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Synthesis of Variously Oxidized Abietane Diterpenes and Their Antibacterial Activities Against MRSA and VRE

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Abstract—Variously oxidized 12 natural abietanes, 6,7-dehydroferruginol methyl ether (**3**), ferruginol (**5**), 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**), royleanone (**9**), demethyl cryptojaponol (**12**), salvinolone (**14**), sugiol methyl ether (**16**), sugiol (**17**), 5,6-dehydrosugiol methyl ether (**19**), 5,6-dehydrosugiol (**20**), 6β-hydroxyferruginol (**23**), and taxodione (**25**) were synthesized. Antimicrobial activities of synthesized phenolic diterpenes and their related compounds against MRSA and VRE were evaluated. Phenols (12-hydroxyabieta-8,11,13-trien-6-one **22** and **23**), catechols (**12** and **14**) and taxodione **25** showed potent activity with 4–10 μg/mL of MIC against MRSA and 4–16 μg/mL of MIC against VRE. (−)-Ferruginol showed more potent activity than natural type (+)-ferruginol. Quinone methide **7** showed the most potent activity with 0.5–1 μg/mL of MIC against both MRSA and VRE.

Introduction

Infections caused by bacteria resistant to multiple antibiotics have been significant problems recently. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are increasingly found worldwide in hospitals. From the search about novel antibiotic compounds, totarol was found to have potent antibacterial activity against MRSA.[1] Evans reported antibacterial activity of totarol, ferruginol and their abietane derivatives against MRSA.[2] Abietane diterpenes are widely distributed natural products in the plant kingdom with various biological activities, e.g. anti-virus,[3,4] antibiotic,[4–9] anti-malarial,[10] anti-oxidant[11] and anti-tumor[12,13] activities. We planned to synthesize variously oxidized abietanes (11-phenol, 11,12-cathecol, *p*-quinone methide, and ketone/alcohol at C-6 and C-7) to examine the structure–activity-relationship against VRE and MRSA. Previously we reported stereoselective synthesis of (+)- and (−)-ferruginol via asymmetric polyene cyclization.[14] In this paper, we report the synthesis of 12 natural abietane-type diterpenes, 6,7-dehydroferruginol methyl ether (**3**),[15] ferruginol (**5**),[14,16,17] 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**),[6] royleanone (**9**),[16] demethyl-cryptojaponol (**12**),[18] salvinolone (**14**),[19,20] sugiol methyl ether (**16**),[21,22] sugiol (**17**),[13,15,21] 5,6-dehydrosugiol methyl ether (**19**),[21,22] 5,6-dehydrosugiol (**20**),[12,21,23] 6β-hydroxyferruginol (**23**),[24] and taxodione (**25**)[12,16,25] using a previously reported synthetic route,[14] together with antimicrobial activity of the synthesized natural diterpenes and the related compounds against MRSA and VRE.

Results and Discussion

Synthetic plan

We reported enantioselective total synthesis of (+)- and (−)-ferruginol via asymmetric polyene cyclization in our previous paper.[14] We thus planned to synthesize 12 natural abietanes from tricyclic compound **3**, as common synthetic intermediate, which could be prepared from acid **1** by two steps. Three synthetic routes (**A**, **B** and **C**) were devised from **3**. The synthetic routes are summarized as follows. The first route (**A**) was branched from **3** to ferruginol **5** which was converted to **7**, **9**, **12** and **14**. The second route (**B**) was branched from **3** to 7-ketone **16** via hydroboration of **3** followed by oxidation

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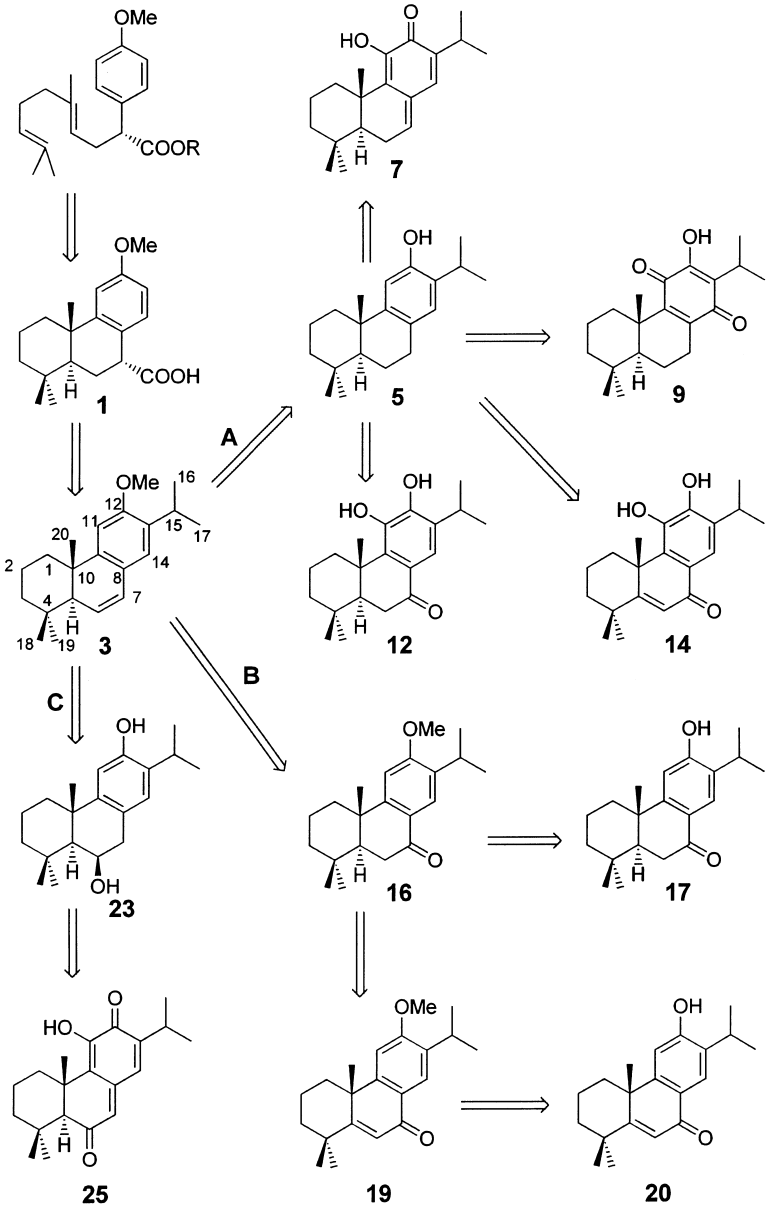
of the products. The ketone **16** was further transformed to **17**, **19** and **20**. The third route (**C**) was branched from **3** to 6-alcohol **23**. The alcohol **23** was oxidized to catechol ester (11-hydroxy-12-benzoyl ester) and finally converted to taxodione (**25**) (Scheme 1).

Tricyclic intermediate 3

Tricyclic intermediate, 6,7-dehydroferruginol methyl ether **3**, was synthesized by two steps from acid **1** which was prepared via polyene cyclization reaction in our previous report.[14] Isopropyl group at C-13 was introduced directly by Friedel–Crafts alkylation of **1** with 2-chloropropane and $AlCl_3$ in dichloromethane to afford **2** (80.9%), which was further decarboxylated with $Pb(OAc)_4$–$Cu(OAc)_2$ in quinoline to give 6,7-dehydroferruginol methyl ether (**3**) (87.4%). Methyl ether **3**, as a common intermediate of our synthesis, was introduced to variously oxidized abietanes. The spectral data of synthetic **3** showed that it is identical with the natural **3** in the literature (Scheme 2).[15]

The first route (A)

Ferruginol (**5**),[14,16,17] 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**),[6] royleanone (**9**),[16] demethylcryptojaponol (**12**)[18] and salvinolone (**14**)[19,20] were synthesized from **3** as follows. The double bond at C6–C7 of **3** was hydrogenated with H_2 and 10% Pd/C in ethyl acetate to yield **4** (quantitative yield). The methyl ether **4** was treated with boron tribromide in dichloromethane at 0–5 °C for 2 h to give ferruginol (**5**)[14,16,17] (94.9%), which was identified by comparing the spectral data with those of natural **5** in the literature. Another experiment for the demethylation of **4** was performed with NaH–EtSH in DMF at 120 °C to give only 40% of **5**. The oxidation



Scheme 1. Synthetic plan of highly oxidized 12 natural abietanes.

of C-11 position of ferruginol (**5**) with benzoyl peroxide (BPO) in chloroform afforded 12-benzoyloxy-11-hydroxyabieta-8,11,13-triene (**6**)[26] (71.4%). The reductive deprotection of benzoyl group at C-12 of **6** with diisobutylaluminum hydride (DIBAL) in THF at −15 °C for 3 h followed by auto-oxidation with air gave 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**)[6] in poor yield (15.1%). We also tried the similar reaction of **6** with lithium aluminum hydride, but resulted in poorer yield of **7** (5.4%). The spectral data of synthetic material **7** were identical with those of natural **7** in the literature.

Treatment of **6** with *meta*-chloroperbenzoic acid (mCPBA) in dichloromethane at room temperature yielded quinone **8** (42.3%),[27] which was further hydrolyzed with $NaHCO_3$ in MeOH–H_2O under reflux to give royleanone (**9**)[16] in 85.0% yield as yellow needles whose spectral properties were identical to those of the literature.

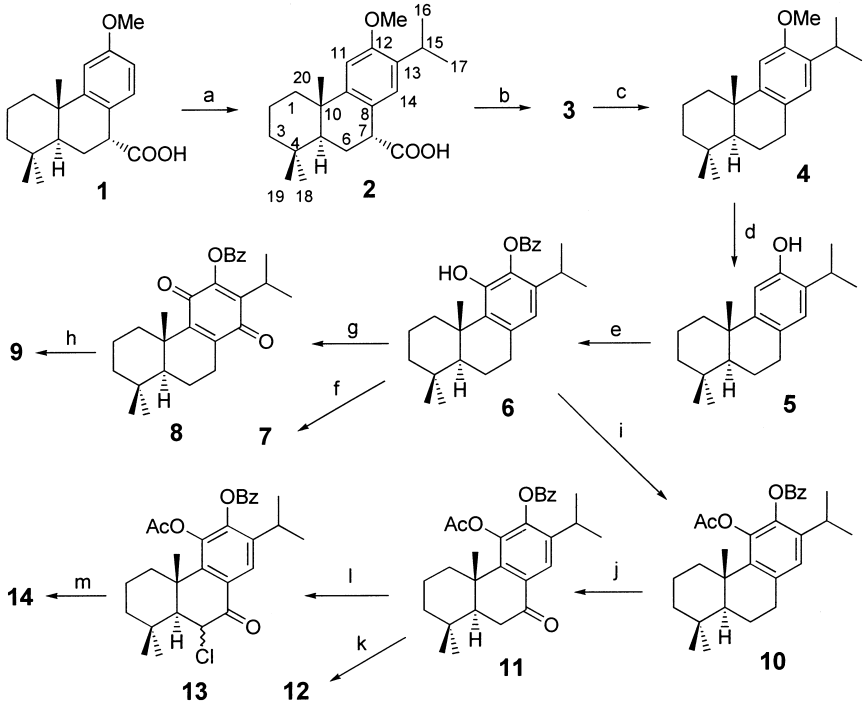
The acetylation of **6** with isopropenyl acetate in refluxing toluene gave an acetate **10** (76.7%), which was oxidized with chromium trioxide in acetic acid to give ketone **11** (65.9%). Ketone **11** was further hydrolyzed with $NaHCO_3$ in MeOH–H_2O to give demethylcryptojaponol (**12**)[18] in quantitative yield whose spectral properties were identical to those of natural **12**.

Treatment of **11** with sulfuryl chloride (SO_2Cl_2) in CCl_4 at 60 °C for 40 h gave **13** (94.9%). Chloroketone **13** was dehydrohalogenated with lithium chloride in refluxing pyridine to give the α,β-unsaturated ketone whose ester groups were hydrolyzed by heating under reflux with $NaHCO_3$ in MeOH–H_2O to afford salvinolone (**14**)[19,20] (87.8%), whose spectral properties were identical to those in the literature (Scheme 2).

The second route (B)

Sugiol methyl ether (**16**),[21,22] sugiol (**17**),[13,15,21] 5,6-dehydrosugiol methyl ether (**19**),[21,22] and 5,6-dehydrosugiol (**20**)[12,21,23] were synthesized from **3** as follows. Hydroboration of **3** with BH_3 in tetrahydrofuran (THF) followed by oxidation with H_2O_2 in NaOH–H_2O gave alcohols (**15a**) of a yellow oil and (**15b**) as colorless needles (1:1) (72.0% total yield of **15a** and **15b** from **3**). The stereochemistry at C-7 of **15a** (7β-H) and **15b** (7α-H) was certified by the splitting pattern of 7-H (**15a**: d, $J = 4.4$ Hz; **15b**: dd, $J = 3.6$, 1.6 Hz). Oxidation of the mixture of alcohols **15a** and **15b** with Jones' reagent in acetone at 0 °C for 20 min gave sugiol methyl ether (**16**)[21,22] in 85.2% yield. Demethylation of **16** with NaH–EtSH in DMF at 120 °C under reflux for 3 h afforded sugiol (**17**)[13,15,21] as colorless needles in satisfactory yield (98.7%). The spectra of the synthetic **16** and **17** were identical in every respect to those of natural compounds, respectively.

Treatment of **16** with sulfuryl chloride in CCl_4 at ambient temperature for 20 h gave **18** (97.7%). Chloride **18** was dehydrochlorinated with lithium chloride in pyridine at 110 °C to give 5,6-dehydrosugiol methyl ether (**19**)[21,22] as needles (85.9%) whose spectral properties were identical to those of natural **19**. Methyl ether **19**

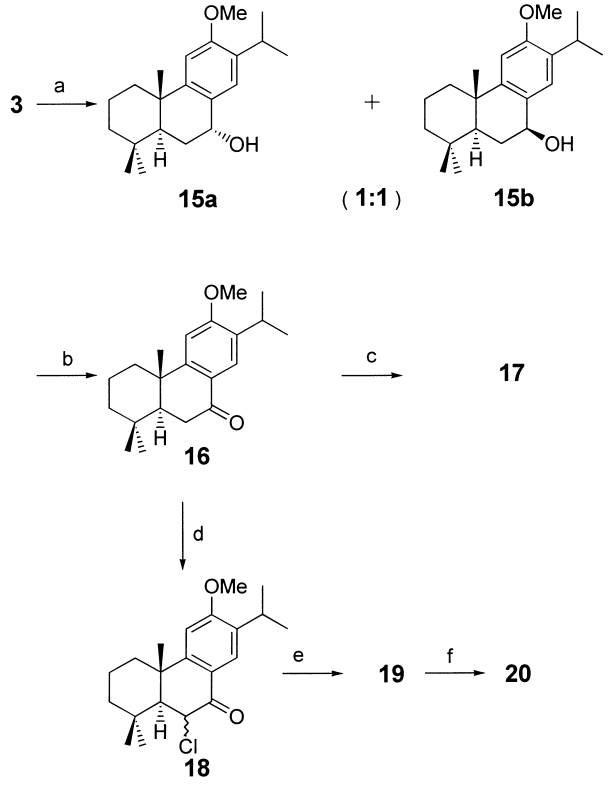


Scheme 2. Reagents and conditions: (a) Me_2CHCl, $AlCl_3$, CH_2Cl_2, 40 °C, 40 h, 80.9%; (b) LTA, $Cu(OAc)_2$, quinoline, 125 °C, 16 h, 87.4%; (c) H_2, Pd/C, EtOAc, rt, 98.3%; (d) BBr_3, CH_2Cl_2, 0–5 °C, 2 h, 94.9%; (e) BPO, $CHCl_3$, rt, 7 h, 71.4%; (f) i. DIBAL-H, THF, −15 °C, 3 h; ii. O_2, two steps, 15.1%; (g) mCPBA, CH_2Cl_2, rt, 12 h, 42.3%; (h) $NaHCO_3$, MeOH–H_2O, reflux, 85%; (i) isopropenyl acetate, TsOH, PhMe, reflux, 5 h, 76.7%; (j) CrO_3, AcOH, rt, 8 h, 65.9%; (k) $NaHCO_3$, MeOH–H_2O, reflux, 96.3%; (l) SO_2Cl_2, CCl_4, 60 °C, 40 h, 94.9%; (m) i. LiCl, pyridine, reflux, 10 h; ii. $NaHCO_3$, MeOH–H_2O, reflux, 1 h, two steps, 87.8%.

was deprotected with the similar procedures as in the case of sugiol to afford 5,6-dehydrosugiol (**20**)[12,21,23] (96.6%), which was identical with the natural compound (Scheme 3).

The third route (C)

6β-Hydroxyferruginol (**23**)[24] and taxodione (**25**)[12,16,25] were synthesized from **3** as follows. The oxidation of **3** with mCPBA in chloroform afforded the crude epoxide, which was further treated with *p*-toluenesulfonic acid in refluxing chloroform to give **21** in 61.4% yield.[27] The demethylation of **21** with boron tribromide in dichloromethane afforded a phenol **22** (60.6%), which was reduced with lithium aluminum hydride to give 6β-hydroxyferruginol (**23**)[24] (80.2%) whose spectral data were identical in every respect to the natural **23**.

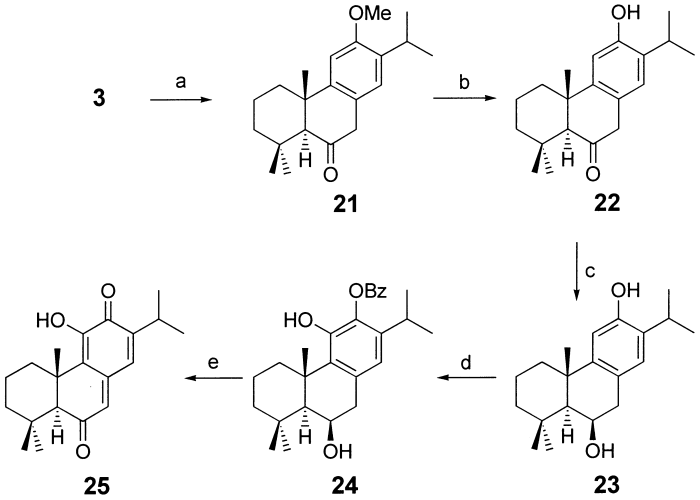


Scheme 3. Reagents and conditions: (a) i. BH_3, THF, rt, 12 h; ii. H_2O_2–30%NaOH, rt, 6 h, two steps, 72%; (b) Jones' reagent, acetone, 0 °C, 20 min, 85.2%; (c) EtSH, NaH, DMF, 120 °C, 3 h, 98.7%; (d) SO_2Cl_2, CCl_4, rt, 20 h, 97.7%; (e) LiCl, pyridine, 110 °C, 5 h, 85.9%; (f) EtSH, NaH, DMF, 110 °C, 3 h, 96.6%.

Oxidation of the phenol at C-11 of **23** with PBO in chloroform yielded intermediate **24** (72.4%)[27] whose benzoyl group was removed reductively with lithium aluminum hydride and subsequent oxidation of the crude catechol using the Jones' reagent afforded taxodione (**25**)[12,16,25] in quantitative yield (Scheme 4).

Antibacterial activities

Antibacterial activities against MRSA and VRE of the synthesized abietane diterpenes and their derivatives were then evaluated. The minimum inhibitory concentrations (MIC) of synthesized phenolic diterpenes and their related compounds against MRSA and VRE were measured (Tables 1 and 2). Compounds in Table 1 exhibited weaker MIC against MRSA and VRE, whereas compounds in Table 2 indicated stronger activity. The MIC of the potent compounds were evaluated against further 2 species of MRSA and 2 species of VRE. In Table 2, all compounds showed comparable activities against 3 species of both bacteria, MRSA and VRE, respectively. Phenols at C-12 showed more potent activity than the methyl ethers (comparing **4** and **5**, **21** and **22**). Catechol **12** showed strikingly increased activity compared with its ester **11**, the MIC reduced from 128 μg/mL to 6 μg/mL for MRSA (664); 128 μg/mL to 8 μg/mL for VanC, respectively. But methyl carnosoate (**26**), which has catechol in C ring together with ester carbonyl group at C-20 position, isolated from *Salvia officinalis*,[28] showed weaker activity. In Table 2, demethylcryptojaponol (**12**), salvinolone (**14**), 12-hydroxyabieta-8,11,13-trien-6-one (**22**), 6β-hydroxyferruginol (**23**) and taxodione (**25**) showed potent activity against



Scheme 4. (a) (i) mCPBA, $CHCl_3$, 3–8 °C, 4.5 h; (ii) TsOH, $CHCl_3$, reflux, 2 h, two steps, 61.4%; (b) BBr_3, CH_2Cl_2, 20 °C, 2.5 h, 60.6%; (c) $LiAlH_4$, THF, reflux, 1 h, 80.2%; (d) BPO, $CHCl_3$, 35 °C, 48 h, 72.4%; (e) (i) $LiAlH_4$, THF, reflux, 1.5 h; (ii) Jones' reagent, acetone, 0 °C, 5 min, two steps, 97.9%.

both bacteria with MIC of 4–10 μg/mL for MRSA and with MIC of 4–16 μg/mL for VRE, respectively. Quinone methide, 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**), showed the most potent activity (0.5–1 μg/mL of MIC) against both MRSA and VRE. Royleanone (**9**), which has *para*-quinone group at C-11 and C-14 position, exhibited weaker antimicrobial activity. Oxidation at C-6 increased the activity (by comparison of **5** with **22** and **23**, **6** with **24**), whereas oxidation at C-7 strikingly decreased the activity (by comparison between **17** and **5**, between **11** and **10**).

From these results, we found that the structure requirements for potent activity can be summarized in three types: (a) quinone methides, (b) catechol with carbonyl function at C-7, (c) alcohol or ketone at C-6 of ferruginol. We also found that most compounds showed comparable activity against both bacteria, MRSA and VRE. As Evans reported that recemic ferruginol (**5**) showed relatively strong activity against MRSA, we evaluated anti-MRSA activity of the three previously synthesized ferruginols, natural (+)-ferruginol, unnatural (−)-ferruginol and (±)-ferruginol. It is interesting that unnatural (−)-ferruginol had the most potent activity of the three against both MRSA and VRE. Evans reported that racemic ferruginol (**5**) showed MIC of 8 μg/mL against their MRSA and totarol was about 4 times more active than racemic **5** against their MRSA with 2 μg/mL of MIC.[2] In our results, natural ferruginol and racemic ferruginol indicated very weaker activity, with 125 μg/mL of MIC for MRSA(664) at least. These differences may be attributed to the difference of the strain of the tested MRSA. Quinone methide **7** showed stronger activity (0.5–1 μg/mL of MIC) compared to vancomycin with about 2–4 times against MRSA and 30–500 times against VRE. This shows the high potential of quinone methide **7** for disinfectant or ointment for MRSA and VRE.

At present, the antibacterial mechanism of tested compounds is not clear; further studies are needed to identify the activity modes.

Table 1. MIC of synthesized phenolic diterpenes and their related compounds with weaker activity against MRSA and VRE

	Strains, MIC (μg/mL)	
Compounds	MRSA664	VanC
1	64	128
2	64	128
3	> 128	> 128
4	> 64	> 64
6	> 64	> 64
8	> 64	> 64
9	32	> 64
10	64	64
11	128	128
13	64	128
15a	> 128	> 128
15b	> 128	> 128
16	> 128	> 128
17	> 128	> 128
18	> 64	> 64
19	> 128	> 128
20	> 64	> 64
21	> 128	> 128
24	32	> 64
26	> 128	> 128

Conclusion

Variously oxidized 12 natural abietans, 6,7-dehydroferrugiol methyl ether (**3**), ferruginol (**5**) (four steps, 66.5%), 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**7**) (six steps, 7.2%), royleanone (**9**) (seven steps, 17.1%), demethylcryptojaponol (**12**) (eight steps, 23.1%), salvinolone (**14**) (nine steps, 20.1%), sugiol methyl ether (**16**) (four steps, 43.3%), sugiol (**17**) (five steps, 41.9%), 5,6-dehydrosugiol methyl ether (**19**) (six steps, 36.3%), 5,6-dehydrosugiol (**20**) (seven steps, 35.1%), 6β-hydroxyferruginol (**23**) (five steps, 21.1%) and taxodione (**25**) (seven steps, 14.9%) were synthesized efficiently from the common intermediate **3** which was synthesized via polyene cyclization. Syntheses of **7**, **12**, **14** and **20** were first performed in this report. Anti-MRSA and anti-VRE activities of natural abietanes and their derivatives were evaluated. Taxodione **25**, phenols (**22** and **23**) and catechols (**12** and **14**) showed potent activity with MIC of 4–10 μg/mL against MRSA and 4–16 μg/mL against VRE. (−)-Ferruginol showed stronger activity than natural (+)-ferruginol. Quinone methide **7** had the most potent activity with MIC of 0.5–1 μg/mL against MRSA and 0.5–1 μg/mL against VRE, suggesting the high potential of **7** for disinfectant or ointment against MRSA and VRE.

Table 2. MIC of synthesized phenolic diterpenes and related compounds with potent activity against MRSA and VRE

	Strains, MIC (μg/mL)					
	MRSA			VRE		
Compounds	MRSA996	MRSA730	MRSA664	VanA	VanB	VanC
7	1	1	0.5	0.5	1	0.5
12	4	4	6	8	8	8
14	6	6	8	16	16	16
22	4	4	4	4	6	6
23	8	8	8	8	16	16
25	10	8	8	4	6	4
Vancomycin	2	2	2	256	128	16
5:(±)-Ferruginol			125			62.5
(+)-Ferruginol			> 125			> 125
(−)-Ferruginol			62.5			31.3

Experimental

General

NMR spectra[29] were measured on a JEOL JNM-EX270 spectrometer (^{1}H: 270 MHz; ^{13}C: 67.8 MHz) and a JEOL JNM AL400 (^{1}H: 400 MHz; ^{13}C: 100 MHz) for samples in $CDCl_3$, C_5D_5N or DMSO-d_6 containing tetramethylsilane as internal standard, *J*-values in Hz. IR spectra were measured on a JEOL JIR-WINSPEC 50 infrared spectrometer, UV spectra on a JASCO UVDEC-460 spectrometer. Mass spectra were recorded on a JEOL JMS-SX102A spectrometer. Melting points (mp) were measured on a MEL-TEMP (Laboratory Device) and were uncorrected. TLC was carried out on Kiesel-gel GF_{254} (0.25 mm thickness). Silica gel 60 (70–230 mesh ASTM) was used for column chromatography.

7α-Carboxyabieta-8,11,13-trien-12-methyl ether (2). Under argon, a mixture of **1** (252 mg, 0.834 mmol) and $AlCl_3$ (550 mg) in dichloromethane (12 mL) was stirred for 10 min and then 2-chloropropane (2.9 mL, 13.4 mmol) was added to the mixture. The mixture was further stirred for 40 h at 40 °C. The reaction was stopped by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (EtOAc). The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to give **2** as oily solid (232 mg, 0.674 mmol, 80.9%): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 6.99 (1H, s), 6.73 (1H, s), 3.84 (1H, d, J = 6.3 Hz), 3.79 (3H, s), 3.21 (1H, sept, J = 6.8 Hz), 2.28–2.18 (2H, m), 2.02–1.89 (1H, m), 1.78–1.57 (3H, m), 1.51–1.36 (2H, m), 1.33–1.23 (1H, m), 1.18 (3H, d, J = 6.8 Hz), 1.16 (3H, d, J = 6.8 Hz), 1.18 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.07, 156.00, 148.65, 134.31, 127.65, 122.05, 106.34, 55.27, 46.79, 44.24, 41.46, 38.54, 38.02, 33.22, 33.01, 29.80, 26.62, 24.85, 22.84, 22.65, 21.64, 19.38; IR (KBr) cm^{-1} 3474, 2929, 1706, 1500, 1459, 1253, 1178; EIMS *m*/*z* (% rel. int.) 344 (M^+, 10), 331 (30), 301 (100), 287 (39), 259 (36), 243 (38), 217 (50), 205 (39), 175 (69), 173 (45), 167 (40), 70 (49); HREIMS *m*/*z* calcd for $C_{22}H_{32}O_3$ 344.2351, found 344.2338; UV λ_{max} nm (EtOH, ε) 207 (1.89×10^4), 277 (2.57×10^3), 285 (2.45×10^3).

6,7-Dehydroferruginol methyl ether (3). A mixture of **2** (233 mg, 0.677 mmol), lead tetraacetate (LTA, 1 g) and $Cu(OAc)_2$ (135 mg) in quinoline (10 mL) was stirred at 125 °C for 16 h under argon. The mixture was acidified with 1 M HCl and was then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a column of silica gel with hexane–EtOAc to yield **3** as yellow oil (176 mg, 0.592 mmol, 87.4%): IR (NaCl) cm^{-1} 2958, 1714, 1604, 1500, 1463, 1051, 892, 850, 767; EIMS *m*/*z* (% rel. int.) 298 (M^+, 100), 283 (30), 241 (45), 216 (65), 213 (43), 199 (34), 173 (34); HREIMS *m*/*z* calcd for $C_{21}H_{30}O$ 298.2297, found 298.2303; UV λ_{max} nm (EtOH, ε) 221 (4.66×10^3), 279 (1.95×10^3).

Ferruginol methyl ether (4). A mixture of Pd/C (80 mg) and **3** (425 mg, 1.426 mmol) in EtOAc (10 mL) was stirred at room temperature under H_2 for 24 h. The mixture was filtered through Celite and the solution was evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to give **4** (421 mg, 1.403 mmol, 98.3%) as pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.83 (1H, s), 6.72 (1H, s), 3.78 (3H, s), 3.21 (1H, sept, J = 6.8 Hz), 2.88–2.73 (2H, m), 2.25 (1H, br d, J = 12.8 Hz), 1.87–1.21 (8H, m), 1.20 (3H, s), 1.18 (3H, d, J = 6.8 Hz), 1.17 (3H, d, J = 6.8 Hz), 0.94 (3H, s) 0.92 (3H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 154.83, 147.95, 133.99, 126.79, 126.29, 106.47, 55.62, 50.53, 41.76, 38.98, 37.92, 33.54, 33.43, 29.93, 26.52, 24.94, 23.02, 22.80, 21.74, 19.47, 19.34; IR (NaCl) cm^{-1} 2958, 1614, 1500, 1463, 1249, 1207, 1164, 1066, 1045, 892, 848; EIMS *m*/*z* (% rel. int.) 300 (M^+, 89), 285 (100), 257 (9), 243 (20), 229 (16), 215 (35), 203 (32), 201 (35), 189 (38), 163 (19), 129 (18), 69 (16), 55 (15); HREIMS *m*/*z* calcd for $C_{21}H_{32}O$ 300.2453, found 300.2431; UV λ_{max} nm (EtOH, ε) 205 (4.22×10^3), 280 (3.59×10^2).

Ferruginol (5). A solution of **4** (299 mg, 0.966 mmol) and boron tribromide (0.35 mL) in dichloromethane (10 mL) was stirred at 0–5 °C for 2 h under argon. The solution was then poured into water and extracted with EtOAc. The combined solution was washed with brine, dried and then evaporated to dryness. The crude product was purified by column chromatography (silica gel, hexane–EtOAc) to give ferruginol (**5**) (262 mg, 0.916 mmol, 94.9%) as oil.

12-Benzoyloxyabieta-8,11,13-trien-11-ol (6). Benzoyl peroxide (279 mg, 1.153 mmol) was added to a solution of ferruginol (**5**) (177 mg, 0.618 mmol) in chloroform (5 mL) and then stirred for 7 h at room temperature until the disappearance of starting material with monitoring by NMR (because of their similar polarity). The reaction was stopped by addition of 0.5 M aqueous sodium thiosulfate (3 mL) and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a column of silica gel with hexane–EtOAc to afford **6** (179 mg, 0.441 mmol, 71.4%) as crystals: mp 133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (2H, d, J = 7.1 Hz), 7.67 (1H, t, J = 7.4 Hz), 7.53 (2H, t, J = 7.5 Hz), 6.60 (1H, s), 5.17 (1H, s), 3.11 (1H, br d, J = 12.4 Hz), 2.89–2.82 (3H, m), 1.82 (1H, br d, J = 12.7 Hz), 1.34 (3H, s), 1.19 (3H, d, J = 6.8 Hz), 1.16 (3H, d, J = 6.8 Hz), 0.96 (3H, s), 0.93 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.91, 145.63, 137.41, 135.61, 134.77, 134.75, 133.93, 130.33, 130.29, 130.27, 128.73, 128.66, 118.53, 52.81, 41.51, 39.60, 39.42, 36.55, 33.76, 32.90, 27.65, 23.09, 23.00, 22.21, 20.17, 19.43, 19.18; IR (KBr) cm^{-1} 3453, 2960, 1743, 1708, 1452, 1425, 1265, 1060, 1024, 711; EIMS *m*/*z* (% rel. int.) 406 (M^+, 23), 215 (9), 189 (12), 128 (10), 106 (25), 105 (100), 77 (61), 51 (11); HREIMS *m*/*z* calcd for $C_{27}H_{34}O_3$ 406.2508, found 406.2484; UV λ_{max} nm (EtOH, ε) 222 (3.73×10^4), 230 (2.10×10^4), 272 (6.64×10^3).

11-Hydroxy-12-oxo-7,9(11),13-abietatriene (7). A solution of DIBAL in toluene (0.096 mmol) was added to a solution of **6** (10 mg, 0.024 mmol) in THF (2 mL) under argon and the solution was stirred at −15 °C for 3 h.

The reaction mixture was extracted with EtOAc–water. The organic layer was washed with brine, dried and evaporated to dryness. The residue was oxidized by air and then chromatographed on a silica gel column with hexane–EtOAc to give **7** (1.1 mg, 0.004 mmol, 15.1%) as oil.

12-Benzoyloxyabieta-8,12-dien-11,14-dione (8). *meta*-Chloroperbenzoic acid (29 mg, 0.168 mmol) was added to a solution of **6** (34 mg, 0.084 mmol) in dichloromethane (3 mL) and the solution was stirred at room temperature for 12 h. The reaction was stopped by addition of aqueous 5% $Na_2S_2O_3$ solution (3 mL). The mixture was extracted with EtOAC and the organic layer was washed with 5% aqueous NaOH and brine successively, dried and evaporated. The residue was chromatographed on a column of silica gel with hexane–EtOAc to yield **8** (14 mg, 0.036 mmol, 42.3%) as yellow crystals: mp 196–197 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (2H, dd, J = 7.9, 1.6 Hz), 7.65 (1H, br t, J = 7.6 Hz), 7.51 (2H, t, J = 7.5 Hz), 3.18 (1H, sept, J = 6.9 Hz), 2.74 (1H, dd, J = 20.2, 5.3 Hz), 2.39–2.29 (1H, m), 1.88 (1H, dd, J = 13.2, 7.2 Hz), 1.28 (3H, s), 1.23 (3H, d, J = 6.9 Hz), 1.20 (3H, d, J = 6.9 Hz), 0.94 (3H, s), 0.89 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.28, 163.98, 134.01, 130.43, 128.65, 128.15, 51.49, 41.37, 38.76, 36.22, 33.59, 33.51, 26.04, 25.08, 21.84, 20.59, 20.32, 18.91, 17.49; IR (KBr) cm^{-1} 2925, 1741, 1664, 1646, 1452, 1236, 1047, 1004, 707; EIMS m/z (% rel. int.) 420 (M^+, 8), 324 (5), 315 (5), 270 (12), 105 (100), 77 (21), 69 (8), 55 (7); HREIMS m/z calcd for $C_{27}H_{32}O_4$ 420.2301, found 420.2288; UV λ_{max} nm (EtOH, ϵ) 233 (1.86×10^4), 263 (1.99×10^4), 333 (3.36×10^2).

Royleanone (9). A solution of **8** (14 mg, 0.033 mmol) and $NaHCO_3$ (43 mg) in MeOH:H_2O (6:1, 7 mL) was refluxed for 1.5 h. The reaction mixture was extracted with EtOAc, and the organic layer was washed with brine, dried and evaporated. The crude product was chromatographed on a column of silica gel with hexane–EtOAc to give **9** (9 mg, 0.028 mmol, 85%) as pale yellow crystals: mp 182–183 °C; IR (KBr) cm^{-1} 3332, 2964, 2919, 2850, 1735, 1652, 1648, 1604, 1459, 1405, 1376, 1253, 736; EIMS m/z (% rel. int.) 316 (M^+, 100), 301 (36), 231 (25), 220 (29), 219 (31), 205 (32), 83 (29), 69 (43), 55 (42); HREIMS m/z calcd for $C_{20}H_{28}O_3$ 316.2038, found 316.2061; UV λ_{max} nm (EtOH, ϵ) 271 (1.11×10^4), 412 (4.5×10^2).

11 - Acetoxy - 12 - benzoyloxyabieta - 8,11,13 - triene (10). Isopropenyl acetate (0.837 mL, 7.7 mmol) and TsOH (17 mg) were added to a solution of **6** (310 mg, 0.763 mmol) in toluene (5 mL). After refluxing for 5 h, the reaction mixture was concentrated and the mixture was chromatographed on silica gel with hexane–EtOAc to afford **10** (262 mg, 0.585 mmol, 76.7%), which was recrystallized from EtOAc to give colorless crystals: mp 178–179 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.19 (2H, d, J = 7.6 Hz), 7.66 (1H, t, J = 7.4 Hz), 7.52 (2H, t, J = 7.9 Hz), 6.92 (1H, s), 2.94–2.78 (3H, m), 1.89 (3H, s), 1.38 (3H, s), 1.21 (3H, d, J = 7.2 Hz), 1.16 (3H, d, J = 7.2 Hz), 0.94 (3H, s), 0.89 (3H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 168.84, 164.62, 141.09, 140.86, 139.66, 139.46, 138.45, 138.22, 135.68, 133.69, 130.15, 129.14, 128.69, 124.60, 51.61, 40.95, 39.56, 36.89, 33.72, 32.44, 27.35, 22.97, 22.07, 21.98, 21.48, 20.44, 20.32, 19.28, 19.16; IR (KBr) cm^{-1} 2962, 1770, 1731, 1600, 1475, 1415, 1369, 1189, 1085, 1014, 917, 879, 709; EIMS m/z (% rel. int.) 448 (M^+, 37), 408 (27), 371 (27), 341 (31), 238 (31), 106 (100), 66 (26); HREIMS m/z calcd for $C_{29}H_{36}O_4$ 448.2614, found 448.2581; UV λ_{max} nm (EtOH, ϵ) 216 (2.35×10^4), 230 (2.49×10^4).

11 - Acetoxy - 12 - benzoyloxyabieta - 8,11,13 - trien - 7 - one (11). Chromium trioxide (57 mg, 0.57 mmol) was added to a solution of **10** (126 mg, 0.281 mmol) in acetic acid (3 mL), and allowed to stand at room temperature for 8 h. The reaction mixture was poured into water and was extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The crude product was purified by column chromatography of silica gel with hexane–EtOAc to afford **11** (86 mg, 0.186 mmol, 65.9%), which was recrystallized from EtOAc to give colorless crsytals: mp 160–161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (2H, d, J = 7.2 Hz), 8.06 (1H, s), 7.69 (1H, t, J = 7.6 Hz), 7.56 (2H, t, J = 7.2 Hz), 2.95 (1H, sept, J = 6.4 Hz), 2.74 (1H, dd, J = 17.8, 4.1 Hz), 2.63 (1H, dd, J = 17.8, 13.6 Hz), 1.93 (3H, s), 1.28 (3H, s), 1.27 (3H, d, J = 6.4 Hz), 1.23 (3H, d, J = 6.4 Hz), 0.95 (6H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.84, 168.03, 164.29, 145.22, 145.08, 144.96, 144.88, 140.51, 140.12, 134.13, 130.74, 130.23, 128.91, 128.55, 124.16, 49.60, 40.70, 40.48, 37.29, 35.75, 33.61, 32.97, 27.66, 23.06, 22.79, 21.47, 20.37, 20.31, 19.02; IR (KBr) cm^{-1} 2964, 1774, 1747, 1689, 1452, 1247, 1197, 1178, 1058, 1024, 711; EIMS m/z (% rel. int.) 462 (M^+, 8), 423 (5), 275 (8), 238 (5), 194 (4), 123 (6), 106 (100), 93 (6), 84 (8), 78 (14), 58 (8), 56 (7); HREIMS m/z calcd for $C_{29}H_{34}O_5$ 462.2406, found 462.2451; UV λ_{max} nm (EtOH, ϵ) 238 (3.55×10^4).

Demethylcryptojaponol (12). Sodium bicarbonate (27 mg, 0.321 mmol) was added to a solution of **11** (11 mg, 0.023 mmol) in MeOH:H_2O (4:1, 5 mL) under argon. After refluxing for 1.5 h, the reaction mixture was extracted with EtOAc and the organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to yield **12** (7 mg, 0.022 mmol, 96.3%) as pale yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (1H, s), 5.65 (1H, s), 5.63 (1H, s), 3.10 (1H, br d, J = 13.2 Hz), 3.02 (1H, sept, J = 6.8 Hz), 2.64 (1H, dd, J = 17.1, 3.2 Hz), 2.54 (1H, dd, J = 17.1, 14.1 Hz), 1.88 (1H, dd, J = 14.1, 3.2 Hz), 1.81–1.73 (1H, m), 1.64–1.43 (4H, m), 1.40 (3H, s), 1.29 (3H, d, J = 6.8 Hz), 1.26 (3H, d, J = 6.8 Hz), 0.98 (3H, s), 0.94 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.86, 146.09, 140.93, 138.48, 131.52, 125.29, 117.94, 50.22, 41.07, 40.19, 36.84, 35.62, 33.53, 33.16, 27.41, 22.55, 22.39, 21.60, 19.11, 18.72.

6-Chloro-11-acetoxy-12-benzoyloxyabieta-8,11,13-trien-7-one (13). SO_2Cl_2 (0.04 mL) was added dropwise to a solution of **11** (37 mg, 0.079 mmol) in CCl_4 (1.5 mL), and the solution was stirred at 60 °C for 40 h. The reaction mixture was concentrated to give the crude product which was chromatographed on a silica gel column with

hexane–EtOAc to yield **13** (37 mg, 0.075 mmol, 94.9%) as colorless oily solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19–8.16 (2H, m), 7.74 (1H, s), 7.69 (1H, t, J = 7.2 Hz), 7.56 (2H, t, J = 7.6 Hz), 4.61–4.56 (1H, m), 2.97 (1H, sept, J = 7.2 Hz), 2.32 (1H, t, J = 4.1 Hz), 2.13–2.10 (1H, m), 1.98 (3H, s), 1.27 (3H, d, J = 7.2 Hz), 1.25 (3H, d, J = 7.2 Hz), 1.21 (3H, s), 1.20 (3H, s), 1.12 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.83, 168.07, 164.40, 145.34, 142.23, 141.25, 140.98, 138.78, 134.22, 131.43, 130.24, 130.20, 128.93, 128.36, 124.94, 56.34, 56.12, 41.64, 41.43, 37.59, 36.56, 35.12, 27.76, 25.69, 25.13, 22.92, 22.57, 20.36, 18.84; IR (NaCl) cm^{-1} 2964, 2931, 2871, 1774, 1745, 1700, 1452, 1369, 1307, 1149, 1079, 904, 860, EIMS m/z (% rel. int.) 497 (M^+, 27), 422 (32), 380 (36), 225 (43), 210 (37), 182 (38), 154 (39), 130 (39), 125 (44), 106 (100), 96 (51), 56 (89); HREIMS m/z calcd for $C_{29}H_{33}ClO_5$ 496.2017, found 496.2012; UV λ_{max} nm (EtOH, ϵ) 231 (1.92×10^4), 259 (1.00×10^4).

Salvinolone (14). Lithium chloride (8 mg, 0.19 mmol) was added to a solution of **13** (14.7 mg, 0.029 mmol) in pyridine (1.5 mL) and the mixture was refluxed for 10 h. The mixture was acidified to acidity slightly with 1 M HCl solution. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried and evaporated. To the residue, a solution of sodium bicarbonate (26 mg, 0.309 mmol) in MeOH:H_2O (6:1, 5 mL) was added and the mixture was refluxed for 1 h under argon. The reaction mixture was extracted with EtOAc and the organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to yield **14** (8 mg, 0.025 mmol, 87.8%) as oily solid: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.72, 175.38, 144.59, 141.32, 137.33, 132.52, 124.01, 123.42, 115.68, 42.24, 40.45, 38.22, 34.35, 33.16, 29.45, 27.46, 24.94, 22.71, 22.56, 18.81.

12-Methoxyabieta-8,11,13-trien-7-ol (15a and 15b). Borane–tetrahydrofuran complex solution (BH_3·THF 1 M, 5.29 mmol) was added to a solution of **3** (157 mg, 0.527 mmol) in THF (20 mL) under argon, and the mixture was stirred for 12 h at room temperature. Water (6 mL), 30% NaOH (12 mL) and 30% H_2O_2 (12 mL) were added to the reaction mixture, and the mixture was stirred for a further 6 h at ambient temperature. The mixture was extracted with EtOAc and the organic layer was washed with brine, dried and evaporated. The crude product was purified by column chromatography (silica gel, hexane–EtOAc) to give 12-methoxyabieta-8,11,13-trien-7α-ol (**15a**) as a pale yellow oil and 12-methoxyabieta-8,11,13-trien-7β-ol (**15b**) as colorless crystals (**15a**:**15b** = 1:1, total 120 mg, 0.379 mmol, 72.0%). **15a** (7β-H): ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.14 (1H, s), 6.71 (1H, s), 4.78 (1H, br s), 3.85 (1H, d, J = 4.4 Hz), 3.80 (3H, s), 3.23 (1H, sept, J = 6.8 Hz), 2.24 (1H, br d, J = 12.3 Hz), 2.02–1.25 (8H, m), 1.21 (3H, d, J = 6.8 Hz), 1.18 (3H, d, J = 6.8 Hz), 1.14 (3H, s), 0.98 (3H, s), 0.93 (3H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 156.66, 148.33, 134.87, 128.28, 127.45, 105.83, 68.01, 55.38, 44.61, 41.60, 38.59, 38.28, 33.24, 33.07, 28.77, 26.66, 24.04, 22.94, 22.58, 21.76, 19.39; IR (NaCl) cm^{-1} 3453, 2958, 1714, 1602, 1500, 1463, 1363, 1243, 1047, 852; EIMS m/z (% rel. int.) 316 (M^+, 100), 298 (57), 273 (64), 241 (57), 213 (60), 192 (88), 171 (41), 69 (25); HREIMS m/z calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2386; UV λ_{max} nm (EtOH, ϵ) 210 (2.12×10^3), 280 (2.97×10^3). **15b** (7α-H): mp 142–143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (1H, s), 6.72 (1H, s), 5.00 (1H, br s), 4.99 (1H, dd, J = 3.6, 1.6 Hz), 3.80 (3H, s), 3.22 (1H, sept, J = 6.8 Hz), 2.47 (1H, br d, J = 13.6 Hz), 2.22 (1H, br d, J = 12.6 Hz), 1.81–1.59 (4H, m), 1.52–1.35 (3H, m), 1.31–1.22 (1H, m), 1.21 (3H, d, J = 6.8 Hz), 1.18 (3H, d, J = 6.8 Hz), 1.16 (3H, s), 1.01 (3H, s), 0.95 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.41, 150.40, 134.47, 128.97, 121.88, 105.94, 81.53, 55.34, 44.43, 41.49, 38.43, 38.29, 33.21, 33.09, 26.58, 24.11, 23.21, 22.90, 22.53, 21.77, 19.33; IR (KBr) cm^{-1} 3415, 2998, 1614, 1571, 1504, 1471, 1162, 1035, 943, 856, 823, 755; EIMS m/z (% rel. int.) 316 (63), 301 (100), 275 (21), 243 (15), 233 (15), 219 (17), 205 (13), 194 (13); HREIMS m/z calcd for $C_{21}H_{32}O_2$ 316.2402, found 316.2361; UV λ_{max} nm (EtOH, ϵ) 230 (6.12×10^3), 279 (1.33×10^3).

Sugiol methyl ether (16). Jones' reagent (0.2 mL) was added to a solution of alcohols **15a** and **15b** (92 mg, 0.291 mmol) in acetone (10 mL) and the mixture was allowed to stand in an ice bath for 20 min. The mixture was extracted with EtOAc and the organic layer was washed with brine and dried. The organic layer was concentrated under vacuum and the crude product was chromatographed on a silica gel column with hexane–EtOAc to yield **16** (78 mg, 0.248 mmol, 85.2%) as colorless crystals: mp 124–125 °C; IR (KBr) cm^{-1} 3030, 2919, 1672, 1594, 1562, 1494, 1305, 1274, 1218, 1187, 1029, 912, 840; HREIMS m/z calcd for $C_{21}H_{30}O_2$ 314.2246, found 314.2258.

Sugiol (17). NaH (65 mg, 2.7 mmol) was added to a solution of EtSH (0.2 mL, 2.7 mmol) in DMF (3 mL) under argon and stirred for 20 min at ambient temperature. To the mixture, **16** (34 mg, 0.108 mmol) in DMF (2 mL) was added and the mixture was stirred for a further 3 h at 120 °C. The reaction was stopped by addition of a saturated solution of NH_4Cl (1 mL) and the mixture was extracted with EtOAc and the organic layer was washed with brine and dried. The organic layer was concentrated and the residue was purified by column chromatography (silica gel, hexane–EtOAc) to afford **17** (32 mg, 0.107 mmol, 98.7%) as colorless crystals: mp 238–239 °C; HREIMS m/z calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2084; UV λ_{max} nm (EtOH, ϵ) 233 (5.01×10^3), 290 (5.57×10^3).

6-Chlorosugiol methyl ether (18). A solution of SO_2Cl_2 (0.3 mL) in CCl_4 (1 mL) was added dropwise to a solution of **16** (55 mg, 0.175 mmol) in CCl_4 (6 mL) under argon and the solution was allowed to react at ambient temperature for 20 h. After the reaction was stopped by addition of water, the mixture was washed with aqueous saturated $NaHCO_3$ solution, and the organic layer was extracted with EtOAc, washed with brine and dried. The organic phase was concentrated to give a crude yellow solid which was chromatographed on a silica gel column with hexane–EtOAc to yield **18** (59 mg, 0.171 mmol, 97.7%) as pale yellow crystals: mp 108–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (1H, s), 6.72

(1H, s), 4.61 (1H, d, $J=9.5$ Hz), 3.91 (3H, s), 3.25 (1H, sept, $J=6.8$ Hz), 2.11 (1H, d, $J=9.5$ Hz), 1.22 (3H, s), 1.22 (3H, d, $J=6.8$ Hz), 1.20 (3H, d, $J=6.8$ Hz), 1.17 (3H, s), 1.11 (3H, s); ^{13}C NMR ($CDCl_3$, 67.8 MHz), δ 193.24, 161.66, 153.81, 135.79, 126.44, 123.75, 103.30, 59.66, 56.49, 55.52, 42.75, 38.80, 37.35, 35.46, 34.87, 26.65, 26.13, 22.53, 22.37, 18.64; IR (KBr) cm^{-1} 2923, 1687, 1606, 1567, 1496, 1469, 1255, 1174, 1049, 908, 858, 642; EIMS *m/z* (% rel. int.) 350 (M + 2, 17), 348 (M^+, 49), 333 (40), 299 (19), 229 (21), 217 (100), 215 (21), 128 (18), 55 (15); HREIMS *m/z* calcd for $C_{21}H_{29}ClO_2$ 348.1856, found 348.1854; UV λ_{max} nm (EtOH, ϵ) 233 (1.08×10^4), 300 (1.08×10^4).

5,6-Dehydrosugiol methyl ether (19). To a solution of **18** (40 mg, 0.115 mmol) in pyridine (6 mL), lithium chloride (244 mg) was added and the mixture was stirred at 110 °C for 5 h. The reaction mixture was acidified with 1 M HCl solution and was extracted with EtOAc. The organic layer was washed with brine and dried. The organic phase was concentrated and the crude product was purified by column chromatography (silica gel, hexane–EtOAc) to give **19** (31 mg, 0.099 mmol, 85.9%) as white crystals: mp 167–168 °C.

5.6-Dehydrosugiol (20). NaH (142 mg, 5.9 mmol) was added to a solution of EtSH (0.44 mL, 5.9 mmol) in DMF (5 mL) under argon and the mixture was stirred for 10 min at ambient temperature. To the mixture, **19** (74 mg, 0.237 mmol) in DMF (3 mL) was added and the mixture was stirred for a further 3 h at 110 °C. The reaction was stopped by addition of aqueous saturated NH_4Cl (1 mL) and the mixture was treated as described for **17** to afford **20** (68 mg, 0.228 mmol, 96.6%) as white crystals: mp 274–275 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.01 (1H, s), 6.86 (1H, s), 6.45 (1H, s), 5.74 (1H, br s), 3.19 (1H, sept, $J=7.0$ Hz), 2.35 (1H, br d, $J=12.5$ Hz), 2.05–1.94 (1H, m), 1.78–1.55 (3H, m), 1.50 (3H, s), 1.45 (1H, dd, $J=14.0$, 4.4 Hz), 1.34 (3H, s), 1.30 (3H, d, $J=7.0$ Hz), 1.28 (3H, d, $J=7.0$ Hz), 1.25 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.46, 173.57, 158.04, 154.10, 133.76, 124.88, 124.28, 123.33, 111.05, 41.19, 40.37, 37.73, 37.56, 32.65, 29.19, 26.95, 22.58, 22.41, 18.69; EIMS *m/z* (% rel. int.) 298 (M^+, 100), 283 (63), 255 (43), 229 (89), 213 (97), 199 (43), 187 (30),165 (22), 69 (43), 55 (21); HREIMS *m/z* calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1958.

12-Methoxyabieta-8,11,13-trien-6-one (21). *meta*-Chloroperbenzoic acid (446 mg) was added to a solution of **3** (321 mg, 1.077 mmol) in chloroform (12 mL) in three portions and the solution was stirred at 3∼8 °C for 4.5 h. After addition of aqueous 5% $Na_2S_2O_3$ solution (3 mL) to stop the reaction, the mixture was extracted with EtOAc. The organic layer was washed with 5% aqueous NaOH and brine successively, dried and evaporated. The crude product was dissolved in chloroform (20 mL) and was refluxed with *p*-toluenesulfonic acid (280 mg) for a further 2 h. The reaction mixture was washed with aqueous saturated $NaHCO_3$ solution and was then extracted with water and EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a silica gel column with hexane–EtOAc to give **21** (208 mg, 0.662 mmol, 61.4%) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (1H, s), 6.79 (1H, s), 3.83 (3H, s), 3.58 (1H, d, $J=21.4$ Hz), 3.51 (1H, d, $J=21.4$ Hz), 3.26 (1H, sept, $J=6.8$ Hz), 2.42 (1H, s), 2.31 (1H, br d, $J=9.5$ Hz), 1.78–1.64 (3H, m), 1.42 (1H, br d, $J=14.6$ Hz), 1.31 (3H, s), 1.30–1.25 (1H, m), 1.20 (3H, d, $J=6.8$ Hz), 1.18 (3H, d, $J=6.8$ Hz), 1.16 (3H, s), 1.08 (3H, s); ^{13}C NMR ($CDCl_3$, 68.7 MHz) δ 210.02, 155.53, 146.86, 135.26, 125.78, 123.81, 105.72, 62.56, 55.61, 44.64, 42.85, 40.67, 38.66, 33.01, 32.70, 26.54, 24.65, 22.92, 22.72, 21.64, 18.79; IR (NaCl) cm^{-1} 2960, 1718, 1600, 1498, 1457, 1249, 1049; EIMS *m/z* (% rel. int.) 314 (M^+, 21), 313 (30), 285 (66), 259 (100), 258 (84), 243 (48), 229 (31), 217 (59), 215 (26), 187 (21), 165 (19), 128 (23), 69 (24); HREIMS *m/z* calcd for $C_{21}H_{30}O_2$ 314.2246, found 314.2242; UV λ_{max} nm (EtOH, ϵ) 216 (1.78×10^4), 243 (6.43×10^3), 276 (1.11×10^4), 333 (7.58×10^3).

12-Hydroxyabieta-8,11,13-trien-6-one (22). To a solution of **21** (297 mg, 0.945 mmol) in dichloromethane (10 mL), boron tribromide (0.27 mL) was added and the solution was stirred for 2.5 h at 20 °C under argon. The reaction was stopped by addition of water (1 mL) and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was concentrated and chromatographed on a silica gel column with hexane–EtOAc to afford **22** (172 mg, 0.573 mmol, 60.6%) as crystals: mp 134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.84 (1H, s), 6.76 (1H, s), 5.72 (1H, br s), 3.57 (1H, d, $J=21.6$ Hz), 3.56 (1H, d, $J=21.6$ Hz), 3.19 (1H, sept, $J=6.7$ Hz), 2.41 (1H, s), 2.21 (1H, br d, $J=10.8$ Hz), 1.75–1.60 (3H, m), 1.41 (1H, br d, $J=13.2$ Hz), 1.31 (3H, s), 1.24 (3H, d, $J=6.7$ Hz), 1.23 (3H, d, $J=6.7$ Hz), 1.13 (3H, s), 1.08(3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.88, 151.78, 147.16, 132.81, 126.03, 123.77, 110.45, 62.56, 44.62, 42.84, 40.27, 38.60, 32.97, 32.66, 26.81, 24.54, 22.76, 22.59, 21.61, 18.71; IR (KBr) cm^{-1} 2927, 1712, 1571, 1513, 1463, 1230, 1174, 1047, 1002, 964; EIMS *m/z* (% rel. int.) 300 (M^+, 89), 285 (100), 257 (45), 243 (45), 215 (38), 201 (30), 173 (26), 159 (21), 128 (23), 69 (16), 55 (16); HREIMS *m/z* calcd for $C_{20}H_{28}O_2$ 300.2089, found 300.2088; UV λ_{max} nm (EtOH, ϵ) 251 (5.85×10^3), 283 (8.77×10^3), 333 (7.95×10^3).

6β-Hydroxyferruginol (23). A mixture of **22** (67 mg, 0.223 mmol) and lithium aluminum hydride (200 mg) in dry THF (10 mL) was refluxed for 1 h. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The residue was chromatographed on a column of silica gel with hexane–EtOAc to give **23** (54 mg, 0.179 mmol, 80.2%) as white crystals: mp 175–176 °C; EIMS *m/z* (% rel. int.) 302 (M^+, 51), 269 (100), 227 (23), 199 (27), 185 (14), 159 (15), 69 (11), 55 (6); UV λ_{max} nm (EtOH, ϵ) 222 (7.19×10^3), 280 (4.78×10^3).

12-Benzoyloxyabieta-8,11,13-trien-6β,12-diol (24). Benzoyl peroxide (66 mg, 0.273 mmol) was added to a solution of **23** (21 mg, 0.069 mmol) in dry chloroform (3 mL) and the mixture was stirred at 35 °C for 48 h. The reaction was stopped by addition of 0.5 M $Na_2S_2O_3$

solution and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried. The solvent was removed and the residue was purified by chromatography on a column of silica gel with hexane–EtOAc to yield **24** (21 mg, 0.050 mmol, 72.4%) as pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (2H, dd, J=8.5, 1.5 Hz), 7.67 (1H, t, J=6.4 Hz), 7.54 (2H, t, J=8.4 Hz), 6.62 (1H, s), 5.32 (1H, br s), 4.65 (1H, d, J=4.0 Hz), 3.17–3.11 (2H, m), 3.03 (1H, br d, J=12.8 Hz), 2.92–2.84 (2H, m), 1.72 (3H, s), 1.28 (3H, s), 1.19 (3H, d, J=6.8 Hz), 1.17 (3H, d, J=6.8 Hz), 1.05 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.86, 145.63, 138.06, 135.38, 134.02, 133.52, 131.18, 130.32, 130.10, 128.78, 128.58, 125.36, 119.44, 65.85, 60.46, 54.33, 42.57, 42.28, 38.92, 38.84, 34.46, 34.34, 34.21, 27.68, 24.17, 23.04, 21.74; IR (NaCl) cm^{-1} 3570, 2925, 2854, 1731, 1265, 706; EIMS m/z (% rel. int.) 422 (M^+, 7), 300 (14), 105 (100), 97 (8), 81 (11), 77 (22), 69 (22), 57 (12), 55 (15); HREIMS m/z calcd for $C_{27}H_{34}O_4$ 422.2457, found 422.2456; UV λ_{max} nm (EtOH, ϵ) 230 (1.32×10^4), 270 (3.59×10^3).

Taxodione (25). Lithium aluminum hydride (17 mg) was added to a dry THF solution (6 mL) of **24** (16.5 mg, 0.039 mmol) under argon and the mixture was refluxed for 1.5 h. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was washed with brine, dried and evaporated. The crude product was dissolved in acetone (3 mL) and was immediately oxidized with the Jones reagent (4 drops) at 0 °C for 5 min. The mixture was neutralized with aqueous saturated $NaHCO_3$ (0.5 mL) and the mixture was extracted with water and EtOAc. The organic layer was washed with brine, dried and evaporated. The crude product was chromatographed on TLC of silica gel with hexane–EtOAc to give **25** (12 mg, 0.038 mmol, 97.9%) as an oily solid: IR (NaCl) cm^{-1} 3326, 2927, 1673, 1616, 1351, 1143, 906; EIMS m/z (% rel. int.) 314 (M^+, 100), 286 (86), 271 (79), 253 (33), 245 (83), 243 (34), 231 (64), 229 (30), 217 (42), 215 (39), 203 (35), 189 (28), 141 (31), 128 (35), 69 (48); HREIMS m/z calcd for $C_{20}H_{26}O_3$ 314.1882, found 314.1881.

Antibacterial activities

Test organisms, three strains of MRSA (MRSA664, MRSA730 and MRSA996) and three strains of VRE (VanA, VanB and VanC) were obtained from Department of Bacterial and Blood Products, National Institute of Infectious Disease of Japan.

Each compound was dissolved in DMSO and diluted in graded concentration with Mueller–Hinton broth. Minimum inhibitory concentrations (MIC) were determined by the broth microdilution method. The overnight broth cultures were diluted to approximately 10^8 CFU (colony forming units) mL^{-1} with water and further diluted to 10^7 CFU mL^{-1} with water. Test inoculum of 10^7 CFU mL^{-1} (5 μL) per spot was applied to 96-well micro-plates containing 0.1 mL of graded concentrations of each compound. After incubation at 37 °C for 18–20 h, the MIC was defined as the minimum concentration of the test compounds that resulted in no visible growth of bacteria, compared with the control which had no test compound. It should be noted that the concentration of DMSO in the medium did not affect the growth of any of the microorganisms tested. The MIC of each compound was determined at least twice.

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29. As the NMR spectral data of the many natural abietanes were recorded in C_5D_5N or DMSO in the literature, the NMR spectral data in $CDCl_3$ were recorded in this report for convenience.