

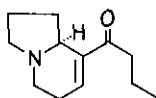
ELAEOCARPUS ALKALOIDS. THE SYNTHESIS OF (±)-ELAEOKANINE A,
(±)-ELAEOKANINE B, AND (±)-ELAEOKANINE C

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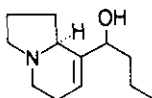
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Abstract---The synthesis of (±)-elaeokanines A, B and C by using compound 2 as
an intermediate is described.

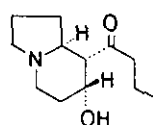
The Elaeocarpus alkaloids have been isolated by Johns et al.¹⁾ from the leaves of Elaeocarpus
species (family Elaeocarpaceae), rain-forest trees which flourish in New Guinea and India.²⁾
All these alkaloids contain the characteristic trans-indolizidine ring system.



elaeokanine A



elaeokanine B



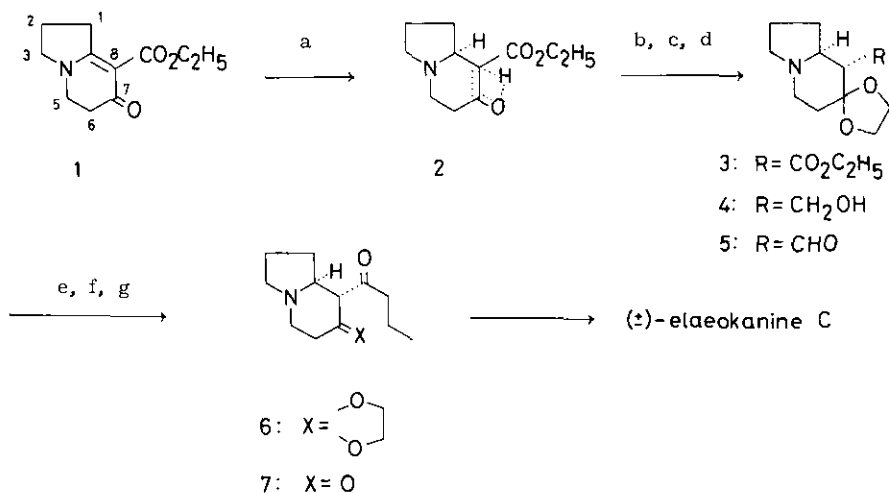
elaeokanine C

Several synthetic methods for indolizidine derivatives have been reported,³⁾ but these
seem inconvenient for Elaeocarpus alkaloids synthesis for lack of suitable functionality and
instability of indolizidine ring for various reagents. For example, Johns et al. reported that
the trans-indolizidine ring in Elaeocarpus alkaloids was easily cleaved when these alkaloids
were treated with an acylating agent^{1a)} and the acylation of the enolate anion of 7-oxo-
indolizidine did not give the desired acylated products with the only exception by 2-methyl-
6-methoxybenzoyl cyanide.⁴⁾ We developed the synthetic methods of indolizidine derivatives
which contained the appropriate functional groups at the C-7 and C-8 positions⁵⁾ and planned
to synthesize the title compounds,⁶⁾ as shown in Schemes I and II, which were isolated from
Elaeocarpus kaniensis Schltr. in 1972.^{1d)}

Recently, Trost et al. reported the synthesis of quinolizidine derivatives from imino-
ethers and α, β -unsaturated ketones.⁷⁾ Extension of this method to 2-ethoxy-1-pyrroline and
ethyl 3-oxo-pentenoate gave the compound 1 in 80% yield [mp. 70.5-71° C; m/e 209(M⁺);

$\nu_{\text{max}}^{\text{CHCl}_3}$ 1710, 1665, 1640, 1560 cm^{-1} ; δ 4.22 (2H, quar, $J=7.1$ Hz, $-\text{COOCH}_2-\text{CH}_3$), 3.59 (2H, t, $J=7.8$ Hz, C_3-H), 3.55 (2H, t, $J=7.8$ Hz, C_5-H), 3.27 (2H, t, $J=7.8$ Hz, C_1-H), 2.59 (2H, t, $J=7.8$ Hz, C_6-H), 2.13 (2H, quin, $J=7.8$ Hz, C_2-H), 1.31 (3H, t, $J=7.1$ Hz, $-\text{COOCH}_2-\text{CH}_3$).

Selective reduction of **1** with LiAlH_4 gave the *trans*-indolizidine **2** in 90% yield [the picrate, mp. 173.5-174, 5°C ; m/e 211 (M^+); $\nu_{\text{max}}^{\text{CCl}_4}$ 3445, 2800-2600 (Bohlmann band), 1740, 1720, 1650, 1615 cm^{-1}]. The compound **2** is one of the versatile intermediates for the synthesis of *Elaeocarpus* alkaloids⁹⁾ and we synthesized (\pm)-*elaeokanine C* as shown in Scheme I by using **2** as a starting material.

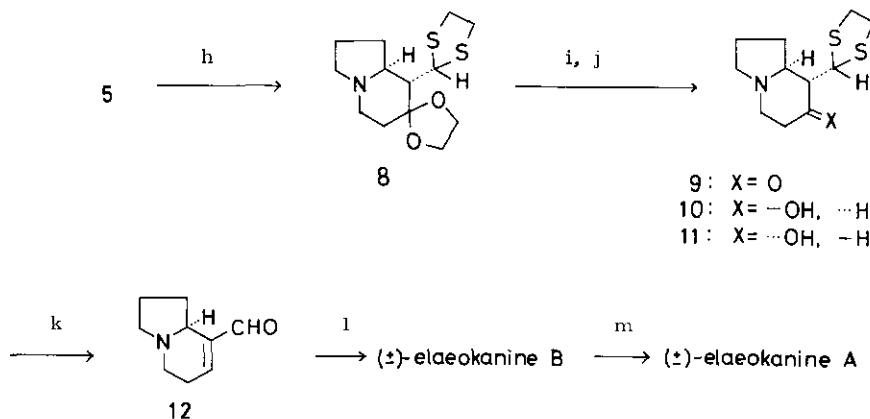


(a) LiAlH_4 (1.5 equiv.), THF, Et_2O , -70°C , 1 hr. (b) $(\text{CH}_2\text{OH})_2$, *p*-TsOH (1.5 equiv.), benzene, 72 hr. (c) LiAlH_4 (1.5 equiv.), THF, Et_2O , reflux 3 hr. (d) NCS, DMS, toluene, CH_2Cl_2 , -25°C , 2.5 hr. (e) *n*-PrMgBr (5.0 equiv.), THF, Et_2O , reflux 3 hr. (f) Jones oxid. (g) 47% aq. HBr, room temperature, 3 hr.

Scheme I

The LiAlH_4 reduction of **3**, which was obtained in 90% yield from **2** by treatment with ethylene glycol, gave the alcohol **4** in 90% yield [mp. $92-93^\circ\text{C}$; m/e 213 (M^+); $\nu_{\text{max}}^{\text{CCl}_4}$ 3550 cm^{-1} ; δ 3.83 (1H, dd, $J=11.5$ Hz, $J=3.0$ Hz), 3.66 (1H, dd, $J=11.5$ Hz, $J=5.0$ Hz), both signals are assigned to $-\text{CH}_2\text{OH}$]. Oxidation of **4** with NCS-DMS gave the aldehyde **5** in 95% yield [m/e 211 (M^+); $\nu_{\text{max}}^{\text{CCl}_4}$ 1730 cm^{-1} ; δ 9.78 (1H, d, $J=1.0$ Hz, $-\text{CHO}$)]. The Grignard reaction of **5** with *n*-PrMgBr followed by the Jones oxidation gave the ketone **6** in 80% yield from **4**

[the picrate, mp. 162.5-163.5°C; m/e 253 (M^+); $\nu_{\max}^{\text{CCl}_4}$ 1715 cm^{-1}]. Hydrolysis of the ethylene ketal in **6** was furnished by treatment with 47% aq. HBr for 3 hr at room temperature and gave **7** in 70% yield, whose spectral data [$\nu_{\max}^{\text{CCl}_4}$ 1720-1680 cm^{-1} (broad); $\lambda_{\max}^{\text{EtOH}}$ 295 nm (ϵ 2860) shifted to $\lambda_{\max}^{\text{EtOH}}$ 308 nm (ϵ 13200) on addition of NaOH] were identical with those reported by Johns *et al.*.^{1d)} The synthesis of **7**, which was already converted into (\pm)-elaeokanine C, thus constitutes a formal synthesis of (\pm)-elaeokanine C.



(h) $(\text{CH}_2\text{SH})_2$ (2.0 equiv.), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.3 equiv.), CH_3COOH , room temperature, 48 hr. (i) 47% aq. HBr, room temperature, 24 hr. (j) LiAlH_4 (1.2 equiv.), THF, Et_2O , reflux 3 hr. (k) MeI, THF, MeCN, HCl, reflux 48 hr. (l) $n\text{-PrMgBr}$ (5.0 equiv.), THF, Et_2O , reflux 3 hr. (m) Jones oxid.

Scheme II

(\pm)-Elaeokanines A and B were synthesized as shown in Scheme II. Treatment of the aldehyde **5** with $(\text{CH}_2\text{SH})_2/\text{BF}_3$ -etherate gave **8** in 95% yield [m/e 283 (M^+); δ 4.92 (1H, s, S-S-H), 3.30-3.13 (4H, m, $-\text{OCH}_2\text{CH}_2\text{O}-$)]. Hydrolysis of the ethylene ketal in **8** with 47% HBr gave the ketone **9** in 90% yield [m/e 243 (M^+); δ 4.95 (1H, d, $J=5.0$ Hz, S-S-H)]. Reduction of **9** with LiAlH_4 gave a mixture of isomeric alcohols **10** [mp. 101-102°C; m/e 245 (M^+); $\nu_{\max}^{\text{CCl}_4}$ 3480 cm^{-1} ; δ 4.90 (1H, s, S-S-H), 4.20-3.70 (1H, m, $\text{C}_7\text{-H}$)] and **11** [mp. 103-104°C; m/e 245 (M^+); $\nu_{\max}^{\text{CCl}_4}$ 3480 cm^{-1} ; δ 4.71 (1H, d, $J=6.0$ Hz, S-S-H), 4.60-4.30 (1H, m, $\text{C}_7\text{-H}$)] in a ratio of 3:2 in 93% yield. Treatment of the mixture of the alcohols **10** and **11** with MeI gave **12**, which was used without further purification in the next step since it decomposed on standing in air. The Grignard reaction of the aldehyde **12** gave (\pm)-elaeokanine

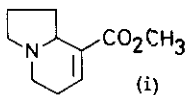
B in 70% yield from the mixture of 10 and 11 [m/e 195 (M^+); $\nu_{\max}^{CCl_4}$ 3150 cm^{-1} ; δ 5.66 (1H, m), 4.04 (1H, m), 0.91 (3H, t, $J=7.0$ Hz)]. Oxidation of (\pm)-elaeokanine B with the Jones reagent gave (\pm)-elaeokanine A in 80% yield [the picrate, mp. 139.5-140.5°C; m/e 193 (M^+); $\nu_{\max}^{CCl_4}$ 1670, 1630 cm^{-1} ; λ_{\max}^{EtOH} 229 nm (ϵ 9800); δ 6.87 (1H, m), 3.50 (1H, m), 2.62 (1H, t, $J=7.0$ Hz), 0.92 (3H, t, $J=7.0$ Hz)]. The spectral data of synthesized elaeokanines are identical with those of the natural products.

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References and Notes

The NMR spectral data of compounds 1, 4, and (\pm)-elaeokanines A and B were taken at 100 MHz and those of other compounds were measured at 60 MHz in $CDCl_3$ using TMS as the internal standard.

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- Compound (i) was prepared by the condensation of 1-pyrroline and methyl 2,4-pentadienoate in 30% yield (T. Watanabe, Y. Nakashita, S. Katayama, and M. Yamauchi, unpublished result). This compound seems most versatile for the synthesis of Elaeocarpus alkaloids, but is far unstable for further reactions.
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- Lions and Willison (ref. 3a) reported that they obtained 6- or 8-ethoxycarbonyl-7-oxo-indolizidine and its mp. was 137°C. We have found the reported compound is actually 6-ethoxycarbonyl-7-oxo-indolizidine and unsuitable for the synthesis of Elaeocarpus alkaloids.
- The synthesis of other Elaeocarpus alkaloids is now in progress.



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