Tetrahedron Letters,Vol.30,No.19,pp 2497-2500,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

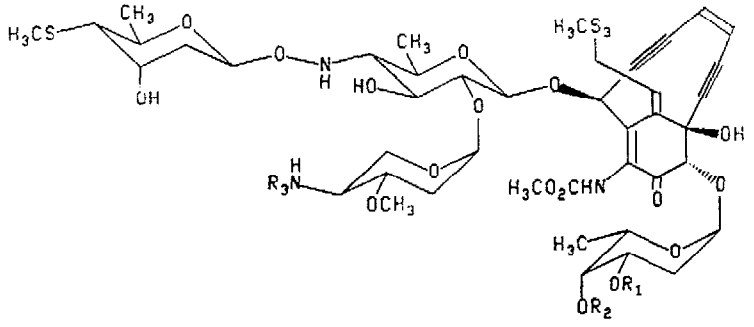
STEREOCHEMICAL STUDIES ON ESPERAMICINS: DETERMINATION OF THE ABSOLUTE CONFIGURATION OF ISOPROPYLAMINO SUGAR MOIETY

J. Golik*, H. Wong, D.M. Vyas, T.W. Doyle

Bristol-Myers Company, Pharmaceutical Research And Development Division
5 Research Parkway, P.O. Box 5100
Wallingford, Connecticut 06492

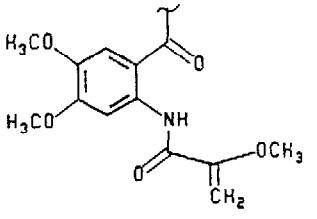
Abstract: The absolute stereochmistry of the isopropylamino sugar moiety of esperamicin A_1 was determined as the α-L-threo-pentopyranosyl by comparing the CD spectra of derivatized methanolysis product 4 with those of two synthesized antipodal glycosides 9 and 11.

The extreme potency of antitumor antibiotics esperamicins[1] produced by Actinomadura verrucosospora is imparted by the unique architecture of carbohydrate side chains. In particular, the stereochemical and functional features of the carbohydrate framework determine their DNA binding affinity [2,3]. Consequently, detailed stereochemical knowledge about the trisaccharide unit of esperamicin A_1 (1) is paramount in understanding the mechanisms of its interaction with DNA.



	R_1	R_2	R_3
Esperamicin A_1 (1):	R	H	$CH(CH_3)_2$
Esperamicin A_2:	H	R	$CH(CH_3)_2$
Esperamicin A_{1b}:	R	H	CH_2CH_3

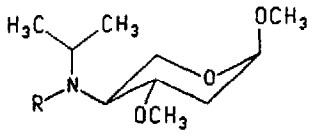
R:

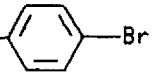


In our earlier studies on the esperamicins A_1, A_2 and A_{1b} structures[4] we had established the relative stereochemistry of the [7,3,1] bicyclic core containing the 1,5 diyne-3-ene system based on the x-ray diffraction data of the esperamicin X fragment[5]. The absolute stereochmistry of the fucosyl residue carrying the anthranilate moiety was also determined by CD spectropolarimetry[6]. The reported gross structure, depicting the relative stereochemistry of the bicyclic core and the

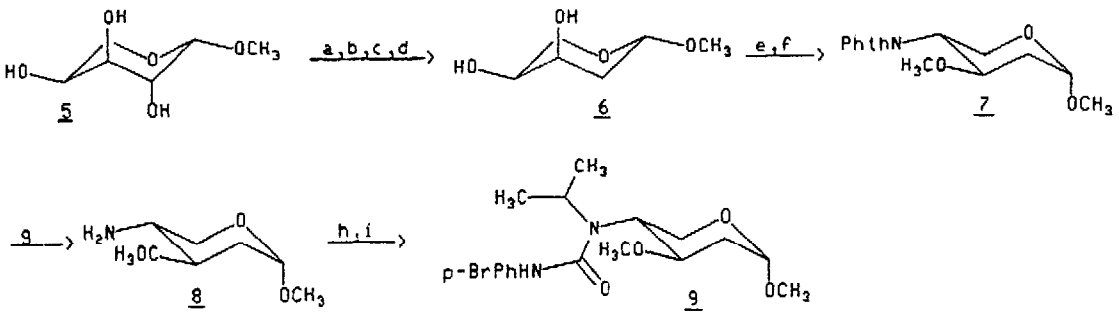
carbohydrate subunits, were assigned on the basis of the ^1H NMR coupling constants. However, the absolute stereochemistry assignment still remained to be established.

In this paper we report the absolute configuration of the isopropylamino sugar[7], a subunit of the trisaccharide of esperamicin A_1. Previous methanolytic degradation studies on N-acetyl-esperamicin A_1 led to the isolation of α and β methyl glycosides of 4-(N-isopropyl-N-acetyl)-2,4-dideoxy-3-O-methyl-threo-pentopyranoside 2. In the present investigation esperamicin A_1 was methanolized with 2M HCl yielding the isopropylamino glycoside 3. For the purpose of obtaining crystals suitable for x-ray



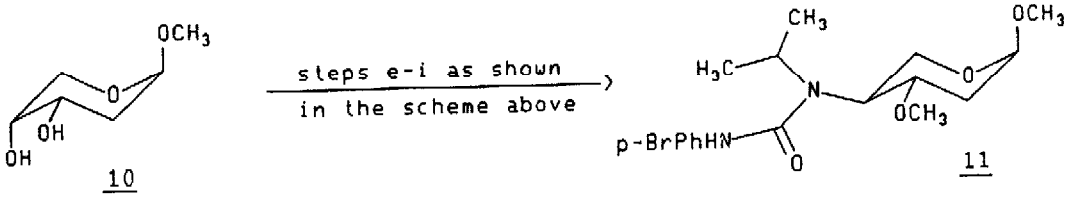
2: R=$COCH_3$
3: R=H
4: R=CONH—  —Br

and a chromophoric derivative acceptable for CD spectropolarimetry 3 was further derivatized to the urea 4 with p-bromophenylisocyanate. Since the poor crystal quality of 4 precluded any x-ray studies we decided to synthesize both D and L antipodes of 4 starting from naturally occuring monosaccharides for spectroscopic comparison. Thus the synthesis of the D-antipode (9) was accomplished from the readily available 1-O-methyl-β-L(+)arabinoside 5 via a known synthetic sequence leading to the 2-deoxy glycoside 6. Partial 3-O-methylation of 6 followed by a subsequent phthalimidation under Mitsunobu reaction conditions yielded 7. Hydrazinolysis of 7 afforded the 4-aminoglycoside 8. This was subjected to a reductive amination reaction yielding the 4-N-isopropylamino glycoside and followed by derivatization with p-bromophenylisocyanate to the urea derivatives 9.



a: 2,2 dimethoxypropane, (80%); b: CS_2, CH_3I, rt., (70%); c: Bu_3SnH, PhH, reflux, (69%); d: HCl, (50%); e: CH_3I, Ag_2O, acetone, rt., (36%); f: phthalimide, Ph_3P, diethyl azodicarboxylate (36%), g: N_2H_4, EtOH, rt., (36%) h: $NaBH_3CN$, acetone, iPrOH, (43%); i: p-BrPhNCO, pyridine, 50°, (51%).

Synthesis of the L-antipode (11) was accomplished from methyl 2-deoxy-α-(D)-ribo-pyranoside 10 in a similar fashion to that described above.



Both synthetic epimers 9 and 11 and the naturally derived product 4 exhibit identical UV, IR, MS, ^{1}H and ^{13}C NMR data[8]. However, the CD spectra (Figure 1) of D and L antipodes show opposite sign of the Cotton effects at λmax=250nm (Δε=±5.7). The CD curve of the natural product 4 is superimposable with that of the L-antipode 11 when measured at the equal concentration and thus its configuration is established to be α-L-threo-pentopyranoside.

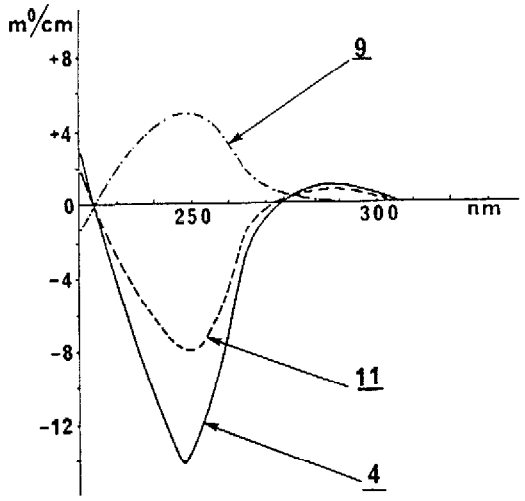


Figure 1. CD spectra of 4, 9, and 11 in MeOH. Sensitivity scale: 2m°/cm; sample concentration - 4:c=0.03 g/L, 9: c=0.018 g/L, 11: c=0.008 g/L.

Further structural studies on the determination of the absolute configuration of the bicyclic core, thiomethyl sugar and hydroxylamino sugar of esperamicin A_1 are ongoing in our laboratory.

References and Footnotes

1. Konishi, M; Saitoh, K.; Ohkuma, H.; Kawaguchi, H.: Japan Kokai 84-232094, Dec. 26, 1984.
2. Long, B.; Golik, J.; Forenza, S.; Dabrowiak, J.C.; Catino, J.J.; Musial, S.T.; Brookshire, K.W.; Doyle, T.W., Proc. Nat'l. Acad. Sci. USA, 1989, 86, 2.

3. Sugiura, Y.; Uesawa, Y.; Takahashi, Y.; Kuwahara, J.; Golik, J.; Doyle, T.W.: Proc. Nat'l. Acad. Sci. USA, 1989 (in press).

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

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

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

7. An identical sugar is present in esperamicin A_2. Its N-ethyl analogs were identified in esperamicin A_{1b} and calicheamicin $\gamma_{1\alpha}$ see: Lee, M.D.; Dunne, T.S.; chang, C.C.; Ellestad, G.A.; Siegel, M.M.; Morton, G.O.; McGahren, W.J.; Borders, D.B.: J. Am. Chem. Soc. 1987, 109, 3466.
Also the N-methyl homolog is present in FR900406 on the basis of its spectral data, see: Kiyoto, S.; Nishikawa, M.; Terano, H.; Koshaka, M.; Aoki, H.; Imanaka, H.; Kawai, Y.; Uchida, I.; Hashimoto, M.: J. Antibiotics 1985, 38, 840.

8. The following spectroscopic data characterize compounds 4, 9, and 11: HR-MS (FAB, CsI/Glycerol) 401.1076 $C_{17}H_{26}N_2O_4Br$ (calc. 401.1062); UV (MeOH), λmax-244nm, ε=15,000; IR(KBr,film) λmax: 3746, 3677, 3334, 3112, 2967, 2934, 2901, 2832, 2248, 1657, 1642, 1590, 1522, 1491, 1445, 1422, 1393, 1378, 1358, 1316, 1288, 1243, 1217, 1200, 1179, 1142, 1128, 1098, 1075, 1052, 1007, 994, 960, 915, 902, 823, 736, 702, 689 cm^{-1}. H^1-NMR (300 MHz, $CDCl_3$): 7.47 (1H,brs); 7.32 (2H,d,9.0Hz); 7.12 (2H,d,9.0Hz); 4.78 (1H,6rd,2.4Hz); 3.88-3.68 (4H,overlapping multiplets); 3.43 (1H,m); 3.39 (3H,s); 3.34 (3H,s); 2.39 (1H,ddd,3.4,4.6,13.4Hz); 1.53 (1H,ddd,3.4,10.6,13.4Hz); 1.41 (3H,d,6.7Hz); 1.33 (3H,d,6.7Hz). ^{13}C-NMR (75.5MHz,$CDCl_3$): 156.3, 138.8, 131.6, 120.8, 114.4, 98.7, 74.3, 59.9, 58.3, 56.7, 55.0, 47.1, 35.2, 23.0, 20.5

(Received in USA 8 February 1989)