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Stereochemical Studies on Esperamicins: Determination of the Absolute Configuration of Hydroxyamino Sugar Fragment.

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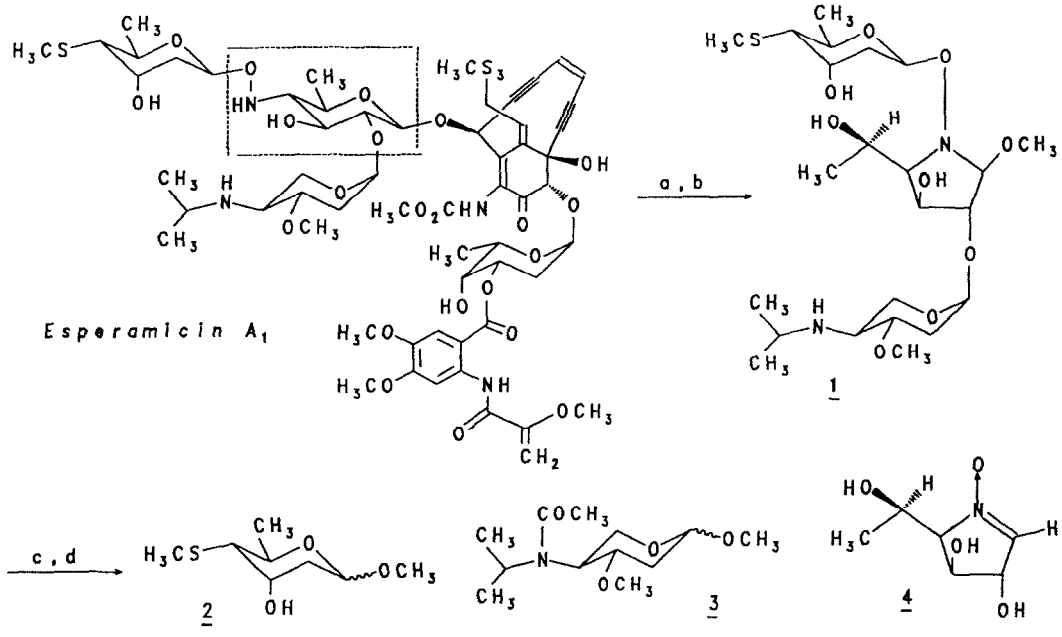
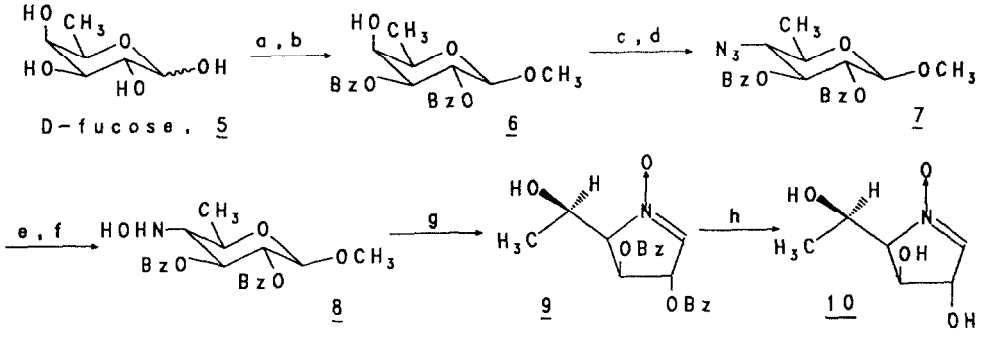
Abstract: The ß-D-gluco-hexopyranose configuration has been assigned for the hydroxyamino sugar fragment of esperamicin A[1]. This determination concluded our study on the absolute configuration of the carbohydrate portion of esperamicins.

Since our first report on the structure elucidation of esperamicins A_1, A_2 and A_{1b} in 1987[1] we have focused our efforts on determination of their absolute configuration. In the course of these studies, involving chemical degradations, spectroscopy and x-ray methods, we have established the L configuration for the 2-deoxyfucose[2], the L configuration for the isopropylamino sugar[3] and the D configuration for the thiosugar[4]. These monosaccharides were isolated during degradative methanolysis of esperamicin A_1. Surprisingly, the hydroxyamino sugar attached at the propargylic position of the bicyclic core resisted extreme glycolytic scission reactions. A disconnection at this glycosidic bond of esperamicin A_1 has been accomplished under basic reductive conditions with sodium borohydride in ethanol.The resulting trisaccharide upon treatment with 5% acetic acid in methanol yielded its methyl glycoside **1**, which has been isolated and characterized by spectroscopy[5]. The assignment of proton NMR coupling constant data for **1** indicates that the hexopyranose ring of the hydroxyamino sugar had rearranged to its N-hexofuranose form. The N-acetylation of **1** with acetic anhydride in methylene chloride in the presence of dimethylaminopyridine and subsequent mild methanolysis with 0.5M hydrochloride in methanol at room temperature afforded a mixture of previously characterized methyl glycosides **2** and **3** in addition to a novel nitrone **4**.



a: $NaBH_4$/EtOH, b: MeOH/AcOH, c: Ac_2O/DMAP/CH_2Cl_2, d: 0.5M HCl/MeOH.

Since the configuration of four asymmetric centers in the hydroxyamino sugar remains unchanged during the ring rearrangement and elimination reactions depicted on the scheme above, the nitrone **4** was valuable for configurational assignment. Due to difficulties in preparation of x-ray quality crystals of the natural nitrone, we synthesized both enantiomers of **4** starting from commercially available D- and L-fucose. This synthesis in the case of D-fucose was accomplished via the following reaction sequence:



a: 0.5M HCl/MeOH, (90%); b: 2eq.BrBzCl/Py, (61%); c: Tf_2O/Py, (quant.); d: $(Bu_4N)N_3$/MeCN, (91%); e: H_2-10%Pd/C, (50%); f: Me_2CO_2/Me_2CO, (14%)[6]; g: 0.1M BCl_3/CH_2Cl_2, (quant.); h: NaOMe/MeOH, (quant.).

As shown above, D-fucose **5** was glycosylated and then selectively benzoylated at the equatorial positions. Subsequent acylation of the axial hydroxyl in **6** with triflic anhydride was followed by transformation of the triflate into equatorial azide **7** with tetrabutylammonium azide under Mitsunobu reaction conditions. Hydrogenation of the azide **7** over 10% palladium on charcoal afforded the 4-amino glycoside which was submitted to oxidation with dimethyldioxirane in acetone at -78°C yielding the 4-hydroxyamino glycoside **8**. Formation of the dibenzoate nitrone **9** occurred spontaneously during demethylation of **8** with 0.1 M boron trichloride in methylene chloride at -78°C. Finally, deprotection of dibenzoate nitrone **9** with sodium methoxide in methanol yielded the desired nitrone **10**. An identical synthetic procedure was applied to L-fucose in order to provide the antipodal nitrone **11**.

Both synthetic epimers and the product derived from esperamicin A_1 exhibit identical UV, IR, MS and NMR data[7], however, the CD spectra of synthetic antipodes show opposite Cotton effects at λmax=271nm. A CD spectrum of the natural nitrone **4** is superimposable with that of 10, which is derived from D-fucose, while the nitrone **11** exhibits the opposite Cotton effect. Thus, the D-gluco configuration for the hydroxyamino sugar has been established.

References and Footnotes

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2. Konishi, M.; Ohkuma, H.; Saitoh, K,; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T.W.: J. Antibiotics 1985, 38, 1605.
3. Golik, J.;Wong, H.; Vyas, D.M.; Doyle, T.W.: Tetrahedron Lett. 1989, 30, 2497.
4. Golik, J.; Doyle, T.W.; Van Duyne, G.; Clardy, J.: Tetrahedron Lett. 1990, 43, 6149.
5. The following spectroscopic data characterize compound **1**: MS: FAB, p-nitrobenzil alcohol, $[MH]^+$, m/z 525, fragment ions m/z 493, 333, 190, 172 161 and 140; NMR: ^1H, 500MHz, $CDCl_3$, 5.27 (1H, dd, J=8.5Hz), 5.00 (1H, dd), 4.89 (1H, brs, exch), 4.51 (1H, brs, exch), 4.40 (1H, d, J=1.7Hz), 4.25 (1H, dq), 4.10 (1H, d), 3.98 (1H, d, J=4.1Hz), 3.88

(1H, d, J=2.6Hz), 3.84 (1H, dq, J=6.2, 4.4Hz), 3.72 (1H, dd, J=11.2, 4.5Hz), 3.47(3H, s) overlap (1H, m), 3.38 (1H, ddd), 3.32 (3H, s), 2.83 (1H, m), 2.82 (1H, dd), 2.71 (1H, ddd), 2.48 (1H, dd, J=10.6, 2.4Hz), 2.21 (1H, ddd, J=13.2Hz), 2.10 (1H, m) overlap (3H, s), 1.58-1.49 (2H, m), 1.36 (3H, d, J=6.2Hz) overlap (3H, d, J=6.5Hz), 1.06 (3H, d, 6.1Hz), 1.05 (3H, d, J=6.3Hz). The coupling constans smaller than 1.7Hz are omitted. ^{13}C, 125MHz, $CDCl_3$, 104.0, 100.0, 97.2, 96.1, 82.6, 76.9, 72.7, 69.3, 67.6, 64.5, 64.4, 63.2, 56.1, 55.7, 55.6, 46.7, 35.4, 34.0, 24.4, 22.7, 19.8, 17.1, 13.8 ppm.

6. A low yield of this step is attributed to overoxidation of the secondary amino group to the respective oxime. Since quantities of **8** were sufficient for our further study we did not optimize reaction conditions. For the oxidation procedure see: Wittman, M.D., Halcomb, R.L., Danishefsky, S.J.: J. Org. Chem. 1990, 55,1981.

7. The following spectroscopic data characterize compounds **4**, **10** and **11** : MS: DCI-isobutane, $[MH]^+$, m/z 162; HR-MS (FAB, CsI/Glycerol) 162.0768 $C_6H_{12}NO_4$ (calc. 162.0766); UV: MeOH, λmax=238nm,ε=5530; CD: MeOH, λmax=271nm, $\Delta\epsilon_{271}$=+0.2 for **4** and **10**, $\Delta\epsilon_{271}$=-0.2 for **11**; IR: KBr, pellet, ν_{max}: 3528, 3422, 3086, 2992, 2926, 2350, 2282, 1614, 1464, 1406, 1384, 1352, 1306, 1272, 1250, 1238, 1206, 1146, 1112, 1098, 1066, 1034, 1020, 958, 920, 904, 858, 806, 774, 690, 624, 550, 536, 518, 478cm^{-1}; NMR: ^1H, 500MHz, CD_3OD, 7.13 (1H,dd,J=1.8, 1.8Hz, H-1); 4.72 (1H,dd,J=3.8, 1.8Hz, H-2);4.47 (1H,dd,J=7.3, 3.8Hz, H-3); 4.42 (1H,dq,J=6.9, 2.4Hz, H-5); 4.02, (1H,dd,J=7.3, 3.8Hz, H-4); 1.43 (3H,d,J=6.9Hz, H-6); ^{13}C, 125MHz, CD_3OD, 140.2, 79.2, 79.1, 77.9, 67.0, 20.2 ppm.

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