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, anti-bacterial, anti-malarial, and anti-tumor activities. Previously, we have reported the total synthesis and the anti-MRSA and anti-VRE activities of 12 various oxidized natural abietanes, 6,7-dehydroferruginol methyl ether, ferruginol (1,5,15—17) 11-hydroxy-12-oxo-7,9(11),13-abietaatriene (2,4) royleanone (16) demethylcryptotaponol (18) salvinolone (9,20) sugiol methyl ether (21,22) 5,6-dehydroferruginol methyl ether (21,22) 5,6-dehydroferruginol (25) and taxodione (3) 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 Asian medicinal plant (*Plectranthus elegans*) used as a remedy for intestinal worms, serious human toxicity may be avoidable. We thus planed to synthesize 11-hydroxy-12-oxo-7,9(11),13-abietaatriene 2 via an efficient route from industrially available dehydroabiatic 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 abietaquione methide for 11-hydroxy-12-oxo-7,9(11),13-abietaatriene 2.

In the previous total synthesis of abietaquione methide 2, we performed ortho-oxidation of ferruginol 1 with dibenzoyl peroxide. 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 dichlorobenzene 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 benzeneselenenic anhydride. 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) and iodobenzone diacate obtaining a complex mixture without the expected structure. Treatment of ferruginol 1 with ceric ammonium nitrate (CAN) was also attempted, but it was not successfully oxidized to 2.

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

After several attempts, we accomplished the synthesis of mCBPO 6 by three reactions (Fig. 2). Method A involved the reaction of two molecules of mCPBA 5 (1.0 eq) with one molecule of DCC 7 (0.52 eq) in dichloromethane (CH₂Cl₂) to give mCBPO 6 (69%). In this reaction, an adduct (A) of mCPBA 5 could be first formed with DCC 7 and was then presumed to react with mCPBA 5 again to form mCBPO 6 along with other unknown compounds supposed to be the result of the oxidation of the dicyclohexylurea part of DCC 7 (Fig. 1).
2-a). Method A needs two molecule of mCPBA 5 to give one mole of mCBPO 6. As the commercial mCPBA contains less than 30% of meta-chlorobenzoic acid (mCBA 8) as an impurity, this method gave an impurity of m-chlorobenzoic anhydride together with unknown yellow compounds. In method B, mCBPO 6 was synthesized from adduct B produced from reaction of mCBA 8 with DCC 7 (1 : 1) in CH₂Cl₂. Adduct B was then treated with mCPBA 5 to give mCBPO 6 (67%) and dicyclohexyl urea (Fig. 2-b). Method C involved the reaction of adduct A with mCBA 8 (Fig. 2-c). Method B gave the most pure white crystals among the three methods.

mCBPO 6 is a diacyl peroxide, but a stable compound throughout the duration of our synthetic research. The obtained solid of mCBPO 6 melted when heated in a glass tube at over 110 °C and exhibited slow foaming. mCBPO 6 could not be reduced with aqueous Na₂S₂O₃ solution, but was reduced with NaBH₄.

ortho-Oxidation of Phenols with mCBPO The ortho-oxidation of phenols (4-methoxyphenol 9, 3-methoxyphenol 10, 2-acetylphenol 11 and 4-nitrophenol 12) by mCBPO 6 was then examined (Fig. 3). Phenols were treated with 1.2 eq of mCBPO 6 in CH₂Cl₂ 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-
methoxy-8,11,16-abietatriene-18-oate. The carboxyl group at C4 of 4 was reduced with LiAlH4 in THF to give an alcohol (17, 94%), 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%). 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 Matsu-shita’s synthesis of tryptoquinones. 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 1H-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 3h. The product (trifluoracetate: 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 mCBPO 6 (0.188 mmol) in CH2Cl2 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 LiAlH4 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.

Although mCBPO is a stable diacylperoxide, one pot ortho-oxidation reaction of phenol with an adduct of mCPBA with DCC was then developed and applied for the synthesis of abietaquinone methide 2. The adduct A of mCBPA with DCC was first synthesized in CH2Cl2 as above (Fig. 6), then ferruginol was added directly to the solution and stirred for
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 LiAlH₄ in tetrahydrofuran (THF) under oxygen for 3 h at ambient temperature gave abietaquione methide directly in 19% yield. The ortho-quinone methide 26, the tautomeric isomer of abietaquione methide 2, was not obtained in this reduction–oxidation step to give quinone methide 2.

Conclusion

We synthesized abietaquione methide 2 efficiently from industrially available dehydroabiatic acid 4 using novel ortho-oxidation reaction of phenol (total yield: 2.4%) with mCBPO. mCBPO is a stable diacetyl peroxide which could be easy synthesized from commercially available mCBA. Ferruginol could be oxidize at ortho-position of the phenol with mCBPO 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 mCBPA 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 (1H: 600 MHz, 13C: 150.9 MHz) spectrometer in CDCl3 using tetramethyilsilane 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 mm, BW-127ZH, Fuji Silysia Chemical Ltd.) was used for column chromatography.

m-Chlorobenzoyl Peroxide (mCBPO) (Method A)

Dicyclohexylcarbodiimide (621.1 mg, 3.01 mmol) was added to a solution of mCBPA (1.000 g, 5.79 mmol) in CH2Cl2 (15 ml) and the mixture 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 Ac2O (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 NaHCO3, and brine. The mixture was filtered out with Celite. The filtrate was evaporated to give white crystals, which were washed with hexane–ethyl acetate to give practically pure mCBPA (942.6 mg, 0.303 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 (2 ml) and Ac2O (1 ml). After stirring for 1 h under argon, the reaction was stopped by addition of 1M HCl followed by extraction with EtOAc. The organic layer was successively washed with 1M HCl, saturated aqueous NaHCO3, and brine, and was dried over MgSO4 and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (3:1) to give a colorless oil of mCBPA (302.3 mg, 0.972 mmol, 67%).

m-Chlorobenzoyl Peroxide (mCBPO) (Method C)

Powder of DCC (3.032 g, 20.00 mmol) was added to a solution of 2-Acetoxy-4-methoxyphenyl 3 (1.33 g, 4.28 mmol) in CH2Cl2 (10 ml) at ambient temperature and the solution was stirred for 20 min under argon. To the solution, mCBPA (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 mCBPA 6 (1.33 g, 4.28 mmol, 67%).

2-Acetoxy-5-methoxyphenyl 3-Chlorobenzoate (15)

To a solution of 4-methoxyphenol 8 (30.0 mg, 0.242 mmol) in CH2Cl2 (3 ml), was added mCBPO (90.20, 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 Ac2O (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 NaHCO3, and brine. The mixture 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 mCBPO 6 (302.3 mmol, 67%).

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 dehydroabiatic acid 4 (21.104 g, 70.24 mmol) under ice cooling. The mixture was heated 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 1M HCl, saturated aqueous NaHCO3, and brine, and was dried over MgSO4 and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (1:1) to give a colorless oil of 16 (324.2 g, 0.101 mmol, 42%); 1H-NMR (CDCl3): δ: 8.14 (1H, dd, J=1.8, 1.8 Hz), 8.05 (1H, d, J=8.8, 1.2 Hz), 7.62 (1H, br, d, J=8.8 Hz), 7.46 (1H, d, J=8.8 Hz), 7.21 (1H, dd, J=8.8 Hz), 6.94 (1H, d, J=8.8 Hz), 6.78 (1H, d, J=2.4 Hz), 3.82 (3H, s), 2.17 (3H, s); 13C-NMR (CDCl3): 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; MS-m/z (%): 322 (M+2, 3), 320 (M+, 6), 278 (37), 139 (100), 111 (25), 69 (15); [α]D26-M (c=0.1) 320.046 (Calcld for C34H24OCl2): 320.045.

8,11,13-Abietatriene-18-ol (17)

Lithium Aluminum hydride (30.2 g, 79.87 mmol) was added to a dry THF (50 ml) solution of dehydroabiatic acid 4 (21.104 g, 70.24 mmol) under ice cooling. The mixture was heated 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 NaHCO3, and brine, and was dried over MgSO4 and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (3:1) to give a colorless oil of 17 (18.847 g, 65.80 mmol, 94%).

18-(p-Toluenesulfonyl)oxo-11,13-17-atrietatriene (18)

p-Toluenesulfonic acid (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 for 10 min 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 NaHCO3, and brine, and was dried over MgSO4 and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1:1) to give a colorless oil of 18 (17.884 g, 65.80 mmol, 94%).

Fig. 6. Synthesis of Abietaquione Methide 2 Using One Pot ortho-Oxidation
19. (3-Chlorobenzenesulfonyl)-8,11,13-abietatriene (24) and 12- (3-Chlorobenzenesulfonyl)-11-hydroxy-8,11,13-abietatriene (25) To a solution of ferruginol (31.5 mg, 0.110 mmol) in CH2Cl2 (3 ml), mpCBPO (58.6 mg, 0.188 mmol) was added. The reaction was stirred for 4 h at ambient temperature under argon. After addition of aqueous Na2SO4, the organic layer was successively washed with Na2SO4 and brine, and was dried over MgSO4 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. 1H-NMR (CDCl3) δ: 8.24 (1H, brs), 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. s), 3.4—3.09 (2H, 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 (1H, s), 1.22 (3H, d, J=7.0 Hz), 1.19 (3H, 1H, d, J=7.0 Hz), 0.991 (3H, s), 0.959 (3H, s). HR-EI-MS (%): 442 (M+2, S), 440 (M+, 11), 288 (17), 286 (61), 273 (11), 271 (85); HR-El-Ms/El: 440.2102 (C27H36O3S440.2385). Abietanequinone Methide (2) Lithium aluminium 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 2 h under oxygen. The reaction was stopped with EtOAc and water, and the mixture was extracted with EtOAc and 10% HCl. The organic layer was successively washed with 1 M HCl, saturated NaHCO3 and brine, and was dried over MgSO4 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%); [α]25 +28.1° (c=0.08 in EtOH) (lit.17 +25.9°).

11-(3-Chlorobenzenesulfonyl)-12-hydroxy-8,11,13-abietatriene (24) and 12- (3-Chlorobenzenesulfonyl)-11-hydroxy-8,11,13-abietatriene (25) Di-cyclohexylcarboxidiimide (23.9 mg, 0.116 mmol) was added to a solution of mpCBPA (19.9 mg, 0.116 mmol) in CH2Cl2 (5 ml), and the mixture was stirred until for 20 min under argon. Ferruginol (2) (26.0 mg, 0.0988 mmol) 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%).

References


