

## Communications to the Editor

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TOTAL SYNTHESIS OF (±)-PANICULIDINE B<sup>1)</sup>

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The first synthesis of (±)-paniculidine B is achieved from 2-nitrotoluene in seven steps with an overall yield of 16%.

KEYWORDS — (±)-paniculidine A; (±)-paniculidine B; 1-methoxyindole; 3-iodo-1-methoxyindole; 4-(1-methoxyindol-3-yl)-2-butanone

Kinoshita and co-workers<sup>2)</sup> isolated paniculidine B from *Murraya paniculata* (Linn.) Jack. and established its structure as 2-methyl-4-(1-methoxyindol-3-yl)-1-butanol. As part of our project for synthesizing 1-methoxyindole alkaloids,<sup>3)</sup> we are greatly interested in this alkaloid. In this report, we describe the first total synthesis of (±)-paniculidine B (1).

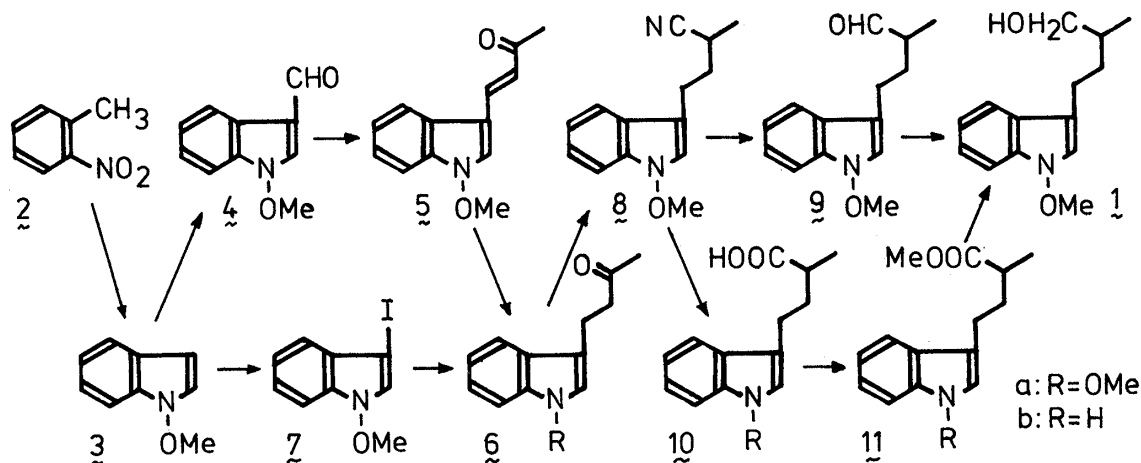
1-Methoxy-3-indolecarbaldehyde (4) is readily available in two steps in 63% overall yield from 2-nitrotoluene (2) according to our synthesis method.<sup>4)</sup> The aldol condensation reaction of 4 with acetone in the presence of 2N-NaOH afforded 4-(1-methoxyindol-3-yl)-3-buten-2-one (5)<sup>5a)</sup> in 96% yield. Subsequent selective hydrogenation of the conjugated double bond in 5 was the most difficult step. Various reduction methods with such reagents as pyridine/ $\text{NaBH}_4$ ,<sup>6)</sup>  $\text{CuI/LiAlH}_4$ ,<sup>7)</sup>  $\text{PdCl}_2/\text{NaBH}_4$ ,<sup>8)</sup>  $\text{Zn(Hg)/HCl}$ ,<sup>9)</sup> etc., were examined but they were found to be unsuccessful due to the intrinsically unstable nature of 1-methoxyindole to reduction, culminating in the formation of demethoxylated products. Among them, catalytic hydrogenation over 10% Pd/C in  $\text{CHCl}_3$  afforded the best result<sup>10)</sup> and the desired 4-(1-methoxyindol-3-yl)-2-butanone (6a)<sup>5b)</sup> and the corresponding demethoxy compound (6b) were obtained in 36% and 16% yields, respectively, though the yield of 6a is still not satisfactory.

The compound (6a) was also produced by the other route. Thus, 3-iodo-1-methoxyindole (7)<sup>5c)</sup> was prepared in 27% yield by the treatment of 1-methoxyindole (2) with  $\text{I}_2/\text{morpholine}$ .<sup>11)</sup> The improved Heck reaction<sup>12)</sup> of 7 with 3-buten-2-ol in the presence of tetra-*n*-butylammonium bromide gave 6a in 36% yield.

Next, the reaction of 6a with TosMIC<sup>13)</sup> proceeded successfully to give 4-(1-methoxyindol-3-yl)-2-methylbutanenitrile (8)<sup>5d)</sup> in 84% yield. Treatment of 8 with DIBAL produced the desired 4-(1-methoxyindol-3-yl)-2-methylbutyraldehyde (9)<sup>5e)</sup> in 88% yield. Subsequent reduction of 9 with  $\text{NaBH}_4$  in MeOH afforded paniculidine B (1) in 98% yield.

It should be noted that alkaline hydrolysis of 8 produced a 49% yield of demethoxy compound (10b), while the desired carboxylic acid (10a)<sup>5f)</sup> was produced in only 22% yield. Both of these carboxylic acids (10a and 10b) were methylated quantitatively with ethereal diazomethane to yield methyl 4-(1-methoxyindol-3-yl)-2-methylbutyrate (11a)<sup>5g)</sup> or paniculidine A (11b), respectively. Reduction of 11a with  $\text{LiAlH}_4$  also afforded paniculidine B (1) in 94% yield.

The UV, MS, and  $^1\text{H-NMR}$  (400 MHz) spectra of the synthetic paniculidine A and B were identical to those of natural products.



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- 5) All melting points are uncorrected.  $^1\text{H-NMR}$  (NMR) spectra were taken in deuterated chloroform (d-C) or carbon tetrachloride (C-T). Chemical shifts are reported in ppm ( $\delta$ ) from TMS. All oily compounds gave satisfactory high MS data and crystalline compounds afforded acceptable combustion data. IR absorption bands are shown in  $\text{cm}^{-1}$ . a) mp 79–81°C. IR (KBr): 1656, 1617. NMR (C-T): 2.18 (3H, s), 3.99 (3H, s), 6.46 (1H, d,  $J=16$  Hz), 6.78–7.26 (3H, m), 7.38 (1H, s), 7.41 (1H, d,  $J=16$  Hz), 7.52–7.80 (1H, m); b) colourless oil. IR (film): 2940, 1708, 1452, 1160. NMR (d-C): 2.08 (3H, s), 2.58–3.08 (4H, m,  $A_2B_2$ ), 3.93 (3H, s), 6.81–7.51 (5H, m); c) mp 45–46°C (unstable colourless prisms). IR (film): 3120, 1570, 1438, 1322. NMR (C-T): 3.96 (3H, s), 6.69–7.34 (5H, m); d) colourless oil. IR (film): 2240, 1450, 1098. NMR (d-C): 1.33 (3H, d,  $J=7$  Hz), 1.79–2.11 (2H, m), 2.60 (1H, sext,  $J=7$  Hz), 2.80–3.04 (2H, m), 4.05 (3H, s), 6.95–7.61 (5H, m); e) colourless oil. IR (film): 2725, 1722, 1453. NMR (C-T): 1.07 (3H, d,  $J=6.5$  Hz), 1.40–2.49 (3H, m), 2.67 (2H, t,  $J=7$  Hz), 3.91 (3H, s), 6.79 (1H, br s), 6.69–7.42 (4H, m), 9.30 (1H, d,  $J=1.5$  Hz); f) colourless oil. IR (film): 3500–2300, 1702, 1450, 1232. NMR (C-T): 1.21 (3H, d,  $J=7$  Hz), 1.44–2.52 (3H, m), 2.69 (2H, t,  $J=7$  Hz), 3.91 (3H, s), 6.61–7.42 (5H, m), 10.49 (1H, br s); g) colourless oil. IR (film): 2940, 1738, 1452, 1204. NMR (C-T): 1.10 (3H, d,  $J=7$  Hz), 1.38–2.44 (3H, m), 2.61 (2H, t,  $J=7$  Hz), 3.53 (3H, s), 3.92 (3H, s), 6.78 (1H, br s), 6.68–7.44 (4H, m).
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