Acknowledgment. We thank Ms. Ruth Nutt and Drs. Roger Freidinger and J. R. Huff for helpful discussions during the course of this work.

Registry No. (±)-**4b**, 77357-58-5; (*R*)-**4b**, 67401-65-4; (*S*)-**4b**, 41844-91-1; (±)-**5b**, 77357-59-6; (*R*)-**5b**, 77447-92-8; (*S*)-**5b**, 77447-93-9; (±)-**6**, 77357-60-9; (*S,S*)-**6**, 77447-94-0; (±)-**7**, 77357-61-0; (*R,R*)-**7**, 77447-95-1; (*S,S*)-**7**, 77447-96-2; (*S,S*)-**9**, 32151-02-3; (±)-**10**, 1670-98-0; (*S*)-**10**, 59190-99-7; (±)-**11**, 77357-62-1; (*S*)-**11**, 77447-97-3.

D. E. McClure,*[23] B. H. Arison
J. H. Jones, J. J. Baldwin
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065, and
West Point, Pennsylvania 19486
Received January 26, 1981

Biomimetic Approach to *Elaeocarpus* Alkaloids. A Synthesis of (±)-Elaeocarpidine

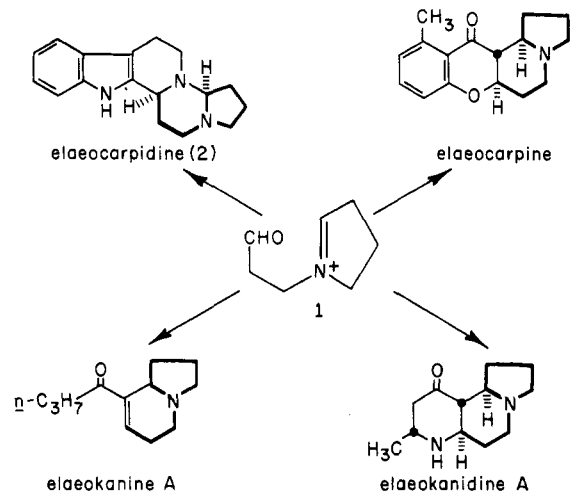
Summary: A short, convergent synthesis of (±)-elaeocarpidine (**2**) is described wherein the final step features a regioselective condensation between tryptamine (**3**) and amine bisacetal **5**. The latter unit is readily assembled from acrolein and cyanide in six steps.

Sir: The *Elaeocarpus* alkaloids comprise a relatively new class of about 20 biogenetically interesting plant products that contain the indolizidine or pyrrolizidine ring system.[1] All of these alkaloids conceivably can arise from a common biosynthetic intermediate, 3-(1-Δ^1-pyrrolinium)propionaldehyde (**1**), which may be derived from ornithine and a three-carbon bioreagent. The incorporation of **1** in several *Elaeocarpus* alkaloids is shown in Scheme I.

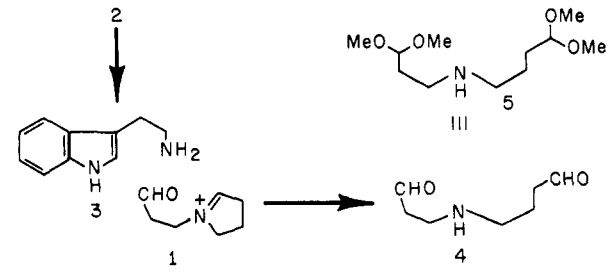
Although several synthesis of selected *Elaeocarpus* alkaloids have been reported,[1-3] none addresses this general biogenesis postulated[4] for these alkaloids. We delineate herein a synthesis of (±)-elaeocarpidine (**2**) involving the in situ generation of **1** and its subsequent condensation with tryptamine (**3**), as shown retrosynthetically in Scheme II.

We anticipated that amine dialdehyde **4**, obtained by hydrolyzing amine bisacetal **5**,[5] would clearly prefer cyclizing to **1** (5-exo-trig[6]) than to the alternative four-membered-ring immonium ion (4-exo-trig) or to reacting intermolecularly with tryptamine (**3**). Furthermore, immonium aldehyde **1**, once formed, is predestined to react with tryptamine (**3**) in the desired regioselective fashion to give elaeocarpidine (**2**).

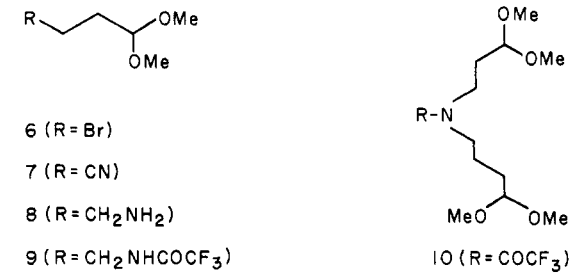
Scheme I



Scheme II



The starting amine bisacetal **5** was synthesized as follows. 3-Bromo-1,1-dimethoxypropane (**6**) was prepared from acrolein (HBr, MeOH, 0 °C; MeOH, 25 °C; 70%)[7] and then converted to 3-cyano-1,1-dimethoxypropane (**7**)[8] (aqueous NaCN, cat. *n*-Bu_3N, reflux, 2 h; 86%).[9] Reduction of **7** to 4-amino-1,1-dimethoxypropane (**8**) was accomplished with $LiAlH_4$ (Et_2O, reflux; 62%)[10] or better with sodium (EtOH, reflux; 77%).[11] Trifluoroacetylation proceeded smoothly to give **9** (TFAA, Et_2O, Et_3N, 0 °C; 25 °C, 2 h; 94%) as an oil [bp 85 °C (0.65 torr)].[12,13]



(1) For a review, see: Johns, S. R.; Lamberton, J. A. *Alkaloids (NY)* **1973**, *14*, 325.

(2) For previous syntheses of **2**, see: (a) Harley-Mason, J.; Taylor, C. G. *J. Chem. Soc., Chem. Commun.* **1969**, 281; (b) Gribble, G. W. *J. Org. Chem.* **1970**, *35*, 1944.

(3) (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972**, *25*, 817. (b) Onaka, T. *Tetrahedron Lett.* **1971**, 4395. (c) Tanaka, T.; Ijima, I. *Tetrahedron* **1973**, *29*, 1285. (d) Howard, A. S.; Meerholz, C. A.; Michael, J. P. *Tetrahedron Lett.* **1979**, 1339. (e) Tufariello, J.; Ali, S. A. *Ibid.* **1979**, 4445. (f) Schmitthenner, H. F.; Weinreb, S. M. *J. Org. Chem.* **1980**, *45*, 3372. (g) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1980**, *14*, 1433. (h) Howard, A. S.; Gerrano, G. C.; Meerholz, C. A. *Tetrahedron Lett.* **1980**, 1373. (i) Watanabe, T.; Nakashita, Y.; Katayama, S.; Yamauchi, M. *Heterocycles* **1981**, *16*, 39.

(4) Onaka, T. *Tetrahedron Lett.* **1971**, 4395.

(5) The acid hydrolysis (pH 5.83) of 4-aminobutyraldehyde diethyl acetal proceeds without nitrogen assistance: Anderson, E.; Capon, B. *J. Chem. Soc., Perkin Trans. 2* **1972**, 515.

(6) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(7) We used a modification of the procedure reported by: Ayer, W. A.; Dawe, R.; Eisner, R.; Furuichi, K. *Can. J. Chem.* **1976**, *54*, 473.

(8) This material can also be purchased from ROC/RIC Corporation, Belleville, NJ.

(9) Procedure of: Reeves, W. P.; White, M. R. *Synth. Commun.* **1976**, *6*, 193.

(10) Lukes, R.; Trojanek, J. *Chem. Listy* **1952**, *46*, 383; *Chem. Abstr.* **1953**, *47*, 4282.

(11) Manske, R. H. F. *Can. J. Res.* **1931**, *5*, 598.

(12) Satisfactory analytical data (combustion or high-resolution mass spectrum) were obtained for this new compound.

0022-3263/81/1946-2433$01.25/0

Alkylation of trifluoroacetamide **9** with bromide **6** was best achieved by using a modification of Nordlander's procedure[14] (KH, THF, 1.1 equiv of 18-crown-6, reflux, 14 h) to afford **10**[12,13] in 72% yield (80% conversion), readily separable from **9** by preparative medium-pressure liquid chromatography (EtOAc/hexane). Hydrolysis of **10** (aqueous NaOH, MeOH, 25 °C; 100%) gave the desired amine bisacetal **5** as an oil [bp 99–114 °C (0.35 torr)].[12,13] Condensation of **5** with tryptamine hydrochloride (**3**) (pH 5.5, citrate–phosphate buffer, MeOH, reflux 3 h;[15] pH 1.5, reflux, 42 h) afforded pure (±)-elaeocarpidine (**2**)[13] (mp 210–212 °C) in 28% yield after column chromatography and recrystallization (hexane/CH_2Cl_2). The material so obtained was identical with authentic material[2b] (TLC, IR, ^{13}C NMR, mmp 209–210 °C, and mass spectrum). The overall condensation is stereoselective because the unknown trans isomer of elaeocarpidine, if formed, would presumably undergo rapid acid-catalyzed equilibration of the aminal linkage to afford the more stable cis isomer **2**.[16]

The application of this methodology to the synthesis of other *Elaeocarpus* alkaloids is under investigation.

Acknowledgment. This investigation was supported in part by Grant CA-24422, awarded by the National Cancer Institute, DHEW, and by Merck Sharp and Dohme Research Laboratories. We also thank Dr. Catherine E. Costello (Massachusetts Institute of Technology) for the high-resolution mass spectra (National Institutes of Health Resource Grant FR00317 from the Division of Research Facilities and Resources).

Registry No. (±)-**2**, 20069-07-2; **3**·HCl, 147733-29-0; **5**, 77357-63-2; **6**, 36255-44-4; **7**, 14618-78-1; **8**, 19060-15-2; **9**, 77357-64-3; **10**, 77357-65-4; acrolein, 107-02-8.

(13) **9**: IR (film) 3320, 2950, 2840, 1715, 1560, 1450, 1375, 1180, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (m, 4 H), 3.38 (s, 6 H), 3.38 (m, 2 H), 4.38 (br t, 1 H), 7.50 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.1, 30.0, 39.7, 53.4, 104.3; mass spectrum, *m/e* 229, 198, 166, 138, 126, 85, 75, 61, 58, 55, 52. **10**: IR (film) 2950, 1680, 1500, 1360, 1310, 1240, 1195, 1125, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 6 H), 3.35 (s, 12 H), 3.35 (m, 4 H), 4.38 (br t, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 23.8, 29.6, 29.8, 29.9, 32.0, 43.1, 46.8, 47.3, 47.6, 47.7, 48.0, 53.1, 53.3, 102.3, 102.6, 104.0, 104.2. **5**: IR (film) 3320, 2920, 2820, 1445, 1370, 1115, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (br s, 1 H), 1.25–1.90 (m, 6 H) 2.30–2.80 (m, 4 H), 3.22 (s, 12 H), 4.32 (br t, 1 H), 4.40 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.5, 30.3, 32.9, 45.3, 49.7, 52.6, 52.8, 74.8, 76.9, 103.5, 104.4; mass spectrum, *m/e* 204, 172, 171, 132, 114, 100, 82. **2**: IR ($CHCl_3$) 3525, 2950, 2845, 1450, 1372, 1356, 1300, 1170 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 19.9, 21.9, 28.7, 29.2, 47.1, 50.3, 51.9, 59.4, 83.7, 108.3, 110.6, 117.9, 119.2, 121.1, 127.3, 134.3, 135.9; mass spectrum, *m/e* 267, 252, 239, 225, 210, 197, 183, 169, 154, 143, 125, 115, 97, 84, 69, 63, 55, 42.

(14) Nordlander, J. E.; et al. *Tetrahedron Lett.* **1978**, 4987.

(15) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032.

(16) A recent example of aminal isomerization is seen in the work of: Thorsett, E. D.; Harris, E. E.; Patchett, A. A. *J. Org. Chem.* **1978**, *43*, 4276.

Gordon W. Gribble,* Richard M. Soll
Department of Chemistry
Dartmouth College
Hanover, New Hampshire 03755
Received December 29, 1980