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# Total synthesis of 5,5',6,6'-tetrahydroxy-3,3'-biindolyl, the proposed structure of a potent antioxidant found in beetroot (*Beta vulgaris*)

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**Abstract**—5,5',6,6'-Tetrahydroxy-3,3'-biindolyl, the proposed structure of a phenolic antioxidant isolated from the red beetroot (*Beta vulgaris*), has been synthesised. The spectroscopic data of the synthetic material is not consistent with that reported for the natural product. © 2004 Published by Elsevier Ltd.

# 1. Introduction

Interest in phenolic antioxidants found in fruits and vegetables has recently increased<sup>1</sup> due to a possibility<sup>2</sup> that they may provide nutritional benefits.<sup>3</sup> A significant proportion of these compounds have been found to be more powerful antioxidants than vitamins C and E, and  $\beta$ -carotene using an in vitro model for heart disease.<sup>4</sup> The antioxidant activity of phenols is mainly due to their reductive properties, however, they also have the capacity for metal chelation.<sup>5</sup>

Ninety-two different phenol-containing plant extracts were recently screened and beetroot peel was shown to have the second-highest dry weight concentration of total phenols.<sup>1a,6</sup> Structural characterisation of these compounds is necessary in order to rationalise their mode of action. Kujala et al. recently isolated a highly unstable phenolic compound from the peel of the red beetroot (*Beta vulgaris*), and proposed its structure to be 5,5',6,6'-tetrahydroxy-3,3'-biindolyl  $1^7$  (Fig. 1), a dimer of 5,6-dihydroxyindole.



Figure 1. 5,5',6,6'-Tetrahydroxy-3,3'-biindolyl (1).

5,6-Dihydroxyindole is an interesting compound, because it plays a central role in melanogenesis<sup>8</sup> (the process by which eumelanin, a black intractable biopigment, is formed from *L*-3,4-dihydroxyphenylalanine<sup>9</sup>). Extra interest in 5,6-dihydroxyindoles has arisen from the recent recognition of their exceptional radical scavenging and photoprotective abilities,<sup>10</sup> which makes them among the most effective endogenous antioxidants.<sup>11</sup> The corresponding 2,2'-linked isomer of **1** is known,<sup>12,13</sup> and forms under oxidative conditions from the monomer.<sup>13</sup> Unsubstituted 3,3'-bisindole is also known<sup>14</sup> and has been synthesised from unsymmetrical coupling partners, a route that does not take advantage of its symmetry.

#### 2. Results and discussion

### 2.1. Retrosynthetic analysis

Towards our goal of synthesising 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1**, we proposed a short symmetrical synthesis that fully exploits its symmetry. This route features an acidcatalysed reductive cyclisation, dehydration and deprotection in the final step that should be compatible with the oxidative lability of the product (Scheme 1). The



Scheme 1. The proposed reductive cyclisation.

Keywords: Antioxidant; Beetroot; Biindolyl; 5,6-Dihydroxyindole.

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Scheme 2. Synthesis of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan (2) from catechol. Reagents and conditions: (i) BnCl, K<sub>2</sub>CO<sub>3</sub>, acetone, 65 °C, 4 days; (ii) NBS, CCl<sub>4</sub>, 80 °C, 1 h; (iii) 70% HNO<sub>3</sub>, AcOH, rt, 2 h; (iv) Bu<sub>6</sub>Sn<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, 120 °C, 48 h; (v) Pd(PPh<sub>3</sub>)<sub>4</sub>, CuBr, THF, 60 °C, 15 h, 10% of 2.

3,4-disubstituted furan **2** was envisaged as an accessible, stable surrogate of the required dialdehyde.

# 2.2. Synthesis of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)-furan 2

**2.2.1.** Double Stille coupling using 3,4-dibromofuran 7. Initially we envisaged that 2 could be obtained from a double Stille coupling of 3,4-dibromofuran 7 and 3,4-dibromofuran 7 and 3,4-dibromofuran 9. Scheme 2).

The preparation of **6** commenced with the reaction of catechol with benzyl chloride and potassium carbonate in acetone, providing 3,4-dibenzyloxybenzene **3** in 87% yield.<sup>15</sup> Bromination with *N*-bromosuccinamide in carbon tetrachloride gave 89% of compound **4**,<sup>15</sup> which was nitrated with 70% nitric acid in 85% yield to afford the *ortho*-substituted aryl bromide **5**.<sup>16</sup> Palladium catalysed tributylstannylation of *ortho*-substituted aryl halides is known to be relatively difficult.<sup>17</sup> However, by employing elevated temperatures and extended reaction times, the *ortho*-substituted tributylstannyl aryl **6** could be formed in 68% yield. The coupling partner, 3,4-dibromofuran **7**, was prepared from (*E*)-2,3-dibromo-2-butene-1,4-diol in 56% yield, using a slight modification of the procedure reported by Rewicki et al.<sup>18</sup>

Stille couplings using electron-withdrawing *ortho*-substituted aryl stannanes are rare.<sup>19</sup> To the best of our knowledge there is only one previously published example in which the substituent is a nitro group.<sup>19a</sup> Initial attempts at the double Stille coupling using Pd(PPh<sub>3</sub>)<sub>4</sub> in dioxane gave no product, with most of the starting materials being recovered. Copper(I) salts have been shown to accelerate Stille reactions,<sup>20</sup> and with the addition of CuBr and THF as the solvent, a small amount of disubstituted furan **2** was isolated in 10% yield together with the monosubstituted furan **8** in 14% yield. In addition 58% of the dimer **9**, which arose from

homocoupling of the tin starting material 6, was obtained from the reaction.

Homocoupling has been observed in Stille reactions<sup>21</sup> and is an oxidative process.<sup>22</sup> Cu(I) alone is also capable of catalysing the reaction, especially when electron withdrawing substituents are present in conjugation with the tin.<sup>23</sup> Rigorous exclusion of oxygen accompanied by the addition of antioxidants, such as 2,6-di-*tert*-butyl-4-methyl phenol, led to no significant reduction of the unwanted product **9**.

Efforts to optimise<sup>24</sup> this reaction by using different catalysts  $(Pd(PPh_3)_4, Pd(PPh_3)_2Cl_2, Pd(dppf)Cl_2, Pd(MeCN)_2 Cl_2, Pd_2(dba)_3), Pd_2(dba)_3 with ligands in different ratios$  $(PPh_3, P(2-furyl)_3, AsPh_3, dppf, 1,3-bis(diphenylphosphino)$ propane), different solvents (toluene, dioxane, THF, NMP,DMF, DMSO), different additives (CuI, CuBr, CuCl, LiCl)and slow addition of the tin starting material**6**led to noimprovement. In all cases, especially with highly polarsolvents, the major product was <math>4,4',5,5'-tetrakisbenzyloxy-2,2'-dinitro-biphenyl **9**. It appears that this unwanted sidereaction is significantly faster than the Stille coupling.

# **2.3.** Initial solutions to the unfavourable double Stille coupling

**2.3.1. 3,4-Diiodofuran.** In the effort to enhance the desired reaction, synthesis of 3,4-diiodofuran as an alternative starting material was investigated, as iodides tend to be more reactive than bromides in Stille reactions.<sup>24</sup> Three syntheses of 3,4-diiodofuran have previously been reported.<sup>25</sup> The most recent protocol, which involves oxidative cyclisation of (*E*)-2,3-diiodo-2-butene-1,4-diol with chromic acid, could not be reproduced in our hands as decomposition of the starting material occurred before oxidation.<sup>26</sup> The other two procedures were either laborious,<sup>25c</sup> or operationally unfavourable,<sup>25b</sup> so more



Scheme 3. Attempted synthesis of 4,5-dibenzyloxy-2-tri-*n*-butylstannylaminobenzene. Reagents and conditions: (i) SnCl<sub>2</sub>, ethyl acetate, MeOH, 70 °C, 1.5 h; or FeCl<sub>3</sub>, activated carbon,  $N_2H_4$ ·H<sub>2</sub>O, MeOH, 70 °C, 15 h; (ii) iron powder, HCl (aq.), EtOH, 80 °C, 3 h; (iii) Bu<sub>6</sub>Sn<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, 120 °C, 48 h.

accessible solutions to the double Stille coupling were investigated in preference.

2.3.2. 4,5-Dibenzyloxy-2-tri-n-butylstannylaminobenzene. It was anticipated that reduction of the nitro group of 4,5-dibenzyloxy-2-tri-n-butylstannylnitrobenzene 6 to an amino group before the Stille coupling could provide two advantages. First, the presence of the mesomerically electron donating amino group might reduce or prevent homocoupling, and second it should make the tin compound more nucleophilic, causing an enhancement of the ratelimiting transmetallation step.<sup>27</sup> However, efforts to reduce the nitro group of arylstannane 6 under different conditions (SnCl<sub>2</sub>, or FeCl<sub>3</sub>, hydrazine and activated carbon) resulted in protodestannylation (Scheme 3). To avoid this unfavourable side reaction, we decided that the nitro group should be reduced prior to the introduction of the tributylstannyl group. Thus, the nitro group of arylbromide 5 was reduced with iron powder and hydrochloric acid in 83%.<sup>28</sup>

Unfortunately, 4,5-dibenzyloxy-2-aminobromobenzene **10** did not undergo the desired stannylation reaction, possibly because the mesomeric electron-donating amino group



Scheme 4. 4,5-Dibenzyloxy-2-aminoiodobenzene (13) from 1,2-dibenzyloxybenzene (3). Reagents and conditions: (i)  $I_2$ , HgO, DCM, rt, 15 h; (ii) HNO<sub>3</sub> (aq.), AcOH, rt, 2 h; (iii) FeCl<sub>3</sub>, activated carbon, N<sub>2</sub>H<sub>4</sub>·H<sub>2</sub>O, MeOH, 70 °C, 8 h; (iv) Bu<sub>6</sub>Sn<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, toluene, 120 °C, 48 h.

might slow down the oxidative addition step in the catalytic cycle. Next, iodide **13** was prepared in the hope that it would be sufficiently reactive to be stannylated (Scheme 4).

Iodination of 1,2-dibenzyloxybenzene **3** was most successful using iodine activated by mercury oxide,<sup>29</sup> yielding 78% of 3,4-dibenzyloxyiodobenzene **11**. Nitration of **11** furnished 94% of nitrobenzene **12**, which was reduced using catalytic iron(III) chloride with activated carbon and hydrazine,<sup>30</sup> giving 4,5-dibenzyloxy-2-aminoiodobenzene **13** in 86% yield. Disappointingly, attempts to exchange the iodine with tributyltin using Pd(PPh<sub>3</sub>)<sub>4</sub> and hexabutylditin proved to be unsuccessful. Significant decomposition of **13** occurred under the reaction conditions.

It became apparent that the best option was to reverse the functional groups in the double Stille coupling. By switching the functional groups, both coupling partners would be electronically favoured—the halide conjugated with an electron withdrawing nitro group and the tin with an electron donating group. Both iodo **12** and bromo **5** versions of the required catechol moiety had already been synthesised, so only 3,4-bis(tri-*n*-butylstannyl)furan needed to be obtained.

**2.3.3. 3,4-Bis**(**tri**-*n*-**buty**]**stanny**]**furan** (14). Wong et al. have reported a synthesis of 3,4-bis(tri-*n*-buty]stannyl)furan 14,<sup>31</sup> but because it is operationally unfavourable and low yielding, the use of 14 in our synthesis did not appeal to us initially. Consequently, we developed an improved synthesis of 3,4-bis(tri-*n*-buty]stannyl)furan 14 (Scheme 5).<sup>32</sup>

This route to **14** involved palladium catalysed addition of hexa-*n*-butylditin to 2-butyne-1,4-diol **15**, followed by oxidative cyclisation and dehydration of (Z)-2,3-bis(tri-*n*-butylstannyl)-2-butene-1,4-diol **16**. This gave the furan **14** in 79% overall yield. With the availability of both **12** and **14**, the coupling reaction was re-investigated.



Scheme 5. An efficient synthesis of 3,4-bis(tri-*n*-butylstannyl)furan. Reagents and conditions: (i) Bu<sub>6</sub>Sn<sub>2</sub>, Pd(MeCN)<sub>2</sub>Cl<sub>2</sub>, THF, rt, 48 h; (ii) IBX, DMSO, THF, rt, 2 h.

# **2.4.** Double Stille coupling using 3,4-bis(tri-*n*-butyl-stannyl)furan 14

Reaction of 3,4-bis(tri-n-butylstannyl)furan 14 with 4,5-dibenzyloxy-2-nitroiodobenzene 12 using  $Pd(PPh_3)_4$  and CuBr in THF (conditions equivalent to those used in earlier attempts), delivered 30% of the disubstituted furan 2 after 15 h. Re-optimising the Stille conditions<sup>24</sup>— $Pd_2(dba)_3$ , AsPh<sub>3</sub> and CuI in DMF-55% of the product was isolated after 15 h, along with recovered starting material. Investigations into methods of generally accelerating this double coupling, led to the development of a new combination of reagents for the Stille coupling reaction. Initial studies have shown that the presence of cesium fluoride in conjunction with copper(I) iodide, as a co-catalyst to Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF, produces a large acceleration of the reaction rate. Fluoride sources have been used before in attempts to accelerate the Stille reaction, but not in conjunction with copper(I) salts.<sup>33</sup> Utilising these new conditions, the desired product 2 was isolated in 92% yield after only 2 h at 40 °C (Scheme 6). The scope of this new combination of reagents is reported elsewhere.34



Scheme 6. Successful double Stille coupling. Reagents and conditions: (i) Pd(PPh\_{3)4}, CuI, CsF, DMF, 40  $^{\circ}$ C, 2 h.

### 2.5. The reductive cyclisation of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan 2

With an effective route to the 3,4-disubstitued furan **2**, the final step (reductive-cyclisation and deprotection) was investigated (Scheme 7).

Unfortunately hydrogenation with palladium on carbon in



Scheme 7. Attempted cyclisation of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan (2). Reagents and conditions: (i)  $H_2$ , Pd/C, AcOH, THF, rt, 15 h.

the presence of acetic acid gave only the deprotected reduced aminophenyl-furan **17** in 94% yield with no evidence of cyclisation. To investigate the conditions required for the desired cyclisation we decided to perform the final three transformations—reduction, cyclisation and deprotection—separately.

Thus, 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** was reduced with tin(II) chloride under non-acidic conditions<sup>35</sup> to give 3,4-bis(3,4-dibenzyloxy-2-aminophenyl)furan **18** in 67% yield (Scheme 8). Reduction with iron powder and HCl later proved to give a higher yield of **18**. Cyclisation was then attempted by heating this compound to reflux in benzene with a catalytic amount of *para*-toluenesulfonic acid and powdered molecular sieves for 2 days. However, this afforded 25% of a solid compound that was clearly not the desired product, along with most of the remaining starting material. After detailed analysis of the spectroscopic data (specifically the NOSEY and HMBC spectra), it became apparent that the product was 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline **19**.



Scheme 8. Product of the cyclisation. Reagents and conditions: (i)  $SnCl_2$ , ethyl acetate, MeOH, 70 °C, 1.5 h, 67%; or iron powder, 38% HCl, EtOH, 80 °C, 3 h; (ii) *p*-TSA, benzene, mol. sieves, 85 °C, 2 days.

The structure of this product was not immediately obvious. The proton and HMQC spectra clearly indicated the structure contained a methylene group with two nonequivalent protons (J=12 Hz). So, initially we speculated the presence of stereocenters or ring systems that were not flat, however, none of these proposed structures fitted all the spectroscopic data. Eventually a deductive, stepwise approach, based on NOE interactions and long range proton-carbon correlations provided the correct structure. The absence of a stereocenter or a non-planar ring system led us to suggest that the observed magnetic nonequivalence of the methylene group is a result of restricted rotation around the aryl-aryl bond. If this were the case then one would expect the chiral environment to degenerate with heating, causing the methylene protons to become equivalent. Recording the proton spectra at increased temperatures demonstrates that the chiral environment is in fact temperature dependent, supporting this proposal (the



Figure 2. Variable temperature proton spectra of  $3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline (19) in DMSO-<math>d_6$ , showing the methylene protons becoming equivalent.



Figure 3. NOE interactions in 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxyquinoline (19).

hydroxyl and amino peaks shift upfield with increased temperature as well) (Fig. 2).

The observed NOE interactions of **19** are indicated below (Fig. 3).

A possible mechanism that explains the formation of **19** from furan **18**, is for the furan to be protonated at C-3, followed by ring-opening of the furan, which could be



Scheme 9. Possible mechanism for the formation of 19.



Figure 4. Crystal structure of 2', 2'', 3', 3''-tetrakisbenzyloxy-dibenzo[c,h][2,6]naphthyridine (20).

facilitated by the nitrogen's lone pair of electrons. An electrocyclic reaction forms the dihydroquinoline, which aromatises to the quinoline through loss of a proton (Scheme 9).

Recrystallisation of **19** did not yield a satisfactory crystal for X-ray diffraction studies, despite a number of attempts. However, we observed the formation of a crystalline material from an aged (3 months) NMR sample of **19** in DMSO- $d_6$ . X-ray diffraction studies of these crystals revealed a symmetrical tetracyclic compound (Fig. 4). The tetracycle **20** is highly crystalline and is only barely soluble in DMSO- $d_6$ , nonetheless a <sup>1</sup>H NMR spectra was obtained and clearly showed that **20** is not the same as the product of the cyclisation reaction, 3-(3,4-dibenzyloxy-2-aminophenyl)-4-(methyl-1-hydroxy)-6,7-dibenzyloxy-quinoline **19**. However, it is reasonable to conclude that the tetracycle **20** was formed from **19** in the solution of DMSO, over a period of 3 months. This transformation would be the result of air oxidation of **19** followed by cyclisation and dehydration (Scheme 10).

The quinoline ring system of 19 is thermodynamically



Scheme 10. Oxidation of 19 followed by cyclisation and dehydration would give 20.



Scheme 11. Attempted cyclisation of the diacylated bisamine 21. Reagents and conditions: (i)  $Ac_2O$ , DMAP,  $Et_3N$ , THF, 15 h; (ii) *p*-TSA, xylene, mol. sieves, 140 °C, 4 days.

stable under the reaction conditions and was not in equilibrium with furan **18**. This problem might be circumvented by making the quinoline formation reversible, which could be achieved by acylating the nitrogen, preventing aromatisation. Treatment of diamine **18** with acetic anhydride, *N*,*N*-dimethylaminopyridine (DMAP) and triethylamine in THF overnight, gave 3,4-bis(3,4-dibenzyl-oxy-2-*N*-acetamidophenyl)furan **21** in 79% yield (Scheme 11).

As before, a solution of **21** and *para*-toluenesulfonic acid in benzene was heated to reflux for 2 days, however, no reaction was observed. Presumably the *N*-acetyl groups were deactivating the nucleophilicity of the nitrogen. Switching to higher boiling xylene as the reaction medium



Scheme 12. The biaryl coupling approach.

did not lead to any product formation. The starting material **21** was recovered in almost quantitative yield. Other possible solutions to the problem of quinoline formation would detract from the efficiency of the original strategy, so a simple route to the target compound was developed using a reductive biaryl coupling of the monomer (Scheme 12).

# 2.6. The reductive biaryl coupling approach

**2.6.1. Synthesis of the monomer.** The monomer **25** was synthesised using slight modifications of previous reactions (Scheme 13)

Protection of 3,4-dihydroxybenzaldehyde with benzyl chloride and potassium carbonate in DMF provided 22 in 99% yield.<sup>36</sup> The protected benzaldehyde 22 was subjected to a Henry reaction by heating to reflux in acetic acid with nitromethane, producing the nitrostyrene derivative 23 in 98% yield.37 Nitration using standard conditions gave 97% of dinitrostyrene 24, which was reductively cyclised to 25 in 61% yield with iron powder in acetic acid. The cyclisation protocol of Borchardt et al. was employed;<sup>38</sup> this includes a non-polar co-solvent like benzene with flash silica. The relatively non-polar starting material and product are maintained in the non-polar solvent, while the silica binds to the polar intermediates, thus minimising the intermolecular reactions involving these intermediates that lead to polymerisation. Although we noticed some improvement in yield over the standard conditions,<sup>38</sup> in our hands the increase was not as dramatic as has been reported elsewhere.38

**2.6.2. Coupling of the monomer.** With the monomer realised, a triisopropylsilyl protecting group was incorporated to sterically direct iodination<sup>39</sup> and stabilise the required iodoindole for the biaryl coupling reaction (Scheme 14)

Deprotonation of indole **25** with *n*-butyllithium followed by addition of triisopropylsilyl chloride gave protected indole **26** in 95% yield. Iodination with mercury acetate and iodine quantitatively yielded the iodoindole **27**.<sup>39</sup> *N*-Iodosuccinimide in THF also afforded **27**, but in a slightly lower yield of 83%. The position of the iodine was confirmed by X-ray crystallography (Fig. 5).

Homocoupling of **27** was initially attempted by formation of the organozinc compound using butyllithium and zinc



Scheme 13. Synthesis of 5,6-dibenzyloxyindole (25). Reagents and conditions: (i) BnCl, K<sub>2</sub>CO<sub>3</sub>, DMF, 120 °C, 15 h; (ii) MeNO<sub>2</sub>, NH<sub>4</sub>OAc, AcOH, 120 °C, 40 min; (iii) 70% HNO<sub>3</sub>, AcOH, rt, 2 h; (iv) iron powder, AcOH, benzene, cyclohexane, SiO<sub>2</sub>, 120 °C, 30 min.



**Scheme 14.** Coupling and deprotection. Reagents and conditions: (i) *n*BuLi, THF, -78 °C, 15 min, then TIPSCl, -78 °C, 2 h; (ii) I<sub>2</sub>, Hg(OAc)<sub>2</sub>, DCM, 0 °C, 2 h, 100%; or NIS, THF, rt, 20 min, 83%; (iii) Pd(PhCN)<sub>2</sub>Cl<sub>2</sub>, TDAE, DMF, 50 °C, 1.5 h; (iv) TBAF, THF, rt, 10 min; (v) H<sub>2</sub>, Pd Black, THF, 18 h.



Figure 5. Crystal structure of 5,6-dibenzyloxy-3-iodo-N-triisopropylsilylindole (27).

chloride, followed by treatment with copper(I) salts.<sup>40</sup> However, reduction of the protected iodoindole **27** to the protected indole **26** was the main reaction. An alternative method for biaryl coupling was investigated using a Grignard reagent and catalytic palladium.<sup>41</sup> Formation of the Grignard reagent by treatment of **27** with <sup>i</sup>PrMgCl, was followed by the addition of a solution of **27** and Pd(dppf)<sub>2</sub>-Cl<sub>2</sub>. This time the coupled product **28** was formed in 19% yield, but again the main product was indole **26**. Eventually, the coupling was achieved in 68% using catalytic Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> and the mild reductant tetrakis(dimethyl-amino)ethylene (TDAE).<sup>42</sup> Desilylation of **28** with tetrabutylammonium fluoride (TBAF) afforded 82% of the benzyl protected bisindole **29**. X-ray diffraction studies

showed indeed the desired product **29** was obtained in the coupling reaction (Fig. 6).

Finally, hydrogenation with catalytic Palladium Black in THF revealed 5,5',6,6'-tetrahydroxy-3,3'-bisindole **1** in 94% yield, the proposed structure of the natural product isolated from beetroot.

# 2.7. Spectroscopic analysis of 5,5',6,6'-tetrahydroxy-3,3'biindolyl 1

The spectroscopic data we obtained from 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1** showed subtle differences to the data recorded from the natural product. A plausible



Figure 6. Crystal structure of 5,5',6,6'-tetrabenzyloxy-3,3'-biindolyl (29).

alternative structure for the natural product is not immediately obvious, and so it remains inconclusive as to whether or not the natural product is 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1**.

**2.7.1. Mass spectrometry.** The high resolution mass spectrum of synthetic 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1** was obtained under electrospray (ES<sup>-</sup>, CV -30) conditions and gave the parent ion as m/z 295.0717, M-H<sup>+</sup> requires m/z 295.0719. High resolution mass measurements on the natural product have only been obtained for fragments corresponding to the monomer.<sup>7</sup> The parent ion apparently was not forthcoming, although on occasion ESI<sup>+</sup> and ESI<sup>-</sup> gave peaks at m/z 297 and 295, respectively.

**2.7.2. UV spectroscopy.** The ultraviolet spectrum of **1** in water showed one  $\lambda_{\text{max}}$  at 302 nm, while the spectrum recorded for the natural product showed two  $\lambda_{\text{max}}$  at 304 and 278 nm.

**2.7.3.** <sup>1</sup>**H** NMR. The <sup>1</sup>H NMR spectrum of **1** in  $D_2O$  showed three signals, but at different chemical shifts to those reported for the natural product in  $D_2O$  (Table 1).

Table 1. Comparison of  ${}^{1}\text{H}$  NMR data from compound 1 and from the natural product

$\delta_{\rm H}$ Compound $1^{\rm a}$	Assignment <sup>b</sup>	$\delta_{\rm H}$ Natural product <sup>c</sup>	Assignment <sup>c</sup>
6.94 (d, <i>J</i> =0.3 Hz)	H7, 7'	7.03 (d, <i>J</i> =0.3 Hz)	H7, 7'
7.13 (d, <i>J</i> =0.3 Hz)	H4, 4'	7.12 (d, <i>J</i> =0.3 Hz)	H4, 4'
7.32 (s)	H2, 2'	7.22 (s)	H2, 2'

<sup>a</sup> Spectra recorded in D<sub>2</sub>O at 500 MHz.

<sup>b</sup> Assigned with the help of HMBC and HMQC experiments.

<sup>c</sup> Taken from Ref. 7.

**2.7.4.** <sup>13</sup>C and HMBC NMR. 5,5',6,6'-Tetrahydroxy-3,3'biindolyl **1** does not dissolve in D<sub>2</sub>O sufficiently to allow the preparation of an adequate sample for <sup>13</sup>C analysis (4000 scans at 500 MHz gave no signals). The natural product, however, is sufficiently soluble in D<sub>2</sub>O to give clear <sup>13</sup>C signals. To prepare a sample of **1** in D<sub>2</sub>O for <sup>13</sup>C analysis, it was necessary to add the D<sub>2</sub>O before all the reaction solvent

(THF) had been removed during work up (see Section 4). Differences are apparent between the  ${}^{13}C$  spectra of 1 and the natural product (Table 2).

Table 2. Comparison of  $^{13}\mathrm{C}$  NMR data from compound 1 and from the natural product

$\delta_{\rm C}$ Compound $1^{\rm a}$	Assignment <sup>b</sup>	$\delta_{\rm C}$ Natural product <sup>c</sup>	Assignment <sup>c</sup>
08.48	C7 7'	101.00	C7 7'
105.19	C4. 4'	103.11	$C_{3}^{\prime}$ , $3'$
109.10	C3. 3'	108.54	C4. 4'
119.50	C3a, 3a'	123.75	C3a, 3a'
121.20	C2, 2'	127.47	C2, 2'
131.57	C7a, 7a'	133.61	C7a, 7a'
139.76	C5, 5′	142.11	C5, 5′
142.21	C6, 6′	144.37	C6, 6′

<sup>a</sup> Spectra recorded in D<sub>2</sub>O at 125.8 MHz.

<sup>b</sup> Assigned with the help of HMBC and HMQC experiments.

<sup>c</sup> Taken from Ref. 7.

In particular the peak assigned as C-3 (109.10 ppm) is clearly observed in the spectrum of  $\mathbf{1}$ , but barely shows up in the natural product spectrum. It is evidently there in the natural product because it gives a correlation in the HMBC spectrum (Fig. 7).

Kujala et al. explain that the virtual absence of the C-3 peak in the <sup>13</sup>C spectrum is due to an extremely long relaxation time. Because the reported recycle time of the <sup>13</sup>C experiment was 3.8 s, we propose instead that the signal was not detected due to broadening under the conditions of the NMR experiment. The HMBC of 1 showed a very similar pattern to the natural product. However, the synthetic compound shows a strong correlation between H4 and C3, where the natural product does not. Furthermore, the correlations from H4 to C5, H7 to C6 and H7 to C7a do not disappear at higher thresholds, as they do in the spectrum of the natural product.<sup>7</sup> There is a difference between the optimised coupling constants in the two HMBC spectra (7.1 Hz for compound 1 vs 8.0 Hz for the natural product), but the difference would seem to be too small to explain the differences in the correlations outlined above. This is because a correlation is strong when its coupling constant is close to the optimised coupling constant used in



Figure 7. Comparison of HMBC spectra from the natural product (left) and from compound 1 (right). The correlations in the natural product spectrum marked with a cross are unsuppressed one-bond couplings.

the HMBC experiment, so the strong correlation seen in the HMBC of 1 between H4 and C3 will have a coupling constant near our optimised coupling constant of 8.0 Hz. Thus, it would be expected to be observed in an HMBC experiment with a similar optimised coupling constant of 7.1 Hz.

**2.7.5.** <sup>1</sup>H NMR and UV under different conditions. Because an alternative structure for the natural product is not immediately obvious, the possibility that the differences in the spectra are due to other reasons was explored. The <sup>1</sup>H NMR spectrum and the UV spectrum of **1** were recorded under a variety of different conditions.

**2.7.6.** <sup>1</sup>**H NMR under different conditions.** As a measure of the differences in the proton NMR spectrum, the three signals from the natural product have an overall spread of ca. 0.2 ppm, while the three signals from 1 have an overall spread of ca. 0.4 ppm. Under acidic or basic conditions (achieved by the addition of various amounts of formic acid—used in the isolation of the natural product—or sodium hydroxide, respectively), more concentrated conditions, doping with MeCN (also used in the isolation procedure), and recording spectra in deuterated methanol or deuterated DMSO, the overall spread of the three signals from 1 remained at ca. 0.4 ppm. Although, not surprisingly, the signals shifted along the spectrum slightly when the conditions were varied.

**2.7.7.** UV spectrum under different conditions. The natural product gives two  $\lambda_{max}$  at 304 and 278 nm. Under neutral conditions 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1** gives one  $\lambda_{max}$  at 302 nm. This  $\lambda_{max}$  shifted to 300 nm in 0.1% formic acid solution and to 324 nm in 0.1% sodium hydroxide solution. There was no appearance of the second reported  $\lambda_{max}$  at 278 nm even when the concentration of acid or base was increased.

**2.7.8.** Oxidation studies. As the differences between in the spectral data of **1** and the natural product persisted despite

the variations in pH, concentration and solvent, we speculated that the natural compound might possibly be an oxidation product of 5,5',6,6'-tetrahydroxy-3,3'-biindolyl **1**. The <sup>1</sup>H NMR and UV spectrum of **1** was recorded every few hours over a period of 24 h. The three signals in the proton NMR spectrum decreased in intensity, but there was no appearance of signals corresponding to the natural product. The UV spectrum also decreased in intensity with no appearance of the reported  $\lambda_{max}$  at 278 nm. To preclude the possibility that the oxidation product that forms might decompose before accumulating to a detectable level, a sample of 1 was oxidised with  $H_2O_2$ . The signals slowly disappeared and a black precipitate was formed over a period of 1 h with no transient intermediate observed by either <sup>1</sup>H NMR or UV. Oxidation with 1 equiv. of dichlorodicyanoquinone (DDQ) in deuterated acetonitrile immediately gave a black precipitate.

### 3. Conclusion

There are clear spectroscopic differences between the natural product and 5,5',6,6'-tetrahydroxy-3,3'-biindolyl 1. Varying the conditions of data collection for 1 did not resolve these differences. Oxidation of 1 gave a black precipitate and no transient intermediate corresponding to the natural product. These observations seem to suggest that the natural product is unlikely to be 5,5',6,6'-tetrahydroxy-3,3'-biindolyl 1. However, there are no obvious alternative structures that are plausible. It is difficult to interpret the HMBC spectrum from the natural product without resorting to a 3,5,6-trisubstituted indole or benzofuran nucleus; however, a benzofuran structural isomer seems biogenetically less likely. The 5,5'- or 6,6'-linked bisindole isomers require a 3-hydroxy group, but these compounds would most likely exist in the keto-form ( $K_{enol}(H_2O)$ ) for indoxyl is 0.086).<sup>43</sup> Thus without further investigation it remains unclear whether or not the natural product is 5,5',6,6'-tetrahydroxy-3,3'-biindolyl 1.

# 4. Experimental

#### 4.1. General experimental

Proton magnetic resonance spectra were recorded on a Brüker DPX200 (200 MHz), Brüker DPX400 (400 MHz), Brüker AMX500 (500 MHz) and Brüker DPX500 (500 MHz) spectrometers at ambient temperatures. Proton spectra assignments are supported by  ${}^{1}\text{H}{-}{}^{1}\text{H}$  COSY where necessary. Chemical shifts ( $\delta_{\rm H}$ ) are reported in parts per million (ppm) and are referenced according to IUPAC recommendations, 2001.<sup>44</sup> Coupling constants (*J*) are recorded to the nearest 0.5 Hz.

Carbon magnetic resonance spectra were recorded on Brüker DPX200 (50.3 MHz), Brüker DPX400 (100.6 MHz), Brüker AMX500 (125.8 MHz) and Brüker DPX500 (125.8 MHz), spectrometers at ambient temperatures. Chemical shifts ( $\delta_C$ ) are reported in parts per million (ppm) and are referenced according to IUPAC recommendations, 2001.<sup>44</sup> Carbon spectra assignments are supported by DEPT analysis and <sup>13</sup>C<sup>-1</sup>H correlations were necessary.

Low resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, a Micromass Platform (APCI) Spectrometer, Micromass Autospec spectrometer (CI<sup>+</sup>) and a micromass ZAB spectrometer (CI<sup>+</sup>, EI). Only molecular ions (M<sup>+</sup>), fragments from molecular ions and other major peaks are reported. High-resolution mass spectra were recorded on a Micromass Autospec spectrometer and are accurate to  $\pm 10$  ppm.

Microanalyses were carried out by Elemental Microanalysis Limited, and are quoted to the nearest 0.1% for all elements except hydrogen, which is quoted to the nearest 0.05%.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer as a thin film between NaCl plates, or as KBr discs. Absorption maxima ( $\nu_{max}$ ) of the major peaks are reported in wavenumbers (cm<sup>-1</sup>).

Ultraviolet spectra were recorded on a Perkin–Elmer Lambda 2 UV/VIS spectrometer in ethanol or water as indicated at ambient temperature. Absorption maxima  $(\nu_{max})$  are reported in nanometers (nm) and extinction coefficients ( $\varepsilon$ ) are quoted to four significant figures.

Melting points were measured using a Cambridge Instruments Gallen<sup>™</sup> III hot stage melting point apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates pre-coated with silica gel 60 F<sub>254</sub> (1.05554). Visualisation was affected by quenching of UV fluorescence ( $\lambda_{max}$ =254 nm), staining with phosphomolybdic acid in ethanol, followed by heating. Retention factors ( $R_f$ ) are reported to two decimal places.

Column chromatography was performed using ICN silica 32-63, 60 Å.

Anhydrous tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl under nitrogen and anhydrous

dichloromethane (DCM) was distilled from calcium hydride under nitrogen. PE refers to the fraction of light petroleum ether boiling between 40 and 60 °C, and was distilled before use. Triethylamine, dimethyl formamide (DMF), dimethyl sulfoxide and *N*-methylpyrrolidine (NMP) were distilled from calcium hydride under argon or reduced pressure and stored over 4 Å molecular sieves under argon until used. Toluene was dried over 4 Å molecular sieves under argon. All water used was distilled except where otherwise indicated. Solvents were evaporated on a Büchi R110 Rotavaporator.

### 4.2. Experimental procedure

**4.2.1. 1,2-Dibenzyloxybenzene (3).** A mixture of catechol (10.0 g, 90.8 mmol), anhydrous  $K_2CO_3$  (38.0 g, 272.5 mmol) and benzyl chloride (31.0 mL, 269.4 mmol) was stirred rapidly in acetone (140 mL) and heated to reflux under argon for 4 days. The mixture was filtered and the solvent removed under reduced pressure. The residue was dissolved in DCM (200 mL) and refiltered, then the solvent was removed under reduced pressure. Recrystallisation from DCM/PE gave **3** (22.9 g, 87%). A small amount was further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid.  $R_f$  0.29 (PE/EtOAc, 9:1); mp 58–59 °C, lit.<sup>15</sup> 58–59 °C;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 5.24 (4H, s, CH<sub>2</sub> of Bn), 6.95–7.00 (2H, m, H4, 5), 7.02–7.06 (2H, m, H3, 6), 7.36–7.57 (10H, m, CH of Bn).

4.2.2. 3,4-Dibenzyloxybromobenzene (4). To a solution of 1,2-dibenzyloxybenzene 3 (10.0 g, 34.4 mmol) in CCl<sub>4</sub> (35 mL) was added NBS (7.4 g, 41.6 mmol). After initiating of the reaction by heating, the heat was removed. The reaction boiled vigorously for 5-10 min without heating. After the reaction subsided, the solution was heated to reflux for 1 h, then diluted with DCM (50 mL), washed with water (100 mL), 1 M NaOH (50 mL) and again with water (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and MgSO<sub>4</sub>, and the solvent removed. The residue was recrystallised from DCM/MeOH to give 4 (11.3 g, 89%). A small amount was further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid.  $R_{\rm f}$  0.32 (PE/ EtOAc, 9:1); mp 62–63 °C, lit.<sup>15</sup> 64–66 °C; *m/z* 386.0756, found 386.0753; microanalysis requires C 65.05, H 4.64, found C 65.08, H 4.59;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.15, (2H, s, CH<sub>2</sub> of Bn), 5.16 (2H, s, CH<sub>2</sub> of Bn), 6.83 (1H, d, J=8.5 Hz, H5), 7.04 (1H, dd, J<sub>1</sub>=8.5 Hz, J<sub>2</sub>=2.5 Hz, H6), 7.12 (1H, d, J=2.5 Hz, H2), 7.33-7.50 (10H, m, CH of Bn).

**4.2.3. 4,5-Dibenzyloxy-2-nitrobromobenzene (5).** 3,4-Dibenzyloxybromobenzene **4** (9.0 g, 24.4 mmol) was dissolved in hot glacial acetic acid (120 mL). The solution was cooled to 35 °C and 70% HNO<sub>3</sub> (7.0 mL, 110.4 mmol) was added over 5 min. A yellow solid was precipitated and the mixture was stirred at room temperature for 2 h. Water (200 mL) was added and the yellow solid collected was dissolved in DCM then washed with  $K_2CO_3$  solution until the aqueous layer remained basic. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give **5** (8.6 g, 85%). A small amount was further purified by column chromatography (PE/EtOAc, 6:1); to give a pale yellow solid.  $R_f$  0.26 (PE/EtOAc, 6:1);

mp 104–105 °C, lit.<sup>16</sup> 105–107 °C;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.18, (2H, s,  $CH_2$  of Bn), 5.21 (2H, s,  $CH_2$  of Bn), 7.20 (1H, s, H6), 7.33–7.47 (10H, m, CH of Bn), 7.65 (1H, s, H-3).

4.2.4. 4,5-Dibenzyloxy-2-tri-n-butylstannylnitrobenzene (6). A solution of 4,5-dibenzyloxy-2-nitrobromobenzene 5 (2.00 g, 4.83 mmol), Bu<sub>6</sub>Sn<sub>2</sub> (3.60 mL, 7.15 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.28 g, 0.24 mol) was heated to reflux in toluene (10 mL) under argon for 48 h. The cooled solution was stirred vigorously with saturated KF solution (10 mL) for 1 h, and then filtered through celite with DCM (100 mL) washings. The filtrate was washed with water (50 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by column chromatography (PE/EtOAc, 9:1) to give 6 (2.05 g, 68%) as a yellow oil.  $R_{\rm f}$  0.46 (PE/EtOAc, 9:1);  $\nu_{\rm max}$ /cm<sup>-1</sup> (thin film) 2955 (s), 2921 (s), 2870 (s), 2852 (s), 1564 (m), 1515 (s, NO<sub>2</sub> str), 1454 (m), 1321 (m, NO2 str), 1272 (s), 1205 (m), 1021 (s), 735 (m), 696 (m); m/z probe ES+ (M(<sup>118</sup>Sn)H<sup>+</sup>-C<sub>4</sub>H<sub>10</sub>) 565.8 (100%), 278.4 (65%), HRMS  $(M(^{118}Sn)H^+ - C_4H_{10})$  requires m/z 566.1504, found 566.1519;  $\delta_{\rm H}$  (400 MHz,  $\bar{\rm CDCl}_3$ ) 0.91 (9H, t,  $J_1$ =7.5 Hz, CH<sub>3</sub>), 1.00–1.20 (6H, m, SnCH<sub>2</sub>), 1.27–1.39 (6H, sextet,  $J_1 = 7.5 \text{ Hz}, CH_2CH_3), 1.39 = 1.60 (6H, m, CH_2CH_2CH_3),$ 5.25, (2H, s, CH<sub>2</sub> of Bn), 5.33 (2H, s, CH<sub>2</sub> of Bn), 7.08 (1H, s, H3), 7.33-7.54 (10H, m, CH of Bn), 8.02 (1H, s, H6);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 11.06 (SnCH<sub>2</sub>), 13.71 (CH<sub>3</sub>), 27.32, (CH<sub>2</sub>CH<sub>3</sub>), 29.06, (CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 70.97 and 71.10 (CH<sub>2</sub> of Bn), 110.1 (C6), 120.3 (C3), 127.0, 127.4, 128.2, 128.2, 128.4, 128.7 and 128.7 (CH of Bn), 133.9 (quat. C), 136.2 and 136.2 (ipso of Bn), 146.6, 148.6 and 153.2 (quat. C).

4.2.5. 3,4-Dibromofuran (7).<sup>15</sup> (E)-2,3-Dibromo-2-butene-1,4-diol (20.0 g, 81.3 mmol) and 7% H<sub>2</sub>SO<sub>4</sub> (50 mL) was added to a flask with distillation apparatus attached. The mixture was rapidly stirred at 110 °C to begin distillation. A solution of K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (25.1 g, 85.4 mmol) and H<sub>2</sub>SO<sub>4</sub> (16.1 mL, 300.4 mmol) in water (160 mL) was then added over 1 h using a dropping funnel while distillation continued. After the chromic acid solution had been added, the mixture was further distilled for one more hour. The product was extracted from the distillate with PE  $(2 \times 100 \text{ mL})$  and the organic layers were washed with sat. Na<sub>2</sub>CO<sub>3</sub> solution, dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Purification by column chromatography (PE) gave 7 (10.3 g 56%) as a colourless liquid.  $R_{\rm f}$  0.46 (PE);  $\nu_{\rm max}/{\rm cm}^{-1}$  (thin film) 3150 (m), 1795 (w), 1639 (w), 1543 (m), 1330 (m), 1215 (m), 1140 (m) 1037 (m), 972 (s), 865 (s), 783 (s), 589 (s); m/z probe CI+ (M(<sup>79,79</sup>Br)<sup>+</sup>) 223.9, HRMS (M(<sup>79,79</sup>Br)<sup>+</sup>) requires m/z 223.8472, found 223.8483;  $\delta_{\rm H}$  (200 MHz, CDCl<sub>3</sub>) 7.46 (2H, s, H2, 5);  $\delta_{C}$  (50.3 MHz, CDCl<sub>3</sub>) 104.0 (C3, 4), 141.6 (C2, 5).

**4.2.6. 3,4-Bis(3,4-dibenzyloxy-2-nitrophenyl)furan (2).** *Method A.* A solution of 3,4-dibromofuran **7** (0.100 g, 0.443 mmol), 4,5-dibenzyloxy-2-tri-*n*-butylstannylnitrobenzene **6** (0.829 g, 1.328 mmol), CuBr (13 mg, 0.089 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.102 g, 0.089 mmol) in THF 5 mL was stirred at 40 °C under argon for 15 h. The mixture was diluted with DCM (50 mL) and water (50 mL) then filtered

through celite. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was purified by column chromatography (DCM/PE, 7:3) to give **2** (33 mg, 10%) as a pale orange solid. Also isolated from the reaction was 3-bromo-4-(3,4-dibenzyloxy-2-nitrophenyl)furan (**8**) (0.030 g, 14%) as a pale orange solid and 4,4',5,5'-tetrakisbenzyloxy-2,2'-dinitro-biphenyl (**9**) (0.258 g, 58%) as a yellow solid.

Method B. A solution of 3,4-bis(tri-n-butylstannyl)furan 14 (1.00 g, 1.55 mmol), 4,5-dibenzyloxy-2-nitroiodobenzene 12 (1.57 g, 3.40 mmol) and CsF (1.06 g, 7.00 mmol) in DMF (20 mL) was sonicated for a few minutes. CuI (0.29 g, 1.52 mmol) and  $Pd(PPh_3)_4$  (0.36 g, 0.31 mmol) were added and the mixture was stirred at 40 °C under argon for 2 h. The mixture was diluted with DCM (50 mL) and water (50 mL) then filtered through celite. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent removed. The residue was purified by column chromatography (DCM/PE, 7:3) to give 2 (1.05 g, 92%) as a pale orange solid.  $R_{\rm f}$  0.44 (DCM/PE, 7:3); mp 55.5–56 °C;  $\nu_{\text{max}}$ /cm<sup>-1</sup> (KBr) 3089 (w), 3063 (w), 3031 (w), 2931 (w), 2867 (w), 1573 (m), 1519 (s, NO<sub>2</sub> str), 1454 (m), 1342 (s, NO<sub>2</sub> str), 1280 (s), 1203 (m), 1086 (m), 1023 (m), 868 (m), 738 (m), 696 (m);  $\lambda_{max}$  (EtOH) 245 ( $\epsilon$ 10,390), 290 ( $\varepsilon$  5200), 340 ( $\varepsilon$  3780); *m*/*z* probe (MNH<sub>4</sub><sup>+</sup>) 752.3 (100%), 702.2 (33%), HRMS ( $MNH_4^+$ ) requires m/z752.2608, found 752.2612; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 5.15, (4H, s, CH<sub>2</sub> of Bn), 5.17 (4H, s, CH<sub>2</sub> of Bn), 6.87 (2H, s, H6', 6"), 7.30–7.53 (24H, m, H2, H5, H3', H3", CH of Bn); δ<sub>C</sub> (100.6 MHz, CDCl<sub>3</sub>) 71.1 and 71.4 (CH<sub>2</sub> of Bn), 110.4 (C3', 3"), 117.0 (C6', 6"), 120.8 and 123.7 (quat. C), 127.2, 127.3, 127.4, 127.5, 128.2, 128.2, 128.3, 128.6 and 128.(CH of Bn), 135.7 and 135.9 (ipso of Bn), 140.0 (C2, 5), 141.6, 147.9 and 152.3 (quat. C) (Fig. 8).



Figure 8.

4.2.7. 3-Bromo-4-(3,4-dibenzyloxy-2-nitrophenyl)furan (8).  $R_{\rm f}$  0.30 (DCM/PE, 6:4); mp 108–109 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$ (KBr) 3147 (w), 3033 (w), 2921 (w), 1588 (m), 1514 (s, NO<sub>2</sub> str), 1452 (m), 1330 (s, NO<sub>2</sub> str), 1292 (s), 1270 (s), 1222 (s), 1063 (s), 1044 (s), 1007 (m), 872 (s), 812 (m), 734 (s), 695 (s), 591 (m); m/z probe CI+ (MH<sup>+</sup>) 480.1 (50%), 452.1 (15%), 353.2 (20%), 336.1 (25%), 279.1 (100%), 263.1 (35%), 108.1 (53%), 91.0 (72%), HRMS (MH<sup>+</sup>) requires m/z 480.0447, found 480.0454;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.25, (2H, s, CH<sub>2</sub> of Bn), 5.26 (2H, s, CH<sub>2</sub> of Bn), 6.85 (1H, s, H6'), 7.33–7.52 (12H, m, H2, H5, CH of Bn), 7.77 (1H, s, H3');  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.2 and 71.4 (CH<sub>2</sub> of Bn), 102.3 (CH), 110.7 (C6'), 116.9 (C3'), 119.7 and 124.3 (quat. C), 127.3, 127.4, 128.3 and 128.7 (CH of Bn), 135.7 and 135.8 (ipso of Bn), 140.3 and 141.5 (C2, 5), 141.6, 148.4 and 152.2 (quat. C) (Fig. 9).



Figure 9.

**4.2.8. 4**,**4**',**5**,**5**'-Tetrakisbenzyloxy-2,**2**'-dinitro-biphenyl (**9**).  $R_{\rm f}$  0.30 (DCM/PE, 8:2); mp 189–190 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$  (KBr) 3063 (w), 3034 (w), 2915 (w), 1574 (m), 1518 (s, NO<sub>2</sub> str), 1454 (m), 1382 (m), 1333 (s, NO<sub>2</sub> str), 1270 (s), 1219 (s), 1066 (m), 1021 (m), 736 (m), 696 (m); *m*/*z* probe CI+ (MNH<sub>4</sub><sup>+</sup>) 686.0 (33%), (MH<sup>+</sup>) 669.0 (8%), 639.0 (16%), 623.0 (40%), 106.2 (100%), 91.2 (96%), HRMS (MNH<sub>4</sub><sup>+</sup>) requires *m*/*z* 686.2502, found 686.2534;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.14, (4H, d, *J*=12.0 Hz, *CH*<sub>2</sub> of Bn), 5.26 (4H, d, *J*=12.0 Hz, *CH*<sub>2</sub> of Bn), 6.66 (2H, s, H6, 6'), 7.33–7.53 (20H, m, *CH* of Bn), 7.89 (2H, s, H3, 3');  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.22 and 71.41 (*C*H<sub>2</sub> of Bn), 110.6 (C3, 3'), 114.8 (C6, 6'), 127.3, 127.5, 128.3 and 128.7 (*C*H of Bn), 129.1 (quat. *C*), 135.6 and 135.9 (*ipso* of Bn), 139.8, 147.9 and 152.8 (quat. *C*).

4.2.9. 4,5-Dibenzyloxy-2-aminobromobenzene (10). To a solution of 4,5-dibenzyloxy-2-nitrobromobenzene 5 (3.0 g, 7.23 mmol) and 35% HCl (3.00 mL) in ethanol (25 mL), was added iron powder (1.21 g, 21.67 mmol). The mixture was heated to reflux under argon for 3 h. The cooled solution was diluted with DCM (100 mL) and water (100 mL), and then filtered through celite, washing with DCM (100 mL). The organic layer was separated and again water (100 mL) was added. K<sub>2</sub>CO<sub>3</sub> was added until no more bubbling occurred and the aqueous layer was basic. The organic layer was separated, dried over Na2SO4/MgSO4 and the solvent removed under reduced pressure. Purification by column chromatography (PE/EtOAc, 8:2) gave 10 (2.3 g, 83%) as a tan solid. *R*<sub>f</sub> 0.19 (PE/EtOAc, 8:2); mp 98–99 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$  (KBr) 3448 and 3366 (w, N–H str), 3063 (w), 3033 (w), 2926 (w), 2868 (w), 1614 (m), 1596 (w), 1508 (s), 1452 (m), 1409 (m), 1381 (m), 1259 (m), 1225 (m), 1210 (m), 1178 (s), 1023 (m), 1007 (m), 982 (m), 917 (m), 873 (m), 846 (m), 763 (m), 750 (m), 734 (m), 700 (s); *m/z* probe  $ES+ (M(^{79}Br)H^+) 384.1 (85\%), HRMS (M(^{79}Br)H^+)$ requires m/z 384.0599, found 384.0595;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 3.64 (2H, br, NH<sub>2</sub>), 5.04, (2H, s, CH<sub>2</sub> of Bn), 5.09 (2H, s, CH<sub>2</sub> of Bn), 6.43 (1H, s, H3), 7.06 (1H, s, H6), 7.30–7.45 (10H, m, CH of Bn);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.31 and 73.07 (CH<sub>2</sub> of Bn), 99.49 (C1), 103.4 (C3), 121.0 (C6), 127.3, 127.7, 127.9, 127.9, 128.4 and 128.5 (CH of Bn), 136.9 and 137.2 (ipso of Bn), 139.1, 142.0 and 149.9 (quat. C).

**4.2.10. 3,4-Dibenzyloxyiodobenzene** (**11**). 1,2-Dibenzyloxybenzene **3** (50 g, 172 mmol), HgO (41 g, 189 mmol), and I<sub>2</sub> (48 g, 189 mmol), were stirred in DCM (700 mL) at room temperature for 24 h. The solution was filtered then washed with sat.  $Na_2S_2O_3$  solution (200 mL). The organic layer was dried over  $Na_2SO_4/MgSO_4$  and the solvent was removed under reduced pressure. Recrystallisation from DCM and MeOH gave **11** (56 g, 78%). A small amount was

further purified by column chromatography (PE/EtOAc, 9:1) to give a white solid.  $R_f 0.33$  (PE/EtOAc, 9:1); mp 63– 65 °C, lit.<sup>29</sup> 65–67 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3062 (w), 3033 (w), 2935 (w), 2870 (w), 1575 (m), 1499 (s), 1454 (m), 1394 (m), 1382 (m), 1247 (s), 1206 (s), 1133 (s), 998 (s), 798 (s), 751 (s), 698 (s); m/z probe CI+ (MNH<sub>4</sub><sup>+</sup>) 434.1 (100%), (MNH<sub>4</sub><sup>+</sup>-I) 308.2 (55%), 290.2 (20%), 108.1 (12%), 91.1 (22%), HRMS (MNH<sub>4</sub><sup>+</sup>) requires m/z 434.0617, found 434.0611; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 5.13 (2H, s, CH<sub>2</sub> of Bn), 5.15 (2H, s, CH<sub>2</sub> of Bn), 6.70 (1H, d, J=8.5 Hz, H5), 7.22 (1H, dd, J<sub>1</sub>=8.5 Hz, J<sub>2</sub>=2.0 Hz, H6), 7.27 (1H, d, J=2.0 Hz, H2), 7.31–7.50 (10H, m, CH of Bn);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.30 and 71.46 (CH<sub>2</sub> of Bn), 83.26 (C1), 117.0 (C5), 124.0 (C2), 127.3, 127.4, 127.9, 128.0, 128.6 and 128.6 (CH of Bn), 130.5 (C6), 136.7 and 136.9 (ipso of Bn), 149.1 and 149.9 (quat. C).

4.2.11. 4,5-Dibenzyloxy-2-nitroiodobenzene (12). 3,4-Dibenzyloxyiodobenzene 11 (50 g, 120 mol) was dissolved in hot glacial acetic (600 mL). The solution was cooled to 35 °C and 70% HNO<sub>3</sub> (35 mL, 552 mmol) was added over 30 min. A yellow solid precipitated and the mixture was stirred at room temperature for 2 h. Water (1 L) was added and the yellow solid collected was dissolved in DCM then washed with sat. K<sub>2</sub>CO<sub>3</sub> solution until the aqueous layer was basic. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give 12 (52 g, 94%). A small amount was further purified by column chromatography (PE/EtOAc, 6:1) to give a yellow solid.  $R_{\rm f}$ 0.27 (PE/EtOAc, 6:1); mp 108.5–109 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3056 (w), 3027 (w), 2899 (w), 2858 (w), 1588 (w), 1575 (m), 1514 (s, NO<sub>2</sub> str), 1498 (s), 1450 (m), 1316 (s), 1266 (s), 1210 (m), 1196 (m), 1011 (m), 859 (m), 749 (m), 732 (m), 699 (m); m/z probe CI+ (MNH<sub>4</sub><sup>+</sup>) 479.0 (20%), (MH<sup>+</sup>) 462.0 (7%), 432.0 (100%), 340.0 (30%), 305.2 (67%), 91.1 (80%), HRMS (MNH<sub>4</sub><sup>+</sup>) requires m/z479.0468, found 479.0452; microanalysis requires C 52.08, H 3.50, N 3.04, found C 52.40, H 3.46, N 3.05;  $\delta_{\rm H}$ (400 MHz, CDCl<sub>3</sub>) 5.19 (2H, s, CH<sub>2</sub> of Bn), 5.20 (2H, s, CH<sub>2</sub> of Bn), 7.33–7.47 (10H, m, CH of Bn), 7.49 (1H, s, C6), 7.68 (1H, s, C3);  $\delta_C$  (100.6 MHz, CDCl<sub>3</sub>) 71.31 and 71.41 (CH<sub>2</sub> of Bn), 77.60 (C1), 111.7 (C3), 125.5 (C6), 127.3, 127.4, 128.4, 128.5, 128.7 and 128.8 (CH of Bn), 135.3 and 135.6 (ipso of Bn), 145.1, 148.5 and 152.6 (quat. C).

4.2.12. 4,5-Dibenzyloxy-2-aminoiodobenzene (13). A mixture of 4,5-dibenzyloxy-2-nitroiodobenzene 12 (2.00 g, 4.33 mmol), activated carbon (0.21 g, 17.50 mmol), and FeCl<sub>3</sub> (70 mg, 0.43 mmol) in MeOH (15 mL) was heated to reflux under argon for 10 min. N<sub>2</sub>H<sub>2</sub>·H<sub>2</sub>O (0.84 mL, 17.23 mmol) was added slowly and the mixture heated to reflux for 8 h. The cooled solution was diluted with DCM (50 mL) and water (50 mL), then filtered through celite, washing with DCM (100 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 8:2) to give 13 (1.60 g, 86%) as a pale yellow solid.  $R_{\rm f}$  0.19 (PE/EtOAc, 8:2); mp 92–94 °C;  $\nu_{max}/cm^{-1}$  (KBr) 3437 and 3353 (m, NH str), 3061 (w), 3032 (w), 2926 (w), 2868 (w), 1609 (m), 1506 (s), 1404 (m), 1381 (m), 1255 (s), 1226 (m), 1210 (m), 1177 (s), 1018 (m), 1006 (m), 982 (m), 847 (m), 765 (m),

750 (m), 731 (m), 700 (s); m/z probe ES+ (MH<sup>+</sup>) 432.1 (100%), (MH<sup>+</sup>-NH<sub>2</sub>) 415.0 (15%), 391.3 (17%), HRMS (MH<sup>+</sup>) requires m/z 432.0461, found 432.0461;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 3.82 (2H, br, NH<sub>2</sub>), 5.04, (2H, s, CH<sub>2</sub> of Bn), 5.09 (2H, s, CH<sub>2</sub> of Bn), 6.43 (1H, s, H3), 7.27 (1H, s, H6), 7.32–7.50 (10H, m, CH of Bn);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.12 (CH<sub>2</sub> of Bn), 72.28 (C1), 73.20 (CH<sub>2</sub> of Bn), 102.3 (C3), 126.8 (C6), 127.3, 127.8, 127.9, 128.0, 128.5 and 128.6 (CH of Bn), 136.9 and 137.3 (*ipso* of Bn), 142.3, 142.3 and 151.0 (quat. C).

**4.2.13. 3,4-Bis(3,4-dihydroxy-2-aminophenyl)furan (17).** 3,4-Bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (51 mg, 0.07 mmol) and AcOH (4  $\mu$ L, 0.07 mmol) were stirred in THF (1 mL) with 10% palladium on carbon (20 mg) under an atmosphere of H<sub>2</sub> for 15 h. The solution was filtered and the solvent removed to give **17** (21 mg, 94%) as a pale yellow solid. The lability of the compound prevented purification. Mp decomposed >190 °C;  $\nu_{max}/cm^{-1}$  (KBr) 3374 (s, br, OH str), 1557 (m), 1514 (s), 1451 (m), 1308 (m), 1243 (m), 1052 (m), 876 (m), 804 (m);  $\lambda_{max}$  (EtOH) 313 ( $\epsilon$  45,850);  $\delta_{\rm H}$  (500 MHz, CD<sub>3</sub>OD) 6.33 (2H, s, H3', 3"), 6.49 (2H, s, H6', 6"), 7.60 (2H, s, H2, 5);  $\delta_{\rm C}$  (125.8 MHz, CD<sub>3</sub>OD), 105.0 (C3', 3"), 110.2 (quat. *C*), 117.8 (C6', 6"), 123.9 (C3, 4), 137.5 and 138.3 (quat. *C*), 141.4 (C2), 146.0 (quat. *C*) (Fig. 10).





**4.2.14. 3,4-Bis(3,4-dibenzyloxy-2-aminophenyl)furan (18).** *Method A.* A solution of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (240 mg, 0.33 mmol) and SnCl<sub>2</sub> (743 mg, 3.92 mmol) in ethyl acetate (1.0 mL) and MeOH (0.5 mL) was heated to reflux for 1.5 h. The solution was poured into a slurry of ice and water (20 mL), and then DCM was added (20 mL). EDTA.2Na was added until the aqueous layer was basic. The mixture was shaken vigorously for a few minutes, and then filtered through celite, washing with DCM (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 1:1) to give **18** (148 mg, 67%) as a pale brown solid.

*Method B.* Iron powder (0.46 g, 8.24 mmol) was added to a solution of 3,4-bis(3,4-dibenzyloxy-2-nitrophenyl)furan **2** (0.76 g, 1.03 mmol) and 35% HCl (1.20 mL) in EtOH (8 mL). The mixture was heated to reflux under argon for 3 h. The cooled solution was diluted with DCM (20 mL) and water (20 mL), and then filtered through celite, washing with DCM (100 mL). The organic layer was separated and again water (20 mL) was added.  $K_2CO_3$  was added until no more bubbling occurred and the aqueous layer was basic. The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub>

and the solvent was removed under reduced pressure. Purification by column chromatography (PE/EtOAc, 1:1) gave 18 (0.61 g, 88%) as a pale brown solid.  $R_{\rm f}$  0.38 (PE/ EtOAc, 1:1); mp 137–138.5 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3455, 3397, 3364 and 3324 (m, NH str), 3061 (w), 3032 (w), 2917 (w), 2867 (w), 1616 (m), 1552 (m), 1505 (s), 1454 (m), 1418 (m), 1370 (m), 1354 (m), 1262 (s), 1204 (s), 1171 (s), 1146 (s), 1054 (m), 1024 (m), 994 (m), 854 (m), 826 (m), 735 (s), 696 (s);  $\lambda_{\text{max}}$  (EtOH) 308 ( $\epsilon$  5560); *m*/*z* probe ES+ (MH<sup>+</sup>) 674.0 HRMS (MH<sup>+</sup>) requires *m*/*z* 675.2859, found 675.2864; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.37 (4H, br, NH<sub>2</sub>), 4.87, (4H, s, CH<sub>2</sub> of Bn), 5.08 (4H, s, CH<sub>2</sub> of Bn), 6.32 (2H, s, H3', 3"), 6.56 (2H, s, H6', 6"), 7.24–7.50 (20H, m, CH of Bn), 7.56 (2H, s, H2, 5);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 71.05 and 72.70 (CH<sub>2</sub> of Bn), 103.3 (C3', 3"), 109.6 (quat. C), 119.4 (C6', 6"), 123.0 (quat. C), 127.2, 127.5, 127.6, 127.8, 128.3 and 128.5 (CH of Bn), 137.2 and 137.7 (ipso of Bn), 139.4 (quat. C), 141.2 (C2, 5), 141.4 and 149.9 (quat. C) (Fig. 11).



Figure 11.

4.2.15. 3-(3,4-Dibenzyloxy-2-aminophenyl)-4-(hydroxymethyl)-6,7-dibenzyloxyquinoline (19). A mixture of 3.4-bis(3.4-dibenzyloxy-2-aminophenyl)furan 18 (500 mg, 0.74 mmol), p-toluenesulfonic acid (70 mg, 0.37 mmol) and powdered molecular sieves (100 mg, 4 Å) in benzene (10 mL) was heated to reflux for 2 days. DCM (20 mL) was added, the mixture filtered, then washed with sat. Na<sub>2</sub>CO<sub>3</sub> solution (10 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give a residue that was purified by column chromatography (PE/EtOAc, 3:7). 19 (125 mg, 25%) was obtained as a white solid, along with recovered starting material (332 mg, 64%). Rf 0.42 (PE/EtOAc, 3:7); mp 183.5–184 °C;  $\nu_{max}$ /cm<sup>-1</sup> (KBr) 3447 and 3355 (m, NH str), 3217 (w), 3028 (m), 2926 (w), 2870 (w), 1623 (s), 1546 (m), 1506 (s), 1454 (m), 1411 (m), 1385 (m), 1358 (m), 1260 (s), 1222 (s), 1208 (s), 1170 (m), 1150 (m), 1058 (m), 1014 (m), 866 (m), 735 (s), 696 (s);  $\lambda_{max}$  (EtOH) 242 ( $\epsilon$ 56,550), 300 (ε 8840), 337 (ε 10,040); m/z probe APCI+ (MH<sup>+</sup>) 675.7 (40%), HRMS (MH<sup>+</sup>) requires *m*/*z* 675.2859, found 675.2861; δ<sub>H</sub> (500 MHz, CDCl<sub>3</sub>) 3.35 (2H, br, NH<sub>2</sub>), 4.55 (1H, br, OH), 4.58 (1H, d, J=12.0 Hz,  $\alpha$ -CH<sub>2</sub>OH), 4.80 (1H, d, J=12.0 Hz,  $\beta$ -CH<sub>2</sub>OH), 5.08 (1H, d, J=12.0 Hz,  $\alpha$ -CH<sub>2</sub> of Bn), 5.10 (1H, d, J=12.0 Hz,  $\beta$ -CH<sub>2</sub> of Bn), 5.18 (1H, d, J=12.0 Hz,  $\alpha$ -CH<sub>2</sub> of Bn), 5.20 (1H, d, J=12.0 Hz,  $\beta$ -CH<sub>2</sub> of Bn), 5.28–5.38 (4H, m, CH<sub>2</sub> of Bn), 6.50 (1H, s, H3), 6.72 (1H, s, H6), 7.28–7.56 (21H, m, H8, CH of Bn), 7.61 (1H, s, H5), 8.46 (1H, s, H2); δ<sub>C</sub> (125.8 MHz, CDCl<sub>3</sub>) 60.0 (CH<sub>2</sub>OH), 70.3, 70.7, 71.2 and 72.5 (CH<sub>2</sub> of Bn), 104.4 (C5), 104.6 (C3), 110.2 (C8), 117.8 (quat. C), 119.3 (C6), 122.6 (quat. C), 127.0, 127.1, 127.3, 127.6, 127.7, 127.8, 127.8, 127.9, 128.3, 128.4, 128.5 and 128.5 (CH of Bn), 136.3, 136.4, 136.9, 137.2, 138.4, 142.1, 142.4 and 145.3

(quat. C), 149.3 (C2), 149.7, 150.1, 151.6 (quat. C);  $\delta_{\rm H}(400 \text{ MHz}, \text{DMSO})$  4.41 (2H, s, NH<sub>2</sub>), 4.62 (1H, dd,  $J_1=11.5 \text{ Hz}, J_2=5.0 \text{ Hz}, \alpha$ -CH<sub>2</sub>OH), 4.70 (1H, dd,  $J_1=$ 11.5 Hz,  $J_2=5.0 \text{ Hz}, \beta$ -CH<sub>2</sub>OH), 4.98 (2H, s, CH<sub>2</sub> of Bn), 5.11 (2H, s, CH<sub>2</sub> of Bn), 5.28 (1H, t, J=5.0 Hz, OH), 5.32 (2H, s, CH<sub>2</sub> of Bn), 5.37 (2H, s, CH<sub>2</sub> of Bn), 6.61 (1H, s, H3), 6.75 (1H, s, H6), 7.28–7.62 (21H, m, H8, CH of Bn), 7.82 (1H, s, H5), 8.37 (1H, s, H2) (Fig. 12).



Figure 12.

4.2.16. 2', 2'', 3', 3''-Tetrakisbenzyloxy-dibenzo[c,h][2,6]naphthyridine (20). 3-(3,4-Dibenzyloxy-2-aminophenyl)-4-(hydroxymethyl)-6,7-dibenzyloxyquinoline **19** (20 mg) was dissolved in DMSO- $d_6$  (0.8 mL), and left standing open to the air for 3 months to give pale yellow crystals of **20.** Due to the crystals being highly insoluble, only a  ${}^{1}$ H NMR spectra was obtainable. Mp 264–265 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$ (KBr) 3428 (br,s), 1620 (w), 1516 (m), 1479 (w), 1448 (m), 1380 (w), 1287 (s), 1242 (m), 1184 (w), 1152 (w), 1026 (s), 824 (w), 727 (m), 693 (m); m/z probe ES+ (MH<sup>+</sup>) 655.1 (30%), 413.0 (20%), 334.9 (68%), 256.8 (80%), 226.7 (94%), 175.6 (100%), HRMS (MH<sup>+</sup>) requires 665.2597, m/z found 665.2602; δ<sub>H</sub> (500 MHz, DMSO-d<sub>6</sub>) 5.43 (4H, s, CH<sub>2</sub> of Bn), 5.53 (4H, s, CH<sub>2</sub> of Bn), 7.31-7.65 (20H, m, CH of Bn), 7.80 (2H, s, H4', 4"), 8.59 (2H, s, H1', 1"), 10.22 (2H, s, H1, H5) (Fig. 13).



Figure 13.

4.2.17. 3,4-Bis(3,4-dibenzyloxy-2-N-acylaminophenyl)furan (21). A mixture of 3,4-bis(3,4-dibenzyloxy-2-aminophenyl)furan 18 (266 mg, 0.39 mmol), acetic anhydride (82 µL, 0.87 mmol), triethylamine (166 µL, 1.19 mmol) and a catalytic amount of DMAP in THF (6 mL) was stirred at room temperature for 15 h. The solvent was removed and the residue was purified by column chromatography (PE/ EtOAc, 1:9) to give 21 (236 mg, 79%) as a pale yellow solid.  $R_{\rm f}$  0.33 (PE/EtOAc, 1:9); mp 64–65 °C;  $\nu_{\rm max}/{\rm cm}^{-1}$ (KBr) 3271 (m, br), 3031 and 2930 (w), 1658 (s, C=O str), 1511 (s), 1454 (m), 1411 (m), 1369 (m), 1251 (s), 1205 (m), 1165 (m), 1146 (m), 1014 (m), 863 (m), 737 (m), 696 (s); m/z probe ES+ (MNa<sup>+</sup>) 780.0 (38%), (MH<sup>+</sup>) 759.0 (70%), HRMS (MH<sup>+</sup>) requires *m*/*z* 759.3070, found 759.3078; microanalysis requires C 75.97, H 5.58, found C 75.70, H 5.54; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 1.83 (6H, s, CH<sub>3</sub>), 4.90 (4H, s, CH<sub>2</sub> of Bn), 5.13 (4H, s, CH<sub>2</sub> of Bn), 6.68 (2H, s, H3', 3"), 7.25–7.48 (22H, m, H2, H5, CH of Bn), 7.52 (2H, s, NH), 7.59 (2H, s, H6', 6");  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 23.94 (CH<sub>3</sub>), 71.01 and 71.87 (CH<sub>2</sub> of Bn), 110.5 (C6'), 116.6 (quat. C), 117.2 (C3', 3"), 122.5 (quat. C), 127.2, 127.5, 127.8, 127.9, 128.4 and 128.5 (CH of Bn), 129.4 (quat. C), 136.8 and 137.1 (*ipso* of Bn), 141.1 (C2, 5), 145.9 and 148.8 (quat. C), 168.7 (C=O) (Fig. 14).



Figure 14.

**4.2.18. 3,4-Dibenzyloxybenzaldehyde** (**22**). A mixture of 3,4-dihydroxybenzaldehyde (5.00 g, 36.20 mmol), K<sub>2</sub>CO<sub>3</sub> (25.02 g, 181.03 mmol) and benzyl chloride (10.00 mL, 86.89 mmol) in DMF (25 mL), was stirred rapidly at 120 °C under argon for 15 h. The solution was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 7:3) to give **22** (11.4 g, 99%) as a white solid.  $R_f$  0.30 (PE/EtOAc, 7:3); mp 84–85 °C, lit.<sup>36</sup> 84–85 °C;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 5.22 (2H, s, CH<sub>2</sub> of Bn), 5.26 (2H, s, CH<sub>2</sub> of Bn), 7.04 (1H, d, *J*=8.0 Hz, H2), 7.31–7.51 (11H, m, H6, CH of Bn), 7.52 (1H, d, *J*=2.0 Hz, H5), 9.83 (1H, s, *H*C=O).

4.2.19. (E)-3,4-Dibenzyloxy-β-nitrostyrene (23). A solution of 3,4-dibenzyloxybenzaldehyde 22 (10.0 g, 31.4 mmol), MeNO<sub>2</sub> (10.2 mL, 188.8 mmol), and NH<sub>4</sub>OAc (9.7 g, 125.8 mmol) in AcOH (100 mL) was heated to reflux for 40 min. Most of the AcOH was removed under vacuum and the residue was dissolved in DCM (100 mL). The solution was washed with sat. K<sub>2</sub>CO<sub>3</sub> solution until the aqueous layer was basic and then with water (100 mL). The organic layer was dried over Na2SO4/MgSO4 and the solvent was removed under reduced pressure to give 23 (11.10 g, 98%) as a bright yellow solid. A small amount was purified by column chromatography (PE/DCM, 3:7) for spectroscopic analysis. Rf 0.38 (PE/DCM, 3:7); mp 115-116.5 °C, lit.<sup>37</sup> 117–118°;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.20, (2H, s, CH<sub>2</sub> of Bn), 5.23 (2H, s, CH<sub>2</sub> of Bn), 6.97 (1H, d, J=8.0 Hz, H5), 7.10 (1H, d, J=2.0 Hz, H2), 7.12 (1H, dd,  $J_1=8.0$  Hz, J<sub>2</sub>=2.0 Hz, H6), 7.33-7.50 (11H, m, β H, CH of Bn), 7.90 (1H, d, *J*=13.5 Hz, α H).

**4.2.20.** (*E*)-4,5-Dibenzyloxy-2,  $\beta$ -dinitrostyrene (24). A mixture of (*E*)-3,4-dibenzyloxy- $\beta$ -nitrostyrene 23 (10.9 g, 30.2 mmol), was dissolved in hot glacial acetic (150 mL). The solution was cooled to 35 °C and 70% HNO<sub>3</sub> (8.7 mL, 137.2 mmol) was added over 15 min. A yellow solid precipitated and the slurry was stirred at room temperature for 2 h. Water (300 mL) was added, and then the yellow solid collected was dissolved in DCM (200 mL) then washed with sat. K<sub>2</sub>CO<sub>3</sub> solution until the aqueous layer was basic. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was recrystallised from DCM/MeOH to give 24

(11.9 g, 97%) as a yellow solid. A small amount was further purified by column chromatography (PE/DCM, 3:7) for spectroscopic analysis.  $R_f$  0.32 (PE/DCM, 3:7); mp 161– 162 °C, lit.<sup>37</sup> 162–163 °C;  $\delta_H$  (400 MHz, CDCl<sub>3</sub>) 5.27 (2H, s, CH<sub>2</sub> of Bn), 5.30 (2H, s, CH<sub>2</sub> of Bn), 6.97 (1H, s, H6), 7.25 (1H, d, *J*=13.5 Hz,  $\beta$  H), 7.34–7.50 (10H, m, CH of Bn), 7.82 (1H, s, H3), 8.55 (1H, d, *J*=13.5 Hz,  $\alpha$  H).

4.2.21. 5,6-Dibenzyloxyindole (25). A mixture of (E)-4,5dibenzyloxy-2,  $\beta$ -dinitrostyrene 24 (5.00 g, 12.30 mmol), iron powder (13.74 g, 246.02 mmol) and SiO<sub>2</sub> (18.50 g) in AcOH (75 mL), benzene (90 mL) and cyclohexane (30 mL) was heated to reflux for 30 min under argon. The mixture was filtered through celite with DCM/EtOAc (1:1) until the washings contained no product by TLC. The solution was washed with K<sub>2</sub>CO<sub>3</sub> solution until the aqueous layer was basic then with water (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. The residue was purified by column chromatography (PE/EtOAc, 3:1) to give 25 (2.47 g, 61%) as a cream solid. R<sub>f</sub> 0.30 (PE/EtOAc, 3:1); mp 111-113 °C, lit.<sup>37</sup> 113–114 °C;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 5.14 (2H, s, CH<sub>2</sub> of Bn), 5.20 (2H, s, CH<sub>2</sub> of Bn), 6.43 (1H, m, H3), 6.92 (1H, d, *J*=0.5 Hz, H7), 7.02 (1H, dd, *J*<sub>1</sub>=2.5 Hz, *J*<sub>2</sub>=3.0 Hz, H2), 7.24 (1H, s, H4), 7.30-7.54 (10H, m, CH of Bn), 8.03 (1H, br, N*H*).

4.2.22. 5,6-Dibenzyloxy-N-triisopropylsilylindole (26). n-BuLi in hexanes (3.90 mL of a 1.62 M solution, 6.32 mmol) was added slowly to a solution of 5,6-dibenzyloxyindole 25 (1.74 g, 5.28 mmol) in THF (20 mL) at -78 °C under argon. After 15 min, TIPSCl (1.58 mL, 7.4 mmol) was added and the solution was stirred for 2 h at -78 °C then 30 min at room temperature. Most of the THF was removed under reduced pressure and replaced with DCM (50 mL). The solution was washed with water (50 mL) dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent removed under reduced pressure to give a residue that was purified by column chromatography (PE/DCM, 6:4). 26 (2.43 g, 95%) was obtained as a white solid.  $R_{\rm f}$  0.18 (PE/ DCM, 6:4); mp 84–85 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 3090 (w), 3062 (w), 3031 (w), 2944 (s), 2865 (s), 1514 (m), 1497 (m), 1482 (s), 1452 (s), 1309 (m), 1263 (m), 1220 (s), 1188 (s), 1161 (s), 1016 (s), 884 (s), 868 (s), 736 (s), 722 (s), 690 (s), 652 (m);  $\lambda_{max}$  (EtOH) 206 ( $\varepsilon$  54,080), 228 ( $\varepsilon$  40,910), 268 ( $\varepsilon$ 6960), 300 ( $\varepsilon$  7420); *m*/*z* probe ES+ (MH<sup>+</sup>) 485.0 (57%), HRMS (MH<sup>+</sup>) requires *m*/*z* 486.2828, found 486.2826; microanalysis requires C 76.65, H 8.09, found C 76.61, H 8.22;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 1.08 (18H, d, J=7.5 Hz, CH<sub>3</sub> of TIPS), 1.52 (3H, heptet, J=7.5 Hz, CH of TIPS), 5.24 (4H, s, CH<sub>2</sub> of Bn), 6.50 (1H, dd, J<sub>1</sub>=3.0 Hz, J<sub>2</sub>=1.0 Hz, H3), 7.01 (1H, d, J=1.0 Hz, H7), 7.12 (1H, d, J=3.0 Hz, H2), 7.19 (1H, s, H4), 7.28–7.57 (10H, m, CH of Bn);  $\delta_{\rm C}$ (100.6 MHz, CDCl<sub>3</sub>) 12.66 (CH of TIPS), 18.05 (CH<sub>3</sub> of TIPS), 71.96 and 72.50 (CH<sub>2</sub> of Bn), 102.5 (C7), 104.4 (C3), 105.6 (C4), 125.3 (quat. C), 127.1, 127.4, 127.5, 127.6 and 128.4 (CH of Bn), 130.3 (C2), 135.3, 138.0, 145.0 and 145.5 (quat. *C*).

**4.2.23. 5,6-Dibenzyloxy-3-iodo-***N***-triisopropylsilylindole (27).** *Method A*. A solution of  $I_2$  (1.62 g, 6.38 mmol) in DCM (200 mL) was added slowly over 1 h to a mixture of 5,6-dibenzyloxy-*N*-triisopropylsilylindole **26** (2.82 g,

5.81 mmol) and Hg(OAc)<sub>2</sub> (2.04 g, 6.40 mmol) in DCM (100 mL) at 0 °C. The mixture was stirred for an additional hour at room temperature, then filtered through celite and washed with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution (50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Purification by column chromatography (PE/DCM, 6:4) gave **27** (3.55 g, 100%) as a cream solid.

Method B. NIS (0.36 g, 1.60 mmol) was added to a solution of 5,6-dibenzyloxy-N-triisopropylsilylindole 26 (0.63 g, 1.30 mmol) in THF (10 mL) at 0 °C and stirred for 30 min. The solution was diluted with DCM (50 mL), washed with sat. Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub> and the solvent was removed under reduced pressure. Purification by column chromatography (PE/DCM, 6:4) gave 27 (0.66 g, 83%) as a cream solid.  $R_{\rm f}$ 0.33 (PE/DCM, 6:4); mp 105–106 °C;  $\nu_{\text{max}}/\text{cm}^{-1}$  (KBr) 2942 (m), 2864 (m), 1496 (m), 1474 (s), 1465 (s), 1454 (s), 1386 (m), 1308 (m), 1200 (s), 1168 (s), 1016 (s), 989 (m), 883 (m), 866 (s), 697 (s);  $\lambda_{max}$  (EtOH) 230 ( $\varepsilon$  21,970), 297 ( $\varepsilon$  6130); *m/z* probe ES+ (MH<sup>+</sup>) 610.7 (40%), (MH<sup>+</sup>-I) 484.4 (75%), HRMS (MH<sup>+</sup>) requires m/z 612.1795, found 612.1791;  $\delta_{\rm H}$  (400 MHz, CDCl<sub>3</sub>) 1.07 (18H, d, J=7.5 Hz,  $CH_3$  of TIPS), 1.49 (3H, heptet, J=7.5 Hz, CH of TIPS), 5.25, (2H, s, CH<sub>2</sub> of Bn), 5.30 (2H, s, CH<sub>2</sub> of Bn), 6.98 (1H, s, H7), 7.03 (1H, s, H4), 7.16 (1H, s, H2), 7.29-7.48 (8H, m, CH of Bn), 7.59 (1H, s, CH of Bn), 7.61 (1H, s, CH of Bn); δ<sub>C</sub> (100.6 MHz, CDCl<sub>3</sub>) 12.62 (CH of TIPS), 17.97 (CH<sub>3</sub> of TIPS), 59.46 (C3), 71.49 and 72.44 (CH<sub>2</sub> of Bn), 102.4 (C7), 105.4 (C4), 127.0, (CH of Bn), 127.0 (quat. C), 127.6, 127.8, 128.5 and 128.5 (CH of Bn), 134.0, (C2), 134.5 (quat. C), 137.6 and 137.7 (ipso of Bn), 146.0 and 146.4 (quat. C).

4.2.24. 5,5',6,6'-Tetrabenzyloxy-N,N'-triisopropylsilyl-3,3'-biindolyl (28). A mixture of 5,6-dibenzyloxy-3-iodo-N-triisopropylsilylindole 27 (0.50 g, 0.82 mmol), tetrakis-(dimethylamino)ethylene (0.38 mL, 1.63 mmol) and Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> (30 mg, 0.08 mmol) was stirred in DMF (4 mL) at 50 °C for 1.5 h under argon. The solution was diluted with DCM (20 mL), washed with water (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>/MgSO<sub>4</sub>, and the was solvent removed under reduced pressure. Purification by column chromatography (PE/DCM, 3:7) gave **28** (269 mg, 68%) as a white gum.  $R_{\rm f}$  0.44 (PE/DCM, 3:7);  $\nu_{\rm max}/{\rm cm}^{-1}$  (thin film) 2946 (s), 2866 (s), 1506 (m), 1470 (s), 1314 (m), 1192 (s), 1151 (s), 1016 (s), 883 (m), 733 (m), 695 (s), 652 (m);  $\lambda_{max}$ (EtOH) 304 ( $\varepsilon$  14,000); *m*/*z* probe (MH<sup>+</sup>) 968.5 (100%), 506.7 (13%), 485.3 (25%), HRMS (MH<sup>+</sup>) requires m/z 969.5422, found 969.5508; microanalysis requires C 76.81, H 7.90, found C 76.76, H 8.03;  $\delta_{\rm H}$  (400 MHz, CDCl\_3) 1.16 (36H, d, J=7.5 Hz, CH<sub>3</sub> of TIPS), 1.58 (6H, heptet, J CH of TIPS), 5.23, (2H, s, CH<sub>2</sub> of Bn), 5.30 (2H, s, CH<sub>2</sub> of Bn), 7.09 (2H, s, CH of Ar), 7.31-7.56 (24, m, Ar CH, Ar CH and CH of Bn);  $\delta_{\rm C}$  (100.6 MHz, CDCl<sub>3</sub>) 12.77 (CH of TIPS), 18.17 (CH<sub>3</sub> of TIPS), 71.78 and 72.55 (CH<sub>2</sub> of Bn), 102.8 and 104.8 (Ar CH), 112.5 and 124.3 (quat. C), 127.1, 127.3, 127.5, 127.6, 127.6, 128.4 and 128.5 (Ar CH, CH of Bn), 135.8 (quat. C), 137.9 and 138.0 (ipso of Bn), 145.2 and 145.7 (quat. C).

**4.2.25. 5**,**5**′,**6**,**6**′-**Tetrabenzyloxy-3**,**3**′-**biindolyl** (**29**). TBAF in THF (0.24 mL of a 1.0 M solution, 0.24 mmol) was

added dropwise to a solution of 5.5'.6.6'-tetrabenzyloxy-N,N'-triisopropyl-3,3'-biindolyl **28** (105 mg, 0.11 mmol) in THF (1 mL) and stirred for 10 min. Cold MeOH (5 mL) was added and the white precipitate was collected, then washed with cold MeOH (10 mL) to give 29 (58 mg, 82%) as a white powder. Mp 225–225.5 °C;  $\nu_{max}/cm^{-1}$  (KBr) 3399 (m, br), 3281 (s, NH str), 3063 (w), 3031 (w), 2935 (w), 2877 (w), 1629 (m), 1508 (m), 1475 (s), 1466 (s), 1454 (m), 1312 (s), 1244 (s), 1189 (s), 1137 (s), 1010 (m), 990 (m), 975 (m), 917 (m), 879 (m), 741 (s), 698 (s);  $\lambda_{\text{max}}$  (EtOH) 300 ( $\epsilon$  6480); *m*/*z* probe ES+ (MNa<sup>+</sup>) 679.3 (57%),  $(MNH_4^+)$  674.3 (56%),  $(MH^+)$  657.3 (100%), HRMS (MH<sup>+</sup>) requires m/z 657.2753, found 657.2765;  $\delta_{\rm H}$ (400 MHz, DMSO) 5.14, (4H, s, CH<sub>2</sub> of Bn), 5.19 (4H, s, CH<sub>2</sub> of Bn), 7.07 (2H, s, H7), 7.28-7.53 (24H, m, H2, H4, CH of Bn), 10.84 (2H, d, J=2.0 Hz, NH);  $\delta_{\rm C}$  (100.6 MHz, DMSO) 71.40 and 72.20 (CH2 of Bn), 98.71 (C7), 106.4 (C4), 110.7 and 120.2 (quat. C), 121.2 (C2), 128.3, 128.4, 128.5, 128.5, 129.1 and 129.2 (CH of Bn), 132.0 (quat. C), 138.6 and 138.9 (ipso of Bn), 144.6 and 146.7 (quat. C).

4.2.26. 5,5',6,6'-Tetrahydroxy-3,3'-biindolyl (1). 5,5',6,6'-Tetrabenzyloxy-3,3'-biindolyl **29** (30 mg, 0.04 mmol) was stirred in THF (1 mL) with Palladium Black (3 mg) under an atmosphere of H<sub>2</sub> for 18 h. The solution was quickly filtered and the solvent removed at 30 °C under reduced pressure to give the target compound 1 (13 mg, 94%) as a greyish orange solid. The solid product did not dissolve in  $D_2O$  sufficiently to allow the preparation of a sample for <sup>13</sup>C NMR analysis (14,000 scans at 500 MHz gave no signals), although it was readily soluble in DMSO- $d_6$ . To prepare a sample in D<sub>2</sub>O, the reaction solution was quickly filtered and most of the THF was removed at 30 °C under reduced pressure. D<sub>2</sub>O (0.8 mL) was added giving a pale orange solution. The remaining THF was removed under reduced pressure leaving an aqueous solution with a milky precipitate (the milky precipitate was soluble in DMSO- $d_6$ and gave clean spectra of the compound showing that the heteroatom protons had been deuterated). This was quickly filtered to give a pale orange aqueous solution.  $\lambda_{max}$  (H<sub>2</sub>O) 302; m/z probe ES- (M-H<sup>+</sup>) 295.07 (100%), HRMS  $(M-H^+)$  requires *m/z* 295.0719, found 295.0717;  $\delta_H$ (500 MHz, D<sub>2</sub>O) 6.94 (2H, s, H7, 7'), 7.13 (2H, s, H4, 4'), 7.32 (2H, s, H2, 2'); δ<sub>C</sub> (125.8 MHz, D<sub>2</sub>O) 98.47 (C7), 105.2 (C4), 109.1 (C3), 119.5 (C3a), 121.2 (C2), 131.6 (C7a), 139.8 (C5), 142.2 (C6);  $\delta_{\rm H}$  (500 MHz, DMSO- $d_6$ ) 6.78 (2H, s, H7, 7'), 7.03 (2H, s, H4, 4'), 7.16 (2H, d, J=2.0 Hz, H2, 2'), 8.23 (2H, s, OH-5), 8.50 (2H, s, OH-6), 10.40 (2H, d, J=2.0 Hz, NH);  $\delta_{\rm C}$  (125.8 MHz, DMSO- $d_6$ ) 98.10 (C7), 105.2 (C4), 110.6 (C3), 119.5 (C2), 119.8 (C3a), 131.5 (C7a), 141.2 (C5), 143.5 (C6).

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#### **References and notes**

- (a) Kähkönen, M. P.; Hopia, A. I.; Vuorela, H. J.; Rauha, J.-P.; Pihlaja, K.; Kujala, T. S.; Heinonen, M. J. Agric. Food Chem. **1999**, 47, 3954–3962. (b) Kujala, T. S.; Loponen, J. M.; Klika, K. D.; Pihlaja, K. J. Agric. Food Chem. **2000**, 48, 5338–5342.
- (a) Temple, N. J. Nutr. Res. 2000, 20, 449–459. (b) Block, G. Nutr. Rev. 1992, 50, 207–213.
- Ames, B. N.; Shigenaga, M. K.; Hagen, T. M. Proc. Natl. Acad. Sci. U.S.A. 1993, 90, 7915–7922.
- Vinson, J. A.; Dabbagh, Y. A.; Serry, M. M.; Jang, J. J. Agric. Food Chem. 1995, 43, 2800–2802.
- Rice-Evans, C.-A.; Miller, N. J.; Bowell, P. G.; Bramley, P.; Pridham, J. B. *Free Radical Res.* **1995**, *22*, 375–383.
- Vinson, J. A.; Yong, H.; Su, X.; Ligia, Z. J. Agric. Food Chem. 1998, 46, 3630–3634.
- Kujala, T.; Klika, K.; Ovcharenko, V.; Loponen, J.; Vienola, M.; Pihlaja, Z. Naturforsch. 2001, 56c, 714–718.
- Prota, G. *Melanins and melanogenesis*; Academic: San Diego, 1992.
- 9. Mason, H. S. In *Pigment cell growth*; Gordan, M., Ed.; Academic: New York, 1953.
- Memoli, S.; Napolitano, A.; d'Ischia, M.; Misuraca, G.; Palumbo, A.; Prota, G. *Biochim. Biophys. Acta* 1996, *1346*, 61.
- Prota, G.; Misuraca, G. In Melanogenesis and malignant melanoma: biochemistry, cell biology, molecular biology, pathophysiology, diagnosis and treatment; Hori, Y., Hearing, V. J., Nakayama, J., Eds.; Elsevier: Amsterdam, 1996; p 49.
- (a) Napolitano, A.; Pezzella, A.; Rosaria, M.; Prota, V.; Prota, G. *Tetrahedron* **1995**, *51*, 5913–5920. (b) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron* **1995**, *51*, 5631–5642.
- Napolitano, A.; Corradini, M.; Prota, G. *Tetrahedron Lett.* 1985, 26, 2805–2808.
- (a) Desarbre, E.; Bergman, J. J. Chem. Soc., Perkin Trans. 1 1998, 2009–2016. (b) Berens, U.; Brown, J.; Long, J.; Selke, R. Tetrahedron: Asymmetry 1996, 7, 285–292.
- Pines, S. H.; Karady, S.; Sletzinger, M. J. Org. Chem. 1968, 33, 1758–1761.
- Lee, F. G. H.; Suzuki, J.; Dickson, D. E.; Manian, A. A. J. Heterocycl. Chem. 1972, 387–392.
- (a) Marshall, J. A. Chem. Rev. 2000, 100, 3163-3185. (b) Li, G.; Bittman, R. Tetrahedron Lett. 2000, 41, 6737-6741.
  (c) Kosngi, M.; Shimuzu, K.; Ohtami, A.; Migita, T. Chem. Lett. 1981, 829. (d) Kosugi, M.; Ohya, T.; Migita, T. Bull. Chem. Soc. Jpn 1983, 56, 3855-3856.
- Gorzynski, M.; Rewicki, D. Liebigs Ann. Chem. 1986, 625-637.
- (a) Scott, T. C.; Söderberg, B. C. G. *Tetrahedron Lett.* 2002, 43, 1621–1624. (b) Albéniz, A. C.; Espinet, P.; Martín-Ruiz, B. *Chem. Eur. J.* 2001, 7, 2481–2489. (c) Furness, M. S.; Robinson, T. P.; Goldsmith, D. J.; Bowen, J. P. *Tetrahedron Lett.* 1999, 40, 459–462. (d) Cuevas, J.-C.; Pat, I. P.; Snieckus, V. *Tetrahedron Lett.* 1989, 30, 5841–5844.
- 20. (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. J. Org. Chem. 1994, 59, 5905-5911.
  (b) Liebeskind, L. S.; Fengi, R. W. J. Org. Chem. 1990, 55, 5359-5364.
- 21. (a) Rossi, K.; Bellina, F.; Raugei, E. Synlett 2000, 1749–1752.
  (b) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. J. Org. Chem. 1993, 58, 5434–5444. (c) Friesen, R. W.; Sturino, C. F. J. Org. Chem. 1990, 55, 2572–2574. (d) Dubois, E.; Beau, J.-M. Tetrahedron Lett. 1990, 31, 5165–5168.
  (e) Farina, V.; Roth, G. P. Tetrahedron Lett. 1991, 32,

4243–4246. (f) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L.; Spririkhin, L. V. *Synthesis* **1989**, 625.

- (a) Shirakawa, E.; Murota, Y.; Nakao, Y.; Hiyama, T. Synlett 1997, 1143–1144.
   (b) Alcaraz, L.; Taylor, R. J. K. Synlett 1997, 791–792.
- 23. Piers, E.; Gladstone, P. L.; Yee, J. G. K.; McEachern, E. J. *Tetrahedron* **1998**, *54*, 10609–10626.
- (a) Farina, V.; Krishnamarthy, V.; Scott, W. J. Organic reactions; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 50. (b) Farina, V.; Krishnan, B. J. Am. Chem. Soc. 1991, 113, 9585–9595. (c) Farina, V.; Buker, S. R.; Benigni, D. A.; Hausk, S. I.; Sapino, C. J. Org. Chem. 1990, 55, 5833–5847. (d) Beletskaya, I. P. J. Organomet. Chem. 1983, 250, 551–564.
- (a) Kraus, G. A.; Wang, X. Synth. Commun. 1998, 28, 1093–1096. (b) Yang, Y.; Wong, H. N. C. Tetrahedron 1994, 50, 9583–9608. (c) Zaluski, M.-C.; Robba, M.; Bonhomme, M. Bull. Soc. Chim. Fr. 1970, 1838–1846.
- Preparation of 3,4-dibromofuran using this method resulted in less than 5% yield in all variations attempted.
- 27. (a) Farina, V.; Krishnan, B. J. Am. Chem. Soc. 1991, 113, 9585–9595. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. J. Am. Chem. Soc. 1987, 109, 2393–2401.
- Tidwell, J. H.; Buchwald, S. L. J. Am. Chem. Soc. 1994, 116, 11797–11810.
- Orito, K.; Hatakeyama, T.; Takeo, M.; Suginome, H. *Synthesis* 1995, 1273–1277.
- Hine, J.; Halm, S.; Miles, D. E.; Ahn, K. J. Org. Chem. 1985, 50, 5092–5096.

- 31. Yang, Y.; Wong, H. N. C. Tetrahedron 1994, 50, 9583-9608.
- 32. Mee, S. P. H.; Lee, V.; Baldwin, J. E. Synth. Commun. 2003, 33, 3205–3209.
- Littke, A. F.; Schwarz, L.; Fu, G. C. J. Am. Chem. Soc. 2002, 124, 6343–6348.
- Mee, S. P. H.; Lee, V.; Baldwin, J. E. Angew. Chem., Int. Ed. 2004, 43, 1132–1136.
- 35. Bellamy, F. D.; Ou, K. Tetrahedron Lett. 1984, 25, 839-842.
- McElhanon, J. R.; Wu, M.-J.; Escobar, M.; Chaudhry, U.; Hu, C.-L.; McGrath, D. V. J. Org. Chem. 1997, 62, 908–915.
- Benigni, J. D.; Minnis, R. L. J. Heterocycl. Chem. 1965, 387–392.
- Sinhahabu, A. K.; Borchardt, R. T. J. Org. Chem. 1983, 48, 3347–3349.
- Bray, B. L.; Mathies, P. H.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. J. Org. Chem. **1990**, 55, 6317–6328.
- 40. (a) Kabir, H.; Miura, M.; Sasaki, S.; Harada, G.; Kuwatani, Y.; Yoshida, M.; Iyoda, M. *Heterocycles* 2000, *52*, 761–774.
  (b) Rajca, A.; Wang, H.; Bolshov, P.; Rajca, S. *Tetrahedron* 2001, *57*, 3725–3735.
- (a) Bumagin, N. A.; Nikitina, A. F.; Beletskaya, I. P. *Russ.* J. Org. Chem. **1994**, 30, 1619–1629. (b) Haung, J.; Nolan, S. P. J. Am. Chem. Soc. **1999**, 121, 9889–9890.
- 42. Kuroboshi, M.; Waki, Y.; Tanaka, H. Synlett 2002, 637-639.
- 43. (a) Capon, B.; Kwok, F.-C. J. Am. Chem. Soc. 1989, 111, 5346–5356. (b) Capon, B.; Kwok, F.-C. Tetrahedron Lett. 1986, 27, 3275–3278.
- 44. Harris, R. K.; Becker, E. D.; De Menezes, S. M. C.; Goodfellow, R.; Granger, P. Pure Appl. Chem. 2001, 73, 1795–1818.