A Practical Synthesis of the C1–C9 Fragment of Dictyostatin

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Dedicated with respect and admiration to Professor Reinhard W. Hoffmann, on the occasion of his 75th birthday

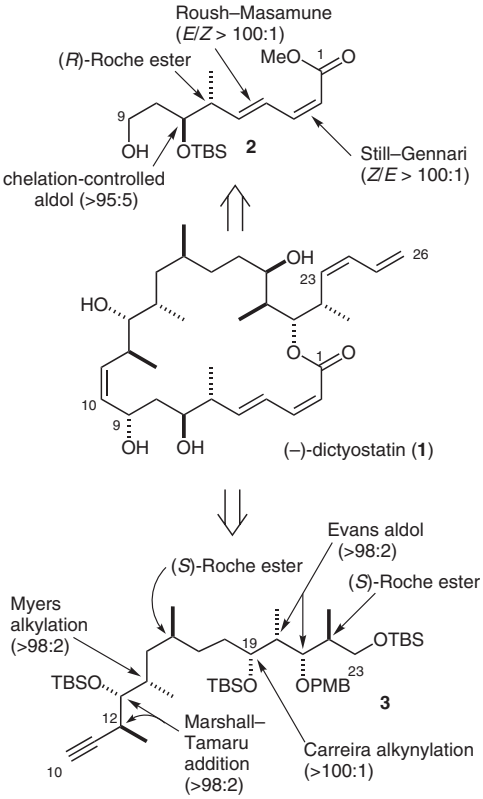
Abstract: A stereoselective synthesis of the C1–C9 fragment of (–)-dictyostatin has been achieved by use of a titanium(IV) chloride mediated chelation-controlled Mukaiyama aldol reaction and two modified Horner–Wadsworth–Emmons olefinations (Roush–Masamune and Still–Gennari).

Key words: antitumor agents, stereoselective synthesis, aldol reactions, titanium, olefination

The sponge-derived macrolide (–)-dictyostatin (**1**, Scheme 1) has been reported to exhibit paclitaxel-like effects on cellular microtubules and to inhibit human cancer cell proliferation at low nanomolar concentrations, with activity somewhat superior to the already very active discodermolide (ED50 0.38 nM, P338 leukemia cells).[1] Moreover, (–)-dictyostatin (**1**) is also extremely active against paclitaxel-resistant cancer cell lines. The structure of (–)-dictyostatin (**1**) with full stereochemical assignment was established by Paterson and co-workers fairly recently (2004),[2] and four total syntheses were completed in the period 2004–2007.[3] A growing number of research groups have recently been involved in targeting this interesting natural product, and the syntheses of several analogues (e.g., normethyldictyostatins, *epi*-dictyostatins),[4] discodermolide/dictyostatin hybrids,[5] and various fragments and synthetic intermediates[6] have been described. The development of a practical and flexible synthesis of (–)-dictyostatin (**1**) is still an important goal, particularly as the natural supply is extremely scarce. With the recent withdrawal of discodermolide from clinical development,[7] the importance of dictyostatin (**1**) further increases.

Our laboratory recently reported a highly stereoselective synthesis of the C10–C23 fragment **3** of (–)-dictyostatin (**1**) (Scheme 1).[6j] We now report on a practical synthesis of the C1–C9 fragment **2** (Scheme 1), containing two of its eleven stereocenters and the (2*Z*,4*E*)-2,4-dienoate unit.

We started our synthesis from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate [(*R*)-Roche ester] (Scheme 2). Conversion of the (*R*)-Roche ester into its benzyl ether with benzyl trichloroacetimidate was followed by lithium aluminum hydride reduction of the ester to give alcohol **4** in 89% overall yield[8] (Scheme 2). Oxidation of alcohol **4** with Dess–Martin periodinane[9] afforded aldehyde **5** in quantitative yield, and, without purification, aldehyde **5** was immediately subjected to a titanium(IV) chloride mediated chelation-controlled Mukaiyama aldol reaction with 1-(*tert*-butyldimethylsiloxy)-1-(*tert*-butylsulfanyl)ethene (Scheme 2).[10] The aldol product **6** was isolated in 94% yield and a 97:3 diastereomeric ratio in favor of the desired stereoisomer. Although it was reported that the two diastereomers could be separated by two consecutive purifications by flash chromatography,[10a] we still observed the presence of some isomer (≤3%) in the ^{13}C NMR spectrum of **6**. However, we decided to continue our synthesis as planned, confident that the minor isomer would be removable at a later stage of the sequence.



Scheme 1 Retrosynthetic approach to fragments C1–C9 (**2**) and C10–C23 (**3**)[6j] of (–)-dictyostatin (**1**), with key reactions involved and associated diastereomeric ratios

Reduction (LAH) of **6** gave diol **7** in 98% yield, and subsequent double silylation of diol **7** led to fully protected triol **8** (98%) (Scheme 2). Benzyl removal was accomplished by hydrogenolysis with Raney nickel in ethanol[11]

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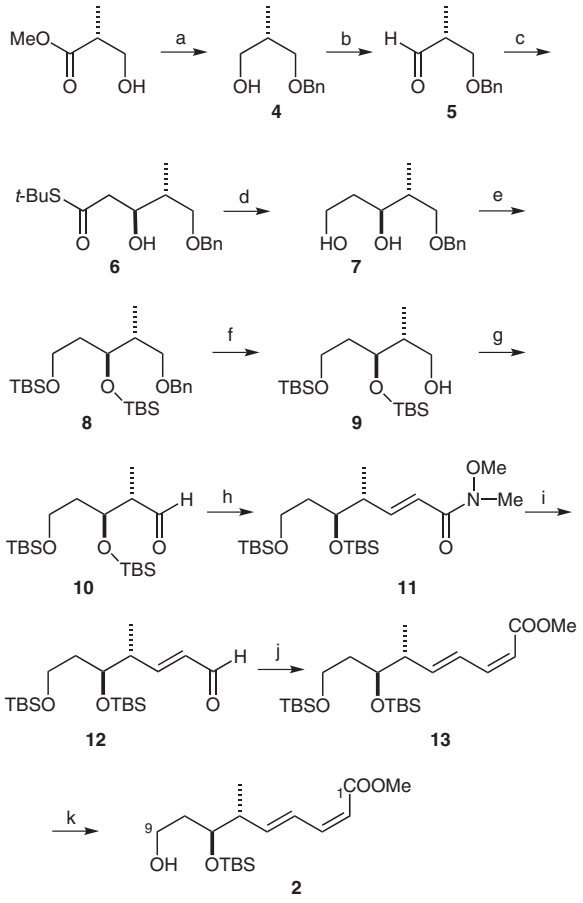

Scheme 2 *Reagents and conditions*: (a) Ref. 8, 89%; (b) DMP, CH_2Cl_2, r.t., 100%; (c) (*t*-BuS)(TBSO)C=CH_2, $TiCl_4$, CH_2Cl_2, –80 °C, 94%, dr 97:3; (d) LAH, THF, r.t., 98%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, –20 °C, 98%; (f) H_2, Raney-Ni, EtOH, r.t., 80%; (g) DMP, CH_2Cl_2, r.t., 100%; (h) $(EtO)_2P(O)CH_2C(O)N(Me)OMe$, LiCl, DBU, MeCN, r.t., 90%; (i) DIBAL-H, THF, –78 °C, 91%; (j) $(F_3CCH_2O)_2P(O)CH_2CO_2Me$, KHMDS, THF, 18-crown-6, –78 °C, 90%; (k) HF·py, THF–py, r.t., 86%.

(80%), and the resulting primary alcohol **9** was oxidized (DMP) to furnish aldehyde **10** in quantitative yield (Scheme 2). Aldehyde **10** was not purified and immediately subjected to a Horner–Wadsworth–Emmons reaction with diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate[12] under Roush–Masamune conditions.[13] The olefination reaction afforded the Weinreb amide **11** in 90% yield as a single *E*-isomer (*E*/*Z* >100:1) (Scheme 2). Diisobutylaluminum hydride reduction gave aldehyde **12** (91%), which was subjected to a Still–Gennari olefination[14] to afford methyl (2*Z*,4*E*)-2,4-dienoate **13** in 90% yield as a single isomer (2*Z*/2*E* >100:1) (Scheme 2).[4d,15] The minor (7*R*)-isomer (≤3%), which originated during the Mukaiyama aldol reaction, was removed at this stage by flash chromatography. Finally, removal of the primary *tert*-butyldimethylsilyl group (HF·py, THF–py) furnished the desired C1–C9 fragment **2** of (–)-dictyostatin in good yield (Scheme 2).[4d]

^{1}H (400.13 MHz) and ^{13}C (100.58 MHz) NMR spectra were recorded on a Bruker Avance-400 spectrometer. The ^{1}H NMR chemical shifts are reported relative to TMS and the solvent resonance was employed as the internal standard ($CDCl_3$, δ = 7.26). The ^{13}C NMR spectra were recorded with complete proton decoupling, with chemical shifts reported relative to TMS and the solvent resonance as the internal standard ($CDCl_3$, δ = 77.0). Infrared spectra were recorded on a standard FT/IR spectrophotometer. Optical rotation values were measured on an automatic polarimeter with a 1-dm cell, at the sodium D line. HRMS was performed on a hybrid quadrupole TOF mass spectrometer equipped with an ESI ion source. A reserpine soln (100 pg/μL, about 100 counts/s, 0.1% HCO_2H–MeCN, 1:1), was used as reference compound (Lock Mass). All reactions were carried out in oven- or flame-dried glassware under a N_2 atmosphere, unless stated otherwise. All commercially available reagents were used as received. All solvents were dried by standard procedures before use. Organic extracts were dried over anhyd Na_2SO_4. Reactions were magnetically stirred and monitored by TLC on silica gel 60 F_{254} precoated glass plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with a ceric ammonium molybdate or $KMnO_4$ solution. Flash chromatography was performed on silica gel (60 Å, particle size 0.040–0.062 mm) by the procedure of Still and coworkers.[16] Yields refer to chromatographically and spectroscopically pure compounds, unless stated otherwise.

(*R*)-3-(Benzyloxy)-2-methylpropionaldehyde (5)

A soln of alcohol **4**[8] (0.4 g, 2.2 mmol) in anhyd CH_2Cl_2 (12.3 mL) was treated at 0 °C with py (0.45 mL, 5.5 mmol) and DMP (1.12 g, 2.64 mmol). The reaction mixture was warmed to r.t. and stirred for 1 h. After completion of the reaction, sat. aq $NaHCO_3$ (38.0 mL) and $Na_2S_2O_3$ (3.99 g, 16.1 mmol) were added. After the mixture had stirred for 30 min, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure; this gave crude aldehyde **5**, which was used without further purification.

Yield: 0.39 g (100%); pale yellow oil; R_f = 0.77 (hexanes–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.65–2.73 (m, 1 H, H–2), 3.66 (dd, *J* = 4.8, 9.2 Hz, 1 H, H-3), 3.72 (dd, *J* = 6.8, 9.2 Hz, 1 H, H-3), 4.55 (s, 2 H, CH_2Ph), 7.10–7.36 (m, 5 H, Ph), 9.75 (s, 1 H, H-1).

S-*tert*-Butyl (3*S*,4*R*)-5-(Benzyloxy)-3-hydroxy-4-methylpentanethioate (6)

A stirring solution of aldehyde **5** (392 mg, 2.2 mmol) in anhyd CH_2Cl_2 (5.0 mL) was treated at –80 °C with $TiCl_4$ (0.49 mL, 2.2 mmol). After a few seconds, a solution of 1-(*tert*-butyldimethylsiloxy)-1-(*tert*-butylsulfanyl)ethene[10] (814 mg, 3.3 mmol) in anhyd CH_2Cl_2 (2.5 mL) was slowly added. After stirring for 2 h at –80 °C, the mixture was quenched with 1 M KOH (18.0 mL). The organic phase was washed with brine (2 × 3 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 85:15); this gave **6** (dr 97:3) as a colorless oil. Further purification by flash chromatography[10a] (benzene–Et_2O, 95:5) did not improve the dr.

Yield: 642 mg (94%); $[\alpha]_D^{20}$ –23.0 (*c* 0.75, CH_2Cl_2); R_f = 0.42 (hexanes–EtOAc, 85:15).

IR ($CHCl_3$): 3470, 2962, 2926, 2860, 1681, 1455, 1364, 1253, 1101 cm^{-1}.

^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.96 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.50 (s, 9 H, *t*-BuS), 1.89–1.97 (m, 1 H, H-4), 2.65 (dd, *J* = 8.0, 15.2 Hz, 1 H, H-2), 2.70 (dd, *J* = 4.0, 15.2 Hz, 1 H, H-2), 3.52 (dd, *J* = 6.4, 9.6 Hz, 1 H, H-5), 3.58 (dd, *J* = 4.8, 9.6 Hz, 1 H, H-5), 4.04 (ddd, *J* = 4.0, 8.0, 6.4 Hz, 1 H, H-3), 4.50 (s, 2 H, CH_2Ph), 7.28–7.39 (m, 5 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.8 (epimer at C-3, ≤3%), 14.5, 30.4, 38.3 (epimer at C-3, ≤3%), 38.6, 49.0, 49.9, 70.8 (epimer at C-3, ≤3%), 73.0, 74.1, 74.4, 126.7, 127.2, 128.7, 138.6, 200.7.

ESI-HRMS: *m*/*z* calcd for $C_{17}H_{26}NaO_3S$: 333.4400; found: 333.4425.

(3*S*,4*R*)-5-(Benzyloxy)-4-methylpentane-1,3-diol (7)

A solution of **6** (500 mg, 1.6 mmol) in anhyd THF (4.0 mL) was added to a cold (0 °C) suspension of LAH (122 mg, 3.2 mmol) in anhyd THF (4.0 mL). The mixture was warmed to r.t. and stirred for an additional 2 h. The solution was cooled to 0 °C and then quenched with H_2O (0.7 mL), 2 M NaOH (1.4 mL), and H_2O (1.4 mL). After vigorously stirring for 1 h, the mixture was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 6:4).

Yield: 352 mg (98%); colorless oil; $[\alpha]_D^{23}$ –21.6 (*c* 0.87, CH_2Cl_2); R_f = 0.50 (hexanes–EtOAc, 6:4).

IR ($CHCl_3$): 3388, 2958, 2924, 2877, 1454, 1364, 1071, 1057, 1028 cm^{-1}.

^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.73–1.82 (m, 2 H, H-2), 1.90–2.00 (m, 1 H, H-4), 2.98 (br s, 2 H, OH), 3.50 (t, *J* = 9.2 Hz, 1 H, H-5), 3.66 (dd, *J* = 4.0, 9.2 Hz, 1 H, H-5), 3.79–3.89 (m, 3 H, H-1 and H-3), 4.55 (s, 2 H, C*H*$_2$Ph), 7.28–7.42 (m, 5 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.1 (epimer at C-3, ≤3%), 14.3, 35.8 (epimer at C-3, ≤3%), 36.6, 39.1, 62.3, 74.2, 75.0 (epimer at C-3, ≤3%), 75.9, 77.5, 128.4, 128.6, 129.2, 138.3.

ESI-HRMS: *m*/*z* calcd for $C_{13}H_{20}NaO_3$: 247.1347; found: 247.1301.

{[(2*R*,3*S*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2-methylpentyloxy]methyl}benzene (8)

A solution of diol **7** (350 mg, 1.56 mmol) in anhyd CH_2Cl_2 (39 mL) was treated at –20 °C with 2,6-lutidine (1.5 mL, 12.5 mmol), followed by TBSOTf (2.7 mL, 3.12 mmol). After stirring for 1 h, the mixture was quenched with sat. aq NH_4Cl (40 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 95:5).

Yield: 692 mg (98%); colorless oil; $[\alpha]_D^{16}$ –7.1 (*c* 0.86, CH_2Cl_2); R_f = 0.60 (hexanes–EtOAc, 95:5).

IR ($CHCl_3$): 3113, 2955, 2928, 2856, 1471, 1254, 1092, 835, 774 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 9 H, *t*-BuSi), 0.89–0.91 (m, 21 H, *t*-BuSi, Me_2Si, Me_2Si), 0.95 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.60–1.67 (m, 2 H, H-4), 1.99–2.05 (m, 1 H, H-2), 3.31 (dd, *J* = 6.8, 9.2 Hz, 1 H, H-1), 3.46 (dd, *J* = 6.4, 9.2 Hz, 1 H, H-1), 3.63–3.76 (m, 2 H, H-3, H-5), 3.89–3.92 (m, 1 H, H-5), 4.51 (s, 2 H, C*H*$_2$Ph), 7.30–7.36 (m, 5 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.6, –3.9, –2.3, 12.2 (epimer at C-3, ≤3%), 13.3, 18.8, 19.0, 26.5, 26.6, 36.4, 39.1 (epimer at C-3, ≤3%), 39.8, 60.9, 70.3 (epimer at C-3, ≤3%), 71.1, 73.5, 73.7, 128.0, 128.1, 129.0, 139.4.

ESI-HRMS: *m*/*z* calcd for $C_{25}H_{48}O_3NaSi_2$: 475.3034; found: 475.3049.

(2*R*,3*S*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2-methylpentan-1-ol (9)

Raney-Ni[11a] was washed with H_2O until the washings were pH neutral, and then rinsed with absolute EtOH (5 × 100 mL). A solution of **8** (690 mg, 1.52 mmol) in absolute EtOH (102 mL) was added, and the mixture was degassed and then purged with H_2 (3×). After stirring for 72 h at r.t., the reaction mixture was filtered through a short pad of Celite, washed with EtOAc (2 × 100 mL), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 10:1).

Yield: 441 mg (80%); colorless oil; $[\alpha]_D^{20}$ –4.0 (*c* 1.11, CH_2Cl_2); R_f = 0.16 (hexanes–EtOAc, 10:1).

IR ($CHCl_3$): 3366, 2956, 2929, 2885, 2858, 1472, 1255, 1094, 836, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H, Me_2Si), 0.12 (s, 6 H, Me_2Si), 0.91 (s, 9 H, *t*-BuSi), 0.92 (s, 9 H, *t*-BuSi), 1.04 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.71–1.82 (m, 3 H, H-2, H-4), 2.61 (br s, 1 H, OH), 3.55 (dd, *J* = 5.6, 11.2 Hz, 1 H, H-5), 3.68 (t, *J* = 6.4 Hz, 2 H, H-1), 3.80 (dd, *J* = 4.0, 11.2 Hz, 1 H, H-5), 3.90–3.94 (m, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –4.0, –3.8, 13.1 (epimer at C-3, ≤3%), 14.9, 18.6, 18.9, 26.5, 26.6, 38.2, 39.3, 40.5 (epimer at C-3, ≤3%), 60.4, 65.9, 73.4 (epimer at C-3, ≤3%), 74.8.

ESI-HRMS: *m*/*z* calcd for $C_{18}H_{42}O_3NaSi_2$: 385.2565; found: 385.2564.

(2*S*,3*S*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2-methylpentanal (10)

A solution of alcohol **9** (0.4 g, 1.1 mmol) in anhyd CH_2Cl_2 (7.0 mL) was treated at 0 °C with pyridine (0.22 mL, 2.8 mmol) and DMP (0.56 g, 1.3 mmol). The reaction mixture was warmed to r.t., and stirred for 2 h. After completion of the reaction, sat. aq $NaHCO_3$ (18.0 mL) and $Na_2S_2O_3$ (2.0 g, 8.0 mmol) were added. After the mixture had stirred for 30 min, the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure; this gave crude aldehyde **10**, which was used without further purification.

Yield: 397 mg (100%); pale yellow oil; R_f = 0.56 (hexanes–EtOAc, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6 H, Me_2Si), 0.10 (s, 6 H, Me_2Si), 0.90 (s, 9 H, *t*-BuSi), 0.91 (s, 9 H, *t*-BuSi), 1.10 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.75–1.82 (m, 2 H, H-4), 2.58–2.59 (m, 1 H, H-2), 3.70–3.73 (m, 2 H, H-5), 4.17–4.19 (m, 1 H, H-3), 9.76 (d, *J* = 1.6 Hz, 1 H, H-1).

(2*E*,4*R*,5*S*)-5,7-Bis(*tert*-butyldimethylsiloxy)-*N*-methoxy-*N*,4-dimethylhept-2-enamide (11)

Diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (0.25 mL, 1.2 mmol), DBU (0.2 mL, 1.3 mmol), and, finally, aldehyde **10** (397 mg, 1.1 mmol) were added to a stirred suspension of LiCl (flame-dried under vacuum before use; 112 mg, 2.6 mmol) in anhyd MeCN (8.7 mL) at r.t. The mixture was stirred at r.t. for 1.5 h and then quenched with H_2O (18 mL). After 15 min, EtOAc (18 mL) was added and the mixture was stirred for an additional 30 min. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 9:1).

Yield: 441 mg (90%); colorless oil; $[\alpha]_D^{23}$ +8.3 (*c* 0.70, CH_2Cl_2); R_f = 0.24 (hexanes–EtOAc, 9:1).

IR ($CHCl_3$): 2955, 2929, 2895, 2886, 2857, 1666, 1636, 1471, 1382, 1255, 1099, 836, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, Me_2Si), 0.07 (s, 6 H, Me_2Si), 0.90 (s, 9 H, *t*-BuSi), 0.91 (s, 9 H, *t*-BuSi), 1.10 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.57–1.69 (m, 2 H, H-6), 2.50–2.59 (m, 1 H, H-4), 3.26 (s, 3 H, NC*H*$_3$), 3.60–3.70 (m, 2 H, H-7), 3.71 (s, 3 H, NOC*H*$_3$), 3.83–3.88 (m, 1 H, H-5), 6.40 (d, *J* = 15.6 Hz, 1 H, H-2), 6.97 (dd, *J* = 8.0, 15.6 Hz, 1 H, H-3), 7.05 (dd, *J* = 7.2, 15.6 Hz, H-3, epimer at C-5, ≤3%).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –3.8, 15.2 (epimer at C-5, ≤3%), 15.6, 18.7, 18.9, 26.6, 26.7, 33.1, 37.5, 43.0, 45.1 (epimer at C-5, ≤3%), 60.6, 62.3, 72.8, 73.1 (epimer at C-5, ≤3%), 119.4, 150.2, 167.6.

ESI-HRMS: *m/z* calcd for $C_{22}H_{47}NNaO_4Si_2$: 468.2936; found: 468.2328.

(2*E*,4*R*,5*S*)-5,7-Bis(*tert*-butyldimethylsiloxy)-4-methylhept-2-enal (12)

A stirred solution of Weinreb amide **11** (400 mg, 0.9 mmol) in anhyd THF (9.4 mL) was treated at –78 °C with 1 M DIBAL-H in hexanes (2.7 mL, 2.7 mmol). After being stirred for 90 min at –78 °C, this solution was poured into a mixture of 1 M aq tartaric acid (12.4 mL) and EtOAc (13.8 mL). After the mixture had stirred for 1 h, the layers were separated, the aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were washed with brine (2 × 25 mL), dried (Na_2SO_4), and evaporated under reduced pressure; this gave crude aldehyde **12**, which was used without further purification.

Yield: 317 mg (91%); pale yellow oil; R_f = 0.81 (hexanes–EtOAc, 6:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, Me_2Si), 0.09 (s, 6 H, Me_2Si), 0.90 (s, 9 H, *t*-BuSi), 0.92 (s, 9 H, *t*-BuSi), 1.14 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.53–1.60 (m, 1 H, H-6), 1.64–1.73 (m, 1 H, H-6), 2.57–2.67 (m, 1 H, H-4), 3.64–3.67 (m, 2 H, H-7), 3.90–3.91 (m, 1 H, H-5), 6.13 (dd, *J* = 7.6, 15.6 Hz, 1 H, H-2), 6.87 (dd, *J* = 7.6, 15.6 Hz, 1 H, H-3), 9.53 (d, *J* = 7.6 Hz, 1 H, H-1).

Methyl (2*Z*,4*E*,6*R*,7*S*)-7,9-Bis(*tert*-butyldimethylsiloxy)-6-methylnona-2,4-dienoate (13)

A solution of $(F_3CCH_2O)_2P(O)CH_2CO_2Me$ (0.18 mL, 0.86 mmol) and 18-crown-6·MeCN (1.20 g, 3.9 mmol) in anhyd THF (15.6 mL) was cooled to –78 °C, and 0.5 M KHMDS in toluene (1.72 mL, 0.86 mmol) was added dropwise. After the mixture had spent a few min at –78 °C, a solution of aldehyde **12** (300 mg, 0.78 mmol) in anhyd THF (6.5 mL) was added dropwise. The mixture was stirred at –78 °C for 1 h and then treated with sat. aq NH_4Cl (20 mL) and Et_2O (20 mL). The layers were separated, the aqueous phase was extracted with Et_2O (2 × 30 mL), and the combined organic extracts were washed with H_2O (2 × 40 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes–EtOAc, 100:5).

Yield: 319 mg (90%); colorless oil; $[\alpha]_D^{22}$ –2.7 (*c* 0.70, CH_2Cl_2); $[\alpha]_D^{24}$ –6.4 (*c* 0.35, $CHCl_3$) {Lit.[4d] $[\alpha]_D^{20}$ –6.6 (*c* = 0.36, $CHCl_3$)}; R_f = 0.35 (hexanes–EtOAc, 100:5).

IR ($CHCl_3$): 3408, 2957, 2927, 2856, 2738, 2710, 2360, 2341, 1722, 1639, 1602, 1471, 1438, 1258, 1194, 1176, 1098, 1030, 835, 806, 775 cm^{-1}.

^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.05 (s, 6 H, Me_2Si), 0.08 (s, 6 H, Me_2Si), 0.90 (s, 9 H, *t*-BuSi), 0.92 (s, 9 H, *t*-BuSi), 1.09 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.55–1.67 (m, 2 H, H-8), 2.47–2.57 (m, 1 H, H-6), 3.63–3.68 (m, 2 H, H-9), 3.75 (s, 3 H, CO_2CH_3), 3.82–3.85 (m, 1 H, H-7), 5.61 (d, *J* = 11.3 Hz, 1 H, H-2), 6.06 (dd, *J* = 8.0, 15.2 Hz, 1 H, H-5), 6.58 (t, *J* = 11.3 Hz, 1 H, H-3), 7.37 (dd, *J* = 11.3, 15.2 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.7, –3.8, 16.1, 18.8, 18.9, 26.6, 37.8, 43.4, 51.7, 60.5, 73.0, 116.0, 127.5, 146.3, 148.2, 167.6.

ESI-HRMS: *m/z* calcd for $C_{23}H_{46}NaO_4Si_2$: 465.2827; found: 465.2823.

Methyl (2*Z*,4*E*,6*R*,7*S*)-7-(*tert*-Butyldimethylsiloxy)-9-hydroxy-6-methylnona-2,4-dienoate (2)

A solution of compound **13** (338 mg, 0.74 mmol) in THF (3.8 mL) at 0 °C was treated with a soln of HF·py in THF–py [16.5 mL, prepared by slow dropwise addition of HF·py (1.3 mL) to a solution of pyridine (5.0 mL) and THF (10.2 mL)]. The reaction mixture was warmed to r.t. and stirred for 8 h. After quenching of the reaction by the addition of sat. aq $NaHCO_3$ (30 mL), the mixture was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with sat. aq $CuSO_4$ (3 × 15 mL) and brine (2 × 40 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Purification by flash chromatography (hexanes–EtOAc, 2:1) gave **2**.

Yield: 218 mg (86%); colorless oil; $[\alpha]_D^{18}$ –10.5 (*c* 1.00, CH_2Cl_2); $[\alpha]_D^{24}$ –14.0 (*c* 0.20, $CHCl_3$) {Lit.[4d] $[\alpha]_D^{20}$ –14.3 (*c* = 0.21, $CHCl_3$)}; R_f = 0.20 (hexanes–EtOAc, 8:2).

IR ($CHCl_3$): 3418, 2954, 2929, 2885, 2857, 1719, 1637, 1601, 1439, 1256, 1197, 1176, 1082, 1031, 1005, 837, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, MeSi), 0.10 (s, 3 H, MeSi), 0.91 (s, 9 H, *t*-BuSi), 1.09 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.63–1.74 (m, 2 H, H-8), 1.98 (br s, 1 H, OH), 2.54–2.59 (m, 1 H, H-6), 3.73 (s, 3 H, CO_2CH_3), 3.69–3.75 (m, 2 H, H-9), 3.85–3.88 (m, 1 H, H-7), 5.61 (d, *J* = 11.2 Hz, 1 H, H-2), 6.02 (dd, *J* = 8.0, 15.6 Hz, 1 H, H-5), 6.56 (t, *J* = 11.2 Hz, 1 H, H-3), 7.38 (dd, *J* = 11.2, 15.6 Hz, 1 H, H-4).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.9, –3.7, 15.4, 18.7, 26.5, 36.3, 43.3, 51.8, 60.7, 74.4, 116.4, 127.6, 146.0, 147.7, 167.6.

ESI-HRMS: *m/z* calcd for $C_{17}H_{32}NaO_4Si$: 351.1962; found: 351.1957.

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