Synthetic Strategies to Terpene Quinones/Hydroquinones

Marina Gordaliza

Farmacy Faculty and Institute of Science and Technology Studies, Campus Miguel de Unamuno, Salamanca University, 37007 Salamanca, Spain; E-Mail: mliza@usal.es; Tel.: +34-923-294528; Fax: +34-923-294515

Received: 26 December 2011; in revised form: 3 February 2012 / Accepted: 3 February 2012 / Published: 14 February 2012

Abstract: The cytotoxic and antiproliferative properties of many natural sesquiterpene-quinones and -hydroquinones from sponges offer promising opportunities for the development of new drugs. A review dealing with different strategies for obtaining bioactive terpenyl quinones/hydroquinones is presented. The different synthetic approaches for the preparation of the most relevant quinones/hydroquinones are described.

Keywords: terpene quinone; terpene hydroquinone; synthesis; chemical modification

1. Introduction

The chemical substances from plants and animals have been and remain to be an important source of drugs and products used in food products, cosmetics and agriculture, amongst other fields. Natural compounds offer an enormous structural diversity and in some cases, a big biological power and thus it is unlikely that the chemistry of synthesis can replace cellular biochemistry as the source of new compound. These observations, in addition to the enormous biodiversity of the planet (plants, sea and microorganisms), which is in a lot of cases inexplored, point to natural compounds as a promising source of drugs [1–45].

Natural products have been a rich source of agents of value to medicine. More than half of the currently available drugs are natural compounds or are related to them, and in the case of cancer this proportion surpasses 60% [4,8]. This situation is accompanied by increasing interest from drug companies and institutions devoted to the search for new drugs [46,47]. Additionally, many new natural compounds of diverse structures have been considered prototypes, leads or heads of series and their later structural modification has afforded compounds with pharmacological activity and extraordinary therapeutic possibilities [11,22,25,26,48].
The research in natural compounds, which is continually expanding and is of enormous interest, explores new compounds coming from different sources, among which the sea could be considered as an almost infinite source of natural resources, some of which have important therapeutic potential [49–126]. The discovery of drugs from marine natural products has enjoyed a renaissance in the past few years. Ziconotide (Prialt®; Elan Pharmaceuticals), a peptide originally discovered in a tropical cone snail, was the first marine-derived compound to be approved in the United States in December 2004 for the treatment of pain [127]. Combination of ziconotide and morphine allows safe and rapid control of oral opioid-refractory malignant pain [128]. In October 2007, trabectedin (Yondelis®; PharmaMar) became the first marine anticancer drug to be approved in the European Union. Trabectedine is an intravenous antineoplastic agent originally derived from the Caribbean marine tunicate Ecteinascidia turbinata and now produced synthetically [129]. Trabectedine shows variable levels of activity against several types of solid tumor including soft tissue sarcoma, ovarian cancer, breast, melanoma, non small lung cancer, prostate and endometrial cancer [130–132]. The drug is especially active in leiomyosarcoma and liposarcoma and is a therapeutic option in the palliative approach to the metastatic uterine leiomyosarcoma patient [133]. Eribulin mesylate (E7389), designed by the Japanese laboratory Eisai (Eisai Research Institute, Andover, MA, USA), shows antitumor properties for the treatment of breast cancer [134]. This is a synthetic analogue of the natural product halichondrin B, isolated from Halichondria okadai (Lissodendoryx sp.), a marine sponge commonly found in Japanese seas; its antitumor activity was discovered in 1986. Eribulin binds to the vinca domain of tubulin and inhibits the polymerization of tubulin and the assembly of microtubules, resulting in the inhibition of mitotic spindle assembly, the induction of cell cycle arrest at G2/M, and, potentially, tumor regression. Eribulin mesylate is now in phase II clinical trials and is active in metastatic or locally advanced breast cancer [135–138].

Excellent reviews on natural compounds of marine origin have been published [49–126] that explore the taxonomy, structural elucidation, role of databases, biosynthetic studies, biomedical potential, synthesis and the technologies necessary for advancing bioactive marine natural product lead compounds into actual pharmaceuticals. Amongst these, the recently published review by Fattorusso et al. [124] particularly stands out.

Among the natural compounds that are receiving an increasing interest we can find the terpenylpurines and the terpenilquinones from marine sources [139,140]. Particularly, the terpenylquinones constitute an interesting group of marine natural product [141–143] for which a wide variety of biological activities have been described, including anti-inflammatory, antifungal, anti-HIV and most often antitumor activities [144,145].

The cytotoxic and antiproliferative properties of many natural sesquiterpene quinones and hydroquinones from sponges of the order Dictyoceratida [71,76,140,144] such as avarol 1, avarone 2, illimaquinone 3, nakijiquinone 4 and bolinaquinone 5 (Figure 1), among others, offer promising opportunities for the development of new antitumor agents [144,145]. This has sparked interest in the chemical composition and cytotoxicity of a large number of marine species that contain metabolites with hybrid structures between terpenes and quinones/hydroquinones [76,140,141,146–150].
Avarol 1 and avarone 2 are the most representative compounds of bioactive terpenequinones. In addition to the above-mentioned pharmacological properties, two monophenyl thioavarol derivatives have recently been described as lacking cytotoxicity, which could point to promising UVB photoprotective agents through the potent inhibition of NF-kappaB activation [151] with a mild antioxidant pharmacological profile. Various formulations with high avarol 1 content have been used for the prevention and treatment of psoriasis, dermatitis, skin cancer, tumors in the gastrointestinal tract, urinary tract and viral infection [152].

It is also important to note the antituberculosis and antimalarial activities of puupehenone 6 [93,153,154], the cardiotonic activity of xestoquinone 7 [155], the antifungal activity of several nakijiquinones 4 [156] and the antiinfective activity of aureol derivatives 9 [157].

Sesquiterpenequinones represent a substance class with increasing pharmacological interest [140]. New developments and new discoveries in the field of terpenequinones continually occur. Recently, neopetrosiquinones A 10 and B 11 (Figure 2), sesquiterpene benzoquinones have been isolated from the deep-water sponge Neopetrosia cf. proxima, of the Petrosiidae family [158]. Neopetrosiquinones A 10 and B 11 inhibit the in vitro proliferation of the DLD-1 human colorectal adenocarcinoma cell line with IC_{50} values of 3.7 and 9.8 μM, respectively, and the PANC-1 human pancreatic carcinoma cell line with IC_{50} values of 6.1 and 13.8 μM, respectively. Neopetrosiquinone A also inhibited the in vitro proliferation of the AsPC-1 human pancreatic carcinoma cell line with an IC_{50} value of 6.1 μM. The compounds are structurally related to known terpene quinine xestoquinone 7. This research is part of the program to identify novel marine natural products with therapeutic properties from a library of extracts of the Harbor Branch Oceanographic Institute (HBOI) [158].
Regarding the mechanism of action of terpenylquinones, the accumulated data about the biological activity of quinone moieties suggest redox processes and/or Michael-type addition-elimination reactions [144]. Their cytotoxicity has been explained in terms of their ability to undergo redox cycling and the generation of reactive oxygen species, which would damage tumor cells [159–161]. NADH/NAD⁺ dehydrogenase reduction of the several terpenylnaphthoquinones increases the rate of oxygen consumption, such rates being higher for quinones with more positive redox potentials. In this process, reactive oxygen species are formed in small amounts, which also correlate with the quinone redox potential. Semiquinone derivatives of these quinones are generated under anaerobic conditions and in the presence of NADH/NAD⁺ dehydrogenase. Since this enzymatic system is found in mitochondria, a possible pathway in the cytotoxic activity of these terpenylnaphthoquinones could be by interference with or the inhibition of mitochondrial respiration, as reported for other naphthoquinone derivatives, in addition to free radical degradation [162,163]. The results obtained with avarol 1 and avarone 2 supported the mechanism of antitumor action via the reactive oxygen radicals [164,165] but there were also indications of the relevance of arylation of biomolecules, such as proteins [144,166,167].

Regarding such terpenquinone structures, many studies have been published addressing the isolation, structural elucidation, activity and mechanisms of action of the compounds [140,143,144,146,147,160]. We present in this review a compilation of the different synthetic approaches for the preparation of the most relevant compounds.

2. Synthetic Approaches Terpenylquinone/Hydroquinone

The synthesis of marine natural products has been widely researched and published in excellent reviews [3,168–183], and is of particular interest in the case of compounds that have some kind of biological or therapeutic activity. The two major obstacles to advancing a natural product lead into drug development are compound supply and adequate structural elucidation. One must not underestimate how much material may be needed. Even the most straightforward courses of pre-clinical studies require hundreds of grams of highly consistent well-characterized product, which represents a major hurdle for natural products derived from non-renewable sources [3]. Therefore, it is of interest to consider the relative role of chemical synthesis in the structure elucidation. Moreover, in the case of revision of relative and absolute configuration, total synthesis is a proven partner for natural product structure elucidation for marine, as well as terrestrial species [169]. Structural misassignments continue
to be made even for recently reported marine natural products, and thus, it seems that the increasingly high-field magnets and sensitive probes do not necessarily attenuate the rate of structural misassignments. Rather, they permit the attempted structure elucidation of increasingly limited quantities of minor components from natural products extracts, as well as larger molecules of greater structural complexity. Therefore, total synthesis of natural products will surely continue to be central to the confirmation of the structure of natural products, as well as providing material for biological testing towards pharmaceutical development, and investigations of biosynthetic pathways [169]. Advances in total synthesis, especially function-oriented syntheses, biosynthetic technologies and genomic research offer new strategies for the medicinal chemical optimization of biologically active secondary metabolites as sources of novel drug leads [3].

In the case of biologically active terpenoquinones, the limited quantities components from the natural sources and the structural complexity are the main problems in continuing the clinical studies. Most of these terpenoquinones are characterised by possessing a quinone fragment attached to a terpenoid, which usually includes a decaline core, mostly with a drimane or rearranged drimane skeleton. Most sesquiterpenoquinone/hydroquinones have been isolated from sponges, although some of them have been described from brown algae [74] and fungi [184]. The initial extract of the natural material usually consists of a complex mixture after fractionation. It may contain small quantities of bioactive substances, often as a mixture with structurally related molecules. The initial concentration of an interesting compound may be too low to be effectively tested in some biological and pharmacological assays. Thus, compounds have become attractive to carry out its total synthesis and obtaining of derivatives to improve the biological properties of natural compounds. Consequently, the development of these marine natural products is highly desirable and worthwhile from the viewpoint of medicinal chemistry and pharmaceuticals.

In the present paper, the most interesting strategies addressed in the total synthesis of sesquiterpenoquinones by terpenic structure coupling to an aromatic ring have been reviewed. In general, the strategies employed in the total synthesis of sesquiterpenoquinones, are as follows:

- Diels-Alder cycloaddition reaction.
- Coupling of the aldehydes with lithiated hydroquinone ether.
- Radical decarboxylation and quinone addition reaction
- Grignard reagent conjugated addition to α,β-unsaturated carbonyl group.
- Reductive alkylation of enones.
- Cross-coupling reaction.
- Furylation of quinones.
- Furan polyene cationic cyclization.

In addition, the application of cell culture for the production of bioactive compounds from sponges is a promising way to utilize the bioactive potential of marine terpenoquinones sources.

3. Diels-Alder Cycloaddition Reaction

The Diels-Alder cycloaddition reaction continues to fuel the imaginations of synthetic chemists engaged in the assembly of complex molecular structures, in particular biologically significant
natural products and provide rich opportunities for the rapid and selective generation of molecular complexity [185].

Mamanuthaquinone 12 is a cytotoxic metabolite collected in the Fiji islands from Fasciospongia sp. [186]. In the first total synthesis of (±)-mamanuthaquinone 12 (Scheme 1) [187] an exothermic Diels-Alder reaction have been used as main reaction, giving the decalin system that already contains the aromatic moiety. The Diels-Alder reaction proceeded via an *exo* transition state, favored by the steric hindrance between the aromatic ring of 13 and a methyl of the cyclohexene 14. This *exo* approach mode reached the desired stereochemistry for mamanuthaquinone 12. With the configuration of the three stereocenters established, the cycloadduct 15 was treated with LiAlH₄ yielding the reduction of the ketone and the demethylation of one methoxyl in the *ortho* position: diastereomers 16a,b. The acetylated derivative 17a,b which Li/NH₃ gave deoxygenation at C-15 and was acetylated in alcohol C-21 leading to 19. Finally, oxidation with CAN, followed by saponification of the acetate at C-21 yielded (±)-mamanutaquinone 12.

**Scheme 1. Synthesis of (±)-mamanuthaquinone 12.**

Starting from natural terpenes, various approaches to terpenoquinones analogues have been reported. The terpene contributes the decalin part that attaches via Diels-Alder cycloaddition to commercial quinones. Thus, some diterpenylquinones/hydroquinones have been prepared through a Diels-Alder cycloaddition between myrceocommunic acid 20 and *p*-benzoquinone 21 or naphthoquinone 22 [149,159,188] (Scheme 2). The natural labdane acid used as starting material was isolated from berries of Juniperus oxycedrus. In order to optimise the synthesis of cycloadduct, two Diels-Alder procedures were considered, one in ethereal solution using BF₃·Et₂O as a catalyst and the
other under Mw irradiation in the absence of solvent. Although the Mw irradiation has the advantage of shortening reaction time, this procedure needs an excess of quinone that impedes the purification of the final product. Several derivatives of cycloadducts 23 and 29 were evaluated in vitro for determining their cytotoxicity against the human cell lines HT-29 (colon carcinoma), A-549 (lung carcinoma) and MEL-28 (malignant melanoma). Some of them were cytotoxic with IC_{50} values under the μM level.

**Scheme 2.** Diels-Alder cycloaddition between myrceocommunic acid and p-benzoquinone/naphthoquinone.
Puupehenones belong to an important class of marine terpenequinone metabolites from *Hyrtios* sp. and other marine sponges [189–192], which are constructed from drimane and polyphenolic moieties. Puupehenones exhibit a wide variety of biological activity including angiogenesis inhibition [193]. The Diels Alder cycloaddition approach has been used to synthesize puupehenone related metabolites [194,195]. Utilizing this, the potent angiogenesis inhibitor 8-epipuupehedione 33 was synthesized from sclareol oxide 30, via *ent*-chromazonarol 32 (Scheme 3); in this case, the methodology used prevents the obtention of the 8-epimer which is formed when the electrophilic cyclization methodology is utilized [196,197]. Microwave-assisted Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene 34 with chromones 35 (Scheme 4) is an expeditious approach to analogues of the puupehenone group 36 of marine diterpenoids [198].

**Scheme 3.** Diels-Alder cycloaddition approach to puupehenone-related metabolites.

![Scheme 3](image)

**Scheme 4.** Microwave-assisted Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene with chromones.

![Scheme 4](image)

The marine (−)-cyclozonarone 37 has been isolated from the Pacific brown algae *Dictyopteris undulata* and possesses a potent feeding-deterrent activity towards young abalones [199]. The total synthesis was achieved starting from albicanol 38 (Scheme 5) [200]. Elimination of water led to drima-(8,12)(9,11)-diene 39, which reacted in the key step of the synthesis, a Diels-Alder reaction, with benzoquinone. Further oxidation led to 37.
Scheme 5. Synthesis of (−)-cyclozonarone 37.

The Diels–Alder cycloaddition between two polygodial-derived dienes 41 and 43 and simple quinones 42 and 22 yield substituted naphthaquinones 40 and anthraquinones 44, some of them with in vitro trypanocide activity (Scheme 6) [201].

Scheme 6. Diels–Alder reaction between polygodial-derived dienes and simple quinones.

Halenaquinone 8, a pentacyclic polyketide isolated from Xestospongia sp. [202], has been synthesized both through a strategy based on an intramolecular inverse-electron-demand Diels–Alder reaction and an intramolecular Heck cyclization [203,204].

4. Coupling of the Aldehydes with Lithiated Hydroquinone Ethers

This strategy is an efficient and general way of accessing drimane-type sequiterpenequinones. The strategy consists on the coupling of an aldehyde as terpene precursor and a lithium anion which carries the quinone structure. The five marine natural products yahazunol 45, zonarone 46, zonarol 47, isozonarone 48 and isozonarol 49 have been synthesised starting from (+)-albicanic acid (+)-51 [205,206]. Yahazunol 45, zonarone 46 and zonarol 47 have been obtained from the East Pacific brown algae Dictyopteris undulata Okamura. Isozonarone 48 and isozonarol 49 have been isolated
from the same species collected in the Gulf of California [207]. These compounds present fungitoxic, anti-inflammatory activities and lock the MCF-7 cells initially in the mitotic phase (G2/M-phase) and induce apoptosis, also blocks the synthesis phase with replication of DNA (S-phase) [72,142,207,208].

**Scheme 7.** Retrosynthesis of yahanuzol 45 and isozonarone 48.

**Scheme 8.** Total synthesis of zonarol 47, isozonarol 49, zonarone 46 and isozonarone 48.
The synthesis of the marine natural products zonarone 46 and isozonarone 48 was achieved via (+)-albicanic acid 51, a sesquiterpene of the drimane type (Scheme 7). Coupling of the appropriate drimane-synthon with lithiated hydroquinone ethers led to sesquiterpene arenes, which were further modified to the target molecules. Stereoselective epoxidation followed by regioselective opening of the oxirane ring yielded yahazunol [205,206]. The key step of the synthesis (Scheme 8) was the coupling of the sesquiterpene part with the lithiated arene unit. The starting quiral aldehydes (+)-albicanal ((+)-52) and (−)-drim-7-en-11-al (−)-50 were obtained from (+)-albicanic acid (+)-51. This chiral synthon was prepared starting from β-ionone via a known route [209]. The di-THP-ether of hydroquine was lithiated with sec-butyllithium and added (+)-albicanal 52, respectively (−)-drim-7-en-11-al 50, to formed lithium organyl. The reaction afforded the benzyl alcohol 54a,b and 56a,b, as coupling products as mixture of diastereoisomers. Removal of the hydroxyl group led to the deoxygenated species zonarol-di-THP-ether 55 and isozonarol-di-THP-ether 57, respectively. Desprotection in presence of oxalic acid [205] gave zonarol 47 and isozonarol 49. Optimized oxidation of zonarol and isozonarol with cerium (IV) ammonium nitrate (CAN) yielded the sesquiterpenequinone zonarone 46 and isozonarone 48.

The synthesis of the marine sesquiterpene quinones (+)-hyatellaquinone 58 and spongiaquinone 60 was respectively achieved starting from the sesquiterpene aldehydes (+)-albicanal 52 and (−)-albicanal 61 (Scheme 9) [210,211]. The sesquiterpene quinone hyatellaquinone has been isolated from the alga Peyssonelia sp. and the marine sponges Hyatella intestinalis [212] and Spongia sp. [211]. Spongiaquinone 60 has been obtained from the sponges Spongia sp. [211] and Stelospongia conulata [213]. These terpenequinone were attractive candidates for pharmacological testing as antitumor, HIV-1 reverse transcriptase inhibitor and immunomodulatory activities [72,142,208].

Scheme 9. Retrosynthesis of hyatellaquinone 58 and spongiaquinone 60.
The synthesis of (+)-hyatellaquinone 58 was achieved starting from the sesquiterpene aldehyde (+)-albicanal 52 (Scheme 10) [210]. Coupling of (+)-albicanal 52 with 2,3,5,6-tetramethoxyphenyllithium 63 led to the aryl-sesquiterpene system 59, which was modified to the target molecule. Furthermore, the first total synthesis of spongiaquinone 60 was carried out starting from (−)-albicanal 61 (Scheme 11) [211] in a reaction sequence encompassing a stereoselective C=C bond hydrogenation and a one-pot AcOH elimination/demethylation reaction.

Scheme 10. Synthesis of (+)-hyatellaquinone 58.

Siphonodictyal C 69, isolated from sponge *Siphonodictyon* sp. [214,215], was tested for its pharmacological activities in assays in search of antiproliferative, cytotoxic, antiphlogistic, antirheumatic and anti-inflammatory drugs [70,208]. Synthesis of siphonodictyal C 69 was achieved via drim-7-en-11-al 70 by coupling with 5-lithium sesamol MEM-ether to the benzylic alcohols (±)-71a,b (Scheme 12) [206,208]. Treatment of (±)-71a,b with *p*-toluenesulfonic acid (PTS) in THF/H$_2$O led to the deprotection of the MEM-group and benzylic dehydration. The formed phenol was rearranged in a six membered cyclic transition state to the alkylidenecyclohexadienone which by reduction with NaBH$_4$ in EtOH yielded the phenol that was deprotonated with *n*-Bu$_4$NOH and the phenolate was methylated with dimethylsulfate (DMS), deprotonated with *n*-BuLi in α-position to the methoxy-group and formylated with DMF to (±)-72. The deprotection of (±)-72 with different reagents always led to decomposition.
Scheme 11. Synthesis of (−)-spongiaquinone 60.

Scheme 12. Synthesis of protected siphonodictyal C 69 via drim-7-en-11-al 70.

In addition, aureol 9 and their analogues were synthesized by coupling of the aldehydes with lithiated hydroquinone ethers using, in this case, a cis-decaline as starting material [216,217]. Aureol was isolated from the Caribbean sponges Smenospongia aurea [218] and Verongula gigantea [219]. Aureol 9 has been shown to exhibit selective cytotoxicity against A-549 human non-small cell lung
cancer cells and antiinfluenza-A virus activity [67,220]. As shown in Scheme 13, the synthesis commenced with the crucial coupling reaction of the cis-fused aldehyde [221,222] previously prepared from the enantiomerically pure (−)-Wieland-Miescher ketone 73 analogue (Figure 3) [223,224] with commercially available 2-bromoanisole.

**Figure 3.** Wieland-Miescher Ketone 73.

![Wieland-Miescher Ketone 73](image)

**Scheme 13.** Synthesis of (+)-arearone 80, (+)-arenarol 81 and (+)-aureol 9 staning from cis-fused decalin.
Thus, the aryllithium generated in situ by treatment of 2-bromoanisole with n-butyllithium in THF was allowed to react with 74 providing an excellent yield of the desired coupling product 75. Simultaneous removal of both the benzylic hydroxyl group and the ethylene acetal moiety in 75 was achieved effectively by initial formation of the corresponding trifluoroacetate 76 followed by reaction under the conditions for hydrogenolysis, which led to the production of the carbonyl group 77. Subsequent methylation of the sterically hindered carbony group in 77 was achieved by employing the Takai procedure [225]. Thus, treatment of 77 with a mixture of dibromoethane, zinc powder and titanium (IV) chloride in THF furnished the exo-olefinic compound 78. The methylation of 77 with Wittig reagent, Peterson’s reagent or Tebbe reagent gave none of desired product 78. Next, deprotection of the methyl ether protecting group of exo-olefin by treatment with lithium n-butylthiolate in hexamethyl-phosphoramide afforded the liberated phenolic compound 79. The pivotal conversion of the phenolic derivative to arenarone 80 was effected by reaction of 79 with molecular oxygen in the presence of salcomine in DMF. Subsequent reduction of the quinone system in arenarone 80 using sodium hydrosulfite gave arenarol 81. By treating of arenarol with BF₃·Et₂O, the desired acid-promoted rearrangement/cyclation reaction was found to proceed, producing aureole 9 with a good stereoselectively in excellent yield [221,222].

**Scheme 14. Enantiospecific synthesis of (+)-puupehenone 6. The arenol oxidative activation route.**

The total synthesis of the (+)-puupehenone 6 was achieved in 10 steps (Scheme 14) by the arenol oxidative activation route [153] starting from commercially available (+)-scclareolide 86. The key feature of this synthesis is the construction of the heterocycle via an intramolecular attack of the terpenoid-derived C-8 oxygen function onto an oxidatively activated 1,2-dihydroxyphenyl unit. The sequiterpene moiety of puupehenone 6 features a normal drimane skeleton annelated to a
shikimate-derived hydroxyquinone unit. The drimane precursor (+)-sclarolide 86 already possesses the correct chirality for three of the four (+)-puupehenone 6 stereogenic centers. It can be purchased from commercial sources or conveniently prepared from labdane 85 [226]. The nucleophilic character of the terpenoid 8-oxygen will serve to mediate the desired heterocyclization by attacking an oxidatively activated 1,2-dihydroxyphenyl unit. The shikimate unit 84 was elaborated from catechol 83 through bromination and benzylolation to give bromide. Coupling of this bromide with aldehyde 87 obtained from (+)-sclarolide 86, was achieved via a standard halogen-metal exchange protocol. A subsequent hydrogenolysis under standard conditions allowed removal of both benzyl protective groups, and the benzylic C-15 hydroxyl group that was unveiled at the previous coupling reaction, to afford the catechol 88 in good yield. The remarkable deprotection-deoxygenation step set the stage for the key oxidative activation of the catechol unit toward intramolecular attack by the drimane 8-oxygen. This activation relied on the use of [bis(trifluoroacetoxy)iodo]benzene (BTI), that as other iodine reagents, constitute today a convenient alternative to the use of toxic heavy metal-based reagents for activating arenols toward oxidative nucleophilic substitution reaction [227,228].

The synthesis of peyssonol A 90 is a special case of fusion between a cis-decalin and the aryl ring [229]. Peissonol A was isolated from the Red Sea marine alga Peyssonelia sp. that has been shown to act as an allosteric inhibitor of the reverse transcriptases of Human Immunodeficiency Virus [212,230]. This compound is the only known natural product possessing a cis-decalin framework likely arising from a halonium-induced cation-π cyclization. As indicated in Scheme 15, the retrosynthetic analysis suggested that the late-stage disconnection on the pendant aryl ring projecting a nucleophilic addition onto the aldehyde 92 to effect its incorporation, might afford the most efficient means to reach a suitable polyene cyclization precursor.

![Scheme 15. Retrosynthetic analysis of peyssonol A 90.](image)

5. Radical Decarboxylation and Quinone Addition Reaction

The application of the Barton’s radical decarboxylation reaction, in which the generated radicals are trapped by a quinone trap, gives rise to addition products in good to excellent yields. This addition
reaction is characterized by good chemoselectivity, taking place only at conjugated and unsubstituted double bonds, and regioselectivity, being strongly influenced by the resonance effect of heteroatoms located on the quinone ring. The synthetic value of this reaction was demonstrated by the synthesis of selected members of a family of quinone sesquiterpenes. Both symmetric and unsymmetric quinones can be used as radical traps and provide facile access to heteroatom-substituted quinone sesquiterpenes. The versatility of our strategy was further expanded by developing reaction conditions that allow subsequent oxygenation of the quinone adducts, providing access to complementary oxygenated structures [231].

Essential to this strategy is a radical addition reaction that permits the attachment of a fully substituted bicyclic core 97 to a variably substituted \( p \)-quinone 98 (Scheme 16). The addition product 96 can be further functionalized, giving access to natural products with a high degree of oxygenation at the quinone unit. The quinone addition reaction is characterized by excellent chemoselectivity, taking place only at conjugated and unsubstituted double bonds, and regioselectivity, being strongly influenced by the resonance effect of heteroatoms located on the quinone ring. These features were successfully applied to the synthesis of avarol 1, avarone 2, ilimaquinone 3 and smenospongidine 116, thereby demonstrating the synthetic value of this method [231].

**Scheme 16.** Strategic bond disconnections of quinone sesquiterpenes.

Avarol 1 and its quinone derivative avarone 2 are secondary metabolites isolated from the marine sponge *Dysidea avara* [232,233]. Both compounds were first discovered as anti-leukaemia agents \textit{in vitro} and \textit{in vivo}, and later it was found that they had an \textit{in vitro} inhibitory capacity against HIV-1. Controlled clinical studies revealed, however, that it was not efficient in the clinical treatment of patients with AIDS. Additionally, the potent T-lymphotropic cytostatic activity shown by avarol 1, and its low toxicity in mice, its ability to cross the blood-brain barrier and its ability to stimulate the synthesis of interferon make both these compounds optimum candidates for transformations aimed at improving their cytostatic and antiviral activity [234–238].
Scheme 17. Total synthesis of avarol 1 and avarone 2 via radical decarboxylation and quinone addition reaction.
The synthetic approach toward the core fragment of avarol and avarone (Scheme 17) began with enantimerically enriched enone 73 (Figure 3), which was readily available through a L-phenylalanine-mediated asymmetric Robinson annulation [239]. The selective protection of the more basic C4 carbonyl group followed by reductive alkylation of the enone functionality with allyl bromide afforded ketone 99. Conversion of ketone 99 to silyl ether 100 was accomplished via a sequence of three steps including ozonolysis of the terminal double bond, reduction of the resulting aldehyde, and selective silylation of the primary alcohol. The C8 ketone functionality that also suffered reduction during the above procedure was subsequently restored upon treatment with Dess-Martin periodinane [240]. Functionalization of C8 stereocenter was achieved by Wittig olefination, followed by a Pd-catalyzed hydrogenation of the resulting exocyclic methylene unit, furnishing alcohol 102. Acid-catalyzed deprotection of the C4 ketal of 102 gave rise to ketone 103, which a second Wittig methylation provided the exocyclic alkene 104. The exocyclic double bond of 104 was isomerized to produce the most substituted alkene 105, which after a two-step oxidation involving Dess-Martin periodinane and sodium chlorite, produced the desired carboxylic acid 106. The stage was now set for the attachment of the aromatic residue on the decalin ring. This was accomplished by DCC-induced esterification of 106 with commercially available 2-mercaptopyridine-N-oxide 108, which furnished the photolabile ester 109. Light-induced decarboxylation of ester 108 in the presence of benzoquinone 21 produced the substituted quinone 110. At this point, brief treatment of 110 with Raney nickel produced synthetic avarol 1 in 84% yield. Consequently, avarone 2 was produced from 1 via heterogeneous oxidation with MnO2.

Scheme 18. Total synthesis of ilimaquinone and smenospongidine.

One of the synthetic strategies to ilimaquinone 3 and smenospongidine 116 is also based on a radical decarboxylation and quinone addition methodology (Scheme 18) [231,241]. These
terpenoquinones were collected from *Hippospongia* sp. [224, 242, 243]. The cytotoxicity against the NCI-H460, HepG2, SF-268, MCF-7, HeLa, and HL-60 human tumour cell lines, the inhibitory effects on the maturation of starfish oocytes, and cell cycle arrest in the HepG2 cell line were evaluated [242].

The chemical structures of ilimaquinone 3 and smenospongidine 116 differ from those of avarone-like molecules at the position of unsaturation of the decalin core and the additional oxygenation at the C21 center of the quinone ring. The application of radical decarboxylation and quinone addition methodology produces quinone 113 from reaction of thiohydroxamic acid derivative with benzoquinone 21. Functionalization of 113 to ilimaquinone 3 is achieved by exploiting the electronic effects of the residual thiopyridyl group. Finally, exposure of 3 to phenylethylamine under basic conditions afforded synthetic smenospongidine 116.

*Ent*-halimic acid 117 is used as starting material for the synthesis of aureole (−)-9, neomammanuthaquinone 120, smenoqualone 121, and cyclosmenospongine 122. The Barton decarboxylation in presence of benzoquinone is the key reaction in this synthesis (Scheme 19) [244].

**Scheme 19.** Retrosynthetic analysis of some sesquiterpenoquinones/hydroquinones from *ent*-halimic acid.

6. **Grignard Reagent Conjugated Addition to α,β-Unsaturated Carbonyl Group**

The total synthesis of (±)-zonarol 47, (±)-isozonarol 49 [205, 206] and (−)-yahazunol 45 [207, 208] also were achieved by Grignard reagent (1,4) conjugated addition to α,β-unsaturated carbonyl group (Schemes 20 and 21) [245].
Scheme 20. Synthesis of yahazunol 45 by Grignard reagent conjugated 1,4-addition to enone 12-nordrim-9-en-8-one.

The synthesis of yahazunol 45 started from (+)-11-hydroxy-12-nordriman-8-one 123 which was transformed with p-toluene sulfonic acid by elimination of water to enone (+)-124. The cuprate catalyzed conjugated 1,4-addition of 2,4-dibenzoxylphenylmagnesium bromide to (+)-12-nordrim-9-en-8-one (+)-124 yielded the enolate anion which was trappe with acetic anhydride. Treatment of the resulting enolacetate (−)-125 with potassium hydroxide in methanol afforded the
ketone (+)-126. Wittig reaction of (+)-126 with PH₃PCH₂ gave (+)-zonarol dibenzyl ether (+)-127. Epoxidation in position 8–12 gave the oxirane ring which was opened with LiAlH₄ to (+)-yahazunol dibenzyl ether. Debenzylation of (+)-10 with H₂ and Pd/C yielded (−)-yahazunol 45 (Scheme 20) [245].

In the synthesis of (±)-zonarol 47 and (±)-isozonarol 49 (Scheme 21), the terpene ketone 128, was prepared following a sequence of reactions [246] from the racemic mixture of the Wieland-Miescher ketone 73 (Figure 3). This ketone and its analogs are of great interest as starting materials to terpenequinones by asymmetric synthesis [223,224,239]. After preparing the Grignard reagent 129, which provides the hydroquinone moiety, it was reacted with the α,β-unsaturated ketone 128, and Ac₂O, yielding the enol acetate obtained by conjugate addition. Treatment of the enol acetate with KOH gave ketone 130, which established the stereochemistry of the molecule. From compound 130, (±)-zonarol 47 and (±)-isozonarol 49, were obtained by two different ways. Wittig reaction, followed by demethylation, zonarol racemate 6 was obtained. By 1,2-addition of organolithium to the ketone 130, (±)-isozonarol 49 was obtained through a tertiary alcohol, which by dehydration gave a mixture of compounds 131 and 132. Finally, the demethylation of the methoxy group by treatment with lithium butanetiolate and HMPA led to (±)-zonarol 47 and (±)-isozonarol 49.

7. Reductive Alkylation of Enones

This strategy to connect the unit to a terpene quinone is based on the alkylation in the reaction medium during metal reduction of a conjugated double bond. Lithium with a solvent proton reduces the double bond through electron transfer giving an enolate. Thus, alkyl halide reaction generates the desired alkylated ketone. In all cases, the α,β-unsaturated ketone that is coupled to the quinone has the (S)-(+)-(Wieland-Miescher diketone 73 as the starting material.

The synthesis of (+)-avarone 2, (+)-avarol 1, (−)-neoavarone, 134 (−)-neovarol 133 and (+)-aureol 9 is a good example of reductive alkylation of enones with bromides (Scheme 22) [247]. Thus, the enone 139 with bromide 140, and applying previously described protocols from the literature [156,239,248–251] gave the exo-olefin 138. The endo-olefin 136 should be accessible from 138 by isomerization at the C4 olefinic double bond.

The synthesis of the decalin derivative 138 (Scheme 23), a common key intermediate for the synthesis of (+)-avarone 2, (+)-avarol 1, (−)-neoavarone 134, (−)-neovarol 133 and (+)-aureol 9, started with the reductive alkylation of enantiomerically pure enone 139 with 2-methoxybromide 140. Thus, treatment of enone 139 with lithium metal in liquid ammonia followed by reaction of the intermediary lithium enolate with bromide 140 provided the expected coupling product 141 as a simple diastereomer. Subsequent methylenation of the sterically hindered carbonyl group in 141 was achieved by employing a combination of Ph₃P+CH₃Br- and t-BuOK furnishing the exo-olefin. To establish the C8 stereogenic center, the ethylene acetal moiety was first removed by acid treatment and the resulting ketone 142 was subjected to hydrogenation, which afforded the product 143 and its C8 epimer 144 after separation by column chromatography on silica gel. Finally, compound 144 was efficiently converted to the desired key intermediate 138 by Wittig methylenation [247].
Scheme 22. Synthetic plan for (+)-avarone 2, (+)-avarol 1, (−)-neoavarone 134, (−)-neovarol 133 and (+)-aureol 9 by enones reductive alkylation.
Scheme 23. Synthesis of key intermediate 138.

The Scheme 24 shows the synthesis of avarol 1 and avarone 2 from key intermediate 138. Isomerization of the *exo*-olefin moiety in 138 to *endo*-olefinic double bond was efficiently achieved by treatment with RhCl$_3$·3H$_2$O. The *endo*-olefin 145 was then converted to avarone 2 and avarol 1 via phenol 146. To construct the quinone system directly, phenol 146 was allowed to react with molecular oxygen in the presence of salcomine, producing (+)-avarone 2. Subsequent treatment of avarone 2 with NaBH$_4$ in THF/H$_2$O resulted in the quinol avarol 1 [247].

Ilimaquinone 3 [224,242] and nakijiquinones 4, 163–165 [252–257] have also been synthesized using this strategy. In the synthesis of (−)-ilimaquinone 3 (Scheme 25) [250,251], compound 147 was treated with Li/NH$_3$ giving the lithium enolate and subsequent treatment with benzyl halide 148 led to the α-alkylation product 149. The configuration of the remaining stereocenter (C-8) was established with a Wittig reaction followed by hydrogenation to yield compound 151 and its diastereomers (3:1). The oxidation of alcohol at C-4 and subsequent formation of the olefin led to 153. Finally, treatment with CAN and Pd (0) in basic medium, yielded (−)-ilimaquinone 3.
Scheme 24. Synthesis of avarol 1 and avarone 2 reductive alkylation of enones.

Scheme 25. Synthesis of ilimaquinone 3 by reductive alkylation of enones.

The reductive alkylation as strategy for building sesquiterpenilquinones has also been used in the synthesis of nakijiquinones [156,252]. From extracts of sponges from the family Spongiidae, collected in Okinawa several nakijiquinones were isolated. Nakijikinones are terpenquinones with an amino
acid on the benzoquinone ring [253–257]. The HER2/Neu receptor tyrosine kinase is hugely overexpressed in about 30% of primary breast, ovary, and gastric carcinomas. Nakijiquinones are the only naturally occurring inhibitors of this important oncogene, and structural analogues of nakijiquinones may display inhibitory properties against another tyrosine kinase receptor involved in cell signaling and proliferation [156]. The synthetic route (Scheme 26), was optimized to obtain nakijiquinone C, using as intermediate the isospongiaquinone 162 and later the strategy was extended to obtain nakijiquinones A-D 4, 163–165.

Scheme 26. Synthesis of isospongiaquinone and nakijiquinone A–D 4, 163–165 by reductive alkylation of enones.
8. Cross-Coupling Reaction

This strategy consists on the application of a (dppf)NiCl$_2$-mediated neopentyl coupling in natural product synthesis and emphasizes the attractive combination of hydroxyl-directed hydrogenation to control stereochemistry followed by a neopentyl coupling to elaborate the carbon skeleton. Retrosynthetic analysis as summarized in Scheme 27 readily dissects arenarol to a neopentyl iodide 166 and 2,4-dimethoxyphenylmagnesium bromide [258]. The neopentyl iodide turn could be derived from the corresponding alcohol 167, assuming that the hydroxyl group could be employed to control the stereochemistry of reduction at an adjacent exocyclic olefin, or the diene alcohol 169, if the hydroxyl group could be employed to fix both adjacent stereocenters. Either olefin could be viewed as a derivative of the decalin 168, depending on the sequence employed to accomplish methylation, introduction of the exocyclic olefin, and for compound 168, reduction of the endocyclic olefin. The synthesis of arenarol, based on this approach, includes both directed introduction of two key stereogenic centers and a (dppf)NiCl$_2$-mediated coupling at a neopentyl center.

Scheme 27. Retrosynthetic analysis of arenarol 81.

Arenarol 81, isolated from *Dysidea* sp. and *Fenestraspongia* sp. [259,260] is a cis-decalin the synthesis of which calls for stereocontrol at two tertiary and two quaternary carbons. These compounds showed cytotoxic activity when assayed against P-388 leukaemia cells, with ED$_{50}$ = 17.5 μg/mL for arenarol 81 and ED$_{50}$ = 1.7 μg/mL for arenarone 80 [259]. Arenarol 81 showed DPPH radical scavenging activity with an IC$_{50}$ value of 19 μM [260]. The Grignard reagent needed for preparation of arenarol 81, (2,5-dimethoxyphenyl)magnesium bromide 129, has been shown to undergo a cross-coupling reaction with neopentyl iodide in the presence of (dppf)NiCl$_2$ and Zn$_2$ dioxane forming the desired coupling product 171. Conversion of 171 to the target compounds required cleavage of the methyl protecting groups. Treatment of compound 171 with ceric ammonium nitrate (CAN) resulted in oxidation to the natural product arenarone 80. Mild reduction of arenarone 80 with Na$_2$S$_2$O$_4$ gave the final target arenarol 81 (Scheme 28).
Scheme 28. Synthesis of arenarone 80 and arenatol 81 by cross-coupling reaction.

9. Furylation of Quinones

This procedure consists on furylation of quinones and hydroquinones through oxidative coupling and Michael addition reactions. Thus, the oxidative coupling reaction of (+) euryfuran with 1,4-quinones in acetic acid yielded euryfuryl-1,4-quinones with leishmanicidal activity. The influence of the solvent to promote the Michael addition and the regioselectivity of the reaction with unsymmetrical quinones are important features that can be useful for the synthesis of new bioactive members of the euryfurylquinones series [261] (Scheme 29). The Michael reaction of (+) euryfuran 172 with activated monosubstituted 1,4-benzoquinones 22 provides a regiospecific access to antiprotozoal active euryfuran derivatives 173 containing a quinone or hydroquinone fragment bond to the 12 position [262]. Access to furylnaphthoquinones from unactivated quinones requires acid-induced conditions. However, oxidative coupling reactions of activate quinones proceed under neutral conditions. Most of the furyl-1,4-quinones exhibited good antiproliferative activity against MCF-7, NCI-H460 and SF-268 cancer cell lines [145].

Scheme 29. Furylation of quinones.
10. Furan Polyene Cationic Cyclization

This strategy is a diversity-oriented synthesis that follows a biomimetic route [263] to marine natural products like liphagal 1, the first member of a new of new liphagane type of meroterpenoid carbon skeleton. Liphagal 180 isolated from the methanol extract of the sponge Aka coralliphaga, collected from reefs in Prince Rupert Bay, Portsmouth, Dominica [264] exhibited impressive biological activity including inhibitory activity against PI3K α (phosphoinositide-3-kinase α) and cytotoxic to LoVo and CaCo human colon, and MDA-468 human breast tumor cell lines [264–266].

Scheme 30. Synthesis of meroterpenoid natural product (±)-liphagal 180 Retrosynthetic analysis by furan polyene cationic cyclization.

Liphagal 180 has a tetracyclic skeleton, harboring a trans-fused 6,7-bicarbocyclic core with three stereogenic centers. The retrosynthetic strategy toward liphagal (Scheme 30) was based on the proposed biogenetic pathway and hinged on a key C–C bond disconnection that mandated connecting a preformed benzofuran precursor 178 with a readily available monoterpenoid 177 to establish the crucial C–C bond and access the framework 8. Further elaboration of 176 into 175 was envisaged to set up the furan polyene cationic cyclization cascade en route to the target. The key furan precursor 178 was to be assessed from a readily available aromatic precursor 179.

11. Application of Cell Culture for the Production of Bioactive Compounds from Sponges

Sponges [phylum Porifera] are a rich source of biologically active and pharmacologically valuable compounds with a high potential to become effective drugs for therapeutic use. However, until now, only a few compounds have been introduced into clinics because of the limited amounts of starting material available for extraction. To overcome this serious problem in line with the rules for a
sustainable use of marine resources, the following routes can be pursued; first, chemical synthesis, second, cultivation of sponges in the sea (mariculture), third, growth of sponge specimens in a bioreactor, and fourth, cultivation of sponge cells in vitro in a bioreactor [267].

Recently, it was demonstrated that the in vitro culture of primmorph from the marine sponge Dysidea avara produces avarol 1. Single cells apparently do not have the potency to produce this secondary metabolite, but the primmorph model is a suitable system for the synthesis of bioactive compounds in vitro [268,269]. In addition, it has also been suggested that some of the bioactive secondary metabolites isolated from sponges are produced by functional enzyme clusters, which originated from the sponges and their associated microorganisms. In order to exploit the bioactive potential of both the sponge and the “symbionts”, a 3D-aggregate primmorph culture system was studied, and it was proved that avarol/avarone is produced by the sponge Dysidea avara. Another promising way to utilize the bioactive potential of the microorganisms is the cloning and heterologous expression of enzymes involved in secondary metabolism [270].

In situ sponge aquaculture is nowadays one of the most reliable methods to supply pharmaceutical companies with sufficient quantities of the target compound. Its use in addition to immortalization of sponge cells by transfection with genomic DNA appears to be a promising way, since recent studies underscore the applicability of this technique for sponges [270].

12. Summary

Sesquiterpenquinones represent a substance class with increasing pharmacological interest. The initial concentration of an interesting compound may be too low to be effectively tested in some biological and pharmacological assays. Thus, the total synthesis of terpenequinones has become attractive in order to obtain the required amounts of compounds natural product analogues with optimized biological properties. Consequently, the development of these marine natural products is highly desirable and worthwhile from the viewpoint of medicinal chemistry and pharmaceuticals. Therefore, total synthesis of natural products will surely continue to be central to confirmation of natural product structure assignment, as well as providing material for biological testing towards pharmaceutical development, and investigations of biosynthetic pathways. The main routes to synthesize terpenequinones/hydroquinones include Diels-Alder cycloaddition reaction, coupling of the aldehydes with lithiated hydroquinone ether, radical decarboxylation and quinone addition reaction, Grignard reagent conjugated addition to α,β-unsaturated carbonyl group, reductive alkylation, cross-coupling reaction, furylation of quinones and furan polyene cationic cyclization. In addition, the application of cell culture for the production of bioactive compound from sponge is a promising way to utilize the bioactive potential of marine terpenoquinones sources.

Advances in total synthesis, especially function-oriented synthesis, biosynthetic technologies, primmorph models and genomic research offer new strategies for the medicinal chemical optimization of biologically active terpenequinones/hydroquinones.

Acknowledgements

The author would like to thank the Regional Government of Castile & Leon (Consejería de Educación, SA-4/2010) and the Ministerio de Ciencia e Innovación CTQ2010-16170.
References

1. Mishra, B.B.; Tiwari, V.K. Natural Product in Drug Discovery: Clinical Evaluations and Investigations. In Opportunity, Challenge, and Scope of Natural Products in Medicinal Chemistry; Tiwari, V.K., Mishra, B.B., Eds.; Research Signpost: Kerala, India, 2011; pp. 1–61.
2. Mishra, B.B.; Tiwa, V.K. Natural products: An evolving role in future drug discovery. Eur. J. Med. Chem. 2011, 46, 4769–4807.
3. Carter, G.T. Natural products and Pharma 2011: Strategic changes spur new opportunities. Nat. Prod. Rep. 2011, 28, 1783–1789.
4. Newman, D.J.; Cragg, G.M. Natural products of therapeutic importance. Compr. Nat. Prod. II 2010, 2, 623–650.
5. Li, J.W.-H.; Vederas, J.C. Drug discovery and natural products: End of an era or an endless frontier? Science 2009, 325, 161–165.
6. Bhakuni, D.S.; Rawat, D.S. Bioactive Natural Products; Springer & Anamaya Publishers: New York, NY, USA, 2005.
7. Harvey, A.L. Natural products as a screening resource. Curr. Opin. Chem. Biol. 2007, 11, 480–484.
8. Newman, D.J.; Cragg, G.M. Natural products as sources of new drugs over the last 25 years. J. Nat. Prod. 2007, 70, 461–477.
9. Newman, D.J.; Cragg, G.M.; Snader, K.M. The influence of natural products upon drug discovery. Nat. Prod. Rep. 2000, 17, 215–234.
10. Newman, D.J.; Cragg, G.M.; Snader, K.M. Natural products as sources of new drugs over the period 1981–2002. J. Nat. Prod. 2003, 66, 1022–1037.
11. Paterson, I.; Anderson, E.A. The renaissance of natural products as drug candidates. Science 2005, 310, 451–453.
12. Wang, B.; Deng, J.; Gao, Y.; Zhu, L.; He, R.; Xu, Y. The screening toolbox of bioactive substances from natural products: A review. Fitoterapia 2011, 82, 1141–1151.
13. Verpoorte, R. Exploration of nature’s chemodiversity: The role of secondary metabolites as leads in drug development. Drug Discov. Today 1988, 3, 232–238.
14. Sticher, O. Natural product isolation. Nat. Prod. Rep. 2008, 25, 517–554.
15. Wilson, Z.E.; Brimble, M.A. Molecules derived from the extremes of life. Nat. Prod. Rep. 2009, 26, 44–71.
16. Bemis, G.W.; Murcko, M.A. The properties of known drugs. 1. Molecular frameworks. J. Med. Chem. 1996, 39, 2887–2893.
17. Ganesan, A. The impact of natural products upon modern drug discovery. Curr. Opin. Chem. Biol. 2008, 12, 306–317.
18. Cragg, G.M.; Newman, D.J. Natural products sources of drugs: Plants, microbes, marine organisms, and animals. Compr. Med. Chem. II 2007, 1, 355–403.
19. Buss, A.D.; Butler, M.S. Natural Product Chemistry for Drug Discovery; RSC Publishing: Cambridge, UK, 2009.
20. Grothaus, G.P.; Cragg, G.M.; Newman, D.J. Plant natural products in anticancer drug discovery. Curr. Org. Chem. 2010, 14, 1781–1791.
21. Chin, Y.-W.; Balunas, M.J.; Chai, H.B.; Kinghorn, A.D. Drug discovery from natural sources. *AAPS J.* **2006**, *8*, E239–E253.

22. Koehn, F.E.; Carter, G.T. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.* **2005**, *4*, 206–220.

23. Balunas, M.J.; Kinghorn, A.D. Drug discovery from medicinal plants. *Life Sci.* **2005**, *78*, 431–441.

24. Jones, W.P.; Chin, Y.-W.; Kinghorn, A.D. The role of pharmacognosy in modern medicine and pharmacy. *Curr. Drug Targets* **2006**, *7*, 247–264.

25. Butler, M.S. The role of natural product chemistry in drug discovery. *J. Nat. Prod.* **2004**, *67*, 2141–2153.

26. Butler, M.S. Natural products to drugs: Natural products derived compounds in clinical trials. *Nat. Prod. Rep.* **2005**, *22*, 162–195.

27. Fabricant, D.S.; Farnsworth, N.R. The value of plants used in traditional medicine for drug discovery. *Environ. Health Perspect.* **2001**, *109*, 69–75.

28. Kinghorn, A.D. The Discovery of Drugs from Higher Plants. In *The Discovery of Natural Products with Therapeutic Potential*; Gullo, V.P., Ed.; Butterworth-Heinemann: Boston, MA, USA, 1994; pp. 81–108.

29. Raviña, E. *The Evolution of Drug Discovery. From Traditional Medicines to Modern Drugs*; Wiley-WCH: Weinheim, Germany, 2010.

30. Bailly, C. Ready for comeback of natural products in oncology. *Biochem. Pharmacol.* **2009**, *77*, 1447–1457.

31. Cragg, G.M.; Grothaus, P.G.; Newman, D.J. Impact of natural products on developing new anti-cancer agents. *Chem. Rev.* **2009**, *109*, 3012–3043.

32. Gordaliza, M. Natural products as leads to anticancer drugs. *Clin. Transl. Oncol.* **2007**, *9*, 767–776.

33. Lee, K.-H. Discovery and development of natural product-derived chemotherapeutic agents based on a medicinal chemistry approach. *J. Nat. Prod.* **2010**, *73*, 500–516.

34. Cragg, G.M.; Newman, D.J. Industrial Applications Natural Products for Medicinal Purposes. Drugs from Nature: Present, Development and Future Prospects. In *Natural Products in the New Millenium: Prospects and Industrial Applications*; Rauter, A.P., Palma, F.B., Justino, J., Araújo, M.E., Dos Santos, S.P., Eds.; Kluwer: Dordrecht, The Netherlands, 2002; pp. 441–461.

35. Newman, J.; Cragg, G. Natural products in medicinal chemistry. *Bioorg. Med. Chem.* **2009**, *17*, 2120.

36. Li, M.-Y.; Xiao, O.; Pan, J.-Y.; Wu, J. Natural products from semi-mangrove flora: Source, chemistry and bioactivities. *Nat. Prod. Rep.* **2009**, *26*, 281–298.

37. Newman, D.J.; Cragg, G.M.; Kingston, D.G.I. Natural Products as Pharmaceuticals and Sources for Lead Structures. In *The Practice of Medicinal Chemistry*; Wermuth, C.G., Ed.; Academic Press: London, UK, 2003; pp. 159–186.

38. Newman, D.J. Natural products as leads to potential drugs: An old process or the new hope for drug discovery? *J. Med. Chem.* **2008**, *51*, 2589–2599.

39. Galm, U.; Shen, B. Natural products drug discovery: The times have never been better. *Chem. Biol.* **2007**, *14*, 1098–1104.
40. Rishton, G.M. Natural products as a robust source of new drugs and drug leads: Past successes and present day issues. *Am. J. Cardiol.* 2008, 101, 43D–49D.

41. Lam, K.S. New aspects of natural products in drug discovery. *Trends Microbiol.* 2007, 15, 279–289.

42. Harvey, A.L. Natural product in drug discovery. *Drug Discov. Today* 2008, 13, 894–901.

43. Butler, M.S. Natural product to drug: Natural products derived compounds in clinical trials. *Nat. Prod. Rep.* 2008, 25, 475–516.

44. Langer, T.; Laggner, C.; Rollinger, J.M.; Stuppner, H. Pharmacophore-based screening for the successful identification of bio-active natural products. *Chimia* 2007, 61, 350–354.

45. Lang, G.; Mayhudin, N.A.; Mitova, M.I.; Sun, L.; van der Sar, S.; Blunt, J.W.; Cole, A.L.; Ellis, G.; Laatsch, H.; Munro, M.H. Evolving trends in the dereplication of natural product extracts: New methodology for rapid, small-scale investigation of natural product extracts. *J. Nat. Prod.* 2008, 71, 1595–1599.

46. Wilson, R.M.; Danishefsky, S.J. Small molecule natural products in the discovery of therapeutic agents: The synthesis connection. *J. Org. Chem.* 2006, 71, 8329–8351.

47. Wilson, R.M.; Danishefsky, S.J. Applications of total synthesis toward the discovery of clinically useful anticancer agents. *Chem. Soc. Rev.* 2007, 36, 1207–1226.

48. Lee, K.-H. Current developments in discovery and design of new drug candidates from plant natural. *J. Nat. Prod.* 2004, 67, 273–283.

49. Hu, G.-P.; Yuan, J.; Sun, L.; She, Z.-G.; Wu, J.-H.; Lan, X.-J.; Zhu, X.; Lin, Y.-C.; Chen, S.-P. Statistical research on marine natural products based on data obtained between 1985 and 2008. *Mar. Drugs* 2011, 9, 514–525.

50. Faulkner, D.J. Marine natural products: Metabolites of marine algae and herbivorous marine molluscs. *Nat. Prod. Rep.* 1984, 1, 251–280.

51. Faulkner, D.J. Marine natural products: Metabolites of marine invertebrates. *Nat. Prod. Rep.* 1984, volume, 1551–1598.

52. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1986, 3, 1–3.

53. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1987, 4, 539–576.

54. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1988, 5, 613–663.

55. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1990, 7, 269–309.

56. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1991, 8, 97–147.

57. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1992, 9, 323–364.

58. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1993, 10, 497–539.

59. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1994, 11, 355–394.

60. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1995, 12, 223–269.

61. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1996, 13, 75–125.

62. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1997, 14, 259–302.

63. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1998, 15, 113–158.

64. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 1999, 16, 155–198.

65. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 2000, 17, 7–5.

66. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 2001, 18, 1R–9R.

67. Faulkner, D.J. Marine natural products. *Nat. Prod. Rep.* 2002, 19, 1–8.
68. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2003**, *20*, 1–48.

69. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2004**, *21*, 1–49.

70. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2005**, *22*, 15–61.

71. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2006**, *23*, 26–78.

72. Blunt, J.W.; Copp, B.R.; Hu, W.P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2007**, *24*, 31–86.

73. Blunt, J.W.; Copp, B.R.; Hu, W.P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2008**, *25*, 35–39.

74. Blunt, J.W.; Copp, B.R.; Hu, W.P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2009**, *26*, 170–244.

75. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2010**, *27*, 165–237.

76. Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2011**, *28*, 196–228.

77. Hill, R.A. Marine natural product. *Annu. Rep. Prog. Chem. Sect. B* **2010**, *106*, 156–173.

78. Bergmann, W.; Feeney, R.J. Contributions to the study of marine products XXXII. The nucleosides of sponges. *I. J. Org. Chem.** **1951**, *16*, 981–997.

79. Molinski, T.F.; Dalisay, D.S.; Lievens, S.L.; Saludes, J.P. Drug development from marine natural products. *Nat. Rev. Drug Discov.* **2009**, *8*, 69–75.

80. Faulkner, D.J. Highlights of marine natural products chemistry (1972–1999). *Nat. Prod. Rep.* **2000**, *17*, 1–6.

81. Proksch, P.; Ebel, R.; Edrada, R.A.; Schupp, P.; Lin, W.H.; Sudarsono; Wray, V.; Steube, K. Detection of pharmacologically active natural products using ecology. Selected examples from Indopacific marine invertebrates and sponge-derived fungi. *Pure Appl. Chem.* **2003**, *75*, 343–432.

82. Proksch, P.; Edrada, R.A.; Ebel, R. Drugs from the seasurrent status and microbiological implications. *Appl. Microbiol. Biotechnol.* **2002**, *59*, 125–214.

83. Jha, R.K.; Xu, Z.R. Biomedical compounds from marine organisms. *Mar. Drugs* **2004**, *2*, 123–146.

84. Smit, A.J. Medicinal and pharmaceutical uses of seaweed natural products: A review. *J. Appl. Phycol.* **2004**, *16*, 245–322.

85. Tan, L.T. Bioactive natural products from marine cyanobacteria for drug discovery. *Phytochemistry* **2007**, *68*, 954–999.

86. Gulder, T.A.M.; Moore, B.S. Chasing the treasures of the sea-bacterial marine natural products. *Curr. Opin. Microbiol.* **2009**, *12*, 252–320.

87. Sabdono, A.; Radjasa, O.K. Microbial symbionts in marine sponges: Marine natural product factory. *J. Coast. Dev.* **2008**, *11*, 57–66.

88. Piel, J. Metabolites from symbiotic bacteria. *Nat. Prod. Rep.* **2004**, *21*, 519–558.
89. Skropeta, D. Deep-sea natural products. *Nat. Prod. Rep.* **2008**, *25*, 1131–1166.
90. Thornburg, C.; Zabriskie, T.M.; McPhail, K.L. Deep-sea hidrotermal: Potencial hot spot for natural products discovery. *J. Nat. Prod.* **2010**, *73*, 489–499.
91. Blunt, J.W.; Munro, M.H.G. *Review of Dictionary of Marine Natural Products*; Chapman & Hall/CRC Press: Boca Raton, FL, USA, 2008.
92. Haefner, B. Drugs from the deep: Marine natural products as drug candidates. *Drug Discov. Today* **2003**, *8*, 536–544.
93. El Sayed, K.A.; El Sayed, P.X.; Shen, X.; Perry, T.L.; Zjawiony, J.K.; Mark, T.C. Marine natural products as antituberculosis agents. *Tetrahedron* **2000**, *56*, 949–953.
94. Vo, T.-S.; Ngo, D.-H.; van Ta, Q.; Kim, S.-K. Marine organisms as a therapeutic source against herpes simplex virus infection. *Eur. J. Phar. Sci.* **2011**, *44*, 11–20.
95. Abad, M.J.; Bermejo, P. Bioactive natural products from marine sources. *Stud. Nat. Prod. Chem.* **2001**, *25*, 683–755.
96. Garson, M.J. Marine natural products as antifeedants. *Compr. Nat. Prod. II* **2010**, *4*, 503–537.
97. Abad, M.J.; Bedoya, L.M.; Bermejo, P. Natural marine antiviral products. *Stud. Nat. Prod. Chem.* **2008**, *35*, 101–134.
98. Carter, B.K. Marine natural products as a source of novel pharmacological agents. *Curr. Opin. Biotechnol.* **1993**, *4*, 275–279.
99. Chapman, D.J. Natural products of marine algae: The interface of chemistry and biology. *Mar. Chem.* **1983**, *12*, doi:10.1016/0304-4203(83)90088-9.
100. Bull, A.T.; Stach, J.E.M. Marine actinobacteria: New opportunities for natural product search and discovery. *Trends Microbiol.* **2007**, *15*, 491–499.
101. Davidson, B.S. New dimensions in natural products research: Cultured marine microorganisms. *Curr. Opin. Biotechnol.* **1995**, *6*, 284–291.
102. Donia, M.; Hamann, M.T. Marine natural products and their potential applications as anti-infective agents. *Lancet Infect. Dis.* **2003**, *3*, 338–348.
103. Glaser, K.B.; Mayer, A.M.S. A renaissance in marine pharmacology: From preclinical curiosity to clinical reality. *Biochem. Pharmacol.* **2009**, *78*, 440–448.
104. Mayer, A.M.S.; Rodriguez, A.D.; Berlinck, R.G.S.; Hamann, M.T. Marine pharmacology in 2005–6: Marine compounds with antihelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Biochim. Biophys. Acta* **2009**, *1790*, 283–308.
105. Kong, D.-X.; Jiang, Y.-Y.; Zhang, H.-Y. Marine natural products as sources of novel scaffolds: Achievement and concern. *Drug Discov. Today* **2010**, *15*, 884–886.
106. Albericio, F.; Álvarez, M.; Cuevas, C.; Francesch, A.; Pla, D.; Tulla-Puche, J. The Sea as a Source of New Drugs. In *Molecular Imaging for Integrated Medical Therapy and Drug Development. Part IV*; Tanaki, N., Kuge, Y., Eds.; Springer: New York, NY, USA, 2010; pp. 237–249.
107. Hill, R.T.; Fenical, W. Pharmaceuticals from marine natural products: Surge or ebb? *Curr. Opin. Biotechnol.* **2010**, *21*, 777–779.
108. Ausubel, J.H.; Crist, D.T.; Waggoner, P.E. Highlights of a Decade of Discovery. *Census of Marine Life*; 2010. Available online: http://www.coml.org/Highlights-2010 (accessed on 1 September 2011).

109. Mayer, A.M.; Glaser, K.B.; Cuevas, C.; Jacobs, R.S.; Kem, W.; Little, R.D.; McIntosh, J.M.; Newman, D.J.; Potts, B.C.; Shuster, D.E. The odyssey of marine pharmaceuticals: A current pipeline perspective. *Trends Pharmacol. Sci.* 2010, 31, 255–265.

110. Fusetani, N. Biotechnological potentials of marine natural products. *J. Biotechnol.* 2008, 136, 17–26.

111. Rana, M.; Hendrik, L. Marine natural products: A new wave of drugs? *Future Med. Chem.* 2011, 3, 1475–1489.

112. Fusetani, N. Antifouling marine natural products. *Nat. Prod. Rep.* 2011, 28, 400–410.

113. Lane, A.L.; Moore, B.S. A sea of biosynthesis: Marine natural products meet the molecular age. *Nat. Prod. Rep.* 2011, 28, 411–428.

114. Proksch, P.; Putz, A.; Ortlepp, S.; Kjer, J.; Baye, M. Bioactive natural products from marine sponges and fungal endophytes. *Phytochem. Rev.* 2010, 9, 475–489.

115. Yoshikazu, S. Natural products from marine derived microorganisms. *J. Synt. Org. Chem. Jpn.* 2010, 68, 534–542.

116. Chakraborty, C.; Hsu, C.-H.; Wen, Z.-H.; Lin, C.-S. Anticancer drugs discovery and development from marine organisms. *Curr. Top. Med. Chem.* 2010, 9, 1536–1545.

117. Jensen, P.R.; Fenical, W. Marine Microorganisms and Drug Discovery: Current Status and Future Potential. In *Drugs from the Sea*; Fusetani, N., Ed.; Karger: New York, NY, USA, 2000; pp. 6–29.

118. Schwartsmann, G.; Brondani, A.; Berlinck, R.G.S.; Jimeno, J. Marine organisms and other novel natural sources of new cancer drugs. *Lancet Oncol.* 2001, 2, 221–225.

119. Simmons, T.L.; Andrianasolo, T.L.; McPhail, K.; Flatt, P.; Gerwick, W.H. Marine natural products as anticancer drugs. *Mol. Cancer Ther.* 2005, 4, 333–342.

120. Nuijen, B.; Bouma, M.; Manada, C.; Jimeno, J.M.; Schellens, J.M.M.; Bult, A.; Beijnen, J.H. Pharmaceutical development of anticancer agents derived from marine sources. *Anticancer Drugs* 2000, 11, 793–811.

121. Imhoff, J.F.; Labes, A.; Wiese, J. Bio-mining the microbial treasures of the ocean: New natural products. *Biotechnol. Adv.* 2011, 29, 468–482.

122. Hester, R.E.; Harrison, R.M.; Andersen, R.J.; Williams, D.E. Pharmaceuticals from the sea. *Chem. Mar. Environ.* 2000, 13, 55–80.

123. Galeano, E.; Rojas, J.J.; Martínez, A. Pharmacological developments obtained from marine natural products and current pipeline perspective. *Nat. Prod. Commun.* 2011, 6, 287–300.

124. Fattorusso, E.; Gerwick, W.H.; Taglialetela-Scafati, O. *Handbook of Marine Natural Products*; Springer: New York, NY, USA, 2012.

125. Besse, J.-P.; Latour, J.-F.; Garric, J. Anticancer drugs in surface waters: What can we say about the occurrence and environmental significance of cytotoxic, cytostatic and endocrine therapy drugs? *Environ. Int.* 2012, 39, 73–86.
126. Radjasa, O.K.; Vaske, Y.M.; Navarro, G.; Vervoort, H.C.; Tenney, K.; Linating, R.G.; Crews, P. Highlights of marine invertebrate-derived biosynthetic products: Their biomedical potential and possible production by microbial associants. *Bioorg. Med. Chem.* 2011, 19, 6658–6674.

127. Miljanich, G.P. Ziconotide: Neural calcium channel blocker for treating severe chronic pain. *Curr. Med. Chem.* 2004, 11, 3029–3040.

128. Alicino, I.; Giglio, M.; Manca, F.; Bruno, F.; Puntillo, F. Intrathecal combination of ziconotide and morphine for refractory cancer pain: A rapidly acting and effective choice. *Pain* 2011, 152, 245–249.

129. Cuevas, C.; Francesch, A. Development of Yondelis® (trabectedin, ET-743). A semisynthetic process solves the supply problem. *Nat. Prod. Rep.* 2009, 26, 322–333.

130. Sanfilippo, R.; Grosso, F.; Jones, R.L.; Banerjee, S.; Pilotti, S.; D’Incalci, M.; Dei Tos, A.P.; Raspagliesi, F.; Judson, I.; Casal, P.G. Trabectedin in advanced uterine leiomyosarcomas: A retrospective case series analysis from two reference centers. *Gynecol. Oncol.* 2011, 123, 553–556.

131. Monneret, C. Impact actuel des produits naturels sur la découverte de nouveaux médicaments anticancéreux. *Ann. Pharm. Fr.* 2010, 68, 218–232.

132. Burge, R.A. Advances in ovarian cancer disease control. *Gynecol. Oncol.* 2012, 124, 5–9.

133. Meoni, G.; Cecere, F.L.; Chaib, I.; Giommoni, E.; di Costanzo, F. Prolonged response to trabectedin in a heavily pretreated patient with metastatic endometrial carcinoma: A case report and literature review. *Gynecol. Oncol. Case Rep.* 2011, 1, 23–25.

134. Alday, P.H.; Correia, J.J. Macromolecular interaction of halichondrin B analogues eribulin (E7389) and E-076349 with tubulin by analytical ultracentrifugation. *Biochemistry* 2009, 48, 7927–7938.

135. Smith, J.A.; Wilson, L.; Azarenko, O.; Zhu, X.; Lewis, B.M.; Littlefield, B.A.; Jordan, M.A. Eribulin binds at microtubule ends to a single site on tubulin to suppress dynamic instability. *Biochemistry* 2010, 49, 1331–1337.

136. Mak, R.G. Eribulin in soft-tissue sarcomas. *Lancet Oncol.* 2012, 12, 988–989.

137. Mak, R.G.; Yeung, B.K.S. Natural product drug discovery: The successful optimization of ISP-1 and halichondrin. *Curr. Opin. Chem. Biol.* 2011, 15, 523–528.

138. Swami, U.; Chaudhary, I.; Ghalib, M.H.; Goel, S. Eribulin—Review of preclinical and clinical studies. *Rev. Oncol. Hem.* 2011, in press.

139. Gordaliza, M. Terpeny-purines from the sea. *Mar. Drugs* 2009, 7, 833–847.

140. Gordaliza, M. Cytotoxic terpene quinones from marine sponges. *Mar. Drugs* 2010, 8, 2849–2870.

141. Fraga, B.M. Natural sesquiterpenoids. *Nat. Prod. Rep.* 2011, 28, 1580–1610.

142. Fraga, B.M. Natural sesquiterpenoids. *Nat. Prod. Rep.* 2008, 25, 1180–1209.

143. Marcos, I.S.; Conde, A.; Moro, R.F.; Basabe, P.; Diez, D.; Urones, J. Quinone/hydroquinone sesquiterpenes. *Mini Rev. Org. Chem.* 2010, 7, 230–254.

144. Bozic, T.; Novakovic, I.; Gasic, M.J.; Juranic, Z.; Stanojkovic, T.; Tufegdzic, S.; Kljajic, Z.; Sladic, D. Synthesis and biological activity of derivatives of the marine quinone avarone. *Eur. J. Med. Chem.* 2010, 45, 923–929.
145. Benites, J.; Valderrama, J.A.; Rivera, F.; Rojo, L.; Campos, N.; Pedro, M.; Nascimento, M.S.J. Studies on quinones. Part 42: Synthesis of furylquinone and hydroquinones with antiproliferative activity against human tumor cell lines. *Bioorg. Med. Chem.* **2008**, *16*, 862–868 and all previous parts.

146. Sladic, D.; Gasic, M.J. Reactivity and biological activity of marine sesquiterpene hydroquinones avarol and related compound from sponges of Order Dictyoceratida. *Molecules* **2006**, *11*, 1–33.

147. Motti, C.A.; Bourguet-Kondracki, M.-L.; Longeon, A.; Doyle, J.R.; Llewellyn, L.E.; Tapiolas, D.M.; Yin, P. Comparison of biological properties of several marine sponge-derived sesquiterpenoid quiNones. *Molecules* **2007**, *12*, 1376–1388.

148. De Rosa, S. Marine Natural Products: Analysis, Structure Elucidation, Bio-Activity and Potential Use as Drug. In *Natural Products in the New Millenium: Prospects and Industrial Applications*; Rauter, A.P., Palma, F.B., Justino, J., Araújo, M.E., Dos Santos, S.P., Eds.; Kluwer: Dordrecht, The Netherlands, 2002; pp. 441–461.

149. Gordaliza, M.; Miguel del Corral, J.M.; Mahiques, M.M.; San Feliciano, A.; García-Grávalos, M.D. Terpenequinone with antitumor activity. *PCT Int. Appl. WO* 9604230 A1, 15 February 1996.

150. Miguel del Corral, J.M.; Gordaliza, M.; Castro, M.A.; Mahiques, M.M.; Chamorro, P.; Molinari, A.; García-Grávalos, M.D.; Broughton, H.B.; San Feliciano, A. New selective cytotoxic diterpenylquinones and diterpenylhydroquinones. *J. Med. Chem.* **2001**, *44*, 1257–1267.

151. Amigo, M.; Terencio, M.; Paya, M.; Iodice, C.; de Rosa, S. Synthesis and evaluation of diverse thio avarol derivatives as potential UVB photoprotective candidates. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2561–2565.

152. Schatton, W.; Schatton, M.; Pietschmann, R. Method for the preparation of compositions with high avarol content from sponge and use for the prevention and treatment of psoriasis and tumors. *Eur. Pat. Appl. EP* 1391197 A1, 25 February 2004.

153. Quideau, S.; Lebon, M.; Lamidey, A.-M. Enantiospecific synthesis of the antituberculosis marine sponge metabolite (+)-puupehenone. The arenol oxidative activation route. *Org. Lett.* **2002**, *4*, 3975–3978.

154. Ciavatta, M.L.; Lopez-Gresa, M.P.; Gavagnin, M.; Melck, D.; Mauzo, E.; Guo, Y.-W.; van Soest, R.; Cimio, G. Studies on puupehenone-metabolites of *Dysidea* sp.: Structure and biological activity. *Tetrahedron* **2007**, *63*, 1380–1384.

155. Nakamura, H.; Kobayashi, J.; Kobayashi, M.; Ohizumi, Y.; Hirata, I. Xestoquinone. A novel cardiotonic marine natural product isolated from the okinawan sea sponge *Xestospongia sapra*. *Chem. Lett.* **1985**, *6*, 713–716.

156. Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. Total synthesis and biological evaluation of the nakiijiquinones. *J. Am. Chem. Soc.* **2001**, *123*, 11586–11593.

157. Hu, J.-F.; Schetz, J.A.; Kelly, M.; Peng, J.-N.; Ang, K.K.H.; Flotow, H.; Leong, C.Y.; Ng, S.B.; Buss, A.D.; Wilkins, S.P.; *et al.* New antinfective and human 5-HT2 receptor binding natural and semisynthetic compounds from the jamaican sponge *Smenospongia aurea*. *J. Nat. Prod.* **2002**, *65*, 476–480.
158. Winder, P.L.; Baker, H.L.; Linley, P.; Guzmán, E.A.; Pomponi, S.A.; Diaz, M.C.; Reed, J.K.; Wright, A.E. Neopetrosiquinones A and B, sesquiterpene benzoquinones isolated from the deep-water sponge Neopetrosia cf. próxima. Bioorg. Med. Chem. 2011, 19, 6599–6603.
159. Schirmer, R.H.; Müller, J.G.; Krauth-Siegel, R.L. Disulfide-reductase inhibitors as chemotherapeutic agents: The design of drugs for trypanosomiasis and malaria. Angew. Chem. Int. Ed. Engl. 1995, 34, 141–154.
160. Monks, T.J.; Hanzlik, R.P.; Cohen, G.M.; Ross, D.; Graham, D.G. Quinone chemistry and toxicity. Toxicol. Appl. Pharmacol. 1992, 112, 2–16.
161. O’Brien, P.J. Molecular mechanisms of quinone cytotoxicity. Chem. Biol. Interact. 1991, 80, 1–41.
162. Alegría, A.; Sánchez, S.; Sánchez-Muñoz, P.; Nieves, I.; Cruz, N.G.; Gordializa, M.; Martín-Martín, M.L. Terpenyllnaphtoquinones are reductively activated by NADH/NADH dehydrogenase. Toxicol. Environ. Chem. 2005, 87, 237–245.
163. Alegría, A.; Cordon, E.; Marcano, Y.; Sanchez, S.; Gordializa, M.; Martín-Martín, M.L. Reductive activation of terpenyllaphtoquinones. Toxicology 2002, 175, 167–175.
164. Schröder, H.C.; Wenger, R.; Gerner, H.; Reuter, P.; Kuchino, Y.; Müller, W.E.G. Suppression of the modulatory effects of the antileukemic and anti-human immunodeficiency virus compound avarol on gene expression by tryptophan. Cancer Res. 1989, 49, 2069–2076.
165. Sladić, D.; Gašić, M.J. Effects of iron(II) compounds on the amount of DNA damage in friend erythroleukemia cells induced by avarol. Role of hydroxyl radicals. J. Serb. Chem. Soc. 1994, 59, 915–920.
166. Novaković, I.; Vučić, Z.; Božić, T.; Božić, N.; Milosavić, N.; Sladić, D. Chemical modification of β-lactoglobulin by quinones. J. Serb. Chem. Soc. 2003, 68, 243–248.
167. Sladić, D.; Novaković, I.; Vučić, Z.; Božić, T.; Božić, N.; Milić, D.; Šolaja, B.; Gašić, M.J. Protein covalent modification by biologically active quinones. J. Serb. Chem. Soc. 2004, 69, 901–907.
168. Sunazuka, T. Total synthesis of natural products for finding pharmaceutical leads. Shinki Sozai Tansaku 2008, 146–153.
169. Suyama, T.L.; Gerwick, W.H.; McPhail, K.L. Survey of marine marine product structure revisions: A synergy of spectroscopy and chemical synthesis. Bioorg. Med. Chem. 2011, 19, 6675–6701.
170. Baran, P.S.; Maimone, T.J.; Richter, J.M. Total synthesis of marine natural products without using protecting groups. Nature 2007, 446, 404–408.
171. Hanessian, S. Structure-based synthesis: From natural products to drug prototypes. Pure Appl. Chem. 2009, 81, 1085–1091.
172. Hashimoto, S. Natural product chemistry for drug discovery. J. Antibiot. 2011, 64, 697–701.
173. Henkel, T.; Brunne, R.M.; Müller, H.; Reichel, F. Statistical investigation into the structural complementarity of natural products and synthetic compounds. Angew. Chem. Int. Ed. 1999, 38, 643–647.
174. Feher, M.; Schmidt, J.M. Property distributions: Differences between drugs, natural products, and molecules from combinatorial chemistry. J. Chem. Inf. Comput. Sci. 2003, 43, 218–227.
175. Morris, J.C.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2011**, *28*, 269–289.
176. Morris, J.C.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2010**, *27*, 1186–1203.
177. Morris, J.C.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2009**, *26*, 245–265.
178. Morris, J.C.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2008**, *25*, 95–117.
179. Morris, J.C.; Nicholas, G.M.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2007**, *24*, 87–108.
180. Nicholas, G.M.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2006**, *23*, 79–99.
181. Nicholas, G.M.; Phillips, A.J. Marine natural products: Synthetic aspects. *Nat. Prod. Rep.* **2005**, *22*, 144–161.
182. Capon, R.J. Marine natural products chemistry: Past, present, and future. *Aust. J. Chem.* **2010**, *63*, 851–854.
183. ApSimon, J.; Thomson, R.H. *The Total Synthesis of Naturally Occurring Quinones in Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons, Inc.: New York, NY, USA, 2007; Volume 8.
184. Fujimoto, H.; Nakamura, E.; Kim, Y.P.; Okuyama, E.; Ishibashi, M.; Sassa, T. Immunomodulatory constituents from an ascomycete, *Eupenicillium crustaceum*, and revised absolute structure of macrophorin D. *J. Nat. Prod.* **2001**, *64*, 1234–1237.
185. Juhl, M.; Tanner, D. Recent applications of intramolecular Diels-Alder reaction to natural product synthesis. *Chem. Soc. Rev.* **2009**, *38*, 2983–2992.
186. Swersey, J.C.; Barrows, L.R.; Ireland, C.M. Mamanuthaquinone: An antimicrobial and cytotoxic metabolite of *Fasciospongia* sp. *Tetrahedron Lett.* **1991**, *32*, 6687–6690.
187. Yoon, T.; Danishefsky, S.J.; de Gala, S. A concise total synthesis of (±)-mamanuthaquinone by using an *exo*-Diels-Alder reaction. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 853–855.
188. Gordaliza, M.; Miguel del Corral, J.M.; Castro, M.A.; Mahiques, M.M.; García-Grávalos, M.D.; San Feliciano, A. Synthesis and bioactivity of new antineoplastic terpenylquinones. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1859–1864.
189. Hamann, M.T.; Scheuer, P.J.; Kelly-Borges, M. Biogenetically diverse, bioactive constituents of a sponge, order Verongida: Bromotyramines and sesquiterpene-shikimate derived metabolites. *J. Org. Chem.* **1993**, *58*, 6565–6569.
190. Kohmoto, S.; McConnell, O.J.; Wright, A.; Koehn, F.; Thompson, W.; Lui, M.; Snader, K.M. Puupehenone, a cytotoxic metabolite from a deep water marine sponge, *Stronglyophora hartmani*. *J. Nat. Prod.* **1987**, *50*, doi:10.1021/np50050a064.
191. Nasu, S.S.; Yeung, B.K.S.; Hamann, T.; Scheuer, P.J.; Kelly-Borges, M.; Goins, K. Puupehenone-related metabolites from two Hawaiian sponges, *Hyrtios* sp. *J. Org. Chem.* **1995**, *60*, 7290–7292.
192. Pina, I.; Sanders, M.L.; Crews, P. Puupehenones congeners from an Indo-pacific *Hyrtios* sponge. *J. Nat. Prod.* **2003**, *66*, 2–6.
193. Castro, M.E.; Gonzales-Iriarte, M.; Barrero, A.F.; Salvador-Tormo, N.; Muñoz-Chapuli, R.; Medina, M.A.; Quesada, A.R. Study of puupehenone and related compounds as inhibitors of angiogenesis. *Int. J. Cancer* **2004**, *110*, 31–38.

194. Alvarez-Manzaneda, E.; Chahboun, R.; Cabrera, E.; Alvarez, E.; Haidour, A.; Ramos, J.M.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Bouanou, H. Diels-Alder cycloaddition approach to puupehenone-related metabolites: Synthesis of the potent angiogenesis inhibitor 8-epipuupedione. *J. Org. Chem.* **2007**, *72*, 3332–3339.

195. Alvarez-Manzaneda, E.; Chahboun, R. Method for the preparation of mero sesquiterpenes from labdane diterpenes. *WO 2009112622 A1*, 17 September 2009.

196. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Herrador, M.; Chahboun, R.; Galera, P. Synthesis and antitumoral activities of marine *ent*-chromazonarol and related compounds. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325–2328.

197. Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Cortes, M.; Armstrong, V. Synthesis and antitumoral activities of puupehedione and related compounds. *Tetrahedron* **1999**, *55*, 15181–15208.

198. Kamble, R.M.; Ramana, M.M.V. Microwave-assisted Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene with chromones—an expeditious approach to analogues of the puupehenone group of marine diterpenoids. *Can. J. Chem.* **2010**, *88*, 1233–1239.

199. Kurata, K.; Taniguchi, K.; Suzuki, M. Cyclozonarone, a sesquiterpene-substituted benzoquinone derivative from the brown alga *Dictyopteris undulata*. *Phytochemistry* **1996**, *41*, 749–752.

200. Schroder, J.; Matthes, B.; Seifert, K. Total synthesis of the marine sesquiterpene quinone (−)-cyclozonarone. *Tetrahedron Lett.* **2001**, *42*, 8151–8152.

201. Cuellar, M.A.; Salas, C.; Cortés, M.J.; Morillo, A.; Maya, J.D.; Preite, M.D. Synthesis and *in vitro* trypanocide activity of several polycyclic drimane-quinone derivatives. *Bioorg. Med. Chem.* **2003**, *11*, 2489–2497.

202. Roll, D.M.; Scheuer, P.J.; Matsutsumoto, G.K.; Clardy, J. Halenaquinone, a pentacyclic polihetide from a marine sponge. *J. Am. Chem. Soc.* **1983**, *105*, 6177–6178.

203. Kienzler, M.A.; Suseno, S.; Trauner, D. Vinyl Quiñónez as Diles-Alder dienes: Concise synthesis of (−)-halenaquinone. *J. Am. Chem. Soc.* **2008**, *130*, 8604–8605.

204. Sutherland, H.S.; Souza, F.E.S.; Rodrigo, R.G.A. A Short synthesis of (±)-halenaquinone. *J. Org. Chem.* **2001**, *66*, 3639–3641.

205. Schröder, J.; Magg, C.; Seiferd, K. Total synthesis of the marine sesquiterpene hydroquinone zonarol and isozonarol and the sequiterpene quinone zonarone e isozonarone. *Tetrahedron Lett.* **2000**, *41*, 5469–5473.

206. Laube, T.; Schröder, J.; Magg, C.; Strhle, R.; Seiferd, K. Total synthesis of yahazunol, zonarone and isozonarone. *Tetrahedron* **2002**, *58*, 4299–4309.

207. Fenical, W.; Sims, J.J.; Squatrito, D.; Wing, R.M.; Radlick, P. Marine natural products VII. Zonarol and isozonarol, fungitoxic hydroquinones from the brown seaweed *Dictyopteris zonarioides*. *J. Org. Chem.* **1973**, *38*, 2383–2386.

208. Laube, T.; Bernet, A.; Dahne, H.; Jacobsen, I.D.; Seiferd, K. Synthesis and pharmacological activities of some sequiterpene quinones and hydroquinones. *Bioorg. Med. Chem.* **2009**, *17*, 1422–1427.
209. Herlem, D.; Kerragoret, J.; Yu, D.; Khuong-Huu, F.; Kende, A.S. Studies toward the total synthesis of polyoxygenated labdanes: Preliminary approaches. *Tetrahedron* **1993**, *49*, 607–618.

210. Bernet, A.; Schroeder, J.; Seifert, K. Synthesis of the marine sesquiterpene quinones hyatellaquinone and spongiaquinone. *Helv. Chim. Acta* **2003**, *86*, 2009–2020.

211. Capon, R.J.; Groves, D.R.; Urban, S.; Watson, R.G. Spongiaquinone Revisited: Structural and Stereochemical studies on marine sesquiterpene/quinones from a Southern Australian marine sponge, *Spongia* sp. *Aust. J. Chem.* **1993**, *46*, 1245–1253.

212. Talpir, R.; Rudi, A.; Kashman, Y.; Loya, Y.; Hizi, A. Three new sesquiterpene hydroquinones from marine origin. *Tetrahedron* **1994**, *50*, 4179–4184.

213. Kazlauskas, R.; Murphy, P.T.; Warren, R.G.; Wells, R.J.; Blount, J.F. New quinones from a dictyoceratid sponge. *Aust. J. Chem.* **1978**, *31*, 2685–2697.

214. Sullivan, B.; Djura, P.; McIntyre, E.; Faulker, J. Antimicrobial constituents of the sponge *Siphonodictyon coralliphagum*. *Tetrahedron* **1981**, *37*, 979–982.

215. Sullivan, B.W.; Faulker, D.J.; Matsumoto, G.K.; Cun-Heng, H.; Cloardy, J. Metabolites of the burrowing sponge *Siphonodictyon coralliphagum*. *J. Org. Chem.* **1986**, *51*, 4568–4573.

216. Nakamura, M.; Suzuki, A.; Nakatani, M.; Fuchikami, T.; Inoue, M.; Katoh, T. A efficient synthesis of (+)-aureol via boron trifluoride etherate-promoted rearrangement of (+)-arenarol. *Tetrahedron Lett.* **2002**, *43*, 6929–6932.

217. Nakatami, N.; Nakamura, M.; Suzuki, A.; Fuchikami, T.; Inoue, M.; Katoh, T. Enantioselective total synthesis of (+)-aureol via a BF$_3$·Et$_2$O-promoted rearrangement/cyclization reaction of (+)-arenarol. *Arkivoc* **2003**, *8*, 45–57.

218. Djura, P.; Stierle, D.B.; Sullivan, B.; Faulkner, D.J.; Arnold, E.; Clardy, J. Some metabolites of the marine sponges *Smenospongia aurea* and *Smenospongia* (ident.Polyfibrospongia) *echina*. *J. Org. Chem.* **1980**, *45*, 1435–1441.

219. Ciminiello, P.; Dell’Aversano, C.; Fattorusso, E.; Magno, S.; Parsini, M. Chemistry of verongida sponges. 10. Secondary metabolite composition of the caribbean sponge *Verongula gigantean*. *J. Nat. Prod.* **2000**, *63*, 263–266.

220. Wright, A.E.; Cross, S.S.; Burres, N.S.; Koehn, F. Antiviral and antitumor terpene hydroquinones from marine sponge and methods of use, *USA. PCT WO 9112250 A1*, 22 August 1991.

221. Katoh, T.; Nakatani, M.; Shikita, S.; Sampe, R.; Ishiwata, A.; Ohmori, O.; Nakamura, M.; Terashima, S. Studies toward the total synthesis of popolohuanone E: Enantioselective synthesis of 8-O-methylpopolohuanone E. *Enantioselective synthesis of* 8-O-methylpopolohuanone E. *Org. Lett.* **2001**, *3*, 2701–2704.

222. Kawano, H.; Itoh, M.; Katoh, T.; Terashima, S. Studies toward the synthesis of popolohuanone E: Synthesis of natural (+)-arenarol related to the proposed biogenetic precursor of popolohuanone E. *Tetrahedron Lett.* **1997**, *38*, 7769–7772.

223. Banerjee, A.K.; Laya-Mimo, M. Synthesis of bioactive terpenes from Wieland-Miescher ketone and its methyl analog. *Anal. Nat. Prod. Chem.* **2000**, *24*, 175–213.

224. Kondracki, M.L.; Guyot, M. Biologically active quinine and hydroquinones sesquiterpenoids from the sponge *Smenospongia* sp. *Tetrahedron* **1989**, *45*, 1995–2004.

225. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. Wittig-type reaction of dimetallated carbodianion species as produced by zinc reduction of gem-polyhalogen compounds in the presence of Lewis acids. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698–1702.
226. Moulines, J.; Lamidey, A.-M.; Desvergnes-Beuil, V. A practical synthesis of Ambrox® from sclareol using no metallic oxidant. *Synth. Commun.* **2001**, *31*, 749–758.

227. Zhdankin, V.V.; Stang, P.J. Recent developments in the chemistry of polyvalent iodine compounds. *Chem. Rev.* **2002**, *102*, 2523–2584.

228. Quideau, S.; Pouységou, L.; Oxoby, M.; Looney, M.A. 2-Alkoxyarenol-derived orthoquinols in carbon-oxygen, carbon-nitrogen and carbon-carbon bond-forming reactions. *Tetrahedron* **2001**, *57*, 319–329.

229. Synder, S.A.; Teitler, D.S.; Brucks, A.P. Simple reagents for direct halonium-induced polyene cyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

230. Loya, S.; Bakhanaskvili, M.; Kashman, Y.; Hizi, A. Peyssonols A and B, two novel inhibitors of the reverse transcriptases of human immunodeficiency virus types 1 and 2. *Arch. Biochem. Biophys.* **1995**, *316*, 789–796.

231. Ling, T.; Poupon, E.; Rueden, E.J.; Kim, S.H.; Theodorakis, E.A. Unified synthesis of quinone sesquiterpenes based on a radical decarboxylation and quinone addition reaction. *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267.

232. Minale, L.; Riccio, R.; Sodano, G. Avarol, a novel sesquiterpenoid hydroquinone with a rearranged drimane skeleton from the sponge *Dysidea avara*. *Tetrahedron Lett.* **1974**, *3401–3404.

233. De Rosa, S.; Minale, L.; Riccio, R.; Sodano, G. The absolute configuration of avarol, a rearranged sesquiterpenoid hydroquinone from a marine sponge. *J. Chem. Soc. Perkin Trans. 1* **1976**, *13*, 1408–1414.

234. Cozzolino, R.; de Giulio, A.; de Rosa, S.; Strazzullo, G.; Gašič, M.J.; Sladić, D.; Zlatović, M. Biological activities of avarol derivatives, 1. Amino derivatives. *J. Nat. Prod.* **1990**, *53*, 699–702.

235. Müller, W.E.G.; Maidhof, A.; Zahn, R.K.; Schröder, H.C.M.; Gasic, M.J.; Heidemann, D.; Bernd, A.; Kurelec, B.; Eich, E.; Seibert, G. Potent antileukemic activity of the novel cytostatic agent avarone and its analogues in vitro and in vivo. *Cancer Res.* **1985**, *45*, 4822–4826.

236. Müller, W.E.G.; Sobel, C.; Sachsse, W.; Diehl-Seifert, B.; Zahn, R.K.; Eich, E.; Kljajić, Z.; Schröder, H.C. Biphasic and differential effects of the cytostatic agents avarone and avarol on DNA metabolism of human and murine T and B lymphocytes. *Eur. J. Cancer Clin. Onc.* **1986**, *22*, 473–476.

237. Müller, W.E.G.; Sobel, C.; Diehl-Seifert, B.; Maidhof, A.; Schöder, H.C. Influence of the antileukemic and anti-human immunodeficiency virus agent avarol on selected immune responses in vitro and in vivo. *Biochem. Pharmacol.* **1987**, *36*, 1489–1494.

238. Sarin, P.S.; Sun, D.; Thornton, A.; Müller, W.E.G. Inhibition of replication of the etiologic agent of acquired immune deficiency syndrome (human T-lymphotropic retrovirus/lymphadenopathy-associated virus) by avarol and avarone. *J. Natl. Cancer Inst.* **1987**, *78*, 663–666.

239. Hagiwara, H.; Uda, H. Optically pure (4aS)-(+) or (4aR)-(−)-1,4a-dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione and its use in the synthesis of an inhibitor of steroid biosynthesis. *J. Org. Chem.* **1988**, *53*, 2308–2311.

240. Dess, D.B.; Martin, J.C. A useful 12-I-5 triacetoxyperiodinane (the Dess-Martin periodinane) for the selective oxidation of primary or secondary alcohols and a variety of related 12-I-5 species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
241. Ling, T.; Poupon, E.; Rueden, E.J.; Theodorakis, E.A. Synthesis of (−)-Ilimaquinone via a radical decarboxylation and quinone addition reaction. Org. Lett. 2002, 4, 819–822.

242. Liu, H.; Wang, G.; Namikoshi, M.; Kobayashi, H.; Yao, X.; Cai, G. Sesquiterpene quinones from a marine sponge *Hippospongia* sp. that inhibit maturation of starfish oocytes and induce cell cycle arrest with HepG2 cells. Pharm. Biol. 2006, 44, 522–527.

243. Kondracki, M.L.; Guyot, M. Smenospongeine: A cytotoxic and antimicrobial aminoquinone isolated from *Smenospongia* sp. Tetrahedron Lett. 1987, 28, 5815–5818.

244. Marcos, I.S.; Conde, A.; Moro, R.F.; Basabe, P.; Diez, D.; Urones, J. Synthesis of quinone/hydroquinone sesquiterpenes. Tetrahedron 2010, 66, 8280–8290.

245. Laube, T.; Beil, W.; Seifert, K. Total synthesis of two 12-nordrimanes and the pharmacological active sesquiteerpene hydroquinone yahazunol. Tetrahedron 2005, 61, 1141–1148.

246. Furuichi, N.; Hata, T.; Soetjipto, H.; Kato, M.; Katsumura, S. Common synthetic strategy for optically active cyclic terpenoids having a 1,1,5-trimethyl-trans-decalin nucleus: Syntheses of (+)-acuminolide, (−)-spongianolide A, and (+)-scalarenedial. Tetrahedron 2001, 57, 8425–8442.

247. Kelly, J.L.; Linn, J.A.; Selway, J.W.T. Synthesis and antirhinovirus activity of 6-(dimethylamino)-2-(trifluoromethyl)-9-(substituted benzyl)-9H-purines. J. Med. Chem. 1989, 32, 1757–1763.

248. Stork, G.; rosen, P.; Goldman, N.; Coombs, R.V.; Tsuji, J. Alkylation and carbonation of ketones by trapping the enolates from the reduction of α,β-unsaturated ketones. J. Am. Chem. Soc. 1965, 87, 275–286.

249. Bruner, S.D.; Radeke, H.S.; Tallarico, J.A.; Snapper, M.L. Total synthesis of (−)-ilimaquinone. J. Org. Chem. 1995, 60, 1114–1115.

250. Poigny, S.; Guyot, M.; Samadi, M. Efficient total synthesis of (−)-ilimaquinone. J. Org. Chem. 1998, 63, 5890–5894.

251. Takahashi, Y.; Ushio, M.; Kubota, T.; Yamamoto, S.; Fromont, J.; Kobayashi, J. Nakijiquinones J–R, Sesquiterpenoid quinones with a qmine residue from Okinawan marine sponges. J. Nat. Prod. 2010, 73, 467–471.
258. Watson, A.T.; Park, K.; Wiener, D.F. Application of the nickel-mediated neopentyl coupling in the total synthesis of the marine natural product arenarol. *J. Org. Chem.* 1995, 60, 5102–5106.

259. Schnitz, F.J.; Lakshmi, V.; Powell, D.R.; van der Helm, D. Arenarol and arenarona: Sesquiterpenoids with rearranged drimane skeletons from marine sponge *Dysidea arenaria*. *J. Org. Chem.* 1984, 49, 241–244.

260. Utkina, N.K.; Denisenko, V.A.; Krasokhin, V.B. Sesquiterpenoids aminoquinones from marine sponge *Dysidea sp.* *J. Nat. Prod.* 2010, 73, 788–791.

261. Valderrama, J.A.; Benites, J.; Cortés, M.; Pessoa-Mahana, H.; Prina, E.; Fournest, A. Studies on quinones. Part. 38: Synthesis and Leishmanicidal activity of sesquiterpene 1,4-quinones. *Bioorg. Med. Chem.* 2003, 11, 4713–4718.

262. Valderrama, J.A.; Benites, J.; Cortés, M.; Pessoa-Mahana, H.; Prina, E.; Fournest, A. Studies on quinones. Part. 35: Studies on quinones. Part 35: Access to antiprotozoal active euryfurylquinones and hydroquinones. *Tetrahedron* 2002, 58, 881–886.

263. Mehta, G.; Likhite, N.S.; Kumar, C.S.A. A concise synthesis of the bioactive meroterpenoid natural product (±)-liphagal, a potent PI3K inhibitor. *Tetrahedron Lett.* 2009, 50, 5260–5262.

264. Marion, F.; Williams, D.E.; Patrick, D.O.; Hollander, I.; Mallon, R.; Kim, S.C.; Roll, D.M.; Feldberg, L.; Soest, R.V.; Andersen, R.J. Liphagal, a selective inhibitor of PI3 kinase α isolated from the sponge *Aka coralliphaga*: Structure elucidation and biomimetic synthesis. *Org. Lett.* 2006, 8, 321–324.

265. Sundstrom, T.J.; Anderson, A.C.; Wright, D.L. Inhibitors of phosphoinositide-3-kinase: A structure-based approach to understanding potency and selectivity. *Org. Biomol. Chem.* 2009, 7, 840–850.

266. Hennessy, B.T.; Smith, D.L.; Ram, P.T.; Lu, Y.; Mills, G.B. Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nat. Rev. Drug Discov.* 2005, 4, 988–1004.

267. Schröder, H.C.; Brümmer, F.; Fattorusso, E.; Aiello, A.; Menna, M.; de Rosa, S.; Batel, R.; Müller, W.E. Sustainable production of bioactive compounds from sponges: Primmorphs as bioreactors. *Prog. Mol. Subcell Biol.* 2003, 37, 163–197.

268. Müller, W.E.; Böhm, M.; Batel, R.; de Rosa, S.; Tommonaro, G.; Müller, I.M.; Schröder, H.C. Application of cell culture for the production of bioactive compounds from sponges: Synthesis of arvarol by primmorphs from *Dysidea avara*. *J. Nat. Prod.* 2000, 63, 1077–1081.

269. De Caralt, S.; Sánchez-Fontenla, J.; Uriz, M.J.; Wijffels, R.H. *In situ* aquaculture methods for *Dysidea avara* (demospongiae, porifera) in the northwestern mediterranean. *Mar. Drugs* 2010, 8, 1731–1742.

270. Müller, W.E.; Grebenjuk, V.A.; Le Pennec, G.; Schröder, H.; Brümmer, F.; Hentschel, U.; Müller, I.M.; Breter, H. Sustainable production of bioactive compounds by sponges—Cell culture and gene cluster approach: A review. *Mar. Biotechnol.* 2004, 6, 105–117.

© 2012 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/3.0/).