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Stereoselective synthesis of (+)-diplodialides-B, C and a formal synthesis of (+)-diplodialide-A by ring-closing metathesis approach☆

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Abstract—Stereoselective synthesis of diplodialides-B and C and the formal synthesis of diplodialide-A are reported. A combination of Jacobsen's hydrolytic kinetic resolution and Sharpless epoxidation is used for the creation of two stereogenic centers, while a ring-closing metathesis strategy was used for the construction of the lactone ring.

1. Introduction

Diplodialide-A **1**, diplodialide-B **2**, diplodialide-C **3**, and diplodialide-D **4** (Fig. 1), the first 10-membered pentaketides, were isolated from the plant pathogenic fungus *Diplodia pinea* (IFO 6472) by Wada and Ishida.[1,2] Among the four, diplodialide-A **1** showed a significant inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm. Wada and Ishida determined the absolute stereochemistry of (9*R*)-**1**, (3*S*,9*R*)-**2** and (3*R*,9*R*)-**3**.[3] Some groups[4] have already reported the synthesis of diplodialides **1**–**3**. Herein, we report the synthesis of **2** and **3** and a formal synthesis of **1**.

Our retrosynthetic analysis revealed that **1** and **3** could be prepared from **2** by simple oxidation and hydrogenation, respectively. Hence, the retroanalysis of **2** indicated that it could be prepared efficiently by RCM protocol from the bis-olefin **5**, which in turn could be realized by Yamaguchi esterification of alcohol **6** and acid **8**. Intermediate **6** was envisaged from (*R*)-propylene oxide **7**, while chiral vinyl alcohol **8** could be produced from epoxy alcohol **9** (Scheme 1).

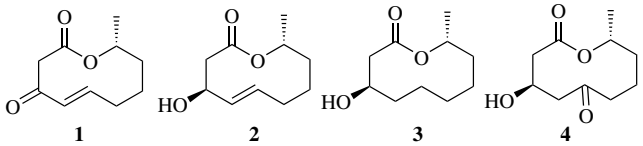

Figure 1.

2. Results and discussion

The synthesis of fragment **6** began by the kinetic resolution of **10** (Scheme 2) under Jacobsen reaction conditions[5] using the (*R*,*R*)-catalyst to give chiral epoxide **7** (42%) and diol **11**. Epoxide **7**, on treatment with protected 1-[(2-propynyloxy)methyl]benzene **A** in the presence of *n*-BuLi and $BF_3{\cdot}Et_2O$ in THF at −78 °C for 3 h, afforded **12** (64%); on reaction with TBDPSCl in CH_2Cl_2 at room temperature gave TBDPS ether **13**. Concomitant removal of the benzyl protecting group and saturation of triple bond with 10% Pd–C/H_2 in MeOH at room temperature gave **14** (93%), which on subsequent oxidation with IBX in DMSO at room temperature afforded aldehyde **15** (90%). Wittig olefination of **15** furnished the corresponding olefin **16** (67%), which on desilylation under neutral conditions using HF-pyridine in THF at room temperature for 12 h afforded **6**, $[\alpha]_D = -15.2$ (*c* 1.1, $CHCl_3$).

The synthesis of alkene **8** began from the known epoxide **9**.[6] Accordingly, reaction of **9** (Scheme 3) with Ph_3P in CCl_4 at reflux gave chloro epoxide **17** (86%), which was subjected to fragmentation with sodium sand in dry ether at room temperature to afford **18** (82%). Vinyl alcohol **18** was treated with TBDPSCl to afford **19** (89%), which was subjected to debenzylation with DDQ in CH_2Cl_2–H_2O to

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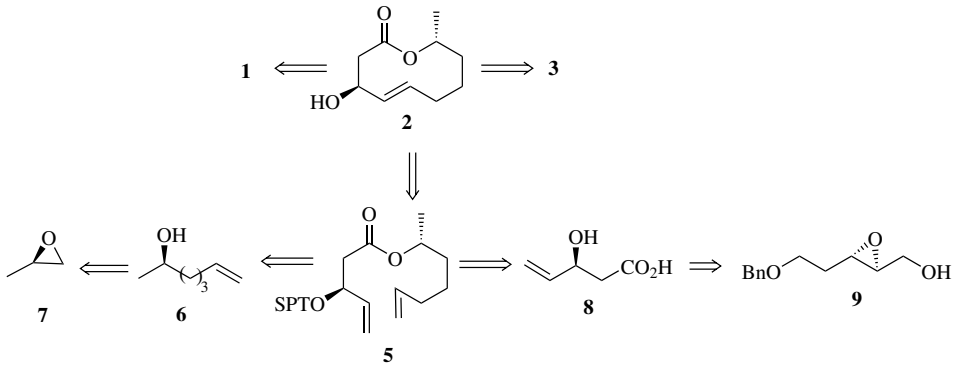
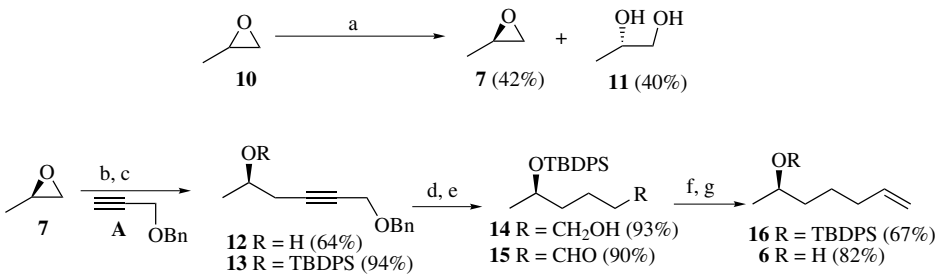
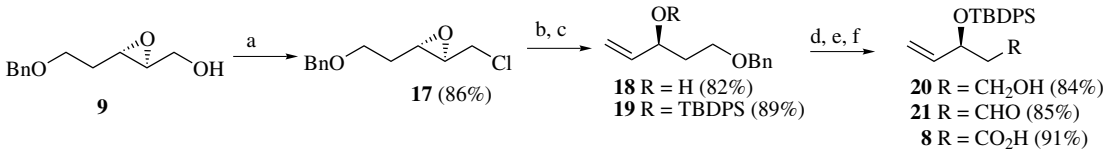


Scheme 1.



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-Jacobsen catalyst, H_2O, rt, 12 h; (b) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 3 h; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h; (d) 10% Pd–C, H_2, MeOH, rt, 12 h; (e) IBX, DMSO, rt, 4 h; (f) $CH_3Ph_3P^+I^-$, *n*-BuLi, THF, −20 °C, 2 h; (g) HF-pyridine, THF, rt, 12 h.



Scheme 3. Reagents and conditions: (a) Ph_3P, CCl_4, relfux, 2 h; (b) Na sand, ether, rt, 6 h; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 2 h; (d) DDQ, CH_2Cl_2–H_2O (19:1) reflux, 4 h; (e) $(COCl)_2$, DMSO, Et_3N, −78 °C, 2 h; (f) Na_2ClO_2, NaH_2PO_4, 2-methyl 2-butene, *t*-BuOH, 10 h.

give **20** (84%). Alcohol **20** on Swern oxidation furnished aldehyde **21**, which on further oxidation with $NaClO_2$ and NaH_2PO_4 in *t*-BuOH gave acid **8** (91%).

The esterification of the two fragments **6** and **8** (Scheme 4) was achieved under Yamaguchi reaction conditions[7] using 2,4,6-trichlorobenzoyl chloride to furnish diene ester **5** (83%). Treatment of **5** with Grubbs (first generation) catalyst under high dilution in CH_2Cl_2 at reflux furnished the unknown dimer as the major product **22**. Hence in order to avoid the formation of this unwanted product, the TBDPS group in **5** was first deprotected using HF–pyridine to give **23**. Diene **23** was treated with Grubb's (first generation) catalyst[8] under high dilution to furnish a 10:1 *E*:*Z* mixture, which on chromatographic purification gave diplodialide-B **2**, $[\alpha]_D = -35.8$ (*c* 0.2, $CHCl_3$); {lit.[3] $[\alpha]_D^{28} = -37.3$ (*c* 0.93, $CHCl_3$)}, whose spectral data were in accordance with the literature data.[3] Similarly, hydrogenation of the *E*/*Z*-mixture of **24** and **2**, using 10% Pd–C in EtOAc, gave diplodialide-C **3**, $[\alpha]_D = -39.75$ (*c* 0.25, $CHCl_3$); {lit.[3] $[\alpha]_D^{28} = -41.0$ (*c* 0.61, $CHCl_3$)}. Likewise, the oxidation of **2** to give diplodialide-A **1** is reported in the literature.[4b] The synthesis of **2** thus formally constitutes the total synthesis of diplodialide-A **1**.

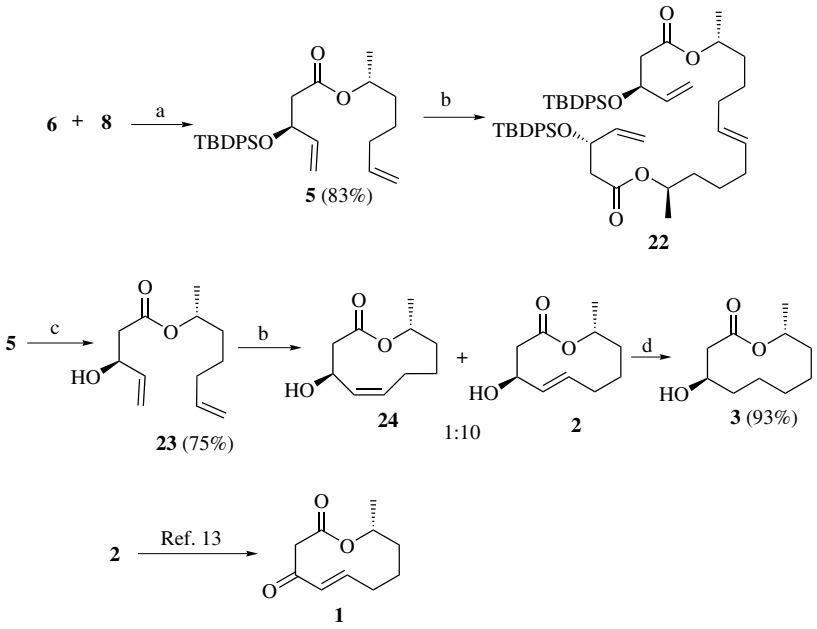
3. Conclusion

In conclusion, a convergent total synthesis of (+)-diplodialide-B and -C has been achieved very efficiently. Both the requisite segments with two stereogenic centers were prepared from Jacobsen and Sharpless reactions, while RCM was used to build the carbon framework.

4. Experimental

4.1. General

All moisture sensitive reactions were performed under a nitrogen atmosphere using flame-dried glassware. The solvents were dried over standard drying agents and freshly distilled prior to use. NMR spectra were recorded on Varian Gemini FT-200 MHz, Unity-400 MHz (21 °C), and In-



Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, THF, Et_3N, rt, 6 h, DMAP, toluene, rt, 14 h; (b) Grubb's catalyst **I**, CH_2Cl_2, reflux, 48 h; (c) HF-pyridine, THF, rt, 12 h; (d) 10% Pd–C, H_2, EtOAc, rt, 4 h.

ova-500 MHz (30 °C) spectrometers, with 7–10 mM solutions in appropriate solvents using TMS as an internal standard. ^{13}C NMR spectra were recorded with complete proton decoupling. Optical rotations were measured with a JASCO DIP-370 instrument, and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a Perkin–Elmer 1310 spectrometer. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system and FABMS were measured using VG AUTOSPEC mass spectrometers at 5 or 7 K resolution using perfluorokerosene as an internal reference. Nomenclature mentioned in Section 3 was adopted from ACD/Name Version 1.0β, Advanced Chemistry Development Inc., and Toronto, Canada. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo.

4.1.1. (*R*)-Propylene oxide 7 and (*S*)-propane 1,2-diol 11. A mixture of (*S*,*S*)-(−)-*N*-*N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.241 g, 0.40 mmol) in toluene (0.5 mL) and acetic acid (0.48 g, 0.80 mmol) was stirred while open to the air for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure and the brown residue was dried under vacuum. The racemic epoxide **10** (11.6 g, 200 mmol) was added in one portion at 0 °C, and water (2.0 mL, 110 mmol) was added dropwise over 5 min. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. (*R*)-Propylene oxide **7** (5.0 g, 43%) $[\alpha]_D = -10.8$ (*c* 1.0, $CHCl_3$) {lit.[5a] $[\alpha]_D^{27} = -11.6$ (neat)} was isolated by distillation from the reaction mixture at atmospheric pressure and diol **11** was removed by vacuum distillation (65 °C) to furnish 40% as colorless liquid, $[\alpha]_D = +15.5$ (neat) {lit.[5b] $[\alpha]_D = +16.0$ (neat)}, ^1H NMR ($CDCl_3$, 300 MHz): δ 1.27 (d, 3H, $J = 6.0$ Hz, $-CH_3$), 2.05 (br s, 1H, OH), 3.55 (t, 2H, $J = 6.0$ Hz, CH_2), 3.90 (q, 1H, $J = 6.0$ Hz, CH); IR (neat) 3440, 3387, 1025, 820 cm^{-1}; EIMS (*m*/*z*): 76 (M^+).

4.1.2. (*R*)-6-Benzyloxy-hex-4-yn-2-ol 12. *n*-BuLi (24.77 mL, 41.37 mmol, 1.6 N hexane solution) was added dropwise to a solution of 1-[(2-propynyloxy)methyl]benzene (5.53 g, 37.93 mmol) in dry THF (40 mL) under an N_2 atmosphere at −78 °C and stirred for 30 min. The reaction mixture was sequentially treated with $BF_3{\cdot}OEt_2$ (4.77 mL, 41.37 mmol) and a solution of (*R*)-propylene oxide **7** (2.0 g, 34.48 mmol) in dry THF (10 mL) after 10 min interval and stirred for an additional 3 h at −78 °C. Saturated $NaHCO_3$ solution (20 mL) followed by saturated NH_4Cl solution (20 mL) was added to the reaction mixture at −78 °C and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3 × 50 mL), washed with water (1 × 20 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by column chromatography (silica gel, EtOAc–hexane, 1.5:8.5) to furnish **12** (4.5 g, 64%) as a yellow syrup. $[\alpha]_D^{27} = -5.9$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.28 (d, 3H, $J = 6.0$ Hz, $-CH_3$), 1.90 (br s, 1H, OH), 2.40 (m, 2H, CH_2), 3.95 (sextet, 1H, $J = 6.0$ Hz, CH), 4.16 (t, 2H, $J = 6.0$ Hz, CH_2), 4.60 (s, 2H, $-CH_2Ph$), 7.30–7.40 (m, 5H, Ar–H); IR (neat) 3447, 2930, 2857, 1465, 1381 cm^{-1}; EIMS (*m*/*z*, %): 204 (M^+) (56), 113 (43), 91 (100).

4.1.3. (*R*)-6-Benzyloxy-hex-4-yn-2-yloxy-*tert*-butyldiphenylsilane 13. To a cooled (0 °C) solution of **12** (3.0 g, 14.70 mmol) in CH_2Cl_2 (20 mL), imidazole (1.49 g, 22.05 mmol) was added followed by TBDPSCl (4.43 g, 16.17 mmol) and stirred for 4 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl solution (15 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layer was washed with water

(1 × 20 mL), brine (1 × 20 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by column chromatography (silica gel, EtOAc–hexane, 0.2:9.8) to give **13** (6.1 g, 94%) as a colorless liquid. $[\alpha]_D^{27} = +18.75$ (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 9H, 3 × CH_3), 1.25 (d, 3H, $J = 6.2$ Hz, –CH_3), 2.40 (m, 2H, CH_2), 4.0 (sextet, 1H, $J = 6.0$ Hz, CH), 4.10 (d, 2H, $J = 6.2$ Hz, CH_2), 4.55 (s, 2H, CH_2), 7.20–7.40 (m, 11H, Ar–H), 7.60–7.70 (m, 4H, Ar–H); IR (neat): 3250, 2851, 1462, 1221, 1087 cm^{-1}; ESIMS (*m*/*z*, %): 443 (M^++1, 56).

4.1.4. (*R*)-5-*tert*-Butyldiphenylsilyloxy-hexan-1-ol 14. To a stirred solution of **13** (3.0 g, 6.78 mmol) in EtOAc (10 mL), 10% palladium adsorbed on carbon (Pd–C) was added and stirred under H_2 atmosphere for 12 h at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to furnish **14** (2.50 g, 93%) as a colorless syrup. $[\alpha]_D^{27} = +9.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 9H, 3 × CH_3), 1.10 (d, 3H, $J = 5.4$ Hz, –CH_3), 1.20–1.50 (m, 6H, 3 × CH_2), 3.50 (t, 2H, $J = 5.4$ Hz, CH_2), 3.81 (sextet, 1H, $J = 5.4$ Hz, CH), 7.25–35 (m, 6H, Ar–H), 7.65–7.75 (m, 4H, Ar–H); IR (neat): 3368, 2934, 2859, 1428, 1108, 1055 cm^{-1}; ESIMS (*m*/*z*, %): 357 (M^+, 42).

4.1.5. (*R*)-6-*tert*-Butyldiphenylsilyloxy-hept-1-ene 16. To a stirred solution of **14** (1.5 g, 4.21 mmol) in dry DMSO (3 mL), IBX (1.77 g, 6.32 mmol) was added at 0 °C and stirred for 6 h at room temperature. The reaction mixture was quenched with satd $NaHCO_3$ solution (5 mL). The crude reaction mixture was filtered and washed with EtOAc (2 × 10 mL). The organic layer was washed with water (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to obtain (*R*)-5-*tert*-butyldiphenylsilyloxy-hexanal **15**.

To a solution of (methyl)triphenylphosphonium iodide (3.0 g, 7.34 mmol) in dry THF (30 mL), *n*-BuLi (4.58 mL, 7.34 mmol, 1.6 M solution in *n*-hexane) was added at −20 °C and stirred for 30 min. A solution of **15** (1.30 g, 3.67 mmol) in THF (15 mL) was added dropwise and stirred for 2 h at room temperature. Saturated aqueous NH_4Cl solution (15 mL) was added and extracted with EtOAc (3 × 20 mL). The organic layer was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by column chromatography (silica gel 60–120 mesh, EtOAc–hexane, 0.1:9.9) to furnish **16** (0.87 g, 67%) as a pale yellow liquid. $[\alpha]_D^{27} = +15.1$ (*c* 1.15, $CHCl_3$), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 9H, 3 × CH_3), 1.07 (d, 3H, $J = 6.0$ Hz, –CH_3), 1.30–1.50 (m, 4H, 2 × CH_2), 1.95 (q, 2H, $J = 6.4$ Hz, CH_2), 3.80 (sextet, 1H, $J = 5.6$ Hz, CH), 4.80–5.0 (m, 2H, olefin), 5.60–5.80 (m, 1H, olefin), 7.20–7.40 (m, 6H, Ar–H), 7.60–7.70 (m, 4H, Ar–H); IR (neat): 3435, 3071, 2932, 1635, 1467, 1134 cm^{-1}; EIMS (*m*/*z*, %): 353 (M^+, 45), 238 (76); Anal. Calcd for $C_{23}H_{32}OSi$ (353): C, 78.35; H, 9.15. Found: C, 78.26; H, 9.08.

4.1.6. (*R*)-Hept-6-en-2-ol 6. A solution of **16** (0.60 g, 1.70 mmol) in dry THF (2 mL) was treated with HF-pyridine and stirred at room temperature for 12 h. The reaction mixture was quenched with satd $NaHCO_3$ solution and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by column chromatography (silica gel 60–120 mesh, EtOAc–hexane, 0.1:9.9) to furnish **6** (0.160 g, 82%) as a pale yellow liquid. $[\alpha]_D^{27} = -13.2$ (*c* 1.1, $CHCl_3$), ^1H NMR ($CDCl_3$, 400 MHz): δ 1.15 (d, 3H, $J = 6.0$ Hz, –CH_3), 1.30–1.60 (m, 4H, 2 × CH_2), 2.00–2.10 (m, 2H, CH_2), 3.70–3.70 (m, 1H, CH), 4.90–5.05 (m, 2H, olefin), 5.70–5.80 (m, 1H, olefin); IR (neat): 3435, 1635, 1455, 1130, 982 cm^{-1}; EIMS (*m*/*z*, %): 137 (M^++Na, 75); Anal. Calcd for $C_7H_{14}O$ (114): C, 73.63; H, 12.36. Found: C, 73.55; H, 12.30.

4.1.7. (2*S*,3*S*)-1-Chloro-2,3-epoxy-5-4-benzyloxy-1-pentane 17. To a stirred solution of epoxide **9** (1.50 g, 7.21 mmol) in dry CCl_4 (10 mL), Ph_3P (3.75 g, 14.42 mmol), and $NaHCO_3$ (0.30 g, 0.72 mmol) were added and heated at reflux for 4 h. CCl_4 was evaporated under reduced pressure and the residue obtained was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 0.5:9.5) to afford **17** (1.40 g, 86%) as a colorless syrup. $[\alpha]_D^{27} = +19.5$ (*c* 1.5, $CHCl_3$), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.70–2.05 (m, 2H, CH_2), 2.85–3.05 (m, 2H, 2 × CH), 3.40–3.60 (m, 4H, 2 × CH_2), 4.44 (s, 2H, –CH_2Ph), 7.22–7.35 (m, 5H, Ar–H); IR (neat): 2920, 2860, 1700, 1520, 1220 cm^{-1}; EIMS (*m*/*z*, %): 227 (M^+, 38), 173 (20), 161 (35), 107 (100).

4.1.8. (3*S*)-3-Hydroxy-5-4-benzyloxy-1-pentene 18. A solution of **17** (1.20 g, 5.30 mmol) in dry ether (10 mL) was added dropwise to a stirred suspension of freshly prepared sodium sand (0.24 g, 10.61 mmol) in dry ether (10 mL) under an N_2 atmosphere at room temperature for 4 h. After complete addition, the reaction mixture was allowed to stir for further 2 h. Then it was carefully quenched with MeOH (10 mL) at 0 °C, diluted with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 1:9) to give **18** (0.83 g, 82%) as a colorless syrup. $[\alpha]_D^{27} = -9.0$ (*c* 0.4, $CHCl_3$), ^1H NMR ($CDCl_3$, 200 MHz): δ 1.60–1.90 (m, 2H, CH_2), 2.70 (br s, 1H, OH), 3.55–3.75 (m, 2H, CH_2), 4.40 (q, 1H, $J = 6.0$ Hz, CH), 4.50 (s, 2H, –CH_2Ph), 5.00–5.30 (m, 2H, olefin), 5.75–5.90 (m, 1H, olefin), 7.20–7.35 (m, 5H, Ar–H); IR (neat): 2950, 2865, 1650, 1560, 1240 cm^{-1}; EIMS (*m*/*z*, %): 192 (M^+, 23); Anal. Calcd for $C_{12}H_{16}O_2$ (192): C, 74.97; H, 8.39. Found: C, 74.94; H, 8.30.

4.1.9. (3*S*)-3-*tert*-Butyldiphenylsilyloxy-5-4-benzyloxy-1-pentene 19. To a stirred solution of **18** (0.50 g, 2.60 mmol) in CH_2Cl_2 (10 mL), imidazole (0.26 g, 3.90 mmol), and TBDPSCl (0.85 g, 3.12 mmol) were added and stirred for 3 h. The reaction mixture was treated with satd NH_4Cl (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was washed with water (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4, evaporated, and the residue obtained was purified by column chromatography (60–120 silica gel, 0.3:9.7 EtOAc–hexane) to furnish **19** (1.0 g, 89%) as a colorless syrup. $[\alpha]_D^{28} = -21.2$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.12 (s, 9H, 3 × CH_3), 1.65–1.95 (m, 2H, CH_2), 3.50–3.75 (m, 2H, CH_2), 4.38 (q, 1H, $J = 5.4$ Hz, CH), 4.50 (s, 2H, –CH_2Ph),

5.05–5.30 (m, 2H, olefin), 5.70–5.80 (m, 1H, olefin), 7.20–7.45 (m, 11H, Ar–H), 7.60–7.70 (m, 4H, Ar–H); IR (neat): 2950, 2865, 1650, 1560, 1240 cm^{-1}; EIMS (*m*/*z*, %): 430 (M^+, 42), 238 (78), 77 (100).

4.1.10. (3*S*)-3-*tert*-Butyldiphenylsilyloxy-5-4-hydroxy-1-pentene 20. To a stirred solution of **19** (0.90 g, 2.94 mmol) in dichloromethane–water (19:1, 10 mL), DDQ (3.33 g, 14.70 mmol) was added and stirred at reflux for 4 h. Satd aq $NaHCO_3$ solution (10 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, and concentrated. The crude residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 0.8:9.2) to afford **20** (0.71 g, 84%) as a yellow syrup. $[\alpha]_D^{28} = -12.1$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.10 (s, 9H, $3 \times CH_3$), 1.60–1.80 (m, 2H, CH_2), 3.50–3.80 (m, 2H, CH_2), 4.40 (q, 1H, $J = 6.1$ Hz, CH), 5.00–5.25 (m, 2H, olefin), 5.70–5.90 (m, 1H, olefin), 7.35–7.45 (m, 6H, Ar–H), 7.65 (m, 4H, Ar–H); IR (neat): 3035, 2860, 1635, 1542, 1244, 1087 cm^{-1}; EIMS (*m*/*z*, %): 363 (M^++Na, 77), 238 (34), 161 (30), 107 (100).

4.1.11. (3*S*)-3-*tert*-Butyldiphenylsilyloxy-pent-5-enoic acid 8. To a stirred solution of oxalyl chloride (0.25 mL, 2.10 mmol), in dry CH_2Cl_2 (10 mL), DMSO (0.26 mL, 4.20 mmol) was added at −78 °C and stirred at the same temperature for 30 min. A solution of **20** (0.60 g, 1.76 mmol) in dry CH_2Cl_2 (20 mL) was added at −78 °C to the reaction mixture and stirred for 2.5 h at the same temperature. Et_3N (2.52 mL, 8.40 mmol) was added at 0 °C and stirred for an additional 30 min. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to give (3*S*)-3-*tert*-butyldiphenylsilyloxy-pent-5-enal **21** (0.51 g, 85%) as a pale yellow syrup.

To a stirred solution of **21** (0.50 g, 1.47 mmol) in *tert*-butanol–water (7:3, 10 mL), sodium chlorite (0.16 g, 1.77 mmol), NaH_2PO_4 (0.27 g, 1.77 mmol), and 2-methyl-2-butene (0.5 mL) were added and stirred at room temperature for 10 h. The reaction mixture was concentrated, the residue dissolved in ethyl acetate (10 mL), washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 2:8) to afford **8** (0.47 g, 91%) as a pale yellow syrup. $[\alpha]_D^{28} = -10.0$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 9H, $3 \times CH_3$), 2.40 (dd, 1H, $J = 3.5$, 7.0 Hz, CH), 2.55 (dd, 1H, $J = 3.0$, 6.5 Hz, CH), 4.55 (q, 1H, $J = 6.5$ Hz, CH), 5.0–5.20 (m, 2H, olefin), 5.80–5.90 (m, 1H, olefin), 7.35 (m, 6H, Ar–H), 7.65 (m, 4H, Ar–H); IR (neat): 3546, 3070, 2934, 2858, 1780, 1589, 1428, 1240 cm^{-1}; EIMS (*m*/*z*, %): 353 (M^++1, 64), 107 (100); Anal. Calcd for $C_{21}H_{26}O_3Si$ (352): C, 71.15; H, 7.39. Found: C, 71.06; H, 7.32.

4.1.12. (1*R*)-1-Methyl-5-hexenyl (3*S*)-3-*tert*-butyldiphenylsilyloxy-4-pentenoate 5. To a stirred solution of **8** (0.20 g, 0.56 mmol) in dry THF (5 mL), Et_3N (0.114 mL, 1.12 mmol) was added at room temperature and stirred for 30 min. A solution of 2,4,6-trichlorobenzoyl chloride (0.137 g, 0.56 mmol) in dry THF (2 mL) was added to the reaction mixture and stirred for 5 h at room temperature. The solvent was evaporated, the residue diluted with toluene (20 mL), and treated with DMAP (0.136 g, 1.12 mmol) and **6** (0.064 g, 0.56 mmol). After 14 h, toluene was evaporated and the crude residue purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 0.4:9.6) to afford **5** (0.105 g, 83%) as a colorless syrup. $[\alpha]_D^{28} = -22.0$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 9H, $3 \times CH_3$), 1.15 (d, 3H, $J = 3.5$ Hz, CH_3), 1.25–1.50 (m, 4H, $2 \times CH_2$), 2.00 (q, 2H, $J = 6.0$ Hz, CH_2), 2.40 (dd, 1H, $J = 3.5$, 7.5 Hz, CH), 2.50 (dd, 1H, $J = 1.7$, 8.5 Hz, CH), 4.55 (q, 1H, $J = 6.0$ Hz, CH), 4.85 (sextet, 1H, $J = 5.8$ Hz, CH), 4.90–5.05 (m, 4H, olefinic), 5.65–5.90 (m, 2H, olefinic), 7.30–7.45 (m, 6H, Ar–H), 7.65 (t, 4H, $J = 3.5$ Hz, Ar–H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.35, 139.5, 138.4, 136.56, 130.0, 127.52, 116.5, 114.8, 72.10, 66.85, 44.40, 35.5, 33.2, 27.26, 20.85; IR (neat): 3540, 3025, 2910, 1777, 1580, 1425, 1240, 1058 cm^{-1}; FABMS (*m*/*z*, %): 451 (M^+, 75), 107 (100); Anal. Calcd for $C_{28}H_{38}O_3Si$ (450): C, 74.62; H, 8.50. Found: C, 74.54; H, 8.42.

4.1.13. Preparation of dimer 22. Ester **5** (0.020 g, 0.047 mmol) dissolved in freshly distilled degassed anhydrous CH_2Cl_2 (100 mL) was treated with Grubbs' catalyst **I** (0.048 g, 0.0589 mmol) and heated at reflux for 2 days under a nitrogen flow until TLC (hexane–EtOAc; 80:20) showed the complete disappearance of the starting material. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2 h under air bubbling in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 0.2:9.8) to furnish **22** (0.027 mg, 70%) as a colorless syrup. $[\alpha]_D^{28} = +18.5$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.05 (s, 18H, $6 \times CH_3$), 1.15 (d, 6H, $J = 6.4$ Hz, $2 \times CH_3$), 1.25–1.50 (m, 8H, $4 \times CH_2$), 1.85–2.05 (m, 4H, $2 \times CH_2$), 2.40 (dd, 4H, $J = 3.5$, 7.5 Hz, $2 \times CH_2$), 4.55 (q, 2H, $J = 7.2$ Hz, $2 \times CH$), 4.80 (sextet, 2H, $J = 5.6$ Hz, $2 \times CH$), 4.90–5.00 (m, 4H, olefinic), 5.22–5.35 (m, 2H, olefinic), 5.70–5.90 (m, 2H, olefinic), 7.25–7.40 (m, 6H, Ar–H), 7.60–7.70 (m, 4H, Ar–H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.5, 139.8, 138.4, 136.2, 131.0, 130.6, 128.6, 127.1, 71.10, 65.7, 45.5, 35.0, 33.1, 27.8, 20.9; IR (neat): 3542, 3020, 2925, 1770, 1610, 1425, 1245, 1052 cm^{-1}; FABMS (*m*/*z*, %): 873 (M^+, 85); Anal. Calcd for $C_{54}H_{72}O_6Si_2$ (873): C, 74.27; H, 8.31. Found: C, 74.50; H, 8.25.

4.1.14. (3*S*)-(*R*)-Hept-6-en-2-yl 3-hydroxy pent-4-enoate 23. A solution of **5** (0.10 g, 1.66 mmol) in THF (1 mL) was taken in a plastic bottle, and HF-pyridine (2–3 drops) was added at 0 °C and stirred at room temperature for 12 h. The reaction mixture was quenched with satd $NaHCO_3$ solution (5 mL) at 0 °C and extracted with EtOAc (2 × 50 mL). The organic layer was washed with satd $CuSO_4$ solution (5 mL), dried over Na_2SO_4, and the residue obtained was purified by column chromatography (sil-

ica gel, 60–120 mesh, EtOAc–hexane, 2:8) to afford **23** (0.035 g, 75%) as a colorless syrup. $[\alpha]_D^{28} = -9.5$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 1.15 (d, 3H, $J = 3.5$ Hz, CH_3), 1.25–1.50 (m, 4H, $2 \times CH_2$), 2.0 (q, 2H, $J = 5.0$ Hz, CH_2), 2.40 (dd, 1H, $J = 3.0$, 6.5 Hz, CH), 2.50 (dd, 1H, $J = 3.5$, 7.0 Hz, CH), 4.55 (q, 1H, $J = 5.2$ Hz, CH), 4.85 (sextet, 1H, $J = 5.6$ Hz, CH), 4.90–5.05 (m, 4H, olefin), 5.65–5.90 (m, 2H, olefin); IR (neat): 3546, 3070, 2934, 2858, 1780, 1589, 1428, 1240 cm^{-1}; EIMS (*m*/*z*, %): 213 (M^++1, 45).

4.1.15. Diplodialide-B 2 [(4*S*,10*R*)-4-hydroxy-10-methyl-3,4,7,8,9,10-hexahydro-2*H*-2-oxecini-ne] and *cis*-isomer 24. Ester **23** (0.010 g, 0.047 mmol) dissolved in freshly distilled degassed anhydrous CH_2Cl_2 (100 mL) was treated with Grubbs' catalyst **I** (0.048 g, 0.0589 mmol) and heated at reflux for 2 days under a nitrogen flow until TLC (hexane–EtOAc; 80:20) showed the complete disappearance of the starting material. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2 h under air bubbling in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane, 3:97) to allow the separation of the desired *trans* stereoisomer (*E*)-**2** (5 mg) and *cis* isomer *Z*-**24** (0.5 mg) as colorless syrups.

First eluted was (4*S*,5*E*,10*R*)-**2** $[\alpha]_D = -35.8$ (*c* 0.2, $CHCl_3$); {lit.[3] $[\alpha]_D^{28} = -37.3$ (*c* 0.93, $CHCl_3$)} ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, 3H, $J = 7.0$ Hz, $-CH_3$), 1.25 (br s, 1H, –OH), 1.40–2.0 (m, 4H, $2 \times -CH_2$), 2.00 (q, 2H, $J = 6.0$ Hz, $-CH_2$), 2.35 (dd, 1H, $J = 3.5$, 7.5 Hz, CH), 2.70 (dd, 1H, $J = 7.5$, 15.86 Hz, –CH), 4.38–4.50 (m, 1H, H-3), 4.70–4.80 (m, 1H, H-9), 5.32–5.55 (m, 2H, H-4, H-5); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.85, 27.26, 33.2, 35.5, 44.4, 66.8, 72.1, 128.2, 132.1, 168.8; IR (neat): 3545, 1720, 1250, 1144, 975 cm^{-1}; FABMS (*m*/*z*, %): 185 (M^++1, 25), 124 (37).

Second eluted was (4*S*,4*Z*,10*R*)-**24** $[\alpha]_D = -15.8$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.18 (d, 3H, $J = 7.0$ Hz, $-CH_3$), 1.40–1.95 (m, 4H, $2 \times -CH_2$), 2.05 (q, 2H, $J = 6.0$ Hz, $-CH_2$), 2.30 (dd, 1H, $J = 3.0$, 6.2 Hz, CH), 2.75 (dd, 1H, $J = 7.0$, 12.1 Hz, –CH), 4.38–4.55 (m, 1H, H-3), 4.75–4.83 (m, 1H, H-9), 5.10 (m, 1H, H-5), 5.25 (m, 1H, H-4); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 20.15, 26.5, 35.0, 44.2, 66.2, 72.0, 128.50, 132.5, 168.0; IR (neat): 3545, 1720, 1250, 1144, 975 cm^{-1}; FABMS (*m*/*z*, %): 185 (M^++1, 25), 124 (37).

4.1.16. Diplodialide-C 3. To a stirred solution of **2** (0.005 g, 6.78 mmol) in EtOAc (2 mL), 10% palladium adsorbed on carbon (Pd–C) was added and stirred under an H_2 atmosphere for 4 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure to obtain **3** (0.004 g, 93%) as a colorless syrup. $[\alpha]_D = -39.7$ (*c* 0.25, $CHCl_3$); {lit.[3] $[\alpha]_D^{28} = -41.0$ (*c* 0.61, $CHCl_3$)} ^1H NMR ($CDCl_3$, 500 MHz): δ 1.27 (d, 3H, $J = 6.6$ Hz, $-CH_3$), 1.30–1.85 (m, 10H, $5 \times -CH_2$), 2.47 (dd, 1H, $J = 9.77$, 15.78 Hz, –CH), 2.68 (dd, 1H, $J = 4.0$, 15.78 Hz, –CH), 4.05–4.13 (m, 1H, H-3), 4.93–5.03 (m, 1H, H-9); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 171.09, 72.41, 69.82, 44.11, 35.48, 31.33, 29.68, 26.70, 21.68, 20.32; IR (neat): 3642, 3435, 1726, 1264, 1140 cm^{-1}; FABMS (*m*/*z*, %): 168 (M^+, 68), 150 (56), 124 (26).

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