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# Stereochemistry of Sagittamide A: Prediction and Confirmation

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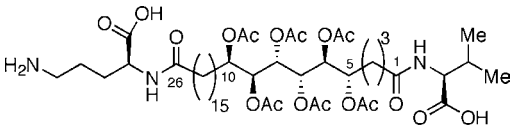
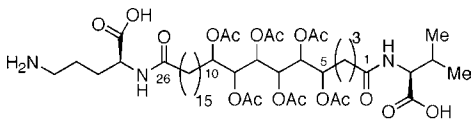
## ABSTRACT



**Sagittamide A**

**The C5–C10 relative stereochemistry of sagittamide A was predicted, with the use of the $^3J_{H,H}$ profiles assembled from the spin-coupling constants reported in the literature. The predicted relative stereochemistry was then confirmed by a total synthesis of two relevant remote diastereomers. The absolute configuration of sagittamide A was established through a detailed $^1$H NMR analysis of the two remote diastereomers, followed by doping experiments of them with the authentic natural product.**

Sagittamides A and B are the marine natural products isolated recently from an unidentified tunicate collected in Micronesia by Lievens and Molinski.[1] These natural products consist of three parts: a long-chain α,ω-dicarboxylic aid (C-26), L-valine, and L-ornithine. The α,ω-dicarboxylic acid moiety of sagittamide A contains a stereocluster of contiguous hexaol peracetate, the stereochemistry of which has not been disclosed. We became interested in the structure of sagittamide A, as the hexaacetate moiety of sagittamide A provides an ideal testing ground for demonstrating the reliability and applicability of the $^3J_{H,H}$ profiles assembled from spin-coupling constants reported in the literature.[2] In this letter, we report the prediction of the relative stereochemistry of the hexaacetate moiety present in sagittamide A by this approach and then the confirmation of the predicted stereochemistry via a total synthesis. The absolute stereochemistry has been established through a detailed analysis of the $^1$H spectra of synthetic sagittamide A and its remote diastereomer.



**Sagittamide A**

By using diastereomeric heptaols as examples, we previously demonstrated that $^3J_{H,H}$ profiles composed of three contiguous spin-coupling constants are, at least to the first order of analysis, sufficient for stereochemical analysis of unknown contiguous polyols.[3] With this demonstration, we felt that the $^3J_{H,H}$ profiles (Figure 1) reported in the preceding paper should be useful for stereochemical analysis of the hexaacetate moiety present in sagittamide A.


**Figure 1.** $^3J_{H,H}$ profiles of the contiguous tetraol peracetate assembled with the use of the spin-coupling constants reported in the literature for the relevant compounds.[2] Abbreviations: A = anti and S = syn.

Thus, following the procedure established for the heptaol case,[3] we analyzed the $^3J_{H,H}$ profile (**A**, Figure 2) of

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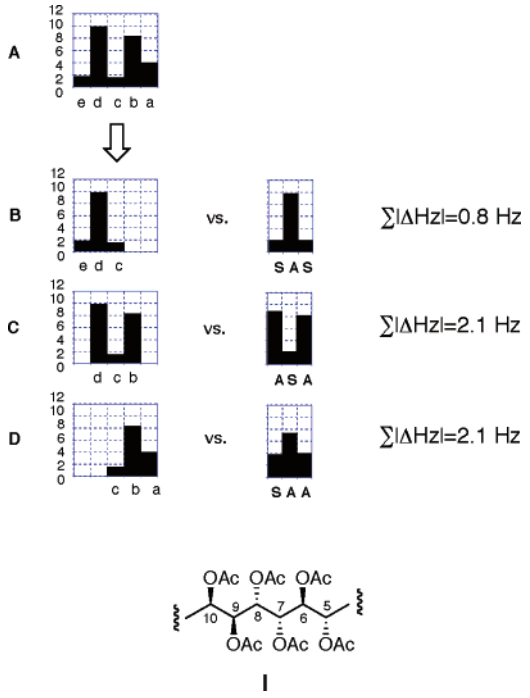
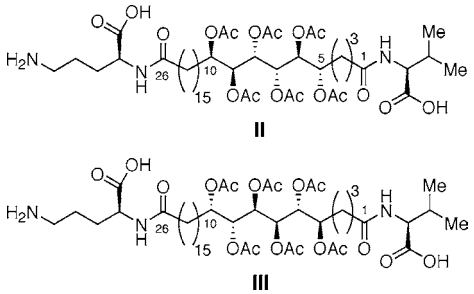



**Figure 2.** Profile analysis of the $^3J_{H,H}$ coupling constants reported for the C5−C10 moiety of sagittamide A.[1] **Panel A:** Overall profile reported where a, b, c, d, and e represent the vicinal spin-coupling constants (Hz) observed for H5/H6, H6/H7, H7/H8, H8/H9, and H9/H10, respectively. **Panel B:** $^3J_{H,H}$ profile composed of the three $^3J_{H,H}$'s of H7/H8−H8/H9−H9/H10; this profile best matches the SAS profile in Figure 1 ($\sum|\Delta Hz| = 0.8$ Hz). **Panel C:** $^3J_{H,H}$ profile composed of the three $^3J_{H,H}$'s of H6/H7−H7/H8−H8/H9; this profile best matches the ASA profile ($\sum|\Delta Hz| = 2.1$ Hz). **Panel D:** $^3J_{H,H}$ profile composed of the three $^3J_{H,H}$'s of H5/H6−H6/H7−H7/H8; this profile best matches the SAA profile ($\sum|\Delta Hz| = 2.1$ Hz). **I**: predicted relative stereochemistry of the C5−C10 moiety of sagittamide A.[4] Abbreviations: A = anti and S = syn.

sagittamide A reported by Lievens and Molinski.[1] The analytical procedure involved: (1) imaginarily dissecting the $^3J_{H,H}$ profile of sagittamide A into three small stereoclusters **B**−**D**, each composed of three contiguous $^3J_{H,H}$ systems and (2) comparing each of the resultant $^3J_{H,H}$ profiles to the $^3J_{H,H}$ profiles of contiguous tetraol peracetates, to predict their relative stereochemistry on the basis of the profile fitness. In this exercise, the profile fitness was assessed by the deviation sum ($\sum|\Delta Hz|$) between the experimental $^3J_{H,H}$'s and the corresponding $^3J_{H,H}$'s in the profile. As discussed in the preceding paper, $\sum|\Delta Hz|$ for a good profile matching is expected to be less than 3.3 Hz. For each of the three comparisons, only one out of the eight subgroups met with the criteria, i.e., SAS subgroup for **B** ($\sum|\Delta Hz| = 0.8$ Hz), ASA subgroup for **C** ($\sum|\Delta Hz| = 2.1$ Hz), and SAA subgroup for **D** ($\sum|\Delta Hz| = 2.1$ Hz), thereby predicting that the C5−C10 relative stereochemistry of sagittamide A corresponds to the one shown as **I** (Figure 2).[4] The predicted stereostructure has no plane of symmetry, even if the difference in the two termini was ignored. Thus, we would expect the $^3J_{H,H}$ profile to have no symmetrical nature, and this trend is clearly recognized in the overall profile shown in **A**.

With the relative stereochemistry at the C5−C10 positions predicted as **I**, sagittamide A should correspond to one of the two diastereomers **II** and **III** because both valine and ornithine were shown to belong to the L-amino acid series.[1] To confirm the predicted relative stereochemistry at the C5−C10 moiety and also to differentiate the two candidates **II** and **III**, we relied on organic synthesis. Specifically, our plan was to synthesize both **II** and **III** and then to develop an analytical method to differentiate them. However, for synthetic economy, we chose to synthesize **II** and the antipode of **III**.



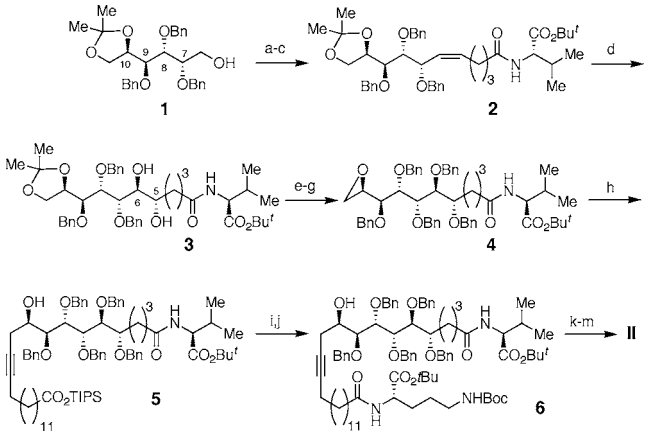

To this end, we chose D-(+)-galactose as the chiral starting material, which contains four out of the six contiguous stereogenic centers present in the $C_{26}$ dicarboxylic acid of **II**. Following literature procedure, D-(+)-galactose was converted to the acetonide alcohol **1** (Scheme 1). Dess−Martin oxidation,[5] followed by Wittig olefination, furnished the desired cis olefin ($J_{5,6} = 11.0$ Hz). After coupling with L-valine *tert*-butyl ester in the presence of the BOP reagent,[6] the olefin **2** was subjected to dihydroxylation (cat. $OsO_4$−NMO in aq dioxane at room temperature), to furnish an 8.3:1 mixture of the expected diols. On the basis of the empirical rule,[7] the stereochemistry of the major product was assigned as indicated. After the newly introduced alcohols were protected as benzyl ethers, **3** was converted to the epoxide **4** under the Mitsunobu conditions.[8]

The next phase of the synthesis was to couple **4** with the lower side chain. Ideally, we hoped to introduce the lower side chain bearing the L-ornithine moiety. Despite a variety of attempts, we were unable to achieve the coupling with a

(1) Lievens, S. C.; Molinski, T. F. *Org. Lett*. **2005**, *7*, 2281.
(2) Seike, H.; Ghosh, I.; Kishi, Y. *Org. Lett*. **2006**, *8*, 3861.
(3) Higashibayashi, S.; Czechtizky, W.; Kobayashi, Y.; Kishi, Y. *J. Am. Chem. Soc*. **2003**, *125*, 14379.

(4) The second best candidate was found to be the SAA ($\sum|\Delta Hz| = 4.9$ Hz) or AAS ($\sum|\Delta Hz| = 4.9$ Hz) subgroup for comparison **B**, the ASS subgroup ($\sum|\Delta Hz| = 5.2$ Hz) for comparison **C**, and the SAS subgroup ($\sum|\Delta Hz| = 4.2$ Hz) for comparison **D**, respectively. However, the degree of profile fitness well exceeds the level of $\sum|\Delta Hz| < 3.3$ Hz for all these cases.
(5) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.
(6) (a) Dormoy, J. R.; Castro, B. In *Encylopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Ltd.: Chichester, U.K., 1995; Vol. 1, pp 301−304. (b) Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett*. **1975**, 1219.
(7) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett*. **1983**, *24*, 3943. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett*. **1983**, *24*, 3947. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.
(8) Hughes, D. L. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 1992; Vol. 42 pp 335−656.

**Scheme 1**[a]




[a] Reagents and conditions: (a) Dess−Martin reagent, $NaHCO_3$, $CH_2Cl_2$, rt; (b) $Br^-(Ph)_3P^+CH_2(CH_2)_3CO_2H$, LiHMDS, THF, 0 °C, then rt; (c) BOP, $^iPr_2NEt$, DMF, 0 °C, then L-valine $^t$Bu ester, rt; (d) $OsO_4$, NMO, aq dioxane, rt; (e) $BnO(C{=}NH)CCl_3$, TfOH, $CH_2Cl_2$/cyclohexane, 0 °C, then rt; (f) AcOH/$H_2O$, rt; (g) DEAD, $PPh_3$, $CHCl_3$, 60 °C; (h) $HC{\equiv}C(CH_2)_{12}CO_2TIPS$, BuLi, $BF_3{\cdot}Et_2O$, $Et_2O$/THF, −95 °C, then −78 °C; (i) TBAF, THF, 0 °C; (j) L-$N^\delta$-Boc-ornithine $^t$Bu ester, EDCI, HOBt, DMF, rt; (k) $H_2$, Pd on C, AcOH/MeOH, rt; (l) $Ac_2O$, py, rt; (m) TFA, $CH_2Cl_2$, rt.

fully functionalized side chain. Thus, we studied the coupling of **4** with the lower side chain bearing a protected carboxylic acid at C26. After much experimentation, it was found that this task could be achieved by a $BF_3-OEt_2$-mediated epoxide opening with the C15 acetylene under the Yamaguchi conditions,[9] to furnish the coupled product **5**. It was critical to generate the boron reagent at −95 °C; when the boron reagent was prepared at −78 °C, a complex mixture containing the desired product, the unreacted epoxide, and unidentified byproducts was obtained. After the TIPS ester was deprotected with TBAF, **5** was coupled with L-$N^\delta$-Boc-ornithine *tert*-butyl ester to give the amide **6**. The amide **6** was uneventfully converted to **II** in three steps.

The product **II** thus synthesized corresponds to one of the two candidates predicted as the structure of sagittamide A. The antipode of the remaining candidate **III** was synthesized via the same route but with the use of D-valine *tert*-butyl ester and D-$N^\delta$-Boc-ornithine *tert*-butyl ester.

With both candidates in hand, we began analytical work. **II** and the antipode of **III** are remote diastereomers (diastereomers due to the stereogenic centers being present outside of a self-contained box).[10] Thus, we anticipate that the NMR characteristics of **II** and **III** are identical or at least very similar. Indeed, the $^1H$ and $^{13}C$ spectra of **II** and the antipode of **III** were found to be virtually identical. Importantly, these NMR characteristics were found to perfectly match the NMR data reported for sagittamide A, thereby confirming the relative stereochemistry at C5−C10 predicted using the $^3J_{H,H}$ profiles assembled from the spin-coupling constants obtained from relevant but scattered literature examples.

(9) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391

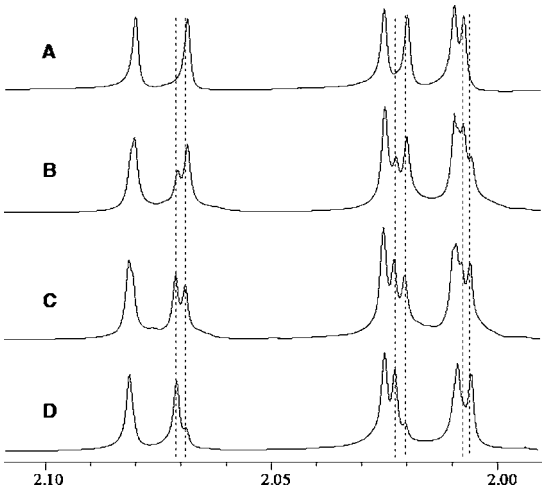



**Figure 3.** Acetate signals in the $^1H$ NMR spectra (600 MHz, $CD_3OD-TFA$) of **II** and the antipode of **III**. **Panel A: II**. **Panel B:** A ca. 3:2 mixture of **II** and **III**-antipode. **Panel C:** A ca. 1:2 mixture of **II** and **III**-antipode. **Panel D: III**-antipode contaminated with a small amount (<10%) of L-valine. *X*-axis represents the chemical shift in ppm.

The remaining task was to develop an analytical method to differentiate **II** and the antipode of **III**. With both remote diastereomers in hand, we closely studied their $^1H$ NMR spectra. As mentioned, both remote diastereomers gave

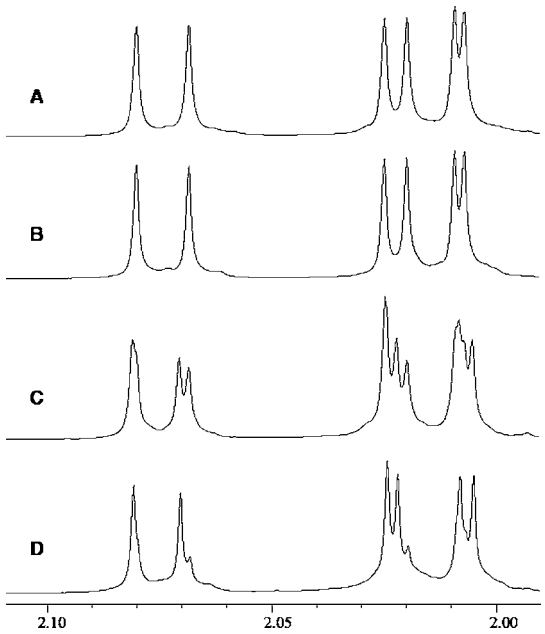



**Figure 4.** Acetate signals in the $^1H$ NMR spectra (600 MHz, $CD_3OD-TFA$) of synthetic and natural sagittamide A. **Panel A: II**. **Panel B: II** doped with approximately 0.5 equiv of natural sagittamide A. **Panel C: III**-antipode doped with approximately 0.5 equiv of natural sagittamide A. **Panel D: III**-antipode contaminated with a small amount (<10%) of L-valine. *X*-axis represents the chemical shift in ppm.

virtually identical $^1$H NMR spectra. However, a clue for the solution was first detected while recording the $^1$H NMR spectrum of the antipode of **III**, which was contaminated with a small amount (<10%) of L-valine.[11] The $^1$H NMR spectrum of this sample clearly indicated that three out of the six acetate signals have a shoulder. Being encouraged with this observation, we then conducted a doping experiment of the antipode of **III** with **II**, thereby unambiguously demonstrating that $^1$H NMR spectroscopy can differentiate the two remote diastereomers in question (Figure 3).[12]

Using this analytical method, we performed two doping experiments (Figure 4). On doping with natural sagittamide A, we observed that none of the acetyl signals were doubled in the **II** series, whereas three out of the six acetyl signals were doubled in the **III**-antipode series,[12] thereby demonstrating that sagittamide A corresponds to the remote diastereomer **II**. Knowing that the absolute configuration of the two amino acids is L,[1] the complete structure of sagittamide A is established as **II**.

In summary, the C5−C10 relative stereochemistry of sagittamide A was predicted, with the use of the $^3J_{H,H}$ profiles assembled from the spin-coupling constants reported in the literature. The predicted relative stereochemistry was then confirmed by a total synthesis of two relevant remote diastereomers. The absolute configuration of sagittamide A was established through a detailed $^1$H NMR analysis of the two remote diastereomers and then by conducting doping experiments of them with the authentic natural product.

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**Supporting Information Available:** Experimental details for Scheme 1; spectroscopic data for compounds **1**−**6**, **II**, and **III**-antipode; $^1$H and $^{13}$C NMR spectra of **II**, **III**-antipode, and natural sagittamide A; and table of $^{13}$C NMR data of **II**, **III**-antipode, and natural sagittamide A along with the $^{13}$C NMR data reported in ref 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Previous work in our laboratory has shown steric and/or stereoelectronic interactions between structural clusters separated by two or more carbons to be negligibly small. This characteristic, referred to as a *self-contained box*, constitutes one of the key foundations for our NMR database approach. For examples, see: (a) Boyle, C. D.; Harmange, J.-C.; Kishi, Y. *J. Am. Chem. Soc*. **1994**, *116*, 4995. (b) Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J. J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc*. **1996**, *118*, 7946. (c) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *Helv. Chim. Acta* **2000**, *83*, 2562. (d) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc*. **2001**, *123*, 2076. Also see ref 3 and references therein.

(11) This was due to a partial epimerization of the D-valine moiety during the preparation of D-valine *tert*-butyl ester.

(12) In addition to the three doubled acetyl signals, the resonance around 2.08 ppm showed a sign of doubling.