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The Synthesis of Novel Isoindoline Nitroxides Bearing Water-Solubilising Functionality

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A range of novel tetramethyl- and tetraethylisoindoline nitroxides, possessing aryl-linked carboxylic acids, amines, alcohols and phosphonic acids were prepared. Notably, the chemistry established for the aromatic dibromination of the tetramethylisoindolines was not easily transferred to the corresponding tetraethylisoindoline system. Instead, various tetraethylisoindoline analogues were accessed by the oxidation of methyl groups attached to the aromatic ring to give the carboxylic acids. The increased steric bulk of the tetraethyl structures should limit bio-reduction and these compounds may have potential as antioxidants.

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Introduction

Nitroxides are stable free-radical species currently utilised in a variety of applications including as synthetic tools.[1–3] Although the piperidine- and pyrrolidine-based nitroxides are the most commonly used, some isoindoline nitroxides possess advantages over these commercially available species. The fused aromatic moiety of isoindoline nitroxides provides structural rigidity and enhanced thermal and chemical stability in polymers.[4,5] They also possess superior electron paramagnetic resonance (EPR) line widths[6] and their structural diversity can easily be expanded by aromatic substitution to generate more complex structures for a range of applications.[7–9]

In biological systems, nitroxides are commonly used as potent antioxidants.[10,11] Their redox- and radical-trapping properties can reduce levels of oxidative stress in cellular systems caused by reactive oxygen species (ROS)[12–16] and they can also provide radio-protection towards ionising radiation.[17–19] Many disease states, such as Alzheimer's disease, Parkinson's disease, cancer and aging, are implicated by increased levels of oxidative stress.

Our group has focused on the use of isoindoline nitroxides to reduce oxidative stress on cells affected by the genetic disease *Ataxia telangiectasia* (A-T). This disease is characterised by neurodegeneration, immunodeficiency and cancer predisposition, and one symptom is elevated levels of ROS.[20] The full potential of isoindoline aminoxyls in this area has been limited somewhat by a lack of structural variation, especially concerning water solubility. To date, the most effective isoindoline nitroxide for reducing radiation-induced oxidative stress on cells affected with A-T is 5-carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (**1**, CTMIO, Figure 1).[13] CTMIO (**1**) has also been used as a successful antioxidant in an A-T mouse model where treated purkinje neurons of A-T-mutated mice displayed increased dendritic growth.[21] In cell viability assays, 5,6-dicarboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (**2**, DCTMIO, Figure 1) has given similar results to CTMIO (**1**).[22]

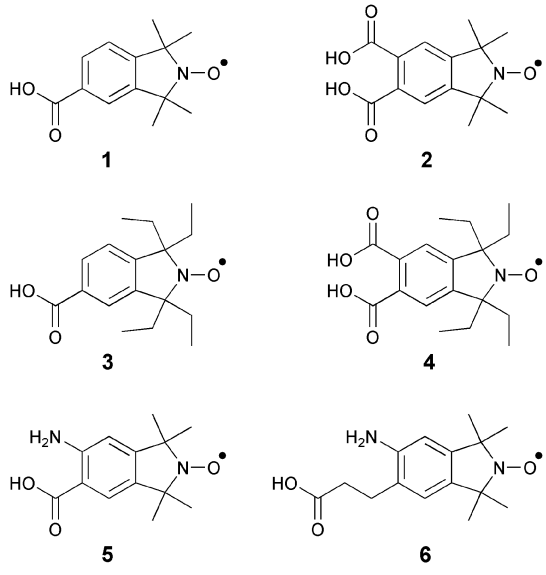

Figure 1. Structural analogues of the parent isoindoline nitroxide CTMIO (**1**).

In order to gain a more detailed insight into the antioxidant behaviour displayed by CTMIO (**1**) in cells affected with A-T and also potentially in other diseases involving oxidative stress, we desired access to new water-soluble de-

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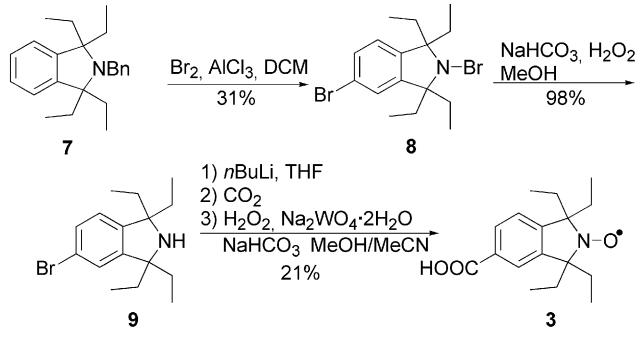
rivatives of CTMIO (**1**). Of particular interest were analogues with bulkier ethyl groups surrounding the nitroxide radical as these should be more resistant to bio-reduction in vivo.[23] Thus, compounds **3** and **4** with one or two carboxylic acid groups on the aromatic ring bearing tetraethyl substitution around the nitroxide moiety were initially targeted. We also sought to prepare amino acid derivatives **5** and **6**, which contain both carboxylic acid and amine groups on the aromatic ring. Herein, we report the synthesis of a range of novel isoindoline nitroxides possessing water-solubilising functionality.

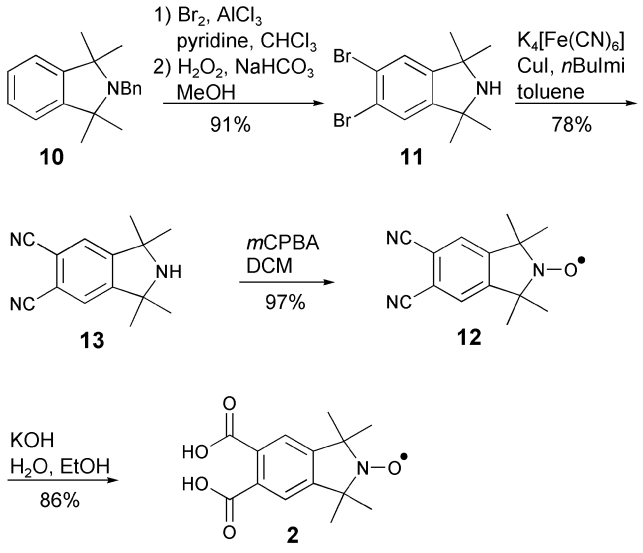
Results and Discussion

To access 5-carboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (**3**, CTEIO), we pursued the route previously used to synthesise CTMIO (**1**).[24] Treatment of 2-benzyl-1,1,3,3-tetraethylisoindoline (**7**) with bromine in the presence of anhydrous aluminium trichloride gave 2,5-dibromo-1,1,3,3-tetraethylisoindoline (**8**) in modest yield (30%) (Scheme 1) after purification by column chromatography to remove the benzaldehyde which results from oxidative cleavage of the benzyl group by bromine.[25] Subsequent reduction of bromoamine **8** with hydrogen peroxide in the presence of sodium hydrogen carbonate afforded 5-bromo-1,1,3,3-tetraethylisoindoline (**9**) in high yield (98%). The corresponding tetramethyl derivative could, at this stage, be separated from the benzaldehyde side-product by acid-base extraction. However, the presence of the more organic solubilising ethyl groups in **9** did not allow this work-up and the removal of benzaldehyde-required chromatography. Lithiation of bromoamine **9**, reaction with carbon dioxide and subsequent oxidation with hydrogen peroxide in the presence of a tungstate catalyst gave the desired nitroxide 5-carboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (**3**) in modest yield (21%).



Scheme 1.

The reported synthesis of DCTMIO (**2**) entails double bromination of 2-benzyl-1,1,3,3-tetramethylisoindoline (**10**) to give dibromoamine **11**,[25] oxidation to the nitroxide,[25] palladium(0)-catalysed coupling of the nitroxide with zinc cyanide to afford dinitrile **12**[26] and final hydrolysis of **12** to furnish DCTMIO (**2**).[27] Optimisation of this procedure for the synthesis of DCTMIO (**2**) was required before it could be applied to prepare 5,6-dicarboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (**4**, DCTEIO). The dibromination of **8** with bromine, aluminium trichloride and catalytic pyridine to give **11** was found to proceed in a significantly higher yield (91% compared to ca. 50% previously)[25] when only 7 equiv. of bromine were used in chloroform rather than carbon tetrachloride (Scheme 2). In our hands, however, the subsequent palladium-catalysed cyanation of **11** or of the corresponding dibromo nitroxide was found to be highly unreliable as repetitive coupling reactions under presumably identical reaction conditions often gave no conversion of the starting material to the desired dicyanides **12** or **13** (yields for both couplings ranged from 0 to 95%).



Scheme 2.

As an alternative, we sought to apply a recently described procedure using copper(I) iodide and *n*-butylimidazole (*n*BuImi) which facilitates the conversion of aryl bromides to benzonitriles in the presence of non-toxic potassium hexacyanoferrate.[28] Initial attempts to convert the dibromo nitroxide to the desired dinitrile nitroxide **12** under these conditions led to a complex mixture of products which may have resulted from the interaction of copper(I) with the nitroxide moiety. Notably, the analogous copper(I)-catalysed coupling reaction of the dibromoamine **11** proceeded smoothly and gave the desired dinitrile **13** in good yield (78%) following recrystallisation to remove an *n*-butylimidazole side-product [possibly a copper(I)–*n*-butylimidazole complex, which could not be removed following acid-base work-up or column chromatography]. Subsequent oxidation of **13** with *m*-chloroperbenzoic acid (*m*CPBA) provided the dinitrile nitroxide **12** in high yield (97%). Final basic hydrolysis of **12** with potassium hydroxide furnished the targeted DCTMIO (**2**) in 86% yield (Scheme 2).

The optimised synthesis for DCTMIO (**2**) could now be investigated as a route towards the preparation of the desired tetraethyl derivative, DCTEIO (**4**). Treatment of 2-benzyl-1,1,3,3-tetraethylisoindoline (**7**) with bromine, aluminium trichloride and catalytic pyridine in chloroform, followed by *N*-bromoamine reduction gave a complex mix-

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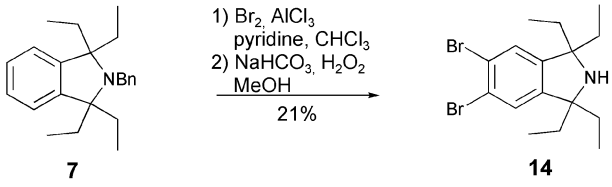
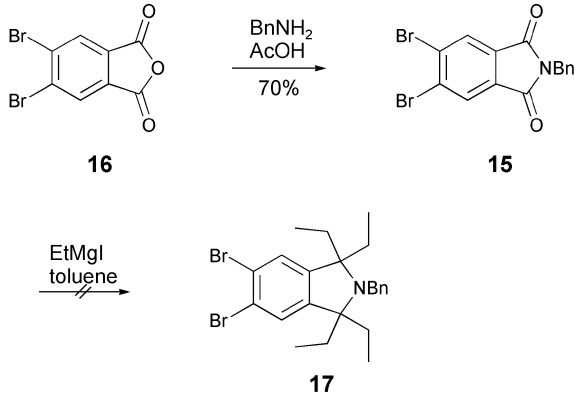
ture of products after analysis by ^{1}H NMR spectroscopy and TLC. However, some of the desired dibrominated product **14** could be isolated from the mixture after an acid-base extraction using diethyl ether in 21% yield (Scheme 3). Further attempts to increase the yield of **14** by varying the equivalents of bromine and/or aluminium trichloride used in the reaction were unsuccessful. Opening of the pyrrolidine ring may have caused the observed mixture of products. Application of milder brominating agents such as *N*-bromosuccinimide or the *N*-bromosuccinimide-bromine system led to no reaction.



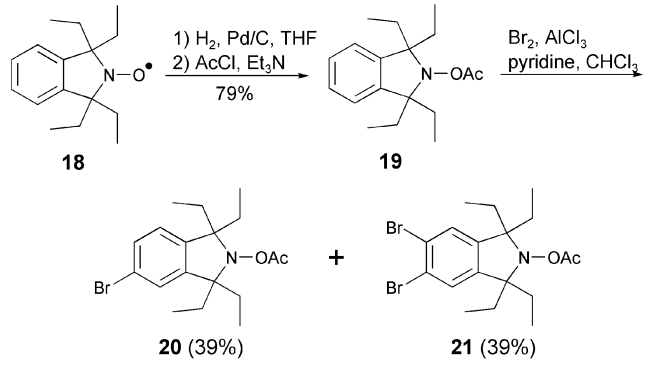
Scheme 3.

Another strategy to prepare **14** involved exhaustive ethylation of an already brominated system. Rassat[29] has previously shown that the monobromo analogue of **15** undergoes tetraethylation with EtMgBr in 25% yield. Thus, we prepared 4,5-dibromophthalic anhydride (**16**) by permanganate oxidation of 4,5-dibromo-*o*-xylene and subsequent cyclisation of the diacid using established literature procedures.[30] The anhydride **16** was easily converted into the corresponding phthalimide **15** (Scheme 4) using benzylamine in acetic acid in good yield (70%), however attempted ethylation of **15** using EtMgI in toluene gave a complex mixture which contained neither the desired product **17** nor the starting material **15**.



Scheme 4.

Following this reaction, it was decided that the ethyl groups must be introduced prior to bromination of the aromatic ring. Therefore, in order to suppress potential ring opening of the tetraethyl-substituted pyrrolidine moiety during the bromination process, the use of a suitable protecting group was required (the benzyl group is known to be cleaved by bromine before aromatic bromination occurs).[25] As the final desired product is a nitroxide, it seemed logical to continue the synthesis with a protected nitroxide. Accordingly, 1,1,3,3-tetraethylisoindolin-2-yloxyl (**18**) was prepared using literature methods by debenzylation of **7** and subsequent oxidation to the nitroxide.[31] Reduction of **18** by hydrogenation to the corresponding hydroxylamine, followed by reaction with acetyl chloride in the presence of base gave the acetyl-protected nitroxide **19** (Scheme 5).[32] Treatment of **19** with bromine, aluminium trichloride and catalytic pyridine, with a prolonged reaction time of 3 d at room temperature, led to the formation of a 1:1 mixture of the mono-brominated and the di-brominated derivatives **20** and **21** (by ^{1}H NMR spectroscopy), which could not be separated by column chromatography. Raising the reaction temperature to 60 °C failed to increase the yield of **21** but increased product decomposition. The mixture of **20** and **21** was submitted to copper(I)-mediated cyano coupling, however a complex mixture was obtained, possibly indicating that the acetyl-protecting group is labile under these reaction conditions. A different approach was therefore required for the introduction of carboxy groups onto the aromatic ring.



Scheme 5.

Another route to aromatic carboxylic acids involves the oxidation of methyl groups attached to the aromatic ring. In our system, an aromatic ring with methyl side chains should be tolerable of the Grignard reaction required to introduce the four ethyl substituents. Oxidation of the methyl groups at a later stage of the synthesis should then afford the desired carboxylic acid groups. Hence, 4,5-dimethylphthalic anhydride (**22**) was prepared according to the literature by a Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene and maleic anhydride,[33] followed by aromatisation using bromine[34] to give **22**. Subsequent reaction of **22** with benzylamine gave 2-benzyl-5,6-dimethylphthalimide (**23**) in an excellent yield (91%) (Scheme 6), which when treated with EtMgI in refluxing toluene afforded 2-benzyl-5,6-dimethyl-1,1,3,3-tetraethylisoindoline (**24**) in a moderate yield (50%). Reaction of **24** with permanganate led to oxidisation of the aromatic methyl moieties as well as the benzyl CH_2 group to give benzamide **25** (75% yield). The same product **25** was obtained when a Jones-oxidation of **24** was performed. Unfortunately, **25** proved to be extremely stable as attempts to hydrolyse the amide group under acidic or basic conditions failed to form the desired amine **26**. To remove the amide group, we reduced **25** with

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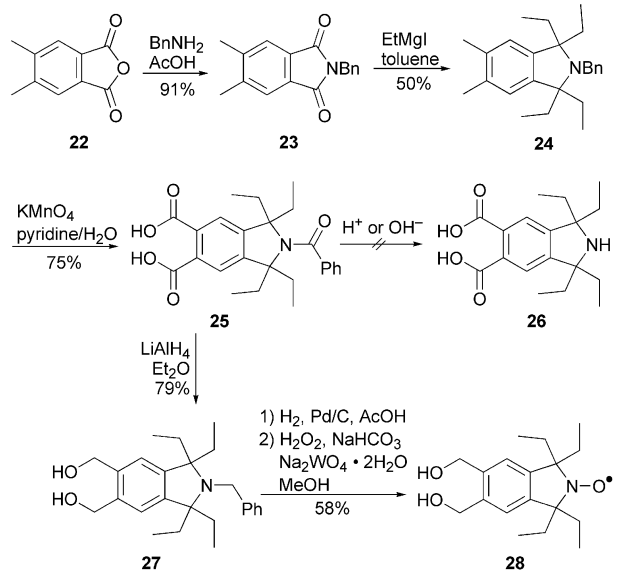
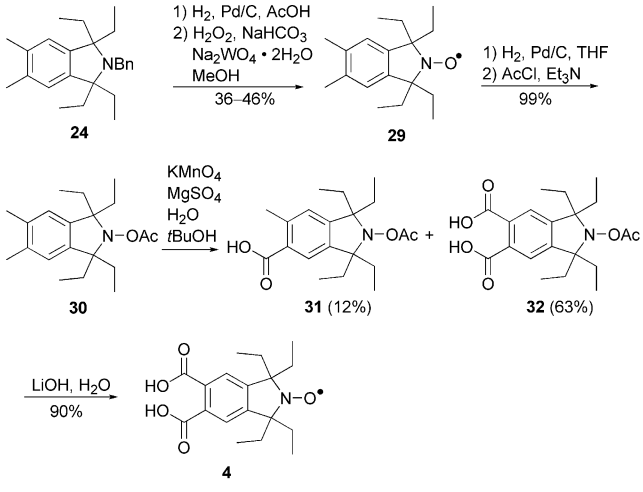
lithium aluminium hydride to afford diol **27** in good yield (79%). Subsequent debenzylation and oxidation to the corresponding nitroxide **28** occurred in moderate yield, however attempts to oxidise the alcohol moieties with permanganate or Jones' reagent to the desired DCTEIO **4** were unsuccessful. Furthermore, attempted oxidation of the nitroxide **29** (formed by hydrogenation and oxidation of **24**, Scheme 7) gave a complex mixture of products under both permanganate and Jones-oxidation conditions.



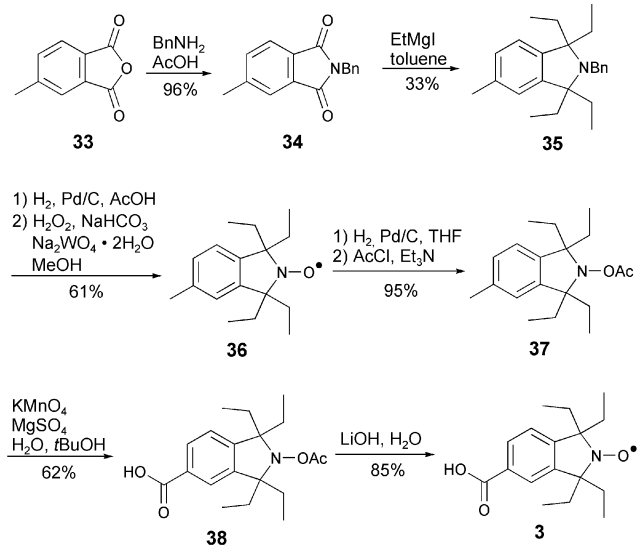
Scheme 6.



Scheme 7.

As the nitroxide moiety was not stable under oxidative conditions, we decided to employ an acetate protecting group, which should be stable during the oxidation provided that it is carried out in the absence of strong acid or base. Reduction of nitroxide **29** to the corresponding hydroxylamine and in situ reaction with acetyl chloride furnished the acetyl-protected nitroxide **30** in high yield (99%) (Scheme 7). Subsequent base-free permanganate oxidation in the presence of magnesium sulfate[35] at 90 °C caused complete decomposition of the starting material **30**. Decomposition could largely be avoided when the oxidation was performed at 70 °C, yet a mixture of the mono-oxidised and di-oxidised products **31** and **32** were obtained in yields of 12 and 63%, respectively. Extending the reaction time along with the repeated addition of extra permanganate failed to increase the conversion of **31** into the di-acid **32**. Fortunately, **32** could be separated by column chromatography and subsequent mild hydrolysis with lithium hydroxide gave the desired 5,6-dicarboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (**4**) in good yield (90%).

In an attempt to improve the yield of CTEIO (**3**), we employed the same route used successfully to prepare DCTEIO (**4**). Commercially available 4-methylphthalic anhydride (**33**) was treated with benzylamine in acetic acid to give 2-benzyl-4-methylphthalimide (**34**) in high yield (96%) (Scheme 8). Exhaustive ethylation of phthalimide **34** with EtMgI afforded 2-benzyl-5-methyl-1,1,3,3-tetraethylisoindoline (**35**) in a modest yield (33%). Transformation to the nitroxide **36** was achieved by cleavage of the benzyl group and oxidation with hydrogen peroxide and sodium tungstate in a 61% yield. Subsequent reduction with hydrogen and reaction with acetyl chloride gave acetate **37**, which underwent permanganate oxidation to yield acid **38** in good yield (62%). Final acetate hydrolysis with lithium hydroxide gave CTEIO (**3**) in high yield (85%). The overall yield for this synthetic route following tetraethylation was significantly higher (≈ 30%, Scheme 8) than that obtained for the initial synthetic pathway (6%, Scheme 1).



Scheme 8.

Another functional group which imparts water solubility is a phosphonic acid. By converting the hydroxy groups of **27** into better leaving groups, the introduction of phosphonate groups can be achieved. Accordingly, the dibromo analogue **39** was formed by reaction of the diol **27** with phosphorus tribromide in DCM (Scheme 9). Heating of **39**

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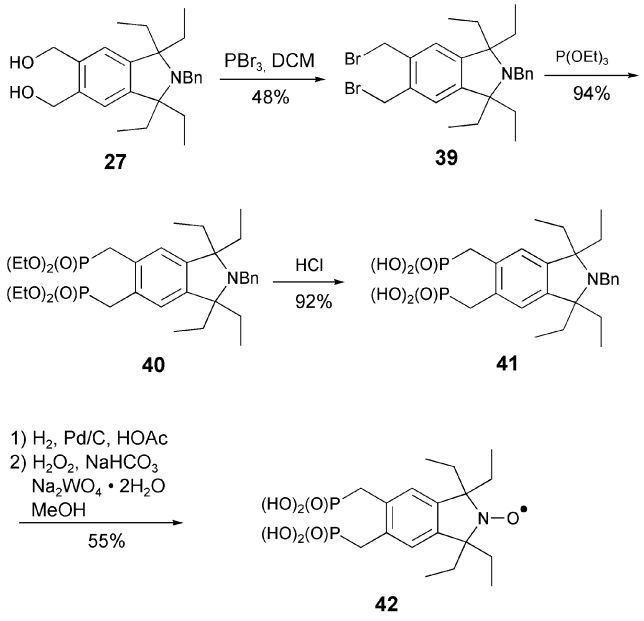
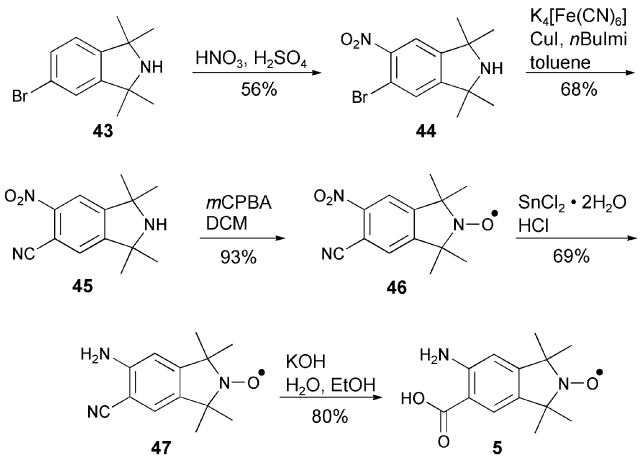
in neat triethyl phosphite gave the diphosphonate **40** in high yield (94%). Acidic hydrolysis gave the corresponding diphosphonic acid derivative **41** which underwent debenzylation and subsequent oxidation to the nitroxide to afford the desired diphosphonic acid nitroxide **42** in moderate yield (55%).



Scheme 9.

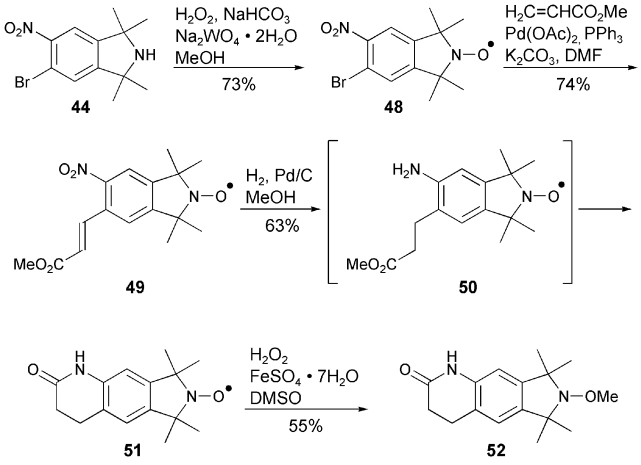
With the targeted CTEIO (**3**) and DCTEIO (**4**) molecules in hand, we turned our attention towards the synthesis of the desired tetramethyl amino acid derivatives **5** and **6**. Nitration of 5-bromo-1,1,3,3-tetramethylisoindoline (**43**) was achieved by treatment with nitric acid in sulfuric acid to give the bromo-nitro nitroxide **44** in moderate yield (56%) (Scheme 10). Initial attempts to form the desired amino acid **5** by lithiation of **44** and subsequent reaction with either solid or gaseous carbon dioxide were unsuccessful, giving only complex mixtures of reaction products. However, copper(I) catalysed cyanation of **44** afforded the cyano-nitro substituted isoindoline **45** which could readily be oxidised to the corresponding nitroxide **46** using *m*-chloroperbenzoic acid (*m*CPBA) in 93% yield. Surprisingly, conversion of the cyano moiety into a carboxylic acid group by basic hydrolysis gave a mixture of compounds and a significant amount of decomposition. Thus, the reverse reaction strategy was pursued and reduction of the nitro moiety was attempted prior to hydrolysis of the cyano group. The reduction of the nitro group was achieved using tin(II) dichloride dihydrate to give the amino-cyano nitroxide **47** in a moderate yield of 69%. Final treatment of **47** with aqueous base led to hydrolysis of the cyano group and the targeted 5-amino-6-carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (**5**) was isolated in 80% yield.

In order to obtain an ethyl-extended version of 5-amino-6-carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (**5**), the bromo-nitro derivative **44** was oxidised to the nitroxide **48**



Scheme 10.

(Scheme 11). Subsequent Pd-catalysed Heck coupling with methyl acrylate provided acrylate **49** in good (74%) yield. Reduction of both the nitro group and the double bond was achieved by palladium-catalysed hydrogenation of **49**, however the desired product **50** could not be isolated as it cyclised immediately to form the corresponding lactam **51**, which could be isolated in a moderate yield of 63%. The formation of **51** was confirmed following the preparation of methoxyamine **52** by the treatment of lactam **51** with methyl radicals generated from dimethyl sulfoxide, ferrous ions and hydrogen peroxide. Unfortunately, the lactam moiety in **51** proved to be extremely stable and could not be opened to the corresponding amino acid derivative **6** by hydrolysis under acidic or basic conditions. In order to avoid lactamisation of **51**, the methyl ester moiety of **49** was first hydrolysed to the corresponding acid in quantitative yield. However, subsequent attempted reduction of both the nitro group and the double bond by hydrogenation gave a crude reaction mixture, which decomposed upon purification by column chromatography. Thus, the targeted 5-amino-6-carboxyethyl-1,1,3,3-tetramethylisoindolin-2-yloxyl (**6**) could not be accessed by this route, however an interesting lactam nitroxide **51** was prepared.



Scheme 11.

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Conclusions

An improved procedure for the synthesis of DCTMIO (**2**) was developed in an overall yield of 59% from 2-benzyl-1,1,3,3-tetramethylisoindoline (**10**). The key step involved dicyanation of the dibromoamine **11** in the presence of copper(I) iodide and *n*-butylimidazole. This route, however, was ineffective for the preparation of DCTEIO (**4**) as the initial dibromination of 2-benzyl-1,1,3,3-tetramethylisoindoline (**7**) was low yielding (21%), possibly due to opening of the pyrrolidine ring. Hence, several alternative routes to **4** were explored. Both tetraethylation of 2-benzyl-5,6-dibromophthalimide (**15**) and cyanide coupling of 2-acetoxy-5,6-dibromo-1,1,3,3-tetraethylisoindoline (**21**) were unsuccessful. Similarly, oxidation of 2-benzyl-5,6-dimethyl-1,1,3,3-tetraethylisoindoline (**24**) and subsequent hydrolysis of the resulting benzamide **25** with acid or base failed to give the desired amine **26**. The desired compound **4** could be obtained by conversion of **24** to the nitroxide, acetate protection of the nitroxide, oxidation of the methyl groups attached to the aromatic ring with permanganate and basic removal of the acetate group in an overall yield of 26% yield (from **24**). CTEIO (**3**) could be prepared from 2-benzyl-1,1,3,3-tetramethylisoindoline (**7**) following monobromination, lithiation and reaction with carbon dioxide, and oxidation to the nitroxide **3** in an overall yield of 6%. This yield could be increased to 30% when the same route used successfully to prepare DCTEIO (**4**), starting from commercially available 4-methylphthalic anhydride (**33**), was employed. A diphosphonic acid nitroxide **42** was also synthesised from diol **27** in 4 steps, in an overall yield of 23%. The first example of an amino acid derived isoindoline nitroxide **5** was prepared from 5-bromo-1,1,3,3-tetramethylisoindoline (**43**) in 5 steps, in a 20% overall yield. The synthesis of the carboxyethyl-extended version **6** of the amino acid **5** was investigated but instead of obtaining **6**, only lactam **51** could be isolated. All of the prepared nitroxides are in the process of being tested as antioxidants in A-T cells and results will be reported shortly.

Experimental Section

General Methods: All air-sensitive reactions were carried out under ultra-high purity argon. Ether and toluene were dried by storage with sodium wire. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketal and dichloromethane (DCM) freshly distilled from calcium hydride. Triethylamine and pyridine were dried by storage with potassium hydroxide. Crystalline $K_4[Fe(CN)_6]\cdot 3H_2O$ was ground to a fine powder and then dried at 80 °C at 0.5 Torr for 10 h. 2-Benzyl-1,1,3,3-tetraethylisoindoline[36] (**7**), 2-benzyl-1,1,3,3-tetramethylisoindoline[37] (**10**), 4,5-dibromophthalic anhydride[30] (**16**), 4,5-dimethylphthalic anhydride[30,33,34] (**22**) and 5-bromo-1,1,3,3-tetramethylisoindoline[25] (**43**) were prepared using established literature procedures. All other reagents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 400 spectrometer and referenced to the relevant solvent peak. Low- and high-resolution mass spectra were recorded at the Australian National University (ANU) using either a Micromass autospec double focusing magnetic sector mass spectrometer (EI^+ spectra) or a Bruker Apex 3 fourier transform ion cyclotron resonance mass spectrometer with a 4.7-T magnet (ESI^+ spectra). Formulations were calculated in the elemental analysis programs of Mass Lynx 4.0 or Micromass Opus 3.6. Fourier transform infrared (FTIR) spectra were recorded on a Nicolet 870 Nexus Fourier Transform Infrared Spectrometer equipped with a DTGS TEC detector and an ATR objective. Elemental analyses were carried out by the University of Queensland Microanalytical Service. Melting points were measured with a GallenKamp Variable Temperature Apparatus by the capillary method and are uncorrected.

2,5-Dibromo-1,1,3,3-tetraethylisoindoline (8): 2-Benzyl-1,1,3,3-tetraethylisoindoline (**7**) (5.00 g, 15.60 mmol) was dissolved in DCM (50 mL) under argon. The solution was cooled on ice and a solution of bromine (1.80 mL, 35 mmol) in DCM (38 mL) was added dropwise, followed by the immediate addition of aluminum trichloride (7.50 g, 56.30 mmol). The solution was stirred at 0 °C for 1 h and then poured onto ice (50 mL). After 30 min of vigorous stirring, the mixture was basified with sodium hydroxide (5 M aqueous solution) and extracted with DCM (3 × 60 mL). The DCM layers were washed with brine (2 × 60 mL) and concentrated at reduced pressure to give an orange oil. Purification by column chromatography (eluent DCM/hexane, 3:7) gave 2,5-dibromo-1,1,3,3-tetraethylisoindoline (**8**) as a pale orange oil (1.90 g, 31%), containing trace amounts (<5% by ^{1}H NMR) of 2,5,6-tribromo-1,1,3,3-tetraethylisoindoline. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.92 (m, 12 H, 4 × CH_3), 1.6–1.79 (m, 8 H, 4 × CH_2), 6.94 (d, J = 8.1 Hz, 1 H, H7), 7.2 (d, J = 1.8 Hz, 1 H, H6), 7.33 (dd, J = 8.1, 1.8 Hz, 1 H, H4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8 (CH_3), 33.58 (CH_2), 33.62 (CH_2), 68.2 (C_{quat}), 68.3 (C_{quat}), 120.3 (C_{quat}) 124.0 (CH), 125.6 (CH), 129.6 (CH), 146.5 (C_{quat}), 150.0 (C_{quat}) ppm. MS (EI): m/z (%) = 389 (40), 387/391 (20) [M^+].

5-Bromo-1,1,3,3-tetraethylisoindoline (9): Sodium hydrogen carbonate (0.40 g, 4.77 mmol) was added to a solution of 2,5-dibromo-1,1,3,3-tetraethylisoindoline (**8**) (1.00 g, 2.57 mmol) in methanol (10 mL). Hydrogen peroxide (30% aqueous solution, ≈ 15 mL) was then added slowly until the observed effervescence ceased (ensuring that some sodium hydrogen carbonate remained). The solution was acidified with hydrochloric acid (2 M aqueous solution) and extracted with DCM (3 × 50 mL). The DCM layers were dried (anhydrous $MgSO_4$) and concentrated in vacuo to give 5-bromo-1,1,3,3-tetraethylisoindoline (**9**) as a pale yellow solid (0.78 g, 98%) containing trace amounts (<5% by ^{1}H NMR) of 5,6-dibromo-1,1,3,3-tetraethylisoindoline (**14**); m.p. > 250 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (br. s, 12 H, 4 × CH_3), 2.1–2.25 (m, 4 H, 2 × CH_2), 2.3–2.45 (m, 4 H, 2 × CH_2), 7.02 (d, J = 8.06 Hz, 1 H, H7), 7.26 (d, J = 1.63 Hz, 1 H, H6), 7.49 (dd, J = 8.04, 1.63 Hz, 1 H, H4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.76 (CH_3), 8.8 (CH_3), 30.73 (CH_2), 30.78 (CH_2), 75.9 (C_{quat}), 76.0 (C_{quat}), 122.4 (C_{quat}), 124.7 (CH), 126.3 (CH), 131.7 (CH), 139.8 (C_{quat}), 143.1 (C_{quat}) ppm. MS (ES): m/z (%) = 310/312 (100) [MH^+]. HRMS: calcd. for $C_{16}H_{25}{}^{81}Br_2N$ [MH^+] 312.1144; found 312.1150. HRMS: calcd. for $C_{16}H_{25}{}^{79}Br_2N$ [MH^+] 310.1170; found 310.1163.

5-Carboxy-1,1,3,3-tetraethylisoindol-2-yloxyl (3): *n*-Butyllithium (1.60 M in hexanes, 5.76 mL, 9.22 mmol) was added slowly to a solution of 5-bromo-1,1,3,3-tetraethylisoindoline (**9**) (1.30 g, 4.19 mmol) in dry THF (12 mL) at –78 °C under argon. After stirring for 10 min, the solution was poured onto a slurry of powdered dry ice and dry THF (40 mL total). The mixture was stirred until it reached room temperature and then concentrated to dryness. The resulting residue was dissolved in diethyl ether (50 mL) and extracted with hydrochloric acid (2 M aqueous solution, 2 × 30 mL).

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The ether layers were dried (anhydrous $MgSO_4$) and concentrated in vacuo. The resulting residue was dissolved in a mixture of methanol (20 mL), water (10 mL) and acetonitrile (15 mL). The solution was treated with sodium hydrogen carbonate (0.29 g, 3.40 mmol) and sodium tungstate dihydrate (0.13 g, 0.38 mmol), followed by the addition of hydrogen peroxide solution (30%, 2.5 mL). The solution was stirred at ambient temperature for 24 h, extra hydrogen peroxide solution (30%, 0.50 mL) added and the solution stirred for a further 72 h. The mixture was basified with sodium hydroxide (2 M aqueous solution) and extracted with diethyl ether (3 × 60 mL) and the ether layers discarded. The basic layers were acidified with hydrochloric acid (2 M aqueous solution) and extracted with diethyl ether (3 × 60 mL). The ether layers were dried (anhydrous $MgSO_4$) and concentrated at reduced pressure to give a yellow oil which solidified upon standing (0.25 g, 21%). Recrystallisation from acetonitrile gave yellow crystals; m.p. 97–99 °C. MS (ES): *m*/*z* (%) = 289 (100) $[M - H]^-$. HRMS (ES): *m*/*z*: calcd. for $C_{17}H_{23}NO_3$ $[(M - H)^-]$: 289.1678; found 289.1679. $C_{17}H_{24}NO_3$ (290.18): calcd. C 70.32, H 8.33, N 4.82; found C 70.29, H 8.35, N 4.77.

5,6-Dibromo-1,1,3,3-tetramethylisoindoline (11): A solution of 2-benzyl-1,1,3,3-tetramethylisoindoline (**10**) (5.31 g, 20.0 mmol, 1.00 equiv.) in $CHCl_3$ (100 mL) was cooled to 0 °C and treated with pyridine (539 μL, 6.67 μmol, 0.33 equiv.). Bromine (7.17 mL, 140 mmol, 7.00 equiv.) was added dropwise and the reaction mixture was stirred for 10 min. $AlCl_3$ (8.00 g, 60.0 mmol, 3.00 equiv.) was added and stirring was continued for 18 h whilst warming to ambient temperature. The reaction mixture was carefully added to 5 M aq. NaOH solution (100 mL) cooled to 0 °C. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were concentrated under reduced pressure. The residue was taken up in MeOH (100 mL) and treated with $NaHCO_3$ (2.52 g, 30.0 mmol, 1.50 equiv.). Hydrogen peroxide (4.12 mL, 40.0 mmol, 30% in H_2O, 2.00 equiv.) was added dropwise. The obtained reaction mixture was stirred for 5 min and then concentrated to ca. 1/3 of its volume. The mixture was cooled to 0 °C, acidified by careful addition of 2 M aq. H_2SO_4 solution (100 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were discarded. The aqueous layer was basified by careful addition of 5 M aq. NaOH solution (pH ≈ 12) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by filtration through SiO_2 (120 g, EtOAc, change to EtOAc/MeOH, 10:1 when product starts to come off) to give 6.08 g of **11** as a pale yellow oil which solidified when kept at ambient temperature (18.3 mmol, 91%). The spectroscopic data acquired for **11** was consistent with that previously reported in the literature.[25]

5,6-Dicyano-1,1,3,3-tetramethylisoindoline (13): 5,6-Dibromo-1,1,3,3-tetramethylisoindoline (**11**) (3.33 g, 10.0 mmol, 1.00 equiv.), $K_4[Fe(CN)_6]$ (1.47 g, 4.00 mmol, 0.40 equiv.) and CuI (190 mg, 1.00 mmol, 10 mol-%) were placed in a pressure tube (20 × 2 cm) and Ar was bubbled through the tube for 10 min. Toluene (5 mL) and *n*-butylimidazole (2.63 mL, 20.0 mmol, 2.00 equiv.) were added and Ar was bubbled through the reaction mixture for 10 min. The tube was sealed, warmed to 160 °C and the reaction mixture was vigorously stirred at this temperature for 3 d. The mixture was cooled to ambient temperature, diluted with H_2O (50 mL) and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was filtered through SiO_2 (150 g, EtOAc) and concentrated in vacuo. The residue (consisting of product and complex-bound *n*-butylimidazole) was recrystallised from hexane/EtOAc (5 mL/5 mL) to give 1.42 g of **13** as pale brown needles (6.30 mmol, 63%). Another 343 mg of product was obtained by evaporation of the mother liquor and treatment of the residue with Et_2O/hexane (1.5 mL/1.5 mL) (1.52 mmol, 15%). ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.49 (s, 12 H, CH_3), 7.55 (s, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, add. DEPT): δ = 31.5 (+, CH_3), 63.4 (C_{quat}, CCH_3), 114.9, 115.7 (C_{quat}, CN, Ar-C), 127.3 (+, Ar-C), 155.0 (C_{quat}, Ar-C) ppm. MS (EI): *m*/*z* (%) = 225 (<1) $[M^+]$, 210 (100) $[M^+ - CH_3]$, 194 (86). HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{15}N_3$ $[M^+]$: 225.1266; found 225.1268. $C_{14}H_{15}N_3 \cdot 0.4H_2O$ (232.50): calcd. C 72.32, H 6.85, N 18.07; found C 72.65, H 6.55, N 17.82.

5,6-Dicyano-1,1,3,3-tetramethylisoindolin-2-yloxyl (12): A solution of 5,6-dicyano-1,1,3,3-tetramethylisoindoline (**13**) (1.76 g, 7.81 mmol, 1.00 equiv.) in CH_2Cl_2 (75 mL) was cooled to 0 °C and treated with *m*-chloroperbenzoic acid (2.25 g, 10.0 mmol, concd. 23% H_2O, 1.28 equiv.). The reaction mixture was stirred at 0 °C for 1 h. The cooling bath was removed and stirring was continued for 2.5 h whilst additional CH_2Cl_2 (25 mL) was gradually added to dissolve precipitating solids. The reaction mixture was washed with 5 M aq. NaOH solution (3 × 50 mL) and brine (75 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from MeCN to give 1.82 g of **12** as yellow needles (7.57 mmol, 97%); m.p. 242–245 °C, (Lit.[26] 243–248 °C). MS (EI): *m*/*z* (%) = 240 (57) $[M^+]$, 225 (26) $[M^+ - CH_3]$, 210 (48), 195 (100), 167 (43). HRMS (EI): *m*/*z*: calcd. for $C_{14}H_{14}N_3O$ $[M^+]$: 240.1137; found 240.1138. $C_{14}H_{14}N_3O$ (240.28): calcd. C 69.98, H 5.87, N 17.49; found C 69.82, H 5.81, N 17.46.

5,6-Dicarboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (2, DCTMIO): A suspension of 5,6-dicyano-1,1,3,3-tetramethylisoindolin-2-yloxyl (**12**) (1.20 g, 5.00 mmol, 1.00 equiv.) in H_2O/EtOH (20 mL/4 mL) was treated with KOH (1.40 g, 25.0 mmol, 5.00 equiv.), warmed to 105 °C and stirred at this temperature for 20 h. The reaction mixture was cooled to ambient temperature and washed with Et_2O (20 mL). The Et_2O-layer was discarded. The aqueous layer was acidified with 3 M aq. HCl solution (pH 2) and extracted with Et_2O (5 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from H_2O/MeCN (5:1) to give 1.19 g of DCTMIO (**2**) as light yellow flakes (4.28 mmol, 86%); m.p. 238–240 °C. MS (EI): *m*/*z* (%) = 278 (5) $[M^+]$. $C_{14}H_{16}NO_5 \cdot H_2O$ (296.30): calcd. C 56.75, H 6.12, N 4.73; found C 56.83, H 6.15, N 4.94.

5,6-Dibromo-1,1,3,3-tetraethylisoindoline (14): 2-Benzyl-1,1,3,3-tetraethylisoindoline (**7**) (1.00 g, 3.11 mmol) was dissolved in chloroform (16 mL) under argon. The solution was cooled to 0 °C and treated with pyridine (83.00 μL, 1.03 mmol) and bromine (2.39 mL, 46.65 mmol). After stirring for 15 min, aluminium trichloride (2.66 g, 19.90 mmol) was added and the solution was stirred at 0 °C for 3 h. The reaction was warmed to ambient temperature for an additional hour then poured into ice/water (100 mL), basified with sodium hydroxide (5 M aqueous solution) and stirred for 30 min. The solution was extracted with DCM (3 × 100 mL), washed with brine, dried (anhydrous Na_2SO_4) and concentrated in vacuo. The resulting residue was dissolved in methanol (30 mL) and sodium hydrogen carbonate (0.10 g, 1.16 mmol) added. The solution was treated with hydrogen peroxide solution (30%, ≈ 4 mL) until the bubbling ceased (and excess sodium hydrogen carbonate remained). The mixture was acidified with sulfuric acid (2 M aqueous solution) and extracted with diethyl ether (2 × 50 mL). The ether layers were discarded. The acid layers were then basified with sodium hydroxide (5 M aqueous solution) and extracted with diethyl ether (3 × 50 mL). The organic layers were washed with brine, dried (an-

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hydrous Na_2SO_4) and concentrated at reduced pressure to give a pale yellow oil (0.26 g, 21%) containing trace amounts (<5% by ^1H NMR) of 5-bromo-1,1,3,3-tetraethylisoindoline (**9**). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.4 Hz, 12 H, 4 × CH_3), 1.5–1.75 (m, 8 H, 4 × CH_2), 7.24 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.8 (CH_3), 33.5 (CH_2), 68.3 (C_{quat}), 122.5 (C_{quat}), 127.5 (CH), 149.0 (C_{quat}) ppm. MS (ES): *m*/*z* (%) = 392 (50), 390 (100), 388 (50) [M^+]. HRMS (EI): *m*/*z*: calcd. for $C_{16}H_{24}{}^{79}Br^{81}BrN$ [M^+]: 390.0255; found 390.0252.

2-Benzyl-4,5-dibromophthalimide (15): Benzylamine (6.00 mL, 54.93 mmol) was added slowly to a slurry of 4,5-dibromophthalic anhydride (5.00 g, 16.34 mmol) in acetic acid (26 mL). The mixture was heated to reflux for 1 h and then poured into an ice/water mixture (80 mL). The resulting solid was collected by filtration and recrystallised from 2-propanol to give a beige powder (4.50 g, 70%); m.p. 207–209 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.34 (s, 2 H, CH_2), 7.28–7.35 (m, 3 H, Ar-H), 7.39–7.43 (m, 2 H, Ar-H), 8.10 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.0 (CH_2), 128.0 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 131.4 (C_{quat}), 131.8 (C_{quat}), 135.8 (C_{quat}), 166.0 (C=O) ppm. MS (EI): *m*/*z* (%) = 396 (80), 394 (100), 392 (80) [M^+]. HRMS: calcd. for $C_{15}H_9{}^{81}Br^{79}BrNO_2$ [M^+] 394.8980; found 394.8984.

2-Acetoxy-1,1,3,3-tetraethylisoindoline (19): A solution of 2-benzyl-1,1,3,3-tetramethylisoindoline (**10**) (1.24 g, 5.03 mmol) in dry THF (20 mL) was treated with palladium (134 mg, 1.26 mmol, 10% on charcoal) and stirred under a balloon of H_2 for 20 min. The reaction mixture was cooled to 0 °C, Et_3N (1.41 mL, 10.10 mmol) and acetyl chloride (0.90 mL, 12.60 mmol) added slowly and the mixture was stirred at 0 °C for 1 h. The cooling bath was removed and stirring was continued for an additional 1.5 h. Ar was bubbled over the mixture for 10 min. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was taken up in EtOAc (50 mL) and washed with water (50 mL) and brine (30 mL). The organic layer was dried with $MgSO_4$ and evaporated at reduced pressure. Recrystallisation from hexane (4 mL) gave **10** as beige needles (0.95 g, 65%); m.p. 91–93 °C.^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (br. t, J = 6.7 Hz, 6 H, 2 × CH_3), 0.81 (br. t, J = 7.2 Hz, 6 H, 2 × CH_3), 1.6–2.07 (m, 8 H, 4 × CH_2), 2.13 (s, 3 H, CH_3), 7.05–7.11 (m, 2 H, Ar-H), 7.24–7.30 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.6 (CH_3), 9.5 (CH_3), 19.4 (CH_3), 28.9 (CH_2), 30.3 (CH_2), 73.7 (C_{quat}), 123.6 (CH), 126.6 (CH), 141.6 (C_{quat}), 170.6 (C=O) ppm. MS (EI): *m*/*z* (%) = 289 (30) [M^+]. $C_{18}H_{27}NO_2$ (289.20): calcd. C 74.70, H 9.40, N 4.84; found C 74.54, H 9.54, N 4.93.

2-Acetoxy-5-bromo-1,1,3,3-tetraethylisoindoline (20) and 2-Acetoxy-5,6-dibromo-1,1,3,3-tetraethylisoindoline (21): A solution of 2-acetoxy-1,1,3,3-tetraethylisoindoline (**19**) (0.145 g, 0.50 mmol) in chloroform (3 mL) was prepared under argon and treated with pyridine (2 drops). Bromine (175 μL, 3.50 mmol) was added and the mixture was stirred for 3 min. Aluminium chloride (233 mg, 1.75 mmol) was added and the mixture stirred for 1 d. Additional aluminium chloride (66.7 mg, 0.50 mmol) and chloroform (1 mL) were added and the mixture stirred for a further 2 d. The mixture was diluted with chloroform (2 mL), cooled on ice and treated with sodium thiosulfate (10% aqueous solution, 10 mL). The phases were separated and the aqueous layer extracted with DCM (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification by silica gel chromatography (eluent hexane/EtOAc, 6:1 → 1:1) gave a brown oil (160 mg, 78%). Analysis by ^1H NMR spectroscopy indicated the formation of **20** and **21** in a 1:1 ratio (based on aromatic protons). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.75–1.0 (m, 4 × CH_3), 1.6–2.05 (m, 4 × CH_2), 2.11 (s, CH_3), 6.94 (d, J = 8.1 Hz, Ar-H for **20**), 7.31 (s, Ar-H for **21**), 7.20 (d, J = 1.7 Hz, Ar-H for **20**), 7.39 (dd, J = 8.1, 1.8 Hz, Ar-H for **20**) ppm.

2-Benzyl-5,6-dimethylphthalimide (23): A suspension of **22** (7.80 g, 44.3 mmol, 1.00 equiv.) in acetic acid (50 mL) was treated with benzylamine (6.28 mL, 57.6 mmol, 1.30 equiv.), warmed to 120 °C and stirred at this temperature for 1.5 h. The mixture was poured onto an ice/H_2O mixture (100 mL) and filtered. The residue was recrystallised from EtOH to yield 10.7 g of **24** as colourless, voluminous crystals (40.3 mmol, 91%). M. p 138–140 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (s, 6 H, CH_3), 4.83 (s, 2 H, CH_2), 7.23–7.35 (m, 3 H, Ar-H), 7.40–7.45 (m, 2 H, Ar-H), 7.61 (s, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, add. DEPT): δ = 20.6 (+, CH_3), 41.5 (–, CH_2), 124.3, 127.7, 128.5, 128.6 (+, 7 C, Ar-C), 130.1, 136.6, 143.7 (C_{quat}, 5 C, Ar-C) ppm. MS (EI): *m*/*z* (%) = 265 (100) [M^+], 247 (78), 236 (58), 222 (67), 133 (59), 104 (67), 91 (44) [$C_7H_7^+$], 77 (42) [$C_6H_5^+$]. HRMS (EI): *m*/*z*: calcd. for $C_{17}H_{15}NO_3$ [M^+]: 265.1103; found 265.1102. $C_{17}H_{15}NO_2$ (265.31): calcd. C 76.96, H 5.70, N 5.28; found C 76.87, H 5.56, N 5.26.

2-Benzyl-5,6-dimethyl-1,1,3,3-tetraethylisoindoline (24): A solution of **23** (7.00 g, 26.38 mmol, 1.00 equiv.) in anhydrous toluene (62 mL) was treated with ethylmagnesium iodide [freshly prepared from ethyl iodide (12.66 mL, 158.29 mmol) and magnesium turnings (7.70 g, 316.59 mmol) in Et_2O (62 mL)]. The Et_2O was distilled off via Dean–Stark. The reaction mixture was heated to reflux, stirred for 3 h and then concentrated to about half of its volume. Hexane (4 × 100 mL) was added, the mixture was filtered through Celite and washed thoroughly with extra hexane (100 mL). The filtrate was passed through a column of basic alumina and concentrated in vacuo to give 4.7 g of **24** as a colourless oil which solidified when kept at ambient temperature (13.46 mmol, 51%); m.p. 98–100 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.80 (t, ^3J = 7.0 Hz, 12 H, CH_2CH_3), 1.45–1.65 (m, 4 H, CH_2CH_3), 1.85–2.00 (m, 4 H, CH_2CH_3), 2.30 (s, 6 H, CH_3), 4.01 (s, 2 H, CH_2), 6.84 (s, 2 H, Ar-H), 7.22–7.40 (m, 3 H, Ar-H), 7.45–7.55 (m, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz, add. DEPT): δ = 9.7 (+, CH_2CH_3), 20.1 (–, CH_2CH_3), 30.3 (+, $PhCH_3$), 46.8 (C_{quat}, CCH_3), 71.1 (–, NCH_2), 124.5, 127.8, 129.3, 133.7 (+, 7 C, Ar-C), 126.5, 142.3, 142.6 (C_{quat}, 5 C, Ar-C) ppm. MS (EI): *m*/*z* (%) = 348 (3) [M^- – H], 320 (100), 236 (58), 91 (47) [$C_7H_7^+$]. HRMS (EI): *m*/*z*: calcd. for $C_{25}H_{34}N$ [M^- – H]: 348.2691; found 348.2690. $C_{25}H_{35}N$ (349.56): calcd. C 85.90, H 10.09, N 4.01; found C 85.76, H 10.36, N 4.00.

2-Benzoyl-1,1,3,3-tetraethylisoindoline-5,6-dicarboxylic Acid (25): A suspension of 2-benzyl-1,1,3,3-tetraethyl-5,6-dimethylisoindoline (**24**) (1.50 g, 4.29 mmol) and sodium hydroxide (1.00 g, 25.00 mmol) in a mixture of pyridine (30 mL) and water (46 mL) was treated portionwise with solid potassium permanganate (12.00 g, 76.00 mmol). The mixture was heated at reflux for 4 d. Ethanol (30 mL) was added, the mixture filtered and the obtained filtrate concentrated at reduced pressure. The resulting residue was dissolved in water (80 mL), acidified with hydrochloric acid (2 M aqueous solution) and extracted with diethyl ether (5 × 100 mL). The combined ether layers were dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a white solid (1.35 g, 75%); m.p. 244–246 °C. ^1H NMR (400 MHz, CD_3OD): δ = 0.7–1.0 (m, 12 H, 4 × CH_3) 1.6–1.75 (br. s, 2 H, CH_2), 1.9–2.1 (br. s, 2 H, CH_2), 2.4–2.7 (br. s, 4 H, 2 × CH_2), 7.4–7.7 (m, 7 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 50 °C): δ = 9.2 (CH_3), 32.6 (br. s, CH_2), 122.4 (Ar-C), 125.2 (Ar-C), 127.4 (Ar-C) ppm. 128.0 (Ar-C), 132.4 (Ar-C), 139.3 (Ar-C), 144.0 (Ar-C), 168.0 (C=O), 169.7 (C=O), C1 and C3 not observed. *m*/*z* (%) = 422 (100) [M^- – H]. HRMS (EI): *m*/*z*: calcd. for $C_{25}H_{28}NO_5$ [M^- – H]: 422.1967; found 422.1954.

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2-Benzyl-1,1,3,3-tetraethyl-5,6-bis(hydroxymethyl)isoindoline (27): 2-Benzoyl-1,1,3,3-tetraethylisoindoline-5,6-dicarboxylic acid (**25**) (1.0 g, 2.36 mmol) was placed in dry diethyl ether (15 mL) and a solution of lithium aluminium hydride (1.0 M in diethyl ether, 21.24 mL, 21.20 mmol) was added slowly. The mixture was heated at reflux for 3 d, cooled and carefully diluted with water (30 mL). The resulting solution was acidified with hydrochloric acid (2 M aqueous solution) and extracted with chloroform (3 × 40 mL). The chloroform layers were washed with brine, dried (anhydrous Na_2SO_4) and concentrated in vacuo to give 2-benzyl-5,6-bis-(hydroxymethyl)-1,1,3,3-tetraethylisoindoline (**27**) as an off-white solid (0.71 g, 79%); m.p. 155–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, J = 7.4 Hz, 12 H, 4 × CH_3), 1.48–1.58 (m, 4 H, 2 × CH_2), 1.87–1.95 (m, 4 H, 2 × CH_2), 4.0 (s, 2 H, CH_2), 4.77 (s, 4 H, 2 × CH_2), 7.04 (s, 2 H, Ar-H), 7.1–7.18 (m, 3 H, Ar-H), 7.44 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7 (CH_3), 30.3 (CH_2), 30.9 (CH_2), 46.7 (CH_2), 64.8 (CH_2), 71.3 (CH), 124.8 (C_{quat}), 126.6 (C_{quat}), 127.8 (C_{quat}), 129.2 (C_{quat}), 137.1 (C_{quat}), 142.1 (C_{quat}), 145.3 (C_{quat}) ppm. MS (EI): m/z (%) = 380 (5) [M – H]$^+$, 352 (75) [M – C_2H_5]$^+$. HRMS: calcd. for $C_{25}H_{34}NO_2$ 380.2590; found 380.2586. $C_{25}H_{35}NO_2$ (381.55): calcd. C 78.70, H 9.25, N 3.67; found C 78.81, H 9.25, N 3.67.

1,1,3,3-Tetraethyl-5,6-bis(hydroxymethyl)isoindolin-2-yloxyl (28): An acetic acid (15 mL) solution containing 2-benzyl-1,1,3,3-tetraethyl-5,6-bis(hydroxymethyl)isoindoline (**27**) (0.55 g, 1.44 mmol) and palladium on charcoal (10%, 36 mg, 33.8 μmol, 2.5 mol-%) was placed under hydrogen (50 psi) in a Parr hydrogenator for 7 h. The solution was filtered through Celite and concentrated at reduced pressure. The residue was dissolved in chloroform (30 mL) and washed with sodium hydrogen carbonate (saturated aqueous solution, 2 × 30 mL) and brine (2 × 30 mL). The organic layer was dried (anhydrous Na_2SO_4) and concentrated in vacuo. The resulting residue was dissolved in methanol (5 mL). Sodium hydrogen carbonate (0.16 g, 1.9 mmol), sodium tungstate dihydrate (0.07 g, 0.2 mmol) and hydrogen peroxide (30%, 1.4 mL, 12 mmol) were added and the solution was stirred at room temperature for 2 d. Additional sodium tungstate dihydrate (0.1 g, 0.29 mmol) and hydrogen peroxide (30%, 2 mL, 17.1 mmol) were added and the solution was stirred for a further 2 d. Water (20 mL) was added and the mixture was acidified with hydrochloric acid (2 M aqueous solution) and extracted with DCM (3 × 30 mL). The DCM layers were washed with brine (2 × 30 mL), dried (anhydrous Na_2SO_4) and concentrated at reduced pressure. Purification by silica gel column chromatography (eluent 70% EtOAc/30% hexane) gave 1,1,3,3-tetraethyl-5,6-bis(hydroxymethyl)isoindolin-2-yloxyl (**28**) as a golden oil which solidified upon standing (0.16 g, 61%); m.p. 114–116 °C. MS (EI): m/z (%) = 306 (15) [M$^+$], 278 (100) [M – C_2H_5]$^+$. HRMS: calcd. for $C_{18}H_{28}NO_3$ 306.2069; found 306.2069. $C_{18}H_{28}NO_3$ (306.42): calcd. C 70.55, H 9.21, N 4.57; found C 70.61, H 9.40, N 4.44.

1,1,3,3-Tetraethyl-5,6-dimethylisoindolin-2-yloxyl (29): The isoindoline derivative **24** (2.15 g, 6.15 mmol, 1.00 equiv.) was dissolved in AcOH (25 mL). Ar was bubbled over the reaction mixture for 10 min. Palladium (328 mg, 308 μmol, 10% on charcoal, 5 mol-%) was added and Ar was again bubbled over the mixture for 10 min. The reaction mixture was set under hydrogen and shaken at 50 psi in a Parr apparatus for 3 h. Ar was bubbled over the mixture for 10 min. The mixture was filtered through Celite and concentrated under reduced pressure. The residue was filtered through SiO_2 (20 g, hexane/EtOAc, 5:1) and the solvents evaporated in vacuo to give 1,1,3,3-tetraethyl-5,6-dimethylisoindoline. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.90 (t, ^3J = 7.0 Hz, 12 H, CH_2CH_3), 1.55–1.80 (m, 8 H, CH_2CH_3), 2.29 (s, 6 H, $PhCH_3$), 6.86 (s, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 9.02 (CH_2CH_3), 20.07 (CH_2CH_3), 33.80 ($PhCH_3$), 68.06 (CCH_2), 123.56, 134.72, 145.26 (3 C, Ar-C) ppm. The residue was dissolved in MeOH (20 mL), treated with $NaHCO_3$ (775 mg, 9.23 mmol, 1.50 equiv.), $Na_2WO_4{\cdot}2H_2O$ (144 mg, 461 μmol, 7.5 mol-%) and then hydrogen peroxide (3.17 mL, 30.8 mmol, 30% in H_2O, 5.00 equiv.) and the reaction mixture was stirred for 1 d. A second portion of $NaHCO_3$ (775 mg, 9.23 mmol, 1.50 equiv.), $Na_2WO_4{\cdot}2H_2O$ (144 mg, 461 μmol, 7.5 mol-%) and hydrogen peroxide (3.17 mL, 30.8 mmol, 30% in H_2O, 5.00 equiv.) was added and stirring was continued for an additional 2 d. The reaction mixture was concentrated to half of its volume, acidified by careful addition of 2 M aq. H_2SO_4 solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was filtered through SiO_2 (40 g, hexane/EtOAc, 5:1) to give 610 mg of **29** as an orange solid (2.22 mmol, 36%). Recrystallisation from EtOAc yielded **29** as orange crystals. On a 2.86 mmol scale, a yield of 46% was obtained; m.p. 127–129 °C. MS (EI): m/z (%) = 274 (35) [M$^+$], 246 (90), 230 (48), 200 (52). HRMS (EI): m/z: calcd. for $C_{18}H_{28}NO$ [M$^+$]: 274.2171; found 274.2174. $C_{18}H_{28}NO$ (274.43): calcd. C 78.78, H 10.28, N 5.10; found C 78.68, H 10.34, N 5.08.

2-Acetoxy-1,1,3,3-tetraethyl-5,6-dimethylisoindoline (30): A solution of the nitroxide **29** (592 mg, 2.16 mmol, 1.00 equiv.) in THF (10 mL) was treated with palladium (57.5 mg, 54.0 μmol, 10% on charcoal, 2.5 mol-%) and stirred under H_2 for 15 min. The reaction mixture was cooled to 0 °C, NEt_3 (602 μL, 4.32 mmol, 2.00 equiv.) and AcCl (383 μL, 5.38 mmol) were added and the mixture was stirred at 0 °C for an 20 min. The cooling bath was removed and stirring was continued for an additional 1 h. Ar was bubbled over the mixture for 10 min. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was taken up in H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (30 g SiO_2, hexane/EtOAc, 10:1) to give 676 mg of the product **30** as a pale yellow, viscous oil which solidifies within a day when kept at ambient temperature (2.13 mmol, 99%); m.p. 80–82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.75–0.85 (m, 6 H, CH_2CH_3), 0.92–1.02 (m, 6 H, CH_2CH_3), 1.60–1.70, 1.70–1.80, 1.80–1.92, 1.92–2.05 (m, 8 H, CH_2CH_3), 2.13 (s, 3 H, CH_3CO), 2.30 (s, 6 H, $PhCH_3$), 6.84 (s, 2 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 1001 MHz, add. DEPT): δ = 8.62, 9.47 (+, CH_2CH_3), 19.44, 20.05 20.08 (+, CH_3CO, $PhCH_3$), 28.88, 30.35 (–, CH_2CH_3), 63.15 (C_{quat}, CCH_2), 124.54 (+, Ar-C), 134.90, 139.23, (C_{quat}, Ar-C), 170.60 (C_{quat}, C=O) ppm. MS (EI): m/z (%) = 316 (44) [M$^-$ – H], 288 (94), 246 (100), 228 (72), 200 (71). HRMS (EI): m/z: calcd. for $C_{20}H_{30}NO_2$ [M$^-$ – H]: 316.2277; found 316.2280. $C_{20}H_{31}NO_2$ (317.47): calcd. C 75.67, H 9.84, N 4.41; found C 75.59, H 10.13, N 4.38.

2-Acetoxy-1,1,3,3-tetraethyl-6-methylisoindoline-5-carboxylic Acid (31) and 2-Acetoxy-1,1,3,3-tetraethylisoindoline-5,6-dicarboxylic Acid (32): A solution of the dimethylaryl derivative **30** (458 mg, 1.44 mmol, 1.00 equiv.) in tBuOH (10 mL) was warmed to 40 °C. The mixture was treated with $MgSO_4$ (177 mg, 720 μmol, 0.50 equiv.) and 0.4 M aq. $KMnO_4$ solution (14.4 mL, 5.76 mmol, 4.00 equiv.), warmed to 70 °C and stirred at this temperature for 7 h. A second portion of 0.4 M aq. $KMnO_4$ solution (7.20 mL, 2.88 mmol, 2.00 equiv.) and tBuOH (5 mL) were added and the mixture was stirred at 70 °C for an additional 17 h. A third portion of 0.4 M aq. $KMnO_4$ solution (7.20 mL, 2.88 mmol, 2.00 equiv.) and tBuOH (5 mL) were added and stirring was continued at 70 °C for an additional 24 h. The reaction mixture was cooled to ambient

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temperature, treated with *i*PrOH (5 mL) and stirred overnight. Celite (4 g) was added, stirring was continued for 1 h and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to half of its volume, acidified with 3 M aq. HCl solution (pH 2) and extracted with Et_2O (5 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (20 g SiO_2, hexane/EtOAc/HOAc, 50:50:1 → EtOAc/HOAc, 100:1) to give 60.2 mg of the monomethyl monocarboxy derivative **31** as a beige powder (173 μmol, 12%), m.p. 145–148 °C and the dicarboxy derivative **32** which was further purified by recrystallisation from EtOAc/hexane to give 345 mg of **32** as a colourless powder (914 μmol, 63%); m.p. 173–175 °C. **31**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.75–0.90 (m, 6 H, CH_2CH_3), 0.90–1.10 (m, 6 H, CH_2CH_3), 1.65–1.85 (m, 4 H, CH_2CH_3), 1.85–2.15 (m, 4 H, CH_2CH_3), 2.14 (s, 3 H, CH_3CO), 2.70 (s, 3 H, $PhCH_3$), 6.98 (s, 1 H, Ar-H), 7.80 (s, 1 H, Ar-H) ppm. The signal of the CO_2H proton could not be assigned. ^{13}C NMR ($CDCl_3$, 100 MHz, add. DEPT): δ = 8.57 (+, CH_2CH_3), 9.35 (br., +, CH_2CH_3), 19.35, 22.50 (+, CH_3CO, $PhCH_3$), 28.93 (br., –, CH_2CH_3), 30.15 (–, CH_2CH_3), 73.59, 73.90 (C_{quat}, CCH_2), 126.79, 126.87 (+, Ar-C), 127.01, 139.65, 140.17, 147.37 (C_{quat}, Ar-C), 170.39, 173.07 (C_{quat}, C=O) ppm. MS (ESI): negative mode *m*/*z* (%) = 346 (100) [M^- – H]. HRMS (ESI): *m*/*z*: calcd. for $C_{20}H_{28}NO_4$ [M^- – H]: 346.20183; found 346.20108. **32:** ^{1}H NMR (CD_3OD, 400 MHz): δ = 0.70–0.95 (m, 6 H, CH_2CH_3), 0.90–1.10 (m, 6 H, CH_2CH_3), 1.65–1.90 (m, 4 H, CH_2CH_3), 1.90–2.15 (m, 4 H, CH_2CH_3), 2.13 (s, 3 H, CH_3CO), 7.49 (s, 2 H, Ar-H) ppm. The signals of the CO_2H protons could not be assigned. ^{13}C NMR (CD_3OD, 100 MHz, add. DEPT): δ = 7.68, 8.31 (+, CH_2CH_3), 17.73 (+, CH_3CO), 28.48, 29.92 (–, CH_2CH_3), 73.79 (C_{quat}, CCH_2), 123.85 (+, Ar-C), 131.74, 144.84 (C_{quat}, Ar-C), 169.80, 170.63 (C_{quat}, C=O) ppm. MS (ESI): negative mode: *m*/*z* (%) = 376 (100) [M^- – H]. HRMS (ESI): *m*/*z*: calcd. for $C_{20}H_{26}NO_6$ [M^- – H]: 376.17601; found 376.17490. $C_{20}H_{27}NO_6$ (377.44): calcd. C 63.65, H 7.21, N 3.71; found C 63.38, H 7.27, N 3.65.

5,6-Dicarboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (4), DCTEIO: A suspension of the dicarboxyisoindoline **32** (175 mg, 464 μmol, 1.00 equiv.) in H_2O (2 mL) was cooled to 0 °C. LiOH (55.6 mg, 2.32 mmol, 5.00 equiv.) was added and the mixture was stirred for 16 h while warming up to amibient temperature. The obtained solution was acidified by addition of 3 M aq. HCl solution (pH 1) and extracted with Et_2O (3 × 8 mL). The combined organic extracts were treated with PbO_2 (27.7 mg, 116 μmol, 0.25 equiv.) and stirred for 20 min. The mixture was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The residue was recrystallised from H_2O/MeCN (6:1.5) to give 139 mg of DCTEIO (**4**) as yellow crystals (416 μmol, 90%); m.p. 186–188 °C. MS (EI): *m*/*z* (%) = 333 (100) [M^- – H]. HRMS (ESI): *m*/*z*: calcd. for $C_{18}H_{23}NO_5$ [M^- – H]: 333.15762; found 333.157623. $C_{18}H_{24}NO_5$ (334.39): calcd. C 64.65, H 7.23, N 4.19; found C 64.70, H 7.40, N 4.27.

2-Benzyl-5-methylphthalimide (34): Benzylamine (10.10 mL, 92.60 mmol) was added to a solution of 4-methylphthalic anhydride (10.00 g, 61.70 mmol) in acetic acid (50 mL). The solution was heated to reflux for 1 h and then poured onto ice/water (150 mL) with stirring. The white precipitate was collected by filtration and recrystallised from ethanol to give fluffy white crystals (14.90 g, 96%); m.p. 128–130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.51 (s, 3 H, CH_3), 4.85 (s, 2 H, CH_2), 7.25–7.36 (m, 3 H, Ar-H), 7.42–7.46 (m, 2 H, Ar-H), 7.51 (dd, *J* = 7.6, 1.1 Hz, 1 H, 6-H), 7.66 (s, 1 H, 4-H), 7.73 (d, *J* = 7.6 Hz, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.0 (CH_3), 41.5 (CH_2), 123.2 (Ar-C), 123.9 (Ar-C), 127.7 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 129.5 (Ar-C), 132.5 (Ar-C), 134.5 (Ar-C), 136.5 (Ar-C), 145.2 (Ar-C), 168.1 (C=O), 168.2 (C=O) ppm. MS (EI): *m*/*z* (%) = 251 (100) [M^+]. $C_{16}H_{13}NO_2$ (251.10): calcd. C 76.48, H 5.21, N 5.57; found C 76.20, H 5.03, N 5.56.

2-Benzyl-1,1,3,3-tetraethyl-5-methylisoindoline (35): A solution of 2-benzyl-5-methylphthalimide (**34**) (10.00 g, 40.00 mmol, 1.00 equiv.) in anhydrous toluene (80 mL) was treated with ethylmagnesium iodide [freshly prepared from ethyl iodide (19.20 mL, 240.0 mmol) and magnesium turnings (11.68 g, 480.0 mmol) in Et_2O (100 mL)]. The Et_2O was distilled off via Dean–Stark. The reaction mixture was heated to reflux, stirred for 3 h and then concentrated to about half of its volume. Hexane (4 × 130 mL) was added, the mixture was filtered through Celite and washed thoroughly with extra hexane (100 mL). The filtrate was passed through a column of basic alumina and concentrated in vacuo to give **35** as a colourless oil (4.5 g, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78 (td, *J* = 7.36, 3.04 Hz, 12 H, 4 × CH_3), 1.45–1.62 (m, 4 H, 2 × CH_2), 1.85–1.95 (m, 4 H, 2 × CH_2), 2.37 (s, 3 H, CH_3), 4.00 (s, 2 H, CH_2), 6.86 (s, 1 H, 4-H), 6.94 (d, *J* = 7.7 Hz, 1 H, 6-H), 7.02 (d, *J* = 7.7 Hz, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.59 (CH_3), 9.62 (CH_3), 21.5 (CH_3), 30.32 (CH_2), 30.34 (CH_2), 46.8 (CH_2), 71.0 (C_{quat}), 71.2 (C_{quat}), 123.1 (Ar-C), 123.9 (Ar-C), 126.47 (Ar-C), 126.48 (Ar-C), 127.7 (Ar-C), 129.2 (Ar-C), 135.0 (Ar-C), 141.7 (Ar-C), 142.5 (Ar-C), 144.7 (Ar-C) ppm. MS (EI): *m*/*z* (%) = 336 (50) [MH^+]. HRMS (ES): *m*/*z*: calcd. for $C_{24}H_{34}N$ [MH^+]: 336.2691; found 336.2690.

1,1,3,3-Tetraethyl-5-methylisoindolin-2-yloxyl (36): 2-Benzyl-5-methyl-1,1,3,3-tetraethylisoindoline (**35**) (0.05 g, 1.49 mmol) was dissolved in AcOH (25 mL). Palladium (10% on charcoal, ≈ 20 mg) was added and the reaction mixture was shaken under hydrogen (50 psi in a Parr apparatus) for 3 h. The mixture was filtered through Celite and concentrated at reduced pressure. The resulting residue was dissolved in DCM (50 mL) and washed with sodium hydrogen carbonate (saturated aqueous solution, 3 × 50 mL). The organic phase was dried (anhydrous Na_2SO_4) and concentrated in vacuo to give a yellow oil (0.35 g). The residue was dissolved in MeOH (10 mL), treated with $NaHCO_3$ (0.13 g, 1.56 mmol) and $Na_2WO_4{\cdot}2H_2O$ (52.5 mg, 168 μmol), and then hydrogen peroxide solution (30%, 1.15 mL, 11.22 mmol) and stirred for 1 d. A second portion of $NaHCO_3$ (0.13 g, 1.56 mmol), $Na_2WO_4{\cdot}2H_2O$ (52.5 mg, 168 μmol) and hydrogen peroxide solution (30%, 1.15 mL, 11.22 mmol) was added and stirring was continued for an additional 2 d. Water (20 mL) was added and the mixture extracted with DCM (3 × 20 mL). The combined organic layers were washed with sulfuric acid (2 M aqueous solution, 2 × 25 mL), dried (anhydrous Na_2SO_4) and evaporated under reduced pressure. The residue was purified by silica gel chromatography (eluent 100% DCM) to give **36** as an orange oil (0.24 g, 61%). MS (ES): *m*/*z* (%) = 283 (20) [MNa^+], 261 (2) [MH^+]. HRMS (ES): *m*/*z*: calcd. for $C_{17}H_{27}NO$ [MH^+]: 261.2093; found 261.2091. $C_{187}H_{26}NO$ (2302.27): calcd. C 78.41, H 10.06, N 5.38; found C 78.62, H 10.23, N 5.58.

2-Acetoxy-1,1,3,3-tetraethyl-5-methylisoindoline (37): A solution of 1,1,3,3-tetraethyl-5-methylisoindolin-2-yloxyl (**36**) (1.00 g, 3.84 mmol) in dry THF (20 mL) was treated with palladium (102 mg, 96.0 μmol, 10% on charcoal) and stirred under a balloon of H_2 for 30 min. The reaction mixture was cooled to 0 °C, Et_3N (1.07 mL, 7.68 mmol) and acetyl chloride (0.68 mL, 9.60 mmol) were added and the mixture was stirred at 0 °C for 30 min. The cooling bath was removed and stirring was continued for an additional 1 h. Ar was bubbled over the mixture for 10 min. The reaction mixture was filtered through Celite and concentrated in vacuo.

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Water (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with Na_2SO_4 and evaporated at reduced pressure. The resulting residue was purified by silica gel chromatography (eluent DCM/hexane, 1:1, sample loaded in DCM) to give **37** as a colourless oil which solidified upon standing (1.10 g, 95%); m.p. 76–78 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.75–0.85 (m, 6 H, 2 × CH_3), 0.9–1.0 (m, 6 H, 2 × CH_3), 1.6–2.05 (m, 8 H, 4 × CH_2), 2.52 (s, 3 H, CH_3), 2.75 (s, 3 H, CH_3), 6.87 (s, 1 H, 4-H), 6.96 (d, J = 7.7 Hz, 6-H), 7.07 (d, J = 7.7 Hz, 7-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.6 (CH_3), 9.4 (CH_3), 19.4 (CH_3), 21.6 (CH_3), 28.9 (CH_2), 30.3 (CH_2), 73.5 (C_{quat}), 73.6 (C_{quat}), 123.4 (CH), 124.0 (CH), 127.5 (CH), 136.2 (C_{quat}), 138.7 (C_{quat}), 141.7 (C_{quat}), 170.6 (C=O) ppm. MS (ES): m/z (%) = 326 (40) [MNa^+], 304 (5) [MH^+]. HRMS (ES): m/z: calcd. for $C_{19}H_{30}NO_2$ [MH^+]: 304.2277; found 304.2280. $C_{19}H_{29}NO_2$ (303.22): calcd. C 75.21, H 9.63, N 4.62; found C 74.10, H 9.69, N 4.53.

2-Acetoxy-1,1,3,3-tetraethylisoindoline-5-carboxylic Acid (38): 2-Acetoxy-1,1,3,3-tetraethyl-5-methylisoindoline (**37**) (0.75 g, 2.47 mmol) was dissolved in *tert*-butyl alcohol (17 mL) and warmed to 40 °C. Magnesium sulfate (0.30 g, 1.24 mmol) and potassium permanganate solution (0.4 M in water, 25 mL, 10.00 mmol) were added and the mixture was heated at 70 °C for 24 h. The solution was cooled, treated with 2-propanol (10 mL) and stirred for 16 h. The mixture was filtered through Celite. The filtrate was concentrated by half, acidified with hydrochloric acid (2 M aqueous solution) and extracted with diethyl ether (4 × 15 mL). The organic layers were dried (anhydrous Na_2SO_4) and concentrated at reduced pressure. Purification of the resulting residue by silica gel chromatography (eluent DCM/EtOAc, 3:2) gave **38** as a white solid. Recrystallisation from hexane/EtOAc gave white prisms (0.51 g, 62%); m.p. 168–170 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81 (br. s, 6 H, 2 × CH_3), 0.98 (br. s, 6 H, 2 × CH_3), 1.62–1.86 (m, 4 H, 2 × CH_2), 1.88–2.1 (m, 4 H, 2 × CH_2), 2.13 (s, 3 H, CH_3), 7.18 (d, J = 8.0 Hz, 1 H, 7-H), 7.82 (1 H, 4-H), 8.04 (d, J = 8.0 Hz, 1 H, 6-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 8.5 (CH_3), 9.3 (CH_3), 19.3 (CH_3), 28.9 (CH_2), 30.2 (CH_2), 73.7 (CH), 74.0 (CH), 123.7 (CH), 125.4 (CH), 128.0 (C_{quat}), 128.9 (CH), 142.3 (C_{quat}), 148.2 (C_{quat}), 170.3 (C=O), 172.1 (C=O) ppm. MS (ES): m/z (%) = 332 (100) [$M - H]^-$. HRMS (ES): m/z: calcd. for $C_{19}H_{26}NO_4$ [$(M - H)^-$]: 332.1862; found 332.1870. $C_{19}H_{27}NO_4$ (333.42): calcd. C 68.44, H 8.16, N 4.20; found C 68.48, H 8.24, N 4.13.

5-Carboxy-1,1,3,3-tetraethylisoindolin-2-yloxyl (3) from (38): 2-Acetoxy-1,1,3,3-tetraethylisoindoline-5-carboxylic acid (**38**) (0.20 g, 0.60 mmol) was suspended in water (4 mL) and the mixture cooled on ice. Lithium hydroxide (71 mg, 2.99 mmol) was added, the ice-bath was removed and the mixture was stirred at room temperature for 16 h. The resulting yellow solution was acidified with hydrochloric acid (2 M aqueous solution) and extracted with diethyl ether (3 × 15 mL). The combined ether layers were treated with lead oxide (71 mg, 0.30 mmol) and stirred for 20 min. The solution was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a yellow oil which solidified upon standing. Recrystallisation from acetonitrile gave yellow crystals (0.15 g, 85%) which displayed identical properties to that synthesised above.

2-Benzyl-5,6-bis(bromomethyl)-1,1,3,3-tetraethylisoindoline (39): Phosphorus tribromide (0.10 mL, 3.10 mmol) was added slowly to an ice-cooled solution of 2-benzyl-1,1,3,3-tetraethyl-5,6-bis(hydroxymethyl)isoindoline (**27**) (0.50 g, 1.31 mmol) in dry DCM (10 mL) under an argon atmosphere. The solution was stirred on ice for 1.5 h, diluted with water (30 mL) and extracted with chloroform (3 × 30 mL). The organic layers were washed with brine, dried (anhydrous Na_2SO_4) and concentrated at reduced pressure. Purification by silica gel chromatography (eluent 30% DCM/70% hexane) gave **39** as a pale yellow solid (0.32 g, 48%); m.p. 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.72–0.8 (m, 12 H, 4 × CH_3), 1.48–1.6 (m, 4 H, 2 × CH_2), 1.85–1.95 (m, 4 H, 2 × CH_2), 3.99 (s, 2 H, CH_2), 4.71 (s, 4 H, 2 × CH_2), 7.04 (s, 2 H, Ar-H), 7.22–7.34 (m, 3 H, Ar-H), 7.41–7.46 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.6 (CH_3), 30.2 (CH_2), 30.9 (CH_2), 46.7 (CH_2), 71.4 (C_{quat}), 125.0 (Ar-C), 126.1 (Ar-C), 126.7 (Ar-C), 127.9 (Ar-C), 129.2 (Ar-C), 134.1 (Ar-C), 146.4 (Ar-C) ppm. MS (EI): m/z = 478/480/476 (85/43/43) [$M^+ - C_2H_5$]. HRMS: calcd. for $C_{25}H_{33}{}^{81}Br_2N$ 480.0548; found 480.0537.

2-Benzyl-5,6-bis(diethoxyphosphorylmethyl)-1,1,3,3-tetraethylisoindoline (40): A solution of 2-benzyl-5,6-bis(bromomethyl)-1,1,3,3-tetraethylisoindoline (**39**) (0.10 g, 0.197 mmol) in triethyl phosphite (85 μL, 0.495 mmol) was heated at 80 °C for 16 h. The excess diethyl phosphite was removed by distillation. Purification of the resulting residue by silica gel chromatography (eluent 100% EtOAc → 10% MeOH/90% EtOAc) gave **40** as a golden oil which solified upon standing (0.11 g, 94%); m.p. 81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (t, J = 7.3 Hz, 12 H, 4 × CH_3), 1.23 (t, J = 7.1 Hz, 12 H, 4 × CH_3), 1.45–1.55 (m, 4 H, 2 × CH_2), 1.85–1.95 (m, 4 H, 2 × CH_2), 3.43 (d, J = 20.1 Hz, 2 H, CH_2), 3.92–4.08 (m, 10 H, 5 × CH_2), 6.95 (d, J = 1.9 Hz, 2 H, Ar-H), 7.2–7.34 (m, 3 H, Ar-H), 7.42–7.46 (m, 2 H, Ar-H) ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.6 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5 (s, CH_3), 16.3 (t, J = 2.8 Hz, P-O-$CH_2C\mathit{H}_3$), 30.3 (s, CH_2), 31.3 (dd, J = 139, 1.6 Hz, P-CH_2), 46.7 (s, CH_2), 62.0 (t, J = 3.3 Hz, P-O-CH_2), 71.1 (s, C_{quat}), 126.3 (s, Ar-C), 126.5 (s, Ar-C), 127.7 (s, Ar-C), 128.2 (s, Ar-C), 129.2 (s, Ar-C), 142.3 (s, Ar-C), 143.8 (s, Ar-C) ppm. MS (EI): m/z (%) = 620 (2) [$M - H]^+$, 592 (100) [$(M - C_2H_5)^+$]. HRMS: calcd. for $C_{33}H_{53}NO_6P_2$ 620.3270; found 620.3264. $C_{33}H_{53}NO_6P_2$ (621.72): calcd. C 63.75, H 8.59, N 2.25; found C 64.03, H 8.61, N 2.21.

2-Benzyl-1,1,3,3-tetraethyl-5,6-bis(phosphonomethyl)isoindoline (41): A solution of 2-benzyl-1,1,3,3-tetraethyl-5,6-bis(diethoxyphosphorylmethyl)isoindoline (**40**) (0.115 g, 0.185 mmol) was heated to reflux in hydrochloric acid (6 M, 4 mL) for 16 h. The solution was concentrated in vacuo and titurated with ethyl acetate (2 × 1 mL) to give **41** as a white solid (0.1 g, 92%); m.p. 280–282 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 1.68 (t, J = 7.2 Hz, 12 H, 4 × CH_3), 2.35–2.45 (m, 4 H, 2 × CH_2), 2.8–2.9 (m, 4 H, 2 × CH_2), 4.12 (d, J = 20.4 Hz, 2 H, CH_2), 4.91 (s, 2 H, CH_2), 7.90 (s, 2 H, Ar-H), 8.13–8.4 (m, 5 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 9.5 (s, CH_3), 29.6 (s, CH_2), 32.7 (d, J = 130 Hz, P-CH_2), 46.1 (s, CH_2), 70.6 (s, C_{quat}), 125.9 (s, Ar-C), 126.7 (s, Ar-C), 127.9 (s, Ar-C), 129.2 (s, Ar-C), 129.8 (d, J = 9.5 Hz, Ar-C), 142.0 (s, Ar-C), 142.2 (s, Ar-C) ppm. MS (ES): m/z (%) = 510 (100) [MH^+]. HRMS: calcd. for $C_{25}H_{38}NO_6P_2$ 510.2174; found 510.2176.

2-Benzyl-5,6-bis(phosphonomethyl)-1,1,3,3-tetraethylisoindolin-2-yloxyl (42): 2-Benzyl-5,6-bis(phosphonomethyl)-1,1,3,3-tetraethylisoindoline (**41**) (85.0 mg, 0.167 mmol) was dissolved in methanol (10 mL) and palladium on carbon (≈ 20 mg) added. The solution was shaken under an atmosphere for hydrogen gas (50 psi) for 6 h, then filtered through Celite and concentrated in vacuo. The resulting residue was dissolved in methanol (5 mL), treated with $NaHCO_3$ (25 mg, 0.298 mmol), $Na_2WO_4{\cdot}2H_2O$ (5 mg, 16 μmol) and then hydrogen peroxide (0.1 mL, 30% in H_2O) and the reaction mixture was stirred for 1 d. A second portion of $NaHCO_3$ (25 mg, 0.298 mmol), $Na_2WO_4{\cdot}2H_2O$ (5 mg, 16 μmol) and hydrogen peroxide (0.1 mL, 30% in H_2O) was added and stirring was continued

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for an additional 2 d. The reaction mixture was concentrated to half of its volume, acidified by careful addition of 2 M aq. H_2SO_4 solution and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried with $MgSO_4$ and evaporated under reduced pressure to give **3** as a white solid (40.0 mg, 55%); m.p. >250 °C (decomp.). MS (EI): *m/z* (%) = 433 (10) [M – H]$^-$. HRMS: calcd. for $C_{18}H_{29}NO_7P_2$ 433.1419; found 433.1437.

5-Bromo-1,1,3,3-tetramethyl-6-nitroisoindoline (44): 5-Bromo-1,1,3,3-tetramethylisoindoline (**43**) (2.01 g, 7.91 mmol) was dissolved in concd. H_2SO_4 (15 mL) and cooled to 0 °C. Nitric acid (3.75 mL, 70% in H_2O) was added and the reaction mixture was stirred at 0 °C for 1 h. The cooling bath was removed and stirring was continued for 4 h. The reaction mixture was cooled to 0 °C, diluted by careful addition of H_2O (20 mL) and basified by careful addition of 10 M aq. NaOH solution (65 mL). The reaction mixture was extracted with Et_2O (1 × 75 mL, 2 × 50 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by filtration through SiO_2 (50 g, EtOAc) and recrystallisation from hexane/EtOAc, 5:1 to give 1.32 g of **44** as yellow crystals (4.41 mmol, 56%); m.p. 136–138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (s, 12 H, Me), 1.85 (br. s, 1 H, NH), 7.44 (s, 1 H, Ar-H), 7.59 (s, 1 H, Ar-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, add. DEPT): δ = 31.5, 31.6 (+, CH_3), 62.9, 63.0 (br., C_{quat}, CCH_3), 113.27 (C_{quat}, Ar-C), 119.2, 128.1 (+, Ar-C), 149.8 (C_{quat}, 2 C, Ar-C) ppm. The signal of the forth quaternary Ar-C could not be assigned. MS (EI): *m/z* (%) = 298/300 (<1/<1) [M$^+$], 283/285 (100/99) [M$^+$ – CH_3], 237/239 (53/52), 158 (76), 143 (46). HRMS (EI): *m/z*: calcd. for $C_{12}H_{15}BrN_2O_2$ [M$^+$]: 298.0317/300.0296; found 298.0314/300.0297, calcd. for $C_{11}H_{12}BrN_2O_2$ [M$^+$ – CH_3]: 283.0082/285.0062, found 283.0086/285.0056. $C_{12}H_{15}BrN_2O_2$ (299.17): calcd. C 48.18, H 5.05, N 9.36; found C 48.29, H 4.71, N 9.28.

5-Cyano-1,1,3,3-tetramethyl-6-nitroisoindoline (45): A solution of 5-bromo-1,1,3,3-tetramethyl-6-nitroisoindoline (**44**) (1.20 g, 4.00 mmol, 1.00 equiv.), $K_4[Fe(CN)_6]$ (295 mg, 800 μmol, 0.20 equiv.) and CuI (76.2 mg, 400 μmol, 10 mol-%) was placed in a pressure tube (10 × 2 cm) and Ar was bubbled through the tube for 10 min. Toluene (3.00 mL, stored over Na) and *n*-butylimidazole (1.05 mL, 8.00 mmol, 2.00 equiv.) were added and Ar was bubbled through the reaction mixture for 10 min. The tube was sealed, warmed to 140 °C and the reaction mixture was vigorously stirred at this temperature for 2 d. The mixture was cooled to ambient temperature, diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was filtered through SiO_2 (60 g, EtOAc) and concentrated in vacuo. The residue (consisting of product and complex-bounded *n*-butylimidazole) was recrystallised from hexane/EtOAc (3:2) to give 580 mg of **45** as yellow needles (2.36 μmol, 59%), m.p. 158–160 °C. Another 88.5 mg of product was obtained as a beige powder by evaporation of the mother liquid and treatment of the residue with Et_2O/hexane (1:1) (361 μmol, 9%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (s, 6 H, Me), 1.54 (s, 6 H, Me), 7.62 (s, 1 H, Ar-H), 8.06 (s, 1 H, Ar-H) ppm. The signal of the Me groups overlapped the signal of the NH proton. ^{13}C NMR ($CDCl_3$, 100 MHz, add. DEPT): δ = 31.4, 31.5 (+, CH_3), 63.2, 63.3 (br., C_{quat}, CCH_3), 107.4, (C_{quat}, CN), 115.4 (C_{quat}, Ar-C), 115. 4, 119.4 (+, Ar-C), 148.7 (C_{quat}, Ar-C), 155.7 (C_{quat}, 2C, Ar-C) ppm. The signal of the forth quaternary Ar-C could not be assigned. MS (EI): *m/z* (%) = 245 (2) [M$^+$], 230 (100) [M$^+$ – CH_3], 184 (73), 169 (37). HRMS (EI): *m/z*: calcd. for $C_{13}H_{15}N_3O_2$ [M$^+$]: 245.1164; found 245.1166, calcd. for $C_{12}H_{12}N_3O_2$ [M$^+$ – CH_3]: 230.0930, found 230.0936. $C_{13}H_{15}N_3O_2$ (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.71, H 6.02, N 17.15.

5-Cyano-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (46): A solution of 5-cyano-1,1,3,3-tetramethyl-6-nitroisoindoline (**45**) (613 mg, 2.50 mmol, 1.00 equiv.) in CH_2Cl_2 (75 mL) was treated with *m*-chloroperbenzoic acid (729 g, 3.25 mmol, concd. 23% H_2O, 1.20 equiv.) and stirred for 1.5 h. The reaction mixture was washed with 2 M aq. NaOH solution (2 × 50 mL) and brine (50 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from MeCN to give 606 mg of **46** as orange needles (2.33 mmol, 93%); m.p. >230 °C (decomp.). MS (EI): *m/z* (%) = 260 (77) [M$^+$], 246 (48), 230 (62), 215 (100). HRMS (EI): *m/z*: calcd. for $C_{13}H_{14}N_3O_3$ [M$^+$]: 260.1035; found 260.1035. $C_{13}H_{14}N_3O_3$ (260.27): calcd. C 59.99, H 5.42, N 16.14; found C 60.16, H 5.31, N 16.10.

5-Amino-6-cyano-1,1,3,3-tetramethylisoindolin-2-yloxyl (47): A suspension of $SnCl_2{\cdot}2H_2O$ (3.38 mg, 1.50 mmol, 3.00 equiv.) in concd. aq. HCl solution (1 mL) was cooled to 0 °C. 5-Cyano-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (**46**) (130 mg, 500 μmol, 1.00 equiv.) was added and the mixture was stirred at 0 °C for 10 min. The cooling bath was removed and stirring was continued for an additional 3 h. The reaction mixture was cooled to 0 °C, basified by careful addition of 5 M aq. NaOH solution (pH 12) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic extracts were washed with brine (25 mL), dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (10 g SiO_2, hexane/EtOAc, 1:1) to give 79.6 mg of **47** as a pale beige solid (346 μmol, 69%); m.p. 198–200 °C. A sample of analytical purity was obtained after recrystallisation from hexane/EtOAc. MS (EI): *m/z* (%) = 230 (57) [M$^+$], 215 (76) [M$^+$ – CH_3], 200 (100), 185 (85). HRMS (EI): *m/z*: calcd. for $C_{13}H_{16}N_3O$ [M$^+$]: 230.1293; found 230.1293. $C_{13}H_{16}N_3O$ (230.29): calcd. C 67.80, H 7.00, N 18.25; found C 67.84, H 7.02, N 18.23.

5-Amino-6-carboxy-1,1,3,3-tetramethylisoindolin-2-yloxyl (5): A suspension of 5-amino-6-cyano-1,1,3,3-tetramethylisoindolin-2-yloxyl (**47**) (70.6 mg, 307 μmol, 1.00 equiv.) in H_2O/EtOH (1 mL/0.2 mL) was treated with KOH (86.4 mg, 1.54 mmol, 5.00 equiv.), warmed to 105 °C and stirred at this temperature for 16 h. The reaction mixture was cooled to ambient temperature, diluted with H_2O and washed with Et_2O (5 mL). The Et_2O-layer was discarded. The aqueous layer was acidified by careful addition of 3 M aq. HCl solution (pH 4) and extracted with Et_2O (4 × 5 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from H_2O/MeCN (2:1) to give 54.2 mg of **5** as yellow, voluminous needles (217 μmol, 71%); m.p. >230 °C (decomp.). MS (EI): *m/z* (%) = 249 (28) [M$^+$], 234 (53) [M$^+$ – CH_3], 219 (100), 204 (53). HRMS (EI): *m/z*: calcd. for $C_{13}H_{17}N_2O_3$ [M$^+$]: 249.1239; found 249.1239. $C_{13}H_{17}N_2O_3$ (249.29): calcd. C 62.64, H 6.87, N 11.24; found C 62.77, H 6.93, N 11.07.

5-Bromo-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (48): A solution of 5-bromo-1,1,3,3-tetramethyl-6-nitroisoindoline (**44**) (598 mg, 2.00 mmol, 1.00 equiv.) in MeOH (10 mL) was treated with $NaHCO_3$ (252 mg, 3.00 mmol, 1.50 equiv.) and $Na_2WO_4{\cdot}2H_2O$ (46.8 mg, 150 μmol, 7.5 mol-%). Hydrogen peroxide (1.03 mL, 10.0 mmol, 30% in H_2O) was added and the mixture was stirred at ambient temperature for 1 d. A second portion of $Na_2WO_4{\cdot}2H_2O$ (46.8 mg, 150 μmol, 7.5 mol-%) and hydrogen peroxide (129 μL, 1.25 mmol, 30% in H_2O) were added and the mixture was stirred for an additional 2 d. After addition of H_2O (20 mL), the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated

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under reduced pressure. The residue was filtered through SiO_2 (20 g, hexane/EtOAc, 1:1 → 1:3) and then recrystallised from EtOAc to give 460 mg of **48** as yellow crystals (1.46 mmol, 73%), m.p. >240 °C (decomp.). $C_{12}H_{14}BrN_2O_3$ (314.16): calcd. C 45.88, H 4.49, N 8.92; found C 46.10, H 4.30, N 8.86.

5-(Methoxycarbonylethenyl)-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (49): 5-Bromo-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (**48**) (408 mg, 1.30 mmol, 1.00 equiv.), potassium carbonate (270 mg, 1.95 μmol, 1.50 equiv.), triphenylphosphane (34.1 mg, 130 μmol, 10 mol-%) and palladium acetate (14.6 mg, 65.0 μmol, 5 mol-%) were placed in a pressure tube (20 × 2 cm) and Ar was bubbled through the tube for 10 min. Methyl acrylate (880 μL, 9.75 mmol, 7.50 equiv.) and dry dimethyl formamide (5 mL) were added and Ar was bubbled through the reaction mixture for 10 min. The tube was sealed, warmed to 110 °C and the reaction mixture was vigorously stirred at this temperature for 3 d (TLC showed no further conversion). The mixture was cooled to ambient temperature, diluted with H_2O (10 mL) and extracted with Et_2O (4 × 10 mL). The combined organic extracts were dried with $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (25 g SiO_2, hexane/EtOAc, 7:1 → 6:1 → 1:1) to give 307 mg of the product **49** as an orange solid (961 μmol, 74%), m.p. 190–192 °C, along with 55.5 mg of unreacted starting material **48** (177 μmol, 14%). MS (EI): *m*/*z* (%) = 319 (100) [M^+], 305 (31) [$M^+ - CH_3$], 289 (17), 258 (24), 243 (42). $C_{16}H_{19}N_2O_5$ (319.34): calcd. C 60.18, H 6.00, N 8.77; found C 60.19, H 6.00, N 8.68.

1,2,3,4,6,8-Hexahydro-6,6,8,8-tetramethyl-2-oxo-7*H*-pyrrolo[3,4-*g*]-quinolin-7-yloxyl (51): A solution 5-(methoxycarbonylethenyl)-1,1,3,3-tetramethyl-6-nitroisoindolin-2-yloxyl (**49**) (0.24 g, 0.75 mmol) and palladium (39.90 mg, 37.5 μmol, 10% on charcoal, 5 mol-%) in methanol (35 mL) was placed under hydrogen gas (50 psi) and shaken in a Parr hydrogenator for 6 h. The reaction mixture was flushed with N_2 gas. Lead oxide (44.9 mg, 87.5 μmol) was added and the mixture was stirred overnight. The resulting mixture was filtered through Celite and the filtrate concentrated at reduced pressure. The residue was purified by column chromatography (20 g SiO_2, hexane/EtOAc, 3:1 → 1:5) to give **51** as a pale beige solid (122 mg, 63%); m.p. 250–252 °C. MS (EI): *m*/*z* (%) = 259 (40) [M^+], 244 (60) [$M^+ - CH_3$], 229 (100). $C_{15}H_{19}N2O_2$ (259.32): calcd. C 69.47, H 7.38, N 10.80; found C 69.29, H 7.52, N 10.61.

1,2,3,4,6,8-Hexahydro-7-methoxy-6,6,8,8-tetramethyl-2-oxo-7*H*-pyrrolo[3,4-*g*]quinoline (52): Hydrogen peroxide solution (30%, 51.5 μL) was added dropwise to a solution of **51** (20.0 mg, 77 μmol) and iron(II) sulfate heptahydrate (55.6 mg, 200 μmol) in DMSO (1 mL). The resulting solution was stirred at room temperature for 1 h and then poured into aqueous sodium hydroxide (1 M, 5 mL). The mixture was extracted with diethyl ether (5 × 4 mL) and the combined organic layers dried (anhydrous $MgSO_4$) and concentrated in vacuo. Purification by silica column chromatography (eluent hexane/EtOAc, 1:1 → 1:2) gave **52** as a beige solid (11.7 mg, 55%); m.p. 220–222 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (br. s, 12 H, 4 × CH_3), 2.64 (t, J = 7.8 Hz, 2 H, CH_2), 2.96 (t, J = 7.1 Hz, 2 H, CH_2), 3.8 (s, 3 H, OCH_3), 6.50 (s, 1 H, Ar-H), 6.89 (s, 1 H, Ar-H), 8.28 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.5 (CH_3), 29.7 (CH_2), 30.8 (CH_2), 65.4 (OCH_3), 66.8 (C_{quat}), 67.0 (C_{quat}), 108.5 (CH), 121.2 (CH), 122.9 (C_{quat}), 136.5 (C_{quat}), 140.1 (C_{quat}), 144.8 (C_{quat}), 171.6 (C=O) ppm. MS (EI): *m*/*z* (%) = 274 (10) [M^+], 259 (100) [$M^+ - CH_3$]. HRMS (ES): *m*/*z*: calcd. for $C_{16}H_{22}N_2O_2$ [$(M - H)^-$]: 274.1681; found 274.1682.

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