Tetrin C, a New Glycosylated Polyene Macrolide Antibiotic Produced by *Streptomyces* sp. GK9244

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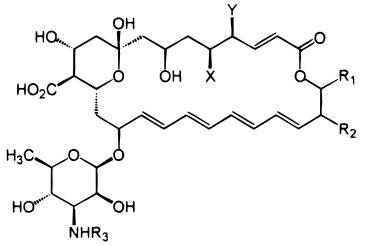
A new antifungal 26-membered polyene macrolide, tetrin C (**1**), has been isolated from *Streptomyces* sp. GK9244. Its structure has been determined by interpretation of NMR data. Compound **1** exhibited antifungal activity against *Mortierella ramannianus* (MIC, 5 μg/mL).

A variety of bioactive 26-membered polyene macrolide compounds including aminosugar mycosamine have been produced from *Streptomyces* spp. since the late 1950s.[1−8] In connection with our research on isolation of novel drugs or lead compounds for prevention and treatment of human fungal diseases we have examined the constituents of *Streptomyces* sp. GK9244 isolated from a soil sample collected in Taejon, Korea.[9,10] *n*-BuOH extraction of a fermentation supernatant of the above species potently inhibited the growth of *Mortierella ramannianus*. Bioassay-guided isolation afforded a new antifungal glycosylated polyene macrolide, tetrin C (**1**). In this paper, we report the isolation and structural elucidation of **1**.

The submerged culture broth (5 L) from a 4-day fermentation of *Streptomyces* sp. GK9244 was centrifuged to separate the mycelial cake. The mycelial cake was stirred in 70% acetone and filtered. The combined filtrates were concentrated, passed through a Diaion HP-20 column, and washed with H_2O followed by MeOH. The MeOH eluate was partitioned between CH_2Cl_2 and 60% MeOH, and between *n*-BuOH and H_2O. The antifungal *n*-BuOH fraction was fractionated by ODS flash chromatography with aqueous MeOH. The 70% MeOH fraction was gel-filtered on Sephadex LH-20 with MeOH to afford an active fraction. This fraction was finally purified by reversed-phase HPLC with 63% MeOH to yield **1** together with the known tetrins A (**2**) and B (**3**), and tetramycins A (**4**) and B (**5**).



1 X, Y=-O-, R_1=CH_3, R_2=CH_3, R_3=H
2 X=OH, Y=H, R_1=CH_3, R_2=CH_3, R_3=H
3 X=OH, Y=OH, R_1=CH_3, R_2=CH_3, R_3=H
4 X=OH, Y=H, R_1=CH_3, R_2=CH_2CH_3, R_3=H
5 X=OH, Y=OH, R_1=CH_3, R_2=CH_2CH_3, R_3=H
6 X, Y=-O-, R_1=CH_3, R_2=CH_3, R_3=Ac

The molecular formula of **1**, $C_{34}H_{49}NO_{13}$, was established on the basis of MS and NMR data. Compound **1** gave peaks at *m/z* 678 for $(M - H)^-$ on negative FABMS. HRFABMS analysis (678.3149, Δ+2.3 mmu) for the molecular ion $(M - H)^-$ confirmed the above formula. The IR spectrum indicated that **1** has OH and/or NH (3450), CO_2H (2750), and lactone (1710). The ^1H NMR spectrum measured in CD_3OD was very similar to that of tetrin B: three methyl doublets (δ 0.95, 1.07, 1.22), eleven oxygenated methines including an anomeric proton at δ 4.64, one nitrogenated methine at δ 3.22, and 10 olefinic protons. The ^{13}C and HMQC NMR data showed a total of 34 carbons including signals for two carbonyls, a hemiketal, twenty-four methines including 10 sp^2 carbons, four methylenes, and three methyl carbons, which accounted for 41 nonexchangeable hydrogen atoms. The molecular formula of **1** corresponded to eleven degrees of unsaturation, seven of which were assignable to 10 olefinic carbons and two carbonyl carbons shown by ^{13}C NMR signals. Since no other sp^2 carbon signals were observed in the NMR spectrum, the remaining four degrees of unsaturation were attributed to four rings.

A mycosamine system (δ 99.3, 69.8, 57.5, 71.6, 74.8, 18.3) and two spin systems (C-2 to C-8 and C-10 to C-27) separated by a quaternary carbon (C-9) at δ 98.1 were revealed by the detailed analysis of H−H COSY, TOCSY, and HMQC spectra. These structural units were readily connected by HMBC[11] cross-peaks: H-7, H-10, H-13/C-9; H-2, H-3, H-25/C-1; H-1′/C-15 and C-5′. An HMBC cross-peak H-11/CO_2H implied that C-12 was also linked to the carboxyl carbon. The locations of hydroxyl groups were determined by a deuterium-induced ^{13}C NMR isotope shift experiment of **1** taken in CD_3OD and CD_3OH. Of the carbons bearing heteroatoms, relatively larger upfield shifts (~0.1 ppm) resulting from deuterium replacements with H were observed on 3′ > 2′ > 7 > 4′ > 11 > 9 listed in order of magnitude, while shifts less than 0.05 ppm at the other oxygenated carbons containing C-4 and C-5 could be attributed to long-range isotope shifts.[12] This indicated an ether-linkage (epoxy group) at C-4 and C-5. Chemical reactivity provided further evidence for the presence of an epoxy functionality since **1** was readily converted to a chlorohydrin (**7**) by HCl in dimethoxyethane/water (2:1) and to a diol monomethyl ether (**8**) by methanolic HCl.

Coupling constants (*J*) were measured for all protons in CD_3OD with the exception of the C-17 to C-22 segment because of a chemical shift overlap of the proton resonances. The coupling constants for this portion of the molecule were obtained in DMSO-d_6, a solvent in which the resonances were better separated on the *N*-acetyl derivative **6**. The geometries of the double bonds and

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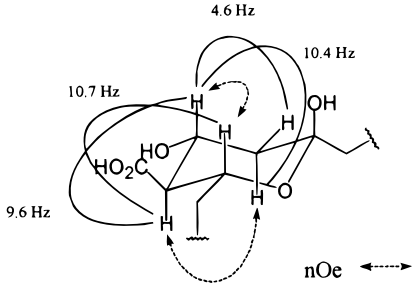
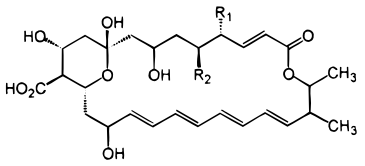


Figure 1. Coupling constants and important NOESY correlations of carboxylic acid group-substituted tetrahydropyran ring in **1**.



7 R_1=Cl, R_2=OH
8 R_1=OMe, R_2=OH

epoxide ring in **6** were concluded to be both trans on the basis of the sizes of the coupling constants. The UV data supported the 16*E*,18*E*,20*E*,22*E*-tetraene system in **1**. The relative configuration of the carboxyl group-substituted tetrahydropyran ring of **1** was confirmed by analysis of $J_{H,H}$ and NOE data, as shown in Figure 1. NOE's observed between H-10ax/H-12 and H-11/H-13 showed that these protons are 1,3-diaxial; thus the tetrahydropyran ring is in a chair conformation with the CO_2H group on C-12 extending equatorially, large $^3J_{H,H}$ values for H-11, H-12 (9.6 Hz) and H-12, H-13 (10.7 Hz) suggested H-11 to be axial so that the hydroxyl group is equatorial. Furthermore, no observation of NOEs between H-13 and/or H-11 and H-8 indicated that the hydroxyl group at C-9 is axial. Therefore, the relative configurations of asymmetric carbons in the tetrahydropyran ring were deduced as 9*S*,*11*R*,*12*S*,*13*R*.* Optical rotation of mycosamine obtained from methanolic hydrolysis (HCl/MeOH) of **1** was indicative to D-mycosamine {authentic $[\alpha]^{22}_D$ −46°(*c* 0.5, EtOH); natural $[\alpha]^{22}_D$ −42°(*c* 0.2, EtOH)}.

The clinical value of polyene macrolide antibiotics lies mainly in their antifungal activity. Other significant biological properties of some of these substances,[13] such as their ability to stimulate the immune response at low concentrations[14] and their action in synergy with other antifungal compounds[15−17] or antitumor drugs,[17,18] have led to their recent stereochemical assignment.[19] Tetrin C (**1**) showed antifungal activity against *M. ramannianus* (MIC, 5 μg/mL), *Penicillium chrysogenum* (10 μg/mL), *Candida albicans* (10 μg/mL), and cytotoxicity (IC_{50}, 4.6 μg/mL) against P388 leukemia cells.

Experimental Section

General Experimental Procedures. UV was recorded on a Hitachi 330 spectrophotometer. IR was measured with a JASCO FT/IR-5300 infrared spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-400 NMR spectrometer at 400 and 100 Hz, respectively. ^{1}H and ^{13}C NMR chemical shifts were referenced to solvent peaks; δ_H 3.5 and δ_C 49.9 for CD_3OD; δ_H 2.49 and δ_C 39.5 for DMSO-d_6. FABMS and HRFABMS were measured with a JEOL JMX-SX 102 mass spectrometer and high-resolution FABMS spectra were determined using a dual-target inlet probe. Optical rotations were performed with a JASCO DIP-371 digital polarimeter. Thin-layer chromatography was carried out on Merck silica gel 60 F_{254} plates, and MPLC and HPLC were carried out on a Waters 510 apparatus.

Organisms and Fermentation. *Streptomyces* sp. GK9244, which was isolated from a soil sample collected in Taejon, Korea, was cultured in the seed medium consisting of glucose 2%, starch 1%, soybean flour 2.5%, yeast extract 0.4%, NaCl 0.2%, K_2HPO_4 0.005%, and beef extract 0.1% (adjusted to pH 7.3 before sterilization). The seed culture was carried out on a rotary shaker (250 rpm) at 28 °C for 24 h in 500-mL Erlenmeyer flasks containing 100 mL of the seed medium. Then, the seed culture (100 mL) was inoculated to a 50-L jar fermenter containing 10 L of the production medium (antifoam 0.08%). Fermentation was carried out at 27 °C for 4 days with aeration (10 L/min.) under constant agitation (250 rpm).

Extraction and Isolation. Isolation of **1** was guided by the use of *M. ramnnianus* as a test organism. The culture broth (5 L) was centrifuged to separate the mycelial cake. The mycelial cake was stirred overnight in 70% acetone and filtered. The filtrate was concentrated *in vacuo* to remove the organic solvent, resulting in an aqueous solution. The combined filtrates were passed through a Diaion HP-20 column, and washed with H_2O followed by MeOH. The MeOH eluate was partitioned between CH_2Cl_2 and 60% MeOH, and between *n*-BuOH and H_2O. The CH_2Cl_2 fraction afforded antibacterial triene antibiotics containing oxazolomycin and 16-methyloxazolomycin.[9,10] The *n*-BuOH fraction showed antifungal activity and was fractionated by ODS flash chromatography with aqueous MeOH. The 70% MeOH fraction was further purified on Sephadex LH-20 with MeOH followed by reversed-phase HPLC with 63% MeOH to yield tetrin C (**1**, 6 mg) together with the known tetrins A and B (**2** and **3**, 12 mg and 90 mg) and tetramycins A and B (**4** and **5**, 15 mg and 13 mg). **1**: pale yellow amorphous solid; $[\alpha]^{23}_D$ +19.3 (*c* 1.5, MeOH); UV (MeOH) λ_{max} (ϵ) 280, 292 (720), 304 (1100), 318 (970) nm; IR (film) ν_{max} 3450, 2750, 1710, 1635, 1580, 1515, 1455, 1180 cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz) δ 6.19−6.62 (7H, overlapped, H-3, and H-17 to H-22), 5.98 (1H, d, *J* = 15.5 Hz, H-2), 5.90 (1H, dd, *J* = 15.4, 8.8 Hz, H-16), 5.77 (1H, dd, *J* = 14.6, 9.0 Hz, H-23), 4.72 (1H, m, H-25), 4.64 (1H, d, *J* = 1.3 Hz, H-1′), 4.57 (1H, ddd, *J* = 8.8, 5.0, 3.1 Hz, H-15), 4.43 (1H, m, H-7), 4.38 (1H, dd, *J* = 10.7, 8.6 Hz, H-13), 4.16 (1H, ddd, *J* = 10.7, 9.6, 4.6 Hz, H-11), 4.06 (1H, dd, *J* = 2.8, 1.3 Hz, H-2′), 3.48 (1H, dd, *J* = 7.5, 1.1 Hz, H-4), 3.39 (1H, m, H-5′), 3.29 (1H, dd, *J* = 9.6, 9.2 Hz, H-4′), 3.21 (1H, dd, *J* = 9.2, 2.8 Hz, H-3′), 2.86 (1H, dd, *J* = 8.2, 1.1 Hz, H-5), 2.51 (1H, m, H-24), 2.20 (1H, dd, *J* = 15.4, 5.0 Hz, H-14), 2.11 (1H, dd, *J* = 17.2, 8.2 Hz, H-6), 2.08 (1H, dd, *J* = 10.7, 9.6 Hz, H-12), 2.03 (1H, dd, *J* = 13.6, 10.7 Hz, H-10), 1.88 (1H, dd, *J* = 13.5, 7.6 Hz, H-8), 1.76 (1H, d, *J* = 13.5 Hz, H-8), 1.66 (1H, ddd, *J* = 15.4, 8.6, 3.1 Hz, H-14), 1.34 (1H, dd, *J* = 13.6, 4.6 Hz, H-10), 1.25 (1H, dd, *J* = 17.2, 10.2 Hz, H-6), 1.21 (3H, d, *J* = 6.5 Hz, H-6′), 1.07 (3H, d, *J* = 6.1 Hz, H-26), 0.95 (3H, d, *J* = 6.3 Hz, H-27). ^{13}C NMR (CD_3OD, 100 Hz) δ 171.4 (s, *C*O_2H), 165.8 (s, C-1), 146.4 (d, C-2), 131−134 (C-17 to C-22), 129.8 (d, C-23), 128.6 (d, C-16), 124.2 (d, C-3), 99.3 (d, C-1′), 98.1 (s, C-9), 76.4 (d, C-15), 74.8 (d, C-5′), 71.6 (d, C-4′), 69.8 (d, C-2′), 69.2 (d, C-13), 67.2 (d, C-25), 66.2 (d, C-7), 65.7 (d, C-11), 58.8 (d, C-5), 57.6 (d, C-12), 57.3 (d, C-3′), 54.7 (d, C-4), 46.8 (t, C-8), 44.1 (t, C-14), 41.7 (t, C-6), 40.6 (d, C-24), 37.6 (d, C-10), 18.3 (q, C-6′), 17.2 (q, C-27), 13.8 (q, C-26); FABMS *m*/*z* 678 $[(M - H)]^-$, 462; HRFABMS *m*/*z* 678.3149 calcd, for $C_{34}H_{48}NO_{13}$ (Δ+2.3 mmu).

N-Acetylation of Tetrin C (6). A mixture of **1** (6 mg) and 0.1 mL of Ac_2O in 1 mL of absolute MeOH was stirred at 0 °C for 2 h while the derivative gradually dissolved. The resulting solution was concentrated at room temperature and the residue was precipitated with ether/hexane (1:1) to give 5.5 mg (85%) of *N*-acetyltetrin C (**6**): ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.59 (1H, d, *J* = 8.4 Hz, 3′-NH), 6.87 (1H, dd, *J* = 15.3, 7.6 Hz, H-3), 6.62 (1H, dd, *J* = 14.6, 10.2 Hz, H-21), 6.45 (1H, dd, *J* = 16.4, 10.1 Hz, H-19), 6.32 (1H, dd, *J* = 16.4, 10.5 Hz, H-18), 6.24 (1H, dd, *J* = 14.6, 10.1 Hz, H-20), 6.16 (1H, dd, *J* = 15.7, 10.5 Hz, H-17), 6.05 (1H, dd, *J* = 14.4, 10.2 Hz, H-22), 6.04 (1H, s, 9-O*H*), 5.94 (1H, dd, *J* = 15.7, 8.8 Hz, H-16), 5.83 (1H, d, *J* = 15.3 Hz, H-2), 5.70 (1H, dd, *J* = 14.4, 9.3 Hz, H-23), 5.24 (1H, d, *J* = 5.0 Hz, 7-OH), 4.78 (1H, d, *J* = 5.5 Hz, 4′-O*H*), 4.69 (1H, d, *J* = 6.3 Hz, 2′-O*H*), 4.60 (1H, m, H-25), 4.54 (1H, d, *J* = 1.2 Hz, H-1′), 4.37 (1H, m, H-7), 4.26 (1H, dd,

J = 10.6, 8.7 Hz, H-13), 3.94 (1H, ddd, J = 10.8, 9.6, 4.5 Hz, H-11), 3.75 (1H, ddd, J = 9.6, 8.4, 2.9 Hz, H-3′), 3.64 (1H, ddd, J = 6.3, 2.9, 1.2 Hz, H-2′), 3.43 (1H, dd, J = 7.6, 1.0 Hz, H-4), 3.19 (1H, m, H-5′), 3.09 (1H, dd, J = 9.6, 5.5 Hz, H-4′), 2.87 (1H, dd, J = 8.3, 1.0 Hz, H-5), 2.39 (1H, m, H-24), 2.22 (1H, dd, J = 10.6, 9.6 Hz, H-12), 2.04 (1H, dd, J = 17.4, 8.3 Hz, H-6), 2.01 (3H, s, NCOCH_3), 1.91 (1H, dd, J = 13.8, 4.5 Hz, H-10), 1.80 (1H, dd, J = 13.6, 7.8 Hz, H-8), 1.64 (1H, d, J = 13.6 Hz, H-8), 1.55 (1H, ddd, J = 15.3, 8.7, 3.0 Hz, H-14), 1.26 (1H, dd, J = 13.8, 10.8 Hz, H-10), 1.22 (1H, dd, J = 17.4, 10.3 Hz, H-6), 1.18 (3H, d, J = 6.3 Hz, H-6′), 1.12 (3H, d, J = 5.9 Hz, H-26), 1.04 (3H, d, J = 6.3 Hz, H-27); FABMS (neg) m/z 720; ^{13}C NMR (CD_3OD, 100 MHz) δ 172.3 (s, CO_2H), 164.7 (s, N$COCH_3$), 163.9 (s, C-1), 148.0 (d, C-3), 135.8 (d, C-17), 134.6 (d, C-22), 132.8 (d, C-21), 131.6 (d, C-20), 131.4 (d, C-19), 130.7 (d, C-18), 129.8 (d, C-21), 129.2 (d, C-23), 125.8 (d, C-2), 99.6 (d, C-1′), 98.4 (s, C-9), 77.2 (d, C-15), 74.5 (d, C-5′), 71.9 (d, C-4′), 71.0 (d, C-2′), 68.8 (d, C-25), 68.7 (d, C-13), 68.1 (d, C-7), 65.6 (d, C-11), 59.2 (d, C-12), 58.2 (d, C-5), 57.2 (d, C-3′), 52.9 (d, C-4), 45.6 (t, C-8), 43.6 (t, C-14), 42.9 (t, C-6), 40.9 (d, C-24), 36.6 (t, C-10), 21.4 (NCOCH_3), 18.6 (q, C-6′), 18.0 (q, C-27), 14.2 (q, C-26).

Conversion of 1 to 7. To a solution of 1.8 mg of **1** in 1 mL of 1,2-dimethoxyethane/H_2O (2:1) was added 0.5 mL of 2 N HCl. The solution was allowed to stir at 60 °C for 4 h, neutralized with potassium carbonate, and evaporated. The residue was partitioned between AcOEt and H_2O. The AcOEt-soluble material was purified by reversed-phase HPLC using MeOH/H_2O (86:14) to obtain 1.3 mg of pure **7**, which showed an $(M - H)^-$ ion at m/z 569 by negative FAB MS. **7**: ^{1}H NMR (CD_3OD, 400 MHz) δ 6.16−6.65 (7H, olefinics), 5.98 (1H, dd, J = 15.4, 8.8 Hz, H-16), 5.78 (1H, d, J = 15.5 Hz, H-2), 5.68 (1H, dd, J = 14.6, 9.1 Hz, H-23), 4.82 (1H, m, H-25), 4.74 (1H, dd, J = 10.2, 6.2 Hz, H-7), 4.65 (1H, dd, J = 6.6, 6.0 Hz, H-4), 4.41 (1H, dd, J = 10.6, 8.7 Hz, H-13), 4.33 (1H, ddd, J = 10.3, 9.1, 4.6 Hz, H-11), 3.46 (1H, ddd, J = 8.8, 5.2, 3.0 Hz, H-15), 2.54 (1H, m, H-24), 2.34 (1H, dd, J = 15.6, 5.2 Hz, H-14), 2.20 (1H, dd, J = 12.8, 10.4 Hz, H-10), 2.12 (1H, dd, J = 10.6, 9.1 Hz, H-12), 2.07 (2H, m, H-6), 1.90 (2H, m, H-8), 1.72 (1H, ddd, J = 15.6, 8.7, 3.0 Hz, H-14), 1.46 (1H, dd, J = 12.8, 4.5 Hz, H-10), 1.09 (3H, d, J = 5.8 Hz, H-26), 0.88 (3H, d, J = 6.3 Hz, H-27).

Conversion of 1 to 8. To a solution of 2.2 mg of **1** in 1 mL of dry MeOH was added 1 mL of methanolic HCl (obtained by treating 2.5 g of thionyl chloride with 25 mL of MeOH). After the solution was stirred at 70 °C for 4 h, the solvent was removed *in vacuo*, and the sample was left under vacuum for 12 h. Purification by reversed-phase HPLC with MeOH/H_2O (86/14) gave 1.6 mg of pure **8**, which showed an $(M - H)^-$ ion at m/z 565 by negative FABMS. **8**: ^{1}H NMR (CD_3OD, 400 MHz) δ 6.16−6.69 (7H, olefinics), 5.98 (1H, dd, J = 15.2, 8.6 Hz, H-16), 5.78 (1H, d, J = 15.5 Hz, H-2), 5.68 (1H, dd, J = 14.6, 9.1 Hz, H-23), 4.82 (1H, m, H-25), 4.74 (1H, dd, J = 10.2, 6.2 Hz, H-7), 4.65 (1H, dd, J = 6.6, 6.0 Hz, H-4), 4.41 (1H, dd, J = 10.6, 8.7 Hz, H-13), 4.33 (1H, ddd, J = 10.3, 9.1, 4.6 Hz, H-11), 3.48 (1H, ddd, J = 8.6, 5.0, 3.0 Hz, H-15), 2.53 (1H, m, H-24), 2.22 (1H, dd, J = 15.6, 5.0 Hz, H-14), 2.12 (1H, dd, J = 12.9, 10.5 Hz, H-10), 2.08 (1H, dd, J = 10.6, 9.2 Hz, H-12), 2.01 (2H, m, H-6), 1.82 (2H, m, H-8), 1.69 (1H, ddd, J = 15.6, 8.8, 3.0 Hz, H-14), 1.42 (1H, dd, J = 12.9, 4.4 Hz, H-10), 1.10 (3H, d, J = 5.9 Hz, H-26), 0.96 (3H, d, J = 6.2 Hz, H-27).

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References and Notes

(1) Pandey, R. C.; German, V. F.; Nishikawa, Y.; Rinehart, K. L., Jr. *J. Am. Chem.* Soc. **1971**, *93*, 3738−3747.
(2) Rinehart, K. L., Jr.; Tucker, W. P.; Pandey, R. C. *J. Am. Chem. Soc.* **1971**, *93*, 3747−3751.
(3) Ceder, O.; Hansson, B.; Rapp, U. *Tetrahedron* **1977**, *33*, 2703−2714.
(4) Gaudiano, G.; Bravo, P.; Quilico, A.; Golding, B. T.; Rickards, R. W. *Tetrahedron Lett.* **1966**, *30*, 3567−3571.
(5) Shenin, Y. D.; Soloviev, V. N.; Nevinskii, A. A. *Acta Chem. Scand.* **1973**, *18*, 72−76.
(6) Pandey, R. C.; Rinehart, K. L, Jr. *J. Antibiotics* **1977**, *30*, 158−162.
(7) Dornberger, K.; Thrun, H.; Radics, L. *Tetrahedron* **1979**, *35*, 1851−1856.
(8) Radics, L.; Incze, M.; Dornberger, K.; Thrun, H. *Tetrahedron* **1982**, *38*, 183−189.
(9) Ryu, G.; Hwang, S.; Kim, S. K. *J. Antibiotics* **1997**, *50*, 1064−1066.
(10) Ryu, G.; Kim, S. K. *J. Antibiotics* **1999**, *52*, 143−149.
(11) Bax, A.; Aszalos, A.; Dinya, Z.; Sudo, K. *J. Am. Chem. Soc.* **1986**, *108*, 8056−8063.
(12) Jeremic, D.; Milosavljevic, S.; Mihalovic, M. L. *Tetrahedron* **1982**, *38*, 3325−3328.
(13) For a review, see: Bolard, J. *Biochim. Biophys. Acta* **1986**, *864*, 257−304.
(14) Little, J. R.; Blanke, T. J.; Valeriote, F.; Medoff, G. *Immune Modulation and Control of Neoplasia by Adjuvant Therapy*; Chirigos, A., Ed.; Raven: New York, 1978; pp 381−387.
(15) Brajtburg J.; Kobayashi, D.; Medoff, G.; Kobayashi, G. S. *J. Infect. Dis.* **1982**, *146*, 138−146.
(16) Hugues, C. E.; Harris, C.; Petersen, L. R.; Gerding, D. N. *Antimicrob. Agents Chemother.* **1984**, *26*, 837−840.
(17) Vertut-Croquin A.; Brajtburg, J.; Medoff, G. *Cancer Res.* **1986**, *46*, 6054−6058.
(18) Henry, N.; Bolard, J. *Syner. Biophys. Acta* **1986**, *854*, 84−92.
(19) For a review, see: Beau, J. M. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; pp 135−182.

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