JOC Article

Efficient Total Syntheses of Phytoalexin and (±)-Paniculidine B and C Based on the Novel Methodology for the Preparation of 1-Methoxyindoles†

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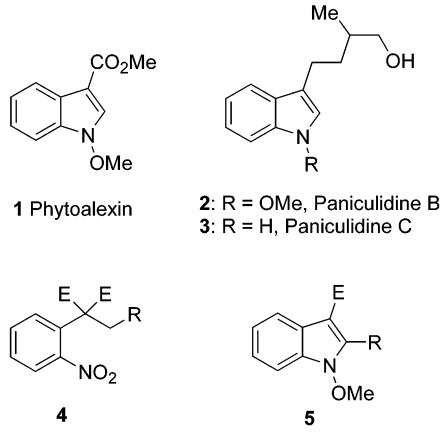
A general route to 2-unsubstituted-1-methoxyindoles, based on our methodology for the synthesis of 1-methoxyindoles, is reported. This synthesis renders accessibility to a variety of natural products possessing the said skeleton. A direct synthesis of phytoalexin (**1**), (±)-paniculidine B (**2**), and (±)-paniculidine C (**3**) is disclosed based on the methodology. The synthesis of paniculidine B (**2**) has been achieved from aldehyde **10** in only two steps in 88% yield and in five steps from a methoxyindole compound **8** obtained using our earlier methodology.

A number of alkaloids possessing a 2-unsubstituted-1-methoxyindole structural framework have been isolated and reported in the literature.[1] These include phytoalexin (**1**), an antifungal metabolite produced by wasabi (*Wasabia japonica*. syn. *Eutrema wasabi*)[2] and paniculidine B (**2**) isolated from *Murraya paniculata* (Linn.) Jack. among many others.[3] Various parts of the latter plant are used as a folk medicine for the treatment of stomachache and toothache and also as a stimulant throughout the areas ranging from India, southeast Asia, southern China, Taiwan, etc. In our previous paper, we have disclosed a new synthesis of substituted 1-methoxyindoles based on a novel methodology.[4] The methodology culminated in the syntheses of a variety of 1-methoxyindoles such as the structure **5** possessing different substituents (R) in the second position starting from simple starting materials such as **4** containing an activated methylene group that in turn are available from aromatic nitrobenzenes.



However, the methodology was not amenable for the syntheses of the large number of natural products possessing 2-unsubstituted-1-methoxyindole skeletons including the title compounds.[5] In an effort to substantiate the usefulness of our earlier methodology for the syntheses of such compounds, we initiated a program to convert the hitherto obtained 1-methoxyindole compounds to the corresponding 2-unsubstituted compounds. To that end, it was envisioned that the decarboxylation of the methoxyindole compound analogous to structure

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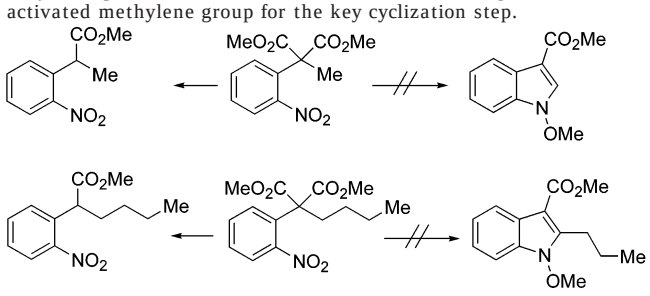
(1) (a) Somei, M. *Heterocycles* **1999**, *50*, 1157. (b) Acheson, R. M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: San Diego, CA, 1990; Vol. 51, pp 105−175.

(2) Soledade, M.; Pedras, C.; Sorenson, J. L. *Phytochemistry* **1998**, *49*, 1959.

(3) Kinoshita, T.; Tatara, S.; Ho, F.-C.; Sankawa, U. *Phytochemistry* **1989**, *28*, 147 and references therein.

(4) (a) Selvakumar, N.; Reddy, B. Y.; Azhagan, A. M.; Khera, M. K.; Babu, J. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7065. (b) Selvakumar, N.; Khera, M. K.; Reddy, B. Y.; Srinivas, D.; Azhagan, A. M.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 7071.

(5) Our efforts to generalize this methodology to the 2-unsubstituted-1-methoxyindole skeleton resulted only in decarboxylated products as shown below. The compound analogous to **4** (R = H and E = CO_2Me) under reaction conditions failed to yield the respective methoxyindole compound analogous to structure **5**. Similarly, the compound **4** (R = *n*-propyl and E = CO_2Me) also resulted in the corresponding decarboxylated product. These results ascertained the requirement of an activated methylene group for the key cyclization step.



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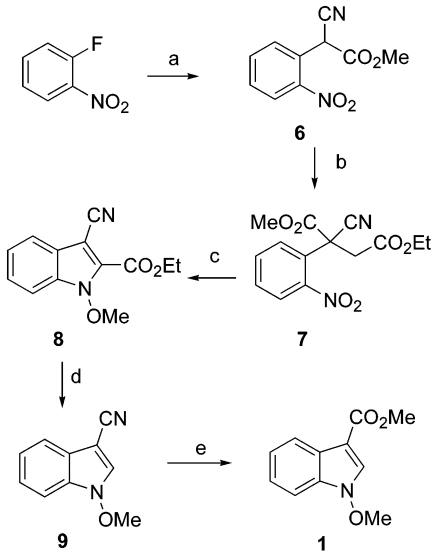
SCHEME 1 [a]



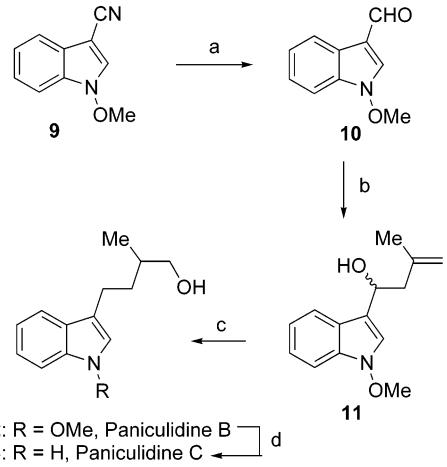
[a] Reagents and conditions: (a) methyl cyanoacetate, NaH, THF, 0 → 60 °C, 79%; (b) K_2CO_3, THF, ethyl bromoacetate, 0 °C → rt, 79%; (c) NaCl, DMSO, 155 °C, 60%; (d) LiOH, 3:1 DMF−H_2O, 0 °C → rt, 80% and then quinoline, Cu powder, 220 °C, 20 min, 88%; (e) MeOH, cat. H_2SO_4, reflux, 72 h, 60%.

5 (R = CO_2Et, E = CN) would lead to the corresponding 2-unsubstituted methoxyindole, which in turn could be elaborated to the natural products. Thus, we now report a method for such conversion and the resultant 2-unsubstituted methoxyindole compound **9** was used as the starting material for the highly efficient total syntheses of phytoalexin (**1**) and (±)-paniculidine B (**2**) and C (**3**).[6]

Results and Discussion

The cyano-ester **6**, prepared along the lines of our previous report,[4] was alkylated with ethylbromoacetate under basic conditions to afford the diester **7** (Scheme 1). The diester **7** underwent smooth rearrangement as reported before leading to the indole 2-carboxylic acid ester **8**. Having the cyano-ester **8** in hand, we turned our attention toward developing an effective method for the decarboxylation of the carboethoxy group in the second position. The hydrolysis of the carboethoxy group was accomplished smoothly following the usual procedure to afford the corresponding acid. At this juncture, literature search for the decarboxylation of indole 2-carboxylic acids revealed that Cu in quinoline at elevated temperature leads to the corresponding indoles in good yields.[7] Thus, heating the acid, obtained from the ester **8**, in doubly and freshly distilled quinoline in the presence of Cu powder neatly afforded the required decarboxylated indole compound **9**. Having succeeded in identifying a method to effect the decarboxylation of the 1-methoxyindole compound **8**, we wished to confirm the structure of the resultant 1-methoxyindole (**9**) unambiguously by converting it to the corresponding ester, which is the naturally occurring phytoalexin (**1**). Thus, the transformation of the nitrile to the carbomethoxy group was smoothly effected by a catalytic amount of sulfuric acid in refluxing methanol.[8] The spectral and analytical data of the synthetic phytoalexin (**1**) were in accordance with literature values in all aspects,[2] confirming the structure of the cyano indole compound **9**.

SCHEME 2 [a]



[a] Reagents and conditions: (a) DIBAL-H, dry PhMe, −78 °C, 20 min, 98%; (b) methallyl chloride, Mg, THF, rt, 3 h, 99%; (c) $NaBH_4$, BF_3·OEt_2, THF then NaOH, H_2O_2, 89%; (d) 10% Pd on charcoal, H_2, MeOH, 94%.

Having identified a method to obtain the cyano indole compound **9** in gram quantities, we turned our attention to complete the synthesis of the target compound **2**. At this stage, the synthesis warranted an introduction of a four-carbon synthon such as methallyl bromide to achieve the natural product **2**. Thus, the nitrile functionality in the indole compound **9** was converted to the corresponding aldehyde **10** under standard conditions setting the stage for introducing the four-carbon fragment (Scheme 2). While our efforts to introduce a four-carbon fragment using the Grignard reagent derived from methallyl bromide failed, the reaction was accomplished neatly with the reagent obtained from methallyl chloride in quantitative yield resulting in the advanced intermediate **11**. Once the alcohol **11** was in hand, only deoxygenation of the benzylic alcohol and a hydroboration of the terminal double bond needed to be achieved to arrive at the target compound. All our efforts to effect the deoxygenation of the alcohol **11**, using reagents such as $NaBH_4$ in TFA,[9] Et_3SiH in TFA,[10] and TMSCI in acetonitrile,[11] resulted in either demethoxylation of the *N*-methoxy group or decomposition. At this juncture, we envisioned that borane derived from the reagent combination of $NaBH_4$ and BF_3·OEt_2 would effect not only the hydroboration of the olefinic functionality in alcohol **11** but also the deoxygenation of the benzylic alcohol group in one pot. Thus, the exposure of alcohol **11** to $NaBH_4$ and BF_3·OEt_2 followed by treatment of the resultant reaction

(6) For a synthesis of this phytoalexin, see: Somei, M.; Tanimato, A.; Orita, H,; Yamada, F.; Ohata, T. *Heterocycles* **2001**, *54*, 425. For a synthesis of paniculidine B, see: Somei, M.; Ohnishi, H. *Chem. Pharm. Bull.* **1985**, *33*, 5147.

(7) For decarboxylation of indole-2-carboxylic acids, see: Jones, G. B.; Chapman. B. J. *J. Org. Chem.* **1993**, *58*, 5558 and references therein.

(8) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1988**, *53*, 4063.

(9) Gribble, G. W.; Leese, R. M. *Synthesis* **1977**, 172.

(10) Patiki, J.; Harvey, R. G. *J. Org. Chem.* **1987**, *52*, 2226.

(11) Sakai, T.; Miyata, K.; Utaka, M.; Jakeda, A. *Tetrahedron Lett.* **1987**, *28*, 3817.

mixture with basic H_2O_2 smoothly afforded paniculidine B (**2**) in good yield. The spectral data of the synthetic compound **2** were in agreement with the data reported for the natural material.[3] The synthesis of the target product **2** has thus been achieved in eight steps in 22.8% overall yield from commercial materials and in only two steps from the known methoxyindole carbaldehyde **10**[6] in an impressive 88.1% yield. It is important to note that the conversion of the carbaldehyde **10** to paniculidine B (**2**) earlier in the literature consumed five steps with a modest overall yield of 25%.[6] In addition, the earlier method needed an expensive reagent in one of the steps and further involved a poor yielding step. In the end, paniculidine B (**2**) was converted to paniculidine C (**3**) under hydrogenolysis conditions in excellent yield. The spectral data of the synthetic paniculidine C (**3**) were in agreement with the data reported for the natural product.[3]

In conclusion, we have reported a method to transform the 2-substituted-1-methoxyindole compounds obtained by using our reported methodology to the corresponding 2-unsubstituted-1-methoxyindole compounds. This opens up a novel route to synthesize all natural products having the 1-methoxyindole skeleton with no substituent in the second position. The usefulness of the procedure was further substantiated with the direct total syntheses of phytoalexin (**1**), paniculidine B (**2**), and paniculidine C (**3**) in good overall yields. Further work to complete the syntheses of other natural products of this class such as methoxybrassinin[12] and lespedamine[13] is underway in our laboratory.

Experimental Section

General. Melting points are uncorrected. Unless otherwise mentioned, all ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. Chemical shifts are reported in δ units with respect to TMS as internal standard. Unless otherwise mentioned all the solvents used were of LR grade. Usually, the flash chromatography was done on silica gel (100−200 mesh), using petroleum ether−ethyl acetate as eluent unless otherwise reported. All the organic extracts were dried over sodium sulfate after workup.

Methyl 2-Cyano-2-(2-nitrophenyl)acetate (6). To a suspension of NaH (60% in oil, 5.64 g, 141 mmol) in dry THF (200 mL) was successively added, at ice bath temperature under argon, methyl cyanoacetate (7.5 mL, 85 mmol) over 5 min followed by 2-fluoronitrobenzene (7.4 mL, 70 mmol). The reaction mixture was refluxed overnight and then allowed to cool to room temperature. The reaction mixture was carefully quenched with saturated NH_4Cl at ice bath temperature and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were washed with water and brine and dried. The residue obtained upon concentration of the solvents was purified by flash column chromatography to give the cyano-ester **6** (12.2 g, 79%) as a pale yellow oil, which solidified upon storing in a refrigerator. Mp: 59 °C. ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H), 5.69 (s, 1H), 7.61−7.79 (m, 3H), 8.25 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 164.0, 147.0, 134.5, 131.6, 130.6, 125.9, 125.0, 114.3, 54.1, 41.0. Mass (CI method): 221 (M^+ + 1), 178. IR (neat): 2959, 2254, 1754 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.53; H, 3.66; N, 12.73. Found: C, 54.29; H, 3.59; N, 12.90.

4-Ethyl 1-Methyl 2-Cyano-2-(2-nitrophenyl)succinate (7). Ethyl bromoacetate (0.9 mL, 8.2 mmol) was added to a mixture of nitro-ester **6** (1.2 g, 5.46 mmol) and potassium carbonate (2.26 g, 16.35 mmol) in dry THF (30 mL) at 0 °C under argon. The reaction mixture was allowed to attain room temperature over 3 h and was stirred for an additional 33 h. The reaction mixture was diluted with ethyl acetate (200 mL) and then washed with water and brine and dried. The residue obtained upon concentration of the solvents was purified by flash column chromatography with petroleum ether−dichloromethane as an eluent to give the diester **7** (1.31 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.3 Hz, 3H), 3.51 and 3.68 (ABq, J = 16.9 Hz, 2H), 3.84 (s, 3H), 4.02−4.15 (m, 2H), 7.62 (dt, J = 1.5 and 7.6 Hz, 1H), 7.75 (dt, J = 1.5 and 7.8 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 8.14 (dd, J = 1.5 and 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 167.8, 165.2, 147.2, 133.9, 131.8, 130.4, 128.0, 126.4, 116.5, 61.4, 54.3, 50.3, 40.5, 13.8. Mass (CI method): 307 (M^+ + 1), 261. IR (neat): 1740, 1534 cm^{-1}.

Ethyl 3-Cyano-1-methoxy-1*H*-2-indolecarboxylate (8). A mixture of cyano-diester **7** (5.0 g, 16.34 mmol) and sodium chloride (475 mg, 8.12 mmol) in dry DMSO (50 mL) was immersed in a preheated oil bath at 150 °C and stirred over a period of 20 min. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (500 mL). The resultant mixture was washed with water and brine and dried. The residue obtained upon evaporation of the solvents was purified by flash chromatography to give the cyano-ester **8** (2.4 g, 60%) as a colorless solid. Mp: 68 °C. ^{1}H NMR ($CDCl_3$): δ 1.50 (t, J = 7.3 Hz, 3H), 4.27 (s, 3H), 4.52 (q, J = 7.2 Hz, 2H), 7.36 (t, J = 6.7 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 157.5, 133.0, 128.8, 127.2, 123.8, 122.9, 120.8, 113.8, 109.8, 88.6, 66.9, 62.3, 14.0. Mass (CI method): 245 (M^+ + 1), 215. IR (KBr): 2223, 1725, 1244 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.96; H, 4.95; N, 11.47. Found: C, 63.58; H, 4.93; N, 11.32.

1-Methoxy-1*H*-3-indolecarbonitrile (9). To a solution of the cyano-ester **8** (1.865 g, 7.64 mmol) in DMF:H_2O (3:1, 30 mL) was added powdered LiOH (549 mg, 22.88 mmol) portionwise at 0 °C. After being stirred for 10 min at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. The reaction mixture was neutralized with 2 N HCl and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine and dried. The residue obtained upon evaporation of the solvents was suspended in ether and filtered to obtain the corresponding cyano-acid (1.322 g, 80%) as a colorless solid. This compound was not stable for analytical purposes and storage, and thus was taken to the next step without further purification and characterization. ^{1}H NMR (DMSO-d_6): δ 4.25 (s, 3H), 7.41−7.78 (m, 4H). Mass (electrospray method): 217 (M^+ + 1). IR (KBr): 3300−2400 (br), 2229, 1673 cm^{-1}.

A mixture of the above acid (1.0 g, 4.63 mmol) and copper power (29 mg, 0.46 mmol) in doubly distilled quinoline (15 mL) was immersed in a preheated oil bath at 220 °C. The reaction mixture was stirred over a period of 20 min at the same temperature and then allowed to attain ambient temperature. The resultant mixture was neutralized with 2 N HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with water and brine and dried. The residue obtained upon evaporation of the solvents was purified by flash chromatography to yield the nitrile **9** (700 mg, 88%) as a light yellow oil that solidified upon storing in a refrigerator. Mp: 60 °C. ^{1}H NMR ($CDCl_3$): δ 4.17 (s, 3H), 7.31−7.43 (m, 2H), 7.52 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.8 Hz, 1H), 7.78 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 130.8, 129.2, 124.5, 124.0, 122.6, 119.9, 115.1, 109.1, 82.3, 67.0. Mass (CI method): 173 (M^++1), 143. IR (neat): 2222, 1238 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.74; H, 4.69; N, 16.28. Found: C, 69.27; H, 5.00; N, 16.26.

(12) Takasugi, M.; Monde, K.; Katsui, N.; Shirata, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 285.
(13) Morimoto, H.; Oshio, H. *Justus Liebigs Ann. Chem.* **1965**, *682*, 212.

1-(1-Methoxy-1*H*-3-indolyl)-3-methyl-3-buten-1-ol (11). To a mixture of magnesium turnings (274 mg, 11.42 mmol) and a crystal of iodine in dry THF (40 mL) was added methallyl chloride (400 μL) under argon. When the reaction mixture turned colorless, it was cooled in an ice bath and then a solution of methallyl chloride (1.7 mL, 11.42 mmol) and 1-methoxyindole-3-carbaldehyde (**10**) (1.0 g, 5.71 mmol) in THF (10 mL) was added over a period of 5 min. After being stirred for 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 3 h. Saturated NH_4Cl was added to the reaction mixture dropwise at the same temperature and the mixture was extracted with ether (3 × 75 mL). The combined organic layers were washed with water (3 × 20 mL) and brine and dried. The residue obtained upon evaporation of the solvents was purified by flash chromatography to yield the alcohol **11** (1.31 g, 99%) as a light yellow oil that is slightly unstable and should be consumed within 2 days. ^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H), 2.10 (br s, D_2O exchangeable, 1H), 2.64 (d, J = 6.8 Hz, 2H), 4.07 (s, 3H), 4.92 (d, J = 6.8 Hz, 2H), 5.16 (t, J = 6.3 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.23−7.30 (m, 2H), 7.43 (d, J = 7.8, 1H), 7.73 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 132.7, 123.9, 122.2, 120.4, 119.3, 119.1, 112.9, 108.3, 68.1, 65.3, 35.4, 33.3, 22.4, 16.5. Mass (CI method): 232 ($M^+ + 1$), 214. IR (neat): 3393 (br), 1450 cm^{-1}. HRMS: calcd for $C_{14}H_{17}NO_2$ 231.1259, found 231.1266.

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Supporting Information Available: Experimental procedure for compounds **1**−**3** and **10** and the ^{1}H NMR and ^{13}C NMR spectra of compounds **1**−**3** and **6**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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