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Synthesis of Spiroketals Related to Griseusin A

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Abstract

The synthesis and attempted functionalization of the spiroketal ring system of the naturally occurring pyranonaphthoquinone antibiotic griseusin A **1** is reported. The unsaturated spiroketals **5,6** were prepared from furonaphthopyran **22**, which in turn was constructed from furonaphthofuran **20.** Addition of 2-trimethylsilyloxyfuran **13** to quinone **19** afforded furonaphthofuran **20**. Initial work using acetylenic quinone **12** afforded a pentacyclic product **15**, where a third Michael reaction of the phenolic hydroxyl group with the α,β-unsaturated ketone moiety had occurred. Modified reaction conditions afforded trimethylsilyl analogue **16**. Naphthoquinone **19**, which bears a 2-alkenyl side chain rather than an acetylene, was synthesized using similar methodology to **12** and subsequently converted to furonaphthofuran adduct **20**. Ceric ammonium nitrate oxidative rearrangement of **20** produced diol **22**, which was then cyclized to spiroketals **5**,**6** under acidic conditions. Reaction of spiroacetals **5**,**6** with osmium tetroxide did not effect the desired hydroxylation of the olefin. Use of cetyltrimethylammonium permanganate as the hydroxylation reagent resulted in reaction with the C5a-C11a double bond affording diols **24**,**25**.

Keywords: spiroketals, pyranonaphthoquinone antibiotics, ceric ammonium nitrate, furonaphthofuran, furonaphthopyran

Introduction

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. They are unique members of the pyranonaphthoquinone family 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** has been confirmed by X-ray analysis of the dibromo derivative [2]. Griseusins A **1** and B **2** are active against gram positive bacteria, pathogenic fungi and yeasts [1] and this, combined with their proposed ability to act as bioreductive alkylating agents [3], makes them attractive synthetic targets.

Despite the interesting biological activity of these compounds, only one total synthesis of griseusin A **1** has been reported to date. Yoshi *et al*. [4] assembled the spiroketal portion of the griseusins *via* cyclization of a δ,δ'-dihydroxyketone in which the oxygenated substituents of the final spiroketal ring were present in the cyclization precursor. Our synthetic approach to griseusin A **1** involves an alternative strategy based on the hydroxylation of an unsaturated spiroketal as a means of introducing the oxygenated substituents at C-3' and C-4'.

We have previously reported [5] a synthesis of the saturated spiroketals **3,4** which contain the basic pentacyclic framework of griseusin A **1**. We now wish to report the synthesis and hydroxylation of unsaturated spiroketals **5,6** which contain the required olefin functionality at C-3'/C-4' for the

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introduction of the hydroxyl and acetoxy groups at these positions.

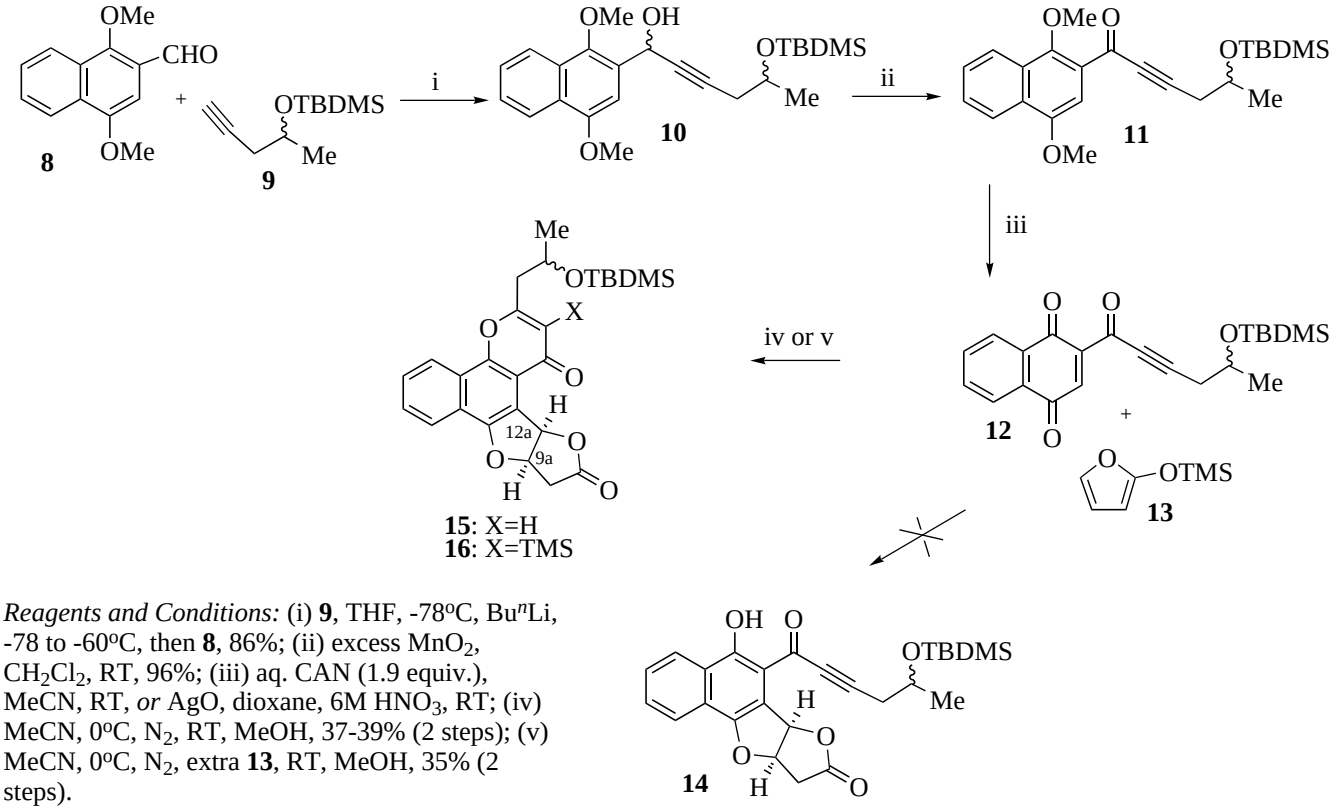
Results and Discussion

Our approach [5] to the griseusin A skeleton involved the ceric ammonium nitrate (CAN) oxidative rearrangement of a furo[3,2-*b*]naphtho[2,1-*d*]furan to a furo[3,2-*b*]naphtho[2,3-*d*]pyran ring system. The furo[3,2-*b*]naphtho[2,1-*d*]furan, in turn, was assembled *via* the addition of 2-trimethylsilyloxyfuran to a naphthoquinone. Based on this strategy which was used successfully in the synthesis of saturated spiroketals **3,4**, our initial approach to introduce the double bond into the spiroketal ring hinged on the synthesis of acetylenic hemiketal **7.** Hydrogenation of **7** followed by acid-catalyzed cyclization would then furnish the unsaturated spiroketals **5,6.**

It was therefore envisaged that hemiketal **7** could be prepared *via* oxidation of furonaphthofuran **14**. Addition of 2-trimethylsilyloxyfuran **13** to naphthoquinone **12** was expected to yield furonaphthofuran **14** (Scheme 1). To this end, acetylenic ketone **11** was prepared [5] by oxidation of acetylenic alcohol **10** which in turn was prepared [5] from acetylene **9** and aldehyde **8**. Oxidative demethylation of **11** to naphthoquinone **12** using ceric ammonium nitrate afforded significant quantities of recovered starting material. Treatment of **11** with silver (II) oxide and nitric acid proved more effective and the resultant naphthoquinone **12** was then treated directly with 2-trimethylsilyloxyfuran **13.** The sole product isolated from these two steps (after purification by flash chromatography) was identified as pentacyclic adduct **15**, rather than the desired furonaphthofuran adduct **14**. Thus an extra conjugate addition reaction of the naphthalene hydroxyl group onto the α,β-unsaturated ketone side chain had occurred.

Disappearance of the absorbance for the acetylene group at 2235 cm^{-1} together with the appearance of a singlet in the vinylic region of the ^{1}H–NMR spectrum at δ_H 6.35 indicated replacement of the acetylene moiety by a vinyl group. The ^{1}H–NMR spectrum indicated the presence of a 1:1 mixture of diastereomers and the ^{13}C–NMR showed the lack of resonances due to acetylenic carbons. The COSY and HETCOR spectra were consistent with the presence of the additional six-membered ring. Adduct **14** was not observed as an intermediate in the reaction mixture, thus suggesting that cyclization to form **15** was facile.

Pentacycle **15** bears a close resemblance to several natural products, notably chromones [6] and the kidamycin antibiotics [7]. When the concentration of 2-trimethylsilyloxyfuran **13** was doubled, an additional product, *C*-trimethylsilyl pentacycle **16,** was formed in 35% yield (based on the amount of starting material recovered) together with **15** (39%) (both as a 1:1 mixture of diastereomers). The relative R_f values (1:1 hexane-ethyl acetate) of **15** and this new compound suggested the formation of a less polar product. The ^{1}H–NMR spectrum of the new product was similar to **15**, how-



Reagents and Conditions: (i) **9**, THF, -78°C, Bu^{n}Li, -78 to -60°C, then **8**, 86%; (ii) excess MnO_2, CH_2Cl_2, RT, 96%; (iii) aq. CAN (1.9 equiv.), MeCN, RT, *or* AgO, dioxane, 6M HNO_3, RT; (iv) MeCN, 0°C, N_2, RT, MeOH, 37-39% (2 steps); (v) MeCN, 0°C, N_2, extra **13**, RT, MeOH, 35% (2 steps).

Scheme 1. *Synthesis of pentacycles **15**, **16***

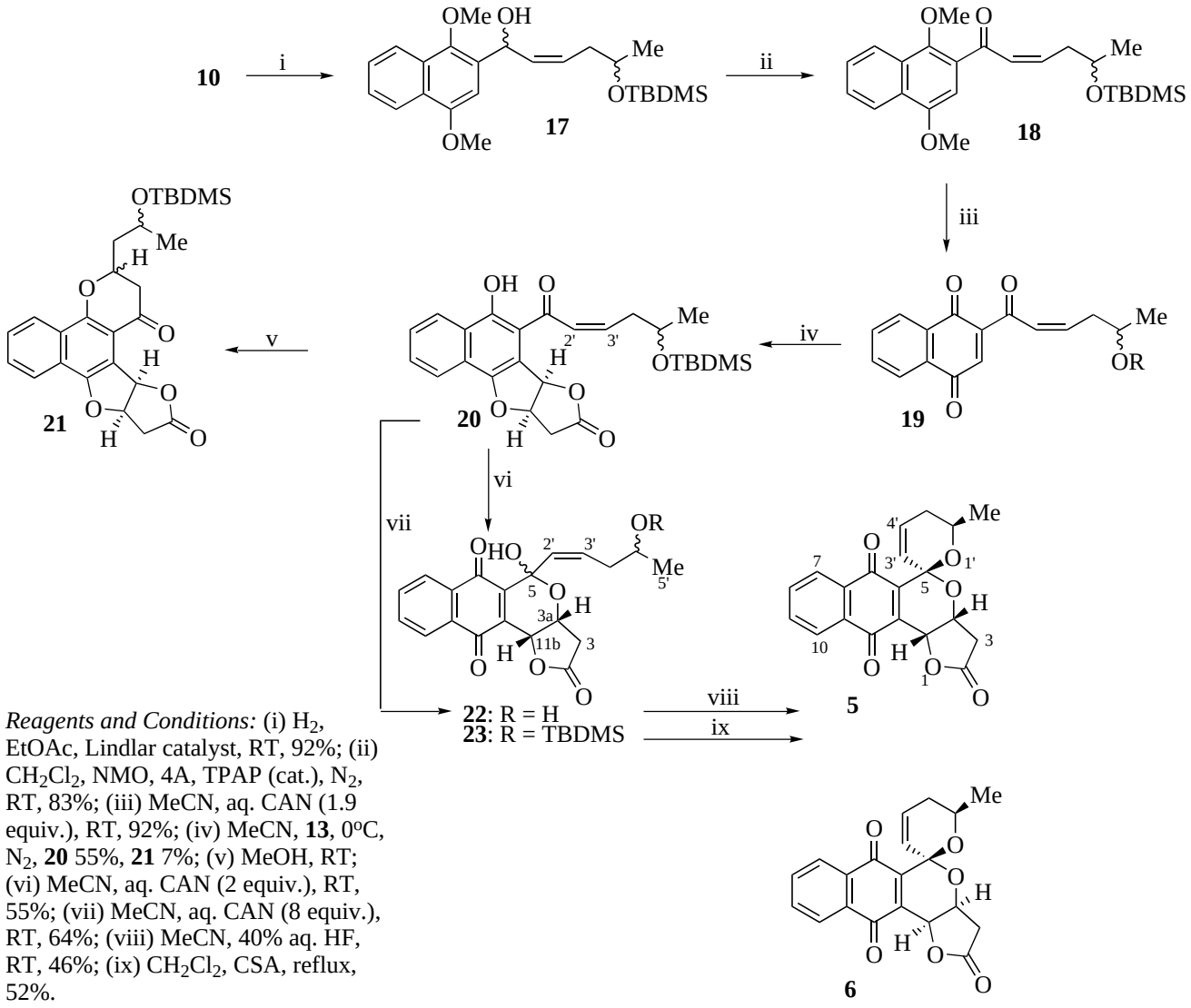
ever, it lacked the resonance for the vinylic proton at δ_H 6.35. The presence of an additional nine-proton singlet at δ_H 0.41 suggested the introduction of a trimethylsilyl group at C-2. The formation of **16** can be rationalized in that attack by the multiple bond on a trimethylsilyl cation rather than a proton occurs in the Michael reaction to form the pyran ring, this presumably being due to the increased concentration of **13** in the reaction mixture.

Due to the additional cyclization taking place to form **15**, a new synthetic strategy was developed (Scheme 2). It was hoped that with a double bond in the side chain, rather than the acetylene group, the additional Michael reaction could be avoided or at least retarded. The double bond would provide the necessary unsaturation in order to elaborate the substituents on the spiroketal ring in the later stages of the synthesis.

Semi-hydrogenation of **10** over a Lindlar catalyst afforded *cis*-olefin **17** in 92% yield. Subsequent oxidation of alcohol **17** to the α,β-unsaturated ketone **18** proved to be difficult. A variety of reagents were tried before a suitable method was found. Activated manganese dioxide required long reaction times and heating under reflux, and resulted in formation of the "double" dehydrogenation product **11**. Barium permanganate, sulphur trioxide-pyridine, Swern conditions, $RuCl_2(PPh_3)_3$, Fetizons reagent, pyridinium chlorochromate and pyridinium dichromate all proved unsatisfactory, giving poor yields or a complex mixture of products.

The oxidation of **17** to **18** was finally solved by using *tetra-n*-propylammonium perruthenate which was developed by Ley and Griffith *et al.* [8] Treatment of **17** with TPAP and co-oxidant *N*-methylmorpholine *N*-oxide at high dilution in dichloromethane afforded ketone **18** cleanly in 83% yield. It was isolated in essentially pure form by filtration of the reaction mixture through a silica gel pad.

With the desired ketone **18** in hand, oxidative demethylation proceeded smoothly and in high yield (92%) to furnish quinone **19**. The optimum conditions found required the use of ceric ammonium nitrate (1.9 equivalents) dissolved in the



Reagents and Conditions: (i) H_2, EtOAc, Lindlar catalyst, RT, 92%; (ii) CH_2Cl_2, NMO, 4A, TPAP (cat.), N_2, RT, 83%; (iii) MeCN, aq. CAN (1.9 equiv.), RT, 92%; (iv) MeCN, **13**, 0°C, N_2, **20** 55%, **21** 7%; (v) MeOH, RT; (vi) MeCN, aq. CAN (2 equiv.), RT, 55%; (vii) MeCN, aq. CAN (8 equiv.), RT, 64%; (viii) MeCN, 40% aq. HF, RT, 46%; (ix) CH_2Cl_2, CSA, reflux, 52%.

Scheme 2. *Synthesis of unsaturated spiroketals **5**, **6**.*

minimum quantity of water needed to dissolve the cerium salt. Not adhering to these conditions resulted in a darkening of the reaction mixture and the appearance of a more polar product, presumably due to loss of the tert-butyldimethylsilyl protecting group. In this oxidation step using CAN, Florisil was used to separate the oxidant from the product. This helped prevent the undesired Michael addition from occurring, which was found to be promoted by both residual CAN and flash silica.

Addition of 2-trimethylsilyloxyfuran **13** to **19** under the usual conditions (0°C, MeCN, N_2) afforded a mixture of adduct **20** and pentacycle **21** in 55 and 7% yield respectively (scheme 2). The maximum yield of the desired adduct **20** was obtained when the reaction mixture was worked up quickly. Long reaction times resulted in complete conversion to **21**. If residual CAN was not removed from the quinone precursor **19** by using Florisil, a second cyclization occurred.

With furonaphthofuran **20** in hand, it was then necessary to effect oxidative rearrangement of this tetracyclic system to the ring system present in the pyranonaphthoquinone antibiotic griseusin A **1**. Treatment of **20** with an excess of ceric ammonium nitrate (8 equivalents) afforded the furo[3,2-b]naphtho[2,3-d]pyran **22**, where oxidative rearrangement was accompanied by loss of the silyl protecting group. The diol **22** was isolated in 64% yield after purification by flash chromatography. Thus the presence of unsaturation in the side chain resulted in lower yields for this oxidation step compared to the saturated analogues [5].

The ^{1}H–NMR spectrum of **22** revealed an upfield shift in the resonances of the bridgehead protons relative to the initial adduct **20**. The coupling constant between the bridgehead protons was reduced from 5.9 to 2.9 Hz, reflecting the presence of 6,5 ring fusion of the terminal rings. The coupling constant observed, $J_{3a,11b}$ 2.9 Hz, matched those obtained for the analogous protons in griseusin A **1** and B **2** [1].

^{1}H–NMR spectroscopy established that diol **22** was in fact a mixture of diastereomers due to the presence of four chiral centres. Whilst the relative stereochemistry of the bridgehead protons at C-3a and C-11b was established as *cis*, a diastereomeric mixture resulted due to lack of control of stereochemistry at the anomeric carbons C-5 and at C-4'.

Having synthesized diol **22** the remaining step required to construction of the griseusin A **1** framework, involving cyclization to form the spiroketal ring. Thus diol **22** was treated with camphor sulphonic acid under gentle reflux to afford spiroketals **5**,**6** in a 3:2 ratio, as measured by integration of the ^{1}H–NMR spectrum. The two spiroketals **5**,**6** were inseparable by flash chromatography, but were readily separated by high-pressure liquid chromatography (HPLC), which also confirmed the 3:2 isomeric ratio. The ^{1}H–NMR spectrum of the isomeric mixture of spiroketals was readily interpreted due to most of the resonances from the individual isomers being distinguishable.

The assignment of structure **5** to the major isomer was based on the spiroketal functional group being formed under thermodynamic control, and that maximum stability is gained by the anomeric effect [9] when the oxygen atom of each pyran ring occupies a position axial with respect to the C-O bond of the adjacent ring. In the case of these spiro[5.5]systems, the *bis*-axial arrangement of spiro C-O bonds is often observed in both saturated and unsaturated systems [10] (Figures 1,2). Comparison of the ^{1}H–NMR chemical shifts for the two spiroketals supported the assigned structures. Thus, spiroketal **6** exhibited a double doublet at δ_H 4.90, which was assigned to the bridgehead proton 3a-H, whilst with the spiroketal **5** this same proton resonated as a double doublet further downfield at δ_H 5.01. The deshielding of 3a-H in the isomer **5** is attributed to the 1,3-diaxial interactions between 3a-H and O-1'. ^{1}H–NMR chemical shift differences and relative positions between **5** and **6** were generally the same as those between saturated isomers **3** and **4** [5].

If the ceric ammonium nitrate mediated oxidative rearrangement of **20** was left for an extended period of time, the mildly acidic conditions not only resulted in cyclization to diol **22**, but also isomerization of the olefin to the *trans* isomer. By combining the inability of the *trans* isomer to cyclize to form a six-membered ring with the use of short reaction times formation of this unwanted by-product was prevented.

The intermediate hemiketal **23** with an intact *tert*-butyldimethylsilyl protecting group, could be formed from adduct **20** in 55% yield by using only two equivalents of ceric ammonium nitrate to rearrange the carbon skeleton. Subsequent deprotection of silyl ether **23** to alcohol **22** using ceric ammonium nitrate was much less efficient than direct conversion of **20** to **22**. Alternative desilylating agents such as tetrabutylammonium fluoride, trifluoroacetic acid and AcOH/THF/H_2O resulted in decomposition or a complex mixture. However, success was finally achieved by using aqueous hydrofluoric acid.

Addition of HF to an acetonitrile solution of **23** effected deprotection and *in situ* cyclization to spiroketals **5**,**6**. In this case, spiroketal **6** was the major isomer formed (**5**:**6** = 3:7). The differing isomeric ratios obtained may be attributed to the spiroketal ring being formed under thermodynamic conditions using ceric ammonium nitrate, whilst the reaction proceeds under kinetic control using hydrofluoric acid. In the synthesis of calyculin A[11], an analogous [6,5] spiroketal ring system was formed under kinetic control by treatment of an acyclic *bis*-triethylsilyl ether with aq. HF. The preference for formation of the less stable kinetic spiroketal in this case "was not readily apparent from the available data, due to a lack of information about the order of ring forming steps during the spirocyclization process" [11]. A similar one step desilylation/cyclization process [12] for avermectin B2a precursors using HF-pyridine in tetrahydrofuran produced the corresponding kinetic cyclization product.

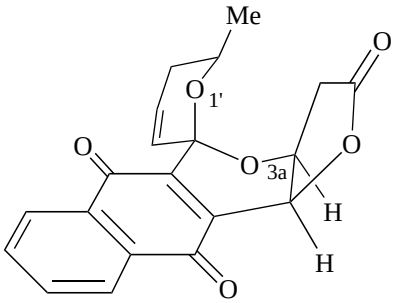
The oxidative rearrangement of the two pentacyclic adducts **15** and **21** was investigated as an alternative route to the griseusin A ring system. Treatment of pentacycles **15** and **21** with ceric ammonium nitrate, however, resulted in

decomposition or the formation of complex mixtures of products. Therefore this avenue was not pursued further.

Unsaturated spiroketal **5** has the same relative stereochemistry at C-3a and C-5 as griseusin A **1**. Efforts were therefore directed towards improvement of the ratio of **5**:**6** by using alternative acidic conditions to effect cyclization to the spiroketal ring system. In the case of the saturated spiroketals **3**,**4**, successful isomerization of **4** to **3** was realized upon treatment of **4** with trifluoroacetic acid in benzene under reflux. Treatment of the unsaturated spiroketals **5,6** with the same conditions, however, resulted in severe decomposition.

With the unsaturated spiroketals **5,6** in hand, it then remained to examine the *syn*-hydroxylation of the double bond. Treatment of **5**,**6** with NMO/OsO_4 resulted in no reaction after 6 h. Addition of more catalyst and oxidant and leaving the reaction overnight resulted in no further change. Use of a trimethylamine *N*-oxide / pyridine system, a method reported to be good for hindered olefins [13], only afforded recovered starting material.

Since osmium tetraoxide did not effect *syn*-hydroxylation of spiroketals **5,6**, attention then turned to the use of cetyltrimethylammonium permanganate (CTAP), $C_{16}H_{33}NMe_3^+MnO_4^-$ [14]. Treatment of **5,6** with CTAP in dichloromethane at room temperature produced a more polar product which exhibited a hydroxyl stretch at 3861-3369 cm^{-1} in the IR spectrum. The vinylic protons, 3'-H and 4'-H were still present in the–NMR spectrum, and hence the C3'-C4' double bond had not been hydroxylated. All the aromatic protons were still present in the product and the chemi-



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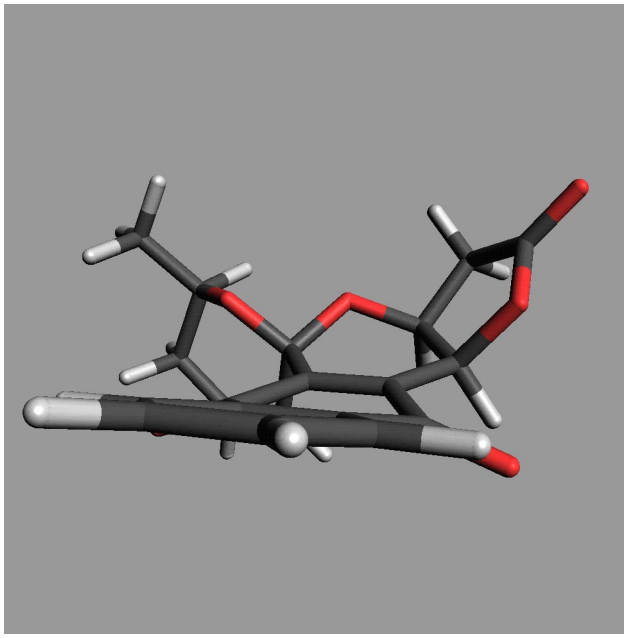
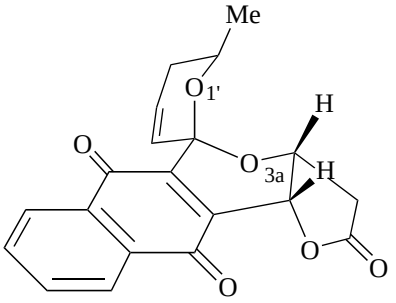


Figure 1



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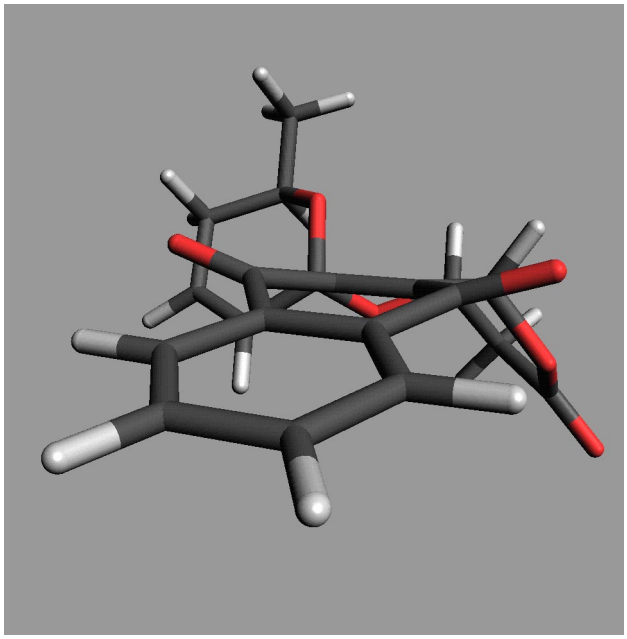


Figure 2

cal shifts for C-6a and C-10a had not significantly changed. It was therefore concluded that the C5a-C11a double bond had undergone hydroxylation. This was supported by the upfield shift of C-5a and C-11a from approximately δ_C 144 and δ_C 136 respectively in **5,6** to δ_C 82, consistent with conversion of sp^2 carbons to oxygen-substituted sp^3 carbons.

Both the ^1H and ^{13}C–NMR spectra indicated the presence of two diastereomers. Hence the reagent had effected dihydroxylation stereoselectively. The structures for spiroketals **5** and **6** were calculated with the semi-empirical method AM1 using the program package VAMP v5.6 [15] (Figure 1, 2). These models predicted that spiroketal **6** would be approached by the CTAP reagent from the lower face of the C5a-C11a double bond, the upper face being sterically hindered by both the lactone and the spiroketal ring (Figure 1). The approach of the electrophile from the lower face affords diol **25**.

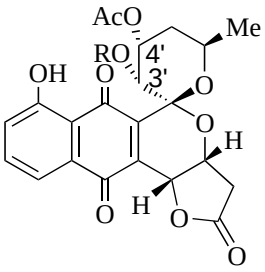
The approach of the hydroxylation reagent to the C5a-C11a double bond in spiroketal **5** was more difficult to predict (Figure 2). There is little difference in steric bulk between the pyran and the lactone. However, the lactone ring does appear to shield the lower face more effectively than the pyran ring does the upper face. Although a definitive assignment of stereochemistry to the diol formed from spiroketal **5** was difficult, it was noted that the resonances for 6'-Me and 6'-H were significantly deshielded compared to these for these protons in diol **25**. This suggested that the newly introduced hydroxyl groups at C-5a and C-11a were *syn* to 6'-Me. Hence structure **24** was tentatively assigned to this second diol.

Based on the results obtained from the dihydroxylation of spiroketals **5**,**6** it appeared that hydroxyl groups on the spiroketal ring in griseusin A **1** would have to be put in place before assembly of the ring itself. Once constructed, unsaturated spiroketal rings present in pyranonaphthoquinones **5**,**6** resist hydroxylation to the extent that other sources of unsaturation on the molecule (C5a-C11a) react instead. This lack of reactivity may well be due to steric effects although electronic factors may also be involved.

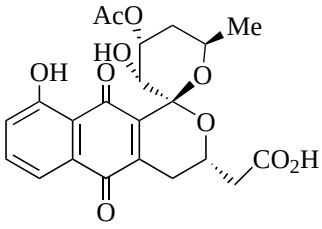
Experimental Section

General Details

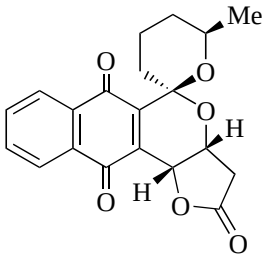
Chemicals and reagents were purchased from the Aldrich Chemical Co. and used without further purification. Melting points were determined on a Kofler hotstage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained at 270 and 67.8 MHz respectively. ^{13}C NMR spectra were assigned with the aid of DEPT spectra. Mass spectra were recorded under electron impact using an ionisation potential of 70 eV and chemical ionisation with ammonia as the reagent gas, or using liquid secondary ionisation mass spectrometry (LSIMS) with either a nitrobenzyl alcohol (NBA) or a 5:1 dithiothreitol:dithioerythritol (DTDE) matrix. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh) with the solvents indicated. Analytical TLC was performed using precoated silica gel plates (Merck Kieselgel 60 F_{254}). THF was distilled from sodium benzophenone ketyl before use. The acetylenic alcohol **10** and the acetylenic ketone **11** were prepared [5] using the procedure previously reported.



Griseusin A 1



Griseusin B 2



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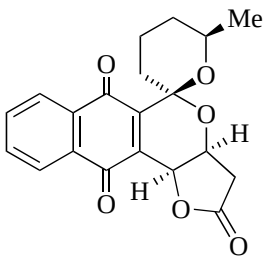

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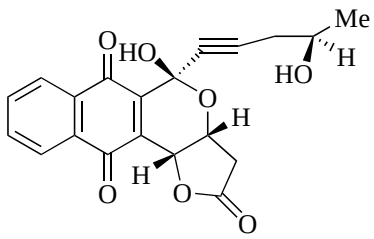

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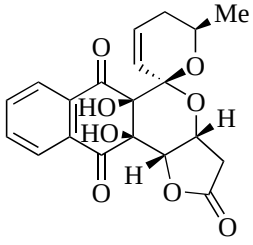

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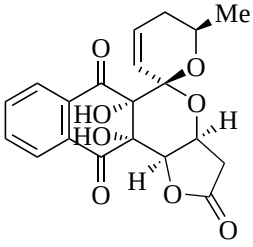

25

(±)-2-(5-tert-Butyldimethylsilyloxy-1-oxohex-2-ynyl)-1,4-naphthoquinone 12

Using Ceric Ammonium Nitrate

A solution of ceric ammonium nitrate (921 mg, 1.67 mmol) in water (7 cm^3) was added dropwise to a vigorously stirred solution of 1,4-dimethoxynaphthalene **11** (364 mg, 0.88 mmol) in acetonitrile (49 cm^3) at room temperature. After 0.25 h the reaction mixture was diluted with dichloromethane (57 cm^3), washed with water (2 × 36 cm^3) and dried over sodium sulphate. Evaporation of the solvent at reduced pressure afforded a mixture (317 mg) of the *title compound* **12** and **11** [*ca.* 1:1 (NMR)] as an orange oil. The mixture was used in the subsequent step without any attempt to separate the two components.

Using Silver(II) Oxide and Nitric Acid

To a mixture of **11** (12 mg, 0.029 mmol), silver(II) oxide (14 mg, 0.11 mmol) and 1,4-dioxane (1.3 cm^3) was added dropwise 6 mol dm^{-3} nitric acid (29 mm^3). The suspension was vigorously stirred until no starting material could be detected by TLC (*ca.* 1 min), poured into dichloromethane (3 cm^3) and washed with water (2 × 1 cm^3). The organic phase was dried over sodium sulphate and the solvent evaporated under reduced pressure to give the *title compound* **12** (15 mg) as an orange oil.
IR (film) 2216 (CºC), 1670 (C=O).
^{1}H NMR (200 MHz; $CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.86 (9H, s, Bu^t), 1.27 (3H, d, *J* 6.1 Hz, Me), 2.55-2.60 (2H, m, CH_2CºC), 3.98-4.16 (1H, m, CHOSi), 7.32 (1H, s, 3-H), 7.64-7.84 (2H, m, 6-H and 7-H), 8.02-8.16 (2H, m, 5-H and 8-H).
MS (EI) *m/z* 384 (M+2H, 4), 327 (M+2H-C_4H_9, 10), 325 (M-C_4H_9, 12), 75 [$(CH_3)_2$SiOH, 74].
HRMS Calcd for $C_{22}H_{26}O_4Si$: (M + 2H), 384.1757. Found: (M + 2H), 384.1733. The crude material was used in the next step without further purification.

(9aR*,12aR*,2'R*)-and (9aR*,12aR*,2'S*)-3-(2-tert-Butyldimethylsilyloxypropyl)-9a,12a-dihydro-1H-furo[2",3":4',5']furo[3',2':3,4]naphtho[1,2-b]pyran-1,11(10H)-dione 15.

*Using the naphthoquinone **12** prepared with the aid of ceric ammonium nitrate*

A solution of 2-trimethylsilyloxyfuran **13** (109 mg, 0.70 mmol) in acetonitrile (3.3 cm^3) was added dropwise to an ice- cooled mixture (*ca.* 1:1) of **12** and **11** (317 mg total mass) in acetonitrile (39 cm^3) under an atmosphere of nitrogen. After 1 h, the reaction was left to warm to room temperature and then methanol (5 cm^3) was added. After a further 30 h, the solvent was removed under reduced pressure to give an orange oil, which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford **11** (173 mg, 48%) and the *title compound* **15** [84 mg, 39% over two steps (based on unreacted **11**)] as a pale yellow oil and as a 1:1 mixture of stereoisomers (^{1}H–NMR). Trituration using ether afforded a colourless solid.
m.p. 186.5-188.5ºC.
IR (film) 1776 (C=O, γ-lactone), 1654s, 1634 (C=O, α,β-unsaturated ketone), 1597 (C=C) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 0.00 (6H, s, $SiMe_2$), 0.80, 0.81 (9H, s, Bu^t), 1.32 (3H, d, *J* 6.2 Hz, Me), 2.84 (2H, d, $J_{1',2'}$ 5.1 Hz, 1'-CH_2), 3.18 (2H, d, $J_{10,9a}$ 4.0 Hz, 10-CH_2), 4.26-4.41 (1H, m, CHOSi), 5.61 (1H, dt, $J_{9a,12a}$ 5.7 and $J_{9a,10}$ 4.0 Hz, 9a-H), 6.35 (1H, s, 2-H), 6.98 (1H, d, $J_{12a,9a}$ 5.7 Hz, 12a-H), 7.74-7.79 (2H, m, 6-H and 7-H), 8.07-8.10 (1H, m, 5-H or 8-H), 8.45-8.49 (1H, m, 8-H or 5-H).
^{13}C NMR (67.8 MHz; $CDCl_3$) -5.0, -4.6 (CH_3, $SiMe_2$), 18.0 (C, *C*Me_3), 24.0 (CH_3, C-3'), 25.7 (CH_3, C*Me*$_3$), 35.6 (CH_2, C-10), 44.6, 44.7 (CH_2, C-1'), 66.8, 67.1 (CH, C-2'), 83.1 (CH, C-9a), 84.6 (CH, C-12a), 110.9 (C, C-12b), 113.2, 113.4 (CH, C-2), 117.3 (C, C-12c), 122.7, 122.8, 122.9, 123.0 (CH, C-5, C-8), 126.4 (C, C-4b, C-8a), 128.8, 129.4 (CH, C-6, C-7), 149.3 (C, C-8b), 155.4 (C, C-4a), 165.7, 165.9 (C, C-3), 174.5 (C, C-11), 177.4 (C, C-1).
MS (EI) *m/z* 466 (M^+, 4), 422 (M-CO_2, 4), 409 (M-C_4H_9, 100), 365 (M-CO_2-C_4H_9, 30), 75 [$(CH_3)_2$SiOH, 25].
Anal. Cald for $C_{26}H_{30}O_6Si$: C, 66.9; H, 6.5. Found: C, 67.15; H, 6.8.

*Using naphthoquinone **12** prepared using silver(II) oxide*

A solution of 2-trimethylsilyloxyfuran **13** (9.0 mg, 0.058 mmol) in acetonitrile (0.3 cm^3) was added dropwise to an ice- cooled solution of crude **12** (15 mg) in acetonitrile (1.8 cm^3) under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (0.4 cm^3) added. After a further 30 h, the solvent was removed under reduced pressure to give an orange oil which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford the *title compound* **15** (5.0 mg, 37% over two steps) as a 1:1 mixture of stereoisomers (^{1}H–NMR).

(9aR*,12aR*,2'R*)- and (9aR*,12aR*,2'S*)-2-Trimethylsilyl-3-(2-tert-butyldimethylsilyloxypropyl)-9a,12a-dihydro-1H-furo[2",3":4",5"]-furo[3',2':3,4]naphtho[1,2-b]pyran-1,11(10H)-dione 16.

A solution of **13** (65 mg, 0.41 mmol) in acetonitrile (1.8 cm^3) was added dropwise to an ice-cooled mixture (79 mg) of **12** and **11** in acetonitrile (10 cm^3) under an atmosphere of nitrogen. After 1 h, the reaction mixture was left to warm to room temperature and then methanol (1.2 cm^3) was added. After stirring for 30 h, the solvent was removed under reduced pres-

sure to give an orange oil, which was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent to afford **11** (22 mg, 24%), the pentacycle **15** [29 mg, 39% over two steps (based on unreacted **11**)] and the *title compound* **16** [30 mg, 35% over two steps (based on unreacted **11**)] as a pale yellow solid and as a 1:1 mixture of stereoisomers (^{1}H-NMR).

m.p. 188.5-190.5°C.

IR (film) 1781 (C=O, γ-lactone), 1643 (C=O, α,β-unsaturated ketone), 1618 (C=C, vinylic) cm^{-1}.

^{1}H NMR (270 MHz; $CDCl_3$) -0.24, -0.23, -0.01, 0.00 (6H, s, 2'-$OSiMe_2$), 0.41 (9H, s, 2-$SiMe_3$), 0.75 (9H, s, Bu^t), 1.32(2) (3H, d, *J* 5.9 Hz, Me), 2.87, 2.89 (1H, dd, J_{gem} 13.9 and $J_{1',2'}$ 7.0 Hz, 1'-H^A), 3.04, 3.07 (1H, dd, J_{gem} 13.9 and $J_{1',2'}$ 8.4 Hz, 1'-H^B), 3.16 (2H, d, $J_{10,9a}$ 3.8 Hz, 10-CH_2), 4.37-4.53 (1H, m, CHOSi), 5.56 (1H, dt, $J_{9a,12a}$ 5.9 and $J_{9a,10}$ 3.8 Hz, 9a-H), 6.95, 6.96 (1H, d, $J_{12a,9a}$ 5.9 Hz, 12a-H), 7.71-7.77 (2H, m, 6-H and 7-H), 8.05-8.08 (1H, m, 5-H or 8-H), 8.43-8.47 (1H, m, 8-H or 5-H).

^{13}C NMR (67.8 MHz; $CDCl_3$) -4.9, -4.7 (CH_3, 2'-$OSiMe_2$), 1.40 (C, 2-$SiMe_3$), 17.9 (C, *C*Me_3), 24.3 (CH_3, C-3'), 25.6 (CH_3, C*Me*$_3$), 35.5 (CH_2, C-10), 44.1 (CH_2, C-1'), 67.7, 68.2 (CH, C-2'), 82.9 (CH, C-9a), 84.7(2) (CH, C-12a), 110.7, 110.8 (C, C-12b), 115.9(2) (C, C-12c), 120.1, 120.2 (C, C-2), 122.6, 122.8, 122.9 (CH, C-5, C-8), 126.2 (C, C-4b, C-8a), 128.6, 129.2 (CH, C-6, C-7), 149.1(2) (C, C-8b), 155.1 (C, C-4a), 168.7, 168.9 (C, C-3), 174.6, 174.7 (C, C-11), 181.4, 181.5 (C, C-1).

MS (EI) *m/z* 538 (M$^+$, 18), 481 (M-C_4H_9, 100), 391 (18), 343 (34), 73 [$(CH_3)_3Si$, 62].

HRMS. Calcd for $C_{29}H_{38}O_6Si_2$: M, 538.2207. Found: M, 538.2201.

(2'Z)-(1'R*,5'R*)- and (1'R*,5'S*)-2-(5-tert-Butyldimethylsilyloxy-1-hydroxyhex-2-enyl)-1,4-dimethoxynaphthalene 17.

To a solution of the acetylene **10** (1.364 g, 3.29 mmol) in ethyl acetate (45 cm^3) was added a Lindlar catalyst (120 mg). The reaction vessel was flushed with hydrogen from a reservoir and the contents stirred at room temperature for 0.5 h. After removal of the catalyst by filtration through a Celite pad the filtrate was concentrated at reduced pressure to give a yellow oil. Purification by flash chromatography, using hexane-ethyl acetate (4:1) as eluent gave the *title compound* **17** (1.261 g, 92%) as a yellow oil and as a 1:1 mixture of stereoisomers (^{1}H–NMR).

IR (film) 3700-3060 (OH), 1635 (C=C) cm^{-1}.

^{1}H NMR (270 MHz; $CDCl_3$) 0.07, 0.08, 0.09 (6H, s, $SiMe_2$), 0.90, 0.91 (9H, s, Bu^t), 1.18, 1.22 (3H, d, *J* 6.2 Hz, Me), 2.22-2.65 (2H, m, =CHC*H*$_2$), 2.90, 2.94 (1H, br.s, OH), 3.89-4.02 (1H, m, CHOSi), 3.91, 3.92 (3H, s, 1-OMe), 4.00 (3H, s, 4-OMe), 5.58-5.69 (1H, m, =C*H*CH_2), 5.83-5.92 (1H, m, C*H*=CHCH_2), 6.03 (1H, d, *J* 7.7 Hz, C*H*OH), 6.94, 6.95 (1H, s, 3-H), 7.44-7.56 (2H, m, 6-H and 7-H), 8.01-8.04 (1H, m, 5-H or 8-H), 8.21-8.24 (1H, m, 8-H or 5-H).

^{13}C NMR (67.8 MHz; $CDCl_3$) -4.6, -4.5 (CH_3, $SiMe_2$), 18.2 (C, *C*Me_3), 23.3, 24.0 (CH_3, C-6'), 25.7, 25.9 (CH_3, C*Me*$_3$), 37.4, 38.1 (CH_2, C-4'), 55.5 (CH_3, 4-OMe), 62.6 (CH_3, 1-OMe), 64.2, 64.8 (CH, C-1'), 68.2, 68.6 (CH, C-5'), 101.7, 101.8 (CH, C-3), 121.9, 122.3 (CH, C-5, C-8), 125.3, 126.5 (CH, C-6, C-7), 126.1 (C, C-2), 128.3, 129.7 (C, C-4a, C-8a), 131.1, 131.5 (CH, C-2'), 133.6, 134.0 (CH, C-3'), 146.1, 152.2 (C, C-1, C-4).

MS (EI) *m/z* 416 (M$^+$, 23), 398 (M-H_2O, 7), 326 (11), 284 (M-$C_6H_{16}OSi$, 10), 201 (26), 159 ($C_8H_{19}OSi$, 20), 119 (100), 75 [$(CH_3)_2SiOH$, 54], 57 (C_4H_9, 8).

Anal. Calcd for $C_{24}H_{36}O_4Si$: C, 69.2; H, 8.7. Found: C, 69.2; H, 8.5.

(2'Z)-(±)-2-(5-tert-Butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-dimethoxy-naphthalene 18.

To a mixture of alcohol **17** (199 mg, 0.48 mmol), 4-methylmorpholine *N*-oxide (84 mg, 0.72 mmol) and powdered 4Å molecular sieves (240 mg) in dichloromethane (20 cm^3) under an atmosphere of nitrogen was added *tetra-n*-propylammonium perruthenate (15 mg, 10 mol %). The reaction mixture was stirred until no starting material was visible (TLC). Filtration of the reaction mixture through a glass frit and then a silica gel pad, followed by concentration of the filtrate at reduced pressure, afforded a yellow oil. Purification by flash chromatography, using hexane-ethyl acetate (95:5) as eluent gave the *title compound* **18** (164 mg, 83%) as a yellow oil.

IR (film) 1643 (C=O), 1594 (C=C) cm^{-1}.

^{1}H NMR (270 MHz; $CDCl_3$) 0.09 (6H, s, $SiMe_2$), 0.90 (9H, s, Bu^t), 1.22 (3H, d, *J* 6.2 Hz, Me), 2.78-3.02 (2H, m, =CHC*H*$_2$), 3.87 (3H, s, 1-OMe), 4.00-4.07 (1H, m, CHOSi), 4.01 (3H, s, 4-OMe), 6.45 (1H, dt, $J_{3',2'}$ 11.7 and $J_{3',4'}$ 7.3 Hz, =C*H*CH_2), 7.05 (1H, s, 3-H), 7.15 (1H, dt, $J_{2',3'}$ 11.7 and $J_{2',4'}$ 1.8 Hz, C*H*=CHCH_2), 7.56-7.60 (2H, m, 6-H and 7-H), 8.16-8.19 (1H, m, 5-H or 8-H), 8.23-8.27 (1H, m, 8-H or 5-H).

^{13}C NMR (67.8 MHz; $CDCl_3$) -4.7, -4.4 (CH_3, $SiMe_2$), 18.1 (C, *C*Me_3), 23.9 (CH_3, C-6'), 25.9 (CH_3, C*Me*$_3$), 39.7 (CH_2, C-4'), 55.7 (CH_3, 4-OMe), 64.2 (CH_3, 1-OMe), 68.3 (CH, C-5'), 102.6 (CH, C-3), 122.4, 123.1 (CH, C-5, C-8), 123.2 (C, C-2), 127.1, 127.6 (CH, C-6, C-7), 128.3, 128.7 (C, C-4a, C-8a), 128.9 (CH, C-2'), 145.4 (CH, C-3'), 151.2, 151.8 (C, C-1, C-4), 193.0 (C, C-1').

MS (EI) *m/z* 414 (M$^+$, 37), 357 (M-C_4H_9, 82), 298 (M-$C_5H_{12}OSi$, 52), 283 (M-$C_6H_{15}OSi$, 37), 267 (M-$C_7H_{19}OSi$, 75), 215 (M-$C_{11}H_{23}OSi$, 46), 159 ($C_8H_{19}OSi$, 32), 133 (60), 117 (34), 75 [$(CH_3)_2SiOH$, 36], 73 (100), 57 (C_4H_9, 10).

Anal. Calcd for $C_{24}H_{34}O_4Si$: C, 69.5; H, 8.3. Found: C, 69.6; H, 8.1.

(2'Z)-(±)-2-(5-tert-Butyldimethylsilyloxy-1-oxohex-2-enyl)-1,4-naphthoquinone 19.

A solution of ceric ammonium nitrate (510 mg, 0.93 mmol) in water (4 cm^3) was added dropwise to a vigorously stirred solution of 1,4-dimethoxynaphthalene **18** (203 mg, 0.49 mmol) in acetonitrile (30 cm^3) at room temperature. After 0.25 h, the reaction mixture was diluted with dichloromethane (30 cm^3), washed with water (2 × 20 cm^3) and dried over sodium sulphate. After removal of residual oxidant by filtration through a Florisil pad the filtrate was concentrated at reduced pressure to give the *title compound* **19** (173 mg, 92%) as an orange oil.
IR (film) 1669 (C=O, quinone and α,β-unsaturated ketone), 1613 (C=C, vinylic) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 0.07, 0.08 (6H, s, $SiMe_2$), 0.89 (9H, s, Bu^t), 1.20 (3H, d, *J* 6.2 Hz, Me), 2.83-2.94 (2H, m, =CHC*H*$_2$), 4.03 (1H, sextet, *J* 5.9 Hz, CHOSi), 6.50-6.68 (2H, m, C*H*=C*H*CH_2), 7.12 (1H, s, 3-H), 7.78-7.82 (2H, m, 6-H and 7-H), 8.08-8.14 (2H, m, 5-H and 8-H).
MS (EI) *m/z* 386 (M+2H, 5), 329 (M+2H-C_4H_9, 8), 327 (M-C_4H_9, 12), 285 (12), 254 (M+2H-$C_6H_{16}OSi$, 8), 215 (13), 186 (M+2H-$C_{11}H_{23}OSi$, 10), 159 ($C_8H_{19}OSi$, 60), 115 (23), 75 [$(CH_3)_2SiOH$, 100], 73 (88).
HRMS. Calcd for $C_{22}H_{28}O_4Si$: (M + 2H), 386.1913. Found: (M + 2H), 386.2053.

(2'Z)-(6bR*,9aR*,5'R*)- and (6bR*,9aR*,5'S*)-6-(5-tert-Butyldimethylsilyloxy-1-oxohex-2-enyl)-6b,9a-dihydro-5-hydroxyfuro[3,2-b]naphtho[2,1-d]furan-8(9H)-one 20.

A solution of **13** (138 mg, 0.88 mmol) in acetonitrile (4.5 cm^3) was added dropwise to an ice-cooled solution of **19** (173 mg, 0.44 mmol), in acetonitrile (23 cm^3) under an atmosphere of nitrogen. After 0.5 h the solvent was removed under reduced pressure to give an orange oil, which was then purified by flash chromatography using hexane-ethyl acetate (4:1) as eluent to afford:

(i) the *title compound* **20** (111 mg, 55%) as an orange semi-solid and as a 1:1 mixture of stereoisomers (^{1}H–NMR). Trituration using hexane-ether (4:1) produced an orange solid.
m.p. 108.0-110.0°C.
IR (film) 3670-3090w (OH), 1785 (C=O, g-lactone), 1630 (C=O, a,b-unsaturated ketone), 1572 (C=C) cm^{-1}.
^{1}H NMR (200 MHz; $CDCl_3$) 0.05, 0.07 (6H, s, $SiMe_2$), 0.87, 0.88 (9H, s, Bu^t), 1.19, 1.20 (3H, d, *J* 6.1 Hz, Me), 2.61-2.88 (2H, m, =CHC*H*$_2$), 3.03-3.32 (2H, m, 9-H and 9-H'), 3.96-4.19 (1H, m, CHOSi), 5.44 (1H, ddd, $J_{9a,6b}$ 5.9, $J_{9a,9}$ 5.9 and $J_{9a,9'}$ 2.7 Hz, 9a-H), 6.35 (1H, d, $J_{6b,9a}$ 5.9 Hz, 6b-H), 6.39-6.54 (1H, m, =C*H*CH_2), 7.07 (1H, dt, $J_{2',3'}$ 12.0 and $J_{2',4'}$ 1.7 Hz, C*H*=$CHCH_2$), 7.57-7.79 (2H, m, 2-H and 3-H), 7.88-7.99 (1H, m, 1-H or 4-H), 8.45-8.56 (1H, m, 4-H or 1-H), 14.79 (1H, s, OH).
^{13}C NMR (67.8 MHz; $CDCl_3$) -4.8, -4.5 (CH_3, $SiMe_2$), 18.1 (C, *C*Me_3), 23.5, 24.0 (CH_3, C-6'), 25.8 (CH_3, C*Me*$_3$), 35.6 (CH_2, C-9), 39.7, 39.8 (CH_2, C-4'), 67.9, 68.2 (CH, C-5'), 81.2 (CH, C-9a), 85.6 (CH, C-6b), 110.1 (C, C-6), 111.2 (C, C-6a), 122.1, 125.3 (CH, C-1, C-4), 124.5, 128.3 (C, C-4a, C-10b), 127.9 (CH, C-2'), 128.4, 130.5 (CH, C-2, C-3), 144.7, 145.5 (CH, C-3'), 150.5 (C, C-10a), 160.7 (C, C-5), 174.1 (C, C-8), 196.0 (C, C-1').
MS (EI) *m/z* 468 (M^+, 34), 411 (M-C_4H_9, 53), 367 (M-C_4H_9-CO_2, 20), 336 (M-$C_6H_{16}OSi$, 17), 295 (M-$C_9H_{21}OSi$, 18), 268 (M-$C_{11}H_{24}OSi$, 17), 159 ($C_8H_{19}OSi$, 100), 95 (38), 73 (87), 43 (CH_3CO, 39).
Anal. Calcd for $C_{26}H_{32}O_6Si$: C, 66.6; H, 6.9. Found: C, 66.5; H, 6.7.

(ii) (3R*,9aR*,12aR*,2'R*)-, (3R*,9aR*,12aR*,2'S*)-, (3S*,9aR*,12aR*,2'R*)- *and* (3S*,9aR*,12aR*,2'S*)-3-(2-tert-Butyldimethylsilyloxypropyl)-2,3,9a,12a-tetrahydro-1H-furo[2",3":4',5']furo[3',2':3,4]naphtho[1,2-b]pyran-1,11(10H)-dione **21** (15 mg, 7%) as a colourless solid and as a mixture of stereoisomers (^{1}H–NMR).
m.p. 131.0-133.0°C; IR ($CHCl_3$) 1780 (C=O, γ-lactone), 1684s, 1675 (C=O, aryl ketone) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 0.08, 0.09(2), 0.010(2) (6H, s, $SiMe_2$), 0.81, 0.82, 0.89, 0.90 (9H, s, Bu^t), 1.27, 1.30 (3H, d, *J* 6.1 Hz, Me), 1.72-2.32 (2H, m, 1'-CH_2), 2.75-2.86 (2H, m, 2-CH_2), 3.14 (2H, d, $J_{10,9a}$ 4.0 Hz, 10-CH_2), 4.14-4.28, 4.33-4.45 (1H, m, CHOSi), 4.79-4.88 (1H, m, 3-H), 5.48-5.54 (1H, m, 9a-H), 6.74(2), 6.79 (1H, d, $J_{12a,9a}$ 5.9 Hz, 12a-H), 7.60-7.72 (2H, m, 6-H and 7-H), 7.94-7.97 (1H, m, 5-H or 8-H), 8.26-8.32 (1H, m, 8-H or 5-H).
^{13}C NMR (67.8 MHz; $CDCl_3$) -4.8, -4.3 (CH_3, $SiMe_2$), 17.9, 18.1 (C, *C*Me_3), 23.6, 23.7, 24.6 (CH_3, C-3'), 25.8 (CH_3, C*Me*$_3$), 35.7 (CH_2, C-10), 42.9, 43.0, 43.1, 43.2 (CH_2, C-2), 44.3, 44.4, 45.0, 45.2 (CH_2, C-1'), 64.2, 65.0 (CH, C-2'), 75.8, 77.2 (CH, C-3), 82.1, 82.3 (CH, C-9a), 85.1 (CH, C-12a), 111.4, 111.5, 111.9 (C, C-12b, C-12c), 122.4, 124.2 (CH, C-5, C-8), 127.0, 127.1, 127.2 (C, C-4b, C-8a), 127.9, 128.0, 129.9 (CH, C-6, C-7), 152.2(2), 152.4 (C, C-8b), 155.6(2), 156.0 (C, C-4a), 174.8(2) (C, C-11), 191.4, 191.6 (C, C-1).
MS (EI) *m/z* 468 (M^+, 47), 411 (M-C_4H_9, 97), 367 (M-C_4H_9-CO_2, 15), 343 (100), 297 (23), 262 (28), 212 (19), 182 (21), 162 (84), 132 ($C_6H_{16}OSi$, 20), 113 (26), 73 (31), 31 (34).
Anal. Calcd for $C_{26}H_{32}O_6Si$: C, 66.6; H, 6.9. Found: C, 66.7; H, 7.1.

(1'Z)-(3aR*,5R*,11bR*,4'R*)-, (3aR*,5R*,11bR*,4'S*)-(3aR*,5S*,11bR*,4'R*)- and (3aR*,5S*,11bR*,4'S*)-3,3a,5,11b-Tetrahydro-5-hydroxy-5-(4-tert-butyldimethylsilyloxypent-1-enyl-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione 23.

A solution of ceric ammonium nitrate (175 mg, 0.32 mmol) in water (1 cm^3) was added dropwise to a solution of **20** (78 mg, 0.16 mmol) in acetonitrile (10 cm^3) at room temperature and the reaction mixture stirred until no starting material could be detected (TLC). The reaction mixture was poured into dichloromethane (17 cm^3), washed with water (5 cm^3) and

dried over sodium sulphate. The solution was filtered through a Florisil pad and the solvent evaporated under reduced pressure to give an orange solid. Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluent gave the *title compound* **23** (43 mg, 55%) as a glassy yellow solid and as a mixture of stereoisomers (^{1}H–NMR).
m.p. 64.5-67.5°C.
IR (CH_2Cl_2) 3671-3122 (OH), 1794 (C=O, γ-lactone), 1671 (C=O, quinone), 1594 (C=C) cm^{-1}.
^{1}H NMR (400 MHz; $CDCl_3$) 0.10, 0.11, 0.12(2), 0.15 (6H, s, $SiMe_2$), 0.91(3) (9H, s, Bu^t), 1.22, 1.27 (3H, d, *J* 6.1 Hz, Me), 2.07-3.05 (2H, m, =CHCH_2), 2.66, 2.73 (1H, d, J_{gem} 17.6 Hz, 3-H^A), 2.95, 2.97 (1H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 5.0 Hz, 3-H^B), 3.95-4.08 (1H, m, CHOSi), 4.96, 5.03 (1H, dd, $J_{3a,3B}$ 5.0 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.30 (1H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 5.67-6.09 (2H, m, C*H*=C*H*CH$_2$), 7.75-7.85 (2H, m, 8-H and 9-H), 8.06-8.15 (2H, m, 7-H and 10-H).
^{13}C NMR (100.6 MHz; $CDCl_3$) -4.8, -4.2 (CH_3, $SiMe_2$), 14.1, 18.1, 22.7 (C, *C*Me$_3$), 23.7, 24.5, 29.3, 29.7 (CH_3, C-5'), 25.7, 25.8, 26.0 (CH_3, C*Me*$_3$), 36.4, 37.4, 40.0, 40.2 (CH_2, C-3'), 36.6, 37.6, 38.4, 38.6 (CH_2, C-3), 65.7, 66.4 (CH, C-3a), 68.4, 69.6 (CH, C-4'), 68.9, 69.1 (CH, C-11b), 92.5, 93.9 (C, C-5), 126.4, 126.7 (CH, C-7, C-10), 130.9, 131.3 (C, C-6a, C-10a), 131.8 (CH, C-1'), 131.8, 132.7 (CH, C-2'), 134.1, 134.4, 134.6, 134.8 (CH, C-8, C-9), 140.0, 140.9 (C, C-11a), 144.8, 144.9, 145.7 (C, C-5a), 174.3, 174.4 (C, C-2), 182.2, 183.2, 183.5, 183.6 (C, C-6, C-11).
MS (EI) *m/z* 483 (M-H, 0.3), 469 (M-CH_3, 1), 440 (M-CO_2, 2), 427 (M-C_4H_9, 46), 409 (13), 383 (M-CO_2-C_4H_9, 40), 339 (10), 295 (24), 265 (10), 159 (M-C_8H_{19}OSi, 74), 115 (25), 103 (14), 95 (8), 75 [$(CH_3)_2$SiOH, 77], 73 (100), 69 (8), 43 (CH_3CO, 9).
Anal. Calcd for $C_{26}H_{32}O_7Si$: C, 64.4; H, 6.7. Found: C, 64.7; H, 6.9.

(1'Z)-(3aR*,5R*,11bR*,4'R*)-, (3aR*,5R*,11bR*,4'S*)-, (3aR*,5S*,11bR*,4'R*)- and (3aR*,5S*,11bR*,4'S*)-3,3a,5,11b-Tetrahydro-5-hydroxy-5-(4-hydroxypent-1-enyl-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione 22.

A solution of ceric ammonium nitrate (282 mg, 0.51 mmol) in water (0.8 cm^3) was added dropwise to a solution of **20** (30 mg, 0.064 mmol) in acetonitrile (3.5 cm^3) at room temperature, and the reaction mixture stirred until no starting material could be detected (TLC, *ca.* 10 min). The mixture was then poured into ethyl acetate (8 cm^3), washed with water (2 × 4 cm^3) and dried over sodium sulphate. The solution was filtered through a Florisil pad and the solvent evaporated under reduced pressure to give an orange solid that was purified by flash chromatography, using hexane-ethyl acetate (1:2) as eluent, to afford the *title compound* **22** (15 mg, 64%) as a yellow solid and as a mixture of stereoisomers (^{1}H–NMR).
m.p. 91.0-95.0°C.
IR (film) 3591-3072 (OH), 1787 (C=O, γ–lactone), 1667 (C=O, quinone), 1592m (C=C) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 1.23 (1H, d, *J* 6.6 Hz, Me), 1.25 (1H, d, *J* 7.0 Hz, Me), 1.30 (0.5H, d, *J* 6.2 Hz, Me), 1.32 (0.5H, d, *J* 7.0 Hz, Me), 2.10-2.68 (2H, m, =CHCH_2), 2.73, 2.76 (1H, d, J_{gem} 17.6 Hz, 3-H^A), 2.99 (0.5H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 4.8 Hz, 3-H^B), 3.00 (0.5H, dd, J_{gem} 17.8 and $J_{3B,3a}$ 4.8 Hz, 3-H^B), 3.84-4.04 (1H, m, C*H*OH), 4.72-4.83 (1H, br.s, OH), 4.99, 5.00 (1H, dd, $J_{3a,3B}$ 4.8 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.30 (1H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 5.67-5.85 (1H, m, C*H*=CHCH$_2$), 5.87-6.00 (1H, m, =C*H*CH$_2$), 6.00-6.22 (1H, br.s, OH), 7.73-7.82 (2H, m, 8-H and 9-H), 8.02-8.13 (2H, m, 7-H and 10-H).
^{13}C NMR (67.8 MHz; $CDCl_3$) 22.9, 23.2, 23.8, 28.6 (CH_3, C-5'), 36.3, 37.1, 40.0 (CH_2, C-3'), 36.6, 38.6, 38.8, 39.1 (CH_2, C-3), 66.5, 66.9 (CH, C-3a), 66.9, 68.2 (CH, C-4'), 68.7, 69.0 (CH, C-11b), 92.3, 93.1 (C, C-5), 126.4, 126.5, 126.6(2) (CH, C-7, C-10), 130.5, 130.7 (CH, C-1'), 131.1(2), 131.9, 132.1 (C, C-6a, C-10a), 132.7, 133.3 (CH, C-2'), 134.0, 134.1, 134.3, 134.4, 134.6, 134.7 (CH, C-8, C-9), 139.3 (C, C-11a), 145.5, 145.8 (C, C-5a), 174.7, 175.4 (C, C-2), 182.4, 182.7, 183.0, 183.3 (C, C-6, C-11).
MS (EI) *m/z* 370 (M$^+$, 6), 354 (M-H_2O, 100), 308 (M-H_2O-CO_2, 21), 295 (61), 286 (M-C_5H_8O, 48), 249 (36), 225 (24), 199 (13), 162 (27), 139 (15), 105 (17), 77 (14) and 43(CH_3CO, 27).
Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.9; H, 4.9. Found: C, 64.6; H, 4.9.

(3aR*,5S*,11bR*,6'R*)-3a,11b,5',6'-Tetrahydro-6'-methylspiro[5H-furo[3,2-b]naphtho[2,3-d]pyran-5',2'-[2H]pyran]-2,6,11(3H)-trione 5 and (3aS*,5S*,11bS*,6'R*)-3a,11b,5',6'-Tetrahydro-6'-methylspiro[5H-furo[3,2-b]naphtho[2,3-d]pyran-5',2'-[2H]pyran]-2,6,11(3H)-trione 6.

Using camphorsulphonic acid

To a solution of **22** (36 mg, 0.097 mmol) in dichloromethane (5 cm^3) was added a catalytic quantity (*ca*. 2 mg) of camphorsulphonic acid. The reaction mixture was heated gently at reflux until no starting material was visible (TLC). Removal of the solvent under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (1:1) as eluent to give the *title compounds* **5** and **6** (18 mg, 52%) as a yellow solid and as a 3:2 (**5***:**6**) mixture of stereoisomers (^{1}H–NMR).
m.p. 229.0-233.0°C; IR (film) 1791 (C=O, γ–lactone), 1672 (C=O, quinone), 1595 (C=C) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 1.30 (1.2H, d, *J* 6.2 Hz, Me), 1.35* (1.8H, d, *J* 6.6 Hz, Me), 2.02-2.17*, 2.26-2.40, 2.60-2.72* (2H, m, 5'-CH_2), 2.71* (0.6H, d, J_{gem} 17.6 Hz, 3-H^A), 2.76 (0.4H, d, J_{gem} 17.7 Hz, 3-H^A), 2.98 (0.4H, dd, J_{gem} 17.7 and $J_{3B,3a}$ 4.7 Hz, 3-H^B), 2.99* (0.6H, dd, J_{gem} 17.6 and $J_{3B,3a}$ 4.9 Hz, 3-H^B), 4.08-4.24 (0.4H, m, 6'-H), 4.31-4.47* (0.6H, m, 6'-H), 4.90 (0.4H, dd, $J_{3a,3B}$ 4.7 and $J_{3a,11b}$ 3.1 Hz, 3a-H), 5.01* (0.6H, dd, $J_{3a,3B}$ 4.9 and $J_{3a,11b}$ 3.0 Hz, 3a-H), 5.32*

(0.6H, d, $J_{11b,3a}$ 3.0 Hz, 11b-H), 5.33 (0.4H, d, $J_{11b,3a}$ 3.1 Hz, 11b-H), 5.63-5.71 (1H, m, 3'-H), 6.19-6.26 (1H, m, 4'-H), 7.73-7.80 (2H, m, 8-H and 9-H), 8.02-8.15 (2H, m, 7-H and 10-H).
^{13}C NMR (67.8 MHz; $CDCl_3$) 21.0, 21.5 (CH_3, CH_3), 29.7, 31.1 (CH_2, C-5'), 36.6 (CH_2, C-3), 65.9, 68.9 (CH, C-6'), 66.3, 66.6 (CH, C-3a), 69.0 (CH, C-11b), 91.5, 92.6 (C, C-5), 125.6, 125.7 (CH, C-3Õ), 126.4, 126.6 (CH, C-7, C-10), 127.6, 129.2 (CH, C-4'), 131.3, 132.2, 133.3 (C, C-6a, C-10a), 134.0, 134.1, 134.5 (CH, C-8, C-9), 135.5, 136.2 (C, C-11a), 144.0, 144.5 (C, C-5a), 174.1, 174.3 (C, C-2), 181.5, 182.3, 183.1, 183.3 (C, C-6, C-11).
MS (EI) *m/z* 352 (M^+, 22), 324 (M-CO, 93), 307 (M-CO_2H, 97), 295 (M-CO-C_2H_5, 75), 279 (M-CO_2-C_2H_5, 34), 251 (M-$C_5H_9O_2$, 29), 238 (M-$C_6H_{10}O_2$, 29), 212 (29), 182 (M-$C_8H_{10}O_4$, 29), 162 (100), 132 (26), 113 (30), 95 (13), 70 (25), 43 (CH_3CO, 26), 31 (46).
Anal. Calcd for $C_{20}H_{16}O_{6:}$ C, 68.2; H, 4.6. Found: C, 67.8; H, 4.9.

Using hydrofluoric acid

To a solution of **23** (18.0 mg, 0.037 mmol) in acetonitrile (3 cm^3) was added dropwise a solution of 40% aqueous hydrofluoric acid (0.10 cm^3) in acetonitrile (1.0 cm^3) until no starting material could be detected (TLC). The reaction mixture was poured into ethyl acetate (5 cm^3), washed with water (2 × 3 cm^3) and dried over sodium sulphate. Removal of solvent under reduced pressure gave a yellow oil that was purified by flash chromatography, using hexane-ethyl acetate (1:1) as eluent to give the *title compounds* **5** and **6** (6.2 mg, 46% over two steps) as a 3:7 (**5**:**6**) mixture of stereoisomers (^{1}H–NMR).

(3aR*,5S*,5aS*,11aR*,11bS*,6'R*)-3a,5a,11a,11b,5',6'-Hexahydro-5a,11a-dihydroxy-6'-methylspiro[5H-furo[3,2-b]naphtho[2,3-d]pyran-5',2'-[2H]pyran]-2,6,11(3H)-trione 24 and
(3aS*,5S*,5aR*,11aS*,11bR*,6'R*)-3a,5a,11a,11b,5',6'-Hexahydro-5a,11a-dihydroxy-6'-methylspiro[5H-furo[3,2-b]naphtho[2,3-d]pyran-5',2'-[2H]pyran]-2,6,11(3H)-trione 25.

To a solution of spiroketal olefins **5** and **6** [8.3 mg, 0.024 mmol as a 4:5 (**5**:**6**) mixture of stereoisomers] in dichloromethane (0.25 cm^3) was added cetyltrimethylammonium permanganate [14] (11.9 mg, 0.030 mmol) and the reaction mixture stirred at room temperature for 3 h. Ether (3 cm^3) was added and the suspension dried over sodium sulphate before being filtered through a silica gel pad. After washing the pad with ether (*ca*. 15 cm^3) and removal of the solvent under reduced pressure, the residue was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluent, to give the *title compounds* **24** and **25** (2.1 mg, 27% based on unreacted **5**,**6**) as a yellow solid and as a 1:1 (**24**:**25**) mixture of stereoisomers (^{1}H–NMR).
m.p. 237.0-239.5ºC.
IR (CH_2Cl_2) 3861-3369 (OH), 1785 (C=O, γ–lactone), 1706s, 1687 (C=O, α-hydroxy aryl ketone) cm^{-1}.
^{1}H NMR (270 MHz; $CDCl_3$) 0.68 (1.5H, d, *J* 6.3 Hz, Me), 0.98 (1.5H, d, *J* 6.6 Hz, Me), 0.82-0.96, 1.20-1.40, 1.48-1.87 (2H, m, 5'-CH_2), 2.73, 2.75 (1H, d, J_{gem} 17.5 Hz, 3-H^A), 2.93(2) (1H, dd, J_{gem} 17.5 and $J_{3B,3a}$ 4.6 Hz, 3-H^B), 3.26-3.40, 3.73-3.89 (1H, m, 6'-H), 3.64-3.81 (1H, m, 2 × OH), 4.42, 4.46 (1H, s, 2 x OH), 4.61, 4.78 (1H, dd, $J_{3a,3B}$ 4.6 and $J_{3a,11b}$ 2.9 Hz, 3a-H), 5.38, 5.41 (1H, d, $J_{11b,3a}$ 2.9 Hz, 11b-H), 5.85-5.95 (1H, m, 3'-H), 5.95-6.03 (1H, m, 4'-H), 7.73-7.82 (2H, m, 8-H and 9-H), 8.02-8.17 (2H, m, 7-H and 10-H).
^{13}C NMR (100.6 MHz; $CDCl_3$) 19.5, 19.9 (CH_3, Me), 29.7, 31.3 (CH_2, C-5'), 37.7, 37.8 (CH_2, C-3), 66.0, 68.8 (CH, C-6'), 67.8, 68.3 (CH, C-3a), 73.9 (CH, C-11b), 80.7, 81.5, 84.2 (C, C-5a, C-11a), 96.2, 97.0 (C, C-5), 122.3(2) (CH, C-3'), 126.2, 126.5 (CH, C-7, C-10), 127.0, 127.3 (CH, C-4'), 129.2, 130.8 (C, C-6a, C-10a), 133.8, 133.9, 134.9, 135.1 (CH, C-8, C-9), 173.9, 174.0 (C, C-2), 188.6, 188.7, 196.3, 196.4 (C, C-6, C-11).
MS (EI) *m/z* 386 (M^+, 2), 277 (37), 257 ($C_{14}H_9O_5$, 6), 204 (13), 192 (21), 162 (8), 113 ($C_6H_9O_2$, 100), 95 (15), 85 (56), 43 (CH_3CO, 29).
HRMS. Calcd for $C_{20}H_{18}O_{8:}$ M, 386.1002. Found: M, 386.0962.
Unreacted spiroketals **5**,**6** (1.1 mg, 13%) were also recovered from the reaction.

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