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

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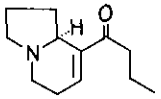
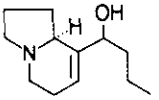
Abstract---The synthesis of (±)-elaeokanines A, B and C by using compound 2 as an intermediate is described.

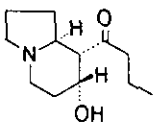
The Elaeocarpus alkaloids have been isolated by Johns et al.[1] from the leaves of Elaeocarpus species (family Elaeocarpaceae), rain-forest trees which flourish in New Guinea and India.[2] All these alkaloids contain the characteristic trans-indolizidine ring system.



elaeokanine A



elaeokanine B

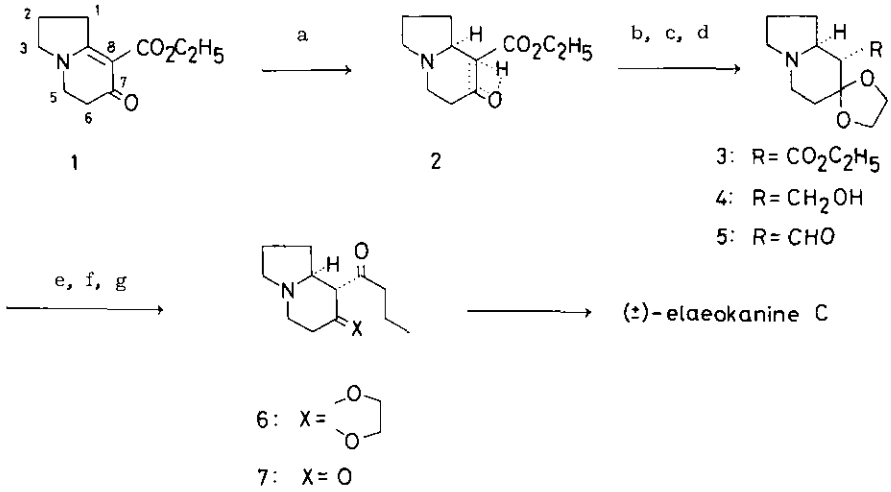


elaeokanine C

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 positions[5] 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^+);

$\nu_{max}^{CHCl_3}$ 1710, 1665, 1640, 1560 cm^{-1}; δ 4.22 (2H, quar, J=7.1 Hz, $-COOC\underline{H}_2-CH_3$), 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, $-COOCH_2-C\underline{H}_3$)]. Selective reduction of 1 with $LiAlH_4$ gave the trans-indolizidine 2 in 90% yield [the picrate, mp. 173.5-174.5°C;[8] m/e 211 (M^+); $\nu_{max}^{CCl_4}$ 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 alkaloids[9] and we synthesized (±)-elaeokanine C as shown in Scheme I by using 2 as a starting material.

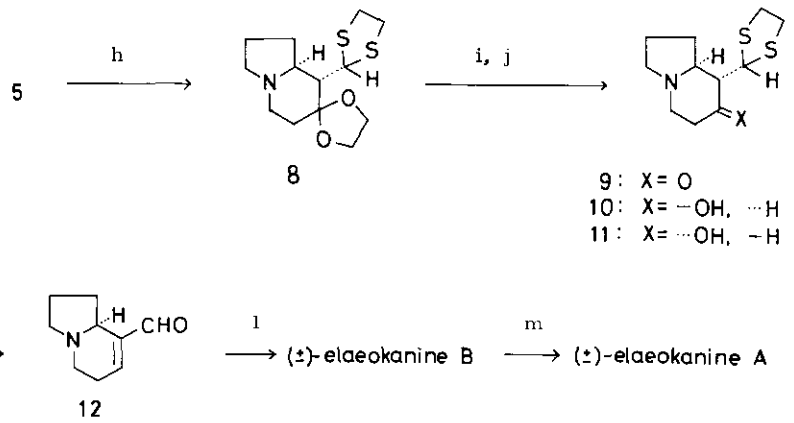


(a) $LiAlH_4$ (1.5 equiv.), THF, Et_2O, -70°C, 1 hr. (b) $(CH_2OH)_2$, p-TsOH (1.5 equiv.), benzene, 72 hr. (c) $LiAlH_4$ (1.5 equiv.), THF, Et_2O, reflux 3 hr. (d) NCS, DMS, toluene, CH_2Cl_2, -25°C, 2.5 hr. (e) n-PrMgBr (5.0 equiv.), THF, Et_2O, reflux 3 hr. (f) Jones oxid.. (g) 47% aq. HBr, room temperature, 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°C; m/e 213 (M^+); $\nu_{max}^{CCl_4}$ 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 $-C\underline{H}_2OH$]. Oxidation of 4 with NCS-DMS gave the aldehyde 5 in 95% yield [m/e 211 (M^+); $\nu_{max}^{CCl_4}$ 1730 cm^{-1}; δ 9.78 (1H, d, J=1.0 Hz, -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^+); $\nu_{max}^{CCl_4}$ 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 [$\nu_{max}^{CCl_4}$ 1720-1680 cm^{-1} (broad); λ_{max}^{EtOH} 295 nm (ε 2860) shifted to λ_{max}^{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 (±)-elaeokanine C, thus constitutes a formal synthesis of (±)-elaeokanine C.



(h) $(CH_2SH)_2$ (2.0 equiv.), BF_3-Et_2O (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-PrMgBr (5.0 equiv.), THF, Et_2O, reflux 3 hr. (m) Jones oxid..

Scheme II

(±)-Elaeokanines A and B were synthesized as shown in Scheme II. Treatment of the aldehyde 5 with $(CH_2SH)_2/BF_3$-etherate gave 8 in 95% yield [m/e 283 (M^+); δ 4.92 (1H, s, ), 3.30-3.13 (4H, m, $-OCH_2CH_2O-$)]. 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, )]. Reduction of 9 with $LiAlH_4$ gave a mixture of isomeric alcohols 10 [mp. 101-102° C; m/e 245 (M^+); $\nu_{max}^{CCl_4}$ 3480 cm^{-1}; δ 4.90 (1H, s, ), 4.20-3.70 (1H, m, C_7-H)] and 11 [mp. 103-104°C; m/e 245 (M^+); $\nu_{max}^{CCl_4}$ 3480 cm^{-1}; δ 4.71 (1H, d, J=6.0 Hz, ), 4.60-4.30 (1H, m, C_7-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 (±)-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 (±)-elaeokanine B with the Jones reagent gave (±)-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 (±)-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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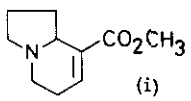
4. A. S. Howard, C. A. Meerholz, and J. P. Michael, Tetrahedron Letters, 1979, 1339.
5. Compound (i) was prepared by the condensation of 1-pyrroline and methyl 2,4-pentadienoate in 30% yield (T. Watanabe, Y. Nakashita, S. Katayama, and M. Yamauchi, unpublished result). This compound seems most versatile for the synthesis of Elaeocarpus alkaloids, but is far unstable for further reactions.



(i)

6. (a). J. J. Tufariello and Sk. A. Ali, Tetrahedron Letters, 1979, 4445; (b). A. S. Haward, G. C. Gerrans, and C. A. Meerholz, ibid., 1980, 21, 1373 have recently described the synthesis of (±)-elaeokanines A, B, and C.
7. B. M. Trost and R. A. Kunz, J. Am. Chem. Soc., 1975, 97, 7152.
8. 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.
9. The synthesis of other Elaeocarpus alkaloids is now in progress.

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