Efficient *ortho*-Oxidation of Phenol and Synthesis of Anti-MRSA and Anti-VRE Compound Abietaquinone Methide from Dehydroabietic Acid

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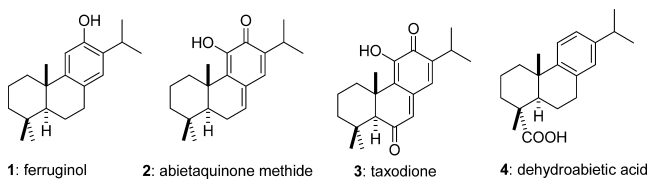
A quinone methide diterpene: abietaquinone methide, which possesses potent anti-methicillin-resistant *Staphylococcus aureus* (MRSA) and anti-vancomycin-resistant *Enterococcus* (VRE) activities, was synthesized *via* efficiently *ortho*-oxidation of ferruginol derived from industrially available dehydroabietic acid. *ortho*-Oxidation of phenols was developed to give mono esters of catechols using a stable diacyl peroxide, bis(4-chlorobenzoyl) peroxide (*m*-chlorobenzoyl peroxide: *m*CBPO) which was synthesized from *meta*-chlorobenzoic acid. Efficient one pot *ortho*-oxidation reaction of phenol with an adduct of *meta*-chloroperbenzoic acid (*m*CPBA) with dicyclohexylcarbodiimide (DCC) was also reported.

Key words anti-methicillin-resistant bacteria; quinone methide; *m*-chlorobenzoyl peroxide; *ortho*-oxidation; anti-methicillin-resistant *Staphylococcus aureus* (MRSA); anti-vancomycin-resistant *Enterococcus* (VRE)

Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are a significant problem in hospitals worldwide. Our group has worked with natural resources to find antimicrobial compounds effective against antibiotic-resistant bacteria. Stable quinone methide compounds have been isolated from various plants and have been shown to display interesting biological activities *e.g.* anti-virus,[1,2] antibiotic,[2—7] anti-malarial,[8,9] and anti-tumor[10—12] activities. Previously, we have reported the total synthesis and the anti-MRSA and anti-VRE activities of 12 variously oxidized natural abietanes[13,14]: 6,7-dehydroferruginol methyl ether,[15] ferruginol (**1**),[15—17] 11-hydroxy-12-oxo-7,9(11),13-abietatriene (**2**),[4] royleanone,[16] demethylcryptojaponol,[18] salvinolone,[19,20] sugiol methyl ether,[21,22] sugiol,[15,20,23] 5,6-dehydrosugiol methyl ether,[21,22] 5,6-dehydrosugiol,[13,22,24] 6β-hydroxyferruginol,[25] and taxodione (**3**)[13,17,26] *via* stereo-selective polyene cyclization. A quinone methide **2** (0.5—1 μg/ml of MIC) and taxodione **3** (4—10 μg/ml of MIC) showed potent activity against both MRSA and VRE among these series of compounds. As the quinone methide **2** was isolated from an east African medicinal plant (*Plectranthus elegans*) used as a remedy for intestinal worms,[4] serious human toxicity may be avoidable. We thus planed to synthesize 11-hydroxy-12-oxo-7,9(11),13-abietatriene **2** *via* an efficient route from industrially available dehydroabietic acid (**4**) in order to provide a larger amount of the sample for further investigations into biological activity and potential application. We propose to adopt the general name of abietaquinone methide for 11-hydroxy-12-oxo-7,9(11),13-abietatriene **2**.

In the previous total synthesis of abietaquinone methide **2**, we performed *ortho*-oxidation of ferruginol **1** with dibenzoyl peroxide.[14] Dibenzoyl peroxide is a well known initiator of polymer synthesis and an effective reagent for *ortho*-oxidation of phenols. However, industrial production of dibenzoyl peroxide was ceased in Japan. Although the various reactions of diacyl peroxides are well known, its application for organic synthesis had been quite limited because of its instability. R. H. Burnell reported the synthesis of **2** through an oxidation using benzeneseleninic anhydride.[27] In order to allow further investigation into the biological activities of quinone methide, *e.g.* anti-MRSA and anti-VRE activities, we planned to develop an efficient *ortho*-oxidation reaction of phenols using a stable and nontoxic reagent. We attempted oxidation of ferruginol with 2-iodoxybenzoic acid (IBX)[28,29] and iodobenzene diacetate,[30,31] obtaining a complex mixture without the expected **2**. Treatment of ferruginol **1** with ceric ammonium nitrate (CAN) was also attempted, but **1** was not successfully oxidized to **2**.



1: ferruginol **2**: abietaquinone methide **3**: taxodione **4**: dehydroabietic acid

Fig. 1. Abietaquinone Methide and Related Compound

Synthesis of *m*CBPO One of the most popular and stable commercially available peracids is *meta*-chloroperbenzoic acid (*m*CPBA **5**). We are therefore interested in the reactivity and the stability of its diacyl peroxide derivative, bis(4-chlorobenzoyl) peroxide (*m*-chlorobenzoyl peroxide: *m*CBPO **6**). The synthesis of *m*CBPO **6** has been reported by several methods, but a practically useful reaction has not been reported. Kubota and Takeuchi reported unexpected formation of *m*CBPO **6** by heating of *m*CPBA **5** in dimethyl formamide (DMF) accompanied by explosion.[32] In 1963, Greene and Kazan reported the synthesis of substituted benzoyl peroxide through the reaction of substituted benzoic acid with dicyclohexylcarbodiimide (DCC **7**) and hydrogen peroxide.[33] They did not, however, report the synthesis of *m*CBPO **6**. We therefore examined the synthesis of *m*CBPO **6** using modifications of this classical reaction.

After several attempts, we accomplished the synthesis of *m*CBPO **6** by three reactions (Fig. 2). Method A involved the reaction of two molecules of *m*CPBA **5** (1.0 eq) with one molecule of DCC **7** (0.52 eq) in dichloromethane (CH_2Cl_2) to give *m*CBPO **6** (69%). In this reaction, an adduct (**A**) of *m*CPBA **5** could be first formed with DCC **7** and was then presumed to react with *m*CPBA **5** again to form *m*CBPO **6** along with other unknown compounds supposed to be the result of oxidation of the dicyclohexylurea part of DCC **7** (Fig.

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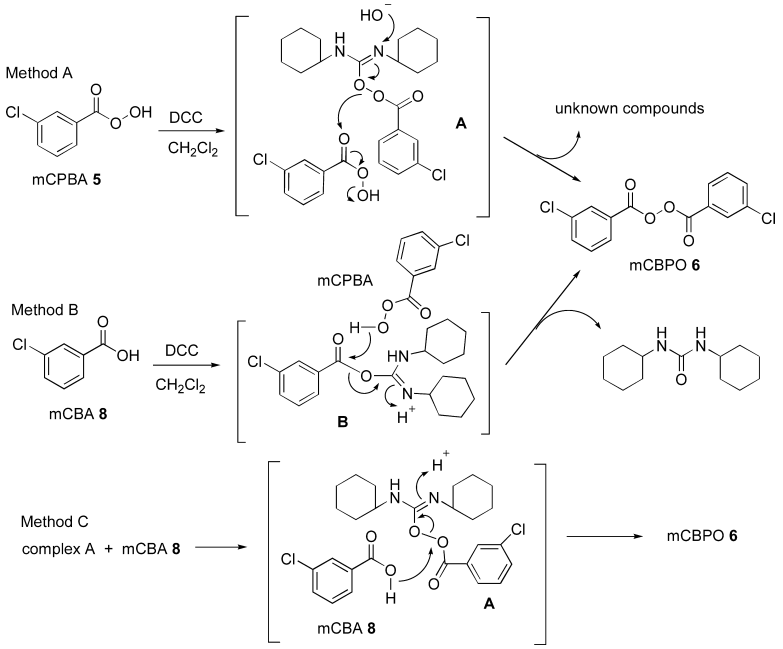

Fig. 2. Synthesis of *m*CBPO

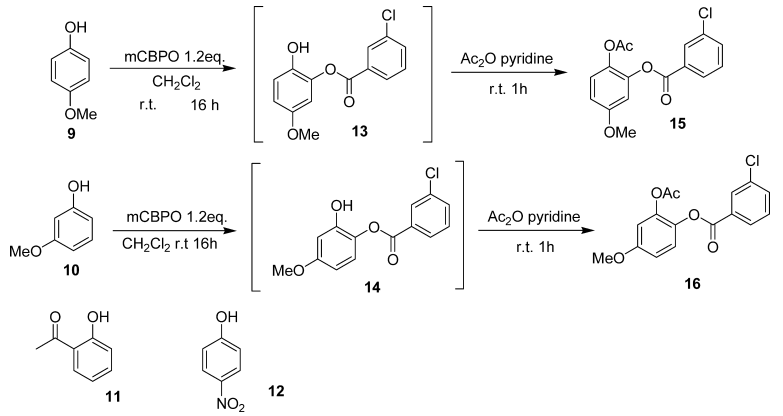

Fig. 3. *ortho*-Oxidation of Phenols with *m*CBPO

2-a). Method A needs two molecule of *m*CPBA **5** to give one mole of *m*CBPO **6**. As the commercial *m*CPBA contains less than 30% of *meta*-chlorobenzoic acid (*m*CBA **8**) as an impurity, this method gave an impurity of *m*-chlorobenzoic anhydride together with unknown yellow compounds. In method B, *m*CBPO **6** was synthesized from adduct **B** produced from reaction of *m*CBA **8** with DCC **7** (1 : 1) in CH_2Cl_2. Adduct **B** was then treated with *m*CPBA **5** to give *m*CBPO **6** (67%) and dicyclohexyl urea (Fig. 2-b). Method C involved the reaction of adduct **A** with *m*CBA **8** (Fig. 2-c). Method B gave the most pure white crystals among the three methods.

*m*CBPO **6** is a diacyl peroxide, but a stable compound throughout the duration of our synthetic research. The obtained solid of *m*CBPO **6** melted when heated in a glass tube at over 110 °C and exhibited slow foaming. *m*CBPO **6** could not be reduced with aqueous $Na_2S_2O_3$ solution, but was reduced with $NaBH_4$.

***ortho*-Oxidation of Phenols with *m*CBPO** The *ortho*-oxidation of phenols (4-methoxyphenol **9**, 3-methoxyphenol **10**, 2-acetylphenol **11** and 4-nitorophenol **12**) by *m*CBPO **6** was then examined (Fig. 3). Phenols were treated with 1.2 eq of *m*CBPO **6** in CH_2Cl_2 at ambient temperature for 16 h. The products (**13**, **14**) were acetylated with acetic anhydride and pyridine. Methoxyphenols **9** and **10** were converted to the *ortho*-oxidation products **15** (42%) and **16** (39%), respectively, whereas **11** and **12** gave complex mixtures and no *ortho*-oxidation products were detected. The lower yields of the reactions of **9** and **10** may be due to the instability of the products, which are catechol derivatives (**13**, **14**).

Synthesis of Ferruginol 1 As stated earlier, an efficient synthetic route of **1** was necessary to provide a larger amount of sample for further investigation into biological activity and potential application. One of the most popular diterpenes is dehydroabietic acid (**4**), which is industrially produced from the pine resin for the synthesis of various medicines and additives of plastics and papers. As dehydroabietic acid **4** has the same carbon skeleton as abietaquinone methide **2**, we selected dehydroabietic acid **4** as the starting material for the synthesis of abietaquinone methide.

The carboxyl group at C4 of **4** was converted to a methyl group according to the procedure of Matsumoto applied in the synthesis of ferruginol methyl ether from methyl 12-

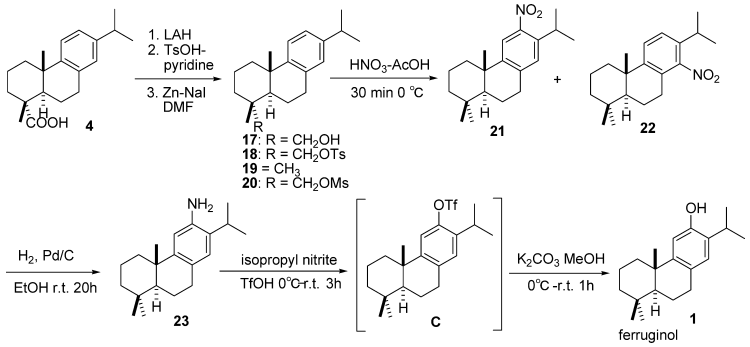

Fig. 4. Synthesis of Ferruginol

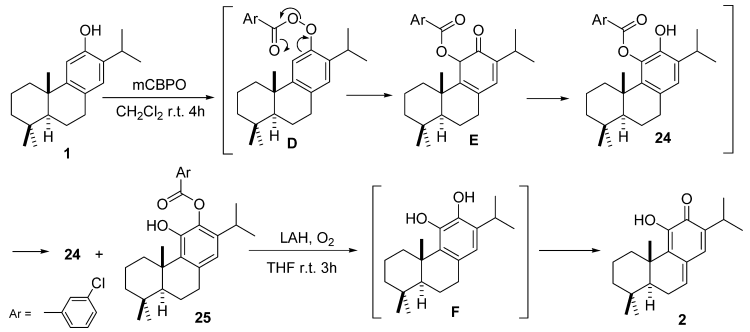

Fig. 5. Synthesis of Abietaquinone Methide **2**

methoxy-8,11,16-abietatriene-18-oate.[34] The carboxyl group at C4 of **4** was reduced with $LiAlH_4$ in THF to give an alcohol (**17**; 94%),[35] which was converted to the tosylate (**18**) with tosyl chloride in pyridine (93%). The tosylate was reduced with Zn powder-NaI in DMF to give the C4-methyl compound: 8,11,13-abietatriene (**19**) (83%).[35] The mesylate (**20**) of the alcohol **17** was also synthesized (93%) and reduced under similar reaction conditions using Zn powder-NaI in DMF, but the yield of the reduction to give 8,11,13-abietatriene **19** (27%) was lower than that of the tosylate.

The hydroxyl group at C12 was introduced by two methods.

1) Friedel-Crafts acylation followed by Baeyer-Villiger reaction; and
2) Nitration-reduction followed by Sandmeyer reaction, which is the application of the procedure used in Matsushita's synthesis of tryptoquinones.[36]

Both synthetic routes successfully gave ferruginol, but the yield of the Baeyer-Villiger reaction of the former route was lower in the larger scale experiments. The latter route was thus selected in this synthesis.

The 8,11,13-abietatriene was nitrated with nitric acid in acetic anhydride to give a mixture (2 : 1) of 12-nitro-8,11,13-abietatriene (**21**) and 14-nitro-8,11,13-abietatriene (**22**) in 70% yield. The products ratio of **21** and **22** was determined by ^{1}H-NMR. As the chromatographic properties of the two nitro-compounds, **21** and **22** were very similar, the mixture was hydrogenated over 10% Pd/C in ethanol without separation to produce a mixture of 12-amino-compound (**23**) (39% in 2 steps) with unreacted 14-nitro-compound **22**. The 12-amino-compound was purified by column chromatography of the mixture. The amino group of **23** was then converted to a phenol as follows. The amino-compound **23** was dissolved in trifluoroacetic acid and then treated with isopentyl nitrite for 3 h.[36] The product (trifluoroacetate: **C**) was hydrolyzed with aqueous sodium carbonate without separation to give ferruginol (**1**) in 87% yield. The total yield of ferruginol **1** was 23% through 7 steps from dehydroabietic acid **4**.

Synthesis of Abietaquinone Methide 2 *via* Oxidation of Ferruginol 1 Oxidation of ferruginol **1** was then examined using the *ortho*-oxidation reaction described above. A solution of ferruginol **1** (0.11 mmol) and *m*CBPO **6** (0.188 mmol) in CH_2Cl_2 was allowed to react at ambient temperature for 4 h. The oxidation of ferruginol occurred at C11 to give a mixture of 11-(3-chlorobenzoyloxy)-12-hydroxy-8,11,13-abietatriene (**24**) and 12-(3-chlorobenzoyloxy)-11-hydroxy-8,11,13-abietatriene (**25**) in 50% yield. 11-(3-Chlorobenzoyloxy)-12-hydroxy-8,11,13-abietatriene **24** could be produced *via* [3.3]sigmatropic shift from the peroxycarboxylate (**D**) of ferruginol **1** as shown in Fig. 5. 12-(3-Chlorobenzoyloxy)-11-hydroxy-8,11,13-abietatriene **25** could be formed *via* intramolecular ester exchange reaction from 11-(3-chlorobenzoyloxy)-12-hydroxy-8,11,13-abietatriene **24**. The mixture of catechol monoesters **24** and **25** was then treated with $LiAlH_4$ in tetrahydrofuran under an oxygen atmosphere for 3 h at ambient temperature to give abietaquinone methide **2** directly in 23% yield. The intermediate catechol **F** could be easily oxidized with oxygen to afford quinone methide **2**. The spectral data of the synthesized quinone methide **2** were identical with previously synthesized abietaquinone methide **2**.[4]

Although *m*CBPO is a stable diacylperoxide, one pot *ortho*-oxidation reaction of phenol with an adduct of *m*CPBA with DCC was then developed and applied for the synthesis of abietaquinone methide **2**. The adduct **A** of *m*CBPA with DCC was first synthesized in CH_2Cl_2 as above (Fig. 6), then ferruginol was added directly to the solution and stirred for

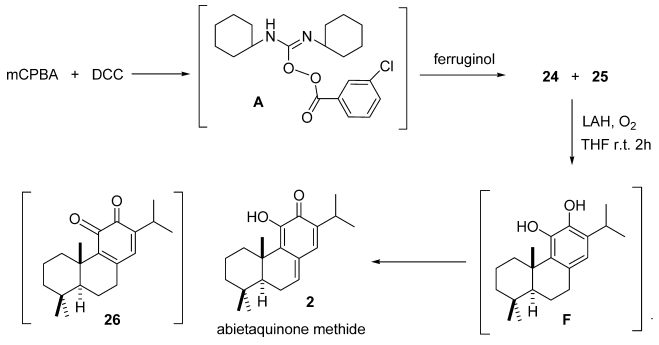

Fig. 6. Synthesis of Abietaquinone Methide **2** Using One Pot *ortho*-Oxidation

15 h. *ortho*-Oxidation reaction of ferruginol occurred and a similar mixture of **24** and **25** was obtained in 58% yield. The mixture was treated with $LiAlH_4$ in tetrahydrofuran (THF) under oxygen for 3 h at ambient temperature gave abietaquinone methide directly in 19% yield. The *ortho*-quinone **26**, the tautomeric isomer of abietaquinone methide **2**, was not obtained in this reduction–oxidation step to give quinone methide **2**.

Conclusion

We synthesized abietaquinone methide **2** efficiently from industrially available dehydroabietic acid **4** using novel *ortho*-oxidation reaction of phenol (total yield: 2.4%) with *m*CBPO. *m*CBPO is a stable diacyl peroxide which could be easy synthesized from commercially available *m*CBA. Ferruginol could be oxidize at *ortho*-position of the phenol with *m*CBPO in a comparable yield with benzoyl peroxide whose industrial production was ceased in Japan. Efficient one pot *ortho*-oxidation reaction of ferruginol with an adduct of *m*CPBA with DCC was also described. This synthetic route is expected to provide large-scale quantities of **2** for further research aimed towards potential application.

Experimental

General Procedures NMR spectra were measured on a JEOL alpha-600 (^{1}H: 600 MHz, ^{13}C: 150.8 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. Optical rotations were measured on a JASCO DIP-360 polarimeter. Melting points (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.

***m*-Chlorobenzoyl Peroxide (*m*CBPO) 6 (Method A)** Dicyclohexylcarbodiimide (621.1 mg, 3.01 mmol) was added to a solution of *m*CPBA (1.000 g, 5.79 mmol) in CH_2Cl_2 (15 ml) and the mixture was stirred at ambient temperature for 105 min under argon. The reaction mixture was concentrated carefully with a rotary evaporator to form a precipitate which was filtered out with Celite. The filtrate was evaporated to give white crystals which were then washed with hexane–ethyl acetate to give practically pure **6** (620.0 mg, 1.99 mmol, 69%) as white crystals (mp 112—113 °C; melted with slow foaming); ^{1}H-NMR ($CDCl_3$) δ: 8.06 (2H, t, J=1.8 Hz), 7.96 (2H, ddd, J=8.1, 1.8, 1.1 Hz), 7.65 (2H, ddd, J=8.1, 1.8, 1.1 Hz), 7.48 (2H, t, J=8.1 Hz); ^{13}C-NMR ($CDCl_3$) δ: 161.80, 135.18, 134.50, 130.25, 129.82, 127.90, 127.11; IR (KBr) cm^{-1}: 3101, 3075, 1791, 1768, 1220, 1006, 811, 723; EI-MS *m/z* (%): 312 (M+2, 10), 310 (M$^+$, 17), 158 (14), 156 (44), 141 (30) 139 (100), 111(33); HR-EI-MS *m/z*: Found, 309.9870 (Calcd for $C_{14}H_8Cl_2O_4$ 309.9800).

***m*-Chlorobenzoyl Peroxide (*m*CBPO) (Method B)** Dicyclohexylcarbodiimide (1.34 g, 6.51 mmol) was added to a solution of *m*CBA (1.000 g, 6.39 mmol) in CH_2Cl_2 (10 ml) at ambient temperature and the solution was stirred for 20 min under argon. To the solution, *m*CPBA (1.12 g, 6.51 mmol) was added and the mixture was stirred for 4 h at ambient temperature under argon. The reaction mixture was concentrated to form a precipitate which was filtered out with Celite. The filtrate was evaporated to give white crystals which were washed with hexane–ethyl acetate to give practically pure **6** (1.33 g, 4.28 mmol, 67%).

***m*-Chlorobenzoyl Peroxide (*m*CBPO) (Method C)** Powder of DCC (598.0 mg, 2.90 mmol) was added to a solution of *m*CBPA (500.0 mg, 2.90 mmol) in CH_2Cl_2 (5 ml) and the solution was stirred at ambient temperature for 20 min under argon. To the solution, *m*CBA (454.1 mg, 2.90 mmol) was added and the mixture was stirred for 145 min under argon. The reaction mixture was concentrated with an evaporator to form a precipitate which was filtered out with Celite. The filtrate was evaporated to give white crystals, which were washed with hexane–ethyl acetate to give practically pure *m*CBPO **6** (302.3 mg, 0.972 mmol, 67%).

2-Acetoxy-5-methoxyphenyl 3′-Chlorobenzoate (15) To a solution of 4-methoxyphenol **8** (30.0 mg, 0.242 mmol) in CH_2Cl_2 (3 ml), was added *m*CBPO (90.2 mg, 0.290 mmol) and the solution was stirred for 16 h under argon. The reaction mixture was evaporated and the residue was dissolved in a solution of pyridine (1 ml) and Ac_2O (0.5 ml). After stirring for 1 h at ambient temperature under argon, the reaction was quenched by addition of 1 M HCl followed by extraction with EtOAc. The organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, and was dried over $MgSO_4$ and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (3 : 1) to give a colorless oil of **15** (30.1 mg, 0.939 mmol, 39%): ^{1}H-NMR ($CDCl_3$) δ: 8.14 (1H, dd, J=1.8, 1.8 Hz), 8.05 (1H, ddd, J=8.1, 1.8, 1.1 Hz), 7.61 (1H, ddd, J=8.1, 1.8, 1.1 Hz), 7.45 (1H, dd, J=8.1, 8.1 Hz), 7.23 (1H, d, J=8.8 Hz), 6.83 (1H, dd, J=8.8, 2.9 Hz), 6.78 (1H, d, J=2.9 Hz), 3.82 (3H, s), 2.17 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.20, 163.28, 157.98, 142.65, 135.66, 134.90, 133.77, 130.78, 130.14, 129.99, 128.21, 123.52, 112.00, 109.20, 55.77, 20.55; EI-MS *m/z* (%): 322 (M+2, 3), 320 (M$^+$, 6), 278 (37), 139 (100), 111 (25), 69 (15); HR-EI-MS *m/z*: 300.0406 (Calcd for $C_{16}H_{13}O_5Cl_2$ 300.0452).

2-Acetoxy-4-methoxyphenyl 3′-Chlorobenzoate (16) To a solution of 3-methoxyphenol **10** (30.0 mg, 0.242 mmol) in CH_2Cl_2 (3 ml), *m*CBPO (94.2 mg, 0.303 mmol) was added and the solution was stirred at ambient temperature for 16 h under argon. The reaction mixture was evaporated and the residue was dissolved in a solution of pyridine (2 ml) and Ac_2O (1 ml). After stirring for 1 h under argon, the reaction was stopped by addition of 1 M HCl followed by extraction with EtOAc. The organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$ and brine, and was dried over $MgSO_4$ and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) to give a colorless oil of **16** (32.4 mg, 0.101 mmol, 42%): ^{1}H-NMR ($CDCl_3$) δ: 8.14 (1H, dd, J=1.8, 1.5 Hz), 8.05 (1H, dd, J=8.8, 1.2 Hz), 7.62 (1H, br d, J=8.1 Hz) 7.46 (1H, dd, J=8.1, 8.1 Hz), 7.21 (1H, d, J=8.8 Hz), 6.84 (1H, dd, J=8.8, 2.4 Hz), 6.78 (1H, d, J=2.4 Hz), 3.82 (3H, s), 2.17 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 168.21, 163.29, 157.98, 142.64, 135.65, 134.89, 133.78, 130.77, 130.14, 129.98, 128.21, 123.53, 112.00, 109.20, 55.78, 20.56; EI-MS *m/z* (%): 322 (M+2, 3), 320 (M$^+$, 13), 278 (57), 141 (55), 139 (100), 111 (39); HR-EI-MS *m/z*: 320.0483 (Calcd for $C_{16}H_{13}O_5Cl_2$ 320.0452).

8,11,13-Abietatriene-18-nol (17) Lithium Aluminum hydride (3.032 g, 79.87 mmol) was added to a dry THF (50 ml) solution of dehydroabietic acid **4** (21.104 g, 70.24 mmol) under ice cooling. The mixture was stirred at 0 °C for 30 min and then at ambient temperature for further 12 h under argon. The reaction mixture was poured into water and extracted with EtOAc. The organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (3 : 1) to give a colorless oil of **17** (18.848 g, 65.80 mmol, 94%).

18-(*p*-Toluenesulfonyloxy)-8,11,13-abietatriene (18) *p*-Toluenesulfonyl chloride (26.157 g, 137.20 mmol) was added to a solution of the alcohol **17** (30.231 g, 105.54 mmol) in pyridine (100 ml) and the solution was stirred at ambient temperature for 2 h under argon. The mixture was poured into 1 M HCl–ice. The mixture was extracted with EtOAc and the organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (10 : 1) to give a colorless oil of **18** (43.467 g, 98.64 mmol, 93%): ^{1}H-NMR ($CDCl_3$) δ: 7.77 (2H, d, J=7.8 Hz), 7.34 (2H, d, J=8.4 Hz), 7.14 (1H, d, J=7.8 Hz), 6.98 (1H, dd , J=8.4, 2.4 Hz), 6.86 (1H, d, J=2.4 Hz), 3.82 (1H, d, J=9.2 Hz), 3.60 (1H, d, J=9.2 Hz), 2.85—2.79 (2H, m), 2.78—2.72 (1H, m), 2.46 (3H, s), 2.24 (1H, br d, J=12.6 Hz), 1.71 (1H, dt, J=13.6, 3.7 Hz), 1.39—1.33

(3H, m), 1.22 (6H, d, J=6.6 Hz), 1.17 (3H, s), 0.88 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 146.69, 145.68, 144.67, 134.54, 133.03, 129.77, 127.91, 126.77, 124.19, 123.87, 77.73, 43.65, 38.00, 37.33, 37.17, 35.03, 33.42, 29.83, 25.20, 23.96, 21.62, 18.87, 18.34, 17.08; IR (NaCl) cm^{-1}: 3004, 2960, 2927, 22864, 1333, 1194, 1173, 960, 852, 818, 687; EI-MS m/z (%): 440 (M^+, 12), 268 (30), 253 (100), 211 (9); HR-EI-MS m/z: 440.2383 (Calcd for $C_{27}H_{36}O_3S$ 440.2385).

18-Methanesulfonyloxy-8,11,13-abietatriene (20) Methanesulfonyl chloride (1.10 ml, 14.17 mmol) was added to a solution of alcohol **17** (3.383 g, 11.81 mmol) in pyridine (10 ml), and the solution was stirred for 2 h under argon. The mixture was poured into 1 M HCl–ice. The mixture was extracted with EtOAc and the organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (10 : 1) to give a colorless oil of **20** (4.004 g, 10.98 mmol, 93%): ^{1}H-NMR ($CDCl_3$) δ: 7.17 (1H, d, J=8.1 Hz), 7.00 (1H, dd , J=8.1, 1.8 Hz), 6.89 (1H, d, J=1.8 Hz), 4.07 (1H, d, J=9.2 Hz), 3.80 (1H, d, J=9.2 Hz), 2.99 (3H, s), 2.92—2.85 (2H, m), 2.82 (1H, sept, J=6.6 Hz), 2.32—2.27 (1H, m), 1.78—1.47 (8H, m), 1.23 (3H, s), 1.22 (6H, d, J=6.6 Hz), 1.22 (3H, s), 0.98 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 146.75, 145.75, 134.49, 126.86, 124.20, 123.94, 76.83, 43.65, 38.07, 37.38, 37.21, 37.16, 35.14, 33.43, 29.93, 25.25, 23.97, 23.94, 18.92, 18.34, 17.09; IR (NaCl) cm^{-1}: 2954, 2870, 1610, 1500, 1464, 1363, 1171, 960, 844, 752; EI-MS m/z (%): 364 (M^+, 17), 353 (22), 286 (27), 261 (39), 254 (100), 156 (17), 69 (14); HR-EI-MS m/z: 364.2081: (Calcd for $C_{21}H_{32}O_3S$ 364.2072).

8,11,13-Abietatriene (19) A dry DMF (15 ml) solution of the tosylate **17** (1.634 g, 3.71 mmol) was stirred with NaI (total 4.058 g, 27.07 mmol) and Zn-powder (total 1.891 g, 28.92 mmol), which was added 4 times at intervals of 7 h at 100 °C for 28 h under argon. After cooling, 1 M HCl was added to the reaction mixture and the resulting precipitate was filtered out. The filtrate was extracted with hexane and the combined organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (100 : 1) to give a colorless oil of **19** (832 mg, 3.077 mmol, 83%).

8,11,13-Abietatriene (19) The mesylate **20** (3.232 g, 8.87 mmol) was dissolved in dry DMF (20 ml) and the solution was stirred at 120 °C with three times addition of NaI (total 2.658 g, 17.73 mmol) and Zn-powder (total 1.159 g, 17.73 mmol) at intervals of 8 h for 26 h under argon. After cool, the reaction mixture was quenched with 1 M HCl and the resulting precipitate was filtered out. The filtrate was extracted with hexane and the organic layer was successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (100 : 1) to give **19** (645.0 mg, 2.38 mmol, 27%).

12-Nitro8,11,13-abietatriene (21) and 14-Nitro8,11,13-abietatriene (22) A solution of nitric acid (0.270 ml) in Ac_2O (2.73 ml) was added to the solution of **19** in Ac_2O with ice cooling and the mixture was stirred at ambient temperature for 45 min under argon. The reaction mixture was poured into water–ice and extracted with EtOAc. The organic layer was successively washed with 1 M NaOH, saturated $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) to give a mixture of **21** and **22** (2 : 1, 410.0 mg, 1.30 mmol, 70%).

12-Amino-8,11,13-abietatriene (23) The suspension of the nitro compounds **21** and **22** (2 : 1, 29.8 mg, 0.0945 mmol) and 10% Pd/C (4 mg) in EtOH (2 ml) was stirred under H_2 at ambient temperature for 23.5 h. After filtration of the Pd/C, the filtrate was evaporated to give a mixture of unchanged **22** and **23** which was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) to give **23** (15.2 mg, 0.0532 mmol, 39% 2 steps from **19**): colorless oil; ^{1}H-NMR ($CDCl_3$) δ: 6.79 (1H, s), 6.58 (1H, s), 3.49 (2H, br), 2.90—2.80 (2H, m), 2.80—2.72 (1H, m), 2.19 (1H, br d, J=12 Hz), 1.87—1.81 (1H, m), 1.77—1.55 (3H, m), 1.48—1.44 (1H, m), 1.39 (1H, dd, J=13.2, 3.7 Hz), 1.32 (1H, dd, J=12.5, 2.2 Hz), 1.31—1.28 (1H, m), 1.25 (3H, d, J=7.0 Hz), 1.22 (3H, d, J=7.0 Hz), 1.17 (3H, s), 0.932 (3H, s), 0.913 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 148.36, 140.98, 130.54, 125.80, 125.66, 111.80, 50.51, 41.80, 38.92, 33.35, 31.60, 29.82, 27.48, 24.81, 22.66, 22.51, 22.35, 21.67, 19.39, 14.15; IR (NaCl) cm^{-1}: 2960, 2872, 2835, 1741, 1666, 1506, 1365, 1240, 1051, 893; EI-MS m/z (%): 285 (M^+, 100), 270 (62), 228 (23), 200 (19), 148 (55); HR-EI-MS m/z: 285.2449 (Calcd for $C_{20}H_{31}N$ 285.2456).

(+)-Ferruginol (12-Hydroxy-8,11,13-abietatriene) (1) To a solution of the 11-amino-compound **23** (700.2 mg, 2.45 mmol) in trifluoroacetic acid (8 ml), isopentyl nitrite (2.43 ml, 14.7 mmol) was added. After stirring for 3 h in an argon atmosphere, methanol (4 ml) and aqueous saturated K_2CO_3 were added and the solution was stirred for further 1 h in argon. The reaction mixture was poured into 3 M HCl–ice and extracted with EtOAc. The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) to give (+)-ferrugonol (**1**) (612.4 mg, 2.14 mmol, 87%): $[\alpha]_D$=+57.6° (c=0.15 in EtOH) (lit.,[13] +55.7).

11-(3-Chlorobenzoyloxy)-12-hydroxy-8,11,13-abietatriene (24) and 12-(3-Chlorobenzoyloxy)-11-hydroxy-8,11,13-abietatriene (25) To a solution of ferruginol (31.5 mg, 0.110 mmol) in CH_2Cl_2 (3 ml), mCBPO (58.6 mg, 0.188 mmol) was added and the mixture was stirred for 4 h at ambient temperature under argon. After addition of aqueous $Na_2S_2O_3$, the organic layer was successively washed with $Na_2S_2O_3$, and brine, and was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (5 : 1) to give a mixture of **24** and **25** (23.3 mg, 0.0548 mmol, 50%): white powder. ^{1}H-NMR ($CDCl_3$) δ: 8.24 (1H, br s), 8.14 (1H, d, J=8.1 Hz), 7.68—7.65 (1H, m), 7.51 (1H, t, J=8.1 Hz), 6.64 (1H, s), 5.12 (1H, br), 3.14—3.09 (1H, m), 2.90—2.82 (3H, m), 1.87—1.84 (1H, m), 1.79—1.70 (2H, m), 1.63—1.52 (4H, m), 1.50—1.46 (2H, m), 1.37 (3H, s), 1.22 (3H, d, J=7.0 Hz), 1.19 (3H, d, J=7.0 Hz), 0.991 (3H, s), 0.959 (3H, s); ^{13}C-NMR ($CDCl_3$) δ: 163.86, 145.54, 137.39, 135.92, 135.04, 134.95, 134.71, 134.03, 130.48, 130.33, 130.12, 128.42, 118.72, 52.73, 41.41, 39.55, 36.53, 33.74, 32.82, 29.68, 27.59, 23.03, 22.90, 22.12, 20.12, 19.33, 19.06; IR (KBr) cm^{-1}: 3460 (br), 2960, 2924, 2864, 1743, 1652, 1423, 1280, 1254, 1217; EI-MS m/z (%): 442 (M+2, 5), 440 (M^+, 11), 288 (17), 286 (61), 273 (11), 271 (85); HR-EI-MS m/z: 440.2102 (Calcd for $C_{27}H_{33}ClO_3$ 440.2118).

Abietaquinone Methide (2) Lithium aluminum hydride (6.3 mg, 0.166 mmol) was added to a solution of **25** and **26** (20.9 mg) in THF (5 ml), and the mixture was stirred for 3 h under oxygen. The reaction was stopped with EtOAc and water, and the mixture was extracted with EtOAc and 1 M HCl. The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$, and brine, and was dried over $MgSO_4$ and evaporated. The product was separated by preparative thin layer chromatography using silica gel (hexane : EtOAc=30 : 1) to give a colorless oil of **2** (3.4 mg, 0.0113 mmol, 23%): $[\alpha]_D$=+28.1° (c=0.08 in EtOH) (lit.,[4] +25.9°).

11-(3-Chlorobenzoyloxy)-12-hydroxy-8,11,13-abietatriene (24) and 12-(3-Chlorobenzoyloxy)-11-hydroxy-8,11,13-abietatriene (25) Dicyclohexylcarbodiimide (23.9 mg, 0.116 mmol) was added to a solution of mCPBA (19.9 mg, 0.116 mmol) in CH_2Cl_2 (5 ml), and the mixture was stirred for 20 min under argon. Ferruginol **2** (26.0 mg, 0.0908 mmmol) was added to the mixture and stirred for 15 h under argon. The reaction mixture was evaporated and the residue was chromatographed on a silica gel column with EtOAc–hexane (10 : 1) to give a mixture of **24** and **25** (22.3 mg, 0.0525 mmol, 58%).

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