First total synthesis of (4R,5R,11S) and (4R,5R,11R)-iso-cladospolide B

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Abstract: The two enantiomers of natural products (4S, 5S, 11R)- and (4S, 5S, 11S)-iso-cladospolide B have been synthesized and their structures unambiguously confirmed by X-ray crystallographic analysis. Key steps of the synthesis include the use of tri-O-acetyl-D-glucal as precursor for a chiral furan diol which, after side chain transformation, underwent singlet oxygen oxidation to afford the target butenolides.

Keywords: Natural products; Singlet oxygen; Butenolide; Total synthesis; Lactones.

Introduction

(4S, 5S, 11R)- and (4S, 5S, 11S)-iso-cladospolide B and cladospolides A-D (Figure 1) are a family of fungal secondary metabolites which were isolated from marine fungi or from soil fungus1. While cladospolides A-D have macrolactonic structures, (4S, 5S, 11R)- and (4S, 5S, 11S)-iso-cladospolide B possess a butenolide moiety and were isolated from Red sea sponge Cladosporium sp. and also from fermentation of the marine fungal species 196S2152. The promising biological profiles of the iso-cladospolide family of natural products have attracted the interest of the synthetic community.3

Results and Discussion

We recently reported the synthesis of natural (4S, 5S, 11R)-iso-cladospolide B (5) and (4S, 5S, 11S)-iso-cladospolide B (6)3b from L-malic acid, confirming unambiguously their structures by X-ray crystallographic analysis. As part of our ongoing program focusing on the use of readily available chiral reagent tri-O-acetyl-D-glucal (9) for the synthesis of natural products4, we now wish to report the synthesis of (4R, 5R, 11S)-iso-cladospolide B (7) and (4R,5R,11R)-iso-cladospolide B (8) using this reagent. Compounds 7 and 8 are the enantiomers of 5 and 6 respectively. Our retrosynthetic basis is outlined in Scheme 1.


We anticipated that furan 11 could be obtained from diol 10, easily available from tri-O-acetyl-D-glucal (9) using a well documented methodology we already employed for the synthesis of chiral compounds\(^5\). Furan 11, on treatment with epoxide 12 would then lead to furan 13 containing the desired iso-cladospolide side chain, hence precursor of 7. Accordingly target compound 7 was prepared as outlined in Scheme 2.

Chiral diol 10 was easily prepared from tri-O-acetyl-D-glucal (9)\(^5\) and the hydroxyl groups were protected as tert-butyldimethylsilyl ethers affording 80% yield of 14. Selective
deprotection of the primary hydroxyl group gave alcohol 15 in 70% yield. TEMPO/Bis(acetoxy)iodobenzene (BAIB) oxidation of 15 followed by Wittig olefination with commercially available ylide 16 afforded a mixture of α,β-unsaturated esters 17 (66%, 2 steps). 17 was subsequently hydrogenated (99%) and reduced by DIBAL to provide 83% of aldehyde 19. Aldehyde 19 underwent an Ohira–Bestmann homologation to give alkyne 11 in 87% yield. Treatment of epoxide 12 with alkyne 11 in the presence of n-butyllithium and BF₃·OEt₃ in tetrahydrofuran gave the alkynol 21 in 97% yield. Protection of the hydroxyl group of 21 followed by catalytic hydrogenation afforded furan 13 in 80% overall yield. Singlet oxygen oxidation of furan 13 affored target compound 7 in 78% yield. The absolute configuration of (4R, 5R, 11S)-iso-cladospolide B (7) was confirmed unambiguously as that shown in Figure 2, by X-ray crystallographic analysis of the crystals obtained by recrystallization from hexane.

Figure 2. X-ray structure (ORTEP) of (4R, 5R, 11S)-iso-cladospolide B (7)

Alkyne 11 was transformed into (4R, 5R, 11R)-iso-cladospolide B (8) using epoxide 23 and following a similar sequence of reactions to that used to prepare its diastereoisomer 7 (Scheme 3).

Conclusion

In conclusion we carried out the synthesis of \((4R, 5R, 11S)\)- and \((4R, 5R, 11R)\)-iso-cladospolide B from cheap and commercially available tri-O-acetyl-D-glucal. By X-ray crystallographic analysis we unambiguously confirmed the structure of \((4R, 5R, 11S)\)-iso-cladospolide. The synthesized compounds are enantiomers of natural products \((4S, 5S, 11R)\)- and \((4S, 5S, 11S)\)-iso-cladospolide B and might be good candidates for biological evaluations. To the best of our knowledge the synthesis and full structure characterization of ent-5 and ent-6 is described here for the first time.

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Experimental Section

General Procedures

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded with a Bruker ARX-400 spectrometer (400 MHz for \(^1\)H NMR, 100.61 MHz for \(^{13}\)C NMR) using TMS as internal standard (Chemical shifts in \(\delta\) values, \(J\) in Hz). Flash chromatography (FC) was performed on silica gel (Merck 60, 230-400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25mm); mass spectra (FAB, EI) were recorded using FISONS VG and electron spray ionization (ESI-MS) spectroscopy was recorded using Bruker FTMS APEXIII. IR spectra were recorded with a JASCO FT/I(R)-6100 spectrophotometer.

\((1'R)-2-[1',2'-bis(tert-butyldimethylsilyloxy)ethyl]furan\) (14).

To a solution of diol 10 (891 mg, 6.95 mmol) in DMF (10 mL) we added imidazole (2.3 g, 35 mmol), DMAP (c.c.) and TBSCl (2.3 g, 15.3 mmol). Then, the mixture was stirred at r.t. for 20 h. EtOAc was added (10 mL) and washed with H\(_2\)O (3 x 10 mL). The organic layer was dried, filtered and concentrated. The residue was chromatographed on silica gel using 1% EtOAc / Hexane affording 14 as a yellowish oil; Yield: 1.9 g (80%); \(R_F = 0.85\) (20% EtOAc/Hexane); [\(\alpha\)]\(_D\)\(^{23}\) + 45.09 (c 1.0, CHCl\(_3\)). IR (NaCl, neat): 2958, 2926, 2857, 1468, 1257 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.37\) (d, \(J = 0.8\) Hz, 1 H, H-5); 6.33 (dd, \(J = 1.8\) Hz, 1 H, H-4); 6.25 (d, \(J = 3.1\) Hz, 1 H, H-3); 4.80-4.70 (m, 1 H, H-1'); 3.80-3.70 (m, 2 H, H-2'); 0.90 (s, 9 H, tBu-TBS); 0.88 (s, 9 H, tBu-TBS); 0.05 (m, 12 H, CH\(_3\)-TBS). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 155.21\) (C-2); 142.45 (CH-5); 110.02 (CH-3); 106.88 (CH-4); 70.07 (CH-1'); 67.02 (CH-2'); 25.91, 25.80 (CH\(_3\)-tBu-TBS); 18.29, 18.26 (C-tBu-TBS); -4.87, -5.06, -5.42, -5.52 (CH\(_3\)-TBS). MS (ESI\(^+\);m/z (%) = 381.20 ([M+Na+2]\(^+\), 9); 380.21 ([M+Na]\(^+\), 100); 374.25 (10); 156.12 (6). HRMS (ESI\(^+\))calcd for C\(_{18}\)H\(_{36}\)NaO\(_3\)Si\(_2\): 379.2095; found: 379.2091.
(2R)-2-(tert-butylidemethylsilyloxy)-2-(2'-furyl)ethanol (15).

To a solution of compound 14 (1.07 g, 3.01 mmol) in THF (18 mL) and pyridine (2.0 mL) cooled to 0 °C was added dropwise, a solution 30% (v/v) HF in pyridine (1.0 mL) and the reaction was stirred for 4 h at the same conditions. Then, EtOAc (38 mL) and sat. aq NaHCO₃ (38 mL) were added and the mixture was stirred for 10 min. The reaction was extracted with EtOAc (3 x 30 mL), dried and the solvent was removed in vacuo. The residue was chromatographed on silica gel using 1% EtOAc / Hexane → 50% EtOAc / Hexane to afford alcohol 15 as a colourless oil. Yield: 330 mg (45%); R<sub>f</sub> = 0.55 (20% EtOAc/Hexane); [α]<sub>23</sub> + 61.42 (c 10.4, CHCl₃). IR (NaCl, neat): 3430, 2952, 2929, 2848, 1470, 1250 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.36 (dd, J = 0.8 Hz, J = 1.8 Hz, 1 H, H-5'); 6.33 (dd, J = 1.8 Hz, J = 3.2 Hz, 1 H, H-4'); 6.27 (d, J = 3.2 Hz, 1 H, H-3'); 4.79 (dd, J = 4.5 Hz, J = 7.0 Hz, 1 H, H-2); 3.80-3.70 (m, 2 H, H-1); 2.36 (s broad, 1 H, -OH); 0.89 (s, 9 H, Bu-TBS); 0.98 (s, 3 H, CH₃-TBS); 0.04 (s, 3 H, CH₃-TBS). ¹³C NMR (100 MHz, CDCl₃): δ = 154.12 (C-2'); 141.91 (CH-5'); 110.21 (CH-3'); 107.22 (CH-4'); 69.27 (CH-2); 65.82 (CH₂-1); 25.76 (CH-3); 18.17 (CH₂-TBS); -4.98, -5.14 (CH₃-TBS). MS (ESI⁺): m/z (%) = 266.12 ([M+Na⁺]+, 12); 265.12 ([M+Na⁺]+, 56); 262.11 (18); 196.11 (100); 185.05 (28). HRMS (ESI⁺): calcd for C₁₂H₂₂NaO₃Si: 265.1230; found: 265.1235.

(4R)-Ethyl 4-(tert-butylidemethylsilyloxy)-4-(2'-furyl)but-2-enolate (17).

To a solution of a solution of alcohol 15 (366 mg, 1.51 mmol) in CH₂Cl₂ (15 mL), were added BAIB (560 mg, 1.73 mmol) and TEMPO (catalytic amount). The reaction was stirred at r.t. for 6 h. Then, (Ethoxycarbonylmethylen)-triphenylphosphoran 16 (788 mg, 2.26 mmol) was added and the reaction was stirred at r.t. for 23 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc (10 mL). The organic layer was washed with sat. aq NaHCO₃ (x10 mL), then with sat. aq NaHCO₃ (3x10 mL) and with brine (3 x 10 mL). The organic layer was dried and the solvent was removed in vacuo, the residue was chromatographed on silica gel using 1% EtOAc / Hexane → 10% EtOAc / Hexane to afford ester 17, as a brown oil. Yield: 307 mg, (66%); R<sub>f</sub> = 0.91 (20% EtOAc/Hexane); [α]<sub>23</sub> + 20.83 (c 4.93, CHCl₃). IR (NaCl, neat): 2952, 2916, 2852, 1794, 1716, 1457 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.38-7.36 (m, 1 H, H-5'); 7.06 (dd, J = 4.2 Hz, J = 15.4 Hz, 1 H, H-3); 6.6-6.14 (m, 3 H, H-3', 4' and 3); 5.82 (d, J = 11.4 Hz, 1 H, H-2); 5.39 (dd, J = 1.7 Hz, J = 4.2 Hz, 1 H, H-2'; 4.22 (m, 2 H, -CH₂O-); 1.30 (t, J = 7.0 Hz, 3 H, CH₃-); 0.91 and 0.69 (2s, 9 H, Bu-TBS); 0.10-0.004 (m, 12 H, CH₃-TBS). ¹³C NMR (100 MHz, CDCl₃): δ = 166.47, 165.62 (C=O); 154.76, 153.69 (C-2'); 148.17, 146.19 (CH-3); 142.29, 142.16 (CH-5'); 120.81, 118.96 (CH-2); 110.35, 110.13 (CH-3'); 107.13, 106.47 (CH-4'); 67.63, 64.29 (CH-4); 60.46, 60.29 (-CH₂O-); 25.76 (CH-3); 18.29, 18.24 (C-3Bu-TBS); 14.24, 14.19 (CH₃-); -4.98, -4.91, -5.11 (CH₃-TBS). MS (ESI⁺): m/z (%) = 391.29 (13); 365.14 (17); 243.14 (14); 196.12 (100). HRMS (ESI⁺): calcd for C₁₆H₂₆O₄Si: 310.1600; found: 310.1607.

Ethyl (4R)-4-(tert-butylidemethylsilyloxy)-4-(2'-furyl)butanoate (18).

To a solution of alkene 17 (503 mg, 1.62 mmol) in hexane (10 mL) was added Pd/C 5 % catalyst (71 mg). The mixture was stirred in H₂ atmosphere at r.t. for 1 h. After filtration, the filtrate was evaporated to afford ester 18 as a yellow oil. Yield: 506 mg, (99%); R<sub>f</sub> = 0.75 (20% EtOAc/Hexane); [α]<sub>23</sub> + 31.59 (c 1.0, CHCl₃). IR (NaCl, neat): 2955, 2932, 2857, 1735, 1467 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.23 (m, 1 H, H-5'); 6.18 (m, 1 H, H-4'); 6.08 (d, J = 3.1 Hz, 1 H, H-3'); 1.49 (m, 1 H, H-4); 0.40 (q, J = 7.1 Hz, 2 H, -CH₂O-); 2.26 (m, 2 H, H-2); 2.01 (m, 2 H, H-3); 1.13 (t, J = 7.2 Hz, 3 H, CH₃-); 0.77 (s, 9 H, Bu-TBS); -
0.05 (s, 3 H, CH₃-TBS); -0.18 (s, 3 H, CH₃-TBS). ¹³C-NMR (100 MHz, CDCl₃): δ = 173.09 (C=O); 156.32 (C-2'); 141.29 (CH-5'); 109.86 (CH-3'); 105.93 (CH-4'); 67.22 (CH-4); 60.03 (-CH₂-O-); 31.71, 29.69 (CH₂-3 and 2); 25.60 (CH₃-Bu-TBS); 17.98 (C-Bu-TBS); 14.05 (CH₃-); -5.20, -5.42 (CH₃-TBS). MS (ESI⁺): m/z (%) = 335.16 ([M+Na]⁺, 31); 317.21 (39); 312.16 ([M⁺, 3); 196.11 (83); 185.11 (22); 181.08 (100); 153.05 (40). HRMS (ESI⁺): calcd for C₁₆H₂₈NaO₄Si: 335.1649; found: 335.1661.

(4R)-4-(tert-butyldimethylsiloxy)-4-(2'-furyl)butan-1-al (19).

To a solution of 18 (530 mg, 1.69 mmol) in CH₂Cl₂ (10 mL) cooled to 78 °C was added, dropwise, Dibal·H 1M in hexane (2.0 mL, 2.03 mmol) and the reaction was stirred for 1 h in the same conditions. Then, BuOMe (2.2 mL) and H₂O (140 µL) were added and the mixture was stirred until the formation a white gel. H₂O (140 µL) and aqNaOH 4 N (140 µL) were added and the mixture was stirred until the formation a white solid. The solvent was removed in vacuo to give a residue which was chromatographed on silica gel using 1% EtOAc / Hexane → 5% EtOAc / Hexane affording aldehyde 19 as a colourless oil. Yield: 378 mg, (83%); Rᵢ = 0.77 (20% EtOAc/Hexane); [α]²²D + 68.32 (c 1.0, CHCl₃). IR (NaCl, neat): 2955, 2929, 2857, 1723, 1467 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 9.77 (t, J = 1.5 Hz, 1 H, H-1); 7.36 (m, 1 H, H-5'); 6.33 (dd, J = 1.8 Hz, J = 3.2 Hz, 1 H, H-4'); 6.21 (d, J = 3.2 Hz, 1 H, H-3'); 4.81 (m, 1 H, H-4); 2.52 (m, 2 H, H-2); 2.14 (m, 2 H, H-3); 0.89 (s, 9 H, Bu-TBS); 0.06 (s, 3 H, CH₃-TBS); -0.06 (s, 3 H, CH₃-TBS). ¹³C-NMR (100 MHz, CDCl₃): δ = 202.31 (HC=O); 156.18 (C-2'); 141.54 (CH-5'); 110.08 (CH-4'); 106.30 (CH-3'); 67.47 (CH-4); 39.60, 29.41 (CH₂-2 and 3); 25.76 (CH₃-Bu-TBS); 18.16 (C-Bu-TBS); -5.02, -5.18 (CH₃-TBS). MS (ESI⁺): m/z (%) = 291.13 ([M+Na]⁺, 1.6); 267.14 ([M-1]⁺, 4); 238.16 (11); 196.11 (100). HRMS (ESI⁺): calcd for C₁₄H₂₆O₃Si: 267.1411; found: 267.1408.

(5R)-5-(tert-butyldimethylsiloxy)-5-(2'-furyl)pent-l-yne (11).

To a solution of aldehyde 19 (378 mg, 1.41 mmol) in MeOH (5 mL) cooled to 0 °C were added methyl 2-diazo-2-(dimethoxyphosphoryl)acetate 22 (1.94 g, 14.08 mmol) in MeOH (10 mL) and K₂CO₃ (2.93 g, 14.08 mmol). The reaction was stirred to r.t. for 3days. Then, sat. Aq NH₄Cl (20 mL) was added and extracted with CH₂Cl₂ (3 x 15 mL). The organic layers were dried, and concentrated. The residue was chromatographed on silica gel using 1% EtOAc / Hexane to afford alkyne 11 as a yellow oil. Yield: 323 mg, (87%); Rᵢ = 0.84 (20% EtOAc/Hexane); [α]²²D + 84.15 (c 0.46, CHCl₃). IR (NaCl, neat): 3312, 2956, 2929, 2857, 1472, 1256 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 7.37 (m, 1 H, H-5'); 6.33 (m, 1 H, H-4'); 6.21 (d, J = 3.2 Hz, 1 H, H-3'); 4.86 (dd, J = 4.8 Hz, J = 7.9 Hz, 1 H, H-5); 2.35 (m, 1 H, H-3); 2.24 (m, 1 H, H-3); 2.07 (m, 1 H, H-4 and 1); 1.96 (m, 2 H, H-4 and 1); 0.89 (s, 9 H, Bu-TBS); 0.10 (s, 3 H, CH₃-TBS); -0.05 (s, 3 H, CH₃-TBS). ¹³C-NMR (100 MHz, CDCl₃): δ = 156.52 (C-2'); 141.47 (CH-5'); 110.01 (CH-3'); 106.03 (CH-4'); 83.93 (C-2); 68.62 (CH-1); 66.86 (CH-5); 35.51 (CH₂-4); 25.79 (CH₃-Bu-TBS); 18.18 (C-Bu-TBS); 14.61 (CH₂-3); -4.95, -5.18 (CH₃-TBS). MS (ESI⁺): m/z (%) = 287.14 ([M+Na]⁺, 100); 265.15 ([M+1]⁺, 10); 247.16 (36); 239.14 (30); 156.12 (75). HRMS (ESI⁺): calcd for C₁₅H₂₄NaO₂Si: 287.1443; found: 287.1437.
(2S, 8R)-8-(tert-butyldimethylsilyloxy)-8-(2'-furyl)oct-4-yn-2-ol (21) and (2R, 8R)-8-(tert-butyldimethylsilyloxy)-8-(2'-furyl)oct-4-yn-2-ol (24)

**General method**

To a solution of alkyne 11 (0.496 mmol) in THF (5 mL) cooled to –78 °C was added, dropwise, n-BuLi in THF 2.5 M (218 µL) and the mixture was stirred for 1 h at the same temperature. Then, (S) or (R)-propylene oxide (42 µL) and BF₃·OEt₂ (69 µL) were added, and the reaction was stirred for 3 h in the same conditions. Sat. aq NH₄Cl (5 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (3 × 5 mL), dried, filtered and concentrated. The residue was purified by chromatography on silica gel using 5% EtOAc / Hexane to afford alcohols 21 or 24 respectively.

(2S, 8R)-8-(tert-butyldimethylsilyloxy)-8-(2'-furyl)oct-4-yn-2-ol (21).

Yield: 97%; Yellow oil; R_F = 0.22 (10% EtOAc/Hexane); [α]D22 + 31.09 (c 4.5, CHCl3). IR (NaCl, neat): 3394, 2956, 2929, 2857, 1506, 1254 cm⁻¹. ¹H-NMR (400 MHz, CDCl3): δ = 7.33 (d, J = 1.0 Hz, 1 H, H-5'); 6.29 (dd, J = 1.8 Hz, J= 3.2 Hz, 1 H, H-4'); 6.17 (d, J = 3.2 Hz, 1 H, H-3'); 4.81 (dd, J = 5.0 Hz, J = 7.9 Hz, 1 H, H-8); 3.90 (qd, J = 5.9 Hz, J = 12.1 Hz, 1 H, H-2); 2.35-2.17 (m, 5 H, H-6, 7 and -OH); 2.01 (m, 1 H, H-3); 1.89 (m, 1 H, H-3); 1.24 (d, J = 6.2 Hz, 3 H, H-1); 0.87 (s, 9 H, 3Bu-TBS); 0.06 (s, 3 H, CH₃-TBS); -0.08 (s, 3 H, CH₃-TBS). ¹³C-NMR (100 MHz, CDCl3): δ = 156.64 (C-2'); 141.39 (CH-5'); 110.00 (CH-3'); 105.92 (CH-4'); 82.24, 76.72 (C-4 and 5); 67.03 (CH-8); 66.55 (CH-2); 36.00, 29.38 (CH₂); 25.77 (CH₃-3Bu-TBS); 22.22 (CH₂-1); 18.18 (C-3Bu-TBS); 14.95 (CH₂); -4.95, -5.20 (CH₃-TBS). MS (ESI⁺): m/z (%) = 345.18 ([M+Na]⁺, 71); 337.17 (5), 191.10 (100). HRMS (ESI⁺): calcd for C₁₈H₃₀NaO₅Si: 345.1856; found: 345.1836.

(2R, 8R)-8-(tert-butyldimethylsilyloxy)-8-(2'-furyl)oct-4-yn-2-ol (24).

Yield: 93%; Yellow oil; R_F = 0.22 (10% EtOAc/Hexane); [α]D22 + 18.63 (c 5.5, CHCl3). IR (NaCl, neat): 3394, 2956, 2929, 2857, 1506, 1254 cm⁻¹. ¹H-NMR (400 MHz, CDCl3): δ = 7.33 (d, J = 0.8 Hz, 1 H, H-5'); 6.29 (dd, J = 1.6 Hz, J= 3.1 Hz, 1 H, H-4'); 6.17 (d, J = 3.2 Hz, 1 H, H-3'); 4.81 (dd, J = 5.0 Hz, J = 7.9 Hz, 1 H, H-8); 3.89 (m, 1 H, H-2); 2.35-2.16 (m, 5 H, H-6, 7 and -OH); 2.01 (m, 1 H, H-3); 1.90 (m, 1 H, H-3); 1.24 (dd, J = 1.1 Hz, J = 6.2 Hz, 3 H, H-1); 0.87 (s, 9 H, 3Bu-TBS); 0.07 (s, 3 H, CH₃-TBS); -0.08 (s, 3 H, CH₃-TBS). ¹³C-NMR (100 MHz, CDCl3): δ = 156.64 (C-2'); 141.39 (CH-5'); 110.00 (CH-3'); 105.92 (CH-4'); 82.22, 76.73 (C-4 and 5); 67.03 (CH-8); 66.55 (CH-2); 35.99, 29.37 (CH₂); 25.77 (CH₃-3Bu-TBS); 22.24 (CH₂-1); 18.17 (C-3Bu-TBS); 14.95 (CH₂); -4.96, -5.20 (CH₃-TBS). MS (ESI⁺): m/z (%) = 345.18 ([M+Na]⁺, 71); 337.17 (5), 191.10 (100). HRMS (ESI⁺): calcd for C₁₈H₃₀NaO₅Si: 345.1856; found: 345.1836.

(1R,7S)-1,7-bis(tert-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (22) and (1R,7R)-1,7-bis(tert-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (25).

**General method**

To a solution of alcohols 21 or 24 (0.301 mmol) in DMF (5 mL) were added imidazole (1.80 mmol), DMAP (catalytic ammount) and TBSCl (0.904 mmol), and the reaction was stirred at r.t. for 5 days. Then, EtOAc was added (5 mL) and the mixture was washed with H₂O (3 × 5 mL). The organic layer was dried, filtered and concentrated to give a residue
which was purified by chromatography on silica gel using 0.5% EtOAc / Hexane affording 22 or 25 respectively.

(1R,7S)-1,7-bis(tert-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (22).

Yield: 89%; Yellow oil; R<sub>f</sub> = 0.77 (10% EtOAc / Hexane); [α]<sup>23</sup><sub>D</sub> = +17.81 (c 10.18, CHCl<sub>3</sub>).

IR (NaCl, neat): 2955, 2928, 2856, 1698, 1540, 1254 cm<sup>-1</sup>. ¹H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.36 (m, 1 H, H-5'); 6.32 (dd, J = 1.7 Hz, J = 3.1 Hz, 1 H, H-4'); 6.19 (d, J = 2.8 Hz, 1 H, H-3); 4.84 (dd, J = 4.8 Hz, J = 7.8 Hz, 1 H, H-1); 3.92 (td, J = 5.8 Hz, J = 11.8 Hz, 1 H, H-7); 2.28 (m, 4 H, H-2 and 3); 2.03 (m, 1 H, H-6); 1.92 (m, 1 H, H-6); 1.26 (d, J = 6.0 Hz, 3 H, H-8); 0.91 (s, 9 H, 'Bu-TBS); 0.89 (s, 9 H, 'Bu-TBS); 0.10 (s, 9 H, CH<sub>3</sub>-TBS); -0.04 (s, 3 H, CH<sub>3</sub>-TBS). ¹³C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 156.79 (C-2'); 141.36 (CH-5'); 109.97 (CH-3'); 105.96 (CH-4'); 80.99, 77.95 (C=C); 68.13 (CH-1); 76.07 (CH-7); 36.02, 29.78 (CH-2); 25.85, 25.80 (CH₃-'Bu-TBS); 23.31 (CH₃-8); 18.20, 18.17 (CH₃-'Bu-TBS); 15.02 (CH₂); -4.69, -4.75, -4.93, -5.17 (CH₃-TBS). MS (ESI<sup>+</sup>): m/z (%) = 459.27 ([M + Na<sup>+</sup>]<sup>+</sup>, 9); 305.20 (100); 196.11 (23); 159.12 (14). HRMS (ESI<sup>+</sup>): calcd for C<sub>29</sub>H<sub>44</sub>NaO<sub>3</sub>Si<sub>2</sub>: 459.2721; found: 459.2728.

(1R,7R)-1,7-bis(tert-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (25).

Yield: 72%; Yellow oil; R<sub>f</sub> = 0.82 (10% EtOAc / Hexane); [α]<sup>25</sup><sub>D</sub> = +14.96 (c 10.06, CHCl<sub>3</sub>).

IR (NaCl, neat): 2955, 2928, 2856, 1698, 1540, 1254 cm<sup>-1</sup>. ¹H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.35 (m, 1 H, H-5'); 6.31 (dd, J = 1.8 Hz, J = 3.1 Hz, 1 H, H-4'); 6.19 (d, J = 3.0 Hz, 1 H, H-3'); 4.84 (dd, J = 4.9 Hz, J = 7.8 Hz, 1 H, H-1); 3.93 (dd, J = 5.7 Hz, J = 11.5 Hz, 1 H, H-7); 2.27 (m, 4 H, H-2 and 3); 2.02 (m, 1 H, H-6); 1.92 (m, 1 H, H-6); 1.25 (d, J = 5.9 Hz, 3 H, H-8); 0.91 (s, 9 H, 'Bu-TBS); 0.89 (s, 9 H, 'Bu-TBS); 0.09 (s, 9 H, CH<sub>3</sub>-TBS); -0.05 (s, 3 H, CH<sub>3</sub>-TBS). ¹³C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 156.77 (C-2'); 141.37 (CH-5'); 109.97 (CH-3'); 105.87 (CH-4'); 80.87, 77.96 (C=C); 68.12 (CH-1); 67.05 (CH-7); 36.02, 29.78 (CH₂); 25.86, 25.81 (CH₃-'Bu-TBS); 23.24 (CH₃-8); 18.21, 18.16 (CH₃-'Bu-TBS); 15.02 (CH₂); -4.68, -4.74, -4.93, -5.16 (CH₃-TBS). MS (ESI<sup>+</sup>): m/z (%) = 459.27 ([M + Na<sup>+</sup>]<sup>+</sup>, 9); 305.20 (100); 196.11 (23); 159.12 (14). HRMS (ESI<sup>+</sup>): calcd for C<sub>29</sub>H<sub>44</sub>NaO<sub>3</sub>Si<sub>2</sub>: 459.2721; found: 459.2728.

(1'R,7'S)-2-[1',7'-bis(tert-butyldimethylsilyloxy)octanoyl]furane (13) and (1'R,7'R)-2-[1',7'-bis(tert-butyldimethylsilyloxy)octanoyl]furane (26).

**General method**

To a solution of 22 or 25 (0.291 mmol) in hexane (5 mL), was added Pd/C 5 % catalyst (6 mg) and the mixture was stirred in H₂ atmosphere at r.t. for 30 min. After filtration, the filtrate was evaporated and the residue was purified by chromatography on silica gel using 0.5% EtOAc / Hexane to afford 13 or 26 respectively.

(1'R,7'S)-2-[1',7'-bis(tert-butyldimethylsilyloxy)octanoyl]furane (13).

Yield: 90%; Yellow oil; R<sub>f</sub> = 0.81 (10% EtOAc / Hexane); [α]<sup>25</sup><sub>D</sub> = +26.55 (c 10.0, CHCl<sub>3</sub>). IR (NaCl, neat): 2928, 2856, 1698, 1540 cm<sup>-1</sup>. ¹H-NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.35 (m, 1 H, H-5); 6.32 (dd, J = 1.8 Hz, J = 3.1 Hz, 1 H, H-4); 6.17 (d, J = 3.1 Hz, 1 H, H-3); 4.68 (m, 1 H, H-1'); 3.78 (m, 1 H, H-7'); 1.83 (m, 3 H, H-2' and 6'); 1.49-1.24 (m, 7 H, H-3', 4', 5' and 6'); 1.13 (d, J = 6.1 Hz, 3 H, H-8); 0.91 (s, 9 H, 'Bu-TBS); 0.90 (s, 9 H, 'Bu-TBS); 0.074 (s, 3 H, CH<sub>3</sub>-TBS); 0.070 (s, 3 H, CH<sub>3</sub>-TBS); 0.06 (s, 3 H, CH<sub>3</sub>-TBS); -0.04 (s, 3 H, CH<sub>3</sub>-TBS). ¹³C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 157.54 (C-2); 141.12 (CH-5); 109.92 (CH-4); 105.50 (CH-3); 68.61 (CH-1'); 68.52 (CH-7'); 39.66, 36.91, 29.46 (CH₂); 25.94, 25.83
(CH$_3$-Bu-TBS); 25.73, 25.41 (CH$_2$); 23.83 (CH$_3$-8'); 18.23, 18.18 (C-1'-Bu-TBS); -4.39, -4.70, -4.87, -5.09 (CH$_3$-TBS). MS (ESI$^+$): m/z (%) = 436.30 ([M + Na]$^+$, 4); 310.22 (29); 309.23 (100); 196.11 (24). HRMS (ESI$^+$): calcd for C$_{24}$H$_{48}$NaO$_3$Si$_2$: 463.3034; found: 463.3036.

**(1'R,7'R)-2-[(1',7')-bis(tert-butyldimethylsilyloxy)octanyl]furan (26)**

Yield: 93%; Yellow iol; R$_F$ = 0.84 (10% EtOAc / Hexane); $[\alpha]_D^{25} + 23.94$ (c3.13, CHCl$_3$). IR (NaCl, neat): 2928, 2856, 1698, 1540 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.35 (dd, J = 0.8 Hz, J = 1.7 Hz, 1 H, H-5); 6.31 (dd, J = 1.8 Hz, J = 3.2 Hz, 1 H, H-4); 6.16 (d, J = 3.2 Hz, 1 H, H-3); 4.67 (m, 1 H, H-1'); 3.77 (m, 1 H, H-7'); 1.80 (m, 2 H, H-2'); 1.46-1.23 (m, 8 H, H-3', 4', 5' and 6'); 1.12 (d, J = 6.1 Hz, 3 H, H-8'); 0.90 (s, 9 H, Bu-TBS); 0.89 (s, 9 H, CH$_3$-TBS); 0.76 (s, 3 H, CH$_3$-TBS); 0.05 (s, 3 H, CH$_3$-TBS); -0.05 (s, 3 H, CH$_3$-TBS). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 157.54 (C-2); 141.14 (CH-5); 109.92 (CH-4); 105.51 (CH-3); 68.64 (CH-1'); 68.53 (CH-7'); 39.66, 36.91, 29.48 (CH$_2$); 25.74, 25.42 (CH$_3$-Bu-TBS); 25.74, 25.42 (CH$_2$); 23.82 (CH$_3$-8'); 18.19 (C-1'-Bu-TBS); -4.39, -4.70, -4.87, -5.08 (CH$_3$-TBS). MS (ESI$^+$): m/z (%) = 436.30 ([M + Na]$^+$, 4); 310.22 (29); 309.23 (100); 196.11 (24). HRMS (ESI$^+$): calcd for C$_{24}$H$_{48}$NaO$_3$Si$_2$: 463.3034; found: 463.3036.

**(4R, 5R, 11S)-iso-cladospolide B (7) and (4R, 5R, 11R)-iso-cladospolide B (8)**

**General method**

To a solution of furane 13 or 26 (0.226 mmol) in MeOH (10 mL) was added Rose Bengal (6 mg) and the resulting pink solution was purged with O$_2$. It was then cooled to –78 °C and DIPEA (0.952 mmol) was added. The mixture was irradiated with a 200W lamp under an atmosphere of O$_2$ for 2 h. After that, the mixture was allowed to reach the r.t. and the MeOH was evaporated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (5 mL) and to the resulting pink solution was added a solution of Oxalic Acid (142 mg, 12 mL H$_2$O), the resulting orange mixture was stirred at r.t. for 2h. After separation of the two phases, the aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic phases were dried, filtered and concentrated in vacuo yielding the expected hydroxybutenolide which was used in the next reaction. To the previous hydroxybutenolide dissolution in MeOH (10 mL) cooled to 0 °C were added CeCl$_3$-7H$_2$O (0.011 mmol) and NaBH$_4$ (0.904 mmol). After the addition, the mixture was stirred under the same conditions for 1 h, after which was added concentrated HCl, dropwise, until pH=1. The mixture was allowed to stir at r.t. for 1 day, after which the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel using 80% EtOAc / Hexane affording iso-cladospolides 7 or 8.

**(4R, 5R, 11S)-iso-cladospolide B (7)**

Yield: 97%; White crystal; R$_F$ = 0.31 (100% EtOAc); $[\alpha]_D^{25}$ + 56.36 (c1.0, CHCl$_3$); [reported synthetic enantiomer of 7$^{3b}$ [\(\alpha\)]$_D$ -73.28 (c1.0, MeOH)]; m.p. 96.7-98.7 °C. IR (NaCl, neat): 3420, 2931, 2857, 1748 cm$^{-1}$. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 7.48 (dd, J = 1.5 Hz, J = 5.8 Hz, 1 H, H-4); 6.20 (dd, J = 2.0 Hz, J = 5.8 Hz, 1 H, H-3); 5.01 (dd, J = 1.8 Hz, J = 2.6 Hz, 1 H, H-5); 3.79 (m, 2 H, H-1' and 7'); 2.60-1.70 (s broad, 2 H, -OH); 1.60 (m, 2 H, H-2'); 1.39 (m, 8 H, H-3', 4', 5' and 6'); 1.20 (d, J = 6.2 Hz, 3 H, H-8'). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 173.08 (C=O); 154.95 (CH-4); 122.69 (CH-3); 86.24 (CH-5); 71.69 (CH-1'); 68.08 (CH-7'); 39.05, 33.10, 29.34, 25.56, 25.43 (CH$_2$); 23.55 (CH$_3$-8'). MS (ESI$^+$): m/z (%) = 229.14 ([M+H]$^+$, 100); 227.12 ([M-I]$^+$, 25); 211.13 ([M-OH]$^+$, 77). HRMS (ESI$^+$): calcd for C$_{12}$H$_{22}$O$_4$:229.1434; found: 229.1432.
(4R, 5R, 11R)-iso-cladospolide B (8)

Yield: 72%; White solid; Rf = 0.28 (100% EtOAc); [α]D23 + 61.05 (c1.0, CHCl3); {reported synthetic enantiomer of 8c [α]D -58.0 (c0.6, MeOH)}; m.p. 82.2-86.0 °C. IR (NaCl, neat): 3420, 2931, 2857, 1748 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, J = 5.7 Hz, 1 H, H-4); 6.19 (dd, J = 1.6 Hz, J = 5.6 Hz, 1 H, H-3); 5.01 (m, 1 H, H-5); 3.78 (m, 2 H, H-1’ and 7’); 2.50-2.06 (s broad, 2 H, -OH); 1.58 (m, 4 H, H-2’ and 6’); 1.49-1.22 (m, 6 H, H-3’, 4’ and 5’); 1.19 (d, J = 6.1 Hz, 3 H, H-8’). ¹³C NMR (100 MHz, CDCl₃): δ = 173.21 (C=O); 154.09 (CH-4); 122.63 (CH-3); 86.31 (CH-5); 71.58 (CH-1’); 68.05 (CH-7’); 39.03, 33.05, 29.30, 25.54, 25.45 (CH₂); 23.51 (CH₃-8’). MS (ESI⁺): m/z (%) = 229.14 ([M+H]+, 100); 227.12 ([M-H]+, 25); 211.13 ([M-OH]+, 77). HRMS (ESI⁺): calcd for C₁₂H₂₁O₄:229.1434; found: 229.1432.

References


8 - Crystallographic data were collected on a Bruker Smart 1000 CCD diffractometer at CACTI (Universidade de Vigo) at 20°C using graphite monochromated Mo Kα radiation (λ = 0.71073 Å), and were corrected for Lorentz and polarisation effects. The frames were integrated with the Bruker SAINT software package and the data were corrected for absorption using the program SADABS. The structures were solved by direct methods using the program SHELXS97. All non-hydrogen atoms were refined with anisotropic thermal parameters by full-matrix least-squares calculations on F2 using the program SHELXL97. Hydrogen atoms were inserted at calculated positions and constrained with isotropic thermal parameters. The structural data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) with reference number CCDC 985353. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ (FAX: (+44) 1223-336-033; E-mail: deposit@ccdc.cam.ac.uk)