First synthetic entry to the trimer stage of 5,6-dihydroxyindole polymerization: *ortho*-alkynylaniline-based access to the missing 2,7′:2′,7″-triindole†

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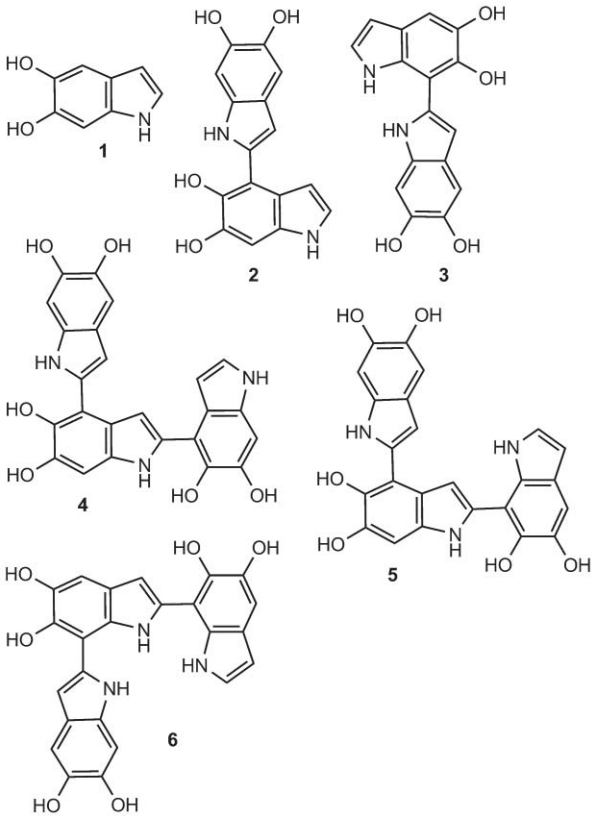
5,6-Dihydroxyindole oligomers are valuable synthetic targets for the structural characterization of eumelanin biopolymers as well as for the realization of bioinspired functional materials. An *ortho*-alkynylaniline-based strategy allowed the first access to a trimer, the missing 5,5′,5″,6,6′,6″-hexaacetoxy-2,7′:2′,7″-triindole, and its detection as a minor intermediate en route from 5,6-dihydroxyindole to eumelanin-like polymers.

The development of efficient and versatile synthetic approaches toward oligomer derivatives of 5,6-dihydroxyindole (**1**) provides a useful strategy to model the complex oxidative process leading to the biosynthesis of eumelanins, the black photoprotective biopolymers of human skin, hair and eyes.[1–3] The oxidative polymerization of **1** to eumelanin proceeds through a range of oligomer intermediates which appear to arise mainly *via* 2,4′- and 2,7′-coupling steps, as indicated by the isolation of biindoles **2** and **3** and triindoles **4** and **5**.[4,5]

Further insights into the structure of the oligomeric species generated during the oxidative polymerization of **1** have been hindered by the marked complexity of the reaction mixtures and the poor isolated yields. The availability of a collection of 5,6-dihydroxyindole oligomers of variable molecular size is therefore pivotal for future advances in the structural characterization of eumelanin biopolymers[6] as well as for the realization of bioinspired functional materials for technological applications, *e.g.* as light-harvesting systems.[7,8] Interest in these synthetic targets is also spurred by the potential of indole-based scaffolds for the preparation of anion sensing architectures.[9–12]

Whereas numerous procedures are available in the literature for the synthesis of biindoles, triindoles and higher indole oligomers,[13–16] the extension to the 5,6-dihydroxyindole series may not be straightforward. Considerable constraints are posed, for example, by the highly oxidizable *ortho*-dihydroxy functionality, which requires careful selection of protecting groups, reagents and reaction conditions. Recently, we reported the first successful approach to a series of dimers of **1**, namely the 2,7′-, 2,2′- and 2,3′-biindoles,[17] which was based on a judicious sequence of Sonogashira coupling and cyclization steps involving suitably protected *ortho*-ethynylaniline intermediates.[18,19]



The versatile methodology developed in that study was envisaged to provide a convenient general strategy toward higher 5,6-dihydroxyindole oligomers. In extending that procedure we report herein the first synthetic approach to a trimer of **1**, namely the 2,7′:2′,7″-triindole **6**. Trimer **6** was an interesting target for the following reasons. Although this structure embodies the characteristic 2,7′-coupling mode of 5,6-dihydroxyindoles,[4] it has never been identified in the oxidation mixtures of **1**, and availability of an authentic standard may guide its detection during the polymerization process. Moreover, preparation of the missing triindole would integrate current knowledge of the structural properties of 5,6-dihydroxyindole oligomers,[20] and would provide a useful starting material for assembling high molecular polymers *via* the oligomer-oligomer coupling approach.[21,22] The triindole skeleton of **6**, featuring three nitrogen groups in a suitable disposition for ion coordination, also offers interesting opportunities for anion sensing.

The synthetic approach to **6** capitalizes on 3,4-diacetoxy-6-ethynyl-2-iodoaniline (**10a**) as the starting material. This key intermediate was readily obtained from commercial 4-nitrocatechol

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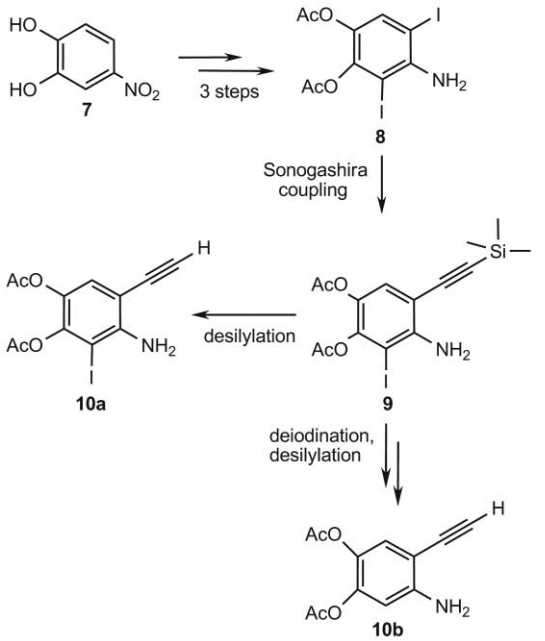
(**7**) by the sequence of reactions reported in the previous study and summarized in Scheme 1.[17]

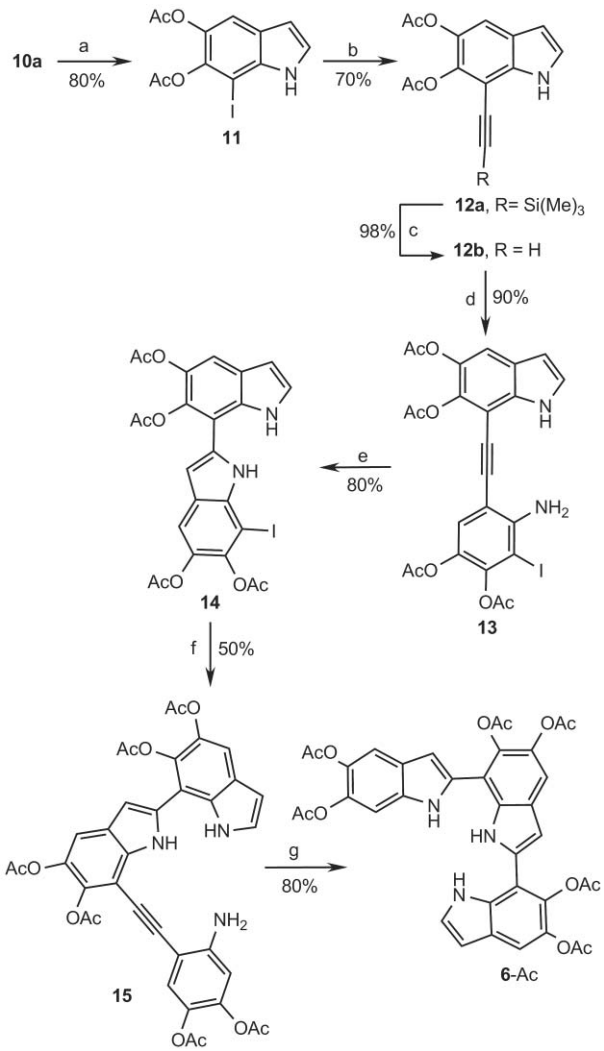


Scheme 1 [16]

Protection of the labile *ortho*-diphenol functionality by acetylation combines the advantage of a decreased aromatic reactivity during the critical iodination steps and the ease of deprotection.[17] Conversion of **10a** to **6** was achieved by the sequence of steps outlined in Scheme 2.

The initial cyclization to 5,6-diacetoxy-7-iodoindole (**11**) was efficiently carried out by an improved procedure which was based on $Cu(OAc)_2$ (0.6 molar eqs.) as catalyst in dry CH_2Cl_2.[23] Under these improved conditions, the reaction proceeded in 18 h and in good yield (80%) without the need for extensive purification steps. Sonogashira coupling on **11** then led to 5,6-diacetoxy-7-ethynylindole (**12b**) which was reacted with the *o*,*o*-diiodoaniline **8**, an intermediate in the synthesis of **10a**, to give the indolylethynylaniline **13**. Surprisingly, cyclization of **13** to 7-iodo-2,7′-biindole **14** proved less efficient than in the case of **10a**, possibly because of steric effects. However, a brief screening of some potential catalysts[24] for *ortho*-alkynylaniline cyclization showed that $AuCl_3$ or $NaAuCl_4{\cdot}2H_2O$, this latter with longer reaction time, could efficiently promote the reaction to give **14** in good yield. A similar sequence of Sonogashira coupling-cyclization steps from **14** eventually led to the desired **6-*Ac***. Structural assignment was secured by extensive 2D NMR[25] and MS analysis also in comparison with trimers **4** and **5**.[26]

To the best of our knowledge, this paper describes the first synthesis of a 2,7′:2′,7″-triindole and provides a simple and versatile procedure for the preparation of indole-based scaffolds with variable substitution patterns. The synthetic approach in Scheme 2 stems largely from the previously reported strategy to isomeric biindoles, however it features some aspects of general interest. In particular, all cyclization steps have been significantly improved with respect to the preceding study,[17] as a result of a



Scheme 2 [27]

systematic screening of different catalysts under various reaction conditions (see ESI†).

Replacement of CuI with $Cu(OAc)_2$[23] increased the yield of conversion of **10a** to **11** from 50% to 80% whereas $AuCl_3$[28] and $NaAuCl_4{\cdot}2H_2O$[29] proved to be superior catalysts for the subsequent cyclization steps leading to the biindole **14** and **6-*Ac***.

We have no clear-cut explanation of why $Cu(OAc)_2$ works only well on the monomer precursor **10a** and less efficiently on the bulkier substrates **13** and **15**, and why $AuCl_3$ and $NaAuCl_4{\cdot}2H_2O$ work better in the latter case. Although gold catalysts have been successfully utilized in the preparation of various indole systems from *ortho*-alkynylanilines,[24,29–32] the use of $AuCl_3$ to promote the cyclization of *ortho*-alkynylanilines has remained so far confined to few examples leading to 2-arylindoles.[28] Key changes introduced in the present methodology with respect to the previous $AuCl_3$ protocol include higher *ortho*-ethynylaniline and catalyst concentration and a lower temperature (45 °C instead of 70 °C) with ultrasound activation, which resulted in shorter reaction times (30–90 min) without the need for extensive chromatographic purification. Comparable results in terms of yields, but with longer reaction time, have been obtained by using $NaAuCl_4{\cdot}2H_2O$ as reported.[29]

The development of a convenient access protocol to **6**, besides the intrinsic synthetic interest, allowed the probing of the generation of this trimer during 5,6-dihydroxyindole polymerization. LC-MS analyses of various oxidation mixtures of **1** under previously reported biomimetic conditions[4,21,22] disclosed the presence of **6** as a minor component of the oligomer intermediates that populate the trimer level, confirming the generation of **4** and **5** as the prevailing isomers (see ESI†). It is concluded that 2,4′- and 2,7′-bonds are of comparable importance in the oxidative dimerization of **1**, but the 2,4′-coupling mode prevails beyond the dimer stage, a finding which may have interesting mechanistic implications for eumelanin build-up.

In conclusion, we have developed an improved *ortho*-alkynylaniline-based procedure for the first synthesis of a 5,6-dihydroxyindole trimer which combines mild, expedient and potentially scaleable protocols with easy-to-perform work-up and satisfactory yields. Assessment of the actual scope of the optimized *ortho*-alkynylaniline cyclization methodology for the preparation of higher indole oligomers is a main goal of ongoing work in our laboratory.

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27 *Reagents and Conditions:* (a) $Cu(OAc)_2$, dry CH_2Cl_2, 55 °C, Ar atm; (b) trimethylsilylacetylene, PPh_3, CuI, $(PPh_3)_2PdCl_2$, TEA/toluene/THF, 60 °C, Ar atm; (c) KF, DMF; (d) **8**, PPh_3, CuI, $(PPh_3)_2PdCl_2$, TEA/toluene/THF, 60 °C, Ar atm; (e) $AuCl_3$, dry EtOH, Ar atm, 45 °C,))); (f) **10b**, PPh_3, CuI, $(PPh_3)_2PdCl_2$, TEA/THF, 60 °C, Ar atm; (g) $AuCl_3$, dry EtOH, Ar atm, 45 °C,))).
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