# Stereoselective Total Synthesis of Stagonolide C

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A convergent and efficient total synthesis of stagonolide C (**1**), a phytotoxic metabolite, was achieved (*Schemes 2* and *3*) The synthesis exploited the high configuration control in the *Prins* cyclization along with alkene rearrangement and ring-closing metathesis as key steps.

**Introduction.** – Naturally occurring ten-membered lactones from fungal metabolites present a wide variety of potent biological properties [1]. Among them, stagonolides A–I [2][3] (*Fig.*) represent a novel family isolated recently from *Stagonospora cirsii*, a fungal pathogen of *Cirsium arvense* causing necrotic lesions on leaves, with interesting phytotoxic properties. When tested by a leaf disk puncture assay at a concentration of 1 mg/ml, stagonolide B–I showed no toxicity to *C. arvense* and *Sonchus arvensis*, whereas stagonolide A was highly toxic. Stagonolides A–I possess interesting structural features, as they are compact, bearing properly placed olefin moieties with well-defined geometry and, therefore, are attractive synthetic targets.

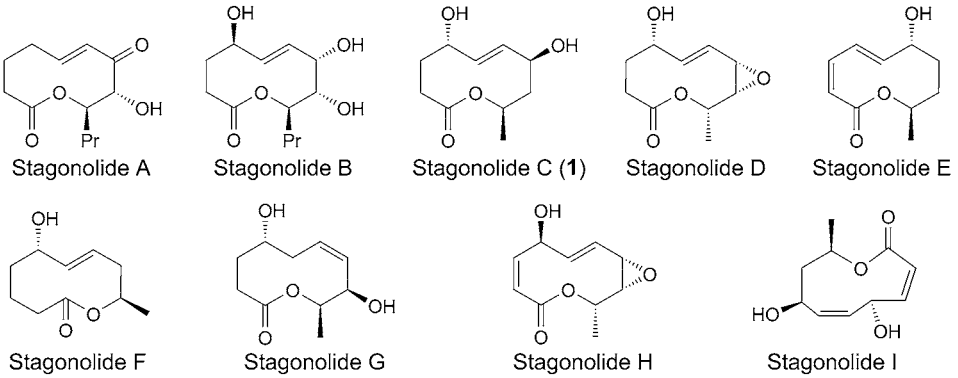


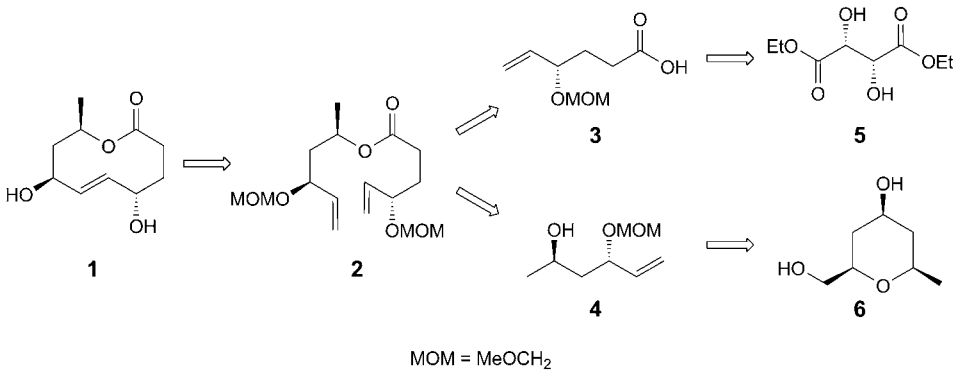

Figure. *Phytotoxic nonenolides*

In continuation of our ongoing program towards synthesis of biologically active compounds, we showed interest in developing a simple and flexible route to the total synthesis of stagonolide C (**1**) [4]. Our group has made a significant effort to explore the utility of the *Prins* cyclization in the synthesis of various polyketide intermediates as

well as for the synthesis of some complex natural products [5][6]. As a part of this program, we now accomplished a stereoselective total synthesis of stagonolide C.

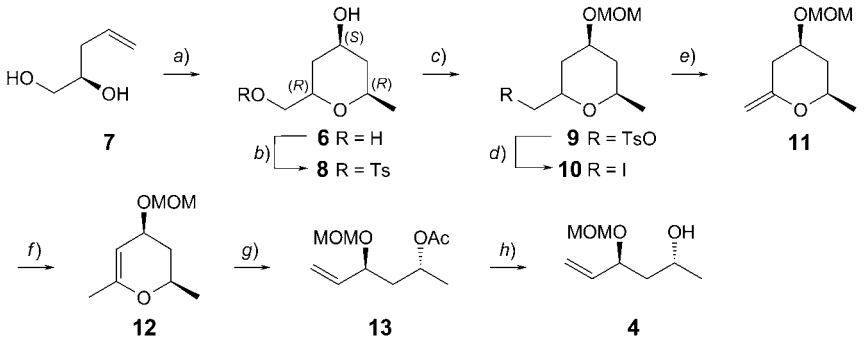
The retrosynthetic analysis delineated in *Scheme 1* indicated that stagonolide C (**1**) could be synthesized by utilizing a ring-closing-metathesis (RCM) protocol from bis-olefin **2**, which in turn could be prepared by esterification of acid **3** with alcohol **4** [4a]. We anticipated that alcohol **4** would be derived from 2*H*-pyran-2-methanol **6**, which in turn could be easily constructed *via Prins* cyclization, in analogy to our previous approach. The second fragment, acid **3**, could easily be derived from (+)-diethyl L-tartrate (**5**).

*Scheme 1*




**Results and Discussion.** – *Prins* cyclization between the known homoallylic alcohol **7** [6d] and acetaldehyde in the presence of trifluoroacetic acid [5] resulted in the trifluoroacetate salt of **6**, which on treatment with $K_2CO_3$ in MeOH gave tetrahydro-4-hydroxy-2*H*-pyran-2-methanol **6** as the only isolable diastereoisomer in 55% yield (*Scheme 2*). The stereochemical aspects of such *Prins* cyclizations and compounds structurally similar to **6** have been discussed in detail previously (for the *Prins* cyclization, see, *e.g.*, [5]) [6]. The primary OH group present in **6** was transformed to its tosylate **8** with TsCl and $Et_3N$ in anhydrous $CH_2Cl_2$, and the secondary OH group was protected as its methoxymethyl ($MeOCH_2$) ether with $MeOCH_2Cl$ and *N*,*N*-diisopropylethylamine ($^iPr_2EtN$) in anhydrous $CH_2Cl_2$ to give **9**. The tosylate group of **9** was substituted by an I-atom on treatment with NaI to give **10**, and subsequent elimination of HI [7] by using NaH in DMF affording the exocyclic alkene **11**, which on column chromatography (CC; $SiO_2$) revealed the rearranged product **12** in 72% yield. To confirm that the HI elimination did not result in the rearranged product, we analyzed the $^1$H-NMR spectrum of the crude product of the elimination reaction, which clearly revealed the presence of two *d* at $\delta$(H) 4.33 and 4.09 ($J = 2.2$ Hz, geminal coupling) and the absence of any characteristic signal for the rearranged product. The substrate **12** was then subjected to ozonolysis to obtain the corresponding (acetyloxy)-substituted aldehyde, which on treatment with methylenetriphenylphosphorane furnished the open-chain olefinic acetate **13** [6e]. Hydrolysis of the acetate group in **13** with $K_2CO_3$ in MeOH provided the corresponding key alcohol **4**.

*Scheme 2*




*a*) MeCHO, $CF_3COOH$, $CH_2Cl_2$, then $K_2CO_3$, MeOH, r.t, 5 h; 55%. *b*) TsCl, $Et_3N$, $CH_2Cl_2$, 0° to r.t., 3 h; 90%. *c*) $MeOCH_2Cl$, $^iPr_2EtN$, $CH_2Cl_2$, 0° to r.t., 6 h; 94%. *d*) NaI, acetone, reflux, 24 h; 95%. *e*) NaH, DMF, r.t., 6 h. *f*) $SiO_2$; 72%. *g*) $O_3$, $Ph_3P$, $CH_2Cl_2$, then $Ph_3P{=}CH_2$, THF, −78° to 0°; 74%. *h*) $K_2CO_3$, MeOH, r.t., 2 h; 96%.

The synthesis of the other key fragment, acid **3**, commenced with a known intermediate **14** [8] (*Scheme 3*). Deprotection of the benzyl ether moiety followed by reduction of the C=C bond of **14** was achieved with Pd/C in the presence of $H_2$ to furnish hydroxy ester **15** in 90% yield. Its primary-alcohol group was successfully converted into an iodo group of **16**, and subsequent reductive elimination was promoted by Zn/EtOH to afford secondary-alcohol derivative **17** [9]. The free OH group of **17** was protected as its $MeOCH_2$ ether **18**, and subsequent saponification of the ester group with 2N NaOH and MeOH afforded acid **3** [10] in 85% yield (*Scheme 3*).

The synthesis of the target compound was successfully completed by combining the two fragments **3** and **4** in a three-step sequence (*Scheme 3*). In analogy to [4a], alcohol **4** was acylated with acid **3** in the presence of dicyclohexylcarbodimide/*N*,*N*-dimethylpyridin-4-amine (DCC/DMAP) to obtain ester **2** [11] in 80% yield. Ester **2** underwent ring-closing metathesis with *Grubbs* 2nd-generation catalyst [12] in boiling $CH_2Cl_2$ to yield (*E*)-diastereoisomer **19** in 60% yield, which was characterized by the usual spectroscopic techniques. The coupling constant of 15.6 Hz between H–C(5) and H–C(6) clearly demonstrated the (*E*)-configuration of the C=C bond. Deprotection of both $MeOCH_2$ ether moieties [13] was carried out with $Me_3SiBr$ in $CH_2Cl_2$ to afford the natural product stagonolide C (**1**). The spectroscopic ($^1$H- and $^{13}$C-NMR) and analytical data were in good agreement with those of the natural product [2][3].

In conclusion, a flexible and efficient synthesis of stagonolide C (**1**) was performed involving *Prins* cyclization and RCM as the key steps. Further applications of the *Prins* cyclization to the synthesis of natural products are in progress and will be disclosed in due course.

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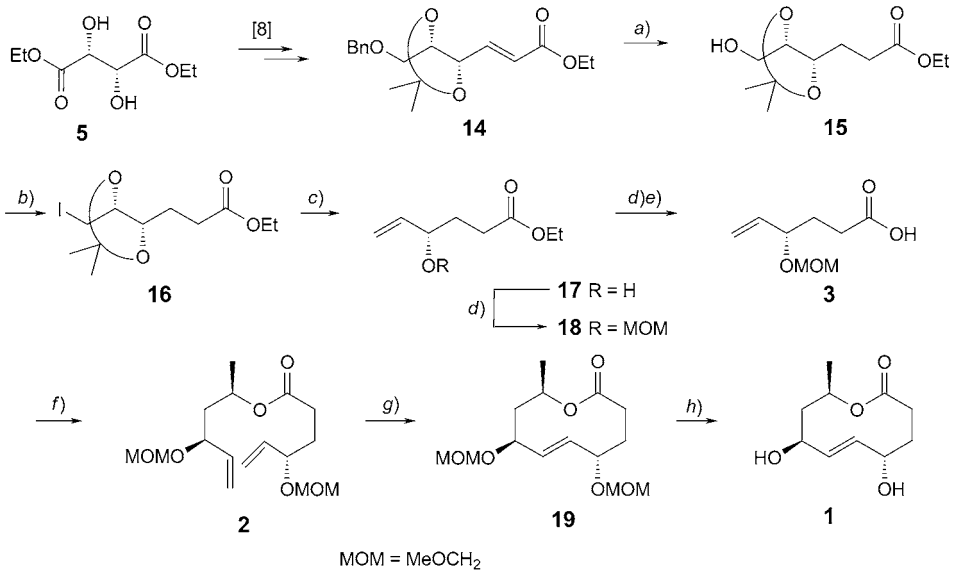
*Scheme 3*




*a*) $H_2$, Pd/C, AcOEt, reflux, 2 h; 90%. *b*) $I_2$, $Ph_3P$, 1*H*-imidazole, THF, 0° to r.t., 4 h; 80%. *c*) Zn, EtOH, reflux, 2 h; 86%. *d*) $MeOCH_2Cl$, $^iPr_2EtN$, *N,N*-dimethylpyridin-4-amine DMAP (cat.), $CH_2Cl_2$, 0° to r.t., 3 h; 82%. *e*) 2N NaOH, MeOH, r.t., 6 h; 85%. *f*) **4**, DCC, DMAP, $CH_2Cl_2$, 0° to r.t., 2 h; 80%. *g*) *Grubbs* 2nd-gen. catalyst, $CH_2Cl_2$, reflux, 24 h; 60%. *h*) $Me_3SiBr$, $CH_2Cl_2$, −40°, 15 min; 76%.

## Experimental Part

*General.* All reactions were carried out under inert atmosphere unless mentioned otherwise following standard syringe septa techniques. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions were monitored by TLC. Column (CC) and flash chromatography (FC): silica gel ($SiO_2$; 60–120 mesh) and neutral alumina, $Et_2O$, AcOEt, and hexane as eluents. TLC: precoated $SiO_2$ *60* $F_{254}$ glass plates (0.5 mm; *Merck*). Optical rotations: *Perkin-Elmer P241* polarimeter and *Jasco-DIP-360* digital polarimeter. IR Spectra: *Perkin-Elmer* FT-IR spectrophotometer; $\tilde{\nu}$ in $cm^{-1}$. $^1H$- and $^{13}C$-NMR Spectra: *Varian-Gemini-200*, *Bruker-Avance-300*, *Varian-Unity-400*, or *Varian-Inova-500* spectrometer; in $CDCl_3$; $\delta$ in ppm rel. to $Me_4Si$ as internal standard, *J* in Hz. MS: *Micro-Mass-VG-7070 H* (EI) and *VG-Autospec-M* (FAB-MS) spectrometer; in *m*/*z*.

*(2*R*,4*S*,6*R*)-Tetrahydro-4-hydroxy-6-methyl-2*H*-pyran-2-methanol* (**6**). $CF_3COOH$ (25 ml) was added slowly to a soln. of the homoallylic alcohol **7** [6d] (2.0 g, 19.60 mmol) and acetaldehyde (3.45 g, 78.40 mmol) in $CH_2Cl_2$ (60 ml) at 25° under $N_2$. The mixture was stirred for 3.0 h, and then sat. aq. $NaHCO_3$ soln. (150 ml) was added and the pH adjusted to >7 by addition of $Et_3N$. The aq. layer was extracted with $CH_2Cl_2$ (4 × 50 ml) and the combined org. layer concentrated. The trifluoroacetate obtained was directly used in the next reaction without purification, *i.e.,* the residue was dissolved in MeOH (50 ml) and stirred in the presence of $K_2CO_3$ (4.50 g) for 0.5 h. The MeOH was then evaporated, and $H_2O$ (30 ml) was added. The mixture was extracted with $CH_2Cl_2$ (3 × 30 ml), the combined org. layer dried ($Na_2SO_4$) and concentrated, and the residue purified by CC $SiO_2$, AcOEt/hexane): **6** (1.57 g, 55%). Colorless liquid. $R_f$ (AcOEt/hexane 6:4) 0.3. $[\alpha]_D^{27} = -13.7$ ($c = 1.34$, $CHCl_3$). IR (neat): 3398, 2925, 2856, 1452, 1363, 1178, 1030, 976. $^1H$-NMR ($CDCl_3$, 200 MHz): 1.09–1.20 (*m*, 2 H); 1.22 (*d*, *J* = 6.04, 3 H); 1.78–1.99 (*m*, 2 H); 3.38–3.62 (*m*, 4 H); 3.75–3.86 (*m*, 1 H). $^{13}C$-NMR (50 MHz, $CDCl_3$): 21.6; 36.5; 42.3; 65.8; 67.3; 67.8; 72.1. HR-ESI-MS: 169.0839 ($[M+Na]^+$, $C_7H_{14}NaO_3^+$; calc. 169.0840)

*(2R,4S,6R)-Tetrahydro-4-hydroxy-6-methyl-2H-pyran-2-methanol 4-Methylbenzenesulfonate* (**8**). To a soln. of **6** (1.5 g, 10.27 mmol) in dry $CH_2Cl_2$ (20 ml), $Et_3N$ (2.87 ml, 20.49 mmol) was added at 0°, followed by TsCl (2.34 g, 12.23 mmol) over 2 h. The mixture was allowed to warm to r.t. and stirred for 3 h. Then, the mixture was treated with aq. 1N HCl (7 ml) and extracted with $CH_2Cl_2$ (3 × 25 ml). The org. layer was washed with sat. aq. $NaHCO_3$ soln. (20 ml) and $H_2O$ (20 ml), the combined org. phase dried ($Na_2SO_4$) and concentrated, and the residue subjected to FC ($SiO_2$, AcOEt/hexane): **8** (2.76 g, 90%). Gummy liquid. $R_f$ (AcOEt/hexane 6:4) 0.6. $[\alpha]_D^{27} = -3.5$ ($c = 0.93$, $CHCl_3$). IR (neat): 3410, 2926, 2855, 1741, 1597, 1451, 1358, 1176, 974 . $^1$H-NMR (300 MHz, $CDCl_3$): 1.15 (*d*, *J* = 5.8, 3 H); 1.37–1.41 (*m*, 2 H); 1.83–1.96 (*m*, 2 H); 2.46 (*m*, 3 H); 3.32–3.45 (*m*, 1 H); 3.48–3.61 (*m*, 1 H); 3.67–3.83 (*m*, 1 H); 3.90–4.02 (*m*, 2 H); 7.32 (*d*, *J* = 8.08, 2 H); 7.79 (*d*, *J* = 8.08, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.32; 21.51; 36.45; 42.26; 67.30; 71.78; 72.02; 72.71; 127.84; 129.70; 132.73; 144.75. HR-ESI-MS: 301.1097 ($[M+H]^+$, $C_{14}H_{21}O_5S^+$; calc. 301.1104).

*(2R,4S,6R)-Tetrahydro-4-(methoxymethoxy)-6-methyl-2H-pyran-2-methanol 4-Methylbenzenesulfonate* (**9**). To a soln. of **8** (2.5 g, 9.13 mmol) in anh. $CH_2Cl_2$ (25 ml) at 0° were successively added $^i$Pr$_2$EtN (8.77 ml, 50.15 mmol), DMAP (cat.), and $MeOCH_2Cl$ (0.8 ml, 25 mmol). The resulting mixture was stirred for 3 h at r.t., the reaction quenched by adding $H_2O$ (15 ml), and the mixture extracted with $CH_2Cl_2$ (3 × 30 ml). The org. extract was washed with brine (15 ml), dried ($Na_2SO_4$), and concentrated and the crude purified by CC ($SiO_2$, AcOEt/hexane): pure **9** (2.68 g, 94%). Liquid $R_f$ (AcOEt/hexane 1:9) 0.5. $[\alpha]_D^{27} = -8.10$ ($c = 1.35$, $CHCl_3$). IR (neat): 2924, 2852, 1598, 1451, 1361, 1178, 1039, 977, 817, 668, 555. $^1$H-NMR (300 MHz, $CDCl_3$): 1.12 (*d*, *J* = 6.23, 3 H); 1.16–1.26 (*m*, 2 H); 1.90 (*dd*, *J* = 1.88, 4.53, 1 H); 1.94 (*dd*, *J* = 1.70, 4.15, 1 H); 2.43 (*s*, 3 H); 3.33 (*s*, 3 H); 3.35–3.43 (*m*, 2 H); 3.51–3.74 (*m*, 2 H); 3.93–4.04 (*m*, 2 H); 4.64 (*s*, 2 H); 7.32 (*d*, *J* = 7.93, 2 H); 7.77 (*d*, *J* = 8.49, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.44; 21.56; 34.15; 39.86; 55.24; 71.90; 72.02; 72.31; 72.86; 94.40; 127.95; 129.71; 132.98; 144.70. ESI-MS: 345 ($[M+H]^+$); 362 ($[M+NH_4]^+$).

*(2R,4S,6R)-Tetrahydro-2-(iodomethyl)-4-(methoxymethoxy)-6-methyl-2H-pyran* (**10**). NaI (10.0 g, 67 mmol) was added to a soln. of **9** (2.3 g, 6.70 mmol) in acetone (40 ml) and the mixture heated to reflux for 24 h. The acetone was then evaporated, and to the residue were added $H_2O$ and $CH_2Cl_2$ (60 ml). The org. layer was dried ($Na_2SO_4$) and concentrated and the residue subjected to CC ($SiO_2$, AcOEt/hexane): **10** (1.90 g, 95%). Colorless liquid. $R_f$ (AcOEt/hexane 1:9) 0.7. IR (neat): 2939, 2885, 1379, 1144, 1099, 914. $^1$H-NMR (300 MHz, $CDCl_3$): 1.26 (*d*, *J* = 6.04, 3 H); 1.88–1.97 (*m*, 2 H); 2.16–2.25 (*m*, 2 H); 3.16–3.21 (*dd*, *J* = 2.45, 5.85, 2 H); 3.31–3.34 (*m*, 1 H); 3.36 (*s*, 3 H); 3.45–3.56 (*m*, 1 H); 3.63–3.80 (*m*, 1 H); 4.69 (*s*, 2 H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 8.84; 21.57; 37.92; 39.83; 55.32; 72.10; 72.51; 75.02; 94.48. ESI-MS: 318 ($[M+NH_4]^+$).

*(2R,4S)-3,4-Dihydro-4-(methoxymethoxy)-2,6-dimethyl-2H-pyran* (**12**). To a soln. of **10** (1.8 g, 6.0 mmol) in DMF (100 ml) at 0° was added NaH (60% in oil; 0.57 g, 24.0 mmol). After 6 h stirring at r.t., the reaction was quenched with $H_2O$ at 0°. The resulting mixture was diluted with AcOEt, the org. phase washed with $H_2O$ and brine, dried ($Na_2SO_4$), and concentrated and the residue purified by CC ($SiO_2$, AcOEt/hexane1:9): **12** (1.26 g, 72%). Colorless clear oil. $R_f$ (AcOEt/hexane 1:9) 0.6. $^1$H-NMR (300 MHz, $CDCl_3$): 1.29 (*d*, 3 H); 1.52–1.63 (*m*, 1 H); 1.73 (*s*, 3 H); 2.06–2.16 (*m*, 1 H); 3.35 (*s*, 3 H); 3.96–4.05 (*m*, 1 H); 4.24–4.31 (*m*, 1 H); 4.53 (*m*, 1 H); 4.66 (*s*, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 19.90; 21.00; 36.46; 55.25; 69.50; 70.95; 95.19; 98.04; 153.44. ESI-MS: 173 ($[M+H]^+$).

*(2R,4S)-4-(Methoxymethoxy)hex-5-en-2-ol Acetate* (**13**). Ozone was bubbled through a soln. of **12** (0.7 g, 4.06 mmol) in $CH_2Cl_2$ (12 ml) at −78° until no starting material was observed by TLC. The mixture was purged with $N_2$ to remove the excess ozone and cooled to 0°, $Ph_3P$ (2.13 g, 8.13 mmol) was added, and the mixture was stirred for 2 h and then concentrated. After adding hexane, the mixture was filtered through a *Celite* pad, which was washed with hexane. The filtrate was dried ($Na_2SO_4$) and concentrated and the crude aldehyde subjected to the next reaction without further purification. A soln. of this aldehyde in dry THF (10 ml) was added at 0° to the ylide generated from methyltriphenylphosphonium chloride (3.36 g, 12.17 mmol) and $^t$BuOK (2.73 g, 24.30 mmol) in dry THF. The mixture was stirred for 2 h at 0° and then the THF was evaporated. AcOEt was (15 ml) added to the residue, the mixture washed with brine (5 ml), the org. phase dried ($Na_2SO_4$) and concentrated and the residue purified by CC ($SiO_2$, AcOEt/hexane): **13** (0.606, 74%, 2 steps). Colorless oil. $R_f$ (AcOEt/hexane 1:9) 0.7. $[\alpha]_D^{27} = -83.4$ ($c = 0.52$, $CHCl_3$). IR (neat): 2929, 1738, 1373, 1244, 1096, 1031. $^1$H-NMR (200 MHz,

$CDCl_3$): 1.23 (*d*, *J* = 6.23, 3 H); 1.66–1.82 (*m*, 2 H); 2.02 (*s*, 3 H); 3.32 (*s*, 3 H); 4.02–4.10 (*m*, 1 H); 4.46 (*d*, *J* = 6.98, 1 H); 4.67 (*d*, *J* = 6.98, 1 H); 5.01–5.11 (*m*, 1 H); 5.16–5.24 (*m*, 2 H); 5.60–5.72 (*m*, 2 H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 20.50; 21.23; 41.95; 55.62; 67.72; 73.66; 93.67; 117.35; 137.84. ESI-MS: 225 ($[M+Na]^+$).

*(2*R*,4*S*)-4-(Methoxymethoxy)hex-5-en-2-ol* (**4**). To a soln. of **13** (0.5 g, 2.47 mmol) in MeOH (10 ml), $K_2CO_3$ (0.6 g, 4.94 mmol) was added. After stirring for 4 h at r.t., the mixture was diluted with $H_2O$ (15 ml) and extracted with $CH_2Cl_2$ (3 × 10 ml). Evaporation of $CH_2Cl_2$ followed by FC ($SiO_2$, AcOEt/hexane): afforded **4** (0.39 g, 96%). Colorless liquid. $R_f$ (AcOEt/hexane 3:7) 0.4. $[\alpha]_D^{27} = -109.2$ (*c* = 1.50, $CHCl_3$). IR (neat): 3414, 2922, 2854, 1460, 1030. $^1$H-NMR ($CDCl_3$, 300 MHz): 1.19 (*d*, *J* = 6.23, 3 H); 1.60–1.66 (*m*, 2 H); 2.55 (br., 1 H, OH); 3.38 (*s*, 3 H); 3.98–4.09 (*m*, 1 H); 4.22–4.20 (*m*, 1 H); 4.52 (*d*, *J* = 6.61, 1 H); 4.65 (*d*, *J* = 6.79, 1 H); 5.15–5.26 (*m*, 2 H); 5.67–5.79 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 23.30; 43.87; 55.68; 64.20; 75.32; 94.25; 116.80; 137.66. ESI-MS: 183 ($[M+Na]^+$).

*Ethyl (4*S*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-propanoate* (**15**). To a soln. of **14** (2.0 g, 6.25 mmol) in AcOEt (30 ml) was added 10% Pd/C, and the mixture was stirred under $H_2$ for 6 h. Then, the mixture was filtered through a small *Celite* pad and the filtrate concentrated. The crude residue thus obtained was purified by CC ($SiO_2$, AcOEt/hexane): **15** (1.30 g, 90%). Colorless liquid. $R_f$ (AcOEt/hexane 3:7) 0.3. $[\alpha]_D^{27} = +20.3$ (*c* = 1.26, $CHCl_3$). IR (neat): 3453, 2985, 2933,1731, 1375, 1219, 1166, 1070, 1040. $^1$H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, *J* = 6.98, 3 H); 1.37 (*s*, 3 H); 1.38 (*s*, 3 H); 1.75–2.00 (*m*, 2 H); 2.25 (br., 1 H, OH); 2.36–2.56 (*m*, 2 H); 3.37–3.64 (*m*, 1 H); 3.70–3.80 (*m*, 2 H); 3.84–3.92 (*m*, 1 H); 4.08–4.15 (*q*, *J* = 7.17, 14.35, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.11; 26.92; 27.18; 27.91; 30.56; 60.43; 61.86; 76.13; 80.98; 108.82; 173.20. ESI-MS: 233 ($[M+H]^+$), 250 ($[M+NH_4]^+$).

*Ethyl (4*S*,5*R*)-5-(Iodomethyl)-2,2-dimethyl-1,3-dioxolane-4-propanoate* (**16**). To a stirred soln. of **15** (1.2 g, 5.17 mmol) in dry THF (20 ml) were added successively, at 0°, 1*H*-imidazole (0.84 g, 12.35 mmol), $Ph_3P$ (1.62 g, 6.40 mmol), and $I_2$ (1.57 g, 6.20 mmol). The resulting mixture was stirred for 2 h at r.t. and then quenched by $H_2O$ (15 ml), and extracted with $CH_2Cl_2$ (3 × 30 ml). The org. layers were washed with brine (15 ml), dried (anh. $Na_2SO_4$), and concentrated. Purification of the crude residue by CC ($SiO_2$, AcOEt/hexane) gave pure **16** (1.41 g, 92%). Colorless liquid. $R_f$ (AcOEt/hexane 1:9) 0.5. $[\alpha]_D^{27} = -19.1$ (*c* = 1.55, $CHCl_3$). IR (neat): 2985, 2934, 1734, 1371, 1242, 1178, 1065, 878. $^1$H-NMR (300 MHz, $CDCl_3$): 1.24 (*t*, *J* = 7.17, 3 H); 1.37 (*s*, 3 H); 1.38 (*s*, 3 H); 1.71–2.02 (*m*, 2 H); 2.36–2.58 (*m*, 2 H); 3.58–3.80 (*m*, 3 H); 3.85–3.93 (*m*, 1 H); 4.12 (*q*, *J* = 7.17, 14.35, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 14.17; 26.98; 27.23; 27.95; 30.61; 60.46; 61.89; 76.15; 80.98; 108.86; 173.21. ESI-MS: 342 ($[M+H]^+$), 365 ($[M+NH_4]^+$).

*Ethyl (4*S*)-4-Hydroxyhex-5-enoate* (**17**). To a soln. of **16** (1.3 g, 3.80 mmol) in EtOH (60 ml), commercial Zn dust (4.79 g, 76.03 mmol) was added. The mixture was refluxed for 2 h and then cooled to 25°. Addition of solid $NH_4Cl$ (6.0 g) and $Et_2O$ (100 ml) followed by stirring for 5 min gave a gray suspension. The suspension was filtered through a pad of *Celite* and the filtrate was concentrated. Purification by FC ($SiO_2$, AcOEt/hexane) gave **17** (0.516 g, 92%). Colorless liquid. $R_f$ (AcOEt/hexane 3:7) 0.4. $[\alpha]_D^{27} = +15.14$ (*c* = 2.85, $CHCl_3$). IR (neat): 3453, 2983, 2929, 1776, 1729, 1424, 1375, 1176, 1018, 930. $^1$H-NMR (300 MHz, $CDCl_3$): 1.17 (*t*, *J* = 6.98, 3 H); 1.89–2.02 (*m*, 2 H); 2.5 (br., OH); 2.31–2.43 (*m*, 2 H); 3.63 (*q*, *J* = 6.98, 13.97, 2 H); 4.85–4.93 (*m*, 1 H); 5.18–5.34 (*m*, 2 H); 5.78–5.89 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 13.99; 18.15; 28.10; 80.40; 117.20; 135.46; 176.90. EI-MS: 158 ($M^+$).

*Ethyl (4*S*)-4-(Methoxymethoxy)hex-5-enoate* (**18**). To **17** (0.40 g, 2.53 mmol) in anh. $CH_2Cl_2$ (10 ml) at 0° were successively added $^i$Pr$_2$EtN (2.66 ml, 15.19 mmol), DMAP (cat.), and $MeOCH_2Cl$ (0.38 ml, 7.58 mmol). The resulting mixture was stirred for 3 h at r.t., the reaction quenched by adding $H_2O$ (10 ml), and the mixture extracted with $CH_2Cl_2$ (3 × 20 ml). The org. extracts were washed with brine (10 ml), dried (anh. $Na_2SO_4$) and concentrated. The crude was purified by CC ($SiO_2$, AcOEt/hexane): pure **18** (0.42 g, 82%). Liquid. $R_f$ (AcOEt/hexane 3:7) 0.7. $[\alpha]_D^{27} = -77.8$ (*c* = 1.6, $CHCl_3$). IR (neat): 2983, 2935, 1736, 1178, 1151, 1095, 1032, 922. $^1$H-NMR (300 MHz, $CDCl_3$): 1.23 (*t*, *J* = 6.98, 3 H); 1.78–1.86 (*m*, 2 H); 2.33 (*t*, *J* = 7.55, 15.10, 2 H); 3.30 (*s*, 3 H); 3.94–4.01 (*m*, 1 H); 4.04–4.11 (*q*, *J* = 6.79, 14.35, 2 H); 4.44 (*d*, *J* = 6.79, 1 H); 4.60 (*d*, *J* = 6.79, 1 H), 5.13–5.21 (*m*, 2 H); 5.56–5.67 (*m*, 1 H). $^{13}$C-NMR ($CDCl_3$, 75 MHz): 14.14; 30.14; 30.25; 55.42; 60.25; 76.13; 93.67; 117.70; 137.54; 173.30. LC/MS: 225 ($[M+Na]^+$).

*(4*S*)-4-(Methoxymethoxy)hex-5-enoic Acid* (**3**). To a soln. of **18** (0.35 g, 1.73 mmol) in MeOH (20 ml), 2N NaOH (10 ml) was added. The mixture was stirred for 6 h at r.t., acidified to pH 4 by adding

1M HCl soln, and extracted with AcOEt (2 × 15 ml). Evaporation of the solvent followed by FC ($SiO_2$, AcOEt/hexane) afforded **3** (0.255 g, 85%). Colorless liquid. $R_f$ (AcOEt/hexane 4:6) 0.3. $[\alpha]_D^{27} = -102.3$ ($c = 0.90$, $CHCl_3$). IR (neat): 3082, 2936, 1711, 1420, 1150, 1095, 1031, 922. $^1$H-NMR (300 MHz, $CDCl_3$): 1.85–1.93 (*m*, 2 H); 2.47 (*t*, *J* = 6.98, 13.59, 2 H); 3.37 (*s*,3 H); 4.02–4.19 (*q*, *J* = 6.98, 13.59, 1 H); 4.53 (*d*, *J* = 6.79, 1 H); 4.69 (*d*, *J* = 6.79, 1 H); 5.19–5.27 (*m*, 2 H); 5.60–5.72 (*m*, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 29.89; 29.95; 55.53; 76.09; 93.7; 117.98; 137.34; 179.27. HR-ESI-MS: 197.0789 ($[M+Na]^+$, $C_8H_{14}NaO_4^+$; calc. 197.0781).

*(1*R*,3*S*)-3-(Methoxymethoxy)-1-methylpent-4-en-1-yl) (4*S*)-(Methoxymethoxy)hex-5-enoate* (**2**). To a stirred soln. of **4** (0.20 g, 1.25 mmol) in $CH_2Cl_2$ (10 ml) was added **3** (0.26 g, 1.50 mmol) followed by DCC (0.515 g, 2.50 mmol) and DMAP [4a] (0.30 g, 2.50 mmol) at r.t. After 2 h stirring the mixture was filtered and the resulting filtrate evaporated. The crude residue was purified by CC ($SiO_2$, AcOEt/hexane): **2** (0.36 mg, 78%). Colorless liquid. $R_f$ (AcOEt/hexane 3:7) 0.7. $[\alpha]_D^{27} = -127.6$ ($c = 0.60$, $CHCl_3$). IR (neat): 2937, 2890, 1732, 1152, 1095, 1031, 922. $^1$H-NMR (300 MHz, $CDCl_3$): 1.24 (*d*, 2 H); 1.72–1.79 (*m*, 2 H); 1.82–1.97 (*m*, 2 H); 2.37–2.43 (*m*, 2 H); 3.33 (*s*, 3 H); 3.38 (*s*, 3 H); 4.49 (*m*, 2 H); 4.47 (*d*, *J* = 6.79, 1 H); 4.53 (*d*, *J* = 6.79, 1 H); 4.67–4.70 (*m*, 2 H); 5.18–5.26 (*m*, 4 H); 5.61–5.73 (*m*, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 20.55; 30.36; 30.47; 42.01; 55.49; 55.49; 67.71; 73.77; 76.28; 93.75; 93.79; 117.34; 117.79; 137.58; 137.89; 172.82. HR-ESI-MS: 339.1770 ($[M+Na]^+$, $C_{16}H_{28}NaO_6^+$; calc. 339.1783).

*(5*S*,6*E*,8*S*,10*R*)-3,4,5,8,9,10-Hexahydro-5,8-bis(methoxymethoxy)-10-methyl-2*H*-oxecin-2-one* (**19**). A soln. of *Grubbs*' 2nd-generation catalyst [4a] (13.4 mg, 20 mol-%) in $CH_2Cl_2$ (10 ml) was added dropwise to a soln. of **2** (0.25 g, 0.79 mmol) in $CH_2Cl_2$ (700 ml). The mixture was stirred under reflux at 45° for 12 h. The solvent was evaporated and the crude product purified by CC ($SiO_2$, AcOEt/hexane): **19** (0.136 mg, 60%). Colorless oil. $R_f$ (AcOEt/hexane 3:7) 0.5. $[\alpha]_D^{27} = -42.8$ ($c = 1.21$, $CHCl_3$). IR (neat): 2928, 2854, 1949, 1859, 1727, 1447, 1372, 1264, 1099, 1033, 801, 756. $^1$H-NMR (300 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.83, 3 H); 1.78–1.90 (*m*, 2 H); 1.98–2.10 (*m*, 3 H); 2.26–2.33 (*m*, 1 H); 3.33 (*s*, 3 H); 3.34 (*s*, 3 H); 4.49 (*m*, 2 H); 4.49 (*d*, *J* = 6.83, 1 H); 4.53 (*d*, *J* = 6.83, 1 H); 4.67–4.70 (*m*, 2 H); 5.37–5.41 (*dd*, *J* = 8.90, 15.61, 2 H); 5.48–5.54 (*dd*, *J* = 9.70, 15.61, 2 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.37; 31.47; 31.97; 41.57; 55.27. 55.39; 67.71; 75.17; 77.85; 92.80; 93.85; 133.24; 135.30; 173.53. HR-ESI-MS: 311.1461 ($[M+Na]^+$, $C_{14}H_{24}NaO_6^+$; calc. 311.1470).

*Stagonolide C* (= *(5*S*,6*E*,8*S*,10*R*)-3,4,5,8,9,10-Hexahydro-5,8-dihydroxy-10-methyl-2*H*-oxecin-2-one*; **1**). $Me_3SiBr$ (1.60 ml, 1.86 mmol) was added dropwise to a cold (−40°) stirred soln. of **19** (90 mg, 0.31 mmol) in $CH_2Cl_2$ (250 ml). The mixture was stirred at −40° for 0.5 h and at 0° for an additional 4 h, poured into sat. aq. $NaHCO_3$ soln., and extracted with $CH_2Cl_2$. The extract was dried ($Na_2SO_4$), and concentrated and the residue subjected to CC ($SiO_2$, AcOEt/hexane): **1** (0.041 mg, 76%). Colorless liquid . $R_f$ (AcOEt/hexane 6:4) 0.3. $[\alpha]_D^{27} = +45.6$ ($c = 1.0$, $CHCl_3$). IR (neat): 3391, 2926, 2856, 1718, 1439, 1368, 1237, 1113, 1043. $^1$H-NMR (300 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.04, 3 H); 1.71–1.92 (*m*, 2 H); 1.98–2.06 (*m*, 3 H); 2.23–2.32 (*m*, 1 H); 4.05–4.16 (*m*, 2 H); 5.09–5.19 (*m*, 1 H); 5.42 (*dd*, *J* = 9.06, 15.86, 1 H); 5.58 (*dd*, *J* = 9.06, 15.86, 1 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 21.38; 31.47; 34.41; 43.37; 67.64; 72.07; 74.47; 133.0; 174.0. HR-ESI-MS: 223.0937 ($[M+Na]^+$, $C_{10}H_{16}NaO_4^+$; calc. 223.0946).

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