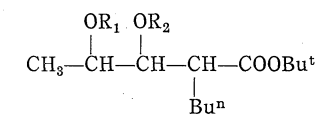
TOTAL SYNTHESIS OF ANTIMYCIN A_3

Sir:

The first total synthesis of antifungal antibiotic antimycin A_3 (blastmycin) in a form of diastereomeric mixture has recently been reported from our laboratory.[1] We now wish to report the total synthesis of natural antimycin A_3 (**1**).[2]

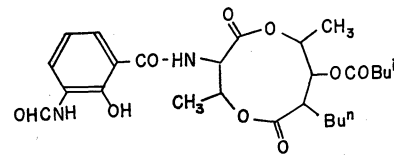
The previous paper[1] showed that the modified REFORMATSKY reaction of 2-benzyloxypropanal with *t*-butyl 2-bromohexanoate afforded the mixture of the diastereomeric *t*-butyl 4-benzyloxy-2-butyl-3-hydroxypentanoate which contained *ca.* 55 % of the major racemic diastereomer (**2**) and **2** could be transformed into the racemate of natural blastmycinone.[3] It has now been found that the preparative isolation of the major diastereomer (**2**) by silica gel column chromatography of the diastereomeric mixture using a solvent system petroleum ether–diisopropyl ether (3 : 1) gave the fraction consisting of **2** contaminated by *ca.* 14 % of the minor diastereomer.[4] This fraction of **2** was O-acylated with isovaleric anhydride in pyridine and the resulted major diastereomer (**3**) corresponding to **2** was isolated as a single racemate by silica gel column chromatography of the reaction product with a solvent system *n*-hexane – diisopropyl ether (10 : 1) in a 75 % yield: b.p. 115~119°C (bath temp./0.002 mmHg); n_D^{22} 1.4708; δ ($CDCl_3$), 1.21 (d, 4-CH_3, J=6.4 Hz), 1.38 (s, O-Bu^t), 3.58 (dq, 4-H, $J_{3,4}$=4.0 Hz) and 5.44 (dd, 3-H, $J_{2,3}$=8.2 Hz).

Anal. Found: C 71.56, H 9.69.
Calcd. for $C_{25}H_{40}O_5$: C 71.39, H 9.58.



2	R_1=PhCH$_2$, R_2=H
3	R_1=PhCH$_2$, R_2=Bu^iCO
4	R_1=H, R_2=Bu^iCO
(+)-**6**	R_1=R_2=H

Hydrogenolysis of **3** over palladium in methanol gave *t*-butyl 2-butyl-4-hydroxy-3-



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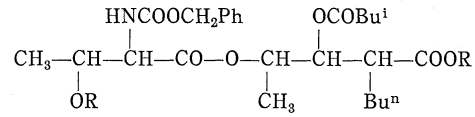
isovaleryloxypentanoate (**4**) in a 90 % yield: δ ($CDCl_3$), 1.18 (d, 4-CH_3, J=6.5 Hz), 3.89 (dq, 4-H, $J_{3,4}$=5.0 Hz) and 5.10 (dd, 3-H, $J_{2,3}$=7.8 Hz).

The racemic 4-hydroxy ester (**4**) was condensed with N-benzyloxycarbonyl-O-*t*-butyl-L-threonine[5] in the presence of N,N′-dicyclohexylcarbodiimide (DCCI) and pyridine to yield a mixture of two optically active diastereomers (**5a**, **5b**). On silica gel column chromatography of the mixture with a solvent system petroleum ether – diisopropyl ether (2 : 1), the less polar diastereomer (**5a**) was effectively separated (29 % from **4**) as a syrup from its more polar isomer (**5b**)*: $[\alpha]_D^{22}$ +10° (*c* 11.4, chloroform).

Anal. Found: C 65.97, H 9.10, N 2.35.
Calcd. for $C_{34}H_{55}NO_9$:
C 65.67, H 8.92, N 2.25.



5a (**5b**) R=Bu^t
9 R=H

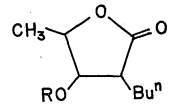
Lithium aluminium hydride reduction of **5a** at −40°C gave the optically active dihydroxy ester [(+)-**6**] (65 %): m.p. 48.0~48.8°C; $[\alpha]_D^{23}$ +16° (*c* 2.4, methanol).

Anal. Found: C 63.66, H 10.74.
Calcd. for $C_{13}H_{26}O_4$: C 63.83, H 10.64.

Hydrolysis of (+)-**6** afforded the hydroxylactone (−)-**7** (67 %): m. p. 50.0~51.0°C; $[\alpha]_D^{20}$ −18° (*c* 1.6, methanol) [Lit.[3], m.p. 49~50°C, $[\alpha]_D^{26}$ −5.27° (*c* 7.8, methanol)]; δ ($CDCl_3$), 1.45 (d, 4-CH_3, J=6.2 Hz), 2.58 (m, 2-H), 3.84 (dd, 3-H, $J_{2,3}$=8.5 Hz) and 4.25 (dq, 4-H, $J_{3,4}$=7.0 Hz); ν_{max}^{KBr} 3470 (OH), and 1745 cm^{-1} (lactone). The IR spectrum (in nujol) of (−)-**7** was identical with that[3] of an authentic sample of natural blastmycinolactol.

* The following data were obtained for isolated **5b**: yield 27 %; $[\alpha]_D^{22}$ −6° (*c* 10.1, chloroform).
Anal. Found: C 65.90, H 8.64, N 2.29. Calcd. for $C_{34}H_{55}NO_9$: C 65.67, H 8.92, N 2.25.

Anal. Found: C 63.06, H 9.51.
Calcd. for $C_9H_{16}O_3$: C 62.76, H 9.36.

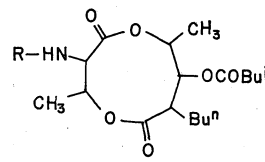


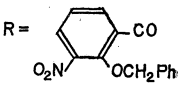
(−)-**7** R= H
(+)-**8** R= COBu^i

Preparation of blastmycinone [(+)-**8**] from the synthetic hydroxylactone (−)-**7** was carried out with isovaleric anhydride and pyridine: $[\alpha]_D^{22}$ +10° (*c* 1.5, chloroform) [Lit.[3], $[\alpha]_D^{25}$ +11.5° (*c* 20.8, chloroform)]. The gas chromatogram (polyester succinate column, He gas) of (+)-**8** showed a single peak having the same retention time as one of the two peaks of natural blastmycinone so that the peak of longer retention time corresponds to the blastmycinone having the O-isovaleryl group.[1) 2c)] The chemical shifts and coupling constants of the ring protons and ring methyl protons in the NMR spectrum ($CDCl_3$) of the synthetic blastmycinone were identical with those in the spectrum* of an authentic sample of natural blastmycinone.

De-*t*-butylation of **5a** with trifluoroacetic acid gave the free acid (**9**), which was cyclized with trifluoroacetic anhydride in benzene at 75°C for 8 hours to afford the intramolecular cyclization product, 3-benzyloxycarboxamido-7-butyl-4, 9-dimethyl-1, 5-dioxa-8-isovaleryloxycyclononane-2, 6-dione (**10**) as a colorless needle in a 1% yield: m. p. 109.0~109.5°C; $[\alpha]_D^{25}$ +70° (*c* 0.5, chlorofrom); δ ($CDCl_3$), 1.25 (d, 9-CH_3, J=6.2 Hz), 1.27 (d, 4-CH_3, J=7.0 Hz), 5.48 (d, NH, $J_{3,NH}$=8.0 Hz) and 5.54 (dq, 4-H, J=8.0 Hz); molecular ion at *m/e* 491.2473 (calcd., 491.2519).

Anal. Found: C 63.65, H 7.41, N 2.61.
Calcd. for $C_{26}H_{37}NO_8$:
C 63.52, H 7.59, N 2.85.



10 R= $PhCH_2OCO$
11 R= 

Removal of the benzyloxycarbonyl group of **10** by hydrogenolysis followed by N-acylation with O-benzyl-3-nitrosalicylic acid N-hydroxysuccinimide ester[8] yield 3-(O-benzyl-3′-nitrosalicylamido)-7-butyl-4, 9-dimethyl-1, 5-dioxa-8-isovaleryloxycyclononane-2, 6-dione (**11**) as a glassy solide in a 65% yield: δ ($CDCl_3$), 1.09 (d, 4-CH_3, J= 7.0 Hz), 1.27 (d, 9-CH_3, J=6.2 Hz), 5.17 (t, 3-H, $J_{3,NH}$=7.6 Hz), 5.55 (dq, 4-H, $J_{3,4}$=7.6 Hz), 7.35 (t, 5′-H, $J_{5',6'}=J_{4',5'}$=8.0 Hz), 7.95 (dd, 4′-H or 6′-H, $J_{4',6'}$=2.0 Hz), 8.03 (d, NH), and 8.25 (dd, 6′-H or 4′-H).

The product (**11**) was again hydrogenolyzed and then N-formylated with 98% formic acid and DCCI. The product was purified by preparative layer chromatography using silica gel with *n*-hexane-ethyl acetate (5: 3) and recrystallization from ether-petroleum ether to afford antimycin A_3 (**1**) as a colorless prism in a 65% yield: m.p. 174~174.5°C [Lit., 174.5~175°C[7], 168~169°C[3], 170.5~171.5°C[8]]; $[\alpha]_D^{24}$ +80°, $[\alpha]_{546}^{24}$ +95°, $[\alpha]_{405}^{24}$ +190° (*c* 0.2, chloroform) [Lit., $[\alpha]_D^{26}$ +79.4° (*c* 1, chloroform)[7], $[\alpha]_D^{26}$ +64.3° (*c* 1.0, chloroform)[8]]; λ_{max}^{MeOH} 225 nm (log ε=4.52) and 320 nm (log ε=3.86); $\nu_{max}^{CHCl_3}$ 3420, 1748, 1703, 1646, 1613 and 1528 cm^{-1}. The NMR spectrum (100 MHz, $CDCl_3$) of the synthetic antimycin A_3 was very similar to that of an authentic sample** of natural antimycin A, and especially, both the spectra were identical with respect to the chemical shifts and coupling constants of the dilactone ring protons and the ring methyl protons which may be closely related to the configuration and conformation in the ring structure***

* The NMR chart was kindly provided by Prof. H. YONEHARA.

** The sample of antimycin A (complex) was generously supplied by the Kyowa Hakko Kogyo Co.: m.p. 139.0~139.5°C; $[\alpha]_D^{24}$ +80°, $[\alpha]_{546}^{24}$ +94°, $[\alpha]_{405}^{24}$ +191° (*c* 0.4, chloroform); molecular ions of the components at *m/e* (relative intensities), 562 (1), 548 (12), 534 (7), 520 (16), 506 (2) and 492 (2).

*** The inspection of the NMR spectra [in $CDCl_3$, C_6D_6 and $(CD_3)_2CO$] of the antimycin A complex revealed that all the antimycin A components had the same stereochemistry in respect of their dilactone rings.

of the natural antimycin A. Molecular ion at *m/e* 520.2412 (calcd., 520.2421).

Anal. Found: C 59.72, H 7.15, N 5.25.
Calcd. for $C_{26}H_{36}N_2O_9$:
C 59.99, H 6.97, N 5.38.

On paper chromatography with a solvent system water – ethanol – acetone (7 : 2 : 1),[8] the synthetic specimen showed on the bioautogram (test organism, *Piricularia orizae*) a single spot corresponding to that of the natural antimycin A_3 in the antimycin A complex.

Minimal inhibitory concentrations (mcg/ml) of the synthetic specimen against test fungi, as compared to those (in parenthesis) of natural antimycin A complex, were as follows: *Candida albicans* 3147, 12.5 (12.5), *Piricularia orizae* 0.025 (0.025) by agar dilution method with 1% glucose nutrient agar, 27°C, 24~70 hours.

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MITSUHIRO KINOSHITA
MASAO WADA
SHIMPEI ABURAGI
SUMIO UMEZAWA

Department of Applied Chemistry,
Keio University, Koganei-shi,
Tokyo, Japan

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4) The minor diastereomer has the Rf-values close to those of the major isomer (**2**) in TLC (silica gel) with several kinds of solvent system, however, it differs from **2** in the NMR spectral feature (in $CDCl_3$).

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