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Enantioselective total synthesis of aigialomycin D

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Abstract—An efficient, convergent approach for the total synthesis of aigialomycin D **1** is described. Key features of the synthetic strategy include (a) a Sharpless asymmetric epoxidation reaction and selective opening of a 2,3-epoxy alcohol to elaborate the two hydroxy-bearing stereogenic centers at the C5′ and C6′ positions; (b) a Kocienski modified Julia protocol to construct the two *E*-configured double bonds; and (c) Yamaguchi macrolactonization to acccess the 14-membered macrocyclic ring.

1. Introduction

The resorcinylic macrolides, a novel family of naturally occurring homologous macrolides, are usually bacterial metabolites with unique chemical structures and potent biological activities (antitumor, antibiotic, and antimalarial).[1] These attractive biological properties of the structurally related macrolactones render them desirable for the total syntheses and serve as excellent scaffolds for the development and validation of new synthetic methodologies.[2]

Aigialomycin D, a new 14-membered resorcyclic macrolide, which was isolated from the mangrove fungus, *Aigialus parvus* BCC 5311,[3] has been shown to possess potent antimalarial activity (IC_{50} value of 6.6 μg/mL against *Plasmodium falciparum* K1) and antitumor activity (IC_{50} value of 3.0 μg/mL against KB cells).[3] The total synthesis of aigialomycin D has been previously reported by Danishefsky.[2f,g] In his approach, all the stereogenic centers were derived from chiral pool starting materials. Herein, we report the enantioselective total synthesis of aigialomycin D utilizing a Sharpless asymmetric epoxidation reaction as the source of chirality from the commercially available starting material propargyl alcohol.

The retrosynthetic analysis is outlined in Scheme 1. We envisioned that aigialomycin D would be derived from a Yamaguchi macrolactonization of **2**, which in turn could be obtained by Kocienski modified Julia coupling of aldehyde **4** with sulfone **3**. Aldehyde **4** could be disconnected between C1′ and C2′ to give aldehyde **6** and sulfone **5**. Sulfones **3** and **5** could be obtained from commercially available (*S*)-butane-1,3-diol **7** and 2,3-epoxy alcohol **8**,[4] respectively.

2. Results and discussion

Our starting point for sulfone **5** was commercially available propargyl alcohol **9** (Scheme 2). Thus, alkylation of **9** with 1-((3-iodopropoxy)methyl)benzene gave propargylic alcohol **10** in 95% yield; this was converted into (*E*)-allylic alcohol **11** in 96% yield by $LiAlH_4$ reduction.[5] Treatment of **11** with Ti(O-*i*Pr)$_4$ and TBHP in the presence of (−)-DIPT ligand under Sharpless AE conditions[6] afforded the epoxy alcohol **8**[4] in 89% yield with excellent (91% ee) selectivity. The titanium-assisted regioselective opening of 2,3-epoxy alcohol **8** with $PhCO_2H$ gave **12** in 75% yield,[7] which was further converted into triol **13** by treatment with EtMgBr.[8] The primary hydroxyl group of **13** was protected as its pivaloyl derivative and the two secondary hydroxyl groups were engaged in an isopropylidene linkage (see **15**). Compound **15** was easily converted into alcohol **16**[2f,g] in excellent yield by a standard hydrogenation procedure. Mitsunobu reaction of **16** with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation of the resultant sulfide furnished sulfone **5** in good yield over two steps.[9]

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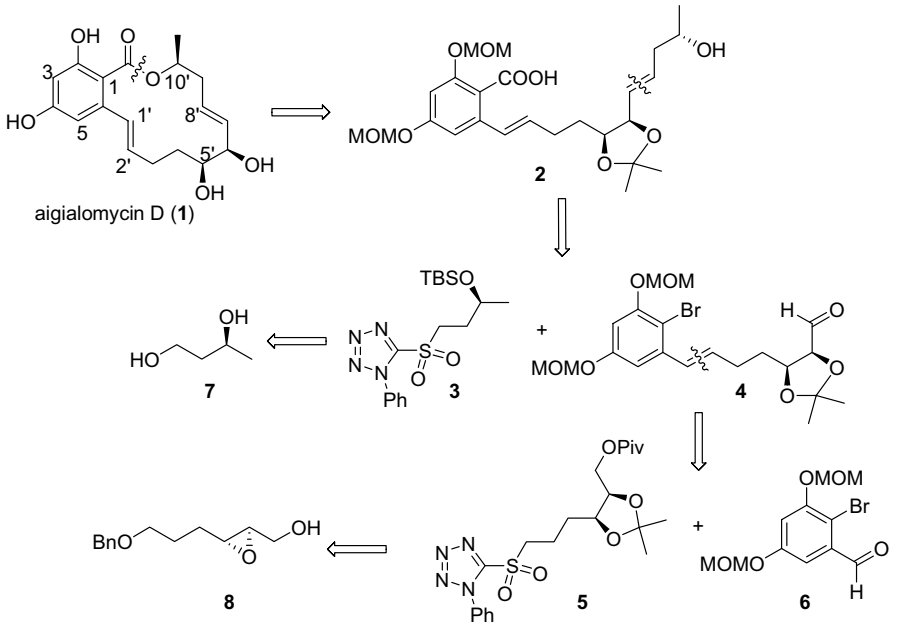
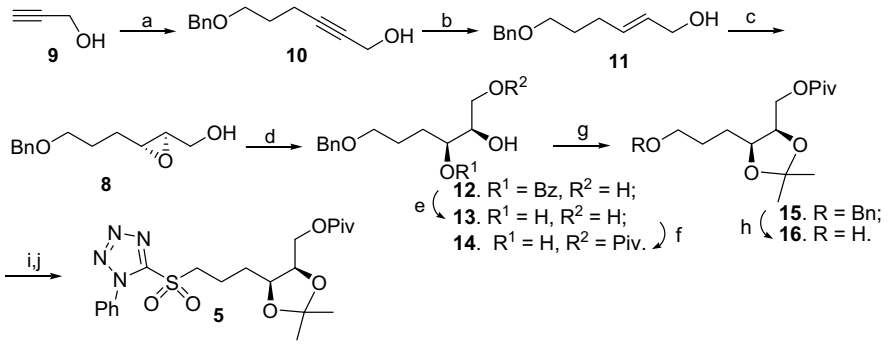
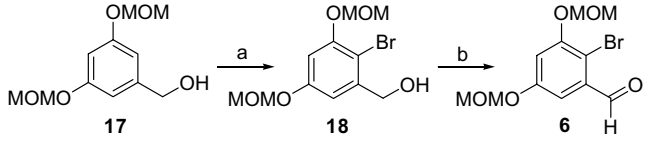


Scheme 1. Retrosynthetic analysis of aigialomycin D **1**.



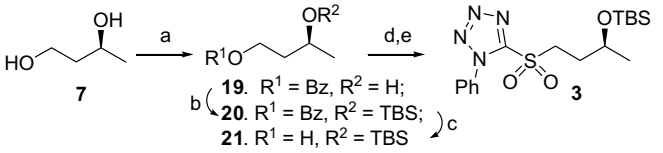
Scheme 2. Reagents and conditions: (a) $BnOCH_2CH_2CH_2I$, BuLi, HMPA, −78 °C, 8 h, 70%; (b) $LiAlH_4$, THF, reflux, 1 h, 96%; (c) $Ti(O\text{-}iPr)_4$, TBHP, (−)-DIPT, cat. CaH_2, CH_2Cl_2, −25 °C, 12 h, 89%; (d) $Ti(O\text{-}iPr)_4$, $PhCO_2H$, CH_2Cl_2, rt, 15 min, 75%; (e) EtMgBr, ether, rt, 1 h, 95%; (f) PivCl, Et_3N, DMAP, CH_2Cl_2, rt, 10 h, 88%; (g) 2-methoxypropene, PPTS, CH_2Cl_2, rt, 5 h, 95%; (h) 10% Pd/C, H_2, EtOH, rt, 4 h, 95%; (i) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C to rt, 1 h; (j) *m*-CPBA, $NaHCO_3$, rt, CH_2Cl_2, 12 h, 81% for two steps.

Aldehyde **6** was readily prepared from alcohol **17** in two steps (Scheme 3): regioselective aromatic bromination with NBS and oxidation with PCC.



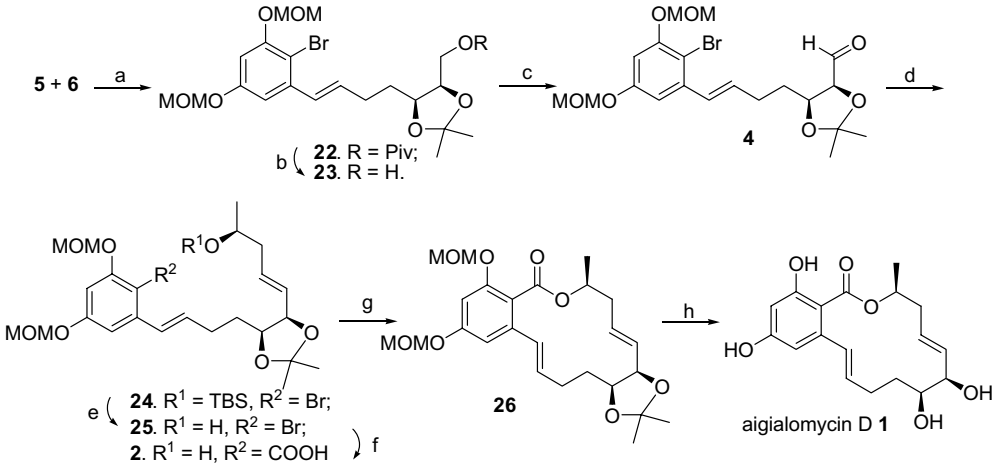
Scheme 3. Reagents and conditions: (a) NBS, $CHCl_3$, rt, 30 min, 98%; (b) PCC, NaOAc, CH_2Cl_2, rt, 4 h, 85%.

The synthesis of sulfone **3** started from commercially available (*S*)-butane-1,3-diol **7** (Scheme 4). Selective protection of the primary hydroxyl group of **7** with BzCl and protection of the secondary hydroxyl group with TBSCl, followed by reductive removal of the benzoate moiety with DIBAL-H, provided alcohol **21**. Mitsunobu reaction of **21** with 1-phenyl-1*H*-tetrazole-5-thiol, followed by oxidation of the resultant sulfide, furnished sulfone **3** in good yield over two steps.[9]



Scheme 4. Reagents and conditions: (a) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 10 h, 80%; (b) TBSCl, $C_3H_4N_2$ (imidazole), DMF, rt, 5 h, 95%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 95%; (d) 1-phenyl-1*H*-tetrazole-5-thiol, DIAD, PPh_3, THF, 0 °C to rt, 1 h; (e) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 12 h, 83% for two steps.

Having completed the synthesis of the key fragments **3**, **5**, and **6**, we needed to couple the three fragments in sequence and carry out subsequent macrolactonization. First, the



Scheme 5. Reagents and conditions: (a) KHMDS, DME, −60 °C to rt, 3 h, 68%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 96%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 85%; (d) **3**, KHDMS, DME, −60 °C to rt, 3 h, 58%, (e) TBAF, THF, rt, 8 h, 95%, (f) *n*-BuLi, CO_2, THF, −78 °C to rt, 2 h, 83%; (g) 2,4,6-trichlorobenzoylchloride, Et_3N, THF, rt, 2 h, then DMAP, toluene, reflux, 36 h, 51%; (h) 0.5 M HCl, H_2O/MeOH, rt, 2 d, 70%.

addition of aldehyde **6** to the potassium salt of sulfone **5** in DME (Scheme 5) provided (*E*)-ene **22** in 68% yield with good stereoselectivity ($E/Z = 95/5$).[9,10] Reductive removal of the pivaloate moiety with DIBAL-H gave **23** in 96% yield, which was oxidized to the corresponding aldehyde **4** under Dess–Martin conditions,[11] then subsequently treated with the potassium salt of sulfone **3** in DME under conventional Julia–Kocienski conditions[9,10] to afford compound **24** with moderate stereoselectivity ($E/Z = 83/17$). Removal of the TBS group in **24** with TBAF and carboxylation with *n*-BuLi and CO_2 afforded acid **2**. Finally, macrolactonization of **2** under Yamaguchi conditions[12] produced macrocyclic lactone **26**,[2f,g] which on subsequent cleavage of the protecting groups[2f,g] afforded target molecule **1**. The physical and spectroscopic data of **1** were identical with those reported.[2f,g,3]

3. Conclusion

In conclusion, we have achieved the enantioselective total synthesis of aigialomycin D with inexpensive commercially available starting materials. Notable features of this approach include a Sharpless asymmetric epoxidation reaction and selective opening of a 2,3-epoxy alcohol to elaborate the two hydroxy-bearing stereogenic centers at the C5′ and C6′ position; application of the Kocienski modified Julia protocol to construct the two *E*-configured double bonds, and Yamaguchi macrolactonization to access the 14-membered macrocyclic ring. Further application of this methodology to the syntheses of other compounds of this family is currently underway in our laboratory.

4. Experimental

4.1. General

Oxygen- and moisture-sensitive reactions were carried out under an argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200–300 mesh). Optical rotations were measured on a Perkin–Elmer model 341 polarimeter. Infrared spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz) or Bruker AM-400 (400 MHz) spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (δ 7.26 for ^1H and 77.0 for ^{13}C).

4.2. 6-(Benzyloxy)hex-2-yn-1-ol 10

To a solution of propargyl alcohol **9** (168 mg, 3.0 mmol) in THF (3 mL) was added *n*-BuLi (2.0 M in petroleum ether, 3.0 mL, 6.0 mmol) at −78 °C. The white suspension was warmed up to 0 °C and stirred for 30 min before adding HMPA (1.5 mL) at −50 °C. Thirty minutes later, 1-((3-iodopropoxy)methyl)benzene (830 mg, 3.0 mmol) in THF (1 mL) was added via a cannula and the mixture was warmed up to rt (8 h) before being quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined, washed with saturated aqueous NaCl solution, and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (5/1) as the eluent to afford **10** as a colorless oil (428 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.77–1.86 (m, 2H), 2.34 (t, 2H, $J = 7.2$ Hz), 3.10 (t, 1H, $J = 5.7$ Hz), 3.56 (t, 2H, $J = 6.3$ Hz), 4.17 (d, 2H, $J = 5.7$ Hz), 4.51 (s, 2H), 7.27–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 28.4, 50.6, 68.4, 72.6, 78.7, 84.9, 127.4, 128.1, 138.0. HRMS (ESI) calcd for $C_{13}H_{16}O_2Na^+$ $[M+Na]^+$ 227.1052, found 227.1047, $\Delta = -2.2$ ppm.

4.3. (*E*)-6-(Benzyloxy)hex-2-en-1-ol 11

To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in THF (10 mL) was added a solution of **10** (428 mg, 2.1 mmol)

in THF (5 mL) dropwise. After the reaction mixture was stirred for 2 h at reflux, water was added. The resulting mixture was filtered through a short pad of Celite and washed with EtOAc (100 mL × 3), and the filtrate was dried over Na_2SO_4. The solvent was removed and the residue purified on a silica gel column using petroleum ether/ethyl acetate (5/1) as the eluent to afford **11** as a colorless oil (415 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (m, 2H), 2.05 (b, 1H), 2.14 (m, 2H), 3.48 (t, 2H, $J = 6.6$ Hz), 4.04 (d, 2H, $J = 4.2$ Hz), 4.50 (s, 2H), 5.64 (m, 2H), 7.27–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 28.9, 63.1, 69.4, 72.6, 127.3, 127.4, 128.1, 129.4, 131.8, 138.3. HRMS (ESI) calcd for $C_{13}H_{16}O_2Na^+$ $[M+Na]^+$ 229.1202, found 229.1206, $\Delta = 1.7$ ppm.

4.4. ((2*R*,3*R*)-3-(3-(Benzyloxy)propyl)oxiran-2-yl)methanol 8

To a suspension of 4-Å molecular sieves (1.5 g) and CaH_2 (84 mg, 2.0 mmol) in 30 mL CH_2Cl_2 were added (−)-diisopropyl tartarate (0.25 mL, 1.2 mmol), Ti(O-*i*Pr)$_4$ (0.30 mL, 1.0 mmol), and ^{t}BuOOH (3.3 M in CH_2Cl_2, 5.15 mL, 17.0 mmol) sequentially at −25 °C. The reaction mixture was stirred for 30 min before **11** (2.06 g, 10 mmol) was added. The reaction mixture was then stored overnight (12 h) in the freezer at −25 °C without stirring. The reaction was then warmed to −20 °C and quenched by the addition of 10% NaOH/saturated aqueous NaCl (4.0 mL). Upon further warming to −10 °C, the reaction was diluted with Et_2O (100 mL), treated with $MgSO_4$ (4.0 g) and Celite (1.0 g), and stirred for an additional 15 min. The reaction mixture was then allowed to settle for 1 h before filtration through Celite using Et_2O and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (3/1) as the eluent to afford **8** as a colorless oil (1.98 g, 89%). $[\alpha]_D^{20} = +28$ (*c* 1.50, $CHCl_3$); lit.[4] (*ent*-**8**) $[\alpha]_D = -29$. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60–1.79 (m, 4H), 2.74 (b, 1H), 2.86–2.89 (m, 1H), 2.91–2.96 (m, 1H), 3.48–3.56 (m, 3H), 3.80 (dd, 1H, $J = 2.4$, 12.6 Hz), 4.49 (s, 2H), 7.25–7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9, 28.3, 55.6, 58.5, 61.6, 69.5, 72.7, 127.5, 128.2, 138.2. HRMS (ESI) calcd for $C_{13}H_{18}O_3H^+$ $[M+H]^+$ 223.1330, found 223.1334, $\Delta = 1.7$ ppm. For the measurement of enantiomeric excess, compound **8** was converted into its benzoate. The enantiomeric purity of the benzoate was estimated to be 91% by chiral HPLC (Chiralcel OD from Daicel Chemical Industries, Ltd, 15% *i*PrOH in hexane, 254 nm, 1 mL/min).

4.5. (2*R*,3*S*)-6-(Benzyloxy)-1,2-dihydroxyhexan-3yl benzoate 12

To a solution of $PhCO_2H$ (262 mg, 2.15 mmol) and **8** (398 mg, 1.79 mmol) in CH_2Cl_2 (10 mL) was added Ti(O-*i*Pr)$_4$ (0.64 mL, 2.15 mmol), and the reaction mixture was stirred for 15 min before ether (50 mL) and 5% H_2SO_4 (6.4 mL) were added. The two-phase mixture was stirred vigorously until two clear layers formed, which were extracted with EtOAc (50 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (2/1) as the eluent to afford **12** as a colorless oil (463 mg, 75%). $[\alpha]_D^{20} = -19$ (*c* 1.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68–1.81 (m, 2H), 1.87–1.95 (m, 2H), 3.50 (m, 3H), 3.56–3.60 (m, 1H), 3.66–3.70 (m, 1H), 3.82–3.88 (m, 2H), 4.48 (s, 2H), 5.16 (m, 1H), 7.26–7.33 (m, 5H), 7.41 (t, 2H, $J = 7.5$ Hz), 7.54 (t, 1H, $J = 7.5$ Hz), 8.04 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 27.1, 62.7, 69.7, 72.6, 72.7, 74.4, 127.4, 127.5, 128.1, 128.2, 129.5, 133.0, 138.1, 166.5. HRMS (ESI) calcd for $C_{20}H_{24}O_5Na^+$ $[M+Na]^+$ 367.1517, found 367.1522, $\Delta = 1.5$ ppm.

4.6. Triol 13

To a solution of 6.0 equiv of EtMgBr, previously formed, was added **12** (688 mg, 2.0 mmol) in 2 mL THF and the reaction mixture was stirred for 2 h before being quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (1/2) as the eluent to afford **13** as a colorless oil (456 mg, 95%). $[\alpha]_D^{20} = -8$ (*c* 1.50, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44–1.49 (m, 1H), 1.61–1.68 (m, 2H), 1.77–1.80 (m, 1H), 3.46–3.51 (m, 3H), 3.64 (m, 3H), 3.89 (m, 1H), 4.10 (m, 2H), 4.72 (s, 2H), 7.24–7.34 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 30.0, 63.2, 70.3, 73.0, 74.2, 127.6, 127.7, 128.4, 137.9. HRMS (ESI) calcd for $C_{13}H_{20}O_4H^+$ $[M+H]^+$ 241.1434, found 241.1429, $\Delta = 2.1$ ppm.

4.7. Pivalate 14

To a solution of triol **13** (456 mg, 1.9 mmol), DMAP (49 mg, 0.4 mmol), and Et_3N (0.57 mL, 4.0 mmol) in 20 mL CH_2Cl_2 was added PivCl (123 μL, 2.0 mmol) at 0 °C. The reaction mixture was warmed to rt overnight (10 h) before being quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (1/1) as the eluent to afford **14** as a colorless oil (542 mg, 88%). $[\alpha]_D^{20} = -20$ (*c* 1.25, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.52 (m, 1H), 1.71–1.81 (m, 3H), 2.89 (d, 1H, $J = 4.8$ Hz), 3.39 (d, 1H, $J = 4.5$ Hz), 3.51 (m, 2H), 3.61 (m, 1H), 3.70–3.73 (m, 1H), 4.20–4.23 (m, 2H), 7.27–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2, 27.1, 29.7, 38.8, 65.6, 70.3, 72.0, 72.9, 73.0, 127.6, 128.3, 137.8, 179.1. HRMS (ESI) calcd for $C_{18}H_{28}O_5Na^+$ $[M+Na]^+$ 347.1830, found 347.1829, $\Delta = -0.3$ ppm.

4.8. ((4*R*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate 15

To a solution of pivalate **14** (542 mg, 1.67 mmol), and PPTS (25 mg, 0.1 mmol) in 10 mL CH_2Cl_2 was added 2-methoxypropene (0.49 mL, 4.0 mmol), and the reaction mixture was stirred for 5 h before being quenched with sat-

urated aqueous $NaHCO_3$ solution, and extracted with EtOAc (30 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (20/1) as the eluent to afford **15** as a colorless oil (577 mg, 95%). $[\alpha]_D^{20} = +13$ (*c* 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.33 (s, 3H), 1.43 (s, 3H), 1.63–1.72 (m, 3H), 1.81–1.87 (m, 1H), 3.46–3.55 (m, 2H), 4.08 (dd, 2H, $J = 0.9$, 2.6 Hz), 4.13–4.23 (m, 2H), 4.50 (s, 2H), 7.26–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 25.9, 26.8, 27.1, 28.1, 38.6, 62.9, 69.7, 72.8, 75.2, 76.9, 108.2, 127.4, 127.5, 128.3, 138.4, 178.1. HRMS (ESI) calcd for $C_{21}H_{32}O_5Na^+$ $[M+Na]^+$ 387.2142, found 387.2146, $\Delta = 1.1$ ppm. For the measurement of the enantiomeric excess, the enantiomeric purity of compound **15** was estimated to be 91% by chiral HPLC (Chiralcel OD from Daicel Chemical Industries, Ltd, 5% *i*PrOH in hexane, 254 nm, 0.8 mL/min).

4.9. ((4*R*,5*S*)-5-(3-Hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate 16

A suspension of benzyl ether **15** (728 mg, 2.0 mmol) and Pd/C (10%, 20 mg) in 5 mL EtOH was flushed with H_2 and then stirred vigorously under balloon pressure. The reaction mixture was stirred for 6 h before being filtered through a Celite pad, which had been moistened with EtOH and Et_3N. The resulting filtrate was concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (8/1) as the eluent to afford **16** as a colorless oil (521 mg, 95%). $[\alpha]_D^{15} = +77$ (*c* 0.9, $CHCl_3$); [lit.[2f,g] +82.4 (*c* 0.07, $CHCl_3$)]. ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.33 (s, 3H), 1.43 (s, 3H), 1.57–1.75 (m, 4H), 2.15 (b, 1H), 3.64–3.68 (m, 2H), 4.05–4.09 (m, 2H), 4.16–4.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 25.8, 27.1, 28.0, 29.9, 38.7, 62.3, 62.8, 75.3, 77.0, 108.3, 178.2. HRMS (ESI) calcd for $C_{14}H_{26}O_5Na^+$ $[M+Na]^+$ 297.1670, found 297.1665, $\Delta = -1.8$ ppm.

4.10. ((4*R*,5*S*)-5-(3-(1-Phenyl-1*H*-tetrazol-5-ylsulfonyl)-propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl pivalate 5

To a solution of **16** (822 mg, 3.0 mmol), PPh_3 (944 mg, 3.6 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (642 mg, 3.6 mmol) in THF (20 mL) was added a solution of DIAD (94%, 0.76 mL, 3.6 mmol) in THF (5 mL) dropwise. The reaction mixture was stirred for 2 h before being quenched with saturated NaCl solution, and extracted with EtOAc (60 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (4/1) as the eluent to afford the corresponding sulfide.

To a solution of the sulfide obtained above in CH_2Cl_2 (30 mL) was added $NaHCO_3$ (554 mg, 6.6 mmol), and then *m*-CPBA (95%, 1.14 g, 6.6 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h before being quenched with saturated $Na_2S_2O_3$ solution and extracted with EtOAc (60 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (4/1) as the eluent to afford **5** as a colorless oil (1.13 g, 81%). $[\alpha]_D^{15} = -8$ (*c* 1.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.31 (s, 3H), 1.41 (s, 3H), 1.68–1.80 (m, 2H), 2.01–2.22 (m, 2H), 3.70–3.92 (m, 2H), 4.04 (d, 2H, $J = 6.0$ Hz), 4.13–4.26 (m, 2H), 7.54–7.61 (m, 3H), 7.66 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 25.2, 26.9, 27.4, 27.8, 38.4, 55.3, 62.3, 74.8, 76.2, 108.4, 124.9, 129.4, 131.2, 132.8, 153.1, 177.7. HRMS (ESI) calcd for $C_{21}H_{30}N_4O_6SNH_4^+$ $[M+NH_4]^+$ 484.2224, found 484.2219, $\Delta = 1.0$ ppm.

4.11. (2-Bromo-3,5-bis(methoxymethoxy)phenyl)methanol 18

To a solution of (3,5-bis(methoxymethoxy)phenyl)methanol **17** (500 mg, 2.2 mmol) in $CHCl_3$ (10 mL) was added NBS (392 mg, 2.2 mmol) portionwise at ambient temperature. The reaction mixture was stirred for 30 min before being quenched with saturated aqueous $NaHCO_3$ solution and aqueous $Na_2S_2O_3$, and extracted with $CHCl_3$ (25 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (5/1) as the eluent to afford **18** as a white solid (664 mg, 98%). Mp: 60–61 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (br s, 1H), 3.43 (s, 3H), 3.48 (s, 3H), 4.65 (s, 2H), 5.13 (s, 2H), 5.20 (s, 2H), 6.76 (d, 1H, $J = 2.7$ Hz), 6.88 (d, 1H, $J = 2.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.0, 56.3, 94.3, 95.0, 103.8, 104.3, 108.8, 141.9, 154.1, 157.1. Calcd for $C_{11}H_{15}BrO_5H^+$ $[M+H]^+$ 307.0180, found 307.0183, $\Delta = 1.0$ ppm.

4.12. 2-Bromo-3,5-bis(methoxymethoxy)benzaldehyde 6

To a solution of **18** (308 mg, 1.0 mmol) in 10 mL CH_2Cl_2 was added $NaHCO_3$ (126 mg, 1.5 mmol), and then PCC (323 mg, 1.5 mmol) at 0 °C. After being stirred for 4 h, the reaction mixture was filtered through a short Celite pad and washed with EtOAc, the filtrate was concentrated under reduced pressure. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (5/1) as the eluent to afford **6** as a white solid (260 mg, 85%). Mp: 80–81 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (s, 3H), 3.51 (s, 3H), 5.17 (s, 2H), 5.25 (s, 2H), 7.07 (d, 1H, $J = 2.7$ Hz), 7.24 (d, 1H, $J = 2.7$ Hz), 10.36 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.2, 56.5, 94.4, 95.2, 108.8, 110.3, 110.4, 134.7, 154.9, 157.2, 191.6. Calcd for $C_{11}H_{13}BrO_5Na^+$ $[M+Na]^+$ 326.9841, found 326.9832, $\Delta = -2.8$ ppm.

4.13. (*S*)-3-Hydroxybutyl benzoate 19

To a solution of (*S*)-butane-1,3-diol **7** (906 mg, 10 mmol), DMAP (244 mg, 2 mmol), and Et_3N (2.8 mL, 20 mmol) in CH_2Cl_2 (20 mL) was added BzCl (1.2 mL, 10.3 mmol) at 0 °C. The reaction mixture was warmed to rt overnight (10 h) before being quenched with saturated aqueous

$NaHCO_3$ solution and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (8/1) as the eluent to afford **19** as a colorless oil (1.55 g, 80%). $[\alpha]_D^{14} = +25$ (*c* 2.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3H, $J = 6.6$ Hz), 1.79–1.98 (m, 2H), 2.36 (b, 1H), 3.94–4.00 (m, 1H), 4.33–4.41 (m, 1H), 4.55–4.63 (m, 1H), 7.43 (t, 2H, $J = 7.5$ Hz), 7.56 (t, 1H, $J = 7.5$ Hz), 8.02 (d, 2H, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 38.1, 62.1, 64.7, 128.3, 129.5, 130.0, 133.0, 166.9. Calcd for $C_{11}H_{14}O_3Na^+$ $[M+Na]^+$ 217.0841, found 217.0849, $\Delta = 3.6$ ppm.

4.14. *tert*-Butyldimethyl silyl ether 20

To a solution of benzoate **19** (1.55 g, 8.0 mmol) and imidazole (1.36 g, 20 mmol) in DMF (5 mL) was added TBSCl (1.44 g, 9.6 mmol) at 0 °C. The reaction mixture was warmed to rt overnight (10 h) before being quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (30/1) as the eluent to afford **20** as a colorless oil (2.34 g, 95%). $[\alpha]_D^{14} = +33$ (*c* 2.05, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.21 (d, 3H, $J = 6.0$ Hz), 1.82–1.92 (m, 2H), 4.01–4.07 (m, 1H), 4.34–4.45 (m, 2H), 7.41–7.46 (m, 2H), 7.53–7.59 (m, 1H), 8.04 (9d, 2H, $J = 8.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.0, −4.4, 18.0, 24.1, 25.8, 38.4, 62.1, 65.2, 128.3, 129.5, 130.4, 132.8, 166.6. Calcd for $C_{17}H_{28}O_3SiNa^+$ $[M+Na]^+$ 331.1701, found 331.1705, $\Delta = 1.2$ ppm.

4.15. Alcohol 21

To a solution of *tert*-butyldimethyl silyl ether **20** (2.34 g, 7.6 mmol) in CH_2Cl_2 (20 mL) was added DIBAL-H (1 M in hexane, 8.4 mL, 8.4 mmol) dropwise at −78 °C. The reaction mixture was stirred for 30 min before being quenched with MeOH and saturated aqueous potassium sodium tartarate solution. The two-phase mixture was stirred vigorously and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, at room temperature, and diluted with ether (150 mL). The organic layer was separated and washed with saturated aqueous NaCl solution (3 × 25 mL). After drying over anhydrous Na_2SO_4, concentration of the residue in vacuo, filtration, and concentration under reduced pressure vacuum, the residue was purified on a silica gel column using petroleum ether/ethyl acetate (8/1) as the eluent to afford **21** as a colorless oil (1.47 g, 95%). $[\alpha]_D^{14} = +25$ (*c* 2.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.86 (s, 9H), 1.16 (d, 3H, $J = 6.3$ Hz), 1.58–1.65 (m, 1H), 1.69–1.75 (m, 1H), 2.82 (b, 1H), 3.64–3.71 (m, 1H), 3.75–3.81 (m, 1H), 4.04–4.10 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.0, −4.4, 17.9, 23.4, 25.7, 40.4, 60.3, 68.2. Calcd for $C_{10}H_{24}O_2SiNa^+$ $[M+Na]^+$ 227.1443, found 227.1445, $\Delta = 0.9$ ppm.

4.16. Sulfone 3

To a solution of **21** (800 mg, 3.9 mmol), PPh_3 (1.2 g, 4.6 mmol), and 1-phenyl-1*H*-tetrazole-5-thiol (0.8 g, 4.5 mmol) in 10 mL THF was added a solution of DIAD (94%, 1 mL, 4.5 mmol) in THF dropwise. The reaction mixture was stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (15/1) as the eluent to afford the corresponding sulfide.

To a solution of the sulfide obtained above in CH_2Cl_2 (15 mL) was added $NaHCO_3$ (0.7 g, 8.3 mmol), and then *m*-CPBA (1.4 g, 8.3 mmol) at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h before being quenched with saturated aqueous $Na_2S_2O_3$ solution, and extracted with EtOAc (50 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (20/1) as the eluent to afford **3** as a colorless oil (1.3 g, 83%). $[\alpha]_D^{15} = 12$ (*c* 1.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 1.20 (d, 3H, $J = 5.7$ Hz), 1.95–2.15 (m, 2H), 3.72–3.91 (m, 2H), 4.01–4.07 (m, 1H), 7.56–7.63 (m, 3H), 7.67–7.71 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.9, −4.4, 17.9, 23.4, 25.7, 31.3, 52.7, 66.2, 125.0, 129.7, 131.4, 133.0, 153.4. Calcd for $C_{17}H_{28}N_4O_3SiSH^+$ $[M+H]^+$ 397.1724, found 397.1721, $\Delta = 0.8$ ppm.

4.17. ((4*R*,5*S*)-5-((*E*)-4-(2-Bromo-3,5-bis(methoxymethoxy)phenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-methyl pivalate 22

To a solution of **5** (466 mg, 1.0 mmol) in DME (3 mL) was added KHMDS (0.89 M in DME, 1.2 mL, 1.1 mmol) at −60 °C. The resultant yellow solution was stirred for 30 min before **6** (306 mg, 1.0 mmol) in DME (2 mL) was introduced via a cannula. The reaction mixture was stirred for 1 h at −60 °C, warmed to rt, and stirred for an additional 2 h before being quenched with saturated aqueous NaCl solution, and extracted with EtOAc (30 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/chloroform/acetone (12/1/1) as the eluent to afford the *Z* isomer [15 mg, 2.8%, ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (ddd, 1H, $J = 7.2$, 11.4, 3.6 Hz), 6.46 (d, 1H, $J = 11.4$ Hz)] and the *E* isomer **22** as a colorless oil (371 mg, 68%) $[\alpha]_D^{14} = +11$ (*c* 1.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.35 (s, 3H), 1.45 (s, 3H), 1.66–1.77 (m, 2H), 2.29–2.50 (m, 2H), 3.46 (s, 3H), 3.50 (s, 3H), 4.09 (d, 2H, $J = 4.8$ Hz), 4.23 (m, 2H), 5.14 (s, 2H), 5.21 (s, 2H), 6.13 (ddd, 1H, $J = 7.2$, 15.9, 1.2 Hz), 6.74 (d, 1H, $J = 3.0$ Hz), 6.77 (d, 1H, $J = 15.9$ Hz), 6.86 (d, 1H, $J = 3.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 27.1, 28.1, 28.4, 29.8, 38.7, 56.1, 56.4, 62.8, 75.1, 76.2, 94.5, 95.1, 103.7, 106.3, 107.3,

108.3, 129.7, 133.0, 139.2, 154.4, 156.9, 178.1. Calcd for $C_{25}H_{37}BrO_8NH_4^+$ $[M+NH_4]^+$ 562.2010, found 562.2014, $\Delta = 0.7$ ppm.

4.18. Compound 23

To a solution of pivalate **22** (120 mg, 0.22 mmol) in CH_2Cl_2 (20 mL) was added DIBAL-H (1 M in hexane, 0.23 mL, 0.23 mmol) dropwise at −78 °C. The reaction mixture was stirred for 30 min before being quenched with MeOH and saturated aqueous potassium sodium tartarate solution. The two-phase mixture was stirred vigorously for 30 min and extracted with EtOAc (30 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (2/1) as the eluent to afford **23** as a colorless oil (96 mg, 95%). $[\alpha]_D^{14} = +13$ (*c* 2.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.47 (s, 3H), 1.60–1.68 (m, 1H), 1.71–1.80 (m, 1H), 2.16 (t, 1H, $J = 6.0$ Hz), 2.27–2.34 (m, 1H), 2.40–2.47 (m, 1H), 3.46 (s, 3H), 3.49 (s, 1H), 3.56 (m, 2H), 4.09–4.25 (m, 2H), 5.14 (s, 2H), 5.20 (s, 2H), 6.13 (ddd 1H, $J = 7.2$, 15.9, 1.2 Hz), 6.74 (d, 1H, $J = 3.0$ Hz), 6.77 (d, 1H, $J = 17.4$ Hz), 6.86 (d, 1H, $J = 3.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 28.1, 28.4, 30.0, 56.0, 56.3, 61.7, 76.0, 77.7, 94.4, 95.0, 103.7, 106.2, 107.2, 108.1, 129.7, 133.0, 139.1, 154.4, 156.9. Calcd for $C_{20}H_{29}BrO_7NH_4^+$ $[M+NH_4]^+$ 478.1435, found 478.1431, $\Delta = 0.8$ ppm.

4.19. Aldehyde 4

To a solution of **23** (92 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (25 mg, 0.3 mmol), and Dess–Martin periodinane (127 mg, 0.30 mmol) in turn at 0 °C. After being stirred for 4 h, the reaction mixture was then diluted with saturated $NaHCO_3$ (aq) (2 mL), saturated $Na_2S_2O_3$ (aq) (2 mL) and stirred for an additional 30 min. The mixture was extracted with CH_2Cl_2 and the organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (4/1) as the eluent to afford **4** as a colorless oil (78 mg, 85%). $[\alpha]_D^{14} = +3$ (*c* 2.25, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.60 (s, 3H), 1.66–1.77 (m, 2H), 2.33–2.46 (m, 2H), 3.46 (s, 3H), 3.50 (s, 3H), 4.27 (dd, 1H, $J = 7.2$, 3.6 Hz), 4.38 (m, 1H), 5.14 (s, 2H), 5.21 (s, 2H), 6.09 (m, 1H), 6.75 (d, 1H, $J = 3.0$ Hz), 6.78 (d, 1H, $J = 15.3$ Hz), 6.86 (d, 1H, $J = 3.0$ Hz), 9.66 (d, 1H, $J = 3.6$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 27.6, 29.0, 29.7, 56.1, 56.4, 77.6, 81.8, 94.5, 95.1, 103.8, 106.3, 107.3, 110.5, 130.1, 132.3, 139.1, 154.4, 156.9, 202.3. Calcd for $C_{20}H_{27}BrO_7H^+$ $[M+H]^+$ 459.1013, found 459.1016, $\Delta = 0.7$ ppm.

4.20. ((*S*,4*E*)-5-((4*R*,5*S*)-5-((*E*)-4-(2-Bromo-3,5-bis(methoxymethoxy)phenyl)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-yloxy)(*tert*-butyl)dimethylsilane 24

To a solution of sulfone **3** (67 mg, 0.17 mmol) in 10 mL DME was added KHMDS (0.89 M in DME, 0.20 mL, 0.19 mmol) at −60 °C. The resultant yellow solution was stirred for 30 min before aldehyde **4** in DME (2 mL) was introduced via a cannula. The reaction mixture was stirred for 30 min at −60 °C, warmed to rt, and stirred for an additional 2 h before being quenched with saturated aqueous NaCl solution, and extracted with EtOAc (10 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified on a silica gel column using dichloromethane/acetone (50/1) as the eluent to afford the *Z* isomer [12.7 mg, 12%, ^1H NMR (300 MHz, $CDCl_3$) 5.47 (dd, 1H, $J = 8.7$, 10.5 Hz), 5.67–5.74 (m, 1H). Calcd for $C_{30}H_{49}BrO_7SiNH_4^+$ $[M+NH_4]^+$ 646.2769, found 646.2755, $\Delta = -2.2$ ppm] and the *E* isomer **24** as a colorless oil (62.3 mg, 58%) $[\alpha]_D^{14} = -17$ (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.12 (d, 3H, $J = 6.0$ Hz), 1.36 (s, 3H), 1.49 (s, 3H), 1.55–1.61 (m, 1H), 1.66–1.72 (m, 1H), 2.21 (t, 2H, $J = 6.6$ Hz), 2.27–2.42 (m, 2H), 3.47 (s, 3H), 3.51 (m, 3H), 3.83–3.89 (m, 1H), 4.10–4.20 (m, 1H), 4.50 (m, 1H), 5.15 (s, 2H), 5.21 (s, 2H), 5.49 (dd, 1H, $J = 9.3$, 15.0 Hz), 5.70–5.78 (m, 1H), 6.09–6.18 (m, 1H), 6.75 (d, 1H, $J = 2.7$ Hz), 6.77 (d, 1H, $J = 15.0$ Hz), 6.87 (d, 1H, $J = 2.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.8, −4.6, 18.1, 23.4, 25.7, 25.8, 28.3, 29.6, 30.1, 42.6, 56.1, 56.4, 68.2, 77.5, 79.5, 94.5, 95.1, 103.7, 106.3, 107.3, 107.9, 127.9, 129.4, 132.2, 133.4, 139.3, 154.4, 156.9. Calcd for $C_{30}H_{49}BrO_7SiNH_4^+$ $[M+NH_4]^+$ 646.2769, found 646.2775, $\Delta = 0.9$ ppm.

4.21. Alcohol 25

To a solution of **24** (45 mg, 0.072 mmol) in THF (2 mL) was added TBAF (28 mg, 0.11 mmol). The reaction mixture was stirred for 8 h before being quenched with saturated aqueous NaCl solution, and extracted with EtOAc (15 mL × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure vacuum. The residue was purified on a silica gel column using ethyl acetate as the eluent to afford **25** as a colorless oil (35.2 mg, 95%). $[\alpha]_D^{15} = -3$ (*c* 0.85, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, 3H, $J = 6.0$ Hz), 1.33 (s, 3H), 1.45 (s, 3H), 2.12–2.39 (m, 4H), 3.43 (s, 3H), 3.47 (s, 3H), 3.78–3.84 (m, 1H), 4.11–4.18 (m, 1H), 4.51 (m, 1H), 5.12 (s, 2H), 5.18 (s, 2H), 5.49–5.76 (m, 2H), 6.05–6.15 (m, 1H), 6.71 (d, 1H, $J = 2.7$ Hz), 6.73 (d, 1H, $J = 15.9$ Hz), 6.84 (d, 1H, $J = 2.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.8, 25.5, 28.2, 29.5, 29.9, 42.0, 55.9, 56.2, 67.0, 77.3, 79.2, 94.3, 95.0, 103.6, 106.2, 107.1, 107.9, 129.0, 129.4, 131.1, 133.2, 139.1, 154.3, 156.8. Calcd for $C_{24}H_{35}BrO_7NH_4^+$ $[M+NH_4]^+$ 532.1904, found 532.1910, $\Delta = 1.1$ ppm.

4.22. Acid 2

To a solution of alcohol **25** (35.0 mg, 0.068 mmol) obtained above in THF (2 mL) was added *n*-BuLi (2.0 M in petroleum ether, 79 μL, 0.16 mmol) at −78 °C. The resultant yellow solution was stirred for 30 min before addition of solid dry ice. The reaction mixture was allowed to warm up to room temperature over 2 h after which time water was added. The aqueous layer was acidified with 1 M HCl to pH 2–3 and then extracted with EtOAc (15 mL × 3). The combined organic extracts were washed with a

saturated NaCl solution, dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuo. The residue was purified on a silica gel column using ethyl acetate as the eluent to afford **2** as a colorless oil (27.3 mg, 79%). $[\alpha]_D^{15} = -20$ (*c* 1.00, acetone). ^{1}H NMR (300 MHz, acetone-d_6) δ 1.13 (d, 3H, $J = 6.0$ Hz), 1.29 (s, 3H), 1.40 (s, 3H), 1.48–1.67 (m, 2H), 2.19–2.35 (m, 4H), 3.36 (s, 3H), 3.40 (s, 3H), 3.78–3.83 (m, 1H), 4.11–4.19 (m, 1H), 4.49 (m, 1H), 5.18 (s, 2H), 5.22 (2,H), 5.47–5.55 (m, 1H), 5.66–5.81 (m, 1H), 6.25–6.39 (m, 1H), 6.53 (d, 1H, $J = 15.9$ Hz), 6.72 (s, 1H), 6.91 (s, 1H). ^{13}C NMR (75 MHz, acetone-d_6): δ 23.4, 25.9, 28.6, 30.7, 30.9, 42.8, 56.2, 56.3, 67.4, 78.2, 80.1, 94.9, 95.4, 103.2, 105.9, 108.2, 108.3, 127.7, 129.7, 131.9, 133.8, 137.5, 155.7, 159.1, 170.3. Calcd for $C_{25}H_{36}O_9Na^+$ $[M+Na]^+$ 503.2252, found 503.2269, $\Delta = 1.4$ ppm.

4.23. Macrolactone 26

To a solution of acid **2** (27.3 mg, 0.057 mmol) in THF (1 mL) were added Et_3N (31 μL, 0.22 mmol) and trichlorobenzoyl chloride (10 μL, 0.06 mmol). The reaction mixture was stirred for 2 h and then diluted with 100 mL anhydrous toluene. The toluene solution was added dropwise (5 mL/h) to a toluene solution (150 mL) of 4-DMAP (53 mg, 0.43 mmol) heated at reflux. After continued heating for 36 h, the reaction mixture was diluted with EtOAc, washed with aqueous $CuSO_4$, dried over anhydrous Na_2SO_4, and the solvent evaporated in vacuo. The residue was purified on a silica gel column using petroleum ether/ethyl acetate (4/1) as the eluent to afford **26** as a colorless oil (17 mg, 51%). $[\alpha]_D^{15} = -120$ (*c* 1.00 $CHCl_3$); [lit.[2f,g] $= -123.8$ (*c* 0.08, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.37 (d, 3H, $J = 6.4$ Hz), 1.47 (s, 3H), 1.49–1.55 (m, 1H), 1.79–1.85 (m, 1H), 2.05–2.12 (m, 1H), 2.30–2.33 (m, 1H), 2.45–2.53 (m, 2H), 3.45–3.48 (m, 6H), 4.18–4.21 (m, 1H), 4.57 (dd, 1H, $J = 5.2$, 9.6 Hz), 5.11–5.21 (m, 4H), 5.32–5.35 (m, 1H), 5.60 (dd, 1H, $J = 15.2$, 9.6 Hz), 5.70–5.76 (m, 1H), 6.14–6.17 (m, 1H), 6.23 (d, 1H, $J = 15.6$ Hz), 6.69 (d, 1H, $J = 1.6$ Hz), 6.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 25.8, 28.5, 28.7, 29.0, 39.5, 56.0, 56.1, 71.6, 77.2, 80.1, 94.3, 94.6, 102.6, 104.8, 108.3, 117.9, 128.4, 129.3, 131.9, 132.3, 136.8, 155.1, 158.9, 167.3. Calcd for $C_{25}H_{34}O_8H^+$ $[M+H]^+$ 463.2326, found 463.2321, $\Delta = 1.1$ ppm.

4.24. Aigialomycin D 1

According to the literature,[2f,g] aigialomycin D **1** was obtained as a white solid (9 mg, 70%). Mp: 84–86 °C. $[\alpha]_D^{15} = -21$ (*c* 0.43, MeOH). IR (KBr) ν_{max} 3338, 1640, 1603, 1318, 1262, 1167, 1013, 968 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6) δ 1.39 (d, 3H, $J = 6.3$ Hz), 1.56–1.62 (m, 1H), 2.13–2.18 (m, 1H), 2.31–2.35 (m, 2H), 2.41–2.46 (m, 1H), 2.53–2.61 (m, 1H), 3.63 (br, 2H), 3.83 (br d, 1H, $J = 4.2$ Hz), 4.36 (br, 1H), 5.41–5.46 (m, 1H), 5.69 (dd, 1H, $J = 5.4$, 15.5 Hz), 5.84–5.94 (m, 1H), 6.10 (ddd, 1H, $J = 5.4$, 15.9, 5.7 Hz), 6.28 (d, 1H, $J = 2.7$), 6.53 (d, 1H, $J = 2.7$), 7.16 (d, 1H, $J = 15.9$), 9.17 (br s, 1H), 11.68 (s, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 19.1, 28.0, 28.6, 38.0, 73.0, 73.2, 76.4, 102.4, 104.4, 107.8, 125.5, 130.7, 133.6, 135.7, 144.3, 163.1, 165.6, 172.1. Calcd for $C_{18}H_{22}O_6Na^+$ $[M+H]^+$ 357.1309, found 357.1310, $\Delta = 0.3$ ppm.

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