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Total synthesis of (+)-Cladospolide D

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Total synthesis of (+)-cladospolide D

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ABSTRACT

The asymmetric total synthesis of cladospolide D, a natural 12-membered macrolide antibiotic, has been accomplished in 12-steps. Sharpless asymmetric dihydroxylation, Grubbs' cross metathesis and Shiina lactonization have been employed as the key reactions for the installation of the desired stereocenter and the construction of the macrolactone framework.

1. Introduction

In 2001, Satoshi Omura et al. have isolated a new 12-membered γ -oxo-lactone, namely cladospolide D, along with two known cladospolides A and B from the fermentation broth of *Cladosporium* sp. FT-0012.¹ Species belonging to the genus *Cladosporium* have also produced a family of other fungal secondary metabolites, cladospolides A-C and *iso*-cladospolide B, which are plant-growth regulators.² Unlike these members, cladospolide D exhibited antimicrobial properties with IC₅₀ values of 0.1 and 29 μ g/mL against *Mucor recemosus* and *Pyricularia oryzae*, respectively. Although, the initial structural determination of cladospolide D was carried out during the isolation, the absolute and relative stereochemistry as well as the stereochemical assignment of the C2-C3 double bond

were correctly determined only after studies on its total synthesis independently by Hou et al.³ and O'Doherty et al.⁴ Later, Kaliappan and Si et al. also achieved the total synthesis of naturally occurring (+)-cladospolide D.⁵ In continuation of our research program on the total synthesis of bioactive natural macrolides,⁶ in particular the cladospolides,⁷ we herein report the asymmetric total synthesis of (+)-cladospolide D.

A retrosynthetic analysis suggests TBS-protected alkenol **7** could be a suitable starting material. Cladospolide D **1** could be prepared by Shiina lactonization of hydroxy acid **6**, which in turn could be obtained from alkenol **7** involving Sharpless asymmetric dihydroxylation for the installation of the C5-hydroxyl group and Grubbs' olefin metathesis to obtain the desired C2-C3 olefin functionality of the target molecule. The above reaction sequence has not been utilized previously for the synthesis of cladospolide D.

Figure 1. Structures of cladospolides A-D and *iso*-cladospolide

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

2. Results and discussion

As shown in Scheme 2, the synthesis of cladospolide D **1** began from the known alkenyl *tert*-butyldimethylsilyl ether **7**, which was obtained readily in two-steps from (*S*)-propylene oxide following the literature.⁸ Sharpless asymmetric

Scheme 2. Synthesis of (+)-cladospolide D **1**

dihydroxylation⁹ of alkene **7** with AD-mix- β , $\text{CH}_3\text{SO}_2\text{NH}_2$ and $t\text{BuOH}/\text{H}_2\text{O}$ (1:1) gave diol **8** in 80% yield as a separable diastereomeric mixture (95:5). Diol **8** was protected as its *para*-methoxybenzylidene acetal **9** in 90% yield, which was subsequently subjected to reductive opening under DIBAL-H in CH_2Cl_2 at -78°C to provide the primary alcohol **10** in 81% yield. Primary alcohol **10** was oxidized using IBX in CH_3CN to give the aldehyde, which upon treatment with vinylmagnesium bromide afforded allylic alcohol **11** as a diastereomeric mixture. To obtain the desired α , β -unsaturated ester, allylic alcohol **11** was subjected to a cross-metathesis reaction with ethyl acrylate using Grubb's second-generation catalyst (G-II),¹⁰ which provided **12** in 90% yield. The hydroxyl group of **12** was oxidized under Dess-Martin periodinane conditions to yield keto-ester **13** in 85% yield. Towards the macrolactonization, deprotection of *tert*-butyldimethyl silyl (TBS) was carried out under aq. HF in CH_3CN to obtain hydroxy keto-ester **14** in 95% yield. Hydrolysis of the ester group of **14** using LiOH in $\text{THF}:\text{H}_2\text{O}$ gave the hydroxyl acid **6** (90%), a key precursor for macrolactonization. Treatment of **6** under Shiina lactonization¹¹ with 2-methyl-6-nitrobenzoic anhydride (MNBA) in the presence of DMAP in toluene provided keto-lactone **15** in 35% yield. Finally, DDQ-mediated deprotection of the *para*-methoxy benzyl group of **15** provided the target molecule, cladospolide D, in 93% yield. The spectroscopic data (IR, ^1H and ^{13}C NMR) of **1** were identical and the specific rotation observed for **1**, $[\alpha]_{\text{D}}^{20} = +55.5$ (c 0.8, CH_3OH), is comparable with the reported data {lit: $[\alpha]_{\text{D}} = +56.0$ (c 1.00, CH_3OH)}.¹

3. Conclusion

In conclusion, the chemistry described herein defines an asymmetric approach for the construction of natural cladospolide D based on a Shiina lactonization strategy involving Sharpless

4. Experimental

4.1. General

All reagents and solvents were of reagent grade and used without further purification unless otherwise stated. All of the reactions were performed under N_2 in flame or oven dried glassware with magnetic stirring. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light and anisaldehyde or potassium permanganate or β -naphthol for visualization. Column chromatography was performed on silica gel (60–120 mesh) using hexanes and ethyl acetate as eluents. Evaporation of the solvents was conducted under reduced pressure at temperatures less than 45°C . IR spectra were recorded on Perkin–Elmer 683, Nicolet Nexus 670 spectrometer. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 solvent on a 300 MHz, 500 MHz and 600 MHz NMR spectrometer. Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (hertz) respectively. Chemical shifts are reported relative to a residual solvent as an internal standard for ^1H and ^{13}C (CDCl_3 : δ 7.26 ppm for ^1H and 77.0 ppm for ^{13}C). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H or LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system. Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2-mL cell with a path length of 1 dm.

4.1.1. (2*R*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol **8**

To a 500 mL round bottom flask, was added 85 mL of $t\text{BuOH}$, 85 mL of H_2O and AD-mix- β (27.3 g, 1.4 g / mmol) and methane sulfonamide (2.6 g, 19.5 mmol). The mixture was stirred at room temperature for 5 min, then cooled to 0°C . To this cooled solution, was added compound **7** (5 g, 19.5 mmol) and stirred for 24 h at 0°C . The reaction was quenched with saturated

sodium sulfite at room temperature. The mixture was diluted with EtOAc (50 mL) and after separation of the layers, the aqueous layer was further extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine solution (40 mL) and dried over Na₂SO₄. The crude mixture was purified by column chromatography (silica gel, 20→30% EtOAc in hexanes) to give compound **8** (4.37 g, 80% yield) as a clear colorless oil. $[\alpha]_{\text{D}}^{25} = +4.4$ (c 0.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 3.84 – 3.51 (m, 3H), 3.37 (dt, *J* = 37.7, 18.8 Hz, 1H), 2.27 – 2.03 (m, 2H), 1.59 – 1.14 (m, 10H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.00 (s, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 72.3, 68.64, 66.9, 39.6, 33.2, 29.7, 25.9, 25.6, 23.8, 21.9, 18.2, -4.4, -4.7; IR (KBr): 3365, 2932, 2858, 1464, 1374, 1253, 1134, 1066, 835, 774 cm⁻¹; MS (ESI): *m/z* 313 (M + Na)⁺; HRMS (ESI): *m/z* calcd for C₁₅H₃₄NaO₃Si (M + Na)⁺: 313.2168, found: 313.2181.

4.1.2. *tert*-Butyl(((2*S*)-7-((4*R*)-2-(4-methoxyphenyl)-1,3-dioxolan-4-yl)heptan-2-yl)oxy)dimethyl silane **9**

To a solution of diol **8** (3 g, 10.3 mmol) in CH₂Cl₂ (30 mL) were added *p*-MeOC₆H₄CH(OMe)₂ (2.1 mL, 0.656 mmol) and PPTS (259 mg, 1.03 mmol) and the resultant solution was stirred at room temperature for 4 h. The reaction mixture was neutralized with saturated NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (2 x 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 2 to 4 % EtOAc/hexanes) gave *p*-methoxybenzylidene acetal **9** (3.8 g, 90%) as a colorless oil; ¹H NMR (500 MHz, CDCl₃): δ 7.45 – 7.35 (m, 2H), 6.94 – 6.84 (m, 2H), 5.81 (d, *J* = 3.6 Hz, 1H), 4.29 – 4.04 (m, 2H), 3.81 (s, 3H), 3.79 – 3.74 (m, 1H), 3.63 (dt, *J* = 8.9, 7.1 Hz, 1H), 1.82 – 1.64 (m, 1H), 1.56 – 1.20 (m, 9H), 1.11 (d, *J* = 6.1 Hz, 3H), 0.88 (d, *J* = 2.7 Hz, 9H), 0.04 (d, *J* = 2.2 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 160.4, 128.1, 113.7, 103.9, 102.9, 70.8, 70.1, 68.6, 55.3, 39.6, 33.5, 29.7, 25.9, 25.8, 25.7, 23.8, 18.2, -4.4, -4.7; IR (KBr): 2930, 2857, 1615, 1516, 1464, 1376, 1250, 1080, 1037, 833, 774 cm⁻¹; MS (ESI): *m/z* 409 (M+H)⁺; HRMS (ESI): *m/z* calcd for C₂₃H₄₁O₄Si (M+H)⁺: 409.2769, found: 409.2780.

4.1.3. (2*R*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)-2-((4-methoxybenzyl)oxy)nonan-1-ol **10**

To a solution of the *p*-methoxybenzylidene acetal **9** (3 g, 7.35 mmol) in CH₂Cl₂ (30 mL) at -78 °C was added DIBAL-H (25% solution in *n*-hexane, 4.52 mL, 8.08 mmol) and the resultant solution was stirred at -78 °C for 2 h. The reaction was then quenched with saturated aqueous potassium sodium tartrate solution (20 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (silica gel, 20 to 30% EtOAc/hexanes) gave the alcohol **10** (2.71 g, 81%) as a colorless oil: $[\alpha]_{\text{D}}^{20} = -1.5$ (c 1.00, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 7.25 – 7.20 (m, 2H), 6.86 – 6.81 (m, 2H), 4.47 (dd, *J* = 49.0, 11.2 Hz, 2H), 3.76 (s, 3H), 3.75 – 3.69 (m, 1H), 3.67 – 3.57 (m, 1H), 3.50 – 3.39 (m, 2H), 1.86 (dd, *J* = 6.9, 4.8 Hz, 1H), 1.50 – 1.16 (m, 9H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), 0.00 (d, *J* = 1.5 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 159.2, 130.5, 129.3, 113.8, 79.4, 71.1, 68.5, 64.2, 55.2, 39.6, 30.7, 29.8, 25.9, 25.6, 25.3, 23.8, 18.1, -4.5, -4.7; IR (KBr): 3424, 2932, 2857, 1613, 1513, 1464, 1250, 1175, 1040, 834, 774 cm⁻¹; MS (ESI): *m/z* 433 (M + Na)⁺; HRMS (ESI): *m/z* calcd for C₂₃H₄₃O₄Si (M+H)⁺: 411.2925, found: 411.2937.

4.1.4. (4*R*,10*S*)-10-((*tert*-Butyldimethylsilyl)oxy)-4-((4-methoxybenzyl)oxy)undec-1-en-3-ol **11**

To a solution of **10** (1.5 g, 3.65 mmol) in MeCN (15 mL) was added IBX (1.53 g, 5.48 mmol) in one portion. The reaction mixture was refluxed for 2 h, cooled to room temperature and filtered over Celite. The filtrate was washed with saturated aq.NaHCO₃ solution (15 mL) and brine solution (15 mL). The solvent was removed under reduced pressure. The aldehyde obtained was dissolved in dry THF (15 mL) and stirred at -78 °C under N₂ (balloon). Vinyl magnesium bromide (1.0 M, in THF, 4.4 mL, 4.41 mmol) was then added slowly, after which the mixture was stirred at the same temperature for 2 h. To the reaction mixture saturated aq.NH₄Cl solution (15 mL) was added, followed by Et₂O (50 mL) and the phases were separated. The organic layer was washed with water (2x15 mL) and brine solution (15 mL) before being dried over anhydrous Na₂SO₄. Removal of the solvent by rotary evaporation and column chromatography on silica gel eluted with 10 % EtOAc in hexanes gave allyl alcohol **11** as a colorless oil (1.1 g, 85%); ¹H NMR (500 MHz, CDCl₃): δ 7.31 – 7.14 (m, 2H), 6.85 (t, *J* = 6.8 Hz, 2H), 5.89 – 5.75 (m, 1H), 5.37 – 5.10 (m, 2H), 4.48 (ddd, *J* = 28.3, 18.9, 10.9 Hz, 2H), 4.27 – 3.93 (m, 1H), 3.81 – 3.65 (m, 4H), 3.33 (ddd, *J* = 17.3, 9.5, 5.0 Hz, 1H), 1.45 – 1.24 (m, 10H), 1.09 – 1.03 (m, 3H), 0.89 – 0.79 (m, 9H), 0.03 – -0.03 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 159.3, 137.7, 136.7, 130.6, 130.4, 129.5, 129.5, 116.8, 116.4, 113.9, 82.0, 81.8, 74.4, 73.5, 72.3, 71.8, 68.8, 55.3, 39.7, 30.4, 29.9, 29.8, 29.3, 26.1, 25.8, 25.7, 25.1, 23.9, 18.2, -4.3, -4.6; IR (KBr): 3455, 2927, 2861, 1513, 1432, 1363, 1283, 1098, 1025, 834, 773 cm⁻¹; MS (ESI): *m/z* 459 (M + Na)⁺; HRMS (ESI): *m/z* calcd for C₂₅H₄₄NaO₄Si (M + Na)⁺: 459.2901, found: 459.2927.

4.1.5. Ethyl (5*R*,11*S*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-5-((4-ethoxybenzyl)oxy)dodec-2-enoate **12**

To a solution of compound **11** (0.9 g, 2.06 mmol) in anhydrous toluene (10 mL) was added ethyl acrylate (2.2 mL, 20.64 mmol) at room temperature. The reaction mixture was degassed under an argon atmosphere during 20 min. To this solution, was added Grubbs second generation catalyst (175 mg, 10 mol%). The resultant mixture was refluxed under an argon atmosphere for 2 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using EtOAc/hexane(10%) as an eluent to give the unsaturated ester compound **12** (0.94 g, 90%) as a colorless liquid; ¹H NMR (500 MHz, CDCl₃): δ 7.23 – 7.17 (m, 2H), 6.94 – 6.87 (m, 1H), 6.86 – 6.81 (m, 2H), 6.08 (m, 1H), 4.55 – 4.35 (m, 2H), 4.24 – 4.10 (m, 3H), 3.81 – 3.63 (m, 4H), 3.48 – 3.26 (m, 1H), 1.64 – 1.45 (m, 2H), 1.45 – 1.16 (m, 10H), 1.07 (dd, *J* = 6.1, 3.5 Hz, 3H), 0.87 – 0.77 (m, 9H), -0.00 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 166.4, 159.4, 147.4, 145.9, 130.1, 130.0, 129.6, 121.8, 113.9, 81.2, 81.1, 72.4, 71.9, 71.6, 68.6, 60.4, 55.3, 39.7, 30.8, 29.9, 29.7, 29.4, 25.9, 25.7, 25.3, 23.8, 18.2, 14.3, -4.3, -4.7; IR (KBr): 3467, 2930, 2856, 1719, 1513, 1303, 1251, 1175, 1039, 834, 773 cm⁻¹; MS (ESI): *m/z* 531 (M + Na)⁺; HRMS (ESI): *m/z* calcd for C₂₈H₄₈NaO₆Si (M + Na)⁺: 531.3112, found: 531.3141.

4.1.6. Ethyl (5*R*,11*S*,*E*)-11-((*tert*-butyldimethylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-4-oxododec-2-enoate **13**

To a stirred solution of alcohol **12** (750 mg, 1.47 mmol) in dry dichloromethane (10 mL) at 0 °C were added NaHCO₃ (248 mg, 2.95 mmol) and Dess-Martin periodinane (938 mg, 2.21 mmol) in one portion. The reaction mixture was stirred for 2 h at room temperature. The reaction was quenched with saturated aqueous Na₂S₂O₃ (10 mL). The layers were separated and the aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by column

chromatography (silicagel, hexanes : EtOAc = 90 : 10) to give ketone **13** (650 mg, 85 %) as a colourless oil. $[\alpha]_D^{20} = +46.8$ (c 1.07, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 7.40 (d, J = 15.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.89 – 6.84 (m, 2H), 6.77 (d, J = 15.8 Hz, 1H), 4.42 (dd, J = 58.0, 11.4 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (dd, J = 8.1, 5.2 Hz, 1H), 3.80 (s, 3H), 3.77 – 3.70 (m, 1H), 1.76 – 1.57 (m, 2H), 1.39 (ddd, J = 16.0, 11.6, 5.4 Hz, 2H), 1.35 – 1.31 (m, 5H), 1.25 (dd, J = 12.6, 6.4 Hz, 4H), 1.10 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.03 (d, J = 3.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 201.4, 165.4, 159.5, 134.7, 131.7, 129.9, 129.2, 113.9, 84.1, 72.3, 68.5, 61.3, 55.2, 39.5, 31.9, 29.4, 25.9, 25.5, 25.1, 23.8, 18.1, 14.1, -4.4, -4.7; IR (KBr): 2934, 2860, 1724, 1701, 1514, 1301, 1251, 1093, 1033, 772 cm⁻¹; MS (ESI): m/z 529 (M + Na)⁺; HRMS (ESI): m/z calcd for C₂₈H₄₇O₆Si(M+H)⁺: 507.3136, found: 507.3117.

4.1.7. Ethyl (5*R*,11*S*,*E*)-11-hydroxy-5-((4-methoxybenzyl)oxy)-4-oxododec-2-enoate **14**

To a flask solution of ketone **13** (530 mg, 1.04 mmol) in MeCN (7 mL) was added 5% HF in H₂O (0.1 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, after which EtOAc (10 mL) was added to dilute the reaction solution. The reaction mixture was washed with saturated NaHCO₃ solution (2x10 mL). The organic layer was dried over Na₂SO₄, filtered, and evaporated under reduced pressure. The crude product was purified using silica gel column chromatography (20% EtOAc in hexanes) to give **14** (390 mg, 95%) as a colorless oil. $[\alpha]_D^{20} = +51.6$ (c 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, J = 15.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.90 – 6.82 (m, 2H), 6.77 (d, J = 15.8 Hz, 1H), 4.54 – 4.33 (m, 2H), 4.30 – 4.24 (m, 2H), 3.91 (dd, J = 8.1, 5.2 Hz, 1H), 3.80 (s, 3H), 3.79 – 3.72 (m, 1H), 1.81 – 1.50 (m, 4H), 1.51 – 1.23 (m, 9H), 1.17 (d, J = 6.2 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 201.5, 165.5, 159.6, 134.7, 131.8, 129.9, 129.2, 113.9, 84.0, 72.3, 68.0, 61.4, 55.3, 39.1, 31.9, 29.2, 25.5, 25.1, 23.5, 14.1; IR (KBr): 3417, 2934, 2860, 1723, 1701, 1513, 1301, 1251, 1179, 1033, 772 cm⁻¹; MS (ESI): m/z 415 (M + Na)⁺; HRMS (ESI): m/z calcd for C₂₂H₃₂NaO₆ (M + Na)⁺: 415.2091, found: 415.2113.

4.1.8. (5*R*,11*S*,*E*)-11-Hydroxy-5-((4-methoxybenzyl)oxy)-4-oxododec-2-enoic acid **6**

A solution of ester **14** (310 mg, 0.79 mmol) in THF/ H₂O (2:1, 8 mL) was treated with LiOH.H₂O (56 mg, 2.37 mmol) at 0 °C. The reaction mixture was then stirred for 1.5 h at room temperature. The reaction was acidified with 10% aq. citric acid (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with brine solution (10 mL), dried over Na₂SO₄ and concentrated in vacuo. The crude acid was purified by silica gel column chromatography (50% ethyl acetate in hexanes) to give compound **6** (259 mg, 90%) as a colorless viscous oil. $[\alpha]_D^{20} = +5.0$ (c 1.25, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.45 (d, J = 15.8 Hz, 1H), 7.21 (d, J = 7.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 15.8 Hz, 1H), 4.44 (dd, J = 30.9, 11.4 Hz, 2H), 3.92 (dd, J = 7.9, 5.3 Hz, 1H), 3.80 (s, 3H), 3.76 (m, 1H), 1.79 – 1.52 (m, 2H), 1.51 – 1.21 (m, 8H), 1.18 (d, J = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 201.3, 168.8, 159.6, 136.2, 130.7, 130.0, 129.2, 113.9, 84.0, 72.4, 68.2, 55.3, 39.1, 31.9, 29.7, 29.2, 25.5, 23.5; IR (KBr): 2927, 2853, 1728, 1706, 1514, 1250, 1250, 1026, 772 cm⁻¹; MS (ESI): m/z 387 (M + Na)⁺; HRMS (ESI): m/z calcd for C₂₀H₂₈NaO₆ (M + Na)⁺: 387.1778, found: 387.1803.

4.1.9. (6*R*,12*S*,*Z*)-6-((4-Methoxybenzyl)oxy)-12-methyloxacyclododec-3-ene-2,5-dione **15**

In a 100-mL two neck flask were placed powdered flame-dried molecular sieves (4 Å, 2 g), DMAP (32 mg, 1.32 mmol) and 2-

methyl-6-nitrobenzoic anhydride (23 mg, 0.32 mmol) under a steady stream of argon. The flask was then charged with dry toluene (70 mL), and a solution of **6** (0.08 g, 0.21 mmol) in dry toluene (30 mL) was added to this suspension using a syringe pump (3 mL/h). After the addition was complete, it was stirred for another 6 h at room temperature. The reaction mixture was diluted with EtOAc (25 mL) and then filtered. The organic phase was washed with saturated aq. NaHCO₃ (2 x 10 mL) and brine solution (10 mL). The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The residue obtained was purified by silica gel column chromatography using petroleum ether:EtOAc (9:1) as eluent to furnish **15** (26 mg, 35%) as a colorless liquid: $[\alpha]_D^{20} = +45.2$ (c 0.55, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ 7.20 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 12.7 Hz, 1H), 6.17 (d, J = 12.7 Hz, 1H), 4.83 (ddd, J = 9.5, 6.2, 3.4 Hz, 1H), 4.43 (s, 2H), 4.11 – 4.00 (m, 1H), 3.74 (s, 3H), 2.07 – 1.48 (m, 5H), 1.49 – 1.24 (m, 5H), 1.21 (d, J = 4.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 202.1, 166.2, 159.5, 134.1, 130.6, 129.7, 129.6, 113.9, 81.2, 73.7, 71.5, 55.3, 33.4, 29.7, 27.0, 25.9, 22.0, 21.3, 20.2; IR (KBr): 2924, 2855, 1729, 1458, 1306, 1249, 1218, 878, 772 cm⁻¹; MS (ESI): m/z 369 (M + Na)⁺; HRMS (ESI): m/z calcd for C₂₀H₂₆NaO₅ (M + Na)⁺: 369.1672, found: 369.1701.

4.2.0. Cladospolide **D 1**

To a solution of **15** (10 mg, 0.03 mmol) in CH₂Cl₂ (3 mL) and pH 7 buffer solution (0.3 mL) was added DDQ (7.8 mg, 0.03 mmol) at 0 °C. The reaction mixture was stirred for 30 min, and then poured into water. The aqueous phase was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were washed with saturated aq. NaHCO₃ (10 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue obtained was purified by column chromatography (silica gel, hexanes: EtOAc = 80:10) to afford **1** (6 mg, 93%) as a colorless oil. $[\alpha]_D^{20} = +55.5$ (c 0.08, CH₃OH); ¹H NMR (300 MHz, CDCl₃): δ 6.35 (d, J = 13.4 Hz, 1H), 6.24 (d, J = 13.4 Hz, 1H), 5.23 – 5.08 (m, 1H), 4.60 (dd, J = 8.0, 3.2 Hz, 1H), 1.89 (dd, J = 13.7, 10.6 Hz, 2H), 1.75 – 1.49 (m, 4H), 1.49 – 1.21 (m, 4H), 1.24 (d, J = 6.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 203.5, 165.4, 133.3, 130.9, 73.5, 71.5, 33.2, 31.1, 23.0, 21.6, 21.5, 20.6; IR (KBr): 3452, 2929, 2845, 1729, 1453, 1118, 1012, 878, 772 cm⁻¹; MS (ESI): m/z 249 (M + Na)⁺; HRMS (ESI): m/z calcd for C₁₂H₁₈NaO₄ (M+H)⁺: 249.1097, found: 249.1102.

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