Tetrahedron 71 (2015) 91–101

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of the carbon skeleton of the griseorhodins

Darcy J. Atkinson [a,b], Daniel P. Furkert [a,b], Margaret A. Brimble [a,b,*]

[a] School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland 1010, New Zealand
[b] Maurice Wilkins Centre for Molecular Biodiscovery, The University of Auckland, 3 Symonds Street, Auckland 1010, New Zealand

ARTICLE INFO

Article history:
Received 13 September 2014
Received in revised form 30 October 2014
Accepted 10 November 2014
Available online 20 November 2014

Keywords:
Griseorhodins
Rubromycins
Spiroketal
Sonogashira coupling

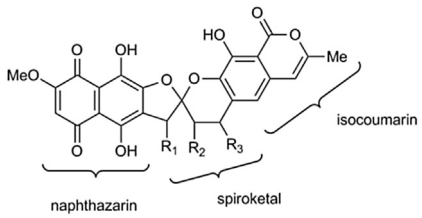
ABSTRACT

A synthetic strategy to access the carbon skeleton of the griseorhodin family of natural products has been developed. The key step involved the acid-mediated spirocyclisation of a highly functionalised dihydroxyketone. The delicate electronic balance between the electron rich naphthalene moiety and the electron-withdrawing isocoumarin ring system were finely tuned to facilitate the acid-mediated spirocyclisation reaction. The development of this synthetic strategy provides a basis for further synthetic investigations towards the more structurally complex griseorhodin natural products.

1. Introduction

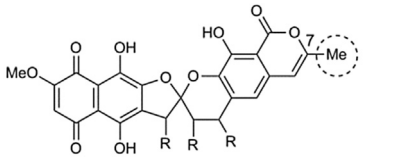
The griseorhodins are a sub class of compounds within the structurally related rubromycin family. They were isolated over several decades with the majority of the compounds isolated from various strains of *Streptomyces*.[1–8] Structurally, griseorhodins **1**–**6** all consist of naphthazarin and isocoumarin moieties linked via a 5,6-spiroketal core (Fig. 1). Piel et al. proposed an absolute configuration of (*S*, *S*, *S*, *S*) for griseorhodin A (**1**) based on quantum-chemical circular dichroism (CD) calculations and experimental CD measurements, however, compounds **2**–**6** currently remain unassigned.[9] The griseorhodins are distinguished from the other members of the larger rubromycin family by the presence of a methyl group at C-7 as opposed to a methyl ester (Fig. 2).

The griseorhodins exhibit antimicrobial activity against a range of bacteria and fungi at micromolar levels.[5,6,8,9] Notably, 8-methoxygriseorhodin C (**4**) exhibits potent activity against strains of MRSA (methicillin resistant *Staphylococcus aureus*, MIC=0.78 μg/mL).[6] These natural products also exhibit cytotoxic activity against KB-nasopharynx cells and HLE (human leukocyte elastase).[5,9]

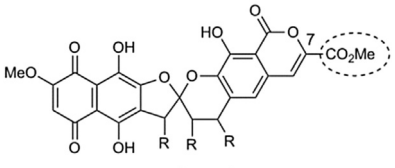


griseorhodin A (**1**) R^1 = OH, R^2, R^3 = 
griseorhodin C (**2**) R^1, R^2, R^3 = OH
griseorhodin G (**3**) R^1, R^2 = OH, R^3 = H
8-methoxygriseorhodin C (**4**) R^1, R^2 = OH, R^3 = OMe
7,8-dideoxygriseorhodin C (**5**) R^1 = OH, R^2, R^3 = H
7,8-dideoxy-6-oxogriseorhodin C (**6**) R^1 = ketone, R^2, R^3 = H

Fig. 1. Structures of the griseorhodins.



griseorhodins



rubromycins

Fig. 2. General structures of the griseorhodins and rubromycins.

* Corresponding author. Tel.: +64 9 373 7599; fax: +64 9 373 7422; e-mail address: m.brimble@auckland.ac.nz (M.A. Brimble).

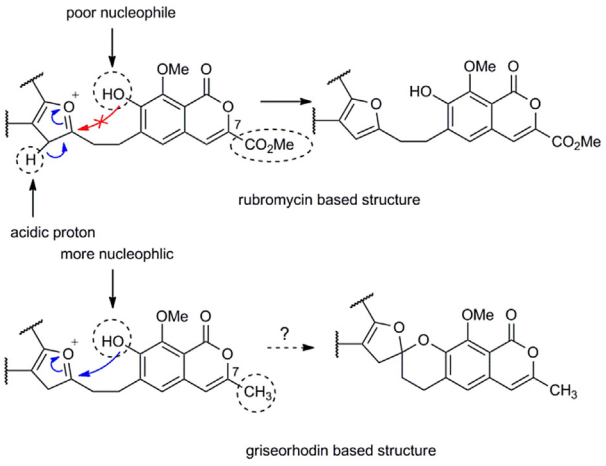
http://dx.doi.org/10.1016/j.tet.2014.11.030
0040-4020/

In addition to their potent antimicrobial and cytotoxic properties, griseorhodins A (**1**) (IC_{50} 12.2 μM) and C (**2**) (IC_{50} 5.87 μM) also inhibit human telomerase.[10] Telomerase is a unique ribonucleoprotein that maintains the ends of chromosomes, through the synthesis of telomeres. Telomeres are short guanine rich sequences, which are repeated at the ends of chromosomes to maintain chromosome length and stability during successive DNA replication.[10] Telomerase is up regulated in 80–90% of cancers while it is almost completely absent in neighbouring healthy somatic cells, therefore, serving as a potential target for the development of new cancer therapeutic agents.[11,12] Structural studies have suggested that the spiroketal moiety of the rubromycins is a key pharmacophore for telomerase inhibition activity.[10]

The rubromycin family has been known for almost 60 years and extensive interest from the synthetic community has led to a large body of literature on the synthesis of various fragments. Three of the natural products have succumbed to total synthesis starting with Danishefsky's seminal preparation of heliquinomycinone.[13] Subsequent syntheses of (±)-γ-rubromycin,[14–18] (±)-δ-rubromycin[19] and an advanced spiroketal intermediate of purpuromycin[20] have now been reported. To date however, synthetic investigations towards the griseorhodin natural products have not been reported.

Initial investigations towards the rubromycins from both Reiβig and Kozlowski centered on acid-mediated spirocyclisation to construct the spiroketal core, but disappointingly these revealed the inability of a fully-substituted isocoumarin to undergo this transformation (Scheme 1). Further investigations revealed that the electron-withdrawing functionality of the isocoumarin had a substantial effect on acid-mediated spirocyclisations, preventing the reaction from proceeding.[21,22] To circumvent this problem, the use of electron-rich isocoumarin precursors and modification of the electrophilic ketone led to the successful formation of spiroketal products.[20,22]

In these previous studies, the synthetic targets all contained the methyl ester functional group at C-7 common to the rubromycin family (Scheme 1). It has been demonstrated that the methyl ester contributes substantially to the reduction in nucleophilicity of the phenol through mesomeric electron-withdrawal, resulting in the formation of benzofuran or degradation products.[21] We hypothesised that exchange of the methyl ester for a methyl group, common to the griseorhodins would remove the electron-withdrawing mesomeric effect, thereby facilitating acid-mediated spirocyclisation to access the griseorhodin spiroketal framework.



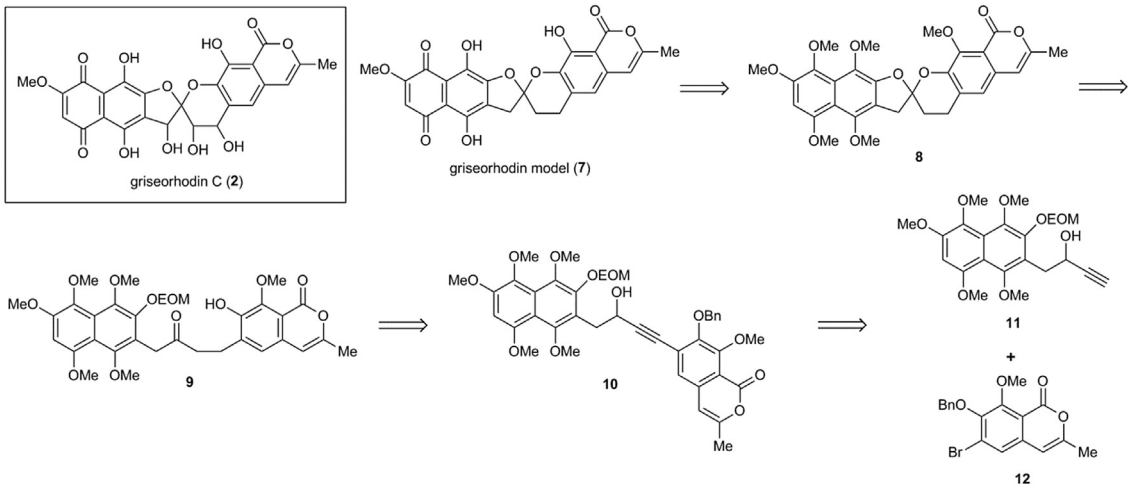
Scheme 1. Comparing reaction pathways for isocoumarins under acidic spirocyclisation conditions.

2. Results and discussion

Given the variability and unknown effects that the modified isocoumarin moiety might confer on the key spirocyclisation reaction, it was decided to initially focus on the synthesis of the model griseorhodin structure (**7**) (Scheme 2). Synthesis of **7** would establish a route that could be readily modified for the preparation of the griseorhodin natural products. Retrosynthetically, griseorhodin model (**7**) arises from hexamethoxy protected spiroketal **8**. An acid-mediated spirocyclisation of a dihydroxyketone precursor **9** would be used to construct the spiroketal core. Dihydroxyketone **9** would in turn be accessed from alkynol **10**. Sonogashira coupling of functionalised naphthalene **11** and isocoumarin **12** would allow for a flexible convergent synthesis providing access to related systems.

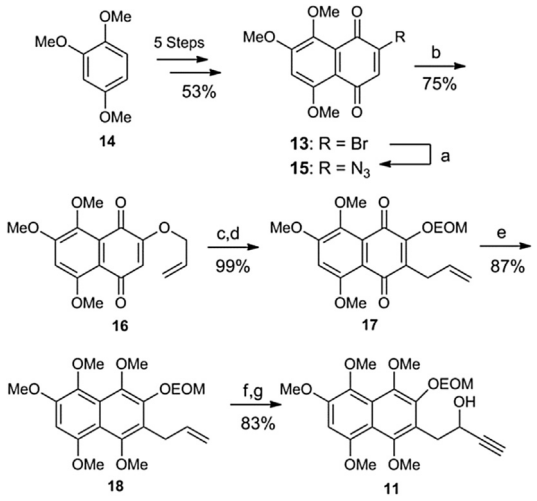
2.1. Synthesis of alkynol 11

Synthesis of alkynol **11** was achieved following an established protocol developed by our group during the formal synthesis of (±)-γ-rubromycin (Scheme 3).[14] Synthesis of intermediate bromoquinone **13** from commercially available 1,2,4-trimethoxybenzene (**14**) was completed in 53% yield over 5 steps. Conversion of bromoquinone **13** to the azidoquinone **15** was



Scheme 2. Retrosynthetic analysis of griseorhodin model (**7**).

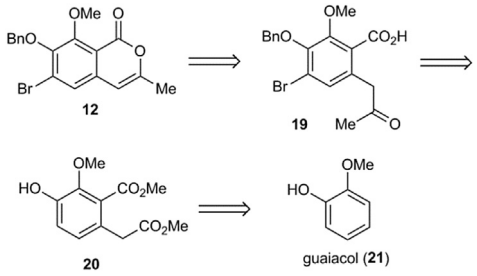
required to ensure regioselective reaction with allyl alcohol.[14] Claisen rearrangement of allyl ether **16** induced by microwave irradiation was then executed followed by protection of the newly-exposed hydroxyl group to afford EOM ether **17** in excellent yield. Reductive dimethylation of **17** then afforded alkene **18**. A one pot dihydroxylation-oxidative cleavage afforded the corresponding aldehyde, which was then converted to desired alkynol **11** upon exposure to excess ethynylmagnesium bromide in tetrahydrofuran.



Scheme 3. Synthesis of alkynol **11**. *Reagents and conditions*: (a) NaN_3, MeCN, rt., 3 days. (b) allyl alcohol, Cs_2CO_3, PhMe, 60 °C, 1 h (c) PhMe, 140 °C, microwave, 200 W, 30 min (d) EOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C→rt., 16 h (e) $Na_2S_2O_4$, TBABr (cat.), THF-H_2O (1:1) 20 min then MeI, Cs_2CO_3, $Na_2S_2O_4$ (cat.), H_2, DMF, 60 °C, 3 h (f) OsO_4 (cat.), 2,6-lutidine, $NaIO_4$, dioxane-H_2O (3:1), rt., 3.5 h (g) ethynylmagnesium bromide, THF, 0 °C→rt., 1 h.

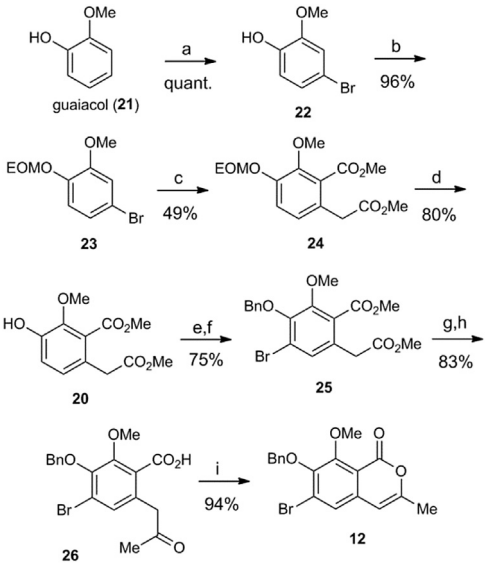
2.2. Synthesis of isocoumarin 12

With naphthalene **11** in hand, attention next focused on the synthesis of isocoumarin **12**. Coupling partner **12** is available from keto-acid **19**, which could be prepared from known phenol **20**, available in turn from guaiacol (**21**) using reported procedures (Scheme 4).[14]



Scheme 4. Retrosynthesis of the isocoumarin coupling partner **12**.

The synthesis of **12** commenced with bromination[23] of guaiacol (**21**) followed by protection of the resultant phenol as an EOM ether **23** (Scheme 5). Regioselective reaction of the intermediate benzyne of **23** with the preformed anion of dimethyl malonate in tetrahydrofuran at −78 °C afforded homophthalic ester **24** in 49% yield as a single product. Acidic cleavage of the EOM group to afford phenol **20** was then required to facilitate the subsequent *ortho*-



Scheme 5. Synthesis of isocoumarin **12**. *Reagents and conditions*: (a) Br_2, CH_2Cl_2, −78 °C → −5 °C, 1 h (b) EOMCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C→rt., o/n. (c) LDA, THF, dimethyl malonate, −78 °C, 1 h then **23**, THF, −78 °C→rt., 1 h (d) $NaHSO_4{\cdot}SiO_2$, CH_2Cl_2, rt., 16 h (e) Br_2, NaOAc, AcOH, rt., 1 h (f) BnBr, K_2CO_3, acetone, reflux, 2 h (g) KOH, EtOH–H_2O (3:1), reflux, 6 h (h) Ac_2O, py, rt., o/n then aq NaOH (1.0 M), 60 °C, 3 h (i) $HClO_4$ (cat.), EtOAc-Ac_2O (5:1), rt., 30 min.

bromination step. Reprotection of the phenol as a benzyl ether afforded homophthalic ester **25** in 75% yield over two steps. Saponification of both esters followed by Dakin-West oxidation afforded keto-acid **26**, which cyclised upon treatment with catalytic perchloric acid in a mixture of EtOAc-Ac_2O (5:1) to afford the desired isocoumarin **12**.

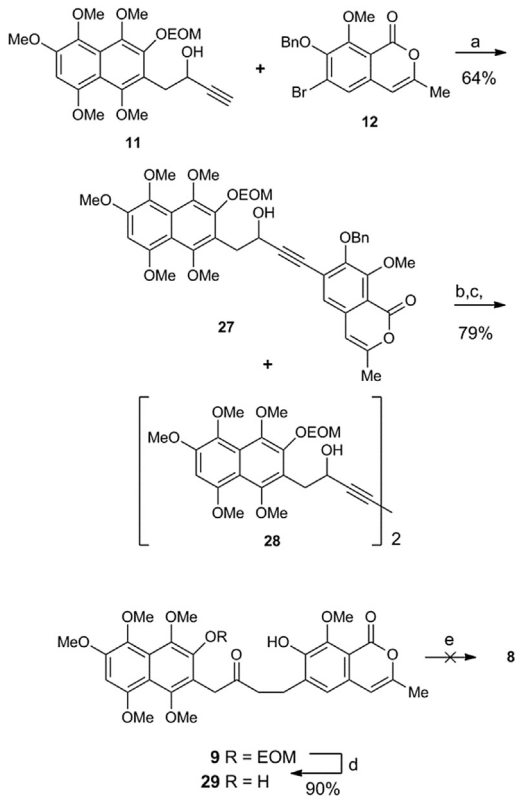
2.3. Coupling of alkynol 11 and isocoumarin 12

With both coupling partners **11** and **12** in hand, attention turned to the Sonogashira coupling and elaboration to spirocyclisation precursor **9** (Scheme 6). Initial attempts to couple alkynol **11** and isocoumarin **12** afforded poor yields of cross-coupled product **27** due to the formation of homo-coupled alkynol product **28**. All attempts to reduce the formation of this undesired product were unsuccessful, therefore, 2 equiv of **11** were required to achieve acceptable yields of the desired cross-coupling product **27**. Synthesis continued with IBX oxidation of the 2° alcohol and treatment of the corresponding ketone with Pd/C under a hydrogen atmosphere, affording ketone **9** in 79% over two steps. Initial attempts to effect spirocyclisation of ketone **9** under acidic conditions were unsuccessful. Exposure of **9** to PPTS in CH_2Cl_2 afforded dihydroxyketone **29** in 90% yield. However, further attempts to effect spirocyclisation of dihydroxyketone **29** using a wide range of both Brønsted and Lewis acids afforded none of the desired spirocyclised product **8**.

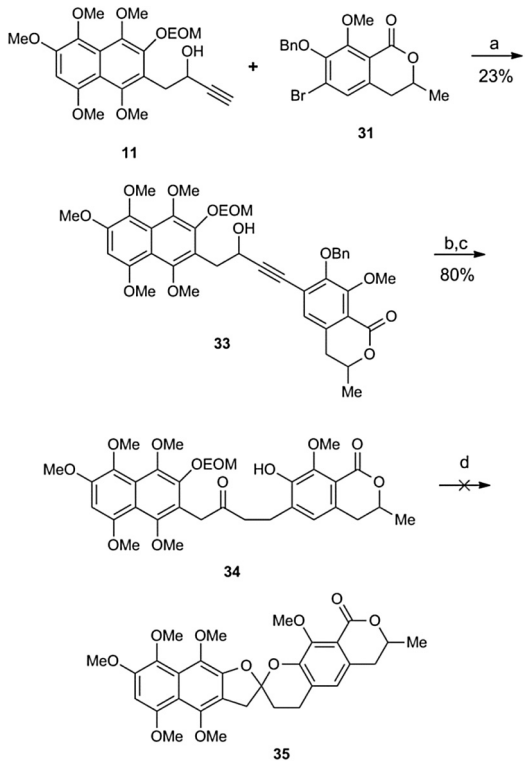
2.4. Isocoumarin precursors

At this stage it was apparent that exchanging the methyl ester for a methyl group at C-7 was not sufficient to facilitate the key spirocyclisation reaction when a fully substituted isocoumarin fragment was in place. As a result, further structural modification of the isocoumarin fragment was required to further probe the functionality, that is, compatible with the key spirocyclisation step.

Consequently, three isocoumarin precursors with differing functionality were synthesised from intermediate keto-acid **26** (Scheme 7). Methylation of keto acid **26** afforded keto ester **30**,



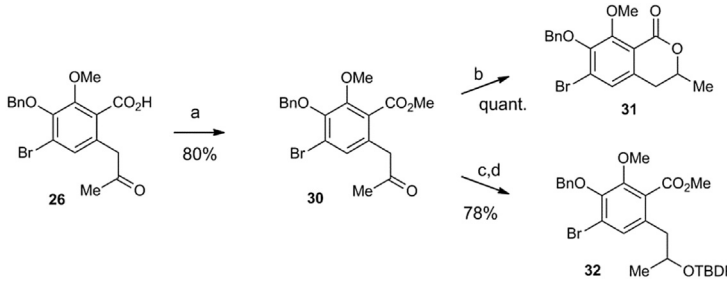
Scheme 6. Synthesis of dihydroxyketone **29** and attempted spirocyclisation. *Reagents and conditions*: (a) $Pd(OAc)_2$, CuI, PPh_3, NEt_3, DMF, rt., 24 h (b) IBX, DMSO, rt., 5 h (c) H_2, Pd/C, EtOAc, rt., 1 h (d) PPTS, CH_2Cl_2, rt., 12 h (e) various Brønsted and Lewis acids.



Scheme 8. Synthesis of **34** and attempted spirocyclisation. *Reagents and conditions*: (a) $Pd(OAc)_2$, CuI, PPh_3, NEt_3, DMF, rt., 24 h (b) IBX, DMSO, rt., 4 h (c) H_2, Pd/C, MeOH, rt., 2 h (d) various Brønsted and Lewis Acids.

which was easily converted to dihydroisocoumarin **31** using $NaBH_4$ and aqueous acid. Alternatively, reduction of keto ester **30** followed by silyl protection of the alcohol affords TBDPS ether **32**. These three compounds (**30**–**32**) were identified as suitable precursors as they contain appropriate functionality for later conversion to the desired fully substituted isocoumarin ring system.

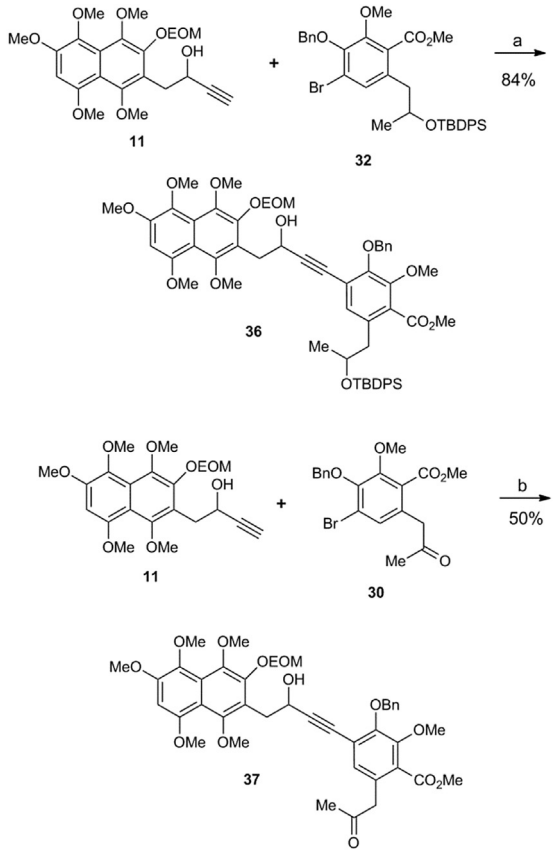
The failure of both lactone-containing isocoumarins **12** and **31** to spirocyclise focused our attention on the open chain precursors **30** and **32**. Attempts to effect Sonogashira coupling of ketone **30** with alkynol **11** using the established conditions were hampered due to undesired lactonisation of **30**. The requirement to use excess alkynol **11** together with the incompatibility of the reaction conditions with ketone **30** necessitated the investigation of alternative cross-coupling conditions.



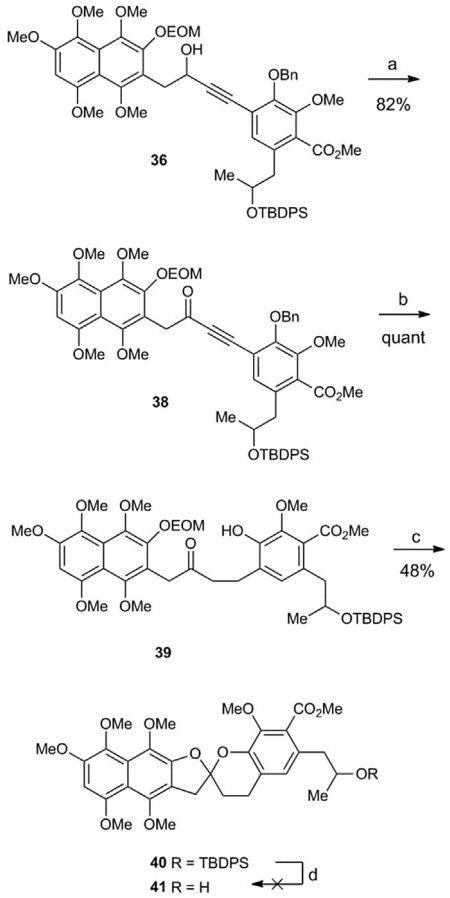
Scheme 7. Synthesis of the three isocoumarin precursor coupling partners **30**–**32**. *Reagents and conditions*: (a) MeI, K_2CO_3, acetone, 50 °C, 3 h (b) $NaBH_4$, THF-MeOH (1:1), 0 °C, 20 min then 1.0 M HCl, 20 min (c) $NaBH_4$, THF-MeOH (1:1), 0 °C, 20 min (d) TBDPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 4 h then rt., o/n.

Attention first turned to the coupling of alkynol **11** with dihydroisocoumarin **31** (Scheme 8). Sonogashira coupling of **31** with alkynol **11** using established conditions proceeded in a poor 23% yield. Despite this, elaboration to mono EOM protected dihydroxyketone **34** was undertaken to investigate the key spirocyclisation step. Once more, under a range of acidic conditions no spirocyclised product was obtained. TLC analysis over the duration of the reaction indicated cleavage of the EOM group but no further products were identified.

Conditions were sought to effect Sonogashira coupling utilising a weak base with the exclusion of a copper co-catalyst in order to minimise the Glaser–Hay homo-coupling of alkynes.[24] Thus, coupling of silyl ether **32** and ketone **30** with alkynol **11** using $Pd(OAc)_2$, 1 1′-bis(di-*tert*-butylphosphino)ferrocene (D^tBuPF) and K_2CO_3 in NMP at elevated temperatures afforded alkynes **36** and **37**, respectively, in moderate to good yield (Scheme 9). Importantly, only 1 equiv of alkynol **11** was required with no evidence for the formation of homo-coupled alkynol **28**.



Scheme 9. Sonogashira coupling of silyl ether **32** and ketone **30** with alkynol **11**. *Reagent and conditions*: (a) $Pd(OAc)_2$, D^tBuPF, K_2CO_3, NMP, 150 °C, 1.5 h (b) $Pd(OAc)_2$, D^tBuPF, K_2CO_3, NMP, 70 °C, 1.5 h.



Scheme 10. Synthesis of spiroketal **40**. *Reagent and conditions*: (a) IBX, DMSO, rt., 5 h (b) H_2, Pd/C, MeOH, rt., 2 h (c) $NaHSO_4{\cdot}SiO_2$, CH_2Cl_2, rt., 6 h (d) $[F^-]$.

Having established access to both coupled products **36** and **37**, elaboration of **36** to the corresponding mono EOM protected dihydroxyketone **39** was performed using the previously developed oxidation/hydrogenation/debenzylation sequence in 82% over two steps (Scheme 10). Ketone **39** was treated with silica-supported $NaHSO_4$[14] to finally afford the desired spiroketal **40** in a moderate 48% yield. However, attempts to cleave the TBDPS group using an array of fluoride sources were unsuccessful, preventing formation of the lactone to complete construction of the isocoumarin fragment.

2.5. Synthesis of griseorhodin model (7)

Given that spirocyclisation of ketone **39** to spiroketal **40** had been demonstrated, attention focused on elaboration of ketone **37** to the griseorhodin natural product framework (Scheme 11). It was envisioned that after spirocyclisation, the methyl ketone could be converted to the isocoumarin ring system by treatment with base. Using the same protocol as previously, ketone **37** was converted to ketone **43** in 85% yield over two steps. Treatment of ketone **43** with silica-supported $NaHSO_4$ was successful in affording spiroketal **44**, albeit in moderate 53% yield. Base-mediated enolate formation and spontaneous lactonisation afforded hexamethoxy spiroketal **8**. Oxidation of the naphthalene ring to the naphthoquinone using conditions described by Kozlowski et al.[20] followed by BCl_3 mediated cleavage of the three methoxy groups finally afforded the desired griseorhodin model spiroketal (**7**) in 58% yield over two steps.

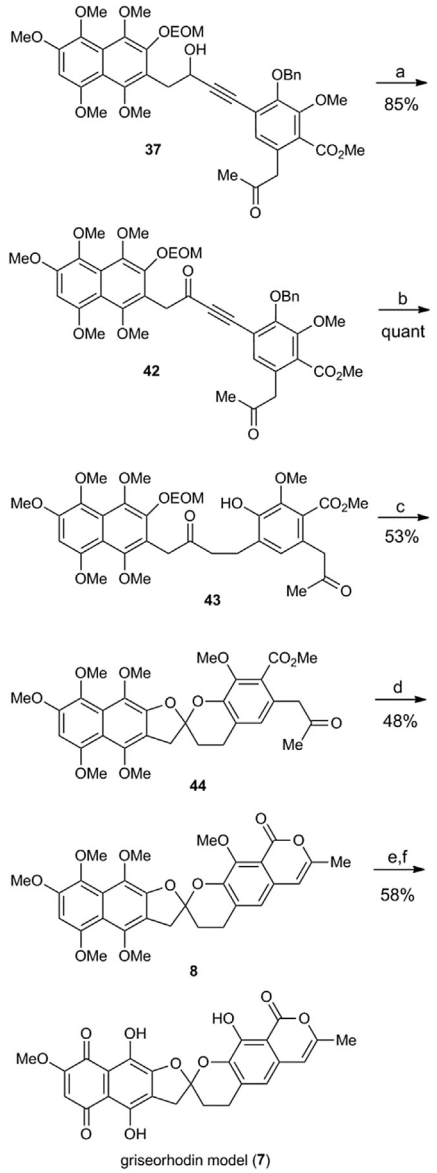
3. Conclusion

A systematic investigation of the functionality used to install the isocoumarin fragment of the griseorhodins determined that the presence of a lactone group is the key structure that prevents successful acid-mediated spirocyclisation of functionalised dihydroxyketones to take place. Use of an open chain isocoumarin precursor however, resulted in the successful synthesis of the griseorhodin model spiroketal (**7**). The use of an acyclic isocoumarin precursor is therefore essential to execute further synthetic work focused on the griseorhodin family of natural products. Continuing investigations into the installation of the oxygen functionality around the spiroketal core that distinguishes each member of the griseorhodin family of natural products, is currently being undertaken in our lab.

4. Experimental section

4.1. General information

Unless otherwise stated, all reactions were performed under an atmosphere of dry nitrogen in oven dried (100 °C) glassware. Commercially available starting materials and reagents were used as received unless otherwise noted. Dioxane and tetrahydrofuran (THF) were freshly distilled over sodium/benzophenone ketyl. Acetonitrile (MeCN), dichloromethane (CH_2Cl_2) and ethanol (EtOH) were freshly distilled from calcium hydride. Triethylamine (Et_3N) was distilled from calcium hydride and stored over potassium hydroxide. Dimethylformamide (DMF) was freshly distilled from molecular sieves (Linde type 4 Å). Reactions performed at low temperature were either cooled with an acetone-dry ice bath to reach −78 °C or a water-ice bath to reach 0 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on E.



Scheme 11. Elaboration of **37** to griseorhodin model (**7**). *Reagents and conditions*: (a) IBX, DMSO, rt., 3 h (b) H_2, Pd/C, MeOH, rt., 2 h (c) $NaHSO_4 \cdot SiO_2$, CH_2Cl_2, rt., 9 h (d) NaH, THF, 0 °C→rt., 30 min (e) DDQ, MeCN−H_2O (10:1), 0 °C, 15 min (f) BCl_3, CH_2Cl_2, 0 °C, 10 min.

Merck silica gel plates using UV light as visualizing agent and an ethanolic solution of vanillin or ammonium molybdate with heat as developing agents. Flash column chromatography was performed using Kieselgel S 63-100 μm (Riedel-de-Hahn) silica gel and the indicated solvent system. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer using a diamond ATR sampling accessory as neat solids or liquids. NMR spectra were recorded at ambient temperature as $CDCl_3$ or MeOD solutions on either a Bruker DRX300 spectrometer operating at 300 MHz for ^1H nuclei and 75 MHz for ^{13}C nuclei, a Bruker DRX400 spectrometer operating at 400 MHz for ^1H nuclei and 100 MHz for ^{13}C nuclei or a Bruker DRX500 spectrometer operating at 500 MHz for ^1H nuclei and 120 MHz for ^{13}C nuclei. All chemical shifts are reported in ppm on the δ scale and were measured relative to the protium solvent in which the sample was analysed ($CDCl_3$: δ 7.26 for ^1H NMR, δ 77.0 for ^{13}C NMR and MeOD: δ 3.31 for ^1H NMR, δ 49.0 for ^{13}C NMR). ^1H NMR data is reported as chemical shift in ppm, followed by multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad or combination thereof), coupling constants where applicable and relative integral. Mass spectra were recorded on a Bruker microTOF QII (electrospray ionisation, ESI) mass spectrometer.

4.2. Methyl 3-(benzyloxy)-4-bromo-2-methoxy-6-(2-methoxy-2-oxoethyl)benzoate (25)

To a stirred solution of phenol **20** (2.0 g, 7.87 mmol) in AcOH (35 mL) was added NaOAc (0.96 g, 12.0 mmol) and a solution of Br_2 (0.44 mL, 8.65 mmol) in AcOH (15 mL) dropwise. The solution was then stirred at rt for 1 h before being concentrated in vacuo. Water (15 mL) was then added to the residue and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexane-EtOAc, 2:1) to afford the aryl bromide (2.41 g, 92%) as a yellow oil that solidified on cooling o/n; Mp=63.0–64.5 °C; *Rf*: 0.33 (hexanes-EtOAc, 2:1); ν_{max}(neat)/cm^{-1} 3409, 2953, 1725, 1580, 1409, 1265, 1135, 1055, 1001, 819; δ_H (400 MHz; $CDCl_3$) 7.19 (s, 1H), 6.56 (br s, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.68 (s, 3H), 3.62 (s, 2H); δ_C (100 MHz; $CDCl_3$) 171.1 (C), 166.6 (C), 146.0 (C), 145.7 (C), 129.8 (C), 126.6 (CH), 124.9 (C), 111.6 (CH), 61.9 (CH_3), 52.2 (CH_3), 52.0 (CH_3), 38.0 (CH_2); *m/z* (ESI+) $[M+Na]^+$ 354.9784 calcd for $C_{12}H_{13}BrNaO_6$ 354.9788.

To a stirred solution of aryl bromide (1.86 g, 5.58 mmol) in acetone (30 mL) was added K_2CO_3 (1.16 g, 8.23 mmol) and BnBr (0.66 mL, 5.58 mmol) and the mixture was heated at reflux for 2 h. The mixture was cooled and filtered through a silica plug and the plug was washed with EtOAc (50 mL). The filtrate was concentrated and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with water (2×8 mL) and the combined aqueous washings were extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate was concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 5:1) to afford the *title compound* **25** (1.96 g, 81%) as a colourless oil; *Rf*: 0.29 (hexanes-EtOAc, 5:1); ν_{max}(neat)/cm^{-1} 3022, 2954, 2942, 2868, 1739, 1727, 1586, 1562, 1470, 1446, 1431, 1398, 1398, 1298, 1267, 1255, 1237, 1168, 1062, 1031, 1017, 987, 940, 913, 819, 804, 791, 735, 696, 677; δ_H (400 MHz; $CDCl_3$) 7.49 (d, *J*=2.0 Hz, 2H), 7.27–7.34 (m, 3H), 7.25, (s, 1H), 4.96 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.61 (s, 3H), 3.59 (s, 2H); δ_C (100 MHz; $CDCl_3$) 170.1 (C), 166.1 (C), 151.6 (C), 148.4 (C), 136.0 (C), 129.9 (CH), 129.0 (C), 128.3 (C), 128.0 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 119.6 (C), 74.6 (CH_2), 61.4 (CH_3), 51.8 (CH_3), 51.5 (CH_3), 37.7 (CH_2); *m/z* (ESI+) $[M+Na]^+$ 445.0256 calcd for $C_{19}H_{19}BrNaO_6$ 445.0257.

4.3. 3-(Benzyloxy)-4-bromo-2-methoxy-6-(2-oxopropyl) benzoic acid (26)

To a stirred solution of ester **25** (1.0 g, 2.36 mmol) in EtOH (20 mL) was added KOH (1.6 g, 28.5 mmol) and water (6.5 mL). The mixture was heated at reflux for 6 h before being cooled to rt and acidified with aqueous HCl (1.0 M, pH=2). The solution was then extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH, 10:1) to afford the homophthalic acid (0.91 g, 98%) as viscous colourless oil that solidified on cooling o/n; Mp=78.0–80.0 °C; *Rf*: 0.30 (CH_2Cl_2–MeOH, 10:1); ν_{max}(neat)/cm^{-1} 3450, 2942, 2507, 1964, 1714, 1670, 1563, 1395, 1266, 1194, 1012, 741; δ_H (400 MHz; MeOD) 7.42 (d, *J*=7.2 Hz, 2H), 7.21–7.28 (m, 4H), 4.87 (s, 2H), 3.80 (s, 3H), 3.62 (s, 2H); δ_C (100 MHz; MeOD) 174.3 (C), 169.8 (C), 152.6 (C),

149.5 (C), 137.6 (C), 131.4 (CH & C), 130.7 (C), 129.4 (CH), 129.3 (2 × CH), 129.2 (2 × CH), 120.3 (C), 76.0 (CH_2), 62.4 (CH_3), 39.0 (CH_2); *m/z* (ESI−) $[M-H]^-$ 392.9992 calcd for $C_{17}H_{14}BrO_6$ 392.9979.

To a stirred solution of homophthalic acid (0.796 g, 2.01 mmol) in Ac_2O (20 mL) was added pyridine (0.47 mL, 5.03 mmol) and stirred at rt for o/n. The excess Ac_2O and pyridine was removed in vacuo and the residue was suspended in aqueous NaOH (20 mL, 1.0 M) and heated at 60 °C for 3 h. The mixture was cooled and acidified using aqueous HCl (1.0 M, pH=2). The aqueous solution was extracted with EtOAc (3×50 mL) and the combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH, 16:1) to afford the *title compound* **26** (0.68 g, 85%) as an orange oil; R_f: 0.21 (CH_2Cl_2–MeOH, 16:1); ν_{max}(neat)/cm^{-1} 3478, 2983, 1713, 1559, 1452, 1371, 1260, 1160, 1064, 998, 698; δ_H (400 MHz; MeOD) 7.56 (d, *J*=7.6 Hz, 2H), 7.36–7.55 (m, 3H), 7.29 (s, 1H), 5.05 (s, 2H), 3.93 (s, 3H), 3.82 (s, 2H), 2.20 (s, 3H); δ_C (100 MHz; MeOD) 208.3 (C), 170.5 (C), 153.9 (C), 150.6 (C), 138.9 (C), 132.7 (CH), 132.3 (C), 132.1 (C), 130.6 (CH), 130.3 (2 × CH), 130.2 (2 × CH), 121.3 (C), 77.0 (CH_2), 63.3 (CH_3), 48.9 (CH_2), 30.5 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 415.0162 calcd for $C_{18}H_{17}BrNaO_5$ 415.0152.

4.4. 7-(Benzyloxy)-6-bromo-8-methoxy-3-methyl-1*H*-isochromen-1-one (12)

To a stirred solution of keto acid **26** (0.57 g, 1.45 mmol) in EtOAc-Ac_2O (30 mL, 5:1) was added $HClO_4$ (3 drops) and stirred at rt for 30 min. Saturated aqueous $NaHCO_3$ (25 mL) was added and the aqueous layer was separated and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 5:1) to afford the *title compound* **12** (0.51 g, 94%) as a yellow solid; Mp=133.4–134.2 °C; R_f: 0.25 (hexanes-EtOAc, 5:1); ν_{max}(neat)/cm^{-1} 2947, 1733, 1666, 1579, 1462, 1376, 1300, 965, 751; δ_H (400 MHz; $CDCl_3$) 7.54 (d, *J*=8.0 Hz, 2H), 7.36–7.42 (m, 3H), 7.30 (s, 1H), 6.07 (s, 1H), 5.09 (s, 2H), 4.00 (s, 3H), 2.24 (s, 3H); δ_C (100 MHz; $CDCl_3$) 158.8 (C), 156.0 (C), 154.9 (C), 148.8 (C), 136.4 (C), 135.9 (C), 128.7 (CH), 128.4 (2 × CH), 128.4 (2 × CH), 126.8 (C), 124.2 (CH), 113.7 (C), 102.1 (CH), 75.6 (CH_2), 62.0 (CH_3), 19.4 (CH_3); *m/z* (ESI+) $[M+H]^+$ 375.0216 calcd for $C_{18}H_{16}BrO_4$ 375.0226.

4.5. Methyl 3-(benzyloxy)-4-bromo-2-methoxy-6-(2-oxopropyl)benzoate (30)

To a stirred solution of acid **26** (1.03 g, 2.62 mmol) in acetone (20 mL) was added K_2CO_3 (0.34 g, 2.88 mmol) and MeI (0.20 mL, 3.14 mmol) and the mixture was heated at 50 °C for 3 h. The mixture was then filtered through a silica plug and the plug washed with EtOAc (40 mL). The filtrate was then concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and washed with water (2×5 mL). The combined aqueous washings were extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 3:1) to afford the *title compound* **30** (0.85 g, 80%) as a yellow oil; R_f: 0.27 (hexanes-EtOAc, 4:1); ν_{max}(neat)/cm^{-1} 2947, 1722, 1559, 1449, 1399, 1288, 1142, 1066, 1011, 826, 735, 697; δ_H (400 MHz; $CDCl_3$) 7.54 (d, *J*=7.2 Hz, 2H), 7.34–7.41 (m, 3H), 7.18 (s, 1H), 5.02 (s, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 3.69 (s, 2H), 2.17 (s, 3H); δ_C (100 MHz; $CDCl_3$) 204.3 (C), 166.9 (C), 152.1 (C), 148.6 (C), 136.3 (C), 130.3 (CH), 129.9 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 120.2 (C), 75.0 (CH_2), 61.8 (CH_3), 52.2 (CH_3), 47.4 (CH_2), 29.4 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 429.0308 calcd for $C_{19}H_{19}BrNaO_5$ 429.0300.

4.6. 7-(Benzyloxy)-6-bromo-8-methoxy-3-methylisochroman-1-one (31)

To a stirred solution of ketone **30** (0.20 g, 0.49 mmol) in MeOH-THF (1:1, 8 mL) at 0 °C was added $NaBH_4$ (20.0 mg, 0.54 mmol) in three portions over 10–15 min. Aqueous HCl (10 mL, 1.0 M) was then added and the mixture stirred vigorously for 20 min before being extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 5:1) to afford the *title compound* **31** (0.19 g, quant) as a colourless oil; R_f: 0.34 (hexanes-EtOAc, 5:1); ν_{max}(neat)/cm^{-1} 3031, 2975, 2950, 2940, 2850, 1715, 1581, 1561, 1453, 1432, 1405, 1373, 1249, 1212, 1076, 1046, 997, 962, 923; δ_H (400 MHz; $CDCl_3$) 7.52 (d, 2H, *J*=7.0 Hz), 7.31–7.36 (m, 3H), 7.18 (s, 1H), 5.02 (s, 2H), 4.49–4.54 (m, 1H), 3.96 (s, 3H), 2.78–2.81 (m, 2H), 1.44 (d, 3H, *J*=6.4 Hz); δ_C (100 MHz; $CDCl_3$) 161.4 (C), 156.2 (C), 149.4 (C), 136.7 (C), 136.2 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.2 (CH), 126.3 (C), 124.0 (C), 118.7 (C), 75.1 (CH_2), 74.2 (CH), 61.8 (CH_3), 34.9 (CH_2), 20.3 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 399.0212 calcd for $C_{18}H_{17}NaBrO_4$ 399.0202.

4.7. Methyl-3-(benzyloxy)-4-bromo-6-(2-((tert-butyldiphenylsilyl)oxy)propyl)-2-methoxybenzoate (32)

To a stirred solution of ketone **30** (0.14 g, 0.35 mmol) in MeOH-THF (3.0 mL, 1:1) at 0 °C was added $NaBH_4$ (14.5 mg, 0.38 mmol) in three portions over 10–15 min. Water (5.0 mL) was then added at the same temperature before the mixture was extracted with EtOAc (3×8 mL). The combined organic extracts were washed with brine (6 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated in vacuo.

The crude alcohol was dissolved in CH_2Cl_2 (4 mL) and cooled to −78 °C. A solution of TBDPSOTf (0.18 g, 0.70 mmol) in CH_2Cl_2 (2 mL) was added followed by 2,6-lutidiene (0.12 mL, 1.04 mmol) and the mixture was stirred at −78 °C for 4 h before being warmed to rt o/n (cooling bath remained in place). Saturated aqueous $NaHCO_3$ (5 mL) was added and the aqueous layer was separated and extracted with CH_2Cl_2 (3×8 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 19:1) to afford the *title compound* **32** (0.14 g, 78%) as a colourless oil; R_f: 0.33 (hexanes-EtOAc, 19:1); ν_{max}(neat)/cm^{-1} 3072, 2941, 2858, 1732, 1560, 1462, 1428, 1400, 1374, 1290, 1267, 1111, 1079, 1011, 994, 822, 739, 702; δ_H (300 MHz; $CDCl_3$) 7.36–7.71 (m, 15H), 7.10 (s, 1H), 5.00 (s, 2H), 4.03–4.10 (m, 1H), 3.91 (s, 3H), 3.83 (s, 3H), 2.73 (dd, *J*=13.6, 6.8 Hz, 1H), 2.65 (dd, 13.6, 6.8 Hz), 0.99–1.02 (m, 12H); δ_C (75 MHz; $CDCl_3$) 167.4 (C), 151.1 (C), 147.5 (C), 136.6 (C), 135.9 (2 × CH), 134.5 (C), 133.9 (C), 133.8 (C), 130.5 (CH), 129.6 (2 × CH), 129.5 (2 × CH), 129.5 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.3 (CH), 127.6 (2 × CH), 127.5 (2 × CH), 119.4 (C), 75.2 (CH_2), 70.1 (CH), 61.9 (CH_3), 52.2 (CH_3), 42.6 (CH_2), 26.8 (3 × CH_3), 23.3 (CH_3), 19.1 (C); *m/z* (ESI+) $[M+Na]^+$ 669.1642 calcd for $C_{35}H_{39}BrNaO_5Si$ 669.1636.

4.8. 7-(Benzyloxy)-6-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-hydroxybut-1-yn-1-yl)-8-methoxy-3-methyl-1*H*-isochromen-1-one (27)

To a mixture of bromide **12** (0.134 g, 0.357 mmol), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol), CuI (8.6 mg, 0.045 mmol), PPh_3 (18.0 mg, 0.089 mmol) in DMF (4 mL, degassed with N_2) was added NEt_3 (0.075 mL, 0.54 mmol) followed by the dropwise addition of alkyne **11** (0.30 g, 0.71 mmol) in DMF (2 mL, degassed with N_2). The mixture was degassed with N_2 for a further 1 h and then stirred at rt for 24 h. Aqueous HCl (5 mL, 1.0 M) was added and the aqueous

layer was separated and extracted with EtOAc (3×8 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 1:1) to afford the *title compound* **27** (0.16 g, 64%) as a yellow oil; R_f: 0.33 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 3462, 2933, 2841, 1733, 1666, 1595, 1454, 1358, 1056, 1005, 521; δ_H (400 MHz; $CDCl_3$) 7.57 (d, J=1.2 Hz, 2H), 7.31–7.41 (m, 3H), 7.09 (s, 1H), 6.66 (s, 1H), 6.07 (s, 1H), 5.37, 5.31 (ABq, J_{AB}=6.0 Hz, 2H), 5.15 (s, 2H), 4.95–5.00 (m, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.97 (s, 3H), 3.87–3.94 (m, 1H), 3.77–3.82 (m, 9H), 3.40–3.42 (m, 2H), 2.23 (s, 3H) 1.26 (t, J=6.8 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 158.7 (C), 154.9 (C), 153.9 (C), 152.7 (C), 151.6 (C), 151.2 (C), 149.7 (C), 148.6 (C), 142.5 (C), 136.7 (C), 136.3 (C), 134.8 (C), 128.3 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 125.9 (C), 125.6 (C), 124.2 (CH), 120.9 (C), 114.2 (C), 113.9 (C), 102.4 (CH), 99.3 (C), 98.6 (CH_2), 96.2 (CH), 79.1 (C), 75.6 (CH_2), 65.5 (CH_2), 62.8 (CH), 62.0 (CH_3), 61.6 (CH_3), 61.5 (CH_3), 61.2 (CH_3), 56.6 (CH_3), 56.5 (CH_3), 33.0 (CH_2), 19.1 (CH_3), 14.9 (CH_3); m/z (ESI+) $[M+Na]^+$ 737.2555 calcd for $C_{40}H_{42}NaO_{12}$ 737.2586.

4.9. 6-(4-(3-(Ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobutyl)-7-hydroxy-8-methoxy-3-methyl-1*H*-isochromen-1-one (9)

To a stirred solution of alkynol **27** (0.27 g, 0.38 mmol) in DMSO (4 mL) was added a solution of IBX (0.42 g, 1.51 mmol) in DMSO (3 mL) and stirred at rt for 5 h. The mixture was diluted with EtOAc (10 mL) and saturated aqueous Na_2SO_3 (10 mL). The aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 1:1) to afford the ketone (0.22 g, 80%) as a yellow oil; R_f: 0.50 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 2932, 2202, 1737, 1668, 1602, 1455, 1358, 1253, 1172, 1105, 1053, 1005; δ_H (400 MHz; $CDCl_3$) 7.50–7.51 (m, 2H), 7.30–7.38 (m, 3H), 6.93 (s, 1H), 6.68 (s, 1H), 5.98 (s, 1H), 5.33 (s, 2H), 5.13 (s, 2H), 4.22 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.96 (s, 3H), 3.78–3.84 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 2.21 (s, 3H), 1.23 (t, J=8.0 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 185.1 (C), 158.5 (C), 155.2 (C), 154.6 (C), 153.1 (C), 152.5 (C), 151.7 (C), 150.2 (C), 147.9 (C), 142.6 (C), 136.5 (C), 136.3 (C), 135.0 (C), 128.7 (2 × CH), 128.4 (2 × CH), 128.4 (CH), 126.3 (C), 125.4 (CH), 123.0 (C), 118.4 (C), 115.8 (C), 114.2 (C), 102.4 (CH), 98.3 (CH_2), 96.1 (CH), 93.5 (C), 85.2 (C), 76.2 (CH_2), 65.7 (CH_2), 62.3 (CH_3), 61.9 (CH_3), 61.8 (CH_3), 61.5 (CH_3), 56.7 (CH_3), 56.7 (CH_3), 41.5 (CH_2), 19.3 (CH_3), 15.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 735.2398 calcd for $C_{40}H_{40}NaO_{12}$ 735.2412.

To a stirred solution of the ketone (0.21 g, 0.30 mmol) in MeOH (6 mL) was added 10% Pd/C (0.11 g, 1.01 mmol) and stirred under a H_2 atmosphere for 1 h. The mixture was filtered through a pad of Celite®, and the pad was washed with EtOAc (30 mL). The filtrate was concentrated in vacuo to afford the *title compound* **9** (0.18 g, 99%) as a yellow oil; R_f: 0.49 (hexanes-EtOAc, 1:2); ν_{max}(neat)/cm^{-1} 3395, 2931, 1715, 1666, 1604, 1479, 1453, 1425, 1383, 1355, 1340, 1208, 1133, 1045, 1003, 935, 732; δ_H (400 MHz; $CDCl_3$) 6.89 (s, 1H), 6.65 (s, 1H), 6.37 (br s, 1H), 6.06 (s, 1H), 5.25 (s, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.93 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.78 (q, J=7.2 Hz, 2H), 3.64 (s, 3H), 2.99–3.03 (m, 2H), 2.88–2.92 (m, 2H), 2.21 (s, 3H), 1.22 (t, J=6.8 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 207.9 (C), 159.7 (C), 153.0 (C), 152.3 (C), 151.2 (C), 150.0 (C), 147.7 (C), 147.0 (C), 146.7 (C), 142.7 (C), 137.0 (C), 136.7 (C), 131.7 (C), 126.0 (C), 121.9 (CH), 119.8 (C), 114.4 (C), 111.2 (C), 103.3 (CH), 98.3 (CH_2), 96.3 (CH), 65.8 (CH_2), 62.4 (CH_3), 62.1 (CH_3), 61.9 (CH_3), 61.6 (CH_3), 56.9 (CH_3), 56.8 (CH_3), 40.8 (CH_2), 39.4 (CH_2), 25.0 (CH_2), 19.3 (CH_3), 15.3 (CH_3); m/z (ESI+) $[M+Na]^+$ 649.2238 calcd for $C_{33}H_{38}NaO_{12}$ 649.2239.

4.10. 7-Hydroxy-6-(4-(3-hydroxy-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobutyl)-8-methoxy-3-methyl-1*H*-isochromen-1-one (29)

To a stirred solution of ether **9** (40.0 mg, 0.064 mmol) in CH_2Cl_2 (3.0 mL) was added PPTS (0.16 g, 0.64 mmol) and stirred at rt for 12 h. The mixture was filtered through a silica plug and the plug was washed with CH_2Cl_2 (15 mL). The solvent was removed in vacuo and the crude product was purified by flash chromatography (hexanes-EtOAc, 1–2) to afford the *title compound* **29** (32.2 mg, 90%) as a yellow oil; R_f: 0.38 (hexanes-EtOAc, 1:2); ν_{max}(neat)/cm^{-1} 3391, 2926, 2850, 1715, 1665, 1607, 1480, 1454, 1357, 1296, 1255, 1210, 1167, 1089, 1007, 988, 942, 878, 817, 734, 657; δ_H (400 MHz; $CDCl_3$) 6.88 (s, 1H), 6.56 (s, 1H), 6.40 (br s, 1H), 6.36 (br s, 1H), 6.05 (s, 1H), 3.99 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.90 (s, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.66 (s, 3H), 2.99–3.03 (m, 2H), 2.91–2.95 (m, 2H), 2.19 (s, 3H); δ_C (100 MHz; $CDCl_3$) 207.8 (C), 159.7 (C), 153.4 (C), 152.2 (2 × C), 151.9 (C), 146.9 (C), 146.6 (C), 146.3 (C), 136.9 (C), 135.0 (C), 131.6 (C), 128.5 (C), 124.7 (C), 121.8 (CH), 114.2 (C), 111.8 (C), 111.2 (C), 103.3 (CH), 94.5 (CH), 62.6 (CH_3), 62.4 (CH_3), 62.3 (CH_3), 61.9 (CH_3), 56.7 (CH_3), 56.6 (CH_3), 40.9 (CH_2), 38.7 (CH_2), 25.0 (CH_2), 19.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 591.1837 calcd for $C_{30}H_{32}NaO_{11}$ 591.1828.

4.11. 7-(Benzyloxy)-6-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-hydroxybut-1-yn-1-yl)-8-methoxy-3-methylisochroman-1-one (33)

To a mixture of bromide **31** (0.17 g, 0.46 mmol), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol), CuI (10.4 mg, 0.055 mmol), PPh_3 (23.1 mg, 0.11 mmol) in DMF (3 mL, degassed) was added NEt_3 (96.0 μL, 0.69 mmol) followed by a solution of alkyne **11** (0.38 g, 0.91 mmol) in DMF (2 mL, degassed) dropwise. The reaction mixture was degassed for a further 1 h and then stirred at rt for 24 h. Aqueous HCl (6 mL, 1.0 M) was added and the mixture extracted with EtOAc (3×8 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 1:1) to afford the *title compound* **33** (76.0 mg, 23%) as viscous orange oil; R_f: 0.23 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 3454, 2980, 1722, 1602, 1456, 1358, 1251, 1056, 1005; δ_H (400 MHz; $CDCl_3$) 7.55 (d, J=7.2 Hz, 2H), 7.30–7.38 (m, 3H), 6.98 (s, 1H), 6.65 (s, 1H), 5.35, 5.29 (ABq, J_{AB}=6.0 Hz, 2H), 5.11 (s, 2H), 4.97–4.98 (m, 1H), 4.52–4.57 (m, 1H), 3.96–3.98 (m, 9H), 3.87–3.92 (m, 2H), 3.78–3.82 (m, 9H), 3.63 (br s, 1H), 3.38–3.41 (m, 2H), 2.77–2.81 (m, 2H), 1.47 (d, J=6.4 Hz, 3H), 1.25 (t, J=7.2 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 161.8 (C), 155.5 (C), 152.9 (C), 152.8 (C), 151.3 (C), 149.9 (C), 148.8 (C), 142.7 (C), 136.9 (C), 136.5 (C), 135.5 (C), 128.5 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 126.2 (CH), 125.8 (C), 123.8 (C), 121.1 (C), 119.3 (C), 114.4 (C), 98.9 (C), 98.8 (CH_2), 96.4 (CH), 79.4 (C), 75.6 (CH_2), 74.4 (CH), 65.7 (CH_2), 63.0 (CH), 62.2 (CH_3), 61.9 (CH_3), 61.8 (CH_3), 61.4 (CH_3), 56.8 (CH_3), 56.7 (CH_3), 35.3 (CH_2), 33.2 (CH_2), 20.5 (CH_3), 15.1 (CH_3). m/z (ESI+) $[M+H]^+$ 717.2898 calcd for $C_{40}H_{45}O_{12}$ 717.2906.

4.12. 6-(4-(3-(Ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobutyl)-7-hydroxy-8-methoxy-3-methylisochroman-1-one (34)

To a stirred solution of alcohol **33** (76 mg, 0.11 mmol) in DMSO (2 mL) was added a solution of IBX (90 mg, 0.32 mmol) in DMSO (3 mL) and stirred at rt for 4 h. Saturated aqueous Na_2SO_3 (4 mL) was added and aqueous layer was separated and extracted with EtOAc (3×5 mL). Combined organic extracts were washed with brine (3 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 1:1) to afford the ketone

(59.0 mg, 80%) as a viscous yellow oil; R_f: 0.26 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 2930, 2197, 1725, 1674, 1599, 1454, 1416, 1357, 1251, 1209, 1122, 1051, 1004, 927, 756, 699; δ_H (400 MHz; $CDCl_3$) 7.48 (d, J=7.2 Hz, 2H), 7.30–7.38 (m, 3H), 6.84 (s, 1H), 6.64 (s, 1H), 5.29 (s, 2H), 5.09 (s, 2H), 4.48–4.56 (m, 1H), 4.19 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.75–3.81 (m, 8H), 3.71 (s, 3H), 2.66–2.81 (m, 2H), 1.47 (d, J=6.4 Hz, 3H), 1.21 (t, 3H); δ_C (100 MHz; $CDCl_3$) 185.2 (C), 161.4 (C), 155.5 (C), 154.0 (C), 153.1 (C), 151.6 (C), 151.0 (C), 147.9 (C), 142.6 (C), 136.6 (C), 136.3 (C), 135.6 (C), 128.7 (2 × CH), 128.5 (2 × CH), 128.4 (CH), 127.0 (CH), 126.3 (C), 121.4 (C), 120.7 (C), 118.5 (C), 114.3 (C), 98.3 (CH_2), 96.1 (CH), 93.4 (C), 85.5 (C), 76.1 (CH_2), 74.5 (CH), 65.7 (CH_2), 62.4 (CH_3), 62.0 (CH_3), 61.8 (CH_3, 61.6 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 41.5 (CH_2), 35.2 (CH_2), 20.5 (CH_3), 15.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 737.2564 calcd for $C_{40}H_{42}NaO_{12}$ 737.2568.

To a stirred solution of the ketone (17.4 mg, 0.024 mmol) in MeOH (3 mL) was added Pd/C (7.0 mg, 0.066 mmol) and stirred under a H_2 atmosphere at rt for 2 h. The mixture was filtered through a silica plug and the plug was washed with EtOAc (20 mL). The filtrate was concentrated in vacuo to afford the *title compound* **34** (15.3 mg, quant) as a viscous yellow oil. R_f: 0.38 (hexanes-EtOAc, 1:2); ν_{max}(neat)/cm^{-1} 3374, 2930, 1715, 1605, 1458, 1357, 1210, 1135, 1053, 1005, 941; δ_H (400 MHz; $CDCl_3$) 6.75 (s, 1H), 6.64 (s, 1H), 6.33 (br s, 1H), 5.25 (s, 2H), 4.50–4.55 (m, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.92 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.75 (q, J=7.2 Hz, 2H), 3.64 (s, 3H), 2.91–2.95 (m, 2H), 2.84–2.89 (m, 2H), 2.74–2.77 (m, 2H), 1.45 (d, J=6.4 Hz, 3H), 1.22 (t, J=7.2 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 208.2 (C), 161.8 (C), 152.9 (C), 151.1 (C), 150.0 (C), 148.2 (C), 147.7 (C), 146.9 (C), 142.6 (C), 136.6 (C), 134.2 (C), 131.4 (C), 125.9 (C), 123.8 (CH), 119.8 (C), 115.0 (C), 114.3 (C), 98.3 (CH_2), 96.2 (CH), 74.9 (CH), 65.7 (CH_2), 62.1 (CH_3), 62.1 (CH_3), 61.8 (CH_3), 61.6 (CH_3), 56.8 (CH_3), 56.7 (CH_3), 41.0 (CH_2), 39.3 (CH_2), 35.2 (CH_2), 24.7 (CH_2), 20.6 (CH_3), 15.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 651.2417 calcd for $C_{33}H_{40}NaO_{12}$ 651.2412.

4.13. Methyl 3-(benzyloxy)-6-(2-((tert-butyldiphenylsilyl)oxy) propyl)-4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-hydroxybut-1-yn-1-yl)-2-methoxybenzoate (36)

To a mixture of $Pd(OAc)_2$ (3.47 mg, 0.015 mmol), 1,1′-bis(di-*tert*-butyl phosphino)ferrocene (8.80 mg, 0.019 mmol), K_2CO_3 (53.0 mg, 0.39 mmol), alkyne **11** (32 mg, 0.077 mmol) and aryl bromide **32** (50 mg, 0.077 mmol) under an argon atmosphere was added NMP (4 mL, degassed with argon). The mixture was heated at 150 °C (sand bath) for 1.5 h and then cooled to rt. The mixture was filtered through a silica plug and the plug was washed with EtOAc (50 mL). The filtrate was washed with water (35 mL), brine (35 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 2:1) to afford the *title compound* **36** (64.0 mg, 84%) as a yellow oil; R_f: 0.52 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 3460, 2930, 2854, 1729, 1600, 1448, 1380, 1357, 1105, 1055, 1005, 940; δ_H (400 MHz; $CDCl_3$) 7.31–7.71 (m, 15H), 6.95 (s, 1H), 6.67 (s, 1H), 5.38, 5.33 (ABq, J_{AB}=8.0 Hz, 2H), 5.10 (s, 2H), 4.97–5.02 (m, 1H), 4.05–4.10 (m, 1H), 3.99 (s, 3H), 3.97 (s, 3H), 3.89 (s, 3H), 3.80–3.83 (m, 14H), 3.59 (d, J=7.2 Hz, 1H), 3.41–3.44 (m, 2H), 2.76–2.81 (m, 1H), 2.61–2.66 (m, 1H), 1.22–1.26 (m, 3H), 1.01–0.99 (m, 12H); δ_C (100 MHz; $CDCl_3$) 167.5 (C), 152.8 (C), 151.3 (C), 151.0 (C), 150.0 (C), 149.8 (C), 148.9 (C), 142.6 (C), 137.0 (C), 136.5 (C), 135.7 (2 × CH), 134.5 (C), 133.8 (C), 132.2 (C), 130.7 (CH), 130.0 (C), 129.5 (2 × CH), 129.4 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.5 (2 × CH), 127.4 (2 × CH), 125.7 (C), 121.2 (C), 119.6 (C), 114.4 (C), 98.8 (CH_2), 96.5 (C), 96.4 (CH), 79.5 (C), 75.4 (CH_2), 70.0 (CH), 65.7 (CH_2), 62.9 (CH), 62.2 (CH_3), 61.7 (CH_3), 61.7 (CH_3), 61.3 (CH_3), 56.8 (CH_3), 56.7 (CH_3), 52.0 (CH_3), 42.6 (CH_2), 33.3 (CH_2), 26.8 (3 × CH_3), 23.1 (CH_3), 19.0 (C), 15.0 (CH_3); m/z (ESI+) $[M+Na]^+$ 1009.4165 calcd for $C_{57}H_{66}NaO_{13}Si$ 1009.4136.

4.14. Methyl 3-(benzyloxy)-6-(2-((tert-butyldiphenylsilyl)oxy) propyl)-4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobut-1-yn-1-yl)-2-methoxybenzoate (38)

To a stirred solution of alcohol **36** (47 mg, 0.061 mmol) in DMSO (1 mL) was added a solution of IBX (60 mg, mmol) in DMSO (1 mL) and stirred at rt for 5 h. Saturated aqueous Na_2SO_3 (2 mL) was added and aqueous layer was separated and extracted with EtOAc (3×3 mL). The combined organic extracts were washed with brine (2 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 2:1) to afford the *title compound* **38** (38.6 mg, 82%) as a yellow oil; R_f: 0.63 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 2940, 2864, 2198, 1734, 1677, 1601, 1454, 1353, 1212, 1111, 1053, 1004, 703; δ_H (400 MHz; $CDCl_3$) 7.30–7.67 (m, 15H), 6.90 (s, 1H), 6.64 (s, 1H), 5.29 (s, 2H), 5.05 (s, 2H), 4.21 (s, 2H), 4.00–4.04 (m, 1H), 3.98 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.74–3.82 (m, 11H), 3.71 (s, 3H), 2.70–2.75 (m, 1H), 2.55–2.60 (m, 1H), 1.18 (t, J=7.0 Hz, 3H), 0.96–0.97 (m, 12H); δ_C (100 MHz; $CDCl_3$) 185.1 (C), 167.1 (C), 153.0 (C), 152.3 (C), 151.6 (C) 150.1 (C), 147.9 (C), 142.5 (C), 136.7 (C), 136.5 (C), 135.9 (2 × CH), 135.8 (CH), 134.5 (C), 133.8 (C), 132.7 (C), 132.5 (C), 131.8 (CH), 129.7 (2 × CH), 129.6 (2 × CH), 128.6 (2 × CH), 128.5 (2 × CH), 128.3 (CH), 127.6 (2 × CH), 127.5 (2 × CH), 126.2 (C), 118.5 (C), 116.7 (C), 114.3 (C), 98.3 (CH_2), 96.3 (CH), 92.4 (C), 86.2 (C), 75.9 (CH_2), 70.0 (CH), 65.7 (CH_2), 62.4 (CH_3), 61.8 (CH_3), 61.8 (CH_3), 61.6 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 52.3 (CH_3), 42.7 (CH_2), 41.6 (CH_2), 26.8 (3 × CH_3), 23.3 (CH_3), 19.1 (C), 15.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 1007.4008 calcd for $C_{57}H_{64}NaO_{13}Si$ 1007.3974.

4.15. Methyl 6-(2-((tert-butyldiphenylsilyl)oxy)propyl)-4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobutyl)-3-hydroxy-2-methoxybenzoate (39)

To a stirred solution of alkyne **38** (75 mg, 0.076 mmol) in MeOH (3 mL) was added Pd/C (10 mg, 0.094 mol) and stirred under a H_2 atmosphere at rt for 2 h. The mixture was filtered through a silica plug and the plug was washed with EtOAc (10 mL). The filtrate was concentrated in vacuo to afford the *title compound* **39** (0.068 mg, quant) as a yellow oil. R_f: 0.20 (hexanes-EtOAc, 2:1); ν_{max}(neat)/cm^{-1} 3376, 2937, 2859, 1725, 1602, 1447, 1356, 1280, 1207, 1109, 1053, 1005, 939, 822, 741, 704, 611; δ_H (400 MHz; $CDCl_3$) 7.29–7.65 (m, 10H), 6.72 (br s, 1H), 6.64 (s, 1H), 6.47 (s, 1H), 5.24 (s, 2H), 4.00 (s, 3H), 3.94–3.99 (m, 4H), 3.90 (s, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.71 (q, J=8.0 Hz, 2H), 3.63 (s, 3H), 2.56–2.85 (m, 6H), 1.20 (t, J=8.0 Hz, 3H), 0.94–0.97 (m, 12H); δ_C (100 MHz; $CDCl_3$) 210.1 (C), 168.1 (C), 153.0 (C), 151.1 (C), 150.0 (C), 147.7 (C), 145.5 (C), 144.8 (C), 142.6 (C), 136.7 (C), 135.9 (4 × CH), 134.7 (C), 134.2 (C), 130.1 (2 × C), 129.4 (2 × CH), 128.2 (CH), 128.0 (2 × CH), 127.4 (2 × CH), 126.2 (C), 126.0 (C), 119.7 (C), 114.3 (C), 98.3 (CH_2), 96.3 (CH), 70.7 (CH), 65.7 (CH_2), 62.1 (CH_3), 61.8 (CH_3), 61.7 (CH_3), 61.6 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 52.0 (CH_3), 42.8 (CH_2), 42.4 (CH_2), 39.2 (CH_2), 26.9 (3 × CH_3), 24.0 (CH_2) 23.1 (CH_3), 19.1 (C), 15.2 (CH_3); m/z (ESI+) $[M+Na]^+$ 921.3852 calcd for $C_{50}H_{62}NaO_{13}Si$ 921.3875.

4.16. Methyl-6-(2-((tert-butyldiphenylsilyl)oxy)propyl)-4′,5′,7′,8,8′,9′-hexamethoxy-3′*H*-spiro[chroman-2,2′-naphtho [2,3-b]furan]-7-carboxylate (40)

To a stirred solution of ketone **39** (52.4 mg, 0.058 mmol) in CH_2Cl_2 (4 mL) was added $NaHSO_4.SiO_2$ (0.40 g) and stirred at rt for 6 h. The mixture was filtered through cotton wool and washed with EtOAc (15 mL) and the filtrate was concentrated in vacuo. The crude

product was purified by flash chromatography (hexanes-EtOAc, 2:1) to afford the *title compound* **40** (23.1 mg, 48%) as a yellow oil; R_f: 0.27 (hexanes-EtOAc, 2:1); ν_{max}(neat)/cm^{-1} 2940, 2895, 1731, 1642, 1604, 1441, 1355, 1255, 1206, 1055, 1006, 873, 823, 704; δ_H (400 MHz; $CDCl_3$) 7.34–7.69 (m, 10H), 6.59 (s, 1H), 6.57 (s, 1H), 4.03–4.06 (m, 1H), 3.97 (s, 6H), 3.84 (s, 3H) 3.79 (m, 3H), 3.64–3.73 (m, 7H), 3.58 (m, 3H), 3.40 (dd, J=16.8, 1.2 Hz), 3.17–3.31 (m, 1H), 2.57–2.76 (m, 3H), 2.39 (ddd, J=13.4, 6.2, 2.2 Hz, 1H), 2.19–2.27 (m, 1H), 0.98–1.01 (m, 12H); δ_C (100 MHz; $CDCl_3$) 168.1 (C), 153.3 (C), 149.9 (C), 149.1 (C), 148.7 (C), 145.2 (C), 143.3 (C), 137.1 (C), 135.9 (4 × CH), 134.8 (C), 134.1 (C), 133.0 (C), 129.4 (4 × CH), 128.9 (C), 127.5 (2 × CH), 127.4 (CH), 127.2 (C), 126.4 (C), 124.0 (C), 117.8 (C), 113.6 (C), 109.8 (C), 95.1 (CH) 70.6 (CH), 61.9 (CH_3), 61.8 (CH_3), 61.7 (CH_3), 61.5 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 51.9 (CH_3), 42.7 (CH_2), 39.6 (CH_2), 29.9 (CH_2), 26.9 (3 × CH_3), 23.3 (CH_3), 21.9 (CH_2), 19.2 (C); *m/z* (ESI+) $[M+Na]^+$ 845.3328 calcd for $C_{47}H_{54}NaO_{11}Si$ 845.3317.

4.17. Methyl-3-(benzyloxy)-4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-hydroxybut-1-yn-1-yl)-2-methoxy-6-(2-oxopropyl)benzoate (37)

To a mixture of $Pd(OAc)_2$ (0.11 g, 0.49 mmol), 1,1′-bis(di-*tert*-butyl phosphino)ferrocene (0.31 g, 0.66 mmol), K_2CO_3 (1.81 g, 13.1 mmol), alkyne **11** (1.38 g, 3.25 mmol) and aryl bromide **30** (1.34 g, 3.25 mmol) under an argon atmosphere was added NMP (12 mL, degassed with argon). The mixture was heated at 70 °C (sand bath) for 1.5 h. After cooling to rt the mixture was filtered through a silica plug and the plug was washed with EtOAc (50 mL). The filtrate was washed with water (2×20 mL) and the combined aqueous washings were extracted with EtOAc (3×30 mL). Combined organic extracts were washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 2:3) to afford the *title compound* **37** (1.2 g, 50%) as a viscous orange oil; R_f: 0.21 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 3438, 2940, 2846, 1721, 1604, 1555, 1448, 1413, 1352, 1285, 1173, 1043, 1007, 820, 733, 698; δ_H (400 MHz; $CDCl_3$) 7.55 (d, J=7.2 Hz, 2H), 7.30–7.39 (m, 3H), 6.99 (s, 1H), 6.65 (s, 1H), 5.35, 5.30 (ABq, J_{AB}=6.0 Hz, 2H) 5.11 (s, 2H), 4.94–4.97 (m, 1H), 3.98 (s, 3H), 3.96 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.77–3.79 (m, 11H), 3.64 (s, 2H), 3.36–3.40 (m, 3H), 2.14 (s, 3H), 1.25 (t, J=7.0 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 204.9 (C), 167.2 (C), 152.9 (C), 152.2 (C), 151.3 (C), 151.3 (C), 149.8 (C), 148.9 (C), 142.7 (C), 136.9 (C), 136.6 (C), 130.6 (CH), 129.1 (C), 128.5 (C), 128.4 (2 × CH), 128.3 (2 × CH), 128.1 (CH), 125.7 (C), 121.2 (C), 120.6 (C), 114.5 (C), 98.8 (CH_2), 97.4 (C), 96.5 (CH), 79.4 (C), 75.4 (CH_2), 65.8 (CH_2), 63.0 (CH), 62.2 (CH_3), 61.8 (CH_3), 61.8 (CH_3), 61.4 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 52.3 (CH_3), 47.8 (C), 33.3 (CH_2), 29.3 (CH_3), 15.1 (CH_3); *m/z* (ESI+) $[M+K]^+$ 785.2555 calcd for $C_{41}H_{46}KO_{13}$ 785.2570.

4.18. Methyl 4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobut-1-yn-1-yl)-3-hydroxy-2-methoxy-6-(2-oxopropyl)benzoate (42)

To a stirred solution of alcohol **37** (1.22 g, 1.63 mmol) in DMSO (10 mL) was added a solution of IBX (1.83 g, 6.52 mmol) in DMSO (10 mL) and stirred at rt for 3 h. The reaction mixture was diluted with EtOAc (10 mL) and saturated aqueous $NaSO_3$ solution (10 mL) was added and the aqueous layer was separated and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 3:2) to afford the *title compound* **42** (1.0 g, 85%) as a yellow oil; R_f: 0.39 (hexanes-EtOAc, 1:1); ν_{max}(neat)/cm^{-1} 2936, 2842, 2200, 1727, 1672, 1599, 1451, 1365, 1258, 1172, 1047, 1003, 733, 698; δ_H (400 MHz; $CDCl_3$) 7.48 (d, J=8.0 Hz, 2H), 7.30–7.37 (m, 3H), 6.77 (s, 1H), 6.64 (s, 1H), 5.29 (s, 2H), 5.07 (s, 2H), 4.17 (s, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.76–3.80 (m, 8H), 3.71 (s, 3H), 3.56 (s, 2H), 2.12 (s, 3H), 1.21 (t, J=8.0 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 204.3 (C), 185.3 (C), 166.8 (C), 153.3 (C), 153.0 (C), 151.6 (C), 151.1 (C), 150.1 (C), 148.0 (C), 142.5 (C), 136.6 (C), 136.3 (C), 131.6 (CH), 131.4 (C), 128.6 (2 × CH), 128.6 (2 × CH), 128.4 (CH), 128.3 (C), 126.2 (C), 118.7 (C), 117.5 (C), 114.2 (C), 98.3 (CH_2), 96.1 (CH), 92.6 (C), 86.2 (C), 75.9 (CH_2), 65.7 (CH_2), 62.4 (CH_3), 61.8 (CH_3), 61.8 (CH_3), 61.5 (CH_3), 56.7 (CH_3), 56.7 (CH_3), 52.4 (CH_3), 47.5 (CH_2), 41.5 (CH_2), 29.4 (CH_3), 15.2 (CH_3); *m/z* (ESI+) $[M+K]^+$ 786.2417 calcd for $C_{41}H_{44}KO_{13}$ 783.2413.

4.19. Methyl 4-(4-(3-(ethoxymethoxy)-1,4,5,6,8-pentamethoxynaphthalen-2-yl)-3-oxobutyl)-3-hydroxy-2-methoxy-6-(2-oxopropyl)benzoate (43)

To a stirred solution of alkyne **37** (0.25 mg, 0.36 mmol) in MeOH (5 mL) was added Pd/C (0.11 mg, 1.01 mmol) and stirred under a H_2 atmosphere and stirred at rt for 2 h. The mixture was filtered through a silica plug and the plug was washed with EtOAc (50 mL). The filtrate was concentrated in vacuo to afford the *title compound* **43** (0.22 g, quant) as a yellow oil. R_f: 0.40 (hexanes-EtOAc, 2:3); ν_{max}(neat)/cm^{-1} 3404, 2935, 2839, 1714, 1601, 1454, 1355, 1344, 1280, 1204, 1047, 1002, 934, 812, 732; δ_H (400 MHz; $CDCl_3$) 6.74 (br s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 5.25 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.92 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.69–3.76 (m, 2H), 3.64 (s, 3H), 2.88 (s, 4H), 2.11 (s, 3H), 1.21 (t, J=7.2 Hz, 3H); δ_C (100 MHz; $CDCl_3$) 209.7 (C), 206.0 (C), 167.6 (C), 153.0 (C), 151.1 (C), 150.0 (C), 147.7 (C), 146.6 (C), 146.0 (C), 142.6 (C), 136.6 (C), 131.1 (C), 128.0 (CH), 126.0 (C), 124.9 (C), 124.6 (C), 119.7 (C), 114.3 (C), 98.3 (CH_2), 96.3 (CH), 65.7 (CH_2), 62.1 (CH_3), 61.8 (CH_3), 61.8 (CH_3), 61.6 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 52.1 (CH_3), 48.2 (CH_2), 42.0 (CH_2), 39.3 (CH_2), 29.2 (CH_3), 24.0 (CH_2), 15.2 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 681.2518 calcd for $C_{34}H_{42}NaO_{13}$ 681.2495.

4.20. Methyl 4′,5′,7′,8,8′,9′-hexamethoxy-6-(2-oxopropyl)-3′*H*-spiro[chroman-2,2′-naphtho[2,3-b]furan]-7-carboxylate (44)

To a stirred solution of ketone **43** (0.13 g, 0.20 mmol) in CH_2Cl_2 (4 mL) was added $NaHSO_4.SiO_2$ (0.25 g) and stirred at rt for 9 h. The mixture was filtered through cotton wool and washed with EtOAc (20 mL). The filtrate was washed with water (2×5 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 2:3) to afford the *title compound* **44** (61.0 mg, 53%) as a yellow oil; R_f: 0.48 (hexanes-EtOAc, 2:3); ν_{max}(neat)/cm^{-1} 2932, 2849, 1723, 1703, 1645, 1602, 1450, 1422, 1353, 1295, 1257, 1225, 1203, 1157, 1108, 1045, 1034, 925, 891, 822, 806; δ_H (400 MHz; $CDCl_3$) 6.75 (s, 1H), 6.60 (s, 1H), 3.97 (s, 6H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.70 (d, J=16.8 Hz, 1H), 3.66 (s, 2H), 3.63 (s, 3H), 3.38 (d, J=16.8 Hz, 1H), 3.31–3.41 (m, 1H), 2.85 (ddd, J=16.4, 5.6, 2.0 Hz, 1H), 2.43 (ddd, J=13.4, 6.0, 2.4 Hz, 1H), 2.25 (ddd, 13.4, 6.0, 2.4 Hz, 1H), 2.16 (s, 3H); δ_C (100 MHz; $CDCl_3$) 206.0 (C), 167.7 (C), 153.3 (C), 150.0 (C), 149.0 (C), 148.8 (C), 146.5 (C), 144.5 (C), 137.1 (C), 133.0 (C), 127.2 (C), 126.6 (C), 126.1 (CH), 125.2 (C), 125.1 (C), 117.6 (C), 113.6 (C), 109.8 (C), 95.1 (CH), 61.9 (CH_3), 61.8 (CH_3), 61.5 (CH_3), 61.3 (CH_3), 56.8 (CH_3), 56.8 (CH_3), 52.1 (CH_3), 47.9 (CH_2), 39.6 (CH_2), 29.7 (CH_2), 29.4 (CH_3), 22.0 (CH_2); *m/z* (ESI+) $[M+Na]^+$ 605.1991 calcd for $C_{31}H_{34}NaO_{11}$ 605.1993.

4.21. 4,5,7,8,9,10′-Hexamethoxy-7′-methyl-3*H*,3′*H*-spiro[naphtho[2,3-b]furan-2,2′-pyrano[4,3-g]chromen]-9′(4′*H*)-one (8)

To a stirred solution of NaH (34 mg, 0.49 mmol, 60% in mineral oil) in THF (4 mL) at 0 °C was added a solution of keto-ester **44** (0.14 mg, 0.25 mmol) in THF (2 mL) and stirred for 5 min then

warmed to rt for 30 min. Saturated aqueous NH_4Cl (10 mL) was added and the aqueous layer separated and extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (hexanes-EtOAc, 2:3) to afford the *title compound* **8** (65.0 mg, 48%) as a pale yellow solid; Mp=88.4–89.2 °C; R_f: 0.48 (hexanes-EtOAc, 2:3); ν_{max}(neat)/cm^{-1} 2932, 2842, 1730, 1604, 1462, 1356, 1235, 1207, 1047, 1008, 925, 821, 617; δ_H (400 MHz; $CDCl_3$) δ 6.84 (s, 1H), 6.58 (s, 1H), 6.05 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.76 (s, 3H), 3.71 (d, *J*=16.8 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 3.45 (d, *J*=16.8 Hz, 1H), 3.38–3.47 (m, 1H), 2.94 (ddd, *J*=17.4, 5.8, 1.8 Hz, 1H), 2.44 (ddd, *J*=13.4, 6.2, 2.2, 1H), 2.34 (ddd, *J*=13.4, 6.2, 2.2 Hz, 1H), 2.17 (s, 3H); δ_C (100 MHz; $CDCl_3$) 159.3 (C), 153.2 (C), 152.6 (2 × C), 149.9 (C), 149.8 (C), 148.8 (C), 145.0 (C), 136.9 (C), 132.8 (C), 132.1 (C), 131.3 (C), 127.0 (C), 119.7 (CH), 117.4 (C), 113.6 (C), 112.5 (C), 109.6 (C), 102.7 (CH), 95.0 (CH), 61.7 (CH_3), 61.6 (CH_3), 61.4 (CH_3), 61.1 (CH_3), 56.7 (CH_3), 56.6 (CH_3), 39.4 (CH_2), 29.3 (CH_2), 22.5 (CH_2), 19.2 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 573.1731 calcd for $C_{30}H_{30}NaO_{10}$ 573.1714.

4.22. 4,9,10′-Trihydroxy-7-methoxy-7′-methyl-3*H*,3′*H*-spiro[naphtho[2,3-b]furan-2,2′-pyrano[4,3-g]chromene]-5,8,9′(4′*H*)-trione (7)

To a stirred solution of naphthalene **8** (60.0 mg 0.11 mmol) in MeCN (4 mL) at 0 °C was added water (0.4 mL) followed by DDQ (61.8 mg, 0.27 mmol) and stirred for 15 min. Water (2 mL) and saturated aqueous $NaHCO_3$ (3 mL) were added and the mixture was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with brine (6 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc, neat) to afford the quinone (31.6 mg, 64%) as a yellow solid; Mp=191.0–193.5 °C; R_f: 0.38 (EtOAc, neat); ν_{max}(neat)/cm^{-1} 2930, 2852, 1729, 1677, 1639, 1585, 1469, 1427, 1364, 1336, 1303, 1228, 1133, 1110, 1054, 1038, 984, 958, 920, 807, 734; δ_H (400 MHz; $CDCl_3$) 6.87 (s, 1H), 6.08 (s, 1H), 5.96 (s, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.71 (d, *J*=17.6 Hz, 1H), 3.45 (d, *J*=17.6 Hz, 1H), 3.32–3.46 (m, 1H), 2.96 (ddd, *J*=17.6, 6.0, 2.0 Hz, 1H), 2.44 (ddd, *J*=13.6, 6.0, 2.0 Hz, 1H), 2.30 (ddd, *J*=13.6, 6.0, 2.0 Hz, 1H), 2.21 (s, 3H); δ_C (100 MHz; $CDCl_3$) 183.7 (C), 179.3 (C), 159.3 (C), 159.2 (C), 155.1 (C), 153.1 (C), 153.1 (C), 149.9 (C), 144.5 (C), 141.8 (C), 132.7 (C), 130.8 (C), 127.1 (C), 125.6 (C), 119.9 (CH), 119.4 (C), 112.9 (C), 110.8 (C), 109.9 (CH), 102.7 (CH), 61.5 (CH_3), 61.2 (CH_3), 60.9 (CH_3), 56.3 (CH_3), 39.9 (CH_2), 29.5 (CH_2), 22.3 (CH_2), 19.3 (CH_3); *m/z* (ESI+) $[M+Na]^+$ 543.1271 calcd for $C_{28}H_{24}NaO_{10}$ 543.1262.

To a stirred solution of the quinone (9.0 mg, 0.017 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added BCl_3 (69 μL, 1.0 M in CH_2Cl_2, 0.069 mmol) dropwise and stirred for 10 min. Water (3 mL) was then added and aqueous layer was separated and extracted with CH_2Cl_2 (3×3 mL). The combined organic extracts were washed with brine (4 mL), dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2–MeOH, 99:1) to afford the *title compound* **7** (7.4 mg, 90%) as a red solid; Mp=278.1–280.2 °C; R_f: 0.65 (CH_2Cl_2–MeOH, 98:2); ν_{max}(neat)/cm^{-1} 2922, 2852, 1686, 1648, 1600, 1442, 1330, 1272, 1237, 1140, 1095, 1058, 940, 922, 882, 803; δ_H (500 MHz; $CDCl_3$) 13.07 (s, 1H), 12.29 (s, 1H), 11.14 (s, 1H), 6.62 (s, 1H), 6.18 (s, 2H), 3.92 (s, 3H), 3.75 (d, *J*=18.0 Hz, 1H), 3.38–3.45 (m, 2H), 2.91 (ddd, *J*=17.4, 6.0, 1.6 Hz, 1H), 2.46 (ddd, *J*=14.0, 6.0, 2.0 Hz, 1H), 2.27–2.34 (m, 1H), 2.26 (s, 3H); δ_C (125 MHz; $CDCl_3$) 183.3 (C), 178.6 (C), 166.9 (C), 159.9 (C), 159.5 (C), 153.8 (C), 152.3 (C), 150.8 (C), 150.0 (C), 138.4 (C), 131.4 (C), 130.5 (C), 123.0 (C), 114.4 (CH), 112.9 (C), 111.8 (C), 110.1 (CH), 106.3 (C), 104.9 (C), 104.1 (CH), 56.7 (CH_3), 39.5 (CH_2), 30.0 (CH_2), 22.3 (CH_2), 19.3 (CH_3); *m/z* (ESI+) $[M+H]^+$ 479.0973 calcd for $C_{25}H_{19}O_{10}$ 479.0966.

Acknowledgements

The authors would like to thank the NZ Foundation for Research, Science and Technology (FRST) for its financial support through the International Investment Opportunities Fund (IIOF).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.11.030.

References and notes

1. Treibs, W.; Eckardt, K. *Naturwissenschaften* **1961**, *48*, 430.
2. Eckardt, K.; Tresselt, D.; Ihn, W. *Tetrahedron* **1978**, *34*, 399–404.
3. Tresselt, D.; Eckardt, K.; Ihn, W. *Tetrahedron* **1978**, *34*, 2693–2699.
4. Eckardt, K.; Tresselt, D.; Ihn, W. *J. Antibiot.* **1978**, *31*, 970–973.
5. Stroshane, R. M.; Chan, J. A.; Rubalcaba, E. A.; Garretson, A. L.; Aszalos, A. A.; Roller, P. P. *J. Antibiot.* **1979**, *32*, 197–204.
6. Yang, J. X.; Fan, S. X.; Pei, H. S.; Zhu, B. Q.; Xu, W. S.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 1277–1279.
7. Suetsuna, K.; Osajima, Y. *Agric. Biol. Chem.* **1989**, *53*, 241–242.
8. Panzone, G.; Trani, A.; Ferrari, P.; Gastaldo, L.; Colombo, L. *J. Antibiot.* **1997**, *50*, 665–670.
9. Yunt, Z.; Reinhardt, K.; Li, A.; Engeser, M.; Dahse, H.-M.; Gütschow, M.; Bruhn, T.; Bringmann, G.; Piel, J. R. *J. Am. Chem. Soc.* **2009**, *131*, 2297–2305.
10. Ueno, T.; Takahashi, H.; Oda, M.; Mizunuma, M.; Yokoyama, A.; Goto, Y.; Mizushina, Y.; Sakaguchi, K.; Hayashi, H. *Biochemistry* **2000**, *39*, 5995–6002.
11. Shay, J. W.; Bacchetti, S. *Eur. J. Cancer* **1997**, *33*, 787–791.
12. Sekaran, V.; Soares, J.; Jarstfer, M. B. *J. Med. Chem.* **2013**, *57*, 521–538.
13. Siu, T.; Qin, D. H.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4713–4716.
14. Rathwell, D. C. K.; Yang, S. H.; Tsang, K. Y.; Brimble, M. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 7996–8000.
15. Akai, S.; Kakiguchi, K.; Nakamura, Y.; Kuriwaki, I.; Dohi, T.; Harada, S.; Kubo, O.; Morita, N.; Kita, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 7458–7461.
16. Wu, K.-L.; Mercado, E. V.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 6114–6117.
17. Wei, L.; Xue, J.; Liu, H.; Wang, W.; Li, Y. *Org. Lett.* **2012**, *14*, 5302–5305.
18. Wilsdorf, M.; Reissig, H.-U. *Angew. Chem. Int. Ed.* **2014**, *53*, 4332–4336.
19. Wang, W.; Xue, J.; Tian, T.; Zhang, J.; Wei, L.; Shao, J.; Xie, Z.; Li, Y. *Org. Lett.* **2013**, *15*, 2402–2405.
20. Lowell, A. N.; Fennie, M. W.; Kozlowski, M. C. *J. Org. Chem.* **2011**, *76*, 6488–6502.
21. Waters, S. P.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 3243–3246.
22. Venkatesh, C.; Reissig, H. U. *Synthesis* **2008**, 3605–3614.
23. Mabic, S.; Lepoittevin, J.-P. *Tetrahedron Lett.* **1995**, *36*, 1705–1708.
24. Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320–3321.