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Synthesis of migrastatin and its macrolide core

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Abstract—Migrastatin and its macrolactone subunit are potent antimetastatic agents. Both were synthesized by using a ring-closing metathesis (RCM) to establish the macrolactone core, and the control of the (*Z*)-trisubstituted double bond at C11–C12 was achieved by using a Still–Gennari olefination.

1. Introduction

Since tumor spreading is responsible for the majority of death cases among cancer patients, the development of therapeutic agents that inhibit tumor metastasis is highly desirable. Such agents could be effective in restraining the formation of new tumor when earlier therapy or surgery has failed, or in increasing the chances of success in containing solid tumors in combination therapy with other agents.

Migrastatin (**1**) is a macrolide natural product isolated from broth cultures of two strains of *Streptomyces* (Fig. 1).[1,2] This product has the potential for metastasis suppression through its ability to inhibit tumor cell migration (IC_{50}=29 μM in mouse breast tumor 4T1 cells) but has no effect on the biosyntheses of DNA, RNA or protein in these cells.[1a] The specific inhibition property of migrastatin in tumor cell migration renders it an interesting target. More recently, it has been shown that migrastatin also inhibits P-glycoprotein and consequently sensitizes drug resistant P-glycoprotein-overexpressing cells to anticancer drugs like taxol, vinblastine or vincristine.[3]

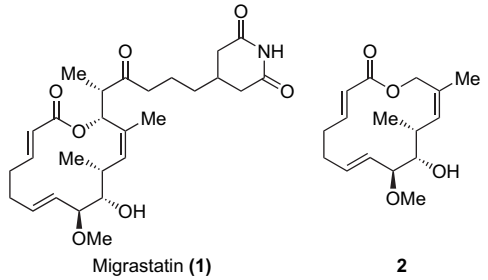

Figure 1. Structure of migrastatin (**1**) and migrastatin analogue **2**.

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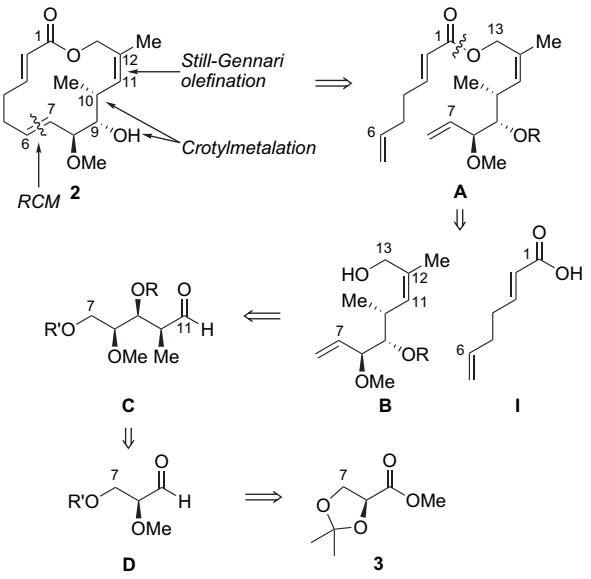
Before our preliminary contribution on the total synthesis of migrastatin,[5] only one total synthesis of migrastatin (**1**) had been achieved.[4] In addition, a library of migrastatin analogues,[6] one of which is the macrolide core of migrastatin **2**, has been found to be 1000 times more active than migrastatin itself, as macrolactone **2** possesses an IC_{50}=22 nM in mouse breast tumor 4T1 cells.[6a] Due to their interesting biological properties, we embarked on the synthesis of migrastatin (**1**) and its macrolactone subunit **2**. In the present work we would like to report the whole study on the total synthesis of migrastatin (**1**), including a new synthesis of the macrolactone subunit **2**. Furthermore, a new approach for the C7–C13 fragment **8**, a common key intermediate for the synthesis of **1** and **2**, will be discussed.

2. Synthesis of the macrolactone 2

The key steps in the synthesis of macrolactone **2** were based on a Still–Gennari olefination to control the (*Z*)-double bond at C11–C12, a ring-closing metathesis (RCM) to establish the macrolactone core and to control the (*E*)-double bond at C6–C7,[7] and a diastereoselective crotylmetalation of a chiral aldehyde to control the stereogenic centers at C9 and C10. As depicted in Scheme 1, the macrocyclic lactone **2** would be the result of a chemoselective RCM applied to diene **A**. This diene would be formed by esterification of 2,6-heptadienoic acid (**I**) with alcohol **B**. The (*Z*)-configuration of the C11–C12 double bond in fragment **B** would be installed by using a Still–Gennari olefination of aldehyde **C**. The construction of **C** relies on the *syn*-selective crotylmetalation of an aldehyde of type **D**, which would be synthesized from the commercially available methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**3**) (Scheme 1).

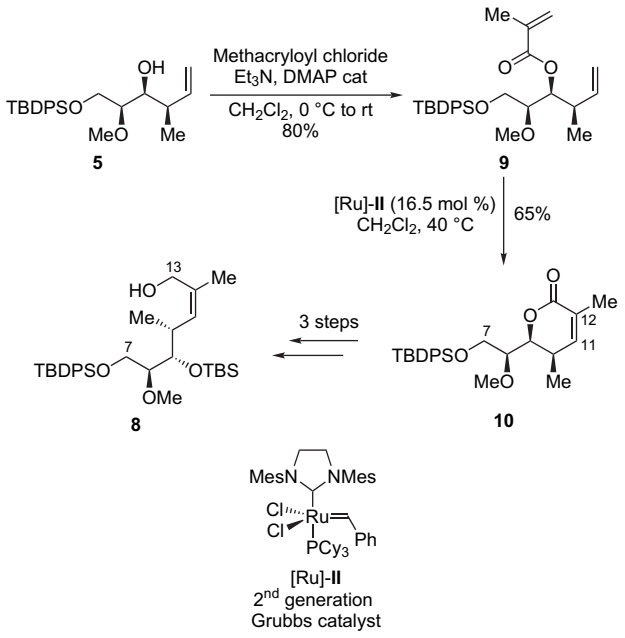
The synthesis of compound **2** started from methyl ester **3**, which was transformed to alcohol **4** in four steps with an overall yield of 58%. After oxidation of alcohol **4** under



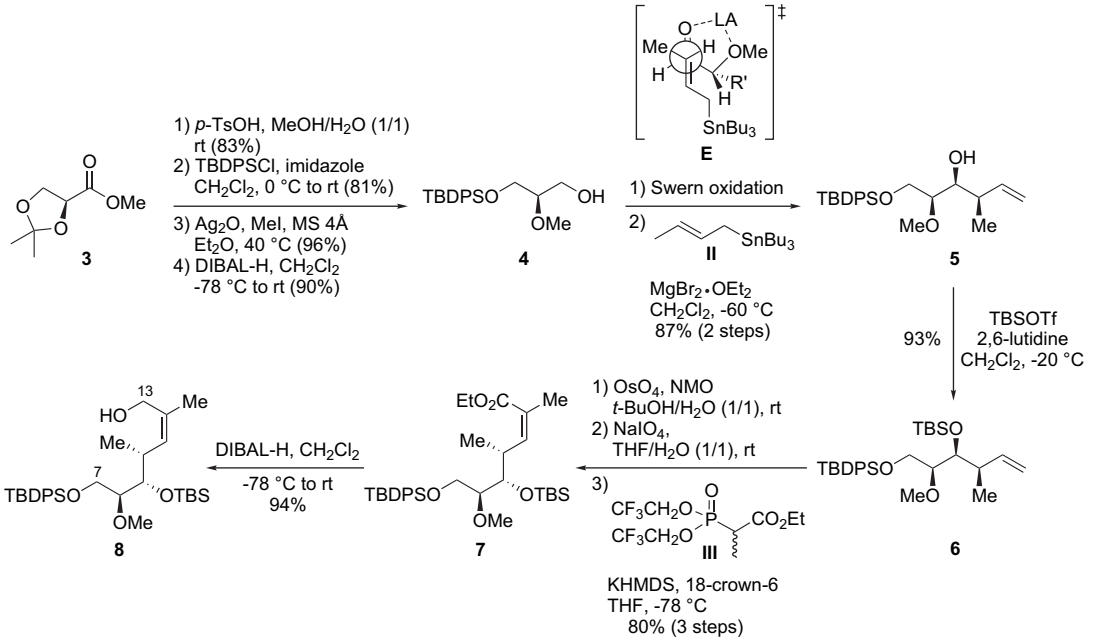
Scheme 1. Retrosynthetic analysis of the macrolide core of migrastatin **2**.

Swern conditions, the obtained crude aldehyde was directly treated with but-2-enyl-[(tri-*n*-butyl)]-stannane **II** (1.5 equiv, CH_2Cl_2, −60 °C) in the presence of $MgBr_2 \cdot OEt_2$ (2.2 equiv) to give the *syn*,*syn*-stereotriad **5** in 87% yield with a good stereocontrol (dr=90/10).[8,9] As described previously,[8] the stereochemical outcome of this addition is likely to be the result of an open-chair transition state of type **E**, in which both the carbonyl and the methoxy groups of the aldehyde are chelated with $MgBr_2 \cdot OEt_2$. After the protection of **5** (TBSOTf, 2,6-lutidine, CH_2Cl_2, −20 °C to 0 °C, 93% yield), olefin **6** was subjected to an oxidative cleavage in a two-step sequence (OsO_4, *N*-methylmorpholine *N*-oxide in *t*-BuOH/water, then $NaIO_4$ in THF/water). The obtained aldehyde was directly treated with Still–Gennari phosphonate **III**[10,11] [**III** (1.2 equiv), KHMDS (1.2 equiv), 18-crown-6 (4.8 equiv), THF, −78 °C, 12 h] to produce the unsaturated ester **7** in 80% yield (from olefin **6**) with a good 97/3 *Z*/*E* ratio.[9] After reduction of **7** with DIBAL-H (2.2 equiv, CH_2Cl_2, −78 °C), allylic alcohol **8** was isolated in 94% yield. Compound **8** corresponds to the C7–C13 fragment of the macrolide core of migrastatin **2**, which was obtained from **3** in 11 steps with an overall yield of 35% (Scheme 2).

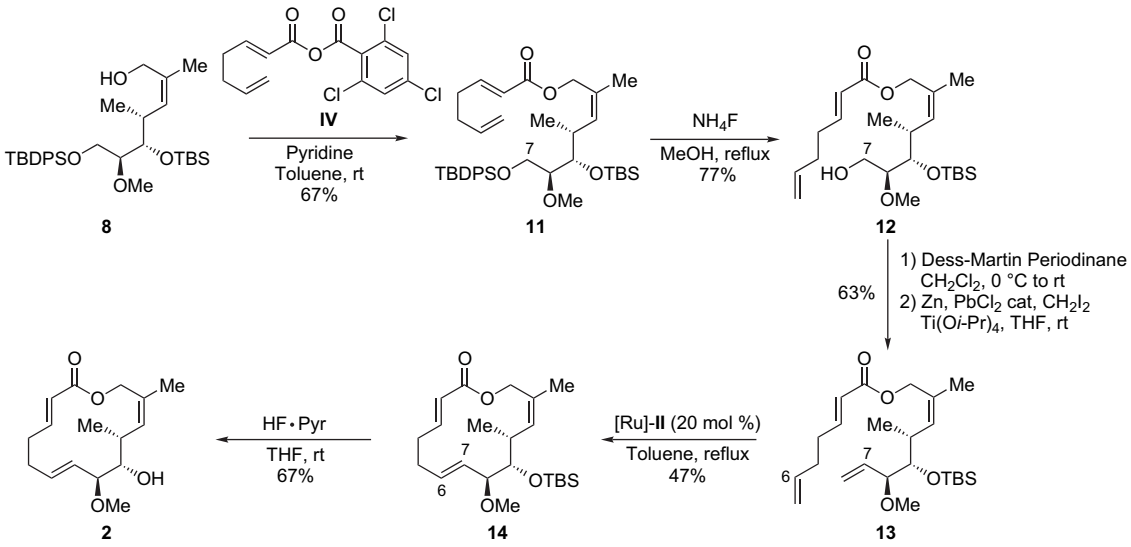
In our previous approach to migrastatin,[5] we explored another access to allylic alcohol **8** using an RCM to establish the (*Z*)-configuration of the C11–C12 double bond (Scheme 3). After esterification of **5** with methacryloyl chloride (Et_3N, DMAP cat, CH_2Cl_2, 0 °C to rt, 80%), diene **9** was



Scheme 3. Other synthetic route to allylic alcohol **8**.



Scheme 2. Synthesis of allylic alcohol **8**.



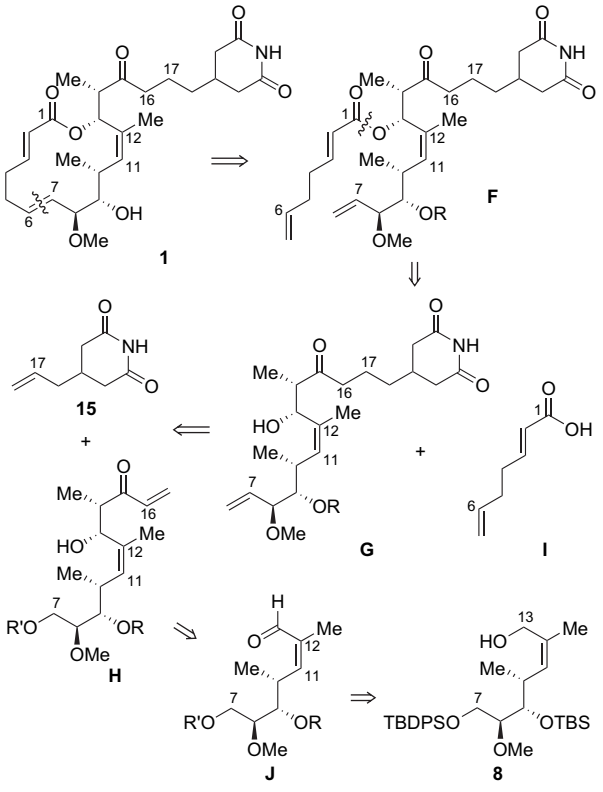
Scheme 4. Completion of the synthesis of macrolactone **2**.

treated with the second generation Grubbs catalyst [Ru]-**II** (16.5 mol %)[12] in refluxing CH_2Cl_2 to afford the unsaturated lactone **10** in 65% isolated yield accompanied by the homodimer of diene **9** in 5% isolated yield. This unsaturated lactone was converted to the (*Z*)-homoallylic alcohol **8** in three steps following Danishefsky's strategy.[6c] This approach led to alcohol **8** in 11 steps and 11% yield from **3**. Thus, our new strategy is more efficient than the previous one for the synthesis of **8** (10 steps, 35% yield).

To complete the synthesis of macrolide **2**, allylic alcohol **8** was then transformed to ester **11** in 67% yield by using the freshly prepared mixed anhydride **IV** (Scheme 4).[13] In order to obtain the RCM precursor **13**, ester **11** was selectively deprotected at C7 (NH_4F, MeOH reflux, 7.5 h) thus producing the primary alcohol **12** in 77% yield.[14] This alcohol was then oxidized with Dess–Martin periodinane and the obtained aldehyde was directly treated under Takai conditions (Zn, $PbCl_2$ cat, CH_2I_2, Ti(O*i*-Pr)$_4$, THF, rt) to afford the expected diene **13** in 63% yield (over two steps).[15,16] As described previously,[6a,c] diene **13** was treated with [Ru]-**II** (20 mol %) in refluxing toluene to produce the macrocyclic lactone **14** in 47% yield, and after deprotection (HF·Py, THF, rt) the macrolide core of migrastatin **2** was obtained in 67% yield. Compound **2** was thus obtained in 17 steps from the commercially available methyl ester **3** with an overall yield of 4%.

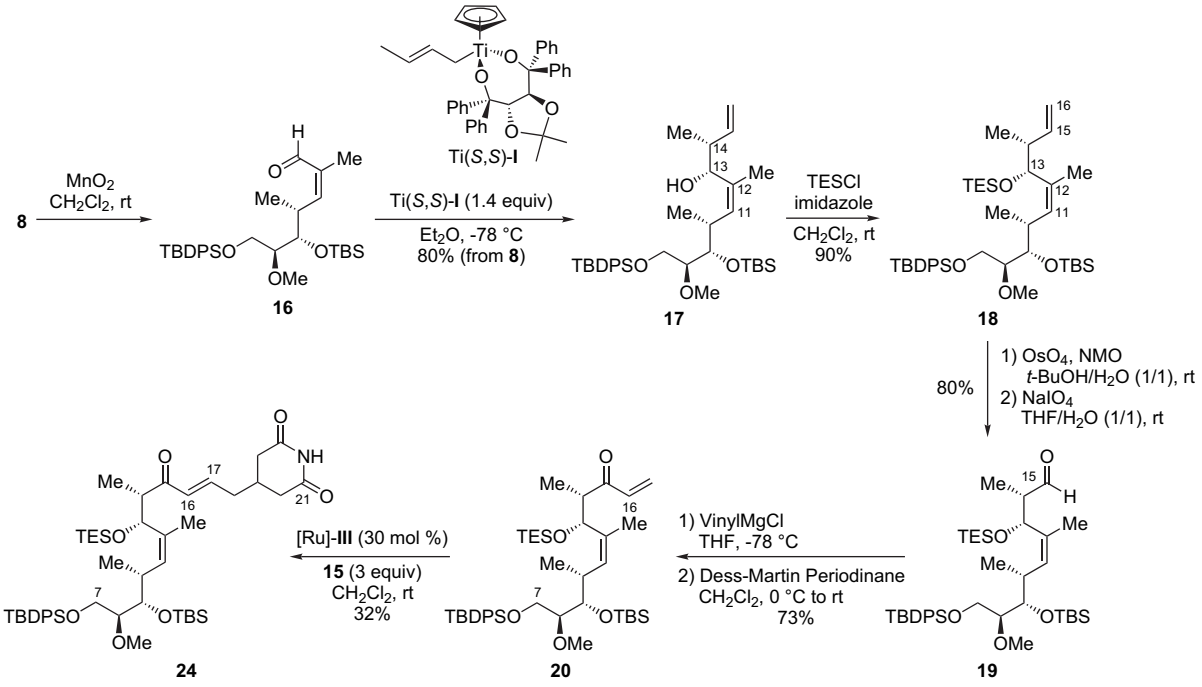
3. Total synthesis of migrastatin (1)

In view of our improved synthesis of the key intermediate **8**, we envisioned a more efficient synthesis of migrastatin (**1**), compared to the one previously reported.[5] The synthesis of migrastatin was envisaged by using a chemoselective RCM applied to diene **F**. This diene would be formed by the esterification of 2,6-heptadienoic acid (**I**) with alcohol **G**, which would be assembled by using a chemoselective cross-metathesis (CM) between allylglutarimide **15** and vinyl ketone **H** (C7–C16 fragment).[17] In this strategy, it would be necessary to perform either a conjugate reduction of the enone or a chemoselective hydrogenation of the enone double bond. In this approach, the glutarimide side chain would be introduced before the C1–C6 fragment **I**. The vinyl ketone **H** would be obtained after functional transformation of an aldehyde of type **J**, which is in turn derived from allylic alcohol **8**. The *anti*-relationship at C13, C14 in fragment **H** would be the result of an *anti*-selective enantio- and diastereoselective crotylmetalation applied to aldehyde **J** (Scheme 5).



Scheme 5. Retrosynthetic analysis of migrastatin (**1**).

As depicted in Scheme 6, the synthesis of migrastatin starts with the oxidation of the previously prepared allylic alcohol **8** to aldehyde **16** (MnO_2, CH_2Cl_2, rt). To control the



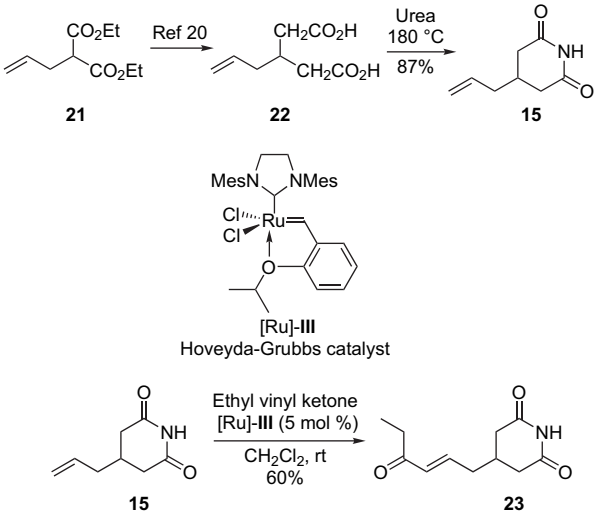
Scheme 6. Synthesis of fragment **24** (C7–C21).

stereogenic centers at C13 and C14, aldehyde **16** was treated with the highly face-selective crotyltitanium complex Ti(*S*,*S*)-**I**,[18] which gave the homoallylic alcohol **17** in 80% yield (from **8**) with good diastereoselectivity (dr=90/10).[9,19] The following step involved the selective oxidative cleavage of the terminal C15–C16 double bond. To protect sterically the internal double bond at C11–C12 from oxidative cleavage, the hydroxy group at C13 in compound **17**, was converted to the bulky triethylsilyl ether **18** (TESCl, imidazole, CH_2Cl_2, rt, 90%). Due to this protection, the C15–C16 double bond was chemoselectively transformed to an aldehyde by using a two-step dihydroxylation/oxidative cleavage sequence (OsO_4, *N*-methylmorpholine *N*-oxide, then $NaIO_4$) to produce aldehyde **19** in 80% yield. This aldehyde was then converted to the α,β-unsaturated ketone **20** in two steps by treatment with vinylmagnesium chloride (THF, −78 °C) followed by oxidation of the resulting allylic alcohol with Dess–Martin periodinane in 73% yield for the two steps.

At this stage, the first CM partner was obtained and the second partner, allylglutarimide **15**, was prepared from the commercially available allyldiethyl malonate **21**. 3-(2-Propenyl)-glutaric acid (**22**) was synthesized from diester **21** in four steps following a previously reported procedure.[20] Diacid **22** was then cyclized to glutarimide **15** by reaction with urea at high temperature (180 °C). In order to test our crucial CM with this glutarimide, **15** was reacted with ethyl vinyl ketone as a test substrate in the presence of Hoveyda–Grubbs catalyst [Ru]-**III** and interestingly, the CM product **23** was isolated in 60% yield (Scheme 7). With the two CM partners in hand, enone **24** (C7–C21 fragment) was synthesized by using a CM reaction.

The CM reaction between vinyl ketone **20** and allylglutarimide **15** was performed in the presence of Hoveyda–Grubbs catalyst [Ru]-**III**, yielding the CM product **24** in a moderate yield of 32% with 60% conversion based on the recovery of the starting material **20** [[Ru]-**III** (30 mol %), **15** (3 equiv), CH_2Cl_2, rt, 72 h] (Scheme 7).[21] We have to point out that during the CM reaction, olefin **15** homodimerized leading to the formation of a white precipitate in the reaction mixture. In our effort to improve the yield of this reaction, we tried to perform the CM under microwave irradiation[22] or in the presence of chlorodicyclohexylborane, previously reported to improve the CM reaction of nitrogen containing substrates,[23] however in both cases, the obtained yields were around 30%.

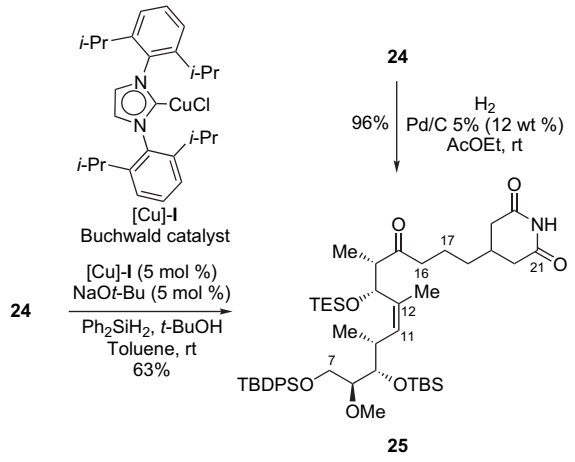
At this stage of the synthesis, the second crucial step to be performed was the selective reduction of the C16–C17 enone



Scheme 7. Synthesis of allylglutarimide **15** and CM with ethyl vinyl ketone.

double bond. A conjugate reduction of this enone was envisaged by using Buchwald copper carbene complex [Cu]-**I** in the presence of a silane as the hydride donor.[24] Therefore, enone **24** was subjected to the conjugate reduction with diphenylsilane in the presence of a catalytic amount of Cu-H species generated in situ from [Cu]-**I** (5 mol %),[25] yielding the corresponding ketone **25** in 63% yield. This copper-carbenic species appears to be a good alternative to the Stryker reagent.[26]

As the bulky TES protecting group at C13 provided a good protection for the C11–C12 trisubstituted double bond during the dihydroxylation step applied to olefin **18**, the chemoselective hydrogenation of the C16–C17 enone double bond was also investigated. Thus, when **24** was treated with hydrogen in the presence of Pd/C, the enone double bond was selectively hydrogenated to afford **25** in 96% yield (Scheme 8).

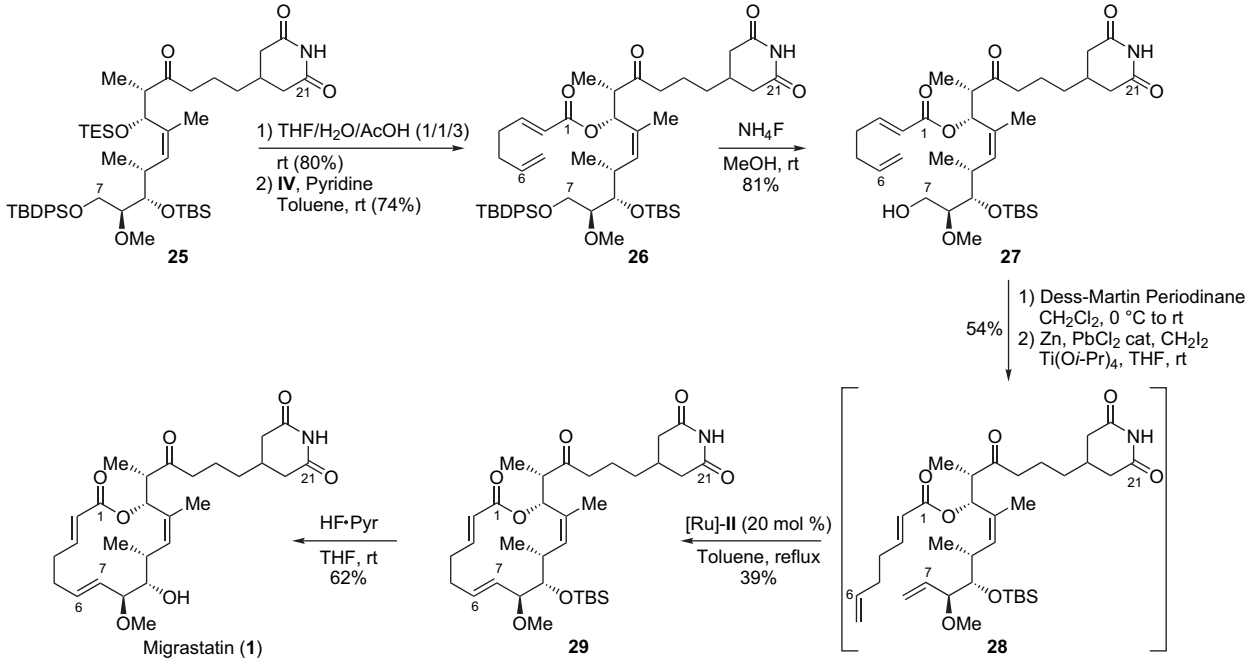


Scheme 8. Synthesis of fragment **25** (C7–C21).

Having synthesized the C7–C21 fragment **25**, the construction of the macrolactone core leading to the complete synthesis of migrastatin could be considered. After a selective deprotection of the hydroxyl group at C13 in compound **25** (THF/H_2O/AcOH, 1/1/3, rt, 80% yield), the obtained alcohol was transformed to ester **26** in 74% yield by using the freshly prepared mixed anhydride **IV** (toluene, rt, 48 h). In order to prepare the RCM precursor **28**, ester **26** was selectively deprotected at C7 by employing ammonium fluoride in methanol providing alcohol **27** in 81% yield. This primary alcohol was then oxidized to the corresponding aldehyde, which was directly treated under the Takai conditions to afford diene **28** in 54% yield (for the two steps). As described previously,[4,6c] diene **28** was treated with [Ru]-**II** (20 mol %) in refluxing toluene to produce macrolactone **29** in 39% yield. Finally, after removal of the last protecting group at C9 by HF·Py in THF, migrastatin (**1**) was isolated in 62% yield (Scheme 9). All the spectral data (^{1}H NMR, ^{13}C NMR, HRMS) and the optical rotation of our synthetic migrastatin matched those reported in the literature.[4,6c]

4. Conclusion

We have developed an efficient access to the C7–C13 fragment of both migrastatin (**1**) and its macrolactone core **2**, involving the use of a *syn,syn*-stereoselective crotylstannylation to control the stereogenic centers present at C9 and C10, and a Still–Gennari olefination to establish the (*Z*)-trisubstituted C11–C12 double bond. The macrolactone core of migrastatin **2** was synthesized in 17 steps from commercially available (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**3**) with an overall yield of 4%. Based on a similar strategy, the total synthesis of migrastatin (**1**) was realized in 27 steps. Synthetic highlights include an enantio- and diastereoselective crotyltitanation to control the stereogenic centers at C13 and C14 as well as a versatile ruthenium-catalyzed CM



Scheme 9. Completion of the synthesis of migrastatin (**1**).

reaction to install the glutarimide side chain, and a RCM to establish the macrolactone core. As the methods employed for the synthesis of **1** and **2** are flexible, they should allow us to access a wide range of migrastatin analogues for biological evaluation.

5. Experimental

5.1. General

All reactions were carried out under argon. Unless specified otherwise, materials were purchased from commercial suppliers and used without purification. THF and diethyl ether were distilled from sodium/benzophenone. CH_2Cl_2, Et_3N, benzene, and toluene were distilled from CaH_2. Flash column chromatography was carried out on Merck Geduran Si60 silica gel (40–63 μm) and analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}). Elemental analyses were performed by the Service de Microanalyse (ICSN-CNRS, Gif sur Yvette). Mass spectra with electronic impact (MS-EI) were recorded from a Hewlett–Packard tandem 5890 GC (12 m capillary column)–5971 MS (70 eV): only selected ions are reported. HRMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris and at the Laboratoire de Spectrométrie de Masse SM^3E de l'Université Pierre et Marie Curie in Paris. Infrared (IR) spectra were recorded on a Bruker TENSOR™ 27 (IRFT), wavenumbers 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 in $CDCl_3$ and data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, sext=sextet, m=multiplet or overlap of non-equivalent resonances, br=broad), integration. ^{13}C NMR spectra were recorded on a Bruker AC 300 at 75 MHz or on a Bruker AVANCE 400 at 100 MHz in $CDCl_3$ and data are reported as follows: chemical shift in parts per million from tetramethylsilane.

5.2. Synthesis of the C7–C13 fragment (8)

5.2.1. Alcohol 4. To a solution of (*S*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**3**) (5.33 g, 33.28 mmol) in a mixture of MeOH (25 mL) and water (25 mL) was added *p*-TsOH (3.47 g, 18.24 mmol). The mixture was stirred at rt for 3 h and then Et_3N (5 mL) was added. After evaporation under reduced pressure, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc; 7/3) to afford (2*S*)-methyl 2,3-dihydroxypropionate (3.32 g, 27.64 mmol, 83%).[27]

To a solution of the above diol (5.95 g, 49.54 mmol) in CH_2Cl_2 (73 mL) at 0 °C, were added imidazole (3.54 g, 52 mmol) followed by *tert*-butyldiphenylsilyl chloride (13.52 mL, 52 mmol). After 6 h at rt, NH_4Cl was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc; 9/1) allowed us to isolate (2*S*)-methyl 3-(*tert*-butyldiphenyl-silyloxy)-2-hydroxypropionate (14.36 g, 40.06 mmol, 81%).

To a solution of freshly prepared Ag_2O (13.96 g, 60.16 mmol) and activated MS 4 Å (3.49 g) in Et_2O (40 mL) was added the above alcohol (14.36 g, 40.06 mmol) followed by iodomethane (22.48 mL, 361 mmol). After 1 h at 40 °C, the mixture was filtered on a pad of Celite and washed with Et_2O. The solvent was removed under reduced pressure to give (2*S*)-methyl 3-(*tert*-butyldiphenylsilyloxy)-2-methoxy-propionate (14.53 g, 39 mmol, 96%).

To a solution of the above ester (14.53 g, 39 mmol) in CH_2Cl_2 (290 mL) at −78 °C, was added dropwise DIBAL-H (86 mL, 1 M in hexanes, 86 mmol). The cooling bath was removed and after 2.5 h at rt, an aqueous 10% HCl solution (115 mL) was slowly added at 0 °C. The aqueous phase was extracted with CH_2Cl_2 and the combined extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc; 9/1) to yield (2*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methoxy-propan-1-ol (**4**) (12.06 g, 35.01 mmol, 90%). $[\alpha]_D^{20}$ +23.1 (*c* 0.54, $CHCl_3$); IR (neat) 3420, 2929, 2957, 1471, 1427, 1108, 1079, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (m, 4H), 7.36–7.43 (m, 6H), 3.68 (m, 4H), 3.37 (s, 3H), 3.37 (m, 1H), 2.05 (m, 1H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.7 (4C), 133.3, 133.2, 129.9 (2C), 127.8 (4C), 81.6, 63.1, 62.7, 58.0, 26.9 (3C), 19.3; EIMS *m/z* 287 ($M-t$-Bu^+), 239, 225, 214, 213, 211, 209, 200, 199, 197, 184, 183, 181, 180, 179, 177, 165, 161, 153, 135, 131, 117, 105, 93, 91, 77. Anal. Calcd for $C_{20}H_{28}O_3Si$: C, 69.72; H, 8.19. Found: C, 69.54; H, 8.21.

5.2.2. Stereotriad 5. To a stirred solution of oxalyl chloride (6.53 mL, 76.12 mmol) in CH_2Cl_2 (520 mL) at −78 °C, was slowly added DMSO (6.87 mL, 96.88 mmol). After 30 min at −78 °C, a solution of alcohol **4** (11.90 g, 34.60 mmol) in CH_2Cl_2 (130 mL) was added and after 20 min at −78 °C, Et_3N (22.62 mL) was introduced. After 30 min at −78 °C, the reaction was slowly warmed to rt and diluted with pentane (100 mL) and brine (100 mL). The aqueous layer was extracted with pentane and the combined organic extracts were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford the corresponding aldehyde, which was used in the next step without further purification.

To a solution of the above crude aldehyde in CH_2Cl_2 (346 mL) at −21 °C, was added $MgBr_2 \cdot OEt_2$ (19.7 g, 76.12 mmol). After 40 min at −21 °C, the reaction was cooled to −60 °C and but-2-enyl-[(tri-*n*-butyl)]-stannane **II** (17.9 g, 51.9 mmol) was added. After 7 h, the reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution (200 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$ and filtered. Purification by flash chromatography on silica gel with 10 wt % finely ground KF[28] (CH_2Cl_2) allowed to isolate (2*S*,3*S*,4*R*)-1-(*tert*-butyldiphenylsilyloxy)-2-methoxy-4-methyl-hex-5-en-3-ol (**5**) (12.01 g, 30.13 mmol, 87%). $[\alpha]_D^{20}$ +15.3 (*c* 1.02, $CHCl_3$); IR (neat) 2929, 2857, 1640, 1590, 1471, 1427, 1390, 1361, 1108, 1079 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.67 (m, 4H), 7.36–7.43 (m, 6H), 5.71 (ddd, *J*=17.6, 10.5, 8.5 Hz, 1H), 5.01–5.10 (m, 2H), 3.80 (dd, *J*=10.5, 5.5 Hz, 1H), 3.73 (dd, *J*=10.5, 4.5 Hz, 1H), 3.50 (td, *J*=7.0, 2.5 Hz,

1H), 3.33 (s, 3H), 3.27 (m, 1H), 2.38–2.49 (m, 2H), 1.09 (d, J=7.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.6, 135.7 (2C), 135.6 (2C), 133.3, 133.2, 129.8 (2C), 127.8 (4C), 115.0, 80.5, 74.8, 63.2, 58.4, 41.5, 26.8 (3C), 19.2, 16.2; HRMS (ESI) calcd for $C_{24}H_{34}O_3NaSi$ [M+Na$^+$] 421.2175. Found 421.2141.

5.2.3. Olefin 6. To a solution of alcohol **5** (4.82 g, 12.09 mmol) in CH_2Cl_2 (120 mL) at −20 °C, was added dropwise 2,6-lutidine (3.52 mL, 30.28 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.57 mL, 24.22 mmol). After stirring for 3 h at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous $NaHCO_3$ solution and warmed at rt. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; from 100/0 to 100/5) furnished (2*S*,3*S*,4*R*)-3-(*tert*-butyldimethylsilyloxy)-1-(*tert*-butyldiphenyl-silyloxy)-2-methoxy-4-methyl-hex-5-ene (**6**) (5.77 g, 11.25 mmol, 93%). $[\alpha]_D^{20}$ +4.4 (*c* 0.5, $CHCl_3$); IR (neat) 2929, 2856, 1472, 1428, 1389, 1361, 1251, 1112, 1075, 1050, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.71 (m, 4H), 7.36–7.45 (m, 6H), 5.88 (m, 1H), 4.93–4.99 (m, 2H), 3.72–3.78 (m, 2H), 3.68 (dd, J=11.1, 5.0 Hz, 1H), 3.27 (s, 3H), 3.14 (m, 1H), 2.42 (m, 1H), 1.06 (s, 9H), 0.96 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9, 135.7 (4C), 133.6, 133.5, 129.7, 129.6, 127.7 (2C), 127.6 (2C), 113.3, 84.1, 75.9, 62.8, 58.4, 40.33, 26.8 (3C), 26.2 (3C), 19.2, 18.5, 14.5, −4.0, −4.4; EIMS *m*/*z* 455 (M−*t*-Bu$^+$), 323, 287, 267, 247, 227, 226, 225, 214, 213, 200, 199, 195, 193, 183, 181, 179, 174, 173, 165, 163, 135, 115, 91, 89, 75, 73, 59.

5.2.4. Ethyl ester 7. To a stirred solution of olefin **6** (5.12 g, 10 mmol) in a mixture of *t*-BuOH (25 mL) and deionized water (25 mL) at rt was added OsO_4 (5.06 mL, 2.5 wt % in *t*-BuOH, 0.4 mmol) followed by *N*-methylmorpholine *N*-oxide (1.2 g, 11 mmol). After 6.5 h the reaction was quenched by the addition of $Na_2S_2O_3$ (11 g) followed by Celite (22 g) and ethyl acetate (25 mL) and the mixture was stirred for 20 min. The reaction mixture was filtered on Celite, the residue was washed with EtOAc, and the solvents were removed in vacuo.

To a solution of the above diol in a mixture of THF (100 mL) and deionized water (100 mL) at rt was added $NaIO_4$ (5.35 g, 25 mmol). After 3 h the mixture was filtered on Celite and the residue was washed with ethyl acetate. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting aldehyde was used in the next step without further purification.

To a solution of phosphonate **III** (4.15 g, 12 mmol) and 18-crown-6 (12.69 g, 48 mmol) in THF (180 mL) at 0 °C, was added dropwise KHMDS (24 mL, 0.5 M in toluene, 12 mmol). After 30 min at 0 °C, the reaction was cooled to −78 °C and the above crude aldehyde in THF (50 mL) was added dropwise via cannula. After 18 h at −78 °C, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (100 mL) and warmed to rt. The mixture was then poured on a mixture of water (200 mL), pentane (150 mL) and Et_2O (150 mL). The aqueous layer was extracted with a mixture of pentane/Et_2O (1/1) and the combined organic extracts were washed with a 5% aqueous $NaHCO_3$ solution and next with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; 100/0 to 100/3) allowed us to isolate (*Z*)-(4*R*,5*S*,6*S*)-5-(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-6-methoxy-2,4-dimethyl-hept-2-enoic acid ethyl ester (**7**) (4.77 g, 7.97 mmol, 80% for the last three steps). $[\alpha]_D^{20}$ −11.2 (*c* 0.91, $CHCl_3$); IR (neat) 2929, 2856, 1713, 1472, 1428, 1370, 1250, 1221, 1195, 1107, 1082, 1055, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.71 (m, 4H), 7.35–7.41 (m, 6H), 5.92 (dd, J=9.5, 1.6 Hz, 1H), 4.05 (m, 2H), 3.78 (dd, J=11.0, 4.3 Hz, 1H), 3.63–3.68 (m, 2H), 3.29 (s, 3H), 3.24–3.34 (m, 1H), 3.16 (m, 1H), 1.86 (d, J=1.3 Hz, 3H), 1.15 (t, J=7.2 Hz, 3H), 1.04 (s, 9H), 0.94 (d, J=6.6 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 146.3, 135.7 (4C), 133.6 (2C), 129.6 (2C), 127.6 (4C), 125.5, 84.6, 75.8, 63.4, 60.0, 58.8, 35.9, 26.8 (3C), 26.2 (3C), 20.8, 19.2, 18.5, 15.0, 14.2, −3.9, −4.6; HRMS (ESI) calcd for $C_{34}H_{54}O_5KSi_2$ [M+K$^+$] 637.3147. Found 637.3150.

5.2.5. Alcohol 8. To a solution of ester **7** (4.21 g, 7.04 mmol) in CH_2Cl_2 (125 mL) at −78 °C, was added dropwise DIBAL-H (15.5 mL, 1 M in hexanes, 15.5 mmol). The cooling bath was removed and after 2 h at rt, the reaction mixture was cooled to −60 °C and then transferred via cannula to a saturated aqueous solution of potassium sodium tartrate. After 2 h stirring at rt, the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (petroleum ether/Et_2O; 8/2) furnished allylic alcohol **8** (3.66 g, 6.59 mmol, 94%). $[\alpha]_D^{20}$ +2.5 (*c* 1.075, $CHCl_3$); IR (neat) 3417, 3071, 2929, 2885, 2856, 1472, 1428, 1389, 1361, 1252, 1189, 1111, 1081, 1026, 1005 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.70 (m, 4H), 7.37–7.45 (m, 6H), 5.15 (d, J=10.0 Hz, 1H), 4.10 (dd, J=12.1, 3.3 Hz, 1H), 3.92 (dd, J=11.5, 6.7 Hz, 1H), 3.78 (dd, J=10.9, 4.8 Hz, 1H), 3.73 (dd, J=11.2, 5.4 Hz, 1H), 3.59 (t, J=5.4 Hz, 1H), 3.26 (s, 3H), 3.21 (q, J=5.1 Hz, 1H), 2.72 (m, 1H), 1.83 (m, 1H, OH), 1.78 (d, J=1.1 Hz, 3H), 1.06 (s, 9H), 0.91 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.7 (4C), 133.6, 133.5 (2C), 132.5, 129.7 (2C), 127.7 (4C), 83.6, 76.2, 62.7, 61.8, 57.8, 34.7, 26.9 (3C), 26.2 (3C), 21.7, 19.2, 18.4, 17.2, −4.0, −4.4; HRMS (ESI) calcd for $C_{32}H_{52}O_4KSi_2$ [M+K$^+$] 595.3041. Found 595.3041.

5.3. Synthesis of macrolide 2

5.3.1. Ester 11. To a solution of alcohol **8** (556 mg, 1 mmol) in toluene (25 mL) at rt was added pyridine (326 μL, 4 mmol) followed by the mixed anhydride **IV** (3 mmol).[13] After stirring for 24 h, the reaction was directly loaded onto a silica gel column and purification by flash chromatography (petroleum ether/Et_2O; 100/0 to 100/3) furnished ester **11** (444 mg, 0.67 mmol, 67%). $[\alpha]_D^{20}$ +1.7 (*c* 0.06, $CHCl_3$); IR (neat) 2956, 2929, 2856, 1721, 1656, 1472,

1428, 1361, 1252, 1194, 1166, 1112, 1083, 1026, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69 (m, 4H), 7.36–7.44 (m, 6H), 6.94 (dt, J=15.4, 7.0 Hz, 1H), 5.74–5.85 (m, 2H), 5.38 (d, J=9.9 Hz, 1H), 4.98–5.08 (m, 2H), 4.70 (d, J=11.8 Hz, 1H), 4.52 (d, J=12.2 Hz, 1H), 3.74 (dd, J=11.0, 5.4 Hz, 1H), 3.68 (dd, J=11.0, 5.1 Hz, 1H), 3.63 (t, J=5.0 Hz, 1H), 3.21 (s, 3H), 3.10 (q, J=5.1 Hz, 1H), 2.76 (m, 1H), 2.26–2.33 (m, 2H), 2.17–2.24 (m, 2H), 1.73 (d, J=1.7 Hz, 3H), 1.05 (s, 9H), 0.93 (d, J=6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 148.3, 137.1, 135.7 (4C), 135.2, 133.6, 133.5, 129.7 (2C), 128.5, 127.7 (4C), 121.6, 115.5, 84.0, 76.2, 63.0, 62.8, 58.4, 34.6, 32.1, 31.5, 26.8 (3C), 26.2 (3C), 21.5, 19.2, 18.5, 16.2, −3.9, −4.4; HRMS (ESI) calcd for $C_{39}H_{60}O_5KSi_2$ [M+K^+] 703.3616. Found 703.3624.

5.3.2. Alcohol 12. To a solution of ester **11** (350 mg, 0.53 mmol) in refluxing MeOH (20 mL) was added NH_4F by portions (466 mg, 3.69 mmol) over 7 h. The reaction mixture was quenched by the addition of a saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; from 100/0 to 50/50) yielded alcohol **12** (175 mg, 0.41 mmol, 77%). $[\alpha]_D^{20}$ +2.4 (c 0.35, $CHCl_3$); IR (neat) 3450, 2922, 2853, 1722, 1657, 1461, 1377, 1362, 1255, 1167, 1157, 1113, 1080, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.91 (dt, J=15.7, 6.6 Hz, 1H), 5.71–5.82 (m, 2H), 5.35 (d, J=9.6 Hz, 1H), 4.94–5.02 (m, 2H), 4.61 (s, 2H), 3.76 (dd, J=11.9, 3.3 Hz, 1H), 3.62 (dd, J=6.5, 3.6 Hz, 1H), 3.56 (dd, J=11.9, 5.0 Hz, 1H), 3.35 (s, 3H), 3.11 (m, 1H), 2.68 (m, 1H), 2.35 (br s, 1H, OH), 2.23–2.28 (m, 2H), 2.15–2.19 (m, 2H), 1.70 (d, J=1.3 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.5, 148.6, 137.0, 135.2, 128.5, 121.5, 115.5, 84.4, 75.6, 63.0, 60.6, 58.1, 34.2, 32.0, 31.5, 26.1 (3C), 21.5, 18.3, 15.3, −4.1, −4.6.

5.3.3. Diene 13. To a solution of alcohol **12** (83 mg, 0.19 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added Dess–Martin periodinane (608 μL, 15 wt % in CH_2Cl_2, 0.29 mmol). After 2 h at rt, the reaction was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution followed by the addition of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding aldehyde, which was used in the next step without further purification.

To an oven-dried tube was added under argon freshly activated Zn (115 mg, 1.76 mmol) and $PbCl_2$ (2.4 mg, 2 wt %/Zn) followed by THF (2 mL). CH_2I_2 (80 μL, 0.98 mmol) was added slowly and after 0.5 h, Ti(O*i*-Pr)$_4$ (57 μL, 0.19 mmol) in THF (200 μL) was added dropwise. After 0.5 h, a solution of the above aldehyde in THF (1.6 mL) was added dropwise at rt. After 0.5 h, the reaction was quenched by the addition of a 5% aqueous Na_2CO_3 solution and the mixture was filtered on a pad of Celite and rinsed with Et_2O. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O; from 100/0 to 90/10) to afford diene **13** (52 mg, 0.12 mmol, 63%, two steps). $[\alpha]_D^{20}$ +3.0 (c 1.15, $CHCl_3$); IR (neat) 2928, 2883, 2855, 2820, 1721, 1656, 1471, 1461, 1379, 1360, 1314, 1251, 1201, 1166, 1125, 1097, 1080, 1025, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.96 (dt, J=15.2, 7.0 Hz, 1H), 5.74–5.87 (m, 2H), 5.62 (m, 1H), 5.43 (d, J=10.0 Hz, 1H), 5.21–5.29 (m, 2H), 4.98–5.08 (m, 2H), 4.61 (d, J=12.0 Hz, 1H), 4.56 (d, J=12.0 Hz, 1H), 3.46 (dd, J=7.3, 3.0 Hz, 1H), 3.36 (app t, J=7.7 Hz, 1H), 3.19 (s, 3H), 2.61 (m, 1H), 2.27–2.33 (m, 2H), 2.18–2.24 (m, 2H), 1.73 (d, J=1.3 Hz, 3H), 0.89–0.91 (m, 12H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 148.5, 137.1, 135.6, 135.1, 128.2, 121.5, 118.8, 115.5, 86.3, 78.4, 63.1, 56.1, 34.3, 32.0, 31.5, 26.2 (3C), 21.5, 18.6, 14.0, −3.8, −4.8; HRMS (ESI) calcd for $C_{24}H_{42}O_4KSi$ [M+K^+] 461.2489. Found 461.2490.

5.3.4. Macrolactone 14.[6c] To a solution of diene **13** (45 mg, 107 μmol) in refluxing toluene (200 mL) was added the second generation Grubbs catalyst [Ru]-**II** (18 mg, 21.2 μmol). After stirring for 20 min, the reaction was cooled to rt and filtered through a pad of silica gel (hexane/EtOAc; 4/1). The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc; from 20/1 to 20/2) to afford macrolactone **14** (20 mg, 51 μmol, 47%). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.81 (dt, J=16.0, 7.5 Hz, 1H), 5.72 (d, J=16 Hz, 1H), 5.48–5.55 (m, 2H), 5.10 (dd, J=15.6, 8.7 Hz, 1H), 4.67 (d, J=15.6 Hz, 1H), 4.61 (d, J=16.0 Hz, 1H), 3.44 (dd, J=8.5, 1.6 Hz, 1H), 3.30 (app t, J=8.4 Hz, 1H), 3.16 (s, 3H), 2.98 (m, 1H), 2.32–2.46 (m, 2H), 2.12–2.30 (m, 2H), 1.63 (s, 3H), 0.91 (s, 9H), 0.82 (d, J=6.9 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 149.9, 132.0, 130.5 (2C), 126.6, 121.9, 85.8, 77.5, 65.6, 55.9, 33.1, 32.5, 30.0, 26.3 (3C), 22.2, 18.7, 12.9, −3.6, −5.0.

5.3.5. Macrolide 2.[6c] To a solution of macrolactone **14** (20 mg, 50.8 μmol) in THF (1.5 mL) was added HF·Py (350 μL). After 16 h at rt, the reaction was quenched by addition of $NaHCO_3$. Water was added to the reaction mixture and the aqueous phase was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; from 9/1 to 8/2) furnished macrolide **2** (9.5 mg, 33.9 μmol, 67%). $[\alpha]_D^{20}$ +80.9 (c 0.47, $CHCl_3$); IR (neat) 3491, 2928, 2877, 1720, 1660, 1440, 1379, 1325, 1248, 1188, 1157, 1100, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.78 (m, 1H), 5.75 (d, J=15.7 Hz, 1H), 5.55–5.63 (m, 2H), 5.10–5.16 (m, 1H), 4.74 (d, J=15.6 Hz, 1H), 4.63 (d, J=15.6 Hz, 1H), 3.39–3.42 (m, 2H), 3.29 (s, 3H), 3.01 (m, 1H), 2.70 (s, 1H), 2.38–2.49 (m, 2H), 2.17–2.33 (m, 2H), 1.68 (s, 3H), 0.88 (d, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.4, 149.5, 133.8, 129.8, 129.5, 127.5, 122.1, 84.6, 76.1, 65.4, 56.2, 32.2, 31.3, 30.0, 22.3, 12.7.

5.4. Synthesis of allylglutarimide 15

3-(2-Propenyl)-glutaric acid **22**[20] (1.81 g, 10.54 mmol) and urea (0.7 g, 11.59 mmol) were heated at 140 °C. After 2 h, the temperature was raised to 180 °C for 20 min. Purification by flash chromatography on silica gel ($CHCl_3$/acetone; 9/1) furnished allylglutarimide **15** (1.40 g, 9.16 mmol, 87%). IR (neat) 3188, 3079, 2903, 1717, 1671, 1641, 1428, 1377,

1288, 1261, 1142, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.45 (br s, 1H, NH), 5.70 (ddt, J=17.1, 10.1, 7.0 Hz, 1H), 5.06–5.14 (m, 2H), 2.65–2.72 (m, 2H), 2.12–2.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (2C), 133.7, 118.5, 38.8, 37.3 (2C), 30.0. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.84; H, 7.05; N, 9.18.

5.5. Synthesis of migrastatin (1)

5.5.1. Alcohol 17. To a stirred solution of alcohol **8** (1.18 g, 2.12 mmol) in CH_2Cl_2 (15 mL) at rt was added MnO_2 (5.1 g). After 24 h, the reaction mixture was filtered on Celite. The solvent was removed in vacuo and aldehyde **16** was used in the next step without further purification.

To a stirred solution of Ti(*S*,*S*)-**I**[18] (2.97 mmol) in Et_2O (48 mL) at −78 °C was added dropwise a solution of the freshly prepared crude aldehyde **16** in Et_2O (15 mL). After 16 h at −78 °C, water (20 mL) was added to the reaction mixture. After stirring for 24 h at rt, the reaction mixture was filtered on Celite and the organic phase was washed with brine and then dried over $MgSO_4$. After evaporation of the solvent, the residue was diluted with pentane (100 mL) and stirred for 2 h. The white precipitate (Taddol) was filtered and pentane was removed in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc; 100/5) furnished alcohol **17** (1.03 g, 1.69 mmol, 80% from **8**). $[\alpha]_D^{20}$ +2.2 (*c* 0.76, $CHCl_3$); IR (neat) 2957, 2929, 2857, 1472, 1428, 1361, 1251, 1190, 1110, 1085, 1054, 1026, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67–7.71 (m, 4H), 7.36–7.45 (m, 6H), 5.59 (ddd, J=17.1, 10.2, 8.7 Hz, 1H), 5.42 (dd, J=10.2, 1.2 Hz, 1H), 5.09–5.16 (m, 2H), 4.05 (d, J=9.4 Hz, 1H), 3.70 (dd, J=11.1, 4.6 Hz, 1H), 3.67 (dd, J=11.0, 5.0 Hz, 1H), 3.52 (dd, J=6.5, 3.0 Hz, 1H), 3.28 (s, 3H), 3.15 (dt, J=6.6, 5.0 Hz, 1H), 2.75 (m, 1H), 2.27 (m, 1H), 1.70 (m, 1H, OH), 1.67 (d, J=1.0 Hz, 3H), 1.06 (s, 9H), 0.91 (d, J=6.6 Hz, 3H), 0.90 (s, 9H), 0.79 (d, J=6.8 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.5, 135.7 (4C), 135.0, 133.5, 133.5, 132.5, 129.8, 129.7, 127.7 (4C), 116.6, 84.7, 76.7, 72.7, 63.5, 58.7, 42.7, 33.3, 26.9 (3C), 26.2 (3C), 19.2, 18.5, 17.8, 16.7, 15.7, −3.8, −4.5; HRMS (ESI) calcd for $C_{36}H_{58}O_4KSi_2$ [M+K^+] 649.3511. Found 649.3514.

5.5.2. Olefin 18. To a solution of alcohol **17** (220 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) at 0 °C, were added imidazole (98 mg, 1.44 mmol) followed by Et_3SiCl (181 μL, 1.08 mmol). After 6 h at rt, water (2 mL) was added to the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; 100/1) allowed us to isolate olefin **18** (235 mg, 0.33 mmol, 90%). $[\alpha]_D^{20}$ −4.9 (*c* 0.68, $CHCl_3$); IR (neat) 2955, 2931, 2877, 2857, 1641, 1590, 1461, 1428, 1376, 1248, 1191, 1110, 1056, 1029, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.68–7.71 (m, 4H), 7.36–7.45 (m, 6H), 5.77–5.86 (m, 1H), 5.25 (d, J=10.3 Hz, 1H), 4.91–4.97 (m, 2H), 4.11 (d, J=8.0 Hz, 1H), 3.73 (dd, J=11.2, 4.7 Hz, 1H), 3.61–3.68 (m, 1H), 3.47 (dd, J=7.4, 2.0 Hz, 1H), 3.29 (s, 3H), 3.15 (m, 1H), 2.58 (m, 1H), 2.23 (app sext, J=7.4 Hz, 1H), 1.63 (s, 3H), 1.07 (s, 9H), 0.91 (s, 9H), 0.86–0.91 (m, 12H), 0.79 (d, J=7.1 Hz, 3H), 0.49 (q, J=8.0 Hz, 6H), 0.04 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.2, 135.7 (2C), 135.6 (2C), 134.6, 133.4 (2C), 132.1, 129.7 (2C), 127.7 (4C), 113.8, 85.1, 76.8, 74.3, 64.2, 59.2, 42.7, 33.1, 26.9 (3C), 26.2 (3C), 19.2, 18.5, 18.2, 16.7, 14.1, 6.9 (3C), 4.9 (3C), −3.9, −4.6; HRMS (ESI) calcd for $C_{42}H_{72}O_4KSi$ [M+K^+] 763.4375. Found 763.4383.

5.5.3. Vinyl ketone 20. To a stirred solution of olefin **18** (548 mg, 0.76 mmol) in a mixture of *t*-BuOH (2 mL) and deionized water (2 mL) at rt was added OsO_4 (383 μL, 2.5 wt % in *t*-BuOH, 0.03 mmol) followed by *N*-methylmorpholine *N*-oxide (89 mg, 0.76 mmol). After 12 h the reaction was quenched by addition of $Na_2S_2O_3$ (800 mg) followed by addition of Celite (2 g) and EtOAc (5 mL) and the mixture was stirred for 20 min. The reaction mixture was filtered on a pad of Celite, the residue was washed with EtOAc, and the solvents were removed in vacuo.

To a solution of the above crude diol in a mixture of THF (7 mL) and deionized water (7 mL) at rt was added $NaIO_4$ (729 mg, 3.4 mmol). After 2 h the reaction mixture was filtered on Celite and the residue was washed with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After a rapid purification by flash chromatography on silica gel (petroleum ether/Et_2O; 9/1) aldehyde **19** (441 g, 0.61 mmol, 80%) was isolated and directly engaged in the following reaction. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.66 (m, 1H), 7.69 (m, 4H), 7.37–7.45 (m, 6H), 5.36 (d, J=10.4 Hz, 1H), 4.60 (d, J=9.2 Hz, 1H), 3.73 (dd, J=11.0, 4.0 Hz, 1H), 3.65 (dd, J=11.0, 5.7 Hz, 1H), 3.47 (d, J=7.4 Hz, 1H), 3.28 (s, 3H), 3.15 (m, 1H), 2.65 (m, 1H), 2.52 (m, 1H), 1.65 (s, 3H), 1.07 (s, 9H), 0.90 (s, 9H), 0.85–0.90 (m, 12H), 0.79 (d, J=7.1 Hz, 3H), 0.51 (q, J=7.9 Hz, 6H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0, 135.7 (2C), 135.6 (2C), 134.1, 133.3, 132.2, 129.8 (2C), 127.7 (4C), 85.1, 76.7, 71.3, 64.0, 59.0, 50.8, 33.1, 26.9 (3C), 26.2 (3C), 22.6, 19.2, 18.5, 17.6, 14.2, 11.1, 6.8 (3C), 4.8 (3C), −3.9, −4.6.

To a solution of the freshly prepared aldehyde **19** in THF (8 mL) at −78 °C was added dropwise vinylmagnesium chloride (1.14 mL, 1.6 M in THF, 1.82 mmol). After 30 min, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution (4.5 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding allylic alcohol, which was used in the next step without further purification.

To a solution of the above alcohol in CH_2Cl_2 (10 mL) at 0 °C was added Dess–Martin periodinane (2.5 mL, 15 wt % in CH_2Cl_2, 1.21 mmol). After 30 min at rt, the reaction was quenched by addition of a saturated aqueous $Na_2S_2O_3$ solution (8 mL) followed by the addition of a saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O; from 100/0 to 100/4) yielded vinyl ketone

20 (331 mg, 0.44 mmol, 73%). $[\alpha]_D^{20}$ −14.1 (*c* 0.46, $CHCl_3$); IR (neat) 2930, 2855, 1699, 1678, 1615, 1589, 1456, 1428, 1377, 1365, 1245, 1188, 1131, 1109, 1051, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72–7.74 (m, 4H), 7.40–7.43 (m, 6H), 6.40 (dd, *J*=17.2, 10.5 Hz, 1H), 6.23 (dd, *J*=17.4, 1.3 Hz, 1H), 5.73 (dd, *J*=10.6, 1.4 Hz, 1H), 5.37 (d, *J*=10.6 Hz, 1H), 4.67 (d, *J*=9.6 Hz, 1H), 3.78 (dd, *J*=11.0, 4.5 Hz, 1H), 3.67 (dd, *J*=11.1, 6.0 Hz, 1H), 3.48 (dd, *J*=7.4, 1.5 Hz, 1H), 3.28 (s, 3H), 3.07–3.20 (m, 2H), 2.74 (m, 1H), 1.67 (s, 3H), 1.08 (s, 9H), 0.91 (s, 9H), 0.88 (d, *J*=6.6 Hz, 3H), 0.82 (d, *J*=6.9 Hz, 3H), 0.82 (t, *J*=7.9 Hz, 9H), 0.45 (q, *J*=8.1 Hz, 6H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 203.5, 137.2, 135.8 (2C), 135.7 (2C), 134.1, 133.5, 133.4, 132.5, 129.7 (2C), 127.7 (4C), 127.5, 85.3, 76.9, 72.7, 64.1, 59.1, 46.8, 33.0, 26.9 (3C), 26.2 (3C), 19.2, 18.5, 17.6, 14.2, 14.1, 6.8 (3C), 4.7 (3C), −3.9, −4.6; HRMS (ESI): calcd for $C_{43}H_{72}O_5Si_3Na$ $[M+Na]^+$: 775.4586. Found: 775.4622.

5.5.4. Enone 24. To a stirred solution of vinyl ketone **20** (98 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) at rt was added allylglutarimide **15** (40 mg, 0.26 mmol) followed by [Ru]-**III** (12 mg, 20 μmol). After 36 h, allylglutarimide **15** (20 mg, 0.13 mmol) and [Ru]-**III** (12 mg, 20 μmol) were added. After 36 h, purification by flash chromatography on silica gel (petroleum ether/EtOAc; from 100/0 to 80/20) yielded the unreacted vinyl ketone **20** (39 mg, 51.9 μmol, 40%) and enone **24** (36.5 mg, 41.6 μmol, 32%). $[\alpha]_D^{20}$ −6.6 (*c* 0.35, $CHCl_3$); IR (neat) 3210, 2931, 2857, 1697, 1627, 1461, 1428, 1370, 1361, 1255, 1191, 1111, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.13 (br s, 1H, NH), 7.73 (m, 4H), 7.41 (m, 6H), 6.69 (dt, *J*=15.5, 6.4 Hz, 1H), 6.25 (d, *J*=15.8 Hz, 1H), 5.37 (d, *J*=10.3 Hz, 1H), 4.54 (d, *J*=9.5 Hz, 1H), 3.78 (dd, *J*=11.0, 4.6 Hz, 1H), 3.67 (dd, *J*=11.1, 5.9 Hz, 1H), 3.48 (d, *J*=7.4 Hz, 1H), 3.27 (s, 3H), 3.16 (m, 1H), 3.01 (m, 1H), 2.65–2.79 (m, 3H), 2.24–2.38 (m, 5H), 1.66 (s, 3H), 1.07 (s, 9H), 0.90 (s, 9H), 0.88 (d, *J*=7.7 Hz, 3H), 0.78–0.85 (m, 12H), 0.45 (q, *J*=8 Hz, 6H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.6, 171.5 (2C), 140.1, 135.8 (4C), 134.3, 134.1, 133.6, 133.5, 132.4, 129.7 (2C), 127.8 (4C), 85.4, 76.9, 72.9, 64.1, 59.1, 47.9, 37.5 (2C), 37.4, 33.1, 29.9, 27.0 (3C), 26.2 (3C), 19.2, 18.5, 17.6, 14.3, 14.1, 6.9 (3C), 4.7 (3C), −3.8, −4.5; HRMS (ESI): calcd for $C_{49}H_{79}O_7NSi_3Na$ $[M+Na]^+$: 900.5062. Found: 900.5040.

5.5.5. Ketone 25. To a stirred solution of enone **24** (78 mg, 88.9 μmol) in EtOAc (2 mL) at rt was added Pd/C 5% (9.5 mg). H_2 was bubbled in the reaction mixture and after 9 h Celite was added. The mixture was filtered on Celite and the solvent was removed in vacuo to yield ketone **25** (75 mg, 85.3 μmol, 96%). $[\alpha]_D^{20}$ −6.6 (*c* 0.99, $CHCl_3$); IR (neat) 3213, 2955, 2932, 2878, 2857, 1709, 1461, 1428, 1377, 1256, 1112, 1056, 1026, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.03 (br s, 1H, NH), 7.70–7.73 (m, 4H), 7.38–7.44 (m, 6H), 5.36 (d, *J*=10.6 Hz, 1H), 4.60 (d, *J*=9.4 Hz, 1H), 3.77 (dd, *J*=11.3, 4.7 Hz, 1H), 3.66 (dd, *J*=11.0, 6.0 Hz, 1H), 3.47 (dd, *J*=7.4, 1.5 Hz, 1H), 3.27 (s, 3H), 3.16 (m, 1H), 2.68–2.80 (m, 4H), 2.43–2.58 (m, 2H), 2.21–2.30 (m, 2H), 2.10–2.19 (m, 1H), 1.63 (s, 3H), 1.53–1.67 (m, 2H), 1.33–1.43 (m, 2H), 1.07 (s, 9H), 0.90 (s, 9H), 0.87 (d, *J*=6.5 Hz, 3H), 0.84 (t, *J*=8.0 Hz, 9H), 0.76 (d, *J*=7.0 Hz, 3H), 0.46 (q, *J*=8.0 Hz, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.7, 172.3 (2C), 135.8 (2C), 135.7 (2C), 134.4, 133.5, 133.4, 132.1, 129.7 (2C), 127.7 (4C), 85.4, 76.9, 72.9, 64.0, 59.1, 49.5, 44.2, 37.8 (2C), 34.4, 33.0, 30.5, 26.9 (3C), 26.2 (3C), 20.1, 19.2, 18.5, 17.5, 14.1, 13.8, 6.8 (3C), 4.7 (3C), −3.9, −4.6; HRMS (ESI) calcd for $C_{49}H_{81}O_7NKSi_3$ $[M+K^+]$ 918.4958. Found 918.4968.

5.5.6. Ester 26. Ketone **25** (115 mg, 0.130 mmol) was stirred in a mixture of acetic acid (3 mL), THF (1 mL), and water (1 mL) at rt. After 6 h, the reaction was quenched by addition of Na_2CO_3. Water was added and the aqueous phase was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes/EtOAc; 7/3) furnished the corresponding alcohol (80 mg, 0.105 mmol, 80%). $[\alpha]_D^{20}$ −5.9 (*c* 1.42, $CHCl_3$); IR (neat) 3468, 2956, 2931, 2857, 1700, 1461, 1428, 1377, 1362, 1257, 1112, 1086, 1056, 1026, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.19 (br s, 1H, NH), 7.68–7.70 (m, 4H), 7.36–7.44 (m, 6H), 5.43 (d, *J*=9.9 Hz, 1H), 4.60 (d, *J*=9.5 Hz, 1H), 3.74 (dd, *J*=11.1, 4.8 Hz, 1H), 3.68 (dd, *J*=11.1, 5.6 Hz, 1H), 3.54 (dd, *J*=6.4, 3.6 Hz, 1H), 3.26 (s, 3H), 3.16 (app q, *J*=5.6 Hz, 1H), 2.67–2.82 (m, 4H), 2.50 (t, *J*=7.1 Hz, 2H), 2.21–2.28 (m, 2H), 2.07–2.17 (m, 2H), 1.66 (s, 3H), 1.57–1.64 (m, 2H), 1.32–1.39 (m, 2H), 1.05 (s, 9H), 0.89–0.91 (m, 3H), 0.89 (s, 9H), 0.83 (d, *J*=6.7 Hz, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.7, 172.2 (2C), 135.7 (4C), 135.4, 133.5, 133.4, 131.9, 129.7 (2C), 127.7 (4C), 84.6, 76.3, 71.8, 63.3, 58.6, 49.3, 42.2, 37.7 (2C), 34.1, 33.5, 30.4, 26.9 (3C), 26.2 (3C), 20.1, 19.2, 18.5, 17.9, 16.2, 13.7, −3.9, −4.5; HRMS (ESI) calcd for $C_{43}H_{67}O_7NKSi_2$ $[M+K^+]$ 804.4093. Found 804.4101.

To a solution of the above alcohol (70 mg, 91.5 μmol) in toluene (840 μL) at rt was added pyridine (30 μL, 0.37 mmol) followed by the mixed anhydride (0.275 mmol).[13] After stirring for 48 h, the reaction was directly loaded onto a silica gel column and purification by flash chromatography (petroleum ether/EtOAc; 9/1 to 7/3) furnished ester **26** (58.8 mg, 67.4 μmol, 74%). $[\alpha]_D^{20}$ −31.7 (*c* 1.08, $CHCl_3$); IR (neat) 2930, 2857, 1723, 1461, 1428, 1378, 1361, 1258, 1150, 1113, 1086, 1057, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (br s, 1H, NH), 7.69–7.72 (m, 4H), 7.35–7.43 (m, 6H), 6.89 (dt, *J*=15.5, 6.4 Hz, 1H), 5.69–5.83 (m, 3H), 5.52 (d, *J*=10.5 Hz, 1H), 4.98–5.06 (m, 2H), 3.80 (dd, *J*=11.1, 4.2 Hz, 1H), 3.73 (dd, *J*=11.1, 5.5 Hz, 1H), 3.56 (dd, *J*=6.8, 2.4 Hz, 1H), 3.27 (s, 3H), 3.18 (m, 1H), 2.85–3.00 (m, 2H), 2.64–2.68 (m, 2H), 2.30–2.45 (m, 2H), 2.15–2.30 (m, 6H), 2.01–2.11 (m, 1H), 1.61 (d, *J*=0.9 Hz, 3H), 1.52 (m, 2H), 1.20–1.27 (m, 2H), 1.07 (s, 9H), 0.93 (d, *J*=6.4 Hz, 3H), 0.89 (s, 9H), 0.87–0.89 (m, 3H), 0.05 (s, 3H), 0.01 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8, 172.0 (2C), 164.6, 148.9, 137.4, 137.0, 135.7 (4C), 133.7, 133.6, 129.6 (2C), 127.7 (4C), 127.0, 121.3, 115.6, 84.9, 76.0, 73.6, 63.5, 58.7, 47.9, 40.4, 37.7 (2C), 34.1, 33.9, 32.0, 31.5, 30.4, 27.0 (3C), 26.2 (3C), 20.1, 19.3, 18.5, 18.0, 14.6, 13.5, −3.8, −4.6; HRMS (ESI): calcd for $C_{50}H_{75}O_8NSi_2Na$ $[M+Na]^+$: 896.4929. Found: 896.4888.

5.5.7. Alcohol 27. To a solution of ester **26** (50 mg, 57.3 μmol) at rt in MeOH (2.5 mL) was added NH_4F

(51 mg, 1.37 mmol). After 18 h, more NH_4F (13 mg, 0.34 mmol) was added. The reaction mixture was quenched by addition of a saturated aqueous $NaHCO_3$ solution (1.5 mL), brine (1.5 mL) followed by EtOAc (6 mL). The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc; 5/5) allowed us to isolate alcohol **27** (29.3 mg, 46.1 μmol, 81%). IR (neat) 2926, 2854, 1702, 1655, 1460, 1428, 1376, 1363, 1245, 1113, 1054, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.12 (br s, 1H, NH), 6.89 (dt, J=15.6, 6.4 Hz, 1H), 5.86 (d, J=10.8 Hz, 1H), 5.69–5.81 (m, 3H), 5.52 (d, J=9.8 Hz, 1H), 4.97–5.04 (m, 2H), 3.90 (dd, J=12.2, 3.1 Hz, 1H), 3.62–3.78 (m, 2H), 3.37 (s, 3H), 3.11 (m, 1H), 3.04 (m, 1H), 2.93 (m, 1H), 2.65–2.70 (m, 2H), 2.48 (t, J=6.9 Hz, 2H), 2.04–2.31 (m, 7H), 1.62 (s, 3H), 1.52–1.62 (m, 2H), 1.25–1.34 (m, 2H), 0.97 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.6, 172.2 (2C), 165.0, 149.1, 138.2, 137.0, 127.4, 121.3, 115.7, 84.5, 76.0, 73.3, 60.0, 58.0, 48.0, 40.2, 37.8 (2C), 34.1, 33.6, 32.0, 31.5, 30.3, 26.1 (3C), 20.2, 18.5, 17.6, 13.5, 13.4, −3.8, −4.6; HRMS (ESI) calcd for $C_{34}H_{57}O_8NKSi$ [M+K^+] 674.3491. Found 674.3496.

5.5.8. Macrolactone 29.[4,6c] To a solution of alcohol **27** (15 mg, 23.6 μmol) in CH_2Cl_2 (4 mL) at 0 °C was added Dess–Martin periodinane (70 μL, 15 wt % in CH_2Cl_2, 35.4 μmol). After 1 h at rt, the reaction mixture was quenched by the addition of a saturated aqueous $Na_2S_2O_3$ solution followed by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding aldehyde, which was used in the next step without further purification.

To an oven-dried tube was added under argon freshly activated Zn (14 mg, 0.21 mmol) and $PbCl_2$ (0.3 mg, 2 wt %/Zn) followed by THF (300 μL). CH_2I_2 (10 μL, 0.12 mmol) was added slowly and after 30 min, Ti(O*i*-Pr)$_4$ (7 μL) was added dropwise. After 30 min, a solution of the above aldehyde in THF (150 μL) was added dropwise at rt. After 1 h, the reaction was quenched by addition of a 5% aqueous Na_2CO_3 solution and the mixture was filtered on Celite and rinsed with EtOAc. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (hexane/EtOAc; 2/1) to afford diene **28** (8 mg, 12.7 μmol, 54% for the two steps) accompanied by a minor impurity. Diene **28** was used in the next step without further purification.

To a solution of diene **28** (8 mg, 12.7 μmol) in refluxing toluene (30 mL) was added second generation Grubbs catalyst [Ru]-**II** (2.5 mg, 2.9 μmol). After stirring for 20 min, the reaction was cooled to rt and filtered through a pad of silica gel (hexane/EtOAc; 1/3). The residue was purified by preparative TLC (hexane/EtOAc; 3/7) to afford macrolactone **29** (3 mg, 5.0 μmol, 39%).[4,6c] $[\alpha]_D^{20}$ +10.0 (*c* 0.12, $CHCl_3$); IR (neat) 2955, 2929, 2856, 1721, 1461, 1377, 1264, 1131, 1115, 1029 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (br s, 1H, NH), 6.52 (m, 1H), 5.52–5.61 (m, 2H), 5.44–5.52 (m, 1H), 5.22 (dd, J=15.4, 5.3 Hz, 1H), 5.09 (d, J=9.4 Hz, 1H), 3.39 (m, 1H), 3.19 (s, 3H), 3.06 (d, J=8.3 Hz, 1H), 2.84–3.00 (m, 2H), 2.66–2.74 (m, 2H), 2.50 (app t, J=7.0 Hz, 2H), 2.38–2.47 (m, 2H), 2.08–2.31 (m, 5H), 1.81 (s, 3H), 1.54–1.66 (m, 2H), 1.31–1.38 (m, 2H), 1.11 (d, J=7.0 Hz, 3H), 0.90 (s, 9H), 0.90–0.92 (m, 3H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.8, 171.8 (2C), 163.8, 150.4, 134.0, 130.2, 129.5, 128.8, 121.9, 83.4, 79.3, 76.9, 56.7, 51.2, 40.3, 37.7 (2C), 34.2, 33.5, 31.2, 30.4, 30.3, 26.3 (3C), 25.7, 20.2, 18.7, 13.6, 13.3, −3.6, −4.9.

5.5.9. Migrastatin (1).[4,6c] To a solution of macrolactone **29** (3 mg, 5.0 μmol) in THF (250 μL) was added HF·Py (50 μL). After 24 h at rt, the reaction was quenched by the addition of Na_2CO_3. Water was added to the reaction mixture and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by preparative TLC (ethyl acetate/hexane; 2/8) furnished migrastatin (1.5 mg, 3.1 μmol, 62%).[4,6c] $[\alpha]_D^{25}$ +11.1 (*c* 0.05, MeOH); IR (neat) 3472, 3220, 2924, 2854, 1715, 1561, 1455, 1378, 1265, 1193, 1150, 1107, 1031, 1014, 982 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (br s, 1H, NH), 6.50 (m, 1H), 5.65 (dd, J=10.4, 1.7 Hz, 1H), 5.59 (dd, J=16.0, 1.4 Hz, 1H), 5.47–5.56 (m, 1H), 5.24 (dd, J=15.5, 5.0 Hz, 1H), 5.09 (d, J=10.0 Hz, 1H), 3.47 (dd, J=9.0, 5.0 Hz, 1H), 3.30 (s, 3H), 3.05 (dd, J=8.6, 2.0 Hz, 1H), 2.87–3.02 (m, 2H), 2.66–2.74 (m, 2H), 2.50 (app t, J=7.0 Hz, 2H), 2.38–2.47 (m, 2H), 2.07–2.30 (m, 5H), 1.86 (d, J=1.2 Hz, 3H), 1.50–1.70 (m, 2H), 1.30–1.39 (m, 2H), 1.12 (d, J=7.3 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.9, 171.8 (2C), 164.0, 150.0, 133.2, 131.3, 130.7, 128.2, 122.3, 82.6, 78.1, 77.3, 57.0, 51.4, 40.1, 37.8 (2C), 34.3, 32.1, 31.2, 30.5, 30.2, 26.1, 20.3, 13.5 (2C); HRMS (DCI$^+$, NH_3): calcd for $C_{27}H_{43}O_7N_2$ [M+NH_4]$^+$: 507.3070. Found: 507.3069.

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