Stereoselective Total Synthesis of Stagonolide E

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An efficient and highly stereoselective synthesis of stagonolide E (**1**) starting from the readily available hexane-1,6-diol (**8**) was accomplished, employing *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* olefination, (*Z*)-selective *Still–Gennari* olefination, and *Yamaguchi* lactonization as key steps.

Introduction. – Macrolides containing a ten-membered ring are known to exhibit several biological activities [1]. Stagonolide E (**1**; *Fig.*) was isolated from *Stagonospora crisii*, which is a fungal pathogen of *Cirsium arvense* and known to produce phytotoxic metabolites [2]. The main metabolite, stagonolide A, exhibits phytotoxic activity [3], stagonolide B (**2**) shows cytotoxic and antimicrobial activities [2], and stagonolide F (**3**) displays antimicrobial activity [2][4]. Intrigued by the biological properties of stagonolides B–F (*Fig.*) and their scarce availability, and due to our continuing interest in the total synthesis of lactone-containing molecules [5], we studied the synthesis of **1**. The total synthesis of stagonolide E (**1**) [6][7] employing *Jacobsen* kinetic resolution and *Yamaguchi* lactonization was reported by *Sabitha et al.*, while *Das* and *Nanda* applied a chemoenzymatic method. *Bernd Schmidt et al.* reported the synthesis of **1** from (3*R*,4*R*)-hexa-1,5-diene-3,4-diol using a key bidirectional olefin-metathesis functionalization of the terminal C=C bonds. *Chattopadhyay et al.* also reported stagonolide E from hept-6-ene-2,5-diol by two lipase-catalyzed acylations to obtain useful chiral intermediates, followed by *Hoveyda–Grubbs*' II catalysis and (*Z*)-selective *Wittig–Horner* reaction as key steps. Herein, we describe a concise synthesis of **1** by using proline-catalyzed *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* (*HWE*) olefination, (*Z*)-selective *Still–Gennari* olefination, and *Yamaguchi* lactonization reactions.

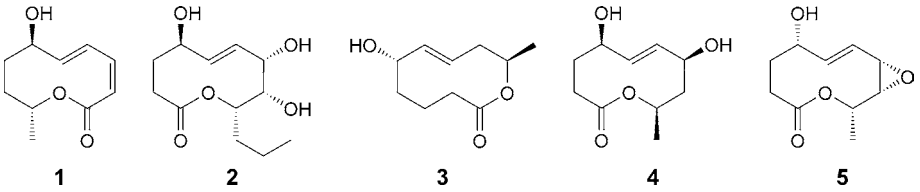
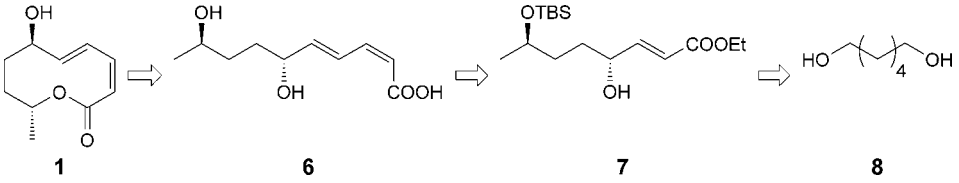


Figure. *Structures of stagonolides E, B, F, C, and D,* **1**–**5**, *respectively*

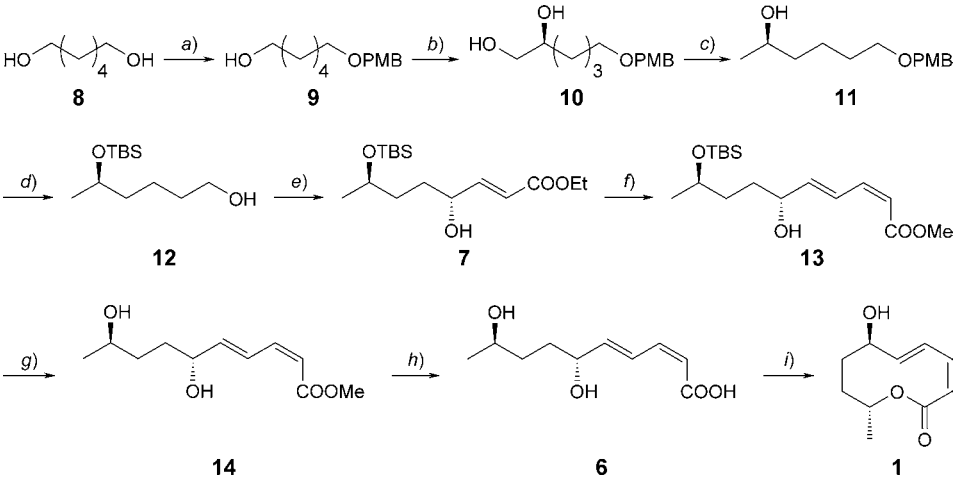
Results and Discussion. – The retrosynthetic analysis of stagonolide E (**1**) is depicted in *Scheme 1*. The target molecule, **1**, can be easily obtained by *Yamaguchi* lactonization of unsaturated acid **6**, which, in turn, can be derived from ester **7** by (*Z*)-selective *Still–Gennari* olefination, and other reactions. Compound **7** can be prepared from hexane-1,6-diol (**8**) using L-proline-catalyzed *MacMillan* α-hydroxylation and *HWE* olefination.

As outlined in *Scheme 2*, stagonolide E (**1**) was synthesized from hexane-1,6-diol (**8**). Initially, **8** was protected as its *p*-methoxybenzyl (PMB) ether (**9**), obtained in 83% yield, with NaH and *p*-methoxybenzyl bromide (PMBBr) [8c] in THF. The primary alcohol **9** was oxidized to the aldehyde using 2-iodoxybenzoic acid (IBX)/DMSO,

Scheme 1. *Retrosynthetic Analysis*



Scheme 2



a) NaH, THF, *p*-Methoxybenzyl bromide (PMBBr), Bu_4NI, 0° to r.t., 1.5 h; 83%. *b*) 1) 2-Iodoxybenzoic acid (IBX), DMSO, CH_2Cl_2, 3 h; 2) PhNO, D-proline, $CHCl_3$, 0°, 2 h; $NaBH_4$, EtOH, 0°, 2 h; AcOH, Zn, 12 h; 65%. *c*) 1) Bu_2SnO, Et_3N, CH_2Cl_2, TsCl, 0° to r.t., 12 h; 2) $LiAlH_4$, THF, reflux, 3 h; 79%. *d*) 1*H*-Imidazole, CH_2Cl_2, (^{t}Bu)Me_2SiCl (TBSCl), r.t., 6 h; 92%; 2) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O 10:1, r.t., 2 h; 93%. *e*) 1) IBX, DMSO, CH_2Cl_2, 0°, 3 h; 90%; 2) PhNO, L-proline, DMSO, 20°, 25 min; $(EtO)_2P(O)CH_2COOEt$, 1,8-diazabicycloundec-7-ene (DBU), LiCl, r.t., 1 h; MeOH, $CuSO_4 \cdot 5\,H_2O$, r.t., overnight; 60%. *f*) 1) Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, −78°, 2 h; 79%; 2) $(CF_3CH_2O)_2P(O)CH_2COOMe$, 18-crown-6, potassium hexamethyldisilazide (KHMDS), anh. THF, −78°, 4 h; 86%. *g*) TsOH, MeOH, 0°, 0.5 h; 89%. *h*) 1) $LiOH \cdot H_2O$, THF/H_2O 1:1, r.t., 8 h; 86%; 2) Et_3N, 2,4,6-trichlorobenzoyl chloride, toluene, DMAP, 80°, 12 h; 58.3%.

which was further subjected to *MacMillan* α-aminoxylation [8d] by using PhNO and D-proline in $CHCl_3$, followed by reduction with $NaBH_4$ in EtOH, to furnish an unstable anilinoxy compound, which was further treated with AcOH and Zn to provide diol **10** in 65% yield. The primary OH group in diol **10** was selectively protected with TsCl and Et_3N in the presence of a catalytic amount of Bu_2SnO in anhydrous CH_2Cl_2, and the Ts-protected intermediate was further treated with $LiAlH_4$ [8e] in anhydrous THF to furnish the secondary alcohol **11** [8] in 79% yield. Protection of the secondary OH group in **11** with (*tert*-butyl)(dimethyl)silyl chloride (TBSCl) and 1*H*-imidazole in CH_2Cl_2 gave the corresponding TBS ether in 92% yield, which was then subjected to PMB deprotection with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2/H_2O at room temperature to give **12** in 93% yield.

The primary alcohol **12** was oxidized with IBX in CH_2Cl_2 to afford the corresponding aldehyde, which was further subjected to sequential α-aminoxylation [9] by using PhNO and L-proline in DMSO, followed by *HWE* reaction to furnish the *O*-amino-substituted allylic alcohol, which was further treated with 20 mol-% of $CuSO_4 \cdot 5\,H_2O$ in MeOH at room temperature to cleave the O–N bond to provide γ-hydroxy-α,β-unsaturated ester **7** in 60% yield [10] with high diastereoselectivity (98% de; *MacMillan* α-hydroxylation; *Scheme 2*).

Ethyl ester **7** was reduced with DIBAL-H (1M in toluene) at $-78°$ to afford an aldehyde, which was further subjected to (*Z*)-selective *Still–Gennari* olefination by employing bis(2,2,2-trifluoroethyl) [(methoxycarbonyl)methyl]phosphonate ($(CF_3CH_2O)_2P(O)CH_2COOMe$), 18-crown-6, potassium bis(trimethylsilyl)amide (KHMDS) in anhydrous THF to furnish (*Z*)-olefinic ester **13** in 86% yield [11]. Then, the TBS protecting group in **13** was removed with TsOH in MeOH to give secondary alcohol **14** in 89% yield. Further, the (*Z*)-configured α,β-unsaturated ester **14** was hydrolyzed with $LiOH \cdot H_2O$ to afford the corresponding acid **6** in 86% yield. Finally, intramolecular lactonization of **6** by employing *Yamaguchi* protocol by using 2,4,6-trichlorobenzoyl chloride in toluene at 80° [12] gave the target natural product, stagonolide E (**1**), in 58.3% yield (*Scheme 2*). The $[\alpha]_D^{25}$ value (-182.4 ($c = 0.5$, $CHCl_3$); -186 ($c = 0.2$, $CHCl_3$) [2]) and spectral data were found to be identical with those of the reported natural product in [2].

Conclusions. – In conclusion, we have achieved a stereoselective total synthesis of stagonolide E (**1**) in a highly concise manner, using easily accessible starting materials. The key steps involved were are *MacMillan* α-hydroxylation, *HWE* olefination, (*Z*)-selective *Still–Gennari* olefination, and *Yamaguchi* lactonization.

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Experimental Part

General. All solvents and reagents were purified by standard techniques. Column chromatography (CC): silica gel (SiO_2; 60–120 mesh). Optical rotations: *Horiba* high sensitive polarimeter; cell length, 1 cm. FT-IR Spectra: *Thermo Nicolet NEXUS 670* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Varian Gemini 500* and *Bruker Avance 300* instrument; δ in ppm rel. to Me_4Si as internal standard, *J* in

Hz. ESI-MS: *Micromass Quattro micro* API mass spectrometer (*Waters*); in *m*/*z*. HR-MS: *QSTAR XL Hybrid* MS/MS system (*Applied Biosystems*, USA); in *m*/*z*.

6-[(4-Methoxybenzyl)oxy]hexan-1-ol (**9**) [8c]. To a soln. of *hexane-1,6-diol* (**8**; 8.0 g, 67.79 mmol) in anh. THF (100 ml) was added NaH (60%, 2.44 g, 45.76 mmol) at 0°, and the mixture was stirred for 30 min at the same temp. Then, PMBBr (9.55 g, 61.01 mmol) was added slowly at 0°, followed by Bu_4NI (cat.), and the mixture was stirred at r.t. for 1 h. After completion of the reaction, cold H_2O was added at 0°, the two layers were separated, and the aq. phase was extracted with AcOEt (3 × 100 ml). The combined org. layers were washed with H_2O and brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (hexanes/AcOEt 7:3) to furnish **9** (13.08 g, 83%). Colorless oil. IR (neat): 3385, 2952, 1720, 1493, 1454, 1220, 1096. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.26 (*d*, *J* = 8.5, 2 H); 6.87 (*d*, *J* = 8.5, 2 H); 4.43 (*s*, 2 H); 3.80 (*s*, 3 H); 3.62 (*t*, *J* = 6.7, 2 H); 3.44 (*t*, *J* = 6.5, 2 H); 1.64–1.53 (*m*, 4 H); 1.42–1.32 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.6; 130.5; 129.1; 113.6; 72.4; 69.9; 62.6; 55.1; 32.5; 29.5; 25.8; 25.4. ESI-MS: 261 ($[M+Na]^+$).

*(2*S*)-6-[(4-Methoxybenzyl)oxy]hexane-1,2-diol* (**10**) [8d]. To a stirred soln. of IBX (7.05 g, 25.21 mmol) in anh. DMSO (7 ml) was added a soln. of **9** (4 g, 16.80 mmol) in anh. CH_2Cl_2 (30 ml) at r.t., and the mixture was stirred for 3 h at r.t. After completion of the reaction, the mixture was filtered, diluted with H_2O (10 ml), and extracted with CH_2Cl_2 (2 × 30 ml). The combined org. extracts were washed with brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a crude aldehyde, which was directly used in the next step.

The aldehyde (3.6 g, 15.25 mmol) was added dropwise to a soln. of PhNO (1.63 g, 15.25 mmol) and D-proline (0.70 g, 6.101 mmol) in $CHCl_3$ (9 ml) at 0°, and the soln. was vigorously stirred at 0° for 2 h. The mixture was transferred dropwise to a soln. of $NaBH_4$ (0.58 g, 15.25 mmol) in EtOH (90 ml) at 0°, and the soln. was stirred at 0° for 2 h, and then concentrated. Sat. $NaHCO_3$ soln. (90 ml) was added, and the mixture was extracted with AcOEt (3 × 50 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOH/AcOH 3:1 (40 ml) and treated with Zn powder (3.3 g, 50.72 mmol), and the mixture was stirred at r.t. for 12 h, then filtered through *Celite*, and concentrated. The crude residue was purified by CC (hexanes/AcOEt 4:6) to give **10** (2.5 g, 65%). Colorless oil. The enantiomeric excess (ee) was determined by chiral HPLC (*CHIRALPAK IA*; 250 × 4.6 mm, 5 μm; mobile phase, 15% ^{i}PrOH in hexane; flow rate, 1 ml min^{-1}; detection, 210 nm; t_R 17.326 min): 98% ee. $[\alpha]_D^{25} = +6.8$ (*c* = 1.0, $CHCl_3$). IR (neat): 3390, 2934, 2861, 1610, 1513, 1249, 1093, 1033, 821. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.25 (*d*, *J* = 8.6, 2 H); 6.87 (*d*, *J* = 8.6, 2 H); 4.42 (*s*, 2 H); 3.80 (*s*, 3 H); 3.72–3.52 (*m*, 2 H); 3.49–3.32 (*m*, 3 H); 2.97 (br. *s*, 1 H); 1.70–1.33 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 130.4; 129.2; 113.7; 72.5; 72.0; 69.8; 66.6; 55.2; 32.7; 29.5; 22.2. ESI-MS: 277 ($[M+Na]^+$).

*(2*R*)-6-[(4-Methoxybenzyl)oxy]hexan-2-ol* (**11**) [8e]. To a cooled (0°) soln. of **10** (2.4 g, 9.523 mmol), a cat. amount of Bu_2SnO (5 mg) and Et_3N (2.64 ml, 21.046 mmol) in CH_2Cl_2 (15 ml), and TsCl (1.81 g, 9.523 mmol) were added portionwise at 0°, and the mixture was stirred at r.t. for 4 h. After completion of the reaction, the mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 50 ml). The org. layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude residue which was purified by CC (hexanes/AcOEt 75:25) to afford the monotosylated product (3.1 g, 80%) as viscous liquid.

To a stirred suspension of $LiAlH_4$ (0.56 g, 14.705 mmol) in anh. THF (30 ml), a soln. of the monotosylated compound (3.0 g, 7.35 mmol) in anh. THF (30 ml) was added dropwise at 0° under N_2, and the mixture was stirred under reflux for 12 h. The mixture was cooled to 0°, treated with sat. aq. Na_2SO_4 soln. (25 ml), filtered, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was purified by CC (hexanes/AcOEt 8:2) to give **11** (1.38 g, 79%). Colorless liquid. $[\alpha]_D^{25} = -3.0$ (*c* = 2.0, $CHCl_3$). IR (neat): 3421, 2934, 2860, 1612, 1513, 1247, 1095, 819. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.28 (*d*, *J* = 8.3, 2 H); 6.90 (*d*, *J* = 8.3, 2 H); 4.45 (*s*, 2 H); 3.81 (*s*, 3 H); 3.79–3.68 (*m*, 1 H); 3.47 (*t*, *J* = 6.4, 2 H); 1.70–1.55 (*m*, 2 H); 1.52–1.33 (*m*, 4 H); 1.18 (*d*, *J* = 6.0, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.8; 130.3; 129.0; 113.5; 72.2; 69.7; 67.4; 54.9; 38.7; 29.3; 23.1; 22.2. ESI-MS: 261 ($[M+Na]^+$).

*(5*R*)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hexan-1-ol* (**12**) [8e]. To a soln. of **11** (1.3 g, 5.46 mmol) in anh. CH_2Cl_2 (15 ml) was added 1*H*-imidazole (0.743 g, 10.92 mmol), and the mixture was stirred for 10 min at 0°. To this soln., TBSCl (0.983 g, 6.55 mmol) was added at 0°, and the mixture was stirred at r.t. for 6 h. After completion of the reaction, the mixture was diluted with H_2O and extracted with CH_2Cl_2

(3×20 ml). The combined org. extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (hexanes/AcOEt 95:5) to give the pure TBS-protected product (1.76 g, 92%) as colorless liquid. Then, to a cooled (0°) soln. of the above TBS-protected compound (1.7 g, 4.83 mmol) in CH_2Cl_2 (15 ml) and H_2O (1.5 ml) was added DDQ (2.2 g, 9.71 mmol), and the mixture was stirred at r.t. for 2 h. After completion of the reaction, sat. $NaHCO_3$ soln. was added, and the aq. layer was extracted with CH_2Cl_2 (2×20 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by CC (hexanes/AcOEt 7:3) to give **12** (1.04 g, 93%). Colorless liquid. $[\alpha]_D^{25} = -5.5$ ($c = 1.0$, $CHCl_3$). IR (neat): 3430, 1263. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.83–3.75 (*m*, 1 H); 3.64 (*t*, $J = 6.2$, 2 H); 1.60–1.52 (*m*, 2 H); 1.50–1.30 (*m*, 4 H); 1.12 (*d*, $J = 6.6$, 3 H); 0.88 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 68.5; 62.6; 39.3; 32.6; 25.8; 23.7; 21.8; 18.0; −4.4; −4.7. ESI-MS: 255 ($[M + Na]^+$).

*Ethyl (2*E*,4*R*,7*R*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4-hydroxyoct-2-enoate* (**7**) [5a]. To a stirred soln. of IBX (1.80 g, 6.46 mmol) in anh. DMSO (2 ml) was added a soln. of **12** (1.0 g, 4.31 mmol) in anh. CH_2Cl_2 (20 ml) at r.t., and the mixture was stirred for 3 h at r.t. After completion of the reaction, the mixture was filtered, diluted with H_2O (10 ml), and extracted with CH_2Cl_2 (2×30 ml). The combined org. extracts were washed with brine (20 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a crude aldehyde, which was directly used in the next step.

To a soln. of the obtained aldehyde (1.2 g, 5.20 mmol) were added PhNO (0.557 g, 5.20 mmol) and L-proline (0.24 g, 2.08 mmol) in anh. DMSO (17.4 ml) at 20°. The mixture was vigorously stirred for 25 min under N_2 and then cooled to 0°. Thereafter, a cooled (0°), premixed soln. of $(EtO)_2P(O)CH_2COOEt$ (3.09 ml, 15.02 mmol), DBU (2.33 ml, 15.02 mmol), and LiCl (0.663 g, 15.02 mmol) in MeCN (17.4 ml) was added quickly (1–2 min). The resulting mixture was allowed to warm to r.t. within 1 h, and the reaction was quenched by addition of ice pieces. MeCN was evaporated under reduced pressure, and the mixture was diluted with H_2O (100 ml) and extracted with Et_2O (3×100 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give a crude product, which was dissolved in MeOH (20 ml) and reacted with $CuSO_4 \cdot 5\ H_2O$ (0.26 g, 1.04 mmol), the mixture was stirred at r.t. overnight, and the reaction was quenched with cold sat. NH_4Cl soln. (15 ml). The mixture was filtered through a *Celite* pad, washed thoroughly with AcOEt (100 ml), concentrated, and extracted with AcOEt (3×75 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude product was then purified by CC (hexane/AcOEt 85:15) to give **7** (0.988 g, 60%). Brown liquid. $[\alpha]_D^{25} = -13.1$ ($c = 0.8$, $CHCl_3$). IR (neat): 3432, 2956, 2932, 2858, 1720, 1657, 1467, 1370, 1256, 1174, 1044, 834, 775. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.93 (*dd*, $J = 15.6$, 4.6, 1 H); 6.06 (*dd*, $J = 15.6$, 2.4, 1 H); 4.30–4.24 (*m*, 1 H); 4.20 (*q*, $J = 7.0$, 2 H); 3.97–3.89 (*m*, 1 H); 1.78–1.52 (*m*, 4 H); 1.29 (*t*, $J = 7.0$, 3 H); 1.16 (*d*, $J = 6.2$, 3 H); 0.9 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.5; 150.2; 120.1; 71.1; 68.4; 60.3; 35.3; 32.2; 25.9; 23.0; 14.3; −4.4; −4.7. ESI-MS: 339 ($[M + Na]^+$).

*Methyl (2*Z*,4*E*,6*R*,9*R*)-9-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-6-hydroxydeca-2,4-dienoate* (**13**). To a cooled (−78°), stirred soln. of **7** (0.6 g, 1.89 mmol) in anh. CH_2Cl_2 (20 ml) was added DIBAL-H (1.0M, 2.08 ml, 2.08 mmol), and the mixture was stirred at the same temp. for 2 h. After completion, the reaction was quenched with sat. potassium sodium tartrate (10 ml), and the mixture was stirred for 0.5 h. The mixture was extracted with CH_2Cl_2 (3×40 ml). The combined org. phases were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. The crude product was purified by CC (hexane/AcOEt 82:18) to give an aldehyde (0.408 g, 79%) as brown liquid.

To a cooled (−78°) soln. of $(CF_3CH_2O)_2P(O)CH_2COOMe$ (0.06 ml, 1.92 mmol) and 18-crown-6 (1.69 g, 6.42 mmol) in anh. THF (15 ml) was added KHMDS (1.54 ml, 1.54 mmol), and the mixture was stirred for 0.5 h. The previously prepared aldehyde (0.35 g, 1.28 mmol) in anh. THF (4 ml) was added, and the mixture was stirred for 4 h at the same temp. After completion, the reaction was quenched with sat. NH_4Cl, and the mixture was extracted with AcOEt. The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by CC (hexane/AcOEt 83:17) to give **13** (362 mg, 86%). Colorless liquid. $[\alpha]_D^{25} = -10.2$ ($c = 0.44$, $CHCl_3$). IR (neat): 3449, 2931, 2857, 1715, 1641, 1604, 1439, 1251, 1176, 999, 964, 830, 770. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.48 (*dd*, $J =$ 16.0, 12.0, 1 H); 6.55 (*t*, $J = 11.0$, 1 H); 6.02 (*dd*, $J = 16.0$, 7.0, 1 H); 5.65 (*d*, $J = 12.0$, 1 H); 4.26–4.19 (*m*, 1 H); 3.93–3.85 (*m*, 1 H); 3.72 (*s*, 3 H); 1.71–1.48 (*m*, 4 H); 1.16 (*d*, $J = 6.0$, 3 H); 0.90 (*s*, 9 H); 0.07

(*s*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.2; 146.4; 144.3; 125.5; 116.8; 71.8; 68.4; 50.8; 35.3; 32.8; 25.8; 23.4; 18.0; −4.5; −4.7. ESI-MS: 351 ($[M+Na]^+$).

Methyl (2Z,4E,6R,9R)-6,9-Dihydroxydeca-2,4-dienoate (**14**). To a cooled (0°) soln. of **13** (250 mg, 0.76 mmol) in MeOH (10 ml) was added TsOH (131 mg, 0.76 mmol), and the mixture was stirred at the same temp. for 0.5 h. After completion, the reaction was quenched with solid $NaHCO_3$, the mixture was filtered, and MeOH was evaporated under reduced pressure to afford a crude product, which was purified by CC (hexane/AcOEt 40:60) to give **14** (145 mg, 89%). Colorless liquid. $[\alpha]_D^{25} = -38.4$ ($c = 0.33$, $CHCl_3$). IR (neat): 3383, 2924, 2856, 1711, 1642, 1602, 1440, 1201, 1177, 1002, 968, 820. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.49 (*dd*, $J = 15.8, 11.3$, 1 H); 6.58 (*t*, $J = 11.3$, 1 H); 6.06 (*dd*, $J = 15.1, 6.0$, 1 H); 5.69 (*d*, $J = 11.3$, 1 H); 4.37–4.30 (*m*, 1 H); 3.91–3.82 (*m*, 1 H); 3.73 (*s*, 3 H); 1.78–1.47 (*m*, 4 H); 1.21 (*d*, $J = 6.0$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.8; 146.2; 144.4; 125.5; 116.9; 71.4; 67.5; 51.2; 34.3; 32.7; 23.1. ESI-MS: 237 ($[M+Na]^+$).

(2Z,4E,6R,9R)-6,9-Dihydroxydeca-2,4-dienoic Acid (**6**). To a soln. of **14** (60 mg, 0.28 mmol) in THF (1 ml) and H_2O (1 ml) was added $LiOH \cdot H_2O$ (58 mg, 1.4 mmol). The mixture was stirred for 8 h at r.t., then concentrated, the residue was diluted with H_2O (3 ml) and acidified with 2N HCl, and the aq. layer was extracted with AcOEt (3 × 15 ml). The combined org. layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (CH_3Cl/MeOH 90:10) to give **6** (48.2 mg, 86%). Colorless gummy liquid. $[\alpha]_D^{25} = -48.3$ ($c = 1.5$, MeOH). IR (neat): 3421, 2922, 2853, 1702, 1640, 1602, 1434, 1378, 1203, 1075, 1007, 969. ^{1}H-NMR (300 MHz, CD_3OD): 7.46 (*dd*, $J = 15.1, 11.3$, 1 H); 6.56 (*t*, $J = 11.3$, 1 H); 6.00 (*dd*, $J = 15.1, 6.0$, 1 H); 5.67 (*d*, $J = 11.3$, 1 H); 4.20–4.10 (*m*, 1 H); 3.76–3.66 (*m*, 1 H); 1.74–1.38 (*m*, 4 H); 1.15 (*d*, $J = 6.8$, 3 H). ^{13}C-NMR (75 MHz, CD_3OD): 171.6; 145.8; 143.4; 127.5; 121.3; 73.0; 68.6; 36.0; 34.4; 23.5. ESI-MS: 223 ($[M+Na]^+$).

(3Z,5E,7R,10R)-7,8,9,10-Tetrahydro-7-hydroxy-10-methyl-2H-oxecin-2-one (= *Stagonolide E*; **1**). To a soln. of **6** (20 mg, 0.10 mmol) and Et_3N (0.08 ml, 0.60 mmol) in anh. THF (3 ml) was added 2,4,6-trichlorobenzoyl chloride (0.08 ml, 0.50 mmol). The resulting mixture was stirred at r.t. for 3 h and was then diluted in toluene (15 ml). The resulting soln. was added dropwise (2 ml h^{-1}) to a diluted soln. of 4-(dimethylamino)pyridine (DMAP; 244 mg, 1.99 mmol) in toluene (110 ml) at 80°. Once the addition was complete, the mixture was stirred for further 12 h at 80°. The mixture was filtered, and the org. layer was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (hexane/AcOEt 80:20) to give **1** (10.6 mg, 58.3%). Colorless liquid. $[\alpha]_D^{25} = -182.4$ ($c = 0.5$, $CHCl_3$; −186 ($c = 0.2$, $CHCl_3$) [2]). IR (neat): 3440, 2927, 2855, 1703, 1601, 1250, 960. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.62 (br. *d*, $J = 11.6$, 1 H); 6.12 (br. *d*, $J = 15.4$, 1 H); 5.85 (*d*, $J = 11.6$, 1 H); 5.74 (*dd*, $J = 15.3, 9.4$, 1 H); 5.03–4.93 (*m*, 1 H); 4.25 (*td*, $J = 9.0, 4.0$, 1 H); 1.94–1.57 (*m*, 4 H); 1.22 (*d*, $J = 6.6$, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 168.1; 140.2; 139.4; 126.5; 125.6; 73.5; 73.2; 37.4; 30.3; 21.3. ESI-MS: 205 ($[M+Na]^+$).

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