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STEREOCHEMICAL STUDIES ON ESPERAMICIN A_1: A SINGLE CRYSTAL X-RAY STRUCTURE OF THIOSUGAR MOIETY

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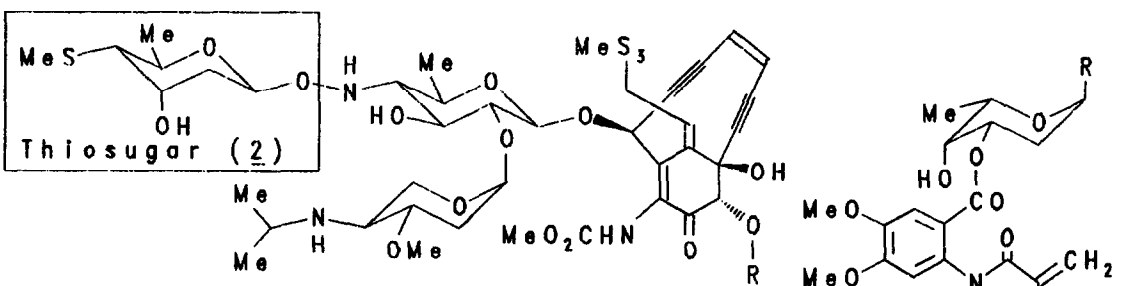
Abstract: A single crystal x-ray diffraction study revealed a β-D-configuration for the 2,4,6-trideoxy - 4 - thiomethyl - ribo - hexopyranose fragment of esperamicin A_1.

The unique structure of enediyne antibiotics,[1] their extreme potency and novel mechanism of cutting DNA have elicited considerable attention among synthetic chemists and biochemists. Esperamicin A_1[2] (1), now in phase I clinical trials, is a member of this class. The subject of this report, the esperamicin methylthiosugar 2, presumably serves as a DNA recognition marker. Hence, the assignment of its absolute configuration is essential for better understanding its role in the interaction of esperamicin A_1 with DNA at the molecular level.

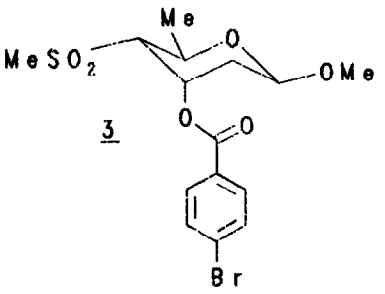


Esperamicin A_1: 1

Previously we had determined the relative configuration of 2 based on ^{1}H-NMR data of esperamicin A_1 and its methanolysis products.[2] The thiol analogue of methylthiosugar has been identified in calicheamicins [3] and recently synthesized by Scharf. [4] More recently, a synthetic route to 2 has been reported in a collaborative study with the Danishefsky group.[5] In order to elucidate its absolute configuration the anomeric mixture of methyl glycosides of 2 (α:β ratio ca. 1:1) obtained by methanoysis of 1 was oxidized with m-chloroperoxybenzoic acid (m-CPBA) in methylene chloride. The resultant sulfones were acylated with p-bromobenzoyl chloride in pyridine at 50°C affording an anomeric mixture of 3-p-bromobenzoate derivatives which were suitable for preparative TLC separation and crystallization.

The β-anomer (3) has been selected for x-ray study. Crystals of 3 grown from ethyl acetate are monoclinic, space group

$P2_1$, with two molecules per unit cell. The structure was solved routinely using direct and heavy atom methods. [6] Full matrix refinement using 2245 unique reflections with $|F_o|>3\sigma$ (F^2) including Freidel pairs gave conventional crystallographic residuals R=0.032, R_w=0.047 for one enantioner and R=0.043, R_w=0.051 for the other. The first enantiomer was chosen as the correct one by Hamilton's significance test at the 0.01 level. A computer generated drawing of the x-ray model is given below, showing the D configuration for the thiosugar.



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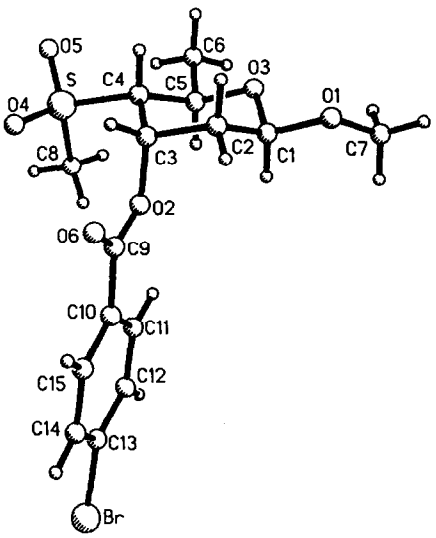

References and Footnotes

1. Enediyne antibiotics, represented by esperamicins, calicheamicins, neocarzinostatin and dynemycins, a novel class of extremely potent cytotoxic natural products are characterized by the presence of enediyne conjugated chromophore which is able to undergo aromatization via bis radical intermediate under physiological conditions. Long, B.H.; Golik, J.; Forenza S.; Dabrowiak, J.C.; Catino, J.J.; Misial, S.T.; Brookshire, K.W.; Doyle, T.W.: Proc. Nat'l. Acad. Sci. USA, 1989, 86, 2.
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