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# SECOISOLANCIFOLIDE AND SECOISOOBTUSILACTONE IN *ACTINODAPHNE LONGIFOLIA*

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**Key Word Index**—*Actinodaphne longifolia*; Lauraceae; isolancifolide; isoobtusilactone; seco-isolancifolide; secoisoobtusilactone.

**Abstract**—Two new compounds, secoisolancifolide and secoisoobtusilactone, were isolated from the leaves of *Actinodaphne longifolia* and the structures established by chemical and spectroscopic data methods.

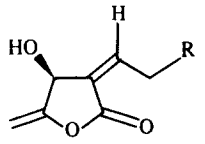
## INTRODUCTION

Previously, we have reported [1] the isolation and the structural determination of the two lactonic compounds, lancifolide (**1**) and isolancifolide (**2**), from *Actinodaphne lancifolia*. In the course of our further investigation of the genus *Actinodaphne*, two new compounds were isolated from *Actinodaphne longifolia* (Blume) Nakai along with isolancifolide (**2**) [1], isoobtusilactone (**4**) [1], sesamin, piperitol, actifolin [2], and three furan derivatives, sesquirosefuran, longifolin, and 8-[2′(3′-methyl)furanyl]-2,6-dimethyl-2,6-octadiene-4-one [3]. We now wish to report the isolation and structural elucidation of these new compounds (**6** and **8**) which are probably precursors of the corresponding lactones (**2** and **4**).

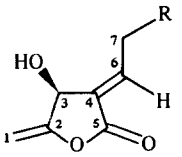
## RESULTS AND DISCUSSION

The ethanol extracts of *A. longifolia* provided isolancifolide (**2**), isoobtusilactone (**4**), secoisolancifolide (**6**) and secoisoobtusilactone (**8**). The known lactonic compounds (**2**, **4**) [1] were identified by direct comparison with authentic samples.

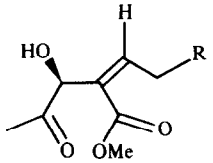
Secoisolancifolide (**6**), $C_{16}H_{28}O_4$, gave IR absorption bands due to the presence of a hydroxy group (3475 $cm^{-1}$), an ester group (1730 $cm^{-1}$), and a carbonyl group (1720 $cm^{-1}$). Acetylation of secoisolancifolide with acetic anhydride and pyridine gave an acetyl derivative (**9**). The $^1H$ NMR spectrum of secoisolancifolide contained the signals for an olefinic proton ($\delta$7.08, *t*, 1H), a methine proton ($\delta$4.90, *d*, 1H), a hydroxy group ($\delta$4.01, *d*, 1H), a methoxy group ($\delta$3.73, *s*, 3H), an acetyl group ($\delta$2.15, *s*, 3H) methylene groups ($\delta$2.35, *q*, 2H and 1.27, *br s*, 14H), and a methyl group ($\delta$0.88, *t*, 3H). In the $^{13}C$ NMR spectrum, all the signals of secoisolancifolide were very similar to those of **2**, except for the presence of those of an acetyl group ($\delta$206.3 and 24.9) instead of the $\gamma$-*exo*-methylene group ($\delta$157.8 and 91.4) observed in **2** (Table 1). These data suggest that secoisolancifolide was a ring-cleavage derivative of **1** or **2** as shown by the formula **5** or **6**, respectively.



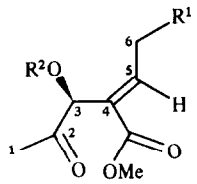
**1** R = $(CH_2)_7Me$
**3** R = $(CH_2)_8$—CH═$CH_2$



**2** R = $(CH_2)_7Me$
**4** R = $(CH_2)_8$—CH═$CH_2$



**5** R = $(CH_2)_7Me$
**7** R = $(CH_2)_8$—CH═$CH_2$



**6** $R^1$ = $(CH_2)_7Me$, $R^2$ = H
**8** $R^1$ = $(CH_2)_8CH$═$CH_2$, $R^2$ = H
**9** $R^1$ = $(CH_2)_7Me$, $R^2$ = Ac

Table 1. $^{13}C$ NMR data of compounds **2**, **4**, **6** and **8**

| Lactones | 2 | 4 | 6 | 8 | Seco-compounds |
|---|---|---|---|---|---|
| C-1 | 91.4 | 91.4 | 24.9 | 24.8 | C-1 |
| C-2 | 157.8 | 157.8 | 206.3 | 206.3 | C-2 |
| C-3 | 66.6 | 66.6 | 73.4 | 73.4 | C-3 |
| C-4 | 127.5 | 127.4 | 129.8 | 129.8 | C-4 |
| C-5 | 166.8 | 166.7 | 166.6 | 166.6 | COOMe |
| C-6 | 150.2 | 150.2 | 149.1 | 149.0 | C-5 |
| C-7 | 31.9 | 33.9 | 31.9 | 33.8 | C-6 |
| $CH_2$ | 29.8 | 29.7 | 29.4 | 29.7 | $CH_2$ |
| | 29.5 | 29.5 | 28.7 | 29.4 | |
| | 29.4 | 29.2 | 22.7 | 28.9 | |
| | 28.4 | 29.0 | | 28.7 | |
| | 22.8 | 28.4 | | | |
| –CH= | | 139.3 | | 139.2 | –CH= |
| $=CH_2$ | | 114.2 | | 114.1 | $=CH_2$ |
| Me | 14.2 | | 14.1 | | Me |
| | | | 52.0 | 52.0 | OMe |

Treatment of isolancifolide (**2**) with hydrogen chloride—methanol afforded a single ester (**6**) which was identical with secoisolancifolide in all respects. Treatment of lancifolide (**1**) also gave a single ester (**5**) which was supposed to be a geometrical isomer of secoisolancifolide. Therefore, the structure of secoisolancifolide was determined to be **6**. The stereochemistry of the C-3 position was assigned as 3*S* by Horeau's method [4]. This compound is not an artifact but a natural product, because it was isolated from both a methanolic and an ethanolic extract of the plant material in identical amounts and no ethyl ester was found.

Secoisoobtusilactone (**8**), $C_{18}H_{30}O_4$, gave IR absorption bands due to the presence of a hydroxy group (3475 $cm^{-1}$), an ester group (1730 $cm^{-1}$) and a carbonyl group (1720 $cm^{-1}$). Its $^1H$ NMR spectrum was very similar to that of **6** except for the presence of an allyl signal ($\delta$5.81, *ddt*, 1H, 4.91–5.03, *m*, 2H, and 2.04, *br q*, 2H) instead of the methyl signal ($\delta$0.88, *t*, 3H) in **6**. In the $^{13}C$ NMR spectrum, all the signals of secoisoobtusilactone were very similar to those of isoobtusilactone (**4**) [5], except for the presence of an acetyl group ($\delta$206.3 and 24.8) instead of the $\gamma$-*exo*-methylene group ($\delta$157.8 and 91.4) observed in **4** (Table 1). These data suggest that secoisoobtusilactone was a ring-cleavage derivative of **3** [6] or **4** as shown by the formula **7** or **8**, respectively.

Treatment of the mixture of obtusilactone (**3**) and **4** (3:1) with hydrogen chloride—methanol afforded a mixture of esters, **7** and **8** (2:1), of which the minor component was identical with secoisoobtusilactone. Therefore, the structure of secoisoobtusilactone was determined to be **8**.

This is the first report of the isolation of *seco* derivatives of $\gamma$-lactones which are often found in other lauraceous plants [1, 5–8].

## EXPERIMENTAL

CC was run on Merck silica gel 60 (230–400 mesh) and florisil (100–200 mesh). TLC was performed on glass plates precoated with Kieselgel 60 $F_{254}$ (Merck). $^1H$ NMR (270 MHz) and $^{13}C$ NMR (25 MHz) spectra were determined in $CDCl_3$. Analytical HPLC, JASCO 880-PV and 875-UV UV detector (254 nm), was conducted on a Develosil pack ODS-5 column (4.6 × 150 mm). The eluent, MeOH–$H_2O$ (3:1), was pumped at 1.0 ml/min. Prep. HPLC was carried on a Develosil pack ODS-10 column (20 × 250 mm) using the same solvent.

*Extraction and separation of compounds. Actinodaphne longifolia* was collected in the Kagoshima prefecture in August 1987. The plant material was divided into leaves (6.0 kg) and wood (3.0 kg). The MeOH extract of the leaves was divided into the *n*-hexane soluble (150 g) and $CHCl_3$ soluble fractions (32 g). The *n*-hexane-soluble fraction was chromatographed on florisil with $C_6H_6$ as an eluent to give sesquirosefuran (1.3 g), longifolin (7.7 g), and a crude mixture (1.0 g) of secoisolancifolide (**6**) and secoisoobtusilactone (**8**). Separation of the mixture (**6** and **8**) by CC on silica gel (*n*-hexane–$Me_2CO$, 9:1) followed by prep. TLC using 5% $AgNO_3$–Kieselgel 60 $F_{254}$ ($CHCl_3$–$Me_2CO$, 19:1) afforded **6** (199 mg) and **8** (12 mg). The $CHCl_3$-soluble fraction was chromatographed on florisil. Elution with $CHCl_3$ afforded an oil (3.7 g), a part of which (0.3 g) was subjected to chromatography on silica gel ($CHCl_3$–$Me_2CO$, 49:1) followed by prep. TLC ($CHCl_3$–$Me_2CO$, 19:1) to give 6 (8 mg). Further elution with $CHCl_3$–$Me_2CO$ (9:1) afforded an oil (1.8 g), which was rechromatographed on silica gel to yield sesamin (8 mg), piperitol (37 mg) and actifolin (24 mg) [2].

The EtOH extract of wood was similarly divided into *n*-hexane soluble (26.8 g) and $CHCl_3$ soluble fractions (12.3 g). The *n*-hexane soluble fraction was chromatographed on a silica gel column. Elution with $C_6H_6$ gave sesquirosefuran (110 mg), longifolin (200 mg), and 8-[2′(3′-methyl)furanyl]-2,6-dimethyl-2,6-octadiene-4-one (63 mg) [3]. Elution with $C_6H_6$–EtOAc (9:1) provided an oil (4 g), a portion (1.2 g) of which was separated by CC on silica gel ($C_6H_6$–EtOAc, 9:1) and further by prep. HPLC (flow rate 9 ml/min) to give isolancifolide (2) (29 mg, $R_t$ 38 min) and isoobtusilactone (**4**) (4 mg, $R_t$ 59 min). A part of the $CHCl_3$-soluble fraction (1.8 g) was separated by CC on silica gel ($CHCl_3$–$Me_2CO$, 19:1) followed by prep. TLC ($C_6H_6$–EtOAc, 9:1) to give a mixture of **2** and **4** (16:1), which was identified with authentic samples [1] by direct comparison of $^1H$ NMR spectra and $R_t$ in HPLC.

The *n*-hexane-soluble fraction (3.0 g) of the EtOH extract of the leaves was also examined, as already described for the MeOH extract, to afford secoisolancifolide (**6**) (4.1 mg). The yield of **6** was about equal to that of the *n*-hexane-soluble fraction of the MeOH extract described above, and no ethyl ester was found in this fraction.

*Secoisolancifolide* (**6**). Colourless oil. $[\alpha]_D$ +102.7° ($CHCl_3$; *c* 0.49); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$; 3475, 1730, 1720, 1650; UV $\lambda_{max}^{EtOH}$ nm; 213; CI-MS (*iso*-$C_4H_9$) *m/z*; 285 $[M+1]^+$; FAB-HRMS *m/z*; 285.2047 ($M^+ + 1$, calcd for $C_{16}H_{29}O_4$: 285.2064); $^1H$ NMR; δ0.88 (3H, *t*, *J* = 6.4 Hz, 14-H), 1.27 (14H, *br s*), 2.15 (3H, *s*, 1-H), 2.35 (2H, *q*, *J* = 7.7 Hz, 6-H), 3.73 (3H, *s*, OMe), 4.01 (1H, *d*, *J* = 4.7 Hz, OH), 4.90 (1H, *d*, *J* = 4.7 Hz, 3-H), 7.08 (1H, *t*, *J* = 7.7 Hz, 5-H); $^{13}C$ NMR: Table 1.

*Secoisoobtusilactone* (**8**). Colourless oil. $[\alpha]_D$ +72.2° ($CHCl_3$; *c* 0.18); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$; 3475, 1730, 1720, 1645; UV $\lambda_{max}^{EtOH}$ nm; 213; CIMS (*iso*-$C_4H_9$) *m/z*; 311 $[M+1]^+$; HRMS *m/z*; 310.2126 ($M^+$, calcd for $C_{18}H_{30}O_4$: 310.2145); $^1H$ NMR; δ1.28 (14H, *br s*), 2.04 (2H, *br q*, *J* = 6.7 Hz, 14-H), 2.15 (3H, *s*, 1-H), 2.35 (2H, *q*, *J* = 7.4 Hz, 6-H), 3.73 (3H, *s*, OMe), 4.01 (1H, *d*, *J* = 4.4 Hz, OH), 4.90 (1H, *d*, *J* = 4.4 Hz, 3-H), 4.91–5.03 (2H, *m*, 16-H), 5.81 (1H, *ddt*, *J* = 17.1, 10.1, 6.7 Hz, 15-H), 7.08 (1H, *t*, *J* = 7.7 Hz, 5-H); $^{13}C$ NMR: Table 1.

*Acetylation of secoisolancifolide.* A mixture of **6** (5 mg), $Ac_2O$ (0.2 ml), and pyridine (0.2 ml) was stirred at room temp. overnight. Work-up in the usual way afforded a colourless oil (**9**, 5 mg): $[\alpha]_D$ +33.2° ($CHCl_3$; *c* 0.25); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$; 1735; UV $\lambda_{max}^{EtOH}$ nm; 211; CIMS (*iso*-$C_4H_9$) *m/z*; 327 $[M+1]^+$; FAB-HRMS *m/z*; 327.2189 ($M^+ + 1$, calcd for $C_{18}H_{31}O_5$: 327.2170); $^1H$ NMR; δ0.88 (3H, *t*, *J* = 6.4 Hz, 14-H), 1.26 (14H, *br s*), 2.16 (3H, *s*, 1-H), 2.20 (3H, *s*, COMe), 2.27–2.40 (2H, *m*, 6-H), 3.78 (3H, *s*, OMe), 6.10 (1H, *s*, 3-H), 7.14 (1H, *t*, *J* = 7.7 Hz, 5-H).

*Methanolysis of lancifolide.* A mixture of **1** (12 mg) and satd HCl–MeOH (1 ml) was stirred at room temp. for 30 min. The reaction mixture was evapd to dryness and then the residue was purified by prep. TLC ($CHCl_3$–$Me_2CO$, 19:1) to afford a colourless oil (**5**, 2.1 mg): $[\alpha]_D$ +204.8° ($CHCl_3$; *c* 0.11); IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$; 3475, 1730; UV $\lambda_{max}^{EtOH}$ nm; 213; FAB-MS *m/z*; 285 $[M+1]^+$; FAB-HRMS *m/z*; 285.2051 ($M^+ + 1$, calcd for $C_{16}H_{29}O_4$: 285.2064); $^1H$ NMR; δ0.88 (3H, *t*, *J* = 6.4 Hz, 14-H), 1.27 (14H, *br s*), 2.20 (3H, *s*, 1-H), 2.54 (2H, *m*, 6-H), 3.74 (3H, *s*, OMe), 4.05 (1H, *br s*, OH), 4.54 (1H, *s*, 3-H), 6.34 (1H, *t*, *J* = 7.7 Hz, 5-H).

*Methanolysis of isolancifolide.* A mixture of **2** (13 mg) was treated in the same way as just described for **1** to afford a colourless oil (**6**, 0.8 mg): $[\alpha]_D$ +222.5° ($CHCl_3$; *c* 0.04); FAB-HRMS *m/z*; 285.2051 ($[M+1]^+$, calcd for $C_{16}H_{29}O_4$: 285.2064). This compound was identical with natural secoisolancifolide (**6**) in all respects (IR, UV, and $^1H$ NMR).

*Absolute configuration of secoisolancifolide by Horeau's method* [4]. A soln of α-phenylbutyric anhydride (185 mg) and **6** (61 mg), in pyridine (2.5 ml) was allowed to stand at room temp. overnight. Excess anhydride was destroyed by adding water (1 ml) and leaving the mixture to stand at room temp. for 6 hr. The soln was extracted with EtOAc. The EtOAc layer was washed with water, and extracted with aq. 5% $NaHCO_3$ and again with $H_2O$. The combined aq. extracts were washed with $CHCl_3$ and acidified with 0.5 M $H_2SO_4$. The acidified soln was extracted with $CHCl_3$ and the $CHCl_3$ extract was dried and evapd. This afforded 117 mg of α-phenylbutyric acid. $[\alpha]_D$ +0.56° ($C_6H_6$; *c* 2.3 ), theoretical $[\alpha]_D$ +21.0°. The optical yield therefore was 2.7%.

*Methanolysis of obtusilactone* (**3**) *and isoobtusilactone* (**4**). A mixture (3:1) of **3** and **4** (16 mg) was treated in the same way as described above for **1** and **2** to afford a colourless oil (2:1 mixture of **7** and **8**, 2.4 mg). The minor component was identical with natural secoisoobtusilactone by direct comparison of $^1H$ NMR and $R_t$ in analytical HPLC (flow rate 1.0 ml/min; **7**: $R_t$ 24.5 min; **8**: $R_t$ 22.9 min).

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