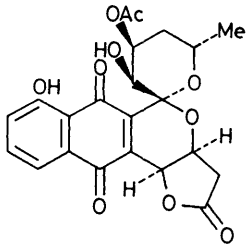
Synthesis of the Griseusin A Ring System

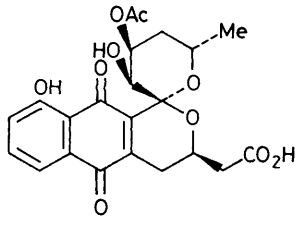
Margaret A. Brimble* and Michael R. Nairn
Department of Chemistry and Biochemistry, Massey University, Palmerston North, New Zealand

An efficient synthesis of the pentacyclic framework (**12**) of the pyranonaphthoquinone antibiotic Griseusin A (**1**) is reported. The key step involves assembly of the furo[3,2-*b*]naphtho[2,3-*d*]pyran (**11**) ring system *via* a ceric ammonium nitrate oxidative rearrangement of the furo[3,2-*b*]-naphtho[2,1-*d*]furan (**10**).

Griseusins A and B, (**1**) and (**2**), isolated from a strain of *Streptomyces griseus*[1] are members of the pyranonaphthoquinone family of antibiotics and are distinguished from the simpler members of the family, kalafungin[2] and the nanomycins A and D[3] by the presence of the 1,7-dioxaspiro[5,5]undecane ring system. Despite the biological activity exhibited by these compounds[1,4] only one synthesis of Griseusin B has been reported, by Yoshii *et al.*[5,6,7] in which the spiroacetal ring system was assembled by an intramolecular ketalization of a δ,δ′-dihydroxyketone derived from a bromohydrin. The γ-lactone present in Griseusin A was then prepared by aerial oxidation of Griseusin B in pyridine. We now wish to report an efficient synthesis of the pentacyclic framework of Griseusin A in which the furo[3,2-*b*]naphtho[2,3-*d*]pyran ring system is assembled *via* a ceric ammonium nitrate oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan (see Scheme). We have recently employed this strategy to synthesize the simpler antibiotic kalafungin.[8]



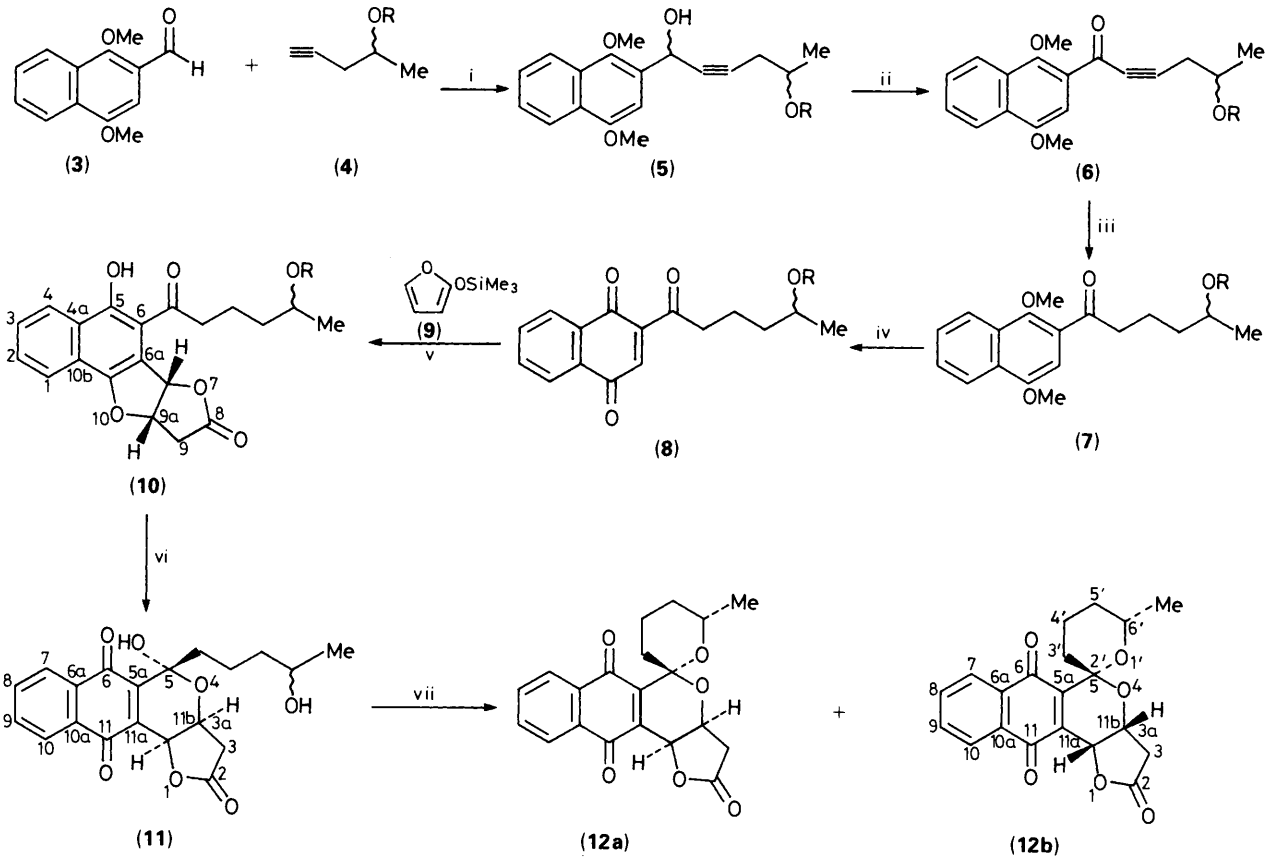
(**1**)



(**2**)

Assembly of the initial furo[3,2-*b*]naphtho[2,1-*d*]furan (**10**) required the synthesis of napthoquinone (**8**) derived from the corresponding dimethyl ether (**7**). Thus, condensation of the lithium acetylide of acetylene (**4**) at −78 °C with 1,4-dimethoxy-2-formylnaphthalene (**3**)[9] afforded an isomeric mixture of the alcohol (**5**)† in 86% yield which upon oxidation using activated manganese dioxide gave the acetylenic ketone (**6**) in 76% yield. Hydrogenation of the acetylene (**6**) over 5% palladium on charcoal in ethyl acetate gave the saturated dimethyl ether (**7**) (93%) which upon careful treatment with ceric ammonium

† All new compounds gave satisfactory spectroscopic and analytical data.



Scheme. *Reagents and conditions:* i, (**4**), BuLi (1.1 equiv.), THF, −78 °C, 1 h, then (**3**), −78 °C to −60 °C, 86%; ii, excess MnO_2 (activated), dichloromethane, room temp., 76%; iii, H_2, 5% Pd on C, ethyl acetate, room temp., 1 h, 93%; iv, ceric ammonium nitrate, (1.9 equiv.), CH_3CN, H_2O, room temp., 0.25 h, 90%; v, CH_3CN, 0 °C, 1 h, then room temp., MeOH, 18 h, 71%; vi, ceric ammonium nitrate (8.0 equiv.), CH_3CN, H_2O, room temp., 0.5 h, 87%; vii, dichloromethane, reflux, camphorsulphonic acid (cat.), 3 days, 64%.

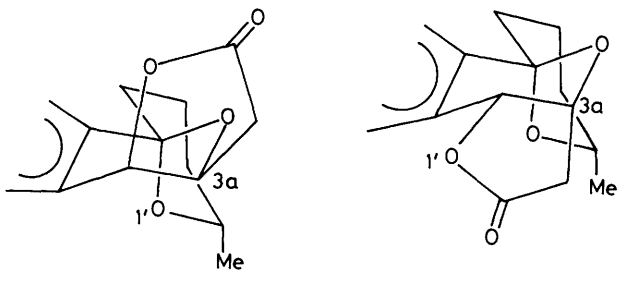
nitrate (1.9 equiv.) in aqueous acetonitrile gave the naphthoquinone (**8**) in 90% yield. The naphthoquinone (**8**) was used in the subsequent step without further purification.

Addition of 2-trimethylsiloxyfuran (**9**) to the naphthoquinone (**8**) effected a furofuran annulation to the furo[3,2-*b*]-naphtho[2,1-*d*]furan (**10**) in 71% yield after isolation by flash chromatography. ^{1}H N.m.r. spectroscopy (270 MHz) established the presence of a 1:1 isomeric mixture which could not be separated by t.l.c. Rearrangement of the isomeric mixture of adducts (**10**) and deprotection of the t-butyldimethylsilyl protecting group was then effected using excess ceric ammonium nitrate (CAN) (8.0 equiv.) to give a 1:1 isomeric mixture (270 MHz ^{1}H n.m.r.) of the furo[3,2-*b*]naphtho[2,3-*d*]pyrans (**11**) in 87% yield after purification by flash chromatography.

Finally treatment of diol (**11**) (1:1 isomeric mixture) in dichloromethane with camphorsulphonic acid (catalytic quantity) after heating under reflux for three days afforded two isomers of spiroacetal (**12**) both as racemic mixtures that in this case were easily separated by flash chromatography {*spiroacetal* (**12a**) (42%), yellow solid, R_F 0.77 [hexane–ethyl acetate (1:1)], m.p. 206—208 °C (Found: C, 67.8; H, 5.2. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); ν_{max}(Nujol) 1 795s (C=O, γ-lactone) and 1 670s (C=O, quinone) cm^{-1}; δ_H(270 MHz; $CDCl_3$) 1.20 (3 H, d, *J* 6.2 Hz, Me), 1.51—1.70 (5 H, m, 5′$_{ax}$-H, 5′$_{eq}$-H, 4′$_{ax}$-H, 4′$_{eq}$-H, and 3′$_{eq}$-H), 2.68 (1 H, ddd, J_{gem} 13.7, $J_{3'ax,4'ax}$ 13.7 and $J_{3'ax,4'eq}$ 4.8 Hz, 3′$_{ax}$-H), 2.75 (1 H, d, J_{gem} 17.4 Hz, 3-H$_A$), 2.98 (1 H, dd, J_{gem} 17.4 and $J_{3,3a}$ 4.9 Hz, 3-H$_B$), 3.86—3.97 (1 H, m, 6′-H), 4.72 (1 H, dd, $J_{3a,3}$ 4.9, and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.31 (1 H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 7.75—7.81 (2 H, m, 8-H and 9-H), and 8.08—8.13 (2 H, m, 7-H and 10-H); *spiroacetal* (**12b**) (22%), yellow solid, R_F 0.66 [hexane–ethyl acetate (1:1)], m.p. 174—177 °C (Found: C, 67.6; H, 5.1. $C_{20}H_{18}O_6$ requires C, 67.8; H, 5.1%); δ_H(270 MHz; $CDCl_3$) 1.16 (3 H, d, *J* 6.2 Hz, Me), 1.52—1.82 (5 H, m, 5′$_{ax}$-H, 5′$_{eq}$-H, 4′$_{ax}$-H, 4′$_{eq}$-H, and 3′$_{eq}$-H), 2.34 (1 H, ddd, J_{gem} 14.1, $J_{3'ax,4'ax}$, 14.1, and $J_{3'ax,4'eq}$ 4.7 Hz, 3′$_{ax}$-H), 2.84 (1 H, d, J_{gem} 17.6 Hz, 3-H$_A$), 2.96 (1 H, dd, J_{gem} 17.6, and $J_{3,3a}$ 5.1 Hz, 3-H$_B$), 4.13—4.17 (1 H, m, 6′-H), 4.60 (1 H, m, 3a-H), 5.33 (1 H, d, $J_{11b,3a}$ 3.3 Hz, 11b-H), 7.72—7.81 (2 H, m, 8-H and 9-H), and 8.07—8.12 (2 H, m, 7-H and 10-H)}.

The stereochemistry* of the two spiroacetals (**12a**) and (**12b**) (see Figure) was assigned on the basis that the spiroacetal functionality is formed under thermodynamic control. Thus, the anomeric effect establishes the formation of the two isomers in which the oxygen of each spiroacetal ring occupies an axial position with respect to the C–O bond of the adjacent ring. Isomer (**12a**) in which the methylene group of the fused γ-lactone occupies an equatorial position at C–3a is favoured over isomer (**12b**) where this methylene group occupying an axial position exhibits unfavourable steric interactions with the oxygen atom (O-1′).

* Similar stereochemical arguments have been described by Yoshii *et al.*[7] Professor Yoshii reported the preparation of isomer (**12a**)[7] with m.p. 107—109 °C for which the ^{1}H n.m.r. data is in agreement with ours but with the omission of a resonance at δ_H 3.86—3.97 assigned to 6′-H. In a private communication Professor Yoshii has acknowledged the omission of this n.m.r. signal and questions the melting point he reported for this isomer.



(12a) (12b)

Figure.

In summary, the successful synthesis of spiroacetal (**12a**) represents an efficient entry to the basic ring system present in the pyranonaphthoquinone antibiotic Griseusin A.

Acknowledgements

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References

1 N. Tsuji, M. Kobayashi, Y. Wakisaka, Y. Kawamura, M. Mayama, and K. Matsumoto, *J. Antibiot.*, 1976, **29**, 7; N. Tsuji, M. Kobayashi, Y. Terui, and K. Tori, *Tetrahedron*, 1976, **32**, 2207.
2 M. E. Bergy, *J. Antibiot.*, 1968, **21**, 454; H. Hoeksama and W. C. Krueger, *ibid.*, 1976, **29**, 704.
3 S. Omura, H. Tanaka, Y. Okada, and H. Marumo, *J. Chem. Soc., Chem. Commun.*, 1976, 320.
4 H. W. Moore, *Science*, 1977, **197**, 527; H. W. Moore and R. Czerniak, *Med. Res. Rev.*, 1981, **1**, 249.
5 Synthesis of (+)-Griseusin A: T. Kometani, Y. Takeuchi, and E. Yoshii, *J. Org. Chem.*, 1983, **48**, 2311.
6 Synthesis of (+)-7-deoxygriseusin A: T. Kometani, Y. Takeuchi, and E. Yoshii, *J. Org. Chem.*, 1982, **47**, 4725.
7 Model work for synthesis of Griseusin A: K. Matsumoto, Y. Takeuchi, K. Takeda, and E. Yoshii, *Heterocycles*, 1981, **16**, 1659.
8 M. A. Brimble, R. Hodges, and S. J. Stuart, *Tetrahedron Lett.*, 1988, **29**, 5987.
9 H. Uno, *J. Org. Chem.*, 1986, **51**, 350.

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