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Tetrahedron 64 (2008) 3343–3350
Tetrahedron
www.elsevier.com/locate/tet

Synthesis of a C8 oxygenated pyranonaphthoquinone: a useful precursor to dimeric pyranonaphthoquinones

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Received 29 October 2007; received in revised form 14 January 2008; accepted 31 January 2008
Available online 6 February 2008

Abstract

The synthesis of a pyranonaphthoquinone bearing an oxygenated substituent at C8 is reported. The oxygen substituent at C8 provides a key functionality for use as a homocoupling precursor for the synthesis of a dimeric pyranonaphthoquinone.

Keywords: Pyranonaphthoquinone antibiotics; Intramolecular cyclization; Nanaomycin

1. Introduction

The class of compounds known as the pyranonaphthoquinone antibiotics are isolated from various strains of bacteria and fungi, the majority being microbial in origin.[1,2] This family of compounds have been shown to exhibit activity against various Gram-positive bacteria, pathogenic fungi and yeasts, as well as antiviral activity. Several pyranonaphthoquinones have also been proposed to act as effective bioreductive alkylating agents.[3,4] More structurally complex members of this class include actinorhodin **1** and crisamicin A **2**, symmetrical dimeric pyranonaphthoquinones linked via a common C8–C8′ biaryl bond (Fig. 1). Given their significant biological activity combined with our continued interest in this class of compounds, we were attracted to the possibility of synthesizing dimeric pyranonaphthoquinones using a late stage homocoupling of their respective monomers. To date, the only successful synthesis of pyranonaphthoquinone dimers is based around early stage homocoupling techniques, including an Ullman coupling to construct the biaryl bond during a racemic synthesis of cardinalin C3[5] and our own success[6a,b] using a Suzuki–Miyaura homocoupling of aryl triflates to access regioisomers of crisamicin A. We herein report our efforts towards the

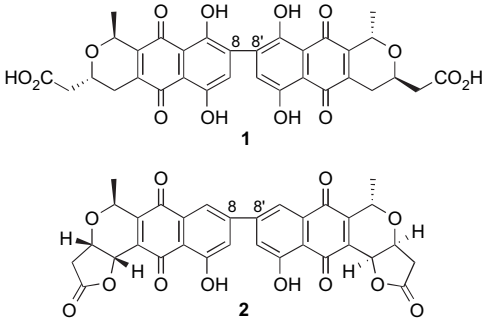

Figure 1.

synthesis of a monomeric pyranonaphthoquinone bearing an appropriately positioned oxygenated substituent at C8 that would provide an appropriate handle for subsequent late stage homocoupling. Thus, triflate **4** was deemed a key precursor to target model dimer **3** and the synthesis of methoxynaphthoquinone **5** is the focus of the work reported herein (Scheme 1).

2. Results and discussion

The retrosynthetic analysis of cis-C8 oxygenated pyranonaphthoquinone **5** is depicted (Scheme 2) and is based on our recently reported enantioselective synthesis of an analogue of deoxynanaomycin A.[7,8] The chosen route hinges on the use of homoallylic acetate **6** in which the stereochemistry at C3

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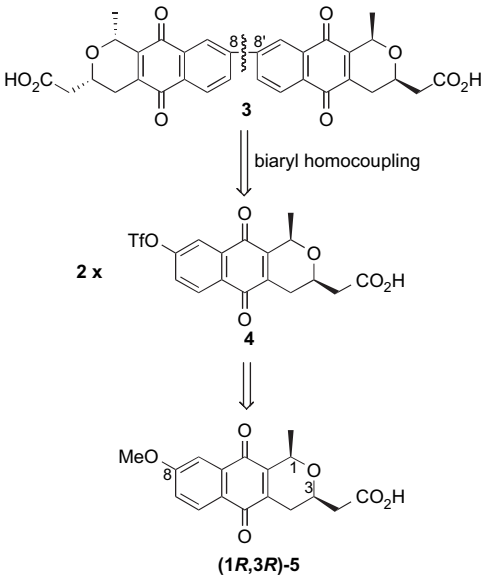
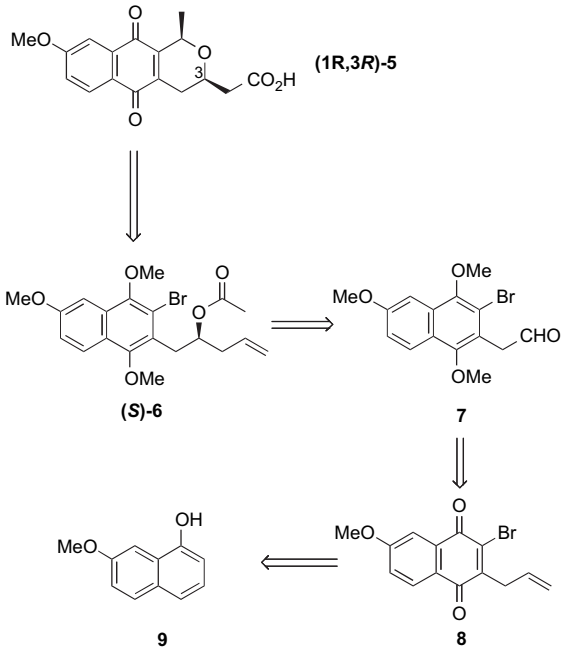
doi:10.1016/j.tet.2008.01.135



Scheme 1.

is established via asymmetric allylation of aldehyde **7**. Aldehyde **7** can be accessed from allylbromonaphthalene **8**, which in turn can be prepared from naphthol **9**. In the key cyclization step, lithium–halogen exchange of (*S*)-6 followed by in situ trapping of the resulting aryllithium with the adjacent acetate triggers an intramolecular cyclization, furnishing pyranonaphthoquinone **5** after oxidation of the allyl side chain (Scheme 2).

Initially, attention focused on the synthesis of racemic homoallylic alcohol *rac*-**17** in order to gauge the viability of the proposed approach. Our initial starting material, 7-methoxynaphthalen-1-ol **9** was accessed using the procedure reported



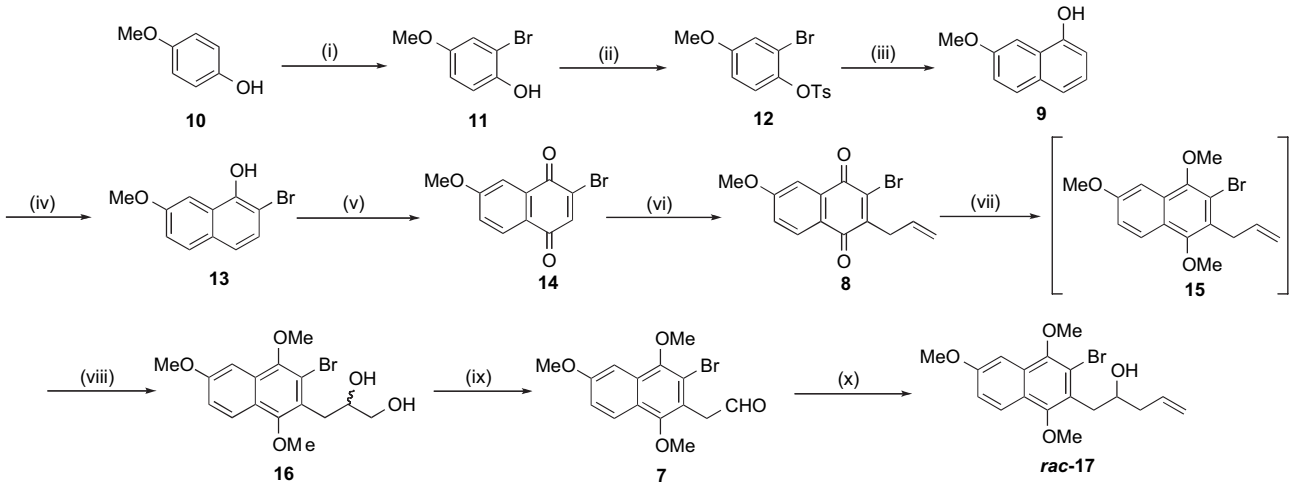
Scheme 2.

by Giles' et al.[9] Thus, regioselective bromination of *p*-methoxyphenol **10** delivered arylbromide **11** that underwent smooth tosylation to tosylate **12** in excellent yield. The benzyne intermediate generated from bromotosylate **12** was treated with excess furan, affording 7-methoxynaphthalen-1-ol **9**. Regioselective bromination[10,11] of naphthol **9** was achieved by treatment with *N*-bromosuccinimide in the presence of a catalytic quantity of diisopropylamine at −30 °C affording arylbromide **13** that underwent oxidation with [bis(trifluoroacetoxy)iodo]-benzene[12] to naphthoquinone **14**. Lewis acid promoted allylation of quinone **14** in the presence of allyltrimethylsilane[13] delivered allylnaphthoquinone **8** after reoxidation of the crude reaction mixture with ferric chloride. Reductive methylation[14] of **8** then provided allylbromonaphthalene **15** that was subjected to immediate dihydroxylation using catalytic quantities of osmium tetroxide with *N*-methylmorpholine *N*-oxide as co-oxidant, furnishing diol **16**. Sodium periodate mediated oxidative cleavage of diol **16** gratifyingly delivered the desired aldehyde **7** in excellent yield. With aldehyde **7** in hand, the allylation could be attempted. Thus, freshly prepared allylmagnesium bromide was added to a solution of aldehyde **7** in diethyl ether, delivering *rac*-**17** in excellent yield (Scheme 3).

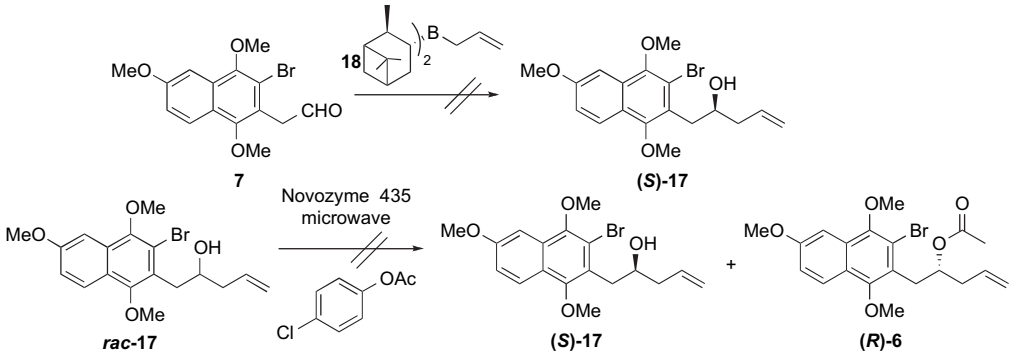
Attention could now be focused towards an asymmetric variant of the allylation reaction. Initially, the popular asymmetric allylation method reported by Brown[15] was investigated. Treatment of (−)-DIP-chloride® with freshly prepared allylmagnesium bromide at 0 °C followed by the addition of aldehyde **7** to a magnesium salt free ethereal solution of the resulting (+)-*B*-allyldiisopinocampheylborane **18** at −78 °C only affording unreacted aldehyde **7**. This result was surprising as the demethoxy analogue of aldehyde **7** previously underwent smooth asymmetric allylation in our hands.[7] Unperturbed by this result, attention turned to the use of our recently disclosed microwave promoted enzymatic resolution of racemic alcohols[16] as a possible method of preparing enantioenriched (*S*)-**17**. Unfortunately, various attempts at resolving racemic homoallylic alcohol *rac*-**17** into (*S*)-**17** and acetate (*R*)-**6** using our microwave assisted Novozyme® 435 protocol failed, with unreacted *rac*-**17** being the only product isolated from the reaction (Scheme 4).

It was decided to continue with the synthesis in racemic form in order to test the viability of the proposed route. Thus, homoallylic acetate *rac*-**6** was prepared in 90% yield from *rac*-**17** using acetic anhydride in dichloromethane in the presence of a catalytic quantity of perchloric acid in excellent yield. *rac*-Homoallylic acetate **17** was then treated with *tert*-butyllithium at −78 °C, gratifyingly undergoing cyclization in situ to afford the unstable lactol **19** that was swiftly converted to the stable *cis*-(±)-naphthopyran **20** in 65% yield over two steps using the triethylsilane promoted reduction reported by Kraus.[17] The NOESY spectrum recorded for **20** confirmed the cis-stereochemistry between 1-H and 3-H.

Dihydroxylation of the allylic group in naphthopyran **20** was achieved with the osmium tetroxide oxidation resulting in an inseparable mixture of 1,2-diols **21** that underwent smooth oxidative cleavage in the presence of sodium periodate

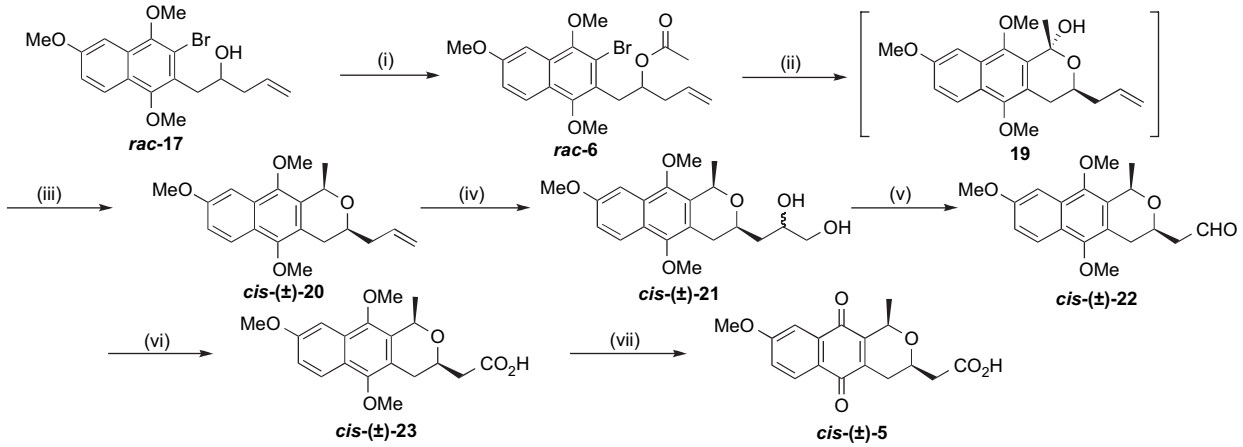


Scheme 3. (i) Br_2, CH_2Cl_2, −5 °C, 1 h, 86%; (ii) *p*-toluenesulfonyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h, 93%; (iii) *n*-BuLi, furan, THF, 30 min, −78 °C to rt, then MeOH, HCl, 80 °C, 2 h, 70%; (iv) NBS, *i*-Pr_2NH, CH_2Cl_2, 1 h, −30 °C, 60%; (v) $PhI(OCOCF_3)_2$, MeCN−H_2O, 1 h, −5 °C, 58%; (vi) allyltrimethylsilane, $MeAlCl_2$, CH_2Cl_2, 2 h, −78 °C then anhydrous $FeCl_3$, MeOH, 6 h, rt, 55%; (vii) $Na_2S_2O_4$, THF−H_2O, *n*-Bu_4NF, KOH, Me_2SO_4, 4 h, 95%; (viii) OsO_4, NMO, acetone−H_2O, 24 h, 0 °C to rt, 80% (1:1); (ix) $NaIO_4$, MeOH−H_2O, 2 h, rt, 99%; (x) allylmagnesium bromide, Et_2O, 6 h, −40 °C to rt, 89%.



Scheme 4.

to furnish aldehyde *cis*-(±)-**22**. The desired transformation into carboxylic acid *cis*-(±)-**23** was accomplished by treatment of a *tert*-butanol solution of aldehyde **22** with sodium chlorite,[18] with a final CAN-mediated oxidative methylation gratifyingly providing pyranonaphthoquinone *cis*-(±)-**5** in 76% yield over the two steps (Scheme 5). Importantly, the NOESY spectrum recorded for **5** confirmed the cis-stereochemistry between 1-H and 3-H.



Scheme 5. (i) Ac_2O, CH_2Cl_2, $HClO_4$, 2 h, rt, 90%; (ii) *t*-BuLi, THF, 1 h, −78 °C; (iii) Et_3SiH, TFA, CH_2Cl_2, 2 h, −78 °C to rt, 65% (over 2 steps); (iv) OsO_4, NMO, acetone−H_2O, 24 h, 0 °C to rt, 86%; (v) $NaIO_4$, MeOH−H_2O, 2 h, rt, 70%; (vi) $NaClO_2$, *t*-BuOH, $NaH_2PO_4\cdot 2H_2O$, cyclohexene, 2 h, rt; (vii) CAN, MeCN−H_2O, 10 min, 0 °C to rt, 76% (over 2 steps).

Unfortunately, all attempts to remove the methoxy group at C8 using a variety of conditions led to degradation of the substrate, thus its conversion to the key homocoupling precursor **4** could not be achieved.

3. Conclusions

The synthesis of a pyranonaphthoquinone bearing an oxygen substituent at C8 has been achieved starting from *p*-methoxyphenol **10**. Although the key homocoupling was not achieved due to the difficulty in removing the protecting group at C8, the synthesis of the monomer **5** provides an important basis for further studies in this area. Synthetic efforts towards an asymmetric synthesis of the key monomeric coupling precursor with a suitably labile protecting group at C8 as well studies on a late stage homocoupling strategy are ongoing.

4. Experimental

4.1. General

All reactions were carried out in flame or oven dried glassware under a dry nitrogen atmosphere. Tetrahydrofuran and diethyl ether were dried over sodium wire. Dichloromethane, pyridine and triethylamine were dried over calcium hydride, and ethanol and methanol were dried over magnesium ethoxide and methoxide. All solvents were distilled prior to use. Flash chromatography was carried out using 0.063–0.1 mm silica gel with the desired solvent. Thin layer chromatography was performed using silica coated aluminium plates (60 F_{254}). Compounds were identified using UV fluorescence and or staining with vanillin in methanolic sulfuric acid, a solution of ammonium heptamolybdate and cerium sulfate in aqueous sulfuric acid, iodine or a solution of potassium permanganate and potassium carbonate in aqueous sodium hydroxide. Low resolution mass spectra were recorded using a VG-70SE spectrometer operating at a nominal accelerating voltage of 70 eV. High resolution mass spectra were recorded at a nominal resolution of 5000–10,000. Infrared spectra were obtained using a Perkin–Elmer Spectrum 1000 series Fourier Transform IR spectrometer as a thin film between sodium chloride plates. NMR spectra were recorded on either a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or using a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. ^{1}H NMR data are reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet), coupling constant (*J* Hz) and assignment. Optical rotations were measured using a Perkin–Elmer 341 polarimeter at λ=598 nm and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

4.1.1. 2-Bromo-4-methoxyphenol **11**[19]

To a solution of 4-methoxyphenol **10** (1.00 g, 8.10 mmol) in dichloromethane (30 mL) was added bromine (0.41 mL, 8.10 mmol) in dichloromethane (6 mL) dropwise at −5 °C. The reaction mixture was stirred for 1 h then quenched with saturated $Na_2S_2O_5$ solution (5 mL), washed with water (40 mL) and dried over anhydrous $MgSO_4$. The organic extract was evaporated under reduced pressure and the residue purified by flash chromatography (20% ethyl acetate/hexanes) to afford the title compound **11** (1.60 g, 7.9 mmol, 86%) as a colourless solid, mp 43–44 °C (lit.[19] mp 42–43 °C); R_f (20% ethyl acetate/hexanes) 0.45; δ_H (400 MHz, $CDCl_3$) 7.01 (1H, d, $J_{3,5}$ 2.9 Hz, 3-H), 6.94 (1H, d, $J_{6,5}$ 9.0 Hz, 6-H), 6.80 (1H, dd, $J_{5,6}$ 9.0 Hz, $J_{5,3}$ 2.9 Hz, 5-H), 5.15 (1H, br s, OH), 3.75 (3H, s, 4-OMe); *m/z* (EI, %) 204 (M^+, ^{81}Br, 50), 202 (M^+, ^{79}Br, 55), 189 (50), 187 (50), 73 (57), 41 (100); HRMS (EI) M^+, Found 203.9614, 201.9635, $C_7H_7^{81}BrO_2$, $C_7H_7^{79}BrO_2$ requires 203.9609, 201.9629. The spectroscopic data was in agreement with that reported in the literature.[19]

4.1.2. 2-Bromo-4-methoxyphenyl-p-toluenesulfonate **12**[9]

To a stirred solution of 2-bromo-4-methoxyphenol **11** (1.60 g, 7.9 mmol) in dichloromethane (25 mL) was added triethylamine (1.30 mL, 9.48 mmol) at 0 °C. A solution of *p*-toluenesulfonyl chloride (1.80 g, 9.48 mmol) in dichloromethane (35 mL) was added dropwise and stirring was continued for 2 h. The mixture was washed with water (25 mL), saturated $NaHCO_3$ solution (25 mL) and brine (25 mL). After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (10% ethyl acetate/hexanes) to afford the title compound **12** (2.62 g, 7.3 mmol, 93%) as colourless needles, mp 74–76 °C (lit.[9] mp 73.5–75 °C); R_f (10% ethyl acetate/hexanes) 0.60; δ_H (400 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.2 Hz, Ar-H), 7.32 (2H, d, *J* 8.2 Hz, Ar-H), 7.22 (1H, d, $J_{6,5}$ 9.0 Hz, 6-H), 7.01 (1H, d, $J_{3,5}$ 3.0 Hz, 3-H), 6.81 (1H, dd, $J_{5,6}$ 9.0 Hz, $J_{5,3}$ 3.0 Hz, 5-H), 3.73 (3H, s, 4-OMe), 2.46 (3H, s, Me); *m/z* (EI, %) 358 (M^+, ^{81}Br, 20), 356 (M^+, ^{79}Br, 20), 281 (10), 279 (10), 203 (95), 201 (100), 175 (10), 173 (10), 91 (35); HRMS (EI) M^+, Found 357.9682, 355.9718, $C_{14}H_{13}^{81}BrO_4S$, $C_{14}H_{13}^{79}BrO_4S$ requires 357.9698, 355.9718. The spectroscopic data was in agreement with that reported in the literature.[9]

4.1.3. 7-Methoxynaphthalen-1-ol **9**[9]

To a solution of tosyl ester **12** (2.8 g, 7.89 mmol) in anhydrous tetrahydrofuran (30 mL) under nitrogen was added furan (5 mL). The mixture was cooled to −78 °C and a solution of *n*-butyllithium in hexanes (6.25 mL, 1.3 M, 8.28 mmol) was added dropwise, stirring was continued for 30 min at −78 °C then the mixture was allowed to warm to room temperature. The reaction was quenched with water (25 mL) and extracted with ethyl acetate (3×25 mL). The organic layer was dried over anhydrous $MgSO_4$ and solvent removed under reduced pressure. The crude material was added to a solution of concd hydrochloric acid (2 drops) in methanol (20 mL) and was heated to reflux for 1 h under nitrogen. After cooling to room temperature, the methanol was removed under reduced pressure and water (20 mL) was added. The crude product was extracted with ethyl acetate (3×20 mL) and dried over

anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography (10% ethyl acetate/hexanes) to afford the title compound **9** (958 mg, 5.5 mmol, 70%) as colourless needles, mp 104–106 °C (lit.[9] mp 105–106 °C); R_f (10% ethyl acetate/hexanes) 0.30; δ_H (300 MHz, $CDCl_3$) 7.69 (1H, d, $J_{5,6}$ 9.0 Hz, 5-H), 7.47 (1H, d, $J_{8,6}$ 2.5 Hz, 8-H), 7.37 (1H, d, $J_{3,4}$ 7.9 Hz, 3-H), 7.17–7.10 (2H, m, 2-H and 6-H), 6.76 (1H, dd, $J_{4,3}$ 7.9 Hz, $J_{4,2}$ 0.8 Hz, 4-H), 5.58 (1H, br s, OH), 3.91 (3H, s, 7-OMe); δ_C (75 MHz, $CDCl_3$) 157.3, 150.5, 130.3, 129.7, 125.2, 123.3, 120.4, 119.2, 109.1, 99.9, 55.4; *m/z* (EI, %) 174 (M^+, 95), 131 (60), 92 (13), 77 (13); HRMS (EI) M^+, Found 174.0683, $C_{11}H_{10}O_2$ requires 174.0681. The spectroscopic data were in agreement with that reported in the literature.[15]

4.1.4. 2-Bromo-7-methoxynaphthalen-1-ol *13*

To a stirred solution of naphthol **9** (250 mg, 1.44 mmol) and *N*,*N*-diisopropylamine (19.9 μL, 0.14 mmol) in dichloromethane (10 mL) was added a suspension of *N*-bromosuccinimide (256 mg, 1.44 mmol) in dichloromethane (10 mL) at −30 °C dropwise. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature then poured into water (20 mL) and acidified to pH 1 with concd sulfuric acid. The crude product was extracted with dichloromethane (3×20 mL) and the combined organic layers were washed with water (3×20 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash chromatography (20% ethyl acetate/hexanes) to yield the title compound **13** (218 mg, 0.86 mmol, 60%) as an off-white solid, mp 87–89 °C; R_f (20% ethyl acetate/hexanes) 0.75; ν_{max} (film) 3268, 1624, 1600, 1510, 1478, 1425, 1219, 1177 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.10 (1H, d, $J_{5,6}$ 8.6 Hz, 5-H), 7.47 (1H, d, $J_{8,6}$ 2.7 Hz, 8-H), 7.42 (1H, d, $J_{3,4}$ 7.9 Hz, 3-H), 7.26 (1H, dd, $J_{6,5}$ 8.6 Hz, $J_{6,8}$ 2.7 Hz, 6-H), 6.67 (1H, d, $J_{4,3}$ 7.9 Hz, 4-H), 3.95 (3H, s, 7-OMe); δ_C (75 MHz, $CDCl_3$) 157.9, 150.3, 128.8, 128.2, 126.8, 126.7, 120.4, 113.4, 109.7, 100.5, 55.5; *m/z* (EI, %) 254 (M $[^{81}Br]^+$, 95), 252 (M $[^{79}Br]^+$, 100), 211 (40), 209 (40), 145 (35), 102 (45); HRMS (EI) M^+, Found 253.9774, 251.9795, $C_{11}H_9^{81}BrO_2$, $C_{11}H_9^{79}BrO_2$ requires 253.9765, 251.9786.

4.1.5. 2-Bromo-7-methoxy-1,4-naphthoquinone *14*

To a solution of naphthol **13** (400 mg, 1.57 mmol) in acetonitrile (20 mL) and water (6 mL) at −5 °C was added [bis(trifluoroacetoxy)iodo]benzene (1.43 g, 3.29 mmol) portionwise over 20 min. After stirring for 30 min at −5 °C, the reaction mixture was allowed to warm to room temperature and stirring continued for 1 h. Saturated $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the mixture extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude product was purified by flash chromatography (10% ethyl acetate/hexanes) to yield the title compound **14** (244 mg, 0.91 mmol, 58%) as a yellow solid, mp 122–124 °C; R_f (10% ethyl acetate/hexanes) 0.60; ν_{max} (film) 1682, 1659, 1601, 1588, 1309, 1265, 738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.03 (1H, d, $J_{5,6}$ 8.6 Hz, 5-H), 7.59 (1H, dd, $J_{8,6}$ 2.6 Hz, $J_{8,5}$ 1.1 Hz, 8-H), 7.46 (1H, s, 3-H), 7.23 (1H, dd, $J_{6,5}$ 8.6 Hz, $J_{6,8}$ 2.6 Hz, 6-H), 3.96 (3H, s, 7-OMe); δ_C (75 MHz, $CDCl_3$) 181.5, 178.0, 164.2, 140.6, 139.1, 132.9, 129.3, 125.2, 120.8, 111.3, 56.0; *m/z* (EI, %) 268 (M $[^{81}Br]^+$, 78), 266 (M $[^{79}Br]^+$, 80), 240 (M $[^{81}Br]^+-O_2$, 10), 238 (M $[^{79}Br]^+-O_2$, 10), 187 (M^+–Br, 100), 159 (40); HRMS (EI) M^+, Found 267.9563, 265.9574, $C_{11}H_7^{81}BrO_3$, $C_{11}H_7^{79}BrO_3$ requires 267.9558, 265.9579.

4.1.6. 3-Bromo-2-allyl-6-methoxy-1,4-naphthoquinone *8*

To a solution of 2-bromo-1,4-naphthoquinone **14** (50 mg, 0.19 mmol) in dry dichloromethane (10 mL) at −78 °C was added allyltrimethylsilane (0.03 mL, 0.19 mmol) followed by a solution of methylaluminium dichloride in hexanes (0.55 mL, 1.0 M, 0.55 mmol). After stirring for 2 h at −78 °C, the reaction mixture was quenched with water (5 mL) and allowed to warm to room temperature. The crude product was extracted with dichloromethane (3×5 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The crude product was dissolved in methanol (10 mL) and a solution of anhydrous $FeCl_3$ (65 mg, 0.40 mmol) in methanol (2 mL) was added and the mixture stirred for 6 h. The methanol was removed under reduced pressure and the crude product was re-dissolved in dichloromethane (15 mL), washed with water (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (10% ethyl acetate/hexanes) to yield the title compound **8** (32 mg, 0.10 mmol, 55%) as a yellow solid, mp 65–67 °C; R_f (10% ethyl acetate/hexanes) 0.55; ν_{max} (film) 1677, 1589, 1497, 1423, 1265, 1067, 1026 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, d, $J_{8,7}$ 8.6 Hz, 8-H), 7.58 (1H, d, $J_{5,7}$ 2.6 Hz, 5-H), 7.19 (1H, dd, $J_{7,8}$ 8.6 Hz, $J_{7,5}$ 2.6 Hz, 7-H), 5.88–5.79 (1H, m, 2-H), 5.21 (1H, dd, $J_{3B,2}$ 10.0 Hz, J_{gem} 1.4 Hz, 3-H_B), 5.12 (1H, dd, $J_{3A,2}$ 10.0 Hz, J_{gem} 1.4 Hz, 3-H_A), 3.94 (3H, s, 6-OMe), 3.60 (2H, dt, $J_{1,2}$ 6.6 Hz, $J_{1,3}$ 1.4 Hz, 1-H); δ_C (75 MHz, $CDCl_3$) 180.4, 177.9, 164.2, 149.2, 138.5, 131.6, 129.6, 128.6, 125.0, 120.7, 118.2, 110.9, 56.0, 35.5; *m/z* (EI, %) 308 (M $[^{81}Br]^+$, 60), 306 (M $[^{79}Br]^+$, 60), 293 (M $[^{81}Br]^+-O$, 18), 291 (M $[^{79}Br]^+-O$, 20), 227 (M^+–Br, 100), 199 (15); HRMS (EI) Found M^+, 307.9883, 305.9883, $C_{14}H_{11}^{81}BrO_3$, $C_{14}H_{11}^{79}BrO_3$ requires 307.9871, 305.9892.

4.1.7. 2-(2,3-Dihydroxyprop-1-yl)-3-bromo-1,4,6-trimethoxynaphthalene *16*

To a solution of 2-allyl-3-bromo-6-methoxy-1,4-naphthoquinone **8** (200 mg, 0.65 mmol) and tetrabutylammonium iodide (10 mg, 0.02 mmol) in THF (15 mL) under nitrogen was added a solution of sodium dithionite (711 mg, 4.05 mmol) in water (7 mL) with vigorous stirring. After 30 min, a solution of potassium hydroxide (439 mg, 7.83 mmol) in water (7 mL) was added dropwise then the reaction mixture was stirred for 1 h followed by addition of dimethylsulfate (1.35 mL, 13.87 mmol). After 4 h stirring, the mixture was quenched with aqueous ammonia (1.5 M, 5 mL) followed by

water (25 mL) and the product was extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with 2 M hydrochloric acid (20 mL), water (3×20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure to obtain crude allyl ether **15**.

To a solution of crude allyl ether **15** (208 mg, 0.62 mmol) in acetone (15 mL) and H_2O (3 mL) was added *N*-methylmorpholine *N*-oxide (122 mg, 0.86 mmol) and the mixture was cooled to 0 °C. After 5 min stirring, a solution of osmium tetroxide (0.06 mL, 0.01 mmol) was added and the mixture gradually warmed to room temperature. The reaction mixture was stirred for 24 h then 33% aqueous Na_2SO_3 solution (5 mL) was added. The mixture was extracted with ethyl acetate (3×20 mL) and the combined organic extracts were washed with water (10 mL) and brine (10 mL). After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (50% ethyl acetate/hexanes) to yield the title compound **16** (183 mg, 0.54 mmol, 80%) as a colourless solid, mp 156–157 °C; R_f (50% ethyl acetate/hexanes) 0.23; ν_{max} (film) 3374, 2305, 1624, 1579, 1421, 1326, 1024, 746 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (1H, d, $J_{8,7}$ 9.2 Hz, 8-H), 7.37 (1H, d, $J_{5,7}$ 2.5 Hz, 5-H), 7.21 (1H, dd, $J_{7,8}$ 9.2 Hz, $J_{7,5}$ 2.5 Hz, 7-H), 4.10–4.00 (1H, m, 2-H), 3.96 (3H, s, 4-OMe or 1-OMe), 3.95 (3H, s, 1-OMe or 4-OMe), 3.93 (3H, s, 7-OMe), 3.72–3.64 (1H, m, 3-H_B), 3.56–3.49 (1H, m, 3-H_A), 3.27–3.09 (2H, m, 1-H); δ_C (75 MHz, $CDCl_3$) 158.6, 151.1, 150.4, 129.7, 124.4, 122.8, 119.6, 117.2, 100.9, 94.0, 71.7, 65.7, 62.4, 60.9, 55.5, 34.1; *m/z* (EI, %) 372 (M $[^{81}Br]^+$, 100), 370 (M $[^{79}Br]^+$, 100), 354 (M $[^{81}Br]-H_2O$, 10), 352 (M $[^{79}Br]-H_2O$, 10), 311 (M $[^{81}Br]-C_2H_5O_2$, 90), 309 (M $[^{79}Br]-C_2H_5O_2$, 90); HRMS (EI) M^+, Found 372.0398, 370.0412, $C_{16}H_{19}^{81}BrO_5$, $C_{16}H_{19}^{79}BrO_5$ requires 372.0395, 370.0416.

*4.1.8. 2-(3-Bromo-1,4,6-trimethoxynaphthalen-2-yl)-ethanal **7***

To a solution of diol **16** (133 mg, 0.36 mmol) in methanol (10 mL) and water (3 mL) at 0 °C was added sodium periodate (92 mg, 0.43 mmol) in several portions at 0 °C. After 2 h stirring at 0 °C, the mixture was warmed to room temperature and extracted with diethyl ether (3×15 mL). The organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by flash chromatography (50% ethyl acetate/hexanes) to yield the title compound **7** (120 mg, 0.34 mmol, 99%) as a colourless liquid; R_f (50% ethyl acetate/hexanes) 0.74; ν_{max} (film) 1721, 1623, 1582, 1496, 1450, 1406, 1076, 1014 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.84 (1H, t, $J_{1,2}$ 1.5 Hz, CHO), 7.95 (1H, d, $J_{8,7}$ 9.2 Hz, 8-H), 7.37 (1H, d, $J_{5,7}$ 2.5 Hz, 5-H), 4.07 (2H, d, $J_{2,1}$ 1.5 Hz, 2-H), 3.97 (3H, s, 4-OMe or 1-OMe), 3.95 (3H, s, 1-OMe or 4-OMe), 3.83 (3H, s, 6-OMe); δ_C (75 MHz, $CDCl_3$) 198.8, 158.9, 152.0, 149.3, 130.2, 124.5, 123.0, 120.4, 119.6, 116.7, 100.9, 62.5, 60.9, 55.5, 45.0; *m/z* (EI, %) 340 (M $[^{81}Br]^+$, 100), 338 (M $[^{79}Br]^+$, 100), 325 (20), 323 (20), 311 (80), 309 (80); HRMS (EI) M^+, Found 340.0124, 338.0163, $C_{15}H_{15}^{81}BrO_4$, $C_{15}H_{15}^{79}BrO_4$ requires 340.0133, 338.0157.

*4.1.9. rac-2-(2-Hydroxy-4-penten-1-yl)-3-bromo-1,4,6-trimethoxynaphthalene **17***

To a stirred suspension of magnesium powder (14 mg, 0.58 mmol) in dry diethyl ether (7 mL) was added a solution of allyl bromide (0.04 mL, 0.45 mmol) in dry diethyl ether (2 mL) dropwise under nitrogen. The reaction mixture was heated to reflux for 1 h then cooled to room temperature. In other flask, aldehyde **7** (70 mg, 0.21 mmol) was dissolved in diethyl ether (10 mL) and cooled to −40 °C. The solution of allylmagnesium bromide was added to aldehyde solution dropwise via syringe. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with H_2O (40 mL) and stirred for 5 min. The mixture was extracted with diethyl ether (3×20 mL), dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford the title compound **17** (70 mg, 0.18 mmol, 89%) as a colourless liquid.; R_f (10% ethyl acetate/hexanes) 0.60; ν_{max} (film) 3584, 2400, 1624, 1580, 1496, 1362, 1031, 1010 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (1H, d, $J_{8,7}$ 9.2 Hz, 8-H), 7.35 (1H, d, $J_{5,7}$ 2.6 Hz, 5-H), 7.18 (1H, dd, $J_{7,8}$ 9.2 Hz, $J_{7,5}$ 2.6 Hz, 7-H), 6.00–5.86 (1H, m, 4-H), 5.22–5.12 (2H, m, 5-H), 4.07–4.01 (1H, m, 2-H), 3.95 (3H, s, 4-OMe or 1-OMe), 3.94 (3H, s, 1-OMe or 4-OMe), 3.90 (3H, s, 6-OMe), 3.14 (2H, d, $J_{1,2}$ 5.9 Hz, 1-H), 2.38 (2H, t, $J_{3,2\ or\ 3,4}$ 6.1 Hz, 3-H), 2.30 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 158.5, 151.4, 149.3, 134.9, 129.5, 125.2, 124.5, 123.0, 119.4, 117.8, 117.4, 100.8, 70.8, 62.2, 60.8, 55.4, 41.9, 37.5; *m/z* (EI, %) 382 (M $[^{81}Br]^+$, 100), 380 (M $[^{79}Br]^+$, 100), 340 (10), 338 (10), 311 (90), 309 (90), 297 (80), 295 (80); HRMS (EI) M^+, Found 382.0610, 380.0617, $C_{18}H_{21}^{81}BrO_4$, $C_{18}H_{21}^{79}BrO_4$ requires 382.0603, 380.0623.

*4.1.10. rac-2-(2-Acetoxy-4-penten-1-yl)-3-bromo-1,4,6-trimethoxynaphthalene **6***

To a solution of homoallyl alcohol *rac*-**17** (70 mg, 0.18 mmol) in dichloromethane (30 mL) was added acetic anhydride (0.02 mL, 0.22 mmol) dropwise with stirring. After stirring for 10 min, a catalytic quantity of perchloric acid (one drop) was added to the reaction mixture and the resulting violet mixture stirred for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with saturated NH_4Cl solution (20 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (30% ethyl acetate/hexanes) to yield the title compound **6** (70 mg, 0.17 mmol, 90%) as a colourless liquid; R_f (30% ethyl acetate/hexanes) 0.60; ν_{max} (film) 2936, 1738, 1622, 1578, 1495, 1227, 1076, 1030 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.93 (1H, d, $J_{8,7}$ 9.2 Hz, 8-H), 7.34 (1H, d, $J_{5,7}$ 2.5 Hz, 5-H), 7.17 (1H, dd, $J_{7,5}$ 2.5 Hz, $J_{7,8}$ 9.2 Hz, 7-H), 5.88–5.75 (1H, m, 4-H), 5.43–5.35 (1H, m, 2-H), 5.10 (1H, dd, $J_{5B,4}$ 19.0 Hz, J_{gem} 1.3 Hz, 5-H_B), 5.07 (1H, dd, $J_{5A,4}$ 10.9 Hz, J_{gem} 1.3 Hz, 5-H_A), 3.94 (3H, s, 4-OMe or 1-OMe), 3.93 (3H, s, 1-OMe or 4-OMe), 3.89 (3H, s, 6-OMe), 3.29 (1H, dd, J_{gem} 13.6 Hz, $J_{1B,2}$

8.1 Hz, 1-H_B), 3.17 (1H, dd, J_{gem} 13.6 Hz, $J_{1A,2}$ 5.4 Hz, 1-H_A), 2.42 (2H, t, J 7.0 Hz, 3-H), 1.89 (3H, s, OCOMe); δ_C (75 MHz, $CDCl_3$) 170.2, 158.5, 151.8, 149.0, 133.9, 129.6, 124.5, 124.3, 123.0, 119.3, 117.6, 117.5, 100.8, 72.6, 62.3, 60.8, 55.4, 38.6, 34.4, 21.0; *m/z* (EI, %) 424 (M^+, ^{81}Br, 48), 422 (M^+, ^{79}Br, 50), 364 (70), 362 (70), 311 (40), 43 ($M^+-C_{18}H_{20}O_4Br$, 100); HRMS (EI) M^+, Found 424.0705, 422.0732, $C_{20}H_{23}^{81}BrO_5$, $C_{20}H_{23}^{79}BrO_5$ requires 424.0708, 422.0729.

4.1.11. *cis-(±)-3-Allyl-5,8,10-trimethoxy-1-methyl-3,4-dihydro-1H-naphtho[2,3-c]pyran* ***20***

Bromo ester *rac*-**6** (70 mg, 0.17 mmol) was dissolved in dry THF (7 mL) under nitrogen atmosphere and the solution cooled to −78 °C. A solution of *tert*-butyllithium in pentane (0.25 mL, 1.3 M, 0.36 mmol) was added dropwise via syringe to the above solution and the resulting dark orange reaction mixture stirred for 1 h at −78 °C. The reaction mixture was quenched with H_2O (5 mL) at −78 °C, warmed to room temperature then extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated to give crude lactol **19**, which was used directly in the next step without further purification due to its instability on silica gel.

To a solution of the crude lactol **19** (57 mg, 0.17 mmol) in dry dichloromethane (10 mL) at −78 °C was added trifluoroacetic acid (0.04 mL, 0.50 mmol) dropwise and the mixture stirred for 15 min. Triethylsilane (0.08 mL, 0.50 mmol) was added dropwise to the reaction mixture at −78 °C and the mixture stirred for 2 h then gradually warmed to room temperature. The reaction mixture was then quenched with ice-water (10 mL) and extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (20% ethyl acetate/hexanes) to give the title compound **20** (35 mg, 0.11 mmol, 65%) as a pale yellow viscous oil; R_f (20% ethyl acetate/hexanes) 0.80; ν_{max} (film) 1736, 1627, 1598, 1499, 1448, 1420, 1342, 1222 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.97 (1H, d, $J_{6,7}$ 9.2 Hz, 6-H), 7.31 (1H, d, $J_{9,7}$ 2.5 Hz, 9-H), 7.13 (1H, dd, $J_{7,6}$ 9.2 Hz, $J_{7,9}$ 2.5 Hz, 7-H), 6.04−5.90 (1H, m, 2-H), 5.20 (1H, q, $J_{1,Me}$ 6.3 Hz, 1-H), 5.17−5.10 (2H, m, 3-H), 3.93 (3H, s, 8-OMe), 3.88 (3H, s, 10-OMe or 5-OMe), 3.84 (3H, s, 5-OMe or 10-OMe), 3.64−3.56 (1H, m, 3-H), 3.06 (1H, dd, J_{gem} 15.5 Hz, $J_{4ax,3}$ 1.6 Hz, 4-H_{ax}), 2.60 (1H, d, J_{gem} 15.5 Hz, 4-H_{eq}), 2.57−2.49 (1H, m, 1-H_B), 2.46−2.35 (1H, m, 1-H_A), 1.68 (3H, d, $J_{Me,1}$ 6.3 Hz, 1-Me); δ_C (75 MHz, $CDCl_3$) 157.8, 149.3, 148.0, 134.7, 131.0, 128.5, 123.9, 122.9, 122.5, 118.6, 117.0, 100.1, 73.3, 71.4, 61.4, 60.4, 55.3, 40.5, 29.6, 22.4; *m/z* (EI, %) 328 (M^+, 60), 313 (M^+−Me, 8), 307 (25), 289 (15), 154 ($M^+-C_9H_{18}O_3$, 100), 136 (70); HRMS (EI) M^+, Found 328.1681, $C_{20}H_{24}O_4$ requires 328.1675.

4.1.12. *cis-(±)-(2′S)-3-(2,3-Dihydroxyprop-1-yl)-5,8,10-trimethoxy-1-methyl-3,4-dihydro-1H-naphtho[2,3-c]pyran and cis-(±)-(2′R)-3-(2,3-dihydroxyprop-1-yl)-5,8,10-trimethoxy-1-methyl-3,4-dihydro-1H-naphtho[2,3-c]pyran* ***21***

To a solution of allylnaphtho[2,3-*c*]pyran **20** (35 mg, 0.11 mmol) in acetone (10 mL) and H_2O (2 mL) was added *N*-methylmorpholine *N*-oxide (23 mg, 0.16 mmol) and cooled to 0 °C. After stirring for 5 min, a solution of osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol) (0.01 mL, 0.002 mmol) was added and the mixture gradually warmed to room temperature. The reaction mixture was allowed to stir for 24 h then 33% aqueous Na_2SO_3 solution (5 mL) was added. The mixture was extracted with ethyl acetate (3×10 mL) and the combined organic extracts were washed with water (5 mL) and brine (5 mL). After drying over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (20% ethyl acetate/hexanes) to yield the title compounds **21** (33 mg, 0.09 mmol, 86%) as colourless viscous oil; R_f (20% ethyl acetate/hexanes) 0.80; ν_{max} (film) 3400, 1627, 1598, 1500, 1448, 1420, 1343, 1222 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.95 (1H, d, $J_{6,7}$ 9.2 Hz, 6-H), 7.30 (1H, d, $J_{9,7}$ 2.5 Hz, 9-H), 7.14 (1H, dd, $J_{7,6}$ 9.2 Hz, $J_{7,9}$ 2.5 Hz, 7-H), 5.29−5.14 (1H, m, 1-H), 4.15−4.05 (1H, m, 2-H), 3.99−3.88 (1H, m, 3-H), 3.92 (3H, s, 8-OMe), 3.86 (3H, s, 10-OMe), 3.83 (3H, s, 5-OMe), 3.74−3.56 (2H, m, 3-H), 3.23 (1H, br s, OH), 3.07−2.96 (1H, m, 4-H_B), 2.77−2.59 (1H, m, 4-H_A), 2.54 (1H, br s, OH), 2.00−1.91 (1H, m, 1-H_B), 1.88−1.79 (1H, m, 1-H_A), 1.67 (3H, d, $J_{1,Me}$ 6.3 Hz, 1-Me); δ_C (75 MHz, $CDCl_3$) 157.7, 157.6, 149.0, 149.1, 147.3, 129.1, 128.4, 128.3, 123.7, 122.74, 122.71, 121.8, 118.6, 118.5, 99.9, 73.8 71.4, 71.3, 71.1, 69.3, 71.6, 66.5, 66.7, 61.2, 60.3, 60.2, 55.1, 38.5, 38.3, 30.2, 29.7, 22.3, 22.2; *m/z* (FAB, %) 362 (M^+, 10), 307 (30), 289 (15), 154 ($M^+-C_9H_{20}O_5$, 100), 136 (70), 107 (25); HRMS (FAB) M^+, Found 362.1731, $C_{20}H_{26}O_6$ requires 362.1729.

4.1.13. *cis-(±)-2-(5,8,10-Trimethoxy-1-methyl-3,4-dihydro-1H-naphtho[2,3-c]pyran-3-yl)ethanal* ***22***

To a solution of diols **21** (33 mg, 0.09 mmol) in methanol (5 mL) and water (1.5 mL) at 0 °C was added sodium periodate (24 mg, 0.11 mmol) in several portions and stirred for 2 h. The reaction mixture was warmed to room temperature and extracted with diethyl ether (3×10 mL). The organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (30% ethyl acetate/hexanes) to yield the title compound **22** (21 mg, 0.062 mmol, 70%) as a colourless solid, mp 129−132 °C; R_f (30% ethyl acetate/hexanes) 0.62; ν_{max} (film) 1725, 1627, 1598, 1500, 1448, 1421, 1343 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.91 (1H, t, $J_{1,2}$ 2.0 Hz, CHO), 7.95 (1H, d, $J_{6,7}$ 9.2 Hz, 6-H), 7.31 (1H, d, $J_{9,7}$ 2.5 Hz, 9-H), 7.14 (1H, dd, $J_{7,6}$ 9.2 Hz, $J_{7,9}$ 2.5 Hz, 7-H), 5.23 (1H, q, $J_{1,Me}$ 6.3 Hz, 1-H), 4.17−4.07 (1H, m, 3-H), 3.93 (3H, s, 8-OMe), 3.87 (3H, s, 10-OMe), 3.85 (3H, s, 5-OMe), 3.09 (1H, dd, J_{gem} 16.2 Hz, $J_{4eq,3ax}$ 2.2 Hz, 4-H_{eq}), 2.85 (1H, ddd, J_{gem} 16.2 Hz, $J_{4ax,3ax}$ 7.9 Hz, $J_{4ax,1}$ 2.2 Hz, 4-H_{ax}), 2.75−2.59 (2H, m, 2-H), 1.65 (3H, d, $J_{Me,1}$ 6.3 Hz, 1-Me); δ_C (75 MHz, $CDCl_3$)

200.9, 157.9, 149.3, 147.5, 129.3, 128.7, 123.9, 122.9, 121.5, 118.8, 100.1, 71.5, 68.9, 61.4, 60.5, 55.3, 49.5, 29.9, 22.3; *m/z* (FAB, %) 330 (M^+, 10), 154 ($M^+-C_8H_{16}O_4$, 100), 136 (70), 120 (15), 107 (23), 89 (20), 77 (20); HRMS (FAB) M^+, Found 330.1461, $C_{19}H_{22}O_5$ requires 330.1467.

4.1.14. cis-(±)-2-(8-Methoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-naphtho[2,3-c]pyran-3-yl)acetic acid ***5***

To a solution of aldehyde **22** (20 mg, 0.06 mmol) in *tert*-butanol (2 mL) were added water (0.5 mL) and cyclohexene (1 mL). After 5 min, sodium chlorite (28 mg, 0.24 mmol) and sodium phosphate monobasic dihydrate (42 mg, 0.31 mmol) were added and the mixture stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C and sodium bisulfite powder (22 mg, 0.20 mmol) was added followed by dilution with saturated sodium phosphate (5 mL). The reaction mixture was extracted with ethyl acetate (3×10 mL), washed with brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to obtain the corresponding crude carboxylic acid **23**.

To a solution of crude carboxylic acid **23** (15 mg, 0.043 mmol) in acetonitrile (5 mL) at 0 °C was added a solution of ceric ammonium nitrate (59 mg, 0.11 mmol) in water (5 mL) dropwise and the mixture allowed to warm to room temperature. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. After evaporation of solvent under reduced pressure, the crude product was purified with flash chromatography (30% ethyl acetate/hexanes) to afford the title compound **5** (11 mg, 0.035 mmol, 76%) as a yellow solid, mp 93–95 °C; R_f (30% ethyl acetate/hexanes) 0.25; ν_{max} (film) 3054, 2987, 2305, 1712, 1595, 1421, 896 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.01 (1H, d, $J_{6,7}$ 8.6 Hz, 6-H), 7.47 (1H, d, $J_{9,7}$ 2.7 Hz, 9-H), 7.16 (1H, dd, $J_{7,6}$ 8.6 Hz, $J_{7,9}$ 2.7 Hz, 7-H), 4.89–4.84 (1H, m, 1-H), 3.94–3.88 (1H, m, 3-H), 3.93 (3H, s, 8-OMe), 2.89 (1H, dd, J_{gem} 18.4 Hz, $J_{4eq,3}$ 2.4 Hz, 4-H_{eq}), 2.81–2.64 (2H, m, 2-H), 2.33 (1H, ddd, J_{gem} 18.4 Hz, $J_{4ax,3}$ 10.4 Hz, $J_{4ax,1}$ 3.8 Hz, 4-H_{ax}), 1.53 (3H, d, $J_{Me,1}$ 6.6 Hz, 1-Me); δ_C (75 MHz, $CDCl_3$) 183.8, 182.7, 175.7, 164.2, 146.0, 141.9, 134.4, 128.8, 125.2, 120.2, 109.7, 70.3, 69.0, 55.9, 40.2, 28.4, 20.7; *m/z* (FAB, %) 317 (M^+, 3), 154 ($M^+-C_6H_{10}O_5$, 100), 136 (75), 107 (25), 89 (25), 77 (20); HRMS (FAB) M^+, Found 317.1026,$C_{17}H_{16}O_6$ requires 317.1025.

Acknowledgements

The authors thank the Department of Chemistry, The University of Auckland for the award of a Departmental Scholarship (P.B.).

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