The chemical structure of antimycins A1 and A3, which are the major components of antibiotic antimycin A complex, had already been established by Van Tamelen, et al., Birch, et al., and Yonehara, et al. The absolute configurations of blastmycinone derived from antimycin A3 (blastmycin) and of the antibiotic itself had been proposed by Endo and Yonehara in 1967. In our recent synthetic studies on antimycin A3, it has been found that the optical behaviors (signs of Cotton effect in CD and of rotational change on addition of base) of the synthetic (−)-blastmycinolactol might not be explained by the lactone configuration proposed for natural blastmycinone by Endo and Yonehara. Furthermore, it had been confirmed by the NMR analyses of the mixture of antimycin lactones and antimycin A complex that all the antimycin lactones and the antimycin A components had the same stereochemistry in respect of their lactone rings and their dilactone rings, respectively.

We now wish to report the absolute configuration of the antimycin lactones and the total absolute configuration of antimycin A as represented in Fig. 1 and Fig. 2, respectively.

The natural (+)-blastmycinone [(+)-1] has recently been synthesized in our laboratory from the synthetic (−)-blastmycinolactol [(-)-2] which was identified with natural (−)-blastmycinolactol. The lactone [(-)-2] was prepared by lithium aluminum hydride reduction of the optically active (+)-diastereomer of tert-butyl 4-(N-benzyloxy-carbonyl-O-tert-butyl-L-threonyloxy)-2-buty1-3-(isovaleryloxy)pentanoate, only this being useful for the total synthesis of natural antimycin A. These experimental results also confirmed that the absolute configuration of the 3-O-acetyl-2-alkyl-3,4-dihydroxypentanoic acid moiety which existed intact in the molecule of antimycin A reflected that of the antimycin lactone derived from the parent antimycin A by saponification.

In order to determine the absolute configuration of antimycin lactones, we decided to use (−)-blastmycinolactol [(−)-2] as a key substance rather than (+)-blastmycinone [(+)-1], because the former had a more favorable structure for optical investigations than the latter.

The ORD and CD curves of (−)-2 in methanol showed a negative Cotton-effect (θ234 = -2870°tr, [θ]222 = -5500) for the lactone n → π* transition. Legrand and Bucourt rules on ring chirality allow the negative sign of the Cotton effect to be predicted for the nonplanar E3 conformation of (−)-2 as shown in Fig. 3. The rotational change ([α]D = -20°) of (−)-2 in methanol on addition of one equivalent of base was observed by Wircor’s method. By application of Hudson’s lactone rule the absolute configuration at the C-4 carbon of (−)-2 was assumed to be “S”.

On the assumption that the molecule of (−)-2 in methanol solution has the conformation and partial configuration at the C-4 carbon described above, a configurational study based on NMR analysis serves to define the configurations at the remained asym-
metric carbons (C-2 and C-3) in (-)-2. The large ring proton coupling constants \( J_{2,3} = 8.2 \) and \( J_{3,4} = 7.5 \) Hz) observed in the spectrum (in CD$_3$OD) of (-)-2 indicated that H-2, H-3 and H-4 protons are all in axial orientation as shown in Fig. 3. The configurations of the C-2 and C-3 carbons were thus deduced as "R" and "R", respectively. The 2(R) configuration was consistent with Okuda's\(^{10}\) and Beecham's observations\(^{11}\) that the negative Cotton effect sign of 1,4-lactones appeared to reflect the "R" configuration at C-2. Furthermore, the 3(R) configuration was also supported by application of the benzoate sector rule\(^{12}\) for the \( p \)-methoxybenzoate of (-)-2 (\( \left[ \alpha \right]_{D}^{23} +42^\circ \), \( \left[ \theta \right]_{25}^{25} +6960 \) for the methoxybenzoate chromophor in methanol).

The absolute configuration of (-)-2 deduced by physical methods (Fig. 3) was finally confirmed through stereospecific synthesis of the enantiomer (12) of (-)-2 as shown in Fig. 4.

Methyl 2,3-anhydro-4,6-O-benzylidene-\( \alpha \)-\( p \)-mannopyranoside(3)\(^{13}\) was treated with excess of butylmagnesium chloride in ether\(^{14}\) to afford methyl 4,6-O-benzylidene-3-C-buty1-3-deoxy-\( \alpha \)-\( p \)-altropyranoside(4) as a syrup in a 69% yield, \( C_{18}H_{26}O_{5}, \left[ \alpha \right]_{D}^{25} +135^\circ \) (c 1.77, chloroform); \( \delta \)(CDCl$_3$), 4.58 (d, H-1, \( J_{1,2} = 1.0 \) Hz) and 5.04 (dd, H-2, \( J_{2,3} = 2.0 \) Hz). Oxidation of 4 with Pfitzner-Moffatt reagent\(^{15}\) gave methyl

\[ \text{Fig. 3.} \]

\[ \text{Fig. 4.} \]

* The natural (+)-blastmycinone\([\text{(+)-1}] \) was shown to have the same conformation in methanol as that of (-)-2 on the basis of its negative Corroox effect sign (\( \left[ \theta \right]_{284}^{284} -1140^\circ \), \( \left[ \theta \right]_{282}^{282} -2510 \) in methanol).

\# Microanalyses agree with the molecular formula shown.
4, 6-O-benzylidene-3-C-butyl-3-deoxy-\(\alpha\)-<\(\alpha\)-d-ribo-hexopyranosid-2-ulose (5) as a syrup in a 90% yield, \(C_{18}H_{24}O_{5}\), \([\alpha]_{D}^{20}+40^\circ\) (c 1.12, chloroform); \(\delta(\text{CDCl}_3)\), 4.57 (d, H-1, \(J_{1,2}=1.0\) Hz). Epi-merization\(^{16}\) of 5 with triethylamine in dimethylformamide afforded methyl 4, 6-O-benzylidene-3-C-butyl-3-deoxy-\(\alpha\)-<\(\alpha\)-d-arabino-hexopyranosid-2-ulose (6) in a 79% yield, \(C_{18}H_{24}O_{5}\), mp 85.0~86.0°C, \([\alpha]_{D}^{20}+39^\circ\) (c 1.12, chloroform); \(\delta(\text{CDCl}_3)\), 4.60 (s, H-1, \(J_{1,2}=0\) Hz). Lithium aluminum hydride reduction of 6 gave methyl 4,6-O-benzylidene-3-C-butyl-3-deoxy-\(\alpha\)-d-glucopyranoside (7), \(C_{18}H_{26}O_{5}\), mp 186.0~186.5°C; \([\alpha]_{D}^{20}+75^\circ\) (c 1.07, chloroform); \(\delta(\text{CDCl}_3)\), 4.69 (d, H-1, \(J_{1,2}=3.4\) Hz); 2-O-acetyl derivative, \(C_{20}H_{28}O_{6}\), mp 74.0~75.0°C; \([\alpha]_{D}^{20}+59^\circ\) (c 0.97, chloroform); \(\delta(\text{CDCl}_3)\), 4.75 (dd, H-2, \(J_{2,3}=8.3\) Hz) and 4.82 (d, H-1, \(J_{1,2}=3.2\) Hz). Treatment of 7 with N-bromo-succinimide in boiling carbon tetrachloride solution\(^{17}\) yielded non-crystalline methyl 4-O-benzoyl-6-bromo-3-C-butyl-3,6-dideoxy-\(\alpha\)-D-glucopyranoside (8) which was reduced with lithium aluminum hydride in tetrahydrofuran to give methyl 3-C-butyl-3,6-dideoxy-\(\alpha\)-D-glucopyranoside (9) in a 50% yield (based on 7), \(C_{18}H_{22}O_{4}\), mp 103.0~104.0°C; \([\alpha]_{D}^{20}+132^\circ\) (c 1.82, chloroform); \(\delta(\text{CDCl}_3)\), 1.25 (d, 5-CH\(_3\)), 2.58 (m, H-2), 3.76 (dd, H-3, \(J_{2,3}=7.0\) Hz), and 4.20 (dq, H-4, \(J_{4,5}=6.0\) Hz). Treatment of 9 with aqueous sodium hydroxide gave a free sugar (11) as a syrup in a 93% yield. Two stage oxidation of 11 with periodate-hypoiodite\(^{18}\) afforded (2S, 3R, 4R)-2-butyl-3,4-dihydroxypentanoic acid-1,4-lactone (12) in a 56% yield, \(C_{6}H_{10}O_{4}\), mp 50.0~51.0°C; \([\alpha]_{D}^{20}+17^\circ\) (c 0.95, methanol); \([\theta]_{254}+3070^\circ\) pk, \(\phi=3470\) (OH) and 1745 cm\(^{-1}\) (lactone); \(\delta(\text{CD}_{3}OD)\), 1.41 (d, 4-CH\(_3\)), 2.60 (m, H-2), 3.76 (dd, H-3, \(J_{2,3}=8.2\), \(J_{3,4}=7.5\) Hz), and 4.20 (dq, H-4, \(J_{4,5}=6.0\) Hz); \(\delta(\text{CDCl}_3)\), 1.45 (d, 4-CH\(_3\)), 2.58 (m, H-2), 3.84 (dd, H-3, \(J_{2,3}=8.5\), \(J_{3,4}=7.0\) Hz), and 4.25 (dq, H-4, \(J_{4,5}=6.2\) Hz). The physical data of 12 indicated that 12 was the enantiomer of the natural (−)-blastmycinolactol([−]−2).

The absolute configurations for the natural blastmycinolactol, blastmycinone and antimycin lactones, therefore, were completely established as 2(R), 3(R), 4(S). The total absolute configuration of antimycin A was determined as shown in Fig. 2 by combination of the known configuration [2(S), 3(R)] for L-threonine and the above-mentioned configuration for antimycin lactone.

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