Triterpenoids with Rare Carbon Skeletons from *Salvia hydrangea*: Antiprotozoal Activity and Absolute Configurations

M. Moridi Farimani,*[,†] M. Babak Bahadori,[†] Salman Taheri,[‡] Samad N. Ebrahimi,[†,‡] Stefanie Zimmermann,[‡,§] Reto Brun,[§] Gholamreza Amin,[‖] and Matthias Hamburger[‡]

[†]Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, G. C., Evin, Tehran, Iran
[‡]Chemistry and Chemical Engineering Research Center of Iran, Tehran, Iran
[‡]Division of Pharmaceutical Biology, University of Basel, Klingelbergstrasse 50, 4056 Basel, Switzerland
[§]Swiss Tropical and Public Health Institute, Socinstrasse 57, CH-4002 Basel, Switzerland
[‖]Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

Ⓢ *Supporting Information*

ABSTRACT: Salvadione C (**1**) and perovskone B (**2**), two new triterpenoids with rare carbon skeletons, were isolated from an antiplasmodial *n*-hexane extract of *Salvia hydrangea*. The absolute configuration was determined by comparison of experimental and calculated electronic circular dichroism (ECD) spectra. In vitro activity against *Plasmodium falciparum* K1 strain, *Trypanosoma brucei rhodesiense* STIB 900 strain, and cytotoxicity in rat myoblast (L6) cells were determined. Compounds **1** and **2** showed in vitro antiplasmodial activity, with IC_{50} values of 1.43 and 0.18 μM and selectivity indices (SI) of 86.2 and 69.6, respectively. IC_{50} values against *T. brucei rhodesiense* were found to be 4.33 and 15.92 μM, respectively.
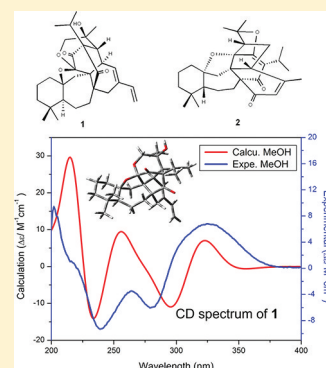
The genus *Salvia* comprises over 1000 species, being the largest genus of the Lamiaceae family. Several *Salvia* species, such as *S. officinalis*, *S. triloba*, *S. miltiorrhiza*, *S. hispanica*, and *S. sclarea*, are cultivated as medicinal plants, spices, and sources of essential oils for the perfume industry.[1] From a phytochemical viewpoint, the genus is characterized by the widespread occurrence of diterpenoids and triterpenoids. Rare classes of terpenoids in *Salvia* include sesterterpenoids[2,3] and some di- and triterpenoids with highly unusual carbon skeletons.[4−7]

In Iran, the genus *Salvia* consists of 58 annual and perennial species, 17 of which are endemic.[8] *S. hydrangea* DC. ex Benth. is a conspicuous aromatic plant that grows widely in Iran, Anatolia, and Transcaucasia.[8] Its common name in Persian is "Gol-e Arooneh", and the aerial parts of the plant have been used in Iranian folk medicine as anti-inflammatory, antispasmodic, carminative, and sedative compounds.[9] Infusions prepared from flowers serve as an anthelmintic and antileishmanial, especially in the Pars province of Iran.[10] Abietane-type diterpenoids have been reported from the roots of the plant. A moderate in vitro antiplasmodial effect of the flower extracts was attributed to a high content in pentacyclic triterpenes, mainly oleanolic acid.[11] *S. hydrangea* is taxonomically close to *S. bucharica*,[8] from which triterpenoids with novel carbon skeletons have been discovered.[6,7,12,13] This prompted

us to investigate *S. hydrangea*. As part of an ongoing screening for new antiparasitic natural products,[14−17] an *n*-hexane extract of *S. hydrangea* was found active against *P. falciparum* and *T. b. rhodesiense*, with IC_{50} values of 3.2 and 18 μg/mL, respectively.

Herein, we report the isolation and structure elucidation of two active compounds, salvadione C (**1**) and perovskone B (**2**), including the determination of their absolute configuration by chiroptical methods.
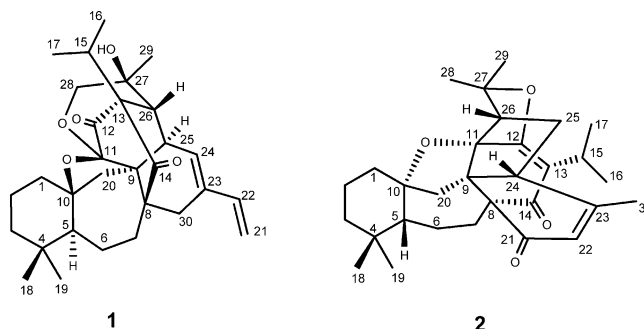
■ RESULTS AND DISCUSSION

Salvadione C (**1**) was isolated as a white, amorphous solid. The molecular formula of $C_{30}H_{40}O_5$ was deduced from HR-ESIMS at m/z 481.2949 $[M + H]^+$ (calcd 481.2965). The IR spectrum showed absorptions of hydroxy (3475 cm^{-1}), carbonyl (1713 cm^{-1}), and olefinic (1610 cm^{-1}) functionalities. The molecular formula accounted for 11 degrees of unsaturation. The ^{13}C NMR spectrum (Table 1) showed 30 carbon signals, which were resolved through a DEPT experiment into 5 methyl, 9 methylene, 6 methine, and 10 quaternary carbons. Thus, 39 hydrogen atoms could be accounted for, while the remaining atom was likely from a hydroxy group. ^{13}C NMR data (Table 1) showed signals for a monosubstituted double bond (δ_C 112.9, 138.5), a trisubstituted double bond (δ_C 131.2, 135.9), and two carbonyl carbons (δ_C 203.6, 209.1). Four carbon signals at δ_C 75.3 (CH$_2$), 76.8 (C), 92.0 (C), and 108.1 (C) indicated the presence of oxygen-bearing sp^3 carbons. The absence of other sp or sp^2 carbon signals implied that the structure of **1** contained seven rings, including two cyclic ethers, which is compatible with the molecular formula of $C_{30}H_{40}O_5$. The ^{1}H NMR spectrum (Table 1) showed resonances of three methyl singlets at δ_H 0.89, 1.04, and 1.31. Resonances of two additional methyl groups at δ_H 1.11 (d, J = 6.9 Hz) and 1.27 (d, J = 6.9 Hz), together with a signal at δ_H 2.29 (sept, J = 6.9 Hz) indicating the presence of an isopropyl moiety. Signals at δ_H 6.34 (dd, J = 17.5, 10.8 Hz), 5.23 (d, J = 17.5 Hz), and 5.05 (d, J = 10.8 Hz) were indicative of a vinyl group. Another olefinic methine signal appeared as a doublet at δ_H 5.68 (J = 6.1 Hz). Comparison of the NMR data of **1** with those of triterpenoids previously isolated from *S. bucharica* indicated that **1** likely had the same carbon skeleton as salvadiol.[7] Notable differences in the ^{13}C NMR spectra of **1** and salvadiol were observed, such as the resonance of an oxygen-bearing methylene carbon at δ_C 75.3 (C-28) replacing a methyl group at δ_C 29.8 in salvadiol. The chemical shifts of C-11, C-26, and C-27 in **1** were observed at δ_C 108.1, 54.9, and 76.8 and thus appeared downfield by ca. 8, 9, and 2 ppm, respectively. In contrast, C-25 in **1** was shifted upfield by ca. 15 ppm and appeared at δ_C 38.4. In the ^{1}H NMR spectrum, the methyl group at δ_H 1.24 (H-28) in salviadiol was replaced in **1** by an AB system (δ_H 3.85 and 3.74, 1H each, both d, J_{gem} = 14.7 Hz), reminiscent of an oxymethylene group attached to a quaternary sp^3 carbon. Along with the additional degree of unsaturation, these spectroscopic data suggested the presence of an oxepane ring through an oxygen bridge between C-11 and C-28. HMBC correlations (Figure 1) confirmed the carbon skeleton of **1**, and the heterocycle was corroborated by connectivities between H-28 (δ_H 3.85 and 3.74) and the C-11 and C-27 carbons (δ_C 108.1 and 76.8, respectively). Unambiguous assignment of ^{1}H and ^{13}C NMR data was achieved by a combination of HMQC, COSY, and HMBC experiments. The relative configuration of **1** was determined from a NOESY spectrum and NOE difference experiments (Figure 2) and was in accord with that of salvadiol, with exception of the newly formed heterocyclic ring.

The absolute configuration of **1** was established by measurement of the ECD spectrum and comparison with calculated ECD data. A conformational search based on the above established relative configuration revealed three conformers within a 3 kcal/mol energy window from the particular global minimum. These conformers were subjected to geometrical optimization and energy calculation using density functional theory (DFT) with the B3LYP function and 6-31G*

Table 1. ^{1}H and ^{13}C NMR Data of Compounds 1 and 2 (CDCl$_3$, 500 MHz for δ_H, 125 MHz for δ_C) [a]

	1			2	
position	δ_H (J, Hz)	δ_C	position	δ_H (J, Hz)	δ_C
1	1.49[b]	41.7	1 α	1.18[b]	42.9
	2.00, br d (12.6)		1 β	1.40[c]	
2	1.28[c]	20.1	2	1.45[c]	20.9
	1.45[b]			1.69[d]	
3	1.47[b]	42.4	3	1.63[d]	42.2
	1.92[d]			1.81[e]	
4		36.4	4		34.1
5	1.27[c]	50.5	5	0.92, dd (3.3, 11.5)	53.7
6	1.88[d]	21.2	6	1.37[c]	19.9
				1.50[c]	
7	1.20[c]	42.0	7 α	2.60, dd (8.5, 15.5)	34.7
	1.88[d]		7 β	1.77[e]	
8		53.0	8		60.2
9		51.3	9		54.6
10		92.0	10		90.1
11		108.1	11		96.3
12		209.1	12		170.2
13		71.1	13		122.0
14		203.6	14		195.5
15	2.29, sept (6.9)	27.3	15	3.11, sept (7.0)	24.6
16	1.27, d (6.9)[c]	20.3	16	1.15, d (7.0)[b]	20.8
17	1.11, d (6.9)	18.8	17	1.08, d (7.0)	20.0
18	0.89, s	33.1	18	0.90, s	32.3
19	1.04, s	22.1	19	0.84, s	22.1
20 α	1.86[d]	42.0	20 α	1.74, d (13.7)	55.8
20 β	1.20[c]		20 β	2.64, d (13.7)	
21	5.05, d (10.8)	112.9	21		196.0
	5.23, d (17.5)				
22	6.34, dd (10.8, 17.5)	138.5	22	5.88, s	125.8
23		135.9	23		156.5
24	5.68, d (6.1)	131.2	24	2.74, br t (10.0)	49.7
25	3.76[e]	38.4	25 α	1.37[c]	34.2
			25 β	2.31, dt (7.4, 12.5)	
26	2.22, s	54.9	26	2.46, dd (7.0, 12.5)	54.8
27		76.8	27		90.3
28 α	3.85, d (14.7)	75.3	28	1.43, s	24.8
28 β	3.74, d (14.7)[e]				
29	1.31, s	26.7	29	1.72, s	27.4
30 α	2.44, d (17.0)	28.1	30	1.79, s	21.9
30 β	2.60, d (17.0)				

[a] δ values were established from HMBC, COSY, and HMQC experiments. [b,c,d,e] Overlapping signals.

in the gas phase combined with calculation of vibrational modes to confirm these minima. No imaginary frequencies were found. Conformation analysis using relative free energies indicated the presence of the two conformers **1a** (98.2%) and **1b** (1.8%) (Figure 3) in the gas phase. Theoretical calculation of ECD spectra of conformers was performed by the time-dependent density function theory (TDDFT) method at B3LYP/6-31G* in MeOH using the SCRF (self-consistent reaction field)
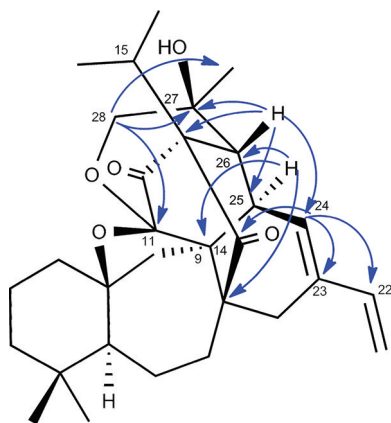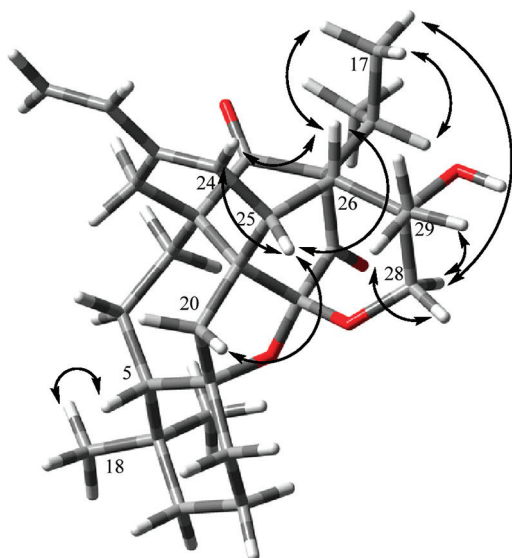
Figure 1. Key HMBC correlations of **1**.

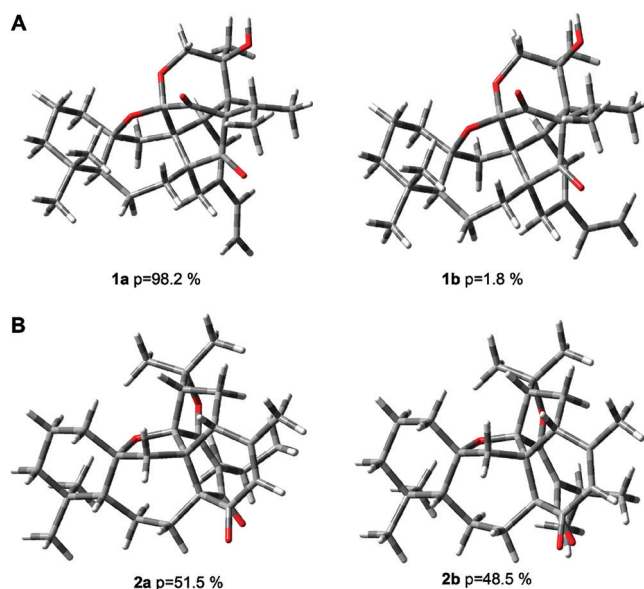**Figure 2.** Key NOE correlations of **1**.

Figure 3. Minimized conformers of **1** and **2** in the gas phase using DFT at the B3LYP/6-31G* level: (A) compound **1**, showing the two conformers **1a,b** within a 3 kcal/mol range from the global minimum, differing only with respect to the orientation of the vinyl group: (B) compound **2**, showing the two major conformers **2a,b**, which according to Boltzmann weighing accounted for the total population and only differed in the orientation of the isopropyl moiety.

method with the CPCM (conductor-like polarizable continuum) model. The overall pattern of calculated ECD spectra was in good agreement with the experimental data (Figure 4). In particular, two negative Cotton effects (CE) were observed at 239 and 279 nm, along with positive effects at 205 and 325 nm. Thus, the absolute configuration of **1** was established as 5S,8R,9S,10S,11R,13R,25R,26R,27S. Salvadione C (**1**) is a new natural product with the same carbon skeleton as salvadiol.

Perovskone B (**2**) was isolated as an amorphous colorless powder. A molecular formula of $C_{30}H_{40}O_4$ was established from its HR-ESIMS (m/z 465.3040 [M + H]$^+$, calcd 465.3005). The IR spectrum showed absorption bands at 1673 and 1110 cm^{-1} indicative of α,β-unsaturated carbonyl and ether functionalities, respectively. The molecular formula accounted for 11 degrees of unsaturation. The ^{13}C NMR spectrum showed 30 carbon signals which originated, according to the DEPT spectrum, from 7 methyl, 7 methylene, 5 methine, and 11 quaternary carbons (Table 1). ^{13}C NMR resonances at δ_C 195.5 (C), 122.0 (C), and 170.2 (C) indicated the presence of an α,β-unsaturated carbonyl containing a trisubstituted double bond. A second α,β-unsaturated carbonyl moiety was characterized by resonances at δ_C 196.0 (C), 125.8 (CH), and 156.5 (C). Three oxygen-bearing quaternary carbons appeared at δ_C 90.1, 90.3, and 96.3. In the DEPT spectrum, all 40 hydrogens could be

accounted for; therefore, the molecule did not contain free hydroxy groups. According to the degree of unsaturation, the structure of **2** was heptacyclic. In the ^{1}H NMR spectrum (Table 1), signals for a proton at δ_H 3.11 (sept, J = 7.0 Hz) and two methyl groups at δ_H 1.08 (d, J = 7.0 Hz) and 1.15 (d, J = 7.0 Hz) showed the presence of a vinylic isopropyl group. Five additional methyl groups appeared as singlets, among these a vinylic methyl resonating at δ_C 1.79. Only one olefinic proton was observed at δ_H 5.88 (s). The ^{1}H and ^{13}C NMR data strongly resembled those of perovskone, a triterpenoid from *Perovskia abrotanoides*,[18] indicating that the two compounds were structurally related. Inspection of the ^{13}C NMR spectra showed the lack of the C-21 methylene group in compound **2** but the presence of an additional carbonyl group (δ_C 196.0). This suggested that the methylene was replaced by a carbonyl group. Indeed, the signals of C-22 (δ_C 125.8) and C-23 (δ_C 156.5) were paramagnetically shifted ($\Delta\delta$ = +5.6 and +20.2 ppm, respectively) in comparison to those of perovskone. Also the resonances of neighboring H-23 (δ_H 5.88), H-30 (δ_H 1.79), and H-24 (δ_H 2.73) were shifted ($\Delta\delta$ = +0.56, +0.29, and +0.31 ppm, respectively). In comparison to perovskone, the C-14 resonance was shifted upfield by ca. 6 ppm and appeared at δ_C 195.5, while the signal of C-8 underwent a downfield shift of ca. 12 ppm (δ_C 60.2). These differences were in agreement with a 1,3-dicarbonyl moiety and suggested that the additional carbonyl group had to be located at C-21. HMBC correlations between H-22 (δ_H 5.88, s), H-30 (δ_H 1.79, s), H-7α (δ_H 2.60, dd), and H-7β (δ_H 1.77, m) and C-21, and between H-22 and C-8 (Figure 5) confirmed the location of the carbonyl group. Unambiguous assignments of NMR data were achieved by a combination of COSY, HMQC, and HMBC experiments, and the relative configuration was deduced from a NOESY spectrum (Figure 6). Diagnostic cross peaks between H-24, H-26, Me-30, H-25β, and H-20α were observed and confirmed their cofacial orientation. In addition, cross peaks between H-5,
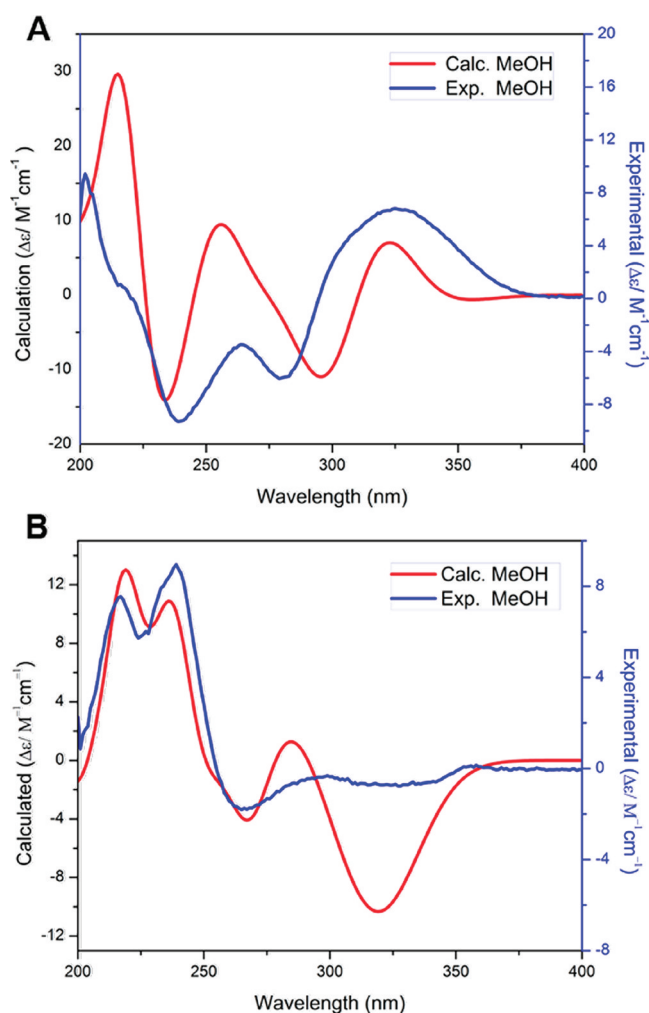
Figure 4. Experimental (blue) and calculated (red) ECD spectra of **1** (A) and **2** (B). Calculated spectra were obtained by using TDDFT at the B3LYP/6-31G* level in MeOH.
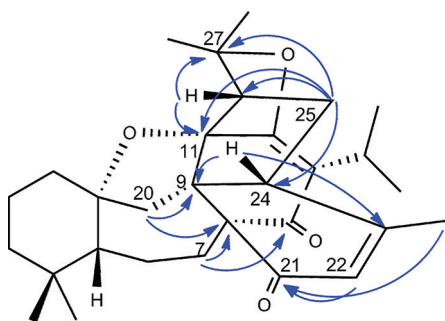

Figure 5. Key HMBC correlations of **2**.

H-20α and H-20β, and Me-18 corroborated the linkage of rings A and B and, hence, the same relative configuration is established as for perovskone.

The absolute configuration of **2** was established by comparison of experimental and calculated ECD spectra. The conformational analysis gave two conformers within a 3 kcal/mol energy window from the particular global minimum. They differed only in the orientation of the isopropyl group attached at C-13 (Figure 3). Conformers were subjected to geometrical optimization and energy calculation using the DFT-B3LYP 6-31G* theoretical level in the gas phase combined with
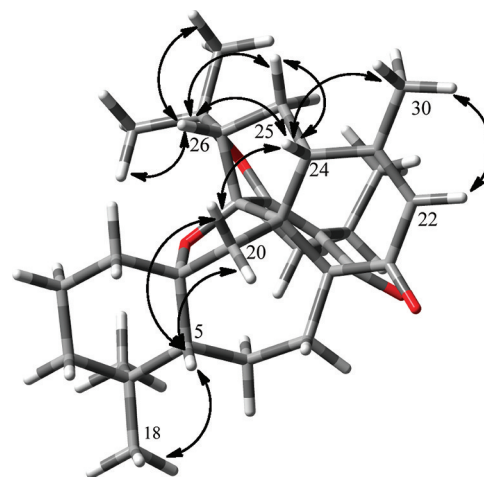

Figure 6. Key NOESY correlations of **2**.

calculation of vibrational modes to confirm these minima. No imaginary frequencies were found. Conformers **2a,b** contributed to 51.5 and 48.5% of the total, respectively. Calculation of the ECD spectra of the conformers was performed as described above. The weighted ECD spectrum in MeOH is shown in Figure 4. The overall patterns of experimental and calculated ECD spectra were in good agreement. Two positive Cotton effects (CE) at 215 and 238 nm along with two negative CEs around 266 nm and in the region 300−350 nm were also found in the calculated spectrum (Figure 4). Differences between calculated and experimental spectra presumably resulted from an overestimation of the UV absorbance in the calculations or may be due to minor differences between calculated and solution conformers.[19,20] Thus, the absolute configuration of compound **2** was established as 5*R*,8*R*,9*R*,10*R*,11*S*,12*R*,26*S*. This new natural product was named perovskone B.

Salvadione C (**1**) and perovskone B (**2**) were tested for in vitro antiplasmodial activity against *P. falciparum* K1 strain. The compounds showed fairly potent activity (IC$_{50}$ values of 1.43 and 0.18 μM, respectively) and good selectivity indices (SI) of 86.2 and 69.6 (Table 2). Against *T. brucei rhodesiense* STIB 900,

Table 2. Activity (IC$_{50}$ in μM with Standard Deviations (SD) and Selectivity Indices (SI)) against *Plasmodium falciparum* K1, *Trypanosoma brucei rhodesiense* STIB 900, and L6 Cells

compd	*P. falciparum*	SI	*T. b. rhodesiense*	SI[a]	L6 cells
1	1.43 ± 0.18	86.6	4.33 ± 0.24	43.2	>90.0
2	0.18 ± 0.002	69.6	15.92 ± 0.72	0.78	5.77 ± 0.41

[a]Selectivity index = IC$_{50}$ of the L6 cells (cytotoxicity) divided by IC$_{50}$ of the parasite.

they exhibited moderate potency (IC$_{50}$ values of 4.33 and 15.92 μM, respectively).

Salvadione C and perovskone B both possess rare carbon skeletons that can be rationalized by a Diels−Alder type addition of an acyclic monoterpene (myrcene for salvadione C and *trans*-β-ocimene for perovskone B) to a diterpenoid[7,18] (Figure 7). The carbon skeletons found in **1** and **2** have been reported once from *S. bucharica* (salvadiol) and *Perovskia abrotanoides* (perovskone), but the scaffold of **1** is new and
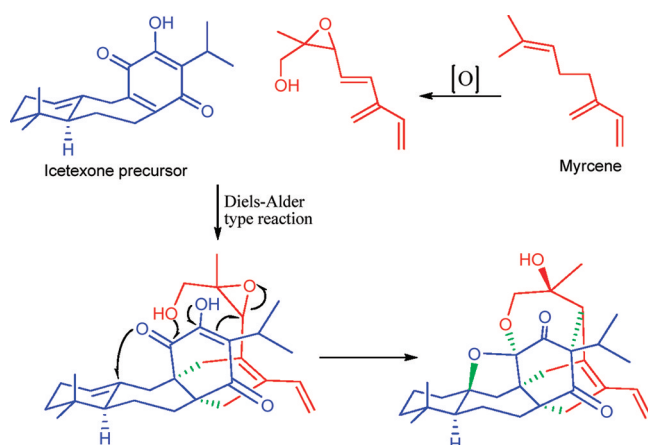
Figure 7. Proposed biogenetic pathway to salvadione C (**1**).

differs in the additional oxepane ring, which confers a high degree of rigidity to the molecule.

In conclusion, fractionation of the antiparasitic *n*-hexane extract of the aerial parts of *S. hydrangea* led to isolation of two new triterpenoids with rare skeletons. Perovskone B (**2**) showed in vitro antiplasmodial activity at submicromolar concentrations and good selectivity. Its druglike physicochemical properties warrant preliminary in vivo testing for exploration of the compound's potential for further investigation.

■ EXPERIMENTAL SECTION

General Experimental Procedures. Optical rotations were measured using a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Bruker Tensor 27 spectrometer. NMR spectra were recorded on Bruker DRX 500 and Avance III 500 spectrometers, using the residual CDCl$_3$ signal (δ_H 7.27/δ_C 77.0) as reference. The 2D NMR experiments (^{1}H−^{1}H COSY, HMQC, HMBC, NOESY) were performed using standard Bruker software. HR-ESIMS spectra were acquired on a Bruker micrOTOF ESI-MS system. ECD spectra of compounds **1** and **2** were recorded in MeOH (40 μg/mL) on an AVIV Model 62ADS CD spectrometer and analyzed with the AVIV 60DS V4.1 software. Silica gel (70−230 and 230−400 mesh, Merck) was used for column chromatography. Preparative TLC was performed on silica gel 60 GF$_{254}$ (Merck). Bands were detected on TLC under UV or by heating after spraying with 5% phosphomolybdic acid in EtOH.

Plant Material. The aerial parts of *S. hydrangea* DC. ex Benth. were collected from the Koohin region in Qazvin province, Iran, in May 2009 and identified by Dr. G. R. Amin. A voucher specimen (6719-TEH) has been deposited at the herbarium of the Faculty of Pharmacy, Tehran University of Medical Sciences.

Extraction and Isolation. The air-dried, powdered aerial parts of *S. hydrangea* (4.5 kg) were extracted successively with *n*-hexane (3 × 25 L), EtOAc (3 × 25 L), and MeOH (3 × 25 L) by maceration at room temperature. Extracts were concentrated in vacuo, to afford dark gummy residues of *n*-hexane (107 g), EtOAc (110 g), and MeOH (280 g) extracts. The *n*-hexane extract was separated on a silica gel column (230−400 mesh, 900 g) with a gradient of *n*-hexane−EtOAc (100/0 to 0/100) as eluent, followed by increasing concentrations of MeOH (up to 5%) in EtOAc. On the basis of TLC analysis, fractions with similar composition were pooled to yield 30 combined fractions. The less polar fractions contained waxes and carotenoids compounds and were not further investigated. Fraction 16 (4.5 g) was separated on a silica gel column with CH$_2$Cl$_2$-Me$_2$CO (98:2), to afford seven fractions (16a−16g). Fraction 16d was further purified by preparative TLC (CH$_2$Cl$_2$−Me$_2$CO (100/3.5)) to afford **1** (11 mg, R_f = 0.72). Fraction 17 (2.2 g) was separated on a silica gel column with CHCl$_3$−Me$_2$CO (97/3) as eluent into seven fractions (17a−17g). Fraction 17a was recrystallized from CHCl$_3$−MeOH to yield 5-hydroxy-4′,7-

dimethoxyflavone (6 mg). Fraction 18 (1.3 g) was separated over a silica gel column with CHCl$_3$−Me$_2$CO (97/3) as eluent, to afford oleanolic acid (25 mg). Fraction 19 (8.5 g) was triturated with Me$_2$CO and MeOH to give β-sitosterol (1 g). Fraction 21 (1.1 g) was separated on a silica gel column (CHCl$_3$−Me$_2$CO (97/3)) into 10 fractions (21a−21j). Fraction 21a was further purified by preparative TLC (CH$_2$Cl$_2$−Me$_2$CO (100/3.5)) to afford **2** (8 mg, R_f = 0.64). Fraction 22 (1.7 g) was triturated with Me$_2$CO, and the insoluble solid was recrystallized from Me$_2$CO to afford salvigenin (120 mg).

Salvadione C (1): white amorphous powder; $[\alpha]^{20}_D$ = +53° (*c* 1.0, CHCl$_3$); IR (KBr) ν_{max} 3475, 2940, 1713, 1610, 1460, 1375, 1225, 1137, 1064 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; CD (MeOH, *c* = 8.3 × 10^{-8} M, 1.0 cm path length) $[\theta]_{202}$ +31 128, $[\theta]_{216}$ +3592, $[\theta]_{229}$ +6677, $[\theta]_{239}$ −30 634, $[\theta]_{262}$ −12 305, $[\theta]_{279}$ −19 987, $[\theta]_{322}$ +22 008; positive HR-ESIMS *m/z* 481.2949 [M + H]$^+$ (calcd for C$_{30}$H$_{41}$O$_5$ 481.2965).

Perovskone B (2): white amorphous powder; $[\alpha]^{20}_D$ = +147° (*c* 0.9, CHCl$_3$); IR (KBr) ν_{max} 2935, 1673, 1455, 1372, 1233, 1110 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; CD (MeOH, *c* = 8.7 × 10^{-8} M, 1.0 cm path length): $[\theta]_{216}$ +24 711, $[\theta]_{239}$ +29 541, $[\theta]_{264}$ −5769, $[\theta]_{324}$ −2430; HR-ESIMS *m/z* 465.3040 [M + H]$^+$ (calcd for C$_{30}$H$_{41}$O$_4$ 465.3005).

Conformational Analysis, Geometrical Optimization, and ECD Calculation. Conformational analysis of **1** and **2** was performed with Schrödinger MacroModel 9.1 software using the OPLS 2005 (optimized potential for liquid simulations) force field in H$_2$O. Conformers occurring within a 3 kcal/mol energy window from the global minimum were chosen for geometrical optimization and energy calculation using density functional theory (DFT) with the B3LYP functional and the 6-31G* basis set in the gas phase with the Gaussian 03 program package.[21] Vibrational analysis was done at the same level to confirm minima. TD-DFT/B3LYP/6-31G*, in the gas phase and in MeOH using the SCRF (self-consistent reaction field) method with the CPCM (conductor-like polarizable continuum) model, was employed to calculate excitation energy (denoted by wavelength in nm) and rotatory strength *R* in dipole velocity (R_{vel}) and dipole length (R_{vel}) forms. ECD curves were calculated on the basis of rotatory strengths using a half-bandwidth of 0.18 eV with conformers of **1** and **2**. The spectra were combined after Boltzmann weighting according to their population contribution.

Antiplasmodial and Antitrypanosomal Assay. Tests of extracts and pure substances were done as previously described.[16] IC$_{50}$ values were calculated from sigmoidal concentration inhibition curves. Assays were run in two independent experiments in duplicate.

■ ASSOCIATED CONTENT

ⓈSupporting Information

Figures giving 1D and 2D NMR spectra for salvadione C (**1**) and perovskone B (**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +98 21 29902679. Fax: +98 21 22431783. E-mail: m_moridi@sbu.ac.ir.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Wu, C. Y.; Li, H. W. *Acta Bot. Yunn.* **1982**, *4*, 97−118.
(2) Moghaddam, F. M.; Farimani, M. M.; Seirafi, M.; Taheri, S.; Khavasi, H. R.; Sendker, J.; Proksch, P.; Wray, V.; Edrada, R. A. *J. Nat. Prod.* **2010**, *71*, 1601−1605.
(3) Rustaiyan, A.; Masoud, S.; Anaraki, M. T. *Nat. Prod. Commun.* **2007**, *10*, 1031−1042.

(4) Xu, G.; Hou, A. J.; Zheng, Y. T.; Zhao, Y.; Li, X. L.; Peng, L. Y.; Zhao, Q. S. *Org. Lett.* **2007**, *9*, 291−293.

(5) Aoyagi, Y.; Yamazaki, A.; Nakatsugawa, C.; Fukaya, H.; Takeya, K.; Kawauchi, S.; Izumi, H. *Org. Lett.* **2008**, *10*, 4429−4432.

(6) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Ali, Z.; Jassbi, A. R.; Abbas, M.; Clardy, J.; Lobkovsky, E.; Tareen, R. B.; Iqbal, M. Z. *J. Org. Chem.* **1999**, *64*, 8465−8467.

(7) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Choudhary, M. I.; Akhtar, F.; Ali, Z.; Iqbal, M. Z. *Tetrahedron Lett.* **1999**, *40*, 7561−7564.

(8) Rechinger, K. H. *Flora Iranica*; Akademische Druck- und Verlagsanstalt: Graz, Austria, 1987; pp 403−476.

(9) Iranian Herbal Pharmacopeia Committee. *Iranian Pharmacopeia*, 1st ed.; Ministry of Health and Medical Education: Tehran, Iran, 2002; Vol. *1*, pp 57−64.

(10) Amin, G. *Popular Medicinal Plants of Iran*; Ministry of Health Publications: Tehran, Iran, 1991; Vol. *1*, p 41.

(11) Sairafianpour, M.; Bahreininejad, B.; Witt, M.; Ziegler, H. L.; Jaroszewski, J. W.; Staerk, D. *Planta Med.* **2003**, *69*, 846−850.

(12) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Jassbi, A. R.; Ahmad, S.; Ali, Z. *Nat. Prod. Sci.* **2000**, *6*, 66−69.

(13) Ahmad, V. U.; Zahid, M.; Ali, M. S.; Ali, Z.; Alam, N.; Tareen, R. B.; Iqbal, M. Z. *Z. Naturforsch., B* **1999**, *54*, 415−418.

(14) Adams, M.; Plitzko, I.; Kaiser, M.; Brun, R.; Hamburger, M. *Phytochem. Lett.* **2009**, *2*, 159−162.

(15) Adams, M.; Zimmermann, S.; Kaiser, M.; Brun, R.; Hamburger, M. *Nat. Prod. Commun.* **2009**, *4*, 1377−1381.

(16) Mokoka, T. A.; Zimmermann, S.; Julianti, T.; Hata, Y.; Moodley, N.; Cal, M.; Adams, M.; Kaiser, M.; Brun, R.; Koorbanally, N.; Hamburger, M., *Planta Med.* DOI: 10.1055/s-0030-1270932.

(17) Ślusarczyk, S.; Zimmermann, S.; Kaiser, M.; Matkowski, A.; Hamburger, M.; Adams, M., *Planta Med.* DOI: 10.1055/s-0030-1270933.

(18) Parvez, A.; Choudhary, M. I.; Akhter, F.; Noorwala, M.; Mohammad, F. V.; Hasan, N. M.; Zamir, T.; Ahmad, V. U. *J. Org. Chem.* **1992**, *57*, 4339−4340.

(19) Kamel, H. N.; Ding, Y.; Li, X. C.; Ferreira, D.; Fronczek, F. R.; Slattery, M. *J. Nat. Prod.* **2009**, *72*, 900−905.

(20) Tayone, W. C.; Honma, M.; Kanamaru, S.; Noguchi, S.; Tanaka, K.; Nehira, T.; Hashimoto, M. *J. Nat. Prod.* **2011**, *74*, 425−429.

(21) Frisch, M. J.; Trucks, H. B.; Schlegel, H. B.; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision D.02*; Gaussian, Inc., Wallingford, CT, 2004.