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The divergent asymmetric synthesis of kalafungin, 5-*epi*-frenolicin B and related pyranonaphthoquinone antibiotics

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ABSTRACT

A divergent, asymmetric method for the synthesis of pyranonaphthoquinones is reported. The synthetic strategy applies a Staunton–Weinreb annulation between substituted *ortho*-toluates and the (*R*)-pyran-2-one **7** to construct the key naphthopyranone intermediates. Stereoselective introduction of either a methyl or propyl C5 alkyl substituent by use of Grignard addition/silane-mediated reduction and a sequence of oxidations gave a series of pyranonaphthoquinones including kalafungin **1**, 5-*epi*-9-methoxykalafungin **34** and 5-*epi*-frenolicin B **24**.

1. Introduction

The pyranonaphthoquinone family of compounds is a class of antibiotics widely dispersed in nature[1] with the majority of members of this group of natural products displaying interesting biological activities.[2] For example, kalafungin **1** (Fig. 1), first isolated in 1968 from *Streptomyces tanashiensis*,[3] is an inhibitor of pathogenic fungi, protozoa, yeasts and Gram-negative bacteria and also possesses cytotoxic activity. Frenolicin B **2**, isolated from a strain of *Streptomyces roseofulvus*,[4] possesses anticoccidial activity and has recently been shown to be a potent inhibitor of the serine/threonine kinase AKT (AKT1 IC_{50}=0.313 μM),[5,6] whilst arizonin B1 **3**[7] and griseusin A **4**[8] both exhibit modest Gram-positive activity.

The redox chemistry of quinone-based therapeutics, such as the anti-cancer agent doxorubicin, is often the basis of their beneficial properties, however, the one-electron reduction of quinones to semiquinone radicals (Scheme 1) and the subsequent generation of reactive oxygen species through redox cycling has been shown to be responsible for their damaging side-effects.[9] Indeed, the major dose-limiting side-effect in the use of doxorubicin in chemotherapy is its cardiotoxicity that results from radical formation. Upon two-electron reduction pyranoquinones such as kalafungin **1** may form their corresponding hydroquinone (Scheme 1), allowing opening of the γ-lactone to take place with resultant generation of a highly reactive *ortho*-quinone methide alkylating species.[10] Strong support for such a bioreductive alkylation mechanism has been demonstrated in the case of frenolicin B **2** wherein alkylation of a cysteine residue at the allosteric T-loop site of an AKT kinase was observed.[6]

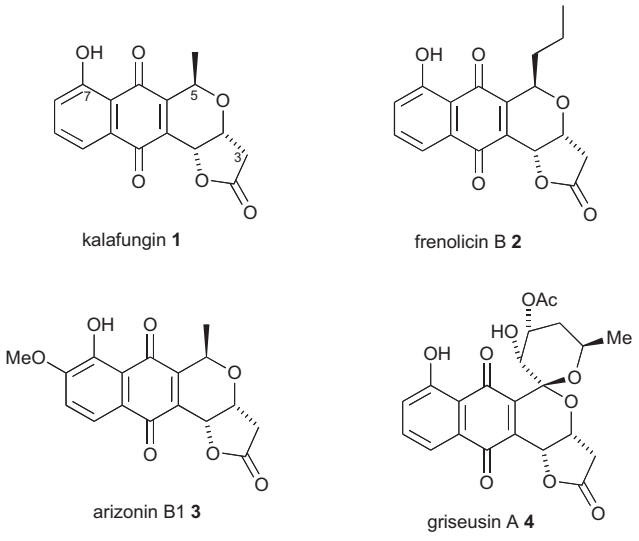

Fig. 1. Naturally occurring pyranonaphthoquinones.

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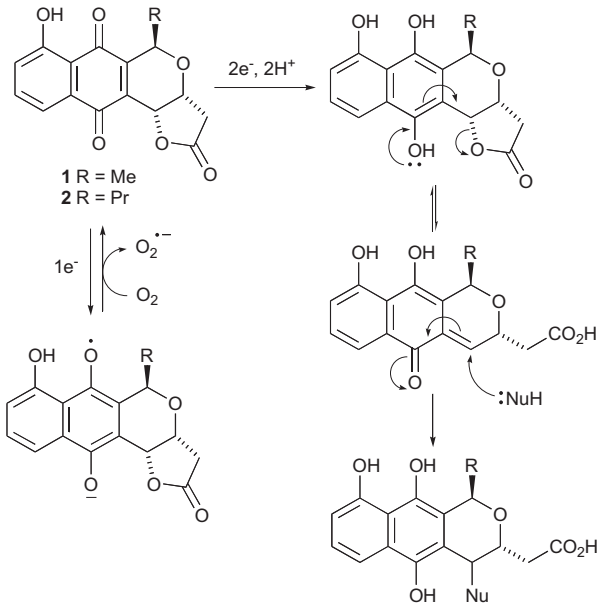


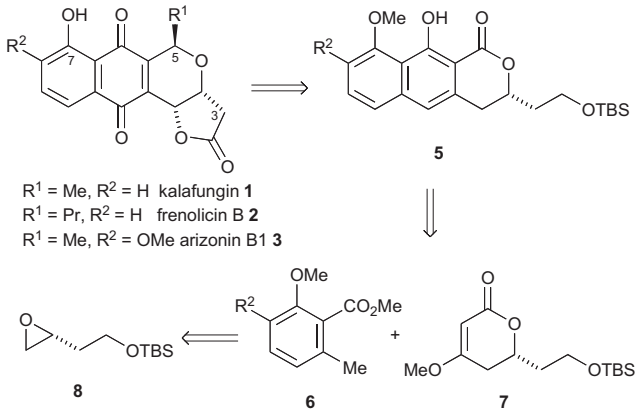
Scheme 1. Redox cycling and bioreductive alkylation mechanisms of pyranonaphthoquinones.

Due to their useful biological activities and interesting structures many synthetic strategies have been developed for the synthesis of pyranonaphthoquinone antibiotics,[11] however, these have often been target specific in nature. The first stereospecific synthesis of kalafungin **1** was achieved by Tatsuta and co-workers[12] employing an enantiodivergent approach that delivered both kalafungin **1** and nanaomycin D *ent*-**1** from a common carbohydrate-derived intermediate. Fernandes and Brückner[13] reported a stereoselective synthesis of kalafungin **1** that used an asymmetric dihydroxylation of an aryl-substituted β,γ-unsaturated ester to generate the γ-lactone ring, followed by oxa-Pictet–Spengler cyclization to complete the tetracyclic framework. The use of an oxa-Pictet–Spengler cyclization to form the pyran moiety allows the incorporation of a variety of substituents at C5, as demonstrated by both Salaski and co-workers[6] and Eid and co-workers[14] in the preparation of frenolicin B analogues. Whilst the first asymmetric synthesis of frenolicin B **2** was described by Kraus,[15] the recently reported kinase inhibitory activity of frenolicin B **2**[5,6] has generated renewed synthetic interest in this compound and its analogues.[6,14,16–18]

Whilst the synthesis of pyranonaphthoquinones using approaches that allow the incorporation of a variety of substituents on either the pyran[6,14] or aromatic ring[19] has been developed, a versatile method that allows structural variation to be readily incorporated on both the pyran and aromatic rings, as part of a single strategy, has not been adequately demonstrated. In pursuit of this goal we recently reported the synthesis of kalafungin **1** using a strategy that should be more widely applicable to the synthesis of a range of pyranonaphthoquinones.[20] Reported here are the full details of our synthesis of kalafungin **1**, along with the extension of this protocol to the synthesis of 5-*epi*-frenolicin B **24** and 5-*epi*-9-methoxykalafungin **34**, demonstrating the versatility of this newly developed strategy for the synthesis of various members of the pyranonaphthoquinone family.

2. Results and discussion

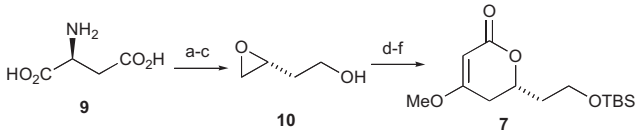
In order to develop a divergent approach to the pyranonaphthoquinone antibiotics we first sought to identify points in the synthesis at which flexibility needed to be incorporated. Comparison of the naturally occurring compounds **1**–**3** (Scheme 2), along with numerous other members of the group, highlights obvious



Scheme 2. Retrosynthetic analysis of pyranonaphthoquinones **1**–**3**.

structural similarities in that they each contain the same tetracyclic core with an oxygen substituent at C7 in the aromatic ring. What differentiates them from one another is the extent of oxygenation on the aromatic ring and the nature of the substituent at C5, which ranges from simple alkyl substitution, as seen in **1**–**3**, through to the more complex spiroacetal system seen in griseusin A **4**. It was reasoned that synthetically a variety of different C5 alkyl groups could be incorporated by addition of a suitable Grignard reagent (R^1MgX) to the naphthopyranone **5** followed by stereoselective reduction of the resultant lactol. Further elaboration may then lead to the pyranoquinones **1**–**3**. Substitution in the aromatic portion of naphthopyranone **5** (e.g., R^2=H, OMe), and hence the ultimate naphthoquinone products, would be determined by the choice of *ortho*-toluate **6** used in a Staunton–Weinreb annulation[21] with the chiral lactone **7**.

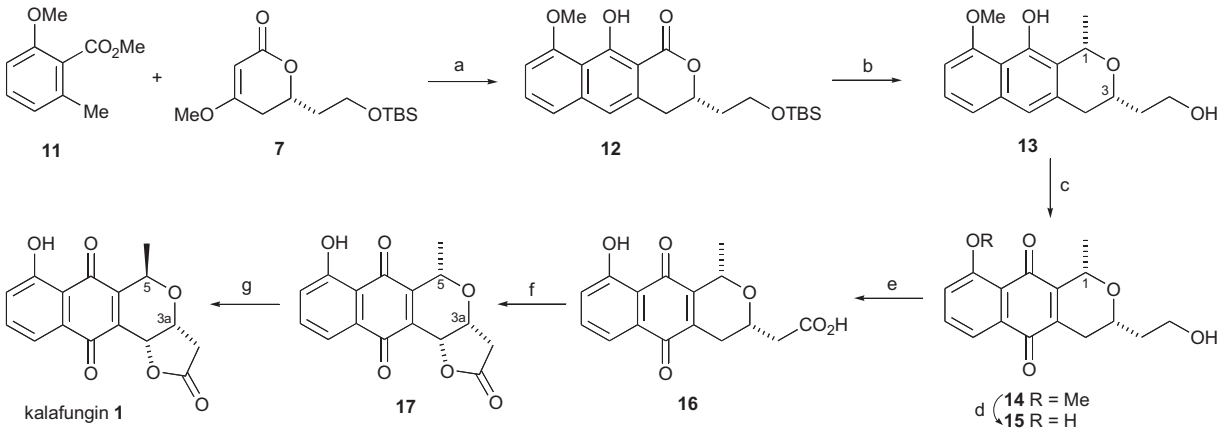
The first target chosen in order to develop and refine the synthetic methodology proposed in Scheme 2 was kalafungin **1**, the simplest γ-lactone-containing member of the pyranonaphthoquinone family. The synthesis of kalafungin **1** began with (*S*)-aspartic acid **9** that was converted into the (*R*)-epoxide **10** (Scheme 3) following the method of Volkmann and co-workers.[22] Protection of the hydroxyl group in **10** followed by opening of the epoxide with the anion of methyl propiolate and exposure of the resulting acetylenic ester to sodium methoxide gave the lactone **7** in 48% yield over the six steps from (*S*)-aspartic acid **9**, as previously reported.[23]



Scheme 3. Reagents and conditions: (a) $NaNO_2$, H_2SO_4, KBr, H_2O, 0 °C, 4 h (91%); (b) $BH_3{\cdot}Me_2S$, THF, −30 °C to rt, 18 h (97%); (c) K_2CO_3, CH_2Cl_2, 72 h (96%); (d) TBSCl, imidazole, CH_2Cl_2, 4 h (98%); (e) methyl propiolate, ^{n}BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 30 min (72%); (f) NaOMe, MeOH, 16 h (80%) (Fig. 1).

Applying Staunton–Weinreb annulation conditions, exposure of toluate **11** to LDA at −70 °C generates the toluate anion, which upon addition of lactone **7** undergoes a tandem Michael addition–Dieckmann cyclization reaction to deliver naphthopyranone **12** in 52% yield (Scheme 4). Careful control of temperature and the use of excess LDA appear crucial for this reaction. Using lower temperatures or longer periods at low temperature lead to formation of the side-product **18** (Fig. 2) in significant quantities (~20%), likely as a result of base-induced elimination.

Addition of methylmagnesium bromide to naphthopyranone **12**, followed by stereoselective reduction of the intermediate lactol



Scheme 4. Reagents and conditions: (a) LDA, THF, −70 to 0 °C, 1 h (52%); (b) (i) MeMgBr, THF, 0 °C, 4 h; (ii) TFA, Et_3SiH, CH_2Cl_2, −60 °C to rt, 2 h; (iii) THF, 2 M aq HCl, 16 h (74%, three steps); (c) (i) NBS, DMF, 18 h; (ii) CAN, H_2O, MeCN, 30 min (85%, two steps); (d) $AlCl_3$, CH_2Cl_2, 2 h (94%); (e) (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 16 h; (ii) $NaClO_2$, ^tBuOH, acetone, H_2O, NaH_2PO_4, 3 h (80%, two steps); (f) (i) O_2, MeOH, pyridine, 60 °C, 14 h; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −45 to 0 °C, 30 min (64%, two steps); (g) H_2SO_4, PhH, 30 min (81%).

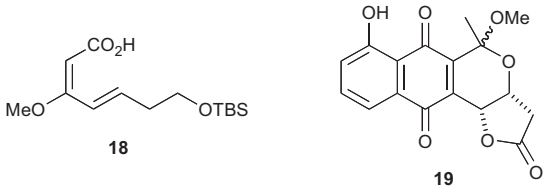


Fig. 2. Elimination product **18** formed during annulation and acetal **19** formed during lactonization.

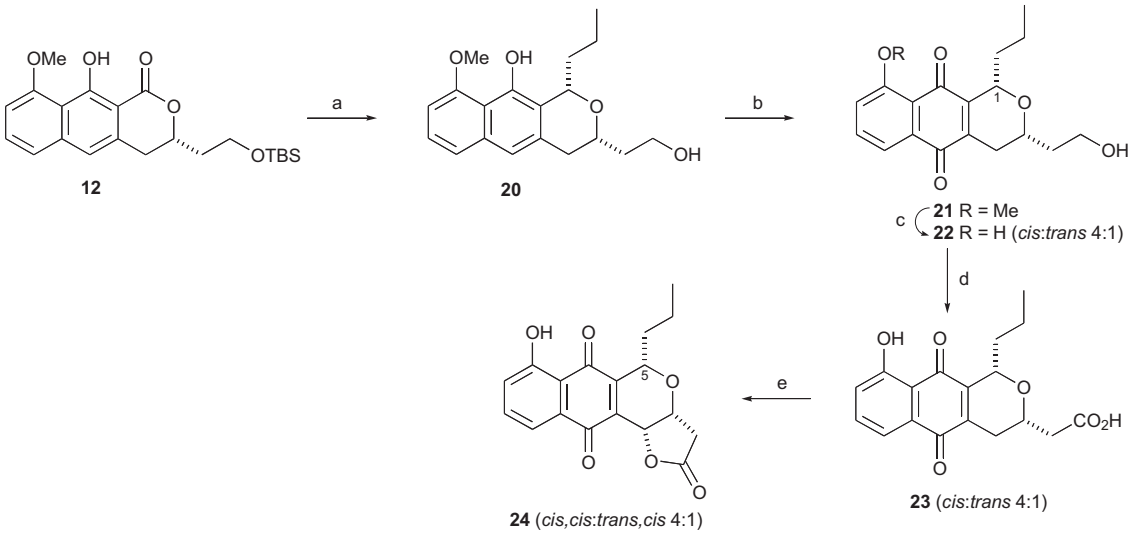
using Et_3SiH/TFA, gave the *cis*-pyran **13** as a single diastereoisomer. The 1,3-cis relationship between the C1 and C3 alkyl substituents was confirmed by the presence of an NOE correlation between the H-1 and H-3 protons, which adopt a 1,3-*pseudo*-diaxial arrangement. With the (1*S*,3*S*)-naphthopyran **13** in hand, all that remains to complete the synthesis of kalafungin **1** is to invert the stereochemistry at the benzylic ether position and effect a series of oxidations. The order in which to execute these operations should be flexible, however, in order to conveniently access stereochemical diversity 'correction' of the stereochemistry at C1 in **13** to that found in kalafungin **1** was left as the final step.

Using a two-step oxidation procedure, bromination of naphthol **13** using *N*-bromosuccinimide followed by exposure of the resulting *p*-bromonaphthol to ceric ammonium nitrate (CAN) gave the naphthoquinone **14**. Subsequent cleavage of the *O*-methyl ether using aluminium chloride[12] delivered **15** in 80% yield over three steps from **13**, with retention of stereochemical integrity. In contrast, partial epimerization at the C1 asymmetric centre was observed when boron tribromide was used to effect demethylation of **14**. Oxidation of the primary alcohol in *cis*-pyran **15** gave the required acid **16** in preparation for lactone formation. The formation of γ-lactones from carboxylic acids such as **16**, via an intermediate quinone methide, is known to proceed in the presence of base and atmospheric oxygen.[24] Exposing a solution of acid **16** in methanol/pyridine to oxygen formed the desired γ-lactone **17**, along with acetal **19** (Fig. 2) resulting from trapping of solvent. The crude mixture of **17** and **19** was reduced using $BF_3{\cdot}Et_2O/Et_3SiH$ to give 5-*epi*-kalafungin **17**.

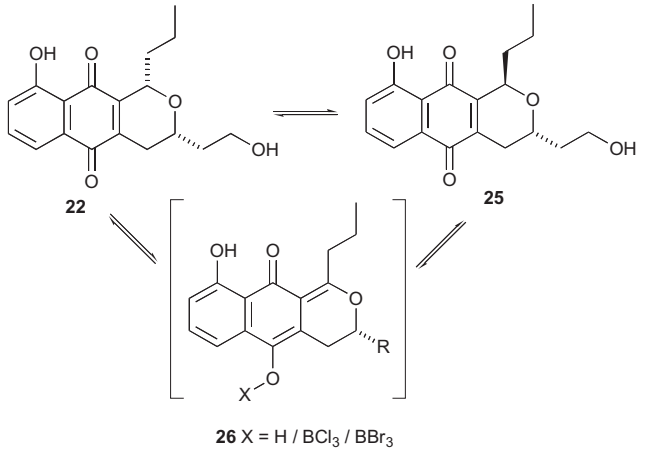
Final conversion into kalafungin **1** was achieved by exposure of **17** to concentrated sulfuric acid, conditions that catalyze inversion of the C5 configuration.[13,24a] Near complete epimerization at C5 to the thermodynamically favoured 5,3a-*trans*-pyran **1** (93:7 mixture of **1**/**17**) was achieved. Epimerization at C5 was clear from examination of the ^1H NMR spectrum in which the signals associated with the protons at C5 and C3a in **1** now appear at δ 5.09 and 4.69, respectively. The corresponding signals for the C5 and C3a protons in **17** appear at δ 4.79 and 4.35, respectively. These downfield shifts have been found to be diagnostic features of trans- versus cis-isomers for closely related γ-lactone-containing systems.[13,24b,25] Importantly, the spectroscopic data for synthetic kalafungin **1**, prepared here from (*S*)-aspartic acid **9**, were in close agreement with the reported data for (+)-kalafungin **1**.[12]

With the synthesis of kalafungin **1** established it was now possible to expand the scope of this technique towards the synthesis of other members of the pyranonaphthoquinone family. The synthetic design used for the preparation of kalafungin **1** incorporates two potentially divergent steps that are clearly amenable to exploitation. The first is the ability to vary the C5 alkyl group, introduced by the use of methylmagnesium bromide in the case of kalafungin **1**, by using different Grignard reagents. As a demonstration of this idea, we sought to prepare analogues in which the C5 group has been varied from the commonly seen methyl substituent, perhaps most significant in this regard being the natural product frenolicin B **2**. Whilst a family of 7-deoxyfrenolicin B analogues possessing a variety of substituents at C5 has been prepared,[6] using the naphthopyranone **12** it should be possible to introduce substituents at C5 whilst retaining the 7-OH group of the frenolicin B **2** naphthoquinone moiety.

Upon addition of propylmagnesium chloride to naphthopyranone **12**, followed by stereoselective reduction of the lactol intermediate, the naphthopyran **20** (Scheme 5) could be isolated in 47% yield as a single diastereoisomer. From this point, by applying a slightly modified reaction sequence to that developed for the synthesis of kalafungin **1**, 5-*epi*-frenolicin B **24** could be prepared as shown in Scheme 5. Thus, oxidation of naphthol **20** gave naphthoquinone **21** in 88% yield, however, attempts to cleave the methyl ether in **21** using aluminium chloride, as was used in the synthesis of kalafungin **1**, were unsuccessful. Boron tribromide has been reported to selectively cleave methyl ethers in related pyranoquinones[25] and, when used in excess, effect both demethylation and epimerization at the benzylic ether position.[25,26] Conversely, it has also been reported that the use of boron tribromide leads to rapid equilibration of *cis*-/*trans*-pyran diastereoisomers.[27] We found that attempted demethylation of **21** under boron tribromide conditions led to formation of complex mixtures. Using the more moderate Lewis acid boron trichloride[27] to form the free phenol **22** from **21** proved to be more effective, however, this still led to partial epimerization at C1 to the more stable trans-isomer **25** (Scheme 6).[28] The conversion of **22** to **25** is likely to occur via the dienol intermediate **26**, with the final mixture of the *cis*-**22**/*trans*-**25** diastereomers being obtained in a 4:1 ratio.



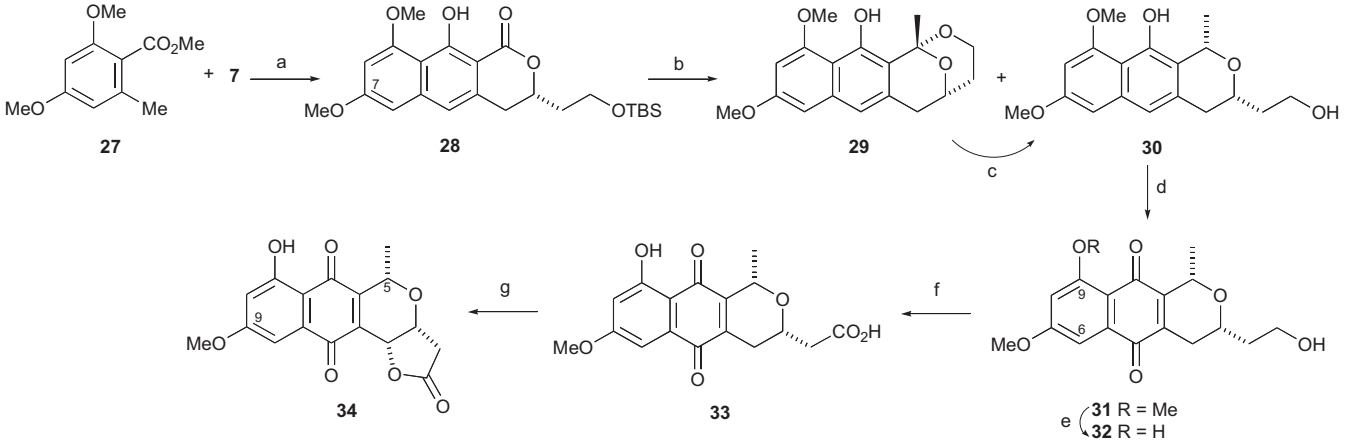
Scheme 5. Reagents and conditions: (a) (i) PrMgCl, THF, −50 °C to 0 °C, 2 h; (ii) TFA, Et_3SiH, CH_2Cl_2, −60 °C to rt, 2 h; (iii) THF, 2 M aq HCl, 1 h (47%, three steps); (b) (i) NBS, DMF, 18 h; (ii) CAN, H_2O, MeCN, 30 min (88%, two steps); (c) BCl_3, CH_2Cl_2, −50 to 0 °C, 1 h (44%); (d) (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 7 h; (ii) $NaClO_2$, ^tBuOH, acetone, H_2O, NaH_2PO_4, 3 h (72%, two steps); (e) (i) O_2, MeOH, pyridine, 65 °C, 10 h; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −45 °C to 0 °C, 30 min (50%, two steps).



Scheme 6. Proposed mechanism for acid-catalyzed epimerization of *cis*-pyran **22** to *trans*-pyran **25**.

Upon oxidation of **22** (4:1 cis/trans mixture), the acid **23** was obtained in 72% yield. The spectroscopic data for **23** were in close agreement with that reported for the corresponding racemic material.[27,29] Final conversion into the required γ-lactone was achieved by heating **23** in a solution of methanol/pyridine in the presence of oxygen, giving 5-*epi*-frenolicin B **24**.[27,30]

As a final demonstration of the intrinsic flexibility of this strategy we planned to take advantage of the potential to incorporate additional substituents on the aromatic portion of the core structure by the use of different *ortho*-toluates in the Staunton–Weinreb annulation step. Unfortunately, methyl 2,3-dimethoxy-6-methylbenzoate **6** (R^2=OMe, Scheme 2) and derivatives thereof failed to react efficiently with the lactone **7**,[31] thus precluding direct access to members of the arizonin family such as **3** using this technique. However, the 2,4-dimethoxy toluate **27** reacted successfully with lactone **7** to give the naphthopyranone **28** in good yield (Scheme 7).[23] From **28**, it was expected that the 9-methoxy analogue **34** could be prepared using the earlier developed sequence. However, the presence of the additional methoxy group at C7 on the aromatic system in **28** resulted in some variation to the expected reactivity in subsequent transformations. Thus, addition



Scheme 7. Reagents and conditions: (a) LDA, THF, −70 to 0 °C, 30 min (36%); (b) (i) MeMgBr, THF, 0 °C, 4 h; (ii) TFA, Et_3SiH, CH_2Cl_2, −60 °C to rt, 2 h; (iii) THF, 2 M aq HCl, 18 h (**29** 30%, **30** 40%, three steps); (c) $NaBH_4$, THF, 2 h (87%); (d) salcomine, MeCN, O_2, 23 h (74%); (e) $AlCl_3$, CH_2Cl_2, 2 h (96%); (f) (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 6 h; (ii) $NaClO_2$, ^tBuOH, H_2O, NaH_2PO_4, 3 h (65%, two steps); (g) (i) O_2, MeOH, pyridine, 60 °C, 10 h; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −45 to 0 °C, 30 min (64%, two steps).

of methylmagnesium bromide to naphthopyranone **28** followed by treatment with Et_3SiH/TFA gave, along with the expected *cis*-naphthopyran **30** in 40% yield, a second product identified as the cyclic acetal **29**. Formation of **29** may result from the lactol initially generated from **28** undergoing oxonium ion formation more readily in the presence of the more electron rich aromatic system, followed by intramolecular trapping by the primary alcohol. The conversion of **29** into the required *cis*-naphthopyran **30** could be effected by reduction of the acetal using sodium borohydride, with the combined yield of naphthopyran **30** being 66% from lactone **28**.

Upon bromination of naphthopyran **30** followed by treatment with CAN, the naphthoquinone **31** could be isolated in a modest 27% yield. A second product was also isolated, the ^{1}H NMR spectrum of which appeared nearly identical to **31** except for the presence of only a single aromatic signal. The spectroscopic data of this second product are consistent with formation of a C6 dimer of **31**, as has been observed to occur with similar naphthopyran systems under these conditions.[32] No further attempt was made to optimize formation of either **31** or the C6 dimer using CAN conditions. Instead, naphthopyran **30** was oxidized with salcomine,[33] resulting in formation of **31** in 74% yield without any trace of dimeric products being formed. Selective cleavage of the 9-*O*-methyl ether in **31** proceeded smoothly using aluminium chloride to give **32** in 96% yield. Oxidation of the primary alcohol in **32** gave the acid **33**, which upon exposure to pyridine and oxygen delivered 5-*epi*-9-methoxykalafungin **34**, a novel analogue of kalafungin **1**.

3. Summary and conclusions

In conclusion, this work constitutes a novel, stereoselective and divergent approach to the synthesis of the pyranonaphthoquinones kalafungin **1**, 5-*epi*-kalafungin **17**, 5-*epi*-9-methoxykalafungin **34** and 5-*epi*-frenolicin B **24**. The late-stage introduction of the C5 alkyl group in this series, via the key naphthopyranone intermediate **12**, demonstrates the potential to incorporate a variety of other substituents at this position by appropriate selection of organometallic reagents. Some flexibility in the choice of *ortho*-toluate used to prepare naphthopyranone intermediates, such as **12** and **28**, using the Staunton–Weinreb annulation has also been demonstrated.[31] With the more biologically active members of the pyranonaphthoquinone family in general possessing the common tetracyclic framework composed of a fused naphthoquinone–pyran–γ-lactone system, the new synthetic strategy demonstrated here, that allows ready access to this pharmacophore whilst allowing variability to be introduced into both the aromatic and pyran rings, will be of significant benefit for accessing many naturally occurring members and analogues of this class of antibiotics.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded using a Varian-500 spectrometer operating at 500 and 125 MHz, respectively. Chemical shifts are given using residual $CHCl_3$ (δ=7.26 for ^{1}H and 77.0 for ^{13}C) as internal standard. Infrared (IR) spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer. Gas chromatography–mass spectrometry (GC–MS) spectra were recorded on an Agilent 7890A GC system using an HP-5MS column (30 m, i.d. 0.25 mm, film thickness 0.25 μm) and 5975C MS system (EI, 70 eV). GC heat programs, method A: $100_5 \rightarrow 250_5$, heating rate 5 °C min^{-1}; method B: $100_5 \rightarrow 250_{30}$, heating rate 10 °C min^{-1}. The retention time (t_R) and selected fragment ions as their mass/charge ratio (m/z) are reported. High-resolution ESI mass spectra (HRMS) were recorded on a Thermo-Finnigan LTQ-FT ICR hybrid mass spectrometer. Specific rotations were measured using a JASCO DIP-1000 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}, c values are given in g 100 mL^{-1}. All moisture sensitive reactions were performed under a dry nitrogen or argon atmosphere in oven-dried or flame-dried glassware. Anhydrous tetrahydrofuran (THF) and dichloromethane were pre-dried over activated alumina under argon. Benzene was distilled from sodium/benzophenone ketyl prior to use. Thin layer chromatography was performed on pre-coated silica plates (Merck 60GF$_{254}$) and compounds were visualized at 254 nm and 365 nm or stained with 20% w/v phosphomolybdic acid in ethanol. Flash column chromatography was performed on silica gel (Kieselgel 60, 230–400 mesh) using the indicated solvent system. Melting points were measured using a Bausch and Lomb hot-stage melting point apparatus and are uncorrected.

4.2. Experimental procedures

*4.2.1. (S)-3,4-Dihydro-10-hydroxy-3-(2-(tert-butyldimethylsilyloxy) ethyl)-9-methoxy-1H-naphtho[2,3-c]pyran-1-one (**12**).* To a solution diisopropylamine (0.750 mL, 5.35 mmol) in THF (40 mL) at −40 °C was added *n*-butyllithium (2.1 M in hexane, 2.55 mL, 5.35 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 5 min. After cooling to −70 °C, methyl 2-methoxy-6-methylbenzoate **11** (482 mg, 2.67 mmol) in THF (5.0 mL) was added and stirring was continued for 10 min at −70 °C. To the resultant red solution was added the (*R*)-lactone **7**[23] (286 mg, 2.67 mmol) in THF (3.0 mL) and the mixture was maintained at −70 °C for 30 min then allowed to warm to 0 °C over 45 min. The reaction was quenched with saturated aq ammonium chloride (20 mL), extracted with ethyl acetate (3×15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/petrol 1:4 to 1:1) gave two main fractions; the first (R_f 0.60 in ethyl acetate/petrol 1:1) contained a mixture of benzoate **11** and naphthalene **12**, the second fraction (R_f 0.35 in ethyl acetate/petrol 1:1) was identified as unchanged lactone 7 (205 mg). The mixed fraction was further chromatographed (dichloromethane then dichloromethane/ethyl acetate 19:1) to afford the benzoate **11** (80 mg) and the *title compound* **12** (414 mg, 39%; 52% based on recovered lactone **7**) as a pale yellow oil; R_f (dichloromethane) 0.20; $[\alpha]_D^{20}$ +16.8 (c 0.94, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (6H, s, $Si(CH_3)_2$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.91–1.97 (1H, m, 3-CH_aH_b), 2.04–2.09 (1H, m, 3-CH_aH_b), 3.00–3.08 (2H, m, 4-H_2), 3.80–3.84 (1H, m, CH_aH_bOSi), 3.86–3.91 (1H, m, CH_aH_bOSi), 4.02 (3H, s, OCH_3), 4.74–4.79 (1H, m, 3-H), 6.83 (1H, d, J 8.1 Hz, 8-H), 6.97 (1H, s, 5-H), 7.23 (1H, d, J 8.1 Hz, 6-H), 7.48 (1H, dd, J 8.1 and 8.1 Hz, 7-H), 13.16 (1H, s, 10-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.4, -5.4, 18.2, 25.9, 33.5, 37.8, 56.2, 58.5, 76.6, 102.4, 106.0, 115.3, 116.0, 119.9, 130.7, 133.6, 139.9, 159.2, 164.0, 171.0; ν_{max} 2928, 1654, 1635, 1572, 1378, 1259, 1171, 1095, 832 cm^{-1}; GC–MS (method A, t_R=26.44 min) m/z 283.0 ([M−119]$^+$, 35%), 281 (58), 247.1 (35), 227.0 (29), 193.0 (43), 145.0 (42), 129.1 (46), 101.1 (100), 75.1 (83), 55.1 (66); HRMS (ESI): found 403.1933, $C_{22}H_{31}O_5Si$ ([M+H]$^+$) requires 403.1935.

*4.2.2. (1S,3S)-3,4-Dihydro-10-hydroxy-3-(2-hydroxyethyl)-9-methoxy-1-methyl-1H-naphtho[2,3-c]pyran (**13**).* To the lactone **12** (380 mg, 0.945 mmol) in THF (15 mL) at −30 °C was added methylmagnesium bromide (3 M in ether, 0.950 mL, 2.85 mmol) dropwise and the solution was allowed to warm to 0 °C. Two further portions of methylmagnesium bromide (each 0.400 mL, 1.20 mmol) were added at 1 h intervals. After 4 h at 0 °C the reaction was quenched with saturated aq ammonium chloride (15 mL), extracted with ethyl acetate (3×15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was dissolved in dichloromethane (20 mL) and cooled to −60 °C. Trifluoroacetic acid (218 μL, 2.84 mmol) in dichloromethane

(1.0 mL) was added dropwise followed by the addition of triethylsilane (483 μL, 3.02 mmol). The solution was allowed to warm slowly to room temperature over 1 h and stirred for a further 1 h. Water (15 mL) was added and after stirring for 15 min the mixture was extracted with dichloromethane (3×10 mL) and the combined organic layers concentrated in vacuo. The resultant oil was dissolved in THF (10 mL) and 2 M aq HCl (2 mL) and stirred at room temperature for 16 h. The mixture was then diluted with water (10 mL), extracted with ethyl acetate (3×15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/petrol 2:3) gave the *title compound* **13** (201 mg, 74%) as a pale yellow oil; R_f (ethyl acetate/petrol 1:1) 0.20; $[\alpha]_D^{25}$ −140 (*c* 1.44, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (3H, d, *J* 6.1 Hz, 1-CH_3), 1.88–1.95 (2H, m, 3-CH_2), 2.71 (1H, dt, *J* 15.4 and 1.0 Hz, 4-H_aH_b), 2.95 (1H, dd, *J* 15.4 and 11.0 Hz, 4-H_aH_b), 3.82–3.87 (1H, m, 3-H), 3.89 (2H, t, *J* 5.6 Hz, CH_2OH), 4.04 (3H, s, OCH_3), 5.25 (1H, q, *J* 6.1 Hz, 1-H), 6.71 (1H, d, *J* 7.6 Hz, 8-H), 7.04 (1H, s, 5-H), 7.24 (1H, dd, *J* 8.2 and 7.6 Hz, 7-H), 7.30 (1H, d, *J* 8.2 Hz, 6-H), 9.63 (1H, s, 10-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 36.0, 37.5, 56.0, 61.6, 71.3, 74.2, 103.2, 113.6, 117.3, 120.9, 121.1, 125.3, 134.9, 135.0, 150.2, 156.0; ν_{max} 3371, 2934, 1634, 1578, 1366, 1352, 1239, 1087, 1064 cm^{-1}; GC–MS (method A, t_R=37.10 min) *m*/*z* 288.1 ($[M]^+$, 33%), 273.1 (100), 227.1 (21); HRMS (ESI): found 289.1434, $C_{17}H_{21}O_4$ ($[M+H]^+$) requires 289.1434.

*4.2.3. (1S,3S)-3,4,5,10-Tetrahydro-3-(2-hydroxyethyl)-9-methoxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran (**14**).* To the naphthol **13** (50.0 mg, 0.173 mmol) in DMF (1.5 mL) was added NBS (32.0 mg, 0.180 mmol) in DMF (0.50 mL) and the solution was stirred in the dark at room temperature for 18 h. Water (10 mL) was added and the mixture was extracted with ethyl acetate (4×5 mL), the combined organic extracts washed with water (4×10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residual yellow oil was dissolved in acetonitrile (2.0 mL) and a solution of ammonium cerium(IV) nitrate (230 mg, 0.420 mmol) in water (0.75 mL) was added dropwise. After stirring for 30 min, water (5 mL) was added and the mixture extracted with chloroform (3×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 95:5) gave the *title compound* **14** (44 mg, 85%) as a yellow oil; R_f (ethyl acetate) 0.35; $[\alpha]_D^{22}$ −196 (*c* 1.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* 6.6 Hz, 1-CH_3), 1.90–1.94 (2H, m, 3-CH_2), 2.32 (1H, ddd, *J* 18.2, 10.4 and 3.6 Hz, 4-H_aH_b), 2.75 (1H, dt, *J* 18.2 and 2.4 Hz, 4-H_aH_b), 3.68–3.73 (1H, m, 3-H), 3.84–3.89 (2H, m, CH_2OH), 3.99 (3H, s, OCH_3), 4.86–4.90 (1H, m, 1-H), 7.28 (1H, d, *J* 8.4 Hz, 8-H), 7.64 (1H, dd, *J* 8.4 and 7.8 Hz, 7-H), 7.73 (1H, d, *J* 7.8 Hz, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 28.2, 37.4, 56.4, 60.6, 70.3, 72.2, 117.8, 119.0, 120.1, 133.8, 134.6, 139.5, 148.2, 159.4, 183.4, 183.8; ν_{max} 3508, 2939, 1651, 1585, 1257, 1057 cm^{-1}; GC–MS (method A, t_R=37.42 min) *m*/*z* 302.1 ($[M]^+$, 100%), 269.1 (23), 257.1 (92), 243.1 (50), 241.1 (26), 229.1 (26); HRMS (ESI): found 303.1227, $C_{17}H_{19}O_5$ ($[M+H]^+$) requires 303.1227.

*4.2.4. (1S,3S)-3,4,5,10-Tetrahydro-9-hydroxy-3-(2-hydroxyethyl)-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran (**15**).* To the methyl ether **14** (110 mg, 0.364 mmol) in dichloromethane (10 mL) was added aluminium chloride (388 mg, 2.91 mmol) and the mixture was stirred at room temperature for 90 min. After addition of water (15 mL) and chloroform (10 mL) the mixture was stirred vigorously for 30 min. Extraction with chloroform (5×10 mL), drying ($MgSO_4$) and concentration in vacuo gave the *title compound* **15** (99 mg, 94%) as a yellow oil that was used without further purification; R_f (ethyl acetate) 0.54; $[\alpha]_D^{23}$ −240 (*c* 0.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, d, *J* 6.6 Hz, 1-CH_3), 1.89–1.95 (2H, m, 3-CH_2), 2.37 (1H, ddd, *J* 18.6, 10.5 and 3.9 Hz, 4-H_aH_b), 2.77 (1H, dt, *J* 18.6 and 2.6 Hz, 4-H_aH_b), 3.69–3.74 (1H, m, 3-H), 3.83–3.91 (2H, m, CH_2OH), 4.85–4.88 (1H, m, 1-H), 7.24 (1H, dd, *J* 8.1 and 1.6 Hz, 8-H), 7.59 (1H, dd, *J* 8.1 and 7.7 Hz, 7-H), 7.62 (1H, dd, *J* 7.7 and 1.6 Hz, 6-H), 11.98 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 28.9, 37.3, 60.6, 69.8, 72.2, 114.9, 119.1, 124.5, 131.7, 136.2, 143.7, 146.0, 161.4, 183.0, 189.0; ν_{max} 3408, 2938, 1659, 1635, 1610, 1455, 1278, 1237, 1055 cm^{-1}; GC–MS (method A, t_R=34.43 min) *m*/*z* 288.1 ($[M]^+$, 100%), 270.1 (50), 255.1 (29), 243.1 (48), 229.1 (39), 227.1 (28), 215.1 (61), 214.1 (84), 213.1 (56), 197.1 (40), 121.1 (34), 115.1 (25); HRMS (ESI): found 289.1071, $C_{16}H_{17}O_5$ ($[M+H]^+$) requires 289.1071.

*4.2.5. (1S,3S)-3,4,5,10-Tetrahydro-9-hydroxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran-3-acetic acid (**16**).* To alcohol **15** (98.0 mg, 0.340 mmol) in dichloromethane (1.0 mL) were added [bis(acetoxy)-iodo]benzene (120 mg, 0.361 mmol) and TEMPO (5.0 mg, 0.032 mmol) and the mixture was stirred at room temperature for 16 h. The reaction mixture was then diluted with aq sodium thiosulfate (5 mL) and extracted with chloroform (4×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue, containing the crude intermediate aldehyde, was dissolved in a mixture of acetone (2.0 mL), *tert*-butanol (4.0 mL) and water (1.0 mL). 2-Methyl-2-butene (1.0 mL) was added followed by sodium dihydrogenphosphate (159 mg, 1.15 mmol) and sodium chlorite (77.0 mg, 0.852 mmol) and the mixture was stirred vigorously for 3 h. After addition of 2 M aq HCl (2.0 mL) the mixture was extracted with chloroform (4×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate) gave the *title compound* 16 (82 mg, 80%) as a yellow solid, mp 99–101 °C (dichloromethane/hexane); R_f (ethyl acetate) 0.24; $[\alpha]_D^{23}$ −173 (*c* 0.32, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, d, *J* 6.6 Hz, 1-CH_3), 2.35 (1H, ddd, *J* 18.5, 10.4 and 3.8 Hz, 4-H_aH_b), 2.69 (1H, dd, *J* 16.1 and 5.2 Hz, 3-CH_aH_b), 2.77 (1H, dd, *J* 16.1 and 7.6 Hz, 3-CH_aH_b), 2.89 (1H, dt, *J* 18.5 and 2.6 Hz, 4-H_aH_b), 3.91–3.99 (1H, m, 3-H), 4.87–4.90 (1H, m, 1-H), 7.25 (1H, dd, *J* 8.2 and 1.5 Hz, 8-H), 7.59 (1H, dd, *J* 8.2 and 7.6 Hz, 7-H), 7.63 (1H, dd, *J* 7.6 and 1.5 Hz, 6-H), 11.97 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 28.5, 40.1, 68.9, 70.0, 115.0, 119.1, 124.5, 131.7, 136.2, 143.2, 146.2, 161.5, 175.7, 182.9, 188.9; ν_{max} 2938, 1712, 1661, 1636, 1611, 1456, 1273, 1238, 1102 cm^{-1}; GC–MS (method A, t_R=35.87 min) *m*/*z* 302.0 ($[M]^+$, 35%), 284.1 (100), 256.0 (27), 243.1 (51), 242.1 (89), 241.1 (69), 227.1 (51), 214.0 (64), 213.0 (45), 139.1 (27), 128.1 (28), 121.0 (40), 115.0 (29); HRMS (ESI): found 301.0725, $C_{16}H_{13}O_6$ ($[M-H]^-$) requires 301.0718.

*4.2.6. 5-epi-Kalafungin (**17**).* A solution of acid **16** (30.0 mg, 0.099 mmol) in methanol (7.0 mL) and pyridine (0.5 mL) was maintained at 60 °C whilst oxygen was bubbled through the solution. After 14 h the solution was concentrated in vacuo then 2 M aq HCl (2.0 mL) was added and the mixture extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was dissolved in dichloromethane (4.0 mL) and cooled to −45 °C. Boron trifluoride diethyl etherate (75 μL, 0.592 mmol) was added and stirring was continued for 10 min. Triethylsilane (144 μL, 0.902 mmol) was added and stirring was continued at −45 °C for 10 min followed by warming to 0 °C over 15 min. Water (5 mL) was added, the mixture vigorously stirred (10 min) then extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate) gave the *title compound* **17** (14 mg, 47%, 64% based on recovered acid **16**) as a yellow oil, R_f (ethyl acetate) 0.65, and recovered acid **16** (8 mg). Data for **17**: $[\alpha]_D^{20}$ −90.5 (*c* 0.24, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64 (3H, d, *J* 6.7 Hz, 5-CH_3), 2.74 (1H, d, *J* 17.3 Hz, 3-H_aH_b), 2.89 (1H, dd, *J* 17.3 and 4.5 Hz, 3-H_aH_b), 4.35 (1H, dd, *J* 4.5 and 2.4 Hz, 3a-H), 4.79 (1H, qd, *J* 6.7 and 1.6 Hz, 5-H), 5.26–5.27 (1H, m, 11b-H), 7.30 (1H, dd, *J* 7.9 and 1.6 Hz, 8-H), 7.67

(1H, dd, *J* 7.9 and 7.5 Hz, 9-H), 7.69 (1H, dd, *J* 7.5 and 1.6 Hz, 10-H), 11.74 (1H, s, 7-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6, 37.2, 68.6, 69.7, 71.1, 115.1, 119.6, 124.8, 131.4, 135.6, 137.0, 150.2, 161.7, 174.2, 181.6, 188.6; ν_{max} 3503, 2927, 1786, 1666, 1644, 1616, 1456, 1283, 1246, 1147, 1037 cm^{-1}; HRMS (ESI): found 299.0568, $C_{16}H_{11}O_6$ ($[M-H]^-$) requires 299.0561.

*4.2.7. Kalafungin (**1**).* To the *cis*-pyran **17** (8.0 mg, 0.027 mmol) in benzene (0.5 mL) at 5 °C was added concentrated H_2SO_4 (10 drops). After 5 min the mixture was warmed to room temperature and stirred for 30 min. After ice (5 g) and ethyl acetate (10 mL) were added the mixture was stirred vigorously (15 min), washed with brine (3×5 mL) and the organic layer dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (dichloromethane/chloroform 4:1 then dichloromethane/chloroform/acetone 80:15:5) gave the *title compound* **1** (6.5 mg, 81%) as a yellow solid as a 93:7 diastereoisomeric mixture of *trans*/*cis* pyrans **1** and **17**; R_f (dichloromethane/chloroform/acetone 80:15:5) 0.40. Data for **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.57 (3H, d, *J* 6.8 Hz, 5-CH_3), 2.71 (1H, d, *J* 17.7 Hz, 3-H_aH_b), 2.96 (1H, dd, *J* 17.7 and 5.1 Hz, 3-H_aH_b), 4.69 (1H, dd, *J* 5.1 and 3.0 Hz, 3a-H), 5.09 (1H, q, *J* 6.8 Hz, 5-H), 5.26 (1H, d, *J* 3.0 Hz, 11b-H), 7.31 (1H, dd, *J* 8.3 and 1.5 Hz, 8-H), 7.67 (1H, dd, *J* 8.3 and 7.6 Hz, 9-H), 7.71 (1H, dd, *J* 7.6 and 1.5 Hz, 10-H), 11.84 (1H, s, 7-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 36.9, 66.2, 66.4, 68.6, 114.8, 119.8, 124.9, 131.5, 135.1, 137.2, 149.7, 161.9, 173.9, 181.5, 188.0; ν_{max} 2927, 1783, 1650, 1621, 1456, 1284, 1243, 1196, 1150 cm^{-1}; HRMS (ESI): found 301.0707, $C_{16}H_{13}O_6$ ($[M+H]^+$) requires 301.0707.

The spectroscopic data (^{1}H and ^{13}C NMR) are in close agreement with the literature.[12]

*4.2.8. (1S,3S)-3-(2-Hydroxyethyl)-9-methoxy-1-propyl-3,4-dihydro-1H-benzo[g]isochromen-10-ol (**20**).* To the lactone **12** (206 mg, 0.510 mmol) in THF (10 mL) at −50 °C was added propylmagnesium chloride (2 M in ether, 1.00 mL, 2.00 mmol) dropwise and the solution was allowed to warm to 0 °C over 1 h. A further portion of propylmagnesium chloride (0.50 mL, 1.00 mmol) was added and after 1 h at 0 °C the reaction was quenched with saturated aq ammonium chloride (10 mL), extracted with ethyl acetate (3×10 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude residue was dissolved in dichloromethane (10 mL) and cooled to −60 °C. Trifluoroacetic acid (114 μL, 1.54 mmol) in dichloromethane (1.0 mL) was added dropwise followed by the addition of triethylsilane (262 μL, 1.64 mmol). The solution was allowed to warm slowly to room temperature over 1 h and stirred for a further 1 h. Water (10 mL) and 2 M aq HCl (5 mL) were added and after stirring for 15 min the mixture was extracted with chloroform (3×10 mL) and the combined organic layers concentrated in vacuo. The resultant oil was dissolved in THF (5.0 mL) and 2 M aq HCl (1.0 mL) and stirred at room temperature for 1 h. The mixture was then diluted with water (10 mL), extracted with chloroform (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/petrol 1:2) gave the *title compound* **20** (76 mg, 47%) as a pale yellow oil; R_f (ethyl acetate/petrol 1:2) 0.25; $[\alpha]_D^{19}$ −200 (*c* 0.62, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 7.3 Hz, CH_3), 1.32–1.39 (1H, m, CH_aH_bCH$_3$), 1.45–1.51 (1H, m, CH$_a$$H_bCH_3$), 1.83–1.90 (1H, m, 1-C$H_aH_b$), 1.91–1.96 (2H, m, 3-$CH_2$), 2.09–2.16 (1H, m, 1-CH$_a$$H_b$), 2.69 (1H, dd, *J* 15.4 and 1.9 Hz, 4-H_aH_b), 2.93 (1H, dd, *J* 15.4 and 11.0 Hz, 4-H_aH_b), 3.82–3.87 (1H, m, 3-H), 3.88–3.90 (2H, m, CH_2OH), 4.05 (3H, s, OCH_3), 5.22–5.24 (1H, m, 1-H), 6.71 (1H, dd, *J* 7.6 and 1.0 Hz, 8-H), 7.04 (1H, s, 5-H), 7.23–7.26 (1H, m, 7-H), 7.31 (1H, dd, *J* 8.3 and 1.0 Hz, 6-H), 9.62 (1H, s, 10-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.6, 36.2, 37.2, 37.5, 56.0, 61.8, 74.39, 74.41, 103.3, 113.6, 117.1, 119.7, 121.1, 125.3, 134.9, 135.6, 150.0, 156.1; ν_{max} 3379, 2928, 1578, 1368, 1353, 1236, 1087, 1065 cm^{-1}; GC–MS (Method B, t_R=27.45 min) *m*/*z* 316.1 ($[M]^+$, 10%), 273.1 (100); HRMS (ESI): found 317.1749, $C_{19}H_{25}O_4$ ($[M+H]^+$) requires 317.1747.

*4.2.9. (1S,3S)-3-(2-Hydroxyethyl)-9-methoxy-1-propyl-3,4-dihydro-1H-benzo[g]isochromene-5,10-dione (**21**).* To the naphthol **20** (31.0 mg, 0.098 mmol) in DMF (1.0 mL) was added NBS (18.5 mg, 0.104 mmol) and the solution was stirred in the dark at room temperature for 18 h. Water (10 mL) was added and the mixture was extracted with chloroform (3×5 mL), the combined organic extracts washed with water (3×10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residual yellow oil was dissolved in acetonitrile (2.0 mL) and a solution of ammonium cerium(IV) nitrate (107 mg, 0.196 mmol) in water (0.20 mL) was added dropwise. After stirring for 30 min, water (10 mL) was added and the mixture extracted with chloroform (3×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 4:1) gave the *title compound* **21** (28 mg, 88%) as a yellow oil; R_f (ethyl acetate/chloroform 4:1) 0.40; $[\alpha]_D^{20}$ −167 (*c* 0.74, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, t, *J* 7.5 Hz, CH_3), 1.40–1.51 (2H, m, CH_2CH$_3$), 1.69–1.76 (1H, m, 1-CH_aH_b), 1.91–1.94 (2H, m, 3-CH_2), 1.96–2.03 (1H, m, 1-CH$_a$$H_b$), 2.30 (1H, ddd, *J* 18.1, 10.5 and 3.9 Hz, 4-H_aH_b), 2.76 (1H, ddd, *J* 18.1, 2.4 and 2.7 Hz, 4-H_aH_b), 3.66–3.71 (1H, m, 3-H), 3.85–3.88 (2H, m, CH_2OH), 4.00 (3H, s, OCH_3), 4.84–4.87 (1H, m, 1-H), 7.28 (1H, dd, *J* 8.6 and 1.1 Hz, 8-H), 7.65 (1H, dd, *J* 8.6 and 7.6 Hz, 7-H), 7.74 (1H, dd, *J* 7.6 and 1.1 Hz, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 18.7, 28.2, 36.2, 37.3, 56.4, 60.9, 72.5, 73.7, 117.8, 119.0, 120.1, 133.9, 134.6, 140.1, 147.6, 159.4, 183.5, 183.6; ν_{max} 3459, 2932, 1723, 1655, 1586, 1271, 1051 cm^{-1}; GC–MS (method B, t_R=27.25 min) *m*/*z* 330.2 ($[M]^+$, 100%), 287.1 (84), 285.1 (61), 269.1 (46), 256.0 (30), 254.0 (29), 243.0 (37), 241.0 (47), 227.0 (39), 128.1 (26), 115.0 (27), 76.0 (26); HRMS (ESI): found 331.1541, $C_{19}H_{23}O_5$ ($[M+H]^+$) requires 331.1540.

*4.2.10. (1S,3S)-9-Hydroxy-3-(2-hydroxyethyl)-1-propyl-3,4-dihydro-1H-benzo[g]isochromene-5,10-dione (**22**).* To the methyl ether **21** (28 mg, 0.085 mmol) in dichloromethane (1.5 mL) at −50 °C was added boron trichloride (1.0 M in dichloromethane, 0.45 mL, 0.45 mmol) and the mixture was allowed to warm slowly to 0 °C over 1 h. After addition of ice (5 g), water (5 mL) and chloroform (5 mL) the mixture was stirred vigorously for 30 min. Extraction with chloroform (3×5 mL), drying ($MgSO_4$) and concentration in vacuo gave a yellow residue. Flash column chromatography (ethyl acetate/chloroform 1:1) gave the *title compound* **22** (12 mg, 44%) as a yellow oil as a 4:1 mixture of *cis*-/*trans*-diastereoisomers; R_f (ethyl acetate/chloroform 4:1) 0.50; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 0.93 (3H, t, *J* 7.5 Hz, CH_3), 1.36–1.58 (2H, m, CH_2CH$_3$), 1.76–1.82 (1H, m, 1-CH_aH_b), 1.88–1.95 (2H, m, 3-CH_2), 2.02–2.09 (1H, m, 1-CH$_a$$H_b$), 2.34 (1H, ddd, *J* 18.5, 10.3 and 4.0 Hz, 4-H_aH_b), 2.78 (1H, ddd, *J* 18.5, 2.6 and 2.6 Hz, 4-H_aH_b), 3.67–3.71 (1H, m, 3-H), 3.86–3.89 (2H, m, CH_2OH), 4.82–4.86 (1H, m, 1-H), 7.24 (1H, dd, *J* 8.0 and 1.5 Hz, 8-H), 7.59 (1H, dd, *J* 8.0 and 7.5 Hz, 7-H), 7.62 (1H, dd, *J* 7.5 and 1.5 Hz, 6-H), 11.98 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer) δ 14.0, 18.6, 29.0, 36.6, 37.3, 60.9, 72.3, 73.1, 114.9, 119.1, 124.5, 131.7, 136.2, 144.4, 145.3, 161.5, 182.8, 189.0; ν_{max} 3460, 2927, 1660, 1637, 1612, 1456, 1279, 1241, 1057 cm^{-1}; GC–MS (method A, t_R=36.67 min) *m*/*z* 316.1 ($[M]^+$, 62%), 273.1 (94), 255.1 (100), 229.1 (56), 227.1 (45), 213.1 (32), 121.0 (28); HRMS (ESI): found 317.1384, $C_{18}H_{21}O_5$ ($[M+H]^+$) requires 317.1384.

*4.2.11. 2-((1S,3S)-9-Hydroxy-5,10-dioxo-1-propyl-3,4,5,10-tetrahydro-1H-benzo[g]isochromen-3-yl)acetic acid (**23**) (1-epi-deoxyfrenolicin).* To alcohol **22** (12.0 mg, 0.038 mmol) in dichloromethane (0.5 mL) were added [bis(acetoxy)-iodo]benzene (14.0 mg, 0.043 mmol) and TEMPO (1.0 mg, 0.006 mmol) and the mixture was stirred at room temperature for 7 h. The reaction mixture was then

diluted with aq sodium thiosulfate (5 mL) and extracted with chloroform (3×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue, containing the crude intermediate aldehyde, was dissolved in a mixture of acetone (0.2 mL), *tert*-butanol (0.5 mL) and water (0.2 mL). 2-Methyl-2-butene (0.1 mL) was added followed by sodium dihydrogenphosphate (18.0 mg, 0.114 mmol) and sodium chlorite (9.0 mg, 0.100 mmol) and the mixture was stirred vigorously for 3 h. After addition of 2 M aq HCl (2.0 mL) the mixture was extracted with chloroform (4×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 2:1) gave the *title compound* 23 (9.0 mg, 72%) as a yellow solid; R_f (ethyl acetate) 0.63; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 0.92 (3H, t, *J* 7.5 Hz, CH_3), 1.31–1.41 (1H, m, CH_aH$_b$CH$_3$), 1.43–1.52 (1H, m, CH$_a$$H_bCH_3$), 1.77–1.84 (1H, m, 1-C$H_aH_b$), 2.02–2.07 (1H, m, 1-CH$_a$$H_b$), 2.29–2.36 (1H, m, 4-$H_aH_b$), 2.70 (1H, dd, *J* 15.8 and 5.8 Hz, CH_aH$_b$CO$_2$H), 2.76 (1H, dd, *J* 15.8 and 7.6 Hz, CH$_a$$H_bCO_2$H), 2.90 (1H, ddd, *J* 18.4, 2.5 and 2.5 Hz, 4-H$_a$$H_b$), 3.89–3.93 (1H, m, 3-H), 4.84–4.86 (1H, m, 1-H), 7.25 (1H, dd, *J* 8.2 and 1.3 Hz, 8-H), 7.59 (1H, dd, *J* 8.2 and 7.6 Hz, 7-H), 7.62 (1H, dd, *J* 7.6 and 1.3 Hz, 6-H), 11.98 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer) δ 13.9, 18.3, 28.5, 36.4, 40.0, 68.7, 73.3, 114.9, 119.1, 124.5, 131.7, 136.2, 143.9, 145.4, 161.5, 175.0, 182.6, 188.9; ν_{max} 2926, 1712, 1661, 1637, 1612, 1456, 1274, 1243 cm^{-1}; HRMS (ESI): found 329.1022, $C_{18}H_{17}O_6$ ([M−H]$^-$) requires 329.1031.

The spectroscopic data (^{1}H and ^{13}C NMR) are in close agreement with the literature.[27,29]

*4.2.12. 5-epi-Frenolicin B (**24**).* A solution of acid **23** (8.0 mg, 0.024 mmol) in methanol (4.0 mL) and pyridine (0.3 mL) was maintained at 65 °C whilst oxygen was bubbled through the solution. After 10 h the solution was concentrated in vacuo then 1 M aq HCl (5.0 mL) was added and the mixture extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was dissolved in dichloromethane (1.5 mL) and cooled to −45 °C. Boron trifluoride diethyl etherate (15.0 μL, 0.119 mmol) was added and stirring was continued for 10 min. Triethylsilane (30.0 μL, 0.188 mmol) was added and stirring was continued at −45 °C for 10 min followed by warming to 0 °C over 15 min. Water (5 mL) was added, the mixture vigorously stirred (10 min) then extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 1:1) gave the *title compound* **24** (4.0 mg, 50%) as a yellow oil; R_f (ethyl acetate/chloroform 1:1) 0.64; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereoisomer) δ 0.91 (3H, t, *J* 7.4 Hz, CH_3), 1.28–1.35 (1H, m, CH_aH$_b$CH$_3$), 1.43–1.49 (1H, m, CH$_a$$H_bCH_3$), 1.91–1.98 (1H, m, 1-C$H_aH_b$), 2.04–2.10 (1H, m, 1-CH$_a$$H_b$), 2.75 (1H, d, *J* 17.5 Hz, 3-H_aH$_b$), 2.88 (1H, dd, *J* 17.5 and 4.5 Hz, 3-H$_a$$H_b$), 4.32 (1H, dd, *J* 4.5 and 2.3 Hz, 3a-H), 4.75–4.78 (1H, m, 5-H), 5.27 (1H, dd, *J* 2.3 and 2.3 Hz, 11b-H), 7.30 (1H, dd, *J* 8.1 and 1.6 Hz, 8-H), 7.67 (1H, dd, *J* 8.1 and 7.5 Hz, 9-H), 7.70 (1H, dd, *J* 7.5 and 1.6 Hz, 10-H), 11.74 (1H, s, 7-OH); ^{13}C NMR (125 MHz, $CDCl_3$, major diastereoisomer) δ 13.9, 18.2, 36.0, 37.3, 69.7, 70.8, 71.8, 115.0, 119.6, 124.8, 131.4, 136.2, 137.1, 149.7, 161.7, 174.3, 181.4, 188.7; ν_{max} 2960, 1787, 1665, 1644, 1617, 1456, 1284, 1247, 1148 cm^{-1}; HRMS (ESI): found 327.0878, $C_{18}H_{15}O_6$ ([M−H]$^-$) requires 327.0874.

The spectroscopic data (^{1}H and ^{13}C NMR) are in close agreement with the literature.[27,30]

*4.2.13. (1S,3S)-3,4-Dihydro-10-hydroxy-3-(2-hydroxyethyl)-7,9-dimethoxy-1-methyl-1H-naphtho[2,3-c]pyran (**30**) and cyclic acetal (**29**).* To the naphthopyranone **28**[23] (300 mg, 0.690 mmol) in THF (15 mL) at −40 °C was added methylmagnesium bromide (3.0 M in ether, 0.70 mL, 2.10 mmol) dropwise and the solution was allowed to warm to 0 °C. Two further portions of methylmagnesium bromide (each 0.35 mL, 1.05 mmol) were added at 1 h intervals. After 4 h at 0 °C the reaction was quenched with saturated aq ammonium chloride (20 mL), extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was dissolved in dichloromethane (15 mL) and cooled to −60 °C. Trifluoroacetic acid (160 μL, 2.08 mmol) in dichloromethane (1 mL) was added dropwise followed by the addition of triethylsilane (355 μL, 2.22 mmol). The solution was allowed to warm slowly to room temperature over 1 h and stirred for a further 1 h. Water (15 mL) was added and after stirring for 15 min the mixture was extracted with dichloromethane (3×10 mL) and the combined organic layers concentrated in vacuo. The resultant oil was dissolved in THF (10 mL) and 2 M aq HCl (5 mL) and stirred at room temperature for 18 h. The mixture was then diluted with water (10 mL), extracted with chloroform (3×10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/petrol 1:2) gave the *title compound* (*pyran*) **30** (88 mg, 40%) as a pale yellow oil, R_f (ethyl acetate/petrol 1:2) 0.17, and the *title compound* (*acetal*) **29** (65 mg, 30%) as a pale yellow oil, R_f (ethyl acetate/petrol 1:2) 0.24. Data for pyran **30**: $[\alpha]_D^{20}$ −105 (*c* 1.60, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (3H, d, *J* 6.3 Hz, 1-CH_3), 1.89–1.94 (2H, m, 3-CH_2), 2.67 (1H, dd, *J* 15.4 and 2.0 Hz, 4-H_aH$_b$), 2.92 (1H, dd, *J* 15.4 and 11.2 Hz, 4-H$_a$$H_b$), 3.82–3.86 (1H, m, 3-H), 3.87 (3H, s, OCH_3), 3.89 (2H, t, *J* 5.5 Hz, CH_2OH), 4.02 (3H, s, OCH_3), 5.21 (1H, q, *J* 6.3 Hz, 1-H), 6.39 (1H, d, *J* 2.2 Hz, 8-H), 6.61 (1H, d, *J* 2.2 Hz, 6-H), 6.93 (1H, s, 5-H), 9.40 (1H, s, 10-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 36.0, 37.5, 55.2, 56.0, 61.4, 71.2, 74.0, 97.1, 98.5, 109.4, 116.4, 118.9, 135.5, 135.6, 150.3, 157.1, 157.4; ν_{max} 3380, 2928, 1630, 1594, 1357, 1264, 1205, 1160 cm^{-1}; GC–MS (method A, t_R=33.76 min) *m*/*z* 318.2 ([M]$^+$, 25%), 303.1 (100); HRMS (ESI): found 341.1359, $C_{18}H_{22}O_5Na$ ([M+Na]$^+$) requires 341.1359; Data for acetal **29**: $[\alpha]_D^{19}$ −24.6 (*c* 0.060, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (1H, dd, *J* 13.7 and 3.0 Hz, 1′-H_aH$_b$), 2.05 (3H, s, 1-CH_3), 2.44–2.51 (1H, m, 1′-H$_a$$H_b$), 2.73 (1H, d, *J* 17.1 Hz, 4-H_aH$_b$), 3.55 (1H, dd, *J* 17.1 and 7.3 Hz, 4-H$_a$$H_b$), 3.57–3.63 (1H, m, 2′-$H_aH_b$), 3.76 (1H, dd, *J* 11.8 and 6.7 Hz, 2′-H$_a$$H_b$), 3.87 (3H, s, 7-$OCH_3$), 4.01 (3H, s, 9-$OCH_3$), 4.49–4.52 (1H, m, 3-H), 6.40 (1H, d, *J* 2.1 Hz, 8-H), 6.60 (1H, d, *J* 2.1 Hz, 6-H), 6.96 (1H, s, 5-H), 9.82 (1H, br s, 10-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.2, 33.3, 55.3, 56.2, 59.1, 66.2, 97.3, 98.4, 109.7, 115.7, 115.9, 136.5, 136.6, 152.2, 157.7, 158.1 (1 signal obscured); ν_{max} 3370, 2939, 1630, 1586, 1364, 1204, 1159, 1100, 1044 cm^{-1}; GC–MS (method A, t_R=33.95 min) *m*/*z* 316.1 ([M]$^+$, 54%), 301.1 (100), 255.1 (54), 254.1 (35), 240.1 (22), 239.1 (25); HRMS (ESI): found 317.1383, $C_{18}H_{21}O_5$ ([M+H]$^+$) requires 317.1384.

*4.2.14. (1S,3S)-3,4-Dihydro-10-hydroxy-3-(2-hydroxyethyl)-7,9-dimethoxy-1-methyl-1H-naphtho[2,3-c]pyran (**30**) (from reduction of acetal **29**).* To the acetal **29** (15.0 mg, 0.047 mmol) in THF at 0 °C was added $NaBH_4$ (40 mg, 1.06 mmol) and the solution was stirred for 1 h. After addition of further $NaBH_4$ (20 mg, 0.53 mmol) the solution was allowed to warm to room temperature and stirred for 2 h. Water was then added followed by 2 M aq HCl and the mixture was extracted with chloroform (3×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/petrol 1:2) gave the *title compound* **30** (13.0 mg, 87%) as a pale yellow oil. The spectroscopic data were identical to that described above.

*4.2.15. (1S,3S)-3,4,5,10-Tetrahydro-3-(2-hydroxyethyl)-7,9-dimethoxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran (**31**).* To the naphthol **30** (35.0 mg, 0.11 mmol) in MeCN (2.5 mL) was added salcomine (7.0 mg, 0.022 mmol) and the mixture was stirred under an atmosphere of oxygen for 23 h. The mixture was filtered through Celite and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 4:1) gave the *title compound* **31** (27.0 mg,

74%) as a yellow solid; R_f (ethyl acetate/chloroform 4:1) 0.40; $[\alpha]_D^{20}$ −161 (*c* 0.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* 6.6 Hz, 1-CH_3), 1.84–1.93 (2H, m, 3-CH_2), 2.31 (1H, ddd, *J* 18.2, 10.5 and 3.8 Hz, 4-H_aH_b), 2.72 (1H, dt, *J* 18.2 and 2.6 Hz, 4-H_aH_b), 3.68–3.72 (1H, m, 3-H), 3.85–3.88 (2H, m, CH_2OH), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.86–4.88 (1H, m, 1-H), 6.71 (1H, d, *J* 2.4 Hz, 8-H), 7.24 (1H, d, *J* 2.4 Hz, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.0, 28.3, 37.4, 55.9, 56.4, 60.8, 70.5, 72.5, 103.1, 104.2, 114.7, 135.6, 139.0, 148.4, 161.7, 164.5, 182.3, 183.9; ν_{max} 3478, 2924, 1647, 1593, 1564, 1318, 1267, 1156, 1048 cm^{-1}; HRMS (ESI): found 333.1331, $C_{18}H_{21}O_6$ ([M+H]$^+$) requires 333.1333.

*4.2.16. (1S,3S)-3,4,5,10-Tetrahydro-9-hydroxy-3-(2-hydroxyethyl)-7-methoxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran (**32**).* To the methyl ether **31** (27.0 mg, 0.081 mmol) in dichloromethane (2 mL) at 0 °C was added aluminium chloride (85 mg, 0.637 mmol) and the mixture was stirred for 30 min, warmed to room temperature and stirred for a further 45 min. After addition of water (5 mL) and chloroform (5 mL) the mixture was stirred vigorously for 30 min. Extraction with chloroform (3×5 mL), drying ($MgSO_4$) and concentration in vacuo gave the *title compound* **32** (25.0 mg, 96%) as a yellow oil that was used without further purification; R_f (ethyl acetate) 0.60; $[\alpha]_D^{20}$ −199 (*c* 0.046, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58 (3H, d, *J* 6.6 Hz, 1-CH_3), 1.91–1.95 (2H, m, 3-CH_2), 2.36 (1H, ddd, *J* 18.6, 10.4 and 3.9 Hz, 4-H_aH_b), 2.74 (1H, dt, *J* 18.6 and 2.6 Hz, 4-H_aH_b), 3.67–3.70 (1H, m, 3-H), 3.85–3.89 (2H, m, CH_2OH), 3.90 (3H, s, OCH_3), 4.83–4.86 (1H, m, 1-H), 6.63 (1H, d, *J* 2.6 Hz, 8-H), 7.18 (1H, d, *J* 2.6 Hz, 6-H), 12.22 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 28.9, 37.3, 56.0, 60.5, 69.9, 72.1, 106.2, 107.7, 109.5, 133.2, 142.8, 146.4, 164.3, 165.8, 182.9, 187.2; ν_{max} 3435, 2928, 1635, 1608, 1387, 1313, 1272, 1207 cm^{-1}; GC–MS (method A, t_R=39.80 min) *m*/*z* 318.1 ([M]$^+$, 100%), 300.1 (28), 273.1 (50), 259.0 (38), 257.0 (24), 245.0 (38), 244.0 (53), 243.0 (40), 151.0 (30); HRMS (ESI): found 317.1031, $C_{17}H_{17}O_6$ ([M−H]$^-$) requires 317.1031.

*4.2.17. (1S,3S)-3,4,5,10-Tetrahydro-9-hydroxy-7-methoxy-1-methyl-5,10-dioxo-1H-naphtho[2,3-c]pyran-3-acetic acid (**33**).* To alcohol **32** (25.0 mg, 0.079 mmol) in dichloromethane (1 mL) were added [bis(acetoxy)-iodo]benzene (28.0 mg, 0.086 mmol) and TEMPO (2.0 mg, 0.013 mmol) and the mixture was stirred at room temperature for 6 h. The reaction mixture was then diluted with aq sodium thiosulfate (2 mL) and extracted with chloroform (4×5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue, containing the crude intermediate aldehyde, was dissolved in a mixture of *tert*-butanol (1.0 mL) and water (0.25 mL). 2-Methyl-2-butene (0.25 mL) was added followed by sodium dihydrogenphosphate (37 mg, 0.24 mmol) and sodium chlorite (18 mg, 0.16 mmol) and the mixture was stirred vigorously for 3 h. After addition of 2 M aq HCl (1.0 mL) the mixture was extracted with chloroform (4×5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate/chloroform 2:1) gave the *title compound* 33 (17.0 mg, 65%) as a yellow solid; R_f (ethyl acetate) 0.45; $[\alpha]_D^{23}$ −157 (*c* 0.33, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (3H, d, *J* 6.4 Hz, 1-CH_3), 2.32 (1H, ddd, *J* 18.3, 10.4 and 3.8 Hz, 4-H_aH_b), 2.67 (1H, dd, *J* 16.1 and 5.2 Hz, 3-CH_aH_b), 2.76 (1H, dd, *J* 16.1 and 7.7 Hz, 3-CH$_a$$H_b$), 2.84 (1H, dt, *J* 18.3 and 2.6 Hz, 4-H_aH_b), 3.89 (3H, s, OCH_3), 3.92–3.96 (1H, m, 3-H), 4.85–4.88 (1H, m, 1-H), 6.62 (1H, d, *J* 2.4 Hz, 8-H), 7.16 (1H, d, *J* 2.4 Hz, 6-H), 12.20 (1H, s, 9-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 28.5, 40.1, 56.0, 68.9, 70.1, 106.3, 107.8, 109.5, 133.2, 142.3, 146.6, 164.3, 165.9, 175.0, 182.8, 187.1; ν_{max} 2918, 1708, 1636, 1607, 1299, 1262, 1205, 1150, 1101 cm^{-1}; HRMS (ESI): found 331.0822, $C_{17}H_{15}O_7$ ([M−H]$^-$) requires 331.0823.

*4.2.18. 5-epi-9-Methoxykalafungin (**34**).* A solution of acid **33** (17.0 mg, 0.051 mmol) in methanol (4.0 mL) and pyridine (0.3 mL) was maintained at 60 °C whilst oxygen was bubbled through the solution. After 10 h the solution was concentrated in vacuo then 2 M aq HCl (2.0 mL) was added and the mixture extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was dissolved in dichloromethane (2.0 mL) and cooled to −45 °C. Boron trifluoride diethyl etherate (25 μL, 0.199 mmol) was added and stirring was continued for 10 min. Triethylsilane (50 μL, 0.313 mmol) was added and stirring was continued at −45 °C for 10 min followed by warming to 0 °C over 15 min. Water (5 mL) was added, the mixture vigorously stirred (10 min) then extracted with chloroform (4×5 mL) and the combined organic layers dried ($MgSO_4$) and concentrated in vacuo. Flash column chromatography (ethyl acetate) gave the *title compound* **34** (7.0 mg, 41%, 64% based on recovered acid **33**) as a yellow oil, and recovered acid **33** (6.0 mg). Data for **34**: R_f (ethyl acetate) 0.50; $[\alpha]_D^{20}$ −60.0 (*c* 0.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (3H, d, *J* 6.7 Hz, 5-CH_3), 2.73 (1H, d, *J* 17.5 Hz, 3-H_aH_b), 2.88 (1H, dd, *J* 17.5 and 4.5 Hz, 3-H_aH_b), 3.94 (3H, s, OCH_3), 4.33 (1H, dd, *J* 4.5 and 2.5 Hz, 3a-H), 4.77 (1H, qd, *J* 6.7 and 1.7 Hz, 5-H), 5.24–5.25 (1H, m, 11b-H), 6.67 (1H, d, *J* 2.5 Hz, 8-H), 7.23 (1H, d, *J* 2.5 Hz, 10-H), 12.01 (1H, s, 7-OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 37.3, 56.2, 68.7, 69.8, 71.0, 106.5, 108.4, 109.8, 133.0, 134.9, 150.8, 164.7, 166.6, 174.3, 181.6, 186.5; ν_{max} 2925, 1790, 1610, 1303, 1265, 1205, 1150 cm^{-1}; HRMS (ESI): found 329.0670, $C_{17}H_{13}O_7$ ([M−H]$^-$) requires 329.0667.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **12**–**17**, **20**–**24**, **29**–**31** and **33**–**34**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.10.012.

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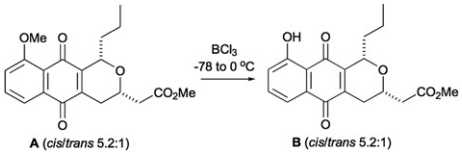

A (*cis*/*trans* 5.2:1) **B** (*cis*/*trans* 5.2:1)

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