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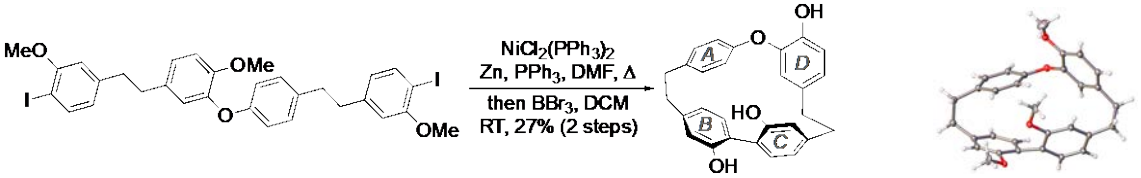

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In memory of Professor Jonathan Williams, a thoughtful and inspirational scientist.

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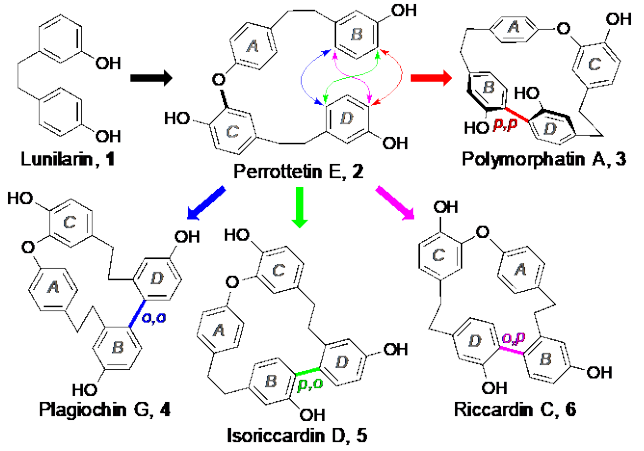
ABSTRACT

Polymorphatin A was reported as a constituent of Marchantia polymorpha in 2007 following much speculation as to its likely existence as a natural product. Interest was rekindled when a claimed total synthesis revealed inconsistencies in spectral data between the synthetic sample and those reported for the natural product. Herein we describe a total synthesis of polymorphatin A, supported by an X-ray crystal structure of its trimethyl ether, that adds further intrigue as our synthetic sample displays physical and spectral characteristics that differ from data provided in the aforementioned reports.

1. Introduction

The macrocyclic bisbibenzyl family of natural products is approaching the landmark of having one hundred identified members.[1,2] All are characterised by the presence of two lunilarin (**1**) sub-units within their core structure, that are connected either directly or via ether linkages to form various macrocycles.[1,2] In turn, each of these macrocycles heads a smaller familial group. For example, in nature the terminal arenes of the lunilarin dimer perrottetin E **2** may be linked oxidatively through their *ortho*- and *para*-carbon centres to form four distinct macrocyclic skeletons **3**-**6** (Scheme 1).[1–4]



Scheme 1. Perrottetin E as the biosynthetic precursor to an array of macrocyclic bisbibenzyls.[3]

When, in the early nineties, Keserü and Nógrádi examined this biosynthetic postulate computationally they suggested that macrocycle **3** was unlikely to be found in nature due to molecular strain.[4] Indeed, they noted that their high "*calculated energy value is probably an underestimate since the minimum energy conformation produced by the program is unrealistic since it contains a bent aromatic ring.*" In 2007 those concerns were largely dispelled with the reported discovery of macrocycle **3** in the ethereal extract of *Marchantia polymorpha L.* by Lou *et al.*, who named it polymorphatin A.[5] Doubts resurfaced three years later when a claimed synthesis of polymorphatin A **3** by Speicher *et al.* found that the physical and spectral characteristics exhibited by their synthetic sample differed markedly from those reported for the natural product.[6]

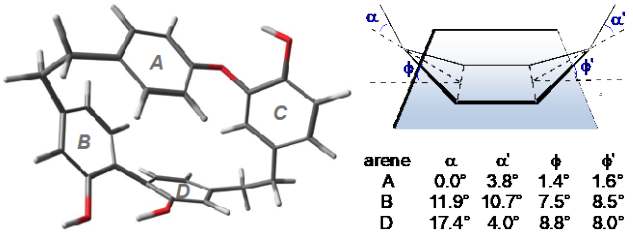


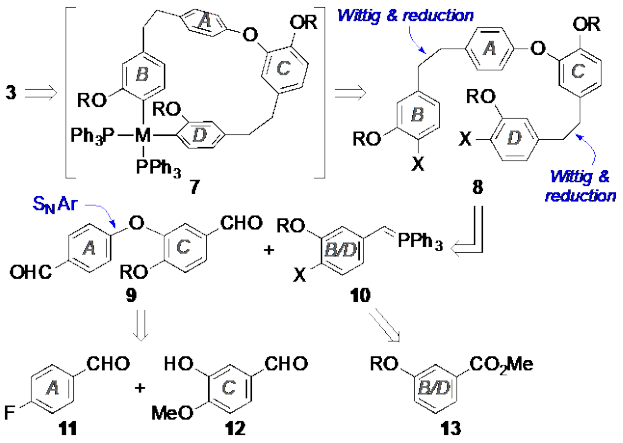
Figure 1. Computationally generated model of polymorphatin A showing significant distortion from planarity in arenes *B* and *D*.[8]

Our own computational analysis of polymorphatin A **3** indicated that strain would cause the arenes in its biaryl subunit

to each adopt boat-like conformations (Figure 1). Past achievements in addressing the synthesis of non-planar aromatic ring systems,[7] prompted us to take up the synthetic challenge of polymorphatin A **3** with the aim of resolving the uncertainties surrounding its identity. Herein we report its total synthesis, supported by an X-ray crystal structure of polymorphatin A trimethyl ether **20**, together with data that conflicts with both of the earlier reports![5]

2. Synthetic strategy

As polymorphatin A **3** contained two non-planar arenes within its macrocyclic core, we decided to adopt a strategy wherein the macrocyclisation step would be used to bend both rings simultaneously. For this to be effective we needed to proceed via an intermediate that could accommodate arenes B and D as planar entities yet had sufficient driving force to bend them when collapsing to form the macrocycle.[7] That assessment led us to the 'biomimetic' disconnection of the biaryl linkage which could be made from a metallamacrocycle akin to **7** in which arenes B and D are both planar.[9] For the tactic to work we needed its collapse by reductive elimination to compete with intermolecular processes such as protonation and dimerization.[7d] A further attractive feature of the strategy was the simplicity with which the required dihalide precursor **8** could be accessed.[10] Here we envisioned a convergent approach whereby biaryl ether **9** would made from aldehydes **11** and **12** by nucleophilic aromatic substitution before the terminal arenes were added by a double Wittig olefination and reduction sequence with ylide **10** (Scheme 2).

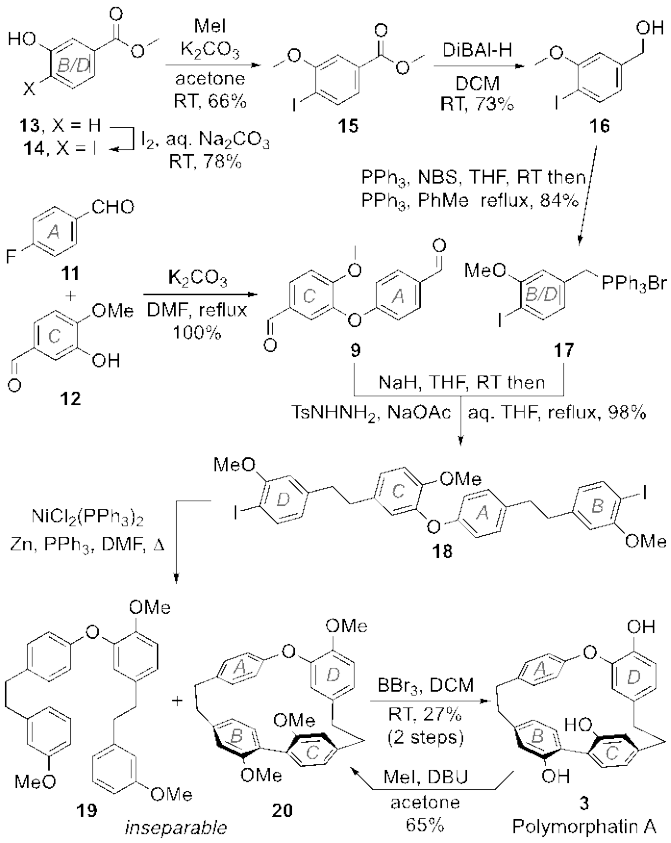


Scheme 2. Strategic and retrosynthetic analysis.

3. Total Synthesis

Thus, bisaldehyde **9** was formed in quantitative yield by heating a DMF solution of isovanillin **12** and 4-fluorobenzaldehyde **11** with potassium carbonate.[11] Contemporaneously, phenol **13** was iodinated (to **14**) and protected as its methyl ether **15**.[12] Ester reduction to alcohol **16**[13] then facilitated formation of phosphonium salt **17** by standard protocols (Scheme 3). Next, the planned double Wittig reaction with *bis*-aldehyde **9** was effected to provide the corresponding *bis*-stilbene in near quantitative yield as a mixture of geometric isomers. These were then transformed into the macrocyclisation precursor **18** by diimide reduction.

Our search for conditions to achieve macrocyclisation of diiodide **18** to polymorphatin A trimethyl ether **20** led us to explore numerous possibilities. For the most part, variants of the Ullmann reaction led to halide reduction and the formation of perrottetin E trimethyl ether **19**,[14,15] as did protocols based on Pd and Fe catalysis.[9,16] Indeed, analysis of crude product mixtures by mass spectrometry failed to provide evidence for the formation of macrocycle **20** in any of these experiments. The situation changed when we switched to using Ni.[17] Although ^{1}H NMR indicated that a complex product mixture had been formed, mass spectrometry revealed the presence of a component with the correct molecular mass for polymorphatin A trimethyl ether **20**.



Scheme 3. Total synthesis of polymorphatin A.

Isolation of that component by column chromatography produced a sample that unexpectedly gave complex ^{1}H and ^{13}C NMR spectra at RT in $CDCl_3$ and d_6-DMSO. The latter simplified greatly on heating to 100 °C (Figure 2), giving data consistent with the formation of polymorphatin A trimethyl ether **20**.

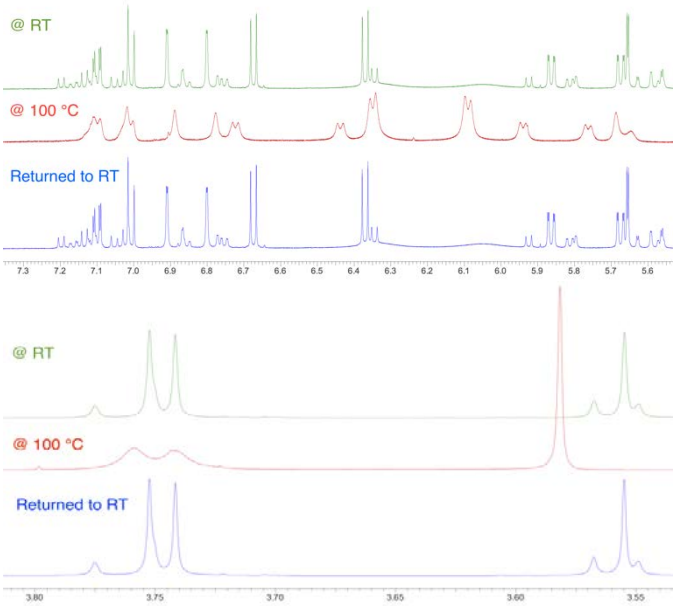
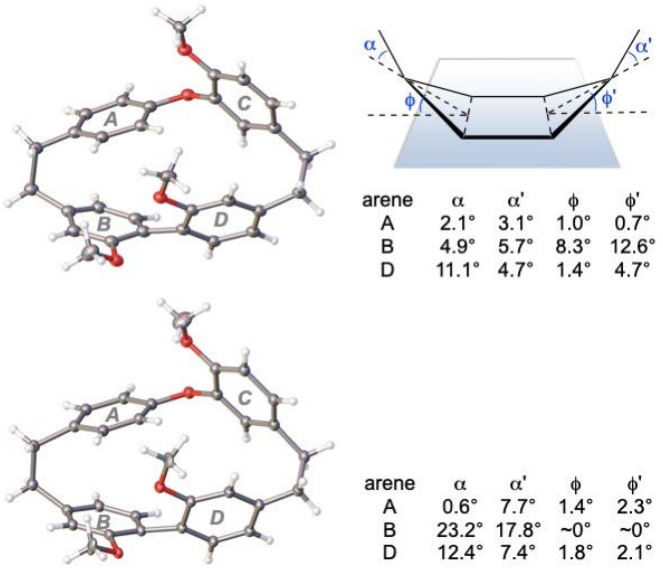


Figure 2. Extracts of VT ^{1}H NMR spectra recorded on polymorphatin A trimethyl ether **20** in d_6-DMSO showing the presence of rotamers in solution.

To confirm the authenticity of our sample, an X-ray crystal structure was obtained (Figure 3) which showed that we had indeed made polymorphatin A trimethyl ether **20**. Notably, it exhibited two crystallographically independent structural forms in the solid state. These differed markedly in respect of their biaryl subunits with arene B adopting a boat-like conformation in one while in the other its benzylic carbons were positioned much further out of the plane.



arene	α	α'	ϕ	ϕ'
A	2.1°	3.1°	1.0°	0.7°
B	4.9°	5.7°	8.3°	12.6°
D	11.1°	4.7°	1.4°	4.7°

arene	α	α'	ϕ	ϕ'
A	0.6°	7.7°	1.4°	2.3°
B	23.2°	17.8°	~0°	~0°
D	12.4°	7.4°	1.8°	2.1°

Figure 3. The two independent forms of polymorphatin A trimethyl ether **20** revealed by X-ray crystallographic analysis (CCDC No. 1517765).

A synthetic sample of polymorphatin A **3**, formed by exposure of its trimethyl ether **20** to boron tribromide, also showed evidence of rotamers in NMR spectra recorded at RT. As before, data recorded on our synthetic sample differed markedly from those reported by Speicher *et al.* in their claimed total synthesis,[6,17] and those reported by Lou *et al.* in the isolation paper.[5] Alas, our synthetic sample of polymorphatin A **3** did not prove amenable to X-ray crystallographic analysis. Consequently, to confirm its identity we took the precaution of reforming its trimethyl ether **20** by exhaustive methylation and showed that data collected on the new sample matched that we had attained previously.

4. Conclusions

In conclusion, we have completed a total synthesis of polymorphatin A **3**.[5,6] Key features are i) the nickel-mediated cross-coupling reaction to effect macrocyclisation and install the distorted arenes[18] and ii) the ease with which the four arene subunits are assembled from simple starting materials.[10] Our synthesis is evidenced by an X-ray crystallographic analysis of polymorphatin A trimethyl ether **20**. The physical and spectral characteristics exhibited by our synthetic samples do not match previously reported data.[5,6,17,19]

5. Experimental section

General experimental.

Melting points were recorded on an Electrothermal IA9100 digital melting point apparatus and are uncorrected. Infrared spectra were recorded neat as thin films or as solid compressions using a Nicolet 380 Laboratory FT-IR spectrometer or a Nicolet iS5 Laboratory FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVIIIHD 400 (400/100 MHz) or a Bruker AVIIIHD 500 (500/125 MHz) spectrometer at 298 K unless stated otherwise. Deuterated chloroform ($CDCl_3$) was supplied by Sigma Aldrich and stored over dried K_2CO_3 to neutralise trace acidity. Assignments were made on the basis of chemical shifts, coupling constants, DEPT-135, COSY, HMQC and comparison with available literature values. High resolution mass spectrometry was performed by Ms Julie Herniman using a MaXis (Bruker Daltonics, Bremen, Germany) mass spectrometer equipped with a time of flight (TOF) analyser. Low resolution mass spectrometry was carried out using electrospray ionisation on a directly injected WATERS quadrupole MSD using ESI+ with MeOH/acetonitrile as solvent. X-ray data were recorded using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature apparatus operating at 100 K.

Thin layer chromatography was carried out on Merck Silica Gel 60 Å F 254 0.2 mm plates, which were visualised under fluorescence UV (254 nm) followed by staining with iodine and/or aqueous 1% $KMnO_4$, methanolic H_2SO_4 or methanolic vanillin. Column chromatography was carried out under slight positive pressure using silica gel with the stated solvent system. Commercial reagents were used without further purification unless stated otherwise. THF and toluene were distilled from sodium under argon. All air sensitive reactions were carried out under argon using flame or oven dried apparatus.

*5.1. Methyl 3-hydroxy-4-iodobenzoate (**14**)*[20]

To a stirred suspension of methyl 3-hydroxybenzoate **13** (10.0 g, 65.7 mmol) in saturated Na_2CO_3 (300 mL) and water (100 mL) was added iodine (16.6 g, 65.7 mmol). After 20 h at RT the product was collected by filtration, washed with water and dried in a desiccator for 5 h to yield the *title compound* **14** (14.3 g, 51.4 mmol, 78%) as a cream solid; MP: 155–157 °C (water) [Lit. 145–148 °C (water)][20]; ν_{max} (solid) 3270 (m), 2950 (m), 1686 (s), 1579 (m), 1433 (m), 1406 (m), 1296 (s), 1239 (s), 1192 (s), 1106 (s), 1016 (m); δ_H (400 MHz, d_6-acetone): 7.52 (1H, d, *J* 8.1 Hz, ArH), 7.15 (1H, d, *J* 2.2 Hz, ArH), 6.60 (1H, dd, *J* 8.1, 2.2 Hz, ArH), 3.70 (3 H, s, OMe), 3.44 (1H, br s, OH); δ_C (100 MHz, d_6-acetone): 167.1 (C), 158.0 (C), 140.9 (CH), 133.0 (C), 123.2 (CH), 116.3 (CH), 91.3 (C), 52.9 (CH_3); *m/z* (ESI+) 279 (100, MH^+); HRMS (ESI+): MH^+, found 278.9513. $C_8H_8IO_3$ requires 278.9509.

*5.2. Methyl 4-iodo-3-methoxybenzoate (**15**)*

To a solution of methyl 3-hydroxy-4-iodobenzoate **14** (13.8 g, 49.6 mmol) in acetone (500 mL) at RT was added K_2CO_3 (20.7 g, 149.8 mmol) and iodomethane (12.4 mL, 199 mmol). After 18 h the solution was filtered through Celite® and the collected solid was washed with acetone (200 mL). The filtrate was concentrated *in vacuo* then the residue was partitioned between water (50 mL) and dichloromethane (100 mL). The aqueous phase was extracted with dichloromethane (3 × 100 mL) then the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to afford the *title compound* **15** (9.54 g, 32.7 mmol, 66%) as a yellow solid; MP 59–60 °C (DCM) [Lit. 50–52 °C (EtOAc/pentane)][12]; ν_{max} 2948 (w), 1716 (s), 1584 (m), 1570 (m), 1460 (m), 1432 (m), 1395 (s), 1285 (s), 1229 (s), 1182 (s), 1105 (s), 1036 (m), 1014 (s); δ_H (400 MHz, $CDCl_3$) 7.84 (1H, d, *J* = 8.1 Hz, ArH), 7.44 (1H, d, *J* = 1.8 Hz, ArH), 7.36 (1H, dd, *J* = 8.1, 1.8 Hz, ArH), 3.93 (3 H, s, OMe), 3.91 (3 H, s, OMe); δ_C (100 MHz, $CDCl_3$) 166.5 (C), 158.1 (C), 139.4 (CH), 131.5 (C), 123.2 (CH), 111.1 (CH), 92.6 (C), 56.4 (CH_3), 52.3 (CH_3); *m/z* (ESI+) 293 (100, MH^+); HRMS (ESI+): $[M+Na]^+$, found 314.9489. $C_9H_9INaO_3$ requires 314.9492.

*5.3. (4-Iodo-3-methoxyphenyl)methanol (**16**)*[13]

To a solution of methyl 4-iodo-3-methoxybenzoate **15** (8.40 g, 28.7 mmol) in DCM (300 mL) at –78 °C was added diisobutylaluminium hydride (1 M in hexanes, 66.1 mL, 66.1 mmol) dropwise over 30 min. The mixture was warmed to RT for 4 h then cooled to –78 °C. MeOH (50 mL) then sat. Rochelle's salt (200 mL) were added cautiously then the solution was slowly warmed to RT. After 5 h the phases were separated, and the aqueous phase was extracted with DCM (3 × 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (20–50% Et_2O in petrol) afforded the *title compound* **16** (5.54 g, 21.0 mmol, 73%) as a pale yellow oil; ν_{max} 3322 (br), 2936 (w), 2863 (w), 1574 (m), 1476 (s), 1459 (s), 1403 (s), 1278 (s), 1254 (m), 1166 (m), 1131 (w), 1037 (s), 1011 (s); δ_H (400 MHz, $CDCl_3$) 7.68 (1H, d, *J* 7.9 Hz, ArH), 6.79 (1H, d, *J* 1.7 Hz, ArH), 6.64 (1H, dd, *J* 7.9, 1.8 Hz, ArH), 4.57 (2H, s, CH_2), 3.83 (3H, s, OMe), 2.62 (1 H, s, OH); δ_C (100 MHz, $CDCl_3$) 158.0 (C), 142.8 (C), 139.1 (CH), 120.6 (CH), 109.3 (CH), 84.4 (C), 64.4 (CH_2), 56.2 (CH_3); *m/z* (EI+) 264 (100, M^+), 247 (45, $[MH–H_2O]^+$), 77 (55%); *m/z* (ESI+) 247 (100, $[MH–H_2O]^+$); HRMS (ESI+): MH^+, found 246.9614. C_8H_8IO requires 246.9610.

*5.4. (4-Iodo-3-methoxybenzyl)triphenylphosphonium bromide (**17**)*

To a solution of 4-iodo-3-methoxybenzyl alcohol **16** (3.61 g, 13.7 mmol) and triphenyl phosphine (4.30 g, 16.4 mmol) in THF (35 mL) at 0 °C was added *N*-bromosuccinimide (2.92 g, 16.4 mmol). After 1 h, the solution was filtered through silica gel (washing through with 25% Et_2O in petrol, 100 mL). The filtrate was concentrated *in vacuo* then dissolved in toluene (35 mL). Triphenylphosphine (3.58 g, 13.7 mmol) was added and the solution heated at reflux for 18 h then cooled to RT. The resulting precipitate was collected by filtration to give the *title compound* **17** (6.82 g, 11.6 mmol, 84%) as a beige solid; MP >300 °C; ν_{max} 2988 (w), 1771 (w), 1701 (m), 1541 (m), 1508 (m), 1437 (m), 1399 (m), 1111 (m), 1032 (m); δ_H (400 MHz, *d*$_6$-DMSO) 7.97–7.88 (3H, m, 3 × ArH), 7.81–7.55 (13H, m, 13 × ArH), 6.52–6.43 (2H, m, 2 × ArH), 5.17 (2H, d, $J_{H\text{-}P}$ 15.8 Hz, $ArCH_2$), 3.41 (3H, s, Me); δ_C (100 MHz, *d*$_6$-DMSO) 157.5 (d, $J_{C\text{-}P}$ 2.9 Hz, C), 139.2 (d, $J_{C\text{-}P}$ 2.9 Hz, CH), 135.1 (d, $J_{C\text{-}P}$ 2.9 Hz, 3 x CH), 134.1 (d, $J_{C\text{-}P}$ 9.5 Hz, 6 x CH), 130.1 (d, $J_{C\text{-}P}$ 12.5 Hz, 6 x CH), 129.7 (d, $J_{C\text{-}P}$ 7.8 Hz, C), 124.8 (d, $J_{C\text{-}P}$ 5.9 Hz, CH), 118.0 (s, CH), 117.6 (s, C), 113.9 (d, $J_{C\text{-}P}$ 5.1 Hz, CH), 86.3 (d, $J_{C\text{-}P}$ 5.1 Hz, C), 55.9 (s, CH_3), 28.1 (d, $J_{C\text{-}P}$ 46.2 Hz, CH_2); δ_P (162 MHz, *d*$_6$-DMSO) δ = 24.0 (s); *m/z* (ESI+) 509 (100, $[M–Br]^+$); HRMS (ESI+): $[M–Br]^+$, found 509.0526. $C_{26}H_{23}IOP$ requires 509.0525.

*5.5. 3-(4-Formylphenoxy)-4-methoxybenzaldehyde (**9**)*

To a solution of isovanillin **12** (5.00 g, 32.8 mmol) and 4-fluorobenzaldehyde **13** (3.9 mL, 36.3 mmol) in DMF (20 mL) was added K_2CO_3 (5.45 g, 39.4 mmol). The solution was heated at reflux for 18 h then cooled to RT, diluted with water (50 mL) and extracted with EtOAc (3 × 80 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (25–75% Et_2O in petrol) afforded the *title compound* **9** (8.42 g, 32.8 mmol, 100%) as a white solid; MP 78–79 °C (Et_2O/petrol) [Lit. 83–85 °C (EtOAc /petrol)][11]; ν_{max} 2838 (w), 2736 (w), 1685 (s), 1597 (s), 1576 (s), 1501 (s), 1431 (m), 1391 (m), 1273 (s), 1210 (s), 1152 (s), 1108 (s), 1015 (m); δ_H 9.92 (1H, s, CHO), 9.88 (1H, s, CHO), 7.84 (2H, d, *J* = 8.8 Hz, 2 × ArH), 7.78 (1H, dd, *J* 8.4, 2.0 Hz, ArH), 7.62 (1H, d, *J* = 2.0 Hz, ArH), 7.16 (1H, d, *J* = 8.4 Hz, ArH), 7.00 (2H, d, *J* = 8.7 Hz, 2 × ArH), 3.89 (3H, s, OMe); δ_C 190.6 (CH), 189.9 (CH), 162.6 (C), 156.7 (C), 143.7 (C), 131.9 (2 × CH), 131.4 (C), 130.4 (C), 129.5 (CH), 122.2 (CH), 116.5 (2 × CH), 112.5 (CH), 56.2 (CH_3); *m/z* (ESI+) 257 (100%, MH^+); HRMS (ESI+): MH^+, found 257.0808. $C_{15}H_{13}O_4$ requires 257.0802.

*5.6. 1-Methoxy-4-(3-methoxyphenethyl)-2-(4-(3-methoxyphenethyl)phenoxy)benzene (**18**)*

To a solution of (4-iodo-3-methoxybenzyl)triphenylphosphonium bromide **17** (6.40 g, 10.8 mmol) in THF (50 mL) at 0 °C was added sodium hydride (60 % in mineral oil; 566 mg, 14.2 mmol). After 30 min, dialdehyde **9** (1.21 g, 4.72 mmol) in THF (10 mL) was added and the mixture was allowed to warm to RT. After 18 h, water (60 mL) was added then the mixture was extracted with diethyl ether (3 × 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (20-100% Et_2O in petrol) afforded a yellow gum that was dissolved in THF (60 mL).[21] Water (60 mL), tosyl hydrazide (8.79 g, 47.2 mmol) and sodium acetate (3.87 g, 47.2 mmol) were added successively then the reaction mixture was heated at reflux for 18 h. On cooling to RT, further water (20 mL) was added then the solution was extracted with Et_2O (3 × 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (20-35% Et_2O:petrol) afforded the *title compound* **18** (3.35 g, 4.65 mmol, 98%) as a white foam; ν_{max} 2931 (w), 2856 (w), 1503 (s), 1467 (m), 1460 (m), 1403 (m), 1267 (s), 1220 (s), 1168 (m), 1124 (m), 1040 (s), 1014 (s); δ_H (400 MHz, $CDCl_3$) 7.65 (1H, d, *J* 7.9 Hz, ArH), 7.62 (1H, d, *J* 7.8 Hz, ArH), 7.09 (2H, d, *J* 8.6 Hz, 2 × ArH), 6.95–6.90 (2H, m, 2 × ArH), 6.81 (2H, d, *J* 8.6 Hz, 2 × ArH), 6.72 (1H, d, *J* 1.7 Hz, ArH), 6.60 (1H, d, *J* 1.8 Hz, ArH), 6.56 (1H, dd, *J* 7.8, 1.8 Hz, ArH), 6.54 (1H, d, *J* 1.7 Hz, ArH), 6.49 (1H, dd, *J* 7.9, 1.9 Hz, ArH), 3.83 (6 H, s, 2 × OMe), 3.80 (3 H, s, OMe), 2.90 (4 H, s, 2 × $ArCH_2$), 2.84 (4 H, s, 2 × $ArCH_2$); δ_C (100 MHz, $CDCl_3$) 157.8 (C), 157.8 (C), 155.9 (C), 149.5 (C), 144.9 (C), 143.7 (C), 143.4 (C), 139.0 (CH), 139.0 (CH), 135.2 (C), 134.1 (C), 129.4 (2 × CH), 124.2 (CH), 122.7 (CH), 122.7 (CH), 120.8 (CH), 117.1 (2 × CH), 112.7 (CH), 111.6 (CH), 111.5 (CH), 82.5 (C), 82.5 (C), 56.1 (CH_3), 56.1 (CH_3), 56.1 (CH_3), 37.8 (CH_2), 37.6 (CH_2), 36.8 (CH_2), 36.6 (CH_2); *m/z* (ESI+) 743 (100, $[M+Na]^+$); HRMS (ESI+): $[M+Na]^+$, found 743.0120. $C_{31}H_{30}I_2NaO_4$ requires 743.0126.

*5.7. Polymorphatin A (**3**) and Perrottetin E (**2**)*

To a solution of $NiCl_2(PPh_3)_2$ (6.95 g, 10.6 mmol) and PPh_3 (5.62 g, 21.4 mmol) in dry DMF (280 mL) was added Zn powder (770 mg, 11.8 g-atom). The reaction mixture was heated to 55 °C for 1 h then a solution of 12,12'-diiodoperrottetin E trimethyl ether **18** (3.19 g, 4.42 mmol) was added. After a further 1 h, the temperature was increased to 100 °C for 18 h. The cooled solution was partitioned between HCl (2 M, 300 mL) and Et_2O (100 mL) then the aqueous phase was separated and extracted with Et_2O (4 × 100 mL). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (25-35% Et_2O in petrol) afforded a colourless gum that was chiefly comprised of polymorphatin A trimethyl ether (**20**, *vide infra*)[22] and perrottetin E trimethyl ether (**19**). The gum was dissolved in DCM (150 mL) at 0 °C then boron tribromide (1 M in DCM, 44.2 mL, 44.2 mmol) was added. After 18 h at RT, water (100 mL) was added then the aqueous phase was separated and extracted with Et_2O (5 × 100 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20–25% EtOAc/hexane) afforded firstly polymorphatin A **3** (503 mg, 1.19 mmol, 27%) as a white solid, MP 160–161 °C

(EtOAc/hexane) [Lit. 234–235 °C (MeOH) and >300 °C][5,6]; ν_{max} 3333 (br) 2925 (w), 2856 (w), 1503 (s), 1440 (m), 1420 (m), 1285 (m), 1268 (w), 1210 (m), 1167 (m); δ_H (400 MHz, *d*$_6$-acetone) 8.48 (2H, br s, 2 × OH), 7.69 (1H, s, OH), 7.01 (1H, d, *J* 7.9 Hz, ArH), 6.94 (1H, dd, *J* 8.3, 2.1 Hz, ArH), 6.85 (1H, dd, *J* 8.0, 2.8 Hz, ArH), 6.83 (1H, d, *J* 8.2 Hz, ArH), 6.61 (1H, d, *J* 7.8 Hz, ArH), 6.51 (1H, d, *J* 7.9 Hz, ArH), 6.43 (1H, d, *J* 2 Hz, ArH), 6.39–6.26 (2H, m, 2 × ArH), 6.21–6.06 (3H, m, 3 × ArH), 5.66 (1H, d, *J* 2.1 Hz, ArH), 3.01–2.45 (8 H, m, 2 × CH_2CH_2); δ_C (100 MHz, *d*$_6$-acetone) 157.2 (C), 154.3 (C), 154.2 (C), 149.2 (C), 142.7 (C), 142.5 (C), 141.4 (C), 134.2 (C), 133.6 (C), 132.8 (CH), 132.7 (CH), 132.1 (CH), 132.0 (CH), 130.5 (CH), 127.3 (CH), 126.1 (C), 125.8 (CH), 125.3 (C), 123.8 (CH), 122.8 (CH), 118.8 (CH), 118.6 (CH), 118.0 (CH), 114.8 (CH), 39.3 (CH_2), 38.7 (CH_2), 37.6 (CH_2), 37.5 (CH_2); *m/z* (ESI+) 425 (100%, MH^+); HRMS (ESI+): MH^+, found 425.1749. $C_{28}H_{25}O_4$ $[M+H]^+$ requires 425.1747; then perrottetin E **2**[2a] (120 mg, 0.28 mmol, 6%) as colourless oil; ν_{max} 3350 (br), 2925 (w), 2858 (w), 1588 (m), 1504 (s), 1455 (m), 1435 (m), 1342 (w), 1272 (m), 1216 (s), 1156 (s); δ_H (400 MHz, $CDCl_3$) 7.16 (1H, t, *J* 7.8 Hz, ArH), 7.12 (1H, t, *J* 7.8 Hz, ArH), 7.11 (2H, d, *J* 8.7 Hz, 2 × ArH), 6.96 (1H, d, *J* 8.2 Hz, ArH), 6.87 (2H, d, *J* 8.7 Hz, 2 × ArH), 6.84 (1H, dd, *J* 8.2, 2.0 Hz, ArH), 6.77 (1H, d, *J* 7.6 Hz, ArH), 6.70–6.63 (4H, m, 4 × ArH), 6.63 (1H, d, *J* 2.1 Hz, ArH), 6.59 (1H, dd, *J* 2.5, 1.5 Hz, ArH), 5.48 (1H, s, OH), 4.89 (1H, br s, OH), 4.85 (1H, br s, OH), 2.95–2.83 (4H, m, 2 × $ArCH_2$), 2.78 (4H, s, 2 × $ArCH_2$); δ_C (100 MHz, $CDCl_3$) 155.4 (C), 155.4 (C), 154.8 (C), 145.3 (C), 143.5 (C), 143.4 (C), 143.2 (C), 136.8 (C), 134.1 (C), 129.8 (2 × CH), 129.5 (CH), 129.4 (CH), 124.3 (CH), 121.0 (2 × CH), 118.7 (CH), 117.8 (2 × CH), 115.8 (CH), 115.5 (CH), 115.4 (CH), 112.9 (CH), 112.8 (CH), 37.8 (CH_2), 37.7 (CH_2), 36.8 (CH_2), 36.7 (CH_2); *m/z* (ESI+) 427 (100, MH^+); HRMS (ESI+): MH^+, found 427.1914. $C_{28}H_{27}O_4$ $[MH]^+$ requires 427.1904.

*5.8. Polymorphatin A trimethyl ether (**20**)*

To a cooled (0 °C) solution of polymorphatin A **3** (35 mg, 0.082 mmol) in acetone (2 mL) were added DBU (0.073 mL, 0.49 mmol) and iodomethane (0.03 mL, 0.49 mmol). After 24 h at RT the reaction mixture was filtered through Celite®, concentrated *in vacuo* and purified by column chromatography (25% Et_2O in hexane) to afford the *title compound* **20** as white solid (25 mg, 65%); MP 130–133 °C (Et_2O/hexane) [Lit. 213 °C][6,17]; ν_{max} 2928 (m), 2854 (s), 1605 (m), 1503 (s), 1462 (m), 1403 (m), 1269 (s), 1220 (m), 1166 (m), 1122 (m), 1039 (s); δ_H (500 MHz, *d*$_6$-DMSO) 7.10 (1H, dd, *J* 8.4, 2.1 Hz, ArH), 7.01 (1H, d, *J* 8.4 Hz, ArH), 6.90 (1H, d, *J* 1.4 Hz, ArH), 6.79 (1H, d, *J* 1.2 Hz, ArH), 6.67 (1H, d, *J* 7.8 Hz, ArH), 6.45–6.20 (2H, v br s, 2 × ArH), 6.37 (1H, d, *J* 7.8 Hz, ArH), 6.18–5.92 (2H, v br s, 2 × ArH), 5.86 (1H, dd, *J* 7.8, 1.5 Hz, ArH), 5.67 (1H, dd, *J* 7.8, 1.4 Hz, ArH), 5.66 (1H, d, *J* 2.1 Hz, ArH), 3.75 (3H, s, OMe), 3.74 (3H, s, OMe), 3.55 (3H, s, OMe), 3.14–2.86 (4H, m, 4 × CHH), 2.70–2.50 (2H, m, 2 × CHH), 2.44–2.22 (2H, m, 2 × CHH) with other signals attributed to rotamer(s); δ_H (500 MHz, *d*$_6$-DMSO, T = 100 °C) 7.09 (1H, m, ArH), 7.00 (1H, br d, *J* 7.9 Hz, ArH), 6.88 (1H, br s, ArH), 6.77 (1H, br s, ArH), 6.71 (1H, br d, *J* 6.9 Hz, Ar*H*), 6.43 (1H, br d, *J* 6.6 Hz, ArH), 6.34 (2H, br d, *J* 7.9 Hz, 2 × Ar*H*), 6.08 (2H, br d, *J* 8.0 Hz, 2 × ArH), 5.93 (1H, br d, *J* 7.4 Hz, Ar*H*), 5.75 (1H, br d, *J* 7.4 Hz, ArH), 5.68 & 5.64 (1H, 2 × br s, Ar*H*), 3.76 (3H, s, OMe), 3.74 (3H, s, OMe), 3.58 (3H, s, OMe), 3.12–2.85 (4H, m, 4 × CHH), 2.68–2.41 (4H, m, 4 × CHH); δ_C (500 MHz, *d*$_6$-DMSO, T = 100 °C) 156.5 (C), 156.2 (C), 156.1 (C), 150.6 (C), 141.3 (C), 140.5 (C), 140.2 (C), 134.2 (C), 133.3 (CH), 133.2 (CH), 132.7 (CH), 131.9 (CH), 131.4 (CH), 129.3 (C), 126.0 (CH), 125.9 (CH), 125.1 (CH), 123.1 (CH), 122.2 (CH), 112.5 (CH), 112.3 (CH), 111.8 (CH), 56.2 (CH_3), 55.8 (CH_3), 55.7 (CH_3), 38.3 (CH_2), 38.2 (CH_2), 37.1 (CH_2), 36.6 (CH_2); *m/z* (ESI+) 467 (100, MH^+); HRMS (ESI+): $[M+Na]^+$, found 489.2044. $C_{31}H_{30}NaO_4$ requires 489.2036; X-ray: CCDC No. 1517765 (Figure 3).

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22. A $CDCl_3$ solution of the gum in an open vial was placed in a pool of hexane within a sealed vial to induce crystallisation of polymorphatin A trimethyl ether **20**. The X-ray crystal structure depicted in Figure 3 was attained from the crystals that formed. Additional characterisation on that solid matched data attained from the sample prepared by exhaustive methylation of polymorphatin A **3**. Three attempts to attain an X-ray crystal structure for polymorphatin A **3** failed.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.