Bioactive Cyclopentenone Derivatives from Marine Isolates of Fungi

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As part of an effort to discover bioactive natural products from marine sources, we investigated the bioactive secondary metabolites from two marine isolates of the fungi, Trichoderma viride and Rhizopus stolonifer. Three cyclopentenones, myrothenones A (1) and B (2) and trichodenone A (3), were isolated from T. viride and two cyclopentenones, 2-bromomyrothenone B (4) and botrytinone (5), were isolated from R. stolonifer. The molecular structures and absolute stereochemistries of the cyclopentenones were determined from chemical and physicochemical evidence, including quantum chemistry calculations, X-ray analysis, and the circular dichroism (CD) exciton chirality method. Myrothenone A (1) displays tyrosinase inhibitory activity, with an \( IC_{50} \) value of 6.6 µM, and is therefore more active than the positive control, kojic acid.

Key Words: Trichoderma viride, Rhizopus stolonifer, Cyclopentenone, Myrothenone, Botrytinone

Introduction

Cyclopentenone is ubiquitous among natural and non-natural organic molecules, and its derivatives play important roles in chemistry and biology because the \( \alpha,\beta \)-unsaturated carbonyl group of cyclopentenone is an electrophilic center susceptible to addition reactions with nucleophiles. Simple cyclopentenones are not only reactive functional groups in biological systems,1 to addition reactions with nucleophiles. Simple cyclopentenones include antimitotic,4 antiinflammatory,7 cyclooxygenase 2 (COX-2) inhibitory,18 cytotoxic,4,6,19 NF-kB inhibitory,10,11 antimicrobial,9,12-15,17 antipigment,12-14 and plant-growth-regulatory activities.12-14,17 The cyclopentenones have several asymmetric centers in the molecule. Therefore, we are interested in their chemical and biological aspect as well as their structure-activity relationships (SARs). As part of an effort to discover biologically active natural products, including cyclopentenones, from marine sources, we investigated the bioactive secondary metabolites of two marine isolates of the fungi, T. viride and R. stolonifer, and isolated three cyclopentenones,20 myrothenones A (1) and B (2) and trichodenone A (3) from T. viride, isolated from the edible marine red alga, Gracilaria verrucosa, and two cyclopentenones,21 2-bromomyrothenone B (4) and botrytinone (5), from R. stolonifer, isolated from the edible marine brown alga, Sargassum horneri.

Experimental

General. Optical rotation was determined on a Perkin Elmer model 341 polarimeter. CD spectra were taken on a JASCO J-715 spectropolarimeter. UV/Visible spectra were measured on a Hitachi U-2001 UV/Vis spectrometer. IR spectra were recorded on a Bruker FT-IR model IFS-88 spectrometer. 1H (400 MHz) and 13C NMR (100 MHz) spectra were obtained on a JEOL JNM-ECP 400 NMR spectrometer, using TMS or solvent peaks as reference standard. MS spectra were obtained on a JEOL JMS-700 spectrometer. Single-crystal X-ray measurements were performed on a Bruker SMART CCD diffractometer.

Fungal isolation and culture. Two fungal strains, MFA811 and MFB063, were isolated from the surface of the edible marine red alga Gracilaria verrucosa and from the surface of the edible marine brown alga Sargassum horneri, collected at Yokji Island of Gyeongnam, Korea in 2008, and identified as T. viride and R. stolonifer based on 18S rRNA analyses (Solgent Co., Ltd., Daejeon, Korea), identities of each 100%, respectively. Two voucher specimens are deposited at Pukyong National University with the code MFA811 and MFB063. Two fungal strains were cultured (1 L × 20) for three weeks (static) at 29°C in SWS medium consisted of soytone (0.1%), soluble starch (1.0%), and seawater (100%).

Extraction and isolation. The cultured media of T. viride and R. stolonifer were filtered through cheesecloth to give
mycelium and broth. The filtered broths were extracted with EtOAc to afford broth extracts of T. viride (1.2 g) and of R. stolonifer (1.0 g), respectively. The broth extract of T. viride was purified by assay-guided fractionation using repeated silica gel flash chromatography (n-hexane in ethyl acetate) and HPLC (ODS-A, MeOH/H2O = 5:1) to yield three cyclo-pentenones, myrothenones A (1) (9.5 mg) and B (2) (10.4 mg) and trichodenone A (3) (4.6 mg). While, the broth extract of R. stolonifer was subjected to silica gel flash chromatography. Elution was performed with n-hexane-EtOAc (stepwise, 0 - 100% EtOAc) to yield four fractions. Fractions 2 and 3 were further purified by HPLC (YMC, ODS-A) utilizing a 30 min gradient program of 50% to 100% MeOH in H2O to furnish 4 (9.3 mg) and 5 (6.6 mg), respectively.

**Myrothenone A (1):** A colorless oil; [α]_D^20 = +61° (c 0.6, MeOH); IR (KBr) 3419, 3240, 1683, 1603, 1554, 1524, 1410, 1318, 1189, 1093, 1005 cm⁻¹; 1H and 13C NMR, see Table 1; EIMS (MeOH); IR (KBr) 3390, 3210, 1630, 1552, 1414, 1271, 1221, 1189, 1078, 1074, 1022 cm⁻¹; 1H and 13C NMR spectral data. See Table 1 for NMR spectral data.

The crystallographic data 2a. C₁₄H₁₂BrNO₃, Mᵣ = 232.16, T = 298 (2) K, λ = 0.71069 Å, monoclinic, P2₁, a = 5.6300 (10), b = 5.6855 (3), c = 20.7151 (3) Å, β = 94.8500 (10), V = 660.6 (2) Å³, Z = 2, dcalc = 1.169 Mg m⁻³, F(000) = 324. The final R and wR values with 3375 Friedel pair reflections (I > 2σ(I)) were 0.0502 and 0.0541, respectively. An absolute structure parameter, χ = -0.02 (1). Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (deposit No. CCDC 256884).

**Synthesis of myrothenone A (1).** Formic acid (0.5 mL) (12.7 mmol) and DCC (5 mg) was added to a solution of myrothenone B (2) (10 mg) (0.5 mmol) in pyridine at 0 °C under N₂ atmosphere, then the mixture was stirred for 3 hours. Work-up of the reaction mixture as described above for p-bromobenzoylation yielded a product, which was purified by column chromatography (n-hexane-EtOAc = 20 : 1) to furnish myrothenone A (8 mg). Synthetic compound was shown to be identical with myrothenone A (1) by TLC, [α]_D, H-NMR and 13C-NMR.

**p-Bromobenzoylation of botrytine (5).** p-Bromobenzoyl chloride (0.3 mL) was added to a solution of botrytine (5) (10 mg) (0.06 mmol) in pyridine (0.5 mL) under N₂ atmosphere, then the mixture was stirred at r.t. for 1 hour. Work-up of the reaction mixture as described above for p-bromobenzoylation yielded products, which were purified by column chromatography (n-hexane-EtOAc = 10 : 1) to furnish p-bromobenzoate derivatives 5a (7 mg) and 5b (2 mg).

**p-Bromobenzoate derivative (5a).** Colorless tetragonal prisms (n-hexane and acetone); CD (MeOH) [α]_D, 1H-NMR and 13C-NMR.

**p-Bromobenzoate derivative (5b).** A amorphous solid (n-hexane and acetone); CD (MeOH) [α]_D, 1H-NMR and 13C-NMR.

**Crystallographic data and data collection parameters.** A colorless tetragonal prism of 5a was obtained by recrystallization from n-hexane and acetone. A single crystal with dimensions of 0.42 × 0.22 × 0.21 mm was used for X-ray diffraction data on Bruker SMART CCD diffractometer employing graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) in the ω-2θ scan mode at 120 K. The data were corrected for absorption (T_max = 0.924 T_min = 0.537) with SADAPs. The structure was solved by a direct

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methods of SHELXS-97, and refined by SHELXL-97 using 3151 reflections \([I > 2.0 \sigma(I)]\) for 263 parameters. The final values are \(R1 = 0.0495\), \(wR2 = 0.1317\), and \(GOF = 1.016\).

**Crystallographic data.** \(C_{21}H_{15}Br_2ClO_5\), triclinic with space group P-1, with \(a = 6.6847(5) \text{ Å}, b = 12.1890(9) \text{ Å}, c = 13.078(1) \text{ Å}, \alpha = 83.984(1)^\circ, \beta = 80.366(1)^\circ, \gamma = 84.514(1)^\circ, V = 1041.5(1) \text{ Å}^3\), and \(Z = 2\). Crystallographic data for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre (deposition number CCDC 615055). Copies of the data can be obtained, free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html, from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; (Fax: +44-1223/336033; E-mail: deposit@ccdc.cam.ac.uk).

**Results and Discussion**

A broth extract of *T. viride* showed antityrosinase activity, which was purified by assay-guided isolation to produce three cyclopentenones derivatives (1-3). Two cyclopentenones, myrothenones A (1) and B (2), were obtained in the form of colorless oils. Myrothenone A (1) is unstable at room temperature, so determination of the structure was commenced from myrothenone B (2).

The molecular formula of 2 was demonstrated to be \(C_{11}H_{9}NO_3\) (four unsaturations) with HRFABMS and \(^{13}C\) NMR methods. The IR absorption spectrum of 2 shows bands characteristic of hydroxyl and amino groups (3390 cm\(^{-1}\)) and enone (1630 cm\(^{-1}\)) functionality. The \(^1\)H and \(^{13}C\) NMR spectra, including DEPT, showed the presence of one carbonyl, one terminal vinyl, one primary amine, one oxygenated sp\(^2\)-quaternary carbon, and one diastereotopic methylene group. However, the assignment of two sp\(^2\)-canbons, \(\delta_c 95.8\) and 174.7, was confused because both signals were observed considerably upfield and downfield, respectively, as signals of double bond. The \(\alpha\) - and \(\beta\)-carbon signals of enamine are deshielded and shielded from the resonance effect of the enamine group, respectively.\(^{22}\) Consideration of the resonance structure of enamine and the two chemical shifts, upfield and downfield, respectively, suggests the presence of an aliphatic enamine group in the molecule. The presence of a 3-aminoenone chromophore is also supported by UV spectral data \([\lambda_{max} 203 \text{ nm (log} \varepsilon 4.1)\] for 263 parameters. Detailed analysis of the spectral data, including 2D NMR data, established the full assignment of the NMR signals and the molecular structure of 2, except for the stereochemistry at the asymmetric center.

To determine the absolute sterechemistry of 2, an X-ray diffraction analysis of the \(p\)-bromobenzoyl derivative, \(3-(p\)-bromobenzyloxy\)myrothenone B (2a), was performed. The crystal structure is shown in Figure 1. The bond distances and angles are all normal. The C-1, C-2, C-3, and C-4 atoms are in a plane, with a maximum deviation of 0.004 Å, and C-5 is displaced toward a beta-orientation from the plane of the other four carbon atoms [diagonal angle : 15.1 (0.5)]. Therefore, cyclopentenone 2 shows a typical envelope geometry. The absolute configuration of the asymmetric center of 2 has been unambiguously determined to be \(5R\) by refinement of the Flack parameter.\(^{23}\)

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**Figure 1.** An ORTEP III drawing of \(p\)-bromobenzoate (2a). Displacement ellipsoids are drawn at 30% probability level.

Myrothenone A (1) is unstable, and the NMR signals measured at room temperature were deformed. Therefore, all the NMR signals were obtained at low temperature (\(-50^\circ \text{C}\)). The HRFABMS and \(^{13}C\) NMR methods established that the molecular formula is \(C_7H_8NO_2\). The general features of its UV, IR, and NMR spectra closely resemble those of myrothenone B (2), except for the appearance of additional signals for one proton and one carbon \([\delta_H 8.11 (H-9), \delta_c 164.1 (C-9)]\) (Table 1). Detailed analyses of the \(^1\)H and \(^{13}C\) NMR spectra of 1, including the results of DEPT, HMOC, and HMBC experiments, suggest that 1 is a formamide derivative of 2.\(^{24}\) The key HMBC correlation from H-9 to C-3 was critical in establishing the location of the aldehyde group, as shown. On the basis of these data, the structure of myrothenone A is proposed to be the 5-ethenyl-3-formamido-5-hydroxy-2-cyclopenten-1-one (1). To clarify the structure of 1, we synthetized 1 from 2 with a formylation reaction using formic acid and 1,3-dicyclohexylcarbodiimide as the base.\(^{25}\) The spectral data for the synthetic compound were identical to those for myrothenone A (1) in all respects. Accordingly, the absolute stereostructure of myrothenone A was determined to be \(5(S)-5\-ethenyl-3\-formamido-5\-hydroxy-2\-cyclopenten-1\-one (1)\. Vinylicyclopentenone analogues have been reported as artifacts and conjugated adducts, but natural products of this class with an amino group (1, 2) are very rare.

During a search for bioactive constituents of marine microorganisms, we isolated two cyclopentenone derivatives, bromomyrothenone B (4) and botryrinone (5), from a broth extract of *R. stolonifer*. Bromomyrothenone B (4) is a colorless oil with isotopic cluster (a ratio of 1:1) at \(m/z\) 217 and 219 in its mass spectrum, suggesting the presence of a bromine atom. The molecular formula of 4 was shown to be \(C_{31}H_{21}BrNO_2\) (four unsaturations) by HREIMS and \(^{13}C\) NMR methods. The IR absorption spectrum of 4 shows bands characteristic of hydroxyl and amino groups (3321 cm\(^{-1}\)) and enone (1630 cm\(^{-1}\)) functionalities. The general features of the UV, IR, and NMR spectra of 4 closely resemble those of myrothenone B (2), except that the NMR signals at C-2 are changed from the sp\(^2\)-methine \([\delta_H 4.70 (s, H-2), \delta_c 95.8 (C-2)]\) of myrothenone B (2) to an sp\(^2\)-quaternary carbon \([\delta_H 86.1 (C-2)]\) in 4. The \(^1\)H and \(^{13}C\) NMR spectra of 4, including DEPT, show a monosubstituted double bond, a tetrasubstituted double bond, a primary amine, an oxygenated quaternary carbon, a carbonyl carbon,
and a diastereotopic methylene. The presence of a 1,2,3,4-tetrasubstituted enone chromophore is further supported by the UV spectral data (210 nm (log ε 3.7), 277 (4.2)) and by the characteristic double bond carbon signals (δ 86.1 (C-2), 169.6 (C-3)) located considerably upfield and downfield.20 Detailed analysis of the 1H and 13C NMR spectra of 4, including the results of DEPT, HMQC, and HMBC experiments, suggest that metabolite 4 is a 2-bromide derivative of myrothenone B (2). The stereochemistry illustrated for 4 is based on optical rotation, which established that myrothenone B (2) and 4 have an identical R configuration at C-5 from the same phase of the optical rotation (α R = 61°), induced mainly by the substituent at C-5, to that of myrothenone B (2) (α R = 35°).20 This conclusion is further supported by a comparison of the CD data for myrothenone B (2) and 4. The CD spectrum of 4 is similar to that of myrothenone B (2) and shows a positive Cotton effect at 289 nm (Δε 2.9) and a negative Cotton effect at 265 (−1.4), indicating that both compounds share the same configuration at the asymmetric center. Based on the evidence described above, the stereostructure of bromomyrothenone B was determined to be (5R)-3-amino-2-bromo-5-ethenyl-5-hydroxy-2-cyclopenten-1-one (4).

Botrytinone (5) is a colorless oil, and a molecular formula of C₃H₁₄O₅, with three degrees of unsaturation, was established by HREIMS and 13C NMR methods. The IR absorption spectrum of 5 shows bands characteristic of hydroxyl (3335 cm⁻¹) and enone (1716 cm⁻¹) functionalities. The 1H and 13C NMR spectra, including DEPT, show one methyl, three oxygenated methines, one trisubstituted double bond, and one carbonyl carbon. Detailed analyses of the 1H and 13C NMR spectra of 5, including the results of COSY and TOCSY experiments, suggest the presence of the functional groups 1-substituted hydroxyethyl, 1,2-disubstituted ethyleneglycol, and 1,3,3-trisubstituted propenone, and the full assignment of the NMR signals. The presence of a 1,3,3-trisubstituted enone chromophore is further supported by a UV absorption band at 225 nm (log ε 3.8). The connection of the functional groups in 5 was determined on the basis of HMBC. Diagnostic HMBC correlations, from H-2 to C-4 and C-5, from H-4 to C-2 and C-3, from H-5 to C-1, from H-6 to C-2, C-3, and C-4, and from H-7 to C-3, showed the connections C1-C5, C3-C4, and C3-C6 in 5. On the basis of all the foregoing evidence, the planar structure was easily determined to be 4,5-dihydroxy-3-(1-hydroxyethyl)-2-cyclopenten-1-one, although the stereochemistry was still not established. To assign the configuration at the asymmetric centers, we analyzed the NOESY data in detail. However, decisive NOE correlations supporting the stereochemistry were not detected. This is because 5 has a flexible side chain with a chiral center, and displayed complex conformational behavior in the NOE experiment. However, the configurations at C-4 and C-5 were considered to be in trans when the coupling constant between H-4 and H-5 in 5 (JH4, H5 = 3.0 Hz) was compared with those of previously reported trans stereoisomers of (+)-terrein (J = 2.3 Hz), cis-terrein diacetate (J = 2.9 Hz),29 and dihydroterrein diacetate (J = 2.9 Hz),29 and the cis stereoisomers of (+)- and (-)-isoterrein (J = 5.7 Hz).12 At the moment, the configuration at C-6 has not been assigned. To determine the configuration at C-6 and to confirm the trans configuration at C-4 and C-5, a quantum chemistry calculation was performed. However, because none of the values calculated were in good agreement with the experimental values, no definitive assignment of the configurations could be made. Therefore, we used an X-ray method to determine the configurations at the asymmetric centers. p-Bromobenzylation of 5 with p-bromobenzoyl chloride in pyridine yielded two unusual p-bromobenzotate-5-chloride derivatives, 5a and its 5-epimer (5b). The two products (5a and 5b) showed coupling constants of JH4, H5 = 3.0 Hz for 5a and JH4, H5 = 5.9 Hz for 5b, indicating trans and cis conformations between H-4 and H-5, respectively.12

### Table 1. NMR Spectroscopic Data (400 MHz, DMSO-d₆) for Myrothenones A (1), B (2), Bromomyrothenone B (4), and Botrytinone (5).a

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*aRecorded in CD3OD at 400 MHz (1H) and 100 MHz (13C) at −50°C.*
The stereochemistry and reaction mechanism were further supported by the CD data for both products (5a, 5b). The CD spectra of 5a and 5b revealed the same negative Cotton effect at 243 nm (Δε = -39.9) and 245 nm (Δε = -1.07), indicating that both products share the same conformation at C-4, retained during the reaction. Therefore, we infer that these two products were formed from the nucleophilic substitution of 5-OH by a chloride ion in the S1 reaction during the benzoylation of 5. Recrystallization of 5a and 5b from n-hexane-acetone only produced crystals of 5a. The crystal structure of 5a, with its relative configuration, is shown in Figure 2. The absolute configuration of 5a was determined with the CD exciton chirality method. The CD spectrum of 5a shows a negative first Cotton effect at 243 nm (Δε = -39.9), attributed to the enone-benzoate chromophores. The π-π* excitation of the enone group is expected to be perturbed mainly by the two allylic 4- and 6-benzoate groups. The dihedral angles between enone and 4- and 6-benzoate are 45.3° and 0.9°, respectively. Therefore, 4-benzoate interacts mainly with the enone π-π* maxima to produce the first negative Cotton effect, which demonstrates the enone-benzoate chirality. This indicates the 4R and 6R configuration in 5a and consequently, the 4R, 5S, and 6R configuration of botrytinone (5). On the basis of these data, the absolute stereostructure of botrytinone was determined to be (4R,5S,6R)-4,5-dihydroxy-3-(1-hydroxyethyl)-2-cyclopenten-1-one (5). The cyclopentenones isolated are small and simple molecules. Therefore, we could easily determine their molecular structures, except that of botrytinone (5). This is because botrytinone (5) has a flexible side chain with an asymmetric center, and exhibited complex conformational behavior in the NOE experiments. We tested the cyclopentenones (1-5) for radical scavenging, antimicrobial, and anti-tumor activities, and they exhibited a weak antityrosinase activity except for compound 1. Myrothecium A (1) shows potent tyrosinase inhibitory activity, with an ED50 value of 6.6 μM, more active than a positive standard, kojic acid (ED50 = 7.7 μM). The cyclopentenones (1-5) have already been isolated from the marine derived fungi, Myrothecium sp. and Botrytis sp., isolated from the marine green alga Enteromorpha compressa. Even though they were isolated from the different genus of the marine-derived fungus, it is likely that they all derive from common or same biogenetic intermediates, presumably as part of a polyketide origin. We are now under extensive examination of cyclopentenones for better biosynthetic pathway, and the results will be reported in due course.

Acknowledgments. This research was supported in part by a grant from Marine Biotechnology Program funded by Ministry of Land, Transport and Maritime Affairs, Republic of Korea and in part by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund)(KRF-2008-314-F00048). Mass spectral data were kindly provided by the Korea Basic Science Institute. The second Brain Korea 21 graduate fellowship grant to students is gratefully acknowledged (0625-B-600285).

References

30. A full list of crystallographic data and parameters is deposited at Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (deposition number CCDC 615055).