

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

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

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



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 polyene 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 puppehenone, 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 tetrahydropyran/dihydropyran 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.

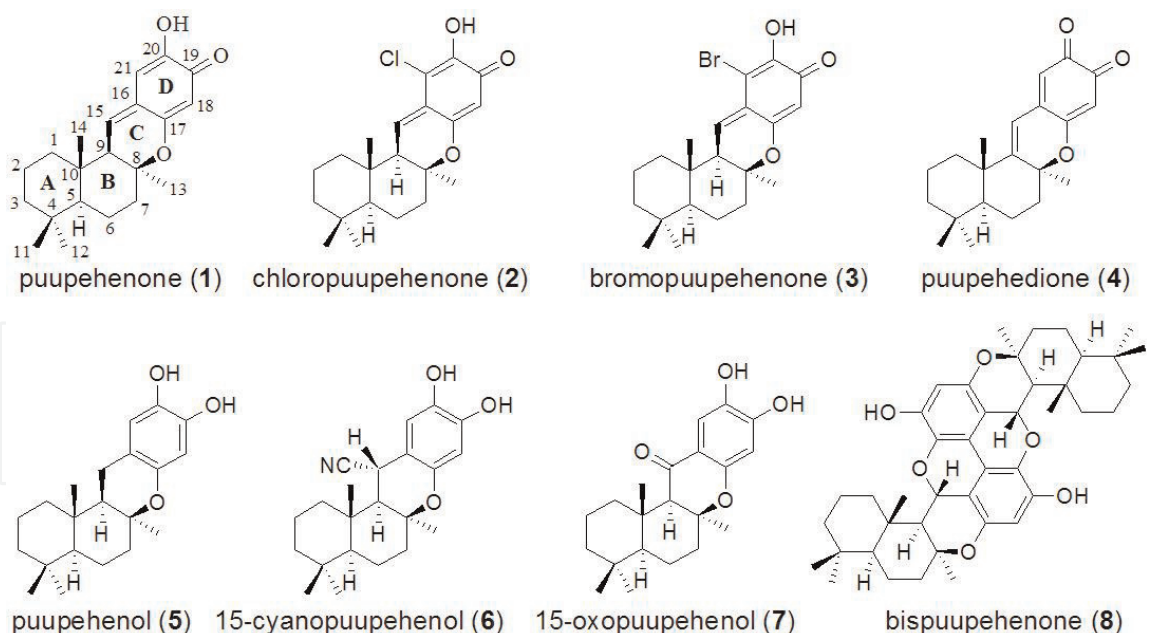


Figure 1.
Representatives of puupehenone-type natural products.

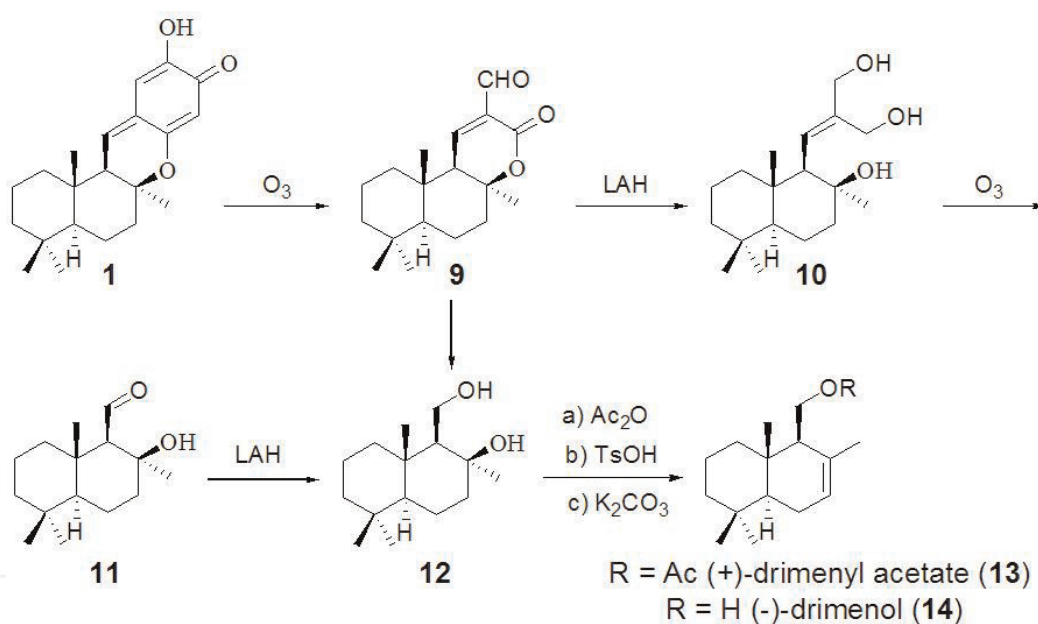


Figure 2.
The confirmation of the absolute configuration of puupehenone by chemical decomposition [18].

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], antimalaria [12], antimitotic [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

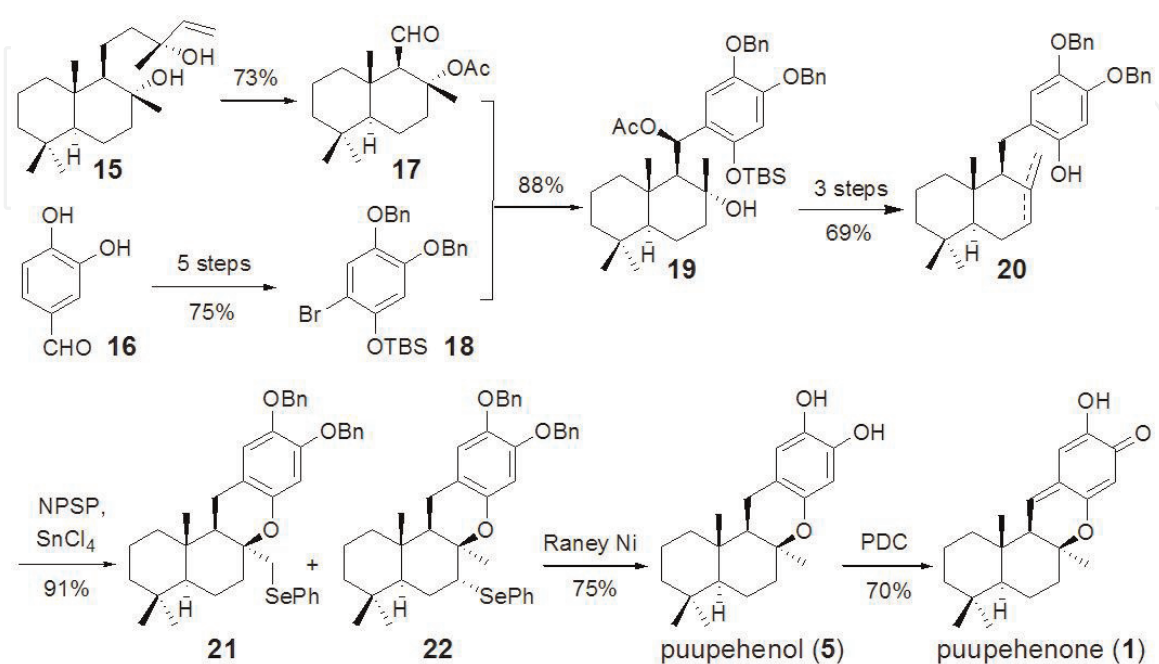


Figure 3.
 Barrero's stereoselective synthesis of puupehenol and puupehenone [33].

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-phenylselenophthalimide) 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 (+)-puupehenone (**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 $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$ in refluxing EtOH resulted in spontaneous cyclization [37], affording a mixture of the puupehedione (**4**) and 8-epi-puupehedione (**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-

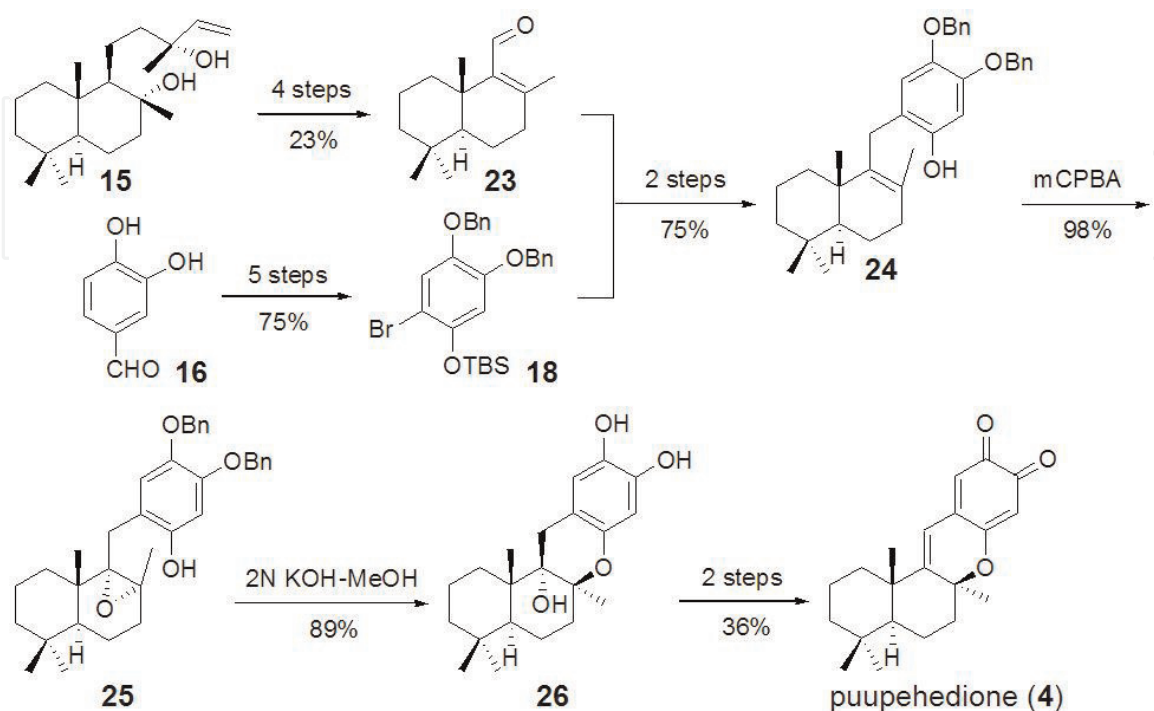


Figure 4.
Barrero's asymmetric synthesis of puupehedione [35].

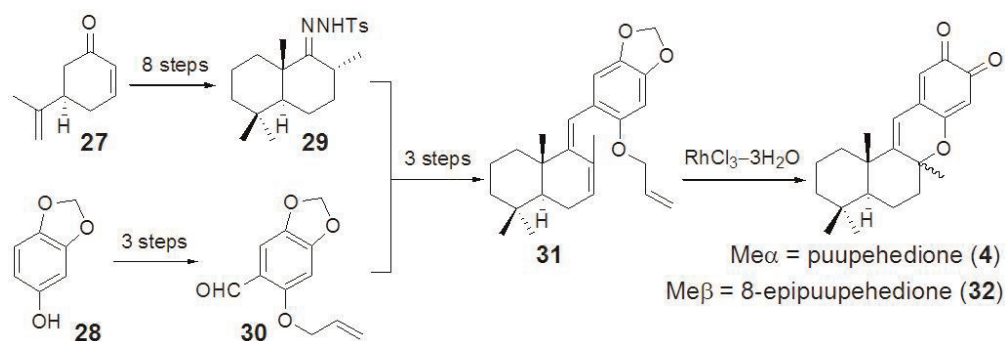


Figure 5.
Maiti's RhCl_3 catalyzed cyclization synthesis of 8-epi-puupehedione [36].

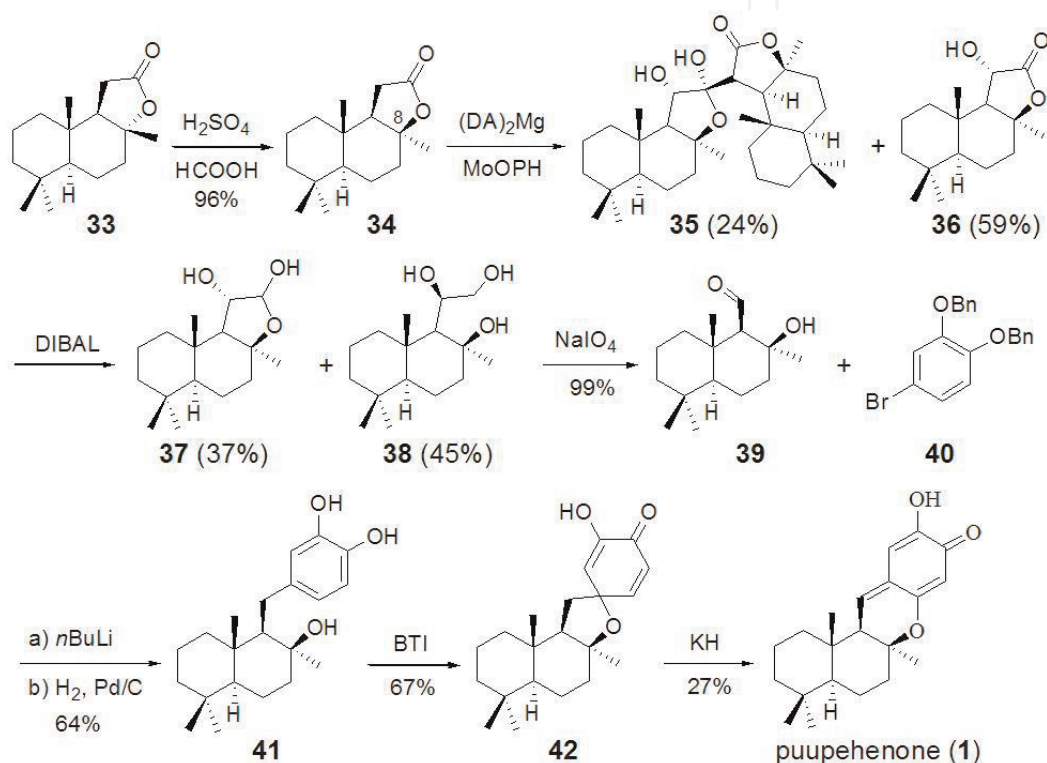


Figure 6.
Quideau's asymmetric synthesis of puupehenone [38].

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 $(\text{DA})_2\text{Mg}$ 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**,

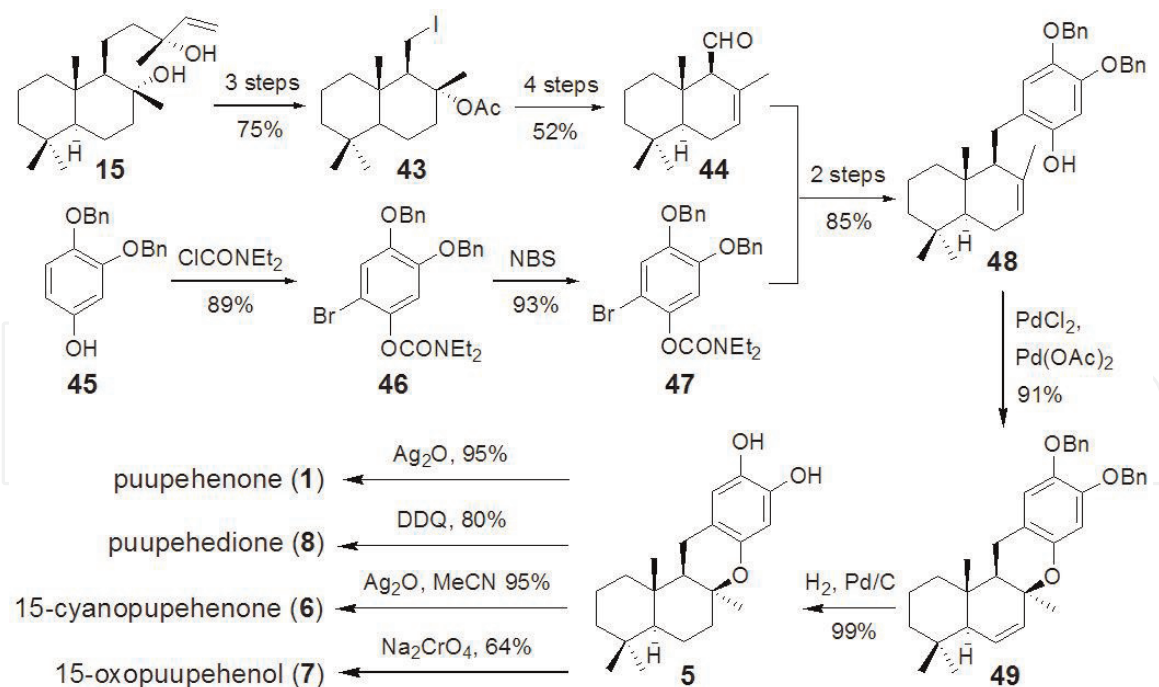


Figure 7. Synthesis of several puupehenone-type natural products by palladium-catalyzed cyclization [39].

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-H₂O, 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 PdCl₂ and Pd(OAc)₂ allowed to obtain the desired C8 α -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-oxopupehenol (**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 α,β -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.

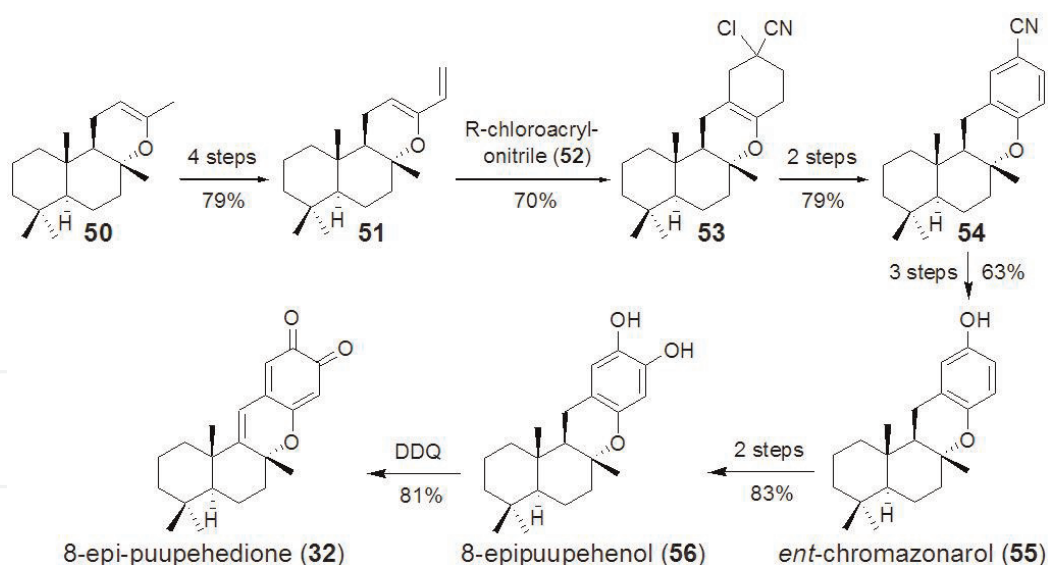


Figure 8.
Synthesis of 8-epi-puupehenone-type compound by Diels-Alder cyclization [41].

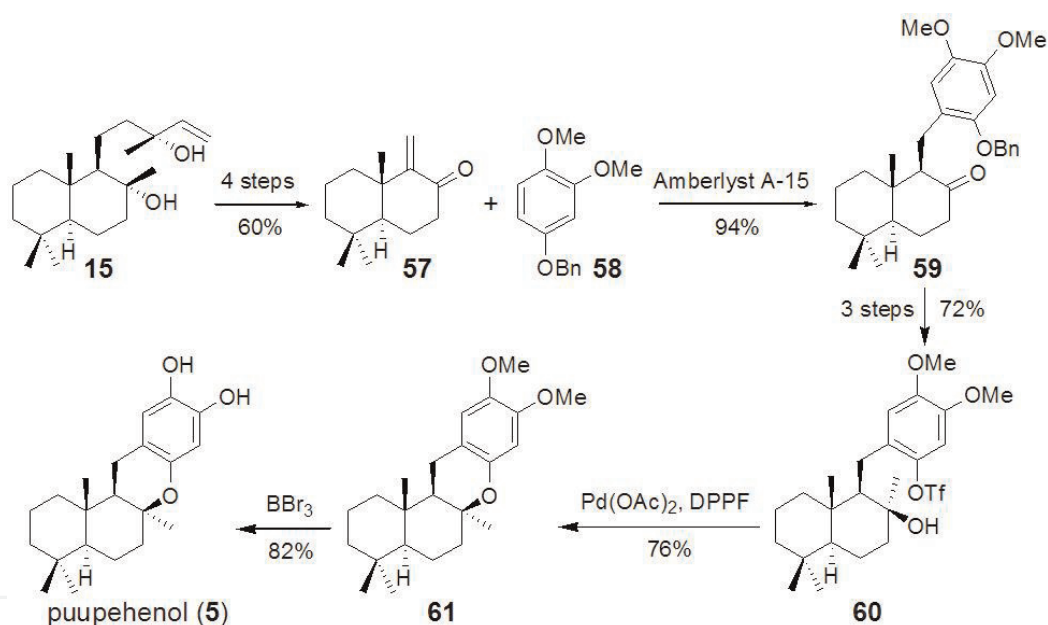


Figure 9.
Synthesis of puupehenol by Friedel-Crafts coupling reaction [42].

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 condition of Amberlyst A-15. Alternatively, treatment of ketone **59** with MeMgBr , further cleavage of the benzyl ether and protection of hydroxyl gave triflate **60** in 72% yield, which was a perfect intermediate for synthesizing puupehenone-type derivatives. Finally, puupehenol (**5**) was achieved in 82% yield by the deprotection of tetracyclic compound **61** obtained by the cyclization of triflate **60** with $\text{Pd}(\text{OAc})_2$, 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

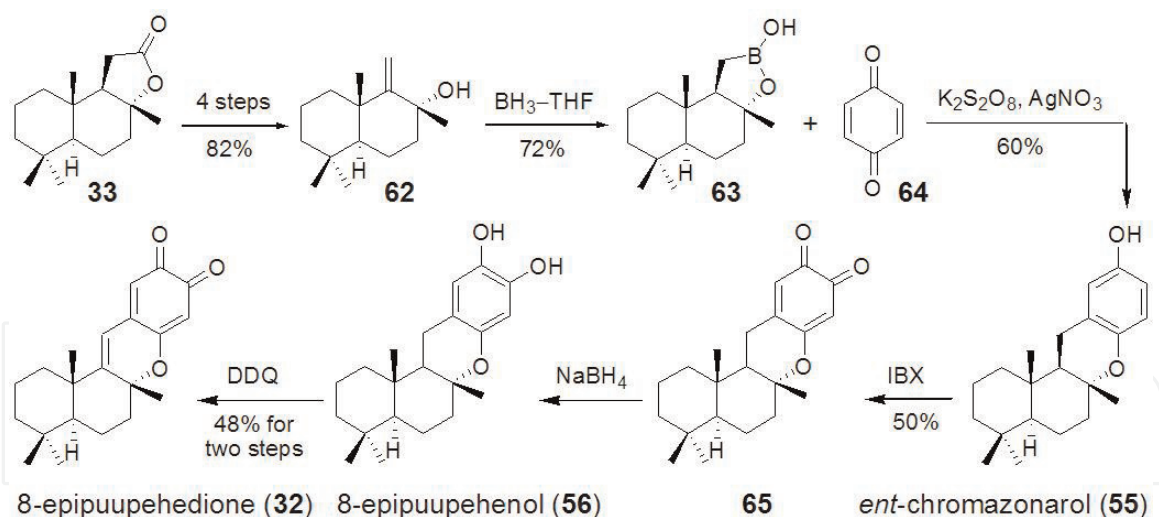


Figure 10.
Baran's synthesis of puupehenone-type natural products [43].

(**Figure 10**). 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 K₂CO₃ in methanol), and hydroboration with BH₃. 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 K₂S₂O₈ and AgNO₃ in PhCF₃/H₂O at 60°C. By following an oxidation-reduction-oxidation procedure, compound **55** was converted into 8-epipuupehedione (**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 C8 α -Me boron-sclareolide is problematic, probably due to its lower stability than its C8 α -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-episclareolide with H₂SO₄ in HCO₂H, α -hydroxylation, reduction with LiH₄Al, 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 KHMDS 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 NaBH₄ 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.

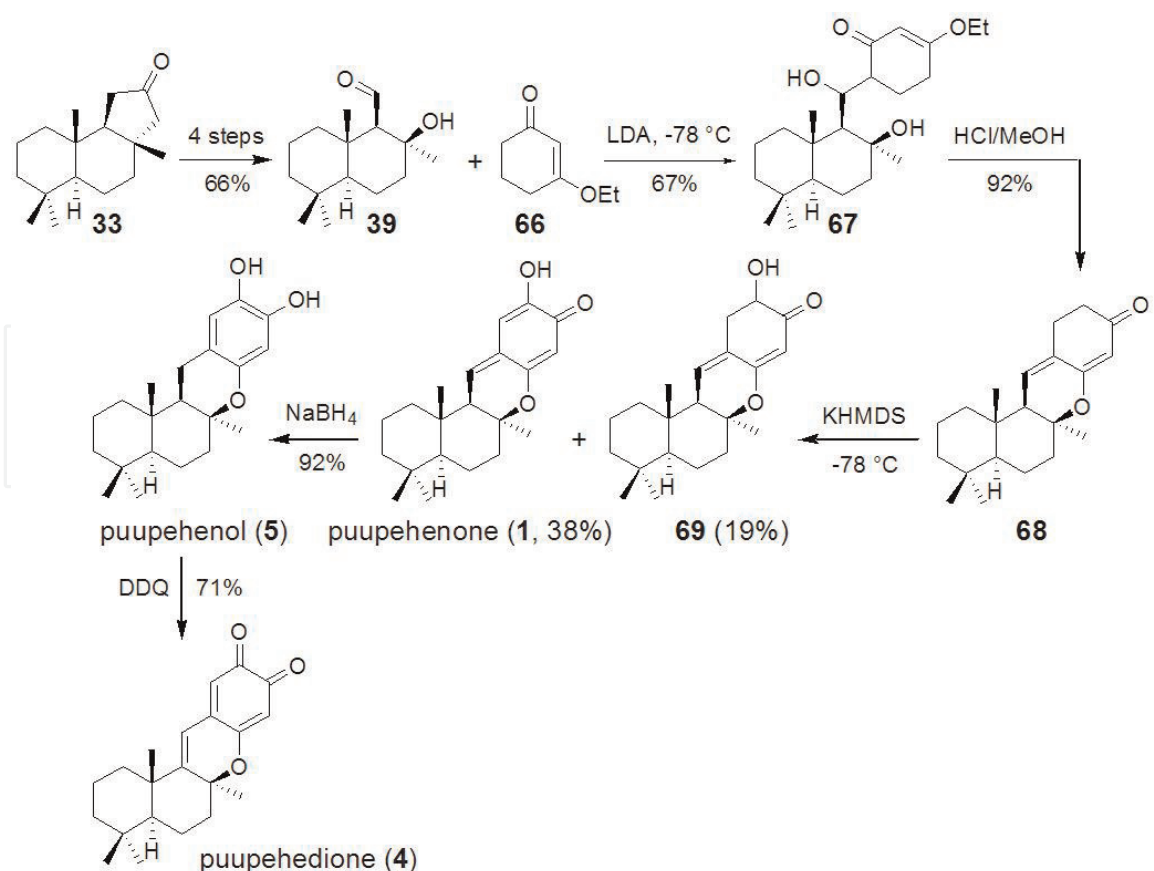


Figure 11.
Wu's synthesis of puupehenone-type natural products [44].

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 drimantal trimethoxystyrene skeleton 71 and 72 were constructed by the palladium-catalyzed cross-coupling reaction of an aryl-iodine and a drimantal hydrazine (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 drimantal 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 oxa-Stork-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 puupehedione (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-puupehedione [46].

Figure 13 shows the synthesis of 8-epi-puupehedione based on the Lewis acid catalyzed cyclization with sclareolide as starting material. Drimantal hydrazone 75 was obtained over four steps, as mentioned above. Then, the key skeleton was obtained by cross-coupling reaction of aryl iodide and drimantal hydrazone 75, yielding intermediates 76 and 77 in 32 and 54% yields, respectively. Allylic product 78 was

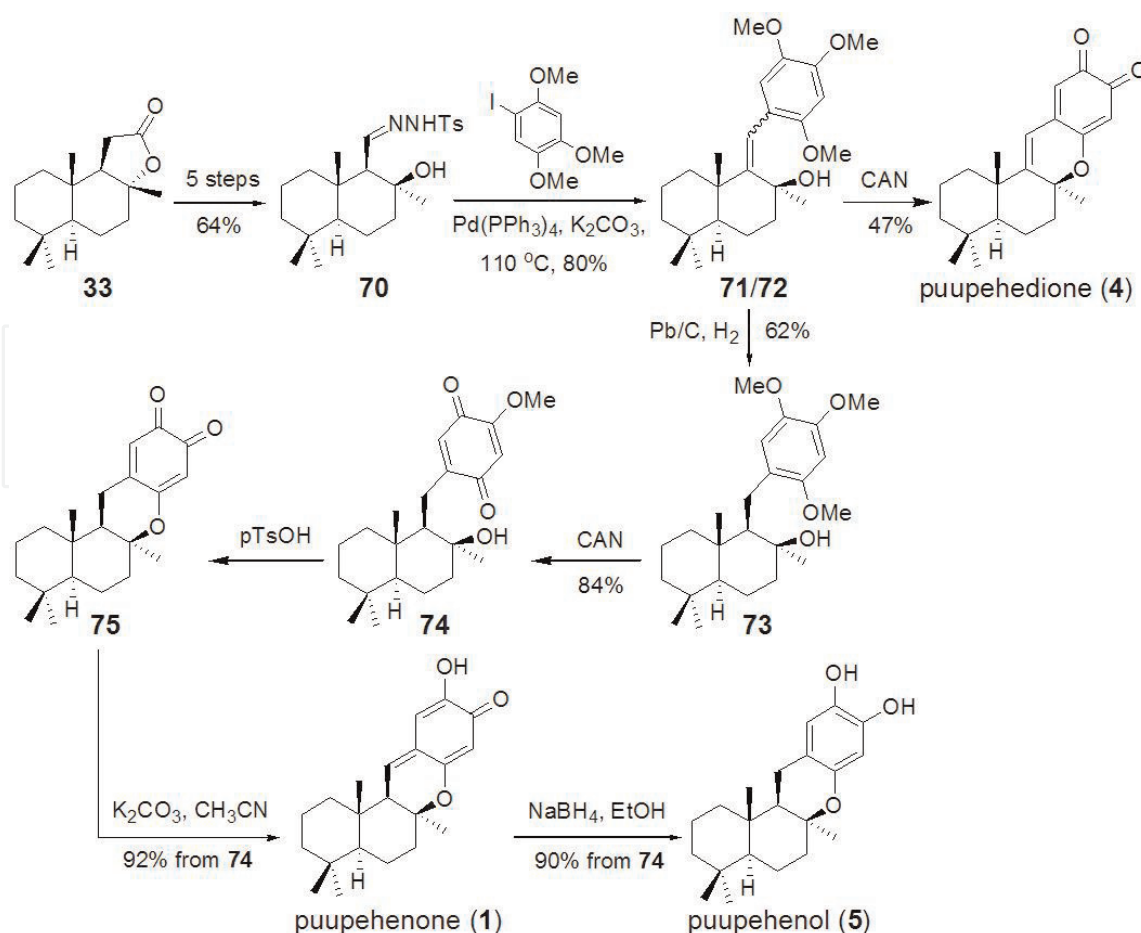


Figure 12.
Wu's synthesis of puupehenone-type natural products [45].

prepared in 91% yield by reduction of compounds 76 and 77 with TFA (trifluoroacetic acid) in the presence of Et_3SiH . 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 $\text{Na}_2\text{S}_2\text{O}_4$ in the presence of tetrabutylammonium bromide (TBAB) and treating 81 with $\text{BF}_3 \cdot \text{Et}_2\text{O}$. 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 oxa-Stork-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_2Cl_2 and H_2O (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.

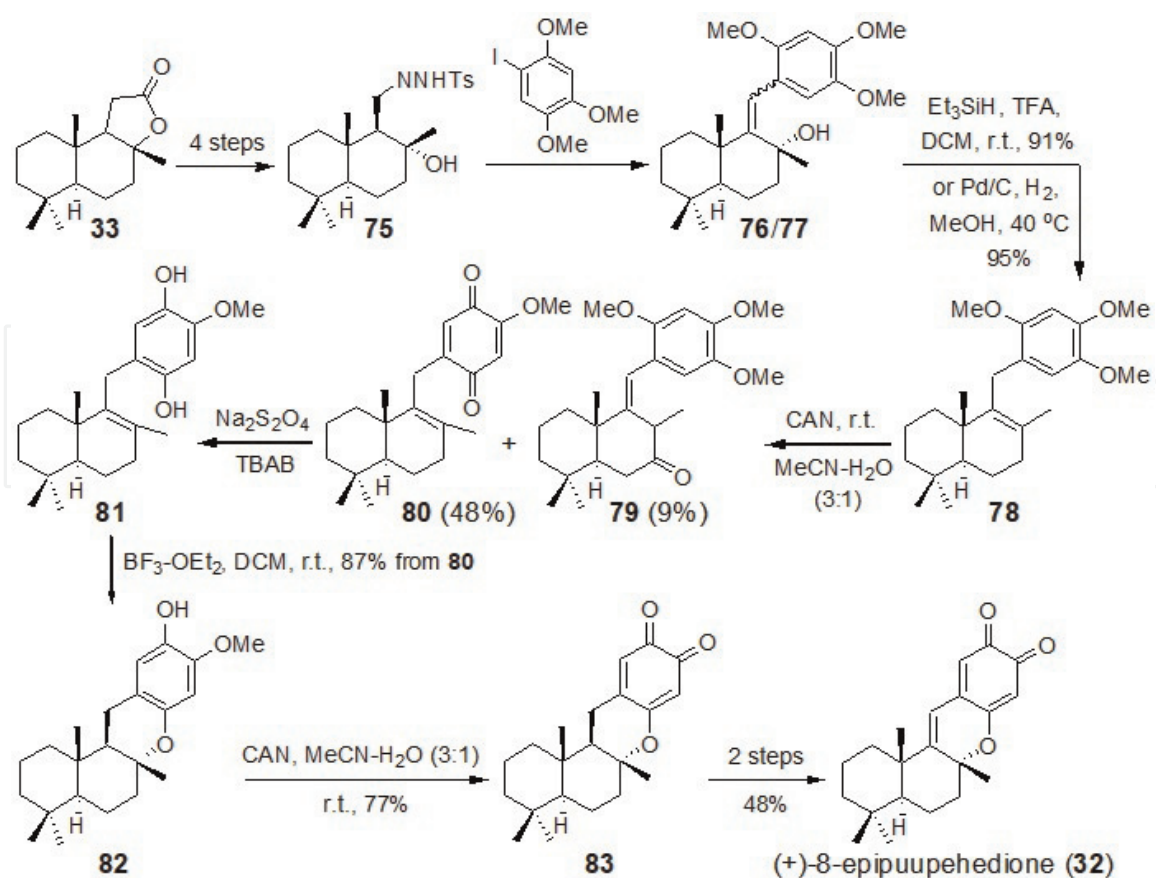


Figure 13.
Wu's synthesis of 8-epi-puupehedione based on the Lewis acid catalyzed cyclization [46].

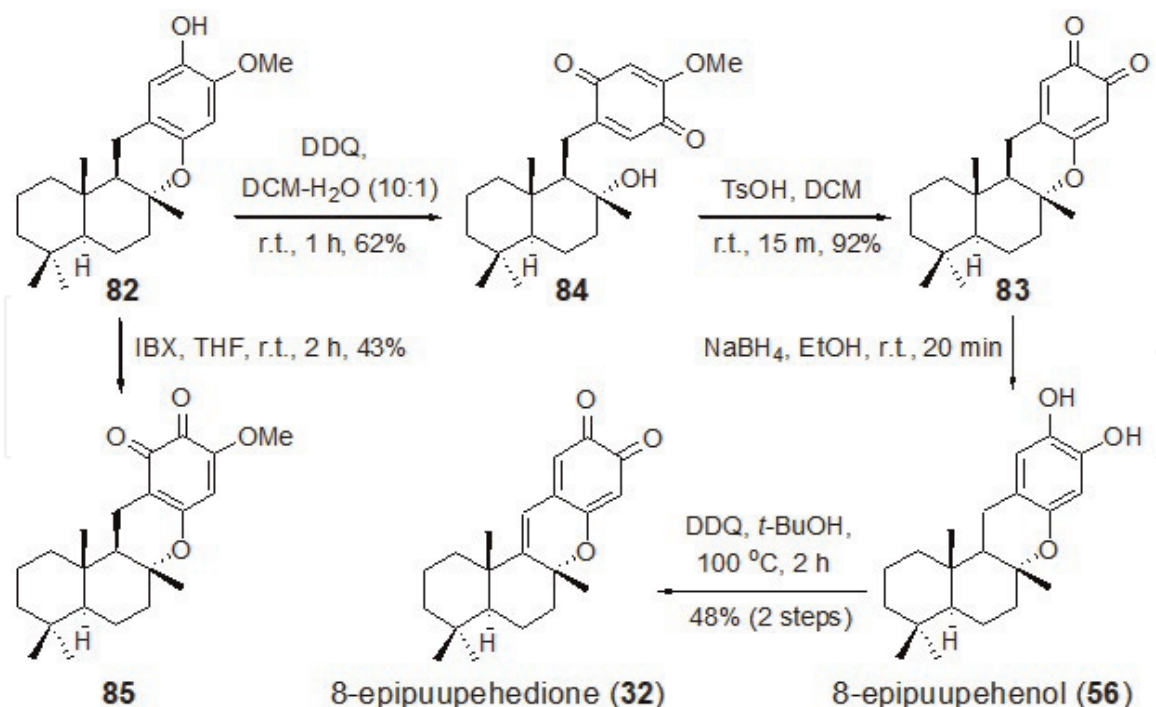


Figure 14.
Wu's synthesis of 8-epi-puupehedione based on the tandem cyclization [46].

As shown in **Figure 16**, the 8-O-acetylhomodrimanic acid (89) was obtained by oxidative degradation of sclareol (15) with potassium permanganate and Ac_2O , and then the key intermediate thiohydroxamic ester 90 was achieved from the coupling of

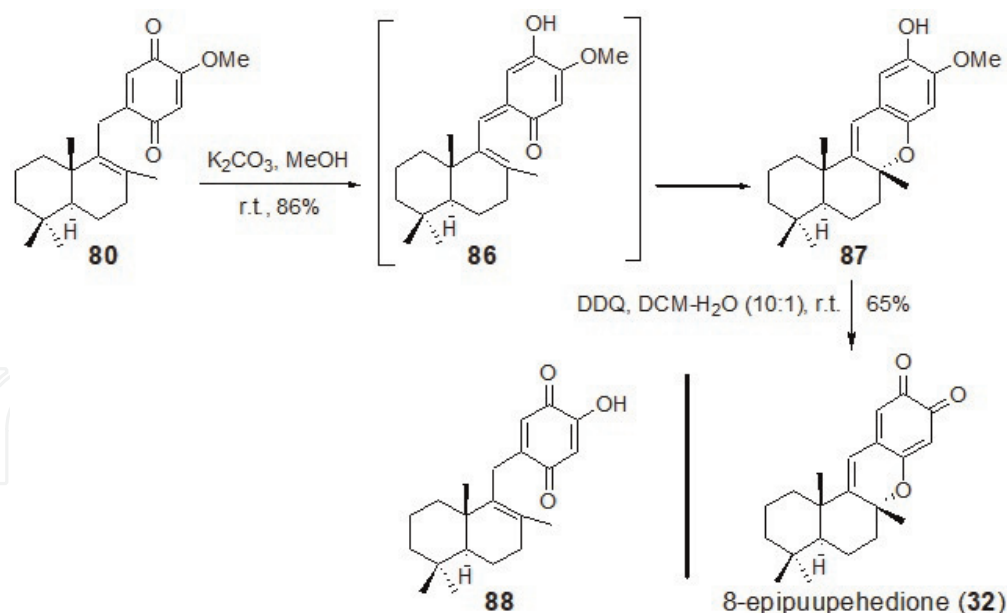


Figure 15.

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

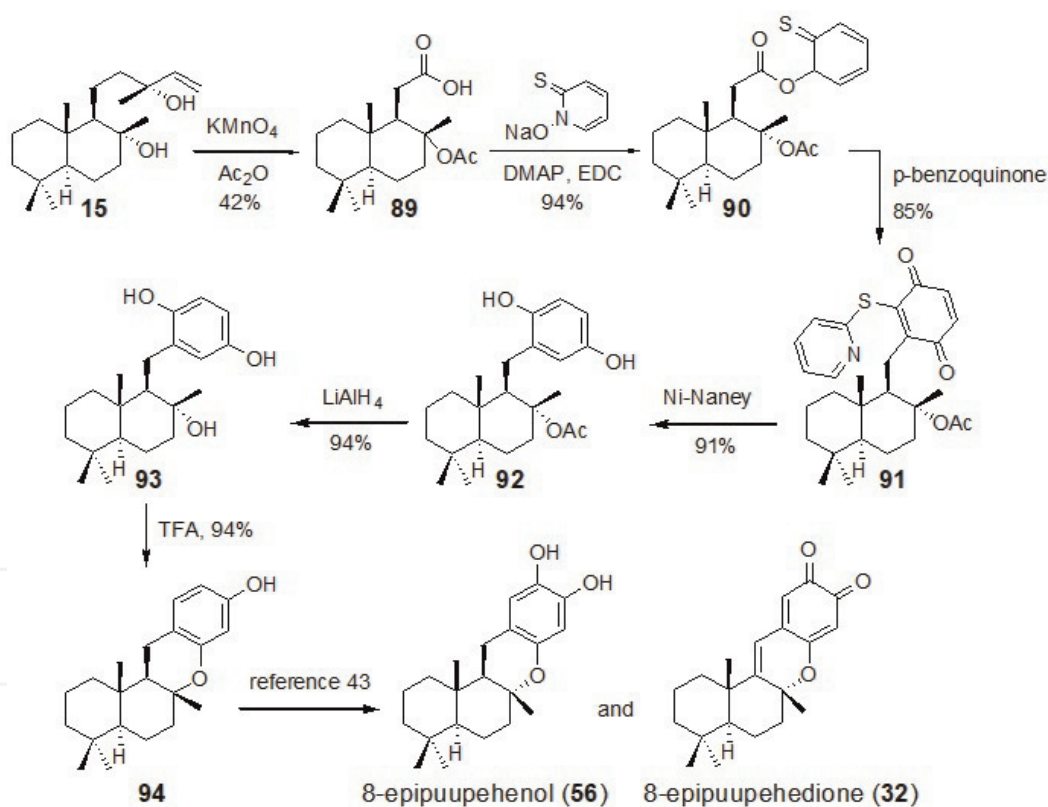


Figure 16.

Li's formal synthesis of 8-epi-puupehenol and 8-epi-puupehedione [47].

8-O-acetylhomodrimanic acid (89) with 2-mercaptopyridine N-oxide under Steglich esterification 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 $LiAlH_4$ gave 93 in 93% yield which was treated with TFA (trifluoroacetic acid) to obtain 94 in excellent yield. Finally, synthesis of

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 linear 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 Et_3SiH and $\text{B}(\text{C}_6\text{F}_5)_3$ and DDQ oxidation (**Figure 17**).

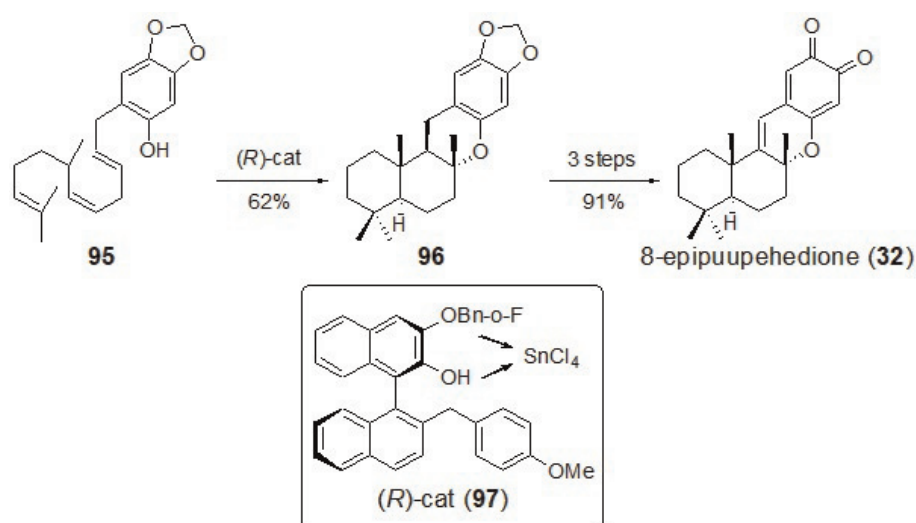


Figure 17.
Yamamoto's synthesis of 8-epi-puupehenone by new type LBA [50].

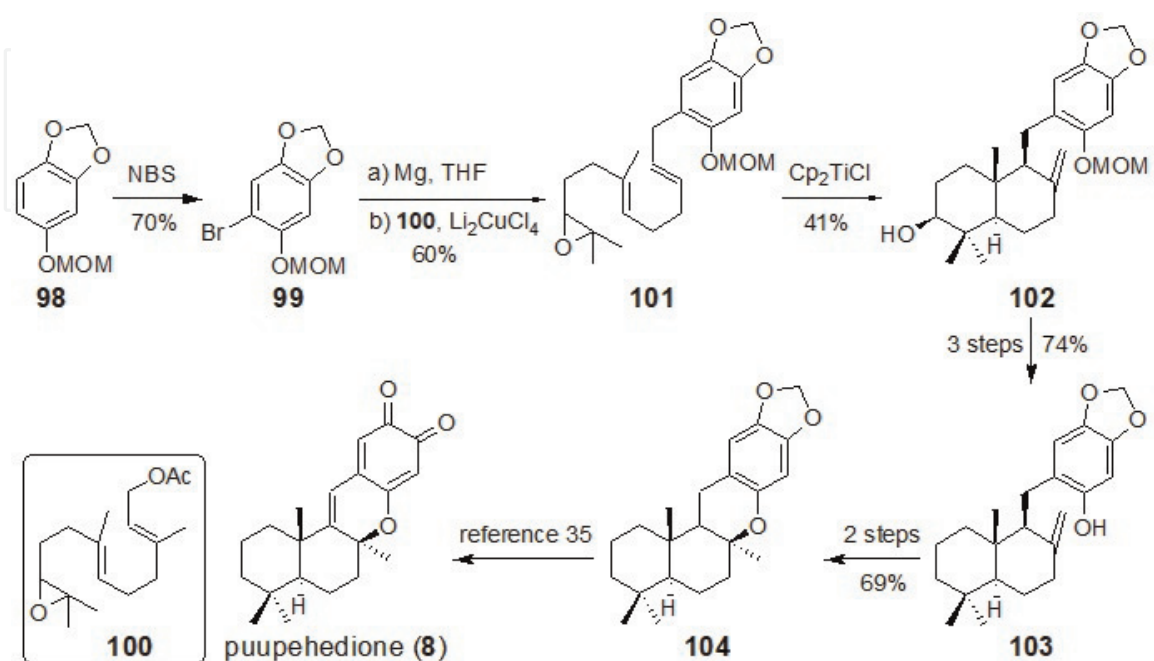


Figure 18.
Gansäuer's formal synthesis of puupehedione [51].

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_2CuCl_4 via copper-catalyzed allylic substitution reaction. Then, the bicyclic alcohol **102** was obtained in 41% yield by Cp_2TiCl -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 yield-ing cleavage of protecting group. Treating **103** with N-(phenylseleno)phthalimide and reduction with Bu_3SnH 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, Friede-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.

IntechOpen


IntechOpen

Author details

Yan-Chao Wu*, Yun-Fei Cheng and Hui-Jing Li
School of Marine Science and Technology, Harbin Institute of Technology, Weihai,
P. R. China

*Address all correspondence to: ycwu@iccas.ac.cn

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

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-gluconase inhibitors. *Khimiya Prirodnikh Soedinenii*. 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/S0040-4039(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/ja.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, Brunne 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 Letters*. 1997;**38**:2325-2328. DOI: 10.1016/S0040-4039(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 puupehedione-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

sesquiterpenes. *Tetrahedron*. 2010;**66**:
8280-8290. DOI: 10.1016/j.tet.
2010.08.038

[50] 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

[51] 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

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