

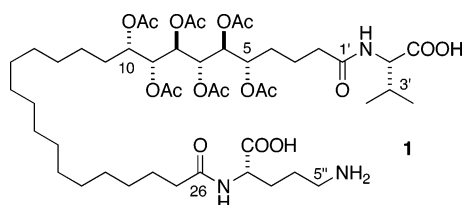
Progressive–Convergent Elucidation of Stereochemistry in Complex Polyols. The Absolute Configuration of (–)-Sagittamide A

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The structure of (–)-sagittamide A (**1**),¹ an unprecedented polyacetoxy, long-chain α,ω -dicarboxylic acid isolated from a tropical didemnid tunicate, was solved by application of conventional 2D NMR spectroscopic methods; however, only partial stereochemistry could be assigned. Although configurations of the terminal amino acids (L-ornithine and L-valine) were determined readily by conventional methods, the contiguous 5,6,7,8,9,10-hexol hexaacetate in **1** represented a significantly more complex NMR problem, in part, because of isolated stereohexad C5–C10 flanked by CH₂ groups² and equivocal interpretations of *J* coupling.

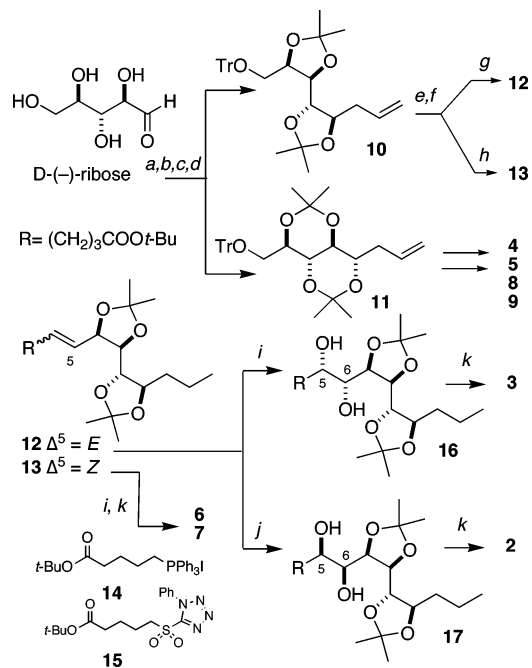


We now report the complete stereostructure of **1** using a *progressive–convergent* approach that integrates three powerful regimens for stereochemical analysis of natural products: use of Murata's *J*-based analysis (³*J*_{HH} and ^{2,3}*J*_{HC}),³ application of Kishi's universal database⁴ (pairwise-comparison of ¹³C NMR chemical shifts with stereo-defined models), and highly sensitive exciton coupling circular dichroism (ECCD).⁵ The integrated approach rapidly converges upon a unique stereochemical assignment for **1** with internal validation.

A basis set of ³*J*_{HH} and ^{2,3}*J*_{CH} values were obtained by 2D heteronuclear 2D NMR experiments of **1** (COSY and HSQMBC, respectively, see Supporting Information (SI)) and used to predict an all anti relative configuration for C6–C9 for **1**. Consequently, the number of remaining possible diastereomers of **1** was reduced from *N* = 32 to 4. A synthetic route to six model compounds, representing permutations of the six stereocenters C5–C10 congruent with those proposed for **1**, was conceived and executed starting with D-xylose (see SI).⁶ To address an equivocal C8 ³*J*_{CH} value in **1**, a parallel set of models **2–9** was also prepared from D-ribose as described below (Scheme 1).

Indium-promoted Barbier reaction of D-ribose with allyl bromide gave a 2:1 mixture of epimeric homoallylic alcohols **10** and **11** after protection. Each acetonide was deprotected and hydrogenated (Pd/C, CF₃CH₂OH, 1 atm H₂)⁸ followed by Swern oxidation to the corresponding C9 aldehydes and homologation using two stereo-complementary methods (*Z*-selective Wittig olefination using phosphonium salt **14** and *E*-selective Julia–Kocienski olefination with tetrazole **15**) to give **12** and **13**.

Scheme 1^a



^a (a) In^o, allyl bromide, H₂O; (b) TrCl, pyridine, reflux 53% (two steps); (c) CSA, acetone, CH₃C(OCH₃)₂CH₃ 58%, **10/11** dr 2:1; (d) SiO₂-HPLC 1:19 EtOAc/hexanes; (e) H₂, 1 atm, Pd/C, CF₃CH₂OH, 35–69%; (f) (i) (COCl)₂, DMSO, CH₂Cl₂, –78 °C (ii) Et₃N; (g) (i) **15**, DME, NaHMDS, –78 °C, (ii) aldehyde, 25%, dr 3:1 (two steps); (h) (i) **14**, THF, NaHMDS, –78 °C, (ii) aldehyde, dr > 19:1, 16% two steps; (i) OsO₄, NMO, acetone, H₂O; dr 1.7:1, 93%; (j) K₃Fe(CN)₆, K₂OsO₄, K₂CO₃ (DHQ)₂PHAL, *t*-BuOH, H₂O, CH₃SO₂NH₂, dr 3.8:1, 86%; (k) 2% TMS–Cl, MeOH, (ii) CH₂N₂, ether/MeOH, (iii) Ac₂O, pyridine 6 h: 22% **3** (three steps), 48% **2** (three steps), 44% **6** (four steps), 26% **7** (four steps).

Stereoselective OsO₄ dihydroxylation¹⁰ of **12** gave diols **16** and **17**. In this manner, *E*- and *Z*-olefins were converted to diol diastereomers and purified by HPLC, prior to deprotection to the hexaols. Peracetylation of each hexaol furnished the eight C7–C9 ribo-model compounds **2–9** and six *xylo*-models (SI). The correct relative configuration of **1** emerged from ¹³C NMR comparisons with the model compounds (Figure 1).⁴

The ¹H and ¹³C NMR spectra of each peracetate model were carefully assigned from COSY and HMBC spectra. Pairwise comparisons of the differences of the ¹³C chemical shifts ($\Delta\delta$) for C4–C11 in model compounds and **1** clearly showed an excellent match for the C8 epimer **6** obtained from D-ribose, but a mismatch for the corresponding *xylo*-C8 epimer (e.g., C8: $\Delta\delta$ = +0.05 and –3.93 ppm, respectively, see SI). A valuable object lesson is revealed here that promotes a *progressive–convergent* approach to stereochemistry. Although anomalous ³*J*_{CH} values in **1** predicted

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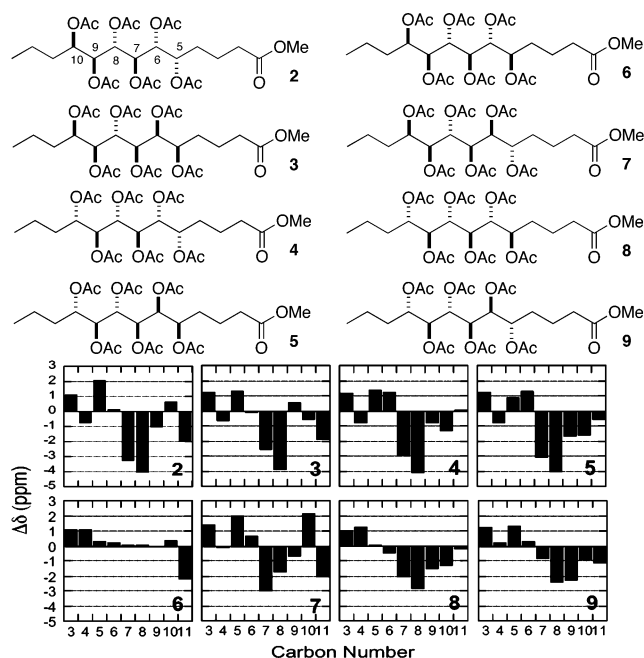


Figure 1. ^{13}C NMR (125 MHz, d_6 -DMSO, $T = 298\text{ K}$) $\Delta\delta$ values ($\delta_{\text{C}1} - \delta_{\text{C}}$ model) of ribo-model compounds **2**–**9**.

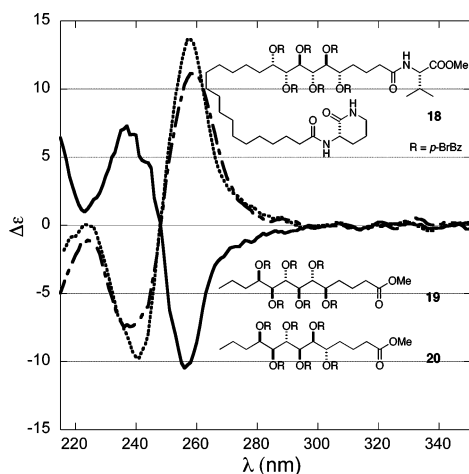


Figure 2. CD spectra of sagittamide A derivative **18** (—), together with models **19** (⋯) and **20** (---), (CH_3CN , $c = 10\ \mu\text{M}$).

an erroneous *xylo*-configuration during *J*-based analysis,¹¹ this was readily rectified in the progressive ^{13}C $\Delta\delta$ analysis allowing reassignment of C8 configuration to that of **6**.

The absolute stereochemistry of **1** was secured by transformation of the natural product, and hexaol diastereomers corresponding to **6** and **7**, to the per-benzoate ester derivatives, **18**, **19**, and **20**, respectively,¹² and comparison of their corresponding CD spectra (Figure 2). Since the fingerprint Cotton effects observed in the CD spectra of **18** and **19** were equal in magnitude but opposite in sign, the absolute configuration of **1** corresponds to *ent*-**19** and is related to *L*-ribose.¹² Thus, the complete configuration of sagittamide A (**1**) is depicted as (5*S*,6*S*,7*S*,8*R*,9*R*,10*S*).

In summary, we have deployed an integrated approach to solve the configuration of sagittamide A (**1**). The power of this triple-

combination of methodologies lies in judicious interpretation of homonuclear 3J and heteronuclear $^{2,3}J$ to provide *partial* stereochemical information which is then used to inform correct choices for synthesis of model compounds to be used in the next stage: ^{13}C NMR comparative analysis.

A significant advantage is gained by a requirement for only a limited subset of stereoisomers without the necessity for synthesis of all 64 possible permutations. The progressive-convergent approach succeeds where other singular methods based on NMR may become irreducibly complex¹³ or rendered equivocal by second-order effects that militate against reliable stereochemical assignments.

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Supporting Information Available: Preparation of *ribo*- and *xylo*-model model compounds, and their stereochemical assignments, $\Delta\delta$'s of *xylo*-models, ^1H , ^{13}C NMR, and MS spectral data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (6) The carbons numbered C7, C8, and C9 in **1** map to C4, C3, and C2 of ribose or xylose, respectively. Thus, the stereochemical descriptors '*xylo*' and '*ribo*' in the context of this work refer to C7–C9 of **1**.
- (7) The configuration of the major isomer was assigned by analogy with the well-known 1,2-*syn*-stereopreference for In^{p} -promoted allylation of aldohexoses [(a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Chem. Org.* **1993**, *58*, 5500–5507. (b) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256–2257] and subsequent conversion to the acetones **10** and **11**.
- (8) Deprotection of **10** and **11** to the corresponding primary alcohols was rapidly effected when $\text{CF}_3\text{CH}_2\text{OH}$ was used as solvent for hydrogenolysis. No reaction was observed in ethanol, even after several days at 3 atm H_2 .
- (9) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, (1), 26–28. Both **14** and **15** were prepared from δ -valerolactone in three and four steps, respectively (see SI).
- (10) Diastereomeric assignments of 5,6-diols were based on the expectation of anti-selectivity of OsO_4 addition to allylic alcohols and confirmed by the outcomes from double-diastereoselection using the Sharpless asymmetric dihydroxylation (Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–547) and observed pseudo- C_2 symmetry in the ^1H and ^{13}C NMR spectra of **2** and **8** (see SI).
- (11) This observation suggests caution in using *J*-based methodology and over-reliance on the underlying assumption of all-staggered conformations and the accuracy of *J*'s measured in strongly coupled contiguous polyols that may not be amenable to first-order spin analysis.
- (12) The lactam-mono methyl ester that formed spontaneously upon treatment of **1** (CH_2N_2 , MeOH-ether, ref 1) and the hexaols corresponding to **6** and **7** were each converted (excess BzCl , pyridine, 40 $^\circ\text{C}$) to hexabenzoylates **17**, **18**, and **19**, respectively, after HPLC purification. Benzoylation at higher temperatures (60–90 $^\circ\text{C}$) led to significant formation of tetrabenzoyloxy-tetrahydrofuran.
- (13) The similarity of CD spectra of diastereomeric **19** and **20** reflect the dominance of the C7–C10 configuration on the Cotton effects.
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