Mayamycin, a Cytotoxic Polyketide from a *Streptomyces* Strain Isolated from the Marine Sponge *Halichondria panicea*

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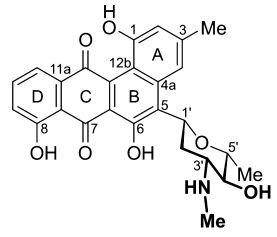
A new benz[*a*]anthracene derivative called mayamycin (**1**) was identified in cultures of *Streptomyces* sp. strain HB202, which was isolated from the marine sponge *Halichondria panicea* and selected because of its profound antibiotic activity. The ability to produce aromatic polyketides was indicated by genetic analyses, demonstrating the presence of a type II polyketide synthase. The production of mayamycin (**1**) was induced by variation of the culture conditions. The structure of **1** was elucidated by HPLC-UV/MS and NMR spectroscopy. Mayamycin (**1**) exhibited potent cytotoxic activity against eight human cancer cell lines and showed activity against several bacteria including antibiotic-resistant strains.

Marine actinomycetes are among the most promising natural producers of new antibiotics with clinical relevance.[1] Therefore, we have performed a systematic analysis of Actinobacteria isolated from marine habitats with regard to their potential to produce biologically active natural products.[2] This strategy included the selection of promising producers based on bioassay-guided analyses and the detection of genes encoding for the biosynthesis of secondary metabolites. Within such an approach, the marine *Streptomyces* sp. strain HB202, which was isolated from the sponge *Halichondria panicea,* showed a wide antibiotic activity spectrum while also containing one type II polyketide synthase gene fragment with a similarity of 92% to the jadomycin polyketide ketosynthase gene from *Streptomyces venezuelae* ISP5230 (AAB36562).[3] Even though many different cultivation experiments were conducted with this strain, stimulation with subinhibitory concentrations of antibiotics was demonstrated,[4] and no aromatic polyketide was observed. The aim of our study was to demonstrate that by further varying the cultivation conditions, strain HB202 has the ability to biosynthesize a type II PKS product.

Previous investigations had demonstrated the production of streptophenazines A−H by *Streptomyces* sp. strain HB202. In this former study, the biosynthesis was induced by subinhibitory concentrations of the antibiotics bacitracin and tetracycline,[4] but no secondary metabolite consistent with the identified iterative PKS gene fragment was observed. To promote the production of additional substances, especially aromatic polyketides, different cultivation conditions were applied, and under one of these applied conditions only one compound, an aromatic polyketide, was produced, which is described here as mayamycin (**1**).



(1'*R**,3'*R**,4'*S**,5'*R**)-mayamycin (**1**)

Cultivation of the bacterium in penicillin flasks containing GYM medium without using shaking conditions led to the production of the new benz[*a*]anthracene derivative mayamycin (**1**). No further compounds were observed under these conditions. The culture broth and cells were homogenized and extracted with EtOAc. The extract was separated by preparative reversed-phase (C_{18}) HPLC to yield **1**.

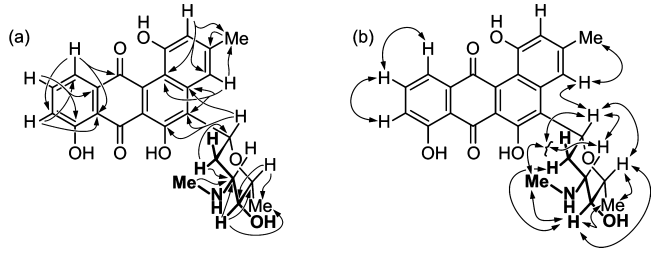


Figure 1. 2D NMR correlations of mayamycin (**1**) relevant for the structure elucidation: (a) HMBC couplings; (b) NOESY correlations.

Mayamycin (**1**) was an amorphous, brown solid with a molecular formula of $C_{26}H_{25}NO_7$, as determined by HRESIMS (*m*/*z* 464.1707 $[M + H]^+$) and verified by ^{13}C NMR and $^1H-^{13}C$ HMBC spectra. According to its UV−vis spectrum, metabolite **1** was likely to belong to the anthraquinone group. This was supported by a set of downfield resonances occurring in the ^{13}C NMR spectrum between δ 100 and 170 ppm, which belonged to aromatic carbon atoms, and by two carbonyl resonances that were observed at δ 194.2 and 188.0 ppm, consistent with a quinone skeleton. According to their chemical shifts, three of the aromatic carbon atoms mentioned above (δ 154.4, 156.5, and 162.9 ppm) carried hydroxy groups. In addition, one methyl residue (2.45, s) attached at C-3 to the aromatic carbon skeleton was observed. Comprehensive analyses of 2D NMR ($^1H-^1H$ COSY, HSQC, $^1H-^{13}C$ HMBC, and NOESY) data showed that compound **1** was an angucycline-type polyketide with a C-glycosidically bound amino sugar. The aromatic protons H-9, H-10, and H-11 were located at the D-ring of the angucycline skeleton and showed HMBC couplings to the remaining carbons (C-7a, C-8, and C11a) of ring D as well as to the carbonyl carbon C-12 of the C-ring (Figure 1). Additionally, $^1H-^1H$ COSY correlations were observed from H-9 to H-10 and from H-10 to H-11. The remaining two aromatic protons together with the methyl group were found to be located at ring A. Long-range H,C-couplings revealed their exact position at this ring (C-2, C-4, and C-3, respectively) (Figure 1). This angucyclinone skeleton of **1** is identical to the known dehydrorabelomycin.[5]

Pivotal correlations that proved the connection site of the amino sugar at C-5 were the long-range H,C-couplings of H-4 to C-5 and C-12b as well as the couplings of H-1′ to C-4a, C-5, and C-6. A

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Table 1. NMR Spectroscopic Data (600 MHz, CD_3OD) for Mayamycin (**1**)

position	δ_C, mult.	δ_H (*J* in Hz)	COSY	HMBC	NOESY
1	156.5, C				
2	114.7, CH	6.74, s		4, 3-CH_3, 12b	
3	143.4, C				
3-CH_3	22.6, CH_3	2.45, s		2, 3, 4	4
4	117.6, CH	8.00, s		2, 3-CH_3, 4a, 5, 12b	3-CH_3, 1′
4a	139.9, C				
5	126.5, C[b]				
6	154.4, C[b]				
6a	138.4/119.4, C				
7	194.2, C				
7a	116.3, C				
8	162.9, C				
9	124.9, CH	7.29, dd (1.2, 8.5)[a]	10	7a, 11	10
10	138.8, CH	7.75, dd (7.5, 8.5)[a]	9, 11	8, 11, 11a	9, 11
11	120.4, CH	7.58, dd (1.2, 7.5)[a]	10	7a, 9, 12	10
11a	137.9, C				
12	188.0, C[b]				
12a	119.4/138.4, C				
12b	117.8, C				
1′	72.8, CH	5.70, dd (11.7, 2.0)	2′a, 2′b	4a, 5, 6	4, 2′a, 2′b, 3′, 5′
2′a	32.9, CH_2	2.35, ddd (13.0, 11.7)	1′, 3′	1′, 3′, 4′	1′, 3′, 3′-*N*-CH_3
2′b	32.9, CH_2	2.27, ddd (13.0, 2.0, 4.8)	1′, 3′	1′, 3′, 4′	1′, 3′, 3′-*N*-CH_3
3′	63.0, CH	3.23, br ddd (4.8, 11.7, 9.0)	2′, 4′		1′, 2′a, 2′b, 3′-*N*-CH_3
3′-*N*-CH_3	31.4, CH_3	2.63, s		3′	2′a, 2′b, 3′, 4′
4′	74.5, CH	3.41, t (9.0)	3′, 5′	3′, 5′, 5′-CH_3	2′a, 3′, 3′-*N*-CH3, 5′, 5′-CH_3
5′	79.2, CH	3.56, dq (9.0, 6.1)	4′, 5′- CH_3	3′, 4′, 5′-CH_3	1′, 4′, 5′-CH_3
5′-CH_3	18.7, CH_3	1.42, d (6.1)	5′	4′, 5′	4′, 5′

[a] *J* values were defined in CD_2Cl_2 because of broad ^1H signals in CD_3OD. [b] Deduced by HMBC correlations.

NOESY correlation between H-4 and H-1′ and the chemical shift of C-1′ (δ 72.8 ppm) confirmed that the amino sugar is attached to the benz[*a*]anthracene skeleton of **1** by a C-glycosidic bond.

Further evaluation of the NMR data showed the amino sugar to be a 2,3,6-trideoxy-3-methylaminopyran. The position of the methylamino residue was evident from the long-range H,C-couplings between the N-CH_3 and C-3′ as well as NOESY correlations between the N-CH_3 and both protons at C-2′. The rest of the structure of the sugar moiety was revealed by long-range H,C-couplings of both protons at H-2′ with C-1′, C-3′, and C-4′, of H-4′ with C-3′, C-5′, and 5′-CH_3, and of H-5′ with C-3′, C-4′, and 5′-CH_3. The methyl group at C-5′ showed HMBC couplings with C-4′ and C-5′. Additionally, a series of $^1H-^1H$ COSY as well as NOESY correlations were observed for the sugar moiety from H-1′ to H-2′a and H-2′b, from H-2′ to H-3′, from H-3′ to H-4′, and from H-4′ to H-5′. The methyl group at C-5′ showed NOESY correlations to H-5′ as well as to H-4′. The chemical shift of C-4′ (74.5 ppm) in combination with the molecular formula of the compound indicated a free hydroxy group at this position. The ^3J-coupling constants of 9.0 Hz for H-5′/H-4′ as well as for H-4′/H-3′ showed axial orientations for these protons. The likewise axial orientation of H-1′ was inferred from the NOE interaction H-3′/H-1′. These results indicate the sugar is *N*-demethylangolosamine, and a relative configuration of (1′*R**,3′*R**,4′*S**,5′*R**) is assigned to mayamycin (**1**). Angolosamine, which has a dimethylamino group, is present in benzanthrins A and B, related compounds that have the same angucyclinone core.[6] Although the absolute configuration has not been determined, the glycoside has been depicted in the D-configuration because in other cases where the configuration of angolosamine has been established D-angolosamine has been present.[7,8]

Most of the reported angucyclines are *O*-deoxyglycosides, and a much smaller group are C-glycosides.[9] In the case of mayamycin (**1**) the sugar binding site is C-5. At this position so far, no C-glycosidic bound sugar is known, although some examples exist with *S*- or *O*-glycosidic bound sugars.[10,11] Deoxyaminosugars are quite frequently found in antibiotics. Examples with D-angolosamine are angolamycin[7] and medermycin.[8] In our case the aminosugar is the mono *N*-demethylated form of angolosamine. Other examples of angucyclines with an aminosugar are the antibiotic P371A[12] and the marmycins.[9]

With regard to the combination of the angucyclinone core structure with this particular aminosugar and the site of glycosylation as well as the character of the glycosylation (C-glycosidic bond) mayamycin (**1**) is unusual compared to previously reported angucycline amino glycoside metabolites.

Members of the angucycline class are polyketide-derived tetracyclic benz[*a*]anthraquinones that exhibit a wide range of biological activities including antibacterial, enzyme-inhibitory, and cytostatic effects.[13] In a previous bioassay-guided approach it was shown that the extract of strain HB202 inhibited the growth of various Gram-positive and Gram-negative bacteria (data not shown). Therefore, the antimicrobial activity of mayamycin (**1**) was analyzed using a wide range of Gram-positive and Gram-negative bacteria and yeast strains. The results revealed strong inhibitory activity against several test strains, including clinically relevant bacteria, such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA), the causative agents of acne vulgaris, *Propionibacterium acnes*, the human skin flora forming bacteria *Dermabacter hominis* and *Brevibacterium epidermidis*, and the phytopathogenic bacterium *Xanthomonas campestris,* as summarized in Table 2. On the other hand, **1** was found to be inactive against the yeast *Candida glabrata* and the fungus *Septoria tritici* as well as the Gram-negative bacteria *Escherichia coli*, *Pseudomonas syringae*, and *Ralstonia solanacearum*. In addition, **1** showed an inhibitory activity against the phytopathogenic oomycete *Phytophthora infestans*, with an IC_{50} value of 15.2 μM (positive control: cycloheximid, IC_{50} 0.36 μM) in a growth-inhibitory assay.

Furthermore, mayamycin (**1**) showed potent *in vitro* cytotoxicity against eight human cancer cell lines (Table 3). The determined IC_{50} values were within a concentration range of 0.13 to 0.33 μM. Mayamycin (**1**) was also cytotoxic toward the mouse fibroblast cell line NIH-3T3. The IC_{50} value of **1** was 0.22 μM. Tamoxifen was used as positive control and showed an IC_{50} value of 23.7 μM.

Experimental Section

General Experimental Procedures. The optical rotation was measured on a Perkin-Elmer model 241. The UV spectra were obtained on a NanoVue (GE Healthcare). NMR spectra were recorded on a

Table 2. Antibacterial Activity of Mayamycin (**1**) against Bacterial Strains

bacterial strains	IC_{50} (μM)	IC_{50} (μM) of the standard
Bacillus subtilis (DSM 347) standard: chloramphenicol	8.0	9.0
Brevibacterium epidermidis (DSM 20660) standard: tetracycline	7.45	13.9
Dermabacter hominis (DSM 7083) standard: tetracycline	8.4	1.2
Klebsiella pneumoniae (ATCC 700603; ESBL)	2.5	n.d.[a]
Propionibacterium acnes (DSM 1897) standard: chloramphenicol	31.2	1.0
Pseudomonas aeruginosa (DSM 50071) standard: chloramphenicol	2.5	27.3
Staphylococcus aureus (ATCC 12600) standard: moxifloxacin	2.5	7.5
Staphylococcus aureus (ATCC 33593; MRSA)	1.25	n.d.[a]
Staphylococcus epidermidis (DSM 20044)	0.31	n.d.[a]
Staphylococcus lentus (DSM 6672) standard: chloramphenicol	8.0	2.3
Xanthomonas campestris (DSM 2405) standard: chloramphenicol	30.0	3.6

[a] n.d. not determined.

Table 3. Cytotoxic Activity of Mayamycin (**1**) in Eight Human Cancer Cell Lines

human cancer cell line	IC_{50} [μM]	IC_{50} [μM] of the standard
HepG2 (hepatocellular carcinoma) standard: tamoxifen	0.2	23.4
HT-29 (colon adenocarcinoma) standard: tamoxifen	0.3	38.6
GXF251L (gastric cancer) standard: adriamycin	0.2	<0.052
LXF529L (non-small-cell lung cancer) standard: adriamycin	0.16	<0.052
MAXF401NL (mammary cancer) standard: adriamycin	0.29	<0.052
MEXF462NL (melanoma cancer) standard: adriamycin	0.13	<0.052
PAXF1657L (pancreatic cancer) standard: adriamycin	0.15	<0.052
RXF486L (renal cancer) standard: adriamycin	0.33	≤0.052

Bruker AV600 spectrometer (600 and 150 MHz for ^{1}H and ^{13}C NMR, respectively), using the signals of the residual solvent protons and the solvent carbons as internal references (δ_H 3.31 and δ_C 49.0 ppm for MeOH-d_4). High-resolution mass spectra were acquired on a benchtop time-of-flight spectrometer (MicrOTOF, Bruker Daltonics) with positive electrospray ionization. Reversed-phase HPLC-UV/MS analysis was performed using a C_{18} column (Phenomenex Onyx Monolithic C18, 100 × 3.00 mm) applying an H_2O (A)/MeCN (B) gradient with 0.1% HCOOH added to both solvents (gradient: 0 min 5% B, 4 min 60% B, 6 min 100% B; flow 2 mL/min) on a VWR Hitachi Elite LaChrom system coupled to an ESI-ion trap detector (Esquire 4000, Bruker Daltonics). Mayamycin (**1**) was detected at 3.0−3.4 min.

Isolation and Identification of *Streptomyces* sp. HB202. The isolation and identification of strain HB202 was described by Mitova et al.[4] The strain was isolated from the marine sponge *Halichondria panicea* collected from the Baltic Sea. The most closely related type strains according to the 16S rRNA gene sequence (1473 bp) were *Streptomyces mediolani* LMG 20093^T (GenBank/EMBL/DDBJ acc. no. AJ781354) with a sequence similarity of 99.9% and *Streptomyces griseus* ATCC 51928^T (GenBank/EMBL/DDBJ acc. no. AF112160) with a sequence similarity of 99.8%.

Detection of Polyketide Synthase Gene Fragments. The PCR approach for the detection of a type II polyketide synthase KS_α domain was performed according to Metsä-Ketelä et al.[14] Sequencing of PCR products was performed using a standard protocol.[15] Comparison of KS_α gene fragments (505 nucleotides) of the marine *Streptomyces* sp. HB202 was accomplished with sequences in the EMBL nucleotide database available online at the European Bioinformatics Institute homepage using the Basic Local Alignment Search Tool (blastx).[16] One of the most closely related sequences was the jadomycin polyketide ketosynthase gene of *Streptomyces venezuelae* ISP5230 (92% similarity; AAB36562).[3]

Cultivation. Cultivation conditions using 500 mL of GYM medium (2 g of glucose, 2 g of yeast extract, 2 g of malt extract, 1 g of $CaCO_3$, 500 mL of water, pH 7.2) in penicillin flasks were the only conditions applied in this study that produced compound **1**. After 7 days a 20 mL sample was extracted with 10 mL of EtOAc. After evaporation of the solvent the extract was redissolved in 200 μL of MeOH. An aliquot of 15 μL was analyzed by HPLC/UV-MS.

Additional cultivation approaches were performed, but no production of **1** was observed under any of the following conditions: Erlenmeyer flasks in GYM, MB (37.4 g of Marine Broth, Difco), and TSB10 medium (3 g of BD trypticase soy broth (TSB), 10 g of NaCl, 1 L of water, pH 7.2) in volumes of 1000, 300, and 25 mL, respectively, under shaking conditions (120 rpm).

Fermentation. For chemical analyses strain *Streptomyces* sp. HB202 was grown in GYM medium for 7 days at 28 °C in multiple 4 L penicillin flasks. Each flask was inoculated with a 3 × 5 cm piece from a GYM agar plate with a 4-week-old culture.

Purification of Mayamycin (1). The culture broth (5 L) was homogenized by Ultra Turrax T25 basic (IKA-Werke GmbH and Co., Staufen, Germany) at 16 000 rpm for 30 s and extracted with 3.5 L of EtOAc. Evaporation of the solvent yielded 400 mg of extract. An aliquot was analyzed with HPLC-MS. The extract was subjected to preparative HPLC (Phenomenex Gemini-NX C18 110A, 100 × 50.00 mm; eluents: H_2O (A), MeCN (B); gradient 0 min 10% B, 17 min 60% B, 22 min 100% B; flow 100 mL/min; UV detection at 236 nm. Mayamycin (166.5 mg) eluted at 8.4−9.0 min).

(1′*R,3′*R**,4′*S**,5′*R**)-Mayamycin (1):** dark brown, amorphous solid; $[\alpha]^{20}_D$ 0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 440 (2.44), 330 (2.78), 301sh (2.68), 230 (3.07); for 1D and 2D NMR data, see Table 1 and SI; HRESIMS *m/z* 464.1707 $[M + H]^+$ (calcd for $C_{26}H_{26}NO_7$, 464.1709).

Antibacterial Activities. Antimicrobial assays were performed using *Bacillus subtilis* (DSM 347), *Brevibacterium epidermidis* (DSM 20660), *Dermabacter hominis* (DSM 7083), *Escherichia coli* K12 (DSM 498), *Propionibacterium acnes* (DSM 1897), *Pseudomonas aeruginosa* (DSM 50071), *Pseudomonas syringae* pv *aptata* (DSM 50252), *Ralstonia solanacearum* (DSM 9544), *Staphylococcus epidermidis* (DSM 20044), *Staphylococcus lentus* (DSM 6672), *Xanthomonas campestris* (DSM 2405), and the yeast *Candida glabrata* (DSM 6425) and *Septoria tritici*. The assays were prepared by transferring 10 μL of a 2 mM methanolic solution of the sample compounds into one well of a 96-well microtiter plate and evaporating the solvent in a vacuum centrifuge. Overnight cultures of the test organisms in tryptic soy broth were diluted to an OD_{600} of 0.02−0.05, and 200 μL of the resulting suspension was added to the wells. After incubating the microtiter plates for 14−16 h at 28 °C, in the case of *Dermabacter hominis* for 24 h at 37 °C, 10 μL of a resazurin solution (0.2 mg mL^{-1} PBS) was added to each well and the plate incubated at 28 °C for 1−2 h. For evaluation of the cell viability the reduction of resazurin to resorufin was assessed by measuring the intensity of fluorescence at $560_{Ex}/590_{Em}$ nm.[17] The resulting values were compared to a positive (50 mg of chloramphenicol or tetracycline for bacteria; 50 mg of cycloheximide for *Candida glabrata*, *Septoria tritici*, and *Phytophtera infestans*) and a negative control (no compound) on the same plate. *Propionibacterium acnes* was grown anaerobically (Anaerocult A mini, Merck) in PYG medium (modified DSMZ medium 104) at 37 °C for 48 h. The bacterial culture was diluted to an OD_{600} of 0.03, 200 μL of the inoculum was added to each well, and the microtiter plate was incubated anaerobically at 37 °C for 48 h.

The assays against *Phytophthora infestans* were prepared by transferring 190 μL of a spore suspension with a concentration of 1 × 10^4 spores/mL into one well of a 96-well microtiter plate, respectively. From a 10 mM DSMO stock solution of mayamycin, a dilution series with PBS buffer was established down to 100 μM. Then 10 μL of this solution was added into the assay. After incubating the microtiter plate for 48 h at 20 °C in the dark, the absorption was measured at 600 nm. As positive control, cycloheximide was used.

The antibacterial assays against the clinically relevant strains *Staphylococcus epidermidis* (clinical isolate, Dr. S. Schubert), *Staphylococcus aureus* (ATCC 12600), *Staphylococcus aureus* (ATCC 33593), *Klebsiella pneumoniae* (ATCC 700603), and *Pseudomonas aeruginosa* (ATCC 10145) were performed as described by Sahly et al., 2003.[18]

Cytotoxic Activities. The sensitivity of the cell lines NIH-3T3, HepG2, and HT-29 to the isolated compound (**1**) was evaluated by monitoring of the metabolic activity using the CellTiter-BlueCell viability assay (Promega). The mouse fibroblast cell line was kindly provided by G. Rimbach (University of Kiel, Germany). The human hepatocellular carcinoma cell line HepG2 and the human colon adenocarcinom cell line HT-29 were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany). HepG2 and NIH-3T3 cells were maintained in RPMI 1640 medium, and HT-29 cells were cultured in Mc Coy's 5A medium. Media were supplemented with 10% fetal bovine serum (Promocell), 100 U/mL penicillin, and 100 μg/mL streptomycin (Invitrogen). The cultures were maintained at 37 °C under a humidified atmosphere and 5% CO_2. The cell lines were transferred twice per week. For experimental procedures, cells were seeded in 96-well plates at concentrations of 7500 cells (NIH-3T3) and 10 000 cells (HepG2 and HT-29) per well. After 24 h incubation the medium was removed, and 100 μL of the test sample adjusted to final concentrations ranging from 10 μM to 40 nM by dilution in growth medium was added to the cells. Each concentration was tested in triplicate. Tamoxifen, as a standard therapeutic drug, was used as positive control. Following sample addition, plates were cultured for 24 h at 37 °C. Afterward, the assay was performed according to the manufacturer's instructions. Fluorescence was measured using the microplate reader Infinite M200 (Tecan) at 560 nm excitation and 590 nm emission. IC_{50} values were calculated using SigmaPlot software.

The *in vitro* cytotoxic activities against the gastric cancer cell line GXF 251 L cells, non-small-cell lung cancer cell line LXFL 529 L, melanoma cancer cell line MEXF 462NL, mammary cancer cell line MAXF 401NL, renal cancer cell line RXF 486 L, and pancreatic cancer cell line PAXF1657L were determined by a modified propidium iodide monolayer assay according to a described procedure by Oncotest GmbH.[19]

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Supporting Information Available: Spectroscopic data and additional information such as NMR spectra (^{1}H, ^{13}C, NOESY, and HMBC) of (2′*R**,4′*R**,5′*S**,6′*R**)-mayamycin (**1**) are available free of charge via the Internet at http://pubs.acs.org.

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