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

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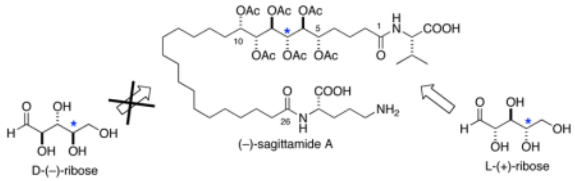
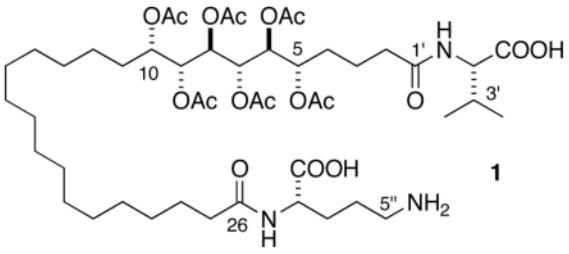
Abstract



The absolute stereostructure of sagittamide A (**1**), a O-hexacetyl long-chain hexahydroxy-α, ω-dicarboxylic acid, was assigned using a progressive-convergent approach that integrates three powerful regimens for stereochemical analysis of acyclic natural products: J-based analysis, ^{13}C NMR universal database comparisons and exciton coupling circular dichroism.

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 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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Supporting Information Available: Preparation of *ribo*- and *xylo*-model model compounds, and their stereochemical assignments, Δδ'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.

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 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 $^{3}J_{HH}$ and $^{2,3}J_{CH}$ values were obtained by 2D heteronuclear 2D NMR experiments of **1** (COSY and HSQMBC, respectively, see Supporting Information) 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 Supporting Information).[6] In order 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[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**.

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 (Supporting information). The correct relative configuration of **1** emerged from ^{13}C NMR comparisons with the model compounds (Figure 1).[4]

The ^{1}H 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 an mismatch for the corresponding *xylo*-C8 epimer (e.g. C8: $\Delta\delta$ = +0.05 and −3.93 ppm, respectively, see Supporting Information). A valuable object lesson is revealed here that promotes a progressive-convergent approach to stereochemistry. Although anomalous $^{3}J_{CH}$'s in **1** predicted 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 ^{3}J 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 sub-set of stereo-model 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Lievens SC, Molinski TF. Org Lett. 2005; 7(11):2281–2284. [PubMed: 15901189]
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. [PubMed: 11674159]
4. (a) Kobayashi Y, Hayashi N, Kishi Y. Org Lett. 2002; 4:411–414. [PubMed: 11820892] (b) Kobayashi Y, Tan CH, Kishi Y. J Am Chem Soc. 2001; 123:2076–2078. [PubMed: 11456839] (c) Kobayashi Y, Lee J, Tezuka K, Kishi Y. Org Lett. 1999; 1:2177–2180. [PubMed: 10836072]
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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°-promoted allylation of aldohexoses [Kim E, Gordon DM, Schmid W, Whitesides GM. J Chem Org. 1993; 58:5500–5507.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 PR, Cole WJ, Kocienski PJ, Morley A. Synlett. 1998; (1):26–28.Both **14** and **15** were prepared from δ-valerolactone in three and four steps, respectively (see Supporting Information).
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 HC, VanNieuwenhze MS, Sharpless KB. 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 Supporting Information.
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) lead 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.

14. Rychnovsky SD, Rogers B, Yang G. J Org Chem. 1993; 58:3511–3515.

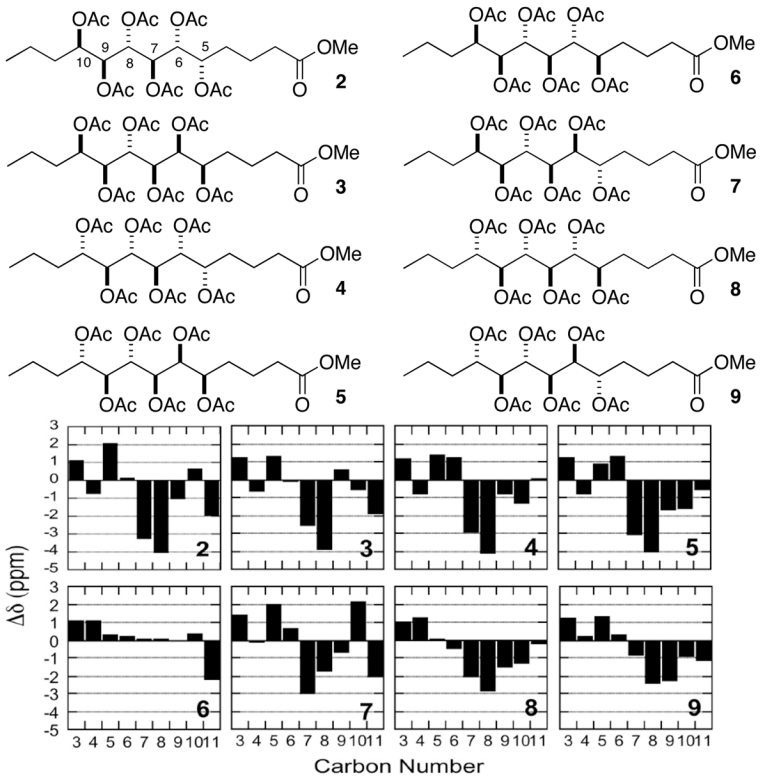


Figure 1.

^{13}C NMR (125MHz, d_6-DMSO, T=298 K) Δδ values (δ_C **1**– δ_C model) of ribo-model compounds **2**–**9**

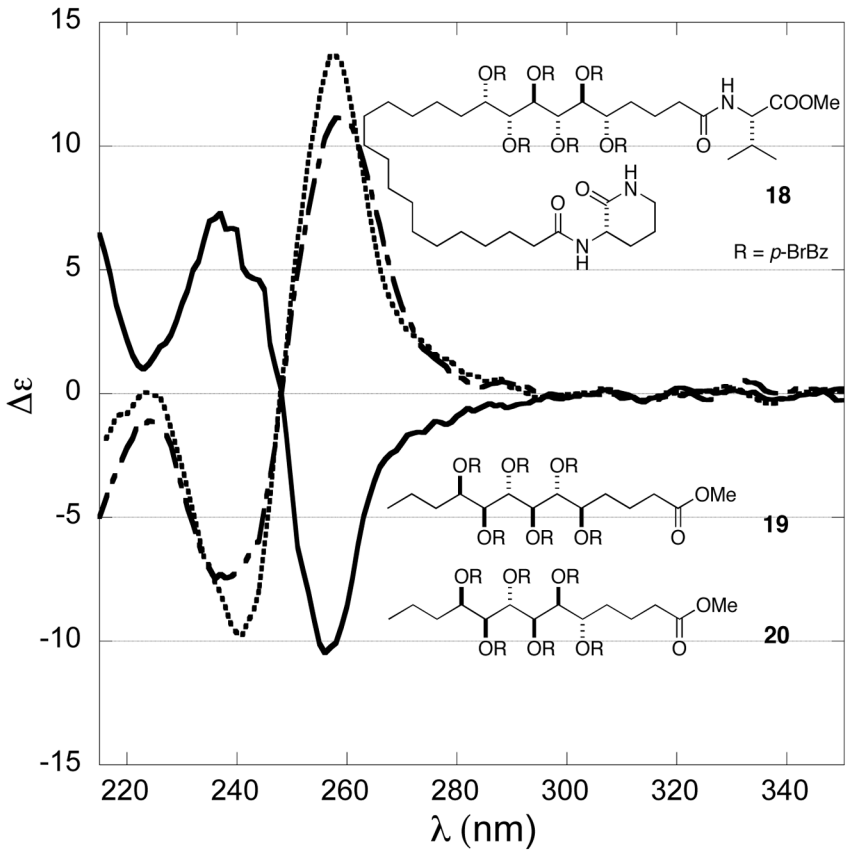
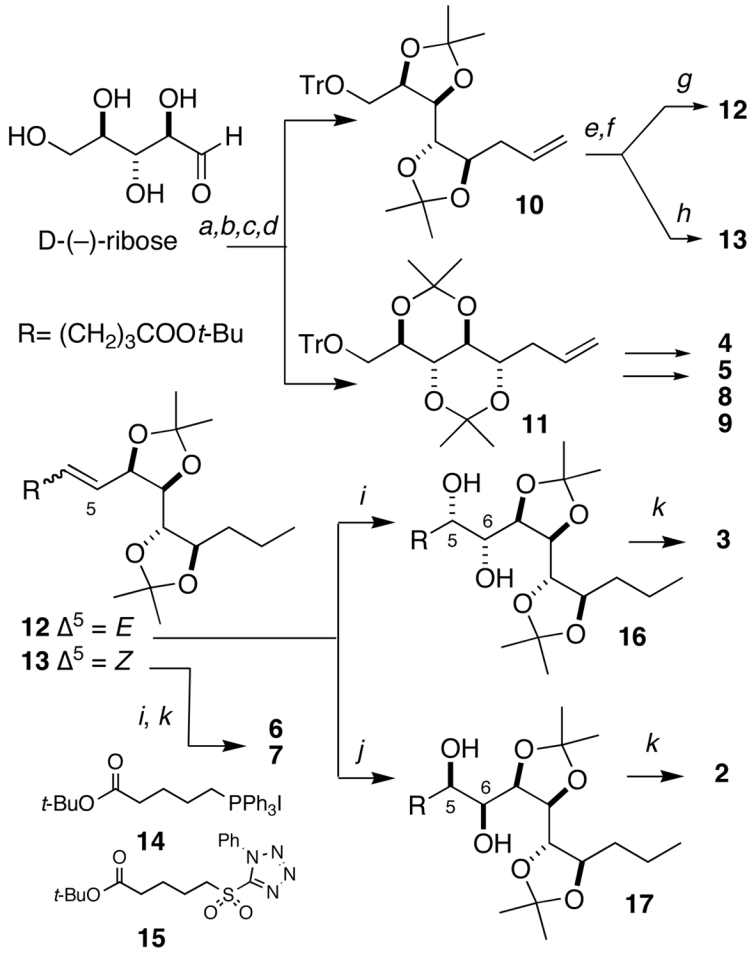


Figure 2.
CD spectra of sagittamide A derivative **18** (—), together with models **19** (…) and **20** (-– -), (CH_3CN, c=10 μM).



Scheme 1.

a) In°, allyl bromide, H_2O; b) TrCl, pyridine, reflux 53% (2 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 (2 steps); h) i. **14**, THF, NaHMDS, −78 °C, ii. aldehyde, dr>19:1,16% 2 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 6h: 22% **3** (3 steps), 48%; **2** (3 steps), 44%, **6** (4 steps), 26%, **7** (4 steps).