A Short Synthesis of Deoxyfrenolicin

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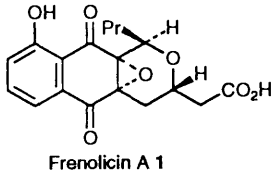
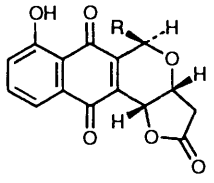
Oxidative rearrangement of furo[3,2-*b*]naphtho[2,1-*d*]furan **8** using CAN provided an efficient route to the hemiacetal **9** which has a three-ring system in common with that in the natural products frenolicin A **1**, frenolicin B **2** and deoxyfrenolicin **3**. Attempted reduction of the hemiacetal **9** to the *cis*-lactone **11** using triethylsilane and trifluoroacetic acid was unsuccessful, however, hydrogenation of the hemiacetal **9** not only effected reduction of the hemiacetal group to a cyclic ether but also hydrogenolysis of the γ-lactone to the ring-opened carboxylic acid which was conveniently characterised as its methyl ester **13**. Deprotection of the methyl ether **13** to the naphthol **15** using boron tribromide also effected *cis-trans* epimerisation at C-1 thus completing a synthesis of deoxyfrenolicin **3** upon hydrolysis of the methyl ester to the carboxylic acid.

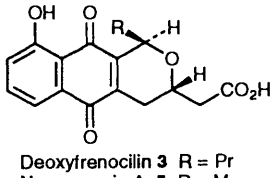
Frenolicins A **1**, B **2** and deoxyfrenolicin **3** are members of the pyranonaphthoquinone family of antibiotics which were isolated from *Streptomyces fradiae*.[1,2] These natural products are closely related to kalafungin[3] **4** and nanaomycin A **5**[4] and are antimicrobial agents[5] which it has been proposed act as bisalkylating agents upon bioreduction, in a similar fashion to the anticancer drug mitomycin.[6]



Frenolicin A **1**



Frenolicin B **2** R = Pr
Kalafungin **4** R = Me

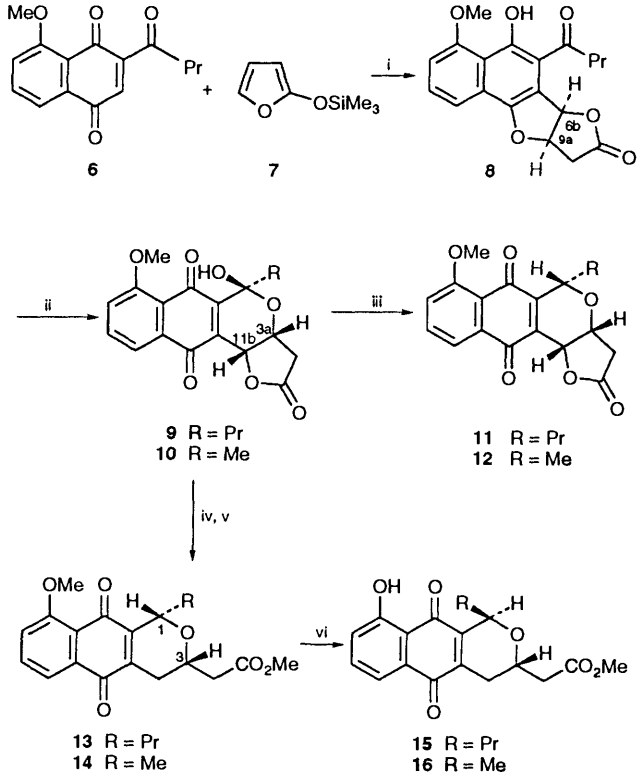


Deoxyfrenocilin **3** R = Pr
Nanaomycin A **5** R = Me

Previous syntheses of the frenolicins have utilised a regioselective alkylation of alkanoyl quinones with allylsilanes,[7] a Diels–Alder cycloadduct of juglone and acetoxybutadiene,[8] a thermal rearrangement of an alkynyl-substituted benzocyclobutenone,[9] a tandem Diels–Alder/retro-Claisen reaction,[10] use of organochromium and organopalladium intermediates[11] and, more recently, a highly regioselective Diels–Alder reaction of a pyranobenzoquinone with 1-(trimethylsilyloxy)butadiene.[12]

We have previously efficiently synthesised[13] a C-5 epimer of kalafungin in which the key step involved oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan which, in turn, was prepared *via* the addition of 2-trimethylsilyloxyfuran to a naphthoquinone. We now report a synthesis of the frenolicin series of antibiotics where we have now extended this methodology to the synthesis of the correct epimer at C-5.

Initial attention focussed on the synthesis of 5-*epi*-7-*O*-methylfrenolicin B **11** (Scheme 1) following our earlier synthesis of 5-*epi*-7-*O*-methylkalafungin **12**. Our critical furofuran annulation required the preparation of the naphthoquinone **6** with the appropriate butanoyl substituent at C-2. This was prepared in six steps from 1,5-dihydroxynaphthalene essentially according to the method of Uno[7] *via* Fries rearrangement of 4-butyryloxy-1,5-dimethoxynaphthalene. The corresponding naphthol from which this latter ester is derived was, in turn, prepared from 1,5-dihydroxynaphthalene according to the method of Rapoport *et al.*[14]



Scheme 1 *Reagents and conditions:* i, MeCN, room temp., then MeOH; ii, cerium(IV) ammonium nitrate (2.0 equiv.), MeCN, H_2O, room temp.; iii, Et_3SiH, CF_3CO_2H, −78 °C to room temp.; iv, H_2, Pd/C, EtOAc; v, CH_2N_2, Et_2O; vi, BBr_3, CH_2Cl_2, −78 to 0 °C.

With the required naphthoquinone in hand, attention turned to the furofuran annulation. Thus, addition of 2-trimethylsilyloxyfuran **7** (2 equiv.) to naphthoquinone **6** in acetonitrile afforded the desired adduct **8** in 60% yield. The bridgehead protons 9a-H and 6b-H resonating as a doublet at δ_H 5.55 and

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a doublet at δ_H 6.45, respectively, were characteristic of the furo[3,2-*b*]naphtho[2,1-*d*]furan system due to their similar chemical shifts and coupling constants observed in the kalafungin work.[13]

Subsequent rearrangement of the adduct **8** to furo[3,2-*b*]-naphtho[2,3-*d*]pyran **9** was then effected using ceric ammonium nitrate (CAN; 2 equiv.) in aqueous acetonitrile at room temperature in 75% yield. The product analysed correctly for $C_{19}H_{18}O_7$ and the mass spectrum exhibited a base peak at *m/z* 315 corresponding to M − C_3H_7 which is consistent with a propyl substituted hemiacetal. The IR spectrum exhibited a broad absorbance at 3435 cm^{-1} due to the hydroxy group, and two strong bonds at 1778 and 1663 cm^{-1} assigned to the carbonyl group of the γ-lactone and quinone, respectively. The ^1H NMR spectrum showed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **8**. Thus, the doublet at δ_H 4.93 assigned to 3a-H and the doublet at δ_H 5.35 assigned to 11b-H were at positions similar to those reported for analogous furo[3,2-*b*]naphtho[2,1-*d*]pyrans.[13]

In order to prepare the natural product frenolicin B **2** reduction of the hemiacetal **9** to a cyclic ether was required. In the natural product, frenolicin B **2** the protons at C-5 and C-3a are *trans* to each other; similarly, in frenolicin A **1** and deoxyfrenolicin **3** the analogous protons at C-1 and C-3 are also *trans* to each other. In our previous synthesis of 5-*epi*-7-*O*-methylkalafungin **12**[13] the analogous hemiacetal **10** was reduced using triethylsilane and trifluoroacetic acid to the cyclic ether **12** (Scheme 1) in which the protons attached to C-5 and C-3a were *cis* to each other. No method was found to effect the conversion of the *cis*-isomers into the *trans*-isomers. This problem needed addressing in the present work.

Attempted reduction of the hemiacetal **9** to the cyclic ether **11** using triethylsilane and trifluoroacetic acid at −78 °C for 2 h afforded a less polar product by TLC. However, upon work-up, attempts to purify this product by flash chromatography led to rapid decomposition. Although the R_F of the compound together with the NMR data obtained from a crude sample suggested that the cyclic ether **11** had formed, it proved unsuitable for characterisation. The instability of the *cis*-lactone product **11** could be due to the fact that the methylene group of the γ-lactone is 1,3-*syn* to the propyl substituent at C-5 thereby causing unfavourable steric interactions. In the analogous C-5 methyl lactone **12**, a smaller methyl group is 1,3-*syn* to the methylene group and the compound in this case is readily isolable and has been fully characterised.[13]

The instability of the *cis*-lactone **11** prompted the use of other methods to effect reduction of the hemiacetal group. Hydrogenation of the hemiacetal **9** in ethyl acetate over palladium on charcoal at room temperature afforded a more polar compound by TLC. Attempts to purify this product proved difficult owing to the low recovery of the material from flash silica. Since the polarity of the product suggested the formation of a carboxylic acid, subsequent treatment with an ethereal solution of diazomethane facilitated purification by flash chromatography to afford the *cis*-methyl ester **13** in 71% yield. Thus, reduction of the hemiacetal group to a cyclic ether together with hydrogenolysis of the γ-lactone had clearly occurred.

It now remained to convert the *cis*-methyl ester **13** into the natural product deoxyfrenolicin **3**. Thus, deprotection of the methyl ether **13** to the corresponding naphthol using boron tribromide also effected epimerisation at C-1 resulting in formation of the *trans*-naphthol ester **15**. Finally, hydrolysis of the methyl ester using potassium hydroxide according to the method of Semmelhack *et al.*[11] afforded the acid deoxyfrenolicin **3**.

The present synthesis of deoxyfrenolicin **3** also constitutes a formal synthesis of frenolicin A **1** and frenolicin B **2** in that deoxyfrenolicin **3** has been converted into frenolicin A **1** by Ichihara *et al.*[8] using *tert*-butyl hydroperoxide and triton B in dioxane–ethanol. In addition, these same authors heated deoxyfrenolicin **3** in chloroform to effect conversion into frenolicin B **2**.

The hydrogenation described herein was also used to prepare nanoamycin A **5** from the hemiacetal **10** which we had previously prepared.[13] Thus, treatment of the hemiacetal **10** with hydrogen over palladium on charcoal followed by esterification using diazomethane afforded the *cis*-methyl ester **14**. Deprotection of the methyl ether **14** and epimerisation at C-1 with boron tribromide afforded the *trans*-ester **16** which has been hydrolysed to the *trans*-acid **5**, nanaomycin A, by Uno[7] using potassium hydroxide.

The major difference in our approach to the frenolicins as opposed to the earlier kalafungin work is the use of palladium on charcoal to effect reduction of the hemiacetal **9** with concomitant opening of the γ-lactone ring. The ring-opened *cis*-methyl ester **13** was then easily epimerised to the more thermodynamically stable *trans*-ester upon treatment with boron tribromide to effect deprotection of the methyl ether. Thus, whereas attempts[13] to epimerise the *cis*-lactone **12** to the *trans*-lactone were unsuccessful it appears that initial ring opening of the γ-lactone apparently facilitates the *cis–trans* epimerisation.

Experimental

M.p.s. were determined on a Köfler hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bio-Rad FTS 40V spectrophotometer as Nujol mulls or thin films between sodium chloride discs. ^1H NMR spectra were recorded at 270 MHz in $CDCl_3$ using tetramethylsilane as internal standard on a JEOL GX270 spectrometer. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL GX270 spectrometer. All *J* values are given in Hz. Mass spectra and accurate mass measurements were recorded on a VG70-250S double focussing magnetic sector mass spectrometer with an ionisation potential of 70 eV. Microanalyses were performed by the microanalytical laboratory, University of Otago. Column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh) with the solvents described.

3-Butyryl-5-methoxy-1,4-naphthoquinone **6**.—3-Butyryl-5-methoxy-1,4-naphthoquinone **6** was prepared from 3-butyryl-1,5-dimethoxy-4-naphthol using ceric ammonium nitrate according to the method of Uno[7] as yellow needles, m.p. 101–102 °C (lit.,[7] m.p. 100–102 °C).

cis-*6b,9a-Dihydro-5-hydroxy-4-methoxy-6-(1-oxobutyl)furo*-[3,2-b]*naphtho*[2,1-d]*furan-8(9H)-one* **8**.—A solution of 2-trimethylsilyloxyfuran **7** (133 mg, 0.85 mmol) in acetonitrile (5 cm^3) was added dropwise to an ice-cooled solution of the naphthoquinone **6** (120 mg, 0.47 mmol) in acetonitrile (40 cm^3) under an atmosphere of nitrogen. Methanol (5 cm^3) was added to the reaction mixture which was then stirred overnight. After this it was evaporated under reduced pressure to give a crude solid which was purified by flash chromatography using hexane–ethyl acetate (2:1) as eluent. Trituration with ether afforded the *title compound* **8** (95 mg, 60%) as colourless needles, m.p. 188–190 °C (Found: C, 66.4; H, 5.1. $C_{19}H_{19}O_6$ requires C, 66.7; H, 5.3%; δ_H[270 MHz; $(CD_3)_2SO$], 0.94 (3 H, t, *J* 7.3, CH_3), 1.67 (2 H, sext., *J* 7.3, CH_2), 2.96 (2 H, d, J_{gem} 19.1, 9-H), 3.06 (2 H, t, *J* 7.3, CH_2CO), 3.30 (1 H, dd, J_{gem} 19.1, $J_{9a,9'}$ 6.6, 9a-H'), 4.08 (3 H, s, OMe), 5.55 (1 H, dd, $J_{9a,6b}$ 5.9, $J_{9a,9'}$ 6.3, 9a-H), 6.45 (1 H, d, $J_{6b,9a}$ 6.3, 6b-H), 7.20, 7.47 (1 H,

d, *J* 8.1, 1-H, 3-H), 7.62 (1 H, t, *J* 8.1, 2-H) and 10.8 (1 H, s, OH); δ_C[67.8 MHz; $(CD_3)_2SO$] 13.7 (q, C-4'), 17.4 (t, C-3'), 35.1 (t, C-9), 45.3 (t, C-2'), 56.5 (q, OMe), 81.9 (d, C-9a), 84.3 (d, C-6b), 108.1, 114.6, (d, C-1, C-3), 115.4, 115.8, 123.6 (s, C-4a, C-6a, C-10b), 129.7 (d, C-2), 149.5 (s, C-10a), 151.4 (s, C-4), 157.3 (s, C-5), 175.2 (s, C-8) and 202.4 (s, C-1'); *m/z* 342 (M^+, 78%) and 299 (M − $CH_2CH_2CH_3$, 100).

3,3*a*,5,11*b*-*Tetrahydro*-5-*hydroxy*-7-*methoxy*-5-*propyl*-2H-*furo*[3,2-b]*naphtho*[2,3-d]*pyran*-2,6,11-*trione* **9**.—To a rapidly stirred solution of compound **8** (156 mg, 0.46 mmol) in acetonitrile (40 cm^3) was added a solution of ceric ammonium nitrate (0.5 g, 0.91 mmol) in water (5 cm^3). The reaction mixture was poured into dichloromethane (150 cm^3) and washed with water (2 × 80 cm^3). The organic layer was then separated, dried (Na_2SO_4), filtered through Florisil, and evaporated under reduced pressure to afford the *title compound* **9** (123 mg, 75%) as yellow needles, m.p. 173–175 °C (decomp.) (Found: C, 63.6; H, 5.2. $C_{19}H_{18}O_7$ required C, 63.7; H, 5.1%); ν_{max}(Nujol)/cm^{-1} 3435 (OH), 1788 (C=O, lactone) and 1663 (C=O, quinone); δ_H(270 MHz; [$^2H_6$]acetone) 0.82 (3 H, t, *J* 7.5, CH_3), 0.96–1.22 (2 H, m, CH_2), 1.78–2.00 (2 H, m, CH_2COH), 2.50 (1 H, d, J_{gem} 17.2, 3-H'), 4.00 (3 H, s, OMe), 4.93 (1 H, dd, $J_{3a,3}$ 4.9 and $J_{3a,11b}$ 3.0, 3a-H), 5.35 (1 H, d, $J_{11b,3a}$ 2.6, 11b-H), 7.58 (1 H, dd, *J* 7.5, 11, 8-H or 10-H), 7.70 (1 H, dd, *J* 6.3, 1.1, 10-H or 8-H), and 7.83 (1 H, t, *J* 8.2, 9-H); *m/z* 358 (M^+, 7%), 340 (M − H_2O, 28) and 315 (M − C_3H_7, 100).

cis-*Methyl* [9-*Methoxy*-1-*propyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-*yl*]*acetate* **13**.—To a solution of compound **9** (70 mg, 0.2 mmol) in ethyl acetate (30 cm^3) was added palladium on charcoal and the reaction mixture was stirred for 1 h under an atmosphere of hydrogen. The reaction mixture was then filtered through Celite and evaporated under reduced pressure to give a yellow solid to which ethyl acetate (20 cm^3) and ethereal diazomethane (1 cm^3) were added with stirring. After evaporation of the mixture under reduced pressure, the crude product was purified by flash chromatography using hexane–ethyl acetate (9:1) as eluent to yield the *title compound* **13** (50 mg, 71%) as a red–brown solid, m.p. 143–145 °C (lit.,[11] m.p. 146–147 °C); δ_H(270 MHz, $CDCl_3$) 0.87 (3 H, t, *J* 7.1, CH_2CH_3), 1.26–1.80 (4 H, m, 2 × CH_2), 2.22 (1 H, ddd, *J* 18, 10, 1.5, 4-pseudoaxial-H), 2.51–2.84 (2 H, m, CH_2CO_2Me and 4-pseudoequatorial H), 3.73 (3 H, s, CO_2Me), 3.99 (3 H, s, OMe), 3.94–4.04 (1 H, m, 3-H), 4.70–4.86 (1 H, m, 1-H), 7.26–7.28 (1 H, m, ArH) and 7.64–7.74 (2 H, m, ArH); *m/z* 358 (M^+, 100%), 315 (M − C_3H_7, 66) and 285 (M − $C_4H_{10}O$, 56). The ^1H NMR data were in agreement with those of the literature.[11]

trans-*Methyl* [9-*Hydroxy*-1-*propyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-*yl*]*acetate* **15**.—To a solution of the methyl ether **13** (46 mg, 0.13 mmol) in dichloromethane (9 cm^3) at −78 °C under argon was added a solution of boron tribromide (321 mg, 1.3 mmol) in dichloromethane (7 cm^3) dropwise over 5 min. The resulting dark red solution was kept at −78 °C for 5 min and then warmed to 0 °C. After 10 min at 0 °C, the orange solution was treated with 5% aqueous sodium hydrogen carbonate (5 cm^3). The yellow aqueous phase was extracted with chloroform (3 × 20 cm^3) until it was nearly colourless. The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a black semi-solid. Flash chromatography of this using hexane–ethyl acetate (4:1) as eluent afforded the *title compound* **15** (38 mg, 86%) as yellow needles, m.p. 136–137 °C (lit.,[11] m.p. 138–138.5 °C); δ_H(270 MHz, $CDCl_3$) 1.00 (3 H, t, *J* 7.1, CH_2CH_3), 1.51–1.80 (4 H, m, 2 × CH_2), 2.28 (1 H, ddd, *J* 10.0, 9.0, 2.5, 4-pseudoaxial H), 2.65 (2 H, d, *J* 6.1, CH_2CO_2Me), 2.82 (1 H, dd, *J* 3.4, 18, 4-pseudoequatorial H), 3.75 (3 H, s, CO_23H_3), 4.18–4.28 (1 H, m, 3-H), 4.80–4.85 (1 H, m, 1-H), 7.23–7.26 (1 H, m, ArH) and 7.57–7.64 (2 H, m, ArH); *m/z* 344 (M^+, 20%), 312 (M − CH_3OH, 10), 301 (M − C_3H_7, 40) and 241 (M − $C_{14}H_9O_4$, 100). The ^1H NMR data were in agreement with those of the literature.[11]

cis-*Methyl* [9-*Methoxy*-1-*methyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-yl]*acetate* **14**.—The title compound **14** was prepared from the hemiacetal **10**[13] (60 mg, 0.19 mmol) by the procedure described for compound **13** as yellow needles (34 mg, 55%), m.p. 110.5–112 °C; δ_H(270 MHz, $CDCl_3$) 1.52 (3 H, d, *J* 6.6, CH_3), 2.28 (1 H, ddd, *J* 18.0, 10.3, 3.7, 4-pseudoaxial H), 2.61 (1 H, dd, *J* 15.7, 3, $CH_ACH_BCO_2Me$), 2.72 (1 H, dd, *J* 15.7, 7.5, $CH_ACH_BCO_2Me$), 2.83 (1 H, dt, *J* 18.0, 2.6 Hz, 4-pseudoequatorial H), 3.73 (3 H, s, CO_2Me), 3.91–3.98 (1 H, m, 3-H), 4.00 (3 H, s, OMe), 4.86–4.90 (1 H, m, 1-H), 7.28 (1 H, d, *J* 8, 6-H or 8-H), 7.65 (1 H, t, *J* 8 Hz, 7-H) and 7.74 (1 H, dd, *J* 8.0, 1.1 Hz, 8-H or 6-H); δ_C(67.8 MHz, $CDCl_3$) 20.6 (q, C-1), 27.9 (t, C-4), 40.3 (q, CH_2CO_2Me), 51.9 (q, CO_2Me), 56.4 (q, OMe), 69.2, 70.5 (d, C-2, C-3), 117.8, 119.0 (d, C-6, C-8), 119.1, 139.2, 143.9, 148.6 (s, 9a, 10a, 4a, 5a), 134.7 (d, C-7), 159.4 (s, C-9), 171.1 (s, CO_2Me) and 183.5, 183.8 (s, C-5, C-10); *m/z* 330 (M^+, 80%), 315 (M − CH_3, 8), 298 (M − CH_3OH, 12), 270 (M − CO_2CH_3-H) and 257 (M − $CH_2CO_2CH_3$, 100). The ^1H NMR data were in agreement with those of the literature.[11]

trans-*Methyl* [9-*Hydroxy*-1-*methyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3*yl*]*acetate* **16**.—The title compound **16** was prepared from methyl ether **14** (34 mg, 0.1 mmol) by the procedure described for compound **15** as yellow needles (29 mg, 89%); m.p. 131–133 °C (lit.,[7] m.p. 133–135 °C); δ_H(270 MHz, $CDCl_3$) 1.58 (3 H, d, *J* 6.6, CH_3), 2.34 (1 H, ddd, *J* 19.1, 10.6, 1.8, 4-pseudoequatorial H), 2.66 (2 H, d, *J* 6.4, CH_2CO_2), 2.82 (1 H, dd, *J* 19.1, 3.3, 4-pseudoequatorial H), 3.75 (3 H, s, CO_2Me), 4.30–4.36 (1 H, m, 3-H), 4.99 (1 H, q, *J* 6.6, 1-H), 7.22–7.27 (1 H, m, 6-H or 8-H), 7.52–7.63 (1 H, m, 7-H) and 7.87–7.90 (1 H, m, 8-H or 6-H); *m/z* 316 (M^+, 66%), 298 (M − H_2O, 17), 284 (M − CH_3OH, 43) and 242 (M − $C_3H_6O_2$, 100). The ^1H NMR data were in agreement with those of the literature.[7,15]

Acknowledgements

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