Total Synthesis of (+)-Cladospolide A

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Abstract: A stereoselective total synthesis of (+)-cladospolide A from D-ribose is described. Key features of the synthesis include olefin cross metathesis and Yamaguchi lactonization.

Key words: cladospolide A, natural products, total synthesis, macrolactone

Cladospolides A–D (**1**–**4**) (Figure 1) belong to a class of 12-membered lactones possessing interesting plant-growth-regulatory as well as plant-growth-promoter activity. Cladospolide A [(–)-**1**] was first isolated[1] from a culture filtrate of the fungus *Cladosporium fulvum* FI-113, it was isolated together with cladospolide B (**3**) and cladospolide C (**2**) from *Cladosporium tenuissimum*,[2] and it was also isolated along with cladospolides B and D from the fermentation broth of *Cladosporium sp.* FT-0012.[3] The structure of (–)-**1** was established by X-ray crystallographic analysis and (–)-**1** was shown to inhibit the root growth of lettuce seedlings.[1] Since the first synthesis by Mori and Maemoto in 1987, a few syntheses of (–)-**1** have appeared in literature.[4] All syntheses involve Yamaguchi lactonization to assemble the macrolactone core. Surprisingly, some of the reported attempts to accomplish macrolactone formation by ring-closing metathesis[4e] reaction were futile, while olefin cross metathesis to construct the macrolactone precursor[4f] resulted in poor yields. Thus, the seemingly trivial assembly of the macrolactone core by RCM always required an arduous detour from the ring-closing-metathesis reaction and olefin-cross-metathesis reaction. We have been interested in the synthesis of natural products of therapeutic significance[5] and recently disclosed the synthesis of cladospolides C (**2**) and B (**3**) using olefin cross metathesis reaction as the key step.[6] Here in we report in detail our efforts in enantiospecific total synthesis of (+)-**1** from D-ribose.

Our strategy for the synthesis of (+)-**1** is depicted in Scheme 1. It was anticipated that the macrolactone (+)-**1** could be synthesized by selective hydrogenation of the electron-rich olefin followed by deprotection of the acetonide in the macrolactone **5**, the formation of which was planned by Yamaguchi lactonization of the hydroxy acid **6**. Synthesis of **6** was envisaged by selective alkene cross metathesis of **7** with (*S*)-hept-6-en-2-ol. Wittig olefination of the aldehyde **8** obtained from D-ribose was chosen as an appropriate transformation for the synthesis of **7**.

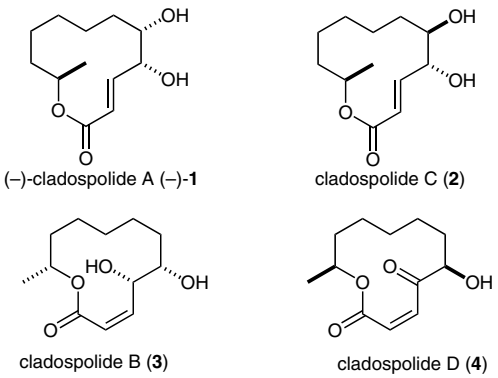
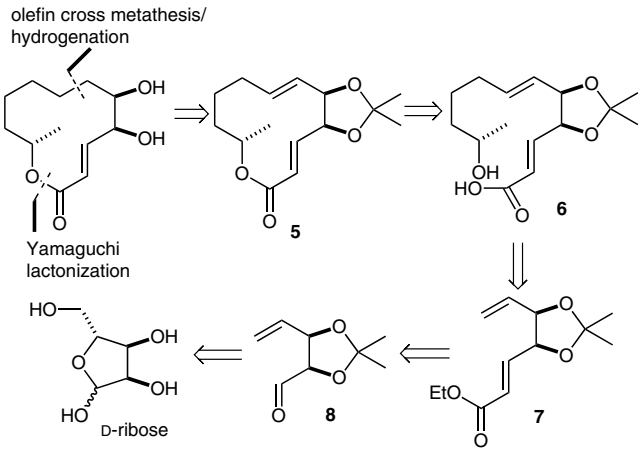


Figure 1 Cladospolides A–D

Accordingly, D-ribose was transformed to the iodide **9** using a known literature procedure.[7] Reaction of **9** with zinc in refluxing ethanol afforded the aldehyde **8**, which on Wittig olefination resulted in the *E*-configured α,β-unsaturated ester **7** in 45% yield over two steps, together with the *Z*-isomer in 22% yield. Olefin cross metathesis reaction of **7** with (*S*)-hept-6-en-2-yl acetate furnished the cross metathesis product **10** in 75% yield.[8] Hydrolysis of both esters with lithium hydroxide furnished the hydroxy acid in **6** in 77% yield. Yamaguchi lactonization of the acid provided the lactone **5** albeit in very low 32% yield. However, selective hydrogenation[9] of the electron-rich olefin in **5** turned out to be difficult and all efforts for the conversion of **5** into the macrolactone **11** were futile (Scheme 2).



Scheme 1 Retrosynthesis for cladospolide A

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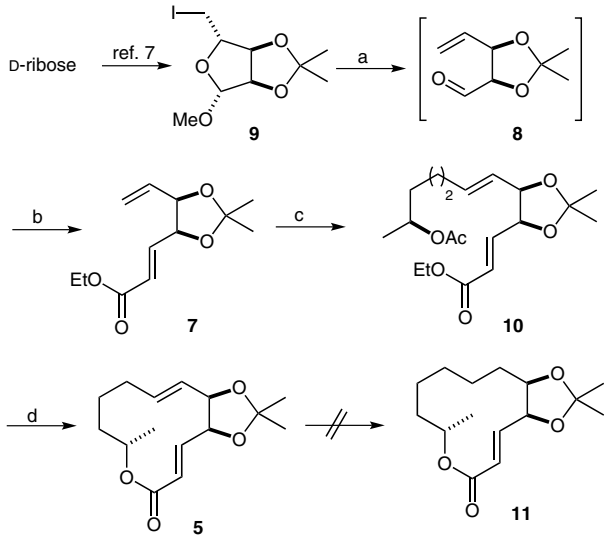
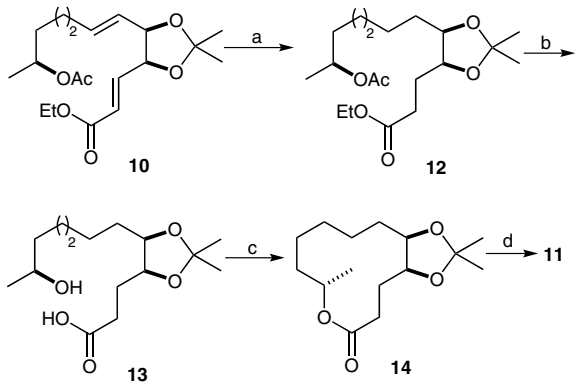


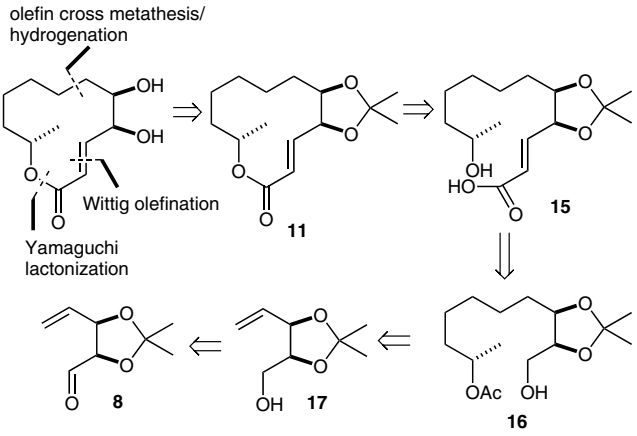
Scheme 2 Synthesis of macrolactone **5**. *Reagents and conditions:* (a) (i) Zn (8 equiv), EtOH, reflux, 1.5 h; (b) $Ph_3P{=}CHCO_2Et$ (2 equiv), toluene, reflux, 2 h, 45% [2 steps for (*E*)-**7**]; (c) (*S*)-hept-6-en-2-yl acetate (2.5 equiv), Grubbs II catalyst (5 mol%), CH_2Cl_2, (0.04 M), reflux, 4 h, 75%; (d) (i) LiOH (5 (equiv), THF–H_2O (2:1), reflux, 5 h, 77%, (ii) 2,4,6-trichlorobenzoyl chloride (1.2 (equiv), Et_3N (1.2 (equiv), DMAP, toluene, reflux, 10 h, 32%.

At this stage, we envisaged the formation of macrolactone **11** by introduction of the unsaturation in the saturated macrolactone **14**. Thus, hydrogenation of **10** with palladium-on-carbon followed by hydrolysis of the ester groups afforded the hydroxy acid **13** in good yield. Yamaguchi lactonization of the hydroxy acid **13** afforded the macrolactone **14** in 65% yield. Introduction of the unsaturation by selenation and oxidative deselenation[10] yielded the unsaturated lactone **11** as an inseparable mixture with the starting lactone **14** (Scheme 3).



Scheme 3 Synthesis of the macrolactone **11**. *Reagents and conditions:* (a) H_2, Pd/C, hexane, 2 h, 95%; (b) LiOH (5 equiv), THF–H_2O (2:1), reflux, 6 h, 88%; (c) 2,4,6-trichlorobenzoyl chloride (1.2 equiv), Et_3N (1.2 equiv), DMAP, toluene, reflux, 10 h, 65%; (d) (i) LDA, PhSeBr, THF, –78 °C; (ii) H_2O_2, pyridine, 0 °C (inseparable mixture with **14**).

Owing to the cumbersome separations involved in the synthesis of **11**, we redrew our retrosynthesis and envisaged the synthesis of **11** by Yamaguchi macrolactone formation of the hydroxy acid **15**. Elaboration of the primary alcohol in **16** by Wittig reaction was planned for the synthesis of **15**. Olefin cross metathesis of **17** with hept-6-en-2-ol followed by hydrogenation should furnish **16**. Formation of **17** from D-ribose is a well-established procedure (Scheme 4).[7]

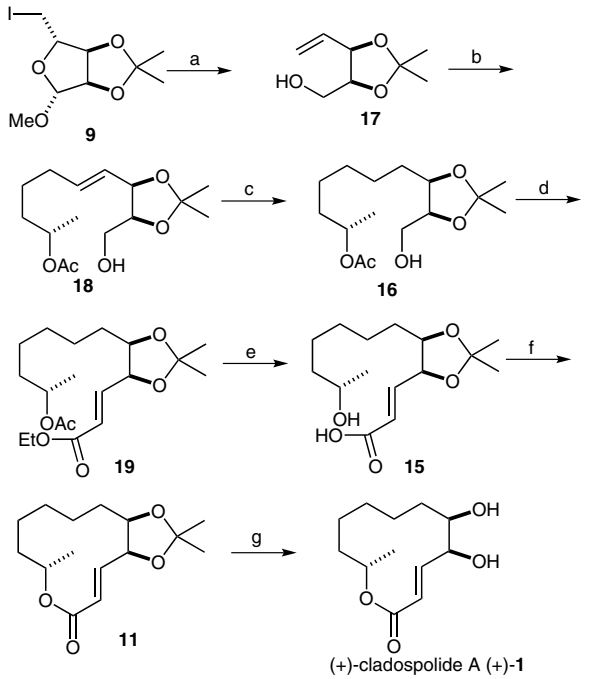


Scheme 4 Revised retrosynthesis for cladospolide A [(+)-**1**]

Accordingly, the synthetic sequence commenced with the reduction of the aldehyde **8** derived from **9** to yield the known alcohol **17** in 74% yield for two steps.[11] Olefin cross metathesis of **17** with (*S*)-hept-6-en-2-yl acetate proceeded smoothly to yield the cross-metathesis product **18** in 76% yield.[8] Hydrogenation of **18** furnished the alcohol **16** in almost quantitative yield. The primary hydroxy group in **16** was oxidized with IBX to the corresponding aldehyde, which on Wittig olefination produced the α,β-unsaturated ester **19** in 72% yield. Saponification of the esters in **19** with lithium hydroxide afforded the hydroxy acid **15** in 93% yield. Using the procedure reported by Mori et al., macrolactone formation under Yamaguchi lactonization conditions yielded the macrolactone **11**, which on deprotection of the acetonide with trifluoroacetic acid furnished (+)-cladospolide A [(+)-**1**] in 54% yield (Scheme 5).

In conclusion, total synthesis of (+)-cladospolide A from D-ribose was accomplished in 11 linear steps in ~9% overall yield. During the course of the synthesis, it was found that the selective hydrogenation of an electron-rich olefin in the macrolactone and the introduction of α,β-unsaturation in the saturated macrolactone to form cladospolide A were difficult. This was overcome by assembly of the hydroxy acid precursor required for the synthesis of the macrolactone by an efficient olefin-cross-metathesis reaction of an alkenol derived from D-ribose. The macrolactone formation was accomplished employing Yamaguchi macrolactonization.

NMR spectra were recorded on a Bruker 400 instrument and MS data were recorded on a Waters Q-TOF machine. Optical rotations were recorded on Jasco-DIP digital polarimeter and IR spectra were recorded on a Jasco infrared spectrophotometer. Column chromatography was performed on silica gel, Acme grade 100–200 mesh;



Scheme 5 Total synthesis of (+)-cladospolide A: *Reagents and conditions:* (a) (i) Zn (8 equiv), EtOH, reflux, 1.5 h, (ii) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 1 h, 74% (2 steps); (b) (*S*)-hept-6-en-2-yl acetate (2.5 equiv), Grubbs' 2nd generation catalyst (5 mol%), CH_2Cl_2, (0.04 M), 40 °C, 4 h, 76%; (c) H_2, Pd/C, hexane, 2 h, 99%; (d) (i) IBX (2 equiv), EtOAc, reflux, 2 h, (ii) $(EtO)_2P(O)CH_2CO_2Et$ (2 (equiv), NaH (1.5 equiv), 0 °C, 1 h, 72% (2 steps); (e) LiOH (5 equiv), THF–H_2O (2:1), reflux, 4 h, 93%; (f) 2,4,6-trichlorobenzoyl chloride (1.2 equiv), Et_3N (1.2 equiv), DMAP, toluene, reflux, 10 h, 46%; (g) TFA, MeCN–H_2O (2:1), 0 °C to r.t., 2 h, 54%.

petroleum ether = PE. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na/benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, all the reactions were performed under inert atmosphere. Iodide **9** was prepared according the procedure described in the literature.[7]

Ethyl (*E*)-3-[(4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)acrylate [(*E*)-7] and Ethyl (*Z*)-3-[(4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]acrylate [(*Z*)-7]

To a soln of the iodide **9** (0.92 g, 2.93 mmol) in abs EtOH (7 mL) was added Zn dust (1.55 g, 23.44 mmol) at r.t. and the mixture was refluxed for 1.5 h (TLC monitoring). When the reaction was complete, the mixture was filtered through a short pad of Celite, and the Celite pad was washed with CH_2Cl_2 (25 mL). The solvent was evaporated and the crude aldehyde thus obtained was used in the next step without purification.

To a stirred soln of the crude aldehyde (obtained above) in anhyd toluene (15 mL) was added $Ph_3PCH{=}CO_2Et$ (1.83 g, 5.27 mmol) under a N_2 atmosphere and the mixture was refluxed for 2 h (TLC monitoring. When the reaction was complete, the mixture was cooled to r.t. and most of the solvent was evaporated off. The crude residue thus obtained was purified by column chromatography (silica gel, PE–EtOAc, 4:1) to afford (*E*)-**7** (0.3 g, 45% for 2 steps) and (*Z*)-**7** (0.146 g, 22%) as colorless oils.

(*E*)-7

$[\alpha]_D^{24}$ –36.4 (*c* 0.7, $CHCl_3$).

IR (neat): 2987, 2937, 2906, 1724, 1661, 1374, 1164, 1048 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.75 (dd, *J* = 15.5, 5.5 Hz, 1 H), 6.03 (dd, *J* = 15.6, 1.2 Hz, 1 H), 5.66 (ddd, *J* = 17.4, 9.8, 7.2 Hz, 1 H), 5.33 (d, *J* = 17.0 Hz, 1 H), 5.23 (d, *J* = 10.2 Hz, 1 H), 4.74 (t, *J* = 6.7 Hz, 1 H), 4.67 (t, *J* = 7.2 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 1.52 (s, 3 H), 1.38 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 143.5, 133.4, 122.7, 119.3, 109.5, 79.7, 77.4, 60.5, 27.7, 25.3, 14.2.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{18}O_4Na$: 249.1103; found: 249.1105.

(*Z*)-7

$[\alpha]_D^{24}$ +195.3 (*c* 1.65, $CHCl_3$).

IR (neat): 2988, 2940, 2906, 1718, 1221, 1191, 1046 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.16 (dd, *J* = 11.6, 7.4 Hz, 1 H), 5.88 (dd, *J* = 11.6,1.3 Hz, 1 H), (5.75–5.57 (m, 2 H), 5.27 (d, *J* = 17.0 Hz, 1 H), 5.15 (d, *J* = 10.3 Hz, 1 H), 4.86 (t, *J* = 7.0 Hz, 1 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 1.54 (s, 3 H), 1.41 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 146.3, 133.9, 121.4, 117.8, 109.1, 79.6, 75.6, 60.3, 27.8, 25.1, 14.2.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{18}O_4Na$: 249.1103; found: 249.1105.

(*S*)-Hept-6-en-2-yl Acetate

To a suspension of CuCN (0.06 g, 2.54 mmol) in THF (2 mL) was added to but-3-enylmagnesium bromide (23 mL of 0.6 M soln in THF, 13.8 mmol) at 0 °C and was stirred for 10 min at the same temperature. (*S*)-Propylene oxide (0.48 mL, 6.9 mmol) was added and the mixture was warmed to r.t. and stirred overnight (TLC monitoring). When the reaction was complete, the mixture was quenched by addition of sat. aq NH_4Cl (15 mL) and it was extracted with Et_2O (3 × 25 mL). The combined ethereal extracts were washed with brine (25 mL) and dried (Na_2SO_4). The solvent was evaporated off carefully at 20 °C and the residue thus obtained was subjected to the next step without further purification.

To a stirred soln of the crude residue (obtained above) in anhyd CH_2Cl_2 (10 mL) were added pyridine (3.56 mL, 44.632 mmol), DMAP (0.27 mg, 2.23 mmol), and Ac_2O (3.40 mL, 33.47 mmol) at 0 °C. The mixture was warmed to r.t. and stirred overnight (TLC monitoring). When the reaction was complete, ice-cold H_2O (10 mL) was added to the mixture, the aqueous layer was extracted with Et_2O (3 × 10 mL), and the combined extracts were dried (Na_2SO_4). Evaporation of Et_2O at 20 °C followed by column chromatography (silica gel, PE–Et_2O, 9:1) furnished (*S*)-hept-6-en-2-yl acetate (0.88 mg, 82% for 2 steps).

$[\alpha]_D^{24}$ +1.34 (*c* 1.1, $CHCl_3$) {Lit.[12] $[\alpha]_D$ +1.50 (*c* 1.58, $CHCl_3$)}.

IR (neat): 3078, 2978, 2864, 1737, 1642, 1373 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.89–5.68 (m, 1 H), 5.07–4.81 (m, 3 H), 2.13–2.10 (m, 2 H), 2.03 (s, 3 H), 1.65–1.34 (m, 4 H), 1.20 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 138.4, 114.7, 70.8, 35.3, 33.5, 24.6, 21.4, 19.9.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_9H_{16}O_2Na$: 179.1048; found: 179.1044.

Ethyl (*E*)-3-{(4*S*,5*R*)-5-[(*S*,*E*)-6-Acetoxyhept-1-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (10)

To a soln of **7** (0.123 g, 0.54 mmol) and (*S*)-hept-6-en-2-yl acetate (0.213 g, 1.35 mmol) in anhyd CH_2Cl_2 (14 mL) was added Grubbs' 2nd generation catalyst (0.025 g, 0.026 mmol) under N_2. The mixture was refluxed for 4 h under N_2 (TLC monitoring). When the reaction was complete, the solvent was evaporated off and the crude product was purified by column chromatography (silica gel, PE–EtOAc, 8.5:1.5) to afford **10** (0.145 g, 75%) as a light-brown oil.

$[\alpha]_D^{24}$ –62.5 (*c* 2.4, $CHCl_3$).

IR (neat): 2985, 2939, 1729, 1664, 1453, 1373, 1254, 1043 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.76 (dd, *J* = 5.3, 15.5 Hz, 1 H), 6.03 (d, *J* = 15.7 Hz, 1 H), 5.83–5.66 (m, 1 H), 5.31 (dd, *J* = 8.1, 15.3 Hz, 1 H), 4.84 (sextet, *J* = 6.1 Hz, 1 H), 4.76–4.58 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 2.13–1.94 (m, 2 H), 1.99 (s, 3 H), 1.59–0.81 (m, 10 H), 1.26 (t, *J* = 7.1Hz, 3 H), 1.18 (d, *J* = 4.8Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 165.9, 144.0, 136.3, 125.4, 122.5, 109.2, 79.6, 77.5, 70.7, 60.4, 35.3, 31.9, 27.8, 25.3, 24.6, 21.3, 19.9, 14.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{30}O_6Na$: 377.1940; found: 377.1942.

(*E*)-3-{(4*S*,5*R*)-5-[(*S*,*E*)-6-Hydroxyhept-1-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylic Acid (6)

To a stirred soln of **10** (0.110 g, 0.31 mmol) in THF (4.0 mL) was added 1 M aq LiOH (2.0 mL, 2.0 mmol) and the mixture was refluxed for 5 h (TLC monitoring). After completion of the reaction, the mixture was diluted with H_2O (5 mL), neutralized with dil. HCl (pH 4), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure and the resulting crude residue was subjected to column chromatography (silica gel, EtOAc) to afford **6** (0.065 g, 77%) as a colorless oil.

$[\alpha]_D^{24}$ –67.1 (*c* 2.6, $CHCl_3$).

IR (neat): 3432, 2931, 1704, 1661, 1377, 1043 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 5.2, 15.5 Hz, 1 H), 6.43 (br s, 2 H), 6.06 (d, *J* = 15.5 Hz, 1 H), 5.80–5.57 (m, 1 H), 5.30 (dd, *J* = 15.4, 8.15 Hz, 1 H), 4.77 (t, *J* = 6.0 Hz, 1 H), 4.69 (t, *J* = 7.5 Hz, 1 H), 3.86–3.70 (m, 1 H), 2.17–2.00 (m, 2 H), 1.58–1.13 (m, 10 H), 1.16 (d, *J* = 6.18 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 146.2, 135.7, 126.1, 121.8, 109.4, 79.5, 77.3, 68.2, 38.2, 32.0, 27.8, 25.3, 24.7, 22.7.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{24}O_5Na$: 307.1521; found: 307.1519.

(3a*S*,4*E*,8*S*,12*E*,13a*R*)-2,2,8-Trimethyl-3a,8,9,10,11,13a-hexahydro-6*H*-[1,3]dioxolo[4,5-*e*]oxacyclododecin-6-one (5)

To a soln of the acid **6** (0.030 g, 0.1 mmol) and Et_3N (0.02 mL, 0.12 mmol) in anhyd THF (1.0 mL) was added 2,4,6-trichlorobenzoyl chloride (0.02 mL, 0.12 mmol) dropwise under an argon atmosphere at 0 °C. The mixture was stirred at r.t. for 2 h and diluted with anhyd toluene (14 mL); it was added dropwise to a refluxing soln of DMAP (0.415 g, 3.4 mmol) in anhyd toluene (33 mL). On completion of the addition, the mixture was refluxed for 10 h, cooled to r.t. and concentrated in vacuo. The resulting residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (10 mL), sat. $NaHCO_3$ (5 mL), and brine (5 mL), and dried (anhyd Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, PE–Et_2O, 9:1) furnished the macrolactone **5** (9 mg, 32%).

$[\alpha]_D^{24}$ –38.4 (*c* 0.9, $CHCl_3$).

IR (neat): 2986, 2938, 1717, 1380, 1252, 1056 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.67 (ddd, *J* = 16.1, 12.4, 3.8 Hz, 1 H), 5.81 (d, *J* = 16.1 Hz, 1 H), 5.82–5.66 (m, 1 H), 5.33 (dd, *J* = 15.9, 5.1 Hz, 1 H), 4.96 (dt, *J* = 16.5, 5.9 Hz, 1 H), 4.85–4.64 (m, 2 H), 2.08–1.93 (m, 2 H), 1.79–1.46 (m, 4 H), 1.59 (s, 3 H), 1.42 (s, 3 H), 1.25 (d, *J* = 10.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 148.2, 134.0, 128.6, 122.3, 110.4, 79.4, 77.6, 73.3, 33.7, 30.8, 28.0, 25.5, 25.3, 18.9.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_4Na$: 289.1416; found: 289.1412.

Ethyl 3-{(4*S*,5*R*)-5-[(*S*)-6-Acetoxyheptyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanoate (12)

To a soln of **10** (0.148 g, 0.42 mmol) in hexane (5 mL) was added 10% Pd/C (7 mg) under an argon atmosphere. The mixture was stirred for 2 h under a H_2 atmosphere (TLC monitoring). When the reaction was complete, the mixture was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (10 mL). Evaporation of solvent followed by column chromatography (silica gel, PE–EtOAc, 8.5:1.5) yielded **12** (0.142 g, 95%) as a colorless oil.

$[\alpha]_D^{24}$ –16.3 (*c* 2.5, $CHCl_3$).

IR (neat): 2982, 2937, 2861, 1736, 1373, 1247, 1163 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.85 (qt, *J* = 12.2, 6.2 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.10–3.90 (m, 2 H), 2.57–2.27 (m, 2 H), 1.99 (s, 3 H), 1.83–1.60 (m, 2 H), 1.54–0.80 (m, 10 H), 1.38 (s, 3 H), 1.29 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H), 1.16 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 170.8, 107.6, 77.8, 76.9, 70.9, 60.3, 35.8, 30.7, 29.4, 29.3, 28.5, 26.2, 25.9, 25.3, 25.2, 21.4, 19.9, 14.2.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{19}H_{34}O_6Na$: 381.2253; found: 381.2249.

3-{(4*S*,5*R*)-5-[(*S*)-6-Hydroxyheptyl]-2,2-dimethyl-1,3-dioxolan-4-yl}propanoic Acid (13)

To a stirred soln of **12** (0.040 g, 0.112 mmol) in THF (3.0 mL) was added 1 M aq LiOH (0.67 mL, 0.67 mmol) and the mixture was refluxed for 6 h (TLC monitoring). After completion of the reaction, the mixture was diluted with H_2O (5 mL), neutralized with dil. HCl (pH 4), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). Solvent was removed under reduced pressure and column chromatography (silica gel, EtOAc) afforded **13** (0.028 g, 88%) as a colorless oil.

$[\alpha]_D^{24}$ –9.5 (*c* 2.8, $CHCl_3$).

IR (neat): 3444, 2933, 1714, 1661, 1379, 1219, 1063 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.14–3.96 (m, 2 H), 3.81–3.77 (m, 1 H), 2.63–2.46 (m, 1 H), 2.45–2.35 (m, 1 H), 1.79–1.64 (m, 2 H), 1.58–1.27 (m, 16 H), 1.17 (d, *J* = 6.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.2, 107.8, 77.8, 76.8, 68.2, 39.1, 30.5, 29.6, 29.3, 28.5, 26.3, 25.9, 25.5, 25.2, 23.3.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{28}O_5Na$: 311.1834; found: 311.1835.

(3a*S*,8*S*,13a*R*)-2,2,8-Trimethyldecahydro-6*H*-[1,3]dioxolo[4,5-*e*]oxacyclododecin-6-one (14)

To a soln of acid **13** (0.062 g, 0.22 mmol) and Et_3N (0.04 mL, 0.27 mmol) in anhyd THF (1.0 mL) was added 2,4,6-trichlorobenzoyl chloride (0.04 mL, 0.27 mmol) dropwise under an argon atmosphere at 0 °C. The mixture was stirred at r.t. for 2 h and diluted with anhyd toluene (27 mL); it was added dropwise to a refluxing soln of DMAP (0.859 g, 7.04 mmol) in anhyd toluene (66 mL). After the addition was complete, it was refluxed for 10 h, cooled to r.t. and then concentrated in vacuo. The resulting residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (10 mL), sat. $NaHCO_3$ (5 mL), and brine (5 mL) and dried (anhyd Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, PE–Et_2O, 9:1) furnished the macrolactone **14** (39 mg, 65%).

$[\alpha]_D^{24}$ –8.6 (*c* 2.2, $CHCl_3$).

IR (neat): 2987, 2939, 2863, 1731, 1246, 1220, 1062 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.93–4.75 (m, 1 H), 4.07–3.90 (m, 2 H), 2.59–2.47 (m, 1 H), 2.36 (td, *J* = 13.1, 2.8 Hz, 1 H), 2.25–2.11 (m, 1 H), 1.81–1.58 (m, 7 H), 1.48–1.03 (m, 4 H), 1.44 (s, 3 H), 1.33 (s, 3 H), 1.23 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 106.8, 79.2, 77.5, 69.8, 33.6, 33.5, 28.5, 27.1, 26.2, 26.1, 25.0, 24.9, 22.4, 20.4.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{15}H_{26}O_4Na$: 293.1729; found: 293.1719.

[(4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)methanol (17)
To a soln of iodide **9** (0.97 g, 3.11 mmol) in abs EtOH (7 mL) was added Zn dust (1.6 g, 24.9 mmol) at r.t. and the mixture was refluxed for 1.5 h (TLC monitoring). When the reaction was complete, the mixture was filtered through a short pad of Celite and the Celite pad was washed with CH_2Cl_2 (25 mL). The solvent was evaporated and the crude aldehyde was used in next step without purification.

To a stirred soln of above crude aldehyde in MeOH (7 mL) was added $NaBH_4$ (0.14 g, 3.73 mmol) portionwise at 0 °C. The mixture was slowly warmed to r.t. and stirred for 1 h (TLC monitoring). When the reaction was complete, most of the solvent was removed under reduced pressure, H_2O (10 mL) was added to the mixture, and it was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried (anhyd Na_2SO_4). Evaporation of solvent followed by column chromatography (silica gel, PE–EtOAc, 1:1) afforded alcohol **17** (0.362 g, 74% for 2 steps) as a colorless oil.

$[\alpha]_D^{24}$ –39.7 (*c* 1.6, $CHCl_3$).

IR (neat): 3446, 2988, 2937, 2882, 1646, 1381, 1217, 1049, 927 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 (ddd, *J* = 17.2, 10.2, 7.3 Hz, 1 H), 5.38 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 10.3 Hz, 1 H), 4.63 (t, *J* = 7.2 Hz, 1 H), 4.25 (q, *J* = 6.0 Hz, 1 H), 3.56 (t, *J* = 5.7 Hz, 2 H), 2.01 (br s, 1 H), 1.50 (s, 3 H), 1.38 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.0, 118.9, 108.9, 78.3 (2 × CH), 62.0, 27.8, 25.2.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_8H_{14}O_3Na$: 181.0841; found: 181.0831.

(*S*,*E*)-7-[(4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]hept-6-en-2-yl Acetate (18)
To a soln of **17** (0.1 g, 0.65 mmol) and (*S*)-hept-6-en-2-yl acetate (0.254 g, 1.63 mmol) in anhyd CH_2Cl_2 (17 mL) was added Grubbs II catalyst (0.028 g, 0.032 mmol) under N_2. The mixture was stirred at 40 °C for 4 h under N_2 (TLC monitoring). When the reaction was complete, the solvent was evaporated and the crude product was purified by column chromatography (silica gel, PE–EtOAc, 1:1) to afford **18** (0.142 g, 76%) as a light-brown oil.

$[\alpha]_D^{24}$ –33.2 (*c* 1.9, $CHCl_3$).

IR (neat): 3460, 2984, 2918, 1731, 1584, 1380 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.78 (dt, *J* = 14.7, 6.7 Hz, 1 H), 5.48 (dd, *J* = 15.4, 8.1 Hz, 1 H), 4.86 (sextet, *J* = 6.4 Hz, 1 H), 4.60 (t, *J* = 7.4 Hz, 1 H), 4.20 (q, *J* = 6.0 Hz, 1 H), 3.55 (t, *J* = 5.3 Hz, 2 H), 2.15–2.04 (m, 3 H), 2.00 (s, 3 H), 1.62–1.30 (m, 10 H), 1.18 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 136.0, 124.9, 108.6, 78.3, 78.2, 70.7, 62.2, 35.3, 32.0, 27.8, 25.2, 24.7, 21.4, 19.9.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{26}O_5Na$: 309.1678; found: 309.1676.

(*S*)-7-[(4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]heptan-2-yl Acetate (16)
To a soln of **18** (0.120 g, 0.42 mmol) in EtOAc (6 mL) was added 10% Pd/C (8 mg) under an argon atmosphere. The mixture was stirred for 2 h under a H_2 atmosphere. After completion of the reaction it was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (10 mL). Evaporation of the solvent followed by column chromatography (silica gel, PE–EtOAc, 7:3) yielded **16** (0.12 g, 99%) as a colorless oil.

$[\alpha]_D^{24}$ –17.2 (*c* 1.2, $CHCl_3$).

IR (neat): 3440, 2935, 1736, 1591, 1374, 1247, 1040 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.86 (sextet, *J* = 6.2 Hz, 1 H), 4.20–4.04 (m, 2 H), 3.63–3.52 (br d, *J* = 4.3 Hz, 2 H), 2.03–2.0 (m, 1 H), 2.0 (s, 3 H), 1.61–1.19 (m, 10 H), 1.45 (s, 3 H), 1.34 (s, 3 H), 1.18 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 108.0, 77.9, 76.9, 70.9, 61.8, 35.8, 29.4, 28.8, 28.3, 26.6, 25.5, 25.2, 21.4, 19.9.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{28}O_5Na$: 311.1834; found: 311.1844.

Ethyl (*E*)-3-{(4*S*,5*R*)-5-[(*S*)-6-Acetoxyheptyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylate (19)
To a stirred soln of the alcohol **16** (0.056 g, 0.19 mmol) in EtOAc (2 mL) was added IBX (0.11 g, 0.38 mmol) and the resulting mixture was refluxed for 2 h. After completion of reaction, the mixture was filtered through a short pad of Celite and the Celite pad was washed with EtOAc (15 mL). The organic layer was washed with sat. $NaHCO_3$ soln (10 mL) and brine (15 mL), and dried (anhyd Na_2SO_4). The crude aldehyde obtained after evaporation of the solvent was used in the next step without purification.

To a slurry of NaH (0.012 g, 60% suspension in mineral oil, 0.28 mmol) in anhyd THF (1 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.08 mL, 0.38 mmol) dropwise at 0 °C and the mixture was stirred at this temperature for 30 min. The crude aldehyde (obtained above) was dissolved in anhyd THF (1 mL) and was introduced into the mixture and stirred at –15 °C for 30 min. It was then warmed to r.t. and stirred for another 30 min at r.t. After completion of reaction (TLC monitoring) it was quenched with sat. NH_4Cl soln (10 mL) and extracted with Et_2O (3 × 10 mL). The combined ethereal extracts were washed with brine (15 mL) and dried (anhyd Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, PE–EtOAc, 9:1) yielded **19** (0.048 g, 72% for 2 steps) as a colorless oil.

$[\alpha]_D^{24}$ –4.6 (*c* 1.2, $CHCl_3$).

IR (neat): 2985, 2939, 2863, 1729, 1659, 1590, 1374, 1250 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 15.6, 6.1 Hz, 1 H), 6.05 (d, *J* = 15.6 Hz, 1 H), 4.86 (sextet, *J* = 12.5, 6.1 Hz, 1 H), 4.63 (t, *J* = 6.2 Hz, 1 H), 4.27–4.10 (m, 3 H), 2.0 (s, 3 H), 1.50 (s, 3 H), 1.36 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.62–1.13 (m, 10 H), 1.18 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 166.0, 143.7, 123.0, 108.8, 78.3, 77.4, 70.9, 60.5, 35.8, 30.4, 29.3, 28.0, 26.2, 25.5, 25.2, 21.4, 19.9, 14.2.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{32}O_6Na$: 379.2097; found: 379.2099.

(*E*)-3-{(4*S*,5*R*)-5-[(*S*)-6-Hydroxyheptyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acrylic Acid (15)
To a stirred soln of **19** (0.046 g, 0.13 mmol) in THF (2.0 mL) was added 1 M aq LiOH (0.8 mL, 0.8 mmol) and the mixture was refluxed for 4 h (TLC monitoring). After completion of the reaction, it was diluted with H_2O (5 mL), neutralized with dil. HCl (pH 4), and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL), and dried (anhyd Na_2SO_4). The solvent was removed under reduced pressure and column chromatography (silica gel, EtOAc) afforded **15** (0.033 g, 93%) as a colorless oil.

$[\alpha]_D^{24}$ +1.1 (*c* 1.35, MeOH) {Lit.[4b] $[\alpha]_D$ –1.1 (*c* 1.30, MeOH) for the enantiomer}.

IR (neat): 3455, 2934, 2860, 1704, 1660, 1461, 1376, 1260, 1039 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.93 (dd, *J* = 15.5, 6.0 Hz, 1 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 5.94–5.50 (br m, 2 H), 4.67 (t, *J* = 6.0 Hz, 1 H), 4.30–4.18 (m, 1 H), 3.85–3.72 (m, 1 H), 1.60–1.20 (m, 10 H), 1.51 (s, 3 H), 1.38 (s, 3 H), 1.18 (d, *J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 146.1, 122.4, 108.9, 78.3, 77.2, 68.2, 39.0, 30.4, 29.4, 28.0 (2 C), 26.1, 25.5, 23.3.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{26}O_5Na$: 309.1678; found: 309.1692.

(3a*S*,8*S*,13a*R*,*E*)-2,2,8-Trimethyl-3a,8,9,10,11,12,13,13a-hexahydro-6*H*-[1,3]dioxolo[4,5-*e*]oxacyclododecin-6-one (11)

To a soln of the acid **15** (0.05 g, 0.17 mmol) and Et_3N (0.04 mL, 0.23 mmol) in anhyd THF (1.5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.04 mL, 0.23 mmol) dropwise under an argon atmosphere at 0 °C. The mixture was stirred at r.t. for 2 h and diluted with anhyd toluene (25 mL); the mixture was added dropwise to a refluxing soln of DMAP (0.74 g, 6.08 mmol) in anhyd toluene (58 mL). After the addition was complete, it was refluxed for 10 h, cooled to r.t., and concentrated in vacuo. The resulting residue was dissolved in EtOAc (25 mL) and washed with 1 M HCl (10 mL), sat. $NaHCO_3$ (5 mL), and brine (5 mL), and dried (anhyd Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, PE–Et_2O, 9:1) furnished the macrolactone **11** (20 mg, 46%).

$[\alpha]_D^{24}$ +15.1 (*c* 0.9, $CHCl_3$) {Lit.[4b] $[\alpha]_D$ –18.4 (*c* 1.44, $CHCl_3$) for enantiomer}.

IR (neat): 2983, 2939, 2869, 1719, 1593 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (dd, *J* = 15.8, 8.9 Hz, 1 H), 6.06 (d, *J* = 15.9 Hz, 1 H), 5.20–5.08 (m, 1 H), 4.70 (dd, *J* = 8.8, 6.3 Hz, 1 H), 4.12 (dd, *J* = 10.1, 6.8 Hz, 1 H), 1.85–1.20 (m, 10 H), 1.50 (s, 3 H), 1.37 (s, 3 H), 1.29 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 145.2, 124.4, 109.5, 79.6, 76.5, 72.8, 33.5, 30.8, 28.2, 28.0, 25.5, 21.9, 20.1, 18.4.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{24}O_4Na$: 291.1572; found: 291.1578.

(5*S*,6*R*,12*S*,*E*)-5,6-Dihydroxy-12-methyloxacyclododec-3-en-2-one [(+)-Cladospolide A, (+)-1]

To an ice-cold soln of macrolactone **11** (16 mg, 0.059 mmol) in MeCN–H_2O (2:1, 1.5 mL) was added TFA (0.08 mL) dropwise. The mixture was slowly warmed to r.t. and stirred for 2 h at the same temperature. Solid $NaHCO_3$ was introduced, the mixture was stirred for 10 min at 0 °C, it was filtered through a short pad of Celite, and the Celite pad was washed with EtOAc (10 mL). The combined organic layers were washed with brine (5 mL) and dried (anhyd Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, PE–EtOAc, 1:4) afforded (+)-**1** (7 mg, 54%) as a colorless solid; mp 91–92 °C [Lit.[4b] mp 92–92.6 °C].

$[\alpha]_D^{24}$ +46.0 (*c* 0.25, $CHCl_3$) {Lit.[4b] $[\alpha]_D$ –49.3 (*c* 0.224, $CHCl_3$) for enantiomer}.

IR (KBr) 3470, 2938, 2858, 1709, 1450 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (dd, *J* = 15.9, 5.7 Hz, 1 H), 6.20 (d, *J* = 15.9 Hz, 1 H), 5.20–5.05 (m, 1 H), 4.60–4.50 (m, 1 H), 3.67 (d, *J* = 9.4 Hz, 1 H), 2.57–2.33 (br s, 2 H), 1.90–1.11 (m, 10 H), 1.28 (d, *J* = 6.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 145.6, 122.3, 74.7, 73.0, 72.9, 32.5, 30.7, 28.1, 25.0, 22.6, 19.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}O_4Na$: 251.1259; found: 251.1251.

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(9) Hydrogenation under a H_2 atmosphere with 10% Pd/C as catalyst afforded the saturated lactone **14** in 99% yield. Use of Pd/$BaSO_4$ as a catalyst in the hydrogenation afforded a lactone in which the electron-deficient double bond was hydrogenated. Hydrogenation did not proceed when $RhCl(PPh_3)_3$ was used as the catalyst. For selective hydrogenation of an electron-rich olefin in a structurally similar macrolactone see: (a) Nishioka, T.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Tetrahedron Lett.* **1998**, *39*, 5597. (b) Yadav, J. S.; Rao, T. S.; Ravinder, K.; Reddy, B. V. S. *Synlett* **2009**, 2828.

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