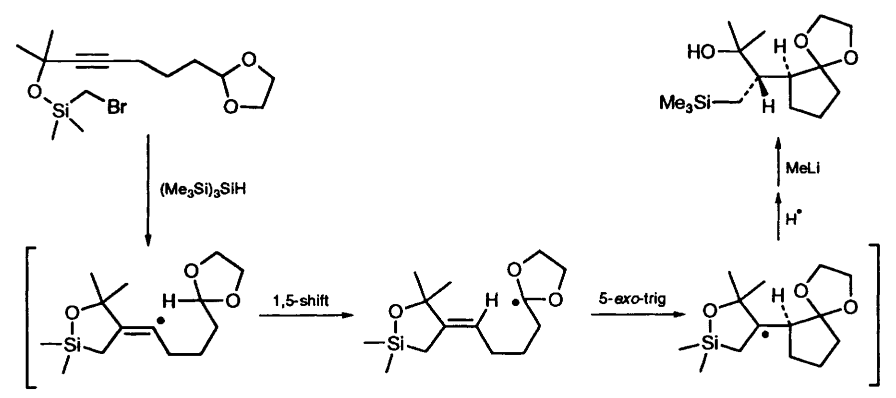
Hydrogen atom transfer reactions are an increasingly important facet to radical cyclisation chemistry, and Malacria has reported an interesting example (**Scheme 2**).[79] In a similar vein, Parsons and Caddick have described a synthesis of spiro-fused cyclopentanones based on 1,5-abstraction from an allylic centre.[80] Finally, radical spirocyclisation has been used by Clive *et al.* in a total synthesis of (±)-fredericamycin A,[81] and the same authors have described a route to the triquinane (±)-cerato-picanol using a radical derived from an epoxide.[82]

3.3 Cationic methods

The conversion of ketones (or their ketals) into cyclopentane 1,3-diones (*e.g.* **93**→**94**) by reaction with 1,2-bis(trimethylsilyloxy)cyclobutene is a well-established tactic in total synthesis. Burnell and co-workers have reported a method for carrying out this transformation in a single step, using an excess of boron trifluoride etherate,[83] and have used the method in a new total synthesis of (±)-penta-lenene.[84] Furthermore, Curran *et al.* have extended the process to include a subsequent 5-*exo* cyclisation onto a pendant alkene or alkyne, giving a diquinane such as **95** (**Scheme 3**).[85,86] The use of



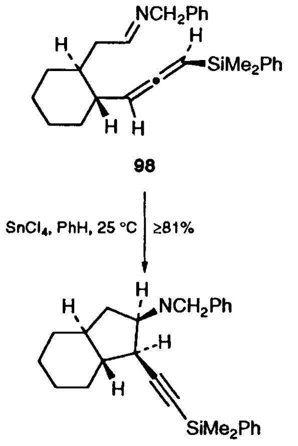
Scheme 3



Scheme 2

1,2-bis(trimethylsilyloxy)cyclopentenes instead gives a bicyclo[4.3.0]nonane product **97**, by way of the 1,3-dione **96**.

One of the most widely used terminating groups for cationic cyclisations remains the allyl or propargyl silane. Amberlyst-15 has been shown to be a simple and effective catalyst for such reactions.[87] Weinreb *et al.* have reported a fascinating synthesis of the natural product papuamine, featuring as a key step a Lewis acid-catalysed imino-ene reaction onto an allenylsilane (**98**→**99**).[88] Such catalysis has also been used effectively in a more straightforward Alder-ene approach to vinyl cyclopentanes.[89,90] Nagao and co-workers have developed a new geminal spiro-*endo* mode of cyclisation of allenyl ketones, which is illustrated for dimethoxyaryl cases by **100**→**101**.[91–93]



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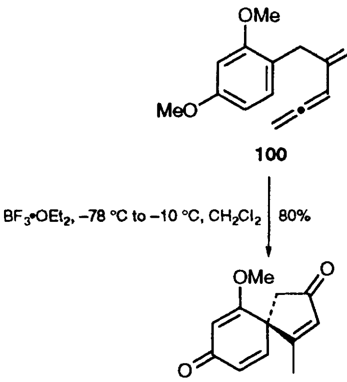
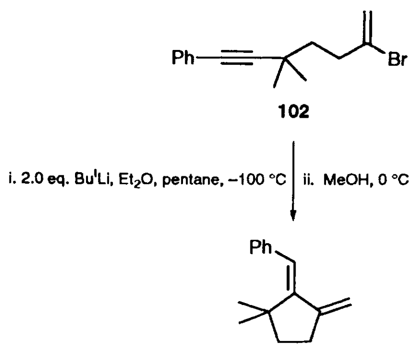


101

3.4 Anionic methods

Cooke *et al.* have extended their work on halogen–metal exchange as an initiator of sequential Michael additions to the formation of bicyclic [4.3.0] and [3.3.0] systems.[94,95] In related work, Ovaska, Bailey and co-workers have devised a synthesis of 1,3-bis-exocyclic dienes **103**, based on 5-*exo*-dig cyclisation of vinyllithiums onto alkynes such as **102**.[96] As with the Pd-catalysed work of Trost,[54] the diene products can be reacted *in situ* with a suitable dienophile, making for a one-pot synthesis of bicyclo[4.3.0]-nonenes.

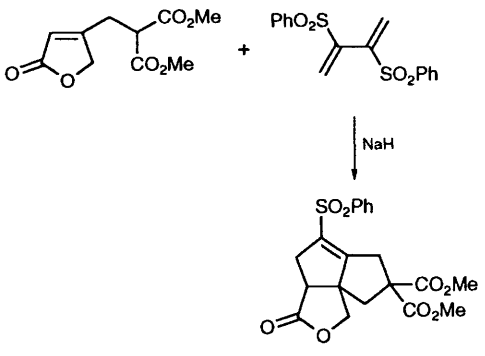


103

94% single isomer

Padwa *et al.* have published a convenient route to bicyclo[3.3.0]octenes **104**, based on an anionic [3+2] cycloaddition step.[97] The same authors have published a route to arylcyclopentones from diazoacetophenones,[98] and Asaoka *et al.* have described a convenient and enantioselective route to a capnellene fragment, based on silyl-directed cyclopentanone enolate alkylation.[99]

Finally, Stang *et al.* have reported a novel route to 2-sulfonyl cyclopentenones **106**, via a tandem Michael addition–carbene insertion methodology starting from γ-ketoethynyl phenyl iodonium triflates **105**.[100,101]



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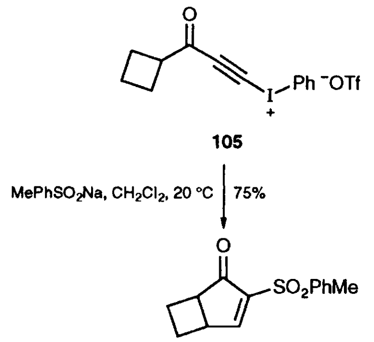
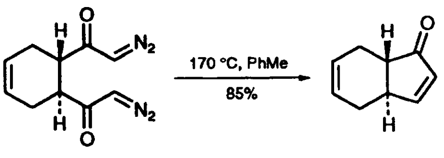


106

3.5 Other routes to five-membered rings

Thermal Wolff rearrangement of the 1,2-bis(diazo-ketone) **107** has been used by Nakatani and co-workers as the basis of a synthesis of *trans*-hydro-1*H*-2-inden-1-one **108**.[102]



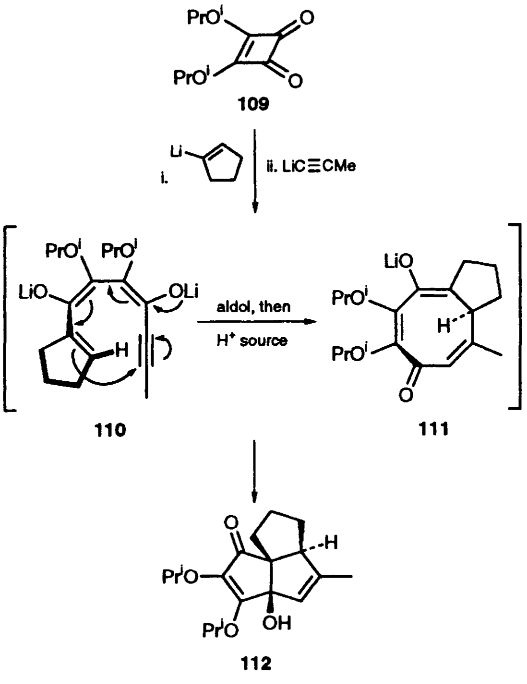
107 **108**

3.6 Polyquinanes and 'cascade' polycyclisations

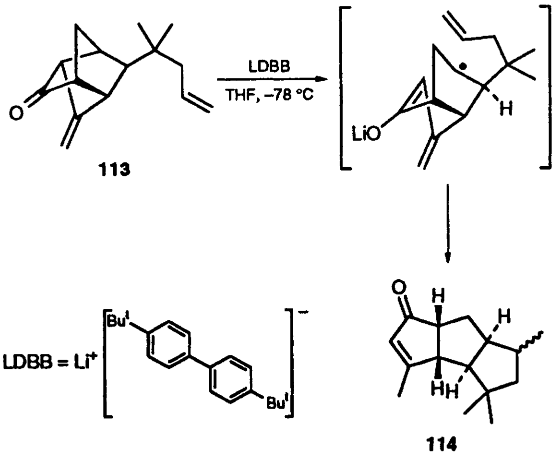
The methods of five-membered ring synthesis detailed so far have all dealt primarily with the formation of single ring. However, the trend in modern organic synthesis is increasingly towards the formation of two or more rings in the same step, whether by conventional means (*e.g.* rearrangements) or by the increasingly popular 'tandem' or 'cascade' processes, wherein the product from the first cyclisation initiates further ring closures. Five membered rings are well suited to the latter, as 5-*exo* cyclisations are usually preferred to 6-*endo*, and 5-*endo* to 4-*exo*, especially in free radical processes, making polyquinane constructions a favourable option.

One of the most useful and rapid rearrangement-based methods is the conversion of squarate esters **109** to diquinanes **112** by sequential treatment with suitable anions. Paquette and co-workers have shown that by using an acetylide as the second anionic component, the regiochemistry of the aldol reaction (**110**→**111**) can be controlled[103,104] (**Scheme 4**; compare this with the work of Hirama *et al.* described in Section 7, *i.e.* **212**→**213**).

Rawal *et al.* have developed a fragmentation route to diquinanes based on the photocycloadducts **113**, which are readily obtainable by a photocyclisation of norbornene derivatives.[105] The radical formed on the diquinane skeleton arising from the initial fragmentation can be trapped with a pendant alkene, allowing the triquinane skeleton **114** to be prepared.[106]



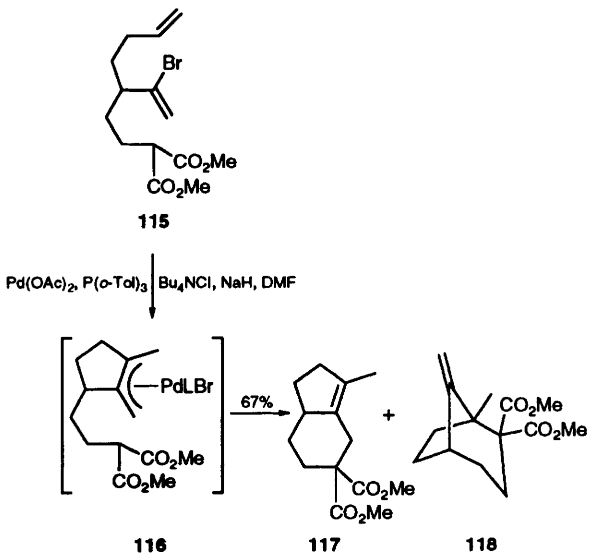
Scheme 4

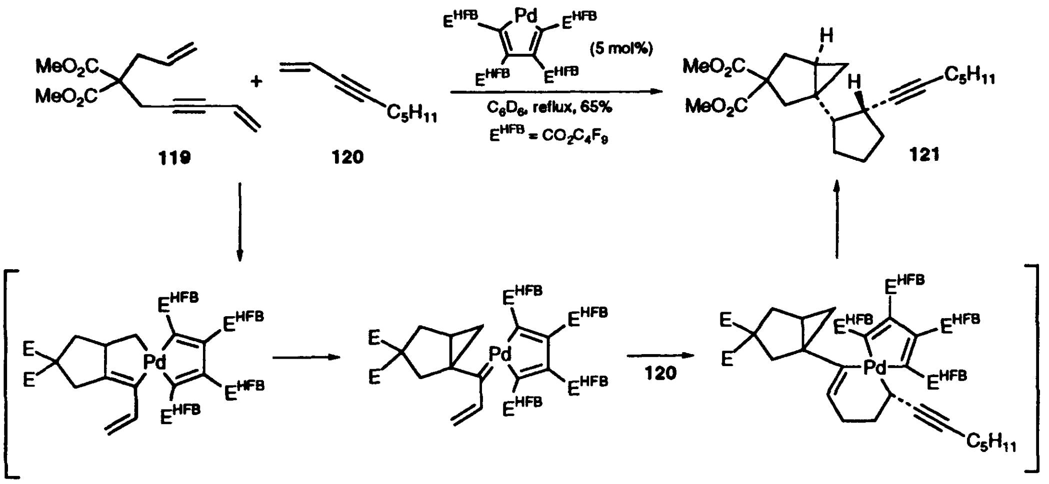


The Heck reaction is a well-established staple of carbocycle synthesis.[107] Weinreb *et al.* have assessed the possibility of carrying out the reaction on a substrate such as **115** which gives rise to a π-allyl Pd complex **116**, which can then be displaced with a soft carbanion.[108] The results confirm that the reaction is possible, but is reduced somewhat in value by the usual problems of α:γ selectivity, giving a mixture of **117** and **118**.

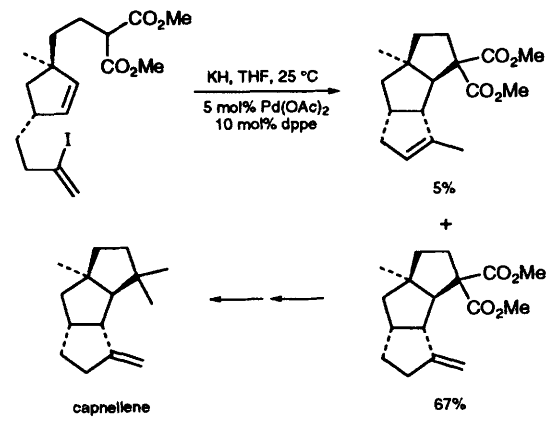
Palladium also features in a fascinating extension to Trost's work of enyne cycloisomerisation; Trost *et al.* have developed a catalyst which allows direct conversion of 1,6-enynes **119** into tricycles **121**, by reaction with 1,3-dienes or 1,3-enynes such as **120** (**Scheme 5**).[109]

The most common ways of effecting 'cascade' reactions involve either free radical intermediates or palladium catalysis. The single exception to appear recently is the use by Negishi *et al.* of an aluminium–titanium reagent to effect the tricyclisation of a triene; selectivity is lacking in this process, however.[110] Of the Pd-catalysed methods





Scheme 5



Scheme 6

the most notable work has been that of Balme and co-workers (**Scheme 6**) which has been used in a total synthesis of (±)-capnellene and, like the work of Weinreb *et al.* cited above, involves the trapping of a Heck reaction product.[111,112] Oppolzer has also made a recent contribution to this field.[113] Of radical cascade methods the work of Pattenden and co-workers is notable. Thus, the 5,7,5-tricycle **123** has been assembled by a macrocyclisation–transannulation approach, starting from the triene **122** (**Scheme 7**).[114,115] Kilburn *et al.* have also made contributions to this field.[116,117]

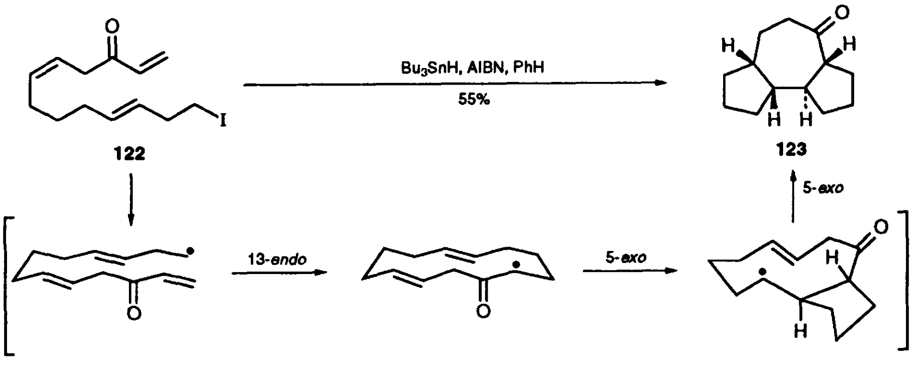
4 Six-membered rings

4.1 Diels–Alder reactions

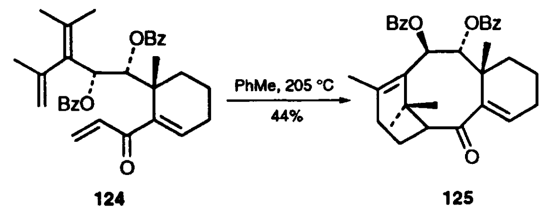
The scope for the intramolecular variant of the Diels–Alder reaction in difficult ring constructions has been further illustrated in Jackson and Shea's synthesis of the highly functionalised taxane intermediate **125** from **124**,[118] and in the elaboration of the steroid–taxane hybrid **126**, described by Danishefsky *et al.*[119] In another neat approach to the taxane ring system Winkler *et al.*[120] have used a combination of inter- and intra-molecular Diels–Alder reactions, *vis* **127**→**128** and **128**→**129**, from readily available precursors; this very direct two step synthesis produces **129** in 50% overall yield and with excellent stereocontrol.

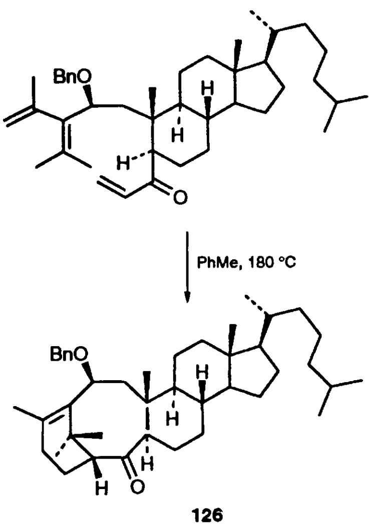
Spino *et al.* have published similar sequential inter- and intramolecular Diels–Alder reactions in their approaches to perhydrophenanthrenes, *viz* **130**→**132** via **131**,[121,122] and to the quassinoids.[123]

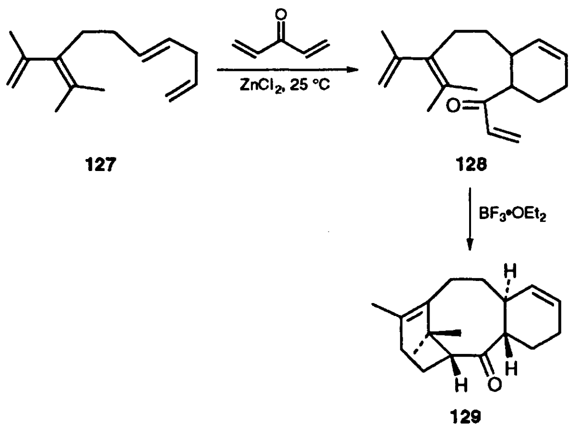
De Clerq and his collaborators have extended their elegant studies on the scope of the intra-

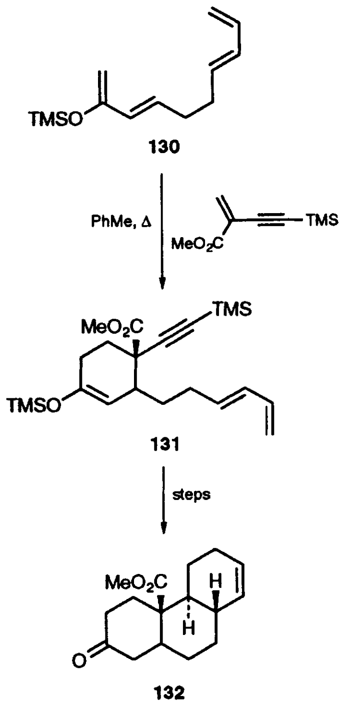


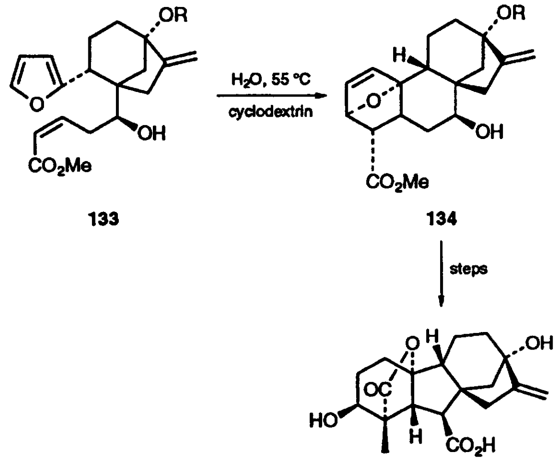
Scheme 7

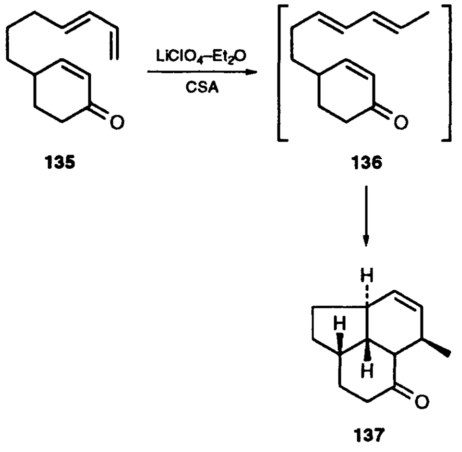








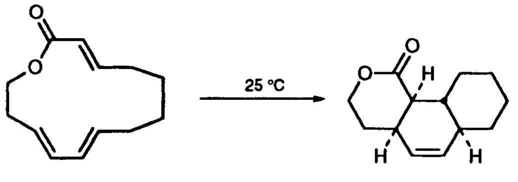




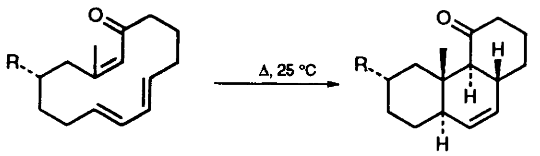
molecular Diels–Alder reaction with furan-dienes, and described a total synthesis of gibberellins A_1 and A_3, based on the cycloaddition **133**→**134** as a key step.[124]

Lithium perchlorate in diethyl ether has been shown to have a profound effect on the reaction rates of many Diels–Alder reactions.[125] Now Grieco *et al.* have shown that catalytic camphorsulfonic acid in 5.0 M lithium perchlorate–diethyl ether solution promotes Diels–Alder reactions of conformationally restricted substrates with concomitant migration of the diene moiety prior to cycloaddition, *viz* **135**→**137** via **136**.[126] In a detailed investigation Gorman and Gassman[127] have studied the influence of alkyl substitution on the ionic intermolecular Diels–Alder reactions of a wide range of methyl analogues of 3*E*,8*E*-1,3,8,10-undecatetraenes; this paper is well worth reading in detail.

The transannular Diels–Alder reaction of the triene **138** produces the *trans-anti-cis* tricyclic lactone **139** as a single cycloadduct in 63% yield;[128] and Takahashi *et al.*[129] have extended their investigation of this approach to polycycle constructions by carrying out detailed studies of the transannular Diels–Alder reactions of the trienones **140**.

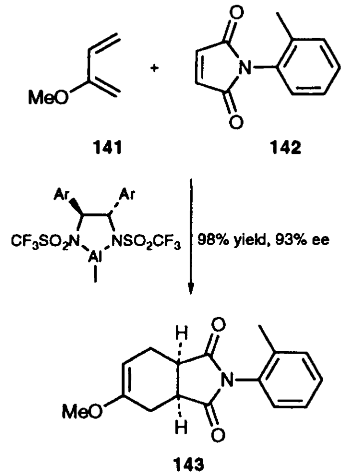


138 **139**



a R = H; **b** R = OH
140

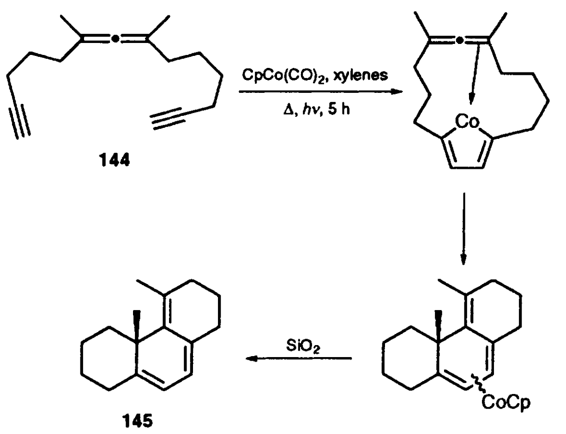
Catalytic enantioselective Diels–Alder reactions are very much in vogue these days. Thus Corey *et al.* have described further aspects of their oxazaborolidine-catalysed reactions,[130] and also the first example of an enantioselective catalytic Diels–Alder reaction of an achiral C_{2v}-symmetric dienophile and an achiral diene, *i.e.* **141** + **142** → **143**.[131] The applications of η^4-diene iron tricarbonyl complexes[132] and of a chiral scandium catalyst[133] in enantioselective Diels–Alder reactions have also been described.

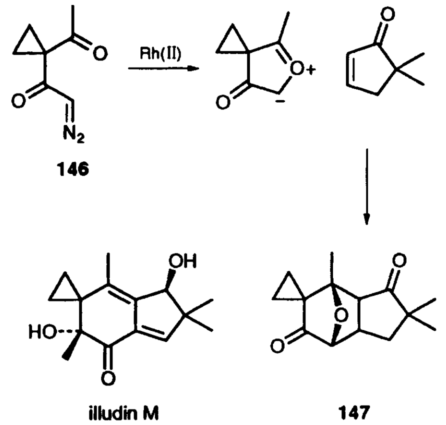


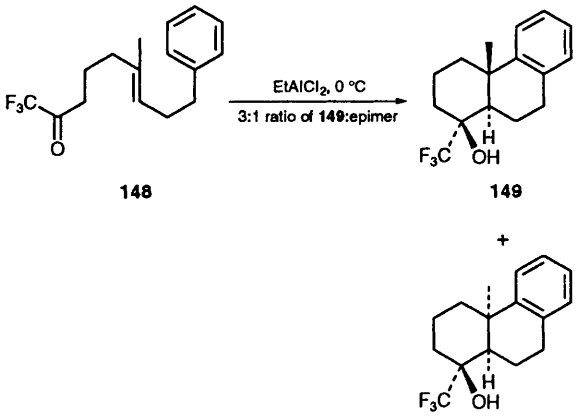
4.2 Other cycloaddition routes

Allenes have been used as new partners in intramolecular cobalt-mediated [2 + 2 + 2] cycloaddition reactions for the first time, leading to facile syntheses of polycycles after decomplexation, *e.g.* **144** → **145**.[134] Padwa *et al.* have shown that dipolar cycloaddition reactions using carbonyl ylides can be used as key steps in the construction of the illudin, ptaquilosin and pterosin families of sesquiterpenes, *e.g.* **146** → **147**.[135,136]

A new sequential carbonyl ene cyclisation/cycloaddition of trifluoromethyl ketones catalysed by Lewis acids has been applied to the synthesis of polycycles, *viz* **148** → **149**.[137] White and Somers[138] have published full details of their approach to the stemodane nucleus based on a hydroxy-directed intramolecular ene reaction.

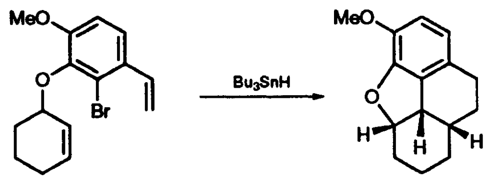






4.3 Free radical cyclisations

A number of interesting 6-*endo* cyclisations leading to six-membered annulated ring systems have been published in recent years. Thus Parker and Fokas[139,140] have used this tactic in their approach to the morphine ring system, *e.g.* **150** → **151**, and Ghatak *et al.*[141] have synthesised a range of linearly condensed hydroaromatic carbocyclic systems, *e.g.* **153** from **152** through 6-*endo*-trig closures. Now Marco-Contelles and colleagues[142] have shown that cyclitols of constitution **155** containing a *trans* 1,3-dioxolane moiety can be produced from



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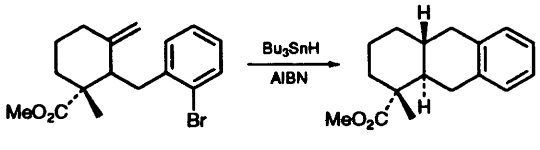

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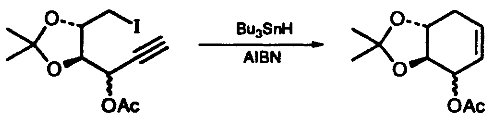
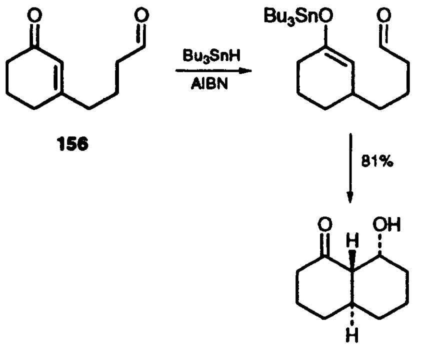


154

155

5-hexenyl radicals derived from **154** by way of a facile 6-*endo*-dig cyclisation.

The addition of Bu$_3$SnH–AIBN to cyclohexenones containing pendant aldehyde functionality leads to a neat synthesis of directed aldols by way of allylic *O*-stannylketyl intermediates, *e.g.* **156**→**157**.[143] Some novel cyclobutanone-based tandem free radical rearrangements,[144] and cyclisations involving methylenecyclopropane derivatives,[145,146] have been used to access certain mono- and bi-cyclic cyclohexanes.



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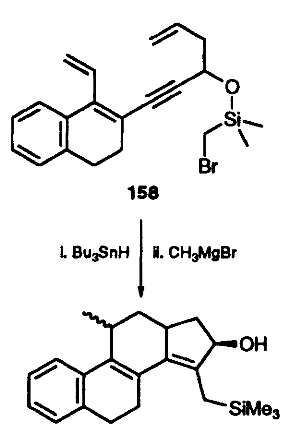
Tandem radical-mediated cyclisations have also been used with silicon tethered precursors, *e.g.* **158**, to access intermediates **159** containing the steroid skeleton.[147] Treatment of appropriately substituted polyene phenylselenyl esters, *e.g.* **160** and **162**, with Bu$_3$SnH–AIBN has been shown to lead to linear and angular six-ring fused carbocycles (such as **163** and the steroidal ring system **161**), via consecutive 6-*endo*-trig mode cyclisations starting from the corresponding polyolefin acyl radical intermediates.[148]



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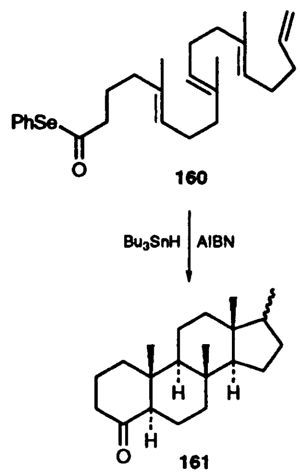

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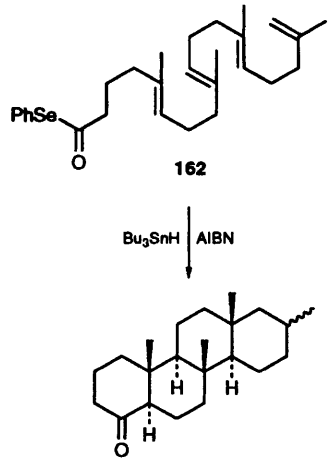

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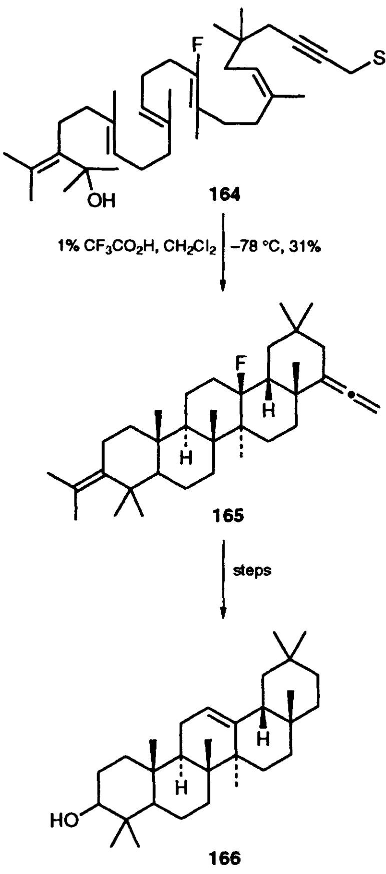
4.4 Electrophilic polyene cyclisations

The elaboration of polycycles based on cyclisations of polyolefinic substrates in the presence of electrophilic reagents, pioneered by W. S. Johnson, has provided organic chemistry with one of its major and enduring synthetic methods. Now Fish and Johnson have described further ramifications of this strategy in synthesis, reporting the first examples of non-enzymatic biomimetic polyene pentacyclisations, *viz* **164**→**165**,[149] and a total synthesis of sophoradiol **166** using the tetramethylallyl cation as a surrogate for the epoxide function as an initiator of the polyene cyclisation.[150] The same research group has also described the use of the allylsilane group as an internal terminator group in polyene



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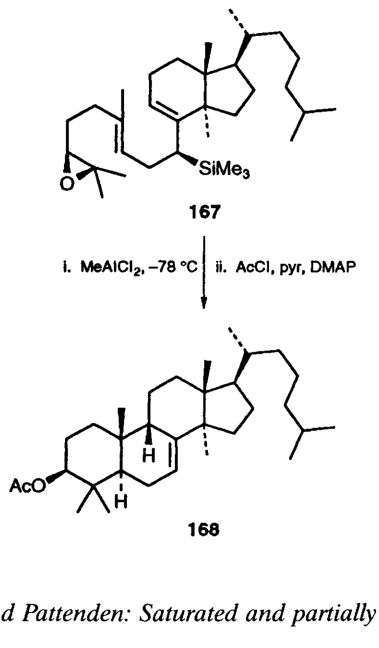
cyclisations,[151] and studies towards the oleanes based on similar polyene cyclisations β-alkynyl involving silane precursors.[152]

Finally, in the first demonstration of a carbocation–olefin cyclisation route to the lanasterol series, Corey *et al.*[153] have described the silicon-assisted double cyclisation **167**→**168**.

4.5 Other routes to six-membered rings

Palladium-catalysed cyclisations remain popular in approaches to six-membered carbocycles. Thus Tietze and Schimpf[154] and Terakado *et al.*[155] have both highlighted the control that can be exercised by the allylsilane moiety in intramolecular Heck reactions, *e.g.* **169**→**170**, and Hatakeyama *et al.*[156] (*cf.* work by Moriarty)[157] have outlined an efficient route to the A-ring synthon **173** for 1α,25-dihydroxyvitamin D$_3$ based on the same Heck reaction, *viz* **171**→**172**.



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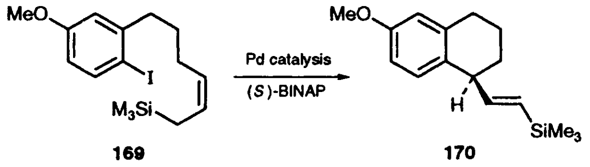

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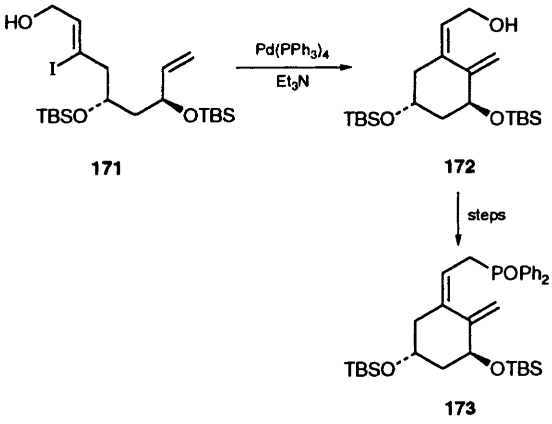

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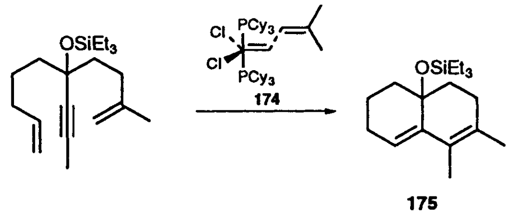
An unusual sequence of ring-closure metathesis reactions from acyclic dienynes, catalysed by the ruthenium carbene complex **174** has been used by Grubbs *et al.*[158] to produce fused bicyclic rings, including the 6,6-fused system **175**.

The first examples of tandem Cope–Cope rearrangements have now been identified, *e.g.* **176**→**178** via **177**,[159] and a range of new tandem anion-induced reactions involving the Michael reaction and the Claisen condensation,[160] the aldol reaction[161] and α-alkylation,[162] have been described.



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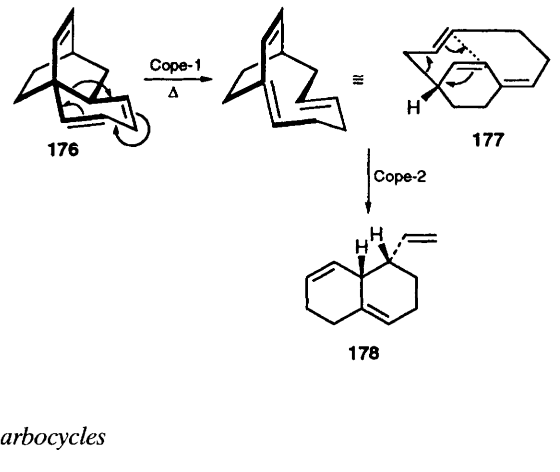

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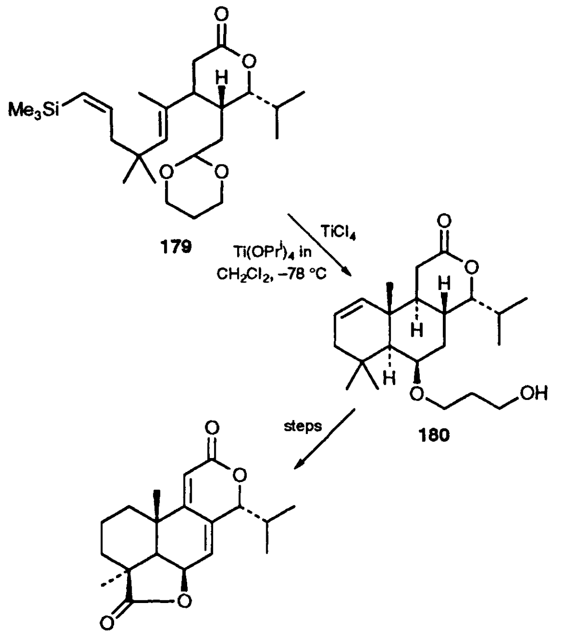
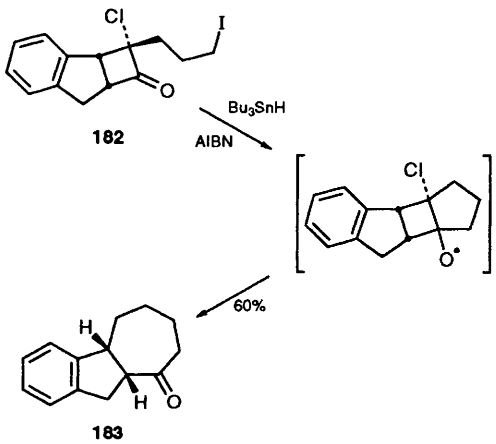
Allyl and vinyl silanes have featured prominently in a range of recently described cationic six-ring cyclisations.[163,164] Perhaps one of the most impressive examples of a vinyl silane-mediated cationic cyclisation is the synthesis of the tricyclic intermediate **180** from **179** described by Burke *et al.*[165] in their approach to an enantioselective synthesis of nagilactone F **181**.



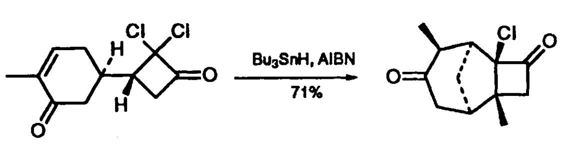
179 **180** **181**

5 Seven-membered rings

Perhaps the most common approaches to seven-membered ring constructions are those utilising ring expansions, which are typically carried out by fragmentation reactions. Thus, Dowd and co-workers have devised a neat synthesis of fused cycloheptanones such as **183** based on radical fragmentation of the alkoxyl radicals derived from cyclobutanones such as **182**.[166] Several strategies for forming the substrates have been devised.[166–168] The same research group has also reported an unusual rearrangement of cyclobutanones **184** to give tricycles **185**.[169]

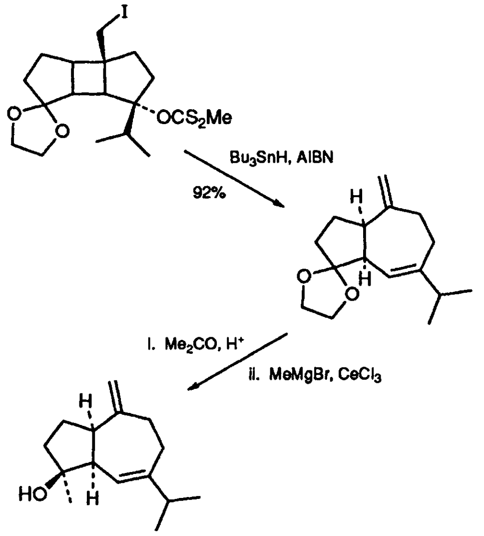


182 **183**



184 **185**

Radical fragmentations of cyclobutanes have also been used by Lange and co-worker, as the basis for the synthesis of 7,5-, 7,6-, 8,5- and 8,6-fused bicyclics.[170] Either tin hydride- or samarium-mediated reductions can be used,[171] and the method has been used in a total synthesis of alismol **186**.[172] Ranu has examined similar radical fragmentations.[173] A thermal diradical fragmentation has been reported by Little and co-worker,[174] where the diradical formed from **187** is converted into **188**, presumably via an hydrogen atom-transfer step.



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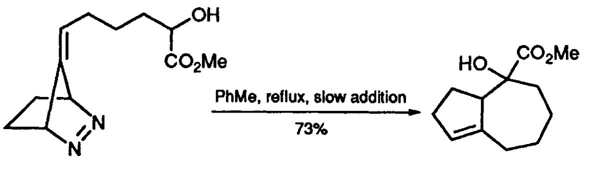
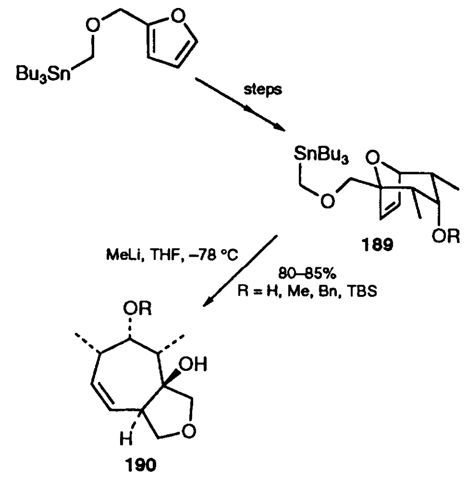
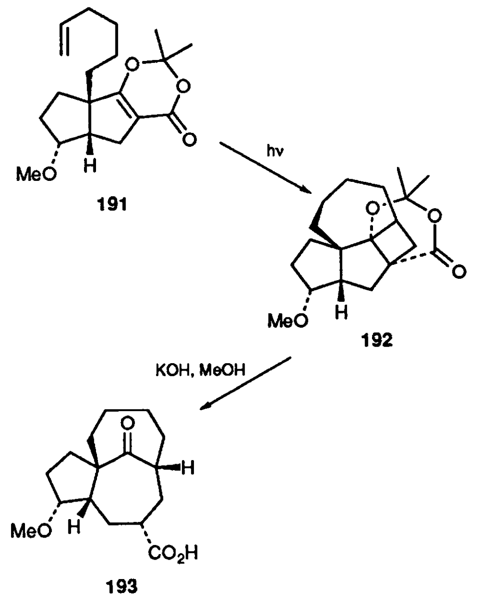


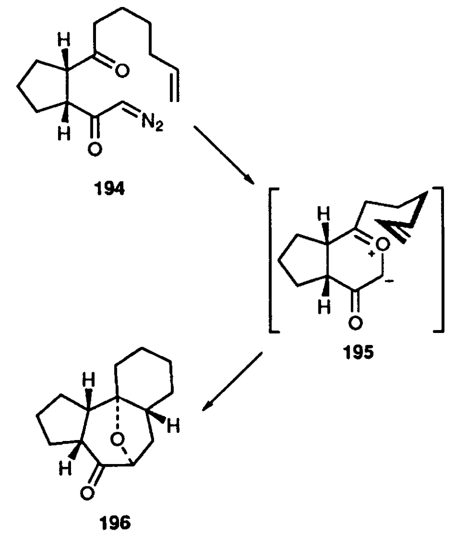
187 **188**

Lautens *et al.* have devised a new route to the 7,5-systems **190**, based on intramolecular ring opening of adducts **189** derived from [4 + 3] cycloadditions to furans.[175] A similar cycloaddition has been used by Harmata and colleagues in a model study for the synthesis of the ingenane carbon skeleton;[176] and an alternative approach to ingenanes has been described by Winkler, Blumberg and co-workers, based on intramolecular [2 + 2] cycloaddition of **191** to give **192**, followed by ring opening under basic conditions to give the tricycle **193**.[177] Similarly, Tochtermann *et al.* have reported a route to the tremulane carbon skeleton based on alkaline rearrangement of oxepines.[178]

McMills *et al.* have described an approach to tigliane diterpenes, based on cyclisation of the oxonium ylide **195** derived from the diazocarbonyl



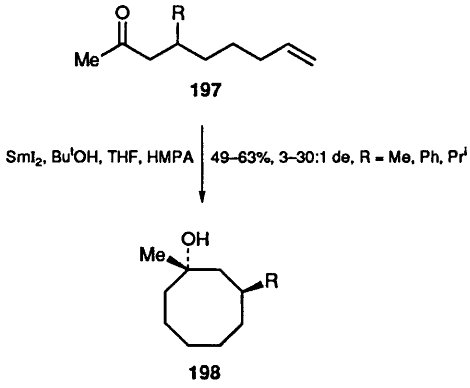




precursor **194**, to give the 5,7,6-tricycle **196**.[179] Finally, two research groups have published studies of cationic cyclisations leading to seven-membered rings: Angle *et al.* have utilised cations derived from *p*-quinonemethides,[180] and Majetich *et al.* have further developed their work on the addition of electron rich aryl systems (in this case furans) to conjugated dienones.[181]

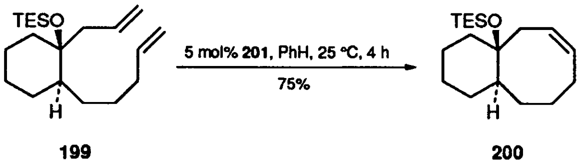
6 Eight-membered rings

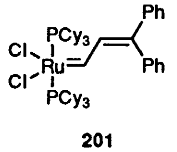
Radical cyclisations are generally not used for eight-membered ring synthesis, owing to the slowness of the ring closure relative to common side reactions. However, Molander and co-worker have shown that ketyl radicals deriving from SmI_2 reduction of ketones can be rendered highly persistent by carrying out the formation under certain conditions.[182] Thus the radical 8-*endo* cyclisation of **197** to **198** is rendered feasible.



Another unusual approach to eight-membered rings has been described by Grubbs *et al.*, who use Ru-catalysed olefin metathesis to effect the conversion of 1,9-dienes into fused cyclo-octenes, *e.g.* **199**→**200**, using complex **201** as the catalyst.[183]

One of the most widely-used routes to cyclooctanes is the use of Ni-catalysed [4+4] cycloaddition of butadienes. In a related process, Harmata *et al.* have shown that cationic [4+3] cycloadditions can be used in similar fashion, *e.g.* by conversion of furan-cyclopentanones **202** into the doubly bridged cyclo-octene **203**.[184] Several researchers have used more standard methods to make eight-ring containing natural products, and of these the most interesting is perhaps Schreiber's use of the Nicholas reaction in the synthesis of (+)-epoxydictymene.[185] Other examples include the use of the Claisen[186] and oxy-Cope[187] rearrangements to effect ring expansion, and the use of sulfone-stabilised carbanion additions to esters.[188]





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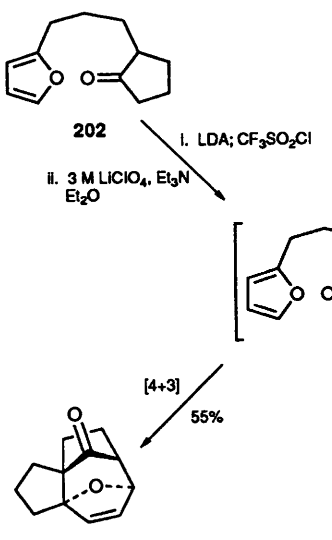
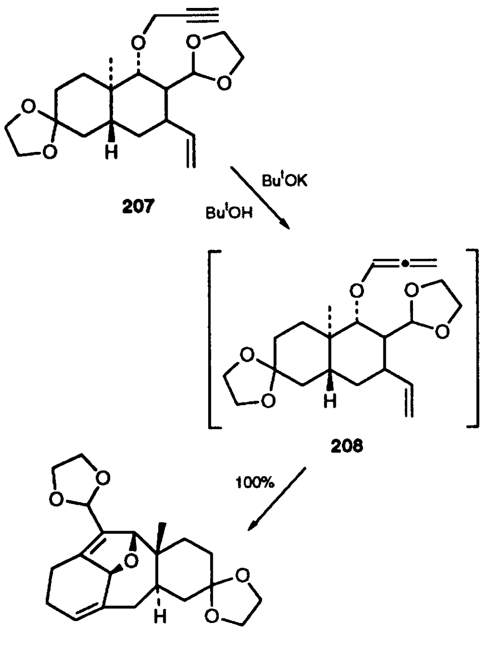


Interest in the much-studied taxane 6,8,6-fused tricyclic carbon skeleton has remained high,[189] culminating in two total syntheses of the valuable anticancer agent Taxol® **204**.[190–195] Both of the synthetic approaches taken are interesting from the point of view of eight-membered ring synthesis, as is the work of Kuwajima *et al.* on the synthesis of taxinine derivatives such as **206**.[196] In the latter work intermediates such as **205** were cyclised in a facile and diastereoselective manner by the use of an appropriate Lewis acid catalyst. In similar work, Swindell *et al.* have reported a synthesis of the eight-membered ring in the taxanes by Ti-mediated pinacol closure,[197] and Romero *et al.* have utilised an intramolecular aldol condensation.[198]

Paquette *et al.* have published more work based on the use of oxy-Cope rearrangements to give the eight-membered ring,[199] as have Martin *et al.*[200] Finally Kanematsu and co-workers have devised a novel route to the taxane carbon skeleton, making use of a tandem [2+2]-cycloaddition–[3,3]-sigmatropic shift process for the conversion of **207** into **209**, via the allenyl intermediate **208**.[201]

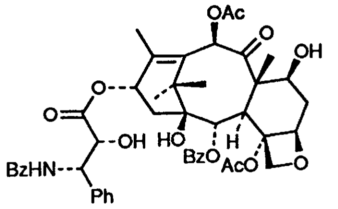


7 Nine-membered and larger rings

Melikyan *et al.* have described an interesting variation on the well-known Nicholas reaction, which allows the cobalt-complexed 1,5-alkadiynes **210** to be cyclised via *β*-alkynyl radical intermediates.[202] Subsequent oxidative decomplexation then gives the cyclic alkadiynes **211**.

Hirama *et al.* have reported a remarkable synthesis of the highly strained nine-membered ring **213** (which rearranges on warming to give the diquinane **214**) by intramolecular acetylide addition in the *ω*-alkadiynal **212**.[203] In related studies, the synthesis of enediyne antibiotics remains an active field, with several research groups reporting new results.[204–207]

The synthesis of medium ring di*enes* has also been investigated by a number of research groups. McMurry and Siemers have reported a total



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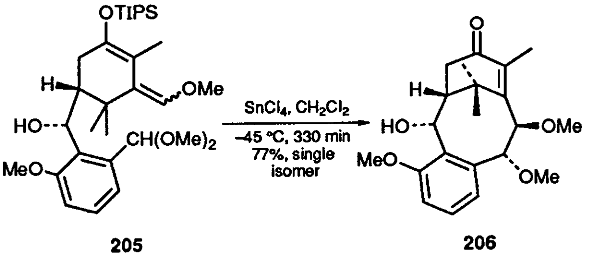

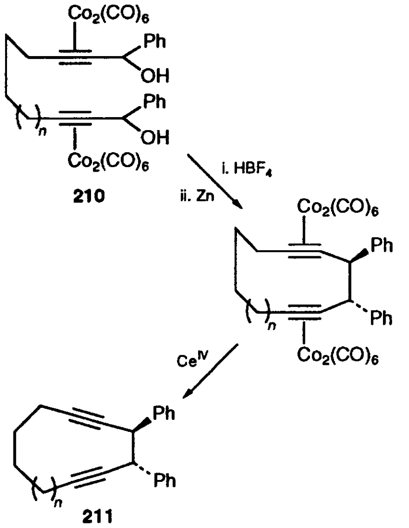

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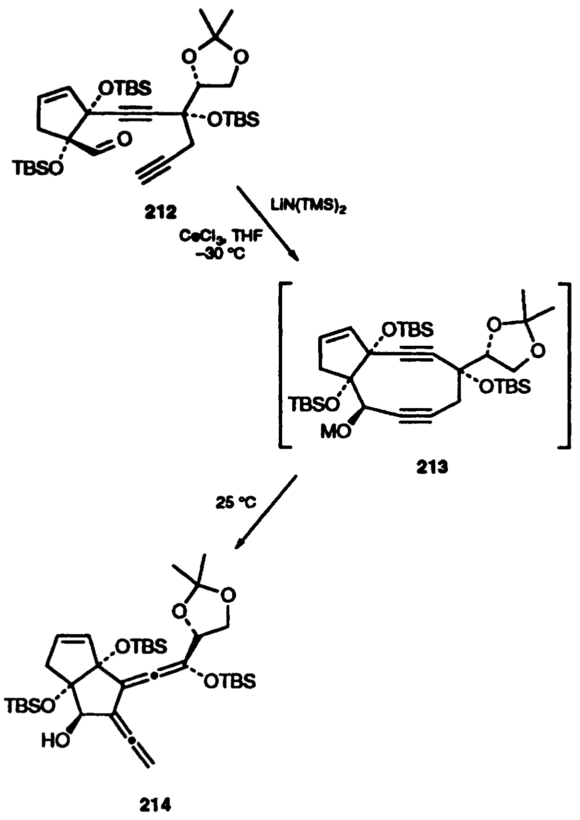
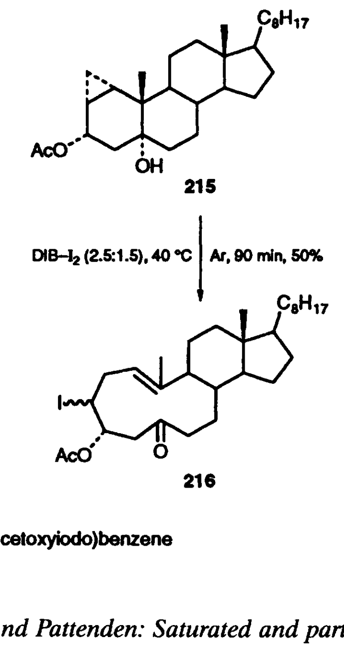


synthesis of periplanone based on intramolecular low-valent titanium coupling of aldehyde and alkenone moieties;[208] and Hodgson *et al.* have described a route into the germancranes, based on a Pd-catalysed vinyl halide–vinyl stannane coupling to the corresponding 1,3-diene.[209] Allyl–allyl cyclisation has also been reported by Takayanagi *et al.*, as part of a total synthesis of the cembranoid sarcophytol A,[210] and by Williams and Coleman as part of a synthesis of neodolabellenol.[211]

As with eight-membered rings, ring expansion remains a popular method for the formation of medium rings. The most notable innovation has been the use by Suárez *et al.* of a tandem alkoxyl radical fragmentation–cyclopropylcarbinyl rearrangement strategy to enable the conversion of decalins such as **215** into the corresponding eleven-membered cyclic ketones such as **216**.[212,213] The oxy-Cope rearrangement has also been used as the basis of a route to the dolabellane carbon skeleton.[214]



DIB = (diacetoxyiodo)benzene

8 General carbocycle synthesis

Although no reviews directly concerned exclusively with carbocycle synthesis have been published, a number of reviews offering partial coverage have appeared. These include reviews of the Heck reaction,[107] particularly in its asymmetric form,[215,216] and a review of synthetic routes to vitamin D.[217]

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