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New dibenzocyclooctadiene lignan from *Schisandra chinensis* (Turcz.) Baill. fruits

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Abstract

Repeated column chromatography using Sephadex LH-20, silica gel (SiO_2), and octadecyl SiO_2 (ODS) as well as preparative HPLC column chromatography led to isolation of a new dibenzocyclooctadiene lignan along with four known ones, gomisin L2 (**1**), L1 (**2**), M1 (**3**), and M2 (**4**). Their chemical structures were fixed based on MS, IR, and NMR data analyses. In addition, the stereochemistry of atropisomers, the absolute configuration of the axial chirality in a biphenyl structure, was confirmed by a CD experiment. The new lignan was named gomisin M3 (**5**).

Keywords: Atropisomer, Axial chirality, Circular dichroism, Dibenzocyclooctadiene lignan, Gomisin M3, *Schisandra chinensis*

Introduction

Schisandra chinensis (Turcz.) Baill. is a deciduous vine wood originated from eastern Asia and is distributed in Korea, China, and Japan [1]. The fruits have been utilized for thousands years as a superior drug for therapy of persistent dyspnoea and cough, frequent urination, severe sweating, shortness of breath, hepatitis, diabetes, and wasting-thirsting disease [2]. In addition, the extracts or metabolites from the plant were reported to have various biological efficacies such as anti-tussive, astringent, tonics [3], antioxidant [4], anti-inflammatory [5], anti-aging [6], anti-tumor [7], and inhibition of platelet aggregation [8] effects. The fruit of *S. chinensis* contains lignans, organic acids, monoterpenes, sesquiterpenes, and triterpenoids as major constituents [9]. It has been reported that the pharmacological functions are mostly attributed to lignans, especially the dibenzocyclooctadiene-type lignans [10]. The lignan content of *Schisandra* fruit has been reported to be high, varying between 7.2 and 19.2% [11, 12]. Lignans are typical component compounds of the *Schisandra* genus plants; among them, the dibenzocyclooctadiene type is the most popular. Upwards of 150 dibenzocyclooctadiene lignans have been reported from Schisandraceae plants [13]. Dibenzocyclooctadiene lignans are categorized further into two series based on stereostructure, *S*- and *R*-biphenyl configuration, because they have biaryl bonds at C-6 and C-6′, and the biphenyl chromophore has no rotational freedom. Therefore, dibenzocyclooctadiene lignans occurred in nature exhibit *S* and *R* configurations because of a chiral biphenyl axis in the structure, resulting to atropisomerism, which is derived from rotation hindrance of single bond. The steric repression barrier to rotation is high enough to permit isolation of the conformers, atropisomers. Enantiomeric compounds can behave differently based on pharmacokinetic setting [14]. One study reported that 8*S*,8′*R*-schisandrin B more potently enhanced cellular glutathione and protection against oxidative injury compared to other diastereomers [15]. In this study, the authors isolated a new dibenzocyclooctadiene-type lignan along with four known ones from the *Schisandra chinensis* fruits and determined the chemical structure, including absolute configuration of the atropisomers,

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through several spectroscopic analyses including a circular dichroism (CD) experiment.

Materials and methods

General experimental procedures

The materials and instruments used in this study were same as previously used ones [16]. And ECD spectra were obtained by Jasco spectropolarimeter J-715, Scan range 200–400 nm, cell length 0.1 cm.

Plant materials

The Department of Herbal Crop Research, RDA, Eumseong, Korea, supplied *S. chinensis* fruits in 2019, as verified by Dr. Jin Tae Jeong, Department of Herbal Crop Research, RDA. A guaranteed sample (KHU-NPCL-1935) is saved in NPCL Laboratory, KyungHee University, Korea.

Extraction and isolation

S. chinensis fruits (5.4 kg, dry weight) were immersed in 70% ethanol (EtOH, 54 L × 3) at 24 °C for one day, followed by filtration and vacuum concentration to yield a brownish residue (1.3 kg). The concentrates were solvent-fractionated using H_2O (4.2 L), EtOAc (4.2 L × 3), and *n*-BuOH (3.4 L × 3) to give the H_2O (SCW, 723 g), EtOAc (SCE, 329 g), and *n*-BuOH (SCB, 247 g) fractions. The column chromatography (CC) for SCE (300 g) was carried out using SiO_2 resin (Fig. 1). The eluate was analyzed through a TLC experiment to yield 12 fractions (SCE-1 – SCE-12). Open CC of fractions 5 (SCE-5) and 7 (SCE-7) using Sephadex LH-20, ODS, and SiO_2 as well as prep-LC using an ODS column (Fig. 1) provided purified lignans, compounds **1**–**5**.

Gomisin L2 (**1**): white powder; TLC (SiO_2) *Rf* 0.38, $CHCl_3$-EtOAc (10:1), (ODS) *Rf* 0.45, acetone–H_2O (3:1); $[\alpha]$D–63.9 (c 0.25, CH_3OH); IR (NaCl) ν_{max} 3435, 2930, 1660 cm^{-1};^{1}H and ^{13}C NMR spectra ($CDCl_3$): Tables 1 and 2. EI-MS: *m/z* 386 $[M]^+$, 354 $[M - CH_3OH]^+$

Gomisin L1 (**2**): white powder; TLC (SiO_2) *Rf* 0.57, $CHCl_3$-EtOAc (10:1), (ODS) *Rf* 0.50, acetone–H_2O (3:1); HPLC tR 22.10 min on YMC Pack ODS-AQ-HG 250 × 20 mm, ACN-H2O (42:58), Flow rate: 15 mL/min; $[\alpha]$D–59.6 (c 0.10, CH_3OH); ECD ($CHCl_3$) 243 ($\Delta\varepsilon$ –1.93), IR (NaCl) ν_{max} 3400, 2924, 1614, 1459 cm^{-1};^{1}H and^{13}C NMR spectra ($CDCl_3$): Tables 1 and 2; positive LR-ESI-MS: *m/z* 387 $[M + H]^+$, 409 $[M + Na]^+$, 795 $[2M + Na]^+$; positive HR-ESI-MS: *m/z* 387.1788 $[M + H]^+$ (calcd for $C_{22}H_{27}O_6^+$, 387.1802).

Gomisin M1 (**3**): white powder; TLC (SiO_2) *Rf* 0.50, $CHCl_3$-EtOAc (10:1), (ODS) *Rf* 0.47, acetone–H_2O (3:1); HPLC t_R 23.70 min on YMC Pack ODS-AQ-HG 250 × 20 mm, ACN-H2O (42:58), Flow rate: 15 mL/min; $[\alpha]$D–14.9 (c 0.30, CH_3OH); IR (NaCl) ν_{max} 3447, 2918, 1614 cm^{-1};^{1}H and^{13}C NMR spectra ($CDCl_3$): Tables 1 and 2; EI-MS: *m/z* 386 $[M]^+$, 370 $[M - CH_4]^+$, 354 $[M - CH_3OH]^+$.

Gomisin M2 (**4**): white powder; TLC (SiO_2) *Rf* 0.55, $CHCl_3$-EtOAc (10:1), (ODS) *Rf* 0.35, acetone–H_2O (3:1); $[\alpha]$D 21.9 (c 0.20, CH_3OH); IR (NaCl) ν_{max} 3321, 2915,1651 cm^{-1};^{1}H and^{13}C NMR spectra ($CDCl_3$): Tables 1 and 2; EI-MS: *m/z* 386 $[M]^+$, 370 $[M - CH_4]^+$, 354 $[M - CH_3OH]^+$.

Gomisin M3 (**5**): white powder; TLC (SiO_2) *Rf* 0.45, CHCl3-EtOAc (10:1), (ODS) *Rf* 0.62, acetone–H_2O (4:1); HPLC t_R 50.20 min on YMC Pack ODS-AQ-HG 250 × 20 mm, ACN-H_2O (42:58), Flow rate: 15 mL/min; $[\alpha]_D$ 16.7 (*c* 0.05, CH_3OH); ECD ($CHCl_3$) 225 ($\Delta\varepsilon$ -25.0), 254 ($\Delta\varepsilon$ 12.3); IR (NaCl) ν_{max} 3448, 2922, 1615, 1460 cm^{-1}; ^{1}H and ^{13}C NMR spectra ($CDCl_3$): Tables 1 and 2; positive LR-ESI–MS: *m/z* 387 $[M + H]^+$, 409 [M

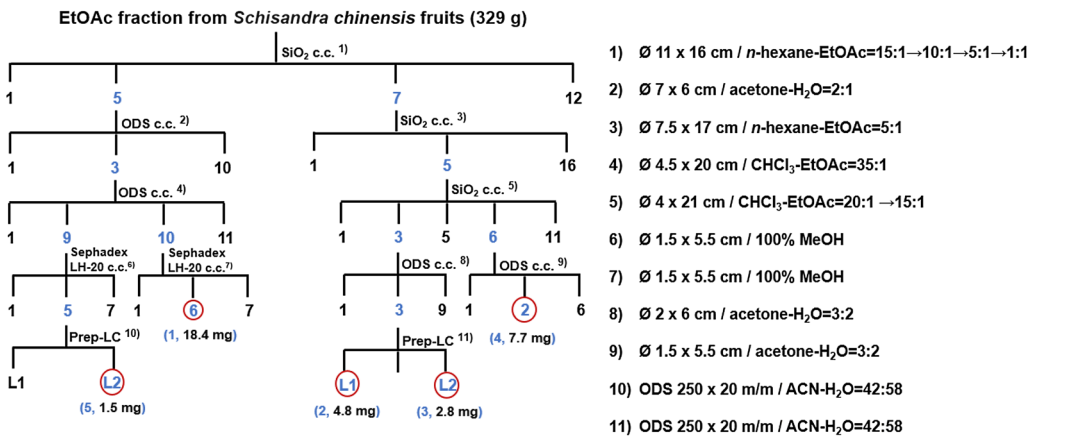

Fig. 1 Isolation of dibenzocyclooctadiene lignans from *Schisandra chinensis* fruits

Table 1 ^{1}H NMR data of dibenzocyclooctadiene lignans from *Schisandra chinensis* fruits (600 MHz, $CDCl_3$, δ_H, coupling pattern, *J* in Hz)

No of H	L2 (1)	L1 (2)	M1 (3)	M2 (4)	M3 (5)
4	6.47, s	6.51, s	6.51, s	6.44, s	6.48, s
6	2.52, dd, 13.8, 7.2 2.44, dd, 13.8, 1.2	2.56, dd, 13.8, 7.2 2.43, dd, 13.8, 1.2	2.24, dd, 13.2, 9.6 2.02, br. d, 13.2	2.17, dd, 13.2, 10.2 2.05, br. d, 13.2	2.24, dd, 13.2, 9.6 2.01, br. d, 13.2
7	1.85, m	1.89, m	1.77, m	1.86 m	1.77, m
8	1.76, m	1.80, m	1.89, m	1.92, m	1.87, m
9	2.22, dd, 13.2, 9.6 2.00, br. d, 13.2	2.30, dd, 13.2, 9.6 2.03, br. d, 13.2	2.57, dd, 13.2, 7.2 2.52, br. d, 13.2	2.58, dd, 13.8, 7.8 2.47, dd, 13.8, 1.8	2.53, dd, 13.2, 7.2 2.46, dd, 13.2, 1.8
11	6.61, s	6.37, s	6.37, s	6.65	6.62, s
17	0.95, d, 7.2	0.99, d, 7.2	0.74, d, 7.2	0.76, d, 7.2	0.72, d, 6.6
18	0.70, d, 7.2	0.73, d, 7.2	0.97, d, 7.2	0.98, d, 7.2	0.96, d, 7.2
1-OMe	3.76	3.87, s	3.86, s	-	3.77, s
12-OMe	3.91	3.89, s	3.88, s	3.89	-
13-OMe	-	3.90, s	3.91, s	3.91	3.93, s
14-OMe	3.49	-	-	3.57	3.51, s
–O–CH_2–O–	5.94, d, 1.2 5.90, d, 1.2	5.97, d, 1.8 5.93, d, 1.8	5.95, br. s 5.92, br. s	6.01, d, 1.8 5.96, d, 1.8	5.95, d, 1.2 5.94, d, 1.2

Table 2. ^{13}C NMR data of dibenzocyclooctadiene lignans from *Schisandra chinensis* fruits (125 MHz, $CDCl_3$, δ_C)

No	L2 (1)	L1 (2)	M1 (3)	M2 (4)	M3 (5)
1	141.40	141.31	141.13	137.00	141.23
2	135.28	135.12	134.78	133.47	134.96*
3	141.23	147.98	148.98	148.59	148.82
4	106.34	106.66	103.59	102.30	103.35
5	132.89	133.26	138.49	138.18	138.20
6	39.11	39.08	35.76	35.75	35.66
7	33.99	34.00	40.89	40.81	40.96
8	40.97	40.94	33.65	33.45	29.89
9	35.20	35.53	39.32	39.16	38.91
10	140.46	140.11	134.64	135.85	135.00*
11	110.41	104.02	107.70	112.50	113.42
12	148.84	151.84	150.54	152.21	147.70
13	137.55	133.26	133.61	140.52	137.83
14	150.47	146.86	147.02	150.49	150.63
15	121.62	115.85	116.76	118.69	122.64
16	121.56	121.48	120.33	121.68	121.56
17	22.05	22.15	13.03	12.89	12.84
18	12.58	12.42	21.65	21.68	21.79
1-OMe	59.85	59.95	59.88	-	59.85
12-OMe	-	55.85	55.82	56.20	-
13-OMe	61.21	61.19	61.13	61.60	61.19
14-OMe	60.32	-	-	61.47	60.31
–O–CH_2–O–	100.99	100.99	100.94	101.48	100.97

* Position might be changed due to chemical shift overlapped

+ Na]$^+$, 795 [2M + Na]$^+$; positive HR-ESI–MS: *m*/*z* 387.1795 [M + H]$^+$ (calcd for $C_{22}H_{27}O_6^+$, 387.1802).

Results and discussion

Solvent extraction of *Schisandra chinensis* fruits, fractionation, and column chromatography for the EtOAc fraction with Sephadex LH-20, silica gel (SiO_2), and octadecyl SiO_2 (ODS) as well as a preparative high performance liquid chromatography (prep-HPLC) yielded a new dibenzocyclooctadiene lignan and four previously reported analogues, which were identified to be gomisin L2 (**1**), gomisin L1 (**2**), gomisin M1 (**3**), and gomisin M2 (**4**) on the basis of MS, IR, and NMR data and comparison with the literature [17–20]. However, spectroscopic data and the procedure of structure determination for gomisin L1 (**2**) previously reported in literature [18] are incomplete and insufficiently described. Therefore, it will be of use for researchers to give complete data and reasonable description for structure determination.

Compound **2**, a white powder, exhibited a molecular ion peak at *m*/*z* 387.1788 [M+H]$^+$ in the positive high resolution ESI–MS, establishing the molecular formula to be $C_{22}H_{26}O_6$ (calcd for $C_{22}H_{27}O_6^+$, 387.1802). The IR bands at 3400 (hydroxy group), 1614, and 1459 cm^{-1} (aromatic moiety) and an orange-blue finding on TLC by spray of 10% sulfuric acid and heating suggested **2** as a dibenzocyclooctadiene lignan. The ^{1}H NMR spectrum (Table 1) displayed two singlet olefinic methine proton signals δ_H 6.51, 6.37 due to two aromatic protons in a biphenyl moiety. As shown by the signals of H-4 and H-11 at different chemical shifts, the biphenyl unit had an asymmetric plane. At the oxygenated field, one dioxygenated methylene proton signal showed germinal coupling at δ_H 5.97 (d, *J* = 1.8 Hz; coupling pattern,

coupling constant in Hz) and 5.93 (d, 1.8), and three methoxy proton signals at δ_H 3.90, 3.89, and 3.87 were observed. At high magnetic field, the following proton signals were identified: two methines at 1.89 (m) and 1.80 (m); two methylenes with germinal coupling at δ_H 2.56 (dd, 13.8, 7.2) and 2.43 (dd, 13.8, 1.2); at δ_H 2.30 (dd, 13.2, 9.6) and 2.03 (br. d, 13.2); and two doublet methyls at δ_H 0.99 (d, 7.2) and 0.73 (d, 7.2). The proton NMR signals of OMe-1 and -14 usually appears at more upfield than those of OMe-2, -3, -12, and -13 owing to a shielding influence by the neighboring phenyl moieties. The former compounds having OMe group at C-1 and -14 usually show the chemical shift of the methoxy group at ca. δ_H 3.55, while the latter compounds having OMe group at C-1, -3, -12, and -13 at ca. δ_H 3.90 [21]. Besides, the proton NMR signals of OMe-1 and -14 are a little shifted to downfield in case of having a dioxymethylene moiety at the next position [9]. Therefore, OMe-1 proton signal was observed at δ_H 3.87. The other two methoxy groups of compound **2** were observed at δ_H 3.90 and 3.89, suggesting that C-14 had a free hydroxyl group. In the ^{13}C NMR spectrum (Table 2), 22 carbon signals were detected including one deoxygenated methylene (δ_C 100.99) and three methoxy (δ_C 61.19, 59.95, 55.85) signals, confirming compound **2** to be a lignan. The carbon signals of the biphenyl moiety were composed of six oxygenated olefinic quaternary carbons (δ_C 151.84, 147.98, 146.86, 141.31, 135.12, 133.26), four olefinic quaternary carbons (δ_C 140.11, 133.26, 121.48, 115.85), and two olefinic methines (δ_C 106.66, 104.02). At high magnetic field, the ^{13}C NMR spectrum showed two methines (δ_C 40.94, 34.00), two methylenes (δ_C 39.08, 35.53), and two methyls (δ_C 22.15, 12.42). The chemical shifts of two methyl carbons appeared over a narrow range (δ_C 12.42 and 22.15), the upfield signal was assigned to be an axial methyl carbon (C-18), and the downfield one to an equatorial methyl carbon (C-17) [22]. Therefore, compound **2** had a *cis*-dimethyl moiety was a cyclooctadiene ring [23]. The abovementioned NMR suggested **2** to be a dibenzocyclooctadiene lignan with three methoxy, one hydroxy, and one dioxymethylene group in the biphenyl moiety. The protection of a hydroxyl group by methyl moiety led to 3–4 ppm downfield shifting of phenyl carbon [21]. Because the oxygenated olefinic quaternary carbons C-12 and C-14 were observed at δ_C 151.84 and 146.86, respectively, C-14 was suggested to have a hydroxyl group. The methoxy carbons next to the biphenyl bond (C-3 and C-12) are upfield shifted by 5 ppm (around δ_C 55) in contrast to those of others (C-1, C-2, C-3, and C-14; about δ_C 60) [21]. The three methoxy carbons were detected at δ_C 61.19, 59.96, and 55.85, suggesting that C-12 has a methoxy group. The chemical shifts of C-1 and C-14 were δ_C 141.31 and 146.86, respectively. The neighboring carbon (C-1) from the dioxymethylene group is observed more upfield than other carbons, such as C-14, indicating the dioxymethylene group at C-2 and C-3 [22]. Additionally, two oxygenated olefin quaternary carbon signals (δ_C 135.12, C-2; 147.98, C-3) showed correlations with dioxymethylene proton δ_H 5.97 and 5.93 signals and an olefin methine proton δ_H 6.51 (H-4) signal in the HMBC spectrum, confirming the position of the dioxymethylene group. These findings established the planar structure of compound **2** (Fig. 2). The absolute configuration of the biphenyl chromophore can be discerned based on the characteristic CD spectra. The *S* configuration derivatives show a (+)-Cotton effect at 210 nm and a (–)-Cotton effect at 240 nm in CD. Conversely, the *R* configuration derivatives yield a CD spectrum with a (–)-Cotton effect at 210 nm and a (+)-Cotton effect at 240 nm [23]. The CD spectrum of **2** gave a negative Cotton effect at 243 nm, proposing **2** to have an *S* configuration in biphenyl structure [24]. In addition, proton signals of H-8 (δ_H 1.80) and H-18 (δ_H 0.73) were upfield-shifted confirming **2** to possess an *S* configuration because an axial methyl group (H-18) or hydrogen (H-8) is shielded by the biphenyl moiety, leading to an upfield effect [20]. Based on these findings, the chemical structure of **2** was identified as (a*S*)-(6*S*,7*R*)-2,3,13-trimethoxy-6,7-dimethyl-5,6,7,8-tetrahydrobenzo[3′,4′]cycloocta[1′,2′:4,5]benzo[1,2-d][1,3]dioxol-1-ol, gomisin L1.

Compound **5**, a white powder, displayed a molecular ion peak *m*/*z* 387.1795 $[M+H]^+$ in the positive high-resolution ESI–MS, establishing the molecular formula to be $C_{22}H_{26}O_6$ (calcd for $C_{22}H_{27}O_6^+$, 387.1802). The IR bands at 3348 (hydroxy group), 1615, and 1460 cm^{-1} (aromatic moiety) and the orange-blue color finding on TLC by spray of 10% sulfuric acid and heating suggested **5** as a dibenzocyclooctadiene lignan. ^{1}H and ^{13}C NMR spectra proposed **5** to be a dibenzocyclooctadiene lignan with three methoxy, one hydroxy, and one dioxymethylene moieties in the biphenyl ring. The ^{1}H NMR chemical shifts at δ_H 3.93 (13-OMe), 3.77 (1-OMe), and 3.51 (14-OMe), as well the ^{13}C NMR chemical shifts at 61.19 (13-OMe), 60.31 (14-OMe), and 59.85 (1-OMe) of three methoxy moieties suggested a hydroxyl moiety at C-12. Additionally, two oxygenated olefin quaternary carbons (δ_C 134.96, C-2; 148.82, C-3) showed correlation with dioxymethylene proton (δ_H 5.95, 5.94) signals and with an olefin methine proton (δ_H 6.48, H-4) signal in the HMBC spectrum, confirming the dioxymethylene moiety to be at C-2 and C-3. The CD spectrum of **5** exhibited a negative Cotton effect at 225 nm and a positive Cotton effect at 254 nm, proposing **5** to have an *R*

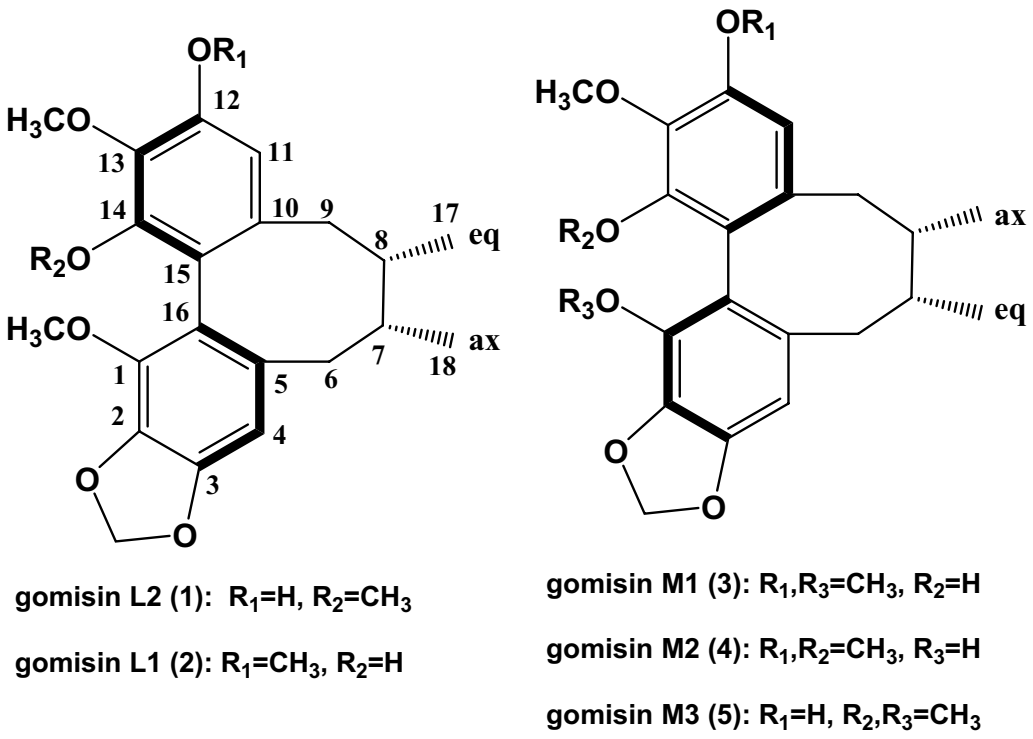

Fig. 2 Chemical structures of dibenzocyclooctadiene lignans from *Schisandra chinensis* fruits

configuration in biphenyl ring structure [17, 18, 24–27]. Taken Additional file 1 together, the chemical structure of **5** was identified as (a*R*)-(6*S*,7*R*)-1,2,13-trimethoxy-6,7-dimethyl-5,6,7,8-tetrahydrobenzo[3',4']cycloocta[1',2':4,5]benzo[1,2-d][1,3]dioxol-3-ol, named gomisin M3.

In the present study, a new dibenzocyclooctadiene lignan (name as gomisin M3) along with four known ones, gomisin L2, L1, M1, and M2, were isolated through repeated column chromatography using silica gel, octadecyl silica gel, and Sephadex LH-20 resins from the EtOAc fraction of *Schisandra chinensis* fruits. Their chemical structures including stereostructure for axial chirality were determined without ambiguity based on the analysis of NMR, IR, MS, and CD data.

Additional information

Additional information (^{1}H and ^{13}C NMR spectra of dibenzocyclooctadiene lignans **1**–**5** accompanies this paper at https://doi.org/ (Additional file 1: Figures S1—S5).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13765-021-00618-1.

Additional file 1: **Figure S1**. 1H- and 13C-NMR spectra of gomisin L2 (1) (600/150 MHz, CD3OD). **Figure S2**. 1H- and 13C-NMR spectra of gomisin L1 (2) (600/150 MHz, CDCl3). **Figure S3**. 1H- and 13C-NMR spectra of gomisin M1 (3) (600/150 MHz, CDCl3). **Figure S4**. 1H- and 13C-NMR spectra of gomisin M2 (4) (600/150 MHz, CDCl3). **Figure S5**. 1H- and 13C-NMR spectra of gomisin M3 (5) (600/150 MHz, CDCl3).

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Authors' contributions
TN N, Y-G L, and N-I B planned the study and wrote the paper. TN N, Y-G L, H-G K, DH Y, and DY L isolated lignans. TN N, Y-G L, and N-I B determined the chemical structure of lignans. JT J collected the fruits of *Schisandra chinensis* and identified. All authors read and approved the final manuscript.

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Availability of data and materials
The data and materials used in this study are available under permission from the corresponding author on reasonable request.

Declarations

Competing interests
There are no conflicts to declare.

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