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# Total Synthesis of Aigialomycin D Using a Ramberg−Bäcklund/RCM Strategy[§]

Lynton J. Baird,[†] Mattie S. M. Timmer,[†] Paul H. Teesdale-Spittle,[‡] and Joanne E. Harvey*,[†]

*School of Chemical and Physical Sciences and School of Biological Sciences, Centre for Biodiscovery, Victoria University of Wellington, P.O. Box 600, Wellington, New Zealand*

*joanne.harvey@vuw.ac.nz*

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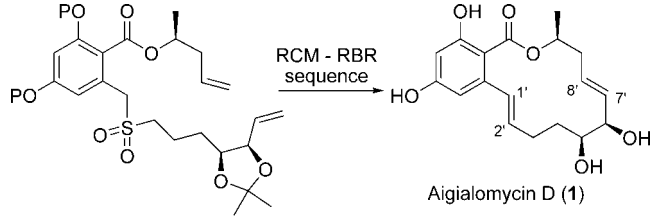
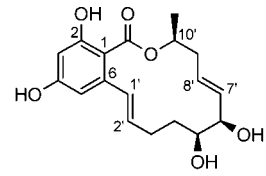


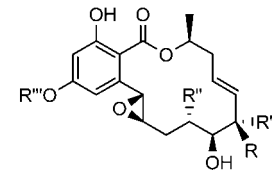

The bioactive resorcylic acid lactone aigialomycin D (**1**) has been synthesized by a novel combination of ring-closing metathesis (RCM) and Ramberg−Bäcklund reactions. This synthetic strategy enables the C1′−C2′ alkene to be masked as a sulfone during formation of the macrocycle by ring closing metathesis at the C7′−C8′ olefin, thus avoiding competing formation of a cyclohexene. A subsequent Ramberg−Bäcklund reaction efficiently produces the C1′−C2′ *E*-alkene. This combined RCM/Ramberg−Bäcklund reaction strategy should be widely applicable to the synthesis of macrocyclic dienes.

## Introduction

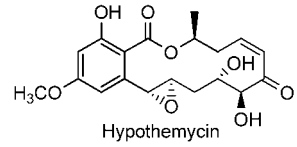
Aigialomycin D (**1**) was isolated in 2002 from the marine mangrove fungus *Aigialus parvus*, along with four other aigialomycins (A−C, E) and the known macrocyclic natural product hypothemycin.[1] These compounds are structurally related to other resorcylic acid macrolactones, such as radicicol, zearalenone, and the pochonins, which are mycotoxins with a diverse array of biological activities and biochemical targets.[2] Aigialomycin D displayed moderate antimalarial activity, with $IC_{50}$ = 6.6 $\mu$g/mL for *Plasmodium falciparum*, and was cytotoxic in some human cell lines, with $IC_{50}$ = 3.0 and 18 $\mu$g/mL in KB and BC-1 cells, respectively.[1] More recently, studies into the molecular targets of aigialomycin D have established that **1** inhibits the kinases CDK1, CDK5, and GSK3 at micromolar levels.[3]

The structure of aigialomycin D and its promising biology have resulted in a flurry of synthetic activity,[4] culminating so far in five reported total syntheses of this intriguing target[3,5] and a number of synthetic analogues.[3,6] Ring-closing metathesis (RCM)[7] has been featured as a theme in several of these




R,R'=O, R''=OH, R'''=$CH_3$: Aigialomycin A
R=H, R'=OH, R''=OH, R'''=$CH_3$: Aigialomycin B
R=H, R'=OH, R''=H, R'''=$CH_3$: Aigialomycin C




synthetic routes, which have generally involved major disconnections at the macrolactone moiety and the two alkenes. Unfortunately, difficulties are encountered when the macrocycle-forming metathesis is performed on a triene precursor in which one of the alkenes of the natural product is already installed, due to the competing facile metathesis process that produces a six-membered ring.[3,6] Therefore, some form of masking of one alkene is required during the RCM, followed by its revelation at a later stage. To this end, Geng and Danishefsky constructed the macrocycle by RCM of a precursor in which the C1′−C2′ olefin was masked as a silyl ether, which would be deprotected and eliminated via Martin's sulfurane prior to appending the aromatic portion using a cycloaddition−cycloreversion se-

[§] We dedicate this article to Professor Richard J. K. Taylor in celebration of his 60th birthday.

[†] School of Chemical and Physical Sciences.

[‡] School of Biological Sciences.

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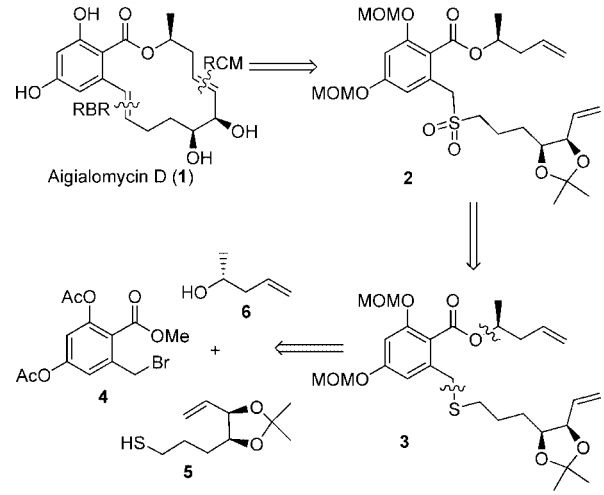
quence.[5a] Winssinger's successful total synthesis invoked elimination of a benzylic phenylselenide to generate the C1′−C2′ alkene after the key RCM.[3] In another approach, Chen and co-workers described the reduction of a macrocyclic C2′-ketone and elimination of the resulting hydroxy group in synthesizing aigialomycin D.[5c]

An alternative solution could involve use of a sulfone-tethered diene in the RCM reaction, followed by its transformation into an *E*-alkene using the Ramberg−Bäcklund reaction. This strategy has the potential to be applied to the synthesis of a wide range of macrocycles containing two or more double bonds.

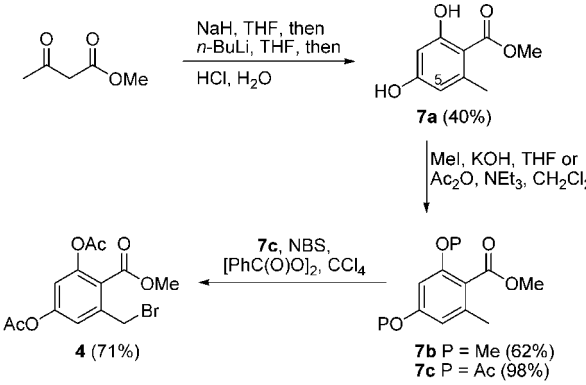
The Ramberg−Bäcklund reaction (RBR)[8] produces an alkene from an α-halo sulfone through formation of an episulfone (thiirane dioxide) and cheleotropic extrusion of $SO_2$.[9,10] Several variations of this methodology have been developed,[10] including Meyers' extension of the RBR,[11] in which α-halogenation of a sulfone is additionally achieved, thus making the conversion of a sulfone into an alkene an efficient one-pot procedure. The RBR has recently been used extensively in *exo*-glycal and *C*-glycoside formation[12] and found application in the synthesis of natural products, dendritic compounds, enediynes, unsaturated amino acids, and other targets.[10,13] In combination with ring-closing metathesis, the RBR has previously been applied to the synthesis of cyclohexadienes and cycloheptadienes.[13b] The sulfone substrate for the Meyers-modified Ramberg−Bäcklund reaction represents a masked alkene, a property that can be exploited in an RCM-based synthesis of macrocyclic dienes, as demonstrated here in the synthesis of aigialomycin D.

We decided to explore the use of the RBR for incorporating the conjugated C1′−C2′ alkene while relying on RCM for installing the C7′−C8′ double bond and closing the macrocycle (Scheme 1). Thus, our retrosynthetic analysis of aigialomycin D led to sulfone-containing diene **2** as a key intermediate by invoking RBR and RCM disconnections. Diene **2** contains a stable precursor to the C1′−C2′ alkene, in the form of a sulfone, expected to be fully compatible with the RCM reaction.[7b] Compound **2** would, in turn, be derived from the thioether **3**, which could be disconnected to the aromatic fragment **4**, thiol **5**, and commercially available homoallylic alcohol **6**. Substitution of the benzylic bromide **4** by thiol **5**, followed by methyl ester hydrolysis and Mitsunobu reaction with alcohol **6**, would deliver the full carbon skeleton **3**, poised for thioether oxidation to sulfone **2**, and the key RCM and RBR sequence.

**SCHEME 1. Retrosynthetic Analysis of Aigialomycin D (1)**




**SCHEME 2. Synthesis of Benzylic Bromide 4**




## Results and Discussion

The benzylic bromide **4** was derived from known methyl orsellinate (**7a**) (Scheme 2). Surprisingly, the synthesis of methyl orsellinate was less facile than expected: the one-pot procedures previously described,[14] which involved sequential treatment of methyl acetoacetate with NaH and BuLi followed by acid-promoted aromatization, initially yielded extremely poor results. Eventually, we discovered that this reaction is highly dependent on the source of the NaH,[15] and addressing this issue improved the reaction sufficiently to afford the required material. Benzylic bromination of either unprotected methyl orsellinate (**7a**) or the dimethyl ether-protected variant (**7b**) was accompanied by large amounts of undesired aromatic bromination at C5. Fortunately, however, acetylation of the phenolic functional groups in **7a** sufficiently deactivated the aromatic ring to allow the desired bromination at the benzylic position of **7c** to proceed efficiently, producing coupling partner **4** in good yield (71%).

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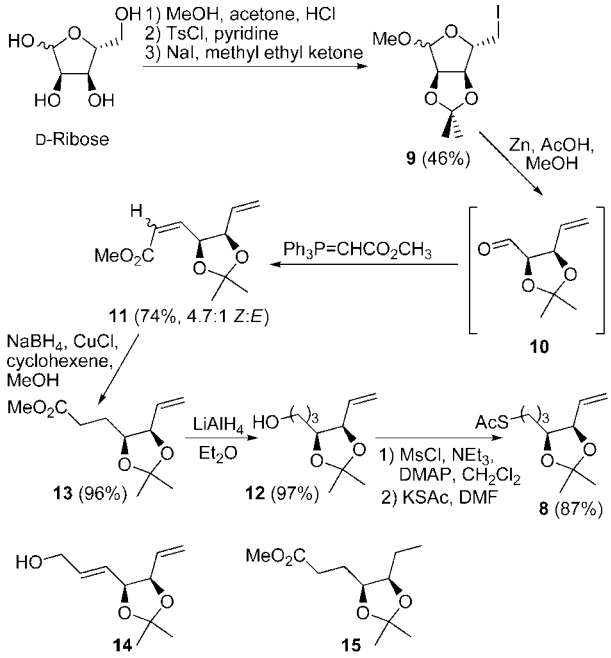
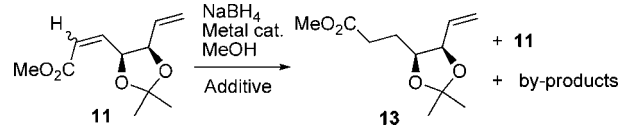
**SCHEME 3. Preparation of Thioacetate 8 from D-Ribose**




Thiol **5** was obtained in its thioacetate-protected form **8** in eight steps from D-ribose via the known aldehyde **10**[16] (Scheme 3). The sequence began with a one-pot methylation and isopropylidenation of D-ribose using methanol and acetone in the presence of hydrochloric acid.[17] The resulting primary alcohol was converted into the corresponding iodide **9**[17] via a tosylate. Vasella reaction[18] of compound **9** led to the ring-opened $\omega$-enal **10**,[16] which underwent a Wittig reaction with the stabilized ylid methyl (triphenylphosphoranylidene)acetate to give the $\alpha,\beta$-unsaturated ester **11** as a 4.7:1 mixture of *Z*- and *E*-isomers.[19]

Methodology was then sought for the selective reduction of the $\alpha,\beta$-unsaturated ester **11** to the saturated primary alcohol **12** while leaving the terminal alkene intact, either in a single step or over two consecutive steps via $\alpha,\beta$-saturated ester **13**. An attempt at performing a one-pot dual reduction of $\alpha,\beta$-unsaturated ester **11** using lithium aluminum hydride afforded poor yields of the desired saturated alcohol **12** and the ester **13** alongside, as major product, the unwanted allylic alcohol **14**. Use of magnesium in methanol[20] did not deliver either desired product **12** or **13**, instead leading to elimination of the isopropylidene group.[21] Therefore, a variety of metal-catalyzed sodium borohydride systems were investigated (Table 1) for the selective reduction of the conjugated alkene within **11** to afford the $\alpha,\beta$-saturated ester **13**, which would be subsequently reduced to alcohol **12** with lithium aluminum hydride. While treatment of $\alpha,\beta$-unsaturated ester **11** with sodium borohydride alone failed to convert the starting material **11** (entry 1), catalysis

**TABLE 1. Metal-Catalyzed $NaBH_4$ Reduction of $\alpha,\beta$-Unsaturated Ester 11**[a]




| entry | metal cat./ additive | isolated yields (%) 13 | 11 | byproducts |
|---|---|---|---|---|
| 1 | none | 0 | 100 | 0 |
| 2 | $NiCl_2$ | 0 | 0 | 84 |
| 3 | $CoCl_2$ | 0 | 0 | 67 |
| 4 | $CuCl_2$ | 45 | 24 | 21 |
| 5 | CuCl | 33 | 47 | 5 |
| 6 | CuCl/cyclohexene | 96 | 0 | 0 |

[a] See the Supporting Information for full details.

by $NiCl_2$[22] (entry 2) or $CoCl_2$[23] (entry 3) led to the isolation of the undesired fully saturated ester **15** (see Scheme 3). Use of $CuCl_2$[24] (entry 4) or CuCl[25] (entry 5) as catalyst provided the sought-after $\alpha,\beta$-saturated ester **13**, albeit contaminated with various byproducts, including the fully saturated ester **15**, unreacted starting material **11**, and compounds lacking the isopropylidene group. Optimization of the most promising results involved using a combination of sodium borohydride and cuprous chloride, with cyclohexene present to trap excess reducing agent and thus prevent over-reduction of the nonconjugated alkene (entry 6). In this way, the $\alpha,\beta$-saturated ester **13** was produced in excellent yield (96%).

Reduction of the ester **13** to alcohol **12** was straightforward and again high yielding. Conversion of this alcohol into the coupling precursor **8** was achieved by mesylation to provide the corresponding sulfonate, followed by reaction with potassium thioacetate. It was found that the thiol coupling partner **5** was unstable to storage and that its in situ preparation from the thioacetate **8** as part of the coupling reaction was therefore preferable.

Preparation of the coupled thioether **16** was achieved through methanolysis of thioacetate **8**, followed by nucleophilic substitution of the benzylic bromide within aromatic fragment **4** by the resultant thiolate (Scheme 4). Concomitant cleavage of the phenolic protecting groups under these basic conditions provided the deacetylated dihydroxybenzoate **16** in excellent yield (86%).

Saponification of the ester group within compound **16** proved problematic: using lithium hydroxide or sodium hydroxide led to significant amounts of the decarboxylated resorcinol **17** (Scheme 4), in keeping with previous reports of decarboxylation occurring in benzoates bearing a free OH group at the ortho position.[26] Lithium ethanethiolate also failed to deliver the desired benzoic acid derivative, returning only starting material **16**. To circumvent these problems, the phenolic groups were protected with methoxymethyl chloride prior to saponification, which now proceeded smoothly with potassium hydroxide. Esterification of the resulting carboxylic acid **18** with 4-penten-

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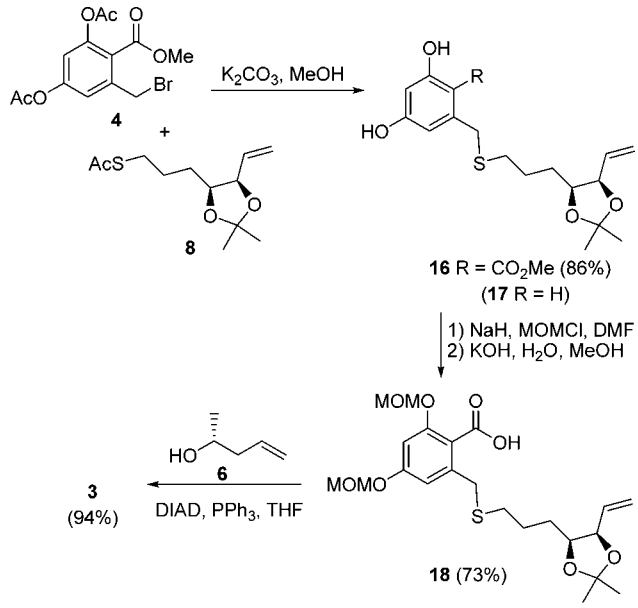
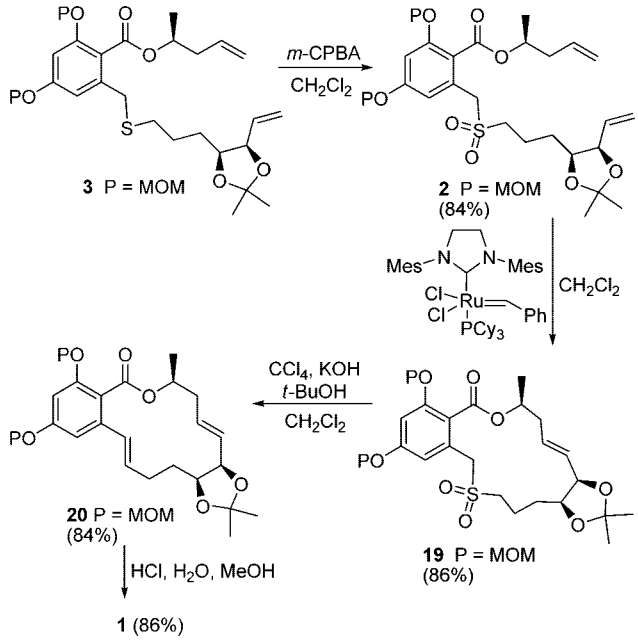
**SCHEME 4. Construction of the Full Carbon Skeleton of Aigialomycin D**




**SCHEME 5**




2-ol using the Mitsunobu protocol gave better yields than the corresponding DCC-promoted coupling. It was also found that the yield of the Mitsunobu reaction was sensitive to the order of reagent addition. Thus, addition of the acid to the preformed triphenylphosphonium-activated intermediate provided the full carbon skeleton of aigialomycin D in its desired (10′*S*)-stereoisomeric form (**3**) and excellent yield.

Oxidation of the thioether **3** to the corresponding sulfone **2** was performed using *m*-CPBA (Scheme 5). The desired sulfone was isolated in 84% yield, and only traces of alkene epoxidation products were observed during this process. Macrocycle formation by ring-closing metathesis proceeded smoothly and rapidly under microwave irradiation, the reaction being completed in 30 min with heating up to 75 °C. The product **19** was isolated in 86% yield, with only the *E*-alkene isomer being observed. In contrast, the conventional reaction resulted only in recovered starting material **2** after 18 h at reflux. The macrocyclic sulfone **19** was subjected to a Ramberg−Bäcklund reaction using Meyers' conditions, which proceeded efficiently with no discernible side products observed in the $^1$H NMR spectrum of the crude reaction mixture. The proposed mechanism involves benzylic chlorination, followed by deprotonation at the non-benzylic sulfone α-center,[9a] episulfone formation[9b,c] by intramolecular displacement of the chloride, and cheleotropic $SO_2$ extrusion.[10] The *E*-alkene **20** was isolated in 84% yield, with no indication of *Z*-isomer formation. The stereoselectivity observed here is particularly gratifying because high stereocontrol is not a guaranteed feature of the RBR in nonconstrained systems.[10]

Interestingly, model reactions of the RBR using benzyl pentyl sulfone (generated from benzyl mercaptan and 1-bromopentane) had produced a complex mixture of products, including the desired alkene plus a halogenated alkene, presumably arising by double halogenation at the benzylic position followed by the standard RBR process.[10] The better outcome from the RBR of macrocycle **19** is consistent with, and extends, the generalization that small- and medium-ring sulfones tend to react more cleanly than acyclic sulfones.[27] The fact that the macrocyclic system reacted so efficiently also highlights the potential utility of the Ramberg−Bäcklund reaction in medium-to-large ring synthesis, a role in which it has found relatively limited use.[28]

Final deprotection of macrocycle **20** was achieved using methanolic aqueous HCl. The resulting material, **1**, obtained in 86% yield, had $^1$H and $^{13}$C NMR data that matched those reported from natural and synthetic aigialomycin D.[1,3]

## Conclusions

Overall, this route to aigialomycin D proceeds in 16 steps (longest linear sequence) from readily available starting materials. The combination of the Ramberg−Bäcklund and RCM reactions proved very effective for producing the diene-containing macrocycle of aigialomycin D, with high yields and complete stereoselectivity observed in these key steps. The preparation of new structural analogs of aigialomycin D for biological screening, and the scope of the RBR/RCM strategy in the synthesis of diene-containing macrocycles are currently being investigated.

## Experimental Section

**Methyl 2,4-Dihydroxy-6-methylbenzoate (Methyl Orsellinate, 7a).** To a suspension of NaH (2.56 g of a 60% dispersion in mineral oil, 64 mmol, washed three times with dry hexanes) in THF (100 mL) at 0 °C was added methyl acetoacetate (5.0 g, 43 mmol) dropwise. The mixture was stirred for 1 h, warming to rt. The reaction was cooled to −78 °C and a 1.6 M solution of *n*-butyllithium in hexanes (25.6 mL, 41 mmol) was added dropwise over 2 h. The reaction was then stirred at rt for 12 h. The reaction mixture was then refluxed for a further 24 h. The cooled orange solution was acidified with 10% HCl to pH 1 and stirred at rt for 12 h. The organic layer was separated, and the aqueous layer was

(27) Page 385 of ref 10a.

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extracted with EtOAc (3 × 75 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified using flash column chromatography (silica, gradient elution 5:1 to 3:1 hexanes/EtOAc) to provide methyl orsellinate (**7a**) as a white solid (1.56 g, 40%): $R_f = 0.44$ (2:1 hexanes/EtOAc); mp 141−142 °C [lit.[29] mp 139−140 °C]. Spectral data matched those reported in the literature.[14a]

**Methyl 2,4-Bis(acetyloxy)-6-methylbenzoate (7c).** To a solution of methyl orsellinate (**7a**) (1.26 g, 6.90 mmol) in $CH_2Cl_2$ (17.5 mL) at rt were added $NEt_3$ (5.76 mL, 41.4 mmol) and acetic anhydride (2.60 mL, 27.6 mmol). The reaction was stirred for 12 h at rt before being quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The organic layer was separated, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by passing it through a short silica column (gradient elution 5:1−2:1 hexanes/EtOAc) with a few drops of AcOH to yield the title compound as a white solid (1.82 g, 98%): $R_f = 0.31$ (2:1 hexanes/EtOAc); mp 53−54 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.89 (d, $J = 2.2$ Hz, 1H), 6.80 (d, $J = 2.2$ Hz, 1H), 3.88 (s, 3H), 2.41 (s, 3H), 2.28 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (75 MHz, CDCl3) $\delta$ 168.9, 168.6, 166.3, 151.7, 149.3, 139.8, 121.3, 114.2, 77.2, 52.2, 21.1, 20.8, 20.5; IR (neat) 3086, 2959, 1781, 1732, 1616, 1587, 1446, 1370, 1280, 1174, 1137, 1098, 1054, 1018, 953, 911 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{14}O_6Na^+$ [M + Na]$^+$ 289.0683, found 289.0685.

**Methyl 2,4-Bis(acetyloxy)-6-(bromomethyl)benzoate (4).** To a solution of **7c** (440 mg, 1.64 mmol) in $CCl_4$ (15 mL) were added NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg), and the reaction mixture was heated to reflux. After 3 h, another portion of NBS (180 mg, 1.01 mmol) and benzoyl peroxide (20 mg) was added to the mixture, and the reaction was heated to reflux for a further 3 h. After this time, the reaction was cooled to rt, the solid succinimide filtered off, and the solvent removed under reduced pressure. The resulting orange oil was purified by flash column chromatography (silica, $CH_2Cl_2$) to yield the title compound **4** as a white solid (400 mg, 71%) and the corresponding dibromide as a white solid (81 mg, 12%). Compound **4**: $R_f = 0.46$ ($CH_2Cl_2$); mp 62−64 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (d, $J = 2.2$, 1H), 6.95 (d, $J = 2.2$, 1H), 4.63 (s, 2H), 3.92 (s, 3H), 2.29 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 168.6, 168.3, 165.2, 152.0, 149.8, 139.3, 123.0, 121.3, 117.0, 52.7, 29.7, 21.1, 20.7; IR (KBr) 3082, 2950, 1770, 1731, 1613, 1434, 1370, 1282, 1187, 1138, 1094, 1033, 1017, 907 cm$^{-1}$; HRMS (ESI) calcd for $C_{13}H_{13}O_6BrNa^+$ [M + Na]$^+$ 366.9793, found 366.9798.

**Methyl (2*Z*,4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hepta-2,6-dienoate [(*Z*)-11] and Methyl (2*E*,4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hepta-2,6-dienoate [(*E*)-11].** To iodide **9** (2.05 g, 6.52 mmol) in MeOH (30 mL) were added activated zinc (3.00 g, 45.9 mmol) and AcOH (100 $\mu$L) before the mixture was refluxed for 4 h. After this time, another portion of zinc (1.50 g, 23.0 mmol) was added and the reaction refluxed for a further 4 h. Once TLC had confirmed the consumption of starting material, the reaction mixture was cooled and filtered through a wad of silica to remove the excess zinc metal and zinc salts. The filtrate was cooled to 0 °C, and methyl (triphenylphosphoranylidene)acetate (2.62 g, 7.83 mmol) was added to the solution. The reaction was allowed to warm over 12 h. The solvent was removed and the crude product partitioned between EtOAc (100 mL) and saturated aqueous $NH_4Cl$ solution (100 mL). The aqueous layer was extracted further with EtOAc (2 × 50 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting pale yellow oil was purified using flash column chromatography (silica,10:1 hexanes/EtOAc) to yield the $\alpha,\beta$-unsaturated ester **11** as a colorless oil [1.06 g, 74% (*Z*/*E* = 4.7:1)]. A portion was subjected to flash column chromatography (silica, gradient elution 10:1−3:1 hexanes/EtOAc) to yield separated samples of (*Z*)-**11** and (*E*)-**11** for characterization. (*Z*)-**11**: $[\alpha]^{22}_D = +216.8$ (*c* 1.00, $CHCl_3$); $R_f = 0.59$ (2:1 hexanes/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.20 (dd, $J = 11.6$, 7.5 Hz, 1H), 5.90 (dd, $J = 11.6$, 1.6 Hz, 1H), 5.68 (td, $J = 7.3$, 1.5 Hz, 1H), 5.66 (ddd, $J = 17.4$, 10.2, 7.2 Hz, 1H), 5.28 (ddd, $J = 17.1$, 1.7, 1.3 Hz, 1H), 5.15 (ddd, $J = 10.3$, 1.9, 1.0 Hz, 1H), 4.87 (tt, $J = 7.1$, 0.9 Hz, 1H), 3.72 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.1, 146.8, 134.0, 121.0, 117.9, 109.2, 79.7, 75.6, 51.5, 27.7, 25.1; IR (KBr) 2985, 2945, 1722, 1648, 1439, 1406, 1381, 1224, 1198, 1179, 1046, 1001, 927, 876, 825 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{16}O_4Na^+$ [M + Na]$^+$ 235.0946, found 235.0942. (*E*)-**11**: $R_f = 0.51$ (2:1 hexanes/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.79 (dd, $J = 15.6$ 5.5 Hz, 1H), 6.08 (dd, $J = 15.6$, 1.6 Hz, 1H), 5.69 (ddd, $J = 17.1$, 10.3, 7.6 Hz, 1H), 5.37 (dd, $J = 17.1$, 1.5 Hz, 1H), 5.27 (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), 1.56 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.4, 143.9, 133.4, 122.2, 119.3, 109.6, 79.8, 77.5, 51.7, 27.7, 25.4.

**Methyl (4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hept-6-enoate (13).** To a solution of $\alpha,\beta$-unsaturated ester **11** (519 mg, 2.45 mmol), CuCl (186 mg, 1.88 mmol), and cyclohexene (960 $\mu$L, 9.43 mmol) in MeOH (40 mL) at −78 °C was added $NaBH_4$ (446 mg, 11.8 mmol). The reaction mixture was left at −78 °C for 1 h, during which time it turned from green to brown. While the mixture was still cold, the solvent was removed on the rotary evaporator. The products were partitioned between saturated aqueous $NH_4Cl$ solution (50 mL) and $Et_2O$ (50 mL). The organic phase was separated, and the aqueous layer was extracted with more $Et_2O$ (4 × 20 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and reduced to give a colorless oil (520 mg, 96%). The product was deemed sufficiently pure by $^1$H NMR for use without further purification: $R_f = 0.46$ (2:1 hexanes/EtOAc); $[\alpha]^{22}_D = -31.0$ (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.82 (ddd, $J = 17.2$, 10.3, 7.6 Hz, 1H), 5.34 (ddd, $J = 17.1$, 1.7, 1.1 Hz, 1H), 5.26 (ddd, $J = 10.3$, 1.6, 0.9 Hz, 1H), 4.54 (dd, $J = 7.5$, 6.4 Hz, 1H), 4.16 (ddd, $J = 8.8$, 6.2, 5.4 Hz, 1H), 3.67 (s, 3H), 2.49 (ddd, $J = 16.3$, 8.3, 6.4 Hz, 1H), 2.40 (ddd, $J = 16.4$, 8.5, 7.4 Hz, 1H), 1.81−1.70 (m, 2H), 1.47 (s, 3H), 1.36 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.6, 133.7, 118.6, 108.4, 79.5, 77.2, 51.7, 30.7, 28.2, 26.2, 25.7; IR (KBr) 2987, 2935, 1736, 1645, 1440, 1371, 1255, 1217, 1162, 1067, 1011, 931, 871 cm$^{-1}$; HRMS (ESI) calcd for $C_{11}H_{18}O_4Na^+$ [M + Na]$^+$ 237.1103, found 237.1100.

**(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hept-6-en-1-ol (12).** To a suspension of lithium aluminum hydride (115 mg, 3.03 mmol) in $Et_2O$ (30 mL) at −10 °C was added methyl ester **13** (540 mg, 2.52 mmol) in $Et_2O$ (15 mL). After 10 min, TLC analysis confirmed that all the starting material had been consumed. The reaction was quenched with wet $Na_2SO_4$, filtered through a pad of Celite, and reduced to dryness to yield alcohol **12** as a colorless oil (458 mg, 97%): $R_f = 0.20$ (2:1 hexanes/EtOAc); $[\alpha]^{22}_D = -6.1$ (*c* 1.00, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.82 (ddd, $J = 17.1$, 10.3, 7.8 Hz, 1H), 5.31 (ddd, $J = 17.1$, 1.6, 1.1 Hz, 1H), 5.24 (ddd, $J = 10.3$, 1.6, 0.9 Hz, 1H), 4.52 (dd, $J = 7.4$, 6.7 Hz, 1H), 4.18 (ddd, $J = 8.5$, 6.2, 5.0 Hz, 1H), 3.68 (t, $J = 5.8$ Hz, 2H), 1.91 (s, 1H), 1.75−1.65 (complex m, 2H), 1.55 (m, 2H), 1.50 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 134.2, 118.4, 108.3, 79.9, 78.2, 62.7, 29.8, 28.3, 27.5, 25.7; IR (KBr) 3435, 2934, 2874, 1644, 1429, 1380, 1248, 1217, 1165, 1047, 1018, 926, 872 cm$^{-1}$; HRMS (ESI) calcd for $C_{10}H_{18}O_3Na^+$ [M + Na]$^+$ 209.1154, found 209.1152.

**(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hept-6-ene-1-methanesulfonate.** To a solution of alcohol **12** (213 mg, 1.15 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C were added $NEt_3$ (320 $\mu$L, 2.30 mmol), DMAP (14 mg, 0.115 mmol), and MsCl (134 $\mu$L, 1.70 mmol). The reaction was allowed to warm to rt and stir for 12 h. After this time, the reaction was deemed complete by TLC (color change from purple to black with anisaldehyde dip). The solvent was removed and the crude product dissolved in EtOAc (20 mL) before being washed with water (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was dried with $MgSO_4$, filtered, and

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concentrated. The resulting oil which was purified using flash column chromatography (silica, gradient elution 3:1−1:1 hexanes/EtOAc) yielded the title compound as a colorless oil (294 mg, 97%): $R_f = 0.26$ (2:1 hexanes/EtOAc); $[\alpha]^{22}_D = -14.3$ (*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), 3.05 (s, 3H), 1.99 (tdd, $J = 12.3, 9.2, 6.2$ Hz, 1H), 1.91−1.82 (m, 1H), 1.62−1.54 (complex m, 2H), 1.52 (s, 3H), 1.41 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6; IR (film) 2994, 2939, 1353, 1248, 1212, 1174, 926, 908, 733 cm$^{-1}$.

**(4*S*,5*R*)-4,5-*O*-(1-Methylethylidene)hept-6-ene-1-thioacetate (8).** To a solution of the mesylate (1.59 g, 6.02 mmol) in DMF (50 mL) at 0 °C was added KSAc (824 mg, 7.23 mmol). The reaction was allowed to warm to rt and stirred for 12 h. The reaction was diluted with $Et_2O$ (100 mL) and $H_2O$ (100 mL). The organic layer was further washed with saturated aqueous $NaHCO_3$ solution (3 × 50 mL) before drying with $MgSO_4$, filtering, and concentrating to give a pale brown oil which was purified using flash column chromatography (silica, gradient elution 20:1−10:1 hexanes/EtOAc) to yield thioacetate **8** as a colorless oil (1.32 g, 90%): $R_f = 0.56$ (2:1 hexanes/EtOAc); $[\alpha]^{22}_D = -9.5$ (*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), 1.36 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 195.8, 134.2, 118.5, 108.3, 79.7, 77.7, 30.6, 29.6, 28.9, 28.2, 26.3, 25.6; IR (film) 2986, 2916, 1692, 1455, 1428, 1379, 1369, 1244, 1216, 1134, 1134, 1048, 1012, 929, 871, 625 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{20}O_3SNa^+$ $[M + Na]^+$ 267.1031, found 267.1028.

**Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-Methylethylidene)-2′-thianon-8′-enyl)-2,4-dihydroxybenzoate (16).** A solution of thioacetate **8** (340 mg, 1.39 mmol) and bromide **4** (485 mg, 1.41 mmol) in dry MeOH (25 mL) was degassed by bubbling dry argon through the solution for 10 min. After this time, $K_2CO_3$ (466 mg, 3.37 mmol) was added, and the reaction was stirred at rt for 12 h. After TLC analysis confirmed the consumption of bromide **4**, the solvent was removed to dryness. The residue was dissolved in EtOAc (50 mL), and saturated aqueous $NH_4Cl$ solution (50 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 25 mL). The organic layers were combined, washed with brine (50 mL), dried with $MgSO_4$, filtered, and reduced to dryness. The crude residue was purified using column chromatography (silica, gradient elution, 5:1−3:1 hexanes/EtOAc) to yield coupled product **16** as a colorless oil (447 mg, 86%): $R_f = 0.33$ (2:1 hexanes/EtOAc); $[\alpha]^{18}_D = -21.5$ (*c* 1.06, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.67 (s, 1H), 6.34 (d, $J = 2.5$ Hz, 1H), 6.31 (s, 1H), 6.28 (d, $J = 2.5$ Hz, 1H), 5.79 (ddd, $J = 17.2, 10.3, 7.8$ Hz, 1H), 5.31 (ddd, $J = 17.1, 1.7, 1.1$ Hz, 1H), 5.25 (ddd, $J = 10.3, 1.5, 0.9$ Hz, 1H), 4.50 (dd, $J = 7.7, 6.4$ Hz, 1H), 4.10 (ddd, $J = 9.1, 6.1, 4.3$ Hz, 1H), 3.93 (d, $J = 13.6$ Hz, 1H), 3.93 (s, 3H), 3.87 (d, $J = 13.6$ Hz, 1H), 2.43 (t, $J = 7.4$ Hz, 2H), 1.76−1.66 (m, 1H), 1.65−1.50 (m, 2H), 1.49 (s, 3H), 1.50−1.40 (m, 1H), 1.38 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 171.3, 165.7, 160.2, 143.9, 133.8, 118.7, 111.1, 108.4, 104.4, 102.5, 79.8, 77.7, 52.2, 37.0, 31.1, 29.5, 28.2, 25.8, 25.7; IR (KBr) 3272, 2988, 2951, 1655, 1621, 1588, 1441, 1381, 1326, 1259, 1210, 1162, 1109, 1031, 1003, 951, 851 cm$^{-1}$; HRMS (ESI) calcd for $C_{19}H_{26}O_6SNa^+$ $[M + Na]^+$ 405.1348, found 405.1345.

**Methyl (6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-Methylethylidene)-2′-thianon-8′-enyl)-2,4-bis(methoxymethoxy)benzoate.** To a solution of compound **16** (621 mg, 1.62 mmol) in DMF (6 mL) at 0 °C was added a 60% dispersion of NaH in mineral oil (163 mg, 4.06 mmol). The reaction was allowed to stir at 0 °C for 20 min before the addition of MOMCl (370 $\mu$L, 4.89 mmol). The reaction mixture was allowed to warm to rt while stirring for 2 h. The reaction mixture was diluted with $Et_2O$ (30 mL) and washed with saturated aqueous $NH_4Cl$ solution (20 mL). The organic layer was separated and the aqueous layer further extracted with $Et_2O$ (2 × 15 mL). The combined organic fractions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil, which was purified using flash column chromatography (silica, gradient elution, 10:1−5:1 hexanes/EtOAc) to afford the desired bis-MOM ether as a colorless oil (562 mg, 74%): $R_f = 0.30$ (2:1 hexanes/EtOAc); $[\alpha]^{18}_D = -30.3$ (*c* 0.08, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.74 (d, $J = 2.2$ Hz, 1H), 6.68 (d, $J = 2.2$ Hz, 1H), 5.79 (ddd, $J = 17.1, 10.3, 7.8$ Hz, 1H), 5.29 (ddd, $J = 17.1, 1.6, 1.1$ Hz, 1H), 5.22 (ddd, $J = 10.3, 1.6, 0.9$ Hz, 1H), 5.161 (s, 2H), 5.157 (s, 2H), 4.47 (dd, $J = 7.6, 6.4$ Hz, 1H), 4.09 (ddd, $J = 8.6, 6.1, 4.7$ Hz, 1H), 3.88 (s, 3H), 3.71 (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), 1.47 (s, 3H), 1.35 (s, H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.9, 158.8, 156.0, 139.4, 134.3, 118.3, 110.6, 108.2, 102.5, 95.0, 94.3, 79.7, 77.8, 77.2 56.3, 56.2, 52.2, 34.0, 31.4, 29.5, 28.2, 25.8, 25.6; IR (neat) 2949, 2906, 1727, 1605, 1434, 1277, 1215, 1144, 1038, 1017, 928, 870 cm$^{-1}$; HRMS (ESI) calcd for $C_{23}H_{34}O_8SNa^+$ $[M + Na]^+$ 493.1872, found 493.1867.

**(6′*S*,7′*R*)-6-(6′,7′-*O*-(1″-Methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoic Acid (18).** To a solution of the bis-MOM methyl ester (455 mg, 0.968 mmol) in 2:1 MeOH/$H_2O$ (15 mL) was added KOH (271 mg, 4.84 mmol), and the reaction mixture was heated to 90 °C for 48 h. After being cooled to rt, the mixture was extracted with $Et_2O$ (20 mL) and the organic layer discarded. The aqueous layer was acidified to pH 6 with an aqueous acetic acid solution (50%, 0.78 mL, 6.8 mmol) and extracted with $Et_2O$ (3 × 15 mL). The combined organic phases were washed with $H_2O$ (4 × 20 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the acid **18** as a colorless oil (434 mg, 98%): $[\alpha]^{20}_D = -32.1$ (*c* 0.2, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.77 (d, $J = 2.3$ Hz, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 5.79 (ddd, $J = 17.2, 10.2, 7.8$ Hz, 1H), 5.28 (ddd, $J = 17.1, 1.6, 1.0$ Hz, 1H), 5.22 (s, 2H), 5.22 (dd, $J = 10.3, 1.6, 0.8$ Hz, 1H), 5.18 (s, 2H), 4.47 (dd, $J = 7.6, 6.4$ Hz, 1H), 4.12 (ddd, $J = 8.4, 6.1, 4.6$ Hz, 1H), 3.96 (d, $J = 13.4$ Hz, 1H), 3.92 (d, $J = 13.4$ Hz, 1H), 3.50 (s, 3H), 3.47 (s, 3H), 2.48 (t, $J = 7.0$ Hz, 2H), 1.74 (m, 1H), 1.64−1.38 (m, 3H), 1.47 (s, 3H), 1.35 (s, 3H); IR (neat) 2908, 2845, 1604, 1586, 1462, 1377, 1277, 1216, 1151, 1028, 1020, 927, 744 cm$^{-1}$; HRMS (ESI) calcd for $C_{22}H_{32}O_8SNa^+$ $[M + Na]^+$ 479.1716, found 479.1720.

**(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1″-Methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate (3).** To a solution of alcohol **6** (147 $\mu$L, 1.43 mmol) and $PPh_3$ (624 mg, 2.38 mmol) in THF (20 mL) at 0 °C was added DIAD (463 $\mu$L, 2.38 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 acid **18** (434 mg, 0.952 mmol) in THF (15 mL) was added dropwise, and the reaction was allowed to stir at rt for 2 days. To the crude reaction mixture was added a small amount of silica gel before removal of solvent. The silica gel was dry loaded onto a column and eluted (gradient elution 20:1−5:1 hexanes/EtOAc) to yield title compound **3** as a colorless oil (468 mg, 94%): $R_f = 0.60$ (2:1 hexanes/EtOAc); $[\alpha]^{18}_D = -34.9$ (*c* 0.18, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.72 (d, $J = 2.2$ Hz, 1H), 6.69 (d, $J = 2.1$ 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 (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 (m, 3H), 2.40−2.33 (m, 1H), 1.72 (m, 1H), 1.60−1.40 (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, 25.8, 25.6, 19.4; IR (neat) 2984, 2906, 2845, 1715, 1604, 1584, 1434, 1380, 1272, 1216, 1149, 1039, 1019, 926 cm$^{-1}$; HRMS (ESI) calcd for $C_{27}H_{40}O_8SNa^+$ $[M + Na]^+$ 547.2342, found 547.2342.

**(4*S*,6′*S*,7′*R*)-Pent-1-en-4-yl 6-(6′,7′-*O*-(1″-Methylethylidene)-2′-thianon-8′-enyl)-2,4-(bismethoxymethoxy)benzoate 2′,2′-Dioxide (2).** To a solution of thioether **3** (122 mg, 0.230 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C was added 75% *m*-CPBA (115 mg, 0.501 mmol). The reaction was allowed to warm to rt while stirring for 2 h. The reaction was quenched with the addition of 20% aqueous $Na_2SO_3$ solution (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (20 mL), dried over $MgSO_4$, filtered, and reduced in vacuo to give a colorless oil. The product was purified by flash column chromatography (silica, gradient elution 3:1−2:1 hexanes/EtOAc) to yield the title compound **2** as a colorless oil (109 mg, 84%): $R_f$ = 0.31 (2:1 hexanes/EtOAc); $[\alpha]^{22}_D$ = −11.0 (*c* 1.05, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.88 (d, *J* = 2.2 Hz, 1H), 6.86 (d, *J* = 2.2 Hz, 1H), 5.85 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.3, 7.7 Hz, 1H), 5.29 (ddd, *J* = 17.1, 1.5, 1.1 Hz, 1H), 5.25−5.20 (m, 2H), 5.18 (s, 2H), 5.17−5.14 (m, 3H), 5.11 (ddt, *J* = 9.0, 2.0, 1.1 Hz, 1H), 4.48 (dd, *J* = 7.5, 6.5 Hz, 1H), 4.38 (d, *J* = 14.1 Hz, 1H), 4.28 (d, *J* = 14.1 Hz, 1H), 4.12−4.07 (m, 1H), 3.47 (s, 3H), 3.46 (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), 2.51−2.44 (m, 1H), 2.42−2.35 (m, 1H), 2.02−1.91 (m, 1H), 1.89−1.80 (m, 1H), 1.52 (tdd, *J* = 11.2, 7.0, 3.9 Hz, 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 (neat) 1708, 1605, 1586, 1285, 1214, 1150, 1122, 1039, 1018, 914, 734; HRMS (ESI) calcd for $C_{27}H_{40}O_{10}SNa^+$ $[M + Na]^+$ 579.2246, found 579.2240.

**(5*S*,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 (19).** To a solution of the diene **2** (55 mg, 99 $\mu$mol) in $CH_2Cl_2$ (20 mL) in a microwave reactor vessel was added a catalytic amount of Grubbs' second-generation catalyst (8.4 mg, 9.9 $\mu$mol). The vessel was flushed with argon before sealing with the cap. The vessel was irradiated for 30 min, heating to 75 °C. The solvent was removed to yield a brown oil. The crude product was purified on a silica column (gradient elution, 5:1−2:1 hexanes/EtOAc) to yield compound **19** as a colorless oil (45 mg, 86%): $R_f$ = 0.14 (2:1 hexanes/EtOAc); $[\alpha]^{22}_D$ = −28.5 (*c* 0.50, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.16 (d, *J* = 2.2 Hz, 1H), 6.85 (d, *J* = 2.2 Hz, 1H), 5.71 (ddd, *J* = 15.2, 9.3, 4.3 Hz, 1H), 5.55 (ddd, *J* = 15.4, 9.4, 1.4 Hz, 1H), 5.29 (m, 1H), 5.21−5.16 (m, 4H), 4.47 (d, *J* = 15.3 Hz, 1H), 4.43 (dd, *J* = 9.3, 5.8 Hz, 1H), 4.13 (d, *J* = 15.1 Hz, 1H), 4.11 (m, 1H), 3.47 (s, 3H), 3.47 (s, 3H), 2.83 (ddd, *J* = 14.6, 11.1, 5.3 Hz, 1H), 2.65 (m, 1H), 2.47 (m, 1H), 2.41 (dd, *J* = 15.5, 9.8 Hz, 1H), 1.75 (m, 1H), 1.67 (m, 1H), 1.62−1.53 (m, 2H), 1.43 (s, 3H), 1.40 (d, *J* = 6.2 Hz, 3H), 1.32 (s, 3H); $^{13}$C NMR (500 MHz, $CDCl_3$) $\delta$ 167.1, 159.3, 156.6, 132.4, 129.0 (2), 118.6, 110.9, 107.9, 103.6, 94.6, 94.4, 76.3, 77.6, 72.3, 56.4, 56.4, 55.4, 51.1, 39.5, 28.3, 27.6, 25.5, 20.8, 18.5; IR (neat) 2982, 2903, 2829, 1708, 1604, 1585, 1277, 1215, 1149, 1122, 1017, 926, 737 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{36}O_{10}SNa^+$ $[M + Na]^+$ 551.1928, found 551.1927.

**(5′*S*,6′*R*,10′*S*)-2,4-Di-*O*-(methoxymethyl)-5′,6′-*O*-(1-methylethylidene)aigialomycin D (20).** To a solution of sulfone **19** (34 mg, 64.4 $\mu$mol) in $^t$BuOH (250 $\mu$L) and $CH_2Cl_2$ (100 $\mu$L) was added powdered KOH (72 mg, 1.29 mmol) at rt. To the resulting suspension was added $CCl_4$ (250 $\mu$mol) dropwise over 2 min. The reaction mixture was then heated to 35 °C for 30 min. After the mixture was cooled to rt, the solvent was removed to dryness and the residue partitioned between saturated aqueous $NH_4Cl$ solution (5 mL) and EtOAc (5 mL). The aqueous layer was further extracted with EtOAc (2 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced. The crude product was purified by flash column chromatography (silica, gradient elution 20:1−5:1 hexanes/EtOAc) to give the title compound **20** as a white solid (25 mg, 84%): $R_f$ = 0.40 (2:1 hexanes/EtOAc); $[\alpha]^{19}_D$ = −118.6 (*c* 0.15, $CHCl_3$) [lit.[5c] $[\alpha]^{19}_D$ = −116.5 (*c* 0.13, $CHCl_3$) and lit.[5a] $[\alpha]^{19}_D$ = −120 (*c* 0.08, $CHCl_3$)]; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.81 (d, *J* = 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.24 (d, *J* = 15.8 Hz, 1H), 6.14 (ddd, *J* = 15.3, 9.6, 4.2 Hz, 1H), 5.74 (ddd, *J* = 15.3, 9.4, 3.5 Hz, 1H), 5.60 (ddd, *J* = 15.4, 9.7, 1.7 Hz, 1H), 5.34 (m, 1H), 5.20−5.12 (m, 4H), 4.57 (dd, *J* = 9.6, 5.4 Hz, 1H), 4.19 (ddd, *J* = 11.6, 5.4, 3.1 Hz, 1H), 3.46 (s, 3H), 3.46 (s, 3H), 2.58−2.44 (m, 2H), 2.31 (m, 1H), 2.11 (m, 1H), 1.80 (m, 1H), 1.49 (m, 1H), 1.47 (s, 3H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.36 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 167.4, 158.9, 155.1, 136.8, 132.3, 131.9, 129.3, 128.4, 117.9, 108.3, 104.8, 102.5, 94.5, 94.3, 80.1, 77.2, 71.6, 56.2, 56.1, 39.5, 29.0, 28.7, 28.6, 25.8, 21.1; IR (neat) 2984, 2897, 1722, 1601, 1579, 1263, 1218, 1148, 1052, 1018, 925 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{34}O_8Na^+$ $[M + Na]^+$ 485.2151, found 485.2147.

**Aigialomycin D (1).** A solution of compound **20** (45 mg, 97.3 $\mu$mol) in 1:1 v/v MeOH/1 M HCl (10 mL) was stirred at rt for 3 days. The reaction mixture was extracted with EtOAc (3 × 10 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and reduced to give aigialomycin D as a white solid (28 mg, 86%): $R_f$ = 0.21 (5% MeOH/$CH_2Cl_2$); $[\alpha]^{19}_D$ = −25.1 (*c* 0.78, MeOH) [lit.[5b] $[\alpha]^{19}_D$ = −21.9 (*c* 0.35, MeOH)]; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 11.66 (s, 1H), 9.25 (brs, 1H), 7.15 (d, *J* = 15.9 Hz, 1H), 6.53 (d, *J* = 2.0 Hz, 1H), 6.28 (d, *J* = 2.0 Hz, 1H), 6.09 (ddd, *J* = 15.9, 5.7, 5.5 Hz, 1H), 5.88 (ddd, *J* = 15.6, 7.4, 1.6 Hz, 1H), 5.69 (ddd, *J* = 15.6, 5.2, 1.2 Hz, 1H), 5.44 (m, 1H), 4.35 (brd, *J* = 4.1 Hz, 1H), 3.82 (brs, 1H), 3.63 (m, 1H), 3.20 (brs, 1H), 2.57 (ddd, *J* = 14.6, 7.4, 3.1 Hz, 1H), 2.43 (m, 1H), 2.36−2.32 (m, 2H), 2.14 (m, 1H), 1.59 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 172.2, 165.8, 163.1, 144.3, 135.7, 133.6, 130.6, 125.4, 107.8, 104.4, 102.5, 76.5, 73.0, 73.0, 37.9, 28.5, 28.0, 19.1; IR (neat) 3338, 2979, 1644, 1608, 1448, 1312, 1259, 1167, 1110, 1018, 972 cm$^{-1}$; HRMS (ESI) calcd. for $C_{18}H_{22}O_6Na^+$ $[M + Na]^+$ 357.1308, found 357.1314. Spectral data matched those reported in the literature.[1]

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**Supporting Information Available:** General experimental methods; full experimental details for all reactions; characterization data for all products; copies of $^1$H NMR spectra for all new compounds; further information on selective conjugate reduction of compound **11**; further information on attempted ester hydrolysis of compound **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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