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Studies towards the biomimetic synthesis of pyridomacrolidin

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Abstract—A possible biomimetic synthesis of pyridomacrolidin has been proposed and experimentally supported by carrying out a model study. Regio and stereospecific [3+2] cycloaddition of an in situ generated unusual di-*tert*-butylated acyl nitrone with *Z*-2-cyclodecenone and subsequent aromatisation was the key step in our proposed biomimetic synthesis. Finally a pyridomacrolidin analogue was prepared via Friedel–Crafts di-de-*t*-butylation of the cycloadduct.

1. Introduction

As part of our ongoing program towards the biomimetic synthesis of pyridone natural products we became particularly interested in a biomimetic synthesis of pyridomacrolidin **2**. Pyridovericin **1** and pyridomacrolidin **2** are novel metabolites isolated in 1998 by Nakagawa and co-workers from the entomopathogenic fungus *Beauveria bassiana* (Fig. 1).[1]

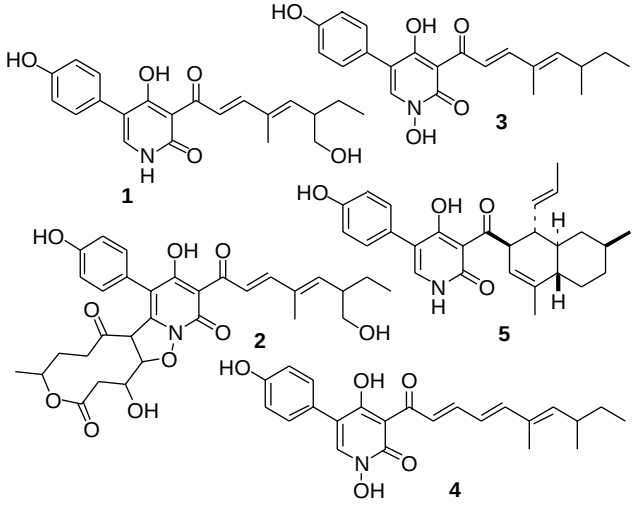

Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related fungal metabolites.

Structurally both pyridovericin **1** and pyridomacrolidin **2** contain the same *p*-hydroxyphenyl pyridone unit present in the related fungal metabolites tenellin **3**,[2] bassianin **4**,[3] and ilicicolin *H* **5**.[4] Chemically this class of compounds has elicited a significant amount of interest as demonstrated by the significant synthetic work already published.[5,6]

Biologically, pyridovericin **1** and pyridomacrolidin **2** have been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100 μg/mL. PTK inhibitors are of potential use as therapeutic agents against a variety of proliferative and inflammatory diseases.[7] In common with several compounds found to inhibit PTKs, pyridovericin **1** and pyridomacrolidin **2** contain a *p*-hydroxyphenyl moiety, which presumably mimics tyrosine. Interest in these type of compounds has largely focused on the determination of the biosynthetic pathway for the generation of tenellin **3**, bassianin **4**, and ilicicolin H **5**.[8–10] Biosynthetically, it has been shown through a series feeding experiments that tenellin **3**, originates from a polyketide chain **6** and the aromatic amino acid L-phenylalanine **7**. Mechanistically, it has been proposed that L-phenylalanine **7** combines with the polyketide **6** unit to generate the acyltetramic acid intermediate **8**. Oxidation of acid **8** could then generates the transient *p*-quinonemethide intermediate **9**, which could undergo a ring expansion to generate the 2-pyridone **10**. Finally, oxidation of the newly formed pyridone unit **10** could generate tenellin **3** (Scheme 1).[7,9]

Although it is believed that the biosynthesis of pyridovericin **1** presumably follows a similar pathway as that of tenellin **3**, the biosynthesis of pyridomacrolidin **2** has not yet been

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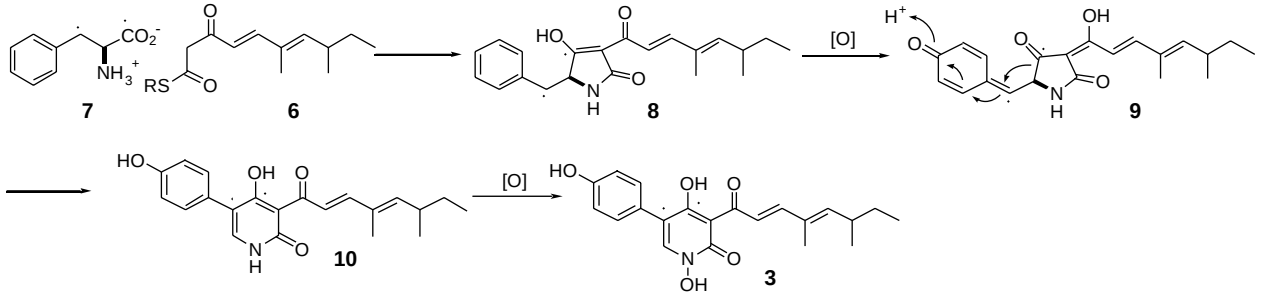
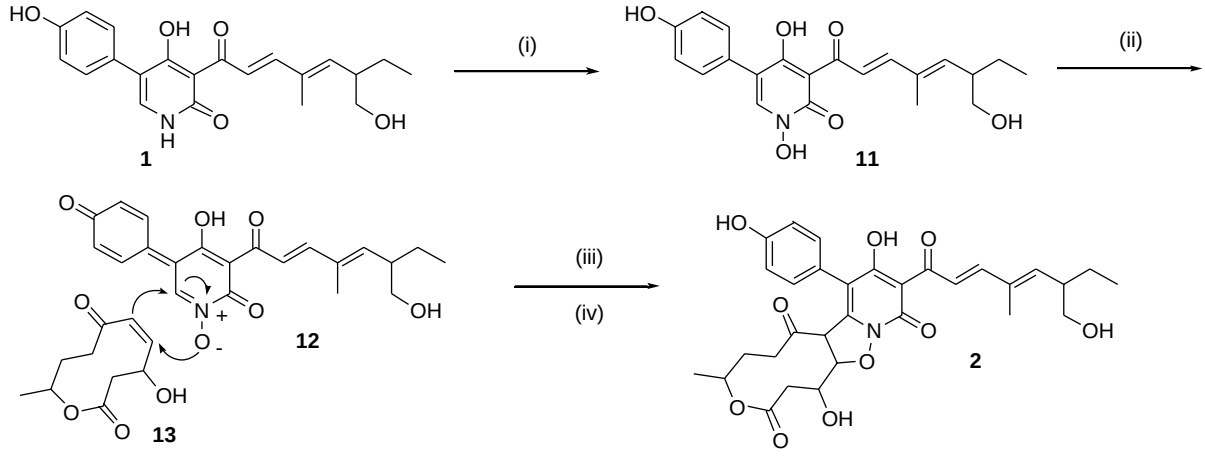


Scheme 1. Proposed biosynthesis of tenellin **3**.

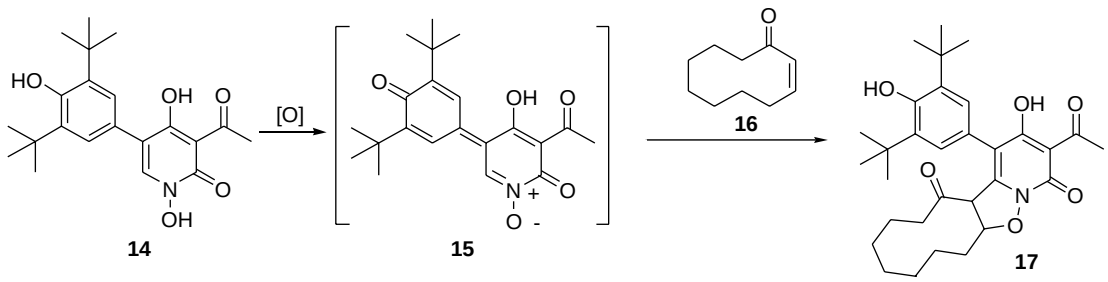


Scheme 2. Proposed biosynthesis of pyridomacrolidin **2**.

elucidated. However, it is possible to propose a biomimetic formation of pyridomacrolidin **2** from the pyridovericin **1** (which was co-isolated from the same fungus) via a number of simple steps (Scheme 2), namely, (i) oxidation of pyridovericin **1** to *N*-hydroxypyridovericin **11**, (ii) further oxidation to the novel acyl nitrone intermediate **12**, (iii) 1,3-dipolar cycloaddition[11] with cephalosporolide B **13**, and (iv) rearomatisation to form pyridomacrolidin **2**. Cephalosporolide B is itself a natural product, isolated independently from the fungus *Cephalosporium aphidicola*,[12] although it has not yet been isolated from *B. bassiana*.

2. Results and discussion

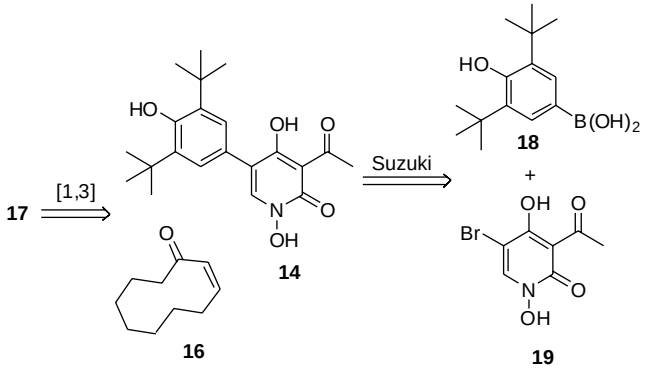
Herein, we would like to describe full details of our studies towards the biomimetic synthesis of pyridomacrolidin **2**, by reporting a model study of an unusual oxidative cyclisation, which supports such an approach to pyridomacrolidin **2**.[13] Although, 1,3-dipolar cycloadditions of nitrones with enones is well documented,[14] as far as we are aware, hitherto, such reactions have not been demonstrated from a nitrone (such as **12**) derived from the oxidation of a 5-(4-hydroxyphenyl)-*N*-hydroxy-2-pyridone (such as **11**). As initial attempts to oxidatively generate and trap unsubstituted quinonoid species similar to **12** were unsuccessful, probably due to competing additions to this highly electron deficient system as well as solubility problems, we chose to block the phenolic *ortho* positions by sterically hindering groups. The introduction of the bulky *t*-butyl groups not only increased the solubility but also provided a protective effect to minimize possible competing side reactions. Moreover, to simplify our task the C-3 side chain of the *N*-hydroxy-2-pyridone **11** was replaced by an acetyl group. Accordingly, compound **14** was targeted for oxidation to produce the corresponding nitrone **15**, from which [3+2] cycloaddition with the simple *Z*-2-cyclodecenone **16**,[15] similar to the desired enone **13** could be attempted. Subsequent aromatisation would afford the cyclised adduct **17**, a pyridomacrolidin analogue (Scheme 3).



Scheme 3.

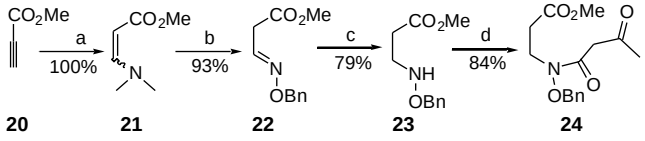
2.1. Total synthesis of di-*t*-butylated-*N*-hydroxy-2-pyridone 14

A retrosynthetic analysis reduced the target compound **14** to a Suzuki cross-coupling between boronic acid **18** and bromide **19** (Scheme 4). The bromide **19** itself should be available following (modification of) methodology developed by Williams et al.[5d]



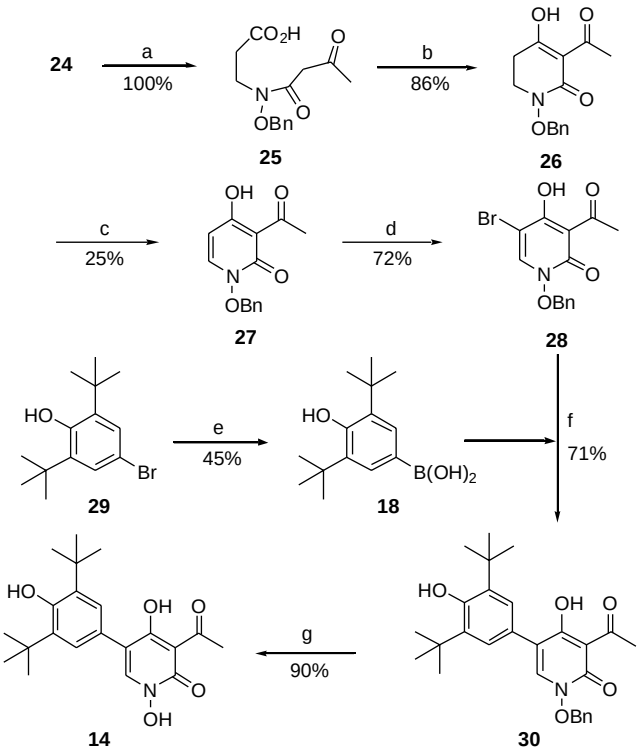
Scheme 4. Retrosynthetic scheme.

The enamine **21**[16] was prepared by passing dimethylamine gas into an ice cooled solution of methyl propiolate **20** in diethyl ether for 1 h, which on subsequent reflux with *O*-benzylhydroxylamine in xylene containing a catalytic amount of camphorsulphonic acid for 24 h afforded the oxime **22**.[17] Sodium cyanoborohydride reduction of the oxime **22** in ethanolic HCl provided the amine **23**. Acylation of the resulting amine **23** with diketene, conducted in anhydrous THF containing triethylamine and a catalytic amount of 4-(dimethylamino)-pyridine, provided the amide **24** in overall good yield (62%) over four steps (Scheme 5).



Scheme 5. Reagents and conditions: (a) $(CH_3)_2NH$, Et_2O, rt, 1 h; (b) H_2NOBn, xylene, cat. CSA, reflux, 24 h; (c) $NaCNBH_3$, EtOH·HCl, rt, 12 h; (d) diketene, cat. DMAP, Et_3N, THF, 0 °C, 30 min.

Ester hydrolysis of the amide **24** was achieved with lithium hydroxide in THF/H_2O (1:1) at rt for 2 h in quantitative yield. The resultant crude carboxylic acid **25** was treated with *N*,*N*′-carbonyldiimidazole (CDI), which after intramolecular cyclisation followed by the addition of sodium hydride yielded the 5,6-dihydropyridone **26**. Unlike the Williams chemistry precedent[5d] attempted oxidation of pyridone **26** with several oxidants (MnO_2, DDQ, *p*-chloranil, Pd/C, H_2SO_4, PhSeCl/LDA then H_2O_2) met with failure. After considerable experimentation, oxidation was achieved with lead tetraacetate[18] in 25% yield [(plus recovered **26** (40%)] to provide pyridone **27**, which on bromination[19] afforded the crucial Suzuki coupling partner **28** in good yield. The phenylboronic acid **18** required for the Suzuki coupling was prepared by the transmetallation of the commercially available 4-bromo-2,6-di-*t*-butylphenol **29** with *t*-butyl lithium and quenching of the organolithium species with triisopropyl borate, followed by acid hydrolysis. Coupling of the bromide **28** and boronic acid **18** was carried out under standard Suzuki conditions in toluene/ethanol (4:1) to yield the *N*-protected pyridone **30** in 44%. The yield of the reaction was later improved to 71% when the solvent was replaced by THF. Deprotection of benzyl group with 10% palladium on carbon in dioxane furnished the *N*-hydroxy-2-pyridone **14** in excellent yield (Scheme 6).

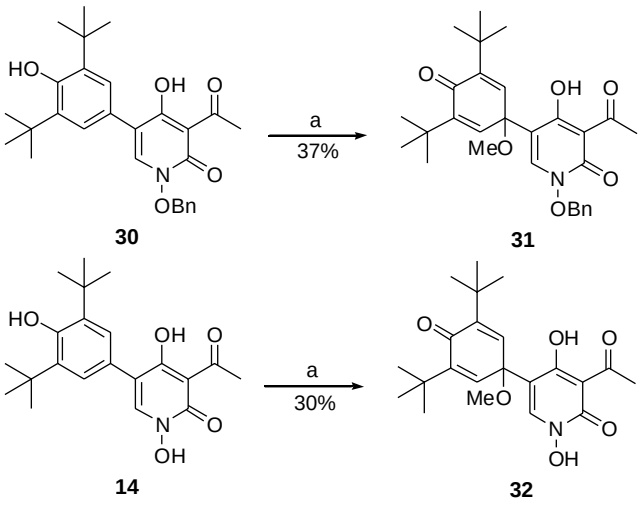


Scheme 6. Reagents and conditions: (a) LiOH, THF, H_2O, rt, 2 h; (b) CDI, THF, 12 h; NaH, rt, 5 h; (c) $Pb(OAc)_4$, benzene, 70 °C, 20 h; (d) Br_2, DCM, reflux, 12 h; (e) *t*-BuLi, $B(OCH(CH_3)_2)_3$, THF, rt, 12 h; (f) $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, reflux, 12 h; (g) 10% Pd/C, dioxane, H_2, rt, 2 h.

2.2. Oxidation of *N*-hydroxy-2-pyridone 14—[3+2] cycloaddition

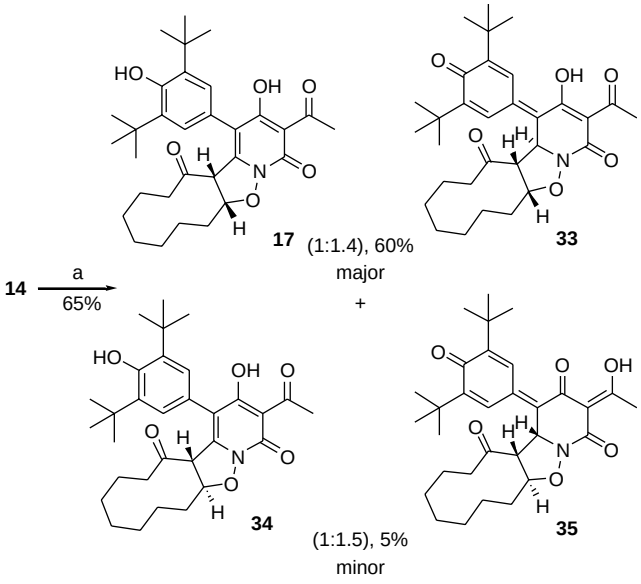
At this stage, in order to find a suitable oxidant, a few model oxidations were conducted on pyridone analogues **14** and **30**. When oxidation of benzyl-protected pyridone **30** was carried out with iodobenzene diacetate[20] in methanol there was obtained the cyclohexadienone **31** in moderate yield. Likewise oxidation of *N*-hydroxy-2-pyridone **14** in methanol gave a similar cyclohexadienone **32** in moderate yield (Scheme 7).

The results of the above oxidation revealed the feasibility of the oxidation of the di-*t*-butylated system, when the oxidation products were trapped by the nucleophilic solvent methanol. We anticipated that if the oxidation could be carried out in the presence of a dipolarophile **16** and in the absence of a nucleophilic solvent, the *N*-hydroxy-2-pyridone **14** after oxidation could undergo [3+2] cycloaddition in situ. Accordingly, oxidation of the *N*-hydroxy-2-pyridone **14** in the presence of *Z*-2-cyclodecenone **16** with



Scheme 7. Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 40 °C, 24 h.

iodobenzene diacetate in DCM at reflux temperature was attempted. Encouragingly, the unstable nitrone **15** formed by the oxidation of hydroxy pyridone **14** underwent [3+2] cycloaddition with enone **16** smoothly to give cyclized products, phenol **17** and quinone methide **33** each with a cis-ring junction in a combined 60% yield. A detailed examination of the crude reaction mixture led us to the discovery of yet two more cyclised products, namely phenol **34** and quinone methide **35** each with a trans ring junction in a 5% combined yield (Scheme 8).[13b]



Scheme 8. Reagents and conditions: (a) $PhI(OAc)_2$, *Z*-2-cyclodecenone **16**, DCM, reflux, 24 h.

2.3. Regio- and stereochemistry

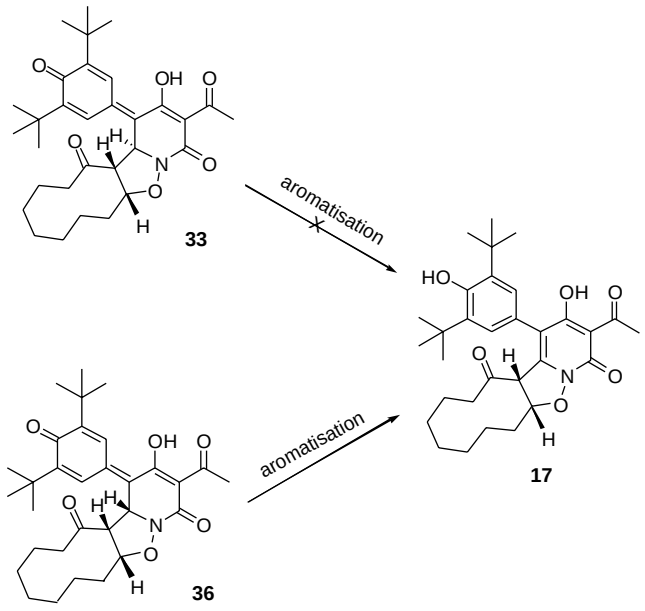
The structures and relative stereochemistry of the major cyclised products **17** and **33** were established by extensive NMR coupling experiments. The stereochemistry at the ring junction was determined as cis based on 1D quantitative NOE[13b] (strong NOE corroboration between the ring junction hydrogens; 11.3% for **17** and 11.0% for **33**), thus retaining the geometry of the enone. Later the structures and relative stereochemistry were unambiguously confirmed by single crystal crystallography.[13] It is clear from the crystal structures that the nitrogen in quinone methide **33** is pyramidal whereas in phenol **17** it is planar. The crystallographic data (of **17** and **33**) also revealed the presence of an intramolecular hydrogen bond between the hydroxyl group at the C-4 of the pyridone ring and the carbonyl oxygen of the neighbouring acetyl group.

The structures and relative stereochemistry of the minor cyclised products were established by NMR coupling experiments. The stereochemistry at the ring junction was determined as trans based on 1D quantitative NOE corroborations (weak NOE corroboration between the ring junction hydrogen; 1.2% for **34** and 2.3% for **35**). The structure and relative stereochemistry of the phenol **34** was further established by single crystal crystallography.[13b] The formation of these products can be rationalized by a two step radical or ionic mechanism. As either mechanisms are non-concerted, the formation of both *syn* and *anti* adducts are possible.

It is noteworthy that there was no evidence for formation of regioisomers arising from the reversed regiochemical pathway for the addition to the double bond, that is, the oxygen of the nitrone was added to the β-carbon of the enone in all cycloadducts. The stereochemistry of the major cyclised products (**17** and **33**) retained the geometry of the enone. No evidence of isomerisation of the enone **16** (>98% *Z*) was observed under the reaction conditions via analysis of recovered unreacted enone. This is consistent with the reaction following a concerted mechanism as the major pathway. The coupling constant of the major cis-fused phenol **17** ($J=7.0$ Hz) rather than the trans-fused phenol **34** ($J=10.5$ Hz) matches closer to the corresponding coupling constant $J=5.9$ Hz of pyridomacrolidin **2**.[1b] So the nitrone **15** derived from *N*-hydroxy-2-pyridone **14** underwent regio- and highly stereospecific [3+2] cycloaddition with enone **16** providing sound evidence for our biomimetic proposal of the pyridomacrolidin formation.

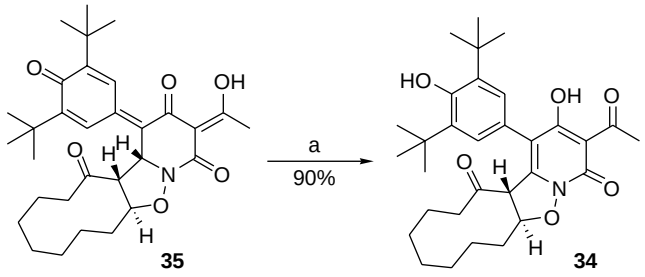
2.4. Equilibration of quinone methides 33 and 35—*exo* and *endo* mode of cycloaddition

The two cyclised products resulted from major cis fusion, **17** and **33** are in fact tautomers. Various attempts to equilibrate the two cyclised products **17** and **33** separately, in aprotic solvent, for example, DCE and protic solvent, for example, *t*-butanol, under acidic condition, for example, trifluoroacetic acid in *t*-butanol (reflux for 24 h), and under basic condition, for example, Hunig's base in *t*-butanol (reflux for 24 h) were unsuccessful. From these results, we rationalized that the products **17** and **33** were generated by means of [3+2] cycloaddition of nitrone **15** with enone **16** in two different modes, that is, *exo* and *endo* cycloaddition pathways providing two different quinone methide adducts **33** and **36** (Scheme 9).



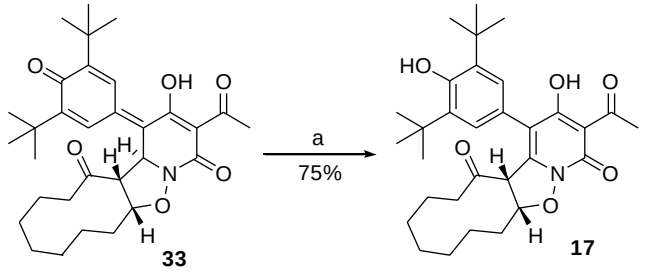
Scheme 9.

It is clear from the crystal structure of quinone methide **33** that it is *exo*. From this observation, we propose that an *endo* quinone methide **36** is formed in situ in the reaction, which subsequently undergoes further aromatization under reaction conditions to provide phenol **17**, while the *exo* adduct **33** remains intact. In this regard the activation energies associated with the aromatisation of **33** and **36** are likely to be different. On the other hand, the *trans* quinone methide **35** could be cleanly transformed into the *trans* phenol **34** by refluxing in *t*-butanol (Scheme 10).



Scheme 10. Reagents and conditions: *t*-butanol, reflux, 24 h.

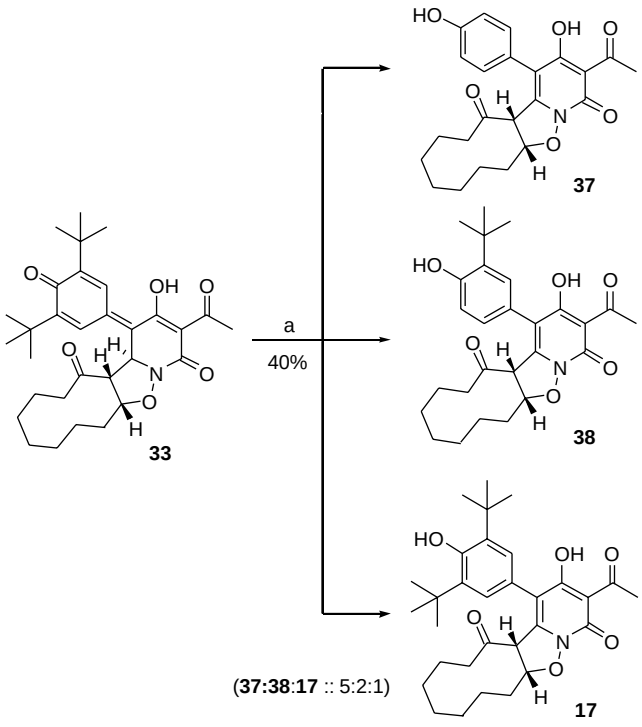
We also attempted the equilibration of *exo* quinone methide **33** using Lewis acid conditions. To our delight quinone methide **33** on treatment with aluminium chloride (2 equiv) in refluxing DCE cleanly transformed into phenol **17** (Scheme 11).



Scheme 11. Reagents and conditions: $AlCl_3$, DCE, reflux, 24 h.

2.5. Friedel–Crafts di-de-*tert*-butylation

Next, we focused our attention towards the removal of *tert*-butyl groups on the phenyl ring of **33** and **17** to produce a true pyridomacrolidin analogue. When *exo* quinone methide **33** was treated with excess of $AlCl_3$ in toluene at 95 °C for 2 days, encouragingly it underwent aromatization and subsequent dealkylation[21] giving the natural product analogue **37** along with mono dealkylated product **38** and phenol **17** in moderate yield (Scheme 12).



Scheme 12. Reagents and conditions: $AlCl_3$, toluene, 95 °C, 2 days.

Phenol **17**, when subjected to the same reaction conditions also underwent dealkylation at a slower rate but in low yield leaving most of the starting material unreacted. Though a few variations of the reaction conditions (use of *t*-butyl cation acceptors like phenol or use of nitromethane[22]) and reagents (Nafion H^+,[23] $AlBr_3$, H_3PO_4[24]) were employed it was not possible to improve the overall yield. Likewise the reaction carried out in anisole in place of toluene with an excess of $AlCl_3$ also found no further improvement.[25] Similarly, although the reaction with a catalytic amount of nitromethane in toluene with excess of $AlCl_3$ was found to be clean, it gave no appreciable improvement in terms of yield. This moderate yield of dealkylation is acceptable if we consider the presence of different functionalities, which survive these rather harsh reaction conditions. The structure of the de-alkylated product **37** was characterized by 2D NMR and was unambiguously determined by single-crystal crystallography (Fig. 2).

2.6. Reactivity of isopropylated-*N*-hydroxy-2-pyridone 43 in oxidative cyclisation

We also investigated the effect of isopropyl groups at C-2 and C-6 of the phenyl ring in our biomimetic oxidative

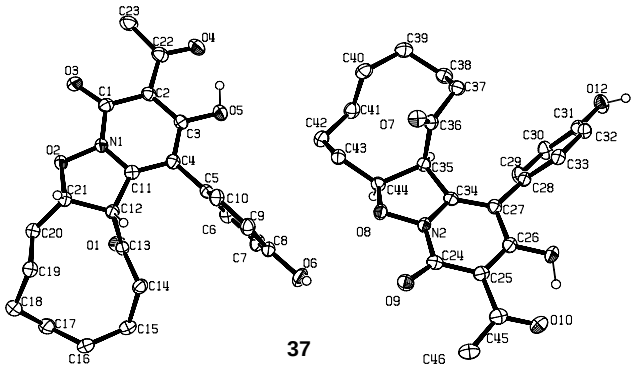
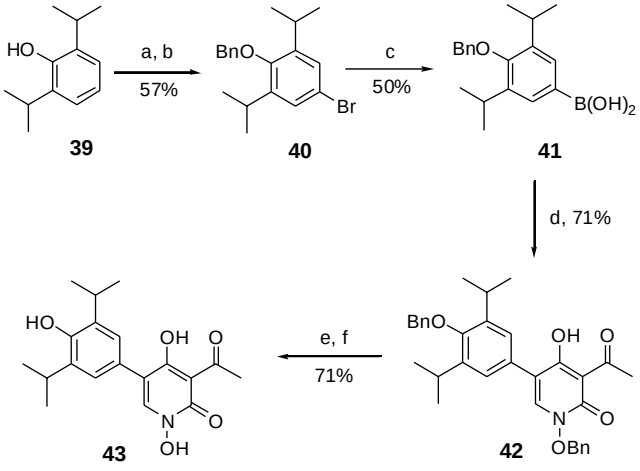


Figure 2. Crystal structure of di-de-*tert*-butylated phenol **37**.

cyclisation. The corresponding *N*-hydroxy-2-pyridone **43** was synthesized by following the methodology in analogy to the synthesis of di-*t*-butylated *N*-hydroxy-2-pyridone **14** from the readily available 2,6-di-isopropylphenol **39** (Scheme 13).



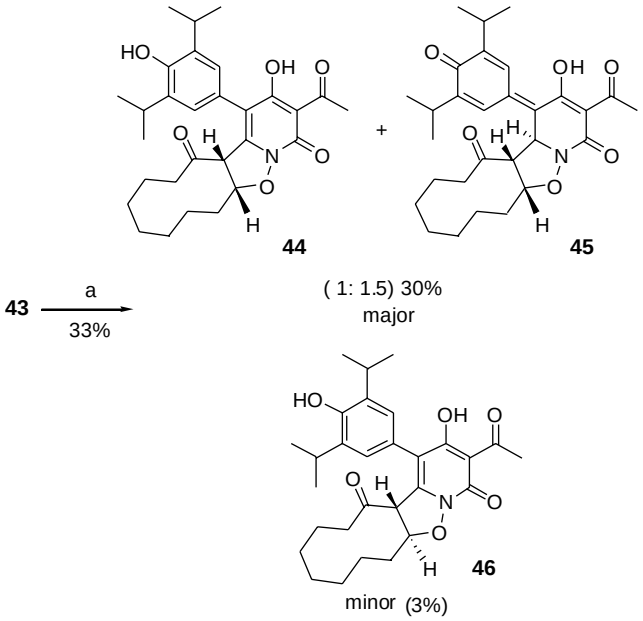
Scheme 13. Reagents and conditions: (a) Br_2, AcOH, rt, 6 h; (b) BnBr, NaH, THF, 40 °C, 12 h; (c) (i) *t*-BuLi, $(MeO)_3B$, THF, rt, overnight; (ii) satd NH_4Cl; (d) $Pd(PPh_3)_4$, Na_2CO_3, toluene: EtOH (4/1), reflux, 12 h; (e) 10% Pd/C, H_2, dioxane, rt, 2 h; (f) 1 M BBr_3 in DCM, DCM, −78 °C, 1 h.

Oxidative cyclisation of isopropylatedpyridone **43** with *Z*-2-cyclodecenone **16** under previously optimised reaction conditions afforded the cyclised products **44**–**46** in 33% combined yield with major products possessing cis ring fusion (Scheme 14).

The structure and relative stereochemistry of all the cyclised products were established by extensive proton coupling experiments and the structure and relative stereochemistry of the phenol **44** was further determined by single crystal crystallography (Fig. 3).

3. Conclusion

We have demonstrated an unusual oxidative cyclisation of the di-*t*-butylated and di-isopropylated *N*-hydroxy-2-pyridones **14** and **43** with *Z*-2-cyclodecenone **16**. This provides strong evidence for our proposed biomimetic



Scheme 14. Reagents and conditions: (a) *Z*-2-cyclodecenone **16**, $PhI(OAc)_2$, DCM, reflux, 24 h.

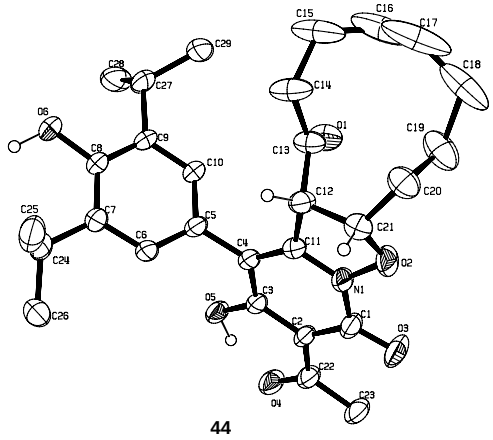


Figure 3. Crystal structure of di-isopropylated phenol **44**.

route to pyridomacrolidin **2** (Scheme 2). The successful oxidative cyclisation with *t*-butylated pyridone **14** in 65% yield and with isopropylated pyridone **43** in 33% yield compared to failure to undergo cycloaddition with unsubstituted pyridone (each with *Z*-2-cyclodecenone **16**) suggests that *t*-butyl or isopropyl groups play a crucial role in allowing the system to undergo oxidation and consecutive cycloaddition. The effect of these alkyl groups is most likely attributable to their ability to prevent possible side reactions of the nitrone intermediate, which might result in its decomposition. It may well be that in an in vivo enzyme mediated oxidation the structure of enzyme binding pocket provides a similar protective effect on the proposed key intermediate **12**. The Friedel–Crafts di-de-*t*-butylation of the phenol **17** in a *tert*-butyl cation acceptor solvent like toluene has been achieved to produce a close pyridomacrolidin **2** analogue.

4. Experimental

4.1. General methods

Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-500, Bruker AV-400, Bruker DPX-400 or Varian Gemini DPX-200 spectrometers. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ^{1}H–^{1}H COSY when necessary. Data are reported in the following manner: chemical shift (multiplicity, coupling constant, integration if appropriate). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in hertz to the nearest 0.5 Hz.

^{13}C NMR spectra were recorded at 50.3, 100.6 and 125.8 MHz using Varian Gemini 200, Bruker AV-400 or Bruker AMX-500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C ^{1}H (HMQC and HMBC) correlations when necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

IR-spectra were recorded as a thin film on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Strong (s) medium (m) and weak (w) absorption bands are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel $60F_{254}$. Column chromatography was carried out on Sorbsil™ C60 (40–63 μm, 230–400 mesh) silica gel.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F. Purification of Laboratory Chemicals, 3rd ed., Pergamon, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 1 mm Hg.

All experiments were carried out under inert atmosphere unless otherwise stated.

4.1.1. 3-Acetyl-5-[(3′,5′-di-*t*-butyl-4′-hydroxy)phenyl]-1,4-dihydroxy-2(1*H*)-pyridone 14. A mixture of 3-acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone **30** (120 mg, 0.26 mmol, 1.0 equiv) and 10% palladium on carbon (120 mg) in dioxane (5 mL) was stirred under a hydrogen (balloon) atmosphere at 25 °C for 2 h. The reaction mixture was filtered, the solid residue was washed with dioxane (20 mL) and the combined filtrates evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 3% ethyl acetate in DCM (silica gel having been pre-washed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C for 24 h)] gave 87 mg (90%) of the desired title compound **14** as a yellow solid, mp 255 °C. ν_{max} (neat)/cm^{-1} 3635w, 3094w, 2958m, 1644s, 1610m, 1547w, 1433m, 1414m, 1237m, 1142m, 909w; δ_H (250 MHz, $CDCl_3$) 1.49 (s, 18H), 2.85 (s, 3H), 5.37 (s, 1H), 7.27 (s, 2H), 7.89 (s, 1H); δ_C (62.5 MHz, $CDCl_3$) 30.6, 32.1, 34.8, 106.3, 114.1, 123.0, 126.4, 134.1, 136.4, 154.4, 157.9, 171.8, 205.9; *m/z* (ESI-) 372 [$(M-H)^-$, 100%]; HRMS: found 372.1805 $(M-H)^-$. $C_{21}H_{26}NO_5$ requires 372.1811.

4.1.2. 3,5-Di-*tert*-butyl-4-hydroxyphenylboronic acid 18. To a −78 °C cooled solution of 4-bromo-2,6-di-*tert*-butyl phenol (1.00 g, 3.51 mmol, 1.0 equiv) in THF (25 mL) was added dropwise a 1.5 M solution of *tert*-butyl lithium in hexanes (7.0 mL, 10.5 mmol, 3.0 equiv). The reaction mixture was stirred for 1 h at 25 °C and then cooled down to −78 °C prior to the addition of tri-isopropyl borate (2.43 mL, 10.5 mmol, 3.0 equiv). The reaction was left overnight at 25 °C prior to the addition of saturated ammonium chloride solution (50 mL). The resulting mixture was stirred at 25 °C for 2 h and the layers separated. The aqueous layer was extracted with ethyl acetate (3× 25 mL) and the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by recrystallization (30% ethyl acetate in hexane) to yield 400 mg (45%) of the title compound **18** as a white solid, mp >250 °C. ν_{max} (neat)/cm^{-1} 3424brm, 2959m, 1599m, 1481m, 1417s, 1343m, 1231s, 1155m, 1122m, 778m; δ_H (400 MHz, $CDCl_3$) 1.55 (s, 18H), 5.64 (s, 1H), 8.13 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 34.2, 132.7, 135.1, 157.9; *m/z* (ESI-) 249 [$(M-H)^-$, 100%]; HRMS: found 249.1658 $(M-H)^-$. $C_{14}H_{22}BO_3$ requires 249.1662.

4.1.3. Methyl-3-(*O*-benzyloxyimino)-propanoate 22.[17] To a solution of methyl-3-(*N*,*N*′-dimethylamino)-2-propeonate **21**[16] (5.52 g, 42.7 mmol) in xylene (50 mL) was added *O*-benzylhydroxylamine (5.26 g, 42.8 mmol, 1.0 equiv) followed by a catalytic amount of camphorsulphonic acid (248 mg, 1.07 mmol, 0.025 equiv). The resulting solution was heated at reflux for 24 h. After cooling to rt (25 °C), the solvent was removed under vacuum, and the crude product was purified by flash column chromatography (silica gel, 10% diethyl ether in 30–40 petroleum ether) to yield the 8.26 g (93%) of the known[17] methyl-3-(*O*-benzyloxyimino)-propanoate **22** as a (1:1.5) mixture of inseparable isomers as a clear oil. ν_{max} (neat)/cm^{-1} 3032m, 2953m, 1743s, 1455m, 1437s, 1350m, 1256m, 1200m, 1172m; δ_H (400 MHz, $CDCl_3$) 3.27 (d, J=6.5 Hz, 0.8H), 3.44 (d, J=5.0 Hz, 1.2H), 3.72 (s, 1.2H), 3.73 (s, 1.8H), 5.09 (s, 0.8H), 5.15 (s, 1.2H), 7.03 (t, J=5.0 Hz, 0.4H), 7.29–7.39 (m, 5H), 7.57 (t, J=6.5 Hz, 0.6H); δ_C (100.6 MHz, $CDCl_3$) 31.3, 34.9, 52.1, 52.2, 75.9, 76.1, 127.9, 128.0, 128.2 (2C), 128.4 (2C), 137.3, 137.5, 143.6, 144.1, 169.6; *m/z* (APCI+) 208 (MH^+, 100%).

4.1.4. Methyl-3-(*O*-benzyloxyamino)-propanoate 23. To a solution of methyl-3-(*O*-benzyloxyimino)-propanoate **22**[17] (8.26 g, 39.9 mmol, 1.0 equiv) in ethanol (80 mL) containing bromothymol blue indicator was added 1 N hydrochloric acid (40 mL) until a yellow precipitate formed. Sodium cyanoborohydride (3.77 g, 60.0 mmol, 1.5 equiv) was then added portionwise to the above reaction mixture at 0 °C. The reaction was then brought to rt, and stirred overnight. The reaction mixture was diluted with water (80 mL) and the aqueous layer extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 30% diethyl ether in 30–40 petroleum ether) to yield 6.63 g (79%) of the title compound **23** as a clear oil. ν_{max} (neat)/cm^{-1} 2951m, 1736s, 1496w, 1438m, 1364m, 1176m, 1018m; δ_H (400 MHz, $CDCl_3$) 2.59 (t, J=7.0 Hz, 2H), 3.08 (t, J=7.0 Hz, 2H), 3.67 (s, 3H), 4.68 (s, 2H), 7.38 (s, 5H); δ_C (100.6 MHz, $CDCl_3$) 32.0, 47.4, 51.6, 76.1, 127.8, 128.3 (2C), 137.7, 172.9; *m/z* (APCI+) 210 (MH^+, 100%).

4.1.5. Methyl-3-(*N*-benzyloxy-*N*-(3-oxo-butyryl)amino)-propanoate 24. To a solution of methyl-3-(*O*-benzylhydroxylamino)propanoate **23** (6.64 g, 31.7 mmol, 1.0 equiv) in THF (65 mL) was added 4-(dimethylamino)pyridine (390 mg, 3.20 mmol, 0.1 equiv), followed by triethylamine (4.42 mL, 31.7 mmol, 1.0 equiv) at 25 °C under argon. Diketene (3.65 mL, 47.6 mmol, 1.5 equiv) was added in small portions over 30 min via syringe pump to the above reaction mixture at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was warmed to 0 °C, stirred for an additional 30 min and the resulting orange solution was diluted with saturated aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 50% diethyl ether in 30–40 petroleum ether) to yield 7.80 g (84%) of the desired title compound **24** as a mixture of inseparable tautomers as a syrupy oil. ν_{max} (neat)/cm^{-1} 2952m, 1736s, 1664s, 1438m, 1361m, 1175m; δ_H (400 MHz, $CDCl_3$) 1.95 (s, 0.5H), 2.15 (s, 2.5H), 2.60 (t, J=7.0 Hz, 0.2H), 2.64 (t, J=7.0 Hz, 1.8H), 3.45 (s, 1.8H, keto tautomer), 3.63, 3.64 (2×s, 3H), 3.94 (t, J=7.0 Hz, 0.2H), 4.01 (t, J=6.5 Hz, 1.8H), 4.81, 4.82 (2×s, 2H), 5.40 (s, 0.2H, enol tautomer), 7.33–7.42 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 22.2, 30.1, 31.5, 31.9, 41.2, 41.5, 49.0, 51.7, 51.8, 76.4, 87.2, 128.6, 128.7, 128.9 (2C), 129.1, 129.4, 133.8, 169.6, 171.9, 201.3; *m/z* (ESI+) 294 (MH^+, 100%); HRMS: found 294.1345 (MH^+). $C_{15}H_{20}NO_5$ requires 294.1341.

4.1.6. 3-(*N*-Benzyloxy-*N*-(3-oxo-butyryl)amino)-propanoic acid 25. To a solution of methyl-3-(*N*-benzyloxy-*N*-(3-oxo-3-butyryl)amino)-propanoate **24** (7.80 g, 26.6 mmol, 1.0 equiv) in a 1:1 mixture of THF and H_2O (150 mL) was added lithium hydroxide monohydrate (5.59 g, 133 mmol, 5 equiv) and the reaction was stirred at 25 °C for 2 h. The reaction mixture was diluted with ethyl acetate (100 mL) and the organic layer was extracted with water (3×100 mL). The combined aqueous extracts were acidified with 1 N hydrochloric acid (50 mL, pH 2.0) and re-extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to yield 7.42 g (100%) of the title compound **25** as a mixture of inseparable tautomers as a gum. The crude product was used for next step without further purification ν_{max} (Neat)/cm^{-1} 3450m, 3034m, 1723s, 1654brs, 1418m, 1185w; δ_H (400 MHz, $CDCl_3$) 1.98 (s, 0.5H), 2.14 (s, 2.5H), 2.64 (t, J=7.0 Hz, 0.35H), 2.69 (t, J=7.0 Hz, 1.65H), 3.46 (s, 1.80H), 3.93 (t, J=7.0 Hz, 0.35H), 4.00 (t, J=6.5 Hz, 1.65H), 4.82, 4.83 (2×s, 2H), 5.40 (s, 0.2H), 7.18–7.59 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 31.4, 31.8, 41.0, 48.9, 76.5 76.6, 87.2, 128.7, 128.8, 128.9, 129.1, 129.2, 129.4, 134.5, 135.2, 169.6, 176.4, 189.1, 191.2, 201.5; *m/z* (ESI+) 280 (MH^+, 100%); HRMS: found 280. 1192 (MH^+). $C_{14}H_{18}NO_5$ requires 280.1185.

4.1.7. 3-Acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone 26. To a solution of 3-(*N*-benzyloxy-*N*-(3-oxobutyryl)amino)propanoic acid **25** (7.42 g, 26.6 mmol, 1.0 equiv) in THF (75 mL) at 0 °C was added portionwise 1,1′-carbonyl diimidazole (5.17 g, 31.9 mmol, 1.2 equiv) and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was cooled to 0 °C and sodium hydride (2.76 g, 69.2 mmol, 2.6 equiv, 60% dispersion in oil) was added portionwise. The resulting mixture was stirred at 25 °C for 5 h. Water (50 mL) was added to the above reaction mixture, which was then acidified with 1 N hydrochloric acid (pH 2.0, 50 mL). The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to afford the crude product, which was purified by flash column chromatography (silica gel, 50% diethyl ether in 30–40 petroleum ether) to yield 6.0 g (86%) of the desired title compound **26** as a white solid and as a (1:1) mixture of tautomers, mp 56–57 °C. ν_{max} (neat)/cm^{-1} 2960m, 1671s, 1555s, 1449m, 1224w; δ_H (400 MHz, $CDCl_3$) 2.52 (t, J= 6.5 Hz, 1H), 2.53 (s, 1.5H), 2.65 (t, J=6.5 Hz, 1H), 2.67 (s, 1.5H), 3.39 (t, J=6.5 Hz, 1H), 3.44 (t, J=6.5 Hz, 1H), 4.99 (s, 1H), 5.03 (s, 1H), 7.34–7.41 (m, 2.5H), 7.42–7.49 (m, 2.5H); δ_C (100.6 MHz, $CDCl_3$) 24.4, 26.8, 33.5, 33.8, 45.7, 46.0, 76.7, 102.1, 105.7, 128.4, 128.6, 128.7, 129.1, 129.6, 129.7, 134.8, 135.6, 165.5, 172.1, 190.3, 192.1, 194.4, 199.5; *m/z* (ESI-) 260 [$(M-H)^-$, 100%]; HRMS: found 260.0928 $(M-H)^-$. $C_{14}H_{14}NO_4$ requires 260.0923.

4.1.8. 3-Acetyl-*N*-benzyloxy-4-hydroxy-2(1*H*)-pyridone 27. To a solution of 3-acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone **26** (1.00 g, 3.83 mmol, 1.0 equiv) in benzene (15 mL) was added lead tetraacetate (1.70 g, 3.83 mmol, 1.0 equiv) and the reaction mixture was stirred at 70 °C for 20 h. After cooling to 25 °C, the reaction mixture was filtered and the solid residue was washed with ethyl acetate (50 mL). The combined filtrates were evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% diethyl ether in 30–40 petroleum ether and 30% ethyl acetate in 30–40 petroleum ether) to afford 250 mg (25%) of the desired title compound **27** as a white solid, mp 105 °C, and 400 mg (40%) of unreacted 3-acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone **26** as a white solid. ν_{max}

(neat)/cm^{-1} 2960m, 1664s, 1613s, 1551m, 1468m, 1386m, 1355m, 1220w, 1165w, 960w; δ_H (400 MHz, $CDCl_3$) 2.80 (s, 3H), 5.22 (s, 2H), 5.69 (d, $J=8.0$ Hz, 1H), 7.18 (d, $J=8.0$ Hz, 1H), 7.41 (s, 5H); δ_C (100.6 MHz, $CDCl_3$) 31.6, 78.9, 98.3, 108.4, 128.9, 129.5, 130.1, 133.4, 142.1, 154.1, 175.6, 204.8; *m/z* (ESI-) 258 [$(M-H)^-$, 100%]; HRMS: found 258.0769 $(M-H)^-$. $C_{14}H_{12}NO_4$ requires 258.0766.

4.1.9. 3-Acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2(1*H*)-pyridone 28. To a solution of 3-acetyl-*N*-benzyloxy-4-hydroxy-2(1*H*)-pyridone **27** (800 mg, 3.09 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise a solution of bromine (0.17 mL, 3.39 mmol, 1.1 equiv) in DCM (0.5 mL) and the resulting mixture was heated at reflux for 12 h. The reaction mixture was cooled down to 25 °C before the addition of water (20 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to afford the crude product which was purified by flash column chromatography (silica gel, 20% diethyl ether in 30–40 petroleum ether) to yield 750 mg (72%) of the desired title compound **28** as a white solid, mp 122 °C. ν_{max} (neat)/cm^{-1} 3082m, 1673s, 1599s, 1528m, 1454m, 1381m, 1223m, 968.5m; δ_H (400 MHz, $CDCl_3$) 2.79 (s, 3H), 5.21 (s, 2H), 7.41 (s, 5H), 7.52 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 31.1, 79.4, 90.1, 107.9, 128.9, 129.8, 130.0, 132.9, 142.5, 157.6, 172.7, 205.7; *m/z* (ESI-) 338, 336 $(M-H)^-$, 100%]; HRMS: found 335.9871 [$M(^{79}Br)-H]^-$ $C_{14}H_{11}BrNO_4$ requires 335.9871.

4.1.10. 3-Acetyl-*N*-benzyloxy-5-[(3′,5′-di-*t*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone 30. To a solution of 3,5-di-*tert*-butyl-4-hydroxyphenylboronic acid **18** (156 mg, 0.62 mmol, 1.0 equiv) and 3-acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2(1*H*)-pyridone **28** (214 mg, 0.63 mmol, 1.0 equiv) in THF (1.25 mL) was added 2 M aqueous sodium carbonate solution (1.25 mL) followed by tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol, 0.05 equiv). The reaction mixture was then heated at reflux for 12 h before cooling to 25 °C and partitioned in a 1:1 mixture of ethyl acetate/water (30 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in DCM) to yield 205 mg (71%) of the desired title compound **30** as a yellow solid, mp 230–232 °C. ν_{max} (neat)/cm^{-1} 3632w, 2957m, 1663s, 1608m, 1536m, 1436m, 1414m, 1376w, 1226m, 1120m; δ_H (400 MHz, $CDCl_3$) 1.42 (s, 18H), 2.86 (s, 3H), 5.29 (s, 2H+OH), 6.95 (s, 2H), 7.21 (s, 1H), 7.39–7.44 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 31.6, 34.2, 78.6, 108.1, 113.3, 122.1, 125.8, 128.9, 129.7, 130.2, 134.0, 135.8, 140.6, 153.8, 158.1, 173.8, 206.1; HRMS: found 462.2271 $(M-H)^-$. $C_{28}H_{32}NO_5$ requires 462.2280.

4.1.11. 3-Acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-1′-methoxy-4′-oxo)-2,5-cyclohexadienyl]-4-hydroxy-2(1*H*)-pyridone 31. To a clear solution of 3-acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone **30** (14 mg, 0.03 mmol, 1.0 equiv) in MeOH (2 mL) was added iodobenzene diacetate (11 mg, 0.033 mmol, 1.1 equiv) and the reaction mixture was stirred at 40 °C for 24 h. After cooling to rt (25 °C), the solvent was removed under vacuum and the residue was dissolved in ethyl acetate (5 mL). The organic layer was washed with water (5 mL), brine (5 mL) dried ($MgSO_4$), filtered and the filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 15% ethyl acetate in 30–40 petroleum ether) to yield 5.5 mg (37%) of quinone methide **31** as a yellow solid, mp 224–225 °C. ν_{max} (neat)/cm^{-1} 2956m, 1731m, 1668s, 1650m, 1635m, 1611m, 1457w; δ_H (400 MHz, $CDCl_3$) 1.23 (s, 18H), 2.77 (s, 3H), 3.15 (s, 3H), 5.26 (s, 2H), 6.02 (s, 2H), 7.32–7.45 (m, 5H), 7.73 (s, 1H); *m/z* (ESI-) 492 [$(M-H)^-$, 100%]; HRMS: found 492.2388 $(M-H)^-$. $C_{29}H_{34}NO_6$ requires 492.2386.

4.1.12. 3-Acetyl-5-[(3′,5′-di-*tert*-butyl-1′-methoxy-4′-oxo)-2,5-cyclohexadienyl]-1,4-dihydroxy-2(1*H*)-pyridone 32. To a solution of 3-acetyl-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-1,4-dihydroxy-2(1*H*)-pyridone **14** (10 mg, 0.027 mmol, 1.0 equiv) in MeOH (2 mL) was added iodobenzene diacetate (9 mg, 0.028 mmol, 1.05 equiv) and the reaction mixture was stirred at 40 °C for 24 h. After cooling to rt (25 °C), the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (5 mL). The organic layer was washed with water (5 mL), brine (5 mL) dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 3–5% methanol in DCM) to yield 3.2 mg (30%) of quinone methide **32** as a yellow solid, mp 235–237 °C. ν_{max} (neat)/cm^{-1} 2956m, 1731m, 1668s, 1650m, 1635m, 1611m, 1457w; δ_H (200 MHz, $CDCl_3$) 1.21 (s, 18H), 2.72 (s, 3H), 3.24 (s, 3H), 5.28 (s, 1H), 6.12 (s, 2H), 8.33 (s, 1H); *m/z* (ESI-) 402 [$(M-H)^-$, 100%]; HRMS: found 402.1921 $(M-H)^-$. $C_{22}H_{28}NO_6$ requires 402.1917.

4.1.13. Preparation of de-*tert*-butylated phenols 37 and 38. To a solution of toluene (2 mL) containing *exo*-quinone methide **33**[13] (20 mg, 0.038 mmol) was added aluminium chloride (23 mg, 0.172 mmol, 4.5 equiv) and stirred the reaction at 95 °C for 2 days. After cooling to rt, the reaction mixture was poured into crushed ice, 1 N hydrochloric acid was added (0.3 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 0.2–1% methanol in DCM as a gradient elution, (Silica gel had been prewashed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C)] to yield 4 mg (25%) of di-dealkylated phenol **37** as a pale brown solid recrystallized from 10% methanol in benzene, mp 202–203 °C, 1.7 mg (10%) of mono-dealkylated phenol **38** as a pale brown solid, mp 196–197 °C and 1.0 mg (5%) of phenol **17**[13] as a pale yellow solid. The structure of phenol **37** was determined by single-crystal crystallography.

Di-de-t-butylated phenol **37**. ν_{max} (neat)/cm^{-1} 3243brm, 2938m, 1704w, 1647s, 1612s, 1541w, 1516m, 1428m, 1272m, 1263m; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.05–1.11 (m, 2H), 1.17–1.28 (m, 1H), 1.30–1.80 (m, 9H), 2.02–2.11 (m, 2H), 2.81 (s, 3H), 4.72–4.78 (m, 1H), 4.94 (d, J=7.0 Hz, 1H), 5.72 (brs, 1H), 6.96 (d, J=8.5 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 22.4, 22.8, 22.9, 23.0, 24.5, 26.8, 31.4, 45.5, 55.9, 84.3, 107.1, 107.8, 116.1, 122.8, 131.3, 144.9, 154.3, 156.3, 173.1, 204.9, 205.4; *m/z* (ESI+) 412 (MH^+, 100%); HRMS: found 412.1755 (MH^+). $C_{23}H_{26}NO_6$ requires 412.1760.

Monode-alkylated phenol **38**. ν_{max} (neat)/cm^{-1} 3243brm, 2939m, 1705w, 1648s, 1613s, 1541w, 1515m, 1428m, 1272m, 1263m; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05–1.11 (m, 2H), 1.17–1.28 (m, 1H), 1.30–1.80 (m, 18H), 2.02–2.13 (m, 2H), 2.82 (s, 3H), 4.75–4.79 (m, 1H), 4.89 (d, J=7.5 Hz, 1H), 5.02 (s, 1H), 6.77 (d, J=8.0 Hz, 1H), 7.01 (dd, J=8.0, 2.0 Hz, 1H), 7.15 (d, J=2.0 Hz, 1H,); *m/z* (ESI-) 466 [$(M-H)^-$, 100%); HRMS: found 466.2231 $(M-H)^-$. $C_{27}H_{32}NO_6$ requires 466.2230.

4.1.14. 4-Benzyloxy-3,5-di-isopropylbromobenzene 40. To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 176 mg, 4.41 mmol, 1.2 equiv) in THF (10 mL) at 0 °C was added dropwise a solution of 4-bromo-2,6-di-isopropylphenol[26] (0.94 g, 3.67 mmol, 1.0 equiv). After stirring for 1 h at 25 °C, the reaction mixture was cooled down to 0 °C prior to the addition of benzyl bromide (0.46 mL, 3.85 mmol, 1.05 equiv). The resulting mixture was stirred at 40 °C for 12 h. The reaction mixture was cooled to rt before the addition of water (20 mL) and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with water (2×10 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 2% diethyl ether in 30–40 petroleum ether) to yield 1.10 g (86%) of title compound **40** as a clear oil. ν_{max} (neat)/cm^{-1} 2963s, 1574m, 1497m, 1456s, 1325s, 1184s; δ_H (400 MHz, $CDCl_3$) 1.25 (d, J=7.0 Hz, 12H), 3.39 (septet, J=7.0 Hz, 2H), 4.83 (s, 2H), 7.27 (s, 2H), 7.41 (t, J=7.0 Hz, 1H), 7.47 (t, J=7.0 Hz, 2H), 7.52 (d, J=7.0 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 23.9, 26.8, 76.5, 118.1, 127.3, 127.4, 128.1, 128.4, 137.3, 144.4, 152.2.

4.1.15. 4-Benzyloxy-3,5-di-isopropylphenylboronic acid 41. To a −78 °C cooled solution of 4-benzyloxy-3,5-di-isopropylbromobenzene **40** (1.00 g, 2.89 mmol, 1.0 equiv) in THF (25 mL) was added dropwise a 1.5 M solution of *tert*-butyl lithium in hexanes (4.04 mL, 6.06 mmol, 2.1 equiv). The reaction mixture was brought to 25 °C and after stirring for 1 h at 25 °C, the reaction mixture was cooled to −78 °C prior to the addition of trimethyl borate (0.97 mL, 8.67 mmol, 3.0 equiv). The reaction was left overnight at 25 °C prior to the addition of saturated ammonium chloride solution (50 mL). The resulting mixture was stirred at 25 °C for 2 h and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by recrystallization (30% ethyl acetate in hexane) to yield 450 mg (50%) of the title compound **41** as a white solid, mp >250 °C. ν_{max} (neat)/cm^{-1} 3377brm, 2961s, 1600m, 1360s, 1316s, 1295s, 1181s, 1022m; δ_H (400 MHz, $CDCl_3$) 1.36 (d, J=7.0 Hz, 12H), 3.49 (septet, J=7.0 Hz, 2H), 4.90 (s, 2H), 7.40 (t, J=7.0 Hz, 1H), 7.47 (t, J=7.0 Hz, 2H), 7.53 (d, J=7.0 Hz, 2H), 8.07 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 24.1, 26.6, 76.4, 127.4, 128.0, 128.6, 131.7, 137.4, 141.5, 157.2; *m/z* (ESI-) 311 [$(M-H)^-$, 100%]; HRMS: found 311.1824 $(M-H)^-$. $C_{19}H_{24}BO_3$ requires 311.1819.

4.1.16. 3-Acetyl-*N*-benzyloxy-5-[(4′-benzyloxy-3′,5′-di-isopropyl)phenyl]-4-hydroxy-2(1*H*)-pyridone 42. To a solution of 4-benzyloxy-3,5-di-isopropylphenylboronic acid **41** (92 mg, 0.29 mmol, 1.0 equiv), and 3-acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2-pyridone **28** (98 mg, 0.29 mmol, 1.0 equiv) in 4:1 mixture of toluene/ethanol (1.25 mL) was added a 2 M aqueous sodium carbonate solution (1.25 mL), followed by tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.014 mmol, 0.05 equiv). The resulting mixture was heated at reflux for 12 h before being cooled to rt and partitioned in a 1:1 mixture of ethyl acetate/water (20 mL). The phases were separated, and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 3% ethyl acetate in DCM) to yield 110 mg (71%) of the title compound **42** as a yellow gum. ν_{max} (neat)/cm^{-1} 2963s, 1668s, 1609s, 1536m, 1454m, 1413m, 1377m, 1308m, 1223m; δ_H (400 MHz, $CDCl_3$) 1.26 (d, J=7.0 Hz, 12H), 2.89 (s, 3H), 3.42 (septet, J=7.0 Hz, 2H), 4.83 (s, 2H), 5.33 (s, 2H), 6.90 (s, 2H), 7.21 (s, 1H), 7.38–7.51 (m, 10H); δ_C (100.6 MHz, $CDCl_3$) 24.1, 26.6, 31.6, 76.5, 78.8, 107.9, 112.6, 124.9, 127.4, 127.9, 128.0, 128.5, 129.0, 129.8, 130.5, 133.7, 137.5, 141.0, 142.0, 153.0, 158.1, 174.0, 206.1; HRMS: found 524.2434 $(M-H)^-$. $C_{33}H_{34}NO_5$ requires 524.2437.

4.1.17. 3-Acetyl-1,4-dihydroxy-5-[(3′,5′-di-isopropyl-4′-hydroxy)phenyl]-2(1*H*)-pyridone 43. A mixture of 3-acetyl-*N*-benzyloxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-4-hydroxy-2(1*H*)-pyridone **42** (100 mg, 0.19 mmol, 1.0 equiv) and 10% palladium on carbon (100 mg) in dioxane (5 mL) was stirred under hydrogen (balloon) atmosphere at 25 °C for 2 h. The reaction mixture was filtered, the solid residue was washed with dioxane (20 mL) and the combined filtrates were evaporated under vacuum to yield 80 mg (96%) of the 3-acetyl-*N*-hydroxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-4-hydroxy-2(1*H*)-pyridone as a yellow solid, mp 202–203 °C. The crude product was used as such for next step without further purification. ν_{max} (neat)/cm^{-1} 3174m, 2963m, 1648s, 1613s, 1429s, 1323m, 1248m, 1212w, 1123m, 722m; δ_H (400 MHz, $CDCl_3$) 1.27 (d, J=7.0 Hz, 12H), 2.83 (s, 3H), 3.48 (septet, J=7.0 Hz, 2H), 4.87 (s, 2H), 7.23 (s, 2H), 7.39 (t, J=7.0 Hz, 1H, 7.45 (t, J=7.0 Hz, 2H), 7.53 (d, J=7.0 Hz, 2H), 7.94 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 22.7, 24.1, 26.7, 76.5, 107.9, 112.6, 125.0, 127.3, 127.9, 128.0, 128.6, 133.9, 137.5, 142.2, 153.2, 158.1, 174.0, 206.1; *m/z* (ESI-) 434 [$(M-H)^-$, 100%]; HRMS: found 434.1964 $(M-H)^-$. $C_{26}H_{28}NO_5$ requires 434.1967.

To a −78 °C cooled solution of 3-acetyl-1,4-dihydroxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-2(1*H*)-pyridone (60 mg, 0.14 mmol, 1.0 equiv) in DCM was added 1 M boron

tribromide in DCM (0.70 mL, 0.70 mmol, 5.0 equiv) and the reaction mixture was stirred at the same temperature for 1 h. Methanol (100 μL) was added to the reaction mixture, which was then stirred for 10 min at the same temperature. The reaction was then further quenched by the sequential addition of water (5 mL) and ethyl acetate (5 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude residue was purified by flash column chromatography [silica gel, 1% methanol in DCM, (silica gel having been prewashed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C)] to yield 35 mg (74%) of the title compound **43** as a yellow solid, mp 201 °C. ν_{max} (neat)/cm^{-1} 3467m, 3166m, 2961m, 1648s, 1602s, 1548m, 1432m, 1416s, 1260w, 1198m, 1146m, 1127m, 723w; δ_H (250 MHz, $CDCl_3$) 1.32 (d, J=7.0 Hz, 12H), 2.85 (s, 3H), 3.20 (septet, J=7.0 Hz, 2H), 5.33 (s, 1H), 7.18 (s, 2H), 7.91 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 22.7, 27.2, 31.7, 106.0, 113.5, 123.7, 124.5, 133.8, 134.5, 150.2, 157.4, 171.5, 205.5; *m/z* (ES-) 344 [$(M-H)^-$, 100%)]; HRMS: found 344.1497 $(M-H)^-$. $C_{19}H_{22}NO_5$ requires 344.1498.

4.1.18. Oxidative cyclisation of di-isopropylated *N*-hydroxy-2-pyridone 43 with *Z*-2-cyclodecenone 16 (44–46). To a mixture of 3-acetyl-1,4-dihydroxy-5-[(3′,5′-di-isopropyl)-4′-hydroxy)phenyl]-2(1*H*)-pyridone **43** (140 mg, 0.41 mmol, 1.0 equiv) and *Z*-2-cyclodecenone[15] (65.4 mg, 0.43 mmol, 1.05 equiv) in DCM (0.026 M) was added iodobenzene diacetate (145 mg, 0.45 mmol, 1.1 equiv) all at once. Immediately the reaction turned to a dark colour. After stirring for 2 h at 25 °C, the reaction was refluxed for 24 h. During the reflux, the colour of the reaction turned into reddish yellow. After cooling to 25 °C, water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 10–30% EtOAc in 30–40 petroleum ether to collect phenol and quinone methides, followed by second purification with DCM for quinone methide and 0–3% EtOAc in DCM as a gradient elution for phenols, (silica gel having been pre-washed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C for 24 h)] to give 36 mg (18%) of *cis*-quinone methide **45** as a reddish-yellow solid, mp 146 °C, 24 mg (12%) of *cis*-phenol **44** as pale yellow solid, re-crystallized from ethyl acetate, mp 262–264 °C, and 5.5 mg (3%) of *trans*-phenol **46** as a pale yellow solid, mp 185–187 °C. *cis*-Quinone methide **45** was equilibrated into *cis*-phenol **44** by treating with aluminium chloride (2 equiv) in DCE at reflux for 24 h.

cis-Phenol **44**. ν_{max} (neat)/cm^{-1} 3398br, 2959s, 2874m, 1706w, 1654s, 1611m, 1541m, 1438m, 1419m, 1297w, 1201w, 1151m: δ_H (400 MHz, $CDCl_3$) 0.98–1.10 (m, 2H), 1.12–1.22 (m, 3H), 1.22–1.31 (d, J=7.0 Hz, 12H), 1.32–1.71 (m, 7H), 2.02–2.12 (m, 2H), 2.80 (s, 3H), 3.16–3.27 (m, 2H), 4.71–4.81 (m, 1H), 4.88 (d, J=7.0 Hz, 1H), 5.10 (s, 1H), 6.94 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 22.1, 22.6, 22.8, 23.1 (2C), 24.4, 27.1, 27.2, 31.5, 45.7, 55.7, 84.1, 107.1, 108.8, 123.1, 134.7, 145.0 (2C), 150.3, 154.3, 173.2, 205.1, 205.5; HRMS: found 494. 2534 $(M-H)^-$. $C_{29}H_{36}NO_6$ requires 494.2543.

cis-Quinone methide **45**. ν_{max} (neat)/cm^{-1} 2962s, 2873m, 1688s, 1620s, 1558m, 1439s, 1387m, 1361m, 1289m, 1078w; δ_H (400 MHz, $CDCl_3$) 0.88–1.01 (m, 1H), 1.02–1.21 (m, 14H), 1.29–1.51 (m, 4H), 1.66–1.70 (m, 2H), 1.82–1.87 (m, 1H), 1.96–2.08 (m, 2H), 2.18–2.26 (m, 1H), 2.49 (dd, J=16.0, 10.5 Hz, 1H), 2.77 (s, 3H), 3.06–3.19 (m, 2H), 3.67 (ca. t, J=9.0 Hz, 1H), 4.29 (ca. t, J=9.0 Hz, 1H), 5.32 (d, J=9.0 Hz, 1H), 6.97 (d, J=2.5 Hz, 1H), 8.41 (d, J=2.5 Hz, 1H); δ_C (100.6 MHz, $CDCl_3$) 21.5, 22.0, 22.3, 23.2, 24.3, 24.6, 25.1, 27.2, 27.3, 27.4, 28.8, 48.3, 61.6, 66.0, 85.7, 107.0, 126.3, 128.5, 129.7, 141.1, 148.5, 150.4, 167.9, 182.1, 185.5, 204.3, 209.5; HRMS: found 494.2540 $(M-H)^-$. $C_{29}H_{36}NO_6$ requires 494.2543.

trans-Phenol **46**. ν_{max} (neat)/cm^{-1} 3400m, 2959s, 2871m, 1711m, 1654s, 1613m, 1542m, 1468s, 1436m, 1295m, 1202m, 1152m, 975m; δ_H (500 MHz, $CDCl_3$) 0.82–0.98 (m, 3H), 1.20–1.31 (m, 6H), 1.27 (d, J=7.0 Hz, 12H), 1.40–1.61 (m, 2H), 1.89–1.98 (m, 2H), 2.28–2.38 (m, 1H), 2.80 (s, 3H), 3.12–3.22 (br m, 2H), 4.64 (d, J=10.5 Hz, 1H), 4.72 (dt, J=10.5, 2.5, Hz, 1H), 4.93 (s, 1H), 6.79 (s, 1H), 6.87 (s, 1H); δ_C (125.8 MHz, $CDCl_3$) 23.4, 23.8, 24.3, 25.4, 25.9, 29.8, 30.6, 30.7, 31.8, 34.7, 34.9, 44.1, 64.1, 87.6, 107.4, 109.4, 122.6, 127.4, 129.7, 136.6, 137.2, 147.0, 154.7, 154.8, 174.1, 205.9, 208.2; HRMS: found $(M-H)^-$ 494.2545. $C_{29}H_{36}NO_6$ requires 494.2543.

4.2. X-ray crystallographic studies

Crystals were grown as described in preparations. Single crystals were mounted on glass fibres using perfluoro-polyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems Cryostream unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo K_α radiation, λ=0.71073 Å). Intensity data were processed using the DENZO-SMN package.

Space groups were assigned by examination of the systematic absence of the intensity data. The structures were solved using the direct-methods program SIR92, which located all non-hydrogen atoms of the organic molecules. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atoms of the organic molecules were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. CH hydrogen atoms were positioned geometrically after each cycle of refinement. 3-Term Chebychev polynomial weighting schemes were applied. The crystal structures are shown as thermal ellipsoid plots (ORTEP-3)[27] at 40% probability.

4.3. Supplementary material

Crystallographic data for compounds **37** and **44** have been deposited with Cambridge Crystallographic Data Centre (Deposition numbers CCDC 292547 and 292548, respectively). Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

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