The Stereoselective Total Synthesis of (+)-Stagonolide B

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Abstract: The stereoselective total synthesis of the nonenolide, (+)-stagonolide B is described. The key steps involve epoxide homologation, hydrolytic kinetic resolution and ring-closing metathesis.

Key words: macrolide, ring-closing metathesis, antifungal, phytotoxic, kinetic resolution

Ten-membered macrolides have attracted significant attention due to their interesting biological properties.[1] A few recent examples include herbarumins I–III and stagonolides A–I (Figure 1). The herbarumins, isolated from the fungus *Phoma herbarum*,[2] display antifungal activity and phytotoxic effects. They also interact with bovine brain caldmodulin and inhibit the calmodulin-dependent enzyme cAMP phosphodiesterase. While there are several reports on the synthesis of herbarumins,[3] only a few contributions on stagonolides have been published which describe total syntheses and biological activity. Stagonolides A–I were isolated from the fungus *Stagonospora cirsii*, a pathogen of the perennial weed *Cirsium arvense*,[4] which results in necrotic lesions on leaves. Stagonolide F displays antifungal, antibacterial and cytotoxic properties.[5] As the biological activity of the other members of this group has not been fully explored due to their limited availability, we decided to target these molecules in order to investigate their biological properties. In continuation of our work on the total syntheses of biologically active lactone-containing natural products,[6] we describe herein a stereoselective total synthesis of stagonolide B (**5**).[7]

Our retrosynthesis of stagonolide B (**5**) is based on a convergent approach wherein two intermediate fragments, **14** and **15**, are coupled by esterification followed by an olefin metathesis to give the required ten-membered cyclic skeleton **13**. Carboxylic acid **14** can be obtained from commercially available butane-1,4-diol or pent-4-en-1-ol. Fragment **15**, with three stereogenic centers, is obtained utilizing a chiral pool approach starting from D-ribose (Scheme 1).

Our initial strategy toward fragment **15** departs from prior work at the readily available epoxide **16** obtained from D-ribose in four steps.[8] Epoxide **16** was treated with ethyl-

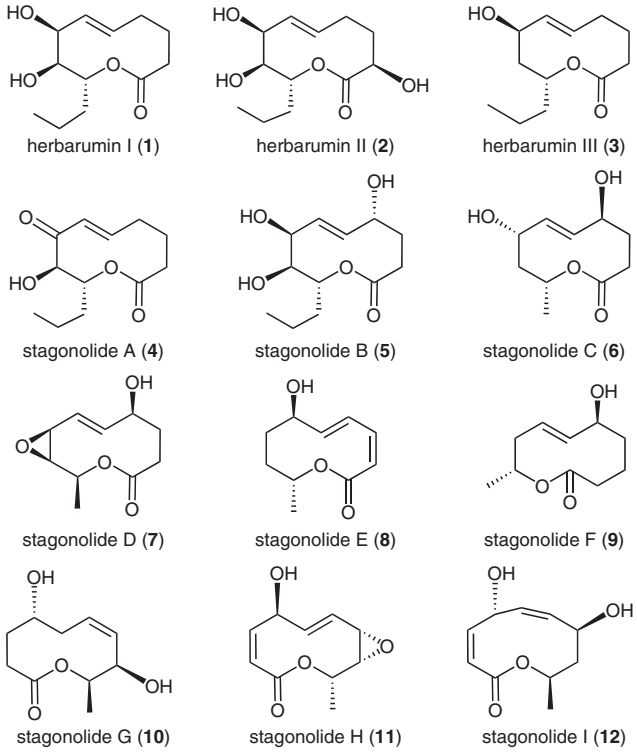
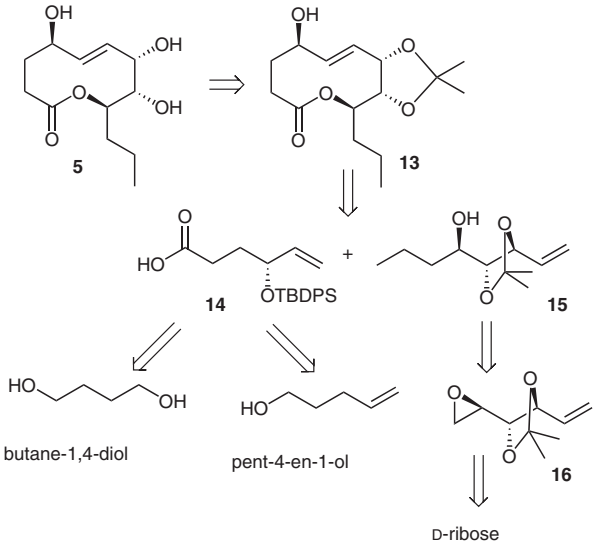


Figure 1 Examples of naturally occurring ten-membered macrolides



Scheme 1 Retrosynthesis of stagonolide B (**5**)

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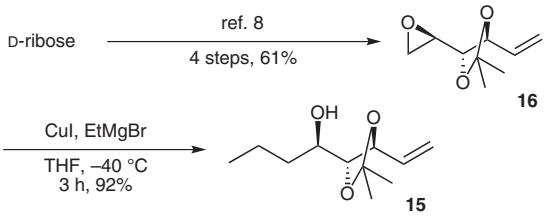
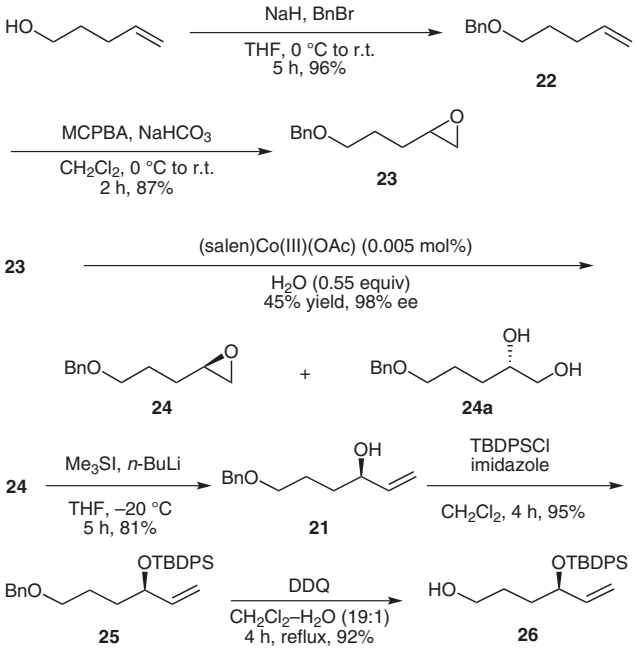
magnesium bromide in the presence of copper(I) iodide to yield the key intermediate **15** in good yield (Scheme 2).



Scheme 2 Synthesis of fragment **15**

The other key fragment, acid **14**, was obtained starting from commercially available butane-1,4-diol as shown in Schemes 3– 5. Accordingly, butane-1,4-diol was monoprotected as the benzyl ether **17**. Oxidation of **17** under Swern conditions[9] gave the corresponding aldehyde which on Wittig homologation with ethyl (triphenylphosphoranylidene)acetate yielded α,β-unsaturated ester **18**. Reduction of the ester functionality with diisobutylaluminum hydride gave alcohol **19**, which was subjected to Sharpless asymmetric epoxidation to yield chiral epoxy alcohol **20**.[10] The epoxy alcohol **20** was treated with iodine, triphenylphosphine and imidazole to give the corresponding epoxy iodide which reacted with zinc in ethanol at reflux temperature to yield the chiral allylic alcohol **21**[11] (Scheme 3).

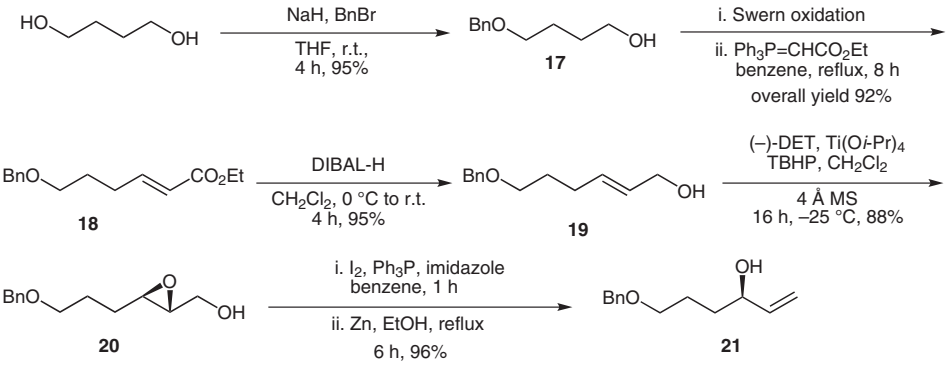
Alternatively, the alcohol **21** could be prepared from commercially available pent-4-en-1-ol as shown in Scheme 4. Thus, pent-4-en-1-ol was protected as the corresponding benzyl ether **22** using sodium hydride and benzyl bromide. Next, the alkene group of **22** was subjected to epoxidation with *m*-chloroperoxybenzoic acid to afford the racemic epoxide **23**. Solvent-free hydrolytic kinetic resolution[12] of **23** employing 0.55 equivalents of water in the presence of 0.005 equivalents of (*R*,*R*)-(–)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(III) acetate [(salen)Co(III)(OAc)] afforded chiral epoxide **24** in 45% yield along with the chiral diol **24a** (42%). The diol **24a** could be converted into the epoxide **24** in three steps.[13] Treatment of epoxide **24** with trimethylsulfonium iodide and *n*-butyllithium provided the chiral secondary allylic alcohol **21**.[14] The hydroxy group was protected as the corresponding *tert*-butyldiphenylsilyl ether to yield **25** which was subjected to debenzylation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the alcohol **26** (Scheme 4).



Scheme 4 Synthesis of alcohol **26**

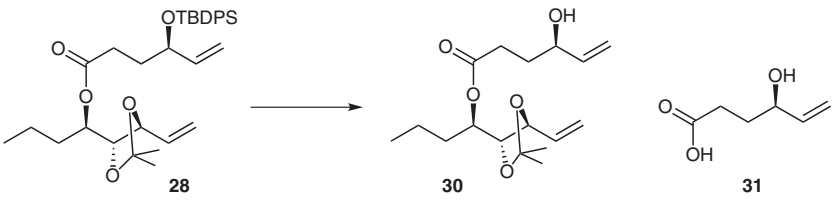
The alcohol **26** was sequentially oxidized to aldehyde **27** with 2-iodoxybenzoic acid (IBX), and then to acid **14** with sodium chlorite ($NaClO_2$) and sodium dihydrogen phosphate (NaH_2PO_4) in *tert*-butanol–water, in an overall 96% yield (Scheme 5).[15] With the two key intermediates, acid **14** and alcohol **15** in hand, the stage was set for coupling these fragments.

Initially, we used the standard procedure to couple acid **14** and alcohol **15** employing *N*,*N*′-dicyclohexylcarbodiimide and 4-(*N*,*N*-dimethylamino)pyridine to give the corresponding ester **28** (Scheme 6). Ring closing metathesis (RCM) on substrate **28** did not proceed to our expectations with both the Grubbs first- and second-generation catalysts. The starting material was recovered even after heating the reaction mixture at reflux for more than 12

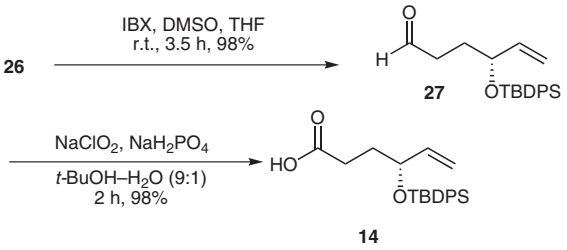


Scheme 3 Synthesis of chiral allylic alcohol **21** starting from butane-1,4-diol

Table 1 Investigation of the Reaction Conditions for the Desilylation of **28**



Entry	Reagents and conditions	Products (yield)
1	HF–py, THF, 0 °C to r.t.	mixture of **15** and **31**
2	Bu_4NF, THF, 0 °C to r.t.	mixture of **15**, **31** and **28**
3	NaH, HMPA, THF, 0 °C to r.t.	mixture of **15** and **31**
4	$Et_3N{\cdot}3HF$, THF, reflux	**30** (91%), **31** (5%)
5	NH_4F, MeOH, reflux	**30** (85%)

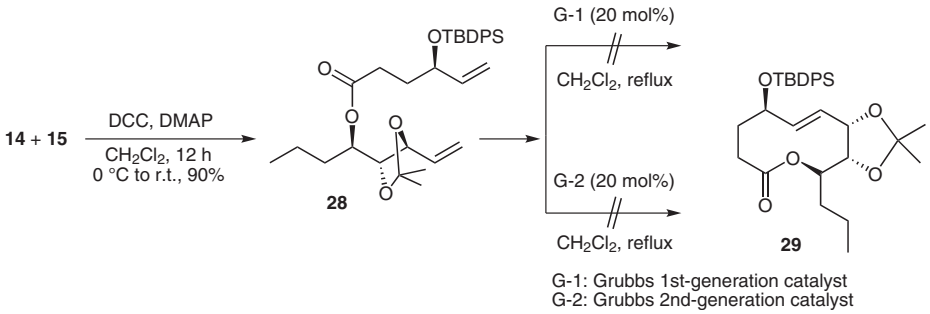


Scheme 5 Preparation of acid fragment **14**

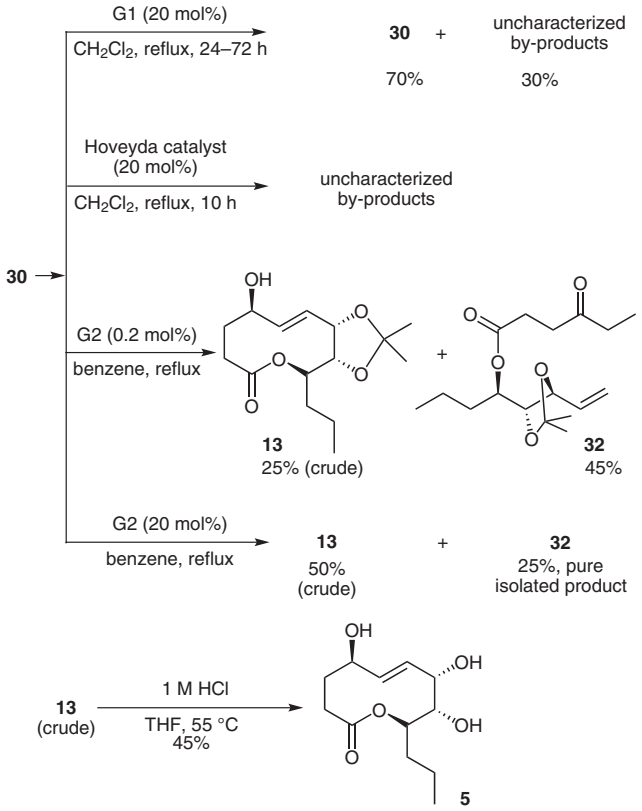
hours in dichloromethane. We reasoned that the presence of the *tert*-butyldiphenylsilyl moiety might be responsible for the failure of the ring-closing metathesis. Hence, we investigated the ring-closing metathesis using deprotected hydroxy compound **30**. Our attempts to desilylate the hydroxy group of **28** with hydrogen fluoride–pyridine, tetrabutylammonium fluoride, or sodium hydride in hexamethylphosphoramide (entries 1–3, Table 1) resulted in ester hydrolysis to return the acid **15** along with the hydroxy acid by-product **31**. After further careful investigations, we found that **28** could be desilyated using triethylamine tris(hydrogen fluoride) ($Et_3N{\cdot}3HF$) in tetrahydrofuran or with ammonium fluoride in methanol (entries 4 and 5, Table 1) to yield the desired product **30**. However, formation of **31** (5%) was observed in the case of the reaction with triethylamine tris(hydrogen fluoride).

Having established the free hydroxy group at the allylic position in compound **30**, the ring-closing metathesis was studied further. Unfortunately, cyclization using the Grubbs first-generation catalyst did not succeed and 70% of the starting material **30** was recovered along with other unidentified by-products. Attempts with Hoveyda catalyst ended up with uncharacterized by-products. However, the reaction was successful using the Grubbs second-generation catalyst to yield the desired acetonide-protected ten-membered macrolide **13**[7] along with ketone **32** as a by-product. On increasing the concentration of the catalyst from 0.2 mol% to 20 mol%, the percentage of the metathesis product was enhanced significantly (25% to 50%). Finally, cleavage of the acetonide group of crude **13** was achieved using hydrochloric acid to yield the target natural product (+)-stagonolide B (**5**) (Scheme 7). The analytical data of the synthetic product was found to be identical with that reported for the natural product.[4a,7]

In conclusion, the stereoselective total synthesis of stagonolide B (**5**) has been achieved. The key steps were Sharpless epoxidation, epoxide homologation, Jacobsen hydrolytic kinetic resolution and Grubbs olefin metathesis. Application of this strategy to the preparation of other



Scheme 6 Synthesis of diene **28** and attempted ring-closing metathesis



Scheme 7 Completion of the synthesis of stagonolide B

stagonolide analogues in order to study their biological activity is currently being pursued.

Column chromatography was performed using silica gel (60–120 mesh, Acme). All solvents were dried and distilled prior to use. IR spectra were obtained on a Perkin-Elmer Infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz instrument at 300 MHz and 75 MHz, respectively, using TMS as an internal standard. Mass spectra (EI) were recorded on a Micromass VG 7070H mass spectrometer. HRMS (ESI) spectra were obtained using a Micromass Quattro LC triple quadrupole mass spectrometer. The optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Enantiomeric excess values were determined by HPLC techniques using a ChiralPak IC 250 × 4.6 mm (5 μm) column. The mobile phase was 10% IPA in hexane with a flow rate of 1.0 mL/min for compound **20** and 20% IPA in hexane for compound **24**.

{(2*R*,3*R*)-3-[(Benzyloxy)propyl]oxiran-2-yl}methanol (20)

To a cooled (–25 °C) suspension of activated, powdered 4 Å MS (4 g) in CH_2Cl_2 (50 mL) were added (–)-DET (1.23 mL, 5.8 mmol), Ti(O*i*-Pr)$_4$ (1.38 mL, 4.6 mmol) and TBHP (21.25 mL, 85.0 mmol). After 20 min, a soln of allylic alcohol **19** (8.0 g, 38.8 mmol) in CH_2Cl_2 (80 mL) was added at –25 °C over 15 min. The resulting mixture was stirred at –25 °C for 12 h and then quenched with a cold soln of $FeSO_4$–tartaric acid (stoichiometric amount) in deionized H_2O. The mixture was stirred vigorously for 30 min and then extracted with Et_2O (3 × 100 mL). The combined organic layer was treated with a cold (0 °C) soln of 30% NaOH (30 mL, w/v) in brine and the mixture stirred for 2 h at r.t. The two layers were separated and the aq layer was extracted with Et_2O (3 × 100 mL). The combined organic layer was washed with brine (100 mL), dried over anhyd Na_2SO_4, filtered and concd. The residue was purified by column chromatography on silica gel (30% EtOAc–hexane) to give **20** (7.60 g, 88%, 90% ee) as a colorless syrup.

$[\alpha]_D^{27}$ +12.0 (*c* 2.0, $CHCl_3$).

IR (neat): 3409, 2920, 2854, 1452, 1364, 1099 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 4.50 (s, 2 H), 3.84 (qd, *J* = 12.6, 2.6 Hz, 1 H), 3.63–3.46 (m, 3 H), 2.97 (dt, *J* = 6.0, 2.3 Hz, 1 H), 2.93–2.88 (m, 1 H), 2.19 (s, 1 H), 1.95 (s, 1 H), 1.85–1.58 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.3, 127.6, 127.5, 72.9, 69.6, 61.6, 58.4, 55.7, 28.4, 26.1.

MS (ES): *m*/*z* = 245 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_3Na$: 245.1148; found: 245.1151.

(3*R*)-6-(Benzyloxy)hex-1-en-3-ol (21)

From butane-1,4-diol according to Scheme 3: To a soln of alcohol **20** (8.0 g, 21.5 mmol) in anhyd benzene (100 mL) were added imidazole (4.39 g, 64.5 mmol), Ph_3P (8.47 g, 32.30 mmol) and I_2 (8.22 g, 32 mmol) at 0 °C. After 5 min, the cold bath was removed and the reaction mixture was stirred for 1 h at r.t. during which time the color changed from brown to bright-yellow and the mixture became highly viscous. The mixture was quenched with sat. aq $Na_2S_2O_3$ soln (50 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layer was washed with sat. aq $Na_2S_2O_3$ soln (100 mL) and brine (100 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. Purification of the crude product by column chromatography on silica gel (20% EtOAc–hexane) afforded the iodo compound (6.88 g, 96%) as a colorless oil. The iodide was heated at reflux with Zn (5.41 g, 82.0 mmol) in EtOH (70 mL) for 6 h after which the reaction mixture was filtered through a pad of Celite which was then rinsed with EtOH. The combined ethanolic layer was dried over anhyd Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel (20% EtOAc–hexane) to give **21** (4.09 g, 96%) as a colorless syrup.

From pent-4-en-1-ol according to Scheme 4: A soln of trimethylsulfonium iodide (3.2 g, 15.6 mmol) (predried by azeotroping with anhyd toluene) in THF (25 mL) was cooled to –20 °C, and *n*-BuLi (8.8 mL, 14.0 mmol, 1.6 M in hexane) was added. The mixture was stirred for 30 min at –20 °C, then epoxy benzyl ether **24** (1 g, 5.2 mmol) in THF (10 mL) was added via syringe, over 20 min, at the same temperature. After addition was complete, the cooling bath was removed and the reaction was allowed to warm to r.t. over 30 min, and then stirred at r.t. for 5 h. The reaction was quenched by the addition of H_2O and then diluted with Et_2O (60 mL). The organic layer was separated, washed with brine (25 mL), dried over anhyd Na_2SO_4, filtered and concd. The residue was purified by column chromatography on silica gel (20% EtOAc–hexane) to give **21** (0.86 g, 81%) as colorless syrup.

$[\alpha]_D^{29}$ –2.7 (*c* 2.0, $CHCl_3$).

IR (neat): 3430, 2922, 2858, 1644, 1454, 1095, 1027 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 5 H), 5.85 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1 H), 5.21 (td, *J* = 17.2, 1.5 Hz, 1 H), 5.08 (td, *J* = 10.4, 1.3 Hz, 1 H), 4.50 (s, 2 H), 4.15–4.06 (m, 1 H), 3.50 (t, *J* = 5.8 Hz, 2 H), 2.57 (br s, 1 H), 1.79–1.53 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.0, 138.0, 128.3, 127.6, 127.5, 114.3, 72.8, 72.5, 70.2, 34.0, 25.6.

MS (ES): *m*/*z* = 229 [M + Na]$^+$.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_2Na$: 229.1199; found: 229.1197.

(3*R*)-{[6-(Benzyloxy)hex-1-en-3-yl]oxy}*tert*-butyldiphenylsilane (25)

To a stirred soln of alcohol **21** (5.0 g, 24 mmol) and imidazole (2.47 g, 29 mmol) in anhyd CH_2Cl_2 (50 mL) at 0 °C was added TBDPSCl (8.0 g, 29 mmol) dropwise, and stirring was continued for 4 h at r.t. The reaction mixture was quenched with H_2O and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with brine (50 mL), dried over anhyd Na_2SO_4 and concd under reduced pressure. Purification by column chromatography using silica gel (2% EtOAc–hexane) furnished silyl ether **25** (10.19 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$ –17.1 (*c* 0.8, $CHCl_3$).

IR (neat): 2970, 2925, 1639, 1217 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.59 (m, 5 H), 7.43–7.23 (m, 10 H), 5.77 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1 H), 4.98 (td, *J* = 10.4, 1.3 Hz, 1 H), 4.95–4.92 (m, 1 H), 4.40 (s, 2 H), 4.17 (q, *J* = 5.3 Hz, 1 H), 3.37–3.26 (m, 2 H), 1.64–1.46 (m, 4 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 136.0, 135.9, 134.8, 129.6, 129.56, 129.5, 128.3, 127.7, 127.54, 127.48, 127.41, 127.39, 114.5, 74.3, 72.7, 70.3, 34.0, 27.1, 26.6, 19.4.

MS (ES): *m*/*z* = 467 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{29}H_{40}NO_2Si$: 462.2823; found: 462.2831.

(4*R*)-4-(*tert*-Butyldiphenylsilyloxy)hex-5-en-1-ol (26)

To a stirred soln of **25** (5.0 g, 11.3 mmol) in CH_2Cl_2–H_2O (60 mL, 19:1) was added DDQ (10.27 g, 45.2 mmol) and the mixture stirred at reflux for 4 h. Sat. aq $NaHCO_3$ soln (30 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layer was washed with H_2O (100 mL) and brine (30 mL), dried over anhyd Na_2SO_4 and concd. The crude residue was purified by column chromatography on silica gel (20% EtOAc–hexane) to afford alcohol **26** (3.66 g, 92%) as a colorless syrupy liquid.

$[\alpha]_D^{25}$ –18.1 (*c* 1, $CHCl_3$).

IR (neat): 3375, 2931, 2857, 1466, 1427, 1111, 1057 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.61 (m, 4 H), 7.47–7.30 (m, 6 H), 5.79 (ddd, *J* = 16.8, 10.6, 6.4 Hz, 1 H), 5.02 (td, *J* = 10.0, 1.3 Hz, 1 H), 4.99–4.95 (m, 1 H), 4.21 (q, *J* = 4.9 Hz, 1 H), 3.49 (t, *J* = 5.8 Hz, 2 H), 1.65–1.41 (m, 4 H), 1.07 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 135.9, 135.8, 134.2, 134.0, 129.6, 129.5, 127.5, 127.3, 114.6, 74.2, 62.9, 33.7, 27.5, 27.0, 19.3.

MS (ES): *m*/*z* = 377 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{22}H_{30}O_2SiNa$: 377.1907; found: 377.1915.

[(Pent-4-enyloxy)methyl]benzene (22)

To a vigorously stirred suspension of freshly activated NaH (3.48 g, 139.5 mmol, 60% w/v dispersion in mineral oil) in anhyd THF (50 mL) was added a soln of pent-4-en-1-ol (10 g, 116.2 mmol) in anhyd THF (70 mL), dropwise at 0 °C. After 30 min, benzyl bromide (16.6 mL, 139.5 mmol) was added and the reaction mixture was stirred at r.t. for 5 h. The reaction was quenched with crushed ice and the product was extracted with Et_2O (3 × 100 mL). The combined organic layer was washed with H_2O (100 mL) and brine (100 mL), and then dried over anhyd Na_2SO_4. After removing the volatiles under reduced pressure, the crude benzyl ether was purified by column chromatography on silica gel (5% EtOAc–hexane) to afford the pure product **22** (19.6 g, 96%) as a colorless liquid.

IR (neat): 3069, 3031, 1640, 1495, 1454, 1362, 1028, 995, 910, 736, 613 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 5.82 (dddd, *J* = 16.8, 13.2, 10.0, 6.6 Hz, 1 H), 5.07–4.91 (m, 2 H), 4.50 (s, 2 H), 3.48 (t, *J* = 6.6 Hz, 2 H), 2.15 (q, *J* = 7.2 Hz, 2 H), 1.78–1.65 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.2, 128.3, 127.6, 127.4, 114.7, 72.8, 69.7, 30.3, 28.9.

2-[3-(Benzyloxy)propyl]oxirane (23)

To a soln of alkene **22** (18.0 g, 102.3 mmol) in anhyd CH_2Cl_2 (150 mL) was added $NaHCO_3$ (17.2 g, 204.6 mmol) followed by MCPBA (26.5 g, 153.4 mmol) and the resulting mixture was stirred at r.t. for 2 h. The mixture was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (3 × 130 mL). The combined organic layer was washed with brine (200 mL) and dried over anhyd Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (10% EtOAc–hexane) to afford the epoxide **23** (17.0 g, 87%) as a colorless oil.

(2*S*)-2-[3-(Benzyloxy)propyl]oxirane (24)

A mixture of (*R*,*R*)-(–)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.26 g, 0.43 mmol), toluene (1 mL) and AcOH (0.1 mL, 1. 73 mmol) was stirred for 1 h at r.t. open to the air. The solvent was removed under reduced pressure and the remaining brown residue was dried under high vacuum. Oxirane **23** (17.0 g, 86.7 mmol) was added in one portion and the mixture was cooled using an ice-bath. H_2O (0.87 mL, 48.7 mmol) was added slowly whilst maintaining the temperature of the reaction mixture below 20 °C. After 1 h, the addition was complete; the ice-bath was removed and the reaction stirred for 24 h at r.t. The product **24** was isolated by column chromatography on silica gel (20% EtOAc–hexane) as a colorless liquid (7.65 g, 45%, 98% ee).

$[\alpha]_D^{25}$ –5.12 (*c* 2.3, $CHCl_3$).

IR (neat): 2929, 2836, 1630, 1347, 1210, 1109, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.20 (m, 5 H), 4.50 (s, 2 H), 3.58–3.44 (m, 2 H), 2.96–2.88 (m, 1 H), 2.72 (t, *J* = 4.9 Hz, 1 H), 2.45 (q, *J* = 2.6 Hz, 1 H), 1.85–1.50 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.2, 127.4, 127.38, 72.7, 69.6, 51.9, 46.9, 29.1, 26.0.

(4*R*)-4-(*tert*-Butyldiphenylsilyloxy)hex-5-enoic acid (14)

To a stirred soln of IBX (3.6 g, 12.80 mmol) in DMSO (7 mL) was added alcohol **26** (3 g, 8.5 mmol) in THF (30 mL) at r.t. After 3 h, the reaction mixture was diluted with Et_2O (50 mL), stirred for 30 min and then filtered through a pad of Celite. The organic layer was washed with sat. aq $NaHCO_3$ soln (50 mL) and brine (50 mL), dried over anhyd Na_2SO_4 and concd to give the crude aldehyde **27** (2.93 g, 98%). Crude **27** was dissolved in *t*-BuOH–H_2O (30 mL, 9:1), cooled to 0 °C, and after 10 min, treated with 2-methyl-2-butene followed by an aq soln of $NaClO_2$ (0.92 g, 9.98 mmol) and NaH_2PO_4 (1.58 g, 9.98 mmol) in H_2O (10 mL). After 2 h, the reaction mixture was quenched with $KHSO_4$ (15 mL, 1 mol/L) and H_2O (10 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na_2SO_4, filtered and concd in vacuo. Flash chromatography of the residue over silica gel (20% EtOAc–hexane) afforded **14** as a colorless oil (3.0 g, 98%).

$[\alpha]_D^{29}$ –19.1 (*c* 1.4, $CHCl_3$).

IR (neat): 3457, 2925, 1710, 1643, 1427, 1112 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.76–7.60 (m, 4 H), 7.50–7.30 (m, 6 H), 5.74 (ddd, *J* = 10.4, 7.0, 6.0 Hz, 1 H), 5.02 (dd, *J* = 17.0, 4.9 Hz, 2 H), 4.26 (q, *J* = 5.3 Hz, 1 H), 2.35 (q, *J* = 7.4 Hz, 2 H), 1.79 (q, *J* = 7.4 Hz, 2 H), 1.06 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 139.5, 135.9, 135.8, 133.9, 133.8, 129.7, 129.5, 127.5, 127.4, 115.4, 73.1, 31.7, 28.9, 27.0, 19.3.

MS (ES): m/z = 391 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{22}H_{28}O_3SiNa$: 391.1705; found: 391.1708.

(1*R*)-1-[(4*R*,5*S*)-2,2-Dimethyl-5-ethenyl-1,3-dioxolan-4-yl]butan-1-ol (15)

To a soln of epoxide **16** (0.6 g, 3.5 mmol) in THF (8 mL) at –40 °C was added CuI (0.13 g, 0.7 mmol) and the mixture was stirred at the same temperature for 15 min. After this time, a cold (22 °C) soln of ethylmagnesium bromide (10.5 mL, 10.5 mmol, 1 M soln in THF) was added via a cannula. The resulting mixture was stirred at –40 °C for 3 h, quenched by the addition of aq NH_4Cl soln and then warmed to 23 °C. The aq layer was separated and extracted with EtOAc (2 × 20 mL), and the combined organic layer was washed with brine (25 mL), dried over anhyd Na_2SO_4 and concd to give the crude product. Silica gel column chromatography (15% EtOAc–hexane) afforded pure **15** (0.649 g, 92%) as a colorless oil.

$[\alpha]_D^{30}$ +8.8 (*c* 1.6, CH_2Cl_2) [Lit.[16] $[\alpha]_D^{20}$ +8.8 (*c* 1.2, CH_2Cl_2)].

IR (neat): 3467, 2983, 2959, 2932, 2873, 1642, 1217, 1065, 872 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.04 (ddd, *J* = 17.2, 10.4, 7.4 Hz, 1 H), 5.43 (d, *J* = 17.2 Hz, 1 H), 5.31 (d, *J* = 10.4 Hz, 1 H), 4.63 (t, *J* = 7.4 Hz, 1 H), 3.97 (dd, *J* = 8.1, 6.4 Hz, 1 H), 3.67 (dt, *J* = 2.6, 2.3 Hz, 1 H), 1.80 (br s, 1 H), 1.69 (m, 1 H), 1.57 (m, 1 H), 1.48 (s, 3 H), 1.45 (m, 1 H), 1.37 (s, 3 H), 1.37 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.7, 118.9, 108.6, 80.7, 78.9, 69.7, 35.8, 27.8, 25.3, 18.3, 14.0.

MS (ES): m/z = 223 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.1305; found: 223.1304.

{(1*R*)-1-[(4*R*,5*S*)-2,2-Dimethyl-5-ethenyl-1,3-dioxolan-4-yl]butyl} (4*R*)-4-(*tert*-butyldiphenylsilyloxy)hex-5-enoate (28)

A soln of acid **14** (1.0 g, 29.4 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C and DCC (0.79 g, 38.2 mmol) was added in several portions during which a white precipitate formed rapidly. After 15 min, a soln of alcohol **15** (0.65 g, 32.34 mmol) in CH_2Cl_2 (8 mL) was added followed by a catalytic amount of DMAP (15 mg). The cooling bath was removed and stirring was continued for 12 h. The soln was filtered and the solvent was removed under reduced pressure. The resulting oil was purified by silica gel column chromatography (2% EtOAc–hexane) to afford ester **28** [0.96 g, 90%, yield based on recovered **14** (0.3 g) and **15** (0.23 g)] as a colorless oil.

$[\alpha]_D^{26}$ –3.2 (*c* 1.8, $CHCl_3$).

IR (neat): 2933, 2861, 2360, 1737, 1427, 1376, 1251, 1217, 1109, 1069 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.59 (m, 4 H), 7.46–7.28 (m, 6 H), 5.86–5.66 (m, 2 H), 5.27 (d, *J* = 17.0 Hz, 1 H), 5.14 (d, *J* = 10.4 Hz, 1 H), 5.07–4.94 (m, 2 H), 4.87 (dt, *J* = 7.5, 4.0 Hz, 1 H), 4.56 (t, *J* = 7.2 Hz, 1 H), 4.31–4.18 (m, 1 H), 4.13 (t, *J* = 7.5 Hz, 1 H), 2.38–2.11 (m, 2 H), 1.75 (q, *J* = 5.7 Hz, 2 H), 1.68–1.51 (m, 2 H), 1.47 (s, 3 H), 1.37 (s, 3 H), 1.35–1.19 (m, 2 H), 1.07 (s, 9 H), 0.89 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.6, 139.6, 135.9, 135.8, 135.8, 133.8, 133.2, 129.6, 129.5, 127.5, 127.4, 118.4, 115.2, 108.7, 78.9, 78.3, 73.3, 71.4, 33.4, 32.0, 29.3, 27.5, 27.0, 25.2, 18.4, 17.9, 14.1.

MS (ES): m/z = 573 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{33}H_{46}O_5SiNa$: 573.3012; found: 573.2999.

{(1*R*)-1-[(4*R*,5*S*)-2,2-Dimethyl-5-ethenyl-1,3-dioxolan-4-yl]butyl} (4*R*)-4-hydroxyhex-5-enoate (30)[7]

To a soln of **28** (1.2 g, 2.2 mmol) in anhyd THF (15 mL) under an N_2 atm was added $Et_3N{\cdot}3HF$ (7.1 mL, 43.6 mmol), and the reaction mixture was heated at reflux for 8 h. The mixture was quenched with aq NH_4Cl soln (30 mL), the phases were separated, and the aq phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extract was dried over anhyd Na_2SO_4 and concd in vacuo to afford an oil which was purified by silica gel column chromatography (20% EtOAc–hexane) to yield **30** (0.62 g, 91%) as a colorless oil.

$[\alpha]_D^{27}$ +20.1 (*c* 2.5, $CHCl_3$).

IR (neat): 3425, 2976, 2860, 1717, 1630, 1378, 1199 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.90–5.73 (m, 2 H), 5.40–5.10 (m, 4 H), 4.93 (dt, *J* = 7.4, 3.6 Hz, 1 H), 4.61 (t, *J* = 7.0 Hz, 1 H), 4.23–4.11 (m, 2 H), 2.48–2.33 (m, 2 H), 2.00 (br s, 1 H), 1.94–1.75 (m, 2 H), 1.74–1.54 (m, 2 H), 1.49 (s, 3 H), 1.37 (s, 3 H), 1.35–1.20 (m, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 140.4, 133.2, 118.5, 115.1, 108.8, 78.8, 78.4, 72.1, 71.9, 33.4, 31.5, 30.3, 27.5, 25.2, 17.9, 14.0.

MS (ES): m/z = 335 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{17}H_{28}O_5Na$: 335.1834; found: 335.1836.

Stagonolide B (5)

Ester **30** (0.04 g, 0.12 mmol) was dissolved in freshly distilled and degassed anhyd benzene (90 mL), then treated with Grubbs 2nd generation catalyst (0.022 mg, 0.025 mmol) and heated at reflux for 6 h under an inert atm. The reaction mixture was evaporated under reduced pressure to give a brown residue which was purified by column chromatography on silica gel (20% EtOAc–hexane) to afford impure **13** (0.018 g, 50%) as a colorless syrup. To a stirred soln of crude **13** (0.018 g, 0.06 mmol) in anhyd THF (5 mL) was added aq HCl (1 M, 0.25 mL) and the mixture was stirred at 55 °C for 10 h (TLC showed complete consumption of the starting material). The mixture was diluted with aq NaOH (1 M, 0.3 mL). The organic layer was separated, dried over anhyd Na_2SO_4, evaporated, and the residue was purified by column chromatography over silica gel (50% EtOAc–hexane) to afford stagonolide B (**5**) (0.007 g, 45%) as a viscous liquid.

$[\alpha]_D^{27}$ +16.0 (*c* 0.2, $CHCl_3$) [Lit.[4a] $[\alpha]_D$ +20 (*c* 0.1, $CHCl_3$)].

IR (neat): 3422, 2933, 2861, 2350, 1734, 1424, 1370, 1251, 1217, 1109, 1069 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.97 (br t, *J* = 16.2 Hz, 1 H), 5.65–5.57 (m, 1 H), 4.92 (td, *J* = 9.8, 2.3 Hz, 1 H), 4.63 (br s, 1 H), 4.54 (br s, 1 H), 3.63–3.53 (m, 1 H), 2.44 (br dd, *J* = 14.1, 13.6 Hz, 1 H), 2.20–2.02 (m, 1 H), 1.99–1.81 (m, 1 H), 1.74–1.45 (m, 3 H), 1.41–1.25 (m, 2 H), 0.92 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 128.0, 127.2, 73.6, 73.1, 70.3, 68.6, 33.6, 31.7, 27.9, 18.0, 13.8.

MS (ES): m/z = 267 $[M + Na]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{12}H_{20}O_5Na$: 267.1203; found: 267.1217.

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