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Synthesis of a regioisomeric analogue of the 3C-protease inhibitor thysanone via a Hauser annulation strategy

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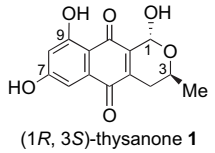
Abstract—Hauser annulation of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** with ethyl acrylate as a method to access activated naphthoquinone **3**, a key intermediate for the synthesis of thysanone **1**, proved unreliable. In contrast to this, Hauser annulation of regioisomeric 3-cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13** with ethyl acrylate proceeded readily affording ethyl 5,7-dimethoxy-1,4-naphthoquinone **12**, after oxidation of the initial dihydroxynaphthalene **16**. Allylation of naphthoquinone **12** followed by reductive methylation and Wacker oxidation afforded ketone **11** that underwent CBS reduction to (2′*S*)-alcohol **19** followed by cyclisation to lactone **20**. Reduction of the lactone followed by oxidative demethylation afforded (1*S*,3*S*)-6,8-dimethoxy-1-hydroxy-3-methylpyrano[2,3-*c*]-1,4-naphthoquinone **22**, a regioisomeric analogue of the 3C-protease inhibitor thysanone **1**.

1. Introduction

Human rhinoviruses belong to one of the largest families of positive strand RNA viruses, the *Picornaviridae*, and are believed to cause up to 50% of common colds.[1] Picornaviruses enter a host cell and instruct it to synthesise a polypeptide essential for continuation of the viral reproductive cycle. The necessary intracellular proteolytic processing of the polypeptide is dependant upon two virally encoded proteases, a 3C-protease and a 2A-protease. Inhibition of the 3C-protease thus provides a potential method to develop therapeutic agents to combat the common cold. Thysanone **1** isolated from *Thysanophora penicilloides*[2] is closely related to the pyranonaphthoquinone family of antibiotics[3] and is one of the few effective inhibitors of human rhinovirus 3C-protease thus providing a lead compound for understanding the mechanism of 3C-protease inhibition.



(1*R*, 3*S*)-thysanone **1**

In one of the reported lengthy total synthesis[4] of thysanone **1**, the (*S*)-stereochemistry at C-3 was derived from ethyl (*S*)-lactate and the stereochemistry of the natural product **1** was established unequivocally to be (1*R*,3*S*). The strategy adopted involved a late stage addition of an oxygenated diene to a bromobenzoquinone unit containing a functionalized pyran ring. A synthesis of an analogue of thysanone[5] has also been reported that contains a hydroxymethyl group rather than a methyl group at C-3 thus providing a handle for the synthesis of tethered mixed mechanism antiviral agents. However, the absolute stereochemistry of the hydroxymethyl group at C-3 was not controlled in this case. We have previously reported[6] the synthesis of 7,9-dideoxy analogues of thysanone in which the stereochemistry at C-3 is controlled by asymmetric dihydroxylation of an allylnaphthalene or via asymmetric reduction of a methyl ketone that was also derived from an allylnaphthalene. We herein report our further synthetic efforts in this area adopting an alternative approach in which the oxygenated naphthoquinone skeleton of thysanone **1** is assembled via annulation of a substituted cyanophthalide with a suitable Michael acceptor.

2. Results and discussion

Our initial attention focused on the synthesis of thysanone **1** in which the stereochemistry at C-3 is established via asymmetric reduction of methyl ketone **2** (Scheme 1). Methyl ketone **2** in turn is available from naphthoquinone **3** that is assembled via Hauser annulation of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** with ethyl acrylate. Hauser annulation[7] has proven to be a reliable method for the synthesis of naphthoquinones and angucyclines,[8] and involves addition of an anion generated from a 3-substituted phthalide to a Michael acceptor followed by expulsion of a leaving group at C-3 to form a 1,4-dihydroxynaphthalene that is readily oxidised to a 1,4-naphthoquinone.

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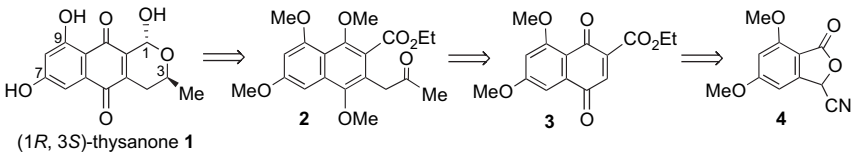


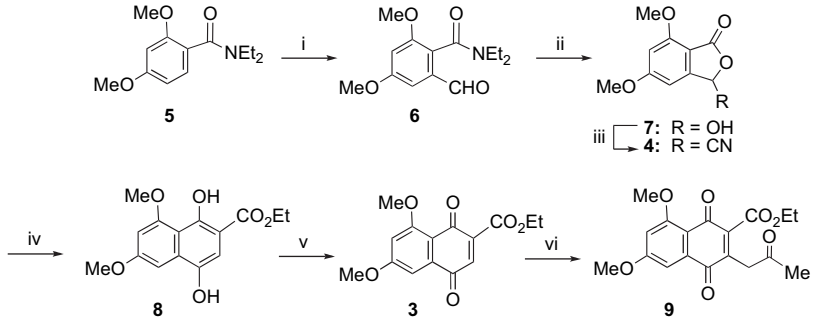
Scheme 1.

3-Cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** was readily prepared from diethyl 2,4-dimethoxybenzamide **5** via *ortho* lithiation followed by quenching the resultant carbanion with DMF providing aldehyde **6**[9] in quantitative yield (Scheme 2). Subsequent treatment of formylbenzamide **6** with acetic acid and 10% HCl under reflux effected hydrolysis and intramolecular cyclisation to give 3-hydroxy-5,7-dimethoxyphthalide **7**.[10] Finally conversion of hydroxyphthalide **7** to cyanophthalide **4**[11] was effected using potassium cyanide and concentrated hydrochloric acid.

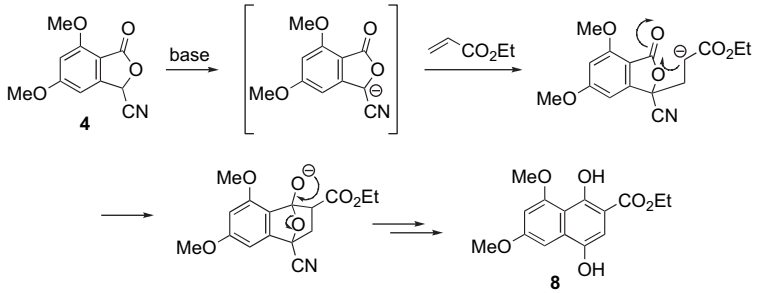
The use of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** in Hauser annulations has not been reported to date, thus a study of the annulation of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** with both acrylonitrile and ethyl acrylate as electrophiles was warranted. Use of LDA (with and without added HMPA), *tert*-butyllithium and lithium *tert*-butoxide in THF, to generate the carbanion at −78 °C using acrylonitrile as the electrophile only afforded the desired annulation product naphthalene in <5% yield. A variety of reaction conditions were then investigated using ethyl acrylate as the Michael acceptor and the best result was obtained using *sec*-butyllithium in THF at −78 °C for 6 h affording the desired naphthalene **8** in 54% isolated yield. When the reaction was carried out using *tert*-butyllithium a lower yield of 41% was observed and use of toluene/THF (2:1) did not offer any improvement. Use of additives such as cerium(III) chloride, tin(II) triflate, HMPA or *trans*-metallation with copper(I) cyanide was ineffective and use of inverse addition techniques, variation of the stoichiometry of the reactants and the reaction temperature and time, likewise did not improve the reaction.

In spite of the difficulties experienced with this key phthalide annulation, the desired product **8** underwent facile oxidation to naphthoquinone **3** in quantitative yield by using a catalytic quantity of cerium(IV) ammonium nitrate (CAN) and *tert*-butyl hydroperoxide.[12] The 2-oxopropyl group was then introduced[13] onto naphthoquinone **3** by using the ylide generated from *N*-acetonylpyridinium chloride. Thus, treatment of naphthoquinone **3** with *N*-acetonylpyridinium chloride[14] and triethylamine in acetonitrile afforded 3-(2′-oxopropyl)-naphthoquinone **9** in quantitative yield.

In order to progress naphthoquinone **9** to thysanone **1**, large quantities of the phthalide annulation product **8** were required. It was therefore disappointing to find that having established conditions to effect the conversion of cyanophthalide **4** to naphthalene **8** on a small scale the reaction was not amenable to scaling up and the reaction proved irreproducible. It was postulated that the two methoxy groups in cyanophthalide **4** are ideally positioned to donate electron density to the carbonyl group of the phthalide thus inhibiting intramolecular attack of the enolate intermediate generated in the initial Michael reaction (Scheme 3). There are several examples of failed Hauser annulations that have been



Scheme 2. Reagents and conditions: (i) ^{t}BuLi, THF, −78 °C, then DMF, 99%; (ii) AcOH, 10% HCl, reflux, 22 h, 85%; (iii) KCN, concd HCl, 0 °C then room temperature, 3 h, 85%; (iv) ^{s}BuLi, THF, −78 °C, 10 min, ethyl acrylate, −78 °C, 6 h, 54%; (v) CAN, ^{t}BuOOH, CH_3CN, 99%; (vi) $pyN^{+}CH_2COCH_3Cl^{-}$, Et_3N, CH_3CN, room temperature, 1 h, 99%.



Scheme 3.

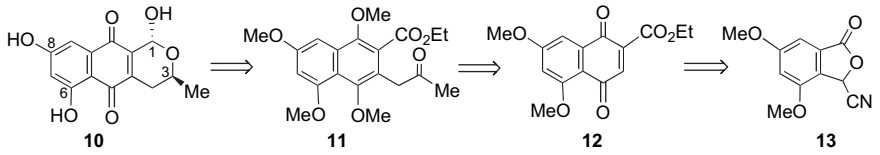
attributed to the inability to induce the initial Michael adduct to undergo cyclisation.[15,16]

Given the problematic Hauser annulation used to access naphthalene **8** in synthetically useful quantities our attention next turned to the synthesis of the 6,8-regioisomer of thysanone **10** via asymmetric reduction of methyl ketone **11** (Scheme 4). Methyl ketone **11** in turn is available from naphthoquinone **12** via Hauser annulation of the regioisomeric 3-cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13**. This revised synthesis would not only provide access to analogues of thysanone for biological evaluation but would also allow us to probe the reason for the failure of cyanophthalide **4** to undergo Hauser annulation with ethyl acrylate that was attributed to the failure of the Dieckmann cyclisation step due to the presence of the methoxy groups at C-5 and C-7.

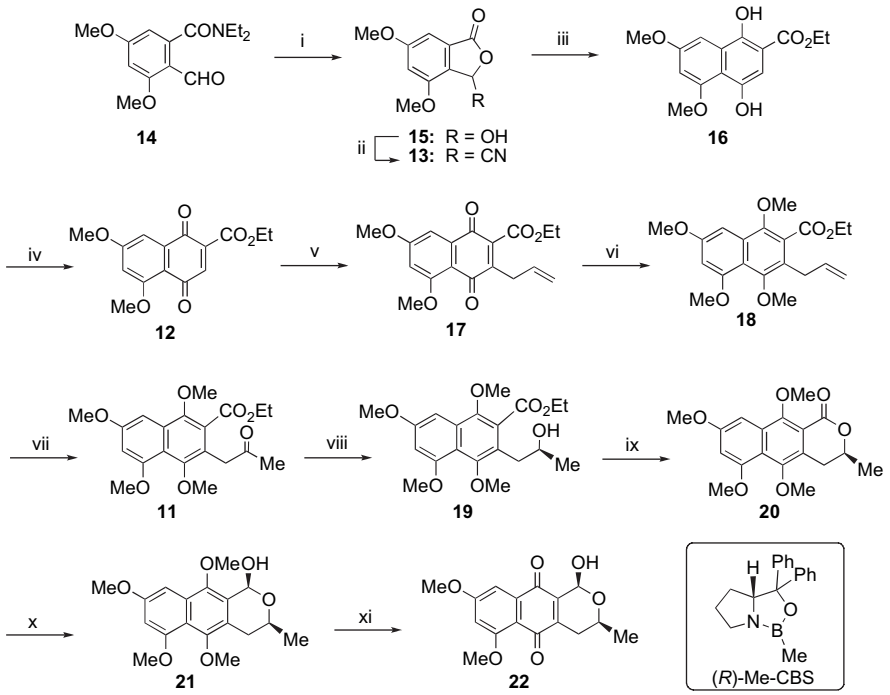
The two methoxy groups in 3-cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13** are *meta* to the phthalide carbonyl group and cannot donate electron density to phthalide carbonyl group thus facilitating the Dieckmann cyclisation step in the Hauser annulation. 3-Cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13** was readily prepared[17] by hydrolysis and cyclisation of formylbenzamide **14** to hydroxyphthalide **15** followed by displacement of the hydroxyl group with potassium cyanide and hydrochloric acid (Scheme 5).

Gratifyingly, treatment of 3-cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13** with *sec*-butyllithium in THF at −78 °C for 3 h followed by reaction with ethyl acrylate proceeded in nearly quantitative yield affording dihydroxynaphthalene **16**. Moreover, and in contrast to the annulation of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4**, no difficulties were encountered when the reaction was carried out on a large scale. Oxidation of dihydroxynaphthalene **16** using silver(I) oxide in toluene afforded naphthoquinone **12** in preparation for appendage of the 2-oxopropyl group. In this case direct introduction of the 2-oxopropyl group using *N*-acetonylpyridinium chloride was unsuccessful thus prompting an alternative strategy to effect this transformation.

Fortunately, the acetonyl group could be introduced in a three-step sequence via introduction of an allyl group at C-3. All attempts to nucleophilic allylation using allyltributyltin resulted in a mixture of unidentifiable compounds. Fortunately, the free radical process[18] involving vinylacetic acid, silver(I) nitrate and ammonium dithionite afforded the allylated naphthoquinone **17** in moderate yield. Reductive



Scheme 4.

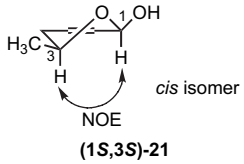


Scheme 5. Reagents and conditions: (i) AcOH, 10% HCl, reflux, 24 h, 99%; (ii) KCN, concd HCl, 0 °C then room temperature, 22 h, 68%; (iii) ^{s}BuLi, THF, −78 °C, 10 min, ethyl acrylate, −78 °C, 2.5 h, 99%; (iv) Ag_2O, toluene, room temperature, 25 h, 73%; (v) vinylacetic acid, CH_3CN, $AgNO_3$, $(NH_4)_2S_2O_8$, 56%; (vi) Bu_4Ni, THF, H_2O, $Na_2S_2O_4$, then KOH, $(CH_3)_2SO_4$, 55%; (vii) CuCl, $PdCl_2$, O_2, DMF, H_2O, 66 h, 72%; (viii) (*R*)-Me-CBS, $BH_3\cdot SMe_2$, THF, −40 °C, 2 h, 97%; (ix) NaH, THF, 1 h, 92%; (x) DIBALH, toluene, −78 °C, 1 h, 99%; (xi) AgO, HNO_3, 1,4-dioxane, 50%.

methylation of the naphthoquinone using sodium dithionite under phase transfer conditions followed by in situ treatment with potassium hydroxide and dimethyl sulfate afforded dimethoxynaphthalene **18**. Finally, Wacker oxidation afforded methyl ketone **11** in good yield.

Introduction of the stereogenic centre at C-3 in the regioisomer of thysanone **10** critically depends on the stereocontrolled reduction of the ketone functionality introduced in the previous step. One method for the asymmetric reduction involves the use of chiral oxazaborolidines and borane as developed by Corey and Helal[19] The optimum procedure for the asymmetric reduction of ketone **11** involved 'in situ' generation of the chiral oxazaborolidine from (*R*)-Me-CBS catalyst (Aldrich, 1 M in toluene) and borane dimethyl sulfide complex in THF followed by the addition of ketone **11** at −40 °C with stirring for 2 h. Work up and purification by flash chromatography afforded the desired alcohol **19** in 97% yield. The enantiomeric excess was determined to be 65% by chiral HPLC (Daicel AD-H column). The (*S*)-configuration was predicted using the transition state model described in the literature[18] for asymmetric reductions of prochiral ketones using this chiral oxazaborolidine. Attempts to improve the enantioselectivity of the asymmetric reduction using alternative chiral reducing agents such as DIP-Cl did not afford any improvement in the enantiomeric excess observed.

The pyran ring was next formed by the treatment of hydroxyester **19** with sodium hydride in THF affording lactone **20** in 92% yield for which the enantiomeric excess was also established to be 65% by chiral HPLC. Reduction of lactone **20** with diisobutylaluminium hydride (1 M in toluene) afforded (1*S*,3*S*)-lactol **21** cleanly in excellent yield. The ^{1}H and ^{13}C NMR spectra displayed only one set of resonances indicating that only one diastereomer had formed. The relative stereochemistry of this product was determined by NOESY NMR experiments, which showed a correlation between H-1 and H-3 clearly establishing that axial hydride addition at C-1 had taken place *syn* to the hydrogen at C-3 affording *cis*-lactol **21** (Fig. 1).



(1*S*,3*S*)-21

Figure 1.

Finally, oxidative demethylation of dimethoxynaphthalene **21** using silver(II) oxide in nitric acid afforded pyranonaphthoquinone **22**, a 6,8-dimethoxy regioisomeric analogue of thysanone. The enantiomeric excess of the final naphthoquinone **22** was also established to be 65% by chiral HPLC.

In summary, the enantioselective synthesis of (1*S*,3*S*)-6,8-dimethoxy-1-hydroxy-3-methylpyrano[2,3-*c*]-1,4-naphthoquinone **22** from *N*,*N*-diethyl 2-formyl-3,5-dimethoxybenzamide **14** was completed in 12 steps. Although, the asymmetric induction for the key stereoselective Corey–Bakshi–Shibata reduction of ketone **11** proceeded in a moderate 65% enantiomeric excess, this optical purity was retained during all subsequent steps. Stereoselective reduction of lactone **20** using DIBALH afforded (1*S*,3*S*)-*cis*-lactol **21** that was readily oxidised to naphthoquinone **22**. Whilst thysanone **1** itself exhibits (1*R*,3*S*)-*trans* stereochemistry we have developed a practical enantioselective synthesis of an analogue of thysanone that contains a regioisomeric substitution pattern in the aromatic ring and differs in the relative stereochemistry between C-1 and C-3. This latter issue will be addressed when the stereogenic centre at C-3 can be introduced with better stereocontrol. In addition, limitations in the use of a Hauser annulation to access the naphthoquinone skeleton of thysanone **1** with the correct oxygenation pattern have been highlighted in this study.

3. Experimental

3.1. General details

All reactions were conducted in flame-dried or oven-dried glassware under a dry nitrogen atmosphere unless otherwise noted. Tetrahydrofuran and diethyl ether were dried over sodium/benzophenone and distilled prior to use. Flash chromatography was performed by using Merck Kieselgel 60 (230–400 mesh) with the indicated solvents. Thin layer chromatography (TLC) was carried out on precoated silica plates (Merck Kieselgel $60F_{254}$) and compounds were visualised by UV fluorescence or by staining with alkaline potassium permanganate solution or vanillin in methanolic sulfuric acid and heating. Infrared spectra were recorded with a Perkin–Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) with the following abbreviations: s=strong, m=medium, w=weak and br=broad. Optical rotations were measured using a Perkin–Elmer 341 polarimeter at l=598 nm and are reported with the units 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker DRX-400 operating at either 400 MHz or 100 MHz, respectively. Alternatively, a Bruker Avance 300 spectrometer operating at either 300 MHz or 75 MHz was used. All chemical shifts are given in parts per million (ppm) downfield from tetramethylsilane as internal standard (^{1}H) or relative to $CDCl_3$ (^{13}C), and J values are given in hertz. ^{1}H NMR data are tabulated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. High-resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. Chemical ionisation (CI) mass spectra were obtained with ammonia as the reagent gas. Fast atom bombardment (FAB) mass spectra were obtained with 3-nitrobenzyl alcohol as the matrix. HPLC was carried out on a Waters 600 system with UV detection at 254 nm using the column and solvent system indicated.

3.2. *N*,*N*-Diethyl 2,4-dimethoxy-6-formylbenzamide (6)

tert-Butyllithium (3.9 mL, 1.05 mol L^{-1} in hexanes, 4.1 mmol) was added to a stirred solution of *N*,*N*-diethyl 2,4-dimethoxybenzamide **5** (870 mg, 3.7 mmol) in tetrahydrofuran (33 mL) at −78 °C under nitrogen. After 15 min, *N*,*N*-dimethylformamide (1.14 mL, 14.7 mmol) was added, and the

mixture was stirred for 1 h at −78 °C and then for 1 h at room temperature. The reaction was quenched with dilute hydrochloric acid (4 mL) with cooling. The solvent was removed under vacuum and the resulting residue was dissolved in dichloromethane (25 mL). The solution was washed with water (20 mL) and saturated sodium chloride (20 mL), and dried (magnesium sulfate). The solvent was removed under vacuum to give a yellow oil that was purified by flash column chromatography on silica (hexanes/ethyl acetate, 2:1) to give *N*,*N*-diethyl 2,4-dimethoxy-6-formylbenzamide **6** (0.98 g, 100%) as a yellow oil. δ_H ($CDCl_3$) 1.02 (3H, t, 7.1 Hz, 2′-H), 1.28 (3H, t, *J* 7.0 Hz, 2″-H), 3.56 (2H, q, *J* 7.0 Hz, 1″-H), 3.82 (2H, q, *J* 7.1 Hz, 1′-H), 3.82 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.70 (1H, d, $J_{5,3}$ 2.3 Hz, 5-H), 7.03 (1H, d, $J_{3,5}$ 2.3 Hz, 3-H), 9.96 (1H, s, CHO). The ^{1}H NMR data were in agreement with the literature.[9]

3.3. 3-Cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one (4)

A solution of *N*,*N*-diethyl 2,4-dimethoxy-6-formylbenzamide **6** (86 mg, 0.32 mmol) in acetic acid (4 mL) and 10% hydrochloric acid (4 mL) was heated under reflux for 22 h. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate (15 mL). The solution was extracted with saturated sodium hydrogen carbonate (3×10 mL). The combined aqueous layers were carefully acidified to pH 2 with concentrated hydrochloric acid. The acidified solution was extracted with ethyl acetate (50 mL), washed with saturated sodium chloride (30 mL), dried (magnesium sulfate) and the solvent was removed under vacuum. Purification of the residue by flash column chromatography (ethyl acetate) gave 3-hydroxy-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **7** as a colourless solid (58 mg, 85%). Melting point 186–189 °C (lit.[10] 183–186 °C). A solution of potassium cyanide (2.3 g, 35.3 mmol) and 3-hydroxy-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **7** (480 mg, 2.3 mmol) in water (8 mL) was cooled to 0 °C. Ice (8 g) and concentrated hydrochloric acid (10.7 mL, 0.12 mol) were added, and the mixture was stirred for 3 h with warming to room temperature. The reaction mixture was extracted with ethyl acetate (20 mL), the organic layer was washed with saturated sodium hydrogen carbonate (15 mL), water (15 mL) and saturated sodium chloride (15 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give a beige solid. Purification by flash column chromatography (dichloromethane) gave 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** as a colourless solid (330 mg, 66%). Melting point 132–133 °C (lit.[11] 134–135 °C). δ_H ($CDCl_3$) 3.94 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.91 (1H, s, 3-H), 6.54 (1H, d, $J_{6,4}$ 1.7 Hz, 6-H), 6.66 (1H, d, $J_{4,6}$ 1.7 Hz, 4-H). The ^{1}H NMR data was in agreement with the literature.[11]

3.4. Ethyl 6,8-dimethoxy-1,4-naphthoquinone-2-carboxylate (3)

sec-Butyllithium (0.17 mL, 0.19 mmol, 1.13 mol L^{-1} in hexanes) was added to a stirred solution of 3-cyano-5,7-dimethoxy-(3*H*)-isobenzofuran-1-one **4** (42 mg, 0.19 mmol) in anhydrous tetrahydrofuran (2 mL) and cooled to −78 °C under nitrogen. The resulting yellow solution was stirred for 10 min and then ethyl acrylate (0.026 mL, 0.24 mmol) in tetrahydrofuran (1 mL) was added. The mixture was stirred at −78 °C for 6 h, quenched with dilute hydrochloric acid (2 mL) and extracted with ethyl acetate (30 mL). The organic layer was washed with water (15 mL) and saturated sodium chloride (15 mL), and dried (magnesium sulfate). Removal of the solvent under vacuum gave a brown oil (69 mg), which was purified by flash column chromatography on silica (hexanes/ethyl acetate 6:1) to give ethyl 1,4-dihydroxy-6,8-dimethoxynaphthalene-2-carboxylate **8** (30 mg, 54%) as a colourless oil that was oxidised directly to naphthoquinone **3**. δ_H 1.41 (3H, t, *J* 5.3 Hz, CH_3), 3.93 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.40 (2H, q, *J* 5.3 Hz, OCH_2), 4.95 (1H, br s, 4-OH), 6.56 (1H, d, $J_{7,5}$ 1.8 Hz, 7-H), 7.07 (1H, d, $J_{5,7}$ 1.8 Hz, 5-H), 7.17 (1H, s, 3-H), 12.27 (1H, s, 1-OH). To a stirred solution of ethyl 1,4-dihydroxy-6,8-dimethoxynaphthalene-2-carboxylate **8** (30 mg, 0.10 mmol) in acetonitrile (7 mL) and water (1 mL) was added a solution of ceric ammonium nitrate (2 mg, 4.0 μmol) in water (1 mL). *tert*-Butyl hydroperoxide (0.059 mL, 0.35 mmol) in acetonitrile (2 mL) was added slowly by syringe pump over 2.5 h. The reaction mixture was stirred for a further 64.5 h and then extracted with dichloromethane (20 mL). The organic extract was washed with water (10 mL) and saturated sodium chloride (10 mL), and dried (magnesium sulfate). The solvent was removed under vacuum to give the *title compound* **3** (29 mg, 99%) as an orange solid. Recrystallisation from hexanes/dichloromethane gave orange crystals. Melting point 136–137 °C. $C_{15}H_{14}O_6$ found 290.0789, requires 290.0790. ν_{max} 2959, 2929, 2872, 1741, 1666, 1464, 1379, 1107. δ_H 1.38 (3H, t, *J* 7.1 Hz, CH_3), 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.39 (2H, q, *J* 7.1 Hz, OCH_2), 6.76 (1H, d, $J_{7,5}$ 2.4 Hz, 7-H), 7.01 (1H, s, 3-H), 7.21 (1H, d, $J_{5,7}$ 2.4 Hz, 5-H). δ_C 14.7 (CH_3, CH_3), 55.4 (CH_3, 6-OCH_3), 56.9 (CH_3, 8-OCH_3), 62.0 (CH_2, OCH_2), 103.8 (CH, C-5), 104.2 (CH, C-7), 113.9 (C, C-8a), 135.2 (C, C-4a), 136.2 (C, C-2), 141.8 (CH, C-3), 160.7 (C-8), 163.8 (C=O_{ester}), 165.9 (C-6), 181.2 (C, C-1), 182.1 (C, C-4).

3.5. Ethyl 3-(2′-oxopropyl)-6,8-dimethoxy-1,4-naphthoquinone-2-carboxylate (9)

To a solution of ethyl 6,8-dimethoxy-1,4-naphthoquinone-2-carboxylate **3** (36 mg, 0.12 mmol) and acetonylpyridinium chloride[14] (21 mg, 0.12 mmol) in acetonitrile (3 mL) under nitrogen in the dark was added triethylamine (0.011 mL, 0.12 mol) in acetonitrile (1 mL). The mixture was stirred at room temperature for 1 h and then most of the solvent was removed under vacuum. The residue was dissolved in dilute hydrochloric acid (5 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was washed with saturated sodium hydrogen carbonate, dried (magnesium sulfate) and the solvent was removed under vacuum to give the *title compound* **9** as an orange solid (43 mg, 99%). Melting point 153–154 °C. $C_{18}H_{18}O_7$ found 346.1051, requires 346.1053. ν_{max} 2925, 2835, 1724, 1654, 1597, 1456, 1408, 1265, 1213. δ_H 1.36 (3H, t, *J* 7.2 Hz, CH_3), 2.26 (3H, s, 3′-H), 3.67 (2H, s, 1′-H), 3.94 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.38 (2H, q, *J* 7.2 Hz, OCH_2), 6.75 (1H, d, $J_{7,5}$ 2.4 Hz, 7-H), 7.24 (1H, d, $J_{5,7}$ 2.4 Hz, 5-H). δ_C 14.1 (CH_3, CH_3), 30.0 (CH_3, C-3′), 41.8 (CH_2, C-1′), 55.9 (CH_3, OCH_3), 56.4 (CH_3, OCH_3), 62.1 (CH_2, OCH_2), 103.7 (CH, C-5 or C-7), 104.5 (CH, C-7 or C-5), 113.7

(C, C8a), 135.1 (C, C4a), 138.1 (C, C2), 142.7 (C, C3), 162.1 (C, C-8), 164.6 (C, C=O_{ester}), 164.9 (C, C-6), 179.2 (C, C-1), 184.6 (C, C-4), 202.2 (C, C-2′).

3.6. *N*,*N*-Diethyl 3,5-dimethoxy-2-formylbenzamide (14)

tert-Butyllithium (2.2 mL, 2.4 mmol) was added to a solution of *N*,*N*-diethyl 3,5-dimethoxybenzamide (0.53 g, 2.3 mmol) in anhydrous tetrahydrofuran (25 mL) at −78 °C. After 5 min, *N*,*N*-dimethylformamide (0.7 mL, 0.90 mmol) was added. Stirring was continued at −78 °C for 30 min and then the reaction was quenched with dilute hydrochloric acid (4 mL) with cooling. The mixture was extracted with ethyl acetate (30 mL), washed with water (20 mL) and saturated sodium chloride (20 mL) and dried (magnesium sulfate) to give a yellow solid (600 mg). Purification by flash column chromatography (dichloromethane) gave the title compound **14** (400 mg, 67%) for which the ^{1}H NMR data were in agreement with the literature.[20]

3.7. 4,6-Dimethoxy-3-hydroxy-(3*H*)-isobenzofuran-1-one (15)

A solution of *N*,*N*-diethyl 3,5-dimethoxy-2-formylbenzamide **14** (1.5 g, 5.7 mmol) in acetic acid (200 mL) and 10% hydrochloric acid (200 mL) was heated under reflux for 24 h. Removal of the solvent under vacuum gave a cream solid, which was dissolved in dichloromethane (150 mL) and then washed with dilute hydrochloric acid (80 mL), water (100 mL) and saturated sodium chloride (100 mL), dried (magnesium sulfate) and the solvent was removed under reduced pressure to give the title compound **15** (1.19 g, 99%) as a beige solid, for which the ^{1}H NMR data was in agreement with the literature.[17] Melting point 164–165 °C (lit.[17] 165 °C).

3.8. 3-Cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one (13)

A solution of potassium cyanide (10.3 g, 0.16 mol) and 4,6-dimethoxy-3-hydroxy-(3*H*)-isobenzofuran-1-one **15** (2.2 g, 10.5 mmol) in water (45 mL) was cooled to 0 °C. Ice (57.5 g) was added followed by concentrated hydrochloric acid (50 mL, 0.55 mmol). After stirring at room temperature for 22 h, the mixture was extracted with dichloromethane (3×30 mL). The organic layer was washed with saturated sodium bicarbonate solution (80 mL), water (100 mL) and saturated sodium chloride (100 mL) and dried (magnesium sulfate). Removal of the solvent under vacuum gave the title compound **13** (1.55 g, 68%) for which the ^{1}H NMR data was in agreement with the literature.[17]

3.9. Ethyl 1,4-dihydroxy-5,7-dimethoxynaphthalenalene-2-carboxylate (16)

To a solution of 3-cyano-4,6-dimethoxy-(3*H*)-isobenzofuran-1-one **13** (2.27 g, 10.4 mmol) in tetrahydrofuran (90 mL) at −78 °C was added *sec*-butyllithium (9.9 mL, 10.4 mmol, 1.05 mol L^{-1} in hexanes). The resulting orange solution was stirred for 10 min and then ethyl acrylate (1.12 mL, 10.4 mmol) was added. After stirring for 2.5 h, dilute hydrochloric acid (15 mL) was added at −78 °C and then the mixture was warmed to room temperature. The aqueous solution was extracted with ethyl acetate (3×50 mL). The organic extracts were washed with water (100 mL) and saturated sodium chloride (100 mL), and dried (magnesium sulfate). The solvent was removed to give the *title compound* **16** as a cream solid (3.03 g, 99%). Melting point 146–147 °C. $C_{15}H_{16}O_6$ found 292.0946, requires 292.0947. ν_{max} 3452, 1729, 1654, 1643, 1619, 1394, 1264, 1214. δ_H 1.43 (3H, t, *J* 7.1 Hz, CH_3), 3.94 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.43 (2H, q, *J* 7.1 Hz, OCH_2), 6.63 (1H, d, *J* 2.2 Hz, 6-H or 8-H), 7.04 (1H, s, H3), 7.31 (1H, d, *J* 2.2 Hz, 8-H or 6-H), 8.62 (1H, s, 4-OH), 11.41 (1H, s, 1-OH). δ_C 14.2 (CH_3, CH_3), 55.6 (CH_3, OCH_3), 56.3 (CH_3, OCH_3), 61.4 (CH_2, OCH_2), 85.7 (CH, C-3, C-6 or C-8), 101.1 (CH, C-6, C-3 or C-8), 104.5 (CH, C-8, C-6 or C-3), 101.2 (C, C-4a or C-8a), 114.6 (C, C-8a or C-4a), 127.8 (C, C-2), 146.0 (C, C-1, C-4, C-5 or C-7), 152.1 (C, C-4, C-1, C-5 or C-7), 156.8 (C, C-5, C-4, C-1 or C-7), 157.9 (C, C-7, C-4, C-5 or C-1), 170.8 (C, C=O).

3.10. Ethyl 5,7-dimethoxy-1,4-naphthoquinone-2-carboxylate (12)

A solution of ethyl 1,4-dihydroxy-5,7-dimethoxynaphthalenalene-2-carboxylate **16** (3.03 g, 10.4 mmol) in toluene (90 mL) was stirred with silver(I) oxide (7.21 g, 31.1 mmol) under nitrogen for 25 h. The silver salts were removed by filtration through Celite, and the solvent was removed under vacuum to give the *title compound* **12** as an orange solid (2.20 g, 73%). Melting point 140–141.5 °C. $C_{15}H_{14}O_6$ found 290.0791, requires 290.0790. ν_{max} 2924, 2854, 1732, 1597, 1461, 1266, 1213, 1024. δ_H 1.39 (3H, t, *J* 7.1 Hz, CH_3), 3.96 (3H, s, 7-OCH_3), 3.98 (3H, s, 5-OCH_3), 4.39 (2H, q, *J* 7.1 Hz, OCH_2), 6.75 (1H, d, $J_{6,8}$ 2.4 Hz, 6-H), 7.16 (1H, s, 3-H), 7.28 (1H, d, $J_{8,6}$ 2.4 Hz, 8-H). δ_C 14.1 (CH_3, CH_3), 56.O (CH_3, 7-OCH_3), 56.5 (CH_3, 5-OCH_3), 62.1 (CH_2, OCH_2), 103.9 (CH, C-8), 104.2 (CH, C-6), 114.2 (C, C-4a), 135.9 (C, C-8a), 136.9 (C, C-2), 141.2 (CH, C-3), 161.9 (C, C-5), 163.2 (C, C=O_{ester}), 165.2 (C, C-7), 181.3 (C, C-1), 182.2 (C, C-4).

3.11. Ethyl 3-allyl-5,7-dimethoxy-1,4-naphthoquinone-2-carboxylate (17)

Ethyl 5,7-dimethoxy-1,4-naphthoquinone-2-carboxylate **12** (1.4 g, 4.8 mmol) in acetonitrile (100 mL) was placed in a three-necked flask fitted with a condenser, rubber septum and a thermometer, and then flushed with nitrogen for 5 min. Silver nitrate (410 mg, 2.4 mmol) in acetonitrile (6 mL) was added to the solution. Upon dissolution of the silver nitrate, vinylacetic acid (0.62 mL, 7.3 mmol) was added. The solution was heated to 60 °C and ammonium dithionite (1.99 g, 8.7 mmol) in water (50 mL) was added dropwise maintaining the internal temperature at 60 °C. After stirring for 2 h, the mixture was cooled to room temperature, poured into cold water and then extracted with ethyl acetate (3×50 mL). The organic layer was washed with saturated sodium hydrogen carbonate (100 mL) and brine (100 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give an orange solid. Purification by flash column chromatography on silica (hexanes/ethyl acetate 5:1) gave the title compound **17** as an orange solid (890 mg, 56%). Melting point 148–149 °C. $C_{18}H_{18}O_6$ found 330.1101, requires 330.1103. ν_{max} 2925, 1731, 1654, 1597, 1265, 1213.

δ_H 1.39 (3H, t, J 7.1 Hz, CH_3), 3.31 (2H, d, $J_{1',2'}$ 6.7 Hz, 1′-H), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.42 (2H, q, J 7.1 Hz, OCH_2), 5.09 (1H, dd, $J_{3'(cis),2'}$ 10.0 Hz, $J_{3'(cis),3'(trans)}$ 1.3 Hz, 3′(cis)-H), 5.18 (1H, dd, $J_{3'(trans),2'}$ 17.1 Hz, $J_{3'(trans),3'(cis)}$ 1.3 Hz, 3′(trans)-H), 5.86 (1H, tdd, $J_{2',3'(trans)}$ 17.1 Hz, $J_{2',3'(cis)}$ 10.0 Hz, $J_{2',1'}$ 6.7 Hz, 2′-H), 6.74 (1H, d, $J_{6,8}$ 2.4 Hz, 6-H), 7.23 (1H, d, $J_{8,6}$ 2.4 Hz, 8-H). δ_C 15.9 (CH_3, CH_3), 35.9 (CH_2, C-1′), 55.8 (CH_3, OCH_3), 56.2 (CH_3, OCH_3), 61.3 (CH_2, OCH_2), 108.3 (CH, C-8), 110.0 (CH, C-6), 116.2 (C, C-2), 118.1 (CH_2, C-3′), 132.7 (CH, C-2′), 134.8 (C, C-8a), 139.7 (C, C-2), 149.8 (C, C-3), 165.4 (C, C-5), 165.8 (C, C=O_{ester}), 170.3 (C, C-7), 181.2 (C, C-1), 181.7 (C, C-4).

3.12. Ethyl 3-allyl-1,4,5,7-tetramethoxynaphthalene-2-carboxylate (18)

To a solution of ethyl 3-allyl-5,7-dimethoxy-1,4-naphthoquinone-2-carboxylate **17** (820 mg, 2.5 mmol) and tetrabutylammonium iodide (97 mg, 2.6 mmol) in tetrahydrofuran (50 mL) and water (25 mL) under nitrogen was added sodium dithionite (2.6 g, 14.9 mmol) in water (30 mL). After stirring the mixture for 15 min, potassium hydroxide (3.20 g, 57.0 mmol) in water (20 mL) was added followed by dimethyl sulfate (4.9 mL, 52.2 mmol). The solution was stirred for 21 h then extracted into dichloromethane (3×40 mL). The organic layer was washed with brine (100 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give a yellow oil. Purification by flash column chromatography on silica (hexanes/ethyl acetate 9:1) gave the *title compound* **18** as a beige wax (500 mg, 55%). $C_{20}H_{24}O_6$ found 360.1571, requires 360.1573. ν_{max} 2936, 1726, 1621, 1342. δ_H 1.41 (3H, t, J 7.1 Hz, CH_3), 3.56 (2H, dt, $J_{1',2'}$ 6.2 Hz, $J_{1',3'}$ 1.6 Hz, 1′-H), 3.78 (3H, s, 4-OCH_3), 3.92 (3H, s, 7-OCH_3), 3.94 (3H, s, 5-OCH_3), 3.98 (3H, s, 1-OCH_3), 4.43 (2H, q, J 7.1 Hz, OCH_2), 4.98–5.06 (2H, m, 3′-H), 5.96 (1H, tdd, $J_{2',3'(trans)}$ 17.0 Hz, $J_{2',3'(cis)}$ 10.2 Hz, $J_{2',1'}$ 6.2 Hz, 2′-H), 6.58 (1H, d, $J_{8,6}$ 2.3 Hz, 8-H), 6.98 (1H, d, $J_{6,8}$ 2.3 Hz, 6-H). δ_c 14.2 (CH_3, CH_3), 31.3 (CH_2, C-1′), 55.4 (CH_3, 7-OCH_3), 56.2 (CH_3, 1-OCH_3), 61.3 (CH_2, OCH_2), 62.67 (CH_3, 4-OCH_3), 62.72 (CH_3, 5-OCH_3), 93.3 (CH, C-6), 100.2 (CH, C-8), 115.4 (CH_2, C-3′), 117.4 (C, C-4a), 123.9 (C, C-2 or C-3), 126.9 (C, C-3 or C-2), 130.7 (C, C-8a), 137.1 (CH, C-2′), 148.4 (C, C-5), 150.9 (C, C-4), 157.4 (C, C-1), 158.4 (C, C-7), 167.8 (C, C=O).

3.13. Ethyl 3-(2′-oxopropyl)-1,4,5,7-tetramethoxynaphthalene-2-carboxylate (11)

A mixture of copper(I) chloride (73 mg, 0.74 mmol) and palladium(II) chloride (23 mg, 0.13 mmol) in *N*,*N*-dimethylformamide (12 mL) and water (2 mL) was stirred under an oxygen atmosphere for 3 h. A solution of ethyl 3-allyl-1,4,5,7-tetramethoxy-1,4-naphthoquinone-2-carboxylate **18** (21 mg, 0.58 mmol) in *N*,*N*-dimethylformamide (8 mL) was added and the mixture was stirred for 66 h under an oxygen atmosphere. Water (80 mL) was added to the reaction followed by dilute hydrochloric acid until the cloudy solution cleared. The mixture was extracted with ethyl acetate (3×30 mL) and the organic phase was washed with water (70 mL) and brine (70 mL) and dried (magnesium sulfate). The solvent was removed under vacuum to give a yellow oil, which was purified by flash column chromatography on silica (hexanes/ethyl acetate 9:1) to give the *title compound* **11** as a pale yellow oil (160 mg, 72%). $C_{20}H_{24}O_7$ found 376.1522, requires 376.1522. ν_{max} 3054, 2928, 1723, 1621, 1343, 1265. δ_H 1.40 (3H, t, J 7.1 Hz, CH_3), 2.16 (3H, s, 3′-H), 3.74 (3H, s, 4-OCH_3), 3.86 (2H, s, 1′-H), 3.93 (3H, s, 7-OCH_3), 3.96 (3H, 1-OCH_3), 3.98 (3H, s, 5-OCH_3), 4.41 (2H, q, J 7.1 Hz, OCH_2), 6.61 (1H, d, $J_{6,8}$ 2.2 Hz, 6-H), 7.02 (1H, d, $J_{8,6}$ 2.2 Hz, 8-H). δ_C 14.1 (CH_3, CH_3), 29.2 (CH_3, C-3′), 42.4 (CH_2, C-1′), 55.4 (CH_3, 7-OCH_3), 56.2 (CH_3, 5-OCH_3), 61.6 (CH_2, OCH_2), 62.2 (CH_3, 4-OCH_3), 62.8 (CH_3, 1-OCH_3), 93.6 (CH, C-8), 100.6 (CH, C-6), 117.4 (C, C-4a), 119.8 (C, C-2 or C-3), 126.0 (C, C-3 or C-2), 131.5 (C, C-8a), 149.1 (C, C-1), 151.3 (C, C-4), 157.3 (C, C-5), 158.8 (C, C-7), 167.6 (C, C=O_{ester}), 206.4 (C, C-2′).

3.14. (2′*S*)-Ethyl 3-(2′-hydroxypropyl)-1,4,5,7-tetramethoxynaphthalene-2-carboxylate (19)

To a stirred solution of (*R*)-Me-CBS catalyst (Aldrich, 1.6 mL, 1.6 mmol, 1 mol L^{-1} in toluene) in tetrahydrofuran (0.5 mL) was added borane dimethyl sulfide (0.16 mL, 1.6 mmol, 10 mol L^{-1} in tetrahydrofuran). After stirring for 15 min, the mixture was cooled to −40 °C and a solution of methyl ketone **11** (30 mg, 0.08 mmol) in tetrahydrofuran (1 mL) was added. After stirring for 2 h, methanol (0.2 mL) was added followed by dilute hydrochloric acid (5 mL) and the mixture was stirred for 5 min. The acidified mixture was extracted with dichloromethane (20 mL), washed with saturated sodium chloride (15 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give a white solid. Purification by flash column chromatography (hexanes/ethyl acetate 3:1) gave the *title compound* **19** as a yellow oil (29 mg, 97%). The enantiomeric excess was determined to be 65% (chiral HPLC, 24 cm×0.4 mm Daicel AD-H column, 90:10 hexanes/*tert*-butyl alcohol, retention time= 44.3 min (major), 62.1 min (minor)). $C_{20}H_{26}O_7$ found 378.1675, requires 378.1678. ν_{max} 3583, 1726, 1620, 1341. δ_H 1.25 (3H, d, $J_{3',2'}$ 6.4 Hz, 3′-H), 1.43 (3H, t, J 7.0 Hz, CH_3), 2.75–2.92 (3H, m, H1′, OH), 3.79 (3H, s 4-OCH_3), 3.92 (3H, s, 7-OCH_3), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.07–4.13 (1H, m, 2′-H), 4.46 (2H, q, J 7.0 Hz, OCH_2), 6.59 (1H, d, $J_{6,8}$ 2.2 Hz, 6-H), 6.98 (1H, d, $J_{8,6}$ 2.2 Hz, 8-H). δ_C 14.2 (CH_3, CH_3), 23.9 (CH_3, C-3′), 37.4 (CH_2, C-1′), 55.3 (CH_3, 7-OCH_3), 56.1 (CH_3, OCH_3), 61.6 (CH_2, OCH_2), 62.0 (CH_3, 4-OCH_3), 62.6 (CH_3, OCH_3), 68.8 (CH, C-2′), 93.2 (CH, C-6 or C-8), 100.4 (CH, C-8 or C-6), 117.3 (C, C-4a), 123.0 (C, C-3), 127.0 (C, C-2), 130.8 (C, C-8a), 148.5 (C, C-1 or C-5), 151.2 (C, C-4), 157.1 (C, C-5 or C-1), 158.5 (C, C-7), 168.3 (C, C=O_{ester}).

3.15. (3*S*)-3-Methyl-5,6,8,10-tetramethoxynaphtho-[2,3-*c*]pyran-1-one (20)

A solution of alcohol **19** (14 mg, 0.4 mmol) in tetrahydrofuran (1.5 mL) was stirred with sodium hydride (11 mg, 0.03 mmol) for 1 h under nitrogen. The reaction was quenched with dilute sulfuric acid (2 mL) and then extracted with ethyl acetate (20 mL). The organic layer was washed with saturated sodium hydrogen carbonate (15 mL) and saturated sodium chloride (15 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give

the *title compound* **20** as a yellow oil (11 mg, 92%). The enantiomeric excess was determined to be 65% (chiral HPLC, 24 cm×0.4 mm Daicel AD-H column, 90:10 hexanes/*tert*-butyl alcohol, retention time=47.9 min (major), 66.8 min (minor)). $C_{18}H_{20}O_6$ found 332.1263, requires 332.1259. ν_{max} 3584, 1724, 1618, 1593, 1340, 1210, 1071. δ_H 1.52 (3H, d, J 7.2 Hz, CH_3), 2.79 (1H, dd, $J_{4A,4B}$ 16.2 Hz, $J_{4A,3}$ 11.0 Hz, 4-H_A), 3.35 (1H, dd, $J_{4B,4A}$ 16.2 Hz, $J_{4B,3}$ 2.5 Hz, 4-H_B), 3.77 (3H, s, 5-OCH_3), 3.95 (3H, s, 10-OCH_3), 3.99 (3H, s, 6-OCH_3), 4.05 (3H, s, 8-OCH_3), 4.52–4.59 (1H, m, 3-H), 6.67 (1H, d, $J_{7,9}$ 1.9 Hz, 7-H), 7.23 (1H, d, $J_{9,7}$ 1.9 Hz, 9-H). δ_C 20.8 (CH_3, CH_3), 29.7 (CH_2, C-4), 55.4 (CH_3, 10-OCH_3), 56.2 (CH_3, 6-OCH_3), 62.0 (CH_3, 5-OCH_3), 62.7 (CH_3, 8-OCH_3), 74.6 (CH, C-3), 94.5 (CH, C-9), 102.0 (CH, C-7), 114.7 (C, C-4a), 119.4 (C, C-5a), 124.5 (C, C-10a), 132.0 (C, C-9a), 148.0 (C, C-5), 155.2 (C, C-10), 157.0 (C, C-6), 158.5 (C, C-8), 163.0 (C, C-1).

3.16. (1*S*,3*S*)-1-Hydroxy-3-methyl-5,6,8,10-tetramethoxypyrano[2,3-*c*]naphthalene (21)

To a solution of lactone **20** (30 mg, 0.09 mmol) in toluene (6 mL) stirred at −78 °C under nitrogen was added diisobutylaluminium hydride (0.083 mL, 0.01 mmol, 20% w/v in toluene). The reaction mixture was stirred for 1 h, and then quenched at −78 °C with water (1 mL) and dilute hydrochloric acid (2 mL). The mixture was extracted with dichloromethane (20 mL), washed with saturated sodium chloride (10 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give the *title compound* **21** as a yellow wax (29 mg, 97%). The enantiomeric excess was determined to be 65% (chiral HPLC 24 cm×0.4 mm Daicel AD-H column, 90:10 hexanes/*tert*-butyl alcohol, retention time=31.0 min (major), 34.0 min (minor)). $C_{18}H_{22}O_6$ found 334.1407, requires 334.1416. ν_{max} 3583, 1623, 1601, 1421. δ_H 1.46 (3H, d, J 6.2 Hz, CH_3), 2.57 (1H, dd, $J_{4A,4B}$ 17.0 Hz, $J_{4A,3}$ 11.6 Hz, 4-H_A), 3.01 (1H, d, $J_{OH,1}$ 3.6 Hz, OH), 3.11 (1H, dd, $J_{4B,4A}$ 17.0 Hz, $J_{4B,3}$ 3.1 Hz, 4-H_B), 3.81 (3H, s, 5-OCH_3), 3.96 (3H, s, 8-OCH_3), 4.00 (3H, s, 6-OCH_3), 4.02 (3H, s, 10-OCH_3), 4.48–4.51 (1H, m, 3-H), 6.39 (1H, d, $J_{1,OH}$ 3.6 Hz, 1-H), 6.57 (1H, d, $J_{7,9}$ 2.3 Hz, 7-H), 6.97 (1H, d, $J_{9,7}$ 2.6 Hz, 9-H). δ_C 21.6 (CH_3, CH_3), 29.9 (CH_2, C-4), 55.3 (CH_3, 8-OCH_3), 56.1 (CH_3, 6-OCH_3), 61.3 (CH_3, 5-OCH_3), 62.0 (CH_3, 10-OCH_3), 62.9 (CH, C-3), 89.1 (CH, C-1), 92.8 (CH, C-9), 99.5 (CH, C-7), 116.9 (C, C-5a), 122.2 (C, C-4a), 126.1 (C, C-10a), 130.1 (C, C-9a), 148.7 (C, C-10), 149.7 (C, C-5), 157.3 (C, C-6), 157.9 (C, C-8).

3.17. (1*S*,3*S*)-6,8-Dimethoxy-1-hydroxy-3-methylpyrano[2,3-*c*]-1,4-naphthoquinone (22)

A solution of tetramethoxypyrano[2,3-*c*]naphthalene **21** (10 mg, 0.03 mmol) in dioxane (5 mL) was stirred with silver(II) oxide (14 mg, 0.1 mmol). Concentrated nitric acid (six drops) was added dropwise with stirring for 1 min and the reaction mixture turned to a deep orange colour. The reaction mixture was filtered through Celite, and the Celite was washed well with dichloromethane (10 mL). The organic layer was washed with water (2×10 mL) and saturated sodium chloride (10 mL), dried (magnesium sulfate) and the solvent was removed under vacuum to give the title compound **22** as an orange oil (4.5 mg, 50%). The enantiomeric excess was determined to be 65% (chiral HPLC, 24 cm×0.4 mm Daicel AD-H column, 90:10 hexanes/*tert*-butyl alcohol, retention time=39.3 min (minor), 42.9 min (major)). $C_{16}H_{16}O_6$ found 304.0946, requires 304.0947. ν_{max} 3406, 2922, 1725, 1654, 1595, 1318, 1260. δ_H 1.39 (3H, d, J 6.3 Hz, CH_3), 2.21 (1H, dd, $J_{4(trans),4(cis)}$ 19.6 Hz, $J_{4(trans),3}$ 10.8 Hz, 4(trans)-H), 2.77 (1H, dd $J_{4(cis),4(trans)}$ 19.6 Hz, $J_{4(cis),3}$ 3.2 Hz, 4(cis)-H), 3.95 (3H, s, 8-OCH_3), 3.97 (3H, s, 6-OCH_3), 4.28–4.36 (1H, m, 3-H), 6.01 (1H, s, 1-H), 6.72 (1H, d, $J_{7,9}$ 2.4 Hz, 7-H), 7.26 (1H, d, $J_{9,7}$ 2.4 Hz, 9-H). δ_C 21.0 (CH_3, CH_3), 29.7 (CH_2, C-4), 56.0 (CH_3, 8-OCH_3), 56.5 (CH_3, 6-OCH_3), 63.0 (CH, C-3), 87.0 (CH, C-1), 103.4 (CH, C-9), 104.2 (CH, C-7), 114.3 (C, C-5a), 135.8 (C, C-9a), 137.8 (C, C-10a), 145.7 (C, C-4a), 162.0 (C, C-6), 164.9 (C, C-8), 182.1 (C, C-5), 183.3 (C, C-10).

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