# Improved Synthesis of Antimycin $A_3$

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(Received July 8, 1978)

An improved synthesis of antimycin $A_3$ was accomplished by a suitable lactonization of 3-*O*-benzyl or 3-*O*-isovaleryl derivative (**10a** or **10b**) of (2*R*, 3*R*, 4*S*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-2-butyl-3-hydroxypentanoic acid, which was synthesized by starting from the corresponding 3-*O*-benzyl or 3-*O*-isovaleryl derivative (**4a** or **4b**) of methyl 2-*C*-butyl-2, 5-dideoxy-β-L-arabinofuranoside, respectively. Acid hydrolysis of **4a** or **4b** followed by reduction with sodium borohydride afforded 3-*O*-benzyl or 3-*O*-isovaleryl-1, 3, 4-pentanetriol (**5a** or **5b**), respectively. Tritylation of **5a** or **5b** followed by succesive 4-*O*-acylation with *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine, detritylation, oxidation with chromium trioxide-acetic acid-pyridine, and de-*t*-butylation gave the hydroxy ester acid **10a** or **10b**, respectively. Lactonization of **10a** or **10b** through its 2-pyridinethiol ester **11a** or **11b** activated with silver perchlorate afforded the corresponding nine-membered dilactone derivative **12a** or **12b** in 33 or 13% yield, respectively. Removal of *N*,*O*-protecting groups of **12a** by hydrogenolysis, followed by successive *N*- and *O*-acylation gave the antimycin $A_3$ precursor, (3*S*, 4*R*, 7*R*, 8*R*, 9*S*)-3-(2-benzyloxy-3-nitrobenzoylamino)-4, 9-dimethyl-7-butyl-8-isovaleryloxy-1, 5-dioxonane-2, 6-dione derived from **12b**.

Antifungal antibiotic antimycin A complex has a unique nine-membered dilactone structure. In the first total synthesis[1,2] of antimycin $A_3$ (**1**), one of the major components of the complex, the dilactone intermediate, (3*S*,4*R*,7*R*,8*R*,9*S*)-3-benzyloxycarbonyl-amino-7-butyl-4,9-dimethyl-8-isovaleryloxy-1,5-dioxonane-2,6-dione (**12b**) was synthesized by lactonization of (2*R*, 3*R*,4*S*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-2-butyl-3-isovaleryloxypentanoic acid (**10b**) prepared by the condensation of (±)-2,3-*threo*-3,4-*erythro*-2-butyl-4-hydroxy-3-isovaleryloxypentanoic acid *t*-butyl ester with *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine. The lactonization of **10b** was effected only with trifluoroacetic anhydride in hot benzene, but the yield of **12b** was extremely poor.[2]

We briefly communicated[3] the synthesis of deisovalerylblastmycin (**2**) which constitutes a new route for the stereospecific synthesis of antimycin A involving an improved lactonization step. We now describe in full the improved synthesis of antimycin $A_3$.[3] Since the first synthesis of antimycin $A_3$, studies have progressed in the field of macrolide synthesis, new lactonization methods being found to be effective for the synthesis of large lactone compounds.[4] It was expected that the yield of the medium lactone ring formation such as lactonization of the hydroxy ester acid **10b** would also be enhanced by appropriate modification in the structure of the reactant or by choice of a more suitable method for lactonization of the reactant.

The structural modification undertaken was an exchange of the 3-isovaleryloxy group of **10b** by benzyloxy group convertible into the former after lactonization. The modified hydroxy ester acid, (2*R*,3*R*,4*S*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-3-benzyloxy-2-butylpentanoic acid (**10a**) was synthesized through the stereospecific route (Fig. 1) starting from the sugar derivative **3**.[5] The route was utilizable for the stereospecific synthesis of **10b**.

Lactonization of **10a** or **10b** through its 2-pyridinethiol ester **11a** or **11b** activated with silver perchlorate by the method of Gerlach and Thalmann[6] effectively afforded the corresponding dilactone intermediate **12a** or **12b** in 33 or 13% yield, respectively. The comparatively high yields are in contrast with the 0.8% yield[2] of **12b** obtained by the trifluoroacetic anhydride method. The dilactone derivative **12a** was converted into the 3-(2-benzyloxy-3-nitrobenzoylamino)-8-hydroxydilactone **15**, a synthetic precursor of the antibiotic deisovalerylblastmycin (**2**).[3] Isovalerylation of **15** afforded the antimycin $A_3$ precursor **16** which had been derived from **12b** *via* the amino dilactone derivative **13b**[2](Fig. 3). The synthesis of antimycin $A_3$ was thus improved through the route *via* **12a** effectively provided by suitable lactonization of the modified hydroxy ester acid **10a**. Moreover, the previous route *via* **12b** was also useful in the antimycin $A_3$ synthesis by the improved lactonization of **10b**.

## Results and Discussion

Methyl 2-*C*-butyl-2,5-dideoxy-β-L-arabinofuranoside (**3**) was converted into the 3-*O*-benzyl derivative **4a** with benzyl bromide and sodium hydride in THF or into the 3-*O*-isovalerate **4b** with isovaleric anhydride in pyridine. Acid hydrolysis of **4a** followed by sodium borohydride reduction gave (2*S*,3*R*,4*S*)-3-*O*-benzyl-2-butyl-1,3,4-pentanetriol (**5a**) in 94% yield. Acid hydrolysis of **4b** followed by reduction with sodium borohydride in 70% ethanol at −10 °C afforded an 8:1 mixture of desired 3-*O*-isovaleryl triol (**5b**) and its positional isomer, 4-*O*-isovalerate (**5b'**)in a total yield of 97%. The formation of **5b'** was probably due to the 3→4 *O*-acylmigration proceeding under basic conditions in the borohydride reduction step.

Tritylation of **5a** with triphenylmethyl chloride in pyridine at 40 °C gave the 3-*O*-benzyl-1-*O*-trityl-1,3,4-pentanetriol (**6a**) quantitatively. Acylation of the 4-hydroxyl group of **6a** with excess *N*-(benzyloxycarbonyl)-*O*-*t*-butyl-L-threonine in the presence of dicyclohexylcarbodiimide (DCCI) and pyridine afforded the condensation product **7a** in 74% yield. Tritylation of the 8:1 mixture of **5b** and **5b'** at room temperature gave 3-*O*-isovaleryl-1-*O*-trityl-1,3,4-pentanetriol (**6b**) in

74% yield after being subjected to chromatography. However, when the reaction with **5b** was conducted at 40 °C, the major product was the isomer, 4-*O*-isovaleryl-1-*O*-trityl-1,3,4-pentanetriol (**6b'**), presumably formed from **6b** by the 3→4 *O*-acyl migration. Condensation of **6b** with the threonine derivative by the DCCI method afforded the ester **7b** in 65% yield.

Detritylation of **7a** and **7b** with 90% acetic acid gave the corresponding alcohols, **8a** and **8b** in 95 and 62.2% yields, respectively. Oxidation of **8a** and **8b** with a mixture of chromium trioxide, acetic acid and pyridine[7] afforded the corresponding ester acids, **9a** and **9b** in 76 and 96% yields, respectively.

The *t*-butyl groups of **9a** and **9b** were removed by treatment with trifluoroacetic acid to give (2*R*,3*R*,4*S*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-3-benzyloxy-2-butylpentanoic acid (**10a**) and (2*R*,3*R*,4*S*)-4-(*N*-benzyloxycarbonyl-L-threonyloxy)-3-isovaleryloxy-2-butylpentanoic acid (**10b**), respectively.

In contrast with **10b**, the modified hydroxy ester acid **10a** afforded no cyclization product on treatment with trifluoroacetic anhydride in hot benzene by the same procedure as that for **10b**.[2] IR spectroscopy revealed that the major product of the reaction was the *O*-trifluoroacetyl derivative of **10a**.

The hydroxy acids **10a** and **10b** were converted into the corresponding 2-pyridinethiol esters, **11a** and **11b** by action of di-2-pyridyl disulfide and triphenylphosphine according to Mukaiyama *et al.*[8] in good yields after being subjected to chromatography. By the method of Gerlach and Thalmann,[6] the intramolecular cyclization of **11a** and **11b** was effected in about 0.01 M benzene solution with a 1.5 equivalent amount of silver perchlorate to yield the corresponding dilactone derivatives, **12a** and **12b** in 33 and 13.4% yields, respectively. In the cyclization of **11a** with silver perchlorate, no formation of intermolecular cyclization product was observed, the hydroxy ester acid **10a** being recoverd in good yield. Cyclization of **11a** carried out in a 0.00 M solution showed no improvement in the yield of **12a**.

According to the method of Corey and Nicolaou,[9] the crude 2-pyridinethiol ester **11a** was refluxed in a 0.005 M xylene solution to afford the sole intramolecular cyclization product in 13.7% yield. The product was distinguishable from **12a** in the ring coupling constants ($J_{7,8}$=4.0 and $J_{8,9}$=9.2 Hz), suggesting that the product might be **12a'**, the 7-epimer of **12a**.

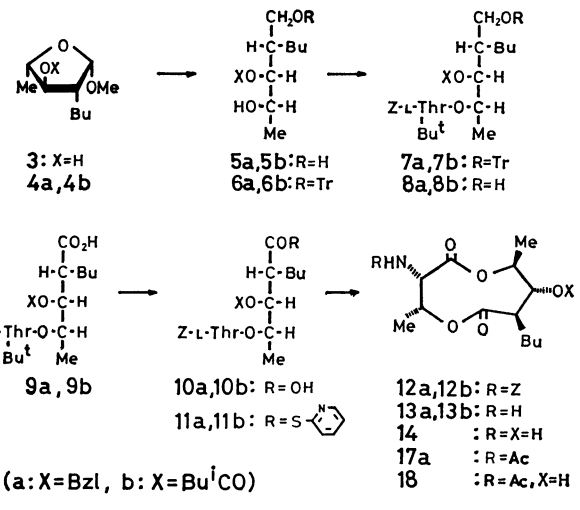


Fig. 1.

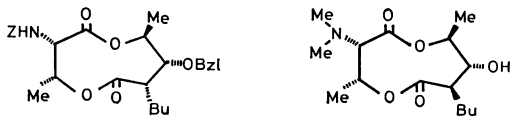


Fig. 2.

Hydrogenolysis of **12a** with palladium black in methanol under hydrogen atmosphere at 50 p.s.i. afforded the *N*-debenzyloxycarbonylated dilactone **13a**, *O*-debenzylation of which was effected *via* the *N*-acetyl derivative **17a** to afford **18**, the *N*-acetyl derivative of the amino hydroxy dilactone **14**. Hydrogenolysis of **12a** with palladium black in methanol containing a small amount of hydrogen chloride under hydrogen atmosphere at 50 p.s.i. gave the hydrochloride of **14**, which was selectively *N*-acylated with 2-benzyloxy-3-nitrobenzoic acid *N*-hydroxysuccinimide ester[10] to afford **15** in 72% yield. On the other hand, hydrogenolysis of **12a** with palladium black in methanol at 40 °C under hydrogen atmosphere at 50 p.s.i. yielded the dimethylamino hydroxy dilactone **19** whose structure was determined by its PMR and mass spectrum.

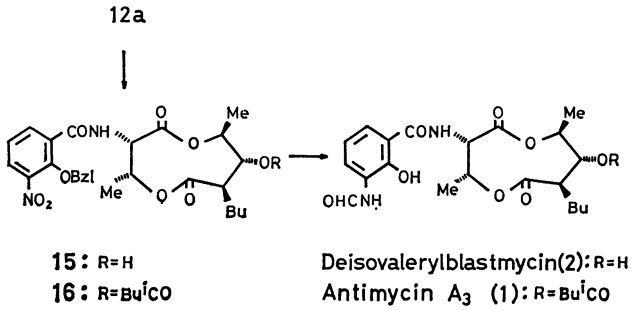


Fig. 3.

The *N*-acylamino hydroxy dilactone **15** was *O*-isovalerylated with isovaleric anhydride in pyridine to afford (3*S*,4*R*,7*R*,8*R*,9*S*)-3-(2-benzyloxy-3-nitrobenzoylamino)-4,9-dimethyl-7-butyl-8-isovaleryloxy-1,5-dioxononane-2,6-dione (**16**),[2] the antimycin $A_3$ precursor, in 88% yield.

## Experimental

Melting points were determined on a micro hot stage and are uncorrected. IR spectra were taken on a Hitachi 225 Spectrophotometer, Mass spectra on a JMS-D-100, and PMR spectra on Varian A-60D and HA-100D Spectrometers using TMS as an internal standard. Optical rotations were measured with a Zeiss Photoelectroic Precision Polarimeter. CD spectra were taken on a JASCO J-20 Spectropolarimeter. TLC was carried out on Wakogel B-5 and silica gel column chromatography on Wakogel C-200 which was activated at 110 °C for 1 h. Concentration was carried out at reduced pressure below 40 °C.

*Methyl 3-O-Benzyl-2-C-butyl-2,5-dideoxy-β-L-arabinofuranoside (4a).* A suspension of 55% NaH (450 mg, 10.3 mmol) in THF(9 ml) was added to a solution of methyl 2-*C*-butyl-2,5-dideoxy-β-L-arabinofuranoside (**3**)[5] (1.29 g, 6.83 mmol) and stirred at room temperature for 2 h. Benzyl bromide (1.22 ml, 10.3 mmol) was added to the mixture and stirred at room temperature overnight. The reaction mixture was poured into cold water (50 ml) and extracted with ethyl acetate. The organic layer was washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel(150 g) with benzene–ethyl acetate (30 : 1) to afford a colorless syrup of **4a** (1.54 g, 81%) : $[\alpha]_D^{21}$ −98°(*c* 1.1, $CHCl_3$); PMR($CDCl_3$) δ 1.32 (d, 4-$CH_3$, $J$=6.4 Hz), 3.44(s, $OCH_3$), 3.36 (dd, H-3, $J_{2,3}$= 4.0, $J_{3,4}$=6.1 Hz), 4.25 (dq, H-4), 4.68 (s, $CH_2Ph$), and 4.76 (d, H-1, $J_{1,2}$=1.8 Hz).

Found: C, 73.65; H, 9.27%. Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%.

*Methyl 3-O-Isovaleryl-2-C-butyl-2,5-dideoxy-β-L-arabinofuranoside (4b).* A mixture of **3** (1.08 g, 5.71 mmol), isovaleric anhydride (1.72 ml, 8.1 mmol) and pyridine (10 ml) was kept at room temperature for 2 days. The reaction mixture was poured into cold water (20 ml) and extracted with chloroform. The combined extracts were washed with saturated aqueous NaCl solution, dried, and evaporated. The residue was chromatographed on silica gel (150 g) with benzene–ethyl acetate(50 : 1) to afford an essentially pure sample of **4b** as a pale yellow syrup (1.52 g, 98%): PMR ($CDCl_3$) δ 0.97[d, 6H, $CH(CH_3)_2$, $J$=6.6 Hz], 1.33 (d, 3H, 4-$CH_3$, $J$=6.5 Hz), 3.40 (s, 3H, $OCH_3$), 4.08 (dq, H-4, $J_{3,4}$=5.9 Hz), 4.61 (dd, H-3, $J_{2,3}$=3.9 Hz), and 4.70 (d, H-1, $J_{1,2}$=1.8 Hz).

*(2S,3R,4S)-3-O-Benzyl-2-butyl-1,3,4-pentanetriol (5a).* A solution of **4a** (1.53 g) in a mixture of dioxane (44 ml) and 1 M HCl (11 ml) was kept at room temperature for 3 days. The reaction mixture was neutralized with solid $NaHCO_3$, the filtrate being evaporated. The residue was chromatographed on silica gel (150 g) with benzene–ethyl acetate (6 : 1) to give the free sugar (1.14 g). Unchanged **4a** recovered on chromatography was again subjected to hydrolysis and chromatography to afford an additional amount of the free sugar (260 mg). The total yield was 1.40 g (97%).

The free sugar (1.40 g, 5.30 mmol) was dissolved in 70% ethanol (28 ml), $NaBH_4$ (100 mg, 2.65 mmol) being added to the solution. The solution was stirred at room temperature for 2 h and then concentrated.The residue was taken in ethyl acetate (50 ml), and the mixture was washed with saturated aqueous NaCl solution, dried, and evaporated to afford a colorless syrup of **5a**(1.37 g, 94% overall yield based on **4a**). A portion of this product was chromatographed on silica gel with benzene–ethyl acetate (6 : 1) to give an analytical sample: $[\alpha]_D^{21}$ +1°, $[\alpha]_{365}^{21}$ −18° (*c* 0.4, $CHCl_3$); PMR ($CDCl_3$) δ 1.31 (d, 4-$CH_3$, $J$=6.4 Hz), 3.52 (dd, H-3, $J_{2,3}$= 3.4 and $J_{3,4}$=6.0 Hz), and 4.73 (s, $CH_2Ph$).

Found: C, 72.22; H, 9.77%. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.

*(2S,3R,4S)-2-Butyl-3-O-isovaleryl-1,3,4-pentanetriol (5b).* A solution of **4b** (1.55 g) in a mixture of dioxane (36 ml) and 2 M HCl (10.7 ml) was kept at 40 °C for 2 days. The reaction mixture was neutralized (pH 4) with solid $NaHCO_3$ and evaporated. The residue was extracted with ethyl acetate and the extract was evaporated. The residual syrup was chromatographed on silica gel (35 g) with benzene–ethyl acetate (15 : 1) to afford a colorless syrup of the free sugar (941 mg, 64%) and **4b** (395 mg, 25.5%). Free sugar: PMR ($CDCl_3$) δ 0.98[d, $CH(CH_3)_2$, $J$=6.8 Hz], 1.33 (d, 4-$CH_3$, $J$=6.3 Hz), 4.25 (dq, H-4, $J_{3,4}$=4.6 Hz), 4.65 (dd, H-3, $J_{2,3}$=3.2 Hz), and 5.22 (d, H-1, $J_{1,2}$=1.9 Hz). A solution of $NaBH_4$(124 mg, 2.17 mmol) in 70% ethanol (2.5 ml) was added under stirring to a solution of the free sugar (847 mg, 3.28 mmol) in 70% ethanol (17 ml) cooled at −10 °C. After being stirred at 0 °C for 1 h, the reaction mixture was neutralized with 2 M HCl and evaporated to dryness. The residue was extracted with ethyl acetate, the combined extracts being washed with saturated aqueous NaCl solution, dried, and evaporated to afford a crude syrup of **5b**(826 mg, 97%), which was used for subsequent synthesis. A portion of this sample (54.5 mg) was chromatographed on silica gel (5.5 g) with benzene–ethyl acetate (3 : 1) to give **5b**($R_f$ 0.12, 43.3 mg, 81%) and its positional isomer, 2-butyl-4-*O*-isovaleryl-1,3,4-pentanetriol (**5b'**) ($R_f$ 0.26, 10 mg, 19%). **5b**: PMR($CDCl_3$) δ 0.98[d, $CH(CH_3)_2$, $J$=6.2 Hz], 1.21(d, 4-$CH_3$, $J$=6.3 Hz), 2.51(s, 2H, OH), *ca.* 3.6(m, 2H, H-1,1'), 4.00(dq, H-4, $J_{3,4}$=7.0 Hz), and 4.91(dd, H-3, $J_{2,3}$=3.8 Hz). Isomer of **5b**: PMR($CDCl_3$) δ 0.98[d, $CH(CH_3)_2$, $J$=6.5 Hz], 1.32(d, 4-$CH_3$, $J$=6.3 Hz), *ca.* 2.1 (m, 2H, OH), *ca.* 3.8(m, 3H, H-1,1',3), and 5.07(dq, H-4, $J_{3,4}$=5.9 Hz).

*(2S,3R,4S)-4-O-(N-Benzyloxycarbonyl-O-t-butyl-L-threonyl)-3-O-benzyl-2-butyl-1-O-trityl-1,3,4-pentanetriol (7a).* Triphenylmethyl chloride (1.68 g, 6.02 mmol) was added to a solution of **5a** (1.34 g, 5.03 mmol) in dry pyridine (6.7 ml) and the solution was allowed to stand at 40 °C overnight. Water (30 ml) was added to the reaction mixutre under cooling and the mixture was extracted with chloroform (20 ml×3). The combined extracts were washed with saturated aqueous NaCl solution, dried and evaporated to afford 1-*O*-tritylated product **6a** (2.56 g, 100%), which was used in the next reaction without purification. A solution of **6a** (2.56 g, 5.03 mmol) in dry ether (3.8 ml) and dry pyridine (0.43 ml) was added to a solution of DCCI (1.14 g, 5.54 mmol) in dry ether (3.1 ml) under ice-cooling. To this solution was added slowly a solution of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine (1.71 g, 5.52 mmol) in dry ether (3.1 ml) under cooling and stirred at 5 °C for 3 days. A solution of DCCI (1.14 g) and pyridine (0.43 ml) in dry ether (3.8 ml) and a solution of the threonine derivative (1.71 g) in dry ether (3.1 ml) were then added successively and the mixture was kept at 5 °C for 3 days. After removal of *N,N'*-dicyclohexylurea (DCU) by filtration, the filtrate was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution, dried, and evaporated. The residue (9 g) was chromatographed on silica gel (450 g) with benzene–ethyl acetate (50 : 1) to give a pure sample of the condensation product **7a**: colorless syrup (2.96 g, 74%); $[\alpha]_D^{21}$ +3°, $[\alpha]_{365}^{21}$ +26° (*c* 0.39, $CHCl_3$); PMR($CDCl_3$) δ 1.07 (s, $OBu^t$), 1.20(d, 4-$CH_3$, $J$=6.3 Hz), 1.29[d, $CH_3$ of threonine, $J$=6.7 Hz], 3.16(d, H-1, $J_{1,2}$=5.2 Hz), 3.72 (dd, H-3, $J_{2,3}$=5.5, $J_{3,4}$=2.8 Hz), 4.56 (ABq, $CH_2Ph$), 5.06(ABq, $CH_2Ph$ of benzyloxycarbonyl), 4.54(dq, H-4), and 5.60(d, NH, $J$=9.2 Hz).

Found: C, 76.76; H, 7.78; N, 2.02%. Calcd for $C_{51}H_{61}NO_7$: C, 76.56; H, 7.69; N, 1.75%.

*(2S,3R,4S)-2-Butyl-3-O-isovaleryl-1-O-trityl-1,3,4-pentanetriol (6b).* a) A solution of the crude **5b**(796 mg, 3.05 mmol) and triphenylmethyl chloride (1.70 g, 6.10 mmol) in dry pyridine (8 ml) was kept at room temperature for 3 days. The reaction mixture was poured into water and extracted with chloroform. The extracts were washed with saturated aqueous NaCl solution, dried, and evaporated to afford a yellow syrup (1.7 g), which was chromatographed on silica gel (150 g) with benzene–ethyl acetate (50 : 1) to afford a homogeneous sample of **6b** [$R_f$ 0.70 (6 : 1 benzene–

ethyl acetate), 1.13 g, 74%]: PMR ($CDCl_3$) $\delta$ 0.95[d, $CH(CH_3)_2$, $J$=6.8 Hz], 1.21 (d, 4-$CH_3$, $J$=7.5 Hz), *ca.* 3.1 (m, 2H, H-1,1'), 5.07(dd, H-3, $J_{2,3}$=4.7, $J_{3,4}$=6.3 Hz), and *ca.* 7.3(m, 15H, $CPh_3$).

Found: C, 78.48; H, 8.30%. Calcd for $C_{33}H_{42}O_4$: C, 78.85; H, 8.42%.

b) A homogeneous sample of **5b** (11.6 mg, 0.0445 mmol) was treated with triphenylmethyl chloride (49.6 mg, 0.178 mmol) in dry pyridine (0.23 ml) at 40 °C for 2 days and the mixture was worked up in the same manner as described above and chromatographed with the same solvent system to afford **6b**($R_f$ 0.70, 9.7 mg, 43.3%) and its isomer, 4-*O*-isovalerate **6b'**($R_f$ 0.80, 12.3 mg, 55%): PMR($CDCl_3$) $\delta$ 0.92[d, $CH(CH_3)_2$, $J$=6.4 Hz], 1.24(d, 4-$CH_3$, $J$=6.1 Hz), *ca.* 2.8(m, 1H, OH), *ca.* 3.3(m, 2H, H-1,1'), *ca.* 3.8(m, 1H, H-3), 4.97(dq, H-4, $J_{3,4}$=5.2 Hz), and *ca.* 7.3(m, 15 H, $CPh_3$).

*(2S,3R,4S)-4-*O*-(*N*-Benzyloxycarbonyl-*O*-t-butyl-*L*-threonyl)-2-butyl-3-*O*-isovaleryl-1-*O*-trityl-1,3,4-pentanetriol (**7b**).* A solution of *N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonine (319 mg, 2.28 mmol) in dry ether (0.7 ml) was added dropwise under stirring to a cooled solution of DCCI (231 mg, 1.12 mmol), **6b** (471 mg, 0.937 mmol), and dry pyridine (0.075 ml, 2.07 mmol) in dry ether (0.62 ml). The mixture was stirred at 0 °C for 3 days, during which time the same amount of DCCI, pyridine, and the threonine derivative were added twice. The reaction mixture was worked up in the same manner as described in the preparation of **7a**. The crude product (5.11 g) was chromatographed on silica gel (80 g) with benzene-ethyl acetate (50 : 1) to afford **7b** (484 mg, 65%) as a syrup: PMR($CDCl_3$), $\delta$ 0.99 [d, $CH(CH_3)_2$, $J$=6.6 Hz], 1.09 (s, $OBu^t$), 1.19(d, $CH_3$ of threonine, $J$=6.5 Hz), 1.21 (d, 4-$CH_3$, $J$=7.6 Hz), 3.09 (m, 2H, H-1,1'), 4.1—4.2(m, 2H, H-2',3'), 5.15(ABq, $CH_2Ph$), 5.2—5.3(m, 3H, NH, H-3,4), and *ca.* 7.4(m, Ph).

Found: C, 74.69; H, 8.00; N, 1.78%. Calcd for $C_{30}H_{49}NO_8$: C, 74.12; H, 8.00; N, 1.76%.

*(2S,3R,4S)-4-*O*-(*N*-Benzyloxycarbonyl-*O*-t-butyl-*L*-threonyl)-3-*O*-benzyl-2-butyl-1,3,4-pentanetriol (**8a**).* A solution of **7a** (1.97 g, 2.47 mmol) in 90% aqueous acetic acid (40 ml) was kept at 40 °C for 15 hr and then evaporated to afford a pale yellow syrup (1.84 g). Chromatography of the syrup on silica gel (100 g) with benzene-ethyl acetate (15:1) gave a colorless syrup of **8a**(1.30 g, 95%): $[\alpha]_D^{21}$ +3°, $[\alpha]_{365}^{21}$ +18° (*c* 0.95, $CHCl_3$).

Found: C, 69.08; H, 8.43; N, 2.44%. Calcd for $C_{32}H_{47}NO_7$: C, 68.91; H, 8.49; N, 2.51%.

*(2S,3R,4S)-4-*O*-(*N*-Benzyloxycarbonyl-*O*-t-butyl-*L*-threonyl)-2-butyl-3-*O*-isovaleryl-1,3,4-pentanetriol (**8b**).* Treatment of **7b** (736 mg) with 90% aqueous acetic acid (16.6 ml) at room temperature for 1 day followed by evaporation afforded a yellow syrup (920 mg), which was chromatographed on silica gel (60 g) with benzene-ethyl acetate (6:1) to give a pure sample of **8b** as a colorless syrup (318 mg, 62.2%): $[\alpha]_D^{23}$ −10°(*c* 2.4, $CHCl_3$); $IR_{max}$($CHCl_3$, 0.1 M) 3500(OH), 3430(NH), and 1715 $cm^{-1}$ (ester and amide); PMR($CDCl_3$) $\delta$ 1.00[d, $CH(CH_3)_2$, $J$=6.5 Hz], 1.16(s, $OBu^t$), *ca* 1.2 (m, 6H, 4-$CH_3$, 3'-$CH_3$), 3.6 (m, 3H, H-1,1', OH), *ca* 4.2 (m, 2H, H-2',3'), 5.16 (s, $CH_2Ph$), 5.2—5.7 (m, 3H, NH, H-3,4), and 7.39 (s, Ph).

Found: C, 65.23; H, 8.78; N, 2.41%. Calcd for $C_{30}H_{47}NO_8$: C, 65.31; H, 8.95; N, 2.54%.

*(2R,3R,4S)-4-(*N*-Benzyloxycarbonyl-*O*-t-butyl-*L*-threonyloxy)-3-benzyloxy-2-butylpentanoic Acid (**9a**).* A solution of **8a** (1.18 g, 2.11 mmol) in a chromium trioxide-acetic acid-pyridine reagent† (26.2 ml, 8.44 mmol) was kept at room temperature overnight. The reaction mixture was diluted with cold water (50 ml) and extracted with ether (20 ml×3). The combined extracts were washed with saturated aqueous NaCl solution, dried, and evaporated. The residual syrup (1.19 g) was chromatographed on silica gel (100 g) with hexane-benzene-acetone-acetic acid (40:20:1:2) to afford a pure sample of **9a**; colorless syrup (920 mg, 76%): $[\alpha]_D^{23}$ +3°, $[\alpha]_{365}^{23}$ +14° (*c* 2.4, $CHCl_3$), PMR($CDCl_3$) $\delta$ 1.09 (s, $OBu^t$), 1.19(d, 4-$CH_3$, $J$=6.5 Hz), 1.31(d, $CH_3$ of threonine, $J$=6.8 Hz), 3.78(dd, H-3, $J_{2,3}$=8.0, $J_{3,4}$=4.2 Hz), 4.66 (ABq, $CH_2Ph$), 5.10(dq, H-4), 5.11(ABq, $CH_2Ph$ of benzyloxycarbonyl), and 5.62(d, NH, $J$=10.0 Hz).

Found: C, 67.27; H, 7.95; N, 2.32%. Calcd for $C_{32}H_{45}NO_8$: C, 67.23; H, 7.93; N, 2.45%.

*(2R,3R,4S)-4-(*N*-Benzyloxycarbonyl-*O*-t-butyl-*L*-threonyloxy)-2-butyl-3-isovaleryloxypentanoic Acid (**9b**).* A sample of **8b** (292 mg, 0.53 mmol) was oxidized with the chromium trioxide reagent (6.6 ml, 2.13 mmol) at room temperature for 1.5 h. Work-up of the product in the same way as in the preparation of **9a** afforded a brown syrup (299 mg), which was chromatographed on silica gel (30 g) with hexane-benzene-acetone-acetic acid (40:20:1:2) to give a pure sample of **9b**(287 mg, 96%) as a colorless syrup: $[\alpha]_D^{22}$ +5.1°(*c* 1.4, $CHCl_3$); PMR($CDCl_3$) $\delta$ 0.99[d, $CH(CH_3)_2$, $J$=6.5 Hz], 1.13(s, $OBu^t$), *ca.* 1.2(m, 6H, 4-$CH_3$, 3'-$CH_3$), *ca.* 4.2(m, 2H, H-2',3'), 5.19(s, $CH_2Ph$), 5.0—5.6(m, 3H, NH, H-3,4), 6.5(br, 1H, COOH), and 7.40(s, Ph).

Found: C, 63.59; H, 8.44; N, 2.61%. Calcd for $C_{30}H_{47}NO_9$: C, 63.69; H, 8.38; N, 2.48%.

*Hydroxy Ester Acid (**10a**).* A solution of **9a**(855 mg) in trifluoroacetic acid (10 ml) was allowed to stand at room temperature for 10 min and then evaporated below 10 °C to afford **10a** (770 mg, quantitative), which was used in the next reactions after being thoroughly dried at 0.01 Torr.

*Hydroxy Ester Acid (**10b**).* Treatment of **9b**(287 mg) with trifluoroacetic acid (3.5 ml) at room temperature for 10 min gave **10b** (248 mg, 96%) after evaporation: IR ($CHCl_3$) 3600—2800(COOH), and 1730 $cm^{-1}$(ester and amide); PMR($CDCl_3$) $\delta$ 1.03[d, $CH(CH_3)_2$, $J$=6.4 Hz], *ca.* 1.3(m, 6H, 4-$CH_3$, 3'-$CH_3$), 4.2—4.5(m, 2H, H-2',3'), 5.20 (s, $CH_2Ph$), 5.1—5.4(m, 2H, H-3,4), *ca.* 5.9(br, 1H, NH), 7.1—7.5(br, 1H, COOH), and 7.41(s, 5H, Ph).

*(3S,4R,7R,8R,9S)-8-Benzyloxy-3-benzyloxycarbonylamino-7-butyl-4,9-dimethyl-1,5-dioxonane-2,6-dione (**12a**).* A sample of **10a** (300 mg, 0.582 mmol) was dissolved in dry benzene (3 ml), triphenylphosphine (458 mg, 1.75 mmol) and di-2-pyridyl disulfide (385 mg, 1.75 mmol) then being added to the solution. After the mixture had been kept for 30 min at room temperature, the reaction mixture was evaporated and the residue (1.2 g) was chromatographed on silica gel (40 g) with benzene-acetone (10:1) to afford the 2-pyridinethiol ester **11a** (160 mg) as a yellow syrup. A solution of silver perchlorate†† (53.5 mg, 0.235 mmol) in dry benzene (0.5 ml) was added to a stirred solution of **11a** (143 mg, 0.235 mmol) in dry benzene (23.5 ml) and the mixture was stirred at room temperature for 1 h. The precipitates were filtered off and washed with benzene. The combined filtrate and washings were evaporated and the residue was chromatographed on silica gel (15 g) with benzene-ethyl acetate (50:1) to afford **12a** (38.6 mg, 33%) as colorless crystals and **10a** (94 mg, 66%). Analytical sample of **12a** was obtained by recrystallization from ethyl acetate as colorless needles: mp 118.5—119.5 °C; $[\alpha]_D^{23}$ +53°(*c* 0.73, $CHCl_3$); IR($CCl_4$,

† The reagent consists of chromium trioxide (1 g), acetic acid (30 ml) and pyridine (1 ml).

†† The silver perchlorate used was thoroughly dried over $P_2O_5$ at 50—60 °C under reduced pressure (1 Torr) for 10 h.

0.1 M) 3432 and 1744 $cm^{-1}$; PMR($CDCl_3$) $\delta$ 1.28(d, 4-$CH_3$, $J$=6.8 Hz), 1.43(d, 9-$CH_3$, $J$=6.5 Hz), 2.46(m, H-7), 3.46(dd, H-8, $J_{7,8}$=9.5 Hz), 4.65(s, $OCH_2Ph$), 4.90(dq, H-9, $J_{8,9}$=9.5 Hz), 4.91(dd, H-3, $J_{3,NH}$=9.0 Hz), 5.12(s, $COOCH_2Ph$), and 5.54(dq, H-4, $J_{3,4}$=7.5 Hz); Found: *m/e* 497.244. Calcd for $C_{28}H_{35}NO_7$: M, 497.2413.

Found: C, 67.50; H, 7.04; N, 2.66%. Calcd for $C_{28}H_{35}NO_7$: C, 67.58; H, 7.09; N, 2.82%.

*Lactonization of* ***10a*** *by Corey-method. (Formation of 7-Epimer* ***12a'****).* Triphenylphosphine (130 mg, 0.494 mmol) and di-2-pyridyl disulfide (109 mg, 0.494 mmol) were added to a solution of **10a** (170 mg, 0.229 mmol) in dry xylene(0.85 ml), which was then stirred at room temperature for 5 h under argon atmosphere. The resulting solution was diluted with dry xylene (60 ml) and refluxed for 72 h under argon. The reaction mixture was evaporated and the residue (400 mg) was chromatographed on silica gel (20 g) with benzene–ethyl acetate (50:1) to afford a syrup of **12a'** (22.4 mg, 13.7%). This was chromatographed twice on silica gel with hexane–acetone (5:1) to give an analytical sample: $[\alpha]_D^{23}$ 0°(*c* 1.65, $CHCl_3$); IR($CCl_4$, 0.1 M), 3435 and 1732 $cm^{-1}$; PMR($CDCl_3$) $\delta$ 1.29(d, 4-$CH_3$, $J$=6.8 Hz), 1.32 (d, 9-$CH_3$, $J$=6.2 Hz), 2.85(m, H-7), 3.72(dd, H-8, $J_{7,8}$= 4.0, $J_{8,9}$=9.2 Hz), 4.55(ABq, H-9), 5.11(s, $COOCH_2Ph$), and 5.15 (dq, H-4).

Found: *m/e* 497.2405. Calcd for $C_{28}H_{35}NO_7$: M, 497.2413.

Found: C, 67.68; H, 7.27; N, 2.58%. Calcd for $C_{28}H_{35}NO_7$: C, 67.58; H, 7.09; N, 2.82%.

*(3S,4R,7R,8R,9S)-3-Benzyloxycarbonylamino-7-butyl-4,9-dimethyl-8-isovaleryloxy-1,5-dioxonane-2,6-dione (****12b****).* Triphenylphosphine (224 mg, 0.930 mmol) and di-2-pyridyl disulfide (205 mg, 0.930 mmol) were added to a solution of **10b** (237 mg, 0.465 mmol) in dry benzene (2.4 ml). After being kept at room temperature for 1 h, the reaction mixture was evaporated and the residue (423 mg) was chromatographed on silica gel (15 g) with benzene–acetone (10:1) to afford a yellow syrup of **11b** (280 mg) containing a small amount of pyridone. The sample of **11b** (130 mg) was dissolved in dry benzene (21.5 ml), a solution of anhydrous silver perchlorate (67 mg) in dry toluene (0.35 ml) being added to the solution. The mixture was stirred at room temperature for 1 h and the insoluble matter was filtered off and washed with benzene. The combined filtrate and washings were evaporated and the residue (159 mg) was chromatographed on silica gel (15 g) with benzene–ethyl acetate (30:1) to afford a crystalline mass of **12b** (14.1 mg, 13.4%). Recrystallization from ether–petroleum ether gave colorless needles: mp 109—110 °C; $[\alpha]_D^{22}$ +55° (*c* 1.24, $CHCl_3$); IR (KBr) 1760, 1738, and 1693 $cm^{-1}$; $[\theta]_{228}^{18}$ −688 (in MeOH); PMR($CDCl_3$) $\delta$ 0.98[d, $CH(CH_3)_2$, $J$=6.5 Hz], 1.26(d, 9-$CH_3$, $J$=6.2 Hz), 1.28(d, 4-$CH_3$, $J$=7.0 Hz), 2.46(m, 1H, H-7), 4.94(dq, H-9, $J_{8,9}$=9.8 Hz), 4.96(dd, H-8, $J_{7,8}$=9.8 Hz), 5.05(dd, H-3, $J_{3,4}$=7.8, $J_{3,NH}$ =8.5 Hz), 5.12(s, $CH_2Ph$), 5.50(d, NH), 5.55(dq, H-4), and 7.34 (s, Ph).

Found: C, 63.74; H, 7.58; N, 2.76%. Calcd for $C_{26}H_{37}NO_8$: C, 63.52; H, 7.59; N, 2.85%.

*(3S,4R,7R,8R,9S)-3-Amino-7-butyl-4,9-dimethyl-8-hydroxy-1,5-dioxonane-2,6-dione (****14****) Hydrochloride.* A solution of **12a** (59.7 mg) in methanol (1 ml) was adjusted to pH 3 with a methanolic hydrogen chloride. The solution was shaken with freshly prepared palladium black in a Paar apparatus under a hydrogen atmosphere (50 p.s.i.) for 1 h. The filtered solution was evaporated to afford the crystalline hydrochloride of **14** (37.3 mg) quantitatively.

*(3S,4R,7R,8R,9S)-3-(2-Benzyloxy-3-nitrobenzoylamino)-4,9-dimethyl-7-butyl-8-hydroxy-1,5-dioxonane-2,6-dione (****15****).* A solution of **14** hydrochloride (37.3 mg, 0.120 mmol), 2-benzyloxy-3-nitrobenzoic acid *N*-hydroxysuccinimide ester (49.3 mg, 0.133 mmol) in dry THF (0.38 ml) was adjusted to pH 8 with triethylamine and kept at 40 °C for 2 days and then evaporated. The residue was chromatographed on silica gel (11 g) with benzene–acetone (6:1) to afford **15** (45.6 mg, 72%) as colorless crystals: mp 164.5—165.5 °C (ethyl acetate–petroleum ether); $[\alpha]_D^{20}$ +35° (*c* 0.71, $CHCl_3$).

Found: C, 61.42; H, 6.19; N, 5.15%. Calcd for $C_{27}H_{32}N_2O_9$: C, 61.35; H, 6.10; N, 5.30%.

*(3S,4R,7R,8R,9S)-3-(2-Benzyloxy-3-nitrobenzoylamino)-4,9-dimethyl-7-butyl-8-isovaleryloxy-1,5-dioxonane-2,6-dione (****16****).* A solution of **15** (9.0 mg, 0.017 mmol) and isovaleric anhydride (0.007 ml, 0.034 mmol) in dry pyridine (0.1 ml) was allowed to stand at room temperature for 5 h and then evaporated. The residue was chromatographed on silica gel with benzene–acetone (6:1) to give **16** (9.1 mg, 88%) as colorless crystals: mp 164.5—165.5 °C; $[\alpha]_D^{18}$ +55° (*c* 0.40, $CHCl_3$) $\delta$ 0.99 [d, $CH(CH_3)_2$, $J$=6.4 Hz], 1.29 (d, 9-$CH_3$, $J$=5.8 Hz), 1.11(d, 4-$CH_3$, $J$=6.8 Hz), 2.5(m, 1H, H-7), 4.86(dq, H-9, $J_{8,9}$=9.9 Hz), 5.06(dd, H-8, $J_{7,8}$=9.8 Hz), 5.19(dd, H-3, $J_{3,4}$=7.5 Hz), 5.16(s, $CH_2Ph$), 5.56(dq, H-4), 7.35 (dd, H-5'), 8.05 (d, 3-NH, $J_{3,NH}$=7.2 Hz), 7.96(dd, H-4' or H-6', $J_{4',5'}$ or $J_{5'6'}$=8.0 Hz), and 8.26 (dd, H-6' or H-4').

Found: C, 61.93; H, 6.74; N, 4.29%. Calcd for $C_{32}H_{40}N_2O_{10}$: C, 62.73; H, 6.58; N, 4.57%.

*(3S,4R,7R,8R,9S)-3-Acetylamino-7-butyl-4,9-dimethyl-8-hydroxy-1,5-dioxonane-2,6-dione (****18****).* A sample of **12a** (30 mg) was hydrogenolyzed with palladium black in methanol at room temperature for 15 min under a hydrogen atmosphere (50 p.s.i.) to afford a colorless syrup of **13a** (21.7 mg). Acetylation of **13a** (21.7 mg) with acetic anhydride (0.012 ml) in methanol (0.44 ml) at room temperature for 2 h gave the 3-*N*-acetyl derivative **17a** (22.1 mg, 91%) as colorless crystals: mp 156—157 °C (ethyl acetate–petroleum ether); $[\theta]_{222}^{20}$ −10660 (MeOH).

Found: C, 65.16; H, 7.68; N, 3.40%. Calcd for $C_{22}H_{31}NO_6$: C, 65.16; H, 7.71; N, 3.45%.

A sample of **17a** (9.9 mg) was hydrogenolyzed for 3 h by the same procedure as described above to afford **18** (7.7 mg) as a colorless solid. Recrystallization from ethyl acetate–petroleum ether gave colorless needles: mp 148 °C (decomp); $[\alpha]_D^{22}$ +68° (*c* 0.54, $CHCl_3$); $[\theta]_{217}^{20}$ −16000 (MeOH); IR ($CCl_4$, 0.1 M) 3540, 3430, 1735, and 1677 $cm^{-1}$; PMR ($CDCl_3$) $\delta$ 1.27(d, 4-$CH_3$, $J$=6.8 Hz), 1.43(d, 9-$CH_3$, $J$= 6.2 Hz), 2.07(s, *N*-Ac), 2.32(m, H-7), 3.56(dd, H-8, $J_{7,8}$= 9.5, $J_{8,9}$=9.5 Hz), 4.81(dq, H-9), 5.10(dd, H-3, $J_{3,4}$=7.8, $J_{3,NH}$=7.8 Hz), 5.55(dq, H-4); $\delta$($CD_3OD$) 1.26(d, 4-$CH_3$, $J$=6.5 Hz), 1.37(d, 9-$CH_3$, $J$=6.2 Hz), 2.02(s, OAc), 2.25(m, H-7), 3.35 (dd, H-8, $J_{7,8}$=9.7, $J_{8,9}$=10.0 Hz), 4.66(dq, H-9), 5.06(d, H-3, $J_{3,4}$=7.5 Hz), and 5.43(dq, H-4).

Found: C, 57.11; H, 7.91; N, 4.37%. Calcd for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44%.

*(3R,4R,7R,8R,9S)-7-Butyl-4,9-dimethyl-3-dimethylamino-8-hydroxy-1,5-dioxonane-2,6-dione (****19****).* A sample of **12a** (42.5 mg) was hydrogenolyzed with palladium black in methanol at 40 °C for 1 h under a hydrogen atmosphere (50 p.s.i.). The product was purified by silica gel chromatography with hexane–acetone (5:1) to give a colorless syrup of **19** (26 mg): *m/e* 301($M^+$); PMR($CDCl_3$) $\delta$ 1.41 (d, 4-$CH_3$, $J$=6.2 Hz), 1.41(d, 9-$CH_3$, $J$=6.0 Hz), 2.25[s, 6H, $N(CH_3)_2$], 3.45(dd, H-8, $J_{7,8}$=9.3, $J_{8,9}$=9.3 Hz), 3.45 (d, H-3, $J_{3,4}$=6.8 Hz), 4.66(dq, H-9), and 5.22(dq, H-4).

The authors wish to thank Dr. Hiroshi Naganawa, Institute of Microbial Chemistry, for the measurements of PMR spectra, Mr. Saburo Nakada for carrying

out the microanalyses, and Mr. Hiromitsu Matsuzaki for his technical assistance. Financial support by the Asahi Glass Foundation for Contribution to Industrial Technology is acknowledged.

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