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Spiroschincarins A–E: Five Spirocyclic Nortriterpenoids from the Fruit of *Schisandra incarnata*

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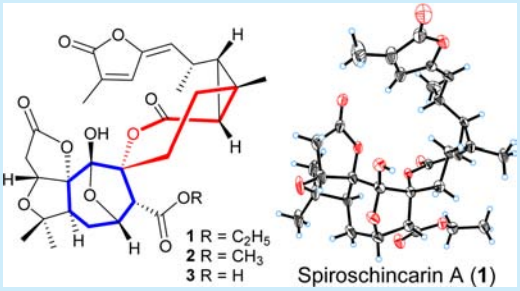
Supporting Information

ABSTRACT: Spiroschincarins A–E (**1**–**5**), five novel spirocyclic schinortriterpenoids featuring a unique 1-oxaspiro[6.6]tridecane motif, were isolated from the fruit of *Schisandra incarnata*. Their structures with absolute configurations were determined by extensive spectroscopic analyses, single-crystal X-ray diffractions, and experimental ECD (electronic circular dichroism). A hypothetical biogenetic pathway of **1**–**5** was postulated.



Widely distributed in China, plants of the *Schisandra* genus are extensively used in traditional Chinese medicine for the treatment of cough, insomnia, chronic dysentery, and premature ejaculation, etc.[1] Considerable chemical research on this genus has resulted in the discovery of a large number of triterpenoids, especially schinortriterpenoids (SNTs).[2] SNTs are a special class of triterpenoids with C26–C29 frameworks, which are characterized by highly oxygenated and complicated polycyclic rings. It has been proposed that they are biogenetically generated from a common cycloartane-type skeleton by 3,4-oxidative cleavage, 9,10-cleavage with ring expansion, decarboxylation at C-18 and/or C-28, and a sequence of oxidations and rearrangements to form various types.[2c] On the basis of their structural features and biogenetic pathways, SNTs have been classified into 18 groups to date,[2c,3] some of which exhibit promising biological effects, such as anticancer and anti-HIV-1 activities,[2c] and their fascinating structures have aroused wide attention in the field of phytochemical research and organic synthesis.[4]

Over the past few years, our group has conducted a series of phytochemical investigations on the plants of *Schisandra* and has succeeded in isolating and characterizing a variety of lignans and triterpenoids with diverse bioactivities.[3b,5] *Schisandra incarnata*, a woody liana, is mainly distributed in the west and southwest of Hubei province, China. Its ripe fruit is used in folk medicine for the treatment of various conditions such as contusion and rheumatism. In our previous studies on the stems and leaves of this plant, a unique schinortriterpenoid featuring a tricyclo-[5.2.1.0^{1,6}]decane-bridged system was isolated.[3b] In continuing research on structurally unique and bioactive products from this species, the chemical constituents of the fruit of *S. incarnata* were investigated. As a result, five novel spirocyclic SNTs, spiroschincarins A–E (**1**–**5**), featuring a unique 1-oxaspiro[6.6]tridecane moiety, were isolated. This paper presents the isolation, structure elucidation, extrapolated biogenetic pathway, and bioactivities of compounds **1**–**5** (Figure 1).

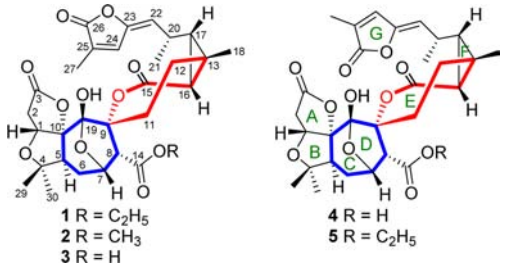


Figure 1. Structures of compounds **1**–**5**.

Spiroschincarin A (**1**) was obtained as colorless needles. Its molecular formula, $C_{31}H_{38}O_{11}$, was established by HRESIMS (*m*/*z* 609.2334, $[M + Na]^+$, calcd for 609.2312) and ^{13}C NMR data, requiring 13 degrees of unsaturation. The IR spectrum suggested the presence of a hydroxyl group (3428 cm^{-1}) and carbonyl groups (1714 and 1748 cm^{-1}). The ^1H NMR data (Table 1) of **1** displayed signals for six methyls at δ_H 1.12 (s), 1.22 (d, J = 6.4 Hz), 1.27 (s), 1.30 (t, J = 7.2 Hz), 1.33 (s), 1.92 (d, J = 1.5 Hz), two oxygenated methines at δ_H 4.45 (ddd, J = 7.1, 4.8, 1.5), 5.04 (d, J = 5.9 Hz), and two olefinic protons at δ_H 5.53 (d, J = 10.7 Hz), 7.58 (br s). The ^{13}C NMR and DEPT spectra of **1** resolved 31 carbon signals including 11 quaternary carbons (two olefinic carbons, four oxygenated carbons, and four ester carbonyl carbons), nine

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Table 1. ^{1}H NMR (600 MHz) Data for 1 and 5 in Methanol-d_4 (δ in ppm, J in Hz)

no.	1	5
1	5.04 d (5.9)	4.97 d (5.9)
2α	2.49 d (18.2)	2.36 d (18.1)
2β	2.92 dd (18.2, 5.9)	3.13 dd (18.1, 5.9)
5	3.11 dd (11.4, 7.4)	3.07 dd (11.0, 7.8)
6α	2.67 dd (14.4, 7.4)	2.63 ddd (14.6, 7.8, 1.6)
6β	1.95 ddd (14.4, 11.4, 4.8)	1.94 ddd (14.6, 11.0, 5.3)
7	4.45 ddd (7.1, 4.8, 1.5)	4.43 ddd (7.1, 5.3, 1.6)
8	3.31 d (7.1)	3.24 d (7.1)
11α	2.42 dd (14.2, 7.0)	2.34 dd (15.1, 7.6)
11β	2.45 m	2.46 dd (15.1, 10.6)
12α	1.89 dd (15.1, 10.2)	2.14 dd (15.4, 10.6)
12β	1.52 dd (15.1, 7.0)	1.54 dd (15.4, 7.6)
16	1.77 d (10.1)	1.73 d (10.1)
17	1.33 overlapped	1.51 t (10.1)
18	1.12 s	1.15 s
20	2.65 m	2.95 m
21	1.22 d (6.4)	1.21 d (6.6)
22	5.53 d (10.7)	5.24 d (8.3)
24	7.58 br s	7.19 d (1.6)
27	1.92 d (1.5)	1.93 br s
29	1.27 s	1.26 s
30	1.33 s	1.30 s
1′	4.25 dq (10.8, 7.2)	4.22 dq (10.8, 7.2)
	3.99 dq (10.8, 7.2)	3.99 dq (10.8, 7.2)
2′	1.30 t (7.2)	1.30 t (7.2)

methines (two olefinic and two oxygenated methines), five methylenes (one oxygenated methylene), and six methyls (Table 2). Taking six degrees of unsaturation occupied by four ester carbonyl and two double bonds into consideration, a heptacyclic structural unit was required for compound **1** to fulfill the unsaturation demand. Detailed examination of the 2D NMR of **1** confirmed the existence of seven rings, A−H.

The HMBC correlations of H-1/C-2, C-3, C-4, C-10; H-2/C-3, C-10; H-5/C-1, C-10; and H-6/C-4, C-5, C-10, combined with the ^{1}H−^{1}H COSY correlations of H-1/H$_2$-2, clearly deduced the parts of rings A and B, which showed the same moiety as preschisanartanin E.[6] The HMBC correlations of H-5/C-6, C-7, C-10; H-7/C-19, coupled with the ^{1}H−^{1}H COSY correlations of H-5/H$_2$-6/H-7, revealed the presence of a six-membered ring C fused with ring B through the bridge between C-5 and C-10. Ring D was established on the basis of the ^{1}H−^{1}H COSY correlation of H-7/H-8 and the HMBC correlations of H-8/C-7, C-9. Subsequently, the HMBC correlation of H-7/C-19 indicated that rings C and D shared the same oxa-bridge hemiketal between C-7 and C-19. The ^{1}H−^{1}H COSY correlation of H-1′/H-2′ and the HMBC correlation of H-1′/C-14 suggested the presence of an ethoxycarbonyl group, the attachment of which at C-8 could be determined by the HMBC correlation of H-8/C-14. Then the HMBC correlations of H-16/C-17; H-17/C-16; H$_3$-18/C-16, C-17 and the ^{1}H−^{1}H COSY correlation of H-16/H-17 indicated the existence of a three-membered carbon ring F. Ring G was deduced to be a α,β-unsaturated γ-lactone moiety by the HMBC correlations of H-24/C-23, C-25, C-26, C-27 and the ^{1}H−^{1}H COSY correlation of H-24/H-27. Furthermore, the linkage of rings F and G was supported by the HMBC correlations shown in Figure 2.

The remaining ring, ring E, was deduced by the following analysis. The HMBC correlations of H-11/C-9, H$_2$-12/C-9, and

Table 2. ^{13}C NMR Data for 1−5 (Methanol-d_4, δ in ppm)[a]

no.	1	2	3	4	5
1	80.9 (d)	80.9 (d)	80.9 (d)	81.0 (d)	81.1 (d)
2	40.3 (t)	40.3 (t)	40.3 (t)	40.1 (t)	40.1 (t)
3	179.4 (s)	179.4 (s)	179.6 (s)	179.3 (s)	179.2 (s)
4	86.7 (s)	86.7 (s)	86.8 (s)	86.8 (s)	86.7 (s)
5	47.4 (d)	47.4 (d)	47.5 (d)	48.1 (d)	47.9 (d)
6	29.7 (t)	29.6 (t)	29.5 (t)	29.0 (t)	29.3 (t)
7	74.9 (d)	74.9 (d)	75.1 (d)	74.8 (d)	74.6 (d)
8	57.5 (d)	57.1 (d)	57.5 (d)	57.6 (d)	57.6 (d)
9	93.2 (s)	93.3 (s)	92.9 (s)	93.2 (s)	93.5 (s)
10	99.5 (s)	99.4 (s)	99.7 (s)	99.4 (s)	99.2 (s)
11	36.5 (t)	36.5 (t)	36.2 (t)	35.5 (t)	35.9 (t)
12	24.6 (t)	24.6 (t)	24.7 (t)	25.1 (t)	25.0 (t)
13	28.7 (s)	28.7 (s)	28.0 (s)	28.8 (s)	29.5 (s)
14	168.9 (s)	169.3 (s)	170.9 (s)	171.4 (s)	169.1 (s)
15	173.8 (s)	173.8 (s)	173.6 (s)	174.6 (s)	174.7 (s)
16	32.4 (d)	32.0 (d)	32.2 (d)	32.7 (d)	32.9 (d)
17	40.6 (d)	40.5 (d)	39.7 (d)	40.4 (d)	41.4 (d)
18	26.3 (q)	26.3 (q)	26.2 (q)	26.6 (q)	26.7 (q)
19	105.2 (s)	105.1 (s)	105.3 (s)	105.5 (s)	105.4 (s)
20	31.0 (d)	31.0 (d)	31.2 (d)	31.4 (d)	31.3 (d)
21	20.2 (q)	20.3 (q)	20.4 (q)	19.6 (q)	19.6 (q)
22	119.2 (d)	119.1 (d)	119.3 (d)	119.8 (d)	119.6 (d)
23	148.7 (s)	148.8 (s)	148.8 (s)	148.4 (s)	148.5 (s)
24	137.3 (d)	137.3 (d)	137.3 (d)	140.5 (d)	140.5 (d)
25	130.9 (s)	130.9 (s)	130.9 (s)	129.3 (s)	129.4 (s)
26	172.8 (s)	172.8 (s)	172.9 (s)	172.9 (s)	172.9 (s)
27	10.6 (q)	10.5 (q)	10.5 (q)	10.3 (q)	10.2 (q)
29	25.4 (q)	25.4 (q)	25.4 (q)	25.2 (q)	25.3 (q)
30	30.2 (q)	30.2 (q)	30.3 (q)	30.4 (q)	30.3 (q)
1′	61.8 (t)	51.7 (q)			61.8 (t)
2′	14.4 (q)				14.3 (q)

[a]Compounds **1**−**5** were recorded at 100 MHz, and the assignments were based on DEPT, HSQC, HMBC, COSY, and NOESY experiments.

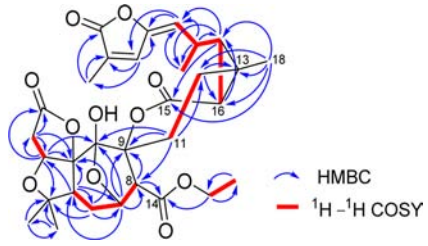

Figure 2. Key HMBC, and ^{1}H−^{1}H COSY correlations of **1**.

H$_3$-18/C-12, C-13, C-16, together with the ^{1}H−^{1}H COSY correlations of H$_2$-11/H$_2$-12, elucidated the structural sequence C-9−C-11−C-12−C-13−C-16. Meanwhile, one ester carbonyl carbon (C-15) was attached to C-16, which was demonstrated by the HMBC correlations of H-17, H3−18/C-15. Taking the final **1** degree of unsaturation into account, compound **1** required another ring, which led to the establishment of the unique seven-membered lactone ring E containing an ester bridge between C-9 and C-15. The interruption of the carbon bond between C-14 and C-15 and the formation of the new ester carbonyl made C-9 to be the spirocyclic center in **1**. Ring E could be further confirmed by single-crystal X-ray crystallographic analysis. From the whole elucidation above, the planar structure of **1** was identified and displayed in Figure 2.

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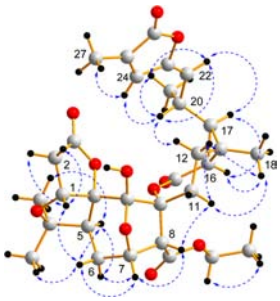

Figure 3. Selected NOESY correlations of compound **1**.

The relative configuration of **1** was deduced by the NOESY correlations (Figure 3). Biogenetically, H-5 was assigned to be α-oriented. The NOESY correlation of H-5/H_3-30 showed Me-30 was α-oriented. H-1 and H-6β were assigned to be β-oriented by the cross-peaks of H_3-29, H-1/H-6β. The NOESY correlations of H-17, H_3-18/H-16; H-8, H_3-18/H-11β and H-8/H-7 suggested that H-16, H-17, H_3-18, H-11β, H-8, and H-7 were oriented on the same face of the molecule. The olefinic group between C-22 and C-23 was deduced to be *E* geometry by the NOESY correlation of H-20/H-24. However, the relative configurations of the two sp^3 quaternary carbons (C-10 and C-19) and the spirocyclic center C-9 were not yet assigned due to the absence of reliable evidence. The relative stereochemistry of C-20 could not be resolved by the NMR data alone, since the σ-bond between C-17 and C-20 has free rotation. In order to determine the relative and absolute configurations, the crystal of **1** was obtained in methanol−water solution by repeated recrystallization. The X-ray diffraction analysis with Cu Kα radiation resulted in a Flack parameter of 0.01 (5) and a Hooft parameter of 0.02 (6),[7] which make the assignment the absolute configuration of **1** 1*R*,5*S*,7*S*,8*R*,9*R*,10*R*,13*R*,16*S*,17*R*,19*S*,20*S* (Figure 4).

Spiroschincarin B (**2**) had a molecular formula of $C_{30}H_{36}O_{11}$ as determined by positive HRESIMS at *m*/*z* 595.2151 ([M + Na]$^+$, calcd for 595.2155) and ^{13}C NMR data, which had the same degrees of unsaturation as **1**. Detailed comparison of the ^{13}C NMR data (Table 2) and 2D NMR spectra of **2** with those of **1** revealed that the structure of **2** was very similar to that of **1**. The only difference was the replacement of the ethoxycarbonyl group in **1** by a methoxycarbonyl group in **2**, which could be deduced by the HMBC correlations of H_3-1′/C-14 and H-8/C-14 in **2**. The absolute configuration of **2** was determined to be 1*R*,5*S*,7*S*,8*R*,9*R*,10*R*,13*R*,16*S*,17*R*,19*S*,20*S* (Figure 5) by X-ray diffraction using Cu Kα radiation with a Flack parameter of 0.04 (15) and a Hooft parameter of 0.03 (14).[7]

Spiroschincarin C (**3**) got the molecular formula of $C_{29}H_{34}O_{11}$ by its HRESIMS at *m*/*z* 581.1969 ([M + Na]$^+$, calcd for 581.1999) and ^{13}C NMR data. Comparison of the NMR data of **3** with that of **1** (Table 2 and Table S3) suggested that they shared the same carbon skeleton, with a major difference of the substituent group at C-8. The ethoxycarbonyl group in **1** was replaced by a carboxyl in **3**, which was confirmed by the HMBC correlation of H-8/C-14. The relative configuration of **3** was determined to be the same as those of **1** and **2** by comparison of their NOESY correlations (Figure S2). An experimental ECD was carried out to determine the absolute configuration of **3**. Compound **3** showed a positive Cotton effect at 272 nm and a negative Cotton effect at 225 nm, which exhibited the same Cotton effect as **1** (Figure 6). Combined with the above-mentioned relative configuration, the absolute configuration of **3** was determined to be the same as that of **1**.

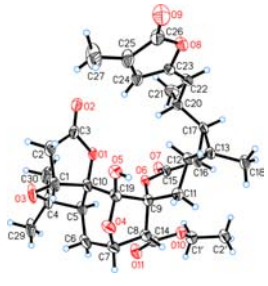

Figure 4. X-ray ORTEP drawing of compound **1**.

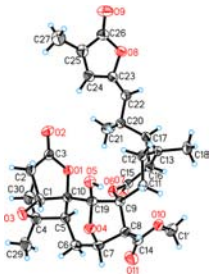

Figure 5. X-ray ORTEP drawing of compound **2**.

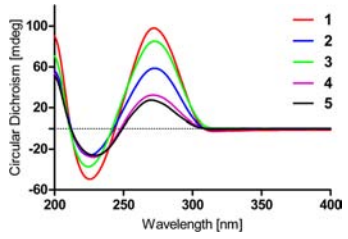

Figure 6. ECD spectra of compounds **1**−**5**.

Spiroschincarin D (**4**) shared the same molecular formula of $C_{29}H_{34}O_{11}$ as **3** based on its HRESIMS at *m*/*z* 581.1979 ([M + Na]$^+$, calcd for 581.1999) and ^{13}C NMR data (Table 2). Careful comparison of the 1D NMR data of **4** with those of **3** suggested that **4** was quite similar to **3**, which was further corroborated by its HSQC, HMBC, and ^{1}H−^{1}H COSY spectra (Figures S47−S49). The only difference between **4** and **3** was the geometry of the olefinic group between C-22 and C-23, which was proved to be *Z* geometry in **4** by the NOESY correlation of H-22 and H-24. Therefore, the molecular structure of **4** was established as shown.

Spiroschincarin E (**5**) had the same molecular formula of $C_{31}H_{38}O_{11}$ as **1** based on its HRESIMS and ^{13}C NMR data (Table 2). The close resemblance between the 1D NMR data (Tables 1 and 2) of **1** and **5** indicated that the structure of **5** was similar to **1**. The double bond between C-22 and C-23 of **5** was determined to be in a *Z* geometry, which was supported by the NOESY correlation of H-22 and H-24.

So far, the structures of **1**−**5** have been derived from the above elucidation. Compounds **1**, **2**, and **5** with ethyl ester or methyl ester units might be artifact products generated during the extraction and isolation procedure when EtOH and MeOH were used. To clarify this possibility, the acetone extract was subjected to HPLC−MS analysis (Supporting Information), and compounds **1**−**5** were detected. Nevertheless, **1**, **2**, and **5** could still be artifacts because of the limitations of the detection method.

Compounds **1**−**5** represent a novel class of triterpenoids wherein they involve a unique 1-oxaspiro[6.6]tridecane moiety.

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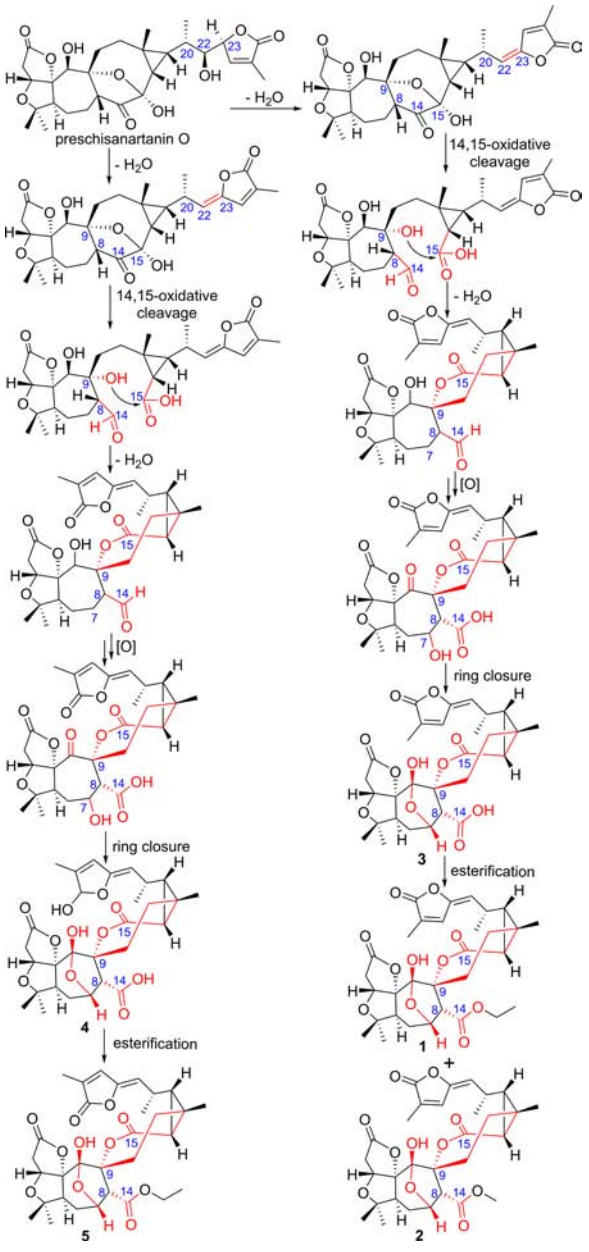
Scheme 1. Hypothetical Biogenetic Pathway for 1−5



The spirocyclic center of C-9, together with an ester bridge between C-9 and C-15 in the seven-membered lactone ring, makes compounds **1**−**5** noteworthy.

The hypothetical biogenetic pathway of compounds **1**−**5** is proposed in Scheme 1. Preschisanartanin O[2c,8] was assumed to be a precursor, and the pathway involved dehydration, oxidative cleavage, and dehydration followed by oxidation and ring closure to form the structures of **1**−**5**.

Compounds **1**−**4** were tested for their cytotoxicity against HepG2, MCF7, and HT-29 human cancer cell lines. However, none showed obvious activity (Table S1). Additionally, **1**−**4** were evaluated for their in vitro immunosuppressive activity (Table S2). Compounds **1** and **2** exhibited weak inhibition with the inhibitory rate of proliferation to be 56.4% and 43.5% against ConA-induced T lymphocyte proliferation at 50 μg/mL concentration, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00250.

Experimental details and full NMR, HRESIMS, ECD, UV, and IR spectra of **1**−**5** (PDF)
X-ray data of **1** and **2** (CIF)

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Notes

The authors declare no competing financial interest.

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