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

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Abstract: The two enantiomers of natural products (4*S*, 5*S*, 11*R*)-and (4*S*, 5*S*, 11*S*)-*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

(4*S*, 5*S*, 11*R*)-and (4*S*, 5*S*, 11*S*)-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 fungus[1]. While cladospolides A-D have macrolactonic structures, (4*S*, 5*S*, 11*R*)-and (4*S*, 5*S*, 11*S*)-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 196S215[2]. 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 (4*S*, 5*S*, 11*R*)-*iso*-cladospolide B (**5**) and (4*S*, 5*S*, 11*S*)-*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 products[4], we now wish to report the synthesis of (4*R*, 5*R*, 11*S*)-*iso*-cladospolide B (**7**) and (4*R*,5*R*,11*R*)-*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.

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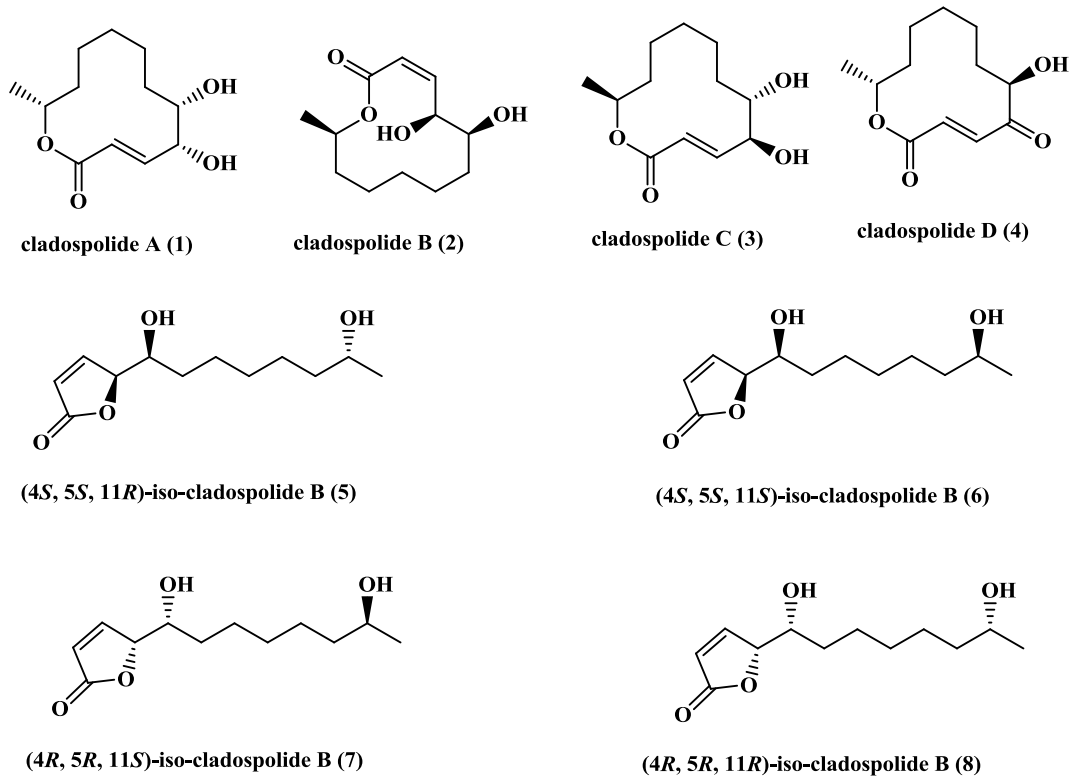
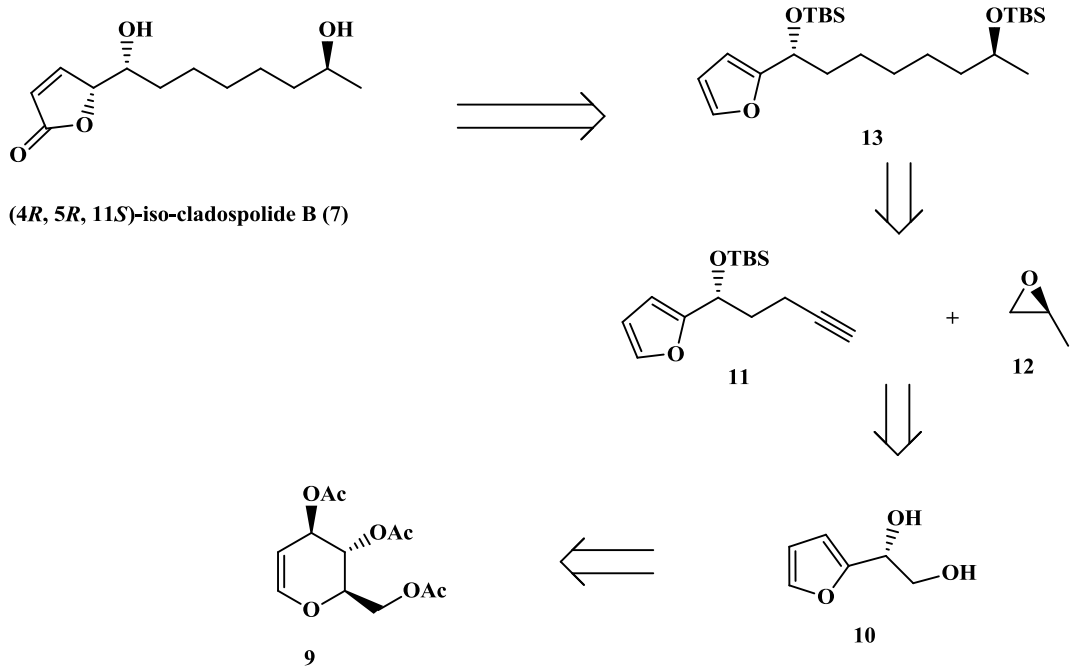
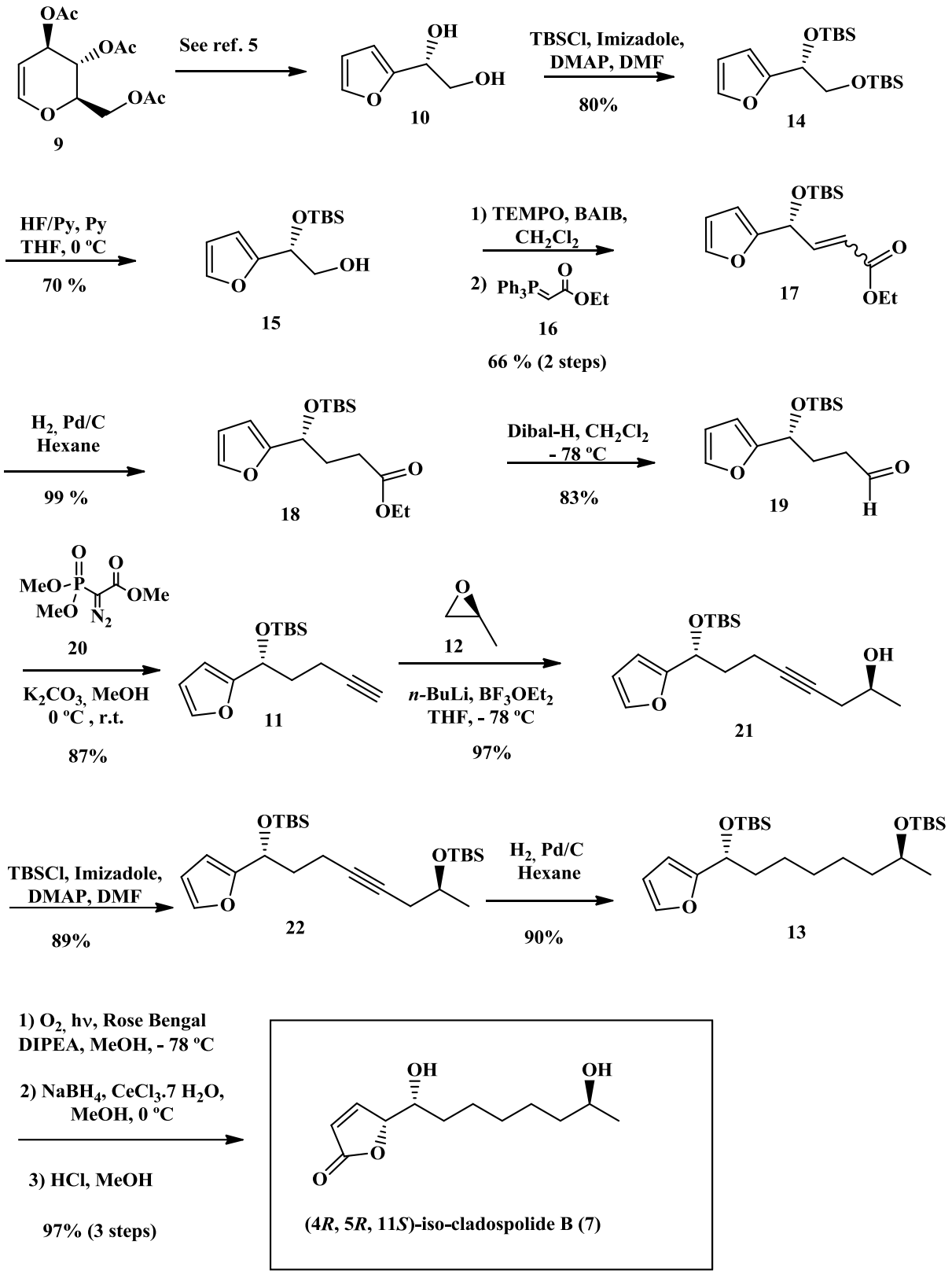


Figure 1. Structures of cladospolides A-D, (4*S*, 5*S*, 11*R*)- and (4*S*, 5*S*, 11*S*)-*iso*- cladospolide B and their respective enantiomers (4*R*, 5*R*, 11*S*)- and (4*R*, 5*R*, 11*R*)-*iso*- cladospolide B.



Scheme 1. Retrosynthetic analysis of (4*R*, 5*R*, 11*S*)-*iso*-cladospolide B (**7**).

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.



Scheme 2. Synthesis of (4*R*, 5*R*, 11*S*)-*iso*-cladospolide B (**7**)

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[6] to give alkyne **11** in 87% yield. Treatment of epoxide **12** with alkyne **11** in the presence of *n*-butyllithium and BF_3-OEt_3 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**[3b,5,7] afforded target compound **7** in 78% yield. The absolute configuration of (4*R*, 5*R*, 11*S*)-*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.[8]

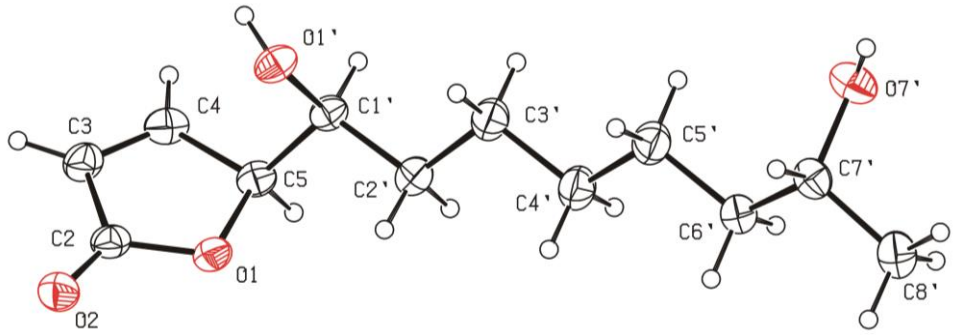
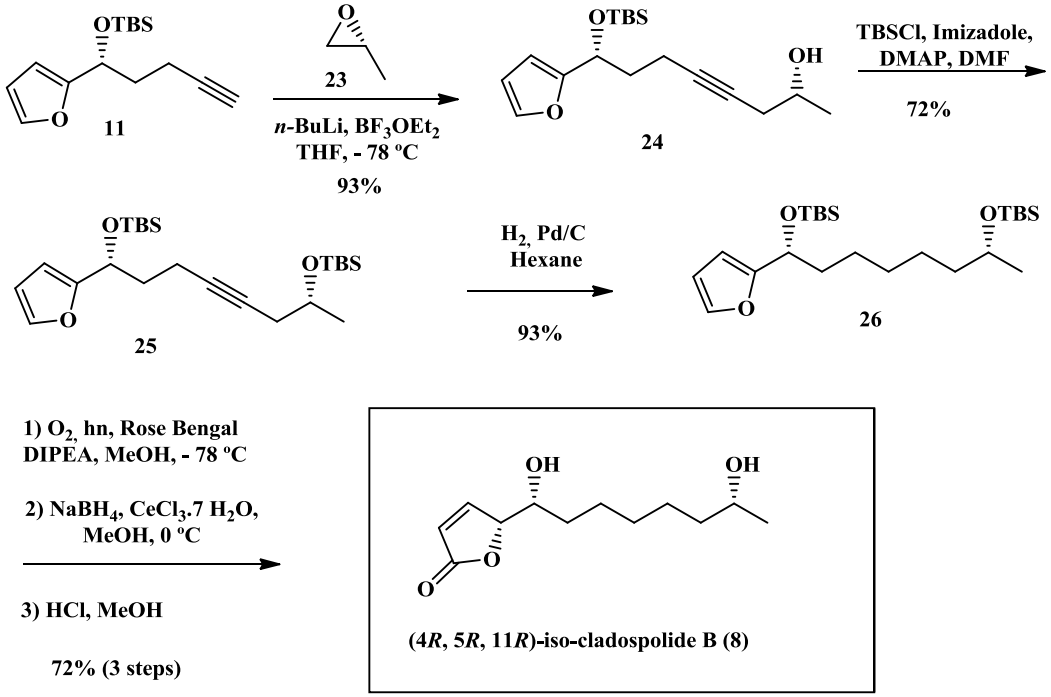


Figure 2. X-ray structure (ORTEP) of (4*R*, 5*R*, 11*S*)-*iso*.cladospolide B (**7**)

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



Scheme 3. Synthesis of (4*R*, 5*R*, 11*R*)-*iso*-cladospolide B (**8**)

Conclusion

In conclusion we carried out the synthesis of (4*R*, 5*R*, 11*S*)-and (4*R*, 5*R*, 11*R*)-*iso*-cladospolide B from cheap and commercially available tri-O-acetyl-D-glucal. By X-ray crystallographic analysis we unambiguously confirmed the structure of (4*R*, 5*R*, 11*S*)-*iso*-cladospolide. The synthesized compounds are enantiomers of natural products (4*S*, 5*S*, 11*R*)- and (4*S*, 5*S*, 11*S*)-*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 δ 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) were 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_2O (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, $CDCl_3$): δ = 7.37 (d, J = 0.8 Hz, 1 H, H-5); 6.33 (dd, J = 1.8 Hz, J = 2.9 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'); 3.84-3.80 (m, 2 H, H-2'); 0.90 (s, 9 H, ^{t}Bu-TBS); 0.88 (s, 9 H, ^{t}Bu-TBS); 0.05 (m, 12 H, CH_3-TBS). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.21 (C-2); 142.45 (CH-5); 110.02 (CH-3); 106.88 (CH-4); 70.07 (CH-1'); 67.02 (CH_2-2'); 25.91, 25.80 (CH_3-^{t}Bu-TBS); 18.29, 18.26 (C-^{t}Bu-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+1]$^{+}$, 29); 379.20 ([M+Na]$^{+}$, 100); 374.25 (10); 156.12 (6). HRMS (ESI^{+}):calcd for $C_{18}H_{36}NaO_3Si_2$: 379.2095; found: 379.2091.

(2*R*)-2-(*tert*-butyldimethylsilyloxy)-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 $NaHCO_3$ (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_F = 0.55 (20% EtOAc/Hexane); $[\alpha]_D^{24}$ + 61.42 (*c* 10.4, $CHCl_3$). IR (NaCl, neat): 3430, 2952, 2929, 2848, 1470, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.09 (s, 3 H, CH_3-TBS); -0.04 (s, 3 H, CH_3-TBS). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.12 (C-2'); 141.91 (CH-5'); 110.21 (CH-3'); 107.22 (CH-4'); 69.27 (CH-2); 65.82 (CH_2-1); 25.76 (CH_3-^{t}Bu-TBS); 18.17 (C-^{t}Bu-TBS); -4.98, -5.14 (CH_3-TBS). MS (ESI^+): *m/z* (%) = 266.12 ($[M+Na+1]^+$, 12); 265.12 ($[M+Na]^+$, 56); 262.11 (18); 196.11 (100); 185.05 (28). HRMS (ESI^+): calcd for $C_{12}H_{22}NaO_3Si$: 265.1230; found: 265.1235.

(4*R*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-4-(2'-furyl)but-2-enoate (17).

To a solution of alcohol **15** (366 mg, 1.51 mmol) in CH_2Cl_2 (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 aq$Na_2S_2O_3$ 15% (3x10 mL), then with sat. aq $NaHCO_3$ (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 **17**, as a brown oil. Yield: 307 mg, (66%); R_F = 0.91 (20% EtOAc/Hexane); $[\alpha]_D^{23}$ + 20.83 (*c* 4.93, $CHCl_3$). IR (NaCl, neat): 2952, 2916, 2852, 1794, 1716, 1457 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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); 6.62-6.14 (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, -CH_2O-); 1.30 (t, J = 7.0 Hz, 3 H, CH_3-); 0.91 and 0.69 (2s, 9 H, ^{t}Bu-TBS); 0.10-0.004 (m, 12 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$):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 (-CH_2O-); 25.74 (CH_3-^{t}Bu-TBS); 18.29, 18.24 (C-^{t}Bu-TBS); 14.24, 14.19 (CH_3-); -4.98, -4.91, -5.11 (CH_3-TBS). MS (ESI^+):*m/z* (%) = 391.29 (13); 365.14 (17); 243.14 (14); 196.12 (100). HRMS (ESI^+):calcd for $C_{16}H_{26}O_4Si$: 310.1600; found: 310.1607.

Ethyl (4*R*)-4-(*tert*-butyldimethylsilyloxy)-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 H_2 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_F = 0.75 (20% EtOAc/Hexane); $[\alpha]_D^{22}$ + 31.59 (*c* 1.0, $CHCl_3$). IR (NaCl, neat): 2955, 2932, 2857, 1735, 1467 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$):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'); 4.69 (m, 1 H, H-4); 4.00 (q, J = 7.1 Hz, 2 H, -CH_2O-); 2.26 (m, 2 H, H-2); 2.01 (m, 2 H, H-3); 1.13 (t, J = 7.2 Hz, 3 H, CH_3-); 0.77 (s, 9 H, ^{t}Bu-TBS); -

0.05 (s, 3 H, CH_3-TBS); -0.18 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (-CH_2O-); 31.71, 29.69 (CH_2-3 and 2); 25.60 (CH_3-^{t}Bu-TBS); 17.98 (C-^{t}Bu-TBS); 14.05 (CH_3-); -5.20, -5.42 (CH_3-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 $C_{16}H_{28}NaO_4Si$: 335.1649; found: 335.1661.

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

To a solution of **18** (530 mg, 1.69 mmol) in CH_2Cl_2 (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, ^{t}BuOMe (2.2 mL) and H_2O (140 µL) were added and the mixture was stirred until the formation a white gel. H_2O (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%); R_F = 0.77 (20% EtOAc/Hexane); $[\alpha]_D^{22}$ + 68.32 (*c* 1.0, $CHCl_3$). IR (NaCl, neat): 2955, 2929, 2857, 1723, 1467 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.06 (s, 3 H, CH_3-TBS); -0.06 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2-2 and 3); 25.76 (CH_3-^{t}Bu-TBS); 18.16 (C-^{t}Bu-TBS); -5.02, -5.18 (CH_3-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 $C_{14}H_{23}O_3Si$: 267.1411; found: 267.1408.

(5*R*)-5-(*tert*-butyldimethylsilyloxy)-5-(2'-furyl)pent-1-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 K_2CO_3 (2.93 g, 14.08mmol). The reaction was stirred to r.t. for 3days. Then, sat. Aq NH_4Cl (20 mL) was added and extracted with CH_2Cl_2 (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%); R_F = 0.84 (20% EtOAc/Hexane); $[\alpha]_D^{23}$ + 84.15 (*c* 0.46, $CHCl_3$). IR (NaCl, neat): 3312, 2956, 2929, 2857, 1472, 1256 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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); 1.96 (m, 2 H, H-4 and 1); 0.89 (s, 9 H, ^{t}Bu-TBS); 0.10 (s, 3 H, CH_3-TBS); -0.05 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2-4); 25.79 (CH_3-^{t}Bu-TBS); 18.18 (C-^{t}Bu-TBS); 14.61 (CH_2-3); -4.95, -5.18 (CH_3-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 $C_{15}H_{24}NaO_2Si$: 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 BF_3OEt_2 (69 µL) were added, and the reaction was stirred for 3 h in the same conditions. Sat. aq NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 x 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.

(2*S*, 8*R*)-8-(*tert*-butyldimethylsilyloxy)-8-(2'-furyl)oct-4-yn-2-ol (21).
Yield: 97%; Yellow oil; R_F = 0.22 (10% EtOAc/Hexane); $[\alpha]_D^{22}$ + 31.09 (*c* 4.5, $CHCl_3$). IR (NaCl, neat): 3394, 2956, 2929, 2857, 1506, 1254 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 1.0 Hz, 1 H, H-5'); 6.25 (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, ^{t}Bu-TBS); 0.06 (s, 3 H, CH_3-TBS); -0.08 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2); 25.77 (CH_3-^{t}Bu-TBS); 22.22 (CH_3-1); 18.18 (C-^{t}Bu-TBS); 14.95 (CH_2); -4.95, -5.20 (CH_3-TBS). Ms (ESI^+): *m/z* (%) = 345.18 ([M+Na] $^+$, 71); 337.17 (5), 191.10 (100). HRMS (ESI^+): calcd for $C_{18}H_{30}NaO_3Si$: 345.1856; found: 345.1836.

(2*R*, 8*R*)-8-(*tert*-butyldimethylsilyloxy)-8-(2'-furyl) oct-4-yn-2-ol (24).
Yield: 93%; Yellow oil; R_F = 0.22 (10% EtOAc/Hexane); $[\alpha]_D^{22}$ + 18.63 (*c* 5.5, $CHCl_3$). IR (NaCl, neat): 3394, 2956, 2929, 2857, 1506, 1254 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.07 (s, 3 H, CH_3-TBS); -0.08 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2); 25.77 (CH_3-^{t}Bu-TBS); 22.24 (CH_3-1); 18.17 (C-^{t}Bu-TBS); 14.95 (CH_2); -4.96, -5.20 (CH_3-TBS). MS (ESI^+): *m/z* (%) = 345.18 ([M+Na] $^+$, 71); 337.17 (5), 191.10 (100). HRMS (ESI^+): calcd for $C_{18}H_{30}NaO_3Si$: 345.1856; found: 345.1836.

(1*R*,7*S*)-1,7-bis(*tert*-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (22) and (1*R*,7*R*)-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 H_2O (3 x 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.

(1*R*,7*S*)-1,7-bis(*tert*-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (22).
Yield: 89%; Yellow oil; R_F = 0.77 (10% EtOAc / Hexane); $[\alpha]_D^{23}$ + 17.81 (*c*10.18, $CHCl_3$). IR (NaCl, neat): 2955, 2928, 2856, 1698, 1540, 1254 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.89 (s, 9 H, ^{t}Bu-TBS); 0.10 (s, 9 H, CH_3-TBS); -0.04 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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); 67.07 (CH-7); 36.02, 29.78 (CH_2-6); 25.85, 25.80 (CH_3-^{t}Bu-TBS); 23.31 (CH_3-8); 18.20, 18.17 (C-^{t}Bu-TBS); 15.02 (CH_2); -4.69, -4.75, -4.93, -5.17 (CH_3-TBS). MS (ESI^+): *m/z* (%) = 459.27 ([M + Na] $^+$, 9); 305.20 (100); 196.11 (23); 159.12 (14). HRMS (ESI^+): calcd for $C_{24}H_{44}NaO_3Si_2$: 459.2721; found: 459.2728.

(1*R*,7*R*)-1,7-bis(*tert*-butyldimethylsilyloxy)-1-(2'-furyl)oct-4-yne (25)
Yield: 72%; Yellow iol; R_F = 0.82 (10% EtOAc / Hexane); $[\alpha]_D^{22}$ + 14.96 (*c*10.06, $CHCl_3$). IR (NaCl, neat): 2955, 2928, 2856, 1698, 1540, 1254 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.89 (s, 9 H, ^{t}Bu-TBS); 0.09 (s, 9 H, CH_3-TBS); -0.05 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2); 25.86, 25.81 (CH_3-^{t}Bu-TBS); 23.24 (CH_3-8); 18.21, 18.16 (C-^{t}Bu-TBS); 15.02 (CH_2); -4.68, -4.74, -4.93, -5.16 (CH_3-TBS). MS (ESI^+): *m/z* (%) = 459.27 ([M + Na] $^+$, 9); 305.20 (100); 196.11 (23); 159.12 (14). HRMS (ESI^+): calcd for $C_{24}H_{44}NaO_3Si_2$: 459.2721; found: 459.2728.

(1'*R*,7'*S*)-2-[1',7'-bis(*tert*-butyldimethylsilyloxy)octanyl]furane (13) and (1'*R*,7'*R*)-2-[1',7'-bis(*tert*-butyldimethylsilyloxy)octanyl]furan (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 H_2 atmosphere at r.t. for 30 min. After filtration, the filtrate was evaporated and the residue was purified by chromatography on silice gel using 0.5% EtOAc / Hexane to afford **13** or **26** respectively.

(1'*R*,7'*S*)-2-[1',7'-bis(*tert*-butyldimethylsilyloxy)octanyl]furan (13)
Yield: 90%; Yellow oil; R_F = 0.81 (10% EtOAc / Hexane); $[\alpha]_D^{25}$ + 26.55 (*c*10.0, $CHCl_3$). IR (NaCl, neat): 2928, 2856, 1698, 1540 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 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, ^{t}Bu-TBS); 0.90 (s, 9 H, ^{t}Bu-TBS); 0.074 (s, 3 H, CH_3-TBS); 0.070 (s, 3 H, CH_3-TBS); 0.06 (s, 3 H, CH_3-TBS); -0.04 (s, 3 H, CH_3-TBS). ^{13}C-NMR (100 MHz, $CDCl_3$): 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 (CH_2); 25.94, 25.83

(CH_3-^{t}Bu-TBS); 25.73, 25.41 (CH_2); 23.83 (CH_3-8'); 18.23, 18.18 (C-^{t}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 $C_{24}H_{48}NaO_3Si_2$: 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); $[\alpha]_D^{23}$ + 23.94 (*c*3.13, $CHCl_3$). IR (NaCl, neat): 2928, 2856, 1698, 1540 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 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, ^{t}Bu-TBS); 0.89 (s, 9 H, ^{t}Bu-TBS); 0.069 (s, 3 H, CH_3-TBS); 0.061 (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, $CDCl_3$): δ = 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); 25.94, 25.83 (CH_3-^{t}Bu-TBS); 25.74, 25.42 (CH_2); 23.82 (CH_3-8'); 18.19(C-^{t}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 $C_{24}H_{48}NaO_3Si_2$: 463.3034; found: 463.3036.

(4*R*, 5*R*, 11*S*)-*iso*-cladospolide B (7) and (4*R*, 5*R*, 11*R*)-*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_2Cl_2 (5 mL) and to the resulting pink solution was added a solution of Oxalic Acid (142 mg, 12 mL H_2O), the resulting orange mixture was stirred at r.t. for 2h. After separation of the two phases, the aqueous phase was extracted with CH_2Cl_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 $CeCl_3 \cdot 7H_2O$ (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**.

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

Yield: 97%; White crystal; R_F = 0.31 (100% EtOAc); $[\alpha]_D^{23}$ + 56.36 (*c*1.0, $CHCl_3$); {reported synthetic enantiomer of **7**[3b] $[\alpha]_D$ -73.28 (c1.0, MeOH)};m.p. 96.7-98.7 ºC. IR (NaCl, neat): 3420, 2931, 2857, 1748 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 ($[M+1]^+$, 100); 227.12 ($[M-1]^+$, 25); 211.13 ($[M-OH]^+$, 77). HRMS (ESI^+): calcd for$C_{12}H_{21}O_4$:229.1434; found: 229.1432.

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

Yield: 72%; White solid; R_F = 0.28 (100% EtOAc); $[\alpha]_D^{23}$ + 61.05(*c*1.0, $CHCl_3$); {reported synthetic enantiomer of **8**[3c] $[\alpha]_D$ -58.0 (c0.6, MeOH)}; m.p. 82.2-86.0 ºC**.** IR (NaCl, neat): 3420, 2931, 2857, 1748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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'). ^{13}C NMR (100 MHz, $CDCl_3$): 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 (CH_2); 23.51 (CH_3-8'). MS (ESI^+): *m/z* (%) = 229.14 ($[M+1]^+$, 100); 227.12 ($[M-1]^+$, 25); 211.13 ($[M-OH]^+$, 77). HRMS (ESI^+): calcd for $C_{12}H_{21}O_4$:229.1434; found: 229.1432.

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