Synthesis of Totarane Diterpenes: Totarol, Maytenoquinone, 6-Deoxymaytenoquinone and 8,11,13-Totaratriene-12,13-diol

Masahiro TADA,* Jun KURABE, Hiroaki YASUE, and Tomohisa IKUTA

Laboratory of Bioorganic Chemistry, Tokyo University of Agriculture and Technology; Fuchu, Tokyo 183–8509, Japan.
Received October 17, 2007; accepted November 24, 2007; published online January 8, 2008

The syntheses of four totarane diterpenes—totarol, 8,11,13-totaratriene-12,13-diol, 6-deoxymaytenoquinone and maytenoquinone—are described. Totarol was synthesized *via* cyclization of a modified polyene. 8,11,13-Totaratriene-12,13-diol was prepared from natural totarol by *ortho*-oxidation with *m*CBPO (*m*-chlorobenzoyl peroxide). Maytenoquinone and 6-deoxymaytenoquinone were synthesized from 8,11,13-totaratriene-12,13-diol. ^{1}H-NMR analysis showed that tautomeric isomerization between 6-deoxymaytenoquinone (2-hydroxy-4-quinone methide) and the *ortho*-quinone was very slow.

Key words synthesis; totarol; maytenoquinone; polyene cyclization; quinone methide; tautomeric isomerization

Infections caused by drug-resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and chloroquine-resistant malaria, are undergoing significant increases worldwide. In previous studies, we reported the syntheses of anti-MRSA and anti-VRE active diterpenes and details of their structure–activity relationships.[1)] Activity was found to vary significantly depending on structure, and two quinone methides, abietaquinone methide[2,3)] (11-hydroxy-12-oxo-7,9(11),13-abietatriene) (**1**) (0.5—1 μg/ml minimum inhibitory concentration (MIC)) and taxodione[4—7)] (**2**) (4—10 μg/ml MIC) showed potent activity against both MRSA and VRE.[1)] In addition, Kubo[8—10)] reported that a migrated abietane (totarane) derivative, totarol (**3**), which was isolated from the bark of *Podocarpus nagi* (Podocarpaceae), showed potent antibacterial activity against MRSA, and Evans reported anti-MRSA activity in totarol (**3**), ferruginol (**4**),[11—18)] and their abietane derivatives.[19)] Totarol was synthesized by three groups.[20—22)] W. E. Campbell reported the isolation of **4** and 8,11,13-totaratriene-12,13-diol (**5**) from *Harpagophytum procumbens* as anti-plasmodial compounds which were active against both chloroquine-resistant and chloroquine-sensitive strains.[23)] Both **4** and **5** showed low cytotoxicity. Maytenoquinone (**7**)[11,24—27)] is an isomeric quinone methide of taxodione **2**. These results suggested to us that phenolic and quinone methide diterpenes show potential as novel treatments for these drug-resistant organisms. We report here syntheses of **3** and **5** and their quinone methide derivatives **7** and 6-deoxymaytenoquinone (**6**) (Fig. 1).[27)]

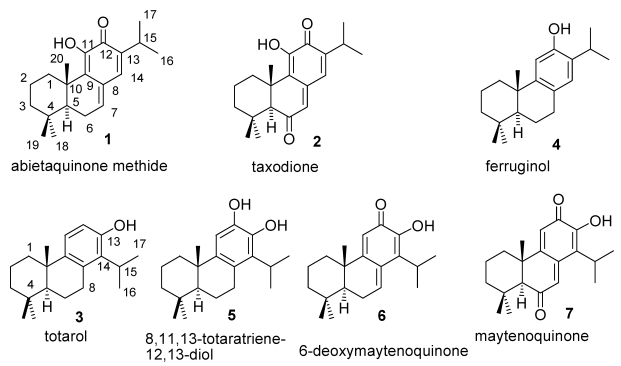

Fig. 1. Phenols and Quinone Methides with Abietane and Totarane Skeletons

Results and Discussion

Totarol We previously reported syntheses of 12 natural abietane diterpenes *via* stereoselective cyclization of a modified polyene.[1)] Totarol **3** has a migrated abietane carbon skeleton (totarane skeleton) which contains an isopropyl group at C-14. Thus, we planned to synthesize totarol **3** *via* cyclization of another modified polyene (**10**).

Polyene **10** was synthesized by alkylation of 2-methoxy-6-methylbenzoic acid (**8**) with lithium diisopropylamide (LDA) and geranyl chloride, followed by esterification with iodomethane and K_2CO_3 in CH_3CN. Polyene **10** was treated with boron trifluoride-diethyl ether ($BF_3 \cdot Et_2O$) in nitromethane to give a mixture of the A/B *trans*-compound **11** and unknown compound **12** in a 3 : 1 ratio (50%). During synthesis of abietanes, we were able to control stereoselectivity in the cyclization of the modified polyene by varying the size of the ester alkyl group on the polyene (Chart 1).[28)]

The mechanism of cyclization of **10** is not clear. When we consider the stepwise mechanism, there are two possible intermediates, **M** and **N** (Chart 2). Intermediate **M** gives the A/B *trans*-compound **11**, while intermediate **N** gives the A/B *cis*-isomer. As the energy difference between the two intermediates was estimated to be quite small, further experiments varying the alkyl group of ester to improve stereoselectivity in the cyclization reaction were not attempted. The crude cyclized product **11** was methylated using methyllithium in tetrahydrofuran (THF) to give acetyl derivative **13** (82%), which was further methylated with methyl magnesium bromide in THF to afford tertiary alcohol **14** (63%). The unknown compound **12** and its derivative were removed during the purification of tertiary alcohol **14** with column chromatography. Dehydration of **14** by heating under reflux in toluene with *p*-toluenesulfonic acid gave isopropenyl compound **15** (83%). After deprotection of the methyl group of **15** with boron tribromide in CH_2Cl_2, the product (**16**) was hydrogenated with H_2-PtO_2 in ethanol for 8 d to give totarol (**3**) (74% from **15**). The A/B *cis*-isomer of totarol, which may be derived from **12**, was not observed in the NMR spectrum of totarol. As natural totarol has recently been offered for sale, the NMR spectrum of synthesized crude totarol was compared with that of natural totarol to confirm that the

* To whom correspondence should be addressed. e-mail: tada@cc.tuat.ac.jp

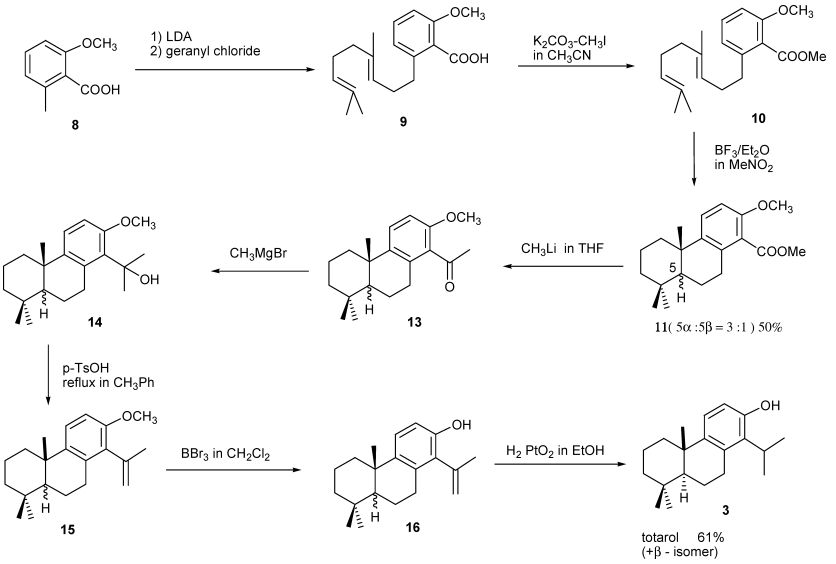

Chart 1. Synthesis of Totarol *via* Polyene Cyclization

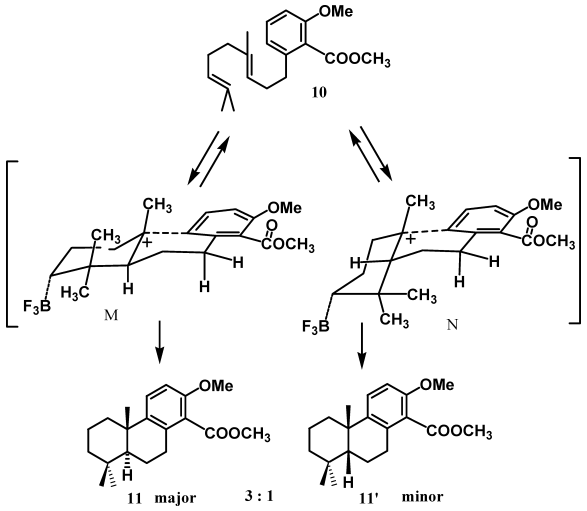

Chart 2. Two Transition States (M and N) in the Cyclization of Polyene **12**

structure was correct.

Maytenoquinone Efficient *ortho*-oxidation of phenol was reported in our synthesis of abietaquinone methide from dehydroabietic acid using a stable diacyl peroxide, *meta*-chlorobenzoyl peroxide (*m*CBPO).[3] Totarol **3** was thus oxidized with *m*CBPO in CH_2Cl_2 for 19 h to afford a mixture of the *ortho*-oxidation product **17** and its isomer **18**, which is thought to be formed by ester exchange reaction of **17**. The mixture was reduced with $LiAlH_4$ in THF for 3 h to give a stable catechol (8,11,13-totaratriene-12,13-diol, **5**) in 60% yield. The spectral features of **5** were identical to those of the plasmodial-active compound which was isolated from *Harpagophytum procumbens* (Devil's claw) by Campbell *et al.*[23] In the synthesis of abietaquinone methide **1**, the intermediate catechol was not isolated because it was easily oxidized to abietaquinone methide **1** with oxygen.[1,3] As catechol **5** is stable under air, it was oxidized with Ag_2O in $CHCl_3$ under reflux for 16 h to give a mixture of two isomers, *ortho*-quinone **19** and quinone methide **6** (14 : 1), in 99% yield.[27] The isomer ratio varied with reaction conditions and reaction time (Chart 3).

When the tautomeric equilibrium between *ortho*-quinone **19** and 2-hydroxy-1,4-quinone methide **6** was investigated using ^{1}H-NMR spectroscopy with acetone as solvent, **19** was found to undergo slow conversion to **6**. The mixture of *ortho*-quinone **19** and quinone methide **6** (14 : 1) was dissolved in acetone and stirred without a catalyst at ambient temperature. After 2 d, the ratio of **19** to **6** was 2.6 : 1; after 7 d, the ratio was 0.9 : 1. This shows that the isomerization reaction of **19** to form **6** is slower than in the case of abietaquinone methide **1**, and that quinone methide **6** is a more stable isomer than quinone **19**. The isomerization of **19** to **6** was also observed on silica gel.

Burnell reported that **6** was prepared by oxidation of catechol **5** with Ag_2O, and maytenoquinone **7** was obtained from quinone methide **6** by auto-oxidation during silica gel column chromatography with slow elution by benzene.[27] In our experiment, both **19** and **6** were obtained by Ag_2O oxidation of **5**, and the equilibrium between the two species was very slow in solution without a catalyst. The isolated quinone methide **6** was oxidized on a short column of silica gel for 45 min under a stream of air from a small air pump, giving maytenoquinone **7**. The spectral properties of **7** were identical to those in the literature.[24,25] The structure–activity relationships and anti-MRSA activities of the synthesized totarane diterpenes and related compounds will be reported elsewhere.

In conclusion, we synthesized four totarane diterpenes. Totarol (**3**) was prepared *via* polyene cyclization; *ortho*-oxidation of totarol with *m*CBPO followed by deprotection gave 8,11,13-totaratriene-12,13-diol (**5**), which was identical to the anti-plasmodial compound isolated from *Harpagophytum procumbens* (Devil's claw). Oxidation of catechol **5** gave two isomers, *ortho*-quinone **19** and quinone methide **6**; isomerization of **19** to **6** took place slowly. Finally, **6** was oxidized to maytenoquinone **7** on silica gel by oxygen.

Experimental

General Procedures NMR spectra were measured on a JEOL alpha-600 (^{1}H: 600 MHz, ^{13}C: 150.8 MHz) or JEOL AL-400 (^{1}H: 400 MHz, ^{13}C: 100.5 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard (*J*-values in Hz). IR spectra were measured on a JEOL JIR-

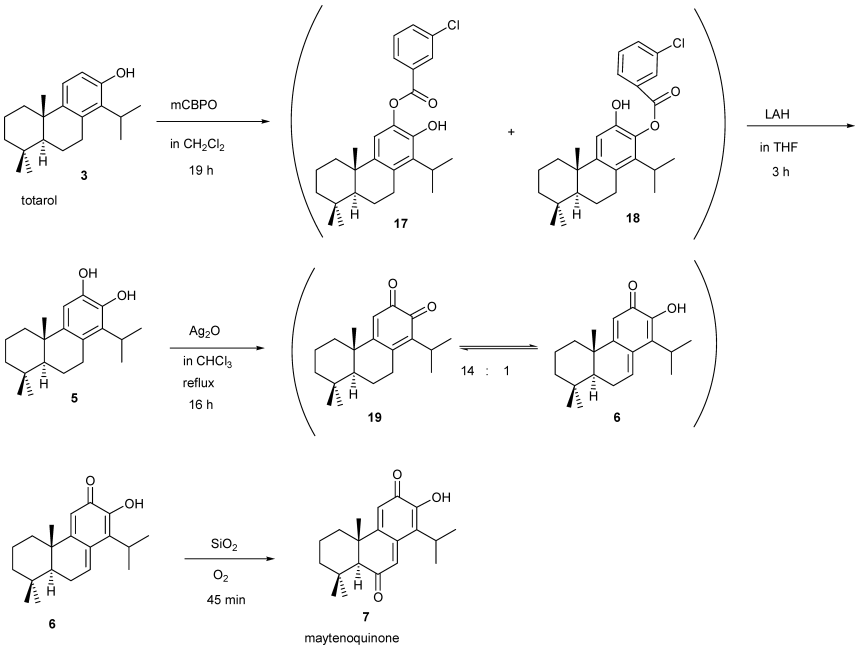

Chart 3. Synthesis of Maytenoquinone

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.

2-(4,8-Dimethylnona-3,7-dienyl)-6-methoxybenzoic Acid (9) To THF (20 ml) solution of diisopropylamine (0.6 ml, 3.89 mmol) and *n*-butyl lithium in hexane (2.7 ml, 3.89 mmol), 2-methoxy-6-methylbenzoic acid **8** (308 mg, 1.85 mmol) in THF (5 ml) was added at −78 °C. The solution was stirred for 30 min and then geranyl chloride (480 mg, 2.80 mmol) in THF (5 ml) was added. The solution was stirred for further 1 h and was allowed to warm up to ambient temperature, and the reaction was stopped with 1 M-HCl. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel column with EtOAc–hexane (1 : 4) to give white crystals of **9** (321 mg: 57% yield): 2-(4,8-Dimethylnona-3,7-dienyl)-6-methoxybenzoic acid (**9**): mp 54—55 °C; ^{1}H-NMR (600 MHz $CDC1_3$) δ: 7.32 (1H, t, J=8.0 Hz), 6.89 (1H, d, J=8.0 Hz), 6.82 (1H, d, J=8.0 Hz), 5.19 (1H, t, J=7.2 Hz), 5.09 (1H, t, J=7.2 Hz), 3.90 (3H, s), 2.79 (2H, t, J=8.0 Hz), 2.31 (2H, q, J=7.3 Hz), 2.08—2.02 (2H, m), 1.99—1.95 (2H, m), 1.68 (3H, s), 1.59 (3H, s), 1.56 (3H, s); ^{13}C-NMR (150 MHz; $CDC1_3$) δ: 169.6, 156.8, 143.2, 136.1, 131.3, 131.1, 124.3, 123.3, 122.9, 121.1, 108.8, 56.2, 39.7, 34.2, 29.8, 26.7, 25.7, 17.6, 15.9; IR (KBr, cm^{-1}) 3077, 2917, 2854, 1697, 1587, 1417, 1402, 1267, 1091, 914, 761, 732, 646; MS (EI) (rel. int. %) 302 (M+8), 259 (77), 215 (82), 166 (78), 148 (94), 109 (25), 81 (34), 69 (100); HR-MS (EI) *m/z*: 302.1845 (Calcd for $C_{19}H_{26}O_3$ 302.1882).

Methy1 2-(4,8-Dimethylnona-3,7-dienyl)-6-methoxy-benzoate (10) To CH_3CN solution (10 ml) of 2-(4,8-dimethylnona-3,7-dienyl)-6-methoxybenzoic acid **9**, K_2CO_3 (431 mg, 3.11 mmol) and CH_3I (0.3 ml, 5.13 mmol) were added and the mixture was heated under reflux for 16 h. The reaction was stopped by addition of water and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The product was chromatographed on a silica gel column with EtOAc–hexane (1 : 7) to give a colorless oil of methy1 2-(4,8-dimethylnona-3,7-dienyl)-6-methoxy-benzoate (**10**) (268 mg, 0.84 mmol, 82%): ^{1}H-NMR (600 MHz: $CDC1_3$) δ: 7.26 (1H, t, J=8.0 Hz), 6.82 (1H, d, J=8.0 Hz), 6.76 (1H, d, J=8.0 Hz), 5.17—5.131 (1H, m), 5.10—5.06 (1H, m), 3.90 (3H, s), 3.81 (3H, s), 2.56 (2H, t, J=8.0 Hz), 2.26 (2H, q, J=7.6 Hz), 2.08—2.03 (2H, m), 1.99—1.94 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.56 (3H, s); ^{13}C-NMR (150 MHz; $CDC1_3$) δ: 168.9, 156.2, 140.8, 136.0, 131.3, 130.2, 124.3, 123.5, 123.3, 121.6, 108.5, 55.9, 52.1, 39.6, 33.7, 29.6, 26.6, 25.6, 17.6, 15.9; IR (NaCl cm^{-1}) 2927, 2865, 1735, 1585, 1471, 1375, 1270, 1189, 1110, 1072, 954, 833; MS (EI) (rel. int. %) 332 (M^+ 7), 285 (11), 241 (36), 215 (89), 179 (64), 148 (81), 81 (26), 58 (100); HR-MS (EI) *m/z* 316.2073 (316.2038 Calcd for $C_{20}H_{28}O_3$).

Methyl 1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-1,1,4a-trimethyl-phenanthrene-8-carboxylate (11), (12) A solution of 2-(4,8-dimethylnona-3,7-dienyl)-6-methoxy-benzoate (**10**) (203 mg) in nitromethane (3 ml) was added to nitromethane (7 ml) solution of $BF_3 \cdot OEt_2$ (0.32 ml, 2.38 mmol) at ambient temperature and the solution was stirred for 15 h at ambient temperature. The reaction was stopped by addition of aqueous saturated $NaHCO_3$ and the mixture was extracted with EtOAc. The solution was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 7) to give white solid of a mixture (3 : 1) of **11** and **12** (115 mg, 0.32 mmol, 50%), **11** (major): ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.25 (1H, d, J=8.4 Hz), 6.72 (1H, d, J=8.4 Hz), 3.89 (3H, s), 3.78 (3H, s), 2.84—2.75 (2H, m), 2.24 (1H, d, J=11 Hz), 1.84 (1H, m), 1.15 (3H, s), 0.93 (3H, s), 0.91 (3H, s); ^{13}C-NMR (150 MHz, $CDC1_3$) δ: 169.3, 153.7, 143.1, 133.3, 126.5, 125.8, 108.8, 55.9, 52.1, 49.9, 41.6, 39.1, 37.5, 33.3, 33.2, 27.4, 24.9, 21.5, 19.3, 18.5; IR (KBr cm^{-1}) 2944, 2846, 1729, 1591, 1486, 1436, 1383, 1207, 1070, 971, 811; MS (EI) (rel. int. %) 332 (M^+ 60), 301 (100), 269 (39), 231 (24), 201 (39), 173 (16), 115 (12), 91 (4), 69 (12); HR-MS (EI) *m/z* 316.2011 (316.2038 Calcd for $C_{20}H_{28}O_3$); **12** (minor): ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.25 (1H, d, J=8.7 Hz), 6.73 (1H, d, J=8.7 Hz), 3.90 (3H, s), 3.79 (3H, s), 1.21 (3H, s), 0.92 (3H, s), 0.90 (3H, s); ^{13}C-NMR (150 MHz, $CDC1_3$) δ: 168.4, 153.6, 136.3, 135.4, 122.9, 108.3, 55.7, 52.1, 49.7, 43.1, 38.1, 36.8, 34.5, 32.6, 23.3, 22.7, 19.1, 17.6, 14.2.

8-Acetyl-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1,1,4a-trimethylphenanthrene (13) To THF (10 ml) solution of CH_3Li (1.8 ml in hexane: 2.05 mmol), THF (5 ml) solution of esters **11** and **12** (121 mg, 0.38 mmol) was added and the mixture was stirred for 15 h at 0 °C. The reaction was stopped by addition of aqueous saturated NH_4Cl and the mixture was extracted with EtOAc. The solution was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 7) to give white solid of **13** (94 mg, 0.31 mmol, 82%): ^{1}H-NMR (600 MHz $CDC1_3$) δ: 7.22 (1H, d, J=8.7 Hz), 6.72 (1H, d, J=8.7 Hz), 3.77 (3H, s), 2.80—2.65 (3H, m), 2.46 (3H, s), 2.24 (1H, d, J=13 Hz), 1.85 (1H, m), 1.16 (3H, s), 0.91 (3H, s), 0.90 (3H, s); ^{13}C-NMR (150 MHz $CDCl_3$) δ: 206.8, 153.2, 143.4, 130.6, 126.0, 125.2, 108.6, 55.6, 49.9, 41.6, 39.2, 37.6, 33.3, 33.2, 32.1, 27.3, 25.0, 21.6, 19.3, 18.8; IR (KBr cm^{-1}) 2940, 2854, 1693, 1589, 1479, 1373, 1270, 1070, 1018, 809, 570; MS (EI) (rel. int. %) 300 (M^+ 90), 285 (100), 273 (28), 241 (27), 215 (95), 179 (39), 148 (57), 109 (22), 91 (16), 69 (76); HR-MS (EI) *m/z* 300.210 (300.2089 Calcd for $C_{20}H_{28}O_2$). Minor: ^{1}H-NMR (600 MHz $CDC1_3$) δ: 6.71 (1H, d, J=8.4 Hz), 3.78 (3H, s), 2.43 (3H, s), 1.12 (3H, s), 0.92 (3H, s); ^{13}C-NMR (150 MHz $CDCl_3$) δ: 213.0, 146.9, 136.5, 134.1, 132.2, 108.1, 100.6, 55.4, 49.6, 43.0, 38.2, 34.4, 32.6, 27.1, 23.2, 22.8, 21.9, 21.0, 19.2, 18.7.

1,2,3,4,4a,9,10,10a-Octahydro-8-(1-hydroxy-1-methylethyl)-7-me-

thoxy-1,1,4a-trimethylphenanthrene (14) To THF solution (10 ml) of CH_3MgBr (1.10 ml in THF: 1.04 mmol), THF (5 ml) solution of 8-acetyl-1,2,3,4,4a,9,10,10a-octahydro-7-methoxy-1,1,4a-trimethylphenanthrene **13** (31 mg, 0.10 mmol) was added and the mixture was stirred for 14 h at 0 °C. The reaction was stopped by addition of 1 M HCl and the mixture was extracted with EtOAc. The solution was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 7) to give white oil of a tertiary alcohol **14** (22 mg, 0.070 mmol, 63%): ^{1}H-NMR (600 MHz $CDCl_3$) δ: 7.17 (1H, d, J=8.7 Hz), 6.80 (1H, d, J=8.7 Hz), 3.85 (3H, s), 3.09—2.98 (2H, m), 2.20 (1H, d, J=13 Hz), 1.87 (1H, m), 1.8—1.5 (3H, m), 1.47 (1H, d, J=14.4 Hz), 1.4—1.2 (3H, m), 1.70 (3H, s), 1.66 (3H, s), 1.19 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C-NMR (150 MHz $CDC1_3$) δ: 155.0, 144.6, 134.6, 134.3, 124.3, 110.3, 75.5, 55.9, 55.8, 49.7, 41.4, 40.0, 38.5, 33.1, 31.9, 31.5, 31.4, 24.9, 21.6, 19.6, 19.5; IR (KBr cm^{-1}) 3502, 2929, 2863, 1585, 1463, 1373, 1249, 1072, 944, 804; MS (EI) (rel. int. %) 316 (2), 299 (15), 298 (45), 283 (76); HR-MS (EI) *m*/*z*: 316.2388 (316.2402 Calcd for $C_{21}H_{32}O_2$).

1,2,3,4,4a,9,10,10a-Octahydro-8-isopropenyl-7-methoxy-1,1,4a-trimethylphnanthrene (15) Toluene (15 ml) solution of a tertiary alcohol **14** (21 mg, 0.066 mmol) and *p*-toluenesulfonic acid (5 mg) was heated under reflux for 15 h under Ar. The reaction was stopped by addition of aqueous saturated NH_4Cl and the mixture was extracted with EtOAc. The solution was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 7) to give colorless oil of 1,2,3,4,4a,9,10,10a-octahydro-8-isopropenyl-7-methoxy-1,1,4a-trimethylphnanthrene **15** (17 mg, 0.05 mmol, 83%): ^{1}H-NMR (600 MHz $CDC1_3$) δ: 7.16 (1H, d, J=8.7 Hz), 6.72 (1H, d, J=8.7 Hz), 6.71 (1H, d, J=8.0 Hz), 5.26 (1H, s), 4.76 (1H, s), 3.77 (3H, s), 2.30—2.26 (1H, m), 2.02—1.9 (4H, m), 1.85 (1H, m), 1.8—1.5 (2H, m), 1.47 (1H, d, J=13.2 Hz), 1.4—1.2 (2H, m) 1.28 (3H, s), 1.19 (3H, s), 0.95 (3H, s), 0.93 (3H, s); ^{13}C-NMR (150 MHz; $CDC1_3$) δ: 153.6, 135.4, 133.5, 129.0, 128.7, 125.9, 114.7, 108.2, 55.6, 49.7, 41.7, 39.3, 37.0, 33.3, 32.7, 29.6, 25.6, 23.1, 21.6, 19.4, 14.0; IR (KBr cm^{-1}) 3075, 2927, 2854, 1645, 1585, 1479, 1263, 1101, 1076, 892, 802; MS (EI) (rel. int. %) 298 (60), 283 (100), 215 (75), 187 (41), 167 (38), 149 (82), 97 (25), 69 (47); HR-MS (EI) *m*/*z*: 298.2301 (298. 2297 Calcd for $C_{21}H_{30}O$).

Totarol (3) To CH_2Cl_2 (13 ml) solution of 1,2,3,4,4a,9,10,10a-octahydro-8-isopropenyl-7-methoxy-1,1,4a-trimethylphnanthrene **15**, BBr_3 (0.01 ml) was added and the solution was stirred for 3 h at 0 °C. The reaction was stopped by addition of CH_3OH and extracted with EtOAc–brine. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 10) to give white oil. The product was dissolved in EtOH (5 ml) and the solution was stirred with PtO_2 (1.5 mg) under H_2 for 8 d. The mixture was filtered through Celite and the solution was evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane to give colorless oil of totarol **3** (7 mg, 0.02 mmol, 74%): ^{1}H-NMR (600 MHz $CDCl_3$) δ: 6.99 (1H, d, J=8.7 Hz), 6.50 (1H, d, J=8.7 Hz), 4.42 (1H, s), 3.34—3.23 (1H, s), 2.93 (1H, d, J=16.8, 6.2 Hz), 2.74 (1H, ddd, J=16.8, 11.7, 7.6 Hz), 2.22 (1H, d, J=6.6 Hz), 1.91 (1H, dd, J=12, 7.8 Hz), 1.46 (1H, d, J=13.2 Hz), 1.68—1.54 (4H m), 1.28—1.20 (2H, m), 1.35 (3H, d, J=7.3 Hz), 1.36 (3H, d, J=7.3 Hz), 1.17 (3H, s), 0.94 (3H, s), 0.91 (3H, s); ^{13}C-NMR (150 MHz $CDCl_3$) δ: 151.9, 143.2, 134.0, 131.0, 23.0, 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 (286.2297 Calcd for $C_{20}H_{30}O$).

(4a*S*,10a*S*)-1,2,3,4,4a,9,10,10a-Octahydro-6,7-dihydroxy-8-isopropyl-1,1,4a-trimethylphenanthrene: 8,11,13-Totaratriene-12,13-diol (5) To a solution of totarol **3** (292.4 mg, 1.02 mmol) in CH_2Cl_2 (5 ml), *m*CBPO (546 mg, 1.75 mmol) was added and the solution was stirred for 19 h at ambient temperature. The reaction mixture was evaporated and the residue was dissolved in THF (5 ml). The solution was cooled in an ice bath and $LiAlH_4$ (133 mg, 3.50 mmol) was added to the solution. The mixture was stirred for 3 h at 0 °C to room temperature. The reaction was stopped by addition of EtOAc and 1 M HCl. The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 5) to give colorless oil of a catechol: 8,11,13-totaratriene-12,13-diol (**5**) (184.4 mg, 0.61 mmol, 60%): ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.69 (1H, s), 5.81 (1H, s), 5.47 (1H, s) , 3.32 (1H, sept, J=7.0 Hz), 3.03—2.64 (2H, m), 2.16—2.05 (1H, m), 1.96 (1H, dd, J= 12.9, 7.8 Hz), 1.84—1.48 (4H, m), 1.42 (3H, d, J=7.0 Hz), 1.41 (3H, d, J=7.0 Hz), 1.38—1.23 (3H, m), 1.20 (3H, s), 1.01 (3H, s), 0.97 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 142.4, 141.0, 131.7, 125.5, 109.2, 49.6, 41.6, 39.5, 37.6, 33.3, 33.2, 28.2, 27.5, 25.1, 21.6, 20.4, 20.4, 19.5, 19.4; IR (NaCl cm^{-1}) 3502, 2933, 2877, 1711, 1605, 1485, 1466, 1441, 1377, 1275, 1190, 1101, 1043, 1007, 947, 866; LR-EI-MS *m*/*z* (%): 302 (88, M^+), 287 (100), 217 (47), 191 (54); HR-EI-MS *m*/*z* (302.4570 for $C_{20}H_{30}O_2$).

***o*-Quinone (19) and 6-Deoxymaytenoquinone (6)** To a solution of the catechol **5** (82.6 mg, 0.273 mmol) in $CHCl_3$ (10 ml), Ag_2O (135.0 mg, 0.583 mmol) was added and the mixture was heated under reflux for 16 h. The mixture was filtered through Celite and the filtrate was evaporated to give a yellow oil of mixture of *o*-quinone **19** and 6-deoxymaytenoquinone **6** (81.0 mg, 0.270 mmol, 99%, **19** : **6**, 14 : 1 by ^{1}H-NMR). The products (167.0 mg, 0.556 mmol) were dissolved in acetone and absorbed on silica gel. The mixture was allowed to stand under air at room temperature for 19 h. The product was extracted with EtOAc and the solution was evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 8) to give yellow solid of *p*-quinone methide **6** (54.6 mg, 0.182 mmol, 33%) and a crude **19** (50.4 mg).

The products (82.6 mg, 0.2.73 mmol) were dissolved in acetone (20 ml) and stirred for 2 d without catalyst at ambient temperature to give 2.6 : 1 mixture of **19** and **6**. The mixture was stirred totally for 7 d and the ratio of **19** and **6** was changed to 0.9 : 1.

o-Quinone (**19**): Reddish oil; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 6.16 (1H, s), 3.01 (1H, sept, J=7.2 Hz), 2.94—2.87 (1H, m), 2.74—2.65 (1H, m), 2.00—1.92 (1H, m), 1.91—1.84 (1H, m), 1.72—1.59 (3H, m), 1.52—1.30 (3H, m), 1.27—1.16 (1H, m), 1.24 (3H, d, J=7.2 Hz), 1.21 (3H, s), 1.20 (3H, d, J=7.2 Hz), 0.95 (3H, s), 0.94 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 181.7, 180.2, 167.094, 145.9, 143.1, 120.8, 46.5, 41.1, 39.5, 38.4, 33.8, 32.7, 27.9, 26.8, 22.4, 21.8, 20.3, 20.0, 18.7, 18.4.

p-Quinone Methide (**6**): Yellow solid mp 96 °C; $[\alpha]_D$ 27.3° (c=0.011 in acetone); ^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.17 (1H, dd, J=6, 2.4 Hz), 6.96 (1H, s), 6.31 (1H, s), 3.12 (1H, sept, J=7.2 Hz), 2.64—2.59 (1H, m), 2.49—2.43 (1H, m), 2.02—1.98 (1H, m), 1.72—1.62 (2H, m), 1.56 (1H, dd, J=11.4, 4.2 Hz), 1.51—1.42 (2H, m), 1.36 (3H, d, J=7.2 Hz), 1.32 (3H, d, J=7.2 Hz), 1.22 (1H, dt, J=13.2, 4.2 Hz), 1.09 (3H, s), 1.00 (3H, s), 0.93 (3H, s); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 181.6, 162.1, 144.7, 143.4, 130.2, 127.1, 117.1, 48.7, 41.4, 38.3, 36.9, 33.3, 32.4, 26.5, 26.4, 22.0, 21.6, 20.4, 18.7; IR (cm^{-1} KBr) 3448, 3327, 3294, 2949, 2929, 2870, 1612, 1549, 1464, 1431, 1377, 1300, 1277, 1277, 1217, 1196, 1109, 887, 714, 623.

Maytenoquinone (7) 6-Deoxymaytenoquinone **6** (18.40 mg, 0.061 mmol) was dissolved in acetone and absorbed on 2 g of silica gel. The silica gel with **6** was packed in a short column. The silica gel mixture was allowed to react with air stream through a small air pump at room temperature for 45 min. The product was extracted with EtOAc and the solution was evaporated. The residue was chromatographed on a silica gel column with EtOAc–hexane (1 : 5) to give orange solid of maytenoquinone **7** (3.7 mg, 0.012 mmol, 20%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.14 (1H, s), 6.61 (1H, d, J=1.2 Hz), 6.40 (1H, d, J=1.5 Hz), 3.06 (1H, sept, J=7.1 Hz), 2.49 (1H, s), 2.03—1.96 (1H, m), 1.80—1.44 (5H, m), 1.36 (3H, d, J=7.1 Hz), 1.31 (3H, d, J=7.1 Hz), 1.26 (3H, s), 1.25 (3H, s), 1.17 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 199.6, 181.3, 161.5, 146.3, 140.3, 131.0, 126.3, 119.9, 62.1, 43.0, 42.5, 37.2, 33.0, 32.9, 26.8, 26.1, 21.7, 20.2, 18.3; IR (KBr cm^{-1}) 3417, 3334, 2929, 2872, 2850, 1670, 1620, 1470, 1419, 1290, 1273, 1225, 1203, 1144, 995, 872, 706, 623, 586, 525, 478.

References

1) Yang Z., Kitano Y., Chiba K., Shibata N., Kurokawa H., Doi Y., Arakawa Y., Tada M., *Bioorg. Med. Chem.*, **9**, 347—356 (2001).
2) Dellar J. E., Cole M. D., Waterman P. G., *Phytochemistry*, **41**, 735—738 (1996).
3) Tada M., Ishimaru K., *Chem. Pharm. Bull.*, **54**, 1412—1417 (2007).
4) Kupchan S. M., Karim A., Marcks C., *J. Am. Chem. Soc.*, **90**, 5923—5924 (1968).
5) Kupchan S. M., Karim A., Marcks C., *J. Org. Chem.*, **34**, 3912—3918 (1969).
6) Lin L., Blasko G., Cordell G. A., *Phytochemistry*, **28**, 177—181 (1989).
7) Sabri N. N., Abou-donia A. A., Assad A. M., Ghazy N. M., El-lakang A. M., Tempesta M. S., Sanson D. R., *Planta Med.*, **55**, 582—582 (1989).
8) Himejima M., Kubo I., *J. Agric. Food Chem.*, **39**, 418—421 (1991).
9) Muroi H., Kubo I., *Biosci. Biotechnol. Biochem.*, **58**, 1925—1926 (1994).
10) Haraguti H., Oike S., Muroi H., Kubo I., *Planta Med.*, **62**, 122—125

(1996).
11) Tezuka Y., Kasimu R., Li J. X., Basnet P., Tanaka K., Namba T., Kadota S., *Chem. Pharm. Bull.*, **46**, 107—112 (1998).
12) Harrison L. J., Asakawa Y., *Phytochemistry*, **26**, 1211—1212 (1987).
13) Sharp H., Latif Z., Bartholomew B., Bright C., Jones C., Sarker S., *Biochem. Syst. Ecol.*, **29**, 215—217 (2001).
14) He K., Zeng L., Shi G., Ghao G., Kolzowski J., Mclaughlin J., *J. Nat. Prod.*, **60**, 38—40 (1997).
15) Ulubelen A., Öksüz S., Kolak U., Birman H., Voelter W., *Planta Med.*, **66**, 627—629 (2000).
16) González A., Aguiar Z., Grillo T., Luis J., *Phytochemistry*, **31**, 1691—1695 (1992).
17) Clarkson C., Campbell W. E., Smith P., *Planta Med.*, **69**, 720—724 (2003).
18) Ulubelen A., Evren N., Tuziaci E., Bozok-Johansson C., *J. Nat. Prod.*, **51**, 1178—1183 (1988).
19) Evans G. B., Furneaux R. H., Gravestock M. B., Lynch G. P., Scott G. K., *Bioorg. Med. Chem.*, **7**, 1953—1964 (1999).
20) Barltrop J. A., Roger N. A. J., *J. Chem. Soc.*, **1958**, 2566—2572 (1958).
21) Matsumoto T., Suetsugu A., *Bull. Chem. Soc. Jpn.*, **52**, 1450—1453 (1979).
22) Marcos I. S., Cubillo M. A., Moro R. F., Diez D., Basabe P., Sanz F., Urones J. G., *Tetrahedron Lett.*, **44**, 8831—8835 (2003).
23) Clarkson C., Campbell W. E., Smith P., *Planta Med.*, **69**, 720—724 (2003).
24) Martin J. D., *Tetrahedron*, **29**, 2553—2559 (1973).
25) Matsumoto T., Ohmura T., Usui S., *Bull. Chem. Soc. Jpn.*, **52**, 1957—1963 (1979).
26) Harrison L., Asakawa Y., *Phytochemistry*, **26**, 1211—1212 (1987).
27) Burnell R. H., Jean M., Marceau S., *Can. J. Chem.*, **66**, 227—230 (1988).
28) Tada M., Nishiiri S., Yang Z., Imai Y., Tajima S., Okazaki N., Kitano Y., Chiba K., *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2657—2664 (2000).