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Synthesis and Absolute Configuration of Hongoquercin A, an Antibacterial Sesquiterpene-Substituted Orsellinic Acid Isolated as a Fungal Metabolite

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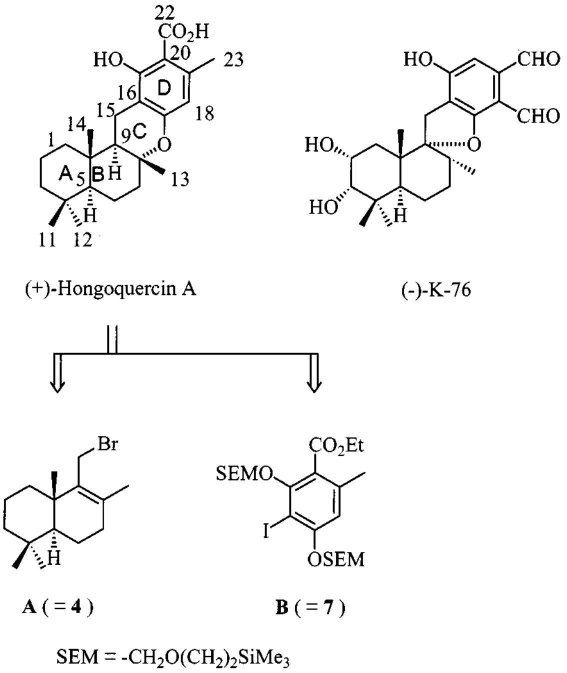
(±)-Hongoquercin A (**1**), the racemate of an antibacterial fungal metabolite, has been synthesized starting from geranylacetone (**2**) and ethyl orsellinate (ethyl 2,4-dihydroxy-6-methylbenzoate, **5**). The structure (±)-**1** has been confirmed by X-ray analysis of its ethyl ester (±)-**10**. Synthesis of the naturally occurring (+)-hongoquercin A from (–)-sclareol (**11**) established its configuration as depicted in **1**.

In 1998, Roll et al. isolated hongoquercin A (**1**) from an unidentified terrestrial fungus as an antibacterial antibiotic against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*.[1] They proposed the structure **1**, i.e. a sesquiterpene coupled with orsellinic acid, for hongoquercin A, including its relative configuration, mainly on the basis of its NMR analysis.[1] Its absolute configuration, however, remained unknown. We became interested in establishing the absolute configuration of the naturally occurring (+)-hongoquercin A (**1**) through its synthesis. This paper describes (i) the synthesis of (±)-**1**, the structure of which was unequivocally established by X-ray analysis of the corresponding ethyl ester (±)-**10**, and (ii) the synthesis of (+)-**1** from (−)-sclareol (**11**), the absolute configuration of which is known. The latter work clarified the absolute configuration of (+)-**1** as depicted.

Our retrosynthetic analysis of **1** is shown in Scheme 1. As in the case of the synthesis of (±)-K-76[2][3] and natural (−)-K-76,[4] the target molecule **1** can be dissected into the sesquiterpene part **A** and the orsellinic acid part **B**, coupling of which would afford the precursor for the closure of the tetrahydropyran C-ring of **1**. Building block **A** is a known compound,[5] while **B** may readily be prepared from the commercially available ethyl orsellinate (ethyl 2,4-dihydroxy-6-methylbenzoate, **5**).

Scheme 2 summarizes our synthesis of (±)-hongoquercin A (**1**). Geranylacetone (**2**) was converted into the known alcohol (±)-**3** according to Mori and Koga[5] in 15% overall yield (5 steps). Treatment of (±)-**3** with phosphorus tribromide afforded the corresponding bromide (±)-**4**,[5] the sesquiterpene part (**A**) of hongoquercin A (**1**). Preparation of the phenolic acid part **B** (= **7**) started from ethyl orsellinate (**5**). Iodination of **5** with benzyltrimethylammonium dichloroiodate[6] furnished the 3-iodo derivative **6**, the phenolic hydroxy groups of which were protected as bis(2-trimethylsilylethyloxy)methoxy (bisSEM) ether functionalities to give **7** (= **B**).



Scheme 1. Retrosynthetic analysis of hongoquercin A

Prior to the successful coupling of (±)-**4** with **7**, various attempts were made to find suitable conditions for coupling of the sesquiterpene part with the phenolic acid part. We first attempted to use a Stille reaction[7] between the allylstannane **C** and **7**. The stannane **C**, however, could not be synthesized. We then tried to generate the anion of **D** in analogy to the McMurry synthesis of (±)-K-76,[3] but unfortunately the protected acetal **D** could not be obtained. Our next attempt was to alkylate the dianion derived from **E** with (±)-**4**. Accordingly, the ethyl ester corresponding to **E** was prepared and then subjected to various hydrolytic

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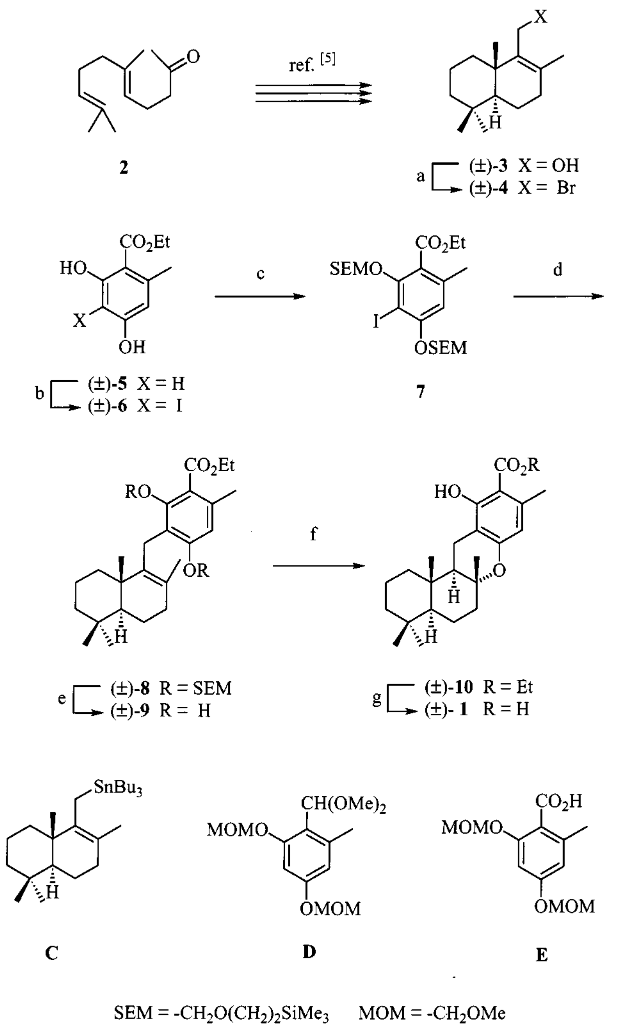


Scheme 2. Synthesis of (±)-hongoquercin A; reagents: (a) PBr_3, Et_2O (quant.); (b) $BnMe_3NICl_2$, $KHCO_3$, CH_2Cl_2/MeOH (73%); (c) NaH, SEMCl, DMF (87%); (d) BuLi, CuCN, THF, (±)-**4** (85%); (e) H_2SO_4, THF/EtOH (87%); (f)(i) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) recrystallization from EtOH (58%); (g)(i) KOH, THF/MeOH/H_2O; (ii) H_3O^+ (96%)

conditions in the hope of hydrolyzing it to **E**. However, all attempts were unsuccessful, and most of the starting material was recovered unchanged. This, we thought, must have been due to steric hindrance caused by the neighboring methoxymethyloxy (MOMoxy) and methyl groups. The above findings led us to the idea of converting **7** to the corresponding lithiate by metal-halogen exchange with butyllithium, considering that neither butyllithium nor the resulting lithiate would be able to attack the severely hindered ester group of **7**.

Lithiation of **7** with 1 equiv. of butyllithium at −78 °C in THF smoothly generated the 3-lithiate. This was treated with copper(I) cyanide to give the corresponding cuprate, treatment of which with (±)-**4** furnished the desired coupling product (±)-**8** in 85% yield. It should be added that direct lithiation of the ethyl ester of **E** with *tert*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in THF[3] gave a product resulting from attack of *tert*-butyllithium at the ester group. The metal-halogen exchange reaction using **7** was therefore the only solution we found for the present coupling problem.

Before formation of the ring C, the SEM protective groups were removed from (±)-**8** by treatment with sulfuric acid in ethanol and THF to give the dihydroxy ester (±)-**9**. Ring-closure of (±)-**9** was accomplished by treatment with boron trifluoride−diethyl ether in dichloromethane to give the desired tetracyclic product (±)-**10** in 58% yield. Fortunately, unlike in the case of the synthesis of (−)-K-76,[4] no spiro product with a benzofuran ring system could be detected on examination of the ^{1}H-NMR spectrum of the crude products. The product (±)-**10** was nicely crystalline and so its structure could be solved by X-ray crystallographic analysis. Its perspective view, as shown in Figure 1(a), was in perfect accord with the structure proposed for hongoquercin A ethyl ester (**10**). The structure (±)-**10** was further supported by the NOE correlations seen in its ^{1}H-NMR spectrum, as indicated in Figure 1(b). Alkaline hydrolysis of (±)-**10** furnished (±)-hongoquercin A (**1**). The overall yield of (±)-**1** was 6% based on geranylacetone (**2**, 10 steps) or 20% based on the commercially available ethyl orsellinate (**6**, 6 steps).

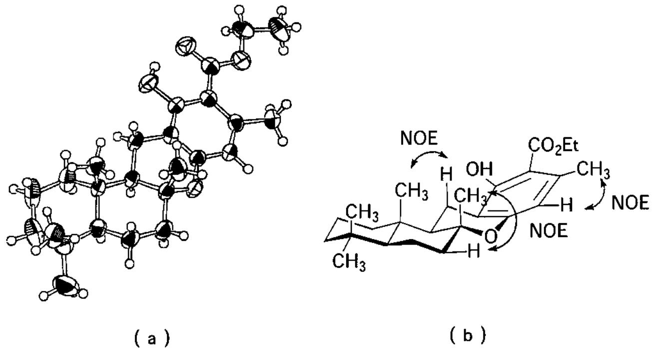
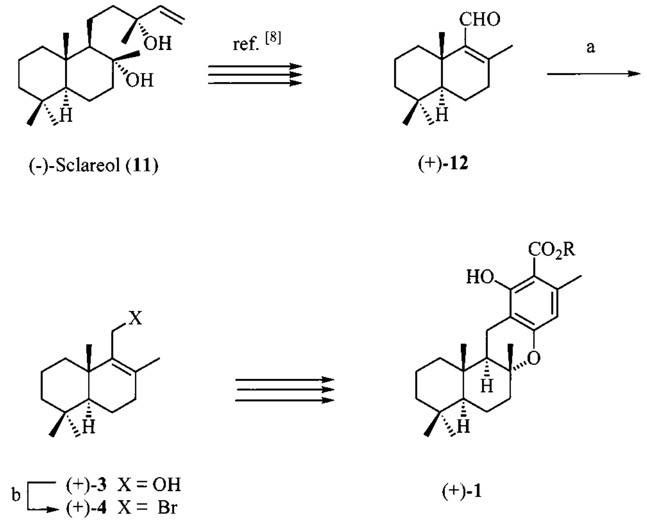


Figure 1. (a) Perspective view of (±)-**10** and (b) NOE correlations between the protons of (±)-**10**

Synthesis of the naturally occurring (+)-enantiomer of hongoquercin A (+)-**1** is summarized in Scheme 3. Commercially available (−)-sclareol (**11**) was oxidatively degraded to the known aldehyde (+)-**12** according to Barrero et al.[8] Reduction of (+)-**12** with diisobutylaluminum hydride gave the known alcohol (+)-**3**,[9] which was treated with phosphorus tribromide to furnish the bromide (+)-**4**. Its conversion to hongoquercin A (**1**) was accomplished via the ethyl ester (+)-**10** in the same manner as for the synthesis of (±)-**1**. It must be noted that the crystals of (+)-**10** [the ethyl ester of (+)-**1**] were needle-shaped but unsuitable for X-ray analysis. The synthesis of (±)-**10** therefore provided all the desired information, having made it possible to rigorously assign its configuration by X-ray analysis. The optically active product **1** was found to be dextrorotatory, $[\alpha]_D^{19} = +148.6$ (MeOH). Accordingly, the absolute configuration of the natural (+)-hongoquercin A (**1**), $[\alpha]_D^{25} = +140.7$ (MeOH), was established as depicted for (+)-**1**. The overall yield of (+)-**1** was 6% based on (−)-sclareol (**11**, 9 steps).



Scheme 3. Synthesis of (+)-hongoquercin A; reagents: (a) *i*Bu_2AlH, toluene (89%); (b) PBr_3, Et_2O (77%)

A brief comment regarding comparison of our synthetic hongoquercin A with the natural product would seem to be necessary. The IR, ^1H- and ^{13}C-NMR spectra of **1** are easily affected by the pH of the solution under examination; the salt of **1** shows spectra different from those of free **1**. This fact complicated our identification. However, direct comparison of the synthetic sample with the natural product (kindly provided by Dr. D. M. Roll and Mrs. S. Kirkwood of Wyeth-Ayerst Research, U.S.A.) fully proved that they were identical on the basis of IR (KBr disc), ^1H-NMR (in $CDCl_3$ or CD_3OD), ^{13}C-NMR (CD_3OD), and CD ($CHCl_3$) comparisons, as well as the mixed melting-point determination.

In conclusion, both (±)- and (+)-hongoquercin A have been synthesized, and the absolute configuration of the latter has been established as 5*R*,8*R*,9*R*,10*S*.

Experimental Section

General: Melting points: Yanaco MP-S3, uncorrected values. − MS: Jeol JMS-SX102A. − IR: Hitachi Perkin−Elmer 1640. − ^1H NMR: Jeol JNM−EX400 (400 MHz) and Jeol JNM-LA500 (500 MHz, $CHCl_3$ at $\delta = 7.26$ or CH_3OD at $\delta = 3.30$ as internal standards). − ^{13}C NMR: Jeol JNM−LA400 (100 MHz) and Jeol JNM-LA500 (125 MHz, $CDCl_3$ at $\delta = 77.0$ or [D_4]methanol at $\delta = 49.0$ as internal standards). − MS: Shimadzu GCMS-QP 2000A and Jeol JMS-SX 102A. − Optical rotation: Jasco DIP-1000. − CD spectrum: Jasco J-725. − CC: Merck Kieselgel 60 Art 1.07734.

Ethyl 2,4-Dihydroxy-3-iodo-6-methylbenzoate (6): To a solution of **5** (3.34 g, 17.0 mmol) in dichloromethane (100 mL) and methanol (80 mL), benzyltrimethylammonium dichloroiodate (5.93 g, 17.0 mmol) was added followed by potassium hydrogen carbonate (5.11 g, 51.0 mmol). The mixture was stirred for 21 h at room temperature. It was then acidified to pH 2−3 with 1 N hydrochloric acid and extracted with dichloromethane. The combined extracts were washed with 5% aqueous sodium thiosulfate and brine, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (150 g) eluting with benzene/acetone (60:1), and recrystallized from *n*-hexane to afford 4.00 g (73%) of **6** as colorless needles; m.p. 111−133°C (decomp.). − IR (KBr): $\tilde{\nu}_{max} = 3430\ cm^{-1}$ (vs, OH), 3340 (br. s, OH), 1620 (s, C=O), 1500 (m, Ar), 1260 (s, C−O), 800 (s). − ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.42$ (t, $J = 7.2$ Hz, 3 H, $CO_2CH_2CH_3$), 2.51 (d, $J = 0.7$ Hz, 3 H, ArMe), 4.42 (q, $J = 7.2$ Hz, 2 H, CO_2CH_2), 5.79 (s, 1 H, 4-OH), 6.47 (d, $J = 0.7$ Hz, 1 H, 5-H), 12.87 (s, 1 H, 2-OH). − ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.2$, 24.2, 61.9, 74.2, 105.8, 110.2, 144.0, 159.4, 163.4, 171.3. − $C_{10}H_{11}O_4$ (322.1): calcd. C 37.29, H 3.44; found C 37.28, H 3.51.

Ethyl 3-Iodo-6-methyl-2,4-bis[2-(trimethylsilyl)ethyloxymethoxy]-benzoate (7): A 60% mineral oil suspension of sodium hydride (1.54 g, 38.5 mmol) was rinsed three times with 10 mL portions of *n*-pentane to remove the mineral oil. Dry *N,N*-dimethylformamide (DMF, 20 mL) was then added, and to this suspension a solution of **6** (4.00 g, 12.4 mmol) in dry DMF (20 mL) was added dropwise at 0°C under argon. The resulting mixture was stirred for 30 min., and then 2-(trimethylsilyl)ethyloxymethyl chloride (4.62 mL, 26.1 mmol) was added dropwise at 0°C. After stirring for 30 min., the pale-yellow mixture was poured into water (120 mL) and extracted with diethyl ether. The combined extracts were washed with water and brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (80 g) eluting with *n*-hexane/diethyl ether (20:1) to afford 6.26 g (87%) of **7** as a colorless oil; $n_D^{25} = 1.5123$. − IR (film): $\tilde{\nu}_{max} = 1730\ cm^{-1}$ (C=O), 1590 (s, Ar), 1250 (s), 1200 (s), 1160 (s), 1090 (s), 1060 (s), 1020 (s, C−O), 920 (s), 860 (s), 840 (s). − ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.00$ (s, 9 H, $SiCH_3$), 0.03 (s, 9 H, $SiCH_3$), 0.95 (m, 2 H), 1.00 (m, 2 H), 1.37 (t, $J = 7.2$ Hz, 3 H, $CO_2CH_2CH_3$), 2.30 (s, 3 H, 6-Me), 3.77 (m, 2 H, OCH_2), 3.87 (m, 2 H, OCH_2), 4.36 (q, 2 H, $J = 7.2$ Hz, CO_2CH_2), 5.13 (s, 2 H, OCH_2O), 5.28 (s, 2 H, OCH_2O), 6.73 (s, 1 H, 5-H). − ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -1.43$, −1.40, 14.2, 17.9, 18.0, 19.9, 61.3, 66.8, 68.0, 82.6, 93.2, 98.7, 112.3, 123.5, 138.3, 155.2, 157.9, 167.0. − $C_{22}H_{39}O_6ISi_2$ (582.6): calcd. C 45.35, H 6.75; found C 45.18, H 6.51.

(4a*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-2,5,5,8a-tetramethyl-1-naphthalenemethanol [(+)-3]: To a solution of (+)-**12**[8] (120 mg, 0.5 mmol) in dry toluene (1.2 mL), DIBAL (1.01 M in toluene, 0.8 mL, 0.8 mmol) was added dropwise at −78°C under argon. After stirring at −78°C for 0.5 h, the reaction was quenched with methanol. The mixture was poured into 1 N hydrochloric acid and extracted with toluene. The combined extracts were washed with 1 N hydrochloric acid and brine, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (1.0 g) eluting with *n*-hexane/ethyl acetate (10:1), and subsequently recrystallized from *n*-pentane to afford 108 mg (89%) of (+)-**3** as a colorless powder; m.p. 115−116°C, ref.[9] 89−90°C. − $[\alpha]_D^{18} = +113$ ($c = 0.14$, $CHCl_3$), ref.[9] $[\alpha]_D^{15} = +105.4$ ($c = 0.13$, $CHCl_3$). Thus, our (+)-**3** showed a slightly higher m.p. and a slightly larger specific rotation value; this might be due to the higher purity of our material. − IR (KBr): $\tilde{\nu}_{max} = 3370\ cm^{-1}$ (s, OH), 1660 (w, C=C), 1000 (s, C=C), 980 (s, C=C). − ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (s, 3 H, 5-Me), 0.89 (s, 3 H, 5-Me), 0.96 (s, 3 H, 8*a*-Me), 1.72 (s, 3 H, 2-Me), 4.04 (d, $J = 11.5$ Hz, 1 H, CH*H*OH), 4.20 (d, $J = 11.5$ Hz, 1 H, C*H*HOH). − ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 18.8$, 18.9, 19.3, 20.7, 21.6, 33.22, 33.24, 33.7, 36.8, 38.0, 41.6, 51.7, 58.3, 132.5, 140.9. − $C_{15}H_{26}O$ (222.4): calcd. C 81.02, H 11.79; found C 80.81, H 11.75.

Ethyl (4a*S,8a*S**)-2,4-Dihydroxy-6-methyl-3-[(3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-1-naphthyl)methyl]benzoate [(±)-9]:** The known (±)-**3** was first prepared from geranylacetone. − (i) *Bromide* (±)-**4:** Phosphorus tribromide (0.27 mL, 2.8 mmol) was added dropwise to a suspension of (±)-**3** (1.79 g, 8.0 mmol) in dry diethyl ether (18 mL) at −20°C under argon. After stirring for a further 15 min., methanol (0.3 mL) and water (2.0 mL) were added dropwise to the colorless solution and the resulting mixture was extracted with diethyl ether. The combined extracts were washed with 5% aqueous sodium hydrogen carbonate solution, water, and brine, dried with magnesium sulfate, and concentrated under reduced pressure to give 2.30 g of crude (±)-**4**, which could only be characterized by IR due to its instability. − IR (film): $\tilde{\nu}_{max}$ = 1650 cm^{-1} (w, C=C), 1220 (s, C−O), 1050 (m, C−O). This unstable colorless oil (±)-**4** was used immediately in the next step without further purification. − (ii) *Coupling Product* (±)-**8:** Butyllithium (1.53 M in hexane, 7.0 mL, 10.7 mmol) was added dropwise to a cooled solution of **7** (6.26 g, 10.7 mmol) in dry tetrahydrofuran (63 mL) at −78°C under argon. After 30 min., the pale-yellow solution was treated with copper(I) cyanide (1.92 g, 21.5 mmol, dried at 120°C for 15 h under reduced pressure) in one portion. The suspension was slowly allowed to warm to −10°C until almost all of the copper(I) cyanide had dissolved and was then cooled to −78°C once more, whereupon a solution of crude (±)-**4** (2.30 g) in dry tetrahydrofuran (18 mL) was added dropwise. The resulting mixture was stirred for 5 h and was then poured into water and extracted with diethyl ether. The combined extracts were washed with water and brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (180 g) eluting with *n*-hexane/ethyl acetate (30:1) to give 4.50 g (85%) of (±)-**8** as a colorless, viscous oil; n_D^{25} = 1.5072. − IR (film): $\tilde{\nu}_{max}$ = 1730 cm^{-1} (vs, C=O), 1600 (m, Ar), 1570 (w, Ar), 1270 (s, Si−CH_3), 1250 (s, C−O), 1060 (vs, C−O), 860 (vs, Ar) 840 (vs, Ar). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.01 (s, 9 H, SiMe), 0.02 (s, 9 H, SiMe), 0.81 (s, 3 H, 5-Me), 0.86 (s, 3 H, 5-Me), 0.89 (s, 3 H, 8a-Me), 0.94 (m, 2 H, $SiCH_2$), 0.99 (m, 2 H, $SiCH_2$), 1.08 (m, 1 H, 8ax-H), 1.13 (dd, *J* = 12.7, 1.7 Hz, 1 H, 4a-H), 1.37 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.32−1.54 (m, 5 H), 1.50 (s, 3 H, 2-Me), 1.63 (br. dd, *J* = 12.7, 8.5 Hz, 1 H, 4eq-H), 1.88 (br. d, *J* = 12.5 Hz, 1 H, 8eq-H), 2.00 (m, 2 H, 3-H), 2.27 (s, 3 H, ArMe), 3.40 (d, *J* = 15.5 Hz, 1 H, $ArCH_2$), 3.49 (d, *J* = 15.5 Hz, 1 H, $ArCH_2$), 3.69 (pseudo t, *J* = 7.6 Hz, 2 H, OCH_2), 3.80 (pseudo t, *J* = 8.6 Hz, 2 H, OCH_2), 4.35 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2), 4.98 (d, *J* = 5.8 Hz, 1 H, OCH_2O), 5.01 (d, *J* = 5.8 Hz, 1 H, OCH_2O), 5.10 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 5.11 (d, *J* = 7.8 Hz, 1 H, OCH_2O), 6.71 (s, 1 H, ArH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = −1.42, −1.37, 14.3, 18.0, 18.2, 19.1, 19.2, 19.8, 20.3, 20.6, 21.7, 24.1, 33.4, 33.5, 34.6, 37.0, 39.4, 41.8, 51.9, 60.9, 66.1, 67.4, 92.7, 99.0, 111.6, 122.7, 123.2, 126.0, 134.6, 137.9, 153.5, 158.0, 168.5. − (iii) *Dihydroxy Ester* (±)-**9:** The colorless oil (±)-**8** (4.48 g) was dissolved in a mixture of ethanol (25 mL) and tetrahydrofuran (25 mL), and then a solution of sulfuric acid (0.7 mL) in ethanol (5 mL) was added at room temperature. The resulting mixture was stirred for 20 h, then neutralized to pH 7−8 with 5% aqueous sodium hydrogen carbonate solution, and extracted with dichloromethane. The combined extracts were washed with brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (100 g) eluting with *n*-hexane/diethyl ether (10:1), and subsequently recrystallized from *n*-hexane to afford 2.35 g (87%) of (±)-**9** as colorless needles, m.p. 130−131°C. − IR (KBr): $\tilde{\nu}_{max}$ = 3330 cm^{-1} (vs, OH), 1650 (s, C=O), 1630 (s, Ar), 1580 (s, Ar), 1250 (s, C−O), 1190 (s), 1020 (m, C−O). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 (s, 3 H, 5-Me), 0.91 (s, 3 H, 5-Me), 1.05 (s, 3 H, 8a-H), 1.11 (ddd, *J* = 13.5, 13.5, 2.5 Hz, 1 H, 8ax-H), 1.13 (ddd, *J* = 13.5, 13.5, 4.7 Hz, 1 H, 6ax-H), 1.18 (dd, *J* = 12.8, 1.9 Hz, 1 H, 4a-H), 1.36 (m, 1 H, 6eq-H), 1.38 (m, 1 H, 7ax-H), 1.41 (t, *J* = 7.0 Hz, 3 H, $CO_2CH_2CH_3$), 1.51 (m, 1 H, 4ax-H), 1.54 (m, 1 H, 7eq-H), 1.66 (m, 1 H, 8eq-H), 1.72 (s, 3 H, 2-Me), 1.75 (m, 1 H, 4eq-H), 2.15 (br. dd, *J* = 9.2, 4.0 Hz, 2 H, 3-H), 2.46 (s, 3 H, ArMe), 3.39 (d, *J* = 17.7 Hz, 1 H, $ArCH_2$), 3.50 (d, *J* = 17.7 Hz, 1 H, $ArCH_2$), 4.39 (q, *J* = 7.0 Hz, 2 H, CO_2CH_2), 6.15 (s, 1 H, ArH), 7.83 (s, 1 H, ArOH), 12.38 (s, 1 H, ArOH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 18.69, 18.71, 19.9, 20.4, 21.7, 24.12, 24.14, 33.1, 33.4, 33.5, 35.7, 39.5, 41.4, 51.5, 61.1, 104.5, 109.5, 112.1, 133.5, 139.9, 140.1, 160.6, 162.7, 172.4. − $C_{25}H_{36}O_4$ (400.6): calcd. C 74.96, H 9.06; found C 75.06, H 8.99.

Ethyl (4a*S*,8a*S*)-2,4-Dihydroxy-6-methyl-3-[(3,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthyl)methyl]benzoate [(+)-9]: According to the preparation of (±)-**9**, (+)-**3** (211 mg) was converted to the bromide, which was coupled with **6** to give 448 mg (77%) of (+)-**8** as a colorless, viscous oil; n_D^{23} = 1.5058; $[\alpha]_D^{18}$ = +39.5 (*c* = 0.63, $CHCl_3$). (+)-**8** (340 mg) was then deprotected to give 170 mg (83%) of (+)-**9** as a colorless, amorphous solid; $[\alpha]_D^{18}$ = +108 (*c* = 0.60, $CHCl_3$). − IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3320 cm^{-1} (vs, OH), 3020 (s, OH), 1640 (s, C=O), 1620 (s, Ar), 1580 (s, Ar), 1190 (s), 1020 (m, C−O). − $C_{25}H_{36}O_4$ (400.6): calcd. C 74.96, H 9.06; found C 74.84, H 9.03.

(±)-Hongoquercin A Ethyl Ester [(±)-10]: Boron trifluoride−diethyl ether (0.2 mL, 1.5 mmol) was added dropwise to a solution of (±)-**9** (2.32 g, 5.8 mmol) in dry dichloromethane (23 mL) at room temperature under argon. After stirring for a further 5 h, the resulting pale-brown solution was diluted with water (10 mL) and extracted with dichloromethane. The combined extracts were washed with water and brine, dried with magnesium sulfate, and concentrated under reduced pressure. The residue was recrystallized from ethanol to afford 1.34 g (58%) of (±)-**10** as a colorless powder, m.p. 139−141°C. − IR (KBr): $\tilde{\nu}_{max}$ = 1650 cm^{-1} (s, C=O), 1620 (m, Ar), 1580 (s, Ar), 1280 (s, C−O). − ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, 12-Me), 0.90 (s, 3 H, 11-Me), 0.91 (s, 3 H, 14-Me), 0.95 (ddd, *J* = 13.1, 13.1, 3.7 Hz, 1 H, 1ax-H), 1.02 (dd, *J* = 12.2, 1.9 Hz, 1 H, 5-H), 1.16 (ddd, *J* = 13.5, 13.2, 3.4 Hz, 1 H, 3ax-H), 1.19 (s, 3 H, 13-Me), 1.35 (ddd, *J* = 13.5, 13.2, 3.4 Hz, 1 H, 3eq-H), 1.40 (t, *J* = 7.1 Hz, 3 H, $CO_2CH_2CH_3$), 1.44 (m, 1 H, 6eq-H), 1.47 (m, 1 H, 2ax-H), 1.54 (dd, *J* = 13.2, 4.9 Hz, 1 H, 9-H), 1.62 (m, 1 H, 7ax-H), 1.66 (m, 1 H, 2eq-H), 1.76 (m, 1 H, 6ax-H), 1.81 (m, 1 H, 1eq-H), 2.06 (ddd, *J* = 12.2, 3.1, 3.1 Hz, 1 H, 7eq-H), 2.29 (dd, *J* = 16.8, 13.2 Hz, 1 H, 15ax-H), 2.46 (s, 3 H, 23-H), 2.68 (dd, *J* = 16.8, 4.9 Hz, 1 H, 15eq-H), 4.38 (q, *J* = 7.1 Hz, 2 H, CO_2CH_2), 6.17 (s, 1 H, 18-H), 12.18 (s, 1 H, 21-OH). − ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3, 14.9, 16.7, 18.5, 19.7, 20.7, 21.6, 24.2, 33.2, 33.4, 37.0, 39.2, 40.9, 41.8, 51.6, 56.1, 61.0, 78.1, 104.0, 108.0, 112.1, 140.0, 157.7, 162.9, 172.3. − $C_{25}H_{36}O_4$ (400.6): calcd. C 74.96, H 9.06; found C 74.67, H 9.13. A sample for X-ray analysis was recrystallized from diethyl ether and dichloromethane to afford colorless plates, m.p. 140−141°C.

X-ray Analysis of (±)-10: $C_{25}H_{36}O_4$, M_r = 400.56, triclinic, space group $P\bar{1}$ bar a = 12.634(2), b = 13.325(3), c = 7.241(4) Å, α = 95.94(3)°, β = 100.52(3)°, γ = 109.74(1)°, V = 1110.0(6) Å^3, Z = 2, D_c = 1.198 Mgm^{-3}, $F(000)$ = 436, μ (Mo-K_α) = 0.792 cm^{-1}. The crystal used for data collection was a colorless plate of approximate dimensions 0.80 × 0.50 × 0.15 mm. All data were obtained with a Rigaku AFC-5S automated four-circle diffractometer using graphite-monochromated Mo-K_α radiation. Unit cell parameters were determined by least-squares refinement of the optimized setting angles of 25 reflections in the range $11.7 < \theta < 18.03°$. The intensities were measured using $\omega/2\theta$ scans up to 50°. Three standard reflections were monitored every 150 measurements. The data were corrected for Lorentz and polarization factors and an absorption correction was applied. Of the 4133 independent reflections collected, 2375 reflections with $I > 2.0\ \sigma(I)$ were used for the structure determination and refinement. The structure was solved by direct methods using the teXsan crystallographic software package.[10] All non-H atoms were located on a Fourier map. The atomic parameters were refined by full-matrix least-squares methods, using anisotropic temperature factors for all non-H atoms. H atoms were placed geometrical positions and were not refined. The final refinement converged with $R = 0.057$ and $Rw = 0.069$ for 266 parameters. Atomic scattering factors were taken from the "International Tables for X-ray Crystallography".[11] Supplementary material available includes lists of atomic coordinates for the non-H atoms and the bond lengths and angles in (±)-**10** with their e.s.d.'s in parentheses.[12]

(+)-Hongoquercin A Ethyl Ester [(+)-10]: According to the preparation of (±)-**10**, (+)-**9** (156 mg) was treated with boron trifluoride−diethyl ether to give 82 mg (53%) of (+)-**10** as a colorless powder; m.p. 169−171°C; $[\alpha]_D^{18} = +131$ ($c = 0.51$, $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max} = 1640\ cm^{-1}$ (s, C=O), 1580 (s, Ar), 1280 (s, C−O), 1270 (s), 1250 (s), 1180 (s), 1130 (s), 1010 (s). − $C_{25}H_{36}O_4$ (400.6): calcd. C 74.96, H 9.06; found C 74.83, H 9.07.

(±)-Hongoquercin A [(±)-1]: The colorless crystalline (±)-**10** (57 mg, 0.14 mmol) was dissolved in a mixture of methanol (1 mL) and tetrahydrofuran (1.5 mL), and then a potassium hydroxide solution (23 mg, 85%, 0.35 mmol, in 1 mL of water) was added and the mixture was stirred for 3 h under reflux. The reaction mixture was subsequently cooled and acidified to pH 2−3, whereupon it was extracted with dichloromethane. The combined extracts were washed with water and brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was chromatographed on silica gel (1.0 g) eluting with *n*-hexane/ethyl acetate (4:1) and subsequently recrystallized from methanol to afford 51 mg (96%) of (±)-**1** as a colorless powder; m.p. 134−138°C. − IR (KBr): $\tilde{\nu}_{max} = 2940\ cm^{-1}$ (s), 2860 (s), 2840 (s), 2690 (m), 2640 (m), 2570 (m), 2520 (m), 1620 (s, C=O), 1580 (s, Ar), 1500 (m), 1460 (m), 1390 (s), 1380 (s), 1320 (m), 1260 (s, C−O), 1180 (s), 1150 (m), 1130 (s), 1080 (m), 1060 (m), 1010 (m), 980 (m), 930 (m), 900 (w), 860 (m), 840 (m), 800 (m), 760 (m), 720 (m), 660 (m), 580 (w), 490 (w), 470 (w). − ^1H NMR (500 MHz, CD_3OD): $\delta = 0.88$ (s, 3 H, 12-Me), 0.91 (s, 3 H, 11-Me), 0.95 (s, 3 H, 14-Me), 1.00 (ddd, $J = 12.9$, 12.9, 3.7 Hz, 1 H, 1ax-H), 1.07 (dd, $J = 12.2$, 1.8 Hz, 1 H, 5-H), 1.18 (s, 3 H, 13-Me), 1.21 (ddd, $J = 13.5$, 13.5, 3.8 Hz, 1 H, 3ax-H), 1.41 (m, 1 H, 3eq-H), 1.44 (m, 1 H, 6eq-H), 1.46 (m, 1 H, 2ax-H), 1.51 (dd, $J = 13.2$, 4.9 Hz, 1 H, 9-H), 1.64 (ddd, $J = 13.2$, 12.5, 3.4 Hz, 1 H, 7ax-H), 1.69 (m, 1 H, 2eq-H), 1.71 (m, 1 H, 6ax-H), 1.77 (m, 1 H, 1eq-H), 2.04 (ddd, $J = 12.5$, 3.1, 3.1 Hz, 1 H, 7eq-H), 2.26 (dd, $J = 16.8$, 13.2 Hz, 1 H, 15ax-H), 2.45 (s, 3 H, 23-Me), 2.63 (dd, $J = 16.8$, 4.9 Hz, 1 H, 15eq-H), 6.10 (s, 1 H, 18-H). − ^{13}C NMR (125 MHz, CD_3OD): $\delta = 15.4$, 17.7, 19.6, 20.8, 21.1, 22.0, 24.2, 33.9, 34.2, 38.1, 40.4, 42.2, 43.0, 53.2, 57.5, 78.9, 108.8, 112.7, 141.7, 158.8, 164.5. − $C_{23}H_{32}O_4$ (372.5): calcd. C 74.16, H 8.66; found C 73.86, H 8.71. − MS: FAB$^-$ found 371.2219 ($C_{23}H_{31}O_4$, $M^+ - H$), calcd. 371.2222.

(+)-Hongoquercin A [(+)-1]: According to the preparation of (±)-**1**, (+)-**10** (65 mg) was hydrolyzed and chromatographed on silica gel (1.0 g) eluting with *n*-hexane/ethyl acetate (4:1) to give 56 mg (93%) of (+)-**1** as a colorless powder; m.p. 147−150°C [natural product: m.p. 135−148°C; mixture m.p. 135−150°C]. − $[\alpha]_D^{19} = +149$ ($c = 0.57$, MeOH). − CD ($c = 1.34 \times 10^{-4}$, $CHCl_3$): $\Delta\varepsilon$ (λ, nm) = +30.1 (277), +15.7 (304) [natural product: +26.2 (276), +14.2 (304)]. − IR (KBr): $\tilde{\nu}_{max} = 2940\ cm^{-1}$ (s), 2860 (s), 2570 (m), 1620 (s, C=O), 1580 (s, Ar), 1500 (m), 1450 (m), 1370 (s), 1260 (s, C−O), 1220 (m), 1180 (m), 1130 (s), 1080 (m), 1000 (m), 930 (m), 900 (w), 850 (m), 810 (m), 760 (m), 720 (m), 660 (m). − ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.85$ (s, 3 H, 12-Me), 0.91 (s, 3 H, 11-Me), 0.92 (s, 3 H, 14-Me), 0.96 (ddd, $J = 13.1$, 13.1, 4.0 Hz, 1 H, 1ax-H), 1.03 (dd, $J = 12.2$, 1.9 Hz, 1 H, 5-H), 1.17 (ddd, $J = 13.5$, 13.5, 4.0 Hz, 1 H, 3ax-H), 1.20 (s, 3 H, 13-Me), 1.36 (ddd, $J = 13.5$, 13.5, 3.0 Hz, 1 H, 3eq-H), 1.40 (m, 1 H, 6eq-H), 1.49 (m, 1 H, 2ax-H), 1.55 (dd, $J = 13.3$, 4.9 Hz, 1 H, 9-H), 1.64 (m, 1 H, 7ax-H), 1.67 (ddd, $J = 13.1$, 13.1, 4.6 Hz, 1 H, 2eq-H), 1.78 (m, 1 H, 6ax-H), 1.81 (m, 1 H, 1eq-H), 2.07 (ddd, $J = 12.5$, 3.1, 3.1 Hz, 1 H, 7eq-H), 2.29 (dd, $J = 16.8$, 13.3 Hz, 1 H, 15ax-H), 2.51 (s, 3 H, 23-Me), 2.69 (dd, $J = 16.8$, 4.9 Hz, 1 H, 15eq-H), 6.21 (s, 1 H, 18-H), 11.86 (s, 1 H, 21-OH). − ^1H NMR (500 MHz, CD_3OD): $\delta = 0.88$ (s, 3 H, 12-Me), 0.91 (s, 3 H, 11-Me), 0.95 (s, 3 H, 14-Me), 1.00 (ddd, $J = 12.9$, 12.9, 3.7 Hz, 1 H, 1ax-H), 1.06 (dd, $J = 12.2$, 1.8 Hz, 1 H, 5-H), 1.18 (s, 3 H, 13-Me), 1.21 (ddd, $J = 13.5$, 13.5, 3.8 Hz, 1 H, 3ax-H), 1.41 (m, 1 H, 3eq-H), 1.44 (m, 1 H, 6eq-H), 1.46 (m, 1 H, 2ax-H), 1.51 (dd, $J = 13.2$, 5.1 Hz, 1 H, 9-H), 1.64 (ddd, $J = 13.2$, 12.5, 3.4 Hz, 1 H, 7ax-H), 1.69 (m, 1 H, 2eq-H), 1.71 (m, 1 H, 6ax-H), 1.77 (m, 1 H, 1eq-H), 2.04 (ddd, $J = 12.5$, 3.1, 3.1 Hz, 1 H, 7eq-H), 2.26 (dd, $J = 16.8$, 13.2 Hz, 1 H, 15ax-H), 2.45 (s, 3 H, 23-Me), 2.63 (dd, $J = 16.8$, 5.1 Hz, 1 H, 15eq-H), 6.10 (s, 1 H, 18-H). − ^{13}C NMR (125 MHz, CD_3OD): $\delta = 15.4$, 17.7, 19.6, 20.8, 21.1, 22.0, 24.2, 33.9, 34.1, 38.1, 40.4, 42.1, 43.0, 53.1, 57.5, 78.9, 104.9 (w), 108.8, 112.8, 141.7, 158.8, 164.5, 175.6 (w). These IR and NMR data are identical to those of the authentic sample of (+)-**1**. − $C_{23}H_{32}O_4$ (372.5): calcd. C 74.16, H 8.66; found C 73.87, H 8.62.

(+)-Hongoquercin A Monopotassium Salt: Potassium carbonate (5 mg, 0.04 mmol) was added to a solution of (+)-**1** (26 mg, 0.07 mmol) in methanol (1 mL) at room temperature. After stirring for a further 0.5 h, the mixture was filtered and the filtrate was concentrated under reduced pressure to afford 29 mg (quant.) of the salt as a colorless powder. − $[\alpha]_D^{20} = +110$ ($c = 0.57$, MeOH). − IR (KBr): $\tilde{\nu}_{max} = 3441\ cm^{-1}$ (br. s), 2937 (s), 2865 (m), 1624 (sh, C=O), 1587 (s, Ar). − ^1H NMR (500 MHz, CD_3OD): $\delta =$ 0.87 (s, 3 H, 12-Me), 0.91 (s, 3 H, 11-Me), 0.94 (s, 3 H, 14-Me), 1.00 (ddd, $J = 13.4$, 13.4, 4.0 Hz, 1 H, 1ax-H), 1.05 (dd, $J = 12.2$, 1.9 Hz, 1 H, 5-H), 1.16 (s, 3 H, 13-Me), 1.20 (ddd, $J = 13.5$, 13.5, 3.5 Hz, 1 H, 3ax-H), 1.40 (m, 1 H, 3eq-H), 1.43 (m, 1 H, 6eq-H), 1.47 (m, 1 H, 2ax-H), 1.51 (dd, $J = 13.4$, 5.0 Hz, 1 H, 9-H), 1.62 (ddd, $J = 13.1$, 12.4, 4.0 Hz, 1 H, 7ax-H), 1.69 (m, 1 H, 2eq-H), 1.75 (m, 1 H, 6ax-H), 1.78 (m, 1 H, 1eq-H), 2.01 (ddd, $J = 12.4$, 3.0, 3.0 Hz, 1 H, 7eq-H), 2.25 (dd, $J = 16.5$, 13.4 Hz, 1 H, 15ax-H), 2.50 (s, 3 H, 23-Me), 2.61 (dd, $J = 16.5$, 5.0 Hz, 1 H, 15eq-H), 5.97 (s, 1 H, 18-H). − ^{13}C NMR (125 MHz, CD_3OD): $\delta = 15.4$, 18.0, 19.6, 20.8, 21.1, 22.1, 23.7, 33.9, 34.1, 38.1, 40.5, 42.3, 43.1, 53.6, 57.6, 78.0, 108.0, 111.2, 111.4, 141.2, 156.1, 162.9, 177.3. − $C_{23}H_{31}O_4K$ (410.6): calcd. K 9.52; found K 9.22. − MS: FAB$^+$: found 410.1868 ($C_{23}H_{31}O_4K$, M^+), calcd. 410.1859.

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