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# Concise, efficient and practical assembly of bromo-5,6-dimethoxyindole building blocks

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ABSTRACT

A concise, efficient and simple route to a series of bromoindole building blocks is described. The synthetic routes are highlighted by purification-free preparation of *o*-nitrocinnamate intermediates and clean, modified Cadogan indole syntheses. The scope of this indole synthesis has been explored and expanded through the use of a range of solvents and easily removable phosphine reagents.



The indole moiety is well recognized as a 'privileged structure' and is undoubtedly one of the most important structural subunits for drug discovery efforts. Moreover, indole core structures are abundant in many naturally occurring compounds from the essential amino acid, tryptophan to alkaloids.[1] Two interesting examples, 5,6-dihydroxyindole (DHI, **1**) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA, **2**) are the basic building blocks found in the photoprotective mammalian pigment, eumelanin.[2] Whilst DHI and DHICA are of little utility due to their propensity to undergo oxidative polymerization in an uncontrolled fashion, it is believed that appropriately protected derivatives of **1** and **2** could be used in the controlled assembly of synthetic eumelanin-like oligomers. The bromo-5,6-dimethoxy derivatives of DHI and DHICA **3**–**9** shown in Figure 1 typify such building blocks and we have recently demonstrated their utility in biindolyl syntheses via Suzuki–Miyaura cross-coupling.[3] However, current approaches to such building blocks are not ideal. For example, previously reported approaches to DHICA derivatives have utilized the Hemetsberger–Knittel indole synthesis.[4] Drawbacks with this approach include hazards associated with the synthesis and manipulation of organic azides on a multigram scale, moderate yielding steps and the potential for side-product formation (e.g., 2*H*-azirines and indole regioisomers) in the thermolysis of azidocinnamates to indoles. In order to address such issues and to develop a standard synthetic strategy for both DHI and DHICA building blocks geared to maximize synthetic efficiency and practical simplicity, we sought to access *o*-nitrostyrene and *o*-nitrocinnamate

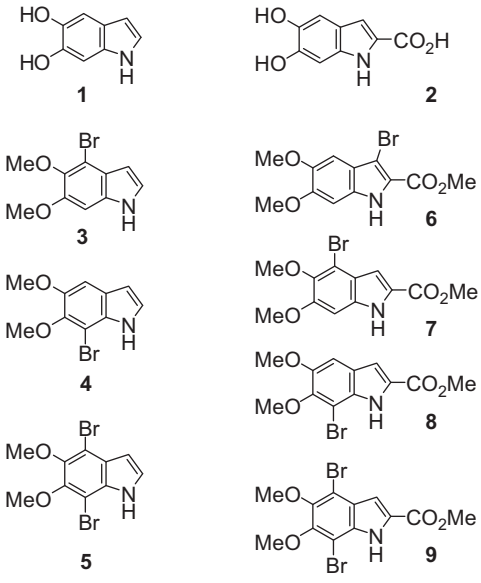


**Figure 1.** 5,6-Dihydroxyindole, 5,6-dihydroxyindole-2-carboxylic acid and bromo-5,6-dimethoxyindole derivatives.

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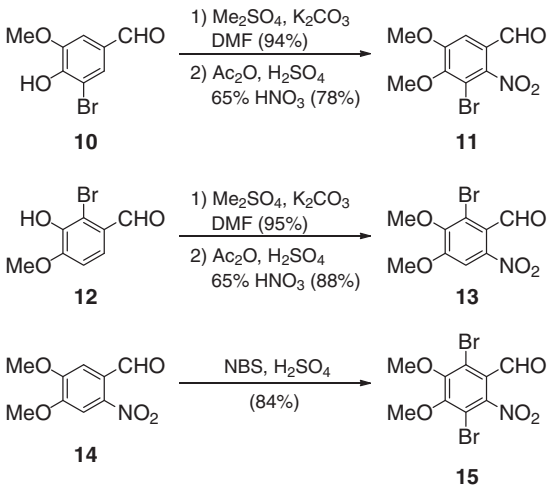



**Scheme 1.** Synthesis of bromo-*o*-nitroveratraldehydes.

intermediates which could be converted into indoles in a manner akin to the Cadogan carbazole synthesis.[5] The protocol was designed to tolerate various reaction conditions with minimal purification steps in order to facilitate optimization and modification during follow-up studies. Accordingly, we herein describe the development of an expedient and practical route to a series of DHI and DHICA derivatives **3**–**9**.

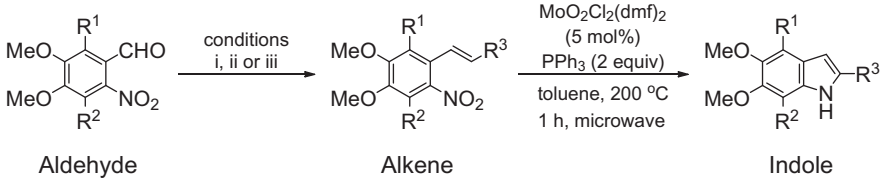
We initiated our study with the synthesis of the bromo-*o*-nitroveratraldehydes (Scheme 1) required for elaboration into the key *o*-nitrostyrene and *o*-nitrocinnamate intermediates. Commercially available 5-bromovanillin (**10**) was methylated using standard conditions to afford 5-bromoveratraldehyde. Subsequent nitration using either 65% nitric acid or 65% nitric acid in acetic acid led to mixtures of compound **11** and the regioisomer 5-bromo-2-nitroveratraldehyde along with 3-bromo-4,5-dinitroveratrole and 3-bromo-5-nitroveratrole which were likely formed through a sequential oxidation/decarboxylation/nitration process similar to the Hunsdiecker reaction. The use of other nitrating conditions such as Claycop in dichloromethane/acetic anhydride also led to mixtures of products.[6] Gratifyingly, nitration of 5-bromoveratraldehyde using Menke conditions ($Ac_2O$/65% $HNO_3$), afforded **11** cleanly as a single product in 78% yield. A similar alkylation, nitration sequence was also used to convert 2-bromoisovanillin (**12**) into compound **13**. Effective dibromination of 6-nitroveratraldehyde (**14**) was achieved with NBS in concentrated sulfuric acid affording 2,5-dibromo-6-nitroveratraldehyde (**15**) in good yield.

With the requisite bromo-*o*-nitroveratraldehydes in hand, attention was turned to the synthesis of the key indole precursors **16**–**23** (Table 1). A Horner–Wadsworth–Emmons protocol utilizing methyl diethylphosphonoacetate and sodium hydride in THF was employed to convert 6-nitroveratraldehyde (**14**) into cinnamate **16** in good yield. Similarly, aldehydes **11**, **13** and **15** were each converted into the corresponding cinnamates **17**–**19** in excellent yields. The efficiency of this concise sequence from commercial starting materials **10**, **12** and **14** to cinnamates **16**–**19** is notable. It can be performed on a multigram scale, no chromatographic purification steps or recrystallizations are required and compounds **16**–**19** are obtained analytically pure.

A Wittig methylenation protocol was adopted for the synthesis of styrenes **20**–**23**. Aldehydes **14** and **11** were smoothly converted into the corresponding styrenes **20** and **21** using *n*-butyllithium and methyltriphenylphosphonium bromide in THF at −78 °C. When the synthesis of *o*,*o*′-disubstituted styrenes **22** and **23** was attempted under similar conditions, the starting aldehydes **13** and **15** were cleanly converted through to 1-bromo-2,3-dimethoxy-5-nitrobenzene and 1,4-dibromo-2,3-dimethoxy-5-nitrobenzene, respectively. These products presumably arise from an ylide-mediated deformylation reaction. Similar deformylation of sterically congested 2-halo-6-nitrobenzaldehydes under basic conditions has been previously reported.[7] Styrenes **22** and **23** could, however, be accessed in modest yield when the ylide was formed with NaHMDS. At this juncture, multigram quantities of all indole precursors **16**–**23** could be readily obtained and conditions for their conversion into indole building blocks **3**–**9** were explored.

The classical conditions for a Cadogan type cyclisation involve heating the substrate with a large excess of a trivalent phosphorous reagent at elevated temperatures.[5] When we attempted the conversion of cinnamate **17** into the indole **8** with any one of trimethyl, triethyl, tributyl or triphenyl phosphite under conventional or microwave heating, complications ensued. Triethyl and tributyl phosphite led to mixtures of **8** and indole side products arising from transesterification reactions. In the case of trimethyl phosphite, the reagent degraded to dimethyl methylphosphonate at the expense of the desired conversion of **17** into **8**. When triphenyl phosphite was employed conversion of **17** into **8** was extremely sluggish and both the starting material and product were observed to decompose over several hours. The use of

**Table 1**
Synthesis of *o*-nitrocinnamates and *o*-nitrostyrenes and conversion into the corresponding indoles




| Entry | Aldehyde | Conditions[a] | $R^1$ | $R^2$ | $R^3$ | Alkene (yield) | Indole (yield) |
|---|---|---|---|---|---|---|---|
| 1 | **14** | i | H | H | $CO_2Me$ | **16** (80%) | **24** (63%) |
| 2 | **11** | i | H | Br | $CO_2Me$ | **17** (99%) | **8** (85%) |
| 3 | **13** | i | Br | H | $CO_2Me$ | **18** (99%) | **7** (92%) |
| 4 | **15** | i | Br | Br | $CO_2Me$ | **19** (90%) | **9** (91%) |
| 5 | **14** | ii | H | H | H | **20** (90%) | **25** (65%) |
| 6 | **11** | ii | H | Br | H | **21** (89%) | **4** (81%) |
| 7 | **13** | iii | Br | H | H | **22** (25%) | **3** (80%) |
| 8 | **15** | iii | Br | Br | H | **23** (32%) | **5** (80%) |

[a] Conditions: (i) methyl diethylphosphonoacetate, NaH, THF, 100 °C, 1 h; (ii) methyltriphenylphosphonium bromide, *n*-BuLi, THF, −78 °C; (iii) methyltriphenylphosphonium bromide, NaHMDS, THF, 25 °C.

**Table 2**
Evaluation of the conditions for the $MoO_2Cl_2(dmf)_2$-mediated conversion of cinnamate **18** into indole **7**

| Entry | Solvent | Phosphine[a] | Temperature (°C) | Time (h) | Yield |
|---|---|---|---|---|---|
| 1 | Toluene | i | 200 | 1 | —[b] |
| 2 | Toluene | ii | 200 | 1 | 51% |
| 3 | Toluene | iii | 200 | 1 | 65% |
| 4 | Toluene | iv | 200 | 1 | 72% |
| 5 | Toluene/THF | v | 160 | 1 | 74% |
| 6 | Toluene | $PPh_3$ | 160 | 1 | 74% |
| 7 | Toluene | iii | 160 | 1 | 3.3 (**7**):1 (**18**)[c] |
| 8 | Toluene | iv | 160 | 1 | 8.6 (**7**):1 (**18**)[c] |
| 9 | MeCN | $PPh_3$ | 160 | 1 | 85% |
| 10 | MeCN | iii | 160 | 1 | 78% |
| 11 | EtOAc | $PPh_3$ | 160 | 1 | 88% |
| 12 | EtOAc | iii | 160 | 1 | 79% |
| 13 | THF | $PPh_3$ | 160 | 1 | 95% |
| 14 | THF | ii | 160 | 1 | 92% |
| 15 | THF | iii | 160 | 1 | 95% |
| 16 | THF | iv | 160 | 1 | 94% |
| 17 | Acetone | $PPh_3$ | 140 | 1 | 84% |
| 18 | Acetone | iii | 140 | 1 | 79% |
| 19 | $CH_2Cl_2$ | $PPh_3$ | 120 | 1.5 | 76% |
| 20 | $CH_2Cl_2$ | iii | 120 | 2 | 77% |
| 21 | $CH_2Cl_2$ | iv | 120 | 2 | 2 (**7**):1 (**18**)[c] |

[a] Phosphines: (i) tris(3-sulfonatophenyl)phosphine trisodium salt hydrate, (ii) diphenyl-2-pyridylphosphine, (iii) 2-(diphenylphosphino)benzoic acid, (iv) 200–400 mesh, 2% divinylbenzene cross-linked, polystyrene-bound triphenylphosphine, (v) 4-diphenylphosphanylbenzoic acid 2-(trimethylsilyl)ethyl ester.
[b] <5% Conversion of **18** into **7**, **18** recovered.
[c] Ratio of product (**7**) to starting material (**18**) determined by analysis of the $^1$H NMR spectrum of the crude reaction mixture.

triphenylphosphine in refluxing *o*-dichlorobenzene, as described by Freeman et al.,[8] was also attempted but resulted only in consumption of **17** with no formation of tractable products. However, the desired transformation was smoothly effected with triphenylphosphine in refluxing toluene over 24 h in the presence of a dioxomolybdenum(VI) catalyst.[9,10]

We envisaged that the efficiency of this modified Cadogan indole synthesis could be improved significantly through the use of microwave heating. Thus, when an homogenous solution of cinnamate **17**, triphenylphosphine (2 equiv) and $MoO_2Cl_2(dmf)_2$ (5 mol %) in toluene in a sealed vessel was heated at 200 °C using microwave heating for 1 h, complete consumption of **17** and clean formation of indole **8** along with triphenylphosphine oxide was observed by GC–MS analysis of the reaction mixture. Gratifyingly, using this protocol, all cinnamates **16**–**19** and styrenes **20**–**23** could be readily converted into the corresponding indoles (**3**–**5**, **7**–**9**, **24** and **25**) in excellent isolated yields (Table 1). The conversion of *o*-nitrostyrenes into indoles described here is particularly noteworthy as similar transformations using classical conditions have been low yielding.[11] Moreover, this method provides a convenient alternative to analogous palladium-mediated processes which often require long reaction times at high temperatures under high pressures of carbon monoxide.[12] Conversion of indole **24** to the 3-bromo derivative **6** as previously described[4] completed the rapid compilation of the requisite DHI and DHICA derivatives **3**–**9**.

With a view to expanding the conditional scope and practical convenience of this indole synthesis, the conversion of cinnamate **18** into indole **7** was studied with a variety of solvent and phosphine combinations (Table 2). Initial investigation of solvent and temperature effects (entries 6, 9, 11, 13, 17 and 19) indicated that the reaction could be carried out efficiently with triphenylphosphine in a variety of polar and non-polar organic solvents at temperatures as low as 120 °C. Most significantly, a variety of other phosphines, which form easily removable phosphine oxide by-products (e.g., by acid wash, base wash or filtration), could be used instead of triphenylphosphine. The use of polystyrene-supported triphenylphosphine (entries 4, 8, 16 and 21) allowed the pure indole **7** to be isolated by simply filtering off the polymer and removing the solvent. Conversely, the use of water soluble tris (3-sulfonatophenyl)phosphine trisodium salt[13] (entry 1) resulted in poor conversion of **18** probably due to the insolubility of the reagent in toluene. When diphenyl-2-pyridylphosphine[14] was used in toluene (entry 2), indole **7** was isolated in moderate yield, though in THF an excellent yield of **7** was obtained (entry 14). Both 4-diphenylphosphanylbenzoic acid 2-(trimethylsilyl)ethyl ester[15] and 2-(diphenylphosphino)benzoic acid (*o*-DPPBA) could be used to good effect in most cases (entries 5, 10, 12, 15, 18 and 20), however, the use of *o*-DPPBA was preferred for both economic and practical reasons. In addition to being commercially available, *o*-DPPBA can be readily prepared from inexpensive bulk chemicals using a large scale, single-step synthesis.[16] Furthermore, it gives rise to an insoluble phosphine oxide by-product which can be easily removed by simple filtration. Significantly, *o*-DPPBA can be used effectively in solvents such as acetonitrile, ethyl acetate and acetone whereas polystyrene-supported triphenylphosphine cannot and thus, it represents a highly valuable and complementary alternative to the polymer-bound reagent for this reaction.

In conclusion, we have described a concise, efficient and practically simple route to a series of DHI and DHICA derivatives **3**–**9**.[17] The syntheses described are highlighted by (a) the preparation of *o*-nitrocinnamates on multigram scale without purification steps, (b) a clean, microwave-mediated, Cadogan type indole synthesis and (c) the use of triphenylphosphine surrogates to simplify isolation of the pure indole products.

## Acknowledgement

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## Supplementary data

Supplementary data (physical data, spectroscopic data and $^1$H and $^{13}$C APT NMR spectra for compounds **3**–**9**, **11**, **13** and **15**–**25**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.076.

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17. *General procedure for nitration under Menke conditions*: To a solution of 5-bromo or 2-bromoveratraldehyde (20 mmol) in $Ac_2O$ (20 mL) was added one drop of concentrated $H_2SO_4$. The resultant solution was stirred at room temperature for 1 h then cooled to 0 °C. $HNO_3$ (65%, 25 mL) was then added dropwise and the reaction mixture was stirred for 16 h. Cold $H_2O$ was added to the thick reaction mixture and the suspension was filtered and dried. The residue was triturated with *n*-hexane containing a few drops of EtOAc and filtered to afford **11** or **13**.
    *Compound* **15:** To a solution of **14** (1.23 g, 5.83 mmol) in concentrated $H_2SO_4$ (5 mL), NBS (3.11 g, 17.48 mmol) was added portion wise over a period of 30 min and the reaction vessel was stoppered and wrapped in aluminium foil to exclude light. The reaction mixture was stirred for 16 h, poured onto cold $H_2O$ (20 mL) and the resultant precipitate filtered and dried. The crude product was triturated with *n*-hexane containing a few drops of EtOAc and filtered to afford **15** as a light yellow solid (1.81 g, 84%).
    *General procedure for Horner–Wadsworth–Emmons reaction*: To a solution of methyl diethylphosphonoacetate (10 mmol) in dry THF (100 mL) at 0 °C was added NaH (1 equiv, 60% dispersion in mineral oil). When the evolution of $H_2$ had ceased (~5 min), the appropriate *o*-nitrobenzaldehyde (**11**, **13**, **14** or **15**) was added and the reaction mixture was heated at reflux for 1 h. After cooling, the solvent was removed in vacuo and the residue was partitioned between EtOAc (100 mL) and $H_2O$ (30 mL). The organic phase was separated, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was triturated with *n*-hexane containing a few drops of EtOAc and filtered to afford the corresponding cinnamates **16**–**19**.
    *Compounds* **20** *and* **21:** To a suspension of pre-dried methyltriphenylphosphonium bromide (3.5 mmol) in THF (10 mL) at −78 °C was added dropwise a solution of *n*-BuLi (2.5 M, 1 equiv). The resultant mixture was stirred at −78 °C for 2 h before a solution of **14** or **11** (2.71 mmol) in THF was added. The mixture was allowed to warm to room temperature and stirring was continued for 16 h. Saturated $NH_4Cl$ solution (15 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL), the organic phase was dried over $Na_2SO_4$ and concentrated in vacuo. Flash chromatographic purification of the residue (*n*-hexane–EtOAc) afforded **20** or **21**.
    *Compounds* **22** *and* **23:** To a suspension of pre-dried methyltriphenylphosphonium bromide (3.5 mmol) in THF (10 mL) at 0 °C was added dropwise a solution of NaHMDS (1 M in THF, 1 equiv). The resultant mixture was stirred at 0 °C for 1 h before a solution of **13** or **15** (2.71 mmol) in THF (10 mL) was added dropwise. The mixture was then stirred at room temperature for 16 h. Saturated $NH_4Cl$ solution (15 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The organic phase was dried over $Na_2SO_4$ and then concentrated in vacuo. Flash chromatographic purification of the residue (*n*-hexane–EtOAc) afforded **22** or **23**.
    *General procedure for the microwave-mediated Cadogan indole synthesis* (Tables 1 and 2): (*NOTE*: Microwave reactions were performed using a Biotage Initiator™ in 2–5 mL reaction vessels). A stirred suspension of the appropriate *o*-nitrostyrene or *o*-nitrocinnamate (0.3 mmol) and phosphine (2.4 equiv) in dry solvent (5 mL) in a microwave reactor vial was purged of oxygen by bubbling argon through the mixture. $MoO_2Cl_2(dmf)_2$ (5 mol %) was added and the vessel sealed. The reaction mixture was heated under microwave irradiation (at the appropriate temperature for the time listed). Work-up for reactions with triphenylphosphine involved removal of the solvent in vacuo and purification by column chromatography (*n*-hexane–EtOAc). Work-up for reactions with polystyrene-supported triphenylphosphine involved filtration and removal of the solvent in vacuo to afford the pure indole. Work-up for reactions with 2-(diphenylphosphino)benzoic acid involved filtration, and if necessary, base washing as previously described.[15] Work-up for reactions with other phosphines were as previously described.[14,15]