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Synthesis of the Macrolactone of Migrastatin and Analogues with Potent Cell-Migration Inhibitory Activity

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The synthesis of the macrolactone core of migrastatin **2**, its potent anti-metastasis analogue **34**, and ester derivatives **35** and **38** are reported. The approach involves the use of a dihydroxylation reaction to establish the desired C-8 stereocenter followed by a metathesis cyclization reaction. The effects of the compounds on the migration and invasion of human breast cancer cells were evaluated by using the wound-healing and the Boyden-chamber cell-migration and cell-invasion assays. The results revealed a high potency of the macrolactones **2** and **34** and the ester analogues **35** and **38**, which suggests they have potential as antimetastatic agents.

Introduction

Migrastatin (**1**) is a natural product isolated from the cultured broth of *Streptomyces* sp. MK 929-43F1 by Imoto and co-workers in 2000 (Figure 1).[1] In 2002, researchers at Kosan Bioscience also isolated this 14-membered macrolactone with a glutarimide-containing side-chain from cultures of *Streptomyces platensis* (NRRL 18993).[2] Migrastatin induces an inhibitory effect on the migration of human tumor cells (IC_{50} = 29 μM in 4T1 cells) and has been considered an attractive lead compound for the treatment of tumor metastasis, thus becoming an interesting target for synthesis.[3–7] These important features of migrastatin have resulted in the partial and total synthesis of this compound as well as the synthesis of closely related analogues by Danishefsky, Cossy, and Das and their co-workers.[8] Among the various compounds of this family, the macrolactone core **2** of migrastatin and its analogue **3** (lacking the double bond between C2 and C3) have exhibited the most potent antitumor activity in 4T1 tumor cells (IC_{50} = 22 and 24 nM, respectively) of all the analogues synthesized to date (Figure 1).

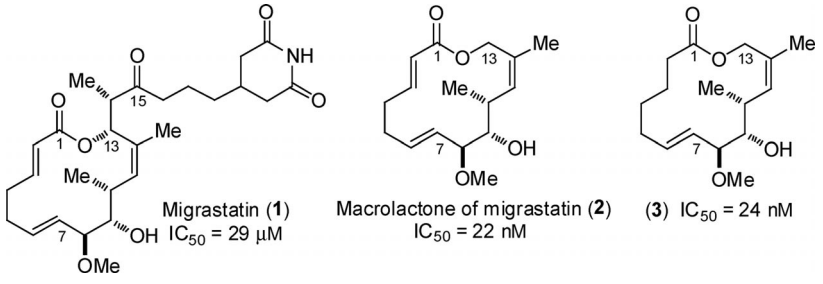

Figure 1. Structures of migrastatin (**1**) and macrolactones **2** and **3**, which exhibit potent antitumor activity in 4T1 mouse breast tumor cells.

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In 2005, Danishefsky and co-workers published the results of initial studies of the mechanism of action of migrastatin analogues.[9a] They reported that these compounds block Rac activation, lamellipodia formation, and cell migration, and that they are associated with the invasion step of the metastatic process.[9,10]

Recently, Chen et al.[11] showed that migrastatin analogues target the actin-binding sites on fascin, a small protein involved in cancer invasion and the metastasis of mul-

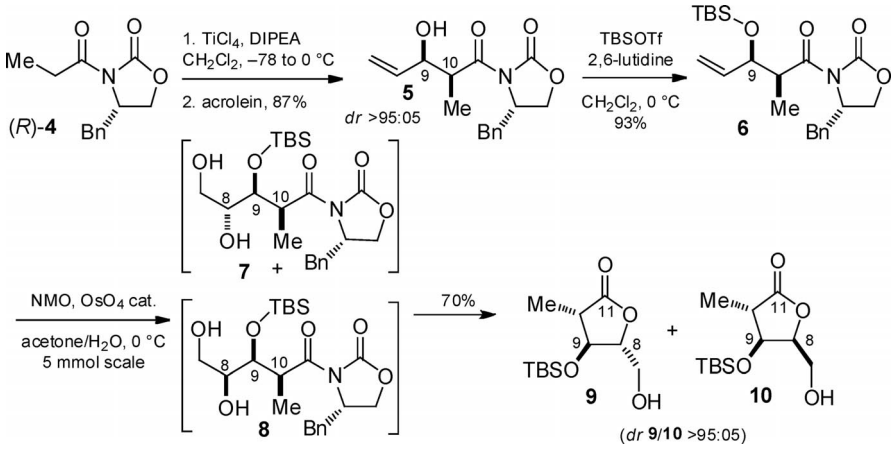
tiple epithelial cancer types.[12] Following this disclosure, Danishefsky and co-workers[13] published a correction to the report of Chen et al., establishing that the molecule in the complex with fascin is a stereoisomer of the cited analogues.

Based on the importance of migrastatin-related compounds as an attractive strategy for the development of novel anticancer therapies and as part of our ongoing research program aimed at discovering new potent cell-migration inhibitors, we report herein the synthesis, spectroscopic and physical characterization, and biological evaluation of the macrolactone of migrastatin and its new analogues.[10–12]

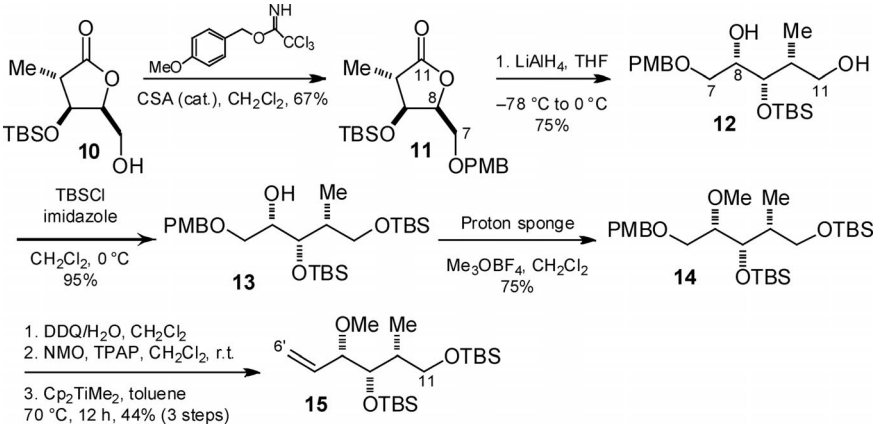
Results and Discussion

Our approach started with an asymmetric aldol addition of the titanium enolate derived from *N*-propionyloxazolidinone (*R*)-**4** to acrolein to give aldol adduct **5** (87% yield, *dr* > 95:5; Scheme 1).[14–16] Protection of the secondary alcohol as its TBS ether cleanly provided aldol **6** in 93% yield, which was smoothly converted into lactones **9** and **10** in 70% yield and with more than 95:5 diastereoselectivity on treatment with 4-methylmorpholine *N*-oxide (NMO) and catalytic amounts of OsO_4 in acetone/H_2O at 0 °C (Scheme 1).[17,18]

At room temperature this process led to the formation of a mixture of lactones **9** and **10** in 77% yield with 74:26 diastereoselectivity. These lactones were readily separated by flash column chromatography, and the oxazolidinone chiral auxiliary was recovered by crystallization from the reaction mixture.[18] We were able to prepare significant amounts of **9** and **10** to proceed with the synthesis. As shown in Scheme 2, treatment of lactone **10** with 4-methoxybenzyl 2,2,2-trichloroacetimidate in the presence of catalytic 10-camphorsulfonic acid (CSA) provided lactone **11** in 67% yield, which, after reduction with $LiAlH_4$, provided primary alcohol **12** in 75% yield. Selective protection of the primary alcohol **12** as its TBS ether (95% yield) followed by methylation with a proton sponge and Me_3OBF_4 gave bis(silyl ether) **14** in 75% yield.[19] Removal of the PMB group with DDQ/H_2O and exposure of the resulting primary alcohol to the oxidation protocol of Ley et al.[20] provided an intermediate aldehyde, which was treated under the olefination conditions of Petasis and Bzowej[21] to give olefin **15** in 44% yield in three steps.



Scheme 1. Preparation of lactones **9** and **10**.



Scheme 2. Preparation of primary olefin **15**.

Efficient selective removal of the primary TBS group in **15** was achieved after treatment with HF–Pyr–THF in THF to give the primary alcohol in 80% yield. Alcohol **16** was treated with TPAP in the presence of NMO followed by phosphonate ester **17** under Ando's conditions[22] to give (*Z*)-α,β-unsaturated ester **18** (*Z*/*E* = 85:15) in 58% yield over the two-step sequence (Scheme 3). Ester **18** was easily converted into allylic alcohol **19**, a key synthetic intermediate, after treatment with DIBAL-H in CH_2Cl_2. The relative stereochemistry of alcohol **19** was confirmed by correlation with the spectroscopic data described in the literature.[8,18]

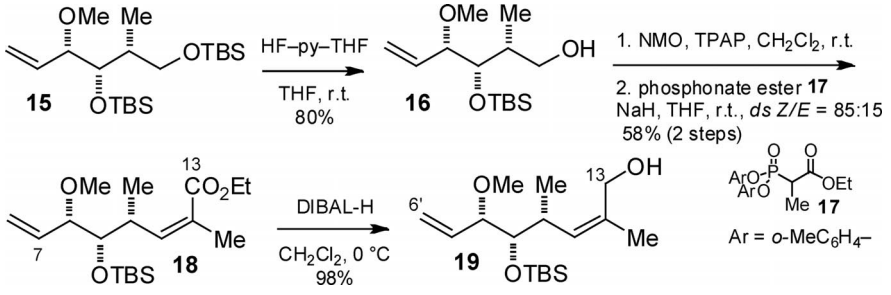
With fragments **19** and **20** in hand we proceeded to assemble the two compounds (Scheme 4). This was accomplished by a peptide-type coupling reaction in the presence of DCC and DMAP to provide ester **21** in 74% yield.[23] Treatment of ester **21** with Grubbs II catalyst in toluene at reflux provided macrolactone **22** in 43% yield.[24]

The conclusion of the synthesis required removal of the TBS protecting group positioned at C-9 to provide the desired macrolactone of migrastatin **2** in 44% yield. The spectroscopic and physical data (^1H and ^{13}C NMR, IR, $[\alpha]_D$, R_f) for **2** were identical in all respects to the published data.[8] The 17-step sequence (longest linear sequence) starting from (*R*)-**4** proceeded in 0.1% overall yield.

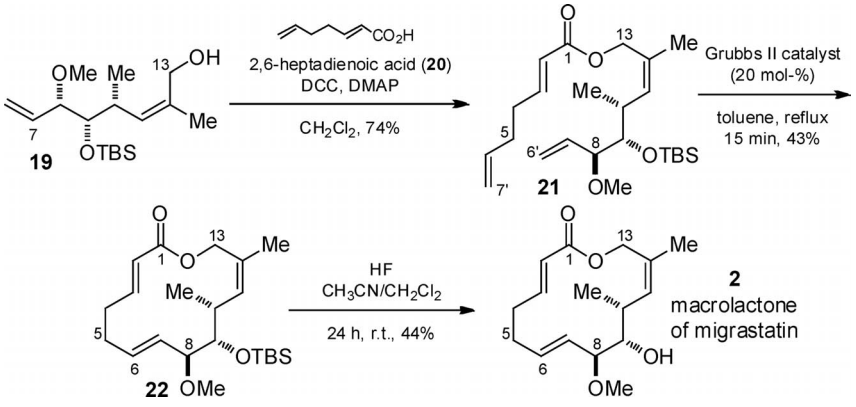
At this stage we decided to prepare the C-8 epimers of macrolactones **2** and **3**. As illustrated in Scheme 5; allylic alcohol **30** was prepared in 13% overall yield in 11 steps starting from lactone **9** in a sequence similar to that employed for the preparation of **19** (Schemes 2 and 3).

To prepare the C-8 epimer of macrolactone **3**, allylic alcohol **30** was coupled with commercially available hept-6-enoic acid (**31**) to give ester **32** in 92% yield (Scheme 6). Treatment of ester **32** with Grubbs II catalyst[24] in toluene under reflux occurred readily to give the desired macrolactone **33** in 80% yield. The last step involved removal of the TBS protecting group to give the new macrolactone **34** in 55% yield. The 17-step sequence starting from (*R*)-**4** proceeded in 3% overall yield and is amenable to a gram scale-up. At this point we decided to remove the TBS protecting group at C-9 in ester **32** to evaluate the potential in vitro activity of the corresponding derivative to inhibit tumor cell migration. For this purpose, ester **35** was prepared in 73% yield after treatment of **32** with HF in CH_3CN/CH_2Cl_2.

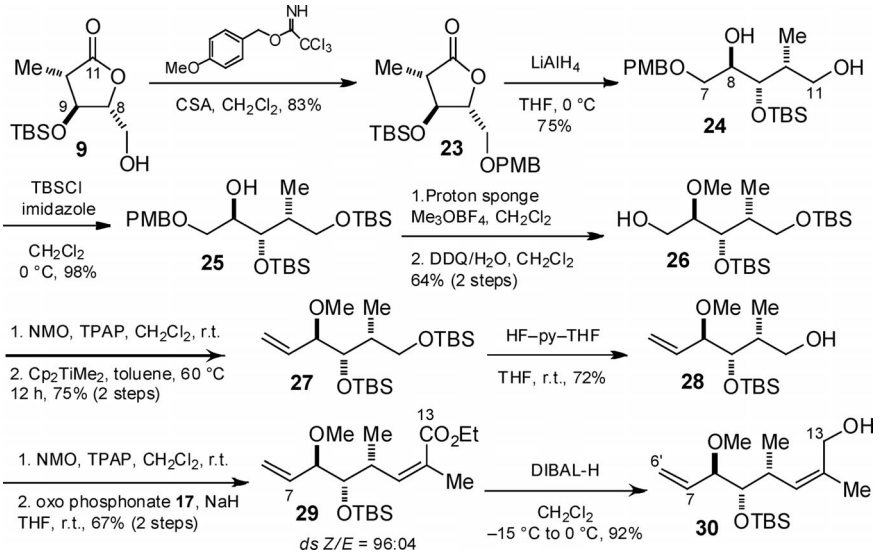
To synthesize the C-8 epimer of macrolactone **2**, allylic alcohol **30** was coupled with carboxylic acid **20** to give ester **36** in 98% yield (Scheme 7). Unfortunately, all our attempts to prepare the corresponding macrolactone **37** by a metathesis reaction failed. As before, we decided to remove the TBS protecting group at C-9 in ester **36** to evaluate the potential of ester **38** to inhibit tumor cell migration. After treatment of **36** with HF in CH_3CN/CH_2Cl_2, ester **38** was prepared in 70% yield.



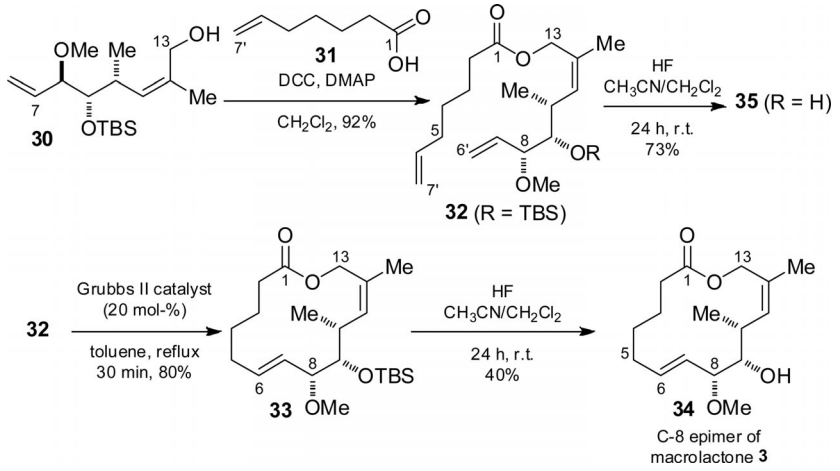
Scheme 3. Preparation of allylic alcohol **19**.



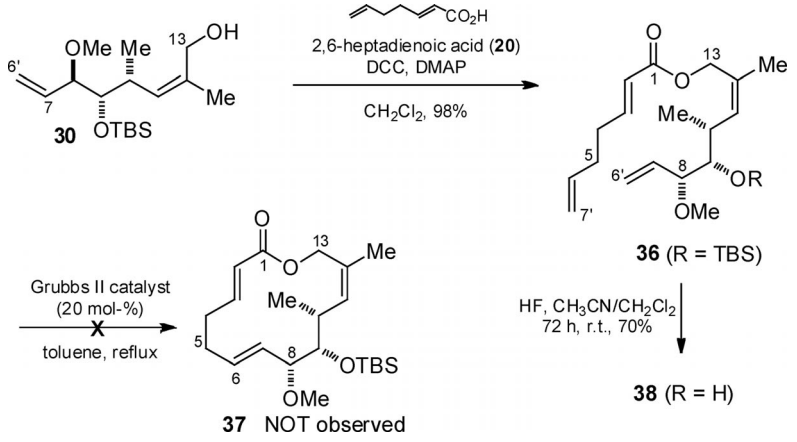
Scheme 4. Synthesis of macrolactone **2**.



Scheme 5. Preparation of allylic alcohol **30**.



Scheme 6. Synthesis of macrolactone **34** and ester **35**.



Scheme 7. Attempts to prepare macrolactone **37** and ester **38**.

Biological Studies

The macrolactones **2** and **34** as well as esters **35** and **38** were evaluated for their in vitro ability to inhibit cell migration by using MDA-MB-231 human breast tumor cells. First, we investigated the effects of these compounds on the migration of tumor cells using the wound-healing assay. Figure 2 shows the high potential of the two macrolactones **2** and **34** to inhibit cell migration in concentrations up to 1 μM.

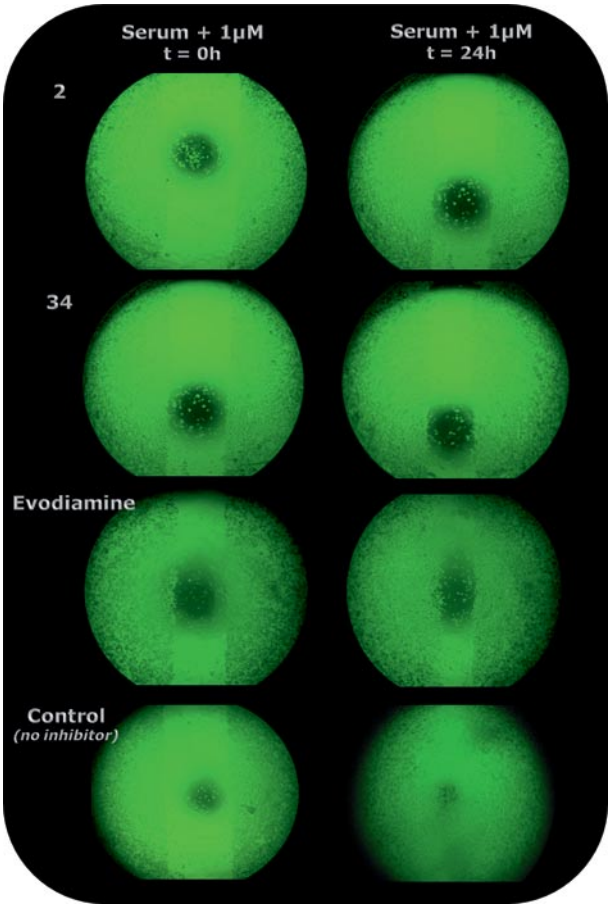


Figure 2. Wound-healing assay results for MDA-MB-231 human breast tumor cells. The figure shows a comparison between the effects of compounds **2** and **34** on the inhibition of tumor-cell migration and those of evodiamine (used as a standard in this study) and a control (no inhibitor). The black dots near the center of the figures refer to the shadow of the microscope light beam (as also in Figure 4). See the Supporting Information for experimental details, including results for esters **35** and **38**.

These results encouraged us to perform the Boyden-chamber cell-migration assay to quantitatively analyze the different effects of the compounds on cell migration and cell invasion (Table 1 and Figure 3). The Boyden-chamber cell-migration assay is based on a chamber of two medium-filled compartments separated by a microporous membrane in which the cells are seeded in the upper compartment and are allowed to migrate through the transwell insert membrane into the lower compartment in which the test compound is present. A medium containing serum is added to the lower chamber. After incubation in the presence of different concentrations of the compounds for 6 h, the number of cells that migrate from the upper chamber through the insert membrane to the lower compartment are counted.[9]

Table 1. Chamber cell-migration and cell-invasion assays with MDA-MB 213 human breast tumor cells.

Compound	IC_{50} [nM][a,b]	IC_{50} [nM][a,c]
2	34 ± 6	7 ± 2
34	14 ± 2	5 ± 1
35	53 ± 8	33 ± 3
38	22 ± 2	9 ± 2
Evodiamine[d]	280 ± 20	590 ± 104

[a] Average of three independent experiments consisting of 6–8 data points (corresponding to 6–8 different concentrations of the compounds). [b] Cell-migration assay. [c] Cell-invasion assay. [d] Used as a standard in all assays.

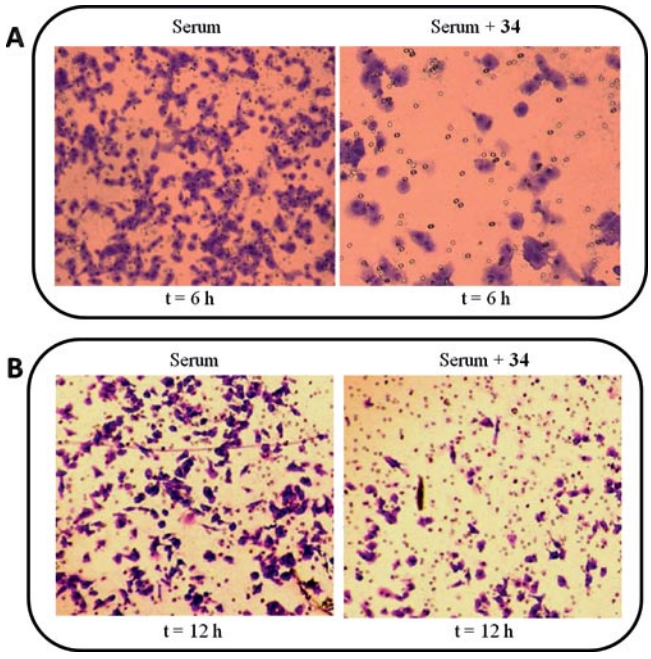


Figure 3. Effect of macrolactone **34** on the cell-migration assay (A) and on Matrigel invasion (B) by using MDA-MB-231 human breast cancer cells. The dark spots refer to the cells that migrated to the lower side of the membrane and were fixed with 100% methanol and then stained with Toluidine Blue. For more details see the Supporting Information (chamber cell-invasion assay).

The results presented in Table 1 and Figure 3 demonstrate the remarkable inhibition of tumor cell migration (MDA-MB-231 cells) exhibited by **2**, **34**, **35**, and **38** with IC_{50} values ranging from 14 to 53 nM. The macrolactone **34** (IC_{50} = 14 nM) was over two-fold more potent than the macrolactone of migrastatin, five-fold more potent than its epimer **3**, and 20-fold more potent than evodiamine, a natural product with potent anti-angiogenic properties[6–11] used as a standard for comparison purposes. Note that the ester analogues **35** and **38** also exhibited high potency with IC_{50} values of 53 and 22 nM, respectively.

Interestingly, the macrolactone of migrastatin **2** and its analogue **3**[8c] (Figure 1) had previously shown excellent inhibition of mouse breast tumor 4T1 cell migration (IC_{50}

values of 22 and 24 nM, respectively). However, the analogue **3** exhibited only moderate inhibition of migration of the human breast cancer cell MDA-MB-435 (IC_{50} = 68 nM) in comparison with the inhibitory effect on the 4T1 mouse breast cancer cell line.[8c] The migratory ability of tumor cells is a requirement for achieving tumor-cell invasion.

We then investigated the effects of compounds **2** and **34** on the invasiveness of the MDA-MB-231 breast cancer cells using an in vitro Matrigel invasion assay, which mimics the in vivo process. This is a modified Boyden-chamber assay that uses a basement membrane matrix preparation (Matrigel) as the matrix barrier (see the Supporting Information for experimental details).

As shown in Table 1, compounds **2**, **34**, **35**, and **38** significantly suppressed the invasion of MDA-MD-231 cells into Matrigel with IC_{50} values of 7, 5, 33, and 9 nM, respectively. The effect of the most potent compound **34** on cell invasion is also depicted in Figure 3. This compound is more than 100-fold more potent than evodiamine. The results obtained with this assay show a strong correlation between the ability of tumor cells to invade in vitro and their invasive behavior in vivo.

The effects of compounds **2**, **34**, **35**, and **38** were further evaluated by using the DU-145 human prostate cancer cells. The tumor cells were treated with increasing concentrations of the compounds up to 1 μM. Even at high concentrations, the compounds were considered inactive, which reveals valuable new information about the selectivity of these compounds for cancer-cell cytotoxicity. These findings confirm previous studies that showed that selectivity for cancer-cell cytotoxicity can be achieved by different synthetic migrastatin analogues such as macroketones, macrolactones, and macrolactams.[8–11]

Figure 4 shows that the macrolactone **34** exhibits no inhibitory effects (similar behavior was observed for compound **2** under the same experimental conditions, see the Supporting Information for details).

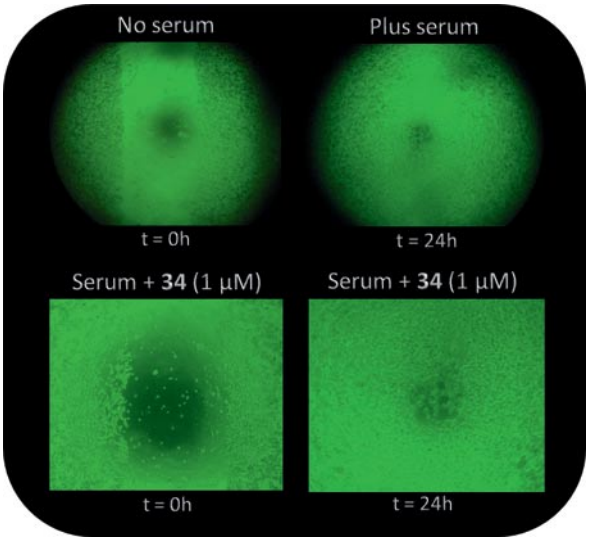


Figure 4. Effect of macrolactone **34** on DU-145 human prostate cancer cells. Wound-healing assay results show that **34** does not inhibit the migration of human prostate tumor cells induced by serum. See the Supporting Information for experimental details.

Conclusions

We have synthesized the macrolactone **2** of migrastatin and its analogues **34**, **35**, and **38**. Notable features of this approach include convergence, a dihydroxylation reaction to establish the desired C-8 stereocenter and a metathesis cyclization reaction in the case of **2** and **34**. This approach compares favorably with previously published routes and, in principle, it is readily applicable to the preparation of additional novel structural analogues. Further optimization of the synthesis as well as application of this strategy to the synthesis of new migrastatin analogues are underway, and the results will be reported in due course. In addition, the macrolactones **2** and **34** as well as esters **35** and **38** exhibit significant in vitro potency against human breast cancer cell migration and invasion, being inactive against human prostate cancer cells. In a very recent report, Chen et al.[11] showed that a macroketone targets and inhibits fascin, providing a novel molecular basis by which migrastatin analogues inhibit tumor-cell migration and invasion. The structure of this molecule was corrected by Danishefsky and coworkers.[13] Owing to our interest in understanding the mechanism of action of our compounds in the inhibition of tumor metastasis, we are also investigating the interaction between our analogue and fascin (see the Supporting Information for details of molecular modeling). Further studies will be required to extend these findings and to determine the ultimate role of the highly active migrastatin-based macrolactones in the inhibition of tumor-cell migration, invasion, and metastasis.

Experimental Section

General: All reactions were carried out under argon or nitrogen in flame-dried glassware. Dichloromethane, toluene, triethylamine, 2,6-lutidine, diisopropylethylamine, *N*,*N*-dimethylformamide, and titanium tetrachloride were distilled from CaH_2. Dimethyl sulfoxide was distilled under reduced pressure from calcium hydride and stored over molecular sieves. THF and diethyl ether were distilled from sodium/benzophenone ketyl. Purification of reaction products was carried out by flash chromatography using silica gel (230–400 mesh). Analytical thin layer chromatography was performed on silica gel 60 and GF (5–40 μm thickness) plates. Visualization was accomplished with UV light and phosphomolybdic acid followed by heating. ^1H and ^1H-decoupled ^{13}C NMR spectra were taken in C_6D_6 or $CDCl_3$ at 250, 300 or 500 MHz (^1H) and 62.5, 75 or 125 MHz (^{13}C). The chemical shifts (δ) are reported in ppm by using the solvent as an internal standard (C_6D_6 at δ = 7.16 ppm and $CDCl_3$ at δ = 7.26 ppm) or with addition of TMS. Data are reported as: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sext = sextuplet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet, qd = quartet of doublets, dsept = doublet of septet, br. d = broad doublet, br. s = broad singlet, dq = doublet of quartet; coupling constant(s) in Hz; integration. IR spectra were recorded with a Perkin-Elmer Paragon 1000 spectrometer and are reported in terms of

frequency of absorption (cm^{-1}). Mass spectra were obtained from LCMS-IT-TOF (225-07100-34) SHIMADZU by electrospray ionization (ESI) techniques and high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) instruments. Optical rotations were measured with a Carl Zeiss Jena Polamat polarimeter with $[\alpha]_D$ values reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g/100 mL.

(*S*)-4-Benzyl-3-[(2*S*,3*R*)-3-hydroxy-2-methylpent-4-enoyl]oxazolidin-2-one (5): Freshly distilled titanium(IV) chloride (0.29 mL, 2.61 mmol) was added dropwise to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one [(*R*)-**4**; 580 mg, 2.48 mmol] in CH_2Cl_2 (25 mL) under argon, and the resulting yellow solution was warmed to 0 °C. After stirring for 5 min, diisopropyl(ethyl)amine (1.08 mL, 6.20 mmol) was added dropwise, and the resulting brown solution was stirred at 0 °C for 1 h. The mixture was cooled to –78 °C, and freshly distilled acrolein (0.25 mL, 3.72 mmol) was added dropwise. After 1 h, the solution was warmed to 0 °C and stirred at that temperature for 12 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The reaction mixture was filtered (Celite), and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine. The organic solution was dried with anhydrous $MgSO_4$ and purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give 624.2 mg of the *syn*-aldol adduct **5** (87%) as a white solid. R_f = 0.27 (40% EtOAc/hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (d, J = 7.0 Hz, 3 H), 2.89–2.77 (m, 1 H), 2.90 (s, 1 H), 3.26 (d, J = 13.4 Hz, 1 H), 3.88–3.86 (m, 1 H), 4.52–4.19 (m, 1 H), 4.51 (br. s, 1 H), 4.73–4.79 (m, 1 H), 5.23 (d, J = 10.7 Hz, 1 H), 5.36 (d, J = 17.0 Hz, 1 H), 5.88–5.82 (m, 1 H), 7.35–7.20 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.91, 37.76, 42.42, 55.12, 66.20, 72.52, 116.33, 127.44, 128.96, 129.41, 134.97, 137.20, 153.09, 176.63 ppm. IR (film): $\tilde{\nu}$ = 3531, 3156, 3032, 2985, 2918, 1780, 1691, 1385, 1211, 1109, 1016, 912, 904 cm^{-1}.

(*S*)-4-Benzyl-3-{(2*S*,3*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpent-4-enoyl}oxazolidin-2-one (6): TBSOTf (0.09 mL, 0.37 mmol) was added dropwise to a solution of *syn*-aldol adduct **5** (100 mg, 0.34 mmol) and 2,6-lutidine (0.05 mL, 0.40 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After 20 min, the reaction was quenched by the addition of water (8 mL), and the organic layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed in sequence with a cold 1% aqueous solution of HCl (3 mL), a saturated aqueous solution of $NaHCO_3$ (3 mL), and brine (3 mL), dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel flash column chromatography (10% EtOAc/hexane) gave the desired product **6** in 93% yield as a colorless oil. R_f = 0.64 (30% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.08 (s, 3 H), –0.06 (s, 3 H), 0.80 (s, 9 H), 1.12 (d, J = 6.9 Hz, 3 H), 2.68 (dd, J = 13.2, 9.9 Hz, 1 H), 3.18 (dd, J = 13.2, 2.93 Hz, 1 H), 3.89 (quint, J = 6.6 Hz, 1 H), 4.10–3.99 (m, 2 H), 4.25 (t, J = 6.2 Hz, 1 H), 4.51 (ddd, J = 9.5, 6.2, 2.9 Hz, 1 H), 5.02 (d, J = 10.2 Hz, 1 H), 5.10 (d, J = 17.2 Hz, 1 H), 5.77 (ddd, J = 17.2, 10.2, 6.2 Hz, 1 H), 7.27–7.11 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = –5.15, –4.44, 12.41, 18.08, 25.73, 37.75, 44.04, 55.60, 65.92, 75.15, 115.68, 127.29, 128.89, 129.43, 135.34, 139.17, 153.16, 174.62 ppm.

(3*S*,4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one (10): A solution of 0.2 M OsO_4 (23.6 mL, 4.72 mmol) was added to a solution of NMO (13.81 g, 118 mmol) in acetone/H_2O (8:1, 200 mL) at 0 °C. After 5 min, a solution of olefin **6** (23.84 g, 59 mmol) in acetone (60 mL) was added slowly (through cannula). The resulting solution was stirred at room temperature for 10 h, and the reaction was quenched by the addition of a 45% aqueous solution of $Na_2S_2O_5$ (118 mL; m/v) and then stirred for 40 min and filtered. The solvent was evaporated, and the aqueous layer was extracted with ethyl acetate (3 × 120 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel flash column chromatography (50% EtOAc/hexane) afforded lactone **9** (8.74 g, 57% yield) and lactone **10** (3.07 g, 20% yield) as a white solid. M.p. 74–76 °C. R_f = 0.40 (30% EtOAc/hexane). $[\alpha]_D^{20}$ = –31 (c = 1.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.90 (s, 9 H), 1.27 (d, J = 7.5 Hz, 3 H), 2.16–2.14 (m, 1 H), 2.67 (quint, J = 6.2 Hz, 1 H), 3.97–3.85 (m, 2 H), 4.28 (t, J = 6.2 Hz, 1 H), 4.50–4.47 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.96, –4.71, 13.44, 17.87, 25.57, 43.36, 61.65, 75.89, 80.65, 177.22 ppm. IR (KBr pellet): $\tilde{\nu}$ = 3460, 3019, 2931, 2860, 1774, 1463, 1386, 1216, 1132, 1051, 931, 838, 779, 669 cm^{-1}. HRMS: calcd. for $C_{12}H_{25}O_4Si$ $[M]^+$ 261.1522; found 261.1699.

(3*S*,4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-[(4-methoxybenzyloxy)methyl]-3-methyldihydrofuran-2(3*H*)-one (11): *p*-Methoxybenzyl 2,2,2-trichloroacetimidate (155 mg, 0.55 mmol) and CSA (3.0 mg, 0.013 mmol) were added to a stirred solution of lactone **10** (120 mg, 0.46 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 12 h. Next, it was diluted with Et_2O (10 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), and H_2O (5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was washed with cold hexane to separate the precipitate. Additional purification by silica gel flash column chromatography (15% EtOAc/hexanes) gave lactone **11** (117.3 mg, 67% yield). R_f = 0.35 (15% EtOAc/hexane). $[\alpha]_D^{20}$ = –25 (c = 1.4, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.23 (d, J = 7.5 Hz, 3 H), 2.72–2.61 (m, 1 H), 3.73–3.70 (m, 2 H), 3.80 (s, 3 H), 4.17 (t, J = 5.6 Hz 1 H), 4.56–4.48 (m, 3 H), 6.87 (d, J = 8.7 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.04, –4.79, 13.17, 17.89, 25.55, 43.49, 55.21, 67.45, 73.23, 75.36, 80.13, 113.74 (2 C), 129.33 (2 C), 129.7, 150.20, 177.73 ppm. IR (film): $\tilde{\nu}$ = 3020, 2956, 2860, 1774, 1645, 1514, 1215, 1134, 1035 cm^{-1}. HRMS: calcd. for $C_{20}H_{33}O_5Si$ $[M]^+$ 381.2097; found 381.2208.

(2*R*,3*S*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-(4-methoxybenzyloxy)-2-methylpentane-1,4-diol (12): $LiAlH_4$ was added (47.0 mg, 1.25 mmol) to a solution of lactone **11** (190 mg, 0.50 mmol) in THF (10 mL) at –78 °C. After 30 min, the reaction was quenched by the addition of an aqueous solution of 0.1 M NaOH (10 mL), and the reaction mixture was stirred for 1 h. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel flash column chromatography (40% EtOAc/hexanes) to give alcohol **12** in 75% yield. R_f = 0.30 (30% EtOAc/hexane). $[\alpha]_D^{20}$ = +11 (c = 1.6, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 0.96 (d, J = 7.3 Hz, 3 H), 1.84–1.73 (m, 1 H), 3.00–2.97 (m, 1 H), 3.48–3.33 (m, 4 H), 3.76 (dd, J = 4.75, 1.5 Hz, 1 H), 3.89–3.85 (m, 2 H), 4.46 (s, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.89, –4.37, 12.89, 18.04, 25.80, 39.79, 55.19, 62.11, 68.24, 70.99, 72.88, 73.11, 113.74, 129.36, 129.91, 159.20 ppm. IR (film): $\tilde{\nu}$ = 3450, 3020, 2956, 2858, 1645, 1514, 1463, 1249, 1218, 1035 cm^{-1}. HRMS: calcd. for $C_{20}H_{37}O_5Si$ $[M + H]^+$ 385.2410; found 385.2464.

(2*S*,3*S*,4*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-1-(4-methoxybenzyloxy)-4-methylpentan-2-ol (13): Imidazole (71 mg, 1.04 mmol)

and TBSCl (128 mg, 0.84 mmol) were added sequentially to a solution of diol **12** (250 mg, 0.65 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The resulting mixture was stirred for 1 h. The solution was diluted with brine (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried with $MgSO_4$, the solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give alcohol **13** in 95% yield as a colorless oil. R_f = 0.50 (30% EtOAc/hexane). $[\alpha]_D^{20}$ = +1 (*c* = 1.4, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.90–0.87 (m, 21 H), 1.83–1.74 (m, 1 H), 3.10–3.02 (m, 1 H), 3.41 (d, *J* = 6.3 Hz, 2 H), 3.57 (dd, *J* = 5.8, 1.3 Hz, 2 H), 3.76–3.74 (m, 1 H), 3.80 (s, 3 H), 3.84–3.80 (m, 1 H), 4.47 (s, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.41, –5.40, –4.48, –4.37, 12.24, 18.24, 18.31, 25.89, 26.00, 40.09, 55.25, 64.40, 70.34, 71.38, 72.68, 72.92, 113.73, 129.33, 130.34, 159.16 ppm. HRMS: calcd. for $C_{26}H_{51}O_5Si_2$ $[M + H]^+$ 499.3275; found 499.3211.

(5*S*,6*R*)-5-[(*S*)-1-Methoxy-2-(4-methoxybenzyloxy)ethyl]-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (14): A proton sponge [1,8-bis(dimethylamino)naphthalene, 1.3 g, 6.06 mmol] and Me_3OBF_4 (0.8 g, 5.4 mmol) were added to a solution of alcohol **13** (1.49 g, 2.98 mmol) in CH_2Cl_2 (55 mL) at room temperature under argon, and the heterogeneous reaction mixture was stirred with protection from light for 12 h. The reaction was quenched by the addition of a cold 1% aqueous solution of HCl (165 mL), and the mixture was extracted with Et_2O (3 × 165 mL). The combined organic layers were filtered through silica, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The resulting mixture was purified by silica gel flash column chromatography (5% EtOAc/hexanes) to give the methylated product **14** in 75% yield. R_f = 0.40 (6% EtOAc/hexane). $[\alpha]_D^{20}$ = –1 (*c* = 1.6, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.06 (s, 3 H), 0.08 (s, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.85–1.71 (m, 1 H), 3.54–3.27 (m, 4 H), 3.41 (s, 3 H), 3.62 (dd, *J* = 10.2, 2.5 Hz, 1 H), 3.80 (s, 3 H), 3.97 (dd, *J* = 6.8, 2.5 Hz, 1 H), 4.44 (d, *J* = 11.8 Hz, 1 H), 4.50 (d, *J* = 11.8 Hz, 1 H), 6.90–6.84 (m, 2 H), 7.28–7.24 (m, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.35, –4.88, –4.02, 10.85, 18.21, 18.34, 25.90, 26.06, 37.42, 55.21, 58.04, 65.69, 69.15, 70.85, 73.05, 83.69, 113.67, 129.23, 130.39, 159.08 ppm. HRMS: calcd. for $C_{26}H_{50}O_5Si$ $[M]^+$ 499.3275; found 499.3211.

(2*S*,3*S*,4*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methoxy-4-methylpentan-1-ol: Compound **14** (1.87 g, 3.65 mmol) was diluted with CH_2Cl_2 (38 mL) and H_2O (2.0 mL), and then DDQ (995 mg, 4.38 mmol) was added at ambient temperature. After 2 h, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution (90 mL) and a saturated aqueous NaCl solution (90 mL) and then extracted with CH_2Cl_2 (3 × 180 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography by using 20% EtOAc/hexane afforded 1.27 g of the corresponding primary alcohol in 88% yield. R_f = 0.60 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –3 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.06 (s, 3 H), 0.09 (s, 3 H), 0.81 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.84–1.74 (m, 1 H), 1.90 (br. s, 1 H), 3.26–3.20 (m, 1 H), 3.42 (s, 3 H), 3.56 (dd, *J* = 11.7, 5.7 Hz, 1 H), 3.51–3.51 (m, 2 H), 3.80 (dd, *J* = 11.7, 3.5 Hz, 1 H), 4.02 (dd, *J* = 6.7, 2.2 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.35, –4.86, –4.09, 10.74, 18.21, 18.29, 25.88, 26.02, 37.20, 58.20, 61.16, 65.63, 70.15, 84.47 ppm.

(5*S*,6*R*)-5-[(*S*)-1-Methoxyallyl]-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (15): At ambient temperature molecular sieves (4 Å) were added to a stirred solution of the previously prepared primary alcohol (1.09 g, 2.78 mmol) in CH_2Cl_2 (56 mL). The mixture was stirred for 15 min before 4-methylmorpholine *N*-oxide (488 mg, 4.17 mmol) was added followed by TPAP (49 mg, 0.14 mmol) after 15 min. The resulting mixture was stirred for 30 min, filtered (Celite), and the filtrate was concentrated to give an intermediate aldehyde. Without purification, Cp_2TiMe_2 (0.5 M, 12 mL) was added to a solution of this aldehyde in toluene (13.7 mL) under argon. The resulting mixture was protected from light and stirred vigorously at 70 °C for 4 h. The mixture was concentrated, and the residue was purified by silica gel flash column chromatography (2% EtOAc/hexane) to afford olefin **15** (538 mg, 50% for two steps). R_f = 0.60 (2% EtOAc/hexane). $[\alpha]_D^{20}$ = –7 (*c* = 1.5, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.76 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.89 (s, 9 H), 1.74–1.62 (m, 1 H), 3.21 (s, 3 H), 3.42–3.33 (m, 2 H), 3.51 (dd, *J* = 9.8, 8.3 Hz, 1 H), 3.80 (dd, *J* = 8.0, 1.7 Hz, 1 H), 5.21 (dd, *J* = 10.3, 2.0 Hz, 1 H), 5.26 (d, *J* = 2.3, 1 H), 5.63–5.48 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.31, –5.08, –3.78, 9.26, 18.22, 18.60, 25.91, 26.18, 38.01, 55.94, 65.69, 73.43, 86.86, 118.49, 135.16 ppm.

(2*R*,3*S*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxy-2-methylhex-5-en-1-ol (16): A solution of HF/pyridine/THF (1:4:5, 14 mL) was added to a stirred solution of TBS ether **15** (538 mg, 1.39 mmol) in THF (18 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h and then diluted with Et_2O (180 mL); powdered $NaHCO_3$ was added until pH = 7. After 10 min, the reaction mixture was filtered and concentrated. Purification by silica gel flash column chromatography (20% EtOAc/hexane) provided alcohol **16** (305 mg, 80% yield). R_f = 0.60 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –9 (*c* = 0.4, CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ = 0.19 (s, 3 H), 0.22 (s, 3 H), 0.83 (d, *J* = 6.8 Hz, 3 H), 1.04 (s, 9 H), 1.74–1.63 (m, 1 H), 3.04 (s, 3 H), 3.52–3.31 (m, 3 H), 3.90 (dd, *J* = 7.5, 2.5 Hz, 1 H), 5.08–5.01 (s, 2 H), 5.56–5.42 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, C_6D_6): δ = –4.72, –3.51, 10.34, 18.85, 26.47, 38.37 55.87, 65.46, 74.61, 86.65, 118.45, 135.53 ppm. HRMS: calcd. for $C_{14}H_{31}O_3Si$ $[M + H]^+$ 275.2042; found 275.2105.

Ethyl (4*R*,5*S*,6*S*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dienoate (18): At ambient temperature molecular sieves (4 Å) were added to a stirred solution of alcohol **16** (123 mg, 0.44 mmol) in CH_2Cl_2 (8.9 mL). The mixture was stirred for 15 min before adding 4-methylmorpholine *N*-oxide (78.8 mg, 0.67 mmol) followed by TPAP (a few crystals) after15 min. The resulting mixture was stirred for 30 min, filtered (plug of silica gel), and the filtrate was concentrated. Ester phosphonate **17** (405 mg, 1.12 mmol) in THF (8 mL) was added to a stirred suspension of 60% NaH (44.6 mg, 1.12 mmol, previously washed with hexane) in THF (4.5 mL) under argon at 0 °C. After stirring at 0 °C for 15 min, a solution of the previously prepared unpurified aldehyde in THF (5.0 mL) was added. The resulting mixture was warmed to ambient temperature and stirred for 12 h. The reaction mixture was diluted with H_2O (15 mL), extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. Purification by silica gel flash column chromatography (5% EtOAc/hexane) gave (*Z*)-unsaturated ester **18** (122.8 mg, 58% yield, two steps). R_f = 0.60 (5% EtOAc/hexane). $[\alpha]_D^{20}$ = –5 (*c* = 1.06, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.029 (s, 3 H), 0.05 (s, 3 H), 0.90 (s, 9 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 1.28 (t, *J* = 7.3 Hz, 3 H), 1.87 (d, *J* = 1.5 Hz, 3 H), 3.19 (s, 3 H), 3.28–3.18 (m, 1 H), 3.40–3.33 (m, 1 H), 3.61 (dd, *J* = 7.5, 2.5 Hz, 1 H), 4.17 (q, *J* = 7.3 Hz, 2 H), 5.31–5.19 (m, 2 H), 5.73–5.56 (m, 1 H), 5.96 (dd, *J* = 9.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.03, –3.82, 12.94, 14.28, 18.52, 20.74, 26.12, 35.32, 55.95, 60.00,

77.5, 86.64, 118.67, 125.27, 134.87, 146.96, 167.87 ppm. IR (film): $\tilde{\nu}$ = 3020, 2929, 2856, 2401, 1701, 1471, 1379, 1215, 1118, 1033, 931, 759, 669 cm^{-1}. HRMS: calcd. for $C_{19}H_{37}O_4Si$ $[M + H]^+$ 357.2461; found 357.2415.

(4*R*,5*S*,6*S*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dien-1-ol (19): A solution of DIBAL-H in toluene (1.5 M, 0.34 mL, 0.51 mmol) was added dropwise to a solution of unsaturated ester **18** (98 mg, 0.204 mmol) in CH_2Cl_2 (1 mL) at –15 °C. After stirring for 1 h, the reaction mixture was warmed to 0 °C, and EtOAc (15 mL) was added. After 30 min, the reaction mixture was warmed to ambient temperature, and a cold solution of aqueous potassium sodium tartrate (10 mL) was added. The resulting mixture was vigorously stirred at ambient temperature until phase separation occurred (about 1 h). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexane) to provide allylic alcohol **19** (63 mg, 0.2 mmol, 98% yield) as an oil. R_f = 0.60 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –2 (*c* = 1.80, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.06 (s, 3 H), 0.92–0.88 (m, 12 H), 1.78 (d, *J* = 1.4 Hz, 3 H), 2.69–2.61 (m, 1 H), 3.22 (s, 3 H), 3.48–3.43 (m, 2 H), 4.00 (dd, *J* = 6.5, 11.7 Hz, 1 H), 4.12 (dd, *J* = 4.9, 11.7 Hz, 1 H), 5.30–5.24 (m, 3 H), 5.73–5.66 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.71, –3.89, 15.28, 18.48, 21.50, 26.09, 34.20, 56.10, 61.71, 78.28, 85.89, 118.52, 133.01, 133.03, 135.12 ppm. IR (film): $\tilde{\nu}$ = 3442, 2931, 2858, 1471, 1254, 1216, 1126, 1004, 933, 835, 730, 669 cm^{-1}.

(*E*)-[(4*R*,5*S*,6*S*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dienyl] Hepta-2,6-dienoate (21): DCC (96.4 mg, 0.467 mmol) and DMAP (14.3 mg, 0.11 mmol) were added to a solution of carboxylic acid **20** (59 mg, 0.0.47 mmol) in CH_2Cl_2 (2 mL) under argon at ambient temperature. A solution of allylic alcohol **19** (73.5 mg, 0.23 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture through cannula. After stirring at that temperature for 12 h, the crude reaction mixture was concentrated. Purification by silica gel flash column chromatography (20% EtOAc/hexane) gave the desired ester **21** (72 mg, 74% yield). R_f = 0.80 (10% EtOAc/hexane). $[\alpha]_D^{20}$ = +4 (*c* = 1.00, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.02 (s, 3 H), 0.05 (s, 3 H), 0.88 (d, *J* = 7.3 Hz, 3 H), 0.90 (s, 9 H), 1.73 (d, *J* = 1.2 Hz, 3 H), 2.32–2.17 (m, 4 H), 2.63–2.57 (m, 1 H), 3.19 (s, 3 H), 3.51–3.35 (m, 2 H), 4.62–4.55 (m, 2 H), 5.08–4.98 (m, 2 H), 5.30–5.25 (m, 2 H), 5.44 (d, *J* = 9.7 Hz, 1 H), 5.87–5.55 (m, 3 H), 6.96 (dt, *J* = 15.6, 6.4 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.86, –3.82, 13.95, 18.52, 21.48, 26.13, 31.47, 32.00, 34.25, 56.04, 63.05, 78.36, 86.25, 115.52, 118.78, 121.51, 128.19, 135.08, 135.57, 137.03, 148.46, 166.55 ppm. IR (film): $\tilde{\nu}$ = 3020, 2931, 2858, 2401, 2360, 1712, 1471, 1215, 1126, 1027, 929, 758, 669 cm^{-1}.

(3*E*,7*E*,9*S*,10*S*,11*R*,12*Z*)-10-[(*tert*-Butyldimethylsilyl)oxy]-9-methoxy-11,13-dimethyl-1-oxacyclotetradeca-3,7,12-trien-2-one (22): Grubbs II catalyst (12 mg, 0.013 mmol) was added to a solution of ester **21** (28.9 mg, 0.068 mmol) in toluene (103 mL) at reflux. After stirring for 15 min, the reaction mixture was cooled to room temperature and filtered through a plug of silica gel (hexane/EtOAc, 4:1). Purification by silica gel flash column chromatography (5% EtOAc/hexane) afforded the desired macrolactone **22** (11.7 mg, 43%). R_f = 0.80 (10% EtOAc/hexane). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.07 (s, 3 H), 0.83 (d, *J* = 6.5 Hz, 3 H), 0.92 (s, 9 H), 1.64 (s, 3 H), 2.21–2.14 (m, 1 H), 2.31–2.21 (m, 1 H), 2.47–2.37 (m, 2 H), 3.03–2.95 (m, 1 H), 3.17 (s, 3 H), 3.33–3.30 (m, 1 H), 3.44 (dd, *J* = 1.5, 8.5 Hz, 1 H), 4.62 (d, *J* = 15.5 Hz, 1 H), 4.68 (d, *J* = 15.5 Hz, 1 H), 5.12 (dd, *J* = 9.0, 15.5 Hz, 1 H), 5.56–5.50 (m, 2 H), 5.73 (d, *J* = 15.5 Hz, 1 H), 6.85–6.79 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.02, –3.56, 12.90, 18.71, 22.17, 26.27, 30.02, 32.46, 33.11, 55.83, 65.57, 77.47, 85.83, 121.82, 126.59, 130.49, 130.50, 132.00, 149.95, 165.39 ppm.

(3*E*,7*E*,9*S*,10*S*,11*R*,12*Z*)-10-Hydroxy-9-methoxy-11,13-dimethyl-1-oxacyclotetradeca-3,7,12-trien-2-one (2): 48% HF (1 drop) was added to a solution of macrolactone **22** (9.5 mg, 0.024 mmol) in CH_3CN/CH_2Cl_2 (2:1; 2.0 mL) at room temperature. After stirring for 24 h, the reaction mixture was diluted with Et_2O and carefully treated with $NaHCO_3$ (pH = 7), filtered, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (EtOAc/hexane 5%) afforded macrolactone **2** (3.1 mg, 44%). $[\alpha]_D^{20}$ = +87.5 (*c* = 0.30, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.5 Hz, 3 H), 1.68 (s, 3 H), 2.31–2.19 (m, 2 H), 2.47–2.38 (m, 2 H), 3.04–2.98 (m, 1 H), 3.28 (s, 3 H), 3.41–3.39 (m, 2 H), 4.63 (d, *J* = 15.5 Hz, 1 H), 4.72 (d, *J* = 15.5 Hz, 1 H), 5.14 (dd, *J* = 15.0, 6.5 Hz, 1 H), 5.63–5.55 (m, 2 H), 5.73 (d, *J* = 16.0 Hz, 1 H), 6.78 (ddd, *J* = 16.0, 8.0, 6.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.67, 22.28, 29.99, 31.37, 32.22, 56.25, 65.41, 76.11, 84.63, 122.16, 127.50, 129.53, 129.82, 133.83, 149.50, 165.35 ppm. HRMS: calcd. for $C_{16}H_{24}O_4Na$ $[M + Na]^+$] 303.1567; found 303.1563.

(3*S*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-(hydroxymethyl)-3-methyldihydrofuran-2(3*H*)-one (9): A solution of 0.2 M OsO_4 in *t*BuOH (2 mL, 0.4 mmol) was added to a solution of NMO (1.17 g, 10.0 mmol) in acetone/H_2O (8:1) at 0 °C. After 5 min, a solution of olefin **5** (2.02 g, 5.00 mmol) in acetone (5 mL) was added slowly. The resulting solution was stirred at room temperature for 10 h and quenched by adding a solution of 45% $Na_2S_2O_5$ (10 mL; m/v), stirred for 40 min, and filtered. The solvent was removed, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel flash column chromatography (50% EtOAc/hexane) to afford lactone **9** (70% yield) as a colorless oil. R_f = 0.58 (30% EtOAc/hexane). $[\alpha]_D^{20}$ = +105 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 1.27 (d, *J* = 7.3 Hz, 3 H), 2.50 (s, 1 H), 2.63–2.58 (m, 1 H), 3.66 (dd, *J* = 13.0, 2.9 Hz, 1 H), 3.97 (dd, *J* = 13.0, 1.6 Hz, 1 H), 4.16–4.10 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.76, –4.35, 12.60, 17.70, 25.52, 44.25, 59.99, 74.15, 84.33, 176.89 ppm. IR (film): $\tilde{\nu}$ = 3450, 3060, 2935, 2858, 1780, 1462, 1403, 1263, 1170, 1120, 1040, 896, 836 cm^{-1}. HRMS: calcd. for $C_{12}H_{25}O_4Si$ $[M]^+$ 261.1522; found 261.1699.

(3*S*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-[(4-methoxybenzyloxy)methyl]-3-methyldihydrofuran-2(3*H*)-one (23): *p*-Methoxybenzyl 2,2,2-trichloroacetimidate (155 mg, 0.55 mmol) and CSA (3.0 mg, 0.013 mmol) were added to a stirred solution of lactone **9** (120 mg, 0.46 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 12 h. Next, it was diluted with Et_2O (10 mL), washed with a saturated aqueous solution of $NaHCO_3$ (5 mL), brine (5 mL), and H_2O (5 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude material was washed with cold hexane to separate the precipitate. Additional purification by silica gel flash column chromatography (20% EtOAc/hexanes), gave lactone **23** (83%) as a yellow oil. R_f = 0.50 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +27 (*c* = 2.5, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.06 (s, 3 H), 0.86 (s, 9 H), 1.23 (d, *J* = 7.3 Hz, 3 H), 2.62–2.50 (m, 1 H), 3.56 (dd, *J* = 11.3, 3.8 Hz, 1 H), 3.71 (dd, *J* = 11.3, 2.3 Hz, 1 H), 3.79 (s, 3 H), 4.12–4.05 (m, 1 H), 4.19–4.14 (m, 1 H), 4.46 (d, *J* = 12 Hz, 1 H), 4.51 (d, *J* = 12 Hz, 1 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 7.23 (d, *J* = 8.8 Hz,

2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.77, –4.31, 12.86, 17.77, 25.58, 44.27, 55.26, 67.16, 73.21, 75.02, 83.44, 113.82, 129.49, 129.56, 159.34, 176.68 ppm. IR (film): $\tilde{\nu}$ = 3001, 2933, 2852, 1784, 1612, 1514, 1457, 1302, 1248, 1171, 1075, 1036 cm^{-1}. HRMS: calcd. for $C_{20}H_{33}O_5Si$ $[M]^+$ 381.2097; found 381.2208.

(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-5-(4-methoxybenzyloxy)-2-methylpentane-1,4-diol (24): $LiAlH_4$ was added (47.0 mg, 1.25 mmol) to a solution of lactone **23** (190 mg, 0.50 mmol) in THF (10 mL) at 0 °C (when using more than 5 mol of lactone **23**, the reaction has to be performed at –78 °C to avoid loss of the TBS group). After 30 min, the reaction was quenched by the addition of an aqueous solution of 0.1 M NaOH (10 mL), and the reaction mixture was stirred for 1 h. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine and dried with $MgSO_4$, concentrated under reduced pressure, and purified by silica gel flash column chromatography (40% EtOAc/hexanes) to give alcohol **24** (75%) as a colorless oil. R_f = 0.30 (40% EtOAc/hexane). $[\alpha]_D^{20}$ = +3 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = –0.04 (s, 3 H), –0.01 (s, 3 H), 0.78 (s, 9 H), 0.83 (d, *J* = 7.3 Hz, 1 H), 1.88 (sextd, *J* = 6.9, 2.4 Hz, 1 H), 2.16 (br. s, 1 H), 2.63 (br. d, *J* = 1.5 Hz, 1 H), 3.39 (dd, *J* = 9.3, 6.9 Hz, 1 H), 3.46–3.44 (m, 2 H), 3.52 (dd, *J* = 9.3, 2.7 Hz, 1 H), 3.75–3.68 (m, 5 H), 4.35 (d, *J* = 11.3 Hz, 1 H), 4.42 (d, *J* = 11.3 Hz, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 7.16 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.50, –4.43, 11.75, 18.12, 25.89, 38.82, 55.22, 65.03, 71.34, 71.94, 73.02, 73.31, 113.81, 129.50, 129.86, 159.27 ppm. IR (film): $\tilde{\nu}$ = 3423, 2931, 2858, 1612, 1514, 1464, 1250, 1090, 1040, 835 cm^{-1}. HRMS: calcd. for $C_{20}H_{37}O_5Si$ $[M + H]^+$ 385.2410; found 385.2464.

(2*R*,3*S*,4*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-1-(4-methoxybenzyloxy)-4-methylpentan-2-ol (25): Imidazole (71 mg, 1.04 mmol) and TBSCl (128 mg, 0.84 mmol) were added to a solution of diol **24** (250 mg, 0.65 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The resulting mixture was stirred for 1 h. The solution was diluted with brine (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried with $MgSO_4$, the solvent was removed under reduced pressure, and the resulting mixture was purified by silica gel flash column chromatography (20% EtOAc/hexanes) to give alcohol **25** in 98% yield as a colorless oil. R_f = 0.61 (40% EtOAc/hexane). $[\alpha]_D^{20}$ = +1 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08–0.05 (m, 12 H), 0.91–0.88 (m, 21 H), 1.92–1.82 (m, 1 H), 2.61 (d, *J* = 2.1 Hz, 1 H), 3.50–3.45 (m, 3 H), 3.60–3.56 (m, 1 H), 3.86–3.81 (m, 5 H), 4.46 (d, *J* = 11.3 Hz, 1 H), 4.53 (d, *J* = 11.3 Hz, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 7.27 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.35, –4.51, –4.35, 11.33, 18.20, 18.25, 25.89, 25.97, 38.35, 55.24, 65.12, 71.30, 72.20, 72.62, 73.00, 113.78, 129.40, 130.15, 159.23 ppm. IR (film): $\tilde{\nu}$ = 3054, 2954, 2930, 2858, 1612, 1514, 1463, 1265, 1092, 1040, 914 cm^{-1}. HRMS: calcd. for $C_{26}H_{51}O_5Si_2$ $[M + H]^+$ 499.3275; found 499.3211.

(2*R*,3*S*,4*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methoxy-4-methylpentan-1-ol (26): A proton sponge [1,8-bis(dimethylamino)-naphthalene, 170 mg, 0.80 mmol] and Me_3OBF_4 (100 mg, 0.70 mmol) were added to a solution of alcohol **25** (200 mg, 0.40 mmol) in CH_2Cl_2 (10 mL) at ambient temperature under argon, and the heterogeneous reaction mixture was stirred with protection from light for 12 h. The reaction was quenched by the addition of a cold 1% aqueous solution of HCl (25 mL), and the mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were filtered through silica gel, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was diluted with CH_2Cl_2 (4 mL) and H_2O (0.2 mL), and then DDQ (100 mg, 0.44 mmol) was added at ambient temperature. After 2 h, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and a saturated aqueous NaCl solution and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were dried with anhydrous $MgSO_4$ and concentrated in vacuo. Purification by silica gel flash column chromatography by using 20% EtOAc/hexane afforded 100.5 mg of **26** in 64% yield for the two-step sequence. R_f = 0.53 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = +1 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 6 H), 0.06 (m, 3 H), 0.10 (s, 3 H), 0.89 (s, 18 H), 0.92 (d, *J* = 7.5 Hz, 3 H), 1.84–1.74 (m, 1 H), 2.09 (s, 1 H), 3.30–3.24 (m, 1 H), 3.42 (s, 3 H), 3.52–3.46 (m, 2 H), 3.70 (t, *J* = 5.8 Hz, 2 H), 3.96 (t, *J* = 4.0 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –5.44, –5.38, –4.77, –4.17, 12.23, 18.19, 18.34, 25.86, 26.03, 38.81, 57.71, 61.30, 65.50, 72.02, 83.69 ppm. IR (film): $\tilde{\nu}$ = 3059, 2960, 2030, 2894, 2858, 1471, 1385, 1265, 1107, 1045 cm^{-1}.

(5*S*,6*R*)-5-[(*R*)-1-Methoxyallyl]-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (27): At ambient temperature molecular sieves (4 Å) were added to a stirred solution of alcohol **26** (50 mg, 0.13 mmol) in CH_2Cl_2. The mixture was stirred for 15 min, before 4-methylmorpholine *N*-oxide (23 mg, 0.20 mmol) was added followed by TPAP (a few crystals) after 15 min. The resulting mixture was stirred for 30 min, filtered (Celite), and the filtrate was concentrated. Without purification, Cp_2TiMe_2 (0.5 M, 0.52 mL, 0.26 mmol) was added to a solution of the resulting aldehyde in toluene (1 mL) and under argon. The resulting mixture was protected from light and stirred vigorously at 60 °C for 4 h. The mixture was concentrated, and the residue was purified by silica gel flash column chromatography (20% EtOAc/hexane) to afford **27** (37.9 mg, 75%). R_f = 0.74 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –10 (*c* = 2.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6 H), 0.04 (s, 6 H), 0.93–0.84 (m, 21 H), 1.89–1.81 (m, 1 H), 3.24 (s, 3 H), 3.52–3.31 (m, 3 H), 3.82–3.80 (m, 1 H), 5.30–5.18 (m, 2 H), 5.76 (ddd, *J* = 17.0, 10.4, 8.0 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –5.36, –5.32, –4.62, –3.61, 11.69, 18.27, 18.43, 25.84, 26.03, 38.42, 56.09, 65.83, 74.26, 85.42, 118.74, 136.20 ppm. IR (film): $\tilde{\nu}$ = 2959, 2930, 2863, 1471, 1391, 1254, 1090 cm^{-1}.

(2*R*,3*S*,4*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxy-2-methylhex-5-en-1-ol (28): A solution of HF/pyridine/THF (1:4:5, 0.8 mL) was added to a stirred solution of TBS ether **27** (30.0 mg, 0.08 mmol) in THF (1.0 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for 12 h, diluted with Et_2O (10 mL), and powdered $NaHCO_3$ was slowly added until pH = 7. After 10 min, the reaction mixture was filtered and concentrated. The crude product was purified by silica gel flash column chromatography on silica gel (20% EtOAc/hexane) to give alcohol **28** (15.8 mg, 72% yield). R_f = 0.30 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –18 (*c* = 1.20, $CHCl_3$). ^{1}H NMR (250 MHz, C_6D_6): δ = 0.13 (s, 3 H), 0.15 (s, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 1.01 (s, 12 H), 1.01 (s, 9 H), 1.99–1.84 (m, 1 H), 3.07 (s, 3 H), 3.47–3.26 (m, 3 H), 3.97–3.93 (m, 1 H), 5.15–5.05 (m, 2 H), 5.81 (ddd, *J* = 17.1, 10.0, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = –4.08, –3.02, 12.61, 19.02, 26.75, 39.52, 56.19, 65.77, 75.80, 85.81, 119.33, 136.94 ppm. IR (film): $\tilde{\nu}$ = 3429, 3019, 2929, 2882, 2858, 2816, 1471, 1248, 1216, 1105, 929, 838, 759, 669 cm^{-1}. HRMS: calcd. for $C_{14}H_{31}O_3Si$ $[M + H]^+$ 275.2042; found 275.2105.

Ethyl (4*R*,5*S*,6*R*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dienoate (29): At ambient temperature, molecular sieves (4 Å) were added to a stirred solution of alcohol **28** (110.0 mg, 0.40 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred for 15 min before 4-methylmorpholine *N*-oxide (71 mg, 0.60 mmol) was added followed by TPAP (a few crystals) after 15 min. The

resulting mixture was stirred for 30 min, filtered (Celite), and the filtrate was concentrated to give an intermediate aldehyde. Phosphonate **17** (40 mg, 1.00 mmol) in THF (8 mL) was added to a stirred suspension of 60% NaH (282 mg, 1.00 mmol, previously washed with hexane) in THF (2 mL) under argon at 0 °C. After stirring at 0 °C for 15 min, a solution of the previously prepared aldehyde in THF (5.0 mL) was added. The resulting mixture was warmed to ambient temperature and stirred for 12 h. The reaction mixture was diluted with H_2O (15 mL), extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel flash column chromatography (5% EtOAc/hexane) to give the (*Z*)-unsaturated ester **29** (95.6 mg, 67% yield over two steps). R_f = 0.72 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –33 (*c* = 1.50, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.89 (d, *J* = 1.5 Hz, 3 H), 3.20 (s, 3 H), 3.24–3.20 (m, 1 H), 3.39 (dd, *J* = 8.0, 3.5 Hz, 1 H), 3.58 (dd, *J* = 7.0, 3.5 Hz, 1 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 5.12 (dd, *J* = 17.5, 2.0 Hz, 1 H), 5.25 (dd, *J* = 10.5, 2.0 Hz, 1 H), 5.76–5.69 (m, 2 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = –4.39, –3.30, 14.20, 16.71, 18.80, 20.98, 26.45, 37.25, 55.51, 60.05, 79.13, 85.66, 119.50, 127.26, 135.18, 144.27, 167.57 ppm. IR (film): $\tilde{\nu}$ = 3019, 2965, 2929, 2858, 1708, 1463, 1373, 1216, 1099, 1027, 837, 739, 669 cm^{-1}. HRMS: calcd. for $C_{19}H_{37}O_4Si$ [M + H]$^+$ 357.2461; found 357.2415.

(4*R*,5*S*,6*R*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dien-1-ol (30): A solution of DIBAL-H in toluene (2.0 M, 0.35 mL, 0.50 mmol) was added dropwise to a solution of unsaturated ester **29** (72 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) at –15 °C. After stirring for 1 h, the reaction mixture was warmed to 0 °C, and EtOAc (15 mL) was added. After 30 min, the reaction mixture was warmed to ambient temperature, and a cold solution of aqueous potassium sodium tartrate (10 mL) was added. The resulting mixture was stirred vigorously at ambient temperature until phase separation occurred (about 1 h). The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (20% EtOAc/hexane) to provide allylic alcohol **30** (57.9 mg, 92% yield) as an oil. R_f = 0.33 (20% EtOAc/hexane). $[\alpha]_D^{20}$ = –35 (*c* = 1.85, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05 (s, 3 H), 0.06 (s, 3 H), 0.90 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 2.59 (br. s, 1 H), 1.79 (d, *J* = 1.4 Hz, 3 H), 2.71–2.56 (m, 1 H), 3.26 (s, 3 H), 3.55–3.45 (m, 2 H), 3.89 (dd, *J* = 11.7, 5.0 Hz, 1 H), 4.17 (d, *J* = 11.7 Hz, 1 H), 5.29–5.04 (m, 3 H), 5.74 (ddd, *J* = 17.3, 10.5, 7.9 Hz, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.54, –3.84, 18.33, 18.39, 21.78, 26.08, 35.63, 56.32, 61.85, 79.46, 85.92, 118.58, 131.57, 133.85, 135.73 ppm. IR (film): $\tilde{\nu}$ = 3396, 3080, 2965, 2931, 2858, 2822, 1462, 1373, 1254, 1100, 1004, 932, 836 cm^{-1}.

(4*R*,5*S*,6*R*,*Z*)-5-[(*tert*-Butyldimethylsilyl)oxy]-6-methoxy-2,4-dimethylocta-2,7-dienyl Hept-6-enoate (32): DCC (92.4 mg, 0.45 mmol) and DMAP (14 mg, 0.11 mmol) were added to a solution of hept-6-enoic acid (**31**; 57.4 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) under argon at ambient temperature. A solution of allylic alcohol **30** (70.4 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added to the reaction mixture through cannula. After stirring at ambient temperature for 12 h, the crude reaction mixture was concentrated. Purification by silica gel flash column chromatography (6% EtOAc/hexane) provided the desired ester **32** (87.2 mg, 92% yield). R_f = 0.85 (5% EtOAc/hexane). $[\alpha]_D^{20}$ = –21 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.04 (s, 3 H), 0.05 (s, 3 H), 0.89 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 1.48–1.35 (m, 2 H), 1.68–1.59 (m, 2 H), 1.72 (d, *J* = 1.3 Hz, 3 H), 2.06 (m, 2 H), 2.32 (t, *J* = 7.7 Hz, 2 H), 2.60–2.45 (m, 1 H), 3.19 (s, 3 H), 3.43 (dd, *J* = 8.5, 3.0 Hz, 1 H), 3.52 (dd, *J* = 7.5, 2.3 Hz, 1 H), 4.45 (d, *J* = 12 Hz, 1 H), 4.60 (d, *J* = 12 Hz, 1 H), 5.29–4.92 (m, 5 H), 5.87–5.68 (m, 2 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = –4.61, –3.68, 17.60, 18.49, 21.49, 24.43, 26.06, 26.15, 28.34, 33.35, 34.12, 35.76, 55.52, 63.35, 78.71, 84.92, 114.68, 119.51, 129.03, 133.89, 134.86, 138.36, 173.63 ppm. IR (film): $\tilde{\nu}$ = 3082, 3025, 2930, 2859, 2401, 1728, 1462, 1423, 1217, 1097, 999, 932, 760 cm^{-1}. HRMS: calcd. for $C_{24}H_{44}O_4SiNa$ [M + Na]$^+$ 447.2901; found 447.2916.

(7*E*,9*R*,10*S*,11*R*,12*Z*)-10-[(*tert*-Butyldimethylsilyl)oxy]-9-methoxy-11,13-dimethyl-1-oxacyclotetradeca-7,12-dien-2-one (33): Grubbs II catalyst (17.2 mg, 0.02 mmol) was added to a solution of ester **32** (43 mg, 0.10 mmol) in toluene (200 mL) at reflux. After stirring for 30 min, the reaction mixture was cooled to room temperature and filtered through a plug of silica gel (hexane/EtOAc, 4:1). Purification by silica gel flash column chromatography (5% EtOAc/hexane) afforded the desired product **32** (32 mg, 80%). R_f = 0.60 (5% EtOAc/hexane). $[\alpha]_D^{20}$ = +19 (*c* = 1.19, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.06 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.78 (d, *J* = 1 Hz, 3 H), 2.41–1.82 (m, 8 H), 2.60–2.59 (s, 1 H), 3.16 (s, 3 H), 3.42 (dd, *J* = 9.0, 1.3 Hz, 1 H), 3.53 (dd, *J* = 9.0, 1.5 Hz, 1 H), 4.14 (d, *J* = 12 Hz, 1 H), 4.59 (d, *J* = 12 Hz, 1 H), 5.20–5.24 (m, 1 H), 5.44–5.34 (m, 1 H), 5.84–5.73 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.74, –3.74, 18.65, 19.48, 22.13, 22.55, 26.26, 28.95, 30.49, 35.09, 36.33, 54.96, 63.66, 79.08, 84.72, 124.89, 128.40, 134.09, 136.08, 173.85 ppm. IR (film): $\tilde{\nu}$ = 3025, 2960, 2930, 2860, 2817, 1732, 1462, 1379, 1250, 1149, 1101, 972, 837, 758, 667 cm^{-1}. HRMS: calcd. for $C_{22}H_{40}O_4SiNa$ [M + Na]$^+$ 419.2588; found 419.2608.

(7*E*,9*R*,10*S*,11*R*,12*Z*)-10-Hydroxy-9-methoxy-11,13-dimethyl-1-oxacyclotetradeca-7,12-dien-2-one (34): A 48% HF solution (1 drop) was added to a solution of macrolactone **33** (32 mg, 0.08 mmol) in CH_3CN/CH_2Cl_2 (2:1; 1.6 mL) at room temperature. After stirring for 24 h, the reaction mixture was diluted with Et_2O and carefully treated with $NaHCO_3$ (pH = 7), filtered, and concentrated under reduced pressure. Purification by silica gel flash column chromatography (EtOAc/hexane 5%) afforded macrolactone **34** (8.6 mg, 40%). R_f = 0.50 (5% EtOAc/hexane). $[\alpha]_D^{20}$ = +38 (*c* = 0.9, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 7 Hz, 3 H), 1.79 (d, *J* = 1 Hz, 3 H), 2.60–1.87 (m, 10 H), 3.27 (s, 3 H), 3.60–3.50 (m, 2 H), 4.19 (d, *J* = 11.6 Hz, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 5.22 (dd, *J* = 11.6, 1.0 Hz, 1 H), 5.42 (dd, *J* = 15.7, 8.5 Hz, 1 H), 5.89–5.78 (m, 1 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 18.70, 22.16, 22.49, 28.61, 30.09, 34.98, 35.04, 55.73, 63.51, 77.23, 83.73, 123.79, 129.37, 132.91, 136.14, 173.74 ppm. IR (film): $\tilde{\nu}$ = 3462, 3003, 2932, 2876, 2823, 1724, 1454, 1252, 1095, 974, 756 cm^{-1}. HRMS: calcd. for $C_{16}H_{26}O_4Na$ [M + Na]$^+$ 305.1723; found 305.1723.

Supporting Information (see footnote on the first page of this article): Experimental procedures and spectroscopic data for the prepared compounds.

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