Syntheses and Antibacterial Activities of Diterpene Catechol Derivatives with Abietane, Totarane and Podocarpane Skeletons against Methicillin-Resistant *Staphylococcus aureus* and *Propionibacterium acnes*

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Natural catechol, quinone and quinone methide diterpenes with abietane (15-deoxyfuerstione, taxodione) and totarane (dispermone, 12,13-dihydroxy-8,11,13-totaratriene-6-one), and podocarpane (nimbidiol, deoxynimbidiol) skeletons were synthesized using *ortho*-oxidation of phenol with *meta*-chlorobenzoyl peroxide. Minimum inhibitory activities of these diterpenes and previously synthesized natural diterpenes were measured against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Propionibacterium acnes*, which cause serious skin infection associated with acne. Abietaquinone methide and 8,11,13-totaratriene-12,13-diol showed potent activities against *S. aureus* (MRSA) and *P. acnes*, and no serious toxicity by oral dose to mice.

Key words quinone methide; catechol; anti-methicillin-resistant *Staphylococcus aureus*; *Propionibacterium acnes*; nimbidiol; 15-deoxyfuerstione

Various infections caused by antibiotic resistant bacteria necessitate the development of new types of antibacterial agents. Skin diseases like acne vulgaris are also known to be caused by the proliferation of various bacteria, especially *Propionibacterium acnes* and *Staphylococcus aureus* on the skin as well as in the foods of young people.[1] Natural catechols were reported to prevent various disease[2,3] together with the anti-oxidant activities.[4] Previously, we reported the total syntheses of variously oxidized twelve abietane diterpenes in racemic modification. In the investigation, we found that (±)-abietaquinone methide [(±)-**1**)] and (±)-taxodione [(±)-**2**)] showed potent anti-bacterial activity against Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[5,6] Isolations and syntheses of natural catechols are troublesome because of their high reactivity with oxygen.[7] Recently, we reported an efficient *ortho*-oxidation of phenols using *meta*-chlorobenzoyl peroxide (*m*CBPO)[8] and its applications for syntheses of optical active natural catechols,[9,10] abietaquinone methide[11] (**1**), 8,11,13-totaratriene-12,13-diol (**5**),[12,13] 6-deoxymaytenoquinone (**6**),[14] 8,11,13-totaratriene-12,13-dione (**10**)[14] and maytenoquinone (**14**).[12,13] There are many catechols with the similar tri-cyclic system of abietane, totarane or podocarpane skeleton. Abietane skeleton (see **1**—**4**) has an isopropyl group at C-13 whereas totarane skeleton (see **5**—**11**) has an isopropyl group at C-14 and podocarpane skeleton (see **12**—**14**) has no isopropyl group (Fig. 1). We have been interested in the implication of the isopropyl substituent on the catechol ring for the biological activities and the reactivity with oxygen. We report here the syntheses of natural abietane derivatives 15-deoxyfuerstione (**3**),[15,16] taxodione (**2**),[17,18] totarane derivatives dispermone (**8**),[13] 12,13-dihydroxy-8,11,13-totaratriene-6-one (**9**)[12] and podocarpane derivatives deoxynimbidiol (8,11,13-podocarpatriene-12,13-diol) (**12**),[19] nimbidiol (**14**).[20] The antimicrobial activities against *P. acnes* and MRSA of compounds **1**—**14** depicted in Fig. 1 are also reported. Toxicity of the most potent compound **1** was evaluated by oral dose to mice.

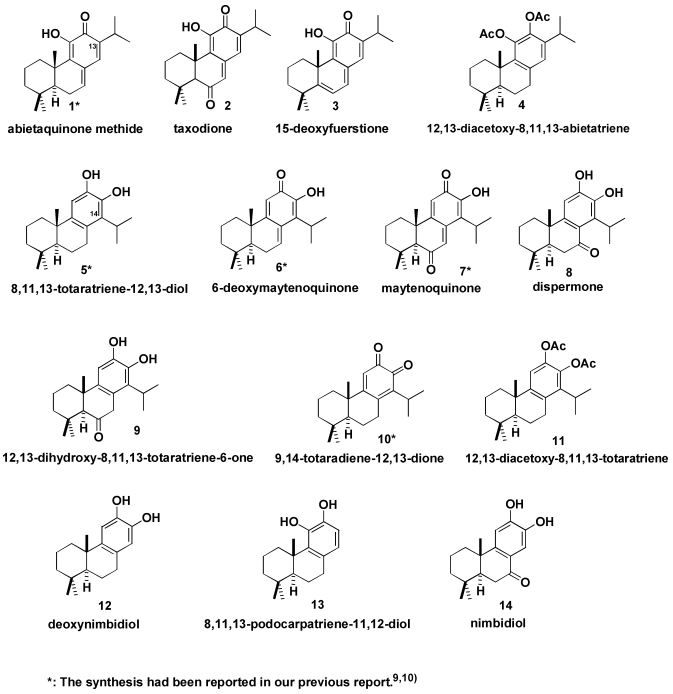

Fig. 1. Synthesized Diterpenes and Related Compounds

Syntheses of Abietane Derivatives, 15-Deoxyfuerstione (3), Taxodione (2) and 11,12-Diacetoxyabieta-8,11,13-triene (4) As ferruginol (**15**) was obtained efficiently from the resin in bark of *Cryptomeria japonica* (Japanese name: sugi),[21] natural **15** could be used for syntheses of variously oxidized abietane and podocarpane catechols. Thus, the synthesis began with the oxidation of **15** with *m*CBPO in CH_2Cl_2 for 20 h affording 12-hydroxy-11-(3-chlorobenzoyloxy)-abieta-8,11,13-triene (**16**). The monoester **16** was reduced with lithium aluminum hydride in tetrahydrofuran (THF) under Ar to give 8,11,13-abietatriene-10,11-diol (**17**) in 52% yield (2 steps from **15**). When this reduction was performed in air, abietaquinone methide **1** was obtained by autooxidation.[9] Diol **17** was oxidized with Ag_2O in CH_2Cl_2 for 40 min to give 8,12-abietadiene-11,12-dione (**18**) (95%) that was heated under reflux in $CHCl_3$ for 70.5 h to give two isomers, **1** (63%) and 6,8,11,13-abietatetraene-10,11-diol (**19**)

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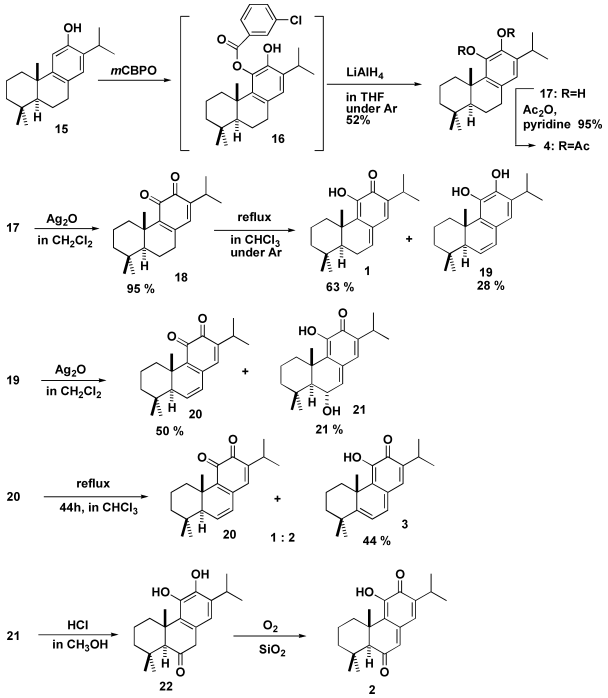

Chart 1. Syntheses of Abietane Compounds **2**, **3** and **4**

(28%). Since **19** was unstable, it was oxidized immediately with Ag_2O in CH_2Cl_2 for 1 h to afford 6,8,12-abietatriene-11,12-dione (**20**) (50%) and taxodone (**21**) (21%).[14] Dione **20** was heated in refluxing $CHCl_3$ for 44 h to give an equilibrium mixture (1 : 2) of **20** and 15-deoxyfuerstione **3** which was separated by silica gel column chromatography to afford **3** in 44% isolated yield. The spectral properties of **3** were identical to those in the literature.[14] Taxodone **21** was converted to taxodione **2** *via* 6-oxo-8,11,13-abietatriene-10,11-diol (**22**) according to the reported procedures.[17] Treatment of **17** with acetic anhydride-pyridine for 5 h under Ar gave 11,12-diacetoxyabieta-8,11,13-triene **4** (95%).

Syntheses of Totarane Derivatives, Dispermone (8), 12,13-Dihydroxy-8,11,13-totaratriene-6-one (9) and 12,13-Diacetoxy-8,11,13-totaratriene (11) As totarol (**23**) was obtained easily from *Thujopsis dolabrata* (Japanese name: hiba),[22] we could use **23** for the syntheses of highly oxidized totaranes (**8**, **9**, **11**) (Chart 2). Synthesis of 8,11,13-totaratriene-12,13-diol **5** from **23** was described in the previous report.[10] The diol **5** was stable in air whereas **17** is easily oxidized to abietaquinone methide **1** in air. We synthesized dispermone **8** from **5**.[12] Esterification of **5** with acetic anhydride in pyridine at ambient temperature for 2.5 h gave 12,13-diacetoxy-8,11,13-totaratriene **11** (99%). Diacetate **11** was oxidized with CrO_3 in acetic acid at ambient temperature for 8 h to afford dispermone diacetate (**24**) (69%). Hydrolysis of **24** in aqueous 1 M NaOH and THF at ambient temperature for 10 h gave **8** (58%). The spectral properties of **8** were identical to those in the literatures.[13,23]

12,13-Dihydroxy-8,11,13-totaratriene-6-one[13] **9** was synthesized from **5** as follows. Oxidation of **5** with Ag_2O gave a mixture of 6-deoxymaytenoquinone **6** and 8(14),9(11)-totaradiene-12,13-dione (**25**) as reported in the literature.[14] The ratio of the produced isomers (**6**, **25**) was changeable (0 : 100—1 : 7) according to the reaction time. The mixture (1 : 15) was oxidized on silica gel in air to produce the equi-

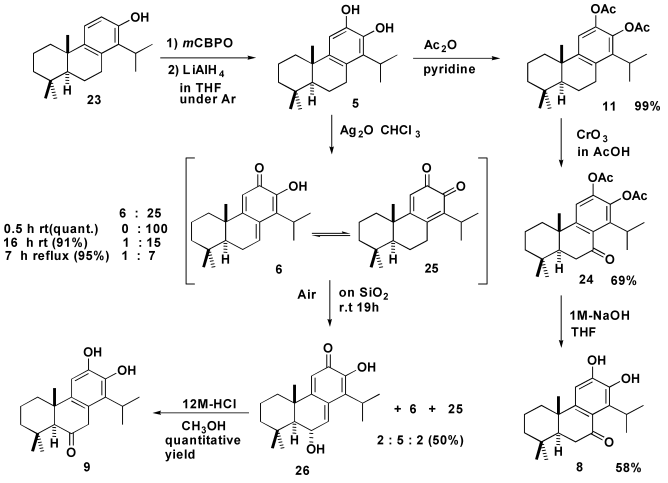

Chart 2. Syntheses of Totarane Compounds **8**, **9** and **11**

librium mixture of 6-deoxymaytenoquinone **6**, **25** and 6,13-dihydroxy-12-oxo-7,9(11),13-totaratriene (**26**) in a ratio of 5 : 2 : 2. The hydroxy quinone methide **26** was treated with 12 M HCl in methanol to give **9** quantitatively.[13]

Syntheses of Podocarpane Derivatives, Deoxynimbidiol (12), 8,11,13-Podocarpatriene-11,12-diol (13) and Nimbidiol (14) Isopropyl group of abietane skeleton is known to be removed *via ipso*-substitution with acetyl group, followed by Baeyer–Villger reaction to give podocarpane skeleton.[24] We thus synthesized highly oxidized podocarpanes (**12**—**14**) from **15**. Ferruginol **15** was heated with iodomethane and potassium *t*-butoxide in refluxing butanol for 11 h under Ar to give ferruginol methyl ether (**27**) (82%). Methyl ether **27** was treated with acetyl chloride and aluminum chloride in dichloromethane at 0 °C to ambient temperature for 11 h to give 12-methoxy-8,11,13-podocarpanetriene-13-yl methyl ketone (**28**) (73%). Baeyer–Villger reaction of methyl ketone **28** with *m*-chloroperbenzoic acid and *p*-toluenesulfonic acid generated 12-methoxy-8,11,13-podocarpanetriene-13-yl acetate (**29**) whose acetoxyl group was easily hydrolyzed under the reaction conditions, giving 12-methoxy-8,11,13-podocarpanetriene-13-ol (**30**) as a major product after the longer reaction time, 14 h (80%).

Deoxynimbidiol **12** was synthesized from methyl ether **30**. Methyl ether **30** was treated with boron tribromide in dichloromethane at 5 °C and gave two catechols, deoxynimbidiol **12** and 8,11,13-podocarpatriene-11,12-diol **13**. The ratio of **13** increased according to the reaction time. At reaction time of 21 h, 89% of **12** and 10% of **13** were obtained, whereas at reaction time of 36 h, 77% of **12** and 22% of **13** were obtained. The diol **13** could be formed by skeletal rearrangement of **12** *via* cations A, B, C. Both of the catechols **12** and **13** are more stable than **17** under air. Since catechols **12** and **13** was decomposed under the reaction conditions with Ag_2O, the quinone or the quinone methide with podocarpane skeleton could not be synthesized.

Nimbidiol **14** was synthesized from **30**. 12,13-Dimethoxy-8,11,13-podocarpanetriene (**31**) was prepared from **30** by the similar procedures in the case of methylation of **15** (72%). Oxidation of dimethyl ether **31** with CrO_3 in acetic acid at ambient temperature for 8 h gave nimbidiol dimethyl ether (**32**) (67%). Deprotection of the methyl ether **32** was per-

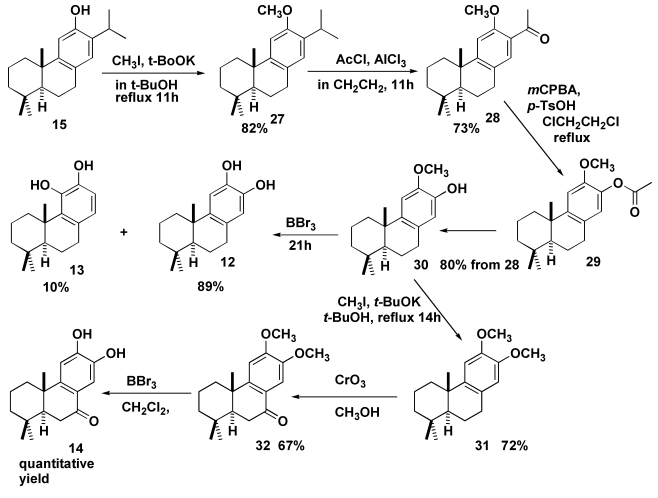

Chart 3. Syntheses of Podocarpane Compounds **12**, **13** and **14**

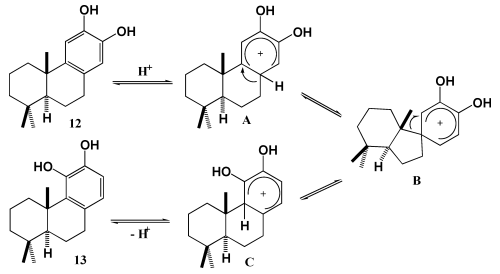

Chart 4. Skeletal Rearrangement between Podocarpane Catechols

formed with BBr_3 in dichloromethane at 5 °C for 28.5 h to give **14** in quantitative yield. The spectral properties of **14** were identical to those in the literature.[20)]

Biological Activities Minimum inhibitory concentration (MIC [μg/ml]) of four abietane compounds, seven totarane compounds and three podocarpane compounds were evaluated against *P. acnes* (ATCC 6919) and *S. aureus* (ME/GM/TC) Resistant (ATCC33592) (MRSA) (Table 1, Fig. 1). The MIC of well-known antibiotics, ampicillin and vancomycin, were measured as the reference compounds against *P. acnes* (ATCC 6919) and MRSA, respectively. Abietane derivatives (**1**—**4**) and totarane derivatives (**5**—**10**) showed potent or moderate antibacterial activities against both bacteria MRSA and *P. acnes*, whereas podocarpane catechols (**12**—**14**) showed moderate activities. The MIC (1 μg/ml) of abietaquinone methide (**1**) and 8,11,13-totaratriene-12,13-diol (**5**) are comparable to Vancomycin against *S. aureus* (MRSA). Diacetate of the catechols with abietane (**4**) and totarane (**11**) showed less antibacterial activities than the other catechol derivatives.

Toxicity of **1** was evaluated by oral dose to mice. No serious change of mice was observed about the body weight and general indications for 7 d after the oral dose of 1000—2000 mg/kg of **1**.

In conclusion, five catechols, **8**, **9**, **12**—**14** and two quinone methide, **2**, **3** and two catechol diesters **4** and **11** were synthesized *via ortho*-oxidation of phenol by efficient oxidation with *m*CBPO. These efficient syntheses of catechols can contribute for the further biological research of catechols. Antibacterial activities of 14 compounds were measured against MRSA and *P. acnes*. Among them, abietaquinone methide (**1**) and 8,11,13-totaratriene-12,13-diol (**5**) showed potent activity against both *S. aureus* (MRSA) and *P. acnes* and **1** showed no serious toxicity by oral dose to mice. In this research, ferruginol **15**, the major constituent in the resin of bark of *Cryptomeria japonica* (Japanese name: sugi), and totarol **23**, the major constituent in leaves of *Thujopsis dolabrata* (Japanese name: hiba) were used as the readily available starting materials for the syntheses. The effective use of these natural resources will contribute for the preservation of the Japanese forest.

Table 1. MIC (μg/ml) of Abietane, Totarane and Podocarpane Derivatives against MRSA and *P. acnes*

Compound	MRSA	*P. acnes*
1	1	1
2	10	10
3	10	3
4	>100	>100
5	1	1
6	3	X
7	1	3
8	10	X
9	3	30
10	3	1
11	>100	>100
12	3	10
13	10	10
14	30	X
Vancomycin	1	X
Ampicillin	X	0.1

X: not measured.

Experimental

General Procedures NMR spectra were measured on JEOL alpha-600 (^{1}H: 600 MHz, ^{13}C: 150.8 MHz) or JEOL AL-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard (*J*-values in Hz). IR spectra were measured on a JEOL JIR-WINSPEC 50 infrared spectrometer. Mass spectra were recorded on a JEOL JMS-SX102A spectrometer. mp were measured on a MEL-TEMP (Laboratory Device) and were uncorrected. TLC was carried out on Silica gel 60 (0.25 mm thickness) with fluorescent indicator (Macherey–Nagel). Silica gel (6 nm, BW-127ZH, Fuji Silysia Chemical Ltd.) was used for column chromatography.

Isolation of Ferruginol (15) The resin of *Cryptomeria japonica* (Japanese name: sugi) was collected in the Fuchu campus of Tokyo University of Agriculture and Technology. The resin (450 mg) was extracted with ethyl acetate (EtOAc) and evaporated. The residue was dissolved in MeOH (10 ml), and the resulting solution was stirred with 5%–Pd/C for 3 d under H_2. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (5 : 1) to give **15** (135 mg, about 30% from the resin) as yellow solids: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.83 (1H, s), 6.63 (1H, s), 4.75—4.18 (1H, br), 3.10 (1H, sept, J=7.0 Hz), 2.89—2.82 (1H, m), 2.81—2.73 (1H, m), 2.20—2.14 (1H, m), 1.88—1.82 (1H, m), 1.77—1.57 (4H, m), 1.49—1.43 (1H, m), 1.41—1.35 (1H, m), 1.34—1.29 (1H, m), 1.24 (3H, d, J=7.0 Hz), 1.23 (3H, d, J=7.0 Hz), 1.17 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 150.65, 148.66, 131.34, 127.30, 126.62, 110.95, 50.34, 41.68, 38.87, 37.50, 33.43, 33.30, 29.75, 26.81, 24.78, 22.73, 22.55, 21.61, 19.31, 19.22; IR (NaCl, cm^{-1}) 3405, 2960, 2923, 2870, 1716, 1616, 1508, 1416, 1373, 1230, 895; MS (electron ionization (EI)) *m*/*z* (%): 286 (M^+, 92), 271 (100), 189 (44), 175 (45), 61 (57); HR-EI-MS (EI) *m*/*z*: 286.2297 (Calcd for $C_{20}H_{30}O$ 286.2297).

Abieta-8,11,13-triene-11,12-diol (17) A solution of **15** (1.312 g, 4.58 mmol) and *m*CBPO (1.572 g, 5.05 mmol) in CH_2Cl_2 (15 ml) was stirred ambient temperature for 20 h under Ar. The reaction mixture was concentrated *in vacuo* and the precipitates were filtered off and washed with hexane. The filtrate was concentrated again *in vacuo* and the residue was

dissolved in tetrahydrofuran (THF) (25 ml). To the solution, $LiAlH_4$ (433.4 mg, 11.4 mmol) was added slowly with cooling in ice-water bath. The reaction mixture was stirred for 7 h at ambient temperature under Ar. The reaction was quenched by slow addition of EtOAc and 1 M HCl with cooling. The mixture was extracted with hexane and the organic layer was washed with 1 M HCl, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (5 : 1) to give **17** (714.9 mg, 52%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.44 (1H, s), 5.63 (1H, br), 4.60 (1H, br), 3.09—3.01 (1H, m), 2.97 (1H, sept, J=6.8 Hz), 2.83—2.75 (2H, m), 1.85—1.67 (2H, m), 1.62—1.41 (4H, m), 1.33 (3H, s), 1.40—1.28 (2H, m), 1.25 (3H, d, J=6.8 Hz), 1.23 (3H, d, J=6.8 Hz), 0.95 (3H, s), 0.92 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 142.85, 138.17, 133.12, 131.41, 129.71, 117.29, 52.81, 41.37, 39.17, 36.74, 33.69, 32.45, 27.26, 22.72, 22.47, 22.11, 20.24, 19.35, 19.29; IR (NaCl, cm^{-1}) 3489, 2956, 2918, 2864, 2841, 1705, 1620, 1568, 1493, 1475, 1462, 1435, 1387, 1367, 1325, 1146, 1095, 1045, 1011, 993, 972, 895, 877, 858, 831, 816, 771, 561, 519, 501; MS (EI) *m/z* (%): 302 (M^+, 100), 287 (65), 285 (17), 272 (13), 257 (16), 245 (14), 231 (34), 229 (23), 217 (75), 205 (77), 191 (93); HR-MS (EI) *m/z*: 302.2252 (Calcd for $C_{20}H_{30}O_2$ 302.2246).

8,12-Abietadiene-11,12-dione (18) To a solution of diol **17** (402.0 mg, 1.33 mmol) in CH_2Cl_2 (10 ml) was added Ag_2O (568.2 mg, 2.45 mmol), and the mixture was stirred for 40 min at ambient temperature under Ar. The mixture was filtered through a pad of Celite and the filtrate was concentrated to give **18** (377.9 mg, 1.26 mmol, 95%) as brown crystals, mp 107—109 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.40 (1H, s), 2.90 (1H, sept, J=6.8 Hz), 2.78—2.66 (1H, m), 2.58—2.34 (2H, m), 1.91—1.80 (1H, m), 1.76—1.33 (4H, m), 1.31—0.97 (3H, m), 1.22 (3H, s), 1.09 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 0.93 (3H, s), 0.88 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 181.19, 180.21, 147.88, 146.57, 144.81, 137.82, 51.23, 41.48, 37.95, 35.96, 33.75, 33.41, 33.34, 26.81, 21.65, 21.38, 21.33, 19.92, 18.79, 18.00; IR (KBr, cm^{-1}) 3442, 3313, 3288, 2966, 2922, 2873, 1647, 1572, 1464, 1390, 1313, 1269, 1174, 1101, 1043, 974, 904, 831, 754, 694, 654, 584, 488, 415, 380; MS (EI) *m/z* (%): 300 (M^+, 100), 285 (72), 257 (27), 244 (23), 229 (79), 215 (51), 204 (60), 189 (32), 187 (20), 171 (18), 149 (46), 129 (12), 95 (12), 81 (25), 69 (12), 55 (14); HR-MS (EI) *m/z*: 300.2069 (Calcd for $C_{20}H_{28}O_2$ 300.2089).

Abietaquinone Methide (1) and Abieta-6,8,11,13-tetraene-11,12-diol (19) *o*-Quinone **18** (315.4 mg, 1.05 mmol) was dissolved in $CHCl_3$ (15 ml) and the solution was refluxed for 72 h under Ar. Quinone methide **1** (63%) and diol **19** were observed by ^{1}H-NMR analysis in a ratio of about 2 : 1. The mixture was separated by column chromatography on silica gel with hexane–EtOAc (8 : 1) to give **1** (198.5 mg, 63%) and **19** (88.3 mg, 28%). Since diol **19** is unstable, only the ^{1}H-NMR could be measured. Abietaquinone methide (**1**): reddish crystals, mp 65—70 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.47 (1H, s), 6.81 (1H, dd, J=6.8, 4.4 Hz), 6.78 (1H, s), 3.07 (1H, sept, J=6.8 Hz), 3.00 (1H, m), 2.58 (1H, ddd, J=20.9, 6.8, 3.9 Hz), 2.40 (1H, ddd, J=20.9, 12.2, 2.9 Hz), 1.72—1.51 (4H, m), 1.46 (1H, m), 1.27 (1H, dt, J=13.2, 3.4 Hz), 1.18 (3H, s), 1.15 (3H, d, J=6.8 Hz), 1.14 (3H, d, J=6.8 Hz), 0.98 (3H, s), 0.93 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 181.23, 149.01, 143.70, 140.31, 135.99, 131.45, 127.15, 50.37, 41.60, 38.50, 36.65, 33.41, 33.18, 26.52, 25.71, 21.97, 21.70, 21.36, 18.81, 18.36; IR (KBr, cm^{-1}): 3527, 3439, 3309, 2956, 2920, 2870, 1608, 1560, 1462, 1439, 1389, 1358, 1257, 1215, 1147, 1111, 1049, 1016, 984, 935, 839, 810, 752, 702, 638, 579, 561, 542, 523; MS (EI) *m/z* (rel. int. %): 300 (M^+, 100), 285 (47), 271 (7), 257 (24), 244 (18), 229 (65), 215 (33), 204 (53), 189 (21), 187 (14), 171 (11), 157 (9), 141 (8), 129 (8), 128 (7), 84 (28), 69 (6), 55 (6); HR-MS (EI) *m/z*: 300.2065 (Calcd for $C_{20}H_{28}O_2$ 300.2089). Abieta-6,8,11,13-tetraene-11,12-diol (**19**): colorless oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.50 (1H, s), 6.43 (1H, dd, J=9.3, 2.9 Hz), 5.85 (1H, dd, J=9.3, 2.9 Hz), 5.59 (1H, br), 5.13 (1H, br), 2.90 (1H, sept, J=6.8 Hz), 2.79 (1H, m), 2.22 (1H, t, J=2.9 Hz), 1.80—1.20 (5H, m), 1.26 (3H, d, J=6.8 Hz), 1.22 (3H, d, J=6.8 Hz), 1.15 (3H, s), 1.03 (3H, s), 0.97 (3H, s).

Abieta-6,8,13-triene-11,12-dione (20) and Taxodone (21) To a solution of **19** (88.3 mg, 0.294 mmol) in CH_2Cl_2 (5 ml) was added Ag_2O (133.3 mg, 0.575 mmol), and the mixture was stirred for 23.5 h at 20 °C under Ar. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **20** (44.0 mg, 50%), **21** (18.4 mg, 20%), and a mixture (7.7 mg, *ca.* 9%) of **3**, **21** and **1**. Abieta-6,8,13-triene-11,12-dione (**20**): brown crystals, mp 120—122 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.57 (1H, d, J=0.98 Hz), 6.53 (1H, dd, J=9.3, 2.9 Hz), 6.23 (1H, dd, J=9.3, 2.9 Hz), 2.93 (1H, double sept, J=6.8, 0.98 Hz), 2.85 (1H, m), 2.12 (1H, t, J=2.9 Hz), 1.73—1.54 (2H, m), 1.49 (1H, m), 1.34—1.20 (2H, m) 1.12 (3H,s), 1.10 (3H, s), 1.01 (3H, s), 1.00 (3H, s), 0.98 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 181.95, 181.86, 147.80, 141.78, 141.36, 139.34, 136.41, 126.77, 52.43, 40.62, 38.34, 34.91, 33.06, 32.59, 27.04, 22.85, 21.49, 21.38, 18.57, 15.33; IR (KBr, cm^{-1}) 3440, 2945, 2866, 2779, 1676, 1639, 1595, 1522, 1466, 1379, 1323, 1304, 1292, 1173, 1093, 920, 839, 808, 690, 604, 536; MS (EI) *m/z* (%): 300 (M^{+2}, 16), 298 (M^+, 11), 270 (76), 255 (100), 241 (20), 227 (40), 213 (24), 199 (45), 185 (43), 171 (27), 157 (34), 143 (18), 128 (20), 115 (13), 91 (9), 83 (8), 69 (11), 55 (8); HR-MS (EI) *m/z*: 298.1942 (Calcd for $C_{20}H_{26}O_2$ 298.1933). Taxodone (**21**): orange solid, mp 139—142 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.49 (1H, s), 6.81 (1H, s), 6.55 (1H, d, J=2.4 Hz), 4.69 (1H, m, J=2.4 Hz), 3.06 (1H, sept, J=6.8 Hz), 2.91 (1H, m), 1.72—1.51 (6H, m), 1.44 (1H, m), 1.32 (1H, m), 1.22 (3H, s), 1.21 (3H, s), 1.15 (3H, s), 1.15 (3H, d, J=6.8 Hz), 1.14 (3H, d, J=6.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 181.68, 149.15, 143.38, 141.94, 135.70, 130.40, 126.21, 70.01, 57.97, 43.17, 40.70, 37.59, 36.68, 34.06, 26.70, 22.80, 21.71, 21.39, 20.79, 18.80; IR (KBr, cm^{-1}): 3437, 3319, 2960, 2879, 1610, 1558, 1448, 1354, 1255, 1205, 1155, 1099, 1057, 976, 914, 636, 704, 575; MS (EI) *m/z* (rel. int. %): 316 (M^+, 100), 298 (30), 283 (27), 273 (31), 255 (20), 245 (34), 220 (67), 219 (63), 205 (47), 191 (28), 177 (30), 173 (22), 161 (18), 129 (13), 128 (10), 115 (9), 83 (9), 69 (16), 55 (12); HR-MS (EI) *m/z*: 316.2038 (Calcd for $C_{20}H_{28}O_3$ 300.2038).

6-Oxo-abieta-8,11,13-triene-11,12-diol (22) A solution of **21** (18.4 mg, 0.058 mmol) in MeOH (8 ml) was acidified with one drop of 12 M HCl and heated at 50 °C for 15 min. The mixture was concentrated *in vacuo* to give **22** (18.4 mg, 0.058 mmol, quantitative yield) as colorless solids: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.40 (1H, s), 5.93 (1H, br), 5.02 (1H, br), 3.70 (1H, d, J=20.0 Hz), 3.37 (1H, d, J=20.0 Hz), 3.24—3.16 (1H, m), 3.03 (1H, sept, J=6.8 Hz), 2.65 (1H, s), 1.81—1.53 (5H, m), 1.35 (3H, s), 1.25 (3H, s), 1.23 (3H, d, J=6.8 Hz), 1.08 (3H, d, J=6.8 Hz), 1.02 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 211.06, 142.80, 138.80, 132.59, 131.73, 126.10, 116.67, 63.26, 46.43, 44.46, 42.41, 37.33, 32.90, 32.72, 27.21, 22.71, 22.45, 21.90, 21.28, 18.97; MS (EI) *m/z* (rel. int. %): 316 (M^+, 100), 301 (60), 283 (17), 273 (86), 259 (14), 245 (19), 231 (57), 217 (28), 203 (16), 189 (13), 175 (9), 161 (8), 149 (8), 129 (6), 128 (6), 91 (7), 69 (17), 55 (6).

Taxodione (2) A solution of diol **22** (18.4 mg, 0.058 mmol) in hexane–EtOAc (10 : 1, 2 ml) was poured on 4 g of silica gel. The mixture was allowed in air for 72 h at ambient temperature. The silica gel was extracted with hexane–EtOAc and the solution was concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **2** (19.7 mg, quantitative yield) as a yellow oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.57 (1H, s), 6.88 (1H, s), 6.21 (1H, s), 3.08 (1H, sept, J=6.8 Hz), 2.94 (1H, m), 2.60 (1H, s), 1.81—1.53 (4H, m), 1.41 (1H, m) 1.27 (6H, s), 1.18 (3H, d, J=6.8 Hz), 1.16 (3H, d, J=6.8 Hz), 1.12 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 201.08, 181.70, 145.32, 144.97, 139.90, 136.15, 133.99, 125.62, 62.96, 42.87, 42.54, 36.99, 33.25, 32.82, 27.13, 22.11, 21.82, 21.64, 21.22, 18.53; IR (NaCl, cm^{-1}): 3323, 2929, 2873, 1728, 1674, 1620, 1460, 1425, 1352, 1292, 1242, 1151, 1053, 980, 914, 858, 810, 731, 652, 579; MS (EI) *m/z* (rel. int. %): 314 (M^+, 100), 299 (20), 286 (55), 271 (58), 269 (43), 245 (38), 229 (55), 215 (22), 199 (36), 187 (16), 185 (15), 171 (14), 157 (12), 128 (11), 109 (10), 91 (6), 69 (10), 55 (6); HR-MS (EI) *m/z* 314.1899 (Calcd for $C_{20}H_{26}O_3$ 314.1882).

15-Deoxyfuerstione (3) A solution of **20** (37.0 mg, 0.124 mmol) in $CHCl_3$ (10 ml) was refluxed for 44 h under Ar. The reaction mixture was concentrated to give a residue constituted of **3** and **20** in a ratio of 2 : 1 by the ^{1}H-NMR analysis. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **3** (16.2 mg, 44%) as a reddish oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.74 (1H, s), 6.93 (1H, s), 6.75 (1H, d, J=6.8 Hz), 6.36 (1H, d, J=6.8 Hz), 3.31 (1H, m), 3.17 (1H, sept, J=6.8 Hz), 2.01—1.88 (1H, m), 1.68—1.58 (3H, m), 1.55—1.36 (1H, m), 1.57 (3H, s), 1.30 (3H, s), 1.23 (3H, s), 1.19 (3H, d, J=6.8 Hz), 1.18 (3H, d, J=6.8 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 178.18, 167.91, 146.23, 141.29, 138.97, 133.02, 128.31, 127.21, 118.08, 43.31, 40.88, 37.99, 34.23, 32.92, 29.95, 26.87, 24.64, 21.89, 21.67, 18.61; IR (NaCl, cm^{-1}): 3284, 2958, 2931, 2875, 1728, 1672, 1595, 1518, 1456, 1356, 1265, 1215, 1165, 1109, 1055, 993, 893, 839, 806, 729, 656; MS (EI) *m/z* (rel. int. %): 298 (M^+, 84), 283 (19), 255 (6), 242 (39), 229 (100), 227 (47), 201 (18), 185 (12), 165 (13), 153 (7), 141 (10), 128 (7), 115 (6), 84 (12); HR-MS (EI) *m/z*: 298.1898 (Calcd for $C_{20}H_{26}O_2$ 298.1933).

11,12-Diacetoxyabieta-8,11,13-triene (4) Diol **17** (96.9 mg, 0.320 mmol) was dissolved in pyridine (1 ml) and Ac_2O (0.5 ml) and the solution was stirred for 5 h under Ar. The reaction was quenched with 1 M HCl and the whole was extracted with EtOAc. The organic layer was washed with 1 M HCl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel column with hexane–EtOAc (5 : 1) to give **4** (117.0 mg, 95%) as colorless crystals, mp

120—122 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.88 (1H, s), 2.93—2.86 (2H, m), 2.85 (1H, sept, J=6.8 Hz), 2.28 (3H, s), 2.27 (3H, s), 1.88—1.79 (1H, m), 1.76—1.37 (5H, m), 1.37—1.26 (2H, m), 1.23 (3H, s), 1.18 (3H, d, J=6.8 Hz), 1.15 (3H, d, J=6.8 Hz), 0.95 (3H, s), 0.91 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 168.65, 168.52, 140.61, 139.21, 138.33, 138.28, 135.61, 124.68, 51.40, 40.83, 39.30, 36.74, 33.60, 33.48, 32.16, 27.21, 22.93, 22.72, 21.86, 21.58, 21.05, 20.34, 19.18, 18.89; IR (KBr, cm^{-1}): 3518, 2983, 2960, 2946, 2927, 2868, 2843, 1776, 1473, 1462, 1435, 1414, 1369, 1338, 1329, 1298, 1242, 1209, 1178, 1149, 1130, 1047, 1016, 972, 916, 879, 870, 793, 598; MS (EI) *m/z* (%): 386 (M^+, 38), 344 (35), 327 (6), 302 (100), 287 (54), 259 (12), 231 (9), 217 (31), 205 (35), 191 (42), 179 (10), 163 (9), 69 (11); HR-MS (EI) *m/z*: 386.2487 (Calcd for $C_{24}H_{34}O_4$ 386.2457).

Isolation of Totarol (23) Leaves of *Thujopsis dolabrata* (Japanese name: hiba) were collected in the Okunoto division of the forest management in Ishikawa prefecture. The leaves (70 g) were extracted with refluxing MeOH. The extract was concentrated *in vacuo* to give 3 g of a residue. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give 0.39 g of crude **23** which was chromatographed on silica gel with hexane–EtOAc (10 : 1) again to give **23** (287.9 mg, 0.4%) as a pale yellow solid: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.99 (1H, d, J=8.1 Hz), 6.50 (1H, d, J=8.1 Hz), 3.29 (1H, s), 2.94 (1H, dd, J=16.9, 6.6 Hz), 2.78—2.72 (1H, m), 2.22 (1H, d, J=12.5 Hz), 1.91 (1H, dd, J=13.2, 8.1 Hz), 1.76—1.56 (3H, m), 1.46 (1H, d, J=13.2 Hz), 1.35 (3H, d, J=7.3 Hz), 1.34 (1H, d, J=7.3 Hz), 1.27 (1H, d, J=13.2 Hz), 1.45—1.20 (5H, m), 1.19 (3H, s), 0.95 (3H, s), 0.91 (3H, s). ^{13}C-NMR (150 MHz $CDCl_3$) δ: 151.9, 143.2, 134.0, 131.0, 123.0, 114.3, 49.6, 41.6, 39.6, 37.7, 33.3, 33.2, 28.7, 27.1, 25.1, 21.6, 20.3, 20.3, 19.5, 19.3; IR (KBr, cm^{-1}): 3420 (br), 2925, 2854, 1704, 1587, 1456, 1365, 1280, 1186, 1103, 1076, 971, 902, 809; MS (EI) (rel. int. %): 286 (75), 271 (100), 269 (15), 203 (62), 201 (77), 189 (48), 175 (94), 149 (16), 91 (7), 83 (10), 69 (32), 55 (18); HR-MS (EI) *m/z*: 286.2315 (Calcd for $C_{20}H_{30}O$ 286.2297).

12,13-Diacetoxytotara-8,11,13-triene (11) A solution of **5** (108.0 mg) in pyridine (1 ml) and acetic anhydride (0.5 ml) was stirred for 3 h under Ar. The reaction was quenched with 1 M HCl and the whole was extracted with EtOAc. The organic layer was washed with 1 M HCl, aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (5 : 1) to give **11** (136.8 mg, 99%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.96 (1H, s), 3.27 (1H, sept, J=7.3 Hz), 2.91 (1H, dd, J=17.6, 6.3 Hz), 2.72 (1H, ddd, J=16.6, 11.2, 8.3 Hz), 2.29 (3H, s), 2.23 (3H, s), 2.18—2.10 (1H, m), 1.97—1.86 (1H, m), 1.79—1.53 (3H, m), 1.50—1.33 (2H, m), 1.32—1.15 (2H, m), 1.24 (3H, d, J=7.3 Hz), 1.22 (3H, d, J=7.3 Hz), 1.20 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 168.58, 168.47, 148.67, 140.39, 138.52, 138.10, 131.42, 117.24, 48.99, 41.32, 39.21, 38.13, 33.23, 33.08, 28.29, 27.43, 24.90, 21.49, 20.89, 20.80, 20.79, 20.74, 19.23, 19.05; IR (NaCl, cm^{-1}): 2939, 2870, 2843, 1774, 1597, 1470, 1458, 1433, 1367, 1300, 1255, 1211, 1182, 1151, 1138, 1119, 1066, 1020, 1011, 962, 939, 916, 889, 864, 733, 584; MS (EI) *m/z* (rel. int. %): 386 (M^+, 15), 344 (44), 329 (7), 302 (100), 287 (71), 217 (16), 205 (11), 191 (23), 175 (6), 149 (11), 69 (8); HR-MS (EI) *m/z*: 386.2500 (Calcd for $C_{24}H_{34}O_4$ 386.2457).

12,13-Diacetoxytotara-8,11,13-trien-7-one (24) To a solution of **11** (136.8 mg, 0.354 mmol) in CH_3CO_2H (3 ml), CrO_3 (106.6 mg, 1.07 mmol) was added and the mixture was stirred for 8 h under Ar. The reaction was quenched with water and the mixture was extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (3 : 1) to give **24** (97.4 mg, 69%) as colorless crystals, mp 142 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.07 (1H, s), 3.76 (1H, sept, J=6.8 Hz), 2.71 (1H, dd, J=19.0, 7.8 Hz), 2.65 (1H, dd, J=18.5, 11.7 Hz), 2.33 (3H, s), 2.27 (3H, s), 2.19—2.09 (1H, m), 1.88 (1H, dd, J=11.7, 7.8 Hz), 1.81—1.46 (4H, m), 1.30—1.23 (1H, m), 1.33 (3H, d, J=6.8 Hz), 1.20 (3H, d, J=6.8 Hz), 1.13 (3H, s), 1.01 (3H, s), 0.92 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 201.27, 168.17, 167.70, 154.51, 144.99, 142.56, 140.02, 131.07, 116.07, 47.16, 41.24, 38.58, 38.33, 38.20, 33.26, 32.04, 28.13, 22.66, 21.48, 21.24, 20.76, 20.68, 18.71; IR (KBr, cm^{-1}): 2933, 2872, 1774, 1682, 1589, 1460, 1371, 1286, 1198, 1014, 914, 783, 729, 598, 555; MS (EI) *m/z* (rel. int. %): 400 (M^+, 54), 385 (9), 358 (84), 341 (12), 316 (100), 299 (64), 283 (79), 261 (15), 233 (14), 219 (41), 213 (25), 179 (19), 175 (8), 161 (5), 69 (12), 55 (6); HR-MS (EI) *m/z*: 400.2229 (Calcd for $C_{24}H_{32}O_5$ 400.2250).

Dispermone (8) Ketone **24** (97.4 mg, 0.243 mmol) was dissolved in MeOH (4 ml) and 1 M NaOH (2 ml) and the solution was stirred for 10 h at ambient temperature under Ar. The reaction was quenched with 1 M HCl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (3 : 1) to give **8** (44.7 mg, 0.141 mmol, 58%) as colorless crystals, mp 200 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.72 (1H, s), 5.85 (1H, br), 5.21 (1H, br), 3.94 (1H, sept, J=7.3 Hz), 2.67 (1H, dd, J=19.0, 6.8 Hz), 2.58 (1H, dd, J=19.0, 12.7 Hz), 2.12 (1H, m), 1.80 (1H, dd, J=12.7, 6.3 Hz), 1.72 (1H, m), 1.67—1.61 (1H, m), 1.55—1.48 (2H, m), 1.45 (3H, d, J=7.3 Hz), 1.33 (3H, d, J=7.3 Hz), 1.26 (1H, dt, J=13.2, 3.9 Hz), 1.09 (3H, s), 0.99 (3H, s), 0.91 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 201.55, 151.07, 147.37, 141.65, 135.61, 125.72, 107.29, 47.72, 41.49, 38.56, 38.41, 38.02, 33.21, 32.23, 27.78, 22.98, 21.35, 21.11, 20.70, 18.98; IR (KBr, cm^{-1}): 3529, 3448, 3059, 2997, 2953, 2879, 2804, 2723, 2675, 2602, 2549, 2465, 1614, 1578, 1497, 1448, 1373, 1286, 1236, 1174, 1093, 1009, 866, 791, 617, 567; MS (EI) *m/z* (rel. int. %): 316 (M^+, 100), 299(51), 283 (72), 273 (5), 259 (10), 245 (7), 231 (41), 219 (38), 213 (36), 205 (17), 179 (21), 175 (7), 161 (6), 83 (5), 69 (14), 55 (5); HR-MS (EI) *m/z*: 316.2051 (Calcd for $C_{20}H_{28}O_3$ 316.2038).

6,13-Dihydroxy-12-oxo-7,9(11),13-totaratriene (26) A mixture of **5** (106.0 mg, 0.35 mmol) and Ag_2O (162.4 mg, 0.71 mmol) in $CHCl_3$ (10 ml) was refluxed for 7 h under Ar. The mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (8 : 1) to give a mixture of **6** and **25** (1 : 7, 99.9 mg, 95%). The product ratio of **6** and **25** was changeable (0 : 100—1 : 7) according to the reaction time. The ratio of **6** : **25** was 0 : 100 for 0.5 h at room temperature (quantitative yield); 1 : 15 for 16 h at room temperature (91%). To a solution of mixture of **6** and **25** (1 : 15, 167.0 mg, 0.556 mmol) in acetone was added silica gel (15 g), and the solvent was evaporated *in vacuo*. The mixture was allowed at room temperature for 19 h under air and then the mixture was chromatographed on silica gel with hexane–EtOAc (8 : 1) to give a mixture of **26**, **6** and **25** in a ratio of 2 : 5 : 2 by ^{1}H-NMR analysis. The mixture was chromatographed again on silica gel with hexane–EtOAc (8 : 1) to give **6** (54 mg, 33%) and **26** (33.3 mg, 19%) as a yellow oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.95 (1H, br), 6.89 (1H, s), 6.26 (1H, s), 4.68 (1H, br d, J=9.5 Hz), 3.11 (1H, sept, J=7.1 Hz), 2.64—2.59 (1H, m), 1.75—1.41 (6H, m), 1.36 (3H, d, J=7.1 Hz), 1.32 (3H, d, J=7.1 Hz), 1.29—1.22 (1H, m), 1.21 (3H, s), 1.18 (3H, s), 1.13 (3H, s); HR-MS (EI) *m/z*: 316.2076 (Calcd for $C_{20}H_{28}O_3$ 300.2038).

12,13-Dihydroxy-8,11,13-totaratriene-6-one (9) A solution of **26** (11.3 mg, 0.0357 mmol) in MeOH (4 ml) was acidified by addition of one drop of 12 M HCl and heated at 50 °C for 15 min. The mixture was evaporated *in vacuo* to give **9** (11.3 mg, quantitative yield) as a yellow solid: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.73 (1H, s), 5.31 (1H, br), 4.91 (1H, br), 3.60 (1H, d, J=21.0 Hz), 3.41 (1H, d, J=21.0 Hz), 3.09 (1H, br sept, J=7.3 Hz), 2.44 (1H, s), 2.23 (1H, m), 1.77—1.53 (5H, m), 1.36 (3H, d, J=7.3 Hz), 1.35 (3H, d, J=7.3 Hz), 1.32 (3H, s), 1.10 (3H, s), 1.07 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 209.84, 141.85, 141.73, 141.08, 131.55, 122.70, 108.47, 61.99, 43.50, 42.59, 40.48, 39.28, 32.78, 32.41, 29.71, 25.10, 21.65, 20.36, 20.21, 18.86; IR (KBr, cm^{-1}): 3537, 3473, 3417, 2927, 2860, 1701, 1614, 1448, 1379, 1311, 1217, 1200, 1099, 939, 876, 852, 696, 623, 474; MS (EI) *m/z* (rel. int. %): 316 (M^+, 100) , 301 (70), 283 (23), 273 (24), 259 (39), 245 (12), 231 (56), 217 (20), 203 (16) , 189 (19), 175 (10), 161 (8), 137 (6), 129 (6), 109 (6), 83 (6), 69 (16), 55 (7); HR-MS (EI) *m/z*: 316.2053 (Calcd for $C_{20}H_{28}O_3$ 316.2038).

12-Methoxyabieta-8,11,13-triene (27) To a solution of **15** (550.9 mg, 1.92 mmol) in *t*-BuOH (8 ml), *t*-BuOK (308.2 mg, 2.75 mmol) was added. After stirring for 10 min under Ar, CH_3I (0.5 ml, 8.03 mmol) was added to the mixture and the mixture was stirred at ambient temperature for 20 min and then refluxed for 2 h under Ar. To the mixture, *t*-BuOK (66.9 mg, 0.596 mmol) was added with ice-cooling. After stirring for 20 min at ambient temperature under Ar, CH_3I (0.3 ml, 4.82 mmol) was added to the mixture again. The mixture was stirred for further 20 min at ambient temperature under Ar, and then the mixture was refluxed for 11 h. The formed precipitates were filtered and washed with hexane, and the combined filtrate was concentrated under vacuo. The residue was acidified with 1 M HCl and the mixture was extracted with hexane. The organic layer was washed with water, aq. $Na_2S_2O_3$, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane to give **27** (474.0 mg, 82%) as a colorless oil: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.83 (1H, s), 6.72 (1H, s), 3.78 (3H, s), 3.22 (1H, sept, J=6.8 Hz), 2.86 (1H, ddd, J=17.1, 7.3, 2.0 Hz), 2.77 (1H, ddd, J=17.1, 11.2, 7.3 Hz), 2.30—2.20 (1H, m), 1.90—1.81 (1H, m), 1.81—1.30 (7H, m), 1.20 (3H, s), 1.19 (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 ($CDCl_3$, 100 MHz) δ: 155.01, 148.06, 134.12, 126.86, 126.38, 106.54, 55.34, 50.50, 41.72, 38.94, 37.84, 33.45, 33.33, 29.82, 26.46, 24.80, 22.89, 22.69, 21.63, 19.35, 19.25;

IR (NaCl, cm^{-1}): 2956, 2945, 2926, 2866, 2843, 1614, 1572, 1500, 1462, 1443, 1404, 1389, 1375, 1362, 1323, 1250, 1207, 1165, 1066, 1055, 1043, 891, 847; MS (EI) *m/z* (%): 300 (M^+, 91), 285 (100), 283 (13), 271 (7), 243 (19), 229 (14), 215 (35), 203 (34), 189 (44), 173 (13), 163 (23), 161 (10), 147 (10), 129 (6), 128 (6), 83 (6), 69 (19); HR-MS (EI) *m/z*: 300.2470 (Calcd for $C_{21}H_{32}O$ 300.2453).

Nimbosone (28) To a solution of **27** (1.7302 g, 5.76 mmol) in CH_2Cl_2 (20 ml), AcCl (2 ml, 0.0281 mol) and $AlCl_3$ (1.6422 g, 0.0123 mol) were added with cooling in ice bath. The mixture was stirred for 2 h at ambient temperature. The reaction was quenched with 1 M HCl and the whole was extracted with EtOAc. The organic layer was washed with 1 M HCl, aq. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **28** (1.2591 g, 73%) as colorless crystals, mp 63—65 °C: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.44 (1H, s), 6.83 (1H, s), 3.87 (3H, s), 2.90 (1H, dd, J=16.9, 6.6 Hz), 2.78 (1H, ddd, J=16.9, 10.9, 8.1 Hz), 2.58 (3H, s), 2.30—2.23 (1H, m), 1.92—1.85 (1H, m), 1.82—1.72 (1H, m) 1.72—1.58 (2H, m), 1.52—1.38 (2H, m), 1.34—1.20 (2H, m), 1.20 (3H, s), 0.95 (3H, s), 0.93 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 199.48, 157.22, 156.41, 130.89, 127.55, 125.50, 107.49, 55.45, 50.00, 41.51, 38.78, 38.49, 33.53, 33.24, 31.76, 29.23, 24.52, 21.65, 19.20, 18.95; IR (KBr, cm^{-1}): 2993, 2980, 2958, 2943, 2920, 2889, 2864, 2841, 1670, 1662, 1603, 1558, 1495, 1470, 1460, 1402, 1352, 1329, 1296, 1265, 1240, 1180, 1034, 993, 972, 914, 850, 677, 604, 565; MS (EI) *m/z* (rel. int. %): 300 (M^+, 94), 285 (100), 271 (9), 257 (7), 243 (14), 229 (16), 217 (45), 203 (48), 189 (35), 187 (12), 173 (12), 163 (9), 128 (8), 115 (7), 83 (6), 69 (16), 55 (7); HR-MS (EI) *m/z*: 300.2101 (Calcd for $C_{20}H_{28}O_2$ 300.2089).

12-Methoxypodocarpa-8,11,13-triene-13-ol (30) A solution of **28** (1.1 g, 3.66 mmol), *m*-chloroperbenzoic acid (65% purity, 1.3079 g, 4.93 mmol) and *p*-toluenesulfonic acid (*p*-TsOH, 52.2 mg, 0.303 mmol) in 1,2-dichloroethane (30 ml) was refluxed for 14 h under Ar. The reaction was quenched with aqueous saturated $Na_2S_2O_3$ and aqueous saturated $NaHCO_3$. The whole was extracted with EtOAc and the organic layer was washed with aqueous saturated $Na_2S_2O_3$, aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **30** (805.3 mg, 80%) as colorless crystals, mp 90—91 °C: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.73 (1H, s), 6.57 (1H, s), 5.45 (1H, br), 3.83 (3H, s), 2.81 (1H, dd, J=16.9, 7.0 Hz), 2.74 (1H, ddd, J=16.9, 11.7, 7.0 Hz) 2.24—2.17 (1H, m), 1.87—1.80 (1H, m), 1.80—1.54 (3H, m) 1.52—1.20 (4H, m), 1.17 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 144.62, 143.10, 141.83, 128.11, 114.20, 106.89, 55.97, 50.57, 41.63, 39.16, 37.53, 33.35, 33.27, 29.85, 24.88, 21.54, 19.31, 19.05; IR (KBr, cm^{-1}): 3521, 3450, 3034, 2993, 2964, 2947, 2918, 2902, 2862, 2839, 1624, 1592, 1506, 1462, 1446, 1439, 1389, 1377, 1363, 1340, 1329, 1281, 1271, 1200, 1138, 1072, 1043, 972, 870, 860, 850, 839, 777, 469; MS (EI) *m/z* (%): 274 (M^+, 97), 259 (100), 257 (6), 231 (8), 217 (8), 203 (21), 189 (54), 177 (31), 163 (40), 151 (9), 137 (10), 131 (9), 115 (5), 69 (23); HR-MS (EI) *m/z*: 274.1909 (Calcd for $C_{18}H_{26}O_2$ 274.1933).

7-Deoxynimbidiol (12) and Podocarpa-8,11,13-triene-11,12-diol (13) Methoxyphenol **30** (119.3 mg, 0.435 mmol) was dissolved in dry CH_2Cl_2 (5 ml) and then a solution of BBr_3 (0.6 ml, 6.35 mmol) in CH_2Cl_2 was added to the solution with cooling in ice bath. The solution was stirred for 21 h at 5 °C under Ar. The reaction was quenched with methanol and water. The whole was extracted with EtOAc and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (5 : 1) to give **12** (101.2 mg, 89%) and **13** (11.6 mg, 10%). 7-Deoxynimbidiol (**12**): colorless crystals, mp 82—85 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.73 (1H, s), 6.51 (1H, s), 5.69 (2H, br), 2.82—2.57 (2H, m), 2.16—1.98 (1H, m), 1.87—1.76 (1H, m), 1.75—1.36 (4H, m), 1.34—1.13 (3H, m), 1.11 (3H, s), 0.92 (3H, s), 0.89 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 143.33, 141.22, 140.89, 128.02, 115.32, 111.60, 50.43, 41.61, 38.92, 37.28, 33.32, 33.26, 29.75, 24.80, 21.53, 19.27, 19.03; IR (KBr, cm^{-1}): 3350, 2927, 2846, 1608, 1516, 1448, 1371, 1273, 1174, 1132, 872, 865, 839, 752; MS (EI) *m/z* (rel. int. %): 260 (M^+, 68), 245 (100), 217 (6), 203 (9), 189 (20), 175 (49), 163 (31), 149 (33), 137 (7), 123 (7), 115 (6), 69 (26), 55 (5); HR-MS (EI) *m/z*: 260.1798 (Calcd for $C_{17}H_{24}O_2$ 260.1776). Podocarpa-8,11,13-triene-11,12-diol (**13**): colorless crystals, mp 110—113 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 6.60 (1H, d, J=8.3 Hz), 6.47 (1H, d, J=8.3 Hz), 5.65 (1H, br), 4.92 (1H, br), 3.19—3.08 (1H, m), 2.87—2.74 (2H, m), 1.86—1.67 (2H, m), 1.60—1.42 (3H, m), 1.34 (3H, s), 1.32—1.18 (3H, m), 0.95 (3H, s), 0.93 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 143.12, 140.38, 135.90, 130.71, 120.25, 112.60, 52.87, 41.43, 39.55, 36.53, 33.73, 32.37, 22.15, 19.97, 19.35, 19.19; IR (KBr, cm^{-1}): 3502, 3446, 2995, 2933, 2860, 1620, 1477, 1371, 1284, 1192, 1036, 906, 800, 735, 511; MS (EI) *m/z* (%): 260 (M^+, 100), 245 (31), 230 (5), 217 (8), 203 (9), 189 (25), 175 (62), 163 (75), 149 (58), 143 (11), 115 (11), 103 (5), 83 (6), 69 (20), 55 (6); HR-MS (EI) *m/z*: 260.1783 (Calcd for $C_{17}H_{24}O_2$ 260.1776).

12,13-Dimethoxypodocarpa-8,11,13-triene (31) To a solution of **30** (119.2 mg, 0.434 mmol) in *t*-BuOH (10 ml), *t*-BuOK (98.8 mg, 0.880 mmol) was added. After stirring for 40 min at ambient temperature, CH_3I (0.5 ml, 8.03 mmol) was added. The reaction mixture was stirred for 30 min and then heated under reflux for 15 h under Ar. After cooling, the reaction mixture was acidified with 1 M HCl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (10 : 1) to give **31** (90.7 mg, 72%) as colorless crystals, mp 45—50 °C: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.76 (1H, s), 6.52 (1H, s), 3.84 (3H, s), 3.82 (3H, s), 2.85 (1H, dd, J=16.9, 7.3 Hz), 2.79 (1H, ddd, J=16.9, 11.0, 7.3 Hz) 2.26—2.19 (1H, m), 1.90—1.83 (1H, m), 1.80—1.56 (3H, m), 1.51—1.44 (1H, m), 1.39 (1H, dt, J=13.2, 3.7 Hz), 1.32 (1H, dd, J=12.5, 2.2 Hz), 1.22 (1H, dt, J=13.9, 3.7 Hz), 1.18 (3H, s), 0.95 (3H, s), 0.92 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 146.91, 146.66, 142.17, 127.31, 111.36, 107.90, 55.99, 55.66, 50.62, 41.60, 39.02, 37.47, 33.34, 33.27, 30.14, 24.74, 21.53, 19.28, 19.10; IR (KBr, cm^{-1}): 2933, 2841, 1608, 1514, 1458, 1385, 1360, 1254, 1211, 1149, 1074, 1043, 970, 852, 771, 584, 486; MS (EI) *m/z*: (%): 288 (M^+, 92), 273 (100), 245 (6), 231 (8), 217 (19), 203 (42), 191 (25), 177 (34), 165 (5), 151 (10), 69 (14); HR-MS (EI) *m/z*: 288.2131 (Calcd for $C_{19}H_{28}O_2$ 288.2089).

12,13-Dimethoxypodocarpa-8,11,13-trien-7-one (32) To a solution of **31** (146.9 mg, 0.508 mmol) in CH_3CO_2H (1 ml), CrO_3 (164.7 mg, 1.65 mmol) was added and the mixture was stirred for 7 h at ambient temperature under Ar. The reaction was quenched with MeOH and water. The mixture was extracted with EtOAc, and the organic layer was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (4 : 1) to give **32** (102.4 mg, 67%) as colorless crystals, mp 96 °C: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.50 (1H, s), 6.81 (1H, s), 3.95 (3H, s), 3.91 (3H, s), 2.71 (1H, dd, J=18.0, 4.4 Hz), 2.61 (1H, dd, J=18.0, 13.7 Hz), 2.29 (1H, m), 1.88 (1H, dd, J=13.7, 4.4 Hz), 1.79 (1H, m), 1.73—1.65 (1H, m), 1.60—1.50 (2H, m), 1.33—1.26 (1H, m) 1.25 (3H, s), 1.00 (3H, s), 0.94 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 198.18, 153.76, 151.27, 147.24, 124.12, 108.52, 105.53, 55.88, 49.83, 41.22, 37.99, 35.81, 33.17, 32.49, 23.14, 21.22, 18.80; IR (KBr, cm^{-1}): 3442, 2999, 2935, 2856, 2632, 1666, 1597, 1510, 1460, 1406, 1354, 1275, 1207, 1163, 1045, 958, 877, 822, 785, 586; MS (EI) *m/z* (%): 302 (M^+, 100), 287 (89), 285 (23), 257 (9), 245 (24), 231 (23), 219 (75), 217 (64), 205 (33), 191 (20), 165 (8), 69 (12); HR-MS (EI) *m/z*: 302.1880 (Calcd for $C_{19}H_{26}O_3$ 302.1882).

Nimbidiol (14) Dimethoxyketone **32** (188.0 mg, 0.622 mmol) was dissolved in dry CH_2Cl_2 (10 ml) and then a solution of BBr_3 (0.3 ml, 3.17 mmol) in CH_2Cl_2 (3 ml) was added to the solution with cooling in ice bath. The solution was stirred for 29 h at 5 °C under Ar and the reaction was quenched with methanol and water. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel with hexane–EtOAc (1 : 1) to give **14** (180.0 mg, quantitatively) as colorless crystals, mp 171—175 °C: ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 8.06 (1H, br), 7.75 (1H, s), 6.88 (1H, s), 6.47 (1H, br), 2.68 (1H, dd, J=18.3, 4.4 Hz), 2.61 (1H, dd, J=18.3, 13.2 Hz), 2.22 (1H, m), 1.86 (1H, dd, J=13.2, 3.7 Hz), 1.75 (1H, m), 1.66 (1H, m), 1.56—1.40 (2H, m), 1.30—1.23 (1H, m), 1.20 (3H, s), 0.98 (3H, s), 0.92 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 200.75, 152.49, 151.34, 142.07, 123.81, 113.57, 110.08, 49.73, 41.29, 37.86, 37.76, 35.92, 33.17, 32.49, 23.17, 21.27, 18.82; IR (KBr, cm^{-1}): 3431, 2997, 2929, 2848, 1653, 1605, 1516, 1454, 1375, 1342, 1292, 1200, 889; MS (EI) *m/z* (rel. int. %): 274 (M^+, 99), 259 (100), 217 (32), 203 (24), 191 (78), 189 (94), 177 (57), 163 (23), 69 (51), 57 (30), 55 (24); HR-MS (EI) *m/z*: 274.1524 (Calcd for $C_{17}H_{22}O_3$ 274.1569).

Methods of Anti-microbial Activities *in Vitro* Assays Minimun inhibitory concentration (MIC μg/ml) of the synthesized fourteen compounds were performed under conditions described in the literatures for each assay against *Propionibacterium acnes* (ATCC 6919)[25] and *Staphylococcus aureus* ME/GM/TC Resistant (ATCC 33592).[26] The synthesized fourteen compounds were tested at half-log concentrations ranging from 0.03 to 100 μg/ml in the *P. acnes* and *S. aureus in vitro* growth inhibition assays.

***Propionibacterium acnes* (ATCC 6919)** Culture Medium: Reinforced Clostridial Medium, Vehicle: 1% DMSO, Incubation Time/Temp: 2 d at 37 °C, Incubation Volume: 3 ml, Time of Assessment: 2 d, Quantitation Method: Turbidity measurement and plating count of subculture.

***Staphylococcus aureus* ME/GM/TC Resistant (ATCC 33592)** Culture

Medium: Mueller–Hinton Broth, Vehicle: 1% DMSO, Incubation Time/Temp: 20 h at 37 °C, Incubation Volume: 1 ml, Time of Assessment: 1 d, Quantitation Method: Turbidity. Measurement.

Toxicity Three groups of each 3 mice were domesticated for 4 d before oral dose. After dose of abietaquinone methide (1000 mg/kg or 2000 mg/kg) in emulsion of carboxymethylcellulose-sodium (0.5%) (Lot. WTL-0593, Wako) or dose of carboxymethylcellulose-sodium (0.5%), the body weights and general indications were observed for 7 d. No significant difference by dose of abietaquinone methide (1000 mg/kg or 2000 mg/kg) was observed from the comparative dose of carboxymethylcellulose-sodium (0.5%).

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