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An efficient total synthesis of 9-methoxycarbazole-3-carbaldehyde based on a novel methodology for the preparation of methoxyindoles☆

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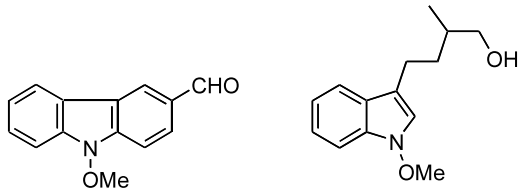
Abstract—A direct synthesis of naturally occurring 9-methoxycarbazole-3-carbaldehyde **1**, based on our methodology for the synthesis of 1-methoxyindoles, is reported. A novel benzannulation strategy was employed using ring closing metathesis as the key step in this total synthesis. The synthesis of the natural product **1** has been achieved in seven steps in 14% overall yield from commercial materials and in only four steps from a methoxyindole compound obtained using the new methodology.

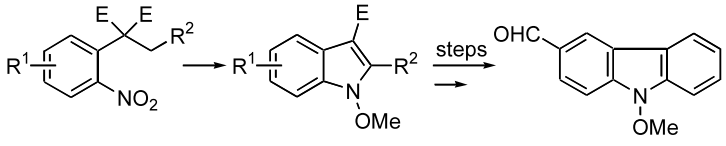
A number of alkaloids possessing a 1-methoxyindole structural framework have been isolated and reported in the literature.[1] These include 9-methoxycarbazole-3-carbaldehyde **1** isolated from *Murraya euchrestifolia* HAYATA (Rutaceae) and Paniculidine B **2** isolated from *Murraya paniculata* (Linn.) Jack.[2,3] 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 areas ranging from India, South-east Asia, southern China, Taiwan etc. In the preceding letter, we disclosed a new synthesis of substituted 1-methoxyindoles based on a novel methodology (Scheme 1).[4] The methodology involves a rearrangement of a nitro compound of type **3** under neutral conditions to a 1-methoxyindole derivative such as **4**. In an effort to substantiate the usefulness of the methodology, we initiated a program towards the total synthesis of the title natural product. To this end, we now report a highly efficient total synthesis of 9-methoxycarbazole-3-carbaldehyde **1** in this communication.[5]



1 9-methoxycarbazole -3-carbaldehyde

2 Paniculidine B

The disconnection of the natural product **1**, illustrated in Scheme 2, led to the indole aldehydes **7** or **8** based on two conceptually different retrosynthetic approaches



3 **4** **1**

E = CO_2Me or CN

Scheme 1.

Keywords: rearrangement; metathesis; alkaloid; decarboxylation; nucleophilic catalysis.

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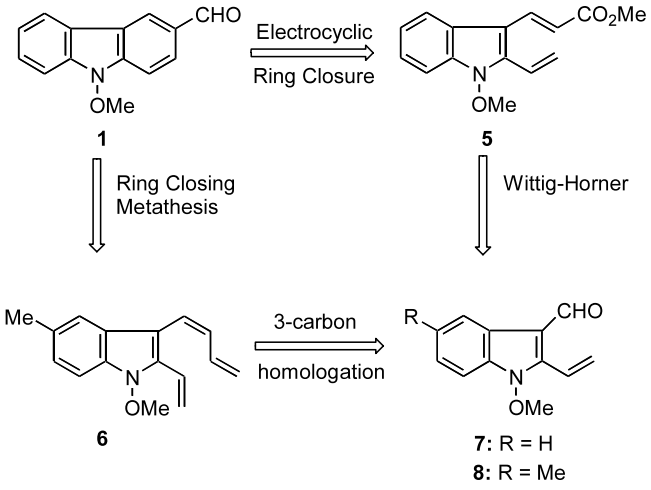
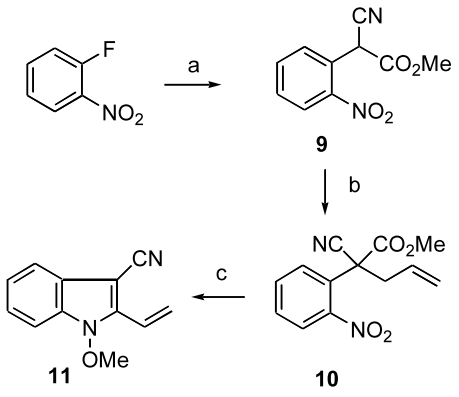


Scheme 2. Retrosynthetic plan for the natural product **1**.

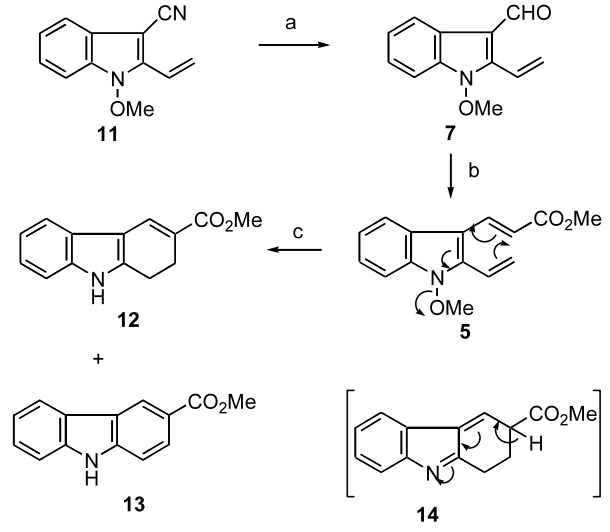
and the aldehydes in turn would be available from our methodology reported in the preceding letter.[4] The first route involved an electrocyclic ring closure of an appropriate unsaturated ester **5** that is accessible from the aldehyde **7** by a Wittig–Horner reaction. The second protocol required a conjugated olefin of type **6** or its equivalent for a ring closing metathesis (RCM) reaction, compound **6** could be easily prepared from the aldehyde **8** by a three carbon homologation procedure. Having conceived two attractive routes for the title compound **1**, we turned our attention towards the preparation of the aldehydes **7** and **8**.

We envisioned that the requisite aldehydes **7** and **8** would be available from nitriles such as **11** by standard reduction procedures (Scheme 3). However, our methodology renders access to only 2-substituted 1-methoxyindole-3-carboxylates but not to 3-substituted nitriles. Thus, we used methyl cyanoacetate instead of dimethyl malonate in the aromatic nucleophilic substitution on 2-fluoronitrobenzene anticipating that the carbomethoxy group would take part in the rearrangement leaving the C-3 nitrile of the resultant indole. Thus, the cyanoester **10**, prepared by the usual reaction sequence,[6] underwent the rearrangement to the required 1-methoxyindole **11** possessing the nitrile substituent at C-3.

With the nitrile **11** in hand, the synthesis of the natural compound **1** was initially attempted by the first route involving electrocyclic ring closure as the key step (Scheme 4). Thus, subjecting aldehyde **7**, obtained by the reduction of nitrile **11**, to Wittig–Horner reaction conditions resulted in the substrate **5** setting the stage for the crucial electrocyclic ring closure reaction. However, all our attempts to effect the ring closure resulted only in the demethoxylated compound **12** along with an appreciable quantity of the corresponding aromatised compound **13**. A mechanism of demethoxylation is illustrated in structure **5** and is believed to go through the intermediacy of structure **14**. It is important to note that precedents exist for such demethoxylations in the literature in the area of methoxyindoles.[7]

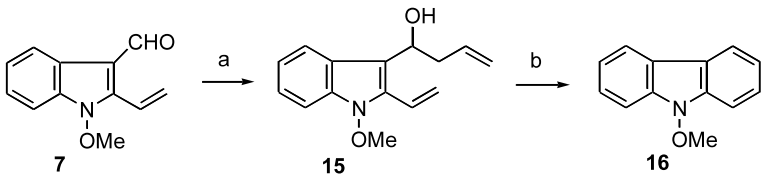


Scheme 3. *Reagents and conditions*: (a) Methyl cyanoacetate, NaH, THF, 0→60°C, 75%; (b) NaH, DMF, allyl bromide, rt, 68%; (c) NaCl, DMSO, 155°C, 72%.



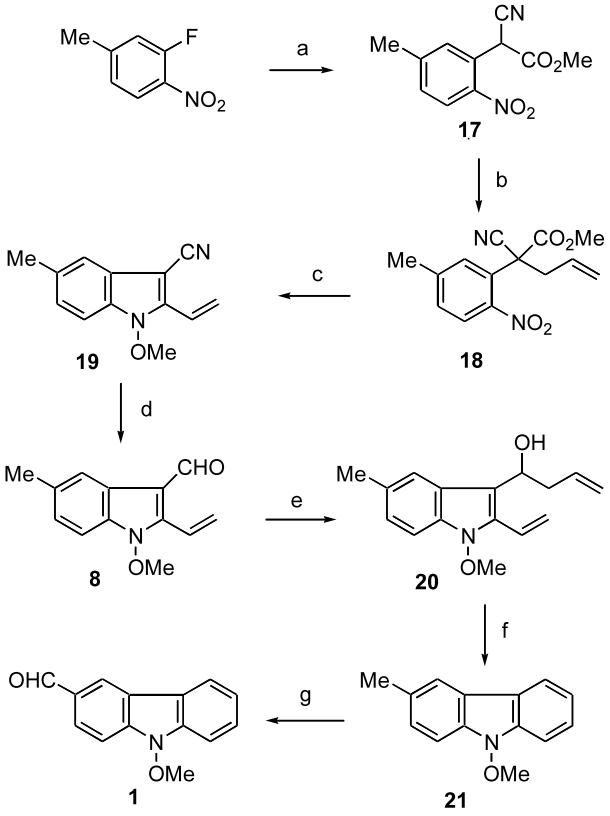
Scheme 4. *Reagents and conditions*: (a) DIBAL-H, dry PhMe, –78°C, 73%; (b) trimethyl phosphonoacetate, NaH, THF, 62%; (c) dry PhMe, reflux.

As the electrocyclic ring closure method failed to deliver the requisite 9-methoxy carbazole skeleton, we turned our attention towards the second route involving RCM as the key step. Because of the ready availability of the aldehyde **7** from Scheme 4, we studied the feasibility of RCM methodology in synthesizing the 9-methoxycarbazole skeleton on this aldehyde as a model system (Scheme 5). Attempted three-carbon homologation of the aldehyde **7** using allyl magnesium bromide failed to yield the desired results. However, the transmetallation of allyltributyltin followed by treatment with aldehyde **7** cleanly afforded the alcohol **15** as a stable oil. It was expected at this stage that the product obtained by the RCM reaction of alcohol **15** would eventually undergo dehydration leading to the corresponding aromatised compound. It was indeed true that treatment of the alcohol **15** with Grubbs' catalyst resulted in smooth cyclisation with concomitant dehydration leading to 9-methoxycarbazole **16** in very good yields.[8]



Scheme 5. *Reagents and conditions*: (a) Allyltributyltin, BuLi, THF, −78°C, 74%; (b) Grubbs' catalyst, CH_2Cl_2, rt→reflux, 66%.

Having established the feasibility of the RCM reaction in effecting the ring closure on the model system, we turned our attention in applying this methodology to the synthesis of the natural compound **1** (Scheme 6). Applying our methodology as in Scheme 3 on commercially available 3-fluoro-4-nitrotoluene resulted in the methoxyindole **19** in much improved yields. Treatment of the nitrile **19** with DIBAL-H cleanly afforded the aldehyde **8**, which was allylated as described in Scheme 5 resulting in the alcohol **20**. The alcohol **20** underwent a smooth RCM reaction as before leading to the carbazole **21** in excellent yield.[9] Among the many methods attempted to convert the aromatic methyl group in **21** to the aldehyde as in **1**, DDQ in acetic acid was particularly impressive affording the target compound in moderate yields.[10] The spectral data of the synthetic compound **1** were in agreement in all aspects with those of the natural material.[2,11] The synthesis of the natural product **1** has thus been achieved in seven steps in 14% overall yield from commercial materials and in only four steps from a methoxyindole compound obtained using our new methodology.



Scheme 6. *Reagents and conditions*: (a) Methyl cyanoacetate, NaH, THF, 0→60°C, 94%; (b) NaH, DMF, allyl bromide, 0°C→rt, 77%; (c) NaCl, DMSO, 155°C, 85%; (d) DIBAL-H, dry PhMe, −78°C, 85%; (e) allyltributyltin, BuLi, THF, −78°C, 83%; (f) Grubbs' catalyst, CH_2Cl_2, rt→reflux, 72%; (g) DDQ, AcOH, rt, 45%.

In conclusion, a direct total synthesis of 9-methoxycarbazole-3-carbaldehyde **1**, based on our methodology reported in the preceding letter,[4] has been achieved using RCM as the key step. The overall process of converting the aldehyde **8** into carbazole **21** constitutes a novel benzannulation strategy. The synthesis of a methoxyindole compound having no substituent in the 2-position and converting such material to the other natural products having a 1-methoxyindole skeleton, particularly paniculidine B **2**, is currently underway, and will be the content of future publications of this laboratory.

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9. Compound **21**: A suspension of Grubbs' catalyst (306 mg, 0.37 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 15 min at rt. To the above suspension was added a solution of the alcohol **20** (910 mg, 3.7 mmol) in dry CH_2Cl_2 (20 mL) dropwise over a period of 10 min under argon. After stirring for a further 30 min at the same temperature, the reaction mixture was refluxed for 16 h and was then allowed to cool to rt. A few drops of water were added to the resultant mixture and the contents were filtered over sodium sulfate. The residue obtained upon concentration of the filtrate was passed through a column of silica gel to afford the compound **21** as a colorless oil (567 mg, 72%). IR (neat, ν cm^{-1}): 1452, 1232 743; δ_H (200 MHz, $CDCl_3$): 8.00 (d, $J=7.3$ Hz, 1H), 7.83 (s, 1H), 7.60–7.15 (m, 5H), 4.10 (s, 3H), 2.53 (s, 3H); δ_C (50 MHz, $CDCl_3$): 21.4, 63.2, 108.2, 108.4, 119.9, 120.3, 120.4, 125.9, 127.4, 129.5, 136.2, 138.2 (signals for two quaternary carbons possibly overlap with other peaks); Mass (EI): 211, 196, 180; HRMS (EI) calcd for $C_{14}H_{13}NO$, 211.0997; found, 211.0997.
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11. Spectral data of synthetic compound **1**: IR (neat, ν cm^{-1}): 1687, 1598, 1234, 745; δ_H (400 MHz, $CDCl_3$): 10.11 (s, 1H), 8.61 (d, $J=1$ Hz, 1H), 8.15 (dd, $J=7.8$ and 1 Hz, 1H), 8.15 (dd, $J=8.3$ and 1.5 Hz, 1H), 7.64–7.56 (m, 3H), 7.40–7.35 (m, 1H), 4.23 (s, 3H); δ_C (50 MHz, $CDCl_3$): 191.5, 140.0, 137.3, 129.3, 127.6, 127.1, 123.8, 121.0, 120.8, 119.5, 108.3, 107.9, 64.1; Mass (EI): 225, 210, 194, 164; HRMS (EI) calcd for $C_{14}H_{11}NO_2$, 225.0790; found, 225.0788.