Enantioselective synthesis of the dimeric pyranonaphthoquinone core of the cardinalins using a late-stage homocoupling strategy†

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Received 5th August 2008, Accepted 1st September 2008
First published as an Advance Article on the web 10th October 2008
DOI: 10.1039/b813605j

The enantioselective synthesis of a dimeric pyranonaphthoquinone closely related to the cardinalins is described. Whilst attempts to effect a double Hauser–Kraus annulation of enone **5** were unsuccessful using both bis-phthalide 4 and bis-sulfone **21**, a single annulation of cyanophthalide **28** with enone **5** furnished functionalised naphthalene **31**. Suzuki–Miyaura homocoupling of the aryl triflate **29** derived from **31** effected a late-stage construction of the biaryl bond and facilitated access to the biaryl **3**. Double stereoselective lactol reduction installed the 1,3-*cis* stereochemistry of the pyran rings and a final double oxidative demethylation step furnished model dimer **1**, completing the enantioselective synthesis of a dimeric pyranonaphthoquinone bearing the core structure of cardinalin 3.

Introduction

Australasian toadstools belonging to the genus *Dermocybe* are a rich source of bioactive secondary metabolites.[1] For example, the deep-red ethanolic extract of the fresh fruit bodies of the New Zealand toadstool *Dermocybe cardinalis* was shown to exhibit significant cytotoxic activity (IC_{50} of 0.47 mg mL^{-1}) against a P388 murine leukaemia cell line. Separation of this extract into its individual components yielded cardinalins 1–6, a series of dimeric pyranonaphthoquinones (Fig. 1).[2a,3] Subsequently, cardinalins 8–12, unique pre-naphthoquinone dehydrodimers were isolated from the same source.[2b]

The common structural feature of cardinalins 1–6 is the presence of two *cis*-1,3-dimethylpyran rings fused to their respective naphthoquinone (or hydroquinone) nuclei. In turn a C8–C8′ biaryl bond present in cardinalins **1–3** affords a bisquinonoid structure that exists as their respective (*aS*)-atropisomers (Fig. 1).

Limited enantioselective syntheses of dimeric pyranonaphthoquinones exist in the literature. In 1987, a relay synthesis of an enantiomer of actinorhodin from a monomeric degradation product confirmed the position of the biaryl bond at C8–C8′.[4] A successful total synthesis of (+)-BE-52440A, a dimeric nanaomycin derivative bridged with sulfur at C4a was disclosed in 2007,[5] and an elegant total synthesis of crisamicin A was recently reported in 2008.[6]

Our longstanding interest in the synthesis of pyranonaphthoquinones[3] combined with the challenging dimeric structure and biological activity of the cardinalins prompted us to instigate a program directed towards their synthesis. Thus, it was decided to initially focus on the asymmetric synthesis of the biaryl core of cardinalin 3, namely model dimeric pyranonaphthoquinone **1**. We therefore herein report the full details of our efficient enantioselective synthesis of the dimeric pyranonaphthoquinone **1**.[7,8]

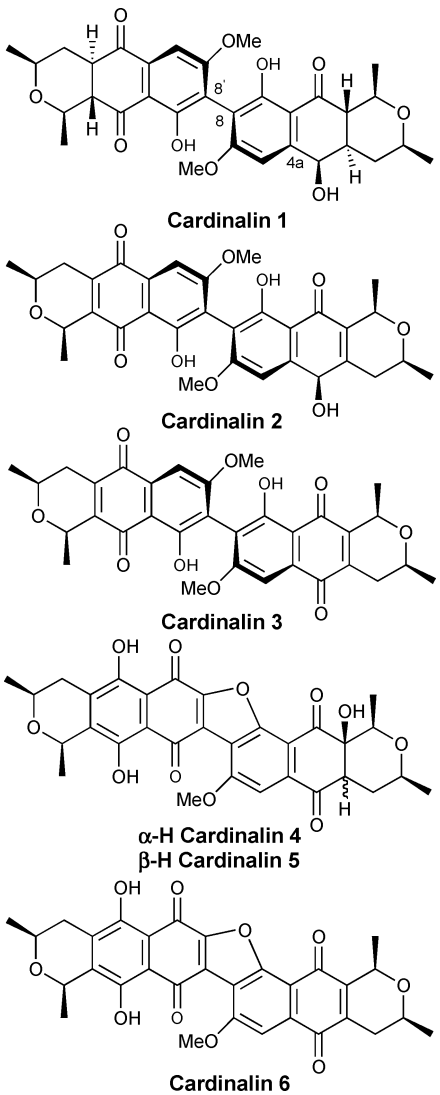

Fig. 1 Cardinalins 1–6.

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† Electronic supplementary information (ESI) available: Additional experimental procedures, NOE data and spectra of compounds **1**, **3**, **12**, **28**, **29**, **30**, **31**, **32** and **33**. See DOI: 10.1039/b813605j

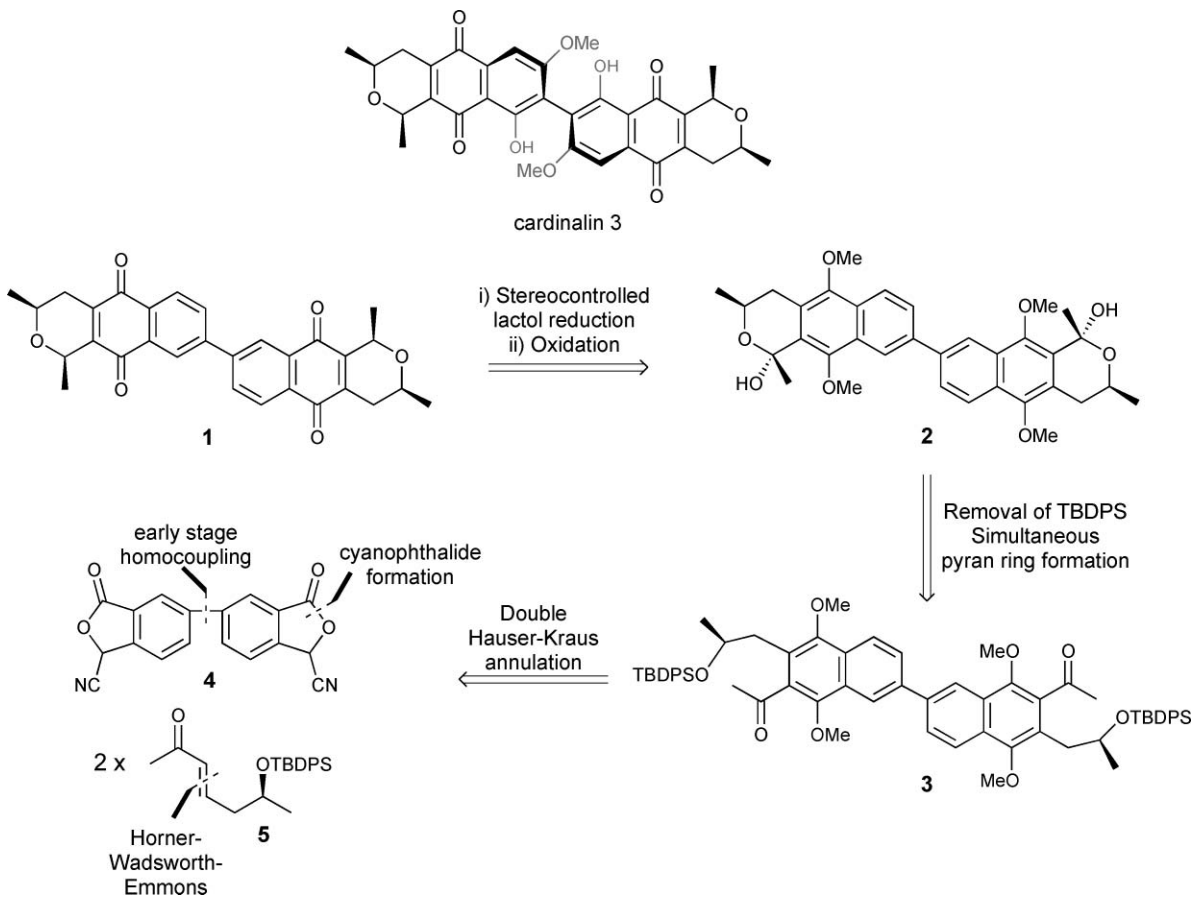
Our initial retrosynthesis (Scheme 1) was based on our methodology for the stereoselective construction of *cis*-1,3-dimethylpyran rings, which has recently been implemented in an enantioselective synthesis of the topoisomerase II inhibitor eleutherin.[9] Thus, in the present work, model dimer **1** was envisioned to be accessible *via* double stereoselective reduction[10] of bis-lactol **2** that in turn would be accessible by double intramolecular pyran ring formation. Biaryl **3** was envisioned to be accessible *via* double Hauser–Kraus annulation[11,12] of bis-cyanophthalide **4** with two equivalents of enone **5**. Thus, our original thoughts were aimed at constructing the key biaryl bond at an early stage of the synthesis with the model dimer **1** being assembled in a tandem fashion. A similar strategy was adopted by de Koning *et al.* for a racemic synthesis of cardinalin 3.[7d]

Results and discussion

The synthesis of bis-cyanophthalide **4** was achieved as follows; *meta*-anisic acid was converted to its diethylamide *via* the acid chloride giving **6**.[13] Boron tribromide mediated methyl ether cleavage gave phenol **7**, which underwent smooth silylation with hexamethyldisilazide furnishing the unstable silyl ether **8**. Anion-induced silyl group migration[14] using *tert*-butyllithium furnished trimethylsilyl aryl **9**. Protection of the free phenol as *tert*-butyldimethylsilyl ether **10** provided an ideal substrate for subsequent directed metalation. With this idea in mind, treatment of the lithium anion derived from **10** with dimethylformamide furnished aldehyde **11**, which underwent concomitant silyl group deprotection *in situ.* Smooth removal of the trimethylsilyl was achieved using caesium fluoride in aqueous dimethylformamide at elevated temperature affording phenol **12** that then underwent smooth conversion to the triflate **13**, the key homocoupling precursor.

Next, the key Suzuki–Miyaura homocoupling step was undertaken. After careful optimization, it was found that microwave irradiation (300 W, 150 °C) of a solution of triflate **13** in dioxane with bis(pinacolato)diboron (0.5 eq.), freshly ground dried potassium carbonate (3 eq.) with $Cl_2Pd(dppf)$ as catalyst (10 mol%) for 30 min gratifyingly afforded in near quantitative yield the homocoupled product **14** in a one-pot operation. Smooth conversion to bis-cyanophthalide **4** was then effected upon treatment with trimethysilylcyanide in the presence of catalytic quantities of potassium cyanide followed by treatment with acetic acid[15] (Scheme 2).

Unfortunately, the route depicted in Scheme 2 only allowed for the preparation of milligram quantities of bis-phthalide **4**. Given the somewhat lengthy synthesis of **4**, a more concise synthesis was designed. By modifying a literature procedure,[16] radical ring-opening of 6-methoxyphthalide[17] with *N*-bromosuccinimide followed by hydrolysis under gentle reflux afforded acid **15**. Facile diethylamide formation gave **16**,[18] which surprisingly, resisted all attempts to effect removal of the methoxy group under Lewis acidic conditions, with extensive degradation occurring in all cases.



Scheme 1 Initial retrosynthesis of model dimer **1**, early stage construction of the biaryl bond.

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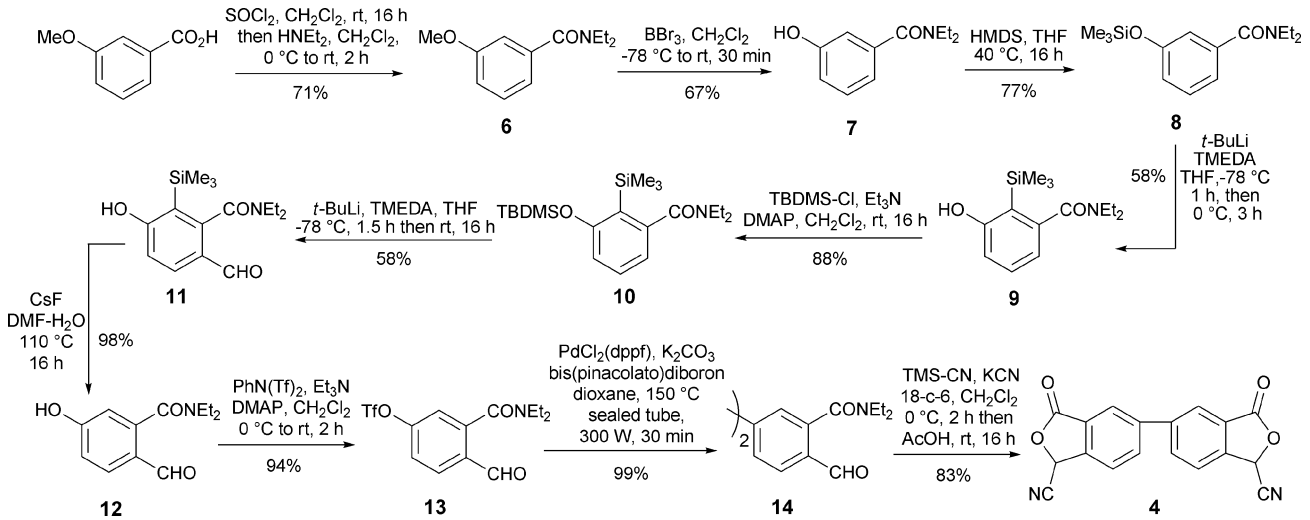
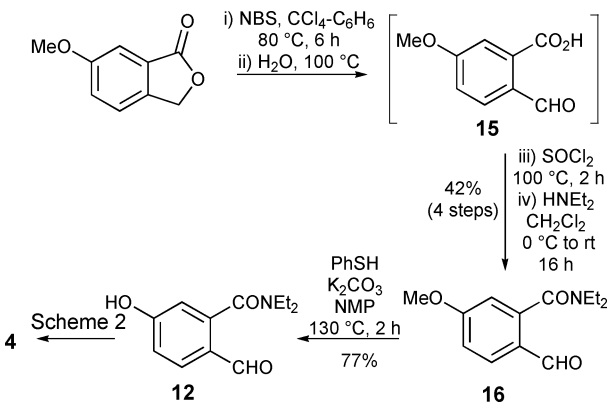


Scheme 2 Synthesis of bis-phthalide **4**.

Pleasingly, the use of thiophenol and potassium carbonate at elevated temperature in *N*-methylpyrrolidone[19] gave the desired phenol **12** in 4 steps compared to the 7-step synthesis described previously (Scheme 3).



Scheme 3 Improved route to key phenol **12**.

With sufficient quantities of bis-phthalide **4** in hand, the key double Hauser–Kraus annulation could be conducted. Initially, the conditions used for the successful Hauser–Kraus annulation in the synthesis of the monomeric pyranonaphthoquinone eleutherin[9] were adopted. A bright-red solution was immediately obtained upon treatment of the bis-cyanophthalide **4** with potassium *tert*-butoxide in THF–DMSO, highly indicative of successful dianion formation. The red colour then disappeared upon addition of two equivalents of the enone **5**,[9] suggesting successful consumption of the dianion. At this stage, only one product was detected by TLC. Attempts to purify the compound only led to degradation of what was assumed to be the bis-hydroquinone product **17**. Further attempts to purify **17** on silica gel, alumina and by crystallisation all met with failure (Scheme 4).

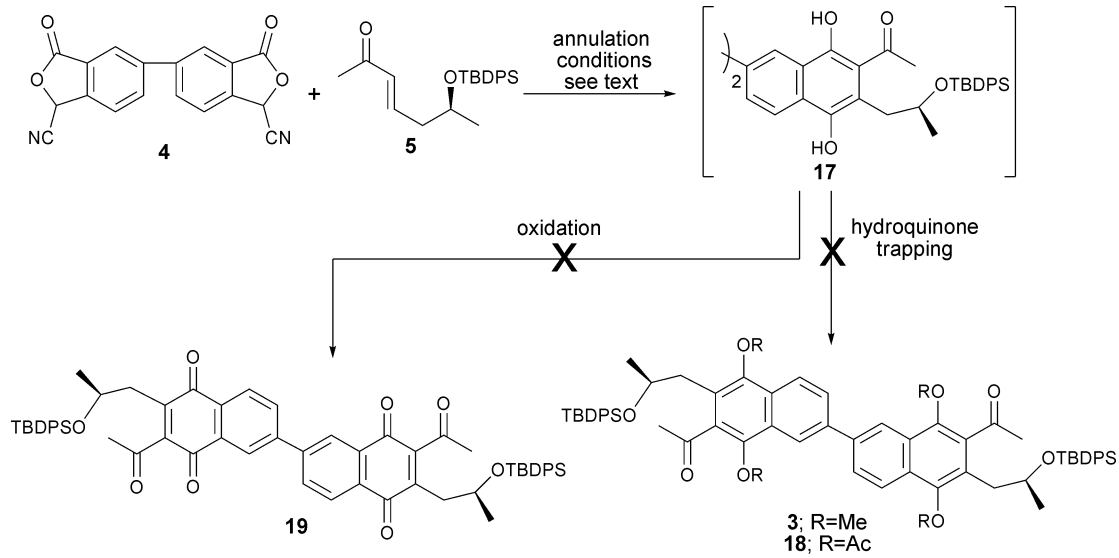
At this stage it was decided to trap the presumably unstable bis-hydroquinone **17** as tetramethyl ether **3** or tetraacetate **18** in order to facilitate purification. Unfortunately, no annulation products were isolated despite subjecting the crude annulation product to a range of reductive trapping conditions.

Our next option was to effect oxidation of **17** to a bis-naphthoquinone, a tactic previously employed by Hauser to facilitate isolation of a double Hauser–Kraus annulation product.[20] To this end, it was hoped that bis-naphthoquinone **19** would be stable enough to be isolated. Again, unfortunately only slow degradation was observed upon subjecting the crude reaction mixture to Fétizons reagent[20] and further oxidants including CAN, AgO, $FeCl_3$, Fremy's salt and molecular oxygen. Changing the base to lithium *tert*-butoxide or LDA offered no improvement.

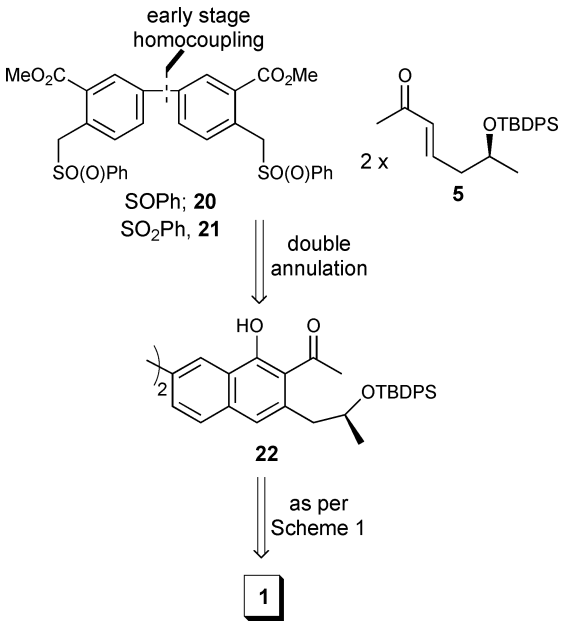
These disappointing results followed similar observations from our laboratory during efforts towards the total synthesis of crisamicin A, wherein double Hauser–Kraus annulation of a bis-cyanophthalide with a carbohydrate-derived enone only proceeded in a poor 23% yield.[21] To date only two double Hauser–Kraus annulations that employ an excess of the electrophilic annulation partner have been reported, including our own.[21] Hauser reported a double annulation during a total synthesis of (±)-biphyscion (36% yield),[20] and a closely related annulation involving the double toluate anion addition of a dimeric orsellinic acid derivative to a lactone electrophile has been reported (9% yield).[22] The paucity of double annulations in the literature combined with our own synthetic difficulties prompted us to modify our initial synthetic route.

Modified double annulation

A variant of the Hauser–Kraus annulation involves the addition of anions stabilised by adjacent sulfur groups to Michael acceptors. Due to the acyclic nature of the Michael donor, phenolic products are produced.[11a] Our attention therefore turned to use of this reaction as it was envisioned the phenolic annulation products would be stable enough to be purified without the need for trapping of the initial annulation product. Thus, a bis-sulfoxide **20** or bis-sulfone **21** were envisioned to be ideal targets to investigate for a double annulation with enone **5**. The resultant bis-naphthol **22** could then undergo a similar series of transformations outlined in Scheme 1 to give the key dimer **1** (Scheme 5). Given that only monomeric Hauser–Kraus-type annulations of sulfoxides and sulfones with electrophiles exist in the literature, the use of



Scheme 4 Failed double Hauser–Kraus annulation.



Scheme 5 Modified double annulation route.

a dimeric sulfone or sulfoxide presented an attractive novel route to bis-naphthalene systems.

Thus, following a closely related literature protocol,[23] 2-methylfuran underwent an aluminium-trichloride-promoted regioselective Diels–Alder reaction with methyl propiolate to provide phenol **23**[24] in moderate yield. Smooth conversion to triflate **24** proceeded under standard conditions. Unfortunately, the Suzuki–Miyaura conditions used successfully for the synthesis of biaryl **14** failed to afford satisfactory yields of the desired homocoupled product **25** despite numerous attempts. However, the use of a nickel-catalyzed protocol reported by Percec *et al.*[25] gave the homocoupled product **25** in 79% yield.

Double radical bromination was effected using *N*-bromosuccinimide in carbon tetrachloride at reflux affording crude dibromide **26** that upon treatment with thiophenol and DBU gave bis-sulfide **27**. Unfortunately, bis-sulfide **27** could not be oxidised cleanly to the bis-sulfoxide **20**, with only a mixture oxidation products being obtained. However, oxidation of **27** with hydrogen peroxide with catalytic quantities of ammonium molybdate[26] did furnish bis-sulfone **21** in excellent yield. Due to the difficulties obtaining bis-sulfoxide **20**, bis-sulfone **21** was decided upon as the annulation target. Thus, treatment of the crude dibromide **26** with sodium salt of benzenesulfinic acid in dimethylformamide gave the bis-sulfone **21** in good overall yield in a convenient one-pot procedure obviating the need to proceed *via* the corresponding sulfide (Scheme 6).

With sufficient quantities of bis-sulfone **21** in hand, the stage was now set for the modified double annulation. Initial treatment of **21** with both lithium and potassium *tert*-butoxide in DMSO and THF led to formation of weakly coloured solutions. Addition of two equivalents of electrophile **5** to these solutions only afforded recovered starting material. However, treatment of **21** with two equivalents of lithium diisopropylamide at −78 °C in THF did lead to a bright orange–red solution that dissipated upon addition of enone **5** with warming to room temperature. Unfortunately however, only unreacted bis-sulfone **21** and enone **5** were isolated from the reaction mixture with no double annulation product **22** being observed.

At this stage, it was concluded that our original plan to construct the biaryl bond at an early stage of the synthesis followed by effecting a double Hauser–Kraus (or closely related) annulation had failed and a different synthetic strategy was sought.

Late-stage homocoupling

Our revised strategy focused on conducting the key homocoupling step to forge the biaryl unit at an advanced stage of the synthesis. Thus, a single Hauser–Kraus annulation of benzyl-protected cyanophthalide **28** with enone **5** was envisioned as the crucial step to construct an appropriately functionalised monomeric naphthalene that could then be smoothly converted to aryl triflate **29** (Scheme 7). Homocoupling of triflate **29** would then provide the biaryl **3** that would undergo a similar synthetic sequence to that

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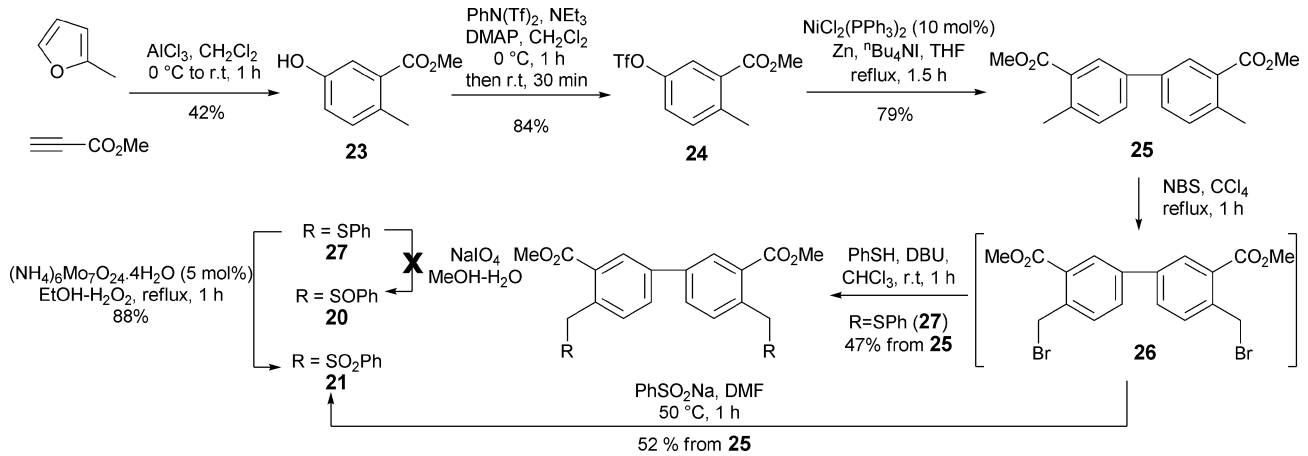
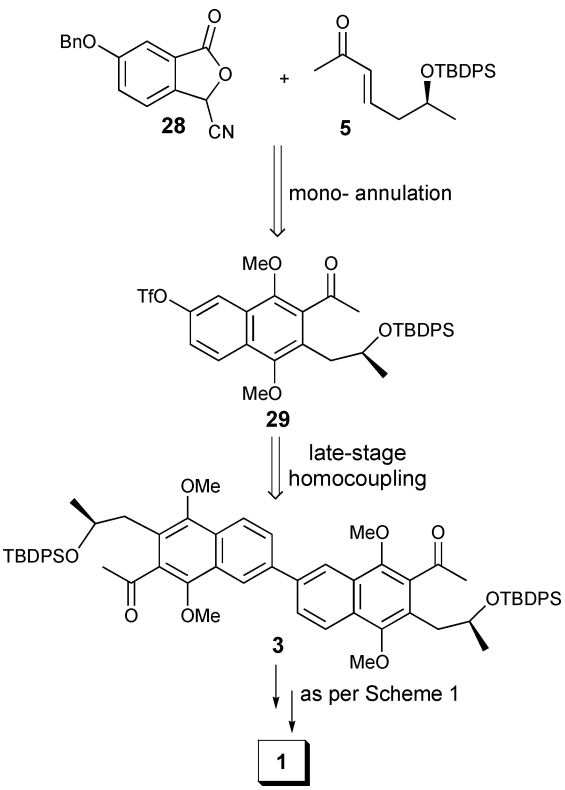


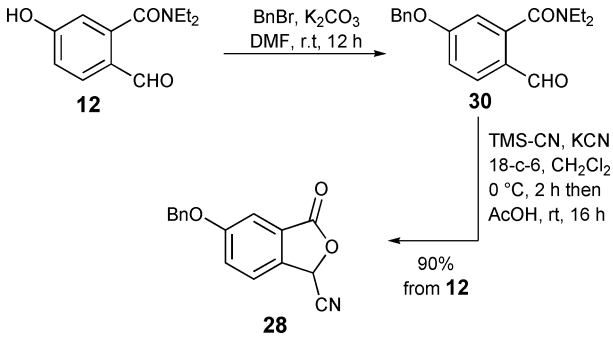
Scheme 6 Synthesis of bis-sulfone **21**.



Scheme 7 Revised strategy, late-stage homocoupling.

in Scheme 1, in which simultaneous construction of both pyran rings would be executed.

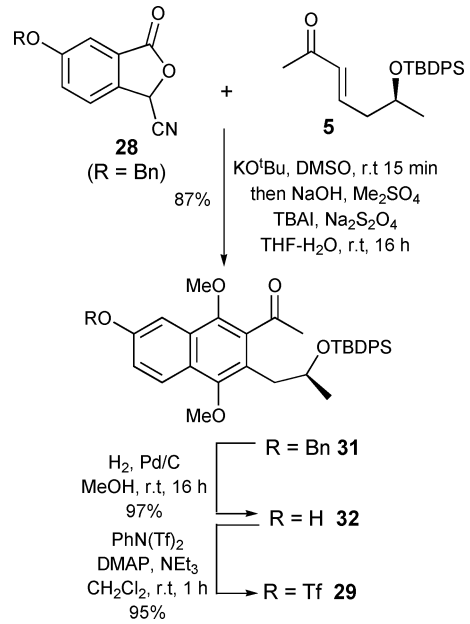
Given the ready availability of chiral enone **5**[9] attention turned to the synthesis of benzyl-protected cyanophthalide **28** that upon annulation with enone **5**, could be easily converted to the aryl triflate **29**, the key substrate for the proposed late-stage homocoupling. Thus, smooth benzylation of the previously synthesised phenol **12** delivered the benzyl ether **30** (Scheme 8). Ring closure using trimethylsilyl cyanide in the presence of catalytic quantities of potassium cyanide and 18-crown-6 then provided the cyanophthalide annulation precursor **28** (Scheme 8).



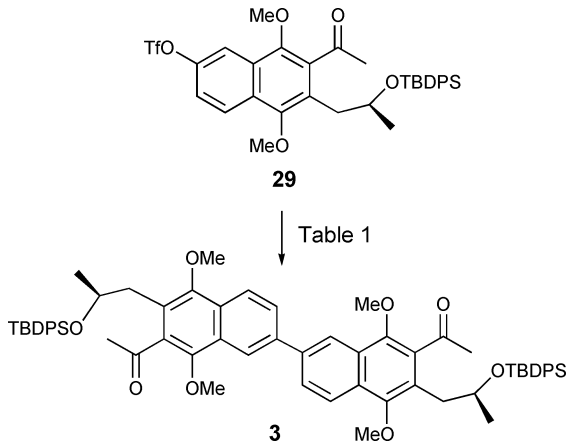
Scheme 8 Synthesis of protected cyanophthalide **28**.

The stage was now set for investigation of the key mono Hauser–Kraus annulation. Thus, reaction of cyanophthalide **28** with enone **5** proceeded smoothly in the presence of potassium *tert*-butoxide in dimethylsulfoxide. Immediate reductive methylation of the crude annulation product using sodium dithionite, sodium hydroxide and dimethylsulfate under phase-transfer conditions gratifyingly furnished the functionalised naphthalene **31**. Facile debenzylation then afforded naphthol **32** that underwent smooth triflate formation using standard conditions furnishing the key aryl triflate homocoupling precursor **29** in excellent overall yield (Scheme 9).

Next, the key homocoupling step was investigated. It was found that use of several literature conditions, including two methods previously used for the synthesis of biaryls **14** and **25**, failed to give satisfactory yields of the desired biaryl **3** (Scheme 10, Table 1). Generally, palladium catalysis (entry 6) was more promising compared to nickel catalysis (entries 1–3). After careful optimization, it was discovered that the yield of the biaryl was highly dependant on the addition of extra phosphine ligand (dppf) to the palladium catalyst and on the concentration of the reactants. Ultimately, it was found that microwave irradiation (300 W, 150 °C) of a 0.26 M solution of triflate **29** in dioxane containing bis(pinacolato)diboron (0.5 eq.), potassium carbonate (3 eq.) with $PdCl_2$(dppf) (10 mol%) as catalyst and additional dppf ligand (10 mol%) for 1 h afforded the homocoupled product in 51% yield (entry 7). This result mirrors similar observations noted on our studies towards the dimeric pyranonaphthoquinone



Scheme 9 Synthesis of aryl triflate **29**.



Scheme 10 Homocoupling of aryl triflate **29**.

crisamicin A[7c] wherein it was observed that homocoupling of highly oxygenated naphthalenes was challenging compared to simpler aryl systems; a sentiment expressed by Yang *et al.* during their recent total synthesis of crisamicin A.[6] With a synthetic route to biaryl **3** successfully established, double pyran ring formation could next be attempted. Treatment of biaryl **3** with an excess of tetrabutylammonium fluoride in tetrahydrofuran effected removal of both *tert*-butyldiphenylsilyl ether protecting groups with concomitant *in situ* cyclisation. Due to the unstable nature of bis-lactol **2** it was immediately reduced to bis-*cis*-1,3-dimethylpyran **33** with trifluoroacetic acid and triethylsilane. The formation of a single symmetrical product was observed in the ^{1}H NMR spectrum that supported the formation of the all *cis*-diastereomer resulting from pseudo-axial delivery of hydride during the reduction step.[10] The 1,3-*cis* stereochemistry was unequivocally confirmed by the NOE correlation between the axial protons at C1 and C3 on the pyran ring (see ESI†) and by X-ray crystallographic analysis[29] (Fig. 2). Finally, facile CAN-mediated oxidative demethylation provided the model dimer **1**, 7,7′-demethoxy-9,9′-deoxycardinalin 3 (Scheme 11).

In conclusion, an efficient synthesis of the dimeric core structure of cardinalin 3 constitutes a novel enantioselective synthesis of a dimeric pyranonaphthoquinone. Attempts to effect a double Hauser–Kraus annulation to access the dimeric naphthoquinone core failed. However, the combined use of a Hauser–Kraus annulation to assemble a monomeric naphthoquinone followed by a late-stage Suzuki–Miyaura homocoupling provided a flexible synthetic strategy for the synthesis of the target dimer **1**. Studies towards the total synthesis of the cardinalins and related dimeric pyranonaphthoquinones using this synthetic strategy are ongoing.

Experimental

General

All reactions were carried out in oven-dried or flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using 0.2 mm Kieselgel F254 (Merck) silica plates and compounds were visualised under 365 nm ultraviolet irradiation followed by staining with either alkaline permanganate or ethanolic vanillin solution. Infrared spectra were obtained using a Perkin-Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Optical rotations were measured

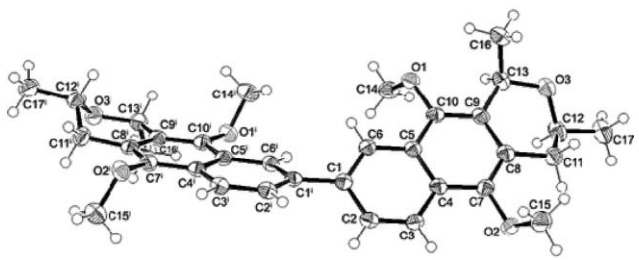


Fig. 2 X-Ray crystal structure of dimer **33**.

Table 1 One-pot homocoupling of aryl triflate **29** to biaryl **3**

Entry	Conditions	Yield of **3** (%)
1	$NiCl_2(PPh_3)_2$, Zn, ^{n}Bu_4NI, THF, reflux, 1.5 h[25]	12
2	$NiCl_2(PPh_3)_2$, Zn, ^{n}Bu_4NI, THF, 1.5 h, microwave 300 W, 100 °C, 15 min	16
3	$NiCl_2$(dppe), Zn, KI, THF, reflux, 3 h[27]	—
4	$Pd(OAc)_2$, ^{n}Bu_4NBr, Et_3N, DMF, 115 °C, 5 h[28]	—
5	$Pd(OAc)_2$, ^{n}Bu_4NBr, K_2CO_3, DMF–H_2O, 115 °C, 5 h[28]	—
6	$PdCl_2$(dppf), bis(pinacolato)diboron, K_2CO_3, dioxane, microwave, 300 W, 150 °C, 1 h	20
7	$PdCl_2$(dppf), dppf, bis(pinacolato)diboron, K_2CO_3, dioxane, microwave, 300 W, 150 °C, 1 h	51

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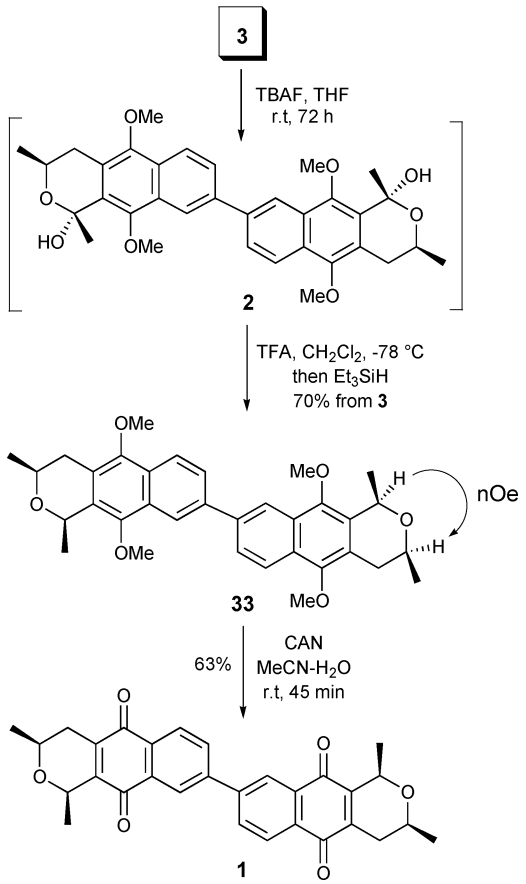

Scheme 11 Synthesis of dimer **1**.

using a Perkin-Elmer 341 polarimeter at $\lambda = 598$ nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on either a Bruker DRX-400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei or on a Bruker Avance 300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C nuclei, respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$–TMS solvent, or the residual chloroform peak at δ 7.25 ppm. The ^{13}C NMR values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C NMR values are reported as chemical shift δ, multiplicity and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (J in Hz) and assignment. Assignments are made with the aid of DEPT 135, COSY, NOESY and HSQC experiments. High-resolution mass spectra were recorded on a VG-70SE mass spectrometer at a nominal accelerating voltage of 70 eV. For all microwave-assisted reactions the CEM Discover system with a circular single mode and focused waves was used, resulting in the formation of a homogeneous field pattern surrounding the sample.

***N*,*N*-Diethyl-2-formyl-5-hydroxybenzamide (12).** To a solution of *N*,*N*-diethyl-2-formyl-5-methoxybenzamide **16**[18] (3.13 g, 13.3 mmol) in *N*-methylpyrrolidone (12 mL) was added potassium carbonate (20 mol%, 2.66 mmol, 367 mg) followed by thiophenol (1.9 mL, 18.6 mmol) and the reaction mixture was heated to 130 °C for 2 h. After cooling to room temperature, sodium hydroxide (1 M, 30 mL) was added and the aqueous layer washed with dichloromethane (3 × 30 mL). The basic aqueous layer was acidified to pH = 2 with concentrated hydrochloric acid and the resulting solution extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash chromatography eluting with hexanes–ethyl acetate (1 : 3) gave the *title compound* (2.26 g, 10.3 mmol, 77%) as a colourless solid, spectroscopic data identical with that reported previously.

***N*,*N*-Diethyl 5-(benzyloxy)-2-formylbenzamide (30).** To a solution of *N*,*N*-diethyl 2-formyl-5-hydroxybenzamide **12** (502 mg, 2.3 mmol) in dry DMF (8 mL) was added potassium carbonate (428 mg, 3.1 mmol) and benzyl bromide (0.32 mL, 461 mg, 2.7 mmol). The reaction mixture was stirred at r.t. for 16 h then water (20 mL) was added. The aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (1:1) to afford the *title compound* (676 mg, 2.2 mmol, 96%) as an off white oil; υ_{max} (oil)/cm^{-1} 3365, 3064, 3034, 2975, 2935, 2754, 1736, 1693, 1633, 1566, 1455, 1381, 1292; δ_H (300 MHz, $CDCl_3$) 0.98 (3 H, t, $^3J_{HH}$ 7.1, NCH_2CH_3), 1.31 (3 H, t, $^3J_{HH}$ 7.1, NCH_2CH_3), 3.09 (2 H, q, $^3J_{HH}$ 7.1, NCH_2CH_3), 3.60 (2 H, br m, NCH_2CH_3), 5.17 (2 H, s, CH_2Ph), 6.89 (1 H, d, $^4J_{HH}$ 2.5, Ar-H), 7.08 (1 H, dd, $^3J_{HH}$ 8.7, $^4J_{HH}$ 2.5, Ar-H), 7.37–7.41 (5 H, m, Ar-H), 7.90 (1 H, d, $^3J_{HH}$ 8.7, Ar-H), 9.91 (1 H, s, CHO); δ_C (100 MHz, $CDCl_3$) 12.6 (NCH_2CH_3), 13.8 (NCH_2CH_3), 39.1 (NCH_2CH_3), 42.9 (NCH_2CH_3), 70.5 (CH_2Ph), 113.0 (CH), 115.4 (CH), 126.0 (C), 127.4 (2 × CH), 128.4 (CH), 128.8 (2 × CH), 132.4 (CH), 135.6 (C), 141.8 (C), 163.2 (C), 168.3 (C=O), 189.0 (CHO); *m*/*z* (EI) 311 (4%, $[M]^+$), 282 (55, $[M - CHO]^+$), 239 (2, $[M - NEt_2]^+$), 91 (100, $[Bn]^+$); HRMS (EI, $[M]^+$) Found 311.1523 Calc. for $C_{19}H_{21}NO_3$ 311.1521.

5-(Benzyloxy)-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (28). *N*,*N*-Diethyl 5-(benzyloxy)-2-formylbenzamide **30** (270 mg, 0.87 mmol) was taken up in dry dichloromethane (5 mL) and cooled to 0 °C. Trimethylsilyl cyanide (0.13 mL, 1.1 eq., 0.95 mmol) was added followed by potassium cyanide (6 mg, 0.1 eq, 0.09 mmol) and 18-crown-6 (10 mg). The reaction mixture was stirred at 0 °C for 1.5 h then at r.t. for 30 min. The reaction mixture was concentrated *in vacuo* and the residue taken up in acetic acid (5 mL) and stirred at r.t. for 16 h. A 1 M aqueous solution of sodium hydroxide (10 mL) was added, followed by ethyl acetate (20 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (3 : 1) to afford the *title compound* (218 mg, 0.82 mmol, 94%) as an off-white solid; m.p. 117–118 °C; υ_{max} (oil)/cm^{-1} 2931, 1786, 1624, 1496, 1465, 1294, 1242, 1044; δ_H (300 MHz, $CDCl_3$) 5.16 (2 H, s, CH_2Ph), 6.02 (1 H, s, CH), 7.39–7.45 (7 H, m, Ar-H), 7.57 (1 H, ddd, *J* 7.7, 1.4, 0.7, Ar-H); δ_C (75 MHz, $CDCl_3$) 65.6 (*C*HCN), 70.8 (CH_2Ph), 109.6 (CH), 114.0 (*C*N), 123.7 (CH), 124.9 (CH), 126.1 (C), 127.6 (2 × CH), 128.6 (CH), 128.9 (2 × CH), 134.0 (C), 135.4 (C), 161.3 (C), 167.5 (C=O); *m*/*z* (EI) 265 (6%, $[M]^+$), 91

(100, [Bn]$^+$), 65 (10); HRMS (EI, [M]$^+$) Found 265.0737 Calc. for $C_{16}H_{11}NO_3$ 265.0738.

(*S*)-1-(7-(Benzyloxy)-3-(2-(*tert*-butyldiphenylsilyloxy)propyl)-1,4-dimethoxynaphthalen-2-yl)ethanone (31). To a solution of potassium *tert*-butoxide (250 mg, 2.2 mmol) in freshly distilled DMSO (5 mL) was added a solution of 5-(benzyloxy)-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile **28** (478 mg, 1.8 mmol) in DMSO (5 mL) followed by a solution of (*S*,*E*)-6-(*tert*-butyldiphenylsilyloxy)hept-3-en-2-one **5** (600 mg, 1.6 mmol) in DMSO (7.5 mL). The reaction mixture was stirred for 30 min then diluted with diethyl ether (50 mL) and quenched by the addition of saturated ammonium chloride (50 mL). The resulting mixture was partitioned between diethyl ether and ammonium chloride and the aqueous layer extracted with diethyl ether (80 mL × 3). The combined organic extracts were washed with water (50 mL × 2), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The resulting residue was taken up in THF–H_2O (5 : 2, 35 mL). Tetrabutylammonium bromide (59 mg, 0.18 mmol) was added, followed by a solution of sodium dithionite (1.78 g, 10.2 mmol) in water (10 mL). The reaction mixture was stirred for 2 h then a solution of sodium hydroxide (1.40 g, 35.0 mmol) in water (15 mL) was added followed by dimethyl sulfate (3.2 mL, 4.27 g, 33.8 mmol). The reaction mixture was stirred at r.t. for 2 h. Water (25 mL) and ethyl acetate (100 mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (80 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (95 : 5) to afford the *title compound* (901 mg, 1.4 mmol, 87%) as a yellow foam; $[\alpha]_D^{25}$ −1.0 (*c* 1.1, CH_2Cl_2); υ_{max} (oil)/cm^{-1} 3070, 3047, 2931, 2856, 1695, 1625, 1590, 1498, 1471, 1454, 1343, 1271, 1206, 1111; δ_H (300 MHz, $CDCl_3$) 0.99 (3 H, d, $^3J_{HH}$ 5.8, CHCH_3), 1.00 (9 H, s, Si(CH_3)$_3$), 2.44 (3 H, s, C=OCH_3), 2.83 (1 H, dd, $^2J_{HH}$ 13.5, $^3J_{HH}$ 7.5, C*H*H), 3.04 (1 H, dd, $^2J_{HH}$ 13.5, $^3J_{HH}$ 6.7, CH*H*), 3.75 (6 H, s, 2 × OCH_3), 4.24 (1 H, ddq, (app. sext.), $^3J_{HH}$ 7.5, 6.7, 5.8, CH), 5.24 (2 H, s, CH_2Ph), 7.23–7.56 (15 H, m, Ar-H), 7.66 (1 H, dd, *J* 7.0, *J* 1.5, Ar-H), 7.67 (1 H, d, *J* 9.2, Ar-H), 7.95 (1 H, d, *J* 9.0, Ar-H); δ_C (75 MHz, $CDCl_3$) 19.1 (*C*-Si), 23.4 (CH*C*H$_3$), 27.0 (C(CH_3)$_3$), 32.8 (C=O*C*H$_3$), 36.9 (CH_2), 61.7 (OCH_3), 63.1 (OCH_3), 69.7 (CH), 70.2 (*C*H$_2$Ph), 102.2 (CH), 120.0 (CH), 121.9 (C), 124.6 (C), 124.7 (CH), 127.4 (2 × CH), 127.5 (2 × CH), 127.7 (2 × CH), 128.1 (CH), 128.7 (2 × CH), 129.3 (CH), 129.4 (CH), 129.6 (C), 134.36 (C), 134.41 (C), 134.78 (C), 135.8 (2 × CH), 135.9 (2 × CH), 136.7 (C), 147.9 (C), 151.7 (C), 157.2 (C), 205.5 (C=O); *m*/*z* (EI) 632 (4%, [M]$^+$), 575 (100, [M − ^{t}Bu]$^+$), 484 (6, [M − Bn − ^{t}Bu]$^+$), 359 (38), 199, (40), 135 (54), 91 (84, [Bn]$^+$); HRMS (EI, [M]$^+$) Found 632.2952 Calc. for $C_{40}H_{44}O_5Si$ 632.2958.

(*S*)-1-(3-(2-(*tert*-Butyldiphenylsilyloxy)propyl)-7-hydroxy-1,4-dimethoxynaphthalen-2-yl)ethanone (32). (*S*)-1-(7-(Benzyloxy)-3-(2-(*tert*-butyldiphenylsilyloxy)propyl)-1,4-dimethoxynaphthalen-2-yl)ethanone **31** (901 mg, 1.42 mmol) was taken up in freshly distilled methanol (50 mL). 10% Palladium on carbon (20 mg) was added and the reaction mixture was stirred under an atmosphere of hydrogen for 18 h. The reaction mixture was filtered through Celite® then concentrated *in vacuo* to yield the *title compound* (746 mg, 1.37 mmol, 97%) as an unstable brown oil that was used directly in the next step without further purification; $[\alpha]_D^{25}$ +4.9 (*c* 5.0, CH_2Cl_2); υ_{max} (oil)/cm^{-1} 3393 (OH), 3071, 2962, 2934, 2894, 1692, 1627, 1591, 1445, 1427, 1354, 1219, 1111; δ_H (300 MHz, $CDCl_3$) 0.98 (9 H, s, C(CH_3)$_3$), 0.99 (3 H, d, $^3J_{HH}$ 5.5, CHCH_3), 2.44 (3 H, s, C=OCH_3), 2.81 (1 H, dd, $^2J_{HH}$ 13.5, $^3J_{HH}$ 7.4, C*H*H), 3.03 (1 H, dd, $^2J_{HH}$ 13.5, $^3J_{HH}$ 6.7, CH*H*), 3.73 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 4.21 (1 H, ddq (app. sext.), $^3J_{HH}$ 7.4, 6.7, 5.5, CH), 5.98 (1 H, s, OH), 7.14 (1 H, dd, *J* 9.0, *J* 2.4, Ar-H), 7.24–7.37 (7 H, m, Ar-H), 7.51 (2 H, dd, *J* 7.9, *J* 1.0, Ar-H), 7.64 (2 H, dd, *J* 7.9, *J* 1.0, Ar-H), 7.92 (1 H, d, *J* 9.0, Ar-H); δ_C (75 MHz, $CDCl_3$) 19.1 (Si(*C*(CH$_3$)$_3$), 23.4 (CH*C*H$_3$), 27.0 (Si(C(*C*H$_3$)$_3$), 32.8 (C=O*C*H$_3$), 36.8 (CH_2), 61.7 (OCH_3), 63.1 (OCH_3), 69.7 (CH), 104.5 (CH), 118.9 (CH), 121.6 (C), 124.4 (C), 125.0 (CH), 127.4 (4 × CH), 129.38 (2 × CH), 129.41 (C), 134.32 (C), 134.35 (C), 134.7 (C), 135.8 (2 × CH), 135.9 (2 × CH), 147.7 (C), 151.8 (C), 154.4 (C), 206.0 (C=O); *m*/*z* (EI) 542 (3%, [M]$^+$), 485 (100, [M − ^{t}Bu]$^+$), 381 (22), 269 (84), 239 (42, [SiPh$_2$^{t}Bu]$^+$), 199 (82), 135 (72); HRMS (EI, [M]$^+$) Found 542.2476 Calc. for $C_{33}H_{38}O_5Si$ 542.2488.

(*S*)-7-Acetyl-6-(2-(*tert*-butyldiphenylsilyloxy)propyl)-5,8-dimethoxynaphthalen-2-yl trifluoromethanesulfonate (29). (*S*)-1-(3-(2-(*tert*-Butyldiphenylsilyloxy)propyl)-7-hydroxy-1,4-dimethoxynaphthalen-2-yl)ethanone **32** (463 mg, 0.85 mmol) was taken up in dichloromethane (4 mL). 4-Dimethylaminopyridine (21 mg, 0.17 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (458 mg, 1.28 mmol) were added followed by freshly distilled triethylamine (0.24 mL, 174 mg, 1.7 mmol). The reaction mixture was stirred at r.t. for 1 h then saturated ammonium chloride (20 mL) was added. The mixture was extracted with ethyl acetate (50 mL × 3) and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (9 : 1) to yield the *title compound* (546 mg, 0.81 mmol, 95%) as a yellow oil; $[\alpha]_D^{25}$ +5.3 (*c* 0.9, CH_2Cl_2); υ_{max} (oil)/cm^{-1} 3073, 2962, 2934, 2858, 1698, 1644, 1496, 1427, 1343. 1212, 1140, 1111; δ_H (300 MHz, $CDCl_3$) 0.97 (9 H, s, SiC(CH_3)$_3$), 0.98 (3 H, d, $^3J_{HH}$ 6.0, CHCH_3), 2.45 (3 H, s, C=OCH_3), 2.86 (1 H, dd, $^2J_{HH}$ 13.5, $^3J_{HH}$ 6.9, CH*H*), 3.06 (1 H, dd $^2J_{HH}$ 13.5, $^3J_{HH}$ 7.1, CH*H*), 3.77 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.25 (1 H, ddq (app. sext.), $^3J_{HH}$ 7.1, 6.9, 6.0, CH), 7.20–7.45 (7 H, m, Ar-H), 7.48 (2 H, dd, *J* 7.7, 1, Ar-H), 7.63 (2 H, dd, *J* 7.7, 1.4, Ar-H), 7.94 (1 H, d, *J* 2.4, Ar-H), 8.11 (1 H, d, *J* 9.2, Ar-H); δ_C (75 MHz, $CDCl_3$) 19.1 (Si(*C*(CH$_3$)$_3$), 23.6 (CH*C*H$_3$), 26.9 (Si(C(CH$_3$)$_3$), 32.7 (C=O*C*H$_3$), 37.1 (CH_2), 61.9 (OCH_3), 63.8 (OCH_3), 69.5 (CH), 114.5 (CH), 120.7 (CH), 125.9 (CH), 126.4 (C), 127.37 (2 × CH), 127.42 (2 × CH), 127.9 (C), 128.1 (C), 129.4 (CH), 129.5 (CH), 134.2 (C), 134.5 (C), 135.6 (C), 135.7 (2 × CH), 135.9 (2 × CH), 147.8 (C), 148.8 (C), 151.6 (C), 204.5 (C=O), triflate carbon not observed; *m*/*z* (CI) 675 (11%, [MH]$^+$), 617 (18), 527 (4, [MH − OTf + H]$^+$), 419 (46), 271 (25), 199 (44), 94 (60), 78 (100, [PhH]$^+$); HRMS (CI, [M]$^+$) Found 675.2072 Calc. for $C_{34}H_{38}F_3O_7SSi$ 675.2059.

1,1′-(6,6′-*bis*((*S*)-2-(*tert*-Butyldiphenylsilyloxy)propyl)-5,5′,8,8′-tetramethoxy-2,2′-binaphthyl-7,7′-diyl)diethanone (3). (*S*)-7-Acetyl-6-(2-(*tert*-butyldiphenylsilyloxy)propyl)-5,8-dimethoxynaphthalen-2-yl trifluoromethanesulfonate **29** (164 mg, 0.24 mmol) was taken up in freshly distilled dioxane (0.9 mL). Potassium carbonate (101 mg, 0.73 mmol), bis(pinacolato)diboron (31 mg, 0.12 mmol) and dppf (13 mg, 0.023 mmol) were added and the resulting suspension degassed under a stream of argon

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for 15 min. $PdCl_2$(dppf) (10 mol%, 20 mg, 0.024 mmol) was added and the reaction mixture was further degassed under a stream of argon for 5 min. The reaction mixture was heated under microwave irradiation in a sealed tube (300 W, 150 °C) for 1 h. After cooling to room temperature, the resulting suspension was diluted with ethyl acetate (15 mL) and water was added (30 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (10 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo.* The residue was purified by flash chromatography eluting with hexanes–ethyl acetate (9 : 1) to give the *title compound* (65 mg, 0.062 mmol, 51%) as a colourless oil; $[\alpha]_D^{25}$ –21.8 (*c* 2.5, CH_2Cl_2); υ_{max} (oil)/cm^{-1} 3070, 3049, 2959, 2932, 2894, 1679, 1588, 1450, 1427, 1348, 1330, 1204, 1112; δ_H (400 MHz, $CDCl_3$) 0.97 (18 H, s, 2 × C(CH_3)$_3$), 0.98 (6 H, d, $^3J_{HH}$ 6.0, 2 × CH_3), 2.48 (6 H, s, 2 × C=OCH_3), 2.90 (2 H, dd, $^2J_{HH}$ 13.4, $^3J_{HH}$ 7.5, 2 × C*H*H), 3.11 (2 H, dd, $^2J_{HH}$ 13.4, $^3J_{HH}$ 6.7, 2 × CH*H*), 3.81 (6 H, s, 2 × OCH_3), 3.90 (6 H, s, 2 × OCH_3), 4.27 (2 H, ddq (app. sext.), $^3J_{HH}$ 7.5, 6.7, 6.0, 2 × CH), 7.27 (4 H, m, Ar-H), 7.38 (8 H, m, Ar-H), 7.54 (4 H, dd, *J* 8.1, 1.3, Ar-H), 7.66 (4 H, dd, *J* 8.1, 1.6, Ar-H), 7.93 (2 H, dd, *J* 8.8, 1.8, Ar-H), 8.15 (2 H, d, *J* 8.8, Ar-H), 8.36 (2 H, d, *J* 1.8, Ar-H); δ_C (100 MHz, $CDCl_3$) 19.1 (2 × Si(*C*(CH_3)$_3$), 23.4 (2 × $CHCH_3$), 27.0 (2 × Si(C(*C*H_3)$_3$), 32.8 (2 × C=O*C*H_3), 37.0 (2 × CH_2), 61.8 (2 × OCH_3), 63.7 (2 × OCH_3), 69.6 (2 × CH), 120.6 (2 × CH), 123.7 (2 × CH), 124.8 (2 × C), 126.8 (2 × CH), 127.4 (8 × CH), 127.9 (2 × C), 128.3 (2 × C), 129.40 (2 × CH), 129.43 (2 × CH), 134.27 (2 × C), 134.31 (2 × C), 134.7 (2 × C), 135.8 (4 × CH), 135.9 (4 × CH), 138.6 (2 × C), 149.3 (2 × C), 151.6 (2 × C), 205.3 (2 × C=O); *m*/*z* (FAB) 1050 (4%, [M]$^+$), 993 (6, [M – C(CH_3)$_3$]$^+$), 795 (14), 397 (10), 197 (40), 135 (100); HRMS (FAB, [M]$^+$) Found 1050.4921 Calc. for $C_{66}H_{74}O_8Si_2$ 1050.4922.

(1*R*,1′*R*,3*S*,3′*S*)-5,5′,10,10′-Tetramethoxy-1,1′,3,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-dibenzo[*g*]isochromene (33). To a solution of 1,1′-(6,6′-*bis*((*S*)-2-(*tert*-butyldiphenylsilyloxy)-propyl)-5,5′,8,8′-tetramethoxy-2,2′-binaphthyl-7,7′-diyl)diethanone **3** (144 mg, 0.14 mmol) in THF (5 mL) was added a 1 M solution of tetra-*n*-butylammonium fluoride (3.0 mL, 3.0 mmol). The reaction mixture was stirred under nitrogen at r.t. for 3 d then concentrated *in vacuo.* The resulting residue was flushed through a pad of silica (hexanes–ethyl acetate 1 : 1–1 : 3). The filtrate was concentrated *in vacuo* and the resulting crude bis-lactol **2** was dissolved in distilled dichloromethane (5 mL) and cooled to –78 °C. Trifluoroacetic acid (0.065 mL, 98 mg, 0.86 mmol) was added dropwise and reaction mixture was stirred for 15 min before addition of triethylsilane (0.13 mL, 94 mg, 0.80 mmol). The reaction mixture was then allowed to reach r.t. over 16 h. Water (20 mL) was added and the mixture extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo* and the resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (7 : 3) to give the *title compound* (52 mg, 0.096 mmol, 70%) as a cream-coloured solid; m.p. 268–269 °C; $[\alpha]_D^{24}$ +36.2 (*c* 0.12, CH_2Cl_2); υ_{max} (CH_2Cl_2)/cm^{-1} 3418, 3053, 2986, 1638, 1421, 1264, 733; δ_H (300 MHz, $CDCl_3$) 1.44 (6 H, d, $^3J_{HH}$ 6.0, 2 × CHC*H*$_3$), 1.73 (6 H, d, $^3J_{HH}$ 6.6, 2 × CHC*H*$_3$), 2.66 (2 H, dd, $^2J_{HH}$ 16.2, $^3J_{HH}$ 11.0, 2 × C*H*$_{ax}$H), 3.11 (2 H, dd, $^2J_{HH}$ 16.2, $^3J_{HH}$ 1.5, 2 × C*H*$_{eq}$H), 3.74 (2 H, m, 2 × C*H*CH$_3$), 3.91 (6 H, s, 2 × OCH_3), 3.95 (6 H, s, 2 × OCH_3), 5.26 (2 H, q, $^3J_{HH}$ 6.6, 2 × C*H*CH$_3$), 7.89 (2 H, dd, $^3J_{HH}$ 8.8, $^4J_{HH}$ 1.6, Ar-H), 8.18 (2 H, d, $^3J_{HH}$ 8.8, Ar-H), 8.37 (2 H, d, $^4J_{HH}$ 1.6, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.8 (2 × CH*C*H$_3$), 22.4 (2 × CH*C*H$_3$), 32.0 (2 × CH_2), 61.1 (2 × OMe), 61.4 (2 × OMe), 69.6 (2 × CH), 71.3 (2 × CH), 120.4 (2 × CH), 122.8 (2 × CH), 125.5 (2 × C), 125.7 (2 × CH), 126.6 (2 × C), 127.7 (2 × C), 129.9 (2 × C), 138.3 (2 × C), 148.8 (2 × C), 149.0 (2 × C); *m*/*z* (EI) 542 (100%, [M]$^+$), 527 (39), 199 (22), 105 (32), 57 (40), 44 (72); HRMS (EI, [M]$^+$) Found 542.2667 Calc. for $C_{34}H_{38}O_6$ 542.2668.

7,7′-Demethoxy-9,9′-deoxycardinalin (1). (1*R*,1′*R*,3*S*,3′*S*)-5,5′,10,10′-Tetramethoxy-1,1′,3,3′-tetramethyl-3,3′,4,4′-tetrahydro-1*H*,1′*H*-8,8′-dibenzo[*g*]isochromene **33** (24 mg, 0.044 mmol) was suspended in acetonitrile (1.5 mL) and a solution of ammonium cerium(IV) nitrate (152 mg, 0.28 mmol) in water (1.25 mL) was added. The reaction mixture was stirred at r.t. for 45 min, then water (5 mL) was added and the whole was extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo*, and the resulting residue was purified by flash chromatography eluting with hexanes–ethyl acetate (4 : 1) to afford the *title compound* (13.5 mg, 0.028 mmol, 63%) as a yellow solid; m.p. 239–240 °C; $[\alpha]_D^{23}$ +356.1 (*c* 0.15, CH_2Cl_2); υ_{max} (CH_2Cl_2)/cm^{-1} 3432, 3025, 1663, 1265, 736, 705; δ_H (400 MHz, $CDCl_3$) 1.40 (6 H, d, $^3J_{HH}$ 6.1, 2 × CHC*H*$_3$), 1.58 (6 H, d, $^3J_{HH}$ 6.5, 2 × CHC*H*$_3$), 2.31 (2 H, ddd, J_{HH} 18.7, 10.2, 4.0, 2 × C*H*$_{ax}$H), 2.82 (2 H, dt, J_{HH} 18.7, 2.5, 2 × C*H*$_{eq}$H), 3.64 (2 H, m, 2 × C*H*CH$_3$), 4.89 (2 H, m, 2 × C*H*CH$_3$), 8.02 (2 H, dd, $^3J_{HH}$ 8.0, $^4J_{HH}$ 1.9, Ar-H), 8.20 (2 H, d, $^3J_{HH}$ 8.0, Ar-H), 8.35 (2 H, $^4J_{HH}$ 1.9, Ar-H); δ_C (100 MHz, $CDCl_3$) 20.8 (2 × CH*C*H$_3$), 21.2 (2 × CH*C*H$_3$), 30.5 (2 × CH_2), 68.7 (2 × CH), 70.0 (2 × CH), 125.0 (2 × CH), 127.3 (2 × CH), 131.4 (2 × CH), 131.9 (2 × C), 133.0 (2 × C), 143.0 (2 × C), 144.2 (2 × C), 147.0 (2 × C), 183.4 (2 × C=O), 183.7 (2 × C=O); *m*/*z* (EI) 482 (100%, [M]$^+$), 467 (20), 237 (15), 199 (20), 131 (21), 91 (99), 77 (25), 57 (37), 40 (85); HRMS (EI, [M]$^+$) Found 482.1720. Calc. for $C_{30}H_{26}O_6$ 482.1729.

Acknowledgements

The authors thank the Royal Society of New Zealand Marsden fund for financial support.

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