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A total synthesis of phomactin A†

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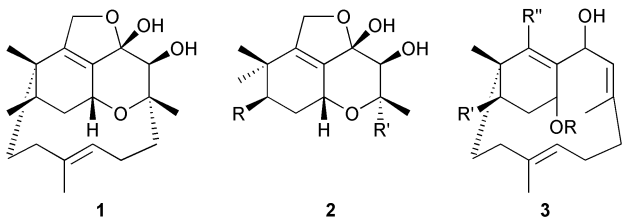
A total synthesis of phomactin A (1) based on a Cr(II)/Ni(II) macrocyclisation from the aldehyde vinyl iodide 11, leading to 12, followed by elaboration of the epoxyketone 16, which then undergoes spontaneous pyran-hemiacetal formation on deprotection, is described.

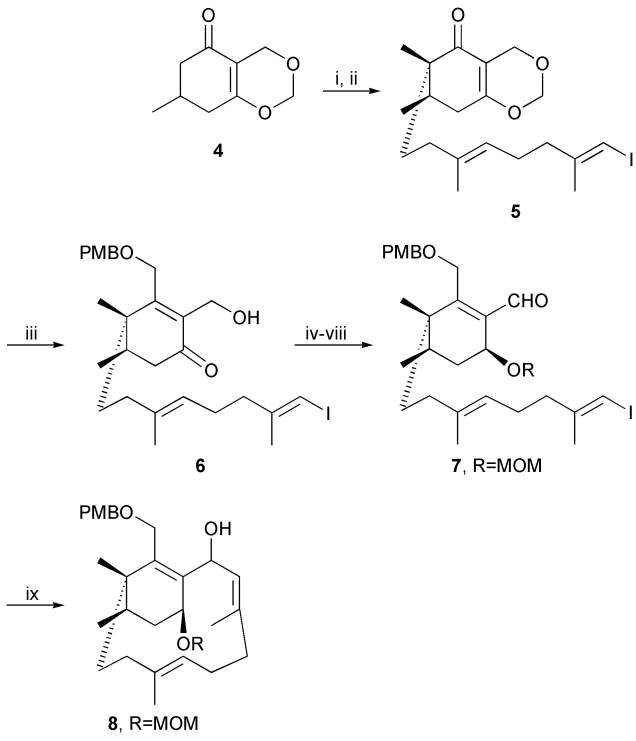
Phomactin A (**1**) and its congeners comprise a novel class of platelet activating factor (PAF) antagonists isolated from the marine fungus *Phoma* sp.[1] With its unusual reduced furanochroman ring system embedded in a macrocyclic bicyclo-[9.3.1]pentadecane core, phomactin A is easily the most structurally complex and synthetically demanding of the phomactins. In previous studies, we and others, have described synthetic routes to both the tricyclic reduced furanochroman **2**[2,3] and the bicyclo[9.3.1]pentadecane unit **3**[4,5] in phomactin A but, hitherto, a total synthesis of this intriguing secondary metabolite has not been forthcoming.[6] We now describe the development of our synthetic investigations, which have culminated in the first total synthesis of phomactin A (**1**).



In an earlier publication[4] we described a strategy to the macrocyclic core in structure **3** based on an intramolecular Cr(II)/Ni(II) mediated coupling reaction[7,8] from an aldehyde vinyl iodide intermediate, *viz.* **7**→**8**. The appropriately oxygenated precursor to **7** was smoothly obtained from the dioxin **4** *via* an alkylation sequence (to **5**), followed by introduction of the PMB hydroxymethyl unit, producing **6**, and manipulation of the functionality in **6**, as summarised in Scheme 1.

To develop this strategy towards an appropriate precursor to phomactin A, we first needed to invert the secondary alcohol centre in **7** prior to the macrocyclisation step. Thus, protection of the free alcohol in **6**, as its *p*-nitrobenzoyl (PNB) ester, followed by reduction of the carbonyl group functionality, under Luche conditions, first led to the β-orientated secondary alcohol **9** exclusively (Scheme 2).[9] Treatment of **9** with thionyl chloride in ether at 0 °C, followed by reaction of the resulting allylic chloride with *p*-methoxybenzyl (PMB) alcohol and *t*-BuOK in the presence of 18-crown-6 (THF, 0 °C), resulted in clean inversion of the secondary alcohol centre in **9** and formation of the corresponding allylic PMB ether **10**, with the required α-stereochemistry, in 56% overall yield.[10,11] Oxidation of **10**, using Dess-Martin periodinane, produced the key aldehyde vinyl iodide intermediate **11** which underwent macrocyclisation in the presence of $CrCl_2$/$NiCl_2$ leading to the doubly allylic alcohol **12**, in an unoptimised 36% yield.[12]

Our strategy for completing the synthesis of phomactin A (**1**) from the secondary alcohol **12** required a stereoselective epoxidation of the adjacent trisubstituted double bond followed by oxidation to the corresponding epoxyketone **16**, deprotection and pyran-hemiacetal ring formation. However, molecular mechanics calculations and NOE experiments suggested that epoxidation of **12** would most probably lead to an epoxide with the incorrect stereochemistry for subsequent conversion into phomactin A.[13] Correspondingly, molecular mechanics calculations on the epimeric alcohol **14** suggested that this compound was conformationally predisposed to formation of the epoxide with the necessary stereochemistry to complete our synthesis of the natural product. Accordingly, we inverted the secondary alcohol centre in **12**, using an oxidation–reduction sequence *via* **13**, leading to **14**. Treatment of **14** with $VO(acac)_2$ and *t*-BuOOH next led to the β-epoxide **15** accompanied by the corresponding *bis*-epoxide **17** which were easily separated by chromatography.[11,14] Oxidation of **15** using Dess-Martin peri-



Scheme 1 *Reagents and conditions*: i, LDA, THF, −78 °C; then MeI, 96%; ii, LDA, DMPU, THF, −78 °C; then (*E*,*E*)-$ICH_2CH_2(CH_3)C{=}CH{-}CH_2CH_2(CH_3)C{=}CHI$, 76%; iii, $PMBOCH_2SnBu_3$, *n*-BuLi, Et_2O, toluene, −78 °C to −25 °C; then 2N HCl, THF, rt, 66%; iv, *p*-NO_2-C_6H_4COCl, Et_3N, DMAP, CH_2Cl_2, −25 °C to 0 °C; v, $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, −78 °C to −40 °C, 75% (2 steps); vi, MOM-Cl, *i*-Pr_2EtN, Bu_4NI, CH_2Cl_2; vii, KOH, MeOH, 87% (2 steps); viii, Dess-Martin periodinane, C_5H_5N, CH_2Cl_2, 0 °C, 98%; ix, $CrCl_2$ (6 eq.), $NiCl_2$ (0.25 eq.), DMSO, 52%.

† Electronic supplementary information (ESI) available: X-ray crystal structure data for the *bis*-epoxide **17**. See http://www.rsc.org/suppdata/cc/b2/b206041h/

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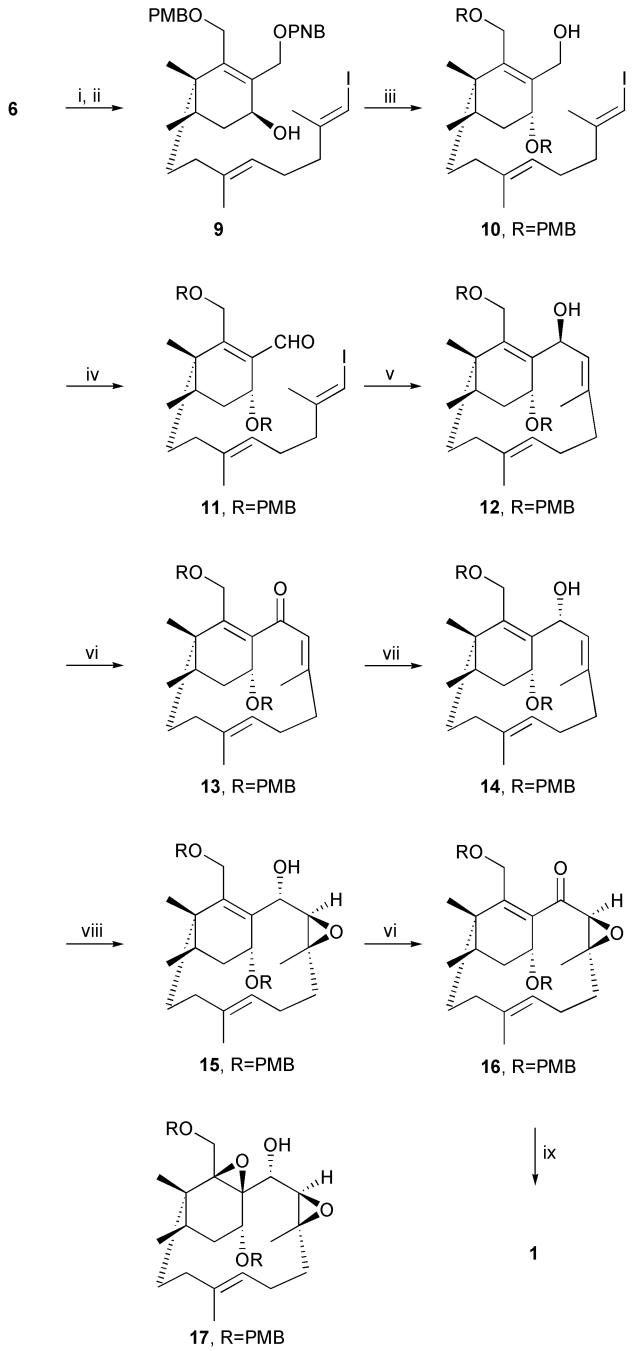

Scheme 2 *Reagents and conditions*: i, *p*-NO_2-C_6H_4COCl, Et_3N, DMAP, CH_2Cl_2, −25 °C to 0 °C; ii, $CeCl_3$·$7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, −78 °C to −40 °C, 75% (2 steps); iii, a) $SOCl_2$, Et_2O, 0 °C to rt; b) PMBOH, *t*-BuOK, 18-C-6, THF, 0 °C to rt, 56% (2 steps); iv, Dess-Martin periodinane, C_5H_5N, CH_2Cl_2, 0 °C to rt, 98%; v, $CrCl_2$ (6 eq.), $NiCl_2$ (1 eq.), DMSO, THF, rt, 36%; vi, Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, quantitative; vii, $CeCl_3$·$7H_2O$, $NaBH_4$, MeOH, CH_2Cl_2, −78 °C to 0 °C, quantitative; viii, $VO(acac)_2$, *t*-BuOOH, PhH, rt, 85%, *ca*. 1:5 (**15** and **17**); ix, DDQ, CH_2Cl_2/H_2O (18:1), 0 °C to rt, 83%.

odinane then produced the epoxyketone **16**, which on treatment with DDQ in CH_2Cl_2 underwent deprotection and spontaneous pyran-hemiacetal ring formation leading to phomactin A (**1**). The synthetic (±)-phomactin A showed NMR spectroscopic data which were superimposable on those of natural phomactin A isolated from *Phoma* sp.[15,16]

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9 The assignment of the β-orientation to the secondary alcohol in **9** followed from an X-ray crystal structure obtained for a related compound (see reference 4).
10 Under the conditions described the alcohol **9** is first converted into the corresponding (β)-allylic chloride which is then inverted using excess alkoxide, with concomitant removal of the *p*-nitrobenzoyl group. See: (*a*) E. S. Lewis and C. E. Boozer, *J. Am. Chem. Soc.*, 1952, **74**, 308; (*b*) C. C. Lee and A. J. Finlayson, *Can. J. Chem.*, 1961, **39**, 260; (*c*) H. R. Hudson and G. R. de Spinoza, *J. Chem. Soc., Perkin Trans. 1*, 1976, 104.
11 The α-stereochemistry of the ether **10** followed from selective NOE enhancements of the corresponding bicyclic alcohol **12** and was later confirmed by an X-ray crystal structure determination of the *bis*-epoxide **17**. *Crystal data*. $C_{36}H_{48}O_7$, M = 592.75, monoclinic, a = 13.2294(7), b = 16.6409(9), c = 15.1000(8) Å, β = 109.075(2)°, U = 3141.7(5) Å^3, T = 150(2) K, space group $P2_1/c$ (No. 14), Z = 4, D_c = 1.253 g cm^{-3}, μ(Mo-Kα) = 0.091 mm^{-1}, 7070 unique reflections measured and used in all calculations. Final R_1 [6512 $F > 4(F)$] = 0.0745 and wR(all F^2) was 0.175. CCDC reference number 188697. See http://www.rsc.org/suppdata/cc/b2/b206041h/ for crystallographic data in .cif or other electronic format.
12 The compound resulting from reduction of the carbon to iodine bond in **11** was isolated as a major by-product (~40–50%).
13 Indeed, treatment of the alcohol **12** with $VO(acac)_2$ and *t*-BuOOH, followed by oxidation and deprotection, as outlined in Scheme 2, led to an epoxy cyclic hemi-acetal which did not undergo pyran formation.
14 Further investigations are underway to improve the selectivity of this reaction and to recycle the *bis*-epoxide **17** to the *mono*-epoxide **15** or the alcohol **14**. It is interesting to note that treatment of the epimeric alcohol **12** under the same conditions led exclusively to the *mono*-epoxide diastereomer of **15**.
15 All new compounds showed satisfactory spectroscopic and mass spectrometry data. Synthetic phomactin A (**1**): oil, δ_H (360 MHz, CD_3OD) 5.36 (1H, br d, J = 12.1 Hz, CH_3C=C*H*CH_2), 4.63 (1H, dd, J = 12.8 and 1.5 Hz, C*H*HOAr), 4.46 (1H, d, J = 12.8 Hz, CH*H*OAr), 4.06 (1H, dt, J = 2.6 and 1.5 Hz, C*H*OC), 3.56 (1H, s, C*H*OH), 2.76 (1H, m, C*H*CH_3), 2.43 (1H, m, CH*H*(CH_3)C=CH), 2.39 (1H, m, CH_3C=CHCH*H*), 1.94 (1H, m, C*H*H(CH_3)C=CH), 1.90 (1H, m, CH_3C=CHC*H*H), 1.73–1.52 (6H, m, C$H_2CH_2(CH_3)$C=C, C=CHCH_2CH_2, and CH_3CHCH_2CHO), 1.65 (3H, s, CH_3C=$CHCH_2$), 1.21 (3H, s, OCCH_3), 0.92 (3H, d, J = 7.2 Hz, CHCH_3), 0.90 (3H, s, CCH_3); δ_C (90 MHz, CD_3OD) 144.6, 131.4, 131.3, 128.8, 81.3, 74.6, 71.9, 62.6, 38.5, 38.0, 37.6, 34.4, 34.2, 27.8, 25.8, 21.9, 19.6, 16.5, 14.9.
16 In $CDCl_3$, instead of CD_3OD, the synthetic phomactin A showed NMR spectroscopic data which were superimposable on those reported for natural Sch 49028 from *Phoma* sp. It is likely therefore, that Sch 49028 is, in fact, phomactin A (**1**) and not the epoxy cyclic hemi-acetal structure reported. See: M. Chu, I. Truumees, I. Gunnarsson, W. R. Bishop, W. Kreutner, A. C. Horan, M. G. Patel, V. P. Gullo and M. S. Puar, *J. Antibiot.*, 1993, **46**, 554.