Tetrahedron 67 (2011) 6644–6648

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Biverlactones A–D, new circumventors of arbekacin resistance in MRSA, produced by *Penicillium* sp. FKI-4429

Masato Iwatsuki [a], Toshiya Ishimori [b], Tsuyoshi Yamamoto [a], Keiko Takata [b], Mihoko Mori [a,c], Kenichi Nonaka [a], Rokuro Masuma [a,c], Yoichi Hayakawa [b], Hideaki Hanaki [a], Kazuro Shiomi [a,c,*], Satoshi Ōmura [a,*]

[a] *Kitasato Institute for Life Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[b] *Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda, Chiba 278-8510, Japan*
[c] *Graduate School of Infection Control Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan*

ARTICLE INFO

Article history:
Received 29 April 2011
Received in revised form 13 May 2011
Accepted 13 May 2011
Available online 20 May 2011

Keywords:
Biverlactone
Penicillium sp.
Circumventors of arbekacin resistance in MRSA

ABSTRACT

Biverlactones, new circumventors of arbekacin resistance in methicillin-resistant *Staphylococcus aureus* (MRSA) were isolated from a culture broth of *Penicillium* sp. FKI-4429. Their structures were elucidated by spectroscopic studies, including various NMR experiments. Biverlactones A–D had novel skeletons, consisting of a lactone ring conjugated with *exo*- or *endo*-olefin, a carboxylic group and a characteristic alkyl side chain in common.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the cause of severe opportunistic infections, particularly in people with compromised immune systems. Recently, it has also been gaining in significance as a cause of serious community-acquired infections among healthy people.[1] Although there are four antibiotics approved as therapeutic agents for MRSA in Japan, namely arbekacin (ABK), vancomycin, teicoplanin, and linezolid, resistant microorganisms against all four have been reported. In particular, ABK-resistant MRSA is an important problem because ABK is used for acute stages of infection. The mechanism of ABK resistance is thought to be via inactivation of ABK caused by bacterial aminoglycoside-modifying enzymes, which phosphorylate and acetylate ABK.[2,3] Consequently, any inhibitor of these enzymes should prove useful for use with ABK to help maintain its effectiveness.

During our screening program to discover new anti-MRSA agents, we discovered four new circumventors of ABK resistance, designated biverlactones A (**1**), B (**2**), C (**3**), and D (**4**), from the culture broth of *Penicillium* sp. FKI-4429 (Fig. 1). In this paper, the physico-chemical properties and structure elucidation of these biverlactones are described.

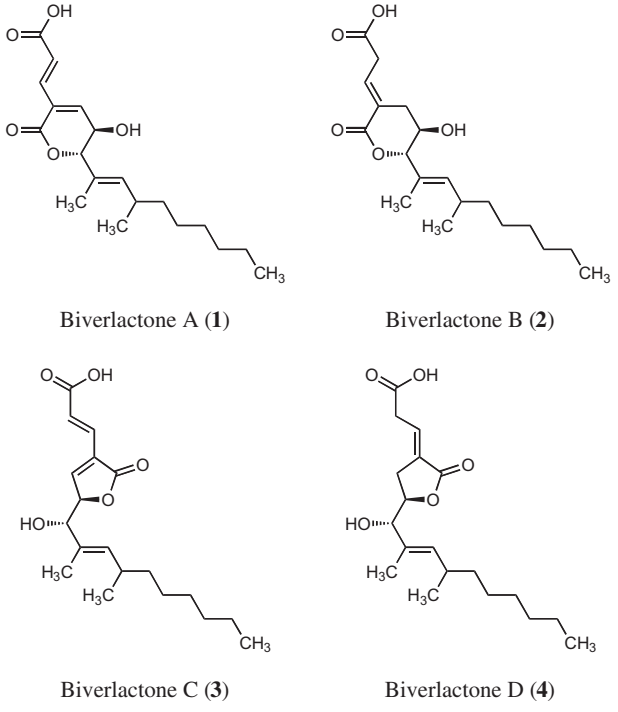

Fig. 1. Structures of biverlactones A–D (**1**–**4**).

*Corresponding authors. E-mail addresses: shiomi@lisci.kitasato-u.ac.jp (K. Shiomi), omuras@insti.kitasato-u.ac.jp (S. Ōmura).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.061

2. Results and discussion

The EtOAc extract of a 6-day culture broth of *Penicillium* sp. FKI-4429 was subjected to column chromatography and HPLC purification to afford **1**–**4** (See Experimental section). Details of taxonomy, fermentation, and bioactivity of the biverlactones will be described elsewhere.[4]

The physico-chemical properties of the biverlactones are summarized in the Experimental section. The compounds are readily soluble in MeOH, $CHCl_3$, and EtOAc, but insoluble in water and *n*-hexane. The IR absorption at 1630–1760 and 3420 cm^{-1} suggested the presence of carbonyl and hydroxy groups. Similarity in physico-chemical properties among the biverlactones strongly suggested that they are structurally related.

Biverlactone A (**1**) was obtained as white powder. The molecular formula of **1** was elucidated by HR-FABMS to be $C_{19}H_{28}O_5$ (*m*/*z* 337.1986 $[M+H]^+$ calcd 337.1956), requiring 6 degrees of unsaturation. The ^1H and ^{13}C NMR spectral data of **1** are listed in Table 1. The ^{13}C NMR, HSQC, and HMBC spectra indicated 19 carbons, which were classified into two carbonyl carbons, four sp^2 methine carbons, two sp^2 quaternary olefinic carbons, two oxygenated sp^3 methine carbons, one sp^3 methine carbon, five sp^3 methylene carbons, and three methyl carbons, thus accounting for 5 degrees of unsaturation. Therefore, the remaining degree of unsaturation should be due to a ring structure. As shown by the bold lines for **1** in Fig. 2, four partial structures **I**–**IV** were revealed by proton spin networks from H-2 (δ_H 6.55) to H-3 (δ_H 7.18), from H-5 (δ_H 7.10) to H-7 (δ_H 4.45), from H-9 (δ_H 5.25) to H_2-11 (δ_H 1.10–1.25) with a branching H_3-19 (δ_H 0.88), and from H_2-15 (δ_H 1.10–1.25) to H_3-16 (δ_H 0.80) in the ^1H–^1H COSY. On the basis of ^1H–^{13}C HMBC experiments, the correlations from H-2 and H-3 to C-1 (δ_C 169.8) and C-4 (δ_C 126.1) indicated one of two carbonyl groups is linked to C-2 or C-3 of **I**. Moreover, the correlations from H-3 to C-5 (δ_C 151.0) and C-17 (δ_C 163.0), from H-5 to C-3 (δ_C 138.0) and C-17 established the linkage among C-3 of **I**, C-5 of **II**, and C-17 through C4, and the linkage between C-1 and C-2. The correlations from H-7 to C-8 (δ_C 128.2), C-9 (δ_C 140.1), and C-18 (δ_C 10.9) and from H-9 (δ_H 5.25) to C-7 and from H_3-18 (δ_H 1.65) to C-7 (δ_C 88.2), C-8, and C-9 revealed that partial structure **II** was connected at C-7 to C-9 of **III** via C-8 with a branching H_3-18. The correlations from H_2-15 and H_3-16 to C-14 (δ_C 32.1) and the ^1H and ^{13}C chemical shifts of C-12 to C-14 methylenes suggested that the partial structures **III** and **IV** were connected via C-12 to C-14. The C2–C3 double bond geometry of **I** was assumed to be 2*E* on the basis of the coupling constants ($^3J_{H\text{-}2,H\text{-}3}$=15.2 Hz). The C8–C9 double bond geometry of **III** was elucidated to be 8*E* by NOE correlation between H_3-18 and H-10 (δ_H 2.38) and gamma effect (C-18: δ_C 10.9).[5] Finally, an ester bond between C-17 and C-7 was suggested by the chemical shift at C-7 (δ_C 88.2) and the difficulty in forming an eight-membered ring via *trans* olefin bond. From all the observations described above, the structure of **1** was elucidated as shown in Fig. 1, consisting of an *endo*-α,β-unsaturated δ-lactone ring, a carboxylic group, and a 4-methyl-2-decen-2-yl moiety. The relative configuration of **1** was determined to be 6*R**,7*S** by a large coupling constant ($^3J_{H\text{-}6,H\text{-}7}$=7.9 Hz), a small coupling constant ($^3J_{H\text{-}5,H\text{-}6}$=1.0 Hz), and NOE correlations for H-6/H-9 and H-7/H_3-18 (Fig. 3).

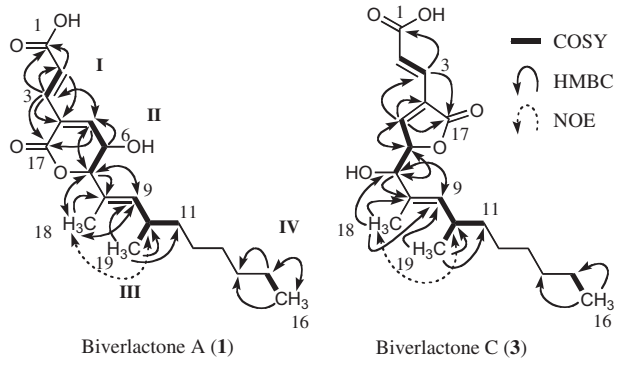

Fig. 2. COSY, HMBC, and NOE correlations of biverlactones A (**1**) and C (**3**).

Table 1
NMR data of biverlactones A (**1**) and C (**3**) in CD_3OD[a]

Position	1		3	
	δ_H	δ_C	δ_H	δ_C
1	–	169.8	–	170.0
2	6.55 (d, 15.2)	123.8	6.90 (d, 16.0)	125.2
3	7.18 (d, 15.2)	138.0	7.36 (d, 16.0)	131.4
4	–	126.1	–	128.1
5	7.10 (d, 1.0)	151.0	7.78 (d, 1.9)	154.8
6	4.52 (dd, 7.9, 1.0)	63.8	5.17 (dd, 5.2, 1.9)	84.2
7	4.45 (d, 7.9)	88.2	4.19 (d, 5.2)	77.0
8	–	128.2	–	132.3
9	5.25 (dq, 9.1, 1.1)	140.1	5.30 (dq, 9.9, 1.1)	135.5
10	2.38 (m)	32.3	2.44 (m)	38.8
11		37.3		33.5
12		27.0[b]		29.0[b]
13	1.10-1.25 (10H, m)	29.0[b]	1.20-1.40 (10H, m)	30.0[b]
14		32.1		33.3
15		22.5		24.1
16	0.80 (3H, t, 6.4)	13.3	0.90 (3H, t, 6.4)	15.0
17	–	163.0	–	171.3
18	1.65 (3H, br. d)	10.9	1.71 (3H, d, 1.1)	13.9
19	0.88 (3H, d, 6.5)	19.9	0.94 (3H, d, 6.5)	21.6

[a]Recorded.at 400 MHz for ^1H and 100 MHz for ^{13}C; Integral, multiplicity, and *J*-values (Hz) are given in parentheses.

[b]Exchangeable.

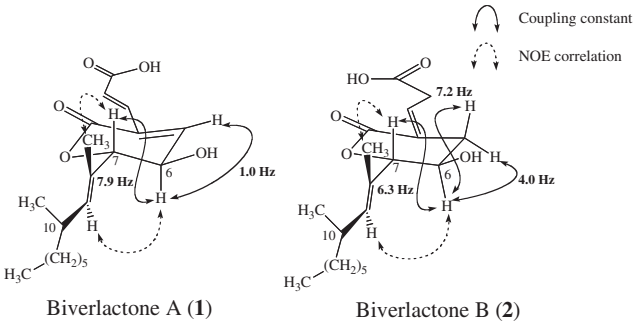

Fig. 3. Determination of relative configurations of biverlactones A (**1**) and B (**2**).

Biverlactone C (**3**) was obtained as white powder. The molecular formula of **3** was elucidated by HR-ESI-MS to be $C_{19}H_{28}O_5$ (*m*/*z* 359.1849 $[M+Na]^+$ calcd 359.1834), representing the same mass units as **1**. The analysis of 1D and 2D NMR revealed **3** has a similar carbon chain to **1**, as shown in Fig. 2. Although the ^1H and ^{13}C NMR spectra of **3** were very similar to those of **1** (Table 1), the chemical shifts of C-6 and C-7 shifted low-field and high-field largely in ^{13}C NMR spectra (C-6, C-7: δ_C 84.2, 77.0 in **3**, δ_C 63.8, 88.2 in **1**), respectively. This observation and the difficulty of forming a seven-membered ring via *trans* olefin bond, suggested the presence of an ester bond between C-17 and C-6. Gradual isomerization between **1** and **3** in methanol (room temperature, 1 week) suggested that the relative configuration of **3** was 6*R**,7*S**. From all these observations, the structure of **3** was elucidated as shown in Fig. 1, consisting of an *endo*-α,β-unsaturated γ-lactone ring, a carboxylic group, and a 1-hydroxy-2,4-dimethyl-2-decen-1-yl moiety.

Biverlactone B (**2**) was obtained as white powder. The molecular formula of **2** was elucidated by HR-ESI-MS to be $C_{19}H_{30}O_5$ (*m*/*z* 361.2001 $[M+Na]^+$ calcd 361.1991), which has an additional H_2 unit compared to **1** or **3**, requiring 5 degrees of unsaturation. The ^1H and ^{13}C NMR spectral data of **2** are listed in Table 2. These data were measured in CD_3OH to prevent the disappearance of active methylene at C-2. The ^{13}C NMR, HMQC, and HMBC spectra indicated 19 carbons, which were classified into two carbonyl carbons, two sp^2 methine carbons, two sp^2 quaternary carbons, two oxygenated sp^3 methine carbons, one sp^3 methine carbon, seven sp^3 methylene carbons, and three methyl carbons, thus accounting for 4 degrees of unsaturation. Therefore, the remaining degree of unsaturation should be due to a ring structure. As shown by the bold lines for **2** in Fig. 4, four partial structures **I**–**IV** were revealed by proton spin networks from H_2-2 (δ_H 3.17, 3.23) to H-3 (δ_H 7.18), from H_2-5 (δ_H 2.48, 2.73) to H-6 (δ_H 4.05), from H-9 (δ_H 5.18) to H_3-19 (δ_H 0.96), and from H_2-15 (δ_H 1.18–1.37) to H_3-16 (δ_H 0.90) in the ^1H–^1H COSY. On the basis of ^1H–^{13}C HMBC experiments, the correlations from H-3 to C-4 (δ_C 126.7) and C-5 (δ_C 30.4), from H-5 to C-4 and C-17 (δ_C 167.9), and from H-2 to C-1 (δ_C 174.1) established the linkage among C-3 of **I**, C-5 of **II**, and C-17 through C-4, and the linkage between C-1 and C-2. The correlations from H-9 to C-7 (δ_C 88.7) and C-18 (δ_C

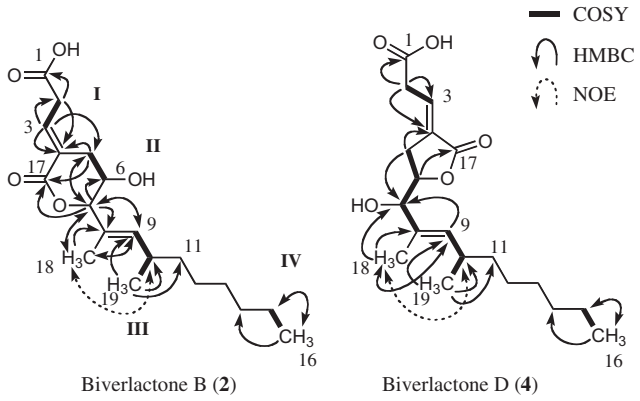

Fig. 4. COSY, HMBC, and NOE correlations of biverlactones B (**2**) and D (**4**).

Table 2
NMR data of biverlactones B (**2**) and D (**4**) in CD_3OH[a]

Position	**2**		**4**	
	δ_H	δ_C	δ_H	δ_C
1	–	174.1	–	172.7
2	3.17 (dd, 18.0, 6.8)	35.1	3.20 (2H, d, 7.0)	48.0
	3.23 (dd, 18.0, 7.0)			
3	7.18 (dddd, 7.0, 6.8, 1.1, 1.0)	140.8	6.80 (tdd, 7.0, 3.1, 2.8)	132.5
4	–	126.7	–	133.4
5	2.48 (ddd, 16.0, 7.2, 1.1)	30.4	2.80 (2H, m)	23.6
	2.73 (ddd, 16.0, 4.0, 1.0)			
6	4.05 (ddd, 7.2, 6.3, 4.0))	64.6	4.71 (ddd, 8.0, 5.9, 4.2)	79.8
7	4.58 (d, 6.3)	88.7	4.16 (d, 4.2)	77.1
8	–	130.3	–	130.4
9	5.18 (dq, 10.3, 0.9)	137.5	5.34 (dq, 10.1, 1.1)	135.3
10	2.45 (m)	33.2	2.43 (m)	33.0
11		28.4		38.7
12		32.9[b]		33.1[b]
13	1.18-1.37 (10H, m)	31.1[b]	1.18-1.37 (10H, m)	30.6[b]
14		28.5		28.6
15		23.6		23.6
16	0.90 (3H, t, 7.0)	14.3	0.91 (3H, t, 6.0)	14.3
17	–	167.9	–	172.7
18	1.68 (3H, br. d)	12.5	1.66 (3H, br. d)	13.7
19	0.96 (3H, d, 6.5)	21.1	0.95 (3H, d, 6.5)	21.2

[a]Recorded.at 400 MHz for ^1H and 100 MHz for ^{13}C; Integral, multiplicity, and *J*-values (Hz) are given in parentheses

[b]Exchangeable.

12.5), from H_3-18 (δ_H 1.68) to C-7, C-8 (δ_C 130.3), and C-9 (δ_C 137.5) and from H-7 (δ_H 4.58) to C-5 (δ_C 30.4) and C-6 (δ_C 64.6) revealed that the partial structure **II** was connected at C-6 to C-9 of **III** via C-7 and C-8. The correlations from H_3-16 (δ_H 0.90) to C-14 and the ^1H and ^{13}C chemical shifts of C-12, C-13, and C-14 suggested that the partial structures **III** and **IV** were connected via C-11 to C-14. The C3-C4 double bond geometry was elucidated as 3*E*, on the basis of the chemical shift of C-3 (δ_H 7.18), compared with literature data of synthetic δ-lactones.[6] The C8–C9 double bond geometry was elucidated as 8*E* by the chemical shift of C-18 (δ_C 12.5) and NOE correlation for H-10/H_3-18. Finally, the ester bond between C-17 and C-7 was established by HMBC correlations from H-7 to C-17 and the chemical shift at C-7 (δ_C 88.7). From all the observations described above, the structure of **2** was elucidated as shown in Fig. 1, consisting of an *exo*-α,β-unsaturated δ-lactone ring, a carboxylic group, and a 4-methyl-2-decen-2-yl moiety. The relative configuration of **2** was determined to be 6*R**,7*S** by large coupling constants ($^3J_{H\text{-}6,H\text{-}7}$=6.3 Hz, $^3J_{H\text{-}5ax,H\text{-}6}$=7.2 Hz) and NOE correlations for H-6/H-9 and H-7/H_3-18 (Fig. 3).

Biverlactone D (**4**) was obtained as white powder. The molecular formula of **4** was elucidated by HR-ESI-MS to be $C_{19}H_{30}O_5$ (*m*/*z* 361.1985 $[M+Na]^+$ calcd 361.1991), the same mass units as **2**. The analysis of 1D and 2D NMR revealed **4** has a similar carbon chain to **2**, as shown in Fig. 4. Although the ^1H and ^{13}C NMR spectra of **4** were very similar to those of **2** (Table 2), the chemical shifts of C-6 and C-7 shifted low-field and high-field largely in ^{13}C NMR spectra (C-6, C-7: δ_C 79.8, 77.1 in **4**, δ_C 64.6, 88.7 in **2**), respectively. This observation and the correlation from H-6 (δ_H 4.71) to C-17 (δ_C 172.7) in HMBC spectra, established the presence of an ester bond between C-17 and C-6. The C3–C4 double bond geometry was determined to be 3*E*, on the basis of the chemical shift of C-3 (δ_H 6.80) compared with literature data of synthetic γ-lactones.[7,8] The C8-C9 double bond geometry was elucidated to be 8*E* by the chemical shift of C-18 (δ_C 13.7) and NOE correlation for H-10/H_3-18. Gradual isomerization between **2** and **4** in methanol (room temperature, 1 week) suggested that the relative configuration of **4** was 6*R**,7*S**. From all the observations described above, the structure of **4** was elucidated as shown in Fig. 1, consisting of an *exo*-α,β-unsaturated γ-lactone ring, a carboxylic group, and an 1-hydroxy-2,4-dimethyl-2-decenyl moiety.

Some fungal metabolites having a 4-methyl-2-decen-2-yl side chain have been reported, such as 4,6-dimethyldodeca-2*E*,4*E*-dienoyl ester of phomalactone from *Phomopsis* sp.,[9] aranorosin from *Pseudoarachniotus roseus*,[10] and gymnastatins from *Gymnascella dankaliensis*.[11] Biverlactones may be biosynthesized from a common hydroxylic acid intermediate, 2-(2,3-dihydroxy-4,6-dimethyl-4-dodecenyl) pentanedioic acid, by polyketide synthase.

The growth of ABK-resistant MRSA was not affected on the agar medium containing 8 μg/mL of ABK. The biverlactones tested only showed an effect on ABK-resistant MRSA by the agar diffusion method when the media contained ABK (Table 3). Thus, biverlactones circumvent ABK resistance in MRSA, and **1** appeared to have the most potent circumvention activity among the compounds tested. These biverlactones are suggested to inhibit aminoglycoside-modifying enzymes by our preliminary examination. In-depth biological study of these biverlactones will be described elsewhere.[4]

Table 3
Circumvention activity of ABK resistance by **1**–**4**

Compound	Amount (μg/disc)	Inhibition zone diameter (mm)	
		−ABK	+ABK (8 μg/mL)
Biverlactone A (**1**)	0.3	No inhibition	12.2
Biverlactone B (**2**)	30	No inhibition	12.5
Biverlactone C (**3**)	3	No inhibition	13.3
Biverlactone D (**4**)	30	No inhibition	12.6

3. Experimental section

3.1. General experimental procedures

NMR spectra were measured on a Varian XL-400 spectrometer with ^1H NMR at 400 MHz and ^{13}C NMR at 100 MHz in CD_3OD (Sigma) or CD_3OH (Sigma). FABMS and ESI-MS spectra were measured on a JEOL JMS AX-505 HA mass spectrometer and a JEOL AccuTOF apparatus. IR spectra (KBr) were taken on a Horiba FT-210 Fourier transform Infrared spectrometer. UV spectra were measured with a Beckman DU640 spectrophotometer. Optical rotation was measured on a JASCO model DIP-181 polarimeter.

3.2. Isolation of biverlactones

The 6-day old culture broth (400 mL) was extracted with ethanol (400 mL) and centrifuged to separate into supernatant and residue. The supernatant was concentrated under reduced pressure to remove ethanol and then extracted with EtOAc (pH 3). The EtOAc extract (192 mg) was dissolved in $CHCl_3$, applied on a silica gel column (20 i.d.×70 mm, Merck) and eluted stepwise with 100:0, 100:1, 50:1, 10:1, 1:1 and 0:100 (v/v) of $CHCl_3$/MeOH solvents. The 10:1 fraction (35.7 mg) was dissolved in a small amount of MeOH and purified by HPLC on XBridge C18 column (10 i.d.×250 mm, Waters) with 50% CH_3CN/0.1% TFA at 4.0 mL/min detected at UV 210 nm. The retention times of biverlactone A (**1**), B (**2**), C (**3**), and D (**3**) were 33, 20, 31, and 27 min, respectively. Each active fraction was concentrated in vacuo to dryness to afford **1** (2.57 mg), **2** (0.71 mg), **3** (1.17 mg), and **4** (2.34 mg) as white powders.

*3.2.1. Biverlactone A (**1**).* White powder; soluble in MeOH, EtOAc, $CHCl_3$, insoluble in H_2O, *n*-hexane; $[\alpha]_D$ +2.03 (*c* 0.15, 22.4 °C, MeOH); UV: λ_{max} 202 nm (ε 67,000), 258 nm (ε 6980) in MeOH; IR (KBr): ν_{max} 3452, 2956, 2925, 2857, 1703, 1639, 1457, 1380 cm^{-1}; ^1H NMR: see Table 1; ^{13}C NMR: see Table 1; HR-FABMS: *m*/*z* 337.1986 $[M+H]^+$ (calcd for $C_{19}H_{29}O_5$, 337.1956).

*3.2.2. Biverlactone B (**2**).* White powder; soluble in MeOH, EtOAc, $CHCl_3$, insoluble in H_2O, *n*-hexane; $[\alpha]_D$ +3.43 (*c* 0.09, 22.9 °C, MeOH); UV: λ_{max} 215 nm (ε 20,500) in MeOH; IR (KBr): ν_{max} 3435, 2956, 2925, 2857, 1743, 1641, 1446 cm^{-1}; ^1H NMR: see Table 2; ^{13}C NMR: see Table 2; HR-ESI-MS: *m*/*z* 361.2001 $[M+Na]^+$ (calcd for $C_{19}H_{30}O_5Na$, 361.1991).

*3.2.3. Biverlactone C (**3**).* White powder; soluble in MeOH, EtOAc, $CHCl_3$, insoluble in H_2O, *n*-hexane; $[\alpha]_D$ +21.0 (*c* 0.04, 23.7 °C, MeOH); UV: λ_{max} 206 nm (ε 67,000), 251 nm (ε 6170) in MeOH; IR (KBr): ν_{max} 3429, 2956, 2925, 2858, 1758, 1705, 1647 cm^{-1}; ^1H NMR: see Table 1; ^{13}C NMR: see Table 1; HR-ESI-MS: *m*/*z* 359.1849 $[M+Na]^+$ (calcd for $C_{19}H_{28}O_5Na$, 359.1834).

*3.2.4. Biverlactone D (**4**).* White powder; soluble in MeOH, EtOAc, $CHCl_3$, insoluble in H_2O, *n*-hexane; $[\alpha]_D$ −0.21 (*c* 0.05, 22.2 °C, MeOH); UV: λ_{max} 214 nm (ε 25,200) in MeOH; IR (KBr): ν_{max} 3444, 2956, 2925, 2858, 1751, 1685, 1633, 1446 cm^{-1}; ^1H NMR: see Table 2; ^{13}C NMR: see Table 2; HR-ESI-MS: *m*/*z* 361.1985 $[M+Na]^+$ (calcd for $C_{19}H_{30}O_5Na$, 361.1991).

3.3. Assay for circumvention activity of arbekacin against MRSA

MRSA TH-1466 strain, a clinical ABK-resistant isolate harboring genes of aminoglycoside-modifying enzymes, was used and anti-MRSA activity was measured as described below.

Agar diffusion method; MRSA was cultured in 4 mL of Mueller–Hinton broth (Difco) at 35 °C for 20 h and adjusted to

1×10^8 CFU/mL. 1-mL portion of culture broth was transferred to a plate (10×14 cm, Eiken Kizai) containing 20 mL of Mueller–Hinton agar (Difco) with or without arbekacin (fin. 8 μg/mL, Meiji Seika), whose concentration has no effect on growth of MRSA. Paper disc (6 mm, Advantec) containing various amounts of a sample were placed on the Mueller–Hinton agar plate and incubated at 35 °C overnight. Anti-MRSA activity was expressed as the diameter (mm) of the inhibition zone.

Acknowledgements

This study was supported, in part, by funds from the Quality Assurance Framework of Higher Education, from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan and by Grant-in-Aid for Scientific Research (C, 21580129) from the Japan Society for the Promotion of Science. We are grateful to Ms. Akiko Nakagawa, Ms. Noriko Sato, and Dr. Kenichiro Nagai (School of Pharmacy, Kitasato University) for mass and NMR spectra measurements.

Supplementary data

UV, IR, ^{1}H NMR, and ^{13}C NMR spectra of biverlactones A (**1**)–D (**4**). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.061. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes

1. Diep, B. A.; Sensabaugh, G. F.; Somboonna, N.; Carlenton, H. A.; Perdreau-Remington, F. *J. Clin. Microbiol.* **2004**, *42*, 2080–2084.
2. Tabata, M.; Shimizu, M.; Araake, M.; Ogawa, H. *Jpn. J. Antibiot.* **2003**, *56*, 36–43.
3. Ishino, K.; Ishikawa, J.; Ikeda, Y.; Hotta, K. *J. Antibiot.* **2004**, *57*, 679–686.
4. In preparation.
5. de Haan, J. W.; van de Ven, L. J. M. *Tetrahedron Lett.* **1971**, *43*, 3965–3968.
6. Lee, J.; Lewin, N. E.; Blumberg, P. M.; Marquez, V. E. *Bioorg. Med. Chem. Lett.* **1994**, *20*, 2405–2410.
7. Yu, J. S.; Wiemer, D. F. *J. Org. Chem.* **2007**, *72*, 6263–6265.
8. Chang, S.-Y.; Cheng, M.-J.; Peng, C.-F.; Chang, H.-S.; Chen, I.-S. *Chem. Biodiversity* **2008**, *5*, 2690–2698.
9. Wrigley, S. K.; Sadeghi, R.; Bahl, S.; Whiting, A. J.; Ainsworth, A. M.; Martin, S. M.; Katzer, W.; Ford, R.; Kau, D. A.; Robinson, N.; Hayes, M. A.; Elock, C.; Mander, T.; Moore, M. *J. Antibiot.* **1999**, *52*, 862–872.
10. Roy, K.; Mukhopadhyay, T.; Reddy, G. C. S.; Desikan, K. R.; Rupp, R. H.; Ganguli, B. N. *J. Antibiot.* **1998**, *41*, 1780–1784.
11. Nimura, A.; Amagata, T.; Minoura, K.; Ito, T. *Tetrahedron Lett.* **1997**, *38*, 5675–5678.