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Synthesis of a Novel Cage Compound via Oxidative Rearrangement of a Dihydronaphthofuran

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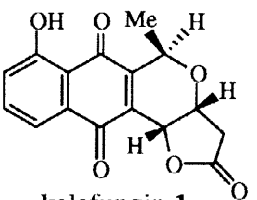
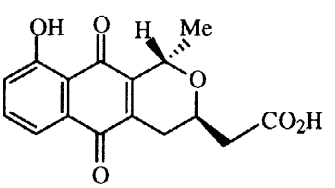
Abstract: Oxidative rearrangement of dihydronaphthofuran **5** with aqueous ceric ammonium nitrate afforded the cage compound **7** which decomposed to diol **8** upon standing at room temperature. An X-ray structure obtained for diol **8** confirmed the formation of this novel cage structure.

INTRODUCTION

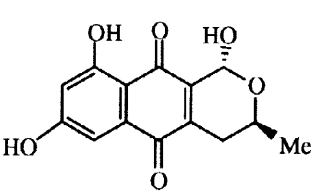
One of our synthetic programs has been directed towards the synthesis of the pyranonaphthoquinone family of antibiotics such as kalafungin **1**[1] and nanaomycin A **2**[2] which have been proposed to act as bioreductive alkylating agents.[3] The key step in our synthetic approach to the basic pyranonaphthoquinone ring system involved the oxidative rearrangement of a furonaphthofuran to a furonaphthopyran.[4] Recent work has been directed towards the synthesis of the human rhinovirus 3C-protease inhibitor thysanone **3**[5] wherein it was envisaged that a similar oxidative rearrangement of dihydronaphthofuran **5** would lead to formation of the thysanone skeleton **6** (Scheme 1). Our synthetic endeavours towards the thysanone skeleton following this strategy are reported herein.



kalafungin **1**



nanaomycin A **2**



thysanone **3**

RESULTS AND DISCUSSION

Dihydronaphthofuran **5** was readily assembled by acid induced fragmentation of the Diels-Alder adduct **4**[6] obtained from addition of 2-formyl-1,4-naphthoquinone to 1-trimethylsilyloxy-1,3-butadiene. Treatment of dihydronaphthofuran **5** with aqueous ceric ammonium nitrate led to formation of the cage compound **7** in 72% yield. After standing in air for several hours the aldehyde proton was absent from the ^{1}H NMR spectrum,

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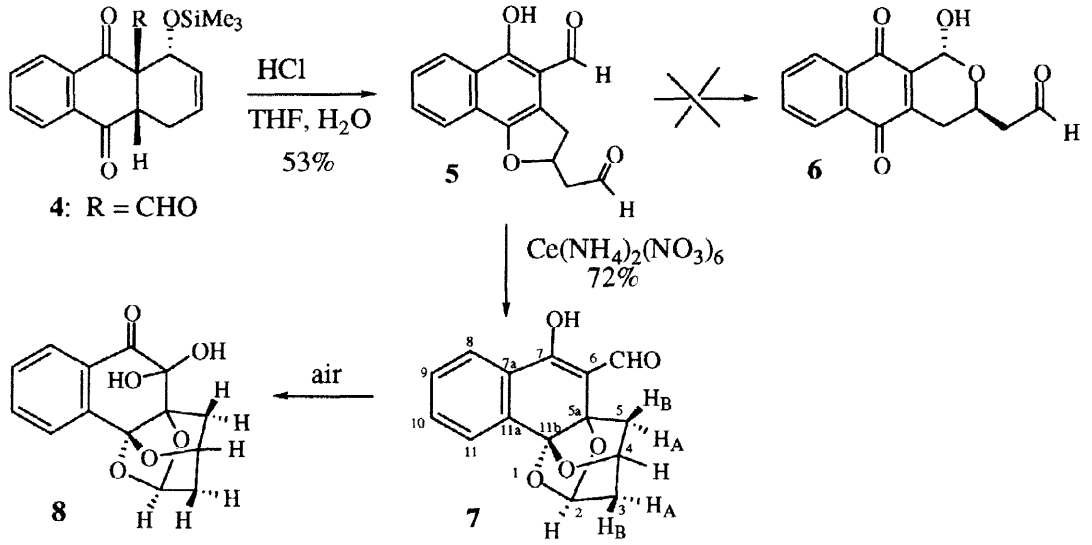
however, the material had the same R_f as **7** upon analysis by tlc. Fortunately, the decomposed material was crystalline and an X-ray structure (Figure 1) not only confirmed the presence of the cage structure but also that the aldehyde group and the potential α-hydrogen had been replaced by hydroxy groups in *gem*-diol **8**.

The formation of cage structure **7** proceeds *via* an intramolecular spiroacetalisation followed by an intramolecular conjugate addition (Scheme 2). The synthesis of **7** represents the first example of this novel highly oxygenated ring system and offers the potential to synthesise other related cage structures based on this oxidative rearrangement.

The conversion of aldehyde **7** to diol **8** is also an interesting reaction and is presumed to proceed *via* autoxidation of the enol **7** as outlined (Scheme 3). The ease with which this auto-oxidation proceeds is noteworthy. Examples of autoxidation of simple enols have been documented in the literature[7] and the intermediacy of four-membered cyclic peroxy hemiacetals in the cleavage step has also been noted.[8] Presumably the hydrate is formed at C-6 due to this carbonyl group being more electrophilic than the carbonyl at C-7.



Scheme 1

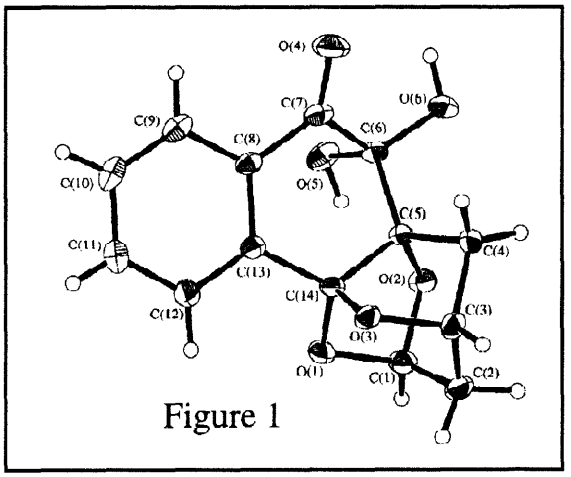
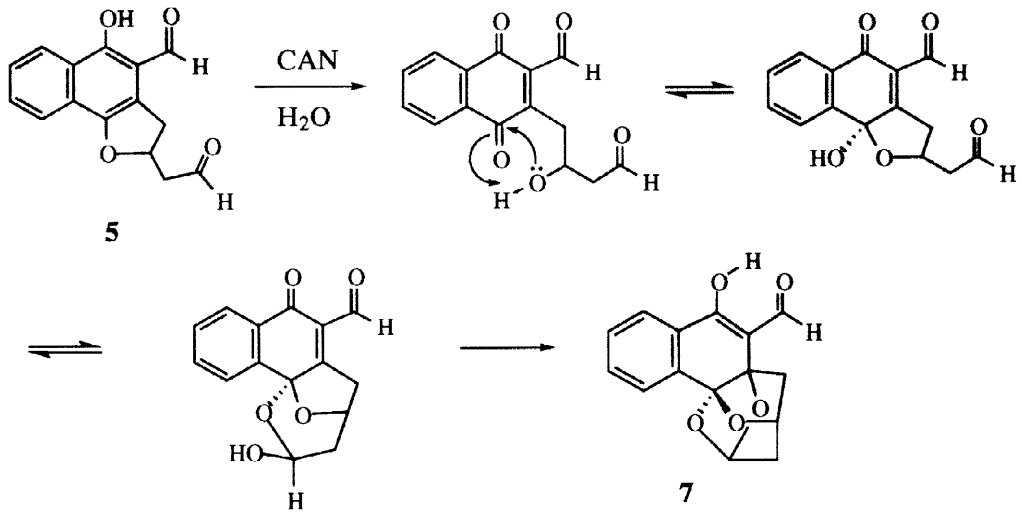
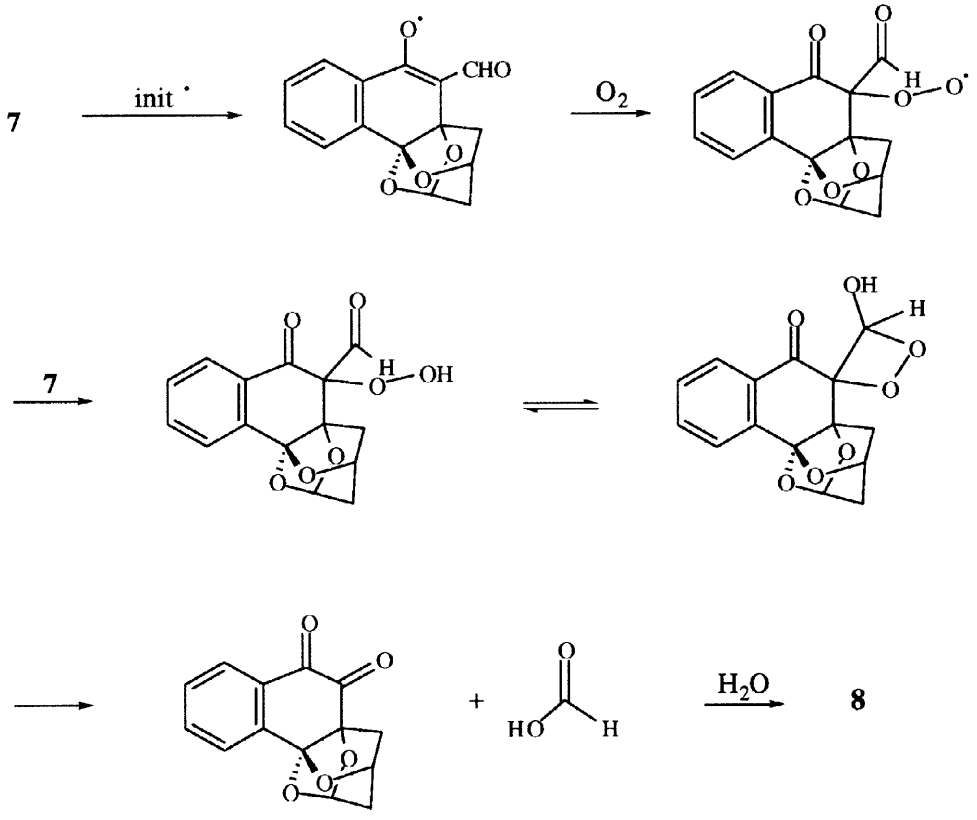


Figure 1



Scheme 2



Scheme 3

EXPERIMENTAL

General Details

Melting points were determined using a Reichert Kofler block and are uncorrected. Infrared absorption spectra were recorded using Perkin Elmer 1600 Series FTIR spectrometer as Nujol mulls or thin films between sodium chloride plates. ^{1}H NMR spectra were obtained using either a Bruker AM 400 or Bruker AC 200 spectrometer. ^{13}C NMR data were recorded using a Bruker AM 400 or Bruker AC 200 spectrometer. ^{13}C NMR spectra were interpreted with the aid of DEPT 135 and DEPT 90 experiments. Low resolution mass spectra were recorded using a VG 70-SE spectrometer operating at an accelerating voltage of 70eV. High resolution mass spectra were recorded at a nominal resolution of 5000 or 10000 as appropriate. Flash chromatography was performed using Merck Kieselgel 60 (230-400 Mesh) with the indicated solvents.

4-Formyl-5-hydroxy-2-(2'-oxoethyl)-2,3-dihydronaphtho[1,2-b]furan **5**

To a solution of the Diels-Alder adduct **4**[6] (0.30 g, 0.92 mmol) in 90% aqueous THF (10 mL) was added concentrated hydrochloric acid (1 mL) and the reaction mixture stirred at room temperature. After 20 min., water (50 mL) was added, the THF removed under reduced pressure and the aqueous layer extracted with chloroform (3 x 50 mL). The organic layer was then washed with water (3 x 20 mL), dried over magnesium sulfate and the solvent removed. The crude product was then purified by flash chromatography using hexane : ethyl acetate (9 : 1 then 2 : 1) as eluent to afford *title compound* **5** (0.117 g, 50%) as a tan solid, m.p. 50-52 °C; (Found: M$^+$, 256.0741. $C_{15}H_{12}O_4$ requires M$^+$, 256.0735); ν_{max} (NaCl plates) (cm^{-1}) 3036-3660 (OH), 1719 (C=O) and 1637 (C=O, *o*-hydroxyaryl aldehyde); δ_H (200 MHz; $CDCl_3$) 2.89 (1H, ddd, J_{gem} 17.4, $J_{1'A,2}$ 6.1 and $J_{1'A,2'}$ 0.8 Hz, 1'-H$_A$), 3.12 (1H, ddd, J_{gem} 17.4, $J_{1'B,2}$ 6.8 and $J_{1'B,2'}$ 1.7 Hz, 1'-H$_B$), 3.14 (1H, dd, J_{gem} 15.6, $J_{3A,2}$ 7.4 Hz, 3-H$_A$), 3.75 (1H, dd, J_{gem} 15.6, $J_{3B,2}$ 9.4 Hz, 3-H$_B$), 5.37-5.52 (1H, m, 2-H), 7.44-7.71 (2H, m, 7-H and 8-H), 7.80 (1H, d, $J_{8,9}$ 8.0 Hz, 9-H), 8.35 (1H, d, $J_{6,7}$ 8.2 Hz, 6-H), 9.92 (2H, bs, 2'-H and CHO), 12.45 (1H, bs, OH); δ_C (100 MHz; $CDCl_3$) 34.7 (CH_2, C-3), 49.8 (CH_2, C-1'), 78.2 (CH, C-2), 110.9 (quat., C-3a), 115.3 (quat., C-4), 121.5 (CH, C-6 or C-9), 124.7 (quat., C-5a or C-9a), 124.9 (CH, C-9 or C-6), 125.4 (quat., C-9a or C-5a), 126.1 (CH, C-7 or C-8), 130.5 (CH, C-8 or C-7), 147.0 (quat., C-9b), 157.9 (quat., C-5), 193.5 (quat., C-2'), 200.0 (CHO); *m/z* (%) 256 (M$^+$, 100), 213 (M-C_2H_3O, 65).

Preparation of 2,5a:4,11b-Diepoxy-6-formyl-7-hydroxy-2,3,4,5-tetrahydronaphth[1,2-b]oxepin **7** *and 2,5a:4,11b-Diepoxy-6,6-dihydroxy-2,3,4,5-tetrahydronaphth[1,2-b]oxepin-7(6H)-one* **8** *(cage compounds)*

To dihydronaphthofuran **5** (0.112 g, 0.44 mmol) in acetonitrile (50 mL) was added 10% aqueous ceric ammonium nitrate (0.48 g, 0.88 mmol) with stirring. After 20 min. the reaction mixture was poured into dichloromethane (30 mL) and water (30 mL). The organic layer was washed with water (3 x 30 mL) and filtered through florisil/magnesium sulfate. The solvent was removed under reduced pressure and the crude product purified by flash chromatography using hexane : ethyl acetate (2 : 1) as eluent to afford aldehyde **7** (0.086 g, 72%) as an orange solid, m.p. 96-98 °C; (Found: M$^+$, 272.0775. $C_{15}H_{12}O_5$ requires M$^+$, 272.0685) ν_{max} (film) (cm^{-1}) 3010-3600 (OH) and 1630-1660 (C=O); δ_H (400 MHz; $CDCl_3$) 1.75 (1H, ddd, J_{gem} 13.3, $J_{3A,4}$ 1.4 and $J_{3A,2}$ 1.4 Hz, 3-H$_A$), 2.09 (1H, ddd, J_{gem} 11.3, $J_{5B,4}$ 5.0, $J_{5B,3B}$ 1.8 Hz, 5-H$_B$), 2.27 (1H, dddd, J_{gem} 13.3, $J_{3B,4}$ 3.6, $J_{3B,5B}$ 1.8 Hz and $J_{3B,2}$ 1.8 Hz, 3-H$_B$), 2.85 (1H, d, J_{gem} 11.3, 5-H$_A$), 4.70-4.72 (1H, m, 4-H), 5.62 (1H, bs, 2-H), 7.56 (1H, ddd, $J_{10,9}$ 7.8, $J_{10,11}$ 7.8 and $J_{10,8}$ 1.4 Hz, 10-H), 7.67 (1H, ddd, $J_{9,10}$ 7.8, $J_{9,8}$ 7.4

and $J_{9,11}$ 1.5 Hz, 9-H), 7.88 (1H, dd, $J_{11,10}$ 7.8 and $J_{11,9}$ 1.5 Hz, 11-H), 8.11 (1H, dd, $J_{8,9}$ 7.4 and $J_{8,10}$ 1.4 Hz, 8-H), 9.40 (1H, s, CHO), 15.3 (1H, bs, OH); δ_C (100 MHz; $CDCl_3$) 33.0 (CH_2, C-5), 46.8 (CH_2, C-3), 75.7 (CH, C-4), 85.4 (quat., C-5a), 101.3 (CH, C-2), 106.4 (quat., C-11b), 109.5 (quat., C-6), 126.5 (CH, C-10), 127.0 (quat., C-7a), 127.1 (quat., C-11a), 127.8 (CH, C-9), 130.7 (CH, C-11), 134.2 (CH, C-8), 171.8 (quat., C-7), 190.3 (CHO); *m/z* (%) 272 (M^+, 20), 254 (M-H_2O, 40), 203 (M-C_4H_6O, 100). This product was then observed to decompose in air to diol **8**, m.p. 116-118 °C, ν_{max} (film) (cm^{-1}) 2841-3797 (OH), 1662 (C=O); δ_H (400 MHz; $CDCl_3$) 1.82 (1H, ddd, J_{gem} 13.4, $J_{3A,4}$ 1.8 and $J_{3A,2}$ 1.2 Hz, 3-H_A), 2.05 (1H, ddd, J_{gem} 12.4, $J_{5B,4}$ 4.8, $J_{5B,3B}$ 1.8 Hz, 5-H_B), 2.28 (1H, dddd, J_{gem} 13.4, $J_{3B,4}$ 3.4, $J_{3B,5B}$ 1.8 Hz and $J_{3B,2}$ 1.8 Hz, 3-H_B), 2.59 (1H, d, J_{gem} 12.4, 5-H_A), 4.50-4.61 (1H, bs, OH), 4.69-4.71 (1H, m, 4-H), 4.79-4.82 (1H, bs, OH), 6.00 (1H, bs, 2-H), 7.55 (1H, ddd, $J_{10,9}$ 7.5, $J_{10,11}$ 7.5 and $J_{10,8}$ 1.0 Hz, 10-H), 7.75 (1H, ddd, $J_{9,10}$ 7.5, $J_{9,8}$ 7.4 and $J_{9,11}$ 1.1 Hz, 9-H), 7.83 (1H, dd, $J_{11,10}$ 7.5 and $J_{11,9}$ 1.1 Hz, 11-H), 7.96 (1H, dd, $J_{8,9}$ 7.4 and $J_{8,10}$ 1.0 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 32.8 (CH_2, C-5), 41.7 (CH_2, C-3), 77.5 (CH, C-4), 89.6 (quat., C-5a), 91.0 (quat., C-6), 105.4 (CH, C-2), 106.7 (quat., C-11b), 127.0 (CH, C-10), 128.0 (CH, C-9), 128.1 (quat., C-11a), 130.4 (CH, C-11), 135.4 (CH, C-8) 135.7 (quat., C-7a), 193.3 (quat., C-7); *m/z* (%) 258 (M-H_2O, 40).

Crystallographic Details for Cage Compound **8**

A colourless blade like crystal was attached to a thin glass fibre and mounted on a Rigaku AFC7R diffractometer employing graphite monochromated Cu-Kα radiation from a rotating anode generator. Primitive triclinic cell constants were obtained from a least-squares refinement using the setting angles of 25 reflections in the range $90.36 < 2\theta < 98.62^{\circ}$. Diffraction data were collected at a temperature of $21 \pm 1^{\circ}C$ using ω-2θ scans to a maximum 2θ value of 130.1°. The intensities of three representative reflections measured every 150 reflections, did not change significantly during the data collection. An analytical absorption correction was applied and the data were also corrected for Lorentz and polarization effects.

All calculations were undertaken with the teXsan[9] crystallographic software package. Neutral atom scattering factors were taken from Cromer and Waber.[10] Anomalous dispersion effects were included in Fcalc[11] and the values for Δf' and Δf" were those of Creagh and McAuley.[12] The values for the mass attenuation coefficients were those of Creagh and Hubbell.[13] The structure was solved by direct methods[14] and expanded using Fourier techniques.[15] Non-hydrogen atoms were modelled with anisotropic thermal parameters. The hydrogen atom sites were located and modelled isotropically. An ORTEP projection of the molecule is provided in Fig. 1.[16]

Crystal data Formula $C_{14}H_{12}O_6$, M 276.25, triclinic, space group $P\bar{1}$(#2), a 7.2844(8), b 12.925(2), c 6.8807(6) Å, α 98.324(9), β 109.234(7), γ 77.31(1) °, V 594.9(1) $Å^3$, D_c 1.542 g cm^{-3}, Z 2, crystal size 0.17 by 0.08 by 0.03 mm, λ(Cu Kα) 1.5418 Å, μ(Cu Kα) 1.042 cm^{-1}, T(analytical)$_{min,max}$ 0.887, 0.975, θ_{max} 65.07, *hkl* range 0 8, -14 15, -8 7, N 2178, N_{ind} 2013(R_{merge} 0.0166), N_{obs} 1612($I > 3.00\sigma(I)$), N_{var} 229, residuals* R(F) 0.0368, $R_w(F)$ 0.0341, $\Delta\rho_{min,max}$ -0.20, 0.21 $e^- Å^{-3}$.

*$R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $R_w = (\Sigma w(F_o - F_c)^2/\Sigma(wF_c)^2)^{1/2}$

$w = 1/[\sigma^2(F_o)]$

Tables of atomic coordinates, bond angles and bond lengths have been deposited at the Cambridge Crystallographic database.

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