We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,500
Open access books available

177,000
International authors and editors

190M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

Approaches to the Total Synthesis of Puupehenone-Type Marine Natural Products

Yan-Chao Wu, Yun-Fei Cheng and Hui-Jing Li

Abstract

Puupehenones have been isolated from the marine sponge Chondrosia chucalla, which belong to a growing family of natural products with more than 100 members. These marine natural products have attracted increasing attention mainly due to their wide variety of biological activities such as antitumor, antiviral, and anti-HIV, and thus offer promising opportunities for new drug development. This chapter covers the approaches to the total synthesis of puupehenone-type marine natural products including puupehenol, puupehenone, puupehedione, and halopuupehenones. The routes begin with the construction of their basic skeletons, followed by the modification of their C- and D-rings. The contents are divided into two sections in terms of the key strategies employed to construct the basic skeleton. One is the convergent synthesis route with two synthons coupled by nucleophilic or electrophilic reaction, and the other is the linear synthesis route with polylene series cyclization as a key reaction.

Keywords: total synthesis, marine natural product, puupehenones, convergent synthesis, linear synthesis

1. Introduction

In recent years, the synthesis and application of marine natural products have become the focus of a much greater research effort, which is due in large part to the increased recognition of marine organisms as a rich source of novel compounds with biological applications [1–4]. The puupehenone-type marine natural products obtained from deep sea sponge have played a very important role in health care and prevention of diseases [5–14].

As shown in Figure 1, the most representative of this natural product family includes puupehenone, halopuupehenones, puupehedione, puupehenol, 15-cyanopuupehenol, 15-oxopuupehenol, and bispuupehenonen. Structurally, puupehenones are tetracyclic compounds consisting of a bicyclic sesquiterpene A- and B-rings and a shikimic acid/O-benzoquinone/O-phenol D-ring connected by tetrahydropryan/dihydropyrpan C-ring. In addition, the chiral center of the C-8 of this series of natural products listed in the figure is 8S, which is also the structural specificity of them.
2. Isolation and biological activities

The natural product puupehenone was first isolated from the Hawaiian sponge *Chondrosia chucalla* by Schauer group in 1979 [15]. Subsequently, it was obtained from sponges such as *Heteronema*, *Hyrtios*, and *Strongylophora* sp. [14, 16, 17]. At that time, the assignment of an absolute stereochemistry to puupehenone was not permitted by spectroscopic analysis or degradative studies. As shown in Figure 2, it was not until 1996 that Capon group [18] used chemical decomposition, ozone oxidative decomposition, and lithium aluminum hydride reduction to finally decompose the natural product into the known structure (+)-drimenyl acetate (13) and (−)-drimenol (14), and since then the absolute configuration of puupehenone has been determined.
Studies show that puupehenone-type marine natural products have antitumor [5–8], anti-HIV [9], anticancer [10], antiviral [11], antimalarial [12], antimite [9, 13], immunomodulation [14], and other important physiological activities. In view of their important biological activities, such natural products have been favored by organic synthetic chemists since their separation.

3. Total synthesis of puupehenone-type marine natural products

Compound supply and appropriate structural analysis are two main barriers to develop a natural product into drug [19–31]. Chemical synthesis of marine natural products could provide the technological base for preparing enough materials for further research of bioactivity [19]. Thus, the total synthesis of puupehenones has been widely researched and published in excellent literature.

In the present chapter, approaches to the total synthesis of puupehenone-type marine natural products have been reviewed. In general, the strategies employed in the total synthesis of puupehenones are as follows:

- Convergent synthesis route with two synthons coupled by nucleophilic or electrophilic reaction.
- Linear synthesis route with polyene series cyclization as a key reaction.

3.1 Convergent synthesis route

Barrero group has been working on the study of total synthesis of puupehenone-type natural products, and has obtained great achievements [32–35]. In 1997, Barrero and coworkers reported the first enantiospecific synthesis of puupehenol and puupehenone in 32 and 22% yield, respectively [33]. As shown in Figure 3, acetoxyaldehyde 17 and aromatic synthon 18 were prepared from commercially available sclareol 15 and veratraldehyde 16 in high yields through a series of
transformations. The acetoxy alcohol 19 was completed by condensation of 17 with the aryllithium derived from 16, and after three steps compound 19 gave the phenolic derivatives 20. Finally, complete diastereoselectivity was achieved by organoselenium-induced cyclization. The treatment of 20 with NPSp(N-phenylelenophthalimide) and SnCl$_4$ obtained a mixture of the selenium derivatives 21 and 22. Treatment with Raney Ni allowed both deprotection of the phenylselenyl group and removal of the benzyl ethers, producing puupehenol (5) as the only product, which was easily oxidized to (+)-puupehenehene (1) in the presence of pyridinium dichromate (PDC).

Besides the above-mentioned research work, in 1999, Barrero group applied a base-mediated cyclization via 8,9-epoxy derivative to achieve the first asymmetric synthesis of puupehedione in 17% overall yield [35]. As shown in Figure 4, Sclareol 15 and veratraldehyde 16 were employed as the starting materials to obtain synthons 23 and 18, which were accordingly converted to the key skeleton 24 in two steps. The treatment of 24 in the presence of mCPBA gave epoxydes 25, and finally alcohol 26 was obtained in high yield when 8a, 9a-epoxyde 25 was treated with KOH in methanol. The subsequent two-step routine transformations, involving dehydration of alcohol 26 and oxidation, gave the target compound puupehedione.

In 2001, Maiti group reported the total synthesis of 8-epi-puupehedione with angiogenesis inhibitory activity [36]. As shown in Figure 5, commercially available carvone (27) and sesamol (28) were converted into tosylhydrazone 29 and aromatic synthon 30 in eight and three steps, respectively. Exposure of the vinyl lithium species, produced by the addition of tosylhydrazone 29 to an excess of n-BuLi, to 30 afforded the diene 31. Then, the cleavage of the O-allyl ether of compound 31 with a catalytic amount of RhCl$_3$-3H$_2$O in refluxing EtOH resulted in spontaneous cyclization [37], affording a mixture of the puupehedione (4) and 8-epi-puuphehedione (32).

In 2002, Quideau and coworkers completed asymmetric total synthesis of puupehenone in 10 steps starting from commercially available (+)-sclareolide [38]. The main feature of this synthesis strategy is an intramolecular attack of the terpenoid-derived C-8 oxygen function onto an oxidatively activated 1,2-
dihydroxyphenyl unit to construct the heterocycle. As shown in Figure 6, the first step in their synthesis is inversion of the configuration at C-8 to construct a C-8 chiral center via simple acid treatment before coupling two key synthons. Subsequent treatment with (DA)$_2$Mg and MoOPH afforded 35 and 36, which were converted into 39 after hydride reduction with DIBAL and oxidation with NaIO$_4$. Then, coupling of aldehyde 15 with bromide 40 was achieved via a standard halogen-metal exchange protocol. Then, the key skeleton catechol 41 was obtained in good yield by a subsequent hydrogenolysis to remove both the benzyl protective groups. Finally, key oxidative activation of the catechol unit toward intramolecular attack by the drimane 8-oxygen and rearrangement with KH accomplished total synthesis of puupehenone.

In 2005, Alvarez-Manzaneda group reported a new strategy toward puupehenone-related natural products based on the palladium(II)-mediated diastereoselective cyclization of a drimenylphenol [39] to complete the first enantiospecific synthesis of 15-oxopuupehenol, together with improved syntheses of 15-cyanopuupehenone, puupehenone and puupehedione. As shown in Figure 7,
The drimane synthon 44 is easily prepared from sclareol (15) in seven steps. According to the procedure reported by Barrero [40], the drimane precursor 43 was prepared over three steps from 15 in 75% overall yield. Treating 43 with t-BuOK in a mixed solvent of DMSO-\(\text{H}_2\text{O}\), followed by oxidative hydroboration, dehydration, and oxidation, afforded synthon 44 in 52% yield over four steps. The new synthon 47 from the 3,4-bis(benzyloxybenzyloxy)phenol (45), in a two-step sequence in 83% overall yield. Then, the key skeleton 48 was obtained by the coupling of 44 and 47. Alvarez-Manzaneda and coworkers realized that catalytic PdCl\(_2\) and Pd(OAc)\(_2\) allowed to obtain the desired \(\alpha\)-Me epimer with complete diastereoselectivity by inducing cyclization, yielding the most satisfactory compounds. Thus, puupehenol (5) was achieved by catalytic hydrogenation of 49, which was obtained in high yield via palladium(II) catalysis of compound 48. Finally, puupehenol (5) can be transformed into 15-oxopuupehenol (7) and the other puupehenone-related natural products.

Continuing their research into the total synthesis of this type of natural product, in 2007, Alvarez-Manzaneda group reported a new synthetic route toward puupehenone-related natural products starting from sclareol oxide (50) [41]. As shown in Figure 8, the key structure 53 was constructed by the coupling of two synthons 51 and 52, based on a Diels-Alder cycloaddition approach. They employed sclareol oxide (50) as starting material to afford 51 over four steps which was treated with dienophile R-chloroacrylonitrile to afford compound 53 utilizing Diels-Alder cycloaddition. Treatment of 53 with DBU in benzene and DDQ in dioxane at room temperature led to aromatic nitrile 54. Then, ent-chromazonarol (55) was obtained over three steps in 63% yield. The oxidation of phenol 55 to the appropriate ortho-quinone precursor of target compound 32 was then addressed.

In 2009, Manzaneda group [42] reported an enantiospecific route toward puupehenone and other related metabolites based on the cationic-resin-promoted Friedel-Crafts alkylation of alkoxyarenes with an \(\alpha,\beta\)-unsaturated ketone 57. As shown in Figure 9, Manzaneda and coworkers developed a very efficient synthesis of compound 57 which is a key synthon employed in the total synthesis of puupehenones, starting from commercially available sclareol (15) in 60% yield.

Figure 7. Synthesis of several puupehenone-type natural products by palladium-catalyzed cyclization [39].
Then, the key intermediate ketone 59 was obtained in high yield and with complete
diastereoselectivity by treatment of 57 with protected phenol 58 under the condi-
tion of Amberlyst A-15. Alternatively, treatment of ketone 59 with MeMgBr, fur-
ther cleavage of the benzyl ether and protection of hydroxyl gave triflate 60 in 72%
yield, which was a perfect intermediate for synthesizing puupehenone-type deriv-
atives. Finally, puupehenol (5) was achieved in 82% yield by the deprotection of
tetracyclic compound 61 obtained by the cyclization of triflate 60 with Pd(OAc)₂,
DPPF (1,1-bis(diphenylphosphanyl) ferrocene), and sodium tertbutoxide in
toluene.

In 2012, Baran group [43] described a scalable, divergent synthesis of bioactive
meroterpenoids via borono-sclareolide (63) of which the preparation requires the
excision of carbon monoxide from 33 and incorporation of BOH in its place.
Thus, compound 63 was accessed from 33 in 59% yield over five steps including Dibal-mediated reduction of 33, Pida/I2-mediated C–C bond cleavage, dehydroiodination, hydrolysis (AgF in pyridine followed by K$_2$CO$_3$ in methanol), and hydroboration with BH$_3$. This strategy constitutes the most efficient synthesis and highest yielding of 63 by far. Then, the key skeleton 55 was synthesized by treating 63 with an excess of 1,4-benzoquinone under the condition of K$_2$S$_2$O$_8$ and AgNO$_3$ in PhCF$_3$/$H_2$O at 60°C. By following an oxidation-reduction-oxidation procedure, compound 55 was converted into 8-epi-pupehedione (32) in 24% yield.

The generation of boron-sclareolide 63 in such a direct manner enables total synthesis of puupehenone-type compounds to be more succinct than those previously established. However, the synthesis of C8α-Me boron-sclareolide is problematic, probably due to its lower stability than its C8α-Me epimer.

In 2017, Wu and his coworkers developed a hemiacetalization/dehydroxylation/hydroxylation/retro-hemiacetalization tandem reaction as the key step to synthesize puupehenone-type marine natural products [44], and this novel synthetic strategy is superior to other reported routes in terms of synthetic steps, purification of the intermediates, and overall yield.

As shown in Figure 11, the key synthon β-hydroxyl aldehyde 39 was accomplished starting from commercially available sclareolide (33) over four steps with an markedly higher overall yield (66%) including the stereospecific 8-episcareolide with H$_2$SO$_4$ in HCO$_2$H, α-hydroxylation, reduction with LiH$_4$Al, and in situ lactol-oxidation/ester-hydrolysis. The key skeleton 67 was constructed by the coupling of aldehyde 39 and ketone 66. Treatment of 66 with LDA in THF at −78°C in the presence of 39 gave 67 in 67% yield. The following hemiacetalization/dehydroxylation/hydroxylation/retro-hemi-acetalization of 67 permitted to produce enone 68 as the only product in 92% yield, which can be converted into α-hydroxylated product 69 in 19% yield and natural product puupehenone (1) in 38% yield when treated with KHMS and subsequent reaction with P(OMe)$_3$. Besides, natural products puupehenol (5) and puupehedione (4) were also achieved in good yield. Reduction of one with NaBH$_4$ gave puupehenol (5) in 92% yield and oxidation of 5 with DDQ afforded puupehedione (4) in 71% yield.

It is worth mentioning that the preparation strategy of the key intermediates 67 can be employed for the total synthesis of haterumadienone- and puupehenone-type natural products without using protecting groups.
In the same year, Wu’s group reported an enantiospecific semisynthesis of puupehedione commencing from sclareolide (33) in only seven steps with an overall yield of 25% [45]. The key drimanal trimethoxystyrene skeleton 71 and 72 were constructed by the palladium-catalyzed cross-coupling reaction of an aryl-iodine and a drimanal hydrazone (70) which was obtained from commercially available sclareolide over five steps. Treatment of compound 70 and aryl iodine in the presence of Pd(PPh₃)₄ and K₂CO₃ in toluene at 110°C afforded key skeletons 71 and 72 in 40 and 45% yields, respectively. Exposure of the mixture of drimanal trimethoxystyrenes 71 and 72 with Pb/C produced compound 73 in 62% yield. Then, the p-benzoquinone (74) can be prepared by treating 73 with CAN (ceric ammonium nitrate) in 84% yield. Treatment of 74 with pTsOH at room temperature produced compound 75 by intramolecular oxastork-Danheiser transposition. Finally, puupehenone (1) was achieved over nine steps in 26% overall yield by exposing the resulting product 75 with K₂CO₃ in an enolization process. Besides, natural product puupehenol (5) can be obtained by reduction of 75 in presence of NaBH₄ in EtOH at room temperature (Figure 12).

Interestingly, natural product puupehediene (4) can be accomplished as the sole diastereoisomer in 47% yield when the mixture of 71 and 72 was treated with CAN at room temperature.

In 2018, Wu and his coworkers reported the divergent synthesis of (+)-8-epi-puupehediene [46]. Figure 13 shows the synthesis of 8-epi-puupehediene based on the Lewis acid catalyzed cyclization with sclareolide as starting material. Drimanal hydrazone 75 was obtained over four steps, as mentioned above. Then, the key skeleton was obtained by cross-coupling reaction of aryl iodide and drimanal hydrazone 75, yielding intermediates 76 and 77 in 32 and 54% yields, respectively. Allylic product 78 was
prepared in 91% yield by reduction of compounds 76 and 77 with TFA (trifluoroacetic acid) in the presence of Et$_3$SiH. Exposure of product 78 to CAN produced compound 80 as the major product in 48% yield, together with byproduct 79 in 9% yield. Then, the cyclization product 8-epi-19-methoxy puupehenol (82) was synthesized in 87% yield from compound 80 over two steps including treating 80 with Na$_2$S$_2$O$_4$ in the presence of tetrabutylammonium bromide (TBAB) and treating 81 with BF$_3$·Et$_2$O. Exposure of 82 to CAN afforded 83 in 77% yield. Finally, 8-epi-puupehedione (32) was completed in 48% overall yield by reducing 83 with NaBH$_4$ and subsequent treatment with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

**Figure 14** shows another synthesis route of 8-epi-puupehedione (32) based on the tandem cyclization. Compound 84 was prepared in 62% yield by a ring opening reaction starting from 8-epi-19-methoxy puupehenol (82) by treatment with DDQ. Then, compound 84 was converted into 83 in 92% yield via an intramolecular oxastork-Danheiser transposition reaction when it was treated with pTsOH. Reduction of 83 with NaBH$_4$ gave 8-epi-puupehenol (56), which can be transformed into 8-epi-puupehedione (32) by oxidation in the presence of DDQ.

**Figure 15** shows an alternative synthesis of (+)-8-epi-puupehedione (32) based on the 6π electrocyclic reaction. Compound 87 was achieved in 86% yield when 80 was reacted with base in MeOH. Then, treatment of 87 with DDQ in a mixed solvent of CH$_2$Cl$_2$ and H$_2$O (10:1, v/v) obtained 8-epi-puupehedione (32) in 65% yield.

In 2018, Li’s group developed an efficient synthesis of 8-epi-puupehenol [47] and central to this strategy is the Barton decarboxylative coupling, comprising a one-pot radical decarboxylation and quinone.
As shown in Figure 16, the 8-O-acetylhomodrimanic acid (89) was obtained by oxidative degradation of sclareol (15) with potassium permanganate and Ac₂O, and then the key intermediate thiohydroxamic ester 90 was achieved from the coupling of
8-O-acetylhomodrimanic acid (89) with 2-mercaptopyridine N-oxide under Steglichesterification conditions. Treatment of Barton ester [48, 49] 90 with 250 W light in the presence of the electron-deficient benzoquinone gave pyridylthioquinone meroterpenoid 91 in 85% yield which was converted into acetate 92 in 91% yield when it was treated with Raney-nickel in EtOH at room temperature. To a solution of compound 92 in anhydrous THF added LiAlH₄ gave 93 in 93% yield which was treated with TFA (trifluoroacetic acid) to obtain 94 in excellent yield. Finally, synthesis of

Figure 15.
Wu’s synthesis of 8-epi-puupehedione based on 6π-electrocyclic reaction [46].

Figure 16.
Li’s formal synthesis of 8-epi-puupehenol and 8-epi-puupehedione [47].
8-epi-puupehenol (56) and 8-epi-puupehedione (32) was accomplished via IBX oxidation, followed by redox manipulation, according to the published literature [43].

### 3.2 Linear synthesis route

In 2004, Yamamoto group [50] developed a liner synthesis route of 8-epi-puupehenone (32) employing a new artificial cyclase 97. Utilizing this cyclase, polycyclic terpenoids bearing a chroman skeleton can be obtained effectively.

8-epi-puupehenone 32 was achieved in 57% overall yield from 95 over four steps. Firstly, treatment of 95 with (R)-catalyst 97 through the enantio- and diastereoselective cyclization gave compound 96 in 62% yield. Then, 96 was transformed into 8-epi-puupehenone 32 through treatment of 96 with DDQ in 1,4-dioxane followed by hydrosilylative acetal cleavage employing Et₃SiH and B(C₆F₅)₃ and DDQ oxidation (Figure 17).

![Figure 17. Yamamoto’s synthesis of 8-epi-puupehenone by new type LBA [50].](image)

Figure 17.
Yamamoto’s synthesis of 8-epi-puupehenone by new type LBA [50].

8-epi-puupehedione (8)
In 2006, Gansäuer and coworkers reported a highly stereoselective and catalytic synthesis strategy for the marine natural product puupehedione (8) [51].

As shown in Figure 18, compound 98 was converted into cyclization precursor 101 over two steps in 42% yield. Bromination of 98 with NBS (N-bromosuccinimide) gave compound 99 in 70% yield and treatment of 100 with Grignard reagent derived from 99 in the presence of Li$_2$CuCl$_4$ via copper-catalyzed allylic substitution reaction. Then, the bicyclic alcohol 102 was obtained in 41% yield by Cp$_2$TiCl-catalyzed epoxypolyene cyclization of 101. The desired building unit 103 was achieved over three steps from compound 102 including deoxygenation of 102 by a Barton-McCombie reaction and high yielding cleavage of protecting group. Treating 103 with N-(phenylseleno)phthalimide and reduction with Bu$_3$SnH obtained compound 104. Then, puupehedione (8) was completed according to the literature published by Barrero [35].

4. Conclusions

Undoubtedly, puupehenone-type marine natural products play a vital role in new drug development. Thus, the total synthesis of puupehenones has become a research hotspot for organic chemists [52]. Recent accomplishments made in total syntheses of puupehenone-type marine natural products are highlighted as above in terms of the employed synthetic strategy. The main routes to synthesize puupehenones include Diels-Alder cycloaddition reaction, coupling of the aldehydes with halogenated aromatic synthon, Friedel-Crafts coupling reaction, hemiacetalization/dehydroxylation/hydroxylation/retro-hemiacetalization tandem reaction, and linear synthesis routes. Advances in total synthesis above offer new strategies for the chemical optimization of biologically active puupehenones.

Acknowledgements

This work was supported by the Natural Science Foundation of Shandong (ZR2019MB009), the Fundamental Research Funds for the Central Universities (HIT.NSRIF.201701), the Science and Technology Development Project of Weihai (2012DXGJ02, 2015DXGJ04), the Natural Science Foundation of China (21672046, 21372054), and the Found from the Huancui District of Weihai City.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.
References

[1] Butler MS. Natural products to drugs: Natural product-derived compounds in clinical trials. Natural Product Reports. 2008;25:475-516. DOI: 10.1039/B514294F

[2] Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981–2002. Journal of Natural Products. 2003;66:1022-1037. DOI: 10.1021/np030096l

[3] Gerwick WH, Fenner AM. Drug discovery from marine microbes. Microbial Ecology. 2013;65:800-806. DOI: 10.1007/s00248-012-0169-9

[4] Jin L, Quan C, Hou X. Potential pharmacological resources: Natural bioactive compounds from marine-derived fungi. Marine Drugs. 2016;14:76. DOI: 10.3390/md14040076

[5] Kohmoto S, McConnell OJ, Wright A. Puupehenone, a cytotoxic metabolite from a deep water marine sponge, Stronglyophora hartman. Journal of Natural Products. 1987;50:336-336. DOI: 10.1021/np50050a064

[6] Pina IC, Sanders ML, Crews P. Puupehenone congeners from an Indo-Pacific Hyrtios sponge. Journal of Natural Products. 2003;66:2-6. DOI: 10.1021/np020279s

[7] Longley RE, McConnell OJ, Essich E. Evaluation of marine sponge metabolites for cytotoxicity and signal-transduction activity. Journal of Natural Products. 1993;56:915-920. DOI: 10.1021/np50096a015

[8] Sova VV, Fedoreev SA. Metabolites from sponges as beta-1,3-glucanase inhibitors. Khimiya Prirodnykh Soedinii. 1990;4:497-500

[9] El Sayed KA, Bartyzel P, Shen XY. Marine natural products as antituberculosis agents. Tetrahedron. 2000;56:949-953. DOI: 10.1016/S0040-4020(99)01093-5

[10] Castro ME, González-Iriarte M, Barrero AF. Study of puupehenone and related compounds as inhibitors of angiogenesis. International Journal of Cancer. 2004;110:31-38. DOI: 10.1002/ijc.20068

[11] John FD. Marine natural products. Natural Product Reports. 1998;15:113-158. DOI: 10.1039/A815113Y

[12] Hamann MT, Scheuer PJ. Cyanopuupehenol, an antiviral metabolite of a sponge of the order Verongida. Tetrahedron Letters. 1991;32:5671-5672. DOI: 10.1016/0040-4039(00)93525-1

[13] Kraus GA, Nguyen T, Bae J. Synthesis and antitubercular activity of tricyclic analogs of puupehenone. Tetrahedron. 2004;60:4223-4225. DOI: 10.1016/j.tet.2004.03.043

[14] Nasu SS, Yeung BK, Hamann MT. Puupehenone-related metabolites from two Hawaiian sponges, Hyrtios spp. The Journal of Organic Chemistry. 1995;60:7290-7292. DOI: 10.1021/jo00127a039

[15] Ravi BN, Perzanowski HP, Ross RA. Recent research in marine natural products: The puupehenones. Pure and Applied Chemistry. 1979;51:1893-1900. DOI: 10.1351/pac197951091893

[16] Bourguet-Kondracki M-L, Debitus C, Guyot M. Dipuupehedione, a cytotoxic new red dimer from a new Caledonian marine sponge Hyrtios sp. Tetrahedron Letters. 1996;37:3861-3864. DOI: 10.1016/0040-4039(96)00700-9

[17] Bourguet-Kondracki M-L, Lacombe F, Guyot M. Methanol adduct of puupehenone, a biologically active derivative from the marine sponge.
Hyrtios species. Journal of Natural Products. 1999;62:1304-1305. DOI: 10.1021/np9900829

[18] Urban S, Capon RJ. Absolute stereochemistry of puupehenone and related metabolites. Journal of Natural Products. 1996;59:900-901. DOI: 10.1021/np9603838

[19] Suyama TL, Gerwick WH, McPhail KL. Survey of marine nature product structure revisions: A synergy of spectroscopy and chemical synthesis. Bioorganic & Medicinal Chemistry. 2011;19:6675-6701. DOI: 10.1016/j.bmc.2011.07.017

[20] Baran PS, Maimone TJ, Richter JM. Total synthesis of marine natural products without using protecting groups. Nature. 2007;446:404-408. DOI: 10.1038/nature05569

[21] Hanessian S. Structure-based synthesis: From natural products to drug prototypes. Pure and Applied Chemistry. 2009;81:1085-1091. DOI: 10.1351/PAC-CON-08-07-12

[22] Hashimoto S. Natural product chemistry for drug discovery. The Journal of Antibiotics. 2011;64:697-701. DOI: 10.1038/ia.2011.74

[23] Morris JC, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2011;28:269-289. DOI: 10.1039/C0NP00066C

[24] Morris JC, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2010;27:1186-1203. DOI: 10.1039/B919366A

[25] Carter GT. Natural products and pharma 2011: Strategic changes spur new opportunities. Natural Product Reports. 2011;28:1783-1789. DOI: 10.1039/C1NP00033K

[26] Henkel T, Brunner RM, Reichel F. Statistical investigation into the structural complementarity of natural products and synthetic compounds. Angewandte Chemie (International Ed. in English). 1999;38:643-647. DOI: 10.1002/(SICI)1521-3773(19990301)38:5<643::AID-ANIE643>3.0.CO;2-G

[27] Capon RJ. Marine natural products chemistry: Past, present, and future. Australian Journal of Chemistry. 2010;63:851-854. DOI: 10.1071/ch10204

[28] Morris JC, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2009;26:245-265

[29] Morris JC, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2008;25:95-117. DOI: 10.1039/B701533J

[30] Morris JC, Nicholas GM, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2007;24:87-108. DOI: 10.1039/B602832M

[31] Nicholas GM, Phillips AJ. Marine natural products: Synthetic aspects. Natural Product Reports. 2006;23:79-99. DOI: 10.1039/B501014B

[32] Barrero AF, Manzaneda EA, Altarejos J. Synthesis of biologically active drimanes and homodrimanes from (−)-sclareol. Tetrahedron. 1995;51:7435-7450. DOI: 10.1016/0040-4020(95)00370-N

[33] Barrero AF, Alvarez-Manzaneda EJ, Chahboun R. Enantiospecific synthesis of (+)-puupehenone from (−)-sclareol and protocatechualdehyde. Tetrahedron. 1997;53:2325-2328. DOI: 10.1016/S0040-4020(97)00305-5

[34] Barrero AF, Alvarez-Manzaneda EJ, Chahboun R. Synthesis of wiedendiol-A and wiedendiol-B from labdane diterpenes. Tetrahedron. 1998;54:5635-5650. DOI: 10.1016/S0040-4020(98)00235-X
[35] Barrero AF, Alvarez-Manzaneda EJ, Chahboun R. Synthesis and antitumor activity of puupehedione and related compounds. Tetrahedron. 1999;55:15181-15208. DOI: 10.1016/S0040-4020(99)00992-8

[36] Maiti S, Sengupta S, Giri C. Enantiospecific synthesis of 8-epipuupehedione from (R)-(-)-carvone. Tetrahedron Letters. 2001;42:2389-2391. DOI: 10.1016/S0040-4039(01)00153-8

[37] Martin SF, Garrison PJ. General methods for alkaloid synthesis. Total synthesis of racemic lycoramine. The Journal of Organic Chemistry. 1982;47:1513-1518. DOI: 10.1021/jo00347a029

[38] Quideau S, Lebon M, Lamidey A-M. Enantiospecific synthesis of the antituberculosis marine sponge metabolite (+)-puupehenone. The arenol oxidative activation route. Organic Letters. 2002;4:3975-3978. DOI: 10.1021/ol026855t

[39] Alvarez-Manzaneda EJ, Chahboun R, Barranco Pérez I, et al. First enantiospecific synthesis of the antitumor marine sponge metabolite (–)-15-oxopuupehenol from (–)-sclareol. Organic Letters. 2005;7:1477-1480. DOI: 10.1021/ol047332j

[40] Barrero AF, Alvarez-Manzaneda EJ, Chahboun R. New routes toward drimanes and nor-drimanes from (–)-sclareol. Synlett. 2000;2000:1561-1564. DOI: 10.1055/s-2000-7924

[41] Alvarez-Manzaneda EJ, Chahboun R, Cabrera E. Diels–Alder cycloaddition approach to puupehenone-related metabolites: Synthesis of the potent angiogenesis inhibitor 8-epipuupehedione. The Journal of Organic Chemistry. 2007;72:3332-3339. DOI: 10.1021/jo0626663

[42] Alvarez-Manzaneda E, Chahboun R, Cabrera E. A convenient enantiospecific route towards bioactive merosesquiterpenes by cationic-resin-promoted Friedel–Crafts alkylation with A,B-enones. European Journal of Organic Chemistry. 2009;2009:1139-1143. DOI: 10.1002/ejoc.200801174

[43] Dixon DD, Lockner JW, Zhou Q. Scalable, divergent synthesis of meroterpenoids via "borono-sclareolide". Journal of the American Chemical Society. 2012;134:8432-8435. DOI: 10.1021/ja303937y

[44] Wang HS, Li HJ, Wu YC. Protecting-group-free synthesis of haterumadienone- and puupehenone-type marine natural products. Green Chemistry. 2017;19:2140-2144. DOI: 10.1039/c7gc00704c

[45] Wang HS, Li HJ, Wu YC. Enantiospecific semisynthesis of puupehenone-type marine natural products. The Journal of Organic Chemistry. 2017;82:12914-12919. DOI: 10.1021/acs.joc.7b02413

[46] Wang HS, Li HJ, Wu YC. Divergent synthesis of bioactive meroterpenoids via palladium-catalyzed tandem carbene migratory insertion. European Journal of Organic Chemistry. 2018;2018:915-925. DOI: 10.1002/ejoc.201800026

[47] Li SK, Zhang SS, Wang X. Expediently scalable synthesis and antifungal exploration of (+)-yahazunol and related meroterpenoids. Journal of Natural Products. 2018;81:2010-2017. DOI: 10.1021/acs.jnatprod.8b00310

[48] Ling T, Xiang AX, Theodorakis EA. Enantioselective total synthesis of avarol and avarone. Angewandte Chemie (International Ed. in English). 1999;38:3089-3091. DOI: 10.1002/(SICI)1521-3773(19991018)38:20<3089::AID-ANIE3089>3.0.CO;2-W

[49] Marcos IS, Conde A, Moro RF. Synthesis of quinone/hydroquinone
Approaches to the Total Synthesis of Puupehenone-Type Marine Natural Products
DOI: http://dx.doi.org/10.5772/intechopen.87927

Ishibashi H, Ishihara K, Yamamoto H. A new artificial cyclase for polyprenoids: enantioselective total synthesis of (−)-chromazonarol, (+)-8-epi-puupehedione, and (−)-11'-deoxytaondiol methyl ether. Journal of the American Chemical Society. 2004; 126:11122-11123. DOI: 10.1021/ja0472026

Gansäuer A, Rosales A, Justicia J. Catalytic epoxypolyene cyclization via radicals: Highly diastereoselective formal synthesis of puupehedione and 8-epi-puupehedione. Synlett. 2006; 2006:927-929. DOI: 10.1055/s-2006-933139

Shen B. A new golden age of natural products drug discovery. Cell. 2015; 163:1297-1300. DOI: 10.1016/j.cell.2015.11.031