# Polyene natural products

**Carl Thirsk and Andrew Whiting**

*Department of Chemistry, Science Laboratories, Stockton Road, Durham, UK DH1 3LE.*
*E-mail: a.whiting@durham.ac.uk*

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## 1.0 Introduction

Natural products containing conjugated alkenyl units represent a large and structurally diverse group of compounds. Particularly significant are those possessing biological activity, including the eicosanoids (the arachidonic acid derivatives such as the leukotrienes and lipoxins),[1] the retinoids,[2] and the polyene macrolides,[3] a large group comprising over 200 members. There are also a considerable number of relatively unexplored polyenes derived from a variety of sources, including marine organisms, fungi, slime-moulds and plants; these polyenes are often produced as a means of chemical defense, and thus also possess potentially useful biological activity.

This review covers the literature from 1971 to the present date. It begins with a brief survey of the major sub-categories of polyene natural products, before focussing on methods used to bring about their synthesis. Heavier emphasis will be given to the synthesis of the polyenes themselves and owing to the vast number of natural products containing multiple double bonds, this review will concentrate only on natural products that contain at least a) three all-*trans* conjugated double bonds, or b) *cis*,*cis* or *cis*,*trans* dienyl units.

## 1.1 Polyenes derived from bacteria

Typically isolated from the *Streptomyces* genera of actinomyces soil bacteria, the polyene and oxopolyene macrolides[4] are relations of the more familiar macrolide antibiotics (for example, the erythromycins) and represent the most important sub-category of polyene natural products. Structurally, they are very large macrocyclic lactones with 22 to 44 membered rings commonplace. The polyenic section usually incorporates between 4 and 8 conjugated double bonds. Oxopolyene macrolides such as roxaticin[5] **1** are characterized by having the polyene in conjugation with the lactone linkage (Fig. 1). Several members of the polyene macrolide family find service as clinically important anti-fungal drugs, notably pimaricin **2**,[6] nystatin $A_1$ **3**[7] and amphotericin B **4**,[8] dubbed 'amphoterrible' due to its high nephrotoxicity.

The ansamycin[9] antibiotics are a growing family of *Streptomyces* metabolites, and many of them possess antibacterial, antifungal or antitumour activity. Ansatrienine A (mycotriene) **5**[10] is one of the first isolated examples, and may be taken as a representative member. Also isolated from *Streptomyces* sp., the manumycins[11,12] (for example, **6** and **7**) are a fairly large and well-studied group of polyenes. This family of antibiotics has attracted considerable attention due to their promising biological activity; manumycin A **6**, the first to be isolated, shows activity towards fungi and L1210 leukemia stem cells in addition to its antibacterial properties.

Isolated in 1994 from the fermentation broth of the gliding bacteria *Sorangium cellulosum*, the disorazoles,[13] of which disorazole $F_2$ **8** is typical, are a group of 29 anti-fungal and cytotoxic macrocyclic dilactones. They are all dimer-like, and are differentiated by the positions and stereochemistries of the double bonds, and in the size of, and nature of the substituents on the macrocyclic core.

Aside from these major classes, there are a host of other bacterially derived polyenes (Fig 2). Xanthomonadin I **9** responsible for the vivid yellow colours of *Xanthomonas* colonies, is a rare example of a compound synthesized by a terrestrial organism that contains bromine.[14] Linearmycin $A_1$ **10**[15] is an unusually long polyene containing thirteen double bonds, whilst the structurally complex polyenes viridenomycin **11**[16] (an antifungal, antibacterial and anti-tumour macrolide) and rapamycin **12**[17] (an antibacterial and immunosuppresive agent) are further examples of *Streptomyces* metabolites.

## 1.2 Polyenes produced by fungi

Pigments derived from fungi tend to be of isoprenoidal origin, not arising from the polyketide metabolic pathways that usually give rise to polyenic compounds. There are a few examples however, and a prominent one is that of fumigillin **13**[18,19] (Fig. 3), a metabolite of *Aspergillus fumigatus* that possesses a wealth of biological activities including amebicidal, anticancer, antiparasitic and antibacterial properties. Also important are the rhizoxins,[20] a family of 16-membered macrolactones isolated from the plant-pathogenic fungus *Rhizopus chinensis*. Rhizoxin **14** is a tubulin binding anti-mitotic agent possessing antifungal and antimicrobial activity in addition to potent *in vitro* cytotoxicity and *in vivo* antitumour activity. It is more potent, yet less toxic than vincristine and has undergone extensive clinical trials. The didesepoxy analogue rhizoxin D[21] has equal potency, but is isolated as a minor component.

## 1.3 Polyenes derived from slime-moulds and plant sources

Slime moulds, often found amongst moist decaying wood and litter in forests, produce yellow cytotoxic substances such as fuligrobin A **15**[22] and physarachrome A **16**[23] (Fig. 4), either as a means of chemical defense, or to function as photoreceptors. Plants synthesize a vast array of polyenic compounds, most familiar of which are the carotenoids[24] (*e.g.* γ-carotene **17**), the most prevalent of all the naturally occurring pigments (Fig 5). The deoxyphorbol ester derivatives **18** and **19** isolated from the caustic sap of the pencil tree, are purported anti-tumour agents.[25] Also shown are several unusual polyenes containing mixed alkene geometries **20**–**22**.[26]

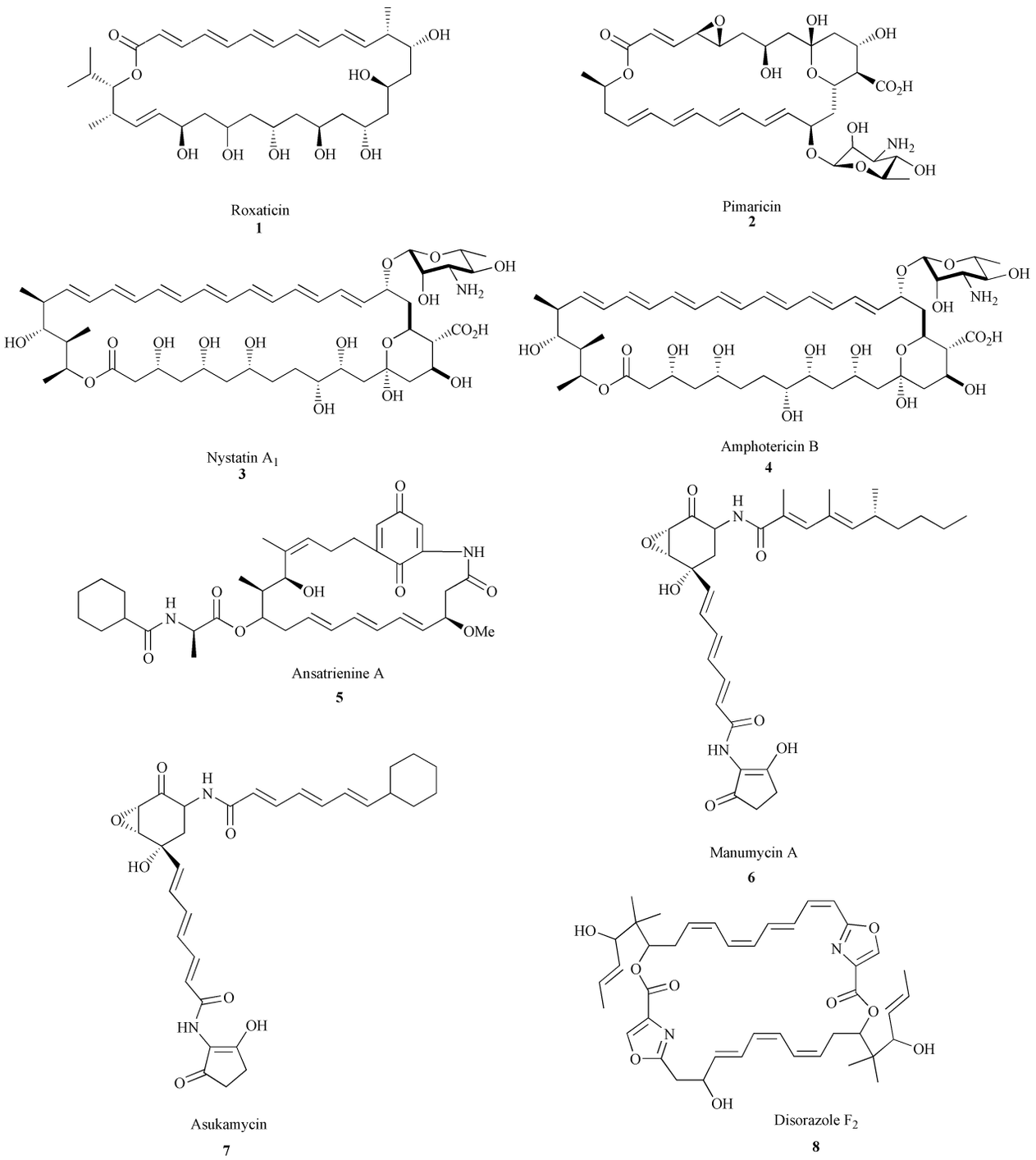
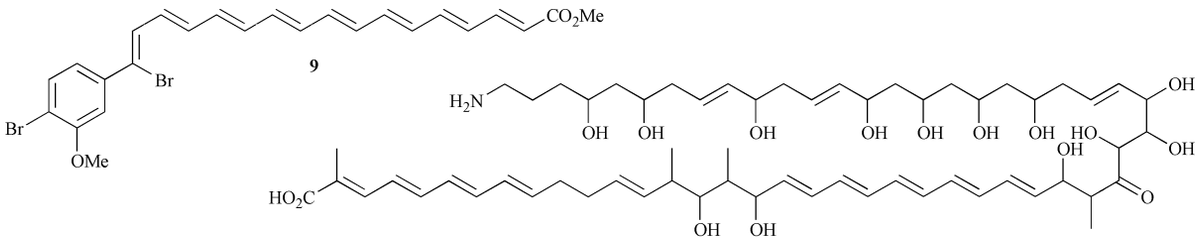



**Fig. 1**

### 1.4 Polyenes derived from marine organisms

Naturally derived polyenes are typically toxic, and often vividly coloured. These two facets are exploited well by many marine organisms which are without the defensive capabilities of many of their larger aquatic cousins. Opisthobranchia for example, a sub-class comprising the sea-slugs and their allies, lack the protection provided by the hard shell typical of most members of the gastropod class, and secrete brightly coloured polyenic ketones, such as the yellow navanones A–C **23**–**25** (named after *Navanax inermis*, an ornately coloured sea-slug found off the Californian coast) which act as alarm pheromones.[27] The cytotoxic aurantosides A and B (**26** and **27**, Fig. 5), obtained from sponges and isolable as orange amorphous powders, are *N*-trisaccharide tetramic acid derivatives possessing activity against P388 and L1210 leukemia cells.[28a] Aurantosides C[28b] and D–F[28c] have also been recently isolated and found to possess biological activity. The antibiotic keronopsins **28**–**31** are produced by *Pseudokeronopsis rubra*, a marine ciliate known for its deep red colour, and are used as chemical weapons against other ciliates and flagellates.[29] Marine dinoflagellates, a type of unicellular aquatic organism possessing both animal and plant characteristics, provide a rich source of structurally diverse natural products with highly specific bioactivity. Certain species produce powerful nerve toxins, and it is these toxins that give rise to the so-called red-tides, formed when the creatures reproduce *en mass* or bloom in shallow waters. The genus *Amphidinium* has been exploited as a source of novel secondary metabolites with unique chemical structures,[30] and amphidinol 3 **32** (Fig 6), an antifungal polyene whose structure was recently elucidated,[31] is a prominent example.

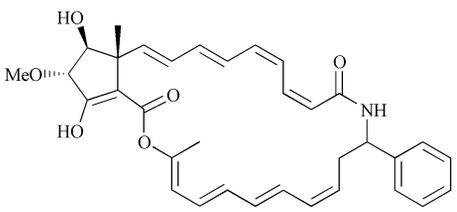


**9**



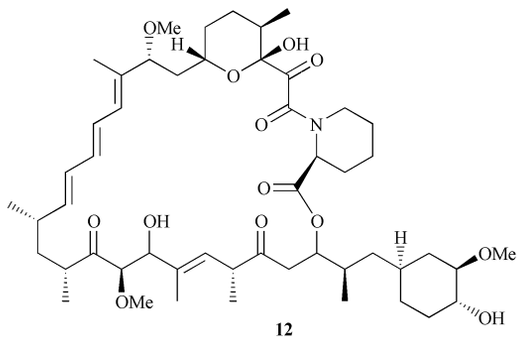
**10**

Linearmycin $A_1$



**11**

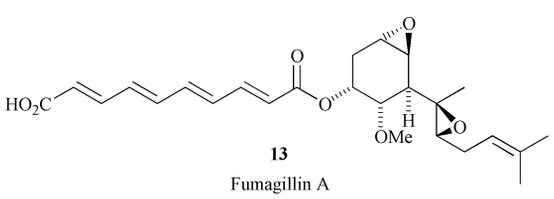
Viridenomycin



**12**

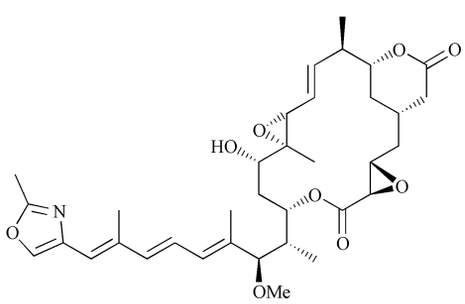
Rapamycin

**Fig. 2**



**13**

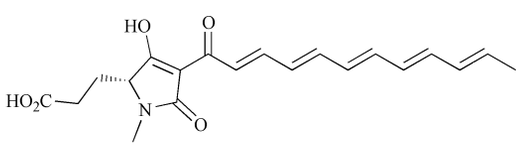
Fumagillin A



**14**

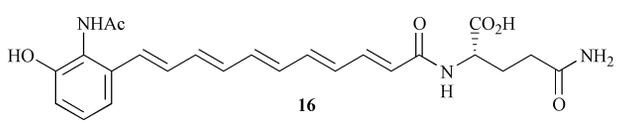
Rhizoxin

**Fig. 3**



**15**

Fuligrobin A



**16**

Physarachrome A

**Fig. 4**

### 1.5 Polyenes produced by animals

The retinoids[2] **33**–**37** (Fig. 7), a collective term for the various synthetic and natural analogs of retinol (vitamin A) **33**, are vitally important during embryo development and throughout post-natal life in humans. The biological roles they play are dependent both on the nature of the R group and on the geometry of the polyene chain. These factors are the reason that they have been the focus of much synthetic attention, and are often used as the first test of a new polyene-assembling methodology.

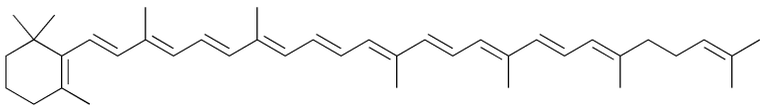
Another important group of polyenic biomolecules are the eicosanoids,[1] comprising the structurally related prostaglandins, prostacyclins, thromboxanes and leukotrienes, which are derived from polyunsaturated fatty acids such as arachidonic acid. These compounds are found in minute quantities in most animal cells, and elicit diverse biological responses in most animals. These effects, together with their small, but complex structures, have made them appealing targets for total synthesis; indeed the only means of obtaining sufficient quantities of eicosanoids for evaluation is through chemical synthesis. Lipoxin A **38** (Fig 7) possesses similar biological properties to the unstable intermediate leukotriene $B_4$, and has been synthesized and evaluated biologically.

### 2.0 Synthesis of polyenes—general strategies

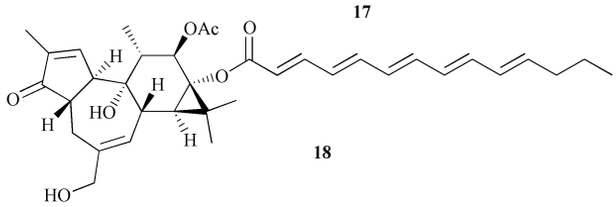
Fig. 8 outlines the most common general strategies taken to date in order to access polyenes.

A few fundamental issues need to be considered when synthesizing polyunsaturated compounds. As a general rule, polyenes of the all-*trans* nature are more stable than those containing *cis*-alkenyl units, hence the latter tend to be more difficult to construct, and especially prone to isomerization. Additionally, when a specific isomer is required, as is usually the case, a method that leads to mixtures of *cis* and *trans* isomers will invariably require a tedious and yield-reducing separation, if separation is possible at all.

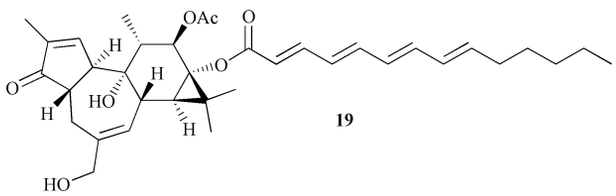
The principal requirements for polyene synthesis are thus 1) a reliable olefination procedure that produces alkenes in high geometric purity, 2) a procedure that allows ready access to either isomer, whilst at the same time being mild and functional group tolerant.



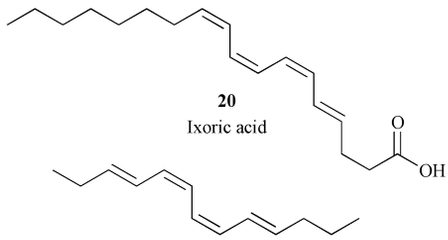
γ-Carotene
**17**



**18**



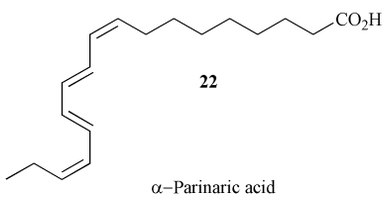
**19**



**20**
Ixoric acid

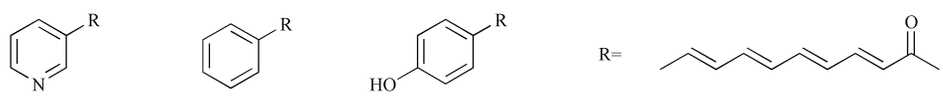


**21**



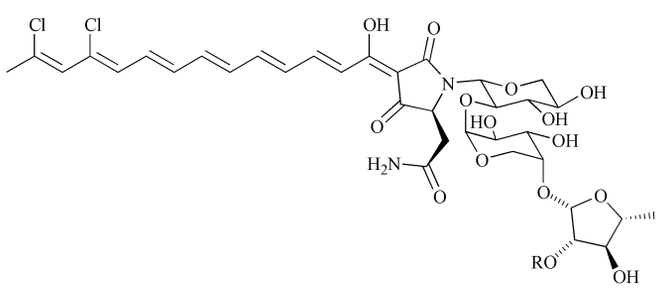
**22**
α–Parinaric acid

**Navanones**



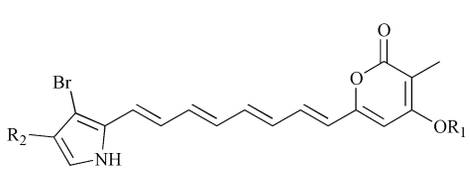
A **23** B **24** C **25**

**Aurantosides**



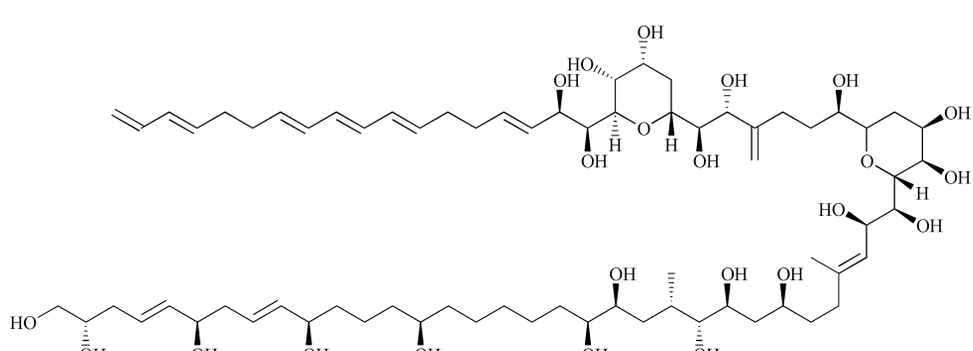
R= Me, Aurantoside A **26**
R=H, Aurantoside B **27**

**Keronopsins**



| $R_1$ | $R_2$ | Keronopsin | |
|---|---|---|---|
| $SO_3Na$ | H | $A_1$ | **28** |
| $SO_3Na$ | Br | $A_2$ | **29** |
| H | H | $B_1$ | **30** |
| H | Br | $B_2$ | **31** |

**Fig. 5**



**32**

**Fig. 6**

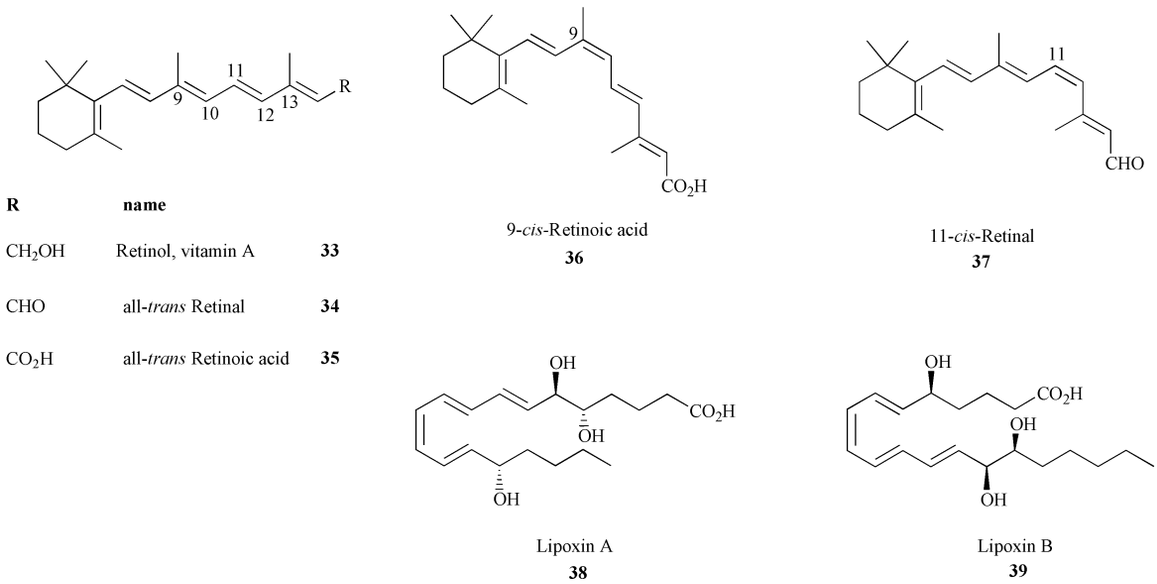



**Fig. 7**

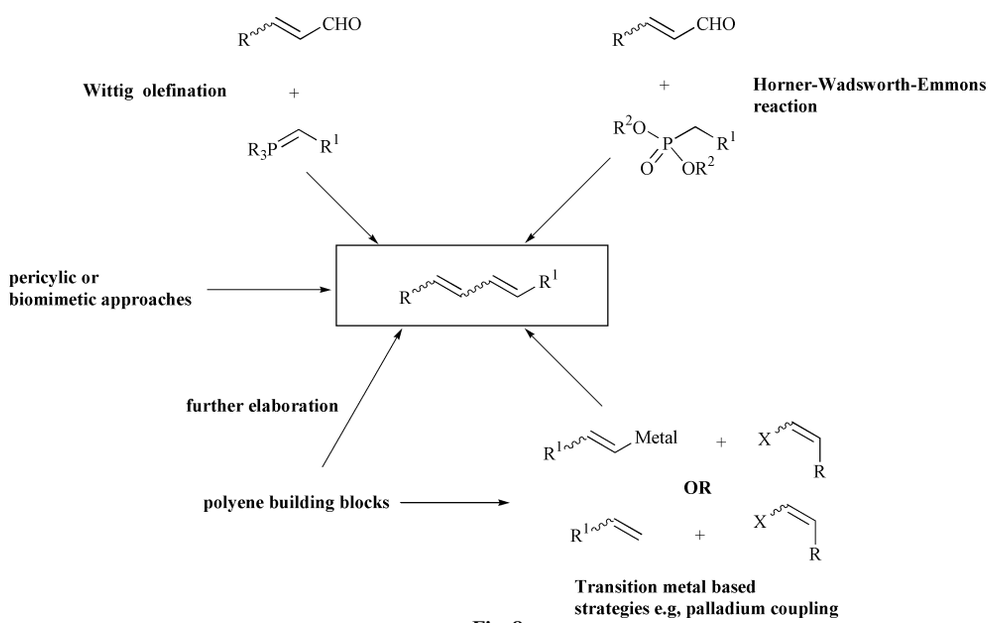



**Fig. 8**

### 2.1 Wittig olefination and Horner–Wadsworth–Emmons procedure

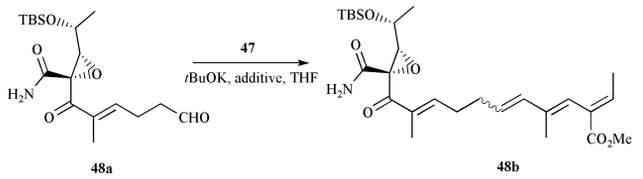
The Wittig reaction[32] has proved historically to be the reaction of choice for the formation of alkenes. It suffers however from a number of disadvantages, the principal one being that it invariably leads to a mixture of isomers, necessitating separation, or isomerization of the unwanted isomer. It also requires preparation of an appropriate ylide, typically requiring a strong base to generate the carbanion, and usually a laborious purification procedure necessary to remove the stoichimetric phosphine oxide by-product. The closely related Horner–Wadsworth–Emmons[33] (HWE) procedure circumvents a number of these problems, and is now increasingly used in all areas of natural product synthesis.

The BASF synthesis of vitamin A, one of the leading methods of production, utilizes Wittig chemistry on a huge scale to produce the precursor retinyl acetate **40** (Scheme 1). A double Wittig reaction was recently employed by Tode's group in the first synthesis of the marine carotenoid crassostreaxanthin B **41** (Scheme 1).[34] Condensation of aldehyde **42** with Wittig salts **43** and **44** led to **41** after deprotection. Wittig chemistry was also employed in the synthesis of the side chain of the novel neuritogenic agent epolactaene **45** (Scheme 2),[35] with the requisite ylide **47** being prepared in six steps starting from known iodoalcohol **46**. Various conditions were examined in order to give the highest $E$ : $Z$ ratio for the Wittig coupling of **47** and **48** (Table 1); use of the tributylphosphonium salt **47b** gave the highest proportion of the $E$ isomer which was separated from the $Z$ isomer by flash chromatography.

As mentioned previously, arachidonic acid metabolites are important due to their intriguing biological properties, and Yadav and co-workers have developed a convergent synthesis of lipoxin A **38** (Scheme 3), with Wittig chemistry being used to install the tetraene portion. Their synthesis involves a specialized ylide **49**, prepared from propargyl alcohol (prop-2–yn-1-ol).[36] In 1991 Pattenden and Patel reported the total synthesis of all-*trans* citreomontanin **52**, a hexaene isolated from *Penicillum pedemontanum* and the putative precursor to citreoviridin and citreoviridinol. This was achieved *via* an iterative sequence involving Wittig coupling between aldehyde and triphenylphosphoranylpropanoate **50**, propanoate reduction, and oxidation to regenerate an aldehyde **51** (Scheme 4).[37]

There are numerous applications of the HWE procedure towards polyene synthesis. A prominent example can be seen in Nicoloau and co-workers' landmark total synthesis of

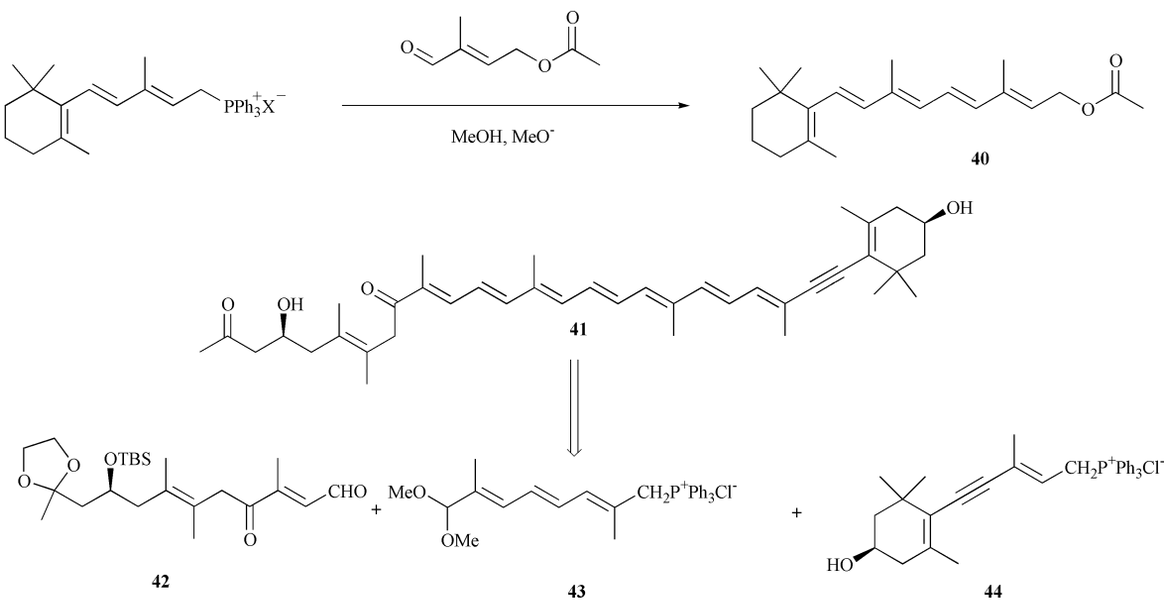
**Table 1**



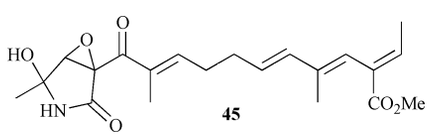

48a 48b

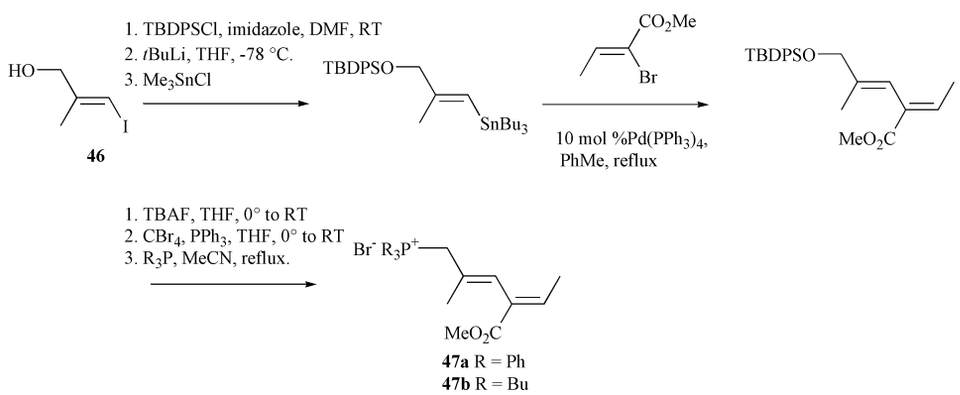
| Ylide | Ylide (equivalents) | Additive | $T$/°C | $E$ : $Z$ Ratio [a] | Yield (%) |
|---|---|---|---|---|---|
| **47a** | 2.4 | None | −78 | — | Trace |
| **47a** | 2.4 | 18-Crown-6–MeCN | −46 | 1 : 1 | 27 |
| **47a** | 5.0 | 18-Crown-6–MeCN | −46 | 1 : 1 | 68 |
| **47b** | 5.0 | 18-Crown-6–MeCN | −46 | 10 : 1 | 69 |

[a] Determined by $^1$H NMR

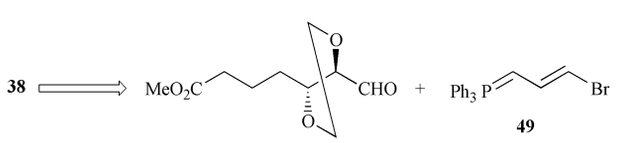



**Scheme 1**



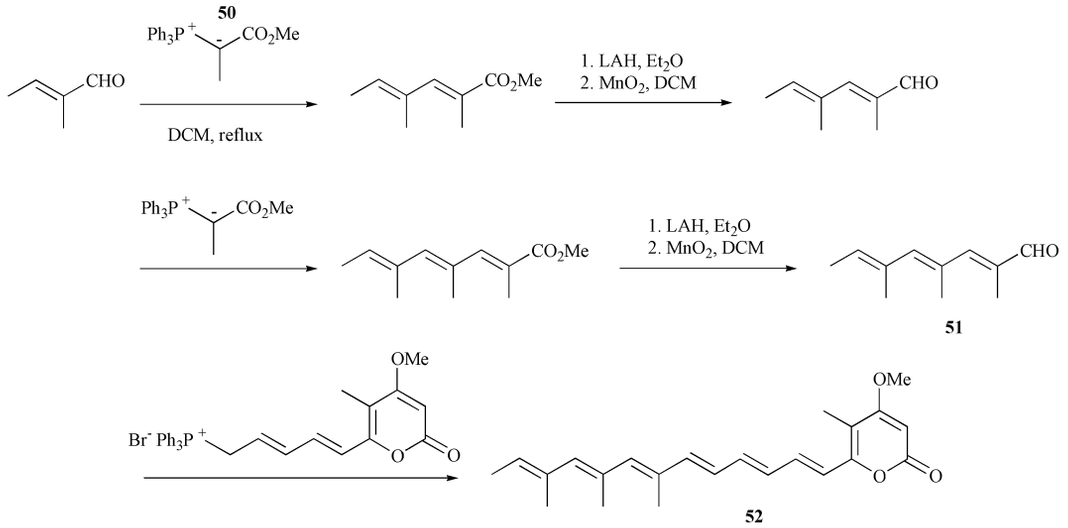




**Scheme 2**

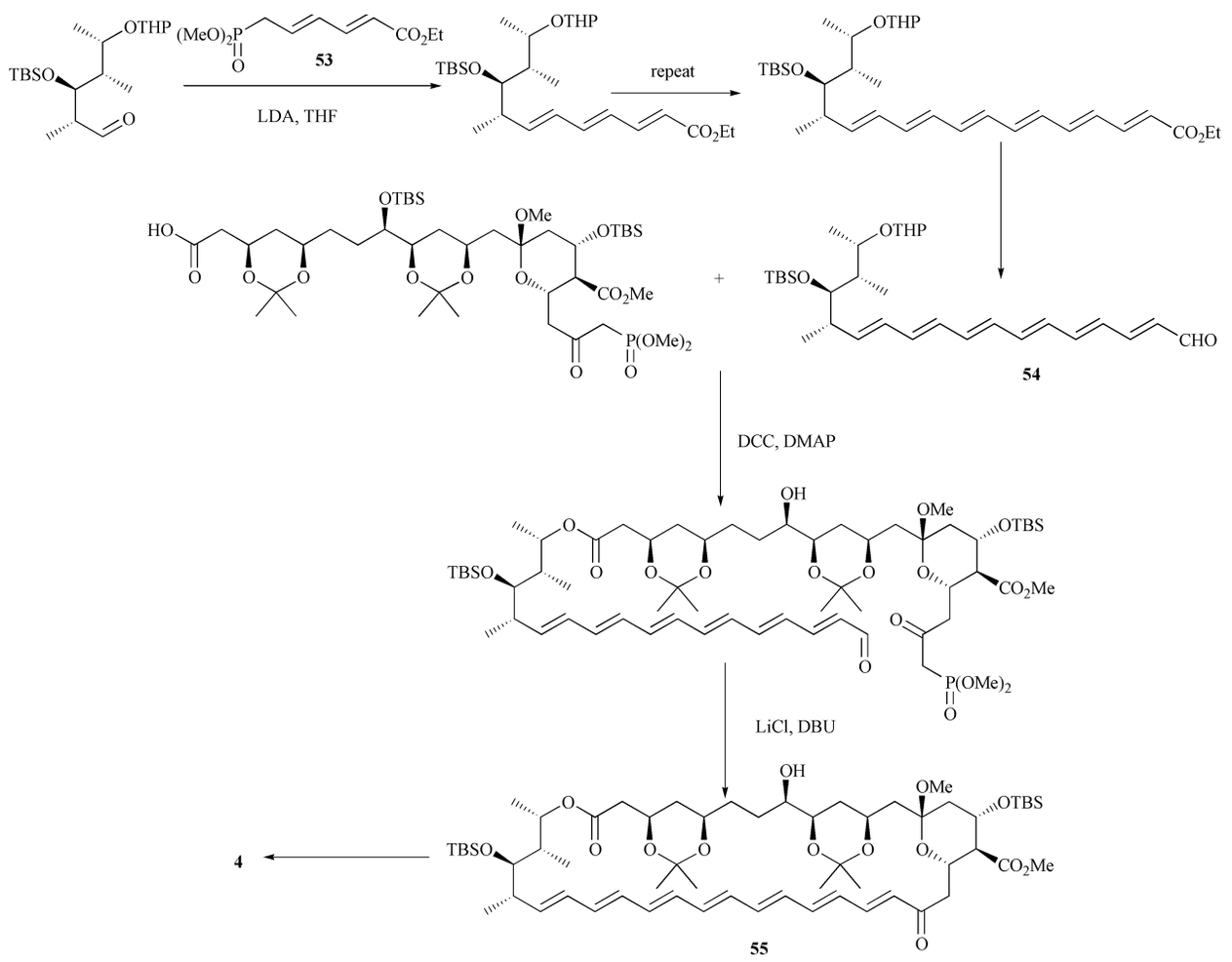



**Scheme 3**

amphotericin B **4**, in which three HWE reactions were used to construct the polyene section (Scheme 5).[38] The first two employed the functionalized phosphonate **53** leading to the acyclic hexaenal **54**, before the third reaction was used to induce ring closure, giving the cyclic heptaene **55**. A similar approach was taken by Mori's group in their recent synthesis of roxaticin **1**.[39]




**Scheme 4**

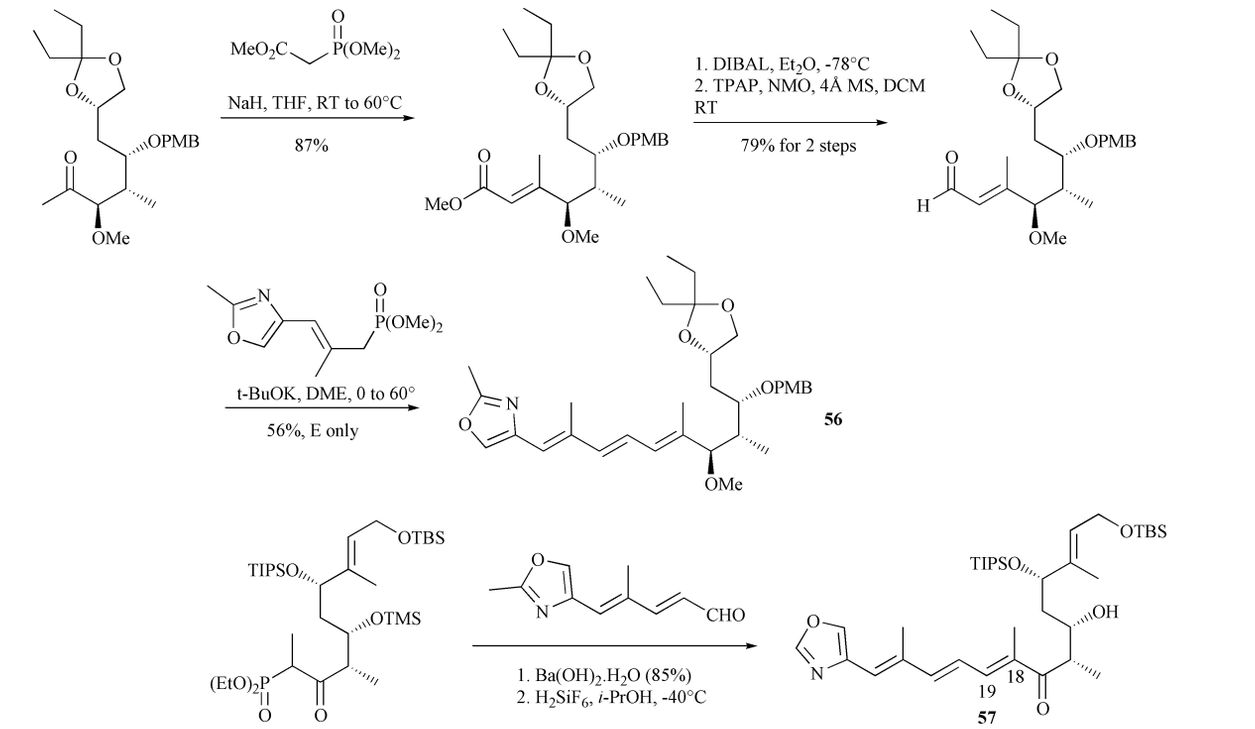



**Scheme 5**

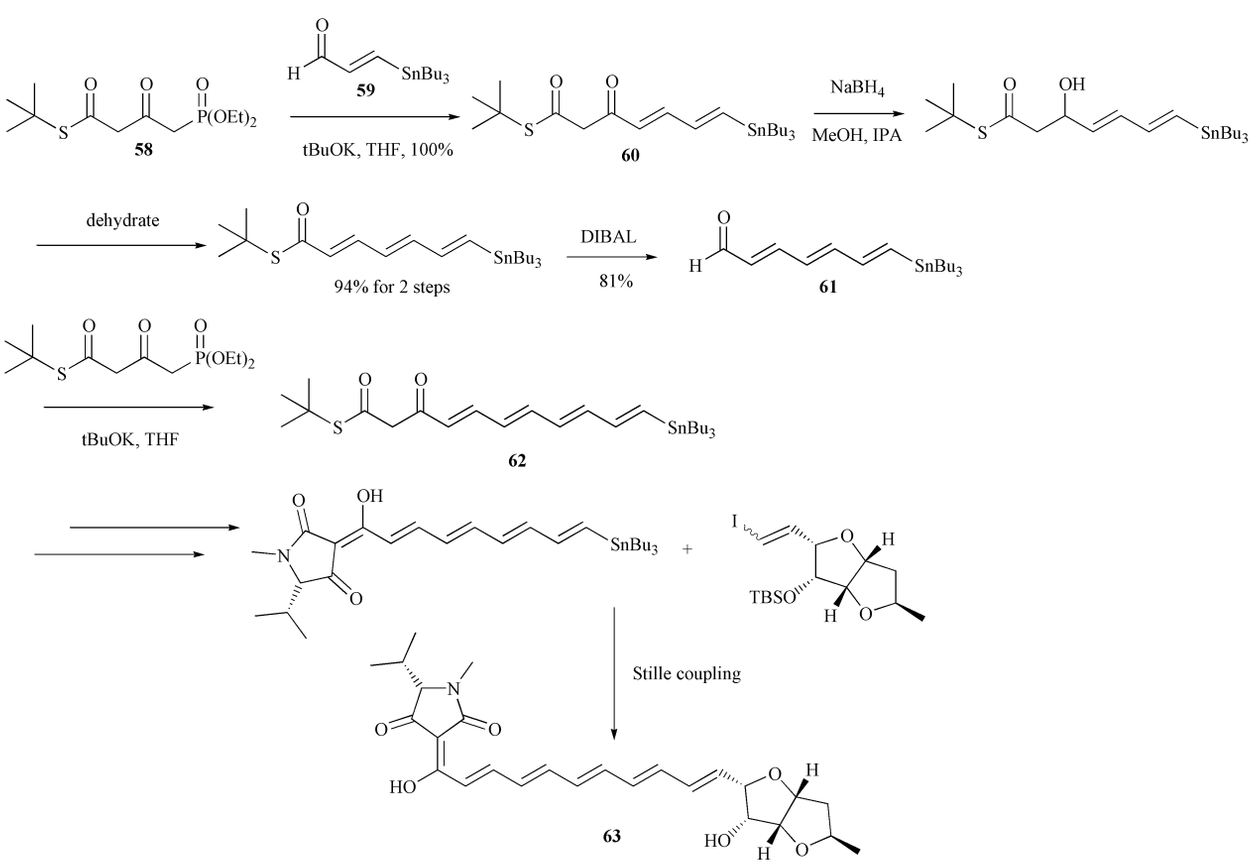
The rhizoxins have attracted considerable attention owing to their remarkable biological activity,[20] and many efforts have been directed towards rhizoxin and its congeners.[40] Burke and co-workers' partial synthesis of rhizoxin[40e] **14** (Scheme 6) used two HWE reactions to form the trisubstituted *E*-olefin **56**.

Leahy and co-workers' total synthesis of rhizoxin D utilizes a similar approach.[41] They explored various routes to the tricky triene oxazole fragment **57** before settling on a HWE reaction between C18 and C19. Ley's group used HWE reactions to install the acyltetramic acid portion of the antibiotic erythroskyrine **63** (Scheme 7).[42,43] They coupled the phosphonate ester **58** with the β-tributylstannyl aldehyde **59** under optimized conditions, giving the dienyl stannane **60** quantitatively as a >30 : 1 mixture of *E*–*Z* isomers. Subjection of trienal **61** and phosphonate **58** to HWE reaction under identical conditions provided the tetraene **62** in high yield and with high selectivity (>30 : 1 *E*–*Z*).

Phosphorous ylide based reactions played a pivotal role in the construction of the macrocyclic lactam cyclamenol A **66** (Scheme 8), recently reported by Nazare and Waldmann.[44] In devising their synthetic strategy, the authors paid particular attention to the polyene section, which comprised one *Z* and six *E* double bonds. It was feared that the *Z* double bond would isomerize, or the polyene skeleton would react further to give a



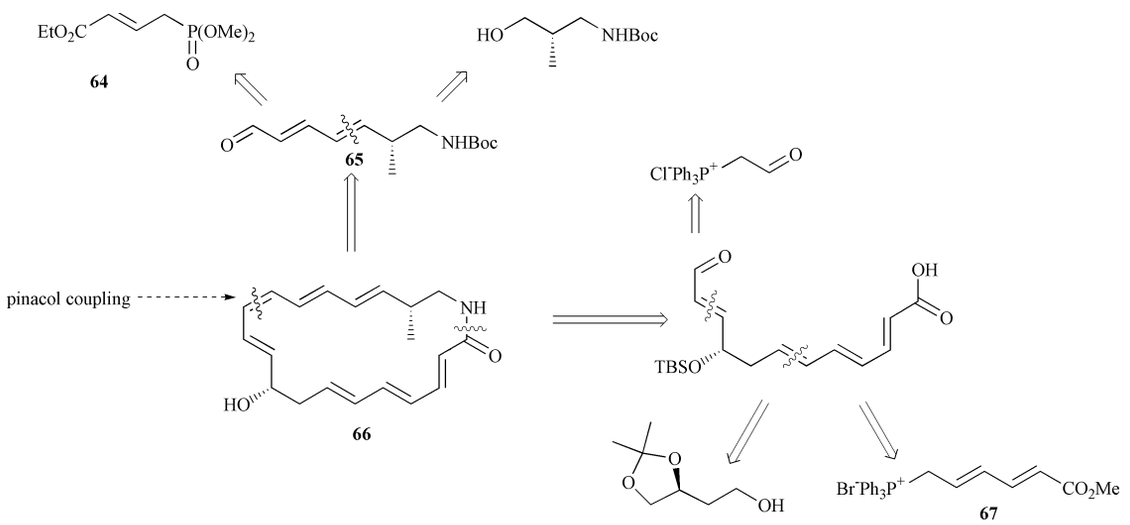

**Scheme 6**



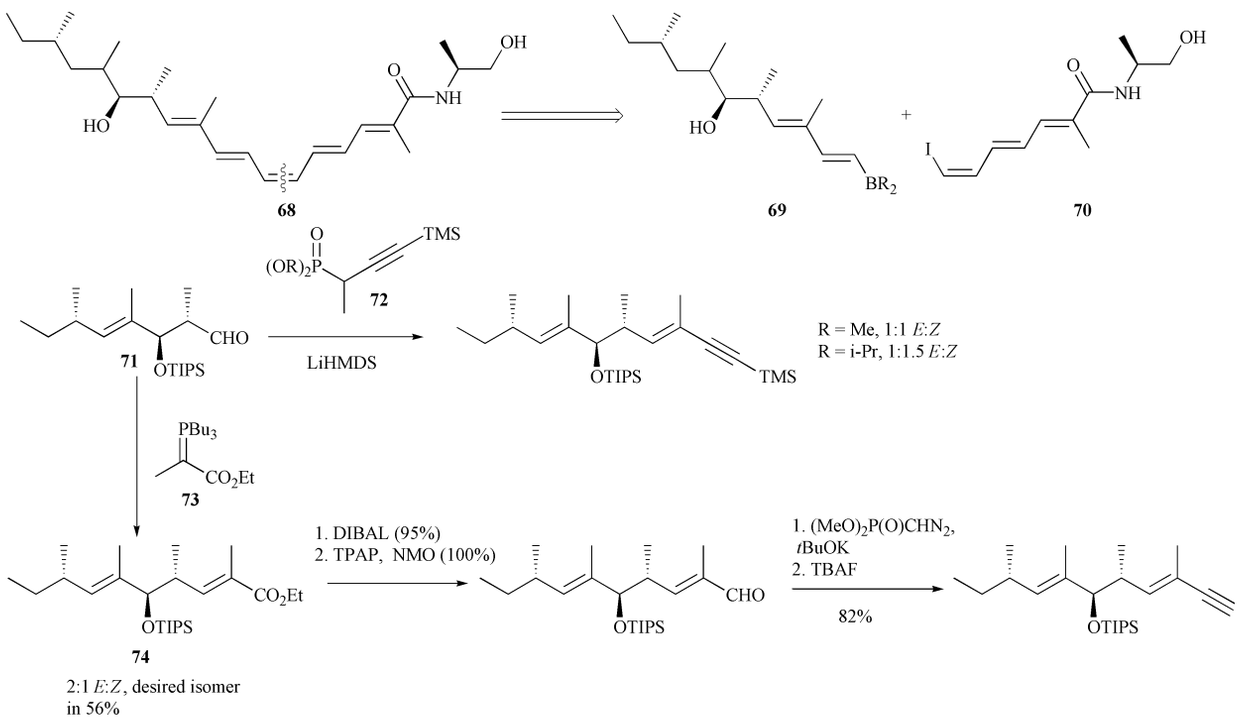

**Scheme 7**

fully conjugated octaene. For this reason, construction of the polyene system was left until late in the synthesis, and the final *Z* double bond was introduced *via* a pinacol coupling, allowing both ends of the acyclic precursor to be tied together through template control. A HWE procedure involving crotonyl phosphonate **64** was used to construct the dienal **65**, whilst a Wittig reaction exploiting the phosphonium salt **67** derived from sorbic acid was used to provide the southern triene.

So far, only examples of the Wittig and HWE reactions leading to all *E* polyenes have been examined; this is mainly due to the inherent *E*-selectivity of these processes. It is possible however, either by changing the nature of the phosphonium salt/phosphonate or by varying the reaction conditions, to bias the outcome towards either alkene isomer. In the first reported synthesis of myxalamide A **68** (Scheme 9), the most abundant of the four myxalamides[45] isolated from the gliding bacteria *Myxococcus xanthus*, Mapp and Heathcock opted to complete the synthesis *via* a Suzuki coupling (see section **2.2**) between

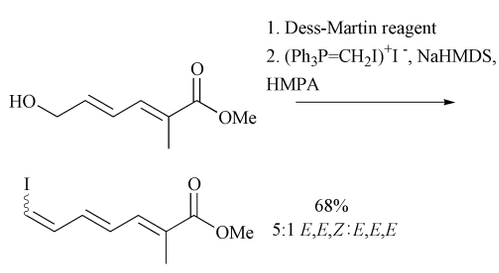



**Scheme 8**



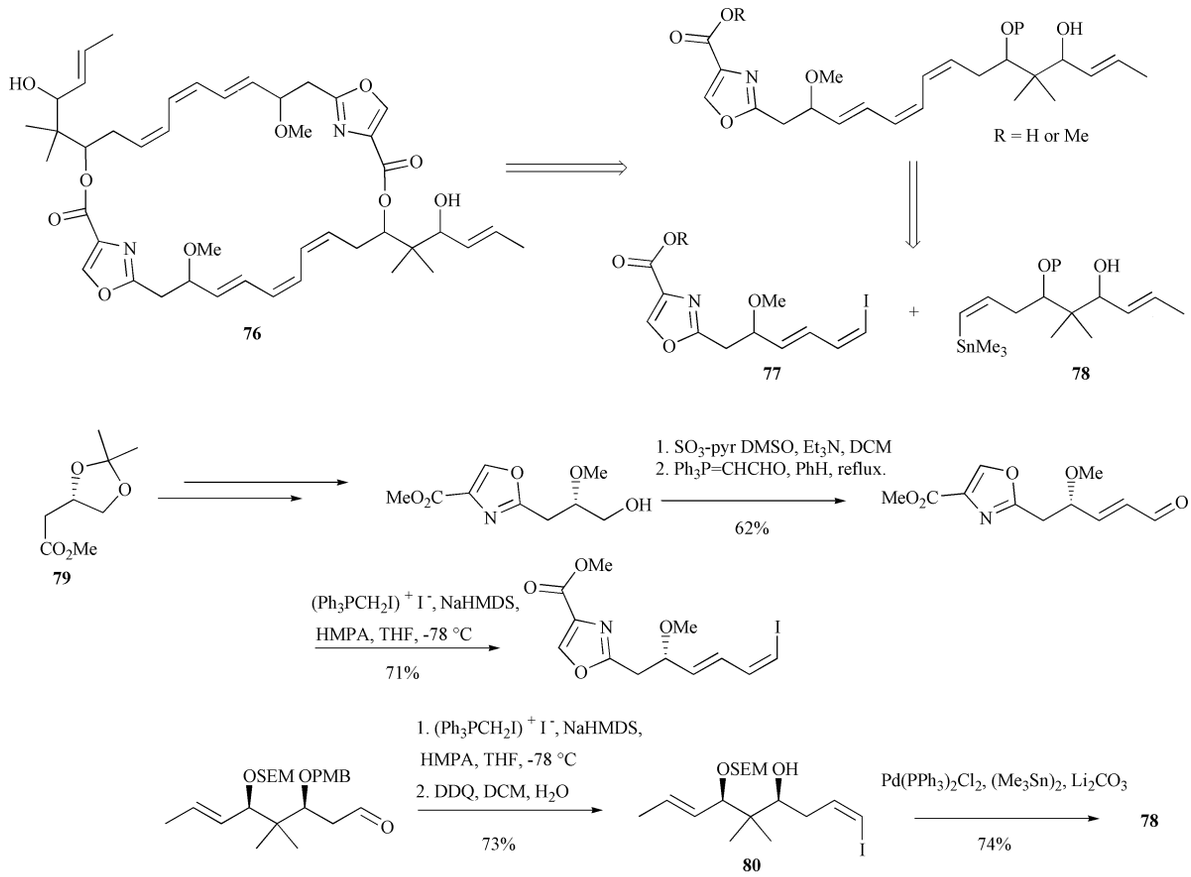

**Scheme 9**

dienylborane **69** and iodotriene **70**.[46] In order to prepare the enyne precursor that would undergo hydroboration to give **69**, they initially attempted to install the triple bond *via* a HWE reaction between aldehyde **71** and phosphonate **72**. However, *E*/*Z* selectivities were not good, and use of the bulkier phosphonate gave greater selectivity, but in the wrong direction. Use of the stabilized ylide **73** gave the unsaturated ester **74** in an improved 2 : 1 (*E*–*Z*) ratio. Synthesis of the triene portion of iodotriene **70** (Scheme 10) required formation of an (*E,E,Z*)-alkenyl unit **75**, with insertion of the *Z*-alkene being accomplished under kinetic conditions through the Stork–Zhao modification of the Wittig reaction.[47] Unfortunately, although the ratio of isomers was acceptable, separation by a variety of methods proved impossible, and the authors were forced to use an alternative approach to this fragment.

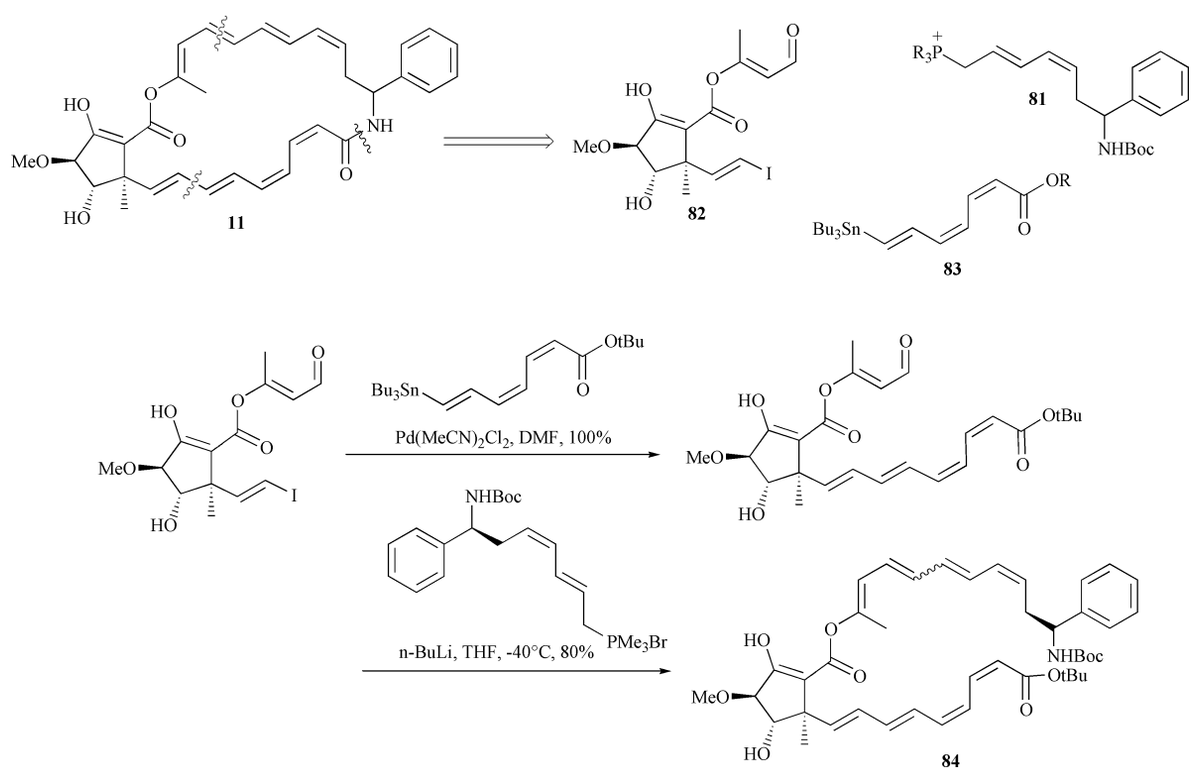



**Scheme 10**

This modification[47] was also employed in Meyers and coworkers' synthesis of the monomeric unit of diorazole $C_1$ **76** (Scheme 11).[48] Here, a palladium coupling reaction was also chosen as the final bond-forming reaction, which retrosynthetically led back to an oxazole containing dienyl iodide **77** and a *cis*-alkenyl stannane **78**. Iodide **77** was assembled from readily available ester **79**, *via* Wittig homologation to insert the *trans* double bond, followed by the Stork–Zhao Wittig modification. This strategy was used again to furnish alkenyl iodide **80**, which gave **78** after the Stille coupling. The same group also recently reported studies towards the total synthesis of viridenomycin[49] **11** (Scheme 12), a large polyene macrolide containing two mixed geometry tetraenes. In their second generation approach, the authors chose to disconnect **11** into three key fragments, allowing these two potentially problematic units to be synthesized in



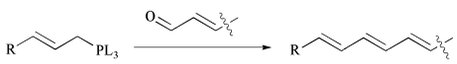

**Scheme 11**



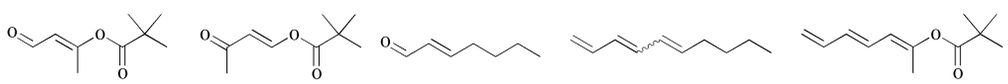

**Scheme 12**

isolation. It was envisaged that **81** would be joined to the core cyclopentenol fragment **82** using phosphonate chemistry and **81** was prepared accordingly, with a kinetic Wittig reaction being used to insert the required *Z*-alkene with good selectivity. The original strategy to use a phosphonate to join **81** and **82** failed in studies using model aldehydes (entries 1 and 2, Table 2), as rearrangement to give a ketone was observed. Use of the semi-stabilized ylide described by Tamura and co-workers[50] gave poor *E*/*Z* selectivity (entries 3 and 4). In the end, the authors used trimethylphosphonium salt **81** (R = Me) to prepare **84**, which gave high selectivity towards the desired *E* isomer. A kinetic HWE reaction was employed to synthesize the trienyl stannane **83** (Scheme 13); use of the electrophilic Still–Gennari phosphonate[51] under kinetic conditions that favour rapid

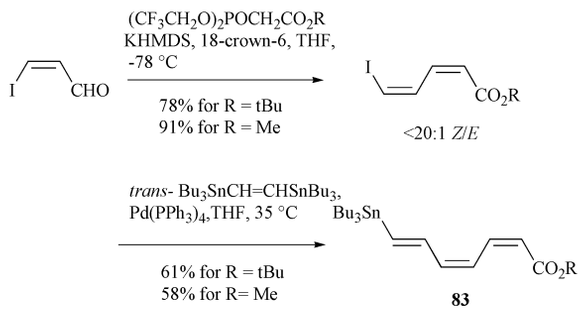
**Table 2**



| Entry | R | $PL_3$ | Base | Aldehyde[a] | Product[a] | Ratio ($E:Z$) |
|---|---|---|---|---|---|---|
| 1 | Me | $PO(OEt)_2$ | KO*t*-Bu | **85** | **86** | — |
| 2 | Me | $PO(OEt)_2$ | *n*-BuLi | **85** | **86** | — |
| 3 | H | $PBu_3$ | KO*t*-Bu | **87** | **88** | 2.6 : 1 |
| 4 | H | $PBu_3$ | *n*-BuLi | **87** | **88** | 2.9 : 1 |
| 5 | H | $PMe_3$ | KO*t*-Bu | **87** | **88** | 3.0 : 1 |
| 6 | H | $PMe_3$ | *n*-BuLi | **87** | **88** | 30 : 1 |
| 7 | H | $PMe_3$ | *n*-BuLi | **85** | **89** | 10 : 1 (90%) |

[a] 

**85** **86** **87** **88** **89**



**Scheme 13**

elimination leads to *Z*-alkenes in excellent isomeric purity. Unfortunately, removal of both *t*-Bu protecting groups proved impossible, and cyclization of **84** was not realized.

Taylor's group recently disclosed a procedure that enables elaboration of haloenals **90** without the need for their isolation.[52] This is useful because whilst such compounds are potentially valuable as polyene building blocks, they are also unstable, difficult to isolate, and have a severe irritant effect on mucous membranes, particularly the bromo and chloro-enals (both isomers of iodopropenal can be prepared readily, but retain lachrymatory properties). Their protocol involves *in situ* manganese dioxide haloenol oxidation, followed by direct Wittig homologation, giving dienyl haloesters **91** that are themselves useful polyene buildings blocks, given that partial reduction of the ester function would allow the process to be repeated (Scheme 14).

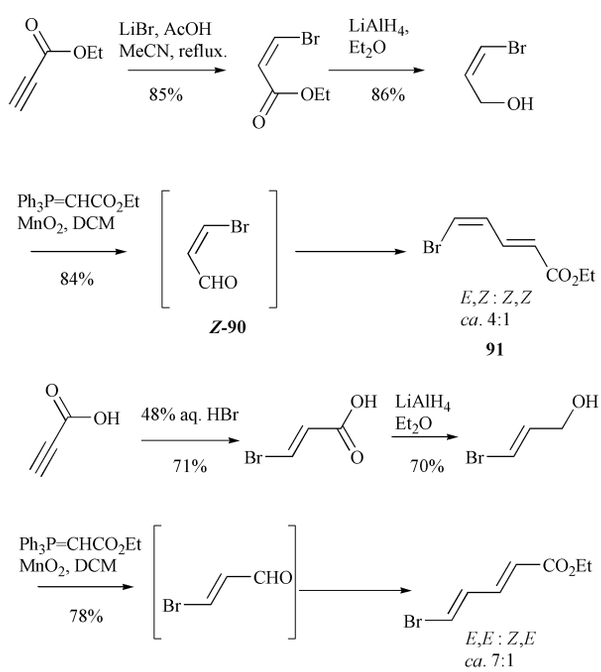
## 2.2 Transition metal based strategies

Representative of these strategies are the palladium cross-coupling reactions, allowing single bond formation between two $sp^2$ centres with excellent stereoselectivity and often under very mild conditions, and without some of the problems encountered with more traditional approaches. The mildness and functional group tolerance of these reactions makes them an ideal way to insert the final 'stitch' in a polyene chain, thus allowing this often troublesome section to be assembled last. The Stille reaction[53] is particularly useful, and typically proceeds with retention of configuration of the alkenyl halide, leading to polyenes of exceptionally high geometrical purity. This reaction has been exploited many times, for example, in Nicolaou and co-workers' synthesis of rapamycin **12**[54] and Panek and Masse's synthesis of mycotrienin I and mycotrienol **92**[55] (Scheme 15), and in the previously discussed syntheses of myxalamide A **68**, viridenomycin **11**, erythroskyrine **63**, and the monomeric moiety of disorazole $C_1$ **76**. Duchene *et al.* have successfully applied Stille methodology to a variety of retinoids, including the trifluoromethyl retinoate **96**,[56] useful as a biological probe (Scheme 16). Their methodology uses enyne

**Table 3**

| Core | Iodide | Retinoid[a] | Yield (%) |
|---|---|---|---|
| **95a** | (*E*)-**98** | All-*trans*-9-Nor-retinoic acid | 50 |
| **95a** | (*Z*)-**98** | (13*Z*)-9-Nor-retinoic acid | 45 |
| **95b** | (*E*)-**98** | All-*trans* retinoic acid | 73 |
| **95b** | (*Z*)-**98** | (13*Z*)-Retinoic acid | 70 |

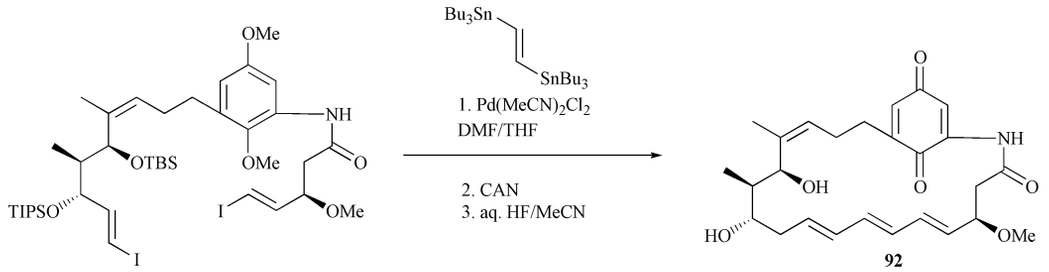
[a] See Fig. 7 for retinoid numbering.



***Z*-90** **91** ***E*-90**

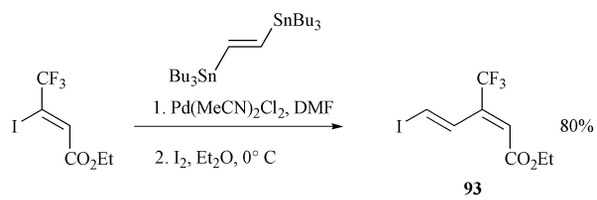
**Scheme 14**

precursor **94** derived from β-ionone,[57] which may either be converted into dienylstannane **95a** by treatment with the Lipshutz reagent[58] in the presence of methanol, or into the trisubstituted vinylstannane **95b** by trapping the intermediate vinylcuprate with methyl iodide. Stille couplings of β-iodovinylic acids **98** derived from tetrolic acid *via* iodides **97**, with stannanes **95** gives the retinoids stereoselectively (Table 3).[59] Fluorine substituted polyenes have traditionally been obtained *via* HWE or Julia reactions, but these methods are hampered by poor *E*/*Z* selectivity, particularly when forming the 9-*trans* trisubstituted double bond common in many retinoids. Yosihara and co-workers have recently described a preparation of 9-*trans*-9-desmethyl-9-fluororetinal **101** and analogues based upon a four component coupling approach.[60] Due to the failure of the 4-hydroxybutynoate **100** to undergo fluorination under reported




92

**Scheme 15**

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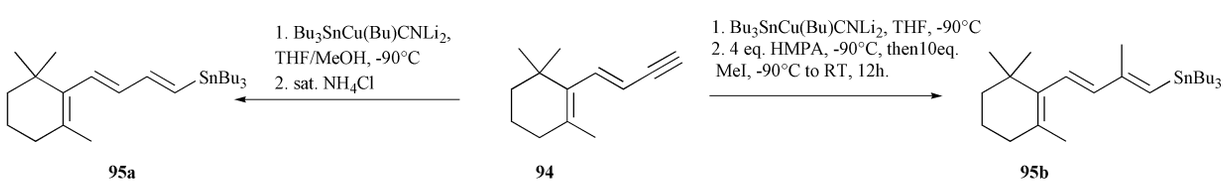
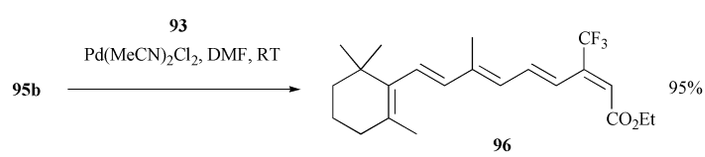
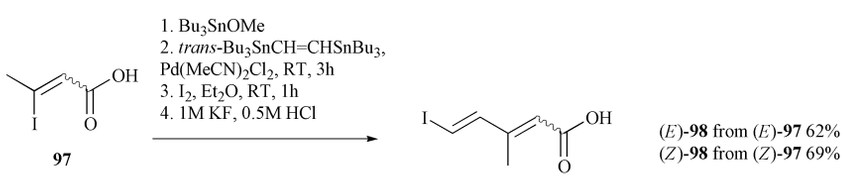


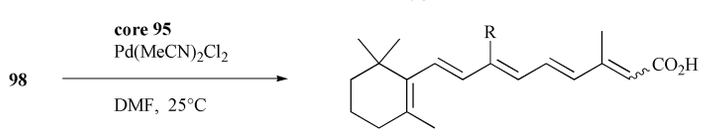

95a 94 95b




96




97 98



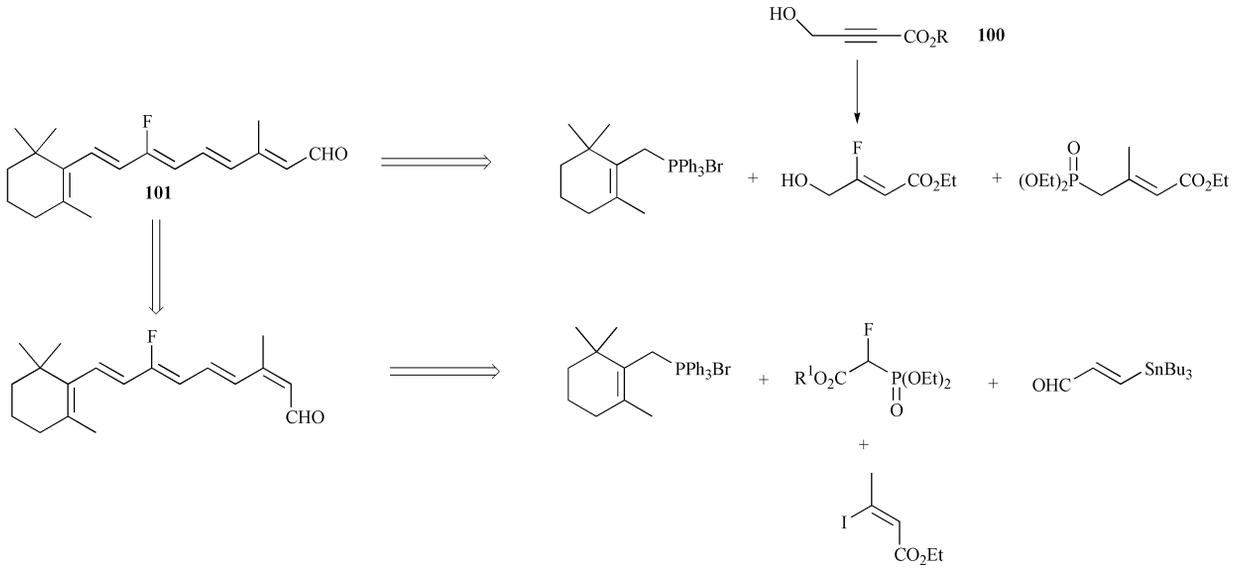

99a-d

**Scheme 16**

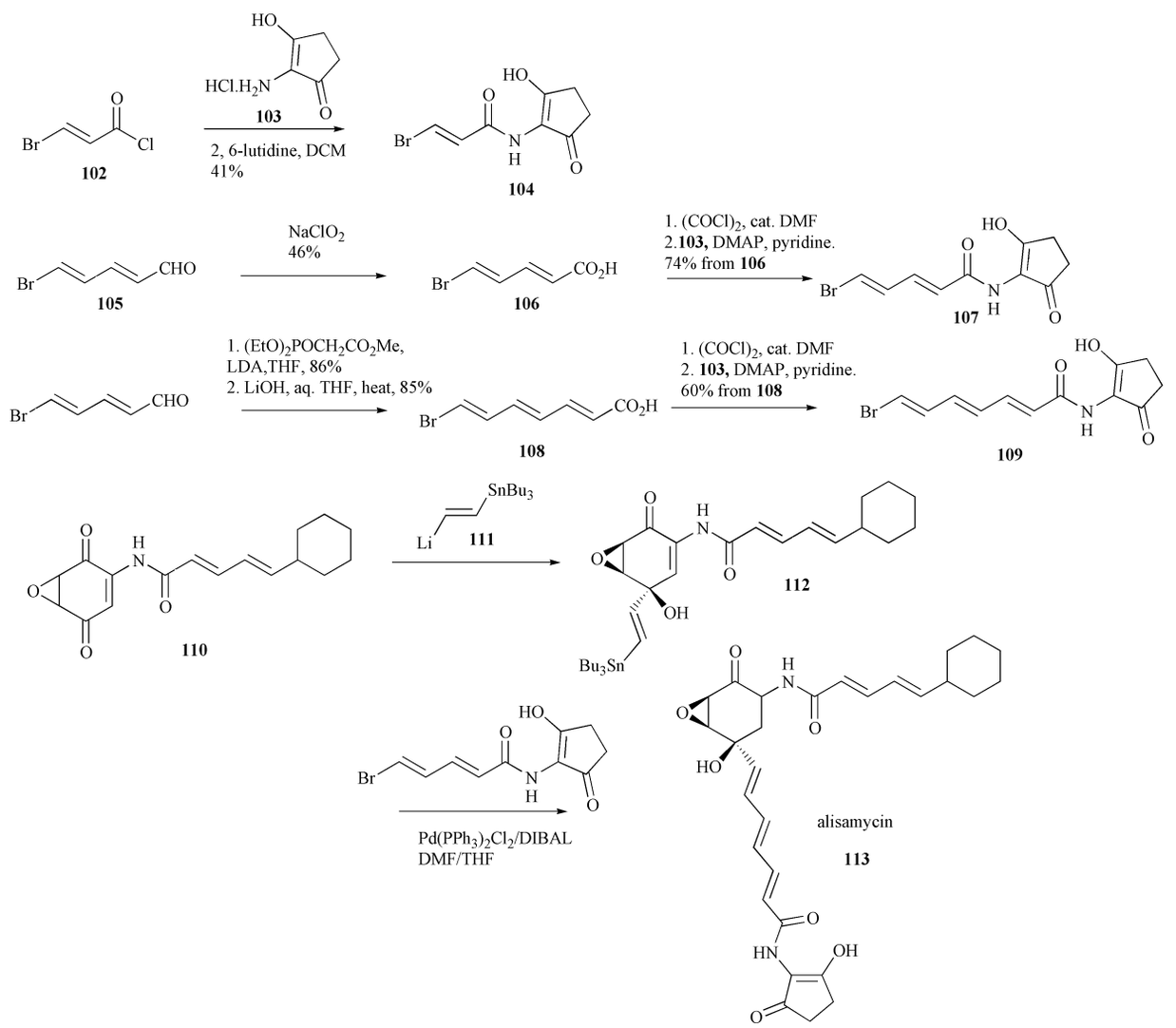
conditions, the second approach utilizing Wittig, HWE and Stille chemistry was successfully adopted (Scheme 17). de Lera and co-workers have also exhaustively examined applications of the Stille reaction for the synthesis of retinoid skeletons. They studied various disconnections and then developed optimized approaches for each strategy, providing useful information regarding the influence of steric factors on the Stille reaction, as well as useful retinoid building blocks.[61]

The first complete synthesis of a manumycin antibiotic was achieved by Taylor and co-workers with alisamycin **113** (Scheme 18).[62] Fundamental to this synthesis was the introduction of the unsaturated 2-amino-3-hydroxycyclopentenone forming the lower polyene chain. This moiety is present in many *Streptomyces* sp. metabolites, notably in many of the manumycin antibiotics. Taylor chose to insert this portion *via* the Stille reaction of 2-amino-3-hydroxycyclopentenone hydrohalides and vinylstannanes, thus treatment of known acyl chloride **102** with key amine hydrochloride **103** (prepared from cyclopentanedione) leads to vinyl bromide **104**. Higher vinylogues **107** and **109**, suitable for synthesizing the manumycins, can be prepared *via* HWE homologation of bromodienal **105**. Elaboration of the quinone **110** with the Corey-Wollenburg reagent[63] **111** gave a mixture of enantiomeric vinylstannanes; Stille coupling of these with bromodiene **107** led to alismaycin and *ent*-alisamycin. Taylor's group have successfully applied this strategy to a great number of the manumycin antibiotics and related polyene natural products.[64]

Like the Stille coupling reaction, the closely related Suzuki reaction[65] has found utility in polyene synthesis. Earlier work towards polyene synthesis was carried out by Suzuki and coworkers, who successfully applied the reaction to the stereoselective synthesis of triene-containing natural products,[66] and later to the synthesis of trisporol B.[67] The Suzuki reaction can operate under extremely mild conditions making it an ideal way to synthesize potentially unstable polyenes. An example of this has already been seen in the total synthesis of myxalamide A, in which the synthesis was completed *via* Suzuki coupling of **69** and **70**.[46] de Lera's group have also presented a detailed study of highly stereoselective retinoid syntheses achieved *via* the thallium-accelerated Suzuki reaction carried out under ambient temperatures. These mild conditions were chosen to be compatible with the known instability of vitamin A and its derivatives. Their approach illustrates the great flexibility offered by the palladium coupling reactions, in that the choice of which

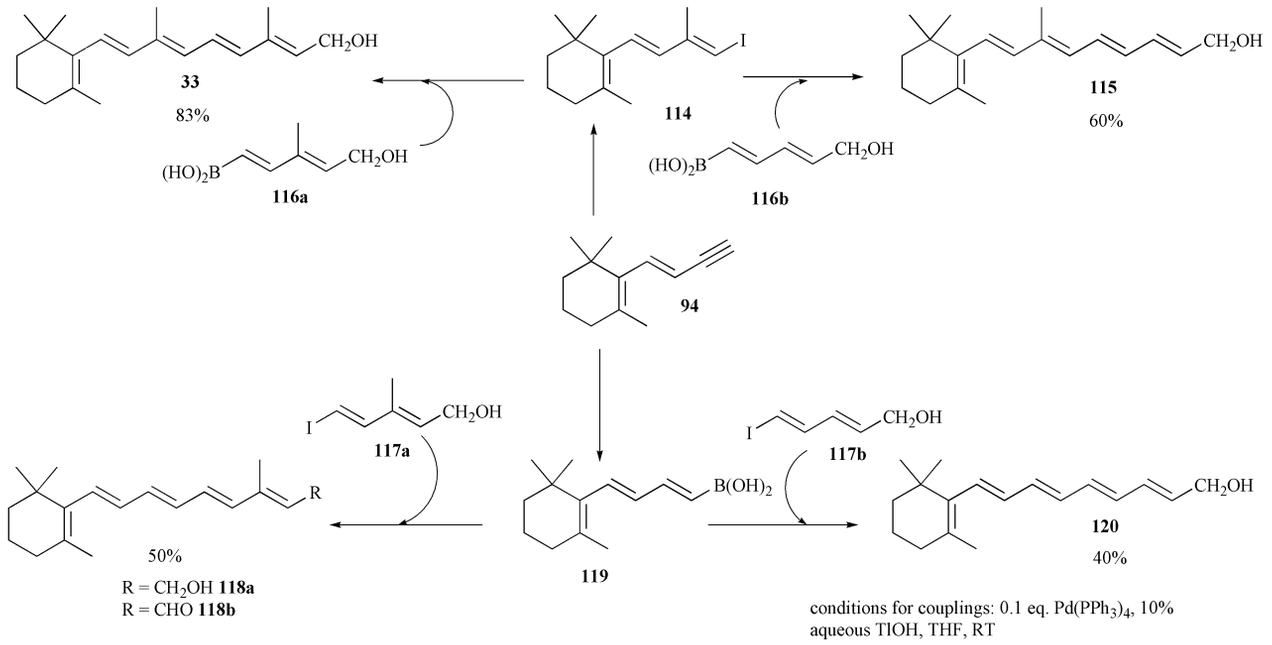


**Scheme 17**



**Scheme 18**

moiety to derive from the alkenyl iodide or alkenylboronic acid is dictated by relative ease of preparation. Preparation of retinol and its 9- and/or 11-desmethyl analogues (Scheme 19) was achieved through coupling of either boronic acids **116** with iodide **114** (also derived from enyne **94**), or with boronic acid **119** and iodides **117**, with total retention of the geometries of the coupling partners. The group have also used Suzuki chemistry for the stereocontrolled preparation of 9-desmethyl-retinoids, useful for bio-organic studies into protein–chromophore steric interactions involved in bacteriorhodopsin photocycles,[68] and more recently have applied Suzuki chemistry to the synthesis of 7-*cis*-retinoids.[69]

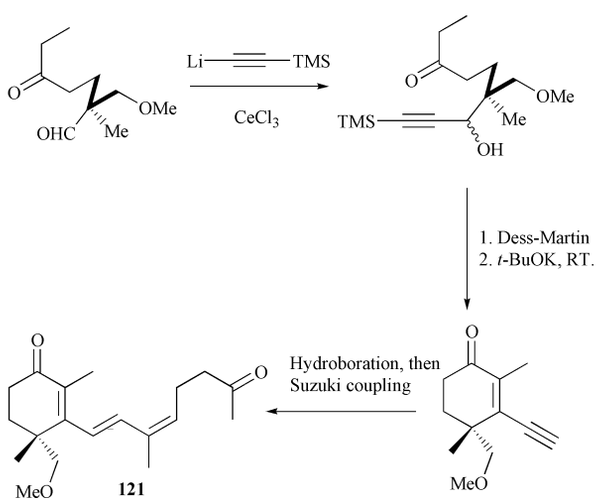



**Scheme 19**

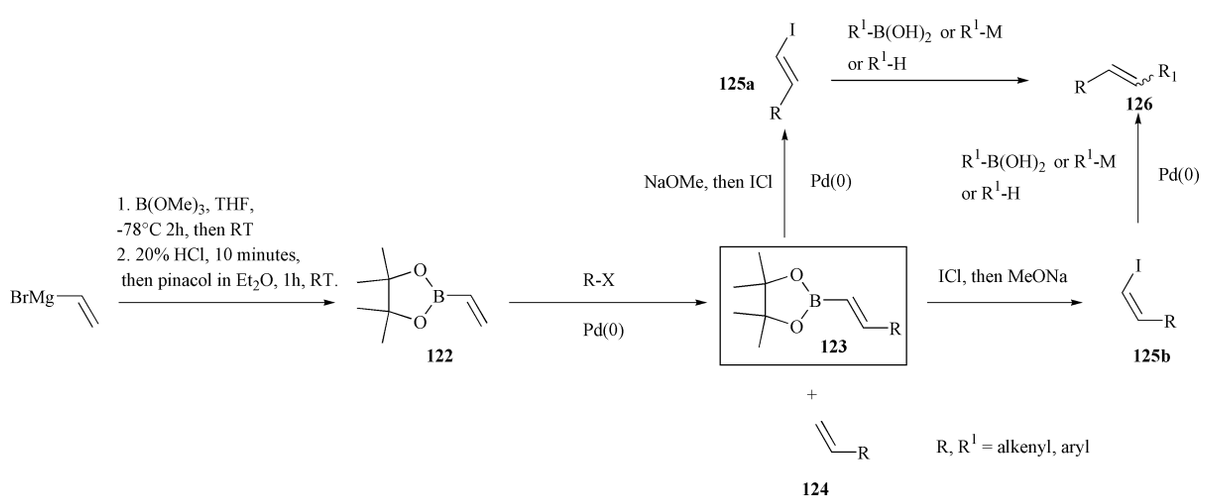
Several groups have been involved in applying Suzuki coupling methodology to leukotriene synthesis, including Sato and co-workers' method for the preparation of $LTB_3$ and $LTB_4$.[70] Using similar conditions, Nicolaou and co-workers have described the synthesis of a range of leukotriene $A_4$ derivatives.[71]

Reeder and Meyers have been involved in the preparation of trisporic acids, a class of $C_{18}$ isoprenoidal fungal hormones, utilizing Suzuki chemistry at a late stage to access the trisporol system (Scheme 20).[72]

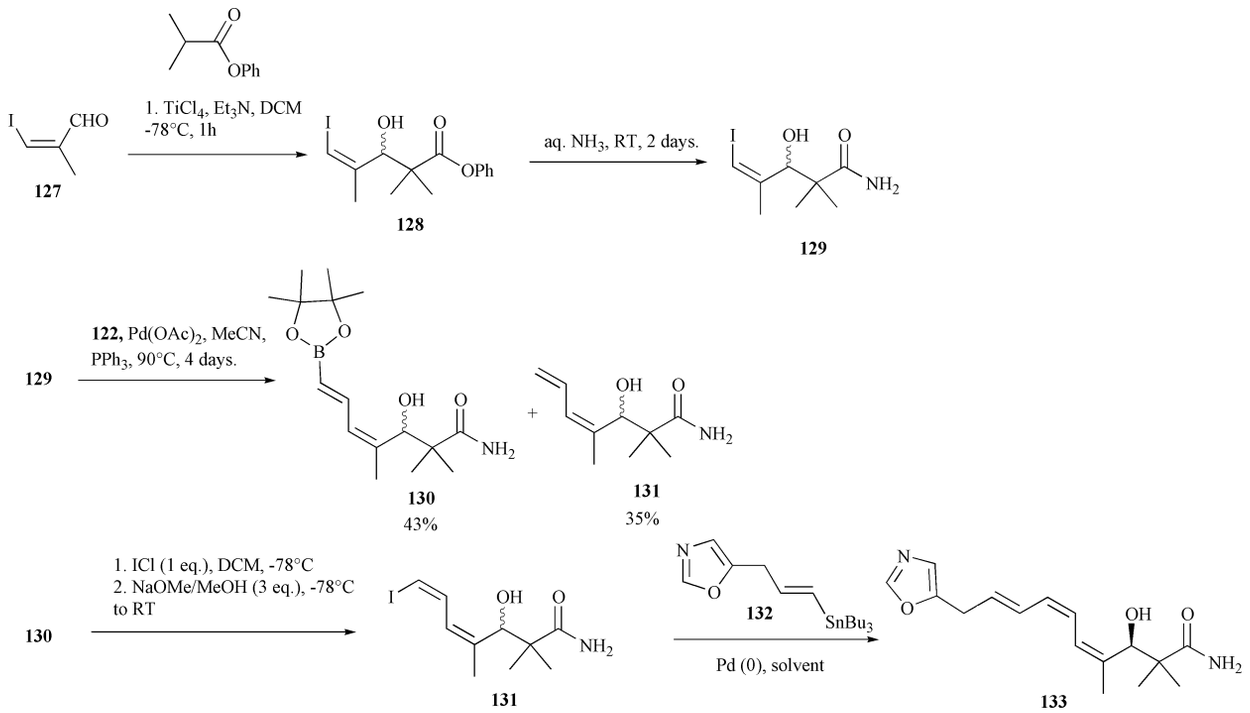
Recently, Hénaff and Whiting reported a highly stereoselective approach to racemic phthoxazolin A **133** using a combination of palladium coupling reactions.[73] Their approach employs the vinylboronate **122** as a useful two-carbon building block for the synthesis of polyenes (Scheme 21).[74] Thus, coupling of **122** with suitable halides leads potentially to Heck or Suzuki products **123** and **124**, the ratio of which is dictated by many factors, including catalyst, solvent, temperature and the presence of additives. Brown and co-workers showed that vinylboronic acids could provide a stereocontrolled route to vinyl iodides, using iodide and sodium hydroxide to effect iododeboronation.[75] The stereochemical course of the process is dictated by the order of addition of the reagents. Pinacol esters were found to be resistant to these conditions, requiring the use of ICl and sodium methoxide.[76] This provides access to vinyl iodides **125**, which may undergo coupling with alkenes or alkenyl metals, leading to dienes **126**. Subsequently, coupling of **126** with **122** leads to trienes if the iodo-deboronation procedure is repeated. Overall, **122** can be considered a vinyl dianion equivalent allowing rapid construction of stereodefined polyene




**Scheme 20**




**Scheme 21**




**Scheme 22**

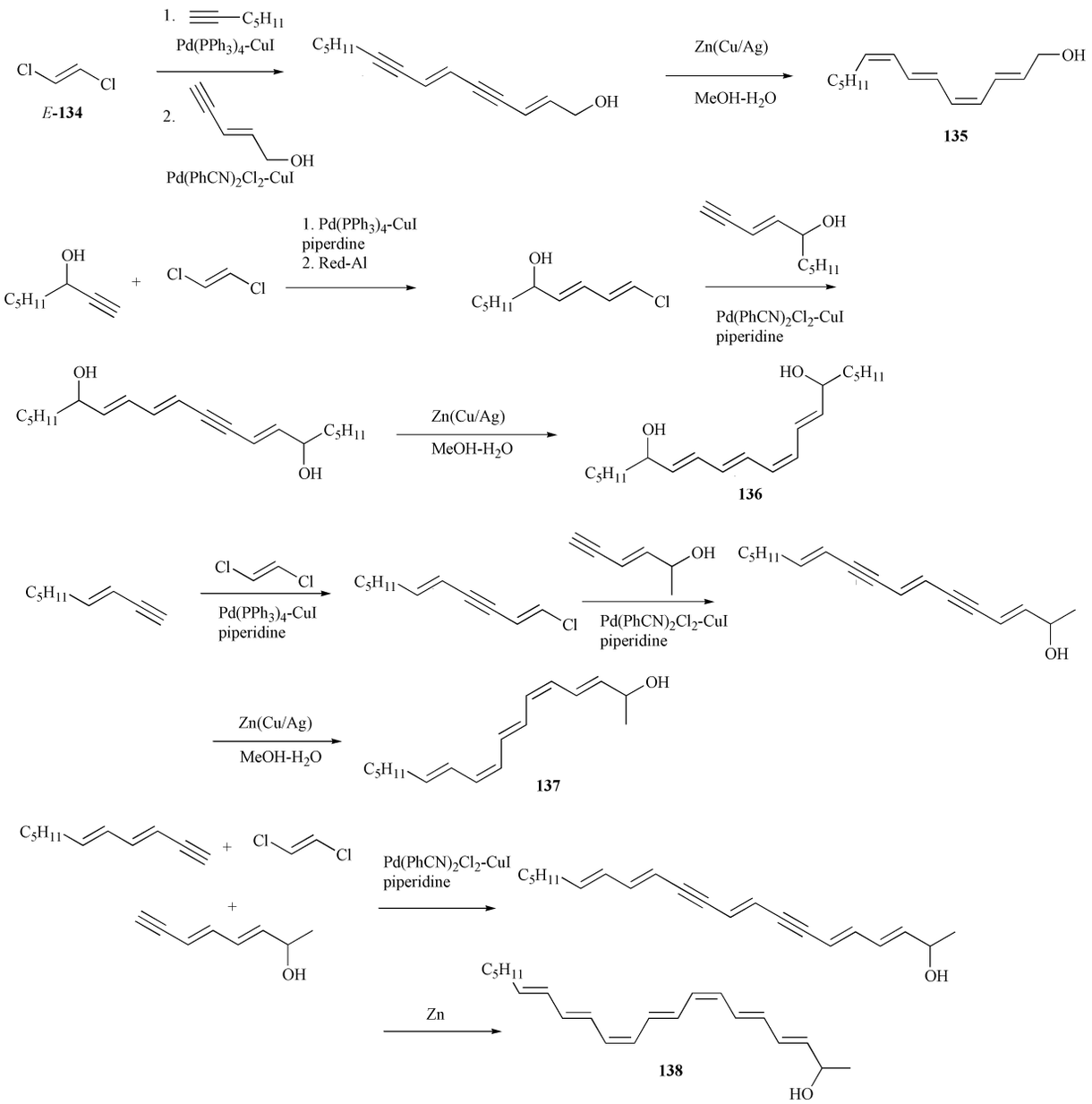
systems. Application of this methodology to the herbicidal agent phthoxazolin A is outlined in Scheme 22. Here, coupling of **122** and amide **129** (prepared from iodide **127** *via* an aldol reaction) demonstrates the functional group tolerance of these reactions, and gives the desired Heck product as the major product. Apart from this notable example, the Heck reaction, in its conventional guise, has found little utility in polyene synthesis. This is partially for the reason that, whilst the Stille reaction usually occurs with retention of stereochemical integrity of the coupling partners, the same cannot be said of the Heck reaction. Pattenden and co-workers recently compared the Heck and Stille reactions in his synthesis of pateamine A, a macrolide containing a (*Z*,*E*)-diene acrylate moiety in its macrocylic core, and found the Stille reaction superior for this very reason.[77]

In contrast, applications of the alkyne coupling variant of the Heck reaction towards polyene synthesis, the so-called Sonagashira coupling,[78] are numerous. Alami's group have devised techniques for the stereocontrolled synthesis of polyenes by sequential coupling of 1,2-dichloroethylenes **134** with a variety of acetylenes; selective reduction of the acetylene then leads to geometrically pure polyenes **135**–**138** (Scheme 23).[79] This methodology was applied to a short synthesis of lipoxin B **39** (Scheme 24). The same group have also developed a related protocol for accessing all-*E* polyenes. This protocol is based around α-chloro-ω-substituted hexatrienes **140**, obtained by two different approaches (Scheme 25). The first uses palladium catalyzed rearrangement of bis-allylic acetates, formed *via* bis-allylic alcohols **139**, whilst the second is based on the stereoselective reduction of homopropargylic alcohols **141** into (*E*)-homoallylic alcohols **142**, followed by elimination. Alcohols such as **142** may also be oxidized to give trienones and trienals, providing useful polyene building blocks having two reactive terminal functions, as the chlorine atom is able to participate in coupling reactions, with, for example, Grignard reagents, providing isomerically pure (*E,E,E*)-diarylhexatrienes **143**. The coupling partner may be acetylenic, as illustrated in a brief, high-yielding synthesis of navanone B **24**.[80]

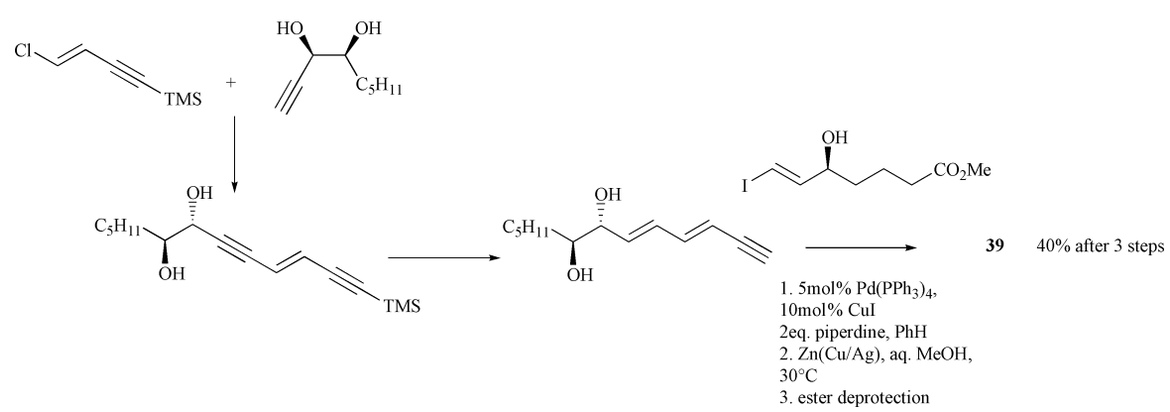
An obvious necessity for the palladium coupling reactions, when stereodefined polyenes are desired, is a stock of geometrically pure alkenyl halide or alkenylmetal. Many techniques giving access to these coupling partners have already been mentioned in this review.

Quintard and co-workers have done work on the regioselectivity of organotin cross-couplings, tuning the reaction conditions in order to obtain the requisite (*E,E*) dienyltin acetals **144** that may then be used to construct polyenic systems (Scheme 26).[81] Uenishi's group have examined the stereoselective hydrogenolysis of 1,1-dibromoalkenes, providing access to (*Z*)-1-bromoalkenes **145** that are useful for (*E,Z*)-diene synthesis.[82] Reduction of conjugated 1,1-dibromoalkenes affords 2-alkenyl or 2-alkynyl-substituted (*Z*)-1-bromo-1-alkenes **146**, useful synthons for polyene construction (Scheme 27). These may then undergo coupling with boronic acids, giving stereodefined trienes such as **148**; coupling with alkynes is also possible. The validity of this approach to polyene synthesis was demonstrated by the synthesis of the unstable polyenes (11*Z*)-retinal and (2*Z*,4*E*,6*E*)-dehydrodendrolasin. The same group has also reported the nickel catalysed coupling of bromoalkenes **147** with Grignard reagents, giving potentially useful allylsilanes **150** when TMS-substituted Grignard reagents are employed, or alkylated 1,3-dienes *e.g.* **149** (Scheme 27).[83] Lipshutz and Lindsley have reported two highly specialized building blocks for the preparation of polyene systems. The first, stannylated dienyne **153**, is readily prepared through reaction of enal **151** with known Wittig salt **152** (Scheme 28). Dienyne **153** undergoes cross-coupling at the vinylstannane end with a variety of halides under different conditions, producing trienyne or tetraenyne products (Table 4).[84]

Elaboration of the alkyne terminus of these products may be carried out either through initial hydrozirconation, transmetallation with aluminium, and trapping of the alane with a suitable electrophile, or *via* direct Negishi carboalumination followed by quenching. Both processes give rapid access to a variety of all-(*E*)-polyenes (Table 5). A synthesis of navenone B **24** is a noteworthy example. The method has further applications to natural products, for instance, preparation of the oxopentaene **156** common to the mycoticins **154** and **155** (Scheme 29). Access to vinylogues of retinoic acid is also possible. Their redesigned trienyne (Scheme 30) **157** incorporates an inversion of polarity relative to **153** due to replacement of the stannyl diene moiety by vinylic bromide. **157** can thus undergo coupling with vinyl and dienylzinc reagents (Table 6). Elaboration of the alkyne terminus in the usual manner, either prior to, or after an initial coupling at the vinyl bromide



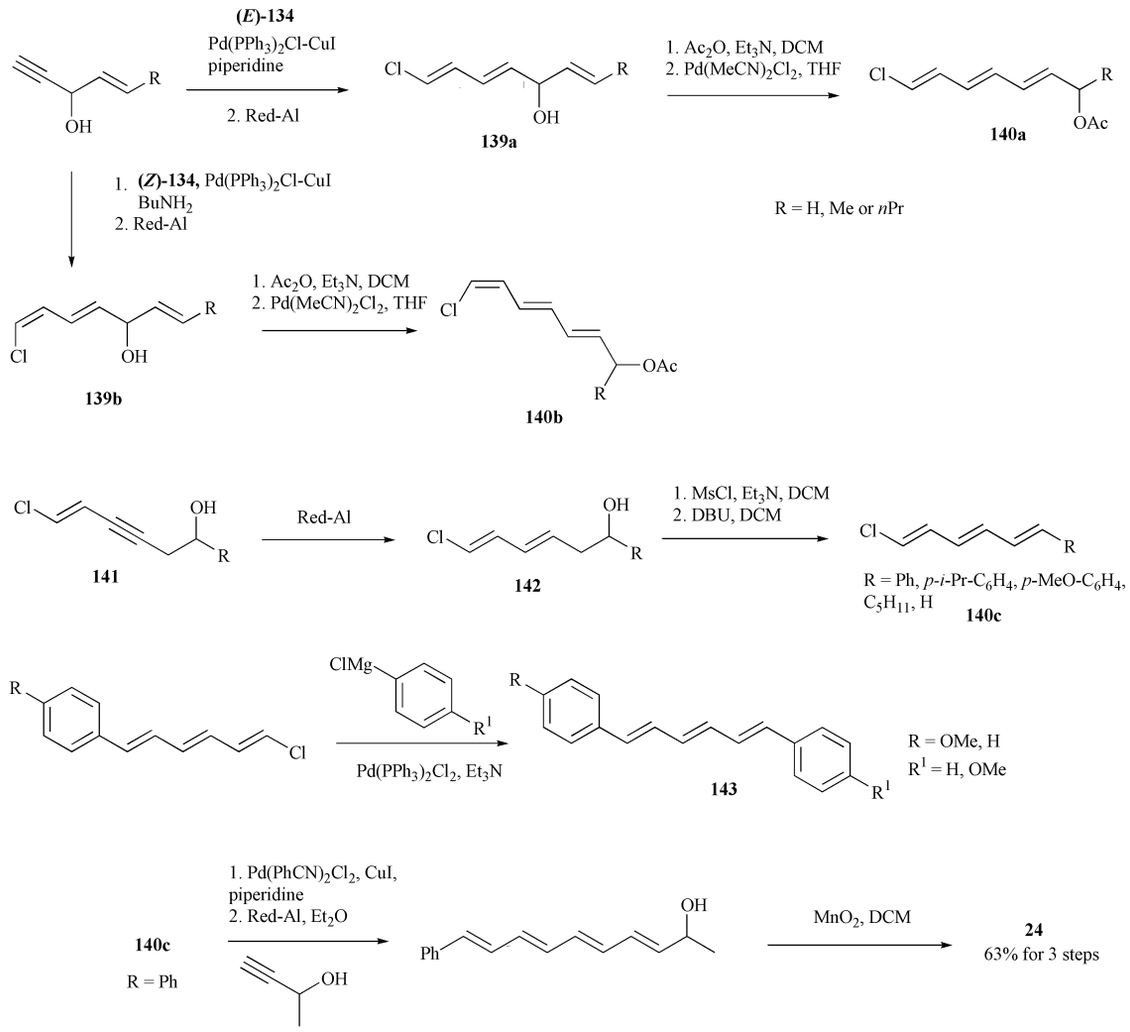

**Scheme 23**



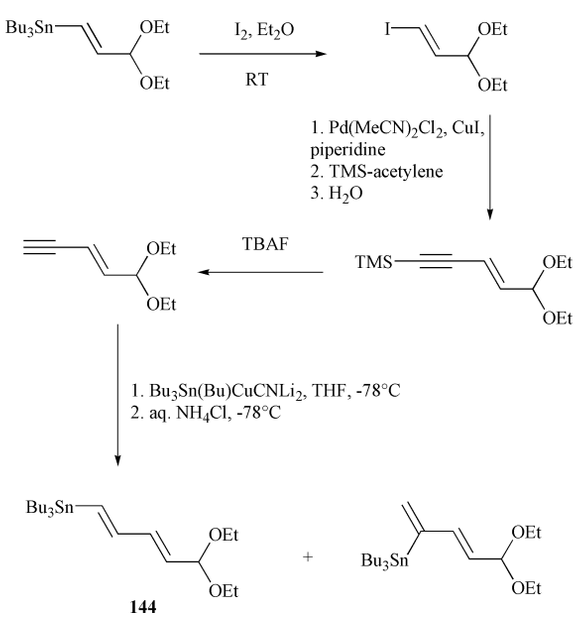

**Scheme 24**

terminus, leads to oxopolyenes, and this approach was applied to a short synthesis of the oxohexaene **159**, common to the dermostatins, of which dermostatin A **160** may be taken as a typical member (Scheme 31).[85]

Zeng and Negishi have formulated a highly efficient and stereoselective procedure for the preparation of both symmetrical and unsymmetrical carotenoids. This procedure is based upon Zr-catalyzed carboalumination of conjugated oligoenynes followed by palladium and zinc catalyzed cross-coupling of the resultant alkenylalanes and allows ready access to members of the retinoid family. The procedure utilizes the two and four carbon synthons **162** and **163** respectively.




**Scheme 25**



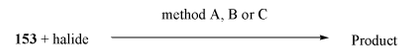

**Scheme 26**

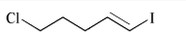
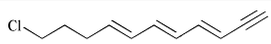
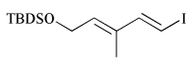
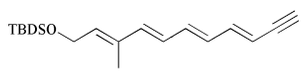
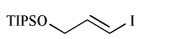
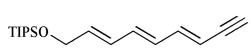
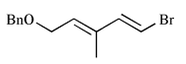
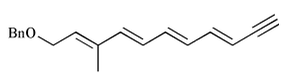
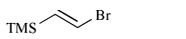
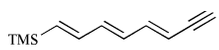
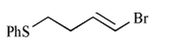
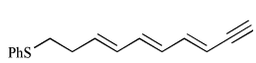
Accordingly, dihaloalkene **162** is readily converted to **163**; with these in hand the authors were able to prepare a variety of carotenoids *e.g.* β-carotene **165** was prepared in 41% overall yield in three linear steps from **94**. In a similar fashion γ-carotene **17** and vitamin A **33** were prepared in good yields (Scheme 32). It is noteworthy that in all cases, ≥99% stereoselectivity towards the drawn isomer was observed, leading to ≥99% isomerically pure polyenes.[86]

Wipf's group have prepared members of the manumycin family, using organozirconocene methodology to build the polyene sections.[87] This approach involves hydrozirconation of a functionalized alkyne *e.g.* **170**, followed by transmetallation with zinc, and *in situ* 1,2-addition of the organozinc reagent to α,β-unsaturated aldehydes. The approach is convergent and can be used to synthesize dienyl and trienyl side chains common to the manumycins, and facilitates analogue preparation. Scheme 33 exemplifies this protocol through the synthesis of the eastern side chain of asukamycin **171** and southern side-chain of nisamycin **172**.

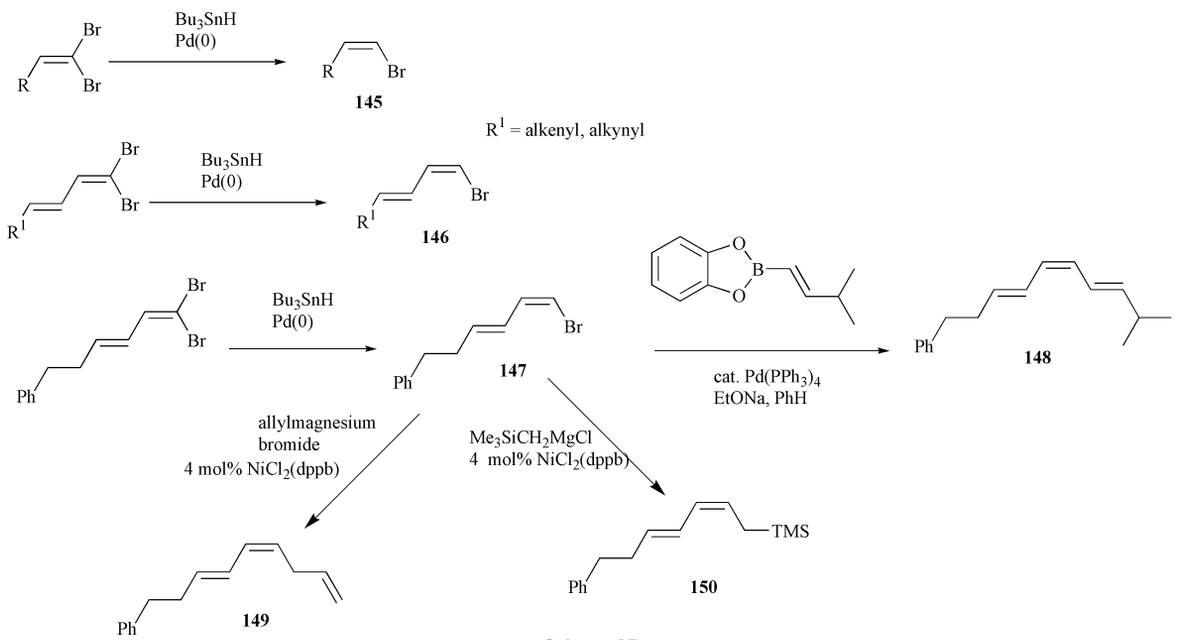
Two recent applications of organoiron methodology towards polyene synthesis have been disclosed (Scheme 34). The first, aimed at stereoselective retinoid synthesis, uses a Peterson reaction between (β-ionylideneacetaldehyde)tricarbonyliron complex **173** and a range of trimethylsilyl derivatives to access retinoid precursors **174**–**177**. Iron complex **175** was subsequently transformed into 11*Z*-retinal **37** by conventional means.[88] The second application employs stoichiometric acyclic dienyl iron complexes. Accordingly, macrolactin A **178** was disconnected into fragments **179** and **181**, with a view to joining them together *via* nitrile oxide–olefin cycloaddition methodology. The (*E*,*Z*)-diene segment of **179** was prepared through addition of the strongly nucleophilic lithium anion of 2-(trimethylsilyl)ethylnitroacetate to the isolable *cisoid* cation **180**, giving an initial mixture of diastereomers that rearranges completely to the (*E*,*Z*) complex upon standing in chloroform.[89]

**Table 4**

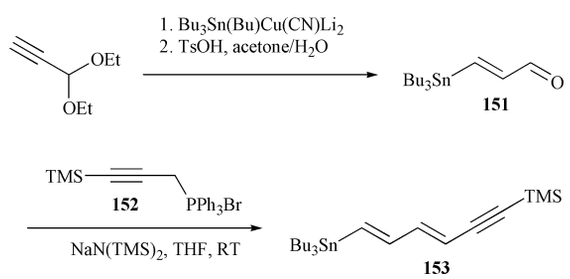



| Halide | Method | Product | Yield (%) |
|---|---|---|---|
|  | A |  | 83 |
|  | A |  | 74 |
|  | A |  | 80 |
|  | A |  | 82 |
|  | B |  | 72 |
|  | C |  | 91 |

Method A: i). BuLi, THF, −78 °C; ii). $ZnCl_2$, 0 °C; iii). $Pd(PPh_3)_4$; iv). $K_2CO_3$, EtOH. Method B: i). 1.5 eq. CuCN, $Pd_2(dba)_3$, $AsPh_3$, NMP, 50 °C; ii). $K_2CO_3$, EtOH. Method C: i). 1.5 eq. CuCN, $Pd_2(dba)_3$, $P(Fur)_3$, NMP, 50 °C; ii). $K_2CO_3$, EtOH.




**Scheme 27**




**Scheme 28**

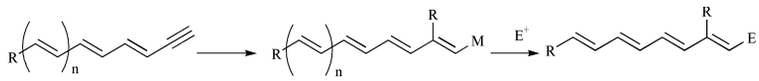
## 2.3 Miscellaneous methods

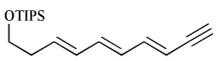
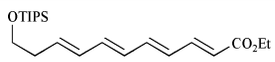
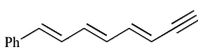
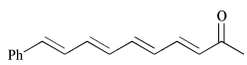
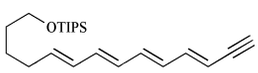
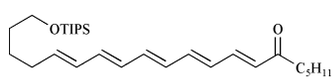
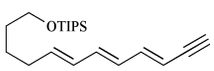
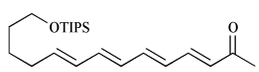
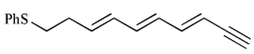
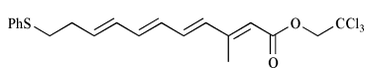
Several new methodologies have emerged recently for the preparation of polyenes. Naso and co-workers have successfully used bis(trimethylsilyl) derivatives to construct a variety of natural products, including the potent leukotriene $B_3$ methyl ester **186** (Scheme 35). Chemoselective acylation of bis(TMS) enyne **182** followed by enantioselective chemical reduction and catalytic hydrogenation of the triple bond leads to *E*,*Z*-diene **183** which is transformed into bromodiene **184**. A similar sequence applied to bis(TMS) acetylene gives **185** which undergoes hydroboration with catecholborane to generate a vinylic boronic ester *in situ*; Suzuki–Miyaura coupling of this with **184** affords, after deprotection, **186** in 41% yield.[90]

In a comparative study of several methods of polyene synthesis, including HWE strategies, an iterative strategy based upon the Wollenburg reagent **187**[91] was found to be superior for the synthesis of the hexaene section of amphotericin B **4** (Scheme 36).[92] This reagent is readily prepared and undergoes transmetallation to give either the lithiated species **188**, or Grignard-type reagents such as **191**, used recently by Rychnovsky's group to install four of the five double bonds of Filipin III **190** (Scheme 36).[93]

Solladié's group have enjoyed much success using reductive elimination as a means of synthesizing polyenes in a stereoselective manner. Their strategy was recently exemplified by the first enantioselective synthesis of the alarm phermomone haminol-1 **192** (Scheme 37). Diyne **194**, obtained through condensation of diacetylene with the appropriate aldehydes, yields the precursor dibenzoate diene **193** under standard conditions, with **192** attained as a single isomer following the reductive elimination step.[94]

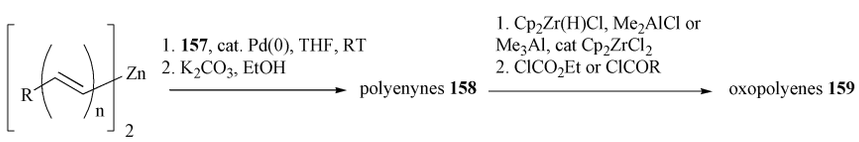
**Table 5**

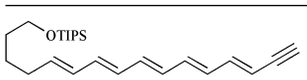
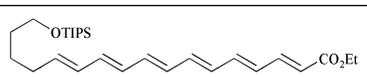
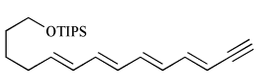
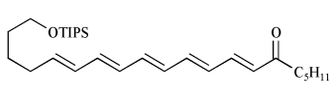
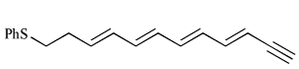
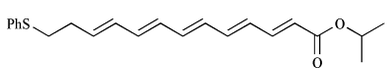
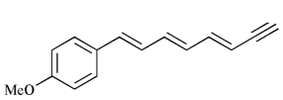
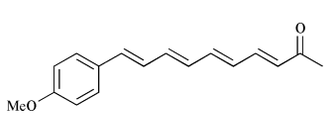
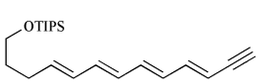
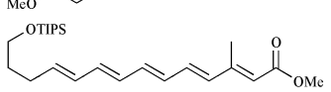


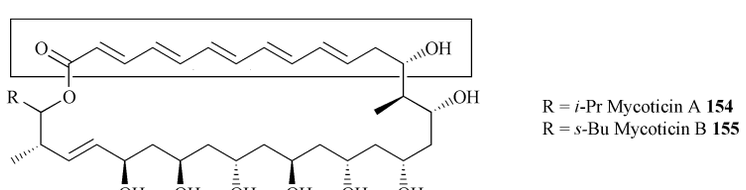
| Substrate[a] | Yield (%) | Metallation/electrophile | Product | Yield (%) |
|---|---|---|---|---|
|  | 70-A | $Cp_2Zr(H)Cl$, DCM, $Me_2AlCl$, 0 °C, $ClCO_2Et$ |  | 71 |
|  | 73-A | $Cp_2Zr(H)Cl$, DCM, $Me_2AlCl$, 0 °C, ClCOMe |  | 82 |
|  | 74-A | $Cp_2Zr(H)Cl$, DCM, $Me_2AlCl$, 0 °C, $C_5H_{11}COCl$ |  | 80 |
|  | 75-A | $Cp_2Zr(H)Cl$, DCM, $Me_2AlCl$, 0 °C, ClCOMe |  | 83 |
|  | 91-B | $Me_3Al$, $Cp_2Zr(H)Cl$, $ClCH_2CH_2Cl$, $ClCO_2CH_2CCl_3$ |  | 73 |

[a] Prepared from **153** and the corresponding vinyl halide by methods A or B, *cf.* Table 4

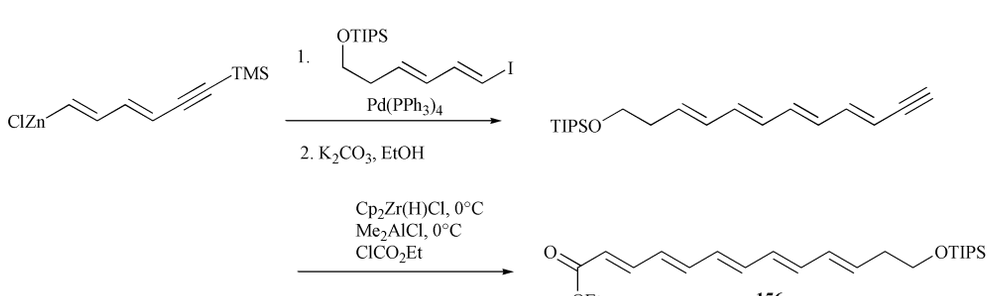
**Table 6**



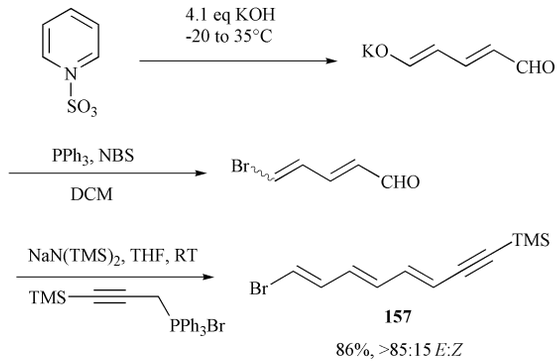
| Polyenyne **158** (from **157**) | Yield (%) | Metallation/electrophile | Oxopolyene **159** (from **158**) | Yield (%) |
|---|---|---|---|---|
|  | 78 | $Cp_2Zr(H)Cl$<br>$Me_2AlCl$<br>$ClCO_2Et$ |  | 68 |
|  | 73 | $Cp_2Zr(H)Cl$<br>$Me_2AlCl$<br>$ClCO_2Et$ |  | 73 |
|  | 80 | cat. $Cp_2Zr_2Cl$<br>$Me_3Al$<br>$ClCO_2$-*i*-Bu |  | 75 |
|  | 85 | $Cp_2Zr(H)Cl$<br>$Me_2AlCl$<br>ClCOMe |  | 70 |
|  | 73 | cat. $Cp_2ZrCl_2$<br>$Me_3Al$<br>$ClCO_2Me$ |  | 74 |



R = *i*-Pr Mycoticin A **154**
R = *s*-Bu Mycoticin B **155**



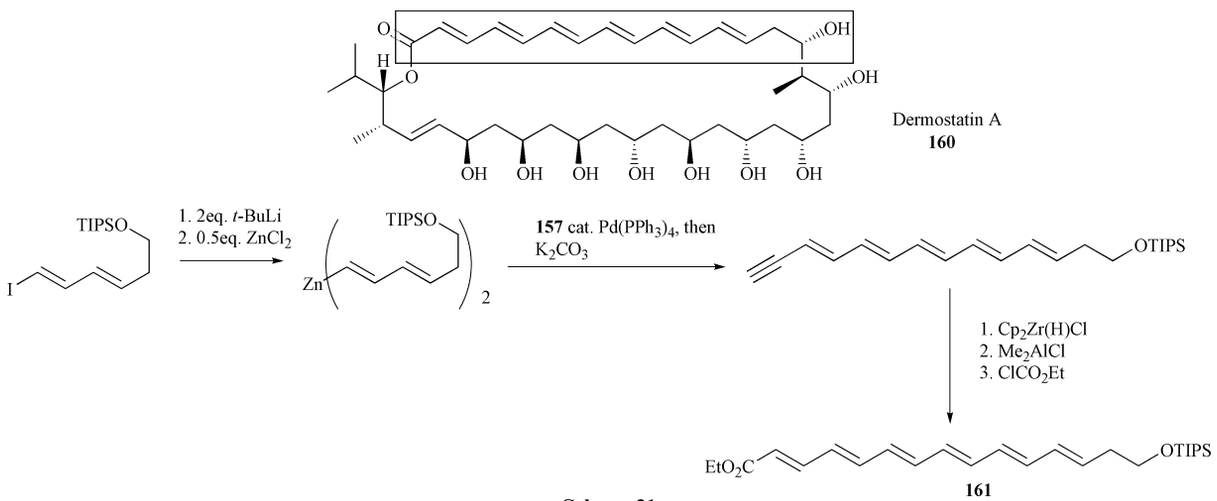
**Scheme 29**



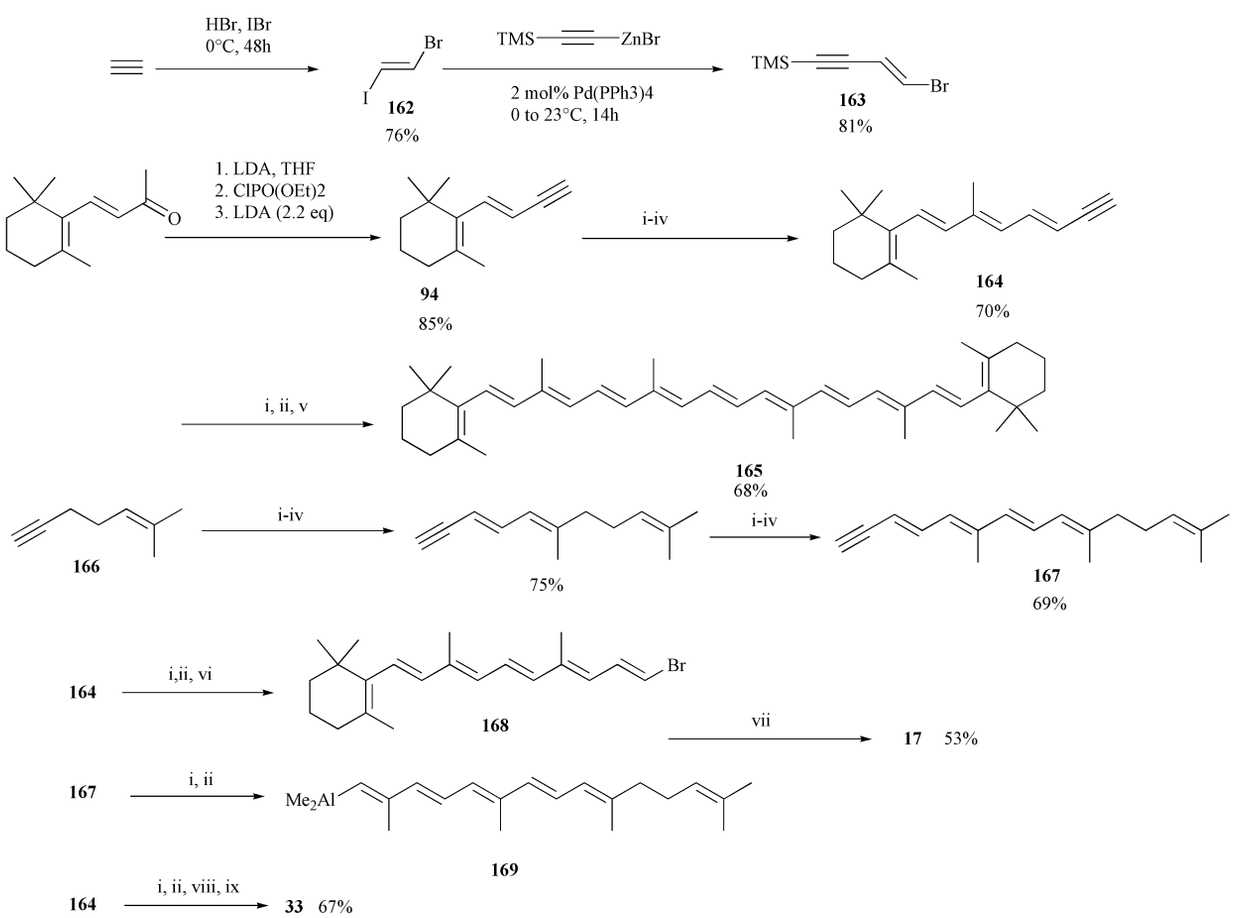

**Scheme 30**

A pericyclic approach to the 9-*cis*-retinoids was recently put forward by de Lera and co-workers (Scheme 38). A domino sequence, involving a reversible [2,3]-allyl sulfenate to allyl sulfoxide rearrangement (**196**–**197**), followed by propargylic sulfenate to vinylallenyl sulfoxide rearrangment (**199**–**200**), and finally, an irreversible, doubly stereoselective [1,5]-hydrogen shift to give **201**. Desulfuration and deprotection afford 9-*cis*-retinoids **36** and **203** (Scheme 38).[95]

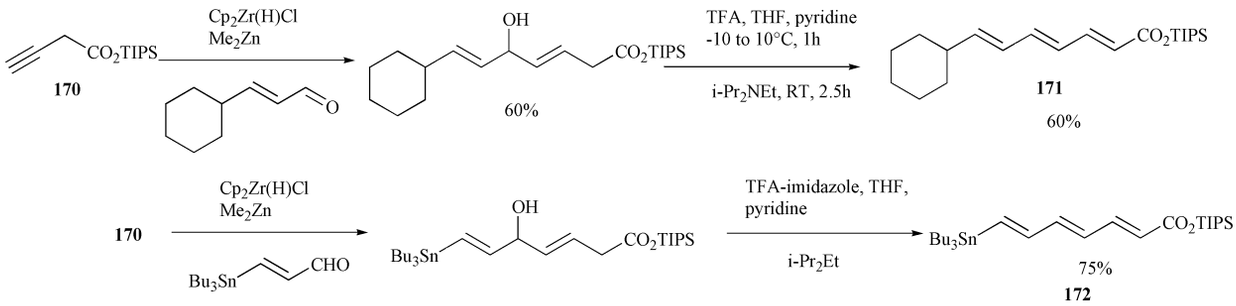
Taylor's group have used pyrylium salts to effect polyene synthesis; treatment of pyrylium tetrafluoroborate **204** with suitable organometallics allows access to a variety of retinoids, including the novel dehydro-demethyl-retinoid **206** (Scheme 39).[96]



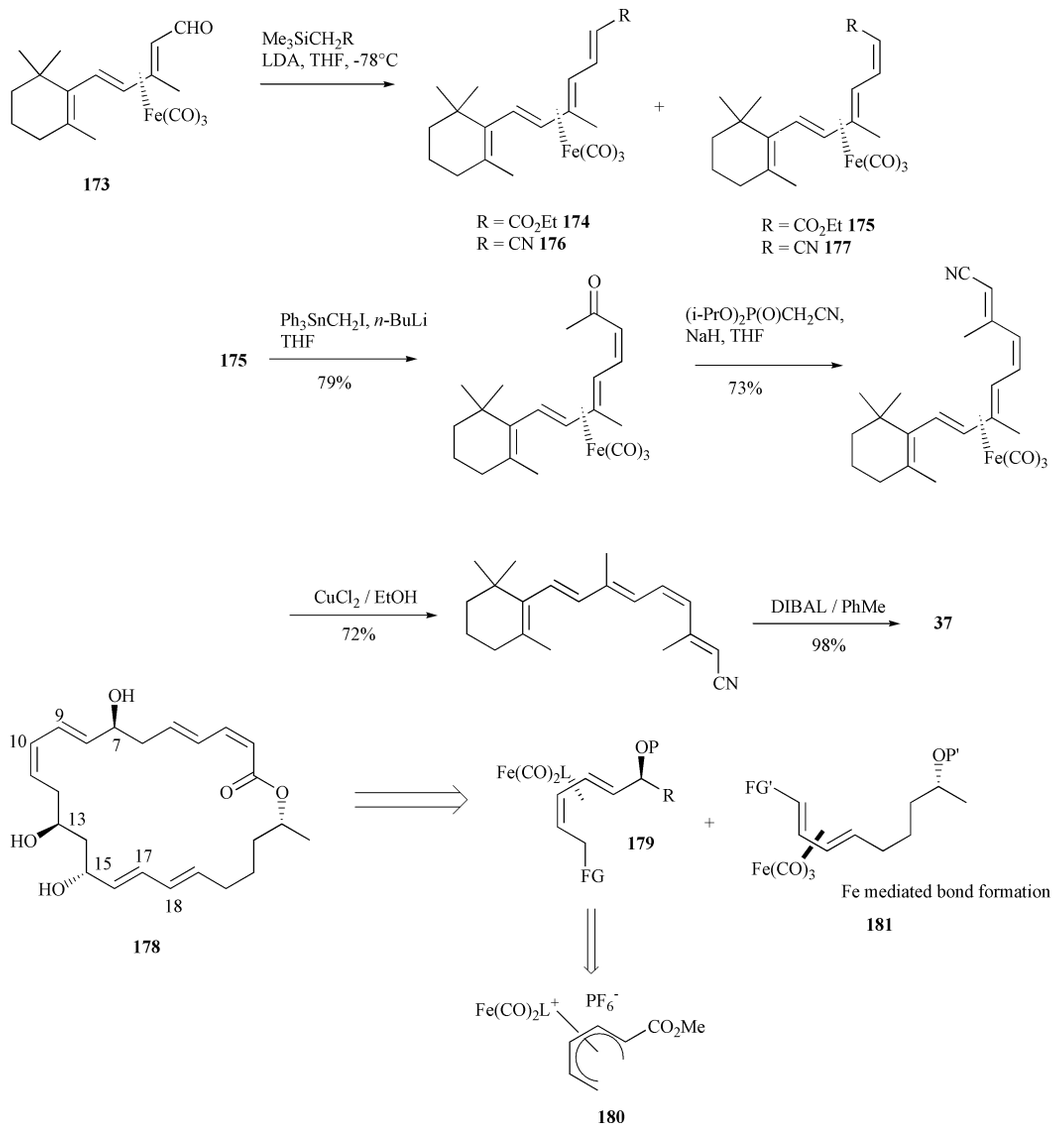

**Scheme 31**




**Scheme 32** *Conditions*: i. $Me_3Al$ (2 eq.), $Cp_2ZrCl_2$ (1 eq.) $(CH_2Cl)_2$, 23 °C, 4 h; ii. evaporation at 50 °C and <0.5 mmHg; iii. **163** (1.05 eq.), $ZnCl_2$ (1 eq.) in THF, 2.5 mol% $Pd_2(dba)_3$, 10 mol% P(Fur)$_3$, DMF, 23 °C, 6 h; iv. $K_2CO_3$, MeOH, 23 °C, 3 h; v. **162** (0.5 eq.), $ZnCl_2$ (1 eq.) in THF, 2.5 mol% $Pd_2(dba)_3$, 10 mol% P(Fur)$_3$, DMF, 23 °C, 8 h; vi. **162** (1.05 eq.), $ZnBr_2$ (1 eq.) in THF, 5 mol% $Pd(PPh_3)_4$, DMF, 23 °C, 2 h; vii. $ZnCl_2$ (1 eq.) in THF, 2.5 mol% $Pd_2(dba)_3$, 10 mol% P(Fur)$_3$, DMF, 23 °C, 6 h; viii. THF, *n*-BuLi (1 eq.), 23 °C, 0.5 h; ix. $(CH_2O)_n$, 23 °C, 5 h. Fur = 2-furyl.



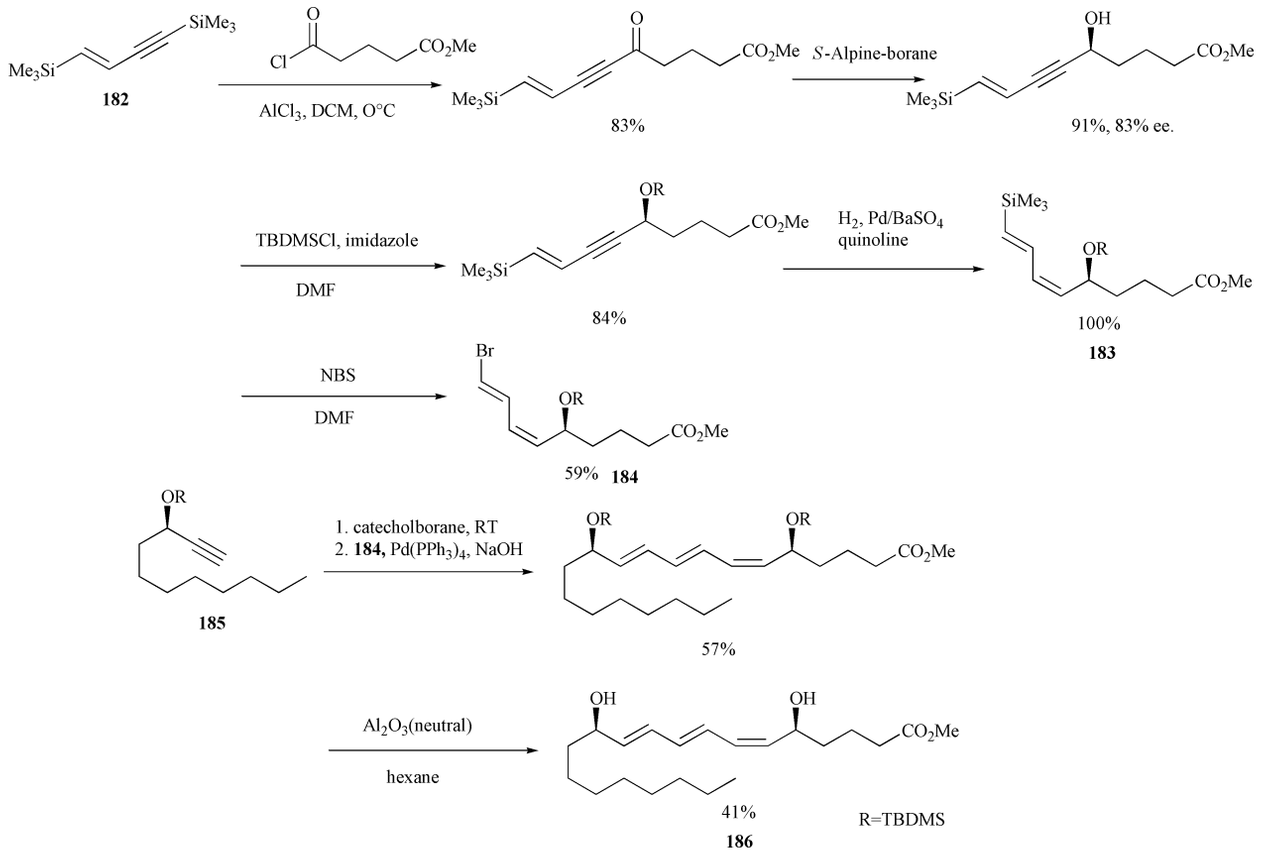

**Scheme 33**



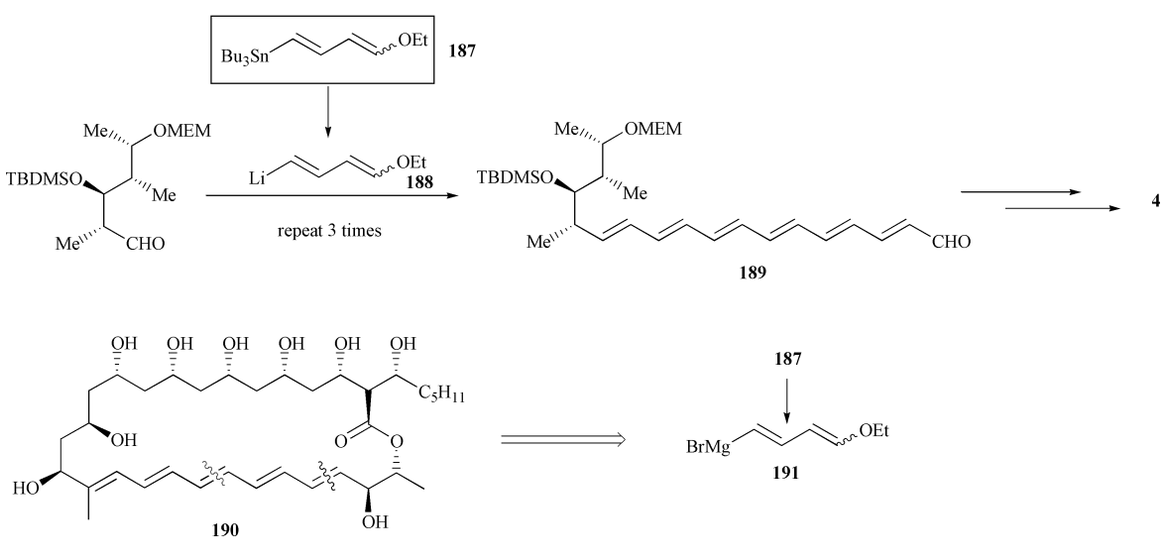

**Scheme 34**

## 3 Conclusion

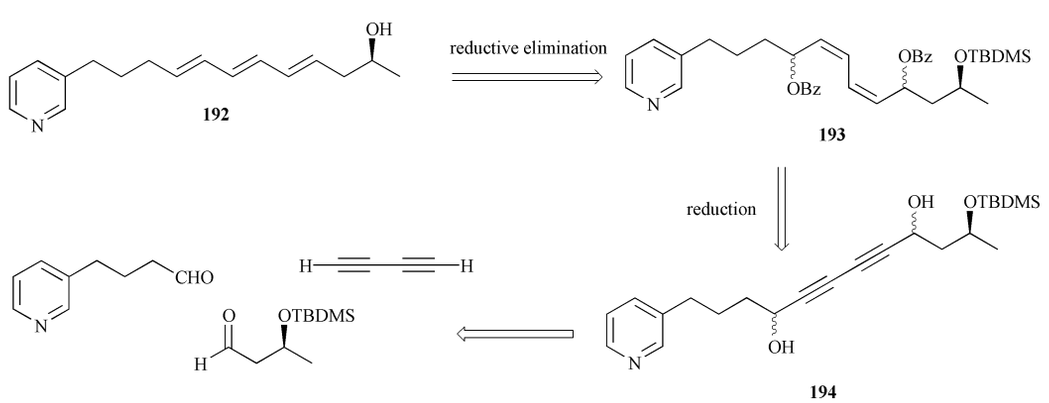
As can be seen from this review, much progress has been made in the area of polyene natural product synthesis over the last 30 or so years, and new methodology is constantly emerging. However, the ability to reliably construct polyenes with absolute control over alkene geometry, particularly for those systems possessing *cis*-alkenyl units, remains an elusive goal. The increasing usage of polyene natural products in medicine, as drugs and as biological probes, as well as the general interest in polyenes for other applications, *e.g.* non-linear optics, should serve to fuel the continuing interest in this area, and help to achieve this goal.



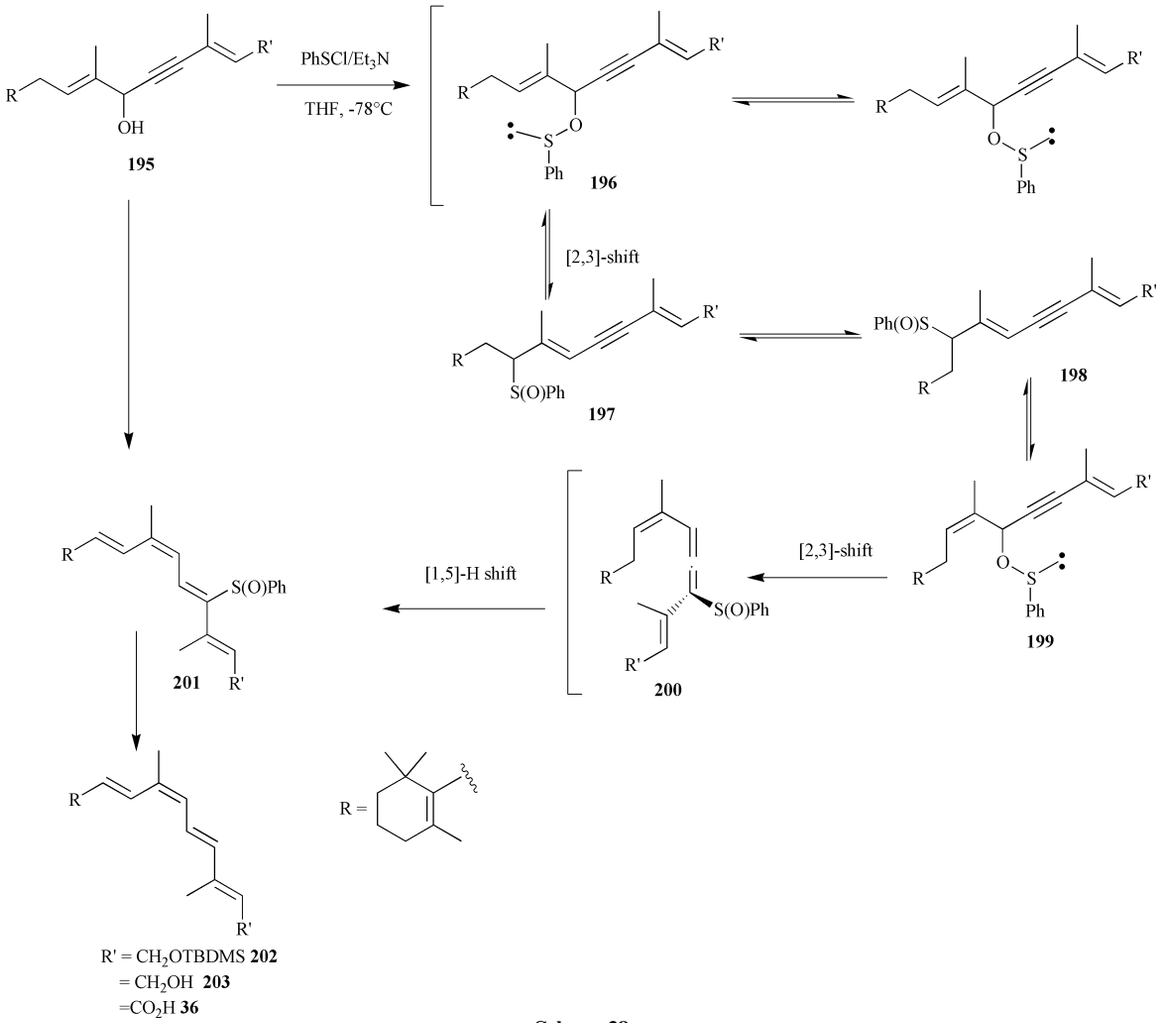

**Scheme 35**



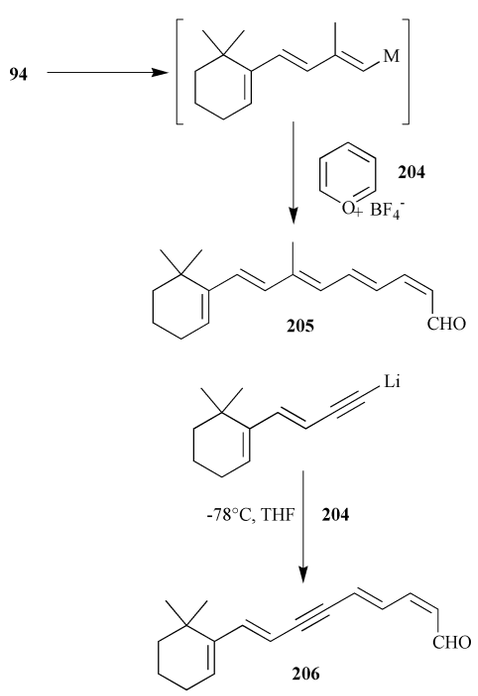

**Scheme 36**




**Scheme 37**




**Scheme 38**




**Scheme 39**

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