Pyranonaphthoquinone Antibiotics. 3. Synthesis of (+)-9-Deoxygriseusin B and Absolute Configuration Revision of Griseusins A and B

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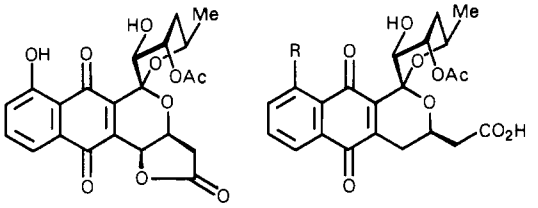
The synthesis of (+)-9-deoxygriseusin B (**3**), a close analogue of the natural product, has been achieved. Coupling of the bromonaphthalene derivative **12** with the chiral carbohydrate precursor **11** followed by oxidation gave the allyl ketone **14**. Intramolecular ketalization of the bromohydrin intermediate **15** derived from **14** afforded the bromo spiro ketal **16**. Treatment of **16** with NaCN and hydrolysis of the cyano group gave the spiro ketal acid **19**, which was converted into the final product **3**. On the basis of the CD spectrum of **3**, which was found to be essentially antipodal to those of griseusins A and B, it was proposed that the original assignment of absolute configuration of the natural products should be revised.

Griseusins A and B, produced by a strain of *Streptomyces griseus*, are members of a growing family of pyranonaphthoquinone antibiotics and are reported to be active against gram-positive bacteria.[1] In 1976, their structures, including absolute configurations, were elucidated as **1** and **2** by Tsuji et al. mainly on the basis of spectroscopic data.[2]



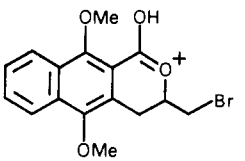
1

2 : R = OH
3 : R = H

Of particular interest, the griseusins contain a unique 1,7-dioxaspiro[5.5]undecane ring system fused to a juglone moiety. Recently, in preliminary investigations, we showed two synthetic approaches[3] to the basic structure of pyranonaphthoquinone antibiotics and also an efficient entry to the pentacyclic framework of griseusins.[4] With these results in hand, we initiated an investigation aimed at the total synthesis of optically active griseusins utilizing an appropriate chiral carbohydrate precursor for the spiropyrano moiety. In this paper, we describe the synthesis of (+)-9-deoxygriseusin B (**3**) and that inspection of the CD spectrum of **3** has led to revision of the absolute configurations originally assigned to griseusins A and B.

The first task in the present study was the preparation of 4,6-dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-L-gulose (**11**) which could serve as the sugar moiety of the griseusins. The chiral aldehyde **11** was synthesized by starting with 6-deoxy-3,5-*O*-isopropylidene-L-gulono-γ-lactone (**4**)[5] as shown in Scheme I. First, the hydroxyl group of **4** was alkylated with chloromethyl methyl ether in the presence of *N,N*-diethylaniline to give the protected lactone **5** in 74% yield. The compound **5** was then reduced with $LiAlH_4$ to produce the diol **6**, which was selectively benzoylated by treatment with 1.2 equiv of benzoyl chloride and 2 equiv of pyridine, affording the monobenzoate **7** in 87% overall yield. Deoxygenation of the secondary hydroxyl group of **7** was carried out by Barton's method.[6] Thus, reaction of **7** with 4 equiv of *N,N'*-thiocarbonyldiimidazole in refluxing 1,2-dichloroethane for 24 h yielded the imidazolide **8**.[7] Crude **8**[8] was treated with *n*-Bu_3SnH in refluxing toluene to give 55% yield of the deoxygenated product **9** accompanied by 27% recovery of **7**.[9] Saponification of **9** with methanolic KOH followed by oxidation of the resulting alcohol **10** by Swern's technique[10] gave the desired aldehyde **11** in 83% yield.

Our approach to (+)-9-deoxygriseusin B (**3**) from 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**12**) is outlined in Scheme II. Reaction of the chiral aldehyde **11** with lithio compound prepared from **12** and *n*-BuLi in THF at −78 °C produced a 2:1 mixture of the epimeric carbinols **13** in 50% yield. The mixture of epimers was subjected to oxidation with PCC to afford the ketone **14** in 52% yield. Construction of the dioxaspiro ring system was achieved by the same method as described in our preceding paper.[4] Reaction of the compound **14** with aqueous *N*-bromoacetamide in the presence of perchloric acid produced a 1:1 mixture of two epimeric bromo ketals **16**. The spiro ketal structure was characterized by the mass spectrum which exhibited the base peaks at *m/e* 351/353 due to the ion **i**. The mixture **16** was then reacted with sodium



(i)

(1) Tsuji, N.; Kobayashi, M.; Wakisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot.* **1976**, *29*, 7.
(2) Tsuji, N.; Kobayashi, M.; Terui, Y.; Tori, K. *Tetrahedron* **1976**, *32*, 2207.
(3) Kometani, T.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1191. Kometani, T.; Takeuchi, Y.; Yoshii, E. *Ibid.* **1981**, 1197.
(4) Masamoto, K.; Takeuchi, Y.; Takeda, K.; Yoshii, E. *Heterocycles* **1981**, *16*, 1659.
(5) Ireland, R. E.; Wilcox, C. L. *J. Org. Chem.* **1980**, *45*, 197.
(6) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
(7) Imidazolide formation did not proceed completely even under prolonged reaction, probably owing to the steric hindrance around the secondary hydroxyl group.
(8) The imidazolide **8** could not be isolated from the mixture by silica gel chromatography because of its instability to silica gel.
(9) Treatment of a dithiocarbonate derivative of **7** with *n*-Bu_3SnH[6] did not give better results, especially in case of large-scale operation.
(10) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

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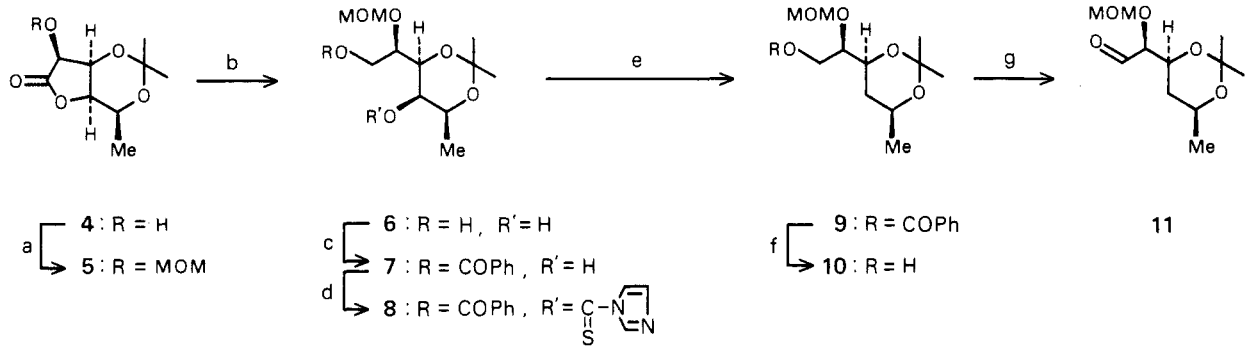
Scheme I[a]

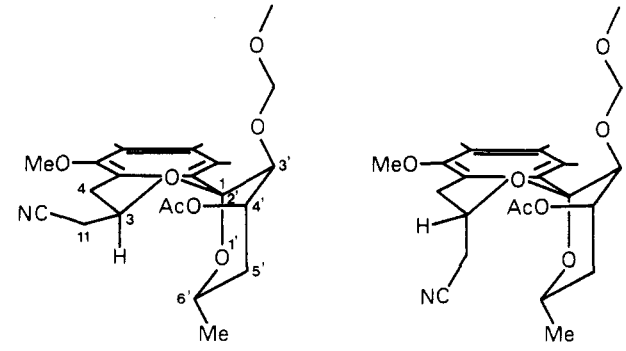


[a] (a) CH_3OCH_2Cl, $PhNEt_2$, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) PhCOCl, pyr, CH_2Cl_2; (d) Im_2CS, $ClCH_2CH_2Cl$; (e) *n*-Bu_3SnH, toluene; (f) KOH, MeOH; (g) Me_2SO, $(COCl)_2$, CH_2Cl_2.

Table I. Selected ^1H NMR (200 MHz) Spectral Data for Compounds 18a and 18b

	chemical shifts, δ (J, Hz)	
atom	18a	18b
H-5′$_{ax}$	1.88 (td, J = 11, 4)	1.87 (td, J = 11, 4)
H-5′$_{eq}$	2.13 (ddd, J = 11, 4, 2)	2.03 (ddd, J = 11, 4, 2)
H-4	2.77 (dd, J = 16, 8)	3.12 (dd, J = 17, 4)
	3.14 (dd, J = 16, 3)	3.32 (dd, J = 17, 5)
H-11	2.81 (dd, J = 16, 2)	2.65 (dd, J = 17, 7)
	2.98 (dd, J = 16, 9)	2.95 (dd, J = 17, 7)
H-3	4.45 (m)	4.89 (m)
H-6′$_{ax}$	4.67 (dqd, J = 11, 6, 2)	4.67 (dqd, J = 11, 6, 2)
H-3′$_{ax}$	5.27 (d, J = 4)	4.94 (d, J = 4)
H-4′$_{eq}$	5.48 (q, J = 4)	5.46 (q, J = 4)

Chart I



18a (1S, 3R) 18b (1S, 3S)

cyanide in DMF at 70 °C for 14 h to give a nitrile mixture of **17a** and **17b** in a ratio of 2.2:1. This isomer ratio could have been further displaced to 14:1 without apparent loss of either isomer by treatment of the product under the same reaction conditions (NaCN/DMF, 70 °C, 14 h). Although these isomers were separable by careful HPLC, TLC with silica gel was not effective for separation, showing a single spot with a variety of solvent systems. However, the nitrile acetates **18a** and **18b** showed distinctly different R_f values on silica gel TLC, and they could have been cleanly separated in pure states.

Having been able to secure the two epimers at this stage and armed with their 200-MHz ^1H NMR data, we proceeded to the determination of their configurations. Among four theoretically possible isomers (1*S*,3*S*, 1*S*,3*R*, 1*R*,3*S*, and 1*R*,3*R*), the two nitrile isomers at hand must be those having distinct conformational stabilities compared to those of the remaining two, since the configurations at C-1 and C-3 should have been established by the equilibration shown in Scheme III. The ^1H NMR spectral data of the nitrile acetates (**18a,b**) shown in Table I are very useful for the determination of the stereochemistries by conformational analysis. As seen from the spin–spin coupling constants between vicinal protons ($J_{3',4'}$ = 4 Hz, $J_{4',5'}$ = 4 Hz, $J_{5',6'}$ = 11, 2 Hz), the sugar moiety of each isomer should have the same $^1C_4$ conformation as proposed for the natural griseusins.[2] This conformation is possible only for the two isomers possessing the 1*S*,3*S* and 1*S*,3*R* configurations, since, for the rest of the possible isomers, there exists severe steric hindrance associated with the ring substituents as shown by Dreiding models.

Here, assignment of 1*S*,3*R* for **18a** and 1*S*,3*S* for **18b** (Chart I) was immediately obtained on the basis of the result of the above equilibration experiment which showed that the major isomer **18a** should have a more stable equatorial C-3 side chain. The NMR data for H-3 also led to the same conclusion: while H-3$_{ax}$ for **18a** was seen at δ 4.45, H-3$_{eq}$ for **18b** was observed at δ 4.89, strongly deshielded by the aromatic ring.

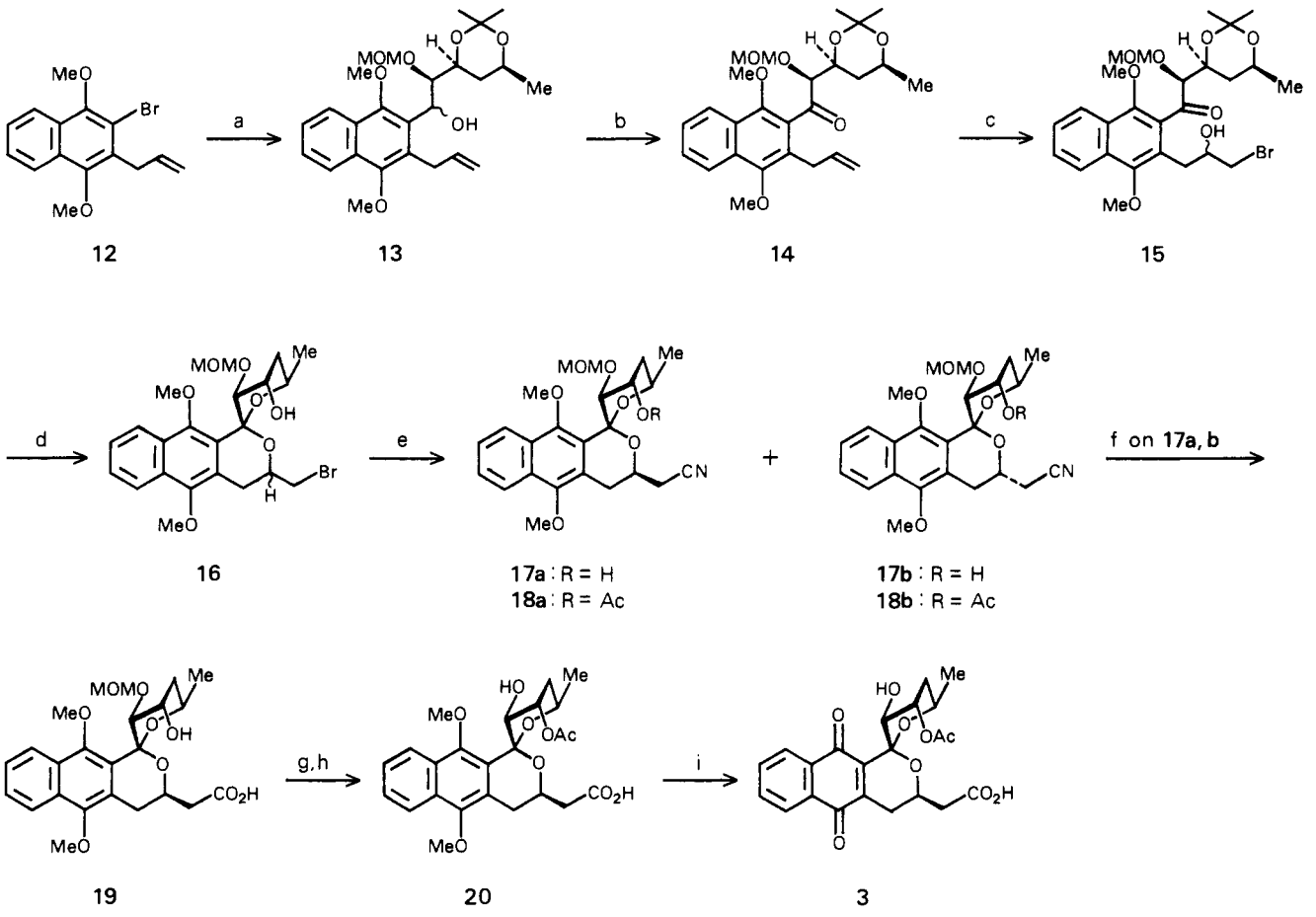
The mixture of nitriles (**17a**/**17b** ratio of 2.2) was subjected to hydrolysis with aqueous KOH in the presence of H_2O_2 to afford the acid **19** as a single product in 84% yield. From the detailed analysis of the 200-MHz ^1H NMR spectrum, the configuration of **19** that was confirmed to be the most stable was 1*S*,3*R*. Thus, epimerization at C-3 also occurred under this basic reaction condition.

For conversion of **19** into the target molecule, we first attempted the procedure shown in Scheme IV. Oxidative demethylation of **19** followed by γ-lactone formation by a known procedure[11] afforded **22**,[12] which was acetylated with Ac_2O–pyridine to yield **23**.[12] Removal of the methoxymethyl group of **23** to give 9-deoxygriseusin A (**24**), however, failed, yielding unidentifiable products. Therefore, we were forced to investigate the alternative route shown in Scheme II. Acetylation of the acid **19** with Ac_2O–pyridine followed by deprotection of the methoxymethyl group with 10% HCl in DME was readily performed to afford the desired acid **20** in 60% yield. Oxi-

(11) Although griseusin B was reported to be transformed to griseusin A quantitatively by air oxidation in pyridine,[2] the 9-deoxy derivative **21** gave the corresponding γ-lactone **22** in low yield under the same conditions.

(12) The ^1H NMR spectral data (200 MHz, $CDCl_3$) of **22** and **23** are as follows. **22**: δ 1.21 (d, 3 H, J = 6 Hz, CH_3), 2.78 (d, 1 H, J = 18 Hz, H-11), 2.91 (s, 3 H, CH_2OCH_3), 3.03 (dd, 1 H, J = 18, 5 Hz, H-11), 4.28 (m, 2 H, H-4′ and H-6′), 4.42 (d, 1 H, J = 7 Hz, OCH_2O), 4.61 (d, 1 H, J = 7 Hz, OCH_2O), 4.80 (d, 1 H, J = 4 Hz, H-3′), 4.81 (m, 1 H, H-3), 5.32 (d, 1 H, J = 3 Hz, H-4), 7.80 (m, 2 H, Ar H), 8.12 (m, 2 H, Ar H). **23**: δ 1.24 (d, 3 H, J = 6 Hz, CH_3), 2.13 (s, 3 H, $COCH_3$), 2.75 (d, 1 H, J = 17 Hz, H-11), 2.82 (s, 3 H, CH_2OCH_3), 3.05 (dd, 1 H, J = 18, 5 Hz, H-11), 4.25 (m, 1 H, H-6′), 4.29 (d, 1 H, J = 7 Hz, OCH_2O), 4.58 (d, 1 H, J = 7 Hz, OCH_2O), 4.80 (dd, 1 H, J = 5, 3 Hz, H-3), 4.85 (d, 1 H, J = 4 Hz, H-3′), 5.33 (d, 1 H, J = 3 Hz, H-4), 5.48 (q, 1 H, J = 4 Hz, H-4′), 7.82 (m, 2 H, Ar H), 8.15 (m, 2 H, Ar H).

Scheme II[a]



[a] (a) *n*-BuLi, **11**, THF; (b) PCC, CH_2Cl_2; (c) NBA, dilute $HClO_4$, acetone; (d) dilute HCl, room temperature; (e) NaCN, DMF; (f) KOH, H_2O_2, EtOH; (g) Ac_2O, pyr; (h) 10% HCl, DME, 50 °C; (i) AgO, 6 N HNO_3, THF.

Scheme III

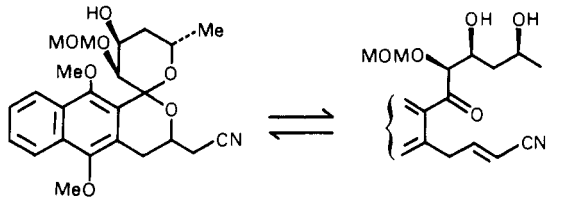
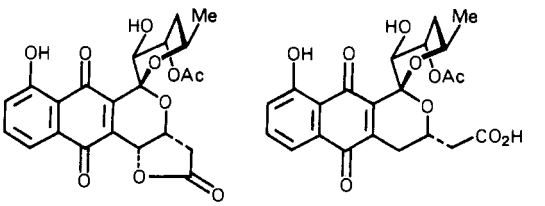
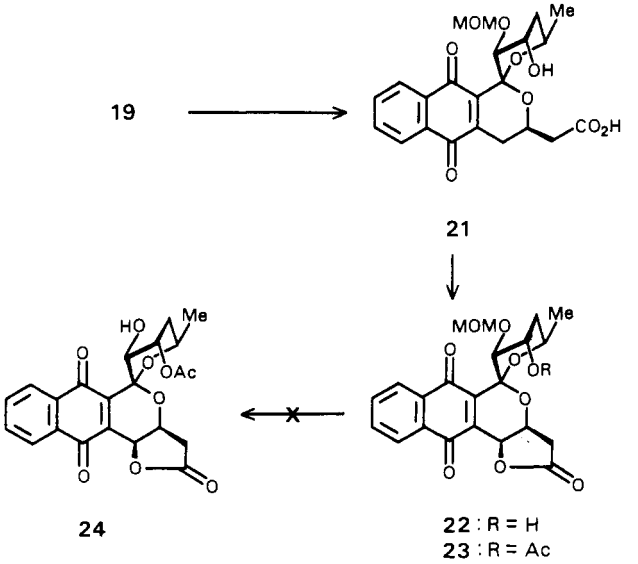


Chart II



Scheme IV



dative demethylation of **20** was successfully achieved by treatment with AgO to produce 9-deoxygriseusin B (**3**) in 72% yield.[13]

Now, at the final stage of the present study, the CD spectrum of the compound **3** was measured for confirmation of the chirality of the spiro ketal moiety, with the expectation that it would be the same as that of natural griseusin B. What turned out was, to our surprise, that they were essentially of mirror-image shape as shown in Figure 1. The only notable spectral differences of **3** from the natural product were hypsochromic shifts and higher

(13) Air oxidation of **3** in pyridine afforded (+)-9-deoxygriseusin A (**24**) in 54% yield. Though this product could not be purified completely, the structure of **24** (mp 145–148 °C) was confirmed by the following spectral data: ^1H NMR (200 MHz) δ 1.23 (d, 3 H, J = 6 Hz, CH_3), 2.14 (s, 3 H, $COCH_3$), 2.74 (d, 1 H, J = 17 Hz, H-11), 3.11 (dd, 1 H, J = 17, 5 Hz, H-11), 4.20 (m, 1 H, H-6′), 4.85 (dd, 1 H, J = 5, 3 Hz, H-3), 4.92 (m, 1 H, H-3′), 5.30 (q, 1 H, J = 4 Hz, H-4′), 5.37 (d, 1 H, J = 3 Hz, H-4), 7.83 (m, 2 H, Ar H), 8.15 (m, 2 H, Ar H); CD (EtOH) $[\theta]_{470}$ 0, $[\theta]_{420}$ 2300, $[\theta]_{370}$ 1600, $[\theta]_{340}$ 0, $[\theta]_{300}$ −7000, $[\theta]_{275}$ −14 400, $[\theta]_{267}$ 0.

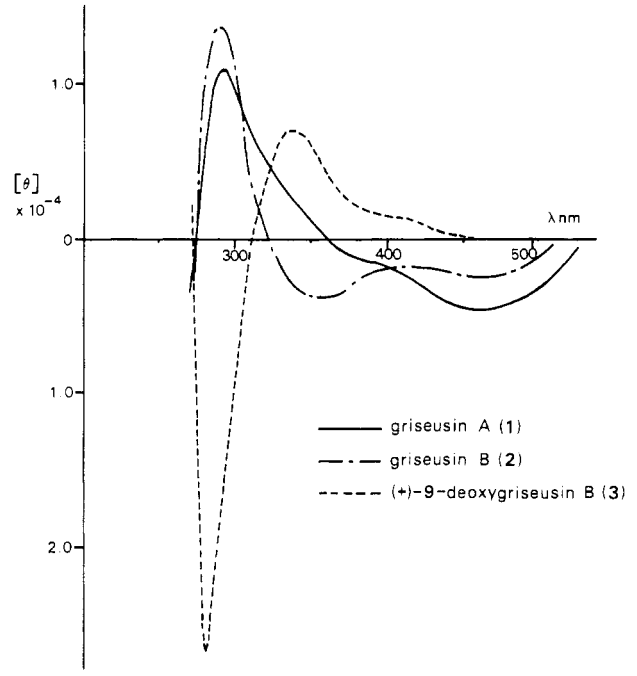


Figure 1. CD spectra of natural griseusins and synthetic (+)-9-deoxygriseusin B (3).

amplitudes of the maxima, presumably due to the lack of a phenolic hydroxyl group. Since our synthetic compound **3** must have the *S* configuration at C-1 as already discussed and since its negative Cotton effect associated with the aromatic absorption near 280 nm is in accord with the prediction from quadrant sector rules,[14] we conclude that the natural griseusins have the 1*R*,3*S* configuration as shown in Chart II.

Experimental Section

Melting points were determined by using a Yanagimoto micro melting point apparatus. All melting points and boiling points are uncorrected. Infrared spectra (IR) were taken on a Hitachi 215 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian XL-200 or a JEOL MH-100 instrument. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi RMU-6MG or a JEOL D-300 spectrometer. Optical rotations were measured on a JASCO DIP automatic polarimeter, and circular dichroism spectra were recorded on a JASCO J-20 spectrometer. Combustion analyses were carried out at the Microanalytical Laboratory of Toyama Medical and Pharmaceutical University. Most reactions were followed by thin-layer chromatography (TLC) with Merck precoated plates (silica gel 60 F_{254}). Preparative TLC was carried out on Merck silica gel 60 $F_{254+366}$. Merck silica gel 60 (70–230 mesh) was used for column chromatography. High-pressure liquid chromatography (HPLC) was carried out on a Waters Model 6000A solvent-delivery system equipped with a Model U6K injector and a Toyo Soda 120ST UV monitor.

6-Deoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-L-gulono-γ-lactone (5). To a solution of 1.13 g (5.6 mmol) of 6-deoxy-3,5-*O*-isopropylidene-L-gulono-γ-lactone (**4**)[5] in 55 mL of CH_2Cl_2 were added 5.80 g (39 mmol) of *N*,*N*-diethylaniline and then 2.26 g (28 mmol) of chloromethyl methyl ether. The reaction mixture was stirred at room temperature for 48 h. The yellowish brown mixture was successively washed with 5% HCl, 5% $NaHCO_3$, and brine and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded a pale yellow solid, which was chromatographed on 10 g of silica gel. Elution with mixtures of ethyl acetate–benzene gave 1.015 g (74%) of the ether **5** as a colorless solid. The analytical sample was obtained by recrystallization from chloroform–hexane as colorless needles: mp 117–118 °C; $[\alpha]^{21}_D$ +47.8° (*c* 3.69, $CHCl_3$); IR (KBr) 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (d, 3 H, *J* = 7 Hz, CH_3), 1.44 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 3.48 (s, 3 H, OCH_3), 4.20 (qd, 1 H, *J* = 7, 2 Hz, H-5), 4.47 (d, 1 H, *J* = 4 Hz, H-2), 4.82 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.98 (d, 1 H, *J* = 6 Hz, OCH_2O); MS, *m*/*e* (relative intensity) 231 ($M^+ - CH_3$, 46), 188 (15), 111 (15), 45 (100). Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.64; H, 7.33.

6-Deoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-D-glucitol (6). To a stirred solution of 1.015 g (4.13 mmol) of the ether **5** in 30 mL of THF at room temperature was added 2.0 g (53 mmol) of $LiAlH_4$ in portions over 5 min, and the mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with 30 mL of saturated aqueous Rochelle salt solution. After extraction of the mixture with $CHCl_3$, the extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The resultant solid was recrystallized from acetone–hexane to give 0.990 g (96%) of the diol **6** as colorless needles: mp 75–76 °C; $[\alpha]^{22}_D$ +50.6° (*c* 2.06, $CHCl_3$); IR (KBr) 3450 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H, *J* = 7 Hz, CH_3), 1.41 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 3.45 (s, 3 H, OCH_3), 4.80 (s, 2 H, OCH_2O); MS, *m*/*e* (relative intensity) 235 ($M^+ - CH_3$, 33), 117 (80), 59 (83), 45 (100). Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.78; H, 8.86. Found: C, 52.48; H, 8.57.

1-*O*-Benzoyl-6-deoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-D-glucitol (7). To a stirred solution of 1.103 g (4.4 mmol) of the diol **6** and 0.7 g (8.8 mmol) of pyridine in 8 mL of CH_2Cl_2 was added 0.744 g (5.3 mmol) of benzoyl chloride in 1 mL of CH_2Cl_2 over 3 min at room temperature. After being stirred for 30 min, the mixture was treated with 2 mL of ethanol and then stirred for 5 min. This mixture was diluted with CH_2Cl_2, washed with 5% HCl, 5% $NaHCO_3$, and brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave a pale yellow oil, which was chromatographed on 20 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 1.35 g (87%) of the monobenzoate **7** as a nearly colorless solid. The analytical sample was obtained by recrystallization from hexane as colorless needles: mp 69.5–70.5°; $[\alpha]^{21}_D$ +28.3° (*c* 6.25, $CHCl_3$); IR (KBr) 3500, 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, 3 H, *J* = 7 Hz, CH_3), 1.44 (s, 6 H, $2CH_3$), 3.44 (s, 3 H, OCH_3), 4.87 (s, 2 H, OCH_2O), 7.60 (m, 3 H, Ar H), 8.18 (m, 2 H, Ar H); MS, *m*/*e* (relative intensity) 339 ($M^+ - CH_3$, 25), 130 (55), 117 (75), 105 (100). Anal. Calcd for $C_{18}H_{26}O_7$: C, 61.00; H, 7.40. Found: C, 61.22; H, 7.48.

1-*O*-Benzoyl-4,6-dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-D-glucitol (9). A mixture of 1.349 g (3.8 mmol) of the monobenzoate **7** and 2.7 g (15 mmol) of *N*,*N*′-thiocarbonyldiimidazole in 20 mL of 1,2-dichloroethane was heated at gentle reflux for 20 h. After removal of the solvent at reduced pressure, the residual oil was partitioned between CH_2Cl_2 and dilute HCl, and then the organic layer was separated, washed with 5% $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 1.6 g of crude imidazolide **8** as a pale yellow oil, which contained a small amount of the starting material **7** as evidenced by TLC: MS, *m*/*e* (relative intensity) 449 ($M^+ - CH_3$, 18), 105 (100), 45 (71).

To a stirred solution of 1.6 g (5.5 mmol) of tri-*n*-butylstannane in 100 mL of refluxing toluene under nitrogen was added 1.6 g of this crude imidazolide **8** in 20 mL of toluene over 30 min. After being heated at reflux for 20 h, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between acetonitrile and hexane, and the hexane layer was separated and then extracted with acetonitrile. The combined acetonitrile layers were washed with hexane and concentrated under reduced pressure to give a pale yellow oil, which was

(14) (a) Kuriyama, K.; Iwata, T.; Moriyama, M.; Kotera, K.; Hamada, Y.; Mitsui, R.; Takeda, K. *J. Chem. Soc. B* **1967**, 46. (b) Snatzke, G.; Hrbek, J., Jr.; Hruban, L. *Tetrahedron* **1970**, *26*, 5013.

(15) Determination of absolute configuration of griseusins by Tsuji et al.[2] is based on conformational analysis and comparison of the CD spectra with that of a closely related compound, actinorhodinindazolquinone, of known absolute configuration. This treatment considered only the chirality of the pyranonaphthoquinone chromophore and is undoubtedly valid for simple pyranonaphthoquinone derivatives such as isoeleutherin,[16] kalafungin,[16] and actinorhodinindazolquinone.[17] For the present case, however, one must evaluate contribution of the additional tetrahydropyrano group in lower left octant.[14]

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chromatographed on 15 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 0.708 g (55%) of the deoxygenated product **9** and 0.36 g (27%) of the starting material **7**. The analytical sample of **9** was obtained by distillation: bp 140–150 °C (1 mmHg; bath temperature); $[\alpha]^{23}_D$ +14.08° (*c* 2.00, $CHCl_3$); IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.18 (d, 3 H, *J* = 7 Hz, CH_3), 1.35 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 3.35 (s, 3 H, OCH_3), 3.79 (m, 1 H, H-2), 4.04 (m, 2 H, H-3 and H-5), 4.37 (dd, 1 H, *J* = 12, 6 Hz, H-1), 4.59 (dd, 1 H, *J* = 12, 3 Hz, H-1), 4.72 (d, 1 H, *J* = 7 Hz, OCH_2O), 4.81 (d, 1 H, *J* = 7 Hz, OCH_2O), 7.54 (m, 3 H, Ar H), 8.05 (m, 2 H, Ar H); MS *m/e* (relative intensity) 323 ($M^+ - CH_3$, 30), 129 (100), 105 (47), 59 (47), 45 (19); exact mass calcd for $C_{17}H_{23}O_6$ ($M^+ - CH_3$) 323.1493, found 323.1501.

4,6-Dideoxy-3,5-*O*-isopropylidene-2-*O*-(methoxymethyl)-L-gulose (11). A solution of 0.60 g (1.78 mmol) of the ester **9** and 4 mL of 5% KOH in 15 mL of methanol was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure to half of the original volume at room temperature. This mixture was then partitioned between ethyl acetate and water, and the aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). After removal of the solvent at reduced pressure, the residue was distilled to afford 0.384 g (92%) of the primary alcohol **10** as a colorless oil: bp 70–80 °C (1 mmHg; bath temperature); $[\alpha]^{21.5}_D$ +33.9° (*c* 3.57, $CHCl_3$); IR (neat) 3450 cm^{-1}; NMR ($CDCl_3$) δ 1.16 (d, 3 H, *J* = 7 Hz, CH_3), 1.35 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 3.36 (s, 3 H, OCH_3), 4.70 (d, 1 H, *J* = 7 Hz, OCH_2O), 4.79 (d, 1 H, *J* = 7 Hz, OCH_2O); MS, *m/e* (relative intensity) 219 ($M^+ - CH_3$, 20), 129 (100), 59 (77), 45 (62).

To a stirred solution of 202 mg (1.6 mmol) of oxalyl chloride in 1.5 mL of CH_2Cl_2 at −50 to −60 °C was added dropwise 248 mg (3.2 mmol) of Me_2SO in 0.5 mL of CH_2Cl_2 over 1 min, and the mixture was stirred for 2 min. A solution of 186 mg (0.8 mmol) of the above alcohol **10** in 1 mL of CH_2Cl_2 was added to the mixture at the same temperature over 2 min. After being stirred at −50 to −60 °C for 15 min, the mixture was treated with 803 mg (8 mmol) of triethylamine and then stirred at the same temperature for 5 min. The reaction mixture was allowed to warm to room temperature and then quenched with 10 mL of water. After the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with 5% HCl, 5% $NaHCO_3$, and brine and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave a pale yellow oil, which was distilled to afford 166 mg (90%) of the aldehyde **11** as a colorless oil: bp 60–70 °C (1 mmHg; bath temperature); $[\alpha]^{23}_D$ +7.57° (*c* 1.93, $CHCl_3$); IR (neat) 1725 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3 H, *J* = 7 Hz, CH_3), 1.35 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 3.37 (s, 3 H, OCH_3), 4.73 (s, 2 H, OCH_2O), 9.66 (d, 1 H, *J* = 2 Hz, CHO); MS, *m/e* (relative intensity) 217 ($M^+ - CH_3$, 21), 129 (35), 59 (63), 45 (100); exact mass calcd for $C_{10}H_{17}O_5$ ($M^+ - CH_3$) 217.1075, found 217.1049. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.71; H, 8.50.

3-Allyl-1,4-dimethoxy-2-[3(*S*),5(*S*)-(isopropylidenedioxy)-2(*S*)-(methoxymethoxy)hexanoyl]naphthalene (14). To a stirred solution of 439 mg (1.43 mmol) of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**12**)[4] in 5 mL of THF at −78 °C under nitrogen was added 1.05 mL (15% in hexane, 1.7 mmol) of *n*-BuLi over 3 min. After being stirred at the same temperature for 10 min, the green solution was treated with a solution of 166 mg (0.72 mmol) of the aldehyde **11** in 2 mL of THF and then stirred at −78 °C for 3.5 h. The pale yellow mixture was quenched with 1 mL of water. The mixture was partitioned between ethyl acetate and water, and the aqueous layer was separated and then extracted with ethyl acetate. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave a pale yellow oil, which was chromatographed on 15 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 166 mg (50%) of the epimeric carbinol **13** as a pale yellow oil, showing two spots on TLC due to two epimers. The analytical samples were obtained by preparative TLC (benzene–ethyl acetate, 5:1) as pale yellow oils. Less polar carbinol: R_f 0.50 (benzene–ethyl acetate, 5:1); NMR ($CDCl_3$) δ 1.20 (d, 3 H, *J* = 7 Hz, CH_3), 1.37 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 2.52 (s, 3 H, CH_2OCH_3), 3.80 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 4.16 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.58 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.90–5.10 (m, 2 H, $CH{=}CH_2$), 5.80–6.20 (m, 1 H, $CH{=}CH_2$), 7.40 (m, 2 H, Ar H), 7.95 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 460 (M^+, 10), 257 (100), 256 (99), 45 (18). More polar carbinol: R_f 0.45 (benzene–ethyl acetate, 5:1); NMR ($CDCl_3$) δ 1.20 (d, 3 H, *J* = 7 Hz, CH_3), 1.24 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 3.33 (s, 3 H, CH_2OCH_3), 3.87 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.49 (d, 1 H, *J* = 7 Hz, OCH_2O), 4.67 (d, 1 H, *J* = 7 Hz, OCH_2O), 4.90–5.25 (m, 2 H, $CH{=}CH_2$), 5.80–6.20 (m, 1 H, $CH{=}CH_2$), 7.45 (m, 2 H, Ar H), 8.00 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 460 (M^+, 12), 257 (100), 256 (99), 45 (20). The ratio of formation was determined from the NMR spectrum of the mixture to be ca. 2:1 by integration of methoxymethyl groups.

To a solution of 0.604 g (2.8 mmol) of PCC in 150 mL of CH_2Cl_2 was added 0.86 g (1.87 mmol) of the above mixture **13** in 20 mL of CH_2Cl_2 at room temperature, and the mixture was stirred for 40 h. The reaction mixture was diluted with 170 mL of ether, stirred with 5 g of Florisil gel for 10 min, and then filtered. Removal of the solvent from the filtrate gave a pale yellow oil, which was chromatographed on 5 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 446 mg (52%) of the ketone **14** as a pale yellow solid. The analytical sample was obtained by recrystallization from ether as colorless cubes: mp 100–101 °C; $[\alpha]^{24}_D$ +42.5° (*c* 0.113, $CHCl_3$); IR (KBr) 1710, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.14 (d, 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 3.14 (s, 3 H, CH_2OCH_3), 3.42 (d, 2 H, *J* = 6 Hz, $CH_2CH{=}CH_2$), 3.84 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.70 (d, 1 H, *J* = 4 Hz, OCH_2O), 4.84 (d, 1 H, *J* = 4 Hz, OCH_2O), 4.90–5.10 (m, 2 H, $CH{=}CH_2$), 5.80–6.90 (m, 1 H, $CH{=}CH_2$), 7.45 (m, 2 H, Ar H), 8.00 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 458 (M^+, 6), 255 (100), 45 (42). Anal. Calcd for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 67.91; H, 7.41.

3(*R*)-(Cyanomethyl)-5,10-dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1(*S*)-spiro-2′-4′(*S*)-acetoxy-3′(*S*)-(methoxymethoxy)-6′(*S*)-methyltetrahydropyran (18a) and 3(*S*)-(Cyanomethyl)-5,10-dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1(*S*)-spiro-2′-4′(*S*)-acetoxy-3′(*S*)-(methoxymethoxy)-6′(*S*)-methyltetrahydropyran (18b). To a stirred solution of 55 mg (0.12 mmol) of the ketone **14** in 10 mL of acetone at 0 °C were added 1 mL of 2.7 N $HClO_4$ and 18.2 mg (0.13 mmol) of NBA. After being stirred at 0 °C for 20 min, the reaction mixture was treated with 1 mL of 10% HCl and then stirred at room temperature for 1 h. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 5% $NaHCO_3$ and brine and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded a pale yellow oil, which was chromatographed on 3 g of silica gel. Elution with mixtures of ethyl acetate–benzene gave 37 mg (62%) of the bromo spiro ketal **16** as a pale yellow oil. Although TLC showed the product to be essentially homogeneous, the NMR spectrum and HPLC (4 mm × 30 cm column, μ-Porasil, $CHCl_3$) clearly indicated that it was a mixture of two epimers (ca. 1:1): MS, *m/e* (relative intensity) 496 and 498 (M^+, 9), 395 and 397 (22), 365 and 367 (20), 351 and 353 (100), 254 (19), 45 (24).

A stirred solution of 35 mg of (0.07 mmol) of the above mixture **16** and 35 mg (0.7 mmol) of NaCN in 3 mL of DMF was heated at 70 °C for 14 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed thoroughly with water and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave a yellow oil, which was chromatographed on 3 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 26 mg (84%) of a mixture of the nitriles **17a** and **17b** as a pale yellow oil. The NMR spectrum and HPLC (4 mm × 30 cm column, μ-Porasil, 100:1 $CHCl_3$–MeOH) indicated that it was a mixture of two epimers (ca. 2.2:1): MS, *m/e* (relative intensity) 443 (M^+, 9), 342 (22), 312 (48), 298 (100), 45 (33).

A solution of 17 mg (0.038 mmol) of the above nitriles (**17a**/**17b** ratio of 2.2) in 1 mL of Ac_2O and 2.5 mL of pyridine was allowed to stand at room temperature for 4 days. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed thoroughly with water and dried ($MgSO_4$). Removal of the solvent gave a pale yellow oil showing two spots on TLC due to the presence of two epimers. The residue was subjected to preparative TLC (ethyl acetate–benzene, 1:1) to afford 8.5 mg (46%) of **18a** and 3.5 mg (19%) of **18b**, R_f 0.30 and 0.40 (benzene–ethyl acetate 1:1), respectively.

18a (colorless needles from ether): mp 180–181 °C; $[\alpha]^{24}_D$ +25.8° (*c* 0.062, $CHCl_3$); IR (KBr) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H, *J* = 6 Hz, CH_3), 1.88 (td, 1 H, *J* = 11, 4 Hz, H-5′$_{ax}$), 2.13 (ddd, 1 H, *J* = 11, 4, 2 Hz, H-5′$_{eq}$), 2.20 (s, 3 H, $COCH_3$), 2.46 (s, 3 H, OCH_2OCH_3), 2.77 (dd, 1 H, *J* 16, 8 Hz, H-4), 2.81 (dd, 1 H, *J* = 16, 2 Hz, H-11), 2.98 (dd, 1 H, *J* = 16, 9 Hz, H-11), 3.14 (dd, 1 H, *J* = 16, 3 Hz, H-4), 3.83 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.11 (d, 1 H, *J* = 8 Hz, OCH_2O), 4.47 (d, 1 H, *J* = 8 Hz, OCH_2O), 4.45 (m, 1 H, H-3), 4.67 (dqd, 1 H, *J* = 11, 6, 2 Hz, H-6′), 5.27 (d, 1 H, H-3′), 5.48 (q, 1 H, *J* = 4 Hz, H-4′), 7.53 (m, 2 H, Ar H), 8.10 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 485 (M^+, 35), 342 (60), 312 (100), 298 (42), 297 (62), 143 (15), 45 (10); exact mass calcd for $C_{26}H_{31}NO_8$ 485.2048, found 485.2066. Anal. Calcd for $C_{26}H_{31}NO_8$: C, 64.31; H, 6.44; N, 2.89. Found: C, 64.61; H, 6.40; N, 2.93.

18b (colorless oil): IR (neat) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, 3 H, *J* = 6 Hz, CH_3), 1.87 (td, 1 H, *J* = 11, 4 Hz, H-5′$_{ax}$), 2.03 (ddd, 1 H, *J* = 11, 4, 2 Hz, H-5′$_{eq}$), 2.17 (s, 3 H, $COCH_3$), 2.41 (s, 3 H, CH_2OCH_3), 2.65 (dd, 1 H, *J* = 17, 7 Hz, H-11), 2.95 (dd, 1 H, *J* = 17, 7 Hz, H-11), 3.12 (dd, 1 H, *J* = 17, 4 Hz, H-4), 3.32 (dd, 1 H, *J* = 17, 5 Hz, H-4), 3.94 (s, 3 H, OCH_3), 3.99 (d, 1 H, *J* = 8 Hz, OCH_2O), 4.01 (s, 3 H, OCH_3), 4.43 (d, 1 H, *J* = 8 Hz, OCH_2O), 4.67 (dqd, 1 H, *J* = 11, 6, 2 Hz, H-6′), 4.89 (m, 1 H, H-3), 4.94 (d, 1 H, *J* = 4 Hz, H-3′), 5.46 (q, 1 H, *J* = 4 Hz, H-4′), 7.53 (m, 2 H, Ar H), 8.07 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 485 (M^+, 37), 342 (58), 312 (100), 298 (40), 297 (65), 143 (17), 45 (13); exact mass calcd for $C_{26}H_{31}NO_8$ 485.2048, found 485.2044.

5,10-Dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1-(*S*)-spiro-2′-[4′(*S*)-hydroxy-3′(*S*)-(methoxymethoxy)-6′-(*S*)-methyltetrahydropyran]-3(*R*)-ylacetic Acid (19). To a stirred solution of 191 mg (0.43 mmol) of the nitriles **17a**/**17b** (ratio of 2.2) in 8 mL of ethanol were successively added 34 mL of 30% KOH and 1 mL of 30% H_2O_2, and the mixture was heated at 40 °C for 1 h. The mixture was then stirred and heated at reflux for 4 h. After being cooled at 0 °C, the mixture was acidified with 10% HCl and extracted with ethyl acetate. The combined organic extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow solid, which was recrystallized from ether to afford 168 mg (84%) of the acid **19** as colorless needles: mp 179–181 °C; $[\alpha]^{24}_D$ +26.8° (*c* 0.164, $CHCl_3$); IR (KBr) 3600–2400, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 3 H, *J* = 7 Hz, CH_3), 2.74 (s, 3 H, CH_2OCH_3), 2.80 (dd, 1 H, *J* = 16, 7 Hz, H-4), 2.87 (d, 2 H, *J* = 9 Hz, H-11), 3.16 (dd, 1 H, *J* = 16, 3 Hz, H-4), 3.90 (s, 3 H, OCH_3), 4.03 (s, 3 H, OCH_3), 4.27 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.52 (d, 1 H, *J* = 6 Hz, OCH_2O), 5.12 (d, 1 H, *J* = 4 Hz, H-3′), 7.55 (m, 2 H, Ar H), 8.10 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 462 (M^+, 10), 361 (20), 331 (19), 317 (100); exact mass calcd for $C_{24}H_{30}O_9$ 462.1888, found 462.1921. Anal. Calcd for $C_{24}H_{30}O_9 \cdot 0.5H_2O$: C, 61.14; H, 6.63. Found: C, 61.31; H, 6.62.

5,10-Dimethoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1-(*S*)-spiro-2′-[4′(*S*)-acetoxy-3′(*S*)-hydroxy-6′-(*S*)-methyltetrahydropyran]-3(*R*)-ylacetic Acid (20). A solution of 168 mg (0.36 mmol) of the acid **19** in 12 mL of Ac_2O and 16 mL of pyridine was allowed to stand at room temperature for 4 days. The reaction mixture was diluted with water and extracted with $CHCl_3$. The combined organic extracts were washed with water and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave a yellow oil, which was dissolved in 3 mL of 10% HCl and 30 mL of dimethoxyethane and stirred at 50 °C for 4 h. The reaction mixture was partitioned between ethyl acetate and water, and the aqueous layer was separated and then extracted with ethyl acetate. The combined organic extracts were washed with water and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded a yellow oil which was subjected to preparative TLC ($CHCl_3$–MeOH, 5:1) to give 100 mg (60%) of the acid **20** as a pale yellow oil: IR (neat) 3700–2400, 1735, 1715 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (d, 3 H, *J* = 7 Hz, CH_3), 2.14 (s, 3 H, $COCH_3$), 2.71 (dd, 1 H, *J* = 16, 12 Hz, H-4), 2.80–2.98 (**ABX** system, 2 H, H-11), 3.21 (dd, 1 H, *J* = 16, 2 Hz, H-4), 3.89 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.34 (**ABX** system, 1 H, H-3), 4.64 (m, 1 H, H-6′), 5.03 (m, 1 H, H-3′), 5.31 (q, 1 H, *J* = 4 Hz, H-4′), 7.52 (m, 2 H, Ar H), 8.07 (m, 2 H, Ar H); MS, *m/e* (relative intensity) 460 (M^+, 10), 317 (62), 316 (100); exact mass calcd for $C_{24}H_{28}O_9$ 460.1732, found 460.1788.

(+)-9-Deoxygriseusin B (3). To a stirred solution of 75 mg (0.163 mmol) of the acid **20** in 5 mL of THF were successively added 200 mg (1.6 mmol) of AgO and 0.5 mL of 6 N HNO_3 at room temperature. After being stirred for 10 min, the mixture was filtered. The filtrate was partitioned between ethyl acetate and water, and the aqueous layer was separated and then extracted with ethyl acetate. The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent afforded a yellow solid, which was recrystallized from acetone–ether, giving 51 mg (72%) of the compound **3** as yellow cubes: mp 196–198 °C; $[\alpha]^{24}_D$ +55.7° (*c* 0.122, DMF); IR (KBr) 3700–2400, 1720, 1665 cm^{-1}; NMR ($CDCl_3$) δ 1.17 (d, 3 H, *J* = 6 Hz, CH_3), 1.88–2.13 (m, 2 H, H-5′), 2.08 (s, 3 H, $COCH_3$), 2.42 (dd, 1 H, *J* = 19, 12 Hz, H-4), 2.74 (dd, 1 H, *J* = 16, 8 Hz, H-11), 2.85 (dd, 1 H, *J* = 16, 4 Hz, H-11), 2.93 (dd, 1 H, *J* = 19, 3 Hz, H-4), 4.24 (m, 1 H, H-3), 4.77 (d, 1 H, *J* = 4 Hz, H-3′), 5.25 (q, 1 H, *J* = 4 Hz, H-4′), 7.73 (m, 2 H, Ar H), 9.06 (m, 2 H, Ar H). Anal. Calcd for $C_{22}H_{22}O_9$: C, 61.39; H, 5.15. Found: C, 61.31; H, 5.24.

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Registry No. **3**, 83312-72-5; **4**, 72251-97-9; **5**, 83312-73-6; **6**, 83312-74-7; **7**, 83333-49-7; **8**, 83312-75-8; **9**, 83312-76-9; **10**, 83312-77-0; **11**, 83312-78-1; **12**, 80089-60-7; **13** (isomer 1), 83312-79-2; **13** (isomer 2), 83376-26-5; **14**, 83333-50-0; **16** (isomer 1), 83312-80-5; **16** (isomer 2), 83377-33-7; **17a**, 83312-81-6; **17b**, 83376-25-4; **18a**, 83377-34-8; **18b**, 83312-82-7; **19**, 83312-83-8; **20**, 83312-84-9; **21**, 83312-85-0; **22**, 83312-86-1; **23**, 83312-87-2; **24**, 83312-88-3; *N,N′*-thiocarbonyldiimidazole, 6160-65-2; griseusin A, 59554-11-9; griseusin B, 59554-12-0.