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Total synthesis of diplodialides C and D

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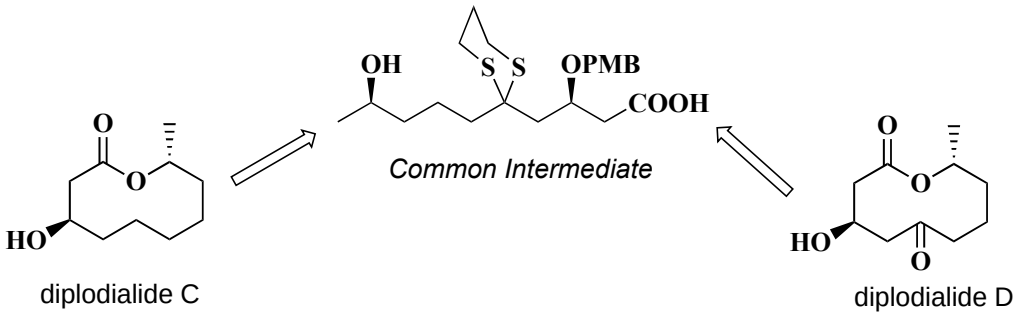
Abstract

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, oxecanones

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]

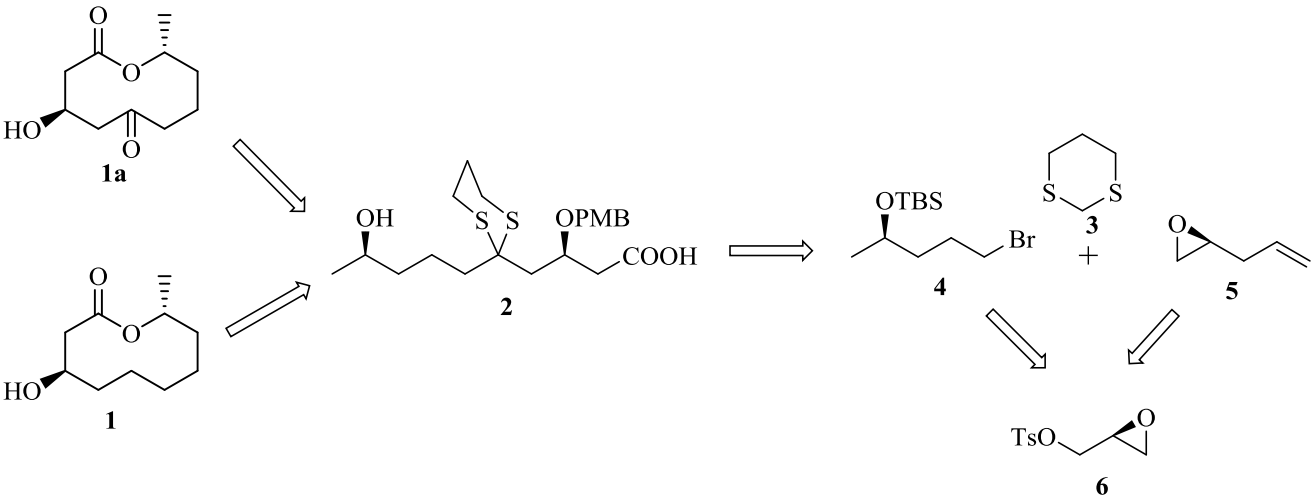
diplodialide C (**1**) diplodialide D (**1a**)

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, Prataparedddy 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.

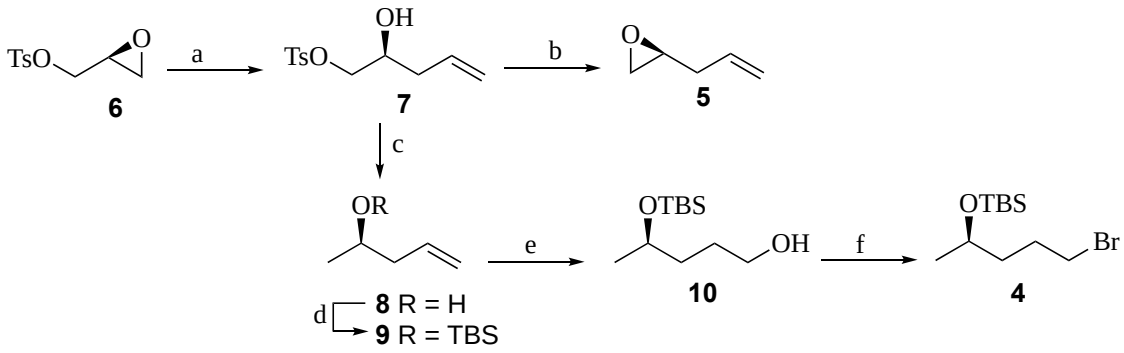
Results and Discussion

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 macrolacton-ization, 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[13] **6** with vinylmagnesium bromide in the presence of CuI in THF, at −10 °C to room temperature, furnishing the tosylate **7** in 84% yield, which on nucleophilic cyclization in the presence of K_2CO_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_2Cl_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_2O_2 to give alcohol **10** in 77% yield. Treatment of alcohol **10** with CBr_4 and PPh_3 in CH_2Cl_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_2CO_3, MeOH, rt, 1 h, 86%; (c) $LiAlH_4$, dry THF, 0 °C to rt, 12 h, 92% (d) TBSCl, imidazole, CH_2Cl_2, rt, 4 h, 87% (e) i) $BH_3.SMe_2$, THF, 0 °C to rt, 4 h, ii) H_2O_2, NaOH, rt, 3 h, 77%; (f) CBr_4, PPh_3, CH_2Cl_2, rt, 3 h, 81%.

Scheme 2. Synthesis of intermediate **4**.

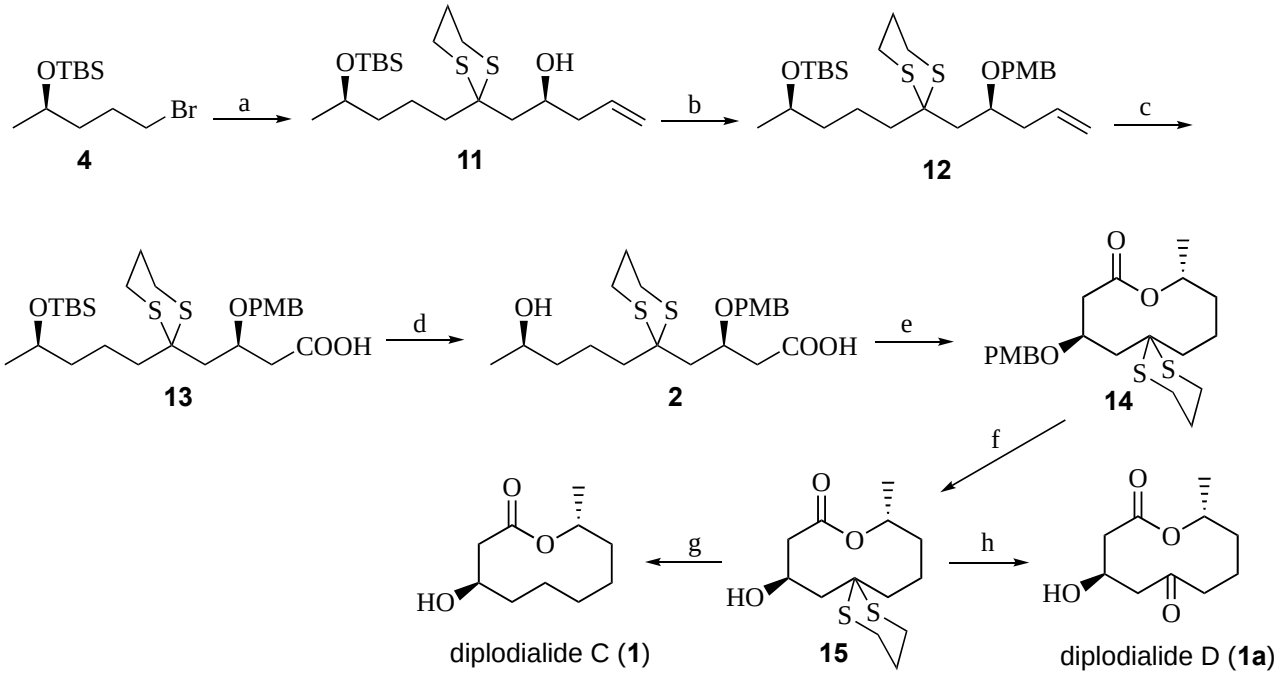
Having both the bromo compound **4** and the epoxide **5** in hand, construction of the macrocyclic framework was achieved as shown in Scheme 3.

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 ^{o}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 NaH_2PO_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_3N 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_2Cl_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_2O[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 ^{o}C to –20 ^{o}C, 3 h, ii) *n*-BuLi, dry THF, –78 ^{o}C to –20 ^{o}C, **5**, 3 h, 74%; (b) PMBBr, NaH, THF, 0 ^{o}C to rt, 8 h, 87%; (c) i) O_3, CH_2Cl_2, Me_2S, -78 ^{o}C, 45 min; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH:water (2:1), 0 ^{o}C to rt, 3 h, 77%; (d) TBAF, dry THF, 0 ^{o}C to rt, 3 h, 91%; (e) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h; ii) DMAP, toluene, 90 °C, 10 h, 71%; (f) DDQ, CH_2Cl_2, rt, 3 h, 91%; (g) Raney Ni, EtOH, 40 ^{o}C, 65%; (h) $CaCO_3$, I_2, THF:H_2O (9:1), 45 ^{o}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. ^{1}H and ^{13}C 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 ^{o}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 ^{o}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 ^{o}C for 2 h. After completion of the reaction, the reaction was quenched with saturated aqueous NH_4Cl, extracted into EtOAc (3 × 30 mL), the combined organic layers was washed with brine, dried over Na_2SO_4 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 ^{o}C was added K_2CO_3 (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 x 30 mL), the combined organic layers was washed with brine, dried (Na_2SO_4), 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. ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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. Na_2SO_4, filtered, and the filtrate was dried (Na_2SO_4) and the residue was concentrated was purified 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 CH_2Cl_2 (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 with aq. NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were washed with water (30 mL), brine (30 mL), dried (Na_2SO_4) 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. $[\alpha]_D^{25}$ +63 (c 0.8, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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-dimethylsulfide (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 H_2O_2 (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 (Na_2SO_4) 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. $[\alpha]_D^{25}$ -12.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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*)-(5-Bromopentan-2-yloxy)(*tert*-butyl)dimethylsilane (4). To a stirred solution of 10 (1.55 g, 7.11 mmol) in CH_2Cl_2 (30 mL), CBr_4 (2.82 g, 8.53 mmol) and Ph_3P (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. ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 67.9, 37.9, 34.3, 29.0, 25.9, 23.6, 18.0, -4.3, -4.7; ESIMS: 281 $(M+ H)^+$.

(*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. NH_4Cl (40 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, 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. $[\alpha]_D^{25}$ –58.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{20}H_{40}O_2S_2Si$: 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-methoxybenzyloxy)pent-4-enyl]-1,3-dithian-2-yl}pentan-2-yloxy) dimethyl-silane (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. NH_4Cl 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 (Na_2SO_4). 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; $[\alpha]_D^{25}$ -26.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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, 9H), 0.23 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 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 $C_{28}H_{48}O_3S_2Si$: C, 64.07; H, 9.22; S, 12.22. Found: C, 64.03; H, 9.25; S, 12.12.

(*S*)-4-{2-[(*R*)-4-(*tert*-Butyldimethylsilyloxy)pentyl]-1,3-dithian-2-yl}-3-(4-methoxybenzyloxy)butanoic acid (13). Ozone was bubbled through a cooled (-78 °C) solution of 12 (1.35 g, 2.57 mmol) in CH_2Cl_2 (20 mL) until a pale blue colour persisted. Excess of ozone was removed with Me_2S (1 mL) and the mixture stirred for 30 min at 0 °C. The reaction mixture was concentrated under reduced pressure to give corresponding aldehyde, which was immediately used for further reaction.

To a cooled (0 ^{o}C) solution of the above aldehyde in *t*-butanol (6 mL), 2-methyl-2-butene (2 mL) was added, followed by a solution of $NaClO_2$ (0.27 g, 3.09 mmol) and NaH_2PO_4 (0.37 g, 3.09 mmol) in water (3 mL) and stirred at rt for 3 h. *t*-Butanol was evaporated and the residue extracted with EtOAc (2 × 20 mL). The organic layers were washed with water (2 ×20 mL), brine (30 mL), dried (Na_2SO_4), evaporated and purified the residue by column chromatography (60-120 silica gel, 30% EtOAc in pet. ether) to furnish **13** (1.08 g, 77%); $[\alpha]_D$ +22.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.19 (d, 2H, *J* 8.8 Hz), 6.81 (d, 2H, *J* 8.8 Hz), 4.51 (d, 1H, *J* 11.1 Hz), 4.44 (d, 1H, *J* 11.1 Hz), 3.81 (m, 1H), 3.72 (s, 3H), 3.63 (m, 1H), 2.91-2.71 (m, 6H), 2.11-1.84 (m, 6H), 1.57-1.38 (m, 4H), 1.14 (d, 3H, *J* 6.0 Hz), 0.89 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 160.1, 129.6, 128.8, 114.1, 75.3, 73.1, 66.3, 61.2, 56.3, 47.1, 43.2, 41.6, 39.3, 27.3, 25.9, 24.6, 24.2, 22.7, 18.8, -4.2, -4.4; ESIMS: 543 $(M+ H)^+$. Anal. Calcd. for $C_{27}H_{46}O_5S_2Si$: 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-methoxybenzyloxy)butanoic acid (2). To a cooled (0 ^{o}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 (Na_2SO_4), evaporated and purified the residue by column chromatography (60-120 silica gel, 55% EtOAc in pet. ether) to give **2** (0.71 g, 91%) as a liquid. ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{21}H_{32}O_5S_2$: C, 58.85; H, 7.53; S, 14.96. Found: C, 58.81; H, 7.58; S, 14.86.

(8*S*,12*R*)-8-(4-Methoxybenzyloxy)-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 Et_3N (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 $NaHCO_3$ (20 mL), 2M aqueous HCl (20 mL), brine (20 mL) and dried (Na_2SO_4). 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 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.23 (d, 2H, *J* 8.6 Hz), 6.82 (d, 2H, *J* 8.6 Hz), 4.86 (m, 1H), 4.51 (d, 1H, *J* 11.2 Hz), 4.44 (d, 1H, *J* 11.2 Hz), 4.13-4.04 (m, 1H), 3.73 (s, 3H), 2.93-2.76 (m, 4H), 2.44-2.28 (m, 2H), 2.04-1.89 (m, 2H), 1.89-1.69 (m, 6H), 1.47-1.30 (m, 2H), 1.17 (d, 3H, *J* 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{21}H_{30}O_4S_2$: C, 61.43; H, 7.36; S, 15.62. Found: C, 61.39; H, 7.32; S, 15.57.

(8*S*,12*R*)-8-Hydroxy-12-methyl-11-oxa-1,5-dithiaspiro[5.9]pentadecan-10-one (15). To a solution of the spiro-dithiane **14** (0.24 g, 0.58 mmol) in aq. CH_2Cl_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_2Cl_2 (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na_2SO_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 (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.91-4.83 (m, 1H), 4.17-3.94 (m, 1H), 2.88-2.74 (m, 4H), 2.71 (dd, 1H, *J* 4.0, 15.1 Hz), 2.44 (dd, 1H, *J* 8.9, 15.1 Hz), 2.03-1.89 (m, 2H), 1.88-1.66 (m, 7H), 1.47-1.38 (m, 1H), 1.18 (d, 3H, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 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 $C_{13}H_{22}O_3S_2$: C, 53.76; H, 7.63; S, 22.08. Found: C, 53.71; H, 7.58; S, 22.02.

Diplodialide C (1). To a stirred solution of lactone **15** (95 mg, 0.32 mmol) in EtOH (2.0 mL) was added freshly prepared Raney 2400 Ni (~1.5 g) in EtOH (2.0 mL) at 25 °C. After stirring at 40 °C for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The residue was purified by column chromatography (60-120 silica gel, 15% EtOAc in pet. ether) to furnish compound 1 (41 mg, 65% yield). $[\alpha]_D$ –41.3 (*c* 0.6, $CHCl_3$); Lit:[4] $[\alpha]_D$ –41.0 ($CHCl_3$); ν_{max} (neat)/cm^{-1} 3645, 3425, 1736, 1244, 1030; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.05-4.94 (m, 1H), 4.15–4.03 (m, 1H), 2.67 (dd, 1H, *J* 4.2, 15.5 Hz), 2.47 (dd, 1H, *J* 9.3, 15.5 Hz), 1.91–1.41 (m, 10H), 1.26 (d, 3H, *J* 6.6 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 72.3, 70.1, 44.1, 35.5, 31.2, 29.6, 26.7, 21.7, 20.2; ESIMS: 209 $(M+ Na)^+$.

Diplodialide 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_2O (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. $Na_2S_2O_3$, filtered through a pad of Celite, and then extracted with EtOAc (3×20 mL), water, brine, dried over Na_2SO_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 (*c* 0.9, $CHCl_3$); Lit:[5] $[\alpha]_D$ +0.8 ($CHCl_3$); ν_{max} (neat)/cm^{-1} 3425, 1735, 1700; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.56 (m,1H), 4.37 (m, 1H), 3.23 (brs, 1H), 2.90 (dd, 1H, *J* 14, 3.2 Hz), 2.60 (dd, 1H, *J* 14.1, 4.2 Hz), 2.57 (d, 2H, *J* 5.6 Hz), 2.44 (m, 2H), 1.88-1.76 (m, 4H), 1.20 (d, 3H, *J* 6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 173.2, 72.6, 65.3, 51.5, 42.6, 41.2, 38.4, 21.6, 20.1; ESIMS: 223 $(M+ Na)^+$.

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Supplementary Material

Compounds characterization and ^1H and ^{13}C NMR spectra for all the intermediates and final compounds are available in the supplementary material.

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