Tetrahedron Vol. 38, No. 17, pp. 2627 to 2633, 1982
Printed in Great Britain.

0040-4020/82/172627-07$03.00/0

A NOVEL TOTAL SYNTHESIS OF ELAEOCARPUS ALKALOIDS

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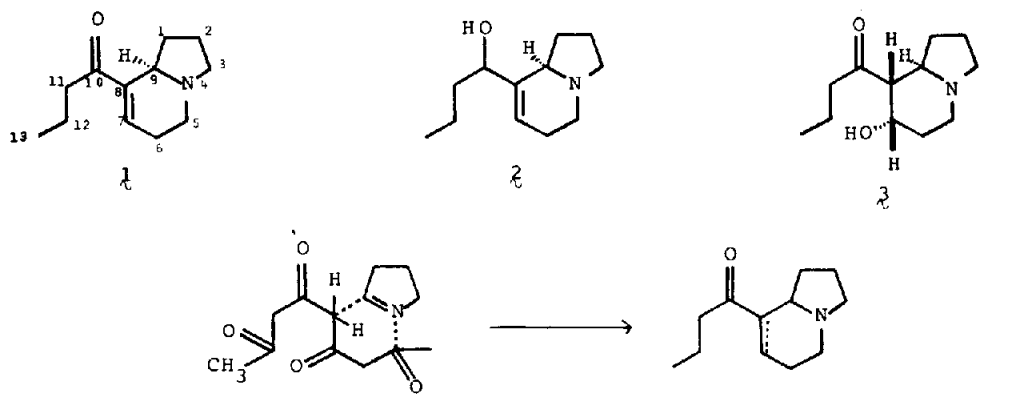
(*Received in Japan 5 June* 1982)

Abstract —— The novel synthesis of elaeocarpus alkaloids has been achieved employing 1,3-dipolar cycloaddition reaction as a key step.

Elaeocarpus alkaloids, such as elaeokanine A(1), B(2) and C(3), isolated from the leaves of Elaeocarpus kaniensis by Johns and his co-workers[1], are known to possess a characteristic trans-indolizidine ring system. These alkaloids can be derived from appropriate condensation of ornithine and a C_8-polyketide, and a biosynthetic scheme for the derivation of these alkaloids has been shown[1] in scheme 1.

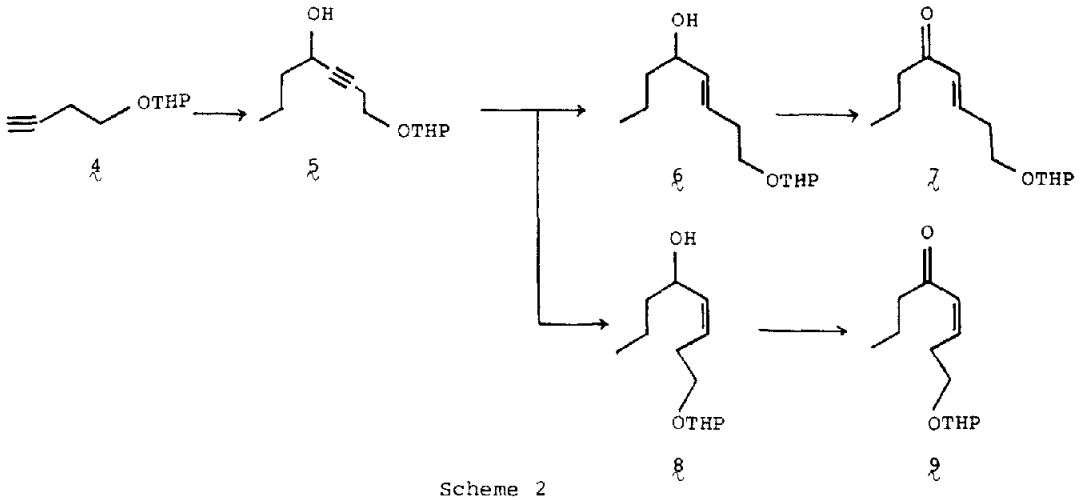
We have planned to synthesize these alkaloids along with the above biosynthetic pathway. For this purpose, the 1,3-dipolar cycloaddition reaction of Δ^1-pyrrolin-1-oxide, which might serve as a chemical equivalent of ornithine, with an appropriate eight-carbons dipolarophile has been investigated. With regard to the synthesis of these alkaloids, many papers[2-9] have appeared to date. In fact, the synthesis of elaeokanine C employing 1,3-dipolar cycloaddition reaction has originally been achieved by Tufariello[5], who however has used Δ^1-pyrrolin-1-oxide and pent-1-ene as starting materials and the C_5 - C_7 carbons have been introduced at the later stage.



Scheme 1

RESULTS AND DISCUSSION

Our requisite enone as a dipolarophile, which would be a substitute of C_8-polyketide was prepared as follows. Butyn-1-ol tetrahydropyranyl ether (4) was treated with n-butyraldehyde in the presence of n-butyllithium to afford the acetylenic alcohol (5), whose reduction with lithium aluminum hydride[10] in tetrahydrofuran gave the trans-olefin (6) in 69 % yield from 4.



4 5 6 7 8 9

Scheme 2

The trans-enone (7) was obtained by treatment of the alcohol (6) with manganese dioxide in petroleum ether in 70 % yield. Whereas the cis-enone (9) was prepared by catalytic reduction of 5 on palladium sulfate[11] and subsequent oxidation of the olefin (8) with manganese dioxide, in 48 % yield from 5.

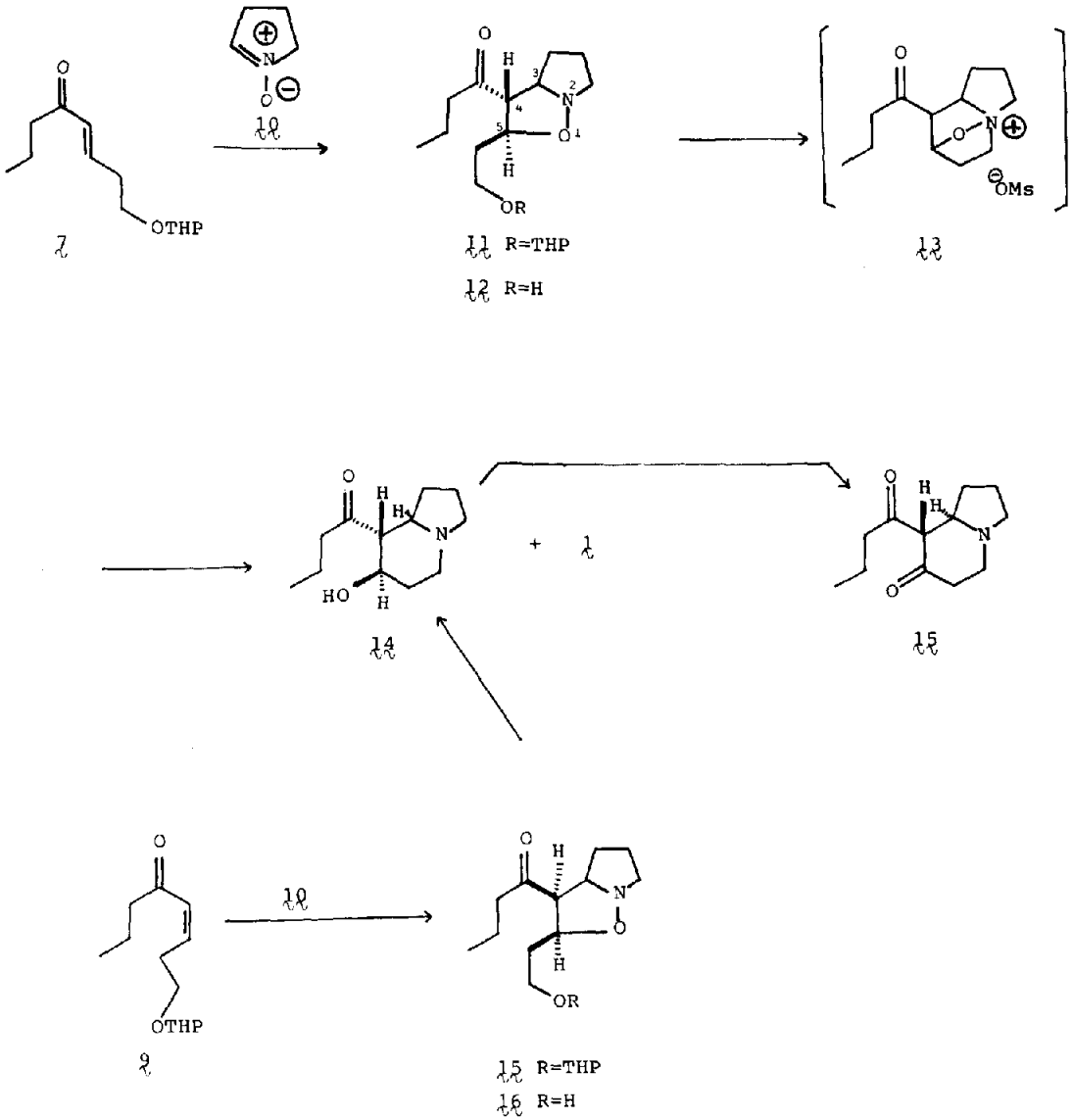
Since the both enones (7 and 9) could be synthesized stereoselectively, the cycloaddition with Δ^1-pyrrolin-1-oxide (10) was then investigated. Based on the mechanistic aspects, the trans-enone would be an appropriate dipolarophile to synthesize elaeokanine C, stereoselectively. Thus, 1,3-dipolar cycloaddition of 7 with 10 was carried out in chloroform to afford the adduct (11) as inseparable stereoisomeric mixtures at the C_3-position of the isoxazolidine ring, in 91 % yield, whose deprotection of tetrahydropyranyl ether with 1 N hydrochloric acid in tetrahydrofuran gave the primary alcohol (12a and 12b). The ratio of 12a : 12b was determined to be 2 : 3 based on its NMR data [δ 4.06 (2/5H, dt, J = 6 and 8 Hz, 3α-H) and 3.97 (3/5H, dt, J = 8 and 8 Hz, 3β-H)], and this ratio was consistent with those reported[12]. Difficulties were initially encountered in the conversion of 12 to 3, e.g. attempted reductive N-O bond cleavage with Raney-nickel, palladium-carbon and zinc powder, followed by selective mesylation of the primary alcohol afforded none of the desired product but complicated mixtures, and mesylation of 12 with methanesulfonyl chloride and triethylamine in methylene chloride again gave rise to the decomposed product.

Whereas, treatment of 12 with methanesulfonyl chloride in pyridine gave the quaternary salt (13), which without isolation was treated with zinc powder in 50 % aqueous acetic acid to yield the β-hydroxy ketone (14) as a major product and a trace amount of elaeokanine A, probably arising from elaeokanine C by dehydration.

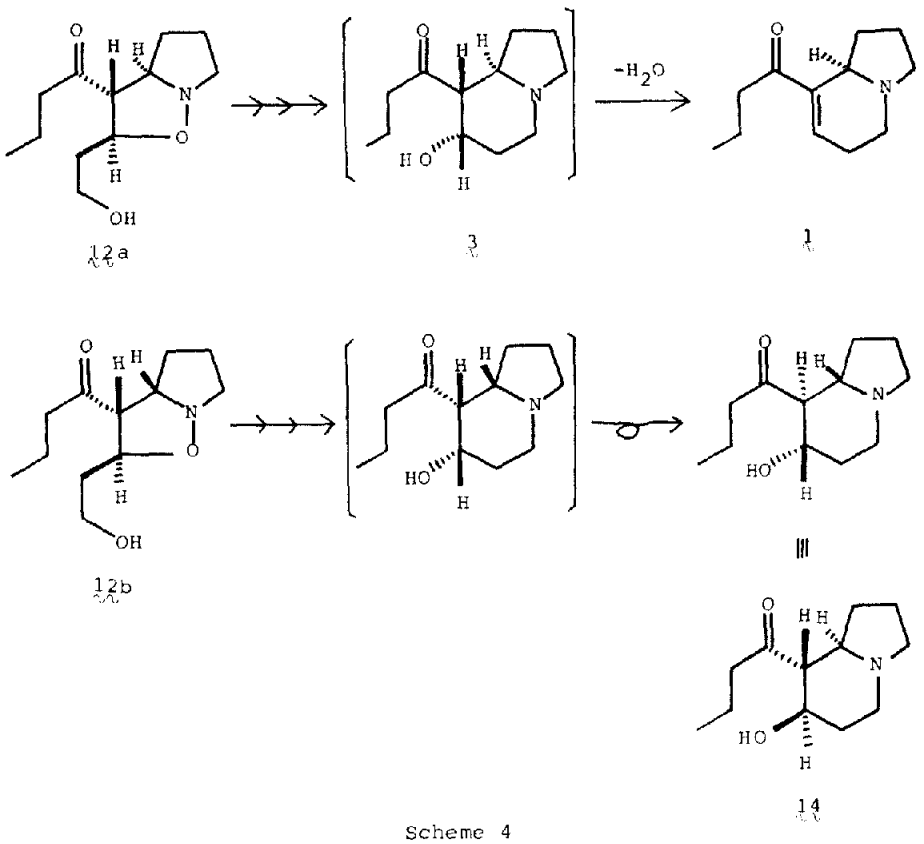
The stereochemistry of the β-hydroxy ketone was assigned to be 14 on the basis of its spectral data and the formation of 14 suggested that the epimerization at the C_4-position of the isoxazolidine (12b) occurred during its conversion into 14 as shown in Scheme 4.

In order to confirm this observation, the cis-enone (9) was treated with 10 to furnish the adduct (15), which was clearly different from 11. After the deprotection of tetrahydropyranyl ether with 1 N hydrochloric acid, the resulting

primary alcohol (16) was converted to the quaternary salt with methanesulfonyl chloride. Reduction of the salt with zinc powder afforded the β-hydroxy ketone (14), in 25.8 % yield, which was identical with the authentic sample obtained from the trans-enone (7) as above. Though the stereoselective synthesis of elaeokanine C has not been successful, 14 was oxidized to the diketone (15) with dimethyl sulfoxide and dicyclohexylcarbodiimide[13] or with Jones reagent. Since the conversion of 15 to elaeokanine B(2) and C(3) has already been reported, this synthesis constitutes a formal total synthesis of elaeokanine alkaloids.



Scheme 3



Scheme 4

EXPERIMENTAL

IR spectra were measured with a 215 Hitachi Grating infrared spectrophotometer and were calibrated with the 1610 cm^{-1} absorption of polystyrene. ^{1}H-NMR spectra were obtained on a JEOL JNM-FX100 spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken with a JEOL JMS-D300 spectrometer.

3-Octyne-1,5-diol 1-tetrahydropyranyl ether (5). To a stirred solution of 3-butyn-1-ol tetrahydropyranyl ether (11.5 g, 74.6 mmol) in tetrahydrofuran (50 ml) was added a solution of n-butyllithium (15 % w/v in hexane; 57.3 ml, 89.5 mmol) at -78°C over the period of 2 hr. After stirring for 0.5 hr, n-butyraldehyde (6.45 g, 89.5 mmol) was added and the resulting mixture was stirred at -78°C for 1.5 hr and was then allowed to warm to 0°C. Water (50 ml) was added and the phases were then separated. The aqueous phase was extracted with ether (2 x 30 ml). The organic phases were combined, washed with saturated aq sodium chloride, dried, and concentrated to give a yellowish oil, which was chromatographed on silica gel (400 g) eluting with CH_2Cl_2-MeOH (19 : 1) to give 5 as a colorless oil (16.5 g, 97.6 %) : IR (film) cm^{-1} 3430 (broad), 2960, 2880, 1030; NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7 Hz), 2.51 (2H, dt, J = 2 and 7 Hz), 2.68 (1H, br s), 3.42 - 3.65 (2H, m), 3.69 - 3.93 (2H, m), 4.34 (1H, br s), 4.64 (1H, m); MS (m/e) 227 (M^+ + 1), 209, 137, 107, 85. Calc for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.91; H, 9.92 %.

3(E)-Octene-1,5-diol 1-tetrahydropyranyl ether (6). To a stirred suspension of lithium aluminum hydride (4.28 g, 113 mmol) in ether (200 ml) was added a solution of 5 (21.3 g, 94 mmol) in ether (30 ml) at room temperature. After stirring for 4 hr at ambient temperature under an atmosphere of nitrogen, the reaction was quenched by the addition of water (20 ml).

The insoluble material formed was filtered off and washed with ether (5 x 39 ml). The combined filtrate was evaporated to give a residue, which was chromatographed on silica gel (500 g) eluting with CH_2Cl_2-acetone (19 : 1) to afford 6 as a colorless oil (15.3 g, 71.1 %) : IR (film) cm^{-1} 3445 (broad), 2940, 2870, 1030, 970; NMR ($CDCl_3$) δ 0.93 (3H, m), 1.78 (1H, br s), 2.34 (2H, dt, J = 6 and 6.5 Hz), 3.30 - 4.20 (5H, m), 4.58 (1H, br m), 5.30 - 5.67 (2H, m); MS (m/e) 211 (M^+-OH), 127, 109, 101, 85. Calc for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.59; H 10.93 %.

5-Oxo-3(E)-octen-1-ol tetrahydropyranyl ether (7). To a stirred suspension of manganese dioxide (20.3 g) in petroleum ether (150 ml) was added 6 (2.5 g, 10.9 mmol) and the mixture was further stirred at ambient temperature for 1 hr. After removal of an insoluble material by filtration, the filtrate was concentrated to the residue, which was chromatographed on silica gel eluting with CH_2Cl_2-acetone (97 : 3) to yield the enone 7 as a colorless oil (1.74 g, 70.2 %) : IR (film) cm^{-1} 2950, 2875, 1680; NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7 Hz), 2.51 (2H, dtt, J = 1.4, 6.5 and 6.5 Hz), 2.52 (2H, t, J = 7.5 Hz), 3.41 - 3.64 (2H, m), 3.76 - 3.99 (2H, m), 4.59 (1H, br m), 6.17 (1H, dt, J = 1.4 and 16 Hz), 6.84 (1H, dt, J = 7 and 16 Hz); MS (m/e) 227 (M^+ + 1), 153, 125, 85. Calc for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.61; H, 10.04 %.

3(Z)-Octene-1,5-diol 1-tetrahydropyranyl ether (8). A mixture of 5 (4.0 g, 17.7 mmol), $PdSO_4 \cdot H_2O$ (400 mg) and pyridine (20 ml) was shaken at ambient temperature under an atmosphere of hydrogen. After an absorption of hydrogen (397 ml, 17.7 mmol) had ceased, the catalyst was filtered off and was washed with benzene (3 x 10 ml). The combined filtrate was concentrated to the residue, which was redissolved in benzene (50 ml). The organic layer was washed with saturated aq potassium hydrogen sulfate and saturated aq sodium chloride, dried, and concentrated to give a residue, which was subjected to column chromatography on silica gel (100 g). Elution with CH_2Cl_2-acetone (19 : 1) afforded 8 as a colorless oil (2.76 g, 68.3 %) : IR (film) cm^{-1} 3450 (broad), 2955, 2870, 1033; NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7 Hz), 2.10 - 2.80 (3H, m), 3.24 - 3.63 (2H, m), 3.68 - 3.96 (2H, m), 4.40 (1H, dt, J = 6.5 and 6.5 Hz), 4.60 (1H, br m), 5.16 - 5.69 (2H, m); MS (m/e) 211 (M^+-OH), 127, 109, 101, 85. Calc for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.09; H, 10.85 %.

5-Oxo-3(Z)-octen-1-ol tetrahydropyranyl ether (9). The oxidation of 8 (4.30 g, 18.8 mmol) with manganese dioxide (40 g) in petroleum ether (150 ml) was carried out as described for 7 to give 9 as a colorless oil (2.78 g, 70.2 %) : IR (film) cm^{-1} 2950, 2875, 1693, 1620, 1032, 985; NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7 Hz), 2.44 (2H, t, J = 7 Hz), 2.93 (2H, ddd, J = 5, 6 and 6.5 Hz), 3.39 - 3.61 (2H, m) 3.71 - 3.94 (2H, m), 4.59 (1H, br m), 6.03 - 6.34 (2H, m); MS (m/e) 227 (M^+ + 1), 209, 153, 125, 85. Calc for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.84; H, 9.99 %.

1,3-Dipolar cycloaddition of 7 : Formation of the isoxazolidine (11). A solution of 7 (1.11 g, 4.90 mmol) and Δ^1-pyrrolin-1-oxide (0.84 g, 9.88 mmol) in toluene (15 ml) was refluxed at ambient temperature in a current of nitrogen for 3 hr. After evaporation of the solvent, the residue was chromatographed on silica gel (100 g) eluting with CH_2Cl_2-acetone (17 : 3) to afford the isoxazolidine (11) as stereoisomeric mixtures at the C_3-position (isoxazolidine numbering) (1.39 g, 91.0 %) : IR (film) cm^{-1} 2950, 2850, 1710, 1033; NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7 Hz), 2.41 (2H, t, J = 7 Hz), 3.14 (2H, t, J = 6.5 Hz), 3.31 - 3.65 (3H, m), 3.73 - 3.98 (3H, m), 4.43 (1H, dt, J = 6 and 8.5 Hz), 4.56 (1H, br m); MS (m/e) 312 (M^+ + 1), 311 (M^+), 310, 228, 152, 86, 85.

Deprotection of tetrahydropyranyl ether of 11. To a stirred solution of 11 (500 mg, 1.61 mmol) in tetrahydrofuran (7 ml) was added 1N HCl (4.5 ml) at ambient temperature. After the stirring had been continued for 5 hr, the solution was basified with sodium carbonate and extracted with ether (3 x 10 ml). The organic layer was washed with saturated aq sodium chloride, dried, and concentrated to give the residue, which was subjected to column chromatography on silica gel (25 g). Elution with CH_2Cl_2-MeOH (9 : 1) afforded the alcohol (12) as a yellowish gum (270 mg, 74.0 %) : IR (film) cm^{-1} 3410 (broad), 2975, 2885, 1710, 1058; NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7 Hz), 2.43 (2H, t, J = 7.5 Hz), 3.16 (2H, m), 3.56 (3/5H, dd, J = 8 and 8 Hz), 3.71 (2H, t, J = 6 Hz), 3.76 (2/5H, dt, J = 6 and 8 Hz), 3.97 (3/5H, dt, J = 8 and 8 Hz), 4.06 (2/5H, dt, J = 6 and 8 Hz), 4.50 (1H, dt, J = 6 and 8 Hz); MS (m/e) 227 (M^+), 154, 143, 138, 128, 125, 112, 110, 86, 85; m/e 227.1509 (calc for $C_{12}H_{21}NO_3$, 227.1520).

1,3-Dipolar cycloaddition of 9 : Formation of the isoxazolidine (15). A solution of 9 (2.50 g, 11.0 mmol) and Δ^1-pyrrolin-1-oxide (1.88 g, 22.1 mmol) in chloroform (30 ml) was stirred at ambient temperature in a current of nitrogen for 3 days and then heated under reflux for 14 hr. After evaporation of the solvent, the residue was chromatographed on silica gel eluting with CH_2Cl_2-acetone (17 : 3) to give the adduct (15) as a colorless gum (3.11 g, 90.4 %) : IR (film) cm^{-1} 2950, 2875, 1710, 1033; NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7 Hz), 2.30 - 2.60 (3H, m), 3.15 (2H, m), 3.48 (2H, m), 3.70 - 4.20 (3H, m), 4.42 (1H, dt, J = 6 and 9 Hz), 4.54 (1H, m); MS (m/e) 312 (M^+ + 1), 311, 310, 228, 210, 154, 86, 85.

Deprotection of tetrahydropyranyl ether of 15. Deprotection of tetrahydropyranyl ether of 15 (2.00 g, 6.42 mmol) with 1 N HCl (15 ml) in tetrahydrofuran (80 ml) was carried out as described above to give the alcohol (16) as a yellowish gum (1.05 g, 71.6 %) : IR (film) cm^{-1} 3390 (broad), 2970, 2880, 1710, 1055; NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7.5 Hz), 2.40 - 2.60 (2H, m), 2.91 (1H, br s), 2.80 - 3.40 (3H, m), 3.50 - 3.80 (2.5H, m), 3.90 - 4.20 (1H, m), 4.50 (0.5 H, dt, J = 5.5 and 8.5 Hz); m/e 227.1537 (calc for $C_{12}H_{21}NO_3$, 227.1520).

7-Epielaeokanine C (14) and elaeokanine A (1). A mixture of 12 (2.0 g, 8.80 mmol), methanesulfonyl chloride (3.02 g, 26.4 mmol) and pyridine (44 ml) was allowed to stand at room temperature for 5 hr. After evaporation of the solvent, the residue was dissolved into 50 % aq acetic acid (44 ml). To the above stirred solution was added zinc powder (8.63 g, 132 mmol) at 50°C and the stirring was continued for 1.5 hr at the same temperature. The resulting solution was cooled to 0°C, diluted with water (30 ml) and basified with Na_2CO_3 to pH 9. After removal of the insoluble material by filtration, the filtrate was extracted with methylene chloride (3 x 40 ml). The organic layer was washed with saturated aq sodium chloride, dried and evaporated to give the residue, which was subjected to column chromatography on silica gel (80 g). Elution with CH_2Cl_2-MeOH (17 : 3) afforded 7-epielaeokanine C (14) as a colorless gum (309 mg, 16.6 %) : IR ($CHCl_3$) cm^{-1} 3420 (broad), 2933, 2807, 2480, 1705, 1375; NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7 Hz), 1.60 (2H, tq J = 7 and 7 Hz), 2.54 (2H, t, J = 7 Hz), 2.55 (1H, dd, J = 10 and 10 Hz), 2.80 - 3.30 (3H, m), 3.87 (1H, dt, J = 5 and 10 Hz); MS (m/e) 211 (M^+), 194, 182, 167, 152, 140, 124, 97; m/e 211.1583 (calc for $C_{12}H_{21}NO_2$, 211.1573). 14 was crystallized as its picrate, m.p. 160 - 161.5°C (from ethanol), calc for $C_{18}H_{24}N_4O_9$: C, 49.09; H, 5.49; N, 12.72. Found: C, 49.00; H, 5.61; N, 12.56 %.

Further elution with CH_2Cl_2-MeOH (17 : 3) gave elaeokanine A (2 mg, 0.1 %), whose spectral data were consistent with those of reported one[1].

The conversion of 16 into 14. The conversion of 16 (300 mg, 1.32 mmol) was

carried out as above by mesylation with methanesulfonyl chloride (455 mg, 3.97 mmol) and a subsequent reduction with zinc powder (1.15 g, 17.6 mmol) in 50 % aq acetic acid (6.6 ml) to afford 14 (72 mg, 25.8 %), which was identical with the authentic sample obtained above.

The oxidation of 14 into 15 with Moffatt reagent. To a solution of 14 (150 mg, 0.71 mmol) in benzene (5 ml) and dimethylsulfoxide (5 ml) containing pyridine (60 mg, 0.76 mmol) and trifluoroacetic acid (40 mg, 0.35 mmol), was added dicyclohexylcarbodiimide (580 mg, 2.81 mmol) and the resulting mixture was stirred at ambient temperature for 15 hr. After evaporation of the solvent, the residue was diluted with water (30 ml) and basified with sodium carbonate to pH 11. Carbon tetrachloride (20 ml) was added into the above mixture and the precipitate was removed off by filtration. The combined filtrate and washings were washed with water, dried, and evaporated to give the residue which was subjected to column chromatography on silica gel (12 g). Elution with CH_2Cl_2-MeOH (9 : 1) afforded the diketone (15) (3 mg, 2 %) : IR (CH_2Cl_2) cm^{-1} 1710, 1620; NMR ($CDCl_3$) δ 0.92 (3H, t, J = 7.5 Hz); MS (m/e) 209 (M^+), 208, 190, 181, 166, 164, 152, 139, 138, 136, 120, 111, 110, 97, 96, 83, 82, 81. These data were consistent with those of reported one[1].

The oxidation of 14 with Jones reagent. To a solution of 14 (50 mg, 0.24 mmol) in acetone (5 ml) was added freshly prepared Jones reagent (0.27 mmol) at 0°C. After stirring at ambient temperature for 3 hr, the mixture was basified with sodium hydrogen carbonate to pH 9 and extracted with methylene chloride (3 x 10 ml). The combined extracts were washed with saturated aq sodium chloride, dried and evaporated to give the residue which was subjected to column chromatography on silica gel (5 g). Elution with CH_2Cl_2-MeOH (9 : 1) afforded the diketone (15) (19 mg, 38.4 %), which was identical with the authentic sample obtained above.

Acknowledgements —— We thank Mrs. T. Ogata, Miss M. Shigetsuna, Miss M. Nagao, Mrs. A. Kumazawa, Miss H. Furuyama, and Miss Y. Narita of Hoshi College of Pharmacy for spectral measurements, microanalyses, and manuscript preparation.

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