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Asymmetric total synthesis strategies of halichlorine and pinnaic acid

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Halichlorine and pinnaic acid are structurally related natural alkaloids isolated from different marine organisms. These two marine alkaloids bearing a 6-azaspiro[4.5]decane skeleton demonstrate a wide range of biological effects. It is this kind of unique structure and potentially valuable biological activity that have prompted strong synthetic interest, making it a research focus in recent years. Since the first total synthesis of halichlorine and pinnaic acid completed by Danishefsky's group, many groups have reported their outstanding synthesis methods especially the asymmetric synthesis strategies. This review summarizes the asymmetric synthesis strategies of halichlorine and pinnaic acid using a 6-azaspiro[4.5] decane skeleton as the key intermediate, which can provide some guidance for related work.

1 Introduction

Halichlorine (**1**) and the pinnaic acid (**2**) are structurally related natural products isolated from different marine organisms (Fig. 1). The marine alkaloid halichlorine (**1**) was isolated from the black sponge *Halichondria okadai* Kadota by Uemure and co-workers in 1996.[1] It selectively inhibits the expression of the inducible cell surface protein VCAM-1 (vascular cell adhesion molecule-1), and can be used to treat atherosclerosis, coronary artery disease, angina pectoris, and non-cardiovascular inflammatory diseases. Then Uemura's Laboratory isolated pinnaic acid (**2**) from the Okinawan bishell *Pinna muricata* in the same year, which was structurally closely related to halichlorine (**1**).[2] Pinnaic acid (**2**) was found to inhibit cytoplasmic phospholipase A_2(cPLA_2) at a semi-inhibitory concentration of 0.2 mm *in vitro*. These two marine alkaloids possess significant biological properties and may have potential for use as biochemical tools or as leads for drug design.

The marine natural products halichlorine (**1**) and pinnaic acid (**2**) have attracted a lot of attention because of their good physiological activities and unique structures, and many research groups have carried out outstanding synthesis research on these two alkaloids. In 2005, Clive's group made a systematic and detailed summary on the synthesis of these two alkaloids.[3] In recent years, lots of new asymmetric synthesis strategies of halichlorine (**1**) and pinnaic acid (**2**) have been reported. This review first summarizes the asymmetric synthesis strategies of halichlorine and pinnaic acid using 6-azaspiro[4.5]decane skeleton as the key intermediate over a span of approximately 20 years (1999–2022), which can provide some guidances for related workers. Furthermore, we also took into account the racemic synthesis work conducted between 2005 and 2022, which was not included in Clive's review. The constructions of 6-azaspiro[4.5]decane framework are the key steps of these asymmetric synthesis methods. In our efforts directed toward the synthesis of these two alkaloids base on the [2,3]-Stevens rearrangement, we have previously disclosed an efficient strategy for construction of the 6-azaspiro [4.5]decane skeleton.[4]

2 Absolute configuration determination and asymmetric synthesis of halichorine

2.1 Absolute configuration determination of halichorine

In 1998, Uemura's Laboratory verified the absolute configuration of **1** through degradation studies (Scheme 1).[5] Methanolysis of **1**, followed by ozonolysis with reductive workup and global acetyl protection of the exposed alcohol functionalities yielded **1.1**. The degradation product was compared with the sample prepared from a known alcohol **1.2**, which it can be obtained from D-(+)-tartaric acid. The hydroxyl group of **1.2** was protected to a THP ether. Then the carbon chain extension product **1.5** was obtained in a high yield with the glycidyl ether **1.4**. Then the final product (*S*)-triacetate **1.1** was obtained by the additional steps, whose NMR spectrum agreed with degradation product of natural halichlorine. It must be noted that the stereochemistry of C(17) is *S* in **1.1** but *R* in halichlorine, although there is no difference in the spatial arrangement of the key atoms. The enantiomer of **1.1** was

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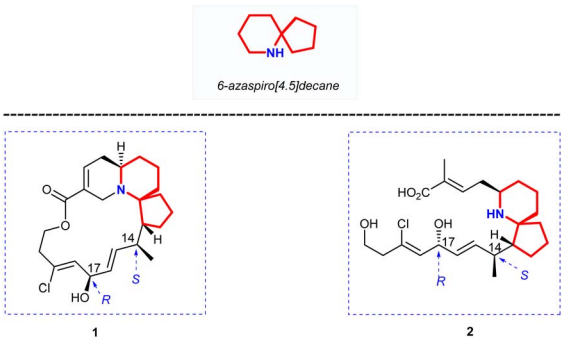


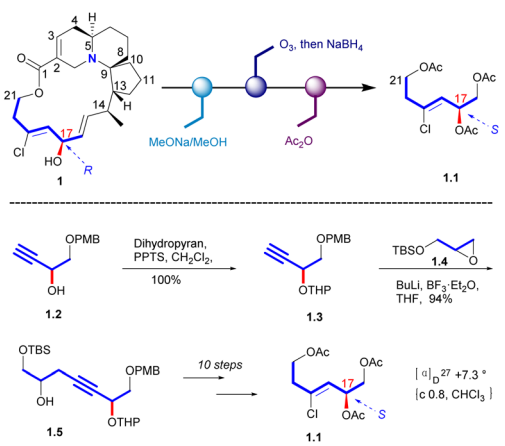
Fig. 1 Structure of halichlorine (**1**) and pinnaic acid (**2**).

made from L-tartaric acid, and HPLC analysis on a chiral column showed that **1.1** from D-tartaric acid corresponds to the degradation product from halichlorine, thereby establishing the absolute configuration of halichlorine, which was subsequently confirmed by the Danishefsky synthesis.[6]

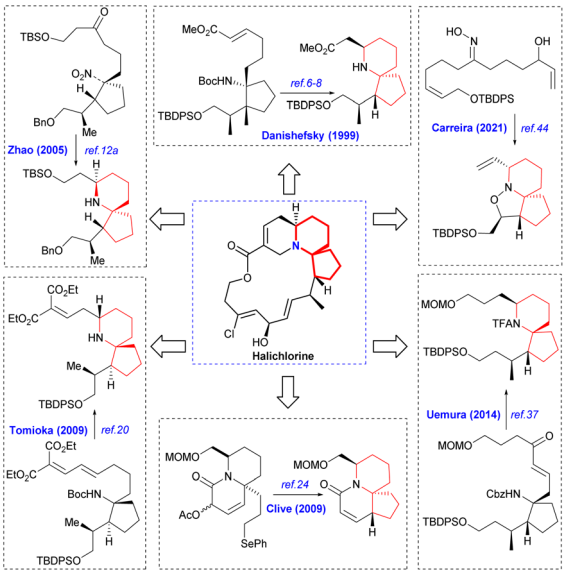
2.2 Asymmetric synthesis of halichorine

Since its initial proposal by Danishefsky in 1999, the synthesis strategy for halichlorine has attracted increasing attention from synthetic scholars. Over the years, numerous research groups have successfully completed the synthesis of halichlorine using various strategies. Each group's research work had their own characteristics in the synthesis strategies employed. We summarized the asymmetric synthesis strategies of halichlorine using 6-azaspiro[4.5]decane skeleton as the key intermediate, in which we can see the subtleties of the synthesis strategies of different research groups (Scheme 2).

2.2.1 Danishefsky's first total synthesis of (+)-halichlorine. In 1999, Danishefsky's Laboratory completed the first asymmetric synthesis of halichlorine.[6–8] The synthesis route started from the simple reaction of γ-keto acid **3.1** with D-(−)-phenylglycinol **3.2** to construct 'Meyers lactam' **3.3**.[9] Under the catalysis of Lewis acid, Meyers lactam reacted with allyl trimethylsilane to generate new lactam **3.4**. Then, the nitrogen



Scheme 1 Confirmation of C17 stereochemistry of halichlorine.

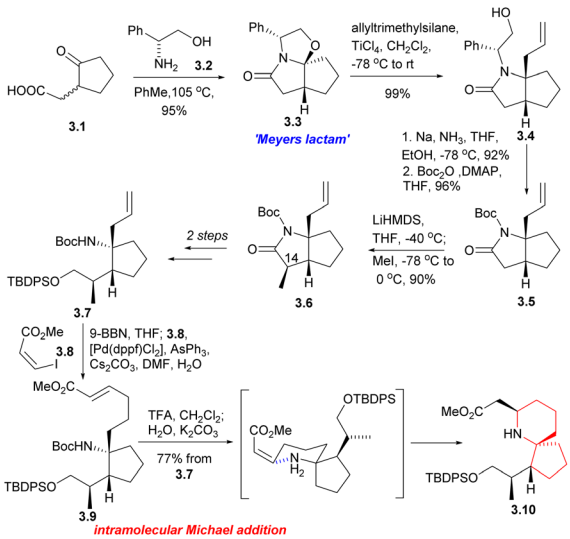


Scheme 2 Asymmetric synthesis of halichorine *via* the 6-azaspiro[4.5] decane skeleton.

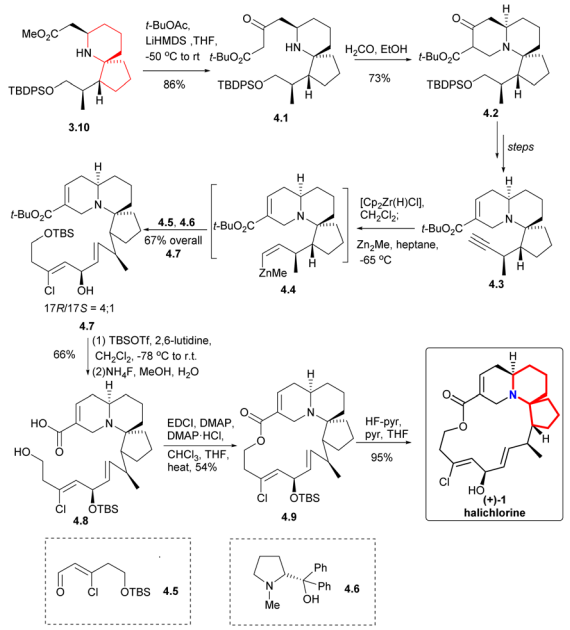
appendage was reduced and removed by the dissolving metal reduction, and the Boc group protection obtained compound **3.5**. **3.6** was obtained by stereoselective methylation from the **3.5** convex structure by introducing C14 methyl.

Then the compound **3.7** was obtained through multiple steps. Compound **3.7** was borohydrided with 9-BBN to obtain borane, and **3.8** was used as coupling agent to have Suzuki coupling reaction with it to extend the side chain (**3.7** → **3.9**). The Boc group was removed by TFA and then neutralized with K_2CO_3, resulting in spontaneous intramolecular Michael addition, providing the 6-azaspiro[4.5]decane skeleton with the desired configuration at C5 (**3.9** → **3.10**). This method is very effective to construct the 6-azaspiro[4.5]decane skeleton and the stereochemistry of the Michael addition presumably results from reaction *via* the conformation that with the larger substituent pseudoequatorial (Scheme 3).

Claisen condensation of **3.10** with *t*-BuOCOMe produced the β-keto ester **4.1** (Scheme 4), which was then subjected to Mannich reaction with formaldehyde to construct the A ring to obtain the compound **4.2**. This process yielded the desired products as a mixture of diastereomer and tautomer. The compound **4.3** was obtained through multiple steps. The terminal alkyne was transformed by zirconation into organozirconium compounds, which were metallized with dimethylzinc to give compounds **4.4**. The resulting zinc substance was successfully coupled with aldehyde **4.5**, and the reaction was carried out in the presence of optical pure amino alcohol **4.6** (ref. 10) to obtain a 4 : 1 mixture of the required 17*R* epimer **4.7** and the corresponding 17*S* epimer (17*R*/17*S* = 4/1). Conversion of the *tert*-butyl ester was accomplished by the action of TBSOTf, which also protected the secondary alcohol.[11] Then the TBS group was removed by NH_4F in aqueous MeOH solution while leaving the protected secondary alcohol intact to obtained **4.8**. At the same time, Keck macrocyclic esterification



Scheme 3 Danishefsky's synthesis of the 6-azaspiro[4.5]decane skeleton of halichlorine.



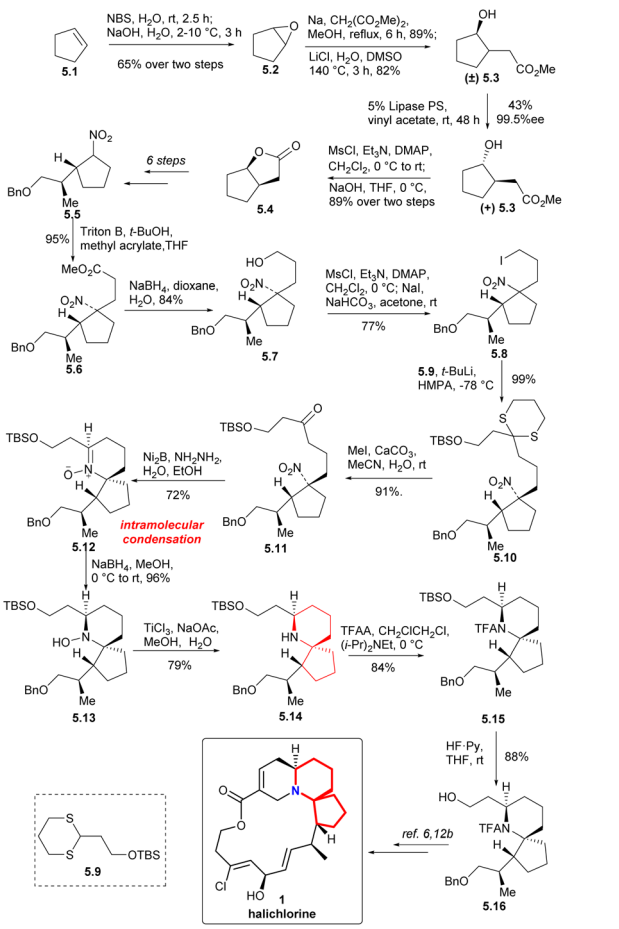
Scheme 4 Danishefsky's synthesis of (+)-halichlorine.

to form 17-OTBS-halichlorine (**4.9**), at staged the 17*R* and 17*S* series (8 : 1 mixture) which were separated, followed by desilylation to give (+)-halichlorine.

2.2.2 Zhao and Ding's formal synthesis of halichlorine. In 2005, Zhao *et al.* constructed the 6-azaspiro[4.5]decane skeleton and achieved the formal synthesis of halichlorine (Scheme 5).[12a] The cyclopentene **5.1** was treated with NBS in water and then with aqeous NaOH at 2–10 °C to afford the epoxide **5.2** in 65% yield. Epoxide was ring-opened with sodium malonic ester to obtain *trans*-diester and then decarboxlated to obtain the corresponding racemic acetates **5.3**. Selective acylation of **5.3** under the control of Lipase PS in vinyl acetate produced the desired product (+) **5.3** (99.5% ee),[13] which was converted to the bicyclolactone **5.4** through mesylation, hydrolysis, and cyclization. Nitro derivative **5.5** was obtained by multi-step transformations of **5.4**. As a good donor, nitro derivative **5.5** underwent very efficient and stereoselective Micheal addition reaction with methyl acrylate. The addition product **5.6** was reduced with sodium borohydride to nitroalcohols **5.7**, followed by iodization to form iodide **5.8**. Dithione **5.9** was coupled with iodide **5.8** afforded **5.10**,[14] and then the thioketal hydrolysis to ketone obtained compound **5.11**.

To form the 6-azaspiro[4.5]decane skeleton by the intramolecular condensation of δ-aminones, the *tert*-nitro in **5.11** must be reduced to an amino group. Ni_2B-hydrazine combination was used to reduce the nitro group to obtain *N*-oxide **5.12**.[15] Reduction of the *N*-oxide **5.12** with $NaBH_4$ (ref. 16 and 17*b*) followed by reduction of the hydroxyl group with $TiCl_3$ (ref. 16*c* and 17) to obtain the 6-azaspiro[4.5]decane skeleton (**5.12** → **5.13** → **5.14**). Compound **5.16** was obtained by *N*-acylation with TFA and deprotection of TBS group (**5.14** → **5.15** → **5.16**). Since the intermediate **5.16** could be transformed to halichlorine,[6,12b] so the formal synthesis of halichlorine was achieved.

2.2.3 Tomioka's formal synthesis of (−)-halichlorine. In 2009, the Tomioka laboratory provided a method to efficiently construct the C9, C13, and C14 contiguous stereogenic centers



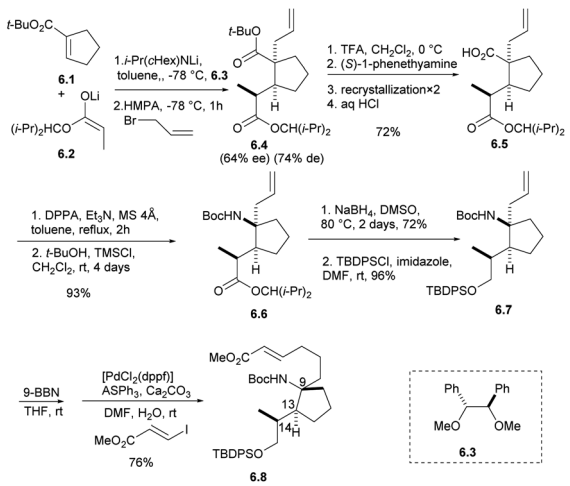
Scheme 5 Zhao and Ding's formal synthesis of halichlorine.

of the key intermediates **6.8** through tandem conjugate addition–alkylation reaction.[18,19] The tricyclic core structure was constructed successfully, and the formal synthesis of (−)-halichlorine was realized.[20]

The synthetic strategy started with the addition of the lithium enolate **6.2** of propionate to **6.1** that would proceed by keeping the methyl group of **6.2** away from the cyclopentene moiety of **6.1** to give enolate intermediate, whose allylation was expected to proceed trans to the introduced propionate giving adduct **6.4**.[21] After the formation of carboxylic acid with TFA, carboxylic acid **6.5** was obtained by optical resolution of (*S*)-1-phenethylamine, and isocyanate was obtained by Curtius rearrangement with DPPA,[22] which was inert to a nucleophilic addition of *t*-BuOH under refluxing conditions. The addition of TMSCl was effective to give Boc-amide **6.6** in 93% yield from **6.4** in two steps. The ester group was reduced by $NaBH_4$ in DMSO and protected by TBDPSCl to obtain the intermediate **6.7**.[7,8] The stereochemistry of **6.7** was confirmed by spectroscopic data and the specific rotation of **6.8**, which was prepared by hydroboration of **6.7** followed by the Suzuki coupling reaction, to be opposite that of natural halichlorin (Scheme 6).

Next, from the compound **6.7**, the Tomioka's group synthesized the tricyclic core of halichlorine by a new strategy. Compound **6.7** hydroboride underwent a Suzuki coupling reaction with dienyl iodide **7.1**, followed by the removal of the Boc group, gave the intramolecular Michael addition product **7.2** in 74% yield in two steps. The next stage was the formation of amides between the secondary amine and the ester moiety. After reduction of the double bond, the monosaponification product was obtained by KOH treatment and subsequent condensation of the amine with the carboxylic acid gave the lactam **7.4** with a tricyclic core of halichlorine (Scheme 7).

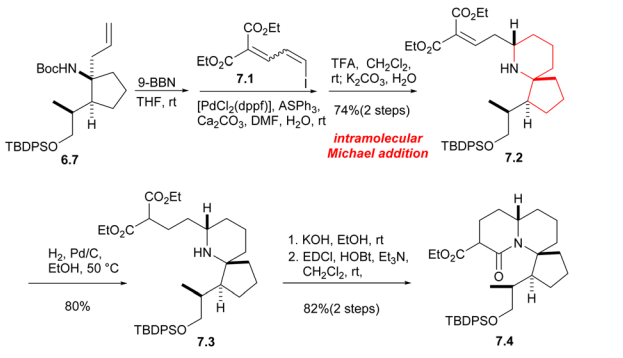
2.2.4 Clive's formal synthesis of (+)-halichlorine. In 2009, Clive' s group synthesized racemic halichlorine based on the method of completely substituted asymmetric center and developed a new route to optically pure piperidines. On the basis of this route, the formal synthesis of (+)-halichlorine was realized.[23,24]



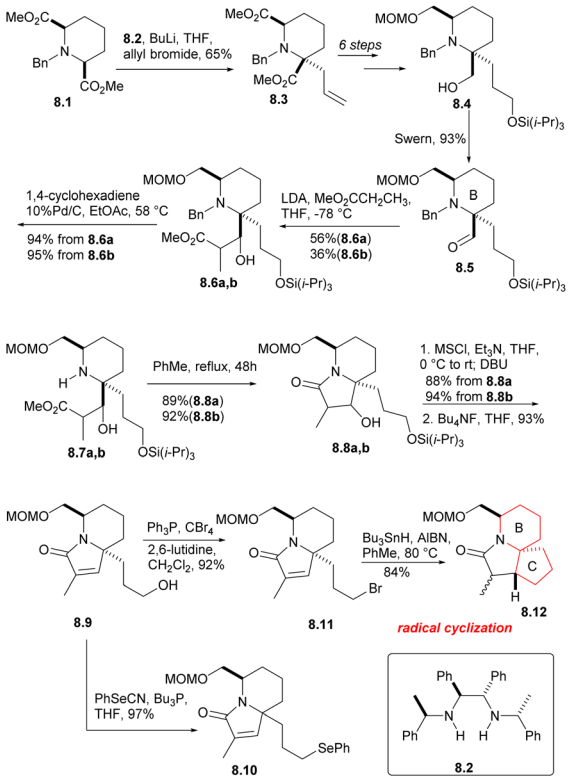
Scheme 6 Tomioka's formal synthesis of (−)-halichlorine.

The *cis*-diester **8.1** was obtained from pyridine 2,6 dicarboxylic acid by esterification, hydrogenation and *N*-benzylation using the methods reported in the literature (Scheme 8). The symmetrical diester **8.1** was then subjected to asymmetric allylation (**8.1** → **8.3**), using the chiral base **8.2** (ref. 25 and 26) and allyl bromide. After a few simple steps, they got the compound **8.4**, and Swern oxidation produced the expected aldehyde **8.5**, which corresponds to the B ring of halichlorine and contains the required stereochemical and structural features. Aldol condensation of aldehyde **8.5** with methyl propionate yielded diastereomer alcohols of **8.6a** and **8.6b**, which were separable, but both can take subsequent reactions without further separation. The *N*-benzyl group was removed by heating with 10% Pd/C in the presence of 1,4-cyclohexadiene, and then the isomeric lactams were formed in the PhMe by heating the hydrogenolysis product (**8.6a,b** → **8.7a,b** → **8.8a,b**). The two lacamides **8.8a,b** afforded the same unsaturated lactam **8.9** *via* mesylation, prolonged heating with DBU in THF an desilication. The hydroxyl of **8.9** was replaced by bromine under the conditions of Ph_3P/CBr_4, then radical cyclization produced the desired the tricyclic lactam **8.12**. However, the stereochemical result at C (17) was unfavorable, the β-isomer required for the main isomer (4 : 1) was the secondary component. Although this isomer ratio could be almost reversed by using the *t*-BuOK/*t*-BuOH equilibrium, the differential isomers were too difficult to separate. As a result, the team decided to utilize the phenylseleno group **8.10**.

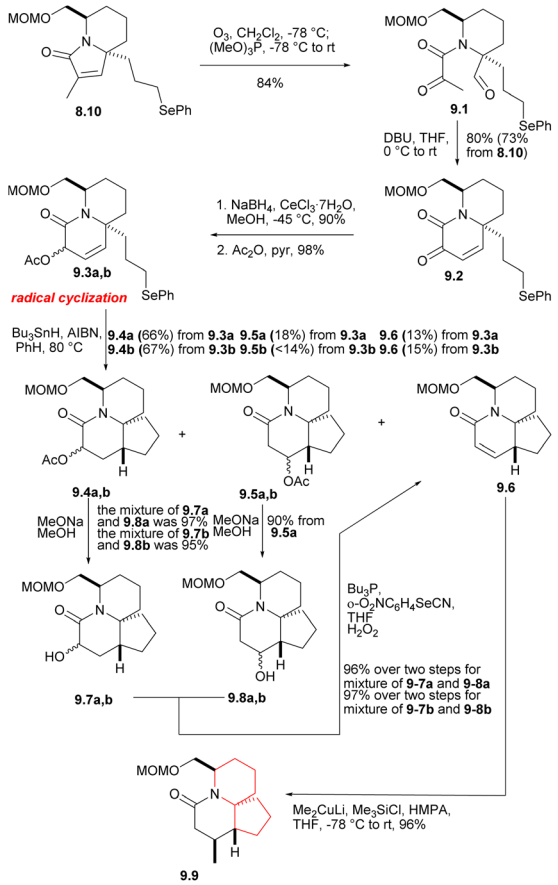
The phenyl selenide **8.10** was subjected to ozonolysis and *in situ* reduction at a low temperature to give tricarbonyl selenide **9.1** (Scheme 9).[27] After treatment with DBU, it underwent consecutive intramolecular aldol condensation and dehydration of hydroxylaldehydes (**9.1** → **9.2**), and was reduced to the corresponding α-hydroxy lactam under Luche condition,[28] which reduced its reactivity. The hydroxyl group was then protected by acetylation to afford **9.3a,b**. In the radical cyclization of **9.3a,b**, the main products were the expected acetates **9.4a** [AcO and C(17*a*)H *syn*] and **9.4b** [AcO and C(17*a*)H *anti*], but the corresponding rearranged acetates[29] **9.5a**, **9.5b** and the enone **9.6** were also isolated. **9.4** were hydrolyzed at a yield of at least 95% to obtain the corresponding alcohol (MeONa, MeOH), and these can be converted to **9.6**, either by mesylation and base



Scheme 7 Construction of the tricyclic core of halichlorine by Tomioka.



Scheme 8 Synthesis of the 6-azaspiro[4.5]decane skeleton of halichlorine.

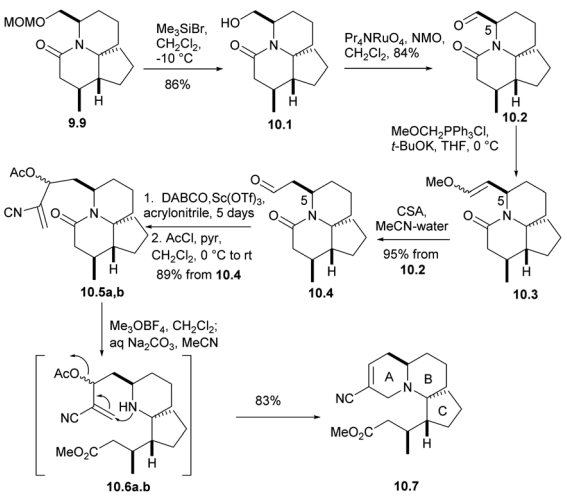


Scheme 9 The exploration of ring C and introduction of the eventual C(17) methyl group.

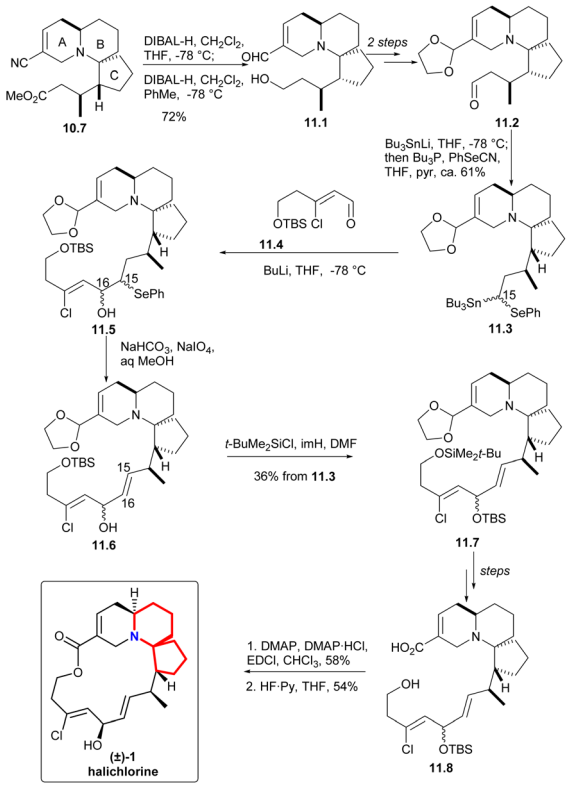
treatment, or treated with o-$(O_2N)C_6H_4SeCN$ and Bu_3P,[30] then oxidized with 30% H_2O_2. **9.5** were hydrolyzed and converted to **9.6**, too. At this stage, they needed to introduce a methyl at the final C(17) position, and the reaction yield of conjugated addition[31] of Me_2CuLi and unsaturated lactam was very high, providing the product saturated lactam **9.9**.

Removing the MOM group of **9.9** *via* Me_3SiBr, *n*-PR_4NRuO_4, oxidizesing the primary alcohol to provide the corresponding aldehyde, $Ph_3P{=}CH(OMe)$ for Wittig olefination(**9.9** → **10.1** → **10.2** → **10.3**), and followed by acid hydrolysis afforded compound **10.4** (aldehyde **10.2** and the formation of enol ethers **10.3** did not cause any epimerization at C5). For the sake of constructing ring A, aldehyde **10.4** underwent a Baylis–Hillman reaction with acrylonitrile to provide the required alcohols at a high yield, and AcCl acetylation instantly converted these alcohols into the corresponding acetate **10.5a,b**. With opening the lactam ring with Meerwein salt $Me_3O^+BF_4^-$, the resulting amines were subjected to spontaneous intramolecular conjugate displacement[32] to unsaturated nitrile **10.7**. At this point, the A, B, and C rings were constructed (Scheme 10).

In the presence of DIBAL-H, nitrile can be reduced to imine, which was then hydrolyzed and reduced to eventually yield alcohol **11.1** (Scheme 11). The processes of multiple steps could afford the compound aldehydes **11.2**. By now the research group hoped to form a carboanion on C15 of halichlorine, which needed to produce selenium-stabilized carbanion and use selenium unit to make C15–C16 double bond. So as to, the stannyl alcohols mixture obtained by treating aldehydes with Bu_3SnLi was immediately converted to the corresponding selenide **11.3**. When the compound was treated with BuLi (to produce the desired selenium-stabilized carbanion[33] by preferential C–Sn heterolysis) and then treated with the known compound **11.4**,[6,34] a mixture of β-hydroxyselenides **11.5** was



Scheme 10 Construction of ring A.

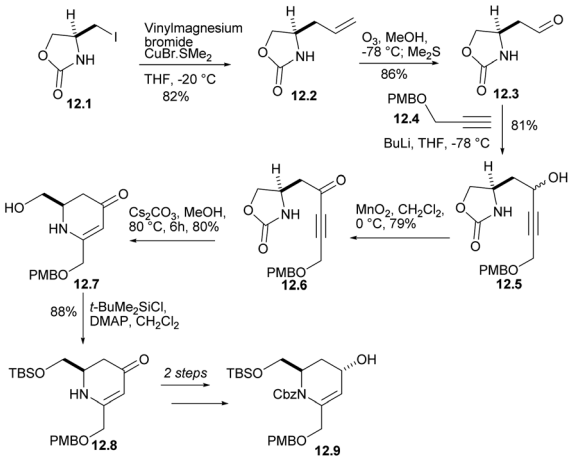


Scheme 11 Clive's total synthesis of (±)-halichlorine.

obtained. The selenium was removed to liberate the double bond to give **11.6** during oxidation. Finally, the hydroxyl group was protected by silylation to obtain **11.7**. By multi-step simple reactions, the hydroxyl and carboxyl groups of the compound **11.8** was cyclized by Keck macrocyclization and deprotected to form (±) halichlorine.

Iodide **12.1** was treated with lithium divinyl cuprate to produce **12.2** (Scheme 12). The terminal double bond of **12.2** performed ozone REDOX and reacted with compound **12.4** (ref. 35) under alkaline conditions to obtain the corresponding alcohols **12.5**, which were oxidized to ketone **12.6**. After treatment with Cs_2CO_3 in MeOH, ketone was converted into dihydropyridinone **12.7** at 80% yield. Each of the steps from L-serine to **12.7** occurred without loss of stereochemical integrity. After several reactions, alcohol **12.9** was obtained.

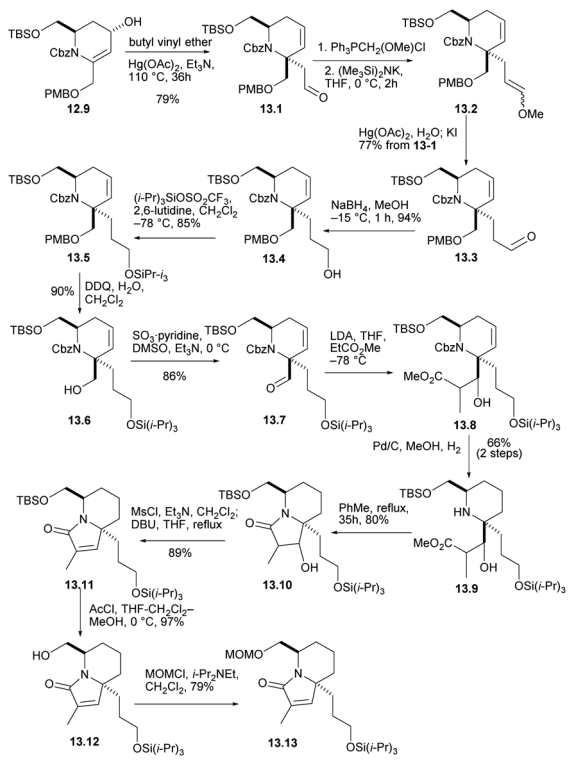
The crucial claisen rearrangement reaction occurred when alcohol **12.9** was heated in butyl vinyl ether in the presence of $Hg(OAc)_2$ and Et_3N, which was finally converted to **13.1** with 79% yield (Scheme 13), and then Wittig enylation reaction occurred, and the enol ether **13.2** was converted into aldehyde **13.3**. This was reduced and silylated (**13.3** → **13.4** →**13.5**). The removal and oxidation of the PMB group gave aldehyde **13.6** and converted it to **13.7**. Condensation of the enolate derived from $EtCO_2Me$ then gave conpound **13.8** and then reduced double bond. When these were heated for 35 h in boiling toluene, the lactam **13.10** were formed in good yield. Mesylation and heating with DBU in THF then converted compound **13.11**. Next, the silicon masking the primary hydroxyl was removed with AcCl



Scheme 12 Synthesis of the precursor to the rearrangement substrate 12.9.

and the resulting alcohol **13.12** was protected as its MOM ether **13.13**. The formation of optically pure **13.13** constitutes a formal synthesis, based on racemic route, of (+)-halichlorine.

2.2.5 Uemura's enantioselective total synthesis of (+)-halichlorine. In 2007, Uemura's group completed the asymmetric total synthesis of pinnaic acid.[36] Then, they continued this route and completed the enantioselective total synthesis of halichlorine based on early result. In this section, we give a detailed report on this total synthesis route of (+)-halichlorine (Scheme 14).[37]

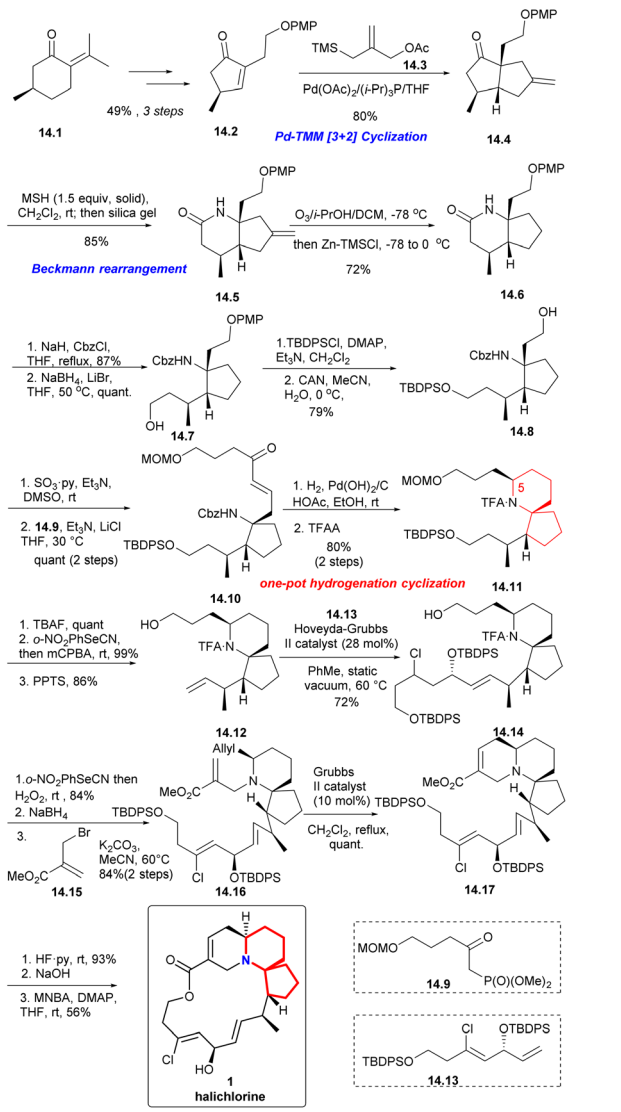


Scheme 13 Preparation of optically pure intermediate.

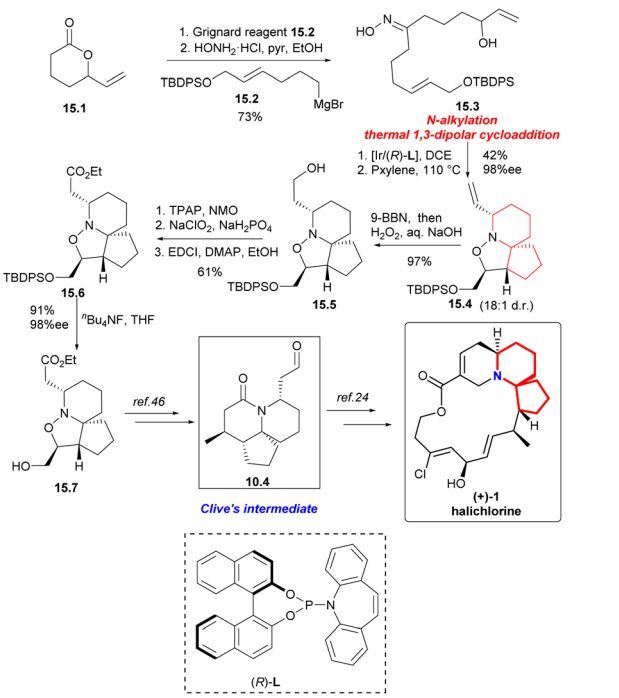
With (*R*)-pulegone **14.1** as the starting material, enone **14.2** obtained through 3 steps in 49% yield. Compound **14.2** reacted with the TMM[38] precursor **14.3** highly selectively and only the diastereomer **14.4** was obtained in 80% yield. After Beckmann rearrangement[39] and a one-pot ozonolysis-Clemmensen reduction process,[40] **14.6** could be obtained in a high yield. Protection of **14.6** with Cbz and reduction with $LiBH_4$ led to compound **14.7**. Then, protection with TBDPS, removal of PMP *via* CAN, Parikh–Doering oxidation and the H–W–E reaction with **14.9** afforded spiro-cyclization precursor **14.10** as the single *trans* isomer (**14.7** → **14.8** → **14.10**). Next, using a one-pot hydrogenation-cyclization[41] efficiently constructed the 6-azaspiro[4.5] decane skeleton with the desired C5 configuration and then TFA protected the amino group to obtained **14.11** through 2 steps in 80% yield. Selective removal of TBS, Grieco elimination[30] and removal of MOM led to terminal olefin (**14.11** → **14.12**). The cross metathesis of **14.12** then proceeded smoothly with the lower-chain unit **14.13** under static vacuum conditions to afford compound **14.14** in 72% yield. Then, **14.14** *via* 3 steps including Grieco elimination,[30] deprotection of TFA and alkylation with bromo-substituted upper-chain unit **14.15** gave compound **14.16** in 84% yield.[42] Six-membered RCM of **14.16** under the conditions reported by Kibayashi *et al.*[12b] afforded the tricyclic compound **14.17** quantitative. Deprotection of the TBDPS groups, basic hydrolysis of the methyl ester and Shiina macrolactonization in overall 56% yield completed the total synthesis of (+)-halichlorine (**14.17** → **1**).

2.2.6 Carreira's formal synthesis of (+)-halichlorine. In 2021, enantioselective and chemoselective iridium-catalyzed *N*-allylation of oximes[43] were described for the first time by the Carreira's Laboratory. The realization of the *N*-allylation/1,3-dipolar cycloaddition reaction sequence provides the azaspirocyclic core in a highly enantioselective and diastereoselective manner. The efficient formal synthesis of Marine natural product (+)-halichlorine demonstrated the synthetic utility of this method.[44]

Synthesis began with the Grignard addition reaction of **15.2** (Scheme 15) and racemic lactone **15.1**.[45] After treatment with hydroxylamine hydrochloride, oxime **15.3** was obtained by two-step separation. Iridium-catalyzed chemoselective *N*-alkylation and thermal 1,3-dipolar cycloaddition reactions provided compound **15.4** with four stereogenic centers with a yield of 42%, 98% ee and 18 : 1 d.r. on 2.5 mmol scale. The compound **15.4** was hydroborated and oxidized to the corresponding primary alcohol **15.5**. The sequence of esterification by Ley oxidation, Pinnick oxidation, and Steglich provided a pathway for ester **15.6** to act as a single diastereomer. Finally, the silyl ether was cracked to obtain alcohol **15.7** with 91% yield,[46] completing the synthesis of (+)-halichlorine.



Scheme 14 Uemura's enantioselective total synthesis of halichlorine.



Scheme 15 Carreira's formal synthesis of (+)-halichlorine.

3. Absolute configuration determination and asymmetric synthesis of pinnaic acid

3.1 Absolute configuration determination of pinnaic acid

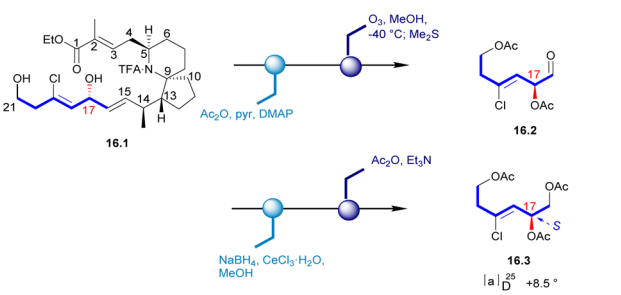
In 1996, Uemura's Laboratory isolated pinnaic acid from the Okinawan bishell *Pinna muricata*, which was structurally closely related to halichlorine. Since only 1 mg of pinnaic acid was isolated from 3000 individual specimens of Okinawa bishell (*Pinna muricata*), it was not possible to correctly establish the stereochemistry of its structure in this case. Until 2001, Danishefsky's Laboratory determined the absolute configuration of pinnaic acid through synthetic method and clarified the stereochemistry of C14 and C17 chiral centers.[47,48] The absolute configuration of the chiral center at C17 was established by degradation studies (Scheme 16). After acetylation of the key intermediate **16.1**, the desired fragment was extracted through ozonolysis, resulting in aldehyde **16.2**. Reduction and final acetylation of **16.2** gave the known compound **16.3** with the absolute configuration determined at C17. This correlation confirmed the absolute configuration of pinnaic acid and thus established the 17*R* configuration, as depicted in (and **2**). The confirmation of the C14 configuration would be seen in subsequent Danishefsky's route.

3.2 Asymmetric synthesis of pinnaic acid

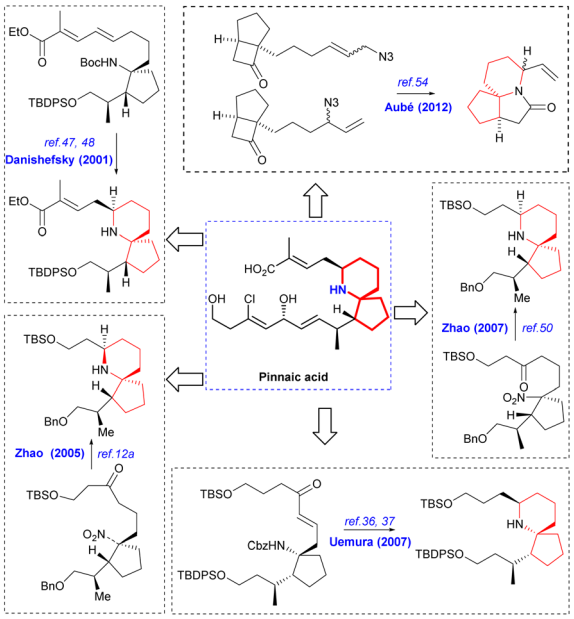
The synthesis of pinnaic acid was initially accomplished by Danishefsky in 2001, and this achievement held reference significance for subsequent researchers working on synthesis. Other research groups have also successfully synthesized the pinnaic acid by constructing the 6-azaspiro[4.5]decane skeleton as the key steps through different strategies (Scheme 17).

3.2.1 Danishefsky's first total synthesis of pinnaic acid. Due to the small amount of pinnaic acid obtained by isolation, the absolute configuration of the compound at C14 and C17 cannot be completely determined. Therefore, Danishefsky conducted a study on the synthesis of all four diastereoisomer derivatives.[47,48]

Compound **3.7** was obtained by a multi-step reaction starting with 'Meyers lactam' **3.3**, which was then borohydrided again, followed by coupling with iodide **18.1** in the presence of palladium(II) catalyst to obtain **18.2** (Scheme 18). Removal of the Boc



Scheme 16 Confirmation of C17 stereochemistry of pinnaic acid.

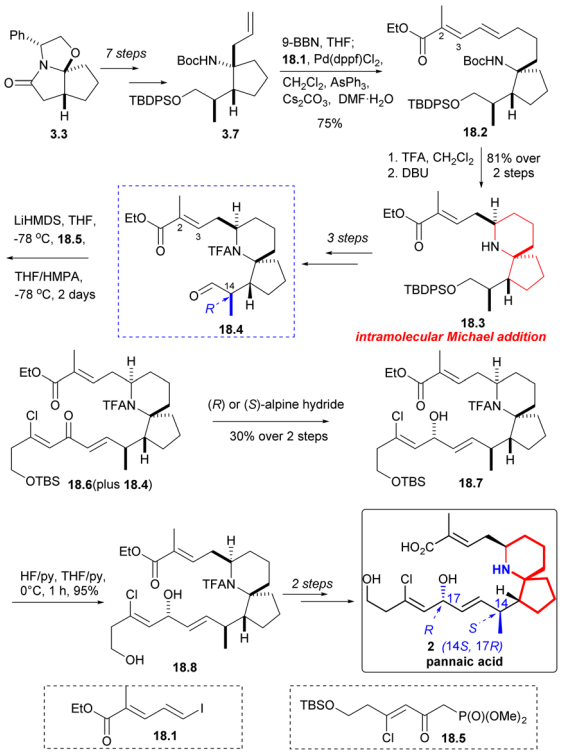


Scheme 17 Asymmetric synthesis of pinnaic acid *via* the 6-azaspiro [4.5]decane skeleton.

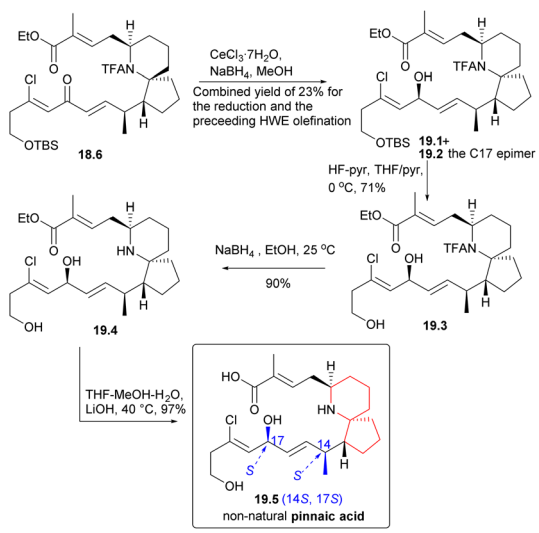
group and treatment with DBU led to clean and stereoselective cyclization while retaining the *E* geometry of the resulting olefin **18.3**. After three steps, the compound **18.4** C(14) isomer was synthesized. The aldehyde **18.4** underwent a H–W–E reaction using known phosphonate **18.5** (ref. 34) to generate α, β - unsaturated ketone **18.6**. The reaction was incomplete and it was challenging to separate the desired product from the initial aldehyde **18.4**. When the mixture of **18.4** and **18.6** was reduced by Alpine hydride,[49] the resulting alcohol **18.7** exhibited the desired C17 configuration, irrespective of whether chiral *R* or *S*-hydride was used. Desilylation (**18.7** → **18.8**) and few steps reaction led to natural pinnaic acid.

During the course of the study, it was discovered that ketone **18.6** predominantly yielded alcohol **19.1** (Scheme 19) and its C17 epimers, alcohol **19.2**, when subjected to Luche reduction conditions. Desilication, *N*-acetyl cleavage, and final ester hydrolysis yielded the non-natural pinnaic acid (**19.2** → **19.3** → **19.4** → **19.5**), whose 1HNMR spectrum was different from that of the natural compound.

Next, Danishefsky intended to prepare the C14 epimer of aldehyde **18.4**. The route began with intermediate **3.6**, which was deprotonated using LiHMDS and then re-deprotonated using BHT. This process led to a significant inversion of stereochemistry at the final C(14) position (**3.6** → **20.1**). The subsequent reactions followed the same procedure as described earlier, and the precursor compound **20.2** of the azabicyclic core was synthesized through a series of straightforward reactions. When treated with DBU, Micheal addition occurred to obtain the 6-azaspiro[4.5]decane skeleton **20.3**, and aldehyde **20.4** was obtained after several steps reactions. The aldehyde **20.4** and phosphonate **18.5** underwent H–W–E reaction in the presence of lithium anion (**20.4** → **20.5**). Hydride reduction was employed once more, but this time without selectivity, resulting



Scheme 18 Danishefsky's synthesis of pinnaic acid and confirmation of C14 stereochemistry.



Scheme 19 Danishefsky's synthesis of non-natural pinnaic acid.

in a mixture of **20.6** and exomer alcohol in a ratio of 1.7 : 1. The diastereomers were subsequently isolated and transformed into non-native pinnaic acids **20.7** and **20.8** (Scheme 20).

After obtaining four diastereomers (**2**, **19.5**, **20.7**, **20.8**), only **2** exhibited spectra that matched the spectral data of native pinnaic acid. The final task was to confirm the absolute configuration of C17, which was accomplished through degradation studies (see: Scheme 16).

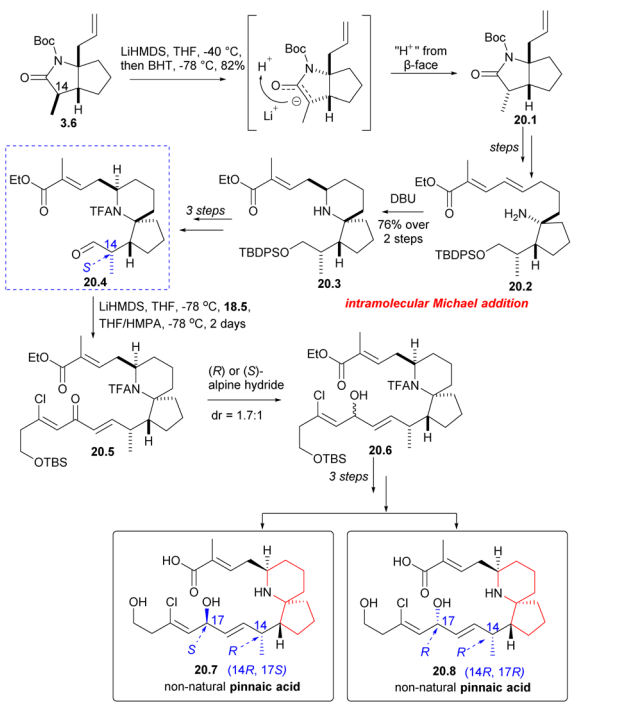
3.2.2 Zhao and Ding's formal synthesis of pinnaic acid. In 2005, Zhao and Ding successfully synthesized the key intermediate **5.16**,[12a] thereby completing the formal synthesis of halichlorine (as described in our previous summary of asymmetric halichlorine synthesis, see: Scheme 5). Following this path, they further synthesized another intermediate **21.3**, which possessed an upper side chain, to achieve the formal synthesis of pinnaic acid.

Compound **21.1** was obtained oxidation of PCC (Scheme 21). Based on **21.1**, they extended its side chain by alkenization. After H–W–E enylation, they constructed (*E*)-C2=C3, which was labelled as **21.2**. and then alcohols were obtained by debenzoylation. The key intermediate **21.3** in Danishefsky route was obtained successfully.

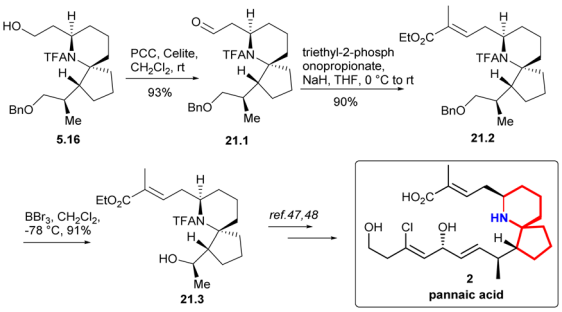
The work of Zhao' s group further enriches the research on the synthesis of halichlorine and pinnaic acid. They presented a novel and efficient method for the highly stereoselective synthesis of azospira rings using mild conditions.

3.2.3 Zhao's enantioselective total synthesis of (−)-pinnaic acid. In 2005, Zhao's group completed the enantioselective synthesis of the 6-azaspiro[4.5]decane,[12a] and one year later, they performed the enantioselective total synthesis of pinnaic acid.[50] In this route, they improved the construction of azaspirocyclic core.

The BINAP–Ru complex has been found to be an efficient catalyst for the asymmetric hydrogenation of β-keto ester.[51] In this synthesis, the catalyst was utilized to hydrogenate γ-ketone ester **22.1** (Scheme 22), resulting in the successful production of bicyclolactone **22.2** with satisfactory results. The asymmetric hydrogenation of racemic γ-keto ester **22.1** was conducted using [(*R*)-BINAP-RuCl$_2$](DMF)n] as a catalyst.



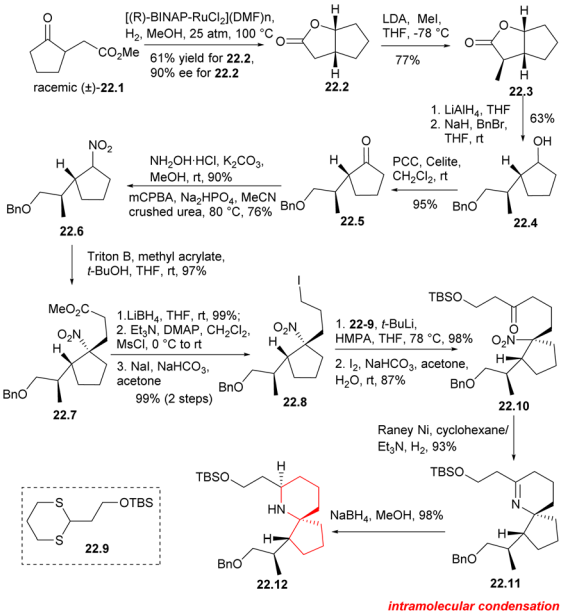
Scheme 20 Danishefsky's synthesis of non-natural pinnaic acids.



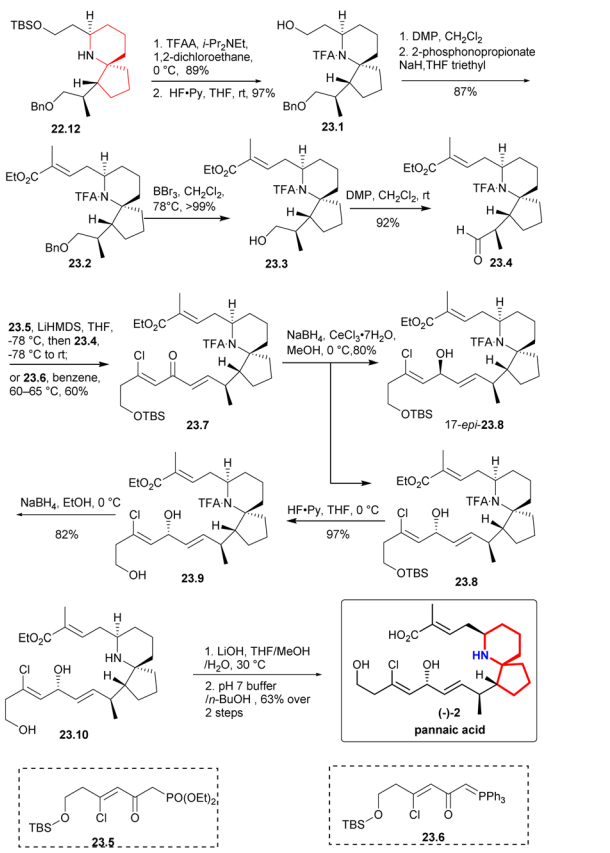
Scheme 21 Zhao and Ding's formal synthesis of pinnaic acid.

The desired (1*R*,5*R*)-lactone **22.2** was obtained in gram scale with a yield of 61% and an enantiomeric excess (ee) of 90%. The yield of the required lactone **22.2** was found to be higher than 50%, suggesting some deracemization of the α-position of the carbonyl group occurred under the reaction conditions. Asymmetric methylation of dicyclolactone **22.2** was carried out at −78 °C using LDA as a non-nucleophilic base, resulting in the formation of **22.3**. LAH was used for reduction, followed by position-selective protection of primary alcohols with benzyl bromide. The secondary alcohols were then oxidized in CH_2Cl_2 using PCC to obtain the desired cyclopentanone **22.5**. Hydroxylamine was condensed with cyclopentanone and then oxidized using *m*-CPBA to give nitrocyclopentane **22.6** with a yield of 64% in two steps.[52] Compound **22.6** was a pair of diastereoisomers without further separation. The Michael addition reaction of nitrocyclopentane with methyl acrylate provided the foundation for the construction of the spirocenter. The desired nitroester **22.7** was obtained with 97% yield as a single diastereoisomer,[12a] which can be explained by assuming that the acrylate approximated the less hindered face of the nitrocyclopentane. The nitroester was reduced with $LiBH_4$, followed by mesylation and iodination to obtaine iodide **22.8**. Subsequently, dithiane **22.9** was subjected to metallization using *t*-BuLi,[14] and then alkylated with iodide **22.8**.[12a,53] Dithiane was then deprotected in the presence of I_2 and $NaHCO_3$ in acetone to obtaine ketone **22.10**, which served as a crucial precursor for the cyclization of the piperidine ring. The nitro group in **22.10** was reduced to an amino group using RANEY® Ni and H_2 at 1 atmosphere pressure, and then the cycloimine compound **22.11** was formed through a simple nucleophilic reaction involving its carbonyl group. Nitrogen spiral ring **22.12** was successfully constructed by reducing cycloimine compound with $NaBH_4$ in mixed solvent.

The secondary amino group was protected by TFAA,[47,48] the TBS group was deprotected to obtain **23.1** (Scheme 23), and the aldehyde was oxidized with DMP and converted into compound **23.2** through H–W–E reaction. Subsequently, benzyl was removed using BBr_3 at −78 °C, the resulting compound was then subjected to DMP oxidation, resulting in the desired aldehyde **23.4**.and DMP oxidation yielded the desired aldehyde **23.4**. A H–W–E reaction was performed between aldehyde **23.4** and Weinreb's phosphonate[34] **23.5** to produce trace products. The desired dienone **23.7** was obtained at a moderate yield (60%) by heating aldehyde **23.4** and phosphorane **23.6** in benzene. Under the Luche reduction



Scheme 22 Construction of the azaspirocyclic core.



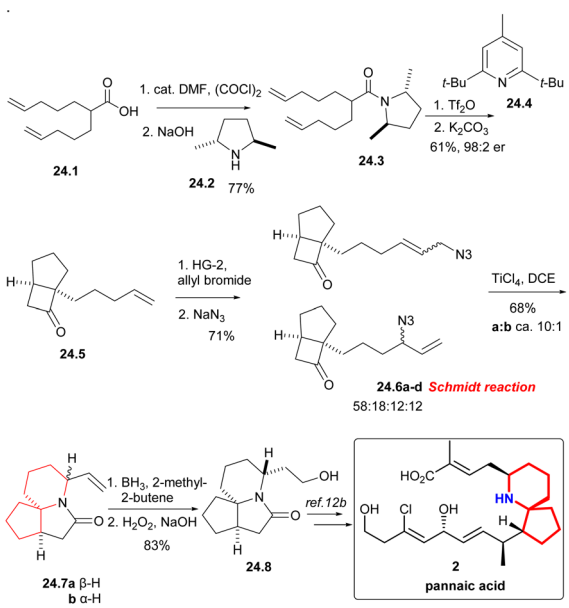
Scheme 23 Zhao's total synthesis of pinnaic acid.

condition,[28] the dienone was converted in a 3 : 1 mixture favoring the desired diastereomer **23.8**. The TBS group was deprotected by HF-Py complex to produce the corresponding alcohol. To obtain lithium carboxylate salt of pinnaic acid, the trifluoroacetamide underwent reductive cleavage, followed by hydrolysis of the ethyl ester in the presence of LiOH. Pinnaic acid was synthesized enantioselectively by dissolving salt in an aqueous buffer solution of pH = 7, extracting it with 1-butanol and purifying it by liquid chromatography.

The highlight of this study was the use of a Ru complex as a catalyst for the asymmetric hydrogenation reaction, and facilitated the formation of the nitrogen azaspirocyclic core through multiple key reactions, leading to a shorter and more efficient synthesis route for pinnaic acid.

3.2.4 Aubé's asymmetric total synthesis of pinnaic acid. Aubé group combined the allyl azide rearrangement with the intramolecular Schmidt reaction to enantioselectively synthesize lactam **24.7**,[54] which was a key intermediate in the synthesis of (±)-pinnaic acid reported by Kibayashi *et al.*[12b]

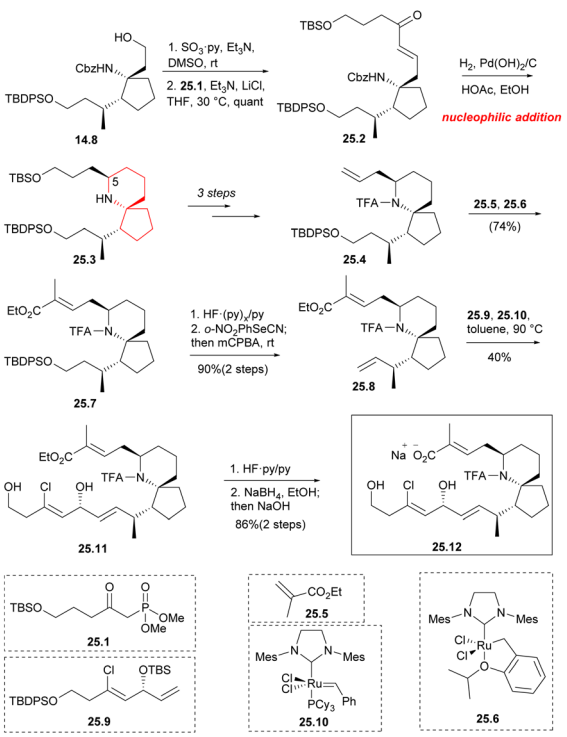
Under the condition of $(COCl)_2$, the known acid **24.1** was converted into the corresponding acyl halide, and then ammonolysis occurred under basic conditions to obtain chiral amides **24.3** (Scheme 24). The asymmetric [2 + 2] cycloaddition of compound **24.3** using Ghosez's protocol,[55] and the obtained intermediate iminium ions were alkaline hydrolyzed to cyclobutanone **24.5**, which continued to undergo cross-metathesis,[56] NaN_3 displacement gave an interconverting mixture of allylic azides **24.6a–d**. The Schmidt reaction of isomeric allyl azides, which was treated with $TiCl_4$, was the key reaction, and the mixture of lactam **24.7a** and **24.7b** can be separated in a *ca.* 10 : 1 ratio. The stereochemistry of the reaction was controlled only by the position of the vinyl in the product. Finally, hydroboration/oxidation gave Kibayashi's pinnaic acid intermediate **24.8** in 83% yield.



Scheme 24 Aubé's formal synthesis of pinnaic acid.

3.2.5 Uemura's asymmetric total synthesis of (−)-pinnaic acid. In 2007, the Uemura group described a novel strategy for asymmetric total synthesis using Pd-catalyzed trimethylenemethane [3 + 2] cyclization (Pd-TMM cyclization).[36] In 2014, they further optimized this route, which achieved total synthesis of pinnaic acid.[37]

Aldehydes were formed by Parkin–Doering oxidation ($SO_3 \cdot Py$, DMSO) from the key intermediate **14.8** and reacted with phosphonate **25.1** (Horner–Wadsworth–Emmons reaction). The product **25.2** was dominated by *E* isomer. This was followed by a series of hydrogenation–cyclization to construct a piperidine ring **25.3** with the desired C5 configuration.[41] It consisted of four successive one-pot transformations: reduction of alkene double bonds; Cbz protective group was removed; formation of intramolecular cyclic imine; stereoselective reduction of imine/enamine intermediates. After multiple steps of reaction, **25.4** was obtained. By combining compound **25.5** (Scheme 25) with 10 mol% Hoveyda–Grubbs second-generation catalyst **25.6** (ref. 57) under reflux conditions, they obtained compound **25.7** with a yield of 74% during the above metathesis. TBDPS deprotection and Grieco elimination[30] were employed to produce terminal olefin **25.8**. This strategy utilized olefin cross-metathesis to establish the C17 center (90% ee) of segment **25.9** before it was incorporated into the spirocyclic core **25.8**. Compound **25.9**, which underwent a six-step transformation, was synthesized from but-3-yn-1-ol. The next step involved repeating the olefin cross-metathesis process. However, in the two precursors **25.8** and **25.9**, there were four different types of carbon–carbon double bonds. It was observed that the two terminal double bonds were more reactive, possibly



Scheme 25 Uemura's total synthesis of (−)-pinnaic acid.

due to spatial factors. This reactivity led to the formation of a single trans isomer **25.11**. The next step performed the olefin cross-metathesis again.[58] However, in the two precursors **25.8** and **25.9**, there were four types of carbon–carbon double bonds. It was observed that the two terminal double bonds were more reactive, possibly due to spatial factors. This reactivity led to the formation of a single trans isomer **25.11**. Compound **25.11** was successively deprotected by the two silyl protecting groups, the TFA amide, and the ethyl ester using common methods[48] to obtain chiral pinnaic acid (**25.12**) in the form of sodium salt.

4. Racemic synthesis of halichlorine and pinnaic acid

In addition to Clive group's review,[3] we also summarized the racemization work of halichlorine and pinnaic acid that was not included.

4.1 Martin's formal synthesis of pinnaic acid and halichlorine

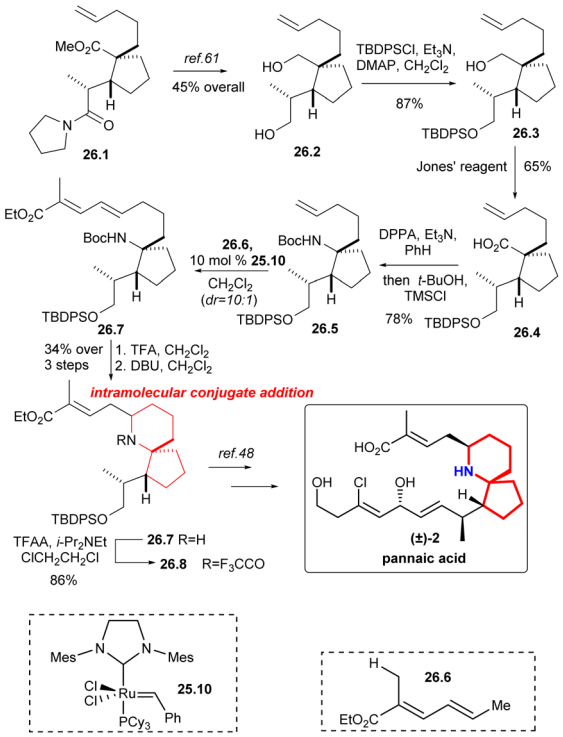
Martin's group synthesized the known intermediates **26.9** and **27.5** to achieve the formal synthesis of halichlorine and pinnaic acid.[59] This route effectively installed the upper chain through the key reaction: cross-olefin-metathesis,[60] which illustrated the utility of selective olefin cross metathesis methodologies for the elaboration of advanced synthetic intermediates in complex molecule synthesis.

The synthesis commenced with the compound **26.1** (Scheme 26), which was converted to alcohol **26.2** by literature.[61] The resulting primary alcohol **26.2** was protected as its *tert*-butyldiphenylsilyl derivative **26.3**. Oxidation with Jones' reagent then generated carboxylic acid **26.4** as expected, which was subjected to a Curtius rearrangement with DPPA[22] and *t*-BuOH to afford **26.5**. At this point cross metathesis of **26.5** with the ester **26.6**, using the Grubbs II catalyst **25.10**,[58] produced the *E*-olefin **26.7**, which upon deprotection of the amino function with TFA and cyclization of the intermediate amino dienoate *via* intramolecular 1,6-conjugate addition to afford piperidine **26.8** in 34% yield for the three steps. The nitrogen was protected as its trifluoroacetate **26.9**, an intermediate in the Danishefsky's synthesis of pinnaic acid.[48]

Compound **27.1** (Scheme 27) was obtained in 89% yield with excellent diastereoselectivity by compound **26.5** and 10 mol% Grubbs II catalyst **25.10**.[58] Carbamate cleavage facilitated spontaneous Michael addition affording spirocycle **27.2**. The reaction of ethyl propiolate in THF with DIBAL-H/NMO complex provided the vinylaluminum reagent.[62] Aldehyde **27.2** was added to the vinylaluminum reagent to gain compound **27.3** as a mixture of diastereomers (dr = 2 : 1). Acetylation of this mixture under standard conditions led to a facile cyclization that provided the known tricycle **27.4**. Final desilylation provided ester **27.5**, a substance synthesized previously by Kibayashi.[12b]

4.2 Clive's total synthesis of (±) halichlorine

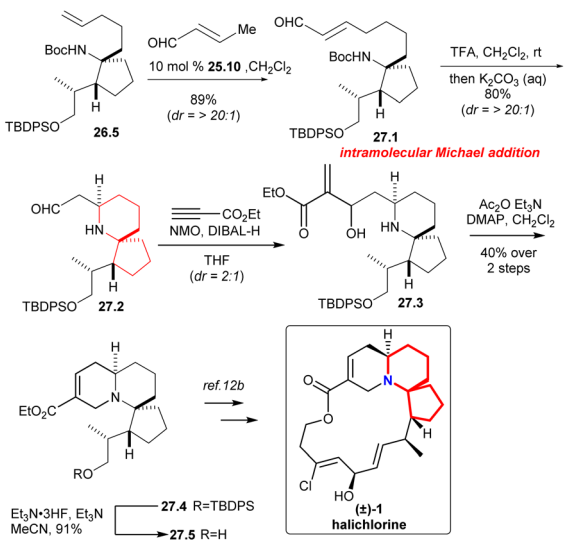
(See 2.2.4).



Scheme 26 Martin's formal synthesis of (±)-pinnaic acid.

4.3 Stockman's formal synthesis of halichlorine

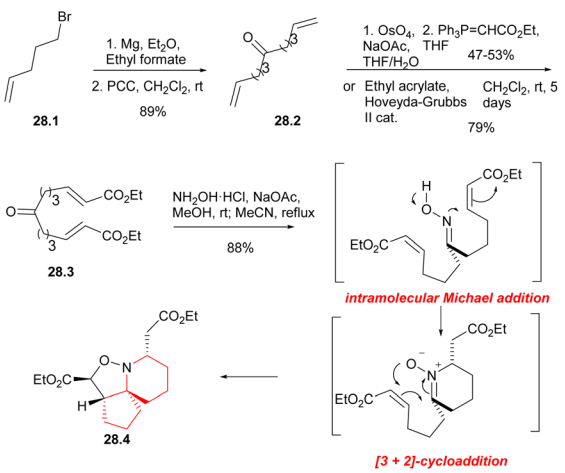
In 2004, Stockman's group reported a concise method for preparing the azaspirocyclic core structure of halichlorine and pinnaic acid with a tandem cascade strategy.[63] In 2012, they improved this strategy and completed the formal synthesis of halichlorine.[46] The resulting synthesis of azaspirocyclic aldehyde **10.4** was an intermediate for the total synthesis of halichlorine by Clive's laboratory.[24]



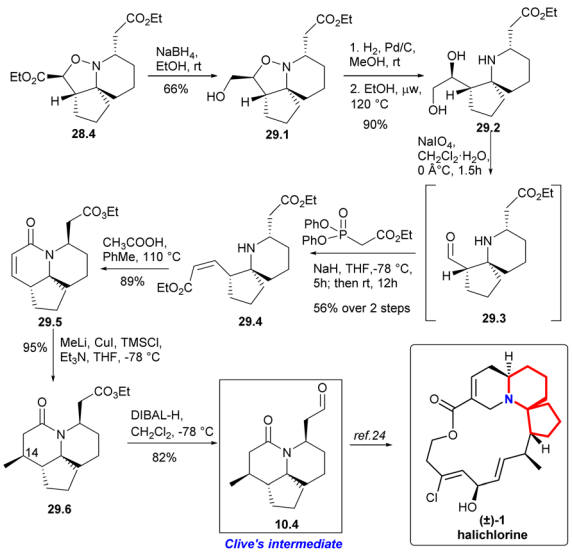
Scheme 27 Martin's formal synthesis of (±)-halichlorine.

By utilizing an electrophilic centrepiece for the two-directional approach, symmetrical alcohol **28.1** (Scheme 28) was successfully synthesized through double addition of pent-5-enyl magnesium bromide on ethyl formate.[64] The alcohol function of **28.1** was then oxidized, resulting in the formation of dialkene **28.2** with a high overall yield. Ketodiester **28.3** could through either the two-directional cross-metathesis method or a two-step approach involving oxidative addition of the alkenes of **28.2** followed by two-directional Wittig homologation. When performed on a 10 g scale, the two-step approach gave the ketodiester **28.3** in 47–53% yield after purification, and was found to be more cost-effective compared to the cross-metathesis route. Upon treatment with hydroxylamine hydrochloride in the presence of sodium acetate, symmetrical ketodiester **28.3** underwent a transformation the [6,5,5]tricycle **28.4** in 88% yield, this transformation was achieved through a tandem oxime formation/Michael addition/1,4-prototopic shift/[3 + 2]-cycloaddition.[65]

The isoxazolidine **28.4** was selectively reduced to **29.1** in ethanol using sodium borohydride[64] and subsequent hydrogenation cleaved the N–O bond, resulting in the formation of diol **29.2** with a quantitative yield (Scheme 29). Ester **29.4** with *Z*-conformation was produced by oxidative cleavage of diol followed immediately by an Ando homologation reaction.[66] It was observed that the reaction yielded the best results when conducted in refluxing toluene with stoichiometric acetic acid, resulting in a high yield of lactam **29.5**. Addition of the Gilman reagent[67] to **29.5** afforded the lactam **29.6** in excellent yield. They found that this reaction required both TMSCl and triethylamine to proceed. With full stereoscopic control of C14 methyl, the ester functional group was converted to the target aldehyde **10.4** using DIBAL-H reduction at low temperature. So they had completed a short and efficient synthesis of Clive's aldehyde **10.4** in 12 steps and 13.2% overall yield from ethyl formate. This study represents the formal synthesis of halichlorine through the rapid and efficient synthesis of Clive aldehyde **10.4**.[24]



Scheme 28 Synthesis of the 6-azaspiro[4.5]decane skeleton of halichlorine.

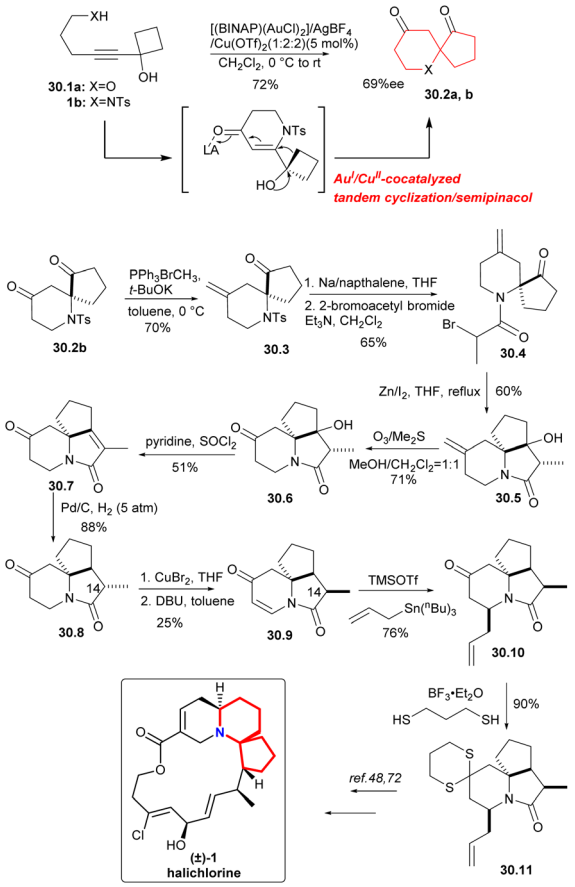


Scheme 29 Stockman's formal synthesis of halichlorine.

4.4 Zhu's formal synthesis of halichlorine

In 2015, a Au^{I}/Cu^{II}-cocatalyzed tandem cyclization/semipinacol reaction[68] had been developed by Zhu's group to provide an effective method for the construction of the 6-aza/oxa-spiro[4.5] decane skeletons. The synthetic utility of the approach was demonstrated by the efficient, formal synthesis of the marine natural product (±)-halichlorine.[69]

The Au^{I}/Cu^{II}-cocatalyzed tandem cyclization/semipinacol reaction was conducted with substrate **30.1a** as the model substrate. After trying many conditions, $[(BINAP)(AuCl)_2]/AgBF_4/Cu(OTf)_2$(1 : 2 : 2) was selected as the catalyst to construct the 6-aza/oxa-spiro[4.5]decane skeletons **30.2a,b** (Scheme 30).[70] The aza-spiro-ketone **30.2b** was subjected to Wittig olefination with Ph_3PBrCH_3 in order to protect the carbonyl group (because the carbonyl group on the piperidine ring would cause side reactions in the subsequent nucleophilic steps), followed by removing the Ts group and amidation with 2-bromoacetyl bromide (**30.2b** → **30.4**). For the construction of tricyclic intermediate **30.5**, the bromine substitute compound **30.4** was subjected to intramolecular Reformatsky reaction with iodine as the initiator in a 60% yield. Ozonolysis and reductive workup gave **30.6**, and dehydration led to amide **30.7**,[71] which gave **30.8** by catalytic hydrogenation. Introduction of the desired carbon–carbon double bond into **30.9** was achieved using copper bromide and DBU, which can get α-bromination compound, and then followed by the elimination reaction. At the same time, the configuration reversion of the C-14 methyl, was also successfully achieved. Subsequently, intermediate **30.10** was obtained by a 1,4-addition of amide **30.9** with allylstannane. Reaction of 4-piperidonone **30.10** with 1,3-propane thiol gave in a 90% yield the expected dithiane **30.11**, they had completed an advanced intermediate reported by Padwa's group,[72] representing a formal synthesis of (±)-halichlorine.



Scheme 30 Zhu's formal synthesis of (±)-halichlorine.

5 Conclusions

In summary, we mainly focus on the construction of the 6-azaspiro[4.5]decane skeleton and provide many brief account of the asymmetric synthesis routes of two marine alkaloids: halichlorine and pinnaic acid. The unique structures and interesting bioactivity of pinnaic acid and halichlorine have motivated the exploration of a number of total syntheses. The synthesis of halichlorine and pinnaic acid was first accomplished by Danishefsky's research group in 1999 and 2001. This groundbreaking work holds great historic significance as it fills a gap in the total synthesis history of these compounds. In this review, we can see from the research works of various groups that the construction of C5, C9 and C13 three stereogenic carbons in the 6-azaspiro[4.5]decane skeleton is somewhat the challenging and key step. And different construction strategies of 6-azaspiro[4.5]decane frameworks of halichlorine and pinnaic acid have been also developed.[73] In addition to the asymmetric synthesis methods summarized in this review, many research groups have also successfully completed the racemic synthesis of the halichlorine and pinnaic acid.[3,24,46,59,69] These outstanding synthetic works make the two alkaloids more attractive. We hope that more relevant researchers will have the courage to challenge and synthesize halichlorine and pinnaic acid in a more concise and efficient way.

Conflicts of interest

There are no conflicts to declare.

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