Pyranonaphthoquinone Antibiotics. 4. Total Synthesis of (+)-Griseusin A, an Enantiomer of the Naturally Occurring Griseusin A

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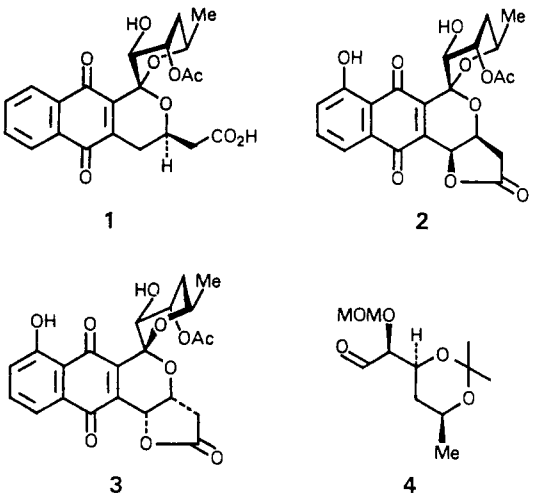
The first total synthesis of (+)-griseusin A (2) has been achieved. The properly functionalized 1,4,5-trihydroxynaphthalene derivative 9 prepared from 3-bromojuglone (7) via 2-allylation with 3-butenoic acid was successively treated with *t*-BuLi and L-dideoxygulose derivative 4 to give the carbinol 10. The corresponding ketone 11 obtained by PCC oxidation was transformed to bromo spiro ketals 12a,b by reaction with aqueous *N*-bromoacetamide followed by acid-catalyzed intramolecular ketalization. Reaction of 12a,b with NaCN and hydrolysis of the resulting nitriles 13 provided a single carboxylic acid, 14, from which (+)-griseusin B (16) was obtained by three steps: O-acetylation, removal of the methoxymethyl group, and AgO oxidation. Finally, (+)-griseusin A, an enantiomer of naturally occurring griseusin A, was obtained by known aerial oxidation in pyridine.

Griseusin A, an antibiotic produced by a strain of *Streptomyces griseus*, is structurally unique among members of a family of pyranonaphthoquinone antibiotics in that it contains a 1,7-dioxaspiro[5.5]undecane ring system.[1] In the previous paper,[2] we reported the chiral synthesis of (+)-9-deoxygriseusin B (1, Chart I) which possessed the same absolute configuration that had been assigned to the naturally occurring griseusin A, and it was proposed on the basis of comparison of their CD spectra that the structure 2 for griseusin A should be revised to the mirror image 3.[3] We have now completed the first total synthesis of (+)-griseusin A (2), the result providing unambiguous evidence to support the previous conclusion.

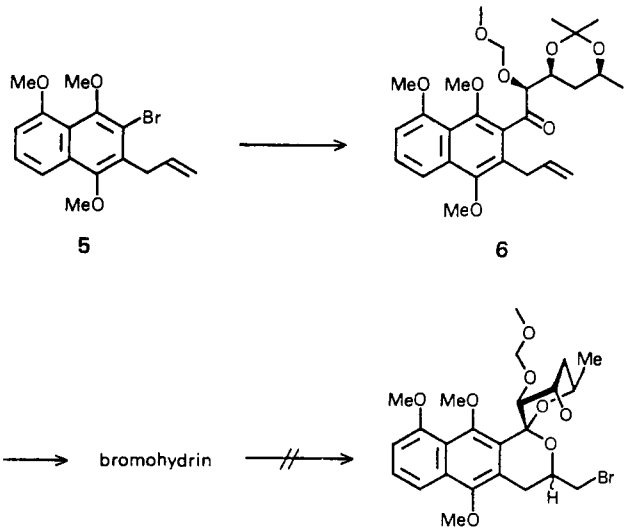
In line with the synthetic strategy for 1, we initiated the synthesis of 2 starting with 2-allyl-3-bromo-1,4,5-trimethoxynaphthalene (5)[4] which would serve as a precursor of the pyranojuglone moiety. Coupling of the lithiation product of 5 with L-dideoxygulose derivative 4[2] followed by oxidation of the resulting carbinol with pyridinium chlorochromate (PCC)[5] afforded the naphthyl ketone 6 (Scheme I). Intramolecular ketalization of the bromohydrin derived from 6, however, could not be achieved under a variety of acidic conditions, presumably owing to the steric hindrance associated with the peri methoxy groups.

In order to overcome the trouble in the crucial step, we sought an alternative protecting group for the peri hydroxyls that would exert no serious steric hindrance in the spiroketalization and fulfil the additional requirements: moderate stability toward acid treatment required for removal of the other protecting groups and feasibility in oxidative generation of the juglone structure. Either the isopropylidene or methylidene group seemed to be a reasonable candidate. On the basis of the model experiments dealing with 1,4,5-trihydroxynaphthalene which showed the isopropylidene group to be more promissing, the selected compound 9 has been prepared as follows (Scheme II).

Chart I



Scheme I



(1) (a) Tsuji, N.; Kobayashi, M.; Wakisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot.* **1976**, *29*, 7. (b) Tsuji, N.; Kobayashi, M.; Terui, Y.; Tori, K. *Tetrahedron* **1976**, *32*, 2207.

(2) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4725.

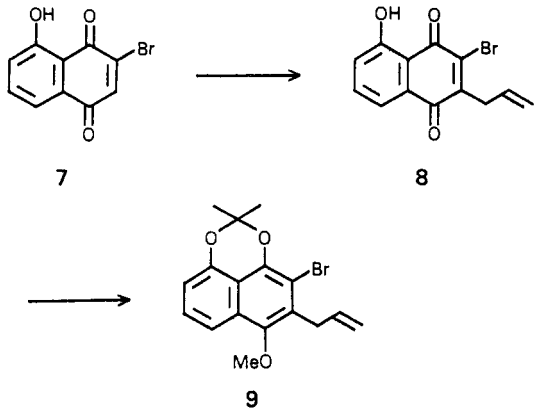
(3) According to a private communication from Dr. Tsuji (Shionogi Research Laboratory, Osaka), his group has recently reached to the same conclusion through X-ray crystallographic study.

(4) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.

(5) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

0022-3263/83/1948-2311$01.50/0

Scheme II



Reaction of 3-bromojuglone (7)[6] with 3-butenoic acid in the presence of silver nitrate and ammonium persulfate at 70 °C for 1.5 h gave 2-allyl-3-bromojuglone (8) in 56% yield. The naphthoquinone 8 was reduced with a large excess sodium hydrosulfite to give the unstable hydroquinone, which was immediately treated with acetone and 2,2-dimethoxypropane in the presence of perchloric acid and then subjected to O-methylation with dimethyl sulfate to afford the acetonide 9 in an overall yield of 63%.

With the properly functionalized naphthalene 9 in hand, we proceeded to the coupling of 9 with L-gulose derivative 4. Treatment of 9 with *t*-BuLi in THF at −78 °C followed by addition of 4 produced the epimeric carbinols 10 in 65% yield. Oxidation of 10 with PCC in dichloromethane at room temperature was extremely slow, giving a 51% yield of 11 with 28% recovery of 10 after 40 h. Addition of HOBr to the olefinic bond of 11 by using aqueous *N*-bromoacetamide followed by selective removal of the acetonide protecting group on the sugar moiety by brief treatment with HCl produced a mixture of the two bromo ketals **12a** and **12b** (ratio = ca. 1:2) in 56% yield. These diastereomers were separated by preparative TLC, and their stereostructures were determined as indicated in the structures (Scheme III) on the basis of their ^{1}H NMR spectral data in which a marked difference in chemical shifts of the H-3 protons due to an anisotropy of the adjacent naphthalene nucleus was diagnostic for the isomers: δ 4.29 for **12a** (H-3_{ax}) and δ 4.78 for **12b** (H-3_{eq}).[7] Reaction of the mixture of **12a** and **12b** with excess sodium cyanide in Me_2SO at 80 °C for 3 h gave diastereomeric nitriles **13** in 83% yield. The nitriles were then hydrolyzed with ethanolic potassium hydroxide in the presence of hydrogen peroxide to afford the carboxylic acid **14** as a single stereoisomer in 61% yield. Epimerization at the C(3) center from a 3*S* to a more stable 3*R* configuration under basic conditions had already been recorded with the 9-deoxy analogue.[2]

Acetylation of 14 with acetic anhydride in pyridine followed by selective removal of the methoxymethyl group with HCl in dimethoxyethane (0.25 N) at 50 °C for 5 h produced the quinone precursor **15** possessing the correct functional groups on the sugar moiety in 58% yield. When treated with silver(II) oxide in the presence of nitric acid,[8] the compound 15 was smoothly oxidized to afford (+)-griseusin B (**16**): mp 208–210 °C; $[\alpha]^{25}_D$ +318° (MeOH);[9] 82% yield. Finally, γ-lactone formation of 16 was accomplished by aerial oxidation in pyridine to give (+)-griseusin A (**2**): mp 161–164 °C; $[\alpha]^{25}_D$ +166° (EtOH);[10] 63% yield. The spectral data (IR, ^{1}H NMR, and mass) and the TLC behavior of the synthetic (+)-griseusin A were identical with those of the naturally occurring (−)-griseusin A, and their CD spectra were mirror images in shape and amplitude.

Experimental Section

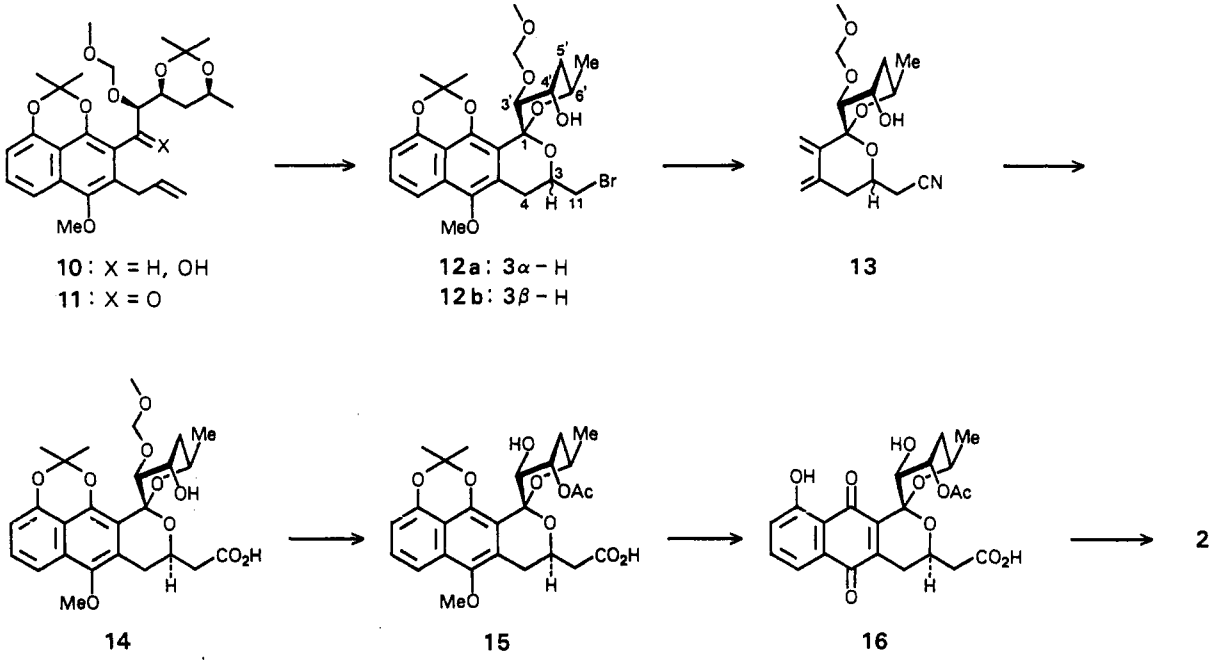
Infrared spectra (IR) were recorded on a Hitachi 215 spectrometer and were calibrated with the 1601-cm^{-1} absorption of polystyrene. Proton nuclear magnetic resonance spectra (NMR) were taken on a Varian XL-200 (200 MHz) or a JEOL MH-100 (100 MHz) spectrometer in deuteriochloroform. Chemical shifts were reported in parts per million (δ) downfield from internal tetramethylsilane. Resonance patterns were reported as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. EI mass spectra (MS) were obtained on a Hitachi RMU-6MG (low resolution) or JEOL JMS-D300 spectrometer combined with a JMA-2000 data processing system (low and high resolutions). Optical rotations were measured on a JASCO DIP automatic polarimeter, and circular dichroism spectra (CD) were recorded on a JASCO J-20 spectrometer. Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of Toyama Medical and Pharmaceutical University. For chromatography, the following adsorbents were used: column, Merck silica gel 60 (70–230 mesh); analytical thin layer, Merck precoated silica gel 60 F_{254} plates; preparative thick layer, Merck silica gel 60 $F_{254+366}$. Dry solvents were obtained by using standard procedures. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in the workup, and removal of the solvents was performed with a rotary evaporator at a reduced pressure.

2-Allyl-3-bromo-5-hydroxy-1,4-naphthoquinone (8). To a stirred suspension of 0.1 g (0.4 mmol) of 3-bromojuglone (7) and 20 mg (0.12 mmol) of silver nitrate in 2 mL of acetonitrile and 0.8 mL of H_2O at 70 °C were added a solution of 51 mg (0.6 mmol) of 3-butenoic acid in 0.4 mL of acetonitrile at once and then a solution of 158 mg (0.7 mmol) of ammonium persulfate in 1.1 mL of H_2O dropwise over 20 min. The mixture was stirred at 75 °C for 1.5 h, diluted with water, and extracted with ethyl acetate. The extract was washed with water and dried. Removal of the solvent under reduced pressure afforded a reddish brown solid, which was chromatographed on 3 g of silica gel. Elution with benzene afforded 65 mg (56%) of the quinone 8 as a red solid. The analytical sample was obtained by recrystallization from benzene as red cubes: mp 100–101 °C; IR (KBr) 1660 cm^{-1}; NMR δ 3.57 (d, 2 H, J = 6 Hz, CH_2), 5.00–5.40 (m, 2 H, CH=CH_2), 5.55–6.66 (m, 1 H, CH=CH_2), 7.10–7.30 (m, 1 H, Ar H), 7.55–7.70 (m, 2 H, Ar H), 11.68 (s, 1 H, OH); MS, *m/e* (relative intensity) 292 and 294 (M^+, 23), 213 (100). Anal. Calcd for $C_{13}H_9O_3Br$: C, 53.27; H, 3.09. Found: C, 53.29; H, 3.09.

2-Allyl-3-bromo-4,5-(isopropylidenedioxy)-1-methoxynaphthalene (9). A solution of 1.0 g (3.4 mmol) of the quinone 8 in 100 mL of ether was vigorously shaken with 50 mL of saturated aqueous sodium hydrosulfite solution. The ethereal solution was washed with water and dried, and the solvent was removed below 15 °C. To a solution of the residue in 25 mL of acetone were added 2.5 mL of 2,2-dimethoxypropane and 0.25 mL of 70% perchloric acid, and the mixture was stirred at room temperature for 15 h under nitrogen. After addition of 1.0 g of $NaHCO_3$, the reaction mixture was stirred for 30 min and filtered, and the filtrate was concentrated to give a brown oil. To a mixture of the residual oil and 5 mL (53 mmol) of dimethyl sulfate was added dropwise 40 mL of 20% KOH over 20 min under nitrogen, and the mixture was stirred at room temperature for 2 h. 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

(6) Hannan, R. L.; Barber, R. B.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2153.
(7) For detailed discussion on the stereochemistry of the spiro ketal moiety, see ref 2.
(8) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(9) Natural griseusin B: mp 210 °C; $[\alpha]^{24.5}_D$ −190.2° (DMF).[1]
(10) Natural griseusin A: mp 165–167 °C; $[\alpha]^{23.5}_D$ −147.8° ($CHCl_3$);[1] $[\alpha]^{25}_D$ −168° (EtOH) measured in our laboratory.

Scheme III



and dried. Removal of the solvent under reduced pressure gave a pale yellow oil, which was chromatographed on 20 g of silica gel. Elution with hexane afforded 750 mg (63%) of the naphthalene **9** as a pale yellow oil. The analytical sample was obtained by distillation: bp 140–150 °C (1 mmHg); NMR δ 1.62 (s, 6 H, 2 CH_3), 3.68 (d, 2 H, J = 6 Hz, CH_2), 4.80–5.10 (m, 2 H, CH=CH_2), 5.70–6.20 (m, 1 H, CH=CH_2), 6.72 (d, 1 H, J = 8 Hz, Ar H), 7.32 (d, 1 H, J = 8 Hz, Ar H), 7.42 (t, 1 H, J = 8 Hz, Ar H); MS, m/e (relative intensity) 348 and 350 (M^+, 100), 333 and 335 (30), 291 and 293 (36), 254 (41). Anal. Calcd for $C_{17}H_{17}O_3Br$: C, 58.47; H, 4.91. Found: C, 58.41; H, 4.98.

2-Allyl-4,5-(isopropylidenedioxy)-3-[3(*S*),5(*S*)-(isopropylidenedioxy)-2(*S*)-(methoxymethoxy)hexanoyl]-1-methoxynaphthalene (11). To a stirred solution of 430 mg (1.23 mmol) of **9** in 5 mL of dry THF at −78 °C under nitrogen was added 0.81 mL (1.7 M in pentane, 1.38 mmol) of *t*-BuLi over 3 min. After being stirred at the same temperature for 10 min, the reddish brown solution was treated with a solution of 114 mg (0.49 mmol) of the aldehyde **4** in 2 mL of dry THF and then stirred at −78 °C for 30 min. The pale yellow mixture was quenched with 1 mL of water and partitioned between ethyl acetate and water. The aqueous layer was separated and extracted with ethyl acetate. The combined organic layers were washed with brine and dried. Removal of the solvent gave a pale yellow oil, which was chromatographed on 5 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 159 mg (65%) of the epimeric carbinol **10** as a pale yellow oil, showing two spots on TLC due to epimers: MS, m/e (relative intensity) 502 (M^+, 23), 299 (100), 298 (98).

To a stirred solution of 102 mg (0.47 mmol) of PCC in 35 mL of CH_2Cl_2 was added a solution of 159 mg (0.32 mmol) of **10** in 7 mL of CH_2Cl_2 at room temperature, and the mixture was stirred for 40 h. The reaction mixture was diluted with 40 mL of ether, stirred with 3 g of Florisil gel for 10 min, and then filtered. Concentration of the filtrate gave a pale yellow oil, which was chromatographed on 3 g of silica gel. Elution with mixtures of ethyl acetate–benzene afforded 81 mg (51%) of the ketone **11** as a colorless oil and 45 mg (28%) of the starting material **10**. For **11**: $[\alpha]^{23}_D$ +57.0° (c 1.28, $CHCl_3$); IR (neat) 1705, 1630 cm^{-1}; NMR δ 1.17 (d, 3 H, J = 6 Hz, CH_3), 1.20 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.69 (s, 6 H, 2 CH_3), 3.32 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.80 (s, 2 H, OCH_2O), 5.00–5.25 (m, 2 H, Ar H); MS, m/e (relative intensity) 500 (M^+, 20), 297 (100); exact mass calcd for $C_{28}H_{36}O_8$ 500.2408, found 500.2425.

3(*R*)-(Bromomethyl)-9,10-(isopropylidenedioxy)-5-methoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1(*S*)-spiro-2′-4′(*S*)-hydroxy-3′(*S*)-(methoxymethoxy)-6′(*S*)-methyltetrahydropyran (12a) and 3(*S*)-(Bromomethyl)-9,10-(isopropylidenedioxy)-5-methoxy-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1(*S*)-spiro-2′-4′(*S*)-hydroxy-3′(*S*)-(methoxymethoxy)-6′(*S*)-methyltetrahydropyran (12b). To a stirred solution of 60 mg (0.12 mmol) of the ketone **11** in 8 mL of acetone at 0 °C were added 0.8 mL of 2.7 N $HClO_4$ and 18.5 mg (0.13 mmol) of *N*-bromoacetamide. After being stirred at 0 °C for 20 min, the reaction mixture was treated with 0.8 mL of 10% HCl and then stirred at room temperature for 30 min. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with 5% $NaHCO_3$ and brine and dried. Removal of the solvent afforded a pale yellow oil, which was chromatographed on 3 g of silica gel. Elution with mixtures of ethyl acetate–benzene gave 36 mg (56%) of a mixture of bromo spiro ketals **12a** and **12b** (ratio ca. 1:2 by NMR). The analytical samples were obtained by preparative TLC (benzene–ethyl acetate, 1:1) as colorless oils.

12a: R_f 0.65 (benzene–ethyl acetate, 1:1); $[\alpha]^{26}_D$ +61.3° (c 0.587, $CHCl_3$); IR (neat) 3550 cm^{-1}; NMR δ 1.24 (d, 3 H, J = 7 Hz, CH_3), 1.56 (s, 3 H, CH_3), 1.78 (s, 3 H, CH_3), 2.11 (ddd, 1 H, J = 13, 4, 2 Hz, H-5′$_{eq}$), 2.74 (dd, 1 H, J = 16, 11 Hz, H-4), 2.97 (s, 3 H, CH_3OCH_2), 3.18 (dd, 1 H, J = 16, 2 Hz, H-4), 3.69 (d, 2 H, J = 7 Hz, H-11), 3.85 (s, 3 H, OCH_3), 4.29 (m, 1 H, H-3), 4.34 (d, 1 H, J = 7 Hz, CH_3OCH_2), 4.53 (d, 1 H, J = 7 Hz, CH_3OCH_2), 4.69 (dqd, 1 H, J = 13, 7, 2 Hz, H-6′), 4.79 (d, 1 H, J = 4 Hz, H-3′), 6.84 (d, 1 H, J = 8 Hz, Ar H), 7.44 (t, 1 H, J = 8 Hz, Ar H), 7.58 (d, 1 H, J = 8 Hz, Ar H); MS, m/e (relative intensity) 538 and 540 (M^+, 31), 393 and 395 (100); exact mass calcd for $C_{25}H_{31}O_8Br$ 538.1203 and 540.1183, found 538.1249 and 540.1227.

12b: R_f 0.60 (benzene–ethyl acetate, 1:1); $[\alpha]^{26}_D$ +52.9° (c 1.27, $CHCl_3$); IR (neat) 3550 cm^{-1}; NMR δ 1.22 (d, 3 H, J = 7 Hz, CH_3), 1.58 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 2.07 (ddd, 1 H, J = 13, 4, 2 Hz, H-5′$_{eq}$), 2.90 (s, 3 H, CH_3OCH_2), 3.10–3.70 (m, 4 H, H-3 and H-11), 3.87 (s, 3 H, CH_3), 4.26 (d, 1 H, J = 7 Hz, CH_3OCH_2), 4.50 (d, 1 H, J = 4 Hz, H-3′), 4.54 (d, 1 H, J = 7 Hz, CH_3OCH_2), 4.65 (dqd, 1 H, J = 13, 7, 2 Hz, H-6′), 4.78 (m, 1 H, H-3), 6.88 (d, 1 H, J = 8 Hz, Ar H), 7.48 (t, 1 H, J = 8 Hz, Ar H), 7.63 (d, 1 H, J = 8 Hz, Ar H); MS, m/e (relative intensity) 538 and 540 (M^+, 30), 393 and 395 (100); exact mass calcd for $C_{25}H_{31}O_8Br$ 538.1203 and 540.1183, found 538.1172 and 540.1183.

9,10-(Isopropylidenedioxy)-5-methoxy-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 (14). A stirred solution of 70 mg (0.13 mmol) of a mixture of the spiroketals **12a**/**12b** and 70 mg (1.4 mmol) of NaCN in 7 mL of Me_2SO was heated at 80 °C for 3 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed thoroughly with water and dried. Removal of the solvent gave a yellow oil, which was chromatographed on 2 g of silica gel. Elution with mixtures of ethyl

acetate–benzene afforded 52 mg (83%) of the nitrile **13** as a pale yellow oil (a mixture of epimers, ratio ca. 2:1 by NMR): MS, *m/e* (relative intensity) 485 (M^+, 35), 340 (100).

To a solution of 52 mg (0.11 mmol) of the above nitrile **13** in 7.5 mL of ethanol were successively added 13 mL of 30% KOH and 2.8 mL of 30% H_2O_2, and the mixture was heated at 40 °C for 1 h and then at reflux for 2 h. After being cooled at 0 °C, the mixture was acidified with 10% HCl and extracted with ethyl acetate. The extract was washed with water and dried. Removal of the solvent gave a pale yellow oil, which was subjected to preparative TLC ($CHCl_3$–MeOH, 9:1) to afford 33 mg (61%) of the acid **14** as a colorless oil: $[\alpha]^{25}_D$ +48.0° (*c* 0.2, $CHCl_3$); IR (neat) 3600–2500, 1725 cm^{-1}; NMR δ 1.21 (d, 3 H, *J* = 6 Hz, CH_3), 1.54 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3), 2.96 (s, 3 H, CH_3OCH_2), 2.70–3.20 (m, 4 H, H-4 and H-11), 3.86 (s, 3 H, OCH_3), 4.36 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.42 (m, 1 H, H-6′), 4.50 (m, 1 H, H-3), 4.55 (d, 1 H, *J* = 6 Hz, OCH_2O), 4.79 (d, 1 H, *J* = 4 Hz, H-3′), 6.84 (d, 1 H, *J* = 8 Hz, Ar H), 7.44 (t, 1 H, *J* = 8 Hz, Ar H), 7.59 (d, 1 H, *J* = 8 Hz, Ar H); MS, *m/e* (relative intensity) 504 (M^+, 67), 359 (100); exact mass calcd for $C_{26}H_{32}O_{10}$ 504.1993, found 504.1976.

9,10-(Isopropylidenedioxy)-5-methoxy-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 (15). A solution of 45 mg (0.09 mmol) of the acid **14** in 6 mL of acetic anhydride and 8 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 extract was washed with water and dried. Removal of the solvent gave a yellow oil, which was dissolved in a mixture of 2 mL of 10% HCl and 20 mL of dimethoxyethane and stirred at 50 °C for 5 h. The reaction mixture was partitioned between ethyl acetate and water, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water and dried. Removal of the solvent afforded a yellow oil, which was subjected to preparative TLC ($CHCl_3$–MeOH, 9:1) to give 26 mg (58%) of the acid **15** as a pale yellow oil: $[\alpha]^{25}_D$ +29.0° (*c* 0.54, $CHCl_3$); IR (neat) 3600–2500, 1735, 1715 cm^{-1}; NMR δ 1.18 (d, 3 H, *J* = 6 Hz, CH_3), 1.59 (s, 3 H, CH_3), 1.72 (s, 3 H, CH_3), 2.15 (s, 3 H, $COCH_3$), 2.70 (dd, 1 H, *J* = 16, 2 Hz, H-4), 2.80-3.00 (**ABX** system, 2 H, H-11), 3.22 (dd, 1 H, *J* = 16, 2 Hz, H-4), 3.88 (s, 3 H, OCH_3), 4.30 (m, 1 H, H-6′), 4.62 (**ABX** system, 1 H, H-11), 4.80 (d, 1 H, *J* = 4 Hz, H-3′), 5.34 (q, 1 H, *J* = 4 Hz, H-4′), 6.85 (d, 1 H, *J* = 8 Hz, Ar H), 7.44 (t, 1 H, *J* = 8 Hz, Ar H), 7.59 (d, 1 H, *J* = 8 Hz, Ar H); MS, *m/e* (relative intensity) 502 (M^+, 27), 359 (93), 358 (100); exact mass calcd for $C_{26}H_{30}O_{10}$ 502.1837, found 502.1820.

(+)-Griseusin A (2). To a stirred solution of 26 mg (0.05 mmol) of the acid **15** in 1.5 mL of THF were successively added 62 mg (0.5 mmol) of AgO and 0.15 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 extracted with ethyl acetate. The combined extracts were washed with water and dried. Removal of the solvent afforded an orange solid, which was subjected to preparative TLC ($CHCl_3$–MeOH, 9:1) to give 19 mg (82%) of (+)-griseusin B (**16**): mp 208–210 °C (MeOH); $[\alpha]^{25}_D$ +318° (*c* 0.071, MeOH); IR (KBr) 3600–2500, 1730, 1640 cm^{-1}; NMR δ 1.21 (d, 3 H, *J* = 6 Hz, CH_3), 1.80–2.15 (m, 2 H, H-5′), 2.12 (s, 3 H, $COCH_3$), 2.43 (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), 2.94 (dd, 1 H, *J* = 19, 3 Hz, H-4), 4.30 (dqd, 1 H, *J* = 13, 6, 2 Hz, H-6′), 4.56 (m, 1 H, H-3), 4.81 (m, 1 H, H-3′), 5.29 (q, 1 H, *J* = 4 Hz, H-4′), 7.30 (m, 1 H, Ar H), 7.62 (m, 2 H, Ar H).

A solution of 19 mg of **16** in 2 mL of pyridine was allowed to stand at room temperature for 15 h. Removal of the solvent afforded an orange residue, which was subjected to preparative TLC (ethyl acetate–benzene, 1:1), giving 12 mg (63%) of (+)-griseusin A (**2**): mp 161–163 °C (MeOH); $[\alpha]^{25}_D$ +166° (*c* 0.038, EtOH); NMR δ 1.22 (d, 3 H, *J* = 6 Hz, CH_3), 1.91 (td, 1 H, *J* = 11, 4 Hz, H-5′$_{ax}$), 2.10 (ddd, 1 H, *J* = 11, 4, 2 Hz, H-5′$_{eq}$), 2.12 (s, 3 H, $COCH_3$), 2.47 (d, 1 H, *J* = 12 Hz, OH), 2.72 (d, 1 H, *J* = 17 Hz, H-11), 3.07 (dd, 1 H, *J* = 17, 5 Hz, H-11), 4.18 (dqd, 1 H, *J* = 11, 6, 2 Hz, H-6′), 4.81 (dd, 1 H, *J* = 5, 3 Hz, H-3), 4.95 (dd, 1 H, *J* = 12, 4 Hz, H-3′), 5.29 (q, 1 H, *J* = 4 Hz, H-4′), 5.31 (d, 1 H, *J* = 3 Hz, H-4), 7.33 (m, 1 H, Ar H), 7.70 (m, 2 H, Ar H), 11.94 (s, 1 H, OH); CD (EtOH) $[\theta]_{525}$ 0, $[\theta]_{500}$ +755, $[\theta]_{465}$ +3750, $[\theta]_{400}$ +1480, $[\theta]_{358}$ 0, $[\theta]_{300}$ −9800, $[\theta]_{287}$ −11 470, $[\theta]_{276}$ 0, $[\theta]_{270}$ +14 000.

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Defensive Metabolites from Three Nembrothid Nudibranchs[1]

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The nembrothid nudibranchs *Tambje abdere*, *T. eliora*, and *Roboastra tigris* all contain tambjamines A–D (**4–7**). The aldehydes **1–3**, produced during extraction with methanol, were key compounds in the structural elucidation. The tambjamines were traced to a food source, the bryozoan *Sessibugula translucens*, and were implicated in the chemical defense mechanism of the *Tambje* species.

Roboastra tigris Farmer 1978[2] is a large carnivorous nembrothid nudibranch that is known to prey on two smaller nembrothid nudibranchs, *Tambje eliora* (Marcus and Marcus, 1967)[3] and *Tambje abdere* Farmer 1978.[2] Methanolic extracts of all three nudibranchs contained the same group of biologically active bipyrroles **1–7** although the aldehydes **1–3** were subsequently shown to be artifacts of the extraction procedure. The tambjamines A–D (**4–7**) were traced to a dietary source, the ectoproct (bryozoan) *Sessibugula translucens* Osburn 1950,[4] and were impli-

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