Total synthesis of diplodialides C and D

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Abstract

A highly convergent, stereoselective total synthesis of diplodialides C and D is described. The protocol involves the use of regioselective ring opening of a chiral epoxide, sequential double alkylation of 1,3-dithiane with a bromide and a chiral epoxide, hydroboration and Yamaguchi macrolactonisation as key steps.

Keywords: Pentaketides, chiral epoxides, Yamaguchi macrolactonisation, macrolides, oxecanoines
**Introduction**

Medium-sized-ring systems, those containing 8 to 11 atoms in the ring, are a subject of continuing interest to organic chemists, as they form the core of many bioactive natural products.\(^1\)\(^-\)\(^3\) Diplodialides (C(1), and D(1a)) are the first 10-membered lactone pentaketides (Figure 1), which were isolated from the plant pathogenic fungus *Diplodia pinea* (IFO 6472) by Wada and Ishida.\(^4\),\(^5\) Diplodialides possess unique biological activity, i.e., inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm. The absolute stereochemistry of diplodialides C and D is (3\(R\), 9\(R\)), as determined by Wada and Ishida.\(^6\)

![Diplodialide C (1) and Diplodialide D (1a)](image)

**Figure 1**

Though devoid of various biological activities, these natural products attracted many synthetic chemists interested in its challenging architecture.\(^7\)\(^-\)\(^{12}\) The first total synthesis of (±)-diplodialide C was reported by Wakamatsu et al.\(^7\) in 1977, using their own methodology, from enediol-bis(trimethylsilyl) ether which is prepared by acyloin condensation of diethyl adipate in the presence of trimethyl chlorosilane and methyl lithium. Later, Sharma et al.\(^11\) reported the stereoselective synthesis of diplodialides-B,C using a combination of Jacobsen’s hydrolytic kinetic resolution and Sharpless epoxidation, further ring-closing metathesis strategy was used for the construction of the lactone ring. Recently, Pratapareddy et al.\(^12\) reported the asymmetric total synthesis of diplodialide C using Grubb’s cross-metathesis reaction as a crucial step. In this context, most of the research groups only focused on the total synthesis of diplodialide A, B and C and to the best of our knowledge, no reports were found in the literature regarding the total synthesis of diplodialide D. Intriguing by this, in this communication, we report our successful total synthesis of diplodialides C 1 and D 1a using sequential double alkylation of 1,3-dithiane with a bromide and a chiral epoxide and Yamaguchi macrolactonisation as the key steps in a simple and highly convergent approach.

**Results and Discussion**

Our retrosynthetic approach to the synthesis of 1 and 1a is outlined in Scheme 1. The target molecules 1 and 1a could be made from a common intermediate, hydroxyacid 2, by intramolecular Yamaguchi macrolactonization, whereas 2 could be synthesized from the coupling reaction of two key fragments: the bromo compound 4 and the chiral epoxide 5, with 1,3 dithiane, while both bromo compound 4 and chiral epoxide 5 could be obtained from the known chiral epoxide 6.
Scheme 1. Retrosynthesis of diplodialides C and D.

As shown in the retrosynthesis (Scheme 1), our approach to the total synthesis of the title molecule was initiated by regioselective opening of the known chiral epoxide\(^\text{13}\) 6 with vinylmagnesium bromide in the presence of CuI in THF, at \(-10^\circ\text{C}\) to room temperature, furnishing the tosylate 7 in 84% yield, which on nucleophilic cyclization in the presence of K\(_2\)CO\(_3\) in MeOH afforded epoxide 5 in 86% yield. On the other hand, tosylate 7 on treatment with LiAlH\(_4\) in THF at 0 °C for 12 h under a nitrogen atmosphere gave 8 in 92% yield, which on subsequent silyl ether formation of the alcohol using TBSCl in the presence of imidazole in CH\(_2\)Cl\(_2\) at 0 °C to rt for 6 h, provided the silyl ether 9 in 87% yield. Next, silyl ether 9 was subjected to hydroboration with BH\(_3\)-DMS followed by treatment with sodium hydroxide and H\(_2\)O\(_2\) to give alcohol 10 in 77% yield. Treatment of alcohol 10 with CBr\(_4\) and PPh\(_3\) in CH\(_2\)Cl\(_2\) at 0 °C to rt for 4 h gave the bromide 4 in 81% yield. The detailed synthetic scheme is depicted in Scheme 2.

Reagents and conditions: (a) vinylmagnesium bromide, copper(I) iodide, dry THF, -10 °C, 2 h, 84%; (b) K\(_2\)CO\(_3\), MeOH, rt, 1 h, 86%; (c) LiAlH\(_4\), dry THF, 0 °C to rt, 12 h, 92% (d) TBSCl, imidazole, CH\(_2\)Cl\(_2\), rt, 4 h, 87% (e) i) BH\(_3\)-SMe\(_2\), THF, 0 °C to rt, 4 h, ii) H\(_2\)O\(_2\), NaOH, rt, 3 h, 77%; (f) CBr\(_4\), PPh\(_3\), CH\(_2\)Cl\(_2\), rt, 3 h, 81%.

Scheme 2. Synthesis of intermediate 4.

Having both the bromo compound 4 and the epoxide 5 in hand, construction of the macrocyclic framework was achieved as shown in Scheme 3.
Sequential double alkylation of 1,3-dithiane \(^{14}\) with the bromide 4 and chiral epoxide 5 led to the alcohol 11 in 74% yield, which on subsequent treatment with PMBBr and NaH in tetrahydrofuran solvent at 0 °C to rt for 8 h afforded 12 in 87% yield. Next, ozonolysis of 12 followed by oxidation of resulting aldehyde with NaClO\(_2\) and Na\(_2\)HPO\(_4\), 2-methyl-2-butene in aqueous t-butanol afforded the acid 13 in 77% yield. In the next step, the silyl protecting group (TBS) was removed from acid 13 using TBAF to afford the desired hydroxy-acid segment 2 in 91% yield.

After successful synthesis of the intermediate 2, the next aim was macrolactonization and further transformation to complete the synthesis of diplodialides C (1) and D (1a). Accordingly, the hydroxy-acid 2 was subjected to macrolactonisation under Yamaguchi high-dilution conditions\(^{15}\) using 2,4,6-trichlorobenzoyl chloride and Et\(_3\)N in dry THF to afford the lactone 14 in 71% yield. Removal of the PMB group from lactone 14 was achieved using DDQ in aq. CH\(_2\)Cl\(_2\) to give the compound 15 in 91% yield.

Finally, removal of the dithiane moiety from 15 under reductive conditions\(^{16}\) furnished diplodialide C (1) in 65% yield. On the other hand, deprotection of the 1,3-dithiane group in compound 15 with CaCO\(_3\) and I\(_2\) in THF:H\(_2\)O\(^{17}\) for 5 h afforded the diplodialide D (1a) in 68% yield. The analytical data of our synthetic compounds are in good agreement with the reported data.\(^4,5\)

Thus, we have accomplished the total synthesis of diplodialides C (1) and D (1a) in an enantioselective way.

**Reagents and conditions:**
(a) 1,3-dithiane, n-BuLi, dry THF, -78 °C to -20 °C, 3 h, ii) n-BuLi, dry THF, -78 °C to -20 °C, 5, 3 h, 74%; (b) PMBBr, NaH, THF, 0 °C to rt, 8 h, 87%; (c) i) O\(_3\), CH\(_2\)Cl\(_2\), Me\(_2\)S, -78 °C, 45 min; ii) NaClO\(_2\), Na\(_2\)HPO\(_4\), 2-methyl-2-butene, t-BuOH:water (2:1), 0 °C to rt, 3 h, 77%; (d) TBAF, dry THF, 0 °C to rt, 3 h, 91%; (e) i) 2,4,6-trichlorobenzoyl chloride, Et\(_3\)N, dry THF, rt, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 71%; (f) DDQ, CH\(_2\)Cl\(_2\), rt, 3 h, 91%; (g) Raney Ni, EtOH, 40 °C, 65%; (h) CaCO\(_3\), I\(_2\), THF:H\(_2\)O (9:1), 45 °C, 3 h, 68%.

**Scheme 3.** Synthesis of diplodialides C (1) and D (1a).
Conclusions

In summary: we have developed a concise and highly convergent approach to the total synthesis of diplodialides C (1) and D (1a). The present strategy involves regioselective ring opening of a chiral epoxide, sequential double alkylation of 1,3-dithiane with a bromide and a chiral epoxide and Yamaguchi macro-lactonisation as the key steps. The syntheses of other related compounds are underway in our laboratory.

Experimental Section

General. All chemicals and reagents were obtained from Aldrich (Sigma-Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualization on TLC was achieved by UV light or iodine indicator. 1H and 13C NMR spectra were recorded on 300 and 75 MHz instruments. Chemical shifts (δ) are reported in ppm downfield from internal TMS standard. ESI spectra were recorded on Micromass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined with an electrothermal melting point apparatus. FT-IR spectra were taken on IR spectrophotometer by using NaCl optics. Optical rotation values are recorded on digital polarimeter at 25 °C.

(S)-2-Allyloxirane (5). Copper iodide (0.75 g, 2.61 mmol) was gently heated under vacuum and slowly cooled under nitrogen atmosphere, then THF (10 mL) was added, the resulting suspension was cooled to −10 °C and vinylmagnesium bromide (43.4 mL, 43.41 mmol, 1.0 M in THF, 1.1 eq) was added at the same temperature while stirring. A solution of epoxide 6 (9.0 g, 39.47 mmol) in dry THF (20 mL) was added to the above reagent and the mixture was stirred at -10 °C for 2 h. After completion of the reaction, the reaction was quenched with saturated aqueous NH4Cl, extracted into EtOAc (3 × 30 mL), the combined organic layers was washed with brine, dried over Na2SO4 and concentrated to give the tosylate 7 (8.47 g, 84%) which was used for the next step without purification.

To a stirred solution of tosylate 7 (4.5 g, 17.57 mmol) in MeOH (20 mL) at 0 °C was added K2CO3 (4.85 g, 35.15 mmol) and the resultant mixture was allowed to stir for 1 h at rt. After completion of reaction as indicated by TLC, the reaction was quenched by the addition of pieces of ice and the MeOH was evaporated. The concentrated reaction mixture was then extracted with EtOAc (3 × 30 mL), the combined organic layers was washed with brine, dried (Na2SO4), and concentrated. The crude product was purified by column chromatography (60-120 silica gel, 5% EtOAc in pet. ether) to afford 5 (1.26 g, 86%) as a colorless liquid. 1H NMR (CDCl3, 300 MHz): δ 5.89–5.71 (m, 1H), 5.19–5.02 (m, 2H), 3.04–2.92 (m, 1H), 2.71 (dd, 1H, J 5.2, 3.9 Hz), 2.44 (dd, 1H, J 5.2, 2.7 Hz), 2.41–2.27 (m, 2H); 13C NMR (CDCl3, 75 MHz): δ 132.8, 117.3, 51.7, 46.1, 39.6.

(R)-tert-Butyldimethyl(pent-4-en-2-yloxy)silane (9). To a stirred suspension of LAH (0.78 g, 20.51 mmol) in dry THF (10 mL), a solution of 7 (3.5 g, 13.67 mmol) in dry THF (15 mL) was added dropwise at 0 °C under a nitrogen atmosphere, and the mixture was stirred at rt for 12 h. The reaction mixture was cooled to 0 °C, treated with saturated aq. Na2SO4, filtered, and the filtrate was dried (Na2SO4) and the residue was concentrated by flash chromatography (60-120 silica gel, 5% EtOAc in pet. ether) to give intermediate 8 (1.1 g, 92%) as a colorless syrup which was used immediately for the next step.

A mixture of the alcohol 8 (1.1 g, 12.79 mmol) and imidazole (1.73 g, 25.58 mmol) in dry CH2Cl2 (30 mL) was treated with TBSCl (3.83 g, 15.34 mmol) at 0 °C under a nitrogen atmosphere and stirred at rt for 4 h. The
reaction mixture was quenched withaq. NH₄Cl solution (10 mL) and extracted with CH₂Cl₂ (2 × 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (60-120 silica gel, 2% EtOAc in pet. ether) to furnish the silane 9 (2.22 g, 87%) as a colorless liquid. [α]D₂⁰ +63 (c 0.8, CHCl₃); ¹HNMR (300 MHz, CDCl₃): δ 5.84 (m, 1H), 5.06-4.89 (m, 2H), 3.83-3.76 (m, 1H), 2.27-2.13 (m, 2H), 1.12 (d, 3H, J 6.1 Hz), 0.89 (s, 9H), 0.11 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 135.7, 116.7, 68.6, 44.4, 25.9, 23.8, 18.1, -4.3, -4.5; ESIMS (m/z): 201 (M + H)⁺, 223 (M + Na)⁺.

(R)-4-(tert-Butyldimethylsilyloxy)pentan-1-ol (10). To a stirred solution of 9 (2.1 g, 10.5 mmol) in dry THF (30 mL) at 0 °C, a solution of borane-dimethyldisulfide (2.0 N solution in THF) (6.3 mL, 12.63 mmol) was added dropwise and allowed to stir for 4 h at rt. After that, the reaction mixture was cooled to 0 °C and treated with 2N NaOH solution (15.7 mL) and H₂O₂ (2.8 mL) dropwise and stirred for 3 h at rt. After the completion of the reaction, it was washed with water and extracted with EtOAc (2 × 50 mL). The organic layers were combined, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by column chromatography (60-120 silica gel, 25% EtOAc in pet. ether) to afford the silyloxy-pentanol 10 (1.76 g, 77%) as a colorless liquid. [α]D₂⁰ -12.3 (c 1.6, CHCl₃); ¹HNMR (CDCl₃, 300 MHz): δ 3.91-3.84 (m, 1H), 3.66-3.53 (m, 2H), 2.37 (brs, 1H), 1.66-1.47 (m, 4H), 1.16 (d, 3H, J 6.1 Hz), 0.89 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 68.5, 62.9, 35.8, 28.7, 26.0, 23.5, 18.1, -4.3, -4.6; ESIMS: 219 (M+H)⁺.

(R)-(S)-5-Bromopentan-2-yloxy)(tert-butyl)dimethylsilane (4). To a stirred solution of 10 (1.55 g, 7.11 mmol) in CH₂Cl₂ (30 mL), CBr₄ (2.82 g, 8.53 mmol) and Ph₃P (2.79 g, 10.66 mmol) were added at 0 °C and stirred at rt for 3 h. The reaction mixture was evaporated and the residue purified by column chromatography (60-120 silica gel, 5% EtOAc in pet. ether) to afford 4 (1.61 g, 81%) as a colourless syrup. ¹HNMR (CDCl₃, 300 MHz): δ 3.89-3.81 (m, 1H), 3.44 (t, 2H, J 6.6 Hz), 1.81-1.69 (m, 2H), 1.55-1.39 (m, 2H), 1.13 (d, 3H, J 6.0 Hz), 0.88 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 67.6, 39.7, 34.3, 29.0, 25.9, 23.6, 18.1, -4.3, -4.7; ESIMS: 281 (M+H)⁺.

(S)-(S)-1-(2-((R)-4-(tert-Butyldimethylsilyloxy)pentyl)-1,3-dithian-2-yl)pent-4-en-2-ol (11). To a stirred solution of 1,3-dithiane (0.7 g, 5.88 mmol) in dry THF at −78 °C, n-BuLi (3.9 mL, 6.42 mmol, 1.6 M in hexane) was added and the reaction mixture was allowed to warm to −20 °C while stirring for 1 h. The mixture was re-cooled to −78 °C and a solution of the bromide 4 (1.5 g, 5.35 mmol) in dry THF (5 mL) was added dropwise. The mixture was warmed to −20 °C stirred for 1 h, then the reaction mixture was again re-cooled to −78 °C, and treated with n-BuLi (3.9 mL, 6.42 mmol, 1.6 M in hexane) and stirred for 1 h at −20 °C. The mixture was re-cooled to −78 °C and a solution of the epoxide 5 (0.45 g, 5.35 mmol) in dry THF (2 mL) was added dropwise. The mixture was warmed to −20 °C stirred for 1 h. After that the reaction was warmed to 0 °C for 1 h and then to ambient temperature for an additional 1 h, quenched with saturated aq. NH₄Cl (40 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography (60-120 silica gel, 10% EtOAc in pet. ether) to afford 11 (1.59 g, 74%) as a colorless syrup. [α]D₂⁰ -58.9 (c 1.0, CHCl₃); ¹HNMR (CDCl₃, 300 MHz): δ 5.91 (m, 1H), 5.04-4.91 (m, 2H), 3.83 (m, 1H), 3.64 (m, 1H), 2.89-2.71 (m, 4H), 2.47-2.36 (m, 1H), 2.31-2.2 (m, 1H), 1.96-1.67 (m, 8H), 1.49-1.37 (m, 1H), 1.33-1.21 (m, 1H), 1.15 (d, 3H, J 6.1 Hz), 0.88 (s, 9H), 0.21 (s, 3H), 0.11 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 135.6, 117.2, 72.3, 68.2, 61.3, 52.1, 40.8, 40.4, 39.2, 26.9, 25.8, 24.4, 24.0, 22.4, 18.1, -4.4, -4.6; ESIMS: 427 (M+H)⁺. Anal. Calcd. for C₂₀H₄₀O₂S₂Si: C, 59.35; H, 9.96; S, 15.84. Found: C, 59.32; H, 9.88; S, 15.76.

tert-Butyl ((R)-5-(2-((S)-2-(4-methoxybenzylloxy)pent-4-en-2-yl)-1,3-dithian-2-yl)pentan-2-yloxy) dimethylsilane (12). To a cooled (0 °C) solution of 11 (1.4 g, 3.46 mmol) in dry THF (10 mL), NaH (0.25 g, 10.38 mmol) was added, the mixture stirred for 30 min and treated with a solution of PMBBr (0.82 g, 4.15 mmol) in dry THF (5 mL). After 7.5 h stirring at rt, the reaction mixture was quenched with sat. NH₄Cl solution (10 mL) and
extracted with EtOAc (2 × 50 mL). The organic layers were washed with water (2 × 10 mL), brine (20 mL) and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue purified by column chromatography (60-120 silica gel, 5% EtOAc in pet. ether) to furnish 12 (1.57 g, 87%) as a yellow liquid; [α]D²⁵ -26.3 (c 0.8, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 7.24 (d, 2H, J 8.7 Hz), 6.86 (d, 2H, J 8.7 Hz), 5.87 (m, 1H), 5.03-4.91 (m, 2H), 4.49 (d, 1H, J 11.1 Hz), 4.41 (d, 1H, J 11.1 Hz), 3.73 (s, 3H), 3.69-3.61 (m, 1H), 3.53-3.44 (m, 1H), 2.91-2.69 (m, 4H), 2.37-2.21 (m, 2H), 1.93-1.59 (m, 9H), 1.29-1.21 (m, 1H), 1.17 (d, 3H, J 6.3 Hz), 0.91 (s, 3H), 0.23 (s, 3H), 0.08 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 160.1, 135.8, 128.9, 128.1, 116.3, 113.8, 79.9, 72.1, 68.0, 59.8, 56.3, 47.1, 40.7, 39.8, 39.1, 26.9, 25.9, 24.3, 24.0, 22.2, 18.2, -4.3, -4.7; ESIMS: 547 (M+ Na)⁺. Anal. Calcd. for C₂₉H₄₈O₅S₂Si: C, 59.69; H, 8.58; S, 14.96. Found 59.8, 56.3, 47.1, 40.7, 39.8, 39.1, 26.9, 25.9, 24.3, 24.0, 22.2, 18.2, -4.3, -4.7; ESIMS: 547 (M+ Na)⁺. Anal. Calcd. for C₂₉H₄₈O₅S₂Si: C, 59.74; H, 8.54; S, 11.81. Found: C, 59.69; H, 8.58; S, 11.77.

(S)-4-[2-[(R)-4-Hydroxypentyl]-1,3-dithian-2-yl]-3-(4-methoxybenzylxy)butanoic acid (2). To a cooled (0 °C) solution of 13 (1.0 g, 1.84 mmol) in dry THF (10 mL) under nitrogen atmosphere, TBAF (3.1 mL, 2.76 mmol) was added and stirred for 3 h. After completion of reaction, reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 × 20 mL). Organic layers were washed with water (2 × 10 mL), brine (10 mL), dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 silica gel, 30% EtOAc in pet. ether) to furnish 2 (0.71 g, 91%) as a liquid. ¹H NMR (CDCl₃, 300 MHz): δ 7.23 (d, 2H, J 8.8 Hz), 6.81 (d, 2H, J 8.8 Hz), 4.49 (d, 1H, J 11.3 Hz), 4.44 (d, 1H, J 11.3 Hz), 3.91 (m, 1H), 3.70 (s, 3H), 3.64 (m, 1H), 2.86-2.70 (m, 5H), 2.47 (dd, 1H, J 5.8, 7.4 Hz), 2.07-1.84 (m, 6H), 1.57-1.39 (m, 3H), 1.31-1.20 (m, 1H), 1.14 (d, 3H, J 6.1 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 160.3, 129.3, 128.8, 114.7, 80.2, 72.1, 67.6, 61.3, 56.1, 47.4, 42.7, 41.3, 39.8, 26.2, 24.5, 23.4, 21.0; ESIMS: 429 (M+ H)⁺. Anal. Calcd. for C₂₁H₂₃O₅S₂: C, 58.85; H, 7.53; S, 14.96. Found: C, 58.81; H, 7.58; S, 14.86.

(8S,12R)-8-(4-Methoxybenzylxy)-12-methyl-11-oxa-1,5-dithiaspiro[5.9]pentadecan-10-one (14). To a stirred solution of the hydroxy-acid 2 (0.4 g, 0.93 mmol) and Et₃N (0.38 mL, 2.80 mmol) in dry THF (5 mL), a solution of 2,4,6-trichlorobenzoyl chloride (0.34 mL, 1.39 mmol) in dry THF (1 mL) was added. The resulting mixture was stirred for 2 h at rt under a nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with toluene (10 mL) and filtered quickly through Celite. The filtrate was added dropwise to a stirred solution of DMAP (0.11 g, 0.93 mmol) in toluene (400 mL) at 90 °C over a period of 10 h. It was cooled, washed with 7% aq NaHCO₃ (20 mL), 2M aqueous HCl (20 mL), brine (20 mL) and dried (Na₂SO₄). The organic layer was evaporated and the obtained residue purified by column chromatography (60-120 silica gel, 12% EtOAc in pet.
ether) to give 14 (0.27 g, 71%) as a syrup. \([\alpha]_D +18.3 \text{ (c } 1.2, \text{ CHCl}_3)\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 7.23 \text{ (d, } 2\text{H, } J 8.6 \text{ Hz}), 6.82 \text{ (d, } 2\text{H, } J 8.6 \text{ Hz}), 4.86 \text{ (m, } 1\text{H}), 4.51 \text{ (d, } 1\text{H, } J 11.2 \text{ Hz}), 4.44 \text{ (d, } 1\text{H, } J 11.2 \text{ Hz}), 4.13-4.04 \text{ (m, } 1\text{H}), 3.73 \text{ (s, } 3\text{H}), 2.93-2.76 \text{ (m, } 4\text{H}), 2.44-2.28 \text{ (m, } 2\text{H}), 2.04-1.89 \text{ (m, } 2\text{H}), 1.89-1.69 \text{ (m, } 6\text{H}), 1.47-1.30 \text{ (m, } 2\text{H}), 1.17 \text{ (d, } 3\text{H, } J 6.0 \text{ Hz})\); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 172.7, 160.3, 128.4, 128.1, 114.4, 79.1, 72.3, 61.3, 55.5, 46.8, 42.3, 39.8, 37.6, 26.5, 24.4, 22.1, 20.3\); ESIMS: 411 (M+ H\(^+\)). Anal. Calcd. for C\(_{22}\)H\(_{30}\)O\(_4\)S\(_2\): C, 61.43; H, 7.36; S, 15.62. Found: C, 61.39; H, 7.32; S, 15.57.

**Diploidialide C (1).** To a stirred solution of lactone 14 (0.24 g, 0.58 mmol) in aq. CH\(_2\)Cl\(_2\) (2 mL, 19:1), DDQ (0.19 g, 0.87 mmol) was added and the mixture stirred at rt for 3 h then quenched with sat. NaHCO\(_3\) solution (1 mL), filtered and washed with CH\(_2\)Cl\(_2\) (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na\(_2\)SO\(_4\)) and evaporated under reduced pressure. The residue was purified by column chromatography (60-120 silica gel, 15% EtOAc in pet. ether) to furnish 15 (0.15 g, 91%) as colourless syrup. \([\alpha]_D +26.8 \text{ (c } 0.8, \text{ CHCl}_3)\); \(^1\)H NMR (CDCl\(_3\), 300 MHz): \(\delta 4.91-4.83 \text{ (m, } 1\text{H}), 4.17-3.94 \text{ (m, } 1\text{H}), 2.88-2.74 \text{ (m, } 4\text{H}), 2.71 \text{ (dd, } 1\text{H, } J 4.0, 15.1 \text{ Hz}), 2.44 \text{ (dd, } 1\text{H, } J 8.9, 15.1 \text{ Hz}), 2.03-1.89 \text{ (m, } 2\text{H}), 1.88-1.66 \text{ (m, } 7\text{H}), 1.47-1.38 \text{ (m, } 1\text{H}), 1.18 \text{ (d, } 3\text{H, } J 6.8 \text{ Hz})\); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 172.8, 159.9, 128.7, 128.4, 114.3, 79.3, 72.1, 61.3, 55.8, 47.1, 42.2, 39.8, 37.7, 26.9, 24.5, 21.9, 20.2\); ESIMS: 291 (M+ H\(^+\)). Anal. Calcd. for C\(_{33}\)H\(_{22}\)O\(_4\)S\(_2\): C, 53.71; H, 7.58; S, 22.02. Found: C, 53.71; H, 7.58; S, 22.02.

**Diploidialide D (1a).** To a solution of compound 15 (0.11 g, 0.37 mmol) and CaCO\(_3\) (0.37 g, 3.79 mmol) in THF/H\(_2\)O (9:1, 2 mL) was added I\(_2\) (0.28 g, 1.11 mmol) at rt. The resulting mixture was stirred at 45 °C for 3 h. The reaction mixture was quenched by adding saturated aq. Na\(_2\)S\(_2\)O\(_3\), filtered through a pad of Celite, and then extracted with EtOAc (3×20 mL), water, brine, dried over Na\(_2\)SO\(_4\) and concentrated. The residue was purified by column chromatography (60-120 silica gel, 15% EtOAc in pet. ether) to furnish compound 1a (51 mg, 68% yield). \([\alpha]_D +1.3 \text{ (c } 0.9, \text{ CHCl}_3)\); Lit:\(^4\) \([\alpha]_D +40.1 \text{ (CHCl}_3)\); \(v_{\text{max}} \text{(neat)/cm}^{-1} 3645, 3425, 1736, 1724, 1030\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 5.05-4.94 \text{ (m, } 1\text{H}), 4.15-4.03 \text{ (m, } 1\text{H}), 2.67 \text{ (dd, } 1\text{H, } J 4.2, 15.5 \text{ Hz}), 2.47 \text{ (dd, } 1\text{H, } J 9.3, 15.5 \text{ Hz}), 1.91-1.41 \text{ (m, } 10\text{H}), 1.26 \text{ (d, } 3\text{H, } J 6.6 \text{ Hz})\); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 171.3, 72.3, 70.1, 44.1, 35.5, 31.2, 29.6, 26.7, 21.7, 20.2\); ESIMS: 209 (M+ Na\(^+\)).

**Supplementary Material**

Compounds characterization and \(^1\)H and \(^13\)C NMR spectra for all the intermediates and final compounds are available in the supplementary material.
References

1. Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. **Nat. Prod. Rep.** **1996**, *13*, 365. [https://doi.org/10.1039/NP9961300365](https://doi.org/10.1039/NP9961300365)

2. Ferraz, H. M. C.; Bombonato, F. I.; Longo, L. S. **Synthesis** **2007**, *3261*. [https://doi.org/10.1055/s-2007-990831](https://doi.org/10.1055/s-2007-990831)

3. Riatto, V. B.; Pilli, R. A.; Victor, M. M. **Tetrahedron** **2008**, *64*, 2279. [https://doi.org/10.1016/j.tet.2007.11.034](https://doi.org/10.1016/j.tet.2007.11.034)

4. Ishida, T.; Wada, K. **J. Chem. Soc., Chem. Commun.** **1975**, *209*. [https://doi.org/10.1039/c39750000209](https://doi.org/10.1039/c39750000209)

5. Wada, K.; Ishida, T. **J. Chem. Soc., Chem. Commun.** **1976**, *340*. [https://doi.org/10.1039/c39760000340](https://doi.org/10.1039/c39760000340)

6. Wada, K.; Ishida, T. **J. Chem. Soc., Perkin Trans. I** **1979**, *1154*. [https://doi.org/10.1039/p19790001154](https://doi.org/10.1039/p19790001154)

7. Wakamatsu, T.; Akasaka, K.; Ban, Y. **Tetrahedron Lett.** **1977**, *18*, 2755. [https://doi.org/10.1016/0040-4039(77)90936-4](https://doi.org/10.1016/0040-4039(77)90936-4)

8. Wakamatsu, T.; Akasaka, K.; Ban, Y. **J. Org. Chem.** **1979**, *44*, 2008. [https://doi.org/10.1021/jo01326a025](https://doi.org/10.1021/jo01326a025)

9. Tsuji, J.; Mandai, T. **Tetrahedron Lett.** **1978**, *19*, 1817. [https://doi.org/10.1016/0040-4039(78)90936-4](https://doi.org/10.1016/0040-4039(78)90936-4)

10. Ishida, T.; Wada. **K. J. Chem. Soc., Perkin Trans. I** **1979**, *323*. [https://doi.org/10.1039/p19790000323](https://doi.org/10.1039/p19790000323)

11. Sharma, G. V. M.; Reddy, K. L. **Tetrahedron Asymm.** **2006**, *17*, 3197. [https://doi.org/10.1016/j.tetasy.2006.11.045](https://doi.org/10.1016/j.tetasy.2006.11.045)

12. Pratapareddy, B.; Sreenivasulu, R.; Hatti, I.; Rao, M. V. B.; Raju, R. R. **Monatsh. Chem.** **2015**, *146*, 1921. [https://doi.org/10.1007/s00706-015-1464-1](https://doi.org/10.1007/s00706-015-1464-1)

13. Brun, E.; Bellosta, V.; Cossy, J. **J. Org. Chem.,** **2015**, *80*, 8668. [https://doi.org/10.1021/acs.joc.5b01323](https://doi.org/10.1021/acs.joc.5b01323)

14. Spracklin, D. K.; Weiler, L. **J. Chem. Soc., Chem. Commun.** **1992**, *1347*. [https://doi.org/10.1039/c39920001347](https://doi.org/10.1039/c39920001347)

15. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. **Bull. Chem. Soc. Jpn.** **1979**, *52*, 1989. [https://doi.org/10.1246/bcsj.52.1989](https://doi.org/10.1246/bcsj.52.1989)

16. Foley, D. A.; O’Leary, P.; Buckley, N. R.; Lawrence, S. E.; Maguire, A. R. **Tetrahedron** **2013**, *69*, 1778. [https://doi.org/10.1016/j.tet.2012.10.083](https://doi.org/10.1016/j.tet.2012.10.083)

17. Raju, A. R. K.; Reddy, R. V.; Rao, V. M.; Naresh, V. V.; Rao, A. V. **Tetrahedron Lett.** **2016**, *57*, 3933. [https://doi.org/10.1016/j.tetlet.2016.04.004](https://doi.org/10.1016/j.tetlet.2016.04.004)