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]
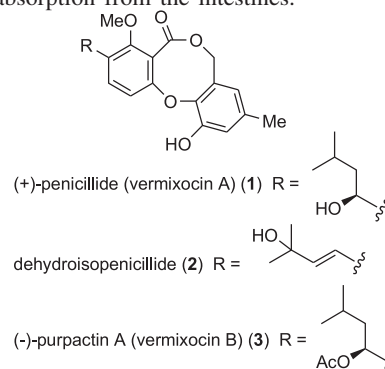
Herein, we wish to review the natural occurrence and biological activities of the eight-, nine- and eleven-membered ring lactones, and to summarize the approaches for their syntheses. For those syntheses already reviewed somewhere else, only a brief discussion of the lactonization step will be presented 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 dibenzodioxocanone 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*.[9] Purpactin A (**3**) was also isolated from *P. purpurogenum* in 1991, and showed inhibitory effect of acyl-CoA-colesterol acyltransferase, an enzyme involved in choslesterol ester accumulation in atherogenesis and in cholesterol absorption from the intestines.[10]

(+)-penicillide (vermixocin A) (**1**) R =

dehydroisopenicillide (**2**) R =

(-)-purpactin A (vermixocin B) (**3**) R =

Penicillide (**1**) and several related compounds were shown to be antagonists of the peptide hormone oxytocin[11] 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 Thailandian plant used in folk medicine as laxative, febrifuge and adstringent.[13]

A total synthesis of (-)-**4** was developed by Delgado and Clardy,[13] 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

manner. The authors used the Corey-Nicolaou protocol[14] 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 triphenylphospine. Deprotection of indole nitrogen atom and hydroxyl groups of the glucoside subunit led to (-)-ovatolide (**4**).
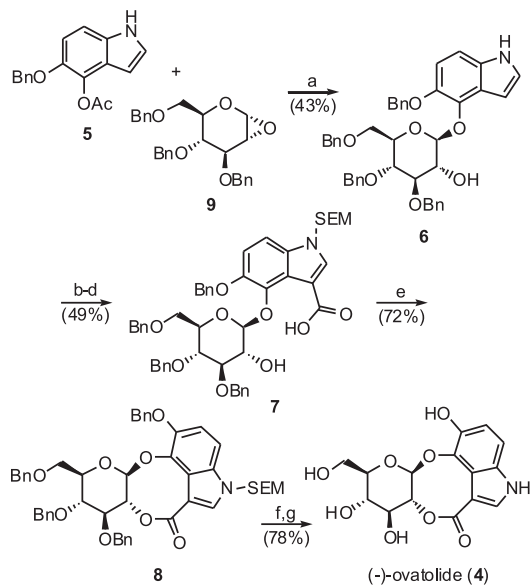
Scheme 1. Reagents and conditions: (a) i: NaOH-Na$_2$S$_2$O$_4$, DMF, 5 ^{o}C, 15 min, ii: 15-crown-5, epoxysugar **9**, DMF, rt, overnight; (b) TFAA, DMF, 5 ^{o}C, 1 h; (c) NaH, THF, 0 ^{o}C, 15 min, then 0.5 N sol. of SEMCl in THF (1.5 equiv.), 5 ^{o}C, 30 min; (d) NaH, DMF, 70 ^{o}C, 15 min; (e) i: pySSpy, PPh$_3$, CH$_2$Cl$_2$, rt 30 min, ii: AgClO$_4$, benzene, reflux, 45 min; (f) MS 4A, THF, NH$_2$CH$_2$CH$_2$NH$_2$, TBAF, 60 ^{o}C, 3 h; (g) Pd(OH)$_2$, EtOAc, AcOH, H$_2$, rt, 2 h
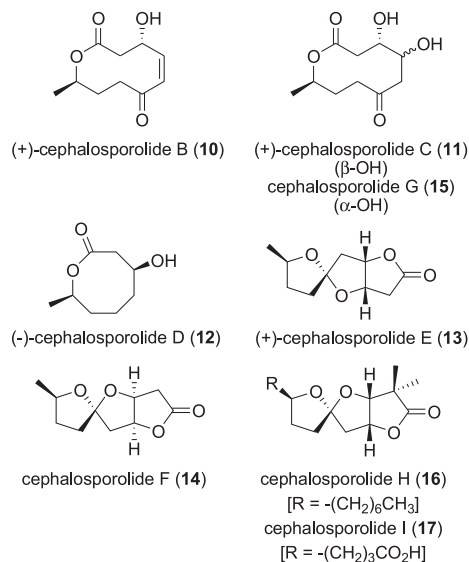
Cephalosporolides

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.[15] 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,[15] 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-memebred 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(OTf)$_4$ as Lewis acid catalyst and *p*-trifluoromethylbenzoic


(+)-cephalosporolide B (**10**)
(+)-cephalosporolide C (**11**) (β-OH)
cephalosporolide G (**15**) (α-OH)
(-)-cephalosporolide D (**12**)
(+)-cephalosporolide E (**13**)
cephalosporolide F (**14**)
cephalosporolide H (**16**) [R = -(CH$_2$)$_6$CH$_3$]
cephalosporolide I (**17**) [R = -(CH$_2$)$_3$CO$_2$H]

anhydride led to the corresponding eight-membered lactones **19a/19b** in 81% yield (Scheme 2).

18a (α-OBn) **19a** (α-OBn) (-)-**12**
18b (β-OBn) **19b** (β-OBn)
(97/3)
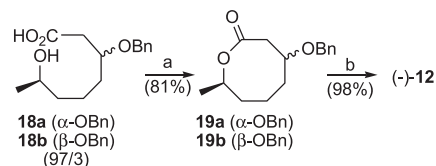
Scheme 2. Reagents and conditions: (a) Hf(OTf)$_4$, (p-CF$_3$C$_6$H$_4$CO)$_2$O, CH$_3$CN, THF, reflux (2.34 mM, slow addition over 15 h period; 81% yield based on 83% conversion); (b) i: H$_2$, Pd/C, EtOH, rt (4/6 mixture of **12**/ent-**12**); ii: recristallization from hexanes

In 2001 Buszek *et al.*[21] synthesized the unnatural (+)-cepalosporolide D (ent-**12**) using the Corey-Nicolaou lactonization method[14] (Scheme 3).


(ent-**12**)
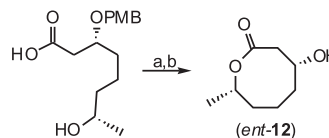
Scheme 3. Reagents and conditions: (a) pySSpy, PPh$_3$, CH$_2$Cl$_2$, rt, 2 h, then AgBF$_4$, toluene, reflux, 12 h (81%); (b) DDQ, CH$_2$Cl$_2$, H$_2$O (yield not given)
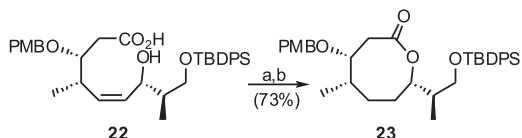
Octalactins

In 1991, the isolation and relative configurations of two lactones, named octalactins A (**20**) and B (**21**), were reported by Tapiolas *et al.*[22] 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.[5] Therefore, only some aspects of the total synthesis will be briefly depicted here.

The first synthesis of both octalactins A (**20**) and B (**21**), which establishes their absolute configurations, was performed by Buszek *et al.*[23] The sequence involves as key step an intramolecular esterification of the ω-hydroxy carboxylic acid **22**, using a slight
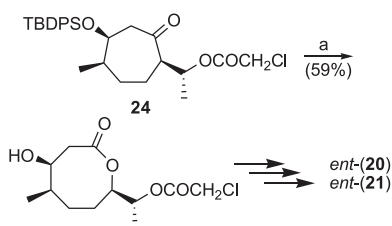
(-)-octalactin A (**20**)

(-)-octalactin B (**21**)
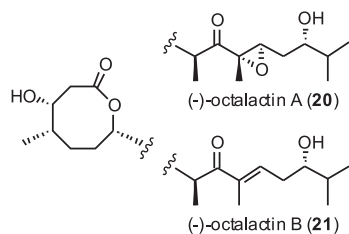
modification of the Corey-Nicolaou protocol,[14] which led to the eight-memebred intermediate **23** in 73% yield (Scheme 4). Thus, **23** could be transformed into (-)-**20** and (-)-**21** after 7 and 6 additional steps, respectively.


Scheme 4. *Reagents and conditions: (a) H_2, Pd/C; (b) i: pySSpy, PPh_3, CH_2Cl_2, rt, 8 h; ii: $AgBF_4$, toluene, 110 °C, 96 h*

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

ent-(**20**)
ent-(**21**)

Scheme 5. *Reagents and conditions: (a) i: HF, CH_3CN, rt, 15 h; ii: 3 M CF_3CO_3H, CH_2Cl_2, -10 °C, 91 h*

The asymmetric total synthesis of both octalactins A and B has also been achieved by O'Sullivan *et al.* in 2004.[25] The eight-memebred lactone core (**27a** or **27b**) was obtained by Claisen rearrangement of alkenyl-substituted cyclic ketene acetal, generated *in situ* by selenoxide elimination of the corresponding selenoacetal **25** or by olefination of the corresponding carbonate **26** using dimethyltitanocene (Scheme 6).
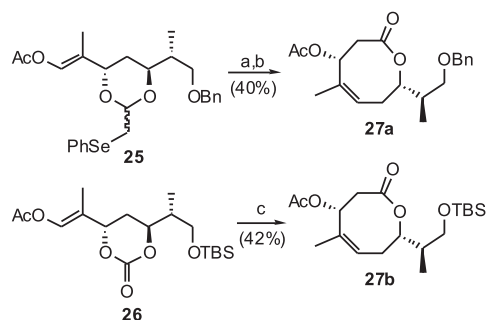
Scheme 6. *Reagents and conditions: (a) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, 22 °C, 1,5 h; (b) 1-*tert-*butyldimethylsiloxy-1-methoxy-ethene, xylene, K_2CO_3, sealed tube, 180 °C, 2,5 h; (c) Cp_2TiMe_2, toluene, reflux, 30 min*

Shiina *et al.*[26] recently reported the synthesis of (-)-octalactin A (**20**) employing a mixed-anhydride lactonization approach to construct the eight-membered ring moiety. Treatment of seco acid **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 **29** in 90% yield (Scheme 7).
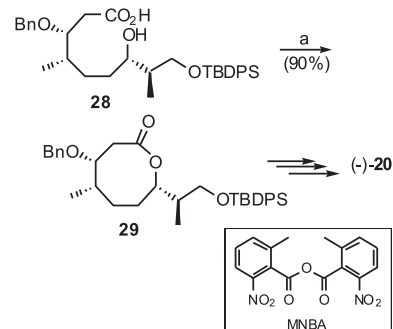

Scheme 7. *Reagents and conditions: (a) MNBA, DMAP (10 mol%) or DMAPO (10 mol%), Et_3N, CH_2Cl_2, rt*

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.*[28] The synthesis initially relied on the preparation of chiral aldehydes **30** and **31**, and phosphonate **33**, as outlined in Scheme 8. Horner-Wadsworth-Emmons reaction of **31** and **33**, followed by desilylation, furnished the β-hydroxy enone **34** as a 95:5 mixture of the E/Z isomers. Evans-Tishchenko coupling of fragment **34** with aldehyde **30**, using preformed samarium(III) catalyst, led to dienoic ester **35** as a single diastereomer. RCM reaction of **35,** using second generation Grubbs catalyst and Ti(O^iPr)$_4$ as Lewis acid, afforded a 1:1 mixture of the eight-membered lactone **37** and the cyclopentene derivative **36**, formed due to a competitive metathesis reaction of the trisubstituted double bond in **35**.

Solandelactones

The solandelactones A-I (**38**-**46**) constitute a group of eight-membered ring lactones isolated in 1996 from *Solanderia secunda*, a dark-brown hydroid found in the shore of Jaeju Island, in Korea. Solandelactones C (**40**), D (**41**), and G (**44**) exhibit moderate inhibitory activity against FPT (farnesyl protein transferase).[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[30] and nine-membered ring halicholactones (described further) are derived from eicosanoid (C_{20})
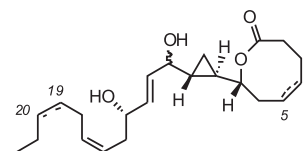
solandelactone A (**38**) (β-OH)
solandelactone B (**39**) (α-OH)
solandelactone C (**40**) (β-OH, $\Delta^{19,20}$)
solandelactone D (**41**) (α-OH, $\Delta^{19,20}$)
solandelactone E (**42**) (α-OH, $\Delta^{4,5}$)
solandelactone F (**43**) (β-OH, $\Delta^{4,5}$)
solandelactone G (**44**) (β-OH, $\Delta^{4,5}$,$\Delta^{19,20}$)
solandelactone H (**45**) (α-OH, $\Delta^{4,5}$,$\Delta^{19,20}$)

solandelactone I (**46**)
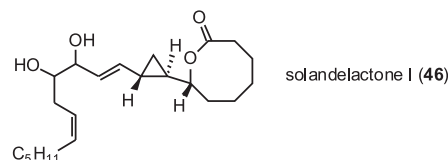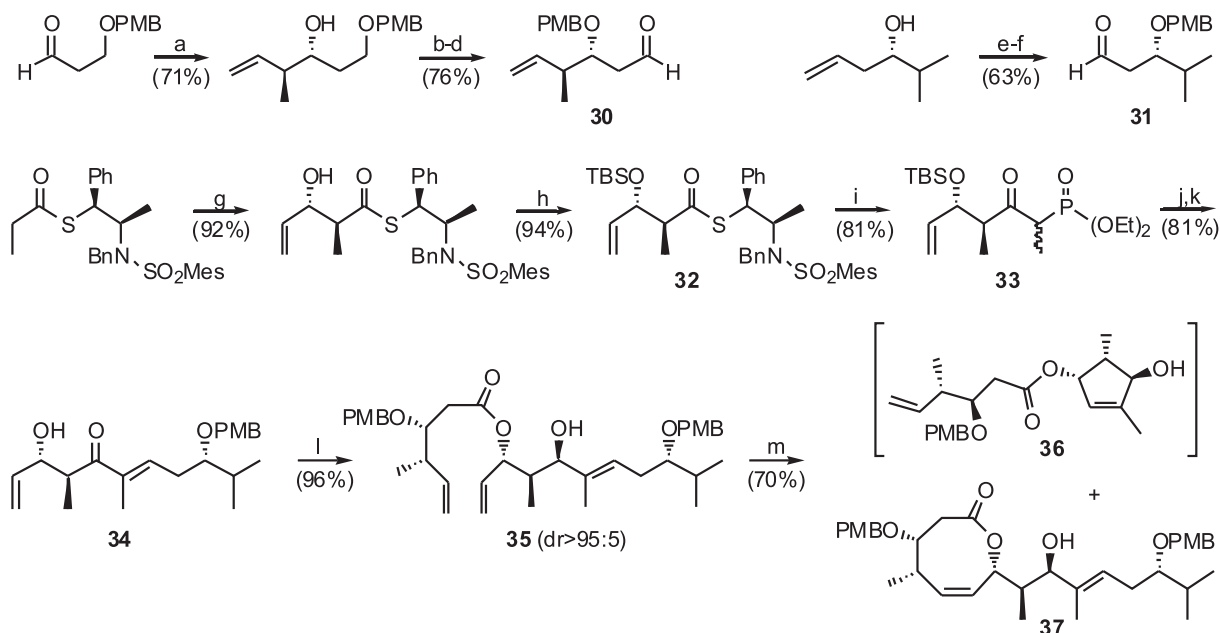
Scheme 8. Reagents and conditions: (a) i: t-BuOK, THF, trans-2-butene, n-BuLi, -78 → -45 °C, 20 min; ii: (-)-Ipc$_2$BOMe, THF, -78 °C, 35 min; iii: BF$_3$.OEt$_2$, THF, -78 °C, 4 h; (b) DDQ, MS 4A, CH$_2$Cl$_2$, 0 °C, 15 min; (c) DIBAL-H, CH$_2$Cl$_2$, 0 °C, 2 h; (d) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, Et$_3$N, -78 °C → rt, 75 min; (e) PMBCl, t-BuOK, DMF, rt, 3 h; (f) cat. OsO$_4$, NaIO$_4$, THF:H$_2$O (4:1) rt, 2 h; (g) i: (ᶜHex)$_2$BOTf, Et$_3$N, CH$_2$Cl$_2$, -78 °C, 2 h; ii: acrolein, -78 → 0 °C, 2 h; (h) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 0 °C, 70 min; (i) i: (OEt)$_2$P(O)CH$_2$CH$_3$; n-BuLi, THF, -78 °C, 1 h; ii: solution of **32** in THF, -78 °C, 1 h; (j) i: Ba(OH)$_2$.8H$_2$O, THF, rt, 30 min; ii: aldehyde **31**, THF:H$_2$O (40:1), rt, 24 h; (k) HF, CH$_3$CN, rt, 15 min; (l) (PhCHO)$_2$SmI.SmI$_3$ (30 mol%), aldehyde **30**, THF, -10 °C, 30 min; (m) 2nd generation Grubbs catalyst, CH$_2$Cl$_2$, Ti(Oi-Pr)$_4$, reflux, 24 h (**36/37** = 1/1)

precursors. The original assigment of C11 of solandelactones E (**42**) and F (**43**) was recently revised by total synthesis.[31,32]
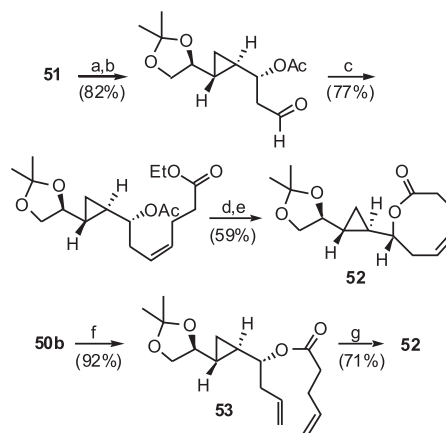
Two different approaches to the synthesis of the cyclopropyl-lactone segment of solandelactones were developed by Varadarajan *et al.*[33] Both strategies were based on the preparation of cyclopropane derivatives **50a/50b**, starting from 2,3-*O*-isopropylidene *D*-glyceraldehyde **47** (Scheme 9). 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 Martin[31] (Scheme 11). The authors synthesized the solandelactone E (**42**) and revised the original assignment for C$_{11}$. 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 C$_{12}$ 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 9. Reagents and conditions: (a) Ph$_3$P=CHCO$_2$Et, benzene, 90 °C, 6 h; (b) DIBAL-H, CH$_2$Cl$_2$, -78→0 °C, 1 h; (c) TBDPSCl, imidazole, CH$_2$Cl$_2$, 0 °C → rt, overnight; (d) Et$_2$Zn, CH$_2$I$_2$, CH$_2$Cl$_2$, -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) H$_2$C=CHCH$_2$MgBr, Et$_2$O, rt, 3 h; (h) Candida cylindracea lipase (CCL), H$_2$C=C(CH$_3$)OAc, hexane, rt, 24 h; (i) DEAD, PPh$_3$, gl. AcOH, THF, 0 °C → rt, overnight

Scheme 10. Reagents and conditions: (a) cat. OsO$_4$, NMO, acetone; (b) silica gel impregnated with NaIO$_4$, CH$_2$Cl$_2$; (c) BrPh$_3$PCH$_2$CH$_2$CO$_2$OEt, NaHMDS, THF, -78 °C → rt; (d) LiOH, MeOH, THF/H$_2$O, rt; (e) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, DMAP, toluene, reflux; (f) H$_2$C=CHCH$_2$CH$_2$C(O)Cl, Et$_3$N, CH$_2$Cl$_2$, 0 °C → rt; (g) 2nd generation Grubbs catalyst, CH$_2$Cl$_2$, 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.*[32] reported the synthesis of solandelactones E (**42**) and F (**43**) and confirmed the hydroxyl configuration at C11, early revised by Davoren and Martin.[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.[35]
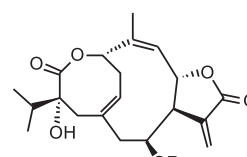
schkuhripinnatolide A (**65**)   R = H

schkuhripinnatolide B (**66**)   R =

schkuhripinnatolide C (**67**)   R =
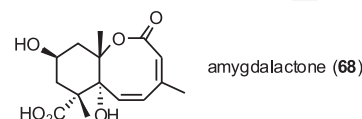
amygdalactone (**68**)

A new unusual sesquiterpene lactone, named amygdalactone (**68**), was isolated from the hulls of almond (*Prunus amygdalus*).[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.
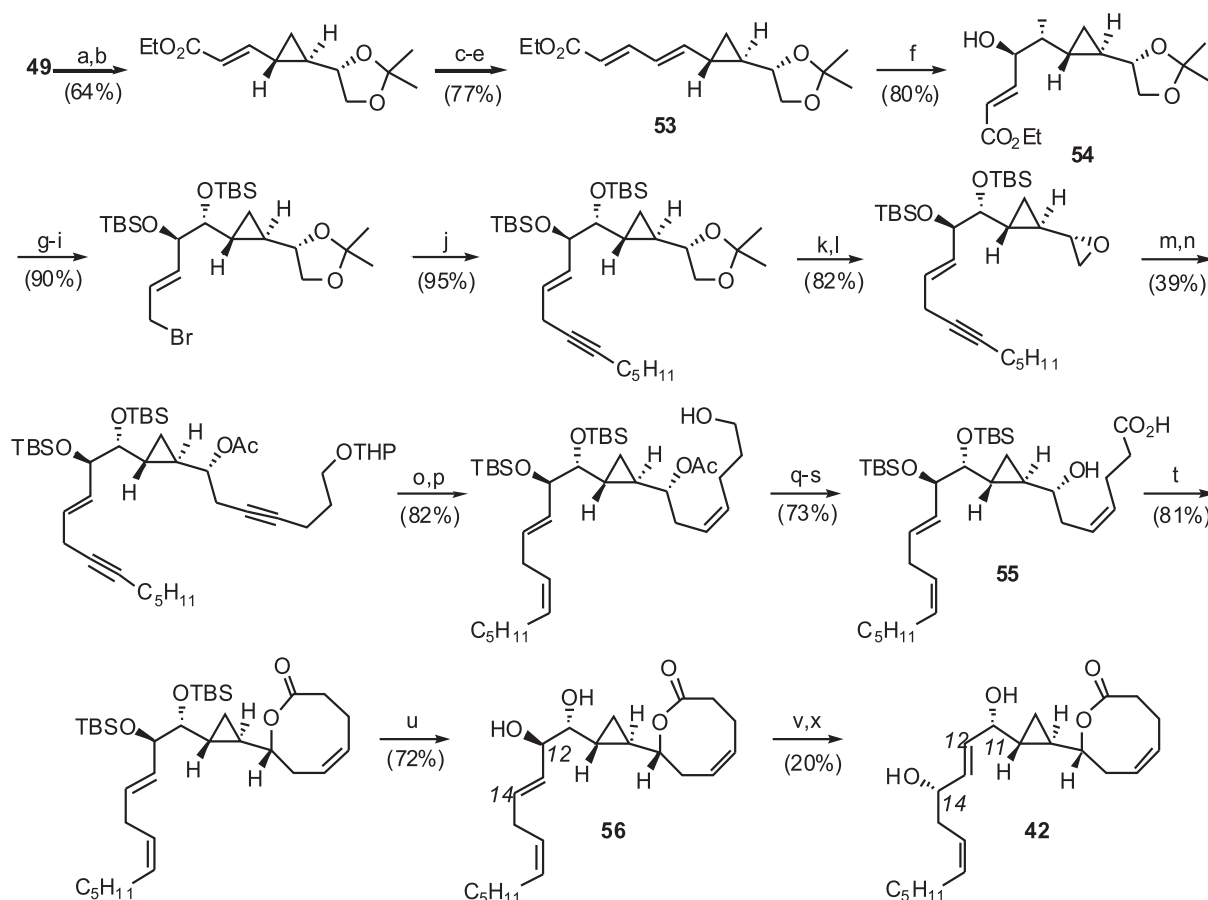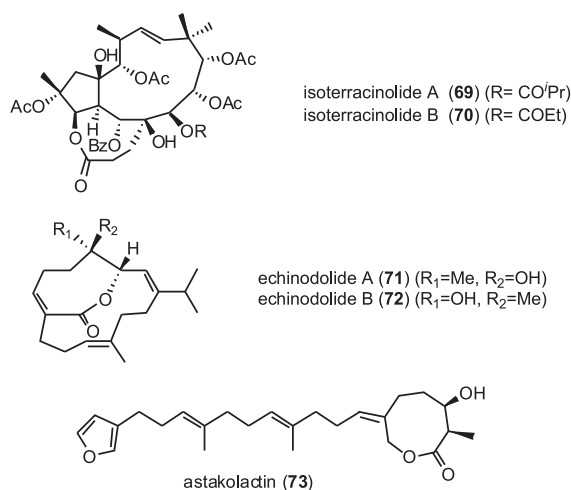

Scheme 11. *Reagents and conditions: (a) trans-(EtO)₂P(O)CH₂CH=CHCO₂Et, LDA, THF, 0 °C (10/1 EE/EZ); (b) Et₂Zn, CH₂I₂, 65 °C, 4 h then 5 °C, 12 h; (c) DIBAL-H, CH₂Cl₂, -78 °C; (d) TPAP, NMO, CH₂Cl₂, rt; (e) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C (10:1 E/Z); (f) K₃Fe(CN)₆, K₂CO₃, K₂OsO₂(OH)₄, (DHQD)₂PHAL, CH₃SO₂NH₂, t-BuOH/H₂O, rt; (g) TBSCl, imidazole, DMF, rt; (h) DIBAL-H, CH₂Cl₂, -78 °C → rt; (i) CBr₄, PPh₃, CH₂Cl₂, rt; (j) n-BuLi, 1-heptyne, CuBr.SMe₂, -78 °C; (k) TFA, H₂O, CH₂Cl₂, rt; (l) NaH, 1-tosylimidazole, THF, 0 °C; (m) i: THPO(CH₂)₃C°CH, n-BuLi, -78 °C, 1 h; ii: BF₃.OEt₂, THF, -78 °C, 45 min, then -100 °C, 2 h; (n) Ac₂O, DMAP, Et₃N, CH₂Cl₂, rt, 3.5 h; (o) p-TsOH, i-PrOH, rt; (p) H₂, Lindlar catalyst, quinoline, MeOH, rt; (q) SO₃.Py, Et₃N, DMSO, CH₂Cl₂, rt; (r) NaClO₂, NaHPO₄, 2-methyl-2-butene, t-BuOH, H₂O, rt; (s) K₂CO₃, MeOH, rt; (t) 2,4,6-trichlorobenzoyl chloride, Et₃N, DMAP, toluene, reflux; (u) TBAF, THF, rt; (v) o-NO₂PhSeCN, Bu₃P, THF, rt, 1 h; (x) H₂O₂, Py, CH₂Cl₂, 0 °C, 5 h*
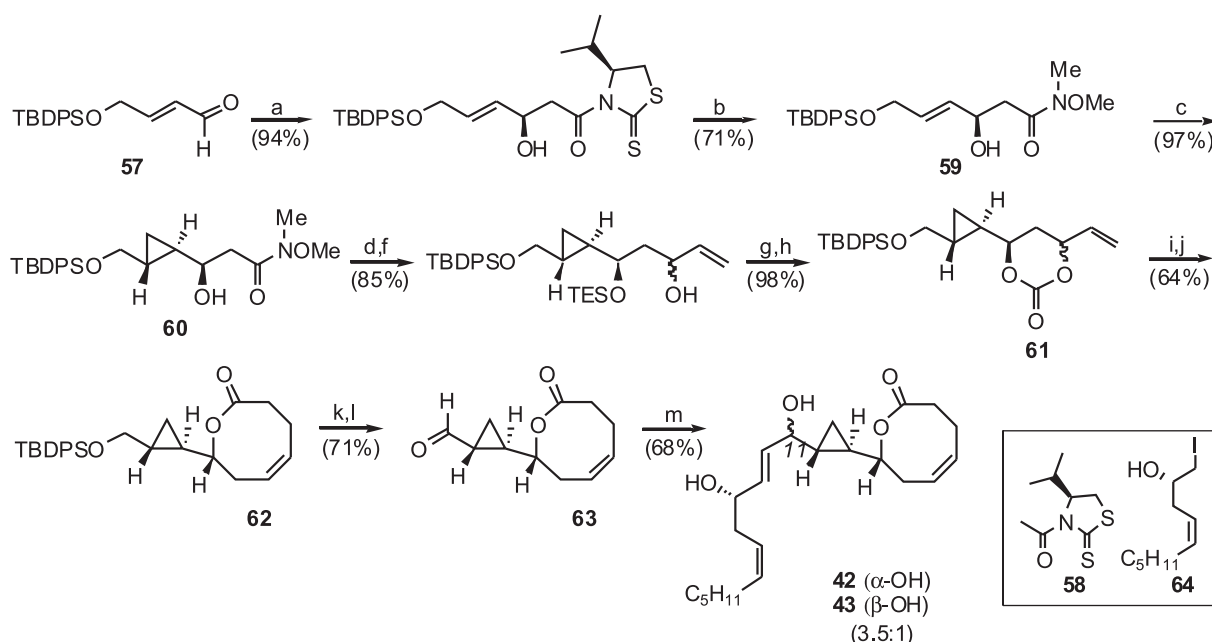
Scheme 12. *Reagents and conditions: (a) 1-(4-isopropyl-2-thioxothiazolidin-3-yl)ethanone (58), TiCl₄, i-Pr₂NEt, CH₂Cl₂, -78 °C, 6 h; (b) MeONHMe.HCl, imidazole, CH₂Cl₂, rt, 16 h; (c) Et₂Zn, CH₂I₂, CH₂Cl₂, -15 °C → rt, 3 h; (d) TESOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 45 min; (e) DIBAL-H, THF, -78 °C, 10 min; (f) H₂C=CHMgBr, THF, -78 °C, 50 min; (g) AcOH/THF/H₂O (6/2/1), rt, 1 h; (h) (Cl₃CO)₂CO, CH₂Cl₂, Et₃N, Py, MS 4A, -78 °C, 30 min; (i) Cp₂TiMe₂, toluene, 100 °C, 2 h (absence of light); (j) toluene, 100 °C; (k) TBAF, THF, rt, 1 h; (l) TPAP, NMO, CH₂Cl₂, MS 4A, rt, 20 min; (m) CrCl₂ (excess), cat. NiCl₂, DMSO, rt, 18 h*

Examples of eight-membered diterpenoid lactones includes the bis-homoditerpenes isoterracinolides A (**69**) and B (**70**) (from *Euphorbia terracina* L.),[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"),[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*.[39] To our knowledge, neither biological tests nor synthetic studies for this metabolite are reported.

isoterracinolide A (**69**) (R= CO^i^Pr)
isoterracinolide B (**70**) (R= COEt)

echinodolide A (**71**) (R₁=Me, R₂=OH)
echinodolide B (**72**) (R₁=OH, R₂=Me)

astakolactin (**73**)

Dimeric lactones

Recently, Dat *et al.*[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 (IC₅₀ of 1.5 and 1.1 µM, respectively).

ardimerin (**74**) R = H

ardimerin digallate (**75**)   R =
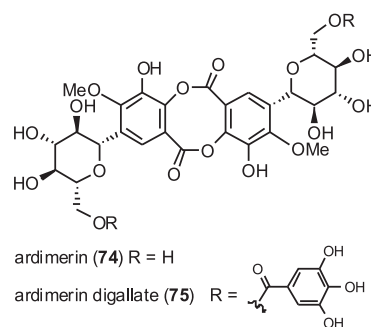
Revised structures

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

Table 1. Revised structures for pueⁿosides A and B, sophoroside A and speciosides A and B[43]

Lactone	R₁	R₂	R₃
(-)-pueroside A	glu⁶-rha	H	H
(-)-pueroside B	glu	Me	glu
(+)-sophoroside A	glu	Me	H
specioside A	glu	H	H
specioside B	H	glu	H

glu = glucose; rha = rhamnose.

Similarly, the structures of gonioheptolides A (**76**) and B (**77**), isolated in 1993 from the stem bark of *Goniothalamus giganteus*,[45] were corrected some years later.[46] Independently, Bermejo *et al.*[47] 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,[48,49] up to 2002, when a revision of the structure of **78** was also reported.[50,51]

gonioheptolide A (**76**) (R₁=H; R₂=Me)
gonioheptolide B (**77**) (R₁=H; R₂=Et)
almuheptolide A (**78**) (R₁=R₂=Me)

almuheptolide B (**79**)
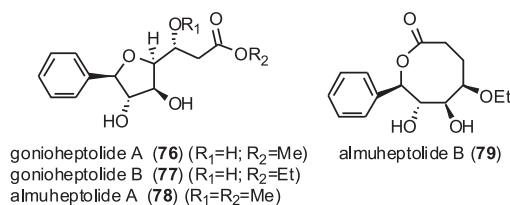
NINE-MEMBERED RING LACTONES

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.[52]

In 1991, the relative stereochemistry of all stereocenters of neohalicholactone (**81**) has been determined by X-ray crystallography as shown below.[53] Some years later, Proteau *et al.*[54] isolated **81** from the brown alga *Laminaria sinclairii*, and its absolute configuration was suggested to be the opposite to that previously postulated.

(-)-halicholactone (**80**)
(-)-neohalicholactone (**81**) ($\Delta^{17,18}$)
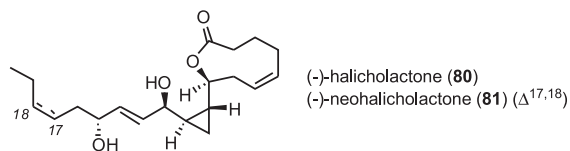
The three total syntheses[55-57] of halicholactone (**80**) and neohalicholactone (**81**) reported in literature will be briefly presented here, since Shiina[5] discussed them in details in his review. A formal synthesis of **80** and **81** was described in 1998.[58]

Critcher *et al.* reported the synthesis of the right-hand hemisphere[59] and the first asymmetric total synthesis of halicholactone (**80**) and neohalicholactone (**81**),[55] confirming the original assignments of absolute configuration of the stereocenters of **81** originally proposed by Yamada and Clardy.[53] They also demonstrated, through the preparation of diastereomers of **81**,[55] that the natural product isolated by Proteau *et al.*[54] 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,[34] led to the nine-membered ring lactone **83**, which could be transformed 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.*[56] and Takahashi *et al.*[57] 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).
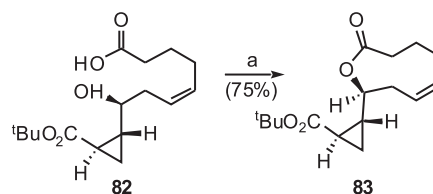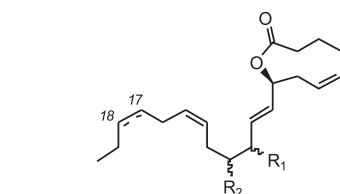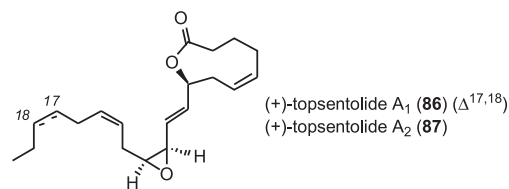
Scheme 13. *Reagents and conditions: (a) i: 2,4,6-trichlorobenzoyl chloride, THF, rt, 2 h; ii: DMAP, toluene, reflux, 6 h*
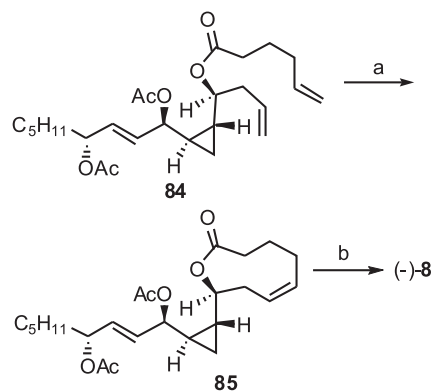
Scheme 14. *Reagents and conditions: (a) 1st generation Grubbs catalyst, Ti(Oi-Pr)₄, CH₂Cl₂ (0.1 mM), reflux, (72% in ref. 56 and 93% in ref. 57); (b) K₂CO₃, MeOH, rt (61% in ref. 56 and 55% in ref. 57)*

Topsentolides

Topsentolides A_1, A_2, B_1, B_2, B_3, C_1, and C_2 (**86-92**) are oxylipins isolated in 2006 from the marine sponge *Topsentia sp.*[60] These lactones exhibit moderate citotoxicity against human solid tumor cell lines. According to the authors, the (+)-topsentolide C_1 (**91**) and (+)-topsentolide C_2 (**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.

(+)-topsentolide A_1 (**86**) ($\Delta^{17,18}$)
(+)-topsentolide A_2 (**87**)

(+)-topsentolide B_1 (**88**) (R₁=β-OH; R₂=α-OH; $\Delta^{17,18}$)
(+)-topsentolide B_2 (**89**) (R₁=β-OH; R₂=α-OH)
(+)-topsentolide B_3 (**90**) (R₁=β-OH; R₂=β-OH)
(+)-topsentolide C_1 (**91**) (R₁=OCH₃; R₂=β-OH; $\Delta^{17,18}$)
(+)-topsentolide C_2 (**92**) (R₁=OCH₃; R₂=β-OH)

Terpenoids

Isotrichogoniolide (**93**)[61] and (+)-sinulariadiolide (**94**)[62] are nine-membered terpenoid lactones, isolated from *Trichogonia sp* and from a coral of the genus *Sinularia*, respectively, and were not synthesized yet.

isotrichogoniolide (**93**)   (+)-sinulariadiolide (**94**)
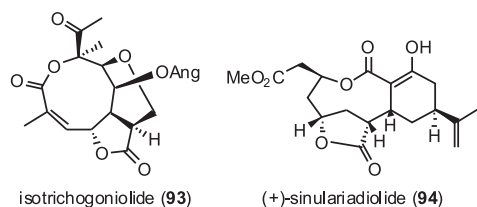
Antimycins

The antimycin-A antibiotics are a series of nine-membered dilactones, which were isolated from a number of *Streptomyces* strains over many decades.[63] A complex mixture of antimycins A_1-A_8 is a specific inhibitor of the electron transfer activity of ubiquinol-cytochrome *c* oxidoreductase.[64] The antimicyns 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.[65]

The main component of this family of peptide alkaloids is the antimycin A_3, 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 antimycins (+)-A_{3a} (**95**) and (+)-A_{3b} (**96**).[66] The slight difference between these two nine-membered dilactones relied upon the ester function at C8: (+)-**95** is a *sec*-butyl ester while the (+)-**96** is the isobutyl analog.


(+)-antimycin A_{3a} (**95**) R = *sec*-butyl
(+)-antimycin A_{3b} (**96**) R = isobutyl
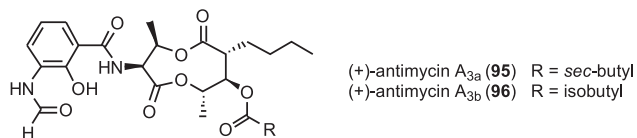
Both racemic[67] and stereoselective synthesis[68] of natural (+)-antimycins A_{3b} (**96**) have been first accomplished by Kinoshita *et al.* Tsunoda group developed an asymmetric aza-Claisen rearrangement of enolates of carboxamides and applied this methodology to the synthesis of both, unnatural (-)-antimycin A_{3b}[69] (*ent*-**96**) and natural (+)-antimycin A_{3a}[70] (**95**), while one approach for (+)-antimycin A_{3b} (**125**) was recently reported.[71] Some formal synthesis of these dilactones are also found in the literature.[72]

Kinoshita *et al.*[68] reported the first asymmetric total synthesis of (+)-antimycin A_{3b} (**96**) as well as the synthesis of one of its diastereomers. Lactonization of (+)-(3S,4R,7R,8R,9S)-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 A_{3b}, starting from the hydroxyacid **97b** (Scheme 16), following the same sequence of reactions outlined in Scheme 15.[68]

The synthesis of unnatural (-)-antimycin A_{3b} (*ent*-**96**) reported by Tsunoda *et al.*[69] started from (R)-(+)-methylbenzylamine, which was transformed in the amide **101** in three steps. The aza-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*-Bu$_3$SnH, afforded the lactones **103a/103b**, which was converted into the desired prenyl ester **104a/104b** along with the butenolide by-product **105**. Mitsunobu reaction[73] 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
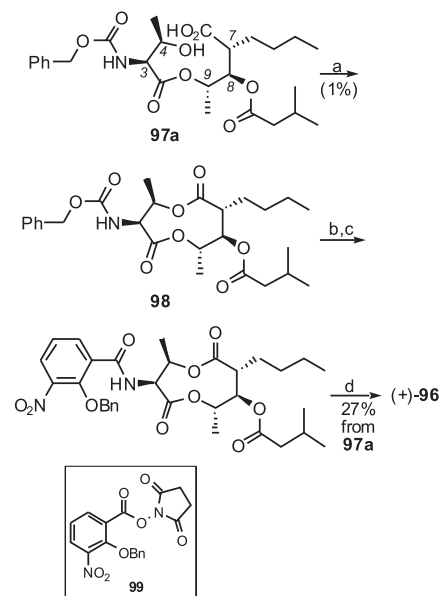
Scheme 15. *Reagents and conditions: (a) i: TFA, rt, 10 min; ii: TTFA, benzene, 65-70 °C, 6 h; (b) palladium black, H$_2$, MeOH, rt, 35 min; (c) i: O-benzyl-3-nitrosalicylic acid N-hydroxysuccinimide ester (**99**), THF, 36 °C, 3 h; ii: Et$_3$N (pH=6), 36 °C, 25 h; (d) i: palladium black, H$_2$, MeOH, rt, 10 min; ii: dicyclohexylcarbodiimide (DCCI), THF, HCO$_2$H, 0 °C, 4 h*
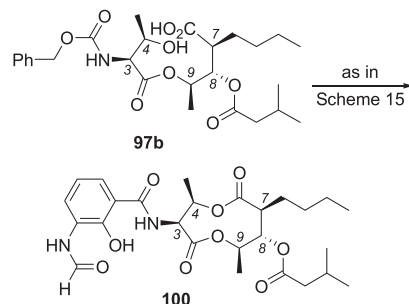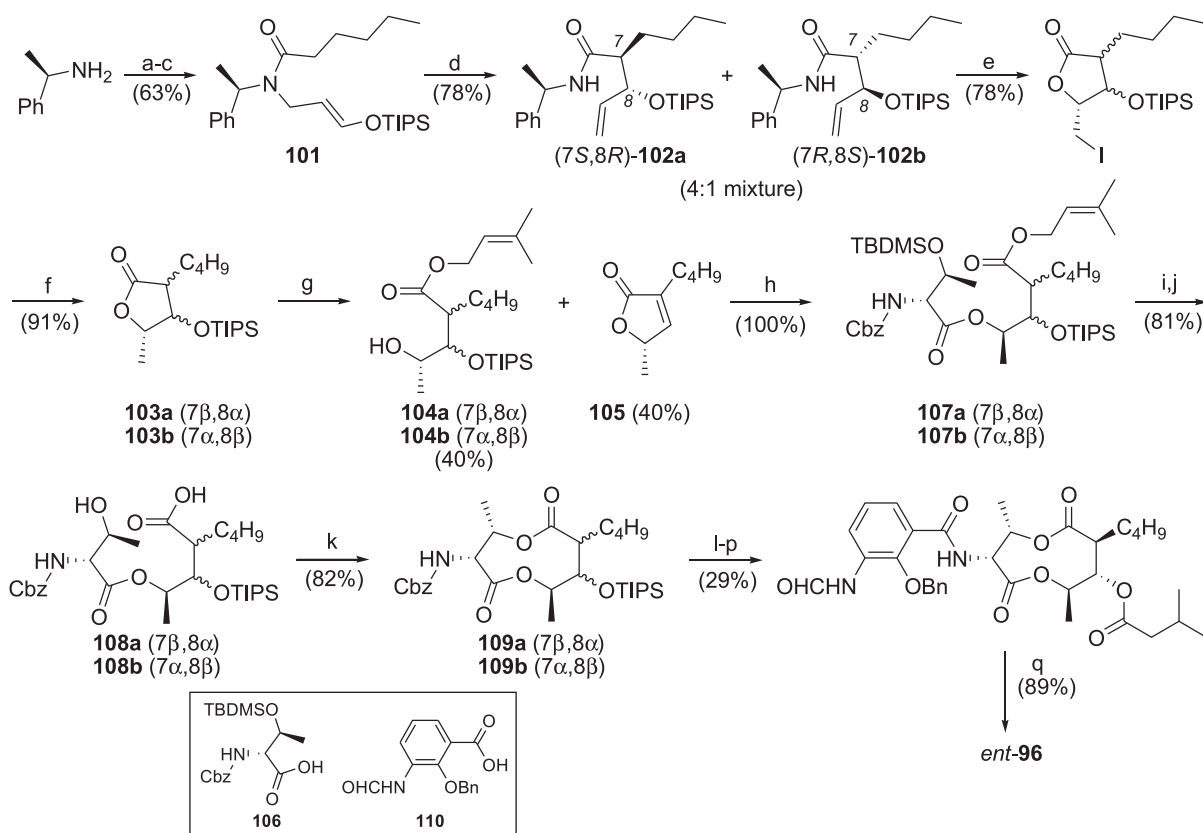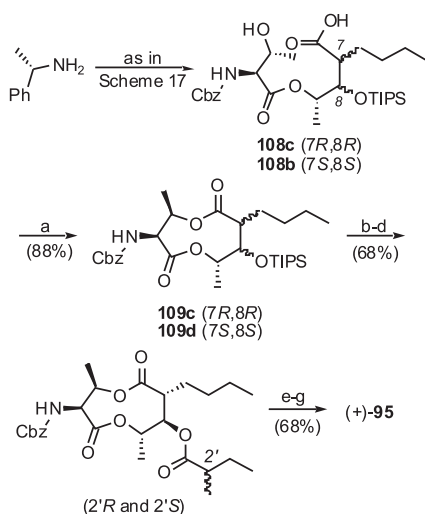

Scheme 16

submitted to the Corey-Nicolaou lactonization[14] to afforded a separable mixture of the nine-membered dilactones **109a/109b**. The unnatural (-)-antimycin A_{3b} (*ent*-**96**) could then be obtained from **109a**, after five additional steps (Scheme 17).

In 2003,[70] the same Japanese group reported the stereoselective synthesis of (+)-antimicym A_{3a} (**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**.[69] Corey-Nicolaou lactonization[14] of **108c/108d**, using Cu(OTf)$_2$.PhH complex instead the explosive AgClO$_4$ metal salt, afforded a separable mixture of the nine-memebered dilactones **109c/109d** in 88% yield. Removal of the TIPS-protecting group, followed by esterification of the free hydroxyl 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[71] synthesized the (+)-antimycin A_{3b} (**96**) using a TiCl$_4$-mediated asymmetric aldolization to construct the C7/C8 stereocenters in **111** with the correct configurations. A lactonization method,[74] based on the activation of the acyl group through the formation of w-hydroxyacid **112** (*via* the formation of

Scheme 17. *Reagents and conditions: (a) TMSOTf, DBU, ether, 0 ºC, 1 h; (b) TIPSOTf, acrolein, 0 ºC ' → rt, 6 h; (c) CH₃CH₂CH₂CH₂CH₂C(O)Cl, Et₃N, CH₂Cl₂, 0 ºC; (d) i: LHMDS, toluene, -78 ºC; ii: 120 ºC, 6 h; (e) I₂, N,N-dimethyl-p-nitroaniline, DME/H₂O (3/2), rt, 3 days; (f) Bu₃SnH, benzene, reflux; (g) i: CsOH, t-BuOH, 0 ºC; ii: prenyl bromide, Py, ether, 0 ºC, 24 h, (h) 106, DEAD, PPh₃, benzene, rt, 24 h; (i) 6 N aq. HCl, EtOH, rt, 24 h; (j) Pd(OAc)₂, PPh₃, Et₃N, HCO₂H, dioxane, 100 ºC, 1 h; (k) i: pySSpy, PPh₃, benzene, rt, 3 h; ii: AgClO₄, benzene, 80 ºC, 2 h; (l) chromatographic separation (isolation of 109a); (m) TBAF, THF, 0 ºC, 5 min; (n) isovaleric anhydride, Py; (o) H₂, Pd/C, AcOEt; (p) 110, water-soluble carbodiimide (WSC), 1-hydroxybenzotriazole (HOBt), N-methylmorpholine (NMM), DMF, rt; (q) H₂, Pd/C, AcOEt*


Scheme 18. *Reagents and conditions: (a) i: pySSpy, PPh₃, benzene, 3 h; ii: Cu(OTf)₂.PhH, benzene, 80 ºC, 3 h; (b) chromatographic separation (isolation of 109c); (c) HF.Py, THF, 23 h; (d) (S)- and (R)-2-methylbutanoic acid, WSC, DMAP, CH₂Cl₂; (e) H₂, Pd/C, AcOEt; (f) 110, WSC, HOBt, NMM, DMF, rt; (q) H₂, Pd/C, AcOEt*

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

Griseoviridin

The macrocyclic peptide (-)-griseoviridin (**115**), isolated from *Streptomyces griseus*, is a broad-spectrum antibiotic, with inhibitory activity toward various pathogenic bacteria and fungi.[75,76] This alkaloid contains, among other functionalities, an unsaturated nine-membered thioether-lactone subunit.
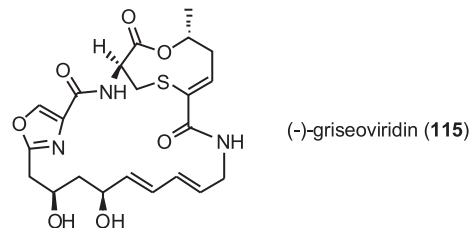
(-)-griseoviridin (**115**)

Several synthetic approaches to the sulfur-containing lactone moiety of griseoviridin have been reported,[77] and a total synthesis of (-)-griseoviridin (**115**) was accomplished by Dvorak *et al.*[78] 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-hydroxyacid **116** to the nine-membered lactone intermediate **117** (with inversion of the configuration of C5) was easily achieved using the Mistunobu protocol.[73]
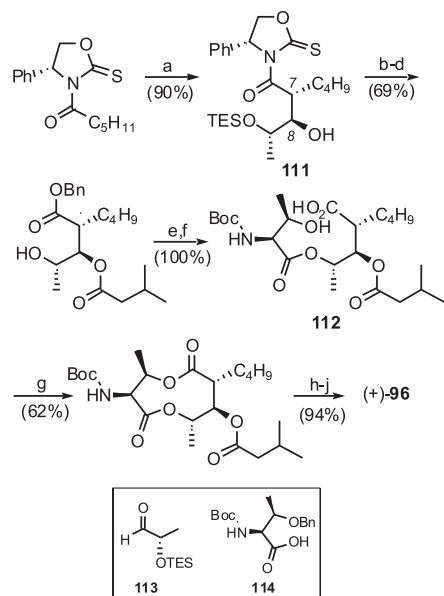
Scheme 19. *Reagents and conditions: (a) i: TiCl$_4$, TMEDA, CH$_2$Cl$_2$, -50 °C, 20 min, then -20 °C, 2 h; ii: TMEDA, -20 °C, 1 h; iii: TES-protected (S)-2-hydroxypropanal (113), -20 °C, 2 h, then -5 °C, 6 h; (b) Me$_2$CHCH$_2$C(O)Cl, Py, DMAP, CH$_2$Cl$_2$, 0 °C, 8 h; (c) BnOH, DMAP, CH$_2$Cl$_2$, rt, 32 h; (d) NaIO$_4$, THF/H$_2$O (3/1), 0 °C, 3 h; (e) i: 114, DCC, CH$_2$Cl$_2$, 0 °C, 50 min; ii: DMAP, rt, 26 h; (f) H$_2$ (30 atm), Pd(OH)$_2$/C, MeOH, 40 °C, 8 h; (g) MNBA, DMAP, toluene, MS 4A, rt, 23 h; (h) TFA, CH$_2$Cl$_2$, 20 °C, 9.5 h; (i) 110, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl), HOBt, NMM, DMF, 30 °C, 23 h; (i) H$_2$, 10% Pd/C, EtOAc, 30 °C, 6.5 h*
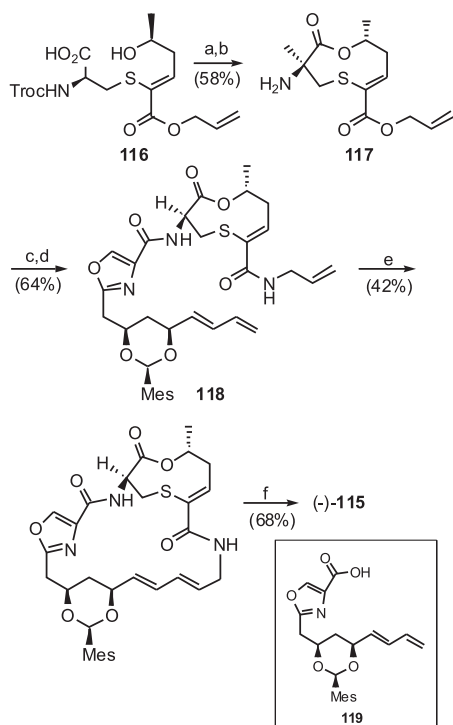
Scheme 20. *Reagents and conditions: (a) DIAD, PPh$_3$, THF; (b) 10% Cd/ Pb, 1 M NH$_4$OAc, THF; (c) 119, N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDCI), HOBt, DMF; (d) Pd(PPh$_3$)$_4$, pyrrolidine, H$_2$C=CHCH$_2$NH$_2$, HOBt, EDCI, DMF; (e) 1st generation Grubbs catalyst, toluene (0,001 M), 100 °C; (f) pyridinium-p-toluenesulfonate (PPTS), acetone/H$_2$O*

Revised structures

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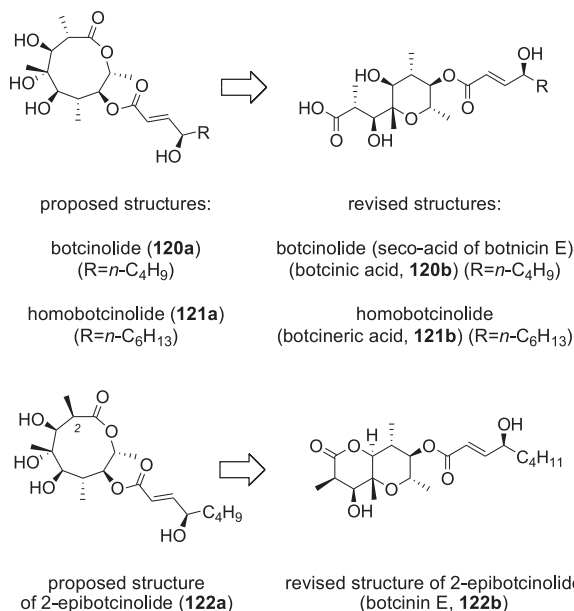

proposed structures:

botcinolide (**120a**)
(R=*n*-C$_4$H$_9$)

homobotcinolide (**121a**)
(R=*n*-C$_6$H$_{13}$)

revised structures:

botcinolide (seco–acid of botnicin E)
(botcinic acid, **120b**) (R=*n*-C$_4$H$_9$)

homobotcinolide
(botcineric acid, **121b**) (R=*n*-C$_6$H$_{13}$)

proposed structure
of 2-epibotcinolide (**122a**)

revised structure of 2-epibotcinolide
(botcinin E, **122b**)

**Figure 1.** *Botcinolide and analogues*

Tani *et al.*[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.[85]

Independently, Shiina *et al.*[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 **124** through the lactonization of seco acid **123** using MNBA as activating reagent (Scheme 21). Epimerization of C2 in **125** 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 γ-lactone **126**.

Concerning the structural misassignments presented above, we would like to reproduce some paragraphs of the fascinating work of Nicolaou and Snyder,[87] entitled *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.
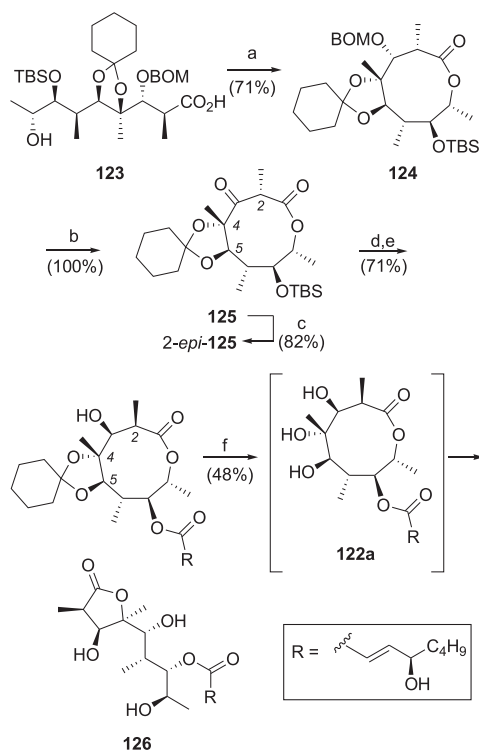
Scheme 21. *Reagents and conditions: (a) MNBA, DMAP, CH₂Cl₂, rt, 4 h (7% of the dimer of **124**); (b) i: H₂, Pd(OH)₂, EtOH, rt, 15 h; ii: TPAP, NMO, MS 4A, CH₂Cl₂, 0 °C, 3 h (**125**/2-epi-**125** = 8/2); (c) preparative TLC; (d) i: NaBH₄, MeOH, 0 °C, 2 h; ii: DHP, CSA, CH₂Cl₂, rt, 1 h; iii: TBAF, THF, 0 °C, 3 h; (e) i: TBS-protected 4-(R)-2-(E)-4-hydroxyoct-2-enoic acid, MNBA, Et₃N, DMAP, CH₂Cl₂, rt, 3.5 h; ii: HF.Py, THF, rt, 3 h; (f) BBr₃, CH₂Cl₂, - 45 °C, 1.5 h*

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.*[88] 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[89-92] of ferrulactone I (**127**) described in literature start from geraniol. The first synthesis of **127** was reported in 1983 by Oehlschlager *et al.*,[89] which obtained the cyclic intermediate **132** by intramolecular alkylation of the ω-bromo-geraniol derivative **131**.

ferrulactone I (**127**)   ferrulactone II (**128**)
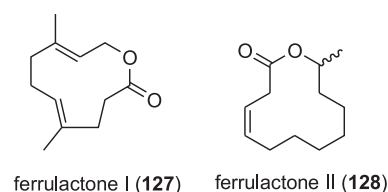
This intermediate was prepared by reaction of geraniol **129** with (phenylthio)acetyl chloride, followed by allylic oxidation in C8 and bromination of the alcohol thus obtained. Finally, desulfurization of **132** afforded the target molecule in 10% global yield (Scheme 22).
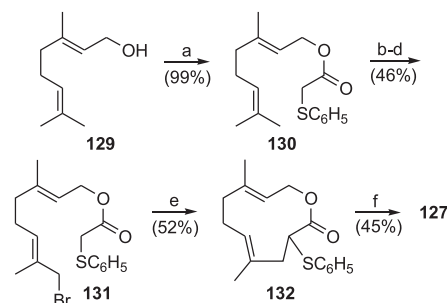
Scheme 22. *Reagents and conditions: (a) C₆H₅SCH₂C(O)Cl, Py, CH₂Cl₂, 0 °C, 3 h; (b) SeO₂, Py, EtOH, reflux, 4.5 h; (c) NaBH₃C≡N, THF, 0 °C, 1 h, then 23 °C for 18 h; (d) CBr₄, PPh₃, Et₂O, 23 °C, 20 h; (e) NaH, HMPA, THF, reflux, 23 h; (f) Ni-Ra, EtOH, rt, 1 h*

In the same paper,[89] an alternative approach to ferrulactone **127** was also described. The key step consists of an intramolecular esterification[93] 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)[93] was used as activating reagent and the temperature of the reaction medium was carefully controlled (Scheme 23).
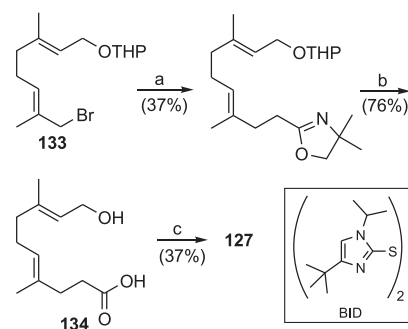
Scheme 23. *Reagents and conditions: (a) 2,4,4-trimethyl-2-oxozoline, n-BuLi, THF, -78 °C, 1 h; (b) i: MeI (excess), rt; overnight; ii: 1 N aq. NaOH, rt, 20 h; iii: Dowex 50W-X8, MeOH, rt, 1 h; (c) i: BID, PPh₃, toluene, -68 °C → -10 °C, 2.5 h; ii: addition of cold toluene, -35 → 23°C, then reflux, 2 h*

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.*[90] (Scheme 24).

Another synthesis of **127** in which the key step is a lactonization of a seco acid was reported by Cheskis *et al.*[91] The Claisen rearrangement of allylic alcohol **136** proceeded stereospecifically to furnish the ester **137** in 95% yield as a single (E,E)-isomer
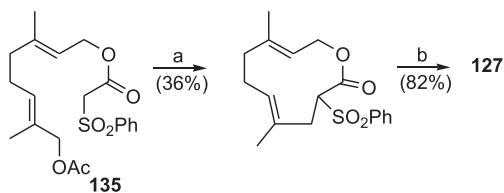
Scheme 24. *Reagents and conditions: (a) i: NaH, THF, 0 °C, 15 min, then rt, 30 min. ii: Pd(PPh₃)₄, bisdephenylphosphineethylene, 0 °C; (b) sodium amalgam, EtOH, AcOH, - 20 °C → rt, 2.5 h*

(Scheme 25). 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]
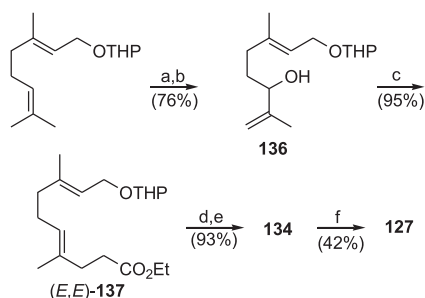
Scheme 25. *Reagents and conditions: (a) MCPBA, AcONa, CH₂Cl₂, 0 °C, 30 min, then 20 °C, 1.5 h; (b) (i-PrO)₃Al, toluene, reflux, 6 h; (c) TMOF, CH₃CH₂CO₂H, 135 °C, 1.5 h; (d) PTSA, Py, EtOH, 55 °C, 4 h; (e) aq. KOH, MeOH, rt, 1 h; (f) BID, toluene, PPh₃, -75 °C, 30 min, then -10 °C, 1.5 h*
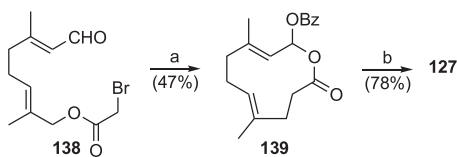
Moriya *et al.*[92] obtained the ferrulactone (**127**) in a short four-step synthesis, also starting from geraniol (Scheme 26). An intramolecular Reformatsky reaction of ω-bromoacetoxy aldehyde **138** led to the eleven-membered lactone intermediate **139**, which was submitted to selective allylic debenzoylation promoted by SmI₂ in THF-HMPA.
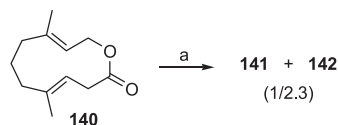

Scheme 26. *Reagents and conditions: (a) SmI₂-THF, BzC(O)Cl, DMAP, rt; (b) SmI₂-THF-HMPA, 2,2-dimethyl propanoic acid, 0 °C*

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 same authors[98] developed a conformational analysis of suspensolide (**140**), by molecular modeling and NMR studies, and concluded that the two most stable conformers have the methyl groups in a *syn* position.

Scheme 27. *Reagents and conditions: (a) BF₃.EtO₂, Et₂O, 23 °C, 0.5 h*

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.[99]

Battiste *et al.*[100] reported a short synthesis of suspensolide (**140**) from mesityl oxide and proved the (3*E*,8*E*)-geometry of the double bonds of this natural product. The key hydroxyacid **143** was submitted to lactonization under Mitsunobu conditions[73] to afford **140** in only 25% isolated yield (Scheme 28).
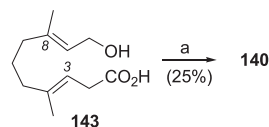
Scheme 28. *Reagents and conditions: (a) DEAD, PPh₃, benzene, rt, 72 h*

In the same year, Mori and Nakazono[101] reported the synthesis of **140** also using the Mitsunobu lactonization[73] 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-monoprotection 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
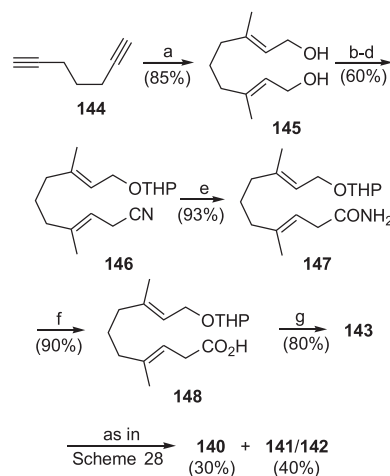
Scheme 29. *Reagents and conditions: (a) i: AlMe₃, ZrCp₂Cl₂, ClCH₂CH₂Cl, 0 °C, 3 h; ii: n-BuLi, THF, (CHO)ₙ, -78 °C, overnight; (b) DHP, Et₂O, PTSA, rt; (c) NCS, CH₂Cl₂, DMS, 0 °C, 1 h; (d) KCN, CH₃CN, 18-crown-6, rt, 12 h; (e) H₂O₂, ,n-Bu₄HSO₄, CH₂Cl₂, 20% aq. NaOH, rt, 8 h; (f) Na₂O₂, H₂O, 80 °C, 8 h; (g) AcOH/THF/Et₂O (4/2/1), 45 °C, 4 h*

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.[103] 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 regio- and stereoselective reduction of the conjugated diene moiety with lithium in liquid ammonia and methanol (Scheme 30).
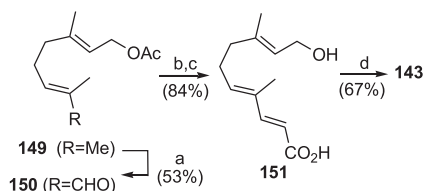
Scheme 30. *Reagents and conditions: (a) SeO$_2$, EtOH, reflux, 1 h; (b) Ph$_3$P=CHCO$_2$Et, 100 °C, 1 h; (c) KOH, H$_2$O, MeOH, 23 °C, 72 h; (d) Li, liq. NH$_3$, MeOH, reflux, 15 min*

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]
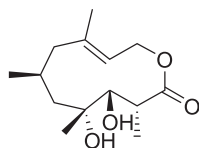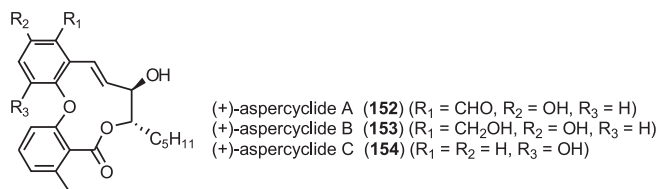

Figure 2. *2,4,6,8-Tetramethyl-3,4-dihydroxydec-8(9)-enolide*

Aspercyclides

Aspercyclides A-C (**152-154**) are biphenylether-lactones isolated from an extract of *Aspergillus sp.*[104] Aspercyclide A (**152**) showed to be inhibitor of the IgE receptor binding (IC$_{50}$ = 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.


(+)-aspercyclide A (**152**) (R$_1$ = CHO, R$_2$ = OH, R$_3$ = H)
(+)-aspercyclide B (**153**) (R$_1$ = CH$_2$OH, R$_2$ = OH, R$_3$ = H)
(+)-aspercyclide C (**154**) (R$_1$ = R$_2$ = H, R$_3$ = OH)

The first reported total synthesis of (+)-aspercyclide C (**154**) was achieved by Fürstner and Müller[105] 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[106] to furnish the dienoic ester **157**. RCM of **157** with second generation
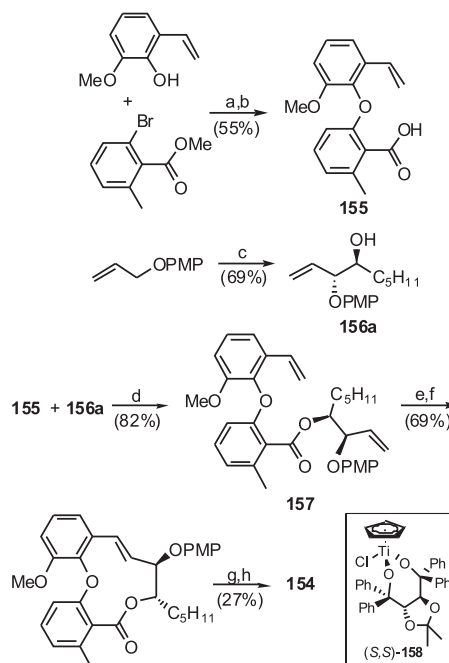
Scheme 31. *Reagents and conditions: (a) CuO, K$_2$CO$_3$, Py, 130 °C; (b) aq. NaOH, MeOH; (c) i: sec-BuLi; ii: hexanal, complex (S,S)-**158**, THF/Et$_2$O, -78 °C; (d) N-methyl-2-chloropyridinium iodide, Et$_3$N, CH$_3$CN, reflux; (e) 2nd generation Grubbs catalyst, toluene, reflux, (f) chromatographic separation; (g) CAN, CH$_3$CN/H$_2$O, 0 °C; (h) BBr$_3$, CH$_2$Cl$_2$, -78 → 0 °C*

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.[107] 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.
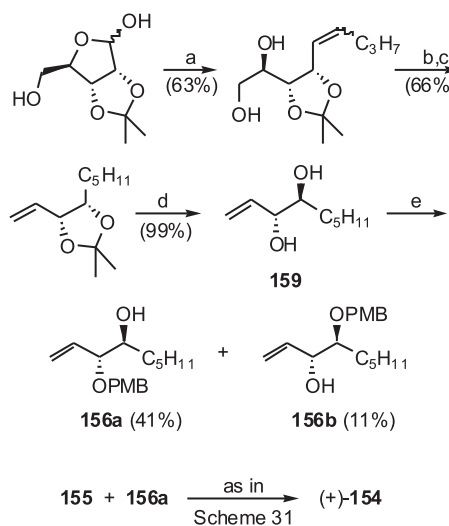
Scheme 32. *Reagents and conditions: (a) Ph$_3$PCH$_2$CH$_2$CH$_2$CH$_3$Br, t-BuOK, THF, 0 °C → rt, 16 h; (b) Ra-Ni, H$_2$, EtOH, rt; (c) i: MsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C, 3 h; ii: Zn, NaI, DMF, 155 °C, 2 h; (d) PTSA, MeOH, rt, 24 h; (e) PMBCl, NaH, DMF, 0 °C → rt, 10 h (20% recovery of **159**); (f)) N-methyl-2-chloropyridinium iodide, Et$_3$N, CH$_3$CN, 120 °C, 1 h; (g) 2nd generation Grubbs catalyst, toluene, reflux, 3 h; (h) BBr$_3$, CH$_2$Cl$_2$, -78 °C, 5 min*

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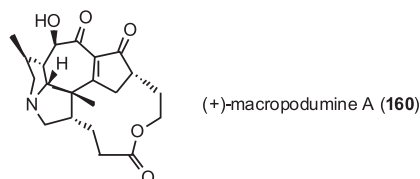
Eight others *Daphniphyllum* alkaloids, namely macropodumines B-I, have also been found in *D. macropodum,*[109] but these molecules are not medium ring lactones. To our knowledge, there are no synthetic approaches for macropodumine A (**160**) described in the literature.

Some eleven-membered dilactone having a pyrrolizidine moiety were isolated from several species of *Crotalaria.*[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,*[111] *C. grahamiana,*[112] *C. crispata,*[113] *C. fulva*[114] and several others species of this genus.[115] Others representative examples of the pyrrolizidine alkaloids with these structure features are dicrolataline (**162**),[116] fulvine (**163**), [113,114] and crispatine (**164**).[111,114]
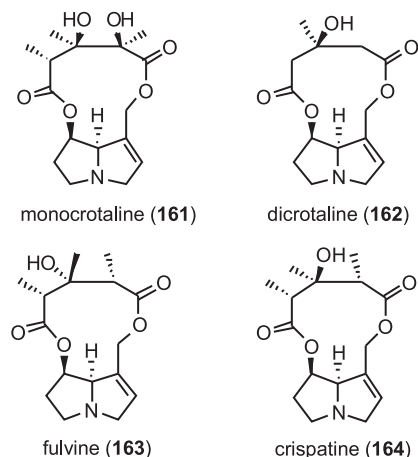

Figure 3. *Some eleven-membered dilactones bearing a pyrrolizidine moiety*

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.*[117] The synthesis of **161**-**164**[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,[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.[3] Nevertheless, the use of the lactonization methods developed by Corey-Nicolaou,[14] Yamaguchi[34] and Mitsunobu[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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