

Meroterpenoid Pigments from *Albatrellus flettii* (Basidiomycetes)

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Dedicated to Professor Conrad Hans Eugster on the occasion of his 85th birthday

Keywords: Natural products / Meroterpenoids / Mushrooms / Quinones / Furans

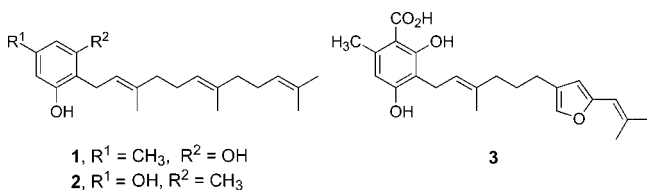
The pigments responsible for the blue colour of the North American polypore *Albatrellus flettii* have been isolated and their structures elucidated by spectroscopic methods. Albatrellin, a dimeric meroterpenoid with a furylbenzoquinone chromophore, is accompanied by its 16-hydroxy and 16-oxo derivatives. The latter has recently been described as grifolone B from a Japanese collection of *A. caeruleoporus*.

Based on the idea that albatrellin is formed in nature by oxidative coupling of a grifolinquinone with the furan derivative cristatin, the blue pigment was synthesized in vitro. The reaction could be applied to the synthesis of several analogues.

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Introduction

Mushrooms of the genus *Albatrellus* (Aphyllphorales) contain meroterpenoids with various biological activities. Grifolin (1)^[1] and neogrifolin (2)^[1b] are the most common metabolites of this type to which other compounds like cristatic acid (3)^[2] are closely related.



Some years ago, we became attracted by the beautiful velvet-blue colour shown by the fruit bodies of *A. flettii* Morse ex Pouzar, a species occurring in the Pacific West of North America^[3] and in West China.^[4] Other species with remarkable blue and greenish tints are *A. caeruleoporus* (Peck) Pouzar and *A. cristatus* (Schaeff.) Kotl. & Pouzar (German: Grüner Kammporling), respectively. In this publication we describe the structural elucidation of the pigments from *A. flettii*.^[5]

Results and Discussion

Isolation and Structural Elucidation of the Pigments

Freshly collected fruit bodies of *A. flettii* were peeled and the blue skins from 1.5 kg of fungi extracted with methanol. TLC of the extract on silica gel revealed the presence of three violet-blue pigments A, B, and C according to increasing polarity. In addition two colourless compounds were identified as grifolin (1) and neogrifolin (2). The pigments were enriched by chromatography of the crude extract on Sephadex LH-20, followed by flash chromatography of the coloured fractions on silica gel. Separation of the individual pigments was achieved by centrifugal thin layer chromatography to yield 12.5 mg of pigment A, 6 mg of pigment B, and 1.3 mg of pigment C. In a separate workup the methanol extract from lyophilized fruit bodies was distributed between water and chloroform. Repeated flash chromatography of the organic phase on silica gel with hexanes/EtOAc yielded grifolin (1, 0.9% of dry weight) and neogrifolin (2, 0.2%), identified by comparison with authentic samples.^[1b]

Solutions of the pigments in chloroform or dichloromethane resemble blue ink; in methanol they appear more violet. According to the great similarity of their UV/Vis spectra with maxima in the range of $\lambda_{\text{max}} = 272\text{--}274$, 395–397, and 530–535 nm (in MeOH) all three pigments must contain the same chromophore. Pigment A, named albatrellin, exhibits a molecular ion peak at $m/z = 680.4061$ in the high-resolution EI-MS, corresponding to the molecular formula C₄₄H₅₆O₆. This indicates that the pigment is a dehydro dimer of grifolin or neogrifolin (C₂₂H₃₂O₂) containing two additional oxygen atoms and two more double-bond equivalents. Intensive [M⁺ + H] and [M⁺ + 2 H] peaks and

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a strong IR absorption at 1650 cm^{-1} are characteristic for a quinone system.

The ^{13}C NMR spectrum of albatrellin exhibits 40 signals and in addition two signals, each representing two identical carbon atoms. According to the DEPT spectrum, 9 methyl, 8 methylene, 8 methine, and 19 quaternary carbon atoms are present. The ^1H -coupled ^{13}C NMR spectrum of albatrellin allows to identify partial structure **A**, which corresponds to cristatin (**8**),^[2] the decarboxylation product of cristatic acid (**3**). Notable are the singlet for the 15'-furan proton at $\delta_{\text{H}} = 6.17\text{ ppm}$ ($\delta_{\text{C}} = 110.9\text{ ppm}$), a multiplet for the 12'-methylene protons at $\delta_{\text{H}} = 1.64\text{ ppm}$ ($\delta_{\text{C}} = 110.9\text{ ppm}$), and a multiplet at $\delta_{\text{H}} = 6.00\text{ ppm}$ ($\delta_{\text{C}} = 114.1\text{ ppm}$), characteristic for the deshielded methine proton at the terminal isobutenyl residue. In addition, the methylresorcinol explains the formation of a strong benzyl ion peak at $m/z = 137$ in the EI-MS. Since in the ^1H NMR spectrum of albatrellin the signal for the furan α -proton is missing, partial structure **A** must be connected through position 21' to the rest of the molecule (Figure 1).

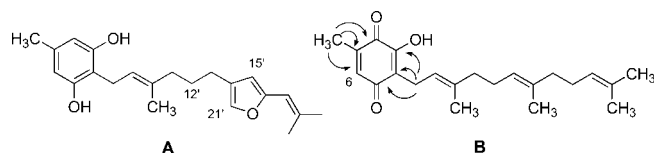
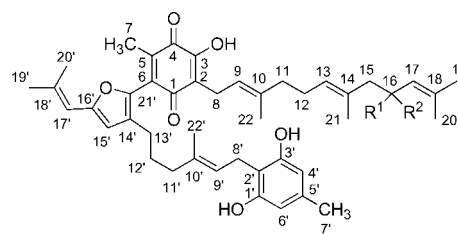


Figure 1. Partial structures **A** and **B** for albatrellin (arrows indicate selected couplings from the ^1H -coupled ^{13}C NMR spectrum).

The remaining NMR signals of albatrellin can be assigned to a 1,4-benzoquinone moiety carrying an intact farnesyl chain as well as a methyl and a hydroxy substituent. In the ^1H -coupled ^{13}C NMR spectrum the quinone carbonyl signal at $\delta_{\text{C}} = 185.2\text{ ppm}$ and the signal of the carbon atom carrying the enolic OH group at $\delta_{\text{C}} = 150.5\text{ ppm}$ appear as triplets with $^3J_{\text{H,C}} = 4.5$ and 5 Hz , respectively, due to coupling with the signals of the methylene protons of the attached farnesyl residue. Similarly, the signals of the second quinone carbonyl group at $\delta_{\text{C}} = 184.1\text{ ppm}$ and a carbon atom at $\delta_{\text{C}} = 135.5\text{ ppm}$ are split into quadruplets with $^3J_{\text{H,C}} = 4$ and 5 Hz , respectively, by interaction with the neighbouring methyl substituent. Considering the two remaining carbon signals at $\delta_{\text{C}} = 120.0\text{ ppm}$ (t, $^2J_{\text{C,H}} = 6.5\text{ Hz}$) and $\delta_{\text{C}} = 137.5\text{ ppm}$ (m) allows the completion of the benzoquinone ring as depicted in partial structure **B**. Combining both partial structures at positions 21' and 6 leads to formula **4** for albatrellin, which is supported by COSY and COLOC experiments.

In pigment **B**, $\text{C}_{44}\text{H}_{54}\text{O}_7$, one of the methylene groups of albatrellin (**4**) has been transformed into a keto group. Its position is indicated by the EI-MS, in which the base peak at $m/z = 83$ ($\text{C}_5\text{H}_7\text{O}$) can be explained by α -cleavage from a terminal $(\text{CH}_3)_2\text{C}=\text{CHCOCH}_2-$ unit. This leads to the structure of 16-oxoalbatrellin (**5**) for this pigment, which is supported by the NMR spectroscopic data. In the ^{13}C NMR spectrum of **5**, the signal of the additional CO group appears at $\delta_{\text{C}} = 200.3\text{ ppm}$, and the neighbouring methylene



albatrellin (**4**), $\text{R}^1 = \text{R}^2 = \text{H}$

5, $\text{R}^1, \text{R}^2 = \text{O}$

6, $\text{R}^1, \text{R}^2 = \text{OH}$

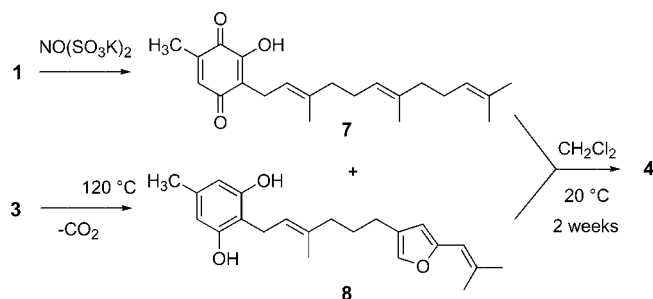
carbon signal suffers the expected downfield shift from $\delta_{\text{C}} = 39.7\text{ ppm}$ in **4** to $\delta_{\text{C}} = 55.1\text{ ppm}$ ($\delta_{\text{H}} = 3.00$). Pigment **5** is identical with grifolinone **B**, a metabolite recently isolated by Asakawa et al.^[6] from a Japanese collection of *A. caeruleoporus*. Interestingly, the monomeric 16-oxogrifolin (grifolinone **A**) was also found in this species. Both compounds inhibit the nitric oxide production in RAW 264.7 cells. The biological activity of albatrellin is unknown.

The most polar pigment **C** of *A. flettii* $\text{C}_{44}\text{H}_{56}\text{O}_7$, possesses one more oxygen atom than albatrellin. The presence of a hydroxy group is indicated by an intense $[\text{M}^+ - \text{H}_2\text{O}]$ ion peak in the high-resolution EI-MS ($m/z = 678$) and NMR spectroscopic data, which reveal the presence of a $(\text{CH}_3)_2\text{C}=\text{CHCHOHCH}_2-$ moiety. Noteworthy is the methine signal at $\delta_{\text{H}} = 4.39\text{ ppm}$ ($\delta_{\text{C}} = 65.7\text{ ppm}$), which appears as triplet of doublets ($J = 8.5, 4.5\text{ Hz}$) due to 3J couplings with the neighbouring CH_2 and CH protons. Since all the other signals agree with those of albatrellin, pigment **C** must possess the structure of a 16-hydroxyalbatrellin (**6**). The limited amount of material as well as the intense colour of this compound prohibited the determination of the chiroptical properties.

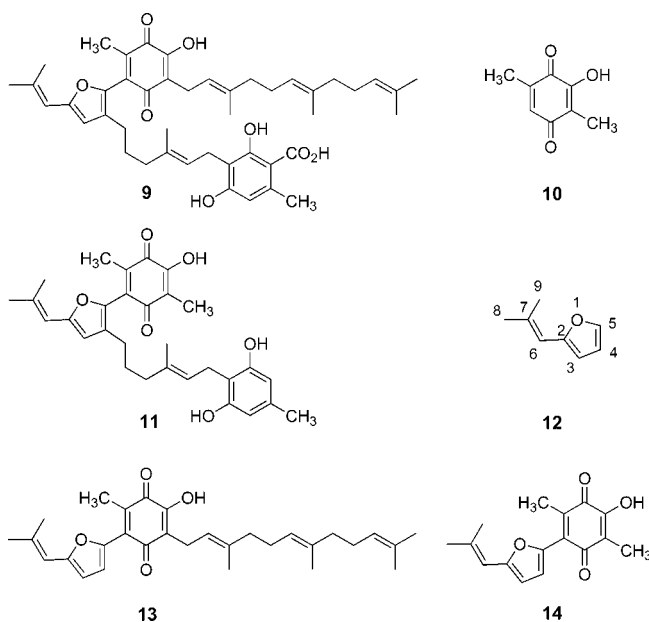
Biomimetic Synthesis of Albatrellin and Some of Its Analogues

The structure of albatrellin (**4**), (Scheme 1) suggests its formation from two components, one derived from grifolin (**1**) and the other from cristatic acid (**3**). To prove this idea experimentally, we prepared the unknown hydroxyquinone **7** from grifolin by treatment with potassium nitrosodisulfonate (Fremy's salt).^[7] Cristatin (**8**) was obtained by thermal decarboxylation of cristatic acid (**3**).^[2] On stirring a 2:1 mixture of **7** and **8** in dichloromethane at room temperature, the solution gradually turned blue and, after two weeks, albatrellin could be isolated in 30% yield. Since each of the starting materials, grifolin (**1**)^[8] and cristatic acid (**3**),^[9] have already been prepared by total syntheses, this constitutes a formal total synthesis of albatrellin.

Similarly, the reaction of quinone **7** with cristatic acid (**3**) yielded 32% of 4'-carboxyalbatrellin (**9**). The latter is rather unstable and suffers easy decarboxylation to albatrellin (**4**) even on standing in the refrigerator. Reaction of 2-hydroxy-3,6-dimethyl-1,4-benzoquinone (**10**)^[10] with cristatin (**8**) afforded the coupling product **11** in 22% yield. On the other hand, reaction of the benzoquinones **7** or **10** with 2-isobut-

Scheme 1. Synthesis of albatrellin (**4**).

enylfuran (**12**)^[11] furnished the corresponding furylquinones **13** and **14** only in 3 and 1.5% yield, respectively. This reflects the importance of the additional alkyl chain at the furan ring for the coupling reaction.^[12] Experiments to enhance the reaction rate by adding Lewis acid catalysts such as BF_3 , ZnCl_2 , AlCl_3 or traces of HCl or AcOH were unsuccessful^[13] and caused the formation of uncharacterized green “polymers” due to the instability of cristatic acid (**3**) under acidic conditions.^[2] The addition of oxidizing agents such as DDQ,^[14] useful for the quinone–furan coupling in simple cases, is known to convert *ortho*-polyprenylated phenols into the corresponding chromenes.^[15]



The reaction between activated benzoquinones and furans has been thoroughly investigated by Eugster and co-workers.^[16] More recently, Valderrama et al.^[3] discovered that nonactivated quinones can be coupled with furans in acetic acid. In the case of cristatin (**8**), this coupling occurs even in dichloromethane without proton catalysis through enhancement of the nucleophilicity at the furan ring by the isobutenyl substituent.

All coupling products including the simplest derivative **14** are blue and exhibit UV spectra similar to those of the albatrellins. This indicates that the colour originates from electronic interactions between the benzoquinone and the

conjugated furan chromophore^[12] and not from a charge transfer interaction of the quinone with the remote resorcinol group.

Experimental Section

General: Evaporation of the solvents was performed under reduced pressure using a rotary evaporator. Column chromatography: Silica gel 60 (Merck), Sephadex LH-20 (Pharmacia). Analytical TLC: Silica gel 60 F₂₅₄ aluminium foils (Merck); solvent system A (v/v): hexanes/EtOAc, 5:1; B: toluene/ HCO_2Et / HCO_2H , 10:5:3; C: CH_2Cl_2 /MeOH, 20:1; D: CH_2Cl_2 ; E: hexanes/EtOAc, 10:2. Preparative centrifugal TLC: Chromatotron 7924T (Harrison Research), silica gel/ CaSO_4 plates, 1–4 mm. UV: Varian Cary 17 spectrophotometer. IR: Perkin–Elmer 1420. NMR: Bruker instruments AC 600, WM 400, AC 200 and WH 90, in CDCl_3 and $[\text{D}_6]\text{acetone}$ with the solvent peak as internal standard. Multiplets due to $^1\text{J}(\text{C},\text{H})$ couplings are indicated by capital letters. EI-MS: A.E.I. MS 50 with data system DS 50, direct inlet (DI) at 70 eV and 180 °C. 2-Hydroxy-3,6-dimethyl-1,4-benzoquinone (**10**)^[10,17] was prepared from 2,5-dimethylbenzoquinone via 1,2,4-triacetoxy-3,6-dimethylbenzene and 3,6-dimethylbenzene-1,2,4-triol according to literature procedures.^[5] 2-(1-Acetoxy-2-methylpropyl)furan was obtained from 2-(1-hydroxy-2-methylpropyl)furan^[11a] in 75% yield by treatment with acetic anhydride/pyridine in the presence of a catalytic amount of DMAP. Cristatic acid (**3**) was isolated from *A. cristatus*.^[2]

Mushrooms: *A. flettii* was collected in September 1987 near Bamfield, Vancouver Island, Canada.

Isolation Procedure: The caps of fresh fruit bodies of *A. flettii* (1500 g) were peeled and the blue skins extracted with MeOH. Concentration of the extracts yielded a brownish black residue (2.99 g), which was divided into two portions and prepurified by gel chromatography on two Sephadex LH-20 columns with MeOH as eluent. Three coloured fractions were obtained, which were flash-chromatographed on silica gel (hexanes/EtOAc, 5:1) to remove **1** and **2**. The separation of the three very similar pigments was achieved by repeated centrifugal TLC chromatography on silica gel (hexanes/EtOAc, 7:1, 5:1, 2:1, and CH_2Cl_2 /MeOH, 20:1). Final purification of each fraction with Sephadex LH-20 (eluent CHCl_3 /MeOH, 1:1) yielded pigments **4** (12.5 mg), **5** (6.6 mg), and **6** (1.3 mg) as dark blue, glass-like solidified oils. For the isolation of **1** and **2**, dried fruit bodies (25.5 g) of *A. flettii* were powdered and extracted with MeOH (2×250 mL). The combined extracts were concentrated under reduced pressure, and the resulting residue was triturated with water (20 mL) to remove mannitol. Extraction of the mixture with CHCl_3 and concentration of the organic phases yielded a residue (0.92 g), which was prepurified by flash chromatography on silica gel (hexanes/EtOAc, 5:2, stepwise gradient to 100% EtOAc). Rechromatography of the grifolin/neogrifolin fractions yielded the pure compounds. Grifolin (**1**): 0.24 g (0.94% of dry weight), R_f (TLC) = 0.71 (hexanes/EtOAc, 10:3), 0.80 (solvent system B). The TLC spot turns carmine-red within a few days, with anisaldehyde/ H_2SO_4 blue-violet, and with sulfovanillin blue, finally blue-green. Neogrifolin (**2**): 0.05 g (0.2% of dry weight), R_f (TLC) = 0.35 (hexanes/EtOAc, 10:3), 0.59 (solvent system B). The TLC spot turns yellowish red within a few days, with anisaldehyde/ H_2SO_4 blue-violet, and with sulfovanillin blue, finally green-brown. Compounds **1** and **2** were identified by direct comparison with authentic samples.^[2]

Albatrellin (4**):** R_f (TLC) = 0.56 (system A), 0.71 (system B). UV/Vis (MeOH): λ_{max} ($\log \epsilon$) = 274 (4.45), 397 (3.56), 535 (3.50) nm.

IR (KBr): $\tilde{\nu}$ = 3420 (s), 2960 (sh), 2920 (s), 2860 (sh), 1650 (s), 1600 (m), 1430 (m), 1370 (m), 1310 (s), 1240 (m), 1160 (w), 1050 (m), 980 (w), 820 (w) cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ = 1.54 (s, 3 H, 21-H), 1.56 (s, 3 H, 20-H), 1.64 (tt, J = 6.5 Hz, 2 H, 12'-H), 1.65 (s, 3 H, 19-H), 1.72 (s, 3 H, 22-H), 1.75 (s, 3 H, 22'-H), 1.89 (s, 3 H, 19'-H), 1.95 (s, 3 H, 20'-H), 1.90–2.05 (m, 10 H, 11-H, 12-H, 15-H, 16-H, 11'-H), 2.02 (s, 3 H, 7-H), 2.18 (s, 3 H, 7'-H), 2.21 (t, J = 7.5 Hz, 2 H, H-13'), 3.16 (d, J = 7 Hz, 2 H, 8-H), 3.32 (d, J = 7 Hz, 2 H, 8'-H), 4.92 (br. s, 2 OH), 5.05 (tm, J = 7 Hz, 2 H, 13-H, 17-H), 5.14 (tm, J = 7 Hz, 1 H, 9-H), 5.17 (tm, J = 7 Hz, 1 H, 9'-H), 6.00 (m, 1 H, 17'-H), 6.17 (s, 1 H, 15'-H), 6.18 (s, 2 H, 4'-H, 6'-H), 7.03 (br. s, 1 OH) ppm. ^1H -coupled ^{13}C NMR (150 MHz, CDCl_3): δ = 13.5 (Q, J = 130 Hz, C-7), 16.0 (Qm*, C-21), 16.1 (Qm*, C-22), 16.2 (Qm*, C-22'), 17.7 (Qm*, C-20), 20.3 (Qm, J = 121 Hz, C-20'), 21.0 (Qt, J = 126, 5 Hz, C-7'), 22.1 (Td, J = 127, 4 Hz, C-8'), 22.3 (Td, J = 130, 4 Hz, C-8), 25.4 (Tm, J = 127 Hz, C-13'), 25.7 (Qm, J = 125 Hz, C-19), 26.5 (Tm*, C-12), 26.7 (Tm*, C-16), 27.2 (Q*, C-19'), 27.8 (Tm, J = 128 Hz, C-12'), 39.1 (Tm*, C-11'), 39.67 (Tm*, C-15), 39.72 (Tm*, C-11), 108.9 (Dquint, J = 158, 6 Hz, C-4', C-6'), 110.3 (m, C-2'), 110.9 (Dm, J = 171 Hz, C-15'), 114.1 (Dsept, J = 154, 6 Hz, C-17'), 119.6 (Dm, J = 155 Hz, C-9), 120.0 (t, J = 6.5 Hz, C-2), 122.1 (Dm, J = 152 Hz, C-9'), 124.1 (Dm, J = 151 Hz, C-13), 124.4 (Dm, J = 151 Hz, C-17), 131.1 (m, C-18), 131.3 (m, C-14'), 135.0 (m, C-14), 135.5 (q, J = 5.5 Hz, C-6), 137.1 (m, C-10), 137.3 (m, C-18'), 137.4 (m, C-5'), 137.5 (m, C-5), 137.9 (m, C-10'), 140.3 (m, C-21'), 150.5 (t, J = 5 Hz, C-3), 154.7 (m, C-1', C-3'), 154.9 (d, J = 10 Hz, C-16'), 184.1 (q, J = 4 Hz, C-4), 185.2 (t, J = 4.5 Hz, C-1) ppm; * signals overlapping. EI MS: m/z (%) = 682 (14.5), 681 (37.2), 680 (78.1) [M^+], 597 (5.9) [$\text{M}^+ - \text{C}_5\text{H}_7\text{O}$], 191.1795 (8.3) [$\text{C}_{14}\text{H}_{23}$], 191.1061 (15.0) [$\text{C}_{12}\text{H}_{15}\text{O}_2$], 177 (11.8) [$\text{C}_{11}\text{H}_{13}\text{O}_2$], 175 (32.7) [$\text{C}_{11}\text{H}_{11}\text{O}_2$], 163 (10.1) [$\text{C}_{10}\text{H}_{11}\text{O}_2$], 149 (9.4) [$\text{C}_6\text{H}_9\text{O}_2$], 137 (100) [$\text{C}_8\text{H}_9\text{O}_2$], 83 (19.8) [$\text{C}_5\text{H}_7\text{O}$], 69 (41.6) [C_5H_9]. HR EI-MS: calcd. for $\text{C}_{44}\text{H}_{56}\text{O}_6$ 680.4077; found 680.4061.

16-Oxoalbatrellin, Grifolinone B (5): R_f (TLC) = 0.42 (system A), 0.57 (system B). UV/Vis (MeOH): λ_{max} ($\log \epsilon$) = 272 (4.37), 395 (4.02), 533 (3.92) nm. IR (KBr): $\tilde{\nu}$ = 3400 (s, br.), 2920 (s), 2860 (sh), 1650 (s), 1620 (s), 1440 (m), 1350 (m), 1310 (s), 1235 (m), 1165 (w), 1090 (w), 1050 (m), 985 (w), 820 (w) cm^{-1} . ^1H NMR (600 MHz, CDCl_3): δ = 1.55 (s, 3 H, 21-H), 1.65 (m, 2 H, 12'-H), 1.70 (s, 3 H, 22-H), 1.74 (s, 3 H, 22'-H), 1.86 (s, 3 H, 19'-H), 1.88 (s, 3 H, 19-H), 1.95 (s, 3 H, 20'-H), 1.95–2.07 (m, 6 H, 11-H, 12-H, 11'-H), 2.03 (s, 3 H, 7-H), 2.13 (s, 3 H, 20-H), 2.16 (s, 3 H, 7'-H), 2.19 (t, J = 7.5 Hz, 2 H, 13'-H), 3.00 (s, 2 H, 15-H), 3.15 (d, J = 7 Hz, 2 H, 8-H), 3.31 (d, J = 7 Hz, 2 H, 8'-H), 5.14 (tm, J = 7 Hz, 1 H, 9-H), 5.16 (tm, J = 7 Hz, 1 H, 9'-H), 5.18 (tm, J = 7 Hz, 13-H), 6.00 (m, 1 H, 17'-H), 6.09 (sept, J = 1 Hz, 1 H, 17-H), 6.17 (s, 1 H, 15'-H), 6.19 (s, 2 H, 4'-H, 6'-H) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ = 13.4 (C-7), 16.0 (C-22), 16.2 (C-22'), 16.4 (C-21), 20.3 (C-20'), 20.8 (C-20), 21.1 (C-7'), 22.1 (C-8'), 22.2 (C-8), 25.4 (C-13'), 26.7 (C-12), 27.3 (C-19'), 27.76 (C-19), 27.84 (C-12'), 39.2 (C-11'), 39.3 (C-11), 55.2 (C-15), 108.8 (C-4', C-6'), 110.5 (C-2'), 111.1 (C-15'), 114.1 (C-17'), 119.6 (C-2), 119.9 (C-9), 122.4 (C-9'), 123.0 (C-17), 128.8 (C-14), 129.3 (C-13), 131.3 (C-14'), 135.5 (C-6), 136.3 (C-10), 136.9 (C-10'), 137.3 (C-5'), 137.37 (C-18'), 137.40 (C-5), 141.4 (C-21'), 150.6 (C-3), 154.8 (C-16'), 154.9 (C-1', C-3'), 156.4 (C-18), 184.1 (C-4), 185.2 (C-1), 200.3 (C-16) ppm. EI MS: m/z (%) = 696 (65.2), 695 (31.7), 694 (67.7) [M^+], 613 (9.7) [$\text{M}^+ + 2 \text{H} - \text{C}_5\text{H}_7\text{O}$], 612 (5.0) [$\text{M}^+ + \text{H} - \text{C}_5\text{H}_7\text{O}$], 611 (5.9) [$\text{M}^+ - \text{C}_5\text{H}_7\text{O}$], 529 (18.4) [$\text{M}^+ - \text{C}_{11}\text{H}_{19}\text{O}$], 203 (4.1) [$\text{C}_{13}\text{H}_{15}\text{O}_2$], 175 (64.2) [$\text{C}_{11}\text{H}_{11}\text{O}_2$], 137 (66.1) [$\text{C}_8\text{H}_9\text{O}_2$], 83 (100) [$\text{C}_5\text{H}_7\text{O}$]. HR EI-MS: calcd. for $\text{C}_{44}\text{H}_{54}\text{O}_7$ 694.3870; found 694.3866.

16-Hydroxyalbatrellin (6): R_f (TLC) = 0.29 (system A), 0.50 (system B). UV/Vis (MeOH): λ_{max} (ϵ_{rel}) = 273 (1.0), 395 (0.17), 530 (0.09) nm. ^1H NMR (600 MHz, CDCl_3): δ = 1.54 (s, 3 H, 21-H), 1.61 (s, 3 H, 20-H), 1.64 (m, 2 H, 12'-H), 1.66 (d, J = 1.5 Hz, 19-H), 1.70 (d, J = 1.5 Hz, 3 H, 22-H), 1.75 (s, 3 H, 22'-H), 1.88 (s, 3 H, 19'-H), 1.95 (s, 3 H, 20'-H), 1.97 (m, 4 H, 11-H, 11'-H), 2.02 (s, 3 H, 7-H), 2.00–2.10 (m, 4 H, 12-H, 15-H), 2.17 (s, 3 H, 7'-H), 2.18 (m, 2 H, H-13'), 3.15 (d, J = 7 Hz, 2 H, 8-H), 3.30 (d, J = 7 Hz, 2 H, 8'-H), 4.39 (td, J = 8, 4.5 Hz, 16-H), 5.15 (m, 4 H, 17-H, 13-H, 9'-H, 9-H), 5.32 (s, OH), 6.00 (sept, J = 1.5 Hz, 1 H, 17'-H), 6.18 (s, 1 H, 15'-H), 6.18 (s, 2 H, 4'-H, 6'-H), 7.05 (br. s, 1 H, OH) ppm. ^{13}C NMR (150 MHz, CDCl_3): δ = 13.4 (C-7), 16.0–16.1 (C-21, C-22, C-22'), 18.2 (C-20), 20.3 (C-20'), 21.1 (C-7'), 22.1 (C-8'), 22.2 (C-8), 25.3 (C-13'), 25.8 (C-19), 26.4 (C-12), 27.3 (C-19'), 27.8 (C-12'), 39.2 (C-11'), 39.5 (C-11), 48.1 (C-15), 65.7 (C-16), 108.8 (C-4', C-6'), 110.5 (C-2'), 111.0 (C-15'), 114.1 (C-17'), 119.8 (Cq), 120.3 (CH), 122.4 (CH), 127.2 (CH), 128.7 (CH), 131.2 (Cq), 131.5 (Cq), 134.4 (Cq), 135.0 (Cq), 135.5 (Cq), 136.7 (Cq), 137.3 (Cq), 137.4 (Cq), 137.5 (C-5'), 140.5 (C-21'), 150.6 (C-3), 154.8 (C-1', C-3', C-16'), 184.1 (C-4), 185.2 (C-1) ppm. EI MS: m/z (%) = 696 (3.4) [M^+], 680 (31.8) [$\text{M}^+ + 2 \text{H} - \text{H}_2\text{O}$], 679 (26.6) [$\text{M}^+ + \text{H} - \text{H}_2\text{O}$], 678 (57.6) [$\text{M}^+ - \text{H}_2\text{O}$], 529 (18.1) [$\text{M}^+ - \text{C}_{11}\text{H}_{19}\text{O}$], 203 (10.8) [$\text{C}_{13}\text{H}_{15}\text{O}_2$], 191 (6.3), 175 (62.0) [$\text{C}_{11}\text{H}_{11}\text{O}_2$], 137 (100) [$\text{C}_8\text{H}_9\text{O}_2$], 83 (75.6) [$\text{C}_5\text{H}_7\text{O}$]. HR EI-MS: calcd. for $\text{C}_{44}\text{H}_{56}\text{O}_7$ 696.4025; found 696.4006.

2-Farnesyl-3-hydroxy-5-methyl-1,4-benzoquinone (7): A solution of **1** (100 mg, 0.31 mmol) in acetone (10 mL) was treated with a solution of potassium nitrosodisulfonate (483 mg, 1.8 mmol) in the minimum amount of water. The mixture was buffered with 0.6 M aqueous KH_2PO_4 (57 mL) and the resulting turbidity removed by addition of acetone. After 16 h of stirring at room temperature in the dark, the reaction was complete. Removal of the acetone under reduced pressure, extraction of the remaining aqueous phase with CHCl_3 (1 $\times$ 100 mL, 2 $\times$ 200 mL) and concentration of the dried (Na_2SO_4) combined extracts yielded the crude product, which was purified by flash chromatography with hexanes/EtOAc (10:2). **7** (76 mg, 73%) was obtained as a yellow solid. R_f (TLC) = 0.71 (system E). UV/Vis (MeOH): λ_{max} ($\log \epsilon$) = 264 (4.17), 312 (sh, 4.20), 403 (4.12) nm. IR (KBr): $\tilde{\nu}$ = 3480 (s), 2970 (m), 2910 (m), 2850 (m), 1655 (s), 1630 (s), 1445 (w), 1390 (m), 1370 (s), 1335 (m), 1305 (s), 1210 (s), 1175 (m), 1080 (w), 1055 (m), 890 (m) cm^{-1} . ^1H NMR (200 MHz, CDCl_3): δ = 1.55, 1.57 (each s, 3 H, 20-H, 21-H), 1.65 (dm, J = 1.4 Hz, 3 H, 19-H), 1.72 (dm, J = 1.4 Hz, 3 H, 22-H), 1.85–2.07 (m, 8 H, 11-H, 12-H, 15-H, 16-H), 2.03 (d, J = 1.7 Hz, 3 H, 7-H), 3.12 (dm, J = 7.5, 0.75 Hz, 3 H, 8-H), 5.05 (tq, J = 6.7, 1.4 Hz, 2 H, 13-H, 17-H), 5.11 (tq, J = 7.3, 1.4 Hz, 1 H, 9-H), 6.48 (q, J = 1.7 Hz, 1 H, 6-H), 6.92 (s, 1 OH) ppm. ^1H -coupled ^{13}C NMR (50 MHz, CDCl_3): δ = 14.9 (Qd, J = 129.5, 5.6 Hz, C-7), 16.1 (Qsext § , J = 125, 4 Hz, C-21), 16.2 (Qsext § , J = 125, 4 Hz, C-22), 17.7 (Qsext, J = 125, 4 Hz, C-20), 21.9 (Td, J = 129.5, 4 Hz, C-8), 25.8 (Q*, J = 127 Hz, C-19), 26.5, 26.8 (each Tm § , J = 128 Hz, C-12, C-16), 39.7 (Tm*, J = 127 Hz, 2 C, C-11, C-15), 119.6 (Dm, J = 155.2 Hz, C-9), 120.4 (m, J = 6.5 Hz, C-2), 124.1, 124.4 (each Dm*, J = 150 Hz, 2 C, C-13, C-17), 131.3 (sept, J = 5.9 Hz, C-18), 135.1 (m, C-14), 135.3 (Dq, J = 164.8, 5.9 Hz, C-6), 137.2 (m, C-10), 141.0 (q, J = 6.9 Hz, C-5), 150.8 ("q", J = 4.8 Hz, C-3), 184.3 (ddq, J = 11.2, 4, 4 Hz, C-4), 187.4 (t, J = 4.8 Hz, C-1) ppm; * overlapping signals; § signals exchangeable. EI MS: m/z (%) = 344 (3.0), 343 (1.6), 392 (4.7) [M^+], 191 (53.7), 153 (38.1), 69 (100).

2-(2-Methylpropenyl)furan (12): 2-(1-Acetoxy-2-methylpropyl)furan (**5** g, 27.4 mmol) was evaporated with a Kugelrohr apparatus at 75 $^{\circ}\text{C}$ and pyrolyzed by flash vacuum thermolysis (FVT) at 500 $^{\circ}\text{C}$

under 10^{-3} mbar. The products were collected in a cool trap, dissolved in *n*-pentane and, for removal of the AcOH, extracted with saturated aqueous NaHCO₃. Evaporation of the solvent yielded **12** as a colourless oil (0.57 g, 17%), which quickly turns brown on air, b.p. 155–156 °C. *R_f* (TLC) = 0.79 (*n*-pentane). ¹H NMR (90 MHz, CDCl₃): δ = 1.87, 1.96 (each br. s, 3 H), 6.06 (m, 1 H, 6-H), 6.15 (d, *J* = 11 Hz, 1 H, 3-H), 6.37 (dd, *J* = 11, 6 Hz, 1 H, 4-H), 7.35 (d, *J* = 6 Hz, 1 H, 5-H) ppm. ¹³C NMR (22 MHz, CDCl₃): δ = 20.1 (C-8), 27.0 (C-9), 107.2 (C-3), 111.0 (C-4), 114.5 (C-6), 135.3 (C-7), 140.5 (C-5), 153.8 (C-2) ppm. EI MS: *m/z* (%) = 122 (100) [M⁺], 107 (56.6), 93 (19.9), 91 (22.3), 81 (22.8), 79 (37.8), 77 (40.6). HR EI-MS: calcd. C₈H₁₀O 122.0732; found 122.0732.

General Procedure for the Synthesis of 4 and Analogues: A solution of the quinone (0.5 mmol) and the corresponding furan (0.25 mmol) was stirred in CH₂Cl₂ or CHCl₃ (50 mL) at room temperature in the dark for three weeks. After removal of the solvent under reduced pressure, the dark brown residue was purified either by flash chromatography on silica gel with CH₂Cl₂/MeOH (**4**: 100:1; **9**: 20:1) or by gel chromatography on Sephadex LH-20 with MeOH.

Albatrellin (4): Obtained from **7** and **8** in 30.2% yield according to the general procedure. All spectroscopic data derived from **4** are in agreement with those of the natural compound.

4'-Carboxyalbatrellin (9): Obtained from **7** and **3** in 32% yield according to the general procedure. Dark blue solidified oil, soluble in CHCl₃ with ink-blue and in MeOH with violet colour. **9** undergoes slow decarboxylation to **4** even in the refrigerator. *R_f* (TLC) = 0.43 (system A), 0.59 (system B). UV/Vis (MeOH): λ_{max} (log ε) = 268 (4.34), 392 (4.29), 530 (4.22) nm. ¹H NMR (600 MHz, CDCl₃): δ = 1.54, 1.57 (each s, 3 H), 1.65 (m, *J* = 6.5 Hz, 2 H), 1.65, 1.70, 1.75, 1.88, 1.95 (each s, 3 H), 1.90–2.02 (m, 10 H), 2.01 (s, 3 H), 2.20 (t, *J* = 7.5 Hz, 2 H), 3.16, 3.35 (each d, *J* = 7 Hz, 2 H), 5.04 (t, *J* = 7 Hz, 2 H), 5.14, 5.16 (each t, *J* = 7 Hz, 1 H), 6.00 (br. s, 1 H), 6.18 (s, 1 H), 6.20 (s, 1 H) ppm. EI MS: *m/z* (%) = 680 (100) [M⁺ – CO₂], 597 (17.2), 177 (50.9), 137 (87.5), 83 (75), 69 (37.5), 44 (75.0).

Model Compound 11: Obtained from quinone **10** and **8** according to the general procedure. Yield 22% after purification by flash chromatography (SiO₂, CH₂Cl₂/MeOH, 20:1). Dark blue solidified oil. *R_f* (TLC) = 0.58 (system B), 0.60 (system C). UV/Vis (MeOH): λ_{max} (log ε) = 275 (4.12), 388 (3.30), 530 (3.24) nm. ¹H NMR (200 MHz, CDCl₃): δ = 1.65 (m, *J* = 7 Hz, 2 H), 1.76, 1.89 (each s, 3 H), 1.96 (s, 6 H), ≈ 2.00 (m, 2 H), 2.03, 2.19 (each s, 3 H), 2.22 (t, *J* = 7.5 Hz, 2 H), 3.32 (d, *J* = 7.2 Hz, 2 H), 5.17 (tm, *J* = 7.2 Hz, 1 H), 6.01 (sept, *J* = 1.5 Hz, 1 H), 6.19 (s, 3 H) ppm. EI MS: *m/z* (%) = 492 (56.5), 491 (7.9), 490 (25.0) [M⁺], 409 (26.5), 283 (31.6), 259 (37.7), 217 (30.6), 175 (100), 137 (100), 83 (67.3). HR EI-MS: calcd. C₃₀H₃₄O₆ 490.2355; found 490.2359.

Model Compound 13: Obtained from **7** and furan **12** according to the general procedure. Yield 3% after purification by flash chromatography (SiO₂, CH₂Cl₂). Dark blue solidified oil. *R_f* (TLC) = 0.93 (system B). UV/Vis (MeOH): λ_{max} (log ε) = 286 (4.32), 380 (3.73), 534 (3.70) nm. ¹H NMR (200 MHz, CDCl₃): δ = 1.56 (br., 6 H), 1.65, 1.75 (each d, *J* = 1.3 Hz, 3 H), 1.90–2.10 (m, 8 H), 1.94, 2.02, 2.35 (each s, 3 H), 3.15 (d, *J* = 6.6 Hz, 2 H), 5.05 (m, 2 H), 5.14 (t, *J* = 6.6 Hz, 1 H), 6.12 (m, 1 H), 6.38, 7.32 (each d, *J* = 4.2 Hz, 1 H) ppm. EI MS: *m/z* (%) = 462 (81.4) [M⁺], 326 (11.6), 311 (100), 272 (17.4), 191 (22.6), 175 (27.3), 137 (81.3). HR EI-MS: calcd. C₃₀H₃₈O₄ 462.2770; found 462.2805.

Model Compound 14: Obtained from **10** and **12** by refluxing the components in CHCl₃ for 16 h. Yield 1.4% after chromatography

on Sephadex LH-20. Violet-blue solidified oil. *R_f* (TLC) = 0.82 (system B), 0.89 (system D). UV/Vis (MeOH): λ_{max} (log ε) = 282 (4.21), 373 (3.66), 530 (3.57) nm. ¹H NMR (400 MHz, CDCl₃): δ = 1.94 (br. s, 3 H), 1.95, 2.03, 2.37 (each s, 3 H), 6.12 (br. “s”, 1 H), 6.39 (d, *J* = 3.7 Hz, 1 H), 7.14 (s, OH), 7.31 (d, *J* = 3.7 Hz, 1 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 8.4, 13.3, 20.7, 27.5, 111.4, 114.3, 116.3, 122.6, 131.1, 132.3, 139.5, 146.4, 151.2, 156.4, 183.5, 186.7 ppm. EI MS: *m/z* (%) = 274 (11.9), 272 (100) [M⁺], 191 (88), 83 (78). HR EI-MS: calcd. C₁₆H₁₆O₄ 272.1049; found 272.1049.

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