

Total Synthesis of Herbimycin A

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General

TLC was performed on Merck 60F₂₅₄ silica gel plates and visualized either with a UV lamp (254 nm), or by using a solution of *p*-anisaldehyde/sulfuric acid/acetic acid in EtOH followed by heating.

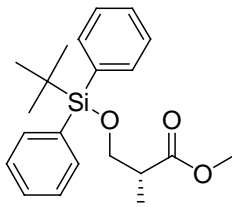
Flash chromatography was performed with Merck Geduran Si60 silica gel (40-63 μ m).

Infrared (IR) spectra were recorded on a Perkin-Elmer 298 or on a Bruker TENSORTM 27 (IRFT), wave-numbers are indicated in cm⁻¹. ¹H NMR spectra were recorded on a Bruker AC 300 at 300 MHz or on a Bruker AVANCE 400 at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non equivalent resonances), integration. ¹³C NMR spectra were recorded on a Bruker AC 300 at 75 MHz or on a Bruker AVANCE 400 at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the solvent as an internal indicator (CDCl₃ δ 77.0 ppm), multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary C, d = CH, t = CH₂, q = CH₃). Mass spectra with electronic impact (MS) were recorded from a Hewlett-Packard tandem 5890A GC (12 m capillary column) – 5971 MS (70 eV). High resolution mass spectra (HRMS) were performed by the Centre de Spectrochimie Organique de l'Ecole Normale Supérieure Ulm

(Paris) or by the Groupe de Spectrométrie de masse de l'Université Pierre et Marie Curie (Paris). Elemental analyses were performed by the Service de Microanalyse of ICSN (Gif sur Yvette, France).

I / Synthesis of the C5-C15 fragment of Herbimycin A

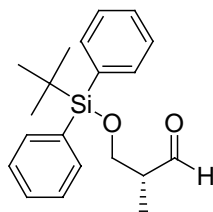
(2R)-Methyl 3-*tert*-butyldiphenylsilyloxy-2-methylpropanoate (**25**):



To a stirring solution of commercially available alcohol **1** (5 mL, 45 mmol, 1 equiv) in CH₂Cl₂ (50 mL) at 0 °C, were successively added imidazole (3.36 g, 49.5 mmol, 1.1 equiv) and *tert*-butyldiphenylsilylchloride (11.7 mL, 45 mmol, 1 equiv) dropwise. The reaction was allowed to warm to rt and stirred for 12 h. The reaction was stopped by addition of an aqueous saturated solution of NaHCO₃ (55 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 120 mL). The combined organic layers were washed with a saturated aqueous solution of NH₄Cl (50 mL), dried with MgSO₄, filtered and concentrated. Crude silyl ether **25** (*ca.* 16.2 g) was obtained as a colorless oil in quantitative yield. Physical and spectral data match those previously reported.¹

C₂₁H₂₈O₃Si; M = 356 g.mol⁻¹; **R_f** = 0.83 (Petroleum ether/Et₂O: 1/1); [**α**]_D²⁰ -13.6 (*c* 2.12, CHCl₃) [litt.¹ [**α**]_D²⁰ -16.4 (*c* 1.18, CHCl₃)]; **IR**: 2932, 2857, 1738, 1428, 1198, 1176, 1106, 823, 738, 700, 612 cm⁻¹; **¹H NMR** (400 MHz): **δ**: 7.70-7.60 (4H), 7.46-7.32 (6H), 3.83 (dd syst AB, 1H, ²*J* = 9.6 and *J* = 7.0 Hz), 3.73 (dd syst AB, 1H, ²*J* = 9.6 and *J* = 5.7 Hz), 3.68 (s, 3H), 2.72 (m, 1H), 1.15 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 9H); **¹³C NMR** (100 MHz): **δ**: 175.4 (s), 135.6 (4d), 133.5 (2s), 129.7 (2d), 127.7 (4d), 66.0 (t), 51.6 (q), 42.4 (d), 26.7 (3q), 19.3 (s), 13.5 (q); **MS** (EI, 70 eV): *m/z* (%): 341 (M-Me⁺, 1), 325 (4), 299 (M-[*t*-Bu]⁺, 100), 269 (5), 251 (4), 237 (11), 213 (87), 193 (12), 183 (44), 153 (15), 135 (10), 105 (15), 91 (6), 77 (5), 57 (3).

(2R)-3-*tert*-Butyldiphenylsilyloxy-2-methylpropanal (**26**):

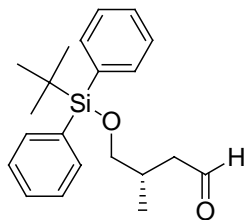


¹ Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096-6107.

To a stirring solution of crude **25** (8.09 g, 22.5 mmol, 1 equiv) in Et₂O (90 mL) at -78 °C, was added slowly a solution of diisobutylaluminum hydride (1M in hexanes, 28 mL, 1.24 equiv). After 1.5 h at -78 °C, the reaction mixture was poured into a well-stirred mixture of sodium potassium tartrate (36 g) in water (130 mL) and hexanes (130 mL). The resulting slurry was stirred until two clear layers separated (approximately 2 h). The layers were separated and aqueous layer was extracted with Et₂O (3 x 150 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification by flash chromatography on silica gel (pentane/Et₂O: 9/1) provided the desired aldehyde **26** (6.85 g, 93%) which crystallized upon standing at -20 °C. Physical and spectral data match those previously reported.²

C₂₀H₂₆O₂Si; M = 326 g.mol⁻¹; **R_f** = 0.68 (Petroleum ether/EtOAc: 8/2); [**α**]_D²⁰ -23.5 (*c* 0.98, CHCl₃) [litt:² [**α**]_D²⁰ -24 (*c* 1, CHCl₃)]; **IR**: 2932, 2857, 1712, 1472, 1427, 1110, 1026, 824, 809, 740, 699, 613 cm⁻¹; **¹H NMR** (300 MHz): δ: 9.76 (d, 1H, *J* = 1.6 Hz), 7.68-7.62 (4H), 7.47-7.34 (6H), 3.91 (dd syst AB, 1H, ²*J* = 10.3 and *J* = 5.1 Hz), 3.84 (dd syst AB, 1H, ²*J* = 10.3 and *J* = 6.4 Hz), 2.56 (m, 1H), 1.10 (d, 3H, *J* = 7.0 Hz), 1.04 (s, 9H); **¹³C NMR** (75.5 MHz): δ: 204.4 (d), 135.6 (4d), 133.2 (2s), 129.8 (2d), 127.8 (4d), 64.2 (t), 48.8 (d), 26.8 (3q), 19.3 (s), 10.3 (q); **MS** (EI, 70 eV): *m/z* (%): 269 (M-[*t*-Bu]⁺, 19), 239 (21), 211 (7), 199 (100), 191 (25), 183 (24), 161 (4), 152 (2), 121 (3), 105 (4), 77 (8), 70 (3), 51 (1).

(3S)-4-tert-Butyldiphenylsilyloxy-3-methylbutanal (2):



To a suspension of methoxymethylphosphonium chloride (22.9 g, 66.8 mmol, 4.5 equiv) in THF (100 mL) was slowly added NaHMDS (2 M in THF, 59.4 mmol, 4 equiv). After 1 h of stirring at -78 °C, a solution of aldehyde **26** (4.84 g, 14.8 mmol, 1 equiv) in THF (35 mL) was added via cannula. The reaction was allowed to stir 1 h at -78 °C and then the cooling bath was removed and the reaction mixture was stirred for 2 h at rt. A saturated aqueous solution of NaHCO₃ (60 mL) was added and the aqueous layer was extracted with Et₂O (2 x 150 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated.

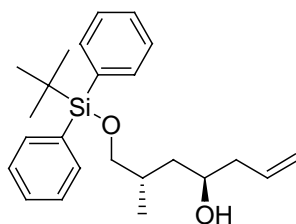
The crude residue was then dissolved in CH₂Cl₂ (150 mL) and THF (37 mL) and an aqueous solution of HCl (5N, 19.3 mL, 6.5 equiv) was added slowly at 0 °C. After 3 h at rt, a saturated aqueous solution of NaHCO₃ was added dropwise (Caution: strong CO₂ release).

² Brünjes, M.; Sourkouni-Argirusi, G.; Kirschning, A. *Adv. Synth. Catal.* **2003**, 345, 635-642.

Aqueous layer was extracted with CH₂Cl₂ (4 x 100 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc: 98/2) provided the desired aldehyde **2** (4.37 g, 86%) as a colorless oil.

C₂₁H₂₈O₂Si; M = 340 g.mol⁻¹; **R_f** = 0.38 (Petroleum ether/EtOAc: 95/5); [**α**]_D²⁰ -1.65 (c 2.51, CHCl₃); **IR**: 2931, 2857, 1724, 1589, 1472, 1427, 1389, 1107, 823, 740, 700, 613 cm⁻¹; **¹H NMR** (300 MHz): δ: 9.78 (t, 1H, *J* = 2.8 Hz), 7.69-7.60 (4H), 7.45-7.33 (6H), 3.58 (dd syst AB, 1H, ²*J* = 9.9 and *J* = 5.0 Hz), 3.44 (dd syst AB, 1H, ²*J* = 9.9 and *J* = 7.0 Hz), 2.60 (m, 1H), 2.41-2.21 (2H), 1.05 (s, 9H), 0.94 (d, 3H, *J* = 6.6 Hz); **¹³C NMR** (75.5 MHz): δ: 202.6 (d), 135.6 (4d), 133.5 (2s), 129.7 (2d), 127.7 (4d), 68.4 (t), 48.2 (t), 31.3 (d), 26.9 (3q), 19.3 (s), 16.8 (q); **MS** (EI, 70 eV): *m/z* (%): 283 (M-[*t*-Bu]⁺, 47), 265 (M-[*t*-Bu]-H₂O⁺, 3), 253 (6), 227 (5), 199 (100), 181 (20), 139 (33), 123 (9), 105 (10), 91 (6), 77 (9).

(4*R*,6*S*)-7-*tert*-Butyldiphenylsilyloxy-6-methylhept-1-en-4-ol (3):

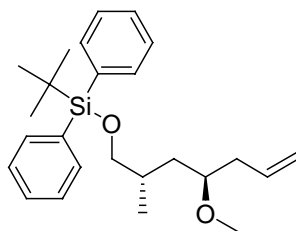


To a stirring solution of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O,O'*]titanium chloride (10.3 g, 16.8 mmol, 1.4 equiv) in anhydrous Et₂O (80 mL) at 0 °C, was added dropwise allylmagnesium chloride (2M in THF, 7.2 mL, 14.4 mmol, 1.2 equiv). After 2.5 h at 0 °C, the reaction mixture was cooled to -78 °C and a solution of aldehyde **2** (4.1 g, 12.0 mmol, 1 equiv) in Et₂O (30 mL) was added dropwise *via* cannula. After 5 h at -78 °C, the reaction was quenched by addition of a 45% aqueous NH₄F solution (58 mL). The reaction mixture was stirred overnight at room temperature and then filtered over Celite. The combined extracts were washed with brine (20 mL), dried with MgSO₄, filtered and concentrated. The residue was then diluted with pentane (60 mL) and filtered to remove (4*S*,*trans*)-2,2-dimethyl- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,3-dioxolane-4,5-dimethanol. ¹H NMR of the crude residue revealed a diastereomeric ratio superior to 95/5. After evaporation, purification of the residue by flash chromatography on silica gel (pentane/EtOAc: 95/5 to 9/1) provided the desired alcohol **3** (4.43 g, 96%) as a colorless oil.

C₂₄H₃₄O₂Si; M = 382 g.mol⁻¹; **R_f** = 0.23 (Petroleum ether/EtOAc: 9/1); [**α**]_D²⁰ -5.74 (c 1.30, CHCl₃); **IR**: 3400, 2930, 2857, 1472, 1427, 1389, 1361, 1107, 913, 823, 739, 700, 613 cm⁻¹; **¹H NMR** (400 MHz): δ: 7.70-7.63 (4H), 7.41-7.34 (6H), 5.84 (m, 1H), 5.15-5.07 (2H), 3.76 (m,

1H), 3.51 (d, 2H, $J = 6.0$ Hz), 2.41 (broad d, 1H, $J = 3.7$ Hz), 2.30-2.12 (2H), 1.89 (m, 1H), 1.51 (ddd syst AB, 1H, $^2J = 14.1$, $J = 9.5$ and $J = 5.7$ Hz), 1.36 (ddd syst AB, 1H, $^2J = 14.1$, $J = 7.5$ and $J = 3.0$ Hz), 1.06 (s, 9H), 0.89 (d, 3H, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (100 MHz): δ : 135.7 (4d), 135.1 (d), 133.6 (2s), 129.7 (2d), 127.7 (4d), 117.7 (t), 69.8 (t), 69.1 (d), 42.7 (t), 41.7 (t), 33.4 (d), 26.9 (3q), 19.3 (s), 17.3 (q); **MS** (EI, 70 eV): m/z (%): 341 (1), 325 (M-[*t*-Bu] $^+$, 2), 307 (2), 283 (3), 263 (1), 253 (1), 239 (3), 229 (8), 199 (100), 181 (13), 139 (13), 109 (51), 85 (11), 67 (30); **Elemental Analysis** Calcd for $\text{C}_{24}\text{H}_{34}\text{O}_2\text{Si}$: C, 75.34; H, 8.96. Found: C, 75.16; H, 8.69.

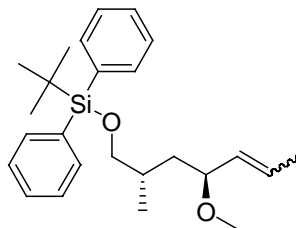
(4*R*,6*S*)-7-*tert*-Butyldiphenylsilyloxy-4-methoxy-6-methylhept-1-ene (4):



To a suspension of potassium hydride (30 % in oil, 4.64 g, 34.8 mmol, 3 equiv) in dry THF (50 mL) at 0 °C, were added iodomethane (3.6 mL, 58.0 mmol, 5 equiv) and, via cannula, a solution of alcohol **3** (4.43 g, 11.6 mmol, 1 equiv) in dry THF (40 mL). The reaction mixture was allowed to warm to rt. Then, the reaction mixture was poured dropwise into a saturated aqueous solution of NaHCO_3 (200 mL). The aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/ EtOAc : 98/2) provided the desired ether **4** (4.47 g, 97%) as a colorless oil.

$\text{C}_{25}\text{H}_{36}\text{O}_2\text{Si}$; $M = 396 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.56$ (Petroleum ether/ EtOAc : 95/5); $[\alpha]_D^{20} -11.1$ (c 1.44, CHCl_3); **IR**: 2930, 2857, 1427, 1090, 998, 912, 822, 739, 700, 613 cm^{-1} ; $^1\text{H NMR}$ (300 MHz): δ : 7.75-7.57 (4H), 7.47-7.24 (6H), 5.78 (m, 1H), 5.11-5.00 (2H), 3.54 (dd syst AB, 1H, $^2J = 9.8$ and $J = 5.3$ Hz), 3.45 (dd syst AB, 1H, $^2J = 9.8$ and $J = 6.4$ Hz), 3.30 (s, 3H), 3.28 (m, 1H), 2.36-2.14 (2H), 1.87 (m, 1H), 1.61 (m, 1H), 1.23 (m, 1H), 1.05 (s, 9H), 0.96 (d, 3H, $J = 6.4$ Hz); $^{13}\text{C NMR}$ (100 MHz): δ : 135.7 (4d), 134.8 (d), 134.1 (2s), 129.6 (2d), 127.6 (4d), 116.9 (t), 78.2 (d), 69.4 (t), 56.3 (q), 38.2 (t), 37.6 (t), 32.4 (d), 27.0 (3q), 19.4 (s), 17.0 (q); **MS** (EI, 70 eV): m/z (%): 355 (2), 339 (M-[*t*-Bu] $^+$, 4), 323 (1), 307 (2), 243 (6), 231 (8), 213 (100), 199 (42), 183 (41), 153 (22), 135 (17), 109 (98), 99 (45), 67 (52), 55 (10); **Elemental Analysis** Calcd for $\text{C}_{25}\text{H}_{36}\text{O}_2\text{Si}$: C, 75.70; H, 9.15. Found: C, 75.48; H, 9.15.

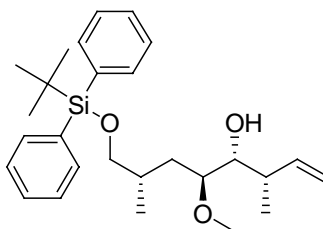
(4*R*,6*S*)-7-*tert*-Butyldiphenylsilyloxy-4-methoxy-6-methylhept-2-ene (5):



To a solution of alkene **4** (3.54 g, 8.95 mmol, 1 equiv) in toluene (100 mL), were added *N*-allyl-*N*-tritylamine (5.35 g, 17.9 mmol, 2 equiv), diisopropylethylamine (1.56 mL, 8.95 mmol, 1 equiv) and second generation Grubbs' catalyst **GII** (152 mg, 0.18 mmol, 2 mol%). After 3.5 h of heating at reflux for 3.5 h, the reaction mixture was concentrated and dissolved in CH₂Cl₂ (120 mL) and water (120 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 70 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc: 98/2) provided the desired alkene **5** (3.48 g, 98%) as a yellow oil.

C₂₅H₃₆O₂Si; M = 396 g.mol⁻¹; **R_f** = 0.58 (Petroleum ether/EtOAc: 95/5); [**α**]_D²⁰ -6.21 (*c* 1.31, CHCl₃); **IR**: 3060, 2950, 2920, 2850, 1660, 1590, 1470, 1430, 1390, 1360, 1190, 1100, 970, 825, 740, 710, 700, 690, 610 cm⁻¹; **¹H NMR** (300 MHz): δ: 7.70-7.63 (4H), 7.44-7.32 (6H), 5.54 (dd, 1H, *J* = 15.5 and *J* = 6.4 Hz), 5.25 (m, 1H), 3.59-3.38 (3H), 3.19 (s, 3H), 1.86 (m, 1H), 1.69 (dd, 3H, *J* = 6.4 and *J* = 1.9 Hz), 1.29-1.11 (2H), 1.06 (s, 9H), 0.98 (d, 3H, *J* = 6.8 Hz); **¹³C NMR** (75.5 MHz): δ: 135.7 (4d), 134.1 (2s), 132.2 (d), 129.5 (2d), 128.5 (d), 127.7 (4d), 80.4 (d), 69.0 (t), 55.7 (q), 39.3 (t), 32.2 (d), 26.9 (3q), 19.4 (s), 17.7 (q), 17.3 (q); **MS** (EI, 70 eV): *m/z* (%): 339 (M-[*t*-Bu]⁺, 2), 323 (1), 307 (6), 239 (3), 213 (28), 199 (15), 183 (21), 135 (9), 109 (100), 85 (11), 67 (19); **Elemental Analysis** Calcd for C₂₅H₃₆O₂Si: C, 75.70; H, 9.15. Found: C, 75.85; H, 9.25.

(3*S*,4*R*,5*S*,7*S*)-8-*tert*-Butyldiphenylsilyloxy-5-methoxy-3,7-dimethyloct-1-en-4-ol (7):



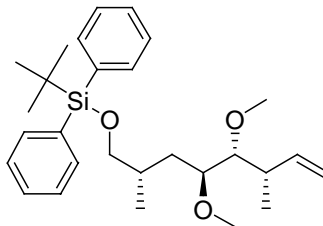
To a solution of alkene **5** (3.47 g, 8.77 mmol, 1 equiv) in acetone and water (9/1, 70 mL) at 0 °C, were added *N*-methylmorpholine *N*-oxide (1.03 g, 8.77 mmol, 1 equiv) and osmium tetroxide (4wt% in water, 1.1 mL, 0.17 mmol, 0.02 equiv). After 16 h of stirring at rt, sodium periodate (7.51 g, 35.1 mmol, 4 equiv) and water (10 mL) were added. After 2.5 h, Na₂S₂O₃ (1.6

g), Florisil (100-200 mesh, 4 g) and water (20 mL) were added and the reaction mixture was stirred for 1 h and then filtered over Celite. After evaporation of organic solvents, the aqueous layer was extracted with Et₂O (2 x 150 mL) and EtOAc (100 mL). The combined organic layers were washed with a saturated solution of Na₂S₂O₃ (40 mL) and with water (20 mL), dried with MgSO₄, filtered and concentrated. The obtained aldehyde was used in the next step without further purification.

To a solution of the *Z*-crotylboronate **6** (0.8M in toluene, 16.1 mL, 13.2 mmol, 1.5 equiv) in toluene (30 mL) at rt, were added activated 4Å molecular sieves (600 mg). After 10 min of stirring at rt, the reaction mixture was cooled to -78 °C and a solution of the crude aldehyde (8.77 mmol, 1 equiv) in toluene (15 mL) was added via cannula. After 17 h of stirring at -78 °C, the reaction mixture was allowed to warm to 0 °C and an aqueous solution of NaOH (2N, 12 mL) was added. After 2h at 0 °C, the reaction mixture was filtered over Celite. The aqueous layer was extracted with Et₂O (4 x 30 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Only one diastereomer was observed by ¹H NMR of the crude residue. Purification of the residue by flash chromatography on silica gel (petroleum ether/Et₂O: 97/3) provided the desired alcohol **7** (2.73 g, 70%) as a colorless oil.

C₂₇H₄₀O₃Si; M = 440 g.mol⁻¹; **R_f** = 0.44 (Petroleum ether/EtOAc: 9/1); [**α**]_D²⁰ -14.1 (*c* 1.24, CHCl₃); **IR**: 3450, 2930, 2857, 1641, 1589, 1461, 1427, 1389, 1084, 915, 822, 739, 700, 613 cm⁻¹; **¹H NMR** (300 MHz): δ: 7.70-7.64 (4H), 7.46-7.32 (6H), 5.63 (ddd, 1H, *J* = 17.3, *J* = 10.2 and *J* = 8.7 Hz), 5.10-4.97 (2H), 3.61 (dd, 1H, *J* = 9.0 and *J* = 3.4 Hz), 3.56 (dd syst AB, 1H, ²*J* = 9.8 and *J* = 5.3 Hz), 3.45 (dd syst AB, 1H, ²*J* = 9.8 and *J* = 6.4 Hz), 3.32 (s, 3H), 3.24 (m, 1H), 2.24 (m, 1H), 2.15 (broad s, 1H), 1.89 (m, 1H), 1.63 (ddd syst AB, 1H, ²*J* = 13.9, *J* = 10.4 and *J* = 3.8 Hz), 1.24 (m, 1H), 1.13 (d, 3H, *J* = 6.8 Hz) 1.06 (s, 9H), 0.93 (d, 3H, *J* = 6.8 Hz); **¹³C NMR** (75.5 MHz): δ: 140.1 (d), 135.7 (4d), 134.1 (2s), 129.5 (2d), 127.6 (4d), 115.2 (t), 80.2 (d), 73.4 (d), 69.8 (t), 57.0 (q), 40.5 (d), 32.1 (d), 30.9 (t), 26.9 (3q), 19.4 (s), 17.4 (q), 16.4 (q); **MS** (EI, 70 eV): *m/z* (%): 365 (M-[*t*-Bu]-H₂O⁺, 1), 351 (M-[*t*-Bu]-MeOH⁺, 28), 333 (1), 323 (2), 299 (10), 243 (7), 225 (6), 213 (59), 199 (100), 183 (31), 167 (9), 153 (25), 135 (47), 99 (72), 93 (17), 85 (15), 69 (16), 55 (27); **Elemental Analysis** Calcd for C₂₇H₄₀O₃Si: C, 73.59; H, 9.15. Found: C, 73.63; H, 9.09.

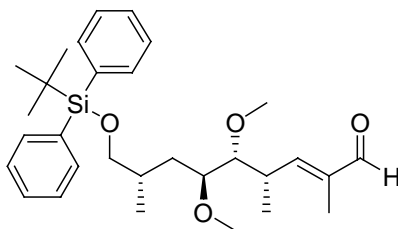
(3*S*,4*R*,5*S*,7*S*)-8-*tert*-Butyldiphenylsilyloxy-4,5-dimethoxy-3,7-dimethyloct-1-ene (27):



To a suspension of potassium hydride (30 % in oil, 5.1 g, 38.1 mmol, 3 equiv) in dry THF (40 mL) at 0 °C, were added iodomethane (4.1 mL, 63.5 mmol, 5 equiv) and, via cannula, a solution of alcohol **7** (5.59 g, 12.7 mmol, 1 equiv) in dry THF (30 mL). The reaction mixture was allowed to warm to rt. After completion of the reaction (TLC), the reaction mixture was poured dropwise into a saturated aqueous solution of NaHCO₃ (200 mL). The aqueous layer was extracted with Et₂O (3 x 200 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/Et₂O: 9/1) provided the desired ether **27** (5.31 g, 92%) as a colorless oil.

C₂₈H₄₂O₃Si; M = 454 g.mol⁻¹; **R_f** = 0.39 (Petroleum ether/EtOAc: 95/5); [**α**]_D²⁰ -3.8 (*c* 2.09, CHCl₃); **IR**: 3070, 2940, 2930, 2850, 1640, 1590, 1460, 1425, 1390, 1190, 1105, 1010, 1000, 915, 825, 745, 710, 700, 690, 610 cm⁻¹; **¹H NMR** (300 MHz): δ 7.72-7.65 (4H), 7.46-7.34 (6H), 5.72 (ddd, 1H, *J* = 17.3, *J* = 10.2 and *J* = 8.3 Hz), 5.07-4.95 (2H), 3.60 (dd syst AB, 1H, ²*J* = 9.8 and *J* = 5.3 Hz), 3.48 (s, 3H), 3.45 (dd syst AB, 1H, ²*J* = 9.8 and *J* = 6.8 Hz), 3.33 (s, 3H), 3.29 (m, 1H), 3.15 (dd, 1H, ²*J* = 7.9 and *J* = 3.0 Hz), 2.28 (m, 1H), 1.93 (m, 1H), 1.66 (ddd syst AB, 1H, ²*J* = 14.3, *J* = 10.6 and *J* = 3.8 Hz), 1.24 (m, 1H), 1.10 (d, 3H, *J* = 6.4 Hz) 1.07 (s, 9H), 0.96 (d, 3H, *J* = 6.8 Hz); **¹³C NMR** (75.5 MHz): δ 141.4 (d), 135.7 (4d), 134.1 (2s), 129.5 (2d), 127.6 (4d), 114.5 (t), 84.6 (d), 80.7 (d), 69.7 (t), 60.6 (q), 57.1 (q), 40.7 (d), 32.6 (d), 32.5 (t), 26.9 (3q), 19.4 (s), 16.8 (q), 16.6 (q); **MS** (EI, 70 eV): *m/z* (%): 399 (1), 365 (M-[*t*-Bu]-MeOH⁺, 13), 355 (11), 333 (2), 323 (2), 309 (3), 297 (3), 283 (6), 243 (6), 213 (82), 199 (33), 183 (32), 167 (26), 153 (26), 135 (72), 99 (100), 67 (17), 55 (12); **Elemental Analysis** Calcd for C₂₈H₄₂O₃Si: C, 73.96; H, 9.31. Found: C, 74.01; H, 9.51.

(*E*)-(4*S*,5*R*,6*S*,8*S*)-9-*tert*-Butyldiphenylsilyloxy-5,6-dimethoxy-2,4,8-trimethylnon-2-enal (9):

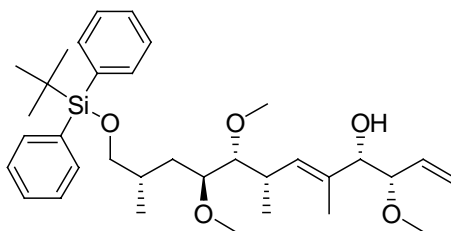


To a solution of alkene **27** (1.16 g, 2.56 mmol, 1 equiv) in a mixture acetone/water (9/1, 25 mL) at 0 °C, were added *N*-methylmorpholine *N*-oxide (330 mg, 2.82 mmol, 1.2 equiv) and osmium tetroxide (4wt% in water, 0.16 mL, 0.025 mmol, 0.01 equiv). After 18 h at rt, sodium periodate (2.19 g, 10.2 mmol, 4 equiv) and water (3 mL) were added. After 2.5 h, Na₂S₂O₃ (1 g), Florisil (100-200 mesh, 1.5 g) and water (10 mL) were added and the reaction mixture was stirred for 1 h and then filtered over Celite. After evaporation of organic solvents, the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with a saturated solution of Na₂S₂O₃ (15 mL) and water (10 mL), dried with MgSO₄, filtered and concentrated. The crude obtained aldehyde was used in the next step without further purification.

To a solution of *N*-(2-triethylsilylpropylidene)-*tert*-butylamine **8** (2.91 g, 12.8 mmol, 5 equiv) in dry THF (40 mL) at 0 °C, was added dropwise *sec*-butyllithium (1.3M in cyclohexane, 9.9 mL, 12.8 mmol, 5 equiv). After 30 min at 0 °C, the reaction mixture was cooled to -78 °C and a solution of the crude aldehyde in dry THF (15 mL) was added via cannula. The reaction was slowly allowed to warm until -20 °C (4.5 h) and water (20 mL) was added to stop the reaction. The aqueous layer was acidified until pH = 4-5 with solid citric acid and extracted with Et₂O (2 x 80 mL). The combined organic layer were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc: 95/5) provided the desired aldehyde **9** (1.18 g, 93%, rd = 4/1) as a yellow-orange oil. (NB: drying under vacuum (0.1 mbar) at 40 °C for 1 h was performed to remove TESOH not separated during purification).

C₃₀H₄₄O₄Si; M = 496 g.mol⁻¹; **R_f** = 0.29 (Petroleum ether/EtOAc: 9/1); **IR**: 2930, 2857, 1687, 1638, 1461, 1428, 1104, 1028, 823, 739, 701, 613 cm⁻¹; **¹H NMR** (300 MHz): δ 9.43 (s, 1H), 7.75-7.54 (4H), 7.48-7.28 (6H), 6.35 (dd, 1H, *J* = 10.5 and *J* = 1.2 Hz), 3.55 (dd syst AB, 1H, ²*J* = 9.8 and *J* = 5.3 Hz), 3.47 (s, 3H), 3.45 (m, 1H), 3.33 (s, 3H), 3.24-3.12 (2H), 2.84 (m, 1H), 1.87 (m, 1H), 1.75 (d, 3H, *J* = 1.1 Hz), 1.70 (m, 1H) 1.15 (m, 1H), 1.14 (d, 3H, *J* = 6.8 Hz), 1.05 (s, 9H), 0.89 (d, 3H, *J* = 6.8 Hz); **¹³C NMR** (75.5 MHz): δ 195.2 (d), 156.3 (d), 138.2 (s), 135.7 (4d), 134.0 (2s), 129.5 (2d), 127.6 (4d), 84.7 (d), 80.9 (d), 69.5 (t), 60.7 (q), 57.4 (q), 36.1 (d), 33.4 (t), 32.4 (d), 26.9 (3q), 19.3 (s), 16.6 (q), 15.9 (q), 9.5 (q); **MS** (EI, 70 eV): *m/z* (%): 439 (M-[*t*-Bu]⁺, 1), 421 (M-[*t*-Bu]-H₂O⁺, 1), 407 (17), 375 (7), 355 (8), 341 (20), 323 (3), 309 (6), 297 (6), 283 (8), 269 (4), 243 (5), 213 (63), 199 (43), 183 (34), 135 (30), 111 (25), 99 (100), 85 (19), 71 (18), 59 (8).

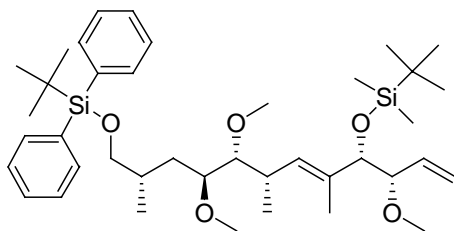
(E)-(3*S*,4*S*,7*S*,8*R*,9*S*,11*S*)-12-*tert*-Butyldiphenylsilyloxy-3,8,9-trimethoxy-5,7,11-trimethyldodec-1,5-dien-4-ol (28):



To a stirred solution of allyl methyl ether (853 mg, 11.85 mmol, 3.3 equiv) in dry THF (13 mL), at $-78\text{ }^{\circ}\text{C}$, was added dropwise *sec*-butyllithium (1.4 M in cyclohexane, 9 mL, 10.8 mmol, 3 equiv). After 30 min at $-78\text{ }^{\circ}\text{C}$, a solution of (+)-*B*-methoxydiisocampheylborane in THF (9 mL, 1 M, 9 mmol, 3 equiv) was added via cannula. After 1 h of stirring at $-78\text{ }^{\circ}\text{C}$, a solution of aldehyde **9** (1.78 g, 3.59 mmol, 1 equiv) in THF (10 mL) was added *via* cannula, followed immediately by the dropwise addition of $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.5 mL, 11.85 mmol, 3.3 equiv). The reaction mixture was allowed to warm slowly to $-50\text{ }^{\circ}\text{C}$ and stirred for 2 h and then to $-5\text{ }^{\circ}\text{C}$. Solvents were evaporated *in vacuo* and pentane and ethanolamine were added at $0\text{ }^{\circ}\text{C}$. After 2.5 h at $0\text{ }^{\circ}\text{C}$, the mixture was filtered through Celite and washed with cold pentane. Purification of the crude residue by chromatography on silica gel (pentane/EtOAc: 95/5) provided the desired alcohol **28** (1.49 g, 73%) as a colorless oil.

$\text{C}_{34}\text{H}_{52}\text{O}_5\text{Si}$; $M = 568\text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.29$ (Petroleum ether/EtOAc: 8/2); $[\alpha]_D^{20} +29.5$ (c 0.63, CHCl_3); **IR**: 3430, 2929, 2856, 1471, 1426, 1386, 1232, 1189, 1153, 1096, 1064, 1006, 972, 927, 872, 817, 799, 741, 702, 689, 613 cm^{-1} ; **^1H NMR** (300 MHz): δ 7.70-7.63 (4H), 7.45-7.31 (6H), 5.53 (ddd, 1H, $J = 17.5$, $J = 10.0$ and $J = 7.7$ Hz), 5.32-5.20 (3H), 3.84 (d, 1H, $J = 8.3$ Hz), 3.59 (dd syst AB, 1H, $^2J = 9.6$ and $J = 5.1$ Hz), 3.51 (app t, 1H, $J = 7.9$ Hz), 3.44 (s, 3H), 3.42 (dd syst AB, 1H, $^2J = 9.6$ and $J = 7.2$ Hz), 3.33 (s, 3H), 3.29 (s, 3H), 3.16 (dt, 1H, $J = 10.5$ and $J = 2.3$ Hz), 3.07 (dd, 1H, $J = 8.5$ and $J = 2.5$ Hz), 2.91 (broad s, 1H), 2.45 (m, 1H), 1.88 (m, 1H), 1.65 (ddd syst AB, 1H, $^2J = 14.4$, $J = 10.5$ and $J = 4.1$ Hz), 1.60 (d, 3H, $J = 1.5$ Hz), 1.14 (m, 1H), 1.05 (s, 9H), 1.03 (d, 3H, $J = 6.8$ Hz), 0.93 (d, 3H, $J = 6.4$ Hz); **^{13}C NMR** (75.5 MHz): δ 135.7 (4d), 134.3 (2s), 134.1 (d), 133.6 (d), 132.5 (s), 129.5 (2d), 127.5 (4d), 119.6 (t), 84.9 (2d), 81.0 (d), 80.4 (d), 69.7 (t), 60.7 (q), 57.0 (q), 56.5 (q), 34.7 (d), 32.7 (t), 32.5 (d), 26.9 (3q), 19.4 (s), 17.0 (q), 16.9 (q), 12.2 (q).

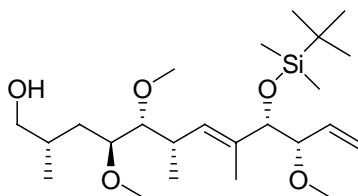
(E)-(3*S*,4*S*,7*S*,8*R*,9*S*,11*S*)-4-*tert*-Butyldimethylsilyloxy-12-*tert*-butyldiphenylsilyloxy-3,8,9-trimethoxy-5,7,11-trimethyldodec-1,5-diene (11):



To a solution of alcohol **28** (1.48 g, 2.62 mmol, 1 equiv) in CH₂Cl₂ (25 mL) at -78 °C were added 2,6-lutidine (1.5 mL, 13.1 mmol, 5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.8 mL, 7.85 mmol, 3 equiv). After 10 h of stirring at -78°C, a saturated aqueous solution of NH₄Cl was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/Et₂O: 95/5) provided the desired silyl ether **11** (1.68 g, 94%) as a colorless oil.

C₄₀H₆₆O₅Si₂; M = 682 g·mol⁻¹; **R_f** = 0.27 (Petroleum ether/EtOAc: 9/1); [**α**]_D²⁰ +11.0 (*c* 6.57, CHCl₃); **IR**: 2929, 2856, 1462, 1428, 1388, 1361, 1249, 1104, 1079, 836, 776, 739, 701, 613 cm⁻¹; **¹H NMR** (300 MHz): δ: 7.74-7.65 (4H), 7.48-7.33 (6H), 5.57 (ddd, 1H, *J* = 17.3, *J* = 10.2 and *J* = 7.4 Hz), 5.29-5.10 (3H), 3.93 (d, 1H, *J* = 7.2 Hz), 3.65 (dd syst AB, 1H, ²*J* = 9.6 and *J* = 4.9 Hz), 3.57-3.42 (2H), 3.49 (s, 3H), 3.33 (s, 3H), 3.32 (s, 3H), 3.23 (m, 1H), 3.12 (dd, 1H, *J* = 8.9 and *J* = 1.8 Hz), 2.44 (m, 1H), 1.94 (m, 1H), 1.72 (ddd syst AB, 1H, ²*J* = 14.3, *J* = 10.6 and *J* = 4.1 Hz), 1.59 (d, 3H, *J* = 1.0 Hz), 1.20 (m, 1H), 1.10 (s, 9H), 1.04 (d, 3H, *J* = 6.5 Hz), 0.98 (d, 3H, *J* = 6.7 Hz), 0.93 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); **¹³C NMR** (75.5 MHz): δ: 135.7 (4d), 135.1 (d), 134.8 (s), 134.1 (2s), 131.5 (d), 129.5 (2d), 127.6 (4d), 117.5 (t), 86.4 (d), 84.8 (d), 81.8 (d), 81.3 (d), 69.7 (t), 60.7 (q), 57.0 (q), 56.9 (q), 34.7 (d), 32.6 (d), 32.5 (t), 27.0 (3q), 25.8 (3q), 19.4 (s), 18.3 (s), 17.1 (q), 16.9 (q), 12.3 (q), -4.6 (q), -4.7 (q); **Elemental Analysis** Calcd for C₄₀H₆₆O₅Si₂: C, 70.33; H, 9.74. Found: C, 70.29; H, 9.72.

(E)-(2*S*,4*S*,5*R*,6*S*,9*S*,10*S*)-9-*tert*-Butyldimethylsilyloxy-4,5,10-trimethoxy-2,6,8-trimethyldodec-7,11-dien-1-ol (12):

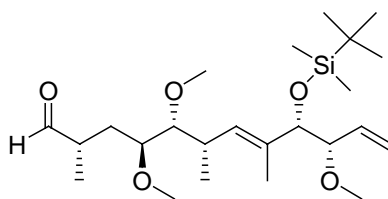


To a solution of silyl ether **11** (509 mg, 0.746 mmol, 1 equiv) in MeOH (10 mL) was added NH₄F (414 mg, 11.2 mmol, 15 equiv). After 6 h of heating at reflux, a second portion of

NH₄F (270 mg, 7.3mmol, 9.8 equiv) was added and the reaction was refluxed for 3.5 h. The reaction was stopped by adding a saturated aqueous solution of NaHCO₃ (15 mL). The aqueous layer was extracted with Et₂O (3 x 50 mL) and EtOAc (2 x 50 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (petroleum ether/Et₂O: 9/1 to 3/7) provided the desired primary alcohol **12** (271 mg, 82%) as a colorless oil. Physical and spectral data match those previously reported.³

C₂₄H₄₈O₅Si; M = 444 g.mol⁻¹; **Rf** = 0.24 (Petroleum ether/Et₂O: 1/1); [α]_D²⁰ +8.1 (c 0.48, CHCl₃); [litt:³ [α]_D²⁰ +6.0 (c 0.50, CHCl₃)]; **IR**: 2929, 2856, 1462, 1428, 1388, 1361, 1249, 1104, 1079, 836, 776, 739, 701, 613 cm⁻¹; **¹H NMR** (400 MHz): δ : 5.49 (ddd, 1H, *J* = 17.3, *J* = 10.3 and *J* = 7.6 Hz), 5.23-5.02 (3H), 3.87 (d, 1H, *J* = 7.2), 3.52-3.41 (2H), 3.48 (s, 3H), 3.37 (m, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 3.21 (m, 1H), 3.12 (dd, 1H, *J* = 9.6 and *J* = 1.3 Hz), 2.83 (broad s, 1H), 2.36 (m, 1H), 1.73-1.53 (2H), 1.52 (d, 3H, *J* = 1.3 Hz), 1.28 (m, 1H), 1.00 (d, 3H, *J* = 6.5 Hz), 0.89 (d, 3H, *J* = 6.7 Hz), 0.86 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); **¹³C NMR** (75.5 MHz): δ : 135.1 (d), 135.1 (s), 130.9 (d), 117.6 (t), 86.3 (d), 84.0 (d), 83.1 (d), 81.6 (d), 68.4 (t), 60.8 (q), 57.0 (q), 56.4 (q), 35.0 (d), 34.2 (d), 33.5 (t), 25.8 (3q), 18.3 (q), 18.2 (s), 17.3 (q), 12.1 (q), -4.8 (q); -4.8 (q); **MS** (EI, 70 eV): *m/z* (%): 373(3), 355 (M-[*t*-Bu]-MeOH⁺, 1), 341 (2), 323 (1), 309 (5), 225 (17), 213 (45), 129 (100), 97 (15), 89 (25), 71 (31), 59 (10); **Elemental Analysis** Calcd for C₄₀H₆₆O₅Si₂: C, 64.82; H, 10.88. Found: C, 64.94; H, 10.81.

(*E*)-(2*S*,4*S*,5*R*,6*S*,9*S*,10*S*)-9-*tert*-Butyldimethylsilyloxy-4,5,10-trimethoxy-2,6,8-trimethyldodec-7,11-dienal (13**):**



To a stirring solution of alcohol **12** (133 mg, 0.30 mmol, 1 equiv) in CH₂Cl₂ (10 mL) were added NaHCO₃ (151 mg, 1.80 mmol, 6 equiv) and Dess-Martin periodinane (381 mg, 0.90 mmol, 3 equiv). After 4 h of stirring, the reaction mixture was diluted with Et₂O (15 mL) and a saturated aqueous solution of NaHCO₃ (8 mL) was added as well as a saturated aqueous solution of Na₂S₂O₃ (8 mL). The reaction mixture was stirred 10 min at rt until two clear layers were obtained. The aqueous layer was extracted with Et₂O (2 x 30 mL). The combined organic layers were washed with a saturated aqueous solution of Na₂S₂O₃ (10 mL) and with a saturated aqueous

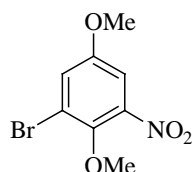
³ Nakata, M.; Osumi, T.; Ueno, A.; Kimura, T.; Tatsuta, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2974-2991.

solution of NaHCO₃ (10 mL), dried with MgSO₄, filtered and concentrated. The crude aldehyde **13** (ca. 130 mg, quant.) was obtained as a colorless oil. Physical and spectral data match those previously reported.³

C₂₄H₄₆O₅Si; M = 442 g.mol⁻¹; **R_f** = 0.80 (Petroleum ether/Et₂O: 1/1); **¹H NMR** (300 MHz): δ: 9.38 (d, 1H, *J* = 3.6 Hz), 5.44 (ddd, 1H, *J* = 17.6, *J* = 9.8 and *J* = 7.6 Hz), 5.25-5.06 (2H), 5.01 (dd, 1H, *J* = 10.2 and *J* = 0.6 Hz), 3.83 (d, 1H, *J* = 7.3 Hz), 3.44 (s, 3H), 3.42 (m, 1H), 3.24 (s, 3H), 3.17 (s, 3H), 3.14-3.01 (2H), 2.39-2.17 (2H), 2.00 (m, 1H), 1.48 (d, 3H, *J* = 1.3 Hz), 1.26 (ddd syst AB, 1H, ²*J* = 14.4, *J* = 5.7 and *J* = 2.3 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.4 Hz), 0.82 (s, 9H), 0.01 (s, 3H), -0.04 (s, 3H); **MS** (EI, 70 eV): *m/z* (%): 371 (7), 339 (4), 307 (1), 251 (3), 225 (9), 175 (9), 159 (60), 127 (100), 115 (31), 99 (40), 89 (38), 71 (63).

II / Synthesis of the Aromatic Core of Herbimycin A

1-Bromo-2,5-dimethoxy-3-nitrobenzene (**15**):



To a stirring solution of 4-methoxy-2-nitrophenol **14** (8.31 g, 49.2 mmol, 1 equiv) in AcOH (50 mL) was added over 40 min a solution of bromine (2.5 mL, 49.2 mmol, 1 equiv) in AcOH (10 mL). After 30 min at rt and 1 h of reflux, the reaction was poured into water (750 mL) acidified with conc. HCl (10 mL). After filtration and drying, the desired 2-bromo-4-methoxy-6-nitrophenol (9.3 g, 76%) was obtained as an orange solid.

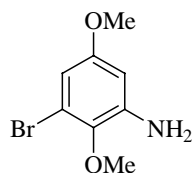
To a stirring solution of 2-bromo-4-methoxy-6-nitrophenol (9.3g, 37.4 mmol, 1 equiv) in dry acetone (200 mL), were added K₂CO₃ (15.5 g, 112.2 mmol, 3 equiv) and Me₂SO₄ (7.1 mL, 74.8 mmol, 2 equiv). After 5 h of heating at reflux, the reaction mixture was concentrated. Purification of the residue by flash chromatography on silica gel (toluene) provided the desired aryl bromide **15** (41.7 mg, 72%) as a yellow solid. Physical and spectral data match those previously reported.⁴

C₈H₈BrNO₄; M = 262 g.mol⁻¹; **F** = 99 °C [litt:⁴ **F** = 98-98.5 °C]; **R_f** = 0.25 (petroleum ether/EtOAc: 98/2); **IR**: 3100, 2943, 2839, 1524, 1474, 1421, 1340, 1228, 1080, 1041, 983, 859, 775, 729, 634, 600 cm⁻¹; **¹H NMR** (300 MHz): δ: 7.34 (d, 1H, *J* = 3.1 Hz), 7.28 (d, 1H, *J* = 3.1 Hz), 3.96 (s, 3H), 3.83 (s, 3H); **¹³C NMR** (75.5 MHz): δ: 155.5 (s), 145.0 (s), 144.5 (s), 123.8 (d), 120.1 (s), 109.2 (d), 62.7 (q), 56.3 (q); **MS** (EI, 70 eV): *m/z* (%): 263 ([M(⁸¹Br)]⁺, 100), 261

⁴ Guay, V.; Brassard, P. *J. Heterocyclic Chem.* **1987**, *24*, 1649-1652.

$([M(^{79}\text{Br})]^+, 100)$, 248 ($[M(^{81}\text{Br})\text{-Me}]^+, 17)$, 246 ($[M(^{79}\text{Br})\text{-Me}]^+, 19)$, 233 (8), 231 (9), 203 (37), 201 (33), 187 (25), 185 (25), 172 (39), 170 (31), 159 (32), 157 (43), 136 (53), 108 (27), 93 (16), 78 (36), 62 (26), 53 (36).

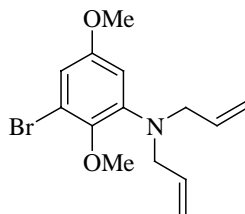
3-Bromo-2,5-dimethoxyaniline (**16**):



To a stirring suspension of nitro compound **15** (4.1 g, 15.6 mmol, 1 equiv) in water (46 mL) were added AcOH (0.6 mL) and iron (powder, 5.74 g). After 1.5 h of heating at reflux, the reaction mixture was filtered. The aqueous layer was basified with a saturated aqueous solution of NaHCO_3 and extracted with EtOAc (2x 200 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated to provide the crude aniline **16** (3.43 g, 94%) which was used in the next step without further purification. Physical and spectral data match those previously reported.⁴

$\text{C}_8\text{H}_{10}\text{BrNO}_2$; $M = 232 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.40$ (petroleum ether/EtOAc: 10/1); **IR**: 3470, 3370, 2936, 2831, 1612, 1569, 1488, 1431, 1221, 1151, 1036, 991, 834, 756, 718, 627 cm^{-1} ; **$^1\text{H NMR}$** (300 MHz): δ : 6.45 (d, 1H, $J = 2.8 \text{ Hz}$), 6.22 (d, 1H, $J = 2.8 \text{ Hz}$), 3.94 (broad s, 2H), 3.76 (s, 3H), 3.69 (s, 3H); **$^{13}\text{C NMR}$** (75.5 MHz): δ : 156.8 (s), 141.7 (s), 138.5 (s), 116.9 (s), 106.9 (d), 101.1 (d), 59.8 (q), 55.6 (q); **MS** (EI, 70 eV): m/z (%): 233 ($[M(^{81}\text{Br})]^+$, 34), 231 ($[M(^{79}\text{Br})]^+$, 34), 218 ($[M(^{81}\text{Br})\text{-Me}]^+$, 99), 216 ($[M(^{79}\text{Br})\text{-Me}]^+$, 100), 190 (11), 188 (10), 175 (6), 173 (6), 122 (6), 109 (5), 94 (16), 78 (6), 65 (4), 53 (6).

N,N-Diallyl-3-bromo-2,5-dimethoxyaniline (**17**):



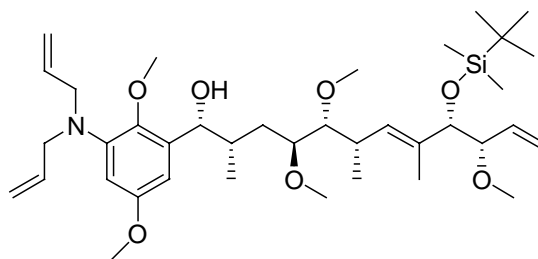
To a stirring solution of the crude aniline **16** (5.16 g, 22.2 mmol, 1 equiv) in DMF (110 mL), were added Na_2CO_3 (10.4g, 97.9 mmol, 4.4 equiv) and allyl bromide (16.2 mL, 186.8 mmol, 8.4 equiv). After 2.5 h of heating at reflux, the reaction mixture was filtered over Celite and the filtrate was poured into water (50 mL). The aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated.

Purification of the residue by flash chromatography on silica gel (pentane/EtOAc : 97/3) provided the desired aniline **17** (6.60, 95%) as a colorless oil.

$C_{14}H_{18}BrNO_2$; $M = 312 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.60$ (petroleum ether/EtOAc: 95/5); **IR**: 3077, 2932, 2833, 1593, 1559, 1478, 1417, 1222, 1173, 1119, 1054, 997, 918, 803, 763, 740, 674, 619 cm^{-1} ; **$^1\text{H NMR}$** (400 MHz): δ 6.65 (d, 1H, $J = 3.0 \text{ Hz}$), 6.41 (d, 1H, $J = 3.0 \text{ Hz}$), 5.78 (m, 2H), 5.21-5.11 (4H), 3.80-3.75 (4H), 3.77 (s, 3H), 3.71 (s, 3H); **$^{13}\text{C NMR}$** (100 MHz): δ 157.8 (s), 147.1 (s), 145.6 (s), 136.6 (2d), 120.1 (s), 119.2 (2t), 111.1 (d), 109.1 (d), 61.3 (q), 57.4 (q), 55.8 (2t); **MS** (EI, 70 eV): m/z (%): 313 ($[\text{M}^{(81}\text{Br})]^+$, 100), 311 ($[\text{M}^{(79}\text{Br})]^+$, 99), 298 ($[\text{M}^{(81}\text{Br})-\text{Me}]^+$, 49), 296 ($[\text{M}^{(79}\text{Br})-\text{Me}]^+$, 49), 282 (66), 280 (59), 272 (52), 270 (58), 256 (50), 240 (55), 230 (80), 228 (83), 190 (93), 176 (57), 160 (43), 150 (39), 133 (30), 117 (18), 104 (21), 77 (24), 53 (20).

III / End of the Synthesis Herbimycin A

(E)-(1R,2S,4S,5R,6S,9S,10S)-9-tert-Butyldimethylsilyloxy-1-(3-diallylamino-2,5-dimethoxyphenyl)-4,5,10-trimethoxy-2,6,8-trimethyldodec-7,11-dien-1-ol (18):

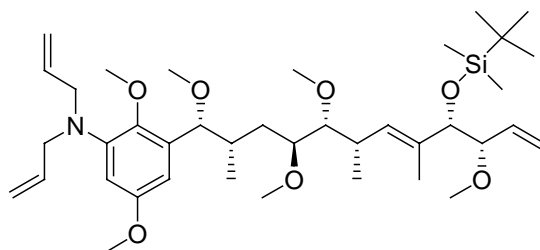


To a solution of aryl bromide **17** (475 mg, 1.52 mmol, 5 equiv) in dry Et_2O (8 mL) at -78°C was added dropwise *n*-butyllithium (2.5M in hexanes, 0.6 mL, 1.5 mmol, 5 equiv). After 30 min at rt, the reaction mixture was cooled to -78°C and a solution of crude aldehyde **13** (0.30 mmol, 1 equiv) in dry Et_2O (4 mL) was added via cannula. After 1.5 h of stirring at -78°C the reaction was stopped by addition of a saturated aqueous solution of NaHCO_3 (10 mL). The aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/ Et_2O : 8/2 to 6/4) provided the desired alcohol **18** (109 mg, 54 %) and its C15 epimer (66 mg, 33%) as yellow oils.

Alcohol **18**: $C_{38}H_{65}NO_7\text{Si}$; $M = 676 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.20$ (Petroleum ether/ Et_2O : 6/4); $[\alpha]_D^{20} +22.5$ (c 4.19, CHCl_3); **IR**: 3450, 2928, 2856, 1594, 1470, 1361, 1249, 1215, 1194, 1172, 1078, 1005, 919, 836, 775, 670 cm^{-1} ; **$^1\text{H NMR}$** (400 MHz): δ 6.58 (d, 1H, $J = 3.0 \text{ Hz}$), 6.36 (d, 1H, $J = 3.0 \text{ Hz}$), 5.76 (m, 2H), 5.52 (ddd, 1H, $J = 17.3$, $J = 10.2$ and $J = 7.5 \text{ Hz}$), 5.23-5.05 (7H), 4.87 (d, 1H, $J = 4.7 \text{ Hz}$), 3.87 (d, 1H, $J = 7.2 \text{ Hz}$), 3.80-3.66 (4H), 3.76 (s, 3H), 3.74 (s, 3H), 3.46 (m, 1H), 3.44 (s, 3H), 3.35 (s, 3H), 3.28 (s, 3H), 3.27 (m, 1H), 3.09 (dd, 1H, $J = 9.0$ and $J = 1.5 \text{ Hz}$), 3.06

(broad s, 1H), 2.39 (m, 1H), 2.01 (m, 1H), 1.71 (ddd syst AB, 1H, $^2J = 14.9$, $J = 10.3$ and $J = 6.4$ Hz), 1.53 (d, 3H, $J = 0.9$ Hz), 1.27 (m, 1H), 0.99 (d, 3H, $J = 6.6$ Hz), 0.86 (s, 9H), 0.78 (d, 3H, $J = 6.8$ Hz), 0.05 (s, 3H), 0.00 (s, 3H); $^{13}\text{C NMR}$ (100 MHz): δ : 155.3 (s), 143.9 (s), 143.7 (s), 137.2 (s), 135.0 (2d), 135.0 (d), 135.0 (s), 131.2 (d), 117.7 (t), 117.2 (2t), 106.8 (d), 104.4 (d), 86.4 (d), 84.6 (d), 82.5 (d), 81.8 (d), 72.5 (d), 60.7 (q), 59.1 (q), 57.1 (q), 56.7 (q), 55.4 (q), 53.8 (2t), 36.5 (d), 34.7 (d), 32.9 (t), 25.8 (3q), 18.2 (s), 17.2 (q), 15.1 (q), 12.1 (q), -4.7 (q), -4.8 (q); **Elemental Analysis** Calcd for $\text{C}_{38}\text{H}_{65}\text{NO}_7\text{Si}$: C, 67.51; H, 9.69; N, 2.07. Found: C, 67.61; H, 9.79; N, 2.01.

(E)-N,N-Diallyl-N-{3-[(1R,2S,4S,5R,6S,9S,10S)-9-tert-butyltrimethylsilyloxy-1,4,5,10-tetramethoxy-2,6,8-trimethyldodec-7,11-dienyl]-2,5-dimethoxyphenyl}amine (29):

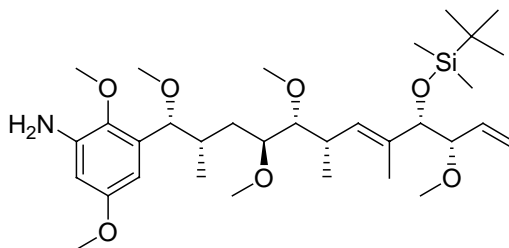


To a stirring solution of alcohol **18** (183mg, 0.27 mmol, 1 equiv) in DMF (4 mL) at 0 °C, were added sodium hydride (60% in oil, 54 mg, 1.4 mmol, 5 equiv) and iodomethane (0.17 mL, 2.7 mmol, 10 equiv). The reaction mixture was allowed to warm slowly to rt and then the reaction was stopped by addition of MeOH (3 mL) and water (7 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/ Et_2O : 9/1 to 8/2) provided the desired ether **29** in quantitative yield and as a colorless oil.

$\text{C}_{39}\text{H}_{67}\text{NO}_7\text{Si}$; $M = 689 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.28$ (Petroleum ether/ EtOAc : 9/1); $[\alpha]_D^{20} +39.9$ (c 1.01, CHCl_3); **IR**: 2928, 2820, 1596, 1465, 1249, 1194, 1101, 1006, 919, 837, 776, 671 cm^{-1} ; **$^1\text{H NMR}$** (400 MHz): δ : 6.48 (d, 1H, $J = 3.0$ Hz), 6.37 (d, 1H, $J = 3.0$ Hz), 5.77 (m, 2H), 5.50 (ddd, 1H, $J = 17.3$, $J = 10.2$ and $J = 7.4$ Hz), 5.20-5.06 (7H), 4.38 (d, 1H, $J = 5.0$ Hz), 3.85 (d, 1H, $J = 7.2$ Hz), 3.81-3.67 (4H), 3.73 (s, 6H), 3.45 (app t, 1H, $J = 7.4$ Hz), 3.40 (s, 3H), 3.27 (s, 6H), 3.22 (s, 3H), 3.17 (m, 1H), 3.04 (dd, 1H, $J = 8.5$ and $J = 2.3$ Hz), 2.41 (m, 1H), 1.92 (m, 1H), 1.65 (ddd syst AB, 1H, $^2J = 14.2$, $J = 10.6$ and $J = 3.4$ Hz), 1.53 (d, 3H, $J = 1.1$ Hz), 1.29 (m, 1H), 0.96 (d, 3H, $J = 6.6$ Hz), 0.86 (s, 9H), 0.82 (d, 3H, $J = 6.8$ Hz), 0.05 (s, 3H), 0.00 (s, 3H); **$^{13}\text{C NMR}$** (100 MHz): δ : 155.4 (s), 145.2 (s), 143.8 (s), 135.4 (s), 135.1 (2d), 135.0 (d), 134.6 (s), 131.6 (d), 117.5 (t), 117.2 (2t), 106.7 (d), 103.8 (d), 86.3 (d), 85.0 (d), 82.6 (d), 81.9 (d), 81.0 (d), 60.6 (q),

59.1 (q), 57.3 (q), 57.1 (q), 56.8 (q), 55.4 (q), 53.8 (2t), 35.5 (d), 34.5 (d), 33.0 (t), 25.8 (3q), 18.2 (s), 16.8 (q), 14.3 (q), 12.2 (q), -4.7 (q), -4.8 (q).

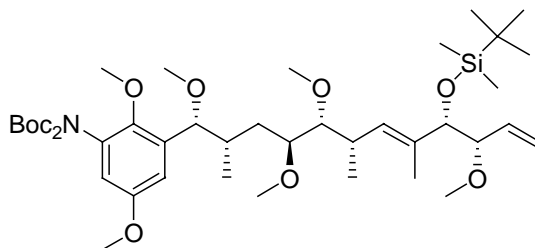
(E)-N-{3-[(1R,2S,4S,5R,6S,9S,10S)-9-tert-Butyldimethylsilyloxy-1,4,5,10-tetramethoxy-2,6,8-trimethyldodec-7,11-dienyl]-2,5-dimethoxyphenyl}amine (19**):**



To a stirring solution of aniline **29** (0.27 mmol, 1 equiv) in CH₂Cl₂ (10 mL) were added *N,N*-dimethylbarbituric acid (169 mg, 1.1 mmol, 4 equiv) and Pd(PPh₃)₄ (47 mg, 0.04 mmol, 0.15 equiv). After 2.5 h of heating at reflux, the reaction was cooled at rt and concentrated *in vacuo*. The residue was dissolved in EtOAc (70 mL) and the resulting organic layer was washed with a saturated aqueous solution of Na₂CO₃ (8 x 10 mL), dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/EtOAc: 7/3) provided the desired aniline **19** (160 mg, 97%) as a yellow oil.

C₃₃H₅₉NO₇Si; M = 610 g.mol⁻¹; R_f = 0.31 (Petroleum ether/Et₂O: 1/1); [α]_D²⁰ +30.7 (c 0.92, CHCl₃); IR: 3450, 3350, 2927, 1615, 1492, 1463, 1352, 1245, 1079, 1003, 836, 775, 670 cm⁻¹; ¹H NMR (400 MHz): δ 6.29 (d, 1H, J = 2.9 Hz), 6.22 (d, 1H, J = 2.9 Hz), 5.50 (ddd, 1H, J = 17.3, J = 10.2 and J = 7.5 Hz), 5.21-5.06 (3H), 4.34 (d, 1H, J = 4.5 Hz), 3.86 (d, 1H, J = 7.2 Hz), 3.76 (broad s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 3.45 (m, 1H), 3.44 (s, 3H), 3.28 (s, 3H), 3.27 (s, 3H), 3.23 (s, 3H), 3.16 (m, 1H), 3.07 (dd, 1H, J = 8.6 and J = 2.2 Hz), 2.42 (m, 1H), 1.98 (m, 1H), 1.71 (ddd syst AB, 1H, ²J = 14.1, J = 10.6 and J = 3.3 Hz), 1.54 (d, 3H, J = 1.0 Hz), 1.33 (m, 1H), 0.98 (d, 3H, J = 6.6 Hz), 0.86 (s, 9H), 0.82 (d, 3H, J = 6.8 Hz), 0.05 (s, 3H), 0.00 (s, 3H); ¹³C NMR (100 MHz): δ 156.3 (s), 140.3 (s), 140.0 (s), 135.1 (s), 135.0 (d), 134.7 (s), 131.5 (d), 117.5 (t), 101.7 (d), 101.0 (d), 86.3 (d), 84.9 (d), 82.4 (d), 81.8 (d), 81.1 (d), 60.7 (q), 59.9 (q), 57.3 (q), 57.1 (q), 56.9 (q), 55.4 (q), 35.4 (d), 34.5 (d), 33.4 (t), 25.8 (3q), 18.2 (s), 16.9 (q), 13.9 (q), 12.2 (q), -4.7 (q), -4.8 (q); **Elemental Analysis** Calcd for C₃₃H₅₉NO₇Si: C, 64.99; H, 9.75; N, 2.30. Found: C, 64.81; H, 9.61; N, 2.27.

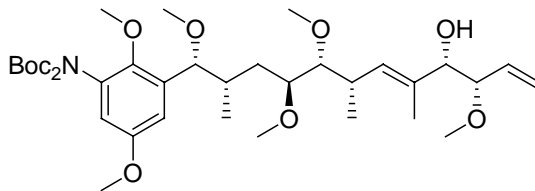
(E)-tert-Butyl N-{3-[(1R,2S,4S,5R,6S,9S,10S)-9-tert-butyldimethylsilyloxy-1,4,5,10-tetramethoxy-2,6,8-trimethyldodec-7,11-dienyl]-2,5-dimethoxyphenyl}biscarbamate (30):



To a stirring solution of aniline **19** (145 mg, 0.237 mmol, 1 equiv) in dry THF (20 mL), were added triethylamine (0.2 mL, 1.4 mmol, 6 equiv), a catalytic amount of *N,N*-dimethylaminopyridine (5 mg) and Boc_2O (155 mg, 0.71 mmol, 3 equiv). After 6 h of heating at reflux, the reaction mixture was concentrated. Purification of the residue by flash chromatography on silica gel (pentane/EtOAc: 9/1 to 8/2) provided the desired biscarbamate **30** (144 mg, 75%) as a yellow oil.

$\text{C}_{43}\text{H}_{75}\text{NO}_{11}\text{Si}$; $M = 809 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.47$ (Petroleum ether/EtOAc: 8/2); $[\alpha]_D^{20} +41.1$ (c 0.54, CHCl_3); $^1\text{H NMR}$ (400 MHz): δ : 6.79 (d, 1H, $J = 3.1$ Hz), 6.51 (d, 1H, $J = 3.1$ Hz), 5.46 (ddd, 1H, $J = 17.2$, $J = 10.3$ and $J = 7.5$ Hz), 5.16-5.01 (3H), 4.35 (d, 1H, $J = 4.0$ Hz), 3.82 (d, 1H, $J = 7.2$ Hz), 3.72 (s, 3H), 3.65 (s, 3H), 3.42 (m, 1H), 3.41 (s, 3H), 3.23 (s, 3H), 3.22 (s, 3H), 3.18 (s, 3H), 3.11 (m, 1H), 3.04 (dd, 1H, $J = 8.8$ and $J = 2.0$ Hz), 2.38 (m, 1H), 1.96 (m, 1H), 1.69 (ddd syst AB, 1H, $^2J = 14.1$, $J = 10.7$ and $J = 2.6$ Hz), 1.50 (s, 3H), 1.36 (s, 18H), 1.32 (m, 1H), 0.94 (d, 3H, $J = 6.6$ Hz), 0.82 (s, 9H), 0.67 (d, 3H, $J = 6.8$ Hz), 0.01 (s, 3H), -0.04 (s, 3H); $^{13}\text{C NMR}$ (100 MHz): δ : 155.2 (s), 151.6 (2s), 147.5 (s), 135.5 (s), 134.9 (d), 134.7 (s), 133.4 (s), 131.5 (d), 117.4 (t), 113.2 (d), 111.8 (d), 86.3 (d), 84.8 (d), 82.5 (d), 82.4 (2s), 81.7 (d), 81.0 (d), 60.8 (2q), 57.4 (q), 57.0 (q), 56.8 (q), 55.6 (q), 34.8 (d), 34.6 (d), 33.6 (t), 27.7 (6q), 25.8 (3q), 18.2 (s), 16.9 (q), 13.3 (q), 12.2 (q), -4.8 (2q); **Elemental Analysis** Calcd for $\text{C}_{43}\text{H}_{75}\text{NO}_{11}\text{Si}$: C, 63.75; H, 9.33; N, 1.73. Found: C, 63.87; H, 9.01; N, 1.71.

(E)-tert-Butyl N-{3-[(1R,2S,4S,5R,6S,9S,10S)-9-hydroxy-1,4,5,10-tetramethoxy-2,6,8-trimethyldodec-7,11-dienyl]-2,5-dimethoxyphenyl}biscarbamate (31):

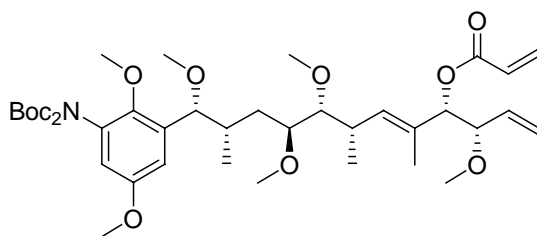


To a stirring solution of silyl ether **30** (74 mg, 0.092 mmol, 1 equiv) in dry THF (4 mL) was added TBAF (1M in THF, 0.9 mL, 0.9 mmol, 10 equiv). After 24 h of stirring at rt, brine

(5 mL) was added and the aqueous layer was extracted with Et₂O (2 x 15 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. The crude alcohol **31** was used in the next step without further purification. A portion of the material was purified for characterization.

C₃₇H₆₁NO₁₁; M = 695 g.mol⁻¹; **Rf** = 0.31 (Petroleum ether/EtOAc: 6/4); [α]_D²⁰ +69.1 (*c* 0.45, CHCl₃); **IR**: 3500, 2929, 2825, 1787, 1752, 1726, 1609, 1519, 1459, 1368, 1276, 1251, 1152, 1096, 1050, 1003, 855, 778, 732 cm⁻¹; **¹H NMR** (400 MHz): δ : 6.78 (d, 1H, *J* = 3.1 Hz), 6.51 (d, 1H, *J* = 3.1 Hz), 5.47 (ddd, 1H, *J* = 17.3, *J* = 10.2 and *J* = 7.8 Hz), 5.26-5.11 (3H), 4.34 (d, 1H, *J* = 4.0 Hz), 3.77 (d, 1H, *J* = 8.1 Hz), 3.72 (s, 3H), 3.64 (s, 3H), 3.43 (m, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 3.23 (s, 3H), 3.18 (s, 3H), 3.08 (m, 1H), 3.03 (dd, 1H, *J* = 8.2 and *J* = 2.4 Hz), 2.85 (broad s, 1H), 2.44 (m, 1H), 1.94 (m, 1H), 1.68 (m, 1H), 1.55 (d, 3H, *J* = 0.7 Hz), 1.35 (s, 18H), 1.35 (m, 1H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.67 (d, 3H, *J* = 6.8 Hz); **¹³C NMR** (100 MHz): δ : 155.2 (s), 151.6 (2s), 147.5 (s), 135.5 (s), 134.2 (d), 133.6 (d), 133.5 (s), 132.5 (s), 119.5 (t), 113.3 (d), 111.9 (d), 85.0 (d), 84.8 (d), 82.4 (2s), 82.4 (d), 80.9 (d), 80.3 (d), 60.9 (q), 60.8 (q), 57.4 (q), 56.9 (q), 56.5 (q), 55.7 (q), 34.9 (d), 34.6 (d), 33.8 (t), 27.8 (6q), 16.9 (q), 13.3 (q), 12.2 (q); **Elemental Analysis** Calcd for C₃₇H₆₁NO₁₁: C, 63.86; H, 8.84; N, 2.01. Found: C, 64.28; H, 8.68; N, 1.99.

(*E*)-(3*S*,4*S*,7*S*,8*R*,9*S*,11*S*,12*R*)-12-[3-bis(*tert*-Butoxycarbonyl)amino-2,5-dimethoxyphenyl]-3,8,9,12-tetramethoxy-5,7,11-trimethyldodeca-1,5-dien-4-yl acrylate (20**):**

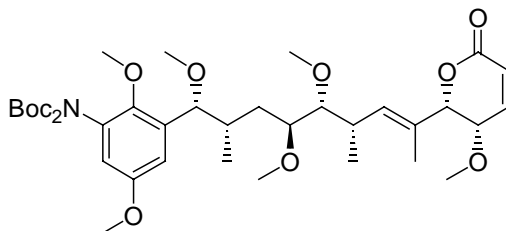


To a stirring solution of crude alcohol **31** (0.092 mmol, 1 equiv) in CH₂Cl₂ (3 mL) at -78 °C, were added diisopropylethylamine (96 μ L, 0.55 mmol, 6 equiv) and acryloyl chloride (22 μ L, 0.27 mmol, 3 equiv). After 6 h of stirring at -78 °C, the reaction was stopped by addition of a saturated aqueous solution of NaHCO₃ (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (pentane/Et₂O: 1/1) provided the desired acryloyl ester **20** (61.4 mg, 89%) as a colorless oil.

C₄₀H₆₃NO₁₂; M = 749 g.mol⁻¹; **Rf** = 0.24 (Petroleum ether/Et₂O: 1/1); [α]_D²⁰ +50.8 (*c* 0.46, CHCl₃); **IR**: 2929, 2825, 1788, 1752, 1725, 1610, 1480, 1368, 1273, 1252, 1187, 1152, 1096,

1049, 1004, 855, 807, 778 cm^{-1} ; $^1\text{H NMR}$ (400 MHz): δ : 6.82 (d, 1H, $J = 3.1$ Hz), 6.54 (d, 1H, $J = 3.1$ Hz), 6.37 (dd, 1H, $J = 17.2$ and $J = 1.4$ Hz), 6.12 (dd, 1H, $J = 17.2$ and $J = 10.4$ Hz), 5.78 (dd, 1H, $J = 10.4$ and $J = 1.4$ Hz), 5.58 (ddd, 1H, $J = 17.3$, $J = 10.2$ and $J = 7.4$ Hz), 5.35-5.18 (3H), 5.15 (d, 1H, $J = 6.8$ Hz), 4.36 (d, 1H, $J = 4.0$ Hz), 3.75 (s, 3H), 3.71 (m, 1H), 3.67 (s, 3H), 3.43 (s, 3H), 3.26 (s, 3H), 3.23 (s, 3H), 3.21 (s, 3H), 3.14-3.02 (2H), 2.43 (m, 1H), 1.97 (m, 1H), 1.69 (m, 1H), 1.62 (d, 3H, $J = 0.9$ Hz), 1.39 (s, 18H), 1.39 (m, 1H), 0.98 (d, 3H, $J = 6.6$ Hz), 0.70 (d, 3H, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (100 MHz): δ : 165.1 (s), 155.2 (s), 151.6 (2s), 147.5 (s), 135.5 (s), 134.0 (d), 133.5 (s), 133.3 (d), 130.6 (t), 130.3 (s), 128.7 (d), 119.2 (t), 113.3 (d), 111.9 (d), 84.9 (d), 83.3 (d), 82.5 (d), 82.4 (2s), 81.0 (d), 80.0 (d), 60.8 (2q), 57.4 (q), 57.0 (2q), 55.6 (q), 34.8 (d), 34.7 (d), 33.8 (t), 27.8 (6q), 16.9 (q), 13.9 (q), 13.2 (q); **Elemental Analysis** Calcd for $\text{C}_{40}\text{H}_{63}\text{NO}_{12}$: C, 64.06; H, 8.47; N, 1.87. Found: C, 64.46; H, 8.84; N, 1.71.

***tert*-Butyl *N*-{2,5-dimethoxy-3-[(*E*)-(1*R*,2*S*,4*S*,5*R*,6*S*)-1,4,5-trimethoxy-8-((2*S*,3*S*)-3-methoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)-2,6-dimethylnon-7-enyl]phenyl}biscarbamate
(21):**

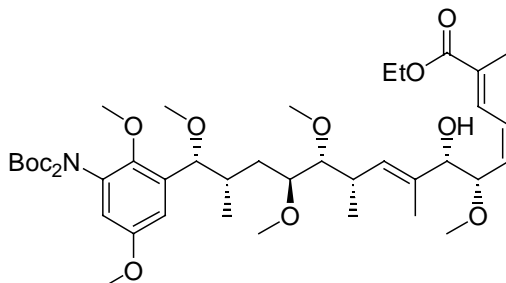


To a stirring solution of acryloyl ester **20** (60 mg, 0.08 mmol, 1 equiv) in dry toluene (30 mL) was added second generation Grubbs catalyst **GII** (8.1 mg, 12 mol%). After 2 h of heating at reflux, a second portion of catalyst **GII** was added (7 mg, 10 mol%) and the reaction was heated at 120 °C for 2 h. After evaporation of toluene, purification of the residue by flash chromatography on silica gel (pentane/Et₂O: 1/1) provided the desired lactone **21** (41.7 mg, 72%) as a colorless oil.

$\text{C}_{38}\text{H}_{59}\text{NO}_{12}$; $M = 721 \text{ g}\cdot\text{mol}^{-1}$; $R_f = 0.15$ (Petroleum ether/EtOAc: 6/4); $[\alpha]_D^{20} +104.1$ (c 0.71, CHCl_3); **IR**: 2931, 2827, 1780, 1722, 1610, 1480, 1368, 1276, 1250, 1152, 1098, 1075, 1050, 1006, 851, 825, 778, 731 cm^{-1} ; $^1\text{H NMR}$ (400 MHz): δ : 6.97 (dd, 1H, $J = 9.8$ and $J = 5.4$ Hz), 6.81 (d, 1H, $J = 3.1$ Hz), 6.54 (d, 1H, $J = 3.1$ Hz), 6.19 (d, 1H, $J = 9.8$ Hz), 5.51 (d, 1H, $J = 10.3$ Hz), 4.67 (d, 1H, $J = 2.3$ Hz), 4.37 (d, 1H, $J = 3.9$ Hz), 3.90 (dd, 1H, $J = 5.4$ and $J = 3.1$ Hz), 3.74 (s, 3H), 3.67 (s, 3H), 3.47 (s, 3H), 3.30 (s, 6H), 3.23-3.16 (2H), 3.21 (s, 3H), 2.57 (m, 1H), 1.98 (m, 1H), 1.74 (m, 1H), 1.73 (s, 3H), 1.38 (s, 18H), 1.38 (m, 1H), 1.04 (d, 3H, $J = 6.6$ Hz), 0.69 (d, 3H, $J = 6.8$ Hz); $^{13}\text{C NMR}$ (100 MHz): δ : 163.1 (s), 155.2 (s), 151.6 (2s), 147.5 (s),

142.1 (d), 135.5 (s), 133.4 (s), 131.1 (d), 128.6 (s), 124.2 (d), 113.2 (d), 112.0 (d), 85.0 (d), 83.0 (d), 82.5 (2s), 82.4 (d), 81.1 (d), 69.7 (d), 60.9 (2q), 57.4 (q), 57.2 (q), 56.9 (q), 55.6 (q), 35.0 (2d), 33.7 (t), 27.8 (6q), 17.2 (q), 13.9 (q), 13.0 (q); **HRMS** : Calcd for C₃₈H₅₉NO₁₂Na (M+Na⁺): 744.39350; Found: 744.39197.

Ethyl (2*E*,4*Z*,6*S*,7*S*,8*E*,10*S*,11*R*,12*S*,14*S*,15*R*)-15-[3-bis(*tert*-butoxycarbonyl)amino-2,5-dimethoxyphenyl]-7-hydroxy-6,11,12,15-tetramethoxy-2,8,10,14-tetramethylpentadeca-2,4,8-trienoate (23**):**



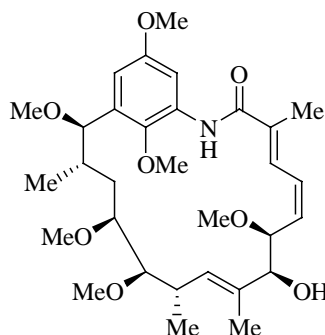
To a stirring solution of lactone **21** (55.7 mg, 0.077 mmol, 1 equiv) in dry Et₂O (8 mL) at -78 °C was added dropwise diisobutylaluminum hydride (1M in hexanes, 0.23 mL, 0.23 mmol, 3 equiv). After 2 h of stirring at -78 °C, the reaction mixture was poured into a well-stirred saturated aqueous solution of sodium potassium tartrate (5 mL). After 2 h of vigorous stirring, two clear layers separated. The aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. The crude lactol was used in the next step without purification.

To a stirring solution of crude lactol (0.077 mmol, 1 equiv) in dry toluene (12 mL) was added the commercially available phosphorous ylide **22** (83.7 mg, 0.231 mmol, 3 equiv). After 3.5 h of heating at reflux, the reaction mixture was concentrated *in vacuo*. ¹H NMR of the crude residue revealed a diastereomeric ratio superior to 9/1. Purification of the residue by flash chromatography on silica gel (pentane/EtOAc: 1/1) provided the desired diene **23** (52.9 mg, 85%) as a colorless oil.

C₄₃H₆₉NO₁₃; M = 807 g.mol⁻¹; **R_f** = 0.52 (Pentane/EtOAc: 1/1); [**α**]_D²⁰ +67.3 (c 1.32, CHCl₃); **IR**: 3500, 2930, 2824, 1785, 1752, 1708, 1609, 1459, 1367, 1247, 1152, 1095, 1050, 855, 779, 745, 732 cm⁻¹; **¹H NMR** (400 MHz): δ 7.47 (d, 1H, *J* = 14.7 Hz), 6.81 (d, 1H, *J* = 3.1 Hz), 6.56 (d, 1H, *J* = 3.1 Hz), 6.51 (m, 1H), 5.49 (t, 1H, *J* = 10.4 Hz), 5.35 (d, 1H, *J* = 9.6 Hz), 4.37 (d, 1H, *J* = 4.0 Hz), 4.26-4.16 (2H), 4.14 (dd, 1H, *J* = 9.0 and *J* = 8.3 Hz), 3.89 (d, 1H, *J* = 7.7 Hz), 3.76 (s, 3H), 3.68 (s, 3H), 3.41 (s, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 3.21 (s, 3H), 3.14 (m, 1H), 3.04 (dd, 1H, *J* = 7.2 and *J* = 3.0 Hz), 2.84 (broad s, 1H), 2.48 (m, 1H), 1.97 (m, 1H), 1.91 (d, 3H, *J* = 0.8 Hz), 1.74-1.60 (2H), 1.60 (d, 3H, *J* = 1.0 Hz), 1.40 (s, 18H), 1.30 (t, 3H, *J* = 7.1 Hz), 0.98 (d, 3H,

$J = 6.7$ Hz), 0.70 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (100 MHz): δ 168.0 (s), 155.2 (s), 151.6 (2s), 147.5 (s), 135.4 (s), 133.6 (d), 133.5 (s), 133.4 (d), 132.2 (s), 131.4 (d), 130.3 (s), 128.8 (d), 113.4 (d), 111.8 (d), 85.3 (d), 82.4 (2s), 82.3 (d), 80.7 (d), 79.7 (d), 79.0 (d), 60.9 (q), 60.8 (t), 60.7 (q), 57.4 (q), 56.9 (q), 56.6 (q), 55.6 (q), 35.0 (d), 34.5 (d), 34.0 (t), 27.8 (6q), 16.6 (q), 14.3 (q), 13.2 (q), 13.0 (q), 12.5 (q); HRMS : Calcd for $\text{C}_{43}\text{H}_{69}\text{NO}_{13}\text{Na}$ ($\text{M}+\text{Na}^+$): 830.46666; Found: 830.46534.

(4E,6Z,8S,9S,10E,12S,13R,14S,16S,17R)-9-Hydroxy-8,13,14,17,20,22-hexamethoxy-4,10,12,16-tetramethyl-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18(22),19-hexaen-3-one (24):



To a stirring solution of biscarbamate **23** (12 mg, 0.015 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C was added trifluoroacetic acid (88 μL , 1.19 mmol, 80 equiv). After 10 min at 0 °C and 1 h at rt, toluene was added and the reaction mixture was concentrated *in vacuo*. Then EtOAc was added (10 mL) and organic layer was washed with a saturated aqueous solution of K_2CO_3 (2 mL) and with brine (2 mL). The organic layer was dried with MgSO_4 , filtered and concentrated to provide the crude deprotected aniline.

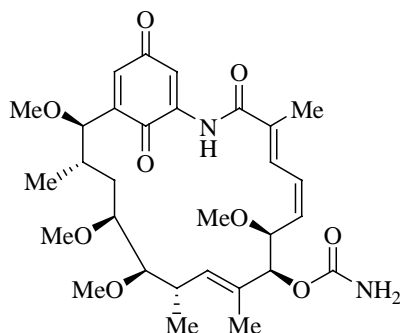
The crude residue was then dissolved in 5 mL of 2:2:1 MeOH/THF/ H_2O (v/v/v) and solid LiOH was added (8.2 mg, 0.34 mmol, 23 equiv). After 60 h of stirring at rt, the reaction mixture was concentrated to evaporate THF and MeOH and an aqueous solution of NaH_2PO_4 (10wt%, 3 mL) was added. The aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2 (5 x 5 mL). The combined organic layers were dried with MgSO_4 , filtered and concentrated to provide the crude carboxylic acid.

The crude residue was then dissolved in dry toluene (19 mL) and diisopropylethylamine (28 μL , 0.24 mmol, 16 equiv) was added. Solid bis(2-oxo-3-oxazolidinyl)phosphinic chloride (6 mg, 0.024 mmol, 1.6 equiv) was added and the reaction mixture was heated at 85 °C for 37 h. During this time, two supplementary additions of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2 x 3mg) were needed to reach completion of the reaction. The reaction mixture was poured into an aqueous solution of NaH_2PO_4 (pH = 4.5, 20 mL) and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried with MgSO_4 , filtered and

concentrated. Purification of the residue by preparative TLC (CH₂Cl₂/MeOH : 9/1) provided the desired macrolactame **24** (6.4 mg, 77%) as a colorless solid. Physical and spectral data match those previously reported.^{3,5}

C₃₁H₄₇NO₈; M = 561 g.mol⁻¹; **R_f** = 0.33 (EtOAc); [**α**]_D²⁰ +71.6 (c 0.40, CHCl₃) [litt.⁵: [**α**]_D²³ +68.2 (c 0.40, CHCl₃)]; **IR**: 3400, 3230, 2927, 2822, 1654, 1591, 1459, 1363, 1197, 1157, 1094, 1049, 1003, 954, 775 cm⁻¹; **¹H NMR** (400 MHz, acetone *d*⁶): δ: 8.40 (s, 1H), 6.76 (broad s, 1H), 6.62 (d, 1H, *J* = 3.1 Hz), 6.35 (app t, 1H, *J* = 11.3 Hz), 6.24 (broad s, 1H), 5.07 (broad s, 1H), 5.05 (broad s, 1H), 4.43 (broad d, 1H, *J* = 4.9 Hz), 3.77 (s, 3H), 3.67 (m, 2H), 3.55 (s, 3H), 3.47 (s, 3H), 3.30 (s, 3H), 3.24 (s, 3H), 3.18 (dd, 1H, *J* = 10.0 and *J* = 1.5 Hz), 3.11 (s, 3H), 3.00 (broad d, 1H, *J* = 5.8 Hz), 2.82 (s, 1H), 2.22 (broad s, 1H), 1.96 (d, 3H, *J* = 0.6 Hz), 1.61 (ddd syst AB, 1H, ²*J* = 14.0, *J* = 9.3 and *J* = 4.3 Hz), 1.32 (m, 1H), 1.15 (s, 3H), 0.95 (d, 3H, *J* = 6.5 Hz), 0.73 (d, 3H, *J* = 6.8 Hz).

(4E,6Z,8S,9S,10E,12S,13R,14S,16S,17R)-8,13,14,17-tetramethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate
(Herbimycin A):



To a stirring solution of macrolactame **24** (8 mg, 0.014 mmol, 1 equiv) in CH₂Cl₂ (2 mL) was added trichloroacetylisocyanate (10 mL, 0.08 mmol, 6 equiv). After 40 min at rt, the reaction mixture was concentrated and MeOH (1.5 mL) and K₂CO₃ (15 mg) were added. After 1.5 h at rt, MeOH was evaporated *in vacuo* and the residue was dissolved in Et₂O (10 mL). The organic layer was washed with water (1 mL) and brine (1 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated to provide the crude carbamate.

The crude carbamate was then dissolved in CH₃CN/H₂O (9/1, 5 mL) and an aqueous solution of cerium ammonium nitrate (1 N, 30 μL) was added at -10 °C. After 1 h at -10 °C, water (2 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (5 x 5 mL). The combined organic layers were dried with MgSO₄, filtered and concentrated. Purification of the

⁵ Carter, K. D.; Panek, J. S. *Org. Lett.* **2004**, *6*, 55-57.

residue by preparative TLC (EtOAc) provided Herbimycine A (2.9 mg, 36%) as a yellow solid. Physical and spectral data match those previously reported^{3,5} or those obtained from a commercially available sample.

$C_{30}H_{42}N_2O_9$; $M = 574 \text{ g.mol}^{-1}$; $R_f = 0.71$ (EtOAc); $[\alpha]_D^{20} +223$ (c 0.14, $CHCl_3$) [Commercially available Herbimycin A: $[\alpha]_D^{20} + 231$ (c 0.05, $CHCl_3$)]; **IR** : 3447, 3360, 2921, 2823, 1736, 1696, 1648, 1609, 1512, 1376, 1312, 1262, 1205, 1075, 999 cm^{-1} ; **1H NMR** (400 MHz): δ : 8.80 (broad s, 1H), 7.34 (d, 1H, $J = 2.5$ Hz), 6.97 (broad d, 1H, $J = 11.7$ Hz), 6.63 (dd, 1H, $J = 2.4$ and $J = 1.5$ Hz), 6.50 (app t, 1H, $J = 11.5$ Hz), 5.86 (dd, 1H, $J = 11.0$ et $J = 6.8$ Hz), 5.66 (broad s, 1H), 5.50 (broad s, 1H), 4.70 (broad s, 2H), 4.50 (broad s, 1H), 4.49 (broad s, 1H), 3.55-3.47 (2H), 3.53 (s, 3H), 3.34 (s, 6H), 3.31 (s, 3H), 2.65 (broad s, 1H), 2.01 (s, 3H), 1.74 (broad s, 1H), 1.65 (broad s, 3H), 1.62 (broad s, 1H), 1.56 (m, 1H), 1.09 (d, 3H, $J = 6.7$ Hz), 0.81 (d, 3H, $J = 6.9$ Hz); **^{13}C NMR** (100 MHz): δ : 188.1 (s), 184.3 (s), 168.9 (s), 155.9 (s), 144.9 (s), 138.4 (s), 137.0 (d), 134.8 (s), 132.8 (d), 131.7 (s), 130.0 (d), 128.4 (d), 125.8 (d), 113.2 (d), 83.6 (d), 82.7 (d), 79.3 (d), 78.5 (2d), 60.0 (q), 58.5 (q), 57.8 (q), 56.1 (q), 37.4 (d), 34.4 (d), 34.1 (t), 16.8 (q), 14.3 (q), 13.8 (q), 12.6 (q); **HRMS** (Cl^- , CH_4): Calcd for $C_{30}H_{46}N_3O_9$ ($M+NH_4^+$): 592.3234; Found: 592.3224.