Enantiodivergent Total Syntheses of Nanaomycins and Their Enantiomers, Kalafungins

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The first, enantiospecific total syntheses of pyranonaphthoquinone antibiotics, nanaomycins D and A, and their enantiomers, kalafungin and 4-deoxykalafunginic acid are described by an "enantiodivergent" strategy from a common optically active intermediate, (1*S*,3*RS*,4*S*)-3,4-dihydro-5,9,10-trimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3,4-diol, which has been derived from L-rhamnose *via* condensation of 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone and methyl 3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosid-2-ulose.

Nanaomycin D[1] (**1**), kalafungin[2] (**2**), granaticin[3] (**3**), medermycin[4] (**4**), and nanaomycin A[5] (**5**) are members of a growing family of pyranonaphthoquinone (benzoisochromanquinone) antibiotics (Chart 1), which have been shown to possess significant antimicrobial activities and potential antitumor activities.[6] Remarkably, nanaomycin D (**1**) and kalafungin (**2**) are enantiomers with each other, and both antipode systems have been found as major constituents of many kinds of pyranonaphthoquinone antibiotics such as **3** and

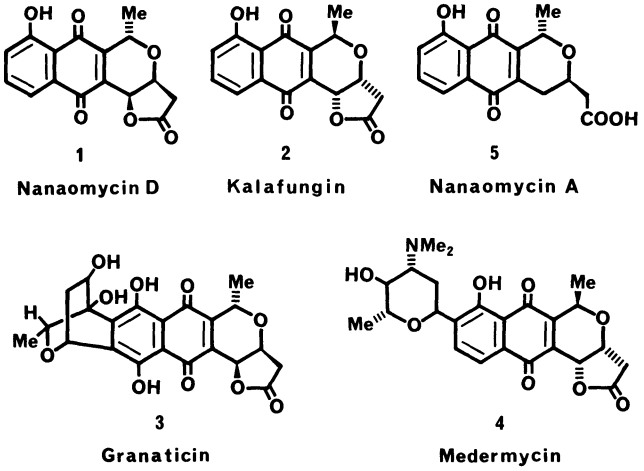


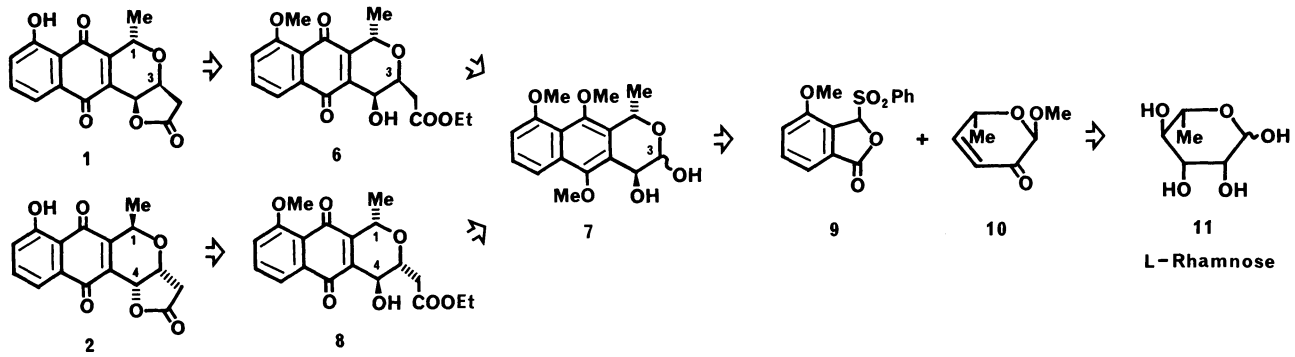
Chart 1.

4. These unique structural features as well as the opportunities to develop synthetic strategies for the construction of more diverse analogs of these interesting antibiotics prompted the immense investigations of their syntheses.[7] No fewer than ten syntheses of racemic nanaomycin A (**5**), in particular, have been described with various strategies,[8] however, stereospecific syntheses of these kinds of optically active antibiotics have not been reported to date. Very recently, the first, total syntheses of natural nanaomycin D (**1**) and kalafungin (**2**) were disclosed in our laboratories.[9]

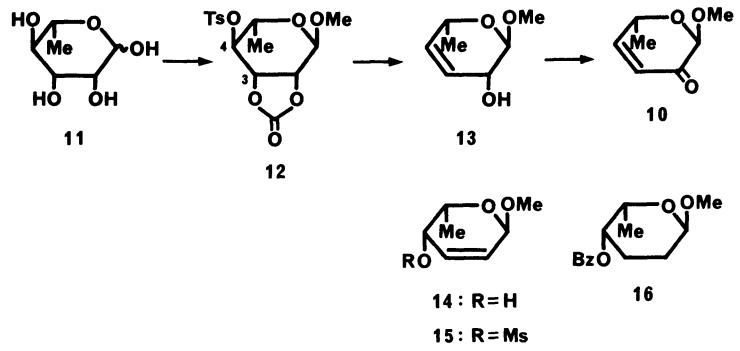
Described herein with full details are the first, enantiospecific total syntheses of nanaomycins D (**1**) and A (**5**), and their enantiomers, kalafungin (**2**) and 4-deoxykalafunginic acid (**5′**) from a common optically active intermediate **7** by the "enantiodivergent" strategy.[10]

The antithetic strategy relating both antipodes **1** and **2** to the starting material, L-rhamnose (**11**) is put forth in Scheme 1. The alcoholysis of the lactone moiety of **1** leads to the hydroxy ester **6**, which in turn leads to the hemiacetal **7** upon application of the indicated retro Michael cyclization and retro Wittig reaction at the C-3 position. On the other hand, the alcoholysis of **2** with the fascinating epimerization at the C-1 and C-4 positions leads to the other hydroxy ester **8**, which returns similarly to the key intermediate **7**. The common intermediate is expected to be derived from condensation of **9**[11] with **10**.

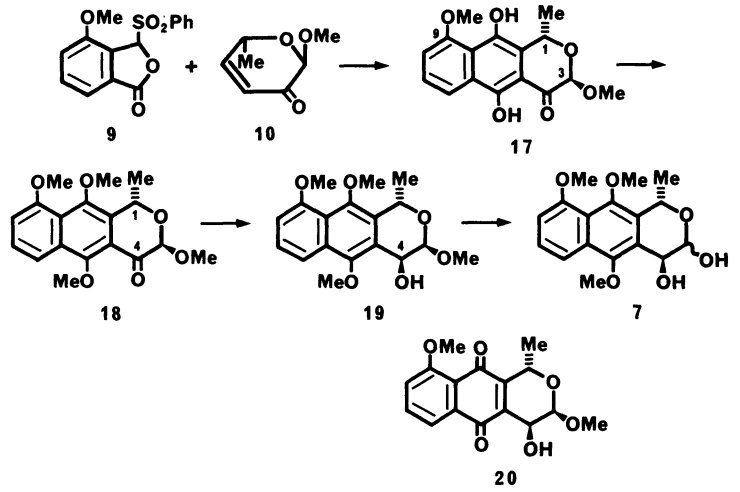
In the synthetic sense (Scheme 2), conversion of L-rhamnose (**11**) to methyl 3,4,6-trideoxy-α-L-*glycero*-hex-3-enopyranosid-2-ulose[12] (**10**) was initially achieved by the following practical procedure. Methyl α-L-rhamnoside, which was prepared from L-rhamnose (**11**), was converted into methyl 2,3-di-*O*-carbonyl-6-



Scheme 1.



Scheme 2.



Scheme 3.

deoxy-4-*O*-tosyl-α-L-mannoside (**12**) in an 80% overall yield by a one-pot reaction with trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of **12** with zinc powder and sodium iodide in refluxing aqueous acetonitrile gave, presumably through the corresponding 3,4-epoxide[13] with removal of the carbonate-protecting group, a mixture of the desired unsaturated alcohol, methyl 3,4,6-trideoxy-α-L-*threo*-hex-3-enopyranoside[12] (**13**) and its migrated alcohol, methyl 2,3,6-trideoxy-α-L-*threo*-hex-2-enopyranoside (**14**) in 60 and 28% yields. Oxidation of **13** with pyridinium chlorochromate afforded the stable α,β-unsaturated ketone (**10**) in an 86% yield. The migrated alcohol **14** was efficiently recycled to **13** along with its C-2 epimeric alcohol in an 85% yield by mesylation to give methyl 2,3,6-trideoxy-4-*O*-mesyl-α-L-*threo*-hex-2-enopyranoside (**15**) followed by exposure to potassium carbonate in aqueous tetrahydrofuran to result in the S_N2' type solvolysis. The mixture thus obtained could be similarly converted into the desired ketone **10**. The stereochemistry of **14** was clarified by the ^{1}H NMR study of the corresponding benzoylated compound, methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-L-*threo*-hexopyranoside (**16**), which existed in the $^1C_4$ conformation.

The other starting material, 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**9**) was synthesized according to the Hauser's conditions.[11]

As shown in Scheme 3, condensation of **10** with the lithium *t*-butoxide generated anion of **9** gave, in an 80% yield, the hydroquinone, (1*S*,3*R*)-5,10-dihydroxy-3,9-dimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]-pyran-4(3*H*)-one (**17**), which was treated with dimethyl sulfate to produce quantitatively (1*S*,3*R*)-3,5,9,10-tetramethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-4(3*H*)-one (**18**). Reduction of **18** with sodium borohydride afforded exclusively (1*S*,3*R*,4*S*)-3,4-dihydro-3,5,9,10-tetramethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-4-ol (**19**) in a 90% yield. The stereoselective hydride delivery is assisted in the desired sense by the *syn* stereodirecting influence of the pyrano oxygen atom[14] as partly depicted in Chart 2, where the C-3 *O*-methyl group would be oriented to be in axial by the anomeric effect[15] as commonly seen in carbohydrates. The (*S*)-con-

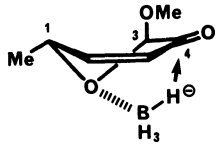
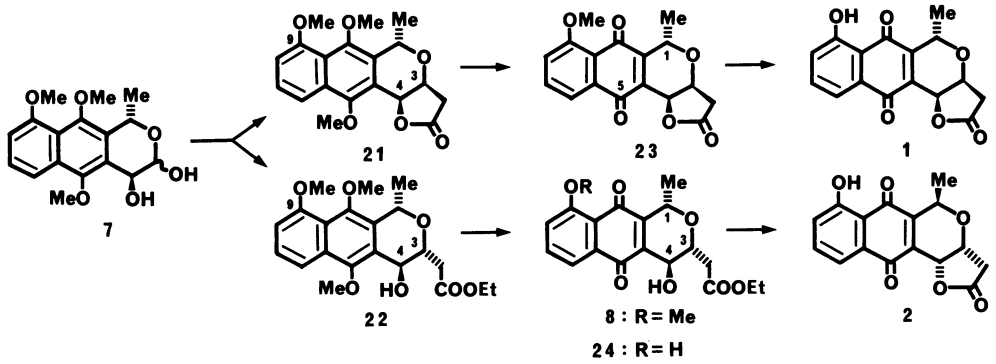


Chart 2.

figuration at the C-4 of **19** was confirmed by the ^{1}H NMR study of the following derivatives **21** ($J_{3,4}$= 3.0 Hz) and **22** ($J_{3,4}$=9.5 Hz), and the reasonable trans-



Scheme 4.

TABLE 1. MINIMAL INHIBITORY CONCENTRATION (mcg/ml) OF **1**, **2**, **5**, **5′**, **21**, **22**, **23**, AND **24**

	1	**2**	**5**	**5′**	**21**	**22**	**23**	**24**
Staphylococcus aureus FDA209P	<0.2	<0.2	<0.2	<0.2	6.25	100	1.56	12.5
Staphylococcus aureus Smith	<0.2	<0.2	<0.2	<0.2	6.25	>100	1.56	3.12
Micrococcus flavus FDA16	<0.2	0.39	0.39	0.78	25	>100	3.12	12.5
Bacillus subtilis PCI219	0.39	<0.2	0.78	0.78	12.5	>100	3.12	6.25
Escherichia coli NIHJ	3.12	6.25	12.5	25	>100	>100	25	100
Shigella dysenteriae JS11910	3.12	1.56	6.25	6.25	100	>100	12.5	25
Mycobacterium smegmatis ATCC607	12.5	6.25	25	25	50	100	>100	12.5

formation from **21** to **1**. Reaction of **19** with ammonium cerium(IV) nitrate[8b] gave the quinone, (1*S*,3*R*,4*S*)-3,4-dihydro-4-hydroxy-3,9-dimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**20**), which was also derived directly from **17** by reduction with sodium borohydride followed by air oxidation. Acid hydrolysis of **20** gave the corresponding hemiacetal, which, however, was not a useful intermediate for the following Wittig reaction, because the reaction afforded several products in low yields. Then, **19** was hydrolyzed with dil. hydrochloric acid, giving quantitatively the key intermediate, (1*S*,3*RS*,4*S*)-3,4-dihydro-5,9,10-trimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3,4-diol (**7**) without epimerization at the C-1 and C-4. The hemiacetal **7** was submitted to Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane in refluxing toluene to give two products as expected:[8b,16] (1*S*,3*S*,4*S*)-3,4,11,12-tetrahydro-5,9,10-trimethoxy-1-methyl-1*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran-12-one (**21**) and ethyl (1*S*,3*R*,4*S*)-3,4-dihydro-4-hydroxy-5,9,10-trimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3-acetate (**22**) in 53 and 41% yields, respectively (Scheme 4). The lactone **21** results from a two-step sequence including the intramolecular Michael cyclization of the intermediary Wittig α,β-unsaturated ester and concomitant lactonization of the resultant 3,4-*cis* hydroxy ester such as **6**. The other 3,4-*trans* hydroxy ester **22** results from the Michael cyclization without lactonization. The lactone **21** was treated with ammonium cerium(IV) nitrate[8b] to give, in a 92% yield, 9-*O*-methylnanaomycin D (**23**), which was equivalent to the structure **6**. The ^{1}H NMR spectrum of **23** has already been superimposable on that of nanaomycin D (**1**) except in the phenyl- and *O*-methyl-signals region. De-*O*-methylation of **23** was attempted with two known reagents, boron tribromide[8c] and aluminium chloride.[8b] Reaction with boron tribromide, however, furnished a mixture of nanaomycin D (**1**) and its brominated product, which were detected by thin-layer chromatography only with a solvent system of dichloromethane–chloroform. De-*O*-methylation with aluminium chloride provided (−)-nanaomycin D (**1**) in a 95% yield as a single product identical in all respects including antibacterial activity (Table 1) with an authentic sample of the natural antibiotic, thereby confirming the absolute structure.

On the other hand, the ester **22** was converted by the aforesaid cerium(IV) oxidative demethylation into ethyl (1*S*,3*R*,4*S*)-3,4,5,10-tetrahydro-4-hydroxy-9-methoxy-1-methyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-acetate (**8**), which was treated with aluminium chloride to give ethyl (1*S*,3*R*,4*S*)-3,4,5,10-tetrahydro-4,9-dihydroxy-1-methyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]-pyran-3-acetate (**24**) in an 84% overall yield. On the final stage, the favored epimerization of the C-1 and C-4 positions was realized by exposure to sulfuric acid[7a] in benzene along with some lactonization, followed by refluxing in toluene to complete the lactonization, affording, in a 92% yield, (+)-kalafungin (**2**) identical with an authentic sample of the natural antibiotic in all respects including antibacterial activity (Table 1). This stereocontrolled epimerization indicated that the C-3 stereochemistry was so vital for the subsequent development of the correct chirality at the C-1 and C-4 positions.

Hydrogenolysis of **1** and **2** furnished quantitatively nanaomycin A (**5**) and its enantiomer, 4-deoxykalafunginic acid (**5′**), respectively, the former of

which was identical with the natural antibiotic. Both compounds **5** and **5'** were readily recycled to **1** and **2**, respectively, by air oxidation.[1] Since compound **5'** has not been in the natural sources yet, these results suggest that, also in the biosynthesis, nanaomycin A (**5**) would be derived from nanaomycin D (**1**) by the appropriate reductase.[17]

The antibacterial activities (Table 1) of **1**, **2**, **5**, **5'**, **21**, **22**, **23**, and **24** revealed that the naphthoquinone and lactone portions were positively required for the appearance of stronger activities.

Thus, both antipodes of antibiotics, (−)-nanaomycins (**1** and **5**) and (+)-kalafungins (**2** and **5'**) have been synthesized from L-rhamnose (**11**) through a common key intermediate **7** in overall yields of approximately 18 and 13%, respectively, by the "enantiodivergent" strategy, which is promising for application to the syntheses of both optical antipodes of the other members of this important class of antibiotics.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR spectra were recorded on a Hitachi Perkin-Elmer 225 spectrometer, UV spectra on JAS·CO UVIDEC-1 spectrometer, and ^{1}H-NMR spectra with TMS as internal standard on a Varian EM-390 (90 MHz) or a JEOL GX-400 (400 MHz) spectrometer. Optical rotations were measured on a JAS·CO DIP-360 photoelectric polarimeter. Silica gel TLC and column chromatography were performed on Merck TLC 60F-254 and Kieselgel 60, respectively. In general, organic solvents were purified and dried by the appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

The starting material, 4-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone (**9**) was prepared according to the published procedure[11] and recrystallized from ethyl acetate–hexane to give needles: mp 189—191 °C.

Methyl 2,3-Di-O-carbonyl-6-deoxy-4-O-tosyl-α-L-mannoside (12). A) Through the Isolated 2,3-Carbonate: A solution of L-rhamnose monohydrate (**11**; 33.7 g) in methanol (169 ml) with 10% methanolic hydrogen chloride solution (2 ml) was refluxed for 72 h. After neutralization with $NaHCO_3$, the precipitated salt was filtered off and the filtrate was evaporated to a residue, which was dissolved in acetone (170 ml). After filtration, the filtrate was evaporated to give a crude solid of methyl α-L-rhamnoside (33 g).

To a stirred and ice-cooled solution of the crude solid (33 g) in pyridine (330 ml) was added dropwise trichloromethyl chloroformate (22.0 ml), and stirring was continued at room temperature for 1 h. After addition of water (7.3 ml), the mixture was evaporated and co-evaporated with toluene to give a residue, which was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The combined organic layers were washed with a saturated aqueous NaCl solution, dried (Na_2SO_4), and evaporated to give a crude solid of the 2,3-carbonate (38 g). A part of the solid was recrystallized from ethyl acetate to afford plates of the 2,3-carbonate: mp 169—171 °C; $[\alpha]_D^{24}$ −59° (*c* 1.0, $CHCl_3$); IR (KBr) 1810 cm^{-1} (carbonate).

A solution of the crude solid (37.8 g) in pyridine (378 ml) was stirred with tosyl chloride (52.9 g) at 60 °C for 36 h. After addition of ethanol (16 ml), the mixture was evaporated to a residue, which was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to a residue, which was chromatographed on silica gel (1330 g) with 6:1 benzene–ethyl acetate to give a solid. Recrystallization from ethyl acetate–ether gave needles of **12** (53.0 g, 80% from **11**): R_f 0.72 (4:1 benzene–ethyl acetate); mp 99.5—101 °C; $[\alpha]_D^{24}$ +23° (*c* 1.0, $CHCl_3$); IR (KBr): 1816, 1792, and 1179 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.38 (3H, d, Me, $J_{5,Me}$=6 Hz), 2.48 (3H, s, Me of Ts), 3.40 (3H, s, OMe), 3.86 (1H, dq, H-5, $J_{4,5}$=9.0 Hz), 4.23—4.72 (3H, m, H-2, 3, and 4), 4.93 (1H, s, H-1), 7.40 (2H, d, Ts, J_{AB}=9 Hz), 7.87 (2H, d, Ts).

Found: C, 50.02; H, 5.09; S, 8.90%. Calcd for $C_{15}H_{18}O_8S$: C, 50.27; H, 5.06; S, 8.95%.

B) Without Isolation of the 2,3-Carbonate: The crude methyl α-L-rhamnoside (49.9 g), which was prepared from L-rhamnose monohydrate (**11**; 50 g) as described above, was dissolved in pyridine (500 ml), and trichloromethyl chloroformate (32.1 ml) was added with cooling. After stirring at room temperature for 2 h, to the reaction mixture was added tosyl chloride (103 g), and stirring was continued at 80 °C for another 24 h. The resulting mixture was worked up as described above to give a solid of **12** (79.6 g, 81%), which was used for the next step.

Methyl 3,4,6-Trideoxy-α-L-threo-hex-3-enopyranoside (13) and Methyl 2,3,6-Trideoxy-α-L-threo-hex-2-enopyranoside (14). To a solution of **12** (70.1 g) in 95% aqueous acetonitrile (700 ml) were added NaI (235 g) and Zn powder (102 g), and the suspension was stirred under argon at 75 °C for 36 h and then cooled to room temperature. The suspension was filtered and the insoluble mass was washed with ethyl acetate. The filtrates and washings were combined, washed with 5% aqueous $Na_2S_2O_3$ solution, dried and evaporated at 85 °C under atmospheric pressure to give a residue. This was chromatographed on silica gel (1400 g) with 7:4 carbon tetrachloride–ethyl acetate to give **13** (16.9 g, 60%) and **14** (7.89 g, 28%) having the R_f-values of 0.26 and 0.20 (2:1 benzene–ethyl acetate), respectively.

13: Oil; bp 90 °C (933 Pa); $[\alpha]_D^{24}$ −206° (*c* 1.0, $CHCl_3$) [lit,[12] $[\alpha]_D^{20}$ −74° (*c* 1, $CHCl_3$)]; IR ($CHCl_3$): 1447, 1402, 1371, and 1345 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$+D_2O): δ=1.29 (3H, d, Me, $J_{5,Me}$=6.5 Hz), 3.49 (3H, s, OMe), 3.76 (1H, broad s, H-2), 4.30 (1H, dq, H-5, $J_{4,5}$=1.5 Hz), 4.71 (1H, s, H-1), 5.90 (2H, apparently s, H-3 and 4, $J_{3,4}$=10.5 Hz).

Found: C, 58.05; H, 8.17%. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39%.

14: Oil [bp 75 °C (400 Pa)], which, after distillation under reduced pressure, was changed to cottony crystals (mp 45—47 °C); $[\alpha]_D^{24}$ +123° (*c* 1.0, $CHCl_3$); IR (KBr): ≈1620, 1441, 1405, 1393, and 1386 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$+D_2O): δ=1.30 (3H, d, Me, $J_{5,Me}$=6.5 Hz), 3.45 (3H, s, OMe), 3.55 (1H, sharp m, H-4, half-width of 10.5 Hz), 4.12 (1H, dq, H-5, $J_{4,5}$=2.2 Hz), 4.85 (1H, d, H-1, $J_{1,2}$=3 Hz), 5.88 (1H, dd, H-2, $J_{2,3}$=10.5 Hz), 6.20 (1H, dd, H-3, $J_{3,4}$=6 Hz).

Found: C, 58.06; H, 8.46%. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39%.

Methyl 2,3,6-Trideoxy-4-O-mesyl-α-L-threo-hex-2-enopyranoside (15). A solution of **14** (152 mg) in pyridine (3.0 ml) was stirred with mesyl chloride (0.10 ml) at room temperature for 30 min. After addition of ethanol (0.076 ml), the

mixture was evaporated to a residue, which was partitioned between ethyl acetate and water. The combined organic layers were evaporated to a residue, which was chromatographed on silica gel (10 g) with 5:1 benzene–ethyl acetate followed by recrystallization from ethyl acetate–hexane to give labile needles of **15** (222 mg, 95%): R_f 0.49 (2:1 benzene–ethyl acetate); mp 97—98 °C; $[\alpha]_D^{24}$ +168° (*c* 1.0, $CHCl_3$); IR (KBr): ≈1630 (olefin), and 1179 cm^{-1} (SO_2); ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.37 (3H, d, Me-5, $J_{5,Me}$=6.5 Hz), 3.06 (3H, s, Ms), 3.45 (3H, s, OMe), 4.26 (1H, dq, H-5, $J_{4,5}$=2.5 Hz), 4.65—4.80 (1H, sharp m, H-4, half-width of 8.0 Hz), 4.92 (1H, d, H-1, $J_{1,2}$=2.0 Hz), 5.95—6.32 (2H, m, H-2 and 3).

Found: C, 43.60; H, 6.08%. Calcd for $C_8H_{13}O_5S$: C, 43.43; H, 5.92%.

*Methyl 4-O-Benzoyl-2,3,6-trideoxy-α-*L*-*threo*-hexopyranoside (16).* A solution of **14** (1.10 g) in pyridine (22.2 ml) was stirred with benzoyl chloride (1.8 ml) at room temperature for 45 min. After addition of ethanol (1 ml), the mixture was evaporated to a residue, which was partitioned between ethyl acetate and a saturated aqueous NaCl solution. The combined organic layers were evaporated to a residue, which was chromatographed on silica gel (95 g) with 10:1 hexane–ethyl acetate to give a syrup of the benzoate (1.73 g, 90.8%): R_f 0.33 (10:1 hexane–ethyl acetate).

A solution of the syrup (235 mg) in ethanol (2.4 ml) was shaken with 5% palladium–carbon and 3-atm hydrogen at room temperature for 12 h, filtered and evaporated to a residue. This was chromatographed on silica gel (23 g) with 10:1 hexane–ethyl acetate to give a syrup of **16** (188 mg, 80%): R_f 0.35 (10:1 hexane–ethyl acetate); $[\alpha]_D^{24}$ −65° (*c* 1.0, $CHCl_3$); IR (neat): 1721, 1605, 1588, 1493, and 1455 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.195 (3H, d, Me-5, $J_{5,Me}$=6.5 Hz), 1.61 (1H, dddd, H-2eq, $J_{1,2eq}$=2 Hz, $J_{2ax,2eq}$=13.5 Hz, $J_{2eq,3ax}$=4.5 Hz, $J_{2eq,3eq}$=2.5 Hz), 1.92 (1H, ddt, H-3eq, $J_{2ax,3eq}$=4 Hz, $J_{3ax,3eq}$= 13.5 Hz, $J_{2eq,3eq}$=$J_{3eq,4}$=2.5 Hz), 2.02 (1H, tt, H-2ax, $J_{1,2ax}$=4 Hz, $J_{2ax,3ax}$=13.5 Hz), 2.155 (1H, ddt, H-3ax, $J_{3ax,4}$=2.5 Hz), 3.41 (3H, s, OMe), 4.11 (1H, dq, H-5, $J_{4,5}$=1.5 Hz), 4.81 (1H, dd, H-1), 5.06 (1H, sharp m, H-4), 7.46 (2H, t, Bz, *J*=6.85 Hz), 7.57 (1H, t, Bz), and 8.12 (2H, d, Bz).

Found: C, 67.15; H, 7.18%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

*Methyl 3,4,6-Trideoxy-α-*L*-*glycero*-hex-3-enopyranosid-2-ulose (10).* *A) From 13*: To a stirred and ice-cooled solution of **13** (487 mg) in dry dichloromethane (9.75 ml) were added Molecular Sieves 3A powder (1.02 g) and pyridinium chlorochromate (1.46 g), and stirring was continued at room temperature for 30 min. The mixture was diluted with ether and passed through a silica-gel column (12 g) with 1:1 chloroform–ether to give eluates containing **10**. The eluates were evaporated at 75 °C under atmospheric pressure, leaving a pale yellow syrup of **10** (0.41 g, 86%), which was used for the next step: R_f 0.72 (2:1 benzene–ethyl acetate).

An analytically pure sample was obtained by distillation under reduced pressure: bp 74 °C (666 Pa); $[\alpha]_D^{24}$ −58° (*c* 1.0, $CHCl_3$)[lit,[12] $[\alpha]_D^{20}$ −93° (*c* 1, MeOH)]; IR (neat) 1762, 1705, 1618, 1450 1390, and 1378 cm^{-1}; ^{1}H-NMR (90 MHz, $CDCl_3$) δ=1.40 (3H, d, Me, $J_{5,Me}$=7.5 Hz), 3.55 (3H, s, OMe), 4.69 (1H, ddq, H-5, $J_{3,5}$=2.5 Hz, $J_{4,5}$=1.5 Hz), 4.73 (1H, s, H-1), 6.06 (1H, dd, H-3, $J_{3,4}$=10.5 Hz), 6.91 (1H, dd, H-4).

Found: C, 58.84; H, 7.26%. Calcd for $C_7H_{10}O_3$: C, 59.15; H, 7.09%.

B) From 15: A solution of **15** (83.3 mg) in 50% aqueous tetrahydrofuran (0.83 ml) was stirred with K_2CO_3 (156 mg) at 50 °C for 9 h. The mixture was partitioned between ethyl acetate and a saturated aqueous NaCl solution, and the combined organic layers were dried and evaporated at 80 °C under atmospheric pressure to give a residue. This was chromatographed on silica gel (3 g) with 2:1 benzene–ethyl acetate to give, after removal of the solvent under atmospheric pressure, a syrup (48.8 mg) containing **13** and its C-2 epimer.

The syrup was oxidized by the procedure described in the preparation (A) to give a syrup of **10** (40 mg, 72% from **15**).

*(1S,3R)-5,10-Dihydroxy-3,9-dimethoxy-1-methyl-1*H*-naphtho-[2,3-c]pyran-4(3*H*)-one (17).* A solution of lithium *t*-butoxide (7.23 mmol) was initially prepared by adding butyllithium (4.50 ml of 1.6 M† solution, 7.23 mmol) to *t*-butyl alcohol (0.75 ml, 7.93 mmol) in tetrahydrofuran (6.85 ml) at 0 °C under argon. This solution was cooled to −78 °C, and **9** (805 mg, 2.65 mmol) was added in one portion with stirring to generate a slurry of the anion. After 15 min, to the stirred slurry was added a solution of **10** (341 mg, 2.40 mmol) in tetrahydrofuran (1.40 ml) at −78 °C, and stirring was continued at this temperature for 15 min and then at room temperature for 3 h under argon. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous NH_4Cl solution, and the combined organic layers were dried and evaporated to a residue. This was chromatographed on silica gel (14 g) with 5:1 hexane–ethyl acetate followed by recrystallization from ethyl acetate to give yellow needles of **17** (580 mg, 80%): R_f 0.34 (4:1 hexane–acetone); mp 123—125 °C; $[\alpha]_D^{24}$ −304° (*c* 1.0, $CHCl_3$); IR (KBr): 1647, 1631, 1610, and 1588 cm^{-1}; UV (MeOH) λ (ε) 221 (24400), 265 (22800), 268 (23400), 321 (2800), 329 (3210), 386 (2440), and 431 nm (5420); ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.73 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 3.60 (3H, s, OMe-3), 4.09 (3H, s, OMe-9), 5.08 (1H, s, H-3), 5.40 (1H, q, H-1), 7.02 and 8.07 (each 1H, dd, H-6 and 8, *J*=8 and 1.5 Hz), 7.40 (1H, t, H-7, *J*=8 Hz), 9.20 and 12.32 (each 1H, s, OH-5 and 10, *vice versa*).

Found: C, 63.44; H, 5.55%. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%.

*(1S,3R)-3,5,9,10-Tetramethoxy-1-methyl-1*H*-naphtho[2,3-c]-pyran-4(3*H*)-one (18).* A solution of **17** (1.10 g) in acetone (22 ml) was stirred with dimethyl sulfate (1.20 ml) and K_2CO_3 (1.75 g) at 40 °C for 12 h. After further addition of dimethyl sulfate (0.60 ml) and K_2CO_3 (874 mg), stirring was continued at 40 °C for another 12 h. The reaction mixture was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution, and the combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to give a yellow syrup of **18** (1.2 g), which was used for the next step.

An analytically pure sample was obtained by a silica-gel column chromatography with 9:1 benzene–ethyl acetate to give a yellow syrup: R_f 0.32 (4:1 hexane–acetone); $[\alpha]_D^{24}$ −154° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1701, 1603, 1578, 1569, and 1449 cm^{-1}; UV (MeOH) λ (ε) 221 (24500), 262 (26100), 295 (3860), 305 (4030), 320 (3540), 379 (3190), and 385 nm (Infl., 3450); ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.69 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 3.55 (3H, s, OMe-3), 3.84 (3H, s, OMe), 4.04 (6H, s, OMe ×2), 4.94 (1H, s, H-3), 5.41 (1H, q, H-1), 7.02 and 7.98 (each 1H, d, H-6 and 8, *J*=8 Hz), 7.46 (1H, t, H-7).

Found: C, 64.80; H, 6.15%. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07%.

*(1S,3R,4S)-3,4-Dihydro-3,5,9,10-tetramethoxy-1-methyl-1*H-

† 1 M=1 mol dm^{-3}.

naphtho[2,3-c]pyran-4-ol (19). A crude sample of **18** (1.20 g) was stirred with $NaBH_4$ (164 mg) in methanol (36 ml) at room temperature for 5 min. The reaction mixture was neutralized with Amberlite CG-50 (H type), filtered and then evaporated to a residue, which was chromatographed on silica gel (50 g) with 1:1 hexane–ethyl acetate followed by recrystallization from ethyl acetate–hexane to afford pale yellow cubics of **19** (1.06 g, 88% from **17**): R_f 0.48 (4:1 benzene–acetone); mp 176—177.5 °C (changed at 168 °C); $[\alpha]_D^{24}$ −97° (*c* 1.0, $CHCl_3$); IR (KBr): 1596, 1572, 1500, 1462, 1448, 1368, and 1266 cm^{-1}; UV (MeOH) λ (ε) 235 (53800), 293 (5620), 307 (7180), 322 (6000), and 337 nm (4740); ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.67 (3H, d, Me-1, $J_{1,Me}$=7.0 Hz), 3.28 (1H, d, OH-4, $J_{4,OH}$=4.0 Hz), 3.62 (3H, s, OMe-3), 3.82, 4.01 and 4.04 (each 3H, s, OMe×3), 4.95 (1H, d, H-3, $J_{3,4}$= 2.0 Hz), 5.07 (1H, dd, H-4), 5.44 (1H, q, H-1), 6.88 and 7.70 (each 1H, d, H-6 and 8, J=8 Hz), and 7.40 (1H, t, H-7).

Found: C, 64.43; H, 6.52%. Cacd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63%.

(1S,3R,4S)-3,4-Dihydro-4-hydroxy-3,9-dimethoxy-1-methyl-1H-naphtho[2,3-c]pyran-5,10-dione (20). *A) From 19*: A solution of **19** (33.5 mg) in acetonitrile (1 ml) was stirred with an aqueous solution (0.48 ml) of ammonium cerium(IV) nitrate (120 mg) at room temperature for 10 min. The reaction mixture was partitioned between ethyl acetate and water, and the combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to a residue. This was chromatographed on silica gel (1.5 g) with 1:1 hexane–ethyl acetate to give a yellow syrup of **20** (28 mg, 91%): R_f 0.19 (2:1 benzen–ethyl acetate); $[\alpha]_D^{24}$−248° (*c* 0.95, $CHCl_3$); IR ($CHCl_3$): 1665, 1660, 1656, 1590, and 1579 cm^{-1}; UV (MeOH) λ (ε) 211 (24500), 248 (14600), 261 (13900), 265 (Infl., 12900), 331 (2480), 385 (Infl., 3830), and 407 nm (4070); ^{1}H-NMR (90 MHz, $CDCl_3$+D_2O): δ=1.50 (3H, d, Me-1, $J_{1,Me}$= 6.5 Hz), 3.53 (3H, s, OMe-3), 3.97 (3H, s, OMe-9), 4.80—5.05 (3H, m, H-1, 3 and 4), 7.20—7.80 (3H, m, H-6,7 and 8).

Found: C, 63.42; H, 5.44%. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30%.

B) From 17: An ice-cooled solution of **17** (28 mg) in methanol (0.56 ml) was stirred with $NaBH_4$ (4.2 mg) for 3 min and then neutralized with Amberlite CG-50 (H type). After filtration, the filtrate was vigorously stirred under atmosphere at room temperature for 12 h and evaporated to a residue, which showed two spots having R_f-values of 0.19 and 0.30 on TLC with 2:1 benzene–ethyl acetate. The R_f 0.19-substance was identical with the aforesaid product **20**. Although the R_f 0.30-substance seemed to be the C-4 epimeric alcohol, it was not further investigated.

(1S,3RS,4S)-3,4-Dihydro-5,9,10-trimethoxy-1-methyl-1H-naphtho[2,3-c]pyran-3,4-diol (7). A sample of **19** (516 mg) was dissolved in a mixture of 0.5 M HCl (20.6 ml) and acetic acid (4.1 ml), and the solution was kept at 75 °C for 2 h. After neutralization with a saturated aqueous $NaHCO_3$ solution, the resulting mixture was extracted with ethyl acetate. The extracts were washed with a saturated aqueous NaCl solution, dried and evaporated to a residue, which was chromatographed on silica gel (20 g) with 3:1 benzene–acetone to give a yellow syrup of **7** (477 mg, 97%): R_f 0.22 (4:1 benzene–acetone); $[\alpha]_D^{24}$ −34° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$); 1597, 1573, 1496, 1450, 1372, and 1339 cm^{-1}; UV (MeOH) λ (ε) 235 (61100), 265 (Infl., 940), 297 (6410), 307 (7920), 322 (6640), 337 (5190), 385 nm (Infl., 313); ^{1}H-NMR (90 MHz, $CDCl_3$+D_2O) δ=1.67 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 3.81, 4.02 and 4.05 (each 3H, s, OMe ×3), 4.90 (1H, sharp d, H-4, $J_{3,4}\cong$1 Hz), 5.30 (1H, sharp d, H-3), 5.48 (1H, q, H-1), 6.90 and 7.72 (each 1H, d, H-6 and 8, J=7.5 Hz), 7.41 (1H, t, H-7).

Found: C, 63.44; H, 6.56%. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29%.

(1S,3S,4S)-3,4,11,12-Tetrahydro-5,9,10-trimethoxy-1-methyl-1H-furo[3,2-b]naphtho[2,3-d]pyran-12-one (21) and Ethyl (1S,3R,4S)-3,4-dihydro-4-hydroxy-5,9,10-trimethoxy-1-methyl-1H-naphtho-[2,3-c]pyran-3-acetate (22). To a solution of **7** (160 mg) in toluene (4.83 ml) was added ethoxycarbonylmethylenetriphenylphosphorane (526 mg), and the mixture was refluxed at 105 °C for 30 h and then evaporated to a residue. This was chromatographed on silica gel (10 g) with 7:1 benzene–ethyl acetate to give **21** (91.6 mg, 53%) and **22** (80.0 mg, 41%) having the R_f-values of 0.44 and 0.57 (3:1 benzene–ethyl acetate), respectively.

21: Pale yellow cubics from ethyl acetate–benzene; mp 232—234 °C (changed at 214 °C); $[\alpha]_D^{24}$−279° (*c* 1.0, $CHCl_3$); IR (KBr): ≈1790, 1591, 1571, 1448, and 1338 cm^{-1}; UV (MeOH) λ (ε) 215 (22300), 235 (45500), 264 (Infl., 2570), 293 (4570), 309 (5860), 324 (4510), and 340 nm (4060); ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.57 (3H, d, Me-1, $J_{1,Me}$=7.0 Hz), 2.71 (1H, d, H-11, $J_{11,11'}$=17.5 Hz, $J_{3,11}$=0 Hz), 2.99 (1H, dd, H-11′, $J_{3,11'}$=5.0 Hz), 3.85, 4.03 and 4.07 (each 3H, s, OMe ×3), 4.75 (1H, dd, H-3, $J_{3,4}$=3.0 Hz), 5.37 (1H, q, H-1), 5.58 (1H, d, H-4), 6.93 and 7.72 (each 1H, d, H-6 and 8, J=8.0 Hz), 7.43 (1H, t, H-7).

Found: C, 66.20; H, 5.87%. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%.

22: Yellow syrup; $[\alpha]_D^{24}$−25° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): ≈1726, 1591, 1567, 1366, and 1335 cm^{-1}; UV (MeOH) λ (ε) 236 (57400), 265 (Infl., 1550), 296 (6130), 308 (7540), 322 (6220), and 337 nm (4670); ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.30 (3H, t, Me of Et, J=7.0 Hz), 1.64 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 2.63 (1H, dd, H-11, $J_{11,11'}$=15.5 Hz, $J_{3,11}$=9.5 Hz), 3.07 (1H, dd, H-11′, $J_{3,11'}$= 3.5 Hz), 3.78 (3H, s, OMe), 3.92 (1H, dt, H-3, $J_{3,4}$=9.5 Hz), 4.00 and 4.01 (each 3H, s, OMe ×2), 4.221 and 4.224 (each 1H, q, CH_2 of Et), 4.77 (1H, d, OH-4, $J_{4,OH}$=1.0 Hz), 4.86 (1H, broad d, H-4), 5.19 (1H, q, H-1), 6.88 and 7.64 (each 1H, d, H-6 and 8, J=8.0 Hz), and 7.40 (1H, t, H-7).

Found: C, 64.31; H, 6.66%. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71%.

9-O-Methylnanaomycin D (23). A solution of **21** (205 mg) in acetonitrile (4.1 ml) was stirred with an aqueous solution (2.6 ml) of ammonium cerium(IV) nitrate (653 mg) at room temperature for 15 min. The reaction mixture was partitioned between ethyl acetate and water, and the combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to a residue. This was chromatographed on silica gel (15 g) with 3:1 benzene–ethyl acetate followed by recrystallization from ethyl acetate–petr. ether to give orange needles of **23** (171 mg, 92%): R_f 0.21 (3:1 benzene–ethyl acetate); mp 214—216 °C (dec.); $[\alpha]_D^{24}$−65° (*c* 0.5, $CHCl_3$); IR (KBr): ≈1786, ≈1658, and 1585 cm^{-1}; UV (MeOH) λ (ε) 212 (21700), 252 (12400), 265 (Infl., 9600), 386 (3390), and 403 nm (3560); ^{1}H-NMR (90 MHz, $CDCl_3$): δ= 1.56 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 2.65 (1H, d, H-11, $J_{11,11'}$= 18 Hz, $J_{3,11}$=0 Hz), 2.96 (1H, dd, H-11′, $J_{3,11'}$=5.0 Hz), 4.05 (3H, s, OMe), 4.69 (1H, dd, H-3, $J_{3,4}$=3 Hz), 5.08 (1H, q, H-1), 5.27 (1H, d, H-4), 7.3—7.9 (3H, m, H-6, 7 and 8).

Found: C, 65.12; H, 4.55%. Calcd for $C_{17}H_{14}O_6$: C, 64.97; H, 4.49%.

Nanaomycin D (1). To a stirred and ice-cooled solution

of **23** (19 mg) in dichloromethane (0.95 ml) was added $AlCl_3$ (190 mg), and stirring was continued at room temperature for 30 min. The reaction mixture was partitioned between chloroform and water, and the combined organic layers were washed with a saturated aqueous NaCl solution, dried and evaporated to a solid, which was recrystallized from ethyl acetate–petr. ether to give dark red rods and/or needles of **1** (17.2 mg, 95%).

An analytically pure sample was obtained by purification on PLC with 3:1 dichloromethane–chloroform followed by recrystallization from ethyl acetate–petr. ether to afford red rods of **1**, which changed into orange needles after a day: R_f 0.41 (3:1 benzene–ethyl acetate); R_f 0.55 (12:4:1 CH_2Cl_2–$CHCl_3$–acetone); red rods: mp 171—173°C (lit,[1] mp 170—173°C); orange needles: mp 196—203°C; $[\alpha]_D^{24}$ −163° (*c* 0.44, $CHCl_3$); IR (KBr): ≈1778, 1766, 1760, 1668, 1651, 1629, and 1452 cm^{-1}; UV (MeOH) λ (ε) 212 (36400), 258 (11200), 265 (Infl., 10200), 385 (Infl., 2890), and 427 nm (4420); ^{1}H-NMR (400 MHz, $CDCl_3$): δ=1.57 (3H, d, Me-1, $J_{1,Me}$=7.0 Hz), 2.71 (1H, d, H-11, $J_{11,11'}$=18 Hz, $J_{3,11}$=0 Hz), 2.97 (1H, dd, H-11′, $J_{3,11'}$=5.0 Hz), 4.69 (1H, dd, H-3, $J_{3,4}$=3.0 Hz), 5.09 (1H, q, H-1), 5.26 (1H, d, H-4), 7.31 and 7.71 (each 1H, dd, H-6 and 8, J=8.0 and 2.0 Hz), 7.68 (1H, t, H-7, J=8.0 Hz), 11.84 (1H, s, OH-9).

Its IR, UV, and ^{1}H-NMR spectra, and antibacterial activity (Table 1) were identical with those of an authentic sample of the natural antibiotic.

Found: C, 64.14; H, 4.02%. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

Ethyl (1S,3R,4S)-3,4,5,10-Tetrahydro-4-hydroxy-9-methoxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran-3-acetate (8). A sample of **22** (271 mg) was treated by the procedure described in the preparation of **23** and then worked up to give an orange syrup of **8** (220 mg, 88%): R_f 0.34 (3:1 benzene–ethyl acetate); $[\alpha]_D^{24}$ −269° (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): 1730, 1656, 1626, 1590, 1471, and 1450 cm^{-1}; UV (MeOH) λ (ε) 211 (22000), 247 (13000), 267 (Infl., 11500), 332 (2150), 385 (Infl., 3670), and 396 nm (3520); ^{1}H-NMR (400 Hz, $CDCl_3$): δ=1.28 (3H, t, Me of Et, J=7.0 Hz), 1.49 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 2.57 (1H, dd, H-11, $J_{3,11}$=9.0 Hz, $J_{11,11'}$=16 Hz), 2.98 (1H, dd, H-11′, $J_{3,11'}$=3.0 Hz), 3.85 (1H, dt, H-3, $J_{3,4}$=9.0 Hz), 4.01 (3H, s, OMe), 4.12 (1H, d, OH-4, $J_{4,OH}$=1.0 Hz), 4.196 and 4.204 (each 1H, q, CH_2 of Et), 4.61 (1H, ddd, H-4, $J_{1,4}$=2.0 Hz), 4.89 (1H, dq, H-1), 7.31 and 7.73 (each 1H, d, H-6 and 8, J=8 Hz), and 7.67 (1H, t, H-7).

Found: C, 63.06; H, 5.65%. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59%.

Ethyl (1S,3R,4S)-3,4,5,10-Tetrahydro-4,9-dihydroxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran-3-acetate (24). A sample of **8** (22.9 mg) was treated by the procedure described in the preparation of **1** and then worked up to give orange crystals of **24** (20.9 mg, 95%): R_f 0.65 (3:1 benzene–ethyl acetate); mp 100—102°C; $[\alpha]_D^{24}$ −433° (*c* 0.5, $CHCl_3$); IR (KBr): 1728, 1634, 1612, 1572, and 1460 cm^{-1}; UV (MeOH) λ (ε) 213 (28000), 250 (8550), 257 (8640), 264 (Infl., 8250), 272 (9280), 385 (Infl., 2860), and 420 nm (3800); ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.29 (3H, t, Me of Et, J=7.0 Hz), 1.52 (3H, d, Me-1, $J_{1,Me}$=6.5 Hz), 2.54 (1H, dd, H-11, $J_{3,11}$=9.0 Hz, $J_{11,11'}$=16 Hz), 2.98 (1H, dd, H-11′, $J_{3,11'}$=3.0 Hz), 3.85 (1H, dt, H-3, $J_{3,4}$= 9.0 Hz), 3.99 (1H, d, OH-4, $J_{4,OH}$=1 Hz), 4.20 (2H, q, CH_2 of Et, J=7.0 Hz), 4.64 (1H, dull d, H-4), 4.87 (1H, dq, H-1, $J_{1,4}$=2.5 Hz), 7.2—7.7 (3H, m, H-6, 7 and 8).

Found: C, 62.21; H, 5.04%. Calcd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.24%.

Kalafungin (2). To a stirred and ice-cooled solution of **24** (16.5 mg) in benzene (0.34 ml) was added conc. H_2SO_4 (0.11 ml), and stirring was continued at room temperature for 30 min. After cooling to 5°C, the reaction mixture was partitioned between ice-cooled ethyl acetate and water. The combined organic layers were washed sequentially with saturated aqueous $NaHCO_3$ and NaCl solutions under ice-cooling, dried and evaporated to a residue, which showed two spots having R_f-values of 0.55 and 0.32 on TLC (12:4:1 CH_2Cl_2–$CHCl_3$–acetone; **24** R_f 0.70). Their R_f-values were identical with those of kalafungin (**2**) and ethyl kalafunginate, the latter of which was derived from kalafungin according to the published procedure.[2b]

The residue was dissolved in toluene (0.4 ml), and the resulting solution refluxed at 105°C for 7 h and then evaporated to a solid, which was recrystallized from ethyl acetate–petr. ether to give red rods of **2** (13.1 mg, 92%).

An analytically pure sample was obtained by purification on PLC with 3:1 dichloromethane–chloroform followed by recrystallization from ethyl acetate–petr. ether to afford red rods of **2**: R_f 0.41 (3:1 benzene–ethyl acetate); R_f 0.55 (12:4:1 CH_2Cl_2–$CHCl_3$–acetone); mp 171—173°C; $[\alpha]_D^{24}$ +160° (*c* 0.30, $CHCl_3$)[lit,[2] mp 163—166°C; $[\alpha]_D^{25}$+159° (*c* 1, $CHCl_3$)].

Its IR, UV, and ^{1}H-NMR spectra, and TLC-behavior were identical with those of the aforesaid nanaomycin D (**1**), and also with those of an authentic sample of the natural kalafungin (**2**). The antibacterial activity was also identical with those of the natural antibiotic as shown in Table 1.

Found: C, 64.19; H, 4.06%. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03%.

Nanaomycin A (5). A solution of **1** (16 mg) in ethanol (3 ml) was shaken with platinum oxide and 3-atm hydrogen at room temperature for 1 h, filtered and evaporated to give orange crystals of **5** (15.7 mg, 98%).

An analytically pure sample was obtained by purification on PLC with 3:2 benzene–acetone followed by recrystallization from ethanol to give orange needles of **5**: R_f 0.20 (3:1 benzene–acetone; **1**: R_f 0.68); mp 179—181°C (lit,[5] mp 178—180°C); $[\alpha]_D^{20}$ −21° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 1714, 1663, 1645, 1620, and 1576 cm^{-1}; UV (MeOH) λ (ε) 248 (11800), 273 (14400), 385 (Infl., 3760), and 420 nm (5450); ^{1}H-NMR (90 MHz, $CDCl_3$): δ=1.58 (3H, Me, $J_{1,Me}$=7 Hz), 2.33 (1H, ddd, H-4, $J_{1,4}$=2 Hz, $J_{3,4}$=10 Hz, $J_{4,4'}$=19 Hz), 2.72 (2H, d, CH_2-11, J=6.5 Hz), 2.87 (1H, dd, H-4′, $J_{3,4'}$=3 Hz), 4.34 (1H, m, H-3), 5.04 (1H, dq, H-1), 7.2—7.7 (3H, m, H-6,7, and 8), 8.8 (1H, broad signal, COOH), 12.03 (1H, s, OH-9).

Its IR, UV and ^{1}H-NMR spectra were identical with the published data of the natural antibiotic.[5]

Found: C, 63.54; H, 4.56%. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.66%.

4-Deoxykalafunginic Acid (Enantiomer of Nanaomycin A) (5′). A sample of **2** (15 mg) was hydrogenated by the procedure described in the preparation of **5** to give orange crystals of **5′** (14.5 mg, 97%), which was purified to afford needles: R_f 0.20 (3:1 benzene–acetone); mp 179—181°C; $[\alpha]_D^{20}$ +21° (*c* 0.4, $CHCl_3$).

Its IR, UV, and ^{1}H-NMR spectra and TLC-behavior were identical with those of nanaomycin A (**5**).

Found: C, 63.44; H, 4.49%. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.66%.

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