JOURNAL OF NATURAL PRODUCTS

Review

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# Spirotetronate Polyketides as Leads in Drug Discovery

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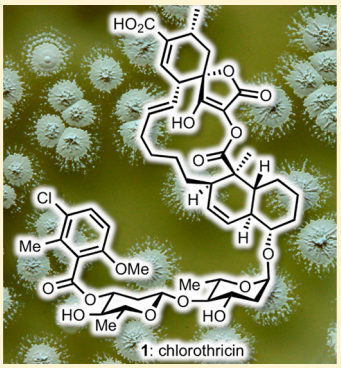
**ABSTRACT:** The discovery of chlorothricin (**1**) defined a new family of microbial metabolites with potent antitumor antibiotic properties collectively referred to as spirotetronate polyketides. These microbial metabolites are structurally distinguished by the presence of a spirotetronate motif embedded within a macrocyclic core. Glycosylation at the periphery of this core contributes to the structural complexity and bioactivity of this motif. The spirotetronate family displays impressive chemical structures, potent bioactivities, and significant pharmacological potential. This review groups the family members based on structural and biosynthetic considerations and summarizes synthetic and biological studies that aim to elucidate their mode of action and explore their pharmacological potential.




## INTRODUCTION

Since the beginning of mankind, organisms producing natural products have provided a reservoir of therapeutic remedies and medicines for various diseases.[1] A subset of these drugs has been classified as antitumor antibiotics based on their ability to "block cell growth by interfering with DNA, the genetic material in cells".[2] Key general features of an antitumor antibiotic include interference with DNA synthesis, membrane transport, and production of reactive oxygen species.[3] One of the most notable examples of an antitumor antibiotic is mitomycin C, a microbial metabolite that is used currently for the treatment of breast and bladder cancer.[4] Among other antitumor antibiotics, daunorubicin and its semisynthetic derivative doxorubicin represent chemotherapeutic leukemia agents in clinical settings.[5]

The search for new antitumor antibiotics led to the discovery of chlorothricin (**1**), a complex polyketide produced by various *Streptomyces* strains.[6] Its intriguing chemical structure and bioactivity defined a new family of microbial metabolites, commonly referred to as spirotetronate polyketides. This family is identified by the presence of a cyclohexene ring spiro-linked to a tetronic acid moiety (Figure 1, fragment A) that is embedded in a macrocycle (Figure 1, fragment B). In several cases, the structure also contains a *trans*-decalin ring (Figure 1, fragment C) and is decorated by various deoxy oligosaccharides (Figure 1, fragment D). In terms of biological profile, spirotetronate polyketides exhibit potent antibacterial and antitumor activities and a documented value as tools in the elucidation of new biological pathways. As such, they represent highly promising leads in drug discovery. To appreciate their untapped potential, in this review we group the known spirotetronates based on common structural elements and biosynthetic considerations. We then discuss the biological profiles and highlight synthetic efforts toward each group.

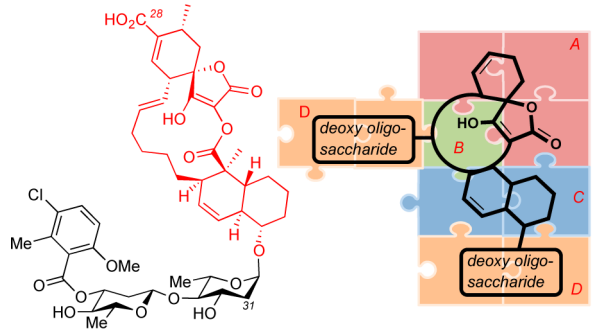



**Figure 1.** Structure of chlorothricin and general structure of spirotetronate polyketides.

## CLASSIFICATION

Recently Süssmuth and co-workers proposed a classification of tetronates based on two main categories: the linear tetronates and the spirotetronates.[7] On the basis of biosynthetic considerations, the latter subgroup can be divided into two classes: class I (generic structure **4**), which contains the spirotetronate moiety within a varying size macrocycle, and class II (generic structure **5**), which additionally contains a decalin moiety (Figure 2). Representative members of the class I spirotetronates in order of increasing macrocyclic length are abyssomicin C (**6**)[8] (containing a $C_{11}$ macrocycle), okilactomycin D (**7**)[9] (containing a $C_{13}$ macrocycle), and spirohexenolide A/B (**8**/**9**)[10] (containing a $C_{15}$ macrocycle).

**Special Issue:** Special Issue in Honor of William Fenical

**Received:** September 26, 2014
**Published:** December 1, 2014

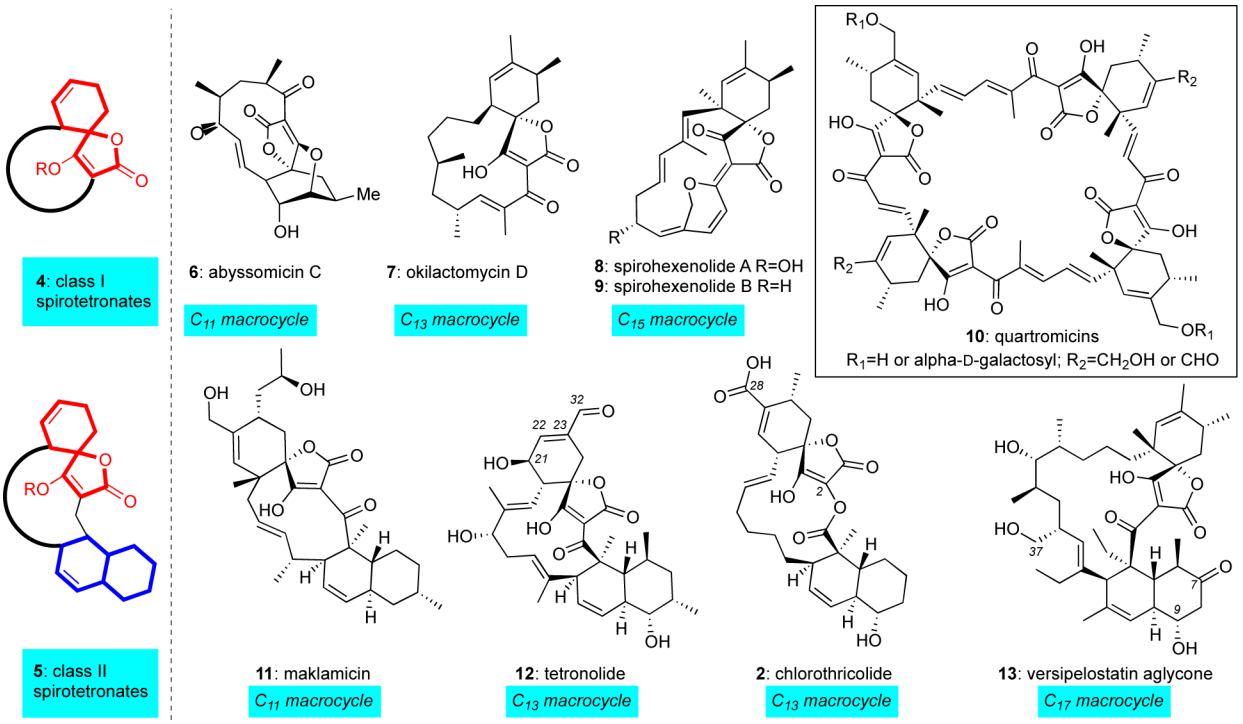



**Figure 2.** Spirotetronate polyketides: general structures and representative members.

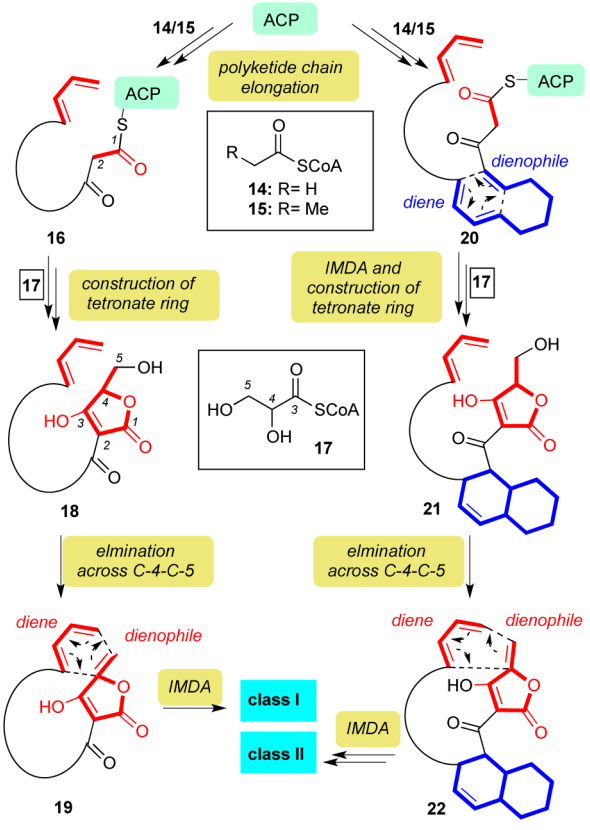
Representative members of the class II spirotetronates include maklamicin (**11**)[11] (containing a $C_{11}$ macrocycle), tetronolide (**12**)[12] (the aglycon of tetrocarcin A containing a $C_{13}$ macrocycle), and chlorothricolide (**2**)[6] (the aglycon of chlorothricin containing a $C_{13}$ macrolactone). In this class is also included versipelostatin aglycone (**13**), which contains the largest $C_{17}$ macrocyclic motif isolated to date.[13] Quartromicins **10**, unusual spirotetronate polyketides containing four spirotetronate subunits, lie outside these two classes due to their peculiar structure[14] and unique biosynthesis.[15] The above classification stems from a common biosynthetic pathway that accounts for construction of these compounds.

## BIOSYNTHESIS OF SPIROTETRONATES

In general, the biosynthesis of spirotetronates occurs through condensation of acetic acid units via the type I polyketide synthase pathway (Scheme 1).[16] As shown in the biosynthesis of abyssomicin C[17] and okilactomycin,[18] construction of the class I spirotetronates proceeds by elongating their carbon chain via incorporation of propanoyl and/or acetyl units (**14**/**15**) to the acyl carrier protein (ACP). This iterative operation forms polyketide chain **16**. Incorporation of a glyceryl unit, via CoA intermediate **17**,[19] forms tetronate **18** likely via a Claisen condensation followed by lactonization. The precise mechanism for the elimination of the C-5 hydroxy group was recently elucidated by the Sun and Leadlay groups and shown to proceed via acetylation and subsequent elimination, thereby forming dienophile **19**.[20] An intramolecular Diels–Alder (IMDA) reaction then generates the characteristic spirotetronate moiety. The resulting substrates subsequently undergo peripheral oxidations to produce the final structures of the natural products.[17a]

The biosynthetic pathways of the class II polyketide spirotetronates have been elucidated for chlorothricin,[21] tetrocarcin A,[22] kijanimicin,[23] and versipelostatin.[24] Following

**Scheme 1. Proposed Biosynthesis of Class I and Class II Spirotetronate Polyketides**




chain elongation, the diene and dienophile groups of **20** undergo an IMDA to construct the characteristic decalin moiety of **21**. Glyceryl CoA (**17**)[19] is then inserted to generate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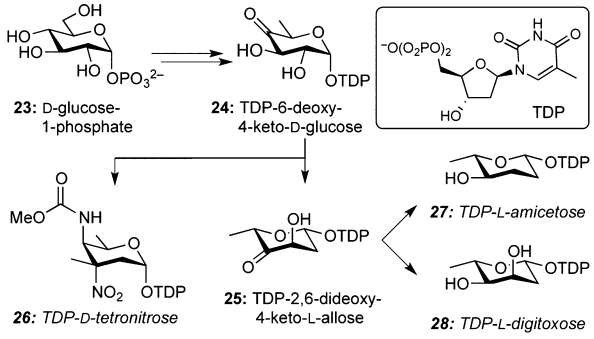
tetronate **22**, which following a second IMDA gives rise to the aglycones of the class II spirotetronates (Figure 2).

Oxidations and/or glycosylations at the periphery of the aglycone lead to various natural products of the class II spirotetronates. For instance, chlorothricolide (**2**), the aglycone of chlorothricin, contains an acyl-oxy tetronic acid moiety. This functionality (i.e., oxygenation at the C-2 position) is proposed to result from a Baeyer−Villiger oxidation that takes place after formation of the spirotetronate motif.[21b,d,e,25] A similar biosynthetic scenario can be proposed for the construction of PA-46101 A and B (see structures **57**/**58**).[26] Another interesting example of post-translational modification is found in the structure of tetronolide (**12**), the aglycone of tetrocarcin A (see structure **47**). Compound **12** is highlighted by an enal functionality at C-22−C-23−C-32. This functionality was proposed to result from oxidation at C-32 to the corresponding aldehyde followed by double-bond migration to C-22−C-23 and further allylic oxidation at C-21.[22a]

Several class II spirotetronates are subject to glycosylation mostly with 2-deoxycarbohydrates such as D-tetronitrose (**26**, D-kijanose), amicetose (**27**), and digitoxose (**28**). These carbohydrates are proposed to arise from thymidine diphosphate (TDP)-6-deoxy-4-keto-D-glucose (**24**), which, in turn, is available from D-glucose-1-phosphate (**23**) (Scheme 2).

**Scheme 2. Biosynthesis of Deoxysugars**




Biosynthesis of the uncommon tetronitrose is proposed to occur from **25** via aminotransferase and methylation, while the precise mechanism for the carbamate biosynthesis still remains elusive.[22a,23,27]

## BIOLOGY OF SPIROTETRONATE POLYKETIDES

The majority of spirotetronates have been subjected to biological assays that aim to define their bioactivity as antibiotic and/or anticancer leads as well as compounds that regulate metabolism. With this in mind, we have grouped these molecules in three major classes that describe the commonality of their bioactivities.

**Spirotetronates as Potential Antibiotic Leads.** *The Abyssomicin Family.* Isolated from a marine *Verrucosispora*, abyssomicin C (**6**) and its atropisomer (**29**) (Figure 3) are the first known natural products to block *para*-aminobenzoic acid (*p*ABA, **41**) biosynthesis.[8,28] *p*ABA is a biosynthetic precursor of folic acid (vitamin $B_9$), and as such, it is essential for DNA synthesis/repair and cell survival (Scheme 3).[29] On the other hand, lack of folic acid is known to induce mutations in DNA resulting in cell death. Importantly, blocking the *p*ABA pathway is detrimental to bacteria but inconsequential to humans since the latter cannot produce folic acid but only absorb it through their diet.[30] Studies on the effect of the abyssomicin motif in

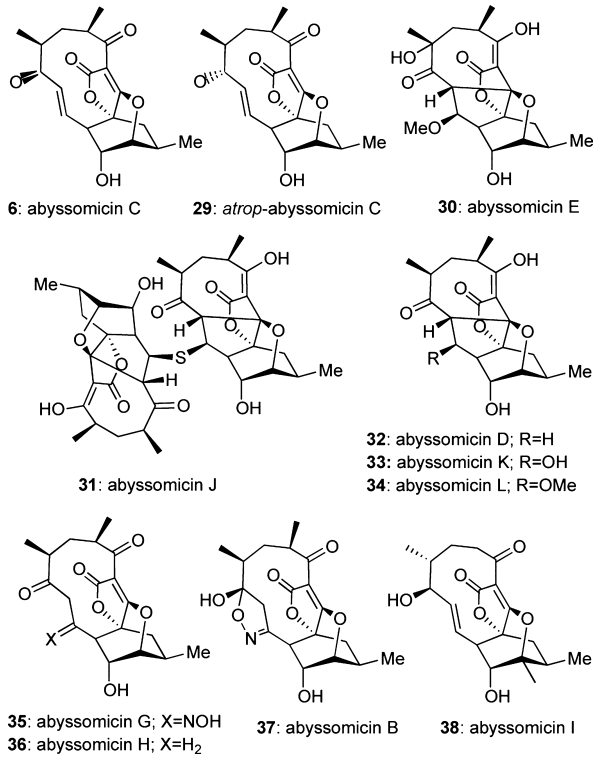
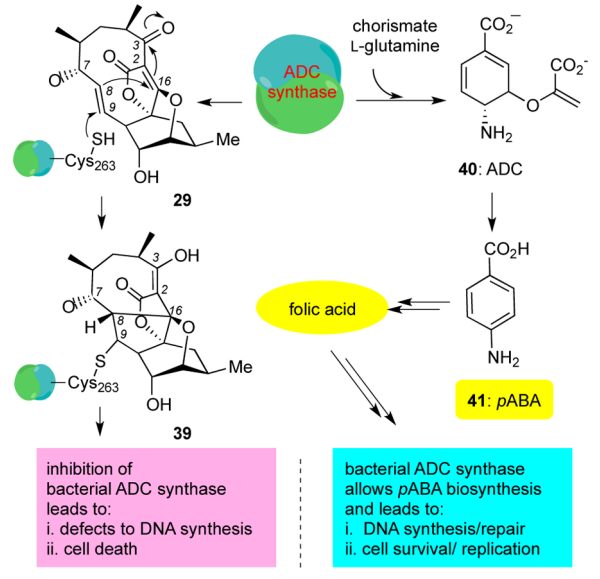



**Figure 3.** Representative structures of the abyssomicin family of spirotetronates.

**Scheme 3. *p*ABA Biosynthesis and Proposed Mode of Action of *atrop*-Abyssomicin C**




*p*ABA biosynthesis have been performed with *atrop*-abyssomicin (**29**) and are highlighted in Scheme 3. Amino-4-deoxychorismate (ADC) synthase, a heterodimeric protein, catalyzes the biosynthesis of amino-4-deoxychorismate (**40**), a synthetic precursor of *p*ABA. Compound **29** was found to covalently react with the Cys-263 of the PabB subunit of ADC synthase at the C-9 enone center. The transiently formed C-8 nucleophile then reacts with the spirotetronate subunit at the C-16 center to form compound **39**, thus irreversibly binding to ADC synthase.[31]


dx.doi.org/10.1021/np500757w | J. Nat. Prod. 2015, 78, 562−575

Several natural products of the abyssomicin family have been tested for their ability to inhibit *p*ABA biosynthesis (Scheme 3). Among them, only abyssomicin C (**6**), *atrop*-abyssomicin C (**29**), and abyssomicin J (**31**) have shown promising bioactivities.[8,28,32] Specifically, **6** and **29** potently inhibit proliferation of methicillin-resistant *Staphylococcus aureus* at MIC values of 5.2 and 3.5 μg/mL, respectively.[8,33] Similar cytotoxicities have been reported against various tuberculosis-related mycobacteria.[32a,b] On the other hand, abyssomicin D (**32**) and related analogues lacking the C-7−C-9 enone motif are inactive, attesting to the biological significance of this functionality.[28,31,32,32c−e] Moreover, most studies indicate that **29** is more potent than **6**. This increased potency has been attributed to an increased conjugation between the C-7 carbonyl group and the C-8−C-9 alkene that renders **29** a stronger Michael acceptor than **6**.[33] The bioactivity of abyssomicin J (**31**), a thioether dimer of the abyssomicin scaffold, can be explained by considering that oxidation of the sulfur accelerates a retro-Michael addition, producing the C-7−C-9 enone functionality in situ. In fact, it has been suggested that **31** is a prodrug of **6**, and as such, it represents a more attractive drug candidate.[32b]

*Kijanimicin (**43**) and Related Class II $C_{13}$ Macrocycles.* Isolated from various *Micromonospora* bacteria, kijanimicin (**43**)[34] and lobophorin B (**42**)[35] are structurally defined by a $C_{13}$ macrocycle (referred to as kijanolide, **44**) in which the C-9 and C-17 hydroxy groups have been glycosylated (Figure 4).

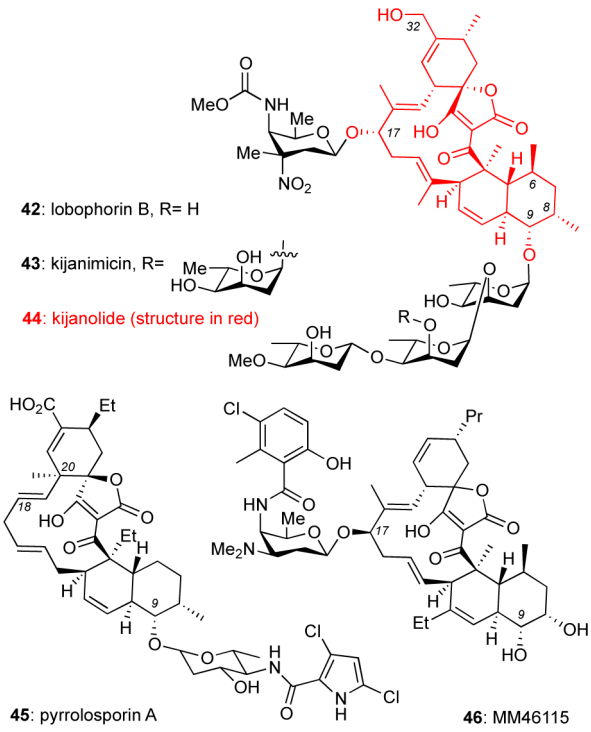



**Figure 4.** Structures of kijanimicin and related class II $C_{13}$ macrocyclic spirotetronates.

Most members of this group show potent activity against Gram-positive bacteria[34e,36] as well as cytotoxicity against various cancer cell lines.[36a,b,37] In addition, kijanimicin was shown to exhibit robust anticancer[38] and antimalarial activities[34e] in mouse models. Moreover, Fenical et al. reported promising anti-inflammatory activities of lobophorins in a mouse ear edema model. Interestingly, this is the first report on the untapped potential of spirotetronates as small-molecule leads against inflammation.[35]

A similar framework is in the structures of pyrrolosporin A (**45**, C-9-glycosylation)[39] and MM46115 (**46**, C-17 glycosylation).[40] The glycopyranose motif of pyrrolosporin is also found in the structures of decatromicin A/B[41] and Nai414-A/B,[42] which also exhibit similar antibiotic activity against various strains of Gram-positive bacteria. In addition to its potent antibiotic activities MM46115 was found to exhibit promising antiviral activities.[40a] Along these lines, the structurally unrelated quartromicins **9**[14a,c] were shown to display potent bioactivity against herpes simplex virus (HSV) and human immunodeficiency virus (HIV) at low μM concentration.[14b]

Recent studies indicate that kijanimicin binds to the TetR family of transcriptional regulators[43] that control expression of various cytoplasmic proteins in prokaryotes. This binding leads to (a) C-9-deglycosylation of kijanimicin, which results in loss of activity, and (b) overexpression of the receptor, thus increasing antibiotic resistance.[44] The structurally related saccharocarcins[45] are subject to a similar mechanism of deactivation and antibiotic resistance.[44,46]

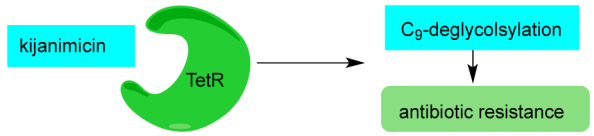



**Figure 5.** Binding of kijanimicin to TetR leads to C-9-deglycosylation and antibiotic resistance.

**Spirotetronates as Potential Anticancer Leads.** *Spirohexenolides A and B (**8**, **9**).* Burkart et al. reported the isolation of spirohexenolides A (**8**) and B (**9**) and their potent cytotoxicities against various cancer cell lines (Figure 2).[10] Subsequent immunoaffinity-fluorescent labeling studies indicated that **8** targets human macrophage migration inhibitory factor (hMIF).[47] This interaction reduces the phosphorylation levels of PI3K/AKT, ultimately leading to a reduction of tumor cell growth (Figure 6).[48] Conjugation of spirohexenolide A with fluorescent tags showed localization in the lysosome of HCT-116 cells, suggesting that spirohexenolides interfere with cellular endocytosis of hMIF.[47]

*Tetronolide-Containing Natural Products.* Isolated from various *Micromonospora* bacteria, tetrocarcin A (**47**, also known as antlermicin A and AC6D)[49] represents the archetype of the tetronolide family of natural products that also includes AC6H (**48**)[50] and arisostatins A (**49**) and B (**50**) (Figure 7).[51] The antibiotic potential of these spirotetronates against several Gram-positive bacteria has been reported.[49a,e,50−52] Animal studies have shown that **47** is about 4 times more potent than the commonly used antibiotic diminazene. Although **47** has a narrow safety margin, it can be used in combination with diminazene, providing a beneficial synergistic effect.[53]

Various reports on the potential anticancer profile of tetrocarcin A and related family members have been published. Initial studies showed tumor reduction in a mouse sarcoma model upon administration of 10 mg/kg of **47** over a period of 6 days. Similar treatment in a mouse leukemia P388 model led to an increased life expectancy.[49b,e] Comparable studies in B16 mouse melanoma showed that the life expectancy more than doubled at a single dose of 27 mg/kg of **47**.[54] Moreover, AC6H **48** exhibited cytotoxicity against P388 leukemia and B16 melanoma cells at 6.25 and 25 μg/mL, respectively.[50] AC6H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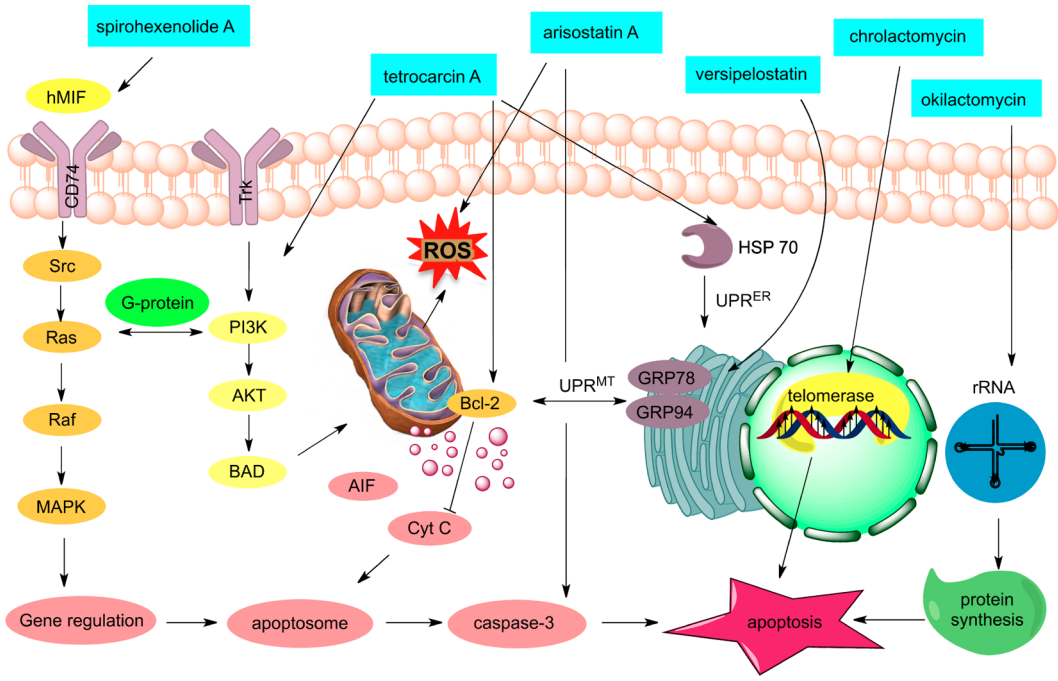


**Figure 6.** Cancer cellular signaling and mode of action of select spirotetronate polyketides.

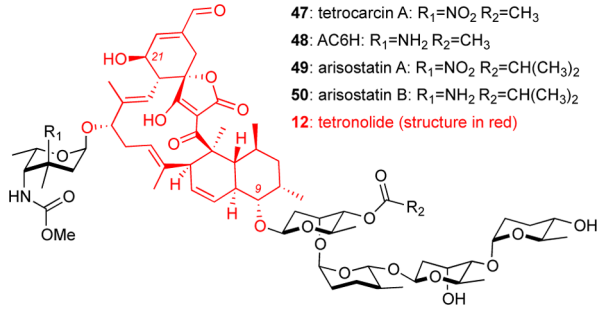


**Figure 7.** Selected structures of tetronolide-containing natural products.

also showed a moderate increase in the life expectancy of a P388 leukemia mouse model albeit less active than tetrocarcin A.[50] Studies in U937 cells indicated that arisostatin A (**49**) is equipotent to tetrocarcin A, while arisostatin B (**50**) was 10-fold less active. Arisostatin A was also found to be active in various breast and lung cancer cell lines at low micromolar concentrations.[51]

Mode-of-action studies in HeLa cells showed that tetrocarcin A (**47**) potently inhibits Bcl-2, an important antiapoptotic protein that is often overexpressed in cancer cells (Figure 6).[55] Although there is no evidence of direct binding to Bcl-2, the phenotypical response induced by **47** is very promising[56] and suggests that this compound represents an important and unexplored lead against cancer.[57]

Studies in lymphoma cells showed that **47** induces a stress response of the endoplasmic reticulum (ER), resulting in upregulation of the heat shock protein HSP70, ultimately triggering cell apoptosis (Figure 6).[58] Studies in breast cancer cells have suggested an alternative mechanism of action of **47** that proceeds by inhibiting phosphorylation of the PI3K/Akt signaling cascade.[59] Although the main cellular target of tetrocarcin A is still under investigation, preclinical studies have demonstrated its potential as a drug against chemo-resistant cancers. In fact, **47** was reported to be more effective than paclitaxel at inducing cell apoptosis in breast cancer cells.[58a,60]

Arisostatin A (**49**) was found to induce cell apoptosis by generating reactive oxygen species (ROS), altering mitochondrial transmembrane potential, and releasing cytochrome *c* (Cyt C) in AMC-HN-4 cells (Figure 6), ultimately leading to activation of caspase-3 and induction of apoptosis. However, Bcl-2 activation was not altered by arisostatin A, indicating a different mode of action from that of **47**.[61]

Screening the potential anticancer and antimicrobial activities of naturally occurring tetrocarcins has produced the main structure–activity relationship (SAR) data for this family. These studies have led to the following observations: (a) the number of carbohydrate units (digitoxose and amicetose) attached at the C-9 center of tetrocarcin A is proportional to its antimicrobial activity;[62,49a,b,e,63] (b) C-21 acetylation and C-9 glycosylation of tetrocarcin A did not significantly affect Bcl-2 activation.[63b] The results suggest that the attachments of amicetose (**27**) and digitoxose (**28**) at the C-9 position of tetrocarcin A enhance its antibacterial profile but have no significant effect on its anticancer potential.[64]

*Versipelostatins.* Versipelostatin A (**51**) was isolated from a strain of *Streptomyces versipellis* (Figure 8).[13,65] Biological studies showed that **51** is the first known molecule to inhibit gene expression of GRP78. Together with its isoform GRP94, these heat shock proteins are induced by stress responses in the endoplasmic reticulum and are essential for cancer cell survival.[13,66] In addition to its role in cancer, ER stress is considered to play a major role in the pathogenesis of various CNS diseases, such as Alzheimer's and Parkinson's disease.[67]

Recent studies have shown that versipelostatin A (**51**) inhibits heat shock proteins and unfolded protein response (UPR) under glucose deprivation conditions.[68] As such, it appears to operate via a different mechanism as compared to that of rapamycin, an FDA-approved immunosuppressive drug that activates GRP78 independently of glucose availability.[69]


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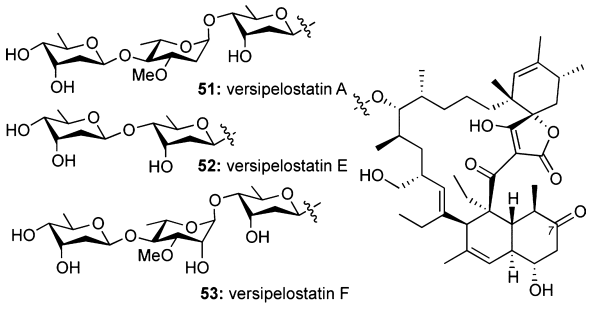


**Figure 8.** Selected members of the versipelostatin family.

Thus, versipelostatin may offer a significant advantage due to its selective effect in hypoglycemic cells.[68] Although there is no information for direct binding of **51** to a protein target, its effect on the UPR signaling pathway offers a novel tool to understand ER-induced stress and pharmacologically regulate related illnesses.[68a,70]

SAR studies on this family have been limited to the bioactivities of naturally occurring versipelostatins.[71] The results show that versipelostatins A (**51**), E (**52**), and F (**53**) are the only biologically active compounds, inhibiting GRP78 expression at low micromolar $IC_{50}$ values.[71b] Interestingly, **53** was found to be 10 times more potent than **51** in GRP78 expression with an $IC_{50}$ of 0.3 $\mu$M.[71a] The data attest to the significance of the glycosylation motif to the GRP78 expression and bioactivity.[71b] In addition to these studies, Takahashi et al. demonstrated the importance of the L-oleandrose sugar for the bioactivity, and changes in the oxidation state of C-7 had no effect on biological activity.[72]

*Okilactomycin (**54**) and Chrolactomycin (**55**).* Okilactomycin (**54**) was isolated from *Streptomyces griseoflavus* and is noted for its potent antitumor activity against Ehrlich ascites carcinoma in vivo at 2.5 mg/kg with a T/C of 145.7% for mice survival.[73] In addition, **54** exhibited in vitro activity against P388 and L1210 leukemia cells, with $IC_{50}$ values of 89 and 216 nM, respectively.[73b] Recently, okilactomycin was shown to inhibit rRNA protein synthesis at low $\mu$M concentrations,[74] suggesting potential applications as an antibacterial agent.[75] Although other natural okilactomycins were found to be inactive,[9] the related chrolactomycin (**55**) was reported to exhibit antibacterial and anticancer activity at a low $\mu$M concentration.[76] It has been reported that **55** inhibits telomerase activity, thus blocking the ability of cancer DNA to replicate.[77] The most recently isolated 6-hydroxy chrolactomycin was less active than **55** against Gram-positive bacteria.[78]

*PA-46101A/B (**57**/**58**), Maklamicin (**11**), and Nomimicin (**59**).* The potent antibiotic properties of PA-46101A (**57**) and B (**58**) have been reported.[26] Recent efforts by Igarashi and co-workers led to the isolation of maklamicin (**11**)[11] and nomimicin (**59**),[79] which contain the smallest macrocyclic ring of the class II spirotetronates. Both compounds display potent activity against many Gram-positive bacteria, while **11** also exhibits moderate antitumor activity against HeLa and MCF7 breast cancer cells.[11,79]

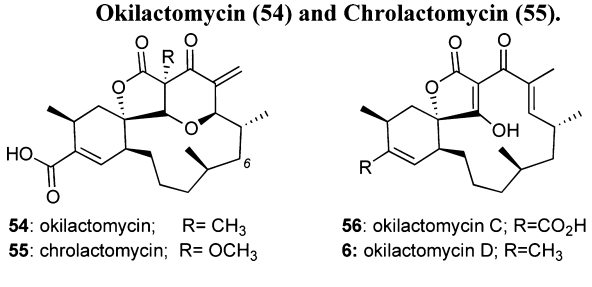


**Figure 9.** Structure of okilactomycin and analogues.

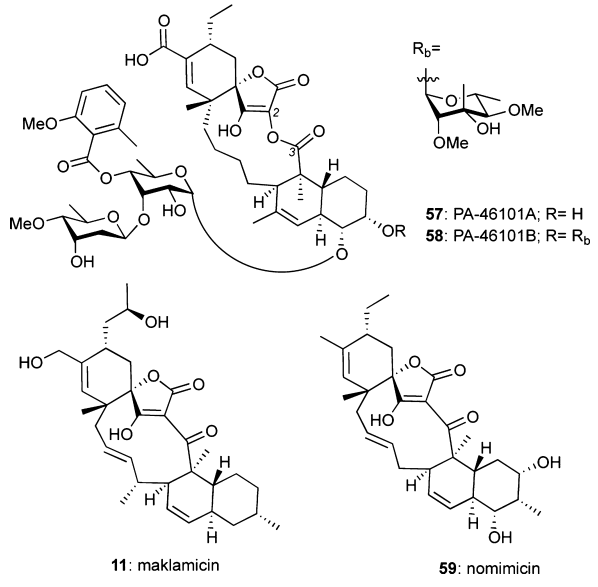


**Figure 10.** Structures of PA46101 A/B, maklamicin, and nomimicin.

**Spirotetronates as Potential Leads in Metabolism and Digestion.** *Chlorothricin (**1**)/A88696C/F (60/61)/Tetronothiodin (**62**).* Chlorothricin (**1**) was shown to inhibit the activity of pyruvate carboxylase,[80] a key enzyme that converts pyruvate to oxaloacetate, thus allowing consumption of glucose through the Krebs cycle (Figure 11). Inhibition of pyruvate

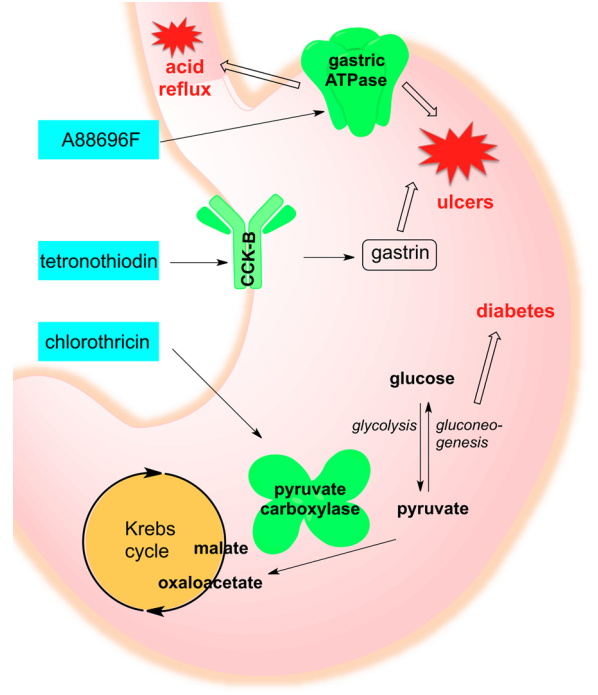


**Figure 11.** Effects of spirotetronate polyketides on metabolic pathways and digestion.


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carboxylase leads to an increase of pyruvate concentration in liver, which through gluconeogenesis accounts for accumulation of glucose, ultimately leading to diabetes.[81] Moreover, an inhibitory effect of **1** on malate dehydrogenase, an enzyme that oxidizes malate to oxaloacetate in the Krebs cycle, has also been reported.[82] It should be noted, however, that the direct cellular target of **1** is under debate and may involve interaction with components in the cell membrane that may account for the observed downstream effects.[83]

Although the potential anticancer properties of chlorothricin (**1**) have not been investigated, C-31 hydroxychlorothricin (Figure 1) was shown to exhibit antitumor activity at 40 mg/kg against implanted Ehrlich carcinoma cells in mice with an $LD_{50}$ of 295 mg/kg.[84] C-28 methyl ester of chlorothricolide (**2**),[85] the aglycone of **1** (Figure 1), also inhibits pyruvate carboxylase albeit at higher concentrations than **1**, suggesting that glycosylation enhances biological activity.[80a]

Efforts to discover new gastric ATP-ase inhibitors[86] led to the isolation of A88696F (**61**) and its dehydroxylated counterpart A88696C (**60**).[87] Hydroxylation at C-3 was found to enhance the biological activities since **61** was the most active, with an $IC_{50}$ at 0.5 $\mu$M, while **60** was considered inactive.[87]

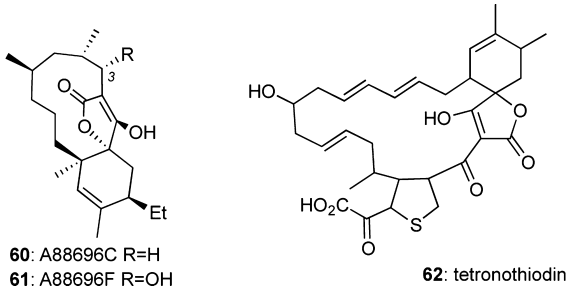



**Figure 12.** Structures of A88696C/F and tetronothiodin.

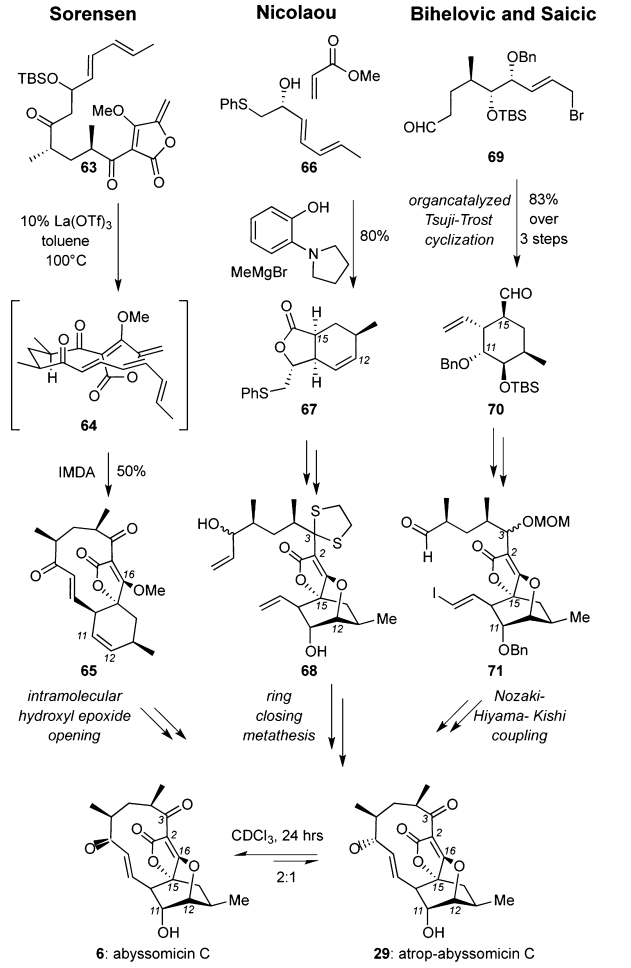
Isolated from a *Streptomyces* species, tetronothiodin (**62**) was shown to inhibit brain-type cholecystokinin (CCK)-B receptor in rat cerebral cortex with an $IC_{50}$ value of 3.6 nM.[88] It is worth noting that CCK receptors are structurally similar to gastrin and are used throughout the central nervous system (CNS) and gastric tract.[89] Interestingly, **62** has 27 000 times higher affinity for CCK-B over CCK-A in rat models.[89a] Thus, in addition to its pharmaceutical promise, **62** could be used as a tool to study the CCK-B/CCK-A signaling pathway.[90]

## SYNTHETIC APPROACHES TOWARD SPIROTETRONATE POLYKETIDES

In this part of the review, we highlight the key steps toward the synthesis of selected spirotetronates. When possible, we compare the various strategies in terms of overall efficiency.

**Class I, $C_{11}$ Spirotetronates: Abyssomicins (6 and 29).** Abyssomicin C (**6**) and its atropisomer **29** contain a rigid oxabicyclo [2.2.2] octane substructure that encapsulates the spirotetronate moiety. To date, three chemical syntheses of **6** and **29** have been reported. The key transformations are highlighted in Scheme 4. Sorensen's group used a biomimetic IMDA to construct spirotetronate moiety **65** from diene **63**. C-11−C-12 epoxidation of **65** followed by C-16 intramolecular enol epoxide opening produced a 1:1 mixture of abyssomicin C (**6**) and *atrop*-abyssomicin (**29**).[91] A similar strategy has been implemented by the Snider[92] and Couladouros[93] groups.

**Scheme 4. Highlights of Abyssomicin C Syntheses**




The Nicolaou group's synthesis of abyssomicin C is highlighted by an intermolecular Diels−Alder cycloaddition that furnishes cyclohexene **67** with the desired stereochemistry (Scheme 4).[33] A ring-closing metathesis (RCM) was used to generate the macrocyclic skeleton of **6** from diene **68**. Interestingly, the authors showed that treatment of **29** with lithium selectride led to formation of abyssomicin D (**32**). Interestingly, this finding supports the notion that abyssomicin C (**6**) is a biosynthetic progenitor of **32** and further validates the proposed mechanism of abyssomicin C deactivation as presented in Scheme 3.[33]

More recently, the groups of Bihelovic and Saicic reported a synthesis of **29**.[94] Key to their approach was a Tsuji−Trost cyclization that constructed cyclohexene **70**. The $C_{11}$ macrocycle of **29** was subsequently formed using an intramolecular Nozaki−Hiyama−Kishi coupling. Interestingly, this strategy produces exclusively *atrop*-abyssomycin C.[94] It is likely that the restricted rotation around the C-2 and C-3 centers, due to the $sp^2$ hybridization, affects the formation of the two isomers. In support of this hypothesis, the Nicolaou group has shown that **29** can be converted to **6** by protonating the C-16 oxygen under mild acidic conditions.[33] Other studies toward the abyssomicin scaffold have been reported in addition to the mentioned total syntheses.[95]

**Class I, $C_{13}$ Spirotetronates: Okilactomycins (54 and 7).** Smith et al. reported the first total synthesis of okilactomycin **54** in 29 steps.[96] Key to the strategy was a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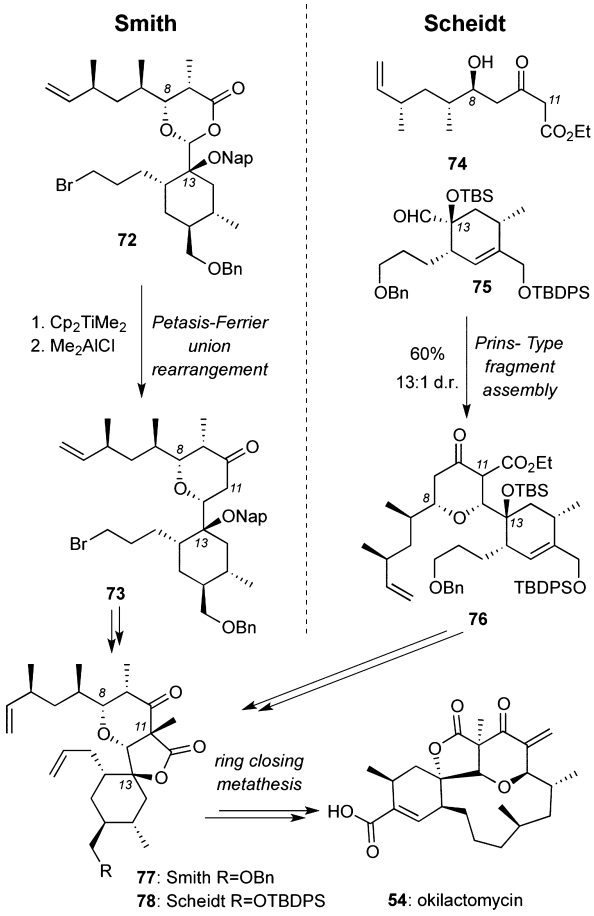
Petasis–Ferrier union/rearrangement of **72**[97] that yielded the 2,6-*cis*-tetrahydropyranone ring **73**. Ring-closing metathesis of **77** using Hoveyda–Grubbs second-generation catalyst was used to construct the 13-membered macrocycle of **54**.[96]

More recently, the Scheidt group also reported a synthesis of okilactomycin. Key to this approach was a Prins-type fragment assembly[98] between cyclohexene **75** and $\beta$-keto-ester **74** that formed the 2,6-*cis*-tetrahydropyranone ring of **76**. Similarly to the Smith approach, an intramolecular ring-closing metathesis using Grubbs second-generation catalyst constructed the macrocycle.[99] Additional synthetic studies toward okilactomycin have been reported by the Yoshii[100] and Paquette groups.[101]

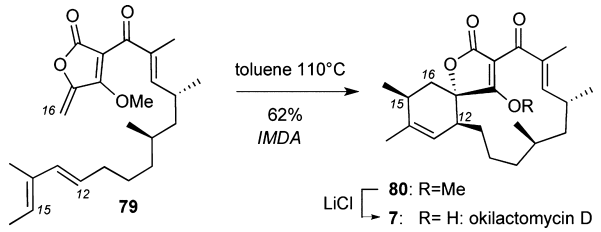
**Scheme 5. Highlights of Okilactomycin Syntheses**



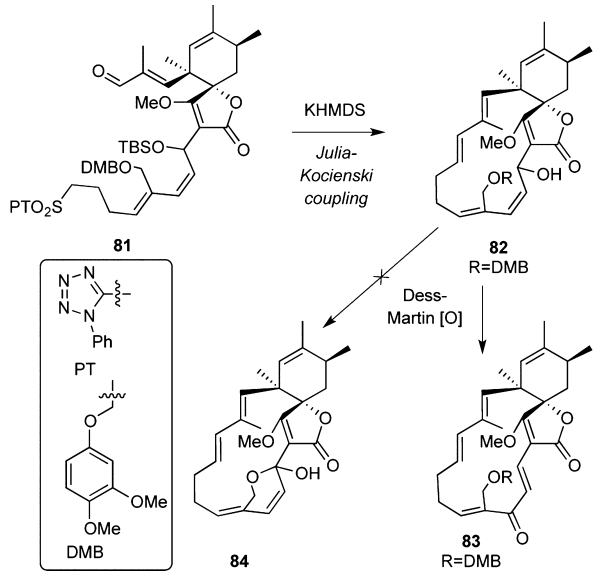

Hoye et al. reported the first total synthesis of (±)/(−)-okilactomycin D (**7**). Key to this strategy was an IMDA cycloaddition that formed spirotetronate **80** from precursor **79**. The overall synthesis proceeds in 13 linear steps (17 total steps) and 17% yield. Remarkably, demethylation of tetronate **80** was efficiently conducted on a 3 g scale.[102]

**Class I, $C_{15}$ Spirotetronates: Spirohexenolides A and B.** The Burkart group reported a strategy toward spirohexenolides based on an intermolecular Diels–Alder cycloaddition (Scheme 7).[103] A ring-closing Julia–Kocienski coupling was applied for the synthesis of macrocycle **82**. Although the projected intramolecular hemiacetalation to **84** failed due to an oxidative rearrangement of **82** to **83**, the overall strategy has successfully installed the major skeletal features of spirohexenolides.[104]

**Scheme 6. Highlights of Okilactomycin D (7) Synthesis**

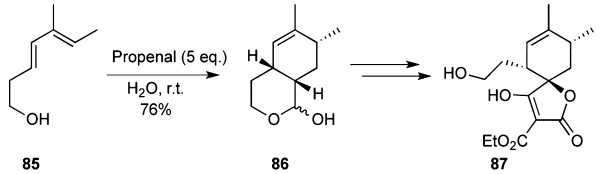



**Scheme 7. Highlights of Synthetic Efforts toward Spirohexenolides**




**Class I, $C_{17}$ Spirotetronates: Tetronothiodin (62).** Structurally tetronothiodin is highlighted by an $\alpha$-acyl tetronic acid moiety and tetrahydrothiophene moiety. Page et al. have reported a synthesis of the spirotetronate subunit isomer **87** using a Diels–Alder reaction with propenal and the hydroxyl diene **85** to install the desired stereochemistry of **86** (Scheme 8). Further functional modifications led to the synthesis of spirotetronate **87**.[105]

**Scheme 8. Synthetic Studies toward Tetronothiodin**




*Class II, $C_{13}$ Spirotetronates: Tetronolide (**12**)/Kijanolide (**44**) and Chlorothricolide (**2**).* To date there are no reported total syntheses of any class II, $C_{13}$ spirotetronates. Several strategies have been employed for the synthesis of tetronolide (**12**), the aglycone of tetrocarcin A (**47**), kijanolide (**44**), the aglycone of kijanimicin (**42**), and chlorothricolide (**2**), the aglycone of chlorothricin (**1**). Tetronolide has been synthesized by Yoshii[106] and Boeckman,[107] while an improved formal synthesis has also been reported by Roush.[108] In general, these strategies rely upon independently constructing the spirotetronate and decalin moieties and then connecting them to form

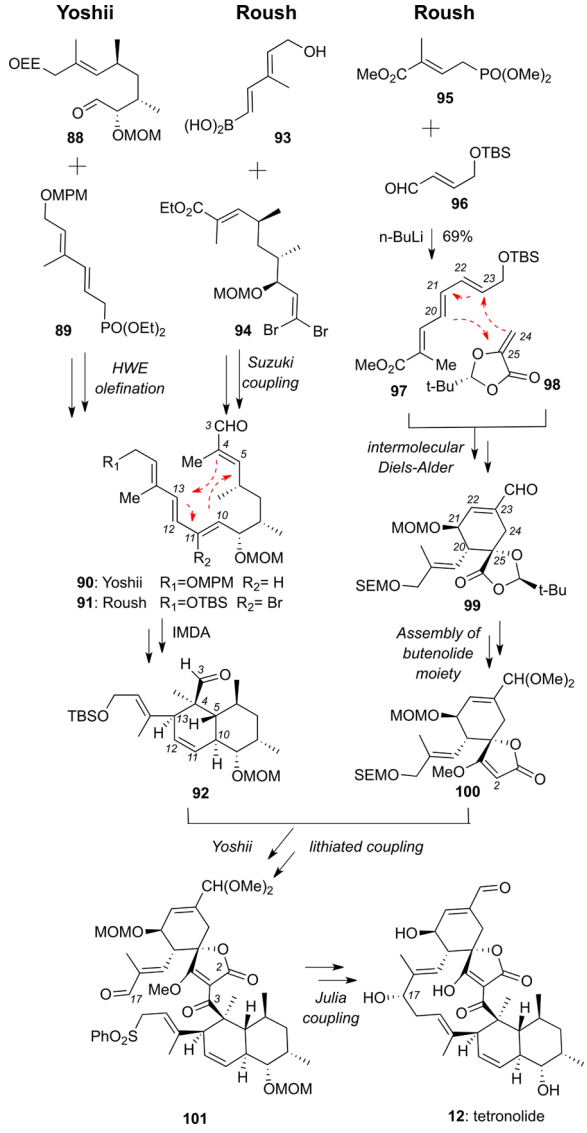

dx.doi.org/10.1021/np500757w | J. Nat. Prod. 2015, 78, 562–575

the $C_{13}$ macrocycle. A remarkable synthesis of chlorothricolide (**2**) was reported by the Roush group.[109]

The Yoshii and Roush syntheses of the decalin moiety **92**, common to both tetronolide and kijanolide, are summarized in Scheme 9. In Yoshii's approach a Horner–Wadsworth–Emmons (HWE) olefination between **88** and **89** was used to construct polyene **90**, which underwent an IMDA reaction to produce decalin **92**.[106,110] The Roush group implemented a Suzuki coupling between **93** and **94** to form polyene **91**, which, following further functionalizations, gave rise to decalin **92** via an IMDA cycloaddition.[108,111] A similar approach toward decalin **92** has been reported by the Marshall group.[112]

A synthetic approach toward spirotetronate **100** has been reported by Yoshii[113] and subsequently optimized by Roush.[108,114] This approach is based on constructing triene **97** via a HWE olefination between **95** and **96**. An intermolecular Diels–Alder of diene **97** and chiral dienophile **98**, followed by oxidative functionalization and double-bond migration, yielded enal **99**. Coupling of lithiated spirotetronate **100** with aldehyde **92** followed by subsequent functionalizations yielded sulfone **101**, which, under Julia coupling conditions, gave rise to the 13-membered macrocycle of **12**.[106]

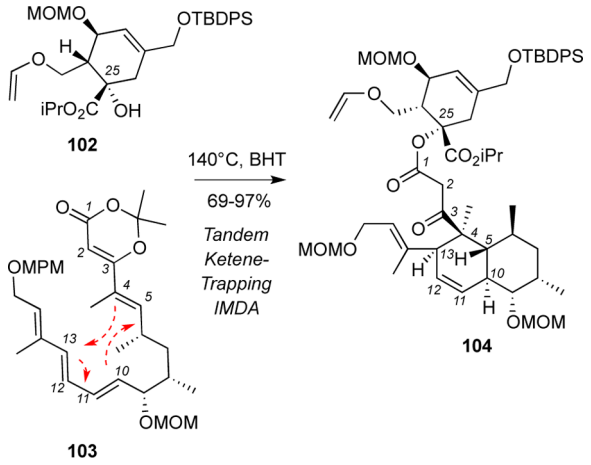
**Scheme 9. Highlights of Tetronolide Syntheses**




Boeckman's group synthesis of **12** is highlighted by a tandem ketene-trapping [4+2] cycloaddition of diene **103** and alcohol **102** to form spirotetronate subunit **104**. Conversion of **104** to tetronolide **12** was accomplished under Julia conditions. Overall, this approach significantly reduces the number of steps required for completion of the tetronolide synthesis.[107,115]

Various synthetic studies toward kijanolide (**44**) have been reported by the groups of Marshall,[116] Yoshii,[117] and Roush.[118] These strategies rely on intermolecular Diels–Alder reactions and ketene-trapping strategy to form the desired macrocycle.[119] Application of a Julia coupling to the synthesis of 28,29-bisnor-(+)-kijanolide has been reported by the Yoshii group.[120]

**Scheme 10. Highlights of the Boeckman Strategy toward Tetronolide**




A tandem intra/intermolecular Diels–Alder reaction between polyene **105** and chiral dienophile **98** was implemented for the synthesis of chlorothricolide (**2**) (Scheme 11). The reaction gave the desired cycloadduct in 40% yield together with partially reacted decalin **107**. Upon treatment with dienophile **98**, **107** was converted to the desired product **106** in 58% yield.[109] Construction of the spirotetronate unit followed by coupling with the allyl ester completed the synthesis of **2**.

A late-stage IMDA reaction was used by Yoshii's group for the synthesis of (±)-24-*O*-methylchlorothricolide (Scheme 12). Although the selectivity of the IMDA reaction was moderate, the overall strategy represents a noteworthy bioinspired approach toward these compounds.[121] The groups of Marshall,[112c,d,122] Ireland,[123] Snider,[124] Schmidt,[125] and Meyers[126] have also reported studies toward the synthesis of **2**.

*Class II, $C_{17}$ Spirotetronates: Versipelostatin (**51**).* Numerous synthetic studies have been reported toward the total synthesis of versipelostatin A (**51**), but to date its total synthesis has not been completed. Kirschning's[127] and Takahashi's[72] groups provided synthetic strategies to the trisaccharide moiety. A synthesis of the versipelostatin (**51**) trisaccharide **114** is shown in Scheme 13.[72] Key to the synthesis is a Schmidt glycosylation of **110** with trichloroacetimidate **111**. The resulting disaccharide **112** was deprotected and coupled with L-oleandrosyl imidate **113** to produce **114** (Scheme 13). Further functionalization of glycosyl **114** and Schmidt glycosylation with acetyl C-7–C-9–C-37 versipelostatin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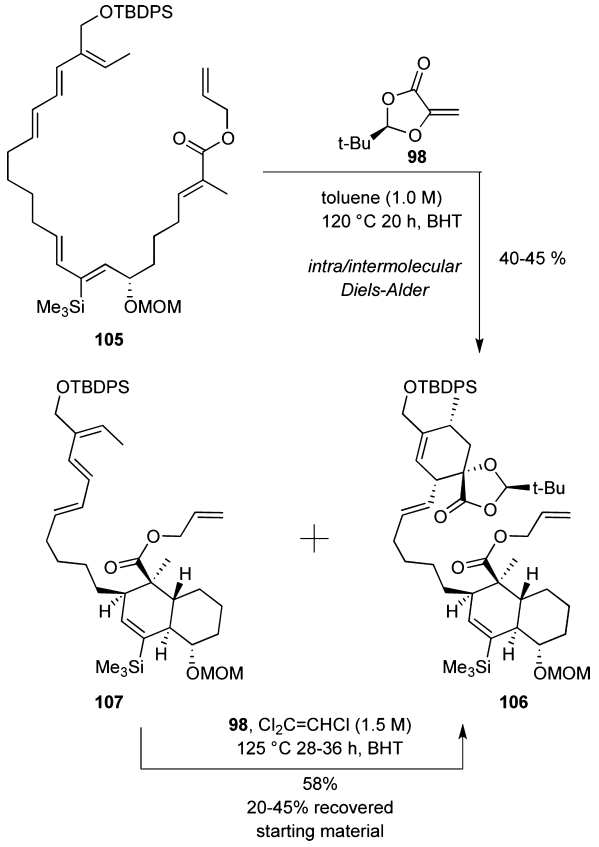
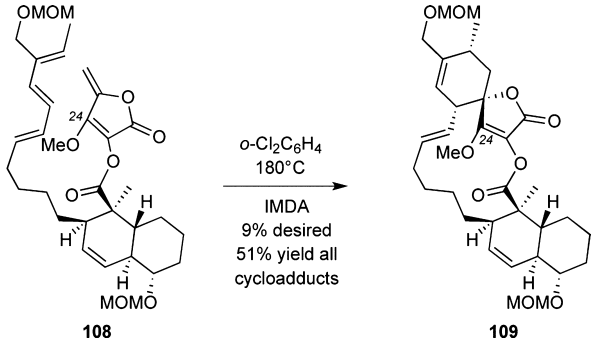
**Scheme 11. Highlights of the Roush Strategy toward Chlorothricolide**



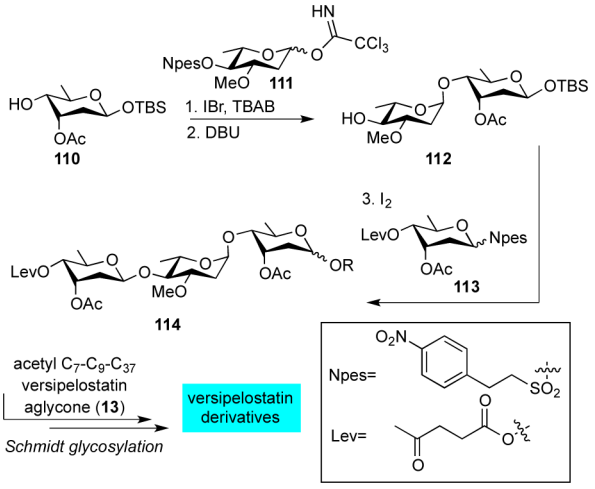

**Scheme 12. Highlights of the Yoshii Strategy toward (±)-24-*O*-Methylchlorothricolide**




aglycone **13** (Figure 2) yielded a versipelostatin derivative used for biological studies. On the basis of NMR and biological consideration, the oleandrose sugar was structurally reassigned from D to L. An alternate strategy used was adding each sugar individually to the versipelostatin aglycone, thus elongating the glycosyl chain.[72] Various approaches toward the spirotetronate unit of the versipelostatin have been reported.[128]

**Quartromicins (10).** A stereocontrolled Diels–Alder reaction has been implemented by the Roush group for the synthesis of the quartromicin spirotetronate unit.[103a,129] In addition, this group reported a strategy of connecting subunits **115** and **116** together using lithium halogen exchange and $CeCl_3$ coupling.[130] Bedel's group offered an alternative strategy of constructing the spirotetronate subunits using RCM, but to

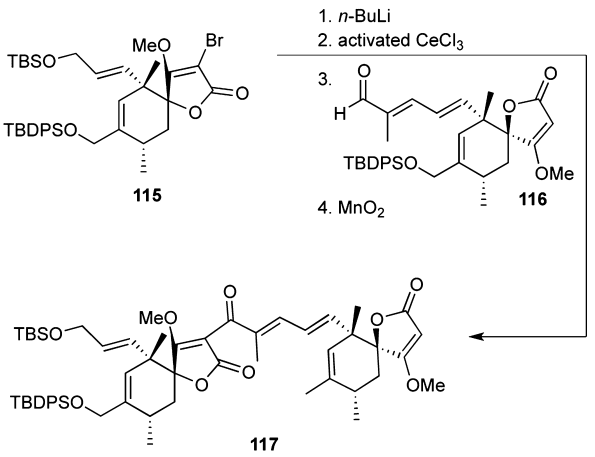
**Scheme 13. Synthetic Studies toward the Glycosyl Moiety of Versipelostatin A**




date no total syntheses of quartromicins have been completed.[131]

**Scheme 14. Connection of Spirotetronates for Quartromicins**

**Quartromicins (10).**




## CONCLUSIONS

The discovery of penicillin revolutionized pharmaceutical research by demonstrating, for the first time, that microorganisms can produce secondary metabolites of value to medicine. Since then, cultured microorganisms have been recognized as prolific producers of secondary metabolites that are used either directly as drugs or have inspired the design of drugs.[66a,132] On the other hand, the intricate structures of these compounds represent exceptional tools to explore new biological pathways and unknown mechanisms of action. These qualities, although scattered, are observed in the family of spirotetronate polyketides and provide evidence for their significant but still untapped pharmacological value.

More than 40 years after the discovery of chlorothricin, the spirotetronate family has grown to include over 70 macrocycles of various sizes that, in certain cases, are decorated with carbohydrate side chains. In addition to their potent antitumor and antibiotic activities, certain spirotetronates were charac-


dx.doi.org/10.1021/np500757w | J. Nat. Prod. 2015, 78, 562–575

terized as "the first" tools to elucidate a biological effect.[8a,55a,66a] For example, versipelostatin was found to induce potent and selective cytotoxicity in glucose-deprived tumor cells.[68] Moreover, abyssomicin C was found to be the first natural product to block *p*ABA biosynthesis, a pathway essential to bacteria but insignificant to humans.[8a] Impressive synthetic and chemical biology efforts were combined to decipher the mode-of-action of abyssomicins at the molecular level.[31,33c] This underscores the enormous significance of the spirotetronate polyketide family to biology in addition to their pharmacological potential.

Several studies have documented the significance of the carbohydrate chains for the observed antibiotic activity of spirotetronates.[44,63b] However, with the exception of abyssomicins, there is no clear understanding of the biological significance of the spirotetronate aglycone core. At present, chemical strategies developed toward the synthesis of spirotetronates have uncovered the value of certain key reactions, such as Diels–Alder cycloaddition, ring -closing metathesis, and Julia olefination. Nonetheless, the vast majority of these strategies have not yielded sufficient amounts of compound for a methodical structure–activity relationship study, thereby hampering rational drug design. It is evident that a methodical fragment-based approach to this structure, in combination with chemical biology studies, will be highly beneficial, as it could reveal the role of the spirotetronate motif, the effect of the macrocyclic size, and the role of the decalin system. In turn, this effort would allow a detailed evaluation and optimization of the spirotetronate pharmacophore. In addition to a dearly needed scalable synthesis,[133] advances in microbial biosynthesis[134] should offer a potential solution to large-scale production or semisynthesis of a lead candidate. A combination of these efforts should unveil the pharmacological value of spirotetronates and would have significant impact in current efforts toward personalized medicine.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

Financial support from the National Institutes of Health (CA 133002) is gratefully acknowledged. We also thank the UCSD Academic Senate and the U.S. Department of Education for a Fellowship to M.H.L. through GAANN grant P200A120223. We thank the National Science Foundation for instrumentation grants CHE9709183 and CHE0741968.

## DEDICATION

Dedicated to Dr. William Fenical of Scripps Institution of Oceanography, University of California–San Diego, for his pioneering work on bioactive natural products.

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