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Synthetic studies towards congeners of phomactin A. Re-examination of the structure of Sch 49028†

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The total syntheses of the epoxy cyclic hemiacetal structures 8 and 9, which are isomeric with the structure 6 proposed for the phomactin known as Sch 49028 isolated from the marine fungus *Phoma* sp. are described. Neither of these structures showed spectroscopic data consistent with those reported for the purported natural product, adding credibility to the proposal that the structure Sch 49028 does not exist in nature and that its NMR spectroscopic data should have been assigned as phomactin A (1).

The phomactins are an intriguing family of diterpenoid natural products isolated from the marine fungus *Phoma* sp.[1] Several of their number show pronounced platelet activating factor (PAF) activity and this feature has captured the attentions of both the medicinal and synthetic chemist.[2] In an earlier publication we described the first total synthesis of phomactin A (**1**),[3] the most structurally complex member of this family of PAF antagonists.

Our synthetic strategy to phomactin A was based on speculation regarding its most likely biosynthesis, and proceeded *via* the oxygenated phomactanes **2** and **3** as key intermediates. It is probable that *in vivo* the congeners phomactin G (**5**) and the metabolite **6**, together with the phomactatriene **4**, which has not yet been isolated from nature, are implicated in the biosynthetic route to phomactin A *via* a sequence of regio- and stereo-selective enzymatic oxidations. The phomactin **6**, known as Sch 49028, was isolated by researchers working at Schering-Plough in 1993,[1c] and it was reported to have a similar level of PAF activity to phomactin A and to phomactin D (**7**) which was the most active metabolite. In our total synthesis of phomactin A, we showed that deprotection of the *bis*-PMB epoxyketone intermediate **2**, using DDQ, gave (±)-phomactin A (**1**) directly with no evidence of the co-formation of the diol intermediate **2** (R = H) or the epoxy cyclic hemiacetal structure **6**, *i.e.* Sch 49028.[3] Indeed, when we recorded the NMR spectrum of synthetic (±)-phomactin A in $CDCl_3$ instead of CD_3OD, the data were identical with those reported for the purported natural Sch 49028 which was also recorded in $CDCl_3$. We concluded therefore that Sch 49028 was incorrectly assigned and that it is most likely phomactin A (**1**), which showed small differences in chemical shift data when the NMR spectrum was recorded in $CDCl_3$ rather than in CD_3OD.[4]

The epoxy cyclic hemiacetal structure **6** assigned to Sch 49028 is intriguing, however, and we were lured into studying the structure in more detail, based on the aforementioned speculative biosynthetic interrelationships. For example, we pondered the possibility that a structure similar to Sch 49028 could be derived from enzymatic oxidation of the phomactatriene **4** {*cf.* phomactin D (**7**)} *in vivo*, and that it had one of the isomeric structures **8** or **9**. To satisfy this curiosity, we have therefore synthesised both **8** and **9** and compared their structures with that proposed for the metabolite Sch 49028.

Thus, a two-step protection–deprotection sequence first converted the previously synthesised cyclohexenol **10**[5] into the cyclohexene methanol **11** which was next oxidised to the corresponding aldehyde **12** (Scheme 1). Macrocyclisation of the aldehyde vinyl iodide **12** using $CrCl_2$ and $NiCl_2$[6] proceeded smoothly and gave only one stereoisomer of the phomactane **13** in 50% yield. NOE studies and a comparison of NMR spectroscopic data with those of related systems prepared previously in our laboratory, confirmed the α-stereochemistry for the newly introduced secondary alcohol group in **13**.[7] Treatment of **13** with *m*-CPBA resulted in the isolation of the β-epoxide **14**, whose formation was accompanied by smaller amounts of regioisomers resulting from simultaneous epoxidations of the other alkene bonds in **13**. Oxidation of the free alcohol group in **14** using Dess–Martin periodinane, followed by deprotection of the silyl ether group in the resulting ketone, then led to the hydroxyl epoxyketone **15** in 89% overall yield. Finally, deprotection of the PMB ether group in **15** was accompanied by spontaneous cyclic hemiacetal ring formation producing the target epoxy cyclic hemiacetal **8**. The structure **8** is isomeric with that assigned to the natural phomactin Sch 49028 (**6**), at its secondary alcohol centre, *i.e.* β- rather than α-, and would not be expected therefore to undergo intramolecular hydroxyl group epoxide cyclisation to an isomer of phomactin A. Inspection of the NMR spectroscopic data for synthetic **8**, in both $CDCl_3$ and CD_3OD, showed that they were at variance with corresponding data reported for Sch 49028, leading us to conclude that the compounds are not the same, *i.e.* Sch 49028 does not have the isomeric epoxy cyclic hemiacetal structure **8**.

We next examined a synthesis of the epoxy cyclic hemiacetal structure **9** having the alternative α-epoxide stereochemistry to that assigned in natural Sch 49028, *cf.* **6**. This synthesis was achieved in a straightforward manner starting from the

† Electronic supplementary information (ESI) available: NMR data for **8** and **9**. See http://www.rsc.org/suppdata/cc/b3/b310753a/

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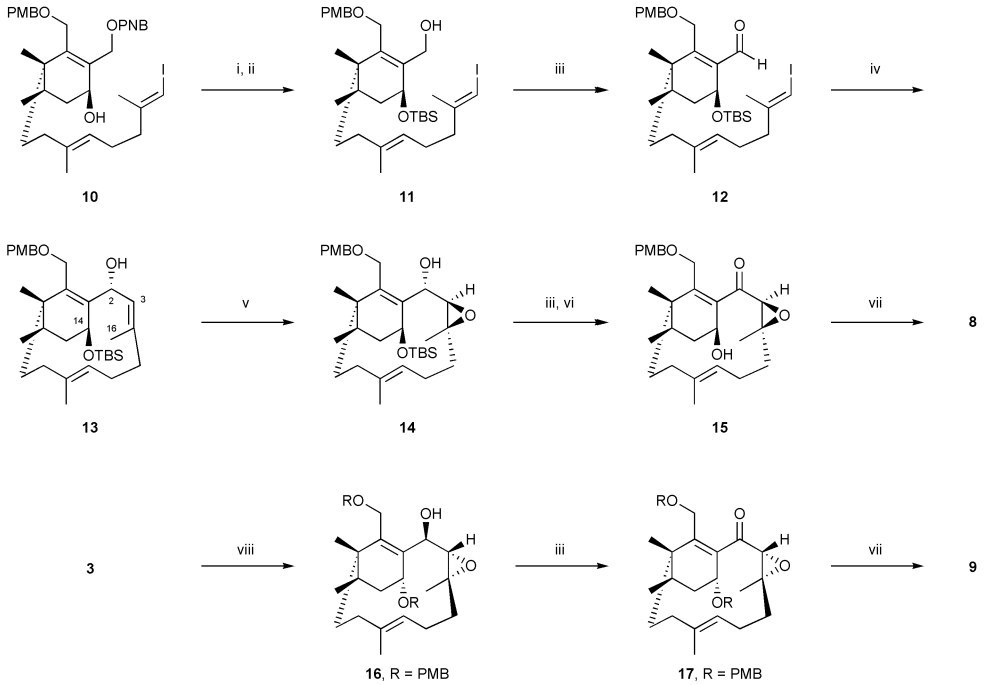

Scheme 1 *Reagents and conditions*: i, TBSCl, imidazole, DMF, 40 °C, 94%; ii, KOH, H_2O, THF, rt, 67%; iii, Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 73–91%; iv, $CrCl_2$ (6 equiv.), $NiCl_2$ (1 equiv.), DMSO, THF, rt, 50%; v, *m*-CPBA, CH_2Cl_2–aqueous phosphate buffer pH 8 (1 : 1), 0 °C, 32%; vi, TBAF, THF, 0 °C to rt, 99%; vii, DDQ, CH_2Cl_2–H_2O (19 : 1), 0 °C to 10 °C, 94–99%; viii, $VO(acac)_2$, *t*-BuOOH, PhH, rt, 82%.

phomactatrienol **3** (R = PMB), with the β-alcohol stereochemistry,[8] which was prepared as an intermediate in our synthesis of phomactin A (**1**).[3] Treatment of the *bis*-allylic alcohol **3** with $VO(acac)_2$ and *t*-BuOOH, followed by oxidation of the resulting epoxy alcohol **16** using Dess–Martin periodinane led to the α-epoxy ketone **17** in 75% yield over the two steps (see Scheme 1). Deprotection of the PMB ether groups in **17** using DDQ in CH_2Cl_2 then gave the epoxy cyclic hemiacetal structure **9**. However, as with the structure **8**, the cyclic hemiacetal diastereoisomer **9** displayed NMR spectroscopic data which did not correspond to the data reported for either Sch 49028 or phomactin A.

The syntheses of the isomeric epoxy cyclic hemiacetals **8** and **9**, and the inconsistency between their NMR data and those reported for Sch 49028 add credence to our earlier conclusion[3] that this metabolite **6** does not actually exist. Sch 49028 has been incorrectly assigned and is, in fact, phomactin A (**1**) rather than the interesting epoxy cyclic hemiacetal structure **6**. Unlike the diastereoisomeric structures **8** and **9**, which can be isolated and characterised, the intermediate corresponding to structure **6** undergoes spontaneous pyran and cyclic hemiacetal formation *in vivo* producing phomactin A (**1**) and would not therefore be expected to be isolatable from nature.

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7 Selective NOE enhancements measured for **13** correlated with the lowest energy conformation of **13** as determined by molecular mechanics calculations. NOE enhancement was observed between H-14 and H-2, H-14 and H-3, and H-14 and H-16.

8 The α-stereochemistry of the secondary ether and the β-stereochemistry of the secondary alcohol in **3** were confirmed by selective NOE enhancements.