Synthesis of Marine Natural Products with Antimalarial Activity

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Abstract: The role played by synthetic organic chemistry of marine metabolites as potential leads for drug discovery of antimalarial agents is discussed. Syntheses of the most promising molecules are summarized, with emphasis on structure-activity relationship (SAR) studies and their mechanism of action.

Key Words: Natural products, marine metabolites, drug discovery, synthesis, retrosynthetic analysis, antiprotozoal, antimalarial, antiplasmodial.

INTRODUCTION

Parasitic diseases occur in people and animals throughout the world, representing a health problem with very limited therapeutic options, most of the available treatments being decades old and suffering from low efficiency, often associated with undesirable side effects. These protozoal infections include malaria, leishmaniasis, trypanosomiasis, African sleeping sickness, giardiasis and amebiasis. They are representative of tropical diseases, but globalization has made them more generic, due to rapid connections among each area in our planet and widespread emigration. Malaria is the most relevant among these diseases. It is the second most infectious disease causing death all over the world and accounts for two million deaths every year and the risk of contracting it involves forty percent of the world population [1]. Most of the malarial protozoa are represented by four *Plasmodium* species: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, added by a few infections reported by *P. knowlesie P. semiovale*. Hopes for eradication are actually dashed by the ability of its most widespread and deadly cause the parasite *P. falciparum* transmitted by the Anopheles mosquito to develop resistance to available drugs, as in the case of chloroquine, the main antimalarial drug used for decades. Recent advantages have been achieved in determining the molecular mechanism of resistance to it [2], able to develop new active agents whose request is not have significant cardiovascular adverse effects shown by quinolines and structurally related drugs [3]. In addition, the resistance of the mosquito vector to the insecticides currently used contributes to complicate the control of the infection, although recent studies have proposed the possible production of a safe and green tool for the control of malaria by using insect fungal pathogens for the control of vector-borne diseases [4]. Another candidate is given by bacteria that establish themselves with an Asian mosquito responsible for transmitting *Plasmodium* sp., as shown by a recent research which opens interesting perspectives in the control of malaria through the production of antiplasmodial molecules or anti-mosquito factors by engineered bacterial strains [5]. The access of an effective vaccine is an urgently needed intervention, but efforts to produce it are still unsuccessful in spite of the remarkable investments [6]. However advances have been made in the understanding of malarial parasite biology with the recent completion of *Plasmodium* genome which has clarified parasite metabolic pathways [7] and shown exciting opportunities for target-based antimalarial drug discovery [8]. Thus, the absence of a vaccine and the development of drug-resistant strains of these parasites, enhance the need of new drugs [9]. A growing tendency is to develop target-specific antimalarial agents, which also include the inhibition of plasmodial farnesyl transferase, proteases, cyclin dependant kinases [10]. Recently, *P. falciparum* choline kinase (PfCK) has been cloned, overexpressed and purified, and a quaternary ammonium compound identified as an inhibitor of this enzyme exhibiting potent antimalarial activity *in vitro* and *in vivo* [11]. In addition, a promising tool for the molecular discovery of new classes of antimalarial drugs has been recently reported based on a virtual screening and in silico design to develop new compounds regarding a quantitative structure-activity relation (QSAR) model [12]. The recent advantages in drug development [13] and the most significant progress of the past ten years have been recently reviewed [14].

In the pressing need of development of efficient therapies, a relevant help comes from natural products, which have always played a pivotal role in medicine and drug discovery [15-17]. Plant derived antimalarial agents have found relevant examples in the alkaloid quinine (**1**) and sesquiterpene lactone artemisinin (**2**) (Fig. **1**) [18, 19].

Metabolites produced by marine organisms represent a relatively novel resource of compounds as potential drug candidates [20]. Although actually only a few drugs from marine sources are in use [21], there are some cases of advanced clinical studies for the treatment of a variety of diseases where they are involved [22]. This is due to a more recent approach to marine natural products than to terrestrial ones, with the potential of this source which is related to the chemical and biological diversity of the immeasurable and

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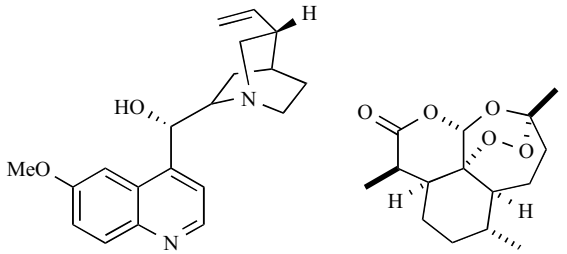


Quinine (**1**) Artemisinin (**2**)

Fig. (1). Chemical structures of antimalarial drugs of natural origin.

still partially unknown marine environment. Marine organisms and specifically porifera (sponges) are interesting mines of bioactive secondary metabolites [23]. The intrinsic peculiarity of secondary metabolites is their very low level in natural resources and it is a great problem to use the marine substances directly for bioassays and therapy. The strategies currently taken into account to resolve this aspect include a higher production based on biosynthesis, gene cloning and expression systems for obtaining secondary metabolites deriving from symbiotic associations [24], cultures of marine microorganisms as new sources of a low but growing number of biologically active compounds [25]. In this context, marine fungi are a source of some molecules showing inhibition to *P. falciparum* [26]. A number of molecules from marine sources have been investigated with the hope to also provide new mechanisms of action and efficient treatments for resistant strains [27]. Even when a natural metabolite shows a good activity (evaluated *in vitro* against whole protozoa with an inhibition of 50% of concentration IC_{50} minor or equal to 1μg/ml and corresponding to 1-4 μM for compounds with molecular weight in the range 1000-250 Dalton, respectively), the development of an antimalarial agent depends then on a concomitant low toxicity towards human cells. Selectivity index (SI), defined as a ratio between cytotoxicity against a mammalian cell line and activity against *Plasmodium,* must be at least higher than ten [7].

Organic synthesis has been applied to confirm chemical structures and/or of the stereochemical assignments made for natural compounds essentially by spectroscopic techniques, or to define absolute configurations, to produce sufficient amounts to be used for a broad biological screening, to furnish analogues for structure-activity relationships (SAR) studies, also by building natural product-like libraries through combinatorial chemistry [28]. Many natural molecules present lipophilic structures responsible for their bioavailability problems when used in human therapy and to resolve this problem organic synthesis can introduce polar and water-soluble functionalities in the core structure of natural compounds, in order to enhance its drug-like properties. Very efficient improvements in the synthetic strategy come from biomimetic approaches and methodologies without using protective groups [29].

The potential applications of marine natural products as anti-infective agents have been recently reviewed [30], as well as antimalarial lead compounds from marine organisms [31, 32] and specifically from porifera (sponges) [33], as well as agents in the perspective of current chemotherapy and prevention of malaria [34]. An overview on the recent synthesis of marine natural products with antibacterial activity was recently reported [35], whereas the synthetic aspects linked to marine metabolites with antimalarial activity are lacking of it. The present review[1] will focus on the role of organic synthesis in the study of marine metabolites whose bioactivity has proved that they are good candidates for antimalarial agents. The syntheses reported in this paper, both as a total approach and an access to analogues, cover relevant literature until 2007 and are only illustrated if previously they haven't been inserted in any cited review articles. They concern those compounds giving direct bioassays on *Plasmodium* strains, whereas the compounds studied only as kinase inhibitors are reported without taking into account the discussion of their syntheses. After a general introduction presenting an actual overview of the topic, the synthetic strategies will be reported in detail with regard to the compounds presented in sections partitioned according to the class of compounds and discussed for their role in revising molecular structure, establishing absolute configuration or for their relevance mainly by retrosynthetic analysis, in terms of biomimetic approach, innovations and effectiveness. When known, the action mechanism is discussed for each class of compounds, as well as the biological activities of synthetic analogues which were compared to the data for natural compounds, the latter ones summarized in a dedicated table.

ENDOPEROXIDES

The action mode of antimalarial artemisinin (**2**) has been studied in detail. It includes the transport of this molecule from the red blood cells of the host into the present *Plasmodium*, where it interacts with Fe^{2+} ions causing the cleavage of the peroxide bond and formation of radicals able to inhibit parasite growth [36]. The knowledge of this mechanism of action has allowed a rational design of some new antimalarial agents bearing an endoperoxide pharmacophore related to natural artemisinin (**2**) [37]. They include semi-synthetic derivatives and fully synthetic peroxides, used for SAR studies by *in vitro* and *in vivo* assays and for the optimisation of their pharmaceutical properties [38, 39].

Naturally occurring peroxides also include metabolites isolated from marine sponge, which have been reviewed as valuable sources in antimalarial and antitumor drug discovery [40]. A specific overview of the metabolites isolated from the marine sponges of the genus *Plakortis* including discussion on structures, stereochemical aspects, pharmacological activity and selected syntheses has been reported [41]. Fattorusso's group has extensively studied cycloperoxides from *Plakortis simplex*, investigating their antimalarial activity [42]. It was noted that the 6-membered endoperoxide compounds (plakortin and dihydroplakortin), but not the 5-membered cycloperoxide (plakortide E), inhibited the growth of cultured *P. falciparum* parasites, both chloroquine-sen-

[1] The molecular configuration of the reported compounds has been reproduced faithfully in agreement with the authors.

The following abbreviations have been adopted in the report of the sequences: Ac = acetyl ; Alloc = (allylloxy)carbonyl; Bn = benzyl; Boc = t-butoxycarbonyl, Bz = benzoyl; CD = circular dischroism; CQ-R= chloroquine resistant; CQ-S = chloroquine sensible; DDQ = dichlorodicyanoquinone; MW = microwave; NOE = Nuclear Overhauser enhancement; PG= protective group; TBDMS = t-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; TFA = trifluoroacetic acid; TMS = trimethylsilyl; Ts = tosyl (*p*-toluensulfonyl);

sitive D10 strain and chloroquine-resistant W2 strain. Both compounds showed similar IC_{50} effects evaluated against D10 (in the range 1263-1117 nM), and W2 (735-760 nM) strains. These results reveal the need of further studies on marine derived cycloperoxides in order to characterize their mechanism of action and identify/synthesize new related compounds with stronger activity. The mechanism of action of plakortin and other endoperoxides is not known, but it could be similar to that for artemisinin, with a lower activity imputable to the dioxane instead of a trioxane moiety as found in plant metabolites.

Peroxyplakoric acid methyl esters A3 (**3**) and B3 (**4**) (Fig. **2**) isolated from a marine sponge of *Plakortis* sp. exhibited good antimalarial activity (Table **1**) with high selective toxicity index between *P. falciparum* and human epideroid carcinoma cells [43].

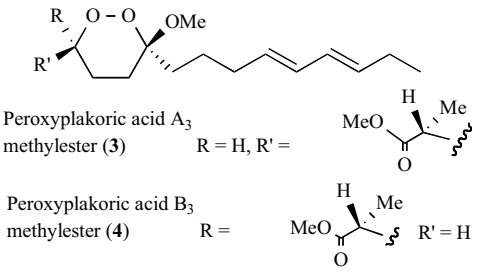


Fig. (2). Chemical structures of peroxyplakoric acid A_3 and B_3 methyl esters.

In order to evaluate the activity of a compound bearing the core peroxide structure, the synthesis of **5** has been developed by M. Kobayashi [43]. In addition, related analogues **6** and **7** [45] were chosen on the basis of calculated Log P, an effective parameter of lipophilicity able to predict both membrane permeability and *in vivo* biological activity of drugs [21]. They were obtained through a common strategy (Scheme **1**). Starting from γ-butyrrolactone, the keto-α,β-unsaturated ester **8** (obtained in four steps and 70% yield), was subjected to oxidation giving the peroxy-hemicetal **9** in 72% yield with H_2O_2/urea/TsOH in MeOH. The intramolecular Michael addition of the peroxy-hemicetal group on the unsaturated ester in **9** furnished the highest yield of **5** by catalytic amount of diethylamine in CF_3CH_2OH, minimizing the formation of the epoxide derivative as by-product [44, 45]. SAR correlation was later studied on the related compounds **11-15**. In order to avoid the opening of the endoperoxide cycle and formation of epoxide as unique by-product by using the classical basic hydrolysis, amides **11-15** were successfully obtained from **6** by a) enzymatic hydrolysis with porcine liver esterase, b) formation of the pentafluorophenoxyester **10** and c) aminolysis through the suitable amine hydrochloride in pyridine [46].

SAR studies on scaffolds from the natural peroxides **3** and **4** indicated: a) the role of side chain R on the bioactivity, with the synthetic compounds **6** and **7,** bearing a C-3 chain as long as the natural or longer respectively, which showed comparable activity with natural **3** and **4**; however, in agreement with the indication from log P prediction, a better selective toxicity for **6** than for **7** was found whereas compound **5** exhibited a low bioactivity; b) the role of the relative stereochemistry at C-3 and C-6 studied for the isomers syn and anti of both **6** and **7** available by HPLC separation, for which the syn-isomers exhibited higher selective toxicity scores than anti isomers; c) no differences in bioactivity and selective toxicity noted for the enantiomeric form of syn-**6** [46]**;** d) the effect of conversion into amide of the ester moiety, which is more easily hydrolyzed in serum and therefore has lower activities *in vivo* system: for each amide analogue **11-15** a lower bioactivity than **6** was observed, but only for **12** and **15** a better stability than **6** was verified in mouse serum [46]. Simple analogues **16-19** (Scheme **2**) have been recently synthesized by Wu under Kobayashi's conditions [44], although evaluation of their antimalarial activity is still lacking [47].

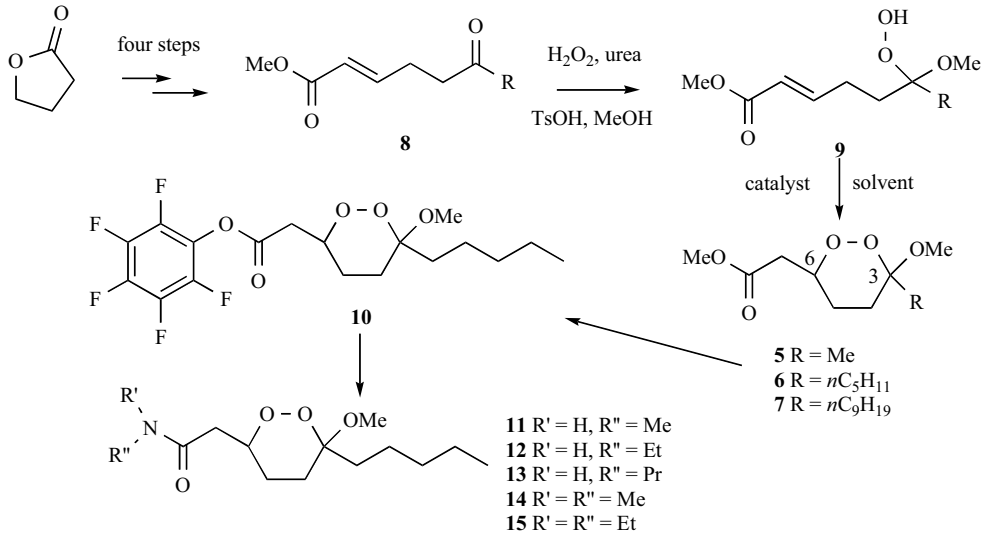
Plakortin (**20**) (Scheme **3**), first isolated from the sponge *Plakortis halichondrioides* [48], was found later in *Plakortis simplex* and its absolute configuration revised as structure **20** reported in scheme **3** by applying Mosher's and Kusumi's methods on suitable degradation products [49]. It showed submicromolar activity against the chloroquine-resistant strain of *P. falciparum* (Table **1**). By using plakortin structure as an antimalarial hit, Taglialatela-Scafati employed standard chemical transformations for preparing a series of analogues for bioactivity studies [50]. Products **21** and **22** through a shortening of the "Western" alkyl chain, derivatives **23-25** by modification of the "Eastern" functionalities and the epoxides **27** and **28** were tested for their antimalarial activity, resulting more potent against chloroquine resistant W2 than chloroquine sensible D10 strains. In addition, small changes in the "Western" alkyl side chain resulted in a decreasing activity. The authors have also performed an interesting computational analysis, in order to define the role played by the conformational parameters of the antimalarial activity for the endoperoxide analogues. The results show that the favourite chair conformation of the dioxane ring is in good agreement with the peroxide ring-constrained conformation of artemisinin. These indications will be better clarified by the mechanism of action for simple endoperoxides related to plakortin under investigation [50]. The activity of plakortin (**20**) and dihydroplakortin resulted significantly higher against chloroquine-resistant than chloroquine-susceptible parasites, following a pattern similar to that of artemisinin, although they were 50-fold less active. Moreover, plakortin and dihydroplakortin showed an additive effect when used in combination with chloroquine [51].

Sigmosceptrellin A was isolated as methyl ester (**31**) (Fig. **3**) from the sponge *Sigmosceptrella laevis* as first example of a nor-sesterterpene from marine and terrestrial sources and its relative configuration established by X-ray diffraction analysis on a derivative [52]. Later, sigmosceptrellin A-C were isolated from the same authors who defined also the absolute configuration of **33** by CD analysis [53]. Sigmosceptrellin A (**32**) and B (**34**) showed both activity against *P. falciparum* (Table **1**) and potent *in vitro* effect against *Toxoplasma gondii* for **34**, associated to low toxicity [54, 55]. The different values of bioactivity for the two isomeric natural compounds **32** and **34** (470 and 1200 ng/ml against D6, respectively; 420 and 3400 ng/ml, resp. against W2 strain) indicated the influence of relative stereochemistry on the antiprotozoal effect shown by these 1,2-dioxane derivatives. Enantio-sigmosceptrellin A methyl ester (**35**), iso-

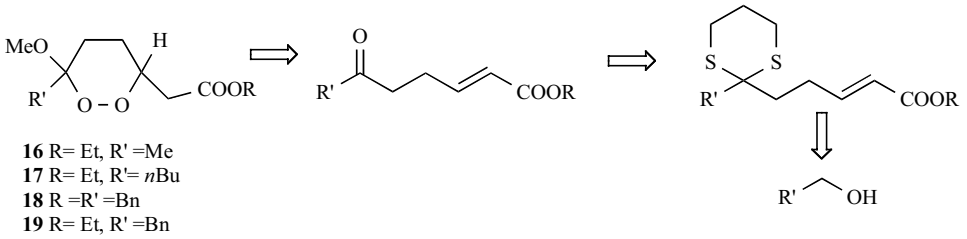
Table 1. Synthesis of Marine Antiprotozoal Compounds and their Analogues

Compound	Natural Source (First Isolation)	Pharmacologic Activity		Chemical Synthesis
		Against *P. falciparum* [a] (strain, IC_{50} in μM)	SI	
Endoperoxides				
Peroxyplakoric acid methyl esters A3 (**3**) and B3 (**4**)	Sponge *Plakortis* sp.	D6 = 0.15	200	Partial [44] Analogues [45-47]
Plakortin (**20**)	Sponge *Plakortis simplex*	W2 (CQ-R) = 0.4 D10 (CQ-S))= 0.87	n.d. n.d.	Analogues [48]
Sigmosceptrellin A (**32**)	Sponge *Sigmosceptrella laevis*	W2 = 1.3 D6 = 1.4	48 43	Partial for config. assignment [57]
Isonitriles				
Axisonitrile-3 ((+)-**38**)	Sponges *Axinella cannabina, Acanthella klethra*	W2 = 0.073 D6 = 0.61	1200 >141	Total of (-)-38 [60]
Kalihinol A (**41**)	*Acanthella* sp.	EC 50 = 12	317;	Analogues [64]
Diisocyanoadocyane (**47**)	Sponges *Adocia* and *Cymbastela Hooperi*	W2 = 0.015 D6 = 0.016	1100 1000	Total [67,68]
Amphilectane diterpenes **60**	Sponges *Adocia* and *Cymbastela Hooperi*	W2 = 0.031 D6 = 0.047	340 230;	Analogues [73]
Amphilectane diterpenes **61**	Sponges *Adocia* and *Cymbastela Hooperi*	W2 = 0.0081 D6 =1.8	>82.6 > 38.5	Analogues [73]
Alkaloids				
Lepadin E (**73**)	ascidian *Didemnum* sp.	NF54= 2.1 K1= 0.95	18 40	Total [81, 82]
Manzamine A (**77**)	sponge genus *Haliclona*, or by bioconversion with *Fusarium* or *Streptomyces*	W2 = 0.015 D6= 0.0082	150 267	Total [93] Analogues [94-97]
(+)-8-Hydroxymanzamine A (**78**)	sponges *Pachypellina, Xestospongia* and *Amphimedon* sp.	W2 = 0.014 D6 = 0.010	138 183	
Manzamine A N-oxide (**79**)	sponge *Xestospongia ashmorica*	W2 = 0.023 D6 = 0.020	323 382	
Phloeodictynes (**95**)	Sponge *Phloeodictyon (= Oceanapia)*	FCB1 = 0.62	46	Total for phloeodictynes A1 [102]
Heptylprodigiosin (**100**)	α-proteobacteria	3D7= 0.068	20	Total and analogues, reviewed in [110]
Cycloprodigiosin (**101**)	Various bacteria	FCR-3= 0.011	n.d.	Total and analogues, reviewed in [110]
Metacycloprodigiosin (**102**) as hydrochloride form	*Streptomyces spectabilis*	K1= 0.011	54	Total and analogues, reviewed in [110]
6-Bromoaplysinopsin (**103**)	anthozoan *Astroides calycularis* and sponge *Smenoospongia aurea*	D6= 1.0	> 14	Total [117] and analogues [116-120]
Miscellaneous				
Xestoquinone (**109**)	Sponge *Xestospongia* sp.	FCB1= 3.0	7	Total [123-127]
Aplasmomycin (**121**)	*Streptomyces* strain	*P. berghei*, 100 mg/Kg (*in vivo*)		Total [129-132]and analogues [133,134]
15-Oxopuupehenol (**132**)	sponge *Hyrtios* sp.	D6 = 5.8 W2 = 3.8	0.2-5.0 0.4-7.6	Total [138] and derivatives [137]

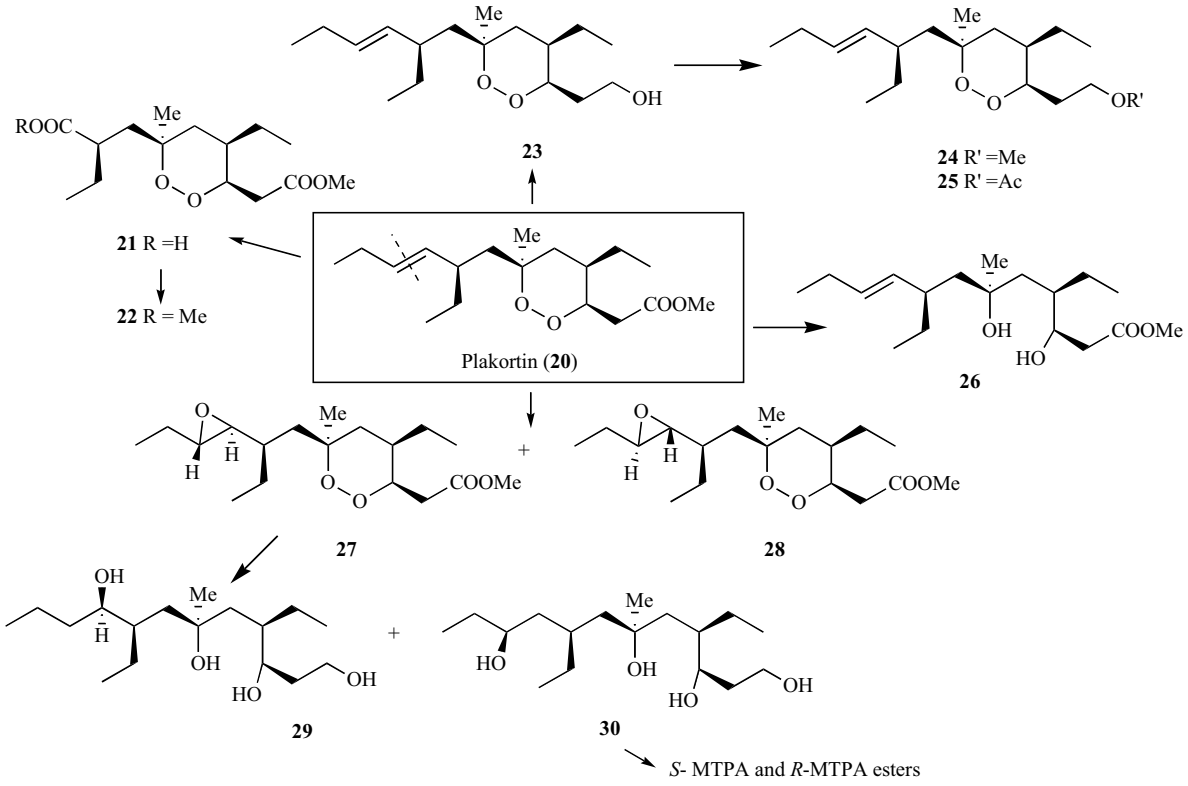
[a] if not otherwise specified.



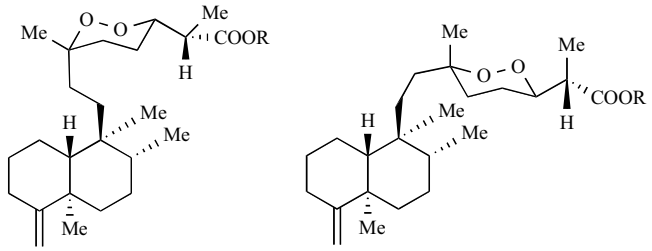
Scheme 1. Synthesis of core structure (**5**) by M. Kobayashi (2001) and analogues of peroxyplakoric acid methyl esters **3** and **4** by the same authors (2002, 2003).



Scheme 2. Retrosynthetic analysis of peroxyplakoric acid analogues by Wu (2006).



Scheme 3. Semisynthetic access of analogues from plakortin (**20**) by Taglialatela-Scafati (2006).



Sigmosceptrellin A (**31**) R= Me methyl ester

Sigmosceptrellin B (**33**) R= Me methyl ester

Sigmosceptrellin A (**32**) R= H

Sigmosceptrellin B (**34**) R= H

Fig. (3). Chemical structures of sigmosceptrellins.

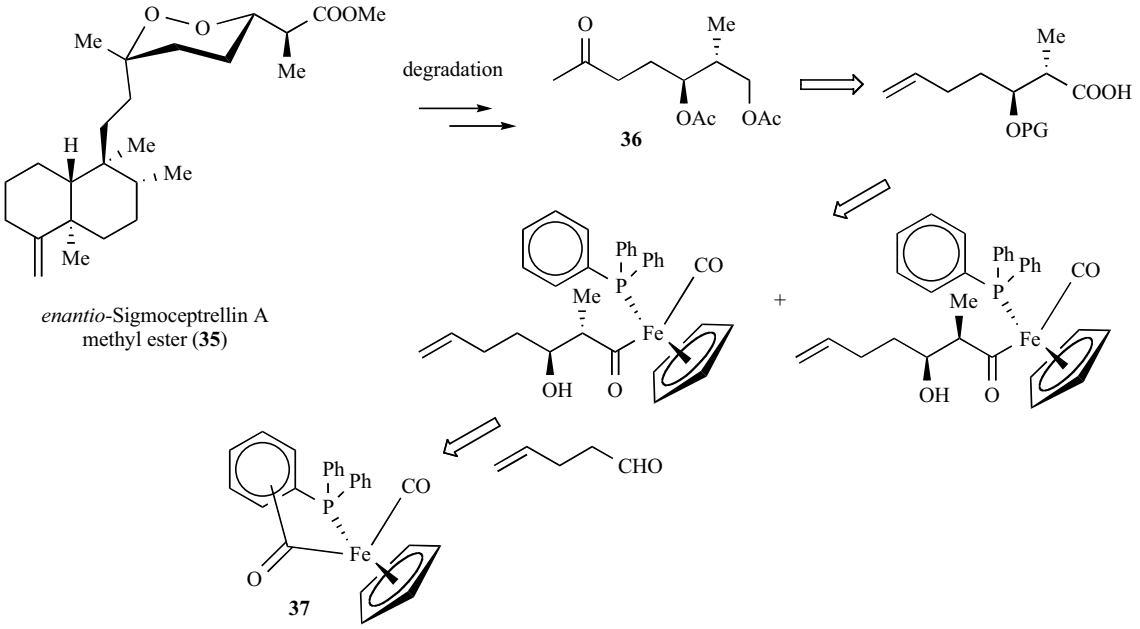
lated from the sponge *Mycale ancorina* [56], was synthesized in an asymmetric way by Davies and Capon in order to achieve an unequivocal assignment of absolute stereochemistry of these marine cyclic peroxides [57]. This strategy involves the three-step degradation of natural **35** to keto diacetate **36**, which was compared to a sample obtained *via* asymmetric synthesis from chiral auxiliary **37** (Scheme **4**). In details, the pivotal step involved an aldol condensation between **37** and 4-pentenal, able to form a pair of erythro and threo isomer with contiguous chiral centres at C-2 and C-3 of known absolute configurations, defined by X-ray crystallographic analysis.

ISONITRILES

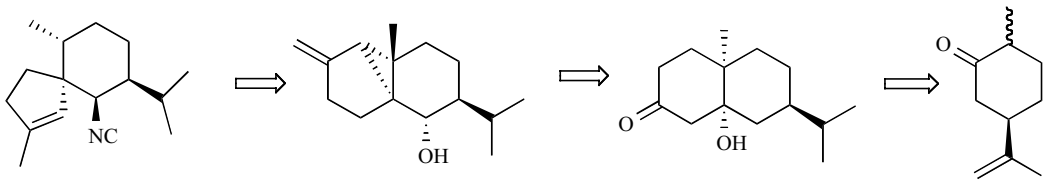
Axisonitrile-3 (**(+)-38**) was first isolated from *Axinella cannabina* as a novel carbon skeleton of spiroxane and its structure (relative stereochemistry) established by X-ray diffraction analysis [58]. It was only on a re-isolated sample from *Acanthella Klethra* that a relevant antimalarial activity was observed, jointly with low cytotoxicity toward cultured KB-3 cells [59] (Table **1**). The natural axisothiocyanate, bearing a isothiocyano group at the place of isocyano in **(+)-38**, was 550- fold less active [58], indicating the decisive role of the substituent on the terpene skeleton, although terpenoids lacking isonitrile groups resulted still active [34]. Caine synthesized the enantiomeric axisonitrile-3 **(-)-38** in 11 steps starting from (+)-dihydrocarvone (**39**) (Scheme **5**). The key step is the opening of the cyclopropane ring in **40** to the corresponding spiro compound occurring stereospecifically (with inversion of configuration) at the tetrasubstituted centre bearing the methyl group. The synthesis established that the absolute configuration of the natural product was opposite to the synthetic compound [60].

Kalihinol A (**41**) is another isonitrile terpenoid isolated from *Acanthella* sp. [61] and showed remarkable *in vitro* activity against *P. falciparum* and low cytotoxicity (Table **1**), which resulted in an antimalarial compound better than a series of related diterpenoids isolated from the same sponge and belonging to the kalihinane class which includes more than 40 members. It is relevant that the bioactivity of kalihinol A was about 30-fold higher than the drug mefloquine taken as a control [62]. Its absolute configuration (1S, 4R, 5R, 6S, 7S, 10S, 11R, 14S) was established by applying the CD exciton chirality method on the bis p-bromobenzamide derivative and this is the first determination of the absolute configuration of a member of kalihinane family [63]. Although the total synthesis of kalihinol A is not yet achieved, an efficient approach to the functionalized decalin core of the molecules as in **42** has been reported by Wood [64]. As illustrated in Scheme **6**, the triene **43**, easily accessible from the 3-methylbutanal, was subjected in sequence to Jones oxidation, intramolecular Diels-Alder cycloaddition and highly diastereoselective epoxidation to obtain compound **44**.

Epimerization of the H in α-position to keto group and olefination of this functionality gave **45**. The successive opening of epoxide to azido-alcohol and the conversion of exo-methylene to tosylaziridine, furnished compound **46** as the major diastereoisomer showing the correct relative con-

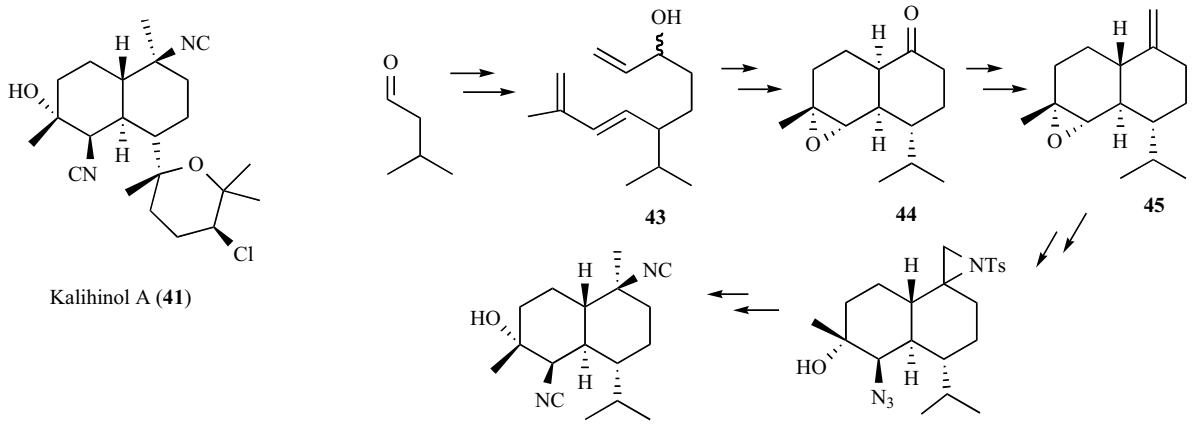


Scheme 4. Absolute configuration of the cycloperoxide moiety in the enantiomer of sigmosceptrellin A methyl ester (**35**) by Davies (1988).



enantio-Axisonitrile-3 (**(-)-38**) **40** (+)-Dihydrocarvone (**39**)

Scheme 5. Total synthesis of enentiomeric (-)-axisonitrile-3 by Caine (1978).



Kalihinol A (**41**) **43** **44** **45** Kalihinol-like (**42**) **46**

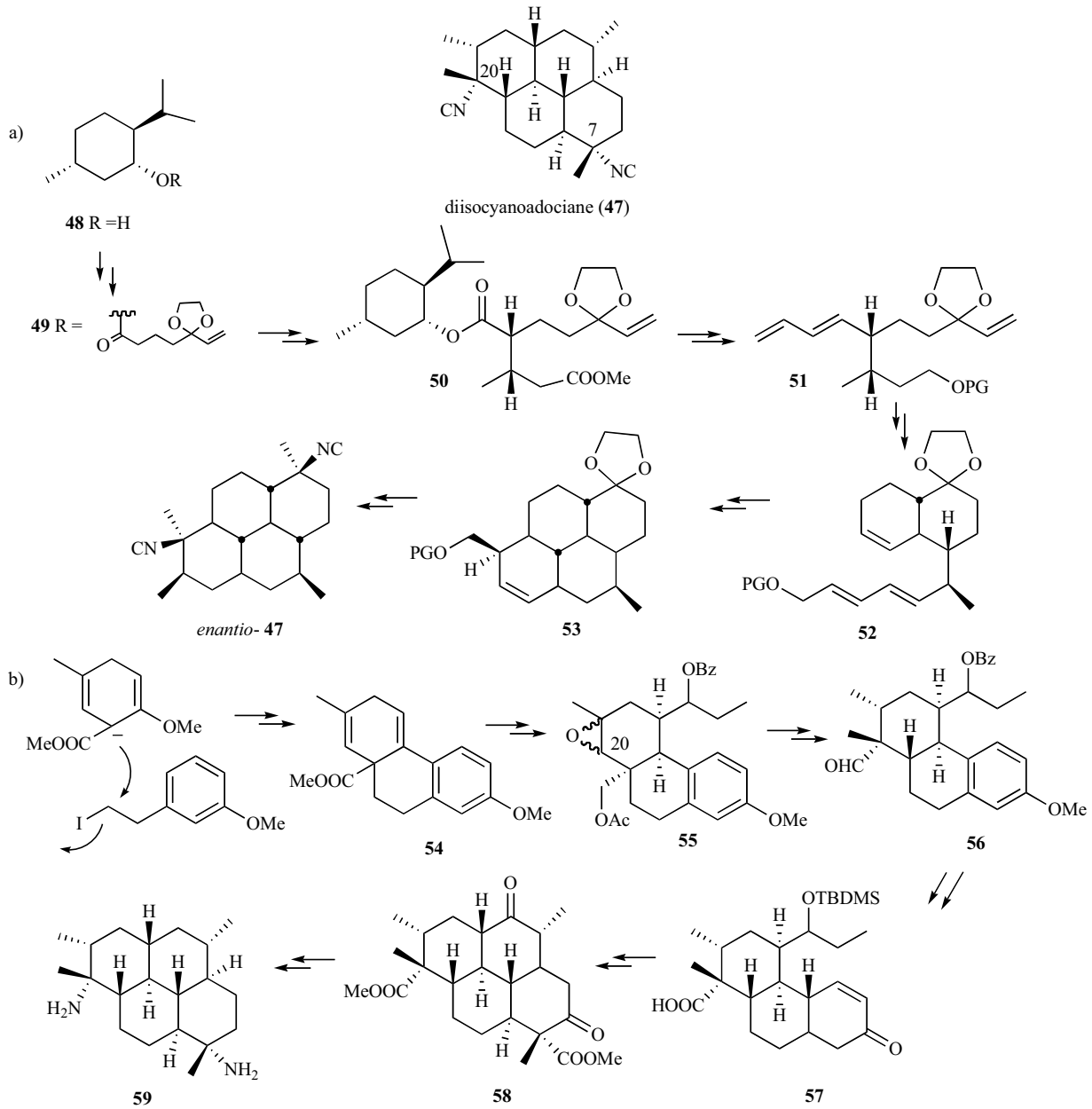
Scheme 6. Synthesis of a kalihinane diperpenoid by Wood (2001).

figuration at all six stereocentres, as deduced by X-ray analysis. Standard conversion of functional groups gave the kalihinol A –like **42** in 11 steps from triene **43** (overall yield 25%).

Diisocyanoadocyane (**47**) (Scheme **7**) was first found from the sponge *Adocia* and its structure established as a unique perhydropyrene skeleton bearing two isonitrile units by X-ray analysis, even if the absolute configuration remained unassigned [65]. It was later isolated by König from the sponge *Cymbastela Hooperi* together with the corresponding C-7 or C-20 isocyano and C-7 isothiocyano compounds; the evaluation of their antiplasmodial activity indicated the C-20 isocyano metabolite and **47** as the most active compounds (Table **1**) [66]. The total synthesis achieved by Corey in 1987 allowed to assign the absolute configuration for natural **47** [67]. The starting reactive (-)-menthol (**48**) was functionalized to vinyl ketal **49** (Scheme **7**). Michael addition of the methyl crotonate was then achieved in enantioselective and diasteroselective way to give major **50** in 8: 1 threo / erythro ratio and 60% ee. The menthol ring employed for inducing asimmetry, was later removed and butadiene unit was introduced by Wittig reaction to furnish diene **51**. It underwent stereospecific internal Diels-Alder addition obtaining the trans-fused adduct, which was elaborated on the alkyl chain to give **52**. Another internal Diels-Alder addition furnished tetracycle **53**, where the suitable functional groups converted to hydroxyl units gave the diisonitrile terpenoid enantio-**47**. This strategy defined unambiguously the absolute configuration of the synthetic product, so that the comparison of its optical activity with the one for natural compound allowed to define the absolute configuration for diisocyanoadocyane (**47**). Very recently, Mander proposed an alternative formal synthesis of racemic diisocyanoadocyane, according to the strategy illustrated in Scheme 7, route b [68]. The first step involved the building of phenanthrene skeleton **54** *via* alkylation followed by intramolecular cyclization, that was functionalized to **55** bearing the optimized protective groups for the successful going on of the synthesis. Opening the epoxide, C-20 functionalization to enolether and methylenation *via* a modified Simmons-Smith reaction gave **56**, which was converted to **57** by standard procedure. After extensive trials, intramolecular Michael reaction gave the tetracyclic diester **58**, the structure of which was confirmed by single-crystal X-ray analysis. By normal conversion, amine groups were located at C-7 and C-20 positions to obtain compound **59**, which was known as a product of hydrolytic degradation of natural diisonitrile **47**, as reported in a biosynthetic study of isocyanides and isothiocyanate from marine sponges [69]. This formal synthesis achieved by Mander allowed to introduce all the 10 stereogenic centres with the correct stereochemistry, although the enantioselectivity remains to be defined.

The amphilectane compounds[2] showed generally a lower activity than the tetracyclic related compounds [70]. Compounds **60** and **61** (Scheme **8**) were first isolated by Wells [71], later from the tropical sponge *Cymbastela hooperi* by

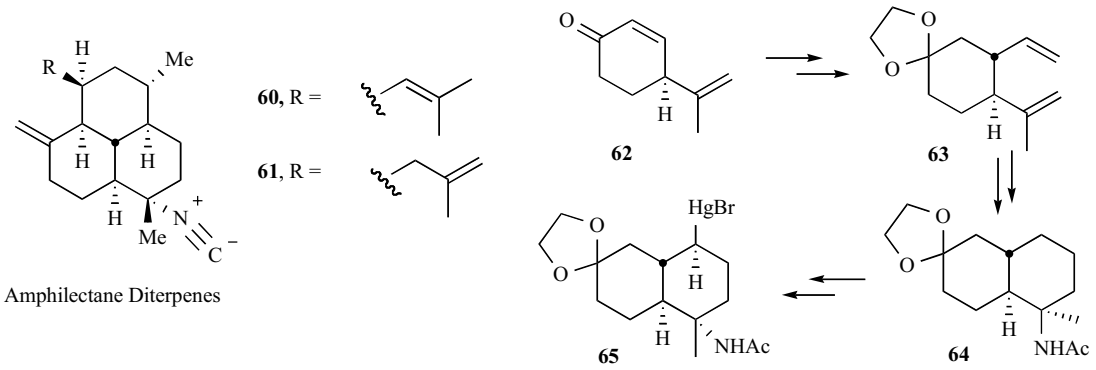
[2] For a rationalization of the trivial/systematic names of the trycyclic diterpenes including this class and neoamphilectane, as well as for the tetracyclic cycloapmhilectane and isocycloamphilectane, see reference 65.



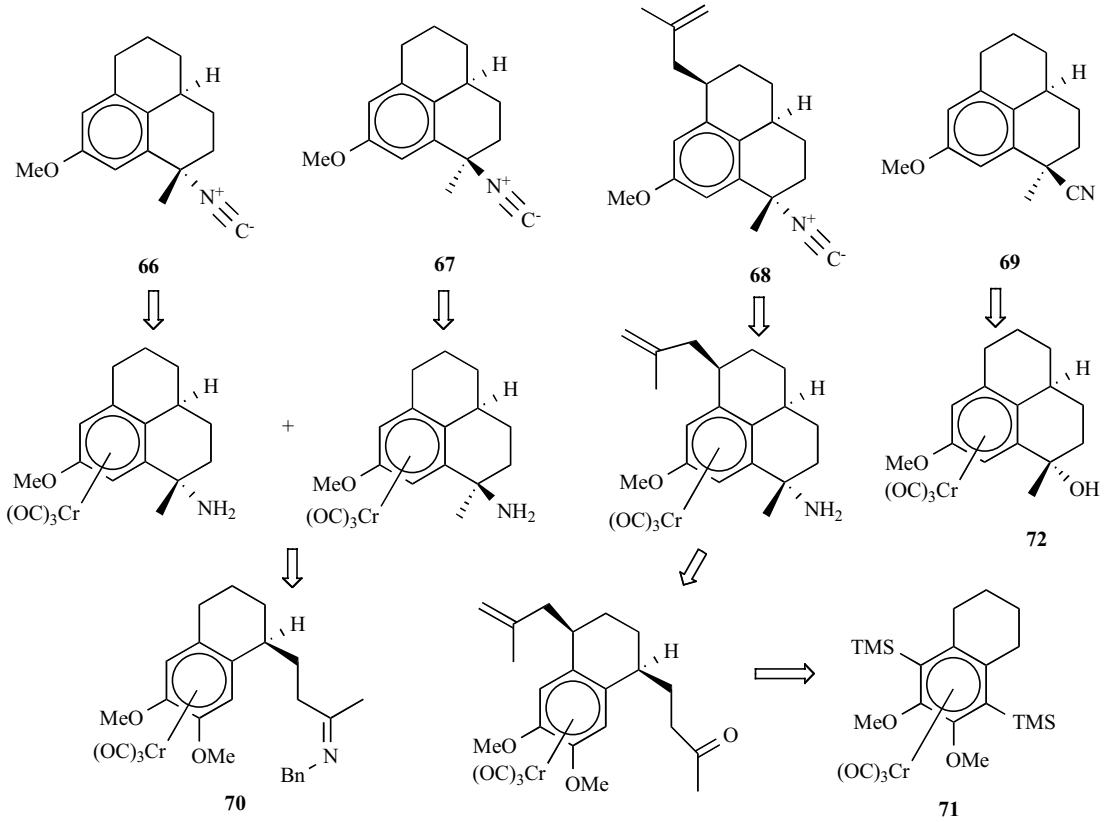
Scheme 7. Total chiral synthesis of diisocyanoadocyane (**47**) by Corey, 1987 (route a) as the first assignment of the absolute configuration and formal total synthesis by Mander, 2006 (route b).

König, who evaluated their antimalarial activity together with a wide series of isocyanate, isothiocyanate and isonitrile diterpenes [65] (Table **1**). The approach to potential intermediates for the synthesis of amphilectane diterpenes was achieved by Albizati [72]. The key compound was enone **62** which was cyclised to **64** *via* **63** and later converted to the organomercuric halide **65** (Scheme **8**). This organomercurial was proposed by the authors as a useful intermediate where several types of functionalities can be introduced for conversion to tricyclic systems present in the structures of amphilectane diterpenes.

Recently, Schmalz has synthesized the analogues **66-69** in a complete diasteroselective way (Scheme **9**) [73]. The starting chiral arene-$Cr(CO)_3$ complex **70** was cyclized by samarium iodide, its benzylic group deprotected affording the pair of diasteroisomeric amines, which were converted to the racemic isonitrile **66** and **67** under standard procedures. By starting from the suitable precursor **71**, racemic product **68** was similarly obtained. Whereas the preparation of **66** using the precursor alcohol **72** was unsuccessful, the latter was able to give racemic nitrile **69** in high yield. This study also deals with the bioactivity investigation of simplified analogues whose skeleton is structurally different from that of the natural antiplasmodial compounds. The inhibition of *P. falciparum* was evaluated against K1 and NF54 strains and all isonitriles **66-68** exhibited significant activity, while the compound **69** containing the unnatural nitrile group, was practically inactive [73]. It is noteworthy that related synthetic amphilectane-type diterpenoids containing an isonitrile



Scheme 8. Synthetic approach to the amphilectane diterpenes by Albizati (1985).



Scheme 9. Retrosynthetic analysis of amphilectane analogues by Schmalz (2002).

unit in C-8, instead of C-7 position as displayed in the natural **60** and **61**, showed antimicrobial activity and were synthesized by Piers [74].

In addition, natural neoamphilectane (corresponding to a tricyclic system formed by two six-membered and one five-membered rings[2]) were also isolated; in particular the isonitrile derivative showed considerable higher antiplasmodial activity than the isonitrile amphilectane **61** [32]. At present, only a synthesis has been reported for the access to neoamphilectane skeleton [75] by exploiting the intramolecular Diels-Alder cycloaddition of fulvene derivatives. Natural isonitriles with amphilectane (**61**) and isocycloamphilectane structures and axisonitrile-3 (**(+)-38**) served as leads for the design of simple synthetic compounds (Fig. **4**) to be used *in vivo* testing [76]. They were synthesized from the easily accessible amines by standard procedures and later tested *in vitro* against NF -54 *P. falciparum* strains; the most active was then selected for *in vivo* assays against multi-drug resistant strain of *P. yoelii* in Swiss mice. Adamantyl isonitrile showed promising activity *in vivo*, although its future development is limited by a poor therapeutic index. Recently, Wright *et al*. have investigated the 3D-QSAR with receptor modelling methodologies on a series of natural antimalarial terpene isonitriles, in order to generate a pharmacophore hypothesis in agreement with the experimental bioactivity [70]. The potent antimalarial diisocyanoadociane (**47**) and axisonitrile-3 (**(+)-38**) interacted with the free heme moiety inhibiting the sequestration of heme into β-hematin (hemozoin), thus preventing free heme detoxification. The study of the mechanism on hemozoin formation is a validated target

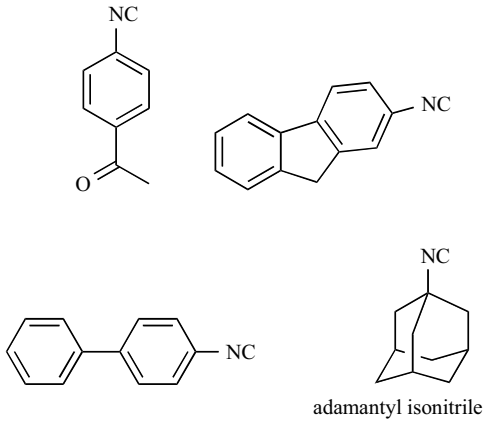


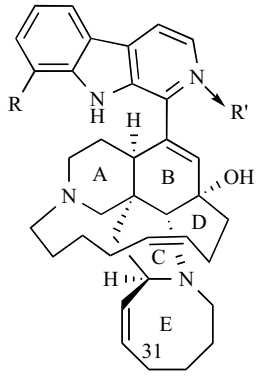
Fig. (4). Chemical structures of synthetic isonitriles.

for most of antimalarial drugs and considered a suitable target for the development of new agents [77-79].

ALKALOIDS

Among the decahydroquinoline alkaloids lepadins, lepadin E (**73**) (Scheme **10**) and its C-2 isomeric lepadin F, isolated from the ascidiana *Didemnum* sp. [80] showed the highest antiplasmodial activity, associated to a low citotoxicity (Table **1**). The biological activity seems to be dependent from C-2 configuration and from the nature of C-3 side chain. While a number of syntheses were reported for the lepadin A-C, the unique synthesis of lepadin E is by Ma [81, 82] and no access is so far known for lepadin F. In the synthetic strategy to lepadin E reported in Scheme **10**, the key intermediate was the bicyclic ketone **74**, obtained by a diasteroselective hydrogenation of the α,β-enone precursor, in turn deriving from an alkylative cyclization of the bromide **75.** This compound was available from the commercial N-Boc–(L)-alanine **76** in five steps by a literature procedure. The total synthesis of (-)-lepadin E also establishes the absolute configuration of the natural product. This strategy was also applied to the access of other members in the lepadin series and should allow the synthesis of many analogues, useful to go through an investigation of their biological activities.

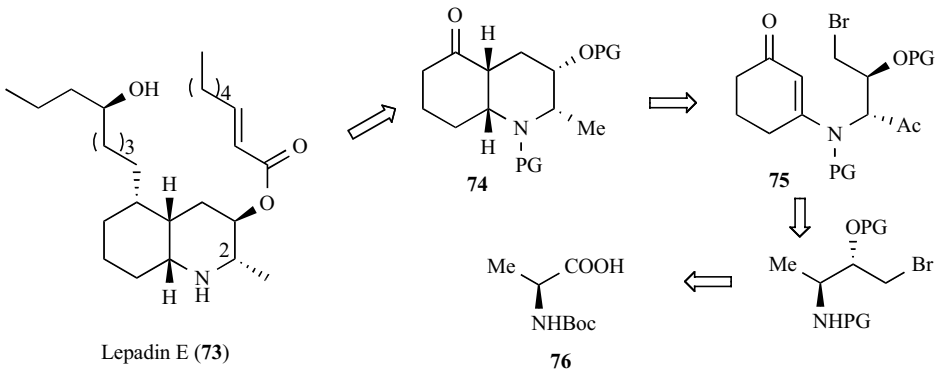
Manzamines represent one of the most promising cases of marine metabolites as leads for the development of drugs against malaria and tuberculosis [83]. A series of these alkaloids has been isolated from different species of sponges, even if this diversity may be due to association of sponges with different microbes, and have been tested against *P. falciparum* [84]. In particular, manzamine A (**77**) (Fig. **5**) was first isolated in 1986 from a sponge of genus *Haliclona* [85], (+)-8-hydroxymanzamine A (**78**) from the *Pachypellina* sp. [86] and manzamine A N-oxide (**79**) from the marine sponge *Xestospongia ashmorica* [87] resulted active against *P. falciparum*.



Manzamine A (**77**) R= H, R' = nihil
(+)-8-Hydroxymanzamine A (**78**) R = OH, R' = nihil
Manzamine A *N*-oxide (**79**) R= H, R' = O

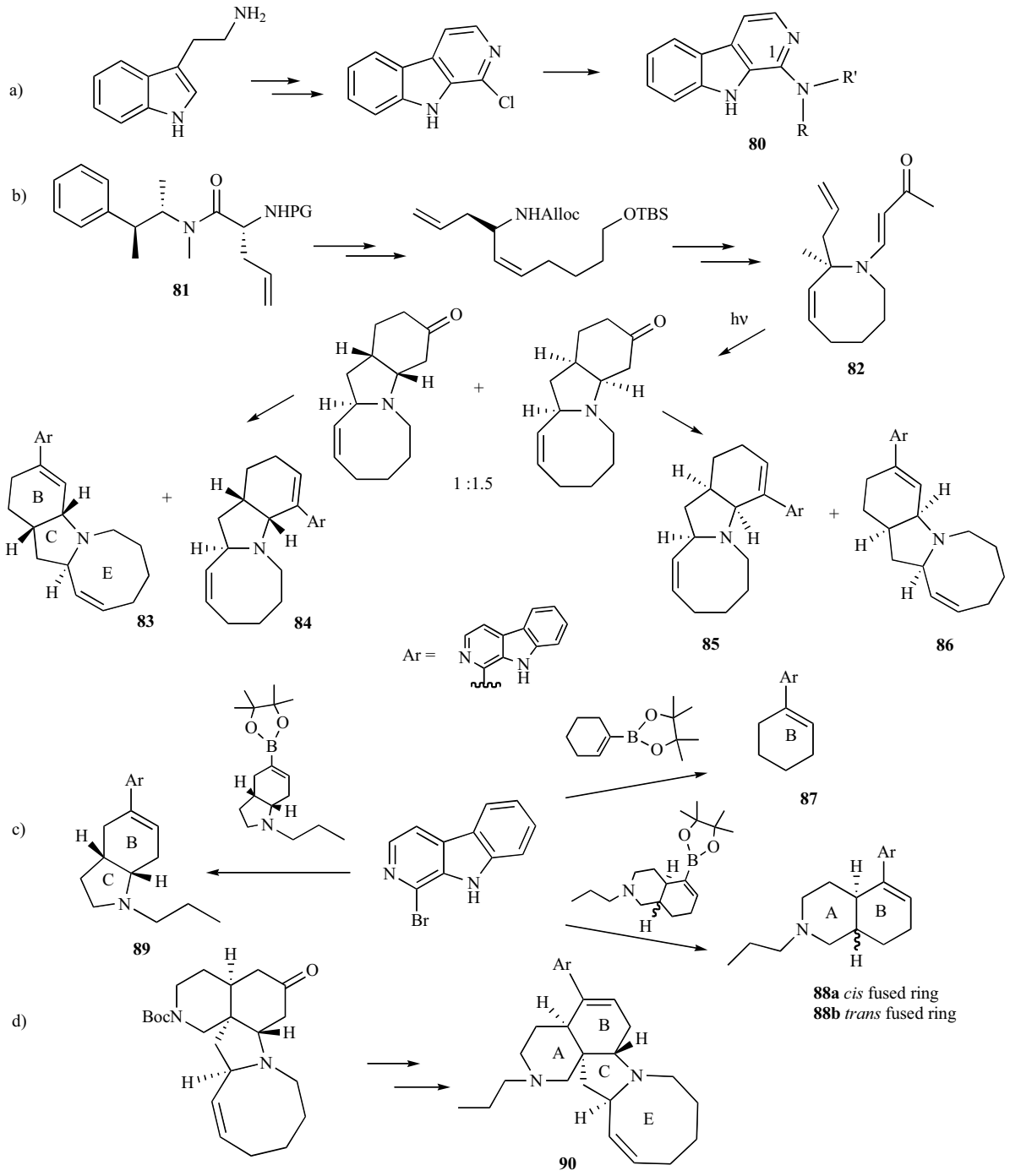
Fig. (5). Chemical structure of manzamines.

Due to their relevant role, it was important to find suitable methods for biological testing and applications. One of the most common manzamine alkaloids, (+)-8-hydroxymanzamine A, can be selectivity converted by a biocatalytic dehydroxylation with *Fusarium* or *Streptomyces* to manzamine A, the latter being a product of great worth because it showed antimalarial activity in murine model bioassays [88]. Even the enantiomeric form of **78**, (-)-8-hydroxymanzamine A, displays *in vivo* a potent antimalarial activity [89]. This evidence makes manzamines more active and less toxic than the currently clinical antimalarial drugs artemisinin and chloroquine. Minimal variations in the structure, such as a keto group in C-31 position of the analogue manzamine F, (Fig. **6**) caused a substantial inactivity [89, 90]. It has been suggested that the antimalarial effect of manzamine A on mice infected with the rodent malaria parasite *P. berghei* is due to an immune-mediated parasite clearance, with suppres-



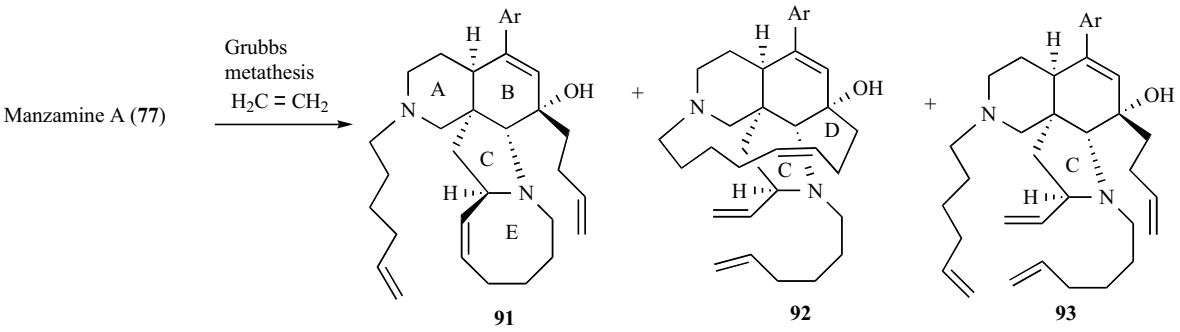
Lepadin E (**73**)

Scheme 10. Retrosynthetic analysis for lepadin E by Ma (2004, 2006).

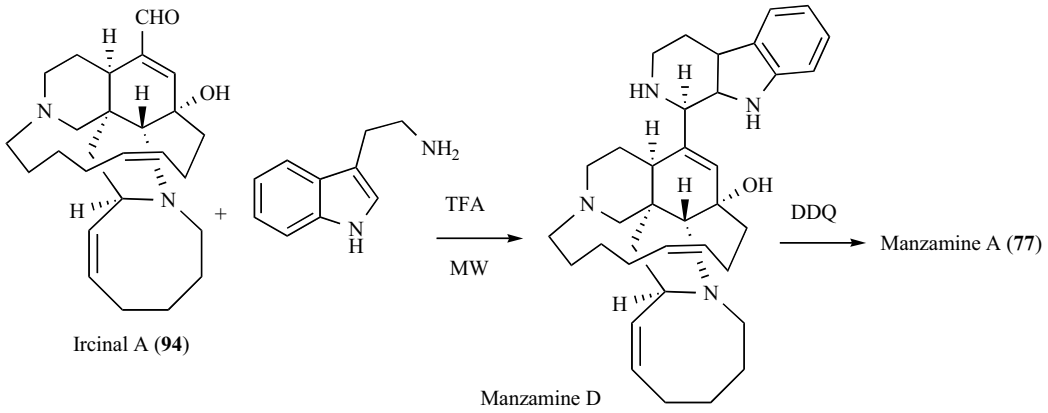


Scheme 11. Synthesis of manzamine analogues: **80** by Coldham (2004), **83-90** by Winkler and Hamann (2006).The ring labels here reported is the same as for manzamine A in Fig. (**6**).

sion of interferon-γ production and an increased production of interleukin-10 and immunoglobulin G [91]. More than 200 papers have been reported until now on this family of bioactive alkaloids, many of them devoted to their synthesis, including the first total synthesis of manzamine A achieved by Winkler at al. in 1998 [92]. In addition a considerable number of overviews summarizing the synthetic strategies to manzamines have been published, among them a recent one by Nishida [93]. A series of twelve 1-amino-substituted β-carboline (**80**, Scheme **11**) were readily prepared by reaction of 1-chloro-β-carboline with the suitable amine and tested as simple analogues of manzamine A and chloroquine. The biological investigation indicated good antiparasitic effect on *P. falciparum*, associated to a significant anticancer activity, which the authors correlate to evidence that such compounds can intercalate DNA [94]. A mini-library of simplified analogues involving the B,C and E tricyclic system was later prepared by Winkler *et al*. [95] with the aim of investigating



Scheme 12. Synthesis of manzamine A derivatives by Winkler and Hamann (2007). The ring labels here reported is the same as for manzamine A in Fig.(**6**). Ar group is the same as reported in Scheme **11**.



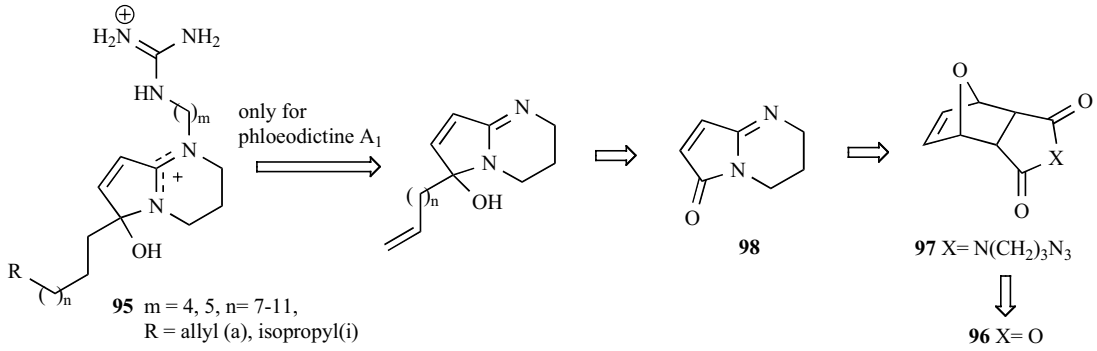
Scheme13. Synthesis of manzamine A by Hamann (2007).

the roles of the A and D rings in manzamine A structure (Fig. **6**). As the main outcome, the antimalarial activity was found to be related to the relative stereochemistry and to the orientation of the β-carboline unit. Starting from amide **81**, the substrate **82** with established absolute stereochemistry was obtained (Scheme **11**) furnishing, after a photochemically activated ring closure process, a diastereoisomeric mixture of tricyclic ketones, later converted to the four analogues **83-86**.

Compound **83**, showing the same relative stereochemistry as in natural product, exhibited the most potent activity, although all the new structures showed lower activities than natural manzamine A against W2 and D6 clones [95]. The involvement of other manzamine rings in determining bioactivity responses has been later investigated by the same authors [96] by using compounds **87-90** (Scheme **11**). Starting from the same 1-bromo-β-carboline, B analogue **87**, cis and trans AB compounds **88a** and **88b**, and BC analogue **89** were synthesized *via* Suzuki coupling of the appropriate boronic esters. Tetracyclic ABCE related compound was prepared in agreement with the first synthesis of manzamine A [92]. By comparison with the latter, a significantly attenuated activity (of ~ 10^3 factor) against W2 and D6 clones was observed for the simplifies molecules **87-89**, whereas the tetracyclic compound **90** resulted the most potent [96]. Recently, the same authors have followed a different strategy for the structural modification of natural manzamine A by using ring-opening olefin metathesis; they obtained the novel analogues **91-93** (Scheme **12**) which were tested, but none of them were more potent than manzamine A [97]. Microwave-assisted Pictet-Spengler reaction between ircinal A (**94**) and tryptamine furnished manzamine D in short reaction times and high product yields, from which manzamine A was obtained by treatment with DDQ [98] (Scheme **13**).

Phloeodictines of type A (**95**) are a class of alkaloids with the unique core structure of a 1,2,3,4-tetrahydropyrrolo [1,2-a]pyrimidinium bearing both a guanidine and an alkyl chains, first isolated from a New Caledonian sponge [99, 100] (Table **1**). Later, at least 25 different components containing many new members of the family were characterised by online liquid chromatography–electrospray mass spectrometric (LC-ESI-MS) analysis and their activity against chloroquine-resistant *Plasmodium falciparum* was investigated. Phloeodictynes[3] proved active, associated to a low value of cytotoxicity (Table **1**), with the inseparable 7: 3 mixture of the components **95** (m=5, n=7, R =i) and (m=4, n=7, R =i) as the most potent. It was noticed that the length of the alkyl chain has greater influence on bioactivity than the nature of its terminal portion whereas methylation of the guanidine moiety decreased the activity [101]. These results indicated these alkaloids as one of the most important marine leads for novel antimalarial agents [32]. The unique synthetic approach to this class of alkloids is due to Neubert and

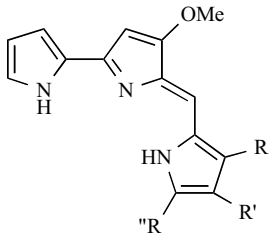
[3] The original phloeodictine naming was changed, due to the lack of providing any appropriate mnemonic aid and of reproducing no trends in chromatographic behaviour, as well as the phloeodictyne substituted phloeodictine as rightly deriving from the name of the sponge, see reference 101.



Scheme 14. Structure of phleodictines **95** and retrosynthetic pathway of phloeodictine A1 (m = 5, n = 9 , R =allyl) by Snider (2003).

Snider, who synthesized phloeodictine A1 in racemic form by a convergent strategy (seven steps, 85% overall yield) [102]. Starting from the furan Diels- Alder adduct **96**, the derived azide **97** was converted to the desired amidine **98** by using a polymer-supported aza-Wittig reaction as key step and a retro Diels-Alder reaction to liberate the double bond. The alkyl chain was then introduced by addition of the Grignard reagent, whereas the guanidine chain came by nucleophilic substitution with the suitable N-Boc-protected guanidine iodide (Scheme **14**).

Prodigiosin family includes red pigments characterized by a common pyrrolylpyrromethene skeleton produced by various bacteria from marine [103] and terrestrial sources, showing a wide range of remarkable biological activities. The chemistry and the biology of these peculiar natural products, including the past popular beliefs ascribing prodigious events to the presence of these metabolites, were recently masterful discussed in a review [104]. Prodigiosin (**99**) and heptylprodigiosin (**100**), the latter isolated from α-proteobacteria [105] (Fig. **6**), exhibited potent antiplasmodial activity, although their high general toxicity precluded any potential development as a clinical agent [106]. The stable fluorescent red pigment cycloprodigiosin as hydrochloric salt (**101**) suppressed T cell proliferation leading to apoptosis



Prodigiosin (**99**) R =H, R' = nC_5H_{11}, R" = CH_3

Heptylprodigiosin (**100**) R =H, R' = nC_7H_{15}, R" = CH_3

Cycloprodigiosin (**101**) R,R' =  , R" = CH_3

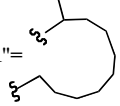
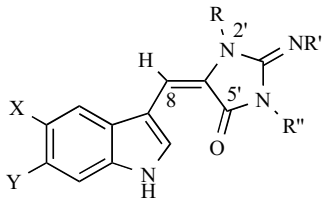
Metacycloprodigiosin (**102**) R,R"=  , R' =H

Fig. (6). Chemical structures of prodigiosins.

[107]. Later, the same authors reported that it showed *in vitro* stronger inhibition of *P. falciparum* than chloroquine (Table **1**) without affecting growth rate of mammalian cells [108]. A related member of this alkaloid class, metacycloprodigiosin (**102**) isolated from a streptomyces found in a soil sample [109, 110] was active against *P. berghei* in mice and inhibited multidrug-resitant strain *P. falciparum*, both *in vitro* and *in vivo*, with a weak cytotoxicity [110].

A series of synthetic approach to some members of prodigiosin family were carried out since 1960, when a partial synthesis allowed to define their correct structure. Recently a comprehensive review of these compounds has been reported, including a discussion of their bioactivities and total synthesis, the latter allowing access to a number of natural prodigiosins and synthetic analogues [111]. Tautomeric equilibria in synthetic compounds containing a phenolic ring as a replacement of the pyrrole-A unit were studied as cromophores in various solvents, with the aim to improve the biological properties (anti-infective, immunosuppressive and anticancer) of prodigiosins [112].

6-Bromoaplysinospin (**103**) (Fig. **7**) belongs to the indole alkaloid class of aplysinopsins. After the first isolations [113, 114] (Table **1**), it was later found in other sponges and corals together with other members of aplysinopsins. By investigation of Porifera metabolites as agents to treat infectious diseases, some aplysinopsins exhibited significant antimalarial activity [115]. In particular, 6-bromoaplysinopsin resulted the most potent against *P. falciparum* (Table **1**), aplysinopsin



6-Bromoaplysinopsin (**103**) X=R'=H, Y=Br, R=R"=Me

Aplysinopsin (**104**) X =Y=R'=H, R=R"=Me

Isoplysin A (**105**) X=Y=R"=H, R=R'= Me

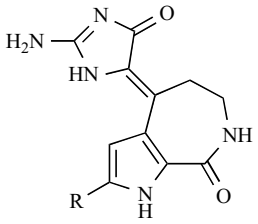
5-Bromoaplysinopsin (**106**) X =Br, Y=R'=H, R=R"=Me

Fig. (7). Chemical structures of aplysinopsins.

(**104**) showed no activities, isoplysin A (**105**) and 5-bromo-aplysinopsin (**106**) showed a moderate effect. Moreover, the latter compound inhibited the antimalarial target plasmepsin II enzyme.

Various synthetic approaches towards these metabolites and their synthetic analogues have been developed, implying base- condensation of indol-3-carboxaldehyde or its 5- or 6-bromo derivatives with a) the suitable five-membered heterocycles to give, by solventless conditions and high stereoselectivity, a product that could be converted in its Z or E isomers by photoisomerisation [116], b) guanidinoacetic acid to be subjected to a subsequent cyclisation [117], c) ethyl azidoacetate converted into iminophosphorane to give a product that was subjected to aza-Wittig-type reaction [118]. A recent review summarizes the syntheses of aplysinopsin and related compounds [119]. It is noteworthy that the assignment of Z/E configurations for aplysinopsins is not trivial, especially for those analogues lacking the methyl group in N-2' because NOE measurements can not provide any configurational information; in these cases different long range H-C(8), C(5') heteronuclear coupling values for E and Z isomers resulted decisive for an unambiguous assignment [116, 120].

Although direct bioactivity is not reported on *Plasmodium* sp., some marine metabolites have shown a potential interest. It is the case of the sponge alkaloids hymenialdisine (**107**), 2-debromohymenialdisine (**108**) (Fig. **8**) and their synthetic 2-substituted derivatives (R= alkyl, phenyl) inhibiting cyclin-dependent kinases (CDKs), which are enzymes well conserved among eukaryotic species and several of them have been isolated from *P. falciparum* [121].



Hymenialdisine(**107**) R= Br

Debromohymenialdisine (**108**) R= H

Fig. (8). Chemical structure of marine alkaloids with CDKs inhibition activity.

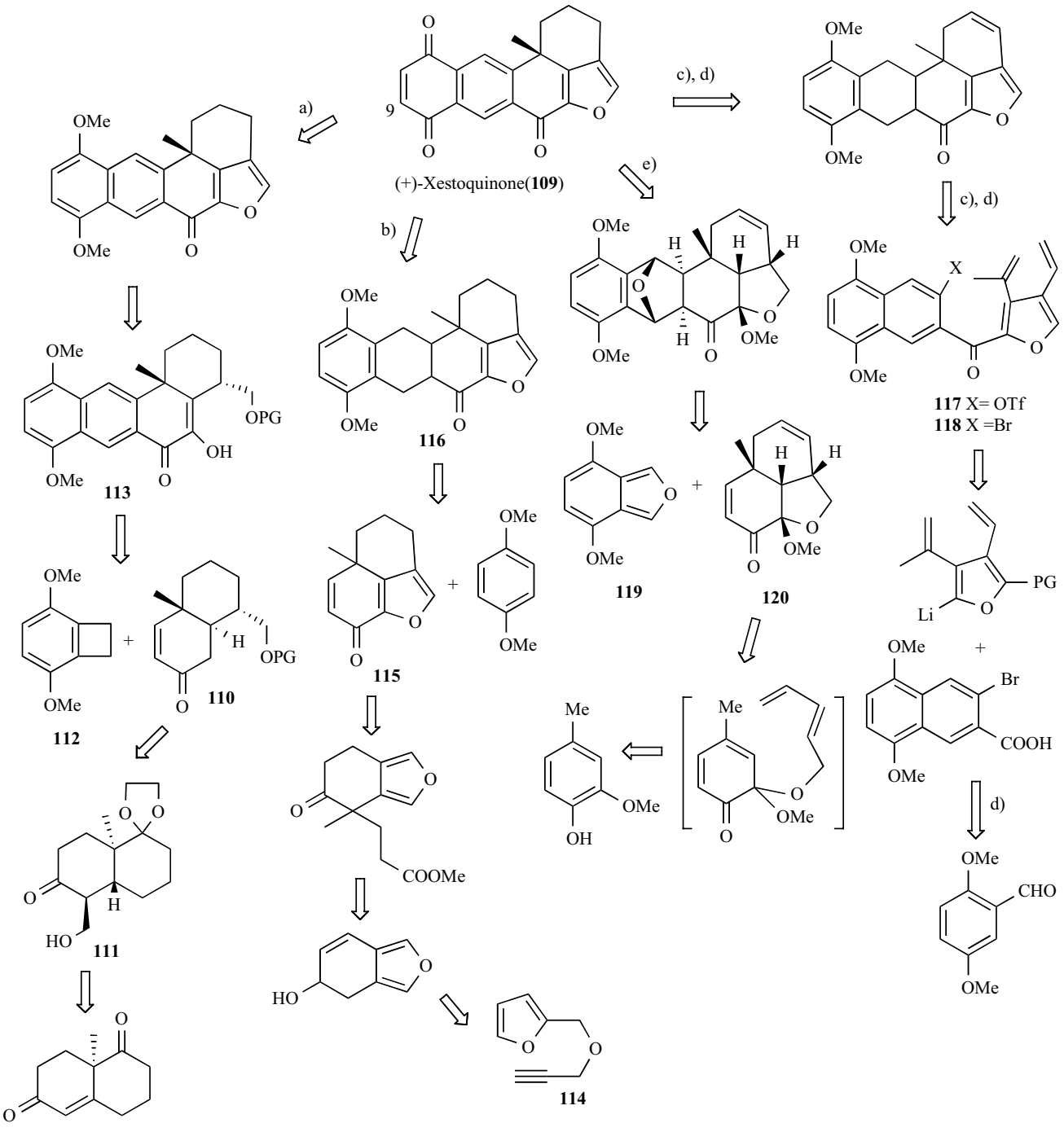
MISCELLANEOUS

A bioassay-guided fractionation of extract of *Xestospongia* sp. led to the isolation of the polyketide xestoquinone (**109**) (Scheme **15**) which a) inhibited Pfnek-1 kinase with an IC_{50} around 1 μM, b) showed moderate *in vitro* antiplasmodial activity (Table **1**) and c) exhibited a weak *in vivo* activity at 5 mg/kg in *P. berghei* NK65 infected mice [122]. The first total synthesis of (+)-xestoquinone was achieved by Harada in 14 steps [123]. Enone **110**, prepared from Wieland- Miescher ketone *via* hydroxyl methyl ketone **111** of known absolute configuration, gave Diels-Alder cycloaddition with dimethoxybenzocyclobutene **112** and finally furnished the cycloadduct **113**. Cyclization to furan unit on this compound allows to obtain the pentacyclic precursor of (+) xestoquinone (Scheme **15**). Its absolute configuration was established by obtaining superimposable CD spectra of synthetic and natural compounds. Later, Kanematsu *et al*. developed a new synthesis, based on their method to convert 2-substituted furan **114** to a 3,4- fused furan *via* intramolecular Diels-Alder cyclization. The product was functionalized to furnish the tricyclic compound **115**, which gave the pentacyclic adduct **116** by Diels- Alder reaction with p-dimethoxybenzene [124]. By a palladium(0)-catalyzed polyene cyclization, the first total asymmetric synthesis of (+)-xestoquinone has been accomplished in 68% ee using in the key step (S)-(+)- 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as the chiral ligand to obtain the cyclization of triflate **117**, whereas poor enantioselectivities were given by the corresponding naphthyl bromide (Scheme **15**, route c) [125]. By using a cascade-type asymmetric Heck reaction of aryl bromide **118** in the presence of a silver salt, the xestoquinone precursor was obtained, as illustrated in route d (63% ee, 39% yield) [126]. Racemic xestoquinone was prepared in overall yield of 18.3% using isobenzofuran **119** and naphthofuranone **120** by the sequence summarized in route e, which furnished also 9- and 10-methoxy derivatives [127].

The first total synthesis of aplasmomycin (**121**, Scheme **16**), a macrolide of mixed biogenesis isolated from a strain of *Streptomyces* which inhibits the growth of gram-positive bacteria and shows *in vitro* and *in vivo* antiplasmodial activity [128], was achieved by Corey [129]. In a retrosynthetic analysis, the $B(OMe)_3$ functionalization of the macrocyle is derived from coupling of two identical C(1)-C(17) fragments **122**, in turn obtained starting from D-mannose and (+)-pulegone (Scheme **16**). In a subsequent formal synthesis, Matsuda synthesized Corey's key intermediate **123** by connecting the two C(3)-C(11) and C(12)-C(17) segments, the latter based on asymmetric reduction of ketone **124** [130]. White used the same disconnection strategy proposed by Corey, but the intermediate **125** was prepared by using enatiomerically pure **126** from HPLC isolation [131].

The aplasmomycin tetrahydrofuran unit was derived by involvement of compound **127** obtained by deiodination and Mitsunobu inversion of **128**, in turn formed by a stereocontrolled 5-endo-cyclization of linear diol **129** from a highly regio- and enantioselective asymmetric dihydroxylation of the diene precursor [132] (Scheme **16**). A series of analogues of the monoterpenic moiety of aplasmomycin were synthesized by Wittig reaction and tested *in vivo* against *P. berghei* yoelli. Some of them (Scheme **17**) showed activities similar to artemisinin (40 mg / kg) [133]. Later, the same authors investigated derivatives of ester **130** as antimalarial agents in chloroquine-sensitive *P. falciparum* strains, observing a dose-dependent inhibition in the range 1mM without showing any toxicity [134].

Bielschowskysin (**131**, Fig. **9**) is a gorgonian-derived diterpene with a highly oxygenated hexacyclic structure based on a previously undescribed ring system, the structure of which established through spectroscopic and X-ray crystallographic analyses. It exhibited activity against *P. falciparum* (IC_{50} 22 μM), but associated to a strong *in vitro* cytotoxicity against small cell lung cancer and renal cancer cells, so

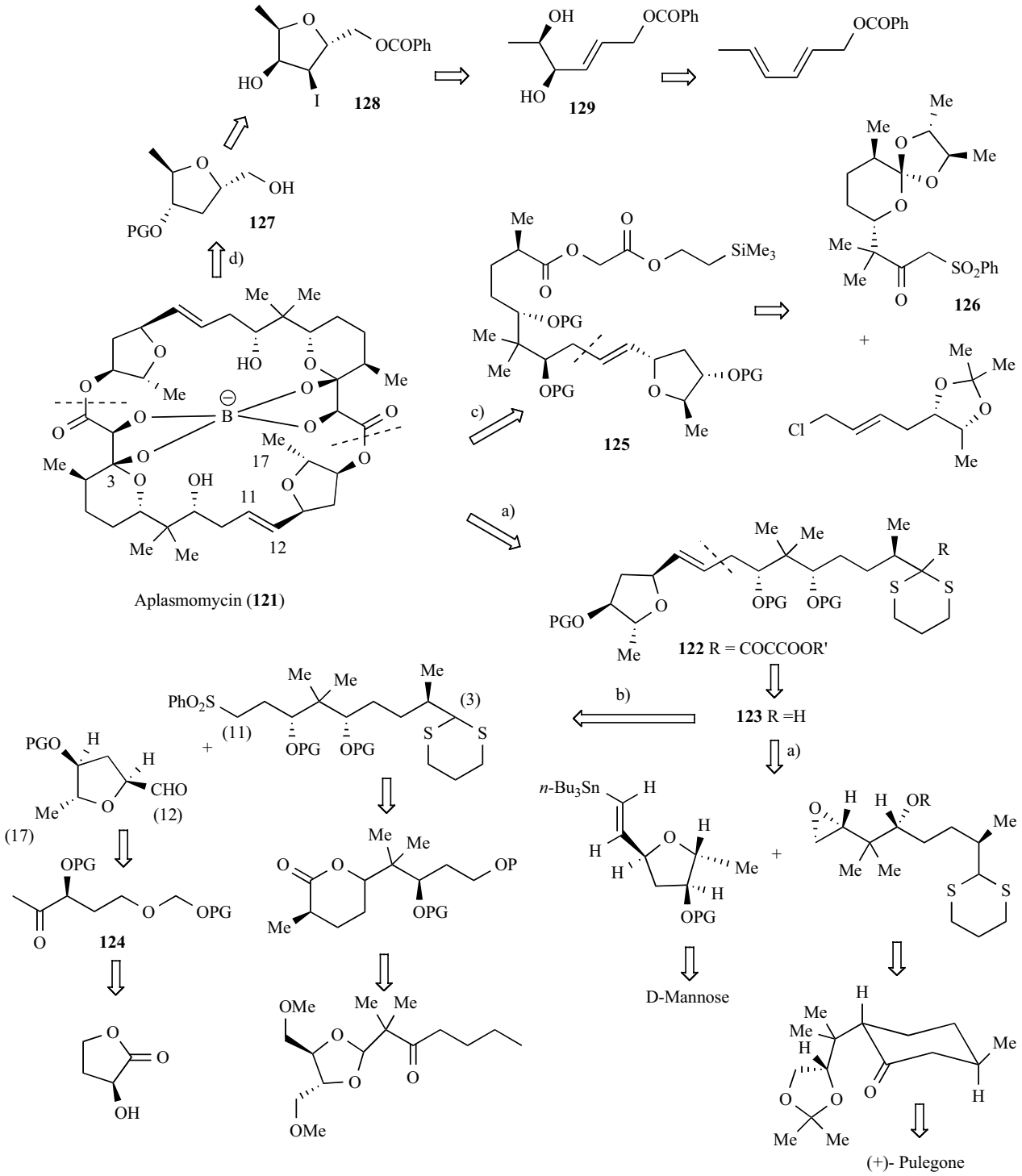


Scheme 15. Synthesis of xestoquinone in chiral form by Harada, 1990 (route a), Kanematsu, 1991(route b), Keay, 1996 (route c), Shibasaki, 1998 (route d), and in racemic form by Rodrigo, 2001 (route e).

that it was not a good candidate as an antimalarial agent due to its very low selectivity index [135].

The sesquiterpene joint to a phenolic moiety, named 15-oxopuupehenol (**132**, Scheme **18**) isolated from sponges *Hyrtios* spp., showed *in vitro* antimalarial activity (Table **1**) [136].

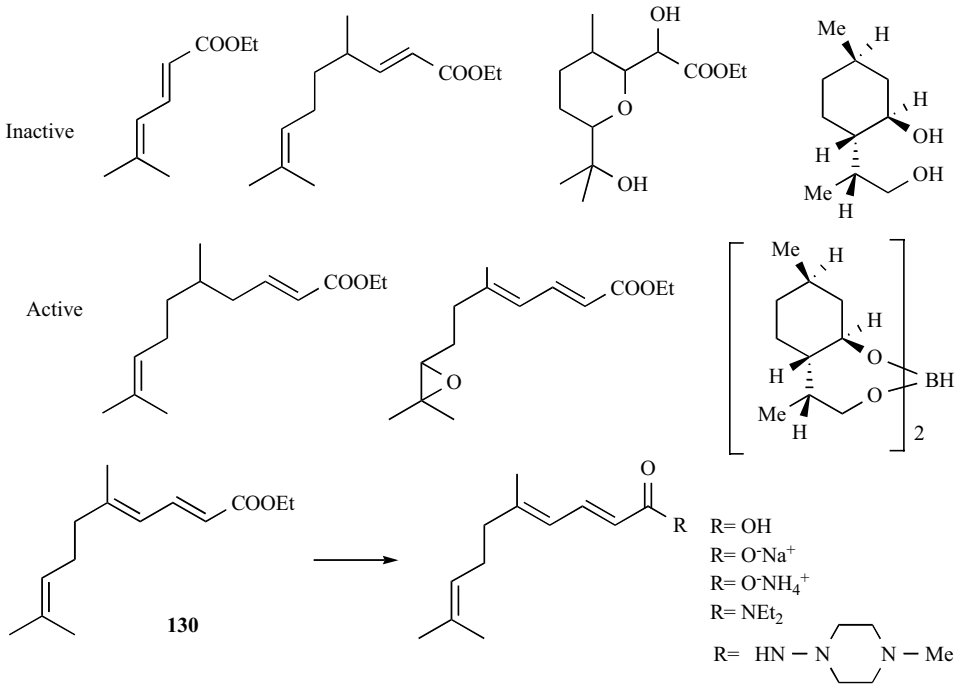
Total synthesis of both enantiomers of methylendioxy derivatives of natural **132** was planned by Arjona in 11 steps. The aromatic unit was introduced starting from sesamol, whereas cyclization of trans,trans-farnesol gave racemic drimenol whose enantiomers were resolved through chromatographic separation of diasteromeric canfanoates (in Scheme **18** is reported the retrosynthetic pathway for only one enan-



Scheme 16. Synthesis of aplasmomycin by a) Corey, 1982 (route a) , Matsuda, 1990 (route b) and White, 1986 (route c) and of the tetrahydrofuran unit by Knight, 2000 (route d).

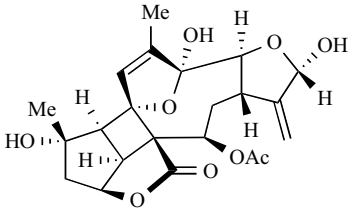
tiomer). However, problems were found related to the deprotection of methylendioxy group in **133**, so that 15-oxopupehenol was not accessible using this sequence. In addition, antimalarial activity of these derivatives was not reported [137]. Recently, the first enantiospecific synthesis of **132** was achieved in 19 steps and 14% overall yield. Starting from (-)-sclareol, the key step is represented by the palladium(II)-mediated diastereoselective cyclization of drimenylphenol **134** (Scheme **18**). In comparison with the previous synthesis by Arjona, here the phenolic groups were protected using the more easily removable benzyl group [138].

Another example is given by α-galactosylceramides. Agelasphin-9b (**135**, Fig. **10**) was isolated as a member of a series of antitumour and immunostimulatory cerebrosides



Scheme 17. Monoterpenic Fragment Analogues of Aplasmomycinby Bhat, 1991 and 1995.

from an Okinawan sponge [139] and was synthesized so that to establish its absolute strereochemistry [140]. Later, the simplified synthetic analogue KNR7000 (**136**) [141] showed a rapid and potent antimalarial activity by an *in vivo* murine model, inhibiting the development of the intrahepatocytic stages of the rodent malaria parasites *P. yoelii* and *P. berghei*. This represents an indirect effect due to the selective activation of Vα14 natural killer T cells which are particularly abundant in liver [142].

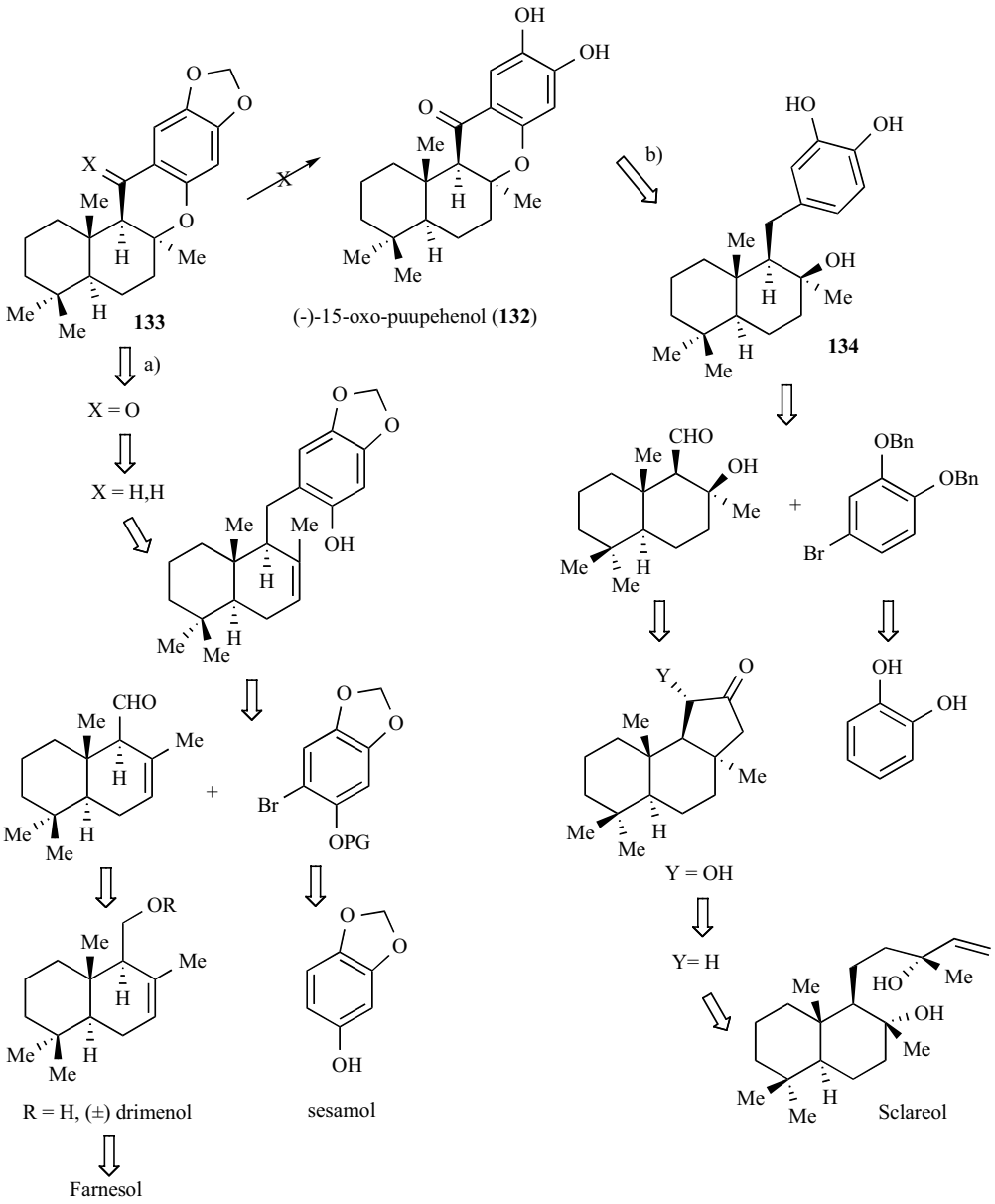


131

Fig. (9). Chemical structure of bielschowskysin.

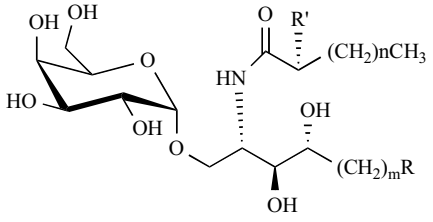
CONCLUSION

In the survey of marine natural products inhibiting *Plasmodium* strains and exhibiting low cytotoxicity in order to represent good candidates for new therapeutical agents, the potential of chemical synthesis has been discussed for a series of compounds. The alkaloid manzamines, representing one of the most promising cases due to their higher and less toxic activity than the currently clinical antimalarial drugs artemisinin and chloroquine, were synthesized and investigated by SAR studies on synthetic analogues, observing that small structural modifications caused a basic substantial inactivity. Concerning other promising molecules, axisonitrile-3, lepadin E and isonitrile diisocyanoadocyane were obtained by total synthesis in enantiomeric form thus establishing their absolute configuration. Amphilectane analogues were synthesized in a complete diasteroselective way, whereas simple synthetic compounds with amphilectane and isocycloamphilectane structures were used for *in vivo* bioassays. Other marine metabolites belonging to the series of the most promising candidates include alkaloid phloeodictines, for which the approach was restricted to the synthesis in racemic form of the component A1 and isonitrile kalihinol A, only the core-structure of which have been so far synthesized. Macrolide aplasmomycin was obtained by total synthesis and a series of analogues bearing a monoterpenic fragment were produced and tested *in vivo*, exhibiting activities similar to artemisinin. Indole alkaloid 6-bromoaplysinospin and phenolic sesquiterpene 15-oxopuupehenol were available by total synthesis, as well as polyketide xestoquinone, inhibiting Pfnek-1 kinase, was obtained both in racemic and in chiral form. Total synthesis of natural *enantio*-sigmosceptrellin A methyl ester has never been obtained, but asymmetric synthesis on its degradation product has allowed an unequivocal assignment of the absolute stereochemistry. Synthetic strategies have given access to analogues of both endoperoxides peroxyplakoric acid methyl esters and plakortin, the latter by a semi-synthetic approach furnishing derivatives where small changes in the alkyl side chain decrease the activity, hence providing useful indications on the mechanism of action for simple endoperoxides related to the natural product. Total synthesis and access to synthetic analogues were also carried out for prodigiosin and heptylprodigiosin, natural pigments exhibiting potent antiplasmodial activity although their high toxicity precluded any potential development as a clinical agent. Synthesis was able to assign absolute strereochemistry of α-galactosylceramides agelasphin-9b and a simplified synthetic analogue showed a potent antimalarial activity *in*



Scheme 18. Synthesis of 15-oxo-puupehenol derivative by Arjona, 1997 (route a) and of the natural compound by Alvarez-Manzaneda, 2005 (route b).

vivo due to an indirect effect as immunomodulator in activation of natural killer T cells.



Agelasphin-9b (**135**) m=11, n =21, R= isopropyl, R'=OH

KRN7000 (**136**) m=11, n =23, R= propyl, R'=H

Fig. (10). Chemical structures of bioactive α-galactosylceramides.

ACKNOWLEDGEMENTS

The authors thank Dr. Boga Carla, Department of Organic Chemistry "A. Mangini", University of Bologna (Italy) for help in providing literature and Dr. Paul Stratton for the careful reading of the manuscript.

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Received: 19 March, 2008 **Revised: 15 April, 2008** **Accepted: 06 May, 2008**

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