ABSOLUTE CONFIGURATIONS OF ANTIMYCIN LACTONES AND ANTIMYCIN A

Sir:

The chemical structure of antimycins A_1 and A_3, which are the major components of antibiotic antimycin A complex, had already been established by VAN TAMELEN, *et al.*[1], BIRCH, *et al.*[2], and YONEHARA, *et al.*[3] The absolute configurations of blastmycinone[3] derived from antimycin A_3 (blastmycin) and of the antibiotic itself had been proposed by ENDO and YONEHARA[4] in 1967. In our recent synthetic studies on antimycin A_3, 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[5] might not be explained by the lactone configuration [**2**(S), **3**(S), **4**(R)] 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[5,6].

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[5] from the synthetic (−)-blastmycinolactol [(−)-**2**] which was identified with natural (−)-blastmycinolactol[3]. The lactone [(−)-**2**] was prepared by lithium aluminum hydride reduction of the optically active (+)-diastereomer of *t*-butyl 4-(N-benzyloxycarbonyl-O-*t*-butyl-L-threonyloxy)-2-butyl-3-(isovaleryloxy)pentanoate, only this being useful for the total synthesis of natural antimycin A_3. These experimental results also confirmed that the absolute configuration of the 3-O-acyl-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 ($[\Phi]_{234}$ −2870°tr, $[\theta]_{222}$ −5500) for the lactone $n-\pi^*$ transition. LEGRAND and BUCOURT rules[7] on ring chirality allow the negative sign of the COTTON effect to be predicted for the nonplaner E_3 conformation of (−)-**2** as shown in Fig. 3. The rotational change ($\Delta[\alpha]_D = -20°$) of (−)-**2** in methanol on addition of one equivalent of base was observed by WITCOP's method[8]. By application of HUDSON's lactone rule[9] 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-

Fig. 1. Antimycin lactone.

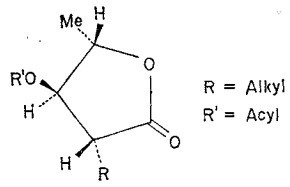
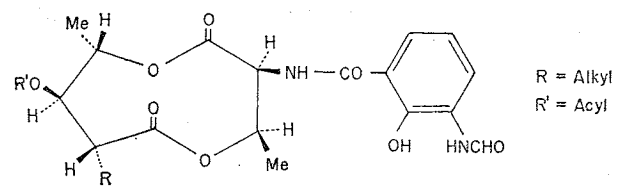


Fig. 2. Antimycin A.



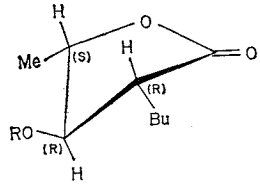
* The authors are indebted to Dr. H. NAGANAWA in the Institute of Microbial Chemistry for the measurements of 100 MHz NMR spectra and his helpful discussions.

** The authors wish to thank Mr. T. TAKAKUWA of Japan Spectroscopic Company for the measurements of ORD and CD.

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_3OD) 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** ($[\alpha]_D^{25}$ +42°, $[\theta]_{256}$ +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.

Fig. 3.

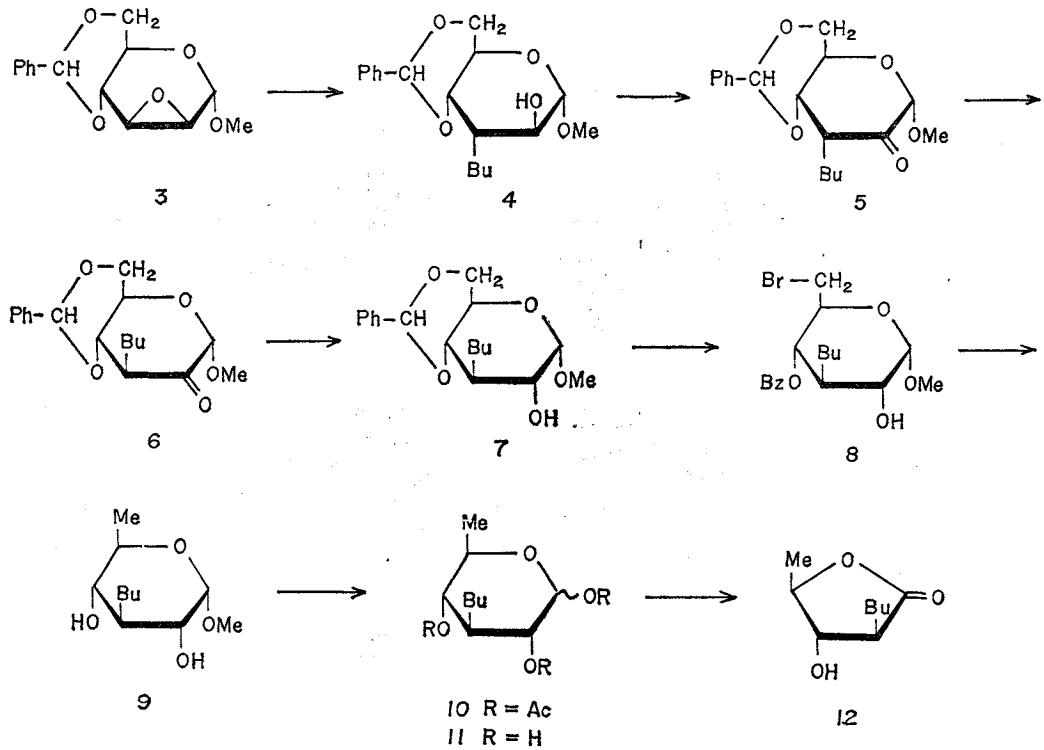


(+)-**1***: R=*i*-BuCO

(−)-**2**: R=H

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside(**3**)[13] was treated with excess of butylmagnesium chloride in ether[14] to afford methyl 4,6-O-benzylidene-3-C-butyl-3-deoxy-α-D-altropyranoside(**4**) as a syrup in a 69 % yield, $C_{18}H_{26}O_5$#, $[\alpha]_D^{18}$ +135° (*c* 1.77, chloroform); δ($CDCl_3$), 4.58 (d, H-1, $J_{1,2}$=1.0 Hz); 2-O-acetyl derivative, δ($CDCl_3$), 4.56 (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

Fig. 4.



* The natural (+)-blastmycinone[(+)-**1**] was shown to have the same conformation in methanol as that of (−)-**2** on the basis of its negative COTTON effect sign ($[\Phi]_{234}$ −1140° tr, $[\theta]_{223}$ −2510 in methanol).

\# Microanalyses agree with the molecular formula shown.

4, 6-O-benzylidene-3-C-butyl-3-deoxy-α-D-*ribo*-hexopyranosid-2-ulose(**5**) as a syrup in a 90% yield, $C_{18}H_{24}O_5$‡, $[\alpha]_D^{18}$ +40° (*c* 1.12, chloroform); ν_{max}^{liq} 1735 cm^{-1} (C=O); δ($CDCl_3$), 4.57 (d, H-1, $J_{1,3}$=1.0 Hz). Epimerization[16] of **5** with triethylamine in dimethylformamide afforded methyl 4, 6-O-benzylidene-3-C-butyl-3-deoxy-α-D-*arabino*-hexopyranosid-2-ulose(**6**) in a 79% yield, $C_{18}H_{24}O_5$‡, mp 85.0~86.0°C, $[\alpha]_D^{18}$ +39° (*c* 1.12, chloroform); ν_{max}^{KBr} 1740 cm^{-1} (C=O); δ($CDCl_3$), 4.60 (s, H-1, $J_{1,3}$=0 Hz). Lithium aluminum hydride reduction of **6** gave methyl 4,6-O-benzylidene-3-C-butyl-3-deoxy-α-D-glucopyranoside(**7**), $C_{18}H_{26}O_5$‡, mp 186.0~186.5°C; $[\alpha]_D^{18}$ +75°(*c* 1.07, chloroform); δ($CDCl_3$), 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; $[\alpha]_D^{18}$ +59° (*c* 0.97, chloroform); δ($CDCl_3$), 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-bromosuccinimide in boiling carbon tetrachloride solution[17] yielded non-crystalline methyl 4-O-benzoyl-6-bromo-3-C-butyl-3,6-dideoxy--α-D-glucopyranoside (**8**) which was reduced with lithium aluminum hydride in tetrahydrofuran to give methyl 3-C-butyl-3,6-dideoxy-α-D-glucopyranoside(**9**) in a 50% yield (based on **7**), $C_{11}H_{22}O_4$‡, mp 103.0~104.0°C; $[\alpha]_D^{18}$ +132° (*c* 1.82, chloroform); δ($CDCl_3$), 1.25 (d, 5-CH_3, J_{5,CH_3}=6.0 Hz) and 4.62 (d, H-1 $J_{1,2}$=3.8 Hz). Acetolysis of **9** with acetic anhydride-sulfuric acid afforded 1, 2, 4-tri-O-acetyl-3-C-butyl-3, 6-dideoxy-D-glucopyranose(**10**) as a crystalline anomeric mixture in a 82% yield. Hydrolysis of **10** 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, 3S, 4R)-2-butyl-3, 4-dihydroxypentanoic acid-1, 4-lactone(**12**) in a 56% yield, $C_9H_{16}O_3$‡, mp 50.0~51.0°C; $[\alpha]_D^{18}$ +17° (*c* 0.95, methanol); $[\Phi]_{234}$ +3070° pk, $[\theta]_{222}$ +5700 (in methanol); ν_{max}^{KBr} 3470 (OH) and 1745 cm^{-1} (lactone); δ(CD_3OD), 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,CH_3}=6.0 Hz); δ($CDCl_3$), 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,CH_3}= 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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(Received March 17, 1972)

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