

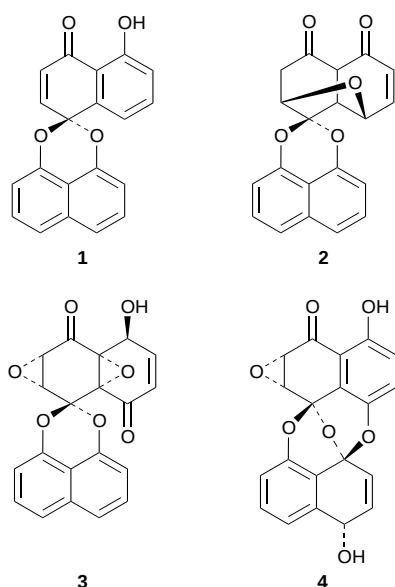
Total syntheses of palmarumycins CP₁ and CP₂ and CJ-12,371: novel spiro-ketal fungal metabolites

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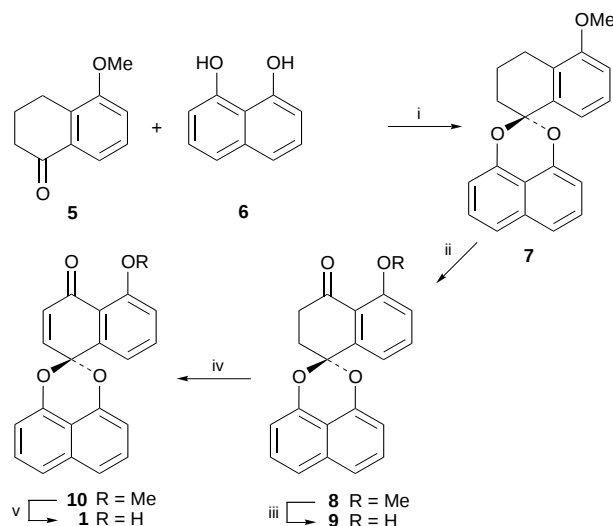
Total syntheses of palmarumycins CP₁ **1** and CP₂ **9** and the structurally related CJ-12,371 **11** are reported, thereby establishing a strategy for the synthesis of further natural products in the palmarumycins, diepoxines and preussomerines family.

The palmarumycins,¹ diepoxines² and preussomerines³ are a structurally remarkable class of natural products isolated from various fungi cultures. They all are graced with a spiro-ketal entity formally derived from naphthalene-1,8-diol **6** and 1,4-naphthoquinone, yet at rich and varied oxidation levels. All three classes of fungal metabolites are undoubtedly closely interrelated biosynthetically and may well be derived from a naphthalene-1,8-diol spiro-ketal with late introduction of the unusual oxygenation patterns. These secondary metabolites are



exemplified by palmarumycin CP₁ **1**, palmarumycin CP₃ **2**, diepoxine σ **3** and preussomerine E **4**, which show diverse biological effects including selective antifungal and antibacterial activities.⁴ Although Wipf and Jung have reported studies towards the synthesis of diepoxine σ **3**⁵ and Krohn *et al.* have reported an elegant biomimetic cyclisation approach to a model spiro-ketal array,⁶ there have been no reports on the total synthesis of any natural product in this intriguing series. Herein we now report the total syntheses of three natural products palmarumycins CP₁ **1** and CP₂ **9** and CJ-12,371 **11**.

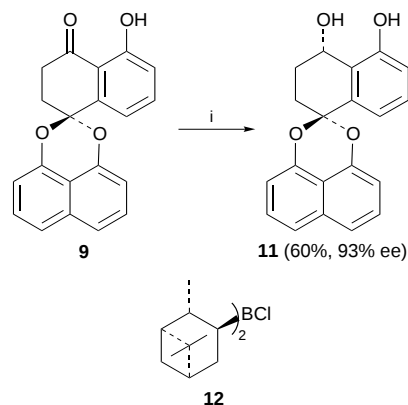
Condensation of 5-methoxytetralone **5** and diol **6**⁷ under acid catalysis gave spiro-ketal **7**† in an 86% yield (Scheme 1). Subsequent benzylic oxidation using bipyridinium chlorochromate⁸ and a 30-fold excess of *tert*-butyl hydroperoxide gave the corresponding ketone **8** in 61% yield. Alternative oxidants including Jones' Reagent or potassium permanganate were much less efficient for the preparation of ketone **8**. Reaction of



Scheme 1 Reagents and conditions: i, TsOH (cat), PhH, Dean-Stark, 48 h, reflux, 86%; ii, CrO₃·HCl·bipy, Bu^tOOH, Celite, PhH, 10 h, room temp., 61%; iii, MgI₂, PhH, 1.5 h, reflux, 84%; iv, DDQ, PhH, 10 h, reflux, 65%; v, *B*-bromocatecholborane, DBU, CH₂Cl₂, 10 min, 5 °C, 50%

the methyl ether **8** with a freshly prepared solution of magnesium iodide⁹ in benzene gave palmarumycin CP₂ **9** (84%). Deprotection using magnesium iodide was found to be far superior to trimethylsilyl iodide (32%) or sodium ethanethiolate (63%).¹⁰ Oxidation of ketone **8** with DDQ¹¹ followed by deprotection of the methyl ether with *B*-bromocatecholborane¹² gave palmarumycin CP₁ **1**, the dehydro analogue of **9**, in 33% yield over two steps.

Finally, palmarumycin CP₂ **9** was converted into its corresponding dihydro derivative **11** (60% yield, 93% ee)§ by asymmetric reduction using (+)-*B*-chlorodiisopinocampheylborane **12**¹³ (Scheme 2). It is germane to mention that reduction presumably takes place *via* intramolecular hydride delivery thereby reversing the absolute stereochemistry of reaction seen



Scheme 2 Reagents and conditions: i, (+)-**12**, THF, room temp., 18 h, then H₂O₂, KOH

with simple alkyl aryl ketones.¹³ The product of reduction, alcohol **11**, is a natural product in its own right named CJ-12,371 **11**,¹⁴ a DNA-gyrase inhibitor isolated from an unidentified fungus (N983-46). The authenticity of both palmarumycins CP₁ **1** and CP₂ **9** were established by comparison of the synthetic compounds with authentic samples (¹H and ¹³C NMR spectroscopy). Unfortunately, we have been unable to obtain an authentic sample of CJ-12,371 **11** and the characterisation of our synthetic material rests on comparison of our data with those published for the natural product.¹⁴

It is clear that the spiro-ketal **7** is a useful intermediate for further redox manipulations and the synthesis of simple palmarumycins. Further studies towards the total synthesis of the more challenging and higher oxidation level diepoxines and preussomerines are currently under investigation and will be reported in due course.

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Notes and References

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‡ All new compounds were fully characterised by spectroscopic data, microanalysis and HRMS

§ The enantiomeric excess was determined by chiral HPLC while the absolute stereochemistry was determined by comparison of the optical rotation [α]_D²⁴ –42.2, (c 0.45 in MeOH)] with the isolated natural product [α]_D²⁴ –46.8 (c 0.23, MeOH)].

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