Recent progress regarding the bioactivities, biosynthesis and synthesis of naturally occurring resorcinolic macrolides

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Macrolides, which comprise a family of lactones with different ring sizes, belong to the polyketide class of natural products. Resorcinolic macrolides, an important subgroup, possess interesting structures and exhibit a wide variety of bioactivities, such as anti-tumor, anti-bacteria, and anti-malaria activities, etc. This review summarizes progress in isolation, bioactivity studies, biosynthesis, and representative chemical syntheses of this group of macrolides in recent decades, encompassing 63 naturally occurring macrolides published in 120 articles.

Keywords: natural product; resorcinolic macrolide; fungal metabolite; bioactivity; anti-tumor; anti-bacteria; anti-malaria; biosynthesis

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Introduction

Natural macrolides produced via polyketide synthase (PKS) pathways are a prolific source of new small-molecule chemical entities for developing clinical drugs. This is not surprising given their diverse pharmacological properties and unexpected structures/skeletons. Among natural macrolides, resorcinolic acid lactones (RALs) and dihydroxyphenylacetic acid lactones (DALs), which are characterized by possessing a macrolide core structure fused to a resorcinol aromatic ring, belong to a unique family of naturally occurring homologous macrolides[1]. Structurally, RALs and DALs are based on a substituted resorcinol fragment fused to the α, β-, and β, γ-positions of the macrocyclic lactone ring, respectively. The generic molecular structures of these compounds are shown in Figure 1. These macrolides, derived from the PKS system in various species of fungi, usually exhibit versatile biological activities, e.g., anti-tumoral, anti-bacterial, and anti-malarial activities[2, 3]. Due to their interesting structures and promising bioactivities, resorcinolic macrolides have attracted extensive attention from pharmacologists, and natural product and synthetic chemists worldwide in recent decades[4, 5].

Since radicicol (1), the first-discovered RAL, was first isolated from the fungus Monocillium nordinii in 1953[2], many natural resorcinol macrolides with remarkable bioactivities have been isolated from diverse fungal sources or synthesized by chemists[6–8]. A topical review by Winssinger and Barluenga that covered the literature up to 2007 dealing with the chemistry and biology of RALs is available[3]. However, knowledge regarding the resorcinol class of macrolides has developed so rapidly in recent years that an updated and state-of-the-art overview is required. This review of the scientific literature and our recent work focuses on reports regarding the isolation, bioactivities, biosynthesis, and some representative chemical syntheses of this class of macrolides that have been published over the last 60 years. More than 60 resorcinolic macrolides are summarized herein, and over 100 references have been cited. For ease of comparison, these natural resorcinolic macrolides are grouped and reviewed according to ring size: four-
teen-membered, twelve-membered, and ten-membered. The names, sources and references of and for these compounds are listed in Table 1.

Structure and bioactivity
Resorcinolic macrolides have been known since the first isolation of radicicol (monorden, 1) in 1953, followed by a DAL (curvularin, 50), which was isolated in 1959. Since then, a variety of this class of macrolides bearing a substituted benzene ring and various sizes of lactone ring equipped with double bonds and oxygen-containing groups (carbonyl, epoxy, or hydroxyl groups) have been identified. Importantly, most of these compounds exhibited various bioactivities, including anti-tumoral, anti-fungal, and enzyme inhibitory activities. Among these secondary metabolites, about five in six macro- lides structurally belong to the RAL group (51 RALs and 12 DALs). Interestingly, ten-membered resorcinolic macrolides are dominated by DALs (2 RALs and 7 DALs). In this section, the structures and bioactivities of fourteen-membered macrocycles (Figure 2) are described first, followed by twelve-membered (Figure 3) and ten-membered macrolides (Figure 4).

Radicicol (1) was initially named monorden in 1953[2]; then, in 1964, the same metabolite isolated from Nectria radicicola was given the formal name of radicicol, and its structure was revised to 1, as shown in Figure 1[5]. Because the structure of monorden was originally incorrect, the name radicicol has prevailed. Radicicol (1) was originally identified as an anti-fungal antibiotic[2]; later, it was identified as having several other bioactivities. For example, radicicol (1) was reported to have a mild sedative activity[46] and was also rediscovered as an inhibitor of the signal transduction of oncogene products (e.g., K-ras and v-Src) in yeast and mammalian cell-based assays in 1992[11, 12]. Importantly, this macrolide was revealed as a potent and selective inhibitor of heat shock protein 90 (Hsp90)[13, 14]. Hsp90 is considered a promising therapeutic target for anticancer drug development because inhibition of Hsp90 results in the simultaneous destabilization and degradation of a wide range of oncogenic proteins, leading to tumor cell growth inhibition and apoptosis[15, 16]. Pearl and coworkers discovered that radicicol inhibits the ATPase activity of Hsp90 via competitive binding to the N-terminal ADP/ATP binding pocket with nanomolar affinity, leading to the inactivation of Hsp90 chaperoning ability[16].

Zearalenone (2) has attracted great attention because it is responsible for the toxicity of an agriculturally damaging fun-

Table 1. Natural resorcinolic macrolides.

| Compounds | Name | Source | References |
|-----------|------|--------|------------|
| 1         | Radicicol | Monocillium nordinii, Nectria radicicola | [2, 9] |
| 2         | Zearalenone | Gibberella zaeae | [17] |
| 3         | LL-Z1640-2 | Lederle Culture Z1640 | [20] |
| 4         | Hypothemycin | Hypomyces tricothecoides, Coriolus versicolor | [23–25] |
| 5         | 4-O-demethylhypothemycin | H tricothecoides DSM 11931 and DSM 11932 | [27] |
| 6–10      | Monocilmins I, II, III, IV, V | Mortlicilliorm nordirii | [28] |
| 11        | Radicicol analogue A | Fungus | [30] |
| 12        | L-783277 | Phoma | [26] |
| 13–17     | Aigialomycins A–E | Aigialus parvus | [25] |
| 18–23     | Pochonins A–F | Pochonia chlamydospora | [6] |
| 24–29     | Pochonins K–P | Pochonia chlamydospora | [31] |
| 30–36     | Paecilomycins A, B, E, F, G–I | Paecilomyces | [32, 33] |
| 37–39     | Cochliomycins A–C | Cochliobolus lunatus | [34] |
| 40–42     | Neocosmosin A–C | Neocosmospora | [35] |
| 43        | Lasiodiplon | Botryodiplodia theobromae, Euphorbia splendens | [36, 37] |
| 44        | de-O-methyllasiodiplon | Botryodiplodia theobromae, Armeba euchroma | [36, 38] |
| 45–46     | (3R,5S)-5-hydroxy-de-O-methylasiodiplon, 6-oxo-de-O-methylasiodiplon | Syncephalastrum racemosum | [41] |
| 47–48     | Trans-resorcylic, cis-resorcylic | Penicillium | [42, 43] |
| 49        | Dihydroresorcylic | Acremonium zaeae | [7] |
| 50–51     | Curvularin, 10,11-dehydrocurvularin | Curvularia, Aspergillus aureofulgens, Alternaria cinerariae, Curvularia eragrostidis, Penicillium, Nectria galliagna, Eupenicillium, Chrysosporium lobatum | [47–55] |
| 52–53     | 11-α-methoxycurvularin, 11-β-methoxycurvularin | Penicillium citreovire | [60] |
| 54        | Citreofuran | Penicillium citreovire | [63, 64] |
| 55–56     | (3R,5R)-sonnerlactone, (3R,5S)-sonnerlactone | Sonneratio apetala | [8] |
| 57        | Sporostatin | Sporormiella | [65, 66] |
| 58–60     | Xestodecalactones A–C | Penicillium of montanense | [67] |
| 61–63     | Xestodecalactones D–F | Corynespora cassiicola | [68] |
Figure 2. Structures of RALs 1–42.
gus\textsuperscript{[17]}. Later, this compound was found to exhibit estrogen agonistic properties by a direct interaction on the estrogen receptor in competition with 17-estradiol\textsuperscript{[18]}. In addition, this compound exhibited anabolic properties, enabling its use as a bovine growth stimulant\textsuperscript{[19]}.

LL-Z1640-2 (3) was found to be competitive with ATP and to irreversibly inhibit TAK1 (IC\textsubscript{50}=8.1 nmol/L)\textsuperscript{[20, 21]}, possibly explaining its effectiveness at preventing inflammation in an animal model. Further biological evaluation indicated that macrolide 3 is also an ERK2 inhibitor (IC\textsubscript{50}=8.0 nmol/L)\textsuperscript{[22]}.

Hypothemycin (4) was originally isolated from the fungus Hypomyces tricothecoides in 1980\textsuperscript{[23]}. Later, this molecule was identified from other genera of fungus, for example in Coriolus versicolor in 1993\textsuperscript{[24]} and in the lignicolous mangrove fungus Aigialus parvus in 2002\textsuperscript{[25]}. This macrolide exhibits anti-fungal\textsuperscript{[20]} and moderate anti-malarial\textsuperscript{[25]} activities, as well as cytotoxicity against various murine and human cell lines\textsuperscript{[26]}. In addition, this compound was found to be an MEK1 inhibitor (IC\textsubscript{50} value, 15 nmol/L)\textsuperscript{[26]}. Further investigation of the fungus H tricothecoides resulted in the isolation of 4-O-demethylhypothemycin (5)\textsuperscript{[27]}, which exhibits potent and selective cytotoxicity against a panel of BRAF mutation human cell lines.

Pochonins A-F (18–23) were obtained from cultures of the clavicipitaceous hyphomycete Pochonia chlamydosporia var catenulata strain P 0297 in 2003\textsuperscript{[6]}. These pochonins inhibited Hsp90 and exhibited antiviral activity against herpes simplex virus 1 (HSV1); pochonin C (20) was the most potent. In 2009, further research on the chemical constituents of the same fungus (P chlamydosporia) led to the isolation of pochonins K-P.
Shinonaga et al evaluated pochonins and related natural analogs with respect to their inhibitory activity against WNT-5A expression and their cytotoxicities against dermal papilla cells. WNT-5A, a secretory glycoprotein, plays a role in the proliferation of dermal papilla cells. A preliminary SAR study implied that the 4,5-epoxide or 4,5-E-olefin moieties might be necessary for radicicol-type macrolides to inhibit WNT-5A expression, and the chlorine atom at the C-13 position might decrease the toxicity against dermal papilla cells.

Paecilomyccins A, B, E, and F (30-33) were isolated from a mycelial solid culture of Paecilomyces sp SC0924 in 2010[32]. Among these molecules, paecilomycin E (32) exhibited potent anti-plasmodial activity against Plasmodium falciparum line 3D7 (IC50 value, 20.0 nmol/L), and paecilomyccins E (32) and F (33) exhibited moderate activity against the P. falciparum line Dd2. One year later, paecilomyccins G-I (34-36) were isolated from a culture broth of the same fungus[33].

Cochliomycins A-C (37-39) were isolated from a culture broth of Cochliobolus lunatus, a fungus obtained from the gor- gonian Dichotella gemmacea that was collected in the South China Sea in 2011[34]. Cochliomycin A (37) exhibited potent anti-fouling activity against the larval settlement of the barnacle Balanus amphitrite and exhibited moderate anti-bacterial activity against Staphylococcus aureus.

Recently, bioassay-guided fractionation of an unidentified species of the fungus Neocosmospora resulted in the isolation of three new RALs, neocosmosins A-C (40-42)[35]; among these, neocosmosin C (42) exhibited potent and full agonistic activity against the human δ-opioid receptor.

The 12-membered lasiodiplodin (43) and de-O-methyllassiodiplodin (44), which were isolated from a culture broth of the fungus Botryodiplodia theobromae (formerly Lasiodiplodia theobromae) for the first time in 1971, were found to exhibit plant growth-regulating properties[36]. Subsequently, both of these RALs have been frequently isolated from various natural sources and determined to have various bioactivities. For example, lasiodiplodin (43), which was isolated from the stems and leaves of Euphorbia splendens, exhibited anti-leukemic activity[37]. De-O-methyllassiodiplodin (44), which is found in the roots of Arnebia euchroma (a traditional Chinese medicine), was found to be responsible, at least in part, for the pharmacological properties of the plant extracts as the result of its efficient inhibition of prostaglandin biosynthesis[38]. Recently, 44 was reported to be a potent inhibitor of pancreatic lipase (PL) (IC50=4.73 μmol/L), an enzyme that plays a key role in the efficient digestion of triglycerides and that is a target for treating obesity[39]. In addition, 44 was found to be a novel, natural, non-steroidal mineralocorticoid receptor (MR) antagonist (IC50=8.93 μmol/L) and an efficient therapeutic target for the treatment of hypertension and other cardiovascular diseases[40]. Furthermore, compound 44 also exhibited cytotoxicity against KB, BC1, and NCI-H187 cell lines with IC50 values ranging from 9.65 to 12.67 μg/mL[41].

Recently, chemical investigation of metabolites of the fungus Syncephalastrum racemosum led to the isolation of two natural RALs, (3R),(5S)-5-hydroxy-de-O-methyllassiodiplodin (45) and 6-oxo-de-O-methyllassiodiplodin (46)[41]. The absolute configuration of 45 was determined using a modified Mosher’s method. Bioassays indicated that 45 was cytotoxic against several tumor cell lines, including cholangiocarcinoma, KKU-M139, KKU-M156, and KKU-M213, with IC50 values in the range of 14-19 μg/mL.

Two isomers, trans-resorcyllide (47) and cis-resorcyllide (48), were isolated independently from various species of the genus Penicillium[42, 43]. The former resorcyllide (47), a plant growth inhibitor, was >10 times more effective than its isomer 48 at inhibiting seedling root elongation. In addition, resorcyllide (47) exhibited cytotoxicity against a panel of tumor cell lines, inhibitory activity against 15-hydroxyprostaglandin dehydro- genase, and anti-microbial activity against Pyricularia oryzae[44]. Cis-resorcyllide (48) inhibited activated factor XIII (FXIIIa), an enzyme that catalyzes a number of covalent cross-linking reactions of fibrin in blood clots[45].

Dihydropseudopsefodiolide (49), which exhibits phytotoxic activity, was recently isolated from fermentation extracts of an endo- phyte Acremonium zeae by Poling et al[7]. The configuration of a methyl group in 49 had been originally determined to be the S configuration; however, the optical rotation sign of naturally isolated 49 [α]25D+15.0 (c 0.33, MeOH) is opposite to that of the recent reported synthetic 49 [α]25D-4.0 (c 0.8, MeOH)[46], indicating that the configuration of naturally isolated 49 most likely needs to be investigated further.

Two DALs, curvularin (50) and 10,11-dehydrocurvularin (51), were reported to be produced by various genera of fungi including Curvularia sp[47, 48], Aspergillus aurofulgens[49], Alternaria cinerariae[50], C eragrostidis[51], Penicillium sp[52], Nectria galligena[53], Eupenicillium sp[54], and Chrysosporium lobatum[55]. Both compounds were found to have a variety of bioactivities. For instance, curvularin (50) is a non-specific phytotoxin that exhibits antibiotic activity against several fungi[56], cytotoxic activity against sea urchin embryogenesis[57] and inhibitory activity against human inducible nitric oxide synthase[58]; its dehydro-derivative 51 acts as a broad-spectrum inhibitor of various cancer cell lines in vitro by overwhelming the heat shock response[59]. In addition, both macrolides exhibited similar levels of cytotoxicity against several human tumor cell lines, such as A549, HeLa, MDA-MB-231, and MCF-7[60]. Other pharmacological studies revealed that 51 was active against COLO 205 (IC50 value, 7.9 μmol/L) and exhibited good superoxide anion scavenging activity (EC50 value, 16.71 μg/ml)[59].

Two epimers, 11-α-methoxycurvularin (52) and 11-β-methoxycurvularin (53), were isolated from the hybrid strain ME 005, which is derived from the fungus Penicillium citreoviride[60]. Both curvularins exhibited considerable cytotoxicity against a panel of human cancer cell lines, including NCI-H460, MCF-7, SF-268, and MIA Pa Ca-2[52, 61]. In addition, these compounds inhibited sea urchin embryogenesis by acting on components of the mitotic apparatus[57] and Hsp90[62]. Another uncommon DAL, citreofuran (54), was produced by a hybrid strain of P citreoviride ME 0005[63, 64]. It is worth noting that 54 is structurally unique within the class of polyketide-derived lactones with respect to its furylphenyl moiety.
Recently, Li et al\(^6\) reported the chemical investigation of the endophytic fungal strain Zh6-B1, which is obtained from the bark of mangrove Sonneratia apetala plants collected from Zhuhai, Guangdong, China; this study led to the isolation of (3R,5R)-sonnerlactone (55) and (3R,5S)-sonnerlactone (56). The absolute configuration of 55 was determined based on single-crystal X-ray spectroscopic data. Both sonnerlactones exhibited weak anti-proliferative activity against multidrug-resistant human oral floor carcinoma cell lines (approximately 42% at 100 μmol/L).

A study of the chemical constituents of Sporormiella sp M5032 resulted in the isolation of sporostatin (57), which was identified as an inhibitor of cyclic adenosine 3',5'-monophosphate phosphodiesterase. Further biological evaluation indicated that 57 is a specific inhibitor of epidermal growth factor (EGF) receptor tyrosine kinase in vitro. The IC\(_{50}\) values reported for this compound were 0.1 μg/mL for EGF receptor kinase, 3 μg/mL for ErbB-2, and 100 μg/mL or greater for other kinases, including the platelet derived growth factor (PDGF) receptor, v-src and protein kinase C \(^6\).

Three DALs, xestodecalactones A–C (58–60), were obtained from an isolate of the fungus Penicillium cf montanense from the marine sponge Xestospongia exigua. Among these metabolites, xestodecalactone B (59) was found to have anti-fungal activity against Candida albicans \(^6\). Chemical investigation of the fungus Corynespora cassiicola resulted in the isolation of xestodecalactones D–F (61–63) \(^6\), whose absolute configurations were determined using the TDDFT ECD (time-dependent density functional theory electronic circular dichroism) method, proving that they belong to the (11S) series of xestodecalactones rather than possessing the (11R) configuration of the former xestodecalactones 58–60.

**Biosynthesis**

Due to the intriguing structures and bioactivities of the above macrolides, it is significant to understand how they are synthesized in nature. To date, research on the biosynthetic pathway of these molecules has attracted great attention from natural product chemists and biologists. Although these macrolides are produced by a variety of different fungal species, they are known to be produced via similar polyketide synthase (PKS) pathways. Of course, subtle differences exist between the biosynthetic pathways for RALs and DALs.

The biosynthesis of zearalenone (2) in Gibberella sp has been well studied. Early labeling and feeding experiments showed that the carbon atoms are derived from acetate and that zearalenol is a precursor of 2 \(^6\). Recently, the biosynthesis of 2 involves two fungal PKSs, PKS4 (a highly reducing PKS, hrPKS), and PKS13 (a nonreducing PKS, nrPKS); these PKSs function collaboratively to yield a macrolactone with a resorcylate core. Gaffoor et al cloned and characterized two genes encoding PKS4 and PKS13 from G zeae to support the view that these two PKSs comprise the core biosynthetic unit for the biosynthesis of 2 \(^73\). Lee et al determined that PKS4 and PKS13 were also required for the synthesis of 2 in G zeae \(^74\). Recently, Zhou et al reconstituted the G zeae PKS13 in vitro and revealed that PKS13 is a highly versatile polyketide macrolactone synthase \(^75\).

The biosynthesis of zearalenone (2) uses a PKS pathway involving the condensation, reduction, and subsequent cyclization reaction \(^73, 75\). The biosynthesis initially involves hrPKS which is a large multi-domain enzyme that condenses and reduces acyl-CoA units to form a hexaketide-thioester chain (C7 to C18). The chain is then transferred to an nrPKS and extended by three additional acetate units (C6 to C1). After the aldol condensation of the unreduced portion (C2 and C7) of the chain, the resorcylate moiety is constructed. Then the intramolecular transesterification between the reduced hydroxy group at C-18 in side chain and thioester functional group at C-1 resulted in the production of zearalenol. Finally, zearalenol is converted to zearalenone (2) in a post-PKS oxidation step \(^6\) (Scheme 1).

The biosyntheses of radicicol (1), hypothemycin (4), and monocillin I (6) have been proven to use a similar pathway involving hrPKS and nrPKS, although there are structural variations that have been attributed to different reduction patterns during the hrPKS step and putative post-PKS enzymatic alterations (eg, epoxidation and halogenation). Reeves et al characterized hypothemycin (4) biosynthesis using heterologous gene expression \(^6\). Hypothemycin biosynthesis has also been studied in considerable detail by the group of Tang-Vederas \(^76\); this group accomplished the complete reconstitution of the PKS Hpm8-Hmp3 activities required in vitro to synthesize RAL \(^76\) and found that β-ketoreductase possesses the ability to reduce the β-ketoacyl intermediates stereospecifically based on substrate chain length \(^76\).

In addition, members of the Tang-Vederas group studied radicicol biosynthesis via the heterologous synthesis of intermediates and analogues \(^79\). Wang et al presented a comparative sequence analysis of the radicicol (1) biosynthetic gene cluster of Chaetomium chiversi by targeting gene disruptions and isolating the corresponding metabolites \(^78\). Zeng et al

![Scheme 1](image)
studied the halogenation mechanism, one of the post-PKS steps. Zhan’s group reconstituted a fungal halogenase, Rdc2, which was isolated from *Pochonia chlamydosporia*, and characterized this enzyme as a halogenase dedicated to radicicol biosynthesis. Schemes 2 and 3 show how various related post-PKS enzymes might be employed to afford the rich diversity of RALs.

The biosynthetic mechanisms of some 14-membered RALs (e.g., zearalenone, hypothemycin, radicicol/monocillin, and dehydrocurvularin) have been rigorously proven by heterologous production and/or *in vitro* experiments. However, lasiodiplodin biosynthesis is still only predicted to involve the steps described above because the corresponding genes and enzymes have not yet been identified and studied. As demonstrated by Takasumi *et al.*[^81], lasiodiplodin (43) was predicted to be biosynthesized by a similar biosynthetic system to that of 14-membered macrolides, such as zearalenone (2) and hypothemycin (4). The presumed entire biosynthetic pathway to lasiodiplodin (43) is outlined in Scheme 4. At the beginning of the pathway, five intact acetate units are condensed by hrPKS to yield a highly reduced pantaketide acyl intermediate. The acyl chain is transferred to nrPKS, which then undergoes three malonyl-CoA condensations and an aldol condensation to yield a resorcylyl intermediate. Then, the intermediate undergoes intramolecular cyclization catalyzed by the enzyme nrPKS, leading to the formation of 44. Finally, O-methylation of the hydroxyl group on C-14 of 44 yields lasiodiplodin (43) in a post-PKS reaction.

Recently, Molnár’s group predicted the biosynthesis of the DAL, 10,11-dehydrocurvularin (51)[^82]. Heterologous expression in *Saccharomyces cerevisiae* of the predicted collaborating hrPKS-nrPKS pair of genes from this cluster yielded 51. This result provides a functional proof of the identity of the cluster and a convenient platform for the production of 51, and in the

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**Scheme 2.** Proposed biosynthetic pathway of hypothemycin (4).

**Scheme 3.** Proposed biosynthetic pathway of radicicol (1) and monocillin I (6).

**Scheme 4.** Proposed biosynthetic pathway of lasiodiplodin (43).
future, its analogs. Importantly, this work established that DALs, like RALs such as monocillin II, are also likely to be produced by iterative fungal PKS pairs; however, the AtCURS pair showed important differences from previously identified RAL synthase systems (Scheme 5). The aromatic ring in natural RALs might be formed by the aldol condensation of C-2 and C-7, whereas the aromatic ring in DALs have been proposed to be formed by the aldol condensation of C-3 and C-8. Understanding these subtle differences in the DAL and RAL biosynthetic systems would help us to further understand the complex programming mechanisms of fungal iterative polyketide synthetic enzymes.

To our knowledge, the biosynthetic pathways of ten-membered resorcinolic macrolides have not yet been reported. Research on the biosynthesis of this class of macrolides is in its infancy, mostly because ten-membered macrolides have only been discovered recently, and their numbers are still limited. However, in the light of their structural similarity, ten-membered RALs and DALs might be produced by a similar biosynthetic system to that of the above multi-membered macrolides. Due to the rapid progress that has occurred in the study of ten-membered RALs and DALs, these compounds will attract further and extensive attention from natural product chemists and biologists in an attempt to understand their biosynthetic pathways.

Chemical synthesis
Unsurprisingly, given their intriguing biological properties and attractive chemical structures, the family of macrolides has also attracted a growing interest in the organic chemistry community. To date, several bioactive natural resorcinolic macrolides or structural analogs, mainly RALs, have been totally synthesized by organic chemists. The general synthetic routes usually involve olefin metathesis catalyzed by Grubbs catalyst as the key step, together with some other classical chemical reactions (such as the Heck coupling reaction, the Witting reaction, the Mitsunobu reaction, the Stille coupling reaction, etc). Due to page limitations, only selected representative examples are described in detail below; citations regarding the syntheses of other resorcinolic macrolides have been listed in the last paragraph of this section.

Widespread interest in the anabolic properties of zearalenone (2) has stimulated chemists to invest much effort into the synthesis of this molecule. Since its first total synthesis was reported in 1967[83], more than ten synthetic strategies for 2 have been designed and reported. Generally, the target macrolide was formed by intramolecular cyclization; however, an alternative position and method for cyclization has now made the total synthesis of 2 attractive. Several different types of ring-closure approaches to synthesizing 2 are illustrated in Figure 5.

Groups at Merck[83] and Syntex[84] proposed the introduction of the double bond using a Wittig reaction in the multistep synthetic routes of the seco acid, but the yields of the following lactonization were very low. Then, Corey et al[85] used new methods for activating carboxylic acids to form lactones with alcohols in remarkably improved yields. The formation of the macrocycle at the position of the ketone group using an internal Dieckmann condensation or an intramolecular alkylation of a protected cyanohydrin was proposed by Hurd[86] and Tsuji[87], respectively. A study reporting formation of the macrocycle via a 14-endo-trig cyclization from an allylic radical intermediate was reported in 1999[88]. Recently, efforts to synthesize 2 have also been reported by other groups. For example, Hegedus[89] applied the Stille coupling reaction to form the macrocycle and employed (R)-propylene oxide as a chiral building block. Nicolau[90] developed a solid-phase strategy, in which cleavage from the polymer resin was combined with the intramolecular coupling reaction. Several total synthetic routes based on a ring-closure metathesis (RCM) as the key step have recently been presented by the groups of Fürstner[4], Yadav[3], and Navarro[90].

As an example, we briefly describe the strategy used in the latest total synthesis of zearalenone (2), as reported by Yadav[3]. Esterification of two fragments, acid 64 and alcohol
afforded the ester 66 in 80% yield under Mitsunobu conditions. Removal of the tetrahydropyranyl group using PPTS yielded alcohol 67, which was converted to intermediate 68 by the key RCM reaction catalyzed by Grubbs’ second-generation catalyst (5 mol%). Oxidation of 68 with IBX yielded the ketone 69, and further demethylation using freshly prepared triiodoaluminate at 10 °C for 45 min yielded 2 in 70% yield (Scheme 6).

In 2004, Danishefsky and co-workers[92, 93] published the first total synthesis of aigialomycin D (16), only two years after the isolation of the aigialomycins. The total synthesis of this macrolide was accomplished via a “ynolide method”; the key features of this synthesis involved using cobalt-complexation-promoted RCM to generate ynolides, followed by a Diels-Alder reaction with disiloxycyclopentadiene to elaborate the benzo system. After masking of the alkyne function in 70 by a dicobalthexacarbonyl complex, the complex was subjected to cyclization using the RCM strategy to produce 71 (Scheme 7). Then, decomplexation enabled a Diels-Alder reaction with the disiloxycyclopentadiene, followed by the elimination of isobutylene to produce the resorcylic macrolide 72. Two phenolic hydroxy groups in 72 were protected, followed by the cleavage of TBS-ether to yield intermediate 73. Finally, dehydration and the following deprotection of all alcohol functions furnished 16 in an overall yield of 8%.

Two years later, another synthetic route for aigialomycin D (16) was reported in 2006 by Winssinger et al[94]. This approach followed a more conventional strategy for introducing the resorcylic acid moiety compared with Danishefsky’s approach, but it also relied on RCM for macrocycle formation. A key point of this synthesis was the application of a selenoether at the benzylic position, which was thought to facilitate subsequent alkylation at this position. Further syntheses of aigialomycin D (16) were completed by the groups of Pan and Harvey[95, 96]. The key features of the Pan approach included the application of two Julia-Kocienski couplings to establish the E geometry of both olefins and a Yamagushi macrolcyclization. The synthetic route developed by Harvey et al included the combination of a Ramberg-Bäcklund reaction and a RCM reaction. Recently, in a more concise synthetic route designed by Barrett et al[97], the entire molecular skeleton of 16 was constructed as linear chain; this chain was subsequently aromatized and cyclized to form 16 in a similar manner to the biosynthetic PKS pathway for assembling RALs.

The first asymmetric total synthesis of de-O-methylasiodiplodin (44), a precursor in the synthesis of lasiodiplodin (43), was published in 1990; this synthesis involved 18 steps with 0.8% overall yield[98]; however, the synthetic route was too complicated, and the yield was too low. A shorter route using the RCM reaction as the key step was reported by Alois Fürstner and Kindler later, in 1996[99]. However, the carboxylation step via a Kolbe-Schmitt reaction under CO₂ (40 atm) and 120 °C for 12 h could not be considered routine for an average synthetic laboratory. In 2011, this compound was synthesized via a more efficient route (Scheme 8) with nine steps in 28.3% overall yield by Jiang et al[40].

Recently, Zhang et al reported the first total synthesis of (S)-dihydroresorcylide (49). The synthetic route starting from

![Scheme 6](image-url)  
Scheme 6. Total synthesis of zearalenone (2) by Yadav.

![Scheme 7](image-url)  
Scheme 7. Total synthesis of aigialomycin D (16) by Danishefsky.
commercially available orcinol monohydrate used 9 steps, including esterification, carbonylation, and the RCM reaction as the key steps (Scheme 9)\(^{[40]}\).

The first synthesis of curvularin (50) via intramolecular Friel-del-Crafts reactions was reported in 1967\(^{[100]}\), and its dimethyl derivative was synthesized in 1980 by Tsuji using the same synthetic protocol\(^{[101]}\). In 2010, this compound was totally synthesized via a concise route involving only six steps with an 8% overall yield; this synthesis established the RAL skeleton in a one-pot, aryne acyl-alkylation reaction\(^{[102]}\). A one-pot silylation-RCM-desilylation procedure used the allylic alcohol 76 as a starting material. Silylation with HMDS, followed by an RCM-generated β-hydroxylactone (77). Noticeably, treatment of the aryne precursor (79) and the β-ketolactone (78) with CsF resulted in the formation of the benzannulated macrolactone (80), which was then converted to curvularin (50) under the hydrogenolysis condition (Scheme 10).

The first total syntheses of the macrocyclic natural products (3R,5R)-sonnerlactone (55) and its epimer (56) were achieved by Thirupathi et al (Scheme 11) in 2011\(^{[103]}\), only one year after the initial isolation. These syntheses were accomplished in eleven steps with 22% overall yield starting from enantiomerically pure (R)-propylene oxide, which was prepared by hydrolytic kinetic resolution. Other key steps involved sharpless
epoxidation, the reductive elimination of iodo epoxide, and construction of the macrolactone using the RCM reaction. One year later, a concise and efficient approach for the synthesis of both sonnerlactones was reported by Yadav et al.[104]. This synthetic approach involved asymmetric allylation, the Alder-Rickert reaction and the Mitsunobu macrolactonization as key steps.

The structure of xestodecalactone A (58) was revised based on a stereoselective asymmetric synthesis reported by Bringmann et al.[105]. Another asymmetric total synthesis of 58 was later accomplished utilizing a Diels-Alder strategy by Danishefsky’s group.[106] The first efficient asymmetric total syntheses of xestodecalactones B (59) and C (60) were accomplished by Liang et al (Scheme 12)[107]. These compounds were synthesized in 10 steps with overall yields of 22% and 20.2%, respectively. The key steps involved the use of Evans oxazolidinone-mediated syn-aldol condensations to establish the C-9 configuration and an intramolecular acylation to form the macrolide ring. Then, in 2012, a convergent chiral pool approach for the total syntheses of 59 and 60 was demonstrated, in which intramolecular acylation reactions constituted the key step.[108] Interestingly, the spectroscopic studies reported by Pal et al suggested that the previously assigned structures for 59 and 60 should be interchanged.

In addition, many other efforts to approach the syntheses of RALs or DALs have been conducted by research groups worldwide. For example, the Lett group reported synthetic routes for a series of RALs, such as radicicol (1), monocillin I (6)[109], LL-Z1640-2 (3), and hypothemycin (4)[110]. In 2004, a modular synthesis of pochonin C (20) was presented by the group of Winssinger[111]; then, concise syntheses of pochonin A (18)[112] and radicicol analog A (11)[113] were reported by the same group. The Altmann group[114] reported the total syntheses of LL-Z1640-2 (3), hypothemycin (4), L-783277 (12), radicicol analog A (11), and aigialomycin D (16). Recently, the asymmetric total syntheses of paecilomycin E (32)[115] and cochliomycin A (37)[116] were achieved by the Nanda group. Stereospecific syntheses of a pair of natural macrolides, trans- and cis-resorcylide (47 and 48), were performed by the Couladouros group[117]. Almost at the same time, the Fürstner group[118] and the Bracher group[119] reported the total synthesis of citreofuran (54). The first efficient stereoselective total synthesis of sporostatin (57) was achieved by the Yadav group[120].

Conclusions
This review summarizes research on the isolation, biological activities, biosynthesis, and representative chemical syntheses of fourteen-, twelve-, and ten-membered resorcinolic macrolides. These natural products have attracted much attention from biologists and chemists because they are isolated from a variety of fungi and possess fascinating molecular architectures and attractive biological activities such as anti-tumoral, anti-bacterial, anti-malarial, and other activities.

Many natural macrolides possessing promising bioactivity should be considered for development as clinical drug candidates. For example, the well-known radicicol (1) and monocillin I (6) exhibit potent inhibitory activity against Hsp90, which is believed to be an efficient target for the treatment of cancer.
In recent years, pharmaceutical industries and institutes have invested great effort in finding novel inhibitors of Hsp90, which has become popular in the search for anti-cancer drugs. Another fungal metabolite, de-O-methylasiodiplodin (44), has been identified as a natural MR antagonist and has provided a novel scaffold for the design of non-steroidal MR inhibitors. Currently, non-steroidal MR antagonists, which might overcome the lack of selectivity exhibited by steroidal MR antagonists, have emerged as other major research targets in the search for anti-hypertension drugs. As presented above, many natural macrolides exhibit promising clinical potential; however, it remains challenging to bring them into clinical trials due to their possible side effects and/or low natural yields.

Fortunately, several natural active RALs and DALs or their structural analogs have been totally synthesized by chemists. Their synthetic routes generally involve the RCM reaction as the key step for constructing the macrocyclic skeleton, thus providing a relatively conventional and mature chemical synthetic strategy for the synthesis of a variety of other biologically important natural resorcinolic macrolides and their structural analogs. This strategy also provides an attractive route for the scale-up synthesis and structure-activity relationship (SAR) study of this class of compounds.

Many of these macrolides are biosynthesized by similar PKS pathways. Although some subtle differences exist between the biosynthetic pathways for RALs and DALs, understanding these differences would help us to further explain the complex programming mechanisms of fungal iterative polyketide synthetic enzymes. Knowledge of the biosynthesis of ten-membered lactones remains limited; however, in light of the structural similarity among these macrolides, ten-membered RALs and DALs might be produced using similar biosynthetic systems as those for other multi-membered macrolides. Generally, this group of metabolites is considered to be produced by a variety of fungi, such as the genera Monocillium, Hypomyces, Pochonia, Penicillium, and etc; however, there is as yet no evidence to support the proposal that the resorcinolic macrolides that have been isolated from plant samples are the metabolites of an endophytic or epiphytic fungus; another challenging task for natural product chemists and biologists is to demonstrate the biosynthetic origin of these macrolides.

Given the ongoing efforts and interest exhibited by chemists and pharmacologists, it is highly probable that further natural or synthetic multi-membered resorcinolic macrolides will enter into clinical trials and that their biosynthetic pathways will be understood clearly in the future.

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