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Sesquiterpenyl indoles†

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The natural product sesquiterpenyl indoles are structural hybrids from farnesyl pyrophosphate and tryptophan or its precursors, often with unusual and complex structural features, many of them with interesting biological activities. In this review the compounds of this class known until now are classified, a biosynthetic approach of each group is proposed and a review of the synthesis or synthetic approaches is communicated.

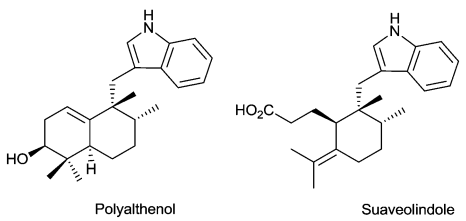
1 Introduction

Alkaloids have been a tempting object of study for researchers due to their multiple biological properties; some of which have been known and used by mankind for medical purposes.[1] A particular and vast group of alkaloids are indole alkaloids, which bears a structural moiety of indole,[2] containing more than 4100 known different compounds, it is one of the largest classes of alkaloids.[3]

Terpenoids are natural products present in nearly all the life forms that have a great number of structural or functional activities.[4] These compounds are the biggest and most diverse natural products group, with more than 65 000 known representatives to date.[5] From several years ago annual revisions of newly isolated terpenoids: monoterpenes,[6] sesquiterpenes,[7] diterpenes,[8] sesterterpenes[9] terrestrial or marine origen[10] and triterpenes[11] have been carried out.

Terpenyl indoles are hybrid natural products from indole alkaloids and terpenoids,[12] extensively studied due to their challenging scaffold structures, complicated frameworks and because they possess significant physiological activities.[13,14] Some of them have even been used in medicine since ancient times, long before their structure was known.[1b]

Among terpenyl indoles, sesquiterpenyl indoles are a small group of natural compounds, though very interesting due to their molecular complexity and wide variety of biological properties, such as antibacterial,[15] anticancer or even anti-HIV.[16] The first known example of a sesquiterpenyl indole compound, is the natural product polyalthenol,[17] isolated in 1976. Since then, several other sesquiterpenyl indoles have been found, mainly from African medicinal plants, especially from *Greenwayodendron suaveolens* (*Polyalthia oliveri* Engl. & Diels). Most of these compounds have been isolated and fully characterised in the decade of the eighties. However, their biological properties remained unknown until two decades later, when



Polyalthenol Suaveolindole

Fig. 1

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† This review is dedicated to Prof. J. G. Urones for his dedication as a teacher, for his guidance and friendship over many years.

antibiotic properties of suaveolindole[18] and polyalthenol[19] (Fig. 1) were reported in 2005 and 2010 respectively.

These results have revived interest in these compounds in recent years, prompting research groups to further investigation of the biological properties, synthesis, biogenesis and sources of isolation of these compounds, so in recent years, sesquiterpenyl indoles have been found not only in plants, but also as secondary metabolites of fungi and bacteria,[15,20] especially from endophytes[16] associated with mangroves. In fact, nearly all of the sesquiterpenyl indoles isolated from mangrove endophytes show antibiotic properties.[20]

2 Classification

Until now there has been no classification of the known sesquiterpenyl indoles. Due to the interesting biological properties, the novelty and structural diversity that some of them show, we considered it to be very interesting to establish a classification of these compounds.

Isidro Sánchez Marcos received his BSc in Chemistry at the University of Salamanca in 1976 and obtained his PhD from the same University in 1979 under the supervision of Professors J. de Pascual Teresa and J. G. Urones. He was promoted to Lecturer in 1986 and to Full Professor in 2010. The area in which he has developed his research is natural products. He has isolated and characterized more than two hundred compounds and described six new carbon skeletons, in more than 170 publications. Now he is interested in the synthesis of bioactive natural products and the synthesis of structural and functional hybrid compounds of antitumoural lipidic ethers and terpenolides.

Rosalina Fernández-Moro gained her PhD in Organic Chemistry, Universidad de Salamanca in 1986 under the supervision of Professor J. G. Urones and Dr P. Basabe. Then she carried out her postdoctoral research with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine of London (1989–1991), obtaining the D.I.C. in September 1991. Currently she is Lecturer in Organic Chemistry at the University of Salamanca, where she is researching the synthesis of bioactive compounds, especially indole alkaloids and organocatalysis.

Isabel Costales received her BSc in Chemistry in 2007 at the University of Salamanca, where she completed her PhD in Organic Chemistry under the supervision of Professors I. S. Marcos and R. F. Moro in 2013. Her research interests are focused on the synthesis of biologically active natural products, especially indole alkaloids. Currently she works in the biotechnology laboratory of a pharmaceutical company.

Dr Pilar Basabe Barcala is Full Professor of Organic Chemistry at the University of Salamanca and obtained her PhD at the same University in 1973 under the supervision of Professors J. de Pascual Teresa and J. G. Urones. She has worked in the field of natural product chemistry and has over 160 publications in the area.

David Diez received his BSc in Chemistry at the University of Salamanca in 1982. In 1986 he completed his PhD at the same University under the supervision of Professors J. G. Urones and I. S. Marcos. Then, he spent a postdoctoral stay (1988–1990, British Council Fellowship) with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine (London) DIC 1991. He became Associate Professor in 1991 at the University of Salamanca and Full Professor in 2008 at the same University. He is co-author of more than 150 papers and he acts as referee for international scientific journals. His current research interests are focused in the transformation of natural products into biologically active compounds, the chemistry of cyclopropanes, sulfones, tetrahydropyrans, chiral amides and recently in organocatalysis.

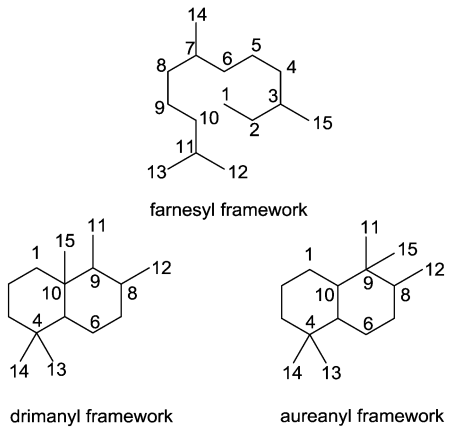


Fig. 2

Herein we show a review of the 43 natural sesquiterpenyl indoles isolated and characterised up to date. The following collection comprises a list of structures, each of which is accompanied by its trivial name and is numbered, along with tables that include the source of isolation, biological activities and the literature. We have classified them attending to their sesquiterpene skeleton, (Fig. 2) and the way this moiety joins to the indole residue.

In this manner the published structures can be classified into three main groups: farnesyl, drimanyl and aureanyl[21] indoles. All the sesquiterpenyl indoles presented in the review that have the terpene part cyclic are drimane or rearranged drimane skeleton, aureane, (Fig. 2) skeleton that arises from 1,2 rearrangements of the drimane skeleton. We proposed the name aureane for the rearranged skeleton considering aureol as one of the first sesquiterpenyl hybrid compound isolated.[22]

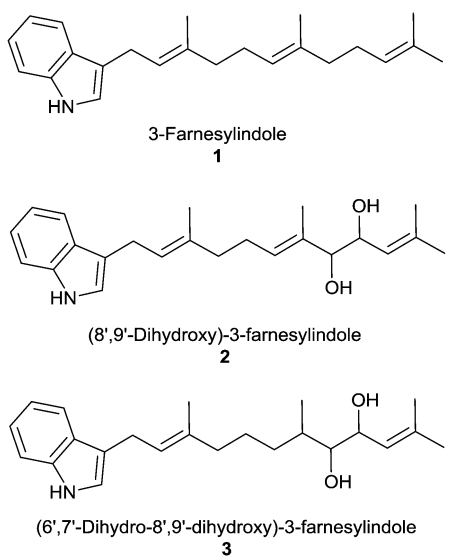


Fig. 3

2.1 Farnesyl indoles

The farnesyl indole group (Fig. 3) is constituted only by three compounds **1**, **2**, **3** isolated from *Uvaria pandensis*, a plant native of Tanzania, of the Annonaceae family. (Table 1)

2.2 Drimanyl indoles

Drimanyl indoles form the most numerous group of sesquiterpenyl indoles. (Table 2) They can be classified as: drimanyl indole simple, pentacyclic drimanyl indoles and diketopiperazinic drimanyl indoles.

2.2.1 Simple drimanyl indole. Only one is known, the indosespene **4**[20] (Fig. 4).

2.2.2 Pentacyclic drimanyl indoles. They are the most numerous group. Their structures can be distinguished by the connection between the drimane and indole fragments. In this manner, several subdivisions can be established:

- driman[11,8-*b*]indoles: **5** and **6** (Fig. 5)
- driman[8,11-*a*]indoles: **7**, **8**, **9**, **10** and **11** (Fig. 6)
- driman[9,12-*b*]indoles: **12**, **13**, **14**, **15** and **16** (Fig. 7)
- driman[12,9-*b*]indoles: **17** (Fig. 8)
- driman[12,11-*b*]indoles: **18**, **19**, **20**, **21**, **22**, **23**, **24**, **25** and **26** (Fig. 9).

Recently, several dimer compounds of the driman[12,11-*b*] indoles, dixiamycines A **25** and B **26**[15] (Fig. 9), have been isolated and characterised. These are the only natural atropoisomers known to possess axial chirality due to a N–N bond, and show more potent antitumoural and antibacterial activities than the corresponding monomers. Compounds belonging to this group can be considered carbazole derivative alkaloids, a very important group of anticancer agents, topoisomerase I/II, telomerase and quinase inhibitors.[23] Due to these very interesting biological properties, many synthetic strategies have been developed[24] for the synthesis of unnatural carbazoles and derivatives.

It is necessary to point out that the group of driman[8,11-*a*] indoles has been the object of careful consideration. The first compounds of this group, named polyavolensin, polyavolensinol and poliavolensinone,[25] were isolated in 1981 from the bark of *Greenwayodendron suaveolens* (previously known as *Polyalthia suaveolens* Engl. & Diels) collected in Nigeria, and their structure and stereochemistry were published based on their NMR data. Later on, in 1982,[26] the same

Table 1 Farnesyl indoles

Farnesyl indoles	Natural source	Activity	References
3-Farnesylindole, **1**	*Uvaria pandensis* Verdc		30
(8′,9′-Dihydroxy)-3-farnesylindole, **2**	*U. pandensis* Verdc		31
(6′,7′-Dihydro-8′,9′-dihydroxy)-3-farnesylindole, **3**	*U. pandensis* Verdc		31

Table 2 Drimanyl indoles

Drimanyl indoles	Natural source	Activity	References
3-Drimanyl indole			
Indosespene, **4**	*Streptomyces* sp. HKI0595	Antimicrobiane	20
Driman[11, 8-*b*]indoles			
Polyveoline, **5**	*Greenwayodendron suaveolens*	Antiparasitic	32, 33
N-Acetylpolyveoline, **6**	*G. suaveolens*	Antiparasitic	33
Driman[8,11-*a*]indoles			
Greenwayodendrin-3-one, **7**	*Greenwayodendron suaveolens*	Antiparasitic	25, 26, 27 and 33
3β-Acetoxy-greenwayodendrine, **8**	*G.* suaveolens	Antiparasitic	25, 26, 27, 29 and 33
3α-Hydroxy-greenwayodendrine, **9**	*G.* suaveolens		27
3β-Hydroxy-greenwayodendrine, **10**	*G. suaveolens*		27
Polysin, **11**	*G. suaveolens*	Antiparasitic	33
Driman[9,12-*b*]indoles			
Lecanindole A, **12**	*Verticillium lecanii*		34
Lecanindole B, **13**	*V. lecanii*		34
Lecanindole C, **14**	*V. lecanii*		34
Lecanindole D, **15**	*V. lecanii*	Progesterone receptor agonist	34
Sespendole, **16**	*Pseudobotrytis terrestris* FKA-25	Cholesterol acetyl transferase and cholesteryl ester synthesis inhibitor	35, 36 and 37
Driman[12,9-*b*]indoles			
Polyavolinamide, **17**	*Greenwayodendron suaveolens*		38
Driman[12,11-*b*]indoles			
Xiamycin A, **18**	*Streptomyces* sp. GT2002/1503, sp. HKI0595, sp. SCSIO 02999	Anti-HIV, antitumoural, antiviric, antimicrobial	15, 16, 20 and 39
Xiamycin A methyl ester, **19**	*Streptomyces* sp. GT2002/1503	Antitumoural	16
Xiamycin B, **20**	*Streptomyces* sp. HKI0595		20
Chloroxiamycin A, **21**	*Streptomyces* sp. SCSIO 02999	Antitumoural, antibacterial	15
Oridamycin A, **22**	*Streptomyces* sp. KS84	Antibiotic	40
Oridamycin B, **23**	*Streptomyces* sp. K 584	Antibiotic	40
Oxiamycin, **24**	*Streptomyces* sp. SCSIO 02999	Antitumoural, antibacterial	15, 39
Dixiamycin A, **25**	*Streptomyces* sp. SCSIO 02999	Antitumoural, antibacterial	15
Dixiamycin B, **26**	*Streptomyces* sp. SCSIO 02999	Antitumoural, antibacterial	15
Diketopiperazinic drimanyl indoles			
Drimentine A, **27**	*Actyniomycetes* MST-8561	Antibiotic, antifungic, anticancer	41
Drimentine B, **28**	*Actyniomycetes* MST-8561	Antibiotic, antifungic, anticancer	41
Drimentine C, **29**	*Actyniomycetes* MST-8561	Antibiotic, antifungic, anticancer	41
Drimentine F, **30**	*Streptomyces* sp. CHQ-64		42
Drimentine G, **31**	*Streptomyces* sp. CHQ-64	Anticancer	42
Drimentine H, **32**	*Streptomyces* sp. CHQ-64		28
Drimentine D, **33**	*Actyniomycetes* MST-8561	Antibiotic, antifungic, anticancer	41
Drimentine E, **34**	*Actyniomycetes* MST-8561	Antibiotic, antifungic, anticancer	41
Indotertine A, **35**	*Streptomyces* sp. CHQ-64		42
Indotertine B, **36**	*Streptomyces* sp. CHQ-64	Anticancer	28, 41

research group published a revised structure of polyavolensin, determined by X-Ray crystallography. In the meantime, another research group reported the isolation of four new sesquiterpenyl indoles from the bark of a Congolese *Greenwayodendron suaveolens* (Engl. & Diels) Verdc. (Annonaceae) that were named greenwayodendrin-3-one **7**, 3β-acetoxy-greenwayodendrine **8**, 3α-hydroxy-greenwayodendrine **9**, and 3β-hydroxy-greenwayodendrine **10**,[27] whose structure and stereochemistry were determined by X-ray crystallography. After comparing the structures of these compounds we have found out that polyavolensin and 3β-acetoxy-greenwayodendrine **8** are actually the same compound, and this happens as well with polyavolensinol and 3β-hydroxy-greenwayodendrine **10**, and with polyavolensinone and greenwayodendrin-3-one **7**. In this work we have decided to keep the names given by Waterman's group,[27] as they suit better the modern name of the parental plant.

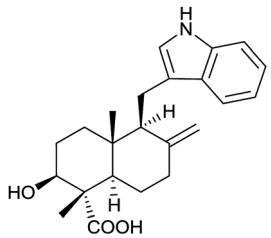
2.2.3 Diketopiperazinic drimanyl indoles. They are a group characterised by the presence of a complete tryptophan unit bonded to a second amino acid, such as valine, leucine or proline, forming a diketopiperazine unit, **27–36** (Fig. 10). Very recently indotertine B **36** has been isolated, with two rotamers characterised **36a** and **36b** about the N–C (O) bond in a 2 : 1 ratio.[28]

2.3 Aureanyl indoles

Aureanyl indoles (Fig. 11) can be divided into three different groups: 3-aureanyl indoles, 2-aureanyl indole and pentacyclic aureanyl indole. (Table 3)

2.3.1 3-Aureanyl indoles (37–41). This group includes the first sesquiterpenyl indole known polyalthenol **37**,[17,19] its isomer isopolyalthenol **38**[29] and the ring A seco-derivatives of the sesquiterpene fragment, suaveolindole **39** and derivatives **40** and **41**.[18,19] (Fig. 11)

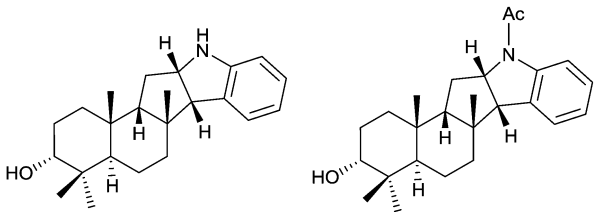
3-Drimanyl indole



Indosespene
4

Fig. 4

Driman[11,8-*b*]indoles

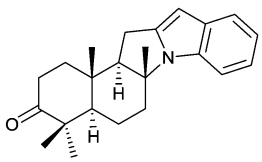


Polyveoline
5

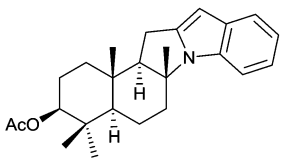
N-Acetylpolyveoline
6

Fig. 5

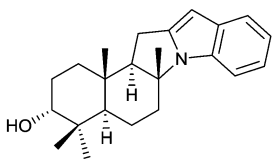
Driman[8,11-*a*]indoles



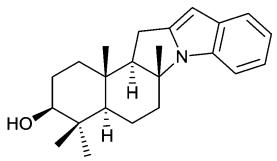
Greenwayodendrin-3-one
(Polyavolensinone)
7



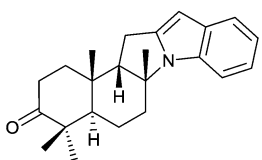
3β-Acetoxy-greenwayodendrine
(Polyavolensin)
8



3α-Hydroxy-greenwayodendrine
9



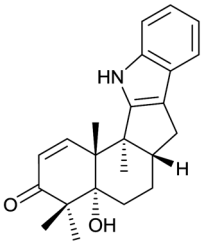
3β-Hydroxy-greenwayodendrine
(Polyavolensinol)
10



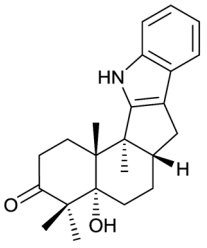
Polysin
11

Fig. 6

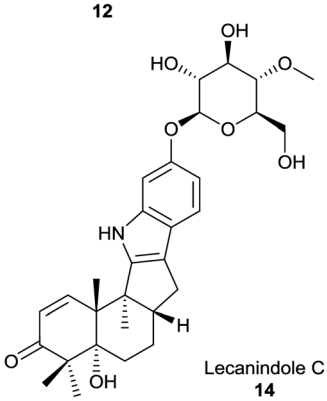
Driman[9,12-*b*]indoles



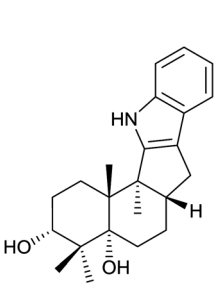
Lecanindole A
12



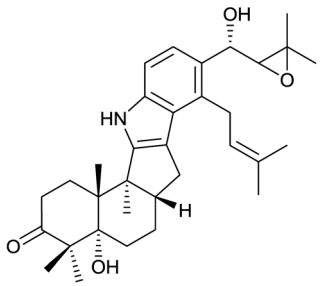
Lecanindole B
13



Lecanindole C
14



Lecanindole D
15



Sespendole
16

Fig. 7

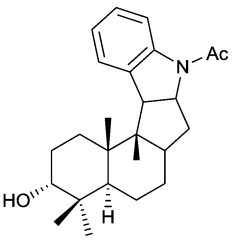
2.3.2 2-Aureanyl indole. Neopolyalthenol **42**, is the only one known.[29] (Fig. 11)

2.3.3 Pentacyclic aureanyl indole. Recently this has been isolated and characterized as the only one pentacyclic aureanyl indole known, until now, that show a new carbon skeleton corresponding to aurean[1,11-*b*]indole and known as pentacyclindole **43**.[19](Fig. 11)

3 Biosynthesis

We now present a biogenetic proposal for all the sesquiterpenyl indoles previously mentioned. Basically, all sesquiterpenyl indoles have the same first biogenetic step that consists of the condensation of an indole moiety and a terpene moiety that, according to isotopic marking and feeding experiments, comes from the mevalonate or non-mevalonate pathway[44,45] to form the terpenyl indole precursor skeleton. Thus, a general biosynthetic scheme for these compounds is depicted in Scheme 1.

Driman[12,9-*b*]indole



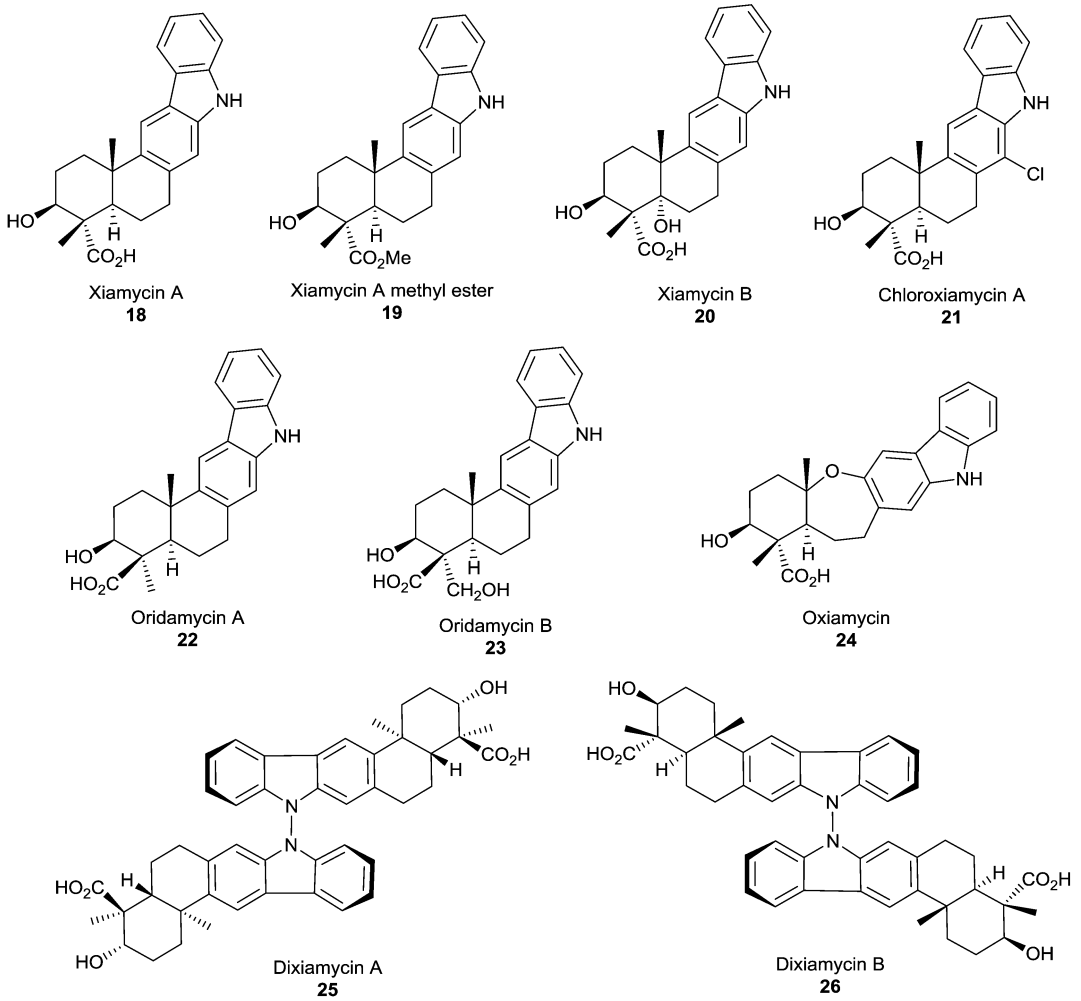
Polyavolinamide
17

Fig. 8

We take as a basis of our proposal the interesting study[45] that Oikawa and co-workers have recently published, in which the biosynthetic route that leads to indole diterpenes is thoroughly explained on a genetic basis, and exemplified with the description of the biogenesis of the natural product paxilline, a diterpene indole tremorgenic mycotoxin. In the same manner Zhang and co-workers recently described the identification and characterisation of eighteen genes involved in the biosynthesis of xiamycin A **18** and oxiamycin **24**.[39]

Herein, the biogenesis of sesquiterpenyl indoles is analogous to the biogenetic pathway of paxilline and xiamycin A **18**, in which several types of gene clusters are involved: a prenyltransferase attaches the terpenyl fragment, farnesyl pyrophosphate (FPP), to indole-3-glycerol phosphate,[46] (Scheme 1) and then a sequence of oxidations and cyclisations promoted by oxygenases and transformant enzymes lead to a wide variety of sesquiterpene indole scaffolds. These cyclisations can occur with different regiochemistries.[47] The structural diversity and stereochemistry of the indole-terpenoid scaffolds resulting would depend on the conformation that the terpene unit adopts before cyclisation.[48] Isotopic marking experiments on diterpenyl indoles, demonstrated that indole-3-glycerol phosphate is the preferred substrate for the enzyme, and not the tryptophan one.[46] For the biosynthesis of the different sesquiterpenyl indoles three pathways A, B and C can be distinguished (Scheme 1).

Driman[12,11-*b*]indoles



Xiamycin A
18

Xiamycin A methyl ester
19

Xiamycin B
20

Chloroxiamycin A
21

Oridamycin A
22

Oridamycin B
23

Oxiamycin
24

Dixiamycin A
25

Dixiamycin B
26

Fig. 9

Diketopiperazinic drimanyl indoles

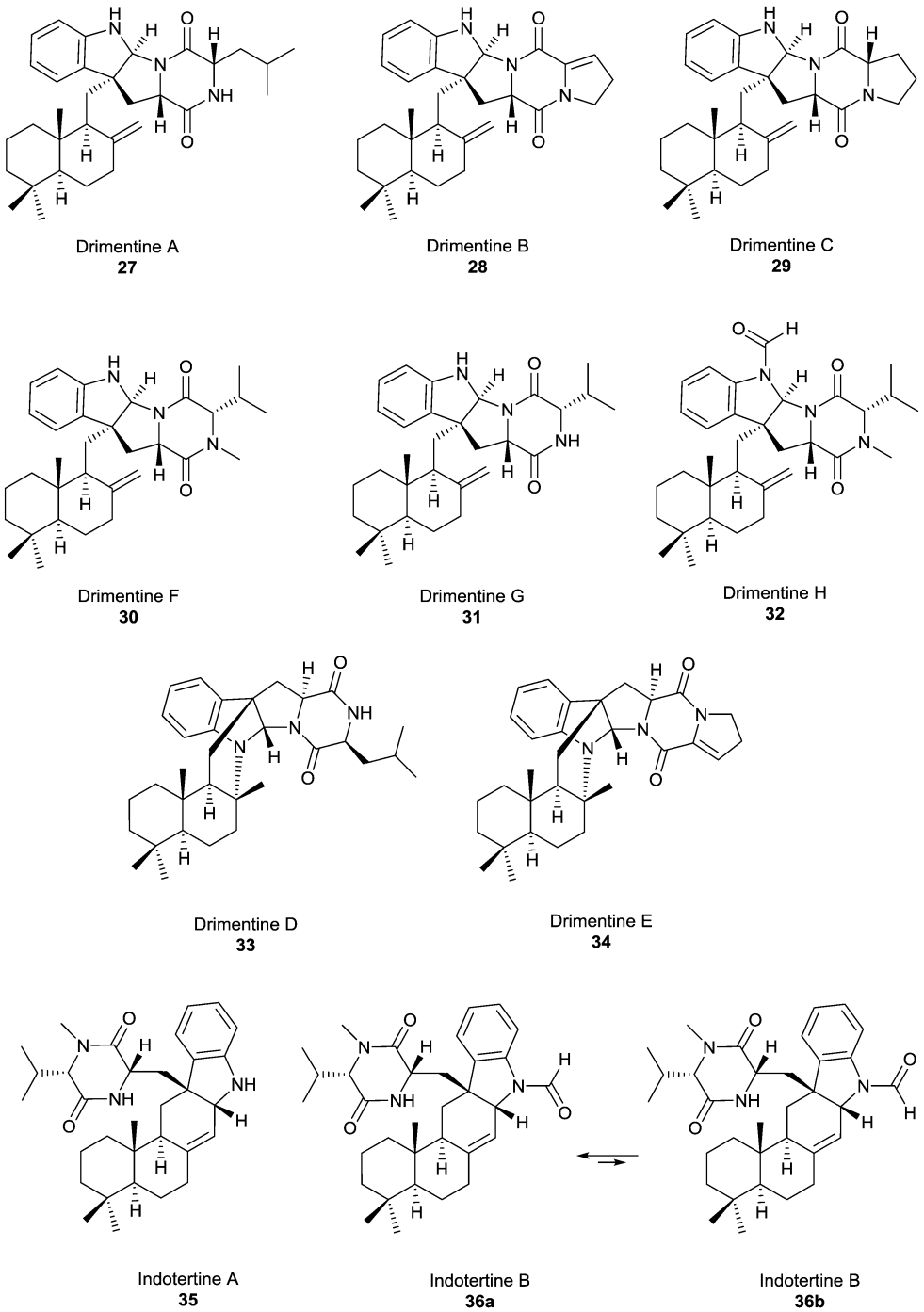


Fig. 10

In pathway A a prenyl transferase inserts a farnesyl diphosphate unit at the C3 position of an indole 3-glycerol phosphate giving an intermediate. Elimination of glyceraldehyde 3-phosphate takes place, leading to a 3-farnesyl indole **I** that can undergo oxidation and cyclisation to afford different sesquiterpenyl indoles, such as 3-drimanyl indole (indosespene **4**), driman[12,11-*b*]indoles **18–26** and driman[9,12-*b*]indoles **12–16**, 3-aureanyl indoles **37–41** and aurean[1,11-*b*]indole (pentacyclindole **43**). In pathway B a different prenyl transferase directly attaches the FPP fragment to the C2 position;[49,50] then a hydride shift from C2 to C3 and elimination of glyceraldehyde 3-phosphate affords the 2-farnesyl indole derivative **II**, an oxidation and cyclisation sequence

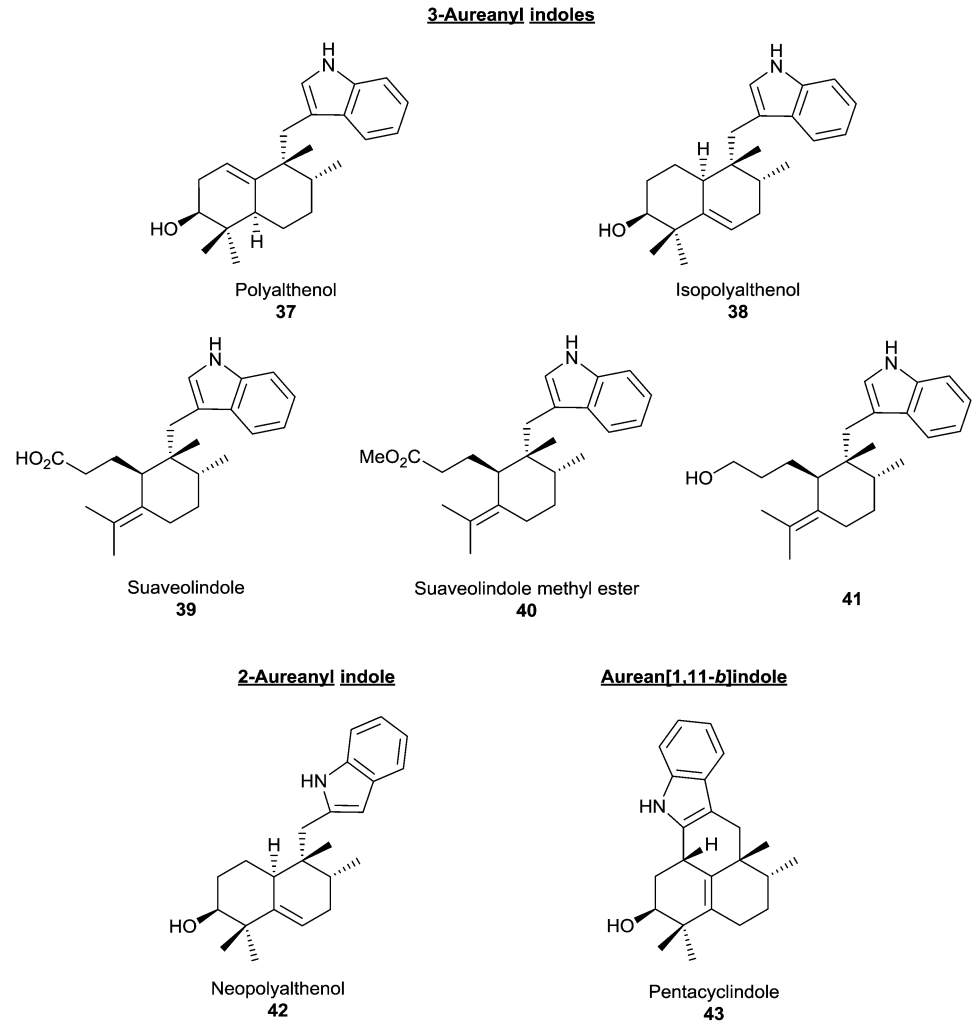
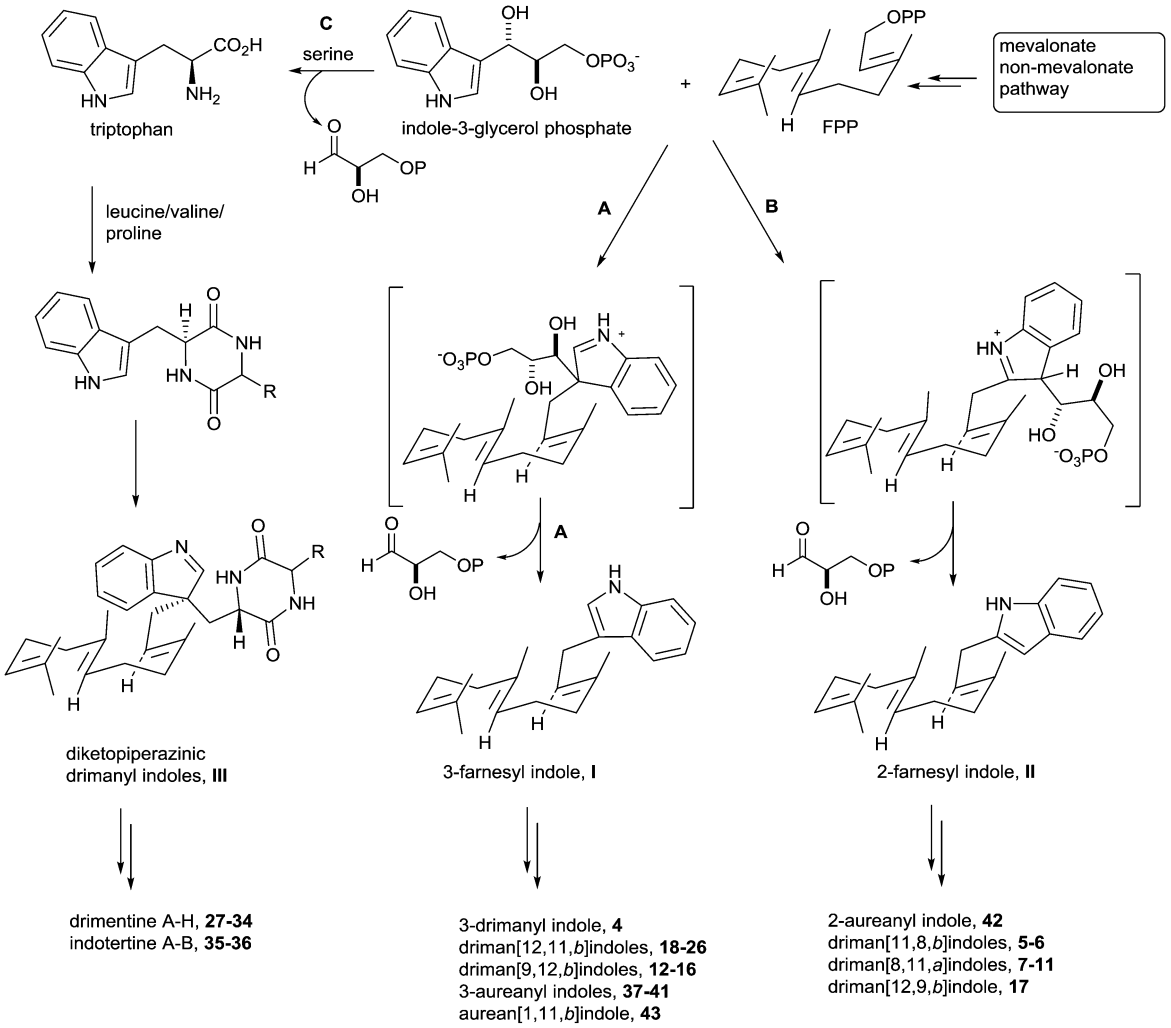


Fig. 11

Table 3 Aureanyl indoles

Aureanyl indoles	Natural source	Activity	References
3-Aureanyl indoles			
Polyalthenol, **37**	*Polyalthia oliveri* Engl. & Diels *Greenwayodendron oliveri* Verdc. *Polyalthia suaveolens*	Antibiotic	17, 19 and 43
Isopolyalthenol, **38**	*Greenwayodendron suaveolens*		29
Suaveolindole, **39**	*G.suaveolens*	Antibiotic	18, 19
Suaveolindole methyl ester, **40**	*G.suaveolens*		19
41	*G.suaveolens*	Antibiotic	19
2-Aureanyl indole			
Neopolyalthenol, **42**	*G. suaveolens*		29
Aurean[1,11-*b*]indole			
Pentacyclindole, **43**	*G. suaveolens*	Antibiotic	19

affords different sesquiterpenyl indoles: 2-aureanyl indole (neopolyalthenol **42**), driman[11,8-*b*]indoles **5–6**, driman[8,11-*a*] indoles **7–11** and driman[12,9-*b*]indole (polyavolinamide **17**). In pathway C an extra amino acid unit is required. Indole 3-glycerol phosphate needs to be converted to tryptophan, then addition of a second unit of an amino acid (proline, valine or leucine) affords the formation of a diketopiperazinic ring. Prenylation at C3 takes place, yielding the diketopiperazinic drimanyl indoles **III**[14] that can undergo oxidation and cyclisation to afford different sesquiterpenyl indoles **27–36.**



Scheme 1

Starting from the main precursors **I**, **II** and **III**, the three biosynthetic pathways will now be commented on in more detail. To avoid numbering confusion, we have kept the drimanyl and aureanyl skeleton numbering as has been already used in section 2.

It is noticeable that, except for the diketopiperazinic drimanyl indoles **27–36** and the 3-farnesyl indoles **1–3**, all the rest present an oxygenated function in C-3 of the sesquiterpenic moiety (C-19 sesquiterpenyl indole). On this basis, we have assumed that biosynthetic pathways A and B, as occurs for paxilline, suffer a series of epoxidation/cyclisation steps.

3.1 Biosynthesis of 3-farnesyl indole derivatives (Pathway A)

Scheme 2 shows the biosynthetic route that leads to 3-farnesyl indole **I** related compounds. Once the acyclic terpenyl precursor **I** is formed, it suffers a selective epoxidation of the terminal double bond[45] to give a terpenyl ω-epoxide, that can adopt two different conformations **44** or **45**.

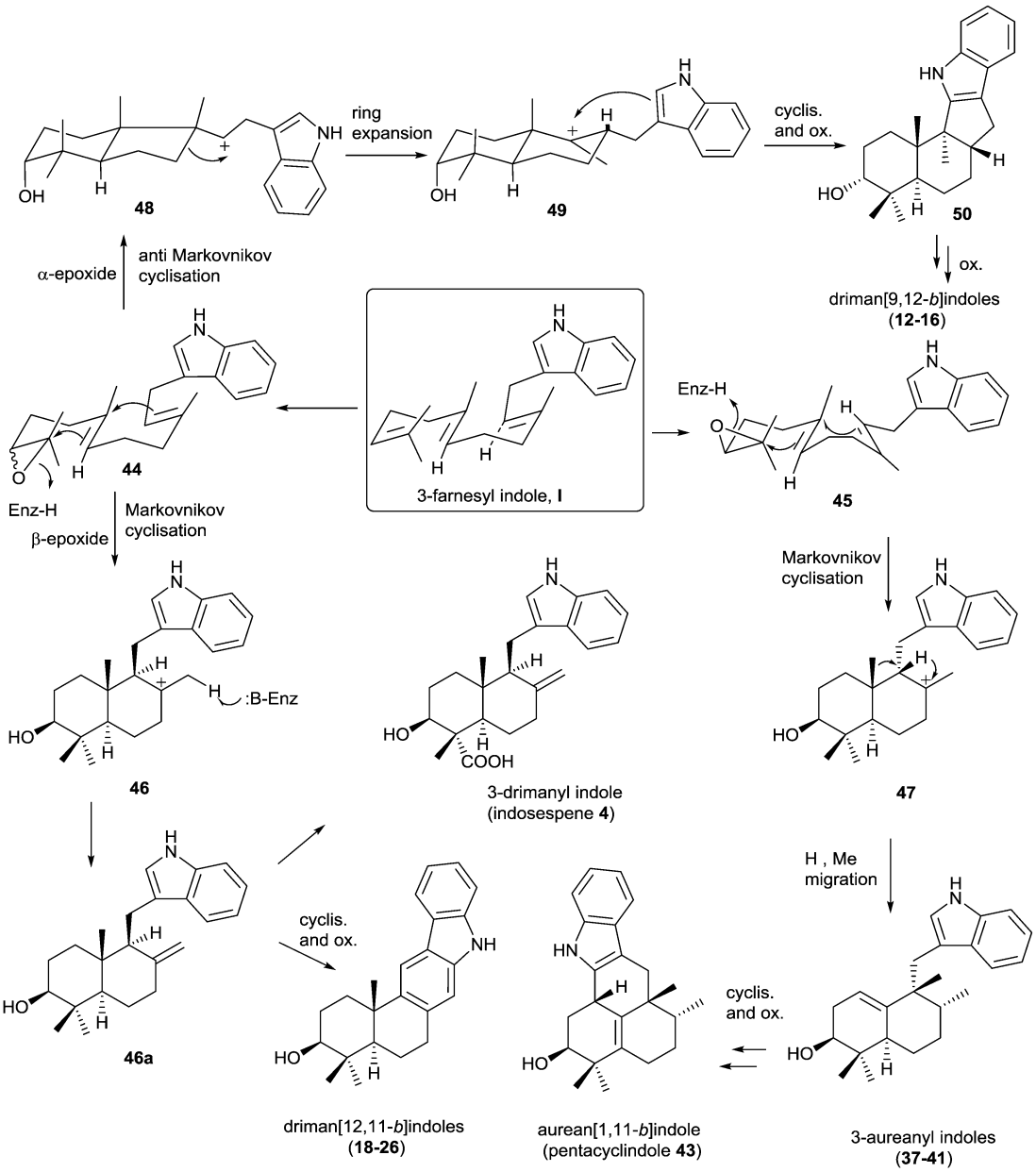
A Markovnikov cyclisation of the terpenyl ω-epoxide when adopting a chair-chair conformation as represented in intermediate **44**, leads to a decalin intermediate **46**. This compound evolves into *exo*-olefin **46a** which would lead to 3-drimanyl indole and by oxidation to indosespene **4**, or by cyclisation with the indole unit to afford driman[12,11-*b*]indoles, and further transformations yield the natural products **18–26.**

It is also possible that the linear ω-epoxide of 3-farnesylindole adopts a chair-boat conformation, as represented by **45**. A Markovnikov cyclisation may afford the decalin intermediate **47** that, after hydrogen and methyl migration, leads to 3-aureanyl indoles **37–41**. Cyclisation and oxidation of the 3-aureanyl indole give the aurean[1,11-*b*]indole (pentacyclindole **43**). To support this, it is worth mentioning that acid catalyzed cyclisation of 3-but-3-enyl indole derivatives[51] have been reported with good yield, affording pentacyclic indole derivatives.[52]

Finally, an anti-Markovnikov cyclisation[46] of the chair-chair ω-epoxifarnesyl indole **44**, gives intermediate **48**, ring expansion leads to **49**, cyclisation with the indole moiety yields **50** and ulterior oxidation produces the driman[9,12-*b*]indoles **12–16.**

3.2 Biosynthesis of 2-farnesyl indole derivatives (Pathway B)

Analogously to pathway A, 2-farnesyl indole **II** is converted to its ω-epoxide, conformers **51** and **52** (Scheme 3). When the terpenyl



Scheme 2

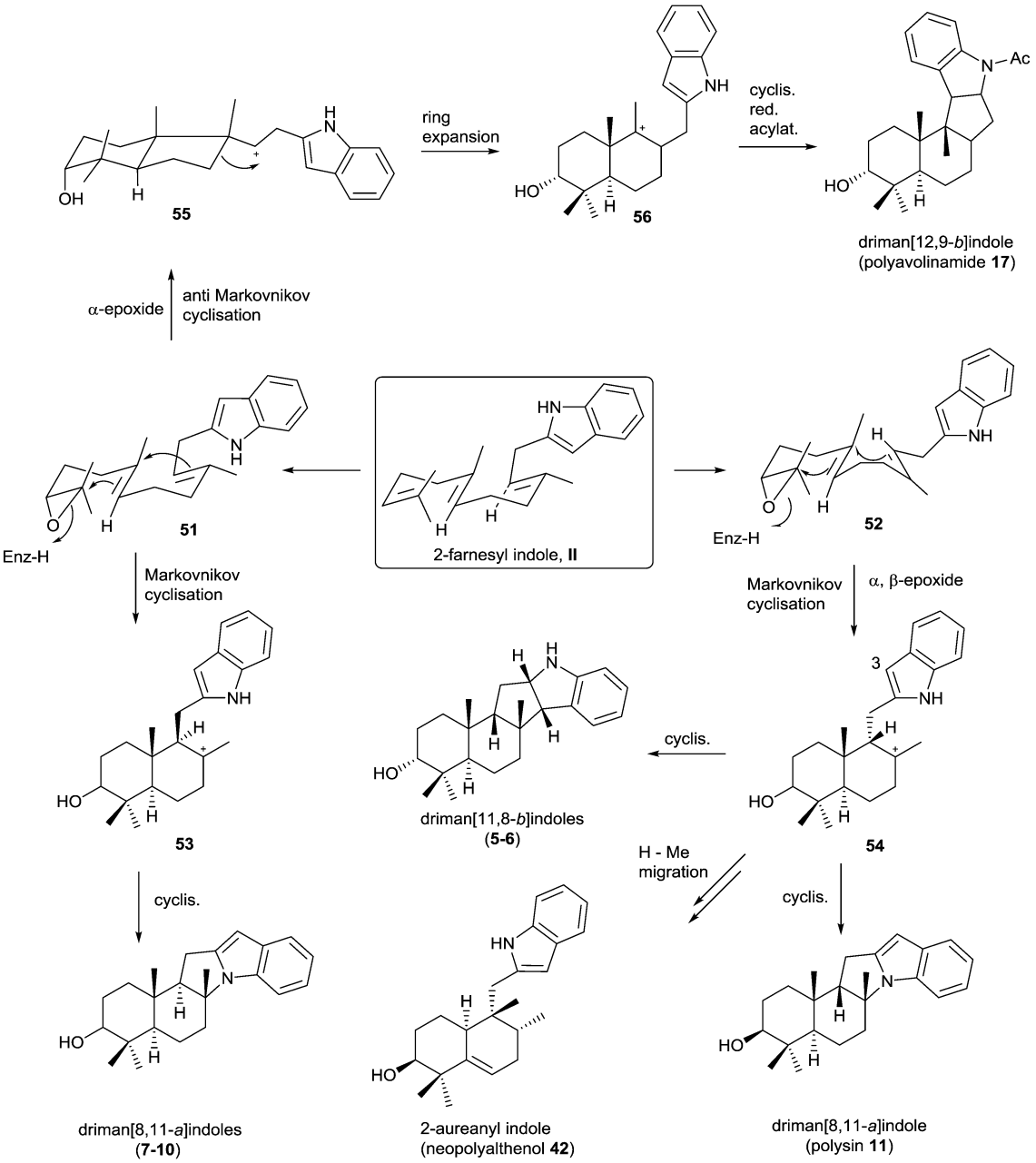
ω-epoxide adopts a chair-chair conformation as represented in **51**, a Markovnikov cyclisation leads to a drimanyl indole intermediate **53** that affords driman[8,11-*a*]indoles **7–10**, it being the N–H bond that is involved in the cyclisation.

When the ω-epoxide of 2-farnesyl indole **II** adopts a chair-boat conformation, **52**, Markovnikov cyclisation gives intermediate **54** that can evolve either hydrogen and undergo methyl migration to 2-aurenyl indole (neopolyalthenol **42**), by cyclisation to the driman[8,11-*a*]indole (polysin **11**) if the N–H bond of the indole participates in the cyclisation, or if C3 is the one involved in the cyclisation to driman[11,8-*b*]indoles **5–6.**

Finally, the anti-Markovnikov cyclisation of **51** leads to intermediate **55**, that after ring expansion produces the decalin **56**, and further cyclisation at C3, reduction and ulterior acylation affords the driman[12,9-*b*]indole, polyavolinamide **17**.

3.3 Biosynthesis of diketopiperazinic drimanyl indoles (Pathway C)

In Scheme 4 the biosynthesis of drimentines A–H, **27–34**, is shown and indotertines A **35**, B **36** (formyl derivative of **35**) from their common precursor **III**. The key intermediate for these natural products is **59**, that can be formed from intermediates **57** or **58**, by cyclisation of the diketopiperazine with the indole moiety before or after the Markovnikov cyclisation of the terpenic moiety of **III**. Deprotonation of **59** would lead directly to drimentines **27–32** and cyclisation with the nitrogen of the indole will give to drimentines **33–34.** During the revision of this work the synthesis of drimentines A **27**, F **30**, G **31** and indotertine A **35** has appeared in the literature.[62] In that work the synthesis of indotertine A **35** is achieved by treatment in acidic



Scheme 3

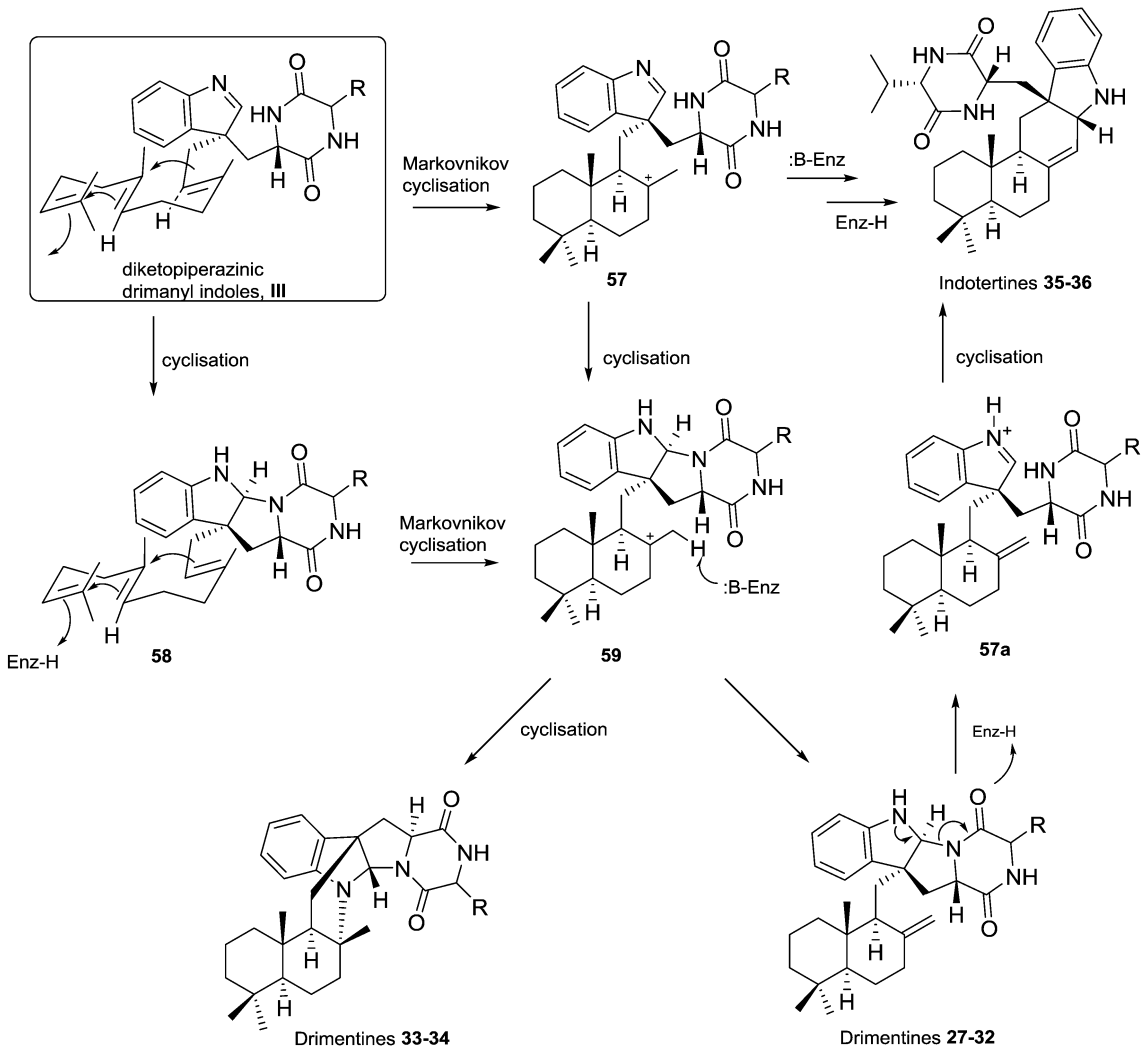
media of drimentine F **30**. In that manner the hypothesis that indotertines proceed biogenetically by acid catalysed cyclisation through the iminium ion **57a** is corroborated. Nevertheless, it can not be ignored that indotertines **35–36** could be formed directly from **57**, by deprotonation followed by acidic cyclisation in the same way as it has been already described in pathway A, Scheme 2, for driman[12,11-*b*]indoles (**18–26**), with no participation of the pirroloindole intermediate **59**.

4 Syntheses and synthetic approximations

Until the moment of sending this manuscript, only two total syntheses of sesquiterpenyl indoles have been published (Fig. 12): 3-farnesyl indole **1**[53] and suaveolindole **39**.[54] During the manuscript revision two new contributions have appeared in the literature, one describing the synthesis of lecanindole D **15**,[61] another reporting the synthesis of drimentines A **27**, F **30**, G **31** and indotertine A **35**.[62] Several syntheses of analogues, of the natural sesquiterpenyl indoles, polyalthenol **37** and polyveoline **5**, that is, 12-*epi-ent*-polyalthenol **60**,[55] 12-*epi-ent*-pentacyclindole **61**[52] and polyveoline analogue **62**,[56] have also been reported, as well as a couple of synthetic approaches towards a non-natural drimanyl indole **63**[57] and sespendole **16**.[58]

4.1 Total synthesis

The first synthesis was communicated in 1985,[59] two years earlier than the isolation and characterization of the natural



Scheme 4

product itself and it is the synthesis of the more simple sesquiterpenyl indole, 3-farnesyl indole **1**. This first total synthesis (Scheme 5) consists on the direct alkylation of indolylmagnesium iodide with *E*,*E*-farnesyl bromide.

Later on, in 2002[53] another synthesis of 3-farnesyl indole **1** (Scheme 6) was published with better global yield. In this manuscript is described the synthesis of a series of alkyl indoles, among them 3-farnesyl indole **1**, by direct alkylation of indoles in position 3 with alkyl halides and zinc triflate, in the presence of tetrabutylamonium iodide and *N*,*N*-diisopropylethylamine.

In 2007 Danishefsky and Velthuisen published the first total synthesis of suaveolindole **39**.[54] In this work the key step is an Ireland–Claisen rearrangement to obtain the terpenic moiety of suaveolindole **39** (Scheme 7).

Addition of an appropriate magnesium derivative to 6-methyl-2-cyclohexen-1-one **64**, followed by oxidation and ulterior ozonolysis of the terminal double bond lead to the intermediate **65** (Scheme 7). Treatment of this compound with 2-iodoaniline and $Pd(OAc)_2$ gave the indole fragment. Protection of the indole unit as its tosyl derivative, 1,4 addition of methyl lithium and trapping of the enolate formed as its triflate, gave intermediate **66**. Carbonylation of **66** takes place in CO atmosphere in the presence of Pd^0 to give, after treatment with MeLi and acetylation, the required substrate **67**. This compound was submitted to an Ireland–Claisen rearrangement by treatment of the allylic acetate **67** with LiHMDS and TMSCl to obtain **68**. An Arndt–Eistert homologation and deprotection of the indole unit gave the natural product (+)-suaveolindole **39**.

Recently Kuwahara and co-workers, based on their experience in the total synthesis of paspalinine,[63] adopted **83** as the key intermediate for the synthesis of racemic lecanindole D (±)-**15**.[61] (Scheme 8) This known compound had been previously prepared in 6 steps from the Wieland–Miescher ketone.[63]

After hydroxyl group protection of **83**, and deprotection of the carbonyl one, the *gem*-dimethyl is introduced to give **84**, that by reduction and epoxidation led to **85**. (Scheme 8). The epoxide reduction permitted the tertiary hydroxyl group followed by protection of the secondary alcohol with TBSOTf, hydrogenolysis for removal of the benzyl group and subsequent oxidation lead to **86**. Treatment of the cyclopropyl ketone intermediate **86** with sodium naphthalenide in THF brought

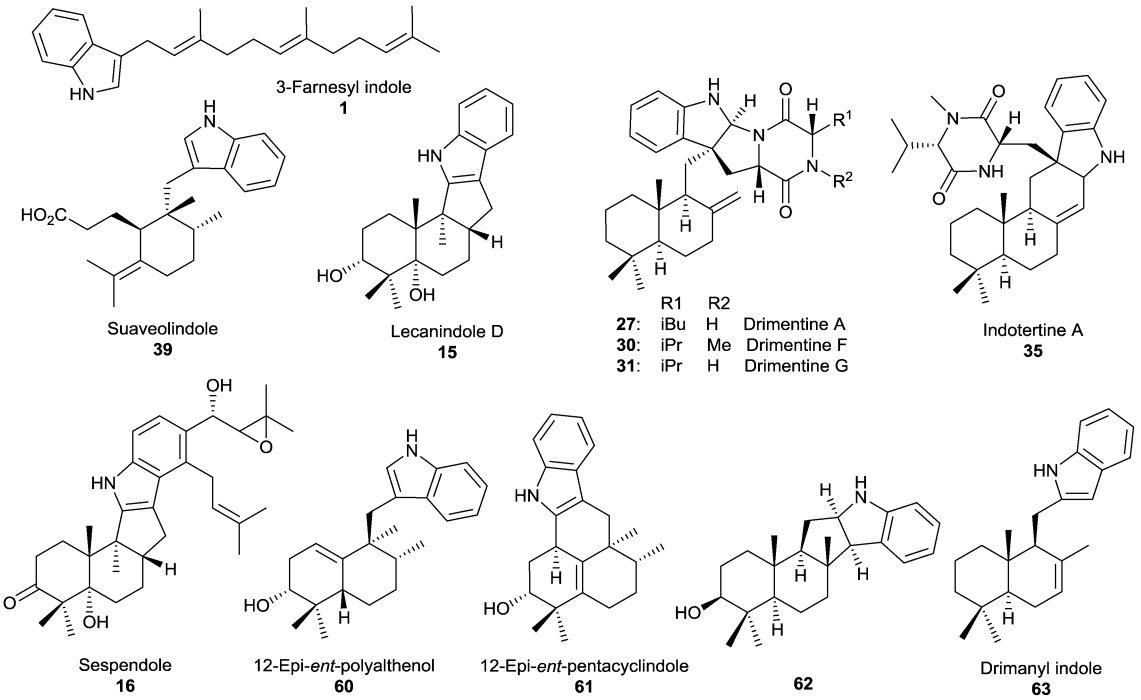
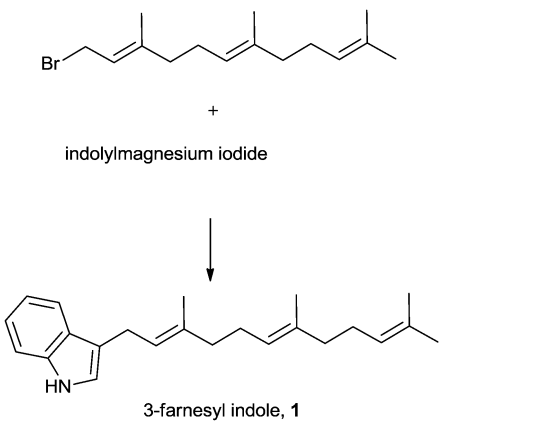
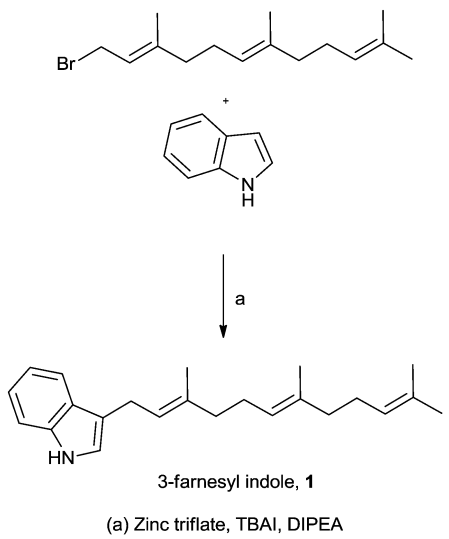


Fig. 12



Scheme 5

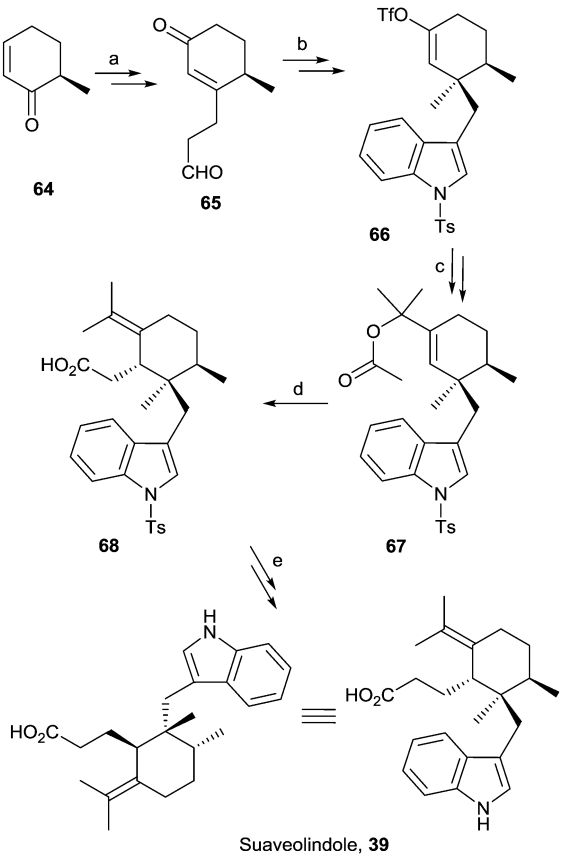


Scheme 6

about reductive cleavage of the cyclopropane ring to generate an enolate intermediate, which was then trapped *in situ* with Comins' reagent to afford enol triflate **87**. Stille coupling of **87** with an *o*-stannylated aniline derivative **88** under Corey's conditions gave **89**. The *o*-alkenyl aniline derivative **89** was then treated with $Pd(OCOCF_3)_2$ in DMSO to furnish an indole ring containing pentacyclic product. Finally, deprotection of the TBS group and removal of the Boc group completed the synthesis of lecanindole D (±)-**15**. The ^1H and ^{13}C NMR spectra of (±)-**15** were identical with those of natural lecanindole D.

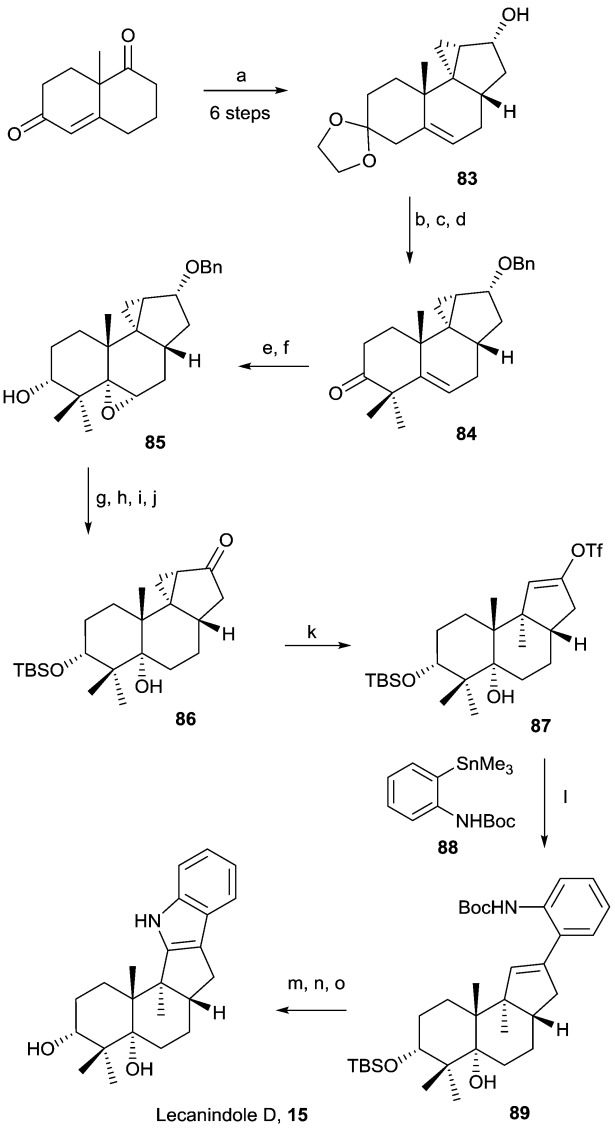
The synthesis of sesquiterpenyl indoles, indotertine A **35**, drimentines A, F, and G **27**, **30** and **31**[62] represent a superb contribution of Li and co-workers to this field (Scheme 9). The key step for the synthesis of drimentines A, F, and G **27**, **30** and **31**, is an intermolecular radical conjugate addition of intermediates **91** and **93** which are readily available from (+)-sclareolide and bis(Boc-L-tryptophan)methyl ester **92** respectively. The synthesis of indotertine A **35** is carried out based in a biosynthetic hypothesis from drimentine F **30**.

After several attempts using different conditions the radical conjugated addition of **91** and **93** was carried out in the presence of $[Ir(ppy)_2(dtbbpy)]PF_6$, blue LED, Et_3N, obtaining **94** in good yield, (ppy= 2-phenylpyridine; dtbbpy= 4,4′-di-*tert*-buthyl-2,2′-bipyridine) (Scheme 9). Boc deprotection with trifluoro acetic acid followed by L-valine and



(a) 1. 4-bromo-1-butene, Mg; 2. PCC; 3. O_3, Me_2S, (41% from **64**); (b) 1. 2-iodoaniline, $Pd(OAc)_2$, DABCO; 2. TsCl; 3. CuI, MeLi; PhNTf; (c) 1. CO, $Pd(PPh_3)_4$; 2. MeLi; 3. Ac_2O, (31% from **65**); (d) LiHMDS, TMSCl, (56%); (e) 1. oxalyl chloride, DMF; 2. CH_2N_2, i-Pr_2EtN; 3. CF_3CO_2Ag; 4. Na, naphtalene, (43% from **68**).

Scheme 7



(a) Ref. 63; (b) NaH, BnI, DMF, (74%); (c) TsOH, MeCN, (47%); (d) ^tBuOK, MeI, ^tBuOH, (67%); (e) L-Selectride, THF, (86%); (f) MCPBA, $CHCl_3$, (66%) ;(g) LAH, (91%); (h) TBSOTf, 2,6-lutidine, (100%); (i) H_2, $Pd(OH)_2$, EtOH, (74%); (j) SO_3·Py, Et_3N, DMSO, (68%); (k) $Na/C_{10}H_8$, isoprene, $ClC_5H_3N(NTf_2)$, HMPA; (l) $Pd(PPh_3)_4$, CuLi, LiCl, DMSO,(76% from **86**); (m) $Pd(OCOCF_3)_2$, NaOAc, DMSO; (n) TBAF/AcOH; (o) SiO_2, (25% from **89**).

Scheme 8

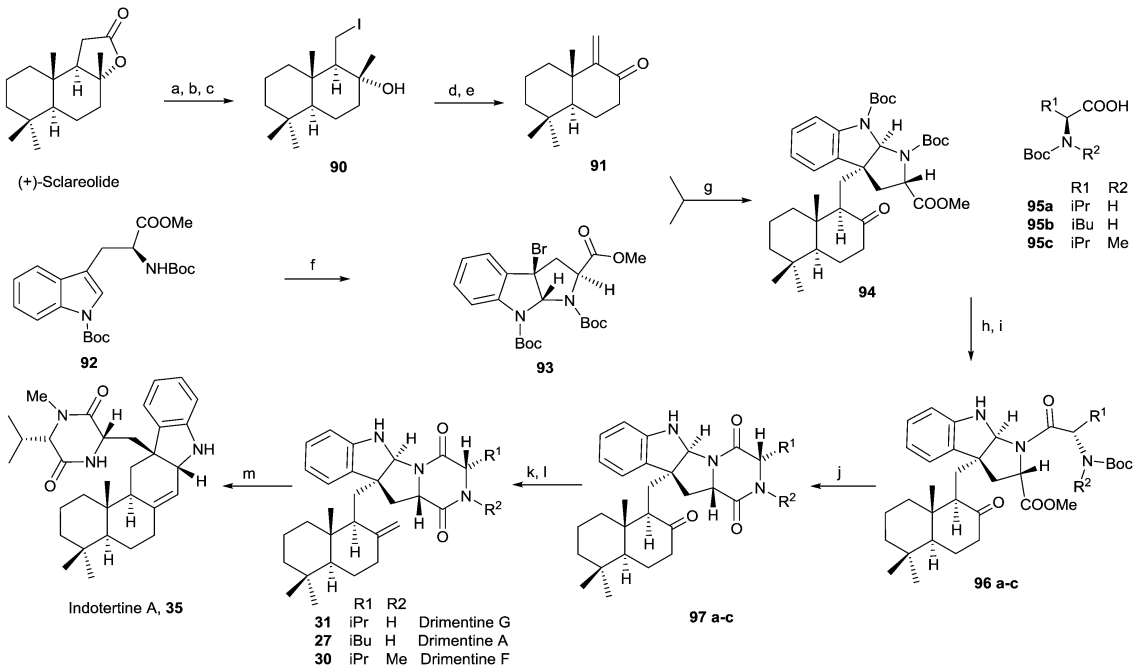
L-leucine derivatives **95a, 95b** and **95c** led to amides **96a–c** that by reaction with trifluoroacetic acid followed by basification with $NH_3 \cdot H_2O$ furnished diketopiperazines **97a–c.** Direct methylenation was not possible in many conditions, so in order to achieve the synthesis of the natural products drimentine G **31,** A **27,** and F **30** it was necessary to use the Grignard reaction and dehydration of the tertiary alcohol formed. Treatment of drimentine F **30** with $Bi(OTf)_3/KPF_6$ smoothly rendered indotertine A **35.**

4.2 Synthetic approaches

Recently Marcos and co-workers reported the synthesis and antitumoural activity of 12-*epi-ent*-polyalthenol **60**[55] a polyalthenol epimer and 12-*epi-ent*-pentacyclindole **61**[52] a pentacyclindole epimer, using *ent*-halimic acid **69**[60] as starting material (Scheme 10). In this synthesis we can distinguish four main steps: (1) preparation of the trinorditerpenyl derivative **70;** (2) oxidation of the C-3 position of the terpenyl fragment giving **71;** (3) incorporation of the indole moiety that led to **60** by Fischer indolization and (4) cyclisation and oxidation to the required indole **61.** This route is summarized in Scheme 10.

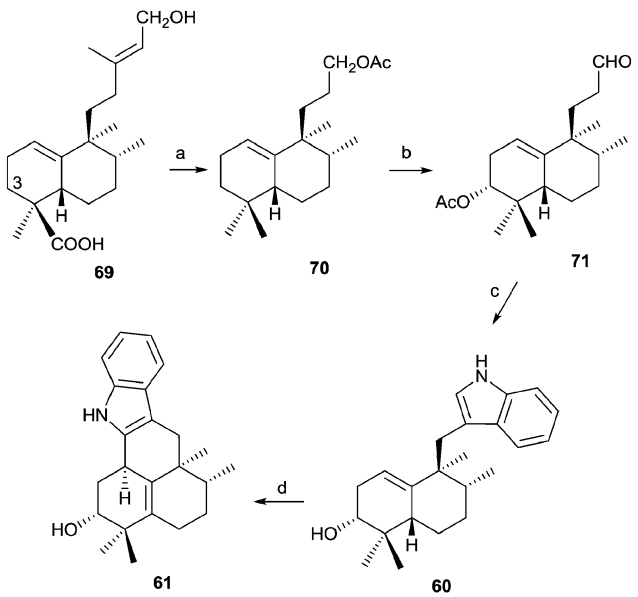
In 1987, Mirand and co-workers[56] reported a synthesis of **62** an analogue (Scheme 11) of the natural product polyveoline **5,** by cyclisation of a 3′-ω-epoxide-2-farnesyl indole.

The first step of this synthesis involves the formation of an *N*-protected-2-farnesylindole **73,** which can be accomplished by treatment of the corresponding *N*-protected indole **72** with *n*-BuLi, followed by treatment with *E,E*-farnesyl bromide (Scheme 11). Formation of the 3′-ω-epoxide **74** was achieved by reaction with NBS and then treatment of the resultant bromohydrine under basic conditions. Cyclisation of the sesquiterpene moiety to yield **75** was carried out by reaction with a Lewis



(a) DIBAL-H; (b) I_2, PIDA; (c) K_2CO_3, MeOH, (78% for the 3 steps); (d) $SOCl_2$, Et_3N, (86%); (e) O_3, Et_3N, (82%); (f) NBS, PPTS, (96%); (g) $[Ir(PPy)_2(dtbbpy)]PF_6$ 2.5%, blue LED, Et_3N, (91%); (h) TFA, (98%); (i) **95a-c**, HATU, iPr_2NEt, or 2,4,6-collidine; (j) 1. TFA, 2. $NH_3{\cdot}H_2O$, (86% for **97a**, 93% for **97b**, 68% for **97c**, over the 2 steps, respectively); (k) $CeCl_3$, MeMgBr, ; (l) $SOCl_2$, Py, (31% for **31**, 25% for **27**, 18% for **30**, over the 2 steps, respectively); (m) $Bi(OTf)_3$, KPF_6,(Conversion of **30** into **35**, 78%).

Scheme 9



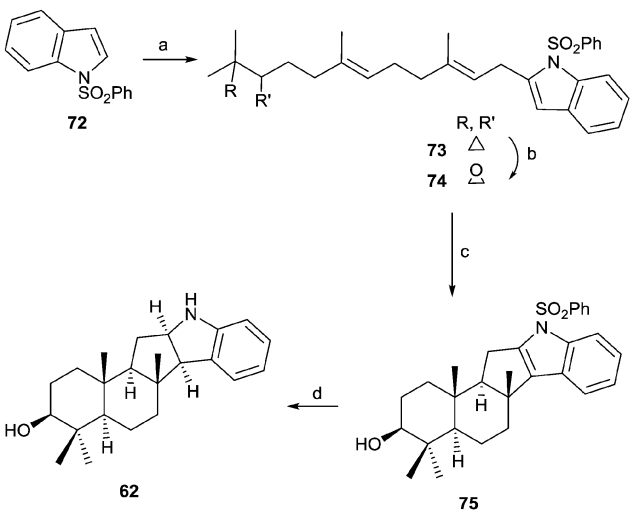
(a) Ref 51 and 60; (b) 1) Na_2CrO_4, NaOAc, Ac_2O, AcOH; 2) $Mn(AcO)_3{\cdot}2H_2O$; 3) $BF_3{\cdot}Et_2O$, 1,2-ethanedithiol; 4) KOH/MeOH; 5) Ni (Raney); 6) Ac_2O, Py; 7) Na_2CO_3; 8) TPAP, NMO, (17% from **70**); (c) 1) phenylhydrazine, AcOH; 2) KOH/MeOH, (77%); (d) 1) Ac_2O, Py; 2) HI, C_6H_6; 3) TPAP, NMO; 4) KOH/MeOH, (57%).

Scheme 10

acid. Finally, *N*-deprotection and reduction of the indole afforded compound **62**.

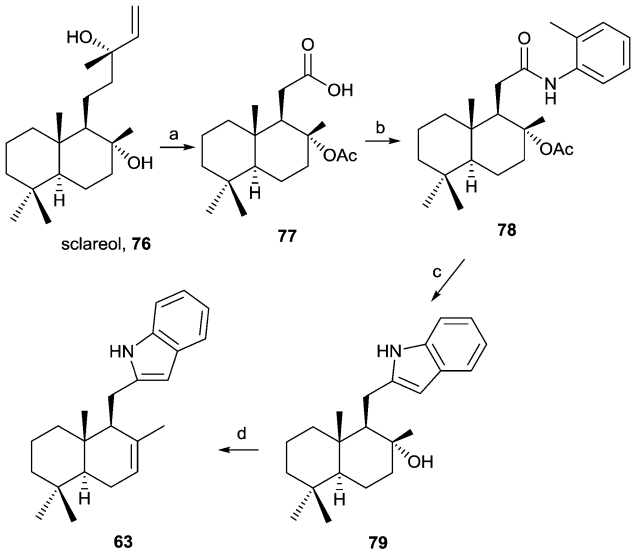
A non-natural indole sesquiterpene neopolyalthenol analogue **63** has been synthesized as well. This compound can be considered as a common intermediate[57] (Scheme 12) in the biosynthesis of neopolyalthenol **42** and greenwayodendrin-like natural indole sesquiterpenes, using sclareol **76** as a starting material.

Sclareol **76** was first oxidized with ruthenium chloride and sodium periodate to give **77** (Scheme 12). Treatment of compound **77** with thionyl chloride and the crude product with *O*-toluidine gave amide **78,** whose reaction with $NaNH_2$ afforded



(a) n-BuLi, then E,E-farnesyl bromide, 70%. (b) 1) NBS; 2) K_2CO_3/MeOH, rt, 1h, 95%. c) $BF_3{\cdot}Et_2O$, 13%. (d) 1) KOH/EtOH, 50%; 2) $NaBH_3CN$/TFA, 65%.

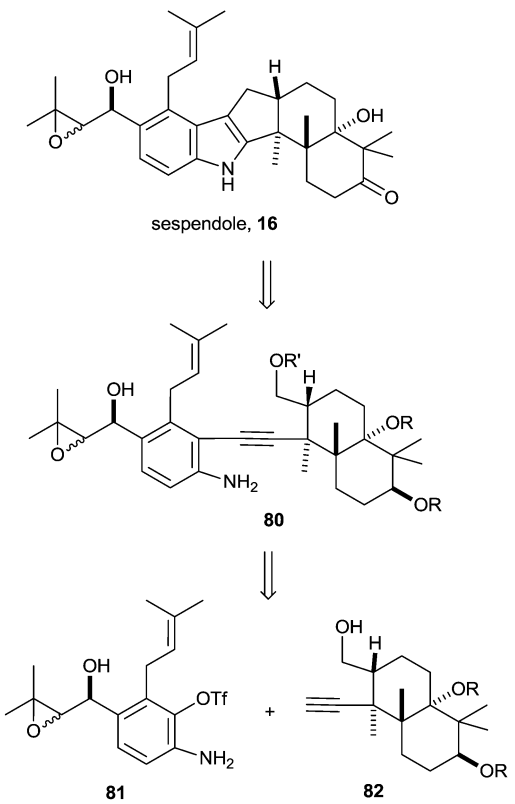
Scheme 11



(a) $RuCl_3$, $NaIO_4$ (30%);. (b) 1) $SOCl_2$; 2) *O*-toluidine, PhMe, K_2CO_3 (70%); (c) $NaNH_2$, $PhNEt_2$ (25%); (d) $SnCl_4$, CH_2Cl_2 (70%).

Scheme 12

79. Finally, dehydration was accomplished by treating **79** with $SnCl_4$, that led to **63**. Further rearrangements and oxidations of the sesquiterpene moiety of compound **63** could lead to neopolyalthenol **42** and the greenwayodendrin compounds.



Scheme 13

More recently there has been an attempt at synthesizing (±)-sespendole **16**.[58] The pentacyclic system synthesis is designed using **80** as an intermediate. Although the challenge of assembling aniline and sesquiterpene fragments **81**[58a] and **82**[58b] to give intermediate **80** has not been possible until date, Scheme 13.

5 Acknowledgements

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