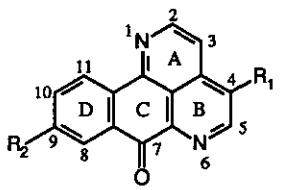
TOTAL SYNTHESIS OF EUPOMATIDINES-1, 2, AND 3

Yoshiyasu Kitahara and Akinori Kubo*
Meiji College of Pharmacy,
1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Abstract — Three aromatic alkaloids, eupomatidines-1 (**1a**), 2 (**1b**) and 3 (**1c**), were synthesized from the corresponding 1,4-naphthoquinones (**2a**, **b**) by hetero Diels-Alder reaction with 2-butenal dimethylhydrazones (**3a**, **b**), followed by one pot annelation of ring A.

In 1991, three aromatic alkaloids, eupomatidines-1 (**1a**), 2 (**1b**), and 3 (**1c**) were isolated from the archaic monogeneric angiosperm family Eupomatiaceae, *Eupomatia bennettii* and *E. laurina*.[1] The structures of eupomatidines-1, 2, and 3 were elucidated by ir, uv, ms and ^{1}H-nmr spectra as 9-methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**1a**), 4-methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**1b**), and 4,9-dimethoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**1c**), respectively.[1] We report here the first total synthesis of eupomatidines-1 (**1a**), 2 (**1b**), and 3 (**1c**).



Eupomatidine-1 (**1a**): $R_1 = H$, $R_2 = OCH_3$
Eupomatidine-2 (**1b**): $R_1 = OCH_3$, $R_2 = H$
Eupomatidine-3 (**1c**): $R_1 = R_2 = OCH_3$

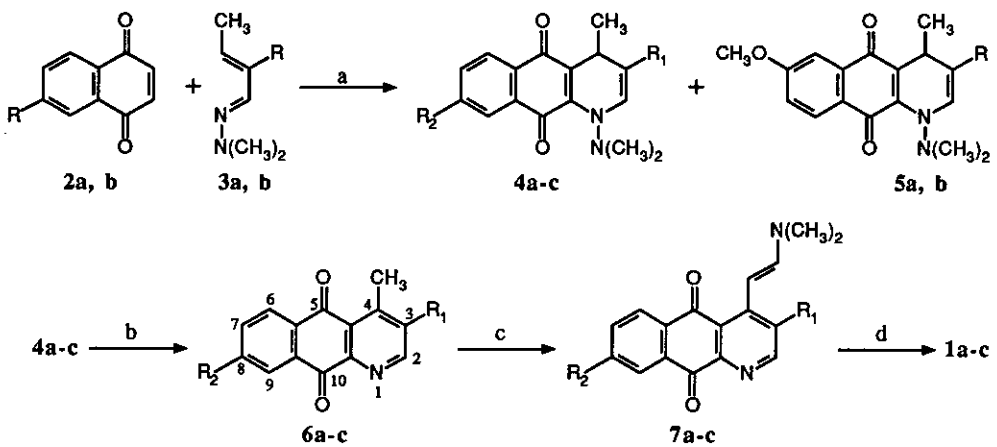
The hetero Diels-Alder cycloaddition[2] of 6-methoxy-1,4-naphthoquinone[3] (**2b**) with 2-butenal dimethylhydrazone[4] (**3a**) in acetonitrile (80°C, 4 h) afforded the corresponding adducts (**4a** and **5a**) as a 3:1 mixture in 48% yield. Oxidation of **4a** by manganese dioxide[2] in chloroform gave 8-methoxy-4-methylbenzo[*g*]quinoline-5,10-dione[5] (**6a**) in 74% yield. The aza-anthraquinone (**6a**) was condensed with dimethylformamide diethylacetal[6] in dimethylformamide to give the enamine (**7a**). Treatment of the crude

enamine (**7a**) with ammonium chloride in refluxing acetic acid[6] afforded the desired 9-methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one (**1a**), *i.e.* eupomatidine-1,[7] in 93% yield from **6a**.

Next, we synthesized eupomatidine-2 (**1b**). The hetero Diels-Alder cycloaddition of 1,4-naphthoquinone (**2a**) with 2-methoxy-2-butenal dimethylhydrazone[8] (**3b**) was carried out in chloroform[9] at 20°C (2 h) to give the corresponding adduct (**4b**)[10] in 79% yield. The adduct (**4b**) was converted to 4-methoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one[11] (**1b**), *i.e.* eupomatidine-2, via **6b**[12] as above in 66% yield from **4b**.

Finally, eupomatidine-3 (**1c**) was prepared. The cycloaddition of 6-methoxy-1,4-naphthoquinone (**2b**) with 2-methoxy-2-butenal dimethylhydrazone (**3b**) in chloroform at 20°C (2 h) afforded the corresponding adducts (**4c**; 57% yield and **5b**; 13% yield). We have found that aza-diene (**3b**) reacts faster than **3a** and under milder conditions towards 6-methoxy-1,4-naphthoquinone (**2b**). The adduct (**4c**) was converted to 4,9-dimethoxynaphtho[1,2,3-*ij*][2,7]naphthyridin-7(7*H*)-one[13] (**1c**), *i.e.* eupomatidine-3, via **6c**[14] as above in 42% yield from **4c**.

The spectroscopic data obtained for **1a-c** were identical to the values reported for the corresponding natural products, eupomatidines-1, 2, and 3 by Carroll and Taylor.[1]



1, 4, 6, 7 **a**: $R_1 = H$, $R_2 = OCH_3$ **2, 3, 5** **a**: $R = H$
b: $R_1 = OCH_3$, $R_2 = H$ **b**: $R = OCH_3$
c: $R_1 = R_2 = OCH_3$

Reagents and Conditions: a) CH_3CN, 80°C, 4 h, or $CHCl_3$, 20°C, 2 h.
b) MnO_2 (large excess), $CHCl_3$, 20°C, 1 h.
c) $(C_2H_5O)_2CH\text{-}N(CH_3)_2$, DMF, 120°C, 30 min.
d) NH_4Cl, CH_3CO_2H, reflux, 30 min.

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REFERENCES AND NOTES

1. A. R. Carroll and W. C. Taylor, *Aust. J. Chem.*, **1991**, *44*, 1615.
2. M. Chigr, H. Fillion, and A. Rougny, *Tetrahedron Lett.*, **1988**, *29*, 5913.
3. J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, **1957**, 2483.
4. T. Severin, G. Wanninger, and H. Lerche, *Chem. Ber.*, **1984**, *117*, 2875.
5. **6a**: mp 212-214°C (CH_2Cl_2-ether). Ms *m/z* (%): 253 (M^+, 100), 225 (29). Ir (KBr): 1686, 1660, 1598, 1578, 1494, 1352, 1306, 1274, 1250, 1162, 1022, 750 cm^{-1}. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 2.928 (3H, s, C_4-CH_3), 4.008 (3H, s, OCH_3), 7.317 (1H, dd, *J*=8.9, 2.6 Hz, C_7-H), 7.508 (1H, d, *J*=4.6 Hz, C_3-H), 7.773 (1H, d, *J*=2.6 Hz, C_9-H), 8.222 (1H, d, *J*=8.9 Hz, C_6-H), 8.895 (1H, d, *J*=4.6 Hz, C_2-H).
6. F. Bracher, *Heterocycles*, **1989**, *29*, 2093.
7. Eupomatidine-1 (**1a**): mp 228-231°C (CH_3OH) [lit.,[1] mp 195-197°C]. Ms *m/z* (%): 262 (M^+, 100), 232 (11), 191 (22). Ir (KBr): 1674, 1602, 1496, 1404, 1380, 1350, 1282, 1022, 838 cm^{-1}. Uv (C_2H_5OH) λ_{max} nm (log ε): 216 (4.48), 221 (4.48), 231 (4.42), 261 (4.26), 286 (4.25), 319 (3.80), 350 (3.52), 437 (3.76). ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 4.015 (3H, s, OCH_3), 7.372 (1H, dd, *J*=8.9, 2.6 Hz, C_{10}-H), 7.665 (1H, d, *J*=5.9 Hz, C_4-H), 7.916 (1H, d, *J*=5.6 Hz, C_3-H), 7.916 (1H, d, *J*=2.6 Hz, C_8-H), 8.779 (1H, d, *J*=8.9 Hz, C_{11}-H), 8.838 (1H, d, *J*=5.9 Hz, C_5-H), 9.134 (1H, d, *J*=5.6 Hz, C_2-H). ^{13}C-Nmr (67.8 MHz, $CDCl_3$) δ: 55.89q, 110.85d, 118.19d, 119.19s, 122.52d, 123.45d, 127.53d, 128.77s, 134.05s, 138.78s, 147.39d, 148.25s, 148.46d, 151.45s, 162.46s, 181.89s.
8. The compound (**3b**) was obtained as an *E*/*Z* mixture (1:1) from 2-butenal dimethylhydrazone (**3a**) in two steps: (i) bromine in methanol; (ii) sodium methoxide in methanol, according to Severin's method.[4] ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 1.742 and 1.769 (3H, d, *J*=7.3 Hz, $C\underline{H}_3$-CH=), 2.854 and 2.939 (6H, s, $(CH_3)_2$N-), 3.623 and 3.708 (3H, s, OCH_3), 4.791 and 5.104 (1H, q, *J*=7.3 Hz, CH_3-C<u>H</u>=), 6.704 and 7.030 (1H, s, CH=N).
9. P. Nebois and H. Fillion, *Tetrahedron Lett.*, **1991**, *32*, 1307.
10. **4b**: mp 172-173°C (ether-hexane). Ms *m/z* (%): 255 (M^+, 9), 240 (100). Ir (KBr): 3356, 1672, 1658,

1594, 1562, 1504, 1368, 1338, 1312, 1288, 1264, 1232, 1194, 1154, 1104, 1004, 794, 724 cm^{-1}. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 1.280 (3H, d, *J*=6.3 Hz, C_4-CH_3), 3.616 (3H, s, OCH_3), 3.970 (1H, q, *J*=6.3 Hz, CH_3-CH), 5.662 (1H, d, *J*=5.0 Hz, C_2-H), 6.703 (1H, br, NH), 7.593 and 7.714 (each 1H, td, *J*=7.6, 1.3 Hz, C_7-H, C_8-H), 8.017 and 8.113 (each 1H, dd, *J*=7.6, 1.3 Hz, C_6-H, C_9-H).

11. Eupomatidine-2 (**1b**): mp 262-265°C (decomp.) (CH_2Cl_2-ether) [lit.,[1] mp 262-265°C (decomp.)]. Ms *m/z* (%): 262 (M^+, 100), 247 (18), 219 (33), 191 (11), 164 (13). Ir (KBr): 1666, 1596, 1570, 1502, 1410, 1378, 1324, 1294, 1280, 1238, 1100, 1040, 1026, 722 cm^{-1}. Uv (C_2H_5OH) λ_{max} nm (log ε): 243 (4.51), 265 (4.25), 333 (3.71), 390 (4.16), 407 (4.14). ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 4.249 (3H, s, OCH_3), 7.690 (1H, ddd, *J*=7.9, 7.6, 1.3 Hz, C_9-H), 7.821 (1H, ddd, *J*=7.9, 7.6, 1.3 Hz, C_{10}-H), 8.016 (1H, d, *J*=5.6 Hz, C_3-H), 8.487 (1H, dd, *J*=7.9, 1.3 Hz, C_8-H), 8.669 (1H, s, C_5-H), 8.879 (1H, dd, *J*=7.9, 1.3 Hz, C_{11}-H), 8.895 (1H, d, *J*=5.6 Hz, C_2-H). ^{13}C-Nmr (67.8 MHz, $CDCl_3$) δ: 56.86q, 114.25d, 120.04s, 125.41d, 128.41d, 128.97d, 130.37s, 131.21d, 132.85s, 134.11d, 135.56s, 141.02s, 146.54d, 150.39s, 152.69s, 180.97s.
12. **6b**: mp 272-275°C (CH_2Cl_2-ether). Ms *m/z* (%): 253 (M^+, 100), 235 (42). Ir (KBr): 1676, 1592, 1546, 1468, 1300, 1282, 1212, 1038, 1018, 950, 798, 720 cm^{-1}. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 2.788 (3H, s, C_4-CH_3), 4.107 (3H, s, OCH_3), 7.75-7.85 (2H, m, C_7-H, C_8-H), 8.2-8.4 (2H, m, C_6-H, C_9-H), 8.658 (1H, s, C_2-H).
13. Eupomatidine-3 (**1c**): mp 278-281°C (decomp.) (CH_2Cl_2-CH_3OH) [lit.,[1] mp 245-248°C (decomp.)]. Ms *m/z* (%): 292 (M^+, 100), 262 (14), 249 (21). Ir (KBr) 1672, 1600, 1574, 1502, 1464, 1436, 1410, 1378, 1322, 1294, 1288, 1240, 1098, 1030, 992, 954, 826 cm^{-1}. Uv (C_2H_5OH) λ_{max} nm (log ε): 218 (4.34), 229 (4.31), 247 (4.42), 269 (4.10), 284 (4.12), 324 (3.67), 335 (3.75), 381 (3.86), 418 (3.87). ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 4.008 (3H, s, C_9-OCH_3), 4.244 (3H, s, C_4-OCH_3), 7.346 (1H, dd, *J*=8.9, 2.6 Hz, C_{10}-H), 7.925 (1H, d, *J*=2.6 Hz, C_8-H), 7.941 (1H, d, *J*=5.9 Hz, C_3-H), 8.651 (1H, s, C_5-H), 8.780 (1H, d, *J*=8.9 Hz, C_{11}-H), 8.834 (1H, d, *J*=5.9 Hz, C_2-H). ^{13}C-Nmr (67.8 MHz, $CDCl_3$-CF_3CO_2D) δ: 56.87q, 58.80q, 115.52d, 117.07d, 118.99s, 119.89s, 122.91d, 129.38d, 130.42d, 133.69s, 134.54s, 137.79d, 138.49s, 149.54s, 155.34s, 162.17s, 177.57s.
14. **6c**: mp 285-288°C (decomp.) (CH_2Cl_2-ether). Ms *m/z* (%): 283 (M^+, 100), 268 (22). Ir (KBr): 1680, 1656, 1598, 1564, 1468, 1440, 1298, 1206, 1102, 1016, 952, 752 cm^{-1}. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 2.779 (3H, s, C_4-CH_3), 3.998 (3H, s, OCH_3), 4.098 (3H, s, OCH_3), 7.283 (1H, dd, *J*=8.6, 2.6 Hz, C_7-H), 7.762 (1H, d, *J*=2.6 Hz, C_9-H), 8.201 (1H, d, *J*=8.6 Hz, C_6-H), 8.618 (1H, s, C_2-H).

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