Non-isoprenoid Polyene Natural Products - Structures and Synthetic Strategies

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This review provides insight into the variety of structures and biological activities found in the non-isoprenoid family of polyene natural products and examines the strategies and synthetic methods applied for the polyenic components in particular by way of examples.

Introduction

The term ‘polyene natural product’ encompasses a large group of compounds with a variety of interesting structures and properties. Of particular interest are those natural products which display biological activity. Whilst a large number of polyenes have been discovered, with over 200 polyenes in the polyene macrolide class alone, they still present a considerable challenge in terms of total synthesis. The construction of longer conjugated polyenes presents a number of obstacles in terms of stereoselectivity, reactivity and product stability. Those natural products containing all-trans polyene moieties tend to be more stable, whilst those containing all-cis olefins, or a mixture of cis and trans double bonds are much more prone to isomerisation and therefore present a greater challenge in terms of their synthesis. Polyenes can be unstable to light and heat, and strongly acidic or basic conditions, often resulting in a need for mild reaction conditions. The traditional method of double bond formation has more generally been achieved using ylide-based Wittig chemistry, with the Horner-Wadsworth Emmons (HWE) employing the mildest conditions. Reasonable levels of stereoselective control are well established within ylide chemistry. There is, though, a need to either separate or subject stereoisomers to isomerisation conditions. With the ever expanding scope of palladium cross coupling chemistry, it has become possible to assemble highly complex conjugated systems with high efficiency and stereoselectivity. In addition, olefin cross metathesis has been used more recently in polyene construction. An interesting question is whether transition metal-based strategies are beginning to take over as the method of choice for polyene construction. This review aims to provide an insight into some of the non-isoprenoid polyene structures discovered to date, and highlight attempts to complete their total synthesis. These non-isoprenoid polyene natural products will be discussed in classes determined by the length of the polyene moieties, with the total synthesis of at least one example in each class discussed in detail. Particular focus is given to the construction of the polyene chains within these natural products, and the strategies and synthetic methods which have been employed to make them. As the class of triene non-isoprenoid natural products is quite large, reasonably simple to construct, and provides enough scope for a review in its own right, this review will begin its focus from tetraene-containing natural products and longer.

Tetraenes

There are a large number of compounds containing the tetraene moiet. These have been isolated from a wide variety of natural sources and display a number of different types of biological activity.

Macroyclic tetraenes

Polyene macrolide structures are often strongly associated with antifungal activity. There are a large number of tetraene polyene macrolides, produced by many different organisms, but often with very similar structures. Some important tetraene polyene macrolides are discussed below and all share common features. The macrocycles are bicyclic, with a larger ring of varied size and a six-membered cyclic ether. In addition, they also all possess an oxygen-linked cyclic six-membered ether substituent, the structure of which is highly conserved. Seven tetraene natural products share the same general structure. One difference, however, is the nature of the amine. Lucensomycin I, otherwise known as etruscomycin, is produced by S. lucensis and contains an epoxide. Arenomycin B 2 is produced by A. tumemacerans var. griseoarencicolor. The family of tetrins A-C have similar structures, with tetrin A 3 and B 4 produced by Streptomyces sp. 8,9 and tetrin C 5 produced by Streptomyces sp. GK9244.10 Tetromycin A 6 and B 7 are both produced by S. noursei var. jenensis.11 Similar structures to these tetraenes include pimarcin 8, AB-400 9, rimodocin 10.
Pimaricin 8, otherwise known as natamycin, is a polyene macrolide produced by S. natalensis, S. chattanoogensis and S. gilveosporus and is used as a natural preservative in the food industry. It is also used as a treatment for fungal keratitis, as well as cutaneous, vaginal and intestinal cancer and antimalarial activity. AB-400 9 is a closely related analogue, produced by Streptomyces sp. RGU5. Rimocidin 10 and rimocidin B 11 and C 12 are all produced by S. diastaticus, and rimocidin is also produced by S. rimosus. CE-108 A 13, B 14 and C 15 are all produced by S. diastaticus var. 108. Larger macrocycles with similar structures include amphotericin A 16 and nystatin 17. Amphotericin A 16 is produced by S. nodosus. Nyastatin 17 is produced by S. noursei and displays broad spectrum antifungal activity and possesses antimalarial activity.

Common to all of the macrocycles above is the all-E configuration of the polyene moieties. Other macrocyclic polyenes are viridenomycin 18 and the marinomycins A-C 19-21, whose total syntheses will be discussed in due course and whose structures are very different to those discussed above.

**Linear tetraenes**

There are a number of linear tetraene natural products and these include fumigillin 22 and lajollamycin 23. These structures share far fewer similarities than those discussed in the macrocyclic tetraenes section above. Fumigillin 22 is produced by Aspergillus fumigans and displays amebicidal, anticancer, antiparasitic and antibacterial properties. It is also an angiogenesis inhibitor. Its structure contains an all E-tetraene and a highly functionalised cyclohexane ring, as well as two epoxide rings. Lajollamycin 23 is produced by Streptomyces nodosus and displays antimicrobial and antitumour activities.
Its structure contains an $E:E:Z:Z$-tetraene, an amide linkage and a conjoined lactam and lactone.

Viridenomycin

Viridenomycin 18 was first reported as a polyene natural product in 1975 by Hasegawa et al., who isolated it from S. viridochromogenes. This compound was shown to have activity against Trichomonas vaginalis and Gram-positive bacteria.\textsuperscript{23} In 1991, a compound was also reported to be isolated from S. gannmycicus and was shown to be identical to 18. The absolute stereochemistry of the compound was not determined, with only the relative stereochemistry of the cyclopentene core known and the relative stereochemistry between the core and benzylic stereocentre.\textsuperscript{24} This macrocycle also contains two tetraenes, one with an $E:E:E:E$-configuration and the other being $E:E:Z:Z$. The macrocycle also contains a functionalised cyclopentene ring and is connected together by a lactam and enol ester. Shortly after, 18 was shown to have anticancer properties, prolonging the lives of mice affected by B16 melanoma and P388 leukaemia.\textsuperscript{25} Two groups have published work pertaining to the synthesis of the polyene portions of viridenomycin 18. Kruger and Meyers attempted two routes,\textsuperscript{24,25} with their disconnection of the macrocycle giving three fragments 24-26 (Scheme 1). The intention was to install the lower ($E:E:E:E$)-tetraene using a Julia olefination and the upper ($E:E:Z:Z$)-tetraene by a palladium catalysed cross coupling and subsequent alkyne reduction. Diene 30 was synthesised successfully using the Stork-Zhao Wittig homologation and then a Stille coupling. The aryl sulfonate was then successfully installed to give 31, ready for an olefination reaction to give the lower tetraene (Scheme 2).

Scheme 1. Kruger and Meyers disconnection of 18

Scheme 2. Synthesis of sulfonate 31
Attempts to build the tetraene using a Julia olefination proved unsuccessful in a closely related model system. This route was put on hold and another investigated. The new route involved construction of the lower tetraene using either Wittig or Horner-Emmons chemistry. Another change was made in the formation of the upper tetraene, where the previously designed alkyne incorporation and reduction was causing concern. Instead, the intention was to undertake direct tetraene formation using a Stille coupling.

In order to make the upper tetraene, trienyl stannane 34 was required. This was made via a Still-Gennari-style phosphonate to afford trans-diene 33 with >20:1 E:Z ratio. Palladium catalysed cross-coupling with distannylethylene gave the desired triene 34 (Scheme 3). Coupling of stannane 34 to give the upper tetraene was successful, giving the desired product 36 in quantitative yield (Scheme 4).

Formation of the lower tetraene to yield the bis-tetraene 38 was then attempted and the bis-tetraene was obtained as a 1:1 mixture of alkene stereoisomers (Scheme 5). Unfortunately, attempts at deprotection and ring closure proved unsuccessful.

Scheme 3. Synthesis of triene 34

Scheme 4. Synthesis of tetraene 36

Scheme 5. Synthesis of bis-tetraene 38
The Whiting group has focussed on Heck-Mizoroki (HM) methodology to build 18,28 with the proposed disconnection strategy for viridenomycin shown in Scheme 6. A model incorporating benzene rings as Z-alkene analogues was also used to identify suitable conditions for the synthesis of the polyene chains. In addition, the northern triene 47 was synthesised using an iterative HM/iododeboronation methodology (Scheme 7).29

Scheme 6. Proposed disconnection strategy for 18

Scheme 7. HM/iododeboronation methodology used in the synthesis of triene 47

Marinomycins A-C
Marinomycins A-C 19-21 are three polyenic macrodiolides isolated by Fenical et al. in 2006 from the saline culture of a new group of marine actinomycetes, Mannispora strain CNQ-140. The marinomycins display antitumour and antibiotic activity. Fenical et al. showed that marinomycin A 19, the most abundant and active of the three natural products, was photochemically converted into an equilibrium mixture of marinomycins A 19, B 20 and C 21 upon exposure to ambient light. As a result, the total synthesis of marinomycin A 19 would also constitute a total synthesis of the two others.30

The marinomycins are characterised by a highly complex 44-membered dimeric molecule, with a monomer consisting of a tetraene conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and connected to a pentahydroxylated
polyketide chain. The variation between the three different marinomycins lies in the stereochemistry of the two double bonds adjacent to the 2-hydroxybenzoic acid groups.

Three groups have either attempted or completed the total synthesis of 19. Nicolaou’s group was the first to synthesise 19 and undertake isomerisation studies to form 20 and 21. The retrosynthesis for 19 involved cleavage of the tetraene to give two monomeric counterparts. Two building blocks were synthesised, diene 48 and enyne 49, which could then be joined together by a palladium catalysed cross coupling. In this synthesis, the tetraenes were built using palladium chemistry, although ylide chemistry was used elsewhere in the synthesis for isolated double bonds. The aryl dienyl bromide 54 was easily made by converting aryl alkyne 50 to the vinyl boronate ester 51, followed by a Suzuki-Miyaura (SM) reaction with trimethylsilyl vinylbromide 52 and subsequent conversion to the desired bromide (Scheme 8). The aryl dienyl iodide was also made, but this compound underwent isomerisation to give the undesired cis-isomer. A Mitsunobu reaction between the carboxylic acid of aryl diene fragment 48 and the hydroxyl of enyne 49 was used to join the building blocks at one end. The first tetraene formation was then undertaken by conversion of the enyne triple bond to a vinyl boronate ester, and subsequent Suzuki coupling with the aryl dienyl bromide (Scheme 9). A further Mitsunobu, followed by another hydroboration/SM sequence was used to close the macrodiolide. The closure was difficult, requiring stoichiometric palladium and 300 equivalents of a thallium base (Scheme 10). Attempts were also made to improve the yield of the cyclisation, investigating the use of both HM and Stille couplings as methods of tetraene formation. Unfortunately, none of these routes were successful and the yield was not improved.

The ability to form marinomycins B 20 and C 21 from A 19 was also demonstrated by exposure to ambient light. Marinomycin A underwent photoinduced isomerisation, giving a ratio of roughly 1.1:1:1.5 (A:B:C respectively) after two hours, as analysed by HPLC. The other groups that attempted the synthesis of marinomycin chose to build the tetraene into a building block, rather than form it during a ring closure. Efforts of the Cossy group have yielded the monomeric counterpart of marinomycin A. The intention was to form a triene building block, with a palladium catalysed cross coupling envisioned to form the tetraene (Scheme 11). Initially, an attempt was made to form the

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**Scheme 8**

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**Scheme 9**

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**Scheme 10**

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**Scheme 11**
boronate ester variant of the triene 64. Unfortunately, stereoselectivity problems led to the concept of a tetraene-forming Suzuki coupling being abandoned for a Stille approach (Scheme 12). The new approach involved a Stille coupling followed by an olefination to give a trienic vinyl stannane 69 (Scheme 13).

Scheme 8. Synthesis of dienyl bromide 54

Scheme 9. Construction of tetraene 56
Scheme 10. Completion of the synthesis of 19

Scheme 11. Envisioned construction of tetraene 60

Triene 69 was then used to complete the monomer synthesis via a Stille coupling with a penta-alkoxyalted alkenyl iodide 70 (Scheme 14). Difficulties in deprotection prevented the completion of the total synthesis of marinomycin A 19 using this route.34,35 In the Evans group, the tetraene was again built before dimerization.36

Scheme 12. Attempted route towards 64
Pentaenes

Macrocyclic pentaenes

Like the tetraene polyene macrolides, there are a number of pentaene containing-compounds with closely related structures. TPU-0043 or chainin 75, filipin III 76 and fungichromin 77 all possess similar structures, varying in the nature of the aliphatic side-chain and in one substituent on the macrocycle. TPU-0043 75 is an antifungal compound produced by Streptomyces sp. TP-A0625 and Chainia minutiscerotica.37 Filipin III 76 is another antifungal produced by S. filipinensis.38 It has also been
shown to have antimalarial activity.\textsuperscript{14} Fungichromin 77 was first isolated from \textit{S. padanus} PMS-702 in 1958\textsuperscript{19} and was also shown to be produced by \textit{S. griseus} in 1980.\textsuperscript{40} A number of apparently different antifungals were isolated in the 1950s, 60s and 70s, all believed to have the same chemical structure as fungichromin. There were, however, inconsistencies in the analytical data [HPLC, \textsuperscript{13}C NMR, circular dichroism (CD) and counter-current distribution (CCD)], which the groups reporting these compounds believed to be due to differing stereochemistry in each of the different compounds. The supposed new compounds discovered were named pentamycin, (isolated in 1958 from \textit{S. penticus})\textsuperscript{41} lagosin (isolated in 1964)\textsuperscript{42} and cogomycin (isolated in 1975).\textsuperscript{43} In 1982, it was shown that these compounds were in fact identical and that the previous inconsistencies in the analytical data were due to differing levels of impurities in the isolated samples. This report also listed \textit{S. cellulosae}, \textit{S. roseoluteus} and \textit{S. fradiae} as the organisms producing fungichromin.\textsuperscript{44}

A compound with a similar structure, but a shorter polyol chain is aurenin 78, an antifungal isolated from \textit{S. aureus}\textsuperscript{45} and later from \textit{Actinomycetes aureorectus}.\textsuperscript{46} Other macrocyclic pentaenes include roflamycoin 79, RK-397 80, roxaticin 81, mycoticins A 82 and B 83, marinisporolides A 84 and B 85, strevertenes A-G 86-92, eurocidin D 93, mirabilin 94 and lienomycin 95. Roflamycoin or flavomycoin 79 is an antifungal isolated from \textit{S. roseoflavus}.\textsuperscript{87} RK-397 80 is another polyene macrolide isolated from a strain of soil bacteria.\textsuperscript{48} This compound, along with attempts made at its total synthesis, are discussed later (vide infra). Roxaticin 81 is an antifungal isolated from streptomycete X-14994.\textsuperscript{49} Mycoticins A 82 and B 83 are compounds with broad antimicrobial properties, isolated from \textit{Streptomyces ruber} (ATCC #3348).\textsuperscript{50}
Marinosporolides A 84 and B 85 are produced by *Marinispora* sp. and display antifungal activity against *Candida* fungi.  

Strevertenes A-G 86-92 are a closely related class of polyene macrolides produced by *Streptoverticillium* sp. LL-30F848. They possess antifungal activity against phytopathogenic fungi.  

Eurocidin D 93 is produced by *Streptoverticillium* sp. and displays antifungal activity against *T. vaginalis*.  

*Mirabilin* 94 and *lienomycin* 95 have more distinct structures from those detailed above. *Mirabilin* possesses a 6-membered cyclic ether as part of its structure, along with a long side chain containing an amide moiety. Produced by *Siliquariaspongia mirabilis*, 94 displays antitumour activity.  

*Lienomycin* is a larger macrocycle and possesses a shorter side-chain, containing a primary amine functionality. Isolated from *Actinomyces diastatochromogenes* var. *lienomycin*, *lienomycin* 95 possesses antifungal, antibacterial and antitumour activity.  

**Linear pentaenes**

Compounds whose pentaene fragments are not contained within a macrocyclic system include mycolactones A 96 and B 97, and spirangiens A 98 and B 99. Mycolactones A and B are produced by *Mycobacterium ulcerans* and *Mycobacterium marinum*. 96 and 97 are believed to be linked to the Buruli ulcer skin disease.  

*Spirangiens* A and B are produced by *Sorangium cellulosum* (strain So ce 90) and are discussed later (*vide infra*).  

**RK-397**

RK-397 80 was isolated from *Streptomyces* sp. in 1993 and displays antifungal activity. In 2009, it was shown to be active against human leukaemia cell lines K-562 and HL-60 at 50 and 25 μg/mL, respectively.  

Five groups have reported efforts towards its total synthesis, but the efforts of the Loh group were towards the polyol chain and are not discussed here. The first total synthesis of 80 was accomplished by Burova and MacDonald in 2004.
This synthesis involved a combination of ylide and palladium chemistry to achieve the synthesis and incorporation of the polyene fragment, involving synthesis of a trienyl building block. This building block was all-trans-7-(tributylstannyl)-2,4,6-heptatrien-1-ol 100 and was originally made in the de Lera group\textsuperscript{60} using Wittig chemistry and a diisobutylaluminium hydride (DIBAL) reduction starting from all-trans-5-(tributylstannyl)-2,4-pentadienal 101 (Scheme 16). The polyol core 103 had already been synthesised, containing a primary alcohol moiety at one end and a vinyl iodide at the other. Esterification of the primary alcohol with diethylphosphonoacetic acid gave phosphonate ester 104 ready for HWE-type ring closure.

Scheme 16. Synthesis of all-trans-7-(tributylstannyl)-2,4,6-heptatrien-1-ol 100

Scheme 17. MacDonald synthesis of 80
The trienyl building block 100 was then installed into the polyol core using a Stille coupling between the tributylstannyl group on the trienyl fragment and the vinyl iodide group on the polyene core. Oxidation of the primary alcohol of the resulting tetraene 105 to the corresponding aldehyde and then Horner-Emmons macrocyclisation under Masamune-Roush conditions gave the tetraacetonide derivative of the natural product 106. Deprotection furnished RK-397 80 (Scheme 17).59 Denmark and co-workers published a total synthesis shortly after MacDonald, in 2005.62 Here, the polyene fragment was fully installed before macrocyclisation was attempted, palladium chemistry was used to build the key tetraenyl intermediate 107 and ylide chemistry to incorporate the polyene into the rest of the molecule. Synthesis of 107 involved sequential palladium-catalysed cross coupling of 1,4-bis-silyl-1,3-butadiene compound 108, first with 3-iodo-2-propenol THP ether 109 and then with ethyl (E)-3-iodoprenoate 110. These reactions proceeded with high yields but poor diastereoselectivity, with mixtures of olefins being obtained. Deprotection and isomerisation to give the all-(E)-tetraenoate using iodine, then conversion to the phosphonate ester gave the desired building block 107 (Scheme 18). This was installed using standard HWE chemistry, then ring closure and deprotection gave RK-397 80.62

In 2007, Sammakia et al. reported a total synthesis of RK-387 8063 using a trienyl aldehyde 113 which was installed onto the polyol core 114 by olefin-cross metathesis with Grubb’s first generation catalyst. HWE yielded the pentaenyl moiety, followed by saponification, Yamaguchi macrolactonisation and global deprotection to yield 80 (Scheme 19). O’Doherty et al. reported a total synthesis of RK-397 80 in 2008. The polyene core, however, was installed using the procedure developed in the Denmark group.62,64

**Spirangien A and B**

The spirangiens A 98 and B 99 were isolated from *Sorangium cellulosum* (strain So ce 90) in 2005 by Niggemann et al.55 Aside from their antifungal properties, these compounds have been investigated for either treatment or prevention of IL-8 or IL-6 mediated disorders.65 The spirangiens are linear polyene natural products, with the polyene moiety having a (4Z,6E,8Z,10E,12Z)-configuration. Three groups have completed the total synthesis of 98 and 99, but only Paterson reports a synthesis of the polyene fragment,66 both Rizzacasa and Ley reported formal total syntheses, but utilised the Paterson methodology.67,68 The total synthesis of spirangien A and B was accomplished by the Paterson group in 2008. A bis-stannylated triene 119 was obtained as the (1E,3Z,5E)-isomer via a (Z)-selective Julia olefination. A Stille coupling furnished the tetraenyl methyl ester 121, with a second Stille coupling forming the pentaene and completing the synthesis of the methyl ester of spirangien A 123 (Scheme 20).66
Scheme 19. Sammakia synthesis of 80

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\begin{align*}
\text{(F)-Bu}_2\text{SnCH=CHCHO} & \quad \text{KHMDS} \\
\text{THF, } -78^\circ \text{C} \rightarrow 20^\circ \text{C} & \quad 68\% \\
& \quad > 20:1 \text{ geometric purity}
\end{align*}
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Scheme 20. Paterson route to the synthesis of 123

Cyclic hexaenes

Hexaenes
Perhaps the most well-known of the cyclic hexaenes are the polyene macrolides dermocorticin A \(124\) and B \(125\), isolated from \(S.\ virdigreseus\) Thirum.\(^6\) Their biological activity and synthesis are discussed later (\textit{vide infra}).

**Linear hexaenes**

The linear hexaenes include the mediomycins A \(126\) and B \(127\), clethramycin \(128\) and etnangien \(129\). The mediomycins and clethramycin are similar in structure. They are all produced by \(S.\ mediocidicus\) ATCC23936 and display a broad spectrum of antifungal activity.\(^7\) Etnangien \(129\) has a different structure, with an unsaturated lactone as part of the compound, isolated from \(Sorangium cellulosum\).\(^8\) Its synthesis is discussed later (\textit{vide infra}).

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**Dermocorticin A and B**

The dermocorticins A \(124\) and B \(125\) were first isolated from \(S.\ virdigreseus\) Thirum. in 1962.\(^6\) These compounds display potent antifungal activity against a number of human pathogens.\(^7\) They have also been used clinically as a treatment for deep vein mycoses.\(^8\) and display anti-proliferative activity against herpes simplex virus (HSV) in H9 cells.\(^9\) Initially, the dermocorticins were thought to be pentene compounds, but their structures were further elucidated and found to contain a hexaene moiety.\(^5,7,6\) Two groups have completed the total synthesis of dermocorticin A \(124\). The Rychnovsky group completed a total synthesis of \(124\) in 2001. This synthesis was analogous to Burova and McDonald’s synthesis of RK-397 \(80\), utilising the tetraene analogue of all-trans-(tributylstannyl)-2,4,6-heptatrien-1-ol \(100\) as reported by de Lera \textit{et al.}\(^6\) and installing it in the same way. The tetraenyl alcohol \(130\) was attached to the polyol \(131\) fragment using a Stille coupling. The primary alcohol of the resulting pentaene \(132\) was then oxidised to give the corresponding aldehyde and the ring closure achieved using the same Horner-Emmons macrocyclisation under Masaume-Roush conditions (Scheme 21).\(^7\)

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**Scheme 21. Rychnovsky synthesis of 124.**
In 2011, the Sammakia group reported a total synthesis, analogous to their synthesis of RK-397 \(80\), using ruthenium cross metathesis for incorporation of the polyene into the polyol core.\(^79,80\) Model studies were undertaken to establish the best polyenyl substrate to undertake the olefin cross metathesis with, finding that the same trienyl aldehyde \(113\) as used in the synthesis of RK-397 was by far the most reactive, and better than the tetraenyl analogue. Application of the first generation Grubbs catalyst gave the desired triene \(135\) in an 82% yield as a 4:1 mixture of olefin isomers distal to the aldehyde. HWE with phosphonate ester \(136\) gave the desired hexaenoate \(137\) which could be isolated in a geometrically pure form. Hydrolysis, Yamaguchi cyclisation and global deprotection gave dermostatin A \(124\) (Scheme 22).\(^79,80\)

**Etnangien**

Etnangien \(129\) was isolated from *Sorangium cellulosum* and found to be active against a range of Gram-positive bacteria.\(^71\) It has also been found to inhibit retroviral RNA and DNA polymerases.\(^81\) Etnangien \(129\) is also reported to have an unstable structure, presumed to be due to the polyene chain. It has only been synthesised by the Menche group,\(^81,82\) which also established the absolute stereochemistry in the process of completing the total synthesis. The synthetic route involves a mixture of ylide and palladium chemistry. The hexaene chain was synthesised from two trienyl building blocks \(142\) and \(148\). Ylide chemistry was used to create diene \(140\), then a series of steps were used to form the macrocycle. Selective removal of the primary TBS group and allylic oxidation were followed by a Takai reaction to install the \(E\)-vinyl iodide \(142\) (Scheme 23). Homologation of alkene \(143\) by olefin cross-metathesis using the Grubbs (II) catalyst gave the required enal \(145\). HWE chemistry furnished the required trienyl stannane \(147\) and tetrabutylammonium fluoride (TBAF) deprotection gave building block \(148\). The side-chain was coupled to the trienyl iodide using a Stille coupling (Scheme 24).\(^81,82\)

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Scheme 22. Sammakia synthesis of 124
Scheme 23. Synthesis of iodide 142

Scheme 24. Completion of the synthesis of 129
Heptaenes

Cyclic heptaenes

One of the most commonly known and widely used polyene natural products is a member of the heptaene polyene macrolide class of compounds, amphotericin B 150 and its derivatives 151-153, which are discussed later (vide infra). The polyene macrolide candidin 154 has a similar structure to amphotericin B, possessing an extra carbonyl moiety on the polyol fragment. It is an antifungal agent produced by S. viridoflavus, and has also been patented as a treatment for mammalian tumours.83,84 Another very closely related structure is mycoheptin 155, produced by Streptoverticillium mycoheptinicum, which displays antifungal activity and is used in the therapy of coccidioidomycosis, histoplasmosis, cryptococcosis, chromomycosis, blastomycosis, aspergillosis, sporotrichosis and candidiasis.85,86 Another class of compounds with very similar structures, all containing a side-chain with a para-amino phenyl ketone group, are hamycin 156, levorin A2 157, partricin A and B 158-159 and 67-121 A and B 160-161. Perimycin A 162, DJ-400 B1 and B2 163-164, FR-008 165 and trichomycin A 166 are also similar. Hamycin 156 is produced by S. pimprina and displays antimicrobial activity against a number of forms of candidiasis and deep-seated mycoses.87 Levorin A2 157, or candidin D, is produced by A. levoris and S. griseus ATCC 3570.
This compound is an antifungal and possesses the ability to inhibit the growth of adenoma prostate.\textsuperscript{88,89} Partricin A and B \textbf{158-159} are produced by \textit{S. aureofaciens} and possess high antifungal activity, particularly against \textit{Candida albicans}, and antiprotozoal activity.\textsuperscript{90} \textbf{67-121} A and B \textbf{160-161} are produced by \textit{Actinoplanes caeruleus} and are antifungals.\textsuperscript{91,92} Perimycin A \textbf{162}, otherwise known as fungimycin, NC-1968 and aminomycin, is an antifungal produced by \textit{S. coelicolor var. aminophilus}.\textsuperscript{93} DJ-400 B\textsubscript{1} and B\textsubscript{2} \textbf{163-164} is produced by \textit{S. Surinam} and displays antifungal activity.\textsuperscript{94,95} FR-008 \textbf{165} is also an antifungal produced by \textit{S. griseus}.\textsuperscript{96} Trichomycin A \textbf{166} is produced by \textit{S. hachijoensis} and is used as a potent clinical drug for the treatment of vaginal infections.\textsuperscript{97}

**Linear heptaenes**

Two interesting linear heptaene structures are peridinin \textbf{167} and fucoxanthin \textbf{168}, which both contain an allene moiety. Peridinin \textbf{167} is produced by \textit{Gonyaulax polyedra} and is believed to possess activity against atherosclerosis, rheumatoid arthritis and cancer. In particular, this compound is believed to reduce membrane permeability to reactive oxygen species.\textsuperscript{98,99} Fucoxanthin is discussed later (vide infra).

**Amphotericin B**

Amphotericin B \textbf{150} and its derivatives \textbf{151-153} have a wide range of biological applications. First reported in 1955, amphotericin B is an antifungal antibiotic produced by \textit{S. nodosus}.\textsuperscript{100} It was tested as early as in 1957 for activity against \textit{Candida albicans},\textsuperscript{101} and has since been shown to have a number of other biological applications, including activity against deep-seated mycotic infections,\textsuperscript{102} activity against intracranial fungal masses,\textsuperscript{103} activity against visceral leishmaniasis,\textsuperscript{104} potential as a treatment for prion infection treatment,\textsuperscript{105} as a malaria treatment in humans and animals,\textsuperscript{14} activity against HSV I, HSV II and hepatitis B,\textsuperscript{7} and as a treatment for severe mucocutaneous candidal infections in the mouth.\textsuperscript{106} Despite being such an important compound, only the Nicolau group has completed the total synthesis of amphotericin B \textbf{150}.\textsuperscript{107} The Negishi group has also completed a synthesis of the polynyl fragment. Completed in 1987, the Nicolau synthesis used ylide chemistry to build up the polynyl fragment. This was achieved via a series of HWE reactions using dienyl phosphonate ester \textbf{170} as a key building block. Ring closure was also accomplished using a HWE reaction (Scheme 25).\textsuperscript{107} The Negishi synthesis of the polynyl fragment \textbf{176} was published in 2013 and utilised HWE, alkyne hydrozirconation, palladium-catalysed Neigishi coupling and HM coupling chemistry.\textsuperscript{108}
The first building block made was a trienyl phosphonate ester 182. The first step involved a hydrozirconation of metallated propargyl alcohol 177, iodinolysis, in situ metallation and then Negishi alkenylation. The next step involved hydrozirconation of the metallated enyne 179 and then another Negishi alkenylation to yield trienyl alcohol 181, which was then converted to the phosphonate ester 182 (Scheme 26). A HM reaction was then used to form dienyl ester 184, which was then reduced and used in a HWE reaction with trienyl phosphonate ester 182 to complete the hexaene fragment 176 (Scheme 27).
**Scheme 25. Nicolaou synthesis of 150**

**Fucoxanthin**

Fucoxanthin 168 is an allenic compound found in brown algae. Its isolation, along with a number of other brown pigments, was reported in the early 1900s.109 Fucoxanthin 168 is a pigment associated with a range of biological activity110 including potential as a treatment for diabetes and obesity,111 as an anti-inflammatory agent,112 into its role in neutrophil modulation,113 into its inhibition of cancer metastasis114 and into its ability to protect against UV-B induced cell damage.115 The synthesis of 168 was first completed by the Ito group in 1994. Construction of the polyene fragment was achieved solely by ylide chemistry, but was hampered by poor selectivity and low yields. This can be seen in the synthesis of building blocks 192 and 195, where diastereomeric ratios of 1:1 or less were achieved (Scheme 28).116,117
Another synthesis was completed by the Katsumara group in 2012.\textsuperscript{118} Again, de Lera group chemistry was used in the construction of a key building block.\textsuperscript{60} A modified version of the de Lera procedure was used to create trienyl iodide 199, which was then coupled with an alkyne to install the epoxycyclohexane group. This was then converted to allenyl building block 203 (Scheme 29).\textsuperscript{119-122} A second benzothiazolylsulfone building block 208 was synthesised and the two building blocks coupled using a Julia olefination which gave a mixture of isomers at the connected olefin, predominantly Z. Deprotection and oxidation of 207 yielded fucoxanthin 168 (Scheme 30).\textsuperscript{118-122}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme26.png}
\caption{Synthesis of phosphonate ester 182}
\end{scheme}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme27.png}
\caption{Synthesis of hexaene 176}
\end{scheme}
Scheme 28. Ito synthesis of 168

Scheme 29. Synthesis of building block 203
Octaenes and above

Those natural products possessing a polyene chain of eight or more conjugated double bonds are dominated by linear structures. To the best of our knowledge, no polyene macrolide structures containing an octaene polyene fragment have been elucidated, nor have any structures for polyene macrocycles containing more than eight conjugated double bonds. Two of these linear polyenes are xanthomonadin 208 and granadaene 209. Xanthomonadin 208 is an octaene bacterial pigment isolated from Xanthomonas juglandis. Its structure was elucidated in 1976 and was later shown to protect against photodamage and also isolated from Xanthomonas oryzae pv. oryzae in 1997. Granadaene 209 is a dodecaene red pigment characteristic of Streptococcus agalactiae, isolated in 2006.
Correlation between polyene chemical structure and biological activity

There has been surprisingly little reported in the literature about the correlation between polyene chemical structure and biological activity. Some work has been done to compare the activity of various polyene macrolides. In a review published by Hamilton-Miller in 1973, it was stated that the biological activity of the polyene macrolides increases with the number of conjugated double bonds.\textsuperscript{127} Several natural product tetraene macrolides, namely pimaricin 8, AB-400 9, rimocidins A-C 10-12 and CE-108s A-C 13-15, were compared with the heptaene macrolide amphotericin B 150 to assess their biological activities on \textit{Trypanosoma cruzi}. These tetraene compounds were found to be less effective, but also less toxic.\textsuperscript{128} Kotler-Braitburg \textit{et al.} attempted to correlate the chemical structures of polyenes and their biological properties by investigating their ability to cause K\textsuperscript{+} leakage and cell death.\textsuperscript{129} The work hypothesised that the polyene macrolides could be categorised into two functionally different groups. Amongst the polyenes in group I was the tetraene pimaricin 8, pentaenes (chainin 75 and filipin 76) and the hexaene (dermostatin A 124), while group II included the heptaenes (amphotericin B 150, amphotericin B methyl ester 151, N-acetylamphotericin B 152, hamycin 154 and candidicidin 156) and one tetraene, nyastatin 17. Group I antibiotics caused potassium ion leakage and cell death or hemolysis at the same concentrations of added polyene, while group II caused considerable potassium ion leakage at low concentrations and cell death or hemolysis at high concentrations.\textsuperscript{129}

A study into the difference between the linear polyenes and the macrocyclic polyenes does not seem to have been undertaken. It appears that in general, the longer chain linear polyenes possess a more diverse range of biological activities, additional to antimicrobial properties, for example fucoxanthin 168, synechoxanthin 208 and xanthomonadin 209, all of which have polyene chains of seven double bonds or greater. As discussed in previous sections (\textit{vide supra}), these compounds have properties such as antioxidant and anti-inflammatory activities and an ability to inhibit cancer metastasis. The link between polyene structure and cancer activity in particular is interesting. Seemingly small changes in structure can impart a significant increase in biological activity. An example of this is the difference in biological activity between RK-397 80 and the mycoticins A and B 82 and 83. RK-397 displays anti-leukaemic activity, whereas the mycoticins only possess antimicrobial activity. The structures are exceptionally similar, differing only in the stereochemistry of the polyol chain and in the absence of a methyl group in the RK-397 structure.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{RK-397.png}
\caption{RK-397}
\end{figure}

Conclusion

The polyene natural products include a wide variety of different structures with a range of biological activities. Total syntheses of a number of interesting compounds have been accomplished using a mixture of ylide chemistry, palladium cross coupling and cross-metathesis. Whilst ylide chemistry was used effectively in a number of total syntheses, there are a number of examples where poor stereoselectivity was a clear issue, for example in the 1994 synthesis of fucoxanthin 168. Palladium chemistry, on the other hand, has given consistently better stereoselectivity in the total syntheses reported. The examples where olefin cross-metathesis was used highlight its potential as an efficient and selective method of polyene synthesis. Despite

Work undertaken by Akiyama \textit{et al.} supported the above theory. Polyene antibiotics were classified according to their synergistic effect on fungi into two groups: a non-heptaene group including pimaricin 8 and filipin 76, and a heptaene group including amphotericin B 150.\textsuperscript{130}
all the research that has been undertaken in this area of polyene natural product synthesis, there is not yet a standout method for the highly stereoselective formation of polyene chains that has completely general application in synthesis, though some methods have clear advantages over others.

In addition, relatively little is understood about the correlation between chemical structure and biological activity as a general phenomenon. Establishment of the structural features which contribute to the activity of the polyene natural products is necessary for a better understanding of this interesting class of compounds.

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References


