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

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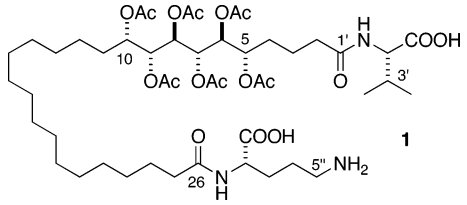
The structure of (−)-sagittamide A (**1**)[1], an unprecedented polyacetoxy, long-chain α,ω-dicarboxylic acid isolated from a tropical didemnid tunicate, was solved by application of conventional 2D NMR spectroscopic methods; however, only partial stereochemistry could be assigned. Although configurations 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 CH_2 groups[2] and equivocal interpretations of *J* coupling.



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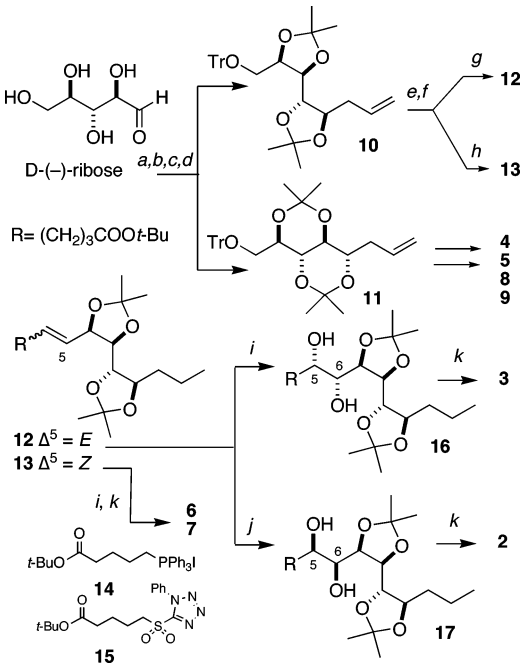
We now report the complete stereostructure of **1** using a *progressive−convergent* approach that integrates three powerful regimens for stereochemical analysis of natural products: use of Murata's *J*-based analysis ($^3J_{HH}$ and $^{2,3}J_{HC}$),[3] application of Kishi's universal database[4] (pairwise-comparison of ^{13}C 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 $^3J_{HH}$ 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 $^3J_{CH}$ 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[7] **10** and **11** after protection. Each acetonide was deprotected and hydrogenated (Pd/C, CF_3CH_2OH, 1 atm H_2)[8] followed by Swern oxidation to the corresponding C9 aldehydes and homologation using two stereocomplementary methods (*Z*-selective Wittig olefination using phosphonium salt **14** and *E*-selective Julia−Kocienski olefination with tetrazole **15**[9]) to give **12** and **13**.

Scheme 1[a]



[a] (a) In°, allyl bromide, H_2O; (b) TrCl, pyridine, reflux 53% (two steps); (c) CSA, acetone, $CH_3C(OCH_3)_2CH_3$ 58%, **10**/**11** dr 2:1); (d) SiO_2-HPLC 1:19 EtOAc/hexanes; (e) H_2, 1 atm, Pd/C, CF_3CH_2OH, 35−69%; (f) (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C (ii) Et_3N; (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) OsO_4, NMO, acetone, H_2O; dr 1.7:1, 93%; (j) $K_3Fe(CN)_6$, K_2OsO_4, K_2CO_3 $(DHQ)_2PHAL$, *t*-BuOH, H_2O, $CH_3SO_2NH_2$, dr 3.8:1, 86%; (k) 2% TMS−Cl, MeOH, (ii) CH_2N_2, ether/MeOH, (iii) Ac_2O, pyridine 6 h: 22% **3** (three steps), 48% **2** (three steps), 44% **6** (four steps), 26% **7** (four steps).

Stereoselective OsO_4 dihydroxylation[10] 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 ^{13}C NMR comparisons with the model compounds (Figure 1).[4]

The ^1H and ^{13}C NMR spectra of each peracetate model were carefully assigned from COSY and HMBC spectra. Pairwise comparisons of the differences of the ^{13}C 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 $^3J_{CH}$ values in **1** predicted

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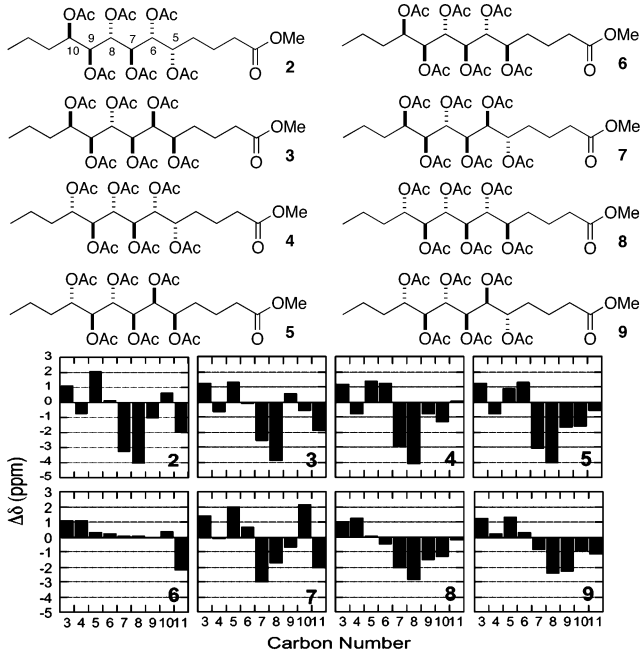

Figure 1. ^{13}C NMR (125 MHz, d_6-DMSO, T = 298 K) $\Delta\delta$ values (δ_C **1**$-\delta_C$ model) of ribo-model compounds **2**−**9**.

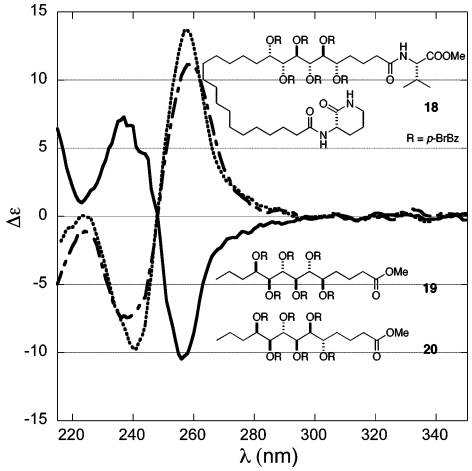

Figure 2. CD spectra of sagittamide A derivative **18** (—), together with models **19** (···) and **20** (- - -), (CH_3CN, c = 10 μM).

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 stereomodel compounds 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 complex[13] 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, ^{1}H, ^{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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(2) All attempts to convert **1** to a C1−O5 δ-lactone (potentially useful for stereochemical assignment) using acid catalysis were unsuccessful.
(3) Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876.
(4) (a) Kobayashi, Y.; Hayashi, N.; Kishi, Y. *Org Lett.* **2002**, *4*, 411−414. (b) Kobayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076−2078. (c) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177−2180.
(5) (a) Vazquez, J. T.; Wiesler, W. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1987**, *109*, 5586−5592. (b) Zhou, P.; Berova, N.; Nakanishi, K.; Knani, M.; Rohmer, M. *J. Am. Chem. Soc.* **1991**, *113*, 4040−4042. (c) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(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°-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 acetonides **10** and **11**.
(8) Deprotection of **10** and **11** to the corresponding primary alcohols was rapidly effected when CF_3CH_2OH 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 ^{1}H 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 °C) to hexabenzoates **17**, **18**, and **19**, respectively, after HPLC purification. Benzoylation at higher temperatures (60−90 °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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