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PAPER

Enantioselective synthesis of pyranonaphthoquinone antibiotics using a CBS reduction/cross-metathesis/oxa-Michael strategy†

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The enantioselective syntheses of deoxydihydrokalafungin (**5**), *cis*-deoxydihydrokalafungin (**6**) and deoxykalafungin (**7**) are reported. The strategy was based on 4 key reactions: (1) CBS reduction of prochiral ketone **10** to introduce chirality at C-1, (2) radical allylation of quinone **9a**, (3) cross-metathesis of dimethoxynaphthalene **13** with methyl acrylate, and (4) intramolecular oxa-Michael addition of alcohol **8** to form the core naphthopyran ring system. This novel approach delivers naphthopyrans possessing the natural *trans*-stereochemistry observed in the pyranonaphthoquinone family of antibiotics.

Introduction

Kalafungin (**1**) was isolated from *Streptomyces tanashienesis* strain *kala* in 1968[1] and is a member of the pyranonaphthoquinone antibiotics.[2] Closely related to **1** is the natural product dihydrokalafungin (**2**),[2] in which the γ-lactone moiety has been replaced with an open chain carboxylic acid (Fig. 1). Nanaomycins D (**3**) and A (**4**) are the enantiomers of **1** and **2**, respectively.[3] Kalafungin displays a range of biological activities *in vitro*, including growth-inhibition of Gram-positive bacteria, protozoa and yeasts.[4] Kalafungin also displays inhibitory activity against L5178Y mouse leukemia cells.[5] Dihydrokalafungin shows strong growth-inhibitory activity against Gram-positive bacteria, dermatophytes and fungi.[6]

The synthesis of pyranonaphthoquinones has attracted considerable attention.[7] In light of the potent biological activity of **1**, and the recent literature identifying pyranonaphthoquinones as a novel class of serine/threonine kinase AKT inhibitors,[8] the synthesis of deoxydihydrokalafungin (**5**) (Fig. 2) was investigated using a novel approach. Initial syntheses of the simpler members of the pyranonaphthoquinones (such as those in Fig. 1) focused on their construction in racemic form,[9] while enantioselective syntheses[10] are rather limited. Previous work in our laboratory has established the synthesis of the C-3 epimer of **5**, *cis*-deoxydihydrokalafungin (**6**) in 82% e.e. using an asymmetric allylation to introduce chirality.[11] Eid *et al.* have reported the synthesis of deoxykalafungin (**7**) in greater than 99% e.e. using an asymmetric dihydroxylation, followed by an oxa-Pictet–Spengler cyclization to form the natural *trans*-stereochemistry in the pyran ring system.[12] However, this approach furnishes the unnatural *cis*-stereochemistry when

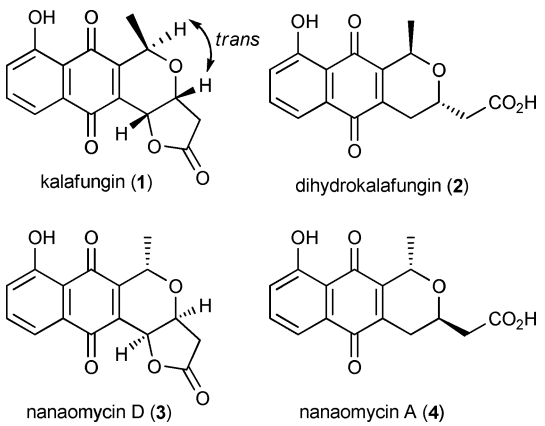

Fig. 1 Monomeric pyranonaphthoquinones.

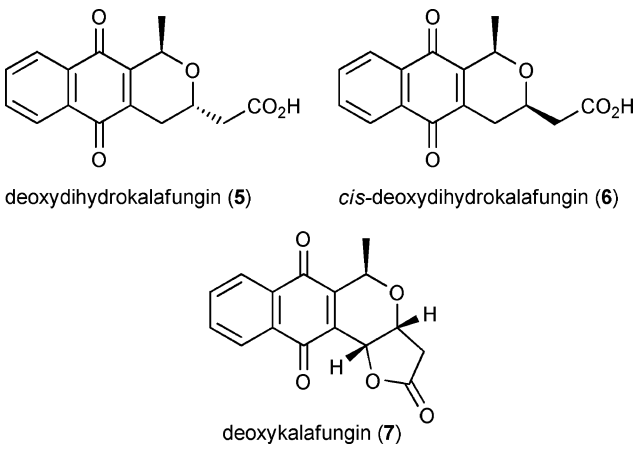

Fig. 2 Deoxykalafungin analogues.

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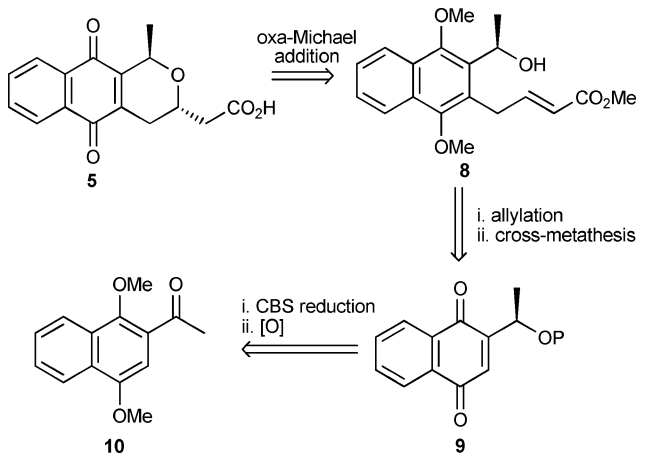
† Electronic supplementary information (ESI) available: Experimental details for **11b, 11c, 9b**, and **9c**, ^{1}H and ^{13}C NMR spectra of all new compounds, chiral HPLC and ^{1}H-^{1}H NOESY characterization data. See DOI: 10.1039/c1ob05595j

applied to the synthesis of the natural product kalafungin (**1**), necessitating the need for an epimerization step.[10c] We herein report the first synthesis of (1*R*,3*S*)-deoxydihydrokalafungin (**5**) and the synthesis of *cis*-deoxydihydrokalafungin (**6**) *en route* to deoxykalafungin (**7**) using a novel Corey–Bakshi–Shibata (CBS) reduction/cross-metathesis/oxa-Michael addition strategy. Furthermore, this novel approach delivers synthetically useful quantities of naphthopyrans possessing the natural *trans*-stereochemistry observed in the pyranonaphthoquinone family of antibiotics, negating the need for a late-stage epimerization.

It was envisaged that the synthesis of **5** could be achieved *via* intramolecular oxa-Michael addition[13] of **8**. It was hoped that the oxa-Michael addition would set up the *trans* substitution pattern of the naphthopyran ring without the need for a late stage epimerization process commonly used in the synthesis of pyranonaphthoquinones.[10] Michael acceptor **8** could be obtained by radical allylation[11,14] of quinone **9** followed by cross-metathesis.[11,15] The chirality in alcohol **9** can be introduced by CBS reduction[16] of the known prochiral ketone **10**[17a] (Scheme 1).



Scheme 1 Retrosynthesis of deoxydihydrokalafungin **5**.

Results and discussion

Prochiral ketone **10** was synthesized from 1,4-naphthoquinone as described previously[17] and attention quickly turned to the enantioselective reduction of **10** using CBS methodology. After considerable experimentation, it was found that the best results were obtained using the method adopted by Giles and Green: adding separate solutions of **10** and $BH_3{\cdot}SMe_2$ in THF to the (*S*)-Me-CBS catalyst at room temperature over 2 min.[18] Using this approach, chiral alcohol **11a** was obtained in excellent yield with an enantiomeric excess of 85%, as determined by chiral HPLC. Subsequent recrystallization of the product (hexanes–ethyl acetate 5 : 1) afforded alcohol **11a** in a pleasing 98–99% e.e.

Next, the radical allylation was attempted. Alcohol **11a** was protected both as a *tert*-butyldimethylsilyl (TBDMS) ether **11b** and an ethoxymethoxy (EOM) ether **11c**. As expected, oxidative demethylation of **11b** and **11c** using ceric ammonium nitrate (CAN)[19] gave the corresponding quinones **9b** and **9c** in good yield. However, when the allylation was examined using silver nitrate, ammonium persulfate and vinylacetic acid in aqueous acetonitrile[11,14] the formation of a complex mixture resulted. Use of allyltrimethylsilane in the presence of the Lewis acid additives Me_2AlCl[20] and $Bi(OTf)_3$[21] was also unsuccessful, resulting only in recovered starting material.

It was therefore decided to attempt allylation of the quinone core in the absence of the alcohol protecting group. Thus, direct CAN oxidation of **11a** furnished quinone **9a** in 93% yield, which was then subjected to the same allylation conditions attempted previously on **9b** and **9c**. Treatment of the crude product with TBDMSOTf followed by flash chromatography afforded the stable allylquinone **12b**. Reductive dimethylation of **12b** gave dimethoxynaphthalene **13** which underwent smooth cross-metathesis[15] with methyl acrylate in the presence of the Grubbs–Hoveyda 2nd generation catalyst providing α,β-unsaturated ester **14** as the thermodynamically favoured *E*-isomer in an acceptable 74% yield (Scheme 2).

With all the requisite functionality for the formation of the naphthopyran ring system now installed in **14**, we were keen to attempt the key oxa-Michael cyclization. With this idea in mind, silyl deprotection and subsequent intramolecular oxa-Michael addition was investigated. Initial results were discouraging: the use of TBAF in THF at room temperature led to degradation of the starting material within 3 h. Pleasingly, it was found that the use of TBAF buffered with acetic acid gave a much cleaner reaction albeit at a far slower reaction rate. To accelerate the reaction, the buffered TBAF was added to neat ester **14** and the solution stirred at 40 °C for 5 days, affording the diastereomeric naphthopyrans **15** and **16** with a combined yield of 84% in a ratio of 1.3 : 1. Diastereomers **15** and **16** were easily separable by flash chromatography.

The relative stereochemistry of the naphthopyran rings was unequivocally established using nOe data. The *trans*-naphthopyran **15** exhibited a strong correlation between the H-3 proton and the C-1 methyl group protons, thus indicating a *trans* relationship between the two ring substituents. In parallel with this assignment, the *cis*-naphthopyran **16** exhibited a nOe correlation between H-1 and H-3, consistent with the proposed *cis* stereochemistry (Fig. 3).

The modest selectivity observed for the *trans*-substituted naphthopyran **15** (approximately 1.3 : 1, *trans* **15**: *cis* **16**) suggests that either the oxa-Michael reaction is irreversible, or that the difference in energy between the *cis*- and *trans*-substituted

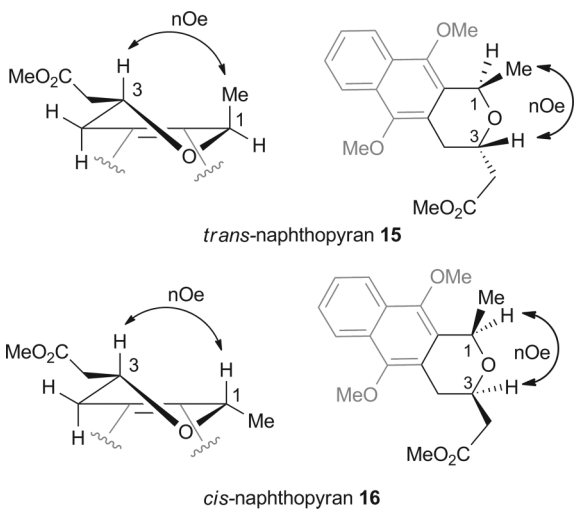
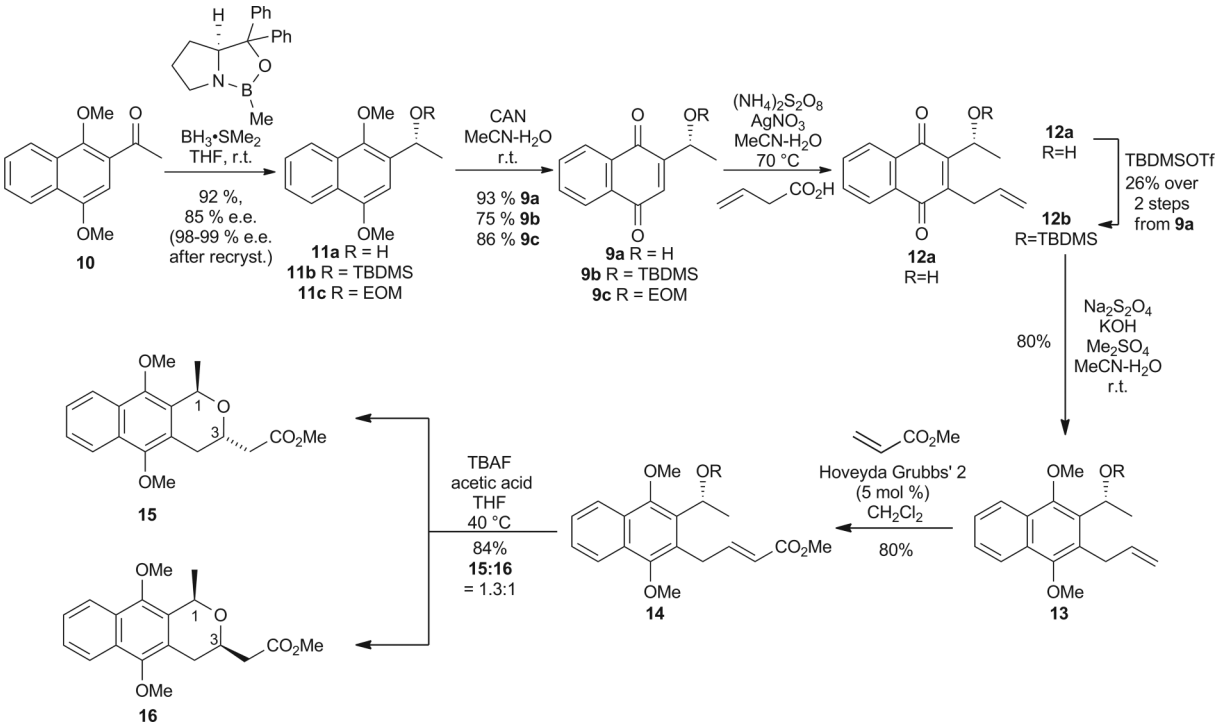


Fig. 3 nOe correlations in naphthopyrans **15** and **16**.

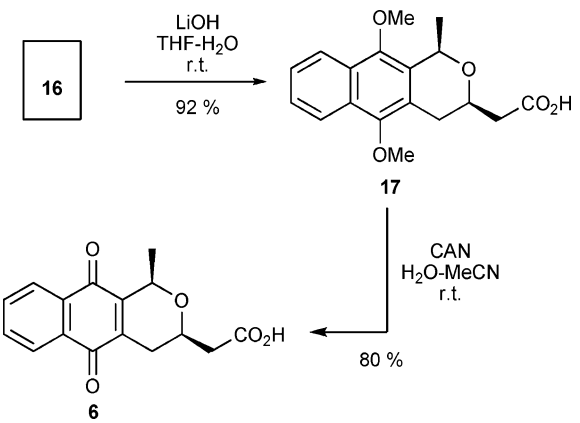


Scheme 2 Preparation of naphthopyrans **15** and **16**.

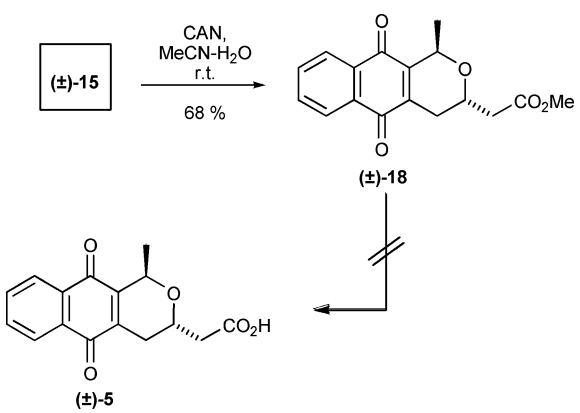
naphthopyrans is not large enough to provide any greater stereocontrol. Attempted equilibration of the 1.3 : 1 mixture of the *cis*- and *trans*-diastereomers using a variety of acidic and basic conditions unfortunately resulted in no change in the diastereomeric ratio.

Despite only observing modest diastereoselectivity in the key oxa-Michael addition we proceeded forward with the proposed synthesis. Straightforward saponification of the *cis*-naphthopyran **16** afforded **17**, an intermediate in our previously reported synthesis of *cis*-deoxydihydrokalafungin (**6**).[11] Oxidative demethylation with CAN provided **6** in 80% yield. The higher enantioselectivity (98% e.e.) obtained in the current work provides an improved synthesis of *cis*-deoxydihydrokalafungin over existing methods (Scheme 3).

In turn, *trans*-naphthopyran **15** was also only two steps away from the target deoxydihydrokalafungin **5**. Oxidative demethylation of a racemic sample of **15** (prepared from (±)-**9a** as shown in Scheme 2) with CAN[19] yielded the literature compound (±)-deoxynanaomycin methyl ester (**18**) in an acceptable 68% yield (Scheme 4).[22] The spectroscopic data gratifyingly matched that reported in the literature.[22] All that remained was to effect cleavage of the methyl ester. Unfortunately, treatment of **18** with LiOH in THF–water resulted in a complex mixture of products. Considering both the limited quantities of material available at this late stage in the synthesis, and the fact that the previous syntheses of (±)-deoxynanaomycin methyl ester did not report conversion to (±)-deoxynanaomycin/deoxydihydrokalafungin,[22] it was decided to reverse the order of the final two steps, aligning the synthetic route with the synthesis of *cis*-deoxydihydrokalafungin shown in Scheme 3.

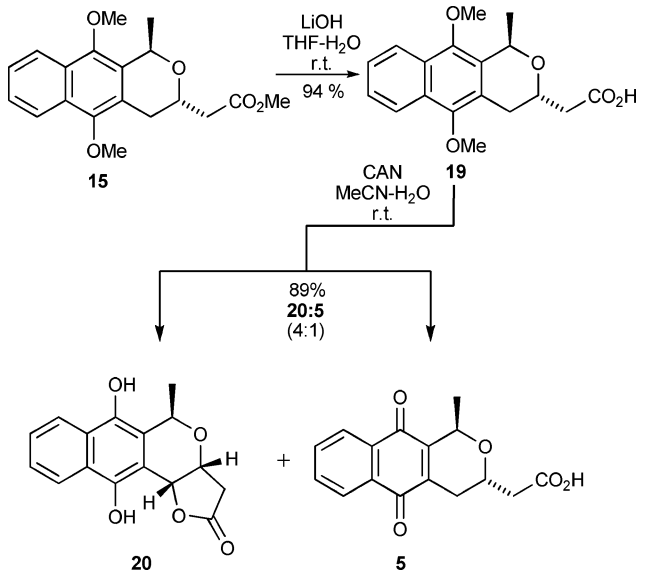


Scheme 3 Synthesis of *cis*-deoxydihydrokalafungin (**6**).



Scheme 4 Failed conversion of (±)-**18** to (±)-**5**.

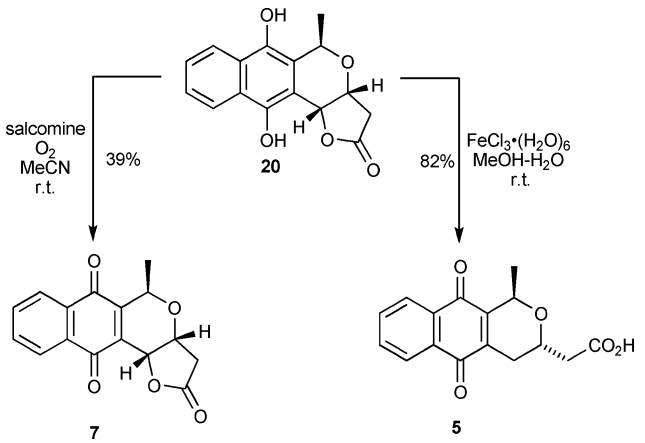
Saponification of enantiopure **15** under standard conditions gave the acid **19** in 94% yield. However, when oxidative demethylation with CAN was conducted, the expected product **5** was not the major product isolated. Surprisingly, the reaction produced an inseparable mixture of hydroquinone **20** and deoxydihydrokalafungin (**5**) in a 4 : 1 ratio (Scheme 5).



Scheme 5 Unexpected formation of hydroquinone **20**.

The unexpected formation of hydroquinone **20** is rationalized as follows: initially deoxydihydrokalafungin **5** is formed *via* oxidative demethylation, but subsequently tautomerises to a quinone-methide intermediate **21**. Intramolecular conjugate addition of the carboxylic acid side chain leads to hydroquinone **20** which contains the fused γ-lactone ring present in kalafungin **1** (Scheme 6). This hypothesis is analogous to the mechanism proposed by Li and Ellison for the conversion of nanaomycin A (the enantiomer of dihydrokalafungin) to nanaomycin D when exposed to air.[9a] Attempted oxidation of the hydroquinone using excess CAN (5 eq.) proved ineffective, causing no change in the product distribution of the reaction.

Despite the failure of CAN in effecting oxidation of hydroquinone **20**, it was envisaged that hydroquinone **20** could be converted to deoxykalafungin (**7**) by oxidation of the hydroquinone moiety using alternative oxidation methods. Attempted oxidation of **20** with Ag_2O resulted in the formation of a complex mixture, however treatment of **20** with ferric chloride resulted in oxidation with concomitant ring opening, thus generating deoxydihydrokalafungin (**5**) in a pleasing 82% yield (Scheme 7). It is postulated that ring opening of the lactone takes place due to coordination of the Lewis acidic $FeCl_3$ to the lactone carbonyl oxygen atom, thus enhancing its ability to act as a leaving group.

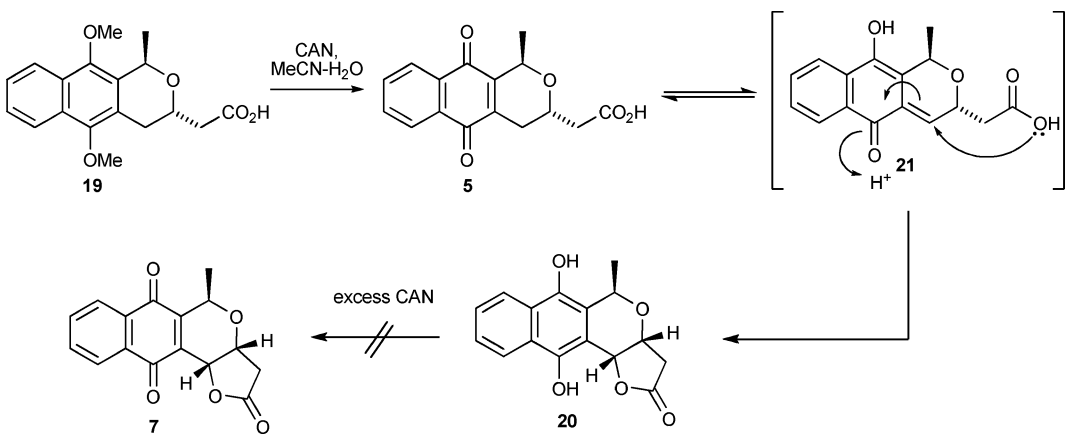


Scheme 7 Synthesis of deoxydihydrokalafungin (**5**) and deoxykalafungin (**7**) from the common hydroquinone precursor **20**.

Attention next turned to the oxidation of hydroquinone **20** to pyranonaphthoquinone γ-lactone deoxykalafungin (**7**). Since the use of ferric chloride had resulted in ring opening, non-coordinating oxidants were sought and the use of salcomine catalysed aerial oxidation was therefore evaluated. Pleasingly, stirring **20** in acetonitrile under an atmosphere of oxygen in the presence of catalytic salcomine afforded deoxykalafungin (**7**) in modest yield (Scheme 7). Comparison of the ^1H and ^{13}C NMR data and the observed optical rotation to that reported in the literature unequivocally confirmed the structure of **7**.[12]

Conclusions

In summary, the enantioselective syntheses of deoxydihydrokalafungin (**5**), *cis*-deoxydihydrokalafungin (**6**) and deoxykalafungin



Scheme 6 Proposed mechanism for the formation of hydroquinone **20**.

(**7**) have been achieved. The chirality at C-1 was introduced using a CBS reduction, providing e.e.'s of 98–99% after recrystallization of the key benzylic alcohol **11a**. The key pyran ring system was formed by radical allylation of quinone **9a**, cross-metathesis of **13** with methyl acrylate and intramolecular oxa-Michael addition upon deprotection of α,β-unsaturated ester **14**. Future work will focus on the extension of this CBS reduction/cross metathesis/oxa-Michael strategy to the synthesis of more complex pyranonaphthoquinones.

Experimental

General

Unless otherwise noted, all non-aqueous reactions and distillations were performed under an atmosphere of dry nitrogen in dry glassware. Commercially available starting materials and reagents were purchased from Acros Organics, Ajax Finechem, Lancaster Synthesis and Sigma–Aldrich and were used as received unless otherwise noted. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran (THF) was freshly distilled over sodium/benzophenone ketyl. Acetonitrile and dichloromethane were freshly distilled from calcium hydride. Diisopropylamine and triethylamine were distilled from calcium hydride and stored over potassium hydroxide. Acetone was freshly distilled from calcium chloride. Dimethylformamide (DMF) was freshly distilled under reduced pressure from molecular sieves (Lindes type 4 Å). Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on E. Merck silica gel plates using UV light as a visualising agent and an ethanolic solution of vanillin or ammonium molybdate with heat as developing agents. Silica gel (0.063–0.1mm) was used for flash column chromatography. NMR spectra were recorded at room temperature in $CDCl_3$, $(CD_3)_2SO$, CD_3OD, CD_3CN or C_6D_6 on a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. The reference peak was set to δ 7.26 and δ 77.0 ($CDCl_3$), δ 2.50 and δ 39.5 ($(CD_3)_2SO$), δ 3.31 and δ 49.0 (CD_3OD), δ 1.94 and δ 188.3 (CD_3CN) and δ 7.16 and δ 128.1 (C_6D_6) for ^{1}H and ^{13}C spectra respectively. Chemical shifts are reported as parts per million (ppm) on the δ scale and coupling constants J, are in hertz (Hz). Multiplicities are reported as "s" (singlet), "d" (doublet), "t" (triplet), "dd" (doublet of doublets), "ddd" (doublet of doublets of doublets), and dt (doublet of triplets). Infrared (IR) spectra were recorded as a thin film on a composite of zinc selenide and diamond crystal on a FT-IR System transform spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained with a nominal resolution of 5000 to 10000.

(+)-2-(1-Hydroxyethyl)-1,4-dimethoxynaphthalene (11a). To a solution of 1 M (*S*)-methyloxazaborolidine in THF (0.9 mL, 0.9 mmol) was added 2-acetyl-1,4-dimethoxynaphthalene **10** (1.0 g, 4.34 mmol) in dry THF (2.5 mL) and $BH_3{\cdot}SMe_2$ (0.29 mL, 3.06 mmol) in dry THF (2.5 mL) simultaneously over two minutes. The solution was stirred at room temperature for 20 min. The reaction mixture was quenched by the addition of MeOH (1 mL) and H_2O (5 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 3 : 1) gave alcohol **11a** (0.93 g, 92%, 85% e.e. rising to 99% e.e. on recrystallization from hexanes–EtOAc 5 : 1) as a colourless solid: $[\alpha]_D^{18}$ = +48 (*c* 1.15 in $CHCl_3$, 96% e.e.); HPLC: column, Chiralpak IC; mobile phase, hexane–isopropanol (65 : 35 v/v); flow rate, 0.5 mL min^{-1}; retention times, 9.8 min (*R*), 11.2 min (*S*); mp 93–97 °C. The spectroscopic data were consistent with the literature.[17a]

(+)-2-(1-Hydroxyethyl)-1,4-naphthoquinone (9a). To a stirred solution of **11a** (0.54 g, 2.2 mmol) in acetonitrile (5 mL) was added a solution of CAN (2.44 g, 4.4 mmol) in water (5 mL). The solution was stirred at room temperature for 30 min, then diluted with water (30 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 5 : 1) gave quinone **9a** (0.42 g, 93%) as a yellow–orange solid: $[\alpha]_D^{18}$ = +7.8 (*c* 1.0 in $CHCl_3$); mp 70–73 °C. The spectroscopic data were consistent with the literature.[17a]

(–)-3-Allyl-2-(1-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-naphthoquinone (12b). A solution of quinone **9a** (0.5 g, 1.5 mmol) in acetonitrile (50 mL) was bubbled with nitrogen gas for 20 min. $AgNO_3$ (0.32 g, 1.9 mmol) was added with light excluded from the reaction vessel. Vinylacetic acid (0.32 mL, 3.7 mmol) and a solution of $(NH_4)_2S_2O_8$ (1.16 g, 4.9 mmol) in water (20 mL) were added and the solution heated to 70 °C and stirred under nitrogen for 16 h. The solution was cooled to room temperature and $AgNO_3$ (0.32 g, 1.9 mmol), vinylacetic acid (0.32 mL, 3.7 mmol) and a solution of $(NH_4)_2S_2O_8$ (1.16 g, 4.9 mmol) in water (20 mL) were added. The solution was heated at 70 °C for 4 h and then the addition of reagents repeated as before. The solution was heated overnight at 70 °C, then cooled to room temperature and extracted with EtOAc (3 × 120 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (50 mL), water (50 mL), dried over $MgSO_4$ and the residue concentrated *in vacuo*.

The crude quinone **12a** was dissolved in dry acetonitrile (6 mL), cooled to 0 °C, and placed under argon. Pyridine (0.24 mL, 3 mmol), and TBDMSOTf (0.63 mL, 2.7 mmol) were added with stirring. The solution was allowed to warm to room temperature and then stirred for 2 h. The solution was quenched by the addition of water (10 mL), and the reaction mixture extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (10 mL), water (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 75 : 1) gave quinone **12b** (0.23 g, 26% over two steps) as a yellow oil: $[\alpha]_D^{18}$ = –102.3 (*c* 1.0 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 3079, 2954, 2930, 2957, 1657, 1595, 1286, 1253, 1087, 989, 871, 833; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.03 (2 H, m, 5-H and 8-H), 8.69–8.66 (2 H, m, 6-H and 7-H), 5.95–5.86 (1 H, m, $CH_2CH{=}CH_2$), 5.52 (1 H, q, J = 6.8 Hz, CHOSi), 5.11–5.02 (2 H, m, $CH{=}CH_2$), 4.03 (1 H, dddd, J = 13.9, 6.5, 1.4, 1.4 Hz, $CH_2CH{=}CH_2$), 3.64 (1 H, dddd, J = 13.9, 5.5, 1.6, 1.6 Hz, $CH_2CH{=}CH_2$), 1.43 (3 H, d, J = 6.8 Hz, CH_3), 0.87 (9 H, s, ^{t}Bu), 0.08 (3 H, s, $SiCH_3$), –0.02 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5 (C=O), 184.7 (C=O), 148.5 (C-Ar), 146.2 (C-Ar), 135.7 ($CH_2CH{=}CH_2$), 133.5 (CH-Ar), 133.4 (CH-Ar), 132.1 (C-Ar), 131.9 (C-Ar), 126.3 (CH-Ar), 126.2 (CH-Ar), 116.7 ($CH{=}CH_2$), 64.4 (CHOSi), 30.4 ($CH_2CH{=}CH_2$), 25.9

(3 × CH_3), 23.9 (CH_3), 18.1 ($\underline{C}(CH_3)_3$), –4.8 ($SiCH_3$), –4.9 ($SiCH_3$); MS (ESI), *m/z* 379 ([M–Na]$^+$, 40%), 357 ([M–H]$^+$, 18), 225 (100); HRMS (ESI) *m/z* for $C_{21}H_{29}O_3Si^+$ [M–H]$^+$ calcd 357.1880, found 357.1883.

(+)-3-Allyl-2-(1-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-dimethoxynaphthalene (13). To a mixture of quinone **12b** (100 mg, 0.28 mmol) and TBAI (10 mg, 0.025 mmol) was added a solution of $Na_2S_2O_4$ (1.7 mmol) in water (1.7 mL) with vigorous stirring. The solution was stirred at room temperature for 10 min, during which time the solution's yellow colour lightened. An aqueous solution of KOH (1.6 mL, 4 M) was added and the solution turned dark red. After a further 10 min, Me_2SO_4 (0.55 mL, 5.8 mmol) was added and the solution stirred at room temperature for 1 h. The solution was quenched by the addition of conc. aq. NH_3 (3 mL) and allowed to stir for 20 min. The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with 2 M HCl (5 mL) and water (5 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (hexane–EtOAc 100 : 1) gave dimethoxynaphthalene **13** (98 mg, 90%) as a colourless oil: $[\alpha]_D^{18}$ = +24.0 (*c* 1.0 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2954, 2931, 2957, 1454, 1355, 1251, 1083, 1017, 972, 834, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.03 (2 H, m, 5-H and 8-H), 7.49–7.46 (2 H, m, 6-H and 7-H), 6.14–6.04 (1 H, m, CH_2CH═CH_2), 5.72–5.65 (1 H, m, CHOSi), 5.04–4.89 (2 H, m, CH_2CH═CH_2), 4.22–4.16 (1 H, m, CH_2CH═CH_2), 3.93 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.77–3.71 (1 H, m, CH_2CH═CH_2), 1.61 (3 H, d, *J* = 7.2 Hz, CH_3), 0.88 (9 H, s, ^{t}Bu), 0.11 (3 H, s, $SiCH_3$), –0.10 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6 (1-C and 4-C), 138.7 (CH_2CH═CH_2), 133.7 (C-Ar), 128.6 (C-Ar), 128.1 (C-Ar), 127.7 (C-Ar), 125.9 (CH-Ar), 125.5 (CH-Ar), 122.8 (CH-Ar), 122.4 (CH-Ar), 114.5 (CH_2CH═$\underline{C}H_2$), 65.6 (CHOSi), 62.9 (OCH_3), 61.8 (OCH_3), 31.0 ($\underline{C}H_2CH$═CH_2), 25.9 (3 × CH_3), 25.2 (CH_3), 18.1 ($\underline{C}(CH_3)_3$), –4.8 ($SiCH_3$), –4.9 ($SiCH_3$); MS *m/z* (ESI) 409 ([M–Na]$^+$, 30%), 255 (100), 223 (10); HRMS (ESI) *m/z* for $C_{23}H_{34}O_3NaSi^+$ [M–Na]$^+$ calcd 409.2169, found 409.2177.

(–)-(*E*)-Methyl 4-(2-(1-(*tert*-butyldimethylsilyloxy)ethyl)-1,4-dimethoxynaphthalen-3-yl)but-2-enoate (14). To a solution of dimethoxynaphthalene **13** (190 mg, 0.49 mmol) in CH_2Cl_2 (2.4 mL) was added methyl acrylate (0.22 mL, 2.4 mmol). The reaction vessel was excluded from light and Hoveyda–Grubbs' 2nd generation catalyst (7.4 mg, 0.024 mmol) was added. The solution was stirred at room temperature for 8 h. A second aliquot of catalyst (7.4 mg, 0.024 mmol) was added and the solution stirred at room temperature overnight, then concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 20 : 1) gave methyl ester **14** (160 mg, 74%) as a pale yellow oil: $[\alpha]_D^{18}$ = –4.2 (*c* 1.1 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2952, 2932, 2856, 1723, 1653, 1436, 1355, 1260, 1164, 1082, 1015, 969, 826, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.00 (2 H, m, 5-H and 8-H), 7.50–7.48 (2 H, m, 6-H and 7-H), 7.21–7.26 (1 H, dt, *J* = 15.6, 5.8 Hz, CH═$CHCO_2Me$), 5.73 (1 H, q, *J* = 6.6 Hz, CHOSi), 5.66 (1 H, dt, *J* = 15.6, 1.8 Hz, CH═$CHCO_2Me$), 4.36–4.30 (1 H, m, CH_2CH═CH), 3.94–3.88 (4 H, m, CH_2CH═CH and OCH_3), 3.86 (3 H, s, OCH_3), 3.66 (3 H, s, OCH_3), 1.54 (3 H, d, *J* = 6.6 Hz, CH_3), 0.85 (9 H, s, ^{t}Bu), –0.09 (3 H, s, $SiCH_3$), –0.11 (3 H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2 (C═O), 152.0 (C-Ar), 149.9 ($\underline{C}H$═$CHCO_2CH_3$), 149.0 (C-Ar), 133.3 (C-Ar), 128.0 (C-Ar), 127.9 (C-Ar), 126.7 (C-Ar), 126.1 (CH-Ar), 126.0 (CH-Ar), 122.9 (CH-Ar), 122.4 (CH-Ar), 120.7 (CH═$\underline{C}HCO_2CH_3$), 65.4 (CHOSi), 62.9 (OCH_3), 61.8 (OCH_3), 51.3 (OCH_3, ester), 29.8 ($\underline{C}H_2CH$═$CHCO_2CH_3$), 25.9 (3 × CH_3), 25.6 (CH_3), 18.1 ($\underline{C}(CH_3)_3$), –4.8 ($SiCH_3$), –4.9 ($SiCH_3$); MS *m/z* (ESI) 445 ([M–H]$^+$, 42%), 313 (100), 253 (30); HRMS (ESI) *m/z* for $C_{25}H_{37}O_5Si^+$ [M–H]$^+$ calcd 445.2405, found 445.2395.

(–)-Methyl 2-[(1*R,3*S**)-5,10-dimethoxy-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (15) and (+)-methyl 2-[(1*R**,3*R**)-5,10-dimethoxy-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]-pyran-3-yl)acetate (16).** Methyl ester **14** (160 mg, 0.36 mmol) was dissolved in 6 mL of a 1 : 1 TBAF (1 M in THF)–acetic acid solution that had been premixed for 1 h. The solution was stirred at 40 °C for five days, during which a further 1.5 mL of TBAF (1 M in THF) solution was added to replace lost solvent. The acetic acid was quenched by the addition of sat. aq. $NaHCO_3$ (3 mL) and the reaction mixture extracted with CH_2Cl_2 (3 × 5 mL). The solvent was removed *in vacuo* to a volume of approx. 2 mL and the solution filtered through a plug of silica. The remaining solvent was removed *in vacuo.* Purification by column chromatography (hexanes–EtOAc 10 : 1) gave *trans*-naphthopyran **15** (54 mg, 45%) and *cis*-naphthopyran **16** (34 mg, 28%) as colourless oils:

Data for 15

$[\alpha]_D^{18}$ = –6.6 (*c* 0.9 in $CHCl_3$); IR (film) ν_{max}/cm^{-1} 2935, 1737, 1593, 1437, 1354, 1278, 1131, 1063, 1008, 773; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01–7.99 (2 H, m, 6-H and 9-H), 7.49–7.45 (2 H, m, 7-H and 8-H), 5.34 (1 H, q, *J* = 6.6 Hz, 1-H), 4.50–4.45 (1 H, m, 3-H), 3.89 (3 H, s OCH_3), 3.88 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3, ester), 3.15 (1 H, dd, *J* = 16.8, 3.2, 4-H), 2.75–2.64 (3 H, m, 4-H and 2 × 2′-H), 1.64 (3 H, d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (C═O), 149.4 (C-Ar), 147.6 (C-Ar), 128.7 (C-Ar), 127.5 (C-Ar) 127.1 (C-Ar), 125.8 (CH-Ar), 125.6 (CH-Ar), 122.7 (C-Ar), 122.2 (CH-Ar), 122.1 (CH-Ar), 69.0 (1-C), 63.8 (3-C), 61.5 (OCH_3), 61.1 (OCH_3), 51.8 (OCH_3, ester), 41.2 (2′-C), 28.6 (4-C), 20.4 (CH_3); MS *m/z* (ESI) 353 ([M–Na]$^+$, 100%), 331 ([M–H]$^+$, 13), 287 (35), 255 (30), 229 (10); HRMS (ESI) *m/z* for $C_{19}H_{23}O_5^+$ [M–H]$^+$ calcd 331.1540, found 331.1537.

Data for 16

$[\alpha]_D^{18}$ = +89.0 (*c* 1.0 in $CHCl_3$), IR (film) ν_{max}/cm^{-1} 2934, 2849, 1739, 1592, 1437, 1353, 1091, 1062, 1007, 772; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06–8.03 (2 H, m, 6-H and 9-H), 7.50–7.46 (2 H, m, 7-H and 8-H), 5.25 (1 H, q, *J* = 6.4 Hz, 1-H), 4.08–4.03 (1 H, m, 3-H), 3.90 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.15 (1 H, dd, *J* = 16.0, 2.0 Hz, 4-H), 2.82–2.65 (3 H, m, 4-H and 2 × 2′-H), 1.66 (3 H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6 (C═O), 149.0 (C-Ar),148.5 (C-Ar), 128.9 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 125.9 (CH-Ar), 125.7 (CH-Ar), 124.4 (C-Ar), 122.2 (CH-Ar), 122.0 (CH-Ar), 71.6 (1-C), 70.2 (3-C), 61.4 (OCH_3), 61.1 (OCH_3, ester), 51.8 (OCH_3), 41.0 (2′-C), 29.9 (4-C), 22.3 (CH_3); MS *m/z* (ESI) 353 ([M–Na]$^+$, 100%), 287 (18), 255 (20), 229 (15); HRMS (ESI) *m/z* for $C_{19}H_{22}NaO_5^+$ [M–Na]$^+$ calcd 353.1359, found 353.1358.

(+)-2-[(1*R,3*R**)-5,10-Dimethoxy-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-3-yl]acetic acid (17).** To a solution of *cis*-naphthopyran **16** (34 mg, 0.1 mmol) in THF (7.7 mL) was added

LiOH (15 mg, 0.36 mmol) in water (1.5 mL). The solution was stirred at room temperature overnight. The reaction mixture was acidified to pH 1–2 with 1 M HCl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give carboxylic acid **17** (30.1 mg, 93%) as a colourless oil: $[\alpha]_D^{18} = +70.1$ (*c* 1.1 in $CHCl_3$, lit. = 59.4, 98% e.e.); HPLC: column, Chiralpak IC; mobile phase, hexane–isopropanol (65: 35 v/v); flow rate, 0.5 mL min^{-1}; retention times, 11.5 min (1*R*, 3*S*), 21.7 min (1*S*, 3*R*); ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–8.03 (2 H, m, 6-H and 9-H), 7.51–7.46 (2 H, m, 7-H and 8-H), 5.28 (1 H, q, *J* = 6.4 Hz, 1-H), 4.09–4.04 (1 H, m, 3-H), 3.91 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 3.19 (1 H, dd, *J* = 16.0, 2.0 Hz, 4-H), 2.87–2.68 (3 H, m, 4-H and 2 × 2′-H), 1.69 (3 H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3 (C═O), 149.1 (C-Ar) 148.6 (C-Ar), 128.6 (C-Ar), 127.6 (C-Ar), 127.5 (C-Ar), 126.0 (CH-Ar), 125.8 (CH-Ar), 124.0 (C-Ar), 122.2 (CH-Ar), 122.1 (CH-Ar), 71.7 (1-C), 70.0 (3-C), 61.4 (OCH_3), 61.1 (OCH_3), 41.0 (2′-C), 29.7 (4-C), 22.4 (CH_3). The spectroscopic data were in agreement with that reported in the literature.[11]

(+)-2-[(1*R,3*R**)-1-Methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-yl]acetic acid (6).** To a stirred solution of carboxylic acid **17** (15 mg, 0.047 mmol) in acetonitrile (5 mL) was added a solution of CAN (65 mg, 0.11 mmol) in water (0.5 mL). The solution was stirred at room temperature for 5 min. The solution was diluted with water (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (5 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes–ethyl acetate 4 : 1) gave pyranonaphthoquinone **6** (11 mg, 80%) as a pale yellow solid: $[\alpha]_D^{18} = +193.7$ (*c* 0.6 in $CHCl_3$, lit. = +148.8[11]); mp 108–110 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08–8.04 (2 H, m, 7-H and 8-H), 7.75–7.70 (2 H, m, 6-H and 9-H), 4.93–4.89 (1 H, m, 1-H), 3.99–3.93 (1 H, m, 3-H), 2.92 (1 H, d, *J* = 18.4 Hz, 4-H), 2.82–2.68 (2 H, m, 2′-H), 2.41–2.33 (1 H, m, 4-H), 1.55 (3 H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.7 (C═O), 183.6 (C═O), 175.8 (C═O), 146.5 (C-Ar), 141.7 (C-Ar), 133.9 (CH-Ar), 133.7 (CH-Ar) 132.4 (C-Ar), 131.7 (C-Ar), 126.3 (CH-Ar), 126.3 (CH-Ar), 70.3 (1-C), 69.0 (3-C), 40.2 (2′-C), 28.4 (4-C), 20.8 (CH_3). The spectroscopic data were consistent with that reported in the literature.[11]

(–)-2-[(1*R,3*S**)-5,10-Dimethoxy-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-3-yl]acetic acid (19).** To a solution of *trans*-naphthopyran **15** (53 mg, 0.18 mmol) in THF (12 mL) was added LiOH (26 mg, 0.62 mmol) in water (2.3 mL). The solution was stirred at room temperature overnight. The reaction mixture was acidified to pH 1–2 with 1 M HCl and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give carboxylic acid **19** (47.6 mg, 94%) as a colourless solid: $[\alpha]_D^{18} = -9.9$ (*c* 1.4 in $CHCl_3$, 99% e.e.); HPLC: column, Chiralpak IC; mobile phase, hexane: THF (90: 10 v/v); flow rate, 0.5 mL min^{-1}; retention times, 21.3 min (*1S*, 3*R*), 22.5 min (1*R*, 3*S*); mp 99–102 °C; IR (film) ν_{max}/cm^{-1} 2943, 2841, 1706, 1591, 1438, 1354, 1230, 1133, 1097, 1080, 1061, 1010, 967; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.00 (2 H, m, 6-H and 9-H), 7.51–7.46 (2 H, m, 7-H and 8-H), 5.28 (1 H, q, *J* = 6.6 Hz, 1-H), 4.51–4.48 (1 H, m, 3-H), 3.91 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 3.19 (1 H, dd, *J* = 16.4, 3.2 Hz, 4-H), 2.77–2.68 (3 H, m, 4-H and 2 × 2′-H), 1.67 (3 H, d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9 (C═O), 149.4 (C-Ar), 147.7 (C-Ar), 128.4 (C-Ar), 127.6 (C-Ar), 127.2 (C-Ar), 125.8 (CH-Ar), 125.7 (CH-Ar), 122.3 (C-Ar), 122.2 (CH-Ar), 121.2 (CH-Ar), 69.2 (1-C), 63.7 (3-C), 61.6 (OCH_3), 61.1 (OCH_3), 41.1 (2′-C), 28.5 (4-C), 20.4 (CH_3); MS (ESI) *m*/*z* 339 ($[M–Na]^+$, 100%), 317 ($[M–H]^+$, 10), 273 (18); HRMS (ESI) *m*/*z* for $C_{18}H_{20}NaO_5^+$ $[M–Na]^+$ calcd 339.1203, found 339.1196.

(3a*R,5*R**,11b*R**)-6,11-Dihydroxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one (20).** To a stirred solution of carboxylic acid **19** (11.5 mg, 0.036 mmol) in acetonitrile (7.5 mL) was added a solution of CAN (48 mg, 0.88 mmol) in water (0.2 mL). The solution was stirred at room temperature for 30 min after which an additional aliquot of CAN (40 mg, 0.073 mmol) in water (0.2 mL) was added. The solution was stirred at room temperature for a further 90 min after which CAN (20 mg, 0.036 mmol) in water (0.2 mL) was added. The solution was stirred for a further 20 min then diluted with water (15 mL). The reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 4 : 1) gave a 4 : 1 mixture of **20** and **5** (9.3 mg, 89%, approx 4 : 1) as a pale yellow solid: IR (film) ν_{max}/cm^{-1} 2981, 2922, 2584, 1722, 1698, 1659, 1625, 1592, 1417, 1292, 1279, 1071, 718; ^1H NMR (400 MHz, DMSO): δ 9.31 (1 H, s, OH), 8.78 (1 H, s, OH), 8.21–8.14 (2 H, m, 7-H and 10-H), 7.53–7.47 (2 H, m, 8-H and 9-H), 5.69 (1 H, d, *J* = 2.6 Hz, 11b-H), 5.35 (1 H, q, *J* = 6.6 Hz, 5-H), 4.82 (1 H, dd, *J* = 4.8, 2.6 Hz, 3a-H), 3.20 (1 H, dd, *J* = 17.2, 4.8 Hz, 3-H), 2.45 (1 H, d, *J* = 17.2 Hz, 3-H), 1.48 (3 H, d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): 176.0 (C═O), 146.1 (C-Ar), 139.5 (C-Ar), 126.4 (C-Ar), 126.0 (CH-Ar), 124.8 (CH-Ar), 124.4 (C-Ar), 122.4 (CH-Ar), 121.9 (CH-Ar), 121.8 (C-Ar), 110.7 (C-Ar), 72.1 (11b-C), 67.0 (5-C), 66.2 (3a-C), 37.5 (3-C), 18.6 (CH_3); MS (ESI) *m*/*z* 309 ($[M–Na]^+$, 100%); HRMS (ESI) *m*/*z* for $C_{16}H_{14}NaO_5^+$ $[M–Na]^+$ calcd 309.0733, found 309.0742.

(–)-2-[(1*R,3*S**)-1-Methyl-5,10-dioxo-3,4,5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-yl]acetic acid (5).** To a solution of hydroquinone **20** (25 mg, 0.09 mmol) in MeOH (9.25 mL), was added a solution of $FeCl_3 \cdot (H_2O)_6$ (50 mg, 0.19 mmol) in water (1 mL). The resultant orange solution was stirred at room temperature for 6 h then diluted with water (5 mL). The reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes–EtOAc 1 : 1) gave (–)-deoxydihydrokalafungin **5** (20.7 mg, 85%) as a pale yellow solid: $[\alpha]_D^{18} = -18.6$ (*c* 0.5 in $CHCl_3$, 99% e.e.); HPLC: column, Chiralpak IC; mobile phase, hexane: THF (90: 10 v/v); flow rate, 0.5 mL min^{-1}; retention times, 69.7 min (1*S*, 3*R*), 72.8 min (1*R*, 3*S*); mp 160–162 °C; IR (film) ν_{max}/cm^{-1} 2927, 2857, 1723, 1663, 1595, 1417, 1329, 1293, 1180, 718; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04–8.07 (2 H, m, 6-H and 9-H), 7.85–7.83 (2 H, m, 7-H and 8-H), 4.92 (1 H, q, *J* = 6.8 Hz, 1-H), 4.40– 4.33 (1 H, m, 3-H), 2.79 (1 H, dd, *J* = 19.0, 3.6 Hz, 4-H), 2.73–2.56 (2 H, m, 2′-H), 2.33 (1 H, ddd, *J* = 18.8, 10.4, 2.0 Hz, 4-H), 1.52 (3 H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.4 (C═O), 183.9 (C═O), 172.1 (C═O), 146.7 (C-Ar), 142.3 (C-Ar), 134.7 (CH-Ar), 134.6 (CH-Ar), 133.0 (C-Ar), 132.9 (C-Ar), 126.7 (2 × CH-Ar), 67.9 (1-C), 64.5 (3-C), 40.9 (2′-C), 28.4 (4-C), 19.6 (CH_3); MS (ESI) *m*/*z* 309

([M–Na]$^+$, 45%), 287 ([M–H]$^+$, 43), 242 (100); HRMS (ESI) *m/z* for $C_{16}H_{15}O_5^+$ [M–H]$^+$ calcd 287.0914, found 287.0908.

(+)-Deoxykalafungin (7). Hydroquinone **20** (21 mg, 0.014 mmol) was dissolved in acetonitrile (8 mL) and flushed with O_2 for ten minutes. Salcomine (40 mg) was added and the solution stirred under a balloon of O_2 for 24 h at room temperature. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. Purification by column chromatography (hexanes–ethyl acetate 2 : 1) afforded (+)-deoxykalafungin **7** (7.4 mg, 35%) as a pale yellow solid: $[\alpha]_D^{18}$ = +98.5 (*c* 0.5 in $CHCl_3$, lit. = +100.1); mp 43–47 °C; ^{1}H NMR (400 MHz, C_6D_6): δ 7.96–7.93 (1 H, m, 7-H or 10-H), 7.83–7.80 (1 H, m, 7-H or 10-H), 7.01–6.94 (2 H, m, 8-H and 9-H), 4.72 (1 H, q, *J* = 6.8 Hz, 5-H), 4.57 (1 H, d, *J* = 2.8 Hz, 11b-H), 3.50 (1 H, dd, *J* = 4.8, 2.8 Hz, 3a-H), 2.24 (1 H, d, *J* = 17.4 Hz, 3-H), 1.94 (1 H, dd, *J* = 17.4, 4.8 Hz, 3-H), 1.06 (3 H, d, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, C_6D_6): δ 182.9 (C═O), 182.1 (C═O), 173.5 (C═O), 148.7 (C-Ar), 134.4 (C-Ar), 133.9 (CH-Ar), 133.6 (CH-Ar), 132.0 (2 × C-Ar), 126.4 (CH-Ar), 126.2 (CH-Ar), 68.4 (CH), 66.5 (CH), 66.4 (CH), 36.8 (CH_2), 18.2 (CH_3). The spectroscopic data were in agreement with that reported in the literature.[12]

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