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# Synthesis of diastereomeric, deoxy and ring-expanded sulfone analogues of aigialomycin D

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ABSTRACT

Several analogues of the fungal natural product aigialomycin D (AmD) have been synthesised. These include the stereoisomer 5′*R*,6′*S*-AmD, 2,4-di-deoxyAmD, 1′,2′,7′,8′-tetrahydroAmD and a 15-membered macrocyclic sulfone. Growth inhibitory activities of these compounds against the HL-60 leukaemic cell line were measured. The ring-expanded sulfone and tetrahydro-analogue were found to have similar $IC_{50}$ values to the natural product, whereas the 5′*R*,6′*S*-stereoisomer was inactive. Energy minimisation of AmD and the synthesised analogues resulted in a range of lowest energy conformers, from planar, open arrangements of the macrocycle in AmD and tetrahydroAmD to bent, L-shaped structures for the sulfone. The synthesis of methyl orsellinate was investigated and optimised as part of this work. A stereo-divergent route to both enantiomers of the diol fragment from D-ribose was also achieved.



## 1. Introduction

The resorcylic acid lactones (RALs, Fig. 1), a class of macrocyclic natural products with a variety of biological actions, have gained widespread attention as leads for drug discovery.[1–3] These mycotoxins[4] have a wide range of activities, from antimalarial (aigialomycin D, paecilomycin E)[5,6] to antifouling (cochliomycin A) properties.[7] With respect to biochemical targets, estrogen agonism (zearalenone)[8] and inhibition of the heat-shock protein HSP90 (radicicol, pochonin D)[9–11] are known within the class, yet the majority of the naturally occurring RALs act as protein kinase inhibitors (hypothemycin, L-783,277, LL-Z1640-2, radicicol A and aigialomycin D).[2,3,12]

The privileged benzo-fused 14-membered macrolactone ring of the RALs represents a rich scaffold for structural variation. This is evidenced biosynthetically by the diversity of natural compounds in this class (see Fig. 1), which differ particularly in the degree and positioning of oxidation and unsaturation about the macrolactone ring. The array of bioactivity noted for these compounds indicates the subtle interplay of the functionality and stereochemistry about the ring system. Further structural variation is available through the preparation of analogues, which has been achieved in a de novo synthetic fashion,[13–15] biosynthetically through heterologous gene expression[16] and by semisynthesis.[17] Notable examples of synthetic analogues include cycloproparadicicol and related species,[13a] pochonin-based macrolactams,[13b,c] oxime derivatives of radicicol,[9,13d] deoxygenated L-783,277 variants,[13e] and alkene-[13f,g] and *O*-modified analogues of the RALs.[2,14]

Through these and other studies, an understanding of the structure–activity relationships for these compounds is beginning to be realised. For instance, the potent kinase inhibitors among this class all have a *Z*-enone moiety at C7′–C8′.[3] In contrast, the C7′–C8′ '*trans*'-configured species radicicol (with its *trans*-epoxide) and pochonin D (with an *E*-alkene) behave as HSP90 inhibitors, binding competitively at the ATP-binding site.[2,18] Among the RALs, aigialomycin D (AmD) seems to be an outlier, in that it has the C7′–C8′ *E*-alkene, is a moderate kinase inhibitor, but does not inhibit HSP90.[13a,14a] Aigialomycin D was originally isolated from a marine mangrove fungus (*Aigialus parvus*)[5] and has subsequently been found in two further fungus species.[6,19] It displays moderate growth inhibitory activity against the human epidermoid carcinoma (KB) and breast cancer (BC-1) cell lines and interacts with kinase targets (CDK1, CDK5, GSK3). Its unusual properties and synthetically tractable structure make it a useful starting point for

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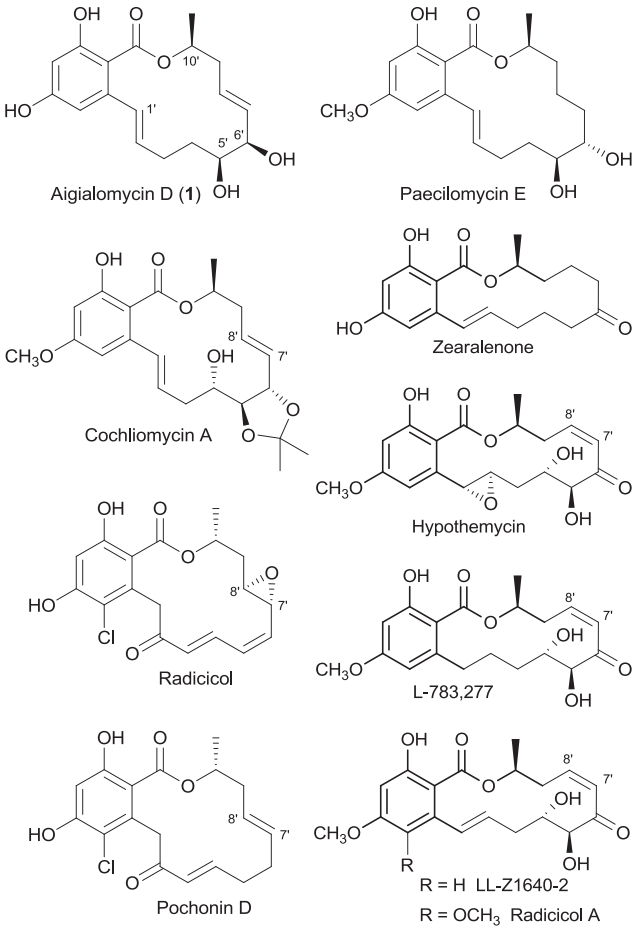



**Fig. 1.** Representative naturally occurring RALs.

novel analogue synthesis. Preparation of new analogues will shed more light on structural features of the RALs required for therapeutic applications.

To this end, we chose to pursue analogues of aigialomycin D differing from the natural material in the stereochemistry at the diol (C5′ and C6′) (analogue **2**) and methyl (C10′) (analogue **3**) substituents, in the degree of unsaturation on the macrocyclic ring (analogue **4**) and in the oxygenation of the aromatic ring (analogue **5**) (Fig. 2). The RAL ring system embodied by AmD is synthetically accessible by numerous diverse routes.[13,14a,20–22] Our total

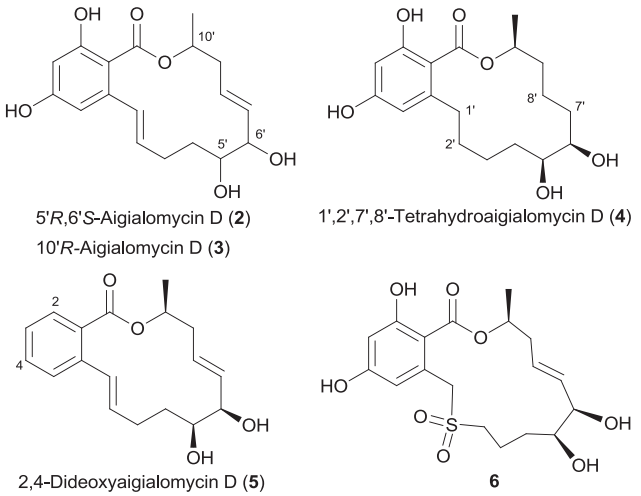


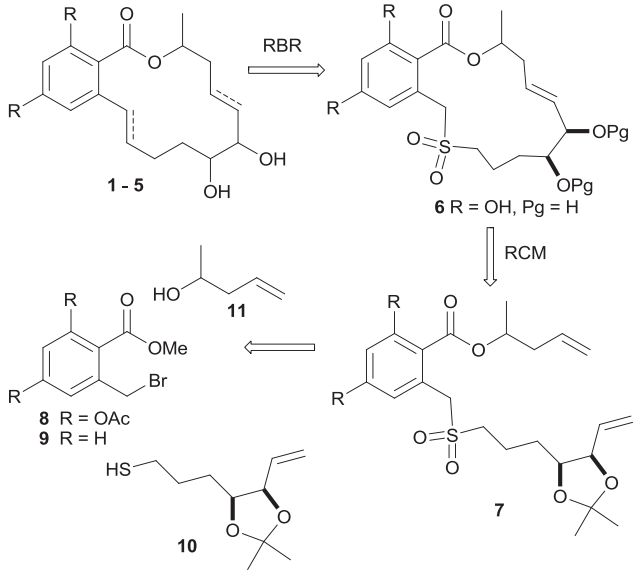

**Fig. 2.** Proposed analogues for this study.

synthesis of AmD[20] invoked a combination of ring-closing metathesis and Ramberg–Bäcklund reactions.[23,24] This strategy prevents the undesired cyclohexene formation that has been observed if metathesis at C7′–C8′ is performed in the presence of the internal C1′–C2′ alkene.[14a,22a,25] A 15-membered sulfone-containing macrolactone is the penultimate intermediate in the synthetic strategy, and its deprotection would afford a novel analogue that is uniquely accessible through this methodology. The sulfone-containing analogue **6**, therefore, was also pursued in this work.

During the course of the present study, Chen and co-workers reported syntheses of two of these AmD-based analogues (**3**, **4**), amongst others.[15] Their analogues were screened against CDK2 (a cyclin-dependent kinase) and MNK2 (a mitogen-activated protein kinase-interacting kinase that phosphorylates the oncogene eIF4E), which are both susceptible to AmD. 10′*R*-AmD (**3**) and 4-*O*-methyl-AmD were found to inhibit CDK2/cyclin A with similar potency to AmD, while 5′,6′-dideoxy-AmD, 5′,6′-acetonido-AmD and 7′,8′-dihydro-AmD were similarly active against MNK2.[26] Tetrahydro AmD (**4**) did not show strong inhibition of either kinase.[15]

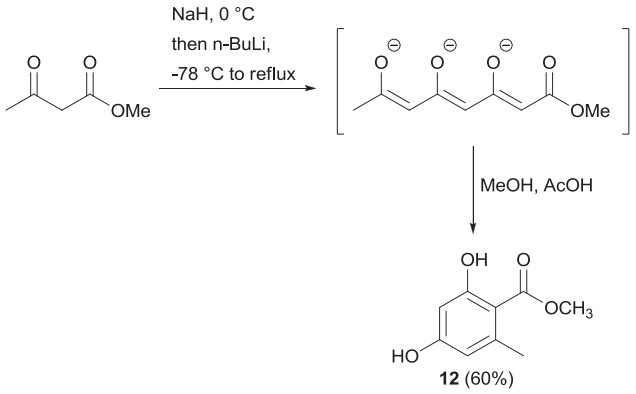
## 2. Results and discussion

The target analogues were prepared using a synthetic strategy related to that already reported by us for the total synthesis of AmD (Scheme 1).[20] The full carbon skeleton, **7**, would be accessed by substitution of the benzyl bromide **8** or **9** with thiol **10**, and esterification with the homoallylic alcohol **11**. Macrocycle formation would be achieved through ring-closing metathesis (RCM) of the benzylic sulfone **7**. A subsequent Ramberg–Bäcklund reaction (RBR) would provide the styrene moiety of analogues **1**–**5**, while the RBR step would be omitted for the sulfone analogue **6**.




**Scheme 1.** Retrosynthesis of proposed analogues **1**–**6**.

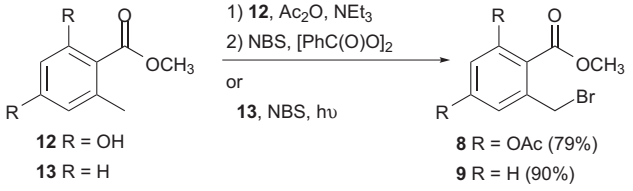
Benzylic bromide **8** was to be prepared from methyl orsellinate (**12**), as before.[20] The latter compound has been prepared numerous times by Claisen self-condensation of methyl acetoacetate and subsequent cyclisation of the resulting triketoester (Scheme 2).[27,28] Good yields are typically obtained by isolating the triketoester and allowing the subsequent cyclisation to occur under (usually) basic conditions.[27,29] A one-pot method, developed to expedite the synthesis, was reported to afford methyl orsellinate in a 60% yield.[28] However, in our hands, the one-pot variant gave consistently poor results (≤40% yield).[20] As part of our analogue studies, we had




**Scheme 2.** Formation of methyl orsellinate (**12**) from methyl acetoacetate.

occasion to revisit the methyl orsellinate synthesis and noticed that degradation of the material was occurring in the cyclisation step. In the one-pot approach, this step is typically achieved with acid in order that the anionic species from the Claisen condensation are quenched. It became apparent that the reported[28] conditions involving addition of dilute HCl were prone to over-acidification, with apparent reversion to methyl acetoacetate as well as production of highly polar materials (thought to be orsellinic acid or an acyclic precursor). Use of a milder acid (aqueous acetic acid) led to improved results (up to 60% isolated yield of methyl orsellinate), although there were indications that hydrolysis of the methyl ester was still occurring. Avoiding the presence of water by quenching with methanol and glacial acetic acid gave improved and consistent results, with methyl orsellinate yields of 60–66% obtained. It is important to note that rapid and complete removal of the acetic acid in the work-up (under reduced pressure) is crucial in order to circumvent hydrolysis of the product **12** and erosion of the isolated yield.

Acetylation and bromination of methyl orsellinate (**12**) afforded **8** as before,[20] albeit in an improved yield (79% over two steps, Scheme 3). Methyl 2-bromomethylbenzoate (**9**) was prepared from methyl 2-methylbenzoate (**13**), in accordance with our reported method,[30] as a precursor to 2,4-dideoxy-AmD (**5**).




**Scheme 3.** Synthesis of benzyl bromides **8** and **9**.

The pseudo-symmetry of D-ribose (**14**) allowed for the stereodivergent preparation of both enantiomers of the diol fragment, **10** (viz. Scheme 1). Optimisation of our earlier route to (5′*S*,6′*R*)-**10**[20] has afforded improved step economy and yield. Thus, D-ribose (**14**) can be converted to methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside in a higher yield (80%) by employing acetyl chloride as an anhydrous source of HCl (Scheme 4). Direct conversion of the resulting primary alcohol to iodide **15**[31] in a single step and high yield (83%) is followed by the Vasella–Wittig reaction sequence, as reported before,[20] to efficiently produce the diene **16**.

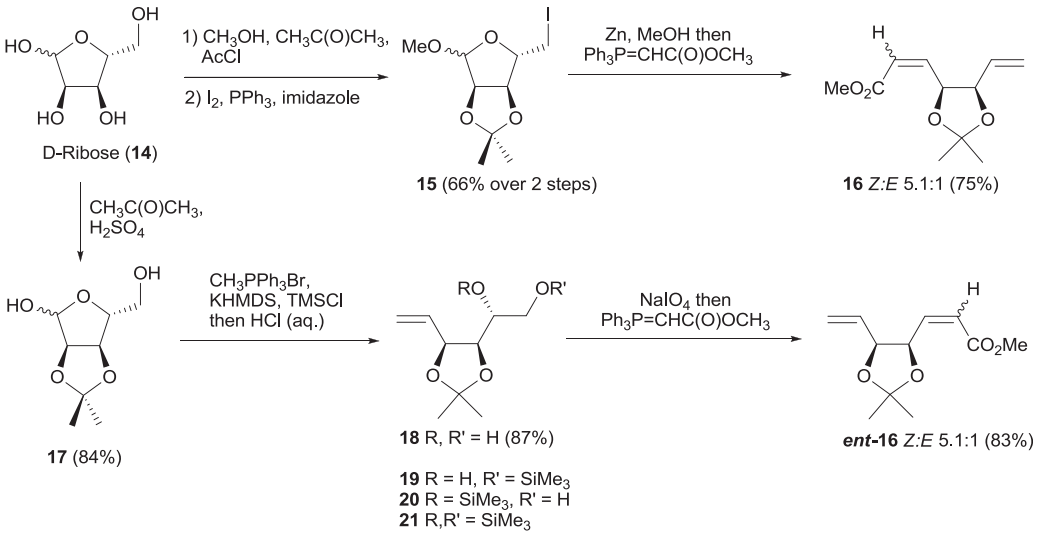
For the enantiomeric series (i.e., synthesis of *ent*-**16**), 2,3-*O*-isopropylidene-D-ribose (**17**) was prepared in high yield from D-ribose (**14**).[32] Hemiacetal **17** was then treated with the ylide derived from methyl triphenylphosphonium bromide. Unfortunately, when potassium *tert*-butoxide,[33] *n*-butyllithium or LDA were employed as the base in this Wittig reaction, none of the desired product **18** was formed, and only starting material was recovered. The discovery that KHMDS afforded traces of trimethylsilylated product **19** led to an optimisation campaign, which culminated in development of a procedure that used a combination of KHMDS and TMSCl for this transformation. The optimised procedure provided a mixture of the desired alkene **18** and mono- and bis-*O*-silylated derivatives **19**–**21**, which was homogenised by treatment with an aqueous acid to afford diol **18**. This desilylation procedure also required care to avoid competing deprotection of the labile acetonide protecting group over time. Ultimately, treatment of the ice-water cooled reaction mixture with aqueous hydrochloric acid for 15–30 min was found to provide **18** in a high (87%) yield. Diol cleavage of **18** with sodium periodate, followed immediately by a Wittig reaction with the stabilised ylide methyl (triphenylphosphoranylidene)acetate produced the α,β-unsaturated ester *ent*-**16** in 83% yield.

The enantiomeric dienes **16** and *ent*-**16** were individually subjected to our optimised conjugate reduction conditions[20] to afford the partially saturated esters **22** and *ent*-**22**, respectively (Scheme 5). High yielding ester reduction (81–97%), mesylation (91–97%) and substitution (82–95%) provided the thioacetates **23**[20] [overall 43% yield from D-ribose (seven steps)] and *ent*-**23** [32% yield from D-ribose (seven steps)].

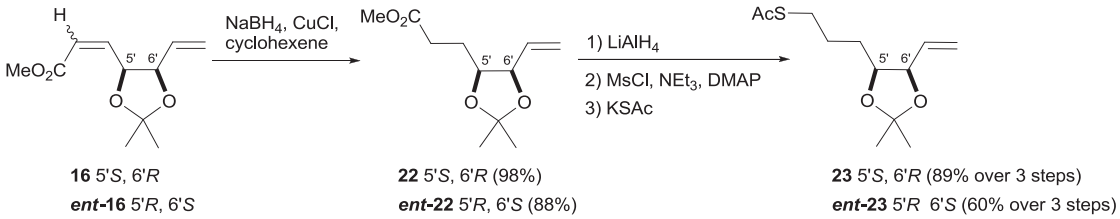
Coupling of the three main fragments was achieved by in situ deacetylation of thioacetates **23** and *ent*-**23** and substitution of the benzylic bromide functionalities within orsellinate **8** or benzoate **9** (Scheme 6). The phenolic groups of the resulting thioethers **24** and *ent*-**24** were reprotected with MOMCl to give **25** and *ent*-**25**, respectively.[20] The methyl esters **25**, *ent*-**25** and **26** were saponified to liberate the corresponding carboxylic acids, which were esterified with the homoallylic alcohols *R*-**11** and *S*-**11** using Mitsunobu chemistry. The resulting products **27**–**30** contained the full carbon skeleton of aigialomycin D and the proposed analogues.

Oxidation of the thioether within compounds **27**–**30** and RCM of the resulting sulfones afforded 15-membered macrocycles **31**–**34** (Scheme 7). Compound **31**, with the natural stereochemistry, was deprotected under acidic conditions to give sulfone analogue **6**. The remaining protected sulfones were subjected to a ring-contractive Ramberg–Bäcklund reaction to provide dienes **35**–**38**. The AmD precursor **35** was hydrogenated and subjected to acid hydrolysis to afford tetrahydroAmD (**4**). Aigialomycin D (**1**) and analogues **2** and **5** were obtained in high yields by global deprotection of **35**, **36** and **38**, respectively, under acidic conditions. In the formation of **2**, a small quantity of a stereoisomer was present in the reaction mixture; this was separable by careful chromatography. It is tentatively proposed to be the 6′-epimer of **2**, i.e., 5′*R*-AmD, which could result from acid-catalysed isomerisation of the allylic alcohol. Surprisingly, deprotection of the 10′*R*-compound **37** under similar conditions but with a prolonged reaction time (5 days) led to an inseparable mixture of two compounds in a low yield. Neither of these displayed the same $^{1}$H NMR signals as analogue **2**, as would be expected for the desired product, **3**, due to the enantiomeric relationship between compounds **2** and **3**. It is tentatively proposed that epimerisation of the allylic alcohol and/or isomerisation of the C7′–C8′ alkene occurred in the acidic conditions over the lengthy reaction time.[34]

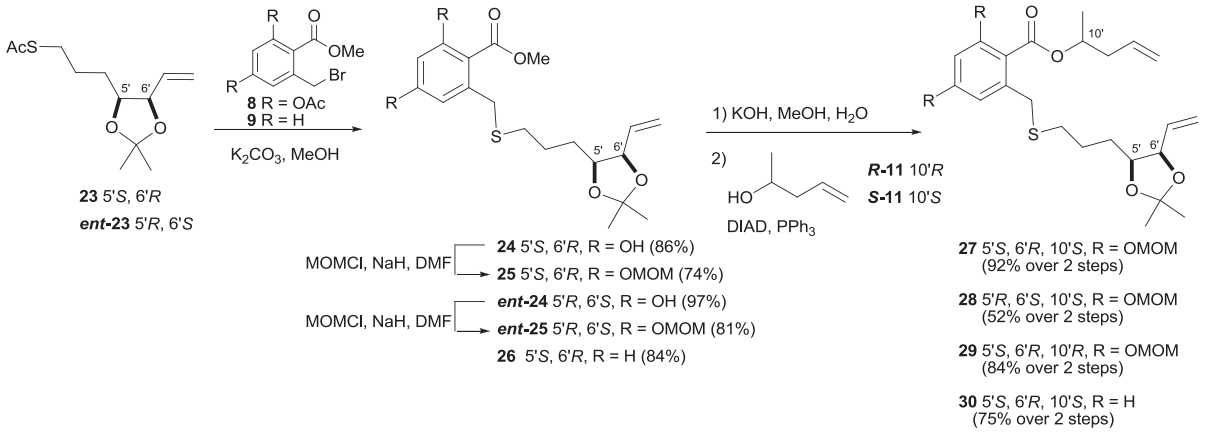
The bioactivities of aigialomycin D and the prepared analogues against the human promyelocytic leukaemia HL-60 cell line were determined using an MTT cell proliferation assay[35] ($n$=1–2 experiments) (Table 1). The measured activity of aigialomycin D towards this cancer cell line was comparable to that reported for KB and BC-1 cells (entry 1).[5] Interestingly, the 15-membered macrocyclic sulfone **6** was similarly potent (entry 2), which perhaps indicates that this compound intercepts a different cellular target to the 14-membered RALs, since kinases




**Scheme 4.** Enantiodivergent synthesis of **16** and *ent*-**16** from D-ribose.




**Scheme 5.** Conversion of **16** and *ent*-**16** into thioacetates **23** and *ent*-**23**.[†]

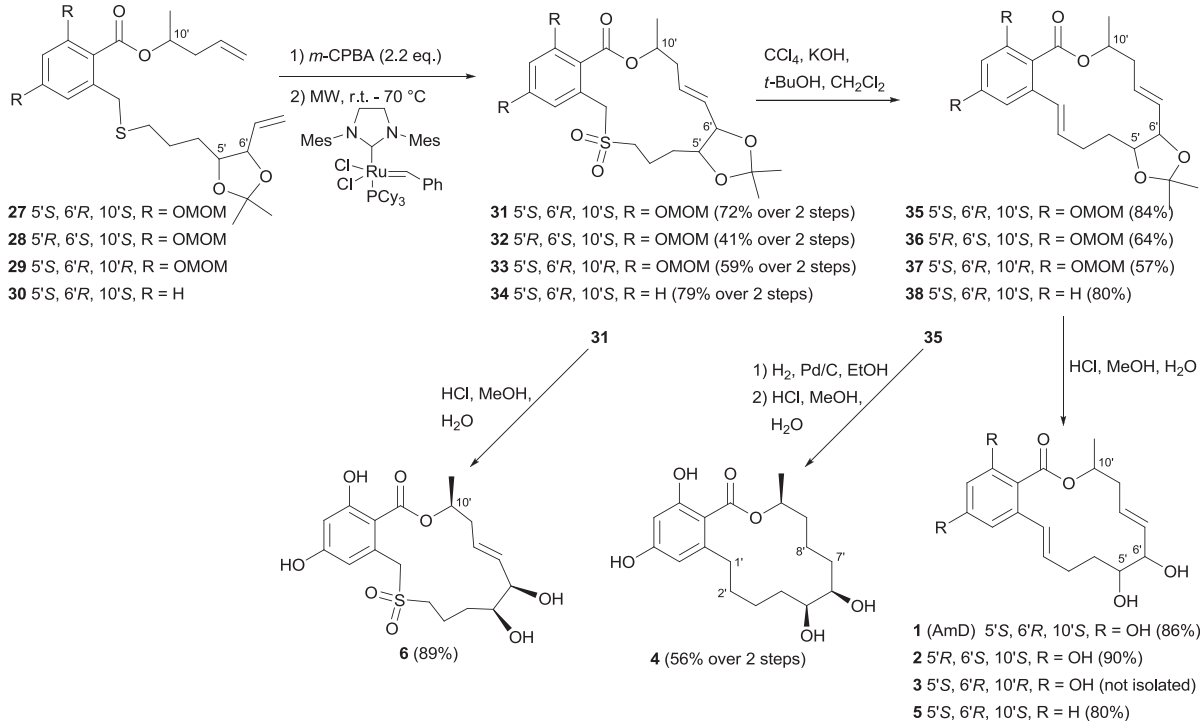



**Scheme 6.** Fragment coupling.[†]

typically have fairly specific substrate requirements.[2,3,15] Saturation of the aigialomycin D macrocycle, providing **4**, led to only a marginal loss of potency (entry 3). Chen and colleagues showed that this compound (**4**) does not inhibit MNK2, a kinase that regulates oncogene eIF4E and is very sensitive to aigialomycin D,[15] and it only demonstrated weak inhibition of CDK2/cyclin A. Thus, its interaction with an alternative target may be responsible for the HL-60 activity. In comparison, the diastereomer of aigialomycin D differing at both diol centres (**2**) had no detectable activity up to 100 μM (entry 4). Unfortunately, 2,4-dideoxy-AmD (**5**) decomposed before it was tested. Interestingly, its precursor, the acetonide-protected sulfone **34**, had growth inhibitory activity (entry 5) similar to the natural product (entry 1) and the resorcylic sulfone **6** (entry 2). Given the similarities in structure and activity of **34** and **6**, it is possible that deprotection of the acetonide occurs in the conditions of the assay.

These results demonstrate the complex and finely tuned nature of the relationship between RAL structure and cytotoxicity. In order to gain a preliminary understanding of the possible reasons for this relationship, the lowest energy conformations of AmD (**1**), its tetrahydro analogue **4**, diol stereoisomer **2** and sulfones **6** and **34** were calculated using a mixed torsional/low-mode sampling conformational search as implemented in MacroModel.[36] For comparison, radicicol was modelled under various conditions and with a number of forcefields. As the OPLS-2005 forcefield with vacuum simulation

[†] Aigialomycin D numbering is used for precursors.




**Scheme 7.** End-game sequence and synthesised analogues.[†]

**Table 1**
Growth inhibitory activity against HL-60 cells

| Entry | Compound | $IC_{50}$ (μM) |
|---|---|---|
| 1 | AmD (**1**) | 12.50 |
| 2 | **6** | 14.30 |
| 3 | **4** | 19.73 |
| 4 | **2** | >100 |
| 5 | **34** | 14.0 |

most accurately reproduced the conformation of radicicol bound to HSP90 (within the pdb file 2WER), this method was chosen for the calculations of the compounds described in our work. For completeness, the simulations were also performed on AmD in a water continuum solvent model, providing comparable results.

The lowest energy conformations calculated for aigialomycin D (**1**) and analogues **2**, **4**, **6** and **34** are shown in Fig. 3. A range of gross conformations is seen, from open, largely planar arrangements in **1**, **2** and **4**, to highly bent in **6** and **34**. For comparison, Karplus and Winssinger have previously defined three favoured conformations for various natural and synthetic RALs based on radicicol[11,9] and pochonins D/E[14c] as:

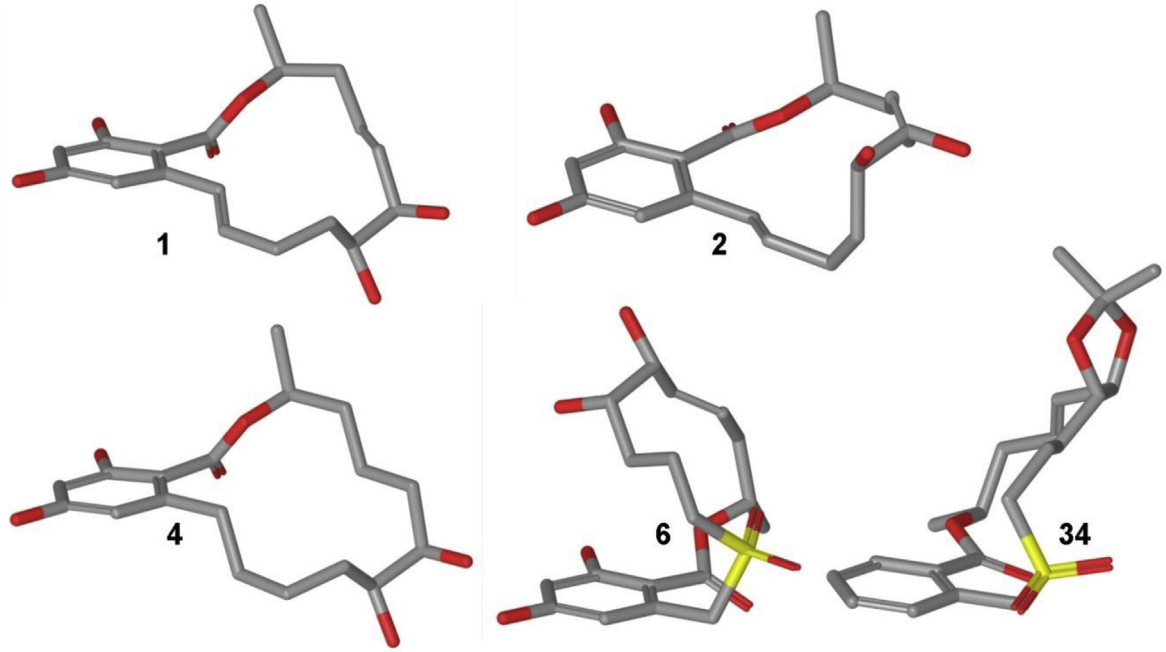



**Fig. 3.** Lowest energy conformations of compounds **1**, **2**, **4**, **6**, **34**.

1) being essentially planar (P-shape);
2) having the macrocyclic ring perpendicular to the aromatic ring with the macrocycle to the right of the aromatic ring and bent in the anti-clockwise direction (L-shape);
3) having the alternative perpendicular arrangement where the macrocycle bends away from the aromatic ring in the clockwise direction (L′-shape).

Of these, molecules that favour the L-shape conformation were found to be active towards HSP90, which corresponds to the conformer modelled[9] and observed in the crystal structure[18] of radicicol in the ATP-binding site of HSP90. Our modelling studies demonstrate that AmD (**1**) favours a fairly planar conformation (akin to the P-shape), as does the hydrogenated analogue **4**. In contrast, the sulfones **6** and **34** favour an L-shape. The 5′*S*,6′*R* diastereomer of AmD, **2**, favours a conformation somewhat different to the natural product that lies between the P- and L-shapes. These data might help to explain the growth inhibition, in that the measured $IC_{50}$ values could result from inhibition of different targets by the various compounds according to their favoured conformations. Thus, AmD (micromolar active) is known to interact with several kinases, while HSP90 inhibition might be the primary interaction for the sulfones **6** and **34** that prefer the L-conformation. The poorly active compound **2** would, by this argument, not be involved in interactions with the kinases or HSP90 due to its conformational profile, with no P- or L-shape conformations available within 5 kJ $mol^{-1}$ of the lowest energy conformer. The situation with tetrahydroAmD is not clear, since the calculated conformers are similar in shape to AmD, yet it was not a potent inhibitor of CDK2 or MNK2 in Chen's study.[15] Assays that allow investigation of the protein targets involved in the cellular interactions are needed in order to clarify the mode(s) of action of these compounds.

## 3. Conclusion

In conclusion, we have synthesised a series of analogues of aigialomycin D using our previously established Ramberg–Bäcklund/RCM strategy. The synthetic approach allowed access to novel sulfone analogues with enlarged 15-membered rings, an analogue with a saturated macrocycle, and diastereoisomeric variants. Determination of the growth inhibitory activity of the analogues against HL-60 cells demonstrated a series of finely tuned structure–activity relationships, with the larger-ring sulfones **6** and **34** and tetrahydroaigialomycin D **4** showing similar activity to the natural product. Molecular modelling provided calculated lowest energy conformers for these compounds that ranged from planar, open macrocycles (for AmD [**1**] and tetrahydroAmD **4**) to bent, L-shaped structures (for sulfones **6** and **34**).

## 4. Experimental section

### 4.1. General information

All reactions were performed under argon in oven-dried or flame-dried glassware using dry solvents and standard syringe techniques. All reagents were of commercial quality unless otherwise specified. MW-assisted reactions were carried out in a Milestone Microsynth reactor, monitored by a fibre optic temperature and pressure probe. $^1H$ and $^{13}C$ NMR spectra were recorded on either a Varian Unity Inova 300 (300 MHz for $^1H$ and 75 MHz for $^{13}C$), or a Varian Unity Inova 500 (500 MHz for $^1H$ and 125 MHz for $^{13}C$) spectrometer. All chemical shifts ($\delta$) were referenced to solvent peaks (for $^1H$ NMR, the corresponding residual protic solvent peaks were used) as follows: for spectra in $CDCl_3$, $^1H$ 7.26 ppm, $^{13}C$ 77.0 ppm; for spectra in acetone-$d_6$, $^1H$ 2.05 ppm, $^{13}C$ 29.8 ppm; for spectra in MeOH-$d_4$, $^1H$ 3.31 ppm, $^{13}C$ 49.0 ppm. Optical rotation was measured on a Perkin–Elmer 241 Polarimeter or a Rudolph Research Analytical Autopol II Polarimeter (sodium lamp) and specific rotation was calculated according to the formula $[\alpha]_D=(\alpha\cdot 100)/c\cdot l$; where concentration ($c$) is given in g/100 mL, pathlength of light ($l$) is in dm and optical rotation ($\alpha$) is in degrees. Infrared spectra were obtained on either a Biorad FTS-7 spectrometer or a Bruker Tensor 27 FTIR spectrometer. High-resolution mass spectrometry (HRMS) was recorded on a Mariner 5158 time-of-flight spectrometer or a Waters Q-TOF Premier™ Tandem Mass Spectrometer.

Lowest energy conformers of aigialomycin D and the analogues studied were obtained by molecular mechanics. Each structure was subjected to exhaustive conformational searching using the mixed torsional/low-mode sampling routine as implemented in MacroModel version 9.7 and visualised in Maestro 9.0. Structures obtained were minimised using the OPLS-2005 forcefield in both vacuum and the GB/SA water continuum solvent model[37] using the Polak–Ribière conjugate gradient (PRCG) method and terminated on a gradient threshold of 0.05 kJ $mol^{-1}$ $Å^{-1}$. The simulation was repeated until the lowest energy structure reported had been replicated at least 100 times and no conformer within 5 kJ $mol^{-1}$ of the lowest energy conformer was obtained fewer than 50 times.

### 4.2. Improved synthesis of methyl 2,4-dihydroxy-6-methylbenzoate (methyl orsellinate, 12)

Methyl acetoacetate (2.00 mL, 18.53 mmol) was added to a stirred solution of NaH (1.12 g, 27.79 mmol, 60% in mineral oil) in THF (40 mL) at 0 °C and allowed to warm to room temperature over 20 min. The solution was then cooled to −78 °C, $^n$BuLi (8.80 mL, 17.61 mmol, 2.0 M in cyclohexane) added and the solution allowed to warm to room temperature. After 17 h the solution was refluxed for 12 h, cooled to 0 °C, slowly quenched with MeOH (20 mL), then acidified to pH 3 with glacial AcOH (ca. 5 mL) and warmed to room temperature. After 18 h, the reaction mixture was concentrated rapidly under reduced pressure to remove all the acetic acid. The residue was extracted with EtOAc (4×40 mL) and the combined organic layers were dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to yield a red solid, which was purified by flash column chromatography (silica, 2:1 hexanes/EtOAc) to afford the desired compound as a colourless solid (1.01 g, 60%). $R_f$=0.45 (2:1 hexanes/EtOAc). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 11.75 (s, 1H), 6.25 (d, $J$=2.5 Hz, 1H), 6.21 (d, $J$=2.5 Hz, 1H), 5.50 (s, 1H), 3.89 (s, 3H), 2.46 (s, 3H). The spectral data matched those reported previously.[28]

### 4.3. Improved synthesis of (2*R*,3*R*,4*S*)-3,4-*O*-(1-methylethylidene)hex-5-en-1,2-diol (18)

KHMDS (13.60 mL, 6.78 mmol, 0.5 M in toluene) was added to a solution of $CH_3PPh_3Br$ (1.85 g, 5.20 mmol) in THF (20 mL) at −78 °C. After 1 h at −78 °C, the reaction was warmed to 0 °C and a solution of the acetonide-protected ribose **17** (430 mg, 2.26 mmol) and TMSCl (0.35 mL, 2.71 mmol) in THF (15 mL) was added. The resulting solution was allowed to warm to room temperature and stirred overnight. It was then cooled to 0 °C and acidified to pH 0–1 with 10% $HCl_{(aq)}$. After 15 min, the aqueous layer was separated and extracted with EtOAc (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant cream-coloured solid purified with flash column chromatography (silica, gradient elution 1:1 to 1:2 hexanes/EtOAc) to afford the desired compound as a clear oil (370 mg, 87%). $R_f$=0.08 (2:1 hexanes/EtOAc). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.96 (ddd, $J$=17.1, 11.0, 6.0 Hz, 1H), 5.41 (d, $J$=17.0 Hz, 1H), 5.26 (d, $J$=11.0 Hz, 1H), 4.65 (t, $J$=6.0 Hz, 1H), 4.09 (dd, $J$=6.4, 8.4 Hz, 1H), 3.75 (m, 1H), 3.62 (m, 2H), 3.20 (br s, 2H),

1.42 (s, 3H), 1.31 (s, 3H). The spectral data matched those reported previously.[32b]

### 4.4. Methyl (2*Z*,4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hepta-2,6-dienoate [(*Z*)-*ent*-16] and methyl (2*E*,4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hepta-2,6-dienoate [(*E*)-*ent*-16]

$NaIO_4$ (841 mg, 3.93 mmol) was added to a solution of diol **18** (370 mg, 1.97 mmol) in MeOH (20 mL). After 3 h, TLC suggested the consumption of starting material. Silica gel was then added and the solution stirred for 30 min, then filtered through a Celite® plug and eluted with MeOH (20 mL). The filtrate was then cooled to 0 °C under argon, $Ph_3P{=}CHCO_2CH_3$ (789 mg, 2.36 mmol) was added and the solution allowed to warm to room temperature. After stirring overnight, the solvent was evaporated under reduced pressure to yield a yellow solid, which was partitioned between EtOAc (20 mL) and satd $NH_4Cl$ (20 mL). The aqueous layer was separated and extracted with EtOAc (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow solid purified with flash column chromatography (silica, gradient elution, 10:1 to 5:1 hexanes/EtOAc) to afford a mixture of the alkene stereoisomers as colourless crystals in oil [346 mg, 83% (*E*/*Z*=1:5.1)]. A sample was further purified with flash column chromatography (silica, gradient elution 10:1 to 5:1 hexanes/EtOAc) for characterisation purposes to afford separated (*E*)-*ent*-**16** as colourless crystals and (*Z*)-*ent*-**16** as a colourless oil. [(*Z*)-*ent*-**16**]: $R_f$=0.59 (2:1 hexanes/EtOAc). $[\alpha]_D^{21}$ −167.4 (*c* 3.00, $CHCl_3$) [cf. lit.[20] for the enantiomer (*Z*)-**16** $[\alpha]_D^{22}$ +216.84 (*c* 1.00, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.20 (dd, *J*=11.5, 7.4 Hz, 1H), 5.90 (dd, *J*=11.8, 1.7 Hz, 1H), 5.68 (ddd, *J*=7.4, 7.2, 1.6 Hz, 1H), 5.66 (ddd, *J*=17.1, 10.4, 7.3 Hz, 1H), 5.26 (ddd, *J*=17.1, 3.0, 1.7 Hz, 1H), 5.15 (ddd, *J*=10.3, 1.6, 1.0 Hz, 1H), 4.86 (ddd, *J*=8.3, 2.2, 1.0 Hz, 1H), 3.72 (s, 3H), 1.54 (s, 3H), 1.41 (s, 3H). [(*E*)-*ent*-**16**]: $R_f$=0.50 (2:1 hexanes/EtOAc). $[\alpha]_D^{21}$ +30.2 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.79 (dd, *J*=15.7, 5.6 Hz, 1H), 6.07 (dd, *J*=15.7, 1.5 Hz, 1H), 5.69 (ddd, *J*=17.1, 10.3, 7.6 Hz, 1H), 5.36 (dd, *J*=17.1, 1.5 Hz, 1H), 5.26 (ddd, *J*=10.3, 1.5, 0.9 Hz, 1H), 4.78 (ddd, *J*=7.0, 5.6, 1.6 Hz, 1H), 4.71 (tt, *J*=7.0, 0.9 Hz, 1H), 3.75 (s, 3H), 1.55 (s, 3H), 1.41 (s, 3H). The spectral data matched those of the enantiomers reported previously.[20]

### 4.5. Methyl (4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hept-6-enoate (*ent*-22)

$NaBH_4$ (162 mg, 4.27 mmol) was added to a solution containing a 1:5.1 mixture of α,β-unsaturated ester isomers (*E*)- and (*Z*)-*ent*-**16** (189 mg, 0.89 mmol), CuCl (88 mg, 0.89 mmol) and cyclohexene (0.36 mL, 3.56 mmol) in $Et_2O$ (5 mL) stirred at −78 °C. After 30 min, TLC suggested the presence of starting material, so additional CuCl (9 mg, 0.09 mmol) and $NaBH_4$ (7 mg, 0.18 mmol) were added. After an additional 15 min, TLC suggested the consumption of starting material. The solvent was then evaporated under reduced pressure to yield a grey solid. The crude mixture was partitioned between EtOAc (10 mL) and satd $NH_4Cl$ (10 mL), and the aqueous layer separated and extracted with EtOAc (2×5 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow oil purified with flash column chromatography (silica, gradient elution, 15:1 to 9:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (167 mg, 88%). $R_f$=0.52 (2:1 hexanes/EtOAc). +27.2 (*c* 2.00, $CHCl_3$) [cf. lit.[20] for the enantiomer **22** $[\alpha]_D^{22}$ −31.0 (*c* 1.00, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.82 (ddd, *J*=17.2, 10.5, 7.7 Hz, 1H), 5.34 (ddd, *J*=17.1, 2.7, 1.2 Hz, 1H), 5.26 (ddd, *J*=10.2, 1.4, 1.0 Hz, 1H), 4.54 (dd, *J*=7.5, 6.4 Hz, 1H), 4.15 (ddd, *J*=8.8, 6.2, 5.4 Hz, 1H), 3.68 (s, 3H), 2.50 (ddd, *J*=16.3, 8.3, 6.4 Hz, 1H), 2.39 (ddd, *J*=16.4, 8.5, 7.4 Hz, 1H), 1.80–1.70 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H). The spectral data matched those of the enantiomer (**22**) reported previously.[20]

### 4.6. (4*R*,5*S*)-4,5-*O*-(1-Methylethylidene)hept-6-en-1-thioacetate (*ent*-23)

A solution of ester *ent*-**22** (296 mg, 1.38 mmol) in $Et_2O$ (10 mL) was added to a suspension of $LiAlH_4$ (315 mg, 8.29 mmol) in $Et_2O$ (15 mL) and stirred at −10 °C. After 30 min, TLC analysis suggested there was remaining starting material, so additional $LiAlH_4$ (44 mg, 1.17 mmol) was added. After an additional 10 min, the reaction was quenched with wet $Na_2SO_4$, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to afford the desired compound (4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hept-6-en-1-ol as a colourless oil (209 mg, 81%). $R_f$=0.10 (2:1 hexanes/EtOAc). $[\alpha]_D^{18}$ +2.5 (*c* 1.00, $CHCl_3$) [cf. lit.[20] for the enantiomer $[\alpha]_D^{22}$ −6.1 (*c* 1.00, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.81 (ddd, *J*=17.1, 10.3, 7.8 Hz, 1H), 5.29 (ddd, *J*=17.1, 1.6, 1.1 Hz, 1H), 5.23 (ddd, *J*=10.3, 1.6, 0.9 Hz, 1H), 4.51 (dd, *J*=7.4, 6.7 Hz, 1H), 4.17 (ddd, *J*=8.5, 6.2, 5.0 Hz, 1H), 3.67 (t, *J*=5.8 Hz, 2H), 1.91 (s, 1H), 1.80–1.60 (m, 2H), 1.55 (m, 2H), 1.49 (s, 3H), 1.37 (s, 3H). The spectral data matched those of the enantiomer reported previously.[20]

MsCl (0.11 mL, 1.48 mmol) was added to solution of the alcohol above (209 mg, 1.12 mmol), $NEt_3$ (0.24 mL, 0.27 mmol) and DMAP (14 mg, 0.11 mmol) in $CH_2Cl_2$ (10 mL) and stirred at 0 °C. TLC analysis suggested the consumption of starting material after 17 h. The solvent was then evaporated under reduced pressure to yield a yellow solid, which was partitioned between EtOAc (20 mL) and water (20 mL). The organic layer was then separated, washed with satd $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow oil purified by flash column chromatography (silica, 3:1 hexanes/EtOAc) to afford the desired compound (4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hept-6-en-1-methanesulfonate as a colourless oil (270 mg, 91%). $R_f$=0.25 (2:1 hexanes/EtOAc). +6.1 (*c* 1.00, $CHCl_3$) [cf. lit.[20] for the enantiomer $[\alpha]_D^{22}$ −14.3 (*c* 1.09, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.84 (ddd, *J*=17.1, 10.3, 7.7 Hz, 1H), 5.33 (ddd, *J*=17.1, 1.6, 1.1 Hz, 1H), 5.30 (ddd, *J*=10.3, 1.6, 0.9 Hz, 1H), 4.57 (dd, *J*=7.5, 6.4 Hz, 1H), 4.30 (dt, *J*=9.9, 6.3 Hz, 1H), 4.25 (ddd, *J*=9.8, 7.0, 6.0 Hz, 1H), 4.19 (ddd, *J*=9.0, 6.2, 4.7 Hz, 1H), 3.01 (s, 3H), 1.99 (tdd, *J*=12.3, 9.2, 6.2 Hz, 1H), 1.88–1.78 (m, 1H), 1.60–1.52 (m, 2H), 1.52 (s, 3H), 1.40 (s, 3H). The spectral data matched those of the enantiomer reported previously.[20]

KSAc (58 mg, 0.51 mmol) was added to a solution of the mesylate above (112 mg, 0.42 mmol) in DMF (4 mL) stirred at 0 °C, then allowed to warm to room temperature. TLC suggested the consumption of starting material after 20 h. The reaction mixture was then partitioned between $Et_2O$ (10 mL) and water (10 mL). The organic layer was then separated, washed with satd $NaHCO_3$ (2×5 mL), brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and the resultant faint yellow liquid purified with flash column chromatography (silica, 10:1 hexanes/EtOAc) to afford the desired compound (4*R*,5*S*)-4,5-*O*-(1-methylethylidene)hept-6-en-1-thioacetate as a colourless liquid (85 mg, 82%). $R_f$=0.60 (2:1 hexanes/EtOAc). +11.5 (*c* 1.00, $CHCl_3$) [cf. lit.[20] for the enantiomer **23** $[\alpha]_D^{22}$ −9.5 (*c* 1.05, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.79 (ddd, *J*=17.1, 9.7, 7.8 Hz, 1H), 5.30 (d, *J*=17.1 Hz, 1H), 5.24 (d, *J*=10.3 Hz, 1H), 4.49 (t, *J*=6.9 Hz, 1H), 4.13 (m, 1H), 2.95–2.83 (m, 2H), 2.32 (s, 3H), 1.80–1.68 (m, 1H), 1.66–1.50 (m, 2H), 1.49–1.41 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H). The spectral data matched those of the enantiomer (**23**) reported previously.[20]

### 4.7. Methyl (6′*R*,7′*S*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thia-non-8′-enyl)-2,4-di(hydroxy)benzoate (*ent*-24)

A solution of thioacetate *ent*-**23** (195 mg, 0.79 mmol) and resorcylic bromoester **8** (339 mg, 0.79 mmol) in MeOH (20 mL) was

degassed by sonicating while flushing with argon for 10 min. $K_2CO_3$ (276 mg, 2.00 mmol) was then added to the reaction mixture. After 24 h, the solvent was evaporated under reduced pressure and the crude product dissolved in EtOAc (20 mL) and satd $NH_4Cl$ (20 mL). The aqueous layer was then separated and extracted with EtOAc (2×15 mL). The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant brown oil purified with flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (321 mg, 97%). $R_f$=0.28 (2:1 hexanes/EtOAc). +25.7 (*c* 1.00, $CHCl_3$) [cf. lit.[20] for the enantiomer **24** $[\alpha]_D^{18}$ −21.5 (*c* 1.06, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.68 (s, 1H), 6.33 (d, *J*=2.5 Hz, 1H), 6.27 (d, *J*=2.5 Hz, 1H), 5.78 (ddd, *J*=17.2, 10.3, 7.8 Hz, 1H), 5.30 (ddd, *J*=17.1, 1.7, 1.1 Hz, 1H), 5.24 (ddd, *J*=10.3, 1.5, 0.9 Hz, 1H), 4.49 (dd, *J*=7.7, 6.4 Hz, 1H), 4.09 (ddd, *J*=9.1, 6.1, 4.3 Hz, 1H), 3.91 (d, *J*=13.6 Hz, 1H), 3.92 (s, 3H), 3.86 (d, *J*=13.6 Hz, 1H), 2.42 (t, *J*=7.4 Hz, 2H), 1.75–1.65 (m, 1H), 1.64–1.49 (m, 2H), 1.48 (s, 3H), 1.49–1.39 (m, 1H), 1.37 (s, 3H). The spectral data matched those of the enantiomer reported previously.[20]

### 4.8. Methyl (6′*R*,7′*S*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di-(methoxymethoxy)benzoate (*ent*-25)

NaH (14 mg, 0.35 mmol, 60% dispersion in mineral oil) was added to a stirred solution of diol *ent*-**24** (54 mg, 0.14 mmol) in DMF (1 mL) at 0 °C. After 20 min, MOMCl (35 μL, 0.42 mmol) was added and the solution allowed to warm to room temperature. After 21 h, the reaction was diluted with satd $NH_4Cl$ (10 mL) and extracted with $Et_2O$ (10 mL, then 2×5 mL). The combined organic layers were then washed with brine (3×5 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow oil purified with flash column chromatography (silica, gradient elution 10:1 to 5:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (54 mg, 81%). $R_f$=0.30 (2:1 hexanes/EtOAc). +34.5 (*c* 1.00, $CHCl_3$) [cf. lit.[20] for the enantiomer **25** $[\alpha]_D^{18}$ −30.3 (*c* 0.08, $CHCl_3$)]. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.73 (d, *J*=2.2 Hz, 1H), 6.67 (d, *J*=2.2 Hz, 1H), 5.78 (ddd, *J*=17.1, 10.3, 7.8 Hz, 1H), 5.28 (ddd, *J*=17.1, 1.6, 1.1 Hz, 1H), 5.21 (ddd, *J*=10.3, 1.6, 0.9 Hz, 1H), 5.16 (s, 2H), 5.15 (s, 2H), 4.46 (dd, *J*=7.6, 6.4 Hz, 1H), 4.08 (ddd, *J*=8.6, 6.1, 4.7 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 2.48–2.40 (m, 2H), 1.77–1.67 (m, 1H), 1.60–1.43 (m, 3H), 1.46 (s, 3H), 1.34 (s, H). The spectral data matched those of the enantiomer (**25**) reported previously.[20]

### 4.9. (4*S*)-Pent-1-en-4-yl (6′*R*,7′*S*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di(methoxymethoxy)benzoate (28)

KOH (98 mg, 1.73 mmol) was added to a solution of ester *ent*-**25** (163 mg, 0.35 mmol) in 2:1 MeOH/$H_2O$ (4 mL) and the stirred solution heated to 80 °C. After 2 days, the solution was washed with $Et_2O$, the aqueous layer acidified to pH=6 with 10% $KHSO_3$ and extracted with $Et_2O$. The latter organic layer was then washed with water (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (6′*R*,7′*S*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di-(methoxymethoxy)benzoic acid as a yellow oil (160 mg), which was used in the next step without further purification. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.79 (d, *J*=2.2 Hz, 1H), 6.75 (d, *J*=2.2 Hz, 1H), 5.81 (ddd, *J*=17.2, 10.2, 7.8 Hz, 1H), 5.30 (ddd, *J*=17.1, 1.6, 1.0 Hz, 1H), 5.25 (s, 2H), 5.22 (dt, *J*=10.3, 0.8 Hz, 1H), 5.18 (s, 2H), 4.49 (dd, *J*=7.6, 6.4 Hz, 1H), 4.14 (ddd, *J*=8.4, 6.1, 4.6 Hz, 1H), 3.98 (d, *J*=13.4 Hz, 1H), 3.94 (d, *J*=13.4 Hz, 1H), 3.52 (s, 3H), 3.49 (s, 3H), 2.50 (t, *J*=7.0 Hz, 2H), 1.76 (m, 1H), 1.66–1.50 (m, 3H), 1.49 (s, 3H), 1.36 (s, 3H). The spectral data matched those of the enantiomer reported previously.[20]

(*R*)-4-Penten-2-ol (43 μL, 0.42 mmol) was added to a stirred solution of $PPh_3$ (230 mg, 0.88 mmol) and DIAD (0.18 mL, 0.88 mmol) in THF (6 mL) at 0 °C. After 20 min, a solution of the benzoic acid above (160 mg, 0.35 mmol) in THF (5 mL) was added and the solution allowed to warm to room temperature. After 24 h, a small portion of silica was added to the solution and the solvent evaporated under reduced pressure. The dry silica was then loaded on a silica column and eluted with 20:1 to 7:1 hexanes/EtOAc to afford the desired compound **28** as a colourless oil (96 mg, 52% over two steps). $R_f$=0.37 (2:1 hexanes/EtOAc). −3.6 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.71 (d, *J*=2.2 Hz, 1H), 6.68 (d, *J*=2.2 Hz, 1H), 5.85 (ddt, *J*=17.2, 10.2, 7.0 Hz, 1H), 5.78 (ddd, *J*=17.9, 10.3, 7.8 Hz, 1H), 5.28 (d, *J*=17.1 Hz, 1H), 5.25–5.20 (m, 2H), 5.15 (s, 2H), 5.14 (m, 2H), 5.13–5.07 (complex m, 2H), 4.46 (dd, *J*=7.3, 6.6 Hz, 1H), 4.09 (ddd, *J*=8.5, 6.0, 4.8 Hz, 1H), 3.73 (d, *J*=13.7 Hz, 1H), 3.69 (d, *J*=13.7 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.51–2.42 (complex m, 3H), 2.40–2.33 (m, 1H), 1.72 (m, 1H), 1.60–1.40 (complex m, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.34 (d, *J*=6.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.9, 158.6, 155.8, 139.0, 134.3, 133.8, 118.4, 118.3, 117.7, 110.4, 108.2, 102.3, 94.7, 94.3, 79.7, 77.8, 71.2, 56.2, 56.1, 40.2, 33.8, 31.6, 29.5, 28.2, 25.9, 25.6, 19.4. IR (KBr): 3094, 2980, 2902, 2840, 1711, 1607, 1584, 1434, 1380, 1213, 1160, 1029, 924 $cm^{-1}$. HRMS (ESI) calculated for $C_{27}H_{40}O_8SNa^+$ $[M+Na]^+$ 547.2342, found 547.2339.

### 4.10. (5*S*,7*E*,9*S*,10*R*)-1,2-(3′,5′-Di-*O*-methoxymethyl)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)pentadec-7-ene 14,14-dioxide (32)

*m*-CPBA (75 mg, 77% w/w, 0.33 mmol) was added to a 0 °C stirred solution of thioether **28** (77 mg, 0.15 mmol) in $CH_2Cl_2$ (4 mL). After 2 h, TLC suggested there was remaining starting material, so additional *m*-CPBA (38 mg, 77% w/w, 0.17 mmol) was added. After 1 h, the reaction was quenched with 20% $Na_2SO_3$ (10 mL), the aqueous layer separated and extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were then washed with $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow oil purified with flash column chromatography (silica, 3:1 hexanes/EtOAc) to afford the desired compound (4*S*)-pent-1-en-4-yl (6′*R*,7′*S*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di(methoxymethoxy) benzoate 2′,2′-dioxide as a colourless oil (50 mg, 61%). $R_f$=0.17 (2:1 hexanes/EtOAc). −2.7 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.87 (d, *J*=2.2 Hz, 1H), 6.85 (d, *J*=2.2 Hz, 1H), 5.84 (ddt, *J*=17.1, 10.1, 7.0 Hz, 1H), 5.74 (ddd, *J*=17.1, 10.3, 7.7 Hz, 1H), 5.29 (dt, *J*=17.0, 1.2 Hz, 1H), 5.25–5.00 (complex m, 8H), 4.46 (app. t, *J*=7.0 Hz, 1H), 4.38 (d, *J*=14.1 Hz, 1H), 4.28 (d, *J*=14.1 Hz, 1H), 4.09 (dt, *J*=7.4, 6.2 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 3.02 (ddd, *J*=13.9, 10.3, 5.9 Hz, 1H), 2.94 (ddd, *J*=13.9, 10.1, 5.7 Hz, 1H), 2.46 (m, 1H), 2.37 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.53–1.48 (complex m, 2H), 1.45 (s, 3H), 1.34 (d, *J*=6.3 Hz, 3H), 1.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.6, 159.0, 156.4, 134.0, 133.6, 128.5, 119.2, 118.5, 117.9, 112.1, 108.4, 104.1, 94.7, 94.3, 79.5, 77.6, 71.7, 56.7, 56.32, 56.28, 51.4, 40.2, 29.3, 28.1, 25.5, 19.4, 18.7. IR (KBr): 3046, 2981, 2908, 2837, 1715, 1605, 1580, 1438, 1389, 1211, 1161, 1025, 924, 766, 746, 667 $cm^{-1}$. HRMS (ESI) calculated for $C_{27}H_{40}O_{10}SNa^+$ $[M+Na]^+$ 579.2240, found 579.2232.

Grubbs' second generation catalyst (8 mg, 0.009 mmol) was added to a solution of the diene above (50 mg, 0.090 mmol) in $CH_2Cl_2$ (20 mL) in a 100 mL Teflon™ reaction vessel. The vessel was then flushed with argon, sealed and heated in a microwave reactor to 75 °C over 2 min, and held at this temperature for a further 28 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the resultant dark green oil purified with flash column chromatography (silica, gradient elution, 5:1 to 1:1 hexanes/EtOAc) to yield a green oil. This green oil was then dissolved in $CH_2Cl_2$ (6 mL), activated carbon added (10 mg) and the solution stirred for 30 min to remove

remaining Grubbs' catalyst by-product. The solution was then filtered through a Celite® plug and evaporated to afford the desired compound **32** as a faint-green oil (32 mg, 67%) $R_f$=0.11 (2:1 hexanes/EtOAc). +50.5 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.98 (d, *J*=2.2 Hz, 1H), 6.86 (d, *J*=2.2 Hz, 1H), 5.86 (ddd, *J*=15.7, 7.0, 6.2 Hz, 1H), 5.68 (dd, *J*=15.6, 8.6 Hz, 1H), 5.39 (dqd, *J*=7.3, 6.4, 3.2 Hz, 1H), 5.21–5.16 (complex m, 4H), 4.52 (dd, *J*=8.6, 6.4 Hz, 1H), 4.41 (d, *J*=14.4 Hz, 1H), 4.17 (m, 1H), 4.14 (d, *J*=14.4 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.08 (ddd, *J*=14.7, 9.8, 4.9 Hz, 1H), 2.86 (m, 1H), 2.50–2.39 (complex m, 2H), 1.86–1.61 (complex m, 4H), 1.47 (s, 3H), 1.42 (d, *J*=6.3 Hz, 3H), 1.34 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.7, 159.1, 156.2, 130.4, 129.4, 128.0, 119.0, 111.7, 108.2, 104.0, 94.7, 94.4, 79.2, 77.0, 72.5, 56.4, 56.3, 56.1, 51.9, 37.7, 28.1, 27.7, 25.4, 20.1, 18.5. IR (KBr): 3035, 2981, 2902, 2821, 1706, 1612, 1582, 1281, 1215, 1142, 1120, 1015, 927, 668 cm$^{-1}$. HRMS (ESI) calculated for $C_{25}H_{36}O_{10}SNa^+$ $[M+Na]^+$ 551.1927, found 551.1925.

### 4.11. (5′*R*,6′*S*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)aigialomycin D (36)

KOH (68 mg, 1.21 mmol) was added to a solution of sulfone **32** (32 mg, 0.06 mmol) in $^t$BuOH (0.25 mL) and $CH_2Cl_2$ (0.10 mL). After 2 min, $CCl_4$ (0.24 mL) was added dropwise and the solution heated to 30 °C. After 30 min, TLC suggested the consumption of starting material. The solvent was then evaporated under reduced pressure, the crude mixture partitioned between EtOAc (5 mL) and satd $NH_4Cl$ (5 mL), the layers separated and the aqueous layer further extracted with EtOAc (2×5 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant brown oil purified with flash column chromatography (silica, 5:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (18 mg, 64%) $R_f$=0.25 (2:1 hexanes/EtOAc). +4.8 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.70 (d, *J*=2.1 Hz, 1H), 6.68 (d, *J*=2.1 Hz, 1H), 6.43 (d, *J*=15.6 Hz, 1H), 6.09 (dt, *J*=15.8, 6.4 Hz, 1H), 5.86 (ddd, *J*=15.6, 7.8, 5.5 Hz, 1H), 5.67 (dd, *J*=15.6, 8.0 Hz, 1H), 5.20–5.10 (complex m, 5H), 4.57 (dd, *J*=7.8, 6.1 Hz, 1H), 4.16 (dt, *J*=7.2, 5.6 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 2.63 (ddd, *J*=15.8, 7.8, 2.9 Hz, 1H), 2.45–2.30 (complex m, 2H), 2.05 (m, 1H), 1.83 (m, 2H), 1.49 (s, 3H), 1.41 (d, *J*=6.3 Hz, 3H), 1.35 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.2, 158.8, 155.4, 137.6, 132.8, 130.3, 128.8, 128.2, 117.4, 107.8, 106.4, 102.5, 94.7, 94.3, 79.6, 78.0, 72.2, 56.2, 56.1, 37.5, 28.3, 28.2, 28.1, 25.6, 20.2. IR (KBr): 3320, 3059, 3024, 2981, 2913, 2877, 1722, 1612, 1580, 1251, 1212, 1142, 1010, 930 cm$^{-1}$. HRMS (ESI) calculated for $C_{25}H_{34}O_8Na^+$ $[M+Na]^+$ 485.2151, found 485.2152.

### 4.12. (5′*R*,6′*S*)-Aigialomycin D (2)

Protected 5′*R*,6′*S*-AmD **36** (17 mg, 0.037 mmol) was stirred in a mixture of MeOH/1 M aqueous HCl (1:1 v/v, 5 mL). After 2 days, TLC suggested full conversion to a single product. The reaction mixture was then extracted with EtOAc (3×10 mL), the combined organic layers were washed with brine (3 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure and the resultant yellow solid purified by flash column chromatography (silica, gradient elution 1–5% MeOH/$CH_2Cl_2$) to yield a mixture of two compounds (ratio 95:5) as a colourless solid (11 mg, 90%). $R_f$=0.45 (9:1 $CH_2Cl_2$/MeOH). A portion was purified by HPLC for characterisation and bioassay [C18 column, 3:1 MeOH/(1% v/v formic acid in $H_2O$) eluent]. For the major compound, proposed to be **2**: $R_t$=13.0 min [C18, 3:1 MeOH/(1% v/v formic acid in $H_2O$) eluent]. +15.6 (*c* 0.20, MeOH). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 11.89 (s, 1H), 9.25 (broad s, 1H), 7.02 (d, *J*=15.3 Hz, 1H), 6.43 (d, *J*=2.2 Hz, 1H), 6.28 (d, *J*=2.5 Hz, 1H), 6.08 (ddd, *J*=15.1, 10.0, 3.4 Hz, 1H), 5.88 (ddd, *J*=15.2, 9.5, 4.5 Hz, 1H), 5.67 (ddd, *J*=15.1, 9.5, 1.7 Hz, 1H), 5.46 (m, 1H), 4.66 (dd, *J*=9.5, 5.9 Hz, 1H), 4.24 (ddd, *J*=11.5, 5.9, 2.5 Hz, 1H), 2.67 (ddd, *J*=15.9, 9.8, 3.4 Hz, 1H), 2.56 (dtd, *J*=15.9, 3.2, 2.6 Hz, 1H), 2.25 (m, 1H), 2.07–1.94 (complex m, 2H), 1.53 (partially obscured m, 1H), 1.50 (d, *J*=6.6 Hz, 3H). $^{13}$C NMR (150 MHz, acetone-$d_6$) $\delta$ 172.3, 166.3, 163.4, 144.7, 132.9, 131.9, 131.5, 128.5, 108.2, 103.8, 102.5, 80.7, 77.7, 72.0, 38.1, 30.4, 28.9, 18.5. IR (KBr): 3300, 3021, 2975, 2921, 1651, 1601, 1410, 1251, 1212, 1142, 1010, 930 cm$^{-1}$. HRMS (ESI) calculated for $C_{18}H_{22}O_6Na^+$ $[M+Na]^+$ 357.1314, found 357.1319.

### 4.13. (4*R*)-Pent-1-en-4-yl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di(methoxymethoxy)benzoate (29)

(*S*)-4-Penten-2-ol (30 μL, 0.28 mmol) was added to a solution of $PPh_3$ (158 mg, 0.60 mmol) and DIAD (120 μL, 0.60 mmol) in THF (5 mL). After 20 min, a solution of the carboxylic acid derived from **25** by saponification[20] (110 mg, 0.24 mmol) in THF (5 mL) was added and the solution allowed to warm to room temperature. After 16 h, silica gel was added to the reaction mixture and the solvent evaporated under reduced pressure. The residue was dry loaded onto a silica column and eluted (gradient elution, 20:1 to 10:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (105 mg, 86%). $R_f$=0.60 (2:1 hexanes/EtOAc). $[\alpha]_D^{22}$ +30.4 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.72 (d, *J*=2.2 Hz, 1H), 6.69 (d, *J*=1.9 Hz, 1H), 5.85 (ddt, *J*=17.2, 10.2, 7.0 Hz, 1H), 5.78 (ddd, *J*=17.7, 10.4, 7.9 Hz, 1H), 5.28 (d, *J*=16.6 Hz, 1H), 5.26–5.07 (complex m, 6H), 5.15 (s, 2H), 4.46 (t, *J*=7.0 Hz, 1H), 4.08 (m, 1H), 3.75–3.67 (complex m, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 2.51–2.41 (m, 3H), 2.37 (m, 1H), 1.71 (m, 1H), 1.60–1.40 (complex m, 3H), 1.46 (s, 3H), 1.34 (s, 3H), 1.33 (d, *J*=6.2 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.1, 158.7, 156.0, 139.2, 134.4, 134.0, 118.6, 118.5, 117.8, 110.5, 108.3, 102.4, 94.9, 94.4, 79.9, 77.9, 71.3, 56.4, 56.3, 40.4, 33.9, 31.7, 29.7, 28.4, 26.0, 25.8, 19.6. IR (KBr): 3464, 3059, 3024, 1956, 1809, 1597, 1489, 1445, 1329, 1157, 1010, 758, 695, 638 cm$^{-1}$. HRMS (ESI) calculated for $C_{27}H_{40}O_8SNa^+$ $[M+Na]^+$ 547.2342, found 547.2338.

### 4.14. (5*R*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Di-*O*-methoxymethyl)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)pentadec-7-ene 14,14-dioxide (33)

*m*-CPBA (62 mg, 0.28 mmol, 77% w/w) was added to a solution of thioether **29** (64 mg, 0.13 mmol) in $CH_2Cl_2$ (4 mL) stirred at 0 °C then allowed to warm to room temperature. After 3 h, the solution was quenched with 20% $Na_2SO_3$ (5 mL), the aqueous layer separated and extracted with $CH_2Cl_2$ (3×5 mL). The combined organic layers were dried with $MgSO_4$, filtered, concentrated under reduced pressure and the resultant colourless oil purified by flash column chromatography (silica, gradient elution, 3:1 to 1:1 hexanes/EtOAc) to afford the desired compound (4*R*)-pent-1-en-4-yl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)-2,4-di(methoxymethoxy)benzoate 2′,2′-dioxide as a colourless oil (53 mg, 78%). $R_f$=0.13 (2:1 hexanes/EtOAc). $[\alpha]_D^{22}$ +54.3 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.87 (d, *J*=2.2 Hz, 1H), 6.85 (d, *J*=2.2 Hz, 1H), 5.85 (ddt, *J*=17.1, 10.1, 7.0 Hz, 1H), 5.78 (ddd, *J*=17.7, 10.4, 7.8 Hz, 1H), 5.29 (dt, *J*=17.1, 1.3 Hz, 1H), 5.26–5.08 (complex m, 7H), 4.46 (t, *J*=7.0 Hz, 1H), 4.38 (d, *J*=14.1 Hz, 1H), 4.28 (d, *J*=14.1 Hz, 1H), 4.10 (dt, *J*=7.3, 6.3 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H). 3.02 (ddd, *J*=13.9, 10.2, 5.7 Hz, 1H), 2.94 (ddd, *J*=13.9, 10.1, 5.7 Hz, 1H), 2.47 (m, 1H), 2.38 (m, 1H), 1.96 (m, 1H), 1.85 (m, 1H), 1.54–1.49 (complex m, 2H), 1.45 (s, 3H), 1.34 (d, *J*=6.3 Hz, 3H), 1.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.6, 159.0, 156.4, 134.0, 133.7, 128.5, 119.3, 118.6, 117.9, 112.2, 108.4, 104.2, 94.8, 94.3, 79.6, 77.6, 71.7, 56.7, 56.4, 56.3, 51.5, 40.2, 29.3, 28.1, 25.5, 19.5, 18.7. IR (KBr): 3042, 2950, 2840, 1716, 1604, 1580, 1438, 1393, 1218, 1162, 1022, 924, 766, 667 cm$^{-1}$. HRMS (ESI) calculated for $C_{27}H_{40}O_{10}SNa^+$ $[M+Na]^+$ 579.2240, found 579.2239.

A 100 mL MW Teflon™ reaction vessel was charged with a solution of Grubbs' second generation catalyst (8 mg, 0.01 mmol) and the diene above (50 mg, 0.09 mmol) in $CH_2Cl_2$ (20 mL), flushed with argon and sealed. The reaction was then heated in a microwave reactor to 75 °C over 2 min and held at this temperature for a further 28 min. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the resultant dark green oil purified by flash column chromatography twice (silica, 1:1 hexanes/EtOAc) to afford the title compound **33** as a colourless oil (36 mg, 76%). $R_f$=0.07 (2:1 hexanes/EtOAc). $[\alpha]_D^{18}$ −41.0 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.98 (d, *J*=2.2 Hz, 1H), 6.86 (d, *J*=2.2 Hz, 1H), 5.86 (ddd, *J*=15.7, 13.2, 6.4 Hz, 1H), 5.68 (dd, *J*=15.6, 8.6 Hz, 1H), 5.39 (m, 1H), 5.21–5.16 (m, 4H), 4.52 (dd, *J*=8.6, 6.4 Hz, 1H), 4.41 (d, *J*=14.4 Hz, 1H), 4.17 (partially obscured m, 1H), 4.14 (d, *J*=14.4 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 3.08 (ddd, *J*=14.7, 9.8, 4.9 Hz, 1H), 2.86 (m, 1H), 2.50–2.39 (complex m, 2H), 1.85–1.60 (complex m, 4H), 1.47 (s, 3H), 1.42 (d, *J*=6.3 Hz, 3H), 1.33 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.7, 159.2, 156.2, 130.2, 129.4, 128.0, 119.0, 111.7, 108.2, 104.0, 94.7, 94.4, 79.2, 72.5, 56.39, 56.36, 56.1, 51.9, 37.7, 28.1, 27.7, 25.4, 20.1, 18.5 (the peak at $\delta$ 77.0 was not resolvable from the solvent peak). IR (KBr): 3021, 2980, 2900, 2822, 1711, 1613, 1582, 1499, 1288, 1218, 1130, 1128, 1014, 926, 665 cm$^{-1}$. HRMS (ESI) calculated for $C_{25}H_{36}O_{10}SNa^+$ $[M+Na]^+$ 551.1927, found 551.1926.

### 4.15. (5′*S*,6′*R*,10′*R*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (37)

KOH (64 mg, 1.14 mmol) was added to a solution of sulfone **33** (30 mg, 0.06 mmol) in $^t$BuOH (0.25 mL) and $CH_2Cl_2$ (0.10 mL) and stirred under argon. After 2 min, $CCl_4$ (22 μL) was added dropwise and the solution heated to 35 °C. After 45 min, TLC suggested the consumption of starting material. The solvent was then evaporated under reduced pressure, the crude mixture partitioned between EtOAc (5 mL) and satd $NH_4Cl$ (5 mL), the layers separated and the aqueous layer extracted with EtOAc (2×5 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated under reduced pressure and the resultant yellow oil purified by flash column chromatography (silica, gradient elution, 9:1 to 4:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (15 mg, 57%) $R_f$=0.30 (2:1 hexanes/EtOAc). $[\alpha]_D^{24}$ −3.9 (*c* 1.00, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.71 (d, *J*=2.1 Hz, 1H), 6.69 (d, *J*=2.1 Hz, 1H), 6.43 (dt, *J*=15.6, 1.3 Hz, 1H), 6.09 (dt, *J*=15.8, 6.4 Hz, 1H), 5.86 (ddd, *J*=15.6, 7.6, 5.9 Hz, 1H), 5.67 (ddt, *J*=15.6, 8.0, 1.3 Hz, 1H), 5.22–5.11 (complex m, 5H), 4.57 (dd, *J*=7.8, 6.0 Hz, 1H), 4.16 (m, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 2.64 (ddd, *J*=15.7, 7.7, 2.8 Hz, 1H), 2.43 (m, 1H), 2.35 (m, 1H), 2.05 (m, 1H), 1.83 (m, 2H), 1.49 (s, 3H), 1.41 (d, *J*=6.3 Hz, 3H), 1.35 (s, 3H). $^{113}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.2, 158.8, 155.4, 137.7, 132.8, 130.3, 128.8, 128.2, 117.4, 107.8, 106.4, 102.5, 94.8, 94.3, 79.6, 78.1, 72.2, 56.2, 56.1, 37.5, 28.4, 28.2, 28.1, 25.6, 20.2. IR (KBr): 3230, 3022, 2975, 2910, 2872, 1721, 1611, 1584, 1495, 1252, 1217, 1144, 1015, 950, 669 cm$^{-1}$. HRMS (ESI) calculated for $C_{25}H_{34}NaO_8Na^+$ $[M+Na]^+$ 485.2151, found 485.2151.

### 4.16. (5*S*,7*E*,9*R*,10*S*)-1,2-(3′,5′-Dihydroxy)benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-dihydroxypentadec-7-ene 14,14-dioxide (6)

To a solution of the protected macrocyclic sulfone **31**[20] (9.5 mg, 0.018 mmol) in MeOH (1 mL) was added 1 M HCl (1 mL). The reaction was stirred at room temperature for 3 days. The reaction mixture was extracted with EtOAc (3×10 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield a colourless oil (6.4 mg, 89%). $[\alpha]_D^{19}$ −7.2 (*c* 0.69, MeOH). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 11.28 (s, 1H), 9.51 (broad s, 1H), 6.63 (d, *J*=2.5 Hz, 1H), 6.41 (d, *J*=2.5 Hz, 1H), 5.79 (ddd, *J*=15.9, 8.5, 4.7 Hz, 1H), 5.72 (dd, *J*=15.9, 6.7 Hz, 1H), 5.46 (m, 1H), 4.88 (d, *J*=13.3 Hz, 1H), 4.76 (d, *J*=13.4 Hz, 1H), 4.20 (m, 1H), 3.94 (broad s, 1H), 3.74 (broad s, 1H), 3.66 (broad m, 1H), 3.16 (dt, *J*=14.5, 6.9 Hz, 1H), 2.87 (partially obscured m, 1H), 2.67 (broad d, *J*=15.0 Hz, 1H), 2.41 (apparent dt, *J*=15.0, 7.4 Hz, 1H), 2.12–2.02 (obscured m, 1H), 1.92–1.79 (m, 2H), 1.57 (m, 1H), 1.43 (d, *J*=6.4 Hz, 3H). $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 171.0, 165.4, 162.7, 135.3, 132.8, 127.4, 114.9, 106.7, 104.3, 76.0, 74.6, 73.9, 57.7, 53.7, 38.2, 31.7, 19.7, 19.0. IR (neat): 3396, 2927, 1711, 1650, 1620, 1597, 1453, 1357, 1304, 1299, 1264, 1173, 1115 cm$^{-1}$. HRMS (ESI) calculated for $C_{18}H_{24}O_8SNa^+$ $[M+Na]^+$ 423.1090, found 423.1082.

### 4.17. 1′,2′,7′,8′-Tetrahydroaigialomycin D (4)

To a solution of unsaturated macrocycle **35**[20] (16 mg, 34.6 μmol) in EtOH (1 mL) was added 10% Pd/C (1.5 mg). The flask was briefly evacuated and flushed with $H_{2(g)}$ by means of a $H_{2(g)}$-filled balloon. The reaction was stirred under the $H_{2(g)}$ atmosphere for 2 h before being filtered through Celite® and concentrated under reduced pressure to yield a colourless oil (14 mg, 87%). This product was carried forward without further purification. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.66 (d, *J*=2.2 Hz, 1H), 6.55 (d, *J*=2.1 Hz, 1H), 5.25 (m, 1H), 5.18–5.10 (complex m, 4H), 4.11–4.06 (complex m, 2H), 3.45 (s, 6H), 2.63 (ddd, *J*=13.6, 11.0, 5.8 Hz, 1H), 2.49 (ddd, *J*=13.7, 10.6, 5.2 Hz, 1H), 1.88–1.66 (complex m, 4H), 1.66–1.50 (complex m, 4H), 1.40 (s, 3H), 1.50–1.30 (complex m, 2H), 1.34 (d, *J*=6.3 Hz, 3H), 1.31 (s, 3H), 1.30–1.19 (complex m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 168.3, 158.6, 155.1, 141.5, 119.1, 109.2, 107.1, 101.0, 94.6, 94.3, 77.7, 77.0, 72.4, 56.2, 56.1, 36.5, 33.2, 31.3, 31.3, 28.4, 27.6, 25.9, 24.7, 23.0, 21.0.

To a solution of the protected hydrogenated material (14 mg, 30.0 μmol) in MeOH (1.5 mL) was added 10% HCl (1.5 mL) and the mixture was stirred at room temperature for 3 days. The reaction mixture was extracted with EtOAc (3×10 mL). The combined organic fractions were washed repeatedly with $H_2O$ (4×10 mL) until the aqueous layer was neutral (pH 7). It was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica, gradient elution 1:1 hexanes/EtOAc to EtOAc) to yield the title compound as a colourless oil (6.5 mg, 64% over two steps). $[\alpha]_D^{19}$ −8.2 (*c* 0.11, MeOH). $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 11.77 (s, 1H), 9.09 (s, 1H), 6.34 (d, *J*=2.5 Hz, 1H), 6.24 (d, *J*=2.5 Hz, 1H), 5.10 (m, 1H), 3.83–3.76 (m, 2H), 3.53 (td, *J*=12.3, 4.0 Hz, 1H), 2.36 (td, *J*=12.1, 4.6 Hz, 1H), 1.92–1.79 (m, 3H), 1.77–1.67 (m, 2H), 1.61 (m, 1H), 1.55–1.35 (m, 6H), 1.33 (d, *J*=6.1 Hz, 3H). $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 172.7, 166.2, 163.1, 149.4, 111.8, 105.2, 101.8, 74.6, 73.9, 69.3, 37.2, 36.5, 34.6, 32.9, 28.3, 26.6, 21.6, 21.0. IR (neat): 3410, 3063, 2943, 2869, 1643, 1607, 1489, 1443, 1312, 1258, 1161, 1009, 759, 698, 638 cm$^{-1}$. HRMS (ESI) calculated for $C_{18}H_{26}O_6Na^+$ $[M+Na]^+$ 361.1627, found 361.1627. The data were consistent with those reported previously.[15]

### 4.18. Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)benzoate (26)

A stirred solution of bromide **9** (531 mg, 2.32 mmol) and thioacetate **23** (566 mg, 2.32 mmol) in MeOH (10 mL) was degassed with argon for 10 min. To this solution was added $K_2CO_3$ (641 mg, 4.64 mmol) and the reaction stirred for 18 h at room temperature. The solvent was removed and the crude residue partitioned between EtOAc (20 mL) and $H_2O$ (20 mL). The aqueous layer was further extracted with EtOAc (3×10 mL). The combined organic fractions were washed with satd $NH_4Cl_{(aq)}$ (10 mL), dried over $MgSO_4$, filtered and reduced to give a colourless oil. The product was purified using flash column chromatography (silica, gradient elution 20:1 to 5:1 hexanes/EtOAc) to afford the desired compound as a colourless oil (683 mg, 84%). $[\alpha]_D^{22}$ −14.6 (*c* 0.55, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.90 (dd, *J*=7.7, 1.1 Hz, 1H), 7.43 (td, *J*=7.6, 1.4 Hz,

1H), 7.33–7.28 (complex m, 2H), 5.78 (ddd, *J*=17.3, 10.3, 7.8 Hz, 1H), 5.29 (d, *J*=17.1 Hz, 1H), 5.22 (d, *J*=10.3 Hz, 1H), 4.46 (dd, *J*=7.9, 6.9 Hz, 1H), 4.12–4.05 (complex m, 3H), 3.90 (s, 3H), 2.45 (td, *J*=7.1, 2.5 Hz, 2H), 1.79–1.67 (complex m, 2H), 1.58–1.45 (complex, partially obscured m, 2H), 1.46 (s, 3H), 1.34 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.8, 140.6, 134.3, 131.7, 131.1, 130.9, 129.5, 127.0, 118.3, 108.2, 79.7, 77.8, 52.1, 34.5, 31.6, 29.5, 28.2, 25.9, 25.6. IR (KBr): 2986, 2938, 1723, 1434, 1379, 1262, 1216, 1123, 1077, 1046, 1011, 928, 872, 769, 716 cm$^{-1}$. HRMS (ESI) calculated for $C_{19}H_{26}O_4SNa^+$ $[M+Na]^+$ 373.1449, found 373.1444; $C_{19}H_{26}O_4SK^+$ $[M+K]^+$ 389.1189, found 389.1189.

### 4.19. (4*S*)-Pent-1-en-4-yl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)benzoate (30)

To a stirred solution of ester **26** (252 mg, 0.72 mmol) in MeOH (5 mL) was added a solution of KOH (202 mg, 3.61 mmol) in $H_2O$ (5 mL), and the reaction was heated at 80 °C for 4 h. The reaction mixture was then cooled to room temperature and washed with $Et_2O$ (2×15 mL). The aqueous layer was acidified to pH 1 with 10% HCl and extracted with $Et_2O$ (3×10 mL). These latter combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the acid as a colourless oil (212 mg, 88%). The product (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)benzoic acid was used in the next reaction without further purification. $[\alpha]_D^{20}$ −26.5 (*c* 0.12, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (dd, *J*=7.8, 1.4 Hz, 1H), 7.49 (td, *J*=7.5, 1.4 Hz, 1H), 7.38–7.32 (complex m, 2H), 5.79 (ddd, *J*=17.2, 10.3, 7.8 Hz, 1H), 5.28 (ddd, *J*=17.1, 1.7, 1.3 Hz, 1H), 5.22 (ddd, *J*=10.3, 1.5, 0.8 Hz, 1H), 4.47 (dd, *J*=7.6, 6.4 Hz, 1H), 4.18 (d, *J*=13.3 Hz, 1H), 4.14 (partially overlapping d, *J*=ca. 13 Hz, 1H), 4.10 (ddd, *J*=8.9, 6.2, 4.3 Hz, 1H), 2.48 (t, *J*=7.1 Hz, 2H), 1.75 (m, 1H), 1.66–1.49 (complex m, 2H), 1.47 (s, 3H), 1.45 (m, 1H), 1.35 (s, 3H). IR (neat): 1692, 1372, 1298, 1267, 1242, 1218, 1046, 913, 873, 733 cm$^{-1}$. HRMS (ESI) calculated for $C_{18}H_{24}O_4SNa^+$ $[M+Na]^+$ 359.1293, found 359.1288.

To a stirred solution of alcohol *R*-**11** (46 μL, 0.446 mmol) and $PPh_3$ (195 mg, 0.744 mmol) in THF (5 mL) at 0 °C was added DIAD (145 μL, 0.744 mmol). The solution was stirred at 0 °C for 20 min, during which time a white precipitate formed. After this time, a solution of the benzoic acid above (100 mg, 0.298 mmol) in THF (2 mL) was added dropwise and the reaction mixture left to stir at room temperature for 16 h. The crude reaction mixture was adsorbed onto silica gel by evaporation of the solvent. The residue was dry loaded onto a silica column and eluted (20:1 hexanes/EtOAc) to yield ester **30** as a colourless oil (103 mg, 85%). $R_f$=0.66 (2:1 hexanes/EtOAc). $[\alpha]_D^{22}$ −21.9 (*c* 0.75, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.86 (dd, *J*=7.7, 1.5 Hz, 1H), 7.41 (td, *J*=7.6, 1.3 Hz, 1H), 7.32–7.27 (complex m, 2H), 5.85 (ddt, *J*=17.2, 10.2, 7.1 Hz, 1H), 5.78 (ddd, *J*=17.1, 9.8, 7.8 Hz, 1H), 5.29 (ddd, *J*=17.1, 1.7, 1.0 Hz, 1H), 5.25–5.19 (complex m, 2H), 5.15 (ddt, *J*=17.1, 1.9, 1.5 Hz, 1H), 5.11 (ddt, *J*=10.2, 1.7, 1.0 Hz, 1H), 4.46 (dd, *J*=7.8, 6.8 Hz, 1H), 4.12 (d, *J*=13.3 Hz, 1H), 4.08 (partially obscured m, 1H), 4.07 (d, *J*=13.2 Hz, 1H), 2.55–2.38 (complex m, 4H), 1.72 (m, 1H), 1.61–1.41 (complex, partially obscured m, 3H), 1.47 (s 3H), 1.37 (d, *J*=6.3 Hz, 3H), 1.35 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.0, 140.4, 134.3, 133.7, 131.5, 130.9, 130.8, 126.9, 118.4, 117.9, 108.2, 79.7, 77.8, 70.9, 40.3, 34.4, 31.6, 29.5, 28.2, 25.9, 25.6, 19.5 (1 C overlapping or missing). IR (neat): 2983, 2934, 1713, 1379, 1260, 1216, 1118, 1072, 1047, 994, 922 cm$^{-1}$. HRMS (ESI) calculated for $C_{23}H_{32}O_4SNa^+$ $[M+Na]^+$ 427.1919, found 427.1914.

### 4.20. (5*S*,7*E*,9*R*,10*S*)-1,2-Benzo-4-oxa-14-thia-3-oxo-5-methyl-9,10-*O*-(1-methylethylidene)-pentadec-7-ene 14,14-dioxide (34)

To a solution of thioether **30** (125 mg, 0.309 mmol) in $CH_2Cl_2$ (7 mL) at 0 °C was added ~75% *m*-CPBA (157 mg, 0.681 mmol). The solution was warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of 20% $Na_2SO_3$ (10 mL). The resulting mixture was stirred for 20 min before the organic layer was separated. The aqueous layer was further extracted with $CH_2Cl_2$ (3×10 mL). The combined organic fractions were washed with satd $NaHCO_{3(aq)}$ (10 mL), dried over $MgSO_4$ and filtered. The crude product was purified using flash column chromatography (silica, 5:1 hexanes/EtOAc), affording the desired compound (4*S*)-pent-1-en-4-yl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-methylethylidene)-2′-thianon-8′-enyl)benzoate 2′,2′-dioxide as a colourless oil (124 mg, 92%). $R_f$=0.39 (2:1 hexanes/EtOAc). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (d, *J*=7.4 Hz, 1H), 7.57–7.51 (complex m, 2H), 7.45 (m, 1H), 5.84 (ddt, *J*=17.2, 10.2, 7.0 Hz, 1H), 5.75 (ddd, *J*=17.2, 9.8, 7.7 Hz, 1H), 5.29 (d, *J*=17.1 Hz, 1H), 5.23–5.16 (partially obscured m, 1H), 5.22 (d, *J*=10.0 Hz, 1H), 5.15 (dd, *J*=17.1 Hz, 1H), 5.11 (d, *J*=10.3 Hz, 1H), 4.94 (d, *J*=13.5 Hz, 1H), 4.84 (d, *J*=13.5 Hz, 1H), 4.49 (apparent t, *J*=6.5 Hz, 1H), 4.09 (apparent q, *J*=6.6 Hz, 1H), 3.06–2.89 (complex m, 2H), 2.50 (m, 1H), 2.43 (m, 1H), 2.07–1.79 (complex m, 2H), 1.55–1.47 (complex m, 2H), 1.44 (s, 3H), 1.37 (d, *J*=6.3 Hz, 3H), 1.33 (s, 3H). IR (neat): 2980, 2928, 1711, 1299, 1268, 1116, 1076, 911, 733 cm$^{-1}$. HRMS (ESI) calculated for $C_{23}H_{32}O_6SNa^+$ $[M+Na]^+$ 459.1817, found 459.1817. This material was used in the next reaction without further characterisation.

To a solution of the diene above (120 mg, 28 μmol) in $CH_2Cl_2$ (55 mL) in a 50 mL Teflon™ reactor vessel was added a catalytic amount of Grubbs' second generation catalyst (23 mg, 28 μmol). The vessel was flushed with argon before sealing and heating at 75 °C for 30 min with microwave irradiation. Once the reaction vessel had cooled to room temperature the cap was removed and the solution transferred to a round bottom flask. The solvent was removed under reduced pressure to yield a brown oil. This material was dry loaded onto a silica column and eluted (10:1 hexanes/EtOAc) to afford the macrocycle **34** as a colourless solid (97 mg, 86%). $R_f$=0.32 (2:1 hexanes/EtOAc). Mp 180–181 °C. $[\alpha]_D^{22}$ −11.3 (*c* 0.54, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (dd, *J*=7.9, 1.4 Hz, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.58 (td, *J*=7.6, 1.5 Hz, 1H), 7.45 (td, *J*=7.7, 1.3 Hz, 1H), 5.94 (d, *J*=14.8 Hz, 1H), 5.83 (ddd, *J*=15.1, 10.2, 3.6 Hz, 1H), 5.49 (ddd, *J*=15.3, 9.6, 1.8 Hz, 1H), 5.40 (m, 1H), 4.42 (dd, *J*=9.6, 5.7 Hz, 1H), 4.13 (dd, *J*=14.8, 1.2 Hz, 1H), 4.07 (ddd, *J*=9.8, 5.6, 3.6 Hz, 1H), 2.57–2.49 (complex m, 3H), 2.42 (dt, *J*=15.6, 10.4 Hz, 1H), 1.68 (m, 1H), 1.61–1.52 (complex m, 2H), 1.43 (partially obscured m, 1H), 1.42 (d, *J*=6.4 Hz, 3H), 1.41 (s, 3H), 1.32 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.3, 133.2, 132.9, 132.8, 131.6, 130.6, 129.4, 128.9, 127.7, 107.8, 79.6, 77.3, 71.2, 54.4, 50.9, 40.6, 28.4, 27.9, 25.6, 21.4, 19.0. IR (neat): 2932, 2879, 1706, 1448, 1295, 1244, 1223, 1109, 1072, 1033, 973, 915, 731 cm$^{-1}$. HRMS (ESI) calculated for $C_{21}H_{28}O_6SNa^+$ $[M+Na]^+$ 431.1504, found 431.1502.

### 4.21. (5′*S*,6′*R*,10′*S*)-2,4-Dideoxy-5′,6′-*O*-(1-methylethylidene)-aigialomycin D (38)

To a solution of sulfone **34** (70 mg, 0.172 mmol) in $^t$BuOH/$CH_2Cl_2$ (0.75 mL/0.30 mL) at room temperature was added powdered KOH (214 mg, 3.82 mmol). To the resulting suspension was added $CCl_4$ (0.75 mL) dropwise over 2 min. The reaction was then heated at 35 °C for 30 min. After cooling to room temperature the solvent was evaporated under reduced pressure and the residue partitioned between satd $NH_4Cl_{(aq)}$ (10 mL) and EtOAc (10 mL). The aqueous layer was further extracted with EtOAc (2×10 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The product was purified using column chromatography (silica, 10:1 hexanes/EtOAc) yielding **38** as a colourless solid (47 mg, 80%). $R_f$=0.61 (2:1 hexanes/EtOAc). $[\alpha]_D^{22}$ −34.8 (*c* 0.59, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.62 (dd, *J*=7.7, 1.1 Hz, 1H), 7.47 (d, *J*=7.9 Hz, 1H), 7.39 (td, *J*=7.4, 1.0 Hz, 1H), 7.25 (td, *J*=7.5, 1.2 Hz, 1H), 6.67 (d, *J*=15.5 Hz, 1H), 6.12 (ddd, *J*=15.3, 9.3, 5.2 Hz, 1H), 5.80 (ddd, *J*=15.4, 6.9, 6.1 Hz, 1H), 5.66 (ddt, *J*=15.4, 8.9, 1.4 Hz, 1H), 5.24 (apparent

sextet, $J$=6.1 Hz, 1H), 4.60 (dd, $J$=8.9, 5.5 Hz, 1H), 4.19 (ddd, $J$=11.5, 5.5, 2.9 Hz, 1H), 2.58–2.54 (complex m, 2H), 2.31 (m, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.64 (m, 1H), 1.48 (s, 3H), 1.40 (d, $J$=6.1 Hz, 3H), 1.36 (s, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 169.6, 136.2, 131.3, 131.1, 130.9, 130.4, 130.1, 129.6, 129.1, 126.9, 125.8, 108.2, 79.7, 77.3, 72.4, 39.5, 29.3, 29.1, 28.5, 25.8, 20.3. IR (neat): 2984, 2936, 1703, 1450, 1379, 1291, 1257, 1216, 1121, 1043, 971 cm$^{-1}$. HRMS (ESI) calculated for $C_{21}H_{26}O_4Na^+$ $[M+Na]^+$ 365.1729, found 365.1722.

### 4.22. 2,4-Dideoxyaigialomycin D (5)

To a solution of macrolide **38** (34 mg, 99 μmol) in MeOH (1.5 mL) was added 1 M HCl (1.5 mL). The reaction was stirred for 2 days at room temperature. The reaction mixture was extracted with EtOAc (3×10 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to dryness. The crude product was purified by flash column chromatography (DIOL silica, gradient elution $CH_2Cl_2$ to 5% MeOH/$CH_2Cl_2$) yielding a colourless solid (26 mg, 80%). $[\alpha]_D^{23}$ −117.0 (*c* 0.02, $CHCl_3$). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.75 (d, $J$=7.8 Hz, 1H), 7.51 (d, $J$=7.9 Hz, 1H), 7.41 (t, $J$=7.6 Hz, 1H), 7.27 (m, 1H), 6.97 (d, $J$=16.2 Hz, 1H), 6.23 (dt, $J$=16.1, 5.4 Hz, 1H), 5.88 (m, 1H), 5.67 (dd, $J$=15.7, 6.0 Hz, 1H), 5.35 (m, 1H), 4.41 (d, $J$=5.5 Hz, 1H), 3.75 (br s, 1H), 2.60 (m, 1H), 2.44 (dd, $J$=15.3, 7.6 Hz, 1H), 2.38 (dd, $J$=11.8, 6.1 Hz, 2H), 2.18 (br s, 1H), 2.09 (m, 1H), 2.04 (s, 1H), 1.65 (m, 1H), 1.39 (d, $J$=6.4 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 169.0, 137.3, 132.5, 132.0, 131.5, 130.5, 130.2, 127.9, 127.8, 126.7, 126.2, 76.0, 73.0, 71.8, 38.0, 27.4, 26.9, 19.7. IR (neat): 3435, 2976, 2932, 1710, 1448, 1357, 1263, 1123, 1076, 977, 756 cm$^{-1}$. HRMS (ESI) calculated for $C_{18}H_{22}O_4Na^+$ $[M+Na]^+$ 325.1416, found 325.1412.

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## Supplementary data

Full details of experimental procedures and spectra for new compounds can be found. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.10.042.

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