Chinese Chemical Letters 31 (2020) 1248–1250

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

# Three unprecedented biphenyl derivatives bearing C6-C3 carbon skeleton from the bark of *Magnolia officinalis* var. *biloba*

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ARTICLE INFO

*Article history:*
Received 19 August 2019
Received in revised form 30 September 2019
Accepted 30 September 2019
Available online 4 October 2019

*Keywords:*
*Magnolia officinalis* var. *biloba*
Biphenyl derivative
Oligomers
C6-C3 subunits
Neuroprotective effect

ABSTRACT

(±)-Magoilgomer A [(±)-**1**] and magoilgomer B (**2**) were identified from the bark of *Magnolia officinalis* var. *biloba*. (+)-**1** and (−)-**1** were a pair of novel biphenyl derivatives featuring three C6-C3 subunits. **2** was an unprecedented adduct containing magnolol and honokiol. These three oligomers possessed new parallel mode which should be biosynthesized from the coupling of three or four C6-C3 subunits. The structures of (±)-**1** and **2** were elucidated based on the spectroscopic data analyses and electronic circular dichroism (ECD) calculations. **2** exhibited neuroprotective effects of oxygen glucose deprivation-induced SK-N-SH cell injury.



*Magnolia officinalis* Rehd. et Wils var. *biloba* (*M. officinalis* var. *biloba*), one kind of plant of *Magnolia* genus, distributed in southern China [1,2]. It has been reported that the main secondary metabolites of *M. officinalis* var. *biloba* [3–5] are neolignanes, phenylethanoid glycosides, alkaloids and meroterpenoids, those compounds showed different biological activities [4–9] including antitumor, PTP1B inhibitory activity, free radical scavenging activity, and neuroprotective activity. The bark of *M. officinalis* var. *biloba*, known as 'Hou Pu' in Chinese, has been used as an important traditional Chinese medicine for the treatment and prevent diseases for centuries in China. This is a part of our continuous endeavor to search for more bioactive metabolites from traditional Chinese medicine. Our group had already reported that novel meroterpenoids with remarkable bioactivity were isolated from the bark of *M. officinalis* var. *biloba* [5]. In our continuous work, three novel compounds (±)-**1** and **2** (Fig. 1) were isolated from the 95% ethanolic extract of the bark of *M. officinalis* var. *biloba*, (±)-**1** possessed three C6-C3 subunits with new parallel approach, **2** was an unprecedented biphenyl derivative with new connection mode between magnolol and honokiol. Hence, the detailed information including isolation, absolute configuration elucidation and bioactivity evaluation of (±)-**1** and **2** was reported.

Compound **1** was obtained as colorless oil, HRESI-MS of **1** showed pseudomolecule ion peak at *m/z* 421.1764 $[M+Na]^+$ revealing a molecular formula of $C_{27}H_{26}O_3$ (calcd. for $C_{27}H_{26}O_3Na$, 421.1774), which suggested 15 degrees of unsaturation. The $^1H$ NMR (Table 1) showed a 1,3,4-trisubstituted benzene ring [$\delta_H$ 6.93 (brs, 1H, H-2′), 6.84 (d, 1H, $J$ = 8.4 Hz, H-5′) and 6.97 (dd, 1H, $J$ = 1.8, 8.4 Hz, H-6′)], a set of 1,4-disubstitued phenyl proton signals at $\delta_H$ 6.63 (d, 2H, $J$ = 8.4 Hz, H-3″, H-5″), 6.92 (d, 2H, $J$ = 8.4 Hz, H-2″, H-6″), and a 1,3,4,5-tetrasubstituted benzene ring proton signals at $\delta_H$ 6.88 (d, 1H, $J$ = 1.8 Hz, H-2), 6.81 (d, 1H, $J$ = 1.8 Hz, H-6), two methylene $\delta_H$ 3.26 (d, 2H, $J$ = 6.6 Hz, H-7), 3.25 (d, 2H, $J$ = 6.0 Hz, H-7′) and 5.03 (d, 1H, $J$ = 7.8 Hz, H-7″). With the help of $^1H$, HSQC, HMBC, and $^1H$-$^1H$ COSY NMR spectra (Figs. S6, S8 – S10 in Supporting information), the $^{13}C$ NMR spectrum gave 18 aromatic carbon signals, six olefin carbons and three $sp^3$ carbon signals.

Along with the $^1H$-$^1H$ COSY cross-peaks (Fig. 2) of H-7/H-8/H-9, H-7′/H-8′/H-9′ and H-7″/H-8″/H-9″, the key HMBC correlations from H-7 to C-6, H-7′ to C-6′, from H-7″ to C-1″ suggested the presence of three C6-C3 subunits (C-1–C-9, C-1′–C-9′ and C-1″–C-9″) [10,11]. The HMBC correlation of H-3′/C-2 indicated two allylbenzene moieties (C-1–C-9 and C-1′–C-9′) conjugated through a carbon-carbon bond between C-3 and C-3′, the HMBC correlations of H-7″/C-4, H-6/C-7″ revealed fragment of C-1″–C-9″ attached at C-5 by a carbon-carbon bond between C-7″ and C-5. Thus, the structure of **1** was established.

The lack of optical activity and no Cotton effects in the ECD spectrum of **1** indicated that **1** was a racemic mixture. Consequently, an AD-H column yielded (+)-**1** ($[\alpha]_D^{20}$ = + 35.8 (*c* 0.10, $CHCl_3$)) and (−)-**1** ($[\alpha]_D^{20}$ = − 36.9 (*c* 0.10, $CHCl_3$)), in an approximate

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https://doi.org/10.1016/j.cclet.2019.09.058
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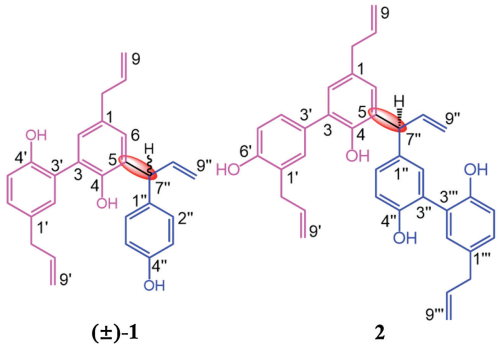
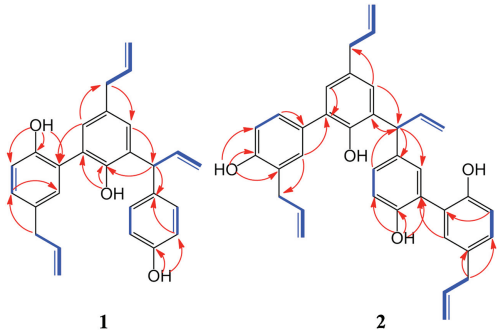


(±)-1 2

**Fig. 1.** Chemical structures of compounds (±)-**1** and **2**.



1 2

**Fig. 2.** Key $^{1}$H-$^{1}$H COSY (▬) and HMBC (◠) correlations of **1** and **2**.

**Table 1**
$^{1}$H (600 MHz) and $^{13}$C NMR (150 MHz) data of compounds **1** and **2** in DMSO-$d_6$.[a]

| Position | **1** | | **2** | |
|---|---|---|---|---|
| | $\delta_H$ ($J$ in Hz) | $\delta_c$ | $\delta_H$ ($J$ in Hz) | $\delta_c$ |
| 1 | | 131.2 | | 130.3 |
| 2 | 6.88, d (1.8) | 128.2 | 6.82, brs | 129.9 |
| 3 | | 128.9 | | 126.2 |
| 4 | | 149.9 | | 149.9 |
| 5 | | 127.5 | | 127.8 |
| 6 | 6.81, d (1.8) | 129.4 | 6.93, brs | 127.7 |
| 7 | 3.26, d (6.6) | 39.1 | 3.27, d (6.6) | 39.3 |
| 8 | 5.87, m | 138.6 | 5.91, m | 137.6 |
| 9 | 5.05, m | 115.8 | 5.01, m | 115.8 |
| 1′ | | 131.0 | | 125.6 |
| 2′ | 6.93, brs | 132.1 | 7.12, brs | 130.8 |
| 3′ | | 126.2 | | 128.2 |
| 4′ | | 152.1 | 6.85, d (8.4) | 128.2 |
| 5′ | 6.84, d (8.4) | 116.1 | 6.75, d (8.4) | 114.8 |
| 6′ | 6.97, dd (1.8, 8.4) | 128.9 | | 154.1 |
| 7′ | 3.25, d (6.0) | 39.4 | 3.27, d (6.6) | 34.3 |
| 8′ | 5.91, m | 138.6 | 5.90, m | 138.6 |
| 9′ | 4.97, m | 115.6 | 4.99, m | 115.8 |
| 1″ | | 133.7 | | 134.2 |
| 2″ | 6.92, d (8.4) | 129.5 | 6.93, brs | 132.1 |
| 3″ | 6.63, d (8.4) | 115.3 | | 127.7 |
| 4″ | | 155.8 | | 152.6 |
| 5″ | 6.63, d (8.4) | 115.3 | 6.85, d (7.8) | 116.0 |
| 6″ | 6.92, d (8.4) | 129.5 | 6.75, brd (7.8) | 129.5 |
| 7″ | 5.03, d (7.8) | 47.1 | 5.05, d (7.2) | 47.1 |
| 8″ | 6.28, m | 141.8 | 6.31, m | 141.8 |
| 9″ | Ha 4.88, dt (1.2, 17.4)<br>Hb 5.10, dt (1.2, 10.2) | 115.6 | Ha, 4.90, brd (16.8)<br>Hb, 5.11, brd (10.2) | 115.7 |
| 1‴ | | | | 131.2 |
| 2‴ | | | 6.93, brs | 132.0 |
| 3‴ | | | | 130.9 |
| 4‴ | | | | 152.2 |
| 5‴ | | | 6.84, d (8.4) | 116.1 |
| 6‴ | | | 6.97, brd (8.4) | 128.9 |
| 7‴ | | | 3.26, d (6.6) | 39.1 |
| 8‴ | | | 5.91, m | 138.7 |
| 9‴ | | | 4.94, m | 115.6 |
| 4-OH | 7.71, s | | | |
| 4′-OH | 10.03, s | | | |
| 6′-OH | | | 9.29, s | |
| 4″-OH | 9.14, s | | 9.11, s | |

[a]NMR data of **1** and **2** were recorded on Bruker AV-600 spectrometer, the assignments were based on 2D NMR spectra.

ratio of 1:1 by chiral-phase HPLC (Fig. 3). The experimental ECD (Fig. 4) of (+)-**1** and (−)-**1** well match with the theoretically calculated ECD of 7″*R*-**1** and 7″*S*-**1**, respectively [12,13]. Thus, the absolute structures of (+)-**1** and (−)-**1** were defined as 7″*R*-**1** and 7″*S*-**1**, respectively.

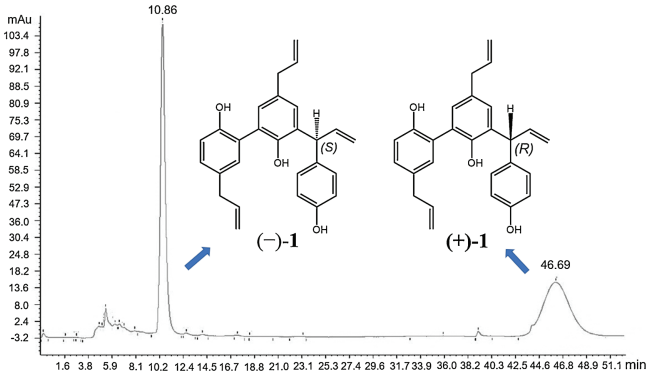



**Fig. 3.** HPLC separation chromatogram of (±)-**1** on the chiral AD-H column.

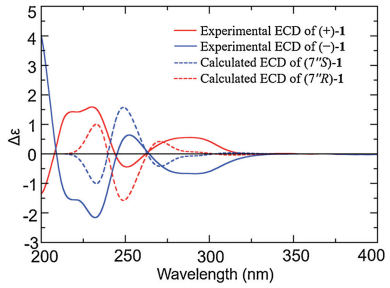



**Fig. 4.** Experimental ECD spectra of (+)-**1** and (−)-**1** and calculated ECD spectra of (7″*R*)-**1** and (7″*S*)-**1**.

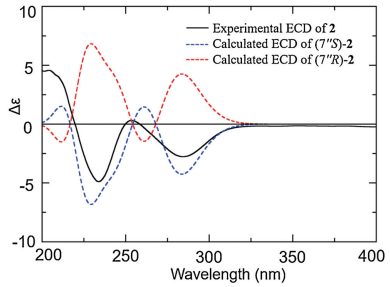



**Fig. 5.** Experimental ECD spectrum of **2** and calculated ECD spectra of (7″*S*)-**2** and (7″*R*)-**2**.

Compound **2**, colorless oil, $[\alpha]_D^{20}$ = − 45.2 (*c* 0.10, $CHCl_3$), the molecular formula, $C_{36}H_{34}O_4$, was deduced by the ion peak (−)-HRESI-MS *m/z* 529.2385 $[M-H]^-$, (calcd. for $C_{36}H_{33}O_4$, 529.2384), revealing 20 degrees of unsaturation. In combination

**Table 2**
Neuroprotective effects of (±)-**1** and **2** on ODG-induced injury of SK-N-SH cells (10 μmol/L).

| No. | Mean ± SD | *P* value | Survival rate |
|---|---|---|---|
| Control | 3.225 ± 0.06 | | |
| Model | 1.619 ± 0.02*** | 0.0000 | 50.2% |
| PHPB | 1.736 ± 0.01### | 0.0000 | 53.8% |
| (+)-**1** | 1.442 ± 0.04## | 0.0020 | 44.7% |
| (−)-**1** | 1.441 ± 0.04## | 0.0020 | 44.7% |
| **2** | 1.884 ± 0.06 | 0.3314 | 58.4% |

***$P < 0.001$ *vs.* Control; ##$P < 0.01$ *vs.* Model, ###$P < 0.001$ *vs.* Model.

**Table 3**
Neuroprotective effects of (±)-**1** and **2** on glutamic acid-induced injury of SK-N-SH cells (10 μmol/L).

| No. | Mean ± SD | *P* value | Survival rate |
|---|---|---|---|
| Control | 1.754 ± 0.03 | | |
| Model | 0.872 ± 0.11*** | 0.0002 | 49.7% |
| PHPB | 0.949 ± 0.06 | 0.3455 | 54.1% |
| (+)-**1** | 0.871 ± 0.05 | 0.6130 | 49.7% |
| (−)-**1** | 0.879 ± 0.01 | 0.6780 | 50.2% |
| **2** | 0.907 ± 0.11 | 0.7243 | 51.7% |

***$P < 0.001$ *vs.* Control.

with the 1D and 2D NMR data (Figs. S14–S18 in Supporting information), the $^{13}$C NMR (Table 1) gave four sp$^3$ carbon signals at 39.3 (C-7), 34.3 (C-7′), 47.1 (C-7″), and 39.1 (C-7‴), three double carbon signals and 24 aromatic carbon signals [including four oxygen-bearing carbons $\delta_C$ 149.9 (C-4), 154.1 (C-6′), 152.6 (C-4″), and 152.2 (C-4‴)]. Analysis of its $^1$H and $^{13}$C NMR (Table 1) data and comparison with $^1$H and $^{13}$C NMR data of **1** suggested **2** containing four C6-C3 subunits.

The planer structure of **2** was constructed basis on 2D NMR data of **2** (Fig. 2), the HMBC correlations from H-6 to C-7 and C-4, H-2′ to C-7′, from OH-6′ to C-1′, C-5′, and C-6′, the $^1$H-$^1$H COSY peaks of H-7/H-8/H-9 and H-7′/H-8′/H-9′ defined two C6-C3 fragments (C-1–C-9 and C-1′–C-9′). The key HMBC correlations from H-2′ to C-3 revealed a bond-bond between C-3 and C-3′ connected the two subunits (C-1–C-9 and C-1′–C-9′) which was described as honokiol [10]. Likewise, along with the $^1$H-$^1$H COSY cross-peaks of H-7″/H-8″/H-9″, H-7‴/H-8‴/H-9‴, the HMBC correlations from H-7″ to C-1″, from OH-4″ to C-3″, C-4″, and C-5″, from H-8‴ to C-1‴, from H-2‴ to C-3‴ gave a magnolol fragment (C-1″–C-9″ and C-1‴–C-9‴) [10], the HMBC correlations from H-7″ to C-5, from H-6 to C-7″ confirmed C-5 of honokiol linked to C-7″ of magnolol fragment. Hence, the structure of **2**, an adduct containing magnolol and honokiol, was established.

The ECD spectrum of **2** (Fig. 5) showed negative Cotton effects in 230 nm and 280 nm, which was similar to the ECD curve of (−)-**1**, indicating that **2** possessed the same absolute configuration as (−)-**1**, moreover, the experimental ECD of **2** well match with the theoretically calculated ECD of 7″*S*-**2**. Thus, the absolute structure of **2** was defined as 7″*S*-**2**.

In this work, the isolated compounds (±)-**1** and **2** were evaluated for their bioactivity. At a concentration of 10 μmol/L, the neuroprotective effects experiment of (±)-**1** and **2** against oxygen glucose deprivation (OGD) and glutamic acid-induced SK-N-SH cell injury [14] indicated that (±)-**1** and **2** exhibited weak neuroprotective effects (Tables 2 and 3). In particular **2** increased the OGD-induced SK-N-SH cell injury from 50.2% to 58.4% which more powerful than positive control drug potassium 2-(1-hydroxypentyl)-benzoate (PHPB, 53.8%).

In summary, we reported (±)-magoilgomer A [(±)-**1**] and magoilgomer B (**2**) isolated from the 95% ethanolic extract of the bark of *M. officinalis* var. *biloba*, (±)-**1** possessed three C6-C3 subunits with new parallel approach, **2** was an unprecedented biphenyl derivative containing magnolol fragment and honokiol fragment. The neuroprotective effects of (±)-**1** and **2** were evaluated. **2** exhibited weak neuroprotective effect of ODG-induced SK-N-SH cell injury.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

This work was supported by the National Natural Science Foundation of China (No. 81730093), the CAMS Innovation Fund for Medical Sciences (No. 2017-I2M-3-010), In Dependent Project of State Key Laboratory of Bioactive Substance and Function of Natural Medicines (No. GTZA201803).

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.058.

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