TOTAL SYNTHESIS OF EUPOMATIDINES-1, 2, AND 3

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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 monogenic angiosperm family Eupomatiaceae, Eupomatia bennetti and E. laurina.1 The structures of eupomatidines-1, 2, and 3 were elucidated by ir, uv, ms and 1H-nmr spectra as 9-methoxynaphtho[1,2,3-i]2,7-naphthyridin-7(7H)-one (1a), 4-methoxynaphtho[1,2,3-i][2,7]naphthyridin-7(7H)-one (1b), and 4,9-dimethoxynaphtho[1,2,3-i][2,7]naphthyridin-7(7H)-one (1c), respectively.1 We report here the first total synthesis of eupomatidines-1 (1a), 2 (1b), and 3 (1c).

The hetero Diels-Alder cycloaddition2 of 6-methoxy-1,4-naphthoquinone3 (2b) with 2-butenal dimethylhydrazone4 (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 dioxide2 in chloroform gave 8-methoxy-4-methylbenzo[g]quinoline-5,10-dione5 (6a) in 74% yield. The aza-anthraquinone (6a) was condensed with dimethylformamide diethylacetal6 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-methoxy-naphtho[1,2,3-ij][2,7]naphthyridin-7(7H)-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(7H)-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(7H)-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.\(^1\)

Reagents and Conditions: a) CH\(_3\)CN, 80°C, 4 h, or CHCl\(_3\), 20°C, 2 h.

b) MnO\(_2\) (large excess), CHCl\(_3\), 20°C, 1 h.

c) (C\(_2\)H\(_3\)O\(_2\))\(_2\)CH-N(CH\(_3\))\(_2\), DMF, 120°C, 30 min.

d) NH\(_4\)Cl, CH\(_3\)CO\(_2\)H, reflux, 30 min.
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REFERENCES AND NOTES

5. 6a: mp 212-214°C (CH₂Cl₂-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. ¹H-Nmr (270 MHz, CDCl₃) δ: 2.928 (3H, s, C₄-CH₃). 4.008 (3H, s, OCH₃), 7.317 (1H, dd, J=8.9, 2.6 Hz, C₇-H), 7.508 (1H, d, J=4.6 Hz, C₃-H), 7.773 (1H, d, J=2.6 Hz, C₉-H), 8.222 (1H, d, J=8.9 Hz, C₆-H), 8.895 (1H, d, J=4.6 Hz, C₂-H).
7. Eupomatidine-l (1a): mp 228-231°C (CH₃OH) [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 (C₂-H₂O) 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). ¹H-Nmr (270 MHz, CDCl₃) δ: 4.015 (3H, s, OCH₃), 7.372 (1H, dd, J=8.9, 2.6 Hz, C₁₀-H), 7.665 (1H, d, J=5.9 Hz, C₄-H), 7.916 (1H, d, J=5.6 Hz, C₃-H), 7.916 (1H, d, J=2.6 Hz, C₈-H), 8.779 (1H, d, J=8.9 Hz, C₁₁-H), 8.838 (1H, d, J=5.9 Hz, C₅-H), 9.134 (1H, d, J=5.6 Hz, C₂-H). ¹³C-Nmr (67.8 MHz, CDCl₃) 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 ¹H-Nmr (270 MHz, CDCl₃) δ: 1.742 and 1.769 (3H, s, CH₃-CH=), 2.854 and 2.939 (6H, d, (CH₃)₂N-), 3.623 and 3.708 (3H, s, OCH₃), 4.791 and 5.104 (1H, q, J=7.3 Hz, CH₃-CH=), 6.704 and 7.030 (1H, s, CH=N).
10. 4b: mp 172-173°C (ether-hexane). Ms m/z (%): 255 (M⁺, 9), 240 (100). Ir (KBr): 3356, 1672, 1658,
11. Eupomatidine-2 (1b): mp 262-265°C (decomp.) (CH2Cl2-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 (C2H5OH) λ_max nm (log ε): 243 (4.51), 265 (4.25), 333 (3.71), 390 (4.16), 407 (4.14). ¹H-Nmr (270 MHz, CDCl3) δ: 4.249 (3H, s, OCH3), 7.690 (1H, d, J=7.9, 7.6, 1.3 Hz, C7-H), 7.821 (1H, d, J=7.9, 7.6, 1.3 Hz, C10-H), 8.016 (1H, d, J=5.6 Hz, C3-H), 8.487 (1H, dd, J=7.9, 1.3 Hz, C8-H), 8.669 (1H, s, C5-H), 8.879 (1H, dd, J=7.9, 1.3 Hz, C11-H), 8.895 (1H, d, J=5.6 Hz, C2-H). ¹³C-Nmr (67.8 MHz, CDCl3) 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 (CH2Cl2-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. ¹H-Nmr (270 MHz, CDCl3) δ: 2.788 (3H, s, C4-CH3), 4.107 (3H, s, OCH3), 7.75-7.85 (2H, m, C7-H, C8-H), 8.2-8.4 (2H, m, C6-H, C9-H), 8.658 (1H, s, C2-H).

13. Eupomatidine-3 (1c): mp 278-281°C (decomp.) (CH2Cl2-CH3OH) [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 (C2H5OH) 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). ¹H-Nmr (270 MHz, CDCl3) δ: 4.008 (3H, s, C9-OCH3), 4.244 (3H, s, C4-OCH3), 7.346 (1H, dd, J=8.9, 2.6 Hz, C10-H), 7.925 (1H, d, J=2.6 Hz, C8-H), 7.941 (1H, d, J=5.9 Hz, C3-H), 8.651 (1H, s, C5-H), 8.780 (1H, d, J=8.9 Hz, C11-H), 8.834 (1H, d, J=5.9 Hz, C2-H). ¹³C-Nmr (67.8 MHz, CDCl3-CD2CO2D) 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, 153.34s, 162.17s, 177.57s.

14. 6c: mp 285-288°C (decomp.) (CH2Cl2-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. ¹H-Nmr (270 MHz, CDCl3) δ: 2.779 (3H, s, C4-CH3), 3.998 (3H, s, OCH3), 4.098 (3H, s, OCH3), 7.283 (1H, dd, J=8.6, 2.6 Hz, C7-H), 7.762 (1H, d, J=2.6 Hz, C9-H), 8.201 (1H, d, J=8.6 Hz, C6-H), 8.618 (1H, s, C2-H).

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