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Total synthesis of pyridovericin

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Abstract—The total synthesis of the naturally occurring kinase inhibitor pyridovericin **1** is reported. A flexible and efficient synthesis has been accomplished in good yield from readily available 2,4-dihydroxypyridine. Pyridovericin is a key intermediate in our proposed biomimetic synthesis of pyridomacrolidin **2**.

As part of our studies towards the synthesis of novel tyrosine kinase inhibitors, we have become particularly interested in the biomimetic synthesis of pyridovericin **1** and pyridomacrolidin **2**. Pyridovericin and pyridomacrolidin are novel metabolites isolated from the entomopathogenic fungus *Beauveria bassiana* in 1998 by Nakagawa and co-workers.[1] Structurally, 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] Biologically, pyridovericin **1** and pyridomacrolidin **2** have been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100 μg/ml[1] making them potential therapeutic leads against a variety of proliferative and inflammatory diseases (Fig. 1).[5]

Interest in this type of compounds has largely focussed on the determination of the biosynthetic pathway for the generation of tenellin **3**, bassianin **4**, and ilicicolin H **5**.[6–8] Biosynthetically, it has been shown through a series of 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** then generates the transient *p*-quinonemethide intermediate **9**, which undergoes a ring expansion to generate the 2-pyridone ring **10**. Finally, oxidation of the newly formed pyridone unit **10** generates tenellin **3** (Scheme 1).[6,8]

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 elucidated. However, it is possible to propose a biomimetic formation of pyridomacrolidin **2** from pyridovericin **1** via a number of simple steps (Scheme 2); (i) oxidation of pyridovericin **1** to hydroxamic acid **11**, (ii) further oxidation to the acyl nitrone intermediate **12**, (iii) 1,3-dipolar cycloaddition[9] with cephalosporolide B **13**, and (iv) re-aromatisation to form pyridomacrolidin **2**. Cephalosporolide B **13** is itself a natural product, and has been independently isolated from the fungus *Cephalosporium aphidicola*,[10] although it has not yet been isolated from *B. bassiana*.

Chemically, this novel class of compounds has elucidated a significant amount of interest as demonstrated by the synthetic work already published.[11–15] Herein, we would like to describe full details of our progress towards the biomimetic synthesis of pyridomacrolidin **2** by reporting a convergent and efficient total synthesis of pyridovericin **1** from readily available starting materials.[16]

Retrosynthetically, we envisaged that the core structure of pyridovericin **1** could be constructed via addition of lithiated pyridine **15** to aldehyde **16**, giving after oxidation the pyridomacrolidin precursor **14**. The organolithium reagent **15** would in turn be generated via metal–halogen exchange from the corresponding bromide **17**, which itself could be synthesised via selective palladium-catalysed

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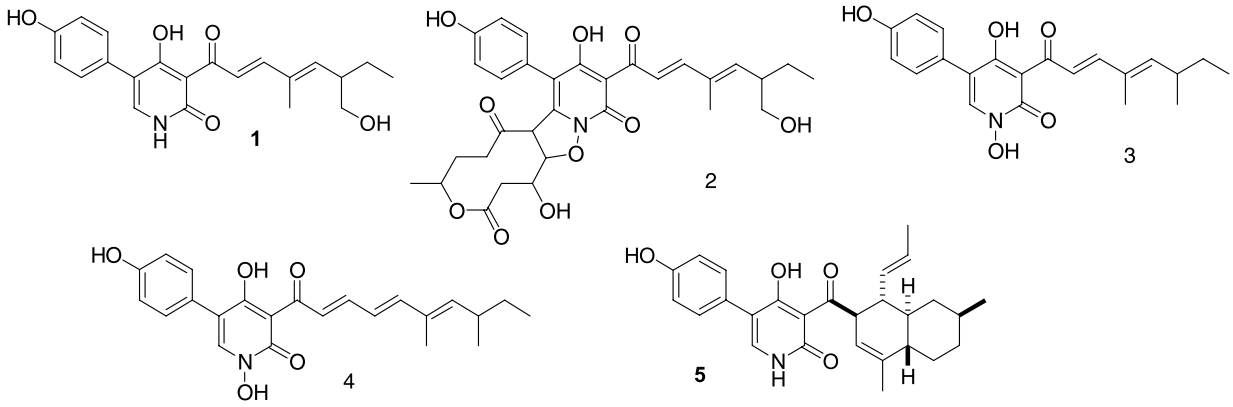
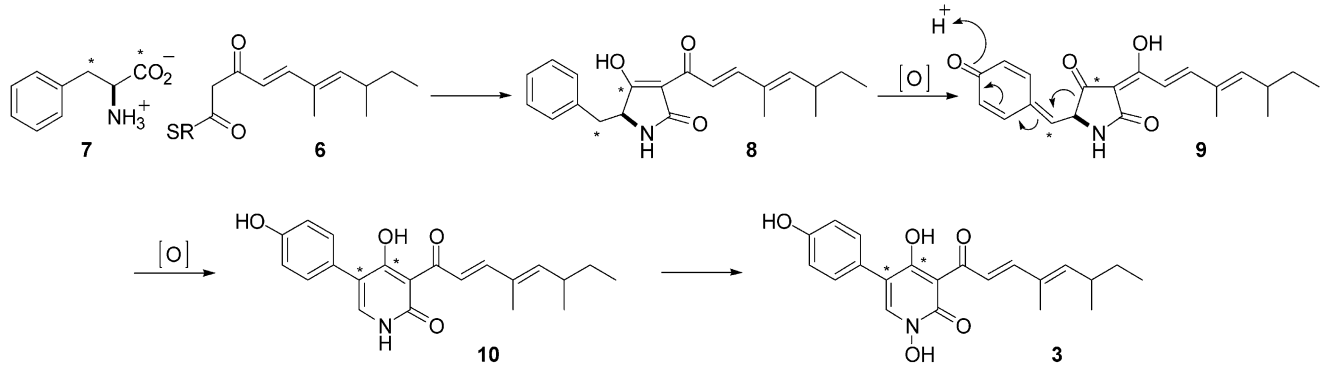
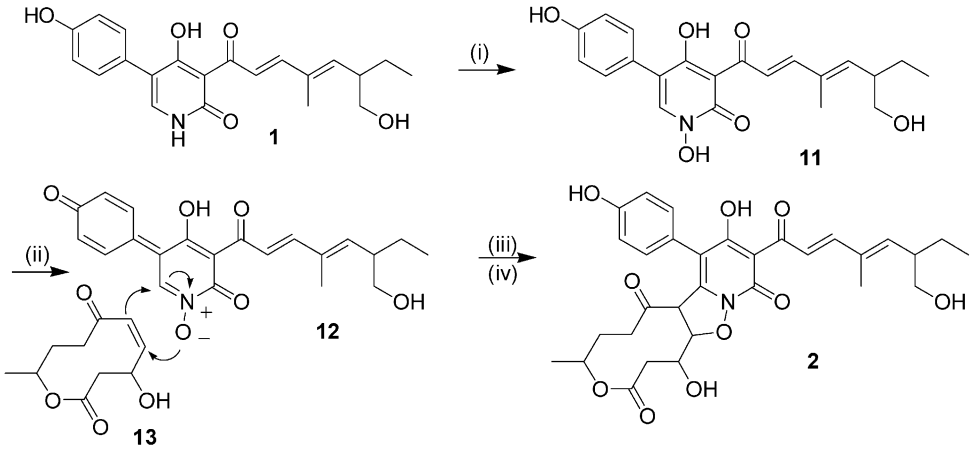


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related analogues.



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

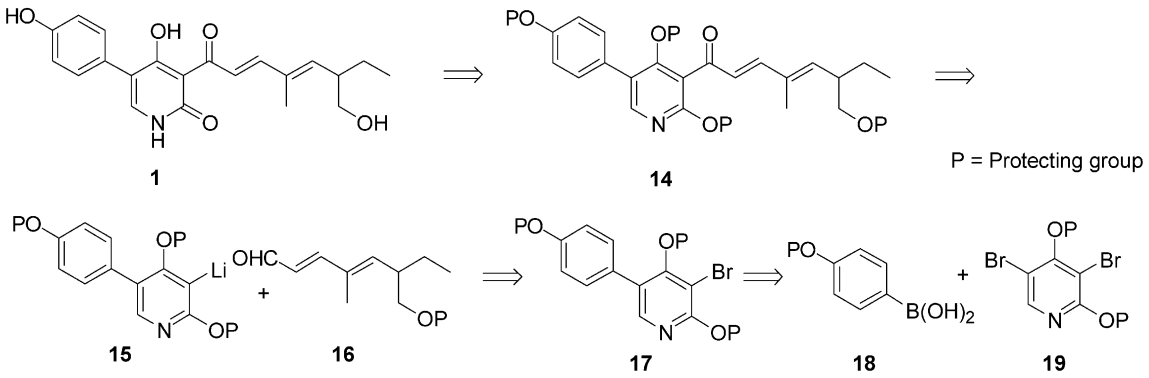


Scheme 2. Proposed biosynthesis of pyridomacrolidin **2**.

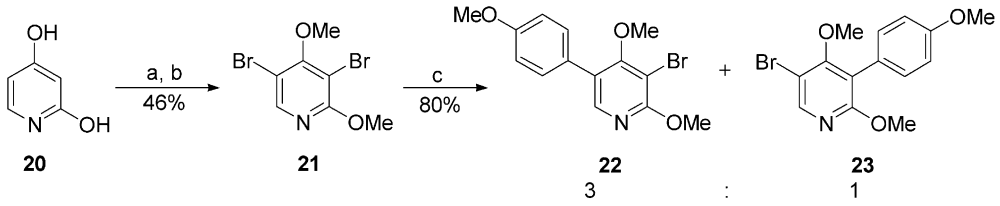
mono-coupling between boronic acid **18** and dibromide **19** (Scheme 3).

Our convergent synthesis began with commercially available 2,4-dihydroxypyridine **20**, which was dibrominated at the C_3 and C_5 positions[17] and then *bis*-O-methylated[18] to give pyridine **21** in good yield. At this stage we decided to perform a model reaction for Suzuki coupling with commercially available 4-methoxyphenylboronic acid. Coupling of bromo pyridine **21** and 4-methoxyphenyl boronic acid under Suzuki-type conditions afforded a separable mixture of coupled adducts **22** and **23**, in which the major product was the desired biaryl **22** (Scheme 4). The regio-selectivity observed in this reaction is consistent with the major coupling being at the less hindered C_5 position (Fig. 2).[19]

At this point, the feasibility of the metal–halogen exchange procedure was tested. Thus, treatment of bromo pyridine **22** with *t*-butyl lithium generated the desired lithiated intermediate **24** which was subsequently trapped with a variety of electrophiles (Table 1).



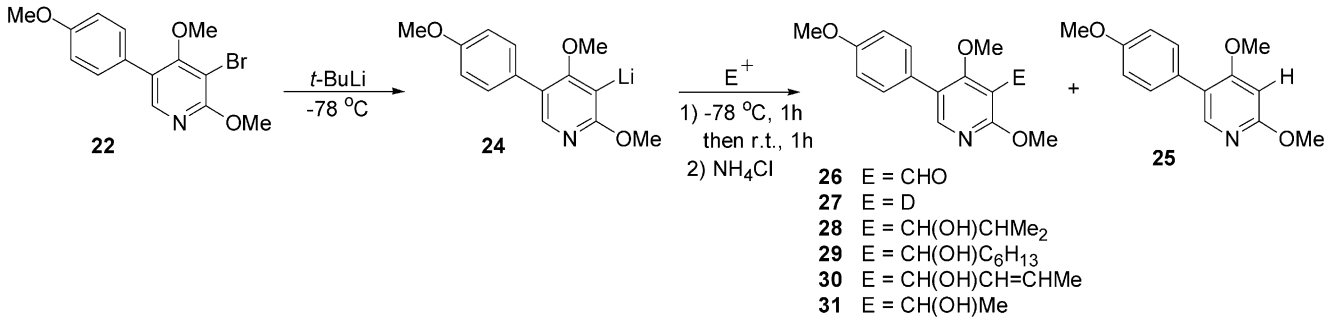
Scheme 3. Retrosynthetic scheme for pyridovericin **1**.

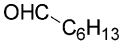
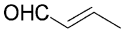


Scheme 4. Reagents and conditions: (a) Br_2(2 eq.), 47% aq. HBr, r.t., 1h; (b) excess MeI, Ag_2CO_3, DCM, r.t., 5 days; (c) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, toluene:ethanol (4:1), reflux, 12h. Synthesis of pyridovericin core synthon **22**.

Figure 2. Observed 2D NOESY's of **22** and **23**.

Table 1. Model additions to lithio-pyridine derivative **24**



Entry	Electrophile	Products (addition/protonation ratio)	Overall yield (%)
1	HCO_2Et	**26**:**25** 32:68	Quantitative
2	D_2O	**27**	96
3		**28**:**25** 95:5	93
4		**29**:**25** 90:10	90
5		**30**:**25** 90:10	92
6		**31**:**25** 40:60	Quantiative

Not surprisingly, suitable electrophiles were aldehydes either lacking or with hindered α-hydrogens (entries 3, 4 and 5). We were particularly encouraged by the addition of crotonaldehyde (entry 5), which resembles aldehyde **16** as the proposed electrophile in our retrosynthetic analysis of pyridovericin **1** (Scheme 3).

After having succeeded in the regio-selective Suzuki coupling and in the introduction of various electrophiles to lithiated pyridine **24**, we focussed our attention towards the synthesis of tetrasubstituted pyridine core of pyridovericin **1**. Synthesis of the required boronic acid coupling partner began with 4-bromophenol **32**, which was readily protected under standard conditions[20] to generate the corresponding benzyl ether in good yield. Metal–halogen exchange followed by treatment with boron triisopropoxide[21] proceeded cleanly to afford, after hydrolysis, the desired boronic acid **33**.

Synthesis of the tetrasubstituted pyridine coupling partner was achieved by the reaction of pyridine **21** and boronic acid **33** under slightly modified Suzuki-type conditions[22] which generated a separable mixture of mono- and bis-coupled adducts **34**-**36** (Scheme 5), in which the major product was confirmed once again by nOe analysis as the desired biaryl **34** (Fig. 3).[19]

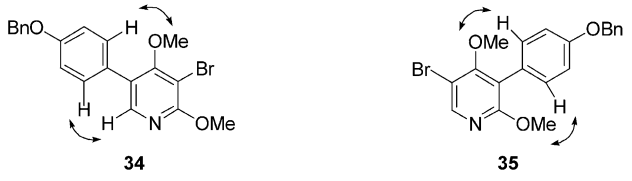


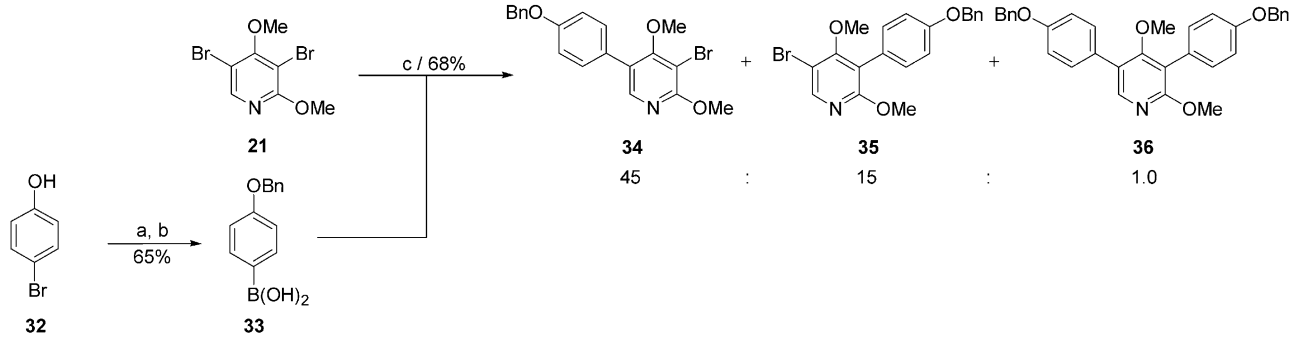
Figure 3. Observed 2D NOESY's of **34** and **35**.

Our synthesis of the C_7–C_{15} side-chain aldehyde began with dimethyl-2-ethylmalonate **37**, which was reduced to the corresponding diol[23] and then monoprotected[24] to afford the desired TBS-silyl ether **38** in good yield. Swern oxidation[25] then Wittig olefination gave ester **39**, which after reduction followed by another Swern oxidation/Wittig olefination sequence gave diene **40** in excellent overall yield. Finally, reduction of the ester to the corresponding alcohol followed by oxidation gave the desired TBS-protected aldehyde intermediate **41**, suitable for coupling to the pyridine unit (Scheme 6).

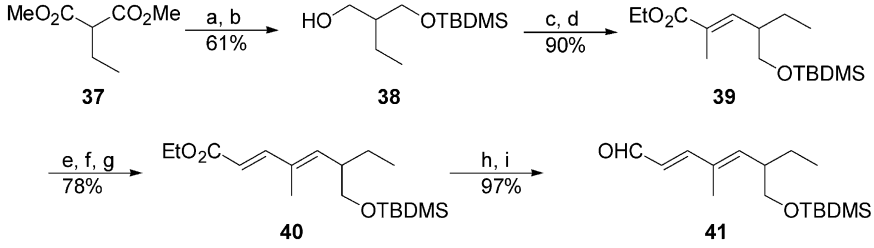
With the benzyl protected pyridine unit **34** and dienal **41** readily available, we focused our attention on the last steps of the synthesis. Thus, metal–halogen exchange of bromopyridine **34** followed by treatment with aldehyde **41** gave the desired alcohol **42**, together with the dehalogenated product **43** (2.6:1) (Scheme 7). The formation of compound **43** is easily explained as the product of the deprotonation of the aldehyde's ε-position or from *t*-butyl bromide by-product by the lithiated pyridine. Subsequent oxidation of alcohol **42** afforded the fully protected pyridovericin **44** in high yield and with no observable side products.

The deprotection of compound **44** at this point proved to be challenging, as most of the methods attempted for removal of the protecting groups either resulted in no reaction or caused complete decomposition of the starting material. It was only after considerable experimentation that it was found that in situ generated trimethylsilyl iodide[26] successfully removed both methyl ethers and TBDMS to afford diol **45**, however the benzyl group was left intact (Scheme 8).

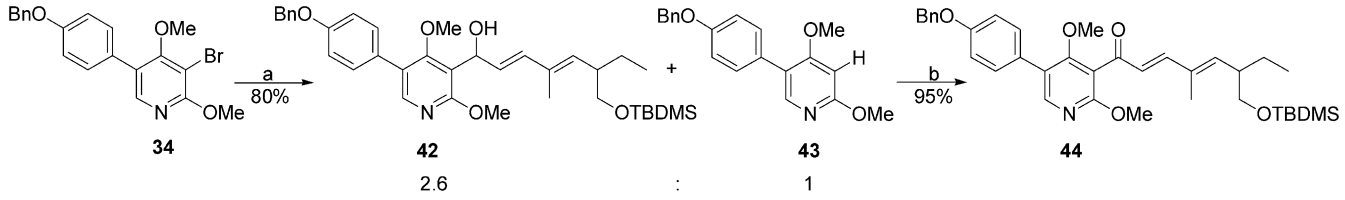
Finally, removal of the adamant benzyl protecting group was carefully effected using boron tribromide,[27] to generate



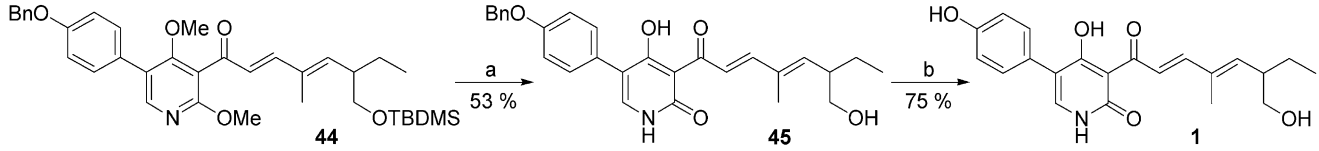
Scheme 5. Reagents and conditions: (a) BnBr, TBAI, NaH, THF, r.t., 4h; (b) (i) $_n$-BuLi, $B(O^iPr)_3$, THF, −78 °C then r.t., overnight; (ii) sat. NH_4Cl; (c) $Pd(PPh_3)_4$, Na_2CO_3, 4:1 toluene:ethanol, reflux, overnight. Modified synthesis of pyridovericin core **34**.



Scheme 6. Reagents and conditions: (a) LAH, THF, r.t., overnight; (b) TBDMSCl, NaH, THF, r.t., overnight; (c) Swern, −78 °C; (d) $PPh_3C(CH_3)CO_2Et$, Benzene, reflux, 20h; (e) Dibal-H, THF; (f) Swern, −78 °C; (g) PPh_3CHCO_2Et, Tol., reflux, 20h; (h) Dibal-H, THF; (i) Swern, −78 °C. Synthesis of TBS-protected aldehyde **41**.



Scheme 7. Reagents and conditions: (a) *t*-BuLi, **41**, THF, −78 °C, 1h then r.t., 1h; (b) MnO_2, DCM, r.t., 48h. Synthesis of protected pyridovericin **44**.



Scheme 8. Reagents and conditions: (a) TMSCl, NaI, MeCN, r.t., 3 days; (b) BBr_3, DCM, −78 °C, 1h. Completion of the synthesis of pyridovericin **1**.

racemic pyridovericin **1** in thirteen steps for the longest linear sequence. The spectral data (^1H, ^{13}C, HRMS, TLC) for synthetic **1** exactly matched that reported for natural pyridovericin **1**.[1] Furthermore, doping experiments of synthetic and natural pyridovericin samples generated a single set of NMR signals.

In conclusion, we have completed the total synthesis of pyridovericin **1** starting from cheap and readily available starting materials. Our synthesis is convergent, fast, efficient and flexible enough to allow for the ready synthesis of a variety of analogues if desired.

1. Experimental

1.1. General

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 DQX-400, Bruker DPX-400, 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 ^1H–^1H COSY where 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 DQX400, Bruker DPX400 and Bruker AMX500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^1H (HMQC and HMBC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

IR-spectra were recorded as a KBr disc or Neat (as indicated) on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Strong (s) and medium (m) absorption bands are reported in wavenumbers (cm^{-1}).

Low resolution mass spectra were recorded on V. G. Micromass ZAB 1F and V. G. Masslab instruments as appropriate with modes of ionisation being indicated as CI, EI, ES or APCI with only molecular ions, molecular ion fragments and major peaks being reported. 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.

Elemental analyses were performed by David Lawrence at Elemental Microanalysis Limited, Okehampton, Devon.

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.

1.1.1. 3,5-Dibromo-2,4-dimethoxy pyridine, 21. To a 0 °C cooled and stirred solution of 2,4-dihydroxy pyridine **20** (4.0 g, 36.0 mmol) in 47% aqueous hydrobromic acid (40 mL) was added bromine (4.1 mL, 79.3 mmol) and the resulting mixture stirred at room temperature for 1 h. The reaction mixture was diluted with water (100 mL), and stirred for further 30 min at room temperature. The solid product was then filtered, washed with water (75 mL), and dried under vacuum. The crude residue was recrystallised from 95% ethanol to afford 7.0 g (72%) of the known[17] 3,5-dibromo-2,4-dihydroxy pyridine as a white solid, mp 245 °C (dec.) (lit.[17] 225–240 °C dec.). ν_{max} (KBr)/cm^{-1} 3101, 2951, 1648, 1618, 1455, 1443, 1429, 1170; δ_H (200 MHz, DMSO) 7.63 (s, 1H); δ_C (50 MHz, DMSO) 161.2, 160.1, 135.8, 98.1, 93.2; *m/z* (CI+) 272 (35%), 270 (MH^+ ^{79}Br ^{81}Br, 65%), 268 (30%), 112 (100%).

A heterogenous mixture of the above described 3,5-dibromo-2,4-dihydroxy pyridine (6.60 g, 24.5 mmol), methyl iodide (15 mL, 245.0 mmol) and silver carbonate (13.54 g, 49.0 mmol) in dichloromethane (500 mL) was stirred at 20 °C for 5 days. The reaction mixture was filtered through celite, and the filtrate evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 2% ethyl acetate in 30–40 petroleum ether) to afford 4.65 g (64%) desired titled product **21** as a white solid, mp 115–116 °C. ν_{max} (KBr)/cm^{-1} 2971, 2939, 1563, 1537, 1463, 1411, 1374, 1296, 1091, 1068; δ_H (200 MHz, $CDCl_3$) 8.17 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H); δ_C (50 MHz, $CDCl_3$) 162.4, 161.4, 147.2, 107.8, 102.4, 60.8, 55.1; *m/z* (CI+) 300 (20%), 298 (MH^+ ^{79}Br ^{81}Br, 60%), 296 (30%), 121 (100%).

1.1.2. 3-Bromo-2,4-dimethoxy-5-(*p*-methoxyphenyl)pyridine, 22; 5-bromo-2,4-dimethoxy-3-(*p*-methoxyphenyl)-pyridine, 23.[19] To a solution of 3,5-dibromopyridine **21** (2.87 g, 9.7 mmol) in a 4:1 mixture of toluene/ethanol (25 mL) was added a 2 M sodium carbonate solution (20 mL), followed by 4-methoxyphenylboronic acid (1.47 g, 9.7 mmol), and tetrakis(triphenylphosphine)palladium(0) (558 mg, 0.5 mmol). The reaction mixture was then refluxed for 12 h, before being cooled back down to room temperature and partitioned in a 1:1 mixture of ethyl acetate/water (100 mL). The phases were separated, and the organic layer dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude residue purified by flash column chromatography (9:1, hexane/ethyl acetate) to afford 1.88 g (60%) of 3-bromo-2,4-dimethoxy-5-(*p*-methoxyphenyl)pyridine **22**, mp 114–115 °C and 626 mg (20%) of 5-bromo-2,4-dimethoxy-3-(*p*-methoxyphenyl)pyridine **23**, mp 119–120 °C as white solids (Fig. 2).

Spectral data for **22**.[19] ν_{max} (KBr)/cm^{-1} 2972, 2935, 2938, 1562, 1514, 1463, 1394, 1117, 1089, 1006; δ_H (400 MHz, $CDCl_3$) 8.01 (s, 1H), 7.44 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 4.05 (s, 3H), 3.86 (s, 3H), 3.54 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 163.1, 160.7, 159.3, 146.1, 130.0, 126.7, 125.8, 114.1, 101.3, 60.3, 55.3, 54.7; *m/z* (APCI+) 326 (MH^+ ^{81}Br, 100%), 324 (80%); HRMS found 324.0242 (MH^+ ^{79}Br). $C_{14}H_{15}BrNO_3$ requires 324.0235. Anal. calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.48; H, 4.38; N, 4.22.

Spectral data for **23**.[19] ν_{max} (neat)/cm^{-1} 2971, 2943, 2939, 1607, 1560, 1510, 1455, 1385, 1379, 1242, 1176, 1089, 1006; δ_H (400 MHz, $CDCl_3$) 8.20 (s, 1H), 7.35 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.47 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.2, 162.1, 159.2, 147.1, 131.5, 123.8, 118.3, 113.6, 108.1, 60.5, 55.2, 54.2; *m/z* (APCI+) 326 (MH^+ ^{81}Br, 100%), 324 (96%); HRMS found 324.0224 (MH^+ ^{79}Br). $C_{14}H_{15}BrNO_3$ requires 324.0235. Anal. calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.86; H, 4.46; N, 4.07.

1.2. General procedure for the synthesis of 3-substituted-2,4-dimethoxy-5-(4-methoxyphenyl)pyridine

A −78 °C solution of 3-bromo-2,4-dimethoxy-5-(4-methoxyphenyl)pyridine **22** (80 mg, 0.25 mmol) in dry THF (2 mL) was slowly treated with 1.7 M *t*-BuLi soln. in pentanes (294 μL, 0.5 mmol). The reaction was then stirred at −78 °C for 10 min before being treated with the freshly distilled electrophile (0.27 mmol), and the resulting mixture stirred at −78 °C for 1 h, then at room temperature for an additional 1 h. The reaction was then quenched with saturated ammonium chloride solution (5 mL) and the mixture extracted with ethyl acetate (2×15 mL) after the addition of water (5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a crude residue, which was purified by flash column chromatography.

1.2.1. 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine, 25 (by-product). ν_{max} (neat)/cm^{-1} 2974, 2946, 1602, 1564, 1488, 1455, 1430, 1372, 1248, 1053, 832; δ_H (400 MHz, $CDCl_3$) 7.95 (s, 1H), 7.38 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.5 Hz, 2H), 6.27 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.0, 164.8, 158.8, 146.7, 130.5, 127.3, 121.3, 113.7, 92.2, 55.4, 55.3, 53.5; *m/z* (APCI+) 246 (MH^+, 100%); HRMS (CI+) found 246.1125 (MH^+) $C_{14}H_{16}NO_3$ requires 246.1130.

1.2.2. 2,4-Dimethoxy-5-(4-methoxyphenyl)pyridine-3-carbaldehyde, 26. The lithiopyridine **24**, was quenched with freshly distilled ethyl formate to afford aldehyde **26** in 32% as a colourless oil. ν_{max} (neat)/cm^{-1} 2952, 2927, 2841, 1692, 1580, 1556, 1470, 1396, 1248, 1090; δ_H (500 MHz, $CDCl_3$) 10.48 (s, 1H), 8.24 (s, 1H), 7.41 (d, J=9.0 Hz, 2H), 7.00 (d, J=9.0 Hz, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H); δ_C (125.8 MHz, $CDCl_3$) 188.8, 167.8, 164.2, 159.4, 153.1, 130.1, 126.3, 124.9, 114.2, 111.7, 61.9, 55.2, 54.4; *m/z* (APCI+) 274 (MH^+, 100%), 246 (10%); HRMS (EI+) found 274.1071 (MH^+) $C_{15}H_{16}NO_4$ requires 274.1079.

1.2.3. 3-Deuterio-2,4-dimethoxy-5-(4-methoxyphenyl)-pyridine, 27. The lithiopyridine **24**, was quenched with D_2O to give pyridine **27** in 96% as a colourless oil. ν_{max} (neat)/cm^{-1} 2974, 2948, 2835, 1596, 1558, 1472, 1419, 1370, 1247, 1221, 1198, 1179, 1095, 1030, 832; δ_H (400 MHz, $CDCl_3$) 7.98 (s, 1H), 7.41 (d, J=8.5 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H); δ_C (100.6 MHz, $CDCl_3$) 165.0, 164.8, 158.8, 146.7, 130.4, 127.3, 121.2, 113.7, 92.1, 55.4, 55.3, 53.5; *m/z* (APCI+) 247 (MH^+, 100%); HRMS (CI+) found 247.1188 (MH^+) $C_{14}H_{15}DNO_3$ requires 247.1193.

1.2.4. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]-2-methylpropan-1-ol, 28. Pyridine **24**, was quenched with freshly distilled *iso*-butyraldehyde to afford alcohol **28** in 88% as a colourless oil. ν_{max} (neat)/cm^{-1} 3357, 2957, 2868, 2836, 1610, 1588, 1559, 1516, 1468, 1413, 1297, 1247, 1107; δ_H (400 MHz, $CDCl_3$) 7.97 (s, 1H), 7.41 (d, J=9.0 Hz, 2H), 6.97 (d, J=9.0 Hz, 2H), 4.66 (dd, J=11.5, 9.0 Hz, 1H), 4.01 (s, 3H), 3.86 (s, 3H), 3.40 (s, 3H), 3.39 (d, J=11.5 Hz, 1H), 2.11 (m, 1H), 1.15 (d, J=7.0 Hz, 3H), 0.80 (d, J=7.0 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 163.5, 161.6, 159.1, 146.8, 129.9, 127.8, 124.5, 117.5, 114.0, 73.3, 60.6, 55.3, 53.6, 34.3, 19.5; *m/z* (APCI+) 318 (MH^+, 100%), 300 (25%).

1.2.5. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]heptan-1-ol, 29. The lithiopyridine **24**, was quenched with freshly distilled heptanal to produce pyridine **29** in

81% as a colourless oil. ν_{max} (neat)/cm^{-1} 3560, 2956, 2928, 2856, 1610, 1589, 1560, 1515, 1468, 1415, 1377, 1107, 1012, 833; δ_H (500 MHz, $CDCl_3$) 7.98 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 5.05 (m, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.42 (s, 3H), 3.41 (d, J=11.5 Hz, 1H), 1.92 (m, 1H), 1.73 (m, 1H), 1.54 (m, 1H), 1.32 (m, 7H), 0.89 (t, J=6.5 Hz, 3H); δ_C (125.8 MHz, $CDCl_3$) 162.9, 161.5, 159.1, 146.5, 129.9, 127.7, 124.6, 118.5, 114.0, 67.6, 60.6, 55.3, 53.6, 37.7, 31.7, 29.0, 26.2, 22.5, 14.1; *m/z* (APCI+) 360 (MH^+, 100%), 342 (35%); HRMS (CI+) found 360.2178 (MH^+) $C_{21}H_{30}NO_4$ requires 360.2175.

1.2.6. (2*E*)-1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]but-2-en-1-ol, 30. The pyridine **24**, was quenched with freshly distilled crotonaldehyde to produce allylic alcohol **30** in 83% as a colourless oil. ν_{max} (neat)/cm^{-1} 3548, 2944, 2918, 2841, 1585, 1463, 1416, 1246, 1034, 1071; δ_H (400 MHz, $CDCl_3$) 7.99 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.97 (d, J=8.5 Hz, 2H), 5.87 (m, 1H), 5.71 (m, 1H), 5.54 (m, 1H), 4.02 (s, 3H), 3.86 (s, 3H), 3.72 (d, J=11.0 Hz, 1H), 3.41 (s, 3H), 1.71 (d, J=6.5 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.9, 161.4, 159.1, 146.9, 132.4, 129.9, 127.5, 126.8, 124.8, 117.5, 114.1, 67.9, 60.7, 55.3, 53.8, 17.7; *m/z* (APCI+) 316 (MH^+, 100%); HRMS (ES+) found 316.1563 (MH^+) $C_{18}H_{22}NO_4$ requires 316.1549.

1.2.7. 1-[2,4-Dimethoxy-5-(4-methoxyphenyl)pyridin-3-yl]ethanol, 31. The lithiopyridine **24**, was quenched with freshly distilled acetaldehyde to yield alcohol **31** in 40% as a colourless oil. ν_{max} (neat)/cm^{-1} 3436, 2957, 2950, 2836, 1610, 1590, 1561, 1470, 1297, 1178, 1055, 1032; δ_H (400 MHz, $CDCl_3$) 7.98 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 5.26 (dq, J=11.5, 6.5 Hz, 1H), 4.03 (s, 3H), 3.86 (s, 3H), 3.63 (d, J=11.5 Hz, 1H), 3.43 (s, 3H), 1.56 (d, J=6.5 Hz, 3H); δ_C (100.6 MHz, $CDCl_3$) 162.7, 161.5, 159.1, 146.6, 129.9, 127.6, 124.8, 119.2, 114.1, 63.6, 60.8, 55.3, 53.7, 23.8; *m/z* (APCI+) 290 (MH^+, 100%), 272 (40%); HRMS (ES+) found 290.1394 (MH^+) $C_{16}H_{20}NO_4$ requires 290.1392.

1.2.8. *p*-Benzyloxyphenylboronic acid, 33. 4-Benzyloxybromobenzene was prepared by following the literature procedure[20] as a white solid, mp 55–56 °C (lit.[20] 60–61 °C); δ_H (200 MHz, $CDCl_3$) 7.40, (m, 7H), 6.90 (d, J=8.0 Hz, 2H), 5.05 (s, 2H); *m/z* (CI) 183 (10%), 121 (100%).

p-Benzyloxyphenylboronic acid, **33** was prepared from 4-benzyloxybromobenzene by following the literature procedure[21] as a white solid, mp 187–192 °C (lit.[21] 189–194 °C); δ_H (250 MHz, $CDCl_3$) 8.20 (d, J=7.0 Hz, 2H), 7.40 (m, 5H), 7.12 (d, J=7.0 Hz, 2H), 5.18 (s, 2H); δ_C (50 MHz, $CDCl_3$) 162.4, 137.6, 136.7, 128.7, 128.1, 127.6, 114.4, 69.9; *m/z* (CI+) 121 (100%).

1.2.9. 3-Bromo-2,4-dimethoxy-5-(*p*-benzyloxyphenyl)-pyridine, 34; 5-bromo-2,4-dimethoxy-3-(*p*-benzyloxyphenyl)pyridine, 35; 3,5-di (*p*-benzyloxyphenyl)-2,4-dimethoxypyridine, 36. A solution of 3,5-dibromo-2,4-dimethoxy pyridine, **21** (2.30 g, 7.74 mmol) and *p*-benzyloxyphenylboronic acid, **33** (1.75 g, 7.68 mmol) in a 4:1 mixture of a toluene/ethanol (22.5 mL) was sequentially treated with tetrakis(triphenylphosphine)palladium(0) (447 mg, 0.39 mmol), 2 M sodium carbonate solution (18 mL), and the resulting mixture refluxed for 12 h. The reaction mixture was cooled to room temperature, and diluted with ethyl acetate (100 mL). The organic layer was washed with water (2×50 mL), brine (50 mL) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the crude product purified by flash column chromatography (silica gel, 4% ethyl acetate in 30–40 petroleum ether), to afford the desired titled products as white solids, **34**, 1.40 g (45%), mp 115–116 °C. **35**, 450 mg (15%), mp 97–99 °C. **36**, 32 mg (1%).

Spectral data for **34**.[19] ν_{max} (neat)/cm^{-1} 2971, 2947, 2939, 1561, 1584, 1514, 1470, 1410, 1379, 1243, 1087, 1006; δ_H (200 MHz, $CDCl_3$) 8.01 (s, 1H), 7.42 (m, 7H), 7.05 (d, J=7.0 Hz, 2H), 5.12 (s, 2H), 4.05 (s, 3H), 3.55 (s, 3H); δ_C (100 MHz, $CDCl_3$) 163.1, 160.8, 158.5, 146.1, 136.8, 130.1, 128.4, 128.1, 127.5, 127.0, 125.8, 114.9, 101.3, 70.0, 60.3, 54.7; *m/z* (CI+) 402 (MH^+ ^{81}Br, 100%), 400 (90%); HRMS (ES+) found 400.0540 (MH^+^{79}Br) $C_{20}H_{19}BrNO_3$ requires 400.0548.

Spectral data for **35**.[19] ν_{max} (neat)/cm^{-1} 2971, 2943, 2939, 1607, 1560, 1510, 1455, 1385, 1379, 1242, 1176, 1089, 1006; δ_H (200 MHz, $CDCl_3$) 8.20 (s, 1H), 7.45 (m, 5H), 7.33 (d, J=7.0 Hz, 2H), 7.05 (d, J=7.0 Hz, 2H), 5.11 (s, 2H), 3.87 (s, 3H), 3.47 (s, 3H); δ_C (100 MHz, $CDCl_3$) 162.7, 158.9, 147.6 (2C), 137.3, 132.0, 129.1, 128.5, 128.1, 124.6, 118.8, 114.9, 108.6, 70.5, 61.0, 54.7; *m/z* (CI+) 402 (MH^+ ^{81}Br, 100%), 400 (90%); HRMS (ES+) found 400.0554 (MH^+^{79}Br) $C_{20}H_{19}BrNO_3$ requires 400.0548.

Spectral data for **36**. δ_H (200 MHz, $CDCl_3$) 8.08 (s, 1H), 7.42 (m, 14H), 7.06 (d, J=7.0 Hz, 4H), 5.11 (s, 4H), 3.92 (s, 3H), 3.23 (s, 3H); *m/z* (CI+) 504 (MH^+, 100%).

1.2.10. 2-(*tert*-Butyldimethylsilanyloxymethyl)-1-butanol, 38. To a 0 °C suspension of 60% sodium hydride (1.88 g, 47.1 mmol) in THF (100 mL), was added dropwise a solution of 2-ethylpropan-1,3-diol[23] (4.90 g, 47.1 mmol) in THF (30 mL) and the reaction mixture stirred at room temperature for 1 h, during which time a large amount of an opaque white precipitate formed. The reaction mixture was cooled to 0 °C and a solution of *tert*-butyldimethylsilyl chloride (7.11 g, 47.1 mmol) in THF (30 mL) was added slowly. The reaction was warmed up and stirred at room temperature overnight, and was then quenched with water (100 mL) and extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed with water (2×100 mL), brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% ethyl acetate in 30–40 petroleum ether) to afford 8.1 g, (79%) of known[24] desired titled product **38** as a clear oil. ν_{max} (neat)/cm^{-1} 3368, 2957, 1472, 1255, 1091, 836; δ_H (200 MHz, $CDCl_3$) 3.80 (m, 4H), 2.92 (dd, J=7.0, 5.0 Hz, 1H), 1.63 (m, 1H), 1.25 (m, 1H), 0.91 (t, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); δ_C (50 MHz, $CDCl_3$) 67.2, 66.4, 43.6, 25.7, 20.6, 18.1, 11.7, −5.57, −5.63; *m/z* (CI+) 219 (MH^+, 100%).

1.2.11. Ethyl-(2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexenoate, 39. To a −78 °C solution of oxalyl chloride (6.62 mL, 75.6 mmol) in

dichloromethane (500 mL) was added dropwise a 1:1 (v/v) solution of DMSO (10.72 mL, 151.2 mmol) in dichloromethane. After stirring at −78 °C for 10 min, a solution of 2-(*tert*-butyldimethylsilanyloxymethyl)-1-butanol, **38** (10.30 g, 47.2 mmol) in dichloromethane (45 mL) was added dropwise and the resulting mixture stirred for 30 min at −78 °C. Triethylamine (42 mL, 302 mmol) was then added slowly, and the reaction raised to room temperature. After stirring for 1 h at room temperature, water (200 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×150 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×150 mL), 5% aq. sodium bicarbonate (2×150 mL), brine (150 mL), and dried ($MgSO_4$). The solvent was then evaporated under vacuum, to afford 10.20 g (100%) of the known[25] 2-(*tert*-butyldimethylsilanyloxymethyl) butyraldehyde, as a clear oil, which was used for next step without further purification; δ_H (250 MHz, $CDCl_3$) 9.69 (d, J=2.5 Hz, 1H), 3.89 (d, J=6.0 Hz, 2H), 2.32 (m, 1H), 1.72 (m, 1H), 1.52 (m, 1H), 0.97 (t, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 204.8, 61.6, 55.8, 25.8, 18.5, 18.2, 11.4, −5.6.

A mixture of 2-(*tert*-butyldimethylsilanyloxymethyl)butyraldehyde (10.20 g, 47.2 mmol) and (carbethoxyethylidene)-triphenylphosphorane (34.2 g, 94.4 mmol) in benzene (250 mL) was refluxed for 20 h. After cooling to room temperature, the solvent was evaporated under vacuum and the residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in 30–40 petroleum ether) to afford 12.75 g, (90%) of the desired titled product **39** as a clear oil. ν_{max} (neat)/cm^{-1} 2959, 1713, 1252, 1230, 1096, 837; δ_H (250 MHz, $CDCl_3$) 6.57 (dq, J=10.5, 1.5 Hz, 1H), 4.22 (q, J=7.0 Hz, 2H), 3.55 (m, 2H), 2.56 (m, 1H), 1.88 (d, J=1.5 Hz, 3H), 1.62 (m, 1H), 1.35 (t, J=7.0 Hz, 3H), 1.32 (m, 1H), 0.90 (s, 9H), 0.88 (t, J=5.5 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); δ_C (50 MHz, $CDCl_3$) 168.2, 143.8, 128.9, 65.6, 60.3, 43.5, 25.8, 24.0, 18.3, 14.3, 12.9, 11.7, −5.4, −5.5; HRMS (CI+) found 301.2190 (MH^+) $C_{16}H_{33}O_3Si$ requires 301.2199.

1.2.12. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dienoicacid ethyl ester, 40. A −78 °C solution of ethyl-(2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexenoate, **39** (9.50 g, 31.7 mmol) in THF (150 mL) was treated dropwise with a 1 M solution of DiBAL-H in hexanes (66.5 mL, 66.5 mmol) and reaction mixture stirred at −78 °C for 2 h. The reaction was then sequentially warmed up to room temperature and then cooled to 0 °C before being quenched with saturated sodium potassium tartrate solution (200 mL) and the resulting mixture stirred for 2 h. Ethyl acetate (150 mL) was then added to the above reaction mixture and the layers separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers washed with brine (150 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 6.70 g (82%) of 4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexene-1-ol, as a clear oil. ν_{max} (neat)/cm^{-1} 3338, 2957, 1255, 1102, 836; δ_H (250 MHz, $CDCl_3$) 5.18 (dq, J=10.0, 1.5 Hz, 1H), 4.05 (m, 2H), 3.48 (m, 2H), 2.37 (m, 1H), 1.72 (brs, 3H), 1.62 (m, 1H), 1.31 (t, J=6.0 Hz, D_2O exchangeable, 1H), 1.12 (m, 1H), 0.91 (s, 9H), 0.87 (t, J=7.5 Hz, 3H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 136.3, 127.8, 69.1, 66.5, 42.3, 25.9, 24.5, 18.4, 14.3, 11.7, −5.3.

To a −78 °C solution of oxalyl chloride (3.53 mL, 40.3 mmol) in dichloromethane (275 mL) was dropwise added a 1:1 (v/v) solution of DMSO (5.71 mL, 80.6 mmol) in dichloromethane (5.71 mL). After stirring for 10 min, a solution of 4-(*tert*-butyldimethylsilanyloxymethyl)-2-methyl-2-hexene-1-ol (6.50 g, 25.2 mmol) in dichloromethane (25 mL) was added dropwise and the resulting mixture stirred for 30 min at −78 °C. Triethylamine (22.4 mL, 161.2 mmol) was then added dropwise and the reaction raised to room temperature. After stirring for 1 h at room temperature, water (150 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×100 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×100 mL), 5% aq. sodium bicarbonate (2×100 mL), brine (100 mL), and dried ($MgSO_4$). The solvent was evaporated under vacuum, to afford 6.45 g (100%) of (2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methylhex-2-enal as a clear oil, which was used for next step without further purification. ν_{max} (neat)/cm^{-1} 2959, 2930, 2858, 1693, 1644, 1472, 1255, 1102, 837; δ_H (250 MHz, $CDCl_3$) 9.45 (s, 1H), 6.33 (dq, J=10.0, 1.5 Hz, 1H), 3.63 (m, 2H), 2.73 (m, 1H), 1.81 (brs, 3H), 1.72 (m, 1H), 1.35 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.03 (s, 6H); HRMS (CI+) found 257.1933 (MH^+) $C_{14}H_{29}O_2Si$ requires 257.1937.

A mixture of (2*E*)-4-(*tert*-butyldimethylsilanyloxymethyl)-2-methylhex-2-enal (6.45 g, 25.1 mmol) and (ethoxycarbonylmethylidene)triphenylphosphorane (17.53 g, 50.2 mmol) in toluene (150 mL) was refluxed for 20 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, and the residue purified by flash column chromatography (silica gel, 5% ethyl acetate in 30–40 petroleum ether) to afford 7.80 g (95%) of the desired titled product, **40** as a clear oil. ν_{max} (neat)/cm^{-1} 2959, 1716, 1625, 1471, 1366, 1298, 1258, 1173, 1100, 1034, 836; δ_H (250 MHz, $CDCl_3$) 7.35 (d, J=15.5 Hz, 1H), 5.82 (d, J=15.5 Hz, 1H), 5.70 (dq, J=10.0 Hz, 1.5 Hz, 1H), 4.24 (q, J=7.0 Hz, 2H), 3.52 (m, 2H), 2.57 (m, 1H), 1.85 (brd, 3H), 1.62 (m, 1H), 1.33 (t, J=7.0 Hz, 3H), 1.23 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); δ_C (50 MHz, $CDCl_3$) 167.6, 149.7, 144.0, 134.0, 115.8, 66.0, 60.2, 43.5, 25.9, 24.4, 18.3, 14.4, 12.8, 11.8, −5.4; HRMS (CI+) found 327.2363 (MH^+) $C_{18}H_{35}O_3Si$ requires 327.2355.

1.2.13. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-4-methylocta-2,4-diene-1-al, 41. A −78 °C solution of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dienoicacid ethyl ester, **40** (7.30 g, 22.4 mmol) in THF (75 mL) was treated dropwise with a 1.5 M solution of DiBAL-H in toluene (31 mL, 46.5 mmol) and reaction mixture stirred at −78 °C for 2 h. The reaction was then warmed up to room temperature, and then cooled back down to 0 °C before being quenched with saturated sodium potassium tartrate solution (100 mL) and the resulting

mixture stirred for 2 h. Ethyl acetate (100 mL) was added to the above reaction mixture and the layers separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers washed with brine (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 6.15 g (97%) of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dien-1-ol, as a clear oil. ν_{max} (neat)/cm^{-1} 3399, 2957, 1719, 1695, 1471, 1387, 1255, 1100, 1006, 776; δ_H (200 MHz, $CDCl_3$) 6.27 (d, J=15.5 Hz, 1H), 5.85 (dt, J=15.5, 7.0 Hz, 1H), 5.24 (brd, J=10.0 Hz, 1H), 4.21 (t, J=6.0 Hz, 2H), 3.47 (m, 2H), 2.51 (m, 1H), 1.79 (d, J=1.0 Hz, 3H), 1.61 (m, 1H), 1.29 (t, J=6.0 Hz, D_2O exchangeable, 1H), 1.21 (m, 1H), 0.91 (s, 9H), 0.87 (t, J=7.0 Hz, 3H), 0.05 (s, 6H); δ_C (50 MHz, $CDCl_3$) 137.0, 135.3, 134.2, 125.4, 66.4, 64.0, 42.9, 25.9, 24.6, 18.4, 13.1, 11.7, −5.3, −5.4; HRMS (CI+) found 285.2253 (MH^+) $C_{16}H_{33}O_2Si$ requires 285.2250.

To a −78 °C solution of oxalyl chloride (0.23 mL, 2.6 mmol) in dichloromethane (25 mL), was dropwise added a 1:1 (v/v) solution of DMSO (0.37 mL, 5.2 mmol) in dichloromethane. After stirring for 10 min, a solution of (2*E*,4*E*)-6-(*tert*-butyldimethylsilanyloxymethyl)-4-methylocta-2,4-dien-1-ol (460 mg, 1.6 mmol) in dichloromethane (2 mL) was added dropwise and the reaction mixture stirred for 30 min at −78 °C. Triethylamine (1.44 mL, 10.4 mmol) was then added dropwise and the reaction brought to room temperature. After stirring for 1 h at room temperature, water (15 mL) was added to the reaction mixture, and the layers separated. The aqueous layer was extracted with dichloromethane (3×15 mL) and the combined organic phases washed with 1 M hydrochloric acid (2×15 mL), 5% aq. sodium bicarbonate solution (2×15 mL), brine (15 mL), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure, to afford 456 mg (100%) the titled desired product, **41** as an oil. The crude product was used for next step without further purification. ν_{max} (neat)/cm^{-1} 2957, 2857, 1683, 1627, 1606, 1471, 1463, 1386, 1361, 1256, 970, 837; δ_H (250 MHz, $CDCl_3$) 9.59 (d, J=8.0 Hz, 1H), 7.16 (d, J=15.5 Hz, 1H), 6.13 (dd, J=15.5, 8.0 Hz, 1H), 5.83 (brd, J=10.0 Hz, 1H), 3.57 (m, 2H), 2.52 (m, 1H), 1.87 (d, J=1.0 Hz, 3H), 1.62 (m, 1H), 1.32 (m, 1H), 0.91 (s, 9H), 0.89 (t, J=7.5 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); δ_C (50 MHz, $CDCl_3$) 194.3, 157.9, 146.6, 134.5, 127.0, 65.8, 43.7, 25.9, 24.3, 18.3, 13.0, 11.7, −5.4.

1.2.14. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dimethoxy-pyridine-3-yl]-4-methylocta-2,4-dien-1-ol, 42 and 5-(*p*-benzyloxyphenyl)-2,4-dimethoxy pyridine, 43. A solution of pyridine, **34** (283 mg, 0.71 mmol) in THF (10 mL) was cooled to −78 °C and was then dropwise treated with a 1.5 M solution of *tert*-butyl lithium in hexanes (0.94 mL, 1.4 mmol). After 30 min, a solution of aldehyde, **41** (200 mg, 0.71 mmol) in THF (2 mL) was added and the resulting mixture stirred at −78 °C for 1 h. The reaction was warmed up to room temperature, and stirred for an additional 1 h. Saturated ammonium chloride solution (10 mL) was then added to the reaction mixture, followed by ethyl acetate (10 mL), and water (10 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (3×15 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford the desired titled product as an approximately (1:1) mixture of inseparable diastereomers, **42** as an oil, 250 mg (58%) and **43**, 50 mg (22%), as a yellow solid.

Spectral data for **42**. ν_{max} (neat)/cm^{-1} 3555, 2954, 1590, 1515, 1469, 1379, 1246, 1086, 833; δ_H (250 MHz, $CDCl_3$) 8.03 (s, 1H), 7.52–7.35 (m, 7H), 7.09–7.07 (d, J=6.5 Hz, 2H), 6.31 (dd, J=15.5, 3.5 Hz, 1H), 5.94 (dd, J=15.5, 7.0 Hz, 1H), 5.69 (dd, J=12.0, 7.0 Hz, 1H), 5.22 (brd, J=10.0 Hz, 1H), 5.13 (s, 2H), 4.07–4.05 (s, 3H), 3.78–3.71 (m, D_2O exchangeable, 1H), 3.51–3.45 (m, 2H), 3.44–3.42 (2× s, 3H), 2.56–2.42 (m, 1H), 1.80–1.78 (s, 3H), 1.72–1.62 (m, 1H), 1.32–1.11 (m, 1H), 0.88–0.78 (m, 12H), 0.04–0.03 (2×s, 3H), 0.01–0.00 (2×s, 3H); δ_C (50 MHz, $CDCl_3$) 163.2, 161.5, 158.4, 147.0, 136.9, 135.8, 135.5, 135.3, 134.3, 130.0, 128.7, 128.1, 127.9, 127.7, 124.9, 117.6, 115.1, 70.1, 68.1, 66.4, 60.8, 53.9, 43.0, 25.9, 24.6, 18.4, 13.2, 11.7, −5.3; HRMS (CI+) found 604.3463 (MH^+) $C_{36}H_{50}NO_5Si$ requires 604.3458.

Spectral data for **43**. δ_H (250 MHz, $CDCl_3$) 7.99 (s, 1H), 7.42 (m, 7H), 7.06 (d, J=9.0 Hz, 2H), 6.31 (s, 1H), 5.13 (s, 2H), 3.99 (s, 3H),3.86 (s, 3H); *m/z* (CI+) 322 (MH^+, 100%).

1.2.15. (2*E*,4*E*)-6-(*tert*-Butyldimethylsilanyloxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dimethoxy pyridine-3-yl]-4-methylocta-2,4-dien-1-one, 44. A suspension of allylic alcohol **42** (185 mg, 0.31 mmol) and activated manganese dioxide, (400 mg, 4.60 mmol) in dichloromethane (10 mL) was stirred at room temperature for 2 days. The reaction mixture was then filtered, and the solid residue washed with dichloromethane (25 mL). The combined filtrates were evaporated under vacuum and the crude residue was purified by flash column chromatography (silica gel, 10% ethyl acetate in 30–40 petroleum ether) to afford 175 mg (95%) of the desired pyridine **44** as a clear gum. ν_{max} (neat)/cm^{-1} 2957, 1651, 1588, 1559, 1514, 1466, 1410, 1379, 1325, 1273, 1247, 1177, 1095, 834; δ_H (250 MHz, $CDCl_3$) 8.12 (s, 1H), 7.42 (m, 7H), 7.06 (d, J=15.5 Hz, 1H), 7.04 (d, J=7.0 Hz, 2H), 6.45 (d, J=15.5 Hz, 1H), 5.70 (d, J=10.0 Hz, 1H), 5.14 (s, 2H), 3.95 (s, 3H), 3.50 (s, 3H), 3.49 (m, 2H), 2.61 (m, 1H), 1.88 (s, 3H), 1.57 (m, 1H), 1.23 (m, 1H), 0.89 (s, 9H), 0.83 (t, J=7.0 Hz, 3H), 0.03 (s, 6H); δ_C (50 MHz, $CDCl_3$) 194.1, 163.0, 161.2, 158.5, 151.6, 148.5, 146.4, 136.9, 134.6, 130.1, 128.7, 128.1, 127.5 (2C), 126.5, 124.2, 115.5, 115.0, 70.1, 65.9, 61.1, 54.0, 43.8, 25.9, 24.3, 18.3, 13.0, 11.8, −5.3; HRMS (CI+) found 602.3303 (MH^+) $C_{36}H_{48}NO_5Si$ requires 602.3302.

1.2.16. (2*E*,4*E*)-6-(Hydroxymethyl)-1-[5-(*p*-benzyloxyphenyl)-2,4-dihydroxypyridine-3-yl]-4-methylocta-2,4-dien-1-one, 45. To a −20 °C solution of pyridine, **44** (50 mg, 0.083 mmol) in acetonitrile (10 mL) was added anhydrous sodium iodide (50 mg, 0.33 mmol) and trimethylsilyl chloride (32 μL, 0.25 mmol) and the reaction slowly brought to room temperature over a period of 4 h.

The reaction was stirred for 3 days at room temperature, and then diluted with ethyl acetate (10 mL) and water (5 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic phases were washed with 5% aq. sodium bicarbonate (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, 2% methanol in chloroform) to afford 20 mg (53%) of the desired pyridone, **45**, as a yellow solid, mp 199–200 °C. ν_{max} (neat)/cm^{-1} 3340, 2923, 1665, 1628, 1512, 1472, 1406, 1324, 1218, 1177, 1036, 827; δ_H (500 MHz, $CDCl_3$) 10.70 (brs, D_2O exchangeable, 1H), 8.01 (d, J=15.5 Hz, 1H), 7.68 (d, J=15.5 Hz, 1H), 7.39 (m, 8H), 7.04 (d, J=8.0 Hz, 2H), 5.84 (d, J=10.0 Hz, 1H), 5.11 (s, 2H), 3.65 (brs, 1H), 3.53 (t, J=8.5 Hz, 1H), 2.70 (m, 1H), 2.03 (s, 3H), 1.57 (m, 1H), 1.37 (brs, D_2O exchangeable, 1H), 1.31 (m, 1H), 0.94 (t, J=7.0 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 195.1, 178.2, 164.0, 159.1, 150.4, 146.0, 138.5, 137.3 (2C), 130.7, 129.1, 128.5, 127.9, 125.6, 124.3, 115.9, 115.3, 107.2, 70.5, 66.5, 44.4, 24.9, 13.7, 12.1; HRMS (CI+) found 460.2123 (MH^+) $C_{28}H_{30}NO_5$ requires 460.2124.

1.2.17. (2*E*,4*E*)-6-(Hydroxymethyl)-1-[5-(*p*-hydroxyphenyl)-2,4-dihydroxypyridine-3-yl]-4-methylocta-2,4-dien-1-one, pyridovericin, 1. A solution of pyridone, **45** (25 mg, 0.054 mmol) in dichloromethane (10 mL) at −78 °C was treated dropwise with a 1 M solution of boron tribromide in dichloromethane (0.54 mL, 0.54 mmol). The reaction was then stirred at −78 °C for 1 h, before methanol (100 μL) was added, and the mixture kept at −78 °C for 10 min. 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 5% aq. sodium bicarbonate (10 mL), brine (10 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude residue was purified by flash column chromatography (silica gel, 3% methanol in chloroform), to afford 15 mg (75%) of pyridovericin **1**, as a yellow solid, mp 203–206 °C (dec.). ν_{max} (neat)/cm^{-1} 3335, 2963, 1665, 1610, 1588, 1489, 1452, 1261, 1225, 1101, 1035, 799; δ_H (500 MHz, DMSO) 17.56 (brs, D_2O exchangeable, 1H), 11.61 (brs, D_2O exchangeable, 1H), 9.48 (s, 1H), 8.00 (d, J=15.5 Hz, 1H), 7.54 (s, 1H), 7.51 (d, J=15.5 Hz, 1H), 7.27 (d, J=8.5 Hz, 2H), 6.78 (d, J=8.5 Hz, 2H), 5.97 (d, J=10.0 Hz, 1H), 4.56 (t, J=5.5 Hz, D_2O exchangeable, 1H), 3.37 (m, 2H), 2.53 (m, 1H), 1.86 (s, 3H), 1.59 (m, 1H), 1.22 (m, 1H), 0.82 (t, J=7.5 Hz, 3H); δ_C (125 MHz, $CDCl_3$) 194.6, 177.7, 162.6, 157.6, 150.3, 148.4, 141.5, 135.4, 130.9, 124.3, 123.9, 115.8, 113.6, 106.7, 64.7, 44.4, 24.9, 13.7, 12.5; HRMS found 370.1664 (MH^+) $C_{21}H_{24}NO_5$ requires 370.1654.

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