CHEMISTRY LETTERS, pp. 423-426, 1990.

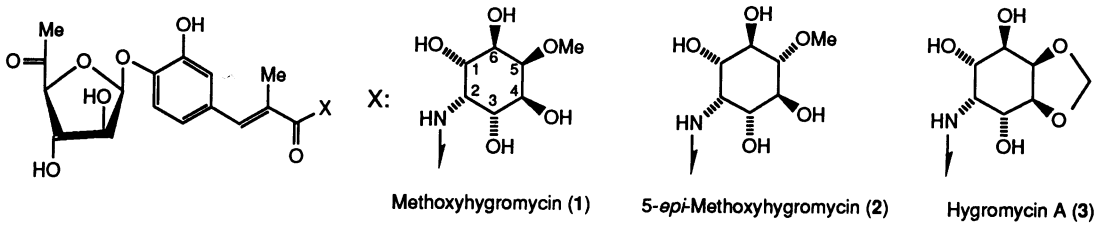
Total Synthesis of Methoxyhygromycin and Its 5-Epimer

Noritaka CHIDA, Keiichi NAKAZAWA, Masami OHTSUKA, Minoru SUZUKI, and Seiichiro OGAWA*
Department of Applied Chemistry, Faculty of Science and Technology
Keio University, Hiyoshi, Kohoku-ku, Yokohama 223

Methoxyhygromycin, an antibiotic having a unique structure among the aminocyclitol antibiotics, and its 5-epimer are first synthesized. This synthesis fully confirmed the proposed structure of the antibiotic and revealed that *neo*-configuration of cyclitol moiety is important for the appearance of antibacterial activity.

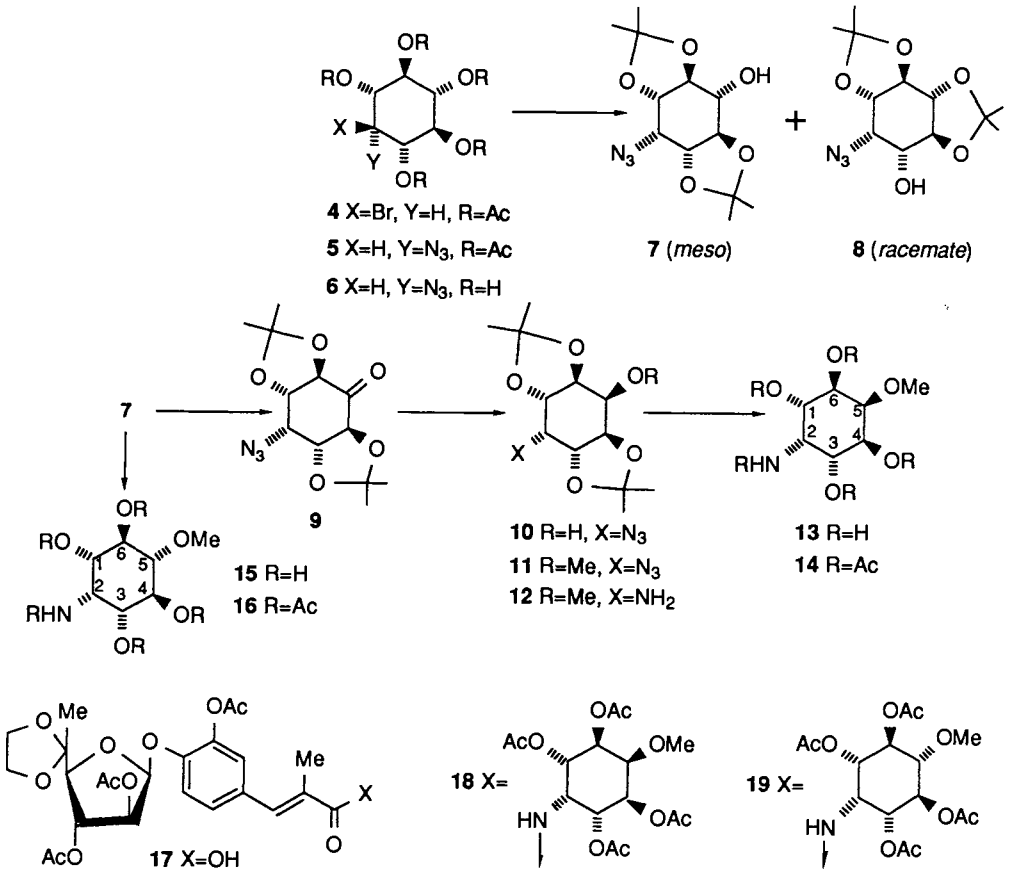
Methoxyhygromycin (**1**) is an antibiotic produced by *Streptomyces* sp. No.207 together with hygromycin A (**3**)[1] and showed antibacterial activity against Gram-positive and negative bacteria. It is also reported that methoxyhygromycin and hygromycin A strongly inactivate hemagglutination by enterotoxic *E. Coli* associated with K 88ab antigen.[1] The structural study was carried out by spectral analyses,[1] and it is shown that methoxyhygromycin has a structure formulated as **1** (Scheme 1), which is very similar to that of hygromycin A,[2,3] (**3**) but posesses a 2-amino-2-deoxy-5-*O*-methyl-*neo*-inositol (**13**) as a cyclitol moiety instead of 1L-2-amino-2-deoxy-4,5-*O*-methylene-*neo*-inositol. In this communication, as a part of synthetic study of aminocyclitol antibiotics related to hygromycin A,[3] we would like to disclose the synthesis and antibacterial properties of methoxyhygromycin (**1**) and its 5-epimer (**2**).

The required 2-amino-2-deoxy-5-*O*-methyl-*neo*-inositol (**13**) for the synthesis of methoxyhygromycin was prepared as illustrated in Scheme 2. The known 1,2,3,4,5-Penta-*O*-acetyl-6-bromo-6-deoxy-*scyllo*-inositol (**4**),[4] readily accessible from *myo*-inositol in one step was chosen as the starting material.



Scheme 1.

Azidolysis and subsequent acetylation of **4** (NaN_3, 10% aqueous DMF, 90 °C, then Ac_2O/py) gave 2-azido derivative with *myo*-configuration (**5**) in 80% yield. Acid hydrolysis of **5** (2 M HCl, EtOH) gave 2-azido-2-deoxy-*myo*-inositol (**6**) in 92% yield, which was then treated with 2,2-dimethoxypropane in the presence of *p*-TsOH (DMF) to give a mixture of compounds **7** and **8**. Separation of this mixture with silica gel column chromatography afforded the desired 1,6:3,4-di-*O*-isopropylidene derivative **7** in 30% yield, along with the racemic isomer **8** (30%). The hydroxyl group in **7** was oxidized [RuO_2 (catalytic amount), K_2CO_3, benzyltriethylammonium chloride, $NaIO_4$, $CHCl_3$-H_2O][5] to give ketone **9** in 88% yield. Stereospecific reduction of **9** was achieved by treatment with L-Selectride in THF to give 75% yield of the alcohol (**10**) with *neo*-configuration as a single product. *O*-Methylation of **10** (NaH, MeI/DMF) gave **11** in 86% yield, azido group of which was then reduced with Raney Ni (atmospheric H_2, EtOH) to afford the amine **12** in 84% yield. Acid hydrolysis of **12** with aqueous acetic acid gave 2-amino-2-deoxy-5-*O*-methyl-*neo*-inositol (**13**) in 92% yield. The structure of **13** was secured by the ^1H NMR spectrum of its peracetyl derivative **14**. The resonance of H-1 and H-3 were observed at δ 5.51 (one dd, J=4.8 and 11.1 Hz), and those of H-4 and H-6 were appeared at δ 5.27 (one dd, J=2.4 and 11.1 Hz). The proton attaching to the carbon bearing acetamido group (H-2) and H-5 were observed at δ 5.07 (dt, $J_{N,H}$=



Scheme 2.

9.9, $J_{1,2}=J_{2,3}=4.8$ Hz) and 4.03 (narrow t, J=2.4 Hz), respectively. These results strongly suggested that compound **14** has a symmetrical *neo*-configuration with methoxy group at C-5 and acetamido group at C-2.

On the other hand, compound **7** was *O*-methylated and the azido group of the product was reduced with Raney-Ni to give, after acid hydrolysis, 2-amino-2-deoxy-5-*O*-methyl-*myo*-inositol (**15**) in 59% overall yield. The ^{1}H NMR spectrum of its peracetyl derivative **16** showed the signals for H-4 and 6 at δ 5.34,(t, J=10.2 Hz), those for H-1 and 3 at δ 5.02 (dd, J=4.5 and 10.2 Hz), those for H-2 at δ 4.91 (dt, J=9.3 and 10.2 Hz), and those for H-5 at δ 3.43 (t, J=10.2 Hz), respectively. These data clearly supported the structure of **16** having a *myo*-configuration.

Condensation of the sugar moiety **17**, which was prepared by our group for the total synthesis of hygromycin A,[3] with **13** was carried out under the conditions of Shioiri's procedure [$(EtO)_2P(O)CN$, Et_3N, DMF][6] to give the condensate, and this was isolated as its peracetyl derivative **18** in 65% overall yield. *O*-Deacetylation and subsequent acid hydrolysis of the ketal group (60% aqueous TFA) gave methoxyhygromycin (**1**) in 44% yield. The ^{1}H and ^{13}C NMR spectral data of **1**[7] were in good accordance with those of natural product.[1]

With the same procedure, the 5-epimer[7] of **1** (**2**) was synthesized from **17** and the amine **15**, in 46% overall yield from **17**. The antibacterial spectra of synthetic methoxyhygromycin (**1**), its 5-epimer[8] (**2**), and natural hygromyin A (**3**) are shown in Table 1. While methoxyhygromycin showed a weak antibacterial activity against some bacteria, the 5-epimer (**2**) possessed almost no activity. From these results, it became clear that the *neo*-configuration in the cyclitol moiety is almost essential for the appearance of the antibacterial activity, and the 4,5-*O*-methylene group in the cyclitol moiety plays an important role for the higher activity in the antibiotic family related to hygromycin A.

Further study preparing new derivatives of hygromycin A is in progress in our laboratory.

TABLE 1.[a] Antibacterial Spectra of Methoxyhygromycin (**1**), Its 5-Epimer (**2**), and Hygromycin A (**3**)

Test Organism	MIC (μg/ml)		
	1	**2**	**3**
S. aureus 209P	>50	>50	25
S. Pyogenes E-14	12.5	>50	3.13
P. multocida P 1059	25	>50	3.13
Pept. anaerobius B-40	12.5	>50	1.56
F. necrophorum VPI 2891	6.25	>50	1.56
M. pulmonis M-53	6.25	100	0.78
M. gallisepticum KP 13	25	>100	0.78

a) The antibacterial activities were measured by an agar dilution method.

We would like to express sincere thanks to Professor T. Beppu and Dr. M. Yoshida (Department of Agricultural Chemistry, Tokyo University) for providing us with ^{1}H and ^{13}C NMR spectra of natural methoxyhygromycin and Dr. S. Harada (Takeda Chemical Industries) for measuring antibacterial activities of compounds **1**, **2**, and **3**.

References

1) M. Yoshida, E. Takahashi, T. Uozumi, and T. Beppu, Agric. Biol. Chem., 50, 143 (1986).
2) K. Kakinuma and Y. Sakagami, Agric. Biol. Chem., 42, 279 (1978).
3) N. Chida, M. Ohtsuka, and S. Ogawa, Chem. Lett., 1988, 969; N. Chida, M. Ohtsuka, K. Nakazawa, and S. Ogawa, J. Chem. Soc., Chem. Commun., 1989, 436.
4) G. E. McCasland and E. C. Horswill, J. Am. Chem. Soc., 75, 4020 (1953).
5) P. E. Morris and D. E. Kiely, J. Org. Chem., 52, 1149 (1987).
6) S. Yamada, Y. Kasai, and T. Shioiri, Tetrahedron Lett., 1973, 1595.
7) **1**: amorphous solid, mp 123-124 °C, $[\alpha]_D^{30}$ -104° (*c* 1.7, H_2O) lit.[1] mp 133-136 °C; ^{1}H NMR (CD_3OD) δ 2.13 (s, 3H), 2.14 (s, 3H), 3.52 (s, 3H), 3.74 (t, 1H, J=2.6 Hz), 3.95-4.15 (m, 4H), 4.20 (dd, 1H, J=4.3 and 6.7 Hz), 4.28 (d, 1H, J=6.7 Hz), 4.36 (dd, 1H, J=6.7 and 6.7 Hz), 4.62-4.64 (m, 1H), 5.63 (d, J=4.3 Hz), 6.90 (dd, 1H, J=1.8 and 7.9 Hz), 6.95 (d, 1H, J=1.8 Hz), 7.23 (s, 1H), and 7.23 (d, 1H, J=7.9 Hz). **2**: amorphous solid, mp 170 °C (dec.), $[\alpha]_D^{25}$ -126° (*c* 0.44, H_2O); ^{1}H NMR (CD_3OD) δ 2.11 (s, 3H), 2.12 (s, 3H), 2.94 (m, 1H), 3.63, (s, 3H), 3.55-4.28 (m, 4H), 4.21 (dd, 1H, J=4.2 and 6.7 Hz), 4.28 (d, 1H, J=6.7 Hz), 4.36 (dd, J=6.7 and 6.7 Hz), 4.60 (m, 1H), 5.62 (d, 1H, J=4.2 Hz), 6.89 (d, J=8.3 Hz), 6.95 (s, 1H), 7.16 (s, 1H), and 7.22 (d, 1H, J=8.3 Hz).
8) Compound **2** has the same structure as that proposed for naturally occurring antibiotic KA-3093 [Japan Unexamined Patent No.99495 (1981)]. However, our synthetic **2** showed almost no antibacterial activity, and the ^{1}H NMR data was not identical with those which have been reported in the patent. Since no detailed properties of KA-3093 is available so far, we could not determine whether **2** is identical with KA-3093 or not.

(Received December 11, 1989)