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Total Synthesis of the Putative Structure of Nagelamide D

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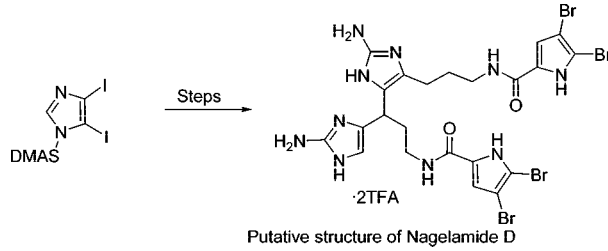
ABSTRACT



A total synthesis of the putative structure of nagelamide D from imidazole is described. A Stille cross-coupling is used to construct the bis imidazole skeleton, and the pyrrolecarboxamides are introduced via a double Mitsunobu reaction using a pyrrolehydantoin derivative. Discrepancies between the published spectroscopic data and that reported in the literature cast doubts either on the assigned structure or the reported data.

The oriodin alkaloids are a growing family of pyrrole-imidazole alkaloids produced by members of the *Agelisida, Axinellida,* and *Halichondrida* orders of marine sponges (Figure 1).[1] These natural products range in complexity from the simple monomeric parent system oroidin (**1**)[2] to the most complex member reported to date, the tetrameric styllisadine A.[3] Formally, these natural products arise from a variety of oxidation and oligomerization pathways of the basic building block oroidin (**1**) and congeners, but little is known about the details of their biosynthesis.[4,5] In large part due to the challenging structural problems presented by the dimeric members of this group, we and others have become interested in developing general synthetic approaches to the pyrrole-imidazole alkaloids including ageliferin (**2**),[6] axinellamine A,[7] palau'amine,[8] and the nagelamides (**3**−**6**).[9−11] The original group of nagelamides is a collection of eight oroidin dimers, which were isolated from an Okinawan marine sponge, *Agelas* sp., by Kobayashi and co-workers.[9] Subsequently, additional members of this subfamily have emerged which reinforce the structural diversity found in the oroidin

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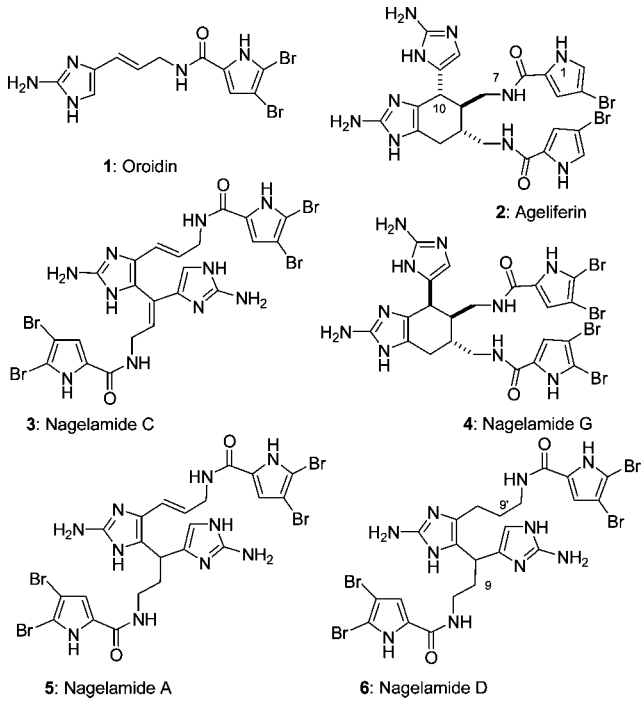

Figure 1. Selected oroidin alkaloids.

natural products.[9b-d] Of the initial collection of natural products, two broad groups of compounds were described reflecting differences in one C−C bond (between C9 and C9′) leading to a polysubstituted tetrahydrobenzimidazole type of system (e.g., ageliferin (**2**) and nagelamide G (**4**)) and the seco systems (e.g., nagelamides A (**5**), C (**3**) and D (**6**)). The examples lacking the additional ring exhibited different levels of oxidation and may in fact serve as biosynthetic precursors to other members of this family. To date, only one total synthesis of a nagelamide, nagelamide E (10-*epi*-**2**) has appeared in the literature, and this was as a byproduct in an approach to ageliferin (**2**).[12] Generally our approaches to the various members of this family of natural products have relied on the elaboration of simple imidazole derivatives as a means to construct highly functionalized imidazole-containing synthons.[11,13] In this manuscript, we describe an application of this strategy in a total synthesis of the reported structure of nagelamide D (**6**).[14]

Retrosynthetically it was envisioned that the core bis imidazole skeleton **7** found in nagelamide D (**6**) would be constructed through an appropriate cross-coupling reaction between an imidazolyl fragment **10** and vinyl fragment **11** (Figure 2). Experience gained in earlier endeavors suggested that (*Z*)-**11** (X = $SnBu_3$) and **10** (Y = I) would serve these roles.[15] Unfortunately, initial attempts to access the (*Z*)-vinylstannane **11** were not successful, and therefore we investigated the preparation of the corresponding and more accessible (*E*)-vinylstannane which upon cross-coupling and

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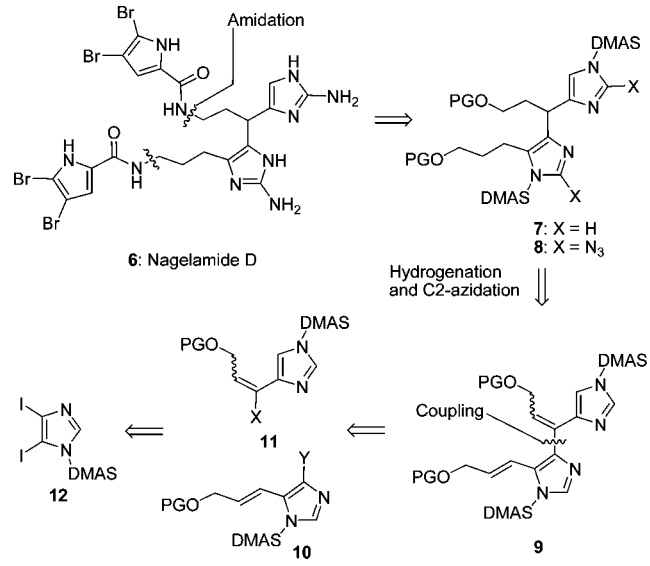
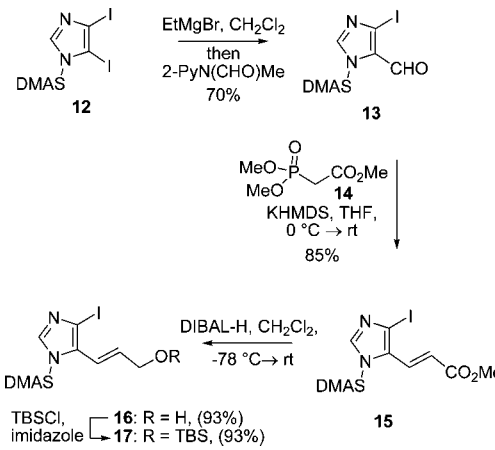


Figure 2. Retrosynthetic analysis of nagelamide D.

reduction would provide the same intermediate **7** suitable for elaboration to **6**. Both cross-coupling fragments can be traced back to the protected diiodoimidazole **12**.[15] Elaboration of the diimidazole core **7** through double C2-amination (Figure 2, **7**→**8**)[16] and double amidation of the diol would provide the complete skeleton of nagelamide D. Reduction of the azides and deprotection would then furnish the natural product **6**.

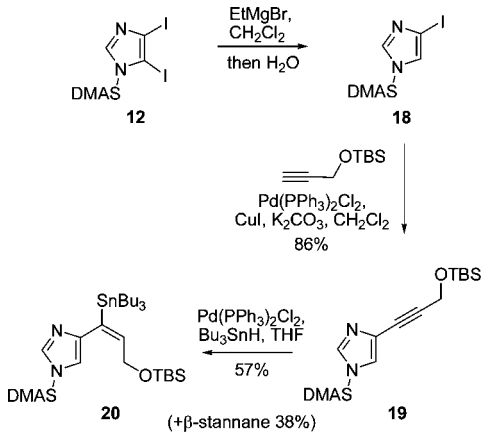
Scheme 1. Preparation of the Imidazolyl Iodide



The imidazolyl iodide component **17** (Scheme 1) was assembled in rapid order from the DMAS-protected 4,5-diiodoimidazole **12** (DMAS = dimethylaminosulfonyl), which can be formylated by metalation at C5 with EtMgBr and treatment with *N*-(2-pyridyl)-*N*-methylformamide forming **13**.[17,18] A Horner-Wadsworth-Emmons reaction provides the acrylate derivative **15**, which can be reduced to the allylic alcohol **16** on treatment with DIBAL. Reaction of allylic

alcohol **16** with TBSCl affords the silyl ether **17** and the first fragment needed for cross-coupling. The (*E*)-vinylstannane **20** was prepared via the hydrostannylation of TBS-protected propargyl alcohol **19** (Scheme 2). Despite extensive

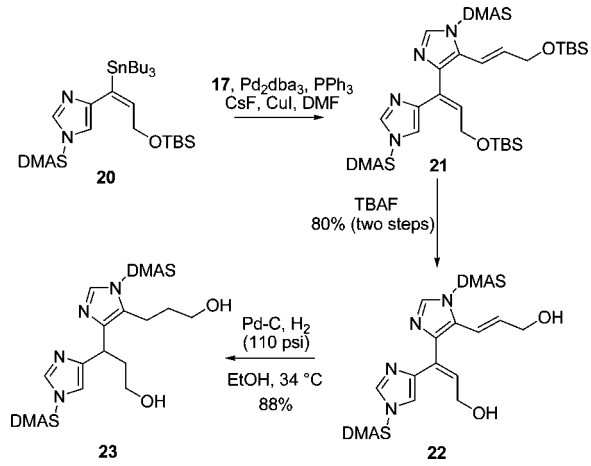
Scheme 2. Preparation of the Vinylstannane



experimentation with conditions and protecting groups, mixtures of the α- and *β*-isomers (~3:2) were always obtained, and unfortunately the regioselectivity of the hydrostannylation reaction could not be improved. The regiochemistry and the stereochemistry of this reaction were determined by the magnitudes of the vicinal coupling constants and Sn/H coupling constants. The imidazole-substituted propargyl alcohol **19** in turn was prepared via a Sonogashira reaction between 4-iodoimidazole **18** and TBS-protected propargyl alcohol.[16]

With the requisite two fragments in hand we began to investigate the cross-coupling reaction, and ultimately determined that the fluoride-mediated Stille cross-coupling conditions reported quite recently by Baldwin and co-workers provided the bis vinylimidazole **22** in good yield after treatment with TBAF to complete the partial desilylation.[19] At this point, catalytic hydrogenation led to saturation of both double bonds to give the diol **23** (Scheme 3),[20] which

Scheme 3. Fragment Assembly and Reduction



was then protected as the bis silyl ether **24** (Scheme 4). Double deprotonation of the imidazole C2 positions with *n*-BuLi and trapping with TsN_3 provides the bis azide **25** in 71% yield (Scheme 4).[16] Deprotection of the silyl ethers occurred on treatment with TBAF leading to the formation of the expected diol **26**. At this stage the introduction of the remaining nitrogen and the two dibromopyrrole moieties was all that remained to complete the synthesis. Strategically, one might envision accomplishing this task by conversion of the primary alcohols to the primary amines via the azide or phthalimide, followed by acylation. However, we had previously demonstrated that the pyrrolecarboxamide moiety could be introduced directly as a pyrrolehydantoin via a Pd-catalyzed allylic substitution reaction.[21,22] Therefore, it was not difficult to envision using a similar type of substrate as a nucleophile in a Mitsunobu reaction. Diol **26** was subjected to a double Mitsunobu reaction with the dibromopyrrolehydantoin derivative **27** leading to **28** (Scheme 4).[23] In order to prevent competitive formation of the iminophosphorane by reaction of the triphenylphosphine with the azide moieties, triphenylphosphine was reacted with DIAD **prior** to introduction of the diol.[24] In this way the full carbon skeleton of nagelamide D was accessed, all that remained to complete the synthesis was deprotection and azide reduction. Exposure of **28** to aqueous sodium hydroxide led to hydrolysis of the ureas, providing the pyrrolecarboxamide **29**. Initial attempts were made to complete the sequence by reduction of the azides with $NaBH_4$, which proceeded uneventfully; however

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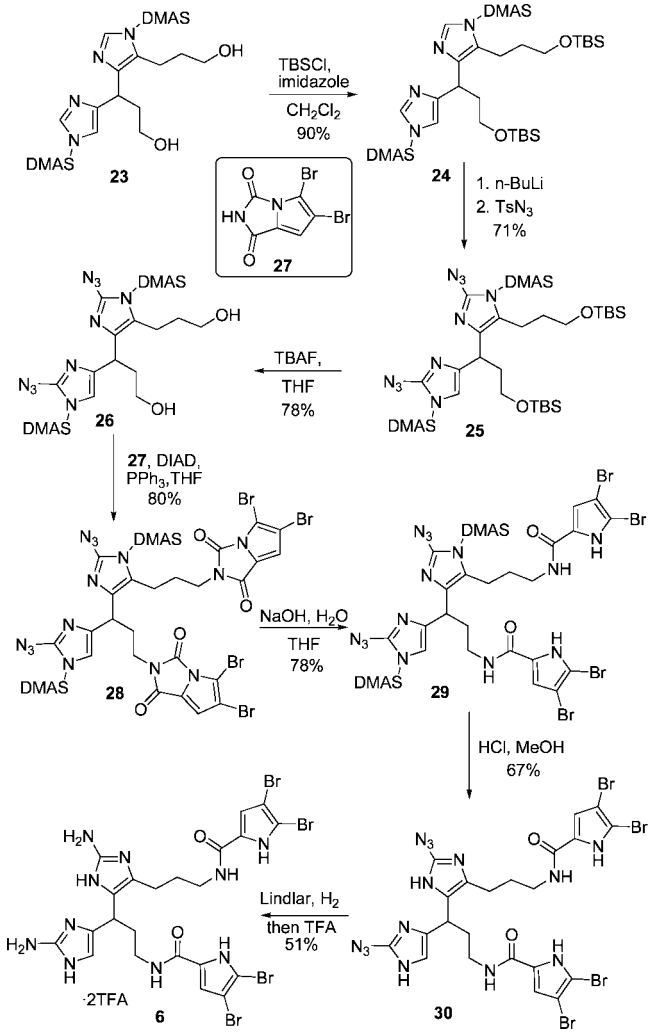
Scheme 4. Completion of the Synthesis



removal of the DMAS-protecting groups at this stage was unsuccessful. Ultimately it was determined that deprotection could be accomplished with azide **29** upon treatment with methanolic HCl providing **30**.[25] Exposure of the bis azide **30** to hydrogen in the presence of the Lindlar catalyst resulted in reduction to the amines and provided nagelamide D (**6**),[16] which was converted to the TFA salt by treatment with TFA.

Somewhat to our surprise, we found on comparison of the spectroscopic data for the synthetic and naturally occurring material that they were not completely identical. In particular in the ^{1}H NMR spectra, there are several notable discrepancies in the signals due to the aliphatic protons, and to a lesser extent in the ^{13}C NMR spectrum for the corresponding carbon atoms. Notably, two of the reported shifts δ_H 2.14/2.72 (nat.) vs 1.68 (syn.) for H9′ and δ_H 3.20−3.30 (nat.) vs 2.40 for H10′ (syn.) are substantially different, whereas our data are very similar to that obtained for dihydrooroidin. A full comparison of the spectroscopic data for nagelamide D, natural and synthetic, in addition to the corresponding data for the related systems archerine nagelamide A (**5**), nagelamide J and dihydrooroidin are provided in the Supporting Information.[9,26,27]

An obvious possible cause of the spectrosopic discrepancy may be a consequence of the concentration differences between the samples used, as Kobayashi and co-workers report isolation of ∼2 mg of nagelamide D (**6**). However, we found essentially no differences in the ^{1}H NMR spectra on serial dilutions down to approximately the same estimated concentration. Addition of a couple of drops of TFA to the final dilution sample exhibited no substantial differences in the ^{1}H NMR spectrum. Prior to conversion of synthetic **6** to the TFA salt, we checked the ^{1}H NMR spectrum of the free base in MeOH-d_4, which exhibited essentially identical chemical shifts to the salt in DMSO-d_6. It appears that neither concentration nor pH make a major difference in the appearance of the ^{1}H NMR spectra.

Similarly, there are discrepancies in the ^{13}C NMR spectra between synthetic and natural nagelamide D, in particular a CH_2 signal is reported at δ_c 16.6 (t), whereas for synthetic material the highest field signal is observed at δ_c 21.1. Based on the same set of comparative molecules, our data appears to be completely consistent with the assigned structure of nagelamide D (see Supporting Information). Unfortunately, we have been unable to obtain a sample or copies of the original NMR data of the genuine natural product from the Kobayashi laboratory to compare the chromatographic and spectroscopic properties of the synthetic and natural material, and therefore we cannot establish the source of this inconsistency at this time. While our work was in progress, we became aware of a biomimetic total synthesis of nagelamide D by the Horne laboratory. It is significant that both the ^{1}H and ^{13}C NMR data reported matches very well with that obtained by us, in spite of there being no common intermediates in either of the two routes until the final compound, indicating that the structural identity of the synthetic material is secure.[14] Therefore, pending additional information we must conclude that either the assigned structure or the reported NMR data is in error, unraveling this may require reisolation and characterization of the natural material.

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Supporting Information Available: Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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