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Synthesis of (±)-Bistellettadine A

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Abstract

Esterification of the trienoic acid with *o*-xylene dibromide gave the bis ester that underwent a templated Diels-Alder reaction to afford the macrodiolide stereospecifically in a single step. The synthesis of bistellettadine A was completed in four steps by hydrolysis and side chain elaboration.

As part of our continuing interest in the synthesis of guanidine-containing alkaloids, we were intrigued by the biologically active, dimeric, tetra guanidines bistellettadines A (**1a**) and B (**2**), which were recently isolated by Fusetani and co-workers from a *Stelletta* sponge collected from Shikine-jima island, 200 km south of Tokyo (see Figure 1).^{1,2} They inhibit Ca^{2+} /calmodulin-dependent phosphodiesterase (40% inhibition at $100\ \mu\text{M}$) and the growth of yeast and *E. coli* at $10\ \mu\text{g}/\text{disk}$. The structures of the bistellettadines were determined by spectroscopic analysis and the *cis* relationship of the two unsaturated side chains on the cyclohexene was established by NOE experiments. Bistellettazine A (**3**), a structurally related dimeric marine natural product with *trans* unsaturated side chains, was isolated by Capon in 2008.^{2f} Dimers **1a** and **2** are probably biosynthesized by a Diels-Alder reaction of two monomers analogous to stellettadine A (**7**)^{2b} (see Scheme 1). The stereochemistry of the Diels-Alder reaction may be controlled in the biosynthesis. However, closely related bis sesquiterpene dimers have been isolated as mixtures of *cis* and *trans* isomers.³ This raises the possibility that the Diels-Alder reactions are not stereoselective and that the *trans* isomer **1b** and the *cis* isomer of **3** were present in the sponges, but were not isolated and characterized.

Mori and co-workers synthesized stellettadine A (**7**)^{2b} by coupling Boc-protected agmatine **4** and acyl chloride **5** to provide the diacylated product **6** in 62% yield (see Scheme 1).⁴ Removal of the Boc group of **6** under acidic conditions followed by treatment of the resulting amine

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Supporting Information **Available**: Complete experimental procedures, tables comparing the spectral data of synthetic and natural products, and copies of ^1H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

with aminoiminomethanesulfonic acid constructed the second guanidine group. The extra acyl group was removed using KOH to afford stellettadine A (**7**) in 56% overall yield from **6**. The yield of this four-step sequence is 35% from **4**, but only 17% based on acyl chloride **5**.

Our retrosynthesis analysis of **1a** is shown in Scheme 2. A Diels-Alder dimerization of two molecules of **8a** or **8b** could give **1a** (after deprotection if **8a** is used). Bis guanidine **8a** will be prepared from trienoic acid **10** resulting from the hydrolysis of ester **11** formed by the Wittig reaction of trienal **12**⁵ and ylide **13**. Alternatively, the Diels-Alder reaction of **10** or **11** could be carried out before introduction of the guanidine side chains to give diacid **9a**, which will then be elaborated to **1a**. We hoped that the carboxylate salt of **10** might orient in water to give selectively the desired Diels-Alder adduct **9a** with cis unsaturated side chains.⁶

Mori's procedure for the introduction of the guanidine side chain of stellettadine A (**7**) that proceeds through a bis acyl guanidine could be used for the conversion of acid **10** to monomer **8b**, but it cannot be used for the conversion of diacid **9a** to **1a**. We therefore needed to develop a more efficient procedure for introduction of the guanidine side chain that does not proceed through a diacylated intermediate analogous to **6**.

Wittig reaction of readily available dienal **12**⁵ and ylide **13** was most effectively carried out in THF at 70 °C for 15 min under microwave irradiation to give **11** in 85% yield (see Scheme 3). The unstable trienoate **11** decomposed partially and gave some Diels-Alder dimer at longer reaction times, higher temperatures, or with traditional heating. Hydrolysis of ester **11** with LiOH in 4:2:1 THF/MeOH/H₂O for 16 h followed by neutralization with 6 M HCl gave crude acid **10**. Coupling⁷ of acid **10** and **14**⁷ in CH₂Cl₂ using DIPEA, EDC and HOBT gave **15** in 59% overall yield from ester **11**, which was treated with bis Boc-protected agmatine **16**,⁸ Et₃N, and AgNO₃ in DMF at 0 °C for 3 h and at 25 °C for 4 h to give **8a** in 77% yield as a 2:3 mixture of tautomers. Deprotection of the Boc groups of **8a** using TFA gave the bis trifluoroacetate salt **8b**. Unfortunately, initial attempts to carry out Diels-Alder dimerizations of either **8a** or **8b** resulted in polymerization of the sensitive trienoyl guanidine.

To establish the structures of the two tautomers of **8a**, we prepared an inseparable 36:64 mixture of the simpler tautomers **17a** and **17b** from tiglic acid using the two-step procedure described above for the conversion of **10** to **8a** (see Scheme 4). The alkene proton at δ 7.08 in the minor isomer **17a** shows a strong NOE only to the geminal methyl group at δ 1.80. However, the alkene proton at δ 6.74 in the major isomer **17b** shows strong NOEs not only to the geminal methyl group at δ 1.87, but also to the N-H proton at δ 12.86. The presence of both tautomers indicates that the N-H exchange is slow on the NMR time scale.⁹ Protonation of both **17a** and **17b** should give the same diacylguanidinium cation. Treatment of the mixture in CDCl₃ with TFA gave **18** as a single compound in which the alkene proton absorbed at δ 6.86.

We then investigated the Diels-Alder dimerization of trienoate ester **11** in organic solvents and the lithium salt of trienoic acid **10** in water. Hydrolysis of **11** with LiOH followed by concentration gave the lithium salt, which underwent a clean Diels-Alder dimerization in water under microwave irradiation at 110 °C for 50 min to give an inseparable 5:4 mixture of crude **9a** and **9b** in 94% yield (see Scheme 5). Heating trienoate ester **11** in toluene at 125 °C for 2 days followed by hydrolysis gave a similar mixture of **9a** and **9b** in comparable yield. An NOE between H-11 and the C-6 methyl group in **9a** suggested that the unsaturated side chains of the major isomer **9a** have the desired cis relationship. NOEs between H-11 and H-5 and between H-12 and the C-6 methyl group established that the unsaturated side chains are trans in the minor isomer **9b**.

Analytical, but not preparative, separation of **9a** and **9b** was achieved on reverse phase silica gel. We therefore coupled the mixture of **9a** and **9b** with **14**, DIPEA, EDC and HOBT to afford an inseparable 5:4 mixture of **19a** and **19b** in 67% overall yield from trienoate ester **11** (see

Scheme 6). Treatment of this mixture with **16**, Et₃N, and AgNO₃ in DMF afforded a 5:4 mixture of **20a** and **20b** in 69% yield. Stirring this mixture in 9:1 CDCl₃/TFA at 25 °C for 4 days cleaved all six Boc groups to give a 5:4 mixture of **1a** and **1b** in 68% yield as the tetra trifluoroacetate salts, which were readily separated by reverse phase HPLC. The ¹H and ¹³C NMR spectra of synthetic **1a** in DMSO-*d*₆ correspond very closely to those of natural **1a**.^{1,10} The spectra of **1b** are very similar except that H-11 is shifted downfield by 0.07 ppm to δ 3.14, the C-6 methyl group is shifted upfield by 0.10 ppm to δ 1.00, C-5 is shifted downfield by 2.7 ppm to δ 153.0 and the C-6 methyl group is shifted upfield by 2.4 ppm to δ 21.7. These shifts are consistent with the upfield shift expected for gauche butane interactions between C-12 and C-5 in **9a** and between C-12 and the C-6 methyl group in **9b**.

Unfortunately, the Diels-Alder dimerization of ester **11** or the salt of acid **10** proceeded cleanly but with poor stereocontrol. Coupling two molecules of acid **10** to a linker by a temporarily tether will form a substrate that can undergo an intramolecular Diels-Alder reaction.¹¹ The tether needs to be easily attached and removed, long enough to accommodate the different lengths of the unsaturated side chains in the Diels-Alder adduct, and yet short enough to facilitate an intramolecular Diels-Alder reaction and favor the formation of the isomer with cis unsaturated side chains. Molecular mechanics calculations suggested that the intramolecular Diels-Alder reaction of **22** should give **23** stereospecifically.¹² We therefore treated acid **10** (2.5-4 equiv) with *o*-xylylene dibromide (**21**) and Cs₂CO₃ in CH₃CN at 85 °C (see Scheme 7). After 3 h, **21** was completely converted to bis ester **22** and ~10% of Diels-Alder product **23** had already formed. Heating for 2 days gave exclusively macrodiolide **23** with the cis configuration of the unsaturated side chains in 42% overall yield from **11** (80% yield from **21**). Remarkably, the intramolecular Diels-Alder reaction proceeded stereospecifically under milder conditions than the intermolecular Diels-Alder dimerization of **10** or **11** to form **23** with a 16-membered ring macrodiolide. The stereochemistry of **23** was established by NOEs between H-11 and the C-6 methyl group. Hydrolysis of **23** using LiOH in 5:2 THF/H₂O at 25 °C for 16 h gave **9a**. Coupling of **9a** with **14** gave **19a** in 57% overall yield from **23**. Reaction of **19a** with **16** gave **20a** in 57% yield, which was deprotected using TFA for 4 days to give **1a** as a single isomer in 68% yield.

In conclusion, trienal **12** has been converted to bistelletadine A (**1a**) in seven steps in 8% overall yield. Remarkably, the templated Diels-Alder reaction of **22** afforded macrodiolide **23** in excellent yield with complete stereocontrol.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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12. MMX calculations using PCMODEL 8.0 (Serena Software: Bloomington, IN) indicated that **23** is >3 kcal/mol more stable than the stereoisomer. Transition state calculations also indicated that the transition state leading to **23** was more stable than that leading to the stereoisomer by >3 kcal/mol.

Figure 1.
Structures of bistellettadines A (**1a**) and B (**2**), *epi*-bistellettadine A (**1b**), and bistellettazine A (**3**).

Scheme 1.
Mori's Synthesis of Stelletadine A (7)

Scheme 2.
Retrosynthesis of (±)-Bistellettadine A (**1a**)

Scheme 3.
Unsuccessful Approach to Bistellettadine A (**1a**)

Scheme 4.
Model Tautomers **17a** and **17b**

Scheme 5.
Diels-Alder Dimerization of **11** to Give **9a** and **9b**

Scheme 6.
Completion of Bistellettadine A (**1a**) Synthesis

Scheme 7. Use of Templated Diels-Alder Reaction to Synthesize Bistellettadine (**1a**)