Synthesis of 12-epi-ent-polyalthenol an antitumour indole sesquiterpene alkaloid

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Biomimetic synthesis of an antitumour indole sesquiterpene alkaloid, 12-epi-*ent*-pentacyclindole

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ABSTRACT

Biomimetic synthesis of 12-epi-*ent*-pentacyclindole **7**, using as key step the cyclization of 12-epi-*ent*-polyalthenol acetate has been carried out. This way, the structure and absolute configuration of the natural product pentacyclindole **1** has been confirmed. The synthesized indole sesquiterpenes **7**, **11** and **12** show cellular proliferation inhibition of a number of human leukaemic and solid tumour cell lines.

1. Introduction

Indole sesquiterpenes represent a group of terpene-alkaloids with diverse biological activities.[1] Pentacyclindole **1**[2] (Fig. 1), is an indole sesquiterpene that shows a new carbon skeleton, being the only natural product with that framework (defined to be all ring systems and the linkers that connect them). In an exhaustive study made throughout the CAS Registry analysing pentacyclindole frameworks,[2,3] 213 compounds with the same graph structure were found, and only 7 that have the same heteroframework. Compound **1** has been recently isolated from *Greenwayodendron suaveolens* roots,[2] along with polyalthenol **2**, suaveolindole **3** and its derivatives **4** and **5** (Fig. 1). In addition, pentacyclindole **1** and polyalthenol **2** present activity against clinical isolates of *Staphylococcus aureus* (MIC_{90} of 8 and 4 μg/ml). Williams and co-workers[2] suggest that **1** is a product of the biosynthetic cyclization between C-2 and C-17 of polyalthenol **2**.

The structural novelty of pentacyclindole **1** and its remarkable antibiotic activity prompted us to start the synthesis of **7** with the aim to add new evidences for the biogenetic route of **1** new framework. In this work we communicate the synthesis of **7** from *ent*-halimic acid methyl ester **8**[4] (Fig. 1). This compound is a natural product with a very well-known structure and stereochemistry that has been used as starting material for the synthesis of a wide variety of natural products,[5] for instance, indole diterpene thiersindole C **9**[6] and the indole sesquiterpene 12-epi-*ent*-polyalthenol **6**,[7] which synthesis confirmed the structure and absolute configuration of the natural product **2**.

2. Results and discussion

The synthesis of **7** using **6** as key intermediate was carried out according to the synthetic route depicted in Scheme 1. Acetylation of **6** with acetic anhydride in pyridine gave the acetylderivative **10** that by treatment with hydroiodic acid in refluxing benzene[8] led to **11**. The HRESMS of **11** shows the same signal at *m*/*z* 402 as **10**, corresponding to the ion with identical atomic mass than the precedent compound **10**. This indicates that the cyclization has taken place between C-2 and C-17, as expected in the reaction of a 3-(but-3-enyl) indole in acidic media,[8] generating three new stereocenters in a single step with total diastereoselection.

Effectively, in the ^1H NMR spectra of **11**, in comparison with the one of **10**, can be appreciated the absence of the signals corresponding to H-2 of the indole ring and the signal corresponding to the olefinic hydrogen at C-17 of **10**. The hexahydrocarbazole structure of **11** and the stereochemistry of the three new stereogenic centres formed was determined by NMR bidimensional experiments $^1H/^{13}C$ (HMQC, HMBC and ROESY). The shield of H-17,

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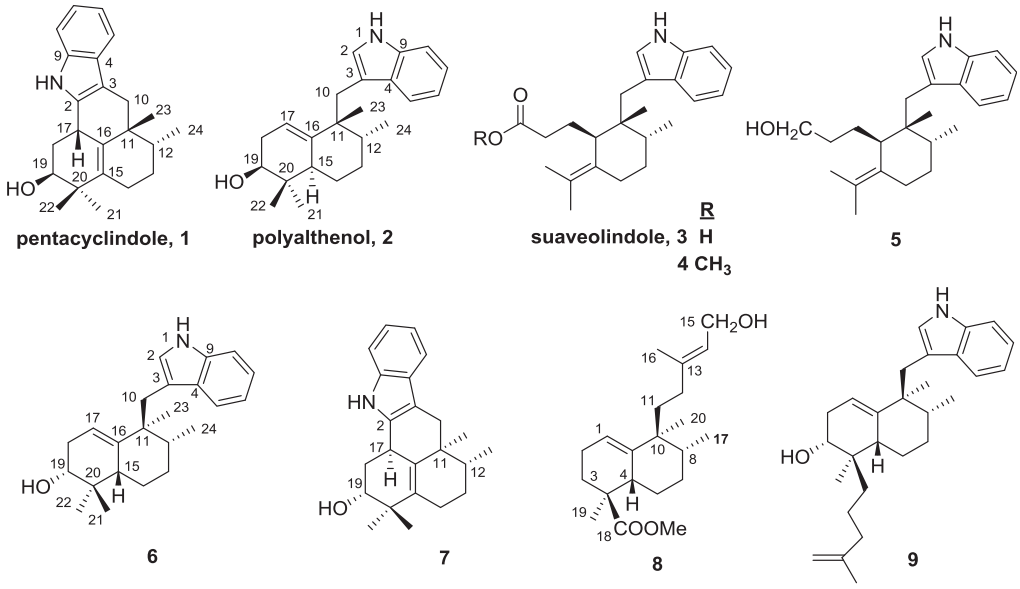
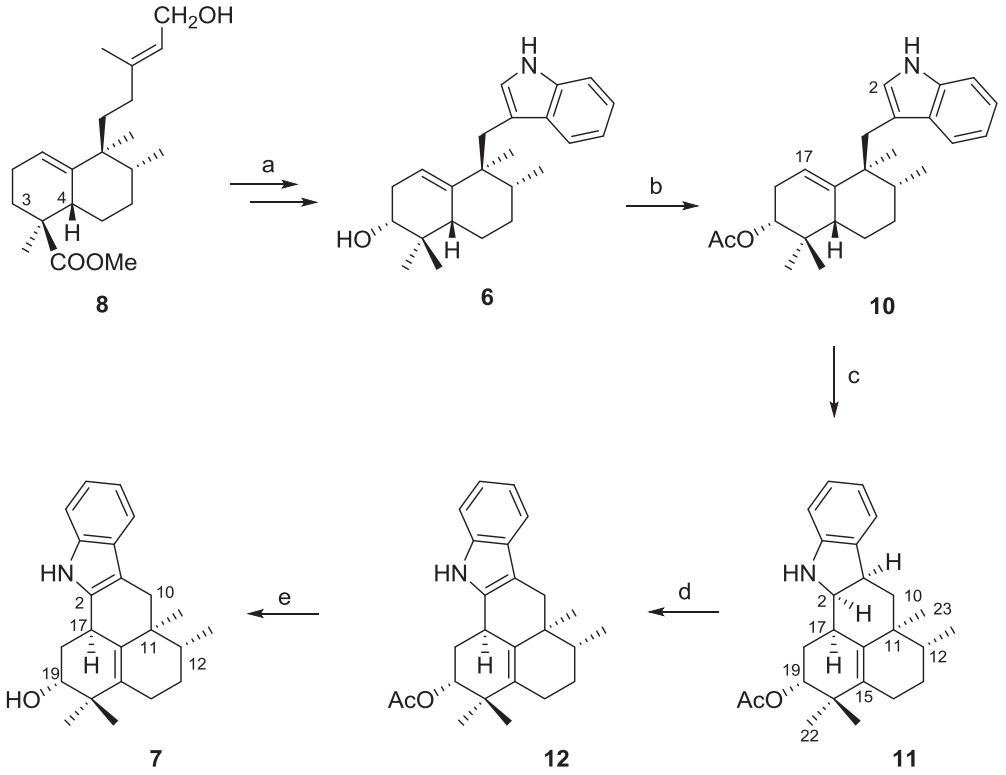


Fig. 1. Pentacyclindole and several structurally related indole sesquiterpenes **1**–**5**, 12-epi-*ent*-polyaltenol **6**, 12-epi-*ent*-pentacyclindole **7**, *ent*-halimic acid methyl ester **8** and thiersindole C **9**.

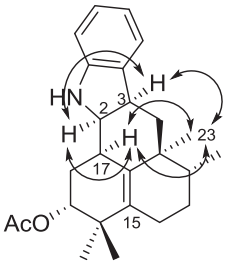


Scheme 1. Reagents and conditions: (a) Ref. 7. (b) Ac_2O, Py, rt, 20 h, 99%. c) HI 57%, C_6H_6, 85 °C, 75 min, 93%. d) TPAP, NMO, 4 Å molecular sieves, DCM, rt, 15 min, 66%. e) 10% KOH/MeOH, rt, 3 h, 93%.

the correlation between C-2 with H-18 and the appearance in the ^{13}C NMR spectra of two quaternary carbons signals at 136.6 and 131.9 ppm corresponding the tetra-substituted olefin Δ^{15} for they show 1,3 correlations with Me-21, Me-22 and Me-23, indicate that the new pentacyclic system was formed. The observed NOEs (Fig. 2) between H-2 with H-3 and H-17, indicate that these hydrogens are located by the same side of the molecule and the NOEs between Me-23 with H-3 and H-17 permit the stereochemistry to be determined as 2*R*, 3*R*, 17*R* for the new stereocentres.

This cyclization reaction can be considered the key step in this biomimetic synthesis of pentacyclindole analogues, and could be used to corroborate other biogenetic routes of other sesqui and diterpeno indoles, such as tubingensin A and B that have been proposed to derive from anominina.[8,9]

Once obtained the pentacyclic system, we proceeded with the oxidation of the indoline **11** to obtain the tetrahydrocarbazolic structure. To achieve this, several methods were tested, such as oxygen, Swern oxidation[10] or CrO_3/Py,[11] but the one that gave



11

Fig. 2. Observed NOE in **11**, which determines the stereochemistry as 2*R*, 3*R*, and 17*R*.

better results was using TPAP with NMO[12] as cooxidant. That permits us to obtain **12** in good yield. The HREIMS of **12** shows a signal at *m*/*z* 400 corresponding to the molecular ion with two mass atomic units less that **11** indicating that the oxidation of the indoline system has taken place. In this case the signal in the ^{1}H NMR for H-17 appears deshielded to 3.65 ppm for being in a benzylic position.

Finally, alkaline hydrolysis of **12** gave **7** (Scheme 1). The ^{1}H NMR spectra in CD_3OD of **7** and pentacyclindole **1** are very similar with the difference in the shield of Me-23 and Me-24 (^{1}H NMR: 1.13 and 1.10 ppm for **1** and 0.99 and 1.05 ppm for **7**). The rest of the signals are equivalent, even the corresponding to the hydrogen at C-19 that Williams and co-workers describe as an 'apparent' *d* of 1.8 Hz and in our compound appears as *dd* of 5.6 and 1.8 Hz. In consequence, **1** and **7** should have an epimeric difference in a position of the terpene bicyclic system. The main differences found between the ^{13}C NMR spectra of **1** and **7** are the shield of the γ-carbons respect to C-12,[13] that is, C-10, C-14, C-16 and C-23, which δ are 30.2, 27.9, 134.3 and 24.3 ppm for **1** and 37.7, 24.9, 133.0 and 20.9 ppm for **7**. These data corroborates that **1** and **7** are epimers at C-12, for when Me-24 is equatorial in **1** has a γ-gauche effect to C-10 shielding it (30.2 ppm), whilst if Me-24 is axial, as it happens in **7** the shielded carbons are C-14 (24.9 ppm), C-16 (133.0 ppm) and C-23 (20.9 ppm). As **7** comes from a natural product, *ent*-halimic acid, of perfectly established structure and absolute configuration,[4] it can be concluded that Me-23 and Me-24 are *trans* in the natural product pentacyclindole **1** (Fig. 3).

that **7**, was obtained from *ent*-halimic acid methyl ester **8**, this compound is 12-epi-*ent*-pentacyclindole and in this manner corroborates that the natural product **1** is of the normal series.

3. Biological activities

The in vitro antitumour activity for these compounds was determined by measurement of their cytostatic and cytotoxic properties in human tumour cell lines by XTT assay (Table 1), as previously reported.[15] The cell lines used were A549 (human lung carcinoma), HL-60 (human myeloid leukaemia) and MCF-7 (human breast adenocarcinoma).

Table 1
In vitro growth inhibitory activity of structurally related compounds to polyalthenol on human tumour cell lines

Compound	IC_{50} (10^{-5} M)		
	A549	MCF-7	HL-60
11	5.9±0.1	3.8±0.3	2.3±0.8
12	5.1±0.4	5.2±0.2	2.1±0.9
7	4.7±0.7	2.2±0.9	1.5±0.7
Doxorubicin	2.5±0.9 (10^{-7})	1.7±0.6 (10^{-7})	1.7±0.6 (10^{-7})

Data are shown as the mean values±S.D. of three independent determinations performed in triplicate. Doxorubicin was used as a positive control.

Cells were incubated in DMEM (A549, MCF-7) or RPMI1640 (HL-60) culture medium containing 10% heat-inactivated foetal bovine serum in the absence and in the presence of the indicated compounds at a concentration range of 10^{-4} to 10^{-9} M in 96-well microtiter plates, and following 72 h of incubation at 37 °C in a humidified atmosphere of air/CO_2 (19/1) the XTT assay was performed. Measurements were done in triplicate and each experiment was repeated three times. The IC_{50} value, defined as the drug concentration required to cause 50% inhibition in the cellular proliferation with respect to the untreated controls, was determined for each compound.

These data show that compounds **11**, **12** and **7** significantly inhibit proliferation of various human tumour cells, including leukaemic and solid tumour cells, with an IC_{50} in the micromolar range (Table 1).

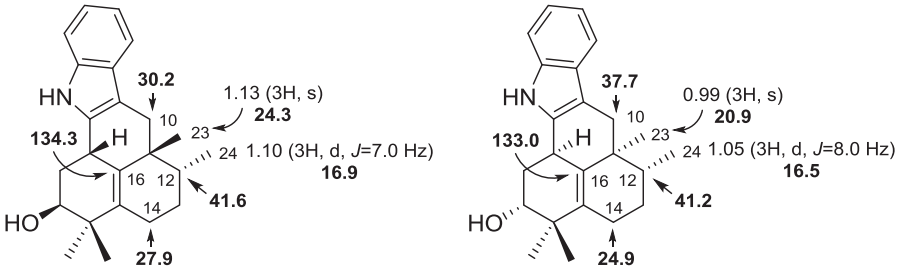


Fig. 3. ^{1}H and ^{13}C NMR values for C-12 and γ-carbons for natural pentacyclindole **1** and synthetic 12-epi-*ent*-pentacyclindole **7**.

There are several examples of this kind of epimery in the literature, such as the sesterterpenolides cladocoran A and B and its 15-epi-derivatives,[5b,14] halimanes and their 8-epi-halimanes[5g] and in polyalthenol and its 12-epi *ent*-polyalthenol.[7]

The difference in the absolute value of the optical rotation between the natural product **1** [α] +69 (*c* 0.3, EtOH) and the synthetic compound **7** [α] −96 (*c* 0.1, EtOH) is of 27° that is in the range for the epimers mentioned before. As the rotation of **1** and **7** is of different sign these compounds are opposite series. Considering

4. Conclusions

A biomimetic synthesis of **7**, the epimer at C-12 of the natural pentacyclindole **1** has been carried out, corroborating this way the structure and absolute configuration of the natural product. The starting material was *ent*-halimic acid methyl ester **8**, and 12-epi-*ent*-polyalthenol **6** was the main intermediate. The key step for the synthesis of the pentacyclic system is the cyclization of a 3-(but-3-enyl) indole derivative by a methodology developed by our group.

Compounds **11**, **12** and **7** inhibit proliferation of various human tumour cells, including leukaemic and solid tumour cells, with an IC_{50} in the range of 25 μM.

5. Experimental

5.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^1H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ parts per million and coupling constants (J) are given in hertz. MS were performed using a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as m/z (% rel. int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin–Elmer 241 polarimeter in 1 dm cells. Diethyl ether and THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under Argon atmosphere.

*5.1.1. Aureanindol-16-ene-19α-yl acetate (**10**).* 24 mg (0.072 mmol) of 12-epi-*ent*-polyalthenol **6** were dissolved in 1 mL of pyridine, 1 mL of Ac_2O was added and the mixture was stirred for 20 h at rt. It was then quenched with crushed ice and extracted with EtOAc. The organic layer was washed with 2 M HCl, 6% aq $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and filtered. Removal of the solvent afforded **10** (24 mg, 99%).

R_f (Hex/EtOAc 8/2)=0.40; IR (film, cm^{-1}): 3420, 3054, 2926, 1735, 1718, 1458, 1376, 1246, 1030; ^1H NMR (200 MHz) δ: 8.02 (1H, br s, NH), 7.60 (1H, d, J=7.0 Hz, H-5), 7.34 (1H, d, J=7.0 Hz, H-8), 7.13 (1H, t, J=7.0 Hz, H-7), 7.10 (1H, t, J=7.0 Hz, H-6), 6.91 (1H, s, H-2), 5.16 (1H, s, H-17), 4.73 (1H, dd, J=8.8 and 5.8 Hz, H-19), 2.90 (2H, br s, H-10), 2.07 (3H, s, *Me*COO−), 0.98 (3H, s, Me-22), 0.89 (6H, s, Me-21 and Me-23), 0.82 (3H, d, J=7.0 Hz, Me-24); ^{13}C NMR (50 MHz) δ: 171.3 (MeCOO−), 142.2 (C-16), 135.8 (C-9), 129.4 (C-4), 123.0 (C-2), 121.7 (C-7), 119.7 (C-5), 119.3 (C-6), 117.7 (C-17), 113.4 (C-3), 111.1 (C-8), 72.2 (C-19), 44.6 (C-20), 44.2 (C-15), 37.4 (C-12), 36.4 (C-11), 35.5 (C-10), 29.6 (C-13), 28.8 (C-18), 28.6 (C-14), 28.5 (C-22), 25.4 (C-21), 24.2 (C-23), 21.6 (*Me*COO−), 16.2 (C-24); HRESIMS.: calcd for $C_{25}H_{33}NO_2Na$ (M+Na): 402.2403; found: 402.2416.

*5.1.2. (2R, 3R, 17R)-2,3-Dihydro-2,17-cyclo-aureanindol-15-ene-19α-yl acetate (**11**).* Compound **10** (21 mg, 0.054 mmol) was dissolved in C_6H_6 (2.7 mL) an HI 57% (10 μL) was added. The mixture was heated up to 85 °C for 1 h 15 min. It was then let to cool to rt, diluted with EtOAc and washed with 10% aq $NaHSO_3$, 6% aq $NaHCO_3$ and brine. It was dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent yielded **11** (19 mg, 93%).

R_f (Hex/EtOAc 9/1)=0.49; [α] +191.1 (c 0.36, $CHCl_3$); IR (film, cm^{-1}): 3350, 2926, 1718, 1375, 1247, 1037, 1018, 738; ^1H NMR (200 MHz) δ: 7.04 (1H, d, J=7.3 Hz, H-5), 7.01 (1H, dd, J=7.6 and 7.3 Hz, H-7), 6.70 (1H, d, J=7.6 Hz, H-8), 6.67 (1H, t, J=7.3 Hz, H-6), 4.97 (1H, dd, J=12.2 and 3.8 Hz, H-19), 4.62 (1H, br s, N–H), 3.77 (1H, dd, J=6.4 and 4.4 Hz, H-2), 3.12 (1H, dt, J=12.4 and 6.2 Hz, H-3), 2.84 (1H, m, H-17), 2.11 (3H, s, *Me*COO−), 1.05 (3H, s, Me-23), 1.02 (6H, s, Me-21 and Me-22), 0.85 (3H, d, J=6.2 Hz, Me-24); ^{13}C NMR (50 MHz) δ: 172.2 (CH_3COO−), 150.5 (C-9), 136.6 (C-15), 135.2 (C-4), 131.9 (C-16), 127.5 (C-7), 123.3 (C-5), 118.4 (C-6), 110.2 (C-8), 77.3 (C-19), 67.6 (C-2), 42.6 (C-10), 40.8 (C-12), 38.5 (C-3), 38.4 (C-20), 33.8 (C-17), 28.3 (C-13), 27.5 (C-18), 26.4 (C-14), 24.5 (C-21), 21.6 (C-22), 20.5 (CH_3COO-), 17.6 (C-23), 16.4 (C-24). HRESIMS: calcd for $C_{25}H_{34}NO$ (M+H): 380.2584; found: 380.2577.

*5.1.3. (17R)-2,17-Cyclo-aureanindol-15-ene-19α-yl acetate (**12**).* A mixture of **11** (18 mg, 0.045 mmol), NMO (18 mg, 0.132 mmol), molecular sieves (57 mg, 500 mg/mmol) and TPAP (catalytic) was dissolved in dry DCM (1.5 mL) and was stirred for 15 min at rt and under Ar atmosphere. The bulk was filtered through silica gel and Celite. The solvent was removed and the crude was purificated through column chromatography (Hex/EtOAc 98:2) to obtain **12** (12 mg, 66%).

R_f (Hex/EtOAc 8/2)=0.52; [α] −168.0 (c 0.1, EtOH); IR (film, cm^{-1}): 3385, 2964, 1926, 1718, 1452, 1375, 1246, 1035, 736; ^1H NMR (400 MHz) δ: 7.75 (1H, br s, N–H), 7.44 (1H, d, J=7.4 Hz, H-5), 7.30 (1H, d, J=7.6 Hz, H-8), 7.12 (1H, dd, J=7.6 and 7.4, H-7), 7.07 (1H, t, J=7.4, H-6), 4.86 (1H, m, H-19), 3.65 (1H, br s, H-17), 2.74 (1H, d, J=15.2, H_A-10), 2.64 (1H, d, J=15.2 Hz, H_B-10), 2.11 (3H, s, *Me*COO−), 1.05 (3H, d, J=6.8 Hz, Me-24), 1.04 (6H, s, Me-21 and Me-22), 1.00 (3H, s, Me-23); ^{13}C NMR (100 MHz) δ: 171.2 (MeCOO−), 136.2 (C-9), 135.6 (C-2), 132.8 (C-15), 131.3 (C-16), 127.3 (C-4), 121.1 (C-7), 119.9 (C-6), 117.7 (C-5), 110.5 (C-8), 108.6 (C-3), 77.0 (C-19), 39.4 (C-12), 38.0 (C-20), 38.0 (C-11), 36.2 (C-10), 29.7 (C-18), 28.9 (C-17), 27.6 (C-21), 27.0 (C-13), 23.4 (C-22), 23.0 (C-14), 21.2 (CH_3COO−), 20.8 (C-23), 15.9 (C-24); HRESIMS: calcd for $C_{25}H_{31}NO_2Na$ (M+Na): 400.2236; found: 400.2236.

*5.1.4. 12-epi-ent-Pentacyclindol (**7**).* Compound **12** (9 mg, 0.024 mmol) was dissolved in 10% KOH/MeOH (2.5 mL) and the mixture was stirred for 3 h at rt. It was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to afford **7** (7 mg, 93%).

R_f (Hex/EtOAc 7/3)=0.45; [α] −96.0 (c 0.1, EtOH); IR (film, cm^{-1}): 3356, 2924, 2852, 1452, 1379, 1261, 1060, 738; ^1H NMR (400 MHz) δ: 7.30 (1H, d, J=7.6 Hz, H-5), 7.25 (1H, d, J=8.0 Hz, H-8), 6.98 (1H, dd, J=8.0 and 7.2 Hz, H-7), 6.91 (1H, dd, J=7.6 and 7.2 Hz, H-6), 4.61 (1H, br s, −OH), 3.77 (1H, m, H-17), 3.57 (1H, dd, J=5.6 and 1.8 Hz, H-19), 2.70 (1H, d, J=14.8 Hz, H_A-10), 2.58 (1H, d, J=14.8 Hz, H_B-10), 2.39 (1H, ddd, J=12.4, 6.8 and 5.6 Hz, H_A-18), 2.04 (2H, m, H-14), 1.98 (1H, m, H_B-18), 1.68 (1H, m, H-12), 1.59 (1H, m, H_A-13), 1.46 (1H, m, H_B-13), 1.10 (3H, s, Me-22), 1.05 (3H, d, J=8.0 Hz, Me-24), 1.00 (3H, s, Me-21), 0.99 (3H, s, Me-23); ^{13}C NMR (100 MHz) δ: 138.3 (C-9), 137.9 (C-2), 135.1 (C-15), 133.0 (C-16), 129.1 (C-4), 121.2 (C-7), 119.3 (C-6), 118.1 (C-5), 111.5 (C-8), 108.6 (C-3), 75.3 (C-19), 41.1 (C-12), 40.2 (C-20), 39.3 (C-11), 37.7 (C-10), 32.7 (C-18), 30.5 (C-17), 28.5 (C-21), 28.4 (C-13), 24.9 (C-14), 23.9 (C-22), 20.9 (C-23), 16.5 (C-24). HRESIMS: calcd for $C_{23}H_{29}NO$ (M+H): 336.2327; found: 336.2330.

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