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A total synthesis of (±)-phomactin A

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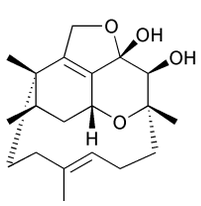
A total synthesis of the PAF antagonist phomactin A (**1**), isolated from the marine fungus *Phoma* sp. is described. The synthesis is based on a Cr(II)/Ni(II) macrocyclisation from the aldehyde vinyl iodide **14**, leading to the key phomactatrienol intermediate **16a**, followed by elaboration of **16a** to the epoxyketone **21**, which undergoes spontaneous pyran and hemiacetal ring formation to **1** on deprotection with DDQ.

Introduction

Phomactin A (**1**) together with its congeners,[1] *e.g.* phomactin D (**2**), phomactin G (**3**), and Sch 49028 (**4**),[2] comprise a novel class of natural products which are selective antagonists of platelet activating factor (PAF). The oxygenated diterpene **1** contains six stereogenic centres, accommodated in an unusual reduced furanochroman ring system, linked by two quaternary centres and making up part of a 12-membered macrocycle. The unique structure of phomactin A, together with the implications that PAF is involved in many inflammatory and respiratory diseases,[3] have combined to make phomactin A, its congeners and its analogues, attractive targets for total synthesis and biological evaluation. In the accompanying paper[4] we summarised our synthetic investigations to the reduced furanochroman[5] and to the bicyclo[9.3.1]pentadecane core unit,[6] *i.e.* **5**, in phomactin A (**1**). In this paper we describe the development of these studies which culminated in the first total synthesis of this intriguing metabolite.[7,8]



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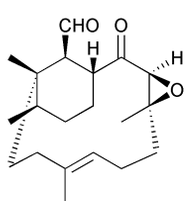

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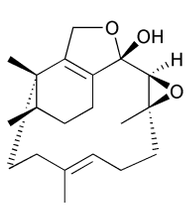

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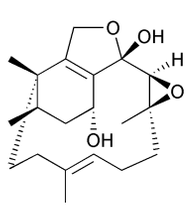
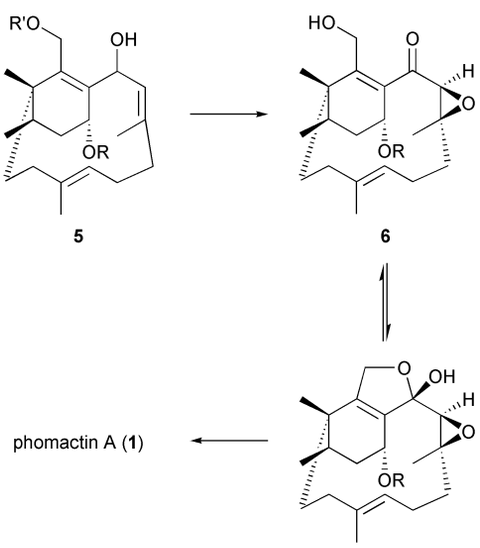


4

Our strategy for synthesising phomactin A, starting from the phomactatriene **5**, was based on speculation regarding its most likely biosynthesis. Thus, we first planned to elaborate the β-oriented epoxyketone **6**, *cf* naturally occurring **4**, from **5**, and then to form the pyran ring in **1** following deprotection and cyclisation of **6**. In model studies, described in the accompanying paper,[4] we showed that the macrocyclic ring in the phomactatriene **5** could be elaborated from the aldehyde vinyl iodide **9** using an intramolecular Cr(II)-mediated coupling reaction, *viz* **9** ⟶ **10**.[9] The aldehyde vinyl iodide **9** was derived from 5-methylcyclohexan-1,3-dione in nine straightforward steps,[4] one of which involved the reduction of the cyclohexenone intermediate **7** under Luche conditions which led exclusively to the β-orientated secondary alcohol **8** in 77% yield.[10] Before we could develop the aforementioned macrocyclisation strategy to phomactin A therefore, we first needed to synthesise an aldehyde vinyl iodide precursor with the correct α-stereochemistry at its secondary alcohol centre, *viz* **14**.



Results and discussion

Attempts to invert the stereochemistry of the β-alcohol group in **8** under the usual Mitsunobu conditions, or *via* the corresponding sulfonate using caesium acetate or superoxide were met with failure. Gratifyingly, however, when the alcohol **8** was treated with thionyl chloride the more reactive β-chloride **11** was produced in almost quantitative yield (Scheme 1).[11] Although we were not able to substitute the chloride in **11** for oxygen using superoxide or zinc oxide, both ammonium acetate and zinc acetate in acetic acid led to **12** with agreeable levels of selectivity (*ca.* 90% α-OH), however in low yields. Finally, displacement of the chloride in **11**, using the potassium salt of *p*-methoxybenzyl alcohol in the presence of 18-crown-6 in THF at 0 °C, with concomitant saponification of the PNB group in the substrate, led to the corresponding PMB ether **13** of the α-secondary alcohol in a satisfying 60% overall yield from the β-alcohol **8**. Oxidation of the primary alcohol **13**, using Dess–Martin periodinane, finally led to the α,β-unsaturated aldehyde **14** whose relative stereochemistry was confirmed by DPFGSE NOSEY studies.

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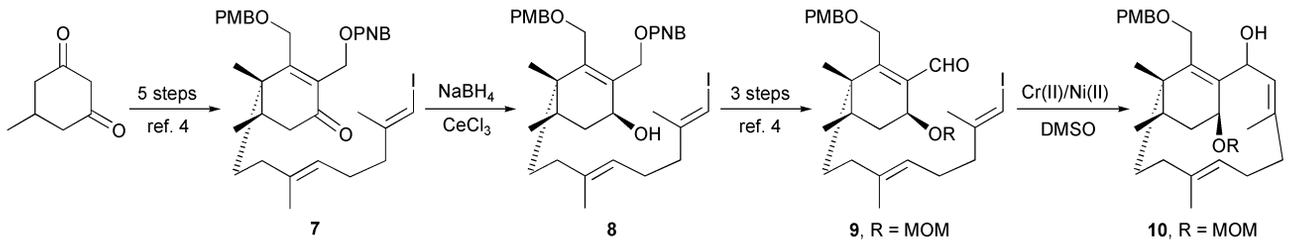
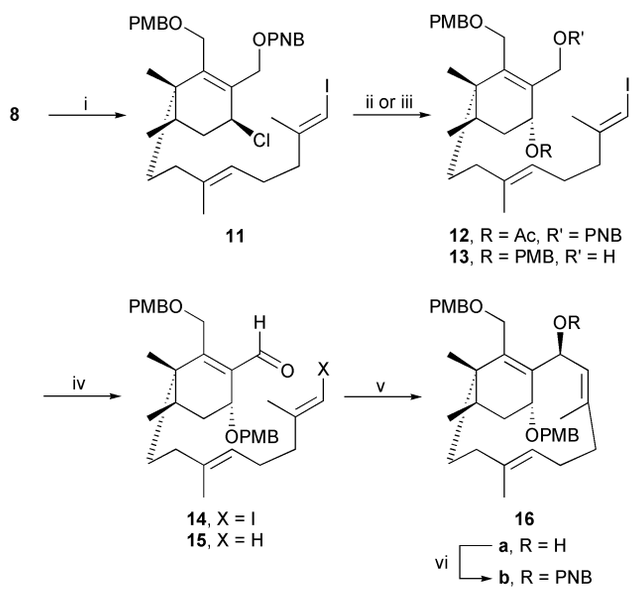
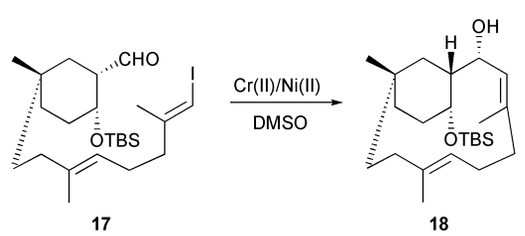


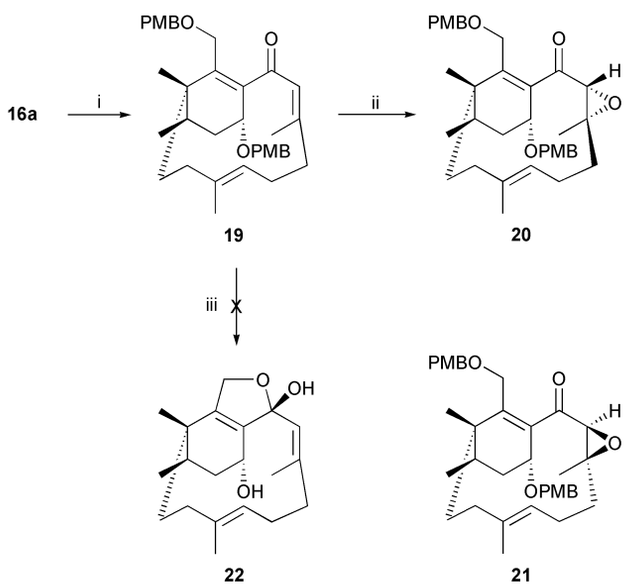
When a solution of the aldehyde vinyl iodide **14** in DMSO and THF was treated with 6 equivalents of $CrCl_2$ and 1 equivalent of $NiCl_2$ it underwent smooth macrocyclisation to a single diastereoisomer of the phomactatriene alcohol **16a** in 58% yield. A small amount (18%) of the product **15** resulting from reduction of the carbon-to-iodide bond in **14** was produced concurrently. The newly produced secondary alcohol group in **16a** was assigned the β-stereochemistry from NOE studies, and was confirmed by carrying out an X-ray crystal structure determination on the corresponding *p*-nitrobenzoate (PNB) derivative **16b**. In later related studies,[12] Mi and Maleczka showed that the substrate **17** underwent a Cr(II)–Ni(II) macrocyclisation leading to the secondary alcohol product **18** with exclusively the α-stereochemistry shown. The β-stereochemistry of the secondary alcohol in **16a**, presumably results from cyclisation of the aldehyde vinyl iodide **14** *via* the *s-trans* conformation, as shown.



Scheme 1 *Reagents and conditions*: i, $SOCl_2$, Et_2O, 0 °C to rt, 97%; ii, NH_4OAc, acetone, rt, 25%; iii, PMBOH, *t*-BuOK, 18-C-6, THF, 0 °C to rt, 62%; iv, Dess–Martin periodinane, C_5H_5N, CH_2Cl_2, 0 °C to rt, 95% (**14**) from **13**; v, $CrCl_2$ (6 eq.), $NiCl_2$ (1 eq.), DMSO, THF, rt, 58%; vi, *p*-NO_2-C_6H_4COCl, Et_3N, DMAP, CH_2Cl_2, −25 °C to 0 °C, 82%.



Having achieved a concise synthesis of the phomactatrienol **16a**, *cf.* **5**, our strategy for completing a synthesis of phomactin A (**1**) required oxidation of the secondary alcohol and a stereoselective epoxidation of the adjacent trisubstituted double bond in **16a** followed by deprotection to the epoxyketone **6**. Further deprotection of the remaining secondary alcohol group in **6** should then lead to the corresponding 1,4-diol which we would expect to undergo spontaneous cyclic hemiacetal and pyran ring formation producing phomactin A (**1**), as discussed earlier. We carried out the aforementioned oxidation–epoxidation steps in two different sequences, as summarised in Scheme 2. Thus, oxidation of the alcohol **16a** using Dess–Martin periodinane led to the corresponding ketone **19** in almost quantitative yield. To our disappointment however, epoxidation of **19** following treatment with *t*-BuOOH and KH in THF gave only the α-epoxy ketone **20**; none of the anticipated β-epoxide **21** could be detected in the crude reaction product.



Scheme 2 *Reagents and conditions*: i, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 97%; ii, KH, *t*-BuOOH, THF, −20 °C to rt, 27%; iii, DDQ, CH_2Cl_2–H_2O (18:1), 0 °C to 10 °C.

We also examined the deprotection of **19** in the hope of preparing the cyclic hemiacetal **22** for later conversion into Sch 49028 (**4**), a possible penultimate precursor to phomactin A (**1**) itself. However, treatment of **19** with DDQ led only to intractable tars and we were not able to find any evidence for the formation of the hydroxy cyclic hemiacetal **22** (Scheme 2).

The formation of the epoxide **20** with the α-stereochemistry from **16a**, *via* **19**, prompted us to examine the conformations of the cyclic systems **16a** and **19** alongside the cyclic hemiacetal **22** and the epimeric secondary alcohol **23** corresponding to **16a**. NOE ^1H NMR studies on the β-alcohol **16a** together with X-ray crystal structure data obtained for the corresponding PNB derivative **16b** suggested that the compound has the conformation (a) shown in Fig. 1. Molecular mechanics

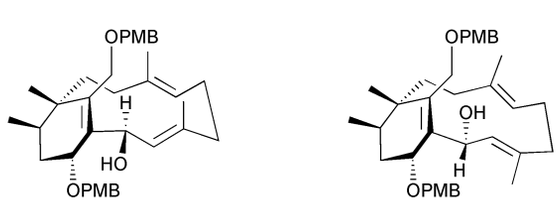
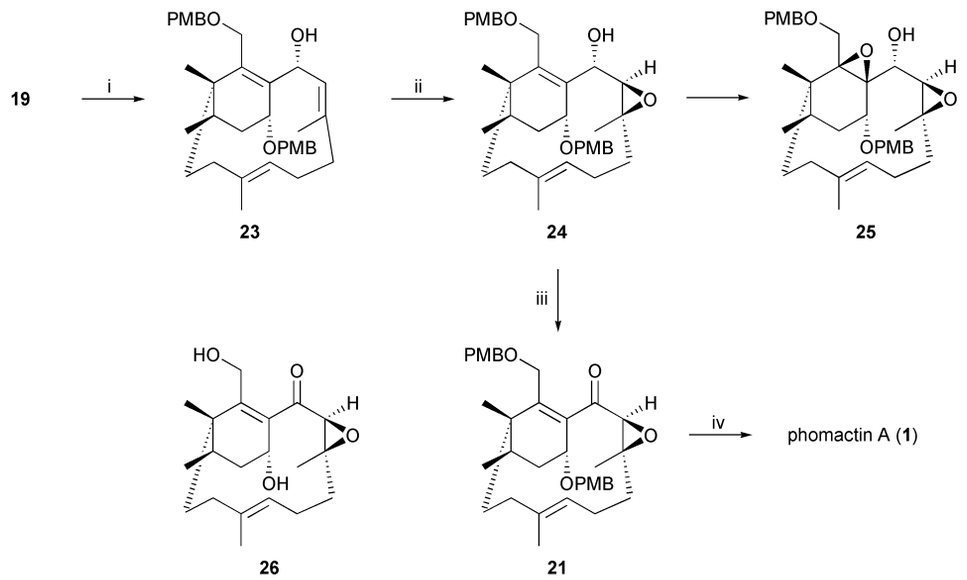


Fig. 1 Conformations of a) the β-, and b) the α-alcohols **16a** and **23**, respectively.



Scheme 3 *Reagents and conditions*: i, $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, −78 °C to 0 °C, 96%; ii, $VO(acac)_2$, *t*-BuOOH, PhH, rt, 86%, *ca*. 1 : 1 (**24** and **25**); iii, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 80%; iv, DDQ, CH_2Cl_2–H_2O (18 : 1), 0 °C to rt, 83%.

calculations,[13] using the MM3 force field,[14] were consistent with this conformation, and showed that the trisubstituted double bond adjacent to the β-alcohol group in **16a** presents only one face to the exterior of the bicyclic ring system. Epoxidation of **16a** followed by oxidation of the intermediate α-epoxy alcohol therefore would be expected to lead only to the α-epoxide **20**. Molecular mechanics calculations also showed that both the enone **19** and the cyclic hemiacetal **22** have conformations closely similar to the β-alcohol **16a**, and would therefore not be expected to act as suitable precursors to phomactin A, as experimental work has demonstrated. However, molecular mechanics calculations on the epimeric α-alcohol **23**, corresponding to **16a**, clearly suggested that this compound was conformationally predisposed (see Fig. 1b) to formation of the correct β-epoxide **24** and precursor to the epoxyketone **21** en route to phomactin A (**1**).

Accordingly, we next converted the β-alcohol **16a** into the corresponding epimeric α-alcohol **23**, by first oxidising **16a** to the ketone **19** and then reducing **19** using $NaBH_4$–$CeCl_3$ (Scheme 3); this procedure gave exclusively the inverted α-alcohol in 96% yield. To our satisfaction, treatment of the α-alcohol **23** with $VO(acac)_2$ and *t*-BuOOH then gave the correct β-orientated epoxide **24**, albeit in only 25% yield. The β-epoxide **24** was accompanied by the corresponding *bis*-epoxide **25** which was produced in equal amounts. The *bis*-epoxide **25** was obtained as colourless crystals, and the β,β-epoxide stereochemistry shown in **25** was established by X-ray crystallography.[7] By inference, and by NMR studies, the *mono*-epoxide **24** was assigned the β-epoxide stereochemistry. Attempts to optimise the yield of the *mono*-epoxide **24** from **23** using, for example, Sharpless asymmetric epoxidation conditions were encouraging but the dearth of material precluded these studies being pursued in depth.

We were now poised to complete our synthesis of phomactin A (**1**) from **24** *via* **21** in line with the biogenetic speculation presented earlier, *cf*. **5**⟶**6**⟶**1**. Oxidation of **24** using Dess–Martin periodinane gave the corresponding epoxyketone **21** in 80% yield. Treatment of the epoxyketone **21** with DDQ in CH_2Cl_2–H_2O at 0 °C resulted in simultaneous deprotection of both the primary and secondary PMB ether groups in the substrate, followed by spontaneous cyclic hemiacetal and pyran ring formation from the presumed diol intermediate **26** leading cleanly and directly to (±)-phomactin A (**1**) in 83% overall yield. The synthetic phomactin A displayed NMR spectroscopic data which were superimposable on those of natural phomactin A isolated from *Phoma* sp.[1] Interestingly, the NMR spectrum of synthetic phomactin A in $CDCl_3$, instead of CD_3OD, was identical with that reported for the co-metabolite designated Sch 49028, *i.e.* **4**, isolated from *Phoma* sp.[2b] It is likely therefore that Sch 49028 has been incorrectly assigned and is in fact phomactin A (**1**) rather than the interesting epoxy cyclic hemiacetal structure **4**.

Experimental

General details

For general experimental details see reference 4.

Energy minimisation and conformational search calculations were performed using Macromodel version 5.5, a molecular modelling program developed by Still and co-workers.[13] The MM3* force field, which was based on the MM3[14] parameter set developed by Allinger and co-workers, was implemented, without solvation, in Macromodel for all calculations. Energy minimisations were conducted using the Polak–Ribiere conjugate gradient (PRCG) first derivative method.[15] Minimum energy conformations were obtained by the Monte Carlo Multiple Minimum (MCMM) conformational search method of Goodman and Still.[16] Ring closure bonds were chosen at a position removed by at least one bond from a functional group. A conformation with a bond closure distance outside 1–2 Å was considered energetically improbable and rejected. Olefins with the *E* configuration were required to be *trans* (180°) and those with the *Z* configuration were required to be *cis* (0°). A conformation with an olefin deviating by more than 90° was considered energetically improbable and rejected. The MMCM search method involved the generation and minimisation of 1,000 starting structures by application of random variations to the internal co-ordinates (torsional angles). Duplicate structures and those greater than 20 kJ mol^{-1} above the global minimum were discarded.

4-Nitrobenzoic acid (±)-(3*S*,4*R*,6*S*)-6-chloro-3-((3*E*,7*E*)-8-iodo-3,7-dimethylocta-3,7-dienyl)-2-(4-methoxybenzyloxymethyl)-3,4-dimethylcyclohex-1-enylmethyl ester 11

Thionyl chloride (430 μL, 5.89 mmol) was added dropwise over 1 minute to a stirred solution of the alcohol **8** (1.11 g, 1.55 mmol) in diethyl ether (26.0 mL) at 0 °C and the mixture was stirred for 1 hour, then allowed to warm to room temperature over 2 hours and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 10% diethyl ether in pentane as eluent to give the *chloride* (1.11 g,

97%) as a colourless oil; ν_{max} (film)/cm^{-1} 2963, 1725, 1610, 1270 and 720; δ_H (360 MHz, $CDCl_3$) 8.26 (2H, d, *J* 8.6, 2 × Ar*H*), 8.15 (2H, d, *J* 8.6, 2 × Ar*H*), 7.26 (2H, d, *J* 8.5, 2 × Ar*H*), 6.85 (2H, d, *J* 8.5, 2 × Ar*H*), 5.83 (1H, br. s, C=C*H*I), 5.22 (1H, d, *J* 12.6, C*H*HOPNB), 5.16 (1H, d, *J* 12.6, CH*H*OPNB), 4.97 (1H, dd, *J* 13.6 and 6.3, C=C*H*), 4.80 (1H, dd, *J* 9.5 and 6.6, C*H*Cl), 4.46 (2H, s, ArCH_2), 4.16 (1H, d, *J* 11.0, OC*H*HC=C), 3.94 (1H, d, *J* 11.0, OCH*H*C=C), 3.79 (3H, s, OCH_3), 2.20–2.12 (3H, m, CH_2C=CHI and CHC*H*H), 2.08 (2H, dt, *J* 14.1 and 6.4, C=CHCH_2), 1.96 (1H, ddd, *J* 24.1, 10.8 and 2.6, CHCH*H*), 1.84–1.72 (2H, m, CH_3C*H* and C*H*HC=CH), 1.82 (3H, d, *J* 1.0, CH_3C=CHI), 1.58–1.40 (3H, m, CH*H*C=CH and C(4°)–CH_2), 1.52 (3H, br. s, CH_3C=CH), 0.99 (3H, s, CH_3–C(4°)), 0.93 (3H, d, *J* 6.5, CH_3CH); δ_C (90 MHz, $CDCl_3$) 164.3 (O*C*=O), 159.3 (Ar–*C*(4°)OCH_3), 150.4 (Ar–*C*(4°)NO_2), 147.6 (*C*=CHI), 146.1 (C=*C*CHCl), 136.2 (Ar–*C*(4°)), 135.8 (Ar–*C*(4°)), 133.3 (*C*=CH), 130.7 (Ar–*C*H), 129.8 (*C*=CCHCl), 129.6 (Ar–*C*H), 123.5 (Ar–*C*H), 122.9 (C=*C*H), 113.8 (Ar–*C*H), 74.8 (C=*C*HI), 72.7 (Ar*C*H_2O), 65.8 (O*C*H_2C=C), 64.4 (*C*H_2OPNB), 58.5 (*C*HCl), 55.2 (O*C*H_3), 41.9 (*C*(4°)–C=C), 39.4 (*C*H_2C=CHI), 38.0 (CH*C*H_2), 35.2 (C(4°)–*C*H_2), 34.3 (*C*H_2C=CH), 32.7 (CH_3*C*H), 26.1 (C=CH*C*H_2), 23.9 (*C*H_3C=CHI), 20.5 (*C*H_3–C(4°)), 16.2 (*C*H_3C=CH), 15.6 (*C*H_3CH); *m*/*z* (ES) 754.2252 (M^+ + Na + MeOH − HCl, 100%, $C_{36}H_{46}INO_7Na$ requires 754.2217).

4-Nitrobenzoic acid (±)-(3*S*,4*R*,6*R*)-6-acetoxy-3-((3*E*,7*E*)-8-iodo-3,7-dimethylocta-3,7-dienyl)-2-(4-methoxybenzyloxymethyl)-3,4-dimethylcyclohex-1-enylmethyl ester 12

Ammonium acetate (50 mg, 0.65 mmol) was added to the chloride **11** (52 mg, 0.071 mmol) at room temperature in a glove bag under an atmosphere of argon. The mixture was diluted with acetone (1 mL) and then stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica using 20% diethyl ether in pentane as eluent to give the *acetate* (14 mg, 25%) as a colourless oil; δ_H (360 MHz, $CDCl_3$) 8.28–8.24 (2H, m, Ar*H*), 8.15–8.12 (2H, m, Ar*H*), 7.23 (2H, d, *J* 8.6, Ar*H*), 6.82 (2H, d, *J* 8.6, Ar*H*), 5.86 (1H, d, *J* 1.1, C=C*H*I), 5.47 (1H, d, *J* 3.1, C*H*OAc), 5.08 (1H, d, *J* 12.7, C*H*HOPNB), 5.04 (1H, t, *J* 5.6, C=C*H*CH_2), 4.85 (1H, d, *J* 12.6, CH*H*OPNB), 4.47 (2H, m, PMBCH_2O), 4.09 (1H, d, *J* 10.4, OC*H*HC=C), 4.02 (1H, d, *J* 10.4, OCH*H*C=C), 3.77 (3H, s, OCH_3), 2.23–2.19 (2H, m, CH_2C=CH), 2.15–2.11 (2H, m, CH_2), 2.07–2.00 (2H, m, CH_2), 1.97 (3H, s, COCH_3), 1.84 (3H, d, *J* 1.1, CH_3C=CHI), 1.78–1.71 (2H, m, CH_2), 1.68–1.66 (3H, m, CH_2 and C*H*), 1.57 (3H, s, CH_3C=CH), 0.90 (3H, d, *J* 6.9, CH_3CH), 0.88 (3H, s, CH_3); *m*/*z* (EI) 782 (M^+ + Na).

[(±)-(3*S*,4*R*,6*R*)-3-((3*E*,7*E*)-8-Iodo-3,7-dimethylocta-3,7-dienyl)-6-(4-methoxybenzyloxy)-2-(4-methoxybenzyloxymethyl)-3,4-dimethylcyclohex-1-enyl]methanol 13

4-Methoxybenzyl alcohol (0.63 mL, 5.0 mmol) was added dropwise over 1 minute to a stirred solution of 18-crown-6 (0.78 g, 3.0 mmol) and potassium *tert*-butoxide (0.43 g, 3.8 mmol) in THF (24 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then a solution of the chloride **11** (1.09 g, 1.48 mmol) in THF (25 mL) was added dropwise *via* cannula over 1 minute at 0 °C. The mixture developed a purple colour and was allowed to warm to room temperature over 5 days. The mixture was quenched with water (40 mL) and the separated aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 1.5% methanol in dichloromethane as eluent to remove the excess 4-methoxybenzyl alcohol. The crude fractions were concentrated *in vacuo* and the residue was purified by flash column chromatography on silica using 30% diethyl ether in pentane as eluent to give the *alcohol* (0.63 g, 62%) as a colourless oil; ν_{max} (film)/cm^{-1} 3454, 2932, 1614 and 1248; δ_H (360 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.4, 2 × Ar*H*), 7.26 (2H, d, *J* 8.4, 2 × Ar*H*), 6.88 (4H, d, *J* 8.4, 4 × Ar*H*), 5.85 (1H, br. s, C=C*H*I), 4.98 (1H, dd, *J* 6.7 and 6.4, C=C*H*), 4.60 (1H, d, *J* 11.4, ArC*H*H), 4.50 (1H, d, *J* 11.1, ArCH*H*), 4.45 (1H, d, *J* 11.1, ArCH*H*), 4.42 (1H, d, *J* 11.4, ArCH*H*), 4.16 (1H, d, *J* 10.5, OC*H*HC=C), 4.12 (1H, d, *J* 11.5, C*H*HOH), 3.98 (1H, d, *J* 11.5, CH*H*OH), 3.95 (1H, br. s, C*H*OPMB), 3.88 (1H, d, *J* 10.5, OCH*H*C=C), 3.81 (6H, s, 2 × OCH_3), 2.82 (1H, br. s, *OH*), 2.22–2.18 (2H, m, CH_2C=CHI), 2.09 (2H, dt, *J* 7.7 and 6.5, C=CHCH_2), 2.07–2.01 (1H, m, CH_3C*H*), 1.89–1.78 (2H, m, C*H*HC=CH and CHC*H*H), 1.84 (3H, s, CH_3C=CHI), 1.53 (3H, s, CH_3C=CH), 1.52–1.35 (4H, m, C(4°)–CH_2, CHCH*H* and CH*H*C=CH), 0.88 (3H, d, *J* 6.8, CH_3CH), 0.84 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 159.4 (Ar–*C*(4°)OCH_3), 159.1 (Ar–*C*(4°)OCH_3), 147.8 (*C*=CHI), 143.2 (C=*C*CHOPMB), 139.1 (Ar–*C*(4°)), 136.6 (Ar–*C*(4°)), 130.9 (*C*=CH), 129.8 (Ar–*C*H), 129.6 (*C*=CCHOPMB), 129.4 (Ar–*C*H), 122.6 (C=*C*H), 113.9 (Ar–*C*H), 113.8 (Ar–*C*H), 74.7 (C=*C*HI), 73.4 (*C*HOPMB), 73.0 (Ar*C*H_2O), 70.7 (Ar*C*H_2O), 66.1 (O*C*H_2C=C), 62.0 (*C*H_2OH), 55.3 (2 × OCH_3), 41.4 (*C*(4°)–C=C), 39.5 (*C*H_2C=CHI), 35.4 (C(4°)–*C*H_2), 34.5 (*C*H_2C=CH), 30.8 (CH*C*H_2), 27.5 (CH_3*C*H), 26.2 (C=CH*C*H_2), 23.9 (*C*H_3C=CHI), 19.4 (*C*H_3–C(4°)), 16.2 (*C*H_3C=CH), 16.0 (*C*H_3CH); *m*/*z* (ES) 711.2567 (M^+ + Na, 100%, $C_{36}H_{49}IO_5Na$ requires 711.2522).

(±)-(3*S*,4*R*,6*R*)-3-((3*E*,7*E*)-8-Iodo-3,7-dimethylocta-3,7-dienyl)-6-(4-methoxybenzyloxy)-2-(4-methoxybenzyloxymethyl)-3,4-dimethylcyclohex-1-enecarbaldehyde 14

Dess–Martin periodinane (354 mg, 0.835 mmol) was added to a stirred solution of pyridine (0.14 mL, 1.7 mmol) and the alcohol **13** (383 mg, 0.556 mmol) in dichloromethane (11.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes, then allowed to warm to room temperature over 60 minutes and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 20% diethyl ether in pentane as eluent to give the *aldehyde* (362 mg, 95%) as a colourless oil; ν_{max} (film)/cm^{-1} 2932, 1674, 1613 and 1247; δ_H (360 MHz, $CDCl_3$) 10.0 (1H, s, C*H*O), 7.26 (4H, d, *J* 8.7, 4 × Ar*H*), 6.89 (2H, d, *J* 8.6, 2 × Ar*H*), 6.86 (2H, d, *J* 8.6, 2 × Ar*H*), 5.85 (1H, br. s, C=C*H*I), 5.00 (1H, app. t, *J* 6.6, C=C*H*), 4.53 (1H, d, *J* 12.2, ArC*H*H), 4.49 (1H, d, *J* 12.2, ArCH*H*), 4.49 (2H, s, ArCH_2), 4.43 (1H, br. s, C*H*OPMB), 4.37 (1H, d, *J* 11.0, OC*H*HC=C), 4.11 (1H, d, *J* 11.0, OCH*H*C=C), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.24–2.18 (3H, m, CH_2C=CHI and CH_3C*H*), 2.10 (2H, dt, *J* 13.9 and 6.5, C=CHCH_2), 1.94 (1H, app. t, *J* 10.8, C*H*HC=CH), 1.84 (3H, s, CH_3C=CHI), 1.79–1.61 (3H, m, CHC*H*H and C(4°)–CH_2), 1.53 (3H, s, CH_3C=CH), 1.51–1.42 (1H, m, CH*H*C=CH), 1.35 (1H, dt, *J* 13.5 and 3.3, CHCH*H*), 0.91 (3H, d, *J* 5.9, CH_3CH), 0.90 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 192.8 (*C*HO), 160.7 (*C*=CCHO), 159.4 (Ar–*C*(4°)OCH_3), 158.9 (Ar–*C*(4°)OCH_3), 147.7 (*C*=CHI), 137.9 (Ar–*C*(4°)), 136.2 (Ar–*C*(4°)), 131.3 (*C*=CH), 129.7 (Ar–*C*H), 129.3 (Ar–*C*H), 122.9 (C=*C*H), 113.9 (Ar–*C*H), 113.6 (C=*C*CHO), 113.6 (Ar–*C*H), 74.8 (C=*C*HI), 73.0 (Ar*C*H_2O), 71.6 (Ar*C*H_2O), 67.9 (*C*HOPMB), 63.8 (O*C*H_2C=C), 55.3 (2 × OCH_3), 43.0 (*C*(4°)–C=C), 39.4 (*C*H_2C=CHI), 35.0 (C(4°)–*C*H_2), 34.7 (*C*H_2C=CH), 31.3 (CH*C*H_2), 27.2 (CH_3*C*H), 26.2 (C=CH*C*H_2), 23.9 (*C*H_3C=CHI), 19.1 (*C*H_3–C(4°)), 16.2 (*C*H_3C=CH), 16.0 (*C*H_3CH); *m*/*z* (ES) 709.2402 (M^+ + Na, 100%, $C_{36}H_{47}IO_5Na$ requires 709.2366).

(±)-(3*E*,7*E*)-(2*S*,11*S*,12*R*,14*R*)-14-(4-Methoxybenzyloxy)-15-(4-methoxybenzyloxymethyl)-4,8,11,12-tetramethylbicyclo-[9.3.1]pentadeca-1(15),3,7-trien-2-ol 16a

Nickel chloride (47 mg, 0.36 mmol) and chromium chloride (221 mg, 1.80 mmol) were added sequentially to a stirred solu-

tion of the aldehyde vinyl iodide **14** (137 mg, 0.20 mmol) in DMSO (45.0 mL) at room temperature in a glove bag under an atmosphere of argon. The mixture was diluted with THF (15.0 mL), then removed from the glove bag, and stirred under a positive pressure of argon for 42 hours. The mixture was cooled to 0 °C and then quenched cautiously with serine (1.0 M in a saturated aqueous solution of $NaHCO_3$, 150 mL). The mixture was stirred vigorously and allowed to warm to room temperature over 1 hour and then diluted with pentane (110 mL). The separated aqueous phase was extracted with diethyl ether (4 × 160 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 30–40–50% diethyl ether in pentane as eluent to give: (i) the *bicyclic alcohol* (64.7 mg, 58%) (eluted second) as a colourless oil, ν_{max} ($CDCl_3$)/cm^{-1} 3556, 3007, 2937, 2839, 1613, 1247 and 1036; δ_H (360 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.6, 2 × Ar*H*), 7.28 (2H, d, *J* 8.5, 2 × Ar*H*), 6.90 (2H, d, *J* 8.6, 2 × Ar*H*), 6.88 (2H, d, *J* 8.5, 2 × Ar*H*), 5.59 (1H, d, *J* 10.4, C=C*H*CHOH), 5.40 (1H, d, *J* 10.4, C=CHC*H*OH), 4.89 (1H, d, *J* 10.2, C=C*H*), 4.64 (1H, d, *J* 11.8, ArC*H*H), 4.50 (1H, d, *J* 11.8, ArCH*H*), 4.47 (1H, d, *J* 11.6, ArC*H*H), 4.35 (1H, d, *J* 11.6, ArCH*H*), 4.32 (1H, br. s, C*H*OPMB), 3.81 (6H, s, 2 × OCH_3), 3.55 (1H, d, *J* 10.7, OC*H*HC=C), 3.43 (1H, d, *J* 10.7, OCH*H*C=C), 2.36–2.14 (3H, m, C=CHC*H*H, CH_3CH and C*H*HC=CH), 2.03 (1H, dd, *J* 11.8 and 3.6, C=CHCH*H*), 2.01–1.98 (2H, m, CH_2C=CHCHOH), 1.83–1.75 (2H, m, CHC*H*H and CH*H*C=CH), 1.64 (3H, s, CH_3C=CHCHOH), 1.57–1.41 (3H, m, C(4°)–C*H*H, CHO*H* and CHCH*H*), 1.47 (3H, s, CH_3C=CH), 1.38 (1H, dd, *J* 13.2 and 3.5, C(4°)–CH*H*), 0.84 (3H, d, *J* 6.8, CH_3CH), 0.74 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 159.2 (Ar–*C*(4°)OCH_3), 158.8 (Ar–*C*(4°)OCH_3), 140.3 (*C*=CCHOH), 139.1 (Ar–*C*(4°)), 133.9 (Ar–*C*(4°)), 132.1 (*C*=CH), 131.6 (*C*=CHCHOH), 130.3 (C=*C*CHOH), 130.0 (C=*C*HCHOH), 129.8 (Ar–*C*H), 128.9 (Ar–*C*H), 128.5 (C=*C*H), 113.8 (Ar–*C*H), 113.7 (Ar–*C*H), 72.9 (Ar*C*H_2O), 70.1 (*C*HOPMB), 69.8 (Ar*C*H_2O), 67.9 (*C*HOH), 65.3 (O*C*H_2C=C), 55.3 (O*C*H_3), 55.2 (O*C*H_3), 41.3 (*C*(4°)–C=C), 38.2 (*C*H_2C=CHCHOH), 34.3 (*C*H_2C=CH), 31.2 (C(4°)–*C*H_2), 30.7 (CH*C*H_2), 26.7 (C=CH*C*H_2), 26.6 (CH_3*C*H), 19.4 (*C*H_3–C(4°)), 16.1 (*C*H_3CH), 15.9 (*C*H_3C=CHCHOH), 14.8 (*C*H_3C=CH); *m*/*z* (ES) 583.3364 (M^+ + Na, 100%, $C_{36}H_{48}O_5Na$ requires 583.3399); and (ii) (±)-(3*S*,4*R*,6*R*)-3-((*E*)-3,7-dimethylocta-3,7-dienyl)-6-(4-methoxybenzyloxy)-2-(4-methoxybenzyloxymethyl)-3,4-dimethylcyclohex-1-enecarbaldehyde, the *alkene* **15** (30.0 mg, 18%) (eluted first) as a colourless oil, ν_{max} (film)/cm^{-1} 3072, 2960, 2932, 1678, 1614 and 1249; δ_H (360 MHz, $CDCl_3$) 10.0 (1H, s, C*H*O), 7.26 (4H, d, *J* 8.5, 4 × Ar*H*), 6.89 (2H, d, *J* 8.7, 2 × Ar*H*), 6.85 (2H, d, *J* 8.7, 2 × Ar*H*), 5.00 (1H, app. t, *J* 6.4, C=C*H*), 4.70 (2H, d, *J* 13.6, C=CH_2), 4.51 (2H, s, ArCH_2), 4.49 (2H, s, ArCH_2), 4.43 (1H, br. s, C*H*OPMB), 4.38 (1H, d, *J* 11.0, OC*H*HC=C), 4.11 (1H, d, *J* 11.0, OCH*H*C=C), 3.82 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 2.24 (1H, dq, *J* 6.8 and 2.6, CH_3CH), 2.10 (2H, app. t, *J* 7.2, C=CHCH_2), 2.04–2.00 (2H, m, CH_2C=CH_2), 1.94 (1H, dd, *J* 12.6 and 3.2, C*H*HC=CH), 1.76–1.70 (1H, m, CHC*H*H), 1.74 (3H, s, C*H*$_3$-C=CH_2), 1.65 (1H, dd, *J* 12.6 and 3.2, CH*H*C=CH), 1.64–1.61 (1H, m, C(4°)–C*H*H), 1.58 (3H, s, CH_3C=CH), 1.50 (1H, dd, *J* 12.6 and 2.9, C(4°)–CH*H*), 1.35 (1H, dt, *J* 13.7 and 3.2, CHCH*H*), 0.91 (3H, d, *J* 6.8, CH_3CH), 0.90 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 192.7 (*C*HO), 160.8 (*C*=CCHO), 159.4 (Ar–*C*(4°)OCH_3), 158.9 (Ar–*C*(4°)OCH_3), 145.7 (*C*=CH_2), 137.9 (Ar–*C*(4°)), 135.2 (Ar–*C*(4°)), 131.3 (*C*=CH), 129.6 (Ar–*C*H), 129.3 (Ar–*C*H), 129.2 (C=*C*CHO), 123.9 (C=*C*H), 113.8 (Ar–*C*H), 113.5 (Ar–*C*H), 109.8 (C=*C*H_2), 73.0 (Ar*C*H_2O), 71.5 (Ar*C*H_2O), 67.9 (*C*HOPMB), 63.8 (O*C*H_2C=C), 55.2 (O*C*H_3), 55.2 (O*C*H_3), 43.0 (*C*(4°)–C=C), 37.7 (*C*H_2C=CH_2), 34.9 (C(4°)–*C*H_2), 34.7 (*C*H_2C=CH), 31.3 (CH*C*H_2), 27.2 (CH_3*C*H), 26.2 (C=CH*C*H_2), 22.5 (*C*H_3C=CH_2), 19.1 (*C*H_3–C(4°)), 16.1 (*C*H_3C=CH), 16.0 (*C*H_3CH); *m*/*z* (ES) 583.3441 (M^+ + Na, 100%, $C_{36}H_{48}O_5Na$ requires 583.3399).

4-Nitrobenzoic acid (±)-(3*E*,7*E*)-(2*S*,11*S*,12*R*,14*R*)-14-(4-methoxybenzyloxy)-15-(4-methoxybenzyloxymethyl)-4,8,11,12-tetramethylbicyclo[9.3.1]pentadeca-1(15),3,7-trien-2-yl ester 16b

4-Nitrobenzoyl chloride (11 mg, 0.06 mmol) was added to a stirred solution of 4-dimethylaminopyridine (0.5 mg, 4 μmol), triethylamine (13 μL, 94 μmol), and the alcohol **16a** (11 mg, 0.02 mmol) in dichloromethane (1.0 mL) at −25 °C. The mixture was allowed to warm to 0 °C over 2 hours and then concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 20–50% diethyl ether in pentane as eluent to give the *ester* (11.7 mg, 82%) which crystallised from diethyl ether–dichloromethane–pentane as colourless crystals; mp 189–191 °C; ν_{max} ($CDCl_3$)/cm^{-1} 3007, 2936, 2858, 1716 and 1610; δ_H (360 MHz, $CDCl_3$) 8.22 (2H, d, *J* 8.8, 2 × Ar*H*), 8.04 (2H, d, *J* 8.8, 2 × Ar*H*), 7.35 (4H, d, *J* 8.5, 4 × Ar*H*), 6.90 (2H, d, *J* 8.5, 2 × Ar*H*), 6.84 (2H, d, *J* 8.4, 2 × Ar*H*), 6.82 (1H, d, *J* 10.6, C=CHC*H*OPNB), 5.88 (1H, d, *J* 10.4, C=C*H*CHOPNB), 4.92 (1H, d, *J* 10.8, C=C*H*), 4.72 (1H, d, *J* 11.4, ArC*H*H), 4.59 (1H, d, *J* 11.6, ArCH*H*), 4.56 (1H, d, *J* 11.4, ArC*H*H), 4.42 (1H, d, *J* 11.6, ArCH*H*), 4.32 (1H, br. s, C*H*OPMB), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.64 (1H, d, *J* 10.5, OC*H*HC=C), 3.52 (1H, d, *J* 10.5, OCH*H*C=C), 2.43–2.20 (3H, m, C=CHC*H*H, CH_3CH and C*H*HC=CH), 2.12–2.01 (3H, m, C=CHCH*H* and CH_2C=CHCHOPNB), 1.88 (3H, s, CH_3C=CHCHOPNB), 1.89–1.80 (2H, m, CHC*H*H and CH*H*C=CH), 1.49 (3H, s, CH_3C=CH), 1.49–1.35 (3H, m, C(4°)–CH_2 and CHCH*H*), 0.86 (3H, d, *J* 6.8, CH_3CH), 0.75 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 163.9 (O*C*=O), 159.4 (Ar–*C*(4°)OCH_3), 158.8 (Ar–*C*(4°)OCH_3), 150.1 (Ar–*C*(4°)NO_2), 141.2 (*C*=CCHOPNB), 138.3 (Ar–*C*(4°)), 136.6 (Ar–*C*(4°)), 136.1 (Ar–*C*(4°)), 132.2 (*C*=CH), 131.4 (*C*=CHCHOPNB), 130.4 (Ar–*C*H), 130.2 (Ar–*C*H), 129.9 (C=*C*CHOPNB), 128.7 (Ar–*C*H), 128.5 (C=*C*H), 125.7 (C=*C*HCHOPNB), 123.4 (Ar–*C*H), 113.8 (Ar–*C*H), 113.6 (Ar–*C*H), 73.4 (Ar*C*H_2O), 73.0 (*C*HOPNB), 70.8 (*C*HOPMB), 70.2 (Ar*C*H_2O), 65.0 (O*C*H_2C=C), 55.3 (O*C*H_3), 55.1 (O*C*H_3), 41.5 (*C*(4°)–C=C), 38.4 (*C*H_2C=CHCHOPNB), 34.4 (*C*H_2C=CH), 31.2 (C(4°)–*C*H_2), 30.5 (CH*C*H_2), 26.9 (C=CH*C*H_2), 26.2 (CH_3*C*H), 19.3 (*C*H_3–C(4°)), 16.2 (*C*H_3C=CHCHOPNB), 16.1 (*C*H_3CH), 14.8 (*C*H_3C=CH); *m*/*z* (ES) 732.3502 (M^+ + Na, 100%, $C_{43}H_{51}NO_8Na$ requires 732.3512).

(±)-(3*E*,7*E*)-(11*S*,12*R*,14*R*)-14-(4-Methoxybenzyloxy)-15-(4-methoxybenzyloxymethyl)-4,8,11,12-tetramethylbicyclo-[9.3.1]pentadeca-1(15),3,7-trien-2-one 19

Dess–Martin periodinane (12.7 mg, 0.03 mmol) was added to a mixture of $NaHCO_3$ (16.8 mg, 0.20 mmol) and the alcohol **16a** (11.1 mg, 0.02 mmol) in dichloromethane (1.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over 90 minutes. The mixture was quenched with saturated aqueous solutions of $NaHCO_3$ (1.0 mL) and $Na_2S_2O_3$ (1.0 mL), and then diluted with diethyl ether (5 mL). The separated aqueous phase was extracted with diethyl ether (3 × 5 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 30–40% diethyl ether in pentane as eluent to give the *enone* (10.9 mg, 97%) as a colourless oil; ν_{max} ($CDCl_3$)/cm^{-1} 2930, 1683 and 1613; δ_H (360 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.6, 2 × Ar*H*), 7.22 (2H, d, *J* 8.5, 2 × Ar*H*), 6.86 (4H, d, *J* 8.5, 4 × Ar*H*), 6.28 (1H, s, C=C*H*C=O), 5.04 (1H, d, *J* 8.6, C=C*H*), 4.55 (1H, d, *J* 11.6, ArC*H*H), 4.39 (1H, d, *J* 11.6, ArCH*H*), 4.30 (2H, s, ArCH_2), 4.15 (1H, br. s, C*H*OPMB), 3.81 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.65 (1H, d, *J* 12.5, OC*H*HC=C), 3.52 (1H, d, *J* 12.5, OCH*H*C=C), 2.29–2.00 (6H, m, C*H*HC=CH, CH_3C*H*, CH_2C=CHC=O and C=CHCH_2), 1.90–1.85 (1H, m, CH*H*C=

CH), 1.74 (1H, br. d, *J* 13.9, CHC*H*H), 1.70 (3H, s, CH_3C=CHC=O), 1.55–1.50 (2H, m, C(4°)–CH_2), 1.48 (3H, s, CH_3C=CH), 1.43 (1H, dd, *J* 13.9 and 3.5, CHCH*H*), 0.85 (3H, d, *J* 7.1, CH_3CH), 0.83 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 201.8 (*C*=O), 159.1 (Ar–*C*(4°)OCH$_3$), 158.8 (Ar–*C*(4°)OCH$_3$), 143.1 (*C*=CC=O), 142.7 (*C*=CHC=O), 140.5 (Ar–*C*(4°)), 133.0 (Ar–*C*(4°)), 131.1 (*C*=CH), 130.6 (C=*C*HC=O), 130.0 (C=*C*C=O), 129.8 (Ar–*C*H), 128.7 (Ar–*C*H), 128.4 (C=*C*H), 113.6 (Ar–*C*H), 113.5 (Ar–*C*H), 73.1 (*C*HOPMB), 72.0 (Ar*C*H$_2$O), 71.0 (Ar*C*H$_2$O), 66.7 (O*C*H$_2$C=C), 55.3 (O*C*H$_3$), 55.2 (O*C*H$_3$), 40.6 (*C*(4°)–C=C), 37.3 (*C*H$_2$C=CHC=O), 33.9 (*C*H$_2$C=CH), 31.5 (C(4°)–*C*H$_2$), 31.1 (CH*C*H$_2$), 27.2 (CH$_3$*C*H), 25.8 (C=CH*C*H$_2$), 19.5 (*C*H$_3$–C(4°)), 17.9 (*C*H$_3$C=CHC=O), 15.5 (*C*H$_3$C=CH), 15.5 (*C*H$_3$CH); *m*/*z* (ES) 581.3226 (M^+ + Na, 100%, $C_{36}H_{46}O_5Na$ requires 581.3243).

(±)-(*E*)-(3*R*,5*S*,12*S*,13*R*,15*R*)-15-(4-Methoxybenzyloxy)-16-(4-methoxybenzyloxymethyl)-5,9,12,13-tetramethyl-4-oxatricyclo-[10.3.1.0^{3,5}]hexadeca-1(16),8-dien-2-one 20

A solution of *tert*-butyl hydroperoxide (5.5 M) in benzene (20 μL, 0.11 mmol) was added to a solution of KH (1 mg, 0.023 mmol) in THF (1.1 mL) at −20 °C. The mixture was stirred at −20 °C for 5 minutes and then added to a solution of the enone **19** (12.3 mg, 0.022 mmol) in THF (1.1 mL) at −20 °C. The mixture was stirred at −20 °C for 2 hours and then allowed to warm to room temperature over 2 days. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica using 30% diethyl ether in pentane as eluent to give the *epoxyketone* (3.4 mg, 27%) as a colourless film; ν_{max} ($CDCl_3$)/cm^{-1} 2929, 1704, 1612 and 1248; δ_H (360 MHz, $CDCl_3$) 7.25 (2H, d, *J* 7.8, 2 × Ar*H*), 7.23 (2H, d, *J* 8.5, 2 × Ar*H*), 6.90 (2H, d, *J* 8.5, 2 × Ar*H*), 6.87 (2H, d, *J* 7.8, 2 × Ar*H*), 5.11 (1H, d, *J* 9.3, C=C*H*), 4.62 (1H, d, *J* 11.2, ArC*H*H), 4.44 (1H, d, *J* 11.2, ArCH*H*), 4.30 (2H, s, ArCH_2), 4.10 (1H, s, C–C*H*C=O), 4.04 (1H, br. s, C*H*OPMB), 3.82 (6H, s, 2 × OCH_3), 3.57 (1H, d, *J* 11.2, OC*H*HC=C), 3.34 (1H, d, *J* 11.2, OCH*H*C=C), 2.37–2.29 (2H, m, C*H*HC=CH and CH$_3$C*H*), 2.24–2.14 (3H, m, C=CHCH_2 and C*H*HC–CHC=O), 1.94 (1H, dd, *J* 12.9 and 8.4, CH*H*C=CH), 1.84 (1H, d, *J* 3.4, CHC*H*H), 1.75–1.59 (2H, m, C(4°)–CH_2), 1.56 (3H, s, CH_3C=CH), 1.49 (1H, dd, *J* 13.7 and 3.4, CHCH*H*), 1.24 (1H, dd, *J* 7.1 and 6.3, CH*H*C–CHC=O), 1.12 (3H, s, CH_3C–CHC=O), 0.91 (3H, d, *J* 6.1, CH_3CH), 0.89 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 204.3 (*C*=O), 159.2 (Ar–*C*(4°)OCH$_3$), 159.1 (Ar–*C*(4°)OCH$_3$), 143.2 (*C*=CC=O), 139.5 (Ar–*C*(4°)), 134.8 (Ar–*C*(4°)), 130.3 (C=*C*C=O), 130.0 (*C*=CH), 129.8 (Ar–*C*H), 129.1 (Ar–*C*H), 126.6 (C=*C*H), 113.8 (Ar–*C*H), 113.7 (Ar–*C*H), 72.6 (*C*HOPMB), 71.9 (Ar*C*H$_2$O), 70.9 (Ar*C*H$_2$O), 66.8 (C–*C*HC=O), 66.4 (O*C*H$_2$C=C), 64.2 (*C*–CHC=O), 55.2 (O*C*H$_3$), 55.2 (O*C*H$_3$), 41.1 (*C*(4°)–C=C), 38.2 (*C*H$_2$C–CHC=O), 34.3 (*C*H$_2$C=CH), 31.8 (C(4°)–*C*H$_2$), 30.8 (CH*C*H$_2$), 27.0 (CH$_3$*C*H), 24.4 (C=CH*C*H$_2$), 19.4 (*C*H$_3$–C(4°)), 15.8 (*C*H$_3$-CH), 15.5 (*C*H$_3$C–CHC=O), 15.4 (*C*H$_3$C=CH); *m*/*z* (ES) 597.3179 (M^+ + Na, 100%, $C_{36}H_{46}O_6Na$ requires 597.3192); and recovered enone (2.9 mg).

(±)-(3*E*,7*E*)-(2*R*,11*S*,12*R*,14*R*)-14-(4-Methoxybenzyloxy)-15-(4-methoxybenzyloxymethyl)-4,8,11,12-tetramethylbicyclo-[9.3.1]pentadeca-1(15),3,7-trien-2-ol 23

Cerium trichloride heptahydrate (11.2 mg, 0.03 mmol) was added to a stirred solution of the enone **19** (10.9 mg, 0.02 mmol) in dichloromethane (0.4 mL) and methanol (0.4 mL) at −78 °C. The mixture was stirred at −78 °C for 15 minutes, then sodium borohydride (3.0 mg, 0.08 mmol) was added and the resulting mixture was allowed to warm to −30 °C over 2 hours and then to 0 °C over 1 hour. The mixture was quenched with a saturated aqueous solution of NH_4Cl (0.5 mL), then allowed to warm to room temperature and diluted with water (1.0 mL). The separated aqueous phase was extracted with dichloromethane (3 × 2.0 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 30–40% diethyl ether in pentane as eluent to give the *alcohol* (10.8 mg, 96%) as a colourless oil; ν_{max} ($CDCl_3$)/cm^{-1} 3406, 2926, 2854 and 1613; δ_H (360 MHz, $CDCl_3$) 7.30 (4H, d, *J* 8.4, 4 × Ar*H*), 6.91 (2H, d, *J* 8.4, 2 × Ar*H*), 6.90 (2H, d, *J* 8.4, 2 × Ar*H*), 5.35 (1H, d, *J* 6.5, C=C*H*CHOH), 4.89 (1H, d, *J* 10.2, C=C*H*), 4.85 (1H, d, *J* 8.7, O*H*), 4.64 (1H, d, *J* 6.5, C=CHC*H*OH), 4.63 (1H, d, *J* 11.6, ArC*H*H), 4.55 (1H, d, *J* 11.2, ArC*H*H), 4.45 (1H, d, *J* 11.6, ArCH*H*), 4.43 (1H, d, *J* 11.3, ArCH*H*), 4.14 (1H, d, *J* 10.9, OC*H*HC=C), 3.84 (1H, obs., C*H*OPMB), 3.84 (6H, s, 2 × OCH_3), 3.64 (1H, d, *J* 10.8, OCH*H*C=C), 2.31 (1H, ddt, *J* 10.3, 8.3 and 7.0, C=CHC*H*H), 2.21–1.97 (5H, m, CH$_3$C*H*, C*H*HC=CH, C=CHCH*H* and CH_2C=CHCHOH), 1.85–1.67 (2H, m, CH*H*C=CH and CHC*H*H), 1.79 (3H, s, CH_3C=CHCHOH), 1.53–1.49 (2H, m, C(4°)–CH_2), 1.52 (3H, s, CH_3C=CH), 1.45 (1H, ddd, *J* 14.0, 13.2 and 3.7, CHCH*H*), 0.85 (3H, d, *J* 6.8, CH_3CH), 0.78 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 159.5 (Ar–*C*(4°)OCH$_3$), 158.8 (Ar–*C*(4°)OCH$_3$), 142.2 (*C*=CCHOH), 141.5 (Ar–*C*(4°)), 132.4 (Ar–*C*(4°)), 132.1 (*C*=CH), 131.3 (*C*=CHCHOH), 130.3 (Ar–*C*H), 129.1 (Ar–*C*H), 128.9 (C=*C*CHOH), 128.4 (C=*C*H), 128.2 (C=*C*HCHOH), 113.9 (Ar–*C*H), 113.6 (Ar–*C*H), 76.1 (*C*HOPMB), 73.9 (*C*HOH), 73.0 (Ar*C*H$_2$O), 70.6 (Ar*C*H$_2$O), 66.8 (O*C*H$_2$C=C), 55.3 (O*C*H$_3$), 55.2 (O*C*H$_3$), 41.8 (*C*(4°)–C=C), 38.6 (*C*H$_2$C=CHCHOH), 34.3 (*C*H$_2$C=CH), 31.7 (C(4°)–*C*H$_2$), 30.8 (CH*C*H$_2$), 26.7 (CH$_3$*C*H), 26.4 (C=CH*C*H$_2$), 19.6 (*C*H$_3$–C(4°)), 16.8 (*C*H$_3$C=CHCHOH), 16.1 (*C*H$_3$CH), 15.0 (*C*H$_3$C=CH); *m*/*z* (ES) 583.3367 (M^+ + Na, 100%, $C_{36}H_{48}O_5Na$ requires 583.3399).

(±)-(*E*)-(2*S*,3*R*,5*R*,12*S*,13*R*,15*R*)-15-(4-Methoxybenzyloxy)-16-(4-methoxybenzyloxymethyl)-5,9,12,13-tetramethyl-4-oxa-tricyclo[10.3.1.0^{3,5}]hexadeca-1(16),8-dien-2-ol 24

A solution of *tert*-butyl hydroperoxide (0.55 M) in benzene (34.5 μL, 0.02 mmol) was added dropwise over 1 minute to a stirred solution of vanadyl acetylacetonate (a few crystals) and the olefin **23** (10.8 mg, 0.02 mmol) in benzene (1.3 mL) at room temperature. The mixture developed an orange colour and was stirred at room temperature for 60 minutes. The mixture was quenched with 3–4 drops of dimethyl sulfide, then stirred for 30 minutes and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 1% triethylamine and 40–60% diethyl ether in pentane as eluent to give: (i) the *epoxy alcohol* (2.7 mg, 25%) (eluted first) as a colourless film, ν_{max} ($CDCl_3$)/cm^{-1} 3424, 3006, 2935, 2860, 1612, 1249 and 1036; δ_H (360 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.5, 2 × Ar*H*), 7.22 (2H, d, *J* 8.5, 2 × Ar*H*), 6.89 (2H, d, *J* 8.7, 2 × Ar*H*), 6.89 (2H, d, *J* 8.7, 2 × Ar*H*), 5.11 (1H, dd, *J* 8.9 and 5.5, C=C*H*), 4.54 (1H, d, *J* 11.3, ArC*H*H), 4.52 (1H, obs., O*H*), 4.52 (1H, obs., ArC*H*H), 4.48 (1H, d, *J* 11.3, ArCH*H*), 4.36 (1H, d, *J* 11.3, ArCH*H*), 4.03 (1H, d, *J* 12.4, OC*H*HC=C), 3.84 (1H, obs., OCH*H*C=C), 3.82 (1H, obs., C*H*OPMB), 3.80 (6H, s, 2 × OCH_3), 3.59 (1H, app. t, *J* 10.3, C*H*OH), 2.94 (1H, d, *J* 10.0, C–C*H*CHOH), 2.36–2.28 (2H, m, C*H*HC=CH and CH$_3$C*H*), 2.10–2.02 (1H, m, C=CHC*H*H), 1.89–1.75 (4H, m, C*H*HC–CHCHOH, C=CHCH*H*, CH*H*C=CH and CHC*H*H), 1.54–1.48 (2H, m, C(4°)–CH_2), 1.46 (3H, s, CH_3C=CH), 1.40 (1H, dd, *J* 16.8 and 3.1, CHCH*H*), 1.14 (3H, s, CH_3C–CHCHOH), 1.07–1.01 (1H, m, CH*H*C–CHCHOH), 0.84 (3H, d, *J* 6.9, CH_3CH), 0.81 (3H, s, CH_3–C(4°)); δ_C (90 MHz, $CDCl_3$) 159.7 (Ar–*C*(4°)OCH$_3$), 158.9 (Ar–*C*(4°)OCH$_3$), 144.0 (*C*=CCHOH), 136.4 (Ar–*C*(4°)), 134.7 (Ar–*C*(4°)), 131.0 (*C*=CH), 130.5 (Ar–*C*H), 129.3 (Ar–*C*H), 128.2 (C=*C*CHOH), 126.6 (C=*C*H), 114.0 (Ar–*C*H), 113.6 (Ar–*C*H), 76.3 (*C*HOPMB), 73.2 (Ar*C*H$_2$O), 73.2 (*C*HOH), 70.9 (Ar*C*H$_2$O), 67.8 (O*C*H$_2$C=C), 65.4 (C–*C*HCHOH), 61.2 (*C*–CHCHOH), 55.3 (O*C*H$_3$), 55.2 (O*C*H$_3$), 42.1 (*C*(4°)–C=C), 37.0 (*C*H$_2$C–CHCHOH), 34.6

(CH_2C=CH), 31.9 (C(4°)–CH_2), 30.5 (CHCH_2), 26.3 (CH_3-CH), 23.6 (C=CHCH_2), 19.5 (CH_3–C(4°)), 18.2 (CH_3C–CHCHOH), 15.8 (CH_3CH), 15.3 (CH_3C=CH); *m/z* (ES) 599.3347 (M^+ + Na, 100%, $C_{36}H_{48}O_6Na$ requires 599.3349); and (ii) the *bis-epoxide* **25** (3.1 mg, 27%) which crystallised from diethyl ether–pentane as colourless crystals, mp 158–159 °C; ν_{max} ($CDCl_3$)/cm^{-1} 3686, 3154, 2933, 1613 and 1249; δ_H (360 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.8, 2 × Ar*H*), 7.25 (2H, d, *J* 8.8, 2 × Ar*H*), 6.89 (2H, d, *J* 8.8, 2 × Ar*H*), 6.88 (2H, d, *J* 8.8, 2 × Ar*H*), 5.25 (1H, br. s, C=C*H*), 4.57 (1H, d, *J* 11.6, ArC*H*H), 4.50 (2H, s, ArCH_2), 4.40 (1H, d, *J* 11.6, ArCH*H*), 3.86 (1H, br. s, C*H*OPMB), 3.82 (3H, s, OCH_3), 3.82 (1H, obs., C*H*OH), 3.81 (1H, obs., OC*H*HC–C), 3.80 (3H, s, OCH_3), 3.77 (1H, d, *J* 5.8, OCH*H*C–C), 3.22 (1H, br. s, O*H*), 2.61 (1H, d, *J* 9.4, C–C*H*CHOH), 2.48 (1H, app. t, *J* 13.6, *H*HC–CH-CHOH), 2.38 (1H, dq, *J* 7.1 and 2.4, CH_3C*H*), 1.94 (1H, dd, *J* 15.3 and 13.1, C*H*HC=CH), 1.86–1.74 (3H, m, H*H*C–CHCHOH and C=CHCH_2), 1.69–1.41 (5H, m, CHCH_2, C(4°)–CH_2 and CH*H*C=CH), 1.38 (3H, s, CH_3C=CH), 1.18 (3H, s, CH_3–C(4°)), 1.04 (3H, s, CH_3C–CHCHOH), 0.71 (3H, d, *J* 7.1, CH_3CH),; δ_C (90 MHz, $CDCl_3$) 159.4 (Ar–*C*(4°)OCH_3), 159.2 (Ar–*C*(4°)OCH_3), 134.5 (Ar–*C*(4°)), 130.3 (Ar–*C*(4°)), 129.9 (Ar–*C*H), 129.4 (Ar–*C*H), 129.4 (*C*=CH), 128.5 (C=*C*H), 113.9 (Ar–*C*H), 113.8 (Ar–*C*H), 79.1 (*C*HOPMB), 73.4 (ArCH_2O), 71.2 (ArCH_2O), 70.2 (C–*C*), 69.9 (*C*HOH), 68.8 (OCH_2C–C), 66.3 (*C*–C), 63.4 (C–*C*H), 61.9 (*C*–CH), 55.3 (2 × OCH_3), 39.0 (*C*(4°)–C–C), 34.4 (C(4°)–CH_2), 34.3 (*C*H$_2$C–CHCHOH), 32.2 (CH_2C=CH), 27.6 (CHCH_2), 25.4 (CH_3CH), 22.5 (C=CHCH_2), 19.8 (CH_3–C(4°)), 19.1 (CH_3C–CHCHOH), 16.7 (CH_3C=CH), 15.0 (CH_3CH); *m/z* (ES) 615.3298 (M^+ + Na, 100%, $C_{36}H_{48}O_7Na$ requires 615.3298); and recovered alcohol (3.7 mg).

(±)-(*E*)-(3*S*,5*R*,12*S*,13*R*,15*R*)-15-(4-Methoxybenzyloxy)-16-(4-methoxybenzyloxymethyl)-5,9,12,13-tetramethyl-4-oxatricyclo[10.3.1.0^{3,5}]hexadeca-1(16),8-dien-2-one 21

Dess–Martin periodinane (7.8 mg, 0.02 mmol) was added to a mixture of $NaHCO_3$ (7.1 mg, 0.08 mmol) and the epoxy alcohol **24** (4.9 mg, 8.5 μmol) in dichloromethane (1.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes and then allowed to warm to room temperature over 3 hours. The mixture was quenched with saturated aqueous solutions of $NaHCO_3$ (1.0 mL) and $Na_2S_2O_3$ (1.0 mL), and then diluted with diethyl ether (3 mL). The separated aqueous phase was extracted with diethyl ether (3 × 6 mL) and the combined organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 30% diethyl ether in pentane as eluent to give the *epoxy ketone* (3.9 mg, 80%) as a colourless oil; ν_{max} ($CDCl_3$)/cm^{-1} 2974, 2935, 2875, 1709, 1612 and 1248; δ_H (500 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.4, 2 × Ar*H*), 7.21 (2H, d, *J* 8.4, 2 × Ar*H*), 6.88 (2H, d, *J* 8.7, 2 × Ar*H*), 6.86 (2H, d, *J* 8.7, 2 × Ar*H*), 5.18–5.16 (1H, m, C=C*H*), 4.50 (1H, d, *J* 11.7, ArC*H*H), 4.48 (1H, d, *J* 11.3, ArC*H*H), 4.35 (1H, app. q, *J* 1.5, C*H*OPMB), 4.30 (1H, d, *J* 11.3, ArCH*H*), 4.22 (1H, d, *J* 11.6, ArCH*H*), 4.01 (1H, d, *J* 15.4, OC*H*HC=C), 3.97 (1H, d, *J* 15.4, OCH*H*C=C), 3.81 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.77 (1H, s, C–C*H*C=O), 2.48 (1H, ddq, *J* 12.8, 2.2 and 7.3, CH_3C*H*), 2.47–2.43 (1H, m, C*H*HC–CHC=O), 1.89–1.83 (3H, m, C=CHCH_2 and CH*H*C–CHC=O), 1.76 (1H, dd, *J* 15.0 and 4.8, C(4°)–C*H*H), 1.74–1.67 (2H, m, CH_2C=CH), 1.52–1.49 (2H, m, CHCH_2), 1.44 (3H, s, CH_3C=CH), 1.40 (1H, dt, *J* 13.6 and 3.3, C(4°)–CH*H*), 1.02 (3H, s, CH_3C–CHC=O), 0.91 (3H, s, CH_3–C(4°)), 0.86 (3H, d, *J* 6.9, CH_3CH); δ_C (125 MHz, $CDCl_3$) 202.0 (*C*=O), 159.4 (Ar–*C*(4°)OCH_3), 158.8 (Ar–*C*(4°)OCH_3), 150.3 (*C*=CC=O), 134.2 (Ar–*C*(4°)), 134.1 (Ar–*C*(4°)), 131.2 (C=*C*C=O), 130.0 (Ar–*C*H), 129.0 (C=*C*H), 128.9 (*C*=CH), 128.8 (Ar–*C*H), 113.8 (Ar–*C*H), 113.5 (Ar–*C*H), 73.1 (*C*HOPMB), 72.3 (ArCH_2O), 70.7 (ArCH_2O), 66.9 (OCH_2C=C), 65.1 (C–*C*HC=O), 64.0 (*C*–CHC=O), 55.3 (OCH_3), 55.2 (OCH_3), 40.8 (*C*(4°)–C=C), 34.7 (CH_2C=CH), 34.0 (CH_2C–CHC=O), 31.4 (CHCH_2), 30.3 (C(4°)–CH_2), 26.9 (CH_3CH), 23.4 (C=CHCH_2), 19.8 (CH_3–C(4°)), 18.6 (CH_3C–CHC=O), 16.2 (CH_3C=CH), 15.0 (CH_3-CH); *m/z* (ES) 597.3197 (M^+ + Na, 100%, $C_{36}H_{46}O_6Na$ requires 597.3192).

(±)-Phomactin A 1

DDQ (3.0 mg, 13 μmol) was added to a stirred solution of the epoxy ketone **21** (3.0 mg, 5.2 μmol) in dichloromethane (0.50 mL) and water (0.03 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hour, then allowed to warm to 10 °C over 90 minutes, and finally to room temperature over 2 hours. The organic layer was separated and the aqueous phase was extracted with dichloromethane (2 × 0.5 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (1.0 mL) and the separated aqueous phase was extracted with dichloromethane (3 × 1.0 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica using 1% triethylamine and 5–15% acetone in dichloromethane as eluent. The pure fractions were concentrated *in vacuo* and the residue was diluted with dichloromethane (1.0 mL) and washed with water (2 × 0.5 mL), then dried over Na_2SO_4 and concentrated *in vacuo* to give (±)-*phomactin A* (1.4 mg, 83%) as a colourless oil; ν_{max} ($CDCl_3$)/cm^{-1} 3604, 2930, 2857, 1602, 1430, 1334, 1232 and 1050; δ_H (500 MHz, CD_3OD) 5.36 (1H, br. d, *J* 12.3, C=C*H*), 4.63 (1H, dd, *J* 12.8 and 1.5, OC*H*HC=C), 4.46 (1H, d, *J* 12.8, OCH*H*C=C), 4.06 (1H, td, *J* 2.6 and 1.5, C*H*OC), 3.56 (1H, s, C*H*OH), 2.76 (1H, ddq, *J* 12.1, 4.4 and 7.0, CH_3C*H*), 2.42 (1H, ddd, *J* 14.8, 13.5 and 4.0, C*H*HC=CH), 2.39 (1H, ddt, *J* 15.1, 5.1 and 12.5, C=CHC*H*H), 1.99–1.89 (2H, m, C=CHCH*H* and CH*H*C=CH), 1.74 (1H, ddd, *J* 15.4, 13.5 and 3.2, C(4°)–C*H*H), 1.71 (1H, ddd, *J* 14.4, 5.1 and 2.6, C*H*HCCHOH), 1.66 (1H, ddd, *J* 14.6, 11.3 and 3.2, CHC*H*H), 1.65 (3H, s, CH_3C=CH), 1.62 (1H, ddd, *J* 14.6, 11.3 and 3.2, CHCH*H*), 1.59 (1H, ddd, *J* 14.4, 12.5 and 5.1, CH*H*CCHOH), 1.51 (1H, dt, *J* 15.4 and 4.0, C(4°)–CH*H*), 1.22 (3H, s, CH_3C-CHOH), 0.92 (3H, d, *J* 7.3, CH_3CH), 0.90 (3H, s, CH_3–C(4°)); δ_C (125 MHz, CD_3OD) 144.6 (*C*=CC(OH)OCH_2), 131.4 (C=*C*H), 131.3 (C=*C*C(OH)OCH_2), 128.8 (*C*=CH), 110.1 (*C*(OH)OCH_2), 81.2 (CH_2*C*CHOH), 74.6 (CH_2C*C*HOH), 71.9 (O*C*H$_2$C=C), 62.6 (*C*HOC), 38.5 (*C*H$_2$CCHOH), 38.0 (*C*(4°)–C=C), 37.6 (*C*H$_2$C=CH), 34.4 (C(4°)–*C*H$_2$), 34.2 (CH*C*H$_2$), 27.8 (CH_3*C*H), 25.8 (C=CH*C*H$_2$), 21.9 (*C*H$_3$–C(4°)), 19.6 (*C*H$_3$CCHOH), 16.5 (*C*H$_3$C=CH), 14.9 (*C*H$_3$CH); *m/z* (CI) 334.2161 (M^+, 8%, $C_{20}H_{30}O_4$ requires 334.2144), 322 (37), 230 (20), 216 (100), 163 (36), 149 (49), 131 (79), 121 (43), 107 (42) and 91 (43); NMR data for phomactin A in deuterochloroform, δ_H (500 MHz, $CDCl_3$) 5.42 (1H, br. d, *J* 11.7, C=C*H*), 4.72 (1H, dd, *J* 13.2 and 1.5, OC*H*HC=C), 4.48 (1H, d, *J* 12.7, OCH*H*C=C), 4.11 (1H, td, *J* 2.5 and 1.5, C*H*OC), 3.77 (1H, br. s, CHO*H*), 3.64 (1H, s, C*H*OH), 2.75 (1H, ddq, *J* 12.0, 4.0 and 7.0, CH_3C*H*), 2.43 (1H, td, *J* 13.9 and 4.0, C*H*HC=CH), 2.33 (1H, ddt, *J* 15.5, 5.5 and 12.0, C=CHC*H*H), 2.04–1.97 (1H, m, C=CHCH*H*), 1.96–1.90 (1H, m, CH*H*C=CH), 1.76 (1H, tdd, *J* 14.6, 5.5 and 2.5, C*H*HCCHOH), 1.71 (1H, ddd, *J* 15.0, 10.8 and 2.5, CHC*H*H), 1.71–1.65 (1H, m, C(4°)–C*H*H), 1.68–1.63 (1H, m, CH*H*CCHOH), 1.63 (3H, s, CH_3C=CH), 1.63–1.58 (1H, m, CHCH*H*), 1.51 (1H, dt, *J* 15.0 and 4.0, C(4°)–CH*H*), 1.24 (3H, s, CH_3CCHOH), 0.92 (3H, d, *J* 6.8, CH_3CH), 0.90 (3H, s, CH_3–C(4°)); δ_C (125 MHz, $CDCl_3$) 144.4 (*C*=CC-(OH)OCH_2), 130.3 (C=*C*H), 129.2 (C=*C*C(OH)OCH_2), 127.4 (*C*=CH), 108.1 (*C*(OH)OCH_2), 79.1 (CH_2*C*CHOH), 74.1 (CH_2-C*C*HOH), 71.6 (O*C*H$_2$C=C), 61.1 (*C*HOC), 37.4 (*C*H$_2$C-CHOH), 36.9 (*C*(4°)–C=C), 36.5 (*C*H$_2$C=CH), 33.6 (C(4°)–*C*H$_2$), 33.0 (CH*C*H$_2$), 26.6 (CH_3*C*H), 24.9 (C=CH*C*H$_2$), 21.6 (*C*H$_3$–C(4°)), 18.9 (*C*H$_3$CCHOH), 16.4 (*C*H$_3$C=CH), 14.6 (*C*H$_3$CH).

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