Tetrahedron Letters, Vol. 33, No. 41, pp. 6049-6052, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Stereochemical Studies on Esperamicins: The Absolute Configuration of Their Bicyclic Aglycone

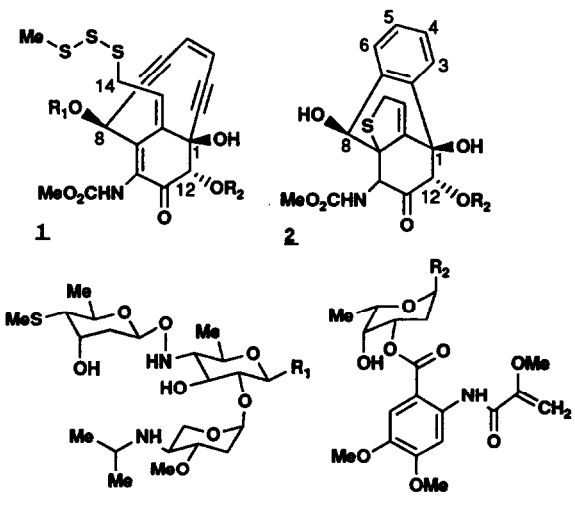
Jerzy Golik*, Bala Krishnan and Terrence W. Doyle
Bristol-Myers Squibb Research Institute, 5 research Parkway, P.O. Box 5100, Wallingford, Connecticut 06492-7660

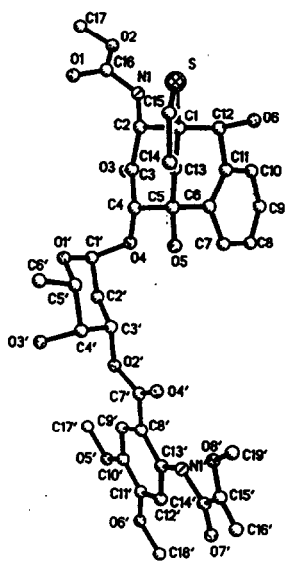
Gregory VanDuyne and Jon Clardy
Cornell University, Department of Chemistry, Baker Laboratory, Ithaca, New York 14853-1301

Abstract: Single crystal x-ray diffraction analyses revealed the relative configuration of esperamicin X and the absolute configuration of 2-deoxy fucose, a fragment present in all known esperamicins. Comparison of the CD curves for esperamicins X and Z gave evidence for their identical chirality. Based on these data the absolute stereochemistry of [7,3,1] bicyclic aglycone of esperamicins has been assigned as C-1 (*S*), C-8 (*S*). and C-12 (*S*).

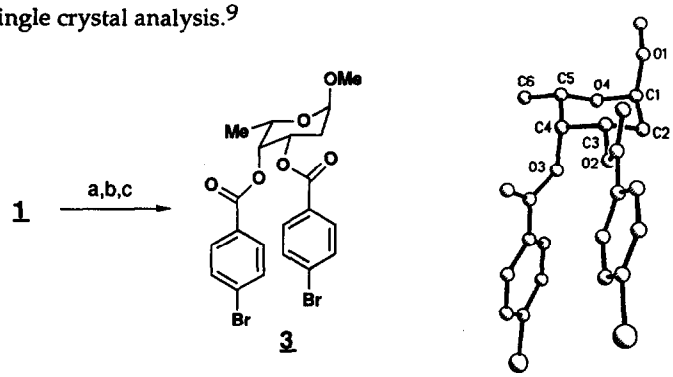
In a series of previously published papers we have presented our studies on the determination of the absolute configuration of the carbohydrate fragments of the esperamicins.[1-6] Here we report the elucidation of the absolute stereochemistry of their highly strained 3-ene-1,5-diyne [7,3,1] bicyclic aglycone.

Our extensive efforts to determine the absolute stereochemistry of esperamicins A_1 (**1**) and A_{1b} by single crystal x-ray diffraction were unsuccessful. Although crystals of esperamicin A_2 were obtained, they failed to diffract x-rays. In contrast, crystals of esperamicin X (**2**) suitable for single crystal x-ray analysis were obtained.[7] Solution of the data set revealed the relative stereochemistry of esperamicin X as shown below in the ORTEP drawing.[8]



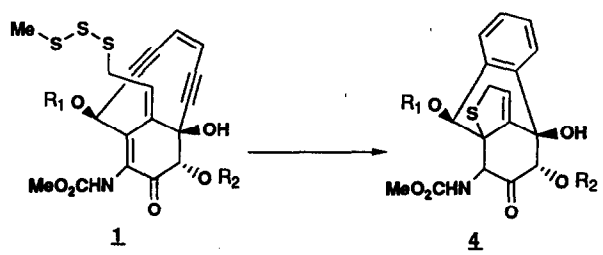


The absolute configuration of esperamicin X was established through determination of the configuration of the 2-deoxyfucoside fragment as L. The α-methyl glycoside of this deoxysugar was obtained upon methanolysis (a. 0.5 M HCl-MeOH) of 2 followed by basic hydrolysis (b. 0.05 M KOH-MeOH). This was then converted to its 3,4-di-p-bromobenzoate derivative (c. p-BrBzCl/Py/DMAP), crystallized, and subjected to a single crystal analysis.[9]

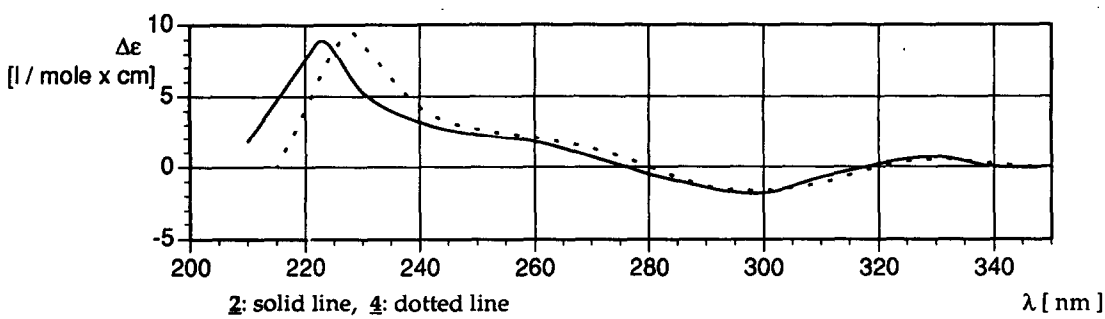


From the data available on the relative configuration of the sugar and the aglycone in 2, the absolute configuration of the aglycone could be assigned as S at C1, C8, and C12.

The correlation of the absolute configuration of esperamicin X (2) and esperamicin A_1 (1) was accomplished as follows. Teatment of 1 under reductive conditions (PPh_3-C_6H_8/ CH_2Cl_2: MeOH) gave esperamicin Z (4) in good yield.[10]



In order to show that the stereochemical assignments made for esperamicin X are also correct for the other members of esperamicin class, we compared the CD spectra of esperamicins X and Z.[11]



Almost identical values of their molar circular dichchroism ($\Delta\varepsilon$) indicated that the chiral centers around the chromophores present in the core of esperamicins X and Z are the same. This assignment concludes our study on stereochemistry of esperamicins.

References and Notes

1. Konishi,M.; Ohkuma, H.; Saitoh, K.; Golik, J.; Dubay G.; Groenewold, G.; Krishnan, B.; Doyle, T. W.: J. Antibiotics 1985, 38, 1605.

2. Golik, J.; Clardy, J.; Dubay G.; Groenewold, G.; , H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh,; Doyle, T.W.: J. Am. Chem. Soc. 1987, 109, 3461.

3. Golik, J.; Dubay G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh,; Doyle, T.W.: J. Am. Chem. Soc. 1987, 109, 3462.

4. Golik, J.; Wong, H,; Vyas, D.M.; Doyle, T.W.: Tetrahedron Lett. 1989, 30, 2497.

5. Golik, J.; Doyle, T.W.; VanDuyne, G.; Clardy, J.: Tetrahedron Lett.: 1990, 43, 6149.

6. Golik, J.; Wong, H.; Krishnan, B.; Vyas, D.M.; Doyle, T.W.: Tetrahedron Lett.: 1991, 32, 1851.

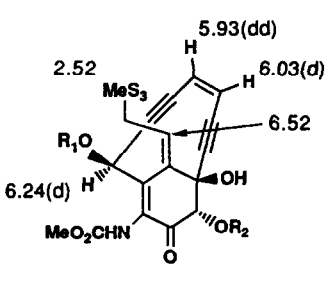
7. Crystal data for 2, ($C_{36}H_{40}N_2O_{14}S$): 0.8x0.5x0.1 mm crystals, grown from aquous acetonitrile, mounted with mother liquor in a thin walled glass capillary, monoclinic, space group $2P_1$, four molecules in the unit cell, a=18.050(2) Å, b=13.862(4) Å, c=20.971(4) Å, β=112.49(2)°. A total 10079 diffraction maxima were measured at room temperature with a Syntex 2P1 diffractometer using graphite monochromated CuKa x-ray and 1° variable speed ω scans for $0<2\Theta\leq114°$ of which 4735 were unique (Rmerge=0.069). The structure was solved by multisolution direct methods using starting sets of tangent refined reflections from the ggg parity group and phases for the rest [SHELXS-86 and SHELXTL-PLUS crystallographic programs written by G. Sheldrick, University of Getingen were used]. The structure was refined with blocked full-matrix least squares with one molecule per block, non-hydrogen thermal parameters and fixed hydrogen atoms. Least squares refinement with 3194 reflections with $|F|>3s(F)$ and $\sin\Theta/l>0.16$ gave conventional crystalographic residuals of R=0.101 and Rw=0.111. The absolute configuration was not determined by the x-ray analysis but was chosen to agree with subsequently elucidated 2-deoxy-α-L-fucose fragment.

8. The numbering system depicted in this ORTEP drawing of esperamicin X is that used for the x-ray analysis. It is inconsistent with that we have accepted for the structural study.

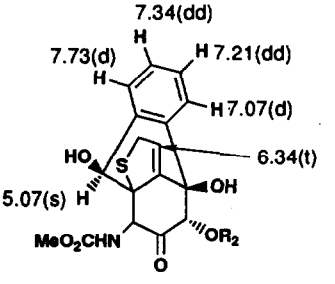
9. Crystal data for 3, $C_{21}H_{20}Br_2O_6$: 0.05x0.2x0.6 mm crystal, grown from ethyl acetate, triclinic, a=7.520(2) Å, b=12.395(5) Å, c=23.337(5) Å, b=12.395(5) Å, c=23.337(5) Å, α=91.56(1)°, β=91.46(1)°, γ=93.75(1)°, space group P1 with the four molecules in the unit cell. A total 8927 unique diffraction maxima were measured with a Nicolet R3m/V diffractometer using graphite monochromated CuKα x-ray and 1° variable speed 2Θ-Θ scans for $0<2\Theta\leq100°$. A total 7810 reflections were judged, $|F|\geq4s(F)$. The eight bromine atoms were located using direct methods and the light atoms were located after several cycles of tangent formula and then Fourier recycling. The

structure was refined with blocked full-matrix least squares with one molecule per block, non-hydrogen atoms with anisotropic thermal parameters and fixed hydrogen atoms to final agreement indices of R=0.056, R_W=0.079 for one enantiomer and R=0.063, R_W=0.086 for the other [SHELXS-86 and SHELXTL-PLUS crystallographic programs written by G. Sheldrick, University of Goettingen were used]. The first enantiomer was chosen as the correct one by Hamiltonian significance test [Hamilton, W.C. Acta Cryst 1965, 18, 502] at the 0.01 level. Refinement of the coefficient of Δf'' with the correct enantiomer gave h=0.95(4) [Rogers, D. Acta Cryct 1981, A37,734].

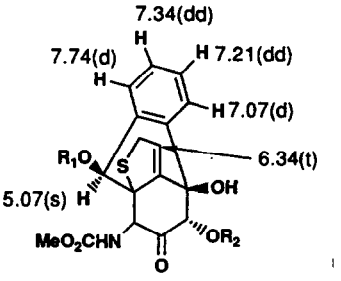
10. The structures of esperamicins A_1 (1), X (2), and Z (4) were examined by NMR. The following diagnostic ^1H NMR resonances reveal differences between esperamicin A_1, X, and Z. Chemical shifts in the core of 2 and 4 are identical.



1



2



4

11. The CD measurements were performed in methanol using a Jasco 500A spectropolarimeter. Diagnostic Cotton effects at λ = 330nm, Δε = + 0.53 l/mole x cm and at λ = 300 nm, Δε = - 1.6 l/mole x cm can be attributed to n - π^* and π - π^* transitions of the carbonyl group and isolated double bond in dihydrothiophene ring, respectively.

(Received in USA 16 June 1992; accepted 16 July 1992)