Bioactive Sesquiterpenes from the Essential Oil of *Thuja orientalis*

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Abstract

A phytochemical investigation on the essential oil of *Thuja orientalis* resulted in the isolation and identification of three new sesquiterpenes, 3α-methoxy-4α-epoxythujopsane (**1**), $\Delta^{3,15}$-4β-epoxythujopsene (**2**), and $\Delta^{3,4}$-thujopsen-2,15-diol (**3**), together with eight known sesquiterpenoids (**4**–**11**). The structures of these new compounds were elucidated based on spectroscopic data analyses including extensive 2D-NMR data and HR-ESIMS. The full assignments of ^{1}H and ^{13}C NMR chemical shifts for thujopsadiene (**4**) were obtained by 2D-NMR for the first time. All compounds (**1**–**11**) showed antiproliferative activities against the SK-OV-3 and SK-MEL-2 cell lines with IC_{50} values of 5.85–28.64 µM. In addition, compounds **1, 3, 4, 7, 8**, and **9** significantly inhibited nitric oxide production in lipopolysaccharide-activated BV-2 cells with IC_{50} values of 3.93–17.85 µM without cell toxicity.

Key words

Thuja orientalis · Cupressaceae · sesquiterpene · cytotoxicity · anti-inflammation

Supporting information available online at http://www.thieme-connect.de/ejournals/toc/plantamedica

Thuja orientalis L. [= *Platycladus orientalis* (L.) Franco, *Biota orientalis* (L.) Endl., Oriental Arborvitae] (Cupressaceae) is a dense, evergreen shrub widely distributed in Korea, China, and Japan, which has been used for treatment of gout, rheumatism, diarrhea, and chronic tracheitis [1,2]. This tree has also been applied as a Korean traditional medicine remedy for hypertension, hematemesis, epistaxis, and hemorrhoids since ancient times [3]. Previous phytochemical investigations on this plant revealed the presence of diverse chemical constituents. In particular, this tree is rich in essential oils that have been used to treat fungus infections, cancer, moles, and parasitic worms [4]. Essential oils of *T. orientalis* contain many mono- and sesquiterpenoids as their chemical constituents [5–9]. But, the chemical constituents of the essential oils have not been the main subject of most researches except for several GC/MS studies [5–9], in which α-pinene, Δ-3-carene, and α-cedrol were reported as the main components without any NMR data analyses.

Our group has conducted a phytochemical investigation on the MeOH extract of the leaves of *T. orientalis* and reported the isolation of 13 diterpenoids including three new diterpenes that were cytotoxic [10]. In our continuing search for structurally interesting and bioactive constituents from *T. orientalis*, we investigated the chemical constituents of its essential oils. The aerial parts of *T. orientalis* (3 kg) were crushed completely and subjected to steam distillation (4 h) in a distillation apparatus. Steam was passed through a vessel containing the plant material-water mixture to yield a condensate. The oils, which are lighter than water, were separated, dried over anhydrous sodium sulfate and stored in a sealed container under N_2 and refrigerated (− 20 °C). The essential oils (300 g) were subjected to silica gel flash column chromatography eluting with *n*-hexane (3 L) to give a crude hexane fraction (100 g). The hexane fraction was separated using repeated silica gel column chromatography, followed by semipreparative HPLC (Supporting Information) to afford three new sesquiterpenes (**1**–**3**), together with eight known sesquiterpenoids (**4**–**11**) (**Fig. 1**). Herein we report the isolation and structural elucidation of isolates (**1**–**11**) and their antitumor and anti-inflammatory activities.

Compound **1** was isolated as a colorless oil with a positive optical rotation ($[\alpha]_D^{25}$ + 7.6). The molecular formula of **1** was determined to be $C_{16}H_{26}O_2$ by HR-ESIMS data at *m/z* 251.2015 $[M + H]^+$ (calcd. for $C_{16}H_{27}O_2$, 251.2011). The ^{1}H NMR spectrum of **1** (**Table 1**) showed four tertiary methyl proton signals at δ_H 1.40 (3H, s), 1.35 (3H, s), 1.02 (3H, s), and 0.56 (3H, s); epoxy proton signals at δ_H 3.09 (1H, dd, *J* = 4.5, 2.0 Hz) and 2.68 (1H, d, *J* = 4.5 Hz); and one methoxy proton signal at δ_H 3.50 (3H, s). In addition, a characteristic signal at δ_H 0.35 (1H, dd, *J* = 10.0, 4.5 Hz) was observed in the ^{1}H NMR spectrum of **1**, suggesting the presence of a cyclo-

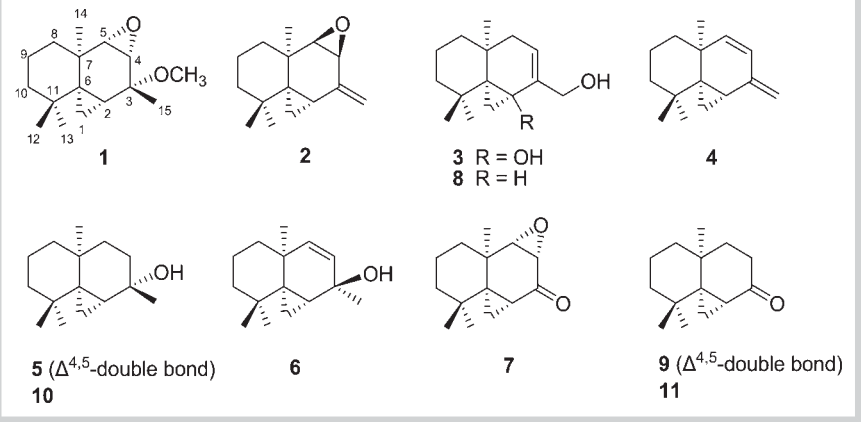

Fig. 1 Chemical structures of **1**–**11**.

Position	1		2	
	δ_H	δ_C	δ_H	δ_C
1	1.35 dd (6.0, 4.5) 0.35 dd (10.0, 4.5)	10.9	1.24 dd (6.0, 4.5) 0.51 dd (10.0, 4.5)	15.2
2	1.32 ddd (10.0, 6.0, 2.0)	26.4	1.79 ddd (10.0, 6.0, 1.5)	24.3
3		72.3		142.4
4	3.09 dd (4.5, 2.0)	58.6	3.42 dd (4.5, 1.5)	56.5
5	2.68 d (4.5)	64.7	2.78 d (4.5)	67.1
6		31.4		34.0
7		32.1		33.1
8	1.54 m 1.34 ddd (13.5, 13.5, 3.5)	36.4	1.54 m 1.34 ddd (13.5, 13.5, 3.5)	35.9
9	1.78 m 1.60 m	17.9	1.78 m 1.57 m	17.9
10	1.51 m 1.22 td (13.5, 3.5)	40.3	1.51 m 1.24 td (13.5, 3.5)	40.0
11		33.6		34.4
12	0.56 s	28.5	0.57 s	28.0
13	1.02 s	26.8	1.02 s	27.2
14	1.35 s	24.9	1.37 s	24.4
15	1.40 s	26.3	5.16 d (1.5) 5.14 d (1.5)	114.1
OCH_3	3.50 s	50.9		

Table 1 ^{1}H and ^{13}C NMR data of compounds **1** and **2** in $CDCl_3$. (δ in ppm, 500 MHz for ^{1}H and 125 MHz for ^{13}C.)[a]

[a] *J* values are in parentheses and reported in Hz; the assignments were based on ^{1}H-^{1}H COSY, HMQC, and HMBC experiments

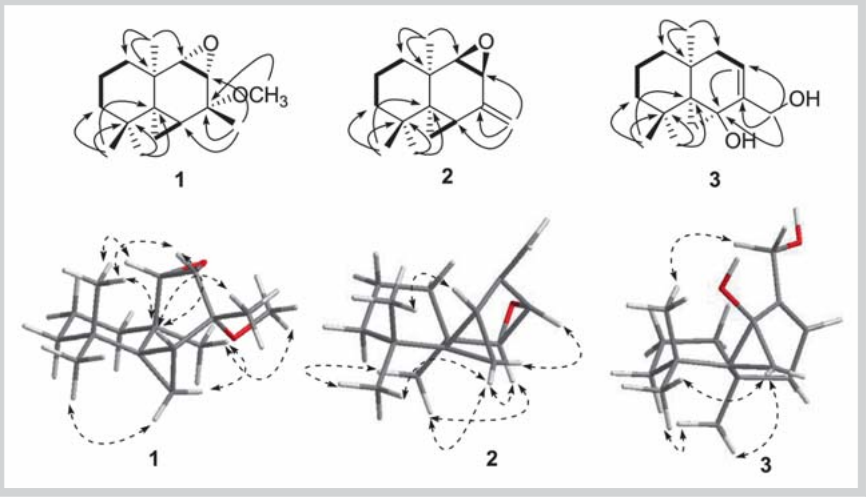

Fig. 2 Key ^{1}H-^{1}H COSY (—), HMBC (→), and NOESY (←– –→) correlations of **1**–**3**.
(Color figure available online only.)

propane ring in the molecule [11]. The ^{13}C NMR spectrum (**Table 1**) in combination with DEPT showed four tertiary methyls, three methines, four methylenes including a characteristic signal for the cyclopropane ring at δ_C 10.9 [11], four quaternary carbons, and one methoxy carbon signals. Overall, inspection of the ^{1}H and ^{13}C NMR data of **1** revealed that these data were similar to those of isolated compound **5**, 3α-hydroxy-4-thujopsene [12], except that the proton and carbon resonances of the double bond in **5** were absent and replaced by resonances of an epoxy group at δ_H 3.09; δ_C 58.6 and δ_H 2.68; δ_C 64.7 and a methoxy group at δ_H 3.50; δ_C 50.9 was present in **1**. In particular, these NMR data of **1** were very similar to those of (+)-thujopsenol-α-epoxide [11], except for the presence of an additional methoxy group in **1**. The HMBC spectrum of **1** displayed key correlations of H-12 (H-13)/C-6, C-10, C-11, of H-14/C-5, C-7, C-8, and of H-15/C-2, C-3, C-4 (**Fig. 2**), which allowed us to confirm the planar structure of **1**. The HMBC correlation of the methoxy group at δ_H 3.50 with C-3 at δ_C 72.3 indicated that the methoxy group was linked to C-3 (**Fig. 2**). The relative configuration of **1** was established by analysis of the NOESY experiment (**Fig. 2**). The NOESY spectrum showed correlations of H-1/H-13, H-1/H-14, H-2/H-12, H-2/H-4, H-4/H-12, and H-5/H-12, but no correlation was observed between H-1 and H-4 or H-5 and between H-14 and H-4 or H-5 (**Fig. 2**). As a result, it was determined that the epoxy group at C4–C5 has an α-configuration. NOESY correlations between the proton signal of the methoxy group and H-14 and between H-2 and H-15 were observed, suggesting the assignment of α-orientation for the methoxy group (**Fig. 2**). According to these data, the structure of **1** was elucidated as 3α-methoxy-4α-epoxythujopsane.

Compound **2** was obtained as colorless oil ($[\alpha]_D^{25}$ – 25.9). Its molecular formula was determined to be $C_{15}H_{22}O$ using positive HR-ESIMS, which showed a positive ion $[M + H]^+$ at *m/z* 219.1748 (calcd. for $C_{15}H_{23}O$, 219.1749). The ^{1}H and ^{13}C NMR data (**Table 1**) of **2** were similar to those of **1**, except that the proton and carbon resonances of the methoxy group and one tertia-

Table 2 ^{1}H and ^{13}C NMR data of compounds **3** and **4** in $CDCl_3$. (δ in ppm, 500 MHz for ^{1}H and 125 MHz for ^{13}C.)[a]

Position	3		4	
	δ_H	δ_C	δ_H	δ_C
1	0.47 dd (9.0, 4.0) 0.34 dd (5.0, 5.0)	8.0	0.72 dd (6.0, 4.5) 0.56 dd (10.0, 4.5)	13.7
2		72.3	1.95 ddd (10.0, 6.0, 4.5)	25.2
3		142.0		144.1
4	5.19 br s	123.5	5.75 d (10.0)	121.7
5	1.77 br d (12.5) 1.61 br d (12.5)	40.7	5.15 d (10.0)	141.9
6		32.8		34.2
7		26.7		39.4
8	1.53 m 1.34 ddd (13.5, 13.5, 4.0)	36.8	1.58 m 1.22 ddd (13.5, 13.5, 3.5)	39.6
9	1.72 m 1.59 m	18.6	1.76 m 1.54 m	18.5
10	1.51 m 1.23 td (13.5, 4.0)	40.3	1.52 m 1.30 td (13.5, 3.5)	40.6
11		33.0		36.8
12	1.07 s	27.2	0.66 s	28.6
13	0.66 s	29.6	1.09 s	27.4
14	1.18 s	26.9	1.25 s	26.3
15	3.61 d (11.0) 3.52 d (11.0)	70.5	4.89 br s 4.72 br s	107.0

[a] *J* values are in parentheses and reported in Hz; the assignments were based on ^{1}H-^{1}H COSY, HMQC, and HMBC experiments

ry methyl group in **1** were absent, and instead, the resonances of characteristic signals for the exomethylene group at δ_H 5.16 and 5.14; δ_C 114.1 was present in **2**. The structure was further confirmed by an HMBC experiment showing the correlations from H-15 (δ_H 5.16 and 5.14) to C-2 (δ_C 24.3), C-3 (δ_C 142.4), and C-4 (δ_C 56.5) (**Fig. 2**). The NOESY spectrum showed correlations of H-1/H-4, H-1/H-5, H-1/H-13, H-1/H-14, H-2/H-12, H-5/H-14, and H-13/H-14, but no correlation was observed between H-2 and H-4 or H-5 or between H-12 and H-4 or H-5 (**Fig. 2**), which allowed us to assign the epoxy group at C4–C5 as having a *β*-orientation. The structure of **2** was thus determined to be $\Delta^{3,15}$-4*β*-epoxythujopsene. A survey of the literature revealed that an isomer of **2** was previously synthesized from mayurone oxide [13].

Compound **3**, isolated as a colorless gum ($[\alpha]_D^{25}$ + 9.2), has the molecular formula $C_{15}H_{24}O_2$, as deduced by the HR-ESIMS data at *m/z* 237.1857 $[M + H]^+$ (calcd. for $C_{15}H_{25}O_2$, 237.1855). Compound **3** had a band at 3357 cm^{-1} (OH) in the IR spectrum. The ^{1}H and ^{13}C NMR spectra (**Table 2**) of **3** were very similar to those of isolated compound **8** [14], except for the resonance attributable to an additional hydroxylated carbon signal at δ_C 72.3. The structure was further confirmed by the ^{1}H-^{1}H COSY, HMQC, and HMBC experiments (**Fig. 2**) where key HMBC correlations from H-4 (δ_H 5.19) to C-2 (δ_C 72.3) and from H-15 (δ_H 3.61 and 3.52) to C-2 (δ_C 72.3) were observed, suggesting that the location of the hydroxylated carbon was at C-2. The relative configuration of **3** was assigned by analysis of the NOESY experiment showing correlations of H-1/H-13, H-1/H-14, H-12/H-15 (δ_H 3.61), and H-13/H-14 (**Fig. 2**). In conclusion, the structure of **3** was established as $\Delta^{3,4}$-thujopsen-2,15-diol.

The known compound thujopsadiene (**4**) was previously identified by GC-MS [15]. In this study, we conducted full assignments of the NMR data for **4** by analyzing its 2D-NMR data (including COSY, HMQC, HMBC, and NOESY) since the NMR data of this compound have not been reported. To the best of our knowledge, the full assignments of the NMR data are reported in this study for the first time.

The known compounds were identified as 3*α*-hydroxy-4-thujopsene (**5**) [12], 3*β*-hydroxy-4-thujopsene (**6**) [12], mayurone oxide (**7**) [13], thujopsen-12-ol (**8**) [14], mayurone (**9**) [12], thujopsan-2*α*-ol (**10**) [16], and dihydromayurone (**11**) [17] by comparison of their spectroscopic data with values reported previously. The relative configurations of the above known compounds were established based on NOESY experiments.

The cytotoxic activities of the isolates (**1**–**11**) were evaluated by determining their inhibitory effects on human tumor cell lines (A549, SK-OV-3, SK-MEL-2, and HCT-15) using the SRB bioassay [18]. The essential oils of this plant have been used to treat cancer [4], and we have recently identified the cytotoxic diterpenoids from this plant [10]. The results (**Table 3**) showed that all compounds, **1**–**11**, displayed significant antiproliferative activities against the SK-MEL-2 cell line with IC_{50} values of 5.85–28.64 µM. Compounds **1, 4**–**7**, and **9** showed cytotoxic activities against the SK-OV-3 cell line with IC_{50} values of 8.46–21.54 µM. But only compounds **5** and **6** were cytotoxic against the A549 and HCT-15 cell lines with IC_{50} values of 13.62–27.12 µM. Based on the data obtained from each group of compounds (A: **1, 5, 6**, and **10**; B: **2** and **4**; C: **7, 9**, and **11**) with the same skeletal structure, the presence of a $\Delta^{4,5}$-double bond in the skeleton of this sesquiterpene may be critical to increase cytotoxic activity against the tested cell lines as compounds **4**–**6** and **9** with the $\Delta^{4,5}$-double bond in each group (A, B, and C) had a higher cytotoxicity, compared to the other compounds, though more related sesquiterpenes need to be tested to confirm this hypothesis. In the same context, the presence of the hydroxyl group at C-2 might be a positive influence on the activity against the SK-MEL-2 cell line considering the biological results of compounds **3** and **8** with the same skeletal structure.

This plant (*T. orientalis*) has been recognized as an herbal medicine for treatment of various inflammatory diseases such as dermatitis, gout, and chronic tracheitis [1,2]. Moreover, the anti-inflammatory effects of *T. orientalis* have been reported through some researches [19,20]. Therefore, we also investigated the anti-inflammatory activities of the isolates (**1**–**11**) in the lipo-

Table 3 Cytotoxic activities of compounds **1–11** isolated from *T. orientalis*.

Compound	IC_{50} (μM)[a]			
	A549	SK-OV-3	SK-MEL-2	HCT-15
1	> 30.0	18.41	7.36	> 30.0
2	> 30.0	> 30.0	25.07	> 30.0
3	> 30.0	> 30.0	9.08	> 30.0
4	> 30.0	16.22	12.16	> 30.0
5	24.19	9.37	8.26	27.12
6	13.62	13.14	5.85	18.04
7	> 30.0	21.54	14.31	> 30.0
8	> 30.0	> 30.0	26.40	> 30.0
9	> 30.0	8.46	7.18	> 30.0
10	> 30.0	> 30.0	28.64	> 30.0
11	> 30.0	> 30.0	27.10	> 30.0
Doxorubicin[b]	0.001	0.002	0.001	0.097

[a] IC_{50} value of compounds against each cancer cell line. IC_{50} value was defined as concentration (μM) causing 50% inhibition of cell growth *in vitro*. [b] Doxorubicin as a positive control

polysaccharide (LPS)-stimulated murine microglia BV-2 cell line. Anti-inflammatory activity was determined by measuring the secreted level of the proinflammatory mediator, nitric oxide (NO), in the medium. Among all tested compounds, compounds **1, 3, 4, 7, 8**, and **9** inhibited NO levels with IC_{50} values of 3.93–17.85 μM without significant cytotoxicity (**Table 4**). In particular, the new sesquiterpenes (**1** and **3**) were more effective than N^G-monomethyl-L-arginine, an inducible NO synthase inhibitor which was tested as a positive control (IC_{50}: 15.26 μM).

Materials and Methods

The aerial parts of *T. orientalis* were purchased at Kyungdong herbal market, Seoul, Korea, in January 2011, and were identified by one of the authors (K.R. Lee). A voucher specimen (SKKU 2011–01) was deposited in the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea. The plant material (3 kg) was crushed and subjected to steam distillation (4 h) in a distillation apparatus to obtain its essential oils (300 g). The essential oils were subjected to silica gel flash column chromatography eluting with *n*-hexane (3 L) to give a crude hexane fraction (100 g). The hexane fraction was applied to repeated column chromatography to purify compounds **1**–**11** (Supporting Information).

A detailed description of the bioassays is available in Supporting Information. The positive controls doxorubicin (purity ≥ 98%) and N^G-monomethyl-L-arginine (purity ≥ 98%) were purchased from Sigma Corporation. The tested compounds were demonstrated to be pure as evidenced by NMR and HPLC analyses (purity ≥ 95%).

Supporting information

The general experimental procedures, isolation details, bioassay protocol, and 1D and 2D NMR spectra for new compounds **1**–**3** are available as Supporting Information.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (20100029358). The authors would like to thank Mr. Do Kyun Kim, Dr. Eun Jung Bang, and Dr. Jung Ju Seo at the Korea Basic Science Institute for the NMR and MS spectral measurements.

Table 4 Inhibitory effect on NO production of compounds **1–11** isolated from *T. orientalis* in LPS-activated BV-2 cells.

Compounds	IC_{50}[a] (μM)	Cell viability[b] (%)
1	3.93	110.2 ± 8.7
2	24.59	102.3 ± 4.4
3	13.50	106.0 ± 2.9
4	15.74	106.1 ± 4.7
5	26.68	99.7 ± 4.4
6	64.58	98.1 ± 1.2
7	16.77	104.1 ± 2.1
8	15.80	105.9 ± 6.1
9	17.85	103.4 ± 2.4
10	35.51	102.8 ± 3.5
11	30.51	104.3 ± 8.3
NMMA[c]	15.26	105.6 ± 2.3

[a] IC_{50} value of each compound was defined as concentration (μM) causing 50% inhibition of NO production in LPS-activated BV-2 cells. [b] Cell viability after treatment with 20 μM of each compound was expressed as a percentage (%) of the LPS only treatment group. The results are expressed as mean ± SD. [c] NMMA as a positive control

Conflict of Interest

All authors declare that there are no conflicts of interest.

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received July 1, 2013
revised September 3, 2013
accepted September 17, 2013

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DOI http://dx.doi.org/10.1055/s-0033-1350952
Published online October 17, 2013
Planta Med 2013; 79: 1680–1684

ISSN 0032-0943

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