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Stereoselective Synthesis and Determination of the Cytotoxic Properties of Spicigerolide and Three of Its Stereoisomers

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General. ^1H NMR spectra (500 MHz) and ^{13}C NMR spectra (125 MHz) were measured at 25 °C. The signals of the deuterated solvent (CDCl_3) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C NMR signals were assigned with the aid of the DEPT pulse sequence. Mass spectra were run using the electron impact mode (EIMS, 70 eV). IR data, which were measured on NaCl plates, are given only for molecules with relevant functional groups. Experiments which required an inert atmosphere were carried out under dry nitrogen in a flame-dried glassware. Et_2O and THF were freshly distilled from sodium/benzophenone ketyl and transferred via syringe. Dichloromethane was freshly distilled from CaH_2 . Tertiary amines were freshly distilled from KOH. Toluene was distilled from sodium wire and stored over molecular sieves. Unless detailed otherwise, "work-up" means pouring the reaction mixture into brine, extraction with solvent (indicated in parenthesis), additional washing with 5% aq NaHCO_3 (if the reaction medium was acidic) or with 5% aq HCl (if the reaction medium was basic), then again with brine, drying over anhydrous Na_2SO_4 and elimination of the solvent under reduced pressure. The obtained material was then chromatographed on a silica gel column (60-200 μm) with the indicated eluent. Where solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent used, and the washings incorporated to the main organic layer. Commercially available reagents were used as received.

Cytotoxicity assays.¹ Lactones **1**, **5**, **6** and **7** were carefully purified by means of HPLC prior to cytotoxicity determinations. The HPLC instrumentation used consisted of a Waters (Millipore Corp., Waters Chromatography Division, Milford, MA) 600E multisolvent delivery system equipped with a Waters W996 diode array detector (254 nm). Control of the equipment, data acquisition, processing, and management of chromatographic information were performed by the Millennium 32 software program (Waters). Purifications were performed on an ISCO Si gel column ($\mu\text{Porasil}$, 10 μm ; 250 $\times$ 10 mm). The elution was isocratic with hexane-EtOAc (3:2) and a flow rate of 3 mL/min. Ellipticine was included as a positive drug control: ED_{50} = 0.17 $\mu\text{g/mL}$ (HCT-15), 0.04 $\mu\text{g/mL}$ (UIO), 0.10 $\mu\text{g/mL}$ (KB), 0.13 $\mu\text{g/mL}$ (OVCAR).

ED_{50} determinations. Nasopharyngeal carcinoma (KB), colon cancer (HCT-15), squamous cell cervix carcinoma (SQC-1 UIO) and ovarian cancer (OVCAR) cell lines were cultured in RMPI 1640 (10 $\times$) medium supplemented with 10% fetal bovine serum and penicillin-streptomycin (0.1%) at 37 °C and 100% relative humidity with 5% CO_2 air. Cells were typically grown to 60-70% confluence; the medium was then changed, and the cells were used for test procedures 1 day later. In each case, 96-well tissue culture plates were used. Test samples were initially dissolved in DMSO, and then diluted tenfold with H_2O . Five-fold serial dilutions (20–0.16 $\mu\text{g/mL}$) were then performed using 10% aqueous DMSO as the solvent (10 μL); 3–5 $\times 10^4$ cells (in 190 μL of media) were added to the 96-well plates and incubations performed for 72 h. All assays were performed in triplicate at 37 °C in a CO_2 incubator with the plates covered by vented plastic lids.

After the incubation period, cells were fixed to the plastic substratum by the addition of 50 μ L of cold 50% aqueous trichloroacetic acid, stained by the addition of 0.4% sulforhodamine B (w/v) dissolved in 1% HOAc (30 min) and washed with 1% aqueous HOAc (4 $\times$). The bound dye was solubilized by the addition of 10 mmol unbuffered Tris base, pH 10 (200 μ L). The absorption was determined at 540 nm using an ELISA plate reader. In each case, a zero-day control was performed by adding an equivalent number of cells to eight wells of each plate and incubating at 37 $^{\circ}$ C for 10 min. The cells were then fixed and processed as described above. Finally, the absorption values obtained with each of the treatment procedures were averaged, and the average value obtained with the zero-day control was subtracted. These values were then expressed as a percentage, relative to the solvent-treated control incubations. Results were expressed as the dose that inhibits 50% control growth (ED_{50}). This value was calculated using nonlinear regression analysis (percent survival versus concentration).

¹Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, 82, 1107-1112.

The compounds described herein have been prepared according to the same procedures described in the main text of the paper.

(4*S*,5*Z*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-7-[(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-1,3]dioxolan-4-yl]-hepta-1,5-dien-4-ol (16). The experimental procedure was the same as for the conversion of **12** into **13** except for the use of (–)-*diisopinocampheyl*boron chloride. Column chromatography on silica gel (hexanes-EtOAc, 9:1) afforded alcohol **16** in 84% yield as a 96:4 mixture of epimers (the major one indicated in Scheme 5): ¹H NMR (500 MHz) δ 5.85 (1H, m), 5.60-5.50 (2H, m), 5.18 (1H, br d, J = 18 Hz), 5.16 (1H, br d, J = 10 Hz), 4.62 (1H, dd, J = 8, 4.5 Hz), 4.50 (1H, m), 3.95-3.85 (3H, m), 2.35-2.25 (2H, m), 1.90 (1H, br s), 1.39 (3H, s), 1.38 (3H, s), 1.19 (3H, d, J = 6 Hz), 0.91 (18H, s), 0.11 (3H, s), 0.09 (9H, s); ¹³C NMR (125 MHz) δ 109.2, 18.2, 18.1 (C), 134.0, 133.4, 131.7, 82.1, 81.8, 69.9, 69.7, 67.0 (CH), 118.5, 42.0 (CH₂), 27.7, 27.6, 26.0, 25.9, 20.0, –4.0, –4.2, –4.3, –4.4 (CH₃). IR (NaCl) 3480 (br, OH) cm^{-1} . HR EIMS m/z (rel. int.) 485.3110 [M^+ –Me] (3), 367 (11), 293 (15), 253 (33), 241 (41), 159 (100), 131 (54), 73 (74). Calcd. for C₂₆H₅₂O₅Si₂–Me, 485.3118.

(1S,2Z,4S)-1-Allyl-4-(tert-butyldimethylsilyloxy)-4-[(4R,5R)-5-[(1S)-1-(tert-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-2-enyl acrylate (17). Alcohol **16** (epimer mixture) was subjected to the same acryloylation procedure as for **13** → **14**. Column chromatography on silica gel (hexanes-EtOAc, 19:1) furnished acrylate **17** in 75% yield as a single diastereoisomer: colorless oil; $[\alpha]_D +2.1$ (c 0.9; CHCl_3). ^1H NMR (500 MHz) δ 6.38 (1H, br d, $J = 17.5$ Hz), 6.10 (1H, dd, $J = 17.2, 10.4$ Hz), 5.81 (1H, br d, $J = 10.4$ Hz), 5.75 (2H, m), 5.55-5.50 (2H, m), 5.15-5.05 (2H, m), 4.69 (1H, t, $J = 6$ Hz), 4.00 (1H, t, $J = 6$ Hz), 3.94 (1H, quint, $J = 6$ Hz), 3.80 (1H, t, $J = 6$ Hz), 2.45 (2H, t, $J = 6.5$ Hz), 1.44 (3H, s), 1.38 (3H, s), 1.19 (3H, d, $J = 6.2$ Hz), 0.92 (9H, s), 0.88 (9H, s), 0.09 (9H, s), 0.01 (3H, s); ^{13}C NMR (125 MHz) δ 165.1, 109.3, 18.2, 18.1 (C), 135.0, 133.0, 128.7, 128.3, 82.2, 81.3, 70.0, 69.4, 69.1 (CH), 130.56, 118.2, 39.3 (CH_2), 27.7, 27.6, 26.0, 25.9, 19.5, -4.2, -4.3, -4.4, -4.6 (CH_3). IR (NaCl) 1726 ($\text{C}=\text{O}$) cm^{-1} . HR EIMS m/z (rel. int.) 539.3207 [$\text{M}^+ - \text{Me}$] (2), 367 (12), 295 (8), 224 (14), 159 (100), 129 (33), 73 (61). Calcd. for $\text{C}_{29}\text{H}_{54}\text{O}_6\text{Si}_2 - \text{Me}$, 539.3224. Anal. Calcd. for $\text{C}_{29}\text{H}_{54}\text{O}_6\text{Si}_2$: C, 62.77; H, 9.81. Found, C, 62.62; H, 9.66.

(6S)-6-[(3S)-3-tert-Butyldimethylsilyloxy-3-[(4R,5R)-5-[(1S)-1-(tert-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-prop-1Z-enyl]-5,6-dihydropyran-2-one (18). Acrylate **17** was subjected to RCM under the same conditions as for **14** → **15**. This afforded α,β -unsaturated lactone **18** in 78% yield as a colorless oil: $[\alpha]_D -10.6$ (c 0.9; CHCl_3). ^1H NMR (500 MHz) δ 6.87 (1H, dt, $J = 9.7, 4$ Hz), 6.05 (1H, br d, $J = 9.7$ Hz), 5.70 (2H, m), 5.21 (1H, dt, $J = 8, 8$ Hz), 4.47 (1H, dd, $J = 8.5, 5.5$

Hz), 3.88 (2H, m), 3.79 (1H, t, $J = 6$ Hz), 2.42 (2H, m), 1.37 (6H, s), 1.20 (3H, d, $J = 6$ Hz), 0.89 (18H, s), 0.10 (3H, s), 0.08 (9H, s); ^{13}C NMR (125 MHz) δ 163.5, 109.3, 18.1, 18.0 (C), 144.4, 135.1, 127.9, 121.8, 82.5, 81.6, 73.9, 70.1, 69.9 (CH), 29.7 (CH₂), 27.7, 27.6, 26.0, 25.9, 20.4, -3.9, -4.2, -4.3, -4.5 (CH₃). IR (NaCl) 1740 (br, C=O) cm^{-1} . HR EIMS m/z (rel. int.) 511.2919 [$\text{M}^+ - \text{Me}$] (6), 469 (14), 411 (28), 367 (32), 267 (50), 159 (100), 73 (36). Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2 - \text{Me}$, 511.2911. Anal. Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2$: C, 61.55; H, 9.57. Found, C, 61.66; H, 9.70.

(6S)-6-[(1Z,3S,4S,5S,6S)-(3,4,5,6-Tetraacetoxyhept-1-enyl)]-5,6-dihydropyran-2-one (5). Cleavage of protecting groups in lactone **18** and subsequent peracetylation was performed as for **15** $\rightarrow$ **1**. Column chromatography on silica gel (hexanes-EtOAc, 7:3) provided **5** in 57% as a colorless oil: $[\alpha]_{589} -44$, $[\alpha]_{578} -48$, $[\alpha]_{546} -56$, $[\alpha]_{436} -108$, $[\alpha]_{365} -207$ (c 0.64; CHCl_3). ^1H NMR (500 MHz) δ 6.90 (1H, dt, $J = 9.8, 4$ Hz), 6.08 (1H, br d, $J = 9.8$ Hz), 5.88 (1H, dd, $J = 10.5, 8$ Hz), 5.60 (1H, t, $J = 10.5$ Hz), 5.52 (1H, dd, $J = 9.8, 7.7$ Hz), 5.45-5.35 (2H, m), 5.28 (1H, br d, $J = 8$ Hz), 4.96 (1H, quint, $J = 6$ Hz), 2.45-2.40 (2H, m), 2.11 (3H, s), 2.07 (3H, s), 2.05 (3H, s), 2.03 (3H, s), 1.20 (3H, d, $J = 6$ Hz); ^{13}C NMR (125 MHz) δ 170.0, 169.9, 169.6, 169.5, 163.2 (C), 144.0, 134.1, 126.9, 121.8, 73.9, 71.0, 69.8, 67.0, 66.0 (CH), 30.0 (CH₂), 21.1, 20.8, 20.7, 20.6, 16.4 (CH₃). IR (NaCl) 1744 (br, C=O) cm^{-1} . HR EIMS m/z (rel. int.) 427.1600 [$\text{M} + \text{H}^+$] (1), 367 (12), 231 (40), 204 (55), 178 (73), 136 (100). Calcd. for $\text{C}_{20}\text{H}_{27}\text{O}_{10}$, 427.1604. Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_{10}$: C, 56.33; H, 6.15. Found, C, 56.61; H, 6.30.

(4R,5E,7S)-7-(tert-Butyldimethylsilyloxy)-7-[(4R,5R)-5-[(1S)-1-(tert-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-1,3]dioxolan-4-yl]-hepta-1,5-dien-4-ol (20). The experimental procedure was the same

as for the conversion **12** → **13**. Column chromatography on silica gel (hexanes-EtOAc, 9:1) afforded alcohol **20** in 80% yield as a 96:4 mixture of epimers (the major one indicated in Scheme 6): ^1H NMR (500 MHz) δ 5.85-5.70 (3H, m), 5.11 (1H, br d, J = 17 Hz), 5.08 (1H, br d, J = 10 Hz), 4.19 (2H, m), 3.93 (1H, t, J = 5.5 Hz), 3.86 (1H, m), 3.80 (1H, t, J = 5.5 Hz), 2.60 (1H, br s), 2.35-2.25 (2H, m), 1.37 (6H, s), 1.18 (3H, d, J = 6 Hz), 0.90 (18H, s), 0.07 (9H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz) δ 109.2, 18.1, 18.0 (C), 135.0, 134.2, 130.3, 82.4, 81.8, 73.9, 70.9, 69.1 (CH), 117.7, 41.7 (CH_2), 27.9 (x 2), 25.9, 25.8, 20.0, -4.0, -4.3, -4.5 (x 2) (CH_3). IR (NaCl) 3470 (br, OH) cm^{-1} . HR EIMS m/z (rel. int.) 485.3113 [$\text{M}^+ - \text{Me}$] (2), 443 (2), 385 (11), 241 (19), 159 (100), 131 (54), 73 (72). Calcd. for $\text{C}_{26}\text{H}_{52}\text{O}_5\text{Si}_2 - \text{Me}$, 485.3118.

(4*S*,5*E*,7*S*)-7-(*tert*-Butyldimethylsilyloxy)-7-{(4*R*,5*R*)-5-[(1*S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-hepta-1,5-dien-4-ol (21**)**. Experimental procedure as for **12** → **13** but using (–)-*diisopinocampheyl*boron chloride. Column chromatography on silica gel (hexanes-EtOAc, 9:1) afforded **21** in 88% yield as a single diastereoisomer: colorless oil; $[\alpha]_{\text{D}} -7.6$ (c 3.6; CHCl_3). ^1H NMR (500 MHz) δ 5.85-5.70 (3H, m), 5.18 (1H, br d, J = 17.5 Hz), 5.15 (1H, br d, J = 10 Hz), 4.25 (2H, m), 3.93 (1H, t, J = 5.5 Hz), 3.90-3.85 (2H, m), 2.40-2.25 (2H, m), 1.80 (1H, br s), 1.39 (6H, s), 1.19 (3H, d, J = 6 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.09 (9H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz) δ 109.3, 18.2, 18.1 (C), 134.6, 134.0, 130.6, 82.3, 81.8, 73.9, 71.0, 69.2 (CH), 118.4, 41.8 (CH_2), 27.9 (x 2), 25.9 (x 2), 20.0, -3.9, -4.2, -4.4 (x 2) (CH_3). IR (NaCl) 3450 (br, OH) cm^{-1} . HR EIMS m/z (rel. int.) 485.3121 [$\text{M}^+ - \text{Me}$] (3), 443 (4), 385 (12), 241 (29), 159 (100), 131 (24), 73 (71). Calcd. for $\text{C}_{26}\text{H}_{52}\text{O}_5\text{Si}_2 - \text{Me}$, 485.3118. Anal. Calcd. for $\text{C}_{26}\text{H}_{52}\text{O}_5\text{Si}_2$: C, 62.35; H, 10.46. Found, C, 62.46; H, 10.64.

(1S,2E,4S)-1-Allyl-4-(tert-butyldimethylsilyloxy)-4-[(4R,5R)-5-[(1S)-1-(tert-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-2-enyl acrylate (22). Alcohol **20** (epimer mixture) was subjected to the same acryloylation procedure as for **13** → **14**. Column chromatography on silica gel (hexanes-EtOAc, 19:1) furnished acrylate **22** in 78% yield as a single diastereoisomer: colorless oil; $[\alpha]_D^{+9.8}$ (*c* 2.5; CHCl₃). ¹H NMR (500 MHz) δ 6.40 (1H, br d, *J* = 17.4 Hz), 6.12 (1H, dd, *J* = 17.4, 10.4 Hz), 5.85-5.75 (3H, m), 5.67 (1H, dd, *J* = 15.5, 6.6 Hz), 5.44 (1H, q, *J* = 6.5 Hz), 5.11 (1H, br d, *J* = 16.5 Hz), 5.09 (1H, br d, *J* = 10 Hz), 4.23 (1H, dd, *J* = 6.5, 4.2 Hz), 3.92 (1H, dd, *J* = 6.2, 4.2 Hz), 3.85 (1H, quint, *J* = 6 Hz), 3.77 (1H, t, *J* = 5.5 Hz), 2.45 (2H, m), 1.38 (3H, s), 1.36 (3H, s), 1.17 (3H, d, *J* = 6 Hz), 0.91 (18H, s), 0.09 (9H, s), 0.05 (3H, s); ¹³C NMR (125 MHz) δ 165.2, 109.1, 18.2, 18.1 (C), 133.0, 132.9, 130.2, 128.7, 81.9, 81.7, 73.9, 73.0, 69.1 (CH), 130.6, 118.2, 39.0 (CH₂), 27.7, 27.6, 26.0 (x 2), 19.9, -4.1, -4.2, -4.3, -4.5 (CH₃). IR (NaCl) 1729 (C=O) cm⁻¹. HR EIMS *m/z* (rel. int.) 539.3232 [*M*⁺-Me] (2), 367 (9), 295 (13), 224 (18), 159 (100), 129 (25), 73 (44). Calcd. for C₂₉H₅₄O₆Si₂-Me, 539.3224. Anal. Calcd. for C₂₉H₅₄O₆Si₂: C, 62.77; H, 9.81. Found, C, 62.79; H, 9.94.

(1S,2E,4S)-1-Allyl-4-(tert-butyldimethylsilyloxy)-4-[(4R,5R)-5-[(1S)-1-(tert-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-2-enyl acrylate (23). Alcohol **21** was subjected to the same acryloylation procedure as for **13** → **14**. Column chromatography on silica

gel (hexanes-EtOAc, 19:1) furnished acrylate **23** in 77% yield: colorless oil; $[\alpha]_D -12.6$ (c 1.8; CHCl_3). ^1H NMR (500 MHz) δ 6.39 (1H, br d, $J = 17.4$ Hz), 6.10 (1H, dd, $J = 17.4, 10.4$ Hz), 5.85-5.65 (4H, m), 5.44 (1H, q, $J = 6.3$ Hz), 5.11 (1H, br d, $J = 16.5$ Hz), 5.09 (1H, br d, $J = 10$ Hz), 4.25 (1H, t, $J = 5$ Hz), 3.90-3.75 (3H, m), 2.45 (2H, t, $J = 6.5$ Hz), 1.37 (6H, s), 1.16 (3H, d, $J = 6$ Hz), 0.90 (18H, s), 0.09 (6H, s), 0.07 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 165.1, 109.1, 18.2, 18.1 (C), 133.0, 132.6, 129.9, 128.6, 81.8, 81.7, 73.5, 72.8, 69.0 (CH), 130.5, 118.1, 38.8 (CH_2), 27.7 (x 2), 26.0 (x 2), 19.8, -4.1, -4.3, -4.5, -4.6 (CH_3). IR (NaCl) 1730 ($\text{C}=\text{O}$) cm^{-1} . HR EIMS m/z (rel. int.) 539.3243 [$\text{M}^+ - \text{Me}$] (12), 497 (10), 367 (34), 295 (66), 237 (74), 224 (92), 159 (88), 129 (100), 73 (82). Calcd. for $\text{C}_{29}\text{H}_{54}\text{O}_6\text{Si}_2 - \text{Me}$, 539.3224. Anal. Calcd. for $\text{C}_{29}\text{H}_{54}\text{O}_6\text{Si}_2$: C, 62.77; H, 9.81. Found, C, 62.66; H, 9.69.

(6R)-6-[(3S)-3-*tert*-Butyldimethylsilyloxy-3-{(4R,5R)-5-[(1S)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-prop-1E-enyl]-5,6-dihydropyran-2-one (24). Acrylate **22** was subjected to RCM under the same conditions as for **14** $\rightarrow$ **15**. This afforded α,β -unsaturated lactone **24** in 77% yield as a colorless oil: $[\alpha]_D +26.3$ (c 0.9; CHCl_3). ^1H NMR (500 MHz) δ 6.88 (1H, m), 6.05 (1H, br d, $J = 9.8$ Hz), 5.92 (1H, br dd, $J = 16, 6.3$ Hz), 5.80 (1H, dd, $J = 16, 5.5$ Hz), 4.98 (1H, dt, $J = 10, 5.5$ Hz), 4.25 (1H, t, $J = 5.5$ Hz), 3.95 (1H, t, $J = 5.5$ Hz), 3.87 (1H, quint, $J = 6$ Hz), 3.79 (1H, t, $J = 5.5$), 2.50-2.40 (2H, m), 1.37 (6H, s), 1.19 (3H, d, $J = 6$ Hz), 0.91 (9H, s), 0.90 (9H, s), 0.09 (3H, s), 0.08 (6H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz) δ 163.8, 109.3, 18.2, 18.1 (C), 144.3, 133.6, 128.9, 121.8, 82.4, 81.7, 77.1, 73.6, 69.1 (CH), 29.7 (CH_2), 28.0, 27.9, 26.0 (x 2), 20.2, -3.9, -4.2, -4.4, -4.5 (CH_3). IR (NaCl) 1725 ($\text{C}=\text{O}$) cm^{-1} . HR EIMS m/z (rel. int.) 511.2927 [$\text{M}^+ - \text{Me}$] (6), 469 (11), 411 (18), 367 (22), 267 (41), 159 (100), 131 (28), 73 (74). Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2 - \text{Me}$, 511.2911. Anal. Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2$: C, 61.55; H, 9.57. Found, C, 61.49; H, 9.50.

(6S)-6-[(3S)-3-*tert*-Butyldimethylsilyloxy-3-{(4R,5R)-5-[(1S)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-prop-1*E*-enyl]-5,6-dihydropyran-2-one (25). Acrylate **23** was subjected to RCM under the same conditions as for **14** → **15**. This afforded α,β -unsaturated lactone **25** in 80% yield as a colorless oil: $[\alpha]_D -8.2$ (c 0.3; CHCl_3). ^1H NMR (500 MHz) δ 6.87 (1H, m), 6.04 (1H, br d, $J = 9.6$ Hz), 5.92 (1H, dd, $J = 15.5, 6.2$ Hz), 5.81 (1H, dd, $J = 15.5, 6$ Hz), 4.98 (1H, dt, $J = 10, 5.2$ Hz), 4.26 (1H, t, $J = 5.3$ Hz), 3.94 (1H, t, $J = 5.3$ Hz), 3.85 (1H, quint, $J = 6$ Hz), 3.79 (1H, dd, $J = 6, 5.3$ Hz), 2.50-2.40 (2H, m), 1.37 (6H, s), 1.19 (3H, d, $J = 6$ Hz), 0.90 (9H, s), 0.89 (9H, s), 0.10 (3H, s), 0.09 (6H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz) δ 163.8, 109.4, 18.2, 18.1 (C), 144.3, 133.8, 129.0, 121.9, 82.2, 81.7, 77.0 (overlapped by CDCl_3 peaks), 73.4, 69.2 (CH), 29.6 (CH_2), 27.9 (x 2), 26.0 (x 2), 20.2, -3.9, -4.2, -4.3, -4.4 (CH_3). IR (NaCl) 1736 (C=O) cm^{-1} . HR EIMS m/z (rel. int.) 511.2924 [$\text{M}^+ - \text{Me}$] (8), 469 (14), 411 (25), 367 (38), 267 (648), 159 (100), 73 (53). Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2 - \text{Me}$, 511.2911. Anal. Calcd. for $\text{C}_{27}\text{H}_{50}\text{O}_6\text{Si}_2$: C, 61.55; H, 9.57. Found, C, 61.71; H, 9.81.

(6R)-6-[(1*E*,3*S*,4*S*,5*S*,6*S*)-(3,4,5,6-Tetraacetoxyhept-1-enyl)-5,6-dihydropyran-2-one (6). Cleavage of protecting groups in lactone **24** and subsequent peracetylation was performed as above for **15** → **1**. Column chromatography on silica gel (hexanes-EtOAc, 7:3) provided (7*E*)-spicigerolide **6** in 46% yield as a colorless oil: $[\alpha]_{589} +24$, $[\alpha]_{578} +26$, $[\alpha]_{546} +30$, $[\alpha]_{436} +67$, $[\alpha]_{365} +145$ (c 1.64; CHCl_3). ^1H NMR (500 MHz) δ 6.88 (1H, m), 6.04 (1H, br d, $J = 9.8$ Hz), 5.94 (1H, br dd, $J = 15.8, 5$ Hz), 5.77 (1H, br dd, $J = 15.8, 7.5$ Hz), 5.35-5.25 (3H, m), 5.00-4.90 (2H, m), 2.50-2.40 (2H, m), 2.11 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.02 (3H, s), 1.21 (3H, d, $J = 6$ Hz); ^{13}C NMR (125 MHz) δ 170.0, 169.9,

169.8, 169.5, 163.3 (C), 144.3, 133.0, 127.2, 121.7, 76.3, 71.0, 70.7, 69.9, 67.1 (CH), 29.1 (CH₂), 21.0, 20.9, 20.7, 20.6, 16.1 (CH₃). IR (NaCl) 1743 (br, C=O) cm⁻¹. HR EIMS *m/z* (rel. int.) 427.1600 [M+H⁺] (1), 367 (10), 231 (42), 204 (30), 178 (75), 136 (100), 129 (67), 107 (48). Calcd. for C₂₀H₂₇O₁₀, 427.1604. Anal. Calcd. for C₂₀H₂₆O₁₀: C, 56.33; H, 6.15. Found, C, 56.61; H, 6.30.

(6S)-6-[(1E,3S,4S,5S,6S)-(3,4,5,6-Tetraacetoxyhept-1-enyl)]-5,6-dihydropyran-2-one (7). Cleavage of protecting groups in lactone **25** and subsequent peracetylation was performed as above for **15** → **1**. Column chromatography on silica gel (hexanes-EtOAc, 7:3) provided lactone **7** in 44% yield as a colorless oil: [α]₅₈₉ -47, [α]₅₇₈ -52, [α]₅₄₆ -59, [α]₄₃₆ -115, [α]₃₆₅ -217 (*c* 0.56; CHCl₃). ¹H NMR (500 MHz) δ 6.86 (1H, m), 6.04 (1H, br d, *J* = 9.7 Hz), 5.93 (1H, dd, *J* = 15.6, 5.8 Hz), 5.76 (1H, dd, *J* = 15.6, 7.5 Hz), 5.33 (1H, dd, *J* = 7.8, 3 Hz), 5.30-5.25 (2H, m), 5.00-4.90 (2H, m), 2.50-2.40 (2H, m), 2.11 (3H, s), 2.08 (3H, s), 2.06 (3H, s), 2.03 (3H, s), 1.20 (3H, d, *J* = 6 Hz); ¹³C NMR (125 MHz) δ 170.1, 170.0, 169.8, 169.6, 163.3 (C), 144.2, 133.1, 127.6, 121.7, 76.5, 71.0, 70.7, 69.8, 67.1 (CH), 29.5 (CH₂), 21.0, 20.9, 20.7 (x 2), 16.1 (CH₃). IR (NaCl) 1742 (br, C=O) cm⁻¹. HR EIMS *m/z* (rel. int.) 427.1612 [M+H⁺] (1), 367 (12), 231 (48), 204 (30), 178 (84), 136 (100). Calcd. for C₂₀H₂₇O₁₀, 427.1604. Anal. Calcd. for C₂₀H₂₆O₁₀: C, 56.33; H, 6.15. Found, C, 56.49; H, 6.28.