Pure Appl. Chem., Vol. 72, No. 9, pp. 1635–1639, 2000.

Synthetic studies toward pyranonaphthoquinone antibiotics*

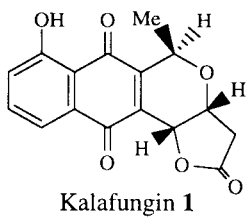
Margaret A. Brimble

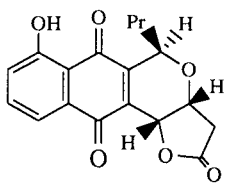
Department of Chemistry, University of Auckland, 23 Symonds St., Auckland, New Zealand

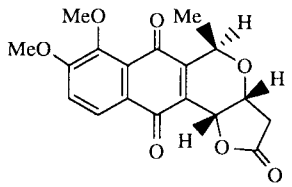
Abstract: A furofuran annulation/oxidative rearrangement strategy was used to construct the basic skeleton of the pyranonaphthoquinone family of antibiotics. This synthetic methodology has been applied to the synthesis of the spiroacetal-containing pyranonaphthoquinone antibiotic griseusin A, to an analog of the *C*-glycoside medermycin, and to a dimeric pyranonaphthoquinone.

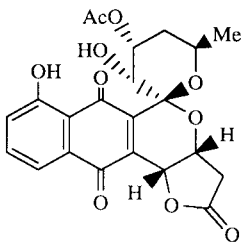
INTRODUCTION

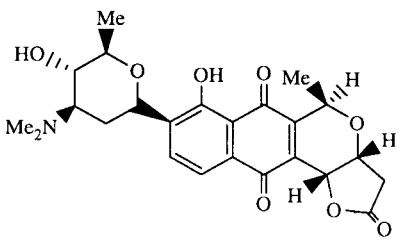
The pyranonaphthoquinone antibiotics [1] have been isolated from various strains of bacteria and fungi of microbial origin and are typified by the presence of a basic naphtho[2,3-*c*]pyran-5,10-dione skeleton. Some members of the family contain an additional γ-lactone ring fused to the dihydropyran moiety. This family of antibiotics exhibits activity against a variety of Gram-positive bacteria, pathogenic fungi, and yeasts, as well as antiviral activity and have attracted considerable synthetic interest [2] due to their proposed ability to act as bioreductive alkylating agents [3] via quinone methide intermediates in a similar manner to the anticancer agent mitomycin C. Some of the simpler pyranonaphthoquinones include kalafungin **1**, deoxyfrenolicin **2** (a coccidiostat), and arizonin **3**, while more complex members of the family include the spiroacetal griseusin A **4**, the C-glycoside medermycin **5**, and the dimeric bacterial pigment, actinorhodin **6** (Scheme 1).

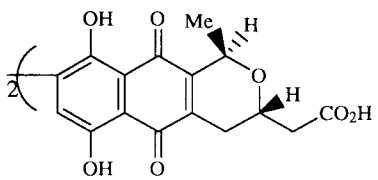

Kalafungin **1**


Frenolicin B **2**


Arizonin C1 **3**


Griseusin A **4**


Medermycin **5**

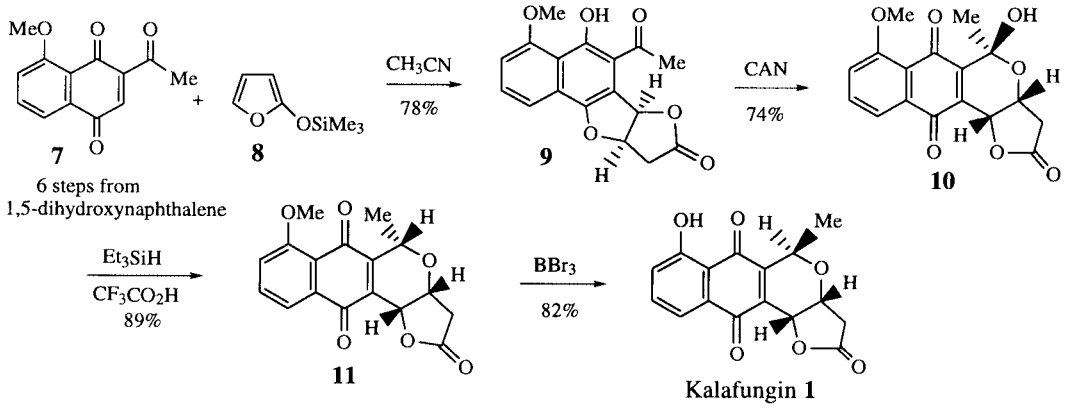

Actinorhodin **6**

Scheme 1

*Lecture presented at the 13th International Conference on Organic Synthesis (ICOS-13), Warsaw, Poland, 1–5 July 2000. Other presentations are published in this issue, pp. 1577–1797.

SYNTHESIS OF KALAFUNGIN

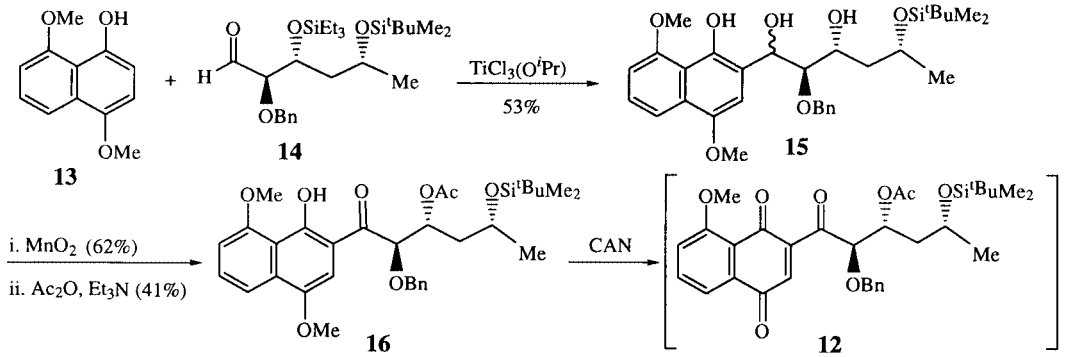
Initial synthetic work developed by this research group [4] established an efficient synthesis of the simpler member of the pyranonaphthoquinone antibiotics, kalafungin **1** (Scheme 2). The key 2-acetyl-1,4-naphthoquinone **7** underwent furofuran annulation with 2-trimethylsilyloxyfuran **8** to furonaphthofuran **9** which then underwent ceric ammonium nitrate (CAN) induced oxidative rearrangement to the desired furonaphthopyran ring system **10**. This lactol **10** was then converted to kalafungin **1** by initial reduction to *cis*-ether **11** followed by concomitant deprotection of the methyl ether and epimerization of the *cis*-ether **11** to the more stable naturally occurring *trans*-ether, kalafungin **1**. This synthetic strategy was then applied to the synthesis of frenolicin B [5] and the arizonins [6].



Scheme 2

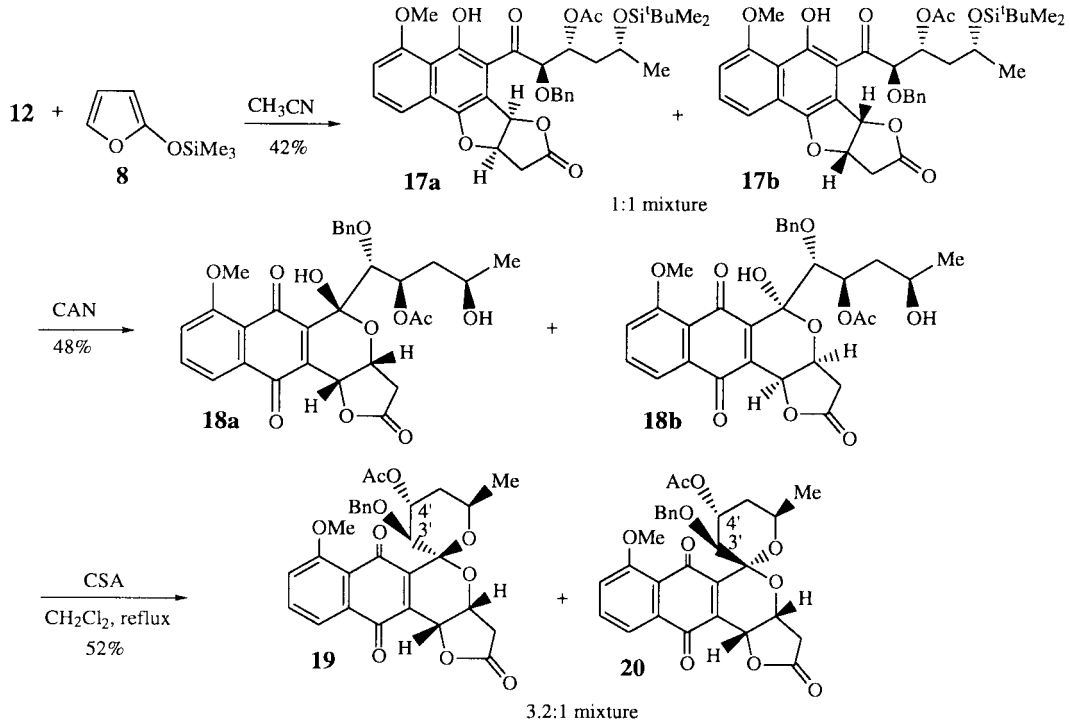
SYNTHETIC STUDIES TOWARDS GRISEUSIN A

Griseusin A **4** was isolated from a soil sample in Peru which had been innoculated with *Streptomyces griseusis* [7] and is a unique member of the pyranonaphthoquinone family of antibiotics in that it contains a 1,7-dioxaspiro[5.5]undecane ring system fused to a juglone moiety. Our initial synthetic approach to griseusin A [8] focused on the assembly of an unsaturated pentacyclic spiroketal which would allow introduction of the oxygenated substituents on the spiroketal ring via hydroxylation. This approach was thwarted, however, when unexpected hydroxylation of the naphthoquinone double bond occurred.



Scheme 3

Our more recent approach to griseusin A **4** (Schemes 3,4) focused on a synthetic strategy wherein the spiroketal-oxygenated substituents were assembled onto an acyclic naphthoquinone precursor **12** which in turn was constructed via addition of a titanium naphtholate derived from naphthol **13** to aldehyde **14**. After conversion of the resultant benzylic alcohol **15** to ketone **16**, subsequent oxidative demethylation afforded the key naphthoquinone **12**. Addition of 2-trimethylsilyloxyfuran **8** to naphthoquinone **12** effected furofuran annulation to a 1:1 inseparable mixture of adducts **17**. Oxidative rearrangement of this mixture of adducts using ceric ammonium nitrate produced lactols **18** which underwent cyclization to a 3.2:1 mixture of spiroacetals **19** and **20** wherein epimerization at C3' had occurred.



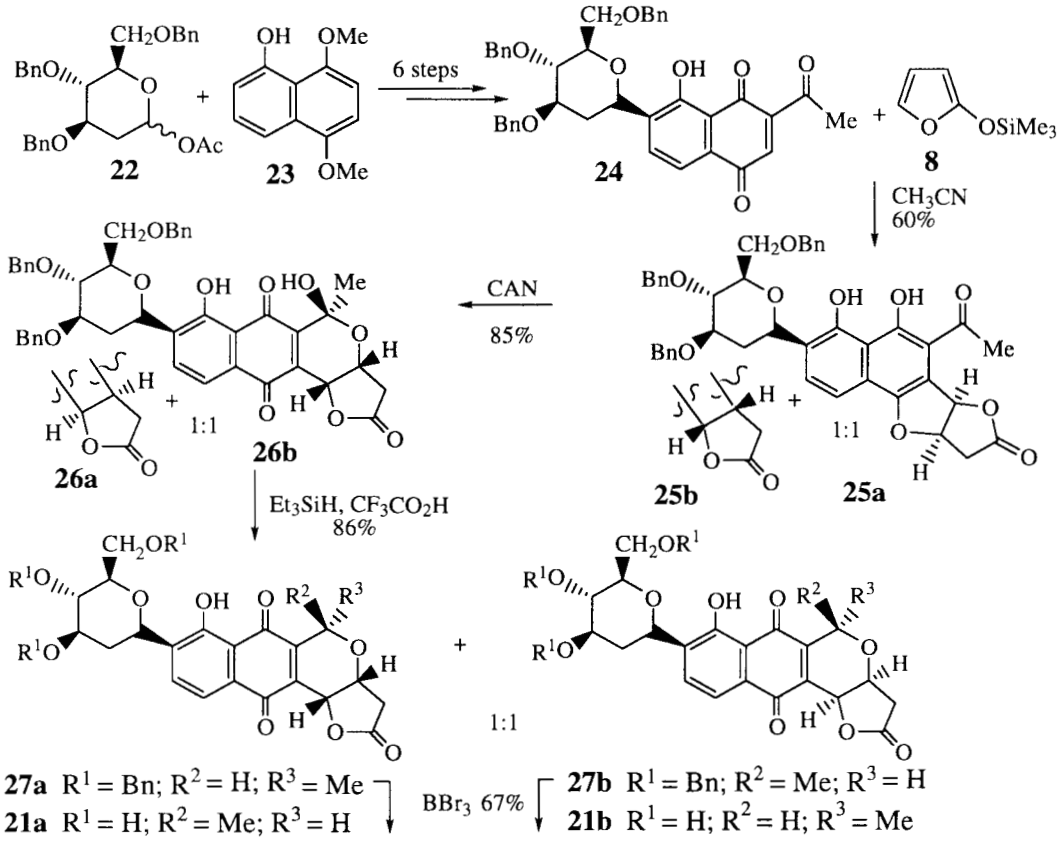
Scheme 4

SYNTHETIC STUDIES TOWARDS MEDERMYCIN

The *C*-glycoside medermycin **5** was isolated from *Streptomyces tanashiensis* [9] and exhibits activity against K-562 human myeloid leukemia and P-388 murine leukemia. To date, only one lengthy synthesis of medermycin **5** has been reported [10], which is not amenable to the synthesis of analogs of medermycin **5**. We have recently completed the synthesis of a 2-deoxyglucosyl analog **21** of medermycin **5** (Scheme 5) using our furofuran annulation—oxidative rearrangement strategy as previously applied to the synthesis of the aglycone, kalafungin **1** [11].

The key *C*-glycosylnaphthoquinone **24** was successfully prepared by *C*-glycosylation of naphthol **23** with glycosyl donor **22** followed by regioselective introduction of the required 3-acetyl group. This strategy was necessitated by the undesired formation of bicyclic acetals in which the glycosyl donor **22** had undergone an unusual 1,6-hydride shift when using 3-substituted naphthols in the *C*-glycosylation step [12]. With the desired *C*-glycosylnaphthoquinone **24** in hand, subsequent addition of 2-trimethylsi-

lyloxyfuran **8** afforded a 1:1 mixture of the furonaphthofuran adducts **25a**,**25b** in moderate yield. Treatment of furo[3,2-b]naphthofurans **25a**,**25b**, with aqueous CAN effected smooth conversion to furonaphthopyrans **26a**,**26b**, which were separable upon purification by low-temperature (–20 °C) flash chromatography. Subsequent reduction of the lactols **26a**,**26b** using triethylsilane and trifluoroacetic acid afforded cyclic ethers **27a**,**27b** which underwent deprotection of the benzyl ethers and epimerization to the more stable *trans* isomers **21a**,**21b** upon treatment with boron tribromide.



Scheme 5

REFERENCES

1. For a recent review of the isolation and biological properties of the pyranonaphthoquinone antibiotics see: M. A. Brimble, L. J. Duncalf, M. R. Nairn. *Nat. Prod. Rep.* **16**, 267 (1999).
2. For a review of the synthesis of the pyranonaphthoquinone antibiotics see: M. A. Brimble, M. R. Nairn, H. Prabaharan. *Tetrahedron*. **56**, 1937 (2000).
3. H. W. Moore and R. Czerniak. *Med. Res. Rev*. **1**, 249 (1981).
4. M. A. Brimble and S. J. Stuart. *J. Chem. Soc., Perkin Trans. I*. 881 (1990).
5. M. A. Brimble and S. M. Lynds. *J. Chem. Soc., Perkin Trans. I*. 493 (1994).
6. M. A. Brimble, S. J. Phythian, H. Prabaharan. *J. Chem. Soc., Perkin Trans. I*. 2855 (1995).
7. N. Tsuji, M. Kobayashi, Y. Terui, K. Tori. *Tetrahedron* **32**, 2207 (1976).
8. M. A. Brimble and M. R. Nairn. *Molecules* **1**, 3 (1996).

9. S. Takano, K. Hasuda, A. Ito, Y. Koide, F. Ishii, I. Haneda, S. Chihara, T. Koyami. *J. Antibiot.* **29**, 765 (1976).
10. K. Tatsuka, H. Ozeki, M. Yamaguchi, M. Tanaka, T. Okui. *Tetrahedron Lett*. **31**, 5495 (1990).
11. M. A. Brimble and T. J. Brenstrum. *Tetrahedron Lett*. **41**, 2994 (2000).
12. M. A. Brimble and T. J. Brenstrum. *Tetrahedron Lett*. **41**, 1107 (2000).