Saturated and partially unsaturated carbocycles

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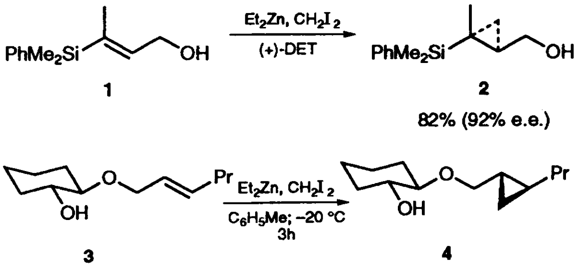
Reviewing the literature published between August 1992 and January 1994

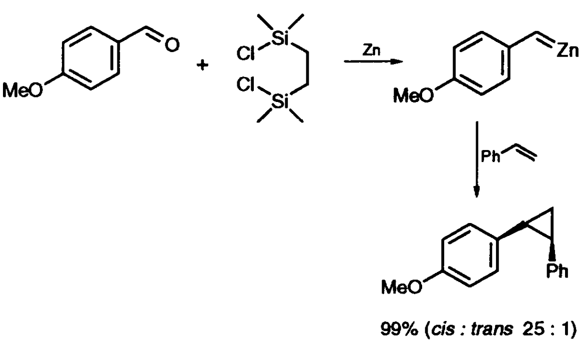
1 Three-membered rings

1.1 Simmons–Smith cyclopropanations

The Simmons–Smith reaction remains one of the most useful procedures for the synthesis of cyclopropane derivatives, and a wide range of chiral auxiliaries for asymmetric Simmons–Smith reactions have been described. In extensions of earlier work, Ukaji *et al.*[1] have now shown that optically active silicon-substituted cyclopropylmethanols can be synthesized using the Simmons–Smith procedure utilizing diethyl tartrate as a chiral auxiliary, *e.g.* **1** → **2** in 92% e.e. Similarly, Charette *et al.*[2] have developed a new and simple auxiliary derived from 1,2-*trans* cyclohexanediol for the Simmons–Smith cyclopropanation of substituted alcohols, *viz.* **3** → **4** (> 20:1 d.s.); related work by the same research group using 2-hydroxy-β-D-glucopyranose as the chiral auxiliary has also been developed this year.[3]



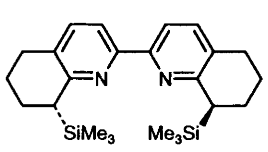
By analogy with the Simmons–Smith reaction, Motherwell and Roberts have extended their earlier work on the deoxygenation of carbonyl compounds and shown that organozinc carbenoid species derived from zinc and chloroalkyl silanes can be trapped with alkenes leading to cyclopropanes in good to excellent yields.[4] The reaction works particularly well using aryl and, in some cases, α,β-unsaturated carbonyl compounds as precursors of the organozinc carbenoid species (**Scheme 1**).



Scheme 1

1.2 Diazoester cyclopropanations

A very wide range of metal complexes are known to catalyse the cyclopropanations of alkenes by diazoesters. Rhodium(III) porphyrin complexes are especially interesting in view of the scope that chiral porphyrins offer in asymmetric cyclopropanations. A transition state model has now been developed for these rhodium-catalysed reactions which provides some level of stereochemical predictive power.[5] In a similar vein, the copper complex of the optically active bipyridine **5**[6] and the chiral cobalt(II) complex **6** from 1(*R*)-3-hydroxymethylenebornane-2-thione[7] have been used as chiral catalysts for the asymmetric cyclopropanations of styrenes and oct-1-ene with ethyl diazoacetate.



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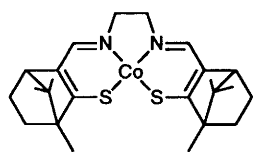

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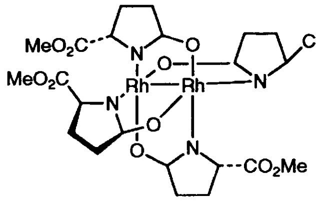
The homoallylic diazoacetates **9** have been shown to undergo enantioselective intramolecular cyclopropanation with the rhodium catalyst **7** leading to the bicyclic cyclopropane **10** in 71–90% e.e. and in 55–80% chemical yield.[8] Other related studies have been described, with allyl diazomalonates, using the chiral phenylalaninol-derived copper catalyst **8**.[9]



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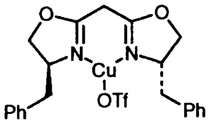

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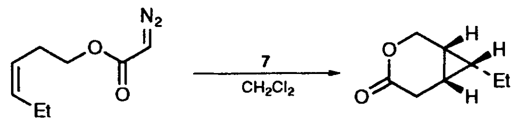
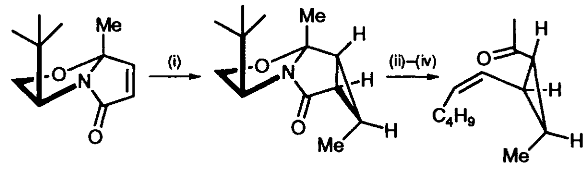


9

10
80% (90% e.e.)

1.3 Other routes to three-membered carbocycles

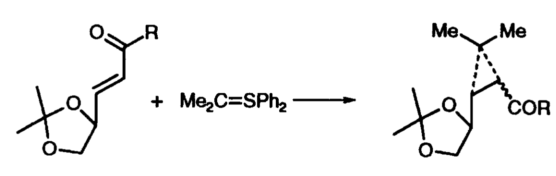
Meyers and his colleagues[10] have described full details of their elegant studies on the synthesis of enantiomerically pure 1,2,3-trisubstituted cyclopropanes based on cycloaddition reactions of sulfur ylides to chiral unsaturated lactams (**Scheme 2**).



Reagents: (i) $Ph_2S{=}CHMe$; (ii) Red-Al; (iii) $BuCH{=}PPh_3$; (iv) H_3O^+

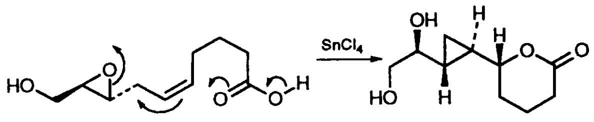
Scheme 2

In related work, Krief and Lecomte[11] have outlined further extensions of their studies of the stereoselective synthesis of cyclopropane derivatives from γ-alkoxy-α,β-unsaturated carbonyl compounds derived from D-glyceraldehyde and sulfur ylides (**Scheme 3**). Developments of earlier strategies towards the synthesis of cyclopropanes, based on a 1,3-elimination protocol, have also been described.[12,13]

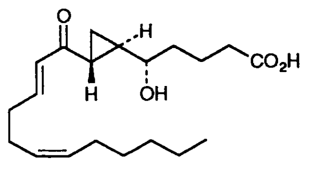


Scheme 3

Two novel cyclopropane ring-forming sequences have been employed in the synthesis of the natural products **13** and **14**. Thus the cyclization step **11** → **12** was used by White and Jensen[14] in their biogenetically patterned synthesis of the cyclopropane-containing eicosanoid **13** produced by the coral *Plexaura homomalla*. Furthermore, the cyclopropane **17** has been produced in one step from the mesylate **15**, presumably *via* the intermediate **16**, during Danishefsky's synthesis of the unusual pentacyclic diterpene mycorin **14**.[15]



11 **12**



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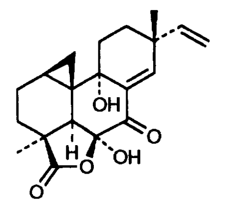

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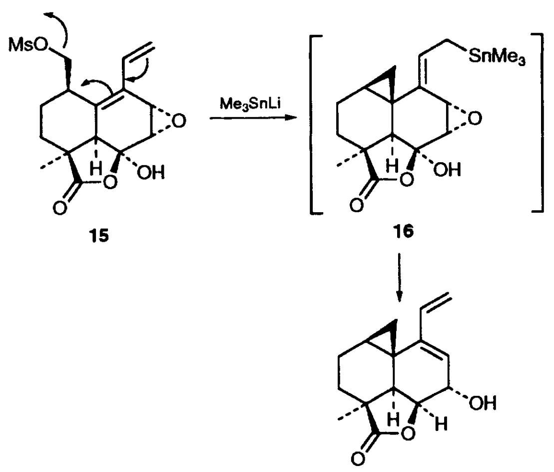
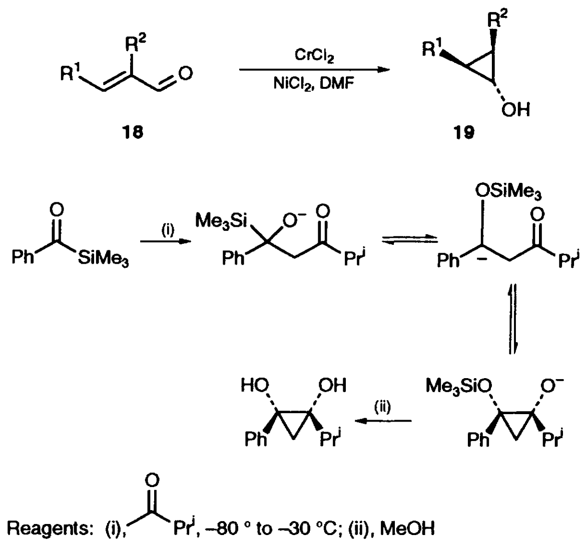


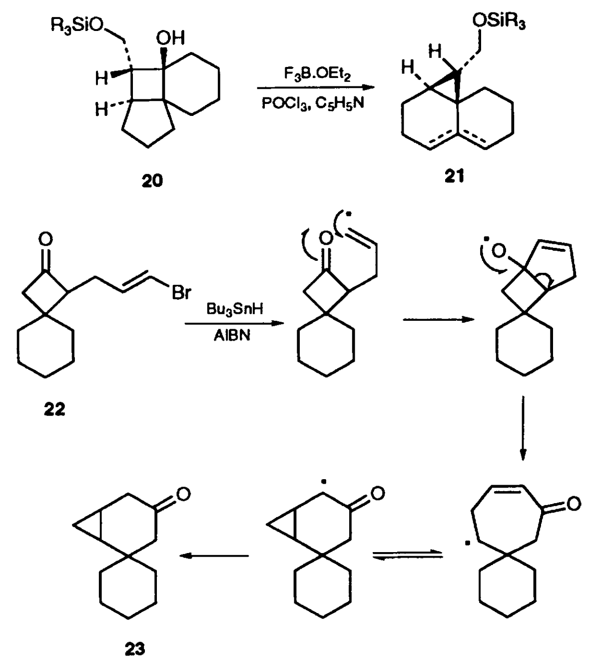
15 **16** **17**

A novel method for the synthesis of cyclopropanols has been described whereby solutions of α,β-unsaturated aldehydes in DMF are simply treated with 2.2 mol of chromium chloride in the presence of 2 mol % nickel(II) chloride at room temperature, *viz.* **18** → **19**.[16] 1,2-Cyclopropanediols are produced when acylsilanes are reacted with ketone enolates; the reaction proceeds *via* Brook rearrangement of the initial 1,2-adduct and subsequent aldol reaction (**Scheme 4**).[17]



Scheme 4

Substituted cyclopropanes of constitution **21** are produced *via* a novel rearrangement when the hydroxylated cyclobutane derivatives **20** are treated with $F_3B \cdot OEt_2$–$POCl_3$ in the presence of pyridine or Raney nickel.[18] Another unusual atom-reorganization sequence has been used by Dowd *et al.* in their synthesis of the β, γ-cyclopropyl ketones **23** by treatment of substituted cyclobutanones of constitution **22** with Bu_3SnH–AIBN (**Scheme 5**).[19]

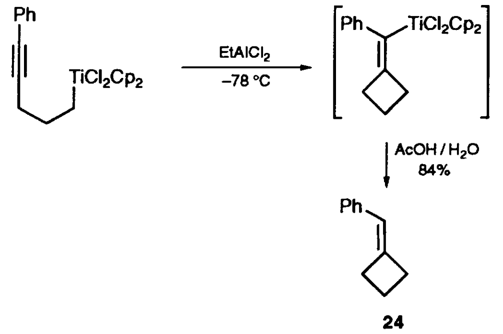


Scheme 5

2 Four-membered rings

2.1 Transition metal based methods

Transition metal based methods form the bulk of new work published in the area of cyclobutane ring synthesis during the period under review. Stille has reported the intramolecular addition of alkyl titanocene complexes to alkynes under Lewis acid catalysis, leading to four-membered rings **24** bearing an exocyclic trisubstituted alkene.[20]



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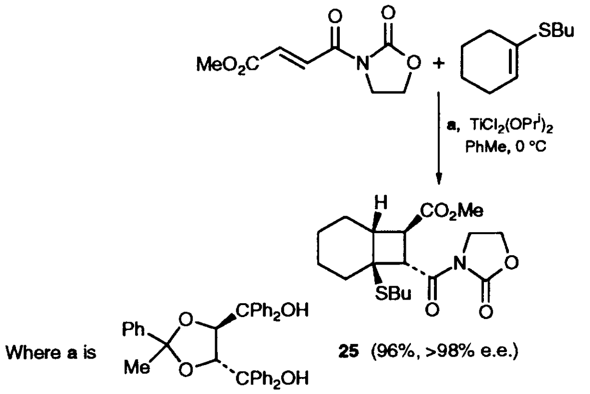
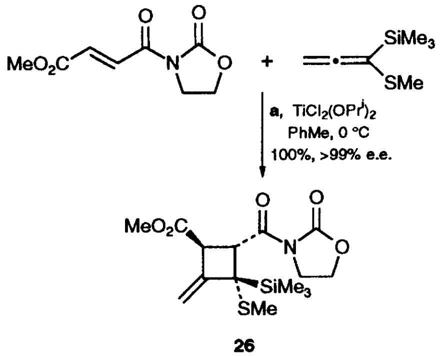
A number of metal-catalysed [2 + 2] methods have also been reported, of which the most interesting is probably that of Narasaka in which sulfur-bearing alkenes, allenes, or alkynes may be reacted with electron-deficient alkenes in the presence of a chiral titanium catalyst to give the corresponding cyclobutanes **25**, *exo*-methylene cyclobutanes **26**, and cyclobutenes **27** with good to excellent enantioselectivity.[21] The use of ketene thiocetals, followed by desulfurization of the resulting adduct, makes for a useful synthesis of cyclobutanones **28**, as does the work of Wulff, which utilizes the reaction of 1,6-enynes with Fischer carbene complexes to give *cis*-[3.2.0]bicycloheptanones **29** in good yields and with good diastereoselectivity for positions α- to the ring junction.[22]





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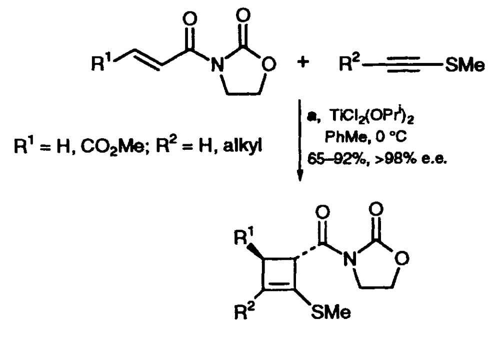

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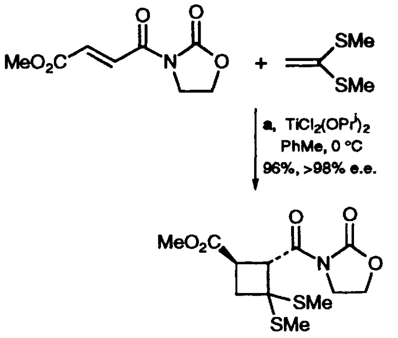

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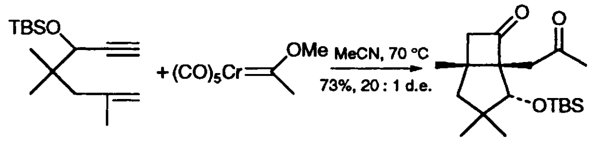

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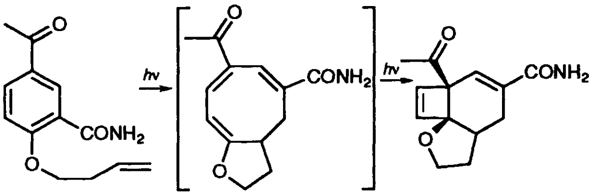
2.2 Photochemical and free radical methods

Wagner *et al.* have reported an interesting synthesis of bicyclo[4.2.0]cyclo-octadienes, based on the intramolecular photoaddition of tethered alkenes to triplet benzenes **30**,[23] and Galatsis *et al.* have devised a modification of the de Mayo reaction which allows the synthesis of bicyclo[4.2.0]cyclooctenones.[24]



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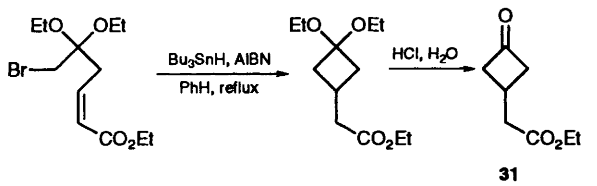
Two unusual examples of cyclobutane ring formation by radical methods have appeared. The first, described by Jung *et al.*, constitutes a route to cyclobutanones **31** *via* the corresponding ketal; 4-*exo-trig* cyclization of the radical onto an alkenoate occurs in the presence of a di-alkoxy substituent but with the free ketone only the product of reduction is formed.[25] The second example relies on electronic rather than steric effects, with the stabilizing effect of methythio- and sulfone-substituents on an intermediate radical promoting 4-*exo* cyclization, to **32**, rather than to the 5-*endo* cyclization products.[26]



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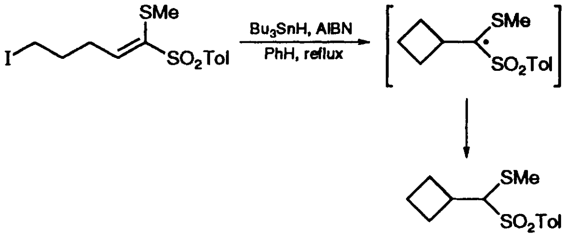

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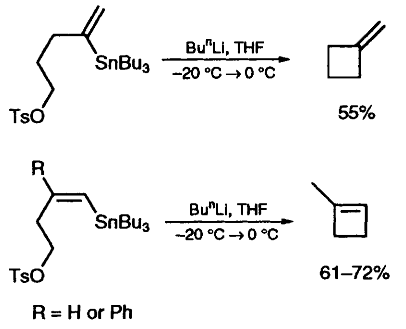
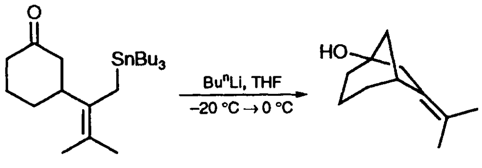
2.3 Other routes to four-membered carbocycles

Barbero *et al.* have reported a remarkable synthesis of both *endo* and *exo* cyclobutenes, based on the fast transmetalation of allyl and vinyl stannanes with alkyl-lithiums at low temperature (**Scheme 6**).[27]



Scheme 6

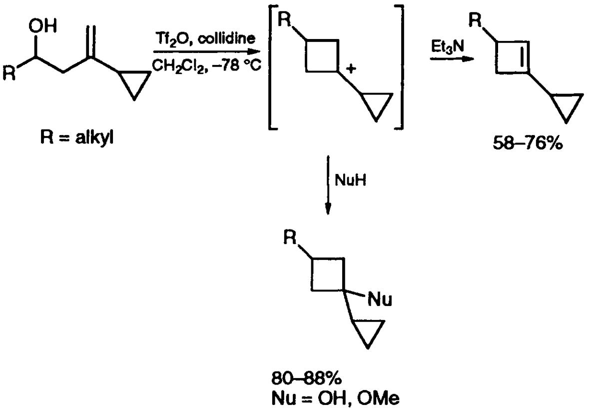
Tin–lithium exchange is so rapid that the reaction can be carried out with Bu^{n}Li in the presence of ketone groups, *viz.* **33** → **34**. Nagasawa and Suzuki have published an effective method for the synthesis of cyclopropyl cyclobutanes and cyclobutenes based on the high stability of cyclopropyl carbocations (**Scheme 7**).[28] Finally, Fukumoto *et al.* have extended their work on tandem intramolecular Michael-aldol reactions to allow the synthesis of polycyclic cyclobutane derivatives **35** which are commonly found in nature.[29]



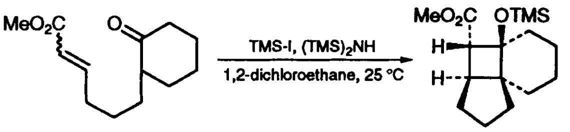
33 **34** (65%)

3 Five-membered rings

A very wide range of methods leading to isolated and to ring-fused substituted cyclopentanes, published



Scheme 7



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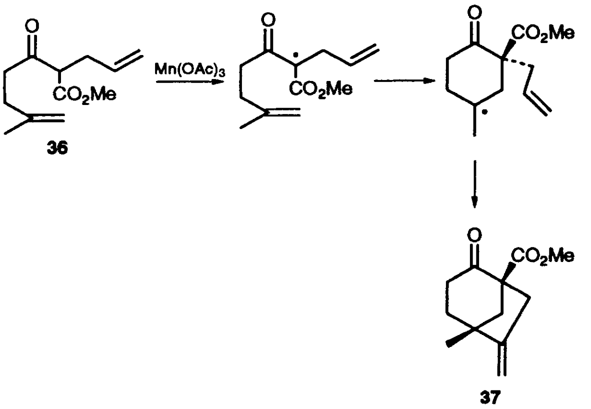
during the period under review, have been based on free radical or transition metal mediated cyclizations. Furthermore, many of these methods have been applied in the area of total synthesis amongst naturally occurring polyquinanes.

3.1 Free radical cyclizations

The enormous scope for oxidative free-radical cyclizations of β-keto esters, 1,3-diones, and 1,3-diesters containing proximate alkene residues, in the presence of $Mn(OAc)_3$ and $Cu(OAc)_2$ has been further delineated, *e.g.* **36** → **37**,[30] and the effects of solvent and ligand on the efficacy of the process have been discussed.[31]



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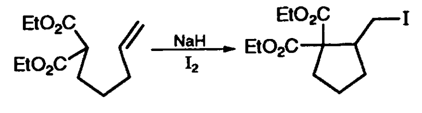
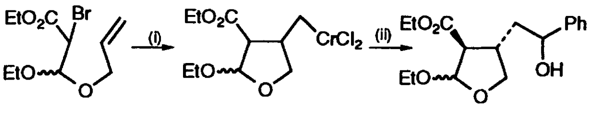
37

Consecutive treatment of appropriately substituted alkenyl malonates with sodium hydride and iodine in THF provides excellent yields of cyclopentanes, *e.g.* **38** → **39**.[32] The reaction also works well in three- and six-, but not four-membered ring formations. Further developments of cobalt(I)-mediated radical cyclizations[33] leading to cyclopentanes have been described, and Schafer *et al.*[34] have described more details of their novel use of $CrCl_3$ [and $Cr(OAC)_2$] in the radical cyclizations of β-halo esters. Thus, after performing the desired radical cyclization, the product radical can be trapped to produce an organochromium intermediate which can then react with electrophiles, *e.g.* aldehydes, leading to substituted adducts (**Scheme 8**).



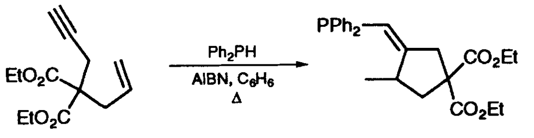
38 **39**



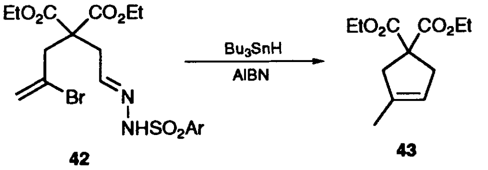
Reagents: (i) $CrCl_3$, $LiAlH_4$, 0 °C; (ii) PhCHO, N_2 25 °C

Scheme 8

The relatively unexplored area of the use of phosphorus-centred radicals in cyclization reactions involving 1,6-diene systems has now been investigated, *viz.* **40** → **41**;[35] so too has the use of arenesulfonyl hydrazones as radical acceptors in the synthesis of unsaturated five-membered carbocycles, **42** → **43**.[36]



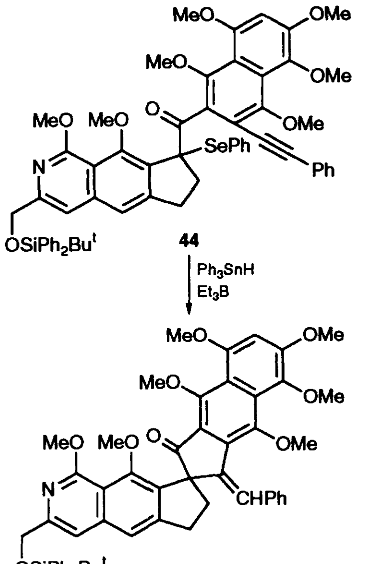
40 **41**



42 **43**

A beautiful illustration of the scope for 5-*exo-dig* radical cyclizations in meaningful target synthesis is contained in the synthesis of the intermediate **45** from **44**, *en route* to the anti-tumour agent fredericamycin A **46**.[37] In addition, the scope for cyclizations of unsaturated ketyl radical anions in natural product synthesis has been neatly summarized by Cossy.[38] Tellurium derivatives, *viz.* **47**, have featured in approaches to substituted cyclopentanes from carbohydrates described by Barton *et al.*,[39] and other approaches to carbocycles from carbohydrates have been published during the period under review.[40]

Allenes and acetylenes have featured prominently in a range of substituted five-membered ring synthesis. Thus, enone radicals generated from the corresponding iodoenones have been found to undergo intramolecular cyclization to tethered trimethylsilyl acetylene side-chains, leading to highly unsaturated cyclic products, *viz.* **48** → **49**.[41]



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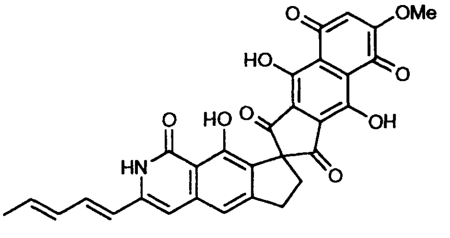
45 (>50%)



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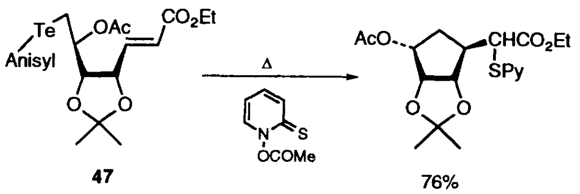

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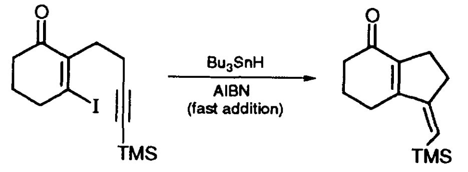
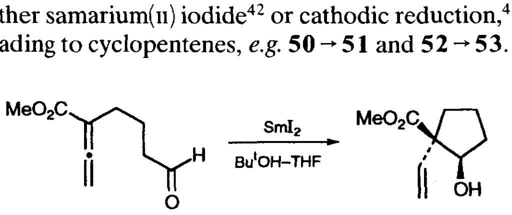
76%



48

49 (85%)

Intramolecular reductive coupling reactions involving carbonyl and allene units have been carried out using either samarium(II) iodide[42] or cathodic reduction,[43] leading to cyclopentenes, *e.g.* **50** → **51** and **52** → **53**.



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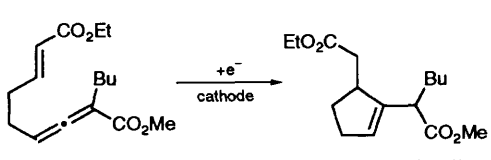
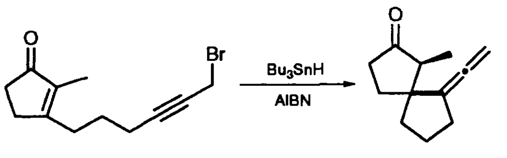
51 (82%)



52

53 (96%)

In addition, Blechert *et al.*[44] have shown that allenylic radicals, generated from propargylic precursors undergo cyclizations onto proximate alkene electrophores, providing a facile synthesis of vinylidene-substituted cyclopentanes, *e.g.* **54** → **55**.



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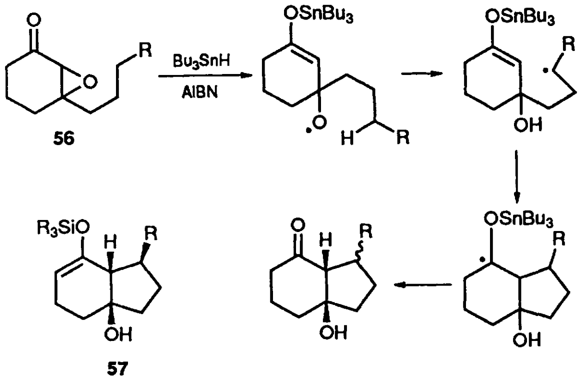
55 (44%)

A neat combination of epoxide ring fragmentation triggered from a ketyl radical, followed by a 1,5-hydrogen abstraction and cyclization provides the basis of a synthesis of ring-fused carbocycles from cyclic α,β-epoxyketones described by Rawal[45] and by Kim[46] and their respective collaborators (**Scheme 9**).

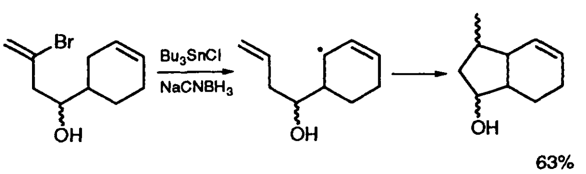


56

57

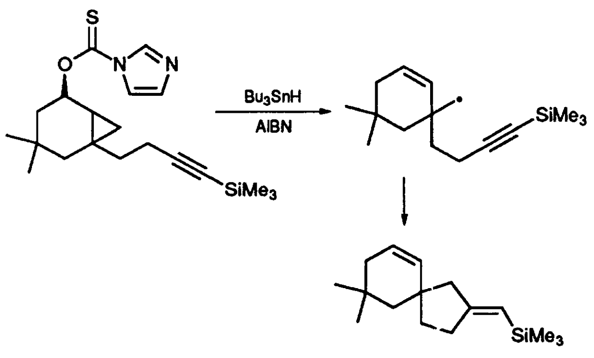
Scheme 9

In extensions of their studies with radical induced epoxide-fragmentations, Rawal and his colleagues have also shown that atom-transfer cyclizations of iodo-epoxides lead to similar angular hydroxy substituted cyclopentanes, whereas Kim and colleagues have demonstrated that treatment of epoxy silyl enol ethers derived from **56** with Bu$_3$SnH-AIBN also provides a useful synthesis of *cis*-fused bicycles of constitution **57**. A 1,5-hdyrogen abstraction protocol, involving a vinyl radical intermediate and an allyl methylene residue, has featured in an approach to 5-ring fused bicycles described by Parsons *et al.*[49] (**Scheme 10**), and Motherwell *et al.*[50] have summarized their novel approach to the construction of bicyclic systems, based on a tandem free radical cyclopropylcarbinyl rearrangement–cyclization strategy, highlighted in **Scheme 11**.



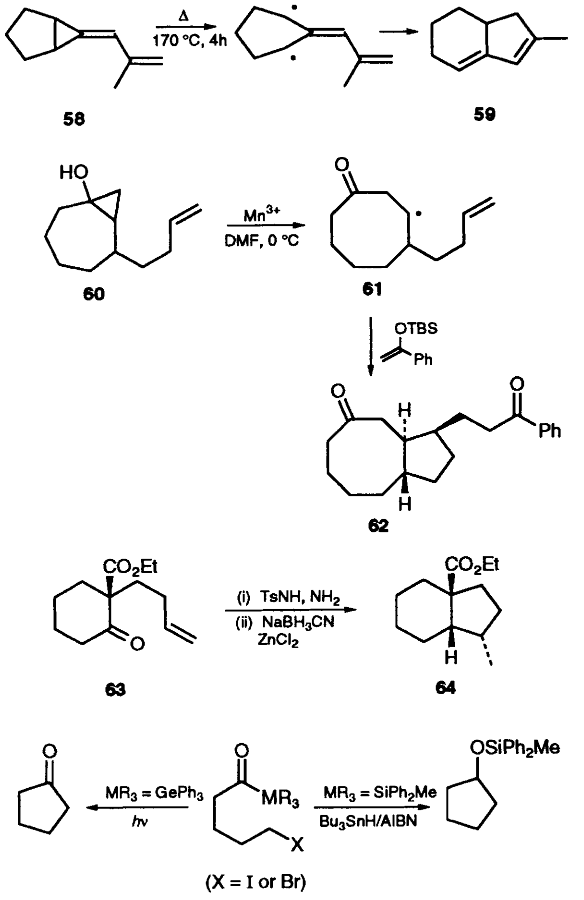
63%

Scheme 10



Scheme 11

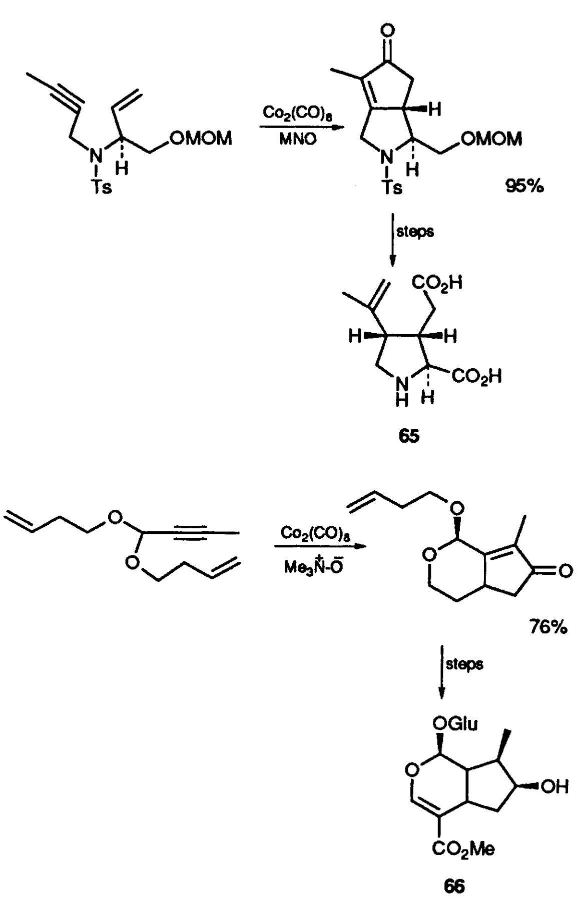
A number of other interesting radical-induced cyclizations, leading to five-membered carbocycles, have been published during the period under review. These include the double ring expansion of the allylidenecyclopropane **58** to **59** at 170°C,[51] the intramolecular cyclization/ring expansion/radical trap sequence **60** → **61** → **62** whereby the cyclopropanol **60** is converted into **62** in the presence of manganese(III) tris-2-pyridine carboxylate[52] or ferric chloride,[53] and the cyclization of the tosylhydrazone derived from **63** in the presence of NaBH$_3$CN-ZnCl$_2$ leading to the bicyclic ester **64**.[54] A further interesting development in cyclopentane ring synthesis is shown by the divergent reaction pathways followed by ω-bromo acylgermanes and acylsilanes in their radical induced cyclizations (**Scheme 12**).[55]



Scheme 12

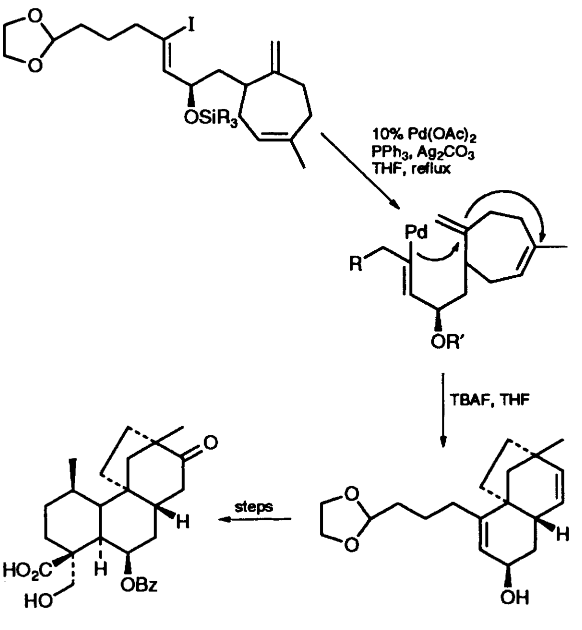
3.2 Transition metal mediated cyclizations

In recent years the Pauson–Khand reaction has emerged as one of the most powerful methods for the synthesis of cyclopentenones. The reaction has also undergone substantial development since its initial report in 1973, including the introduction of new promoters and new metal carbonyl precursors for the source of CO. Dimethyl sulfoxide can now be added to the list of promoters for the reaction,[56] so too can W(CO)$_5$.THF,[57] Mo(CO)$_6$,[58] and Mo$_2$Cp$_2$(CO)$_4$[59] as precursors to the intermediate alkyne complexes and source of CO. The effects of coordinating ligands in the homo and bis-homopropargylic position of a 1,6-diene precursor have also been examined;[60] so too has a solid phase variant of the Pauson–Khand reaction.[61] Reports of successful Pauson–Khand reactions with electron-deficient alkynes have been published,[62,63] and the reaction has played a pivotal role in the recent synthesis of (−)-α-kainic acid **65**[64] and of (±)-loganin **66**[65] (**Scheme 13**).



Scheme 13

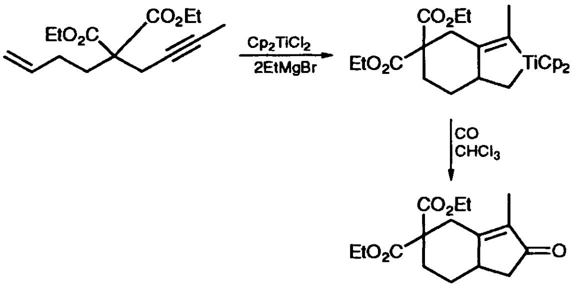
Applications of palladium-catalysed reactions leading to polycycle constructions are ubiquitous in contemporary organic synthesis. Thus, Trost and his colleagues have published more details of their atom-economical cyclo-isomerizations of enediynes,[66] and of their zipper reactions[67] leading to ring-fused cyclopentanes, under palladium catalysis. They have also demonstrated the compatibility and effect of carbonyl, carboxylic acid, and ketal functionality in these catalysed enyne cyclizations.[68,69] Overman has published a useful review of his early work on Heck-type polyene cyclizations of organopalladium intermediates,[70] and has also described a neat total synthesis of (±)-scopadulcic acid A **67** using an intramolecular double-Heck cyclization to form the B–D rings in this complex tetracyclic diterpene structure, with complete stereochemical control (**Scheme 14**).[71,72] Grigg *et al.* have also published full details of their contemporaneous synthetic studies on the intramolecular Heck reaction, featuring anion capture,[73] which adds further credence to this powerful method for the construction of novel polycycles.



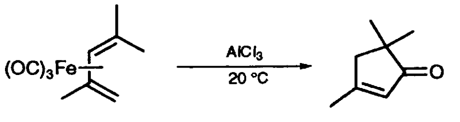
67

Scheme 14

Buchwald *et al.*[74,75] have highlighted the use of a combination of Cp_2TiCl_2 with two equivalents of EtMgBr as an effective cocktail for the reductive cyclization of enynes to bicyclic titanacyclopentanes; reactions of the latter with CO then lead to cyclopentenones in good yield (**Scheme 15**).
The cyclocarbonylation of acyclic 1,3-dienes *via* their tricarbonyl iron complexes has also resurfaced as a route to cyclopentenones, *viz.* **68** → **69**.[76]

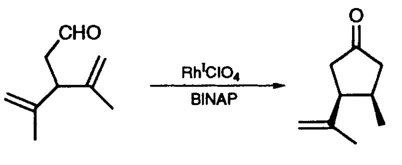


Scheme 15



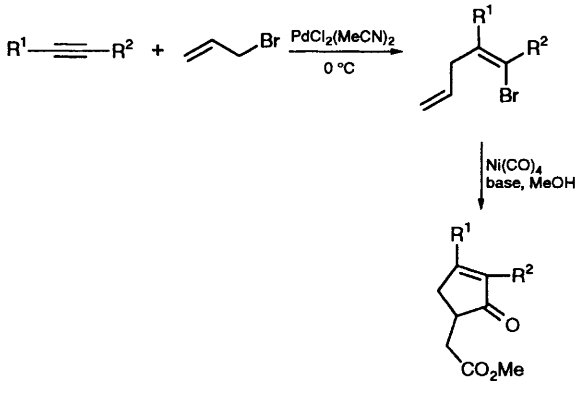
68 **69** (>95%)

Further details on the scope and limitations of the synthesis of cyclopentenones involving reactions between cyclopropylcarbene-chromium complexes and alkynes have been disclosed,[77] and highly diastereo- and enantio-selective cyclizations of substituted penten-4-als using a chiral rhodium(I) complex leading to cyclopentanones have been published (**Scheme 16**).[78]

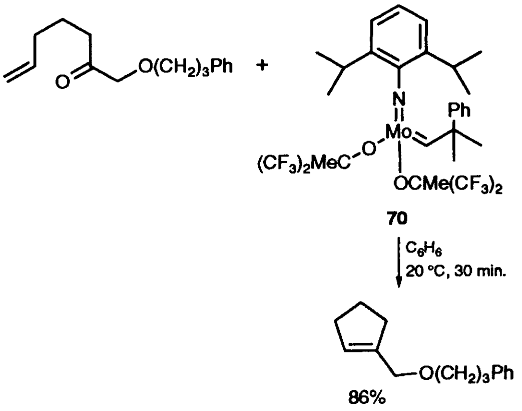


Scheme 16

A number of [3 + 2] type cycloaddition reactions bear witness to the use of this strategy in the synthesis of cyclopentenones (**Scheme 17**),[79–81] and the use of the molybdenum alkylide **70** in effecting the novel olefin metathesis/carbonyl olefination route to cyclopentenes is, to say the least, intriguing.[82]

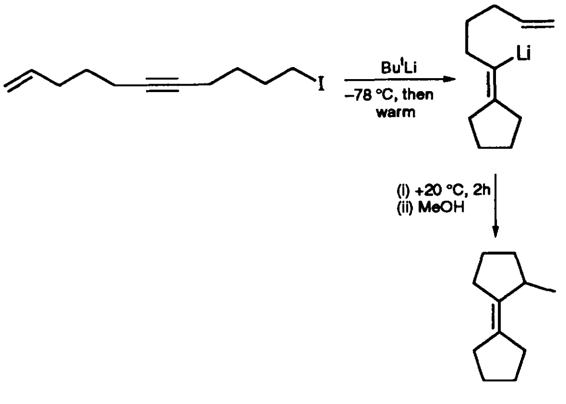


Scheme 17



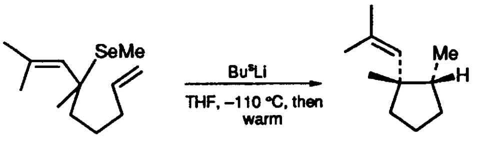
3.3 Other routes to five-membered carbocycles

The scope for intramolecular additions of the carbon-to-lithium bond into unactivated carbon-to-carbon double bonds, leading to cyclopentylmethyl lithiums, has received considerable attention in recent years. 5-*exo-dig* Cyclizations are also possible, and these reactions can be effected in tandem with 5-*exo-trig* processes (**Scheme 18**).[83]

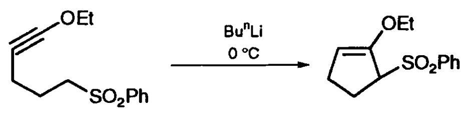


Scheme 18

In a similar vein Krief *et al.*[84] have shown that ω-alkenyl allyl-lithiums also undergo facile cyclizations with high regio- and stereo-control (**Scheme 19**), and usefully functionalized cyclopentanes are produced when stabilized organolithiums are added intramolecularly to alkoxyacetylenes (**Scheme 20**).[85]

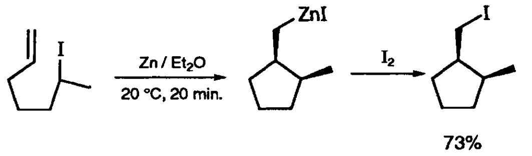


Scheme 19

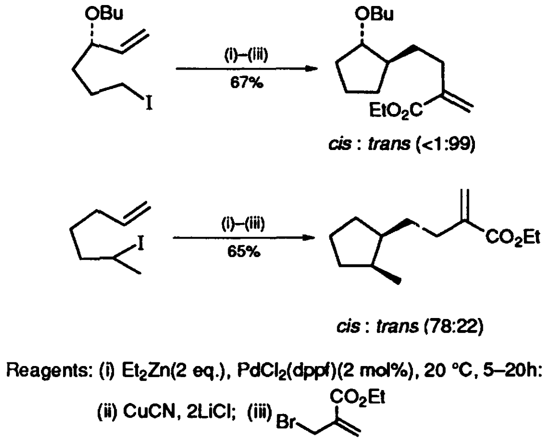


Scheme 20

Recent advances in the accessibility of organozinc compounds have prompted Normant, and others, to examine the intramolecular cyclizations of a range of suitably functionalized alkenyl zinc derivatives, with some interesting and useful results emerging (**Scheme 21**).[86, 87] Related studies by Knochel *et al.*[88, 89] have shown that intramolecular carbozincation reactions of alkenes can be dramatically accelerated by the addition of small amounts of Pd^{II} or Ni^{II} complexes. These novel ring closures, which are probably radical in nature, lead to organometallic intermediates which can subsequently be trapped with a range of electrophiles (**Scheme 22**).



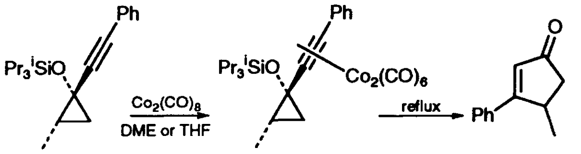
Scheme 21



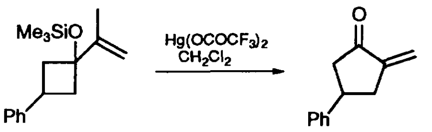
Reagents: (i) Et_2Zn(2 eq.), $PdCl_2$(dppf)(2 mol%), 20 °C, 5–20h: (ii) CuCN, 2LiCl; (iii) Br, CO_2Et

Scheme 22

A number of methods are available for the synthesis of cyclopentane derivatives *via* ring expansion processes of three- and four-membered ring systems. To add to this list are the rearrangement of cobalt complexed alkynyl cyclopropanols shown in (**Scheme 23**)[90, 91] and the ring expansions of alk-1-enyl-cyclobutan-1-ols under Hg^{2+} catalysis illustrated in the conversion of **71** into **72**.[36]



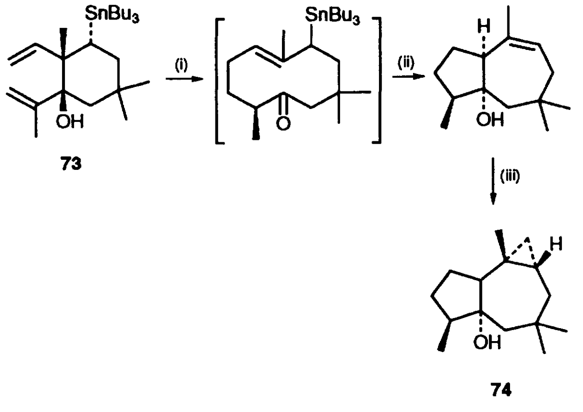
Scheme 23



71 **72**

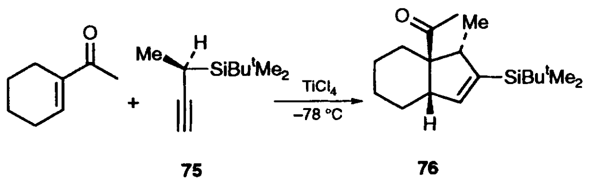
The novel use of an anionic oxy-Cope rearrangement, from **73**, in combination with a transannular cyclization has culminated in a neat synthesis of the 5,7-ring-fused terpene (±)-africanol **74**, described by White *et al.* (**Scheme 24**).[92, 93]

Danheiser and his colleagues[94, 95] have extended their studies of [3 + 2] annulation reactions involving allenylsilanes, and now shown that allyl and propargyl silanes can take part in the reactions, leading to usefully functionalized cyclopentanes, *e.g.* **75** → **76**.



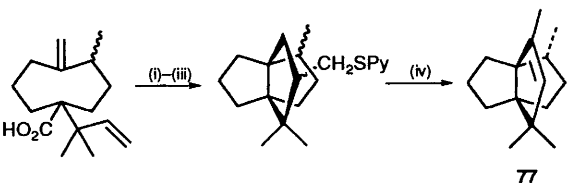
Reagents: (i) KH, ether, 25 °C, 3h; (ii) Na/$C_{10}H_8$, THF; (iii) CH_2I_2, Et_2Zn, 0 °C

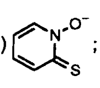
Scheme 24



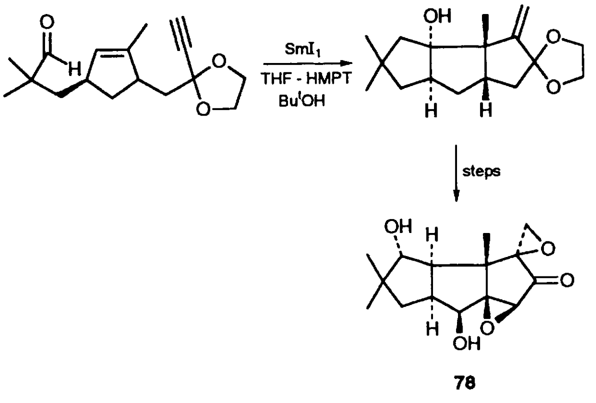
3.4 Polyquinanes

Interest in the biological activity and structural novelty of natural products like hirsutic acid, pentalenene, and modhephene has sustained activity in the synthesis of linear, angular, and propellane-type triquinanes. Furthermore, a number of the strategies used towards these intriguing compounds have been very much based on the burgeoning interests in free radical and transition metal mediated cyclopentane ring-forming reactions, discussed earlier in this section. Thus, Curran and Shen have published full details of their approach to (±)-modhephene **77** based on tandem transannular radical cyclizations (**Scheme 25**),[96] and Weinges *et al.* have demonstrated the scope for radical cyclizations in the presence of samarium iodide in their approach to coriolin **78** (**Scheme 26**).[97]

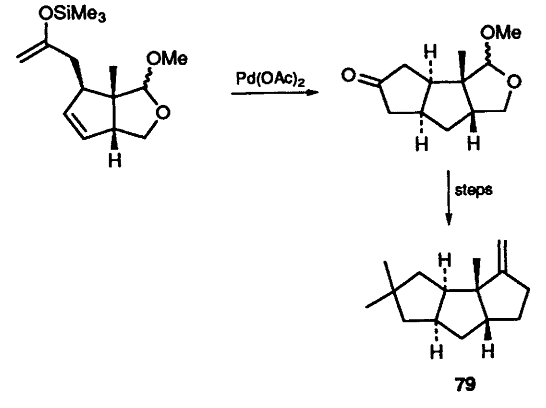


Reagents: (i) ClCOCOCl; (ii)  ; (iii) 100 °C; (iv) steps

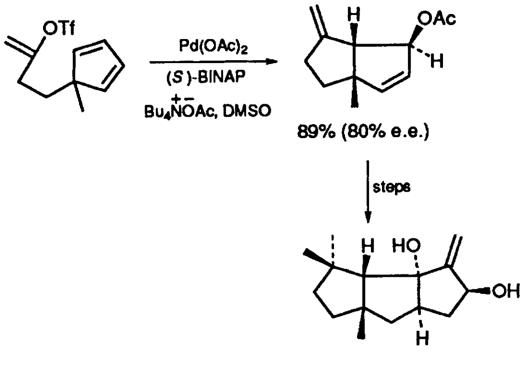
Scheme 25



Scheme 26



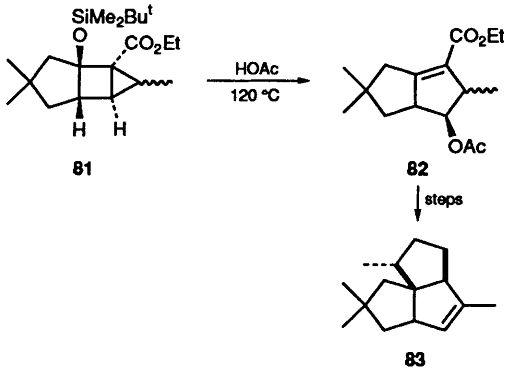
Scheme 27

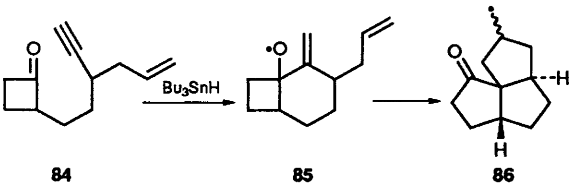


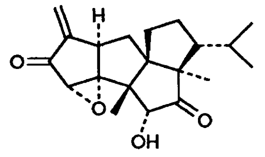
Scheme 28

A Pd^{2+} promoted cyclization provides a cornerstone in Fukumoto's synthesis of (±)-hirsutene (**79**, **Scheme 27**),[98,99] and an asymmetric Heck-reaction/anion-capture process features in an approach to capnellenols, *via* **80**, presented by Shibasaki *et al.* (**Scheme 28**).[100] Both the Pauson–Khand[101] reaction and tandem cyclizations of 5-hexenyl lithiums[102] have been used in other approaches to angular and linear polyquinanes.

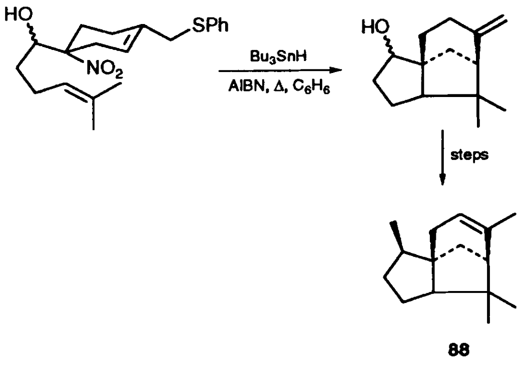
The interesting ring cleavage reaction **81** → **82** is the key step in a new synthesis of (±)-pentalenene **83** presented by Franck-Neumann *et al.*,[103] and an unusual oxyradical fragmentation radical-transannulation–cyclization sequence, *i.e.* **84** → **85** → **86**, has been investigated as an alternative approach to **83**.[104] A range of other routes to polyquinane constructions have been published during the period under review,[105–109] and a total synthesis of (±)-crinipellin B **87** has also been described.[110]






87

An interesting new approach towards the tricyclo [5.3.1.0^{1,5}]undecane ring system found in α-cedrene **88** relies on the tandem radical cyclization reaction shown in **Scheme 29**, which proceeds *via* an addition–elimination mechanism.[111]



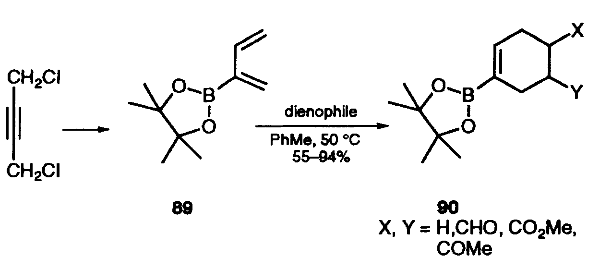
Scheme 29

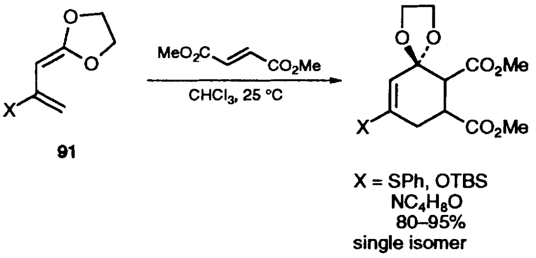
4 Six-membered rings

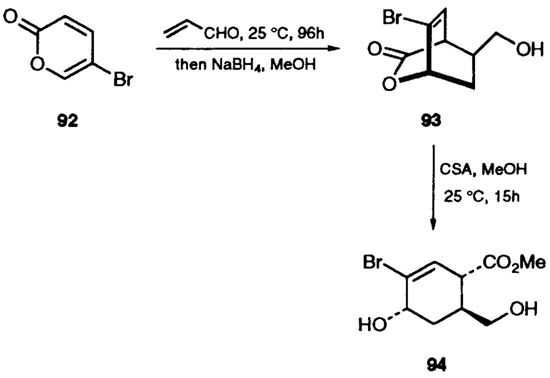
4.1 Diels–Alder reactions

The Diels–Alder reaction retains its central role in the synthesis of six-membered rings, with several new modifications being developed, particularly in the field of asymmetric synthesis.

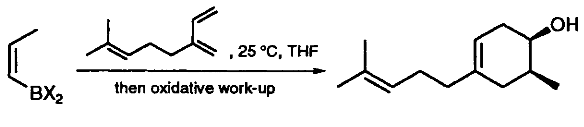
A number of new diene variants have been reported, of which the most generally useful may prove to be the butadienyl boronate species **89** described by Miyaura and Suzuki.[112] This highly reactive diene leads to adducts of the type **90**, and provides a useful route into cyclic alkenyl boronates which are otherwise difficult to obtain. Welker has reported similar results with cobalt-substituted butadienes.[113] Konopelski has extended his work on vinylketene acetals to 3-substituted cases **91**, although quite reactive dienophiles are still needed.[114] The useful 2-pyrone equivalent **92** has been prepared and investigated in Diels–Alder reactions, where the conditions for the cycloadditions are much milder than is usual for pyrone additions.[115] The conversion of the product **94** obtained on acidolysis of the adduct **93** into an intermediate in the synthesis of a vitamin D_3 analogue has also been described. An example of the use of tethered vinylallenes and dienes (which allows the construction of two rings simultaneously) has been reported.[116]





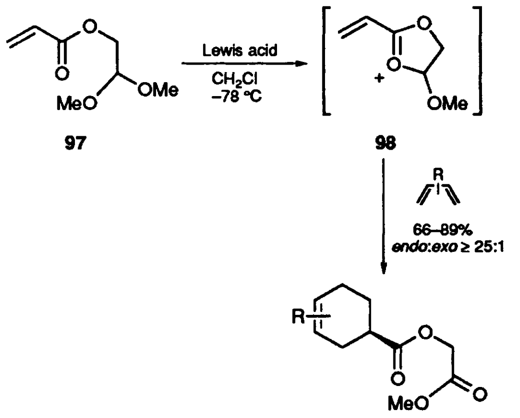


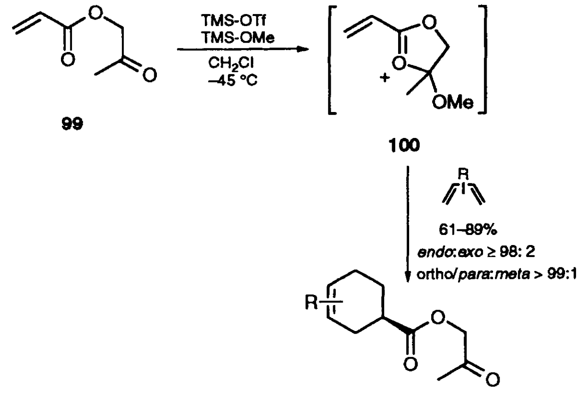
As with dienes, the use of boron-substituted dienophiles such as **95**, followed by appropriate manipulation of the adducts **96**, has been reported, most notably by Singleton;[117–120] both this and the related work of Vaultier[121] are beset by problems of regioselectivity, although there are indications that these problems can be overcome. If this is indeed the case the method provides a useful route to cyclic boranes. Saigo and his co-workers have reported a novel method for producing highly electron-deficient dienophiles whereby the acrylate-acetal **97** is first converted into the species **98**, which then reacts readily with a range of dienes under milder conditions

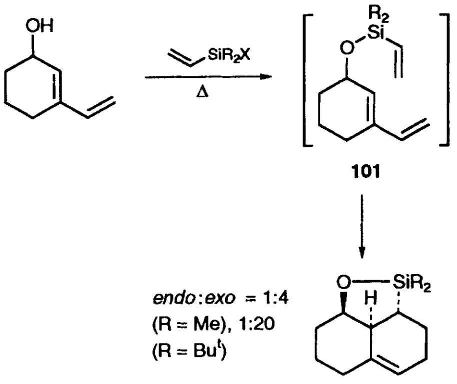


95 **96** (75%, single regioisomer)

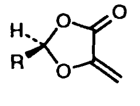
than are usually needed for Lewis acid catalysed acrylate cycloadditions.[122] The related cationic species **100** may be formed *in situ* from the ketone **99** by the action of TMS-OTf and TMS-OMe and then used in a similar manner.[123] Sieburth *et al.* have described the use of *in situ* formed vinylsilane dienophiles such as **101** in intramolecular Diels–Alder reactions; by careful choice of the alkyl groups on silicon, excellent *exo:endo* selectivity can be obtained.[124] Roush has prepared the unusual dienophile **102** as an intermediate in the synthesis of kijanolide.[125]







Two examples of the use of the allenes **103** and **104** as dienophiles in natural product synthesis have been reported,[126, 127] and Kim has investigated the scope for cyclic sugar-derived dienophiles such as **105**. These dienophiles react with five- or six-membered ring cycloalkadienes to give single stereoisomers of the resulting adducts, which can then be converted into highly substituted cyclopentanols or cyclohexanols such as **106**.[128]



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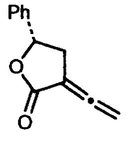
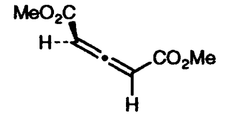


103



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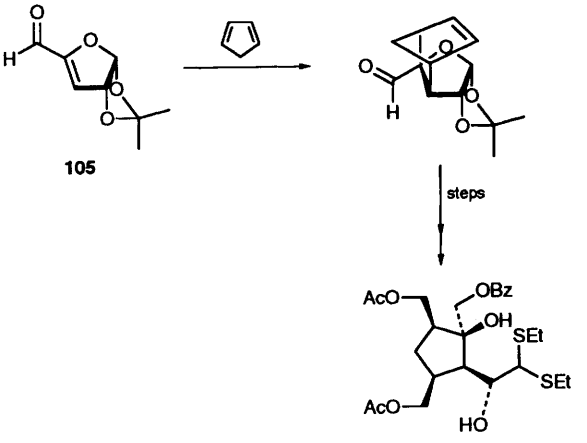
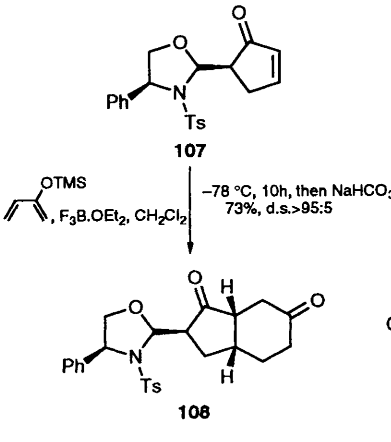


106

A number of new chiral auxiliaries for dienophiles have been reported.[129, 130] Thus, Hoffmann *et al.* have described the use of *N*-sulfonyloxazolidines in conjunction with cyclopentanones, illustrated by **107** → **108**, and Nouguier *et al.* have used arabinose derivatives such as **109**. In addition, Yamamoto *et al.* have described a strategy for increasing the effectiveness of chiral menthyl esters by the use of bulky Lewis acids.[131]



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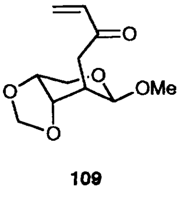
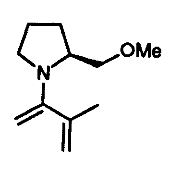


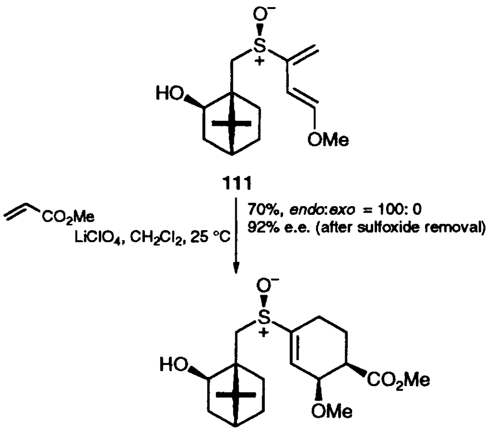
109

Interestingly, the less usual course of placing chiral auxiliaries on the diene component has also seen significant progress this year. Enders has used chiral, proline-derived 2-amino-1,3-butadienes, such as **110**,

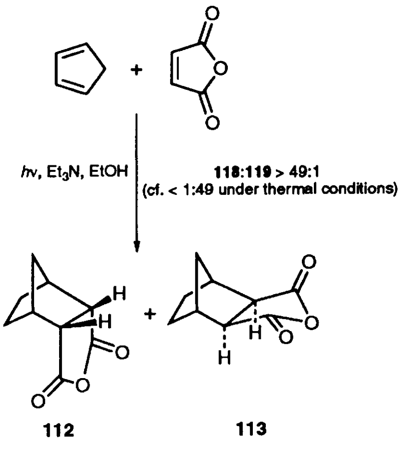


110

for both carbo- and hetero-cycloadditions,[132] whilst Jones and Aversa have studied the use of chiral sulfoxide-bearing dienes.[133] The latter researchers obtained excellent results in the optimization of Lewis acid conditions in the case of **111**.



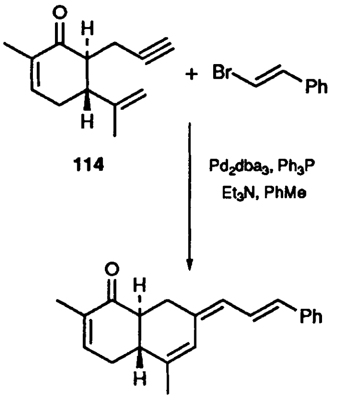
Perhaps one of the most interesting general developments in the area of Diels–Alder reactions is the demonstration by Pandey that reactions between cyclic dienes and dienophiles can be forced to give predominantly the product of *exo*-addition (*e.g.* **113**) by carrying out the reaction under photolytic conditions.[134] If this method proves to have general application it should be of considerable value, given the normal tendency towards predominantly *endo*-addition products, *e.g.* **112**. A number of new or improved Lewis acid catalysts for Diels–Alder reactions have been reported; these include the bulky MAD and MABr aryloxyaluminium reagents of Yamamoto,[135] examples of catalysis on solid supports,[136, 137] and the use of scandium triflate.[138] Asymmetric catalysis has seen little genuinely new work; however, the basic staples of metal-complexed chiral binaphthols[139, 140] and the chiral oxaborolidinone work of Corey[141] have seen further development. The latter has been extended to reactions with furan, providing a useful route into chiral cyclohexanols.[141]



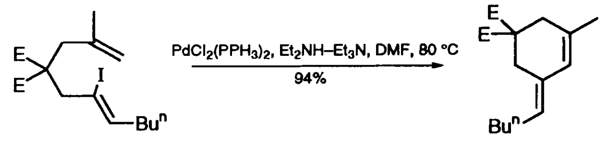
112 **113**

4.2 Transition metal mediated cyclizations

As in previous years palladium has been the dominant metal used in transition-metal based syntheses of six-membered rings published during the period covered by this report, with several descriptions of coupling to sp^2 centres. Trost has published a study of intramolecular palladium-catalysed intramolecular carbametalations of 1,6-enynes, wherein the regioselectivity of addition is shown to be dependent on the substitution pattern of the alkyne, with monosubstituted alkynes such as **114** giving exclusively the product **115** of 6-*endo* cyclization.[142] Another example of *endo* cyclization of alkenyl palladium intermediates has been reported by Negishi, *viz.* **116** → **117**, although evidence is presented which indicates that the reaction in fact proceeds *via* the *exo*-mode of bicyclization followed by cyclopropanation and then rearrangement.[143]

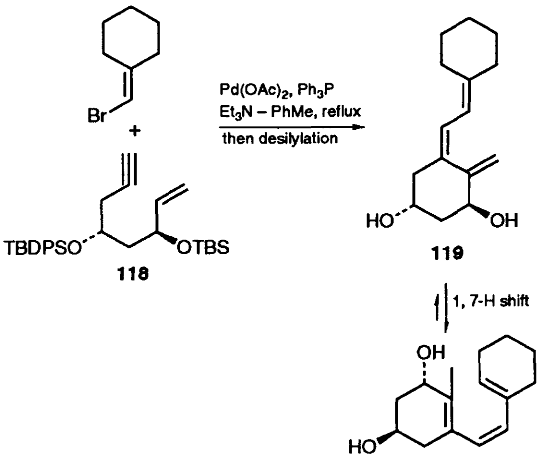


115



116 **117**

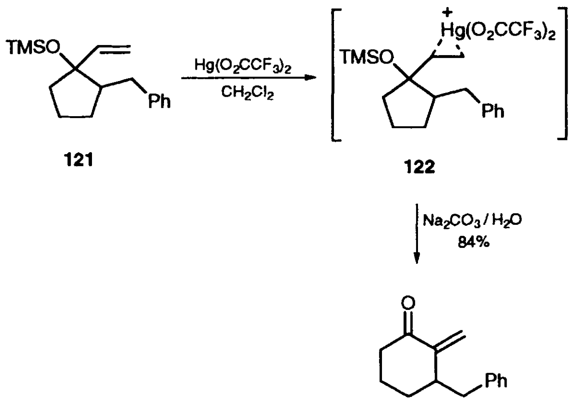
The recent revival of synthetic interest in the vitamin D carbon skeleton (following the discovery of immunosuppressant and anti-cancer properties in analogues) has led several research groups to approach the A-ring (with its two *exo*-alkene groups) *via* palladium-based methodology of similar type to that described above for **114** → **115**.[144] Interestingly, attempts to form the triene system in **119** *via* the cycloisomerization of a suitable enyne **118** followed by trapping of the intermediate vinyl palladium species with a vinyl halide were hampered by a tendency towards isomerization in the product, *viz.* **119** → **120**; however, less ambitious approaches based on initial formation of the *exo*-diene structure followed by triene synthesis by more conventional methods have been more successful.[145-147] Other metal-mediated research of note includes Kim's ring expansion method for 1-alkenyl cyclopentanols **121** *via* the corresponding mercurinium ion **122**.[148] The method may also be applied to the synthesis of five-, seven-, and eight-membered rings (see Section 3.2).



118

119

120

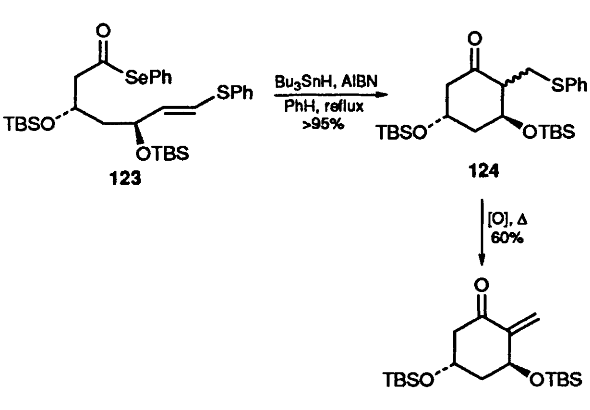


121

122

4.3 Free radical cyclizations

Cyclizations of simple heptenyl radicals are, in general, an unreliable method of forming six-membered rings, owing to a tendency for competing side-reactions (7-*endo* cyclization, 1,5-hydrogen abstraction, and simple reduction) to both decrease the chemical yield and possibly introduce problems in purification. However, by attaching suitable substituents to either the radical centre of the acceptor site, it is possible to minimize or even eliminate such complications. For example, the propensity of acyl carbon atoms, acting as either radical centres or radical acceptors, to selectively form six-membered-ring cyclic ketones is emerging as a useful addition to more established methods of annulation. Crich has described the use of the acyl radial cyclization route in an alternative approach, *viz.* **123** → **124**, to the vitamin D A-ring discussed in Section 4.2.[149] The clean 6-*exo* addition to the alkene **123** seen here is also apparent in other work.[150]

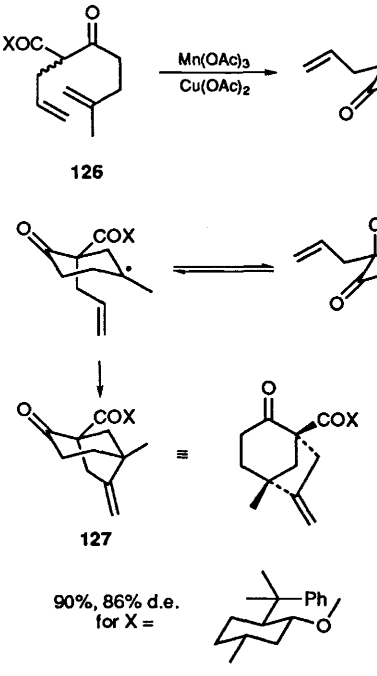


123

124

125

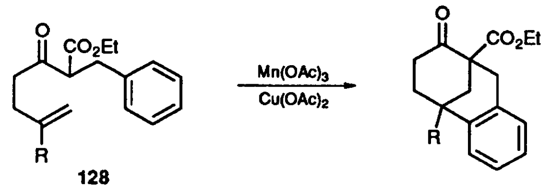
In a related study, Crich has demonstrated that (at least in arylacyl cases) acyl tellurides are a viable alternative to acyl selenides as a source of acyl radicals.[151] Another case in point is the use of copper-manganese reagents to generate radicals at *β*-dicarbonyl centres. This method has been investigated by Snider, yielding some fascinating results. Such radicals favour 6-*endo* cyclization over 5-*exo* in many circumstances, and as such are a potentially useful tool for the synthesis of cyclohexanones. In the case of **126** a tandem process occurs, giving the product **127** *via* the mechanism indicated in **Scheme 30**.[152] By careful choice of the chiral auxiliary 'X' in **126** synthetically useful yields and diastereomeric excesses can be obtained. Snider has also described the control of regioselectivity by the use of chloroalkenes for cases where either 7-*endo* or 5-*exo* cyclizations are serious side-reactions.[153] The case of the latter is exemplified by the conversion of **128** into **129**. Finally, an unusual route to six-membered rings has been reported by Kilburn,[154] based on radical addition to methylene cyclopropanes such as **130**.



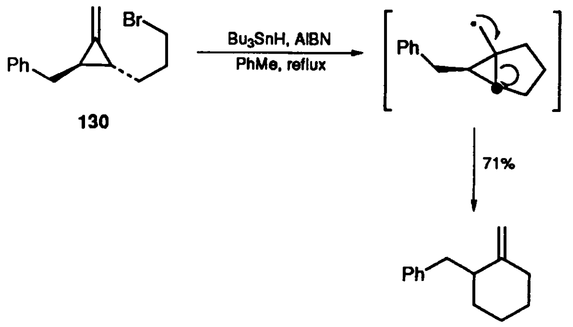
126

127

Scheme 30



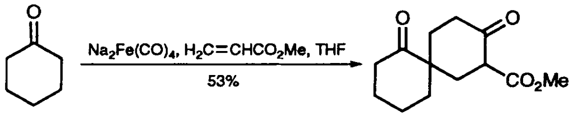
128 **129**



130

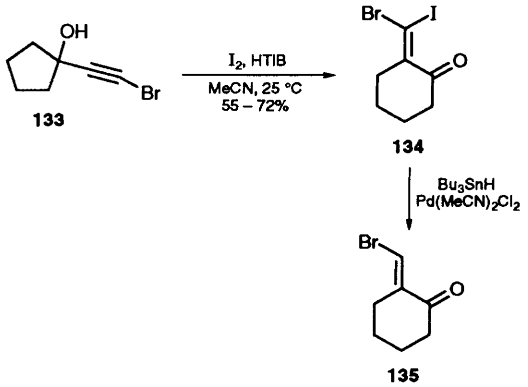
4.4 Other routes to six-membered rings

Anionic methods remain popular in six-membered ring constructions, with the familiar Michael and Dieckmann reactions seeing further development. Periasamy has described a general method for the introduction of cyclohexyl rings at the α-methylene centre in ketones, esters, lactones, and nitriles, utilizing a one-pot combination of the two, *e.g.* **131** → **132**.[155]

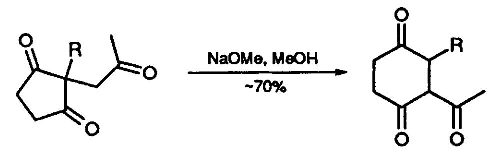


131 **132**

New ring-expansion methods have also been reported. Thus, McNelis has shown that treatment of alkynyl cyclopentanols **133** with iodine and Koser's reagent gives cleanly and in good yield the methylene cyclohexanone **134** with a doubly halogenated alkene. Subsequent selective reduction of the iodine moiety in **134** gives the stereodefined bromide **135**.[156] Schick has reported an unusual ring-expansion of the 1,3-cyclopentanediones **136** to the corresponding 1,4-cyclohexanediones **137**;[157] the reaction is unusual in that cleavage of 1,3-cyclopentanediones is usually seen under alkaline conditions.

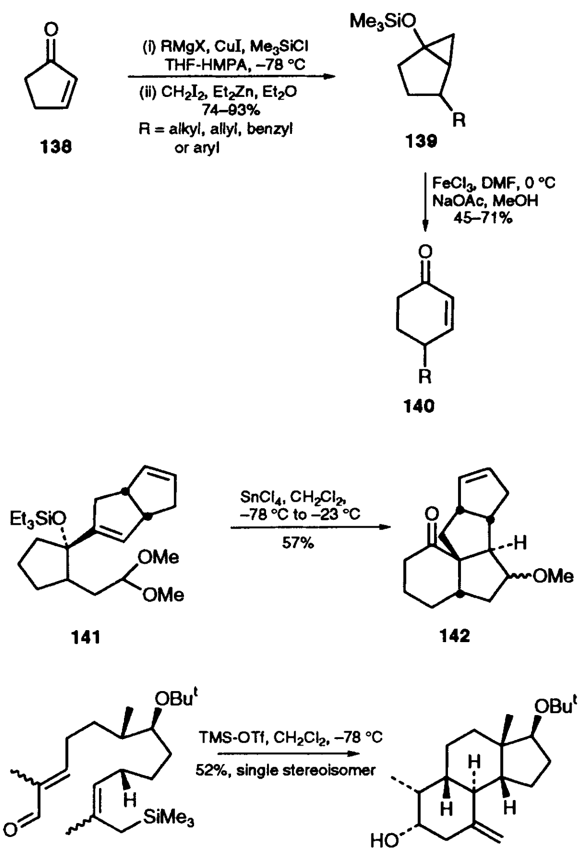


133 **134** **135**



136 **137** (R = 1 ° alkyl)

Cationic methods, particularly those mediated by Lewis acids, are increasing in popularity. Thus Booker-Milburn has reported the preparation of cyclohexenones **140** from cyclopentenones **138** by iron-catalysed ring expansion of siloxybicyclo-[3.1.0]cyclohexane intermediates **139**,[158] and Overman has demonstrated that the Prins-pinacol rearrangement can be usefully applied to the synthesis of quite complex structures such as **142** following simple treatment of the vinyl (siloxycylopentane) **141** with tin tetrachloride.[159] Finally, Lewis-acid catalysed asymmetric ene[160] and carbonyl ene reactions have seen further development, the latter forming part of a remarkable (and highly stereoselective) tandem process with the Sakurai reaction (**Scheme 31**).[161]

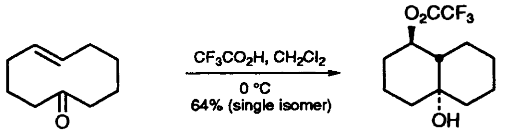


138 **139** **140** **141** **142**

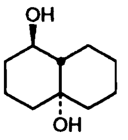
Scheme 31

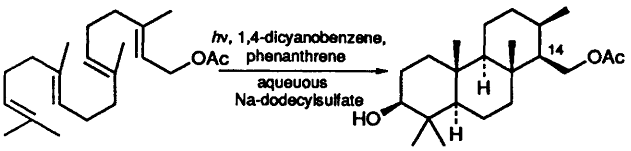
4.5 Fused six-membered rings

The majority of the methods used for six-membered-ring annulation are equally applicable to the synthesis of six-membered-ring containing bicycles and polycycles, by the simple expedient of using a cyclic substrate. Such simplicities are not covered in this section, which instead highlights cases of 'one-pot' formation of two or more rings, where at least one is six-membered. Transannular ring contractions of medium-rings provide one such approach, as illustrated by the work of White,[162] in which treatment of the cyclododecenone **143** with acid gives the *trans*-decalin system **144**. Note that under radical conditions (Bu_3SnH or SmI_2) the 7,5-ring system is favoured. Other transannular work includes the continuing research of Deslongchamps into intramolecular Diels–Alder syntheses of polycycles, which has been self-summarized.[163] Roush has also made a recent contribution to this field.[164] An increasingly popular alternative to transannulation reactions for polycycle synthesis is the use of 'cascade' cyclizations, as described for five-membered rings in Section 3. An excellent example of this has been reported by Demuth,[165] wherein the polyene **145** is cyclized to the tricycle **146** under single-electron transfer conditions. This fascinating process is suggested to proceed *via* radical cation intermediates (as would be expected from the reaction conditions), and represents an alternative to the classical cationic means of achieving 'biomimetic' polycyclization. Although the yield of **146** is low, there remains considerable scope for optimization.



143 **144**

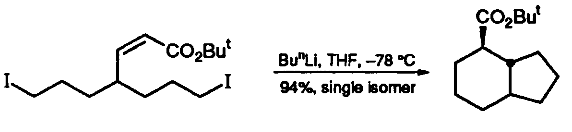




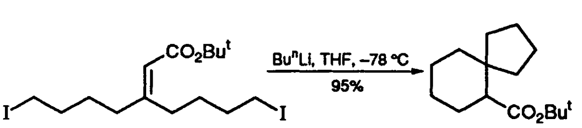
145

146
18%, + 6%
of C-14 epimer

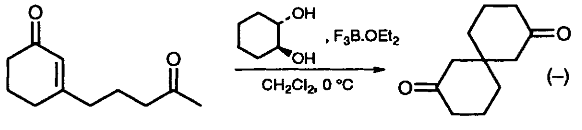
A 'tandem' approach to decalins **147** and spiro 6,5-systems **148** has been described by Cooke.[166] The method is dependent on the rapid halogen–metal exchange (presumably *via* single-electron transfer) between alkyl iodides and Bu^nLi, and appears to be remarkably efficient. Another route (asymmetric in this case) to spiro-bicycles has been reported by Sakai,[167] utilizing chiral diol auxiliaries to allow the synthesis of **149** in chiral form. A method for the selective formation of *cis* or *trans* decalins *via* samarium-mediated cyclization has been reported,[168] where the stereocontrol is proposed to arise by intramolecular samarium chelate formation between the carbonyl and hydroxyl groups; thus the hydroxyl groups in **150**, **151**, and **152** are all *syn*, to each other.



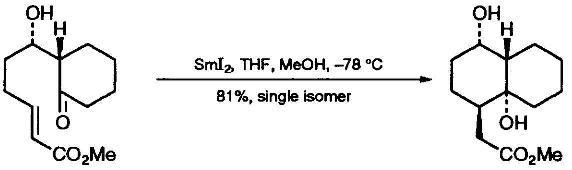
147



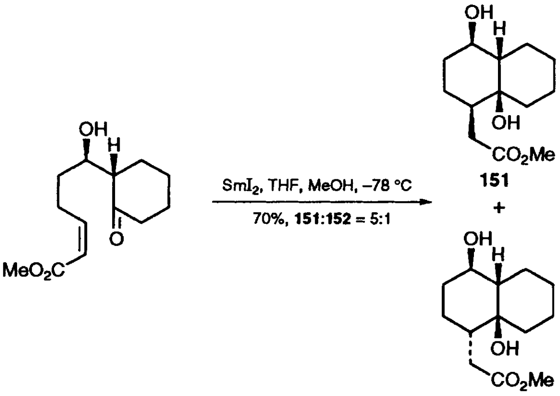
148



149 (86% yield
85% e.e.)

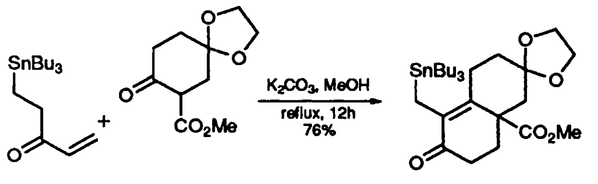


150



151 + **152**

'Appendage' bicyclization (*i.e.* attaching a bifunctional synthon to a monocycle and then closing a second ring *in situ*) continues to attract interest. Fuchs has developed the four carbon appendage **153** as a means of preparing highly functionalized allylic stannanes such as **154** *via* the classical Robinson annulation.[169] The survival of **154** under the alkaline conditions of the annulation is noteworthy (the equivalent silane is hydrolyzed). Finally, Piers has

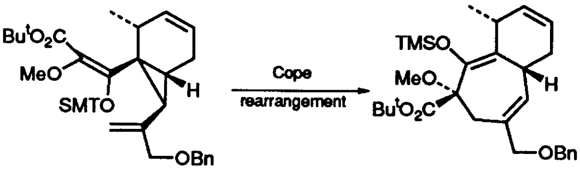


153 **154**

reported a simple method of *exo*-alkenyl cyclohexane synthesis based, like that of Pulido mentioned in Section 2, on the fast transmetalation of vinyl stannanes with alkyl-lithiums.[170]

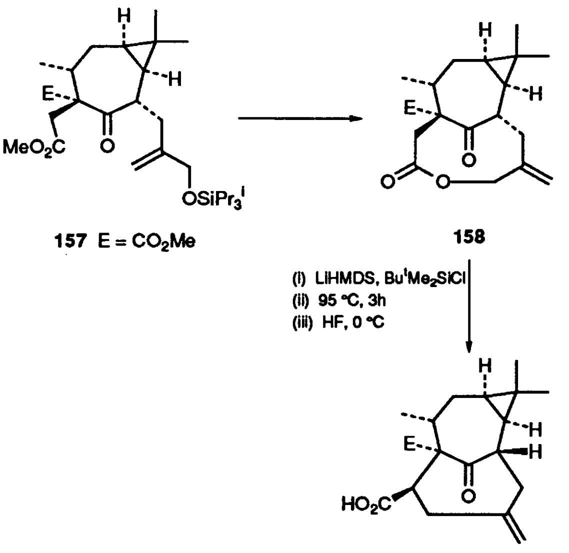
5 Seven-membered rings

Without doubt one of the most effective methods for the synthesis of seven-membered rings to be utilized in recent years has been the Cope rearrangement of *cis*-divinylcyclopropanes, *e.g.* **155** → **156**. The only limitation to this method of synthesis is the availability of the *cis*-divinylcyclopropanes. In a concise review Davies[171] has now drawn together the main features of the conversions to demonstrate how the *cis*-divinylcyclopropanation/Cope-rearrangement can be effected in tandem, leading to highly functionalized seven-membered rings, often with excellent control of both relative and absolute stereochemistry.



155 **156 (87%)**

The equally familiar Claisen rearrangement, but used in the form of a ring-contraction strategy, has been used in a most elegant fashion to elaborate the novel 7,7-fused bicyclic ring portion **159** in the ingenane family of natural products, *viz.* **157** → **158** → **159**.[172]

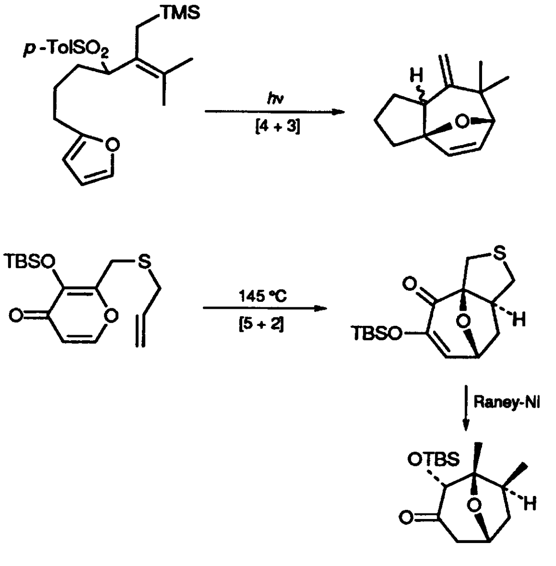


157 E = CO_2Me

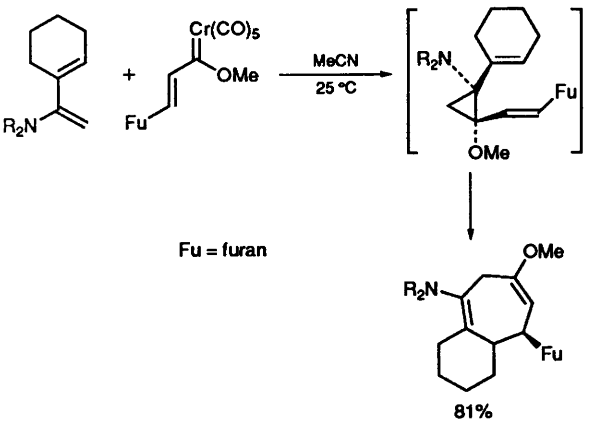
158

159 (88%)

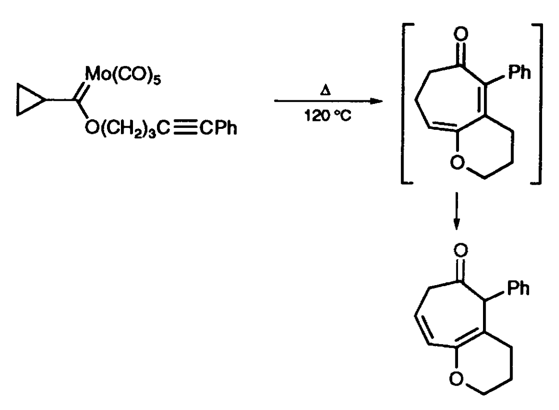
Cycloaddition reactions based on [4 + 3] and [5 + 2] annulations leading to seven-membered rings have featured prominently in the recent literature, and two further examples of these reactions described during the period under review are collected in **Scheme 32**.[173-176] The unusual reaction between 2-aminobuta-1,3-dienes and vinylchromium Fischer type carbenes, which can be regarded as a [4 + 3] cycloaddition, also provides an interesting route to seven-membered rings (**Scheme 33**).[177] Furthermore, in a modification of the more familiar Dötz reaction, Herndon *et al.*[178, 179] have now shown that cycloheptadienones can be obtained by the reaction of cyclopropylcarbene molybdenum or tungsten complexes with alkynes according to **Scheme 34**.



Scheme 32

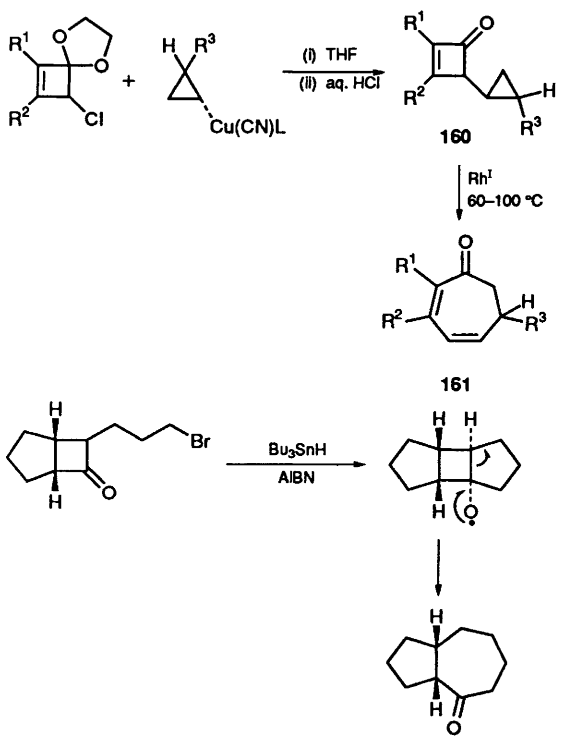


Scheme 33



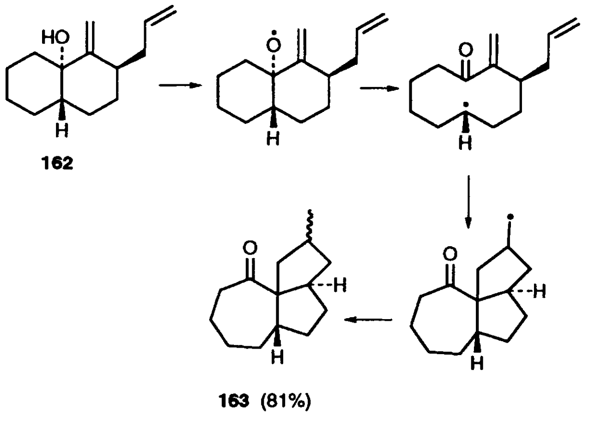
Scheme 34

Ring-enlargement reactions are often used in synthesis, and two new sequences used in seven-membered ring constructions are the rhodium(I)-catalysed ring fusion **160** → **161**[180] and the free-radical ring expansion of fused cyclobutanones described by Dowd *et al.*[181] and highlighted in **Scheme 35**.



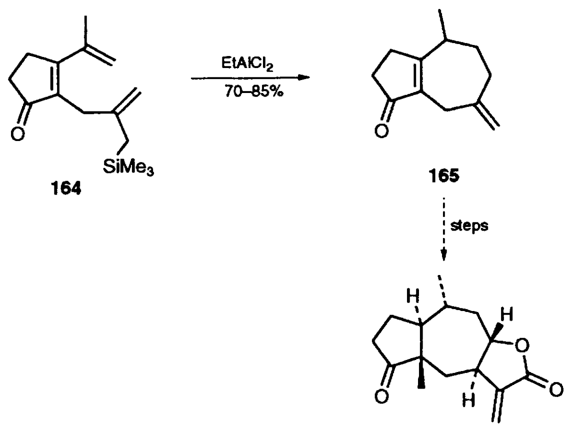
Scheme 35

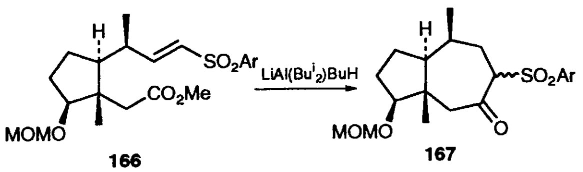
A further illustration of the scope for tandem free-radical reactions in seven-membered ring synthesis is shown by the cascade fragmentation–transannulation process triggered by treatment of the bicyclic dienol **162** with iodosylbenzene diacetate/iodine, leading to the 7,5,5,-tricycle **163** in 80% yield (**Scheme 36**).[182] Other radical-based procedures, involving acyl radical[183] and organocobalt intermediates,[184] leading to the synthesis of linear fused seven-membered ring systems have also been described.



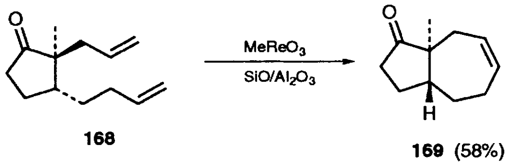
Scheme 36

Majetich *et al.*[185] have published full details of their allylsilane-based annulation strategy to construct perhydroazulenes, *viz.* **164** → **165**, and Jones *et al.*[186] have described an approach to the same ring system based on some novel cyclizations involving sulfones, *e.g.* **166** → **167**.



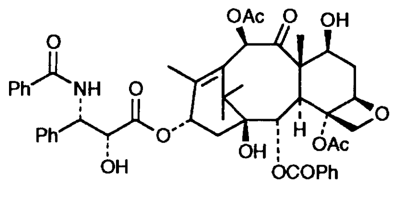


Ring-opening reactions of oxabicyclo[3.2.1]octanes leading to functionalized cycloheptenes and cycloheptadienes have been summarized,[187] and the neat metathesis reaction **168** → **169** has been highlighted as a route to hydroazulenes.[188]



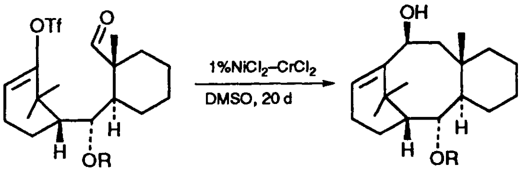
6 Eight-membered rings

Much of the recent spate of activity in approaches to the synthesis of eight-membered rings stems from interest in taxol **170** and its promising anticancer activity. A concise review of approaches to taxanes has recently been published in *Contemporary Organic Synthesis*.[189] Recent additions to these approaches are

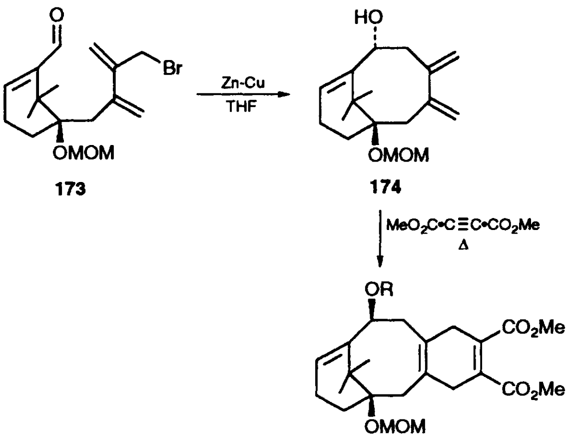


170

the intramolecular Ni^{II}-Cr^{II} mediated coupling reaction shown by **171** → **172**,[190] and the intramolecular nucleophilic allylic bromide-aldehyde addition reaction **173** → **174** promoted by a Zn-Cu couple.[191]



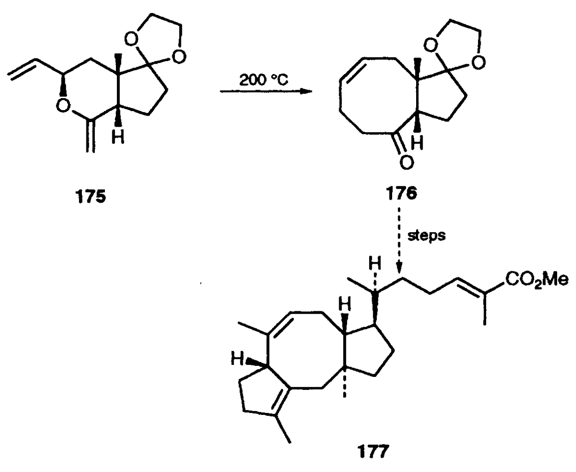
171 **172** (50%)



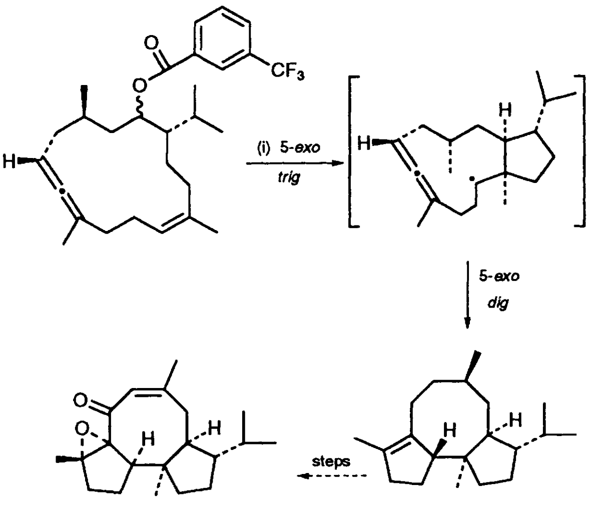
173 **174**

The Claisen rearrangement of **175** → **176** has featured in Paquette's approach to the 5,8,5-ring fused diterpene (+)-ceroplastol I **177**,[192] and Myers and Condroski[193] have outlined a neat radical-based transannular strategy in their novel synthesis of the tobacco isolate (±)-7,8-epoxy-4-basnien-6-one **178** (**Scheme 37**).

In other approaches to eight-membered ring constructions published during the period covered by this review, efficient intramolecular [4 + 4] photocycloadditions between 2-pyrones and furan have been presented,[194] Funk has extended his work on Claisen rearrangements to enol phosphates,[195] and Inoue *et al.*[196] have used a modified de Mayo photochemical reaction in an approach to (±)-precapnelladiene found in marine coral.



175 **176** **177**



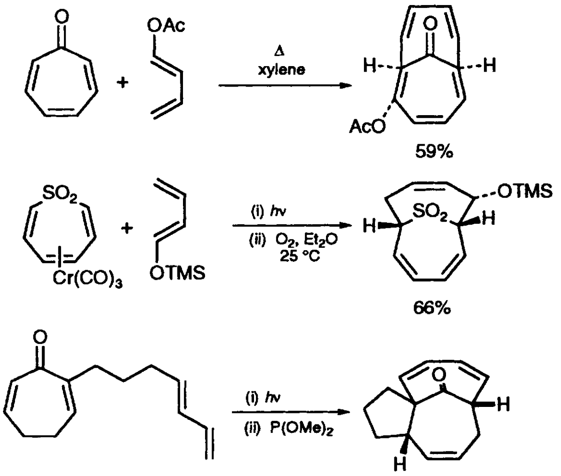
178

Reagent: (i) *N*-methylcarbazole, 1,4-cyclohexadiene, THF–H$_2$O, *hv*

Scheme 37

7 Ten-membered and larger rings

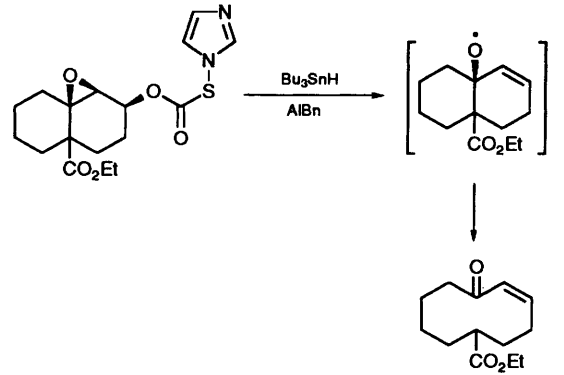
In so-called higher order cycloaddition reactions, Rigby and co-workers[197] have summarized numerous examples of [6π + 4π] cycloadditions which can be effected either thermally, photochemically, or by employing a chromium metal catalyst (**Scheme 38**); related [6π + 2π] cycloaddition reactions have also been highlighted by Rigby and co-workers.[198]



Scheme 38

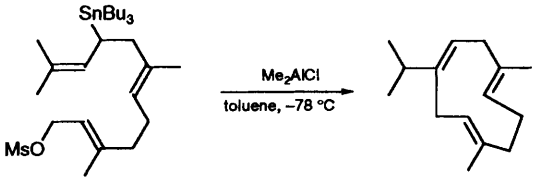
The directed ring-opening of epoxycarbinyl radicals set in decalin ring systems, followed by fragmentation of the resulting oxy-centred radicals, has been used as an approach to substituted cyclodecanones (**Scheme 39**),[199, 200] and related work involving radical intermediates from homoallylic alcohols has been presented.[201]

A biogenetically inspired synthesis of humulene **180** from farnesol has been described by Corey *et al.*[202] which incorporates the trick of utilizing an allylic

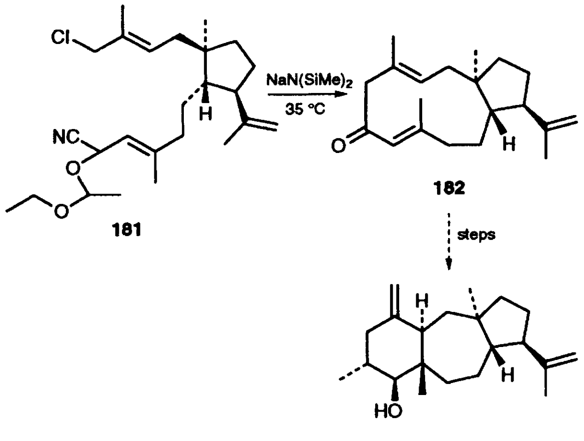


Scheme 39

Bu_3Sn to lower the activation energy in the cyclization of **179** → **180** in the presence of dimethylaluminium chloride at − 78°C. The cyclization of **181** to the eleven-membered ring intermediate **182** has been used in the biogenetically patterned synthesis of the clavularanes **183** described by Williams *et al.*[203]



179 **180**

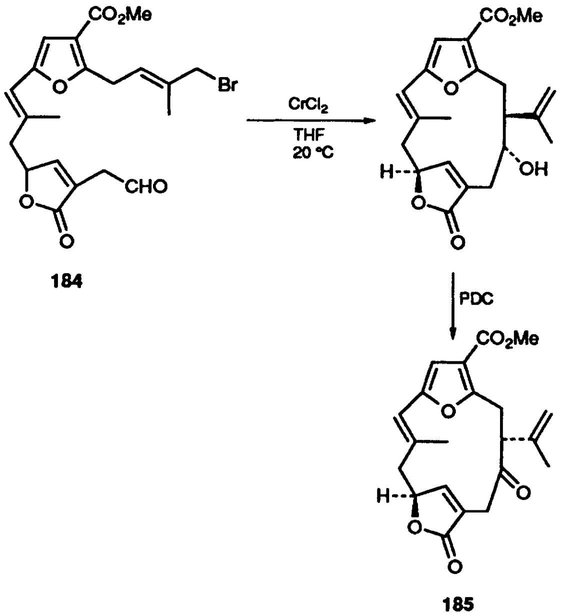


181 **182** **183**

In Paquette's synthesis of the fourteen-membered furanocembrane acerosolide **185**, the crucial cyclization step was achieved by treatment of the allylic bromide **184** with the reducing cocktail of $CrCl_3$ and $LiAlH_4$.[204]

8 General carbocyclic ring synthesis

In addition to those reviews already sited, Tietze and Beifuss[205] have produced a useful review of sequential (tandem/domino/cascade) ring-forming reactions in organic synthesis, which nicely complements the book written by T.-L. Ho covering the same area.[206] Roxburgh has reviewed the synthesis of medium-sized rings by ring expansion reactions,[207] and Paquette and Stirling[208] have presented a useful exposé of the intramolecular S_N1 reaction and some of its applications to ring synthesis. A general account of stereo-electronic effects in the formation of five- and six-membered rings, and the role of so-called Baldwin's rules, has been presented,[209] and Petasis and Patane[210] have provided an excellent account of the synthesis of eight-membered carbocycles.



184 **185**

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