CHEMICAL REVIEWS

Review

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Brevianes Revisited

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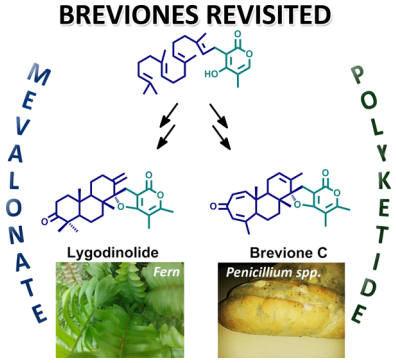

CONTENTS

1. INTRODUCTION. ISOLATION, AND STRUCTURAL TYPES

Breviones are a new family of secondary metabolites that were originally isolated from the New Zealand endemic fungus *Penicillium brevicompactum* var. Dierckx.[1,2] These compounds are generally characterized by a new carbon skeleton, which we have named breviane, that has three possible structural variations: breviane, *abeo*-breviane, and *abeo*-norbreviane (Figure 1). However, brevianes are not the only meroterpenoids with a terpene moiety linked to an α-pyrone ring. Meroditerpenes, oxalicines, and decaturins also show a similar structure. Sesquiterpenic meroterpenoids, pyripyropenes, and arisugacins respond to the same pattern. All of these compounds are of interest, not only because of their unusual backbones but also because of the biological activities they have shown. Hence, we had an interest in reviewing and presenting all together the literature published on these compounds to give an overall view of the state of the art on their chemistry.

This review covers the literature published on meroterpenes with a breviane-like skeleton up to December 2012. It describes the compounds isolated from natural sources, their biogenesis and bioactivity, and the methods used to synthesize them. Special attention has been paid to structure−activity relationship studies (SAR) in section 4.4.

Brevianes present a basic diterpenic tricyclic core (rings A, B, and C) that is mevalonic in origin and is similar to that of perhydrophenanthrene. The core bears four methyl groups at positions C4, C8, C10, and C13 and has defined stereochemistry at positions C5, C8, C9, C10, and C14 (Figure 1). The C1′−C7′ side chain has been proposed to have a polyketide biosynthetic origin and is joined to the diterpenic moiety through carbons C2′−C15′. The cyclization and lactonization of this part of the molecule leads to the characteristic breviane spiranic ring fused to the α-pyrone (rings D and E, Figure 2). The main distinctive feature of 3(4→18)-*abeo*-brevianes is the expansion of ring A to a cycloheptene ring, a change that modifies the methyl group at C18. Finally, in 3(4→18)-*abeo*-1′-norbrevianes, the methyl group at C1′ is lost——usually modified as a carbonyl group——and the α-pyrone ring is expanded to an oxepane ring. The numbering presented here is consistent with this mixed biogenetic hypothesis and is the system used in all the latest papers on the isolation and synthesis of brevianes and related compounds.

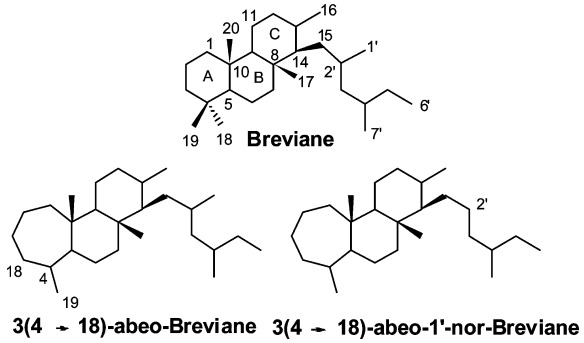

Figure 1. Basic breviane skeletons.

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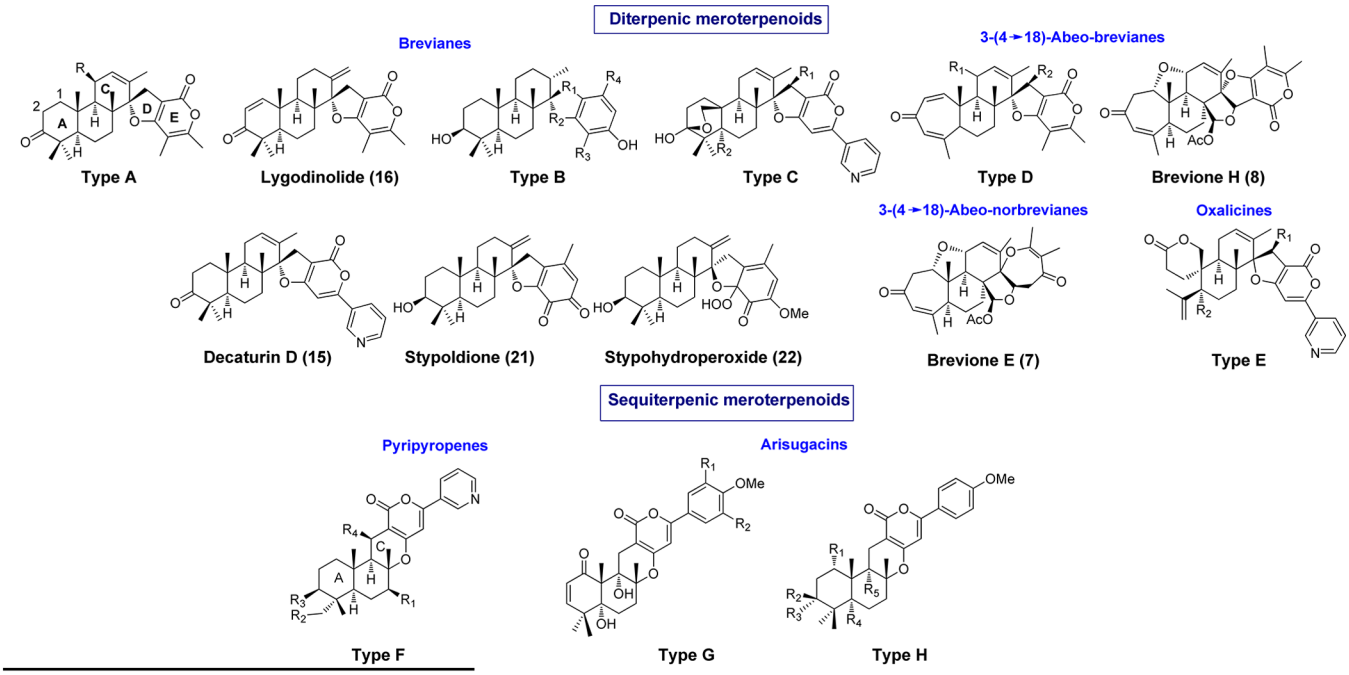

Type A: Brevianes

R	Compound	
H	Brevione A, Δ(1,2)	(**1**)
H	Brevione B	(**2**)
OH	Brevione I, Δ(1,2)	(**9**)
OH	Brevione J	(**10**)

Type B: Brevianes

R_1	R_2	R_3	R_4	Compound	
CH_2	O	H	Me	Stypodiol	(**17**)
O	CH_2	H	Me	*Epi*-stypodiol	(**18**)
CH_2	O	OH	Me	Δ(13,16) Stypotriol	(**19**)
CH_2	O	OH	CHO	Stypotriolal	(**20**)

Type C: Decaturins

R_1	R_2	Compound	
H	OH	Decaturin A	(**12**)
OH	H	Decaturin B	(**13**)
H	H	Decaturin C	(**14**)

Type D: Abeo-brevianes

R_1	R_2	Compound	
H	H	Brevione C	(**3**)
βOH	H	Brevione F	(**5**)
αOH	H	Brevione G	(**6**)
O	H	Brevione K	(**11**)
H	Me	Brevione D	(**4**)

Type E: Oxalicines

R_1	R_2	Compound	
OH	H	Oxalicine A	(**23**)
OH	OH	Oxalicine B	(**24**)
H	OH	15-Deoxyoxalicine B	(**25**)
H	H	15-Deoxyoxalicina A	(**26**)

Type F: Pyripyropenes

R_1	R_2	R_3	R_4	Compound	
OAc	OAc	OAc	OH	Pyripyropene A	(**27**)
OPr	OAc	OAc	OH	Pyripyropene B	(**28**)
OAc	OPr	OAc	OH	Pyripyropene C	(**29**)
OAc	OAc	OPr	OH	Pyripyropene D	(**30**)
H	H	OAC	H	Pyripyropene E	(**31**)
H	H	OPr	H	Pyripyropene F	(**32**)
H	H	OAc	OH	Pyripyropene G	(**33**)
H	H	OPr	OH	Pyripyropene H	(**34**)
OPr	OPr	OPr	OH	Pyripyropene I	(**35**)
OAc	OPr	OPr	OH	Pyripyropene J	(**36**)
OPr	OAc	OPr	OH	Pyripyropene K	(**37**)
OPr	OPr	OAc	OH	Pyripyropene L	(**38**)
OAc	OPr	OAc	H	Pyripyropene M	(**39**)
OPr	H	OPr	OH	Pyripyropene N	(**40**)
OAc	H	OAc	H	Pyripyropene O	(**41**)
OPr	H	OAc	H	Pyripyropene P	(**42**)
OPr	H	OAc	OH	Pyripyropene Q	(**43**)
OAc	OH	OPr	OH	Pyripyropene R	(**44**)

Type G: Arisugacins

R_1	R_2	Compound	
OMe	OMe	Arisugacin A	(**45**)
H	OMe	Arisugacin B	(**46**)

Type H: Arisugacins

R_1	R_2	R_3	R_4	R_5	Compound	
H	O	O	OH	H	Arisugacin C	(**47**)
H	H	OAc	OH	OH	Arisugacin D	(**48**)
H	H	OH	OH	H	Arisugacin E	(**49**)
H	OH	H	H	H	Arisugacin F	(**50**)
H	O	O	H	H	Arisugacin G	(**51**)
OH	H	OAc	OH	OH	Arisugacin H	(**52**)

Figure 2. Breviones and related compounds isolated from fungi and higher plants.

Breviones were originally described as a family of compounds by the group of Macias et al.,[1,2] who reported breviones A–E (**1**–**4** and **7**). Recently, the discovery of breviones F–H (**5**, **6**, **8**) and I–K (**9**–**11**) from a *Penicillium* species (MCCC 3A00005) isolated from West Pacific deep sea marine sediments,[3,4] has been added to this family. Finally, the

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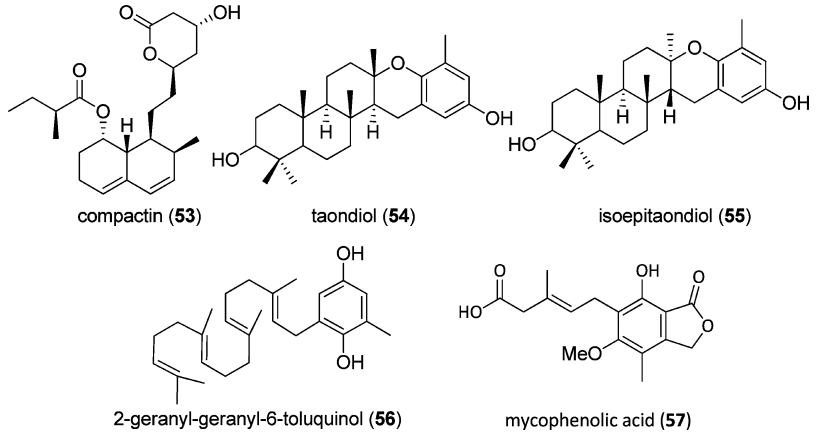

Figure 3. Related meroterpenes, precursor, and micophenolic acid.

decaturins A–D (**12**–**15**) were isolated from *Penicillium decaturense* and *Penicillium thiersii*.[5,6] The most distinctive feature of decaturins is the presence of a pyridine ring attached to the α-pyrone moiety, and in three examples (decaturins A–C, **12**–**14**) the carbonyl and the C20 methyl groups are also modified as a hemiketal bridge. Despite the fact that these compounds lack the two methyl groups at the α-pyrone ring, they should be considered as brevianes and not as norbrevianes, as discussed later in the section related to their possible biogenetic pathways (Figure 2).

From nonfungal sources, one compound with the breviane skeleton, named lygodinolide (**16**), has been described from the fern *Lygodium flexuosum*.[7] Other brevianes, named stypols (**17**–**19**, **21**), have been isolated from the tropical brown alga *Stypopodium zonale* (Lamouroux) Papenfuss[8,9] and, more recently, from the brown alga *Taonia atomaria*[10] (Figure 2). More recently, the unusual compounds stypotriolal (**20**) and stypohydroperoxide (**22**) were isolated from the brown alga *Stypopodium flabelliforme*, along with the known compounds stypoldione (**21**) and epistypodiol (**18**).[11] These compounds are brevianes by virtue of the number of carbons on the side chain, but the α-pyrone ring has been replaced by a benzene or an *o*-quinone ring.

A family of compounds named oxalicines (**23**–**26**) has been isolated from *P. thiersii*. These have a structure similar to that of breviones, but ring A has been cleaved and the methyl group C20 has been modified to render a spirolactone ring at C10. These compounds also present the typical spiranic ring fused to the α-pyrone and an additional pyridine ring as a substituent in the pyrone ring, as in the case of decaturins.[5,6,12]

Finally, pyripyropenes A–R (**27**–**44**), obtained from *Aspergillus fumigatus*,[13,14] and arisugacins (**45**–**52**), obtained from *Penicillium* sp. FO-4259,[15] are potent cholesterol acyltransferase (ACAT) and acetylcholinesterase (AChE) inhibitors, respectively.[16] Instead of the typical diterpenic moiety, these compounds contain a sesquiterpene unit linked to a pyrone ring, which in turn is adorned with a nicotinate (pyripyropenes) or benzene (arisugacins) subunit, and both sets of compounds lack the oxygenated spirocenter typical of breviones. Compactin (**53**) (Figure 3), obtained from *P. brevicompactum*, is another example of a sesquiterpene linked to a β-hydroxylated-γ-lactone ring[17] and this system could render the pyrone ring upon dehydrogenation.

2. BIOACTIVITY

Brevianes are of interest not only because of their structural features but also because of their bioactivity and possible ecological roles, yet the relatively recent discovery of these compounds has not allowed a high number of studies on this subject. However, the examples that have been reported are very promising in terms of their possible uses.

The extract of the fern *Lygodium flexuosum* is known in Indian folk medicine as a potent abortive.[18] Strong postcoital antifertility activity has been reported in rats and mice for the EtOH and EtOH/water (7:3) extracts and also for the EtOH/water extract in rabbits.[18] However, attempts to use the pure compound lygodinolide (**16**) have not been reported to date.

Breviones C (**3**) and E (**7**) have shown phytotoxic activity on etiolated wheat coleoptiles,[2] but other results regarding their possible phytotoxic or fungicidal activities have not been reported.

Decaturins have been reported to be strongly insecticidal. In particular, decaturins B (**13**) and D (**15**) and oxalicines A (**23**) and B (**24**) showed potent antiinsectan activity against *Spodoptera frugiperda*, with dramatic reductions in the growth rate observed when it was tested at a dietary level of 100 ppm.[6]

Some stypols (**17**–**19**, **21**) showed potent deleterious effects against the herbivorous fish *Eupomucentrus leucostictus*, with stypotriol (**19**) and stypoldione (**21**) being especially toxic. While not toxic, stypodiol (**17**) induces intense hyperactivity. It has been suggested that this effect is partly responsible for the "escape" behavior observed in fishes under controlled aquarium conditions.[9] Stypoldione (**21**) effectively inhibits synchronous cell division in fertilized sea urchin (*Strongylocentrus purpuratus* Stimpson) eggs with an ED_{50} of 1.1 μg/mL.[10] This compound appears to act by inhibiting tubulin polymerization, thus making it a promising candidate as an anticancer drug. In addition, stypodiol (**17**) and stypoldione (**21**) show remarkable antioxidant properties through radical-scavenging activity in addition to structurally related (non-spiro-containing) mixed meroditerpenoids taondiol (**54**) and iso-*epi*-taoindiol (**55**) (Figure 3).[10]

Stypotriolal (**20**) showed moderate neurotoxic activity against the mouse neuro-2a cell line, while stypotriolal and stypohydroperoxide (**22**) caused modulation of intracellular Ca^{2+} in rat cerebellar granule neurons (CGN).[11] The biphasic curve shown by **20** is consistent with action on a ligand-gated or voltage-gated ion channel. Stypoldione (**21**) also proved to

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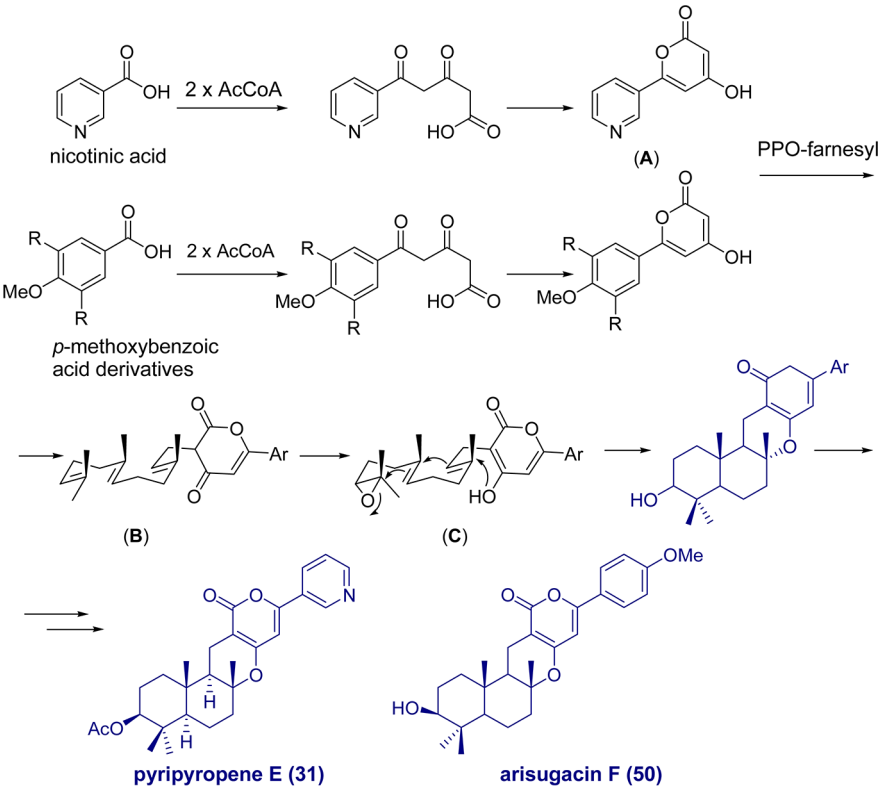
Scheme 1. Biogenetic Pathway for Pyripyropenes and Arisugacins



be slightly active toward CGN and the suggested mode of action is not associated with sodium channels.[11]

Despite the variety of biological activities shown by breviones and structurally related compounds, their relatively recent isolation has precluded in-depth studies on their ecological role, the main requisites needed for the bioactivity or their possible use as drugs. Recently, some structure−activity relationship (SAR) studies have been performed on the diterpenic moiety,[19] but further investigations are required. The relatively complex nature of these compounds in comparison with their low number of carbons, the high number of chiral centers, and the high degree of functionalization make them attractive candidates for such studies.

It seems reasonably clear that stypols play a defense role in the algae from which they were isolated. However, the situation is less clear in the case of the different *Penicillium* strains. The deleterious effects shown by some breviones and decaturins may indicate an active role as mycotoxins. However, the presence of these compounds outside the producing organism needs to be documented before such a function can be unequivocally assigned. This is the case for the fern *L. flexuosum*, for which only the deleterious effects of the extracts have been reported,[18] but the activity of the pure compound lygodinolide (**16**) has not been described.

Regarding the possible medicinal activities of these compounds, breviones F (**5**), G (**6**), and H (**8**) showed weak inhibitory activity on the growth of HeLa cells and brevione F (**5**) weakly inhibited replication of human immunodeficiency virus type 1 (HIV-1).[3]

ACAT is a desirable target in drug design, as it catalyzes the formation of cholesterol esters from cholesterol and fatty acids. Thus, ACAT inhibitors have potential beneficial effects in coronary atherosclerosis. Pyripyropenes have been reported as potent ACAT inhibitors.[20] Extensive QSAR studies with pyripyropenes have resulted in the synthesis of more than 300 pyripyropene derivatives and the modeling of the receptor's cavity.[14]

Another important target is that related to arisugacins and Alzheimer's disease (AD). In this field, AChE has attracted particular attention since the approval by the U.S. Food and Drug Administration (FDA) of several AChE inhibitors for the treatment of AD.[21,22] In this respect, a survey of over 10 000 soil isolates containing actinomycetes and fungi led to the isolation of arisugacins A (**45**) and B (**46**) from a *Penicillium* spp. culture broth,[23] and these were reported to be potent AChE inhibitors.[15,24] The discovery of arisugacins and pyripyropenes illustrates the potency and importance of fungal metabolites as a source of new drugs and also demonstrates the possibilities of meroditerpenoids.

3. BIOGENETIC PATHWAY

The mixed biogenetic origin of breviones from mevalonate and acetate pathways has been proposed by several authors[2,9] and is in good agreement with the biogenetic pathway proposed for other meroterpenes such as pyripyropenes and arisugacins.

3.1. Sesquiterpenic Meroterpenoids. Pyripyropenes, and Arisugacins

Metabolites of mixed origin are not unusual, but the combination of a pyrone ring (acetate pathway in origin) and a terpene is uncommon. The fungal metabolites pyripyropenes and arisugacins are good examples of this combination of features. These are two families of meroterpenoids that contain a sesquiterpene unit instead of a diterpenic unit, as is the case with breviones. As mentioned in section 1, pyripyropenes were isolated from the fungus *Aspergillus fumigatus*, while arisugacins

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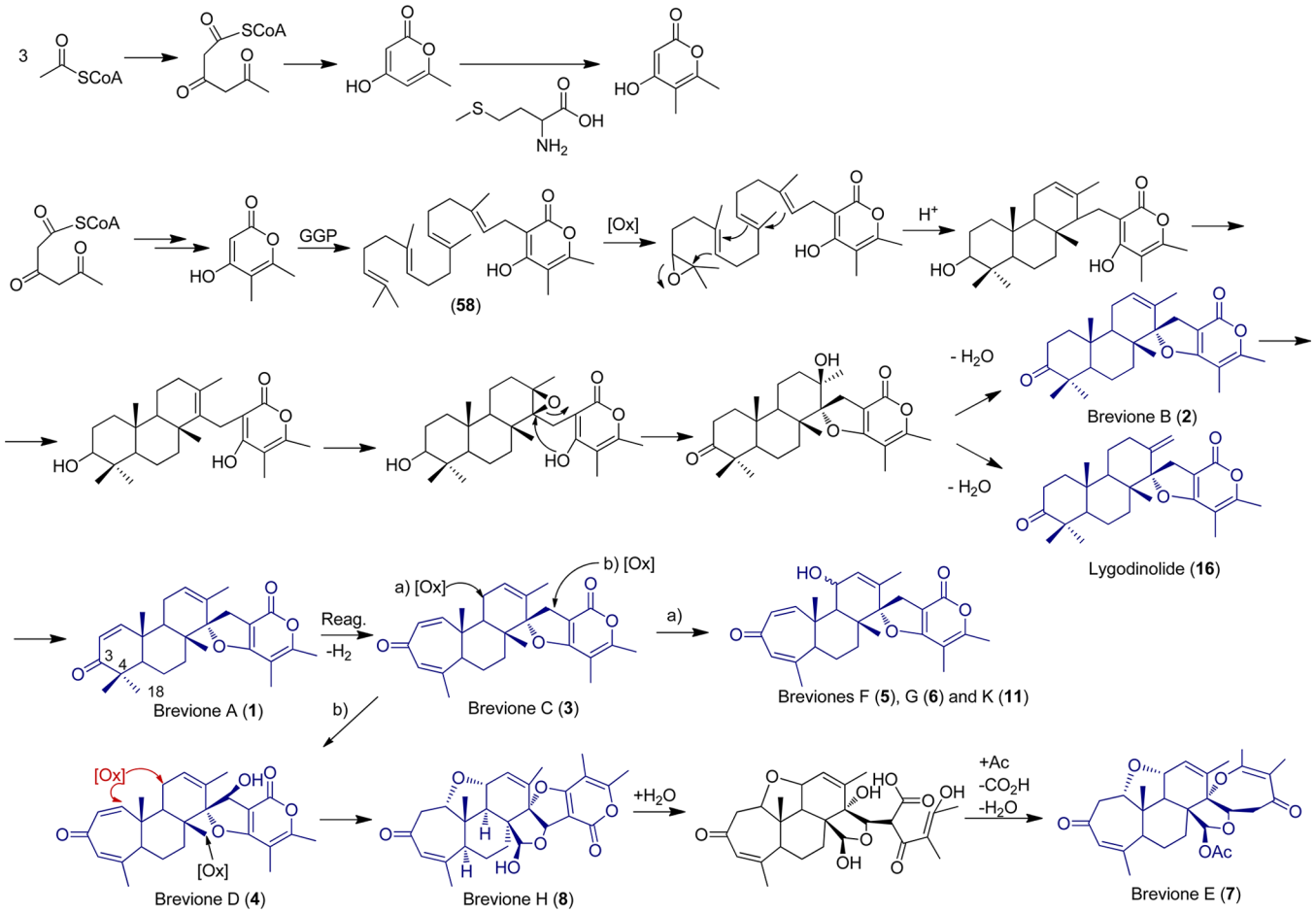
Scheme 2. Biogenetic Hypothesis for Breviones[a]



[a](a) Allylic oxidation at ring C leads to breviones F (**5**) and G (**6**). (b) Oxidation at ring D is the key step leading to breviones D (**4**) and H (**8**) and *abeo*-norbrevione E (**7**).

are *Penicillium* spp. metabolites. A similar biogenetic pathway has been proposed for both families.

Feeding experiments using ^{13}C-labeled acetate, mevalonolactone and nicotinic acid established the following biosynthetic sequence for pyripyropenes: (1) condensation of two acetate units with nicotinic acid leads to the pyridine-α-pyrone moiety (A); (2) this moiety links to a pyrophosphate-farnesyl molecule (B) that (3) undergoes epoxidation and *trans*-cyclization (C) as for any other sesquiterpene molecule to render the basic pyripyropene E (**31**).[14] In the case of arisugacins (**47**−**52**), a similar biogenetic pathway has been proposed with the difference that a benzoic acid derivative and two acetate units yield the benzyl-α-pyrone moiety (Scheme 1).[25]

3.2. Diterpenic Meroterpenoids: Breviones of Fungal Origin

A similar combination of acetate and mevalonate pathways has also been proposed for breviones.[2,9] In this case, the combination of three acetyl-CoA moieties and cyclization renders the $\alpha,\beta,\gamma,\delta$-unsaturated lactone (Scheme 2). The additional methyl group is delivered by methionine to yield the final pyrone ring, a situation that was also proposed for mycophenolic acid (MPA, **57**) (Figure 3),[26] another *Penicillium* metabolite of mixed origin.

A mixed-origin metabolite arising from the addition of the α-pyrone ring to one molecule of geranylgeranyl pyrophosphate (GGP) should be placed at the beginning of the brevione biosynthetic pathway in a similar way to that proposed for pyripyropenes. This hypothesis is supported by the isolation of 2-geranylgeranyl-6-toluquinol (**56**) (Figure 3) from the alga *Stypopodium zonale*.[27] However, the isolation of a similar metabolite with a pyrone ring (**58**) has not been reported to date for any *Penicillium* or other fungus species. The cyclization of such a metabolite would lead to the breviones (see section 3.3).

Either epoxidation followed by an *all-trans* geranylgeranyl-cyclase enzymatic reaction or acid-catalyzed cyclization will lead to the tricyclic diterpenic core of brevianes (breviones, stypols, and decaturins). The advantage of the epoxidation pathway is that the hydroxyl group at C3 is already introduced and only a simple oxidation is needed to render the carbonyl group. The acid-catalyzed mechanism is also feasible, but this requires a harsh oxidation to render the same cyclohexanone ring A. Isomerization of the double bond and epoxidation will allow ring cyclization to give rise to the spirofuran ring D. Dehydration of the alcohol will yield either brevione B (**2**) or lygodinolide (**16**) (Scheme 2). Thus, brevione B (**2**) can be considered as the source member of the brevione family in fungi.

The 3-(4→18)-*abeo*-brevianes will arise due to cleavage of the C3−C4 bond followed by rearrangement of the methyl group C18 and dehydrogenation, thus rendering the expanded

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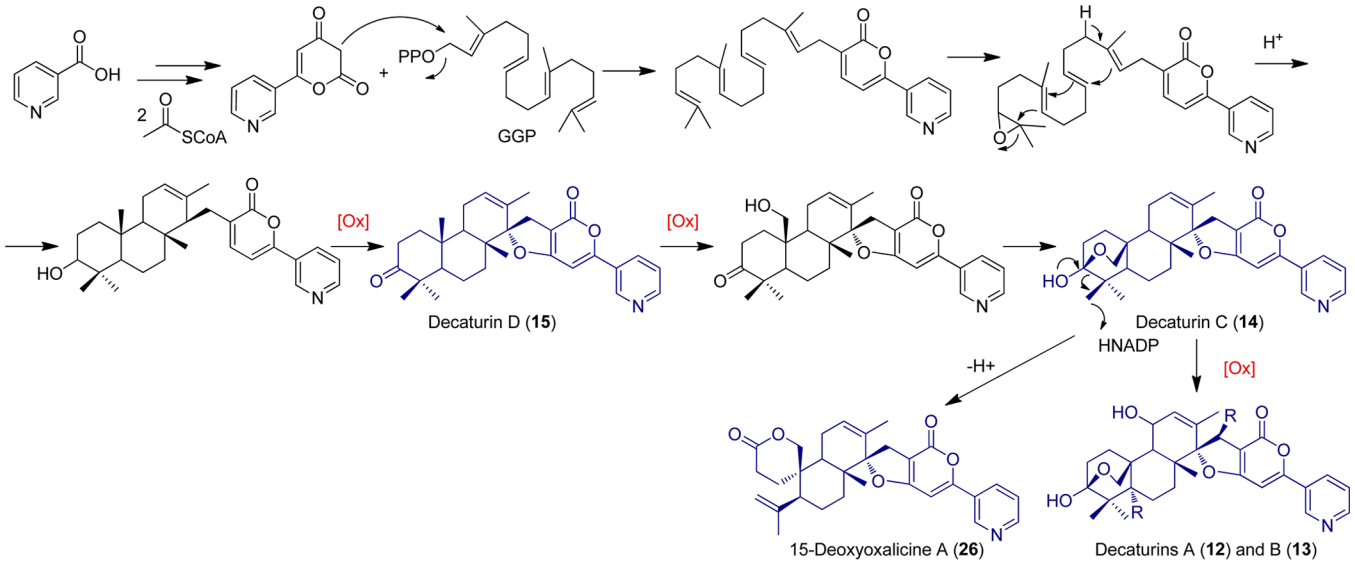
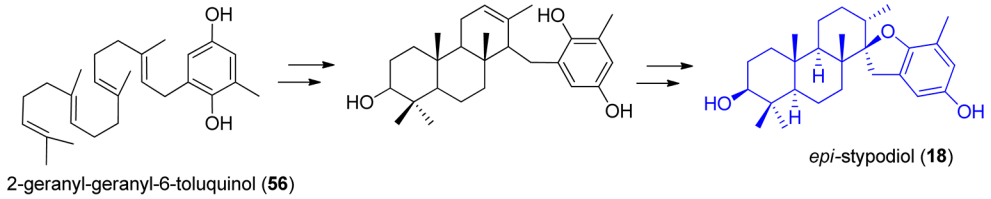
Scheme 3. Biogenetic Pathway Proposed for Decaturins and Oxalicines



Scheme 4. Biogenetic Hypothesis for Stypols



brevione C (**3**). Subsequent oxidations at different positions will lead to the other *abeo*-breviones. Finally, the only member of the *abeo*-norbreviane family known to date could arise from the ring opening, subsequent decarboxylation, and ring closing etherification of the pyrone ring in brevione H (**8**) to render brevione E (**7**).

Breviones are not the only meroterpenoids that have been isolated from *Penicillium* spp. The isolation of compactin (**53**)[17] (Figure 3) illustrates the fact that different linear terpenes (in this case a sesquiterpene) may be assembled with a pyrone moiety undergoing cyclization to render compactin (**53**) or breviones, pyripyropenes, arisugacins, etc. In this case, compactin has undergone cyclization but the lactone ring is not dehydrogenated and the spiro ring is not present.

Finally, decaturins will respond to a similar biogenetic pathway in which formation of the polyketide moiety will start with the addition of two units of acetylcoenzyme A (AcCoA) to a nicotinic acid molecule, as proposed for pyripyropenes (Scheme 3). In this case, the delivery of a methyl group from methionine is not necessary, in contrast to the case of breviones.

3.3. Brevianes of Plant Origin

Investigations into the marine sea grass *S. zonale* led to the isolation of stypols **17**−**20**,[8−11] which bear the typical brevione backbone. The isolation from the same algae of 2-geranylgeranyl-6-toluquinol (**56**)[27] supports the biogenetic hypothesis proposed previously for fungal breviones (Scheme 4). Moreover, linear meroditerpenes of this class with different degrees of oxidation at the side chain and the aromatic ring have been reported in many algae species.[28]

3.4. The Case of Oxalicines

In view of the structure of oxalicines, it is unlikely that rearrangement of the pyrophosphate-geranyl precursor, oxidation of the methyl group, and subsequent lactonization necessary to change the tricyclic core ring structure would take place at the beginning of the biosynthetic pathway. Rather, decaturins A−C should be considered as the most likely biogenetic precursors because they already contain the methyl group modified as a hemiketal (decaturin C, **14**). This hemiketal group can readily undergo oxidative cleavage between carbons C3 and C4, followed by lactonization, to render oxalicines (Scheme 3). Consequently, decaturin C (**14**) should be named as the precursor of 15-deoxyoxalicin A (**26**).

4. SYNTHESIS OF BREVIANES

The total synthesis of brevianes has been achieved and published for breviones A−C (**1**−**3**), lygodinolide (**16**), stypoldione (**21**), decaturins, arisugacins, and pyripyropenes. Reviews on the synthesis and biological properties of breviones (including stypoldiones),[29] arisugacins, and pyripyropenes[14,16] have been published. A route toward the formal synthesis of *abeo*-brevianes has also been disclosed recently.[30] However, a review that addresses all of these materials together has not been published to date. The approaches and retrosynthetic analyses used in each case are different. However, a common feature of all approaches is to split the molecule into the diterpenic moiety and the pyrone ring (Scheme 5). As far as the *abeo*-breviane skeleton is concerned, the two contributions on the synthesis of this unit both involve the initial formation of the breviane perhydrophenanthrene core but then use different strategies to obtain the expanded cycloheptanone ring. The

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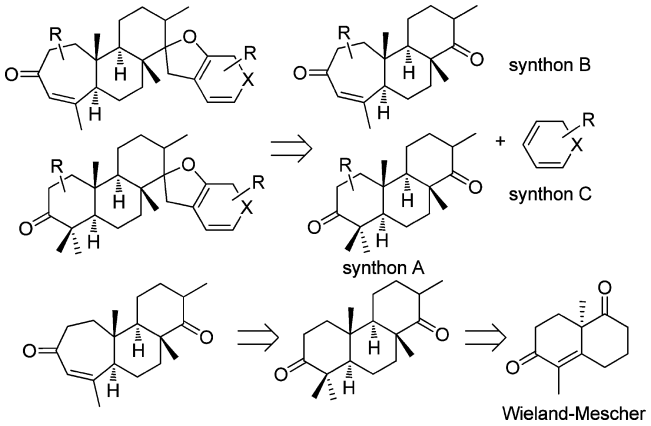
Scheme 5. Common Synthetic Plan



main differences concern the coupling between the diterpenic unit and the aromatic moiety (α-pyrone, pyridyl-α-pyrone, phenol, or *o*-quinone). The strategy selected by each author determines the position of the double bonds in ring C and also the protecting groups required. Accordingly, the methodologies used to build up the pyrone ring and the tricyclic diterpenic core (western half) will be discussed separately, as will the way in which the two units are linked. Some comments on the synthesis of the sesquiterpenic meroterpenoids, pyripyropenes, and arisugacins will also be made.

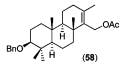
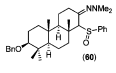
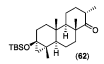
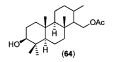
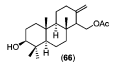
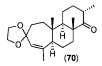
4.1. Stypols and Breviones: Synthesis of the Western Half

The strategies used to build up the diterpenic half in breviones and stypols are summarized in Table 1. The first synthesis of racemic (±)-14-deoxystypoldione was reported by Mori and Koga,[31] and this was soon followed by the enantioselective synthesis of (−)-stypoldione (**21**).[32,33] The construction of ring C in the enantioselective approach was achieved through the $SnCl_4$-catalyzed[34] ring closure in which the final stereochemistry of the methyl group is governed by the angular methyl group between rings A and B, which forces an α orientation of the side chain (entry 1). However, the yield obtained for this process was not very high (37%).

The synthesis of Falck et al.[35] uses decaline **59** as starting material (entry 2). The starting material was obtained from the commercial triterpene 18β-glycyrrhetinic acid by Jones oxidation and this compound comprises rings A and B. The most remarkable aspect of the synthesis is the ring expansion scheme followed to obtain ring C. To pursue this objective, a transannular hydroboration from the less hindered α face of decaline **59** followed by carbonylation of the resulting borane gave the correct stereochemistry at the third angular methyl group. A cyclopentenone was obtained, and treatment of this compound with (phenylthiomethylidene)triphenylarsorane ($Ph_3AsCHSPh$) yielded a labile exocyclic epoxysulfide that easily rearranged to the phenyl cyclohexanone thioether. This compound was transformed into the α-phenylsulfoxide hydrazine **60** depicted in Table 1 (entry 2), which was ready to be incorporated into the aromatic ring (see section 4.3).

One of the advantages of the synthetic approach of Abad et al.[36] toward (−)-stypoldione (**21**) is that it uses the readily available (+)-carvone (**61**) as the starting material for this enantioselective synthetic design (entry 3). In this case, the carbonyl group is protected as an OTBS-cyclopropane system. Construction of the tricyclic core was achieved through thermal ring-closing rearrangement of a triene precursor, a process that gave rise to rings A and B with the correct orientation at all stereocenters.

Table 1. Synthetic Approaches to the Diterpenic Moiety of Stypols, Breviones, and Decaturin D

Entry	Starting material	Methodology	End product	Ref.
1		$SnCl_4$ cat. ring closing		Mori & Koga[32,33]
2		ring expansion		Falck et al.[35]
3		thermal rearrangement		Abad et al.[36]
4		photoinduced electron transfer		Xing & Demuth[37]
5		Cp_2TiCl_2 catalyzed		Justicia et al.[38]
6				Takikawa et al.[40]
7		enzymatic resolution		Takikawa et al.[41]
8				Macías et al.[30]
9				Shishido et al.,[44]

The novelty in the approach used by Xing and Demuth[37] is that it uses photoinduced free radical chemistry (entry 4). Biomimetic light-induced radical cationic cyclization allowed the tricyclic core of stypoldione (**64**) to be obtained quantitatively in one impressive single step. Thus, starting from geranylgeranyl acetate (**63**) and using catalytic amounts of biphenyl and 1,4-dicyano-2,3,5,6-tetramethylbenzene (TMDCB) as radical promoters, photoinduced electron transfer (PET) yielded the corresponding acetylated tricyclic moiety (**64**). It is noteworthy that the use of a protic solvent probably induced the folding of the chain in the correct conformation to obtain the desired stereochemistry at all chiral centers.

Closely related to the previous biomimetic approach, titanocene-catalyzed cyclization of epoxypolyenes was the

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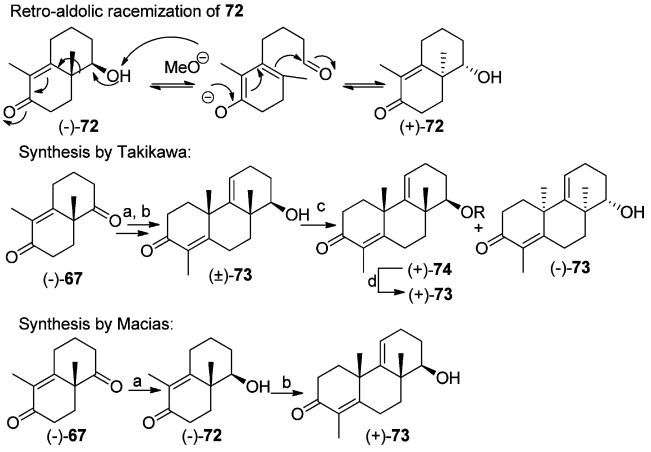
strategy selected by Justicia et al.[38] in another example of step economy (entry 5). The methodology represents an improvement on previous procedures, in which stoichiometric amounts of titanocene were needed.[39] Treatment of the epoxypolyene yields an unsaturated compound (**66**) that is closely related to the one obtained by Xing and Demuth,[37] but in this case 31% overall yield was obtained.

Regarding breviones, there is a clear separation between the perhydrophenanthrene-like and the expanded *abeo*-breviane skeletons. In the former case, the common retrosynthetic analysis includes a double Robinson annulation. Control of the stereochemistry to render the Wieland–Mescher ketone uses a typical approach with L-valine to obtain the correct orientation of the methyl group that will end up as C-17 in the breviane skeleton. However, major problems were encountered in the second annulation, where racemization due to retro-aldolic reactions occurred. This problem was solved in the first instance using enzymatic resolution.

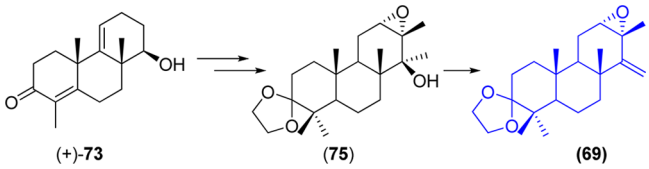
The first synthesis of brevione B was carried out in a racemic form (entry 6),[40] and this was soon followed by the first enantioselective synthesis (entry 7), which employed an enzymatic resolution of the retro-aldolic racemic mixture to give 50% yield of the desired isomer (−)-D with 98.8% enantiomeric excess (ee).[41] Our own route toward the synthesis of the western half of *abeo*-breviones overcame the retro-aldolic reaction, which causes racemization by a single change in the order of reactants, a situation that forced us to carry out the annulation first (entry 8). Under these conditions the base was not allowed to undergo the undesired retro-aldolic reaction, thus enabling the first direct enantioselective synthesis of synthon (+)-**70** in one step fewer and with 80% ee (Scheme 6).[19,30]

Scheme 6. Enantioselective Synthesis of Synthon (+)-73



The synthetic route of Takikawa takes the synthon (+)-**73** to the final epoxide (**69**), which is ready for the coupling with synthon C through classical procedures involving Li/NH_3 methylation, reduction, protection of the carbonyl group, and oxidation to render **75** (Scheme 7).[42] This compound is a key point as it opens the route to **69**, which incorporates all of the required stereocenters and functional groups needed for the coupling reaction (see section 4.3). This intermediate was also used to carry out the first enantioselective synthesis of natural (+)-decaturin D (**15**).[42] Takikawa and co-workers[43] have recently carried out the first synthesis of decaturin C (**14**) using the same methodology.

Scheme 7. Synthesis of Natural (+)-Decaturin D (15)



4.2. *abeo*-Breviones: Synthesis of the Western Half

Recently, the total synthesis of brevione C (**3**) has been disclosed.[44] Previously, only one approach to the synthesis of expanded *abeo*-breviones had been published and this involved a methodology based on a ring-expansion strategy using a Lewis acid-catalyzed diazoalkane addition (Scheme 8).[30] This methodology has been previously shown to be useful to obtain cycloheptanones from cyclohexanones.[45] The reaction proceeds via a Tiffeneau–Demjanov-type intermediate and Pd-catalyzed oxidative dehydrosilylation of the TMS intermediate in a one-pot experiment. Unexpectedly, the reaction was light-sensitive and this allowed control over the regiochemistry of the resulting double bond. The best yields and regioselectivity in the desired isomer were obtained by carrying out the reaction in the absence of light.

As can be observed, the regioselectivity of the reaction changes markedly in the absence of light (Scheme 8, entry 2), which for some reason favors homologation at the most hindered carbon (pinacolinic cleavage b). When the reaction was carried out in light, the type a pinacolinic cleavage prevailed and the ratio between the two regioisomers was opposite to that obtained in the dark. Previous reports on the influence of light on this process have not been published. Also, under dark conditions benzoquinone (BQ) cannot be excited to the triplet state (^{3}BQ) and direct Pd-catalyzed desilylation instead of β-dehydrosilylation occurred to give the corresponding cycloheptanone. Under light conditions, ^{3}BQ reacted with the palladium-silyl enol ether intermediate of the ring expansion and the β-dehydrosilylation products were obtained.

Recently, Shishido and co-workers[44] published the total enantiocontrolled synthesis of breviones A–C (**1**–**3**). The starting point was, as in other previous approaches, the optically pure Wieland–Mescher ketone (Table 1, entry 9). However, the authors' choice in this case was a Baeyer–Villiger oxidation. The corresponding lactone was subjected to ester cleavage and reduction/oxidation (two steps) of the alkenyl methyl ester yielded an alkenyl aldehyde. The 7-endo-trig-cyclization was successfully achieved by use of *tert*-dodecanethiol and a radical initiator [1,1′-azobis(cyclohexane-1-carbonitrile), V-40] to yield the cycloheptenone depicted in Scheme 8 as a single product and in good yield.

4.3. Sesquiterpenic Meroterpenoids: Synthesis of the Western Half

Several excellent reviews have been published on the synthesis of sesquiterpenic meroterpenoids arisugacins and pyripyropenes.[14,16] However, recent data have not been reviewed and we will briefly cover this information and the latest developments in this area.

In the case of the merosesquiterpenoid pyripyropene A, the reported strategy again involved the (+)-Wieland–Mescher Ketone (WMK, **76**) as the starting point to yield the alcohol **77** that, after several steps including a Pd-catalyzed carbonylation and classical chemistry, led to compound **78**, which is ready for incorporation of the pyridine-α-pyrone moiety (Scheme 9).

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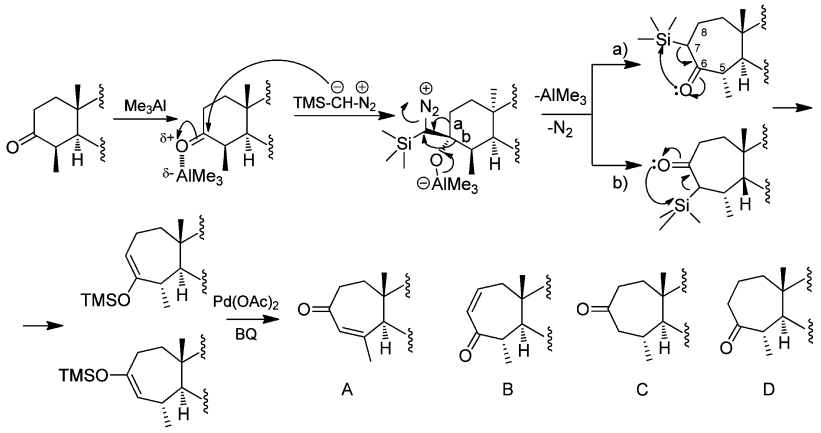
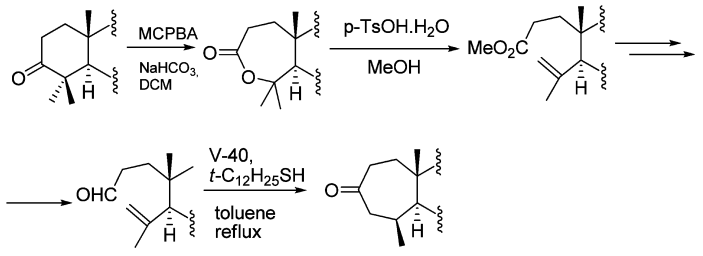
Scheme 8. Strategies for Ring Expansion Leading to the *abeo*-Breviane Skeleton[a]

Macias' approach:



Conditions/ratio	A	B	C	D
daylight	2	3		
dark			3	1
λ < 300 nm	1	4	3	4

Shishido's approach



[a] (a) Light-sensitive Tiffeneau–Demjanov ring expansion toward the western half of *abeo*-breviones (adapted from Macias et al.).[30] (b) Endo-trig cyclization of the alkenyl aldehyde (adapted from Yokoe et al.).[44]

The synthesis of **78** was also carried out by Justicia et al.,[46] who used the titanocene-catalyzed cascade cyclization procedure that was successfully used in their approach to stypoldione (Table 1, entry 5).[47] In this case, the use of Ti(III) allowed synthon **80** to be obtained and Pd-catalyzed remote functionalization of **81** led to **83**, which is structurally close to **78**.

Other approaches involve biomimetic strategies such as that used for the synthesis of pyripyropenes E and similar to that previously discussed for stypoldione (Table 1, entry 4). In this particular case, the sequence involves the synthesis of an epoxide derivative of a geranyl-type precursor that bears the desired nicotinoyl moiety (**84**) (Scheme 9).[48] Lewis acid (BF_3·Et_2O)-catalyzed biomimetic cyclization led to intermediate **85**, which——after another cyclization to the α-pyrone ring with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and acetylation——afforded pyripyropene E directly.

The biomimetic approach has also been successfully used in the formal synthesis of pyripyropene A (**27**) (Scheme 9) using the same acidic conditions as for pyripyropene E (**31**).[49] The reaction yielded the final intermediate **83**, which is ready for coupling with the pyrone ring following the procedure of

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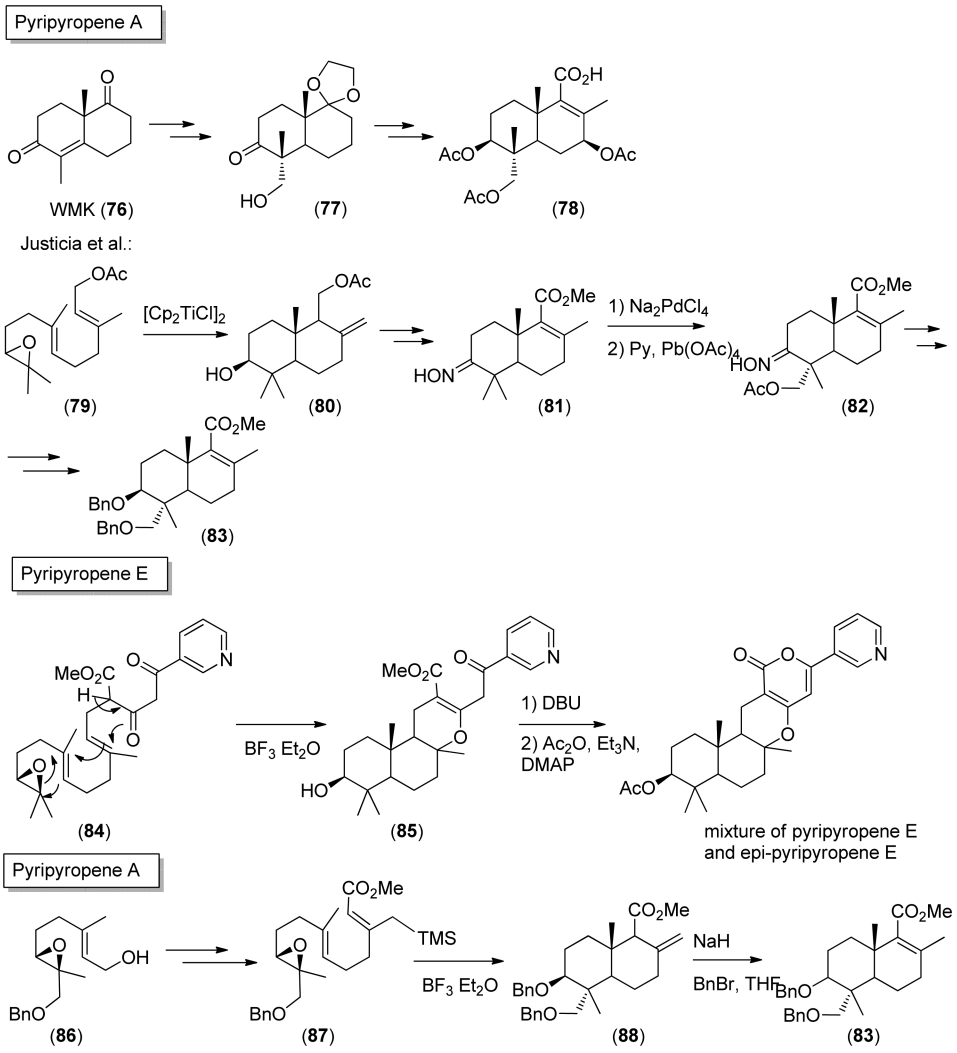
Scheme 9. Pyripyropene Synthesis



Sunazuka and co-workers (section 4.4, Scheme 10). In this case, the authors were aware that allyl silanes bearing ester groups are sufficiently nucleophilic to undergo epoxy-olefin cyclization under acidic conditions.[50]

For the synthesis of arisugacins, the approach of Sunazuka et al.[51] is conceptually similar to their synthetic pathway to pyripyropene A, but in this case α-ionone (**89**) was used as the starting material to gain access to the hemiketal (**90**) (Scheme 10). The key synthon is an α,β-unsaturated aldehyde (**91**) rather than the α,β-unsaturated carboxymethyl ester **83** and, of course, the chemistry used to gain access to the synthon is different. Sunazuka successfully carried out two different approaches to the arisugacin framework, which in one case bore an epoxide moiety at ring B.

On the other hand, two different approaches have been used by Jung and Min[52] to access the sesquiterpenic unit of arisugacins through concerted intramolecular reactions. One approach is based on an intramolecular Diels–Alder reaction with furan (IMDAF), which was previously optimized for this skeleton,[53] and the other was based on the 6π-electrocyclization of a triene followed by singlet oxygen cycloaddition. Both methods provide a synthon similar to **91** but in a more advanced oxidation step. However, the route involving endoperoxide **97** was not ultimately explored at the coupling stage. In contrast, synthon **103**, arising from the 6π-electrocyclization/oxygen cycloaddition strategy, was successfully used in the coupling steps with the α-pyrone ring, even though these units were not ultimately incorporated into arisugacins.

4.4. Structure–Activity Relationship Studies with Pyripyropenes

Pyripyropenes are among the best ACAT inhibitors found in nature, and their activity is in the nanomolar range.[54] In view of the high ACAT activity shown by pyripyropenes, several structure–activity relationship (SAR) studies with structural analogues of pyripyropenes have been undertaken. The main issue in these studies is to obtain enough starting material to carry out the synthesis of as many derivatives as possible. Usually, pyripyropene A was used as the starting material in such studies, as it can be obtained in relatively large amounts by culturing. Structural modifications have been made during the course of several studies in an effort to study the influence of side chains, the degree of oxidation at ring C, and the importance of the type of aromatic rings attached to the pyrone moiety. Furthermore, in some studies pyripyropenes have been used as starting materials in approaches toward arisugacins and arisugacin analogues.

(1) Upon using pyripyropene A as the starting material, selective deacetylation with DBU led to a secondary, sterically

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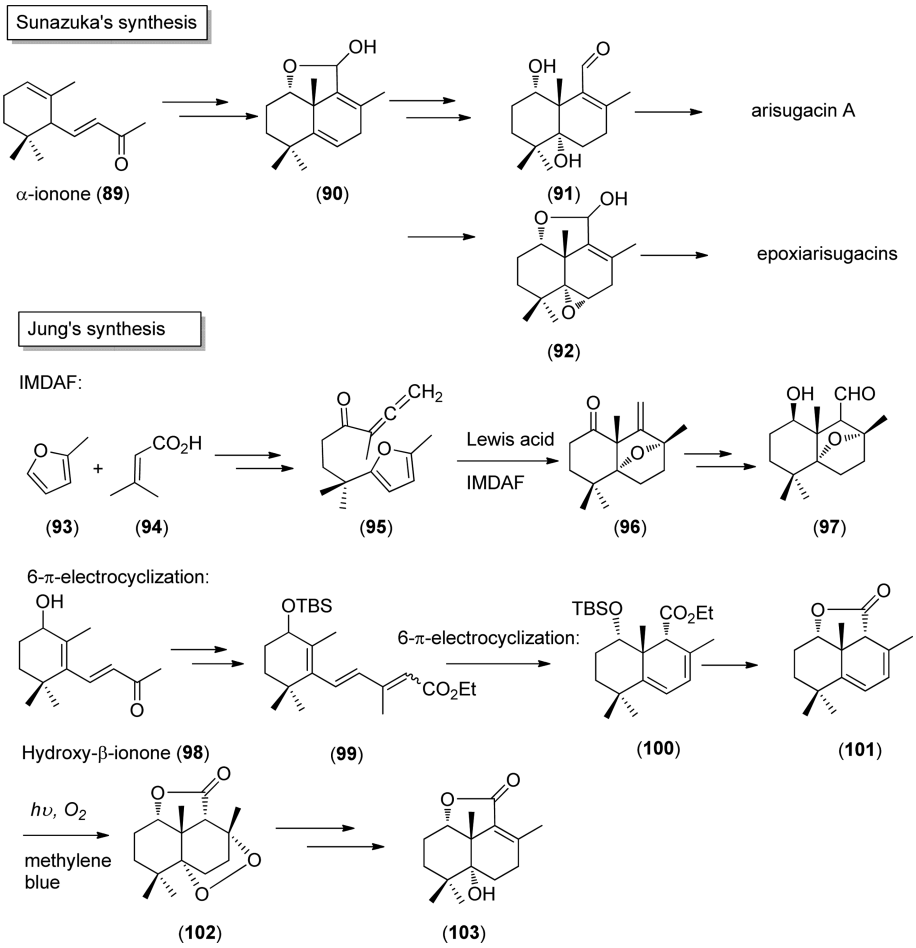
Scheme 10. Synthesis of Arisugacins



unhindered alcohol. This alcohol was used to introduce carboxylic esters in a homologous series from two to eight carbons, plus palmitoleic and branched alkylic, alkenylic, and benzoic esters.[55,56] The highest activity was obtained for the valeroyl ester, with the IC_{50} values following a parabolic curve through the series of compounds. Even though these results are in good agreement with Hansch's model and show that these modifications should not affect the intrinsic activity at the target site, the authors did not comment on this particular issue. Lipophilia seems to be the factor that governs the changes in the activity in this series and one would expect a quantitative SAR correlation between log *P* and the IC_{50} value.

(2) The selectivity of 96 semisynthetic derivatives prepared from fungal pyripyropene A toward ACAT1 and ACAT2 isoenzymes was investigated in a cell-based assay with ACAT1- and ACAT2-expressing CHO cells.[57] Eighteen derivatives, including PR-71 (7-O-isocaproyl derivative), showed much more potent ACAT2 inhibition (IC_{50} 6.0−62 nM) than pyripyropene A (IC_{50} 70 nM). Among the compounds tested, however, natural pyripyropene A showed the highest selectivity toward ACAT2, with a selectivity index (SI) of >1000, followed by PR-71 (SI = 667).[57]

(3) A SAR study on the cytotoxicity of pyripyropene acyl derivatives on drug-resistant cancer cell lines has been published.[58] A relationship between the ACAT and cytotoxic activities was not found. However, several pyripyropene derivatives exhibited enhanced cytotoxic activity against vincristine- and adriamycin-resistant cell lines, with the benzoyl derivative identified as being especially active. The degree of oxidation at ring C also proved to be of great importance for the cytotoxic activity, with the fully dehydrogenated system being the most active, followed by acetylated and hydroxylated ring types and, finally, the γ-pyrone ring (Figure 4).

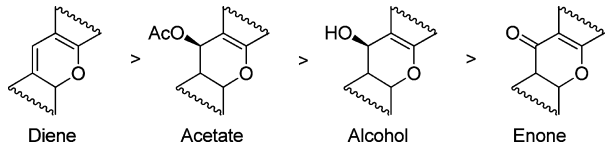


Figure 4. Increasing order of cytotoxic activity of pyripyropenes depending on the degree of oxidation at ring C.

(4) Substitution of the N atom at the pyridyl group resulted in lower activity by more than 2 orders of magnitude. The same effect was produced by a change in the position of the N atom, replacement of the pyridyl with a benzene ring, or replacing the O in the α-pyridine ring by a N. **These results indicate that the pyridine-pyrone moiety is essential for the activity.**[59]

(5) An evaluation was carried out on 48 pyripyropene A derivatives in which the two hydroxyl groups at ring A had been modified as 1−11 cyclic acetals and the hydroxyl group at ring C was either free, acetylated, or had a valeroyl side chain.[60] These changes were made on the basis of previously obtained results.[55] Once again the results clearly show that when the hydroxyl group at C-7 is free, the compounds remain inactive,

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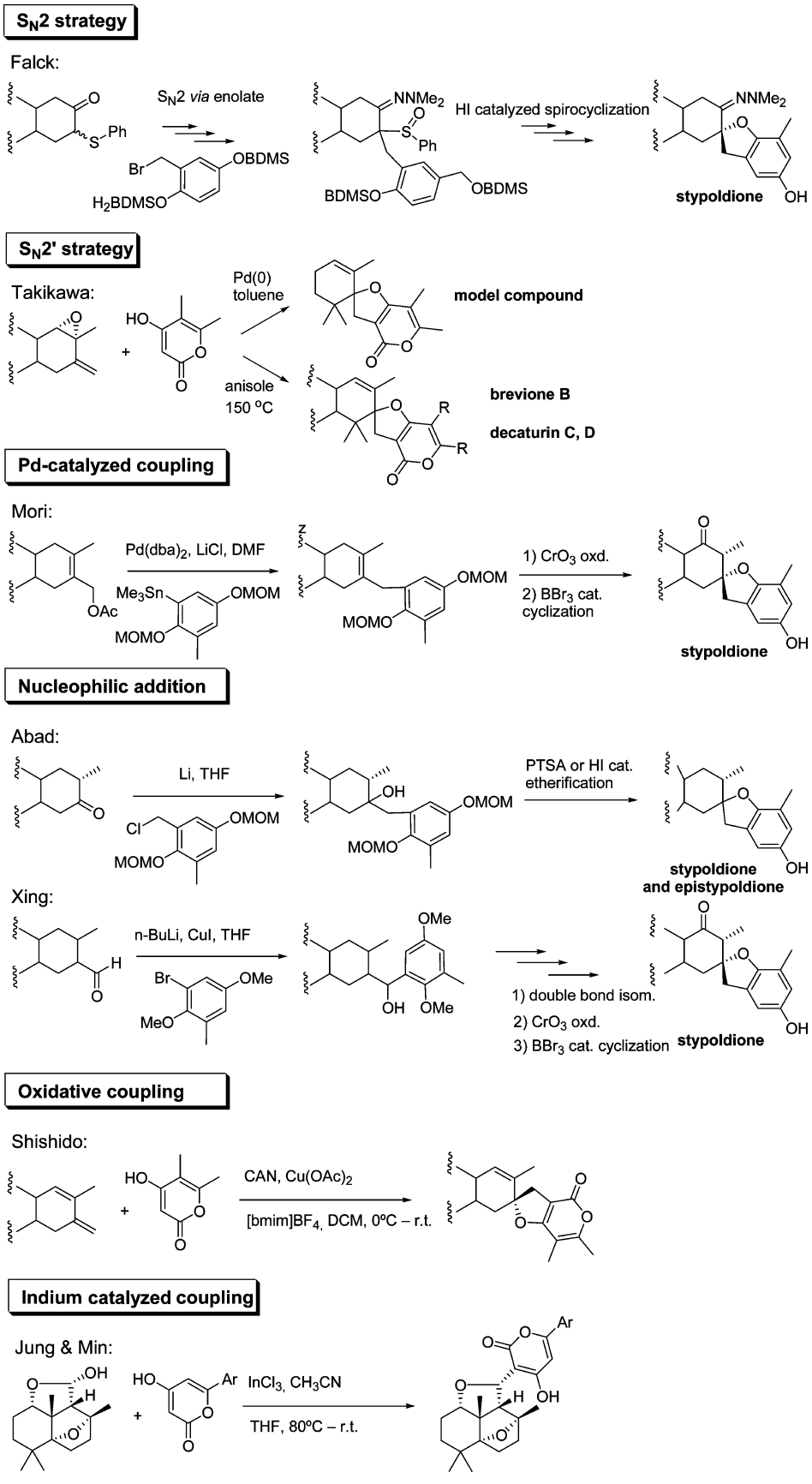
Scheme 11. Coupling between Sesquiterpenic or Diterpenic Moiety and Pyrone Ring



regardless of the substituents in the hemiketal ring (substituted aromatic rings, methyl, ethyl, isopropyl, *tert*-butyl, allyl), and that the acetyl esters can be converted into ketals with retention of the activity as long as the C7-OH group is esterified. It

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therefore seems that it is not only lipophilia that plays a role in this series but also the presence of hydrophobic areas in certain parts of the molecule that match with the active pocket of the enzyme. Furthermore, the presence of a hydrophobic area in the β face of the ring A and/or the ketal ring seems to be important to improve the activity as the aromatic acetal derivatives of substituted benzaldehydes are the most active compounds.[60]

(6) Esterification of the four hydroxyl groups of pyripyropene A led to the following types of esters (52 derivatives tested in total):

(a) Pr, *n*Bu, *n*Val, *i*Bu at C1, C7, C11; C13 free, and all hydroxyl groups free (4). **The compound with all hydroxyl groups free was almost inactive**, whereas the triacyl derivatives were at least 1 order of magnitude less active than pyripyropene A.[61]

(b) Substitution with a longer acyl group at C11 (Ac, *n*Pr, *n*Bu, *n*Val, *i*Bu) or C-13 (Ac, Pr, *n*Bu, *i*Bu) while the other hydroxyls are acetylated resulted in diminution of the activity. **Substituent at C-11 should not be bulky and C-13 hydroxl group should be free.**

(c) **Substitution at the C-7 hydroxyl group is crucial for the activity.**

(7) Surprisingly, arisugacins and pyripyropenes are closely structurally related compounds with totally different biological activities. While pyripyropenes are acyl-CoA:cholesterol transferase (ACAT) inhibitors, arisugacins are acetylcholinesterase (AChE) inhibitors. The main structural differences arise from the aromatic ring substituent attached to the pyrone moiety (pyridine in pyripyropenes, phenyl for arisugacins). While pyripyropene A is available at gram scale, arisugacins can be obtained only in small amounts. Thus, pyripyropene A was converted into a mixed pyripyropene/arisugacin-like compound by removing and replacing the pyridine ring by a substituted phenyl or a different pyridyl ring. The new compounds did not show significant AChE activity, with the exception of the 4-pyridyl derivative, and marginal AChE activities were found for "pyripyropenes" bearing an arisugacin-like phenyl ring. Despite the low activities, it was shown that pyripyropenes can be converted into AChE inhibitors.[62]

(8) Conversely, replacement of the pyridyl by an aryl group in pyripyropene resulted in ca. 100-fold loss of the ACAT activity, thus showing the importance of this moiety for the activity.[63]

4.5. Coupling Strategies

Coupling between the sesquiterpenic or diterpenic moiety and the pyrone ring is achieved through three main strategies that involve metal-catalyzed or S_N2 reactions (Scheme 11).

Metal-catalyzed strategies have been tried unsuccessfully with palladium for breviones and decaturins,[40−42] while the palladium-catalyzed Stille coupling reaction of arylstannanes has been used to achieve the synthesis of stypoldiones.[32,33] A strategy involving S_N2' nucleophilic additions to epoxides was used by Takikawa et al.[40,41] to access brevione B. Surprisingly, the Pd(0)-catalyzed S_N2' coupling reaction worked well with the simplified model compound, but steric demands led to failure when the brevione precursor was treated under the same conditions, with the reaction giving a β-enone at ring C as a consequence of the hydride β-elimination of the π-allylpalladium complex.[41] The conversion was successfully achieved and the reaction proceeded smoothly under thermal conditions without addition of Pd(0) or Lewis acid or base, and the best results were obtained with anisole as solvent. The same procedure was successfully used to achieve the first enantioselective synthesis of decaturin D.[42] In both cases the use of anisole as solvent gave the best yields, followed by xylene. The use of solvents such as pyridine, diphenyl ether, chlorobenzene, or nitrobenzene yielded only small amounts or traces of the desired furospiranic compound, thus illustrating the importance of solvent effects in this process.

On the other hand, strategies such as benzyllithium nucleophilic additions to carbonyl groups have been used in the synthesis of stypoldione.[36,64] Similar strategies, but using organocopper aryl complexes and an aldehyde, were used by Xing and Demuth[37] in the synthesis of stypoldione (**21**).

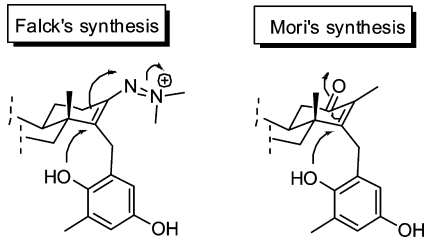
The use of S_N2 reactions is well illustrated by Falck's approach to stypoldione (Scheme 11). In this case the enolate was generated in the diterpenic half of the molecule and reacted with the appropriate benzyl bromide derivative. Mild acidic conditions (HI) led to removal of the sulfoxide moiety from the hydrazine group and this was followed by intramolecular axial attack of the nucleophilic oxygen in the aromatic ring to give spiroketalization.[35]

Finally, the recently published synthesis of brevione C by Shishido and co-workers[44] addresses this question from a different viewpoint (Scheme 11). In this case, the authors' use of oxidative radical coupling with ceric ammonium nitrate (CAN) yielded the desired product in 65% yield as a separable 10:1 diastereomeric mixture. However, the best yields and diastereoselectivities were obtained with a mixture of CAN and $Cu(AcO)_2$ and an ionic liquid ($[bmim]BF_4$)/dichloromethane (DCM) mixture.

The control of the stereochemical pathway toward preparation of the correct enantiomer at the spiranic center was not always totally successful, and a mixture of the two enantiomers was often obtained.

Falck's synthesis rendered only the natural enantiomer, and the stereochemical pathway in this process is governed by the methyl group located close to the benzyl moiety (Scheme 12), which was also the case in Mori's and Xing's approaches to stypoldione.

Scheme 12. Stereoselective Spirocyclization to Stypoldiones



The approach of Abad et al.[64] led to a mixture of enantiomeric precursors of stypoldione and *epi*-stypoldione, which in turn provided the corresponding target compounds when treated under acidic conditions (Scheme 11). Finally, the published syntheses of brevione B and decaturin D also led to mixtures of the two enantiomers.

As can be seen, the strategies used for spirocyclization are not particularly abundant, but this is also true for the synthetic procedures published to date for meroditerpenes with a furospiranic ring. More work is needed to open up new enantioselective synthetic routes toward these interesting and promising compounds.

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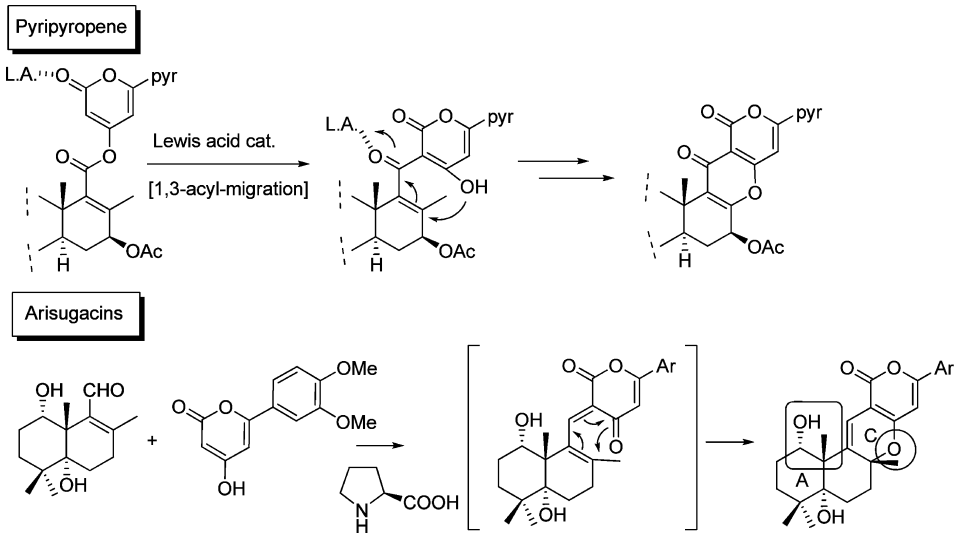
Scheme 13. Synthesis of γ-Pyrone Ring in Pyripyropenes and Arisugacins



Regarding the synthesis of the γ-pyrone ring in pyripyropenes, Sunazuka and co-workers[65] envisaged a direct linkage between the nicotin-hydroxy-α-pyrone subunit and the sesquiterpenic moiety in trifluoroacetic or Lewis acid ($AlCl_3$) (Scheme 13). The mechanism is proposed to proceed through an O-acylation, followed by in situ 1,3-acyl-migration and 1,4-cyclization. This approach differs from that used later by the same author to gain access to arisugacins.[51] In this case a Knoevenagel-type condensation was carried out between the α,β-unsaturated aldehyde and the α-pyrone ring, which carried the appropriate substituents in the aromatic ring, in the presence of L-proline. Elimination of the proline moiety and electrocyclic ring closure led to the appropriate precursor of arisugacin A. However, epoxidation at the double bond failed and no reaction occurred, a finding attributed to the steric hindrance of the axial face neighboring α-hydroxyl and β-methyl groups. Consequently, the authors changed the stereochemistry of the hydroxyl group to β, and epoxidation then took place. Reduction of the hydroxyl group in the appropriate enantiomer by use of Et_3SiH was followed by functionalization at ring A to render arisugacin A. The same strategy was used to obtain arisugacin E (Scheme 13).

Another strategy used to access arisugacin A involved an indium-catalyzed coupling between a lactol and the pyrone ring, which was thought to proceed via an oxocarbonium intermediate.[66] Unfortunately, all attempts to cleave the lactol ring failed, and the synthesis of arisugacin A could not be completed.

5. CONCLUSIONS

Meroterpenes are a family of compounds from mixed biogenetic pathways and they have great potential as drug leads. The biological activity of pyripyropenes and their potential as ACAT and AChE inhibitors make their synthesis attractive, and this also highlights the desirability of exploring the potential of other members of the family such as breviones. The complexity of these molecules and their synthesis has led to the development of useful synthetic tools, especially for coupling of the diterpenic and polyketide (pyrone) rings and the spirocycle. From the biogenetic point of view, it seems that sesquiterpenic and diterpenic meroterpenes could have similar biogenetic pathways. Accordingly, both merosesquiterpenes and meroditerpenes could be included in one single class of natural products.

In summary, meroterpenes with a spirocycle and a pyrone ring are attractive targets for synthesis and biological evaluation, especially regarding their ACAT and AchE potential.

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Notes

The authors declare no competing financial interest.

Biographies

Francisco A. Macías was born in La Línea de la Concepción, Cádiz, Spain (1956). He was a Visiting Associate Professor in the Department of Chemistry at Louisiana State University, Baton Rouge, LA, for five years, where he established a strong collaboration program with Professor Nikolaus H. Fischer in the field of Allelopathy. Presently, he is Professor of Organic Chemistry at the University of Cadiz, Spain, since 2000. He has been honored with the 1999 Rhône-Poulenc Rorer Award, Amsterdam, The Netherlands, from the Phytochemical Society of Europe (PSE), and the 2011 Molish Award, Guangzhou, China, from the International Allelopathy Society (IAS). Their general philosophy is to learn from Nature: "If we know the way that plants made possible their inter- and intra-specific relationship within a specific ecosystem, we can mimic certain processes and think in natural

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applications as natural herbicides, natural insecticides, etc." His research interest are related to different aspects of allelopathy including higher plants and microorganisms, studies on natural and modified ecosystems, and development of new methodologies for allelopathic studies including mode of action. He heads the Cadiz Allelopathy Group, which is a pioneer in Europe in allelopathic studies from the organic chemistry viewpoint with a multidisciplinary structure. During this period, his group has isolated, identified, characterized or synthesized, and tested the bioactivity of more than 1600 potential allelochemicals and derivatives belonging to a wide range of chemical families as aglycons and/or glycosides (simple phenolics; coumarins; flavonoids; lignans; terpenoids: mono-, sesqui-, di-, spirodi-, mero- and triterpenoids; steroids; benzoxazinoids; and others) that allow the corresponding structure–activity relationship studies (SAR) to be carried out. He is an author of 10 international patents. His publications exceed 210, with book chapters; he has coedited two books on recent advances in allelopathy, supervised 22 doctoral theses, and delivered more than 200 lectures.

Ceferino Carrera (Torrecera, Spain, 1974) obtained his B.Sc. and M.Sc. in chemistry at the University of Cadiz, Spain, where he also received his Ph.D. in 2009, supervised by Professor Francisco A. Macías and Professor Juan Carlos G. Galindo. His dissertation focused on the synthesis of the diterpenic moiety of breviones. His research, performed in the Cádiz Allelopathy Group, is related to synthesis, bioactivity evaluation, and structure–activity relationship studies on allelochemicals. Since 2010 he has worked as an assistant researcher of The Agrifood Campus of International Excellence at the Andalusian Centre of Viniculture Research. His current research focuses on agrifood chemistry and natural products.

Juan Carlos G. Galindo (Ibarra, Ecuador, 1965) is Associate Professor of Organic Chemistry at the University of Cadiz, Spain, since 2001. He finished his studies in chemistry at the University of Cadiz in 1988, where he also earned his Ph.D. in 1993 with a thesis in allelopathy; his was the first Ph.D. thesis in this subject presented in Spain. He was a postdoctoral visiting professor at the NPURU USDA-ARS facilities at the University of Mississippi, Oxford, MS, in 1997, working on mode of action of allelopathic sesquiterpene lactones. His research interests cover all aspects of chemical ecology, with special emphasis on allelopathy. He has conducted two research campaigns in Antactica, working on the chemistry of lichens and research projects on isolation, chemical characterization, and synthesis of allelopathic agents, structure–activity relationship studies, and bioassays. He has published more than 50 papers and book chapters, coedited two books in the series Recent Advances in Allelopathy, delivered more than 80 presentations (posters and invited and plenary talks), and supervised three Ph.D. theses. He was Treasurer of the International Allelopathic Society for 1994–1999. At present he is a regional representative at the Phytochemical Society of Europe (PSE).

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