

First Synthesis of Aminobisabolene

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Two routes for the synthesis of aminobisabolenes were developed. One is the divergent course which completes the first synthesis of the target molecules. Another synthetic route is the biomimetic approach based on the hypothesis of biosynthesis.

Two types of aminobisabolenes (**1** and **2**) were isolated from marine organisms, and their structures were elucidated by X-ray diffraction as shown in Fig. 1.¹⁾ These molecules have the bisabolene skeleton with interesting amino moiety attached to a quaternary carbon atom at C-7 and represents a family of aminobisabolene including functionalized members, such as aminobisabolanol **3** and isoaminobisabolanol **4**.²⁾

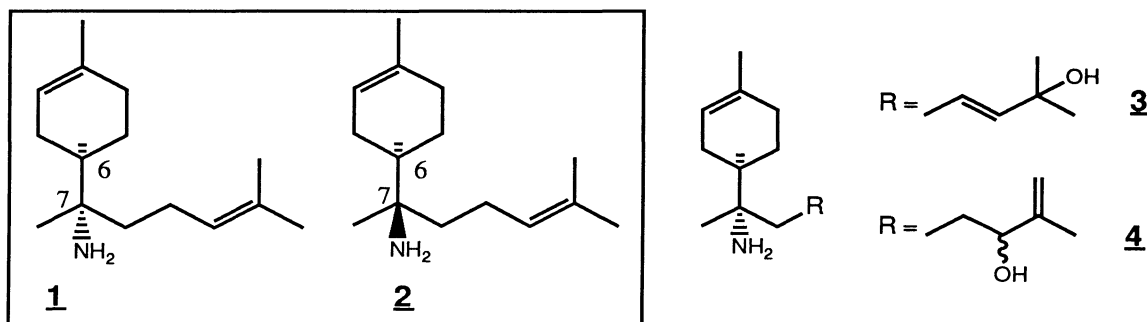


Fig. 1.

Retrosynthetic analysis shown in Fig. 2 leads to the divergent route for the synthesis of this aminobisabolene family.

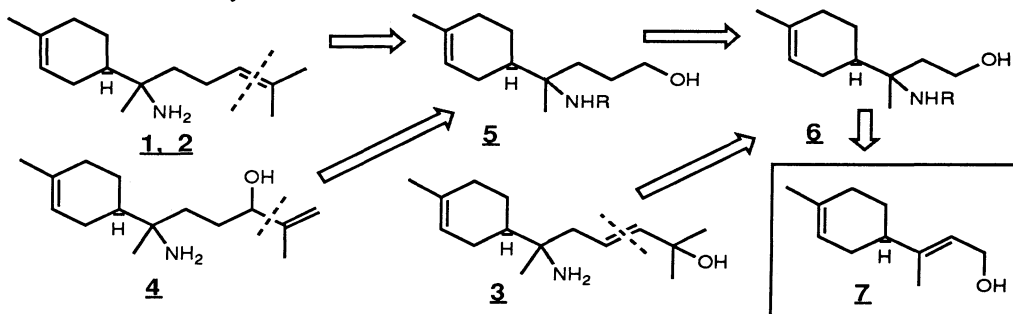


Fig. 2.

The crucial step of this plan was the construction of quaternary carbon atom at C-7. Indeed, this was achieved by use of hetero-Claisen rearrangement of an allyl imidate (Overman

reaction).³⁾ Treatment of ally alcohol **7**⁴⁾ with sodium hydride followed by trichloroacetonitrile in ether at 0 °C gave the unstable imidate, which was immediately heated in toluene at reflux for 5 h to provide **8** in 45% yield.⁵⁾ Initial efforts to functionalize terminal double bond of **8** for subsequent conversion to an aldehyde by the reported procedures were unsuccessful.⁶⁾ Ultimately, the desired functionalization was realized by the use of disiamylborane freshly prepared from sodium borohydride, boron trifluoride etherate and 2-methyl-1-butene in tetrahydrofuran.⁷⁾ Reaction of **8** with disiamylborane at -20 °C for 48 h followed by oxidative work up with 2 M NaOH and 30% hydrogen peroxide provided the alcohol **9** and starting material **8** in 57% and 17% yields (conversion yield 66%). Swern oxidation⁸⁾ of **9** followed by Wittig olefination with methylenetriphenylphosphorane in THF (initially at -78 °C then at room temperature) produced olefin **10** in 79% yield.

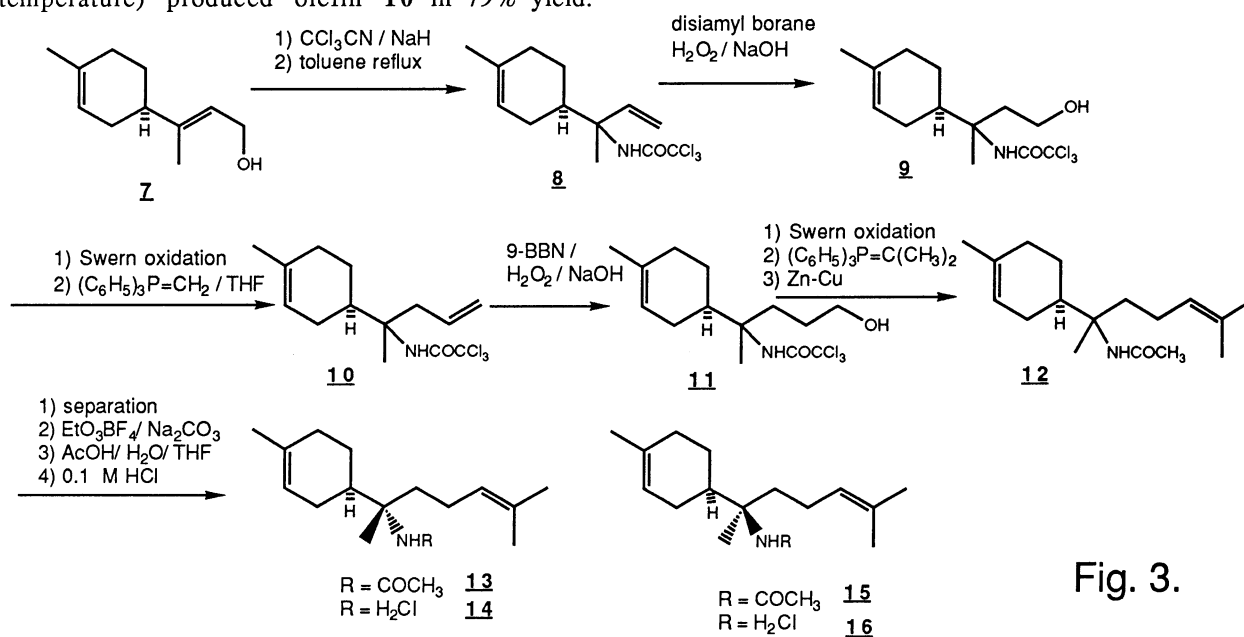
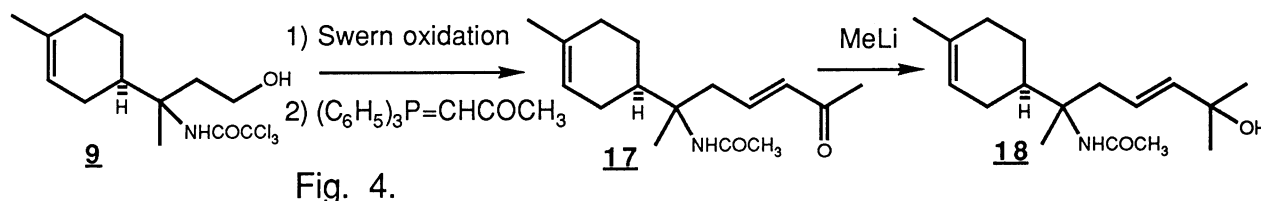


Fig. 3.

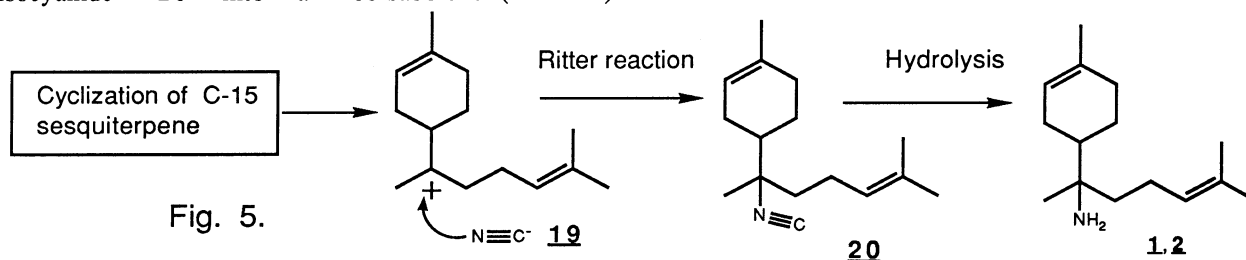
Reaction of **10** with 9-BBN in THF at 0 °C proceeded smoothly to provide the alcohol **11** in 85% yield after oxidative work up (2 M NaOH, 30% hydrogen peroxide) and chromatographic purification. Conversion of **11** to **12** in 22% overall yield was accomplished by the sequence: 1) Swern oxidation, 2) Wittig reaction with isopropylidenetriphenylphosphorane in THF, 3) conversion of trichloroacetyl moiety to acetyl with zinc-copper couple.

In this stage, we finally succeeded in separating the isomers at C-7, and each acetamide (**13** and **15**) was obtained in pure form. Treatment of acetamide **13** with Meerwein's reagent gave the corresponding imino ether which was successively treated with acetic acid in aqueous tetrahydrofuran,⁹⁾ and 0.1 M hydrogen chloride to furnish aminobisabolene hydrochloride **14** in 46% yield. The same sequences provided **16** in 57% overall yield starting from **15**. Acetamide **13** and amine hydrochloride **14** were indistinguishable from those derived from natural product (200 MHz ^1H NMR, TLC behavior), and spectral data (200 MHz ^1H NMR) of acetamide **15** and amine hydrochloride **16** were in good agreement with that reported in the literature.¹⁰⁾ Since conversion of amine hydrochloride to aminobisabolene has been already reported,^{1b)} this synthesis represents the first synthesis of aminobisabolene.

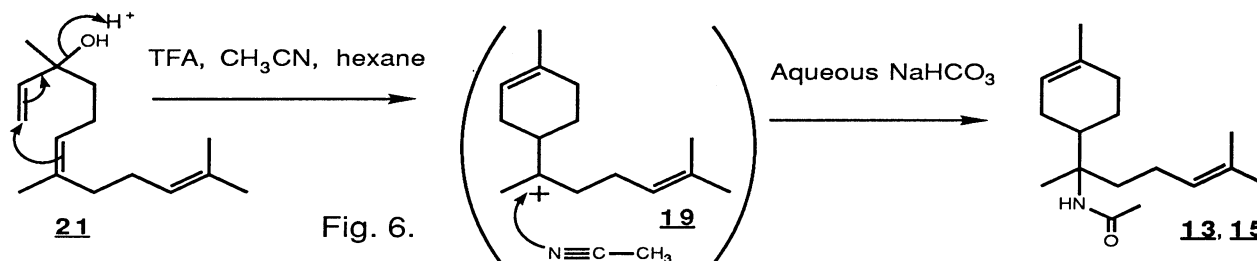
The usefulness of this divergent route was demonstrated in the conversion of **9** to **18** which was a crucial intermediate of aminobisabolene **3** (Fig 4). Swern oxidation of **9** followed by Wittig reaction with triphenylphosphoraneacetylmethylene gave α, β -unsaturated ketone **17** in 55% yield. This ketone was further transformed into allyl alcohol **18** with methyllithium in 22% yield. Further transformation of this compound to natural aminobisabolene **3** is now under investigation.



With authentic sample of aminobisabolenes (**1** and **2**) in hand, we finally turned our attention to the biomimetic approach. Scheuer reported the isolation of isocyanobisabolene **20**^{1b)} which seemed to be a precursor of aminobisabolene.¹¹⁾ The probable biosynthetic pathway will be as follows; 1) cyclization of sesquiterpene precursor such as farnesol or nerolidol, 2) capture of the resulting carbenium ion intermediate **19** by the ambident nucleophile cyanide (Ritter type reaction) to provide the isocyanide **20**,¹²⁾ 3) hydrolysis of isocyanide **20** into aminobisabolene (**1** and **2**).



Based on this hypothesis, nerolidol **21**¹³⁾ was treated with trifluoroacetic acid in acetonitrile and hexane (two phase system) at 0 °C for 24 h, and the reaction mixture was hydrolyzed with aqueous sodium bicarbonate.¹⁴⁾ Purification of the crude product by chromatography followed by recrystallization furnished acetamidobisabolene (**13** and **15**) in 3% yield (the product ratio was 2 : 3). The probable reaction mechanism of this reaction was shown in Fig. 6.



An efficient one step construction of the whole structure of aminobisabolene has now been achieved. Further progress of this biomimetic synthesis will be reported in due course.

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References

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- 4) Allyl alcohol **7** was prepared from 4-acetyl-1-methylcyclohexene in two steps as a mixture of Z and E isomers (1 : 5). See the reference; F. Delay and G. Ohloff, *Helv. Chim. Acta.*, **38**, 369 (1979).
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- 10) ^1H NMR (200 MHz, CDCl_3) of **15**; d 1.22(3H, s), 1.60(3H, s), 1.63(3H, s), 1.67(3H, s), 1.93(3H, s), 5.10(2H, brn), 5.35(1H, brs).
 ^1H NMR (200 MHz, CDCl_3) of **16**; d 1.32(3H, s), 1.61(3H, s), 1.62(3H, s), 1.65(3H, s), 5.07(1H, brs), 5.34(1H, brs), 8.3(2H, br).
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