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Syntheses of Palmarumycin CP_1 and CP_2, CJ-12,371 and Novel Analogues

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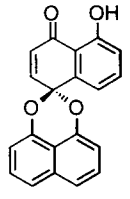
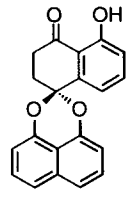
Abstract: Total syntheses of the title fungal metabolites are described *via* a route which utilises initial acetalisation with 1,8-dihydroxynaphthalene followed by elaboration of the ring A functionality. Novel analogues are also reported.

A new family of bioactive natural products has recently been isolated all of the members of which contain a 1,8-dihydroxynaphthalene derived spiroacetal unit linked to a second, more elaborately oxidised naphthalene moiety (Figure, **1** - **7**).[1-5] The palmarumycins (*e.g.* **1** - **4**), the largest group with *ca.* twenty members, were isolated from the endophytic fungus *Coniothyrium palmarum* and a related *Coniothyrium* species and were shown to possess antibacterial, antifungal and herbicidal activity.[1] CJ-12,371 (**5**) is closely related structurally and is a DNA gyrase inhibitor.[2] Other members of this family contain epoxide groups:[3] the Schering-Plough compounds (*e.g.* **6**) are phospholipase D inhibitors,[3a] whereas diepoxin α (**7**)[3b] is a representative member of another large group of related diepoxide antibiotics (which includes cladospirone bisepoxide[3c]) which also exhibit antitumour activity. The preussomerins (*e.g.* **8**)[4,5] are a closely related, though structurally more complex, group of fungal metabolites which act as novel inhibitors of *ras* farnesyltransferase, and thus are of interest in terms of their potential in cancer chemotherapy.[5]

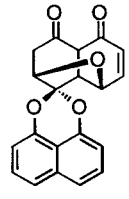
Figure



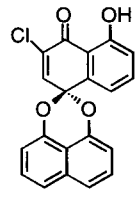
Palmarumycin CP_1 (**1**)



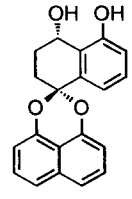
Palmarumycin CP_2 (**2**) Deoxypreussomerin B



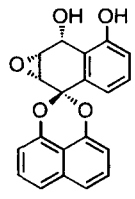
Palmarumycin CP_3 (**3**)



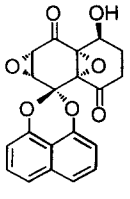
Palmarumycin C_1 (**4**)



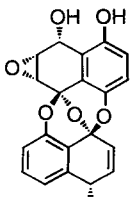
CJ-12,371 (**5**)



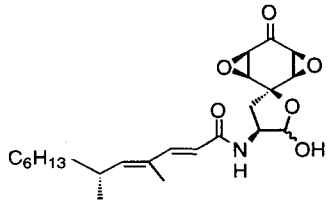
Sch 53,823 (**6**)



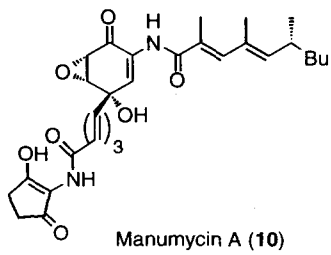
Diepoxin α (**7**) (Sch 53,516)



Preussomerin A (**8**)



Aranorosin (**9**)



Manumycin A (**10**)

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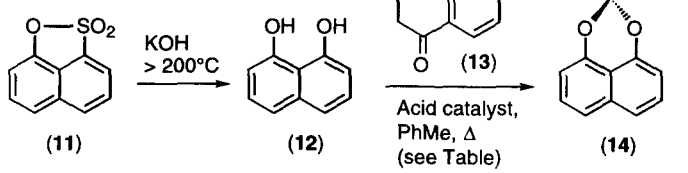
PII: S0040-4039(98)00896-X

We became interested in the dihydroxynaphthalene natural products as part of our programme to prepare novel diepoxide antibiotics (*e.g.* aranorosin **9**[6]) and *ras* farnesyltransferase inhibitors (*e.g.* manumycin A **10**[7]). Until recently, the only synthetic publications in the spiroacetal area involved preliminary model studies towards the diepoxins[8] and the biomimetic cyclisation of a *Coniothyrium* metabolite to generate a non-natural spirocyclic 1,8-dihydroxynaphthalene acetal.[9] However, Barrett *et al.* have recently reported[10] the total syntheses of palmarumycin CP_1 and CP_2, and CJ-12,371 and this has prompted us to describe our own research in this area.

We initially investigated a biomimetic cyclisation approach with little success and so turned our attention to a route in which the dihydroxynaphthalene derived spiroacetal unit is introduced at the start of the synthetic route. In view of the absence of this type of moiety in the synthetic literature we first carried out the model studies shown in Scheme 1.[11]

Scheme 1



Table

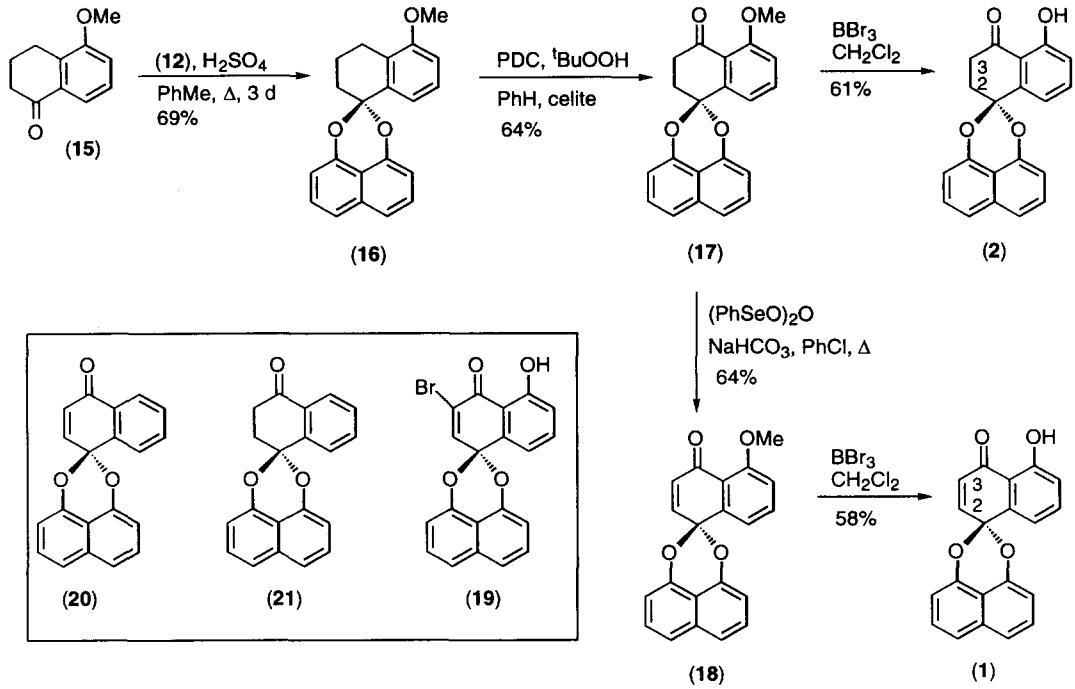
Acid catalyst	Yield (**14**)
Amberlite 15	22%
pTSA	40%
Montmorillonite K10	44%
H_2SO_4	64%
CF_3SO_3H	74%

There are numerous procedures for the conversion of commercially available 1,8-naphthosultone **11** into diol **12** in the recent literature but, in our hands, the most efficient procedure is that described by Erdmann in 1888[12] which allows multigram quantities to be prepared in good yield (86% on a 10 g scale). The reaction between diol **12** and tetralone **13** to give spiroacetal **14** proved to be surprisingly difficult and forcing conditions were required (Table). The optimum procedure required treatment with 0.2 equivalents of triflic or conc. sulfuric acid in refluxing toluene until the reaction was complete (*ca.* 3 days).[13]

We were then in a position to utilise this method to prepare natural products (Scheme 2). Commercially available 5-methoxytetralone (**15**) was converted into spiroacetal **16** in good yield using the conditions described above. Benzylic oxidation was achieved using excess pyridinium dichromate and *t*-butyl hydroperoxide[14] giving **17** in 64% yield (93% based on recovered starting material). Direct dehydrogenation of **17** to **18** was achieved in 64% yield by treatment with benzeneseleninic anhydride[15] using sodium bicarbonate to prevent acetal hydrolysis. Demethylation of **17** and **18** giving palmarumycin CP_2 (**2**) and CP_1 (**1**), respectively, was accomplished using boron tribromide. In the latter case vinyl bromide **19** was obtained as a byproduct: this is the bromo analogue of palmarumycin C_1 (**4**). The authenticity of **1** and **2** was confirmed by comparison of their NMR data with those reported [*e.g.* CP_1: δ_H 6.37 (1 H, d, *J* 10.5 Hz, H-3), 7.03 (1 H, d, *J* 10.5 Hz, H-2). Lit.[1] 6.36 (1 H, d, *J* 10.6 Hz, H-3), 7.02 (1 H, d, *J* 10.4 Hz, H-2). CP_2: δ_H 2.50 (2 H, t, *J* 6.5 Hz, CH_2-2), 2.85 (2 H, t, *J* 6.5 Hz, CH_2-3). Lit.[1] 2.49 (2 H, t, *J* 6.5 Hz, CH_2-2), 2.85 (2 H, t, *J* 6.5 Hz, CH_2-3)].

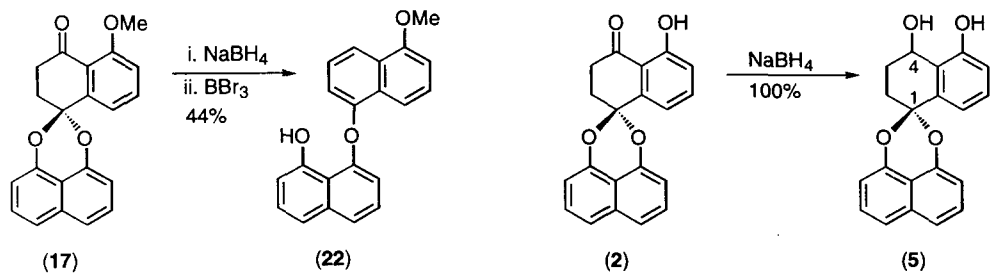
The sequence illustrated in Scheme 2 is extremely straightforward and can be used for the preparation of a range of novel analogues simply by variation of the ketone starting material. Thus, using similar methodology, tetralone **13** was converted into the deoxy-ring B palmarumycin analogues **20** and **21**.

Scheme 2



Finally, we investigated reductive processes to access CJ-12,371 (Scheme 3). Borohydride reduction of **17** proceeded quantitatively but attempted demethylation of the alcohol resulted in ring A aromatisation and acetal cleavage to give **22**. We therefore reduced palmarumycin CP_2 (**2**) with sodium borohydride producing (±)-CJ-12,371 (**5**) in quantitative yield [δ_C 60.9 (C-4), 100.0 (C-1). Lit.[2] δ_C 61.0 (C-4), 100.0 (C-1)].

Scheme 3



We are currently developing asymmetric reduction and epoxidation procedures for use in this programme and utilising these with the methodology described above to prepare the other natural products shown in the Figure.

Acknowledgements

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References and Notes

1. Krohn, K.; Michel, A.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1093; **1994**, 1099; Krohn, K.; Beckmann, K.; Flörke, U.; Aust, H.-J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Tetrahedron* **1997**, *53*, 3101.
2. Sakemi, S.; Inagaki, T.; Kaneda, K.; Hirai, H.; Iwata, E.; Sakakibara, T.; Yamauchi, Y.; Norcia, M.; Wondrack, L. M.; Sutcliffe, J. A.; Kojima, N. *J. Antibiotics* **1995**, *48*, 134.
3. (a) Chu, M.; Patel, M. G.; Pai, J.-K.; Das, P. R.; Puar, M. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 579.
   (b) Schlingmann, G.; West, R. R.; Milne, L.; Pearce, C. J.; Carter, G. T. *Tetrahedron Lett.* **1993**, *34*, 7225; Schlingmann, G.; Matile, S.; Berova, N.; Nakanishi, K.; Carter, G. T. *Tetrahedron* **1996**, *52*, 435.
   (c) Petersen, F.; Moerker, T.; Vanzanella, F.; Peter, H. H. *J. Antibiotics* **1994**, *47*, 1098 see also Chu, M.; Truumees, I.; Patel, M. G.; Gullo, V. P.; Puar, M. S. *J. Org. Chem.* **1994**, *59*, 1222.
4. Weber, H. A.; Baenziger, N. C.; Gloer, J. B. *J. Am. Chem. Soc.* **1990**, *112*, 6718; Weber, H. A.; Gloer, J. B. *J. Org. Chem.* **1991**, *56*, 4355.
5. Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bils, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J. Org. Chem.* **1994**, *59*, 6296;
   Omura, S.; Takeshima, H. *Drugs of The Future* **1994**, *19*, 751.
6. McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385.
7. Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem. In press.*
8. Wipf, P.; Jung, J.-K. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 764.
9. Krohn, K.; Beckmann, K.; Aust, H.-J.; Draeger, S.; Schulz, B.; Busemann, S.; Bringmann, G. *Liebigs Ann./Recueil* **1997**, 2531.
10. Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809.
11. All new compounds were fully characterised by high field ^{1}H- and ^{13}C-NMR spectroscopy and by elemental analysis and/or high resolution mass spectrometry.
12. Erdmann, H. *Liebigs Ann.* **1888**, *247*, 306.
13. Representative acetalisation procedure: A mixture of diol **12** (150 mg, 0.937 mmol), tetralone **13** (126 μL, 0.937 mmol) and toluene (20 mL) was heated under Dean-Stark conditions collecting a small amount of solvent (*ca.* 5 mL). The mixture was cooled to 60 °C and triflic acid (28 mg, 0.187 mmol) added. The mixture was heated under reflux and monitored by TLC until completion (3 d). Triethylamine was then added to the cooled mixture. Evaporation of the solvent and purification by column chromatography (PE-Et_2O,98:2) gave **14** (200 mg, 74%) which was recrystallised (MeOH) to afford colourless crystals, m.p. 140-141°C (MeOH); R_f 0.39 (PE-EtOAc, 98:2) [HRMS (CI): calc. for $C_{20}H_{17}O_2$, 289.12285. Found: MH^+, 289.12302], which was fully characterised spectroscopically.
14. Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048.
15. Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2209.