Studies toward the Total Synthesis of Amphidinolide N and Goniodomin A

博士論文（要約）

Studies toward the Total Synthesis of Amphidinolide N and Goniodomin A

（アンフィジノリド N およびゴニオドミン A の全合成研究）

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Amphidinolide N (**1**, Figure 1), which was isolated from the cultured *Amphidinium* sp. (Y-5 strain) by the Kobayashi group in 1994, is the most potent cytotoxic member of the amphidinolide family discovered so far, and its IC_{50} values against murine lymphoma L1210 and human epidermoid carcinoma KB cells are 0.05 and 0.06 ng/mL, respectively.[1] The gross structure of amphidinolide N, including its partial stereochemical assignment, was proposed on the basis of 2D NMR spectroscopic studies. The structure has recently been revised, and the relative configuration has been reported.[2] Amphidinolide N consists of a 26-membered macrolide skeleton containing a six-membered hemiacetal, 2,5-*trans*-disubstituted tetrahydrofuran, allylic epoxide, and 13 stereogenic centers. Although several synthetic studies of amphidinolide N have been reported to date,[3] complete stereostructure of **1** has not been elucidated yet. We previously reported the synthesis of the tetrahydrofuran **2**.[4] However, it was unable to establish the synthetic route to the C8–C29 segment of **1**.

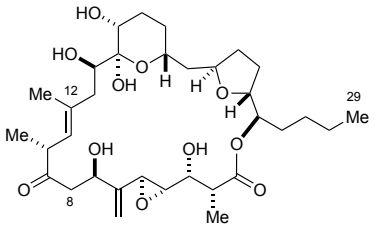
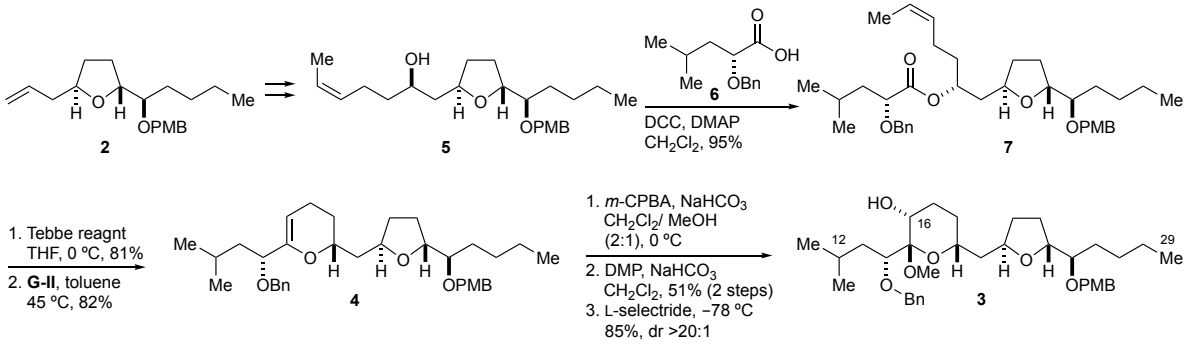


Figure 1. amphidinolide N (**1**)

Here the author reports his efforts toward a stereocontrolled synthesis of the C8–C29 model compound **3**, which involves the construction of the challenging six-membered acetal unit of amphidinolide N (Scheme 1). The key features of the synthesis are a Tebbe methylenation/ring-closing metathesis sequence[5] to construct a dihydropyran ring **4** and a late-stage introduction of the oxygen functionalities at C15 and C16 with *m*-CPBA.[6]



Scheme 1. Synthesis of the C8–C29 model compound **3**

Goniodomin A (**8**, Figure 2) is a marine polyether macrolide, which was isolated as a potent antifungal substance from the dinoflagellate *Alexeandrium hiranoi* by Murakami and coworkers.[7] We previously assigned the complete stereostructure of **8** on the basis of 2D NMR analysis, degradation experiments of the authentic sample, and synthesis of model compounds.[8] Aiming at the determination of complete stereostructure of goniodomin A, we have been engaged in the total synthesis of **8**.[9] Although we have achieved the synthesis of a seco-acid, our previous efforts on its macrolactonization were fruitless.[10]

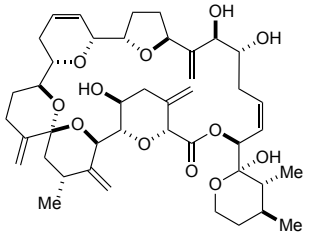
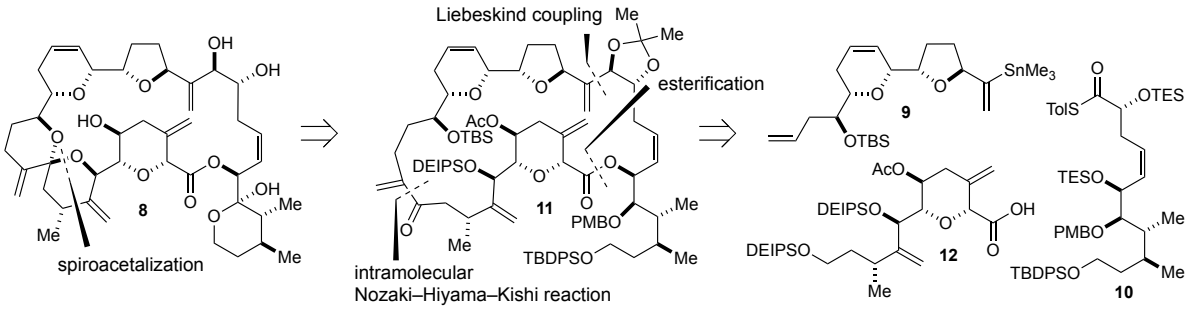


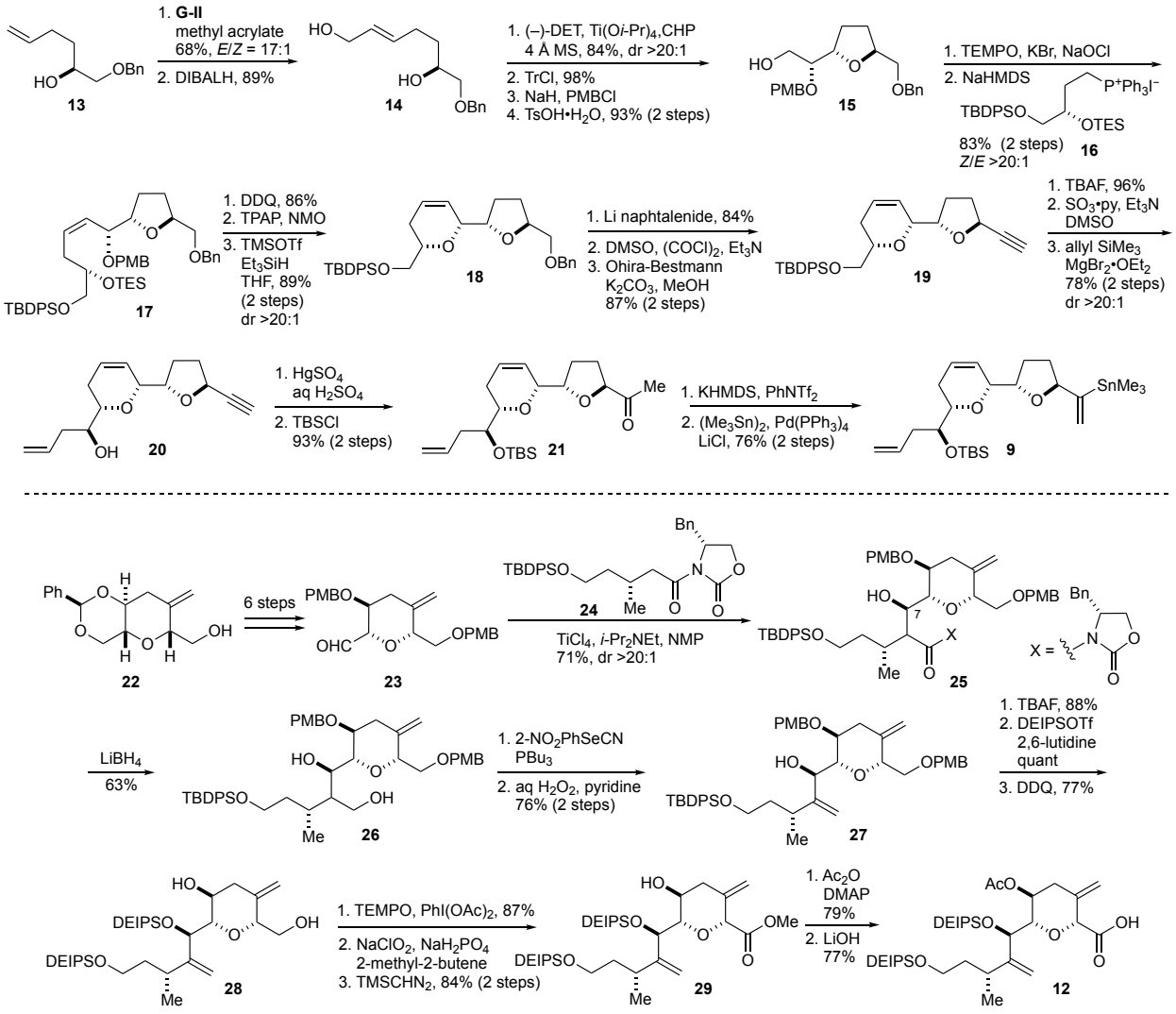
Figure 2. goniodomin A (**8**)

Here the author reports his studies toward the total synthesis of goniodomin A based on newly devised convergent strategy, which featured a palladium-catalyzed coupling[11] of vinylstannane **9** with thioester **10**, and an intramolecular Nozaki–Hiyama–Kishi (NHK) reaction[12] for the construction of the macrocyclic skeleton **11** (Scheme 2).



Scheme 2. Synthesis plan of goniodomin A

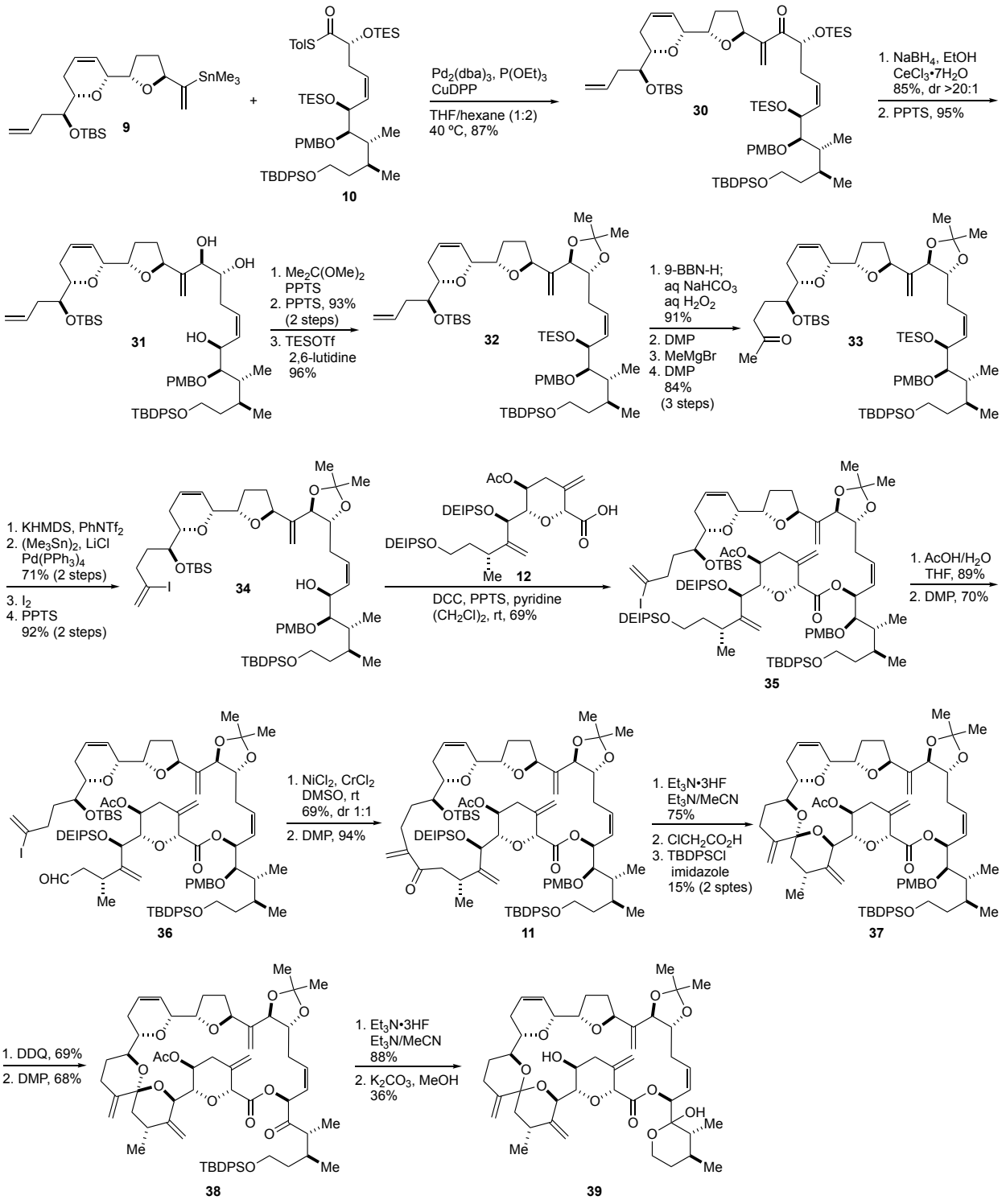
The author established scalable synthetic routes to vinylstannane **9** and carboxylic acid **12**. The synthesis of vinylstannane **9** involved a Wittig reaction and a reductive cycloetherification for the construction of the dihydropyran ring.[13] The synthesis of carboxylic acid **12** utilized a titanium-enolate mediated aldol reaction[14] for stereocontrolled installation of the acyclic moiety with a correct configuration of the C7 stereogenic center (Scheme 3).



Scheme 3. Synthesis of vinylstannane **9** and carboxylic acid **12**

The author next focused his attention on the formation of the macrocyclic skeleton of goniodomin A. Palladium-catalyzed cross-coupling[11] of vinylstannane **9** with thioester **10** gave advanced intermediate **30**, which was further elaborated to aldehyde **36** in 16 steps. Intramolecular NHK reaction[12] of **36** successfully afforded the corresponding cyclization product, which was oxidized to give enone **11**. Desilylation and subsequent acid treatment led to the corresponding spiroacetal as a mixture of diastereomers. The two diastereomers were separated by column chromatography on silica gel after silylation to afford natural (11*S*)-spiroacetal **37**. Formation of a hemiacetal, followed by removal of the acetyl group provided alcohol **39** as an inseparable mixture of isomers. Unfortunately, the ^{1}H NMR spectrum of **39** was different from that of the authentic derivative.[8] The author

inferred that the originally proposed relative configuration of goniodomin A might be incorrectly assigned.



Scheme 3. Synthesis of spiroacetal **39**

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