Ann Microbiol (2010) 60:249–253
DOI 10.1007/s13213-010-0034-3

ORIGINAL ARTICLE

Chemical constitutes from endophytic *Streptomyces* sp. W5 isolated from *Trewia nudiflora* L.

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Received: 9 October 2009 / Accepted: 2 March 2010 / Published online: 25 March 2010

Abstract Strain W5 was isolated from stem of *Trewia nudiflora* L. and identified as a member of *Streptomyces* according to its 16S rDNA partial sequence. From extracts of fermentation medium of W5, a new γ-butyrolactone (**1**), together with nine known compounds [2-methyl-2,5-bornandiol (**2**), dimeric dinactin (**3**), (*R*)-2-((2*R*,5*S*)-tetrahydro-5-(2-oxopropyl)furan-2-yl)propanoic acid (**4**), 2-(5-(2-acetoxypropyl)-tetrahydrofuran-2-yl) propanoic acid (**5/6**), (±)-homononactic acid (**7/8**), (±)-nonactic acid (**9/10**)] was isolated. Their structures were elucidated on the basis of extensive spectroscopic data.

Keywords *Streptomyces* sp. W5 · *Trewia nudiflora* L. · 16S rDNA · Chemical constitute · Spectroscopic data

Introduction

Endophytic microorganisms take up residence in the tissues of almost all plants, usually causing no apparent symptoms of disease (Sturz et al. 2000; Tan and Zou 2001). The endophyte/host relationship is believed to be complex and probably varies from host to host and microbe to microbe (Sturz et al. 2000). Many are able to synthesize bio-active compounds that can be used by the plant for defence against pathogenic microorganisms and/or insect and vertebrate herbivores (Owen and Hundley 2004). Some of these compounds had been proven useful for novel drug discovery (Owen and Hundley 2004; Ryan et al. 2008). *Trewia nudiflora* L. (Euphorbiaceae, distributed mainly in southwest of China, India and Malaysia) is a rich source of maytansinoids (Powell et al. 1982, 1983). Up to now, no evidence has been found that maytansinoids were present in the individual plant and in cell culture (Pullen et al. 2003). Endophytes, however, may be responsible for biosynthesis of maytansinoids because several types of ansamysins isolated to date are well-known bacterial metabolites (Higashide et al. 1977; Yu et al. 2002; Snipes et al. 2007). To understand whether biosynthesis of maytansinoids is associated with endophytes, an endophytic microorganism was isolated from *Trewia nudiflora* L. As part of our investigation into the chemical constituents of endophytic microorganisms from this plant, we investigated the secondary metabolites produced by *Streptomyces* sp. W5. Herein, we report the identification of strain W5, and the isolation and structural elucidation of compounds **1-10**, including a new γ-butyrolactone (**1**).

Materials and methods

Microorganism isolation and identification

Stems of *Trewia nudiflora* L. were obtained from the greenhouse of the Kunming Institute of Botany (Yunnan Province, P.R. China) in October 2003. Stem (0.5–1.5 cm in diameter) was surface-sterilized by washing with 75% ethanol (1 min), then rinsed twice with sterile water followed by submersion in 1% sodium hypochlorite and 0.12% mercuric chloride (50 ml, 1:1, v/v) (6 min), before

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being rinsed with sterile water seven times. After washing with sterile water, the stem was cut longitudinally into segments (0.2 cm thickness) under sterile conditions and placed on YMG medium (0.4% yeast extract, 1% malt extract, 0.4% glucose and 1.5% agar, pH 7.2), and incubated at 28°C until colony or mycelium surrounding the segments appeared. After culturing for a further 10 days, a strain had appeared and was isolated from the sterilized stem. This organism—named W5—has been deposited at the Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, P.R. China.

Pulverized mycelia of W5 was lysed for 2 h by exposure to 1% SDS in buffer A (500 mM Tris-HCl, pH 8.0, 20 mM EDTA, 10 mM NaCl) containing 200 mg/ml proteinase K (Merck, Darmstadt, Germany). The samples were extracted by phenol/chloroform (1:24, v/v) treatment (3×), precipitated with isopropanol, rinsed DNA in 75% aqueous ethanol (2×), air-dried and dissolved in buffer B (10 mM Tris-HCl, pH 8.0, 1 mM EDTA, pH 8.0).

For polymerase chain reaction (PCR) amplification of 16S rRNA partial sequence, the primer pair 27F and 1492R was used to target bacterial genomes (Lane et al. 1985). The reaction system contained DNA template (100 ng), primers (0.5 mM), dNTP (0.2 mM), 10× *Ex-Taq* buffer (Takara, Tokyo, Japan), and *Ex-Taq* (1.25 U; Takara) was incubated in a thermal cycler (Eppendorf, http://www.eppendorf.com/). Conditions consisted of 10 min of predenaturation at 95°C, 30 cycles of 40 s of denaturation at 95°C, annealing at 55°C for 40 s, elongation at 72°C for 90 s, plus 1 additional cycle with a final 10-min chain elongation. The 1.5 kb PCR products were purified on a UNIQ-10 column using a DNA gel-extraction kit (Shanghai Sangon Biotechnology, Shanghai, P.R. China), and ligated into pMD18-T vector (Takara). Chemically competent *Escherichia coli* DH10B was prepared, and plasmids were introduced by a standard method (Sambrook and Russell 2001). Three randomly picked clones were sequenced on an ABI PRISM 3730 sequencer (Applied Biosystems, Foster City, CA) to verify the insert fragment. The partial 16S rDNA sequence was assembled using Vector NTI Advance 10 software (http://www.invitrogen.com), and blasted against the latest GenBank database, using BLASTn (http://www.ncbi.nlm.nih.gov).

Spectroscopic measurements and chromatography

Column chromatography (CC) was performed on silica gel H (200–300 mesh, 10–40 μm; Qingdao Marine Chemical Factory, China), on Sephadex LH-20 (Amersham Pharmacia, Uppsala, Sweden); on reverse-phase C_{18} (RP-18) silica gel (40–70 μm, Merck); thin layer chromatography (TLC) was performed on silica gel GF_{254} (10–40 μm, Qingdao). All solvents were distilled before use. UV Spectra: Shimadzu 2401PC spectrophotometer; λ_{max} log (ε) in nm. IR Spectra: Bio-Rad FTS-135 spectrophotometer with KBr discs; in cm^{-1}. Optical rotation: Jasco DIP-370 polarimeter. NMR Spectra: Bruker AM-400 or DRX-500 spectrometers; chemical shifts δ in ppm rel. to Me_4Si, coupling constants *J* in Hz. HR-ESI, ESI-MS and FAB-MS: Finnigan LCQ-Advantage and VG Auto-Spec-3000 mass spectrometers, respectively; in *m/z*.

Extraction and isolation of compounds

Strain W5 was cultured on YMG solid medium (20 L) for 14 days at 28°C. The culture was extracted five times with EtOAc-MeOH-AcOH (80:15:5, v/v) exhaustively to give an extract (5.307 g). The extract was subjected to medium pressure liquid chromatography (MPLC) over RP-18 silica gel (40–75 μm, 160 g) eluted with H_2O, 30, 50, 70 and 100% MeOH (3 L each gradient) to yield five fractions. The 50% MeOH fraction (1.7 g) was subjected to CC (silica gel; $CHCl_3$/MeOH, 20:1→1:1) to afford four fractions: Fr-1–Fr-4. Fr-1 (275 mg) was subjected to CC (silica gel; $CHCl_3$/MeOH 20:1→10:1) to afford Fr-1-1 to Fr-1-4, and further purified by CC over Sephadex LH-20 eluted with MeOH to provide **2** (2 mg), **4** (4 mg), **5/6** (8 mg), **7/8** (35 mg), **9/10** (5 mg), respectively. Fr-4 (16 mg) was subjected to CC (silica gel; $CHCl_3$/MeOH, 20:1→10:1) to afford Fr-4-1, then Fr-4-1 was further purified by column chromatography over Sephadex LH-20 eluted with MeOH to provide **1** (2 mg). The 70% MeOH fraction (380 mg) was subjected to CC over Sephadex LH-20 eluted with MeOH to afford two fractions: Fr1 and Fr2. Fr2 was further chromatographed on silica gel using petroleum ether/acetone/formic acid gradient system (from 20:1:0.1 to 5:1:0.025) to afford Fr2-1, then Fr2-1 was further subjected to column chromatography over Sephadex LH-20 eluted with acetone to provide **3** (25 mg).

Results and discussion

Identification of strain W5

Based on its partial sequence of the 16S rRNA gene, the strain W5 was identified as a member of the genus *Streptomyces* and its 16S rDNA partial sequence was submitted to GenBank under accession number EU429478.

Structure determination of compounds 1-10

Compound **1** was obtained as white amorphous power. [α]=−61.7 (*c*=0.21, MeOH). UV (MeOH): 220 (2.85). IR (KBr): 3,423, 2,932, 1,753, 1,181. Its molecular formula was determined to be $C_{15}H_{28}O_5$ by ESI-MS (*m/z* 311

Table 1 ^{1}H- (400 MHz) and ^{13}C-NMR (100 MHz) data of compound **1** (In CD_3OD; δ in ppm, *J* in Hz)

Position	δ(H)	δ(C)	HMBC
1	–	179.5	–
2	2.60 (dd, *J*=6.6, 3.2)	49.5	1,3,5,6,7
3	2.68-2.71 (m)	42.2	1,2,5,6
4	4.43 (t, *J*=8.3, H_α)	70.9	1,3,5
	4.10 (dd, *J*=8.9, 6.0, H_β)		1,2,3,5
5	3.63 (dd, *J*=5.8, 3.2)	63.6	2,3,4
6	3.84–3.87 (m)	72.4	1,3,7,8
7	1.72–1.75 (m)	35.1	8,9
	1.54–1.58 (m)		6,8,9
8	1.48–1.52 (m)	27.3	7
	1.35–1.37 (m)		–
9	1.27–1.30 (m)	30.6	7
10	1.38–1.40 (m)	25.3	11,12
	1.34–1.36 (m)		–
11	1.31–1.33 (m)	31.3	10,12
12	1.43–1.46 (m)	44.8	10,11,13
	1.40–1.42 (m)		11,13
13	–	71.5	–
14	1.17 (s)	29.1	12,13
15	1.17 (s)	29.1	12,13

$[M+Na]^+$), which was further confirmed by HR-ESI-MS (*m/z* 327.1569 $[M+K]^+$, calc. 327.1573). The IR spectrum of **1** showed absorption at 3,423 cm^{-1} and 1,753 cm^{-1} indicative of the presence of hydroxyl and carbonyl groups, respectively. The ^{13}C-NMR spectrum of **1** showed 15 carbon signals, which were identified with the assistance of its DEPT spectrum as two methyls, eight methylenes, three methines, and two quaternary carbons. From the NMR spectra (Table 1), compound **1** was suggested to be a butanolide compound (Yamada et al. 1987; Kondo et al. 1989). In the HMBC spectrum of **1**, correlations between H-4 (δ_H 4.10) and the C-atoms at δ_C 179.5 (C-1), 49.5 (C-2), and 42.2 (C-3); between H-3 and the C-atoms at δ_C 179.5 (C-1) and 49.5 (C-2); between H-2 and the C-atoms at δ_C 179.5 (C-1) and 42.2 (C-3) to establish the linkage of the lactone unit. Moreover, other HMBC data (Table 1) confirmed the presence of a tail of long fatty chain: correlation between the protons of Me(C-14/C-15) and C-atoms at δ_C 71.5 (C-13) and 44.8 (C-12), correlation between H-12 (δ_H 1.43-1.46) and C-atoms at δ_C 25.3 (C-10), 31.3 (C-11), 71.5 (C-13), and other correlations (Table 1). The coupling constant between H-2 and H-3 was 6.6 Hz and this value suggested that the configuration of two substituents on butanolide ring is cis (Yamada et al. 1987). Therefore, compound **1** was identified as cis-2-(1′,8′-dihydroxy-8′-methylnonyl)-3-hydroxymethylbutanolide (Fig. 1).

Compound **2**

White amorphous power, [α]=−4.2 (c=0.24, MeOH). ^{1}H-NMR (500 MHz, CD_3OD) δ: 0.79 (s, Me-1′), 0.89 (s, Me-7′), 1.12 (s, Me-7″), 1.28 (dd, *J* = 11.5, 4.0, H_β-6), 1.30 (s, Me-2′), 1.75 (t, *J*=4.5, H-4), 1.79 (d, *J* = 13.1, H_α-3), 1.82 (t, *J* = 11.5, H_α-6), 2.12 (d, *J* = 13.1, H_β-3), 4.25–4.27 (m, H-5); ^{13}C-NMR (100 MHz, CD_3OD) δ: 10.7 (C-1′), 21.6 (C-7″), 22.6 (C-7′), 26.0 (C-(2′), 38.1 (C-3), 42.0 (C-6), 51.0 (C-7), 52.6 (C-4), 54.3 (C-1), 70.6 (C-5), 80.0 (C-2). ESI-MS: 185 $[M+H]^+$. The compound was identified as 2-methyl-2,5-bornandiol (**2**; Fig. 1) (Tang et al. 2000).

Compound **3**

Pale yellow oil, [α]=0.0 (c=0.55, MeOH). ^{1}H-NMR (500 MHz, CD_3OD) δ: 0.94 (t, *J*=7.5, CH_2CH_3-8′), 1.07 (d, *J* = 7.0, Me-2), 1.09 (d, *J* = 7.0, Me-2′), 1.22 (d, *J* = 10, Me-8), 1.30-1.32 (m, CH_2CH_3-8′), 1.42-1.45 (m, CH_2CH_3-8′), 1.50-1.53 (m, H_β-5, H_α-7, H_β-5′), 1.61-1.65 (m, H_β-4, H_β-4′, H_α-7′), 1.67-1.70 (m, H_β-7), 1.76-1.78 (m, H_β-7′),

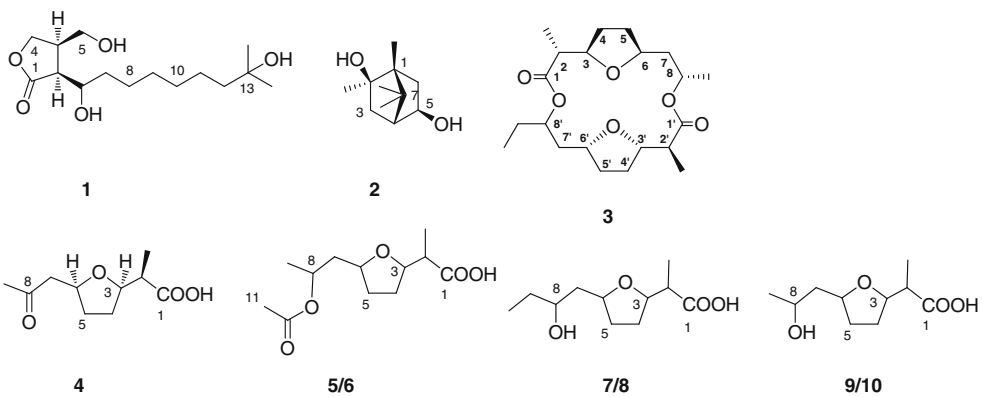

Fig. 1 Structures of compounds **1**–**10**

1.96–1.98 (m, H_{α}-4, H_{α}-4′), 2.00-2.03 (m, H_{α}-5, H_{α}-5′), 2.41–2.43 (m, H-2, H-2′), 3.89–3.91 (m, H-6), 3.94–3.96 (m, H-3′), 3.98–4.00 (m, H-6′), 4.02–4.05 (m, H-3), 4.80–4.83 (m, H-8′), 4.97–4.99 (m, H-8); ^{13}C-NMR (100 MHz, CD_3OD) δ: 10.3 (CH_2CH_3-8′), 13.9 (Me-2), 14.0 (Me-2′), 20.7 (Me-8), 29.3 (C-4), 29.6 (C-4′), 31.6 (CH_2CH_3-8′), 32.4 (C-5), 32.4 (C-5′), 43.8 (C-7), 44.1 (C-7′), 47.3 (C-2), 47.5 (C-2′), 70.7 (C-8), 71.3 (C-8′), 77.6 (C-6), 78.0 (C-6′), 82.2 (C-3′), 82.3 (C-3), 176.3 (C-1), 176.6 (C-1′). ESI-MS: 383 $[M+H]^+$. Compound **3** was determined to be dimeric dinactin (**3**; Fig. 1) by comparison their spectroscopic data with the corresponding literature data (Zhao et al. 2005).

Compound **4**

Pale yellow oil, [α]=−13.3 (c=0.35, MeOH). ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.11 (d, *J*=7.0, Me-2′), 1.53-1.56 (m, H-4), 1.64–1.66 (m, H-5), 1.84–1.87 (m, H-4), 2.07–2.09 (m, H-5), 2.16 (s, Me-9), 2.53-2.56 (m, H-2), 2.59–2.61 (m, H-7), 2.74–2.76 (m, H-7), 4.07–4.10 (m, H-3), 4.20–4.23 (m, H-6); ^{13}C-NMR (100 MHz, CD_3OD) δ: 13.9 (C-2′), 29.3 (C-4), 30.5 (C-9), 31.9 (C-5), 46.7 (C-2), 48.5 (C-7), 76.9 (C-6), 81.7 (C-3), 178.6 (C-1), 210.2 (C-8). ESI-MS: 201 $[M+H]^+$. Based on its spectroscopic data, the compound was considered to be (*R*)-2-((2*R*,5*S*)-tetrahydro-5-(2-oxopropyl)furan-2-yl)propanoic acid (**4**; Fig. 1) (Arco et al. 1976).

Compounds **5/6**

Inseparable mixture of two enantiomers, pale yellow oil, [α]=+3.1 (c=0.5, $CHCl_3$). ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.11 (d, *J*=7.0, Me-2′), 1.23 (d, *J*=6.3, Me-9), 1.53–1.56 (m, H-4), 1.66–1.69 (m, H-5), 1.75–1.76 (m, H-7), 1.95–1.98 (m, H-4), 2.01 (s, Me-11), 2.03–2.05 (m, H-5), 2.43–2.45 (m, H-2), 3.88–3.91 (m, H-3), 3.95–3.97 (m, H-8), 3.99–4.01 (m, H-6); ^{13}C-NMR (100 MHz, CD_3OD) δ: 13.9 (C-2′), 20.8 (C-11), 21.3 (C-9), 29.4 (C-4), 32.2 (C-5), 43.5 (C-7), 46.8 (C-2), 70.6 (C-8), 77.5 (C-3), 82.1 (C-3), 172.6 (C-10), 178.7 (C-1). ESI-MS: 245 $[M+H]^+$. Two configurations were reported for this type compound: (−)-nonactic acid and (+)-nonactic acid, and the configurations were determinated by their optical rotation. Prikrylova et al. (1994) suggested nonactic acid and homononactic acid are mixtures of (+)- and (−)-enantiomers, and (±)-enantiomers was predominance in the mixture based on the optical rotations. So, according to the optical rotation and the reference (Prikrylova et al. 1994), they were identified to be 2-(5-(2-acetoxypropyl)-tetrahydrofuran-2-yl) propanoic acid (**5/6**; Fig. 1) (Gombos et al. 1975), with (+)-enantiomers predominating over (−)-enantiomers.

Compounds **7/8**

Pale yellow oil, [α]=+5.0 (c=0.80, $CHCl_3$). the mixture of two enantiomers: (+)-homononactic acid and (−)-homononactic acid. ^{1}H-NMR (500 MHz, CD_3OD) δ: 0.95 (t, *J*=7.4, Me-10), 1.11 (d, *J*=7.0, Me-2′), 1.43–1.46 (m, H-9), 1.56–1.64 (m, H-4, H-5), 1.65–1.67 (m, H-7), 2.00−2.03 (m, H-4, H-5), 2.43–2.46 (m, H-2), 3.96–3.98 (m, H-3), 4.04–4.06 (m, H-8), 4.08–4.10 (m, H-6); ^{13}C-NMR (100 MHz, CD_3OD) δ: 10.3 (C-10), 13.9 (C-2′), 29.5 (C-4), 31.6 (C-9), 32.3 (C-5), 44.1 (C-7), 46.8 (C-2), 71.3 (C-8), 78.0 (C-6), 82.0 (C-3), 178.7 (C-1). ESI-MS: 217 $[M+H]^+$. According to their optical rotation and the reference (Prikrylova et al. 1994), the two compounds were determined to be (±)-homononactic acid (**7/8**; Fig. 1), with (+)-homononactic acid predominating over (−)-homononactic acid.

Compounds **9/10**

Pale yellow oil, [α]=−8.0 (c=0.35, $CHCl_3$). The mixture of two enantiomers. ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.12 (d, *J*=7.1, Me-2′), 1.17 (d, *J*=6.3, Me-9), 1.59–1.61 (m, H-4,H-5), 1.66–1.68 (m, H-7), 1.99–2.02 (m, H-4, H-5), 2.43–2.46 (m, H-2), 3.87–3.90 (m, H-3), 3.98–4.01 (m, H-8), 4.03–4.05 (m, H-6); ^{13}C-NMR (100 MHz, CD_3OD) δ: 13.9 (C-2′), 24.1 (C-9), 29.5 (C-4), 32.3 (C-5), 46.2 (C-7), 46.8 (C-2), 66.2 (C-8), 78.0 (C-6), 82.0 (C-3), 178.8 (C-1). ESI-MS: 203 $[M+H]^+$. The two compounds were identified as (±)-nonactic acid (**9/10**; Fig. 1) by comparison their spectroscopic data with literature data (Prikrylova et al. 1994), with (−)-nonactic acid predominaing over (+)-nonactic acid.

Despite the current use of synthetic products in many fields today, natural products still retain an immense impact on modern medicine and agriculture due to their unique features. As a huge and relatively untapped source of new medicinal and agricultural products, endophytic microbes showed enormous potential in the search for natural products. In the present work, ten compounds were obtained from the endophytic bacteria *Streptomyces* sp. W5 isolated from *Trewia nudiflora* L. Among them, compound cis-2-(1′,8′-dihydroxy-8′-methylnonyl)-3-hydroxymethylbutanolide (**1**) was a new compound. The unique butanolide skeleton of compound **1** is known as an inducer of secondary metabolism and/or morphological development in *Streptomyces* (Yamada et al. 1987; Nihira et al. 1988).

Acknowledgments This work was partly supported by the Natural Science Foundation of Yunnan Province (2007C096M), and the Chinese Academy of Sciences projects (XiBuZhiGuang to Peiji Zhao), and grants from the Young Academic and Technical Leader Raising Foundation of Yunnan Province (2009CI071).

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