Spirolactones: Recent advances in natural products, bioactive compounds and synthetic strategies

Spirolactones: Recent Advances in Natural Products, Bioactive Compounds and Synthetic Strategies.

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Abstract: ***Background:*** The spirocyclic compounds have always aroused a great interest because this motif is present as structural core in a number of natural products and bioactive compounds. In particular, the spirolactone moiety has been recognized in a wide array of natural and non-natural scaffolds showing a variety of useful pharmacological properties.

Methods: Extensive literature search using SciFinder (Databases: CA Plus, CAS Registry, CAS React, Chemlist, Chemcat and Medline) and Web of Science (Database: Web of Science Core Collection).

Results: Nowadays, many efforts are devoted to the discovery of new natural products containing the promising spirolactone framework and to the disclosure of the potential bioactivities of these chemical entities. Moreover, the medicinal relevance of many spirolactones makes these scaffolds attractive targets for the design and development of innovative and efficient synthetic strategies, enabling the construction of complex and variably substituted products.

Conclusion: This review gives an overview on the recent advances in the spirolactones field, in terms of new compounds isolated from natural sources, recently determined bioactivity profiles and innovative synthetic approaches. The collected data demonstrate the key role played by spirolactones in medicinal chemistry and the great attention still devoted by the scientific community to these compounds.

Keywords: spirolactones, natural products, bioactivity, stereoselective synthesis, quaternary stereocenters, spirocyclization.

1. INTRODUCTION

Much attention has always been addressed to spirocyclic compounds because the spiro-junction is present in the core of a number of natural and non-natural bioactive products [1-19]. In addition, spiro-compounds have proved to be very interesting for technological fields such as optoelectronics [20-21]. Among the spirocyclic architectures, the spirolactone moiety is particularly present in natural and non-natural species characterized by pharmacological properties [3-4,6,22-23]. For this reason, many efforts are still devoted to the discovery of new natural products containing this promising framework and to the disclosure of the potential bioactivities of these chemical entities. Moreover, the medicinal relevance of many spirolactones has made these scaffolds attractive targets for the design and development of innovative and efficient synthetic strategies, enabling the construction of complex and variably substituted products. On one hand the need for more potent and selective, as well as less toxic, drugs has conferred a key role to the spirolactones synthesis, on the other hand their stereoselective construction remains still challenging, because of the sterically constrained spiro architecture and the presence of at least a quaternary stereogenic center.

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The aim of this review is to give an overview on the recent advances in the spirolactones field, in terms of new compounds isolated from natural sources, recently determined bioactivity profiles and innovative synthetic approaches. The review will be divided in three main sections: natural products, bioactive synthetic compounds and innovative synthetic strategies. For the first two sections, the sub-sections will be defined according to the biological properties of the compounds. The third section will be organized in accordance with the reaction categories.

2. NATURAL PRODUCTS

Historically, natural products were one of the main sources of bioactive species, which established the basis for drug discovery and development [24-31]. Considering the new drugs approved from 1981 to 2007 [25], almost half were natural products-based leads. Nevertheless, in the past two decades, the main direction of drug discovery left the natural sources, due to the difficulty in finding unexplored materials and isolating adequate amount of compound. In addition, molecular biology techniques and combinatorial chemistry experienced a strong growth, allowing to create wide libraries of synthetic drug-like compounds. More recently, there was a renewed and growing interest in natural products, caused by the recognition of the exceptional structural diversity provided by the natural sources.

Natural occurring spirolactones represent a broad family of compounds, characterized by a huge structural diversity (Fig. 1) and a wide range of different biological activities. In the

following sections, the recently discovered spirolactone-containing natural products will be presented, sorted by bioactivity profile.

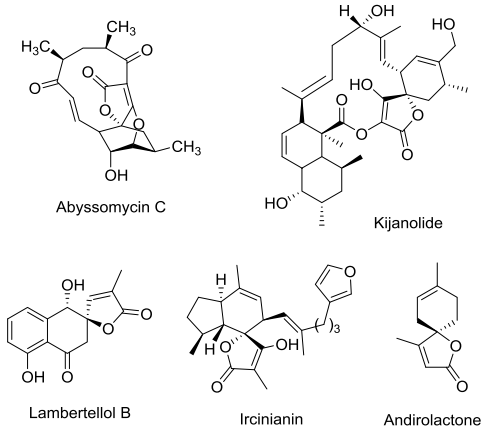


Fig. (1). Examples of natural products containing spirolactone framework.

2.1. Antibiotic Compounds.

To face and defeat many infections caused by multiresistant Gram-positive bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), still there are few therapeutic options. As a consequence, many efforts have been devoted to the discovery of new antibiotics.

In 2004, Süssmuth and co-workers focused their investigations on rare actinomycetes from the deep-sea plain and they screened them for inhibitors of *p*-aminobenzoate (*p*ABA) biosynthesis, a part of the tetrahydrofolate biosynthesis present in many microorganisms but not in humans. The authors identified a new family of polycyclic polyketide-type antibiotics, named abyssomicins (Fig. 2), representing the first compounds from a bacterial source able to inhibit the *p*ABA biosynthesis [32].

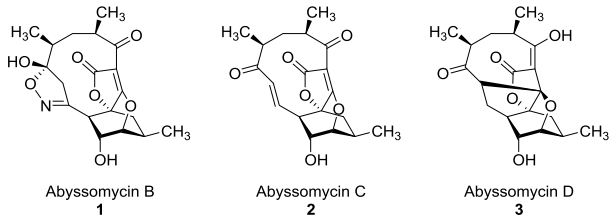


Fig. (2). Structures of antibacterial abyssomicins B (**1**), C (**2**), and D (**3**).

Within this family, only abyssomicin C (**2**) revealed to be active against Gram-positive bacteria, including *Staphylococcus aureus* strains. The minimal inhibition concentrations (MIC) against MRSA and an other multiresistant (including vancomycin-resistant) *S. aureus* strain were 4 μg/mL and 13 μg/mL, respectively [33]. Although abyssomicins are relatively small molecules, they are characterized by many ring systems (four in **2** and five in **1** and **3**), quarternary carbons, and other stereocenters. In particular, all these scaffolds share the tetronic acid motif of ring B spiro-combined with the oxabicyclooctane ring system of rings C and D. The authors found similarities between the oxabicyclooctane system and both the chorismate conformation and the transition-state of synthetic derivatives of chorismate mutase inhibitors. Furthermore, the absence of the Michael acceptor system in the inactive abyssomicins B (**1**) and D (**3**) led the authors to postulate that this Michael system is directly involved in the mechanism of action of abyssomicin C (**2**) by covalent trapping of a nucleophilic side chain in the target enzyme.

Another natural product family, showing promising antimicrobial activity against Gram-positive bacteria including MRSA, consists of lactonamycins (**4**, Fig. 3). They were isolated for the first time in 1996 and are characterized by a five-membered lactone-unit (ring F) spiro-grafted with the 2,3-dihydronaphthalene-1,4-dione system (C,D rings). In 2003, lactonamycin Z (**4a**, Fig. 3) was identified among the metabolites produced by strain AK 623 of *Streptomyces sanglieri* [34]. This scaffold is characterized by the peculiar α-2,6-dideoxy-ribohexose sugar unit. Considering the only weak antibacterial activity of **4a** with respect to the previously isolated lactonamycin, it can be deduced that the antibiotic properties of this class of natural compounds are significantly affected by the nature of the sugar moiety and the α-2,6-dideoxy-ribohexose unit drops the bioactivity.

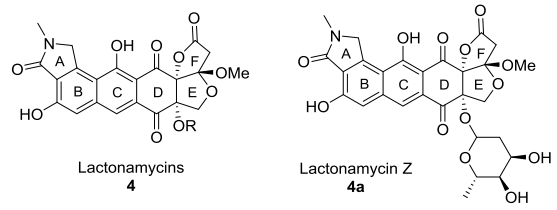


Fig. (3). Structure of antibacterial lactonamycins **4.**

Very recently (2015), Cech *et al.* identified the new antibiotic spirolactone chaetocuprum (**5**, Fig. 4), provided by a fungal endophyte from the roots of a wild-harvested yerba mansa (*Anemopsis californica*), which was used by the tribes of North America to treat inflammations and infections [35]. Compound **5** was active against *S. aureus* (IC_{50} = 50 mg/mL), but a complete growth inhibition was not observed (MIC > 50 mg/mL). No activity was recorded against Gram-negative bacterium *P. aeruginosa* (MIC > 200 mg/mL). The spirolactone **5** was produced by fungal endophyte *Chaetomium cuprum*. Previous studies on the metabolites of *Chaetomium* genus allowed to isolate other spirolactones. The recent use of epigenetic modifiers, such as histone deacetylase and/or DNA methyltransferase inhibitors, in fungal cultivation provided access to cryptic secondary metabolites, otherwise suppressed or hidden under standard culture conditions. Applying this approach to the cultivation of *Chaetomium indicum* led Asai and Oshima to isolate the two epimers spiroindicumides A and B (**6** and **7**, respectively; Fig. 4), characterized by an unprecedented spirolactone core [36]. The bioactivity profile of these new natural products is not reported yet.

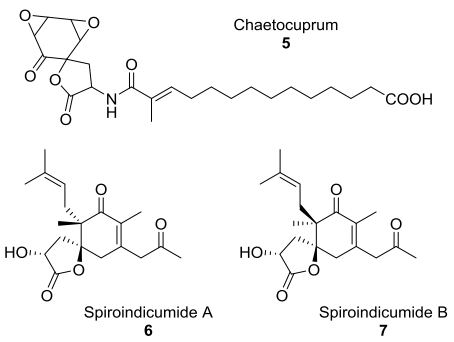


Fig. (4). Structures of antibiotic chaetocuprum (**5**), spiroindicumide A (**6**), and spiroindicumide B (**7**).

2.2. Antifungal and Antiparasitic Compounds.

Spirolactones lambertellols are known to cause mycoparasitism of *Lambertella sp*. against *Monilinia sp*. on apple fruits. Lambertellols A and B (**8** and **9**, respectively; Fig. 5) compose a diastereomeric pair of unique 4,8-dihydroxy-2,3,4-trihydronaphthalene-1-one, featured by the spiro-butenolide unit at C3 position [37]. Interestingly, the two isomers interconvert one into the other *via* a *retro*-Michael reaction of carboxy group at C3 followed by a *re*-Michael addition from the opposite side of the double bond. Lambertellols A and B revealed to inhibit the growth of spores of *Cochlibolus miyabeanus* (IC_{50} = 0.5 μg/mL). The same authors that discovered lambertellols A and B [37] shortly after isolated lambertellol C (**10**, Fig. 5) from a fermentation broth of *Lambertella sp.* 1346 [38]. This compound is a labile congener of lambertellols A and B existing as a racemic mixture. A more in-depth discussion of the biological properties of these natural compounds proved to be difficult due to their instability.

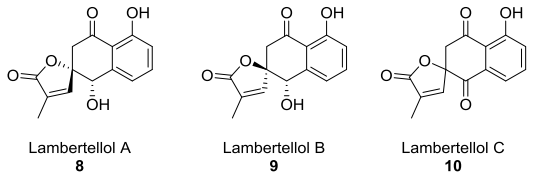


Fig. (5). Structures of antifungal lambertellols A (**8**), B (**9**), and C (**10**).

Still concerning the wide field of bioactive secondary metabolites produced by fungal endophytes, in 2011 Feng and co-workers isolated and characterized massarigenin D (**11**), spiromassaritone (**12**) and paecilospirone (**13**, Fig. 6) [39]. These three spirolactones, featured by a spiro-5,6-ring system and by the γ-methylene lactone moiety, were yielded by *Massrison* sp. strain isolated from wild *Rehmannia glutinosa*, an important Chinese traditional herb. All the compounds exhibited *in vitro* antifungal activity against various pathogens (MIC values ranging from 0.25 to 32 μg/mL), with spiromassaritone (**12**) showing a higher potency in all the bioassays. These findings seem to suggest that the tricyclic scaffold present in **12** enables an improvement of the antifungal properties.

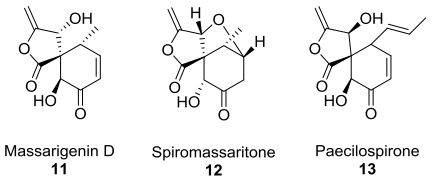


Fig. (6). Structures of antifungal massarigenin D (**11**), spiromassaritone (**12**) and paecilospirone (**13**).

The naphthalenone derivative perenniporide A (**14**, Fig. 7) was isolated in 2012 from the fermentation of a strain of *Perenniporia* sp. fungus [40]. In the same extract, naphthalenone derivatives perenniporides B-D were also identified, but perenniporide A **14** was the only spirolactone-containing compound. The antifungal activity of these new products was tested against a panel of five plant pathogens and the inhibitory properties of **14** was significant in all the cases (MIC values from 10 to 20 μg/mL). Conversely, perenniporides B-D were inactive. This behavior supports the key role played by the spirolactone framework as pharmacophore.

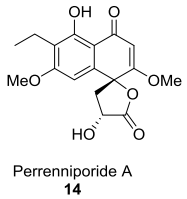


Fig. (7). Structure of antifungal perrenniporide A (**14**).

Plumericin (**15**, Fig. 8) and the related iridoid allamandin (**17**) are terpenoids, isolated for the first time with other congeners in 1951 [41,44] and 1974 [42], respectively. The bioactivity profile of these compounds revealed to be very interesting and drew much attention. Plumericin (**15**) showed antifungal, antimicrobial, and antitumor properties [43], whereas allamandin (**17**) was active *in vivo* against P-388 leukemia in the mouse and inhibited *in vitro* the growth of human carcinoma KB cells [42]. Recently (2011), the *in vitro* antifungal activity of plumericin (**15**) and isoplumericin (**16**) from *Plumeria bicolor* was assessed against *Candida* species and *Cryptococcus* neoformans [45]. Moreover, both compounds were found to be significantly active against *Leishmania amazonensis* axenic amastigotes (IC_{50} = 0.21 μM for **15** and 0.28 μM for **16**; reference compound: amphotericin B, IC_{50} = 0.52 μM) [46]. However, bioassays on *Leishmania amazonensis in vitro* infected macrophages revealed that plumericin **15** reduced the infection similarly to the commonly used drug amphotericin B (IC_{50} of 0.9 μM for **15** and 1 μM for amphotericin B), whereas isoplumericin **16** exhibited a high toxicity against macrophages. This divergent behavior demonstrated that the antileishmanial activity of these natural products was strongly influenced by the geometry of the exocyclic double bond present on the

spirolactone moiety. Anyway, this kind of scaffold is quite rare in nature, so that the authors admitted that reliable structure–activity relationships could be established only on a wider set of compounds.

In 2011, the antiparasitic activity of plumericin (**15**) and isoplumericin (**16**) was extended to *Leishmania donovani* [47]. Also in this case, plumericin **15** showed the highest inhibition properties, with IC_{50} of 3.17 and 1.41 μM against promastigote and amastigote forms, respectively. Correspondingly, isoplumericin **16** showed IC_{50} of 7.2 and 4.1 μM. The cytotoxicity in murine macrophage model was assessed, with CC_{50} values of 20.6 μM for **16** and 24 μM for **15**. For the most potent compound plumericin **15** a microscopic evaluation of the treated promastigote parasites was also carried out, showing notable morphological changes. Concerning the SAR analysis, the authors supposed that the bioactivity of this class of molecules could be ascribed to the α-methylene γ-lactone unit, which could act as Michael-acceptor in the presence of biological nucleophiles. Furthermore, being the cytotoxicity low, this behavior should be selectively exerted in protozoans cells.

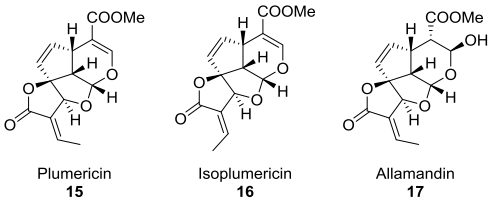


Fig. (8). Structures of plumericin (**15**), isoplumericin (**16**), and allamandin (**17**).

Another natural product containing the spirolactone moiety and showing antiparasitic activity was secochiliolide acid (**18**, Fig. 9). It was first isolated from *Nardophyllum lanatum* and the related species *Chiliotrichum rosmarinifolium* [48], and, more recently, also from the Patagonian shrub *Nardophyllum bryoides* [49]. In addition to moderate cytotoxic effects on a human pancreatic adenocarcinoma cell line [49], in 2013 secochiliolide acid (**18**) revealed interesting inhibitory properties on *Trypanosoma cruzi* epimastigotes, with an IC_{50} of 2 μg/mL comparable to the activity of commercial drug benznidazole (IC_{50} = 2.5 μg/mL) [50]. Moreover, **18** is extractable in large amount from *Nardophyllum bryoides* and it offers several functionalization possibilities. The same authors synthesized some derivatives showing trypanocidal properties (IC_{50} = 2-7 μg/mL). Comparing the bioactivity of the obtained compounds it could be deduced that the carboxylic group was not essential, whereas the tetrasubstituted exocyclic double bond was required. It is noteworthy that nowadays the discovery of new chemical entities with trypanocidal activity is still a challenge, because of the significant side effects characterizing the currently used drugs.

The spirolactone structural motif is present in an other natural trypanocidal compound, named psilostachyin (**19**, Fig. 9), a sesquiterpene lactone extracted from *Ambrosia tennuifolia* and other plants of the same genus [51]. On the basis of its marked *in vitro* activity against trypomastigote forms of *Trypanosoma cruzi* (IC_{50} = 0.76 μg/mL), psilostachyin (**19**) was employed in *in vivo* assays exhibiting promising bioactivity results and no toxicity. Lastly, this compound revealed to exert a significant antiparasitic activity also against *Leishmania* sp. promastigotes (IC_{50} = 0.12 μg/mL). Psilostachyin (**19**) was isolated and tested along with peruvin, a structurally similar sesquiterpene lacking the spirolactone moiety. Both the trypanocidal and the leishmanicidal activities were higher for psilostachyin, confirming the peculiar role of the spirolactone framework.

Very recently (2015), Shoyama and co-workers isolated a novel anti-trypanosomal iridoid, molucidin (**20**, Fig. 9), from the leaves of *Morinda lucida*, a Ghanaian medicinal plant [52-54]. The strong bioactivity (IC_{50} = 1.27 μM) and the promising selectivity of **20** made it a good drug candidate. This natural compound is characterized by a spirolactone tetracyclic iridoid skeleton, structurally related to plumericin (**15**, Fig. 8) and congeners, already mentioned as antifungal and leishmanicidal agents. The substituent present on the exocyclic double bond represents the main structural difference between **20** and **15-16**, demonstrating to affect and direct the bioactivity. In this regard, a conformational analysis revealed similarities between the aromatic portions of molucidin **20** and anti-trypanosomal oregonin, suggesting a common biological target [54].

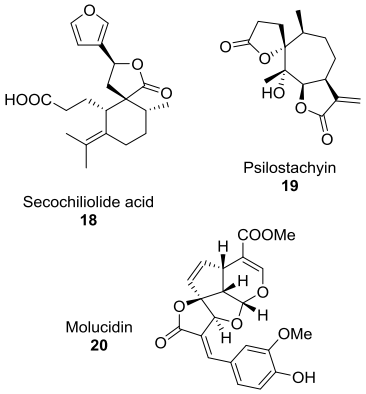


Fig. (9). Structures of antiparasitic secochiliolide acid (**18**), psilostachyin (**19**), and molucidin (**20**).

2.3. Anti-inflammatory Compounds.

Although the spiro-2(5*H*)-furanone moieties are scarcely present in the natural extracts, in 2010 Zhang *et al*. isolated and determined the structure of abiespiroside A (**21**, Fig. 10), the unique sesquiterpenoid spirolactone produced by *Abies dalavayi*, tall trees living exclusively in China at a height between 3300 and 4000 meters [55]. The novel 6/6/5 ring system structurally characterizes this natural compound, that exhibits anti-inflammatory activity. In particular, it significantly inhibits (inhibition rate of 35.0% at 100 μg/mL) the LPS-stimulated nitric oxide release in RAW264.7 macrophages, phenomenon involved in many inflammatory diseases, such as arthritis.

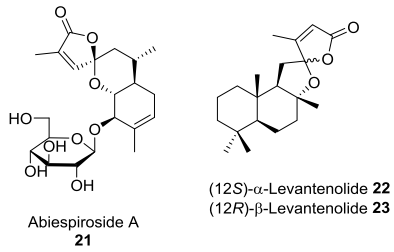


Fig. (10). Structures of anti-inflammatory abiespiroside A (**21**), α- (**22**) and β- (**23**) levantenolides.

Levantenolides [56-57] (**22** and **23**, Fig. 10), extracted from Turkish tobacco, belong to a family of labdane-derivatives that revealed to be able to reduce the LPS-induced production of nitric oxide and pro-inflammatory cytokines [58], thus becoming good candidates as anti-inflammatory agents.

An interesting family of bioactive natural products consists of the *Stemona* alkaloids, characterized by polycyclic complex architectures. They were recently classified into eight structurally different groups [59], and the compounds of the stemonamine group (Fig. 11) share the cyclopenta[1,2-*b*]pyrrolo-[1,2-*a*]azepine nucleus. The extracts from the *Stemonaceae* family were traditionally used for the treatment of respiratory diseases, such as pertussis and tuberculosis, and also as vermifuges and insecticides in eastern Asian countries. Therefore, it is not surprising that some pure alkaloids display a significant antitussive activity [60]. For example, for maistemonine (**24**) an ID_{50} of 0.16 mmol/kg was determined in guinea pig citric acid-induced cough model [61]. This natural compound was first isolated in 1991 from the roots of *Stemona mairei* [62]. Its peculiar scaffold, including an azatetracyclic 7/5/5/5-ring system and an α-methyl-γ-butyrolactone moiety, is present also in other alkaloids of this family, among which stemonamide (**25**) and isomaistemonine (**26**). A related 7/5/5-ring system spiro-grafted with a lactone unit characterizes the two epimeric *Stemona* alkaloids stemonidine (**27**, Fig. 11) and stemospironine (**28**) [63]. Also stemospironine (**28**) showed good antitussive properties (ID_{50} = 0.13 mmol/kg) [61].

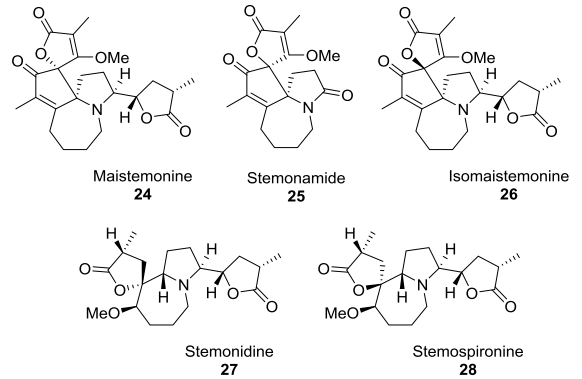


Fig. (11). Structures of *Stemona* alkaloids maistemonine (**24**), stemonamide (**25**), isomaistemonine (**26**), stemonidine (**27**), and stemospironine (**28**).

2.4. Anti-viral Compounds.

The hydrophobic natural product biyouyanagin A (**29**, Fig. 12) was isolated from an extract of leaves of *Hypericum chinense* L. var. *salicifolium* in 2005 [64]. In its peculiar scaffold the sesquiterpene, the cyclobutane, and the spirolactone structural units are present. Compound **29** showed a relevant and selective anti-HIV activity, inhibiting HIV replication in H9 lymphocytes with an EC_{50} value of 0.798 μg/mL and inhibiting uninfected H9 cell growth with IC_{50} values >25 μg/mL. Moreover, it was found that **29** reduced the LPS-induced cytokine production (at 10 μg/mL, IL-10 = 0.03; IL-12 = 0.02; tumor necrosis factor-α (TNF-α) = 0.48) [65]. In 2007, Nicolaou *et al*. reported the total synthesis of both the (24*S*) and (24*R*) epimers of biyouyanagin A in their enantiopure form and, therefore, the complete structural elucidation of the natural compound [65]. The same authors synthesized also a series of analogues designed with the aim to study the substituents effect at C-3, C-7, C-19, and C-22 positions [66]. Moreover, simplified substructures were also obtained to identify the active pharmacophores. All the products were tested as HIV-1 replication inhibitors in MT-2 lymphocytes and the corresponding cytotoxicities were evaluated in non-infected MT-2 lymphocytes using the TZM-bl/luciferase assay. Biyouyanagin A (**29**) displayed a significant activity (IC_{50} = 26 μM) and low toxicity (TI = 7.5), and the synthetic analogues exhibited similar properties. The authors demonstrated that the bioactivity of the natural product likely originates from its hyperolactone C (**30**) structural domain (**30**: IC_{50} = 29 μM against HIV-1 infected cells, CC_{50} = 925 μM) [64,67-68]. Afterwards, Nicolaou and co-workers ascertained also that biyouyanagin A (**29**) was active against lymphocytic choriomeningitis virus in the middle micromolar range [69]. In this case, hyperolactone C (**30**) and its analogues did not show significant activity.

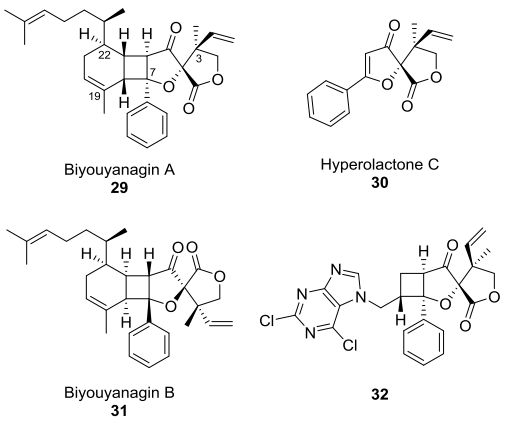


Fig. (12). Structures of anti-viral biyouyanagin A (**29**), hyperolactone C (**30**), biyouyanagin B (**31**) and synthetic analogue **32**.

Following the discovery of biyouyanagin A (**29**), Kashiwada and co-workers identified in the extracts of *Hypericum chinense* also biyouyanagin B (**31**, Fig. 12), a diastereoisomer of biyouyanagin A [70]. In 2010, Nicolaou

et al. described the total synthesis and the derived structural revision of biyouyanagin B [71]. The same authors subjected both biyouyanagins A (**29**) and B (**31**) to a neutralization assay using the clone HIV-1_{HxB2}, demonstrating that **31** (IC_{50} = 42.90 μM) was a more potent inhibitor than **29** (IC_{50} = 123.4 μM) [69]. The developed synthetic approach allowed to obtain a library of biyouyanagins derivatives and analogues, among which **32** showed the best bioactivity (IC_{50} = 7.00 μM). This finding seemed to suggest that the substituted cyclohexene moiety was not essential, whereas the crucial pharmacophores should be included in the remaining spiro tricyclic framework.

From the plants of the genus *Schisandra*, traditionally employed in the Chinese folk medicine, was isolated a series of nortriterpenoids [72], some of which exhibit anti-HIV properties and low cytotoxicity.
Micrandilactones B and C (**33** and **34**, respectively; Fig. 13), produced by *Schisandra micrantha*, possess a peculiar highly oxygenated norcycloartane skeleton [73]. Compound **34** showed an EC_{50} value of 7.71 μg/mL for the inhibition of HIV-1_{IIIB} induced syncytium formation combined with a minimal cytotoxicity (> 200 μg/mL). Considering that micrandilactone B (**33**) exerted only a weak activity against HIV-1, it could be concluded that the epoxidation of C14-C15 bond significantly worse the anti-HIV-1 properties.

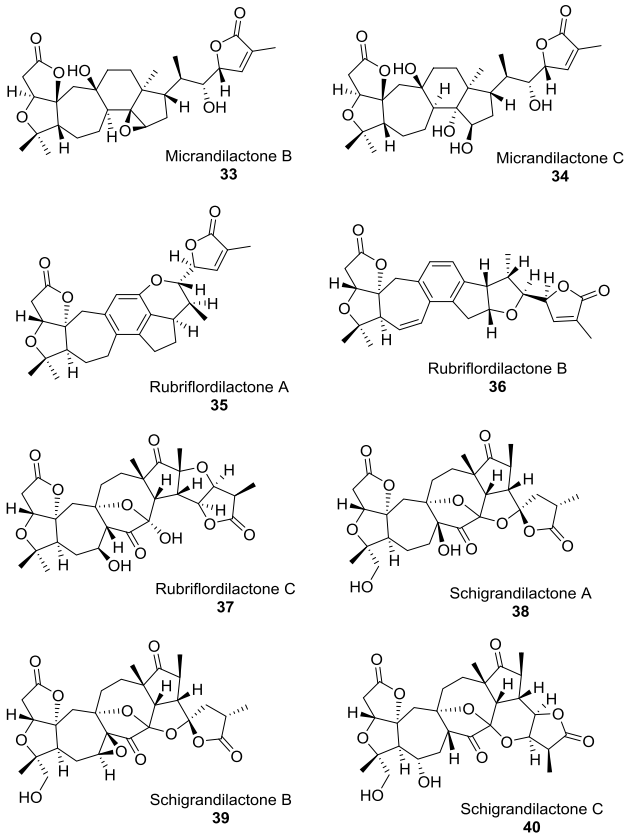


Fig. (13). Structures of anti-viral micrandilactones B (**33)** and C (**34)**, rubriflordilactones A (**35**), B (**36**), and C (**37**), schigrandilactones A (**38**), B (**39**), and C (**40**).

Rubriflordilactones A (**35**) and B (**36**) were isolated from the extracts of *Schisandra rubriflora* [74]. These two highly unsaturated bisnortriterpenoids are characterized by a modified aromatic ring D. Compound **35** displayed only a poor anti-HIV-1 activity. Conversely, compound **36** exhibited a significant HIV-1-inhibition (EC_{50} = 9.75 μg/mL) and low cytotoxicity (CC_{50} = 120.7 μg/mL). From the same natural source Zhu and Sun obtained rubrifloradilactone C (**37**, Fig. 13), which showed an even better anti-HIV-1 activity (EC_{50} = 5.18 μg/mL) and cytotoxicity (CC_{50}) against C8166 cells with a value of 77.54 μg/mL [75]. The authors performed also a theoretical investigation of key steps in the biosynthetic pathway for schisanartane nortriterpenoids formation.

Continuing their investigation on bioactive natural compounds produced by plants of the genus *Schisandra*, in 2009 Sun *et al*. identified three new nortriterpenoids, named schigrandilactones A-C (**38-40**, Fig. 13), in the extracts of *Schisandra grandiflora* [76]. The new products were tested for their ability to prevent the cytopathic effects of HIV-1 in C8166 cells, and they showed EC_{50} values of 80.2, 20.8, and 5.1 μg/mL, respectively. Schigrandilactones A and B (**38** and **39**) are structurally very similar, differing only for the epoxide present on C7-C8 bond of **39**, functionality that seems to increase the anti-viral potency.

2.5. Cytotoxic and Anti-Cancer Compounds.

Since many years, one of the areas that has aroused most interest in the scientific community is the search for new and more effective anti-cancer drugs. Natural products have always played a major role in this field. In particular, several spirolactones extracted from natural sources display cytotoxic effects and could be exploited as anti-cancer drugs.

Some of the already mentioned natural spiro-derivatives possess also the significant ability to selectively inhibit the growth of cancer cells.
The antimicrobial agent lactonamycin Z (**4a**, Fig. 3) was tested for its antitumor activity on different human cell lines: gastric adenocarcinoma (HMO2), breast carcinoma (MCF 7), and hepatocellular carcinoma (Hep G2). The inhibitory effect was strong on HMO2 (IC_{50} = 0.19 μg/mL), whereas it was less pronounced on MCF 7 and Hep G2 cells [34].

Antifungal lambertellols A and B (**8** and **9**, Fig. 5) expressed a weak cytotoxity against P388 murine leukemia (IC_{50} = 12 μg/mL for **8** and 15 μg/mL for **9**) [37].

The cytotoxic effects of antifungal massarigenin D (**11**), spiromassaritone (**12**) and paecilospirone (**13**, Fig. 6) were investigated on four cell lines: L 02 (human normal liver cells), HepG 2, MCF 7 and A 549 (lung carcinoma). Compound **12** showed the highest activity (IC_{50} against HepG 2 = 5.6 μg/mL) but no selectivity, whereas **13** revealed to be an active (IC_{50} against A 549 = 6.8 μg/mL) and more selective agent [39].

The antifungal iridoids plumericin, isoplumericin and allamandin (**15-17**, Fig. 8) displayed anti-tumor activity against human carcinoma of the nasopharnyx (KB) with

ED_{50} of 2.7, 2.6 and 2.1 μg/mL, respectively [42]. Considering that the natural iridoids allamandicin (**17a**, Fig. 14) and allamdin (**17b**) extracted from *Allamanda cathartica* Linn. were inactive (ED_{50} > 10 μg/mL), it could be supposed a considerable pharmacophoric role played by the exocyclic double bond linked to the spirolactone moiety.

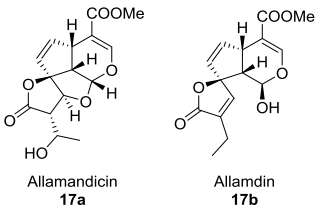


Fig. (14). Structures of inactive allamandicin (**17a**) and allamdin (**17b**).

Trypanocidal secochiliolidic acid (**18**, Fig. 9) was tested on LM3 (murine lung adenocarcinoma) and PANC1 (human ductal pancreatic carcinoma) cells. Although the activity of **18** is only moderate, these results are very promising, because it is abundantly present in the natural extracts and it can be transformed into pharmacologically more effective compounds [49].

Biyouyanagin A (**29**, Fig. 12), already known as anti-viral agent, was subjected to cytotoxicity assays against a series of human tumor cell lines, including multidrug-resistant (MDR) KB cancer cells [70]. **29** demonstrated a certain inhibitory activity on all the tested cell lines (IC_{50} values ranging from 16.6 to 38.8 μg/mL) and, in particular, its cytotoxicity against MDR KB-C2 cells resulted increased in the presence of colchicine (colchicine alone was inactive at the same concentration). A similar behavior was observed for the structurally simpler hyperolactones C (**30**, Fig. 12) and A (**41**, Fig. 15) [67], suggesting that the common spirolactone moiety should have a crucial role in the establishment of this kind of bioactivity.

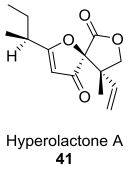


Fig. (15). Structure of cytotoxic hyperolactone A (**41**).

The anti-HIV-1 agent rubriflordilactone C (**37**, Fig. 13) showed a remarkable cytotoxicity against two human tumor cell lines: K562 (myelogenous erythroleukemia) and HepG 2, with IC_{50} values of 0.14 and 0.54 μg/mL, respectively (*cis*-platin: IC_{50} = 0.40 and 0.59 μg/mL, respectively) [75]. The structural related anti-viral nortriterpenoids schigrandilactones A and B (**38** and **39**, respectively; Fig. 13), tested for their cytotoxicity against the same tumor cells, displayed IC_{50} values of 0.13 and 3.19 μg/mL for K562 cells and of 0.19 and 0.20 μg/mL for HepG 2 cells, respectively [76]. Thus, schigrandilactone A **38** revealed to be a potent cytotoxic agent against both the tumor cell lines, whereas schigrandilactone B **39** was selective for HepG 2. This different behavior seems to derive only from the presence of the epoxy group on C7-C8 position.

In 2007, Krohn and Nahar discovered a new highly cytotoxic iridoid, named prismatomerin (**42**, Fig. 16), produced by *Prismatomeris tetrandra*, belonging to the family of Rubiaceae [77-78]. This compound contains an additional aromatic ring with respect to the spirolactone-iridoids plumericin and isoplumericin (**15** and **16**, respectively; Fig. 8), being structurally more strictly related to anti-trypanosomal molucidin (**20**, Fig. 9). Prismatomerin (**42**) was tested against a panel of 60 human tumor cell lines and it exhibited a remarkable anti-cancer activity (IC_{50} against L-929 = 0.21 μM, IC_{50} against KB-3-1 = 0.41 μM, IC_{50} against A-549 = 1.41 μM, IC_{50} against SW-480 = 0.060 μM). The growth inhibition (GI) in leukemia cell lines was high (GI_{50} < 10 nM). Most of the solid tumor cells were slightly less sensitive (GI_{50} < 10 nM to 2 μM), with renal cancer cell lines representing the most sensitive group. Regarding the solid tumors, product **42** was able not only to inhibit the growth but also to kill the cancer cells. The authors investigated also the mode of action of prismatomerin (**42**) and hypothesized that the product acts as antimitotic agent, altering the spindle formation without directly affecting the microtubules. Concerning the structure-activity relationships, the tetracyclic scaffold equipped with the exocyclic double bond, featuring plumericin **15**, isoplumericin **16**, allamandin **17**, and prismatomerin **42**, demonstrated to maintain anti-cancer properties regardless of the olefin substitution.

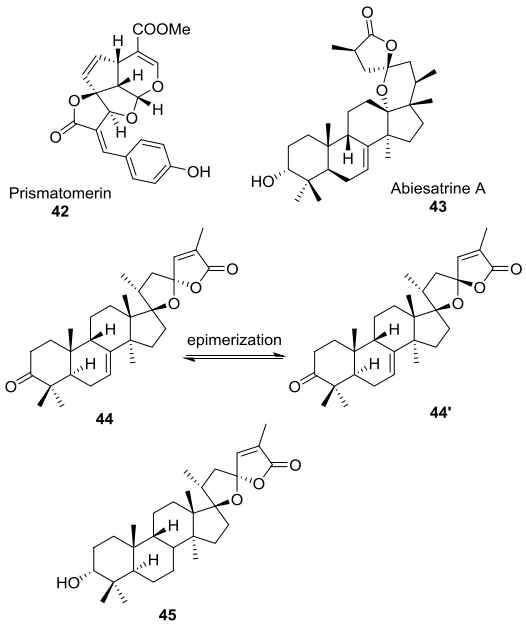


Fig. (16). Structures of cytotoxic prismatomerin (**42**), abiesatrine A (**43**), and epimeric mixtures **44** and **45**.

A few years later (2010), the spiro-lanostane abiesatrine A (**43**, Fig. 16) was identified in the $CHCl_3$ fraction of the EtOH extract of *Abies georgei* [79]. Although abiesatrine A

(**43**) and anti-inflammatory abiespiroside A (**21**, Fig. 10) are both produced by plants of the *Abies* genus, they share a quite limited structural portion, which, however, comprises the spirolactone framework. Abiesatrine A (**43**) exhibited significant anti-tumor effects on QGY-7703 (human hepatocellular carcinoma) cell line (IC_{50} = 9.3 μg/mL). Among the triterpenes lanostanes extracted from *Abies georgei*, only **43**, characterized by the spirolactone unit, displayed significant anti-cancer properties.

Very recently (2016), phytochemical studies on Chinese *Abies faxoniana* allowed to identify two new spirolactone-type triterpenoids (**44** and **45**, Fig. 16) both present in the natural extracts as inseparable epimeric mixtures [80]. The epimerization concerns the spiro C-23 ketal carbon and the epimers interconversion occurs in solution. The **44**/**44**' mixture reveled to be cytotoxic, with remarkable IC_{50} values of 10.0 and 12.3 μM against Huh-7 (hepatocyte-derived carcinoma) and SMMC-7721 (human hepatocellular carcinoma) cells, respectively. The C3-oxo-containing **44** was significantly more active than the C3-hydroxyl-containing **45**. This trend was followed also by other structurally related natural products obtained from *Abies faxoniana*.

Several structural similarities can be noticed in the cytotoxic natural spirolactones (**43**, **44** and **45**) produced by the plants of the *Abies* genus. The main differences are located in the spirobicyclic portion: the lactone is β,α-unsaturated in **44** and **45**, whereas the double bond is absent in abiesatrine A (**43**). Moreover, the spiro-junction involves a 5/6-ring system in **43** and a 5/5-ring system in **44** and **45**.

Sun and co-workers thoroughly studied the secondary metabolites extracted from the Chinese herbs of the genus *Isodon* [81].

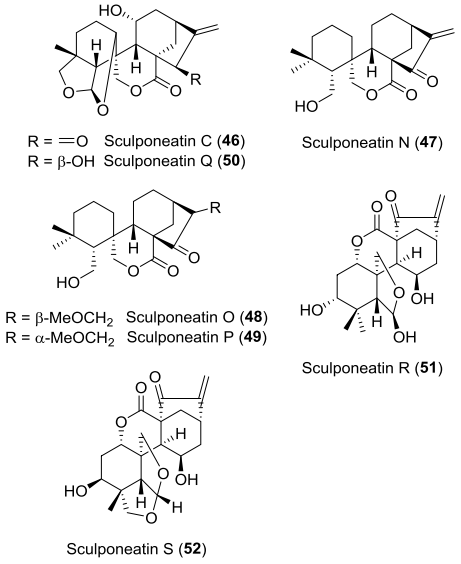


Fig. (17). Structures of sculponeatin C (**46**), and sculponeatins N-S (**47-52**).

They isolated a series of *ent*-kauranoids with significant cytotoxicity [82-84], among which a remarkable antitumor activity (IC_{50} against K562 = 0.29 μM, IC_{50} against HepG 2 = 0.33 μM) was exhibited by sculponeatin C (**46**, Fig. 17), characterized by a spirolactone type 6,7-*seco*-*ent*-kaurane scaffold [85]. In 2010, the authors identified six new 6,7-*seco*-*ent*-kaurane diterpenoids, sculponeatins N-S (**47-52**, respectively; Figure 17), in the extracts of *Isodon sculponeatus* [85]. The cytotoxicity of these natural products was evaluated against K562 and HepG 2 human tumor cell lines and the results revealed to be particularly good for spirolactone sculponeatin N (**47**), displaying IC_{50} values of 0.21 and 0.29 μM, respectively. Comparing the bioactivities of the isolated compounds, the authors inferred that the presence of the α,β-unsaturated ketone plays an important role in the cytotoxicity establishment, but the substituents distribution also affects the activity.

As already mentioned, a plethora of bioactive natural compounds have been extracted from the plants of the *Isodon* genus [81]. Besides diterpenoids *ent*-kauranoids sculponeatins (**46-52**, Fig. 17), also spirolactones trichorabdal A and B (**53** and **54**, respectively; Figure 18) [86-88] and shikodonin (**55**) [89] exert a tumor growth inhibition *in vivo* in mice, while longikaurin E (**56**) [90] and maoecrystals Z and V (**57** and **58**, respectively) [91-92] are cytotoxic *in vitro* against a series of human cancer cell lines.

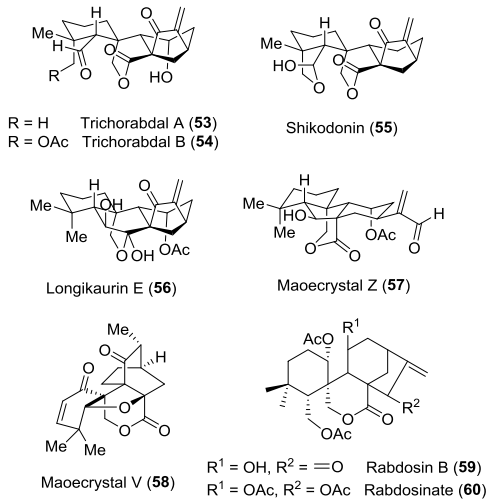


Fig. (18). Structures of cytotoxic trichorabdals A and B (**53** and **54**), shikodonin (**55**), longikaurin E (**56**), maoecrystals Z and V (**57** and **58**), rabdosin B (**59**) and rabdosinate (**60**).

The last examples of cytotoxic natural products generated by plants of the *Isodon* genus is represented by rabdosin B (**59**, Fig. 18) and rabdosinate (**60**). These two *ent*-kaurenes spirolactone-type diterpenoids were recently (2008) extracted from the leaves of *Isodon japonica* and assayed on three human tumor cell lines: HepG 2, HL-60 (Human promyelocytic leukemia) and GLC-82 (Lung adenocarcinoma) [93-94]. The activity of rabdosin B (**59**, IC_{50} = 8.95, 10.22, 4.47 μmol/L, respectively) was three times higher than that of rabdosinate (**60**) on all the tested cell lines. With the aim of studying the cytotoxicity mechanism of these diterpenoids, the authors evaluated their

DNA damage potential on HepG 2 cells, which retain many characteristics of hepatocytes with hepatocellular carcinoma, one of the most common malignant neoplasms of the liver. Both the compounds **59** and **60** induced DNA damages, confirming rabdosin B more active than rabdosinate. The results led the authors to infer that the *exo*-methylene cyclopentanone framework was crucial for spirolactone-type *ent*-kaurene diterpenoids to exert cytotoxicity and DNA damage potential. Furthermore, it was found that spirolactone-type diterpenoids **59** and **60** displayed higher cytotoxicity (and DNA damage potential) than similar enmein-type diterpenoids (epinodosin and epinodosinol), demonstrating that the spirolactone skeleton itself strongly concurred to endow high cytotoxicity properties.

Lin and Shi in 2012 detected in the EtOAc-soluble lipophilic fraction of the ethanolic extract of *Machilus yaoshansis* bark two butenolide derivatives, featuring an unusual 5'*H*-spiro-[bicyclo[2.2.2]oct[2]ene-7,2'-furan]-5'-one skeleton and a long linear alkyl chain [95]. These tricyclic compounds were named yaoshanenolides A and B (**61** and **62**, respectively; Fig. 19) and were tested on adenocarcinomic human alveolar basal epithelial cells (A549). They showed non-selective cytotoxicity with IC_{50} values of 5.1-6.6 μM (camptothecin used as positive control, IC_{50} = 0.16-11.3 μM).

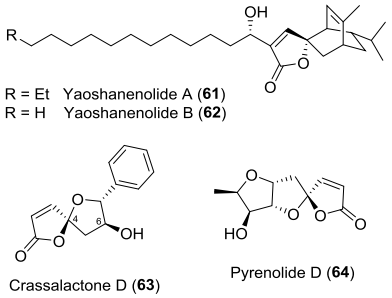


Fig. (19). Structures of cytotoxic yaoshanenolides A and B (**61** and **62**), crassalactone D (**63**), and pyrenolide D (**64**).

From an ethyl acetate extract of the leaves and twigs of *Polyalthia crassa* the styryl lactone (+)-crassalactone D (**63**, Fig. 19) was isolated for the first time [96]. It was the only spirocompound present in the analyzed mixture, containing several different lactones. The natural product **63** was assayed on a panel of mammalian (human and rat) cancer cell lines (P-388, KB, Col-2, BCA-1, Lu-1, ASK) and it exhibited a broad cytotoxicity against almost all the tested cells (ED_{50} = 1.1-4.0 μg/mL).

Pyrenolide D (**64**, Fig. 19) is characterized by a highly oxygenated tricyclic spiro-γ-lactone framework, which largely repeats the structural core of (+)-crassalactone D (**63**). It was isolated from the phytopathogenic fungus *Pyrenophora teres* and showed cytotoxicity against HL-60 cells at IC_{50} = 4 μg/mL [97].

Bakkenolides belong to the bakkanes family, sesquiterpenes structurally characterized by a *cis*-hydrindane scaffold and a spiro-β-methylene-γ-lactone moiety (Fig. 20) [98]. Some bioactivities were discovered for bakkenolides, including cytotoxicity. For example, bakkenolide A (**65**, Fig. 20) was first isolated from *Petasites japonicas* [99] and revealed to be cytotoxic to several cancer cell lines (IC_{50} against HEp2 = 0.8 μg/mL, IC_{50} against HeLa = 1 μg/mL, IC_{50} against HeLu = 5 μg/mL, IC_{50} against RE 1 = 18 μg/mL, IC_{50} against BHK 21/C13 = 20 μg/mL, IC_{50} against Hood = 40 μg/mL) [100]. In particular, normal and 'transformed' cells derived from different organisms were tested, showing that the human cell lines were more sensitive than rodent cells to compound **65**. Moreover, bakkenolide A exhibited a promising selectivity, with an ED_{50} against human carcinomas cells (HEp2 and HeLa) around 1 μg/mL, five-fold lower than the corresponding value on 'non-transformed' human cell line (HeLu). Concerning the SAR analysis, the authors noticed that many cytotoxic sesquiterpene lactones contained an α,β-unsaturated system, which therefore was suggested as key pharmacophore. Conversely, bakkenolide A **65** showed comparable cytotoxicity properties although characterized by a β-methylene-γ-lactone moiety.

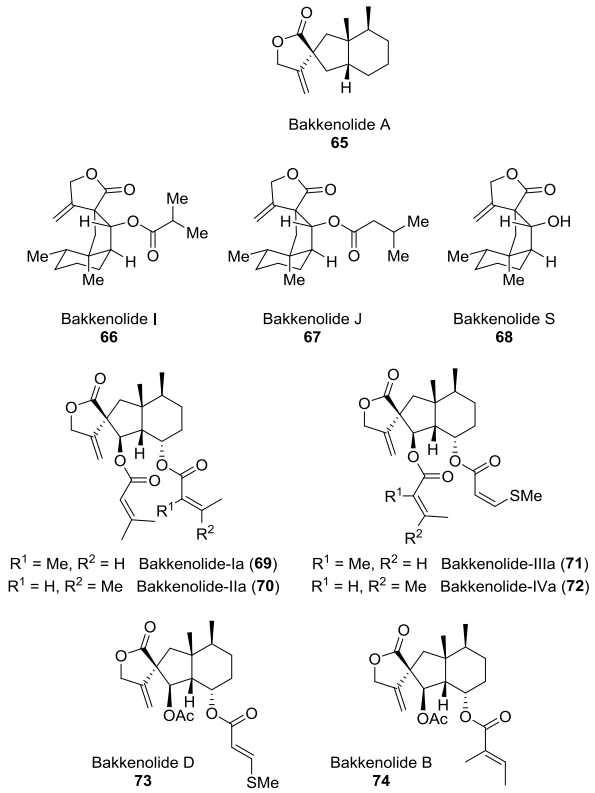


Fig. (20). Structures of selected members of bakkenolides family.

As previously mentioned, members of the bakkenolides family show not only cytotoxic effects, but also other promising bioactivities. In 2009, the results of a study were published, demonstrating for the first time the neuroprotective and antioxidant properties *in vitro* of four bakkenolides extracted from *Petasites tricholobus*: bakkenolide-Ia, bakkenolide-IIa, bakkenolide-IIIa and bakkenolide-IVa (**69-72**, respectively; Fig. 20) [101]. In

2011, Guo and co-workers evaluated the anti-allergic activity of a bakkenolides extract derived from *Petasites tricholobus* in an allergic rhinitis model in rats [102]. The major components of the mixture were bakkenolide D, bakkenolide B, bakkenolide-IIIa and bakkenolide-IVa (**73**, **74**, **71** and **72**, Fig. 20).

2.6. Anti-Diabetic Compounds.

In 1997, Ramakrishna *et al*. isolated mumbaistatin (**75**, Fig. 21) from the Indian microorganism *Streptomyces sp*. DSM 11641 [103]. On the basis of the structure determination [104], it was supposed that this natural polyketide product exists as equilibrium between the "open" diketo (**75a**) and the "closed" spiroketal lactone (**75b**) form.
The diketo form (**75a**) of mumbaistatin is one of the most potent inhibitor (IC_{50} = 5 nM) of glucose-6-phoshate translocase 1 (G6P-T1) [104], whereas the spiroketal lactone form (**75b**) was one thousand times less active. From a structural point of view, mumbaistatin displays no similarities with the few previously reported G6P-T1 inhibitors. G6P-T1 is part of the enzymatic system involved in both pathways of the hepatic glucose production, gluconeogenesis and glucogenolysis. Therefore, inhibition of G6P-T1 could represent a promising therapeutic approach to non-insulin dependent type II diabetes mellitus [105].

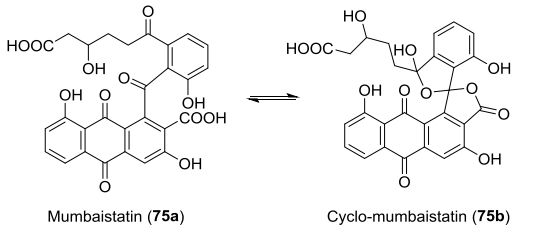
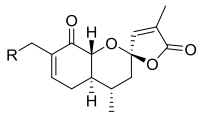


Fig. (21). Structure of glucose-6-phoshate translocase 1 inhibitor mumbaistatin (**75**) as mixture of two equilibrating forms.

As already mentioned, plants of the *Abies* genus are an extraordinary source of pharmacologically useful natural compounds. *A. beshanzuensis* M. H. Wu is a rare and endangered tree present only in a remote Chinese region. Very recently (2016), Hu *et al*. isolated from the bark of this plant four enone-containing sesquiterpenoids, among which the two spirolactones beshanzuenones C and D (**76** and **77**, Fig. 22) [106]. The same authors performed also the structure elucidation, deducing a bisabolane-type sesquiterpenoid spirolactone skeleton, similar to the aglycon of abiespiroside A (**21**, Fig. 10), produced by *Abies dalavayi* [55]. The bioactivity studies on these natural products revealed that they significantly inhibited human protein tyrosine phosphatase 1B (PTP1B), an important enzymatic target for the treatment of type-II diabetes and obesity. The IC_{50} values were 16.6 μg/mL for **76** and 10.6 μg/mL for **77** (oleanolic acid used as control: IC_{50} = 1.52 μg/mL).



R = OH **76**
R = H **77**

Fig. (22). Structures of the two spirolactones (**76** and **77**) isolated from *Abies beshanzuensis.*

2.7. Miscellaneous Bioactivities.

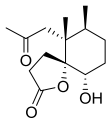
2.7.1. Insecticides.

The extracts of *Stemona* roots, containing a broad family of natural alkaloids involving several spirolactones [59-63], are widely employed as bio-insecticides. Nevertheless, accurate correlations between the activity against a specific insect and the pure natural compound are missing [107].

Bakkenolide A (**65**, Fig. 20), already mentioned as cytotoxic agent [99-100], was also reported as insect antifeedant [98].

2.7.2. Ca^{2+} Antagonists.

Pathylactone A (**78**, Fig. 23) is a natural γ-spirolactone norsesquiterpenoid isolated form the soft coral *Paralemnalia thyrsoides* and reported as Ca^{2+} antagonist [108]. In 2002, Coelho *et al*. proposed the total synthesis of racemic pathylactone A, suggesting that the assignment of the spectral data of the natural compound needed a revision [109].



Pathylactone A
78

Fig. (23). Structure of Ca^{2+} antagonist pathylactone A (**78**).

2.7.3. Autophagy-Modulating Agents.

Autophagy is a catabolic process of the cells, consisting of the capture of cytoplasmic proteins and organelles into vesicles (autophagosomes and then lysosomes) to be degraded and recycled. This mechanism supports cells survival during starvation and is involved in immunity processes, degradation of invading agents, and some neurodegenerative pathologies. The autophagy phenomenon is not fully understood yet, so that compounds able to activate or inhibit this process could be very useful and therapeutically promising.

Fairly recently (2008), clionamine D (**79**, Fig. 24) was extracted from the South African marine sponge *Cliona celata* [110]. Preliminary results suggested that this compound was able to induce autophagy. Clionamines A-D combine some rare structural characteristics. In fact, very few natural 3-aminosteroids are known and, in particular, the

spiro-bislactone motif present in clionamine D has no precedent in both natural and synthetic steroids.

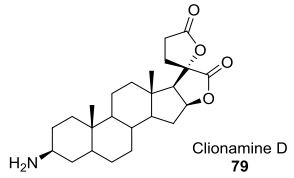


Fig. (24). Structure of autophagy-inducing compound clionamine D (**79**).

2.7.4. Tremorgenic Mycotoxins.

Tremorgenic mycotoxins are a family of indole alkaloids able to arouse tremors in vertebrate animals by affecting the central nervous system. Some structurally different natural products possess this ability, among which the quinazoline-containing alkaloids tryptoquialanine and tryptoquivaline (**80** and **81**, respectively; Fig. 25). They are produced by fungi *Aspergillus clavatus* [111] and *Penicillium* spp [112-113]. These natural products are characterized by a quinazoline ring and a 6/5/5-imidazoindolone system, bridged through a spiro-γ-lactone. Driven by the interest on these tremorgenic mycotoxins, in 2011 Tang *et al*. identified the fungal gene cluster from *P. aethiopicum* involved in the biosynthesis of tryptoquialanine (**80**) and they proposed a related biosynthetic pathway for this compound [114].

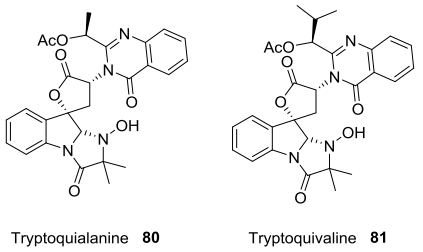


Fig. (25). Structure of tremorgenic mycotoxins tryptoquialanine (**80)** and tryptoquivaline (**81)**.

2.8. Potentially Bioactive Natural Products.

Some spirolactone-containing compounds were isolated from natural extracts and structurally characterized, but the possible bioactivity profile was not established yet.

Syringolides 1 and 2 (**82** and **83**, Fig. 26) are produced by some plant pathogens as signal molecules (elicitors), which are recognized by resistant plants triggering the defense response. Sims *et al*. isolated syringolides from plant pathogen *P. syringae* pv. *tomato* [115-116]. From the same culture were also isolated different metabolites, among them secosyrins 1 and 2 (**84** and **85**, Fig. 26), sharing with syringolides the 1,7-dioxaspiro[4.4]nonane system [117]. Although secosyrins are not active as elicitors, they are biogenetically correlated with syringolides.

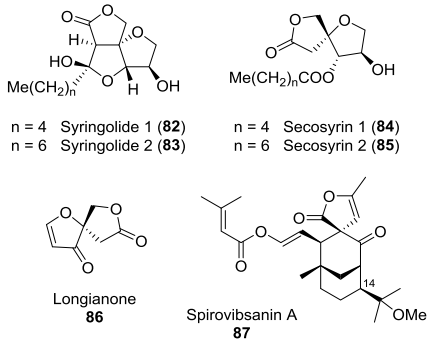


Fig. (26). Structure of syringolides 1 and 2 (**82** and **83**), secosyrins 1 and 2 (**84** and **85**), longianone (**86**), and spirovibsanin A (**87**).

The 1,7-dioxaspiro[4.4]nonane system is present also in longianone (**86**, Fig. 26), a natural compound that some authors proposed as precursor of secosyrins and syringolides in the biosynthetic pathway. Longianone was isolated from cultures of fungus *Xylaria longiana* [118]. In 2012, Perali *et al*. accomplished the first stereoselective synthetic approach to longianone [119], enabling the identification of the absolute stereochemistry of the natural product.

Spirovibsanin A (**87**, Fig. 26), extracted from *Viburnum awabuki* [120], shows a unique architecture, significantly different from the other members of vibsanin family. In fact, it is a 18-norditerpene containing the peculiar bicyclo[3.3.1] nonane spiro-γ-lactone scaffold. Considering that many vibsanin-type natural products, biosynthetically related with spirovibsanin A (**87**), possess a different configuration at C-14, synthetic efforts were devoted also to ascertain the stereochemistry of **87** at this position. Williams and co-workers reported on the total synthesis of (±)-5,14-bis-*epi*-spirovibsanin A, confirming the relative stereochemistry previously assigned to spirovibsanin A (**87**) [121-122].

A series of spirolactones was extracted from the fruits of *Vitex rotundifolia*, among them norlabdane-type diterpenes vitexifolin D (**88**, Fig. 27), vitexifolin E (**89**), trisnor-γ-lactone (**90**) and isoambreinolide (**91**) [123]. The structurally related spirolactone vitedoin B (**92**, Fig. 27) was isolated from *Vitex negundo* [124].

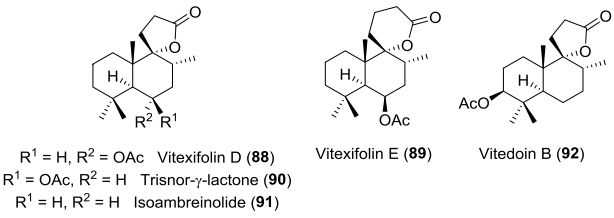


Fig. (27). Structures of spirolactones extracted from the fruits of *Vitex* spp.

Two novel 19-*nor*-3,4-*seco*-lanostane-type triterpenoids, sablacaurin A and B (**93** and **94**, respectively; Fig. 28), were

discovered as metabolites produced by plants of *Sabal causiarum* and *Sabal blackburniana*, respectively [125].

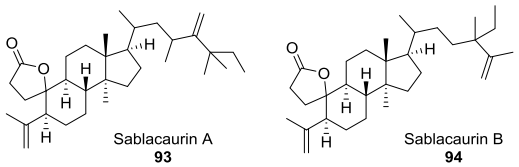


Fig. (28). Structures of spirolactones extracted from the plants of *Sabal causiarum* and *Sabal blackburniana*.

Novel natural spirolactone-containing compounds were disclosed also in very recent years, witnessing the interest in this class of molecules.

In 2013, Tezuka and co-workers studied the components of the extracts of Indonesian *Curcuma heyneana*, traditionally used as medicinal plant [126]. Two new epimeric spirolactones, curcumanolides C and D (**95** and **96**, respectively; Fig. 29), were found in the mixture, along with the already known epimers curcumanolides A and B (**97** and **98**, respectively; Fig. 29) [127].

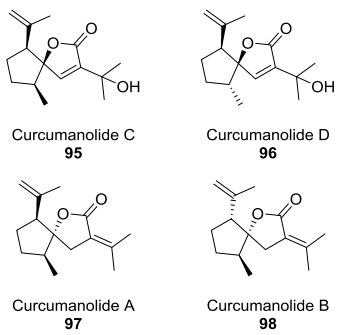


Fig. (29). Structures of spirolactones extracted from *Curcuma heyneana*.

In 2014, aspergiloid I (**99**, Fig. 30) was identified by Tan and Ge in the culture broth of *Aspergillus* sp. YXf3, an endophytic fungus associated with *Ginkgo biloba* [128]. This norditerpenoid showed an unusual 6/5/6-tricyclic skeleton, involving an α,β-unsaturated spirolactone unit. This peculiar architecture belongs to a new subclass of norditerpenoids. Aspergiloid I was tested as cytotoxic agent, antioxidant, acetylcholinesterase-, α-glucosidase-, and topoisomerase IIα-inhibitor, antimicrobial and antifungal, but no significant bioactivity was recognized.

The α,β-unsaturated spirolactone moiety characterizes also the natural epimers **100** and **101** (Fig. 30), recently (2015) extracted by Fuchino *et al*. from the fruits of *Cinnamomum inunctum*, a folk medicine plant in Myanmar [129].

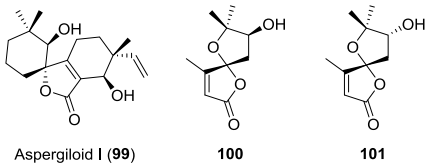


Fig. (30). Structures of recently extracted natural compounds characterized by α,β-unsaturated spirolactone moiety.

3. BIOACTIVE SYNTHETIC COMPOUNDS.

As previously underlined, in the last two decades the synthetic contribution to the identification of new drugs became predominant [26,28-30,130-135]. This approach showed many advantages, among them the possibility to introduce several different structural modifications, with the aim to improve not only the potency of the lead but also its pharmacodynamics and pharmacokinetics. The advances in both combinatorial chemistry and instrumental technology allowed to obtain wide libraries of products to be subjected to biological screening, thus increasing the chances of identifying novel drug-candidates. Moreover, the development of innovative and efficient synthetic strategies enabled the easy achievement of large product quantities, essential for the bioactivities tests, the clinical trials and the market entry.

In conclusion, the synthetic approach to "druggable" compounds, complementary to the isolation of new potentially bioactive natural products, allowed to identify and produce many lead molecules very popular on the market and, nowadays, this approach is widely employed. In this section, it will be overviewed the most important and recently introduced synthetic bioactive spirolactones, sorted by their bioactivity properties.

3.1. Cardiovascular Diseases.

It was demonstrated that a disorder in the endogenous aldosterone regulation system is involved in the occurrence of several cardiovascular diseases, such as heart fibrosis, myocardial failure and essential hypertension [136]. Therefore, the aldosterone receptor antagonists (ARAs) belonging to the spirolactone family are employed since many years for the therapy of the aldosterone excess disorders [137-139]. More recently, it was confirmed the beneficial effect of their use in combination with other therapies for the treatment of several cardiovascular diseases.

Almost all the spirolactone-based ARAs are synthetic compounds featured by a steroidal structure (Fig. 31). Within this family, the most commonly used spironolactone (**102**, Fig. 31) demonstrated to be able to prevent myocardial fibrosis in rats with unilateral renal ischemia or hyperaldosteronism, although the altered arterial pressure and the ventricular hypertrophy resulted still present [140]. **102** was extensively employed for many Na^+-retaining diseases, such as congestive heart failure [141-142] and liver cirrhosis, and also for essential hypertension treatment [143]. Very recently (2016), it was reported that spironolactone

(**102**) is able to reduce renal fibrosis by inhibiting the endothelial–mesenchymal transition process [144]. Spironolactone (**102**) is rapidly metabolized and it was suggested that its active metabolite was the more persistent canrenone (**103**, Fig. 31), administered also directly [145-147]. Eplerenone (**104**, Fig. 31) was more recently added to the bioactive spirolactone-ARAs family. It is characterized by the presence of a 9,α11α-epoxy group absent in the parent spironolactone scaffold. Eplerenone (**104**) revealed to be less potent but more selective than spironolactone (**102**), allowing a reduction of the side effects [148-153].

The spirolactone class of ARAs exerts its bioactivity through the competitive inhibition of the binding of aldosterone to the mineralocorticoid receptor (MR). In 2007, Rafestin-Oblin and co-workers exploited a mutant of the MR (MR_{S810L}) to stabilize the spironolactone-MR complex and to crystallize the corresponding ligand-binding domain [154]. It was possible to identify the crucial contacts between some key receptor-aminoacids and specific substituents of spironolactone (**102**). In particular, the authors suggested that the γ-lactone on C17 is responsible for the antagonist activity, whereas the potency of different spirolactones is related to the nature of the C7 substituent and, therefore, to its ability to adapt to the ligand-binding domain. For example, spironolactone (**102**) and RU26752 (**105**, Fig. 31), characterized by a thioacetyl group and a propyl group at C7, respectively, bind and inhibit the MR_{WT} more efficiently than mexrenone (**106**, Fig. 31) and canrenone (**103**), bearing at the same position a methyl ester and no substituent, respectively [155].

Essential hypertension is related also to dysfunction of dopamine D_2 receptors (D_2Rs) and, therefore, to an increased oxidative stress. Since D_2Rs are involved in the aldosterone regulation, spirolactones demonstrated to be able to counteract some effects of the ROS (reactive oxygen species) production in mice [156].

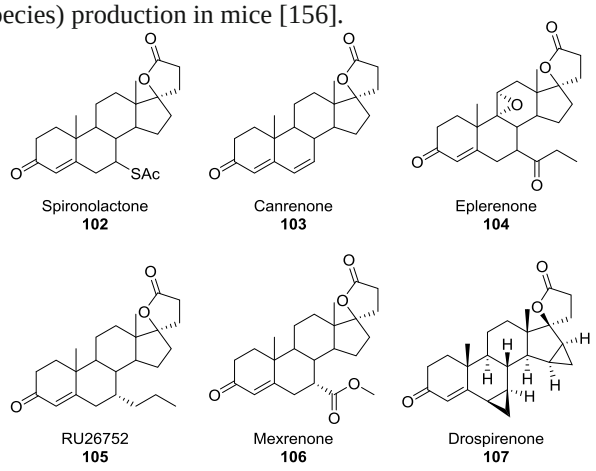


Fig. (31). Structures of mineralocorticoid receptors antagonists belonging to the spirolactone family.

A structurally related steroidal mineralocorticoid receptor antagonist is drospirenone [157] (**107**, Fig. 31), a progestogen which does not provide many side effects typical of the previously mentioned ARAs [139]. In fact, drospirenone in humans acts as progesterone receptor agonist and androgen receptor antagonist, without affecting the glucocorticoid receptor and the estrogen receptor. Thanks to its anti-mineralocorticoid properties, drospirenone (**107**) slightly reduces body weight and blood pressure. Furthermore, its pharmacodynamics [158], similar to that of progesterone, suggests a possible use of this spirolactone in postmenopausal women under hormone treatment with the aim of decreasing cardiovascular morbidity [159].

3.2. Contraceptives and Hormonal Therapeutic Agents.

Synthetic progestins are widely employed in contraception, hormone replacement therapy and for other gynecological indications. The previously mentioned anti-mineralocorticoid drospirenone (**107**, Fig. 31) displays also anti-androgenic properties and, combined with other active ingredients, is sold as oral contraceptive [158,160-162].

Norethisterone (NET, **108**, Fig. 32), a 19-nortestosterone derivative, was used as first generation contraceptive, but, because of its retained androgenic activity, several structural modifications were studied. In particular, with the aim of increasing the progestagenic activity and decreasing the androgenic properties, a six-membered-spiromethylene lactone was introduced in 17-position, and some alkylic chains were varied on C-11 (**109**, Fig. 32) [163].

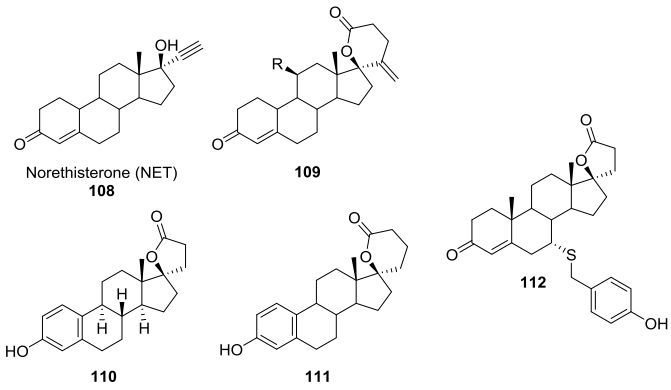


Fig. (32). Structures of contraceptives belonging to the spirolactone family.

The progestagenic binding properties of the 17-spiro compounds (**109**) resulted higher than those of the corresponding 17α-ethynyl derivative (**108**). The ethyl, ethenyl and ethynyl substituents (-R) conferred the greatest activities in ovulation inhibition tests. Considering the low side-effects (very weak androgenic and glucocorticoid properties) these six-membered spiromethylene lactones revealed to be very selective and therefore promising agents as contraceptives, for either oral and/or subcutaneous administration.

It was demonstrated that spirolactones characterized by the C18- and C19-steroid architecture are potent inhibitors of

type 2 17β-HSD [164-166], a dehydrogenase involved in the regulation of steroidal hormones. 17β-HSD inhibitors are therapeutically useful for the treatment of estrogen- and androgen-sensitive pathologies. In particular, product **110** (Fig. 32) showed one of the highest activity (IC_{50} = 0.27 μM) and acted as a reversible inhibitor. The authors demonstrated that: *i)* the spiro-γ-lactone moiety was a key pharmacophore for the type 2 17β-HSD inhibition; *ii)* the alkylation of the phenolic oxygen decreased the bioactivity and the bulkiest groups provided the lowest inhibition properties; *iii*) the double bonds introduction into A ring decreased the inhibition; *iv*) the presence of a thio-group at C7 improved the activity [164]. As a confirmation, the C19-steroidal inhibitor **112** (Fig. 32), bearing 17-spiro-γ-lactone and *para*-hydroxy-benzylthio group at 7α-position, showed an IC_{50} value of 0.5 μM against type 2 17β-HSD [165]. Afterwards, a small library of spiro-γ-lactones and spiro-δ-lactones at position C17 was synthesized [167]. A careful structure–activity relationship study established that: *i*) the 17β-*O*-isomer of spiro-γ-lactone is more potent than the corresponding 17α-*O*-analogue; *ii*) the carbonyl function is essential, being the corresponding ether analogue almost inactive; *iii*) the spiro-δ-lactone framework displays improved bioactivity with respect to the spiro-γ-lactone; *iv*) substituents, ie steric hindrance, on the spiro-δ-lactone ring lower the inhibition. The spiro-δ-lactone **111** (Fig. 32) resulted the best type 2 17β-HSD inhibitor (*K*i = 29 nM), acting as a reversible non-competitive inhibitor.

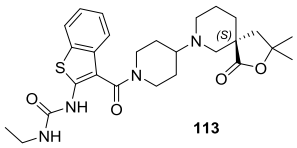
The spiro-δ-lactone moiety revealed to be a crucial subunit, present in several inhibitors of 17β-HSD, not only type 2 but also type 5 [168-169].

Hartmann and Marchais-Oberwinkler in 2011 designed and synthesized new non-steroidal spiro-δ-lactones as type 2 17β-HSD inhibitors, potentially useful against osteoporosis [170]. However, these compounds showed low stability and weak bioactivity (25% of inhibition tested at 1 μM).

3.3. Obesity and Diabetes Treatment.

In the obesity treatment and body weight regulation, a significant role was played by the acetyl-CoA carboxylases (ACCs) inhibitors. ACCs are enzymes promoting the carboxylation of acetyl-CoA to malonyl-CoA, a key intermediate in the regulation of the fatty acid metabolism. Therefore, the ACCs inhibition, by means of a decreased malonyl-CoA formation, should reduce the fatty acid production, enhance the fatty acid oxidation, and improve insulin sensitivity and obesity. In rodents and humans, the ACCs are present as two different isoforms (ACC1 and ACC2) and some studies propose the dual inhibition as therapeutic approach to obesity and insulin resistance, especially for type 2 diabetes.

In 2003, it was reported the co-crystallyzed structure of human ACC2 carboxyl transferase domain complexed with a potent ACC1/2 dual inhibitor. On the basis of the derived model, Yamashita *et al*. proposed in 2011 the spirolactone **113** (Fig. 33), characterized by a 2-ureidobenzothiophene moiety, as ACC1/2 dual inhibitor (IC_{50} = 32 nM for ACC1, IC_{50} = 5.4 nM for ACC2) [171]. The absolute stereochemistry of the product revealed to be particularly important, since the (*R*)-configured enantiomer was much less active.



113

Fig. (33). Structure of ACC1/2 dual inhibitor **113**.

3.4. Anti-Cancer Compounds.

Some synthetic or semi-synthetic spirolactones exert anti-cancer properties. This is the case of products **115** and **116** obtained by Zhang and Xu in 2012 starting from the natural product oridonin **114** (Fig. 34) [172]. Being Taxol the reference compound (IC_{50} against A549 = 3.46 μM, IC_{50} against Bel-7402 = 1.89 μM), the keto-derivative **115** showed comparable cytotoxic activity on A549 (adenocarcinomic human alveolar basal epithelial) cells (IC_{50} = 4.58 μM), and slightly lower activity on Bel-7402 (human hepatocellular carcinoma) cells (IC_{50} = 5.03 μM). Even better results were achieved with a series of 14-O-derivatives of **115**. The same research group synthesized also a family of 14-O-derivatives of **116** and the most promising product **117** (Fig. 34) revealed to be more active than Taxol against K562 (human myelogenous leukemia) and Bel-7402 cells (IC_{50} = 0.39 μM and 1.39 μM, respectively) [173]. Concerning the mechanism of action, compound **117** induced apoptosis at low micromolar concentrations in Bel-7402 cell line. At last, very recently (2016), these authors introduced on the 14-hydroxyl of precursors **115** and **116** a series of furoxan-based NO donors, obtaining a new family of nitric oxide-releasing spirolactone-type diterpenoid derivatives [174]. The design of these hybrids resulted from the known ability of high concentrations of NO and its metabolic derivatives (reactive nitrogen species, RNS) to alter functional proteins, enabling bioregulation and cytotoxicity, especially in tumor cells. The obtained scaffolds were more potent than precursors **115**, **116** and oridonin **114**. The highest antiproliferative activity was observed for compound **118** (Fig. 34), tested on four different human cancer cell lines (IC_{50} = 1.74 μM against K562, 3.75 μM against CaEs-17, 1.16 μM against MGC-803, 0.86 μM against Bel-7402). For this product was also recorded a high NO-releasing ability.

A second example of bioactive semi-synthetic spirolactone is product **119** (Fig. 34), obtained by Trajkovic, Ferjancic and Saicic starting from an extract of European yew *Taxus baccata* [175]. This compound is an analogue of the well-known anti-cancer paclitaxel and it is characterized by a C,D-spiro junction and by a lactone D-ring. Although the SAR studies did not assign a defined role to the paclitaxel oxetane D-ring, the analogues without this moiety generally lost their cytotoxicity. On the contrary, compound **119** possessed an activity only one order of magnitude lower than paclitaxel. Moreover, the authors suggested that this

molecule acted through a mechanism involving mTOR inhibition-dependent autophagy, different from the typical mode of action of the bioactive taxoids (apoptosis induced by binding to tubulin, stabilization of the microtubules, and arrest of the cell cycle in the G2/M phase).

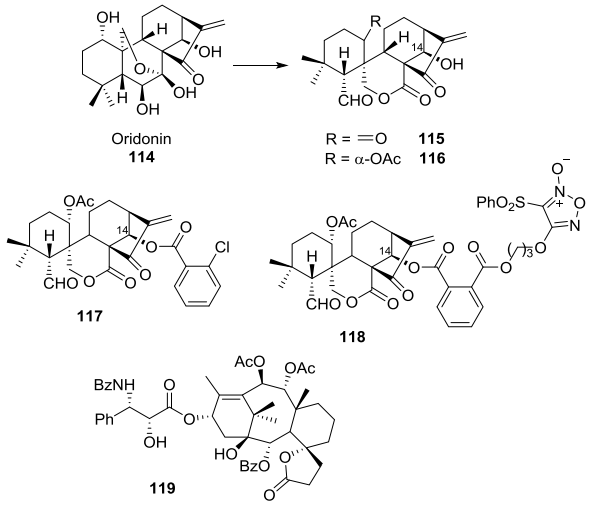


Fig. (34). Structure of cytotoxic agents **114-119**.

3.5. Insecticides.

Some semi-synthetic spirolactones showed antifeedant and insecticide properties [176-177].

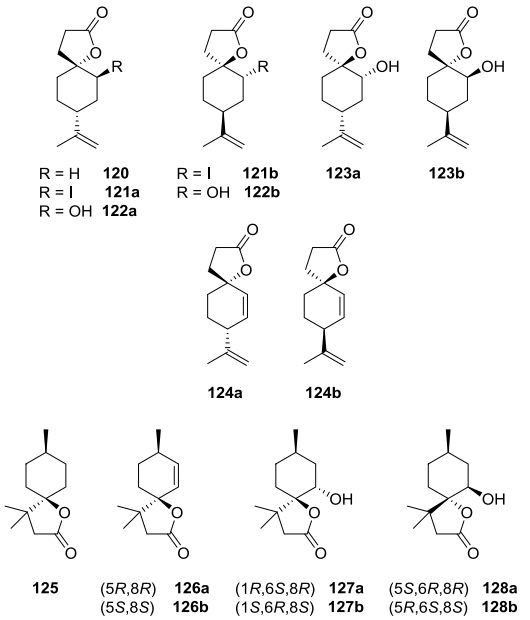


Fig. (35). Structures of spirolactones with antifeedant and insecticidal properties.

For example, in the series of bicyclic terpenoid lactones **120-124** (Fig. 35) derived from limonene, product **124a** revealed to be an excellent antifeedant agent against pest *Tribolium confusum*, whereas the enantiomer **124b** and the hydroxy-derivatives **122** and **123** showed only a slightly lower activity [178]. Conversely, the saturated compound **120** was moderately active and the iodo-derivatives **121** were inactive. The antifeedant properties were significantly affected by the absolute stereochemistry of the compounds (in general, *8R* configuration provided better results) and the presence of double bonds (**124**) improved the activity.

Afterwards (2008), the same research group synthesized novel spirolactones (**125-128**, Fig. 35) starting from pulegone and isopulegol, and characterized by a *p*-menthane system [179]. The authors studied the antifeedant effects of these spiro-compounds on the lesser mealworm *Alphitobius diaperinus*, a dangerous pest for poultry farms. They observed that the introduction of the lactone system did not increase the activity respect to the starting pulegone and isopulegol. On the other hand, the presence of a hydroxy group significantly enhanced the antifeedant properties of the corresponding spirolactone (products **127-128**, Fig. 35). The same family of bicyclic spirolactones was tested also against pest *Myzus persicae* [180]. The preingestional, ingestional, and postingestional phases of feeding were studied and the most deterrent compounds were δ-hydroxy-γ-spirolactones **127b** and **128b** (Fig. 35). Also in this case, the absolute and relative stereochemistry played a crucial role and the lactone moiety was confirmed as essential for the antifeedant activity.

Recently, spirocyclic derivatives of tetronic acid were designed, synthesized and exploited as miticides (**129-130**, Fig. 36) [181-182]. Spiromesifen **130a** is active against white flies (*Bemisia* spp., *Trialeuroides* spp.) and several spider mites (*Tetranychus* and *Panonychus* spp.) [183], and it is characterized by a novel mode of action involving the fat synthesis inhibition in pests.

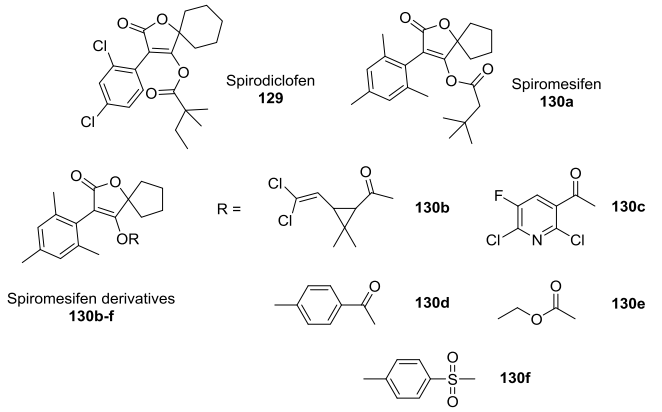


Fig. (36). Structures of insecticide spirolactones **129-130**.

In 2009, in order to improve the effectiveness and broaden the activity spectrum of spiromesifen, Cheng *et al*. synthesized a series of spiromesifen-derivatives (**130b-f**, Fig.

36) [184]. Product **130f** showed a high inhibition (70.8%) against diamondback moth *P. xylostella* (6.9% for spiromesifen, at concentration 600 mg/L). Preliminary tests suggested that also derivatives **130b-e** acted as better acaricides than spiromesifen **130a**.

4. SYNTHETIC STRATEGIES.

As demonstrated by the great number of scientific publications reported in the recent years, spirolactones still represent important target scaffolds, due to their abundant presence among natural and synthetic bioactive compounds [3-4,6,22-23]. For this reason, both the isolation of novel spirocyclic natural lactones and the development of innovative synthetic strategies towards these scaffolds underwent a significant growth in recent years. Previously published reviews admirably covered the synthetic approaches to spirolactones proposed up to the end of 2010 [185-186,2,6]. Therefore, this paper will give an overview of the more recent advances in the construction of spirolactones, with particular attention to the enantioselective protocols. The scientific contributions will be sorted in accordance with the reaction categories.

4.1. Dearomatization.

In 2008, the pioneering work of Kita *et al*. described the first oxidative dearomatization of substituted phenols affording chiral spirolactones with high enantioselectivities (up to 86% *ee*, Fig. 37) [187-188]. The reaction was promoted by 0.55 equivalents of the chiral iodine(III) reagent **131**, which could be used in catalytic amount if generated *in situ* from **132** and *meta*-chloroperbenzoic acid (*m*CPBA). In 2010, Ishihara and co-workers proposed the more flexible and stereoselective chiral pre-catalyst **133**, which allowed to reach enantioselectivities up to 92% *ee* in the same reaction [189-190].

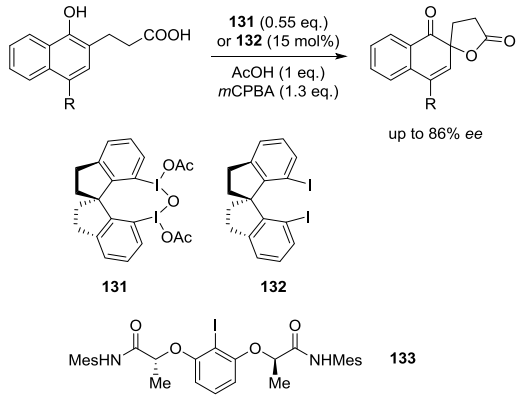


Fig. (37). Oxidative dearomatization proposed by Kita in 2008 and improved by Ishihara in 2010.

Nachtsheim's group accomplished the oxidative spirocyclization of 2-(4-hydroxybenzamido)acrylates to δ-spirolactones promoted by a stoichiometric amount of hypervalent iodine(III) reagent PIFA (phenyliodine bis(trifluoroacetate)) in fluorinated solvents (Fig. 38) [191].

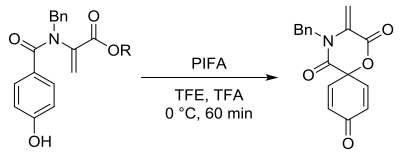


Fig. (38). Oxidative dearomatization proposed by Nachtsheim in 2012.

In 2015, Ohmori and Suzuki exploited the oxidative dearomatization process promoted by $PhI(OCOCF_3)_2$ to accomplish the total synthesis of perenniporide A (**14**, Fig. 7) and related compounds (Fig. 39) [192].

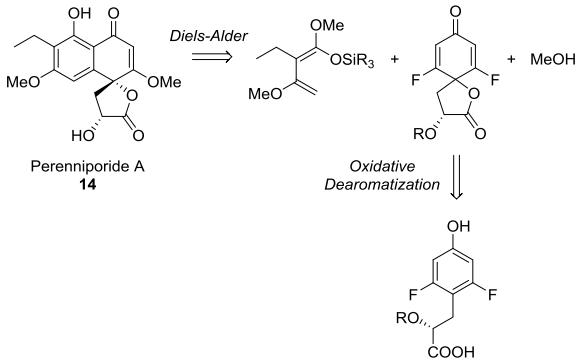


Fig. (39). Perenniporide A (**14**) total synthesis *via* oxidative dearomatization proposed by Ohmori and Suzuki in 2015.

A different dearomatization approach was developed by Vadola *et al*. in 2014 [193]. They proposed to exploit a gold-based π-acidic catalyst to activate the alkyne of an aryl alkynoate ester and induce the spirocyclization (Fig. 40). In this way, it was avoided the waste of a stoichiometric amount of halogenating reagent usually employed in the common halo-spirocyclization of alkynyl arenes. The selective formation of the spirolactone product required the presence of an equivalent of water and of the *p*-methoxy substituent on the substrate.

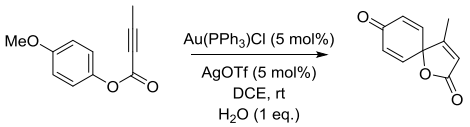


Fig. (40). Oxidative dearomatization mediated by a gold complex proposed by Vadola in 2014.

4.2. Radical Transformations.

The first total synthesis of racemic maoecrystal V (**58**, Fig. 18) was provided by Li and Yang in 2010 [194], followed by

the contributes of Danishefsky in 2012 [195], and Zakarian in 2013 [196]. Recognizing the structural similarity existing between many bioactive diterpenoids originated by *Isodon* plants, Reisman and co-workers focused their attention on the development of a general synthetic strategy, applicable to the construction of several different *ent*-kauranoids [197]. In 2011, they proposed the first enantioselective total synthesis of (−)-maoecrystal Z (**57**), based on the diastereoselective achievement of a key spirolactone intermediate exploiting a Ti-mediated reductive coupling (Fig. 41) [198]. Properly modified, the same approach was used also to accomplish the total syntheses of (−)-trichorabdal A (**53**) and (−)-longikaurin E (**56**) [199].

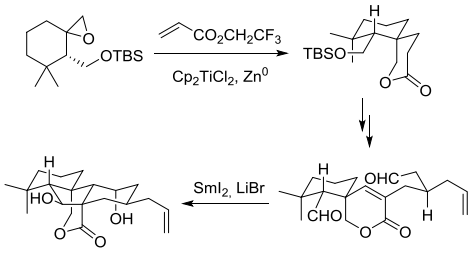


Fig. (41). The key steps in the enantioselective synthesis of (-)-maoecrystal Z (**57**) proposed by Reisman in 2011.

The interest in natural compounds belonging to the bakkanes family led to the development of a series of synthetic strategies [98,200-201]. In 2010, Scheidt *et al*. proposed the catalytic enantioselective total syntheses of bakkenolides I, J, and S (**66**-**68**, Fig. 20) [202]. The *N*-heterocyclic carbene catalysis was exploited for the key step of 1,3-diketone desymmetrization, providing the hydrindane core (Fig. 42). Afterwards, the spirolactone construction was diastereoselectively promoted by $Mn(OAc)_3$.

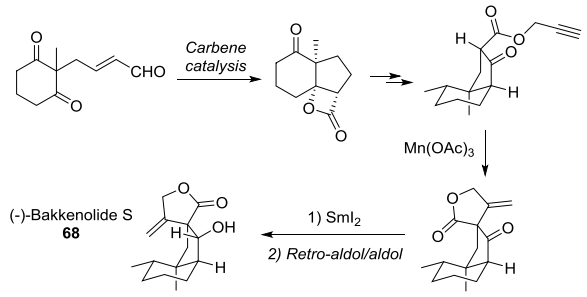


Fig. (42). The key steps in the enantioselective total synthesis of (-)-bakkenolide S (**68**) proposed by Scheidt in 2010.

In 2014, Shi and Tian developed an efficient synthesis of clionamine D (**79**, Fig. 24) (10 steps, 51% overall yield), which could be exploited as precursor for the construction of other members of the clionamine family [203]. The key step of the synthetic strategy was the insertion of the peculiar spirobislactone moiety, accomplished through a $Mn(OAc)_3$-mediated radical [3 + 2] cycloaddition (Fig. 43).

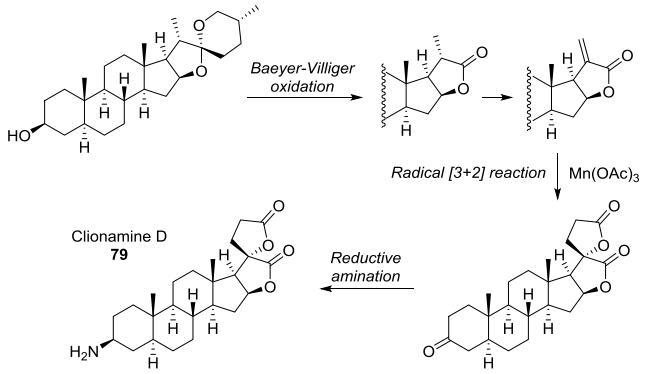


Fig. (43). Synthesis of clionamine D (**79**) *via* $Mn(OAc)_3$-mediated radical [3 + 2] cycloaddition proposed by Shi and Tian in 2014.

In 2014, bis(cyclopentadienyl) titanium(III) chloride (Cp_2TiCl) was exploited as radical generator by Roy and co-workers to develop a mild and efficient intermolecular tandem radical process, starting from a Baylis–Hillman adduct and an epoxide to obtain a δ-spirolactone (Fig. 44) [204].

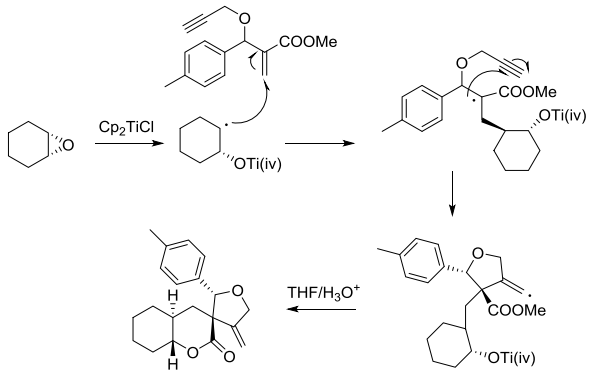


Fig. (44). Probable mechanism of the intermolecular tandem radical process proposed by Roy in 2014.

Vanelle in 2012 resumed a previously reported Mn(III)-based free-radical cyclization applying it to benzylmalonate and methylenecyclohexane as 1,1-disubstituted alkene (Fig. 45) [205].

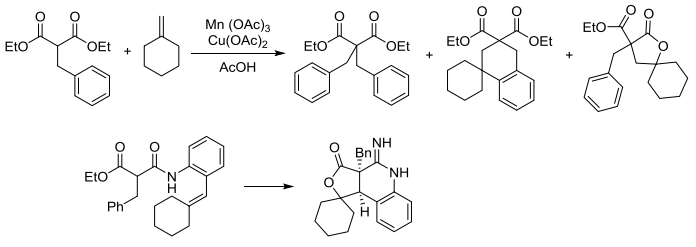


Fig. (45). Mn(III)-based free-radical cyclization proposed by Vanelle in 2012, applied to benzylmalonate and β-oxoamide.

Three different products were obtained, among them a spirolactone system. By replacing the malonate with a β-oxoamide incorporating a C-C double bond, the authors carried out an intramolecular version of the same process.

4.3. One-Pot Transformations.

In the last decades, the multicomponent reactions, the tandem and the domino sequences attracted much interest and were widely developed because of their high efficiency and selectivity. This approaches meet very well the requirements of the stereoselective synthesis of complex spirolactones, often characterized by polycyclic structures with several stereocenters, besides the spiro quaternary center.

4.3.1. 1,3-Dicarbonyl Compounds.

Coquerel and Rodriguez in 2009 proposed the diastereoselective synthesis of spiro δ-lactones through a microwave-assisted one-pot sequence, consisting of an intermolecular cross-metathesis followed by an intramolecular organocatalyzed Michael addition (Fig. 46a) [206]. Interestingly, the Hoveyda-Grubbs precatalyst could work not only as ruthenium-based catalyst, but also as *N*-heterocyclic carbene organocatalyst in the Michael addition step. Afterwards (2011), the same research group developed a Wolff rearrangement/α-oxo ketene trapping/cross metathesis/Michael addition sequence, starting from 2-diazo-1,3-dicarbonyl compounds, (homo)allylic alcohols and acrylic substrates (Fig. 46b) [207]. γ- and δ-spirolactones were diastereoselectively obtained.

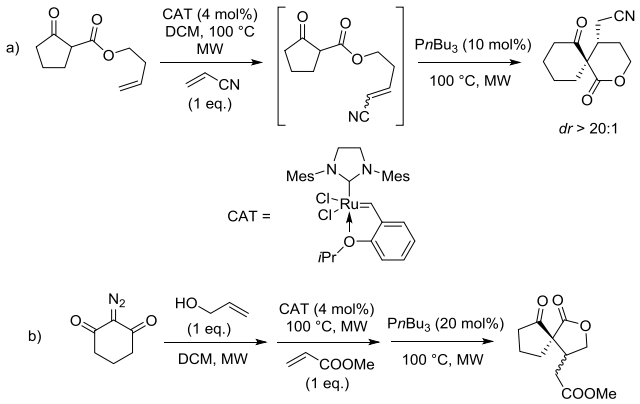
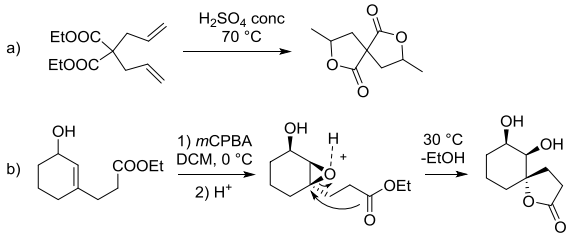


Fig. (46). The two microwave-assisted one-pot sequences developed by Coquerel and Rodriguez: a) cross-metathesis/intramolecular Michael addition, b) Wolff rearrangement/α-oxo ketene trapping/cross metathesis/Michael addition.

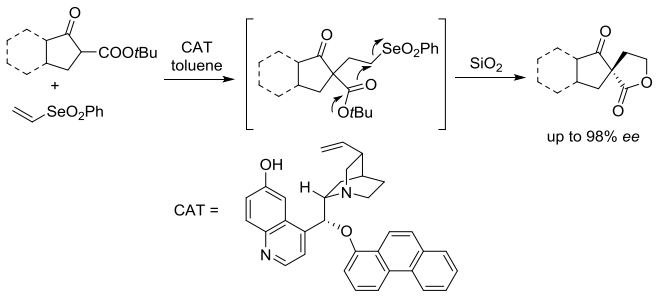
In the same year (2011), Kotha subjected diene diesters substrates to acidic hydrolysis conditions obtaining spiro



bislactones in good yields (Fig. 47a) [208]. Yeh and Wang (2013) described a similar one-pot process in which the alkene was first epoxidized and then the acidic conditions led to the spirocyclization (Fig. 47b) [209].

Fig. (47). Acidic catalyzed addition/hydrolysis sequences. Carboxylate addition to double bonds (a) and epoxide (b).

Regarding enantioselective transformations, in 2011, Marini *et al*. reported on a highly enantioselective one-pot synthesis



of spirolactones accomplished thanks to an organocatalytic Michael addition/spirocyclization sequence (Fig. 48) [210]. A cyclic β-ketoester and a vinyl selenone were the starting materials, the first conjugate addition was mediated by a bifunctional organocatalyst and the subsequent spirocyclization was promoted by silica gel.

Fig. (48). Organocatalyzed Michael addition/spirocyclization sequence proposed by Marini in 2011.

Immediately afterwards (2012), Gade and colleagues presented a different approach to highly enantioselective synthesis of spirolactones/bi-spirolactones [211].

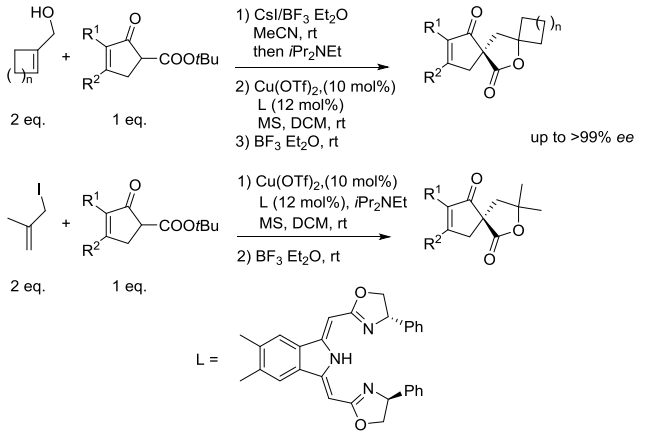


Fig. (49). One-pot copper-catalyzed alkylation and subsequent cyclization proposed by Gade in 2012.

Also in this case β-ketoesters were used as substrates, which were subjected to one-pot copper-catalyzed alkylation and subsequent cyclization (Fig. 49).

In 2016, the cooperative indium(III)/silver(I) system was exploited by Youn *et al*. to synthesize different five-membered heterocycles, including spirolactones (Fig. 50) [212]. As in some previous examples (Fig.s 46, 47a, 48, and 49), even in this case 1,3-dicarbonyl compounds were reacted with olefins, but herein an oxidative coupling/annulation sequence was accomplished. The authors suggested that radical intermediates were involved in the reaction mechanism.

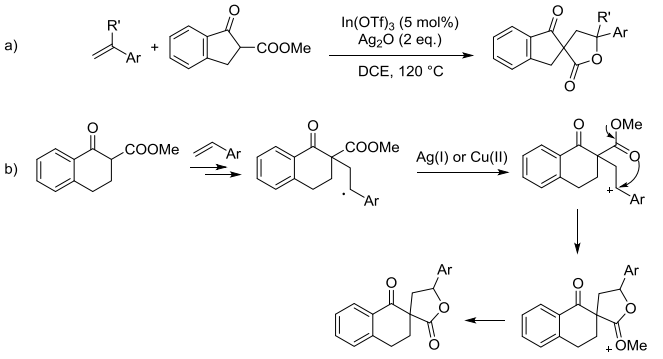


Fig. (50). One-pot oxidative coupling/annulation sequences proposed by Youn to synthesize: a) 2-oxaspiro[4.4]nonane-1,6-diones, b) 2-oxaspiro[4.5]decane-1,6-diones.

4.3.2. Spiroketal Lactones.

An unusual synthetic approach to [5,5]-γ-spiroketal-γ-lactones was described in 2009 by Vassilikogiannakis [213]. 2-(γ-hydroxyalkyl)furans underwent a one-pot photooxygenation/intramolecular nucleophilic opening/dehydration sequence leading to the desired products in high yields (Fig. 51). The strategy was successfully applied to the synthesis of natural bioactive compounds: three epimers of pyrenolide D (**64**, Fig. 19) and two epimers of crassalactone D (**63**, Fig. 19).

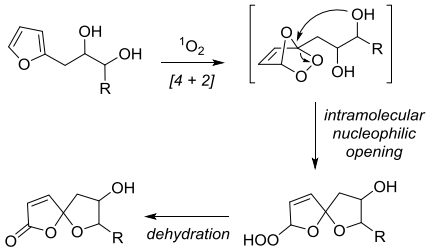


Fig. (51). One-pot photooxygenation/intramolecular nucleophilic opening/dehydration sequence proposed by Vassilikogiannakis in 2009.

In the same year Yang *et al*. reported the first asymmetric total synthesis of (+)-crassalactone D (**63**), based on the Sharpless enantioselective dihydroxylation of a *trans*-olefin synthesized on this purpose, followed by an oxidative spirocyclization [214]. In 2012, Bermejo presented an alternative approach to 1,6-dioxaspiro[4.4]non-3-en-2-ones *via* bromoetherification of dihydroxybutenolides [215]. This synthetic route allowed to accomplish the asymmetric total synthesis of 6-*epi*-crassalactone D.

Concerning (+)-pyrenolide D (**64**), the first total synthesis was reported by Gin and co-workers in 2001 [216], which effectively exploited the stereoselective oxidative ring contraction of a suitable glycal substrate, incorporating three stereocenters (Fig. 52). The development of this process allowed also to assign the absolute stereochemistry of natural product **64**.

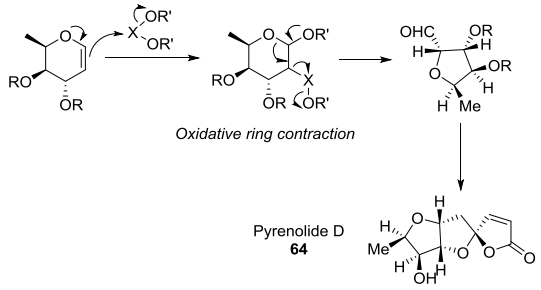


Fig. (52). Stereoselective oxidative ring contraction exploited by Gin in 2001 to synthesize pyrenolide D (**64**).

In 2011, Mohapatra *et al*. achieved the total syntheses of (+)-pyrenolide D (**64**) and (−)-4-*epi*-pyrenolide D starting from a 5-deoxy-D-xylose derivative [217]. In this carbohydrate-based strategy, the spiro-system was introduced *via* an oxidative spiroketalization mediated by *m*CPBA. The most recent contribution (2013) comes from Du and co-workers, obtaining (+)-pyrenolide D (**64**) and its spiroketal epimer from D-xylose in seven steps [218].

Many efforts were devoted to the total synthesis of analogues of mumbaistatin (**75**, Fig. 21), but the correctly functionalized core of the compound was not achieved.

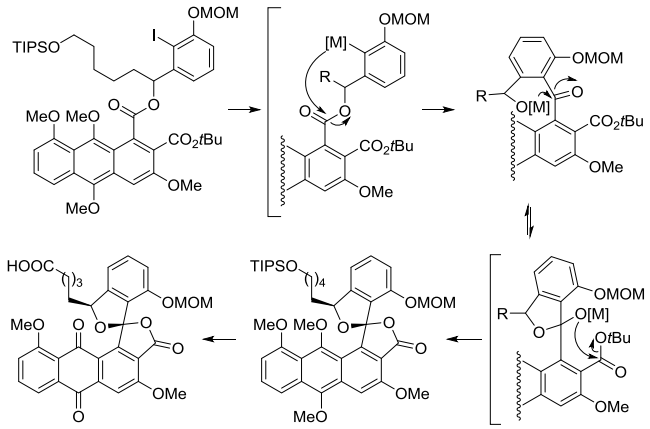


Fig. (53). Anionic homo-Fries rearrangement proposed by Schmalz in 2011 to synthesize cyclo-mumbaistatin analogues.

Recently (2011), Schmalz and co-workers proposed a novel approach providing close analogues of cyclo-mumbaistatin (**75b**) [219]. The key synthetic step was an anionic homo-Fries rearrangement providing the tetra-*ortho*-substituted benzophenone core, which spontaneously converted into the spiroketal lactone form (Fig. 53).

In 2009, Shi *et al*. reported on the Lewis acid-promoted synthesis of 1,6-dioxa-spiro[4.4]non-3-en-2-ones starting from diethyl 2-oxomalonate or ethyl 2-oxoacetate and 1-cyclopropyl-2-arylethanones (Fig. 54) [220]. The overall one-pot transformation consisted of: *i)* a nucleophilic cyclopropane ring-opening by water, *ii)* an aldol reaction, *iii)* an intramolecular transesterification.

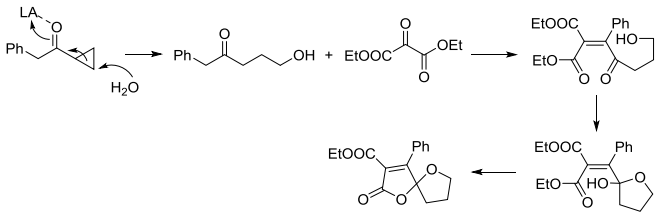


Fig. (54). One-pot cyclopropane ring-opening/aldol reaction/intramolecular transesterification sequence proposed by Shi in 2009.

In 2013, Fañanás and Rodríguez developed the first multicomponent organocatalyzed enantioselective synthesis of spiroacetals (Fig. 55) [221]. The three-component coupling reaction occurred between alkynols, arylamines and glyoxylic acid, promoted by the couple (JohnPhos)AuMe and (*R*)-BINOL-based phosphoric acid as catalytic system. The authors hypothesized that: *i)* the cycloisomerization of alkynol provided an intermediate exocyclic enol ether, *ii)* the condensation of glyoxylic acid with the amine yielded an intermediate imine, *iii)* the reaction between the two intermediates led to the final product [5,5]-spiroacetal.

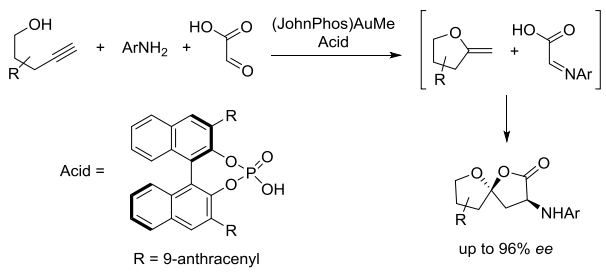


Fig. (55). One-pot enantioselective synthesis of [5,5]-spiroacetals proposed by Fañanás and Rodríguez in 2013.

A metal-free stereoselective synthesis of sugar-derived γ-spiroketals was reported by Sridhar and colleagues in 2015 [222]. Spiro cyclopropanecarboxylic acids bearing a carbohydrate system were treated with catalytic BF_3 Et_2O, triggering a one-pot ring-opening/cyclization sequence and affording the desired 1,6-dioxa[*n*,5]-spiroketal butyrolactones (n = 5, 6) (Fig. 56). The synthesis of pyrenolide D analogues was also accomplished.

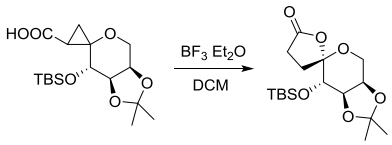


Fig. (56). One-pot ring-opening/cyclization sequence affording sugar-derived γ-spiroketals proposed by Sridhar in 2015.

Very recently (2016), Waymouth and Dai reported a palladium-catalyzed cascade process based on the carbonylative spirolactonization of hydroxycyclopropanols, which enables the efficient construction of oxaspirolactones moieties present in many natural products [223]. In particular, the innovative protocol (Fig. 57) was applied to the synthesis of α-levantanolide and α-levantenolide (**22**, Fig. 10) in two and four steps, respectively.

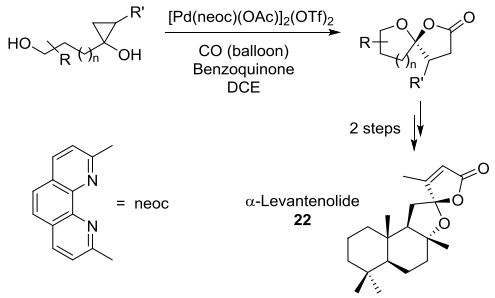


Fig. (57). α-Levantenolide (**22**) synthesis based on carbonylative spirolactonization of hydroxycyclopropanols proposed by Waymouth and Dai in 2016.

4.3.3. Miscellaneous One-Pot Transformations.

In 2002, Coelho *et al*. proposed the total synthesis of racemic pathylactone A (**78**, Fig. 23) [109].

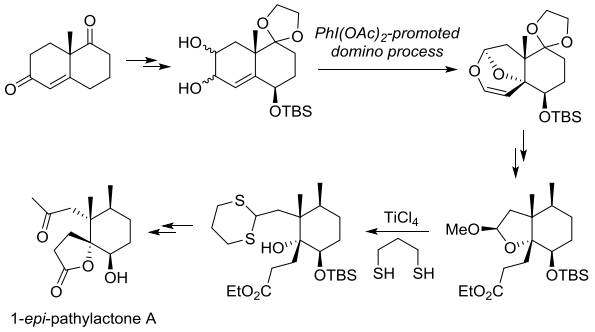


Fig. (58). Enantioselective total synthesis of 1-*epi*-pathylactone A proposed by Arseniyadis in 2007.

In 2007, Arseniyadis and co-workers described the first enantioselective total synthesis of 1-*epi*-pathylactone A, achieved exploiting a $PhI(OAc)_2$-promoted domino process (Fig. 58) [224]. It was confirmed that the initial stereochemical assignment at C1 of pathylactone A was incorrect [224-225].

In 2011, Maghsoodlou described a one-pot three component protocol, which provided polycyclic spirolactones starting from aromatic ketones derived from 11*H*-indeno[1,2-*b*]quinoxalin-11-one, dimethyl acetylenedicarboxylate and *N*-heterocycles (Fig. 59) [226]. The authors obtained excellent yields under mild conditions and no activators were required.

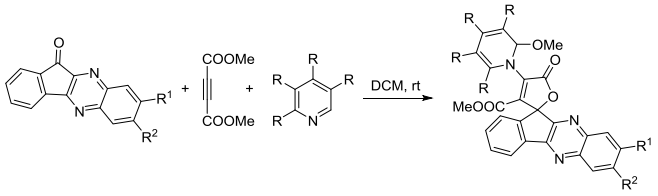


Fig. (59). One-pot three component protocol providing polycyclic spirolactones proposed by Maghsoodlou in 2011.

Sugar fused β-disubstituted γ-butyrolactones were stereoselectively synthesized by Sridhar and co-workers in 2012 [227]. First, a sugar derived cyclopropanecarboxylate was subjected to a bromonium ion mediated solvolytic ring opening. The obtained intermediate underwent a one-pot dehydrohalogenation, an intramolecular oxa-Michael addition, an ester hydrolysis and a spirocyclization (Fig. 60).

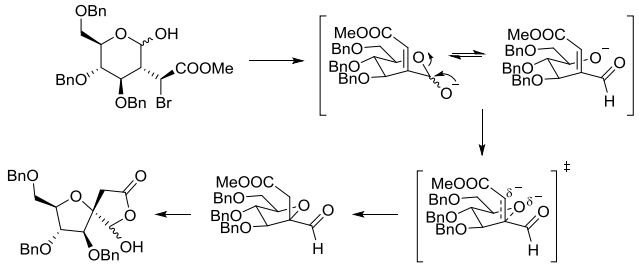


Fig. (60). One-pot dehydrohalogenation/intramolecular oxa-Michael addition/ester hydrolysis/spirocyclization proposed by Sridhar in 2012.

In 2012, Chouraqui and Parrain accomplished an efficient one-pot cascade (Fig. 61) enabling a concise route to the ABCD polycyclic core of micrandilactone B (**33**, Fig. 13) [228]. Three rings and a quaternary spirocenter were sequentially built one-pot. A final oxa-Michael reaction completed the B ring.

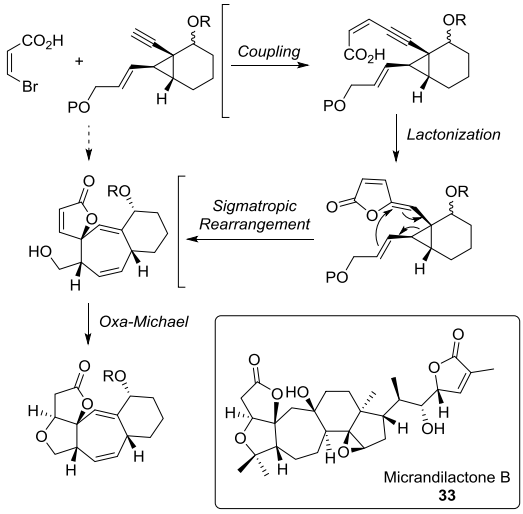


Fig. (61). One-pot cascade proposed by Chouraqui and Parrain in 2012.

Very recently (2016), Quintavalla and co-workers described the first enantioselective organocatalyzed synthesis of 3-spiro-α-alkylidene-γ-butyrolactone oxindoles (Fig. 62) [229]. β-nitro oxindoles were reacted with aldehydes in the presence of a bifunctional thiourea as catalyst. An aldol/lactonization/elimination domino sequence provided the desired spirolactones with good stereocontrol.

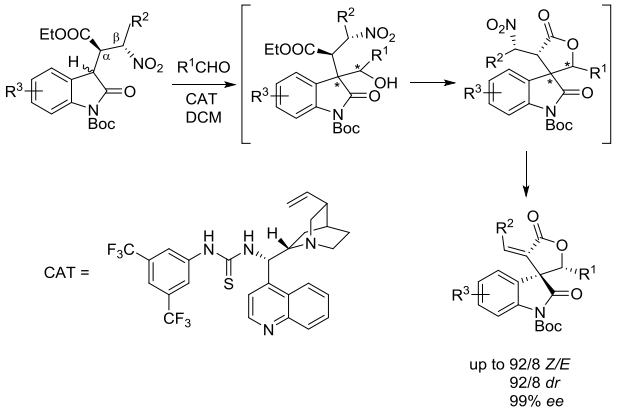


Fig. (62). One-pot aldol/lactonization/elimination domino sequence proposed by Quintavalla in 2016.

4.4. Annulation Processes.

In 2005, one year after the discovery of the potent antibiotic activity of abyssomicin C (**2**, Fig. 2), Sorensen *et al.* reported an efficient asymmetric synthesis of this natural product (Fig. 63) [230]. The key intramolecular Diels–Alder reaction, followed by a cycloisomerization, was exploited to construct the crucial spiro junction involving the lactone unit. The authors also envisaged that such a transformation could be involved in the biogenesis of the compound. In the same years, slightly different strategies were proposed by Snider [231] and Couladouros [232], which also described the abyssomicin D (**3**) carbon skeleton construction.

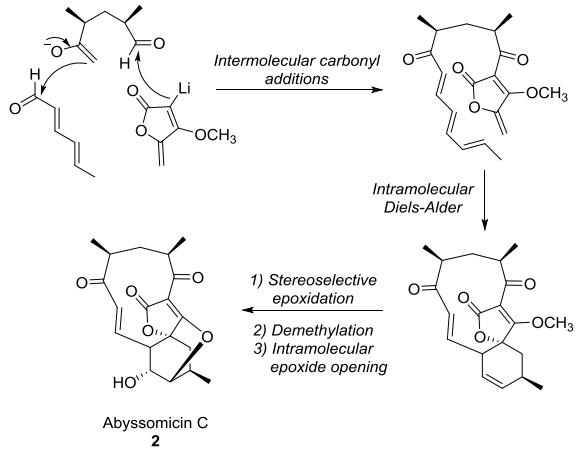


Fig. (63). Abyssomicin C (**2**) asymmetric synthesis proposed by Sorensen in 2005.

In 2012, Commeiras and Parrain proposed a rapid approach to the CDEF ring system of lactonamycinone, the aglycone of the antimicrobial lactonamycins (**4**, Fig. 3), exploiting an intramolecular oxa-Michael addition anticipated by a highly chemo- and diastereoselective intermolecular Diels-Alder cycloaddition, which built the spiro system (Fig. 64) [233].

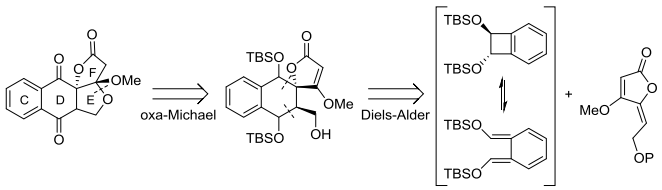


Fig. (64). Diastereoselective approach to lactonamycinone proposed by Commeiras and Parrain in 2012.

In 2010 the same authors proposed an intermolecular Diels-Alder reaction to diastereoselectively synthesize lambertellol (Fig. 5) cores [234]. The developed approach, similar to that for the construction of lactonamycinone (Fig. 64), involves also δ-substituted γ-alkylidenebutenolides as dienophiles, providing access to decorated tricyclic spirolactones otherwise difficult to achieve.

Chouraqui and Commeiras in 2013 reported on a diastereoselective rhodium(II)-catalyzed [3+2]-cycloaddition, leading to polycyclic spirolactones [235]. The intramolecular version of the developed 1,3-dipolar cycloaddition occurred on a suitably synthesized 2-diazo-1,3-ketoester containing the γ-alkylidenebutenolide moiety as dipolarophile (Fig. 65a). The authors extended the protocol also to the corresponding intermolecular process (Fig. 65b). In both cases, the (5,7) structural core of natural products produced by *Schisandra* genus was achieved.

Feng's group in 2014 reported the first enantioselective catalytic hetero-Diels-Alder reaction between Brassard's dienes and isatins, catalyzed by Mg(II)/*N*,*N*'-dioxide complexes (Fig. 66) [236]. Chiral spiro δ-lactones bearing two contiguous stereocenters were obtained with excellent yields and stereocontrol. A predominant Diels–Alder reaction path was found by the authors.

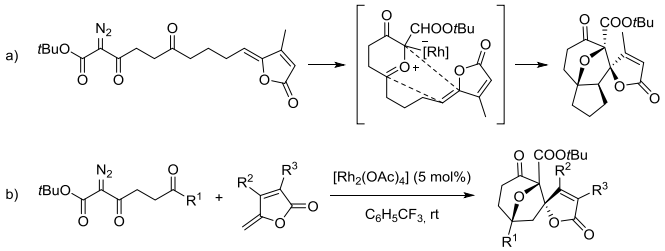


Fig. (65). Diastereoselective rhodium(II)-catalyzed [3+2]-cycloadditions proposed by Chouraqui and Commeiras: a) intramolecular version, b) intermolecular version.

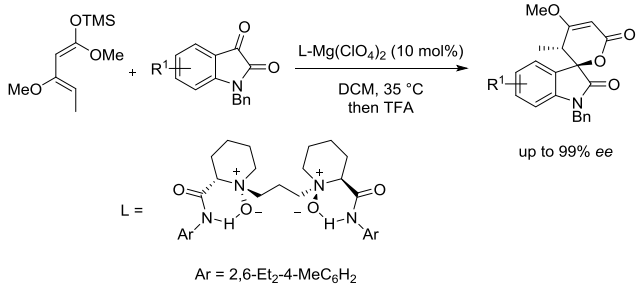


Fig. (66). Enantioselective catalytic hetero-Diels-Alder reaction catalyzed by Mg(II)/*N*,*N*'-dioxide complexes proposed by Feng in 2014.

In the same year (2014) Glorius's group proposed to exploit the umpolung NHC/Brønsted acid dual catalysis to achieve the enantioselective synthesis of spirocyclic oxindoles starting from β,β-disubstituted enals and isatins ([3+2]-annulation; Fig. 67) [237].

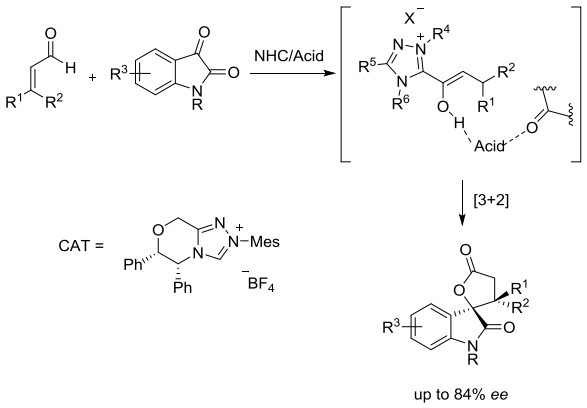


Fig. (67). Enantioselective NHC/Brønsted acid catalyzed [3+2]-annulation proposed by Glorius in 2014.

The products were characterized by two congested adjacent quaternary stereocenters and the employed Brønsted acid played a crucial role not only for the reactivity but also for the process stereocontrol.

Inspired by the Glorius research work, in 2016 Zhou and Liu proposed the construction of spiro δ-lactones through a formal [4+2]-annulation of β-methyl substituted enals and isatins (Fig. 68) [238]. The umpolung NHC-catalysis was used to activate the remote enal γ-carbon.

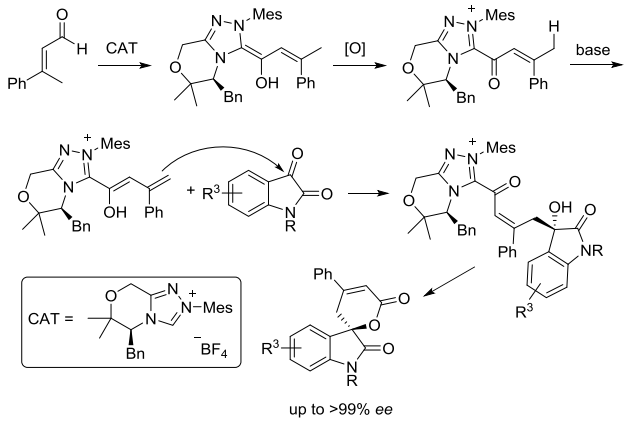


Fig. (68). Enantioselective NHC-catalyzed [4+2]-annulation proposed by Zhou and Liu in 2016.

Considering the pharmacological relevance of sculponeatin N (**47**, Fig. 17), recently (2014) it was achieved its total synthesis. The synthetic approach developed by Zhai consisted of: *i)* a regio- and stereoselective aldol/epimerization/lactonization sequence to install the quaternary C10 stereocenter; *ii)* an intramolecular Diels−Alder reaction to simultaneously construct the B and C rings; *iii)* a radical cyclization to obtain the D ring (Fig. 69) [239].

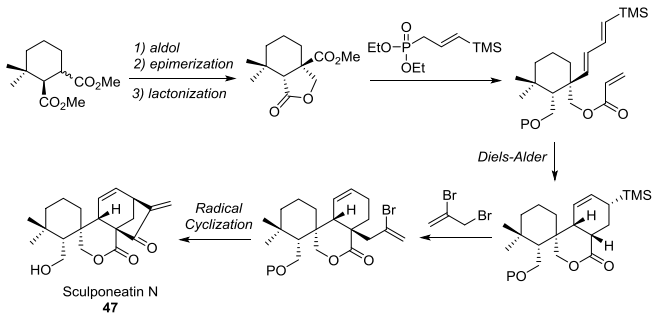


Fig. (69). Sculponeatin N (**47**) total synthesis proposed by Zhai in 2014.

4.5. Miscellaneous Spirolactones Syntheses.

Hyperolactone C (**30**, Fig. 12) attracted much attention due to its anti-HIV activity [64]. Several total syntheses were proposed in the last 15 years [240], among which the catalytic asymmetric syntheses developed by Xie and co-workers (Fig. 70) [241-242], and the oxonium ylide formation–rearrangement sequences reported by Hodgson *et al*. (Fig. 71) [240,243-244].

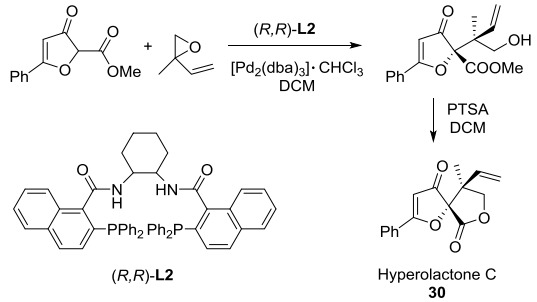


Fig. (70). Catalytic asymmetric synthesis developed by Xie for the hyperolactone C (**30**).

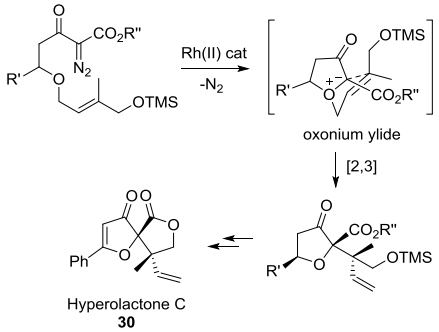


Fig. (71). Oxonium ylide formation–rearrangement sequence reported by Hodgson for the hyperolactone C (**30**) synthesis.

Synthetic approaches to steroidal spirolactone-based ARAs were developed starting from the late 1950s. Recently, some

innovative strategies were applied to the achievement of these compounds. Concerning drospirenone (**107**, Fig. 31), in 2008 Bandini *et al*. developed an approach based on a cross-metathesis reaction to introduce the ester function on the C17 quaternary spirocenter (Fig. 72). It was avoided the use of protecting groups and heavy metal-based oxidants [245].

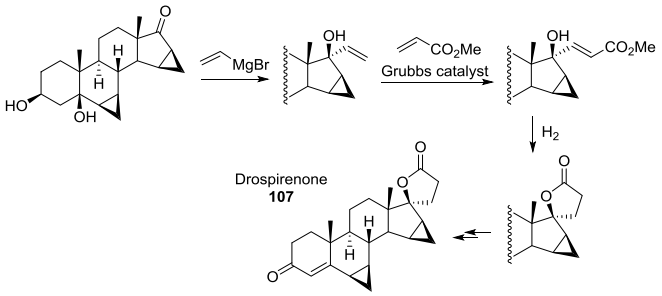


Fig. (72). Drospirenone (**107**) synthesis proposed by Bandini in 2008.

In 2013, Li and Jiang proposed an alternative stereospecific synthesis, in which the reduction of the C7-tertiary alcohol with the mild system ZnI_2/Et_3SiH and the tandem oxidation/cyclopropanation sequence represent the key steps [246]. In the same year, Molinari and co-workers accomplished a biocatalytic transformation of 1,4-diols and γ-lactols into γ-lactones, and the process was applied to the drospirenone preparation [247]. Very recently (2015), Santhamma *et al*. reported a synthetic strategy exploiting the addition of the acetylide anion of propiolate esters to the C17 ketone of steroids [248].

In 2013, the synthesis of spirolactones *via* ruthenium(0)-catalyzed hydrohydroxyalkylation of acrylates was proposed by Krische and colleagues (Fig. 73) [249]. The process proceeded smoothly employing vicinal diols or corresponding oxidized analogues (α-hydroxy ketones, vicinal diketones) demonstrating to be independent from the redox level of the reagents.

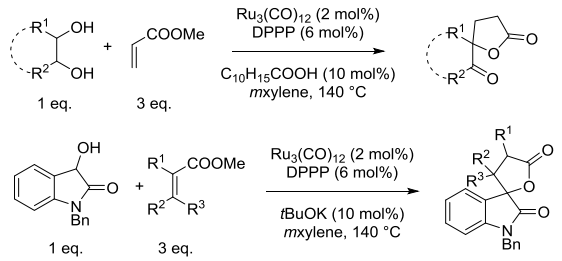


Fig. (73). Ruthenium(0)-catalyzed hydrohydroxyalkylation of acrylates proposed by Krische in 2013.

In 2014, Chahboun and Manzaneda focused their interest on the synthesis of natural spirolactones extracted from the fruits of *Vitex rotundifolia* [250-251]. In particular, they developed a useful approach to the spirolactonization step, consisting of subjecting the proper unsaturated carboxylic acid to iodine and triphenylphosphine under mild reaction conditions (Fig. 74). This strategy was successfully applied to accomplish the first syntheses of (-)-isoambreinolide (**91**, Fig. 27), (+)-vitexifolin D (**88**) and (+)-vitedoin B (**92**).

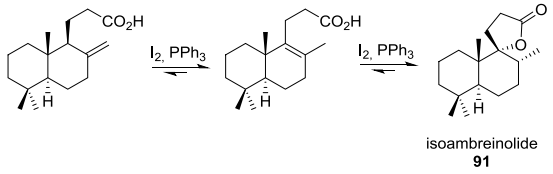


Fig. (74). Iodine/triphenylphosphine-based spirolactonization proposed by Chahboun and Manzaneda in 2014.

Yang *et al*. proposed in 2014 the construction of cyclopropene spirolactones *via* CuBr-promoted dimerization of diphenylcyclopropenones (Fig. 75) [252]. A first demethylation released a nucleophilic phenol group leading to the cyclopropene ring opening. A second demethylation enabled the oxidative cyclization, which provided the final benzofuran-containing spirolactone.

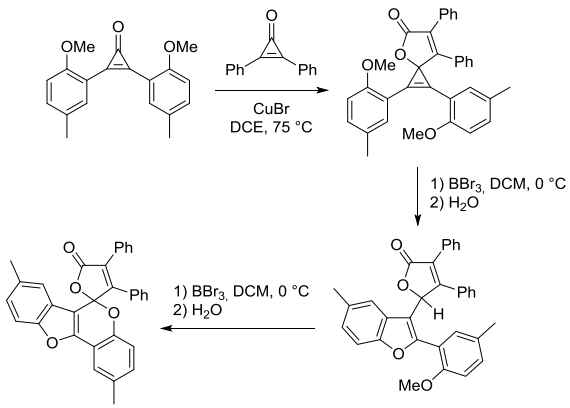


Fig. (75). Construction of spirolactones *via* CuBr-promoted dimerization of diphenylcyclopropenones, followed by two demethylation steps.

In the same year (2014), Doisneau and Beau reported on the synthesis of spiro-δ-lactones α-*C*-sialosides by means of reductive samariation of the substrates glycosyl 2-pyridylsulfides or acetates (Fig. 76) [253].

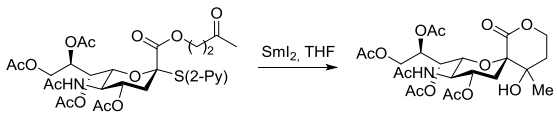


Fig. (76). Synthesis of spiro-δ-lactones α-*C*-sialosides *via* reductive samariation proposed by Doisneau and Beau in 2014.

In 2014 Thomson proposed an alternative synthesis of sculponeatin N (**47**, Fig. 17). The key steps of the strategy (Fig. 77) were the Nazarov and metathesis reactions, enabling the diastereocontrolled introduction of the C8 and C10 quaternary stereocenters, and the reductive radical cyclization, assembling the bicyclo[3.2.1]octane framework [254].

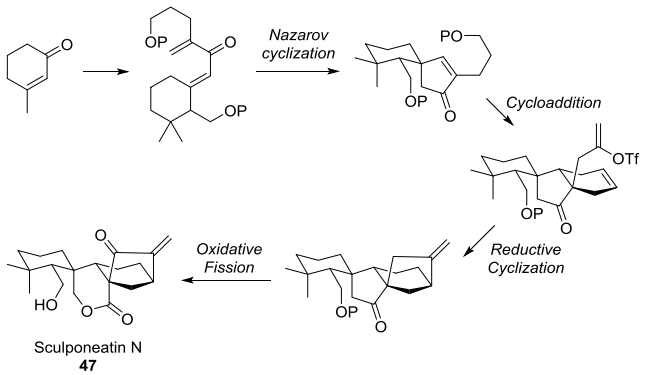


Fig. (77). Sculponeatin N (**47**) total synthesis proposed by Thomson in 2014.

In 2015, Jia and You synthesized a sesquiterpenoid library consisting of curdione and curcumalactone derivatives through a combination of chemical and biological transformations [255]. In particular, curdione-based compounds were converted into the corresponding curcumalactone derivatives exploiting an acid-mediated intramolecular "ene" rearrangement (Fig. 78).

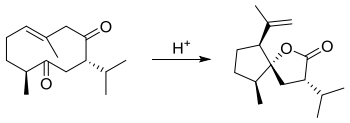


Fig. (78). Curcumalactone derivatives synthesized through an acid-mediated intramolecular "ene" rearrangement proposed by Jia and You in 2015.

CONCLUSION

Spirolactone moiety proved to be a privileged framework due to its ubiquitous presence in many classes of pharmacologically relevant compounds. These scaffolds show a wide range of biological activities and, although they are characterized by a huge structural diversity, in most cases the spirolactone unit is involved in the pharmacophoric system. Considering their medicinal significance, the spirolactones represent an important target not only for the identification of new natural products, but also in the synthetic chemistry field. In fact, primary goals are: *i)* the introduction of structural modifications on known drugs to improve their potency and selectivity; *ii)* the development of innovative and more efficient synthetic strategies to increase the structural diversity and the industrial productivity. This review collects the recent advances in spirolactones discovery and synthesis, demonstrating the great attention still devoted by the scientific community to these compounds.

LIST OF ABBREVIATIONS

ACC = acetyl-CoA carboxylase

CC_{50} = half maximal cytotoxic concentration

Cp = cyclopentadienyl

DCE = dichloroethane

DCM = dichloromethane

DPPP = 1,3-Bis(diphenylphosphino)propane

EC_{50} = half maximal effective concentration

ED_{50} = effective dose, for 50% of people receiving the drug

eq. = equivalents

EtOAc = ethyl acetate

GI = growth inhibition

G6P-T1 = glucose-6-phoshate translocase 1

IC_{50} = half maximal inhibitory concentration

ID_{50} = infective dose causing 50% of exposed individuals to become ill

LPS = lipopolysaccharide

*m*CPBA = *meta*-chloroperoxybenzoic acid

Mes = methanesulfonyl

MIC = minimal inhibition concentration

MR = mineralocorticoid receptor

MRSA = methicillin-resistant *Staphylococcus aureus*

MS = molecular sieves

MW = microwaves

NHC = *N*-Heterocyclic Carbene

*p*ABA = *para*-aminobenzoate

PIFA = phenyliodine bis(trifluoroacetate)

rt = room temperature

SAR = structure-activity relationship

TFA = trifluoroacetic acid

TFE = trifluoroethanol

THF = tetrahydrofuran

TI = therapeutic index

CONFLICT OF INTEREST

The author declares no competing financial interest.

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