Free radical-mediated macrocyclisations and transannular cyclisations in synthesis

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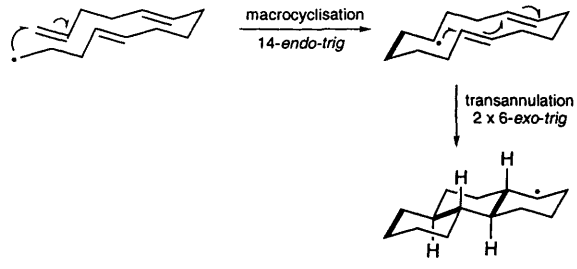
Reviewing the literature published up to January 1997

1 Introduction

When the history of the main developments occurring in synthetic organic chemistry during the last twenty years of the twentieth century is written, free radical chemistry will occupy a prominent position. To say that developments in this area have occurred at an explosive pace would be an understatement. Many review articles[1] and several books[2] bear witness to this fact. The construction of five- and six-membered rings, either in separate or multistep processess (or in tandem radical reactions)[3] has dominated many of these developments. Furthermore, guidelines for understanding the stereoelectronic factors involved in these five- and six-membered free radical ring constructions are now well developed.[4] Until the pioneering work of Porter *et al.*, first published in 1986,[5] and the applications in natural products synthesis from our research group,[6] few practising synthetic chemists would have entertained using free radical protocols in the construction of macrocyclic frameworks, *i.e.* 10- to 20-membered rings. This situation has now changed dramatically. In addition, macrocycles provide a template for studies of radical-mediated transannular cyclisations leading to the synthesis of a wide variety of smaller ring-fused polycycles. Finally, when the principles of free radical macrocyclisation are combined with radical-mediated transannular cyclisation, in a single operation, a powerful cascade strategy becomes available for the synthesis of polycycles from relatively simple acyclic precursors, *viz.* **Scheme 1**.



Scheme 1 Radical-mediated macrocyclisation followed by successive transannular cyclisations

The broad aim of this Review is to reflect upon, and to summarise, the main developments that have taken place in the applications of free radical chemistry to (i) the synthesis of macrocycles; (ii) the elaboration of polycycles by transannular cyclisations, and finally (iii) the synthesis of polycyclic arrays by cascade macrocyclisation–transannulation processes, over the past decade. In order to keep the Review to an acceptable length, coverage has been focused on carbocyclic ring constructions.

2 Free radical-mediated macrocyclisations

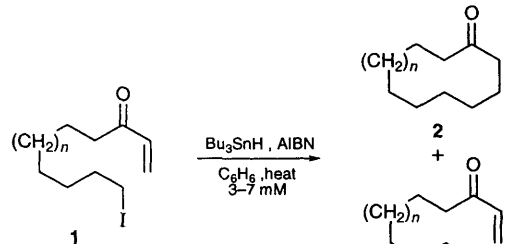
2.1 Cyclisations onto activated carbon–carbon bonds

Pioneering studies into the feasibility of free radical-mediated macrocyclisations were published by Porter *et al.* in the late 1980s.[5,7–9] Utilising previous mechanistic work concerning the electronic and steric effects that dominate intermolecular radical additions to carbon–carbon double bonds, these authors were able to define the criteria necessary to achieve radical cyclisation to produce macrocycles of ten members and larger. To summarise the main

findings, Porter and co-workers showed the following: (i) As the majority of carbon-centred radicals are nucleophilic, then activation of the carbon–carbon double bond undergoing addition by the radical, using an electron withdrawing substituent (typically a carbonyl moiety), was necessary to achieve smooth intramolecular macrocyclisation (*cf.* **Scheme 1**). (ii) In common with other macrocyclisation techniques, high dilution conditions using Bu_3SnH–AIBN gave improved yields of macrocyclised products by lowering the probability of competing bimolecular processes, most notably the direct reduction of the initially formed radical by tin hydride. Optimum conditions were found to include low concentration of the cyclisation precursor (3–7 mM) and occasionally slow addition of the tributylin hybride. (iii) In general alkyl iodides gave improved yields of cyclised products over the corresponding bromide precursors, presumably due to poor propagation at the alkyl bromide–stannyl radical step with the latter under the high dilution conditions.

In the first successful study of radical macrocyclisation Porter *et al.* examined the cyclisation of a series of acyclic ω-iodoenones **1** (**Scheme 2**).[5] These radical precursors underwent intramolecular *endo-trig* macrocyclisation, when subjected to the optimum conditions outlined above, to generate the respective macrocyclic ketones **2** in moderate to good yield together with the acyclic products **3** resulting from direct reduction of the initially formed alkyl radical by tin hydride. Additionally, it was found that the two analogues of the precursor **1** (n = 5) containing unsaturation in the tether between the radical and the activated olefin gave yields of macrocyclised products (76–78%) above that achieved with the saturated analogue (63%). This finding also holds true for many other macrocyclisation methods. Indeed it was subsequently shown by the same research group that, even when the unsaturation in the tether allowed a competitive 6-*exo-trig* cyclisation onto an electron rich olefin, macrocyclisation could be achieved successfully.[8]

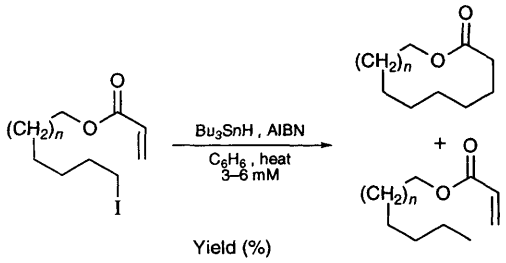
In a continuation of these studies Porter and Chang later demonstrated that intramolecular free



		Yield (%)	
n	Ring size	2	3
1	10	15	27
5	14	63	22
9	18	54	16

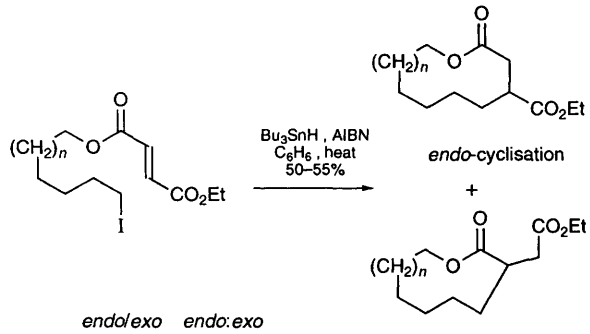
Scheme 2

radical additions to acrylate (**Scheme 3**) and fumarate (**Scheme 4**) esters could be used to produce 11- to 20-membered macrolides in fair to good yields.[7] Once again the major side-product was found to be acyclic material resulting from direct reduction of the carbon–iodine bond, which was observed even under high dilution conditions. Improved yields were obtained with a tertiary iodide precursor owing to the fact that the cyclisation could be carried out at a much lower concentration (0.7 mM, *cf.* 3–6 mM) for the primary iodides), due to the enhanced reactivity of this system towards the stannyl radical.



		Yield (%)	
n	Ring size	Cyclic	Acyclic
2	11	15–25	23–28
3	12	27–29	27–29
6	15	45	12
7	16	50–55	18–21
11	20	47–56	19

Scheme 3



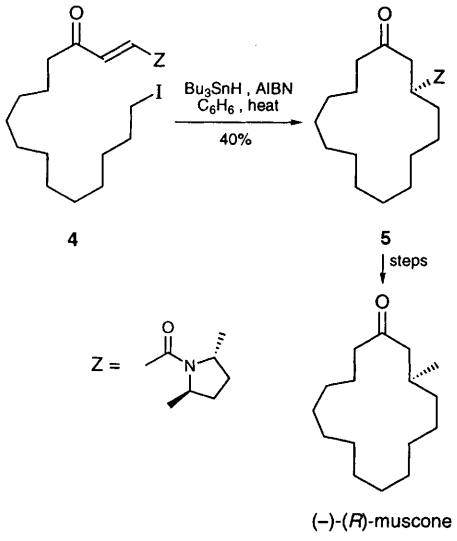
	endo/*exo*	*endo*:*exo*
n	Ring size	Ratio
3	12/11	5:1
4	13/12	5:1
7	16/15	2.5:1
11	20/19	1.1:1

Scheme 4

The results of the macrocyclisations with the iodofumarates (**Scheme 4**) were of particular significance as they demonstrated that *endo*-cyclisation modes were favoured over *exo*-cyclisation. This trend was especially marked in the formation of intermediate sized rings (12- and 13-membered) suggesting that it was due to the increased enthalpic destabilisation by transannular steric effects in the

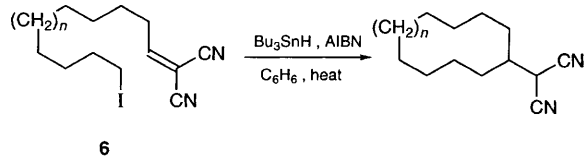
exo-cyclisation mode. This factor allowed the authors to propose the guideline that '*endo*-cyclisation modes are favoured' in radical macrocyclisations.

Porter and colleagues were able to use this propensity of fumarate systems for *endo*-macrocyclisation in a total synthesis of (−)-(*R*)-muscone (**Scheme 5**).[9] Thus, treatment of the iodide precursor **4**, containing the C_2-symmetric pyrrolidine substituent on the fumarate system, with tributyltin hydride and AIBN in refluxing benzene led to a highly diastereo- and regio-selective 15-*endo-trig* cyclisation to generate the macrocycle **5**. Straightforward functional group manipulations then gave natural (−)-(*R*)-muscone. It should be noted that this was one of the first examples of asymmetric induction in a radical cyclisation reaction.



Scheme 5

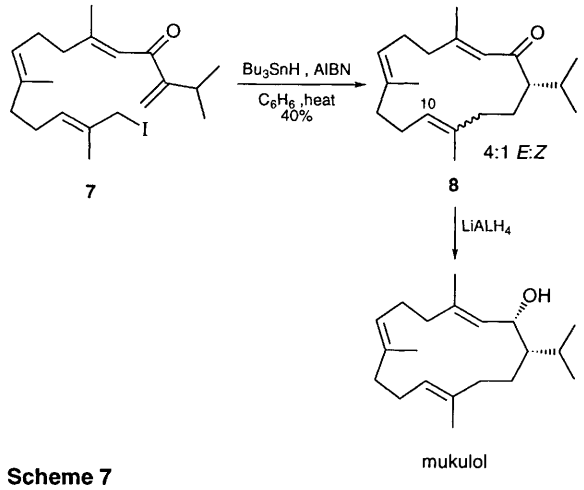
Subsequent investigations by Porter *et al.* revealed that the preference for *endo*-macrocyclisation held general for nearly all systems investigated.[8] Indeed even in systems where *exo*-attack was electronically favoured *exo*-macrocyclisation could only be achieved in one case, using the highly activated dicyano system of the precursor **6** (**Scheme 6**). Attempted cyclisation of other analogous substrates only resulted in the isolation of acyclic reduced products or products resulting from addition of tin to the olefinic site.



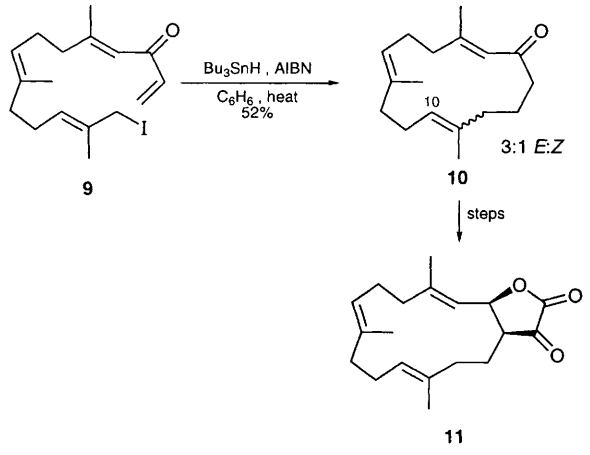
n	Ring size	Yield (%)
3	12	<5
7	16	35
11	20	50

Scheme 6

Following on from these fundamental studies by Porter *et al.* advances began to be made by other research groups in the application of free radical-based macrocyclisations towards natural product synthesis. Pattenden and co-workers were one of the first to exploit such a strategy in their synthesis of the natural marine cembranoids mukulol (**Scheme 7**) and the lactone **11** (**Scheme 8**) isolated from *Comiphora mukul* and *Sinularia mayi* respectively.[6a,10] In this approach 14-*endo-trig* cyclisation of the allyl radical generated from the all-*E*-iodotetraenone **7** (prepared from farnesal) gave a 40% yield of the cyclotetradecatrienone **8** as a 4:1 mixture of the separable 10*E* and 10*Z* isomers respectively. The observed double bond isomerisation can be explained by allylic transposition of the radical prior to the macrocyclisation. Subsequent reduction of the all-*E*-trienone isomer of **8** with lithium aluminium hydride then provided the diterpene mukulol. In an analogous approach the lactone **11** was also synthesised *via* a 14-*endo-trig* cyclisation of the all-*E*-tetraenone **9** to generate the macrocyclic trienone **10** in 52% overall yield and as a separable 3:1 mixture of the 10*E* and 10*Z* isomers (**Scheme 8**). The all-*E*-isomer of **10** had previously been used in a synthesis of the lactone **11** and as such Pattenden's



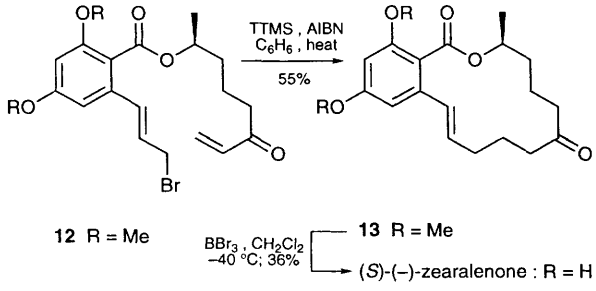
Scheme 7



Scheme 8

work represented a formal synthesis of this cembranoid.

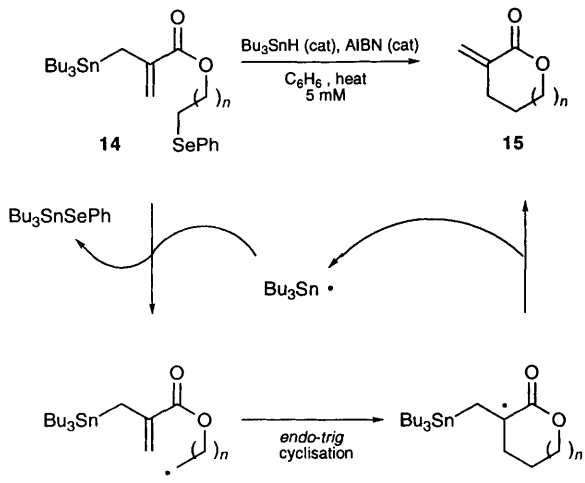
Pattenden and Hitchcock employed a similar strategy, involving the 14-*endo-trig* macrocyclisation of a cinnamyl radical, as the key step in one of the first asymmetric syntheses of the mycotoxin (−)-zearalenone isolated from the fungus *Gibberella zeae* (**Scheme 9**).[6b,11] In this system it was found preferable to generate the radical from the *E*-allyl bromide **12** using tris(trimethylsilyl)silane (TTMS) and catalytic AIBN under high dilution conditions in order to decrease the amount of acyclic product formed *via* direct reduction of the initially formed radical. Cyclisation under these modified conditions produced (*S*)-(−)-zearalenone dimethyl ether **13** in 55% yield, and subsequent reaction with boron tribromide afforded the natural product.



Scheme 9

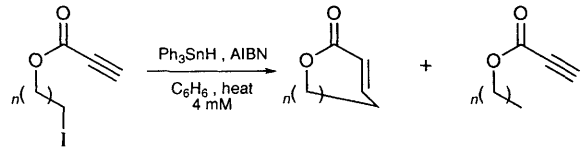
A different and ingenious approach to suppress the direct reduction often seen in radical macrocyclisations was reported contemporaneously by Baldwin and co-workers[12] in their synthetic approach to 10- to 15-membered α-methylene lactones **15** (**Scheme 10**). By incorporating an allylstannane moiety at the olefin acceptor of the acyclic precursor **14**, these authors were able to effect macrocyclisation *via* an intramolecular *endo-trig* S_H2' reaction using only a catalytic amount of tributyltin hydride and thus eliminating the competitive reduction pathway. The radical chain is propagated by *in situ* fragmentation of the radical formed from the cyclisation step to produce the chain carrier stannyl radical. Attempts to synthesise analogous six- to nine-membered lactones using this strategy met with failure however, giving only low yields of dimeric dilactones and/or AIBN derived adducts. This outcome was presumably due to the necessity of these substrates to adopt an unfavourable s-*E*-conformation to accommodate the transition state required for radical cyclisation.

Baldwin *et al.* were also the first to show that a propiolate moiety could be used as the electrophore in a 'Porter type' macrocyclisation.[13] Thus reaction of a series of ω-iodopropiolate esters **16** with triphenyltin hydride and catalytic AIBN under high dilution conditions generated 14- to 16-membered α,β-unsaturated lactones in good yields (**Scheme 11**). Attempts to prepare the analogous 10- to 13-membered lactones proved unsuccessful, with only



n	Ring size	Yield of **15** (%)
5	10	54
6	11	46
7	12	61
8	13	50
9	14	80
10	15	72

Scheme 10

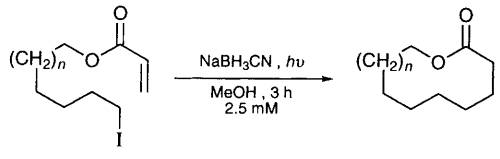


n	Ring size	Yield (%) Cyclic	Acyclic
5	10	—	87
6	11	—	84
7	12	—	78
8	13	traces	76
9	14	48	37
10	15	60	31
11	16	55	29

Scheme 11

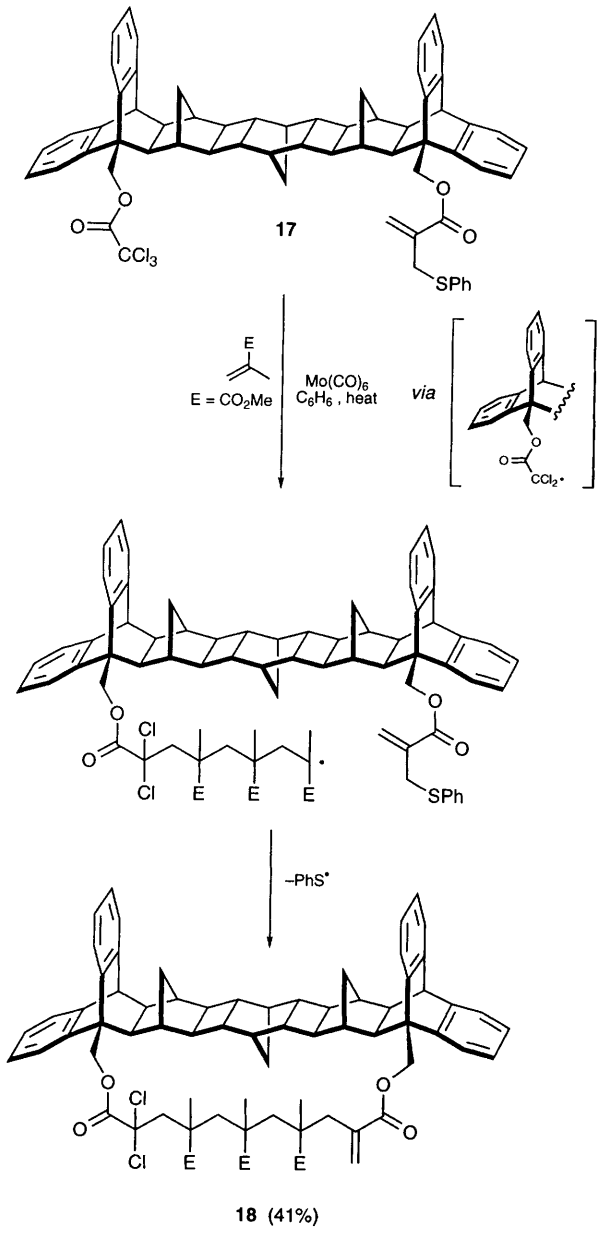
acyclic reduction products being isolated. As anticipated the reaction was regiospecific for *endo-dig* macrocyclisation, but more unexpected was the stereospecific nature of the process with only the *trans*-α,β-unsaturated lactones produced. This latter observation can be explained by inversion of the kinetically favoured *cis*-cyclised product to the thermodynamically favoured *trans*-isomer prior to hydrogen abstraction from the tin hydride, which is presumably slow under the high dilution conditions. In accordance with the guidelines set out in Porter's pioneering studies, the iodo substrates were found to give superior yields when compared to the corresponding bromides and, also in this study, to the selenides.

Kurata and co-workers[14] have reported the use of a modification of the conditions originally pioneered by Porter[7] for the macrocyclisation of ω-iodoacrylates. These new reaction conditions do not suffer from the problems of the competing reductive pathway (**Scheme 12**). Thus photostimulation of a methanolic solution of the precursors in the presence of metal hydride complexes such as $NaBH_3CN$, $NaBH_4$ and KBH_4 gave the macrocyclised products in excellent yields, together with smaller amounts of dimeric dilactone species. Other metal hydrides that were tested resulted only in reduction of the ester group. Compared to the standard tin hydride reaction conditions this modified procedure gave significantly higher yields for the macrocyclisation reaction and was also successful in producing medium sized lactones (10- to 12-membered) which had been isolated in only very low yield by Porter *et al.* Additionally, acyclic material resulting from reduction of the initially formed alkyl radical composed less than 5% of the products from the reaction. The authors postulated that the cyclisation reaction proceeds by a radical chain mechanism involving the cyanoborane radical anion (BH_3CN^-).



n	Ring size	Yield of **2** (%)
1	10	74
2	11	73
3	12	79
4	13	81
5	14	82
6	15	86
7	16	90

Scheme 12

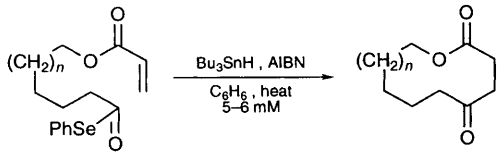


Scheme 13

Feldman *et al.*[15] were quick to exploit the effectiveness of radical macrocyclisation in a conceptually new strategy, which they termed 'template-controlled oligomerisation', towards the challenges posed by the construction of repeating segments within structurally complex molecules. Their approach used a radical macrocyclisation as the 'stop message' (*i.e.* termination event) to control the length of the oligomeric product formed by radical-mediated telomerisation carried out on a template of fixed size (**Scheme 13**). Thus, using the suitably functionalised template **17** containing a trichloroacetate 'starter' unit together with an allyl thioether moiety incorporated at the olefinic 'terminator' unit, these authors were able to control the $Mo(CO)_6$-initiated free radical polymerisation of methyl methacrylate (MMA). The reaction produced the cyclised material **18** containing only three MMA monomers in 41% yield together with 26% of products from uncontrolled polymerisation. Therefore, Feldman *et al.* had engineered an unprecedented and very impressive 26-*endo-trig* macrocyclisation. In addition, it was found that the formation of **18** proved to be somewhat stereoselective with only six of the possible eight stereoisomers being formed, in unequal amounts, suggesting that this novel strategy could possibly be applied to the formation of stereodefined oligomers. Porter and colleagues[16] attempted to produce such systems employing a similar strategy which they termed 'addition–cycliation–transfer' (ACT). Again a macrocyclisation step was used successfully to control the length of the oligomer produced by a polymerisation process carried out on fixed size templates.

Inclusion of chiral directing groups, either in the template itself or attached to the methacrylate unit, led to the stereoselective formation of oligomers having defined non-isostatic geometries.

Acyl radicals (which are most conveniently generated from phenyl selenylesters) show nucleophilic properties and reactivity similar to those of alkyl radicals and would thus be expected to participate in radical macrocyclisations onto electron deficient olefins. That this is indeed the case was first demonstrated by Boger and Mathvink[17] who showed that a series of ω-phenyl selenoester acrylates **19** gave rise to good yields of 11- to 20-membered macrolides *via endo-trig* cyclisation when treated with tributyltin hydride and AIBN under high dilution conditions (**Scheme 14**). No evidence of acyclic products arising from either the direct reduction of the acyl radical intermediate or of the alkyl radical produced by decarbonylation of the acyl radical was seen with these substrates. In an additional study the same authors were also able to show that, in accordance with the guidelines laid down by Porter *et al.*, unsaturation in the tether increased the efficacy of macrolide formation and that macrocyclisation could successfully compete with 6- or 7-*exo-trig* and 7-*endo-trig* cyclisation onto unactivated (*i.e.* electron rich) olefins. In one case Boger *et al.* encountered difficulties in attempting to form a macrocycle *via* an *exo-trig* cyclisation onto a β-substituted olefin and could only recover the product resulting from decarbonylation of the acyl radical.



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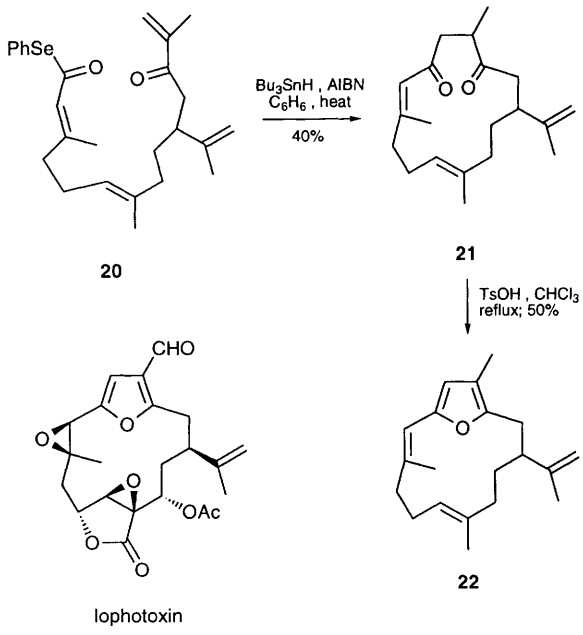
n	Ring size	Yield (%)
2	11	47
3	12	46
5	14	55
7	16	68
11	20	57

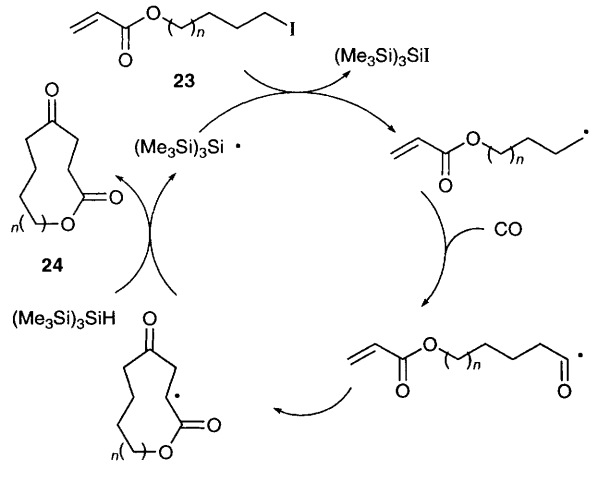
Scheme 14

Soon after publication of Boger's work with acyl radical-mediated macrocyclisations Astley and Pattenden[18] reported the first application of this strategy towards natural products in their synthesis of the furanocembranoid ring system found in lophotoxin, a potent neurotoxic substance isolated from gorgonium (soft) corals. Thus 14-*endo-trig* cyclisation of the phenyl selenoester precursor **20** under standard conditions was shown to generate the macrocycle **21** in 40% yield (**Scheme 15**). Subsequent treatment of **21** with toluene-*p*-sulfonic acid then produced the core furanocembranoid unit **22** which is common to lophotoxin and its relatives.



Scheme 15

Sonoda and co-workers[19] have also been able to effect acyl radical macrocyclisations using a slightly different approach wherein the acyl radical was generated by intermolecular carbonylation of an alkyl radical with carbon monoxide (**Scheme 16**). Subsequent intramolecular cyclisation then generated the macrocyclic systems. Thus treatment of a series of ω-iodo-acrylate esters **23** with



n	Ring size	Yield of **24** (%)
1	9	—
2	10	28
3	11	68
5	13	70
7	15	61
8	16	50
9	17	78

Scheme 16

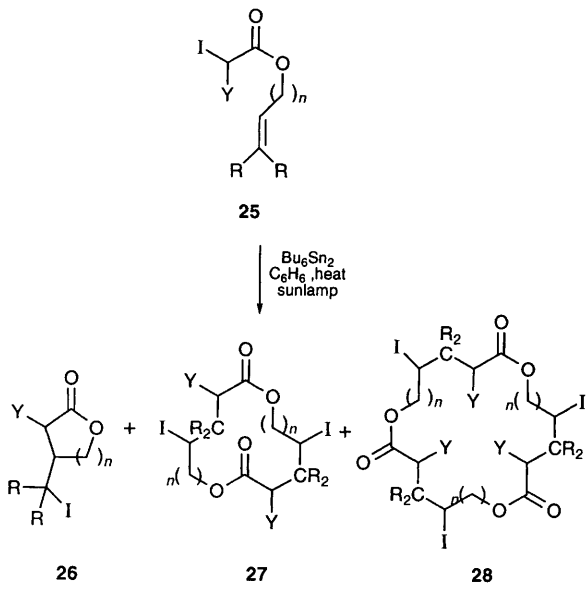
tris(trimethylsilyl)silane and AIBN in the presence of CO generated the 10- to 17-membered oxolactone products **24** in moderate to good yields. Optimum conditions for the reaction included the use of positive CO pressures (30 atm) as well as low concentration of the precursor (0.5–1 mM) both of which disfavour side-product formation due to competing bimolecular processes. In addition to the oxolactone product **24** minor amounts of the macrocyclic lactone, produced by competing cyclisation of the initially formed alkyl radical, were isolated from these reactions.

2.2 Cyclisations onto unactivated carbon–carbon bonds

Following the initial work of Porter *et al.*, wherein one of the guidelines proposed for radical macrocyclisation was the use of an electron deficient carbon–carbon double (or triple) bond as the radical acceptor, most research groups have employed such an activated electrophore. However a number of studies in this rapidly growing field have shown that the original criterion of Porter for activation is not a prerequisite for all radical macrocyclisations.

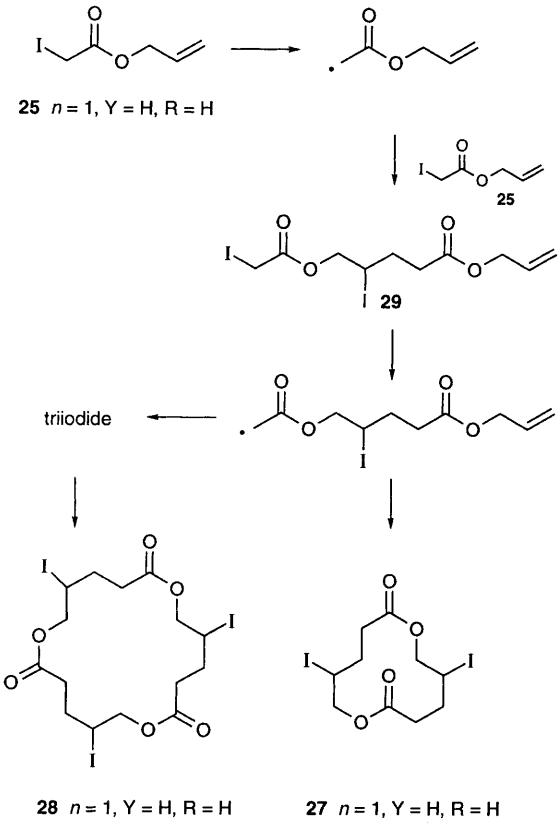
Electrophilic radicals, although encounterd less commonly than their nucleophilic counterparts, can occur if the radical centre is adjacent to an electron withdrawing substituent such as a carbonyl moiety. It can be envisaged that these electron deficient radicals have the potential to undergo macrocyclisation onto unactivated (*i.e.* electron rich) olefins. The first indications of this possiblity came from observations made by Barth and Yang during their studies on the radical cyclisations of α-fluoro-α-iodo and α-iodo esters.[20] In the course of their work towards the synthesis of the unsubstituted and α-fluoro lactones **26** *via* 5- and 6-*exo-trig* cyclisation of the corresponding precursors **25** these authors observed the unexpected formation of the macrocyclic di- and tri-lactones **27** and **28** respectively (**Scheme 17**). Their observations were explained by a mechanism involving intermolecular addition of the initially formed radical to give the acyclic dilactone **29** followed by generation of a new electrophilic radical and subsequent *endo-trig* macrocyclisation onto the electron rich double bond giving **27** (**Scheme 18**). Formation of the trilactone product **28** follows a similar pathway.

Curran and Seong were first to carry out the controlled macrocyclisation of an electrophilic radical which they generated from an iodomalonate system.[21] After an unsuccessful initial study into macrocyclisation using iodomalonic esters these authors were able to achieve efficient 18-*endo-trig* cyclisation onto an unactivated olefin using the iodomalononitrile **30**, with the reaction being carried out under the atom transfer conditions pioneered by the same research group (**Scheme 19**). In order to purify the cyclised product **31** from oligomeric material the mixture was treated with two equivalents of tin hydride which surprisingly

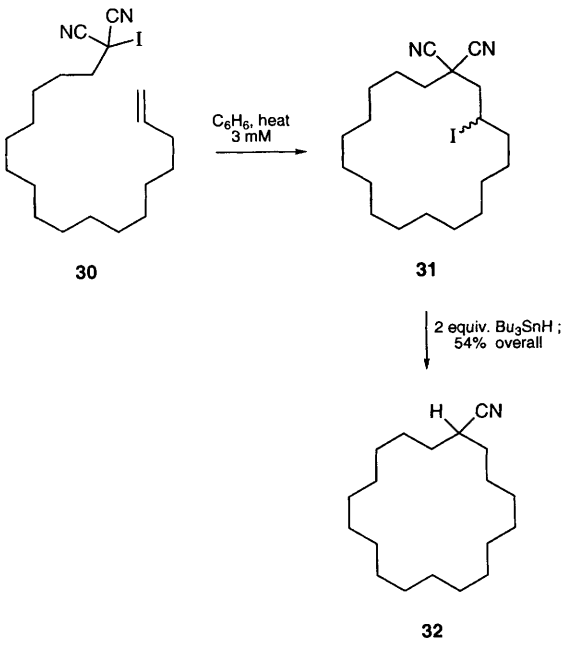


			Yield (%)		
n	Y	R	**26**	**27**	**28**
1	F	H	—	56	—
1	H	H	19	38	17
1	F	Me	68	—	—
1	H	Me	62	—	—
2	H	H	7	66	26

Scheme 17



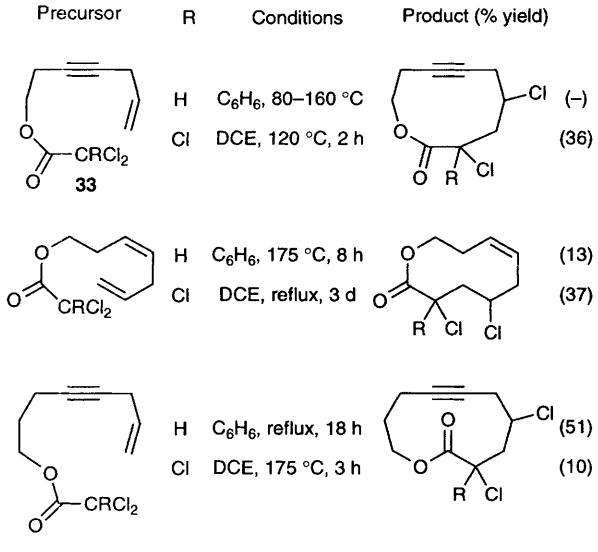
Scheme 18



Scheme 19

resulted in the isolation of the macrocyclic *mono*nitrile **32** in 54% overall yield from **30**. This final reaction represented an unprecedented reductive removal of the nitrile group using tin hydride.

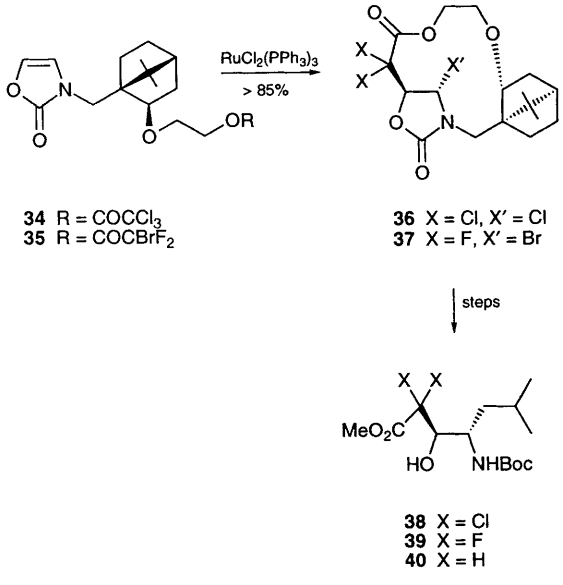
Analogous macrocyclisations of electrophilic radicals have been reported by Speckamp and co-workers to effect the formation of lactones.[22] Thus, treatment of a series of ω-unsaturated di- and tri-chloroacetates, *e.g.* **33** with a Cu(bipy)Cl catalyst generated *in situ* from CuCl and 2,2′-bipyridine (bipy) in either benzene or dichloroethane (DCE) generated the corresponding 10- and 11-membered chlorolactones in moderate yields (**Scheme 20**).



Scheme 20

Again *endo*-cyclisation was favoured and additionally it was found to be essential for the tether connecting the ester and olefin moieties to contain unsaturation in order to produce these entropically disfavoured products (fully saturated analogues gave rise only to telomers). The authors proposed that cyclisation occurs *via* radicals coordinated to the copper centre of the catalyst whereby carbon–carbon bond formation takes place within the coordination sphere of the metal complex. This templating action effectively shields the molecule from the rest of the species in the mixture thereby allowing the macrocyclisation to be carried out at relatively high concentrations of up to 100 mM.

Kunieda and co-workers[23] have used a similar metal-catalysed radical cyclisation in their synthesis of the *N*-Boc methyl ester derivative **40** of the unusual amino acid statine, as well as the 2,2-dichloro and -difluoro analogues **38** and **39**, respectively (**Scheme 21**). Using a Ru^{II}-catalysed procedure these authors were able to achieve an extremely high regio- and diastereo-selective 12-*endo-trig* cyclisation of the chiral trichloro- and bromodifluoro-acetates **34** and **35**. The enantiopure oxazolidin-2-ones **36** and **37** thus obtained were transformed into the (3*S*,4*S*)-statine derivatives **38**–**40**. The high stereoselectivity observed in these macrocyclisations can be rationalised by assuming a favoured conformation of the precursors **36** and **37** where the two amide carbonyl groups adopt an *anti*-coplanar conformation.



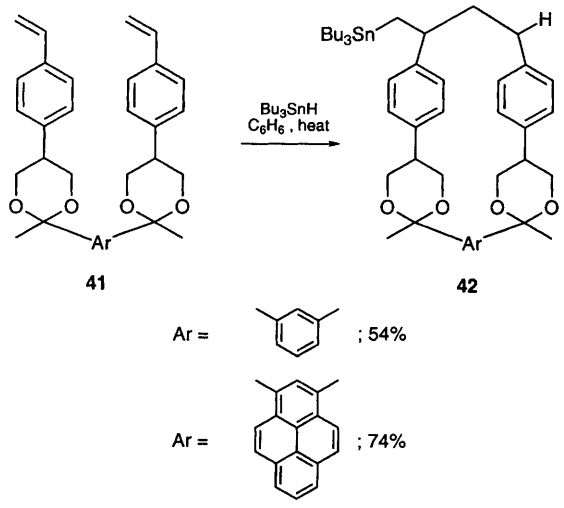
34 R = $COCCl_3$
35 R = $COCBrF_2$

36 X = Cl, X′ = Cl
37 X = F, X′ = Br

38 X = Cl
39 X = F
40 X = H

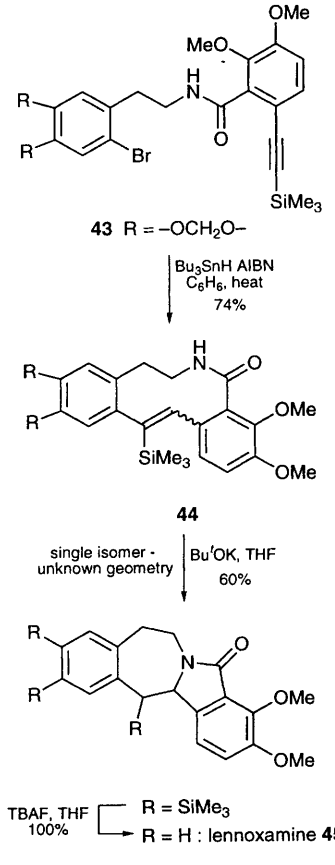
Scheme 21

One last example of macrocyclisation onto an unactivated carbon–carbon double bond has been reported by Shea *et al.*[24] These authors were able to produce the 22-membered macrocycles **42** upon treatment of the styrene bis-ketals **41** with tributyltin hydride in refluxing benzene (**Scheme 22**).

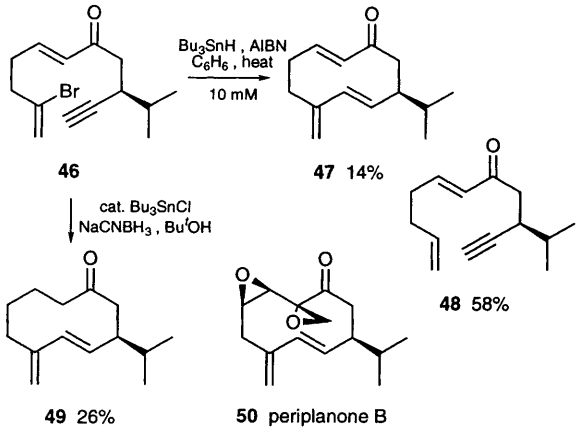


Scheme 22

Two examples of 10-*endo-dig* macrocyclisations onto unactivated carbon–carbon triple bonds have been reported. Thus, Castedo and co-workers[25] used such a reaction in their synthesis of the isoindolobenzazepine alkaloid lennoxamine **45** (**Scheme 23**) whereby cyclisation of the aryl radical generated from the bromide **43** onto the silylated alkyne electrophore generated the macrolactam core (*i.e.* **44**) of **45** in 74% yield. Subsequent base-induced transannular cyclisation *via* nucleophilic attack of the nitrogen atom, followed by desilylation, then produced the natural product. Parsons and his colleagues have reported the first example of a macrocyclisation utilising an alkenyl radical during their initial studies towards a synthesis of the sesquiterpene periplanone B **50** (**Scheme 24**).[26]



Scheme 23



Scheme 24

Treatment of the vinyl bromide **46** with tributyltin hydride produced the cyclodecadiene **47** in a moderate 14% yield together with a large amount of the reduced acyclic product **48**. The use of 'non-reducing' tin hydride conditions (catalytic tributyltin chloride and $NaCNBH_3$) gave an improved yield of cyclised material **49** in which, however, the α,β-unsaturated unit in the precursor had been reduced.

A number of other radical-mediated macrocyclisations have been reported. These have been harnessed in tandem with transannular radical reactions leading to the generation of a range of polycyclic systems including those found in the important natural products brefeldin and Taxol. These reactions are dealt with in Section 4.

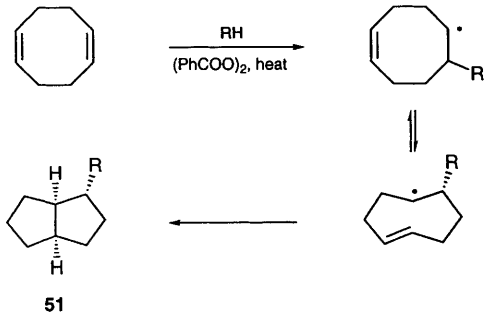
3 Free radical-mediated transannular cyclisations

Transannulation reactions lead to the formation of a covalent bond between atoms on opposite sides of a ring compound. They occur frequently in medium (8- to 12-membered) rings and can involve carbonium ion,[27] carbanion[28] and carbene[29] intermediates as well as radical intermediates. A range of pericyclic transannulation processes has also been developed recently.[30] The first examples of free radical-mediated transannulation reactions were reported in 1964 during studies of the additions of radicals to cycloocta-1,5-diene.[31,32] These reactions have now become part of the day-to-day armoury of the synthetic chemist and they are used frequently as a key stratagem in polycyclic natural product synthesis. This section of the Review will highlight the developments that have occurred since 1964 by

discussing the subject according to the size of the cycloalkene from which the transannular cyclisation is effected.

3.1 Cyclooctenes

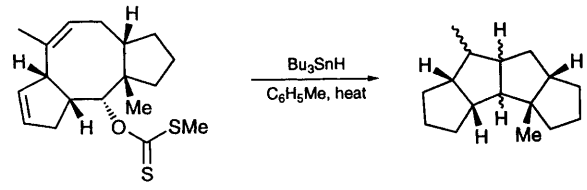
Cycloocta-1,5-diene was the first medium ring synthetic 1,5-diene to become available in sufficient quantity to examine its radical-mediated transannulation chemistry in a systematic manner. Thus, Dowbenko[31] and Friedman,[32] in independent investigations, showed that when solutions of cycloocta-1,5-diene in chloroform, aliphatic aldehydes, or *N*-alkylformamides were heated under reflux in the presence of benzoyl peroxide, transannular 1,5-cyclisations occurred leading to *exo*-substituted bicyclo[3.3.0]octane derivatives **51** in good yields, *i.e.* 40–70% (**Scheme 25**). Although no definitive mechanistic studies have been described for these transannulation reactions, it seems likely that they proceed by a series of radical addition–elimination sequences to the *Z*-double bonds in the cyclooctadiene which lead ultimately to a cyclooctene radical intermediate having the most favourable geometrical orientation for facile transannulation. In **Scheme 25**, this radical intermediate is shown with an *E*-double bond favouring formation of the *exo*-substituted (*cis*) bicyclo[3.3.0]octane products, although there is no reason to believe that a concerted process is not involved or indeed that the transannulation reaction does not involve a radical intermediate accommodating the corresponding *Z*-double bond. Later studies, with the cyclooctenyl xanthate **52**[33] and with suitably substituted cyclooacta-1,5-dienes, *viz.* **54**,[34] demonstrated that such transannulation reactions across cyclooctenes could have scope in the synthesis of linear-fused triquinanes, *e.g.* **53** and **55** respectively, although the yields and stereoselectivities in these reactions were not altogether encouraging.



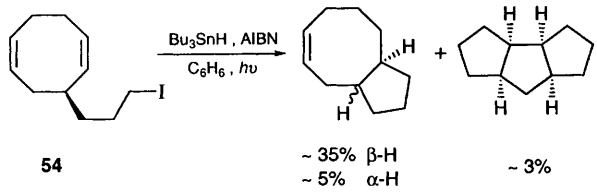
51

Scheme 25

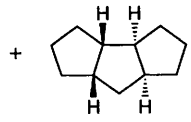
Transannulation reactions involving cyclooctenes where the acceptor double bond is exocyclic have been exploited in two interesting synthetic approaches to 3,3,3-propellane and to angular triquinane-containing natural sesquiterpenes. Thus Curran and Shen[35] have described a synthesis of (±)-modhephene **60a** and its epimer involving the



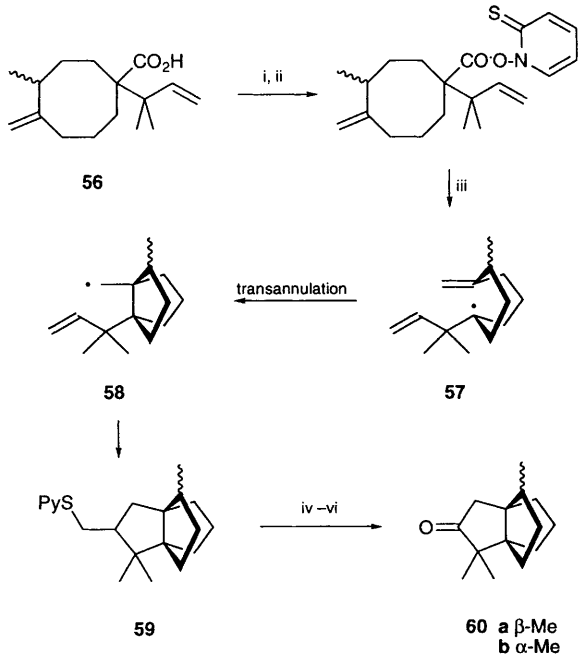
52 **53**



54 ~ 35% β-H ~ 5% α-H ~ 3%



55 ~ 5%



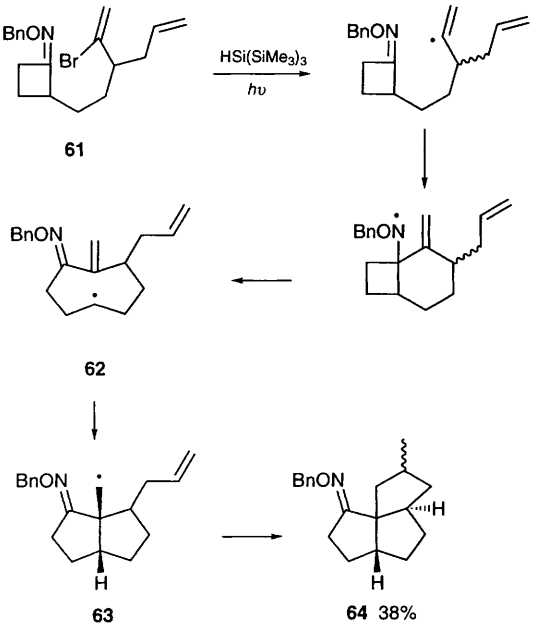
56 **58** **57** **59** **60** a β-Me b α-Me

Scheme 26 *Reagents*: i, $(COCl)_2$; ii,  ; iii, heat, 110 °C, C_6H_6; iv, $NaIO_4$; v, heat, 130 °C; vi, $RuCl_3$, $NaIO_4$.

tandem transannulation–radical cyclisation sequence **57**→**58**→**59** triggered by the Barton thiohydroxamate method from the methylenecyclooctanecarboxylic acid starting material **56** (**Scheme 26**).

Furthermore, in our own studies of cascade radical fragmentation–transannulation reactions in polycycle constructions, it has been shown that when the vinyl bromide-substituted cyclobutanone oxime

61 is irradiated with a sunlamp in the presence of $(Me_3Si)_3SiH$, the angular triquinane **64** is produced in 38% yield. The remarkable conversion features the 5-*exo-trig* transannulation **62**→**63**, as a key step (**Scheme 27**).[36]



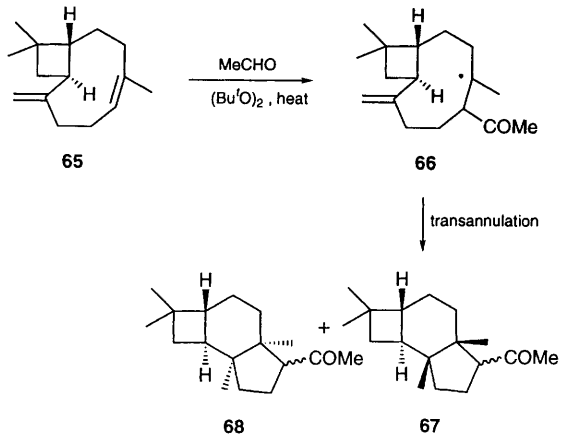
Scheme 27

3.2 Cyclononenes

Surprisingly few studies of radical-mediated transannular cyclisations involving cyclononene precursors have been described, although several studies of tandem macrocyclisation–transannulation reactions involving cyclononene radical intermedidates have been investigated (see Section 4). Some of the most remarkable (electrophilic) transannulation cyclisations have been uncovered during the treatment of natural caryophyllene **65** with mineral acids, and it is perhaps not surprising therefore that radical-induced rearrangements with the substrate have also been examined. Thus, it has been shown that when caryophyllene is heated with acetaldehyde (six equivalents) in the presence of di-*tert*-butyl peroxide (10 equivalents) at 125–130 °C for 3 h in a sealed tube it is converted into a mixture of the 4,6,5-tricycles **67** and **68** in a combined yield of 54%.[37] These tricycles all result from addition of an acetyl radical to the trisubstituted double bond in caryophyllene, leading to the intermediate **66**, followed by transannular cyclisation, as depicted in **Scheme 28**.

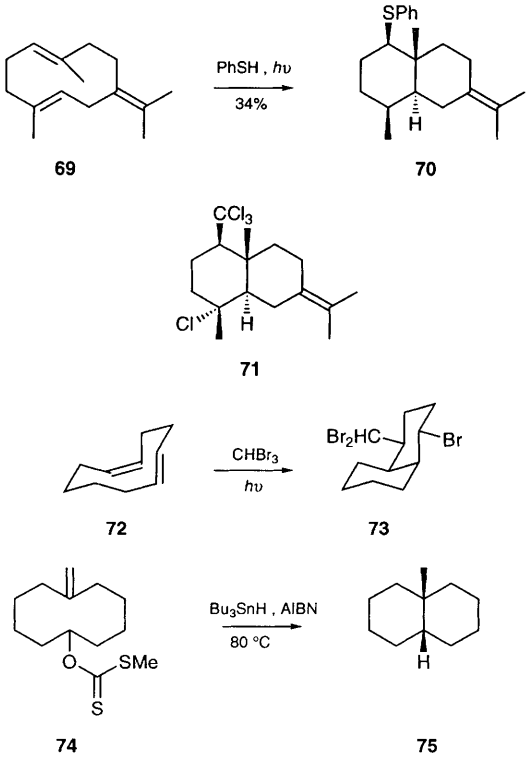
3.3 Cyclodecenes

Transannular cyclisation reactions involving carbonium ions generated within cyclodecenes have been studied extensively, as a consequence of their



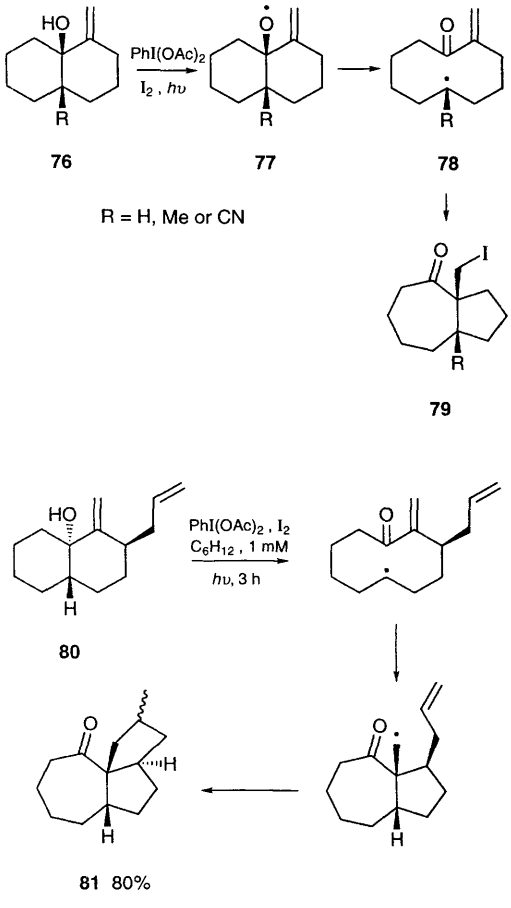
Scheme 28

relevance to our understanding of the biosynthesis of polycyclic sesquiterpenes.[27] In early parallel studies of the additions of radicals to the naturally occurring cyclodecadiene germacrene **69**, Sutherland *et al.*[38] were able to demonstrate that the direction and stereoselectivity of these radical cyclisation reactions were closely similar to those effected by electrophiles. Thus, irradiation of germacrene with benzenethiol in cyclohexane produced the bicyclo[4.4.0]decane **70** (34%) of defined stereochemistry, and irradiation of **69** in carbon tetrachloride led to **71** in 32% yield; the formation of the transannular carbon–carbon bonds and the C–SPh and C–CCl_3 bonds in **70** and **71** were considered to be in concert with each other. In



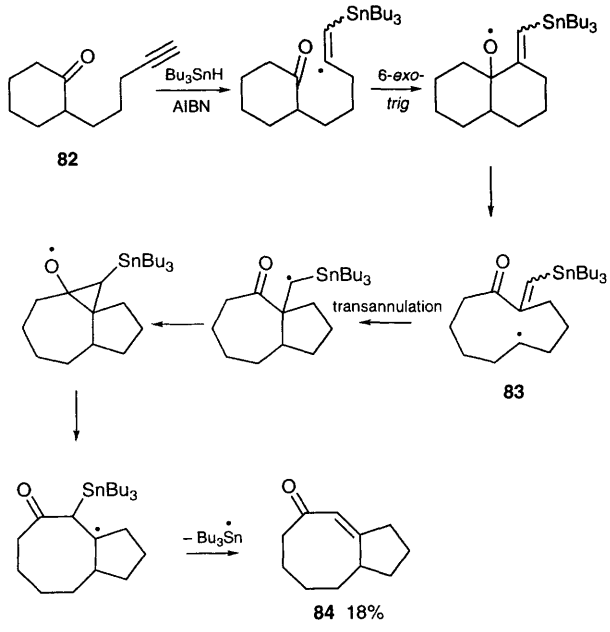
other early studies of radical transannulation reactions within cyclodecenes, Traynham and Hsieh[39] found that the photoinitiated addition of bromoform to *cis,trans*-cyclodeca-1,5-diene **72** led exclusively to the substituted *cis*-decalin **73** in 45% yield. Interestingly, transannulation from the methylenecyclodecane radical produced from **74** has also been found to lead to predominantly the *cis*-decalin **75**.[40]

Hydroazulenones (bicyclo[5.3.0]decanones) **79** are produced in a neat way when the unsaturated decanols **76** are treated with (diacetoxyiodo)-benzene and iodine, by a sequence that involves β-fission of the oxyl radical intermediate **77** followed by radical-mediated transannulation from **78** and quenching of the product radical with iodine.[41] Extension of this strategy to the further substituted decanol **80** provides a powerful method of elaborating the tricycle **81** in a single step in 80% overall yield (**Scheme 29**).[42] In a not too dissimilar sequence



Scheme 29

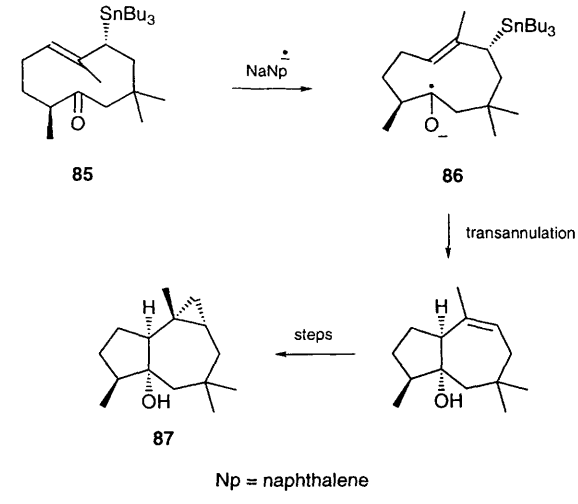
of reactions to those leading to **81** from **80**, Nishida *et al.*[43] have found that when the acetylene ketone **82** is treated with Bu_3SnH–AIBN it is converted into the bicyclo[6.3.0]undecenone **84** in one step in 18% yield. This novel conversion is thought to occur *via* a transannulation pathway involving the cyclo-



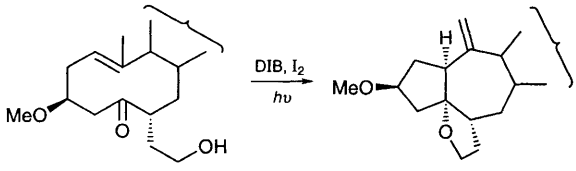
Scheme 30

decanone radical **83** as key intermediate (**Scheme 30**).

In an interesting synthesis of the sesquiterpene africanol **87**, J. B. White *et al.*[44] have shown that the required *cis*-geometry in this bicyclo[5.3.0]decane-based natural product can be incorporated by transannular cyclisation of the allylstannane-functionalized cyclodecenone **85** using sodium naphthalene radical anion in tetrahydrofuran and involving the ketyl radical **86** as central intermediate (**Scheme 31**). An analogous ketyl radical intermediate has been implicated in the transannular cyclisation of the steroidal cyclodecenone **88** to the substituted bicyclo[5.3.0]decane **89** by photolysis using (diacetoxyiodo)benzene and iodine.[45]



Scheme 31

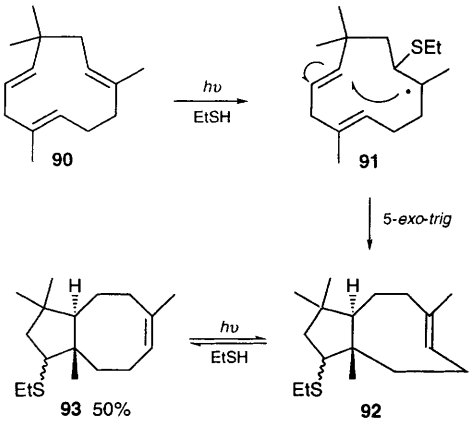


88 89

DIB = (diacetoxyiodo)benzene

3.4 Cycloundecenes and cyclododecenes

The 11-membered ring hydrocarbon humulene **90** plays a central role as a key intermediate in the biosynthesis of several families of sesquiterpenes, *e.g.* the triquinanoid capnellanes, pentalenanes, hirsutanes; also the caryophyllenes, sterpuranes, illudanes and africananes. Furthermore, many of these biosynthetic transannular electrophilic processes have now been mimicked in the laboratory using either humulene itself or one of its three mono-epoxides.[27] By contrast, until very recently, radical-mediated transannular reactions involving humulene had not been reported. It has now been shown that when humulene **90** is treated with ethanethiyl radicals it undergoes facile radical transannulation producing the novel 5,8-ring fused bicycle **93** in 50% yield.[46] The sulfide **93** presumably results from selective addition of an ethanethiyl radical to the C8–C9 double bond in humulene, leading initally to the 11-ring radical intermediate **91**. This addition is followed by a 5-*exo-trig* transannulation giving rise to the linear and *trans*-ring fused 5,8-bicycle **92**. An addition–elimination of EtS$^{\bullet}$ to the trisubstituted double bond in the eight-membered ring of **92** then results in its ($E \rightleftharpoons Z$) equilibration, leading to the product observed (**Scheme 32**). The $E \rightleftharpoons Z$ equilbration in **92** could also occur prior to the transannulation reaction **91**→**92** or in concert with it. The substituted 5,8-ring system **93**, which can be readily converted into the



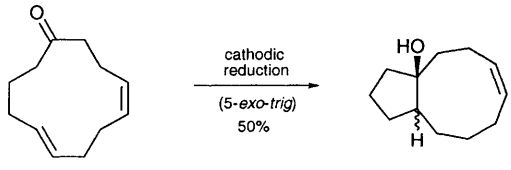
90 91 93 50% 92

Scheme 32

94 95

hydrocarbon **94**, is similar structurally to that found in the natural sesquiterpene junipediol **95**.

The importance of ketyl radical intermediates in transannulation reactions has already been mentioned in Section 3.3. Such intermediates can also be generated by cathodic reduction of ketones, and when this technique is applied to 4*Z*,8*E*-cyclododeca-4,8-dien-1-one **96**, transannular cyclisation ensues leading to the formation of a 3:2 mixture of *cis*- and *trans*-isomers of the bicyclo[7.3.0]dodecenol **97** in a combined yield of 50%.[47]



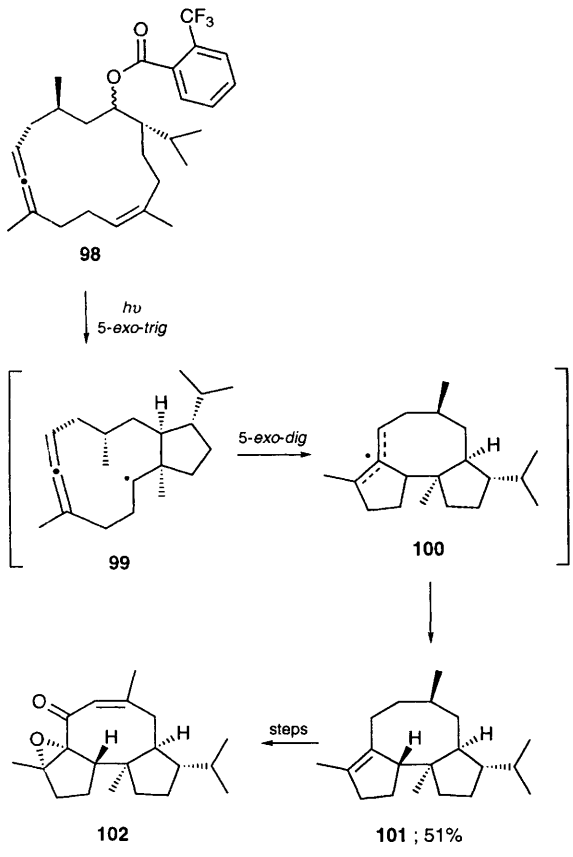
96 97

3.5 Cyclotetradecenes

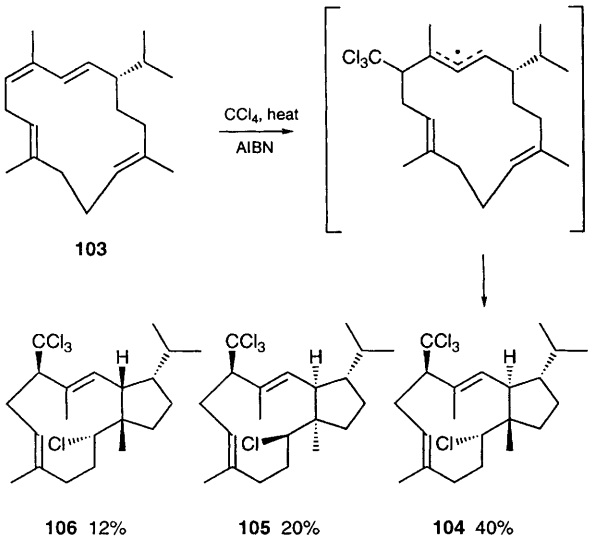
In a superb illustration of the scope for, not one but, two radical-mediated transannulation reactions in synthesis, Myers and Condroski[48] have shown that when the allene-based macrocyclic alcohol ester **98** is irradiated it undergoes sequential 5-*exo-trig* and 5-*exo-dig* transannular cyclisations leading to the 5,8,5-based tricycle **101** in an impressive 51% overall yield. The allene unit in **98** was incorporated in order to make the second transannulation, *i.e.* **99**→**100**, favourable. This second transannulation produced a mixture of alkene positional isomers of the tricyclic product **100** which could be readily equilibrated upon heating in thiophenol–heptane at 50 °C for 0.5 h to produce the single isomer **101**. Manipulation of **101** then led to a synthesis of the natural diterpene 7,8-epoxy-4-basmen-6-ene **102** (**Scheme 33**). Few additional studies of radical-mediated transannular reactions amongst cyclotetradecenes have been carried out, but the aforementioned investigation was firmly based on model studies with natural cembrene **103** which was shown to undergo a selective 5-*exo-trig*–11-*endo-trig* transannulation on heating with carbon tetrachloride in the presence of AIBN, leading to a mixture of the bicyclic products **104**, **105** and **106**.

3.6 Cycloheptadecatrienes

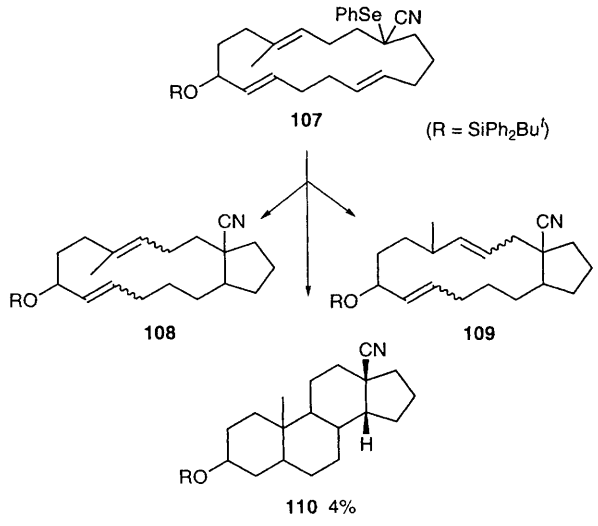
In studies designed to test the scope for multiple transannulation reactions leading to steroid ring constructions, both Curran *et al.*[49] and our own research group have independently examined the



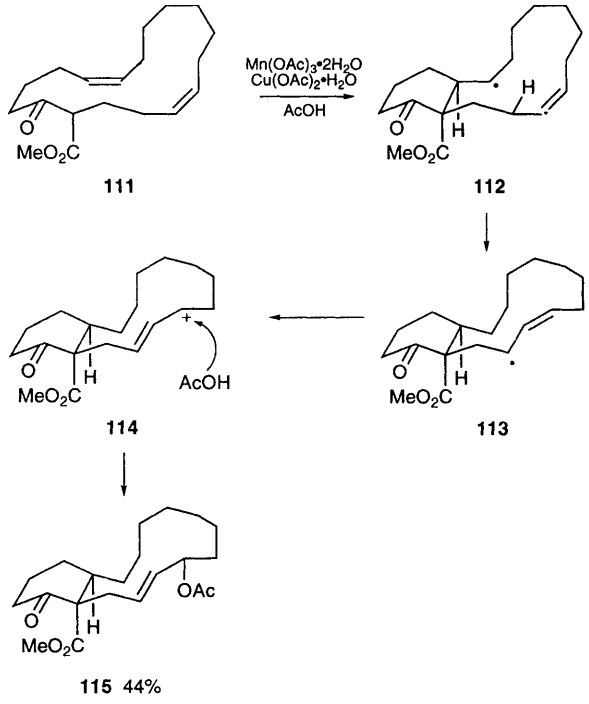
Scheme 33



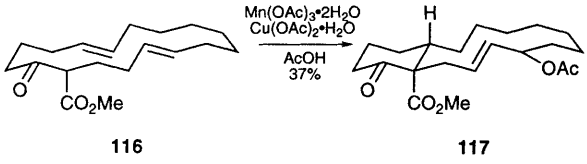
triple transannular radical cyclisation of several substituted cycloheptadecatriene systems (see also Section 4). Thus, Curran and Jahn have demonstrated that when the phenylselanyl polyene macrocycle **107** is treated with Bu_3SnH at low concentration, work up followed by repeated separation using HPLC allows the isolation of a meagre amount (*ca.* 4%) of a single tetracyclic product of unassigned configuration and given structure **110**. The main products of the reaction were the monocyclised compounds **108** and **109** resulting from extensive double bonds migration and isomerisation involving 1,5-hydrogen transfer processes.



In investigations of *oxidative* transannulation reactions, using manganese(III) acetate, Jones and Pattenden[50] have encountered similar problems with competing 1,5-hydrogen transfer processes. Thus, when the *Z,Z*-macrocyclic diene β-keto ester **111** was treated with $Mn(OAc)_3$–$Cu(OAc)_2$ it underwent transannulation to **112**, followed by 1,5-hydrogen abstraction (to **113**), allylic transposition and oxidation (to **114**) and final trapping with acetic acid leading to the bicyclic product **115** in 44% yield

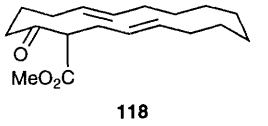


(**Scheme 34**). Likewise the corresponding *E,E*-macrocyclic diene **116** led to the geometrical isomer **117** of **115** (37%) on similar treatment with $Mn(OAc)_3$–$Cu(OAc)_2$. In only one case studied so far has it been possible to effect oxidative radical-mediated transannular cyclisation in this series, *i.e.* the conversion of **118** into **119** in a disappointing 8% yield.

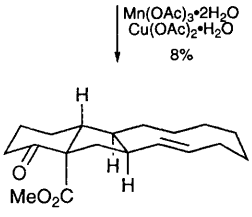


116 **117**

Scheme 34



118



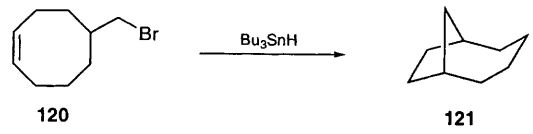
119

Thus the aforementioned studies have demonstrated that multiple radical transannulations within 17-membered rings are severely hampered by competing transannular 1,5-hydrogen transfer processes. Until these limitations can be overcome, therefore, a practical synthesis of steroid constructs based on the proposition of multiple transannulations would seem a long way off.

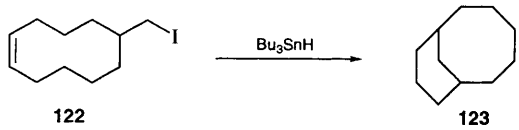
3.7 Other radical-mediated transannular cyclisations

A variety of other radical-mediated transannular cyclisation reactions has been examined including approaches to bicyclo[3.2.1]octanes, bicyclo[4.2.1]nonanes,[51] and to bicyclo[5.3.1]decanes[52] from appropriate halomethylcycloalkenes, *e.g.* **120**→**121** and **122**→**123**. Photolysis of bulnesene **124** with dimethyl disulfide followed by desulfurisation of the product (presumably **125**) also leads to the tricycle **126** *via* a radical transannulation pathway.[53]

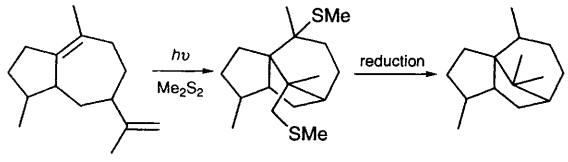
Fraser-Reid *et al.*[54] have described a neat radical-mediated transannular cyclisation, *viz.* **127**→**128**, as part of their approach towards the tricyclic dihydrofuran portion of the natural insecticide azadirachtin.



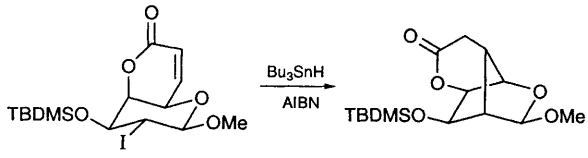
120 **121**



122 **123**



124 **125** **126**

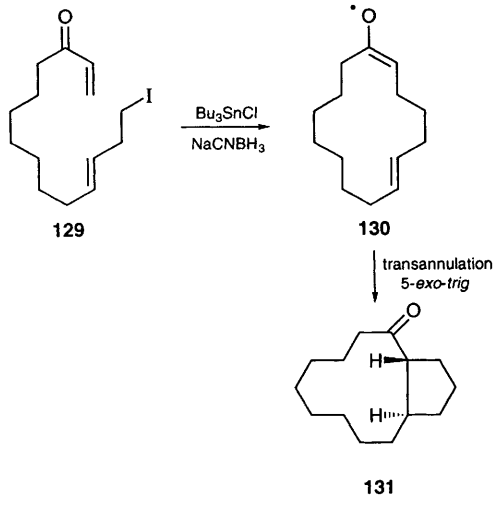


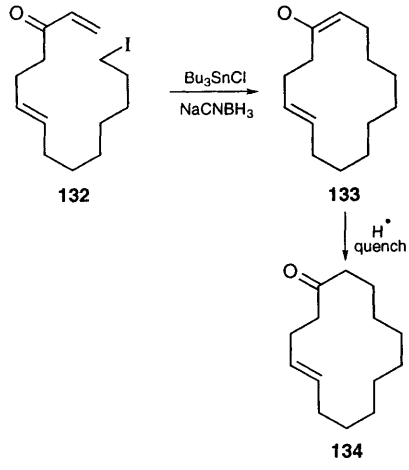
127 **128**

4 Cascade radical-mediated macrocyclisation–transannulation reactions

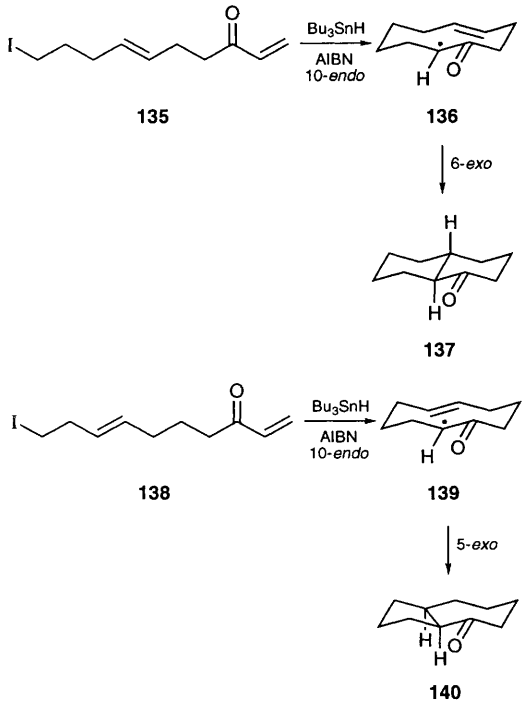
The elaboration of ring-fused carbocycles based on cascade radical macrocyclisation–transannular processes from simple acylic precursurs (**Scheme 1**) would appear to offer a unique opportunity for the rapid, stereocontrolled synthesis of a wide range of functionalised polycyclic arrays. Porter *et al.*[8] were the first to demonstrate this opportunity when they showed that the iododienone **129** underwent macrocyclisation–transannulation in the presence of Bu_3SnCl–$NaCNBH_3$ producing a *cis/trans* mixture of the 5,11-bicyclic ketone **131** in 30% yield. In the same study it was shown that the isomeric dienone **132** only underwent macrocyclisation to the 14-ring γ-unsaturated ketone **134**, which can be understood if one assumes that the γ-ketone radical intermediate resulting from the macrocyclisation is delocalised into the carbonyl, *viz.* **133**, preventing it from assuming a favoured transition state for 5-*exo*-transannulation. In the case of transannulation from the radical **130** the correct transition state can be attained since the partial bond of the •C–C=O unit is incorporated in the more flexible 11-membered ring (**Scheme 35**).

Following the aforementioned observation our own research group synthesised a wide variety of *E*-iododienones with a view to examining their cascade radical-mediated macrocyclisation–transannulations leading to a variety of smaller 6,6-, 7,5- and 5,5-bicyclic compounds.[55,56] Thus treatment of the iododienone **135** with Bu_3SnH–AIBN led to the decalone product **137**, resulting from tandem

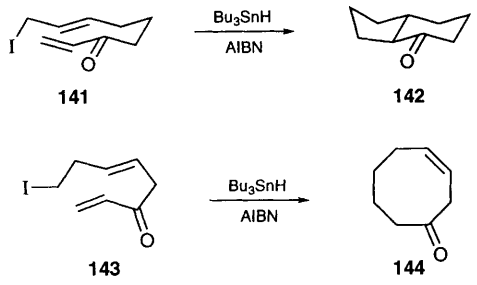




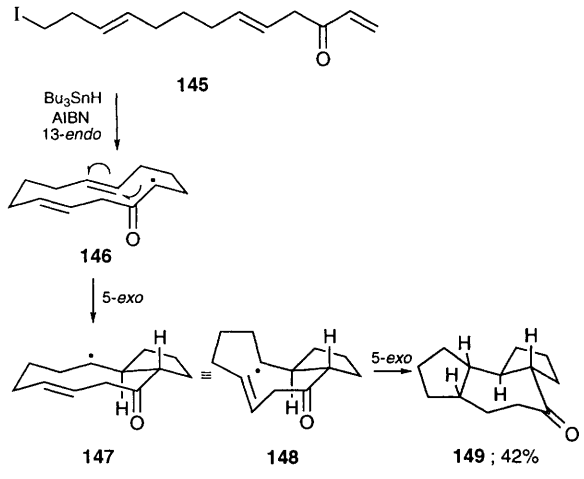
Scheme 35



10-*endo-trig* macrocyclisation–6-*exo-trig* transannulation, in 72% yield. In a similar manner the iododienones **138** and **141** led to the bicycles **140** and **142**, respectively, in 50–68% yield, whereas the iododienone **143** produced only *Z*-cyclooct-3-enone **144** on treatment with Bu_3SnH–AIBN.

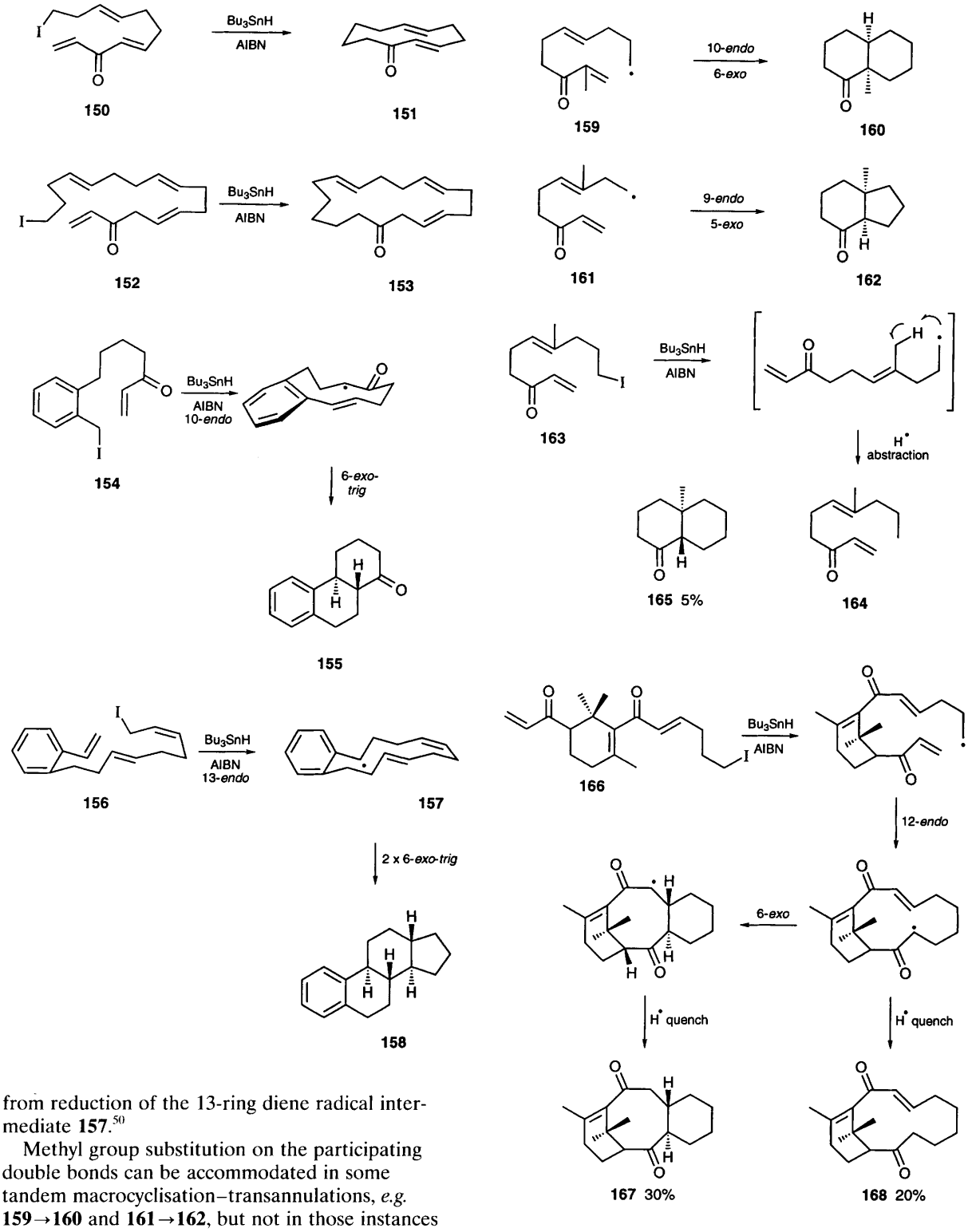


In a highly satisfying and novel sequential 13-*endo* macrocyclisation followed by two successive 5-*exo-trig* transannulation processes, *viz.* **145**→**146**→**147**/**148**→**149**, the iodotrienone **145** was converted into the angular 5,7,5-ring fused tricyclic ketone **149** in 42% yield on reaction with Bu_3SnH–AIBN (**Scheme 36**).[55,56] A range of other iodopolyenones was investigated but these either led to products of reduction or of macrocyclisation, *e.g.* **150**→**151**; **152**→**153**, instead of polycycle construction. The differing reaction pathways followed by the various iodopolyenones used in our studies were rationalised in terms of conformational preferences of the macrocyclic α-keto radical intermediates, *e.g.* **136** and **139**, involved in the various cyclisations, supported by some preliminary MM2 studies and calculations.

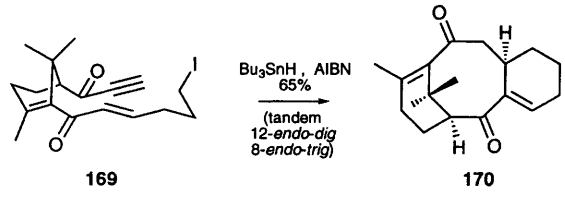


Scheme 36

In other studies directed towards steroid constructions, the substituted benzyl iodide **154** has been shown to undergo tandem 10-*endo*–6-*exo* bicyclisation to the *trans*-fused tricycle **155**, but attempts to cyclise the iodotriene **156** to the tetracycle **158** instead produced largely the product



Scheme 37

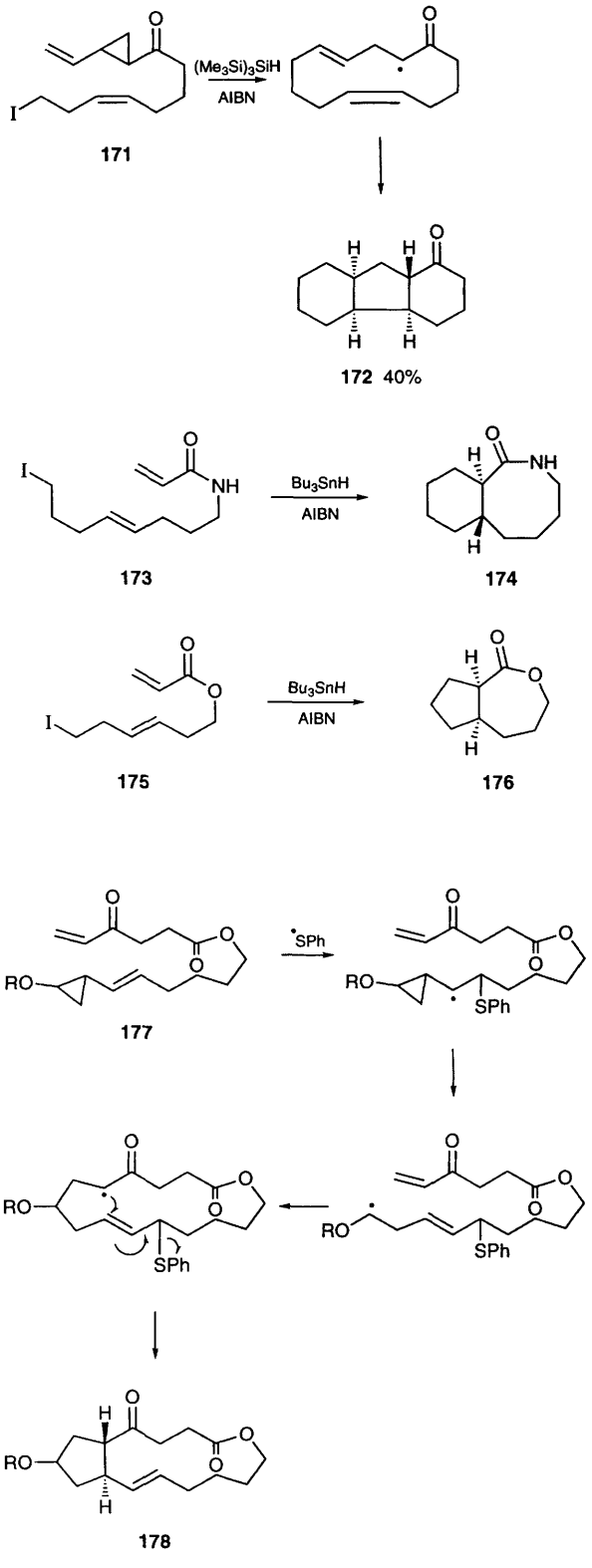


from reduction of the 13-ring diene radical intermediate **157**.[50]

Methyl group substitution on the participating double bonds can be accommodated in some tandem macrocyclisation–transannulations, *e.g.* **159**→**160** and **161**→**162**, but not in those instances where competing H-abstraction processes are able to dominate, *i.e.* **163**→**164**, with only 5% of formation of **165**.[57]

Pattenden and Hitchcock[58] have designed a synthesis of the taxane ring system **167**, based on a cascade 12-*endo*–6-*exo*-bicyclisation from the iododienedione **166**, containing an intact A-ring. This bicyclisation was shown to proceed reasonably smoothly in the presence of Bu_3SnH–AIBN producing the tricycle **167** in *ca.* 30% yield, accom-

panied by the intermediate bicycle (**168**, 20%) and the product of direct reduction (**Scheme 37**). The ynone **169** corresponding to **166** was found to cyclise even more smoothly leading to the tricyclic system **170** in *ca.* 65% yield.[59]



Scheme 38

The cyclopropane ring can also become involved in cascade macrocyclisation–multiple transannulation reactions, as evidenced by the novel one-pot conversion of **171** into **172** (40%)[60] in the presence of $(Me_3Si)_3SiH$–AIBN, and ring-fused lactams and lactones can also be produced by way of similar diastereoselective, cascade pathways, *viz.* **173**→**174** and **175**→**176**.[61]

Finally, a highly facile synthesis of the brefeldin ring system **178** has been developed by Feldman *et al.*[62] involving the macrocyclisation–transannulation sequence from the vinylcyclopropane **177** in the presence of a catalytic amount of phenylthiyl radical (**Scheme 38**).

5 Acknowledgements

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