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An efficient and practical total synthesis of aigialomycin D

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Abstract—An efficient and practical total synthesis of aigialomycin D **1** is described. This concise synthetic route features the use of readily available starting materials with the key transformations being the formation of the macrocycle by RCM under microwave irradiation conditions to effect complete *E*-selectivity, and regio- and stereospecific formation of the 1′,2′-double bond. The synthesis of aigialomycin D is achieved with the longest linear sequence of only 11 steps and an overall yield of 19%.

1. Introduction

Aigialomycin D **1**, which possesses potent antitumour (IC_{50}: 3.0 μg/ml against KB cells) and anti-malarial activity (IC_{50}: 6.6 μg/ml against *Plasmodium falciparum*), is a member of a group of 14-membered resorcinylic macrolides isolated from the marine mangrove fungus *Aigialus parvus* BCC 5311.[1] Some kinases, in particular cyclin-dependant kinase (CDK) and glycogen synthase kinase (GSK-3), have recently been identified as its antitumor targets of action.[2] Three synthetic routes to aigialomycin D **1** have been reported so far. The first total synthesis was described by Danishefsky et al. using a novel 'ynolide' protocol for the formation of the resorcinylic unit.[3] Subsequently, Pan[4] and Winssinger[2] reported two more synthetic routes using the Sharpless asymmetric epoxidation to introduce the 5′,6′-diol unit, and either the Julia–Kocienski reaction[4] or selenium/sulfur chemistry[2] to install the 1′,2′-double bond. In Winssinger's work, some aigialomycin D analogues have also been synthesised using solid-phase synthetic strategies.[2]

In view of the biological activities, the lack of analogues with structural diversity for structure–activity relationship studies and the potential to develop more potent lead compounds, we have independently conceived an efficient and practical total synthetic route to aigialomycin D **1** from readily available starting materials. In this paper, we report an efficient, stereospecific and practical synthesis of aigialomycin D **1** with a longest linear sequence of only 11 steps in 19% overall yield.

Keywords: Aigialomycin D; Macrolide; D-Erythronolactone; Ring closing metathesis.
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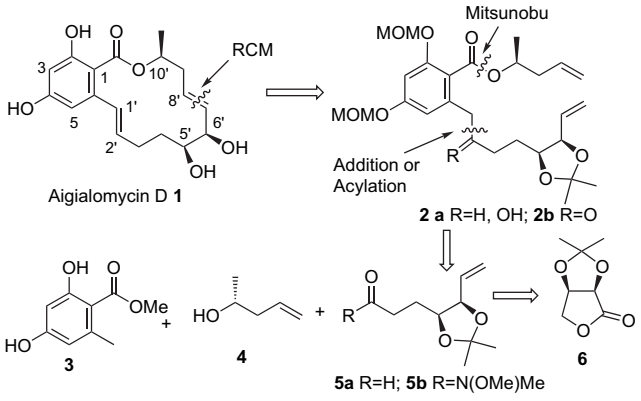
2. Results and discussion

Our synthetic route to aigialomycin D **1** (Scheme 1) was designed in conjunction with our recent efforts in the exploration of new synthetic applications of D-(−)-erythronolactone as a chiral building block. Disconnection of the target compound **1** revealed three key fragments **3**–**5**. The aromatic portion **3** could be easily accessed by a reported cyclodimerization of methyl acetoacetate[5] whilst the key $C_{2'}$–$C_{7'}$ fragment **5** would be derived from D-(−)-erythronolactone acetonide **6**, thus should provide the 5′,6′-diol with the desired configuration. The formation of the ester linkage was to be effected by the Mitsunobu reaction[6] of **3**, after phenolic group protection and saponification to its carboxylic acid, with the commercially available *R*-alcohol **4**, and the installation of the $C_{2'}$–$C_{7'}$ portion to be carried out at the benzylic position either by addition to the aldehyde **5a** or acylation with the Weinreb amide[7] **5b**, respectively, after lithiation

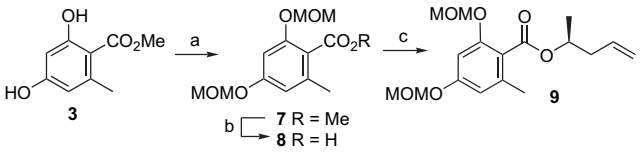


Scheme 1. Retrosynthetic analysis of aigialomycin D **1**.

at the benzylic position. The macrocyclisation would then be achieved by a ring closing metathesis (RCM) on intermediate **2** and the 1′,2′-alkene to be formed by regio- and stereoselective dehydration of the 2′-alcohol. Final global deprotection should complete a practical and efficient synthesis of aigialomycin D **1**.

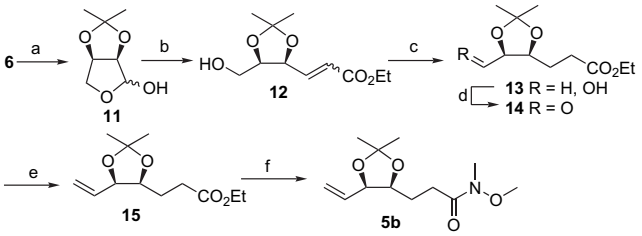
Our synthesis began with methyl orcillinate **3**, which was conveniently prepared by cyclodimerization of methyl acetoacetate in large scales according to a reported protocol.[5] To couple **3** with the alcohol **4**, the phenolic groups were protected as its bis-MOM ether **7**,[8] which was saponified to give the desired acid **8** after acidification. It is noteworthy that the acid is unstable under acidic conditions and undergoes fast deprotection of one of the MOM protecting groups. Therefore only weak organic acids, such as acetic acid, should be used for the acidification and the crude product should be used after workup.

Coupling of the acid **8** with the alcohol **4** under Mitsunobu conditions proceeded smoothly, affording the desired ester **9** in 86% yield (Scheme 2). At this point, the feasibility of coupling the ester **9** with the aldehyde **5a** by a benzylic lithiation–addition reaction was examined. Disappointingly, reaction of the 1′-lithiated **9** with *n*-butyraldehyde as a model substrate afforded only the δ-lactone **10**,[9] apparently formed by intramolecular lactonisation after the addition reaction had taken place. As a result, the aldehyde addition approach was abandoned and the acylation methodology with the Weinreb amide **5b** to be investigated.



Scheme 2. Reagents and conditions: (a) MOMCl, NaH, THF, rt, quant.; (b) KOH, MeOH/H_2O (1:1), reflux then HOAc, pH 6, 99%; (c) DIAD, Ph_3P, **4**, THF, rt, 86%.

The synthesis of the required Weinreb amide **5b** for the acylation approach is shown in Scheme 3. The acetonide **6**, which is commercially available or readily prepared following the literature procedures,[10] was reduced using DIBAL-H to provide the known lactol **11**,[10] which was converted to the ester **15** following a modified route described for its enantiomer.[11] Thus, treatment of **11** with ethyl(triphenylphosphoranylidene)acetate in the presence of a catalytic amount of benzoic acid afforded the α,β-unsaturated ester **12** as a 1:2 mixture of *E*- and *Z*-isomers in 73% yield. Without separating the two isomers, the double bond in **12** was saturated under catalytic hydrogenation conditions to give the alcohol **13**, which was oxidized to the aldehyde **14** under the buffered pyridinium chlorochromate (PCC) conditions.[11] Wittig reaction on the aldehyde **14** with methylenetriphenylphosphorane, generated by treatment of methyl triphenylphosphonium bromide with *n*-butyllithium, afforded the alkene **15** in 71% yield. Conversion of **15** to the Weinreb amide **5** was attempted following a general protocol developed by Williams et al. by reacting **15** with methoxymethylamine hydrochloride in the presence of isopropylmagnesium chloride.[12] This, however, resulted in deprotection of the acetonide, presumably due to the acidic nature of methoxymethylamine hydrochloride. After much experiment, it was eventually found that changing the order of reagent addition sequences by treatment of methoxymethylamine hydrochloride with 2 equiv of isopropylmagnesium chloride followed by addition of the ester **15** gave the desired amide **5b** in 96% yield.

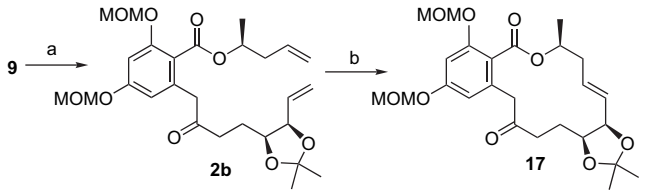


Scheme 3. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C then MeOH, 92%; (b) $Ph_3P{=}CHCO_2Et$, $PhCO_2H$ (0.2 mol %), CH_2Cl_2, reflux, *E*/*Z*=1:2, 73%; (c) H_2 (1 atm), 10% Pd/C (cat.), EtOH, 97%; (d) PCC, NaOAc, 4 Å MS, CH_2Cl_2, rt, 80%; (e) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, −30 °C to rt, 71%; (f) MeONHMe·HCl, *i*-PrMgCl, THF, −20 °C to rt, 96%.

With both the ester **9** and the Weinreb amide **5b** in hand, the crucial acylation step was examined. To our delight, lithiation of **9** at the 1′-position using LDA at −78 °C followed by reacting with the Weinreb amide **5b** provided the desired ketone **2b** in 82% yield. At this stage, attempted reduction of the 2′-carbonyl group with sodium borohydride led to the cleavage of the ester linkage and formation of δ-lactone **16**[13] instead of the required alcohol **2a**, indicating again the facile intramolecular attack of the 2′-alkoxy anion on the ester moiety. It was envisaged that reduction after formation of the macrocycle could avoid this problem as the macrocyclic ring strain would prevent the 2′-alkoxy anion from approaching close enough to attack the ester.

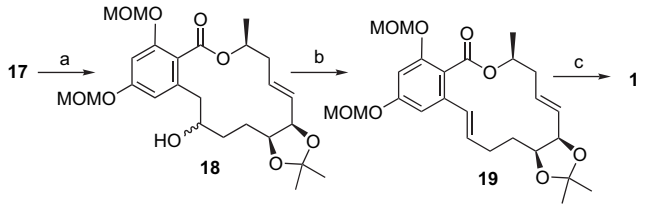
The macrocyclisation of **2b** by RCM following a reported protocol[3] afforded the cyclised product **17** in 86% yield but with an *E*/*Z* ratio of only 5.7:1 as was evident from its ^{1}H NMR spectrum. As the two stereoisomers were inseparable by column chromatography, alternative conditions were sought to improve the *E*-selectivity in this reaction. Inspired by reports[14] that RCM under microwave (MW) irradiation improves the yield as well as the reaction efficiency, it was considered that RCM of **2b** under MW irradiation at higher temperature could improve the selectivity by favouring the thermodynamically more stable *E*-isomer. Indeed, when the cyclisation precursor **2b** (0.005 M in CH_2Cl_2) was subjected to MW irradiation with Grubbs II catalyst (10 mol %) at 100 °C for only 30 min (see Section 4.1.9), the cyclised product **17** was obtained in 98% yield with complete *E*-selectivity (Scheme 4), which was evident from only one set of olefinic signals in the ^{1}H NMR spectrum characterised by a 15.0 Hz coupling constant.

Having achieved the macrocyclization, the ketone **17** was reduced under standard conditions with sodium borohydride to give the desired alcohol **18** as expected, in contrast to the result before formation of the macrocycle.[13] At this point, a formal synthesis of aigialomycin D **1** has been achieved as the alcohol **18** has been used in Danishefsky's synthesis of aigialomycin D **1**.[3]



Scheme 4. Reagents and conditions: (a) LDA, −78 °C, THF then **5b**, 82%; (b) CH_2Cl_2 (0.005 M), Grubbs II catalyst (10 mol %), MW irradiation, 100 °C, 30 min, 98%, *E* only.

To install the 1′,2′-*E*-double bond, the alcohol **18** was treated with Martin's sulfurane dehydrating reagent[15] following a literature protocol.[3] However, this led to the formation of the desired product **19** but mixed with the decomposed sulfurane reagent, which were not separable in our hands. As a result, alternative dehydration conditions were examined. After screening a number of conditions, we were delighted to find that mesylation of the alcohol **18** followed by elimination with DBU under reflux afforded cleanly the desired alkene **19** in 74% yield with complete regio- and *E*-selectivity, characterised by a 15.4 Hz coupling constant at the newly formed 1′,2′-double bond. Final global deprotection of both the MOM and the acetonide protecting groups with aqueous hydrochloric acid in methanol[3] afforded aigialomycin D **1** in 91% yield (Scheme 5) with all the analytical data in agreement with those reported.[1,3,4]



Scheme 5. Reagents and conditions: (a) $NaBH_4$, MeOH/H_2O (4:1), rt, quant.; (b) (i) MsCl, Et_3N, DMAP (10 mol %), CH_2Cl_2; (ii) DBU, toluene, reflux, 74% over two steps; (c) 1 N HCl/MeOH (1:1), rt, 48 h, 91%.

3. Conclusion

In conclusion, we have developed a highly efficient, practical and stereospecific total synthesis of aigialomycin D **1** with the longest linear sequence of 11 steps and an overall yield of 19%. This synthesis features the use of D-(−)erythronolactone to introduce the 5′,6′-chiral diol unit, formation of the macrocycle by RCM under microwave conditions to achieve complete *E*-selectivity of the 7′,8′-double bond with high yields and effective regio- and stereo-controlled installation of 1′,2′-double bond from the alcohol **18** by mesylation and elimination. This facile regio- and stereo-controlled formation of *E*-styrene motif, which combines acylation at the benzylic position, reduction and elimination, should find use in the synthesis of other biologically active, *E*-styrene motif containing phenolic macrolides such as LL-Z1640-2,[16] queenslandon[17] and oximidines.[18] Using the pivotal ketone intermediate **17**, a series of aigialomycin D derivatives and analogues have been prepared and are currently being screened for antitumor and anti-malarial activities. The results will be disclosed in due course.

4. Experimental

4.1. General

Melting points were measured on a Büchi B-540 capillary melting point apparatus and are uncorrected. $^1H/^{13}C$ NMR spectra were recorded at 400/100 MHz on a Bruker Advance 400 spectrometer in $CDCl_3$ unless otherwise stated, using either TMS or the undeuterated solvent residual signal as the reference. IR spectra were measured on a Bio-Rad FTS 3000MX FTIR spectrometer as liquid film or evaporated film. Optical rotations were measured using a Jasco P-1030 polarimeter. Elemental analyses were performed on a EuroEA 3000 Series CHNS Analyzer. Mass spectra were run by the electron impact (EI, 70 eV) mode on a Thermo Finnigan MAT XP95 mass spectrometer, or by the electro spray ionisation (ESI) or the electro spray ionization-time-of-flight (ESI-TOF) mode on an Agilent 6210 mass spectrometer. Microwave reactions were carried out using a MicroSYNTH® multimode microwave system (Milestone Inc., USA) with built-in temperature and pressure sensors and programmable control software for reaction parameters. Solvents for moisture sensitive reactions were taken from a Glasscontour solvent purification system under nitrogen. Commercially available reagents were used as received unless otherwise indicated. Flash column chromatography purification was carried out either manually or by using a Biotage SP1™ purification system by gradient elution.

4.1.1. 2,4-Bis(methoxymethoxy)-6-methylbenzoic acid 8. To a solution of bis-MOM protected methyl ester **7**[8] (1.35 g, 5.0 mmol) in MeOH (20 mL) were added KOH (1.40 g, 25.0 mmol) and H_2O (20 mL) at room temperature. The reaction mixture was heated at 90 °C for 2 days under argon. After cooling to room temperature, the mixture was acidified to pH 6 with acetic acid aqueous solution (50%; v/v, 3.9 mL, 34 mmol) and extracted with EtOAc (3×100 mL). The combined organic phases were washed with H_2O (2×50 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the acid **8** as a colourless oil (1.27 g, 99%), which was pure as judged by its ^1H NMR spectrum and used immediately for the next step. R_f (EtOAc/*n*-hexane, 1:1) 0.28; IR (film) 3020, 2963, 2402, 1698, 1606, 1448, 1398, 1317, 1294, 1215, 1150, 1047, 1029, 928 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.61 (s, 1H), 5.24 (s, 2H), 5.18 (s, 2H), 3.52 (s, 3H), 3.48 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 159.5, 156.6, 141.7, 116.0, 112.1, 101.4, 95.5, 94.2, 56.7, 56.3, 21.5; MS (EI) *m/z* 256.1 (M^+); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_6$ (M^+) 256.0947, found 256.0953.

4.1.2. (*S*)-Pent-4-en-2-yl 2,4-bis(methoxymethoxy)-6-methylbenzoate 9. To a solution of **8** (1.02 g, 4.0 mmol), (*R*)-pent-4-en-2-ol **4** (0.52 g, 6.0 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) in anhydrous THF (20 mL) was added dropwise a solution of DIAD (1.86 g, 9.2 mmol) in THF (5 mL) at room temperature. After stirring for 2 days under argon, the solvent was removed under reduced pressure. The residue was absorbed on silica gel (5 g), followed by flash column chromatographic purification (SiO_2, EtOAc/*n*-hexane, 5–70% gradient) to afford **9** (1.12 g, 86%) as a colourless oil. R_f (EtOAc/*n*-hexane, 1:9) 0.25; $[\alpha]_D^{24}$ +11.7 (*c* 0.10, $CHCl_3$); IR (film) 2828, 2362, 1718, 1607, 1483,

1451, 1149, 1104, 1051, 1026, 994, 923, 838, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.66 (d, 1H, J=2.1 Hz), 6.54 (d, 1H, J=2.1 Hz), 5.84 (tdd, 1H, J=7.00, 10.2, 17.2 Hz), 5.24 (qt, 1H, J=6.3, 12.6 Hz), 5.08–5.14 (m, 6H), 3.46 (s, 6H), 2.33–2.50 (m, 2H), 2.29 (s, 3H), 1.33 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 158.5, 155.2, 137.6, 133.8, 119.1, 117.7, 110.6, 101.1, 94.6, 94.3, 70.9, 56.1, 56.0, 40.2, 19.7, 19.5; MS (EI) m/z 324.2 (M^+); HRMS (EI) m/z calcd for $C_{17}H_{24}O_6$ (M^+) 324.1573, found 324.1572.

4.1.3. Ethyl 3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate 12. To a solution of (2*R*,3*R*)-2,3-*O*-isopropylidene-D-erythrose **11**[10] (4.74 g, 29.6 mmol) in CH_2Cl_2 (150 mL) were added methyl (triphenylphosphoranylidene)acetate (12.5 g, 36.0 mmol) and benzoic acid (0.10 g, 0.82 mmol). The solution was heated under reflux for 17 h until TLC showed that the lactol **11** had been consumed. The solvent was evaporated and the residue was triturated with 30% ether in hexane (4×100 mL). The combined extracts were evaporated and the residue was purified by column chromatography on silica gel by gradient elution with ether–hexane (2:1) to give the isomeric mixture (*E*/*Z*=1:2) of the unsaturated ester **12**[10a] (4.96 g, 73%) as a liquid. *Z*-Isomer: R_f (EtOAc/*n*-hexane, 1:1) 0.43; IR (film) 3441, 2986, 2938, 1714, 1645, 1456, 1416 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, 1H, J=7.0, 11.6 Hz), 5.93 (dd, 1H, J=1.7, 11.6 Hz), 5.60 (ddd, 1H, J=1.7, 7.0, 7.2 Hz), 4.58 (ddd, 1H, J=3.8, 5.1, 7.2 Hz), 4.15 (q, 2H, J=7.1 Hz), 3.56 (dd, 1H, J=3.8, 11.8 Hz), 3.44 (dd, 1H, J=5.1, 11.8 Hz), 2.14 (br s, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 147.3, 121.1, 108.9, 78.8, 74.9, 61.5, 60.7, 27.4, 24.7, 14.2; *E*-isomer: R_f (EtOAc/*n*-hexane, 1:1) 0.33; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, 1H, J=5.6, 15.6 Hz), 6.13 (dd, 1H, J=1.6, 15.6 Hz), 4.81 (ddd, 1H, J=1.6, 5.7, 7.1 Hz), 4.37 (m, 1H), 4.15 (q, 2H, J=7.1 Hz), 3.56 (dd, 1H, J=3.8, 11.8 Hz), 3.44 (dd, 1H, J=5.1, 11.8 Hz), 1.89 (br s, 1H), 1.50 (s, 3H), 1.38 (s, 3H), 1.27 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 142.1, 123.3, 109.7, 78.4, 62.0, 60.8, 27.8, 25.4, 14.4; MS (EI) m/z 215.1 $(M-CH_3)^+$; HRMS (EI) m/z calcd for $C_{11}H_{18}O_5$ $(M-CH_3)^+$ 215.0919, found 215.0916.

4.1.4. Ethyl 3-((4*S*,5*R*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate 13. To a solution of the unsaturated ester **12** (7.20 g, 31.3 mmol) in ethanol (150 mL) was added 10% Pd on charcoal (1.50 g). The black mixture was evacuated and back-filled with hydrogen for four cycles and then stirred under H_2 (ca. 1 atm) for 2.5 h. The mixture was diluted with ethanol (100 mL) and filtered through a pad of Celite®, and the residue was washed with ethanol (2×30 mL). The filtrates were evaporated under reduced pressure to give the hydroxy ester **13** as a liquid (7.04 g, 97%). R_f (EtOAc/*n*-hexane, 2:1) 0.42; $[\alpha]_D^{28}$ −21.4 (*c* 2.04, EtOH) [lit.[11] *ent*-**13** $[\alpha]_D^{28}$ +22.5 (*c* 2, EtOH)]; IR (film) 3514, 2986, 2937, 1733, 1448, 1373, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09–4.18 (m, 4H), 3.63 (d, 2H, J=4.5 Hz), 2.51 (td, 1H, J=7.2, 14.8 Hz), 2.38 (td, 1H, J=7.2, 14.8 Hz), 2.14 (br s, 1H), 1.80–1.83 (m, 1H), 1.43 (s, 3H), 1.33 (s, 3H), 1.23 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 108.2, 77.7, 75.9, 61.5, 60.4, 31.1, 28.0, 25.4, 24.6, 14.1; MS (EI) m/z 217.1 $(M-CH_3)^+$; HRMS (EI) m/z calcd for $C_{11}H_{20}O_5$ $(M-CH_3)^+$ 217.1076, found 217.1063.

4.1.5. Ethyl 3-((4*S*,5*S*)-5-formyl-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate 14. To a stirred suspension of PCC (6.22 g_s, 28.8 mmol), sodium acetate (0.24 g, 2.85 mmol) and 4 Å molecular sieves (2.68 g) in CH_2Cl_2 (90 mL) was added the hydroxyl ester **13** (2.68 g, 11.55 mmol) in CH_2Cl_2 (10 mL) dropwise. The suspension was stirred at ambient temperature for 3 h. The solvent was removed under reduced pressure and the residue extracted with diethyl ether (4×100 mL). The combined extracts were filtered through a silica gel column and further eluted with diethyl ether. Evaporation of the solvent under reduced pressure provided the aldehyde **14** (2.13 g, 80%), which was used in the next step. R_f (EtOAc/*n*-hexane, 2:1) 0.50; IR (film) 3004, 2253, 1730, 1465, 1383, 1235 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.67 (1H, d, J=3.1 Hz), 4.38 (ddd, 1H, J=3.8, 7.2, 10.8 Hz), 4.30 (dd, 1H, J=3.1, 7.2 Hz), 4.14 (q, 2H, J=7.1 Hz), 2.38–2.54 (m, 2H), 1.91–1.99 (m, 1H), 1.72–1.82 (m, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.26 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 172.6, 110.7, 81.8, 77.4, 60.6, 30.9, 27.5, 25.3, 25.2, 14.1.

4.1.6. Ethyl 3-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanoate 15. To a solution of the aldehyde **14** (2.85 g, 12.39 mmol) in THF (20 mL) cooled to −30 °C was added a solution of methylenetriphenylphosphorane (generated at −30 °C by treatment of methyl(triphenyl)-phosphonium bromide (16.8 g, 48.0 mmol) with *n*-butyllithium (17.5 mL of 1.6 M solution in hexanes, 28.0 mmol)) in THF (150 mL) under argon. After being stirred at −30 °C for 30 min, the mixture was allowed to warm to room temperature and stirred for a further 2 h. The mixture was poured into diethyl ether (100 mL) and stirred for 10 min. Evaporation of the solvents followed by flash column chromatography (SiO_2, Et_2O/*n*-hexane 1:1) provided the alkene **15** (2.00 g, 71%) as a colourless liquid. R_f (EtOAc/*n*-hexane, 1:1) 0.61; $[\alpha]_D^{28}$ −20.6 (*c* 2.05, EtOH) [lit.[11] *ent*-**15** $[\alpha]_D^{23}$ +20.6 (*c* 1.5, EtOH)]; IR (film) 3010, 2986, 2936, 1737, 1449, 1371, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, J=7.6, 10.3, 17.5 Hz), 5.33 (d, 1H, J=17.5 Hz), 5.25 (d, 1H, J=10.3 Hz), 4.53 (dd, 1H, J=6.8, 7.6 Hz), 4.09–4.17 (m, 3H), 2.33–2.51 (m, 2H), 1.71–1.77 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 1.25 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 133.8, 118.6, 108.4, 79.5, 77.2, 60.4, 30.9, 28.1, 26.0, 25.6, 14.2; MS (EI) m/z 213.1 $(M-CH_3)^+$; HRMS (EI) m/z calcd for $C_{12}H_{20}O_4$ $(M-CH_3)^+$ 213.1118, found 213.1127.

4.1.7. *N*-Methoxy-*N*-methyl-3-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)propanamide 5b. To a slurry of Me(MeO)NH·HCl (1.24 g, 12.73 mmol) in THF (25 mL) was added a solution of *i*-PrMgCl in THF (12.73 mL of 2.0 M solution, 25.5 mmol) at −20 °C under argon. The mixture was stirred for 20 min to form a homogeneous solution to which a solution of the ester **15** (1.16 g, 5.09 mmol) in THF (10 ml) was added dropwise via a cannula. The reaction mixture was stirred at −20 °C for 1 h before being quenched with saturated NH_4Cl aqueous solution (10 mL). Upon warming to room temperature, the mixture was extracted with diethyl ether (2×30 mL). The combined extracts were washed with brine and dried ($MgSO_4$). Evaporation

of the solvent followed by purification by flash column chromatography (SiO_2, EtOAc/*n*-hexane 1:1) provided the amide **5** (1.19 g, 96%) as a colourless oil. R_f (EtOAc/*n*-hexane, 3:1) 0.45; $[\alpha]_D^{24}$ −27.3 (*c* 0.27, EtOH); IR (film) 2988, 2938, 2252, 1650, 1427, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J*=7.6, 10.3, 17.3 Hz), 5.33 (d, 1H, *J*=17.3 Hz), 5.26 (d, 1H, *J*=10.3 Hz), 4.55 (dd, 1H, *J*=6.5, 7.6 Hz), 4.19 (ddd, 1H, *J*=4.6, 6.5, 9.5 Hz), 3.69 (s, 3H), 3.18 (s, 3H), 2.47–2.65 (m, 2H), 1.72–1.82 (m, 2H), 1.49 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 134.0, 118.5, 108.3, 94.4, 79.6, 77.6, 61.2, 28.5, 28.2, 25.72, 25.68; MS (EI) *m/z* 228.1 $(M-CH_3)^+$; HRMS (EI) *m/z* calcd for $C_{12}H_{21}NO_4$ $(M-CH_3)^+$ 228.1236, found 228.1228.

4.1.8. (*S*)-Pent-4-en-2-yl 2,4-bis(methoxymethoxy)-6-(4-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2-oxobutyl)benzoate 2b. *n*-Butyllithium (1.56 mL of a 1.6 M solution in hexane, 2.50 mmol) was added to diisopropylamine (0.42 mL, 3.0 mmol) in THF (5 mL) at −20 °C and the solution was stirred for 10 min. The resulting LDA solution was added to the ester **9** (0.33 g, 1.00 mmol) in THF (3 mL) at −78 °C, followed by immediate addition of the Weinreb amide **5b** (0.29 g, 1.20 mmol) in THF (3 mL). The resulting mixture was stirred for 10 min at −78 °C and then quenched by addition of aqueous NH_4Cl solution (3 mL). Upon warming to room temperature, the mixture was extracted with EtOAc (3×50 mL) and washed with H_2O (20 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to afford the crude product, which was purified by flash column chromatography (SiO_2, EtOAc/*n*-hexane, 5–100% gradient) to provide the ketone **2b** (0.42 g, 82%) as a colourless oil. R_f (EtOAc/*n*-hexane, 1:1) 0.67; $[\alpha]_D^{24}$ −6.5 (*c* 0.31, $CHCl_3$); IR (film) 2986, 1716, 1606, 1450, 1381, 1283, 1237, 1150, 1023, 924, 830, 803 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, 1H, *J*=2.1 Hz), 6.53 (d, 1H, *J*=2.1 Hz), 5.73–5.89 (m, 2H), 5.07–5.32 (m, 9H), 4.49 (dd, 1H, *J*=6.7, 7.2 Hz), 4.08–4.13 (m, 1H), 3.74 (d, 1H, *J*=16.4 Hz), 3.67 (d, 1H, *J*=16.4 Hz), 3.47 (s, 3H), 3.46 (s, 3H), 2.51–2.68 (m, 2H), 2.31–2.48 (m, 2H), 1.65–1.71 (m, 2H), 1.45 (s, 3H), 1.33 (s, 3H), 1.30 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 171.0, 170.0, 158.9, 156.2, 135.0, 134.0, 133.8, 118.4, 117.6, 111.3, 102.5, 94.7, 94.3, 79.5, 77.2, 71.1, 60.3, 56.2, 56.1, 47.9, 40.1, 38.3, 28.1, 25.5, 24.6, 21.0, 19.4, 14.1; MS (EI) *m/z* 506.2 (M^+); HRMS (EI) *m/z* calcd for $C_{27}H_{38}O_9$ (M^+) 506.2516, found 506.2503.

4.1.9. Macrolactone 17. To a solution of the ketone **2b** (0.15 g, 0.30 mmol) in anhydrous CH_2Cl_2 (60 mL, 0.005 M) in a 100 mL Teflon® vessel (supplied by the manufacturer) was added Grubbs II catalyst (0.025 g, 0.03 mmol, 10 mol %). The vessel was immediately sealed and secured onto the vessel holder in the reactor chamber together with a 100 mL reference vessel, which was charged with CH_2Cl_2 (60 mL) and connected to the temperature and pressure sensors. The vessels were heated to 100 °C for 30 min by programming the system, and selecting temperature and reaction time as the control parameters. After the heating was completed, the vessels were allowed to cool to room temperature before being removed from the reactor chamber. The mixture in the reacting vessel was transferred to a round bottomed flask and the solvent was removed under reduced pressure to afford the crude cyclisation product, which was purified by flash column chromatography (SiO_2, EtOAc/*n*-hexane, 10–100% gradient) to give the macrolactone **17** as a light purple oil (0.14 g, 98%). R_f (EtOAc/*n*-hexane, 1:1) 0.50; $[\alpha]_D^{26}$ +41.6 (*c* 0.339, $CHCl_3$); IR (film) 2982, 1718, 1605, 1585, 1270, 1218, 1148, 1102, 1042, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 1H), 6.53 (s, 1H), 5.77 (dd, 1H, *J*=6.8, 15.0 Hz), 5.53 (dd, 1H, *J*=9.0, 15.0 Hz), 5.33 (dd, 1H, *J*=6.3, 12.4 Hz), 5.14 (s, 4H), 4.47 (dd, *J*=6.4, 9.0 Hz), 4.10–4.15 (m, 1H), 3.82 (d, 1H, *J*=15.2 Hz), 3.42–3.49 (m, 7H), 2.30–2.60 (m, 4H), 1.91–1.99 (m, 1H), 1.68–1.77 (m, 1H), 1.44 (s, 3H), 1.39 (d, 3H, *J*=6.3 Hz), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 167.8, 158.9, 155.9, 133.8, 132.4, 129.0, 118.7, 110.7, 108.0, 102.1, 94.5, 94.2, 82.7, 76.3, 71.6, 56.2, 56.1, 47.2, 39.3, 37.6, 28.0, 25.2, 23.7, 20.8; MS (EI) *m/z* 478.2 (M^+); HRMS (EI) *m/z* calcd for $C_{25}H_{34}O_9$ (M^+) 478.2203, found 478.2203.

4.1.10. Macrolactone 18. To a solution of the macrolactone **17** (0.065 g, 0.14 mmol) in MeOH/H_2O (v/v=4:1, 5 mL) was added $NaBH_4$ (0.020 g, 0.54 mmol) portionwise at room temperature. The reaction mixture was stirred for 30 min and quenched with saturated NH_4Cl aqueous solution (3 mL). The solution was extracted with EtOAc (3×30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the macrolactone **18**[3] as a colourless oil (0.067 g, 100%); R_f (EtOAc/*n*-hexane, 1:1) 0.36; $[\alpha]_D^{26}$ −26.2 (*c* 0.52, $CHCl_3$); IR (film) 3489, 2934, 1718, 1604, 1583, 1449, 1399, 1379, 1269, 1216, 1147, 1040, 972, 923, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, 1H, *J*=2.1 Hz), 6.66 (d, 1H, *J*=2.1 Hz), 5.72 (dd, 1H, *J*=6.8, 15.4 Hz), 5.59 (dd, 1H, *J*=9.2, 15.4 Hz), 5.35 (dd, 1H, *J*=6.2, 12.5 Hz), 5.14 (s, 4H), 4.55 (dd, *J*=6.2, 9.2 Hz), 4.18–4.23 (m, 1H), 3.89 (br s, 1H), 3.46 (s, 6H), 2.81 (dd, 1H, *J*=4.8, 14.1 Hz), 2.71 (dd, 1H, *J*=6.1, 14.1 Hz), 2.43–2.46 (m, 2H), 1.67–1.80 (m, 4H), 1.46 (s, 3H), 1.38 (d, 3H, *J*=6.2 Hz), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 158.6, 155.4, 138.0, 132.2, 130.2, 119.3, 110.6, 107.7, 101.4, 94.5, 94.3, 79.6, 77.2, 71.5, 70.0, 56.2, 56.1, 41.1, 39.6, 31.8, 28.1, 25.3, 24.7, 21.0; MS (EI) *m/z* 480.2 (M^+); HRMS (EI) *m/z* calcd for $C_{25}H_{36}O_9$ (M^+) 480.2359, found 480.2358.

4.1.11. Macrolactone 19. To a solution of the macrolactone **18** (0.19 g, 0.39 mmol) in dry CH_2Cl_2 (5 mL) were added Et_3N (0.56 mL, 3.96 mmol) and DMAP (4 mg, 0.3 mol, 10 mol %) at room temperature under argon. To this mixture was added freshly distilled methanesulfonyl chloride (0.062 mL, 0.79 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the crude mesylate was dissolved in toluene (20 mL) with DBU (0.59 mL, 3.96 mmol) added. The mixture was heated to reflux at 120 °C overnight. Toluene was removed under reduce pressure and the organic material was extracted with EtOAc (3×30 mL). The combined organic phases were washed with water, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, EtOAc/*n*-hexane, 10–100% gradient) to afford the macrolactone **19**[3] as a colourless oil (0.14 g, 74%); R_f (EtOAc/*n*-hexane, 1:1) 0.48; $[\alpha]_D^{22}$ −116.5 (*c* 0.13, $CHCl_3$) [lit.[3] −120 (*c* 0.08, $CHCl_3$)

and lit.[4] −120 (*c* 1.00, $CHCl_3$)]; IR (film) 2927, 1721, 1601, 1576, 1456, 1378, 1261, 1217, 1147, 1051, 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, 1H, *J*=2.0 Hz), 6.68 (d, 1H, *J*=2.0 Hz), 6.24 (d, 1H, *J*=15.4 Hz), 6.14 (ddd, 1H, *J*=4.0, 8.7, 15.4 Hz), 5.73 (ddd, 1H, *J*=3.6, 9.1, 15.5 Hz), 5.59 (dd, 1H, *J*=9.6, 15.5 Hz), 5.30–5.37 (m, 1H), 5.16 (s, 4H), 4.56 (dd, *J*=5.4, 9.6 Hz), 4.16–4.21 (m, 1H), 3.45 (s, 6H), 2.45–2.55 (m, 2H), 2.29–2.32 (m, 1H), 2.07–2.11 (m, 1H), 1.80–1.85 (m, 1H), 1.49–1.55 (m, 1H), 1.46 (s, 3H), 1.36 (d, 3H, *J*=6.2 Hz), 1.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.9, 155.2, 136.8, 132.3, 131.9, 129.3, 128.5, 117.9, 108.3, 104.8, 102.6, 94.6, 94.3, 80.2, 77.3, 71.6, 56.2, 56.1, 39.5, 29.0, 28.7, 28.6, 25.9, 21.2; MS (ESI) *m/z* 463.4 $(M+H)^+$, 485.4 $(M+Na)^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{34}O_{98}Na$ $(M+Na)^+$ 485.2146, found 485.2147.

4.1.12. Aigialomycin D 1. To a solution of macrolactone **19** (0.13 g, 0.29 mmol) in MeOH (5 mL) was added HCl (1 N, 5 mL) and the mixture was stirred at room temperature for 2 days. The mixture was extracted with EtOAc (3×10 mL), and the combined organic phases were washed with water until neutral, dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford the crude product, which was purified by flash column chromatography (SiO_2, EtOAc/*n*-hexane, gradient 50%–100%) to afford aigialomycin D **1**[1,3,4] as a white solid (0.089 g, 91%). Mp 85.6–87.2 °C; R_f (EtOAc) 0.52; $[\alpha]_D^{25}$ −21.9 (*c* 0.35, MeOH); IR (film) 3391, 1646, 1456, 1312, 1259, 1167, 1110, 972 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3) δ 11.67 (s, 1H), 9.23 (br s, 1H), 7.16 (d, 1H, *J*=15.9 Hz), 6.53 (d, 1H, *J*=2.5 Hz), 6.28 (d, 1H, *J*=2.5 Hz), 6.10 (ddd, 1H, *J*=5.7, 5.9, 15.9 Hz), 5.87 (dddd, 1H, *J*=1.4, 7.3, 7.3, 15.6 Hz), 5.69 (dd, 1H, *J*=5.1, 15.6 Hz), 5.40–5.47 (m, 1H), 4.36 (br d, *J*=4.7 Hz), 3.78 (br s, 1H), 3.63–3.66 (m, 1H), 2.55 (ddd, *J*=3.3, 7.4, 14.6 Hz), 2.32–2.36 (m, 2H), 2.11–2.19 (m, 1H), 1.58–1.61 (m, 1H), 1.39 (d, 3H, *J*=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 165.9, 163.3, 144.4, 135.8, 133.7, 130.8, 125.6, 108.0, 104.5, 102.7, 76.7, 73.4, 73.1, 38.1, 28.7, 28.1, 19.2; MS (ESI) *m/z* 333.2 $(M-H)^+$; HRMS (ESI-TOF) *m/z* calcd for $C_{18}H_{23}O_6$ 335.1489 $(M+H)^+$, found 335.1499.

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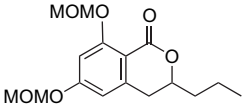
References and notes

1. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M. *J. Org. Chem.* **2002**, *67*, 1561.
2. Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 3951.
3. (a) Geng, X.; Danishefsky, S. J. *Org. Lett.* **2004**, *6*, 413; (b) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881.
4. Lu, J.; Ma, J.; Xie, X.; Chen, B.; Shea, X.; Pan, X. *Tetrahedron: Asymmetry* **2006**, *17*, 1066.
5. Chiarello, J.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 41.
6. (a) Mitsunobu, O. *Synthesis* **1981**, 1; (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
7. (a) Moulin, E.; Barluenga, S.; Winssinger, N. *Org. Lett.* **2005**, *7*, 5637; (b) Moulin, E.; Zoete, V.; Barluenga, S.; Karplus, M.; Winssinger, N. *J. Am. Chem. Soc.* **2005**, *127*, 6999.
8. Dodd, J. H.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1982**, *47*, 4045.
9. The reaction was carried out by treatment of **9** with LDA at −78 °C followed by the addition of *n*-butyraldehyde.



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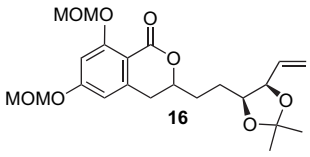
10. (a) Gypser, A.; Peterek, M.; Scharf, H.-D. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1013; (b) Cohen, N.; Banner, B.; Lopresti, R.; Wong, F.; Rosenberger, M.; Liu, Y.; Thom, E.; Liebman, A. *J. Am. Chem. Soc.* **1983**, *105*, 3661.
11. Batty, D.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3193.
12. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
13. The reduction was carried out with sodium borohydride in methanol/water (4:1). Formation of the δ-lactone **16** was evident by the loss of the characteristic signals of the ester portion in **2b**.



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14. For examples: (a) Mayo, K. G.; Nearhoof, E. H.; Kiddle, J. J. *Org. Lett.* **2002**, *4*, 1567; (b) Yang, C.; Murray, W. V.; Wilson, L. J. *Tetrahedron Lett.* **2003**, *44*, 1783; (c) Ronald, G.; Martin, W.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 4899; (d) Thanh, G. V.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 9091; (e) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, O. C. *J. Org. Chem.* **2003**, *68*, 9136; (f) Salim, S. S.; Bellingham, R. K.; Brown, R. C. D. *Eur. J. Org. Chem.* **2004**, 800; (g) Appukkuttan, P.; Dehaen, W.; Van Der Eycken, E. *Org. Lett.* **2005**, *7*, 2723; (h) Comer, E.; Organ, M. G. *J. Am. Chem. Soc.* **2005**, *127*, 8160.
15. (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327; (b) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.
16. Sellès, P.; Lett, R. *Tetrahedron Lett.* **2002**, *43*, 4621 and references cited therein.
17. Hoshino, Y.; Ivanova, V. B.; Yazawa, K.; Ando, A.; Mikami, Y.; Zaki, S. M.; Karam, A. Z.; Youssef, Y. A.; Grafe, U. *J. Antibiot.* **2002**, *55*, 516.
18. Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153.