Isolation and synthesis of two antiproliferative calamenene-type sesquiterpenoids from *Sterculia tavia* from the Madagascar Rain Forest ☆

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ABSTRACT

Investigation of the endemic Madagascan plant *Sterculia taiva* Baill. (Malvaceae) for antiproliferative activity against the A2780 ovarian cancer cell line led to the isolation of two new bioactive calamenene-type sesquiterpenoids, named tavinin A (**2**) and *epi*-tavinin A (**3**) together with the known sesquiterpenoid mansonone G (**1**). The structures of the two new compounds were elucidated based on analysis of their 1D and 2D NMR spectra and mass spectrometric data, and were confirmed by de novo synthesis. The three isolated sesquiterpenoids (**1–3**) had modest antiproliferative activities against the A2780 ovarian cancer cell line, with IC_{50} values of 10.2, 5.5 and 6.7 µM, respectively.

1. Introduction

Discovering antiproliferative natural products from both tropical dry forests and rainforests of Madagascar has been one of the objectives of our group's involvement for more than 15 years in the International Cooperative Biodiversity Group (ICBG) program.[1] As a part of this research, an EtOH extract from the bark of *Sterculia tavia* Baill. (Malvaceae) from the rain forest of northern Madagascar was found to exhibit antiproliferative activity against the A2780 human ovarian cancer cell line, with an IC_{50} value of 14 µg/mL. The Malvaceae family is a family of flowering plants containing over 200 genera with close to 2300 species.[2] *Sterculia*, one of the largest genera of this family, is a rich source of alkaloids, saponins and flavonoid glycosides, which are well-known for their broad range of bioactivity, including antimicrobial, antifungal, insecticidal, cytotoxic, antioxidant, and anti-inflammatory activities among others.[3] Although the genus *Sterculia* has been well investigated, the present species is endemic to Madagascar and has not been explored for its phytochemical composition and biological activity. The EtOH extract of *S. tavia* was thus selected for bioassay-guided fractionation to isolate its antiproliferative components.

2. Results and discussion

The EtOH extract of the bark part of the *S. tavia* was subjected to liquid–liquid partitioning to give an active dichloromethane fraction with an IC_{50} value of 9.6 µg/mL. Bioassay-guided separation, including LH-20 size-exclusion, normal-phase silica gel chromatography, and C-18 reverse-phase HPLC, was used to obtain the known cadinane-type sesquiterpenoid mansonone (**1**), and the two new calamenene-type sesquiterpenoids designated tavinin A (**2**) and *epi*-tavinin A (**3**) as the major antiproliferative constituents of the extract. Herein, we report the structural elucidation and synthesis of the two new compounds.

Compound **1** was identified as the cadinane-type sesquiterpenoid mansonone G (6-hydroxy-5-isopropyl-3,8-dimethyl-naphthalene-1,2-dione) by comparison of its chemical and spectroscopic data with those reported in the literature.[4]

Tavinin A (**2**), $[\alpha]_D^{21}$ +15° (*c* 1.2, MeOH), was isolated as a light yellow oil. Its positive ion HRESIMS revealed quasi-molecular ion peaks at *m/z* 293.1399 [M+H]$^+$ and 315.1194 [M+Na]$^+$, corresponding to a molecular formula of $C_{16}H_{20}O_5$, with seven degrees of unsaturation. Based on the similarity of the NMR spectral data of **2** and those of compound **1**, compound **2** was identified as a sesquiterpenoid with a similar carbon skeleton. The six aromatic ^{13}C NMR resonances: *δ* 162.9, 145.3, 127.8, 123.1, 116.7 and 107.4, as well as the two singlet signals (Table 1) observed in the aromatic region of its ^{1}H NMR spectrum (*δ* 7.64 and 7.37), revealed the

Table 1
NMR spectroscopic data for **2** and **3** in acetone-d_6 (600 MHz)

Position	2		3	
	δ_H (J in Hz)	δ_C[a], type	δ_H (J in Hz)	δ_C[a], type
1	–	73.8, C	–	74.7, C
2	–	204.0, C	–	208.2, C
3	–	196.7, C	–	200.7, C
4	–	88.9, C	–	91.2, C
5	7.64 s	127.8, CH	7.68 s	128.1, CH
6	–	116.7, C	–	116.9, C
7	–	162.9, C	–	163.2, C
8	7.37 s	107.4, CH	7.33 s	108.0, C
9	–	145.3, C	–	144.8, C
10	–	123.1, C	–	122.8, C
11	2.52 sept	36.1, CH	2.35 sept	35.6, CH
12	0.67 d (J = 6.7 Hz)	15.4, CH₃	0.81 d (J = 6.7 Hz)	15.6, CH₃
13	0.88 d (J = 6.7 Hz)	15.9, CH₃	0.90 d (J = 6.7 Hz)	16.2, CH₃
14	1.62 s	28.1, CH₃	1.86 s	27.4, CH₃
15	2.27 s	15.1, CH₃	2.27 s	15.1, CH₃
16	4.04 s	55.5, CH₃	4.05 s	55.5, CH₃

[a] The ^{13}C NMR spectral data were generated from gHSQC and gHMBC spectra.

Table 2
Antiproliferative activity of compounds **1–3** and synthetic intermediates **7–12** against A2780 ovarian cancer cells

Compound	IC_{50} (μM)
1	10.2 ± 0.9
2	5.5 ± 0.9
rac-**2**	5.9 ± 0.7
3	6.7 ± 0.3
rac-**3**	6.3 ± 0.4
7	>50
8	>50
9	33.9 ± 1.5
10	4.0 ± 0.5
11	22.1 ± 3.4
12	35.5 ± 2.7
Paclitaxel	0.028 ± 0.003

presence of a tetrasubstituted benzene ring with two protons located in the *para*-position.[5] The presence of two deshielded carbon signals at δ 204.0 and 196.7, as well as the compound's IR absorption (ν_{max} = 1659 cm^{-1}), indicated the presence of two

hydrogen-bonded carbonyl groups in the structure. Since the benzene rings and two carbonyl groups contribute four and two degrees of unsaturation, respectively, the remaining one was assigned to a ring. The above data indicated that the basic skeleton of **2** was that of an oxygenated calamenene-type sesquiterpenoid.[6] The methyl proton signal located at δ 2.27 and the methoxy proton at δ 4.04 (both singlets) were assignable to a C-6 methyl carbon and to the carbon of a C-7 methoxyl group of the benzene ring. This assignment was supported by HMBC correlations (Fig. 1a) between H-15 (δ 2.27) and C-7 (δ 162.9) and the C-5 methine carbon (δ 127.8), and between H-16 (δ 4.04) and C-7. An oxygen-bearing quaternary carbon (δ 88.9, C-4) was determined to be attached to C-10 of the benzene ring (δ 123.1) due the presence of a ^3J HMBC crosspeak between the methine proton at H-5 and C-4. The ^{1}H NMR spectrum exhibited resonances at δ 0.67 (d, J = 6.7 Hz, H-12) and δ 0.88 (d, J = 6.7 Hz, H-13) for the two methyl groups of an isopropyl group, and these showed COSY correlations with a methine proton at δ 2.52 (sept, J = 6.8 Hz, H-11). The ^3J HMBC correlation between the protons of one of the doublet methyl groups (H-12/H-13) and the carbon at δ 88.9 allowed us to determine the connection of the isopropyl unit to be at C-4. Moreover, the ^2J HMBC correlation observed between the protons at δ 1.62 (H-14) and C-1, the ^3J HMBC crosspeaks between H-14 and C-9 (δ 145.3) and between H-14 and one carbonyl carbon at δ 204.0 (C-2), as well as the ^3J HMBC correlations between the septet methine proton (H-11) and the carbon at δ 196.7 (C-3), allowed us to determine the location of a second oxygen-bearing quaternary carbon (δ 73.8) and the two carbonyl carbons to be at C-1, C-2 and C-3, respectively. The relative configuration of **2** (Fig. 1a) as well as the assignment of the aromatic methyl and methoxy groups to C-6 and C-7, respectively, rather than the reverse, was deduced by the interpretation of the results of the 1D NOE-difference experiment. When the H-14 protons (δ 1.62) were irradiated, only the signal at δ 7.37 (H-8) was amplified (1.23%). Similarly, irradiation of H-11 (δ 2.52) only enhanced the aromatic signals at δ 7.64 (H-5) by 3.18%.

The second compound isolated, *epi*-tavinin A (**3**), $[\alpha]_D^{21}$ +8° (c 1.2, MeOH) had the same molecular formula ($C_{16}H_{20}O_5$) as **2** by interpretation of its HRESIMS data. The NMR spectroscopic data of compound **3** were very similar to those of **2** except for the ^{1}H chemical shifts of H-11, H-12, H-13 and H-14. Compounds **2** and **3** were thus assigned as a pair of diastereomers differing in one of their two stereogenic centers (C-1 and C-4). The relative configuration of **3** was determined in the same manner as that of **2**. Irradiation of H-14 in a 1D NOE-difference experiment enhanced the signals of *both* H-8 and H-11 by 1.32% and 1.35%, respectively, indicating a *syn* relationship between the methyl and *iso*propyl groups in **3**. Based on these observations, the relative configurations of C-1 and C-4 of compound **2** were assigned as R^* and R^* while those of C-1 and C-4 of **3** were assigned as S^* and R^*.
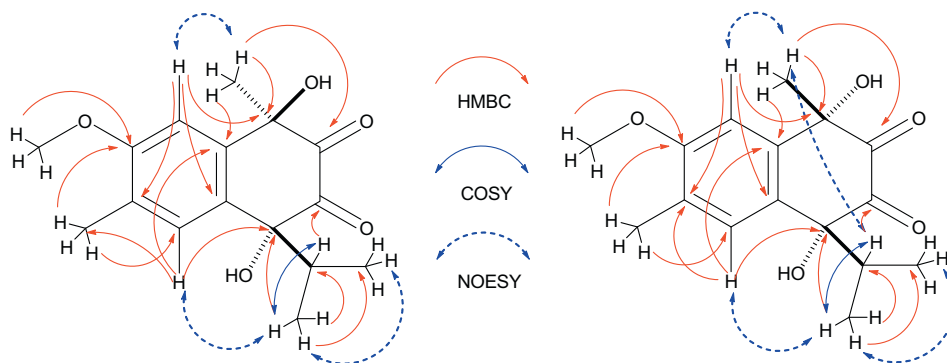

Figure 1. (a) HMBC, COSY, and NOESY correlations of **2**; (b) HMBC, COSY and NOESY correlations of **3**.

The structures of compounds **2** and **3** were confirmed by synthesis (Scheme 1). The synthesis initially followed McCormick's method for the synthesis of lacinilene C methyl ether (**10**) from 2-methylanisole.[7] The literature procedure was modified by running the Grignard reaction to convert the known ketoester **4** to 5-isopropyl-5-(4-methoxy-3-methylphenyl)-dihydrofuran-2-one (**6**) at low temperature, which increased the yield of **6** from 20% to 42% and of the reduction byproduct **5** from 23% to 30%. Dihydrofuranone **6** was then converted to cycloalkene **7**, diol **8**, and ketone **9** as previously described,[7] except that conversion of **8** to **9** was carried out using the sulfur trioxide pyridine complex instead of the Swern oxidation originally used.[7] Oxidation of the carbon–carbon double bond of compound **10** to triol **13** could not be accomplished directly with osmium tetroxide in the presence of N-methylmorpholine N-oxide because of the electron deficient nature of the αβ-unsaturated double bond. The ketone **10** was thus reduced to alcohol **11**[8] by Luche reduction[9] in a yield of 90.3%. The product appeared to consist of a single compound as judged by HPLC and by the presence of only one singlet for H-2 in its ^{1}H NMR spectrum, presumably because the orientation of the hydride ion attack was governed by complexation of the borohydride with the adjacent C-1 hydroxyl group. Oxidation of **11** with osmium tetroxide in the presence of N-methylmorpholine N-oxide afforded tetraol **12** as a mixture of stereoisomers. Without separation of this mixture, the tetraols **12** were further oxidized by the sulfur trioxide pyridine complex to give a mixture of four diones as two pairs of enantiomers in the relatively low yield of 43.2%. The diones were separated by HPLC to afford synthetic racemic **2** and synthetic racemic **3**. The structures of the natural products isolated were confirmed by comparison of their ^{1}H NMR, UV spectrometric and HRESIMS data with those of their synthetic counterparts.

3. Bioassay data

The isolated tavinin A (**2**) and *epi*-tavinin A (**3**), the synthetic compounds *rac*-**2** and *rac*-**3** as well as the intermediates involved in the synthetic route were tested for antiproliferative activity against the A2780 ovarian cancer. As listed in Table 2, both natural

products **2** and **3** showed weak inhibition of the A2780 ovarian cancer cells, with IC$_{50}$ values of 5.5 and 6.7 μM, respectively. The synthetic compounds *rac*-**2** and *rac*-**3** had identical values within experimental error, indicating that bioactivity is not dependent on stereochemistry in this series. Among the synthetic intermediates, only lacinilene C methyl ether (**10**, IC$_{50}$ value of 4.0 μM) was of comparable potency to the natural products; the other calamenene-type sesquiterpenoid intermediates were less active or inactive. The cytotoxic activity of compound **10** may be due to the presence of an α,β-unsaturated ketone function in the molecule; such groups are electrophilic and are able to bind to receptors, leading to facile reactions with protein thiols, and ultimately to induction of apoptosis.[10]

4. Experimental section

### 4.1. General experimental procedures

Optical rotations were recorded on a JASCO P-2000 polarimeter. IR spectroscopic data were measured on a MIDAC M-series FTIR spectrophotometer. NMR spectra were recorded in acetone-d_6 or CDCl$_3$ on Bruker Avance 500 or Bruker Avance 600 spectrometers. The chemical shifts are given in δ (ppm), and coupling constants (J) are reported in Hz. Mass spectra were obtained on an Agilent 6220 LC–TOF–MS in the positive ion mode.

4.2. Antiproliferative bioassays

Antiproliferative activities were obtained at Virginia Tech against the drug-sensitive A2780 human ovarian cancer cell line[11] as previously described.[1c]

4.3. Plant material

A sample of the bark parts of *Sterculia tavia* Baill. was collected in October 2005. The sample was collected from a tree 24 m high, with yellowish seeds and light brown fruits. The collection was made in the rainforest 8 km from Ankijabe, in the Daraina region
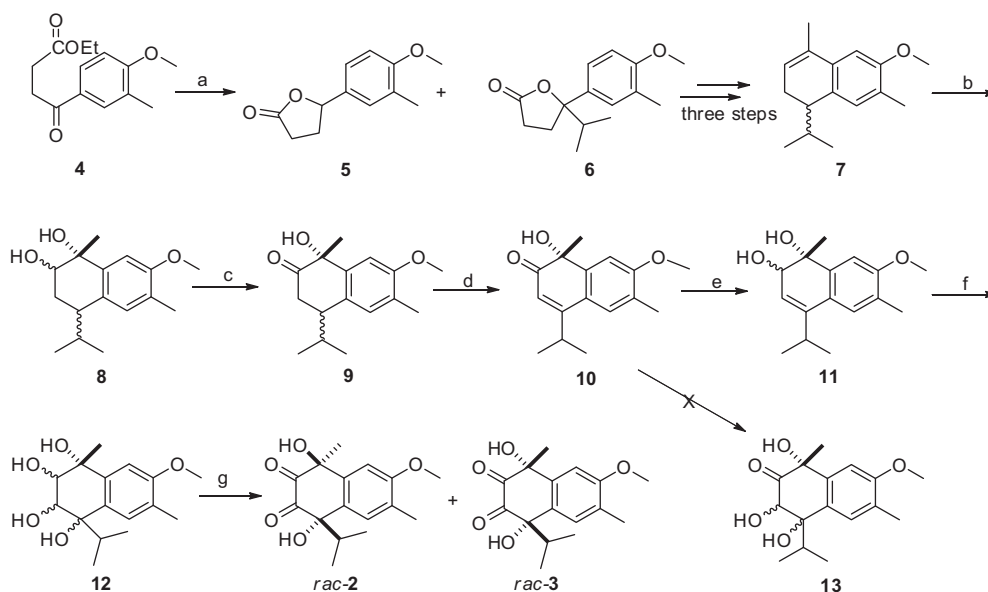
Scheme 1. Synthesis of compound **2** and **3**. Reagents and conditions: (a) isopropylmagnesium chloride, THF, −15 °C, 1 h, 42.1%; (b) 2% Osmium teroxide, N-Methyl-morpholine-N-oxide (NMO), dichloromethane, rt, 48 h, 75.4%; (c) sulfur trioxide–pyridine complex, dichloromethane, 0 °C, 2 h, 91.9%; (d) 2,3-dichloro-5,6-dicyanobenzo-quinone (DDQ, benzene), reflux, 24 h, 58%; (e) NaBH$_4$, CeCl$_3$, 7H$_2$O, rt, 5 min, 90.3%; (f) 2% Osmium tetroxide, N-methyl-morpholine-N-oxide (NMO), dichloromethane, rt, 48 h; (g) sulfur trioxide–pyridine complex, dichloromethane, 0 °C, 2 h, 13% (*rac*-**2**) 10% (*rac*-**3**).

of Madagascar, at coordinates 13°16′12″S 049°36′40″E and elevation 617 m. Voucher specimens have been deposited at the Parc Botanique and Zoologique de Tsimbazaza (TAN), at the Centre National d'Application des Recherches Pharmaceutiques in Antananarivo, Madagascar (CNARP), the Missouri Botanical Garden in St. Louis, Missouri (MO), and the Muséum National d'Histoire Naturelle in Paris, France (P), voucher Sennen Randrianasolo et al. 533.

4.4. Extraction and isolation

Dried bark parts of S. tavia (252 g) were ground in a hammer mill, then extracted with EtOH by percolation for 24 h at room temperature to give the crude extract MG 3532 (5.2 g), of which 1.42 g was shipped to Virginia Tech for bioassay-guided isolation. A 1.4 g sample of MG 3532 (IC$_{50}$ 14 µg/mL) was suspended in aqueous MeOH (MeOH/H$_2$O 9:1, 100 mL), and extracted with hexane (3 × 100 mL portions). The aqueous layer was then diluted to 60% MeOH (v/v) with H$_2$O and extracted with dichloromethane (DCM) (3 × 150 mL portions). The hexane fraction was evaporated in vacuo to leave 497.5 mg of material with IC$_{50}$ = 15 µg/mL. The residue from the DCM fraction (213.5 mg) had an IC$_{50}$ of 9.6 µg/mL, and the remaining aqueous MeOH fraction had an IC$_{50}$ >20 µg/mL. LH-20 size exclusion open column chromatography (DCM/MeOH = 1:1) of the DCM fraction was used to obtain six fractions, of which the two most active fractions F3 (67.7 mg) and F4 (51.4 mg) had IC$_{50}$ values of 5.9 and 4.8 µg/mL, respectively. Fraction F4 was then applied to a silica gel column with elution by hexane/EtOAc, 7:3 to give seventeen fractions, of which fraction 4 (2.3 mg) was the most active (IC$_{50}$ 3.7 µg/mL), and yielded compound 1 (1.5 mg, IC$_{50}$ 2.5 µg/mL) on chromatography on C-18 HPLC with elution by 85% MeOH in water, with the retention time of 14.9 min. Fraction F3 was also applied to a silica gel column with elution by hexane/EtOAC = 4:1 to give six fractions, of which fraction 5 (26.2 mg) was the most active (IC$_{50}$ 2.7 µg/mL). Compounds 2 (0.32 mg, IC$_{50}$ 1.7 µg/mL) and 3 (0.28 mg, IC$_{50}$ 1.9 µg/mL), with retention times of 14.7 and 15.2 min, respectively, were obtained by using C-18 HPLC eluted by 70% MeOH in water to purify fraction 5.

4.5. (1R,4R)-1,4-dihydroxy-1-isopropyl-6-methoxy-4,7-dimethylnaphthalene-2,3(1H,4H)-dione (2, Tavinin A)

Light yellow oil; $[\alpha]_D^{21}$ +15 (c 1.2, MeOH); UV (MeOH) λ_{max} (ε) 207 (3.20), 232 (2.35), 280 (1.62); IR ν_{max} cm^{-1}: 3418, 2926, 1659, 1463, 1052 cm^{-1}. ^{1}H NMR (600 MHz, acetone-d_6), and ^{13}C NMR (125 MHz, acetone-d_6), see Table 1; HRESIMS m/z 315.1194 [M+Na]$^+$ (calcd for C$_{16}$H$_{20}$NaO$_5$, 315.1208).

4.6. (1R,4S)-1,4-dihydroxy-1-isopropyl-6-methoxy-4,7-dimethylnaphthalene-2,3(1H,4H)-dione (3, Epi-Tavinin A)

Light yellow oil; $[\alpha]_D^{21}$ +8 (c 1.2, MeOH); UV (MeOH) λ_{max} (ε) 207 (3.20), 232 (2.35), 280 (1.62); IR ν_{max} cm^{-1}: 3432, 2932, 1671, 1459, 1078 cm^{-1}. ^{1}H NMR (600 MHz, acetone-d_6), and ^{13}C NMR (125 MHz, acetone-d_6), see Table 1; HRESIMS m/z 315.1201 [M+Na]$^+$ (calcd for C$_{16}$H$_{20}$NaO$_5$, 315.1208).

4.7. Synthesis of 4-hydroxy-4-(4-methoxy-3-methylphenyl)-5-methyl-hexanoic acid lactone (6)

Ketoester 4[12] (500 mg) was dissolved in 50 mL of THF, and the solution cooled to −15 °C. Isopropyl magnesium chloride (1.5 mL of a 2.0 M solution in THF) was added during a 15 min period. After stirring for 2 h, the mixture was dried under reduced pressure, and 50 mL of saturated NH$_4$Cl solution was added. The aqueous solution was extracted with 50 mL Et$_2$O three times, and the extracts

were washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated to afford 468 mg brown oil, which was refluxed together with 500 mg KOH in 100 mL 95% EtOH for 4 h. The EtOH was removed from the mixture under reduced pressure, 100 mL of water was added, and the resulting mixture was extracted three times with 50 mL Et$_2$O. The aqueous portion was acidified to pH 1 with HCl and stirred at rt for 2 h. The acidified solution was extracted three times by another 50 mL of Et$_2$O, and the ethereal potion was washed with saturated Na$_2$CO$_3$ and NaCl solution, respectively, dried by Na$_2$SO$_4$ and concentrated under reduced pressure to afford 313 mg of a yellow oil. Chromatographic purification of the crude lactone (50 g of silica gel; eluted with EtOAc/hexane, 3:7) afforded 167 mg of compound 6 (R$_f$ 0.56, silica gel TLC, EtOAc/hexane, 3:7) and 140 mg of compound 5 (R$_f$ 0.40). The NMR and mass spectrometric data were consistent with the data reported.[7]

4.8. 1,2,3,4-Tetrahydro-1,2-dihydroxy-4-isopropyl-7-methoxy-1,6-dimethylnaphthalenes (8)

This compound was prepared from 4-hydroxy-4-(4-methoxy-3-methylphenyl)-5-methyl-hexanoic acid lactone (6) in four steps as previously described; its spectroscopic data matched the literature data.[7]

4.9. l-Hydroxy-4-isopropyl-7-methoxy-1,6-dimethyl-2-naphthalenone (10)

Diol mixture 8 (50 mg) was dissolved in 50 mL of CH$_2$Cl$_2$ and the solution cooled to 0 °C. Sulfur trioxide pyridine complex (150.6 mg) was added to the solution during a 5 min period. After stirring for 2 h, 50 mL of saturated Na$_2$CO$_3$ solution was added, and the layers were separated. The aqueous layer was extracted with 50 mL of CH$_2$Cl$_2$ three times, and the combined organic layers were washed with saturated NaCl solution, dried over Na$_2$SO$_4$, and concentrated under reduced pressure to afford 45.3 mg of ketone 9 as a yellow oil. The crude ketone and 56.6 mg dichlorodicyanobenzoquinone were stirred in 50 mL of benzene for 24 h at room temperature, after which the solvent was evaporated under reduced pressure. The resulting oil was purified by column chromatography (50 g of silica gel; eluted with EtOAc/hexane, 2:3) to give 28.9 mg (58%) of compound 10 (R$_f$ 0.40). The NMR and mass spectrometric data were consistent with the reported data.[7]

4.10. 4-Isopropyl-7-methoxy-1,6-dimethyl-1,2-dihydronaphthalene-1,2-diol (11)

Compound 10 (26.0 mg) was dissolved in 25 mL of 0.4 mM methanolic CeCl$_3$·7H$_2$O at room temperature, and 1 equiv of NaBH$_4$ (3.8 mg) was added to the solution. After stirring for 5 min, the mixture was dried under reduced pressure, redissolved in 25 mL of water and extracted three times with 25 mL of dichloromethane. The organic portion was washed with saturated NaCl solution, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The resulting light yellow oil was purified by column chromatography (50 g of silica gel; eluted with EtOAc/hexane, 2:3) to afford 23.7 mg (90%) of diol 11. The product appeared to consist of a single compound as judged by HPLC and by the presence of only one singlet for H-2 in its ^{1}H NMR spectrum, presumably because the orientation of the hydride ion attack was governed by complications of the borohydride with the adjacent C-1 hydroxyl group. m/z 262.1658; ^{1}H NMR (CDCl$_3$) δ 7.12 (H-8, s, 1), 7.06 (H-5, s, 1), 5.56 (H-3, br s, 1), 4.48 (H-2, br s, 1), 3.86 (H-16, s, 3), 2.87 (H-11, sept, 1, J = 6.65), 2.19 (H-15, s, 3), 1.30 (H-14, s, 3), 1.19 (H-12, d, 3, J = 6.68), 1.06 (H-13, d, 3, J = 6.68); ^{13}C NMR (CDCl$_3$) δ 157.5 (C-7, C), 142.6 (C-4, C), 142.2 (C-9, C), 126.2 (C-5, CH), 125.2 (C-10, C),

125.2 (C-6, C), 121.7 (C-3, CH), 105.7 (C-8, CH), 77.1 (C-2, CH), 77.0 (C-1, C), 55.7 (C-16, CH$_3$), 28.2 (C-11, CH); 22.7 (C-14, CH$_3$), 21.6 (C-12, CH$_3$), 20.8 (C-13, CH$_3$), 16.4 (C-15, CH$_3$).

4.11. 1,4-Dihydroxy-1-isopropyl-6-methoxy-4,7-dimethylnaphthalene-2,3-diones *rac*-2 and *rac*-3

Diol **11** (22.0 mg) was dissolved in 6 mL of acetone and 2.5 mL of water and the solution cooled to −25 °C. *N*-methylmorpholine N-oxide (0.05 mL of a 50% solution in water) and 0.1 mL of 2% osmium tetroxide aqueous solution were then added under nitrogen. The mixture was allowed to warm to room temperature and stirred for an additional 48 h, and then 50 mg of Na$_2$S$_2$O$_4$ was added. The acetone was removed under reduced pressure, the pH was adjusted to 2 by HCl, and the solution was extracted with 20 mL dichloromethane three times. The combined extracts were washed with saturated NaCl solution, dried by Na$_2$SO$_4$ and concentrated under reduced pressure to afford product **12** as a light brown oil The crude product was oxidized directly with sulfur trioxide pyridine complex as described in the synthesis of compound **10** above. The resulting 6.6 mg of light brown oil was applied to C-18 HPLC and eluted by 68% MeOH in water to afford 3.2 mg of light yellow oil (*rac*-**2**) and 2.5 mg of light yellow oil (*rac*-**3**), at retention times of 19.5 and 20.7 min, respectively. The NMR and mass spectrometric data of both compounds were identical to those of the corresponding natural products.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.10.012. These data include MOL files and InChiKeys of the most important compounds described in this article.

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