Pergamon

Tetrahedron Letters 41 (2000) 9105–9107

TETRAHEDRON LETTERS

Novel synthetic approaches to the palmarumycin skeleton

Ian G. C. Coutts,[a,*] Robert W. Allcock[a] and Hans W. Scheeren[b]

[a]*Department of Chemistry and Physics, Nottingham Trent University, Clifton Lane, Nottingham NG11 8NS, UK*
[b]*Department of Organic Chemistry, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands*

Received 24 July 2000; revised 14 September 2000; accepted 20 September 2000

Abstract

Oxidation of readily available aminonaphthols **7a** and **7b** with activated manganese dioxide gives palmarumycin analogues **8a** and **8b** in good yield. The related benzoquinone monoacetals **10a–c** undergo cycloaddition with 3-methoxy-2-pyrone at high pressure to give adducts **12a–c**, also possessing the palmarumycin framework.

Keywords: quinones; acetals; Diels–Alder reactions.

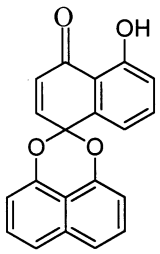
The palmarumycins are a group of fungal metabolites isolated[1] from *Coniothyrium* sp. Compound **1**, palmarumycin CP_1, may be regarded as the parent member of the series, with others displaying a range of hydroxylation, unsaturation or epoxidation. Several of the series exhibit antibacterial, anti-fungal, or potentially anti-cancer activity.

Palmarumycin CP_1 is a 5-hydroxy-1,4-naphthoquinone in which the 1-carbonyl has formed a *spiro*-acetal with naphthalene-1,8-diol, and represents a rare example of a naturally-occurring quinone monoacetal in which the acetal is derived from *phenolic* hydroxyls, a class of compound in which we have long been interested.[2] Adding to this our current involvement with antifungal compounds,[3] we have initiated a programme of evaluating palmarumycin analogues as anti-infective agents.

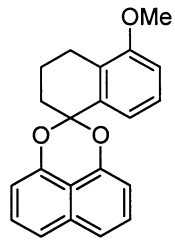
The combination of biological activity and unusual structure of this family of compounds has attracted the attention of several groups. Published syntheses have used two routes for constructing the key acetal linkage. In the first,[4,5] 5-methoxytetralone undergoes slow acid-catalysed reaction with naphthalene-1,8-diol to give ketal **2**, which is converted to **1** by judicious oxidation and demethylation. An alternative, biomimetic approach[6] involves the multi-stage synthesis of diphenol **3**, which, on treatment with phenyliodonium diacetate, undergoes oxidative coupling to **4**; this is then further oxidised to CP_1.

* Corresponding author. Fax: +44 115 8486636; e-mail: ian.coutts@ntu.ac.uk

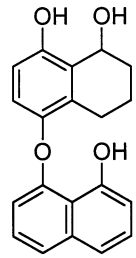
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01625-7



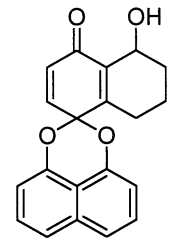
1



2

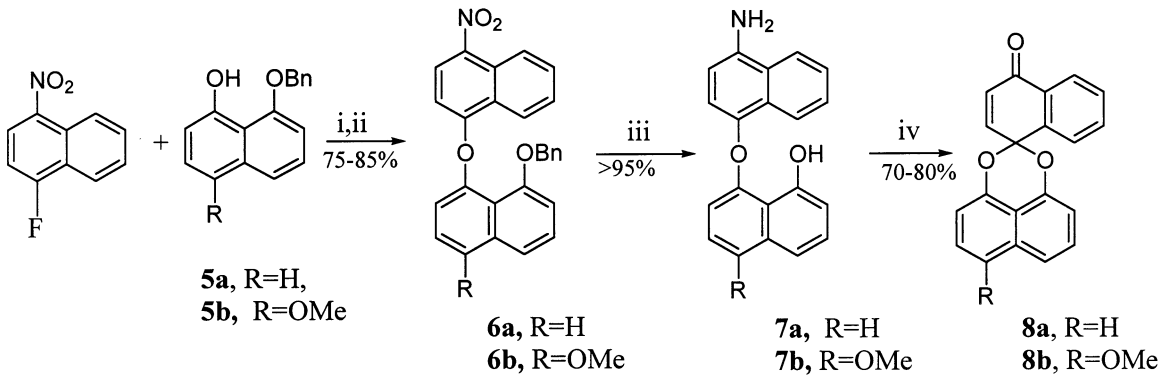


3



4

Our approach to the palmarumycin skeleton (Scheme 1) exploits the synthesis of quinone ketals by the oxidation of aryloxyanilines.[7] Reaction of naphthalene-1,8-diol with benzyl chloride/K_2CO_3/butanone gives in high yield 1-benzyloxy-8-hydroxynaphthalene **5a** which, on treatment with 1-fluoro-4-nitronaphthalene in DMSO, affords dinaphthyl ether **6a**. This is converted quantitatively by hydrogenation to aminophenol **7a**, which, on immediate oxidation with activated manganese dioxide, gives *deoxy*-CP_1 **8** in 80% yield. The same sequence, starting with the known[8] 1-benzyloxy-5-methoxy-8-naphthol **5b**, allows ready access to **8b**, a regioisomer of *O*-methyl-CP_I, in comparable yield.

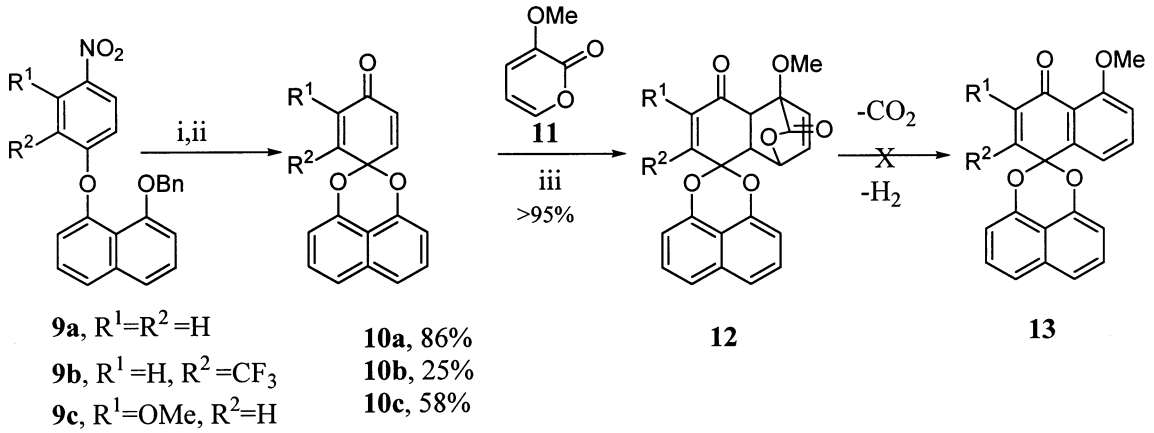


Scheme 1. (i) NaH/THF; (ii) DMSO; (iii) H_2/Pd/C; (iv) MnO_2/benzene

Scheme 1 provides an efficient synthesis of **8a**,**b**, useful substrates for modifications such as reduction or epoxidation. It does not, however, allow for the introduction of a hydroxyl group *peri* to the quinone carbonyl, as the requisite 5-alkoxy-1-fluoro-4-nitronaphthalene would be difficult to prepare. An alternative strategy, shown in Scheme 2, is to attempt to incorporate the hydroxyl by a Diels–Alder approach. Here, 3-methoxy-2-pyrone **11** is used as a synthon for 1-hydroxybutadiene (adducts formed using 3-hydroxy-2-pyrone[9] proved to be unstable). It was hoped that subsequent decarboxylation and oxidation of adducts **12** would lead to compounds **13**, substituted analogues of *O*-methyl CP_1, which could be demethylated if required.

Reaction of **5a** with appropriately substituted 4-fluoronitrobenzenes gave virtually quantitative yields of ethers **9a**–**c**, which were efficiently converted as before to the benzoquinone acetals **10a**–**c**.

Mono-acetals of quinones[10] or quinoneimines[11] are much less reactive dienophiles than their parent quinones, but undergo cycloaddition more readily at high pressure.[12] When equimolar



Scheme 2. (i) H_2/Pd/C; (ii) MnO_2/benzene; (iii) 12–15 kbar

mixtures of acetals **10a**, **10b** or **10c** and pyrone **11** were maintained at 12–15 kbar, adducts **12a–c** were formed quantitatively, and as single regio- and stereoisomers. Although not entirely unambiguous, the ^{1}H and ^{13}C NMR spectra of the adducts suggest that they are *endo* products, with the substituent orientation as shown in the Scheme.

Thermal cycloaddition was less efficient. Prolonged reaction of acetal **10a** with **11** in refluxing benzene resulted in an equilibrium mixture, from which adduct **12a** could be isolated in 55% yield. In higher boiling solvents there was evidence of extensive decomposition.

Attempts to eliminate carbon dioxide from the adducts thermally, or with acid or base catalysis, led to retro-Diels–Alder reaction or to decomposition, although aromatisation of **12a** and **12b** occurred cleanly in the mass spectrometer. These results, however, illustrate the potential of this approach to palmarumycin analogues for structure–activity studies, and the reaction of **12** and related acetals with a variety of dienes is under current investigation.

The significant anti-microbial activity of several of the acetals and derived adducts will be reported separately.

References

1. Krohn, K.; Michel, A.; Florke, U.; Aust, H.-J.; Draeger, S.; Schulz, B. *Liebigs Ann. Chem.* **1994**, 1093 and 1099.
2. (a) Coutts, I. G. C.; Humphreys, D. J.; Schofield, K. *J. Chem. Soc. (C)* **1969**, 1982. (b) Coutts, I. G. C.; Hamblin, M. R.; Welsby, S. E. *J. Chem. Soc., Perkin Trans 1* **1981**, 493.
3. Coutts, I. G. C.; Bulpitt, P. C. A.; Cummins, P. J.; Buckley, G. A.; Mills, S. D. *Pestic. Sci.* **1997**, *51*, 99.
4. Barrett, A. G. M.; Hamprecht, D.; Meyer, T. *Chem. Commun.* **1998**, 809.
5. Ragot, J. P.; Steeneck, C.; Alcaraz, M.-L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1073.
6. Wipf, P.; Jung, J.-K. *J. Org. Chem.* **1998**, *63*, 3530.
7. Coutts, I. G. C.; Pavlidis, V. H.; Reza, K.; Southcott, M. R.; Wiley, G. *Tetrahedron Lett.* **1997**, *38*, 5563.
8. Hart, D. J.; Mannino, A. *Tetrahedron* **1996**, *52*, 3841.
9. Okamura, H.; Morishige, K.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1998**, *39*, 1211.
10. (a) Carreno, M. C.; Farina, F.; Galan, A.; Ruano, J. L. *J. Chem. Res.* **1979**. (b) Carreno, M. C.; Farina, F.; Galan, A.; Ruano, J. L. G. *J. Chem. Res.* **1981**, 370.
11. Coutts, I. G. C.; Culbert, N. J.; Edwards, M.; Hadfield, J. A.; Musto, D. R.; Pavlidis, V. H.; Richards, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1892.
12. (a) Kerr, M. A. *Synlett* **1995**, 1165. (b) Jarvo, E. R.; Boothroyd, S. E.; Kerr, M. A. *Synlett* **1996**, 897.