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Absolute Configuration of Staurosporine By X-Ray Analysis

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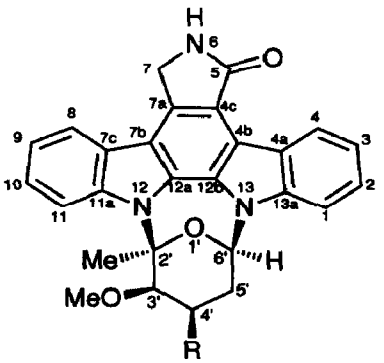
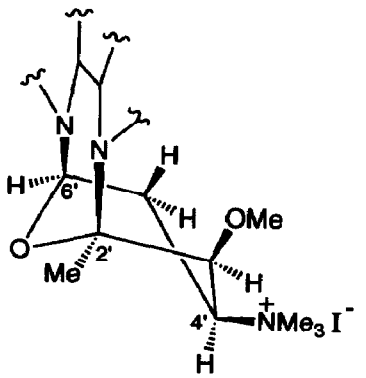
Abstract: The stereostructure of staurosporine (**1**) was determined absolutely to be 2'*S*, 3'*R*, 4'*R*, 6'*R*-configurations by means of X-ray crystallographic analysis of 4'-*N*-methylstaurosporine methiodide (**2**)

Staurosporine (**1**), isolated from Saccharothrix sp. AM-2282,[1] has very interesting biological activities such as antimicrobial,[1a] hypotensive,[2a] cell cytotoxic,[2b] inhibitor of protein kinase C,[2b] and platelet aggregation.[2c] Its attractive structure presents a challenging target of its total synthesis to many synthetic chemists.[3] But its absolute configuration remained unclarified, and only the relative stereochemistry have been elucidated by X-ray crystallographic analysis of its methanol solvate by us[5] and also by ^{1}H- and ^{13}C-NMR assignments using a combination of one- and two-dimensional NMR techniques, including HMQC and HMBC.[4] In our previous work[5], we could not obtain suitable crystals of staurosporine for determination of the absolute configuration.

Therefore it is very necessary to elucidate its absolute configuration. After various efforts, we were able to get good crystals of 4'-*N*-methylstaurosporine methiodide (**2**), which was prepared from **1** with methyl iodide in the presence of tributylamine in DMF at room temperature: colorless amorphous, mp 262°C (decomp.) (dioxane/H_2O), $[\alpha]_D^{24}$+45.7° (c=0.105, DMF), IR (KBr) ν 1645 cm^{-1}, MS *m/z* [M-I] 495, $[M+Na]^+$ 645 (for $C_{30}H_{31}N_4O_3I$ 622).

Compound **2** has a heavy atom in a molecule, and thereby we could solve the absolute configurations. Plate-like single crystals of **2** was obtained by slow evaporation of a saturated solution in a mixture of dioxane-water (1:1) at room temperature. By using direct methods, the crystal structure,[6] built up of one crystallographically independent molecule, was refined through full-matrix least-squares calculation to a final R factor of 0.066. The absolute configuration was determined through refinement of the inverted configuration (R=0.113).





1 R = –NHMe

2 R = $-N^{+}(Me)_3\ I^{-}$

3 R = $-N^{+}H_2Me\ Cl^{-}$

4

Scheme 1

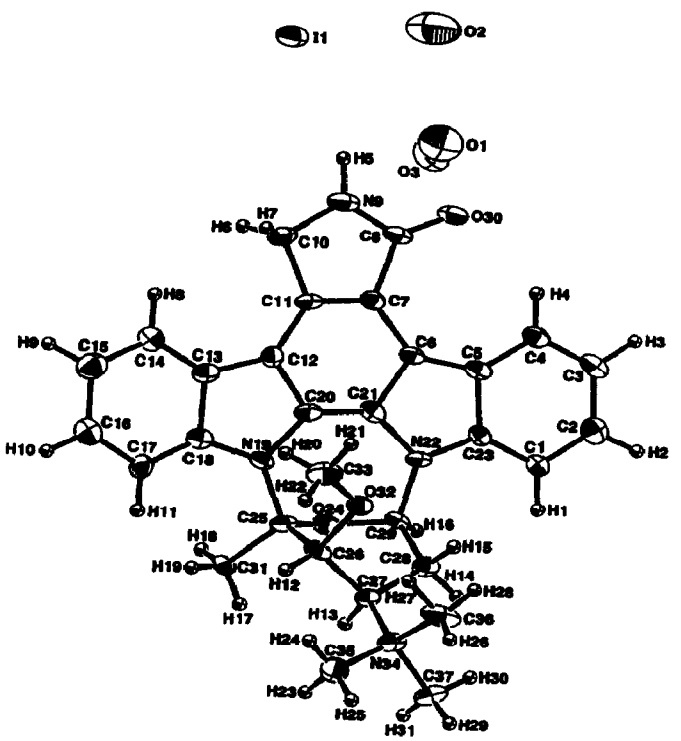
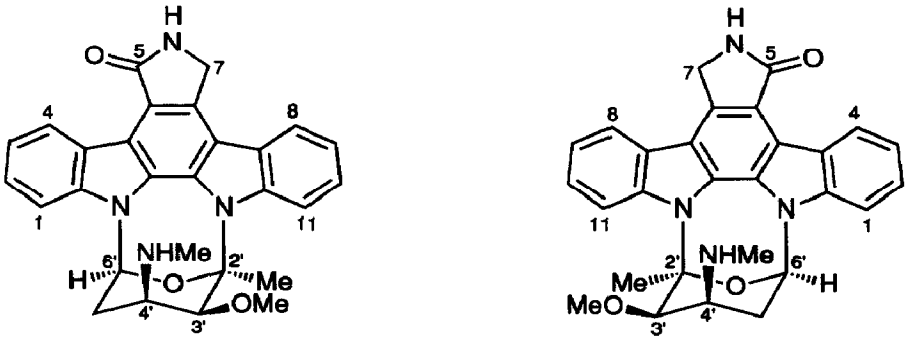


Fig. 1

From the result of the X-ray data for **2** (Fig. 1), the absolute stereostructure of **1** was confirmed to be the 2'*S*, 3'*R*, 4'*R*, 6'*R*-configurations, and the conformation of aminosugar moiety of **2** adopts boat form (**4**) in solid state. It is interesting that the conformation of aminosugar moiety of **2** and **3**,[7] both compounds have 4'-ammonium group, are same boat form in solid and in liquid state, respectively. It is noteworthy that the stereostructural notation for staurosporine which has been in common use hitherto should be revised as shown in Scheme 2 in line with the result obtained above.

The absolute configurations of four related compound of **1** have also been determined from the above result as follows, RK-286C,[8] 7-oxostaurosporine (RK-1409)[9] and 11-hydroxystaurosporine,[10] which are the same stereochemistry with **1**, have 2'*S*, 3'*R*, 4'*R*, 6'*R*-configurations, whereas RK-1409B,[11] 3'-epimer of RK-286C, has 2'*S*, 3'*S*, 4'*R*, 6'*R*-configurations.



Scheme 2

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6. Crystal data were : **2**, $C_{30}H_{31}N_4O_3I \cdot 3H_2O$, Monoclinic, $P2_1$ (No. 4), Z=2; a=13.740 (3), b=7.150 (2), c=15.626 (1)Å, β=106.601 (9)°, V=1471.2 (4)Å^3, D_c=1.527 g • cm^{-3}, μ (CuKα)=90.31 cm^{-1}. Intensity data were collected at room temperature with graphite monochromated Cu-Kα radiation (λ=1.54178Å) on a Rigaku AFC-5R diffractometer; $2\theta_{max}$ =140.3°. Of 6112 measured reflections, 5371 had I>3σ (I), and 4153, including Bijvoet pairs, were independent and were used in the structure analysis. The structure was solved by direct methods and refined to R=0.066 and Rw=0.069 using the TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985). Hydrogen atoms were incorporated at fixed positions with C-H=1.0Å. The absolute configuration was confirmed by refining the inverted configuration which converged to a higher residual of 0.113 (0.128). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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