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THE STRUCTURE OF ACUMYCIN

A 16-MEMBERED RING MACROLIDE ANTIBIOTIC

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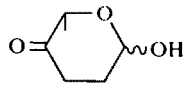
Abstract—The structure of acumycin, an antibiotic isolated from *Streptomyces griseoflavus*, was determined from spectroscopic and X-ray studies. Acumycin was found to be a 16-member ring macrolide with two sugars attached. One of the sugars had earlier been shown to be D-mycaminose. From the known absolute configuration of D-mycaminose we have been able to determine the absolute stereochemistry of acumycin. The stereochemistry in acumycin is compared with the predictions based on a biogenetic model proposed by Celmer. Acumycin because of its large number of chiral centers provided the most demanding test of the model to date and the model was found to be consistent with the experimental results from acumycin in every detail but one. These results suggest a refinement of Celmer's model for 16-member ring macrolides.

The macrolide antibiotics[1] have played a central role in the chemistry of natural products over the past three decades. Several members of this family are the most complex natural products whose structures have been elucidated by spectroscopic and chemical methods. More recently X-ray crystallography and solution NMR have been utilized to determine the stereochemistry and conformations of these highly substituted, large ring systems. The biogenesis of the macrolides was the subject of many hypotheses which have subsequently been tested in numerous biosynthetic studies. Recently the macrolide antibiotics have been the goal of several elegant synthetic studies. Many of these areas of macrolide chemistry have been reviewed.[2-7]

In 1962, Bickel *et al.* isolated an antibiotic from *Streptomyces griseoflavus* which they called acumycin.[8] From the results of combustion and functional group analyses, spectroscopic studies and some preliminary chemical reactions it appeared that acumycin was another member of the macrolide family of antibiotics and that it might be related to magnamycin (also called carbomycin).[1,9] Acumycin may be crystallized from ethyl acetate to yield prismatic crystals, m.p. 230–233°. Results from elemental analysis suggested that acumycin had the molecular formula $C_{38}H_{61}NO_{12}$ (MW 723).[8] However, the mass spectrum of acumycin did not show any peak at *m/e* 723, but it did show a significant peak at *m/e* 709. The mass spectral results along with the analytical data lead to the molecular formula $C_{37}H_{59}NO_{12}$ for acumycin. This formula was verified by a high resolution mass measurement of the peak at *m/e* 709. A preliminary X-ray crystallographic study of acumycin had also led to a molecular weight of 708 ± 2 for acumycin. All of this evidence was consistent with the molecular formula of $C_{37}H_{59}NO_{12}$ for acumycin.

The IR spectrum of acumycin has a weak band at 2725 cm^{-1} which is indicative of an aldehyde group in the molecule. A one-proton singlet at δ 9.72 in the ^1H NMR spectrum (Fig. 1) verifies the presence of an aldehyde. The IR spectrum of acumycin has bands at 1685 and 1615 cm^{-1} which may be attributed to an α,β-unsaturated ketone moiety. A strong absorption in the UV spectrum at 241 nm (ε 15,500) corroborates the presence of a conjugated enone. The ^1H NMR spectrum of acumycin has an AB quartet (J = 16 Hz) at δ 6.49 which suggests that the double band of the enone is trans disubstituted.

Mild acid hydrolysis of acumycin yielded a hexose[8] which was subsequently shown to be 2,3,6-trideoxyhexopyranos-4-ulose (**1**). This sugar derivative has also been isolated from the antibiotics



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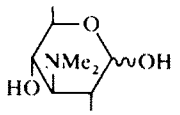

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cenerubin A[1] and B-58941,[11] and it has been synthesized.[12] Vigorous acid hydrolysis of acumycin yielded D-mycaminose (**2**).[8] The structure, including absolute stereochemistry, of D-mycaminose has been

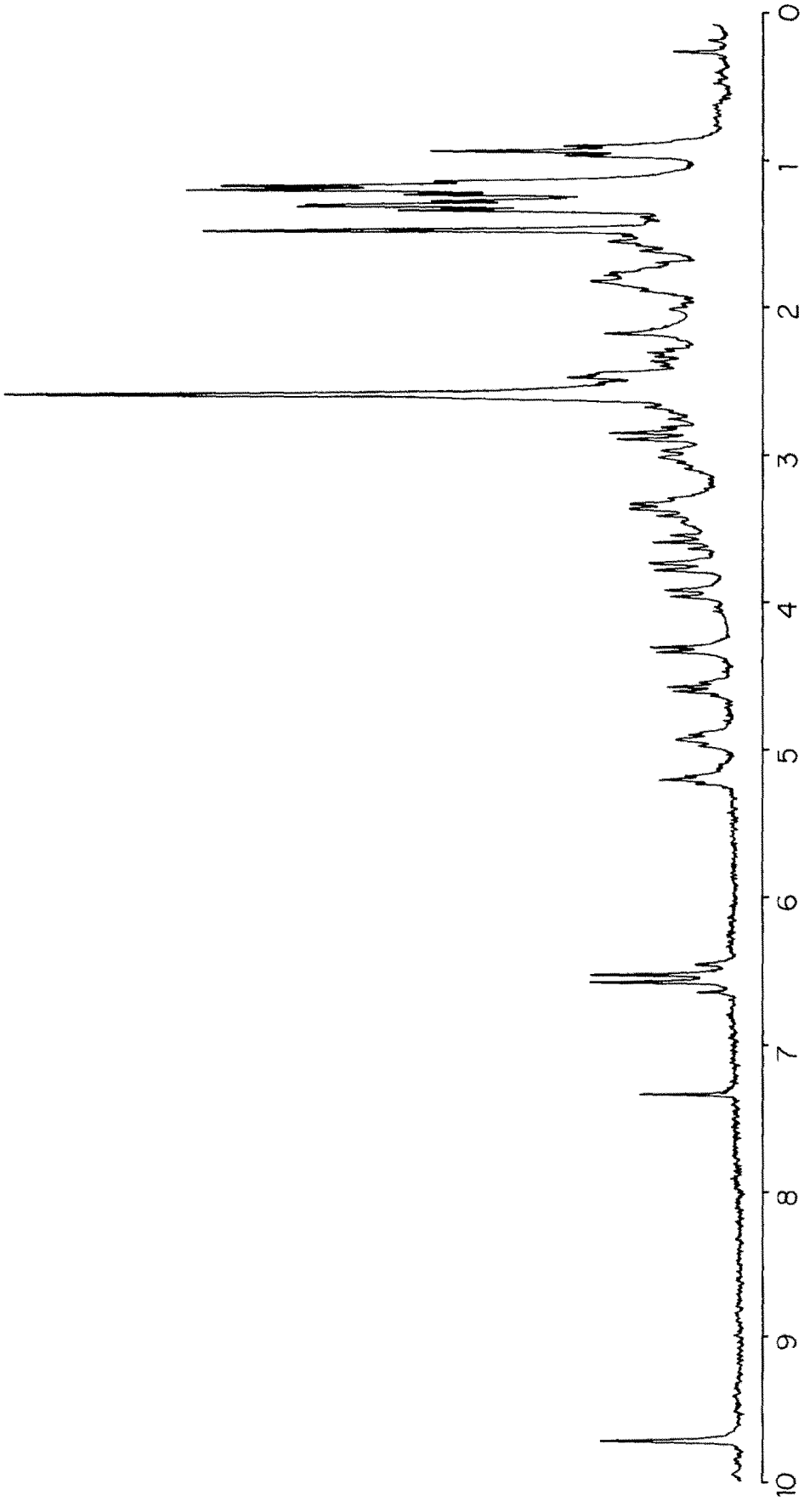
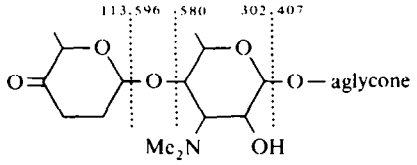


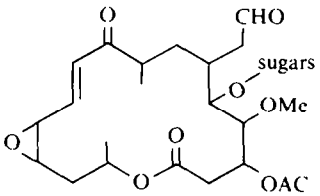
Fig. 1. 220 MHz ^{1}H NMR spectrum of acumycin in $CDCl_3$.

determined by chemical degradation,[13] ^{1}H NMR spectroscopy,[14] and synthesis.[15] The six-proton singlet at δ 2.56 in the ^{1}H NMR spectrum was assigned to the dimethylamino group in acumycin.[8] The results of pK_a measurements of acumycin and its hydrolysis products led to the suggestion that the two sugar moieties were linked together in acumycin.[8] The mass spectrum of acumycin supports this finding. Significant peaks occur at *m/e* 596, 580, 407, 302 and 113. The following fragmentation scheme can accommodate formation of these ions, and their composition was confirmed by high resolution mass measurements.



Kuhn-Roth oxidation indicated that acumycin possesses *seven* C-Me groups.[8] The ^{1}H NMR spectrum of acumycin also suggested that there are a large number of C-Me groups in the molecule. A three-proton triplet (J = 7 Hz) at δ 0.87 could be assigned to the Me of an Et side chain. In addition the ^{1}H NMR spectrum has a three-proton singlet at δ 1.41 and a series of signals between δ 1.0 and 1.4 attributed to five additional Me groups.

Originally, Woodward suggested that the macrolide antibiotics were synthesized in nature by the condensation of acetate and propionate units.[1] This hypothesis has been confirmed for a number of macrolides.[3,6,7] If we assume that acumycin has the same basic carbon framework as magnamycin A (3)



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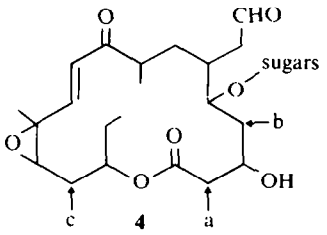
and the additional Me groups in acumycin are incorporated as propionate units in place of acetate units, we arrive at the following possible structures (4) for acumycin. There are three possibilities which could not be distinguished from the available data. In addition we have no experimental evidence for any of



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(Me groups at two of a, b, or c sites)

the relative stereochemical arrangements around the aglycone ring, except for the trans geometry of the double band. At this stage we turned to X-ray crystallography to provide insight about the structure of acumycin and to obtain some information about the stereochemistry of the substituents on the aglycone.

The X-ray structure was determined from orthorhombic crystals and the results are given in Fig. 2. Table 1 contains the fractional coordinates and errors for acumycin. Since the absolute stereochemistry of D-mycaminose is known,[16] the absolute stereochemistry of each asymmetric center in acumycin was established. First we note that the terminal hexose is (5*S*)-2,3,6-trideoxyhexopyranos-4-ulose and the sugar is linked via an α-glycosidic linkage to C-4 of D-mycaminose. The mycaminose in turn is linked to the aglycone via a β-glycosidic bond. The stereochemistry of the macrolide ring can be specified as 3*R*, 4*S*, 5*S*, 6*R*, 8*R*, 12*S*, 13*S*, 14*S*, 15*R*. The X-ray structure of acumycin contains all of the structural features anticipated from the spectral data and the two additional methyl groups are located at sites b and c in 4.

Acumycin is another member of the 16-member ring macrolides and it has the same gross structure as the aglycones in antibiotic B-58941,[11] cirramycin A,[17] and rosamicin.[18] In fact acumycin has the same structure,

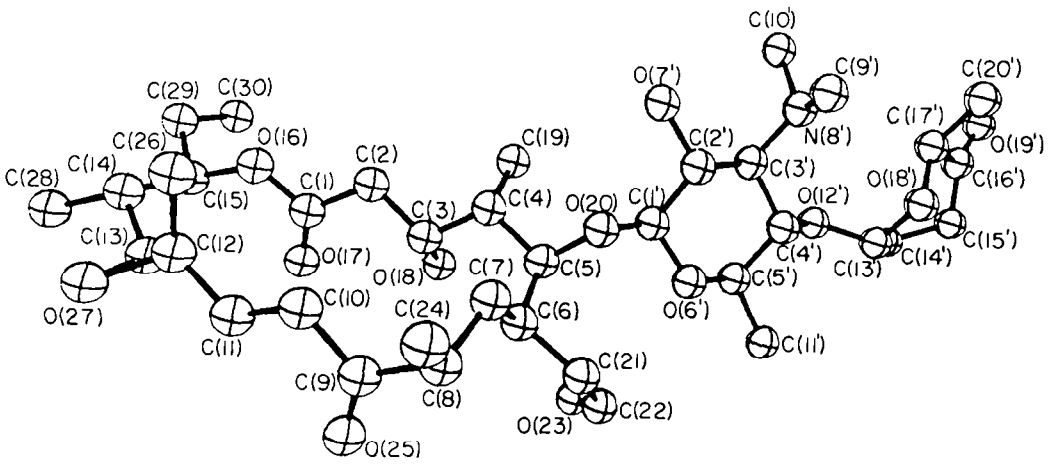


Fig. 2. X-ray structure of acumycin.

Table 1. Final fractional coordinates for acumycin. The primed numbers designate sugar atoms. The hydrogens are given the same numbers as the atoms to which they are bonded. In parentheses following each coordinate is the estimated standard deviation of its least significant figure

C(1)	.0854(3)	.4071(3)	-.77309(7)
C(2)	.1359(3)	.3239(3)	-.74349(7)
C(3)	.1907(3)	.3919(3)	-.71022(7)
C(4)	.2513(3)	.3037(3)	-.68225(7)
C(5)	.3254(3)	.3691(2)	-.65113(6)
C(6)	.4308(3)	.4635(2)	-.66395(6)
C(7)	.5348(3)	.4073(3)	-.69004(7)
C(8)	.6182(3)	.4998(3)	-.71196(7)
C(9)	.5387(3)	.5621(3)	-.74198(7)
C(10)	.4853(3)	.4855(3)	-.77246(7)
C(11)	.4168(3)	.5342(3)	-.80016(7)
C(12)	.3579(3)	.4655(3)	-.83121(7)
C(13)	.2278(3)	.5115(3)	-.84553(7)
C(14)	.1245(3)	.4315(3)	-.86437(7)
C(15)	.0126(3)	.4040(3)	-.83664(7)
O(16)	.0758(2)	.3457(2)	-.80472(4)
O(17)	.0563(2)	.5124(2)	-.76925(5)
O(18)	.0863(3)	.4609(2)	-.69193(6)
C(19)	.1439(4)	.2177(3)	-.66712(9)
O(20)	.3956(2)	.2763(1)	-.63004(4)
C(21)	.5017(3)	.5209(3)	-.63081(7)
C(22)	.4231(5)	.5975(3)	-.60591(9)
O(23)	.3133(4)	.6284(3)	-.60984(9)
C(24)	.7402(4)	.4349(4)	-.72835(9)
O(25)	.5179(3)	.6717(2)	-.74125(6)
C(26)	.3991(4)	.3357(3)	-.83732(9)
O(27)	.3477(2)	.5398(2)	-.86509(5)
C(28)	.0689(4)	.4984(4)	-.89826(8)
C(29)	-.0933(4)	.3164(3)	-.84958(8)
C(30)	-.2019(4)	.2940(5)	-.82118(10)
C(1')	.3465(3)	.2507(3)	-.59514(7)
C(2')	.3962(3)	.1257(3)	-.58415(7)
C(3')	.3491(3)	.0924(3)	-.54537(7)
C(4')	.3869(3)	.1961(3)	-.51905(7)
C(5')	.3458(4)	.3221(3)	-.53365(7)
O(6')	.4004(2)	.3383(2)	-.57015(4)
O(7')	.3460(3)	.0343(2)	-.60877(5)
N(8')	.3931(3)	-.0258(3)	-.53180(7)
C(9')	.2992(8)	-.1256(4)	-.53951(12)
C(10')	.5302(6)	-.0572(5)	-.54070(11)
C(11')	.3992(6)	.4283(3)	-.51138(8)
O(12')	.3149(2)	.1775(2)	-.48519(5)
C(13')	.3897(4)	.1814(4)	-.45264(8)
C(14')	.2883(5)	.1811(4)	-.42114(8)
C(15')	.3426(5)	.1031(6)	-.38935(9)
C(16')	.3591(5)	-.0233(5)	-.40329(13)
C(17')	.4217(5)	-.0323(5)	-.44058(11)
O(18')	.4807(3)	.0820(3)	-.44983(6)
O(19')	.3225(4)	-.1121(5)	-.38633(15)
C(20')	.5267(9)	-.1329(9)	-.44203(16)
H(2A)	.206(5)	.267(4)	-.755(1)
H(2B)	.064(4)	.278(4)	-.736(1)
H(3)	.112(4)	.446(4)	-.698(1)
H(4)	.318(3)	.255(3)	-.695(1)
H(5)	.258(3)	.411(3)	-.635(1)
H(6)	.378(3)	.534(3)	-.677(1)
H(7A)	.486(3)	.352(3)	-.709(1)
H(7B)	.597(3)	.348(2)	-.676(1)
H(8)	.647(4)	.567(3)	-.695(1)
H(10)	.499(2)	.395(2)	-.771(1)
H(11)	.404(3)	.626(3)	-.799(1)
H(13)	.188(3)	.587(3)	-.832(1)
H(14)	.169(3)	.351(3)	-.871(1)
H(15)	-.023(3)	.487(3)	-.828(1)
H(19A)	.081(5)	.251(4)	-.652(1)
H(19B)	.102(4)	.162(4)	-.688(1)
H(19C)	.185(4)	.155(4)	-.651(1)
H(21A)	.546(4)	.449(3)	-.616(1)
H(21B)	.589(4)	.569(3)	-.637(1)
H(22)	.469(3)	.634(3)	-.579(1)
H(24A)	.787(6)	.493(5)	-.744(1)
H(24B)	.798(5)	.405(5)	-.709(1)
H(24C)	.705(4)	.348(3)	-.743(1)
H(26A)	.366(4)	.289(4)	-.816(1)
H(26B)	.359(4)	.292(4)	-.857(1)
H(26C)	.492(4)	.337(4)	-.837(1)
H(28A)	.030(4)	.582(4)	-.891(1)
H(28B)	.149(4)	.517(4)	-.913(1)
H(28C)	-.010(5)	.451(4)	-.909(1)
H(29A)	-.133(4)	.341(4)	-.871(1)
H(29B)	-.057(4)	.236(4)	-.856(1)
H(30A)	-.241(5)	.376(4)	-.817(1)
H(30B)	-.267(5)	.230(4)	-.831(1)
H(30C)	-.161(5)	.260(4)	-.797(1)
H(1')	.246(3)	.253(3)	-.594(1)
H(2')	.498(3)	.124(3)	-.584(1)
H(3')	.243(3)	.092(3)	-.543(1)
H(4')	.482(3)	.197(2)	-.515(1)
H(5')	.243(4)	.318(4)	-.535(1)
H(9'A)	.293(5)	-.147(5)	-.565(1)
H(9'B)	.322(5)	-.198(4)	-.528(1)
H(9'C)	.213(5)	-.091(5)	-.531(1)
H(10'A)	.583(4)	.010(4)	-.529(1)
H(10'B)	.546(5)	-.143(5)	-.531(1)
H(10'C)	.545(5)	-.071(4)	-.570(1)
H(11'A)	.390(4)	.497(4)	-.522(1)
H(11'B)	.349(5)	.424(4)	-.487(1)
H(11'C)	.510(5)	.416(4)	-.512(1)
H(13')	.449(4)	.260(3)	-.452(1)
H(14'A)	.263(4)	.278(4)	-.415(1)
H(14'B)	.202(4)	.143(3)	-.431(1)
H(15'A)	.416(5)	.146(5)	-.382(1)
H(15'B)	.279(5)	.106(5)	-.370(1)
H(17')	.352(4)	-.044(4)	-.458(1)
H(20'A)	.490(6)	-.194(5)	-.430(1)
H(20'B)	.575(5)	-.134(5)	-.464(1)
H(20'C)	.597(6)	-.107(5)	-.423(1)

devoid of stereochemical detail, as antibiotic B-58941. A comparison of the published physical and spectroscopic properties indicates that these two antibiotics are identical.

Stereochemistry. Celmer has proposed a stereochemical model for the macrolide antibiotics based on biogenetic considerations.[7] This model predicts the *absolute* configuration of the macrolide sugars, including glycosidic linkages, and the absolute configuration of every chiral center on the aglycone. The Celmer model has been remarkably successful. The model is consistent with the stereochemistry of every single chiral center in the 12- and 14-member ring macrolides.[7] In fact, it has been so successful that every "exception" to the model was subsequently reinvestigated and the original stereochemical assignment was found to be in error.

The X-ray structure reported here is the first X-ray structure of 16-member ring macrolide with the sugars attached and thus allows us to test all aspects of the Celmer stereochemical model as it applies to the 16-lactones. First, Celmer suggests that if a macrolide has a sugar at C-5 of the aglycone, the sugar should be of the D-series. Acumycin has D-mycaminose linked to C-5 of the macrolide ring. In addition, the model predicts that this sugar should form a β-glycosidic link to the lactone ring. The above X-ray results confirm this prediction for D-mycaminose. The model goes on to predict that there are two possible sites for attachment of an L-sugar, should the antibiotic contain one. These sites are (i) β to the site of attachment of the D-sugar to the lactone ring, or (ii) on C-4 of D-mycaminose. Furthermore, the model predicts that this L-sugar should be joined to the site (i) or (ii) via an α-glycosidic bond. The X-ray results show that the configuration and location of the 2,3,6-trideoxyhexopyranos-4-ulose is in full accord with these predictions. In summary, the Celmer model for the location, configuration and

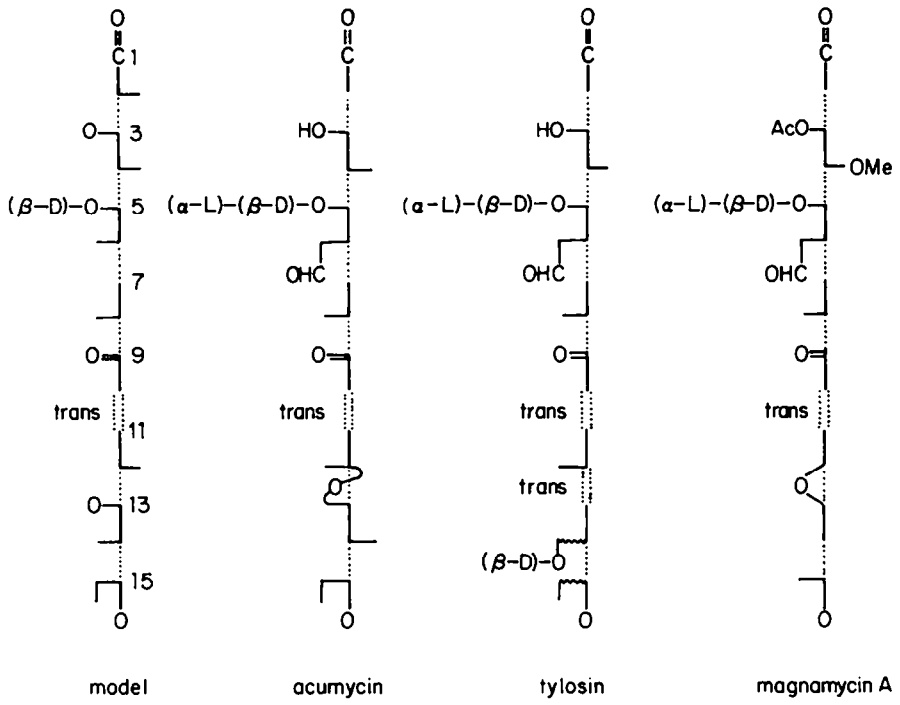


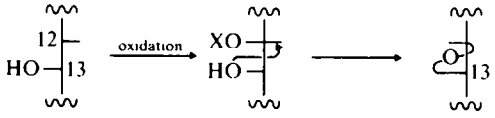
Fig. 3. Celmer's stereochemical model for 16-member macrolides and the absolute stereochemistry of acumycin, tylosin and magnamycin A (Fisher projection), all shown in Fisher projection.

geometry of the glycosidic linkages for the carbohydrate moieties in the macrolides is totally consonant with the X-ray structural results for acumycin.

The Celmer model also predicts the chirality at the asymmetric centers in the macrolide ring.[7] This model is based on a biogenetic proposal for the stereospecific addition of acetate or propionate units in the biosynthesis of the macrolide ring. The model for the 16-member ring lactones is shown above (Fig. 3). In this model the aglycone is considered to be formed from seven "propionate" units and one "acetate" unit. It was recognized that some of the propionate units might be replaced by acetate units which would remove a chiral center for each replacement. Also, Celmer noted that extra oxygens were occasionally found attached to the even-numbered carbons (model in Fig. 3). It was reasoned that these oxygens were introduced late in the biosynthetic pathway. Since most oxygenases involve retention of configuration,[19] it was a straightforward matter to incorporate these extra oxygens at any of the methyl substituted carbons in the lactone ring.

Figure 3 shows the absolute stereochemistry of the aglycone of acumycin (drawn in a Fisher projection) and compares this structure with the Celmer model for the 16-member lactones. Carbon atoms 3 and 4 are the first asymmetric centers in the lactone ring of acumycin and their absolute configuration is in accord with the model. The next four-carbon unit in acumycin, C-5 and C-6 and the side-chain aldehyde, is a feature which is unique to the 16-member macrolides. The biosynthetic origin of this fragment appears to involve incorporation of a butyrate unit[20] rather than a propionate unit. Nevertheless, the configuration at C-5 and C-6 of acumycin agrees with the model. The stereochemistry of the methyl at C-8 is also in agreement with the model. Celmer suggests that the olefinic bonds in the aglycone should be trans and the C-10,11 double bond of acumycin is. Thus, the six asymmetric centers and the geometry of the double band from C-1 to C-11 of acumycin are in full agreement with the predictions based on the Celmer model.

Carbon-12 is a special case with the branching methyl and an "extra" oxygen. As pointed out above, in the model these "extra" oxygens are introduced with retention of configuration. In this case, it would appear that the stereochemistry at C-12 is a violation of the model. However, this oxygen is unique in that it forms an epoxide bridge to C-13 and the configuration at C-13 agrees with the model. The epoxide formation might involve an inversion of configuration at C-12 as shown schematically in **5**.



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The configuration at C-14 is *S* and this is a clear violation of the predictions based on the model! There appears to be no apparent resolution of this problem within the framework of the current model. The configuration of this center (where it is substituted) is not known for any of the other 16-member ring macrolides (vide infra). Finally the configuration of C-15 in acumycin agrees with Celmer's model.

To date there are only two substitution patterns found for the 16-member ring lactones in the macrolide antibiotics. The two basic structures differ only in the number of acetate versus propionate units in the lactone skeleton. Acumycin is a member of the group which contain five propionate units, two acetate units, and a butyrate unit in the aglycone. Magnamycin A (3)[1,9,21] is an example of the second family which contain only one propionate unit, six acetate units, and one butyrate unit in the aglycone.

As we see in Fig. 3, the stereochemistry of C-14 in acumycin conflicts with the predictions of Celmer's model. Unfortunately the stereochemistry of this center is not known for any of the antibiotics directly related to acumycin, namely, antibiotic B-5894,[11] cirramycin A_1,[17] rosamicin,[18] and antibiotic M-4365 A_2.[22] There are other 16-member ring macrolides related to acumycin, in that the aglycone of these antibiotics can be considered to consist of five propionate units, one acetate, and one butyrate. The most extensively studied member of this group is tylosin[23] and the stereochemistry of carbons 1–13 have been proposed.[23c] These results based on chemical degradation and spectroscopic studies are in agreement with the Celmer model (Fig. 3). Unfortunately there is no data available on the absolute stereochemistry at C-14 and C-15 in tylosin or in any of its related antibiotics. Hence, we are unable at this time to define the scope of the exception to Celmer's model found at C-14 in acumycin.

The second family of 16-member macrolides represented by magnamycin[1,9,21] includes leucomycin A_3,[24] niddamycin[25] and spiramycin III.[26] The absolute stereochemistry in this family is known from chemical studies in the case of magnamycin[1,21] and from X-ray studies in the case of leucomycin A_3.[24] Again we see complete agreement between the observed configuration and the predictions of Celmer's model for all of the asymmetric centers. Note that C-14 is unsubstituted in this family.

In summary the X-ray structural data for acumycin have allowed the most extensive evaluation of Celmer's stereochemical model[7] to date. The model and experimental results were consistent in all aspects but one. The significance of this single known exception to Celmer's model must await further structural studies on related macrolides. But these results suggest that the Celmer model may have to be refined in extending the model to C-14 in the 16-membered ring macrolides.

EXPERIMENTAL

A 100-mg sample of crude acumycin (m.p. 215 219 , dec) was chromatographed on 50 g of silica gel and the product was eluted with EtOAc. The fractions with high concentrations of acumycin were combined. The solvent was removed under reduced pressure and the resulting colourless oil was immediately dissolved in a minimum volume of hot EtOAc. When the solution cooled 30 mg of pure acumycin crystallized, m.p. 230 233 , dec (lit. m.p. 233–237 , dec[11]). These crystals were of sufficiently high quality to be used directly in the X-ray study.

The mass spectrum (AEI MS-9 mass spectrometer operating at 70 eV) had the following peaks *m/e* 709 (10), 693 (1), 691 (1), 596 (0.5), 580 (0.5), 407 (1), 302 (4), 286 (16), 174 (11), 173 (14), 122 (12), 115 (20), 114 (21), 113 (23), 109 (20), 98 (14) and 87 (100). High resolution mass measurement gave 709.4031, calc. for $C_{37}H_{59}NO_{12}$: 709.4037. (Found: C, 62.64; H, 8.31; N, 1.90). Calc. for $C_{37}H_{59}NO_{12}$: C, 62.60; H, 8.37; N, 1.9.

X-ray structure determination. Preliminary X-ray photographs showed orthorhombic symmetry for acumycin crystals. Accurate unit cell constants, determined from a least-squares fit of fifteen diffractometer measured 2θ-values, were **a** = 9.996 (2), **b** = 10.892 (2) and **c** = 36.315 (6) Å. Systematic extinctions, chirality and an observed density of 1.19 g/cm^3 were uniquely accommodated by space group $P2_12_12_1$ with one molecule of $C_{37}H_{59}NO_{12}$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114$ were recorded by an automated four-circle diffractometer using an ω-scan technique and graphite monochromated CuKα (1.54178 Å) radiation. Of the 3064 reflections surveyed, 2581 (84%) were judged observed after correction for Lorentz, polarization and background effects ($|F_0| \geq 3\sigma(F_0)$).

The angular dependence of the scattering was removed as the data were converted to normalized structure factors and the 350 largest of these were assigned phases using a multisolution weighted tangent formula approach.[27] An E-synthesis computed from the best solution showed a plausible 24 atom fragment. This fragment was used in a tangent formula recycling procedure and the improved phases yielded a synthesis from which 40 of the atoms could be identified.[28] These atomic coordinates were refined by a least-squares procedure and a subsequent electron density synthesis revealed all 50 non-hydrogen atoms.[29] H atoms were located in a difference synthesis and full-matrix least-squares refinements converged to a final crystallographic discrepancy index of 0.041 for the observed reflections.[30]

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