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An approach to an enantioselective synthesis of crisamicin A via a novel double Hauser–Kraus annulation strategy

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Abstract

A double Hauser–Kraus annulation between biscyanophthalide **4** and the D-mannose derived enone **39** provides access to an advanced intermediate **54** that is an excellent scaffold to effect an enantioselective total synthesis of crisamicin A **1**.

Keywords: Pyranonaphthoquinone antibiotics; Crisamicin A; Hauser–Kraus annulation

1. Introduction

The pyranonaphthoquinone (or isochromanquinone) family of antibiotics exhibits activity against a variety of Gram-positive bacteria, pathogenic fungi and yeasts,[1,3b] and has been proposed to act as bioreductive alkylating agents.[2] Whilst the synthesis of monomeric members of this important family of antibiotics is well documented,[3] the enantioselective total synthesis of a naturally occurring dimeric pyranonaphthoquinone antibiotic has yet to be achieved.[4] Herein we document our efforts towards an asymmetric synthesis of a key dimeric pyranonaphthoquinone antibiotic, crisamicin A (Fig. 1). Crisamicin A **1** was isolated from the microorganism *Micromonospora purpureochromogenes*[5] and exhibits activity against B16 murine melanoma cells, and the herpes simplex and vesicular stomatitis viruses.[6] To date, the total synthesis of crisamicin A has yet to be achieved.

Our earlier synthetic work towards **1** utilized a novel furofuran annulation-oxidative rearrangement strategy, but this route only facilitated access to regioisomers of crisamicin A.[4b,c] Recently, our attention has focused on a new retrosynthesis based around late stage construction of the pyran ring (Scheme 1). It was envisioned that crisamicin A **1** could be accessed via a key double Hauser–Kraus annulation[7] between biscyanophthalide **4** and enone **5**. This would give rise to the double annulated product **3** that upon removal of the protecting groups would undergo hydroxyl unmasking and in situ intramolecular lactol formation under thermodynamic control forming bis-*cis*-lactol **2**. Silane mediated lactol reduction followed by hydroquinone oxidation and treatment with Lewis acid to remove the methyl ethers with concomitant epimerization to the desired *trans*-ether would furnish crisamicin A **1**.

The synthesis of monomeric quinone-containing natural products using the Hauser–Kraus annulation is widespread,[8] but to date only one isolated example of a double Hauser–Kraus annulation has been reported during a total synthesis of biphyscion,[9] and a closely related double annulation has been successfully employed during the total synthesis of dimeric orsellinic acid derivatives.[10] Notably, both of these aforementioned routes employ cyclic enones as Michael acceptors in the respective double annulation reactions, as opposed to our proposed use of a chiral acyclic enone of type **5**.

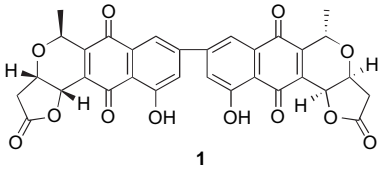

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Figure 1.

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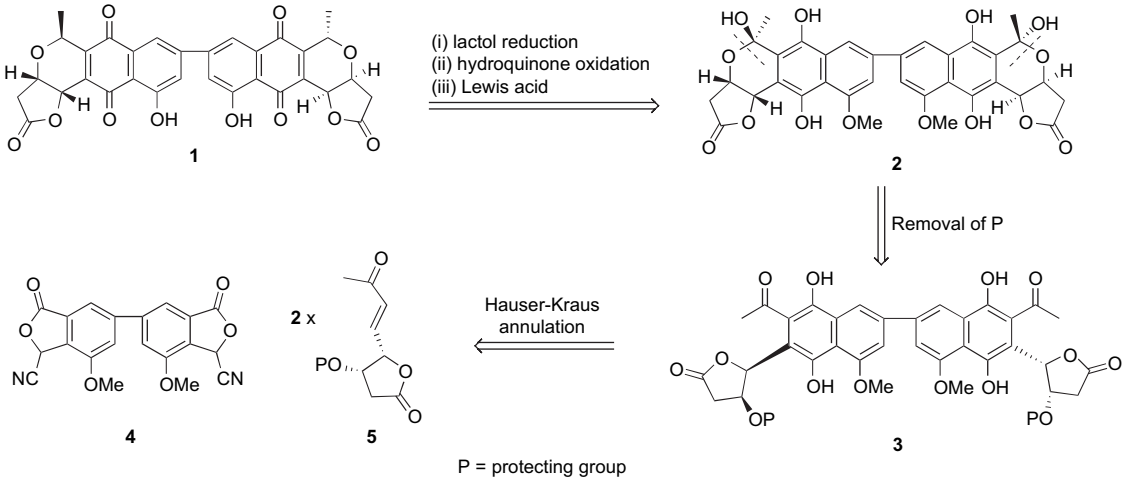
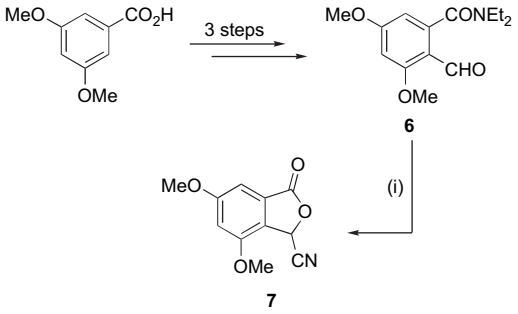


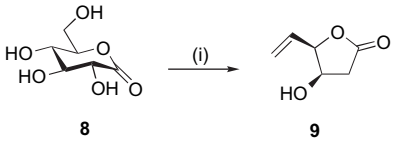
Scheme 1.

In order to test the viability of our approach, we first set out to assess the ability of enones such as **5** to undergo Hauser–Kraus annulation with a monomeric phthalide. We chose the 4,6-dimethoxyphthalide **7** for this purpose as it possesses the same substitution pattern on the aryl ring as biscyanophthalide **4**, wherein the biaryl bond is replaced with a methoxy group. To this end, formamide **6**, prepared from 3,5-dimethoxybenzoic acid in three steps as previously described,[11] was treated with trimethylsilyl cyanide in the presence of catalytic quantities of potassium cyanide and 18-crown-6[12] to effect cyclization furnishing the desired dimethoxycyanophthalide **7**[11] in excellent yield (Scheme 2).



Scheme 2. (i) TMS-CN, KCN, 18-c-6, CH_2Cl_2, 0 °C, 2 h then AcOH, rt, 16 h, 98%.

With the synthesis of the monomeric model phthalide in hand, attention next turned to the synthesis of a suitably protected enone of type **5**. It became clear from surveying the literature that the best route to enone **5** was likely to be a carbohydrate-derived synthesis. Unfortunately, a highly promising report that D-glucono lactone **8** could be readily transformed into lactone **9**[13] could not be repeated in sufficient yield or purity in our hands after numerous attempts (Scheme 3). Lactone **9** possesses the opposite absolute stereochemistry to that of crisamicin A, but at this stage it was decided to lay foundations for our proposed route and if it were successful, the use of the expensive L-sugar (D-mannose 500 g, NZ$698; L-mannose, 5 g, NZ$600) would be conducted providing enones with the correct absolute stereochemistry.



Scheme 3. (i) HBr (30% in acetic acid) then Zn, AcOH, 7%.

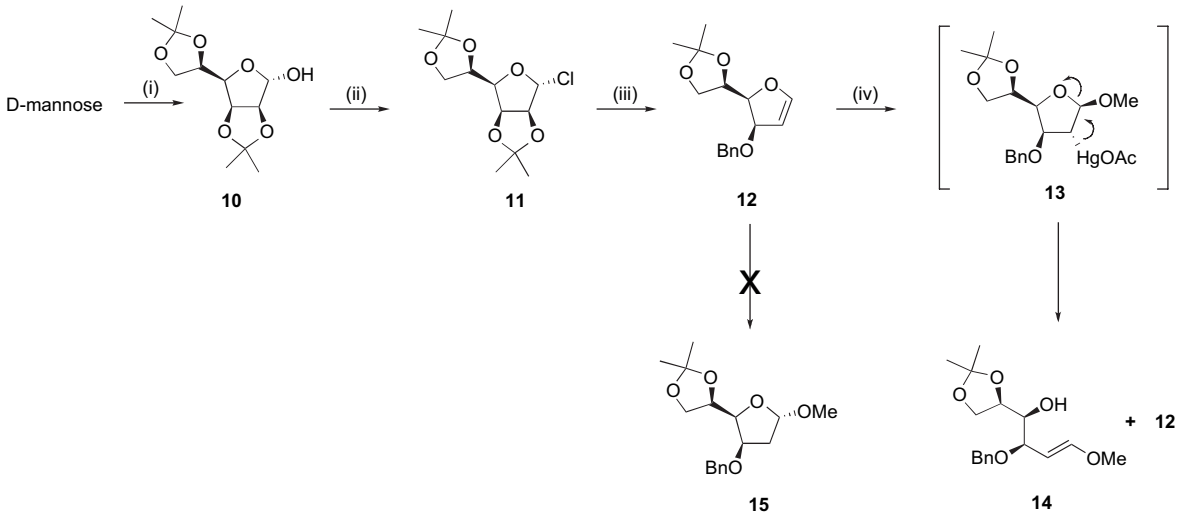
Given that lactones possess relatively acidic protons adjacent to the carbonyl, it was thought that this may have a detrimental effect on the Hauser–Kraus annulation as the reaction is traditionally carried out in the presence of a strong base. Therefore, the use of a suitably protected lactol was deemed more compatible for the Hauser–Kraus annulation step and oxidation to the desired lactone could then be effected after successful annulation.

With these ideas in mind attention focused on the synthesis of methyl acetal **15**, starting with a large-scale iodine-mediated protection of D-mannose to furnish the protected sugar **10**.[14] Chlorination of **10** furnished **11** that underwent sodium-mediated elimination followed by benzyl protection giving the known furanoid glycal **12** in good yield.[14] Unfortunately, all attempts to effect a mercury mediated glycosidation followed by in situ reduction of the carbon–mercury bond led to facile elimination of the intermediate **13** and the isolation of the ring opened product **14**. None of the desired product **15** was obtained (Scheme 4).

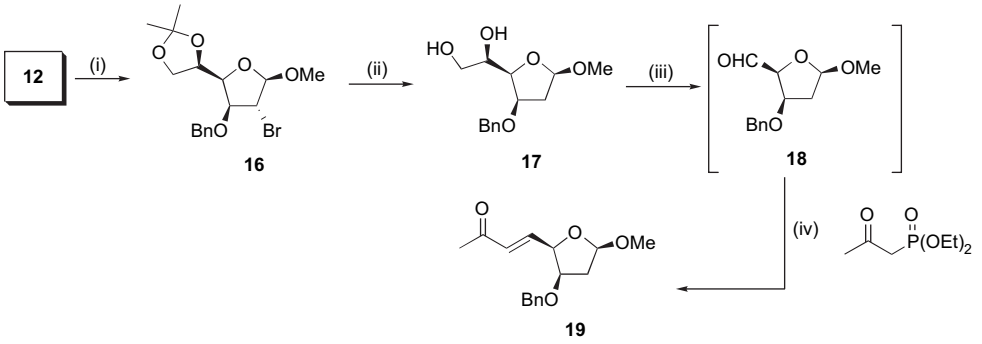
In contrast, bromo-glycosidation of **12** furnished the bromide **16** in good yield.[15] Deprotection of **16** under acidic conditions, followed by hydrogenation yielded diol **17**.

Oxidative cleavage then afforded the aldehyde **18** that was immediately subjected to a Horner–Wadsworth–Emmons olefination with diethyl (2-oxopropyl)phosphonate to give the desired enone **19** containing a protected lactol functionality (Scheme 5).

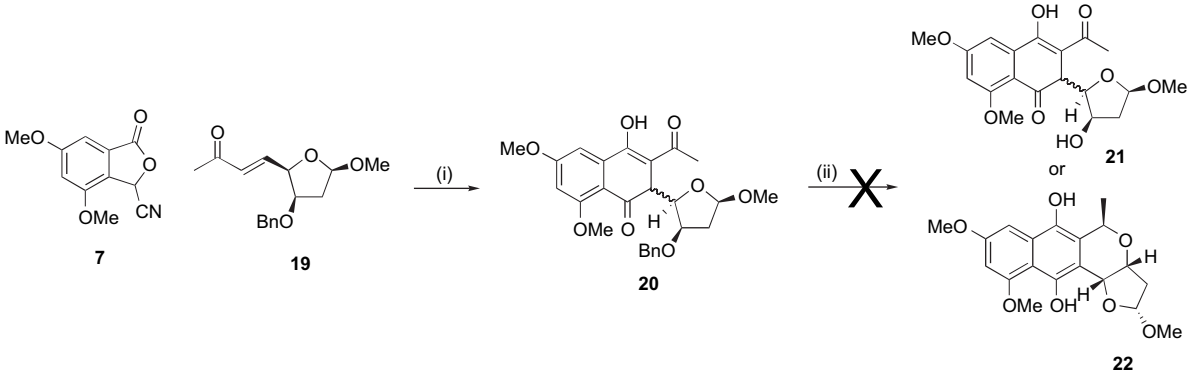
Attention next focused on the key Hauser–Kraus annulation. Enone **19** and model phthalide **7** underwent annulation



Scheme 4. (i) I_2, acetone, rt, 2 h, 85%; (ii) TsCl, Et_3N, DMAP, CH_2Cl_2, rt; (iii) Na, naphthalene, THF, 0 °C to rt then NaH, BnBr, Bu_4NI, 0 °C to rt, THF, 62% over two steps; (iv) $Hg(OAc)_2$, $CaCO_3$, MeOH–THF (1:1), 0 °C, then KI, 15% (**14**/**12**=1:4).



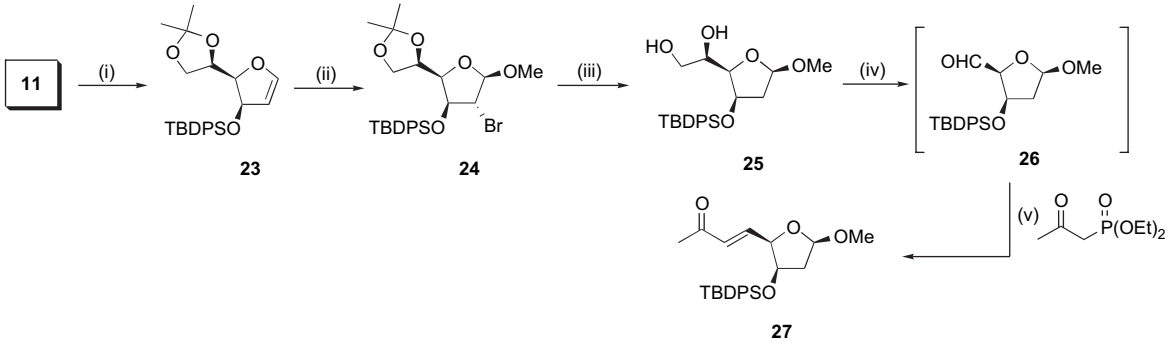
Scheme 5. (i) NBS, MeOH–MeCN, 0 °C to rt, 69% (dr=92:8); (ii) AcOH–H_2O (4:1), 40 °C then H_2, Pd/C, Et_3N, 62% over two steps; (iii) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 95% (crude); (iv) NaH, THF, 0 °C to rt, 63%.



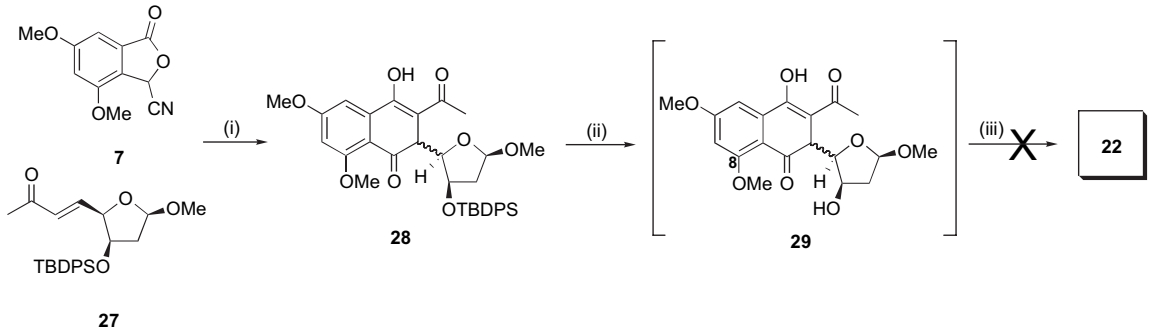
Scheme 6. (i) KO^{t}Bu, DMSO, rt, 78% (dr=65:35); (ii) H_2, Pd/C, EtOAc, rt.

with potassium *tert*-butoxide in dimethylsulfoxide, resulting in formation of the non-aromatized adduct **20** as a 65:35 mixture of diastereomers. The stereochemistry of the major product was not determined. Unfortunately, attempted unmasking of the hydroxyl group via hydrogenation did not afford either deprotected alcohol **21** or tetrahydropyran derivative **22**, and only decomposition was observed (Scheme 6).

At this stage it was decided to change the protecting group from benzyl ether **19** to silyl ether **27** (Scheme 7). Thus, sodium-mediated elimination of chloride **11** followed by silylation gave the *tert*-butyldiphenylsilyl ether **23** that underwent smooth bromo-glycosidation delivering bromide **24**. Acetonide removal under acidic conditions, followed by hydrogenation yielded the diol **25**. Sodium periodate mediated oxidative



Scheme 7. (i) Na, naphthalene, THF, 0 °C to rt then TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 59% over two steps; (ii) NBS, MeOH–MeCN, 0 °C to rt, 87% (dr=84:16); (iii) AcOH–H_2O (4:1), 40 °C then H_2, Pd/C, Et_3N, 23% over two steps; (iv) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 100%; (v) NaH, THF, 0 °C to rt, 63%.

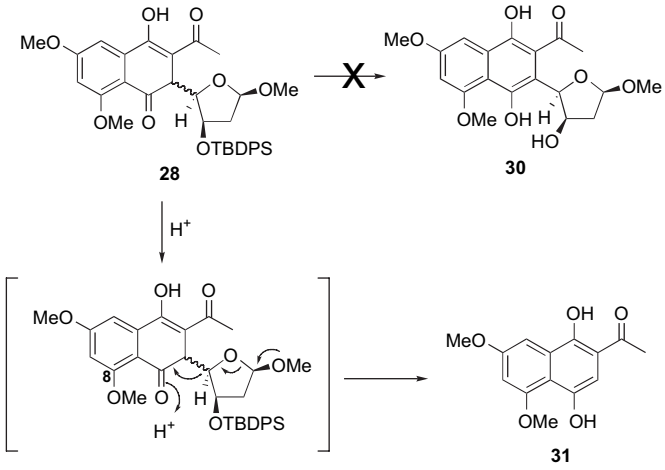


Scheme 8. (i) KO^{t}Bu, DMSO, rt, 66%; (ii) TBAF, DMF, rt, 52%; (iii) Et_3SiH, TFA, CH_2Cl_2, −78 °C to 0 °C.

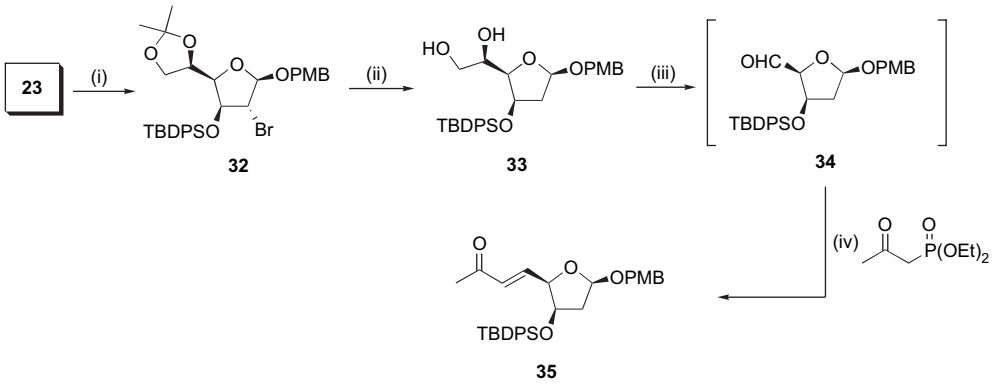
cleavage then gave aldehyde **26** that was immediately subjected to Horner–Wadsworth–Emmons olefination delivering the desired enone **27** (Scheme 7). Hauser–Kraus annulation between enone **27** and model phthalide **7** was next performed, again resulting in the formation of non-aromatized adduct **28** as a single diastereomer. Treatment of **28** with tetrabutylammonium fluoride gave a more polar product thought to be **29** upon analysis of the crude reaction mixture by ^{1}H NMR. However, all attempts to form the desired pyran product **22** from the crude reaction mixture led to degradation (Scheme 8).

At this stage it was thought that effecting aromatization of the adduct **28** prior to further manipulation would facilitate future steps in the synthesis. Attempts to rearomatize **28**, including the use of several bases in the presence of dimethyl sulfate (to trap the resulting hydroquinone), TBDPSCl and 2,6-lutidine, or tosic acid led to recovered **28**. Various oxidants were also tried in an attempt to isolate the quinone, also to no avail. Unfortunately, treatment with acid promoted elimination to dihydronaphthoquinone **31** as the sole product (Scheme 9). This observation suggests that the presence of the methoxy group on the lactol prevents the desired aromatization from taking place and the tetrahydrofuran ring eliminates faster than the product tautomerizes to the stable aromatic enol form. Based on this observation, it was decided to prepare an enone in which the lactol was protected so that it could be liberated under non-acidic conditions and hence does not eliminate to compounds of type **31** during aromatization.

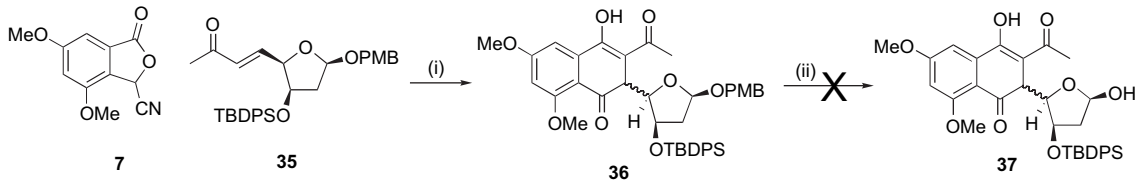
Thus, the synthesis of the PMB-protected enone **35** was undertaken. Use of *para*-methoxybenzyl alcohol (PMBOH) in the bromo-glycosidation step furnished the desired adduct **32**. After acid mediated acetonide deprotection, use of the radical initiator Et_3B–O_2 at −78 °C effected debromination to furnish the diol **33** in excellent yield. Oxidative cleavage and immediate olefination of aldehyde **34** gave the desired enone **35** (Scheme 10). PMB-protected enone **35** then underwent smooth Hauser–Kraus annulation with phthalide **7** giving the non-aromatized product **36** as a single diastereomer. However, all attempts to remove the PMB group under neutral



Scheme 9.



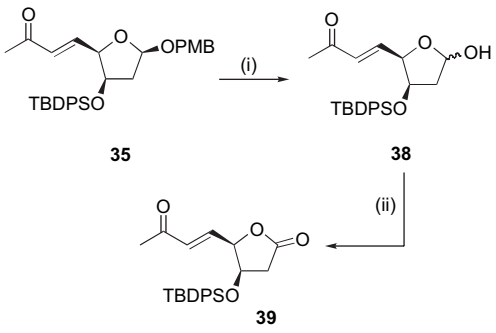
Scheme 10. (i) NBS, PMBOH, MeCN, 0 °C to rt, 72% (dr=84:16); (ii) AcOH–H_2O (4:1), 40 °C then Bu_3SnH, Et_3B, air, CH_2Cl_2, −78 °C, 83% over two steps; (iii) $NaIO_4$, SiO_2, CH_2Cl_2, rt, 100% (crude); (iv) NaH, THF, 0 °C to rt, 63%.



Scheme 11. (i) KO^{t}Bu, DMSO, rt, 53%; (ii) DDQ, CH_2Cl_2–H_2O (19:1).

oxidative conditions (DDQ, phosphate buffer) failed, with only starting material being isolated (Scheme 11). To circumvent this problem, it was decided to remove the PMB group and effect oxidation to the lactone prior to the annulation step and hence conduct the Hauser–Kraus annulation with lactone instead of a protected lactol. Thus, oxidative removal of the PMB group in **35** with DDQ under buffered conditions furnished lactol **38** that underwent smooth PCC mediated oxidation to the lactone **39** (Scheme 12).

Gratifyingly, lactone **39** underwent smooth Hauser–Kraus annulation with phthalide **7** to give the non-aromatized product **40** in excellent yield as a single diastereomer. Aromatization could be successfully achieved upon exposure to boron trifluoride etherate followed by immediate trapping of the resulting unstable hydroquinone with acetic anhydride, affording the aromatized, stable monoacetate **41** in 53% yield over two steps after flash chromatography. Exposure of **41** to HF–pyridine gave an inseparable mixture of uncyclized (**42**) and cyclized *cis*-lactol (**43**) products in a 4:1 ratio as



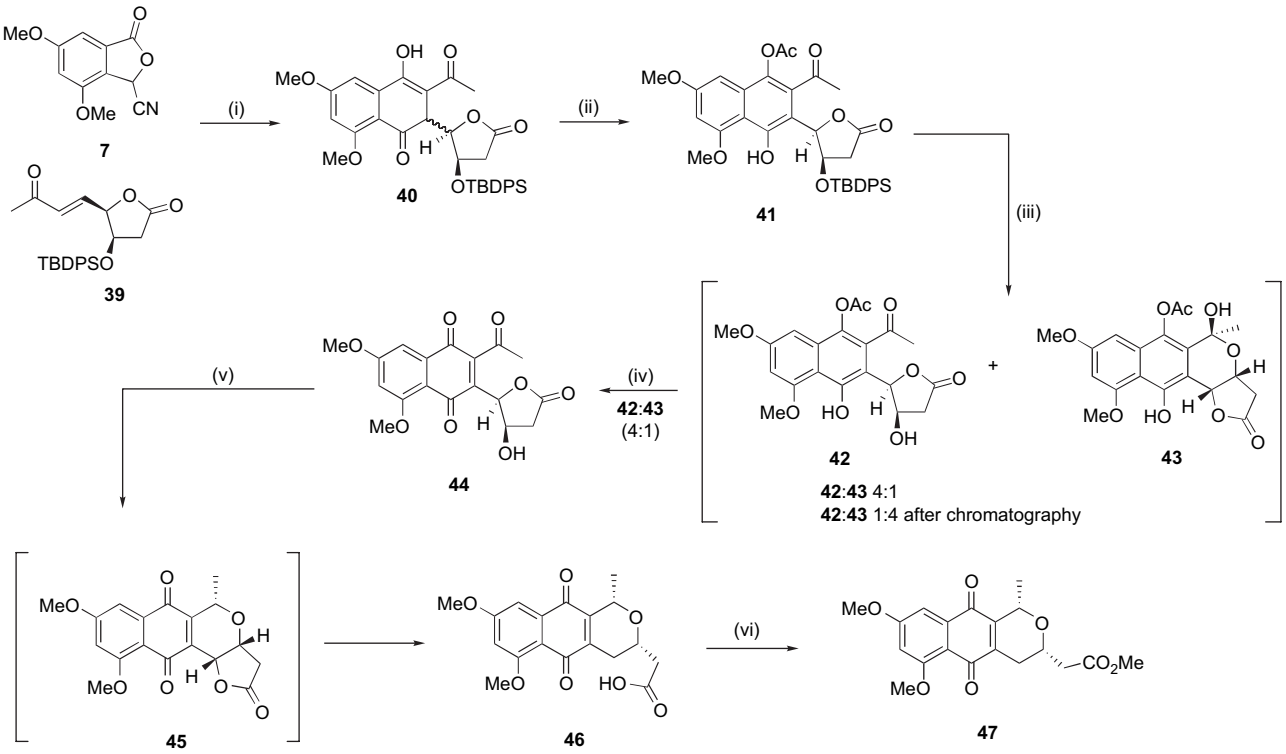
Scheme 12. (i) DDQ, CH_2Cl_2–H_2O (19:1), pH=7, 78% (*anti*/*syn*=56:44); (ii) PCC, NaOAc, MS 4 Å, 91%.

determined by ^{1}H NMR spectroscopy. Although silica gel chromatography did not allow separation of the two compounds, it did facilitate further cyclization of **42** to **43** giving a ratio of 1:4 in favour of the cyclized product **43**, as determined by ^{1}H NMR spectroscopy. The structure of **43** was also postulated to exist as a single cis-diastereomer from spectroscopic studies presumably as fluoride-induced deprotection of **41** liberates the hydroxyl group, which undergoes cyclization under thermodynamic control.[16a]

For the synthetic route to progress, CAN oxidation of the crude mixture of **42/43** (4:1, pre-silica treatment) was necessary, affording quinone **44** in 38% yield over two steps from monoacetate **41**. Cyclization of **44** and concomitant triethylsilane mediated reduction[16b] successfully reduced the intermediate lactol in a stereospecific manner, but unfortunately none of the desired product **45** was obtained. Rather, carboxylic acid **46** formed wherein ring opening of the lactone moiety had taken place. Attempted recyclization of acid **46** based on the literature precedent[17] using methanol and oxygen only afforded the methyl ester **47** (Scheme 13). Despite this, an enantioselective route to a monomer closely related to the crisamicins had been achieved.

At this stage, synthetic studies were directed towards the dimeric structure. Our attention therefore turned to the synthesis of the key biscyanophthalide **4**.

Thus, 3,5-dimethoxybenzoic acid was converted to the diethylamide **48**,[18] which was selectively monodeprotected with boron tribromide at high dilution in dichloromethane. The resulting phenol **49** was then readily converted to triflate **50**. After much optimization, it was found that treatment of a dioxane solution of triflate **50** with precisely 0.5 equiv of bis(pinacolato)diboron, freshly ground dried potassium carbonate under Pd(dppf)Cl_2 catalysis at 100 °C for 3 h resulted



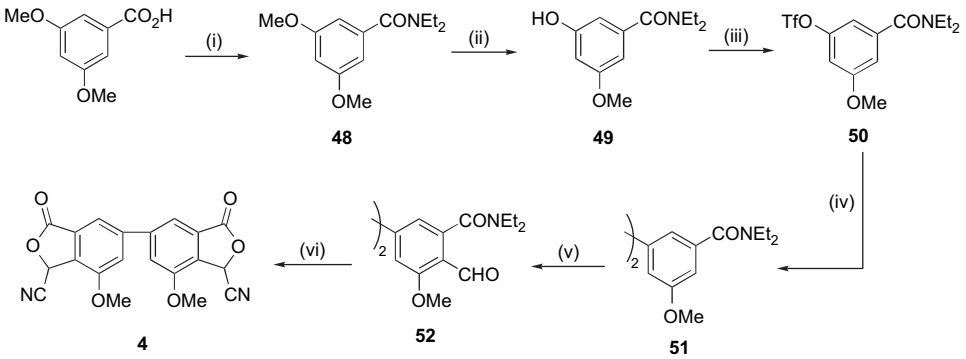
Scheme 13. (i) KO^{t}Bu, DMSO, rt, 80%; (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C to 0 °C then Ac_2O, py, −10 °C to rt, 53% over two steps; (iii) HF·Py, THF, rt, then SiO_2 (**42**/**43**=4:1); (iv) CAN, MeCN−H_2O (2:1), 38% from **41**; (v) $BF_3{\cdot}Et_2O$ (10 equiv), Et_3SiH (10 equiv), CH_2Cl_2, −78 °C to rt, 63%; (vi) MeOH, O_2, dark, 32%.

in a quantitative yield of the homocoupled product **51** in a one-pot, one-step operation. Next, the combined directing ability of the methoxy and the diethylamide functionalities facilitated dilithiation followed by treatment with dimethylformamide to afford the bisformyl derivative **52** in excellent yield. Subsequent biscyanophthalide formation then gave **4**, also in good yield (Scheme 14).

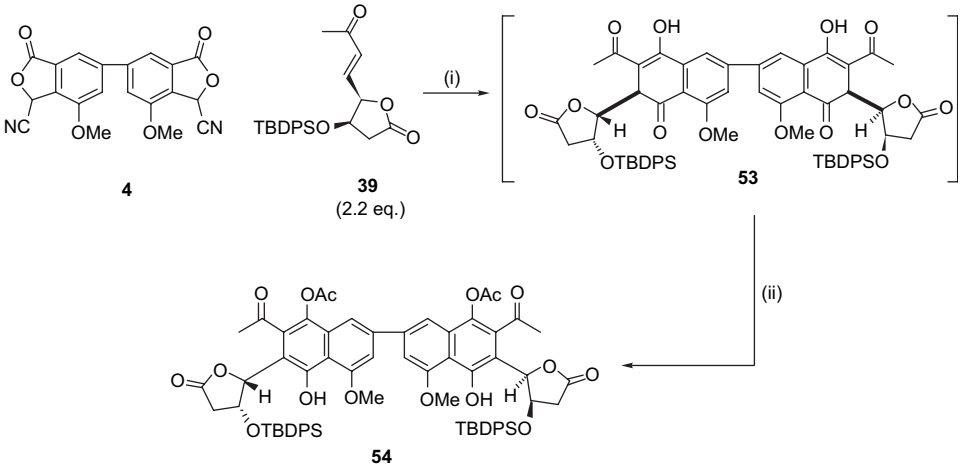
Finally, attention focused on the key double Hauser−Kraus annulation, based on the successful model annulation between monomeric cyanophthalide **7** and enone **39**. Thus, the dianion of biscyanophthalide **4** generated with excess potassium *tert*-butoxide was treated with 2 equiv of enone **39** providing the highly unstable adduct **53** that was immediately subjected to our established acetylation protocol, gratifyingly providing diacetate **54**, albeit in 23% yield over the two steps. To the best of our knowledge, this result represents the first successful double Hauser−Kraus annulation using an acylic Michael acceptor (Scheme 15).

2. Conclusions

The synthesis of an advanced intermediate **54** that provides an excellent basis for an asymmetric total synthesis of crisamicin A has been achieved. Key steps included construction of the biaryl bond using a one-pot, one-step Suzuki−Miyaura homocoupling and a double Hauser−Kraus annulation between a biscyanophthalide **4** and a carbohydrate (mannose) derived acyclic enone **39**. Difficulties encountered in performing



Scheme 14. (i) $SOCl_2$, CH_2Cl_2, rt, 16 h then $HNEt_2$, CH_2Cl_2, 0 °C to rt, 2 h, 71%; (ii) BBr_3, CH_2Cl_2, −78 °C, 1 h, 72%; (iii) $PhN(OTf)_2$, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 89%; (iv) $Pd(dppf)Cl_2$, dppf, K_2CO_3, bis(pinacolato)diboron, dioxane, 100 °C, 3 h, 100%; (v) ^{t}BuLi (4 equiv), TMEDA, THF, −78 °C, then DMF, rt, 16 h, 92%; (vi) TMS-CN, KCN, 18-c-6, CH_2Cl_2, 0 °C, 2 h then AcOH, rt, 16 h, 81%.



Scheme 15. (i) KO^{t}Bu, DMSO, rt; (ii) $BF_3 \cdot Et_2O$, CH_2Cl_2, −78 °C to 0 °C then Ac_2O, py, −10 °C to rt, 23% over two steps.

the double annulation reaction on a large scale and good yield have so far prevented the conversion of biaryl **54** to crisamicin A and work towards this end is ongoing.

3. Experimental

3.1. 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, respectively. 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 is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint., quintet), coupling constant (J in hertz) 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.

*3.1.1. 3-Cyano-5,7-dimethoxy-(3H)-isobenzofuran-1-one (**7**)[11]*

N,*N*-Diethyl 2,4-dimethoxy-6-formylbenzamide **6** (234 mg, 0.87 mmol) was taken up in dichloromethane (5 mL) and cooled to 0 °C. Trimethylsilyl cyanide (0.13 mL, 1.1 equiv, 0.95 mmol) was added followed by potassium cyanide (6 mg, 0.1 equiv, 0.09 mmol) and 18-crown-6 (10 mg). The reaction mixture was stirred at 0 °C for 1.5 h then at room temperature for 30 min. The reaction mixture was concentrated in vacuo and the residue taken up in acetic acid (5 mL) and stirred at room temperature for 16 h. Sodium hydroxide (1 M, 10 mL) was added, followed by ethyl acetate (20 mL). The layers were separated and the aqueous layer extracted with ethyl acetate (3×20 mL). 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* **7** as a colourless solid (330 mg, 66%), mp 132−133 °C (lit.[11] 134−135 °C). δ_H (300 MHz, $CDCl_3$) 6.66 (1H, d, J 1.7, CH), 6.54 (1H, d, J 1.7, CH), 5.91 (1H, s, CH), 3.98 (3H, s, OMe), 3.94 (3H, s, OMe). Spectroscopic data consistent with the literature.[11]

*3.1.2. (3aS,4S,6R,6aS)-6-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]-dioxol-4-ol (**10**)[14]*

To a suspension of D-mannose (15 g, 83.3 mmol) in acetone (0.75 L) was added iodine (4.3 g, 16.8 mmol) and the mixture was stirred for 2 h at room temperature. The reaction mixture was quenched at 0 °C with sodium thiosulfate (200 mL) and sodium bicarbonate (200 mL) then extracted with chloroform (500 mL). After three washings with sodium bicarbonate, the organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo to give the *title compound* as a pale yellow solid (19.2 g, 89%), which was used without further purification in the next step. δ_H (400 MHz, $CDCl_3$) 5.38 (1H, d, J 2.4, CH), 4.81 (1H, dd, J 6.0, 3.6, CH), 4.62 (1H, d, J 6.0, CH), 4.40−4.38 (1H, m, CH), 4.18 (1H, dd, J 7.2, 3.6, CH), 4.06−3.99 (2H, m, CH_2), 2.57 (1H, br s, CH), 1.46 (3H, s,

Me), 1.45 (3H, s, Me), 1.38 (3H, s, Me), 1.32 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 112.4, 108.9, 100.9, 85.3, 79.9, 79.5, 73.2, 66.3, 26.7, 25.8, 25.1. 24.4. Spectroscopic data consistent with the literature.[14]

3.1.3. (3aS,4R,6R,6aS)-4-Chloro-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]-dioxole (**11**)[14]

To a solution of bisacetonide **10** (6.5 g, 25.0 mmol) in dichloromethane (150 mL) were added successively at room temperature, DMAP (1.83 g, 15.0 mmol), tosyl chloride (5.72 g, 30.0 mmol) and triethylamine (3.5 mL, 25.0 mmol). After 3 h stirring at room temperature, the solution was hydrolyzed with sodium bicarbonate (100 mL) and then extracted with diethyl ether (3×100 mL). The combined organic layers were washed with saturated copper sulfate (100 mL) and brine (2×50 mL), dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale yellow oil. Purification by flash chromatography on silica gel eluting with hexanes–ethyl acetate (9:1) gave the *title compound* as a viscous amber-coloured oil (4.3 g, 62%). δ_H (400 MHz, $CDCl_3$) 6.07 (1H, s, CH), 4.96 (1H, d, *J* 5.6, CH), 4.89–4.87 (1H, m, CH), 4.44–4.40 (1H, m, CH), 4.21 (1H, dd, *J* 11.2, 3.6, CH), 4.10 (1H, dd, *J* 8.8, 6.0, CH), 4.02 (1H, dd, *J* 8.8, 4.4, CH), 1.47 (3H, s, Me), 1.46 (3H, s, Me), 1.39 (3H, s, Me), 1.33 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 113.2, 109.4, 97.5, 89.1, 82.3, 78.5, 72.3, 66.7, 27.0, 25.9, 25.2, 24.7. Spectroscopic data consistent with the literature.[14]

3.1.4. (R)-4-((2S,3R)-3-(Benzyloxy)-2,3-dihydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**12**)[14]

To a solution of naphthalene (5.93 g, 46.3 mmol) in dry THF (300 mL) were added at room temperature small pieces of sodium (3.55 g, 154.3 mmol) previously dipped in methanol and rinsed with diethyl ether. After 20 min the solution turned deep green and the stirring was continued for 1.5 h. A solution of compound **11** (4.3 g, 15.4 mmol) in dry THF (50 mL) was then added at 0 °C over 5 min. The reaction mixture was allowed to warm up to room temperature and after stirring for 10 min, the mixture was carefully hydrolyzed with water (25 mL) then poured into diethyl ether (300 mL). After washing with brine, dried using $MgSO_4$, filtered and concentrated in vacuo afforded the crude alcohol as a pale yellow oil for use directly in the next step without further purification. To a suspension of sodium hydride (95%, 507 mg, 20.1 mmol) in THF (20 mL) was added at 0 °C a solution of the crude alcohol (15.4 mmol) in THF (30 mL). After 15 min at 0 °C, benzyl bromide (2.4 mL, 20.1 mmol) and tetrabutylammonium iodide (285 mg, 0.77 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was hydrolyzed with water and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with hexanes–ethyl acetate (95:5→4:1) to afford the *title compound* as a pale yellow oil (3.44 g, 62% over two steps from **11**). δ_H (400 MHz, $CDCl_3$) 7.32–7.24 (5H, m, Ar–H), 6.62 (1H, d, *J* 2.4, CH), 5.29 (1H, t, *J* 2.8, CH), 4.66–4.62 (1H, m, CH), 4.55–4.46 (3H, m, 3×CH), 4.44 (1H, dd, *J* 5.2, 4.4, CH), 4.12–4.09 (1H, m, CH), 3.99–3.94 (1H, m, CH), 1.47 (3H, s, Me), 1.40 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 150.3, 138.2, 128.1, 127.4, 127.3, 108.5, 101.7, 83.9, 79.1, 73.0, 70.9, 65.9, 26.6, 25.3. Spectroscopic data consistent with the literature.[14]

3.1.5. (E,1S,2R)-2-(Benzyloxy)-4-methoxy-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**14**)

To a solution of glycal **12** (100 mg, 0.36 mmol) in a mixture of THF–methanol (1:1, 4 mL) was added mercury diacetate (138 mg, 0.43 mmol) at room temperature. After 2.5 h the mixture was diluted with diethyl ether and treated with 2.5 M aqueous potassium iodide (10 mL). The mixture was decanted and the organic layer was washed with saturated sodium thiosulfate, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with hexanes–ethyl acetate (8:2) to give the recovered starting material **12** (77 mg, 77%) and the *title compound* as a colourless oil (17 mg, 15%). ν_{max} (film) 3160, 2963, 1699, 1450, 1354, 1283, 1167, 1110, 741 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30–7.26 (5H, m, Ar–H), 6.56 (1H, d, *J* 12.8, H-4), 4.85 (1H, dd, *J* 12.8, 9.5, H-3), 4.63 (1H, d, *J* 11.8, OCH_AH_BPh), 4.37 (1H, d, *J* 11.8, OCH_AH_BPh), 4.16 (1H, q, *J* 6.4, H-4′), 4.04 (1H, dd, *J* 8.4, 6.2, H_AH_B-5′), 3.98 (1H, dd, *J* 8.4, 6.3, H_AH_B-5′), 3.87 (1H, dd, *J* 9.5, 3.5, H-2), 3.59 (3H, s, OMe), 3.57 (1H, dt, *J* 7.0, 3.5, H-1), 2.47 (1H, d, *J* 7.4, O*H*), 1.40 (3H, s, C2′-C_AH_3), 1.35 (3H, s, C2′-C_BH_3); δ_C (100 MHz, $CDCl_3$) 152.0, 138.3, 128.4 (2C), 127.8 (2C), 127.6, 109.0, 99.2, 76.4, 75.8, 75.6, 69.2, 66.3, 56.0, 26.7, 25.5; *m/z* (CI, NH_3) 309 (MH^+, 1), 219 (10), 201 (40), 169 (25), 143 (13), 128 (29), 127 (45), 111 (41), 108 (29), 101 (100), 91 (41), 73 (38), 71 (15); HRMS (CI) MH^+; found: 309.1696. $C_{17}H_{25}O_5$ requires: 309.1702.

3.1.6. (R)-4-((2R,3S,4R,5R)-3-(Benzyloxy)-4-bromotetrahydro-5-methoxyfuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**16**)

To a solution of glycal **12** (297 mg, 1.09 mmol) and methanol (0.44 mL, 10.9 mmol) in acetonitrile (5 mL) was added *N*-bromosuccinimide (204 mg, 1.14 mmol) at 0 °C. The solution was stirred for 1 h at room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane (15 mL), washed with saturated sodium thiosulfate, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes–ethyl acetate (9:1) to give the *title compound* as a colourless oil (293 mg, 69%, dr 92:8). *Major diastereomer*: ν_{max} (film) 2978, 2929, 1450, 1368, 1251, 1209, 1152, 1109, 1049, 957, 851, 737 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar–H), 5.17 (1H, s, H-5′), 4.71 (1H, d, *J* 12.0, OCH_AH_BPh), 4.56 (1H, d, *J* 12.0, OCH_AH_BPh), 4.51 (1H, dd, *J* 6.1, 5.0, H-2′), 4.39 (1H, q, *J* 6.3, H-4), 4.19 (1H, dd, *J* 4.8, 0.8, H-3′), 4.13 (1H, s, H-4′), 4.10 (1H, dd, *J* 8.6, 6.3, H_AH_B-5), 4.05 (1H, dd, *J* 8.6, 6.3, H_AH_B-5), 3.41 (3H, s, OMe), 1.45 (3H, s, C2-C_AH_3), 1.38 (3H, s, C2-C_BH_3); δ_C (100 MHz, $CDCl_3$) 137.3, 128.4 (2C),

127.9, 127.8 (2C), 110.7, 108.8, 83.8, 82.0, 73.8, 72.3, 66.8, 55.9, 50.1, 26.7, 25.4; *m/z* (CI, NH_3) 389 (MH^+, 4), 387 (MH^+, 4), 316 (7), 315 (7), 299 (13), 297 (13), 173 (26), 149 (22), 132 (12), 111 (13), 108 (27), 101 (59), 91 (100); HRMS (CI) MH^+; found: 389.0790, 387.0812. $C_{17}H_{24}^{81}BrO_5$, $C_{17}H_{24}^{79}BrO_5$ requires: 389.0787, 387.0807.

*3.1.7. (R)-1-(2R,3R,5R)-3-(Benzyloxy)tetrahydro-5-methoxyfuran-2-yl-ethane-1,2-diol (**17**)*

Compound **16** (304 mg, 0.78 mmol) was stirred for 16 h at room temperature in 60% aqueous acetic acid (25 mL). Azeotropic removal of the acetic acid with toluene under reduced pressure gave the crude bromo-diol as a colourless oil. The residue was dissolved in methanol (3 mL), then treated with triethylamine (0.15 mL) and Pd/C 10% (83 mg, 0.078 mmol). The mixture was vigorously stirred under a hydrogen atmosphere (1 atm) for 20 h, then filtered through a pad of Celite® and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes–ethyl acetate (1:1) to give the *title compound* as a colourless oil (130 mg, 62%) for use immediately in the next step. ν_{max} (film) 3413, 2920, 1494, 1450, 1353, 1208, 1038, 941, 735, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.39–7.29 (5H, m, Ar–H), 5.00 (1H, dd, *J* 4.8, 3.2, H-5′), 4.71 (1H, d, *J* 11.6, OCH_AH$_B$Ph), 4.41 (1H, d, *J* 11.6, OCH$_A$$H_B$Ph), 4.33 (1H, dt, *J* 5.8, 4.0, H-1), 4.07–4.01 (2H, m, H-2′ and H-3′), 3.85 (1H, dd, *J* 11.2, 2.8, H_AH$_B$-2), 3.72 (1H, dd, *J* 11.2, 5.2, H$_A$$H_B$-5), 3.37 (3H, s, OMe), 3.19 (1H, br s, O*H*), 2.23–2.04 (3H, m, H-4′ and O*H*); δ_C (100 MHz, $CDCl_3$) 137.2, 128.7 (2C), 128.1, 127.8 (2C), 105.0, 80.1, 78.2, 71.7, 70.8, 64.3, 55.5, 37.3; *m/z* (CI, NH_3) 286 ($M+NH_4^+$, 11), 254 (100), 237 (27), 129 (15), 111 (38), 108 (20), 100 (19), 91 (53); HRMS (CI) $M+NH_4^+$; found: 286.1650. $C_{14}H_{24}NO_5$ requires: 286.1655.

*3.1.8. (E)-4-((2R,3R,5R)-3-(Benzyloxy)tetrahydro-5-methoxyfuran-2-yl)but-3-en-2-one (**19**)*

To a suspension of silica gel (0.75 g) in dichloromethane (12.5 mL) previously treated with a 0.65 M aqueous solution of sodium periodate (1.6 mL, 1.04 mmol) was added a solution of diol **17** (100 mg, 0.37 mmol) in dichloromethane (3.5 mL). After 20 min at room temperature the suspension was filtered and concentrated to give the crude intermediate aldehyde **18** as a pale yellow oil. Then, to a suspension of sodium hydride (11 mg, 0.44 mmol, 95% dispersion in mineral oil) in THF (1 mL) was added dropwise at 0 °C a solution of diethyl (2-oxopropyl)phosphonate (86 mg, 0.44 mmol) in THF (3 mL). When the base had dissolved and the evolution of gas had ceased, a solution of crude aldehyde **18** (0.37 mmol) in THF (3 mL) was added. The cooling bath was removed and the solution was stirred for 2 h at room temperature, then diluted with diethyl ether, washed successively with ammonium chloride, brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale yellow oil. Purification by flash chromatography eluting with hexanes–ethyl acetate (3:2) gave the *title compound* as a colourless oil (61 mg, 60%). $[\alpha]_D^{25}$ +26.7 (*c* 1.3, CH_2Cl_2); ν_{max} (film) 2907, 1670, 1631, 1450, 1358, 1251, 1209, 1102, 1028, 978, 943, 737, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ar–H), 6.93 (1H, dd, *J* 16.4, 6.2, H-4), 6.29 (1H, dd, *J* 16.0, 1.6, H-3), 5.08 (1H, dd, *J* 5.6, 2.4, H-5′), 4.63 (1H, dt, *J* 6.0, 1.2, H-2′), 4.54 (1H, d, *J* 12.8, OCH_AH$_B$Ph), 4.46 (1H, d, *J* 12.8, OCH$_A$$H_B$Ph), 4.21–4.17 (1H, m, H-3′), 3.46 (3H, s, OMe), 2.30 (3H, s, H-1), 2.30–2.14 (2H, m, H-4′); δ_C (100 MHz, $CDCl_3$) 198.5, 143.9, 137.6, 131.8, 128.4 (2C), 127.8, 127.6 (2C), 105.2, 81.3, 78.3, 71.7, 55.9, 38.3, 26.9; *m/z* (EI) 276 (M^+, 1), 190 (17), 146 (10), 99 (18), 92 (17), 91 (100), 87 (70), 65 (11), 59 (64), 43 (16); HRMS (EI) M^+; found: 276.1362. $C_{16}H_{20}O_4$ requires: 276.1362.

*3.1.9. 3-Acetyl-2-((2R,3R,5R)-3-(benzyloxy)tetrahydro-5-methoxyfuran-2-yl)-4-hydroxy-6,8-dimethoxynaphthalen-1(2H)-one (**20**)*

To a solution of 1,3-dihydro-5,7-dimethoxy-3-oxoisobenzofuran-1-carbonitrile **7** (26 mg, 0.121 mmol) and enone **19** (40 mg, 0.145 mmol) in DMSO (5 mL) was added dropwise a solution of potassium *tert*-butoxide (19 mg, 0.157 mmol) in DMSO (3 mL). After 30 min the orange solution was cooled in an ice bath, diluted with diethyl ether (5 mL) and quenched with saturated ammonium chloride. The mixture was decanted and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography eluting with hexanes–ethyl acetate (6:4→4:6) gave the *title compound* as a yellow oil (44 mg, 78%, dr=65:35). *Major diastereomer*: ν_{max} (film) 2919, 2843, 1784, 1680, 1587, 1337, 1240, 1216, 1160, 1087, 1052, 941, 733 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.51–7.49 (2H, m, Ar–H), 7.37–7.26 (3H, m, Ar–H), 7.23 (1H, d, *J* 2.4, H-5), 6.60 (1H, d, *J* 2.4, H-7), 4.92 (1H, dd, *J* 6.5, 1.3, H-5′), 4.70 (2H, s, OCH_2Ph), 4.44 (1H, d, *J* 9.1, H-2), 4.00–3.88 (2H, m, H-2′ and H-3′), 3.93 (3H, s, Ar–OMe), 3.90 (3H, s, Ar–OMe), 3.34 (3H, s, C5′-OMe), 2.41 (3H, s, COMe), 2.25–2.00 (2H, m, H_2-4′); δ_C (100 MHz, $CDCl_3$) 201.3, 194.9, 167.7, 164.9, 161.1, 138.4, 128.24, 128.17 (2C), 127.9 (2C), 127.4, 114.9, 108.1, 104.9, 102.4, 101.6, 83.2, 76.1 (2C), 71.6, 56.2, 55.9, 48.6, 38.0, 30.3, 26.1; *m/z* (EI) 468 (M^+, 2), 273 (15), 268 (12), 262 (41), 91 (100), 87 (23), 59 (24), 43 (16); HRMS (EI) M^+; found: 468.1779. $C_{26}H_{28}O_8$ requires: 468.1784.

Minor diastereomer (C2 epimer): δ_H (400 MHz, $CDCl_3$) 7.40–7.22 (5H, m, Ar–H), 7.07 (1H, d, *J* 2.3, H-5), 6.63 (1H, d, *J* 2.3, H-7), 4.93 (1H, dd, *J* 5.7, 2.4, H-5′), 4.45 (1H, d, *J* 11.8, OCH_AH$_B$Ph), 4.16 (1H, d, *J* 11.8, OCH$_A$$H_B$Ph), 4.08–3.88 (3H, m, H-2, H-2′ and H-3′), 3.93 (3H, s, Ar–OMe), 3.90 (3H, s, Ar–OMe), 3.37 (3H, s, C5′-OMe), 2.22 (3H, s, COMe), 2.20–2.03 (2H, m, H_2-4′).

*3.1.10. (R)-4-((2S,3R)-3-(tert-Butyldiphenylsilyloxy)-2,3-dihydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**23**)*

To a solution of naphthalene (7.12 g, 55.6 mmol) in dry THF (350 mL) were added at room temperature small pieces of sodium (4.26 g, 185.2 mmol) previously dipped in methanol and rinsed with diethyl ether. After 20 min the solution turned deep green and stirring was continued for 1.5 h. A solution of compound **11** (5.2 g, 18.7 mmol) in dry THF (50 mL) was

then added at 0 °C over 5 min. The temperature was then allowed to warm to room temperature and after 10 min the mixture was carefully hydrolyzed with water (50 mL) then poured into diethyl ether (300 mL). After washing with brine, drying over $MgSO_4$, filtration and concentration in vacuo the crude alcohol was afforded as a pale yellow oil for use directly in the next step without further purification. To a solution of the crude alcohol (18.7 mmol) in dichloromethane (190 mL) was added at 0 °C imidazole (1.66 g, 24.4 mmol) and TBDPSCl (6.4 mL, 24.4 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The solution was poured into water (200 mL) and extracted with dichloromethane (3×100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale yellow oil. The residue was purified by flash chromatography eluting with hexanes–ethyl acetate (9:1) to afford the *title compound* as a colourless oil (3.25 g, 59% over two steps from **11**). $[\alpha]_D^{25}$ −53.3 (*c* 0.92, $CHCl_3$); ν_{max} (film) 2927, 2855, 1606, 1425, 1367, 1255, 1212, 1147, 1103, 1064, 941, 847, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.72–7.62 (4H, m, Ar–H), 7.44–7.38 (6H, m, Ar–H), 6.46 (1H, d, *J* 2.7, H-5′), 4.96 (1H, ddd, *J* 7.0, 2.7, 0.6, H-4′), 4.69–4.64 (2H, m, H-4 and H-2′), 4.29 (1H, dd, *J* 6.8, 5.1, H-3′), 4.22 (1H, dd, *J* 8.4, 6.8, H_AH_B-5), 4.08 (1H, dd, *J* 8.4, 6.3, H_AH_B-5), 1.48 (3H, s, C2-C_AH_3), 1.39 (3H, s, C2-C_BH_3), 1.06 (9H, s, $OSiMe_3$); δ_C (100 MHz, $CDCl_3$) 149.3, 135.94 (2C), 135.90 (2C), 134.1, 133.2, 129.8, 129.7, 127.7 (2C), 127.5 (2C), 108.7, 104.6, 84.7, 74.2, 73.2, 66.1, 26.9 (3C), 26.5, 25.0, 19.2; *m/z* (CI, NH_3) 425 (MH^+, 1), 309 (22), 241 (21), 216 (20), 199 (31), 169 (22), 128 (30), 111 (69), 101 (100), 94 (36), 78 (57), 72 (19); HRMS (CI) MH^+; found: 425.2151. $C_{25}H_{33}O_4Si$ requires: 425.2148.

*3.1.11. (R)-4-((2R,3S,4R,5R)-3-(tert-Butyldiphenylsilyloxy)-4-bromotetrahydro-5-methoxyfuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**24**)*

To a solution of glycal **23** (1.98 g, 4.66 mmol) and methanol (1.9 mL, 47.1 mmol) in acetonitrile (20 mL) was added *N*-bromosuccinimide (880 mg, 4.95 mmol) at 0 °C. The solution was stirred for 1.5 h at room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane (30 mL), washed with saturated sodium thiosulfate and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a mixture of two diastereomers (84:16). The residue was purified by flash chromatography on silica gel eluting with hexanes–ethyl acetate (9:1) to give the *title compound* as a colourless oil that solidified on standing (1.23 g, 97%, dr=82:16). *Major diastereomer*: mp 75–80 °C, $[\alpha]_D^{25}$ +4.3 (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$) 2985, 2929, 2855, 1638, 1468, 1425, 1379, 1368, 1205, 1109, 1049, 943, 968 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.76–7.73 (4H, m, Ar–H), 7.43–7.39 (6H, m, Ar–H), 5.01 (1H, s, H-5), 4.56 (1H, d, *J* 4.5, H-3), 4.54 (1H, dt, *J* 7.2, 6.4, H-4′), 4.38 (1H, dd, *J* 7.2, 4.5, H-2), 4.20 (1H, dd, *J* 8.4, 6.4, H_AH_B-5′), 4.10 (1H, dd, *J* 8.4, 6.2, H_AH_B-5′), 3.57 (1H, s, H-4), 3.34 (3H, s, C5-OMe), 1.47 (3H, s, C2′-C_AH_3), 1.38 (3H, s, C2′-C_BH_3), 1.11 (9H, s, $OSiMe_3$); δ_C (100 MHz, $CDCl_3$) 136.1 (2C), 136.0 (2C), 133.6, 132.5, 130.0, 129.9, 127.8 (2C), 127.6 (2C), 110.3, 109.0, 83.5, 78.7, 73.5, 67.4, 55.1, 53.4, 26.8 (3C), 26.7, 25.4, 19.2; *m/z* (CI, NH_3) 554 ($M+NH_4^+$, 1), 552 ($M+NH_4^+$, 1), 521 (10), 519 (10), 505 (12), 503 (12), 447 (70), 445 (70), 423 (54), 237 (55), 230 (29), 213 (38), 199 (44), 183 (23), 135 (23), 101 (100), 78 (51); HRMS (CI) $M+NH_4^+$; found: 554.1780, 552.1769. $C_{26}H_{39}^{81}BrNO_5Si$ requires: 554.1760, $C_{26}H_{39}^{79}BrNO_5Si$ requires: 552.1781.

*3.1.12. (R)-1-((2R,3R,5R)-3-(tert-Butyldiphenylsilyloxy)-5-methoxytetrahydrofuran-2-yl-1,2-diol (**25**)*

Bromide **24** (1.85 g, 3.45 mmol) was stirred for 16 h at room temperature in 75% aqueous acetic acid (160 mL) and then for 3 h at 40 °C under reduced pressure (300 mbar). Azeotropic removal of the acetic acid with toluene under reduced pressure gave the crude bromo-diol as a colourless oil. The residue was dissolved in methanol (15 mL), and then treated with triethylamine (0.62 mL, 4.42 mmol) and 10% Pd/C (360 mg, 0.34 mmol). The mixture was stirred vigorously under a hydrogen atmosphere (1 atm) for 4 days, then filtered through a pad of Celite® and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes–ethyl acetate (1:1) to give the *title compound* as a colourless oil (326 mg, 23%). ν_{max} (film) 3427, 2987, 2857, 1474, 1419, 1399, 1208, 1009, 950, 719, 694 cm^{-1} $[\alpha]_D^{25}$ −37.7 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.72–7.66 (4H, m, Ar–H), 7.66–7.39 (6H, m, Ar–H), 4.73 (1H, dd, *J* 5.6, 4.0, H-5), 4.56 (1H, q, *J* 6.9, H-3), 4.24–4.19 (1H, m, H-1′), 3.95 (1H, dd, *J* 9.0, 6.2, H-2), 3.91–3.87 (1H, m, H_AH_B-2′), 3.81–3.77 (1H, m, H_AH_B-2′), 3.53 (1H, d, *J* 2.8, O*H*), 3.32 (3H, s, C5-OMe), 2.43 (1H, br s, O*H*), 1.87 (1H, ddd, *J* 13.8, 7.5, 5.6, H_AH_B-4), 1.81 (1H, ddd, *J* 13.8, 6.9, 4.0, H_AH_B-4), 1.25 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 135.9 (2C), 135.5 (2C), 132.7, 132.1, 130.21, 130.17, 128.0 (2C), 127.8 (2C), 104.5, 78.8, 73.6, 70.7, 64.1, 55.6, 39.5, 26.8 (3C), 19.0; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 439 ($M+Na^+$, 12), 416 (M^+, 40), 387 (11), 223 (23), 203 (47), 199 (60), 197 (57), 137 (57); HRMS (FAB^+) M^+; found: 416.2007. $C_{23}H_{32}O_5Si$ requires: 416.2019.

*3.1.13. (E)-4-((2R,3R,5R)-3-(tert-Butyldiphenylsilyloxy)-5-methoxytetrahydrofuran-2-yl)but-3-en-2-one (**27**)*

To a suspension of silica gel (1.5 g) in dichloromethane (11 mL) previously treated with sodium periodate (0.65 M, 1.5 mL, 1.0 mmol) was added a solution of diol **25** (310 mg, 0.744 mmol) in dichloromethane (7 mL). After 3 h at room temperature the suspension was filtered and concentrated to give the crude intermediate aldehyde **26** as a pale yellow oil. Then, to a suspension of sodium hydride (95%, 23 mg, 0.89 mmol) in THF (2 mL) was added dropwise at 0 °C a solution of diethyl (2-oxopropyl)phosphonate (173 mg, 0.89 mmol) in THF (5 mL). When the base had dissolved and gas evolution had ceased, a solution of crude aldehyde **26** (0.744 mmol) in THF (5 mL) was added. The cooling bath was removed and the solution was stirred for 2.5 h at room temperature and then diluted with diethyl ether. The organic phase was washed successively with saturated ammonium chloride and brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale

yellow oil. Purification by flash chromatography eluting with hexanes–ethyl acetate (4:1) gave the *title compound* as a colourless oil (230 mg, 73%). $[\alpha]_D^{25}$ +15.7 (*c* 1.0, $CHCl_3$); ν_{max} 2926, 2857, 1673, 1424, 1361, 1254, 1108, 1032, 976, 737, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.65–7.60 (4H, m, Ar–H), 7.44–7.36 (6H, m, Ar–H), 6.97 (1H, dd, *J* 16.2, 6.3, H-4), 6.21 (1H, dd, *J* 16.2, 1.2, H-3), 4.93 (1H, dd, *J* 5.7, 3.6, H-5′), 4.50 (1H, dt, *J* 7.0, 5.9, H-3′), 4.40 (1H, dt, *J* 6.3, 1.2, H-2′), 3.42 (3H, s, C5′-OMe), 2.26 (3H, s, COMe), 2.12 (1H, ddd, *J* 13.6, 7.0, 5.8, H_AH_B-4′), 1.94 (1H, ddd, *J* 13.6, 5.6, 3.6, H_AH_B-4′), 1.05 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 198.5, 144.8, 135.8 (2C), 135.7 (2C), 133.3, 133.1, 132.4, 130.0, 129.9, 127.8 (2C), 127.7 (2C), 104.9, 81.3, 73.4, 55.5, 40.5, 26.8 (3C), 26.6, 19.1; *m/z* (CI, NH_3) ($M+NH_4^+$, 442, 19), 394 (34), 393 (100), 375 (23), 289 (52), 216 (28), 196 (33), 153 (67), 137 (63), 78 (28); HRMS (CI) $M+NH_4^+$; found: 442.2398. $C_{25}H_{36}NO_4Si$ requires: 442.2414.

*3.1.14. 3-Acetyl-2-((2R,3R,5R)-3-(tert-butyldiphenylsilyloxy)-5-methoxy-tetrahydrofuran-2-yl)-4-hydroxy-6,8-dimethoxynaphthalen-1(2H)-one (**28**)*

To a solution of 1,3-dihydro-5,7-dimethoxy-3-oxoisobenzofuran-1-carbonitrile **7** (98 mg, 0.446 mmol) and enone **27** (227 mg, 0.534 mmol) in DMSO (20 mL) was added dropwise a solution of potassium *tert*-butoxide (65 mg, 0.58 mmol) in DMSO (10 mL). After 30 min the orange solution was cooled in an ice bath, diluted with diethyl ether and quenched with saturated ammonium chloride. The mixture was decanted and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (8:2) gave the *title compound* as a yellow oil (182 mg, 66%). $[\alpha]_D^{25}$ −35.6 (*c* 0.9, $CHCl_3$); ν_{max} (film) 2933, 2852, 1784, 1682, 1587, 1455, 1240, 1216, 1160, 1108, 1053, 952, 841, 699 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92–7.86 (4H, m, Ar–H), 7.45–7.35 (6H, m, Ar–H), 7.22 (1H, d, *J* 2.3, H-5), 6.57 (1H, d, *J* 2.3, H-7), 4.76 (1H, dd, *J* 6.5, 1.3, H-5′), 4.58 (1H, d, *J* 9.2, H-2), 4.18–4.16 (1H, m, H-3′), 3.91 (3H, s, Ar–OMe), 3.85 (3H, s, Ar–OMe), 3.76 (1H, dd, *J* 9.2, 3.2, H-2′), 3.33 (3H, s, C5′-OMe), 2.57 (3H, s, COMe), 1.90–1.85 (1H, m, H_AH_B-4′), 1.70 (1H, ddd, *J* 14.5, 6.4, 5.2, H_AH_B-4′H), 1.18 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 201.4, 194.5, 167.6, 164.7, 161.1, 138.3, 136.7 (2C), 136.6 (2C), 134.3, 132.6, 129.7, 129.4, 127.5 (2C), 127.2 (2C), 114.8, 108.0, 104.6, 102.4, 101.5, 82.8, 71.4, 56.2, 56.1, 55.8, 48.1, 40.6, 27.2 (3C), 26.4, 19.5; *m/z* (CI, NH_3) 616 (MH^+, 10), 584 (10), 507 (10), 465 (22), 268 (20), 200 (20), 199 (100), 135 (10), 77 (12); HRMS (CI) M^+; found: 616.2487. $C_{35}H_{40}O_8Si$ requires: 616.2493.

*3.1.15. (R)-4-((2R,3S,4R,5R)-4-Bromo-3-(tert-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**32**)*

To a solution of glycal **23** (3.19 g, 7.51 mmol) and *p*-methoxybenzyl alcohol (5.2 g, 37.6 mmol) in acetonitrile (32 mL) was added *N*-bromosuccinimide (1.40 g, 7.89 mmol) at 0 °C. The solution was stirred for 1.5 h at room temperature and the solvent was evaporated. The residue was dissolved in dichloromethane (50 mL), washed with saturated sodium thiosulfate and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash chromatography eluting with hexanes–ethyl acetate (9:1) to give the *title compound* as a colourless oil (3.49 g, 72%, dr=84:16). *Major diastereomer*: $[\alpha]_D^{25}$ −45.3 (*c* 3.1, CH_2Cl_2); ν_{max} (film) 2926, 2857, 1611, 1510, 1247, 1212, 1170, 1111, 1046, 941, 844, 817, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72–7.69 (4H, m, Ar–H), 7.42–7.25 (8H, m, Ar–H), 6.88 (2H, d, *J* 8.7, Ar–H), 5.20 (1H, s, H-5′), 4.67 (1H, d, *J* 11.3, C5′OCH_AH_BAr), 4.57–4.50 (2H, m, H-3′ and H-4), 4.42–4.37 (1H, m, H-2′), 4.40 (1H, d, *J* 11.3, C5′OCH_AH_BAr), 4.17 (1H, dd, *J* 8.5, 6.4, H_AH_B-5), 4.12 (1H, dd, *J* 8.5, 6.3, H_AH_B-5), 3.81 (3H, s, Ar-OMe), 3.67 (1H, s, H-4′), 1.46 (3H, s, C2CA_H_3), 1.36 (3H, s, C2CB_H_3), 1.04 (9H, s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 159.3, 136.14 (2C), 130.06 (2C), 133.6, 132.4, 129.9 (2C), 129.6 (2C), 129.5, 127.72 (2C), 127.66 (2C), 113.7 (2C), 109.0, 108.6, 83.7, 78.9, 73.6, 69.7, 67.4, 55.3, 53.9, 26.82 (3C), 26.76, 25.3, 19.3; *m/z* (EI) 642 (M^+, 1), 640 (M^+, 1), 627 ($M^{+\bullet}$–Me, <1), 625 ($M^{+\bullet}$–Me, <1), 199 (5), 149 (3), 122 (10), 121 (100), 101 (2). HRMS (EI) M^+; found: 642.1834, 640.1866. $C_{33}H_{41}^{81}BrO_6Si$ requires: 642.1835, $C_{33}H_{41}^{79}BrO_6Si$ requires: 640.1856.

*3.1.16. (R)-1-((2R,3R,5R)-3-(tert-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-ethane-1,2-diol (**33**)*

The bromide **32** (2.55 g, 4.00 mmol) was stirred for 7 h at 45 °C under reduced pressure (300 mbar) in 80% aqueous acetic acid (140 mL). Azeotropic removal of the acetic acid with toluene under reduced pressure gave the crude bromo-diol as a colourless oil that was used for the next step without further purification. To a solution of crude bromo-diol (3.81 mmol) in dichloromethane (200 mL) was added at −78 °C tributyltin hydride (1.54 mL, 5.72 mmol) and triethylborane (1.0 M in *n*-hexane, 0.8 mL, 0.76 mmol). Air was then injected into the solution with a needle (10 mL). The addition of triethylborane followed with air was repeated every 30 min (three times). The mixture was then allowed to warm to room temperature then treated with NaOH (1 M, 60 mL) and vigorously stirred for 2 h. The mixture was decanted and the aqueous layer extracted with dichloromethane (3×). The combined organic layers were washed with saturated ammonium chloride and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography eluting with hexanes–ethyl acetate to give the *title compound* as a colourless oil (597 mg, 83% over two steps from **32**). $[\alpha]_D^{25}$ −88.6 (*c* 1.4, CH_2Cl_2); ν_{max} (film) 3412, 2928, 2853, 1609, 1585, 1510, 1463, 1425, 1300, 1245, 1106, 1031, 817, 701 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.71–7.65 (4H, m, Ar–H), 7.68–7.34 (6H, m, Ar–H), 7.23 (2H, d, *J* 8.6, Ar–H), 6.86 (2H, d, *J* 8.6, Ar–H), 4.94 (1H, dd, *J* 5.6, 3.9, H-5′), 4.67 (1H, d, *J* 11.3, OCH_AH_BAr), 4.56 (1H, q, *J* 6.7, H-3′), 4.35 (1H, d, *J* 11.3, OCH_AH_BAr), 4.31–4.24 (1H, m, H-1), 3.98 (1H, dd, *J* 9.0, 6.1, H-2′), 3.96–3.76 (2H, m, CH_2), 3.78 (3H, s, ArOMe), 3.48 (1H, d, *J* 2.8, O*H*), 2.40–2.30 (1H, m, O*H*), 1.93 (1H,

ddd, *J* 13.9, 6.5, 4.0, H_AH_B-4′), 1.86 (1H, ddd, *J* 13.9, 7.5, 5.9, H_AH_B-4′), 1.07 (9H, s, $SiMe_3$); δ_C (75 MHz, $CDCl_3$) 159.2, 136.0 (2C), 135.6 (2C), 132.7, 132.1, 130.1 (2C), 129.5 (2C), 128.0 (2C), 127.8 (2C), 113.7 (2C), 102.4, 79.2, 73.7, 70.7, 69.7, 64.2, 55.2, 39.6, 26.9 (3C), 19.0; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 545 ($M+Na^+$, <1), 203 (4), 199 (8), 197 (8), 122 (100), 121 (100), 91 (4). HRMS (FAB^+), $M+Na^+$, found: 545.2342. $C_{30}H_{38}NaO_6Si$ requires: 545.2335.

*3.1.17. (E)-4-((2R,3R,5R)-5-(4-Methoxybenzyloxy)-3-(tert-butyldiphenylsilyloxy)tetrahydrofuran-2-yl)but-3-en-2-one (**35**)*

To a suspension of silica gel (2.3 g) in dichloromethane (18 mL) previously treated with sodium periodate (0.65 M, 2.3 mL, 1.5 mmol) was added a solution of diol **33** (597 mg, 1.14 mmol) in dichloromethane (10 mL). After 5 h at room temperature the suspension was filtered and concentrated to give the crude intermediate aldehyde **34** as a pale yellow oil. Then, to a suspension of sodium hydride (95%, 35 mg, 1.37 mmol) in THF (3 mL) was added dropwise at 0 °C a solution of diethyl (2-oxopropyl)phosphonate (266 mg, 1.37 mmol) in THF (8 mL). When all the base had dissolved and the evolution of gas had ceased, a solution of crude aldehyde **34** (1.14 mmol) in THF (8 mL) was added. The solution was stirred for 30 min at 0 °C and then diluted with diethyl ether. The organic phase was washed successively with saturated ammonium chloride and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography on silica gel eluting with hexanes–ethyl acetate (8:2) gave the *title compound* as a colourless oil (482 mg, 80%). $[\alpha]_D^{25}$ −4.6 (*c* 1.1, CH_2Cl_2); ν_{max} (film) 2929, 2851, 1677, 1609, 1514, 1425, 1358, 1248, 1109, 1024, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64–7.59 (4H, m, Ar–H), 7.44–7.25 (8H, m, Ar–H), 6.99 (1H, dd, *J* 16.2, 6.4, H-4), 6.88 (2H, d, *J* 8.6, Ar–H), 6.22 (1H, dd, *J* 16.2, 1.0, H-3), 5.13 (1H, dd, *J* 5.6, 3.4, H-5′), 4.78 (1H, d, *J* 11.3, OCH_AH_BAr), 4.49 (1H, br s, *J* 6.2, H-3′), 4.45 (1H, d, *J* 11.3, OCH_AH_BAr), 4.42 (1H, dt, *J* 6.3, 1.0, H-2′), 3.80 (3H, s, ArOMe), 2.21 (3H, s, H_3-C1), 2.17–2.10 (1H, m, H_AH_B-C4′), 2.04 (1H, ddd, *J* 13.7, 5.4, 3.4, H_AH_B-C4′), 1.03 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 198.5, 159.2, 144.8, 135.8 (2C), 135.7 (2C), 133.3, 133.0, 132.4, 130.0, 129.90, 129.86, 129.5 (2C), 127.8 (2C), 127.7 (2C), 113.7 (2C), 102.8, 81.6, 73.4, 69.5, 55.3, 40.7, 26.7 (3C), 26.6, 19.1; *m/z* (CI, NH_3) 548 ($M+NH_4^+$, <1), 216 (10), 199 (10), 196 (12), 139 (14), 137 (26), 122 (15), 121 (100), 78 (14); HRMS (CI) $M+NH_4^+$; found: 548.2824. $C_{32}H_{42}NO_5Si$ requires: 548.2832.

*3.1.18. 3-Acetyl-2-((2R,3R,5R)-3-(tert-butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)tetrahydrofuran-2-yl)-4-hydroxy-6,8-dimethoxynaphthalen-1(2H)-one (**36**)*

To a solution of 1,3-dihydro-5,7-dimethoxy-3-oxoisobenzofuran-1-carbonitrile **7** (54 mg, 0.25 mmol) and enone **35** (158 mg, 0.30 mmol) in DMSO (10 mL) was added dropwise a solution of potassium *tert*-butoxide (35 mg, 0.30 mmol) in DMSO (5 mL). After 30 min the orange solution was cooled in an ice bath, diluted with diethyl ether and quenched with saturated ammonium chloride. The mixture was decanted and the aqueous layer extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil. Purification by flash chromatography eluting with hexanes–ethyl acetate (8:2) gave the *title compound* as a yellow solid (96 mg, 53%). $[\alpha]_D^{25}$ −13.3 (*c* 1.3, CH_2Cl_2); ν_{max} ($CHCl_3$) 3390, 2929, 2851, 1787, 1680, 1585, 1510, 1457, 1425, 1336, 1241, 1212, 1159, 1106, 1035, 950, 819, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92 (2H, dd, *J* 7.7, 1.9, Ar–H), 7.85 (2H, dd, *J* 8.0, 1.2, Ar–H), 7.45–7.17 (9H, m, Ar–H), 6.90–6.88 (2H, m, Ar–H), 6.57 (1H, d, *J* 2.3, H-7′), 4.98 (1H, d, *J* 5.7, H-5′), 4.70 (1H, d, *J* 11.3, OCH_AH_BAr), 4.62 (1H, d, *J* 9.5, H-C2), 4.32 (1H, d, *J* 11.3, OCH_AH_BAr), 4.14 (1H, t, *J* 3.8, H-3′), 3.92 (3H, s, OCH_2Ar), 3.85–3.83 (6H, 2s, C6-OMe and C8-OMe), 3.76 (1H, dd, *J* 9.5, 3.1, H-2′), 2.59 (3H, s, COMe), 1.98 (1H, d, *J* 14.5, H_AH_B-C4′), 1.73 (1H, ddd, *J* 14.5, 6.7, 5.2, H_AH_B-4′), 1.16 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 201.6, 194.5, 167.5, 164.7, 161.1, 159.1, 138.2, 136.7 (2C), 136.6 (2C), 134.3, 132.4, 130.0, 129.7, 129.3 (3C), 127.6 (2C), 127.0 (2C), 114.8, 113.7 (2C), 108.1, 102.8, 102.4, 101.5, 83.1, 71.3, 70.4, 56.2, 55.8, 55.3, 48.2, 40.7, 27.2 (3C), 26.6, 19.5; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 722 ($M^{+\bullet}$, <1), 585 (2), 383 (9), 262 (5), 197 (4), 122 (11), 121 (100); HRMS (FAB^+) M^+; found: 722.2903. $C_{42}H_{46}O_9Si$ requires: 722.2911.

*3.1.19. (E)-4-((2R,3R)-3-(tert-Butyldiphenylsilyloxy)-5-hydroxy-tetrahydrofuran-2-yl)but-3-en-2-one (**38**)*

To a solution of **35** (25 mg, 0.05 mmol) in a mixture of dichloromethane (1 mL) and phosphate buffer (pH 7.4, 0.05 mL) was added DDQ (18 mg, 0.08 mmol). After stirring vigorously at room temperature for 2 h, the mixture was hydrolyzed with saturated sodium bicarbonate and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (3:2) gave the *title compound* as a colourless oil (15 mg, 78%), and as a mixture of two anomers (*anti*/*syn*, 56:44). ν_{max} (film) 3407, 2926, 2857, 1673, 1632, 1427, 1358, 1254, 1108, 1039, 976, 820, 740, 702 cm^{-1}; *m/z* (CI, NH_3) ($M+NH_4^+$, 4), 393 (10), 274 (31), 216 (71), 199 (62), 198 (23), 196 (100), 155 (23), 139 (59), 137 (84), 94 (26), 78 (51); HRMS (CI) $M+NH_4^+$; found: 428.2242. $C_{24}H_{34}NO_4Si$ requires: 428.2257.

anti: δ_H (400 MHz, $CDCl_3$) 7.62–7.60 (4H, m, Ar–H), 7.44–7.38 (6H, m, Ar–H), 6.78 (1H, dd, *J* 11.6, 5.7, H-4), 6.22 (1H, dd, *J* 16.1, 1.4, H-3), 5.68 (1H, dt, *J* 5.4, 3.1, H-5′), 4.70 (1H, dt, *J* 6.0, 4.7, H-3′), 4.62 (1H, dt, *J* 5.4, 1.4, H-2′), 2.83 (1H, d, *J* 3.2, O*H*), 2.20 (3H, s, C1), 2.16–2.09 (1H, m, H_AH_B-C4′), 1.93 (1H, ddd, *J* 13.8, 6.0, 2.8, H_AH_B-C4′), 1.05 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 198.2, 143.3, 135.71 (2C), 135.69 (2C), 133.3, 132.9, 131.8, 130.02, 130.00, 127.83 (2C), 127.77 (2C), 97.9, 80.5, 74.7, 43.0, 26.8 (3C), 26.7, 19.1.

syn: $[\alpha]_D^{25}$ +66.7 (*c* 1.2, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.62–7.60 (4H, m, Ar–H), 7.44–7.38 (6H, m, Ar–H), 6.72 (1H, dd, *J* 5.8, 16.0, H-4′), 6.32 (1H, dd, *J* 16.0, 1.4, H-3), 5.43 (1H, dd, *J* 11.5, 4.8, H-5′), 4.54 (1H, dt, *J* 4.1, 1.5,

H-3′), 4.37 (1H, ddd, *J* 5.8, 3.9, 1.4, H-2′), 3.87 (1H, d, *J* 11.5, C5′O*H*), 2.15 (3H, s, H_3-C1), 2.11 (1H, d, *J* 13.8, H_AH_B-4′), 2.01 (1H, dt, *J* 13.8, 4.6, H_AH_B-4′), 1.07 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 197.9, 143.2, 135.9 (2C), 135.8 (2C), 132.3, 132.04, 131.98, 130.33, 130.31, 128.0 (4C), 99.5, 83.4, 74.7, 42.6, 27.2, 26.9 (3C), 19.1.

*3.1.20. (4R,5R,1′E)-4-(tert-Butyldiphenylsilyloxy)-5-(3-oxobut-1-enyl)dihydrofuran-2(3H)-one (**39**)*

PCC (1.52 g, 7.04 mmol), anhydrous sodium acetate (577 mg, 7.04 mmol), 4 Å MS (1.8 g) and anhydrous dichloromethane (14 mL) were placed in a light protected flask and stirred under a nitrogen atmosphere for 10 min. A solution of lactol **38** (688 mg, 1.68 mmol) in dichloromethane (8 mL) was added. After 2 h at room temperature the mixture was diluted with diethyl ether (50 mL) and filtered through a Florisil® pad to give the *title compound* as a colourless oil (620 mg, 91%). $[\alpha]_D^{25}$ +49.7 (*c* 3.5, CH_2Cl_2); ν_{max} (film) 2954, 2926, 2857, 1788, 1677, 1639, 1424, 1358, 1257, 1150, 1105, 1025, 980, 948, 820, 740, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.60–7.57 (4H, m, Ar–H), 7.48–7.37 (6H, m, Ar–H), 6.79 (1H, dd, *J* 16.1, 5.7, H-1′), 6.33 (1H, dd, *J* 16.1, 1.3, H-2′), 4.88 (1H, dt, *J* 5.1, 1.3, H-5), 4.66 (1H, dt, *J* 5.0, 3.4, H-4), 2.52 (1H, dd, *J* 17.4, 5.3, H_AH_B-C3), 2.46 (1H, dd, *J* 17.4, 3.3, H_AH_B-C3), 2.31 (3H, s, C4′), 1.05 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 197.1, 174.0, 138.9, 135.6 (4C), 132.5, 132.3, 132.0, 130.4 (2C), 128.0 (4C), 82.5, 71.2, 38.3, 27.4, 26.7 (3C), 19.1; *m/z* (CI, NH_3) 426 ($M+NH_4^+$, 6), 309 (9), 216 (23), 199 (65), 110 (23), 109 (23), 108 (20), 94 (60), 93 (35), 78 (100); HRMS (CI) $M+NH_4^+$; found: 426.2103. $C_{24}H_{32}NO_4Si$ requires: 426.2101.

*3.1.21. (4R,5R)-5-(3-Acetyl-4-hydroxy-6,8-dimethoxy-1-oxo-1,2-dihydronaphthalen-2-yl)-4-(tert-butyldiphenylsilyloxy)dihydrofuran-2(3H)-one (**40**)*

To a solution of potassium *tert*-butoxide (104 mg, 0.88 mmol) in DMSO (8 mL) was added at room temperature a solution of 1,3-dihydro-5,7-dimethoxy-3-oxoisobenzofuran-1-carbonitrile **7** (193 mg, 0.88 mmol) in DMSO (11 mL) followed by a solution of enone **39** (300 mg, 0.734 mmol) in DMSO (11 mL). After 10 min the orange solution was cooled in an ice bath, diluted with diethyl ether and quenched with saturated ammonium chloride. The mixture was decanted and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give the *title compound* as a yellow solid (440 mg, 81%), which was used for the next step without further purification. A sample was purified for analytical purposes by flash chromatography eluting with hexanes–ethyl acetate (7:3). $[\alpha]_D^{25}$ +15.4 (*c* 2.0, CH_2Cl_2); ν_{max} ($CHCl_3$) 3372, 2926, 2857, 1791, 1684, 1587, 1455, 1323, 1243, 1139, 1107, 1035, 948, 737, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.92–7.87 (2H, m, Ar–H), 7.70–7.66 (2H, m, Ar–H), 7.48–7.41 (6H, m, Ar–H), 7.25 (1H, d, *J* 2.4, H-5′), 6.60 (1H, d, *J* 2.4, H-7′), 4.62 (1H, d, *J* 10.4, H-2′), 4.39 (1H, t, *J* 3.3, H-4), 4.25 (1H, dd, *J* 10.4, 2.7, H-5), 3.93, 3.88 (6H, s, 2 ArOMe), 2.44 (3H, s, COMe), 2.36 (1H, d, *J* 17.3, H_AH_B-C3), 2.18 (1H, dd, *J* 17.3, 4.2, H_AH_B-C3), 1.18 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 195.5, 192.4, 173.7, 170.2, 165.2, 161.1, 138.1, 136.4 (2C), 135.8, 135.7 (2C), 133.5, 131.4, 130.2, 130.0, 127.9 (2C), 127.8 (2C), 106.3, 102.8, 101.9, 84.3, 70.7, 56.3, 55.9, 47.7, 39.4, 27.0 (3C), 25.2, 19.5; *m/z* (EI) 566 (23), 480 (24), 479 (64), 465 (12), 300 (19), 200 (19), 199 (100), 134 (38), 69 (41), 57 (64), 55 (62), 43 (64), 41 (64); HRMS (EI) MH^+; found: 601.2254. $C_{34}H_{37}O_8Si$ requires: 601.2258.

*3.1.22. 2-Acetyl-3-((2R,3R)-3-(tert-butyldiphenylsilyloxy)-5-oxo-tetrahydrofuran-2-yl)-4-hydroxy-5,7-dimethoxy-naphthalen-1-yl acetate (**41**)*

To a solution of crude **40** (0.734 mmol) in dichloromethane (15 mL) was added at −78 °C boron trifluoride diethyl etherate (186 μL, 1.47 mmol). The temperature was raised to −10 °C over 20 min, then after 10 min at this temperature pyridine (6 mL) and acetic anhydride (4 mL) were added and the mixture was stirred at room temperature for 5 h. The reaction was quenched with water and extracted with dichloromethane (3×30 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (7:3) gave the *title compound* as a yellow oil (250 mg, 53%). *Major diastereomer*: $[\alpha]_D^{25}$ +46.2 (*c* 2.1, CH_2Cl_2); ν_{max} (film) 3358, 2940, 2857, 1777, 1701, 1628, 1587, 1469, 1424, 1368, 1195, 1170, 1146, 1108, 1042, 1007, 907, 820, 733, 702 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.41 (1H, s, C4-O*H*), 7.59–7.10 (10H, m, Ar–H), 6.51 (1H, d, *J* 2.2, Ar–H), 6.48 (1H, d, *J* 2.2, Ar–H), 5.63 (1H, d, *J* 4.2, H-2′), 4.95 (1H, dt, *J* 7.2, 4.9, H-3′), 4.00 (3H, s, C5-OMe), 3.89 (3H, s, C7-OMe), 2.72 (1H, dd, *J* 17.9, 7.7, H_AH_B-C4′), 2.52 (3H, s, C2-COMe), 2.47 (1H, dd, *J* 17.9, 5.0, H_AH_B-C4′), 2.36 (3H, s, OCOMe), 1.05 (9H, s, $SiMe_3$); δ_C (100 MHz, $CDCl_3$) 203.3, 175.4, 168.9, 159.4, 157.5, 151.4, 135.7 (4C), 133.6, 133.5, 133.4, 132.4, 130.4, 129.8, 129.5, 127.7 (2C), 127.4 (2C), 111.4, 110.8, 99.2, 93.3, 84.4, 73.8, 56.5, 55.4, 38.8, 32.4, 26.8 (3C), 20.6, 14.2; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 643 (MH^+, 20), 273 (12), 120 (12), 89 (22); HRMS (FAB^+) MH^+; found: 643.2358. $C_{36}H_{39}O_9Si$ requires: 643.2363.

*3.1.23. 2-Acetyl-3-((2R,3R)-3-hydroxy-5-oxotetrahydrofuran-2-yl)-5,7-dimethoxynaphthalene-1,4-dione (**44**)*

To a solution of **41** (64 mg, 0.093 mmol) in THF (6 mL) placed in a polypropylene flask was added HF·Py (1.5 mL). After stirring at room temperature for 6 h the solution was poured carefully into saturated sodium bicarbonate. The mixture was decanted and the organic layer was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a mixture of **42** and **43** (4:1) (60 mg), which was used without further purification for the next step. A sample was purified by flash chromatography on silica gel eluting with ethyl acetate–hexanes (1:1→2:3) to give a mixture of **42** and **43** (1:4).

To a solution of a mixture of **42** and **43** (4:1, 150 mg, 0.4 mmol) in acetonitrile (20 mL) was added at room temperature a solution of ceric ammonium nitrate (640 mg, 1.17 mmol) in water (10 mL). After stirring for 15 min the solution was quenched with saturated sodium bicarbonate and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (1:1→1:1+1% MeOH) gave the *title compound* as a yellow oil (44 mg, 38% over two steps starting from **41**). ν_{max} (film) 3289, 2909, 1731, 1689, 1599, 1478, 1499, 1375, 1312, 1274, 1251, 1190, 1100, 747 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, d, *J* 2.4, H-8), 6.75 (1H, d, *J* 2.4, H-6), 5.40 (1H, d, *J* 3.6, H-2′), 4.58 (1H, dt, *J* 8.1, 4.0, H-3′), 3.99 (3H, s, ArOMe), 3.97 (3H, s, ArOMe), 3.02 (1H, dd, *J* 18.4, 8.3, H_AH_B-C4′), 2.61 (1H, dd, *J* 18.4, 4.2, H_AH_B-C4′), 2.51 (3H, s, C2-COMe); δ_C (100 MHz, $CDCl_3$) 201.9, 183.3, 183.2, 173.8, 169.9, 162.3, 142.4, 135.8, 134.9, 113.2, 104.5, 104.0, 83.9, 72.3, 56.6, 56.2, 35.7, 31.7; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 361 (MH^+, 1), 273 (3), 219 (4), 124 (10), 120 (13), 91 (18), 90 (20), 89 (29); HRMS (FAB^+) MH^+; found: 361.0865. $C_{18}H_{17}O_8$ requires: 361.0923.

3.1.24. 2-((1S,3S)-6,8-Dimethoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-benzo[g]isochromen-3-yl)-acetic acid (*46*)

To a solution of quinone **44** (38 mg, 0.105 mmol) in dichloromethane (5 mL) was added at −78 °C boron trifluoride diethyl etherate (134 μL, 1.05 mmol) followed by triethylsilane (168 μL, 1.05 mmol). The solution was stirred at −78 °C for 15 min then allowed to warm to room temperature over 30 min. The dark red mixture was then concentrated in vacuo and purified by flash chromatography eluting with hexanes–ethyl acetate–methanol (10:10:1) to afford the *title compound* as a red-orange solid (23 mg, 63%). ν_{max} (CH_2Cl_2) 2923, 1720, 1647, 1593, 1454, 1424, 1349, 1325, 1274, 1250, 1198, 1159 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.21 (1H, d, *J* 2.4, H-9′), 6.73 (1H, d, *J* 2.4, H-7′), 4.89–4.80 (1H, m, H-1′), 3.96 (3H, s, ArOMe), 3.95 (3H, s, ArOMe), 3.96–3.84 (1H, m, H-3′), 2.91 (1H, dt, *J* 18.6, 2.6, H_AH_B-C4′), 2.76 (1H, dd, *J* 16.0, 7.4, H_AH_B-C2), 2.69 (1H, dd, *J* 16.0, 5.4, H_AH_B-C2), 2.25 (1H, ddd, *J* 18.6, 10.5, 3.7, H_AH_B-C4′), 1.52 (3H, d, *J* 6.6, C1′-Me); δ_C (75 MHz, $CDCl_3$) 183.7, 181.5, 174.4, 164.7, 161.8, 143.7, 143.5, 136.3, 114.1, 104.0, 103.1, 70.0, 69.2, 56.4, 55.9, 40.1, 28.4, 20.5; *m/z* (FAB^+, glycerol) 347 (MH^+, 1), 75 (29); HRMS (FAB^+) MH^+; found: 347.1123. $C_{18}H_{19}O_7$ requires: 347.1131.

3.1.25. Methyl 2-((1S,3S)-6,8-dimethoxy-1-methyl-5,10-dioxo-3,4,5,10-tetrahydro-1H-benzo[g]isochromen-3-yl)-acetate (*47*)

A solution of quinone **46** (21 mg, 0.061 mmol) in methanol (20 mL) protected from light was stirred for 6 weeks and oxygen was bubbled daily through the solution. The solvent was then removed in vacuo and the crude mixture purified by flash chromatography eluting with hexanes–ethyl acetate–methanol (20:20:1) to afford the *title compound* as a red-orange oil (7 mg, 32%). $[\alpha]_D^{20}$ −206 (*c* 0.7, CH_2Cl_2); ν_{max} (film) 2933, 2843, 1736, 1649, 1590, 1562, 1455, 1431, 1323, 1271, 1250, 1198, 1153, 1105, 1063 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.21 (1H, d, *J* 2.4, H-9′), 6.71 (1H, d, *J* 2.4, H-7′), 4.85–4.78 (1H, m, H-1′), 3.97 (3H, s, ArOMe), 3.95 (3H, s, ArOMe), 3.97–3.89 (1H, m, H-3′), 3.73 (3H, s, CO_2Me), 2.86 (1H, dt, *J* 18.8, 2.6, H_AH_B-C4′), 2.71 (1H, dd, *J* 15.7, 7.8, H_AH_B-C2), 2.62 (1H, dd, *J* 15.7, 5.2, H_AH_B-C2), 2.26 (1H, ddd, *J* 18.6, 10.5, 3.8, H_AH_B-C4′), 1.50 (3H, d, *J* 6.8, C1′-Me); δ_C (100 MHz, $CDCl_3$) 183.8, 181.6, 171.2, 164.6, 161.7, 143.9, 143.7, 136.3, 114.0, 103.9, 103.0, 69.9, 69.4, 56.4, 55.9, 51.8, 40.4, 28.4, 20.5; *m/z* (FAB^+, *m*-nitrobenzylalcohol) 361 (MH^+, 40), 360 (M^+, 17), 149 (12), 120 (12); HRMS (FAB^+) MH^+; found: 361.1287. $C_{19}H_{21}O_7$ requires: 361.1287.

3.1.26. N,N-Diethyl 3,5-dimethoxybenzamide (*48*)[18]

3,5-Methoxybenzoic acid (12.0 g, 65.7 mmol) was taken up in dichloromethane (100 mL) and cooled to −10 °C. Thionyl chloride (5.3 cm^3, 72.3 mmol) was added dropwise and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was concentrated in vacuo with azeotropic removal of the residual thionyl chloride with toluene (2×50 mL). The resulting crude acid chloride was taken up in dichloromethane (100 mL) and cooled to 0 °C. A solution of diethylamine (20 mL) in dichloromethane (20 mL) was added dropwise, the reaction mixture warmed to room temperature and stirred for 2 h. Glacial acetic acid (30 mL) was added and the reaction mixture was diluted with dichloromethane (100 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (2:1) gave the *title compound* (10.4 g, 46.6 mmol, 71%) as a yellow oil. ν_{max} (film) 2945, 1680 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.45 (2H, d, *J* 2.2, Ar–H), 6.40 (1H, t, *J* 2.2, Ar–H), 3.81 (6H, s, 2×OMe), 3.52–3.39 (2H, br m, CH_2), 3.27–3.20 (2H, br m, CH_2), 1.24–1.10 (3H, br m, Me), 1.12–1.06 (3H, br m, Me). Spectroscopic data consistent with the literature.[18]

3.1.27. N,N-Diethyl 3-hydroxy-5-methoxybenzamide (*49*)

N,*N*-Diethyl 3,5-dimethoxybenzamide **48** (3.01 g, 12.7 mmol) was dissolved in dichloromethane (250 mL). The solution was cooled to −78 °C, boron tribromide (20 mL, 20 mmol) was added dropwise and the reaction mixture stirred for 1 h. The reaction was quenched by the addition of HCl (1 M, 50 mL). The aqueous layer was extracted with dichloromethane (2×50 mL) and the combined organic extracts were washed with brine, dried with $MgSO_4$, concentrated and purified by flash column chromatography (hexane–ethyl acetate 1:1) to give the *title compound* as white crystals (2.10 g, 9.42 mmol, 72%), mp 103–105 °C. ν_{max} (CH_2Cl_2) 3414, 2977, 1635, 1428, 1381, 1364, 1258, 1159, 1119 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.29 (1H, s, OH), 6.36–6.33 (1H, m, Ar–H), 6.45–6.36 (1H, m, Ar–H), 6.34–6.32 (1H, m, H-4), 3.71 (3H, s, OMe), 3.57–3.46 (2H, q, *J* 6.7, CH_2), 3.32–3.20 (2H, q, *J* 6.7, CH_2), 1.26–1.19 (3H, t, *J* 6.7, Me), 1.14–1.05 (3H, t, *J* 6.7, Me); δ_C (100 MHz, $CDCl_3$) 172.4, 161.1, 158.8, 138.1, 107.1, 103.8, 103.1, 55.7, 43.9, 39.6, 14.6, 13.2; HRMS (EI) M^+; found: 223.1210; $C_{12}H_{17}NO_3$ requires: 223.1208.

3.1.28. 3-Diethylcarbamoyl-5-methoxyphenyl trifluoromethanesulfonate (**50**)

N,*N*-Diethyl 3-hydroxy-5-methoxybenzamide **49** (3.12 g, 14.0 mmol) and *N*-phenyltrifluoromethanesulfonimide (5.09 g, 14.2 mmol) was dissolved in dichloromethane (150 mL) and cooled to −20 °C. Triethylamine was added and the reaction was allowed to warm to room temperature. After 3 h the reaction was complete as determined by TLC analysis and the mixture was washed with saturated ammonium chloride, dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography (hexanes–ethyl acetate 4:1 to 1:1) gave the *title compound* (4.01 g, 11.3 mmol, 80%) as a light yellow oil. ν_{max} (film) 3486, 2976, 1736, 1634, 1426, 1326, 1213, 1141, 1053, 961, 833, 802, 761 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.94 (1H, dd, *J* 1.7, 1.3, Ar–H), 6.86 (1H, dd, *J* 1.3, 0.9 Ar–H), 6.83–6.80 (1H, m, Ar–H), 3.85 (3H, s, OMe), 3.63–3.43 (2H, br m, CH_2), 3.35–3.15 (2H, br m, CH_2), 1.30–1.16 (6H, br m, 2×Me); δ_C (75 MHz, $CDCl_3$) 168.7, 161.0, 149.8, 140.0, 112.1, 111.3, 108.4, 55.9, 43.3, 39.6, 14.1, 12.9, triflate carbon not observed; HRMS (EI) M^+; found: 355.0702. $C_{13}H_{16}F_3NO_5S$ requires: 355.0701.

3.1.29. 5,5′-Dimethoxy-biphenyl-3,3′-dicarboxylic acid bisdiethylamide (**51**)

3-Diethylcarbamoyl-5-methoxyphenyltrifluoromethane sulfonate **50** (3.98 g, 11.2 mmol), bis(pinacolatodiboron) (1.39 g, 5.53 mmol), potassium carbonate (4.94 g, 36.2 mmol), 1,1′-bis(diphenylphosphino)-ferrocene (295 mg, 0.54 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (5 mol %, 435 mg, 0.54 mmol) were dissolved in dioxane (120 mL) and heated to reflux for 3 h. The mixture was cooled to room temperature and diluted with ethyl acetate (100 mL). The mixture was washed with water (2×100 mL) and the water was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Further purification by flash column chromatography (hexane–ethyl acetate 1:1) gave the *title compound* as white crystals (2.08 g, 5.05 mmol, 90%), mp 125–127 °C. ν_{max} (film) 3054, 2986, 1772, 1626, 1422, 1265, 736 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.14–7.12 (4H, m, H-2, H-2′, H-4 and H-4′), 6.89 (2H, dd, *J* 3.5 and 1.4, H-6 and H-6′), 3.87 (6H, s, 2×OMe), 3.64–3.46 (4H, br m, 2×CH_2), 3.39–3.21 (4H, br m, 2×CH_2), 1.31–1.19 (6H, br m, 2×Me), 1.18–1.06 (6H, br m, 2×Me); δ_C (100 MHz, $CDCl_3$) 171.2 (2C), 160.4 (2C), 142.6 (2C), 139.5 (2C), 117.8 (2C), 114.2 (2C), 111.3 (2C), 43.7 (2C), 39.7 (2C), 14.7 (2C), 13.4 (2C); HRMS (EI) M^+; found: 412.2356. $C_{24}H_{32}N_2O_4$ requires: 412.2362.

3.1.30. 4,4′-Diformyl-5,5′-dimethoxy-biphenyl-3,3′-dicarboxylic acid bisdiethylamide (**52**)

Biaryl **51** (1.65 g, 4.00 mmol) and TMEDA (3.5 mL) were dissolved in THF (100 mL) and the solution was cooled to −78 °C. ^{t}BuLi (11 mL 1.6 M, 17.6 mmol) was added dropwise and the mixture was stirred for 1 h. Freshly distilled DMF (12 mL) was added and the reaction was allowed to warm slowly to room temperature and was left to stir for 15 h. At 0–5 °C the mixture changed colour from dark brown to yellow. The mixture was poured into 1 M HCl (200 mL). The aqueous phase was extracted with ethyl acetate (5×50 mL). The combined organic phase was extracted with sodium bicarbonate (2×50 mL), brine, dried ($MgSO_4$) and concentrated to afford light brown crystals. Recrystallization from ethyl acetate gave the *title compound* as white crystals (1.62 g, 3.69 mmol, 92%), mp 248–250 °C. ν_{max} (CH_2Cl_2) 3468, 2991, 2912, 2878, 2245, 1696, 1651, 1599, 1419, 1280 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.51 (2H, s, CHO and C′HO), 7.15 (2H, d, *J* 1.2, H-2 and H-2′), 7.04 (2H, d, *J* 1.2, H-6 and H′-6), 4.02 (6H, s, 2×OMe), 3.61 (4H, br q, *J* 7.2, 2×CH_2), 3.11 (4H, q, *J* 7.2, 2×CH_2), 1.35 (6H, t, *J* 7.2, 2×Me), 1.03 (6H, t, *J* 7.2, 2×Me); δ_C (75 MHz, $CDCl_3$) 188.7 (2C), 169.3 (2C), 162.5 (2C), 146.7 (2C), 140.2 (2C), 121.1 (2C), 118.2 (2C), 110.6 (2C), 56.3 (2C), 42.6 (2C), 38.8 (2C), 13.6 (2C), 12.1 (2C); HRMS (EI) MH^+; found: 439.2327. $C_{26}H_{33}N_2O_6$ requires: 439.2339.

3.1.31. 7,7′-Dimethoxy-3,3′-dioxo-1,3,1′,3′-tetrahydro-[5,5′]biisobenzofuranyl-1,1′-dicarbonitrile (**4**)

A solution of **52** (62 mg, 0.12 mmol) in dichloromethane (10 mL) was cooled to 0 °C. Trimethylsilyl cyanide (48 μL, 0.36 mmol), potassium cyanide (1.6 mg, 1.6 mmol) and 18-crown-6 (2 mg) were added and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated in vacuo and the resulting residue taken up in glacial acetic acid (5 mL) then stirred at room temperature for 16 h. The resulting mixture was partitioned between ethyl acetate (25 mL) and sodium hydroxide solution (1 M, 25 mL) then the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (1:4) gave the *title compound* (37 mg, 82%). ν_{max} (CH_2Cl_2) 3555, 2989, 2941, 2912, 1741, 1449, 1363, 1241, 747 cm^{-1}; δ_H (300 MHz, d_6-DMSO) 8.00 (2H, br s, H-4 and H-4′), 7.86 (2H, br s, H-6 and H′-6), 6.89 (2H, s, C*H*CN), 4.13 (6H, s, 2×OMe); δ_C (75 MHz, d_6-DMSO) 167.4, 154.3, 144.2, 129.2, 126.2, 117.1, 116.3, 114.0, 64.4, 56.8; HRMS (EI) MH^+; found: 377.0775. $C_{20}H_{13}N_2O_6$ requires: 377.0773.

3.1.32. 7,7′-Diacetyl-6,6′-bis((2R,3R)-3-(tert-butyldiphenylsilyloxy)-5-oxotetrahydrofuran-2-yl)-5,5′-dihydroxy-4,4′-dimethoxy-2,2′-binaphthyl-8,8′-diyl diacetate (**54**)

To a solution of biscyanophthalide **4** (16 mg, 0.043 mmol) and enone **39** (39 mg, 0.095 mmol) in DMSO (3 mL) was added dropwise a solution of potassium *tert*-butoxide (10 mg, 0.086 mmol) in DMSO (2 mL). After 10 min the orange solution was cooled in an ice bath, diluted with diethyl ether and quenched with saturated ammonium chloride. The mixture was decanted and the aqueous layer was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil (**53**, 31 mg).

The crude compound **53** (31 mg, 0.027 mmol) was dissolved in dichloromethane (2 mL) and a solution of boron trifluoride diethyl etherate (4.1 μL, 0.033 mmol) in dichloromethane (0.5 mL) was added at −78 °C. The temperature was then raised to 0 °C over 30 min, then pyridine (0.5 mL) and acetic anhydride (0.3 mL) were added and the mixture was stirred at

room temperature for 5 h. The reaction was hydrolyzed with water and hydrochloric acid (10%) then extracted with dichloromethane (3×5 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with hexanes–ethyl acetate (7:3→1:1) gave the *title compound* as a yellow oil (11 mg, 23% from **4**). ν_{max} (film) 3379, 2954, 2940, 2837, 1765, 1700, 1651, 1584, 1519, 1444, 1424, 1368, 1199, 1179, 1149, 1110, 1055, 1007, 910, 820, 735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.51 (2H, br s, 5-O*H* and 5′-O*H*), 7.73–7.09 (24H, m, Ar–H), 5.86 (2H, br s, H-2″ and H-2‴), 5.03 (2H, br s, H-3″ and H-3‴), 4.18 (6H, s, 4-OMe and 4′-OMe), 2.65 (6H, s, 7-COMe and 7′-COMe), 2.52–2.37 (4H, m, H-4″ and H-4‴), 2.41 (6H, s, 8-OCOMe and 8′-OCOMe), 0.82 (18H, s, 2×$SiMe_3$); δ_C (100 MHz, $CDCl_3$) 201.2 (2C), 174.3 (2C), 169.2 (2C), 139.7 (6C), 135.93 (4C), 135.87 (4C), 135.0 (2C), 133.0 (2C), 132.5 (2C), 130.0 (2C), 129.6 (2C), 128.0 (4C), 127.8 (4C), 127.3 (4C), 114.5 (2C), 113.5 (4C), 105.1 (2C), 82.5 (2C), 70.5 (2C), 56.7 (2C), 38.7 (2C), 30.3 (2C), 26.4 (6C), 20.6 (2C), 18.8 (2C); MS (FAB^+, *m*-nitrobenzylalcohol) 1223 (MH^+, 9), 198 (22), 197 (33), 89 (24); HRMS (FAB^+) MH^+; found: 1223.4226. $C_{70}H_{71}O_{16}Si_2$ requires: 1223.4281.

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