# The Migrastatin Family: Discovery of Potent Cell Migration Inhibitors by Chemical Synthesis

Christoph Gaul,[a] Jón T. Njardarson,[a] Dandan Shan,[b] David C. Dorn,[c] Kai-Da Wu,[c] William P. Tong,[d] Xin-Yun Huang,[b] Malcolm A. S. Moore[c] and Samuel J. Danishefsky*[,a,e]

[a]*Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021,* [b]*Department of Physiology, Weill Medical College of Cornell University, 1300 York Avenue, New York, New York 10021,* [c]*Laboratory of Developmental Hematopoiesis, Cell Biology Program, Sloan-Kettering Institute for Cancer Research, New York, New York 10021*

[d]*Analytical Core Facility, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021,* [e]*Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, New York 10027*

**E-mail:s-danishefsky@ski.mskcc.org*

## Supporting Information

**Analytical Equipment**: Optical rotations were measured on a JASCO DIP-370 digital polarimeter at rt. Concentration (*c*) in g/100 ml and solvent are given in parentheses. Infrared spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer neat or as a film in $CHCl_3$ (NaCl plates). Absorption bands are noted in $cm^{-1}$. $^1$H- and $^{13}$C-NMR spectra were recorded on a Bruker AMX-400 or a Bruker DRX-500 spectrometer in $CDCl_3$. Chemical shifts ($\delta$-values) are reported in ppm with residual undeuterated $CHCl_3$ as the internal standard (referenced to 7.26 ppm for $^1$H-NMR and 77.0 ppm for $^{13}$C-NMR). Coupling constants (*J*) (H,H) are given in Hz, spectral splitting patterns are designated as singulet (s), doublet (d), triplet (t), quadruplet (q), multiplet or more overlapping signals (m), apparent (app), broad signal (br). Low resolution mass spectra (ionspray, a variation of electrospray) were acquired on a Perkin-Elmer Sciex API 100 spectrometer. Samples were introduced by direct infusion. High resolution mass spectra (fast atom bombardment, FAB) were acquired on a Micromass 70-SE-4F spectrometer. Flash chromatography (FC) was performed with E. Merck silica gel (60, particle size 0.040-0.063 mm). Preparative thin layer chromatography (TLC) was performed with Whatman Partisil Plates (10x10 cm, 60 Å, 200 μm).

**Techniques, Solvents, and Reagents**: Reactions involving air or moisture-sensitive reagents or intermediates were performed under argon or nitrogen atmosphere in glassware which had been heat gun or flame-dried under high vacuum. Indicated reaction temperatures refer to those of the reaction bath, while room temperature (rt) is noted as 22 °C. Preparative reactions were stirred magnetically. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), methylene chloride ($CH_2Cl_2$), and toluene were obtained from a dry solvent system (activated alumina columns, positive pressure of argon). All other solvents were used as received in Sure/Seal bottles (Aldrich). Triethylamine

($Et_3N$), diisopropylethylamine (*i*-$Pr_2NEt$), pyridine, 2,6-lutidine, and chlorotrimethylsilane (TMSCl) were distilled from $CaH_2$ immediately prior to use. All other reagents were purchased from Aldrich at the highest commercial quality and used without further purification, with the exception of the Stryker reagent which was purchased from Fluka, the RCM catalysts **16** and **17** which were purchased from Strem, and biotin-dPEG$_4$-hydrazide which was purchased from Quanta Biodesign.

**Vinyl Carbinol 19**: Compound **19** was prepared using a slightly modified literature procedure by Madsen.[1]

Preparation of the divinylzinc reagent: To vinylmagnesium bromide (294 mL, 294 mmol, 1.0M in THF) was added slowly a solution of anhydrous $ZnCl_2$ (20.0 g, 147 mmol, beads) in THF (100 mL) to yield a dark brown solution of divinylzinc in THF (with some precipitate).

Preparation of vinyl carbinol **19**: To a solution of dimethyl 2,3-*O*-isopropylidene-L-tartrate **18** (8.58 g, 39.3 mmol) in toluene (100 mL) at –78 °C was added slowly DIBALH (90 mL, 90.0 mmol, 1.0M in toluene). The reaction mixture turned into a white slurry during the course of the addition. After stirring for 3 h (the reaction temperature has to be kept at –78 °C to prevent overreduction), the divinylzinc solution as prepared above was added to the reaction mixture via cannula over 45 min. After stirring for another 30 min, the reaction mixture was warmed to rt and stirred for 4 h. The reaction mixture was then carefully (!) treated with saturated aqueous $NH_4Cl$ solution and 20% aqueous Na/K-tartrate solution. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 4:1) afforded vinyl carbinol **19** (6.28 g, 75%, diastereoselectivity > 90%) as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.04-5.94 (m, 2H), 5.40 (d, $J$ = 17.3, 2H), 5.30 (d, $J$ = 10.5, 2H), 4.19-4.16 (m, 2H), 3.89-3.87 (m, 2H), 2.91 (br s, 2H), 1.42 (s, 6H).

**1,2-Diol 20**: The preparation of compound **20** has been reported before by Chang,[2] but experimental details have not been provided.

To a solution of vinyl carbinol **19** (6.28 g, 29.2 mmol) in DMF (100 mL) at 0 °C was added NaH (2.58 g, 64.5 mmol, 60% dispersion in mineral oil) and, 5 min later, MeI (4.38 mL, 70.3 mmol). The reaction mixture was warmed to rt, stirred for 45 min, and then treated with 2M $NH_4OH$. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in MeOH (150 mL) and 2M HCl (50 mL) and heated to reflux for 2

[1] Jorgensen, M.; Iversen, E. H.; Paulsen, A. L.; Madsen, R. *J. Org. Chem.* **2001**, *66*, 4630.
[2] Lee, W. W.; Chang, S. *Tetrahedron: Asymmetry* **1999**, *10*, 4473.

h. The reaction mixture was cooled to rt, treated with saturated aqueous $Na_2CO_3$ solution and diluted with $Et_2O$. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 2:1) afforded 1,2-diol **20** (4.72 g, 80%) as a colorless oil. $[\alpha]_D$ +31.0° (*c* 1.77, $CHCl_3$); IR (neat) 3454, 3078, 2982, 2936, 2824, 1643, 1420, 1192, 1102, 992; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.77-5.71 (m, 2H), 5.36-5.32 (m, 4H), 3.81 (app t, *J* = 6.3, 2H), 3.76 (d, *J* = 5.5, 2H), 3.32 (s, 6H), 2.96 (br s, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.08, 119.27, 86.65, 71.23, 57.15; MS (ESI) 225 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{10}H_{18}O_4Na$ [M+$Na^+$] 225.1103, found 225.1079.

**Butadiene 3**: Compound **3** was prepared using modified literature procedures.[3]
To a suspension of NaH (4.40 g, 110 mmol, 60% dispersion in mineral oil) in toluene (90 mL) and MeOH (0.1 mL) at 0 °C was added a mixture of 3-pentanone (10.6 mL, 105 mmol) and methyl formate (8.00 mL, 130 mmol) over 1 hr. The reaction mixture was warmed to rt, stirred for another 3 h, and then diluted with $Et_2O$. The suspension was filtered and the precipitate was washed with $Et_2O$. The resulting crude sodium salt of 1-hydroxy-2-methyl-1-penten-3-one was dissolved in DMSO (100 mL) and $Me_2SO_4$ (9.16 mL, 97.0 mmol) was added at rt. After stirring for 30 min, the reaction mixture was treated with 2M $NH_4OH$ and diluted with $Et_2O$. The organic layer was separated, washed with $H_2O$ and saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure to afford 1-methoxy-2-methyl-1-penten-3-one (8.27 g, 74%). To a solution of 1-methoxy-2-methyl-1-penten-3-one (2.60 g, 20.3 mmol) in $Et_2O$ (12.0 mL) was added $Et_3N$ (7.08 mL, 50.8 mmol) and TMSOTf (3.68 mL, 20.3 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for another 3 h, and then poured onto a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure to afford butadiene **3** (3.66 g, 90%). $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 6.35 (s, 1H), 4.75 (q, *J* = 6.9, 1H), 3.63 (s, 3H), 1.66 (s, 3H), 1.62 (d, *J* = 6.9, 3H), 0.22 (s, 9H).

**Dihydropyrone 21**: To a solution of diol **20** (2.55 g, 12.6 mmol) in $CH_2Cl_2$ (130 mL) at 0 °C was added $Na_2CO_3$ (1.40 g, 13.2 mmol) and $Pb(OAc)_4$ (5.87 g, 13.2 mmol). The reaction mixture was warmed to rt, stirred for 25 min, and then treated with ethylene glycol (300 μL). After stirring for another 5 min, the reaction mixture was filtered through a Celite pad. The filtrate was washed with saturated aqueous $NaHCO_3$ solution and saturated aqueous NaCl solution and dried

[3] Danishefsky, S. J.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry Jr., P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

($MgSO_4$). The obtained solution of α-methoxy-α-vinyl aldehyde **2** in $CH_2Cl_2$ was cooled to –78 °C, and then $TiCl_4$ (2.77 mL, 25.2 mmol) and butadiene **3** (6.06 g, 30.3 mmol) were added. After stirring for 20 min, the reaction mixture was treated with MeOH (5 min), followed by the addition of saturated aqueous $NaHCO_3$ solution and 20% aqueous Na/K-tartrate solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (130 mL) and TFA (13 mL) and stirred for 1 hr. Toluene (50 mL) was added and the reaction mixture was concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 20:1 → 10:1 → 7:1) afforded dihydropyrone **21** (4.31 g, 87%) as a colorless oil. $[\alpha]_D$ +77.1° (*c* 2.00, $CHCl_3$); IR (neat) 2980, 2938, 2883, 2827, 1785, 1671, 1622, 1602, 1460, 1387, 1305, 1214, 1176, 1085, 1010; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.36 (s, 1H), 5.63-5.54 (m, 1H), 5.48-5.43 (m, 2H), 4.25 (dd, *J* = 8.6, 2.9, 1H), 3.88 (app t, *J* = 8.5, 1H), 3.37 (s, 3H), 2.44 (dq, *J* = 7.2, 2.9, 1H), 1.68 (s, 3H), 1.07 (d, *J* = 7.2, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 198.99, 160.75, 131.79, 122.06, 112.51, 82.69, 81.99, 56.37, 40.62, 10.42, 9.96; MS (ESI) 219 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{11}H_{16}O_3Na$ [M+$Na^+$] 219.0997, found 219.0991.

**Diol 25**: To a solution of dihydropyrone **21** (4.30 g, 21.9 mmol) in THF (50 mL) at –10 °C was added MeOH (977 μL, 24.1 mmol) and $LiBH_4$ (12.1 mL, 24.1 mmol, 2M in THF). After stirring for 10 min, the reaction mixture was carefully treated with 0.2M HCl (25 mL) and stirring was continued for another 20 min. Then the organic layer was separated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude alcohol **22** was dissolved in THF (280 mL) and $H_2O$ (28 mL), and champhorsulfonic acid (1.02 g, 4.38 mmol) was added. After refluxing for 2 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude lactol **23** was dissolved in THF (60 mL) and $H_2O$ (15 mL), and $LiBH_4$ (12.1 mL, 24.1 mmol, 2M in THF) was added at rt. After stirring for 15 min, the reaction mixture was treated with 0.2M HCl (35 mL) and stirring was continued for another 20 min. Then the organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 4:1 → 2:1 → 1:1) afforded diol **25** (2.34 g, 53%) as a colorless oil. $[\alpha]_D$ +40.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3621, 3565, 3444, 3012, 2934, 2868, 1449, 1393, 1238, 1083; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.74-5.67 (m, 1H), 5.33-5.25 (m, 2H), 5.16 (d, *J* = 10.2, 1H), 4.12 (d, *J* = 11.9, 1H), 3.95 (d, *J* = 11.9, 1H), 3.48 (dd, *J* = 8.1, 5.4, 1H), 3.26 (app t, *J* = 5.5, 1H), 3.23 (s, 3H), 2.74-2.68 (m, 1H),

2.57 (br s, 2H), 1.79 (d, $J$ = 1.4, 3H), 0.98 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.32, 135.20, 130.41, 119.51, 83.42, 77.44, 61.51, 55.93, 34.80, 21.89, 16.85; MS (ESI) 223 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{11}H_{20}O_3Na$ [M+$Na^+$] 223.1310, found 223.1301.

**Dimeric Acetal 24**: The Ferrier rearrangement described above was carried out at a concentration of 0.07M. When the Ferrier rearrangement was conducted at a concentration of 0.30M, the formation of a side product, which corresponds to dimeric acetal **24**, was observed. Compound **24** was isolated after FC (hexane/EtOAc 20:1 → 10:1) in 15-20% yield as a white crystalline solid. M.p. 83-85 °C; $[\alpha]_D$ –161.3° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3003, 2910, 2816, 1446, 1382, 1317, 1211, 1088, 965; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.67-5.59 (m, 4H), 5.39-5.28 (m, 6H), 3.93 (dd, $J$ = 8.4, 2.9, 2H), 3.57 (app t, $J$ = 8.2, 2H), 3.32 (s, 6H), 1.94-1.91 (m, 2H), 1.74 (s, 6H), 0.91 (d, $J$ = 6.8, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 134.66, 132.01, 129.40, 119.11, 93.37, 83.15, 72.19, 56.79, 30.44, 18.81, 12.78; MS (ESI) 401 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{22}H_{35}O_5$ [M+$H^+$] 379.2485, found 379.2486.

**Monoprotected Diol 26**: To a solution of diol **25** (364 mg, 1.82 mmol) in $CH_2Cl_2$ (8 mL) at rt was added 2,6-lutidine (530 µL, 4.55 mmol) and TBSOTf (961 µL, 4.19 mmol). After stirring for 20 min, the reaction mixture was treated with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 30:1) afforded the corresponding diprotected diol (731 mg, 94%) as a colorless oil. $[\alpha]_D$ +0.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2929, 2856, 1472, 1253, 1076; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.67-5.60 (m, 1H), 5.29-5.21 (m, 3H), 4.14 (d, $J$ = 11.8, 1H), 4.04 (d, $J$ = 11.8, 1H), 3.43 (dd, $J$ = 7.2, 2.9, 1H), 3.37 (app t, $J$ = 7.5, 1H), 3.21 (s, 3H), 2.60-2.56 (m, 1H), 1.72 (d, $J$ = 0.9, 3H), 0.91-0.89 (m, 21H), 0.05-0.04 (m, 12H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.44, 133.27, 131.41, 118.43, 86.20, 78.68, 61.91, 56.17, 33.85, 26.17, 25.93, 20.99, 18.56, 18.36, 14.13, –3.82, –4.80, –5.29; MS (ESI) 451 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{23}H_{48}O_3Si_2Na$ [M+$Na^+$] 451.3040, found 451.3054.

A solution of the diprotected diol (731 mg, 1.71 mmol) in HOAc (9 mL), THF (3 mL), and $H_2O$ (3 mL) was stirred at rt for 8 h. The reaction mixture was neutralized with solid $Na_2CO_3$ and diluted with $H_2O$ and $Et_2O$. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1 → 5:1) afforded monoprotected diol **26** (456 mg, 85%) as a colorless oil. $[\alpha]_D$ +3.8° (*c* 1.85, $CHCl_3$); IR (neat) 3352, 2957, 2930, 2857, 1472, 1462, 1250, 1127, 1081, 1028; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.73-5.66 (m, 1H), 5.30-5.24 (m, 3H), 4.12 (dd, $J$ = 11.8, 4.9, 1H), 4.00 (dd, $J$ = 11.8, 6.5, 1H),

3.48-3.43 (m, 2H), 3.22 (s, 3H), 2.69-2.61 (m, 1H), 1.78 (d, $J$ = 1.1, 3H), 1.68 (br t, 1H), 0.90-0.89 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.15, 133.05, 118.54, 85.89, 78.28, 61.76, 56.12, 34.23, 26.11, 25.64, 21.53, 18.49, 15.32, –3.88, –4.70; MS (ESI) 337 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{17}H_{34}O_3SiNa$ [M+Na$^+$] 337.2175, found 337.2162.

**Propionyl Oxazolidinone 28**: Compound **28** was prepared by reaction of (*R*)-(+)-4-benzyl-2-oxazolidinone with BuLi and propionyl chloride in THF according to standard literature procedures.[4]

**Aldol Product 29**: To a solution of alcohol **26** (189 mg, 0.601 mmol) in $CH_2Cl_2$ (4 mL) at rt was added Dess-Martin periodinane (280 mg, 0.661 mmol). After stirring for 50 min, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield crude aldehyde **27**. IR (neat) 2958, 2936, 2891, 2858, 1674, 1467, 1378, 1249, 1126, 1093, 1031; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 10.06 (s, 1H), 6.51 (dd, $J$ = 10.7, 1.5, 1H), 5.63 (ddd, $J$ = 17.4, 10.5, 7.9, 1H), 5.32-5.25 (m, 2H), 3.56 (dd, $J$ = 6.6, 3.8, 1H), 3.45 (app t, $J$ = 7.3, 1H), 3.42-3.35 (m, 1H), 3.20 (s, 3H), 1.75 (s, 3H), 1.03 (d, $J$ = 6.6, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 191.36, 153.37, 134.76, 133.96, 119.12, 85.73, 78.03, 56.21, 33.15, 26.05, 18.44, 16.37, 14.73, –3.84, –4.85.

The crude aldehyde **27** was dissolved in EtOAc (2 mL) and added to neat propionyl oxazolidinone **28** (210 mg, 0.902 mmol). The reaction mixture was then treated at rt with anhydrous $MgCl_2$ (57 mg, 0.601 mmol), $Et_3N$ (210 μL, 1.50 mmol), and TMSCl (153 μL, 1.20 mmol). After stirring for 36 h, the reaction mixture was filtered through a silica plug ($Et_2O$) and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in MeOH (3 mL), treated with TFA (1 drop) and stirred for 10 min. Toluene (3 mL) was added and the reaction mixture was concentrated under reduced pressure. Purification of the crude product by FC (hexane/ $CH_2Cl_2$ 1:1 → $CH_2Cl_2$) afforded aldol product **29** (219 mg, 67%) as a colorless oil. $[\alpha]_D$ –16.1° (*c* 1.77, $CHCl_3$); IR (neat) 3505, 2920, 2856, 1782, 1699, 1453, 1384, 1258, 1208, 1125, 1079, 1020; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.35-7.26 (m, 5H), 5.64 (ddd, $J$ = 17.6, 10.3, 7.6, 1H), 5.56 (d, $J$ = 10.2, 1H), 5.37 (dd, $J$ = 10.4, 1.8, 1H), 5.30 (dd, $J$ = 17.4, 1.8, 1H), 4.73-4.69 (m, 2H), 4.22-4.16 (m, 2H), 4.14-4.08 (m, 1H), 3.46 (dd, $J$ = 8.0, 1.8, 1H), 3.39 (app t, $J$ = 8.0, 1H), 3.36 (dd, $J$ = 14.1, 3.8, 1H), 3.21 (s, 3H), 2.81 (dd, $J$ = 13.6, 9.6, 1H), 2.75-2.68 (m, 1H), 2.39 (br s, 1H), 1.75 (s, 3H), 1.02 (d, $J$ = 7.0, 3H), 0.92 (s, 9H), 0.91 (d, $J$ = 6.0, 3H), 0.07

[4] Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(s, 3H), 0.04 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 176.48, 153.94, 135.68, 135.35, 134.76, 131.41, 129.52, 128.94, 127.29, 119.26, 86.43, 78.16, 72.78, 66.06, 56.01, 55.76, 41.09, 37.74, 33.44, 26.16, 18.60, 17.16, 14.48, 13.60, –3.74, –4.86; MS (ESI) 546 [M+H$^+$]; HRMS (FAB) calcd. for $C_{30}H_{48}NO_6Si$ [M+H$^+$] 546.3251, found 546.3251.

**Primary Alcohol 31**: To a solution of aldol product **29** (215 mg, 0.394) in $CH_2Cl_2$ (5 mL) at rt was added imidazole (107 mg, 1.58 mmol) and TESCl (198 μL, 1.18 mmol). After stirring for 12 h, the reaction mixture was treated with $H_2O$ and diluted with $CH_2Cl_2$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the TES-protected aldol product **30**. The crude product **30** was dissolved in THF (5 mL), and MeOH (64 μL, 0.394 mmol) and $LiBH_4$ (35 mg, 1.58 mmol) were added at rt. After stirring for 1 h, the reaction mixture was treated with 0.5M NaOH. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1) afforded primary alcohol **31** (159 mg, 83%) as a colorless oil. $[\alpha]_D$ +10.9° (*c* 2.38, $CHCl_3$); IR (neat) 3460, 2970, 2930, 2880, 1460, 1380, 1250, 1130, 1060, 1020; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.60-5.53 (m, 1H), 5.35-5.26 (m, 3H), 4.31 (d, *J* = 9.1, 1H), 3.68-3.58 (m, 2H), 3.42-3.34 (m, 2H), 3.20 (s, 3H), 3.13 (app d, *J* = 7.0, 1H), 2.65-2.59 (m, 1H), 1.94-1.88 (m, 1H), 1.67 (d, *J* = 1.2, 3H), 0.94 (t, *J* = 8.0, 9H), 0.93-0.91 (m, 12H), 0.70 (d, *J* = 7.1, 3H), 0.58 (q, *J* = 8.0, 6H), 0.04 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.10, 133.66, 133.46, 118.84, 86.46, 78.30, 76.58, 68.33, 56.08, 38.87, 33.24, 26.13, 18.58, 17.70, 14.25, 12.64, 6.75, 4.74, –3.85, –4.89; MS (ESI) 509 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{26}H_{54}O_4Si_2Na$ [M+Na$^+$] 509.3458, found 509.3468.

**Glutarimide Aldehyde 5**: Compound **5** was synthesized according to a literature procedure.[5]

**Enone 33**: To a solution of primary alcohol **31** (142 mg, 0.292 mmol) in $CH_2Cl_2$ (5 mL) at rt was added Dess-Martin periodinane (136 mg, 0.321 mmol). After stirring for 45 min, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. In a separate flask, dimethyl methylphosphonate (316 μL, 2.92 mmol) in THF (2 mL) at –78 °C was treated with BuLi (1.64 mL, 2.62 mmol, 1.6M in hexane). After stirring for 20

[5] Egawa, Y.; Suzuki, M.; Okuda, T. *Chem. Pharm. Bull.* **1963**, *11*, 589.

min, the crude aldehyde obtained from the Dess-Martin oxidation was dissolved in THF (1mL) and added to the reaction mixture. The reaction mixture was warmed to 0 °C, stirred for 15 min, and then treated with saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was dissolved in $CH_2Cl_2$ (5 mL), and Dess-Martin periodinane (136 mg, 0.321 mmol) was added at rt. After stirring for 20 min, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (1x) and EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude phosphonate **32** was put under high vacuum for 1 hr. To a solution of the crude product **32** in MeCN (5 mL) at rt was added anhydrous LiCl (25 mg, 0.583 mmol) and DBU (87 μL, 0.583 mmol). After stirring for 10 min, a solution of glutarimide aldehyde **5** (136 mg, 0.875 mmol) in MeCN (1 mL) was added. After stirring for 1 h, the reaction mixture was treated with saturated aqueous $NH_4Cl$ solution and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 4:1 → 2:1) afforded enone **33** (105 mg, 57%) as a colorless oil. $[\alpha]_D$ +4.4° (*c* 1.69, $CHCl_3$); IR (neat) 2955, 2931, 2877, 2855, 1722, 1698, 1628, 1461, 1377, 1288, 1254, 1128, 1066, 1035; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.91 (br s, 1H), 6.71-6.67 (m, 1H), 6.26 (d, *J* = 15.9, 1H), 5.65 (ddd, *J* = 17.4, 10.4, 8.4, 1H), 5.41-5.36 (m, 2H), 5.29 (dd, *J* = 17.4, 1.6, 1H), 4.62 (d, *J* = 9.3, 1H), 3.43 (app d, *J* = 7.2, 1H), 3.38-3.33 (m, 1H), 3.21 (s, 3H), 3.09-2.99 (m, 1H), 2.75-2.66 (m, 3H), 2.36-2.28 (m, 5H), 1.66 (s, 3H), 0.91 (s, 9H), 0.87-0.82 (m, 15H), 0.46 (q, *J* = 7.9, 6H), 0.05 (s, 3H), –0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 202.98, 171.17, 140.21, 134.99, 134.43, 134.09, 132.47, 119.18, 86.57, 78.53, 72.86, 55.97, 47.67, 37.47, 37.43, 37.27, 33.22, 29.82, 29.69, 26.13, 18.59, 14.18, 12.53, 6.76, 4.71, –3.83, –4.91; MS (ESI) 636 [M+H$^+$]; HRMS (FAB) calcd. for $C_{34}H_{62}NO_6Si_2$ [M+H$^+$] 636.4116, found 636.4116.

**Secondary Alcohol 34**: To a solution of enone **33** (101 mg, 0.159 mmol) in toluene (4.5 mL) at rt was added the Stryker reagent (156 mg, 0.079 mmol, dark red solid if quality is good). After stirring for 3.5 h, hexane (3 mL) was added, and the reaction mixture was exposed to air, stirred for 20 min, and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 6:1 → 2:1) afforded the corresponding saturated ketone as a colorless oil. $[\alpha]_D$ +7.7° (*c* 3.00, $CHCl_3$); IR (neat) 3217, 2954, 2932, 2877, 1713, 1459, 1377, 1253, 1126, 1061, 1035, 1006; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (br s, 1H), 5.63 (ddd, *J* = 17.0, 10.0, 8.2, 1H),

5.40-5.36 (m, 2H), 5.28 (dd, $J$ = 17.0, 1.8, 1H), 4.55 (d, $J$ = 9.4, 1H), 3.41 (dd, $J$ = 8.2, 1.2, 1H), 3.35 (app t, $J$ = 8.2, 1H), 3.19 (s, 3H), 2.82-2.64 (m, 4H), 2.60-2.41 (m, 2H), 2.29-2.23 (m, 2H), 2.18-2.10 (m, 1H), 1.62 (d, $J$ = 1.2, 3H), 1.61-1.53 (m, 2H), 1.43-1.34 (m, 2H), 0.92-0.90 (m, 12H), 0.86 (t, $J$ = 7.8, 9H), 0.77 (d, $J$ = 7.0, 3H), 0.46 (q, $J$ = 7.8, 6H), 0.03 (s, 3H), –0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 213.45, 172.06, 134.91, 134.57, 132.25, 119.24, 86.58, 78.52, 72.90, 55.94, 49.29, 44.53, 37.75, 34.32, 33.18, 30.44, 26.11, 19.97, 18.57, 17.16, 13.90, 12.46, 6.75, 4.71, –3.85, –4.93; MS (ESI) 638 [M+H$^+$]; HRMS (FAB) calcd. for $C_{34}H_{64}NO_6Si_2$ [M+H$^+$] 638.4272, found 638.4273.

A solution of the saturated ketone in HOAc (3 mL), THF (1 mL), and $H_2O$ (1 mL) was stirred at rt for 2 h. The reaction mixture was neutralized with solid $Na_2CO_3$ and diluted with $H_2O$ and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 4:1 → 1:1) afforded secondary alcohol **34** (68 mg, 82%) as a white foam. $[\alpha]_D$ +1.0° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3601, 3366, 3035, 2931, 2861, 1708, 1455, 1378, 1249, 1120, 1026; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 8.22 (br s, 1H), 5.63-5.56 (m, 1H), 5.48 (d, $J$ = 9.3, 1H), 5.33 (dd, $J$ = 10.3, 1.5, 1H), 5.27 (dd, $J$ = 17.2, 1.5, 1H), 4.60 (d, $J$ = 9.8, 1H), 3.42-3.35 (m, 2H), 3.18 (s, 3H), 2.79-2.63 (m, 4H), 2.58-2.54 (m, 2H), 2.29-2.23 (m, 2H), 2.18-2.10 (m, 1H), 1.95 (br s, 1H), 1.67 (d, $J$ = 1.0, 3H), 1.66-1.59 (m, 2H), 1.42-1.37 (m, 2H), 0.91 (s, 9H), 0.89 (d, $J$ = 6.6, 3H), 0.87 (d, $J$ = 7.1, 3H), 0.05 (s, 3H), 0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 214.01, 172.21, 135.51, 134.72, 131.56, 119.19, 86.30, 78.26, 71.69, 55.98, 48.87, 42.70, 37.73, 37.70, 34.08, 33.26, 30.32, 26.11, 20.07, 18.55, 17.35, 13.87, 13.63, –3.79, –4.90; MS (ESI) 546 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{28}H_{49}NO_6SiNa$ [M+Na$^+$] 546.3227, found 546.3227.

**2,6-Heptadienoic Acid 6**: Compound **6** can be prepared by γ-alkylation of crotonic acid with allyl bromide.[6] However, it was found that the procedure described below is more convenient for larger scale preparations of 2,6-heptadienoic acid **6.**

To a solution of oxalyl chloride (3.36 mL, 39.2 mmol) in $CH_2Cl_2$ (100 mL) at –78 °C was added DMSO (5.56 mL, 78.3 mmol). After stirring for 5 min, 4-penten-1-ol (2.00 mL, 19.6 mmol) was added, and after another 15 min $Et_3N$ (13.6 mL, 97.9 mmol) was added. The reaction mixture was warmed to rt and then treated with 0.1M HCl. The organic layer was separated, washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and treated with $Ph_3PCHCO_2t$-Bu (7.38 g, 19.6 mmol) at rt. The reaction mixture was stirred for 5 h and then treated with saturated aqueous

[6] Katzenellenbogen, J. A.; Crumrine, A. L. *J. Am. Chem. Soc.* **1976**, *98*, 4925; Ahmar, M.; Duyck, C.; Fleming I. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2721.

$NH_4Cl$ solution and diluted with $CH_2Cl_2$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was filtered through a silica plug ($CH_2Cl_2$/pentane 1:1) to give *t*-butyl (*E*)-2,6-heptadienoate. To a solution of this ester in $CH_2Cl_2$ (40 mL) was added TFA (5 mL) at rt. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 15:1 → 5:1) afforded 2,6-heptadienoic acid **6** (1.67 g, 68%) as a colorless oil. $^1$H-NMR (400 MHz, $CDCl_3$) $\delta$ 7.12-7.05 (m, 1H), 5.88-5.76 (m, 2H), 5.08-5.02 (m, 2H), 2.37-2.32 (m, 2H), 2.26-2.21 (m, 2H).

**Formation of the mixed anhydride**: To a solution of 2,6-heptadienoic acid **6** (68 mg, 0.535 mmol) in toluene (1 mL) at rt was added 2,4,6-trichlorobenzoyl chloride (84 μL, 0.535 mmol) and *i*-$Pr_2$NEt (89 μL, 0.508 mmol). The reaction mixture was stirred for 3 h and then used as it is as a stock solution (0.54M) for the subsequent acylation reactions.

**Unsaturated Ester 35**: To a solution of alcohol **34** (41 mg, 0.078 mmol) in toluene (0.1 mL) at rt was added pyridine (25 μL, 0.313 mmol) and the mixed anhydride[7] (460 μL, 0.235 mmol, 0.54M in toluene). After stirring for 24 h, the reaction mixture was directly loaded onto a silica column and purified by FC (hexane/EtOAc 10:1 → 4:1 → 2:1) to afford unsaturated ester **35** (33 mg, 67%) as a colorless oil. $[\alpha]_D$ –29.0° (*c* 1.00, $CHCl_3$); IR (neat) 3214, 3081, 2930, 2856, 1722, 1452, 1377, 1256, 1126, 1028; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.87 (br s, 1H), 6.89 (app dt, *J* = 15.5, 6.8, 1H), 5.81-5.62 (m, 4H), 5.61 (dd, *J* = 10.3, 1.2, 1H), 5.38 (dd, *J* = 10.3, 1.8, 1H), 5.32 (dd, *J* = 17.3, 1.4, 1H), 5.03-4.98 (m, 2H), 3.43-3.39 (m, 2H), 3.21 (s, 3H), 3.00-2.85 (m, 2H), 2.72-2.68 (m, 2H), 2.56-2.44 (m, 2H), 2.30-2.24 (m, 4H), 2.23-2.08 (m, 3H), 1.62 (s, 3H), 1.61-1.58 (m, 2H), 1.36-1.32 (m, 2H), 0.94 (app t, *J* = 7.2, 6H), 0.90 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 211.20, 171.83, 164.68, 148.92, 137.72, 136.96, 134.57, 127.00, 121.15, 119.23, 115.60, 86.28, 78.39, 73.79, 56.03, 47.39, 41.45, 37.72, 34.16, 33.84, 31.97, 31.46, 30.40, 26.21, 26.13, 20.10, 18.59, 17.70, 13.72, 12.66, –3.76, –4.94; MS (ESI) 654 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{35}H_{57}NO_7SiNa$ [M+$Na^+$] 654.3826, found 654.3835.

**TBS-Migrastatin 37**: To a solution of unsaturated ester **35** (29 mg, 0.046 mmol) in refluxing toluene (100 mL) was added Grubbs-II catalyst **16** (8 mg, 0.0092 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 1:3). Purification of the crude product by FC (hexane/EtOAc 5:1 → 2:1 → 1:1) afforded TBS-

[7] See above for the preparation of a stock solution of the mixed anhydride in toluene.

migrastatin **37** (19 mg, 69%) as a white solid. $[\alpha]_D$ +13.7° (*c* 0.50, $CHCl_3$); $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.77 (br s, 1H), 6.54-6.48 (m, 1H), 5.59 (d, *J* = 15.7, 1H), 5.56 (d, *J* = 10.7, 1H), 5.51-5.45 (m, 1H), 5.22 (dd, *J* = 15.4, 4.6, 1H), 5.08 (d, *J* = 9.5, 1H), 3.39 (dd, *J* = 8.1, 4.6, 1H), 3.19 (s, 3H), 3.03 (app d, *J* = 7.8, 1H), 2.98-2.92 (m, 1H), 2.91-2.85 (m, 1H), 2.73-2.68 (m, 2H), 2.50 (app t, *J* = 6.9, 2H), 2.44-2.40 (m, 2H), 2.29-2.09 (m, 5H), 1.81 (d, *J* = 1.1, 3H), 1.64-1.57 (m, 2H), 1.37-1.31 (m, 2H), 1.11 (d, *J* = 7.2, 3H), 0.92-0.90 (m, 12H), 0.04 (s, 3H), –0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.81, 171.82, 163.80, 150.36, 133.94, 130.17, 129.49, 128.78, 121.88, 83.37, 79.25, 76.82, 56.68, 51.15, 40.24, 37.70, 37.68, 34.17, 33.47, 31.15, 30.36, 30.27, 26.29, 20.12, 18.63, 13.61, 13.30, –3.61, –4.95; MS (ESI) 626 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{33}H_{53}NO_7SiNa$ [M+$Na^+$] 626.3489, found 626.3489.

**Migrastatin 1**: To a solution of TBS-migrastatin **37** (19 mg, 0.032 mmol) in THF (1.5 mL) at rt was added HF•pyridine (0.25 mL). After stirring for 15 h, the reaction mixture was carefully treated with MeOTMS (3 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 2:1 → 1:1 → 1:2) afforded migrastatin **1** (13 mg, 85%) as a white solid. $[\alpha]_D$ +12.6° (*c* 0.50, MeOH); $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.82 (br s, 1H), 6.49 (ddd, *J* = 15.7, 10.5, 3.7, 1H), 5.64 (dd, *J* = 10.7, 1.2, 1H), 5.58 (dd, *J* = 15.7, 1.2, 1H), 5.54-5.48 (m, 1H), 5.24 (dd, *J* = 15.5, 4.7, 1H), 5.08 (d, *J* = 10.0, 1H), 3.47 (dd, *J* = 8.7, 4.7, 1H), 3.30 (s, 3H), 3.03 (dd, *J* = 8.7, 1.7, 1H), 2.99-2.87 (m, 2H), 2.80 (br s, 1H), 2.73-2.68 (m, 2H), 2.50 (app t, *J* = 6.9, 2H), 2.44-2.39 (m, 2H), 2.28-2.17 (m, 4H), 2.16-2.08 (m, 1H), 1.86 (d, *J* = 1.2, 3H), 1.69-1.55 (m, 2H), 1.41-1.30 (m, 2H), 1.12 (d, *J* = 7.2, 3H), 0.96 (d, *J* = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.88, 171.78, 163.86, 150.01, 132.99, 131.17, 130.46, 127.87, 122.08, 82.39, 77.92, 76.92, 56.93, 51.18, 39.88, 37.68, 37.66, 34.12, 31.93, 31.08, 30.34, 30.09, 25.99, 20.09, 13.39; MS (ESI) 512 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{27}H_{39}NO_7Na$ [M+$Na^+$] 512.2624, found 512.2604.

**6-Heptenoyl Chloride 38**: To a solution of 6-heptenoic acid (251 μL, 1.85 mmol) in $CH_2Cl_2$ (5 mL) at rt was added oxalyl chloride (476 μL, 5.55 mmol) and DMF (1 drop). After stirring for 1 hr, the reaction mixture was concentrated under reduced pressure and put under high vacuum for 15 min. The residual yellow oil was dissolved in $CH_2Cl_2$ (3 mL) and used as a stock solution (0.62M) for the subsequent acylation reactions.

**Ester 39**: To a solution of alcohol **34** (37 mg, 0.070 mmol) in $CH_2Cl_2$ (2 mL) at rt was added DMAP (17 mg, 0.139 mmol) and 6-heptenoyl chloride[8] **38** (202 μL, 0.125 mmol, 0.62M in $CH_2Cl_2$). After stirring for 2 h, the reaction mixture was treated with 0.1M HCl and diluted with

[8] See above for the preparation of a stock solution of 6-heptenoyl chloride **38** in $CH_2Cl_2$.

$CH_2Cl_2$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1 → 4:1 → 2:1) afforded ester **39** (31 mg, 69%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 8.22 (br s, 1H), 5.79-5.72 (m, 1H), 5.67-5.61 (m, 2H), 5.55 (d, *J* = 10.3, 1H), 5.36 (dd, *J* = 10.3, 1.3, 1H), 5.30 (d, *J* = 17.1, 1H), 5.00-4.92 (m, 2H), 3.40-3.37 (m, 2H), 3.20 (s, 3H), 2.93-2.85 (m, 2H), 2.71 (dd, *J* = 17.0, 4.0, 2H), 2.55-2.42 (m, 2H), 2.29-2.21 (m, 2H), 2.19-2.11 (m, 3H), 2.09-2.00 (m, 2H), 1.60 (s, 3H), 1.59-1.51 (m, 5H), 1.47-1.42 (m, 1H), 1.38-1.32 (m, 2H), 0.92-0.90 (m, 15H), 0.05 (s, 3H), –0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 211.06, 172.07, 171.68, 138.28, 137.75, 134.48, 126.86, 119.24, 114.73, 86.25, 78.39, 73.62, 56.01, 47.13, 41.67, 37.70, 34.18, 34.08, 33.78, 33.28, 30.41, 28.21, 28.18, 26.11, 24.38, 20.12, 18.56, 17.61, 13.73, 12.64, –3.78, –4.97; MS (ESI) 656 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{35}H_{59}NO_7SiNa$ [M+$Na^+$] 656.3959, found 656.3956.

**TBS-2,3-Dihydromigrastatin 40**: To a solution of ester **39** (31 mg, 0.048 mmol) in refluxing toluene (100 mL) was added Grubbs-II catalyst **16** (8 mg, 0.0094 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 1:3). Purification of the crude product by FC (hexane/EtOAc 5:1 → 2:1 → 1:1) afforded TBS-2,3-dihydromigrastatin **40** (23 mg, 79%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.90 (br s, 1H), 5.65-5.57 (m, 2H), 5.35 (dd, *J* = 15.7, 5.1, 1H), 5.20 (d, *J* = 9.2, 1H), 3.43-3.40 (m, 1H), 3.23-3.20 (m, 1H), 3.21 (s, 3H), 3.03-2.98 (m, 1H), 2.95-2.91 (m, 1H), 2.73-2.69 (m, 2H), 2.59-2.43 (m, 2H), 2.33-2.22 (m, 4H), 2.17-2.07 (m, 3H), 1.75 (d, *J* = 0.9, 3H), 1.61-1.55 (m, 5H), 1.40-1.35 (m, 3H), 1.07 (d, *J* = 7.2, 3H), 0.94 (d, *J* = 6.8, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.63, 171.84, 171.80, 134.70, 131.22, 129.51, 128.39, 82.98, 79.10, 76.46, 56.49, 51.24, 40.62, 37.74, 37.69, 34.18, 33.35, 33.18, 31.11, 30.37, 26.29, 25.76, 25.16, 22.80, 20.18, 18.71, 13.66, 13.12, –3.56, –4.97; MS (ESI) 628 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{33}H_{55}NO_7Na$ [M+$Na^+$] 628.3646, found 628.3644.

**2,3-Dihydromigrastatin 41**: To a solution of TBS-2,3-dihydromigrastatin **40** (23 mg, 0.038 mmol) in THF (1.5 mL) at rt was added HF•pyridine (0.3 mL). After stirring for 15 h, the reaction mixture was carefully treated with MeOTMS (4 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 2:1 → 1:1 → 1:2) afforded 2,3-dihydromigrastatin **41** (15 mg, 81%) as a white foam. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.97 (br s, 1H), 5.68-5.60 (m, 2H), 5.34 (dd, *J* = 15.6, 5.6, 1H), 5.19 (d, *J* = 9.7, 1H), 3.49-3.46 (m, 1H), 3.33 (s, 3H), 3.22 (app d, *J* = 9.1, 1H), 3.07-3.00 (m, 1H), 2.98-2.91 (m, 1H), 2.72 (dd, *J* = 17.1, 2.3, 2H), 2.59-2.50 (m, 1H), 2.49-2.40 (m, 1H), 2.30-2.04 (m, 7H), 1.79 (d, *J* = 1.3, 3H), 1.63-1.56 (m, 4H), 1.55-1.48 (m, 1H), 1.42-1.35 (m, 3H), 1.09 (d, *J* = 7.2, 3H), 0.99 (d, *J* = 6.9,

3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.64, 171.88, 171.73, 133.95, 132.35, 130.27, 128.05, 81.92, 77.42, 76.45, 56.70, 51.38, 40.37, 37.73, 37.68, 34.15, 32.50, 31.72, 30.45, 30.35, 25.94, 24.80, 22.33, 20.16, 13.22, 13.20; MS (ESI) 514 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{27}H_{41}NO_7Na$ [M+$Na^+$] 514.2781, found 514.2768.

***N*-Methyl-2,3-Dihydromigrastatin 42**: To a solution of 2,3-dihydromigrastatin **41** (4 mg, 0.0081 mmol) in acetone (0.4 mL) at rt was added MeI (excess) and $Cs_2CO_3$ (excess). After stirring for 4 h, the reaction mixture was concentrated under reduced pressure to a volume of ca. 0.2 mL. Purification of the residual solution by preparative TLC (hexane/EtOAc 1:2) afforded *N*-methyl-2,3-dihydromigrastatin **42** (3.5 mg, 85%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.68-5.61 (m, 2H), 5.34 (dd, $J$ = 15.6, 5.6, 1H), 5.19 (d, $J$ = 9.6, 1H), 3.49-3.46 (m, 1H), 3.33 (s, 3H), 3.22 (app d, $J$ = 9.1, 1H), 3.14 (s, 3H), 3.07-3.01 (m, 1H), 2.95-2.89 (m, 1H), 2.82-2.78 (m, 2H), 2.58-2.50 (m, 1H), 2.49-2.42 (m, 1H), 2.33-2.27 (m, 2H), 2.25-2.04 (m, 5H), 1.79 (d, $J$ = 1.3, 3H), 1.65-1.52 (m, 5H), 1.47-1.42 (m, 1H), 1.37-1.31 (m, 2H), 1.09 (d, $J$ = 7.2, 3H), 0.99 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.67, 172.20, 171.72, 133.93, 132.35, 130.33, 128.06, 81.92, 77.45, 76.47, 56.72, 51.38, 40.44, 38.75, 38.71, 34.27, 32.51, 31.73, 30.47, 29.34, 26.36, 25.94, 24.81, 22.33, 20.09, 13.23; MS (ESI) 528 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{28}H_{43}NO_7Na$ [M+$Na^+$] 528.2937, found 528.2939.

**Unsaturated Ester 43**: To a solution of alcohol **26** (109 mg, 0.346 mmol) in toluene (1 mL) at rt was added pyridine (84 μL, 1.04 mmol) and the mixed anhydride[9] (1 mL, 0.535 mmol, 0.54M in toluene). After stirring for 12 h, the reaction mixture was filtered through a silica plug (hexane/EtOAc 30:1). Purification of the crude product by FC (pentane/$CH_2Cl_2$ 3:1 → 2:1) afforded unsaturated ester **43** (70 mg, 48%) as a colorless oil. $[\alpha]_D$ +2.6° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2934, 2882, 2851, 1705, 1653, 1470, 1381, 1246, 1126, 1079, 1026; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 6.99-6.93 (m, 1H), 5.86-5.76 (m, 2H), 5.66-5.59 (m, 1H), 5.44 (d, $J$ = 9.5, 1H), 5.29-5.22 (m, 2H), 5.07-4.99 (m, 2H), 4.61 (d, $J$ = 12.1, 1H), 4.57 (d, $J$ = 12.1, 1H), 3.47 (dd, $J$ = 7.2, 2.9, 1H), 3.37 (app t, $J$ = 7.7, 1H), 3.19 (s, 3H), 2.63-2.59 (m, 1H), 2.33-2.28 (m, 2H), 2.24-2.19 (m, 2H), 1.73 (d, $J$ = 1.3, 3H), 0.91 (d, $J$ = 6.6, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 166.57, 148.47, 137.05, 135.58, 135.10, 128.21, 121.52, 118.79, 115.53, 86.26, 78.37, 63.07, 56.06, 34.26, 32.02, 31.48, 26.15, 21.49, 18.54, 13.96, –3.80, –4.85; MS (ESI) 445 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{24}H_{43}O_4Si$ [M+$H^+$] 423.2931, found 423.2929.

**TBS-Migrastatin Core 44**: To a solution of unsaturated ester **43** (35 mg, 0.083 mmol) in refluxing toluene (125 mL) was added Grubbs-II catalyst **16** (14 mg, 0.017 mmol). After stirring

[9] See above for the preparation of a stock solution of the mixed anhydride in toluene.

for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 4:1). Purification of the crude product by FC (hexane/EtOAc 20:1) afforded TBS-migrastatin core **44** (18 mg, 55%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 6.85-6.79 (m, 1H), 5.74 (d, $J$ = 15.9, 1H), 5.56-5.50 (m, 2H), 5.12 (dd, $J$ = 15.5, 8.7, 1H), 4.68 (d, $J$ = 15.8, 1H), 4.62 (d, $J$ = 15.8, 1H), 3.44 (dd, $J$ = 8.3, 1.4, 1H), 3.33-3.30 (m, 1H), 3.17 (s, 3H), 3.03-2.97 (m, 1H), 2.47-2.36 (m, 2H), 2.31-2.24 (m, 1H), 2.21-2.14 (m, 1H), 1.64 (s, 3H), 0.92 (s, 9H), 0.83 (d, $J$ = 6.8, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 165.37, 149.91, 131.98, 130.48, 126.58, 121.83, 117.57, 85.82, 77.49, 65.56, 55.83, 33.11, 32.46, 30.01, 26.27, 22.17, 18.71, 12.90, –3.57, –5.02; MS (ESI) 417 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{22}H_{38}O_4SiNa$ [M+Na$^+$] 417.2437, found 417.2456.

**Migrastatin Core 45**: To a solution of TBS-migrastatin core **44** (18 mg, 0.0457 mmol) in THF (1.5 mL) at rt was added HF•pyridine (0.3 mL). After stirring for 14 h, the reaction mixture was carefully treated with MeOTMS (4 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1 → 5:1) afforded migrastatin core **45** (8.5 mg, 66%) as a colorless oil. $[\alpha]_D$ +106.0° ($c$ 0.50, $CHCl_3$); IR ($CHCl_3$) 3567, 2933, 2881, 1716, 1602, 1448, 1393, 1255, 1107, 1052; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 6.81-6.75 (m, 1H), 5.73 (d, $J$ = 15.9, 1H), 5.62-5.55 (m, 2H), 5.14 (dd, $J$ = 15.2, 6.8, 1H), 4.72 (d, $J$ = 15.6, 1H), 4.63 (d, $J$ = 15.6, 1H), 3.42-3.38 (m, 2H), 3.28 (s, 3H), 3.03-2.97 (m, 1H), 2.69 (br s, 1H), 2.47-2.38 (m, 2H), 2.32-2.18 (m, 2H), 1.68 (s, 3H), 0.88 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 165.36, 149.52, 133.85, 129.79, 129.51, 127.50, 122.15, 84.62, 76.09, 65.40, 56.25, 32.20, 31.34, 29.99, 22.27, 12.66; MS (ESI) 303 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{16}H_{24}O_4Na$ [M+Na$^+$] 303.1571, found 303.1572.

**Ester 46**: To a solution of alcohol **26** (275 mg, 0.874 mmol) in $CH_2Cl_2$ (3 mL) at rt was added DMAP (214 mg, 1.75 mmol) and 6-heptenoyl chloride[10] **38** (2.5 mL, 1.57 mmol, 0.62M in $CH_2Cl_2$). After stirring for 20 min, the reaction mixture was treated with 0.1M HCl and diluted with $CH_2Cl_2$. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 30:1) afforded ester **46** (302 mg, 82%) as a colorless oil. $[\alpha]_D$ +3.0° ($c$ 0.50, $CHCl_3$); IR ($CHCl_3$) 2980, 2933, 2863, 1722, 1458, 1382, 1252, 1112, 1024; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.83-5.75 (m, 1H), 5.66-5.59 (m, 1H), 5.43 (d, $J$ = 9.5, 1H), 5.30-5.23 (m, 2H), 5.03-4.94 (m, 2H), 4.56 (d, $J$ = 12.0, 1H), 4.51 (d, $J$ = 12.0, 1H), 3.46 (dd, $J$ = 7.2, 2.9, 1H), 3.37 (app t, $J$ = 7.7, 1H), 3.20 (s, 3H), 2.61-2.57 (m, 1H), 2.32 (app t, $J$ = 7.5, 2H), 2.06 (app q, $J$ = 7.2, 2H), 1.74 (d, $J$ = 1.2, 3H), 1.68-1.62 (m, 2H), 1.45-

[10] See above for the preparation of a stock solution of 6-heptenoyl chloride **38** in $CH_2Cl_2$.

1.39 (m, 2H), 0.91 (s, 9H), 0.90 (d, $J$ = 6.5, 3H), 0.05 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.65, 138.40, 135.59, 135.10, 128.12, 118.77, 114.67, 86.24, 78.36, 63.11, 56.07, 34.24, 34.17, 33.35, 28.35, 26.15, 24.46, 21.45, 18.54, 13.98, –3.80, –4.85; MS (ESI) 447 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{24}H_{44}O_4SiNa$ [M+Na$^+$] 447.2906, found 447.2893.

**TBS-Macrolactone 47**: To a solution of ester **46** (95 mg, 0.224 mmol) in refluxing toluene (450 mL) was added Grubbs-II catalyst **16** (38 mg, 0.045 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 5:1). Purification of the crude product by FC (hexane/EtOAc 30:1) afforded TBS-macrolactone **47** (67 mg, 76%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.71-5.65 (m, 1H), 5.56 (d, $J$ = 10.0, 1H), 5.28 (dd, $J$ = 15.7, 8.0, 1H), 4.52 (d, $J$ = 13.9, 1H), 4.35 (d, $J$ = 13.9, 1H), 3.46 (dd, $J$ = 7.7, 2.6, 1H), 3.39 (app t, $J$ = 7.8, 1H), 3.20 (s, 3H), 2.85-2.82 (m, 1H), 2.42-2.36 (m, 1H), 2.26-2.20 (m, 1H), 2.18-2.14 (m, 1H), 2.11-2.06 (m, 1H), 1.77-1.72 (m, 1H), 1.71 (d, $J$ = 1.1, 3H), 1.62-1.50 (m, 2H), 1.46-1.40 (m, 1H), 0.91 (s, 9H), 0.88 (d, $J$ = 6.8, 3H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.74, 134.81, 133.62, 128.75, 126.14, 85.42, 77.78, 65.01, 55.97, 34.31, 34.01, 29.37, 27.34, 26.16, 23.36, 23.09, 18.58, 13.86, –3.78, –4.96; MS (ESI) 419 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{22}H_{40}O_4SiNa$ [M+Na$^+$] 419.2594, found 419.2601.

**Macrolactone 48**: To a solution of TBS-macrolactone **47** (179 mg, 0.452 mmol) in THF (6 mL) at rt was added HF•pyridine (in the beginning: 0.6 mL, after a total of 15 h: an additional 0.6 mL, after a total of 25 h: an additional 0.3 mL). After stirring for a total of 40 h, the reaction mixture was carefully treated with MeOTMS (12 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1 → 5:1) afforded macrolactone **48** (120 mg, 94%) as a white crystalline solid. $[\alpha]_D$ +115.3° ($c$ 1.00, $CHCl_3$); IR ($CHCl_3$) 3567, 3016, 2933, 2858, 1724, 1450, 1387, 1317, 1258, 1145, 1115, 979; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.74-5.67 (m, 2H), 5.23 (dd, $J$ = 15.7, 7.7, 1H), 4.54 (d, $J$ = 13.1, 1H), 4.29 (d, $J$ = 13.1, 1H), 3.46-3.39 (m, 2H), 3.30 (s, 3H), 2.82-2.77 (m, 1H), 2.44-2.39 (m, 1H), 2.26-2.15 (m, 2H), 2.03-1.97 (m, 1H), 1.74 (d, $J$ = 0.9, 3H), 1.74-1.70 (m, 1H), 1.60-1.52 (m, 2H), 1.36-1.32 (m, 1H), 0.93 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.69, 135.19, 134.39, 129.02, 127.14, 83.82, 75.91, 64.76, 56.34, 34.23, 32.06, 29.88, 27.20, 23.40, 23.27, 12.81; MS (ESI) 305 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{16}H_{26}O_4Na$ [M+Na$^+$] 305.1719, found 305.1729.

**Acetylated Macrolactone 49**: To a solution of macrolactone **48** (4.5 mg, 0.016 mmol) in $CH_2Cl_2$ (0.75 mL) at rt was added DMAP (6 mg, 0.048 mmol) and AcCl (3.5 μL, 0.048 mmol). After stirring for 24 h, the reaction mixture was concentrated under reduced pressure to a volume of ca. 0.2 mL. Purification of the residual solution by preparative TLC (hexane/EtOAc 2:1)

afforded the acetylated macrolactone **49** (4 mg, 76%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.78-5.72 (m, 1H), 5.37 (dd, $J$ = 15.7, 8.2, 1H), 5.28 (d, $J$ = 10.0, 1H), 4.89 (dd, $J$ = 8.0, 3.6, 1H), 4.56 (d, $J$ = 13.2, 1H), 4.32 (d, $J$ = 13.2, 1H), 3.57 (app t, $J$ = 8.1, 1H), 3.23 (s, 3H), 3.02-2.97 (m, 1H), 2.46-2.41 (m, 1H), 2.25-2.19 (m, 2H), 2.11 (s, 3H), 2.10-2.05 (m, 1H), 1.81-1.75 (m, 1H), 1.71 (d, $J$ = 0.9, 3H), 1.61-1.53 (m, 2H), 1.43-1.39 (m, 1H), 0.95 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.61, 170.82, 135.23, 132.14, 127.76, 82.63, 76.83, 64.69, 56.46, 34.30, 32.10, 29.58, 27.02, 23.39, 23.04, 21.10, 14.85; MS (ESI) 347 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{18}H_{28}O_5Na$ [M+Na$^+$] 347.1834, found 347.1848.

**Oxidized Macrolactone 50**: To a solution of macrolactone **48** (7 mg, 0.025 mmol) in $CH_2Cl_2$ (1.5 mL) at rt was added Dess-Martin periodinane (12 mg, 0.027 mmol). After stirring for 4 h, the reaction mixture was concentrated under reduced pressure to a volume of ca. 0.2 mL. Purification of the residual solution by preparative TLC (hexane/EtOAc 1:1) afforded oxidized macrolactone **50** (5 mg, 72%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.92-5.86 (m, 1H), 5.73 (d, J = 9.9, 1H), 5.34 (dd, $J$ = 15.5, 8.0, 1H), 4.54 (d, $J$ = 11.6, 1H), 4.37 (d, $J$ = 8.0, 1H), 4.31 (d, $J$ = 11.6, 1H), 3.71-3.65 (m, 1H), 3.32 (s, 3H), 2.41-2.36 (m, 1H), 2.27-2.21 (m, 1H), 2.20-2.16 (m, 1H), 2.06-1.99 (m, 1H), 1.81 (s, 3H), 1.68-1.60 (m, 2H), 1.58-1.51 (m, 1H), 1.41-1.33 (m, 1H), 1.19 (d, $J$ = 7.1, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 207.91, 173.74, 138.30, 130.64, 130.42, 124.64, 86.15, 62.75, 56.65, 41.61, 34.04, 30.35, 26.64, 23.40, 23.18, 18.89; MS (ESI) 303 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{16}H_{24}O_4Na$ [M+Na$^+$] 303.1572, found 303.1588.

**Hydrolyzed Core 51**: To a solution of macrolactone **48** (5 mg, 0.018 mmol) in MeOH (1.5 mL) at rt was added 0.5M NaOH (0.3 mL). After stirring for 2 h, the reaction mixture was concentrated under reduced pressure to a volume of ca. 0.5 mL, diluted with $CH_2Cl_2$, and acidified with 1M HCl (2 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to afford hydrolyzed core **51** (4 mg, 77%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.75-5.70 (m, 1H), 5.34 (dd, $J$ = 15.5, 8.7, 1H), 5.23 (d, $J$ = 10.1, 1H), 4.15 (d, $J$ = 11.8, 1H), 3.97 (d, $J$ = 11.8, 1H), 3.47-3.44 (m, 1H), 3.29-3.26 (m, 1H), 3.23 (s, 3H), 2.74-2.69 (m, 1H), 2.36 (app t, $J$ = 7.4, 2H), 2.14 (app q, $J$ = 7.1, 2H), 1.82 (d, $J$ = 1.2, 3H), 1.69-1.63 (m, 2H), 1.51-1.45 (m, 2H), 0.99 (d, $J$ = 6.7, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 177.87, 136.20, 134.96, 130.90, 127.34, 83.24, 77.55, 61.56, 55.65, 34.56, 33.59, 31.81, 28.38, 24.13, 22.00, 16.39; MS (ESI) 323 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{16}H_{28}O_5Na$ [M+Na$^+$] 323.1834, found 323.1840.

**Allylic Azide 52**: To a solution of alcohol **26** (300 mg, 0.954 mmol) in toluene (3 mL) at rt was added DBU (214 μL, 1.43 mmol) and diphenylphosphoryl azide (308 μL, 1.43 mmol). After

stirring for 5 h, the reaction mixture was treated with saturated aqueous $NH_4Cl$ solution and diluted with $Et_2O$. The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 30:1) afforded allylic azide **52** (281 mg, 87%) as a colorless oil. Compound **52** should be used immediately for the subsequent steps to avoid double bond isomerization. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.68-5.60 (m, 1H), 5.52 (d, $J$ = 10.0, 1H), 5.32-5.25 (m, 2H), 3.81 (d, $J$ = 13.0, 1H), 3.66 (d, $J$ = 13.0, 1H), 3.45 (dd, $J$ = 7.1, 3.0, 1H), 3.39 (app t, $J$ = 7.5, 1H), 3.21 (s, 3H), 2.56-2.52 (m, 1H), 1.77 (d, $J$ = 1.2, 3H), 0.93-0.90 (m, 12H), 0.06 (s, 3H0, 0.04 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.97, 135.19, 127.27, 118.81, 86.04, 78.39, 56.13, 51.46, 34.40, 26.14, 22.21, 18.53, 14.43, –3.80, –4.77; MS (ESI) 362 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{17}H_{33}N_3O_2SiNa$ [M+Na$^+$] 362.2240, found 362.2239.

**Amide 53**: To a solution of azide **52** (184 mg, 0.542 mmol) in THF (5 mL) at 70 °C was added $PPh_3$ (249 mg, 0.949 mmol) and $H_2O$ (49 μL, 2.71 mmol). After stirring for 4 h, the reaction mixture was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in $CH_2Cl_2$ (5 mL) and treated with *i*-$Pr_2NEt$ (378 μL, 2.17 mmol), 6-heptenoic acid (147 μL, 1.08 mmol), and EDC (207 mg, 1.08 mmol). After stirring for 30 min, the reaction mixture was concentrated under reduced pressure to a volume of ca. 1 mL. Purification of the residual solution by FC ($CH_2Cl_2$ → $CH_2Cl_2$/$Et_2O$ 10:1) afforded amide **53** (211 mg, 92%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.83-5.74 (m, 1H), 5.70-5.64 (m, 1H), 5.41 (br s, 1H), 5.32-5.23 (m, 3H), 5.01-4.93 (m, 2H), 3.86 (dd, $J$ = 14.1, 5.6, 1H), 3.79 (dd, $J$ = 14.1, 5.5, 1H), 3.47-3.37 (m, 2H), 3.21 (s, 3H), 2.61-2.56 (m, 1H), 2.19-2.15 (m, 2H), 2.08-2.04 (m, 2H), 1.68 (d, $J$ = 1.3, 3H), 1.67-1.59 (m, 2H), 1.45-1.38 (m, 2H), 0.91-0.89 (m, 12H), 0.06 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 172.79, 138.44, 135.10, 133.94, 129.82, 118.66, 114.66, 86.01, 78.22, 56.11, 39.84, 36.65, 34.26, 33.44, 28.52, 26.11, 25.25, 21.93, 18.50, 14.76, –3.83, –4.77; MS (ESI) 446 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{24}H_{45}NO_3SiNa$ [M+Na$^+$] 446.3066, found 446.3065.

**TBS-Macrolactam 54**: To a solution of amide **53** (105 mg, 0.248 mmol) in refluxing toluene (350 mL) was added Grubbs-II catalyst **16** (42 mg, 0.050 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 1:2). Purification of the crude product by FC (hexane/EtOAc 2:1) afforded TBS-macrolactam **54** (59 mg, 60%) as a colorless oil. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.81-5.75 (m, 1H), 5.46 (d, $J$ = 9.9, 1H), 5.36 (dd, $J$ = 15.9, 6.0, 1H), 5.30 (br s, 1H), 3.77 (dd, $J$ = 13.9, 3.5, 1H), 3.66 (dd, $J$ = 13.9, 5.4, 1H), 3.48-3.44 (m, 2H), 3.21 (s, 3H), 2.63-2.58 (m, 1H), 2.21-2.08 (m, 3H), 2.05-1.98 (m,

1H), 1.73 (d, $J$ = 1.1, 3H), 1.65-1.49 (m, 3H), 1.39-1.32 (m, 1H), 0.92-0.90 (m, 12 H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.26, 134.11, 133.90, 129.03, 128.54, 84.80, 77.46, 56.29, 41.41, 36.01, 34.48, 29.59, 27.45, 26.11, 24.68, 24.32, 18.56, 14.77, –3.92, –4.93; MS (ESI) 418 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{22}H_{41}NO_3SiNa$ [M+Na$^+$] 418.2753, found 418.2752.

**Macrolactam 55**: To a solution of TBS-macrolactam **54** (91 mg, 0.230 mmol) in THF (3 mL) at rt was added HF•pyridine (in the beginning: 0.4 mL, after a total of 18 h: an additional 0.15 mL). After stirring for a total of 21 h, the reaction mixture was carefully treated with MeOTMS (5 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 1:1 → 1:2) afforded macrolactam **55** (52 mg, 81%) as a colorless oil. $[\alpha]_D$ +101.3° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3566, 3444, 3021, 2936, 2828, 1658, 1504, 1478, 1398, 1229, 1088, 979; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.79-5.73 (m, 1H), 5.66 (d, $J$ = 10.2, 1H), 5.24 (dd, $J$ = 15.8, 7.5, 1H), 5.12 (br s, 1H), 3.91 (dd, $J$ = 13.7, 4.1, 1H), 3.50-3.46 (m, 2H), 3.34-3.30 (m, 1H), 3.31 (s, 3H), 2.89 (br s, 1H), 2.56-2.52 (m, 1H), 2.32-2.25 (m, 2H), 2.16-2.11 (m, 1H), 1.96-1.89 (m, 1H), 1.77 (d, $J$ = 1.1, 3H), 1.73-1.51 (m, 3H), 1.37-1.32 (m, 1H), 0.94 (d, $J$ = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.36, 135.52, 133.77, 129.89, 128.73, 83.21, 76.38, 56.45, 41.40, 35.95, 32.27, 29.86, 27.00, 24.82, 24.42, 13.03; MS (ESI) 304 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{16}H_{27}NO_3Na$ [M+Na$^+$] 304.1888, found 304.1889.

**Allylic Bromide 56**: To a solution of alcohol **26** (325 mg, 1.03 mmol) in $CH_2Cl_2$ (10 mL) at rt was added solid supported $PPh_3$ (excess until reaction complete) and $CBr_4$ (478 mg, 1.44 mmol). After stirring for 15 min, the reaction mixture was filtered through a cotton plug and concentrated under reduced pressure to yield the allylic bromide **56**. $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.67 (ddd, $J$ = 17.2, 10.3, 8.3, 1H), 5.41 (dd, $J$ = 10.0, 0.9, 1H), 5.31 (dd, $J$ = 10.3, 2.0, 1H), 5.27 (dt, $J$ = 17.2, 1.0, 1H), 3.94 (s, 2H), 3.55 (dd, $J$ = 7.2, 3.0, 1H), 3.39 (app t, $J$ = 7.4, 1H), 3.21 (s, 3H), 2.63-2.56 (m, 1H), 1.81 (d, $J$ = 0.9, 3H), 0.93 (d, $J$ = 6.4, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 136.35, 135.20, 129.64, 118.82, 86.09, 77.57, 56.15, 34.68, 32.34, 26.13, 21.91, 18.50, 13.54, –3.83, –4.82.

**β-Ketosulfone 57**: To a solution of methyl phenyl sulfone (1.43 g, 9.14 mmol) in THF (15 mL) at –15 °C was added BuLi (6.28 mL, 10.0 mmol, 1.6M in hexane). After stirring for 30 min, the reaction mixture was cooled to –78 °C and ethyl 6-heptenoate (802 μL, 4.57 mmol) was added. The reaction mixture was warmed to rt and then treated with saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Purification of the crude product by FC (hexane/EtOAc 5:1) afforded β-ketosulfone **57** (1.12 g, 92%) as a white solid. $^{1}$H-NMR (500 MHz, $CDCl_3$) $\delta$ 7.88-7.86 (m, 2H), 7.68-7.65 (m, 1H), 7.58-7.54 (m, 2H), 5.79-5.71 (m, 1H), 5.00-4.92 (m, 2H), 4.14 (s, 2H), 2.70-2.67 (m, 2H), 2.05-2.00 (m, 2H), 1.58-1.52 (m, 2H), 1.38-1.32 (m, 2H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 197.99, 138.14, 134.19, 129.25, 129.06, 128.17, 114.73, 66.70, 44.12, 33.26, 27.85, 22.42; MS (ESI) 289 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{14}H_{18}O_3SNa$ [M+$Na^+$] 289.0874, found 289.0882.

**Ketone 58**: To a solution of β-ketosulfone **57** (685 mg, 2.57 mmol) in toluene (5 mL) at rt was added DBU (385 μL, 2.57 mmol). After stirring for 50 min, a solution of crude allylic bromide **56** in toluene (5 mL) was added and the reaction mixture was stirred for another 45 min. The reaction mixture was concentrated under reduced pressure to a volume of ca. 1 mL and the residual solution was filtered through a silica plug (hexane/EtOAc 7:1). To a solution of crude alkylated sulfone in MeOH (10 mL) at rt was added $Na_2HPO_4$ (366 mg, 2.57 mmol) and 10% Na/Hg (474 mg, ca. 2.06 mmol). After stirring for 3 h, the reaction mixture was filtered through a cotton plug and $H_2O$ was added to the filtrate. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 30:1) afforded ketone **58** (258 mg, 61%) as a colorless oil. $^{1}$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.82-5.75 (m, 1H), 5.67-5.60 (m, 1H), 5.29-5.18 (m, 3H), 5.02-4.93 (m, 2H), 3.41 (dd, *J* = 7.2, 2.8, 1H), 3.37 (app t, *J* = 7.6, 1H), 3.20 (s, 3H), 2.52-2.47 (m, 1H), 2.44-2.38 (m, 4H), 2.28-2.18 (m, 2H), 2.06 (app q, *J* = 7.1, 2H), 1.64 (d, *J* = 1.2, 3H), 1.62-1.56 (m, 2H), 1.41-1.35 (m, 2H), 0.90 (s, 9H), 0.87 (d, *J* = 6.7, 3H), 0.05 (s, 3H), 0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 210.57, 138.45, 135.30, 131.81, 131.30, 118.53, 114.64, 86.27, 78.61, 56.10, 42.64, 41.23, 34.05, 33.50, 28.46, 26.16, 26.12, 23.27, 23.11, 18.55, 14.05, –3.79, –4.79; MS (ESI) 445 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{25}H_{46}O_3SiNa$ [M+$Na^+$] 445.3114, found 445.3095.

**TBS-Macroketone 59**: To a solution of ketone **58** (258 mg, 0.610 mmol) in refluxing toluene (1200 mL) was added Grubbs-II catalyst **16** (104 mg, 0.122 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 2:1). Purification of the crude product by FC (hexane/EtOAc 20:1) afforded TBS-macroketone **59** (194 mg, 81%) as a colorless oil. $^{1}$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.67-5.61 (m, 1H), 5.32 (dd, *J* = 15.7, 6.7, 1H), 5.26 (dd, *J* = 9.8, 0.9, 1H), 3.41-3.36 (m, 2H), 3.21 (s, 3H), 2.55-2.49 (m, 1H), 2.46-2.41 (m, 1H), 2.39-2.33 (m, 1H), 2.32-2.18 (m, 5H), 2.14-2.10 (m, 1H), 1.68-1.63 (m, 1H), 1.67 (d, *J* = 1.3, 3H), 1.62-1.53 (m, 2H), 1.51-1.46 (m, 1H), 0.90 (s, 9H), 0.89 (d, *J* = 6.8, 3H), 0.05 (s, 3H), 0.00 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 211.96, 133.10, 131.91, 131.68, 129.87, 84.77, 79.32, 56.24, 41.44, 40.91, 34.32, 30.25, 28.74, 26.84, 26.15, 23.15, 22.85, 18.60,

12.78, –3.85, –5.03; MS (ESI) 417 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{23}H_{42}O_3SiNa$ [M+$Na^+$] 417.2801, found 417.2819.

**Macroketone 60**: To a solution of TBS-macroketone **59** (194 mg, 0.492 mmol) in THF (15 mL) at rt was added HF•pyridine (3.5 mL). After stirring for 15 h, the reaction mixture was carefully treated with MeOTMS (25 mL) and concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 10:1 → 4:1) afforded macroketone **60** (124 mg, 90%) as a colorless oil. $[\alpha]_D$ +77.6° (*c* 0.50, $CHCl_3$); IR (neat) 3566, 3022, 3015, 2975, 2937, 2879, 1700, 1448, 1384, 1237, 1109, 1085, 979; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.72 (ddd, *J* = 15.0, 8.5, 6.0, 1H), 5.37 (dd, *J* = 10.0, 0.9, 1H), 5.31 (dd, *J* = 15.6, 7.8, 1H), 3.47 (app t, *J* = 8.5, 1H), 3.36 (dd, *J* = 9.2, 1.2, 1H), 3.31 (s, 3H), 2.78 (br s, 1H), 2.51-2.45 (m, 2H), 2.37-2.32 (m, 2H), 2.26-2.16 (m, 5H), 1.69 (d, *J* = 1.3, 3H), 1.68-1.59 (m, 2H), 1.55-1.50 (m, 2H), 0.95 (d, *J* = 6.8, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 212.10, 135.23, 132.91, 130.26, 129.22, 83.69, 77.62, 56.45, 42.08, 40.67, 32.57, 30.33, 28.57, 27.01, 23.22, 23.14, 12.61; MS (ESI) 303 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{17}H_{28}O_3Na$ [M+$Na^+$] 303.1936, found 303.1938.

**Secondary Alcohols 61 and 62**: To a solution of alcohol **26** (360 mg, 1.15 mmol) in $CH_2Cl_2$ (5 mL) at rt was added Dess-Martin periodinane (970 mg, 2.29 mmol). After stirring for 1 h, the reaction mixture was treated with saturated aqueous $Na_2S_2O_3$ solution and saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to afford the corresponding aldehyde **27**. Crude product **27** was dissolved in $Et_2O$ (12 mL) and *i*-PrMgCl (2.90 mL, 5.80 mmol, 2M in THF) was added at –78 °C. After stirring for 5 h, the reaction mixture was treated with saturated aqueous $NH_4Cl$ solution. The organic layer was separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude product by FC (toluene/EtOAc 19:1) afforded (*S*)-secondary alcohol **61** (186 mg, 50%) and (*R*)-secondary alcohol **62** (134 mg, 36%) as colorless oils.

**(*S*)-Secondary Alcohol 61**: IR (neat) 3476, 2956, 2929, 2884, 2857, 1471, 1462, 1378, 1251, 1127, 1096, 1080, 1032, 1006; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.78-5.68 (m, 1H), 5.31-5.23 (m, 3H), 3.98 (d, *J* = 9.8, 1H), 3.51-3.48 (m, 2H), 3.24 (s, 3H), 2.73-2.68 (m, 1H), 1.78-1.69 (m, 1H), 1.66 (s, 3H), 1.60 (br s, 1H), 1.03 (d, *J* = 6.4, 3H), 0.91 (s, 9H), 0.89 (d, *J* = 6.0, 3H), 0.73 (d, *J* = 6.9, 3H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.37, 134.58, 133.16, 118.24, 85.74, 77.85, 75.73, 56.23, 33.64, 30.96, 26.13, 19.51, 18.93, 18.48, 17.56, 15.66, –3.86, –4.57; MS (ESI) 379 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{20}H_{40}O_3SiNa$ [M+$Na^+$] 379.2644, found 379.2663.

**(*R*)-Secondary Alcohol 62**: IR (neat) 3378, 2955, 2931, 2919, 2872, 1466, 1455, 1378, 1249, 1119, 1096, 1079, 1026; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.59 (ddd, $J$ = 17.3, 10.3, 8.2, 1H), 5.40 (dd, $J$ = 10.3, 1.4, 1H), 5.31 (dd, $J$ = 10.2, 1.5, 1H), 5.27 (dd, $J$ = 17.3, 1.4, 1H), 3.97 (d, $J$ = 9.2, 1H), 3.43 (dd, $J$ = 7.4, 2.2, 1H), 3.37 (app t, $J$ = 8.1, 1H), 3.21 (s, 3H), 2.67-2.62 (m, 1H), 1.80-1.73 (m, 1H), 1.67 (d, $J$ = 1.5, 3H), 1.37 (br s, 1H), 1.04 (d, $J$ = 6.5, 3H), 0.91 (s, 9H), 0.90 (d, $J$ = 6.6, 3H), 0.76 (d, $J$ = 6.6, 3H), 0.05 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 135.02, 134.13, 133.88, 118.86, 86.39, 78.35, 75.92, 56.06, 33.16, 31.52, 26.15, 19.52, 19.34, 18.59, 17.68, 13.74, –3.80, –4.84; MS (ESI) 379 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{20}H_{40}O_3SiNa$ [M+Na$^+$] 379.2644, found 379.2643.

**(*S*)-Isopropyl Ester 63**: To a solution of alcohol **61** (55 mg, 0.154 mmol) in toluene (0.4 mL) at rt was added pyridine (62 μL, 0.772 mmol) and the mixed anhydride[11] of 6-heptenoic acid and 2,4,6-trichlorobenzoyl chloride (1.5 mL, 0.75 mmol, 0.50M in toluene). After stirring 15 h, the reaction mixture was directly loaded onto a silica column and purified by FC (toluene) to afford (*S*)-isopropyl ester **63** (54 mg, 75%) as a colorless oil. IR (neat) 2928, 2830, 1732, 1470, 1378, 1247, 1125, 1096, 1032; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.81-5.76 (m, 2H), 5.41 (d, $J$ = 10.4, 1H), 5.31 (dd, $J$ = 10.3, 2.0, 1H), 5.24 (app d, $J$ = 17.2, 1H), 5.17 (app d, $J$ = 9.9, 1H), 5.00 (app d, $J$ = 17.1, 1H), 4.94 (d, $J$ = 5.8, 1H), 3.59 (dd, $J$ = 8.0, 1.8, 1H), 3.32 (app t, $J$ = 8.4, 1H), 3.20 (s, 3H), 2.73-2.68 (m, 1H), 2.28 (app t, $J$ = 7.5, 2H), 2.08-2.04 (m, 2H), 1.91-1.88 (m, 1H), 1.66-1.59 (m, 3H), 1.61 (s, 3H), 1.44-1.41 (m, 1H), 0.91 (d, $J$ = 8.3, 3H), 0.90 (s, 9H), 0.84 (d, $J$ = 6.7, 3H), 0.77 (d, $J$ = 6.9, 3H), 0.04 (s, 3H), –0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 172.48, 138.46, 135.43, 135.32, 129.62, 118.71, 114.62, 86.92, 78.07, 77.52, 77.34, 55.83, 34.42, 33.39, 33.27, 29.71, 28.38, 26.22, 24.66, 19.22, 18.53, 18.36, 12.69, –3.80, –4.96; MS (ESI) 489 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{27}H_{50}O_4SiNa$ [M+Na$^+$] 489.3376, found 489.3362.

**(*R*)-Isopropyl Ester 66**: Preparation performed exactly as for (*S*)-isopropyl ester **63**, affording (*R*)-isopropyl ester **66** in 70% yield. IR (neat) 2956, 2928, 2856, 1732, 1469, 1462, 1370, 1249, 1129, 1032; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.81-5.74 (m, 1H), 5.61 (ddd, $J$ = 17.6, 10.6, 7.6, 1H), 5.45 (d, $J$ = 9.4, 1H), 5.33 (dd, $J$ = 10.4, 1.9, 1H), 5.29 (dd, $J$ = 17.0, 1.9, 1H), 5.15 (app d, $J$ = 9.8, 1H), 4.99 (dd, $J$ = 17.0, 1.9, 1H), 4.95-4.93 (m, 1H), 3.40-3.38 (m, 2H), 3.21 (s, 3H), 2.82-2.76 (m, 1H), 2.29 (app t, $J$ = 7.5, 2H), 2.08-2.03 (m, 2H), 1.97-1.90 (m, 2H), 1.64-1.61 (m, 1H), 1.61 (d, $J$ = 1.3, 3H), 1.43-1.36 (m, 2H), 0.92 (d, $J$ = 6.6, 3H), 0.91 (s, 9H), 0.89 (d, $J$ = 6.6, 3H), 0.79 (d, $J$ = 6.0, 3H), 0.05 (s, 3H), 0.01 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 172.82, 138.47, 135.59, 134.68, 129.61, 118.97, 114.63, 86.41, 78.32, 77.72, 56.06, 34.42, 33.65, 33.38, 29.71,

[11] The preparation of the mixed anhydride of 6-heptenoic acid and 2,4,6-trichlorobenzoyl chloride was performed exactly as for the mixed anhydride of 2,6-heptadienoic acid and 2,4,6-trichlorobenzoyl chloride (see above).

28.35, 26.18, 24.58, 19.38, 18.96, 18.61, 18.19, 12.89, –3.76, –4.91; MS (ESI) 489 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{27}H_{50}O_4SiNa$ [M+$Na^+$] 489.3376, found 489.3363.

**(*S*)-Isopropyl Macrolactone 65**: To a solution of (*S*)-isopropyl ester **63** (25 mg, 0.053 mmol) in refluxing toluene (100 mL) was added Grubbs-II catalyst **16** (9 mg, 0.0107 mmol). After stirring for 15 min, the reaction mixture was cooled to rt and filtered through a silica plug (hexane/EtOAc 1:3). After evaporation of the solvent, crude product **64** was dissolved in THF (3 mL) and treated with HF•pyridine (0.75 mL) at rt. After stirring for 40 h, the reaction mixture was carefully treated with MeOTMS (6 mL) and concentrated under reduced pressure. Purification of the crude product by FC ($CH_2Cl_2$/EtOAc 9:1) afforded (*S*)-isopropyl macrolactone **65** (12 mg, 65%) as a colorless oil. $[\alpha]_D$ +25.1° (*c* 0.32, $CHCl_3$); IR (neat) 3479, 2967, 2926, 2876, 1724, 1448, 1373, 1257, 1237, 1091; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.70 (ddd, *J* = 15.4, 8.5, 5.3, 1H), 5.33 (dd, *J* = 10.0, 0.9, 1H), 5.30 (d, *J* = 7.0, 1H), 5.19-5.13 (m, 1H), 3.40-3.30 (m, 2H), 3.28 (s, 3H), 2.99-2.95 (m, 1H), 2.76 (br s, 1H), 2.36-2.24 (m, 2H), 2.20-2.08 (m, 2H), 1.99 (app dt, *J* = 7.0, 6.9, 1H), 1.69 (d, *J* = 1.3, 3H), 1.62-1.52 (m, 4H), 0.94 (d, *J* = 7.0, 3H), 0.91 (d, *J* = 6.6, 3H), 0.86 (d, *J* = 6.9, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 172.97, 135.94, 133.83, 130.09, 127.75, 86.47, 78.70, 55.98, 33.99, 32.80, 30.38, 29.82, 27.34, 22.57, 21.38, 19.09, 18.05, 15.20; MS (ESI) 347 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{19}H_{32}O_4Na$ [M+$Na^+$] 347.2198, found 347.2187.

**(*R*)-Isopropyl Macrolactone 68**: Preparation performed exactly as for (*S*)-isopropyl macrolactone **65**, affording (*R*)-isopropyl macrolactone **68** in 66% yield. $[\alpha]_D$ +21.3° (*c* 0.09, $CHCl_3$); IR (neat) 3499, 2967, 2926, 2866, 1729, 1453, 1383, 1257, 1111; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.65 (app dt, *J* = 15.5, 7.5, 1H), 5.58 (dd, *J* = 10.7, 1.3, 1H), 5.35 (dd, *J* = 15.5, 6.0, 1H), 4.87 (d, *J* = 7.6, 1H), 3.49 (dd, *J* = 9.1, 6.0, 1H), 3.34 (s, 3H), 3.27 (br d, *J* = 8.8, 1H), 3.13-3.07 (m, 1H), 2.86 (br s, 1H), 2.34-2.15 (m, 4H), 2.06-1.99 (m, 1H), 1.76 (d, *J* = 1.6, 3H), 1.75-1.58 (m, 3H), 1.47-1.41 (m, 1H), 0.98 (d, *J* = 7.0, 3H), 0.93 (d, *J* = 6.7, 3H), 0.92 (d, *J* = 6.7, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 172.50, 132.45, 132.08, 131.58, 128.26, 82.45, 80.74, 77.44, 56.67, 33.00, 32.66, 31.76, 30.56, 25.57, 24.91, 22.44, 19.02, 18.96, 13.20; MS (ESI) 347 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{19}H_{32}O_4Na$ [M+$Na^+$] 347.2198, found 347.2196.

**Macrocyclic Secondary Alcohol 69 (diastereomeric mixture)**: To a solution of macroketone **60** (4 mg, 0.014 mmol) in MeOH (0.3 mL) at rt was added $NaBH_4$ (2 mg, 0.042 mmol). After stirring for 5 min, the reaction mixture was carefully treated with 1M HCl (1 mL) and stirring was continued for another 20 min. Then the reaction mixture was diluted with EtOAc, the organic layer was separated, and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford

a diastereomeric mixture of macrocyclic secondary alcohol **69** (4 mg, 95%) as a colorless oil. IR (neat) 3405, 2931, 2922, 2856, 1446, 1380, 1106, 1090; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.66-5.59 (m, 2H), 5.32 (app t, $J$ = 8.4, 2H), 5.27-5.19 (m, 2H), 3.83-3.72 (m, 2H), 3.49 (s, 1H), 3.46-3.40 (m, 2H), 3.36 (app t, $J$ = 10.0, 1H), 3.30 (s, 6H), 2.74 (br s, 2H), 2.59-2.46 (m, 2H), 2.31-2.26 (m, 2H), 2.19-2.06 (m, 2H), 2.02-1.90 (m, 2H), 1.83-1.72 (m, 4H), 1.70 (s, 6H), 1.68-1.13 (m, 12H), 0.94 (app t, $J$ = 6.3, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 136.43, 136.22, 134.53, 134.21, 129.52, 129.40, 129.28, 129.19, 84.38, 84.14, 77.51, 77.42, 71.17, 70.66, 56.28, 56.22, 33.36, 33.30, 32.87, 32.50, 32.21, 32.16, 30.47, 30.34, 26.93, 26.91, 26.83, 25.50, 23.46, 23.37, 21.90, 19.67, 12.58, 12.44; MS (ESI) 305 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{17}H_{30}O_3Na$ [M+$Na^+$] 305.2093, found 305.2103.

**Macrocyclic Tertiary Alcohol 70 (diastereomeric mixture)**: To a solution of macroketone **60** (5.5 mg, 0.020 mmol) in THF (0.4 mL) at 0 °C was added MeMgBr (66 μL, 0.200 mmol, 3M in $Et_2O$). After stirring for 5 min, the reaction mixture was treated with saturated aqueous $NH_4Cl$ solution and diluted with EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford a diastereomeric mixture of macrocyclic tertiary alcohol **70** (6.0 mg, 95%) as a colorless oil. IR (neat) 3434, 2933, 2856, 1460, 1448, 1117, 1083; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.66-5.60 (m, 2H), 5.34-5.31 (m, 2H), 5.24-5.17 (m, 2H), 3.46-3.32 (m, 6H), 3.30 (s, 6H), 2.80-2.70 (m, 2H), 2.61-2.51 (m, 2H), 2.30-2.26 (m, 2H), 2.17 (br s, 1H), 2.14-2.01 (m, 2H), 1.95-1.82 (m, 2H), 1.77-1.60 (m, 2H), 1.70 (s, 6H), 1.58-1.36 (m, 8H), 1.34-1.14 (m, 5H), 1.20 (s, 6H), 1.02 (app t, $J$ = 7.2, 2H), 0.94-0.92 (m, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 136.55, 136.44, 134.45, 134.35, 129.44, 129.32, 84.34, 84.24, 72.90, 72.80, 56.27, 56.23, 38.71, 38.60, 38.48, 38.43, 32.10, 32.09, 30.92, 30.56, 29.69, 29.32, 29.24, 27.41, 27.37, 26.79, 24.27, 23.34, 23.33, 21.91, 21.14, 12.64, 12.57; MS (ESI) 319 [M+$Na^+$]; HRMS (FAB) calcd. for $C_{18}H_{32}O_3Na$ [M+$Na^+$] 319.2249, found 319.2264.

**Macrocyclic $CF_3$-Alcohol 71 (major)**: To a solution of macroketone **60** (10 mg, 0.036 mmol) and $TMSCF_3$ (27 μL, 0.180 mmol) in THF (0.6 mL) at rt was added a catalytic amount of TBAF. After stirring for 1 h, the reaction mixture was treated with excess TBAF and stirred for another 5 h. The reaction mixture was concentrated under reduced pressure. Purification of the crude product by FC (hexane/EtOAc 3:1) afforded a diastereomeric mixture of alcohol **71** (10 mg, 80%) as a colorless oil. Further purification by FC (hexane/EtOAc 7:1 → 3:1) provided the major isomer **71** in pure form as a colorless oil. IR (neat) 3409, 2963, 2931, 2922, 1457, 1244, 1150, 1112; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.64 (ddd, $J$ = 17.2, 9.4, 5.1, 1H), 5.34 (d, $J$ = 10.7, 1H), 5.19 (dd, $J$ = 17.2, 8.2, 1H), 3.43 (app t, $J$ = 9.0, 1H), 3.36 (app d, $J$ = 9.5, 1H), 3.30 (s, 3H),

2.87 (br s, 1H), 2.56-2.47 (m, 1H), 2.31-2.26 (m, 1H), 2.11-2.03 (m, 1H), 2.00-1.84 (m, 2H), 1.71-1.68 (m, 2H), 1.69 (s, 3H), 1.69-1.38 (m, 4H), 1.30-1.22 (m, 2H), 0.99 (app t, $J$ = 7.3, 1H), 0.93 (d, $J$ = 7.0, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 136.38, 133.31, 129.78, 129.45, 83.77, 56.33, 32.00, 31.02, 30.41, 29.72, 26.99, 25.09, 23.93, 23.27, 20.20, 19.63, 12.74; MS (ESI) 373 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{18}H_{29}F_3O_3Na$ [M+Na$^+$] 373.1966, found 373.1971.

**Macrooxime 72 (diastereomeric mixture)**: A solution of macroketone **60** (5 mg, 0.018 mmol) and $NH_2OH$•HCl (12 mg, 0.178 mmol) in pyridine (0.3 mL) was heated to 45 °C for 3 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by FC (hexane/EtOAc 1:1) to afford a diastereomeric mixture of macrooxime **72** (4 mg, 70%) as a colorless oil. IR (neat) 3326, 2930, 1447, 1109, 1086, 981; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 5.72-5.64 (m, 2H), 5.37 (d, $J$ = 9.1, 2H), 5.31-5.25 (m, 2H), 3.50-3.45 (m, 2H), 3.38-3.35 (m, 2H), 3.32 (s, 6H), 2.82 (br s, 2H), 2.62-2.57 (m, 2H), 2.43-2.36 (m, 2H), 2.29-2.04 (m, 14H), 1.76 (d, $J$ = 1.6, 3H), 1.71 (d, $J$ = 1.8, 3H), 1.56-1.48 (m, 6H), 1.27-1.24 (m, 2H), 0.97 (d, $J$ = 6.8, 3H), 0.96 (d, $J$ = 6.8, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 161.91, 161.66, 135.46, 135.30, 134.03, 133.76, 129.76, 129.64, 129.29, 129.19, 83.93, 83.89, 77.65, 77.48, 56.42, 33.66, 32.57, 32.51, 32.42, 30.62, 30.41, 30.29, 28.22, 27.01, 26.94, 26.70, 26.64, 24.42, 23.51, 23.13, 12.67; MS (ESI) 318 [M+Na$^+$]; HRMS (FAB) calcd. for $C_{17}H_{29}NO_3Na$ [M+Na$^+$] 318.2045, found 318.2049.

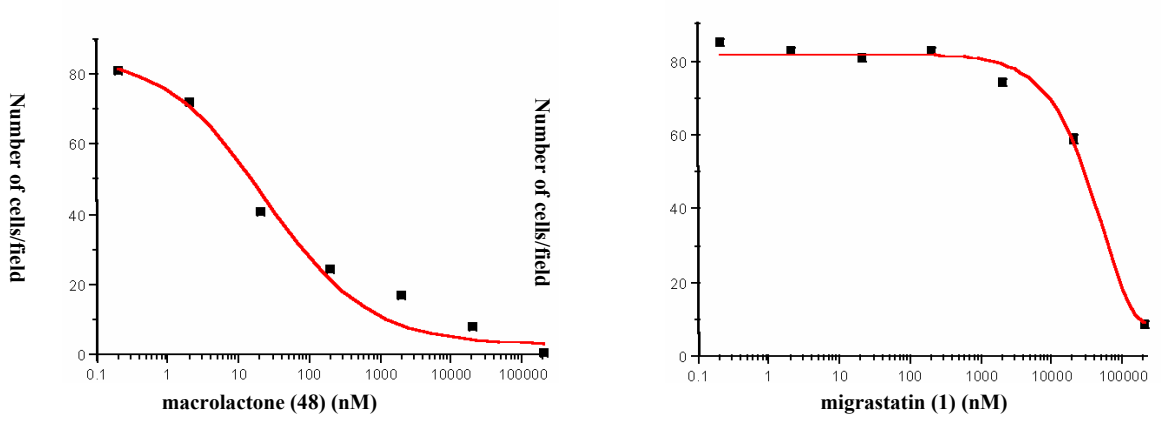
**Biotinylated Macrohydrazone 73 (diastereomeric mixture)**: A solution of macroketone **60** (6 mg, 0.021 mmol) and biotin-dPEG$_4$-hydrazide (13 mg, 0.026 mmol) in EtOH (0.3 mL) was heated to 55 °C for 1 h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by FC ($CH_2Cl_2$/MeOH 4:1) to afford a diastereomeric mixture of biotinylated macrohydrazone **73** (12 mg, 75%) as a colorless oil. IR (neat) 3291, 2930, 2872, 1703, 1691, 1680, 1668, 1540, 1459, 1261, 1104; $^1$H-NMR (500 MHz, $CDCl_3$) $\delta$ 9.56 (s, 0.4H), 9.50 (s, 0.4H), 9.23 (s, 0.6H), 9.10 (s, 0.6H), 6.77-6.73 (m, 2H), 6.58 (s, 0.6H), 6.50 (s, 6H), 6.12 (s, 0.4H), 6.08 (s, 0.4H), 5.70-5.63 (m, 2H), 5.42-5.34 (m, 2H), 5.32-5.25 (m, 2H), 5.18 (s, 0.8H), 5.04 (s, 1.2H), 4.50-4.47 (m, 2H), 4.37-4.32 (m, 2H), 3.83-3.79 (m, 4H), 3.68-3.55 (m, 32H), 3.48-3.41 (m, 6H), 3.39-3.28 (m, 8H), 3.16-3.14 (m, 2H), 2.97-2.89 (m, 5H), 2.82 (s, 0.6H), 2.78 (s, 0.4H), 2.74-2.70 (m, 2H), 2.64-2.56 (m, 4H), 2.30-2.22 (m, 10H), 2.20-2.02 (m, 4H), 2.17 (s, 3H), 1.77 (s, 3H), 1.75-1.64 (m, 12H), 1.25-1.24 (m, 2H), 0.95 (d, $J$ = 7.0, 3.6H), 0.92 (d, $J$ = 6.6, 2.4H); $^{13}$C-NMR (125 MHz, $CDCl_3$) $\delta$ 173.95, 173.74, 173.33, 173.22, 163.73, 163.67, 163.49, 160.94, 160.65, 156.08, 155.65, 135.39, 135.02, 134.78, 133.92, 133.65, 132.80, 132.62, 130.73, 130.61, 129.71, 129.56, 129.39, 128.99, 128.92, 83.99, 83.83, 83.79, 83.70, 77.64, 77.53, 77.46, 77.41, 70.42, 70.38, 70.14, 70.04, 69.92, 61.77, 61.73, 60.08, 56.46, 56.40, 40.61, 40.54, 39.13, 39.10, 36.29, 35.86, 35.77, 33.17, 32.68, 32.44, 30.92, 30.67, 30.46, 30.36, 29.68, 28.07, 27.41,

26.88, 26.81, 26.58, 25.51, 25.45, 24.59, 23.63, 23.49, 23.26, 12.71, 12.66; MS (ESI) 768 [M+H$^+$]; HRMS (FAB) calcd. for $C_{38}H_{66}N_5O_9S$ [M+H$^+$] 768.4581, found 768.4581.

## Materials and methods for mouse breast tumor cell and HUVEC cell studies:

**Chamber Cell Migration Assay (Tables 1 and 3)**: Cell migrations were assayed with Boyden chambers [8.0 μm pore size, polyethylene terephthalate membrane, FALCON cell culture insert (Becton-Dickinson)]. 4T1 mouse breast tumor cells or HUVECs were trypsinized and counted. 300 μl of 5-10x $10^4$ cells in serum-free medium was added to the upper chamber and 500 μl of medium with 10% fetal bovine serum (FBS) was added to the lower chamber. The transwells were incubated for 6-8 h at 37 °C with different concentrations of chemical compound in both upper and lower chamber. Cells on the inside of the transwell inserts were removed with a cotton swab, and cells on the underside of the insert were fixed and stained. Photographs of three random regions were taken and the number of cells was counted to calculate the average number of cells that have transmigrated.

As an example, the outcome of the 4T1 tumor cell migration assay with macrolactone **48** and migrastatin **1** is shown below.

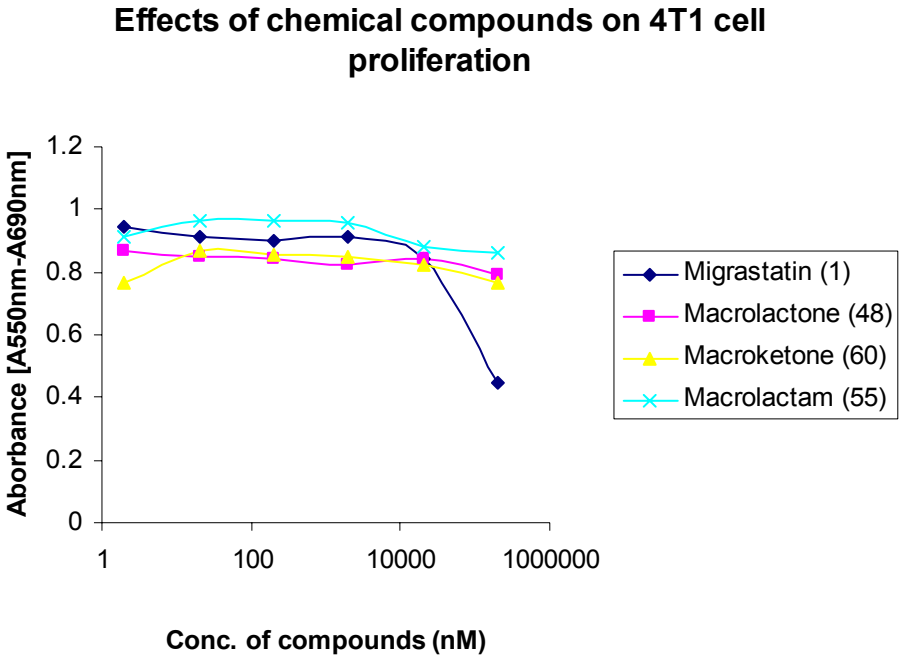



**Mouse Plasma Stability Studies (Table 2)**: *HPLC conditions*: The sample was injected and separated using an Inertsil ODS3 6u 3x 150 mm column with a mobile phase of MeCN and water (50% for migrastatin) at a flow of 0.4 mL/min, monitored at 220 nm at 0.02 AUFS (the retention time for migrastatin is ca. 4 min, the identity of this peak was confirmed by mass spectral

analysis). *Incubation and sample preparation conditions*: A solution (ca. 30 mM) of chemical compound (Table 2) in DMSO was prepared. 2 μL of the solution was added to a mixture containing 200 μL of mouse plasma and 800 μL of PBS. The resulting solution was put into a water bath at 37 °C, and 100 μL of sample was withdrawn at 10, 20, 30, 45, and 60 min. The precipitate was removed by centrifugation and 20 μL of the supernatant was injected onto the HPLC.

**Cell Proliferation Assay**: 4x $10^4$ of 4T1 tumor cells in RPMI-1640 medium containing 10% FBS were seeded into wells of 96-multiwell plates (Becton-Dickinson) in the presence or absence of chemical compounds and then incubated at 37 °C for 48 h. An MTT kit (Cell Proliferation Kit I, Roche) (a colorimetric assay) was used to quantify cell proliferation and viability. The number of living cells, thus the total metabolic activity, directly correlates to the amount of purple formazan crystals formed (monitored by the absorbance).

The outcome of the 4T1 tumor cell proliferation assay with migrastatin **1**, macrolactone **48**, macrolactam **55**, macroketone **60** is shown below.



## Materials and methods for human cancer cell studies:

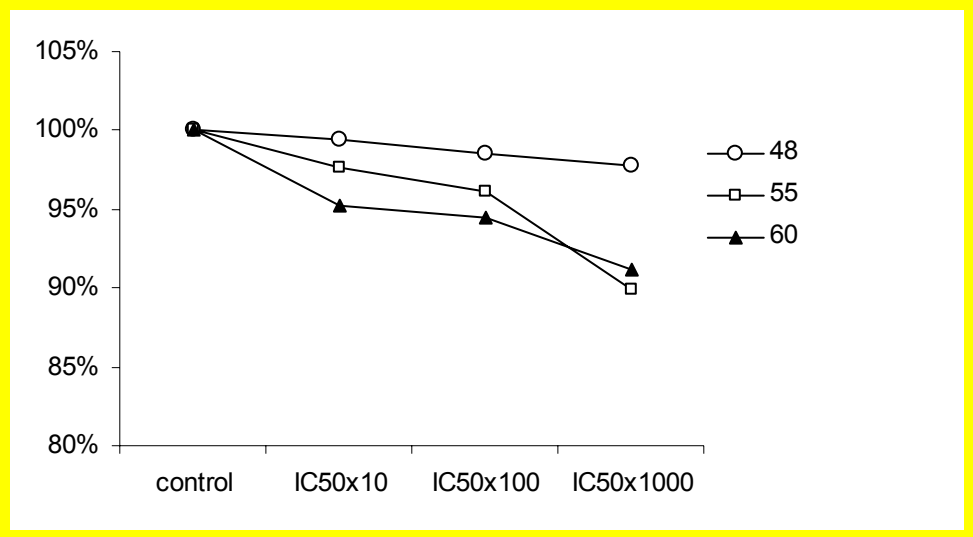
**Cell culture:** The human ovarian cancer cell lines Ovcar3 and IGROV were grown in M5 media. The colon cell lines HT 29 and HCT 116 were cultivated in DMEM containing 10% FCS in a humidified environment at 37°C. Myeloma cell lines CAG (obtained from The Myeloma Institute for Research and Therapy, University of Arkansas) and RPMI8226 as well as lymphoma cell line RL were maintained at RPMI1640 medium containing 10% FCS. All cell lines were acquired from the ATCC if not otherwise stated.

**Migration Assays.** Cell migrations were assayed with 8 µm of microporous 6.5-mm transwell plates (Corning). 200µl of 2 x $10^5$ cells in serum-free RPMI1640 medium containing 0.5% BSA were added to the upper chamber and 600µl of medium with 10% fetal bovine serum was added to the lower chamber. Transwells were incubated for 6 hours at 37°C for liquid tumor cells (RL, RPMI8226 and CAG) and for 12 hours for solid tumors (HT29, HCT 116, IGROV and Ovcar3) with following concentrations of chemical compounds in both upper and lower chambers (2,3-dihydro-migrastatin core (**48**): 240nM, migrastatin lactam (**55**): 2,550nM, migrastatin ketone (**60**): 1,000nM). Cells migrated to the lower wells were collected and counted for liquid tumors, solid tumors were processed as previously described.[28] Data shown are representative of at least three experiments.

**Wound Healing Assay.** The tumor cells were seeded into 24-multiwell plates (Becton-Dickinson) and cultivated until the cells formed a confluent monolayer. Wounds were set by horizontally scratching the monolayer with a sterile pipette tip. The cells were thereafter washed twice with Phosphate Buffered Saline (PBS) to remove detached cells. Growth media was then added containing different concentrations of the chemical compound and incubated at 37°C (2,3-dihydro-migrastatin core (**48**): 240 and 2,400nM, migrastatin lactam (**55**): 2,550 and 25,500nM, migrastatin ketone (**60**): 1,000 and 10,000nM) . The cells were photographed at the beginning of the experiment and after 24 and 48h to assess the progression of cell migration into the wound.

**Cell proliferation assay**. 5x$10^3$ CAG cells were plated into wells of 96 multi-well plates (Becton-Dickinson) using RPMI with 10% FCS (Sigma) as growth media in the presence or absence of chemical compounds and then incubated at 37°C for 72 hours. In the last 20 hours,

sodium 3'-[1-(phenylamino-carbonyl)-3,4-tetrazolium]-bis (4-methoxy-6-nitro) benzene sulfonic acid hydrate (XTT) was added and optical absorbance at 490nm were measured. As reference wavelength 650nm was used. The number of living cells, thus the total metabolic activity, directly correlates to the amount of orange formazan formed. The result was expressed as percentage of the control.




$IC_{50}$: DMC (**48**) = 24nM, macroketone (**55**) = 100nM and macrolactam (**60**) = 255nM.