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NOTE

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A Practical Total Synthesis of (+)-Antimycin A_9

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Abstract (+)-Antimycin A_9 (AA_9) isolated from a cultured broth of *Streptomyces* sp. K01-0031 was synthesized *via* an asymmetric aldol reaction using Oppolzer's sultam as a chiral auxiliary.

Keywords asymmetric synthesis, asymmetric aldol reaction, antimycin A_9, antibiotics

The antimycin A (AA) family isolated from *Streptomyces* sp. possesses significant biological activities [1], such as antifungal, insecticidal, and anticancer, as well as an inhibitory activity against ubiquinol-cytochrome *c* oxidoreductase. Among the AA family, AA_3 is one of the most active agents and has been widely used in biological and biochemical studies. On the contrary, (+)-AA_9 (Figure 1) recently isolated from a cultured broth of *Streptomyces* sp. K01-0031 together AA_{3a}, AA_{3b}, AA_4, and AA_7 by Kitasato's groups showed more potent nematocidal and insecticidal activities against *Caenorhaditis elegans* and *Artemia salina* than other known antimycins [1b]. Thus, involving the discovery of new compounds, investigation of the AA family is still continued because of their characteristic biological activities. For precise biological and biochemical investigations, the supply of each pure component of the AA family seems to be very important. However, since the isolation of each pure component from a cultured broth is possible only with intensive effort [2], the pure material of each component is not practically available for biological and biochemical studies. Therefore, the Antimycin A complex (mixture of AA family purchased from Sigma Co.) was used in most biological and biochemical studies.

Due to their outstanding bioactivities and unique structures, the antimycin family has attracted much interest from synthetic organic chemists [3]. Up to now three groups accomplished enantioselective total synthesis of AA_{3b} (previous name AA_3) [3b~e]. However, the synthesis of other antimycins has not been performed and further effort directed to a practical and economical synthesis is still needed to supply sufficient amounts of pure antimycins for the biological investigations.

In the previous paper, we reported the synthesis of (+)-AA_{3a} and (+)-AA_{3b} using an asymmetric aza-Claisen rearrangement, although the overall yield was low [3c, d]. To develop a practical synthetic route of antimycins, we reconsidered the synthetic route and found that an asymmetric aldol reaction using Oppolzer's sultam as a chiral auxiliary was quite effective to construct the C-7 and C-8 asymmetric centers. Utilizing this methodology, we performed the first and efficient synthesis of (+)-AA_9, which is the first antimycin having an aromatic 8-acyl residue. The results are reported herein.

Sultam amide **2** reacted with aldehyde **3** under the modified [4] Oppolzer's conditions to give the desired aldol adduct **4** and its stereoisomer [5] in 82% yield (ratio=98/2)

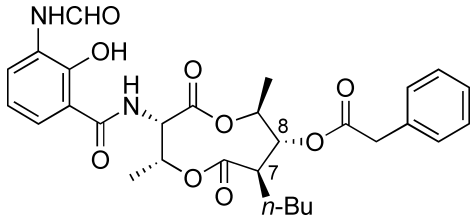

Fig. 1 Structure of antimycin A_9.

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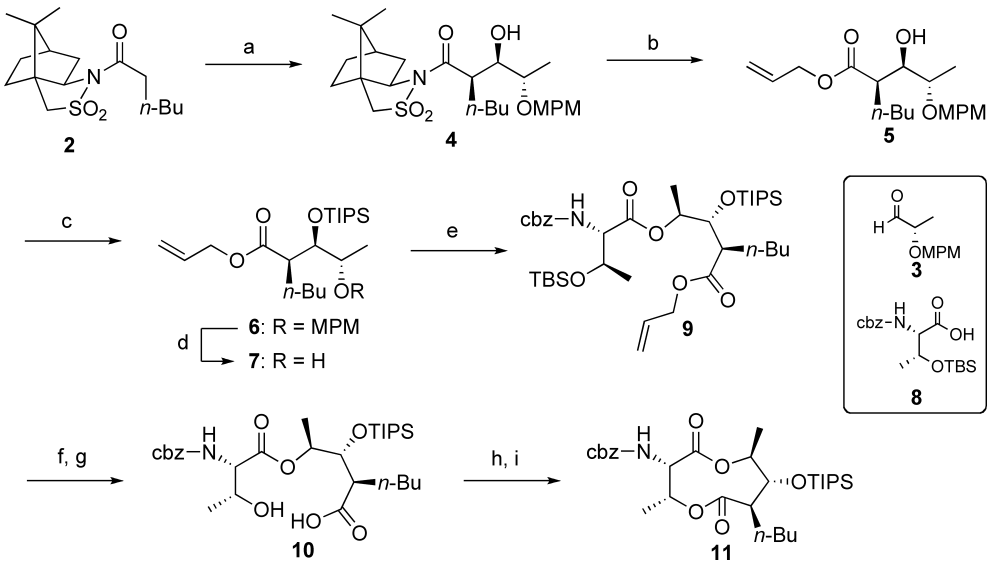


Scheme 1

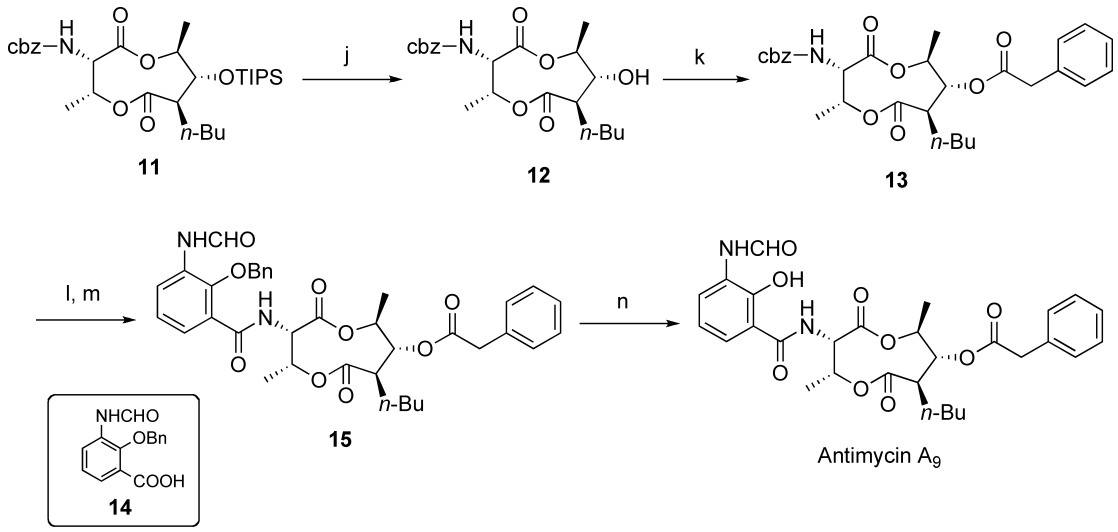
Reagents and conditions: (a) (i) *n*-Bu_2BOTf, DIPEA, CH_2Cl_2, 0.5 hours, −5°C; (ii) **3**, 1 hour, −78°C, 82% (98/2); (iii) recryst.; (b) Ti(O-*i*Pr)$_4$, MS 4A, allyl alcohol, 150°C, 48 hours, 74%; (c) TIPSOTf, DIPEA, CH_2Cl_2, r.t., 4 hours, 99%; (d) DDQ, CH_2Cl_2/H_2O, r.t., 0.5 hours; (e) (i) **8**, 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, r.t., 0.5 hours; (ii) DMAP, Tol, r.t., 15 hours, 2 steps 84%; (f) 6 M HCl, EtOH, r.t., 24 hours, quant.; (g) $Pd(PPh_3)_4$, PPh_3, pyrrolidine, CH_3CN, 0°C∼r.t., 7 hours; (h) 2,2′-dipyridyl disulfide, PPh_3, Tol, r.t., 3 hours, 2 steps 91%; (i) $(CuOTf)_2 \cdot C_6H_6$, Tol, 80°C, 3 hours, 87%.

[6]. The best results were obtained with 1.5 equivalents of dibutylboron trifluoromethanesulfonate (*n*-Bu_2BOTf), 2.0 equivalents of diisopropylethylamine (DIPEA), and 2.5 equivalents of **3**. The pure **4** (>99% de) afforded by recrystallization (63% isolated yield) was converted to allyl ester **5** by heating at 150°C with allyl alcohol in the presence of titanium isopropoxide [Ti(O-*i*Pr)$_4$] and molecular sieves 4 Å (MS 4A) (74%) [7].

After protection of the hydroxy group by triisopropylsilyl (TIPS) group, the *p*-methoxyphenylmethyl (MPM) group was removed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to yield alcohol **7**. Condensation of **7** with L-threonine derivative **8** [8] proceeded satisfactorily under Yamaguchi conditions to give **9** in 84% yield (2 steps) [9]. Removal of the TBS group with 6 M HCl followed by palladium(0)-catalyzed deprotection [$Pd(PPh_3)_4$, PPh_3, pyrrolidine] of the allyl ester provided the *seco* acid **10**. *Via* conversion of **10** to the 2-pyridinethiol ester, lactonization was accomplished by heating at 80°C in toluene with copper(I) trifluoromethanesulfonate-benzene complex [$(CuOTf)_2$·PhH] under high dilution conditions to give dilactone **11** in 79% yield (4 steps from **9**) [10].

The TIPS group of lactone **11** was removed smoothly using hydrogen fluoride pyridine (HF·Py) at r.t. to provide alcohol **12** (98% yield), which was esterified with phenylacetic acid in the presence of *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride [water-soluble carbodiimide (WSC)] and 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) in CH_2Cl_2 to provide ester **13** in excellent yield (92%). The benzyloxycarbonyl (cbz) group of **13** was removed by hydrogenolysis (Pd-C in THF) to give an amine, which was successfully acylated with **14** (See the experimental section.), using WSC, 1-hydroxybenzotriazole hydrate (HOBt), and *N*-methylmorpholine (NMM) in DMF to give **15**. Removal of the benzyl protecting group of **15** by hydrogenolysis with Pd-C in ethyl acetate led cleanly to the target molecule (+)-antimycin A_9 (69% yield from **13**), mp 151.0∼152.0°C, $[\alpha]_D^{22}$ +82.1 (*c* 0.17, CH_3OH), whose physical properties compared well with those in the literature [1b] [mp 134∼139°C, $[\alpha]_D^{25}$ +83.6 (*c* 0.157, CH_3OH)].

Thus, the asymmetric aldol reaction using Oppolzer's sultam provided a practical and economical synthetic route (15 steps, overall yield 24%) to (+)-antimycin A_9, which could be obtained in pure form on a 300 mg scale in this synthesis. Further synthetic studies of not only the AA family but also their analogs and investigation of their biological activities are now in progress.



Scheme 2

Reagents and conditions: (j) HF·Py, THF, r.t., 3 hours, 98%; (k) phenylacetic acid, WSC, DMAP, CH_2Cl_2, r.t., 1 hour, 92%; (l) H_2, Pd/C, THF, r.t., 2 hours; (m) **14**, WSC, HOBt, NMM, DMF, r.t., 24 hours, 2 steps 77%; (n) H_2, Pd/C, EtOAc, r.t., 2 hours, 89%.

Experimental

(3a*S*,6*R*,7a*R*)-1-{2,5-Dideoxy-4-*O*-[(4-methoxyphenyl)-methyl]-2-butyl-L-arabinoyl}hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole-2,2-dioxide (4)

To a suspension of **2** (1.02 g, 3.25 mmol) in CH_2Cl_2 (10 ml) were added dibutylboron trifulate (4.8 ml, 1 M in CH_2Cl_2, 4.8 mmol) and DIPEA (1.15 ml, 6.6 mmol) at −5°C. After stirring at −5°C for 0.5 hours and then cooling to −78°C, a solution of **3** (1.58 g, 8.13 mmol) in CH_2Cl_2 (5 ml) was added dropwise to the mixture over 1 hour. The resulting mixture was treated with a phosphate buffer (pH 6.8) and saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (5.22 g) was purified by silica gel column chromatography (toluene/AcOEt) to give the aldol adduct **4** (1.33 g, 82%) as colorless needles; mp 102.1∼103.2°C (hexane/EtOAc); $[\alpha]_D^{22}$ −48.8 (*c* 1.0, $CHCl_3$); IR (neat) cm^{-1}: 3509, 2958, 1686, 1512, 1333; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.29 (2H, d, *J*=8.5 Hz), 6.87 (2H, ddd, *J*=9.5, 0.4, 4.8 Hz), 4.57 (1H, d, *J*=11.5 Hz), 4.39 (1H, d, *J*=11.3 Hz), 3.97 (1H, ddd, *J*=6.4, 4.9, 1.9 Hz), 3.86 (1H, t, *J*=6.3 Hz), 3.80 (3H, s), 3.57∼3.41 (4H, m), 2.87 (1H, d, *J*=1.6 Hz), 2.05 (2H, d, *J*=6.3 Hz), 1.94∼1.80 (3H, m), 1.39∼1.18 (11H, m), 1.17 (3H, s), 0.98 (3H, s), 0.83 (3H, t, *J*=6.8 Hz); MS (EI) *m/z* 507 (M^+), 353, 342, 257, 216, 121 (base peak); HRMS (EI) *m/z* 507.2661 (507.2655 calcd for $C_{27}H_{41}O_6NS$).

(*R*)-Allyl-2-[(1*R*,2*S*)-1-hydroxy-2-(4-methoxybenzyloxy)-propyl]hexanoate (5)

To a suspension of **4** (202 mg, 0.4 mmol) and 4 Å MS (386 mg) in allyl alcohol (4 ml) was added Ti(*i*-Pro)$_4$ (300 μl, 1.2 mmol) at r.t., and the mixture was heated at 150°C for 48 hours. The resulting mixture was treated with saturated aqueous NH_4Cl and then filtered through a pad of Celite. The filtrate was extracted with AcOEt, and the extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (302 mg) was purified by silica gel column chromatography (hexane/EtOAc) to give the allyl ester **5** (104 mg, 74%) as a colorless oil; $[\alpha]_D^{21}$ +27.3 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3502, 2955, 2360, 1728, 1612, 1586, 1512, 1172, 1073, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, dt, *J*=9.0, 2.7 Hz), 6.88 (2H, dt, *J*=9.0, 2.7 Hz), 5.87 (1H, ddt, *J*=17.1, 10.2, 6.0 Hz), 5.39 (1H, ddt, *J*=17.1, 1.5, 1.5 Hz), 5.23 (1H, ddt, *J*=10.2, 1.2, 1.2 Hz), 4.55 (2H, ddd, *J*=6.0, 1.2, 1.2 Hz), 4.51 (1H, d, *J*=11.4 Hz), 4.39 (1H, d, *J*=11.1 Hz), 3.88 (1H, dd, *J*=6.9, 5.1 Hz), 3.80 (3H, s), 3.45 (1H, qd, *J*=5.1, 0.9 Hz), 2.58 (1H, ddd, *J*=10.2, 6.9, 4.5 Hz), 1.54∼1.82 (2H, m), 1.21 (3H, d, *J*=6.0 Hz), 1.18∼1.36 (4H, m), 0.88 (3H, t, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.2, 131.9, 130.2, 129.4, 118.5, 113.7, 74.7, 73.4, 70.0, 65.0, 55.2, 47.6, 29.5, 27.8, 22.6, 14.1, 13.9; MS (CI) *m/z* 350 (M^+), 288, 243, 213, 196, 185, 163, 121 (base peak); HRMS (CI) *m/z* 350.2086 (M^+) (350.2093 calcd for $C_{20}H_{30}O_5$).

(*R*)-Allyl-2-[(1*R*,2*S*)-2-(4-methoxybenzyloxy)-1-(triisopropylsilyloxy)propyl]hexanoate (6)

To a solution of **5** (66.8 mg, 0.19 mmol) in CH_2Cl_2 (1 ml) were added DIPEA (100 μl, 0.57 mmol) and TIPSOTf (104 μl, 0.39 mmol) successively at 0°C. After stirring at r.t. for 4 hours, the reaction mixture was quenched with the addition of saturated aqueous NH_4Cl, and the resulting mixture was extracted with ether. The extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (142 mg) was purified by silica gel column chromatography (hexane/AcOEt) to give the TIPS ether **6** (95.4 mg, 99%) as a colorless oil; $[\alpha]_D^{24}$ +10.2 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 2943, 1732, 1613, 1512, 1463, 1247, 1106, 1034; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (2H, dt, *J*=9.0, 2.7 Hz), 6.85 (2H, dt, *J*=8.7, 3.0 Hz), 5.85 (1H, ddt, *J*=17.1, 10.2, 6.0 Hz), 5.29 (1H, ddt, *J*=17.4, 1.8, 1.2 Hz), 5.20 (1H, ddt, *J*=10.5, 1.5, 1.2 Hz), 4.50 (2H, dd, *J*=5.7, 1.2 Hz), 4.44 (1H, d, *J*=11.7 Hz), 4.37 (1H, d, *J*=11.1 Hz), 4.13 (1H, dd, *J*=7.2, 2.7 Hz), 3.80 (3H, s), 3.40 (1H, qd, *J*=6.3, 2.7 Hz), 2.49 (1H, ddd, *J*=11.1, 7.5, 3.6 Hz), 1.57～1.82 (2H, m), 1.17 (3H, d, *J*=6.3 Hz), 1.05～1.32 (24H, m), 0.87 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 158.9, 132.1, 130.8, 129.2, 118.2, 113.5, 76.4, 70.1, 64.9, 55.2, 50.5, 30.0, 29.0, 22.6, 18.3, 14.0, 13.1; MS (CI) *m*/*z* 507 ($[M+H]^+$), 463, 399, 369, 3269, 241, 163, 121 (base peak); HRMS (CI) *m*/*z* 507.3514 ($[M+H]^+$) (507.3505 calcd for $C_{29}H_{51}O_5Si$).

(*R*)-Allyl-2-{(5*S*,8*S*,9*R*)-5-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-11,11-diisopropyl-8,12-dimethyl-3,6-dioxo-1-phenyl-2,7,10-trioxa-4-aza-11-silatridecan-9-yl}hexanoate (9)

Deprotection of **6**

To a solution of **6** (2.01 g, 3.97 mmol) in CH_2Cl_2 (40 ml) were added dist. water (2.2 ml) and DDQ (988 mg, 4.4 mmol) at r.t., and the mixture was stirred for 0.5 hours at same temperature. The reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$, filtered, and concentrated to give the crude deprotected alcohol of **7** (1.54 g).

Preparation of a Mixed Anhydride of **8**

To a solution of **8** (2.91 g, 7.93 mmol) in THF (15 ml) were added NEt_3 (2.2 ml, 16 mmol), and 2,4,6-trichlorobenzoyl chloride (1.8 ml, 12 mmol) at 0°C. After stirring at r.t. for 1.5 hours, the resulting mixture was filtered and concentrated to give a mixed anhydride of **8**.

Condensation of the Alcohol and the Mixed Anhydride

To a solution of the crude alcohol in toluene (20 ml) were added DMAP (781 mg, 6.4 mmol), NEt_3 (550 μl, 3.95 mmol), and a solution of the mixed anhydride in toluene (20 ml) successively at 0°C. The resulting mixture was stirred at r.t. for 16 hours and quenched with the addition of dist. water. The resulting mixture was extracted with ether, and the organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue (5.36 g) was purified by silica gel column chromatography (hexane/EtOAc) to give the diester **9** (2.44 g, 84%, 2 steps) as a colorless oil; $[\alpha]_D^{23}$ +0.52 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 2946, 2865, 1730, 1504, 1463, 1378, 1311, 1252, 1170, 1103; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24～7.44 (5H, m), 5.91 (1H, ddt, *J*=17.1, 10.2, 6.0 Hz), 5.44 (1H, br d, *J*=9.6 Hz), 5.32 (2H, ddt, *J*=17.1, 1.5, 1.5 Hz), 5.24 (1H, ddt, *J*=10.5, 1.2, 1.2 Hz), 5.19 (1H, d, *J*=12.0 Hz), 5.06 (1H, d, *J*=12.0 Hz), 4.84 (1H, qd, *J*=6.3, 1.8 Hz), 4.49～4.65 (2H, m), 4.40 (1H, qd, *J*=6.0, 1.5 Hz), 4.19 (1H, dd, *J*=9.9, 1.5 Hz), 4.13 (1H, dd, *J*=7.5, 1.8 Hz), 2.48 (1H, ddd, *J*=10.5, 7.5, 3.9 Hz), 1.60～1.80 (2H, m), 1.27 (3H, d, *J*=6.3 Hz), 1.19 (3H, d, *J*=6.0 Hz), 1.02～1.38 (25H, m), 0.88 (3H, t, *J*=6.6 Hz), 0.80～0.92 (9H, m), −0.08～0.06 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 170.0, 156.5, 136.2, 131.2, 128.5, 128.1, 118.7, 75.8, 74.5, 68.8, 67.1, 65.2, 59.9, 50.7, 29.8, 29.2, 25.6, 22.5, 21.1, 18.2, 17.8, 13.8, 13.5, 13.0, −4.5, −5.1; MS (FAB) *m*/*z* 759 ($[M+Na]^+$), 678, 544, 480, 448, 369, 241, 91 (base peak); HRMS (FAB) *m*/*z* 758.4465 ($[M+Na]^+$) (758.44591 calcd for $C_{39}H_{69}NO_8Si_2Na$).

Benzyl-(3*S*,4*R*,7*R*,8*R*,9*S*)-7-butyl-4,9-dimethyl-2,6-dioxo-8-(triisopropylsilyloxy)-1,5-dioxonan-3-ylcarbamate (10)

Desilylation of **9**

To a solution of **9** (125 mg, 0.17 mmol) in EtOH (1.5 ml) was added 6 M HCl (185 μl) at r.t., and the mixture was stirred for 24 hours. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ether, and the organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue (119 mg) was purified by silica gel column chromatography (hexane/ether) to give a desilylated alcohol (105 mg, quant.) as a colorless oil; $[\alpha]_D^{22}$ −12.1 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3444, 2944, 2867, 1729, 1515, 1456, 1382; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28～7.42 (5H, m), 5.91 (1H, ddt, *J*=17.1, 10.2, 6.0 Hz), 5.53 (1H, br d, *J*=12.6 Hz), 5.33 (1H, ddt, *J*=17.1, 1.5, 1.5 Hz), 5.25 (1H, ddt, *J*=10.5, 1.2, 1.2 Hz), 5.17 (1H, d, *J*=12.6 Hz), 5.09 (1H, d, *J*=12.0 Hz), 4.90～5.05 (1H, m),

4.58 (2H, ddd, J=6.0, 1.2, 1,2 Hz), 4.22～4.42 (2H, m), 4.10 (1H, dd, J=6.0, 3.6 Hz) 2.46～2.66 (1H, m), 1.62～1.82 (2H, m), 1.26 (3H, d, J=6.3 Hz), 1.24 (3H, d, J= 6.3 Hz), 1.02～1.40 (25H, m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 170.2, 156.5, 136.1, 131.8, 128.4, 128.0, 127.9, 118.7, 75.9, 74.7, 67.7, 67.0, 65.3, 59.3, 50.4, 29.9, 29.0, 22.5, 19.6, 18.1, 15.3, 13.8, 12.9; MS (CI) m/z 622 ($[M+H]^+$), 578, 514, 470, 369 (base peak), 329, 285, 241, 195, 131, 91; HRMS (CI) m/z 622.3759 ($[M+H]^+$) (622.3774 calcd for $C_{33}H_{56}NO_8Si$).

Preparation of Seco Acid **10**

To a solution of the desilylated alcohol (81.2 mg, 0.13 mmol) in acetonitrile (1 ml) were added $Pd(PPh_3)_4$ (4.2 mg, 3.6 μmol), PPh_3 (1.8 mg, 6.7 μmol) and pyrrolidine (10 μl, 0.15 mmol) successively at 0°C. Since the alcohol still remained after stirring at r.t. for 3 hours (monitored by TLC), the same amount of the reagents were added to the mixture. After additional stirring for 4 hours, the resulting mixture was treated with 15% HCl aq. and NaCl. The resulting was extracted with CH_2Cl_2, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (110 mg) was purified by silica gel column chromatography (hexane/acetone) to give the crude seco acid **10** (78.8 mg).

Conversion of **10** to Pyridinethiol Ester

To a solution of the crude seco acid **10** in toluene (1 ml) were added PPh_3 (131 mg, 0.595 mmol) and PySSPy (156 mg, 0.6 mmol) at r.t., and the mixture was stirred for 3 hours. After concentration the residue was purified by silica gel column chromatography (hexane/acetone) to give the pyridinethiol ester (81.5 mg, 91%, 2 steps) as a pale yellow oil; $[\alpha]_D^{22}$ −22.3 (c 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3375, 2943, 2866, 2360, 1698, 1511, 1454, 1421, 1318, 1201, 1164, 1116, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54～8.62 (1H, m), 7.75 (1H, td, J=7.5, 1.8 Hz), 7.61 (1H, d, J=9.0 Hz), 7.24～7.42 (6H, m), 5.70 (1H, br d, J=9.7 Hz), 5.04～5.22 (3H, m), 4.04～4.46 (3H, m), 2.74～3.24 (2H, m), 1.68～1.92 (2H, m), 1.34 (3H, br d, J=6.3 Hz), 1.23 (3H, d, J=6.3 Hz), 1.02～1.48 (25H, m), 0.90 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 170.4, 156.5, 151.1, 150.2, 137.2, 136.2, 130.1, 128.4, 128.1, 127.9, 123.6, 76.1, 74.6, 67.6, 67.0, 59.3, 59.1, 31.5, 29.6, 29.3, 27.6, 22.5, 19.8, 18.2, 15.4, 14.0, 13.0; MS (CI) m/z 675 ($[M+H]^+$), 567, 520, 419, 366, 311, 283, 245, 208, 155, 112 (base peak), 91; HRMS (CI) m/z 675.3483 ($[M+H]^+$) (675.3499 calcd for $C_{35}H_{55}N_2O_7SSi$).

Lactonization

To a warmed solution of $(CuOTf)_2{\cdot}C_6H_6$ (561 mg, 1.0 mmol) in toluene (1 liter) at 80°C was added dropwise a solution of the pyridinethiol ester (657 mg, 0.97 mmol) in toluene (20 ml) over 2 hours. The resulting mixture was stirred for 1 hour at same temperature and filtered through a pad of silica gel. The filtrate was concentrated, and the residue (913 mg) was purified by silica gel column chromatography (hexane/AcOEt) to give the 9-membered dilactone **11** (476 mg, 87%) as a colorless oil; $[\alpha]_D^{24}$ +36.3 (c 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 2944, 2867, 2360, 1740, 1509, 1103, 1057, 1013; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24～7.46 (5H, m), 5.71 (1H, br d, J=7.8 Hz), 5.53 (1H, quintet, J=6.9 Hz), 5.11 (2H, s), 4.95 (1H, t, J=8.1 Hz), 4.76 (1H, quintet, J=6.0 Hz), 3.83 (1H, t, J=8.7 Hz), 2.31 (1H, dt, J=14.7, 9.3 Hz), 1.58～1.82 (2H, m), 1.39 (3H, d, J=6.3 Hz), 1.25 (3H, d, J=6.9 Hz), 1.02～1.42 (23H, m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.1, 155.4, 135.9, 128.4, 128.1, 127.9, 78.9, 76.8, 70.7, 67.1, 54.7, 53.2, 29.6, 29.0, 22.4, 18.5, 18.1, 14.7, 13.7; MS (CI) m/z 564 ($[M+H]^+$), 520, 456, 419 (base peak), 329, 278, 236; HRMS (CI) m/z 564.3342 ($[M+H]^+$) (564.3356 calcd for $C_{30}H_{50}NO_7Si$).

Benzyl-(3*S*,4*R*,7*R*,8*R*,9*S*)-7-butyl-8-hydroxy-4,9-dimethyl-2,6-dioxo-1,5-dioxonan-3-ylcarbamate (12)

To a solution of **11** (449 mg, 0.80 mmol) in THF (4 ml) was added HF·pyridine (4 ml) at r.t. After stirring at r.t. for 3 hours, the mixture was poured into saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The oreganic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (414 mg) was purified by silica gel column chromatography (hexane/EtOAc) to give the alcohol **12** (320 mg, 98%) as colorless needles; mp 104.5～105.0°C (hexane/EtOAc); $[\alpha]_D^{23}$ +47.4 (c 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3360, 2956, 1701, 1519, 1361, 1267, 1227, 1177, 1045; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28～7.42 (5 H, m), 5.42～5.64 (2H, m), 5,11 (2H, s), 4.92 (1H, t, J=8.4 Hz), 4.68～4.85 (1H, m), 3.44～3.62 (1H, m), 2.30 (1H, ddd, J=11.1, 9.6, 3.3 Hz), 2.24～2.42 (1H, m), 1.58～1.86 (2H, m), 1.41 (3H, d, J=6.3 Hz), 1.27 (3H, br d, J=5.7 Hz), 1.14～1.36 (4H, m), 0.88 (3H, t, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.3, 155.6, 135.8, 128.5, 128.3, 128.0, 76.2, 70.8, 67.3, 54.9, 52.0, 29.4, 28.6, 22.5, 18.3, 14.9, 13.8; MS (CI) m/z 408 ($[M+H]^+$), 390, 364, 300, 263, 236, 208, 173, 91 (base peak); HRMS (CI) m/z 408.2010 ($[M+H]^+$) (408.2022 calcd for $C_{21}H_{30}NO_7$).

(2*R*,3*S*,6*S*,7*R*,8*R*)-3-(Benzyloxycarbonylamino)-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl 2-Phenylethanoate (13)

To a solution of **12** (334 mg, 0.82 mmol) in CH_2Cl_2 were

added phenyl acetic acid (227 mg, 1.7 mmol), WSC (240 mg, 1.3 mmol) and DMAP (50.9 mg, 0.42 mmol) successively at r.t. The mixture was stirred for 1 hour and treated with saturated aqueous $NaHCO_3$. The resulting mixture was extracted with AcOEt, and the organc extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (480 mg) was purified by silica gel column chromatography (hexane/AcOEt) to give the ester **13** (423 mg, 98%) as colorless needles; mp 154.5～155.0°C (hexane/CH_2Cl_2); $[\alpha]_D^{20}$ +59.0 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3335, 2955, 2359, 1735, 1696, 1533, 1194, 1132, 1073, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22～7.41 (10H, m), 5.43～5.62 (2H, m), 5.11 (2H, br s), 4.73～5.03 (3H, m), 3.64 (2H, s), 2.42 (1H, ddd, *J*=12.6, 10.2, 2.4 Hz), 1.50～1.68 (1H, m), 1.26 (3H, br d, *J*=6.6 Hz), 1.11 (3H, d, *J*=6.3 Hz), 0.96～1.22 (4H, m), 0.80 (3H, t, *J*=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.1, 170.0, 155.4, 135.9, 133.1, 129.1, 128.6, 128.5, 128.2, 128.0, 127.4, 75.9, 74.1, 70.9, 67.2, 54.7, 49.9, 41.4, 29.0, 27.8, 22.2, 17.5, 14.6, 13.7; MS (CI) *m*/*z* 526 ($[M+H]^+$, base peak), 418, 381, 291, 236, 155, 91; HRMS (CI) *m*/*z* 526.2422 ($[M+H]^+$) (526.2440 calcd for $C_{29}H_{36}NO_8$).

2-(Benzyloxy)-3-methanamidobenzoic Acid (14)

2-Hydroxy-3-nitrobenzoic Acid to Benzyl 2-(Benzyloxy)-3-nitrobenzoate

To a solution of 2-hydroxy-3-nitrobenzoic acid (5.16 g, 27.3 mmol) in THF (43 ml) were added triphenylphosphine (21.2 g, 81.9 mmol) and benzyl alcohol (8.5 ml, 81.9 mmol) at r.t., and then a solution of diethyl azodicarboxylate (13 ml, 81.9 mmol) in THF (28 ml) was added dropwise to the mixture over 2 hours. The reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with AcOEt. The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The residue (52 g) was purified by silica gel column chromatography (hexane/EtOAc) to give the crude benzyl 2-(benzyloxy)-3-nitrobenzoate (10.3 g).

Benzyl 2-(Benzyloxy)-3-nitrobenzoate to Benzyl 3-Amino-2-(benzyloxy)benzoate

A mixture of crude benzyl 2-(benzyloxy)-3-nitrobenzoate (5 g, *ca.* 13.8 mmol) and iron powder (4.6 g, 82.6 mmol) in 50% EtOH aq. (40 ml, 1/1, v/v) was heated at 100°C, and then conc. H_2SO_4 in 50% EtOH aq. (287 μl/1.38 ml) was added. After refluxing for 2 hours, the resulting mixture was treated with saturated aqueous $NaHCO_3$ and then filtered through a pad of Celite. The filtrate was extracted with EtOAc, and the organic extracts were dried over Na_2SO_4, filtered, and concentrated to give the crude benzyl 3-amino-2-(benzyloxy)benzoate (4.38 g).

Benzyl 3-Amino-2-(benzyloxy)benzoate to 3-Amino-2-(benzyloxy)benzoic Acid

To a solution of benzyl 3-amino-2-(benzyloxy)benzoate (2.4 g, *ca.* 7.2 mmol) in 50% EtOH aq. (30 ml, 1/1, v/v) were added 6 M NaOH (4.8 ml, 14.8 mmol) at 0°C. After stirring at r.t. for 20 hours, the mixture was diluted with H_2O and EtOAc. The organic layer was extracted with 0.5 M NaOH and the combined aqueous layers were washed with ether. After acidifing with 2 M HCl, the acidic aqueous layer was extracted with AcOEt. The combined organic extracts were washed with a phosphate buffer (pH 6.8), dried over Na_2SO_4, filtered, and concentrated to give 3-amino-2-(benzyloxy)benzoic acid (1.74 g, 93%, 3 steps from 2-hydroxy-3-nitrobenzoic acid).

3-Amino-2-(benzyloxy)benzoic Acid to **14**

To a solution of formic acid (235 μl, 6.15 mmol) in CH_2Cl_2 (5 ml) was added *N*,*N*′-dicyclohexylcarbodiimide (1.3 g 6.15 mmol) at 0°C. After stirring at 0°C for 0.5 hours, a solution of 3-amino-2-(benzyloxy)benzoic acid (1.07 g 4.1 mmol) in CH_2Cl_2 (20 ml) was added dropwise to the mixture over 20 minutes, and the mixture was stirred for 1 hour at r.t. The reaction mixture was filtered and the filtrate was concentrated. The residue was diluted with ether and extracted with aqueous $NaHCO_3$. The combined aqueous layers were washed with ether and acidified with 6 M HCl. The acidic aqueous layer was extracted with EtOAc, and the organic extracts were dried over Na_2SO_4, filtered, and concentrated to give formylamide **14** (1.04 g, 93%) as a brown powder (rotamer mixture); mp 170.0～171.5°C; IR (KBr) cm^{-1}: 3346, 2769, 1700, 1645; ^1H NMR (200 MHz, DMSO d_6) δ: 13.0 (1H, br s), 9.71, 9.71 (total integr. 1 H, s, br d, *J*=11.8 Hz), 8.51, 8.35, 8.32, 7.61～7.12 (total integr. 9H, br d, *J*=10.6 Hz, d, *J*=1.0 Hz, dd, *J*=8.0, 1.6 Hz, m), 4.96, 4.93 (total integr. 2H, s, s); MS (EI) *m*/*z* 227 (M^+), 181, 135, 106, 91 (base peak); HMRS (EI) *m*/*z* 271.0837 (271.0844 calcd for $C_{15}H_{13}NO_4$).

(2*R*,3*S*,6*S*,7*R*,8*R*)-3-[2-(Benzyloxy)-3-methanamidophenylamido]-8-butyl-2,6-dimethyl-4,9-dioxo-1,5-dioxonan-7-yl 2-Phenylethanoate (15)

A mixture of **13** (424 mg, 0.81 mmol) and Pd/C (catalytic amount) in THF (2.5 ml) was stirred under H_2 atmosphere for 2 hours in the dark. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. To a solution of the residual oil in DMF (2.5 ml) were added 3-formamidesalicylic acid derivative **14** (395 mg, 1.5 mmol), WSC (239 mg, 1.3 mmol), HOBt (223 mg, 1.5 mmol), and NMM (625 μl, 5.7 mmol) successively at r.t. After stirring

for 24 hours, the reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue (502 mg) was purified by silica gel column chromatography (hexane/EtOAc) to give the amide **15** (391 mg, 77%, 2 steps) as a colorless solid (rotamer mixture); mp 137.5～139.5°C; $[\alpha]_D^{24}$ +34.2 (*c* 1.0, $CHCl_3$); IR (ATR) cm^{-1}: 3302, 2955, 1739, 1686, 1645, 1518, 1189, 1129, 1024; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 and 8.42 (total integr. 1H, br d, *J*=11.1 Hz and dd, *J*=8.1, 1.5 Hz), 8.02～8.20 and 7.20～7.60 (total integr. 14H, m and m), 7.81 and 7.72 (total integr. 1H, br d, *J*=6.3 Hz and dd, *J*=8.1, 1.8 Hz), 5.66 and 5.64 (total integr. 1H, quintet, *J*=7.2 Hz and quintet, *J*=7.2 Hz), 5.31 and 5.28 (total integr. 1H, t, *J*=7.8 Hz and t, *J*=9.6 Hz), 5.15 (1H, d, *J*=11.4 Hz), 5.03 (1H, t, *J*=9.9 Hz), 4.85 (1H, d, *J*=11.4 Hz), 4.80～4.96 (2H, m), 3.66 (2H, s), 2.45 (1H, t, *J*=9.9 Hz), 1.50～1.66 (1H, m), 1.25 (3H, d, *J*=6.6 Hz), 1.16 (3H, d, *J*=6.0 Hz), 0.98～1.30 (5H, m), 0.81 (3H, t, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 172.3, 170.2, 170.0, 164.7, 164.3, 161.1, 158.6, 146.6, 146.0, 135.1, 133.1, 134.4, 133.1, 131.3, 129.3, 129.1, 129.0, 128.8, 128.7, 127.4, 126.3, 126.1, 125.6, 125.4, 124.8, 121.7, 78.6, 78.2, 76.0, 71.0, 70.9, 54.0, 50.0, 41.5, 29.1, 27.9, 22.2, 17.6, 15.0, 13.7; MS (CI) *m/z* 645 ($[M+H]^+$), 555, 418, 355, 337, 291 (base peak), 228, 195, 155; HRMS (CI) *m/z* 645.2792 ($[M+H]^+$) (645.2811 calcd for $C_{36}H_{41}N_2O_9$).

Antimycin A_9

A mixture of **15** (358 mg, 0.56 mmol) and Pd/C (catalytic amount) in EtOAc (3 ml) was stirred under H_2 atmosphere for 2 hours. The mixture was filtered through a pad of Celite, and the filtrate was concentrated. The residue (295 mg) was purified by silica gel column chromatography (hexane/EtOAc) to give antimycin A_9 (284 mg, 89%) as a pale yellow solid (rotamer mixture); mp 151.0～152.0°C; $[\alpha]_D^{22}$ +82.1 (*c* 0.17, MeOH); IR (ATR) cm^{-1}: 3372, 2957, 2872, 2360, 2341, 1745, 1530, 1364, 1182; ^1H NMR (600 MHz, $CDCl_3$) δ 12.61 and 12.47 (total integr. 1H, s and s), 8.09 and 8.50 (total integr. 1H, d, *J*=11.0 Hz and br s), 8.55 (1H, d, *J*=10.2 Hz), 8.11 and 7.83 (total integr. 1H, br s and br d, *J*=10.2 Hz), 7.32～7.38 (2H, m), 7.26～7.32 (3H, m), 7.24 (1H, dd, *J*=8.0, 0.8 Hz), 7.10 and 6.91 (total integr. 1H, d, *J*=7.7 Hz and d, *J*=7.7 Hz), 6.90 (1H, t, *J*=8.2 Hz), 5.75 and 5.71 (total integr. 1H, q, *J*=6.9 Hz and q, *J*=7.1 Hz), 5.32 and 5.27 (total integr. 1H, t, *J*=7.7 Hz and t, *J*=7.4 Hz), 5.09 and 5.05 (total integr. 1H, t, *J*=10.2 Hz and t, *J*=10.2 Hz), 4.93 (1H, dq, *J*=6.6, 6.3 Hz), 3.67 (2H, s), 2.49 (1H, ddd, *J*=13.2, 10.2, 2.7 Hz), 1.54～1.62 (1H, m), 1.30 (3H, d, *J*=6.6 Hz), 1.15 (3H, d, *J*=6.3 Hz), 1.10～1.24 (4H, m), 1.00～1.08 (1H, m), 0.81 (3H, t, *J*=7.1 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 170.2, 170.0, 169.3, 159.2, 150.7, 133.0, 129.2, 128.8, 127.5, 127.4, 124.7, 120.0, 118.9, 112.5, 75.8, 74.7, 70.8, 53.5, 50.1, 41.5, 29.1, 27.9, 22.3, 17.6, 14.9, 13.7; MS (FAB) *m/z* 577 ($[M+Na]^+$), 555 ($[M+H]^+$), 413, 391, 265, 154, 55 (base peak), 41; HRMS (FAB) *m/z* 555.2314 ($[M+H]^+$) (555.2342 calcd for $C_{29}H_{35}N_2O_9$).

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