A Stereoselective Aldol Approach for the Total Synthesis of Herbarumin I and Stagonolide A

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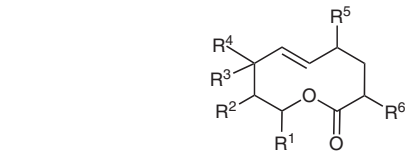
Abstract: A stereoselective total synthesis of phytotoxic compounds herbarumin I and stagonolide A has been achieved utilizing Crimmin's protocol for non-Evans *anti*-aldol approach and a ring-closing olefin metathesis reaction as the key steps.

Key words: macrolide, phytotoxic, Evans aldol, olefin metathesis

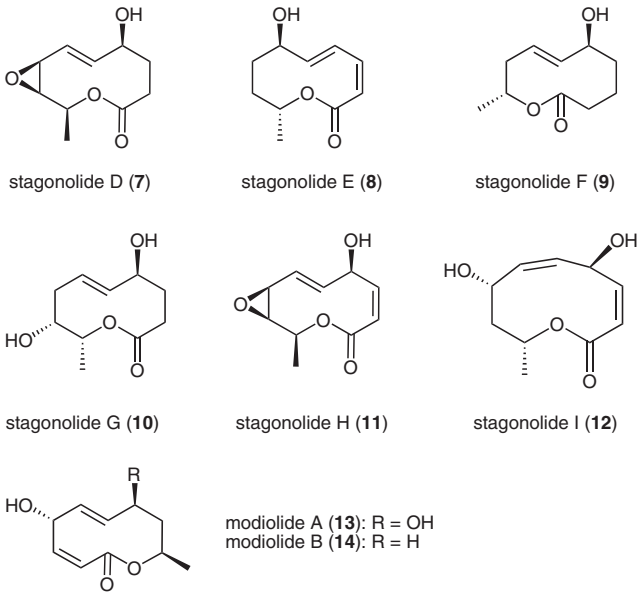
Recently, there has been increased attention in ten-membered ring containing macrolides that display potent biological activity.[1] Herbarumins I–III,[2] stagonolides A–I,[3] and modiolides A and B[4] are recent examples that have been isolated and found to display potent biological activity (Figure 1). Herbarumins I–III have been isolated from fermentation broth and mycelium of the fungus *Phoma herbarum* and were found to show phytotoxic effects against the seedlings of *Amaranthus hypochondriacus* at very low concentrations. Herbarumin I also displayed potent antifungal activity. Stagonolide A isolated recently from the fungus *Stagonospora cirsii*, a pathogen of *Cirsium arvense* was found to cause necrotic lesions on leaves. The impressive biological activity and scarce availability of these natural materials have attracted several synthetic chemists to take up their total synthesis for further evaluation towards biological screening.[5–9]

In continuation of our programme towards the total synthesis of natural products containing lactone moieties,[7k,8d,10] we have recently described the total synthesis of herbarumin I and stagonolide A following a chiron approach.[5g] Herein, we describe a stereoselective aldol route for the total synthesis of herbarumin I and stagonolide A.

Our synthetic strategy relies on Crimmins' protocol for non-Evans *anti*-aldol product starting from *n*-butyraldehyde to generate two chiral centers. The third chiral center is created by a stereoselective Grignard reaction and is then followed by the well-known ring-closing-metathesis reaction to obtain the desired skeleton for the target molecule. Thus, our retrosynthetic analysis revealed a key fragment **15** which could be coupled to hex-2-enoic acid and subjected to intramolecular Grubbs metathesis reaction followed by benzyl deprotection to realize the target molecule herbarumin I (**1**). The key fragment **15** was obtained from **16** in a four-step sequence involving auxiliary cleavage to yield the aldehyde, Grignard reaction with vinylmagnesium bromide followed by benzyl protection and TBS-deprotection. The compound **16** in turn was obtained by modified Evans aldol reaction of *n*-butyraldehyde with (*S*)-2-(benzyloxy)-1-(4-benzyl-2-thioxooxazolidin-3-yl)ethanone (Scheme 1).



herbarumin I (**1**): R^1 = α-Pr, R^2 = β-OH, R^3 = α-H, R^4 = β-OH, R^5 = H, R^6 = H
herbarumin II (**2**): R^1 = α-Pr, R^2 = β-OH, R^3 = α-H, R^4 = β-OH, R^5 = H, R^6 = β-OH
herbarumin III (**3**): R^1 = α-Pr, R^2 = H, R^3 = α-H, R^4 = β-OH, R^5 = H, R^6 = H
stagonolide A (**4**): R^1 = α-Pr, R^2 = β-OH, R^3 = O, R^4 = O, R^5 = H, R^6 = H
stagonolide B (**5**): R^1 = α-Pr, R^2 = α-OH; R^3 = β-H, R^4 = α-OH, R^5 = β-OH, R^6 = H
stagonolide C (**6**): R^1 = α-Me, R^2 = H, R^3 = α-OH, R^4 = β-H, R^5= β-OH, R^6 = H



stagonolide D (**7**) stagonolide E (**8**) stagonolide F (**9**)

stagonolide G (**10**) stagonolide H (**11**) stagonolide I (**12**)

modiolide A (**13**): R = OH
modiolide B (**14**): R = H

Figure 1 Ten-membered-ring-containing macrolides

Accordingly, our synthesis started with *n*-butyraldehyde which was subjected to Crimmins' protocol[11] for non-Evans *anti*-aldol reaction with (*S*)-2-(benzyloxy)-1-(4-benzyl-2-thioxooxazolidin-3-yl)ethanone (**17**) in the presence of titanium(IV) chloride and (–)-sparteine at –78 °C to give the corresponding chiral α,β-dihydroxy amides **18** and **18′** as a mixture of diastereomers (non-Evans-*anti*/Evans-*anti*, 95:5) in 65% yield. The diastereomeric ratios were determined by combined analysis of crude ^{1}H NMR

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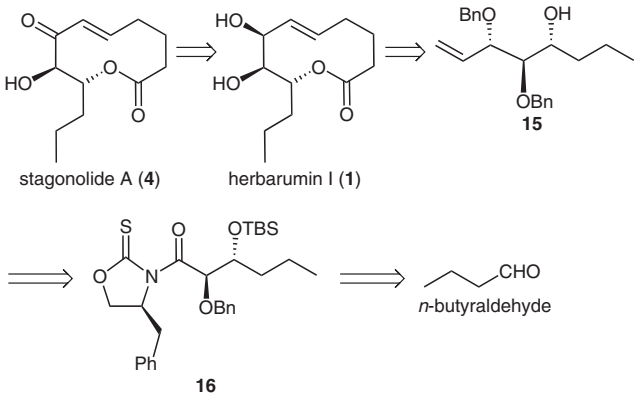
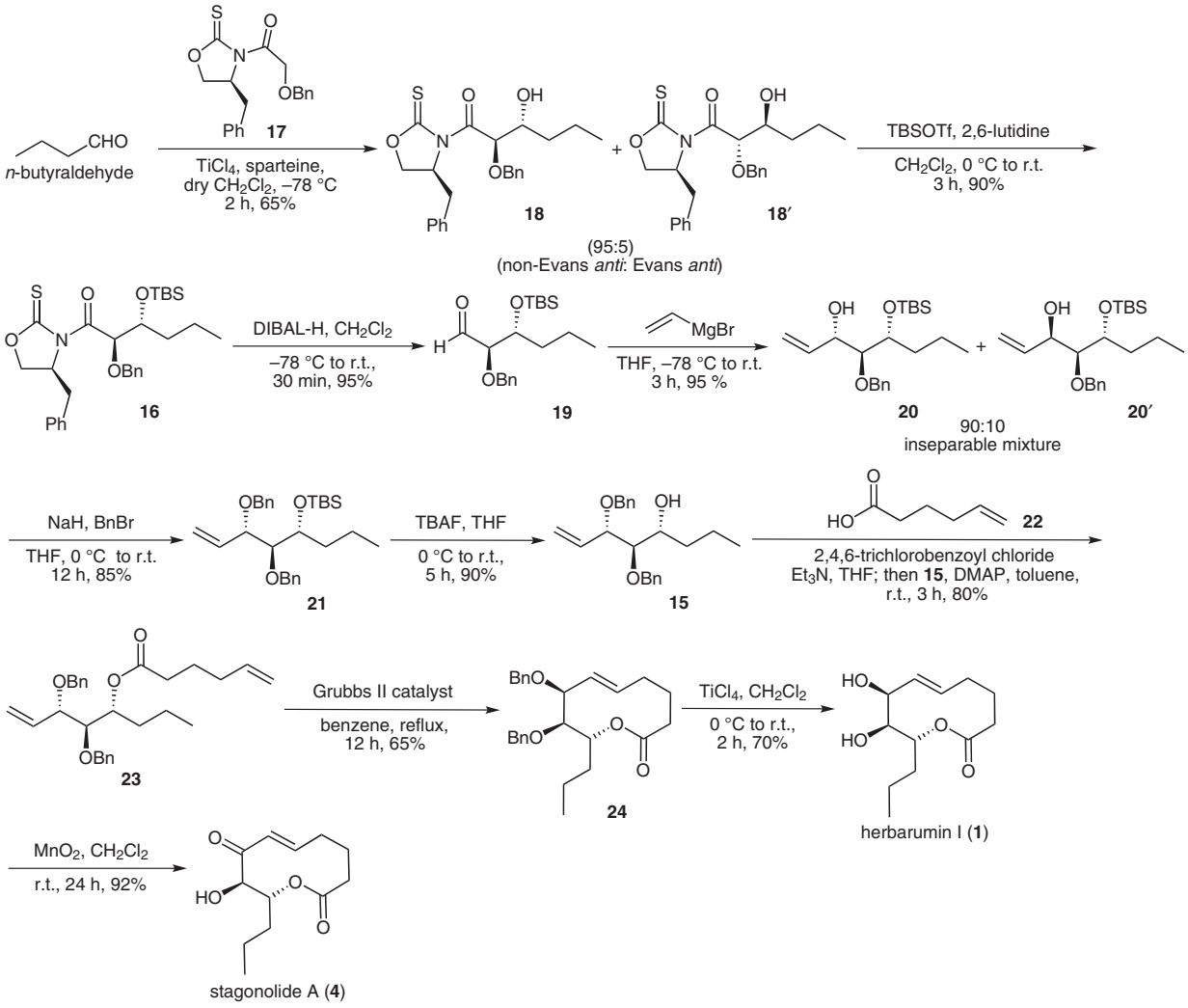


Scheme 1 Retrosynthesis

spectroscopy and LCMS analysis. Due to difficulties in separating *anti*-aldol products from the starting material, we carried out the TBS-protection directly with *tert*-butyldimethylsilyl triflate to afford the corresponding TBS ether **16**. Treatment of compound **16** with diisobutylaluminum hydride afforded aldehyde **19**, which was then subjected to Grignard reaction with vinylmagnesium bromide at –78 °C to room temperature to yield corresponding allylic alcohols **20** and **20′** as an inseparable mixture of diastereomers (*anti*/*syn*, 90:10) in 95% yield.[12] However, upon protection of the secondary alcohol with benzyl bromide, the desired product **21** (85%) was easily separated. TBS deprotection with tetrabutylammonium fluoride yielded the intermediate **15**. With the key intermediate **15** in hand, the stage was set for coupling with hex-5-enoic acid (**22**) and to proceed further for ring-closing metathesis. Thus, coupling of alcohol **15** with hex-5-enoic acid (**22**) proceeded smoothly under Yamaguchi's conditions employing trichlorobenzoyl chloride and 4-(dimethylamino)pyridine to yield diolefin **23**.[13] Ring-closing metathesis of compound **23** worked well with Grubbs' 2nd-generation catalyst in benzene at reflux temperature for 12 hours to yield the desired *trans*-isomer **24** as the major product.[14] Deprotection of the two benzyl moieties was achieved using titanium(IV) chloride[15] to yield herbarumin I (**1**). Consequently herbarumin I (**1**) was converted into stagonolide A (**4**) on allylic oxidation with manganese dioxide, thus, we have also accomplished the total synthesis of stagonolide A (Scheme 2). The products herbarumin I (**1**) and stagonolide A (**4**) obtained were characterized by spectroscopic analysis and also confirmed by



Scheme 2 Total synthesis of herbarumin I (**1**) and stagonolide A (**4**)

comparing the data with the earlier known literature and was found to be identical in all respects.[2,3,5,8d]

In conclusion, we have achieved the total synthesis of herbarumin I and stagonolide A by utilizing Crimmins' protocol for non-Evans *anti*-aldol product, stereoselective Grignard reaction, and Grubbs' olefin metathesis as the key steps with an overall yield of 12.6% and 11.6% for herbarumin I (**1**) and stagonolide A (**4**), respectively.

Column chromatography was performed using silica gel 60–120 mesh. All the solvents were dried and distilled prior to use. IR spectra were recorded on a Perkin-Elmer Infrared spectrophotometer as KBr wafers or neat or in $CHCl_3$ as a thin film. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 MHz instrument using TMS as an internal standard. Mass spectra were recorded on Micro mass VG 7070H mass spectrometer for EI, VG Autospec mass spectrometer for FABMS and micromass Quatro LC triple quadrupole mass spectrometer for ESI analysis. The optical rotations were recorded on Jasco DIP-360 digital polarimeter. PE = petroleum ether.

(*S*)-2-(Benzyloxy)-1-(4-benzyl-2-thioxooxazolidin-3-yl)ethanone (17)

To a stirred soln of 2-(benzyloxy)acetic acid (17.20 g, 103.0 mmol) and DMF (0.394 mL, 5.10 mmol) in anhyd CH_2Cl_2 (100 mL) at 0 °C under N_2 was added slowly 2.0 M oxalyl chloride in CH_2Cl_2 (9.5 mL, 112.0 mmol). The resulting mixture was allowed to warm up to 25 °C and stirred for 1 h. Evaporation of most of the solvents yielded the crude 2-(benzyloxy)acetyl chloride, which was added to a stirred soln of (*S*)-4-benzyloxazolidine-2-thione (10.00 g, 51.0 mmol) and 1.6 M *n*-BuLi in hexanes (38.1 mL, 61.0 mmol) in anhyd THF (200 mL) at –78 °C under N_2. The mixture was allowed to warm up to r.t. and stirred for 1.5 h. The mixture was quenched with sat. $NaHCO_3$ (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine (2 × 60 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 80:20) to afford pure **17** (12.5 g, 71%) as a colorless solid; **17** could also be recrystallized (Et_2O–*n*-hexane) for enhanced purity.

$[\alpha]_D^{25}$ +59.4 (*c* 1.1, $CHCl_3$).

IR (KBR): 3029, 2919, 1710, 1494, 1366, 1325, 1208 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.19 (m, 10 H), 5.02 (dd, *J* = 29.4, 18.1 Hz, 2 H), 4.94–4.86 (m, 1 H), 4.67 (s, 2 H), 4.37–4.30 (m, 2 H), 3.31 (dd, *J* = 12.8, 3.0 Hz, 1 H), 2.82–2.71 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.3, 170.5, 136.7, 134.5, 129.0, 128.6, 128.1, 127.7, 127.6, 127.0, 73.0, 71.1, 71.0, 59.3, 37.0.

MS (ESI): *m*/*z* = 364 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_3S$: 364.0983; found: 364.0986.

(2*R*,3*R*)-2-(Benzyloxy)-1-[(*S*)-4-benzyl-2-thioxooxazolidin-3-yl]-3-hydroxyhexan-1-one (18)

To a stirred soln of **17** (3.0 g, 8.79 mmol) in anhyd CH_2Cl_2 (25 mL) at –78 °C under N_2 was added $TiCl_4$ (1.17 mL, 10.5 mmol) dropwise and the resulting reddish brown color soln was allowed to stir for 10 min. Then a freshly prepared soln of 2.0 M (–)-sparteine in CH_2Cl_2 (2.41 mL, 10.5 mmol) was added dropwise and stirring was continued for an additional 40 min. Additional $TiCl_4$ (2.25 mL, 20.2 mmol) was added to the enolate mixture, the mixture was stirred for 1 min, and a freshly distilled soln of butyraldehyde (1.05 mL, 11.4 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at this temperature for 15 min, and then the reaction was quenched by the addition of aq sat. NH_4Cl (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (anhyd Na_2SO_4), filtered, and concentrated to afford the diastereomeric mixture **18**/**18′** (2.4 g, 65%) ratio non-Evans *anti*/Evans *anti*, 95:5 (determined by combined analysis of crude ^1H NMR spectroscopy and LCMS). The diastereomeric mixture was used directly in the next step without further purification.

(2*R*,3*R*)-2-(Benzyloxy)-1-[(*S*)-4-benzyl-2-thioxooxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)hexan-1-one (16)

To a stirred soln of aldol compound **9** (1.0 g, 2.4 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C under N_2 was added 2,6-lutidine (0.36 mL, 3.1 mmol) and TBSOTf (0.83 mL, 3.6 mmol) sequentially and the mixture was stirred at r.t. for 3 h. Then the mixture was quenched with aq sat. $NaHCO_3$ (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with 10% $NaHSO_4$ (2 × 10 mL) and brine (1 × 20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 95: 5) to afford **16** (1.15 g, 90%) as a yellow oil.

$[\alpha]_D^{25}$ +50.3 (*c* 2.8, $CHCl_3$).

IR (neat): 2956, 2930, 2858, 1704, 1366, 1323, 1196, 1155, 834 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.15 (m, 10 H), 6.24 (d, *J* = 5.2 Hz, 1 H), 4.73–4.68 (m, 1 H), 4.58–4.46 (m, 2 H), 4.26–4.21 (m, 1 H), 4.12 (dd, *J* = 9.3, 3.1 Hz, 1 H), 3.89 (t, *J* = 8.3 Hz, 1 H), 3.31 (dd, *J* = 12.4, 3.1 Hz, 1 H), 2.51 (ABq, *J* = 12.4, Hz, 1 H), 1.81–1.71 (m, 1 H), 1.63–1.55 (m, 1 H), 1.54–1.44 (m, 2 H), 0.95 (t, *J* = 7.2 Hz, 3 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.8, 173.4, 137.8, 135.3, 129.2, 129.0, 128.4, 128.2, 127.9, 127.3, 78.1, 73.6, 72.9, 70.4, 60.3, 37.7, 35.1, 25.8, 17.6, 14.4, –4.35, –4.31.

MS (ESI): *m*/*z* = 528 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{42}NO_4SiS$: 528.2603; found: 528.2612.

(2*R*,3*R*)-2-(Benzyloxy)-3-(*tert*-butyldimethylsilyloxy)hexanal (19)

To a stirred soln of **16** (1.5 g, 2.8 mmol) in anhyd CH_2Cl_2 (15 mL) at –78 °C under N_2 was added dropwise 20% DIBAL-H in toluene (4.07 mL, 5.7 mmol). The resulting mixture was stirred at –78 °C for 30 min. Then the mixture was quenched with sat. sodium potassium tartrate soln (5 mL) and allowed to warm up to r.t. and stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh; PE–EtOAc, 97: 3) to afford pure **19** (0.9 g, 95%) as a yellow oil.

$[\alpha]_D^{25}$ +16.1 (*c*, 3.0, $CHCl_3$).

IR (neat): 2957, 2932, 2859, 1731, 1463, 1364, 1254, 1122, 835, 776 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 2.2 Hz, 1 H), 7.39–7.28 (m, 5 H), 4.63 (ABq, *J* = 11.8 Hz, 2 H), 4.06–4.00 (m, 1 H), 3.69 (dd, *J* = 2.2, 3.5 Hz, 1 H), 1.71–1.57 (m, 1 H), 1.54–1.41 (m, 1 H), 1.40–1.22 (m, 2 H), 0.92–0.86 (m, 12 H), 0.07 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.2, 137.3, 128.3, 128.0, 127.8, 86.0, 72.7, 73.5, 35.8, 25.7, 18.8, 18.2, 14.0, –4.6, –4.7.

MS (ESI): *m*/*z* = 359 $[M + Na]^+$.

(3*S*,4*S*,5*R*)- and (3*R*,4*S*,5*R*)-4-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)oct-1-en-3-ol (20 and 20′)

To a stirred soln of aldehyde **19** (1.40 g, 4.1 mmol) in anhyd THF (13 mL) at –78 °C under N_2 was added dropwise 1.0 M vinylmagnesium bromide in THF (12.00 mL, 12.00 mmol). The resulting mixture was warmed up to r.t. and stirred for 3 h and then it was quenched with sat. aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, PE–EtOAc, 90:10) to afford a pure, inseparable diastereomeric mixture of **20** and **20′** (1.45 g, 95%) as a yellow oil; *anti*/*syn* 90:10.

$[\alpha]_D^{25}$ –9.3 (*c* 3.5, $CHCl_3$).

IR (neat): 3449, 2955, 2929, 2858, 1638, 1462, 1077, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 6.08–5.85 (m, 1 H), 5.41–5.29 (m, 1 H), 5.24–5.16 (m, 0.9 H), 5.14–5.08 (m, 0.1 H), 4.78–4.54 (m, 2 H), 4.29–4.13 (m, 1 H), 3.94–3.84 (m, 0.9 H), 3.82–3.75 (m, 0.1 H), 3.35–3.30 (m, 0.9 H), 3.29–3.25 (m, 0.1 H), 2.79 (d, *J* = 4.5 Hz, 0.3 H, OH), 2.37 (d, *J* = 3.5 Hz, 0.7 H, OH), 1.72–1.50 (m, 1 H), 1.49–1.28 (m, 3 H), 0.96–0.86 (m, 12 H), 0.12–0.06 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major and minor) = (138.2, 138.4), (137.9, 139.3), (128.2, 128.3), (127.9, 127.8), (127.7, 127.5), (115.6, 116.4), (84.4, 84.0), (74.1, 73.9), (73.5, 73.4), (71.8, 72.6), (35.7, 35.1), (25.86, 25.85), (18.3, 19.1), (18.2, 17.9), (14.25, 14.24), (–4.4, –4.61), (–4.5, –4.64).

MS (ESI): *m*/*z* = 365 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{37}O_3Si$: 365.2511; found: 365.2519.

[(4*R*,5*S*,6*S*)-5,6-Bis(benzyloxy)oct-7-en-4-yloxy]*tert*-butyldimethylsilane (21)

To a well-stirred soln of NaH (0.219 g, 5.4 mmol) in anhyd THF (5 mL) at 0 °C under N_2 atmosphere, a soln of mixture of compounds **20** and **20′** (1.0 g, 2.74 mmol) in anhyd THF (5 mL) was added dropwise. After 30 min, a soln of BnBr (0.45 mL, 3.80 mmol) in anhyd THF (4 mL) was added dropwise and the mixture was allowed to warm up to r.t. and stirred for 12 h. The mixture was quenched with ice flakes and extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with brine (1 × 20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, 230–400 mesh, PE) to afford pure **21** (1.07 g, 85%) as a yellow oil.

$[\alpha]_D^{25}$ +23.0 (*c* 0.7, $CHCl_3$).

IR (neat): 3449, 2926, 2856, 1635, 1459, 1252, 1107, 832, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 10 H), 5.96–5.84 (m, 1 H), 5.38–5.28 (m, 2 H), 4.73 (ABq, *J* = 12.0 Hz, 2 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 3.94–3.86 (m, 2 H), 3.58–3.54 (m, 1 H), 1.67–1.55 (m, 1 H), 1.40–1.20 (m, 3 H), 0.91–0.81 (m, 12 H), 0.05 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.8, 128.2, 128.1, 127.8, 127.7, 127.4, 127.2, 118.7, 84.2, 80.4, 74.0, 72.5, 70.1, 34.2, 29.6, 25.9, 18.1, 14.3, –4.2, –4.4.

MS (ESI): *m*/*z* = 455 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{43}O_3Si$: 455.3011; found: 455.2989.

(4*R*,5*R*,6*S*)-5,6-Bis(benzyloxy)oct-7-en-4-ol (15)

To a stirred soln of **21** (0.55 g, 1.21 mmol) in anhyd THF (5 mL) at 25 °C was added TBAF (3.6 mL, 3.63 mmol) and the mixture was stirred for 5 h. Then it was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 90:10) to afford pure **15** (0.37 g, 90%) as a yellow oil.

$[\alpha]_D^{25}$ –4.4 (*c* 2.2, $CHCl_3$).

IR (neat): 3452, 2956, 2924, 2862, 1637, 1456, 1069, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 10 H), 5.97–5.87 (m, 1 H), 5.38–5.29 (m, 2 H), 4.72–4.52 (m, 3 H), 4.35 (d, *J* = 12.4 Hz, 1 H), 4.02 (t, *J* = 5.8 Hz, 1 H), 3.71–3.65 (m, 1 H), 3.37 (t, *J* = 5.8 Hz, 1 H), 2.45 (d, *J* = 5.1 Hz, 1 H, OH), (1.57–1.42 (m, 1 H), 1.40–1.23 (m, 3 H), 0.89 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 119.1, 82.8, 80.9, 73.7, 70.8, 70.5, 34.9, 29.6, 18.7, 14.0.

MS (ESI): *m*/*z* = 363 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{28}NaO_3$: 363.1931; found: 363.1941.

(4*R*,5*S*,6*S*)-5,6-Bis(benzyloxy)oct-7-en-4-yl Hex-5-enoate (23)

To a stirred soln of hex-5-enoic acid (**22**, 0.139 mL, 1.17 mmol) in anhyd THF (7 mL) under N_2 was added Et_3N (0.181 mL, 1.29 mmol) and 2,4,6-trichlorobenzoyl chloride (0.183 mL, 1.17 mmol) at r.t. The resulting mixture was allowed to stir at r.t. for 2 h and then it was filtered through a pad of silica gel. The filtrate was concentrated to dryness to give the acid anhydride. The residue was dissolved in toluene (8 mL) and **15** (0.40 g, 1.17 mmol) and DMAP (0.717 g, 5.88 mmol) were added. The mixture was stirred at r.t. for 3 h and then it was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 95:5) to afford pure **23** (0.41 g, 80%) as a yellow oil.

$[\alpha]_D^{25}$ +28.0 (*c* 0.6, EtOH).

IR (neat): 2926, 2864, 1730, 1638, 1455, 1067, 737 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 10 H), 5.93–5.68 (m, 2 H), 5.39–5.26 (m, 2 H), 5.05–4.95 (m, 3 H), 4.73 (ABq, *J* = 11.7 Hz, 2 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.37 (d, *J* = 11.7 Hz, 1 H), 3.87 (t, *J* = 6.7 Hz, 1 H), 3.65 (dd, *J* = 3.2, 6.6 Hz, 1 H), 2.29–2.11 (m, 2 H), 2.09–2.02 (m, 2 H), 1.86–1.63 (m, 3 H), 1.62–1.49 (m, 1 H), 1.42–1.14 (m, 2 H), 0.87 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 138.6, 138.2, 137.6, 135.0, 128.2, 128.1, 127.9, 127.8, 127.5, 127.4, 119.4, 115.3, 82.7, 82.4, 74.8, 74.0, 70.4, 33.6, 33.0, 30.6, 23.9, 18.7, 13.8.

MS (ESI): *m*/*z* = 459 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{36}NaO_4$: 459.2511; found: 459.2501.

(8*S*,9*S*,10*R*,*E*)-8,9-Bis(benzyloxy)-10-propyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (24)

A soln of **23** (0.065 g, 0.149 mmol) and Grubbs II catalyst (0.029 mmol) in degassed anhyd benzene (125 mL) was refluxed for 12 h under an argon atmosphere; the mixture was concentrated in vacuo. The residue was purified by column chromatography (silica gel, PE–EtOAc, 92:8) to afford pure **24** (0.039 g, 65%); as a yellow oil.

$[\alpha]_D^{25}$ +47.0 (*c* 2.5, $CHCl_3$).

IR (neat): 2923, 2853, 1736, 1458, 1260, 1093, 1022, 800 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 10 H), 5.76–5.59 (m, 1 H), 5.46 (td, *J* = 9.2, 2.6 Hz, 1 H), 5.38 (d, *J* = 15.4 Hz, 1 H), 4.78 (d, *J* = 12.6 Hz, 1 H), 4.58 (d, *J* = 12.6 Hz, 1 H), 4.40 (ABq, *J* = 11.7 Hz, 2 H), 4.31–4.25 (m, 1 H), 3.33 (dd, *J* = 9.4, 2.0 Hz, 1

H), 2.45–2.26 (m, 2 H), 2.03–1.78 (m, 4 H), 1.73–1.58 (m, 2 H), 1.51–1.21 (m, 2 H), 0.90 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.8, 129.7, 128.3, 128.1, 127.9, 127.7, 127.6, 127.4, 127.2, 125.1, 80.8, 74.7, 72.0, 71.9, 70.1, 34.6, 33.7, 33.6, 29.6, 24.3, 17.7, 14.0.

MS (ESI): m/z = 431 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{32}NaO_4$: 431.2198; found: 431.2190.

(8*S*,9*S*,10*R*,*E*)-8,9-Dihydroxy-10-propyl-3,4,5,8,9,10-hexahydro-2*H*-oxecin-2-one (Herbarumin I; 1)

To a stirred soln of **24** (0.025 g, 0.061 mmol) in anhyd CH_2Cl_2 (5 mL) at 0 °C under N_2 was added $TiCl_4$ (0.013 mL, 0.122 mmol) and the resulting mixture was allowed to stir at r.t. for 2 h. The mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$ (2 × 5 mL) and brine (1 × 10 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel, PE–EtOAc, 80:20) to afford pure herbarumin I (**1**) (0.009 g, 70%) as a colorless solid.

$[\alpha]_D^{25}$ +13.0 (*c*, 0.3, EtOH).

IR (neat): 2958, 2923, 2854, 1716, 1440, 1359, 1255, 1203, 1089, 806 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (dd, J = 15.8, 0.7 Hz, 1 H), 5.56–5.44 (m, 1 H), 4.94 (td, J = 9.6, 2.4 Hz, 1 H), 4.42 (br s, 1 H), 3.50 (dd, J = 9.8, 2.0 Hz, 1 H), 2.46–2.27 (m, 3 H), 2.06–1.86 (m, 3 H), 1.64–1.50 (m, 2 H), 1.45–1.21 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 130.5, 124.9, 73.6, 73.3, 70.1, 34.4, 33.6, 33.3, 24.6, 18.0, 13.8.

MS (ESI): m/z = 251 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$calcd for $C_{12}H_{20}NaO_4$: 251.1259; found: 251.1264.

(9*R*,10*R*,*E*)-9-Hydroxy-10-propyl-4,5,9,10-tetrahydro-2*H*-oxecin-2,8(3*H*)-dione (Stagonolide A; 4)

To a stirred soln of herbarumin I (**1**, 0.03 g, 0.13 mmol) in CH_2Cl_2 (6.0 mL) was added MnO_2 (0.229 mg, 2.60 mmol) at 25 °C and the mixture was stirred at this temperature for 24 h. The mixture was filtered through a pad of Celite, the solvent was concentrated under reduced pressure, and the resulting residue was purified by column chromatography (silica gel, PE–EtOAc, 90:10) to afford pure stagonolide A (**4**) (0.027 g, 92%) as a colorless solid.

$[\alpha]_D^{25}$ –59.5 (*c* 0.2, EtOH).

IR (neat): 3417, 2960, 2930, 2869, 1727, 1692, 1632, 1438, 1398, 1152, 1075, 824 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (d, J = 16.0 Hz, 1 H), 6.37–6.24 (m, 1 H), 4.65 (dt, J = 9.6, 2.4 Hz, 1 H), 4.05 (dd, J = 9.5, 6.2 Hz, 1 H), 2.47–2.55 (m, 1 H), 2.44 (d, J = 5.7 Hz, 1 H), 2.13 (dd, J = 14.0, 2.3 Hz, 1 H), 2.05 (m, 1 H), 2.03–1.86 (m, 3 H), 1.73–1.58 (m, 1 H), 1.50–1.24 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.6, 174.1, 143.1, 131.9, 76.5, 74.5, 34.2, 34.0, 33.5, 25.0, 18.0, 13.7.

MS (ESI): m/z = 249 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{18}NaO_4$: 249.1102; found: 249.1095.

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