

Cytotoxic Quassinoids and Tirucallane-Type Triterpenes from the Woods of *Eurycoma longifolia*

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New cytostatic quassinoids, 6 α -hydroxyeurycomalactone (1), longilactone (2) and 14,15 β -dihydroxyklaineaneone (3) were isolated from the woods of *Eurycoma longifolia* (Simaroubaceae) with three cytotoxic quassinoids, 11-dehydroklaineaneone (4), eurycomalactone (5) and 5,6-dehydroeurycomalactone (6), and with seven cytotoxic tirucallane-type triterpenes, niloticin (7), dihydroniloticin (8), piscidinol A (9), bourjotinolone A (10), 3-episapelin A (11), melianone (12) and hispidone (13). All of them showed potent cytotoxic activity against P388 and KB cells.

Keywords quassinoid; triterpene; cytotoxic activity; *Eurycoma longifolia*; Simaroubaceae

As part of our program on research of antitumor compounds from natural products, we earlier reported on cytotoxic quassinoids and squalene-type triterpene ethers from *Eurycoma longifolia*.^{1,2} Further purification of the active components providing cytotoxicity led us to isolate some quassinoids and tirucallane-type triterpenes from the woods of *E. longifolia*. In this paper, structural elucidation of the cytotoxic principles including some new quassinoids is reported.

Cytotoxic activities of methanol extract of *E. longifolia* were concentrated in the methylene chloride soluble fraction, which showed cytotoxicity of IC₅₀ 2.4 μ g/ml against

chinese hamster V-79 cells.³ Repeated chromatographic purification with the guidance of bio-assay against V-79 cells led to isolation of three new quassinoids, 6 α -hydroxyeurycomalactone (1), longilactone (2) and 14,15 β -dihydroxyklaineaneone (3), three known quassinoids (4—6), and seven known tirucallane-type triterpenes (7—13).

Compound 1, named as 6 α -hydroxyeurycomalactone and with the molecular formula, C₁₉H₂₄O₇, was obtained as colorless needles, mp 234—236 °C, [α]_D +180.4° (*c* = 0.18, CHCl₃). Carbon-13 nuclear magnetic resonance (¹³C-NMR) spectrum of 1 indicated that 1 possesses a C₁₉-quassinoid type skeleton like eurycomalactone. In the

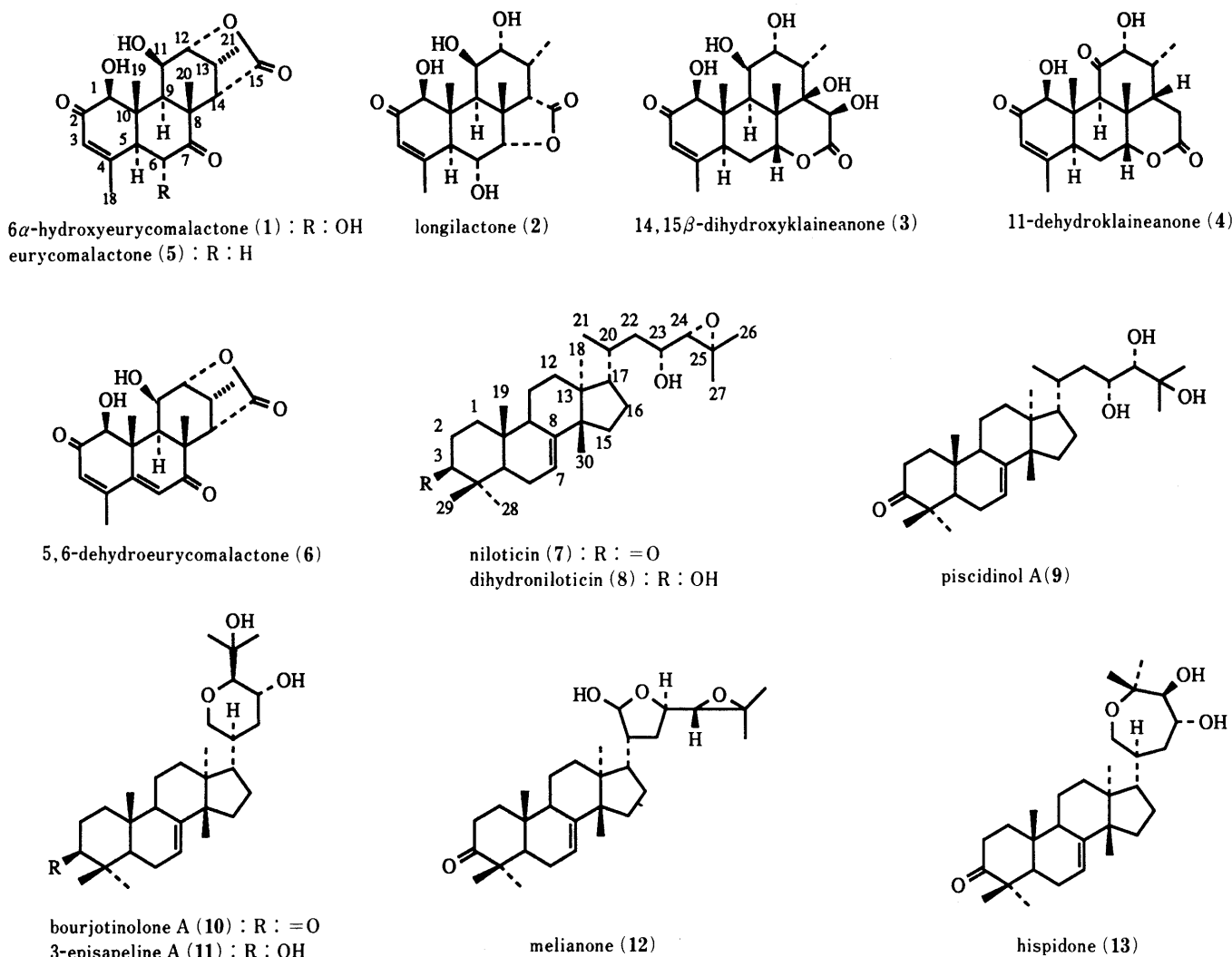


Fig. 1. Molecular Structures of Compounds 1—13 Isolated from the Woods of *E. longifolia*

proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectrum, the feature that a proton assignable to H-12 did not couple to H-13 due to the vertical dihedral angle also supported presence of this skeleton. The origin of an additional oxygen atom was found to be a hydroxyl group attached at C-6 because of the aromatic solvent induced shift⁴⁾ of H-6 ($\Delta\delta$ pyridine- d_5 - CDCl_3 , 0.47 ppm) and the coupling relationship to H-5. The configuration of this hydroxyl group was determined to be α by the coupling constant (11.3 Hz) between H-5 and H-6. This data was sufficient to corroborate the structure of **1** as 6 α -hydroxyeurycomalactone.

Compounds **2** and **3** were determined to be new quassinoids, longilactone and 14,15 β -dihydroxyklaineaneone, respectively, which were reported as our earlier communication.¹⁾ Longilactone is a new C_{19} -type quassinoid forming a lactonic linkage at C-7 rather than C-12.

Compounds **4**, **5** and **6** were identical with 11-dehydroklaineaneone,⁵⁾ eurycomalactone^{6,7)} and 5,6-dehydroeurycomalactone,^{7,8)} respectively, by comparison of the spectral data.

Three tirucallane-type triterpenes (**7**, **8** and **9**) were established as niloticin,⁹⁾ dihydroniloticin⁹⁾ and piscidinol A,¹⁰⁾ respectively. Recently, the stereostructure of niloticin has been positively determined by X-ray analysis.¹¹⁾ Reduction of **7** with sodium borohydride gave **8** and cleavage of epoxide by 0.1 N sulfuric acid gave **9**. So, ambiguous stereostructures of **8** and **9** were determined by the above conversion (Fig. 1). Compounds **10** and **11** were established as bourjotinolone A¹²⁾ and 3-episapelin A,¹³⁾ both of which formed an ether linkage. The configuration of hydroxyl group at C-3 of 3-episapelin A must be β due to the splitting pattern (dd, $J=4.2$, 11.1 Hz) of H-3 (δ 3.24). This was the first time compound **11** has been isolated as natural product.¹³⁾ Compounds **12** and **13** were identical with melianone¹⁴⁾ and hispidone.¹²⁾

Complete ^1H and ^{13}C assignments of **1**–**5** and ^{13}C of **7**–**13** were made by a combination of ^1H – ^1H correlated spectroscopy (COSY), ^1H – ^{13}C COSY and ^1H – ^{13}C long range COSY (COLOC) spectra (see Experimental section).

All of the compounds obtained at this time showed cytotoxic activity against P388 and KB cells (Table I). In the quassinoids, there was no marked propensity between structures and activities. Comparison of **3** and **4**, however, showed that hydroxyl groups at C-11 and/or C-14 may

provide a structural requirement for potent activity. In the tirucallane-type triterpenes, cytotoxicities of sapelins A and B have been reported by Sandmann and McHugh.¹⁵⁾ A series of tirucallane-type triterpenes (**7**–**13**) also showed moderate cytotoxic activity.

Experimental

All melting points were recorded on a Yanagimoto MP-3 micromelting point apparatus and are uncorrected. The spectral data were obtained on the following instruments: optical rotation on a JASCO DIP-4, infrared spectrum (IR) on a JASCO A-302, ultraviolet spectrum (UV) on a Hitachi 557, NMR on a Bruker AM 400 and mass spectrum (MS) on a Hitachi M-80. Medium-pressure liquid chromatography (MPLC) was carried out on a CIG column system (Kusano Scientific Co., Tokyo) packed with 10 μm silica gel as the stationary phase. Reversed phase high pressure liquid chromatography (HPLC) was carried out on a YMC R and D column packed with 5 μm octadecyl silica (ODS) and an Inertsil PREP-ODS packed with 10 μm ODS.

Bioassay of Cytotoxic Activity against V-79, P388, and KB Cells See previous paper.¹⁶⁾

Extraction and Isolation The woods of *E. longifolia* collected in Indonesia (4.5 kg) were extracted with hot methanol three times and concentrated to give a methanolic extract (192 g). This extract was successively partitioned into methylene chloride, *n*-butanol and water. The cytotoxic activity was concentrated in the methylene chloride soluble fraction, which was subjected to silica gel column chromatography using a methylene chloride–methanol gradient system. Further chromatographic purification of the active fraction by silica-MPLC (*n*-hexane–ethyl acetate solvent system) and ODS-HPLC (methanol–water and acetonitrile–water solvent system) led to the isolation of 6 α -hydroxyeurycomalactone (**1**: 25 mg), longilactone (**2**: 18 mg), 14,15 β -dihydroxyklaineaneone (**3**: 215 mg), 11-dehydroklaineaneone (**4**: 12 mg), eurycomalactone (**5**: 53 mg), 5,6-dehydroeurycomalactone (**6**: 2 mg), niloticin (**7**: 1.5 g), dihydroniloticin (**8**: 40 mg), piscidinol A (**9**: 55 mg), bourjotinolone A (**10**: 12 mg), 3-episapelin A (**11**: 43 mg), melianone (**12**: 78 mg) and hispidone (**13**: 30 mg).

6 α -Hydroxyeurycomalactone (**1**): Colorless needles, mp 234–236 °C, $[\alpha]_D^{25}$ 180.4° ($c=0.17$, CHCl_3). High-MS: Calcd 364.1522 for $\text{C}_{19}\text{H}_{24}\text{O}_7$ (M^+), Found 364.1526. MS m/z (%): 364 (M^+ , 4), 111 (100). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.18 (3H, d, $J=7.0$ Hz, H-21), 1.30 (3H, s, H-19), 1.62 (3H, s, H-20), 1.83 (1H, d, $J=3.6$ Hz, H-9), 2.27 (3H, brs, H-18), 2.69 (1H, br d, $J=11.4$ Hz, H-5), 2.92 (1H, m, H-13), 2.92 (1H, m, H-14), 3.18 (1H, d, $J=5.8$ Hz, OH-11), 3.98 (1H, brs, H-1), 4.09 (1H, d, $J=2.5$ Hz, OH-6), 4.36 (1H, d, $J=4.5$ Hz, H-12), 4.52 (1H, d, $J=1.2$ Hz, OH-1), 4.58 (1H, dd, $J=11.3$, 2.5 Hz, H-6; d, $J=11.3$ Hz in addition of D_2O), 4.80 (1H, dd, $J=4.3$, 3.6 Hz, H-11; t, $J=4.3$ Hz in addition of D_2O), 6.14 (1H, br d, $J=2.5$, 1.3 Hz, H-3). $^1\text{H-NMR}$ (pyridine- d_5) δ ppm: 1.06 (3H, dd, $J=6.9$, 2.0 Hz, H-21), 1.64 (3H, brs, H-19), 1.74 (3H, brs, H-20), 2.30 (1H, brs, H-9), 2.40 (3H, s, H-18), 2.95 (1H, br d, $J=10.5$ Hz, H-5), 3.20 (1H, br q, $J=12.4$, 5.5 Hz, H-13), 3.26 (1H, s, H-14), 4.15 (1H, brs, H-1), 4.48 (1H, br d, $J=4.8$ Hz, H-12), 5.05 (1H, br d, $J=11.6$ Hz, H-6), 5.44 (1H, brs, H-11), 6.25 (1H, brs, H-3), 6.30 (1H, d, $J=5.5$ Hz, OH-11). $^{13}\text{C-NMR}$ (CDCl_3) δ ppm: 13.6 (C-19), 16.5 (C-21), 23.2 (C-18), 24.8 (C-20), 31.9 (C-13), 47.8 (C-8), 48.6 (C-14), 49.6 (C-10), 53.4 (C-9), 57.0 (C-5), 69.6 (C-6), 70.0 (C-11), 81.1 (C-1), 82.9 (C-12), 125.5 (C-3), 165.0 (C-4), 175.3 (C-15), 197.1 (C-2), 207.3 (C-7). IR (KBr) cm^{-1} : 3550, 1775, 1715, 1670. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 242 (3.97).

11-Dehydroklaineaneone (**4**): Colorless needles, mp 141–142 °C, $[\alpha]_D^{25}$ –14.2° ($c=0.11$; MeOH). High-MS: Calcd 362.1727 for $\text{C}_{20}\text{H}_{26}\text{O}_6$ (M^+), Found: 362.1720. MS m/z (%): 362 (M^+ , 100), 344 (45). $^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.12 (3H, s, H-20), 1.13 (3H, d, $J=5.9$ Hz, H-21), 1.21 (3H, s, H-19), 1.80 (1H, ddd, $J=12.7$, 6.6, 3.1 Hz, H-14), 1.95 (3H, s, H-18), 2.00 (1H, td, $J=12.7$, 2.0 Hz, H-6a), 2.20 (1H, dt, $J=14.5$, 3.2 Hz, H-6e), 2.29 (1H, qd, $J=7.6$, 3.1 Hz, H-13), 2.69 (1H, dd, $J=19.4$, 6.6 Hz, H-15a), 2.90 (1H, br d, $J=11.7$ Hz, H-5), 3.70 (1H, dd, $J=19.4$, 12.7 Hz, H-15e), 3.73 (1H, s, H-9), 3.86 (1H, d, $J=3.0$ Hz, H-12), 4.02 (1H, s, H-1), 4.38 (1H, t, $J=3.1$ Hz, H-7), 6.04 (1H, dd, $J=2.7$, 1.3 Hz, H-3). $^{13}\text{C-NMR}$ (CDCl_3) δ ppm: 9.6 (C-19), 13.3 (C-21), 22.4 (C-20 or 18), 22.7 (C-20 or 18), 25.2 (C-6), 28.9 (C-15), 35.2 (C-13), 40.0 (C-8), 42.6 (C-5), 45.1 (C-14), 45.9 (C-10), 46.4 (C-9), 81.7 (C-7), 82.1 (C-12), 84.5 (C-1), 124.9 (C-3), 163.1 (C-4), 170.8 (C-16), 197.2 (C-2), 210.1 (C-11). IR (KBr) cm^{-1} : 3530, 1740, 1720, 1680. UV $\lambda_{\text{max}}^{\text{MeOH}}$ (log ϵ): 237 (4.00).

Eurycomalactone (**5**): Colorless needles, mp 239–240 °C, $[\alpha]_D^{25}$ 96.6° ($c=0.18$, CHCl_3). MS m/z (%): 348 (M^+ , 10), 330 (17), 95 (100).

TABLE I. Cytotoxic Activities of Compounds **1**–**13** against P388 and KB Cells (IC_{50} $\mu\text{g/ml}$)

Compound	P388	KB cells
1	0.25	0.44
2	1.3	3.4
3	0.29	0.38
4	1.8	1.6
5	0.90	1.3
6	1.0	1.7
7	1.5	8.3
8	20	0.55
9	1.2	5.0
10	4.5	5.0
11	14	9.0
12	0.83	7.7
13	5.0	7.0

¹H-NMR (CDCl₃) δ ppm: 1.14 (3H, d, *J* = 7.0 Hz, H-21), 1.23 (3H, s, H-19), 1.54 (3H, s, H-20), 1.86 (1H, d, *J* = 10.3 Hz, H-9), 1.93 (3H, brs, H-18), 2.75 (1H, dd, *J* = 15.2, 4.9 Hz, H-6e), 2.77 (1H, dd, *J* = 16.3, 12.9 Hz, H-6a), 2.87 (1H, dd, *J* = 11.0, 4.0 Hz, H-5), 2.90 (1H, m, H-13), 2.93 (1H, brs, H-14), 3.14 (1H, d, *J* = 5.7 Hz, OH-11), 4.03 (1H, brs, H-1), 4.35 (1H, brd, *J* = 4.7 Hz, H-12), 4.49 (1H, brs, OH-1), 4.77 (1H, brdd, *J* = 8.8, 5.2 Hz, H-11), 6.09 (1H, brs, H-3). ¹³C-NMR (CDCl₃) δ ppm: 12.1 (C-19), 16.6 (C-21), 21.8 (C-18), 23.6 (C-20), 32.3 (C-13), 36.2 (C-6), 46.9 (C-8), 49.0 (C-14), 49.3 (C-5), 51.1 (C-10), 52.9 (C-9), 69.8 (C-11), 81.2 (C-1), 83.1 (C-12), 124.4 (C-3), 162.2 (C-4), 176.1 (C-15), 197.4 (C-2), 205.4 (C-7). IR (KBr) cm⁻¹: 3560, 1772, 1715, 1672. UV λ_{max}^{MeOH} (log ε): 239 (4.01).

5,6-Dehydroeurycomalactone (6): Colorless needles, mp 285–286 °C, [α]_D -34.2° (*c* = 0.38, MeOH). MS *m/z* (%): 346 (M⁺, 9), 317 (100). ¹H-NMR (CDCl₃) δ ppm: 1.19 (3H, d, *J* = 6.9 Hz, H-21), 1.45 (3H, s, H-19), 1.53 (3H, s, H-20), 2.16 (3H, s, H-18), 2.33 (1H, d, *J* = 3.8 Hz, H-9), 2.71 (1H, d, *J* = 6.0 Hz, OH-11), 2.94 (1H, dd, *J* = 13.9, 7.0 Hz, H-13), 3.00 (1H, d, *J* = 1.2 Hz, H-14), 4.20 (1H, d, *J* = 1.4 Hz, H-1), 4.38 (1H, brs, OH-1), 4.38 (1H, dd, *J* = 5.5, 1.4 Hz, H-12), 4.90 (1H, dd, *J* = 9.8, 4.7 Hz, H-11), 6.24 (1H, s, H-6), 6.29 (1H, brs, H-3). IR (CHCl₃) cm⁻¹: 3480, 1789, 1680. UV λ_{max}^{MeOH} (log ε): 288 (4.22).

Niloticin (7): Colorless needles, mp 139–141 °C, [α]_D -76.7° (*c* = 0.09, CHCl₃). MS *m/z* (%): 456 (M⁺, 12), 369 (100). ¹³C-NMR (CDCl₃) δ ppm: 12.8 (C-19), 18.3 (C-11), 19.8 (C-26), 19.8 (C-21), 21.6 (C-29), 21.8 (C-18), 24.4 (C-6), 24.6 (C-28), 24.9 (C-27), 27.4 (C-30), 28.8 (C-16), 33.6 (C-20), 33.7 (C-15), 34.0 (C-12), 34.9 (C-2), 35.0 (C-10), 38.6 (C-1), 40.7 (C-22), 43.6 (C-13), 47.9 (C-4), 48.5 (C-9), 51.2 (C-14), 52.4 (C-5), 53.3 (C-17), 60.2 (C-25), 66.4 (C-24), 69.3 (C-23), 116.0 (C-7), 145.7 (C-8), 216.8 (C-3). IR (KBr) cm⁻¹: 3390, 1707.

Dihydroniloticin (8): Colorless needles, mp 178–179 °C, [α]_D -48.0° (*c* = 0.08, CHCl₃). MS *m/z* (%): 458 (M⁺, 17), 371 (100). ¹³C-NMR (CDCl₃) δ ppm: 13.2 (C-19), 14.8 (C-29), 18.2 (C-11), 19.9 (C-26), 20.0 (C-21), 21.8 (C-18), 24.0 (C-6), 24.9 (C-27), 27.3 (C-30), 27.7 (C-28), 27.8 (C-16), 28.8 (C-2), 33.7 (C-20), 33.8 (C-15), 34.1 (C-12), 35.0 (C-10), 37.3 (C-1), 39.1 (C-4), 40.9 (C-22), 43.7 (C-13), 49.0 (C-9), 50.8 (C-5), 51.3 (C-14), 53.4 (C-17), 60.3 (C-25), 68.6 (C-24), 69.4 (C-23), 79.3 (C-3), 118.1 (C-7), 145.7 (C-8). IR (KBr) cm⁻¹: 3500.

Piscidinol A (9): Colorless needles, mp 79–81 °C, [α]_D -76.7° (*c* = 0.62, CHCl₃). MS *m/z* (%): 474 (M⁺, 7), 441 (15), 369 (100). ¹³C-NMR (CDCl₃) δ ppm: 12.7 (C-19), 18.3 (C-11), 18.9 (C-21), 21.5 (C-29), 22.0 (C-18), 24.3 (C-6), 24.5 (C-28), 26.2 (C-26), 27.3 (C-27), 27.3 (C-30), 28.4 (C-16), 33.7 (C-20), 33.8 (C-15), 34.0 (C-12), 34.9 (C-2), 35.0 (C-10), 38.5 (C-1), 40.5 (C-22), 43.5 (C-4), 47.8 (C-13), 48.4 (C-9), 51.2 (C-14), 52.3 (C-5), 53.8 (C-17), 69.7 (C-23), 74.3 (C-25), 75.1 (C-24), 117.9 (C-7), 145.7 (C-8), 217.0 (C-3). IR (KBr) cm⁻¹: 3450, 1710.

Bourjotinolone A (10): Colorless needles, mp 110–111 °C, [α]_D -42.6° (*c* = 1.2, CHCl₃). MS *m/z* (%): 472 (M⁺, 2), 439 (10), 110 (100). ¹³C-NMR (CDCl₃) δ ppm: 12.8 (C-19), 18.2 (C-11), 21.6 (C-18), 22.3 (C-29), 24.0 (C-26), 24.4 (C-6), 24.6 (C-28), 27.4 (C-16), 27.5 (C-30), 28.5 (C-27), 33.0 (C-12), 34.0 (C-15), 35.0 (C-2), 35.1 (C-10), 36.5 (C-22), 37.5 (C-20), 38.6 (C-1), 43.3 (C-13), 44.8 (C-17), 47.9 (C-4), 48.5 (C-9), 51.3 (C-14), 52.4 (C-5), 64.6 (C-23), 70.1 (C-21), 74.2 (C-25), 86.5 (C-24), 118.1 (C-7), 145.7 (C-8), 216.8 (C-3). IR (KBr) cm⁻¹: 3430, 1715.

3-Episapelin A (11): Colorless needles, mp 204–205 °C, [α]_D -5.2° (*c* = 0.5, CHCl₃). MS *m/z* (%): 474 (M⁺, 28), 441 (50), 383 (100). ¹³C-NMR (CDCl₃) δ ppm: 13.1 (C-19), 14.7 (C-29), 18.0 (C-11), 22.3 (C-18), 24.0 (C-6), 24.0 (C-26), 27.3 (C-30), 27.5 (C-16), 27.6 (C-28), 27.7 (C-2), 28.5 (C-27), 33.1 (C-12), 33.9 (C-15), 35.0 (C-10), 36.5 (C-22), 37.3 (C-1), 37.5 (C-20), 39.0 (C-4), 43.4 (C-13), 44.8 (C-17), 48.9 (C-9), 50.7 (C-5), 51.3 (C-14), 64.6 (C-23), 70.1 (C-21), 74.6 (C-25), 79.3 (C-3), 86.5 (C-24), 118.1 (C-7), 145.5 (C-8). IR (KBr) cm⁻¹: 3410.

Melianone (12): Colorless needles, mp 214–215 °C, [α]_D -63.3°

(*c* = 0.12, CHCl₃). MS *m/z* (%): 470 (M⁺, 11), 437 (50), 383 (70), 105 (100). ¹³C-NMR (pyridine-*d*₅) δ ppm: 12.7 (C-19), 18.0 (C-11), 19.5, 19.6 (C-26), 21.5 (C-18), 22.8, 23.5 (C-29), 24.6 (C-6), 24.9 (C-27), 25.1 (C-28), 27.4, 27.7 (C-30), 27.5, 27.8 (C-16), 31.6, 31.8 (C-22), 32.2 (C-12), 34.2, 34.7 (C-15), 35.0, 36.0 (C-2), 35.2 (C-10), 38.4 (C-1), 44.0, 44.2 (C-13), 45.7, 47.6 (C-17), 47.8 (C-4), 48.6 (C-9), 50.3, 51.1 (C-20), 51.3 (C-14), 52.5, 52.6 (C-5), 56.8, 57.0 (C-25), 66.1, 68.6 (C-24), 77.2, 78.9 (C-23), 97.8, 102.4 (C-21), 118.3 (C-7), 146.0, 146.5 (C-8), 215.2 (C-3). IR (KBr) cm⁻¹: 3450, 1710.

Hispidone (13): Colorless needles, mp 106–107 °C, [α]_D -40.8° (*c* = 0.33, CHCl₃). MS *m/z* (%): 472 (M⁺, 3), 381 (100). ¹³C-NMR (CDCl₃) δ ppm: 12.8 (C-19), 18.1 (C-11), 21.6 (C-18), 22.2 (C-29), 22.3 (C-26), 24.4 (C-6), 24.5 (C-28), 26.3 (C-27), 27.4 (C-30), 28.1 (C-16), 32.6 (C-12), 34.0 (C-15), 34.9 (C-2), 35.0 (C-10), 37.4 (C-22), 38.5 (C-1), 38.5 (C-20), 43.3 (C-13), 47.5 (C-17), 47.9 (C-4), 48.4 (C-9), 51.3 (C-14), 52.4 (C-5), 64.4 (C-21), 68.5 (C-23), 76.2 (C-25), 80.7 (C-24), 118.0 (C-7), 145.7 (C-8), 217.0 (C-3). IR (KBr) cm⁻¹: 3460, 1710.

Conversion of Niloticin to Dihydroniloticin A methanol solution of niloticin (5 mg) was treated with an excess of sodium borohydride. After workup in the usual way, the product was extracted with methylene chloride to give dihydroniloticin (5 mg).

Conversion of Niloticin to Piscidinol A Niloticin (5 mg) in tetrahydrofuran–water (9:1) was treated with 0.1 N sulfuric acid for 6 d. The reaction mixture was neutralized and extracted with methylene chloride. This organic layer was concentrated and purified by MPLC (*n*-hexane : ethyl acetate = 65 : 35) to give piscidinol A (4.7 mg).

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