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Stereoselective total synthesis of stagonolide E

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ABSTRACT

The first total synthesis of a 10-membered macrolide, stagonolide E is described from readily available 4-penten-1-ol. The synthetic strategy involves Jacobsen's kinetic resolution, Sharpless epoxidation, Stille–Gennari, and Yamaguchi lactonization as key reactions.

Ten-membered macrolides such as aspinolide A,[1] putaminoxin,[2] and nonenolide[3] have been isolated from fungal sources and are known to possess potent biological properties. Stagonolides A–I[4] (Fig. 1) represent a family of novel 10-membered ring lactones produced recently from *Stagonospora cirsii*, a fungal pathogen of *Cirsium* arvense causing necrotic lesions on leaves. Among them stagonolide A was found to be phytotoxic and stagonolide B exhibited potent antifungal, antibacterial, and cytotoxic activities. The scarce availability of these macrolides coupled with their interesting biological profile continued to attract the attention of synthetic chemists. However, syntheses of some members of this class of compounds have been reported.[5] To the best of our knowledge, so far no synthesis has been reported for **8**. Our continued interest on the synthesis of 10-membered lactones[6] led us to take up the synthesis of stagonolide E. Herein we report a simple route to the total synthesis of stagonolide E starting from readily available 4-penten-1-ol.

Retrosynthetically (Scheme 1), we envisaged that the target molecule **8** can be obtained from seco acid **13** by Yamaguchi lactonization followed by MOM deprotection. The seco acid **13** in turn can be made from aldehyde **14** using Stille–Gennari reaction. Compound **14** can be obtained from **15** by dihydroxylation and cleavage of the diol, while the allylic alcohol **15** is readily obtained from 4-penten-1-ol by standard transformations.

Accordingly, the synthesis began with the known secondary alcohol **17**[6b] prepared from 4-penten-1-ol **16**. The secondary alcohol **17** was protected as TBS ether using *t*-butyldimethylsilyl chloride and imidazole in CH_2Cl_2 at rt to afford product **18** in 95% yield (Scheme 2). Removal of benzyl ether using Li in liq NH_3 provided primary alcohol **19** in 75% yield, which was oxidized to the corresponding aldehyde under Swern oxidation conditions. The aldehyde was homologated by a two-carbon Wittig ylide (etoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux for 3 h to furnish α,β-unsaturated ester **20**. The ester group in compound **20** was reduced to alcohol **21** in 85% yield using DIBAL-H in dry CH_2Cl_2 at °C to rt for 2 h. Sharpless asymmetric epoxidation[7] of **21** ((−)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide) afforded epoxy alcohol **22** in 75% yield (95% ee). The epoxy alcohol **22** was converted to the corresponding epoxy iodide **23** by treating with iodine, triphenylphosphine, and imidazole in a mixture of diethylether and acetonitrile in 3:1 ratio at 0 °C to rt in 90% yield. Compound **23** was converted to a secondary allylic alcohol **24** in 80% yield by refluxing with activated zinc[8] in ethanol. The resulting alcohol **24** was protected as its MOM ether using MOMCl, *N*,*N*-diisopropylethyl amine in CH_2Cl_2 to afford **15** in 80% yield. The terminal olefin in **15** was subjected to dihydroxylation with OsO_4 to give vicinal diol, which on oxidative cleavage with $NaIO_4$ provided an aldehyde. A two-carbon extension of the aldehyde using triphenylphosphoranylideneacetaldehyde ($Ph_3P{=}CHCHO$) afforded **14** in 73% yield. Applying the Stille–Gennari[9] reaction to compound **14** provided ester **27** using methyl *P*,*P*′-bis(2,2,2-trifluoroethyl)phosphonoacetate in the presence of NaH at −78 °C with excellent stereoselectivity (*Z*,*E*/*E*,*E* 95:5) in 80% yield. Cleavage of the TBS ether in **27** using TBAF in THF afforded **28** in 70% yield. Hydrolysis of ester **28** using LiOH provided seco acid **13** in 90% yield followed by Yamaguchi lactonization (2,4,6-trichlorobenzoylchloride in refluxing toluene) to provide macrolactone **29** (ee >95%). Finally, removal of MOM group under neutral conditions completed the synthesis of the target molecule, stagonolide E **8**

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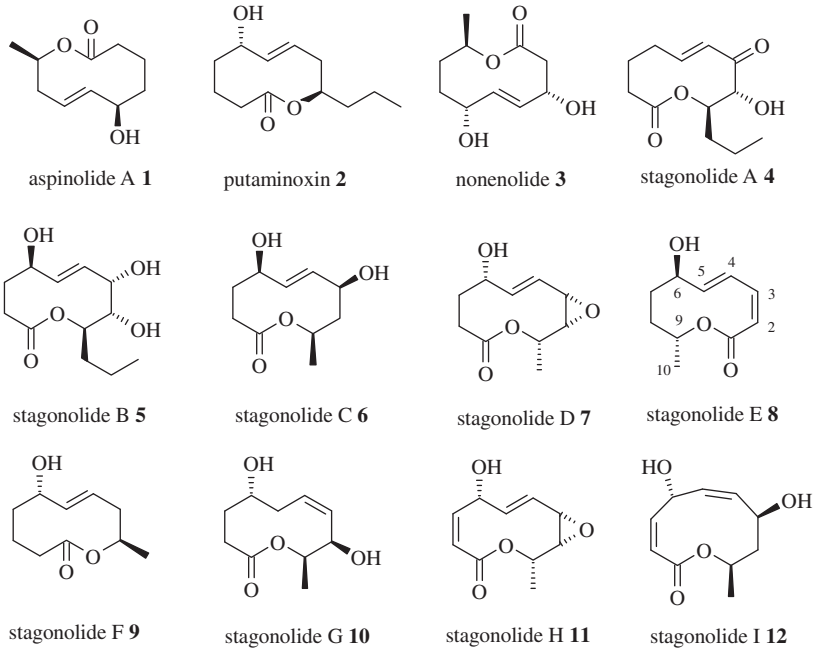
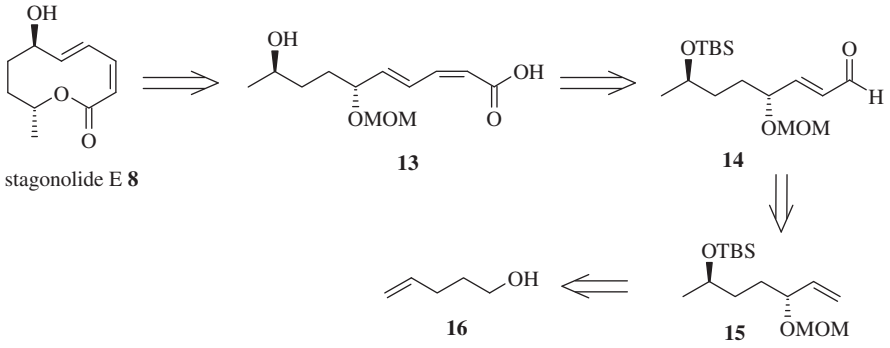


Figure 1. Stagonolides A–I.



Scheme 1. Retrosynthesis.

in 60% yield. The IR, ^{1}H NMR, ^{13}C NMR, and mass data of the synthetic **8** was in good accordance with those of the natural product.

In the DQFCOSY-(600 MHz, $CDCl_3$, 27 °C) spectrum of stagonolide E (Fig 1, structure **8**), couplings between H-2 with H-3 and H-4 with H-5 and a weak coupling between H-3 and H-4 were observed. In addition to this, a coupling was observed between H-5 and a proton of HO–CH-6 carbon. In the HSQC-(600 MHz, $CDCl_3$) spectrum, the four protons of dienyl system and adjacent HO–C-6 coupled with the signals observed at 140.2, 139.4, 126.5, 125.6, (C-5, C-3, C-4, and C-2), and 73.5 (C-6). The observed values of the synthetic compound **8** were matched with the reported values of the natural product.[4b]

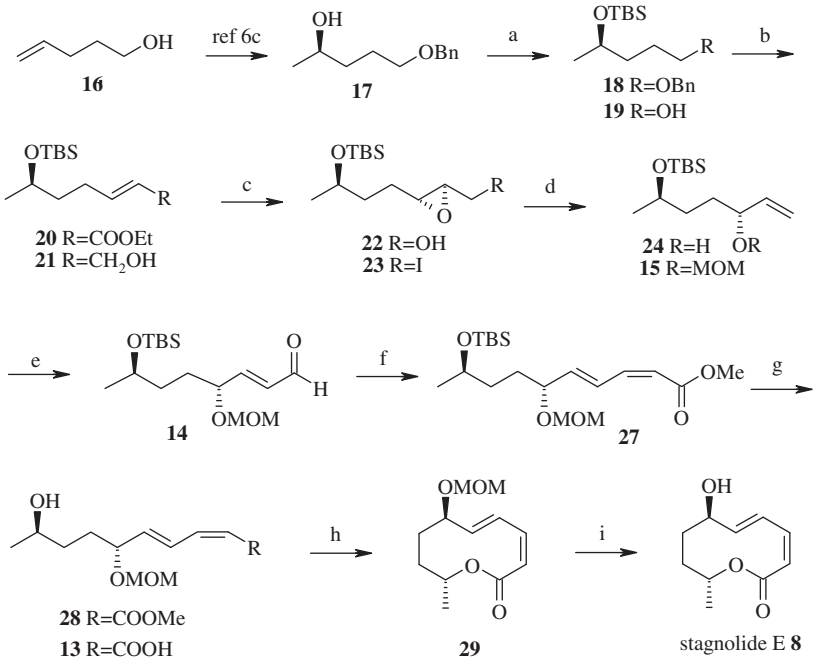
In conclusion, a simple route to the first total synthesis of stagonolide E is reported utilizing Jacobsen's kinetic resolution, Sharpless epoxidation, Stille–Gennari, and Yamaguchi lactonization as key steps. Selected spectral data

((2R, 3R)-3-((R)-3-(tert-butyl dimethylsilyloxy)butyl)oxiran-2-yl)methanol (**22**). $[\alpha]_D^{25}$: +12.0 (c = 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.04 (d, 6H, J = 2.2 Hz), 0.89 (s, 9H), 1.14 (d, 3H, J = 6.0 Hz), 1.41–1.70 (m, 4H), 2.86 (m, 1H), 2.92 (m, 1H), 3.61 (m, 1H), 3.78–3.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.7, −4.3, 22.3, 23.8, 28.0, 35.7, 56.1, 58.5, 61.7, 68.1; IR (neat): 3442, 2930, 2858, 1465, 1252, 834, 774 cm^{-1}; HRMS: m/z [M+1]$^+$ calcd for $C_{13}H_{28}O_3Si$: 261.1936; found: 261.1932.

(3R, 6R)-6-(tert-butyldimethylsilyloxy)hept-1-en-3-ol (**24**). $[\alpha]_D^{25}$: −5.6 (c = 1.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.05 (d, 6H, J = 6.8 Hz), 0.90 (s, 9H), 1.15 (d, 3H, J = 6.0 Hz), 1.44–1.66 (m, 4H), 3.80–3.92 (m, 1H), 4.00–4.14 (m, 1H), 5.04–5.28 (dd, 2H, J = 10.6, 17.3 Hz), 5.77–5.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.5, 21.6, 23.3, 33.0, 35.4, 68.5, 73.2, 114.3, 141.2; IR (neat): 3411, 2930, 2858, 1253, 1096, 835, 774 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{13}H_{28}O_2SiNa$: 267.2879; found: 267.2883.

(4R, 7R, E)-7-(tert-butyldimethylsilyloxy)-4-(methoxymethoxy)-oct-2-enal (**14**). $[\alpha]_D^{25}$: +22.5 (c = 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 0.05 (d, 6H, J = 2.0 Hz), 0.90 (s, 9H), 1.14 (d, 3H, J = 6.0 Hz), 1.35–1.83 (m, 4H), 3.36 (s, 3H), 3.74–3.84 (m, 1H), 4.24–4.35 (m, 1H), 4.6 (m, 2H), 6.16–6.28 (dd, 1H, J = 7.1, 7.7 Hz), 6.60–6.71 (dd, 1H, J = 6.0, 5.8 Hz), 9.8 (d, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): −4.8, −4.4, 23.8, 25.8, 30.8, 34.8, 55.7, 68.2, 75.5, 95.0, 132.0, 156.7, 193.3; IR (neat): 2954, 2931, 2889, 2857, 1696, 1042, 835, 774 cm^{-1}; HRMS: m/z [M+Na]$^+$ calcd for $C_{16}H_{32}O_4SiNa$: 339.1305; found: 339.1298.

(2Z, 4E, 6R, 9R)-methyl 9-(tert-butyldimethylsilyloxy)-6-(methoxymethoxy)deca-2,4-dienoate (**27**). $[\alpha]_D^{25}$: +46.1 (c = 1, $CHCl_3$); ^{1}H



Scheme 2. Reagents and conditions: (a) (i) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt, 30 min, 95%; (ii) Li, liq NH3, dry THF, 10 min, rt, 75%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (ii) Ph_3P=CHCOOEt, benzene, reflux, 3 h, 90% (over two-steps); (iii) DIBAL-H, CH_2Cl_2, 0 °C to rt, 2 h, 85%; (c) (i) (−)-DET, $Ti(O^iPr)_4$, cumene hydroperoxide, 4°A MS, CH_2Cl_2, −20 °C, 5 h, 75%; (ii) I_2, Ph_3P, imidazole, ether:acetonitrile (3:1), 0 °C to rt, 1 h, 90%; (d) (i) activated Zn, EtOH, reflux, 1–2 h 80%; (ii) MOMCl, *N*,*N*-diisopropylethyl amine, dry CH_2Cl_2, 0 °C, 4 h, 80%; (e) (i) OsO_4 (0.1 M solution in toluene), NMO, acetone/H_2O (4:1), overnight; (ii) $NaIO_4$, THF/H_2O (2:1), 15 min 85%; (iii) Ph_3P=CHCHO, CH_2Cl_2, rt, 8 h, 73%; (f) $(CF_3CH_2O)P(O)CH_2CO_2Me$, NaH, dry THF, −78 °C, 2 h, 80%; (g) (i) TBAF, THF, 0 °C, 1 h, 70%; (ii) LiOH·H_2O, THF/MeOH/H_2O (3:1:1), 0 °C–rt overnight, 90%; (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, reflux, 9 h, 70%; (i) $CeCl_3{\cdot}7H_2O$, CH_3CN/MeOH (2:1), 48 h, reflux, 60%.

NMR (300 MHz, $CDCl_3$): 0.04 (s, 6H), 0.88 (s, 9H), 1.12 (d, 3H, J = 6.2 Hz), 1.39–1.78 (m, 4H), 3.33 (s, 3H), 3.70 (s, 3H), 3.73–3.81 (m, 1H), 4.06–4.14 (m, 1H), 4.56 (d, 1H, J = 7.1 Hz), 4.66 (d, 1H, J = 7.1 Hz), 5.68 (d, 1H, J = 11.5 Hz), 5.88 (dd, 1H, J = 8.0, 15.0 Hz), 6.57 (t, 1H, J = 11.5 Hz), 7.47 (dd, 1H, J = 11.5, 15.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): −4.7, −4.4, 24.0, 26.0, 31.6, 35.2, 51.2, 55.5, 68.4, 76.2, 94.2, 117.5, 128.0, 143.5, 144.0, 166.5; IR (neat): 3426, 2930, 2857, 1720, 1176, 1037, 833, 773 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{19}H_{36}O_5SiNa$: 395.1041; found: 395.1048.

(2Z, 4E, 6R, 9R)-methyl 9-hydroxy-6-(methoxymethoxy)deca-2,4-dienoate (**28**). $[\alpha]_D^{25}$: +43.2 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.20 (d, 3H, J = 6.2 Hz), 1.46–1.80 (m, 4H), 3.38 (s, 3H), 3.73 (s, 3H), 3.78–3.89 (m, 1H), 4.14–4.26 (m, 1H), 4.57 (d, 1H, J = 6.8 Hz), 4.68 (d, 1H, J = 6.8 Hz), 5.70 (d, 1H, J = 11.3 Hz), 5.91 (dd, 1H, J = 6.8, 15.5 Hz), 6.57 (t, 1H, J = 11.3 Hz), 7.50 (dd, 1H, J = 11.5, 15.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 23.5, 31.6, 34.7, 51.2, 55.6, 67.7, 76.2, 94.3, 117.7, 128.0, 143.1, 144.0, 166.6; IR (neat): 3432, 2932, 1716, 1200, 1035 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{13}H_{22}O_5Na$: 281.2781; found: 281.2774.

(3Z, 5E, 7R, 10R)-7-(methoxymethoxy)-10-methyl-7,8,9,10-tetrahydrooxecin-2-one (**29**). $[\alpha]_D^{25}$: +47.4 (c = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (d, 3H, J = 6.2 Hz), 1.57–1.94 (m, 4H), 3.35 (s, 3H), 4.15 (td, 1H, J = 4.0, 9.0 Hz), 4.53 (d, 1H, J = 6.8 Hz), 4.70 (d, 1H, J = 6.6 Hz), 5.00 (m, 1H), 5.64 (dd, 1H, J = 9.6, 15.4 Hz), 5.85 (d, 1H, J = 10.5 Hz), 6.16 (d, 1H, J = 15.1 Hz), 6.62 (d, 1H, J = 10.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 21.4, 29.7, 39.0, 55.5, 73.1, 73.2, 95.0, 124.1, 128.1, 138.5, 140.6, 168.0; IR (neat): 3456, 2931, 1710, 1253, 1045 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{18}O_4Na$: 249.1041; found: 249.1048.

(3Z, 5E, 7R, 10R)-7-hydroxy-10-methyl-7,8,9,10-tetrahydrooxecin-2-one (stagonolide E) (**8**). $[\alpha]_D^{25}$: −181 (c = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (d, 3H, J = 6.6 Hz), 1.57–1.94 (m, 4H), 4.25 (td, 1H, J = 4.0, 9.0 Hz), 4.98 (m, 1H), 5.74 (dd, 1H, J = 9.4, 15.3 Hz), 5.85 (d, 1H, J = 11.6 Hz), 6.12 (br d, 1H, J = 15.4 Hz), 6.62 (br d, 1H, J = 11.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 21.3, 30.3, 37.4, 73.2, 73.5, 125.6, 126.5, 139.4, 140.2, 168.1; IR (neat): 3447, 2924, 2853, 1704, 1257 cm^{-1}; HRMS: *m/z* $[M+Na]^+$ calcd for $C_{10}H_{14}O_3Na$: 205.0851; found: 205.0845.

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