NATURAL OCCURRENCE, BIOLOGICAL ACTIVITIES AND SYNTHESIS OF EIGHT-, NINE-, AND ELEVEN-MEMBERED RING LACTONES

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NATURAL OCCURRENCE, BIOLOGICAL ACTIVITIES AND SYNTHESIS OF EIGHT-, NINE-, AND ELEVEN-MEMBERED RING LACTONES. The natural occurrence, biological activities and synthetic approaches to natural eight-, nine-, and eleven-membered lactones is reviewed. These medium ring lactones are grouped according to ring size, and their syntheses are discussed. The structures of some natural products early identified as medium-ring lactones were revised after total synthesis.

Keywords: medium ring lactones; synthesis; natural products.

INTRODUCTION

About ten years ago, Kao et al.1 wrote: “The chemical synthesis of functionalized eight-membered ring lactones (2-oxocanones) is extremely challenging, and virtually no functionalized eight-membered ring lactones are known among natural products.” In fact, these lactones, as well as those of nine- and eleven-membered ring, are not so abundant in the Nature as their congeners containing a ten-membered ring.2

Recently, the synthetic approaches toward the naturally occurring ten-membered ring lactones (decalactones) were revised by us.3 More specifically, Riatto et al.4 reviewed the synthetic studies of decarestrictine family, an important class of decalactones. Another recent review, dealing with the total syntheses of some eight- and nine-membered ring lactones, was published by Shiina.5 Herein, we wish to review the natural occurrence and biological activities of the eight-, nine- and eleven-membered ring lactones, and to summarize the approaches for their syntheses. For those syntheses already reviewed somewhere else, only a brief discussion of the lactonization step will be presented here, in order to provide a global panorama to the reader. Beyond the scope of this review are the synthetic unnatural eight-, nine- and eleven-membered lactones.

EIGHT-MEMBERED RING LACTONES

Penicillide and derivatives

The dibenzodioxocane named (+)-penicillide (1) was first isolated in 1974, by Sassa et al.,6 from Penicillium sp. Later, this metabolite was found, along with dehydroisopenicillide (2), in the extract of Talaromyces derxii, and its absolute configuration was established.7 In 1992, Proksa et al.8 reported the isolation of the metabolites vermixocins A and B, from P. vermiculatum. Recently, the structures of vermixocins A and B were determined as being the same as those of penicillide (1) and (-)-purpactin A (3), respectively, which were isolated from P. simplicissimum.6 Purpactin A (3) was also isolated from P. purpurogenum in 1991, and showed inhibitory effect of acyl-CoA-cholesterol acyltransferase, an enzyme involved in cholesterol ester accumulation in atherogenesis and in cholesterol absorption from the intestines.10

Penicillide (1) and several related compounds were shown to be antagonists of the peptide hormone oxytocin11 as well as inhibitors of cholesterol ester transfer protein (CETP). Inhibition of CETP may have a beneficial action in enhancing high-density lipoprotein cholesterol (HDL) levels.12 Epidemiological studies show that low levels of HDL is a risk factor for the development of coronary heart diseases.

Although several research groups deal with the biological aspects of penicillide and its derivatives,11 there is no report, to our knowledge, concerning the total synthesis of these compounds.

Ovatolide

(-)-Ovatolide (4) is a tetracyclic indole alkaloid bearing an eight-membered ether-lactone, found in the leaves of Bridelia ovata, a Thaiandian plant used in folk medicine as laxative, febrifuge and adstringent.13

A total synthesis of (-)-4 was developed by Delgado and Clardy,15 as summarized in Scheme 1. The β-glucosidic linkage of 6 was constructed via the reaction of the 4-hydroxy-5-(benzyloxy)indole derived from 5 with the epoxysugar 9, in a regio- and stereocontrolled

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1 In memoriam
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manner. The authors used the Corey-Nicolaou protocol in the lactonization step, and the eight-membered lactone 8 was obtained in 72% yield after treatment of 7 with 2,2'-dipyridyl disulfide (pySSpy) and triphenylphosphine. Deprotection of indole nitrogen atom and hydroxyl groups of the glucoside subunit led to (-)-ovatolide (4).

Cephalosporolides

A group of five lactones, called cephalosporolides B-F (10-14), was produced by fermentation of the fungus Cephalosporium aphidicola, and their structures were elucidated by Ackland et al., in 1985. Later, cephalosporolide G (15) was isolated from the same fungus by Farooq et al.,16 along with the known decalactone diplodialide B 17 and Z-3-methylpent-2-en-1,5-dioic acid. More recently, Li et al.18 reported the isolation of cephalosporolides H (16) and I (17) from lyophilized culture broth of the fungus Penicillium sp. Three of these metabolites are ten-membered ring lactones (cephalosporolides B, C and G), one is an eight-membered ring lactone (cephalosporolide D), and the others (cephalosporolides E, F, H and I) are spiroketal lactones.

According to the authors, cephalosporolides E (13) and F (14) are probably artefacts of the isolation procedure, arose from cephalosporolide C (11) through a sequence involving an opening of the ten-membered ring of 11 followed by relactonization and acetal formation.

In 2005, Oller-López et al.19 isolated 13 and 14 in the broth culture of the entomoparasitic deuteromycete Beauveria bassiana and found a biosynthetic precursor of these lactones, the butyrolactone bassianolone, which showed antimicrobial activity against gram-positive cocci and fungi. To our knowledge, the biological activities of cephalosporolides were not yet evaluated.

The only reported synthesis of (-)-cephalosporolide D (12), allowing the determination of its relative and absolute stereochemistry, was developed by Shiina et al.20 The lactonization of the hydroxy-acids 18a/18b were performed employing different protocols. The use of Hf(OOTf) as Lewis acid catalyst and p-trifluoromethylbenzoic anhydride led to the corresponding eight-membered lactones 19a/19b in 81% yield (Scheme 2).

Octalactins

In 1991, the isolation and relative configurations of two lactones, named octalactins A (20) and B (21), were reported by Tapiolas et al. These highly functionalized eight-membered ring compounds are produced by an actinomycete collected from the surface of a mexican gorgonian octocoral of the genus Pacifigorgia. Octalactin A (20) showed significant in vitro cytotoxicity against some tumor cell lines, while its olefin analogue B was inactive in the cytotoxic assays.

The four total syntheses of octalactins found in the literature,23-26 as well as some formal syntheses and related model studies,27 were exhaustively discussed by Shiina, in his recent review. Therefore, only some aspects of the total synthesis will be briefly depicted here.

In 2001 Buszek et al.21 synthesized the unnatural (+)-cephalosporolide D (ent-12) using the Corey-Nicolaou lactonization method (Scheme 3).

Ottlanatins
modification of the Corey-Nicolaou protocol,\textsuperscript{14} which led to the eight-membered intermediate \textit{23} in 73\% yield (Scheme 4). Thus, \textit{23} could be transformed into \textit{(-)-20} and \textit{(-)-21} after 7 and 6 additional steps, respectively.

McWilliams and Clardy\textsuperscript{24} reported a total synthesis of the unnatural \textit{(+)-octalactin A (\textit{ent-20})} and \textit{(+)-octalactin B (\textit{ent-21})}, using a Baeyer-Villiger expansion of the cycloheptanone derivative \textit{24} using unbuffered trifluoroperoxyacetic acid (Scheme 5).

The asymmetric total synthesis of both octalactins A and B has also been achieved by O’Sullivan et al. in 2004.\textsuperscript{25} The eight-membered lactone core (\textit{27a} or \textit{27b}) was obtained by Claisen rearrangement of alkenyl-substituted cyclic ketene acetal, generated \textit{in situ} by selenoxide elimination of the corresponding selenoacetal \textit{25} or by olefination of the corresponding carbonate \textit{26} using dimethyltitanocene (Scheme 6).

Shiina et al.\textsuperscript{26} recently reported the synthesis of \textit{(-)-octalactin A (20)} employing a mixed-anhydride lactonization approach to construct the eight-membered ring moiety. Treatment of seco acid \textit{28} with 2-methyl-6-nitrobenzoic anhydride (MNBA) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine 1-oxide (DMAPO) afforded the eight-membered lactone \textit{29} in 90\% yield (Scheme 7).

More recently, an approach to the functionalized eight-membered ring core of octalactins, based on a sequential Evans-Tishchenko and ring closing metathesis (RCM) reactions, was developed by Aird et al.\textsuperscript{28} The synthesis initially relied on the preparation of chiral aldehydes \textit{30} and \textit{31}, and phosphonate \textit{33}, as outlined in Scheme 8. Horner-Wadsworth-Emmons reaction of \textit{31} and \textit{33}, followed by desilylation, furnished the \(\beta\)-hydroxy enone \textit{34} as a 95:5 mixture of the E/Z isomers. Evans-Tishchenko coupling of fragment \textit{34} with aldehyde \textit{30}, using preformed samarium(III) catalyst, led to dienoic ester \textit{35} as a single diastereomeric. RCM reaction of \textit{35}, using second generation Grubbs catalyst and Ti(O\textit{i}Pr)\textsubscript{4} as Lewis acid, afforded a 1:1 mixture of the eight-membered lactone \textit{37} and the cyclopentene derivative \textit{36}, formed due to a competitive metathesis reaction of the trisubstituted double bond in \textit{35}.

**Solandelactones**

The solandelactones A-I (\textit{38-46}) constitute a group of eight-membered ring lactones isolated in 1996 from \textit{Solanderia secunda}, a dark-brown hydroid found in the shore of Jaeyeu Island, in Korea. Solandelactones C (\textit{40}), D (\textit{41}), and G (\textit{44}) exhibit moderate inhibitory activity against FPT (farnesyl protein transferase).\textsuperscript{29} These compounds are lactonized cyclopropyl docosanoids, being probably the first examples of marine oxylipins bearing a C22 carbon skeleton. The biosynthetically related six-membered ring constanolactones A and B\textsuperscript{30} and nine-membered ring halicholactones (described further) are derived from eicosanoid (C\textsubscript{20})
precursors. The original assignment of C11 of solandelactones E (42) and F (43) was recently revised by total synthesis.31,32 Two different approaches to the synthesis of the cyclopropyl-lactone segment of solandelactones were developed by Varadarajan et al.33 Both strategies were based on the preparation of cyclopropane derivatives 50a/50b, starting from 2,3-O-isopropylidene D-glyceraldehyde 47 (Scheme 9). Then, 51 could be converted into the eight-membered ring core of solandelactones (52) via a lactonization key step, under Yamaguchi conditions,34 or through a ring-closing metathesis of the dienoic ester 53 (Scheme 10).

The first total synthesis of a solandelactone was recently reported by Davoren and Martin31 (Scheme 11). The authors synthesized the solandelactone E (42) and revised the original assignment for C11. Thus, 2,3-O-isopropylidene glyceraldehyde 49 was converted in the diene 53, which was selectively dihydroxylated using AD-mix β to furnish the diol 54 as a single diastereomer. A thirteen-step sequence of reactions led to the seco acid 55, which could be submitted to the Yamaguchi lactonization protocol,34 followed by TBAF-mediated deprotection of TBS ethers, affording the eight-membered lactone 56. The 1,3-transposition of the C12 allylic alcohol could be achieved by treatment of 56 with o-nitrophenylselenocyanate and tri-n-butylphosphine, leading to the activation and inversion of the less-hindered alcohol to furnish a

Scheme 8. Reagents and conditions: (a) i: t-BuOK, THF, trans-2-butene, n-BuLi, -78 → -45 °C, 20 min; ii: (-)-Ipc2BOMe, THF, -78 °C, 4 h; (b) DDQ, MS 4A, CH2Cl2, 0 °C, 15 min; (c) Dibal-H, CH2Cl2, 0 °C, 2 h; (d) (COCl)2, DMSO, CH2Cl2, Et3N, -78 °C → rt, 75 min; (e) PMBCl, t-BuOK, DMF, rt, 3 h; (f) cat. OsO4, NaIO4, THF, H2O (4:1) rt, 2 h; (g) i: (+-Hex)2BOTf, Et3N, CH2Cl2, -78 °C, 2 h; ii: acrolein, -78 → 0 °C, 2 h; (h) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 70 min; (i) i: (OEt)2P(O)CH2CH3; n-BuLi, THF, -78 °C, 1 h; ii: solution of 32 in THF, -78 °C, 1 h; (j) i: Ba(OH)2.8H2O, THF, rt, 30 min; ii: aldehyde 31, THF, H2O (40:1), rt, 24 h; (k) HF, CH2CN, rt, 15 min; (l) (PhCHO)2SmI3 (30 mol%), aldehyde 30, THF, -10 °C, 30 min; (m) 2nd generation Grubbs catalyst, CH2Cl2, Ti(O-i-Pr)4, reflux, 24 h (36/37 = 1/1)

Scheme 9. Reagents and conditions: (a) Ph,P=CHCO2Et, benzene, 90 °C, 6 h; (b) Dibal-H, CH2Cl2, -78 → 0 °C, 1 h; (c) TBDPSCl, imidazole, CH2Cl2, 0 °C → rt, overnight; (d) Et3N, CH2Cl2, -78 °C, 4 h, then 0 °C, 20 h; (e) TBAF, THF, 0 °C, 1 h, then rt, overnight; (f) IBX, DMSO, THF, rt, 6 h; (g) H2C=CHCH2Br, Et3N, CH2Cl2, 0 °C → rt, overnight; (h) Candida cylindracea lipase (CCL), CH2Cl2, 0 °C, 24 h; (i) DEAD, PPh3, gl. AcOH, THF, 0 °C → rt, overnight

Scheme 10. Reagents and conditions: (a) cat. OsO4, NMO, acetone; (b) silica gel impregnated with NaIO4, CH2Cl2, (c) BrPh,PCH2CH,CO2Et, NaHMDS, THF, -78 °C → rt; (d) LiOH, MeOH, THF, H2O, rt; (e) 2,4,6-trichlorobenzoyl chloride, Et3N, DMAP, toluene, reflux; (f) H2C=CHCH2CH3, CH2Cl2, 0 °C → rt; (g) 2nd generation Grubbs catalyst, CH2Cl2, Ti(O-i-Pr)4, reflux, 50 h
selenide, which was converted into the solandelactone E (42) after hydrogen peroxide-mediated oxidation followed by a [2,3]-sigmatropic rearrangement of the intermediate allylic selenoxide.

Recently, White et al.\textsuperscript{32} reported the synthesis of solandelactones E (42) and F (43) and confirmed the hydroxyl configuration at C11, early revised by Davoren and Martin.\textsuperscript{31} The synthesis starts with an asymmetric aldol reaction between the titanium enolate derived from 58 and the achiral aldehyde 57, followed by cyclopropanation of the Weinreb amide 59 to furnish the cyclopropane intermediate 60 as a single diastereomer (Scheme 12). Conversion of 60 to the key cyclic carbonate 61 was achieved in five steps. Olefination of 61, followed by a Holmes-Claisen rearrangement of the corresponding ketene acetal, led to the desired eight-membered lactone core of solandelactones 62. Coupling of 63 with the acyclic side chain fragment 64 (obtained from (S)-methyl 3,4-dihydroxybutanoate in nine steps) using NHK reaction led to a mixture of C11 epimeric solandelactones E (42) and F (43), in a 3.5:1 ratio, respectively.

**Terpenoids**

Some terpenoids bearing an eight-membered ring lactone are described in literature, such as the sesquiterpenes schkuhripinnatolides A-C (65-67), which were isolated from the aerial parts of Schkuhria pinnata collected from Namibia.\textsuperscript{35}

A new unusual sesquiterpene lactone, named amygdalactone (68), was isolated from the hulls of almond (Prunus amygdalus).\textsuperscript{36} Amygdalactone represents a new class of sesquiterpene bearing an octalactone ring system. The cytotoxicity of this compound toward K562, P3HR-1 and CEM leukemia cancer cell lines was evaluated and the results showed very low inhibition rate. There is no synthesis described.

**Scheme 11.** Reagents and conditions: (a) trans-(EtO)\textsubscript{2}P(O)CH\textsubscript{2}CH=CHCO\textsubscript{2}Et, LDA, THF, 0 °C (10/1 EE/EZ); (b) Et\textsubscript{2}Zn, CH\textsubscript{2}I\textsubscript{2}, 65 °C, 4 h then 5 °C, 12 h; (c) Dibal-H, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C; (d) TAP, NMO, CH\textsubscript{2}Cl\textsubscript{2}, rt; (e) (EtO)\textsubscript{2}P(O)CH\textsubscript{2}CO\textsubscript{2}Et, NaH, THF, 0 °C (10/1 EE/EZ); (f) K\textsubscript{2}Fe(CN)\textsubscript{6}, K\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}OsO\textsubscript{2}(OH)\textsubscript{4}, (DHQD)\textsubscript{2}PHAL, CH\textsubscript{3}SO\textsubscript{2}NH\textsubscript{2}, t-BuOH/H\textsubscript{2}O, rt; (g) TBSCI, imidazole, DMF, rt; (h) Dibal-H, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C → rt; (i) CBr\textsubscript{4}, PPh\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}, rt; (j) n-BuLi, 1-heptyne, CuBrSMe\textsubscript{2}, -78 °C; (k) TFA, H\textsubscript{2}O, CH\textsubscript{2}Cl\textsubscript{2}, rt; (l) NaH, 1-tosylimidazole, THF, 0 °C; (m) i: THPO(CH\textsubscript{2})\textsubscript{3}CºCH, n-BuLi, -78 °C, 1 h; ii: BF\textsubscript{3}.OEt\textsubscript{2}, THF, -78 °C, 45 min, then -100 °C, 2 h; (n) Ac\textsubscript{2}O, DMAP, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, rt, 2.5 h; (o) p-TsOH, i-PrOH, rt; (p) H\textsuperscript{2}, Lindlar catalyst, quinoline, MeOH, rt; (q) SO\textsubscript{3}.Py, Et\textsubscript{3}N, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, rt; (r) NaClO\textsubscript{2}, NaHPO\textsubscript{4}, 2-methyl-2-buten, t-BuOH, H\textsubscript{2}O, rt; (s) K\textsubscript{2}CO\textsubscript{3}, MeOH, rt; (t) 2,4,6-trichlorobenzoyl chloride, Et\textsubscript{3}N, DMAP, toluene, reflux; (u) TBAF, THF, rt; (v) o-NO\textsubscript{2}PhSeCN, Bu\textsubscript{3}P, THF, rt, 1 h; (x) H\textsubscript{2}O\textsubscript{2}, P\textsubscript{2}O\textsubscript{5}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 5 h
Examples of eight-membered diterpenoid lactones includes the bis-homoditerpenes isoterracinolides A (69) and B (70) (from Euphorbia terracina L.),\textsuperscript{37} and the cembrane diterpenes echinodolides A (71) and B (72), isolated from the Brazilian medicinal plant Echinodorus macrophyllus (also known as “chapéu-de-couro”),\textsuperscript{38} used in traditional medicine in the treatment of hepatitis and rheumatism. To our knowledge, there is no report concerning the synthesis and the biological activities of these compounds.

Astakolactin (73) is a sesterterpene isolated in 2003 from the mediterranean sponge Cacospongia scalaris.\textsuperscript{39} To our knowledge, neither biological tests nor synthetic studies for this metabolite are reported.

Diterpene lactones

Recently, Dat et al.\textsuperscript{40} isolated the dimeric lactones ardimerin (74) and ardimerin digallate (75) from the extracts of Ardisia japonica, a plant used in Oriental traditional medicine as antitussive and diuretic, as well as to stop uterine bleeding. The diolide 75 showed in vitro inhibitory effect of HIV-1 and HIV-2 RNase H (IC\textsubscript{50} of 1.5 and 1.1 μM, respectively).

Revised structures

The structures of some natural products early identified as being eight-membered rings were revised later. Thus, the initially proposed structures for puerosides A and B\textsuperscript{41}, sophoroside A\textsuperscript{42} and speciosides A and B\textsuperscript{43} were showed to be butenolides (Table 1).\textsuperscript{44}

<table>
<thead>
<tr>
<th>Lactone</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>R\textsubscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>pueroside A</td>
<td>glu\textsuperscript{-}</td>
<td>rha</td>
<td>H</td>
</tr>
<tr>
<td>pueroside B</td>
<td>glu</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>sophoroside A</td>
<td>glu\textsuperscript{-}</td>
<td>Me</td>
<td>H</td>
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<tr>
<td>specioside A</td>
<td>glu</td>
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<td>H</td>
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<tr>
<td>specioside B</td>
<td>H</td>
<td>glu</td>
<td>H</td>
</tr>
</tbody>
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Revised structures for puerosides A and B, sophoroside A and speciosides A and B\textsuperscript{43}
Similarly, the structures of gonioheptolides A (76) and B (77), isolated in 1993 from the stem bark of *Goniothalamus giganteus*, were corrected some years later. Independently, Bermejo et al. have isolated from *Goniothalamus arvensis* two compounds with spectroscopic data very similar to those observed for the gonioheptolides, and called them almuheptolide A (78) and B (79). These metabolites have been cited in some other papers, up to 2002, when a revision of the structure of 78 was also reported.

**NINE-MEMBERED RING LACTONES**

**Halicholactone and neohalicholactone**

The eicosanoid oxylipins (-)-halicholactone (80) and (-)-neohalicholactone (81) were isolated from the marine sponge *Halichondria okadai* (Kadota) collected at Daiozaki, Japan. Halicholactone (80) exhibited weak inhibitory activity against lipoxygenase of guinea pig polymorphonuclear leukocytes.

In 1991, the relative stereochemistry of all stereocenters of neohalicholactone (81) has been determined by X-ray crystallography as shown below. Some years later, Proteau et al. isolated 81 from the brown alga *Laminaria sinclairii*, and its absolute configuration was suggested to be the opposite to that previously postulated. The three total syntheses of halicholactone (80) and neohalicholactone (81) reported in literature will be briefly presented here, since Shiina discussed them in details in his review. A formal synthesis of 80 and 81 was described in 1998. Critcher et al. reported the synthesis of the right-hand hemisphere and the first asymmetric total synthesis of halicholactone (80) and neohalicholactone (81), confirming the original assignments of absolute configuration of the stereocenters of 81 originally proposed by Yamada and Clardy. They also demonstrated, through the preparation of diastereomers of 81, that the natural product isolated by Proteau et al. was, in fact, a C15 epimer of this nine-membered lactone.

The synthetic strategy was based on the preparation of the key intermediate 83. The lactonization of seco acid 82, using the Yamaguchi protocol, led to the nine-membered ring lactone 83, which could be converted into (-)-halicholactone (80) and (-)-neohalicholactone (81) in six additional steps (Scheme 13).

The others two synthetic approaches to (-)-halicholactone (80) were reported by Takemoto et al. and Takahashi et al. The authors used as key step the ring-closing metathesis of dienoic ester 84, using first generation Grubbs catalyst and titanium isopropoxide as Lewis acid, to achieve the nine-membered lactone 85, which could be converted into (-)-80 by hydrolysis of the acetyl protecting groups (Scheme 14).

**Topsentolides**

Topsentolides A₁, A₂, B₁, B₂, B₃, C₁, and C₂ (86-92) are oxylipins isolated in 2006 from the marine sponge *Topsentia sp*. These lactones exhibit moderate citotoxicity against human solid tumor cell lines. According to the authors, the (+)-topsentolide C₁ (91) and (+)-topsentolide C₂ (92) are suspected to be artefacts formed during the extraction with methanol. Synthetic approaches to these nine-membered lactones were not found in the literature.

**Terpenoids**

Isotrichogoniolide (93) and (+)-sinulariadiolide (94) are nine-membered terpenoid lactones, isolated from *Trichogonia sp* and from a coral of the genus *Sinularia*, respectively, and were not synthesized yet.
Antimycins

The antimycin-A antibiotics are a series of nine-membered dilactones, which were isolated from a number of Streptomyces strains over many decades. A complex mixture of antimycins A₁–A₈ is a specific inhibitor of the electron transfer activity of ubiquinol-cytochrome c oxidoreductase. The antimycins have also other biological properties such as antifungal activity, inhibition of enzymatic activity as well as the ability to induce the death of cancer cells.

The main component of this family of peptide alkaloids is the antimycin A₈, which had been considered as an unique compound until 1988, when analytical investigations using HPLC techniques revealed that this natural product is, in fact, a mixture of the diastereomers. Lactonization of (+)-(3S,4)-hydroxyacid to the desired natural (+)-antimycin A₃a and (+)-(3S,4)-hydroxyacid to the unnatural (-)-antimycin A₃b was recently reported. Some formal synthesis of these dilactones are also found in the literature.

Both racemic and stereoselective synthesis of natural (+)-antimycin A₃b (96) have been first accomplished by Kinosita et al. Tsunoda group developed an asymmetric aza-Claisen rearrangement of enolates of carboxamides and applied this methodology to the synthesis of both, unnatural (-)-antimycin A₃b (ent-96) and natural (+)-antimycin A₃b (95), while one approach for (+)-antimycin A₉b (125) was recently reported. Some formal synthesis of these dilactones are also found in the literature.

Kinosita et al. reported the first asymmetric total synthesis of (+)-antimycin A₉b (96) as well as the synthesis of one of its diastereomers. Lactonization of (+)-(3S,4R,7R,8S,9R,10S)-hydroxyacid 97a afforded the nine membered dilactone 98 in only ca. 1% yield. A sequence of reactions on the amino group at the C3 position led to the desired natural (+)-96 (Scheme 15).

Similarly, the authors could prepare the unnatural diastereomer (+)-(3S,4R,7S,8S,9R)-100 of (+)-antimycins A₉b, starting from the hydroxyacid 100b (Scheme 16), following the same sequence of reactions outlined in Scheme 15.

The synthesis of unnatural (-)-antimycin A₉b (ent-96) reported by Tsunoda et al. started from (R)-(++)-methylbenzylamine, which was transformed in the amide 101 in three steps. The aa-Claisen rearrangement of 101 led the expected amide as a mixture of four stereoisomers, from which the main isomers 102a and 102b could be obtained as a unseparable 4:1 mixture, respectively. Iodolactonization of 102a/102b, followed by reduction with n-Bu₃SnH, afforded the lactones 103a/103b, which was converted into the desired prenyl ester 104a/104b along with the butenolide by-product 105. Mitsunobu reaction of 104a/104b with N,O-protected D-threonine (106) led to a mixture of the diesters 107a and 107b. Hydrolysis of TBDMs and prenyl protecting groups was easily achieved to furnish the seco acids 108a/108b, which was submitted to the Corey-Nicalou lactonization to afforded a separable mixture of the nine-membered dilactones 109a/109b. The unnatural (-)-antimycin A₉b (ent-96) could then be obtained from 109a, after five additional steps (Scheme 17).

In 2003, the same Japanese group reported the stereoselective synthesis of (+)-antimycim A₉b (95) and established the absolute configuration at the C2′ position on the acyloxy side chain. The authors used (S)-(++)-methylbenzylamine for the preparation of the seco acids 108c/108d, following the same sequence of reactions early used for the synthesis of unnatural ent-96. Corey-Nicalou lactonization of 108c/108d, using Cu(OTf)₂·PhH complex instead the explosive AgClO₄ metal salt, afforded a separable mixture of the nine-memebred dilactones 109c/109d in 88% yield. Removal of the TIPS-protecting group, followed by esterification of the free hydroxy group of 109c with (S)- and (R)-2-methylbutanoic acid allowed the establishment of the S-configuration at the C2′ position in the natural (+)-95 (Scheme 18).

More recently, Wu and Yang synthesized the (+)-antimycin A₉b (96) using a TiCl₄-mediated asymmetric aldolization to construct the C7/C8 stereocenters in 111 with the correct configurations. A lactonization method, based on the activation of the acyl group through the formation of w-hydroxyacid 112 (via the formation of...
Griseoviridin

The macrocyclic peptide (-)-griseoviridin (115), isolated from *Streptomyces griseus*, is a broad-spectrum antibiotic, with inhibitory activity toward various pathogenic bacteria and fungi. This alkaloid contains, among other functionalities, an unsaturated nine-membered thioether-lactone subunit.

Several synthetic approaches to the sulfur-containing lactone moiety of griseoviridin have been reported, and a total synthesis of (-)-griseoviridin (115) was accomplished by Dvorak et al. in 2000 (Scheme 20). The authors used the RCM of 118, followed by acid removal of the diol protecting group, to obtain the macrocycle (-)-115 as a single diastereomer. It is noteworthy that the lactonization of ω-hydroxycarboxylic acid 116 to the nine-membered lactone intermediate 117 (with inversion of the configuration of C5) was easily achieved using the Mistunobu protocol.

a mixed anhydride after treatment with 2-methyl-6-nitrobenzoic anhydride, MNBA), was used to construct the nine-membered dilactone moiety (Scheme 19).
Revised structures

In 1993, Cutler et al.\textsuperscript{79} isolated a bioactive product from a strain of the fungus \textit{Botrytis cinerea} and named it botcinolide. The structure of this compound was determined as being a polyhydroxylated nine-membered ring lactone (120a, Figure 1).\textsuperscript{80} A homologue of botcinolide, called homobotcinolide (121a), was isolated by these authors in 1996.\textsuperscript{81} The isolation of other botcinolide derivatives was also reported by Collado et al.\textsuperscript{82,83}

Tani et al.\textsuperscript{84} reinvestigated the spectroscopic data reported for botcinolide and some derivatives, and revised their structures (Figure 1). They found that botcinolide, originally reported as the nine-membered lactone (120a), is in fact the seco acid of botnicin E, as well as the structure of 2-epibotcinolide (122a) was revised as being the same as that of botcinin E (122b). In addition, botcinolide was renamed botcinic acid (120b) and the name of homobotcinolide was also changed to botcineric acid (121b).

An approach toward the synthesis of the lactone moiety of the unnatural pseudo 2-epi-8-epibotcinolide was reported by Chakraborty and Goswami.\textsuperscript{85}

Independently, Shiina et al.\textsuperscript{86} recently achieved the total synthesis of the pseudo 2-epibotcinolide (122a) and showed that the proposed structures for this compound and related ones are doubtful. The authors prepared the nine-membered lactone core through the lactonization of seco acid using MNBA as activating reagent (Scheme 21). Epimerization of C2 in smoothly took place on silica gel to afford the 2-epi-125 in 82% yield. Deprotection of the diol at C4-C5 led to the unstable pseudo 2-epibotcinolide (122a), which underwent facile translactonization to the corresponding \(\gamma\)-lactone (126).

Concerning the structural misassignments presented above, we would like to reproduce some paragraphs of the fascinating work of Nicolaou and Snyder,\textsuperscript{87} entitled \textit{Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation}:

“Although the past half century has witnessed a remarkable improvement in our ability to isolate and characterize complex natural products, mistakes are still a relatively common occurrence.
However, (...) this state of affairs is far from catastrophic. Indeed, structural misassignments clearly provide opportunities for synthetic chemists to make discoveries through total synthesis, and certainly show that there is still adventure to be had in the process of structure assignment. (...) we can be certain that as long as chemists continue to isolate new and diverse substances from nature, there will be plenty of challenges for our intellectual and physical skills. Moreover, much new science awaits discovery during the struggle to synthesize such new molecular puzzles”.

Eleven-membered ring lactones

Few examples of eleven-membered lactones are found in Nature, similarly to what occurs with the eight- and nine-membered ones. Besides some structurally more complex pyrrolizidinic and daphniphyllum alkaloids, there are two insect pheromones - the ferrulactone I and the suspensolide - and three fungal metabolites - the aspercyclides A-C - described in the literature.

Ferrulactone I

In 1983, Wong et al. reported the isolation of two lactones from the frass of Cryptolestes ferrugineus (Stephens), the rusty grain beetle. These compounds, named ferrulactone I (127) and ferrulactone II (128), are aggregation pheromones produced by the male insects, and bear an eleven- and a twelve-membered ring lactone, respectively.

All the syntheses described in literature start from geraniol. The first synthesis of 127 was reported in 1983 by Oehlschlager et al., which obtained the cyclic intermediate 132 afforded the target molecule in 10% global yield (Scheme 22).

This intermediate was prepared by reaction of geraniol 129 with (phenylthio)acetyl chloride, followed by allylic oxidation in C8 and bromination of the alcohol thus obtained. Finally, desulfurization of 132 afforded the target molecule in 10% global yield (Scheme 22).

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In the same paper, an alternative approach to ferrulactone 127 was also described. The key step consists of an intramolecular esterification of the dienoic acid 134, prepared by formal addition of acetate anion equivalent to tetrahydropyranyl-protected 8(E)-bromo-geraniol 133. The best yield obtained for the eleven-membered lactone 127 was 37%, when bis(4-tert-butyl-N-isopropylimidazol-2-yl)disulfide (BID) was used as activating reagent and the temperature of the reaction medium was carefully controlled (Scheme 23).

The cyclization of 135 under the action of zerovalent palladium, followed by sodium amalgam-promoted desulfurization of the eleven-membered lactone intermediate, also afforded the ferrulactone I (127), as described by Kukovinets et al. (Scheme 24).

Another synthesis of 127 in which the key step is a lactonization of a seco acid was reported by Chesiks et al. The Claisen rearrangement of allylic alcohol 136 proceeded stereospecifically to furnish the ester 137 in 95% yield as a single (E,E)-isomer.
Removal of THP protecting group followed by ester hydrolysis led the ω-hydroxyacid 134, which was submitted to latonization using BID, similarly to what was previously reported by Oehlschlager et al.90

Moriya et al.92 obtained the ferrulactone (127) in a short four-step synthesis, also starting from geraniol (Scheme 26). An intramolecular Reformatsky reaction of ω-bromoacetoxy aldehyde 138 led to the eleven-membered lactone intermediate 139, which was submitted to selective allylic debenzoylation promoted by SmI2 in THF-HMPA.

Suspensolide

Suspensolide (140), which is a regioisomer of ferrulactone I (127), was isolated in 1988 from the male Caribbean fruit fly Anastrepha suspensa (Loew), together with anastrephin (141) and epianastrephin (142).94 Later, 140 was reported to be also produced by A. ludens,95 and A. fraterculus.96 Studies concerning some biosynthetic aspects of suspensolide (140) were published by Battiste et al.97 Thus, acid-catalyzed rearrangement of 140 to anastrephin (141) and epianastrephin (142) was carried out by treatment with BF3.Et2O, as depicted in Scheme 27.

The complete assignments of the 1H-NMR and 13C-NMR spectra of the lactones suspensolide (140), anastrephin (141) and epianastrephin (142) have been accomplished by Baker and Heath.73 Battiste et al.100 reported a short synthesis of suspensolide (140) from mesityl oxide and proved the (3E,8E)-geometry of the double bonds of this natural product. The key hydroxyacid 143 was subjected to lactonization under Mitsunobu conditions73 to afford 140 in only 25% isolated yield (Scheme 28).

In the same year, Mori and Nakazono101 reported the synthesis of 140 also using the Mitsunobu lactonization73 of 143, which afforded the desired eleven-membered lactone in a very poor yield (ca. 9%). The key hydroxyacid 143 was prepared from geraniol in a fifteen-step sequence of reactions.

A stereospecific synthesis of suspensolide (140) was achieved by Del Vecchio and Oelschlager.102 The synthesis started with 1,6-heptadiyne which was converted into the diol 145 by a double carboalumination with in situ conversion to a dialanate intermediate followed by reaction with paraformaldehyde (Scheme 29). THP-protection of 145, conversion of free hydroxyl group to chloride and cyanide substitution under phase-transfer conditions led to the nitrile 146, which could not be directly hydrolyzed to the corresponding carboxylic acid without isomerization of the double bond. Thus, 146 was alternatively converted into the amide 147 followed by a very mild hydrolysis, leading to the desired acid 148. Lactonization of 143 under Mitsunobu conditions,73 as already reported by Battiste et al.,100 also led to suspensolide 140 in poor yield.
yield (30%), along with a mixture of anastrephin (141) and epianastrephin (142), in 40% isolated yield.

A stereoselective four-step synthesis of the 10-hydroxy-4,8-dimethyl-3(E),8(E)-dienoic acid (143), precursor of suspensolide (140), was described in 1996. The authors used the regioselective oxidation of the methyl group of geranyl acetate 149 with selenium oxide to obtain the aldehyde 150 in 53% yield. Wittig reaction followed by saponification led to the trienoic acid 151, which could be converted into the desired seco acid 143 by a region- and stereoselective reduction of the conjugated diene moiety with lithium in liquid ammonia and methanol (Scheme 30).

It is of note that an eleven-membered lactone (2,4,6,8-tetramethyl-3,4-dihydroxydec-8(9)-enolide), structurally related to suspensolide, was recently isolated from the fungus Botrytis cynerea (Figure 2), along with some botcinolide derivatives.83

The first reported total synthesis of (+)-aspercyclide C (154) was achieved by Fürstner and Müller through a kinetically controlled RCM reaction to form the eleven-membered ring (Scheme 31). The straightforward preparation of diaryl acid 155 was possible by an Ullmann coupling of a bromide with a phenol, followed by saponification of the ester function. An anti-selective oxy-allylation reaction led to the aliphatic fragment 156a, upon treatment of PMP-protected allyl alcohol with hexanal, a strong base and the (S,S)-158 complex. Esterification of acid 155 with alcohol 156a was performed using the Mukaiyama method to furnish the dienoic ester 157. RCM of 157 with second generation Grubbs catalyst afforded the eleven-membered unsaturated lactones as a 5:1 mixture of E and Z isomers, respectively. Chromatographic separation followed by deprotection of hydroxyl groups of the E-isomer led to the (+)-aspercyclide C (154).

Recently, a formal synthesis of (+)-aspercyclide C (154) was reported. The preparation of the PMB-protected linear fragment 156a was done using D-ribose acetonide as chiral pool (Scheme 32). Monoprotection of diol 159 led to a mixture of products, from which the desired product 156a could be isolated in only 41% yield.

**Scheme 30.** Reagents and conditions: (a) SeO₂, EtOH, reflux, 1 h; (b) Ph₃P=CHO₂Et, 100 oC, 1 h; (c) KOH, H₂O, MeOH, 23 °C, 72 h; (d) Li, liq. NH₃, MeOH, reflux, 15 min

**Scheme 31.** Reagents and conditions: (a) CuO, K₂CO₃, Py, 130 °C; (b) aq. NaOH, MeOH; (c) i: sec-BuLi; ii: hexanal, complex (S,S)-158, THF/Et₂O, -78°C; (d) N-methyl-2-chloropyridinium iodide, Et₂N, CH₂CN, reflux; (e) 2nd generation Grubbs catalyst, toluene, reflux; (f) chromatographic separation; (g) CAN, CH₂CN/H₂O, 0 °C; (h) BBr₃, CH₂Cl₂, -78 → 0 °C

**Scheme 32.** Reagents and conditions: (a) Ph₃PCH₂CH₂CH₂Br, t-BuOK, THF, 0 °C → rt, 16 h; (b) Ra-Ni, H₂, EtOH, rt; (c) i: MsCl, Et₃N, CH₂Cl₂, 0 oC, 3 h; ii: Zn, NaI, DMF, 155 °C, 2 h; (d) PTSA, MeOH, rt, 24 h; (e) PMBCl, NaH, DMF, 0 °C → rt, 10 h (20% recovery of 159); (f) N-methyl-2-chloropyridinium iodide, Et₂N, CH₂CN, 120°C, 1 h; (g) 2nd generation Grubbs catalyst, toluene, reflux, 3 h; (h) BBr₃, CH₂Cl₂, -78 °C, 5 min

**Figure 2.** 2,4,6,8-Tetramethyl-3,4-dihydroxydec-8(9)-enolide

**Aspercyclides**

Aspercyclides A-C (152-154) are biphenylether-lactones isolated from an extract of Aspergillus sp. Aspercyllide A (152) showed to be inhibitor of the IgE receptor binding (IC₅₀ = 200 μM), thus having a moderate anti-inflammatory effect. Compounds with this biological action may be efficacious in the treatment of allergic diseases such as asthma and rhinitis.

![Chemical structure of Aspercyclides](image-url)
Mukaiyama coupling\textsuperscript{106} of alcohol 156a with acid 155 (see Scheme 31), second generation Grubbs catalyst-mediated RCM of the dienoic ester intermediate and PMB-deprotection led to (+)-aspercyclide C (154), following a similar sequence of reactions early described by Fürstner and Müller.\textsuperscript{105}

**Alkaloids**

In 2006, the alkaloid (+)-macropodumine A (160) was isolated from the stem of *Daphniphyllum macropodum*, a plant used in Chinese traditional medicine in the treatment of inflammations.\textsuperscript{108} This metabolite has a fused pentacyclic system including an eleven-membered lactone, a structure feature never found before within the *Daphniphyllum* alkaloid family.

![Macropodumine A (160)](image)

Eight others *Daphniphyllum* alkaloids, namely macropoduminines B-I, have also been found in *D. macropodum*,\textsuperscript{109} but these molecules are not medium ring lactones. To our knowledge, there are no synthetic approaches for macropodumine A (160) described in the literature.

Some eleven-membered dilactone having a pyrrolizidine moiety were isolated from several species of *Crotalaria*.\textsuperscript{110} The hepatotoxic and carcinogenic monocrotaline (161) (Figure 3) is the most abundant alkaloid in this family of secondary metabolites, being isolated from *C. lechnaultii*,\textsuperscript{111} *C. grahamiana*,\textsuperscript{112} *C. crispatula*,\textsuperscript{113} *C. fulva*,\textsuperscript{114} and several others species of this genus.\textsuperscript{115} Others representative examples of the pyrrolizidine alkaloids with these structure features are dicrolatine (162),\textsuperscript{116} fulvine (163),\textsuperscript{113,114} and crispatine (164).\textsuperscript{113,114}

![Figure 3. Some eleven-membered dilactones bearing a pyrrolizidine moiety](image)

The natural occurrence and biological properties of these eleven-membered dilactones, among others pyrrolizidine compounds, were reviewed in the series articles published in the journal *Natural Products Reports*.\textsuperscript{117} The synthesis of 161-164\textsuperscript{118} and related dilactone pyrrolizidine alkaloids will not be discussed here.

**CONCLUSION**

This review has attempted to summarize the natural occurrence, the biological properties as well as the enormous efforts toward the synthesis of the natural eight-, nine-, and eleven-membered lactones known to date.

In contrast to what was stated by Kao in 1997,\textsuperscript{1} this challenging class of natural products has been stimulating chemists to develop new methodologies to construct the medium ring lactone core. Thus, several successful syntheses of the title compounds can be found in the literature.

It must be highlighted the increasing use of RCM to achieve the medium ring lactones, as already observed for the synthetic approaches to the ten-membered ring lactones, recently reviewed by us.\textsuperscript{1} Nevertheless, the use of the lactonization methods developed by Corey-Nicolau,\textsuperscript{14} Yamaguchi\textsuperscript{34} and Mitsunobu\textsuperscript{73} is still remarkable.

Although much success has been obtained in the syntheses described here, many of the natural eight-, nine-, and eleven-membered lactones have never been synthesized. Thus, we hope to see new exciting synthetic studies reported soon.

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**REFERENCES**