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Sequosempervirin A, a novel spirocyclic compound from *Sequoia sempervirens*

Yu-Mei Zhang,[a] Ning-Hua Tan,[a,*] Min He,[a] Yang Lu,[b] Su-Qin Shang[b] and Qi-Tai Zheng[b]

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, 650204 Kunming, Yunnan, People's Republic of China*

[b]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, 100050 Beijing, People's Republic of China*

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Abstract—A novel spirocyclic compound (4*R*)-4-(4-hydroxy-benzyl) spiro [4,5] dec-1-en-8-ol (sequosempervirin A) was isolated from the branches and leaves of *Sequoia sempervirens*. Its structure and relative stereochemistry were mainly determined by MS, 2D NMR and X-ray means, which is the first naturally occurring norlignan containing one spirocycle with C6 (cyclohexane)–C2–C3–C6 skeleton.

Taxodiaceae, with 9 genera, 14 species and 12 variations, is distributed in the North Temperate Zone.[1] According to the literatures, many types of compounds have been isolated from Taxodiaceae, including terpenoids,[2–4] lignans,[5] flavonones,[6] in which some compounds showed bioactivities, such as antifungal,[7] antibacterial[8] and antitumour.[9,10] *Sequoia sempervirens* (Lamb.) Endl., the only species in *Sequoia* genus, is distributed naturally at the seashore of California in the US. It is one of the famous fast growing trees in the world and can grow up to 110 m high in California.[1] Chemical constituents of *S. sempervirens* were seldom reported before. As a part of serial investigations on Taxodiaceae and in order to seek more novel bioactive compounds, we carried out an extensive chemical study on *S. sempervirens*, and obtained a novel spirocyclic compound named sequosempervirin A from the acetone extracts for the first time. The details showed as follows.

The dried and powdered branches and leaves (11.9 kg) of *S. sempervirens*[11] were extracted with petroleum ether, acetone and methanol for three times under reflux, respectively. The extracts were concentrated in vacuo and afforded 156 g of petroleum ether extracts, 214 g of acetone extracts and 524 g of methanol extracts. The acetone extracts were subjected to silica gel column chromatography using $CHCl_3$, $CHCl_3$–Me_2CO (9:1–1:1), Me_2CO and MeOH as eluents to give 23 fractions. Fraction 17 was further chromatographed on silica gel column using $CHCl_3$–CH_3OH (9:1) and gel Sephadex LH-20 column using CH_3OH–H_2O (1:1) to yield sequosempervirin A (26 mg).

Sequosempervirin A[12] was found to possess the molecular formula of $C_{17}H_{22}O_2$ by HR +TOF MS (found 281.1511 $[M+Na]^+$, calcd 281.1517), which was confirmed by ^{13}C and DEPT NMR spectra. Its IR spectrum indicated absorption bands for hydroxyl (3426 cm^{-1}) and double bond (1630 cm^{-1}). Its UV spectrum revealed the presence of phenyl group (203, 225, 280 nm). The ^1H and ^{13}C spectra (Table 1) showed the presence of 6 methylenes [δ_C 37.5 (t, C-3), 31.5 (t, C-6), 32.2 (t, C-7), 28.1 (t, C-9), 33.0 (t, C-10), 36.1 (t, C-11); δ_H 2.15–2.16 (1H, m, H-3a), 1.99–2.03 (1H, m, H-3b), 1.69–1.71 (2H, m, H-6), 1.84–1.87 (1H, m, H-7a), 1.55–1.63 (1H, m, H-7b), 1.84–1.87 (1H, m, H-9a), 1.26–1.31 (1H, m, H-9b), 1.84–1.87 (1H, m, H-10a), 1.17–1.18 (1H, m, H-10b), 2.79 (1H, dd, $J = 2.77$, 13.08 Hz, H-11a), 2.21 (1H, t, $J = 12.83$ Hz, H-11b)], 8 methines [δ_C 139.6 (d, C-1), 129.3 (d, C-2), 50.6 (d, C-4), 68.3 (d, C-8), 130.7 × 2 (d, C-13, C-17), 116.0 × 2 (d, C-14, C-16); δ_H 5.85 (1H, d, $J = 5.64$ Hz, H-1), 5.62–5.63 (1H, m, H-2), 1.99–2.03

Keywords: *Sequoia sempervirens*; Taxodiaceae; Spirocyclic compound; Norlignan; Sequosempervirin A.

* Corresponding author. Tel./fax: +86-871-5223800; e-mail: nhtan@mail.kib.ac.cn

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Table 1. NMR data and 2D NMR correlations of sequosempervirin A (in $CDOD_3$; 400 MHz for δ_H, 100 MHz for δ_C; δ in ppm, J in Hz; TMS)

Position	δ_C	δ_H	^{1}H–^{1}H COSY	HMBC
1	139.6 d	5.85 (d, 5.64)	H-2	H-2, 3, 10
2	129.3 d	5.62–5.63 (m)	H-1	H-1, 3
3	37.5 t	2.15–2.16 (m) 1.99–2.03 (m)	H-4	H-2, 11
4	50.6 d	1.99–2.03 (m)	H-3, 11	H-2, 11
5	50.9 s			H-1, 4, 6, 10
6	31.5 t	1.69–1.71 (m)	H-7	H-7
7	32.2 t	1.84–1.87 (m) 1.55–1.63 (m)	H-6, 8	H-6
8	68.3 d	3.84–3.86 (m)	H-7	H-6, 10
9	28.1 t	1.84–1.87 (m) 1.26–1.31 (m)	H-10	H-10
10	33.0 t	1.84–1.87 (m) 1.17–1.18 (m)	H-9	H-9
11	36.1 t	2.79 (dd, 2.77, 13.08) 2.21 (t, 12.83)	H-4	H-4, 13, 17
12	134.2 s			H-11, 13, 17
13	130.7 d	6.97 (d, 8.37)	H-14	H-11
14	116.0 d	6.68 (d, 8.41)	H-13	H-13
15	156.3 s			H-14, 16
16	116.0 d	6.68 (d, 8.41)	H-17	H-17
17	130.7 d	6.97 (d, 8.37)	H-16	H-11

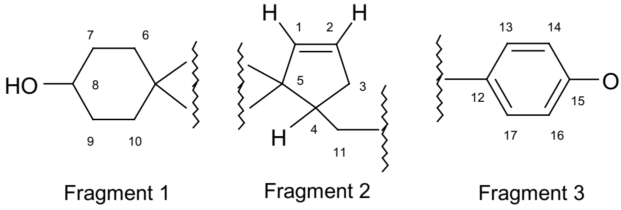

Figure 1. Fragments of sequosempervirin A.

(1H, m, H-4), 3.84–3.86 (1H, m, H-8), 6.97 (2H, d, $J = 8.37$ Hz, H-13, H-17), 6.68 (2H, d, $J = 8.41$ Hz, H-14, H-16)] and 3 quaternary carbons [δ_C 50.9 (s, C-5), 134.2 (s, C-12), 156.3 (s, C-15)]. On the basis of HMQC, ^{1}H-^{1}H COSY and HMBC spectral data, the following fragments 1–3 were assigned (Fig. 1).

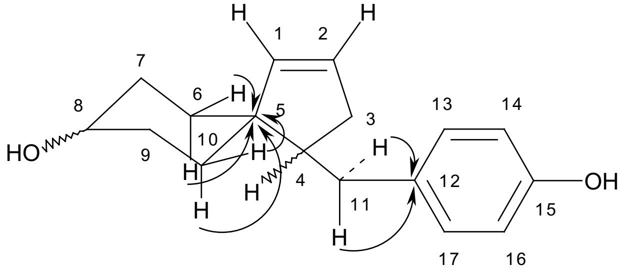

Figure 2. Key HMBC correlations of sequosempervirin A.

In the HMBC spectrum δ_C 134.2 (s, C-12) showed cross-peaks to δ_H 2.79 (1H, dd, $J = 2.77$, 13.08 Hz, H-11a) and 2.21 (1H, t, $J = 12.83$ Hz, H-11b), which indicated

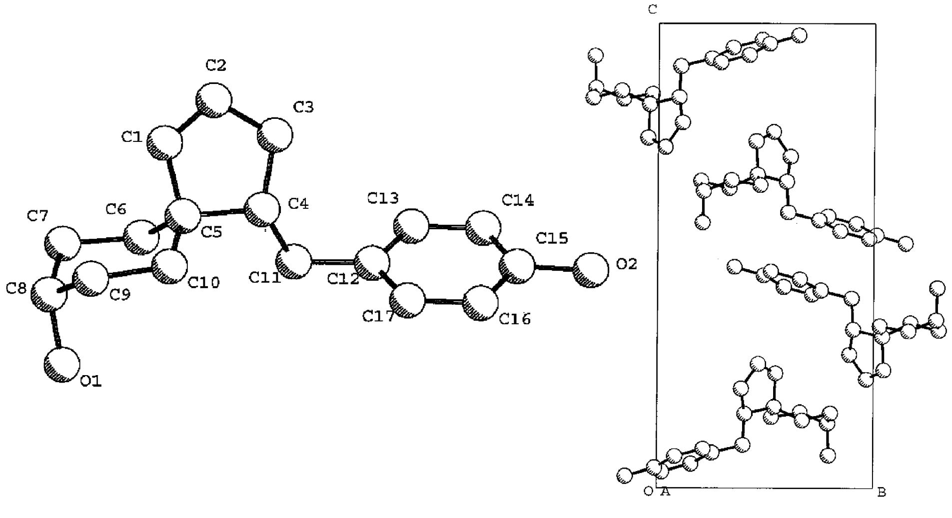

Figure 3. X-ray crystallographic structure of sequosempervirin A.

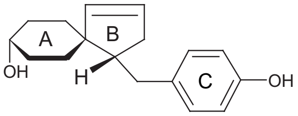

Figure 4. Structure of sequosempervirin A.

that fragment 2 was linked with fragment 3 at C-11; δ_C 50.9 (s, C-5) showed cross-peaks to δ_H 1.69–1.71 (2H, m, H-6), 1.84–1.87 (1H, m, H-10a) and 1.17–1.18 (1H, m, H-10b), which indicated that fragment 2 was linked to fragment 1 at C-5 by one spirocycle. Therefore the structure of this compound was determined as 4-(4-hydroxy-benzyl) spiro [4,5] dec-1-en-8-ol, in which the stereochemistry of C-4, C-5 and C-8 could not be deduced from the NMR spectra (Fig. 2).

Fortunately, the compound was obtained as colourless plate-like crystals from CH_3OH. The analysis of the single crystal X-ray diffraction[13] of the compound not only confirmed the presence of the spirocycle at C-5, but also established the stereochemistry of C-4 as *R* and C-8 in the α-orientation. Thus the structure was finally determined as (4*R*)-4-(4-hydroxy-benzyl) spiro [4,5] dec-1-en-8-ol, and named sequosempervirin A. The results are shown in Figures 3 and 4.

According to the literatures, some of sesquiterpenes and diterpenes with one spiro [4,5] decane group were isolated from nature,[14,15] and a few compounds with one spiro [4,5] decane group were synthesized.[16] Thus we can conclude that sequosempervirin A is the first naturally occurring norlignan containing one spirocycle with C6 (cyclohexane)–C2–C3–C6 skeleton.

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11. The branches and leaves of *S. sempervirens* (Lamb.) Endl. were collected in Kunming Botany Garden, Yunnan Province, People's Republic of China, in August 2002. It was identified by associated Professor Z. S. Yue, Kunming Botany Garden, Kunming Institute of Botany, Chinese Academy of Sciences, People's Republic of China. A voucher specimen (No 0040453) was deposited in the herbarium of Kunming Institute of Botany.
12. Sequosempervirin A: $C_{17}H_{22}O_2$, colourless plate-like crystals (MeOH), mp: 172–174 °C; $[\alpha]_D^{26}$ +24.7 (*c* 0.6, MeOH); UV (MeOH) λ_{max} ($\log\varepsilon$): 203 (3.91), 225 (3.76), 280 (3.10) nm; IR (KBr) ν_{max}: 3426, 2928, 2854, 1630, 1514, 1446, 1367, 1243, 1173, 1037, 997, 909, 817, 741, 714, 611 cm^{-1}; ^1H NMR and ^{13}C NMR data, see Table 1; EI MS *m*/*z*: 258 $[M]^+$ (13), 240 (4), 200 (3), 186 (8), 148 (9), 133 (17), 107 (100), 91 (20), 77 (15), 67 (4); HR +TOF MS *m*/*z*: 281.1511 $[M+Na]^+$, calcd 281.1517.
13. A colourless plate-like crystal of dimensions $0.15\times0.25\times1.00$ mm was used for X-ray diffraction on a MAC DIP-2030K diffractometer with Mo Kα radiation and graphite monochromator by maximum 2θ value of 50.0°. The total number of independent reflections was 1871, of which 1460 were observed ($[|F|^2 \geqslant 8\sigma(|F|^2)]$). Crystal data: molecular formula $C_{17}H_{22}O_2$, $M = 258.36$, orthorhombic system, space group: $P2_12_12_1$, $a = 7.220$ (1), $b = 9.684$ (1), $c = 21.198$ (2) Å, $V = 1482.1$ (2) $Å^3$, $Z = 4$, $d = 1.158\,g\,cm^{-3}$. The structure was solved by the direct method (SHELX-86[17]) and expanded using difference Fourier techniques, refined by the full-matrix least-squares method (NOMCSDP[18]). Hydrogen atoms were fixed at calculated positions. The final indices were $R_f = 0.076$, $R_w = 0.070$ ($w = 1/\delta|F|^2$). Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 233368. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-0-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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