ORGANIC LETTERS
2012
Vol. 14, No. 1
166–169

Hydrangenone, a New Isoprenoid with an Unprecedented Skeleton from *Salvia hydrangea*

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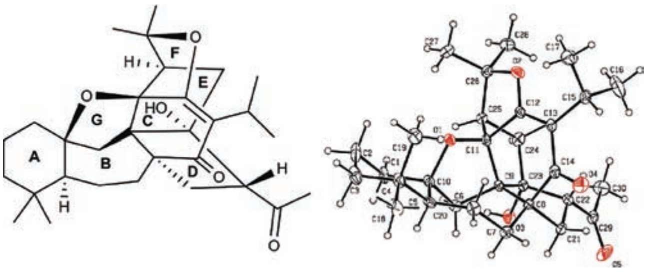
Received November 2, 2011



Hydrangenone, a new heptacyclic isoprenoid with a 6/7/6/5/5 membered carbon ring skeleton, was isolated from the aerial parts of *Salvia hydrangea.* The structure was established by extensive NMR spectroscopic methods. The relative and absolute configuration of 1 was assigned by NOESY and X-ray crystallographic analysis and by comparison of experimental and calculated electronic circular dichroism (ECD) spectra. Compound 1 showed in vitro antiplasmodial activity, with an IC_{50} value of 1.4 μM against *P. falciparum*. A plausible biosynthetic pathway of 1 was also proposed.

The genus *Salvia* is a rich source of structurally diverse terpenoids.[1] One of the most distinguishing features of *Salvia* species is their ability to synthesize isoprenoids with unusual scaffolds.[2] In a project directed at structurally interesting bioactive metabolites from Iranian Lamiaceae, we studied *Salvia hydrangea*. This species is popularly known in Persian as “Gol-e Arooneh”. It grows widely in Iran, Anatolia, and Transcaucasia,[3] and its flowers are used in popular Iranian medicine as an anthelmintic and antileishmanial.[4] We recently identified two new antiplasmodial isoprenoids, perovskone B and salvadione C, from this plant.[5] Further examination of the *n*-hexane extract of

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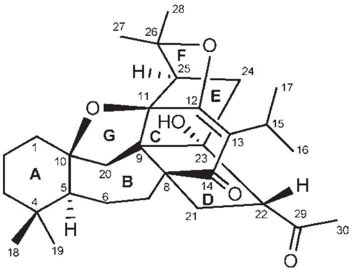
10.1021/ol202953b

S. hydrangea led to the isolation of hydrangenone (**1**), an isoprenoid with an unprecedented skeleton which is characterized by an unusual arrangement of 6/7/6/5/5 membered carbon rings fused with two tetrahydrofuran rings.

The aerial parts of *S. hydrangea* DC. ex Benth. were collected from the Koohin region in Qazvin province, Iran, in May 2009. The dried plant material (4.5 kg) was extracted with *n*-hexane (3 × 25 L). Fractionation of the *n*-hexane extract (107 g) by column chromatography on silica gel (*n*-hexane/EtOAc step gradient) afforded 30 fractions. Fraction 20 (1.1 g) was separated on a silica gel column [$CHCl_3$/Me_2CO (97:3)] into 10 fractions (20a−20j). Fraction 20b was further purified by preparative TLC on silica gel [CH_2Cl_2/Me_2CO (97:3)] to afford **1** (6 mg, R_f = 0.45).



1

Hydrangenone (**1**) was obtained as colorless needles ($CHCl_3$).[6] A molecular formula of $C_{30}H_{42}O_5$ was established from its HR-ESIMS (*m*/*z* 505.2902 $[M+Na]^+$, calcd 505.2924). The molecular formula accounted for 10 degrees of unsaturation. Absorption bands at 3440, 1707, and 1611 cm^{-1} in the IR spectrum implied the presence of OH, carbonyl, and olefinic functionalities, respectively. The ^{13}C NMR spectrum showed resonances of 30 carbons attributable by the DEPT spectrum to seven methyl, eight methylene, four methine, and 11 quaternary carbons (Table 1). Thus, 41 hydrogen atoms could be accounted for, while the remaining one was likely from a hydroxyl group. ^{13}C NMR resonances at δ_C 202.1 (C), 123.3 (C), and 172.5 (C) suggested the presence of an α,β-unsaturated ketone moiety containing a trisubstituted double bond and an oxygen substituent at the β-position. The resonance at δ_C 212.0 (C) was indicative of a second carbonyl group. Four carbon signals at δ_c 87.9 (C), 90.0 (C), 90.9 (C), and 93.6 (C) suggested the presence of oxygen bearing sp^3 carbons. The absence of other sp or sp^2 carbon signals and the 10 degrees of unsaturation implied that **1** contained seven rings, including two cyclic ethers. The ^1H NMR spectrum (Table 1) showed resonances of five methyl singlets at δ_H 0.82, 0.84, 1.35, 1.66, and 2.11. Resonances of two additional methyl groups at δ_H 1.13 (d, J = 7.1 Hz) and 1.20 (d, J = 7.1 Hz), together with a signal at δ_H 3.24 (sept, J = 7.1 Hz) indicated the presence of an isopropyl moiety.

Comparison of the NMR data of **1** with those of isoprenoids previously isolated from *S. hydrangea* suggested structural similarities with perovskone B.[5] Notable differences in the NMR spectra of **1** and perovskone B were observed, suggesting a five-membered ring D in **1** instead of a six-membered ring as in perovskone B. Hence, structure determination mainly focused on confirmation of ring D and of its connectivity to rings B, C, and E.

Unambiguous assignment of NMR data was achieved by a combination of COSY, HSQC, and HMBC experiments in $CDCl_3$ and C_6D_6. HMBC data (correlations from H-20β to C-9, C-8, and C-23, and from H-24β to C-23, C-9, and C-25) revealed the connectivity between $C_{20}-C_9-C_{23}-C_{24}-C_{25}$ (Figure 1). Correlations of H-7β and H-21β with C-8, C-9, and C-14, respectively, indicated that the tertiary carbon C-8 was a bridgehead between C-7, C-9, C-14, and C-21. HMBC correlations of H-22 with C-21, C-23, and C-29, and of H-21β with C-8, C-9, C-14, C-22, and C-23, respectively, confirmed the presence of a five-membered ring D. The acetyl group was located at C-22 according to the HMBC cross peaks of H-22 and H-21α with C-29, and also of H-30 with C-29 and C-22. HMBC correlations of H-25 with C-11, C-12, and C-26 confirmed the nature of ring E.

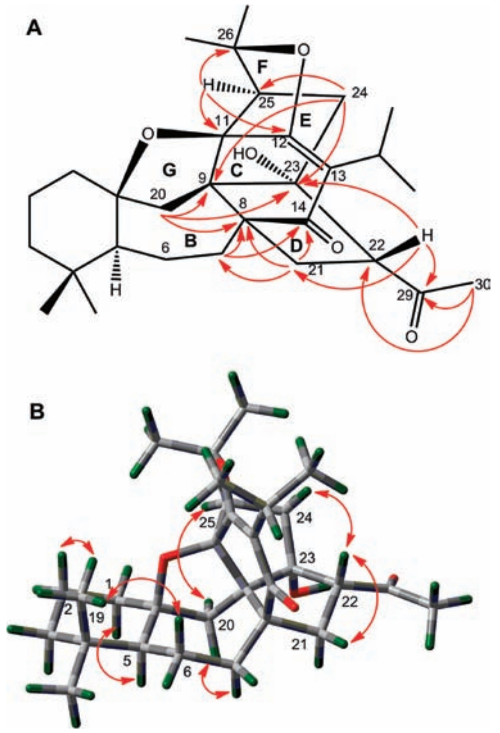


Figure 1. (A) Key HMBC and (B) NOESY correlations of **1**.

The relative configuration of **1** was deduced from a NOESY spectrum (Figure 1). NOESY correlations between H-5, H-1α, H-6α, and H-20α, as well as between Me-19, H-2β, and H-6β corroborated the linkage of rings A and B. Diagnostic cross peaks between H-22, H-21β, and H-24β were observed and confirmed their cofacial orientation. Equally, an NOESY cross-peak between

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[6] Hydrangenone (**1**): Colorless crystal; $[\alpha]^{20}_D$ +51.9 (*c* 0.27, $CHCl_3$); IR (KBr) ν_{max} 3440, 2937, 1707, 1611, 1457, 1370, 1230, 1110 cm^{-1}; for ^1H and ^{13}C NMR data, see Table 1; CD (MeOH, *c* = 1.0 × 10^{-6} M, 0.1 cm path length): $[\theta]_{202}$ +4797, $[\theta]_{243}$ −29336, $[\theta]_{266}$ −33773, $[\theta]_{318}$ + 27521; $C_{30}H_{42}O_5$ was established from its HR-ESIMS (*m*/*z* 505.2902 $[M+Na]^+$, calcd 505.2924).

Table 1. ^{1}H and ^{13}C NMR Data of Compound **1**[a]

	CDCl$_3$		Benzene-d_6	
Position	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1α	1.12[b]	42.7, t	1.17, dt (3.0, 13.5)	42.3, t
1β	1.37, br d (12.6)		1.39[b]	
2α	1.46[b]	20.1, t	1.48[b]	19.8, t
2β	1.60[b]		1.88, tq (3.5, 13.5)	
3α	1.64[b]	43.0, t	1.58[b]	42.5, t
3β	1.68[b]		1.70[b]	
4		34.5, s		33.9, s
5	1.01, m	53.6, d	0.88,[b] dd (4.5, 12.5)	53.0, d
6α	1.70[b]	22.8, t	1.65[b]	22.5, t
6β	1.33[b]		1.40[b]	
7α	1.75, br t (14.0)	44.1, t	1.67,[b] dd (11.5, 14.0)	44.1, t
7β	2.13,[b] dd (7.8, 14.5)		2.05,[b] dd (8.0, 14.0)	
8		66.3, s		66.1, s
9		55.4, s		54.8, s
10		90.0, s		89.3, s
11		93.6, s		93.1, s
12		172.5, s		170.9, s
13		123.3, s		122.8, s
14		202.1, s		200.6, s
15	3.24, sept (7.1)	24.6, d	3.70, sept (7.0)	24.7, d
16	1.20, d (7.1)	20.7, q	1.50, d (7.0)[b]	20.5, q
17	1.13,[b] d (7.1)	20.3, q	1.45,[b] d (7.0)	20.1, q
18	0.84, s	32.3, q	0.85,[b] s	31.8, q
19	0.82, s	21.6, q	1.01, s	21.3, q
20α	2.38, d (14.0)	43.1, t	2.08, d (14.0)	42.8, t
20β	2.18, d (14.0)		2.45, d (14.0)	
21α	2.00, dd (11.7, 13.8)	44.3, t	2.02,[b] dd (11.5, 14.0)	43.8, t
21β	2.63, dd (5.8, 11.7)		2.80, dd (5.0, 11.5)	
22	2.35[b]	62.7, d	2.42, dd (5.0, 14.0)	62.2, d
23		87.9, s		87.4, s
24α	1.47[b]	34.8, t	1.41[b]	34.5, t
24β	2.35[b]		2.62, dd (8.0, 12.5)	
25	2.77, dd (8.0, 11.5)	56.9, d	2.52, dd (8.0, 11.5)	56.5, d
26		90.9, s		89.7, s
27	1.35,[b] s	24.7, q	1.11, s	23.8, q
28	1.66,[b] s	27.4, q	1.57,[b] s	26.7, q
29		212.0, s		210.2, s
30	2.11,[b] s	30.8, q	1.72,[b] s	29.5, q
23-OH	3.86, s		6.36, s	

[a] Spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. [b] Overlapping signals.

H-25 and H-20β confirmed their location on the same face of the molecule. However, we were not able to establish the relative configuration at C-23. A single-crystal X-ray study of **1** clarified the α-orientation of OH-23 and unambiguously confirmed the structure of **1** (Figure 2).[7]

Electronic circular dichroism (ECD) is a powerful chiroptical tool for determination of the absolute configuration in natural products.[8] 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 X-ray relative configuration revealed seven 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 function theory (DFT) with the B3LYP function and 6-31G* in the gas phase combined with calculation of vibrational modes to confirm these minima. No imaginary frequencies were found. Conformational analysis using relative free energies indicated the presence of one predominant conformer (100%) in the gas phase. Theoretical calculation of ECD spectra of this conformer was performed by the time-dependent density function theory (TDDFT) method at B3LYP/6-31G* in MeOH using the SCRF (Self-consistent reaction field) 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 3). In particular, two negative Cotton effects (CE) were observed at 225, 279 nm, along with positive effect at 320 nm. Thus, the absolute configuration of **1** was established as 5*S*, 8*R*, 9*R*, 10*S*, 11*R*, 22*R*, 23*R*, 25*R*.

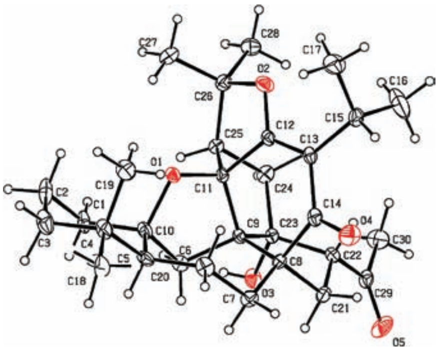


Figure 2. Single-crystal X-ray struture of **1**.

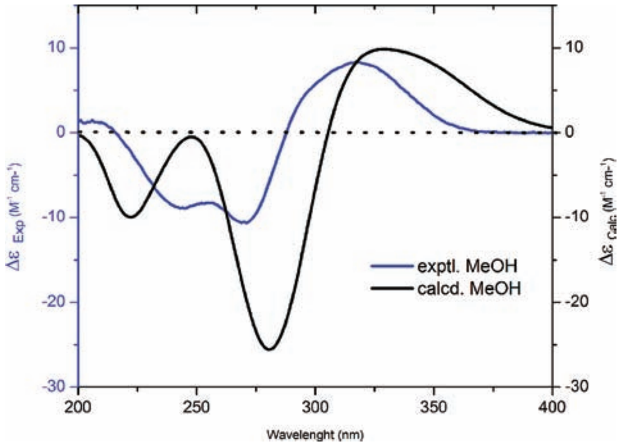
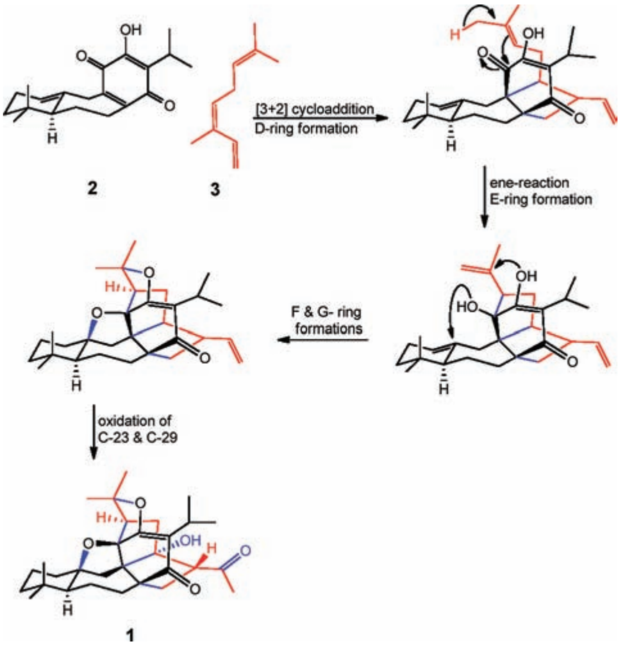


Figure 3. ECD spectra of **1**: experimental ECD (blue) and calculated ECD in MeOH(black).

Scheme 1. Plausible Biogenetic Pathway of **1**



Hydrangenone (**1**) was tested for in vitro antiplasmodial activity against the *Plasmodium falciparum* K1 strain. The compound showed a moderate activity and selectivity index (IC_{50} 1.4 μM, SI = 6, cytotoxicity in rat myoblast (L6) cells). The positive control, artesunate, had an IC_{50} of 0.1 μM.

Hydrangenone (**1**) represents the first example of a new 6/7/6/5/5 membered carbon ring framework. A plausible biogenetic pathway toward this new skeleton bears close similarities to the proposed formation of some other rare isoprenoids in *Salvia* species (Scheme 1).[2c−2d,5,9] However, while these previously described isoprenoids could be explained by a Diels−Alder reaction between a monoterpene and a diterpenoid, hydrangenone (**1**) is probably formed via a [3 + 2] cycloaddition type reaction between a putative icetexone precursor (**2**) and *trans*-β-ocimene (**3**) to assemble the five-membered ring D. An intramolecular ene-type reaction[10] would then form the key C(11)−C(25) bond of carbocyclic ring E, and successive formation of the two tetrahydrofuran rings would complete the heptacyclic scaffold. Finally, two oxidation steps on C-23 and C-29 would lead to hydrangenone (**1**). The complex fusion of rings B−G confers a high degree of rigidity to the molecule.

Acknowledgment. Financial support by the Shahid Beheshti University Research Council is gratefully acknowledged.

Supporting Information Available. Experimental procedure, 1D and 2D NMR spectra, and X-ray data (CIF file) of hydrangenone (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Crystallographic data for **1**: $C_{30}H_{42}O_5$, MW = 482.64, orthorhombic, space group $P2_12_12_1$, a = 8.3674(5) Å, b = 10.8816(10) Å, c = 28.719(2) Å, V = 2614.9(3) Å^3, Z = 4, Dc = 1.229 g/cm^3, crystal dimensions 0.40 × 0.17 × 0.16 mm^3 were used for measurements on an STOE-IPDSII with a graphite monochromator (ω-scans, $2\theta_{max}$ = 56.36°), Mo Kα radiation. The total number of reflections measured was 12011, of which 6886 were unique. Final indices: R_f = 0.0691, R_w = 0.1090 for reflections with $I > 2\sigma(I)$. The crystal structure (**1**) was solved by direct methods using SHELX-97 (Sheldrich, G. M. University of Gottingen: Gottingen, Germany, 1990) and expanded using difference Fourier techniques, refined by SHELX-97 (Sheldrich, G. M. 1997). Crystallographic data for the structure of **1** have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC851279). Copies of these data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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