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Synthesis of Analogues of Griseusin A

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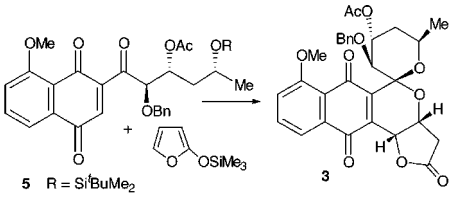
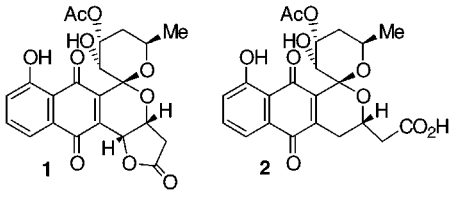
ABSTRACT



The synthesis of pyranonaphthoquinone-spiroacetals (3 and 4), which are synthetic analogues of the pyranonaphthoquinone antibiotic griseusin A (1) is reported. The oxygenated substituents on the spiroacetal ring were introduced onto the key naphthalene intermediate (5) using an *anti* asymmetric aldol reaction. The pyranonaphthoquinone skeleton was then assembled via furofuran annulation to naphthoquinone (22) to construct a furonaphthofuran ring followed by oxidative rearrangement to the furonaphthopyran ring.

Griseusins A (**1**) and B (**2**) were isolated[1] from a soil sample collected in Peru which had been innoculated with *Streptomyces griseus* K-63 and are unique within the pyranonaphthoquinone family[2] of antibiotics in that they contain a 1,7-dioxaspiro[5.5]undecane ring system fused to a juglone moiety. The absolute configuration of griseusin A (**1**) was initially erroneously assigned by comparison of CD spectra with other pyranonaphthoquinones of known absolute configuration; however, X-ray crystallographic analysis of a 6,8-dibromoderivative[3] later established the absolute stereochemistry to be as depicted in structure (**1**).



Despite their reported antimicrobial activity[1] and their proposed ability to act as bioreductive alkylating agents,[4] only one total synthesis of griseusins A (**1**) and B (**2**) has been reported to date.[5] Yoshii et al.[5] assembled the spiroacetal ring of griseusin A (**1**) starting from an appropriate carbohydrate precursor; however, the required functionalization of the initial carbohydrate involved a lengthy process.

Our initial synthetic effort[6] toward griseusin A (**1**) focused on the hydroxylation of an unsaturated spiroacetal as a means to introduce the oxygenated substituents onto the spiroacetal ring. The basic griseusin A framework was assembled via oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan which in turn was assembled by addition of 2-[(trimethylsilyl)oxy]furan to a 1,4-naphthoquinone bearing an α,*β*-unsaturated ketone at C-2. This approach was thwarted, however, when hydroxylation of the final unsaturated spiroacetal unexpectedly occurred on the C5a−C11a naphthoquinone double bond.

We herein report a synthesis of spiroacetals (**3**) and (**4**),[7] adopting this furofuran annulation/oxidative rearrangement strategy wherein the spiroacetal oxygenated substituents are assembled onto an acyclic naphthalene intermediate (**5**) at

(1) (a) Tsuji, N.; Kobayashi, M.; Wakisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot. (Tokyo)* **1976**, *29*, 7. (b) Tsuji, N.; Kobayashi, M.; Terui, Y.; Tori, K. *Tetrahedron* **1976**, *32*, 2207.

(2) Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep*. **1999**, *16*, 267.

(3) Tsuji, N.; Kamagauchi, T.; Nakai, H.; Shiro, M. *Tetrahedron Lett*. **1983**, *24*, 389.

(4) (a) Moore, H. W. *Science* **1977**, *197*, 527. (b) Moore, H. W.; Czerniak, R. *Med. Res. Rev*. **1981**, *1*, 249.

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(6) Brimble, M. A.; Nairn, M. R. *Molecules* **1996**, *1*, 3.

(7) All new compounds gave satisfactory spectroscopic and analytical data.

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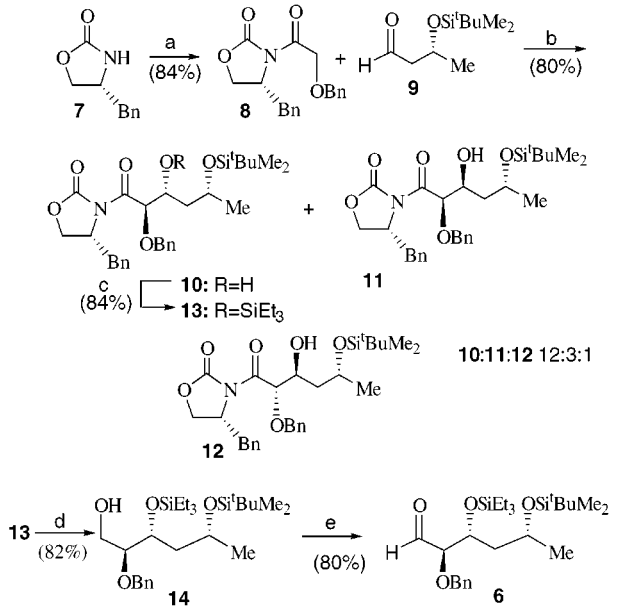
an early stage in the synthesis. This approach provides a non-carbohydrate-derived synthesis of analogues of griseusin A (**1**).

The functionality on the C3 side chain of the key naphthalene (**5**) was derived from aldehyde (**6**). In turn the required (2*R*,3*R*,5*R*)-aldehyde (**6**) was prepared via *anti* aldol condensation of acyloxazolidinone (**8**) [derived from oxazolidinone (**7**)[8]] with (3*R*)-aldehyde (**9**) (Scheme 1). Aldehyde (**9**) was readily available from commercial (3*R*)-ethyl 3-hydroxybutanoate by protection of the hydroxyl group as a *tert*-butyldimethylsilyl ether, lithium borohydride reduction of the ester to an alcohol,[9] followed by oxidation (TPAP, NMO) to the aldehyde (**9**).[10]

Scheme 1



a. ^{n}BuLi, -78°C, $BnOCH_2COCl$. b. $Sn(OTf)_2$, CH_2Cl_2, Et_3N, -78°C then **9**, TMEDA. c. Et_3SiCl, imidazole, DMF. d. $LiBH_4$, THF, 0°C. e. TPAP, NMO, CH_2Cl_2.

Precedent for the desired *anti* aldol coupling between oxazolidinone (**8**) and aldehyde (**9**) was based on work by Evans et al.[11] using tin(II) enolates of oxazolidinones in the presence of TMEDA. Thus, the stannous enolate of oxazolidinone (**8**) [generated using Et_3N and $Sn(OTf)_2$] was reacted with aldehyde (**9**) in the presence of TMEDA to afford an 80% yield of the aldol products (**10**, **11**, and **12**) in a 12:3:1 ratio. The aldol products (**10**, **11**, and **12**) were separated by flash chromatography and the 2′,3′-*anti* stereochemistry of the major product (**10**)[12] was supported by the magnitude of the 2′,3′-vicinal coupling constant ($J_{2',3'}$ 7.7 Hz) which was similar to that observed in analogous aldol products.[10,13] Furthermore the 3′,5′-*syn* stereochemistry of aldol adduct (**10**) was confirmed by ^{13}C NMR analysis[14] of the acetonide derivative (**15**) which was formed after removal of the chiral auxiliary (Figure 1). The stereochemistry of the minor aldol products (**11** and **12**) was established in a similar manner.

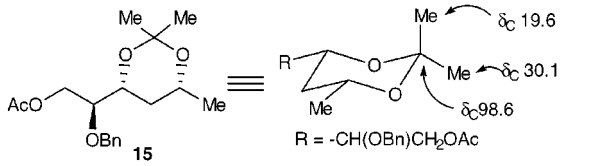


Figure 1.

Reductive removal of the chiral auxiliary from the triethylsilyl ether (**13**) of major aldol adduct (**10**) afforded alcohol (**14**) which underwent oxidation to aldehyde (**6**) using TPAP/NMO without epimerization.

Union of aldehyde (**6**) to a naphthalene fragment with the oxygenation pattern required for assembly of naphthol (**5**), initially focused on the use of the organometallic reagents derived from 3-bromo-1,4,5-trimethoxynaphthalene. This approach resulted in substantial quantities of 1,4,5-trimethoxynaphthalene being recovered from the reaction together with elimination of the β-triethylsilyloxy group from the aldehyde. The three oxygenated substituents on the naphthalene ring resulted in a marked increase in the basic character of the naphthyl anion[15] such that protonation by the aldehyde was occurring.

In light of the difficulties experienced with the above approach, we next decided to effect C-arylation of aldehyde (**6**) using a titanium naphtholate generated from naphthol (**16**). This strategy was based on work by Bigi et al.[16] and Casiraghi et al.,[17] who have effected regiospecific ortho-arylation of α-alkoxy and α-amino carbonyl compounds.

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(9) Mori, K.; Maemoto, S. *Liebigs Ann. Chem.* **1987**, 863.
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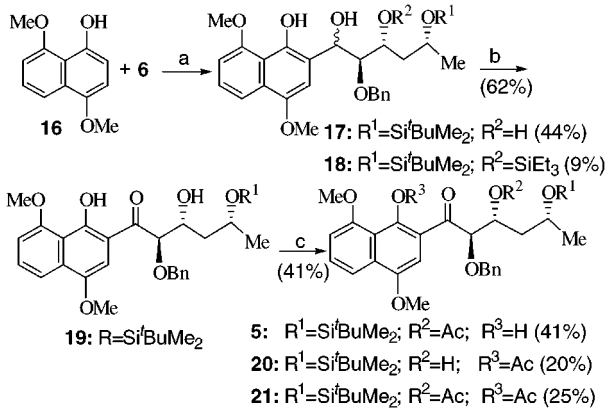
(11) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961.

(12) Compound **10** was obtained as a colorless oil. R_f: 0.56 (7:3 light petroleum−ethyl acetate). Found: C, 66.0; H, 7.4; N, 2.6%. $C_{29}H_{41}NO_6Si$ requires C, 66.0; H, 7.8; N, 2.65%. $[\alpha]_D$: −56.11 (*c* 1.788, $CHCl_3$). υ_{max} (film), cm^{-1}: 3589−3280 (m, OH), 1784 (s, O*C*=*O*N), 1703 (s, N*C*=*O*C), 1389 (m, C−N), and 1105 (m, C−O). δ_H (200 MHz, $CDCl_3$): 0.08 (6H, s, $SiMe_2$), 0.86 (9H, s, Bu^t), 1.18 (3H, d, $J_{6',5'}$ 6.2 Hz, H6′), 1.67 (1H, ddd, J_{gem} 14.3, $J_{4'A,3'}$ 9.7, and $J_{4'A,5'}$ 9.7 Hz, H4′^{A}), 1.94 (1H, ddd, J_{gem} 14.3, $J_{4'B,3'}$ 3.8 or 1.6, and $J_{4'B,5'}$ 1.6 or 3.8 Hz, H4′^{B}), 2.60 (1H, dd, J_{gem} 13.6 and *J* 9.9 Hz, CHC*H*^{A}Ph), 3.15 (1H, dd, J_{gem} 13.6 and *J* 3.3 Hz, CHC*H*^{B}Ph), 3.54 (1H, d, *J* 2.2 Hz, OH), 3.94−4.01 (1H, m, H3′), 4.01−4.17 (3H, m, H5, H5′), 4.53−4.69 (1H, m, H4), 4.61 (2H, s, OCH_2Ph), 5.31 (1H, d, $J_{2',3'}$ 7.7 Hz, H2′), and 7.17−7.41 (10H, m, Ph). δ_C (50 MHz, $CDCl_3$): −5.0, −4.2 (CH_3, $SiMe_2$), 17.6 (quat., *C*Me_3), 24.2 (CH_3, C6′), 25.6 (CH_3, C*Me*$_3$), 37.7 (CH_2, $CHCH_2Ph$), 42.2 (CH_2, C4′), 55.2 (CH, C4), 66.2 (CH_2, C5), 69.6 (CH, C5′), 72.6 (CH, C3′), 72.8 (CH_2, OCH_2Ph), 78.8 (CH, C2′), 127.0, 127.8, 128.1, 128.2, 128.6, 129.2 [CH, 2 × Ph, 135.1 (quat., $CHCH_2$*Ph*), 137.1 (quat., OCH_2*Ph*), 153.3 (quat., C2), and 172.1 (quat., C1′). *m*/*z* (LSIMS, NBA matrix): 528 (MH^+, 18%).
(13) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem Soc.* **1992**, *114*, 9434.
(14) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.
(15) Jung, M. E.; Hagenah, J. A. *J. Org. Chem.* **1987**, *52*, 1889.
(16) (a) Bigi, F; Casnati, G.; Sartori, G.; Araldi, G. *Gazz. Chim. Ital.* **1990**, *120*, 413. (b) Bigi, F.; Casnati, G.; Sartori, G.; Araldi, G.; Bocelli, G. *Tetrahedron Lett.* **1989**, *30*, 1121. (c) Bigi, F.; Casnati, G.; Sartori, G.; Dalprato, C.; Bortolini, R. *Tetrahedron Asymmetry* **1990**, *1*, 861.

In the present work the desired benzylic alcohols (**17** and **18**) were prepared in moderate yield by addition of the titanium naphtholate, generated from naphthol (**16**) and $TiCl_3(O^iPr)$, to aldehyde (**6**) (Scheme 2). Precise reaction

Scheme 2



a. $TiCl_3(O^iPr)$, CH_2Cl_2, 0°C, 9 min. b. MnO_2, CH_2Cl_2. c. Ac_2O, Et_3N.

conditions were developed for this step to minimize formation of an unwanted biarylmethane byproduct.[18]

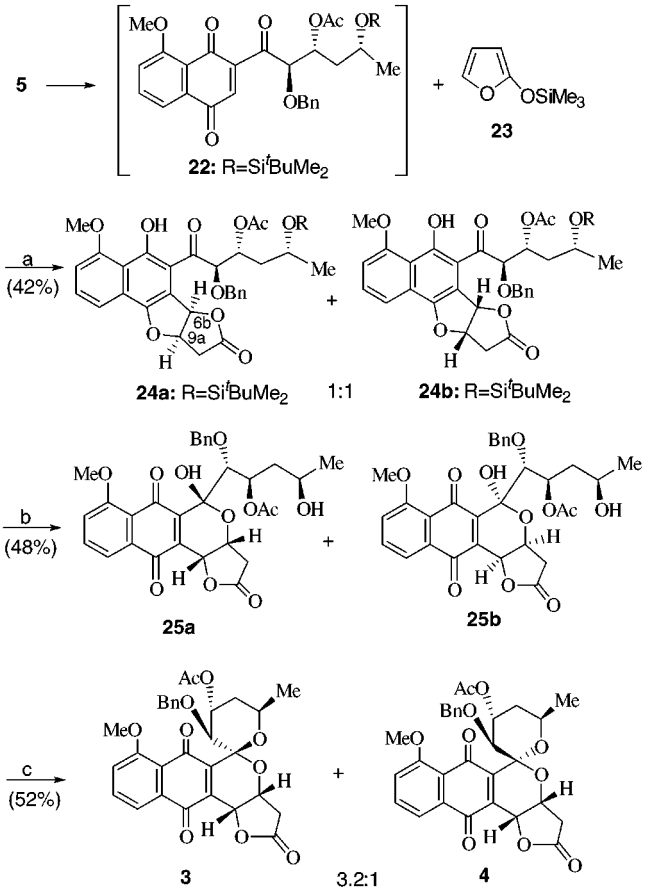
With alcohol (**17**) in hand, oxidation with manganese dioxide provided ketone (**19**) which afforded acetates (**5** and **20**) and diacetate (**21**) upon treatment with Ac_2O and Et_3N. Naphthyl acetate (**20**) isomerized to the desired alkyl acetate upon treatment with guanidine in ethanol.

The key naphthol (**5**) underwent oxidation with CAN to the sensitive naphthoquinone (**22**) which was treated directly with 2-[(trimethylsilyl)oxy]furan (**23**) to afford furonaphthofuran (**24**) (Scheme 3). Characteristic doublets at δ 6.36 and δ 6.69 (both with $J_{6b,9a}$ 5.9 Hz) were assigned to the bridgehead proton H-6b of the individual adduct isomers, clearly establishing that furofuran annulation had taken place. However, the 1:1 ratio of these two doublets indicated that bulky benzyloxy group at C2′ on naphthoquinone (**22**) failed to influence any stereocontrol in the ensuing annulation.

Addition of excess CAN to the isomeric mixture of adducts (**24**) followed by immediate treatment with 5% HF effected oxidative rearrangement and deprotection of the *tert*-butyldimethylsilyl ether, affording lactol (**25**). The stereochemistry assigned to lactol (**25**) was established by analogy to related compounds[19] wherein the hydroxyl group at C-5 is axial and *syn* to the bridgehead proton H-3b. A more detailed assignment of stereochemistry as either isomer **25a** or **25b** was not made. In any event, the final cyclization to a spiroacetal allowed a more detailed analysis of the stereochemistry.

Finally treatment of lactol (**25**) with a catalytic quantity of camphorsulfonic acid in dichloromethane effected spiro-

Scheme 3



a. CAN, CH_3CN, H_2O then **23**. b. CAN, CH_3CN, H_2O then 5% HF. c. CSA, CH_2Cl_2.

cyclization to a 3.2:1 mixture of spiroacetals (**3**) and (**4**) in 52% yield.[20] The magnitude of the vicinal coupling constant, $J_{3',4'}$ 9.8 Hz, in both isomers clearly established that the benzyloxy and acetate groups were diequatorial. An nOe effect between H-4′ and 6′-Me was also observed in both spiroacetals (**3** and **4**) (Figure 2).

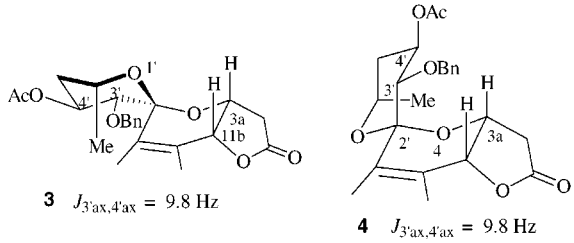


Figure 2.

The stereochemistry obtained for spiroacetals (**3** and **4**) can be rationalized via epimerization at C-3′ which leads to isomers in which the two bulky substituents at C-3′ and C-4′ can adopt more favorable equatorial positions. Assignment

(17) (a) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919. (b) Cornia, M.; Casiraghi, G. *Tetrahedron* **1989**, *45*, 2869. (c) Casiraghi, G.; Bigi, F.; Casnati, G.; Sartori, G.; Soncini, P.; Fava, G. G.; Belichi, M. F. *J. Org. Chem.* **1988**, *53*, 1799.

(18) Brimble, M. A.; Oppen, E. *Synth. Commun.* **1997**, *27*, 989.

(19) Brimble, M. A.; Duncalf, L. J.; Phythian, S. J. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1399.

of the stereochemistry at the spirocenter is mainly made on the basis that the bridgehead proton H-11b of the major isomer (**3**) is *syn* to O-1′ and is deshielded compared to the same proton in the minor isomer (**4**). H-3′ is also more deshielded in the minor isomer (**4**) due to the BnOC−H bond being antiperiplanar to the C2′-O4 bond. Efforts to prevent epimerization at C3′ in the spirocyclization step were unsuccessful.

In summary, a synthesis of pyranonaphthoquinone-spiroacetals (**3** and **4**) which are closely related to griseusin A (**1**) and B (**2**) has been presented. The epimerization observed in the final spirocyclization step demonstrates that subtle stereoelectronic effects provide the driving force for the stereochemistry observed in the final spiroacetals.

Acknowledgment. This work was supported by an Australian Research Council Small Grant and The University of Sydney.

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(20) Spiroacetals **3** and **4** were isolated as a 3.2:1 mixture of stereoisomers as an oil. Found: M^+H, 549.1747; $C_{30}H_{28}O_{10}$ requires M^+H, 549.1761. δ_H (400 MHz, $CDCl_3$): 1.37* (0.7H, d, $J_{5',4'}$ 5.8 Hz, Me), 1.42 (2.3H, d, $J_{5',4'}$ 6.1 Hz, Me), 2.00, 2.03* (3H, s, $COCH_3$), 2.00−2.03 (1H, m, H5′^{A}), 2.10−2.13 (1H, m, H5′^{B}), 2.68* (0.24H, d, J_{gem} 17.6 Hz, H3^A), 2.74 (0.76H d, J_{gem} 17.6 Hz, H3^A), 3.00 (1H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 4.9 Hz, H3^B), 3.47 (0.76H, d, $J_{3',4'}$ 9.8 Hz, H3′), 3.52* (0.24H, d, $J_{3',4'}$ 9.8 Hz, H3′), 3.98, 4.00* (3H, s, OMe), 4.21−4.28 (1H, m, H4′), 4.67 (0.76H, d, J_{gem} 11.3 Hz, OC*H*^{A}Ph), 4.68−4.70 (0.76H, m, H3a), 4.74* (0.24H, d, J_{gem} 11.1 Hz, OC*H*^{A}Ph), 4.92 (0.76H, d, J_{gem} 11.3 Hz, OC*H*^{B}Ph), 4.94−4.96* (0.24H, m, H3a), 4.95* (0.24H, d, J_{gem} 11.1 Hz, OC*H*^{B}Ph), 5.20−5.25 (1H, m, H6′), 5.27* (0.24H, d, $J_{11b,3a}$ 2.8 Hz, H11b), 5.31 (0.76H, d, $J_{11b,3a}$ 2.8 Hz, H11b), 7.30−7.36 (6H, m, H8, Ph), 7.47 (1H, t, $J_{9,8}$ 8.0 and $J_{9,10}$ 8.0 Hz, H9), and 7.75 (1H, d, $J_{10,9}$ 8.0 Hz, H10). The asterisks (*) denote resonances for the minor isomer **4**.