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Asymmetric Total Synthesis of (−)-Pironetin Employing the SAMP/RAMP Hydrazone Methodology**

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Dedicated to Professor Alain Krief on the occasion of his 65th birthday

Abstract: A convergent asymmetric total synthesis of pironetin (**1**), a polyketide with immunosuppressive, antitumor, and plant-growth regulating activities is described. The synthesis was realized by coupling between the C_8–C_{14} **2** and C_7–C_2 **15** fragments, respectively, by using a Mukaiyama-aldol reaction. The stereogenic centers of each fragment were generated by employing the SAMP/RAMP hydrazone (SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine, RAMP = (*R*)-1-amino-2-methoxymethylpyrrolidine) methodology as a key step. An asymmetric α-alkylation of diethyl ketone permitted the introduction of the C_{10} stereogenic center of **2**, whereas the stereocenters C_4 and C_5 of **15** were installed by an asymmetric aldol reaction. Finally, the formation of the α,β-unsaturated δ-lactone was achieved by ring-closing metathesis in the presence of catalytic amounts of titanium tetraisopropoxide.

Keywords: aldol reaction · asymmetric synthesis · hydrazones · metathesis · natural products · pironetin

Introduction

Pironetin (**1**) (PA-48153C) was first isolated in 1993 by Yoshida et al.[1] from the fermentation broth of *Streptomyces prunicolor* PA-48153, and then in 1994 by Kobayashi and co-workers[2] from *Streptomyces* sp. NK10958. This natural lactone displays very interesting and diverse biological activities. Pironetin shows a potent immunosuppressive effect on the responses of both T and B-lymphocytes to mitogens, whereas immunosuppressants cyclosporin A (CsA) and FK-506 only antagonize T-cell activation.[1a] Apart from being an immunosuppressive agent with an original mode of action, pironetin also exhibits a strong regulating activity in plant growth.[2] More importantly, it has recently been identified as a strong antitumor agent, which influences the dynamic of the tubulin-microtubules system inhibiting the polymerization of tubulin.[3] Its uniqueness comes from its ability to bind covalently to the α-subunit of tubulin in contrast to colchicin, vinblastin, or rhizoxin which bind to different sites of β-tubulin.[3e] Based on all these characteristics, pironetin **1** is considered to be a very attractive research target and several total syntheses have already been described in the literature.[4] However, this metabolite suffers from problems of toxicity and side effects; therefore, some structural modifications of the natural product have been studied in order to reduce its toxicity and increase its specificity.[3]

Due to its unique properties and low extraction yields from nature, it was our aim to establish an efficient total synthesis of pironetin **1**, which also enabled an easy access for the preparation of other structural analogues. We envisaged its synthesis by employing the SAMP/RAMP hydrazone (SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine, RAMP = (*R*)-1-amino-2-methoxymethylpyrrolidine) alkylation[5] and aldolization[5a,6] methodology developed earlier by our group.

Our retrosynthetic analysis was initially based on the asymmetric aldol reaction between the ketone **2** and the lactone-aldehyde **3**, in which the stereogenic center C_{10} could be introduced by hydrazone α-alkylation, and the C_4 and C_5 centers by a hydrazone aldol reaction (Scheme 1).

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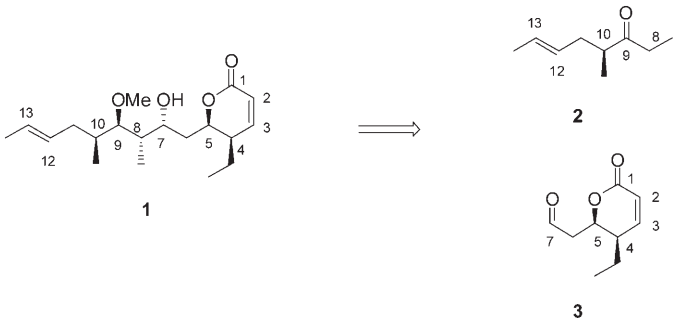
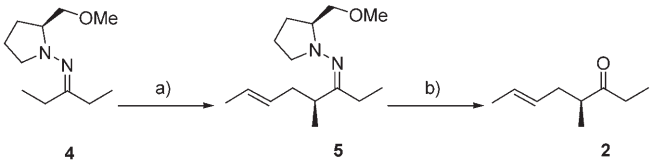
[**] SAMP = (*S*)-1-amino-2-methoxymethylpyrrolidine
RAMP = (*R*)-1-amino-2-methoxymethylpyrrolidine



Scheme 1. Retrosynthetic analysis of pironetin.

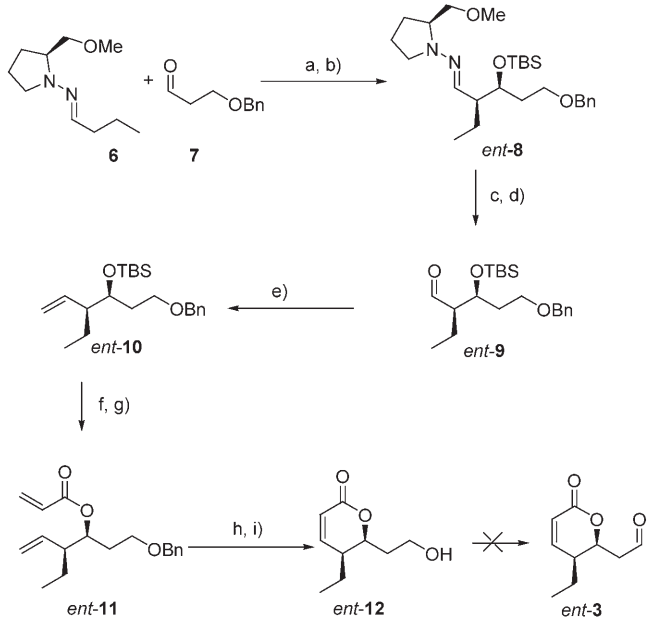
Results and Discussion

For the synthesis of ketone **2**, the stereogenic center at C_{10} was generated by asymmetric α-alkylation of 3-pentanone via its SAMP-hydrazone derivative **4** with (*E*)-crotylbromide. After removal of the chiral auxiliary from the product hydrazone **5** by standard acidic conditions in a two-phase system, ketone **2** was obtained with 98% *ee* (*ee* = enantiomeric excess) and with good yield over two steps (Scheme 2).



Scheme 2. Synthesis of the α-alkylated ketone **2**: a) 1) LiTMP, THF, 0°C, 30 min; 2) (*E*)-crotylbromide, −110°C; b) pentane/4 N HCl, RT, 1 h, 78% over two steps, 98% *ee* (CSP GC analysis, Lipodex E).

To introduce the stereogenic centers C_4 and C_5 of the lactone aldehyde building block *ent*-**3**,[7] we used the *syn*-selective asymmetric aldol reaction via titanium azaenolates of SAMP hydrazones.[5a,7] Butanal SAMP hydrazone **6** was treated with titanium tetrachloride and Hünig's base to provide the titanated hydrazone as a deep-red solution in dichloromethane. Subsequent trapping with the aldehyde **7**, followed by protection as a TBS (TBS = *tert*-butyldimethylsilyl) ether, furnished the *syn*-configured SAMP hydrazone *ent*-**8** as the major diastereomer ($de = 55\%$, $de \geq 96\%$ after HPLC, $ee = 96\%$; de = diastereomeric excess) with good yield. Oxidative cleavage of the chiral auxiliary by using magnesium monoperoxyphthalate hexahydrate (MMPP)[8] afforded the corresponding nitrile without racemization in 92% yield. Its reduction with DIBAL-H (DIBAL-H = diisobutylaluminum hydride), followed by Wittig olefination of the corresponding aldehyde *ent*-**9** gave the olefin *ent*-**10** in good yield. After TBS deprotection and esterification with acrylic acid, the diene precursor of the metathesis *ent*-**11** was isolated in 75% yield over two steps. Ring-closing metathesis of the acrylate *ent*-**11** with Grubbs first-generation catalyst (0.2 equiv) in the presence of titanium tetraisopropoxide (0.5 equiv), followed by deprotection of the benzyl group permitted access to the lactone alcohol *ent*-**12** (Scheme 3).[9]

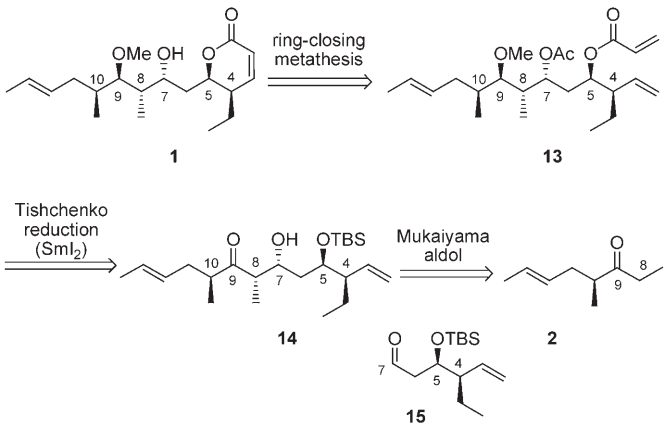


Scheme 3. Attempts to synthesize the aldehyde *ent*-**3**: a) $TiCl_4$, DIPEA (DIPEA = diisopropyl ethyl amine), dichloromethane, −78°C→RT; b) TBSOTf, lutidine, dichloromethane, −78°C, 80% over two steps, 96% *ee*, 55% *de* ($de \geq 96\%$ after HPLC); c) MMPP, EtOH, buffer pH 7, RT, 92%; d) DIBAL-H, THF, 0°C→RT, 86%; e) $Ph_3P{=}CH_2$, THF, −78°C→RT, 92%; f) TBAF, THF, RT, 97%; g) acrylic acid, DMAP, DDC, dichloromethane, 0°C→RT, 77%; h) Grubbs first-generation catalyst, $Ti(OiPr)_4$, dichloromethane, reflux, 96%; i) $TiCl_4$, dichloromethane, 0°C→RT, 91%.

Several oxidation attempts were studied on **12** by using classical conditions, such as pyridinium chlorochromate,[10] pyridinium dichromate,[11] DMP (DMP = Dess–Martin periodinane),[12] TPAP/NMO (TPAP = tetra-*n*-propylammonium perruthenate, NMP = *N*-methyl-2-pyrrolidinone)[13] and the Swern oxidation.[14] Unfortunately, only traces of aldehyde were observed and were accompanied by decomposition products of the starting alcohol in all cases. Consequently, we had to modify our first strategy.

In the new approach, the lactone formation was envisaged at the end of the synthesis by means of a transition-metal-catalyzed ring-closing metathesis of the diene **13**. We considered a Mukaiyama-aldol reaction between the alkylated ketone **2** and the aldehyde **15** to create the C_7–C_8 bond. The stereogenic center at C_9 may be controlled by a samarium-iodide-mediated Tishchenko reduction of the β-hydroxyketone **14** (Scheme 4).

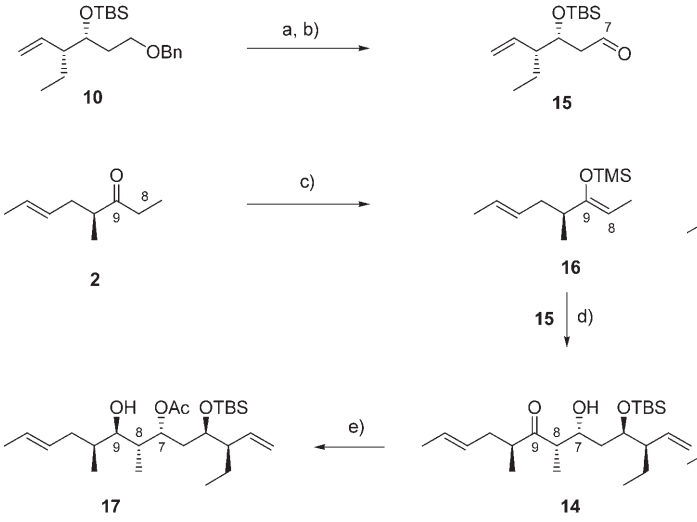
For the synthesis of the aldehyde **15**, planned to be used in the aldol reaction with **2**, the benzyl group of **10** was removed with calcium in liquid ammonia, and the resulting primary alcohol was oxidized under Swern conditions to



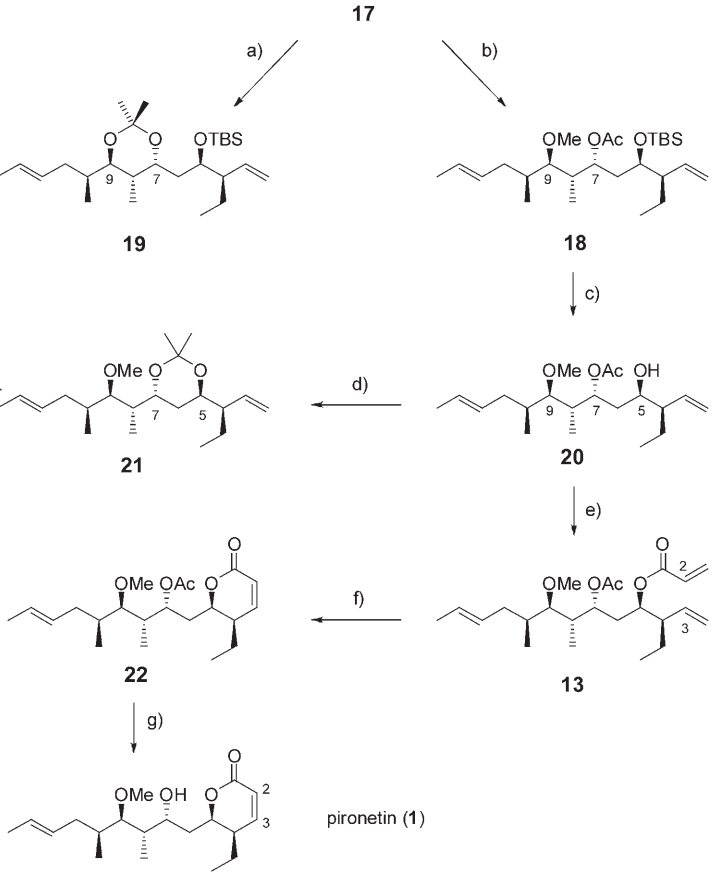
Scheme 4. Retrosynthetic analysis of the new approach.

afford the desired aldehyde **15** in 83% yield over two steps. Deprotonation of the ketone **2** by using diphenyltetramethyldisilazane and *n*-butyllithium followed by trapping with a mixture of trimethylsilyl chloride and triethylamine furnished the *Z* enolate **16**, which was used directly in a Mukaiyama-aldol reaction in the presence of $BF_3{\cdot}Et_2O$ with the aldehyde **15** to provide the β-hydroxyketone **14** in 52% yield.[15] Subsequent samarium-iodide-mediated Tishchenko reduction introduced the stereogenic center C_9 to give **17** with an excellent *anti* selectivity of 96% *de* in 90% yield (Scheme 5).[16]

The resulting alcohol **17** was easily converted to the acetonide **19** in two steps by removal of the acetate group and acetonide formation to determine the configuration. The *anti* relationship between C_9 and C_7 was established by ^{13}C NMR spectroscopy (the acetonide methyl group chemical shifts of **19**, $\delta = 23.8$ and 26.0 ppm). The alcohol on C_9 was converted to the methyl ether by using proton sponge and Meerwein's reagent (Me_3OBF_4) in dichloromethane.[17] The cleavage of the TBS ether[18] furnished the alcohol **20**, which was then treated with acryloyl chloride in THF in the presence of triethylamine to give the ester **13**.[19] ^{13}C NMR spectroscopic analysis of the acetonide methyl group chemical shifts ($\delta = 24.9$ and 25.0 ppm) of **21**, easily achieved from **20** in two steps, proved the *anti* relationship between C_7 and C_5. The formation of the δ-lactone was carried out by employing the ring-closing metathesis with Grubbs first-generation catalyst and a catalytic amount of titanium isopropoxide.[9] Finally, the removal of the acetate group provided the title natural product pironetin (**1**) in 80% yield (Scheme 6).[4g]



Scheme 5. Introduction of the stereogenic centers C_7, C_8, and C_9. a) $NH_{3(liq)}$, Ca, THF, −78°C; b) DMSO, Et_3N, SO_3–pyridine complex, RT, 83% over two steps; c) 1) diphenyltetramethyldisilazane, *n*BuLi, THF, −78°C; 2) TMSCl, Et_3N, 5 h, RT; d) $BF_3{\cdot}OEt_2$, dichloromethane, −78°C , 92% (mixture of diastereomers, 57% of the desired one); e) CH_3CHO, SmI_2, THF, −15°C, 90%, 96% *de* (determined by NMR spectroscopy).



Scheme 6. Final steps of the pironetin synthesis: a) 1) KOH, MeOH, RT; 2) DMP (DMP = 2,2-dimethoxypropane), PPTS (PPTS = pyridinium *p*-toluene sulfonate), dichloromethane, 0°C→RT, 72% over two steps; b) Me_3OBF_4, proton sponge, 40°C, 53%, 69% based on the recovered starting material; c) acetone/6 N HCl, RT, 60%, 79% based on the recovered start material; d) 1) KOH, MeOH, RT; 2) DMP, PPTS, dichloromethane, 0°C→RT, 60% over two steps; e) acrylic acid chloride, Et_3N, THF, 0°C, 48% (not optimized); f) Grubbs first-generation catalyst, $Ti(OiPr)_4$, dichloromethane, reflux, 32% (not optimized); g) MeOH/3 N HCl, 60°C, 80%.

Conclusion

A convergent asymmetric total synthesis of pironetin (**1**) has been accomplished. The creation of the stereogenic centers at C_8, C_4, and C_5 were realized by employing the SAMP/RAMP hydrazone alkylation and aldolization methodology. The formation of the C_7–C_8 bond was carried out by a Mukaiyama-aldol reaction between ketone **2** and aldehyde **15**, which installed the stereogenic centers C_4 and C_5 simultaneously. The last stereogenic center C_9 was introduced by means of a samarium-mediated Tishchenko reduction and the formation of the α,β-unsaturated δ-lactone was achieved by ring-closing metathesis. Our new approach should permit easy access to various stereoisomers and structural analogues. Indeed, all the configurations of the stereogenic centers of pironetin can be simply controlled by auxiliary exchange between SAMP and RAMP in the alkylation and aldol reactions or by modification of the experimental conditions for the aldol reaction between the fragments **2** and **15** as well as for the reduction of the β-hydroxy ketone. Moreover, as it has already been described by our laboratory, the asymmetric α-alkylation of ketones by means of the SAMP/RAMP hydrazone methodology allows the introduction of a large variety of substituents R_1 in the C_{10} position.[5] In the same way, different R_2 groups may be envisaged at the C_4 position by employing other aldehydes rather than butyraldehyde in the aldol reaction.

Experimental Section

General methods: Solvents were dried and purified prior to use. THF was freshly distilled over sodium lead alloy under argon. Dichloromethane, dimethyl sulfoxide (DMSO), and triethylamine were distilled over CaH_2 and stored under argon. Acetone was distilled over P_2O_5 and stored under argon. Methanol was distilled over magnesium. Et_2O, pentane, and EtOAc were distilled over KOH, CaH_2, and K_2CO_3, respectively. Analytical glass-backed TLC plates (silica gel 60 F_{254}) and silica gel (60, 40–63 μm) were purchased from Merck, Darmstadt. Reagents of commercial quality were used from freshly opened containers unless otherwise stated. Optical rotations were measured on a Perkin–Elmer P241 polarimeter and with solvents of Merck UVASOL quality. Microanalyses were obtained with a Heraeus CHN-O-RAPID, Vario EL elemental analyzer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian VXR 300, Gemini 300 (both 300 and 75 MHz), Varian Inova 400 (400 MHz and 100 MHz), or Varian Unity 500 (500 and 125 MHz) with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer FTIR 1760 spectrometer. Mass spectroscopy was carried out on a Varian MAT 212, EI 70 eV, 1 mA and a Finnigan MAT SSQ 7000, CI 100 eV (relative intensities are reported in brackets). High-resolution mass spectra were recorded on a Finnigan MAT 95.

(*E*)-(*S*)-4-Methyloct-6-en-3-one (2): A dry, argon flushed 1 L Schlenk round-bottomed flask equipped with a magnetic stirring bar was filled with 2,2,6,6-tetramethylpiperidine (TMP, 114 mmol, 1.5 equiv) and anhydrous THF (220 mL). The reaction mixture was cooled to 0 °C and *n*BuLi (114 mmol, 1 equiv) was added dropwise. The orange solution was stirred for 30 min and a solution of SAMP hydrazone **4** (15 g, 76.0 mmol, 1.0 equiv) in THF (20 mL) was added at 0 °C. After stirring for 4 h at the same temperature, the mixture was cooled to −110 °C and (*E*)-1-bromobut-2-ene (68 mmol, 0.9 equiv) was slowly added in order to maintain the low temperature. After stirring for a further 30 min at −110 °C, the mixture was allowed to warm up to room temperature overnight. The reaction was quenched with pH 7 buffer solution (330 mL) and then diluted with Et_2O (200 mL). The aqueous phase was extracted with Et_2O (3 × 150 mL), the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting crude ketone hydrazone **5** was diluted in pentane (140 mL) and cooled to 0 °C. An aqueous solution of HCl (4 N, 60 mL) was added and the reaction mixture was vigorously stirred at room temperature for 1 h. The aqueous layer was separated, extracted with Et_2O (3 × 50 mL), and the organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by silica-gel flash chromatography (pentane/Et_2O 100:0, 95:5) to afford the alkylated ketone **2** (7.5 g, 78% over two steps) as a clear liquid. $[\alpha]_D^{24} = +23.9$ ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 5.49–5.39 (m, 1H), 5.36–5.26 (m, 1H), 2.59–2.50 (m, 1H), 2.43 (dq, ^3J(H,H) = 7.1, 2.2 Hz, 2H), 2.33–2.24 (m, 1H), 2.06–1.97 (m, 1H), 1.62 (dd, ^3J(H,H) = 6.2, 1.2 Hz, 3H), 1.04 (d, ^3J(H,H) = 7.1 Hz, 3H), 1.02 ppm (t, ^3J(H,H) = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.8$, 128.2, 127.3, 46.4, 36.3, 34.6, 18.1, 16.3, 7.9 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3022$, 2970, 2934, 2857, 1714, 1457, 1413, 1376, 1106, 1021, 969 cm^{-1}; MS (EI): *m*/*z* (%): 140 $[M]^+$, 112, 111, 83, 83, 67, 57, 56, 55, 53; elemental analysis calcd (%) for $C_9H_{16}O$ (140.12): C 77.09, H 11.50; found: C 76.83, H 11.38.

[(2*S*,3*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2-ethylpent-(*E*)-ylidene][(*R*)-2-methoxymethylpyrrolidin-1-yl]amine (*ent*-8): $TiCl_4$ (6.00 mmol, 1.2 equiv) was added dropwise over 15 min at −78 °C to a solution of hydrazone **6** (921 mg, 5.00 mmol, 1 equiv) in dichloromethane (7.5 mL) under argon. The dark-red solution was stirred for 30 min and then diisopropylethylamine (6.00 mmol, 1.2 equiv) was added over 15 min. The reaction mixture was stirred for 30 min at −78 °C, then for 2 h at room temperature, and recooled to −78 °C. After the addition of the aldehyde **7** (4.0 mmol, 0.8 equiv) dissolved in dichloromethane (1.5 mL), the solution was allowed to warm up to room temperature over 16 h and then quenched with a saturated solution of ammonium fluoride (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product (thick-dark-brown oil) was used in the next step without purification. 2,6-Lutidine (20.0 mmol, 4 equiv) was added to a stirred solution of crude aldol product (5.0 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) under argon, followed by the dropwise addition of TBSOTf (15.0 mmol, 3 equiv) at −78 °C. After stirring for 2 h at the same temperature (TLC control), the mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product as a dark-brown syrup. Purification by flash chromatography on silica gel (pentane/Et_2O 90:10, 80:20) gave the TBS-protected product *ent*-**8** as a pale-yellow oil (1.85 g, 80% over two steps, *de* = 55%, ≥96% after HPLC). $[\alpha]_D^{28} = -63.8$ ($c = 1.09$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$–7.23 (m, 5H), 6.56 (d, ^3J(H,H) = 6.6 Hz, 1H), 4.50 (d, ^3J(H,H) = 12.0 Hz, 1H), 4.46 (d, ^3J(H,H) = 12.0 Hz, 1H), 3.93–3.88 (m, 1H), 3.62–3.49 (m, 3H), 3.44–3.29 (m, 3H), 3.36 (s, 3H), 2.75–2.67 (m, 1H), 2.27–2.20 (m, 1H), 1.98–1.70 (m, 6H), 1.52–1.42 (m, 2H), 0.88 (s, 9H), 0.89 (t, ^3J(H,H) = 7.4 Hz, 3H), 0.05 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 139.3, 138.4, 128.1, 127.4, 127.3, 74.9, 72.8, 71.7, 67.1, 63.3, 59.1, 50.2, 50.0, 33.8, 26.6, 25.9, 22.02, 21.6, 18.1, 12.2, −4.4, −4.5 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3088$, 3064, 2956, 2929, 2856, 2727, 1946, 1726, 1692, 1601, 1496, 1461, 1407, 1381, 1362, 1340, 1302, 1254, 1198, 1099, 1056, 1029, 1006, 973, 939, 905, 837, 801, 776, 698, 676, 609, 465 cm^{-1}; MS (EI): *m*/*z* (%): 462 $[M]^+$, 420, 418, 286, 280, 269, 204, 185, 175, 173, 139, 117, 115, 114, 101, 1001, 91, 89, 82, 75, 73, 71, 70, 59, 55, 45; HRMS: *m*/*z*: calcd for $C_{26}H_{46}N_2O_3Si$: 462.3278 $[M]^+$; found: 462.3276.

(2*R*,3*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)-2-ethylpentanal (*ent*-9): SAMP hydrazone *ent*-**8** (7.15 g, 15.45 mmol, 1.0 equiv) in MeOH (100 mL) was added to a solution of MMPP (32.81 mmol, 2.1 equiv) in a mixture of MeOH (130 mL) and pH 7 buffer solution (130 mL) at 0 °C. The heterogeneous solution was stirred at the same temperature for 6 h, followed by dilution with Et_2O (310 mL) and brine (70 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under

reduced pressure. Purification by flash chromatography on silica gel (pentane/Et_2O 90:10) afforded the corresponding nitrile (4.95 g, 92%) as a colorless oil. $[\alpha]_D^{28} = -10.2$ ($c = 1.09$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.32–7.18$ (m, 5H), 4.46 (d, $^3J(H,H) = 11.8$ Hz, 1H), 4.39 (d, $^3J(H,H) = 11.8$ Hz, 1H), 3.93 (td, $^3J(H,H) = 10.2$, 6.6 Hz, 1H), 3.51 (t, $^3J(H,H) = 5.8$ Hz, 2H), 2.58 (ddd, $^3J(H,H) = 8.5$, 6.9, 4.9 Hz, 1H), 1.86–1.78 (m, 2H), 1.60–1.48 (m, 2H), 1.04 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.84 (s, 9H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.3$, 128.5, 127.7, 120.7, 73.1, 69.0, 65.9, 41.5, 34.1, 25.8, 21.6, 18.0, 12.2, −4.6 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3088$, 3065, 3031, 2956, 2931, 2882, 2858, 2801, 2240, 1496, 1463, 1408, 1386, 1363, 1310, 1256, 1208, 1100, 1051, 1029, 1008, 940, 839, 804, 778, 727, 699, 672 cm^{-1}; MS (EI): m/z (%): 347 $[M]^+$, 290, 92, 73; elemental analysis calcd (%) for $C_{20}H_{33}NO_2Si$ (347.57): C 69.11, H 9.57, N 4.03; found: C 69.12, H 9.81, N 4.49.

DIBAL-H (1.0 M in heptane, 15.5 mmol, 1.35 equiv) was added to a solution of the nitrile derived from *ent*-**8** (4.0 g, 11.51 mmol, 1.0 equiv) in anhydrous THF (23 mL) under argon at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched with a solution of tartaric acid (1 M in water, 57 mL) and Et_2O (23 mL). The heterogeneous solution was stirred for 1 h. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the organic solutions were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (pentane/Et_2O 90:10) afforded the aldehyde *ent*-**9** (3.44 g, 86%) as a colorless oil. $[\alpha]_D^{28} = -23.2$ ($c = 1.21$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.80$ (d, $^3J(H,H) = 2.2$ Hz, 1H), 7.37–7.25 (m, 5H), 4.50 (d, $^3J(H,H) = 11.8$ Hz, 1H), 4.45 (d, $^3J(H,H) = 11.8$ Hz, 1H), 4.21 (td, $^3J(H,H) = 8.8$, 4.4 Hz, 1H), 3.52 (t, $^3J(H,H) = 5.8$ Hz, 2H), 2.34 (ddd, $^3J(H,H) = 6.9$, 4.7, 2.2 Hz, 1H), 1.91–1.82 (m, 2H), 1.79–1.66 (m, 2H), 0.91 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 205.6$, 138.5, 128.6, 127.8, 73.2, 69.7, 66.8, 59.5, 34.6, 26.1, 18.4, 18.1, 12.7, −4.2 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3088$, 3065, 3031, 2956, 2929, 2857, 2711, 1723, 1496, 1462, 1407, 1383, 1362, 1309, 1256, 1208, 1187, 1101, 1055, 1006, 940, 838, 777, 736, 698, 669, 465 cm^{-1}; MS (EI): m/z (%): 279 $[M-C_5H_{11}]^+$, 92, 91, 75, 73; elemental analysis calcd (%) for $C_{20}H_{34}O_3Si$ (350.57): C 68.52, H 9.78; found: C 68.43, H 9.90.

[(1*S*,2*S*)-1-(2-Benzyloxyethyl)-2-ethyl-but-3-enyloxy]-*tert*-butyldimethylsilane (*ent*-10): *t*BuLi (17.22 mmol, 6 equiv) was slowly added to a suspension of Ph_3PCH_3Br (17.22 mmol, 6 equiv) in anhydrous THF (23 mL) under argon at −78 °C. The orange solution was stirred 30 min at −78 °C and for 30 min at room temperature until it became homogenous. The reaction mixture was cooled to −78 °C and aldehyde *ent*-**9** (1.0 g, 2.87 mmol, 1 equiv) dissolved in THF (8.6 mL) was added. The reaction was allowed to warm up to room temperature overnight and was then quenched with water (23 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/Et_2O 100:0, 95:5) afforded *ent*-**10** (971 mg, 97%) as a colorless oil. $[\alpha]_D^{28} = -7.4$ ($c = 1.07$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35–7.25$ (m, 5H), 5.65 (ddd, $^3J(H,H) = 17.0$, 10.4, 8.5 Hz, 1H), 5.06 (dd, $^3J(H,H) = 10.4$, 2.2 Hz, 1H), 4.98 (ddd, $^3J(H,H) = 17.0$, 2.2, 1.0 Hz, 1H), 4.51 (d, $^3J(H,H) = 12.0$ Hz, 1H), 4.45 (d, $^3J(H,H) = 12.0$ Hz, 1H), 3.77 (ddd, $^3J(H,H) = 7.4$, 5.2, 3.85 Hz, 1H), 3.53 (t, $^3J(H,H) = 7.1$ Hz, 2H), 2.06–1.95 (m, 1H), 1.85–1.63 (m, 2H), 1.56–1.42 (m, 1H), 1.30–1.16 (m, 1H), 0.88 (s, 9H), 0.85 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.05 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.2$, 138.7, 128.4, 127.7, 127.5, 116.1, 72.9, 72.2, 67.1, 51.8, 33.5, 26.0, 22.8, 18.2, 12.1, −4.2, −4.5 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3068$, 3030, 2957, 2929, 2857, 2800, 1640, 1496, 1462, 1455, 1407, 1379, 1362, 1307, 1255, 1205, 1096, 1058, 1029, 1005, 939, 878, 836, 775, 734, 697, 665 cm^{-1}; MS (EI): m/z (%): 279 $[M-C_5H_9]^+$, 173, 131, 117, 107, 101, 91, 75, 73, 59; elemental analysis calcd (%) for $C_{21}H_{36}O_2Si$ (348.59): C 72.35, H 10.41; found: C 71.84, H 10.84.

Acrylic acid (1*S*,2*S*)-1-(2-benzyloxyethyl)-2-ethyl-but-3-enyl ester (*ent*-11): A solution of tetrabutylammonium fluoride (TBAF, 1 M in THF, 16.4 mmol, 5.9 equiv) was added to a solution of *ent*-**10** (970 mg, 2.78 mmol, 1.0 equiv) in THF (13 mL) under argon at room temperature. The reaction mixture was stirred for 16 h and was then quenched by addition of water (13 mL), followed by extractions with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (pentane/Et_2O 60:40) to give the corresponding alcohol (620 mg, 97%) as a colorless oil. $[\alpha]_D^{23} = +2.0$ ($c = 1.13$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37–7.27$ (m, 5H), 5.65 (ddd, $^3J(H,H) = 17.0$, 10.2, 9.3 Hz, 1H), 5.10 (dd, $^3J(H,H) = 10.2$, 2.0 Hz, 1H), 5.04 (ddd, $^3J(H,H) = 17.0$, 2.0, 0.8 Hz, 1H), 4.52 (s, 3H), 3.75–3.61 (m, 3H), 1.98 (dtd, $^3J(H,H) = 13.2$, 6.9, 3.6 Hz, 1H), 1.83 (d, $^3J(H,H) = 14.8$, 6.0, 4.4, 2.0 Hz, 1H), 1.75–1.61 (m, 2H), 1.30–1.19 (m, 1H), 0.80 ppm (t, $^3J(H,H) = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.2$, 138.1, 128.6, 127.7, 127.9, 117.2, 74.0, 73.6, 69.8, 52.9, 34.0, 23.3, 12.1 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3067$, 2960, 2929, 2872, 1639, 1496, 1479, 1454, 1421, 1364, 1310, 1242, 1206, 1029, 1000, 914, 737, 698, 462 cm^{-1}; MS (EI): m/z (%): 234 $[M]^+$, 165, 107, 92, 91, 65; elemental analysis calcd (%) for $C_{15}H_{22}O_2$ (234.33): C 76.88, H 9.46; found: C 76.58, H 9.61.

Dropwise 1,3-dicyclohexylcarbodiimide (DCC, 29.07 mmol, 4.0 equiv) and the alcohol obtained from *ent*-**10** (1.7 g, 7.26 mmol, 1.0 equiv) were added successively to a solution of acrylic acid (29.05 mmol, 4.0 equiv) and 4-dimethylaminopyridine (DMAP, 8.73 mmol, 1.2 equiv) in dichloromethane (22 mL) under argon at 0 °C. The solution was stirred at 0 °C for 10 min and was then allowed to warm up to room temperature overnight. The mixture was filtered through Celite, washed with dichloromethane (15 mL), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (pentane/Et_2O 80:20) to give the diene *ent*-**11** (1.55 g, 77%) as a colorless oil. $[\alpha]_D^{23} = -10.1$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34–7.24$ (m, 5H), 6.38 (dd, $^3J(H,H) = 17.3$, 1.4 Hz, 1H), 6.10 (dd, $^3J(H,H) = 17.3$, 10.4 Hz, 1H), 5.80 (dd, $^3J(H,H) = 10.4$, 1.4 Hz, 1H), 5.56 (ddd, $^3J(H,H) = 17.0$, 10.4, 9.2 Hz, 1H), 5.14–5.06 (m, 1H), 5.04 (dd, $^3J(H,H) = 17.0$, 0.8 Hz, 1H), 4.46 (s, 2H), 3.53–3.41 (m, 2H), 2.25–2.16 (m, 1H), 2.05–1.75 (m, 2H), 1.59–1.46 (m, 1H), 1.35–1.20 (m, 1H), 0.85 ppm (t, $^3J(H,H) = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.1$, 138.6, 138.0, 130.8, 128.8, 127.8, 127.6, 117.9, 74.0, 73.4, 67.2, 50.2, 32.0, 23.3, 12.0 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 2963$, 2931, 2874, 1723, 1638, 1619, 1496, 1454, 1405, 1363, 1270, 1195, 1101, 1046, 1029, 985, 918, 866, 809, 737, 698, 461 cm^{-1}; MS (EI): m/z (%): 288 $[M]^+$, 187, 146, 110, 107, 105, 95, 92, 91, 82, 79, 69, 68, 67, 65, 55; elemental analysis calcd (%) for $C_{18}H_{24}O_3$ (288.38): C 74.97, H 8.39; found: C 74.72, H 8.83.

(5*S*,6*S*)-5-Ethyl-6-(2-hydroxyethyl)-5,6-dihydropyran-2-one (*ent*-12): $Ti(OiPr)_4$ (2.69 mmol, 0.5 equiv) was added to a stirred solution of diene *ent*-**11** (1.55 g, 5.37 mmol, 1.0 equiv) in dichloromethane (107 mL) under argon at room temperature. The resulting solution was refluxed at 40 °C for 2 h and then Grubbs first-generation catalyst (1.09 mmol, 0.2 equiv) in dichloromethane (50 mL) was added. The reaction mixture was stirred at reflux for an additional 48 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (pentane/Et_2O 50:50) to provide the lactone (1.34 g, 96%) as a brown oil. $[\alpha]_D^{23} = -63.3$ ($c = 0.75$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37–7.26$ (m, 5H), 6.99 (dd, $^3J(H,H) = 9.9$, 6.0 Hz, 1H), 6.03 (dd, $^3J(H,H) = 9.9$, 0.8 Hz, 1H), 4.67 (dt, $^3J(H,H) = 9.6$, 3.8, 1H), 4.54 (d, $^3J(H,H) = 11.8$ Hz, 1H), 4.49 (d, $^3J(H,H) = 11.8$ Hz, 1H), 3.73–3.62 (m, 2H), 2.29–2.23 (m, 1H), 2.12–2.0 (m, 1H), 1.92–1.83 (m, 1H), 1.72–1.60 (m, 1H), 1.56–1.42 (m, 1H), 0.95 ppm (t, $^3J(H,H) = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.7$, 150.8, 138.4, 128.6, 127.9, 127.8, 121.0, 78.9, 73.5, 66.3, 38.8, 32.0, 21.0, 11.3 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3030$, 2964, 2932, 2876, 1724, 1496, 1455, 1385, 1366, 1311, 1250, 1258, 1101, 1028, 954, 823, 699 cm^{-1}; MS (EI): m/z (%): 260 $[M]^+$, 187, 154, 147, 125, 109, 107, 97, 96, 95, 94, 92, 91, 81, 79, 69, 67, 65, 57, 55, 53; HRMS: m/z: calcd for $C_{16}H_{20}O_3$: 260.1112 $[M]^+$; found: 260.1412.

$TiCl_4$ (1 M in dichloromethane, 10.4 mmol, 3.0 equiv) was slowly added to a solution of the benzyl-protected lactone alcohol (900 mg, 3.45 mmol, 1.0 equiv) in dichloromethane (32 mL) under argon at 0 °C. After stirring for 10 min at 0 °C and 6 h at room temperature, the reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (40 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL) and the combined organic layers were washed with brine (50 mL), dried over

$MgSO_4$, filtered, and concentrated in vacuo. Purification by silica-gel flash chromatography (Et_2O 100%) gave the desired product *ent*-**12** (535 mg, 91%) as a colorless liquid. $[\alpha]_D^{23} = -79.2$ ($c = 1.00$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.04$ (dd, $^3J(H,H) = 9.6$, 3.3 Hz, 1H), 6.03 (d, $^3J(H,H) = 9.6$ Hz, 1H), 4.71 (dt, $^3J(H,H) = 10.2$, 3.6, 1H), 3.92–3.78 (m, 2H), 2.63 (s, 1H; OH), 2.40–2.25 (m, 1H), 2.04 (m, 2H), 1.65 (m, 2H), 0.95 ppm (t, $^3J(H,H) = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.5$, 150.7, 120.4, 77.6, 58.5, 38.4, 33.8, 20.7, 10.9 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3419$, 3016, 2967, 1883, 1711, 1623, 1463, 1387, 1258, 1057, 1016, 922, 826, 755, 667 cm^{-1}; MS (EI): *m/z* (%): 152 $[M-H_2O]^+$, 141, 125, 97, 96, 95, 82, 81, 73, 68, 67, 57, 54, 53; elemental analysis calcd (%) for $C_9H_{14}O_3$ (170.21): C 63.51, H 8.29; found: C 63.28, H 8.88.

(3*R*,4*R*)-3-(*tert*-Butyldimethylsilanyloxy)-4-ethyl-hex-5-enal (15): Benzyl ether **10** (675 mg, 1.91 mmol, 1.0 equiv) in THF (50 mL) was added to a dark-blue solution of calcium metal (19.4 mmol, 10 equiv) in liquid ammonia (10 mL) and anhydrous THF (25 mL) under argon at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and was then quenched by the addition of solid NH_4Cl (25 g). The ammonia was allowed to evaporate while the reaction was gradually warmed up to room temperature and then a saturated aqueous solution of NH_4Cl was added. The aqueous phase was extracted with Et_2O (3×40 mL) and the organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. After a short filtration on silica gel (pentane/Et_2O 80:20), the corresponding alcohol (500 mg, quantitative, clear oil) was directly used in the next step. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.54$ (ddd, $^3J(H,H) =$ 17.1, 10.4, 8.7 Hz, 1H), 5.03 (dd, $^3J(H,H) = 10.4$, 2.2 Hz, 1H), 4.95 (ddd, $^3J(H,H) = 17.1$, 2.2, 1.0 Hz, 1H), 3.77–3.70 (m, 2H), 3.65 (dt, $^3J(H,H) =$ 11.4, 5.7 Hz, 1H), 2.11–2.00 (m, 1H), 1.70–1.60 (m, 2H), 1.53–1.43 (m, 1H), 1.20–1.06 (m, 1H), 0.83 (s, 9H), 0.80 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.03 (s, 3H), 0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 138.6$, 116.5, 73.8, 60.1, 51.3, 35.0, 25.9, 23.2, 18.0, 12.0, −4.5, −4.4 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3343$, 3075, 2956, 2860, 1639, 1467, 1418, 1382, 1254, 1082, 914, 838, 775, 668, 490 cm^{-1}; MS (CI): *m/z* (%): 259 $[M+1]^+$, 243, 189, 173, 131, 127, 109, 83.

DMSO (8 mL) and Et_3N (9.69 mmol, 5.0 equiv) were added to a solution of the alcohol (500 mg, 1.94 mmol, 1.0 equiv) in dichloromethane (8 mL) under argon. The solution was cooled to 0 °C and SO_3–pyridine complex (9.69 mmol, 5 equiv) was added. After 30 min of stirring, the reaction mixture was diluted with Et_2O (20 mL) and washed with a saturated solution of NH_4Cl (15 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (pentane/Et_2O 95:5, 90:10) afforded the aldehyde **15** (414 mg, 83% over two steps) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.81$ (t, $^3J(H,H) = 2.3$ Hz, 1H), 5.56 (ddd, $^3J(H,H) = 17.3$, 10.4, 8.8 Hz, 1H), 5.13 (dd, $^3J(H,H) = 10.4$, 1.9 Hz, 1H), 5.05 (ddd, $^3J(H,H) = 17.3$, 1.9, 0.8 Hz, 1H), 4.11 (td, $^3J(H,H) = 6.3$, 4.8 Hz, 1H), 2.57 (ddd, $^3J(H,H) = 16.0$, 6.3, 2.7 Hz, 1H), 2.48 (ddd, $^3J(H,H) = 16.0$, 4.7, 1.9 Hz, 1H), 2.14–2.06 (m, 1H), 1.62–1.52 (m, 1H), 1.28–1.17 (m, 1H), 0.88 (s, 9H), 0.87 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.09 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.3$, 138.2, 117.5, 70.8, 52.5, 48.3, 25.8, 23.0, 18.0, 11.9, −4.5, −4.4 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 3077$, 2954, 2862, 2719, 1727, 1466, 1380, 1255, 1091, 1003, 920, 838, 777, 673, 552 cm^{-1}; MS (CI): *m/z* (%): 257 $[M+1]^+$, 241, 213, 199, 187, 159, 125, 127, 107, 81.

(*E*)-(5*S*,7*S*,8*R*,10*R*,11*R*)-10-(*tert*-Butyldimethylsilanyloxy)-11-ethyl-8-hydroxy-5,7-dimethyltrideca-2,12-dien-6-one (17): *n*BuLi (3.86 mmol, 2.0 equiv) was added to a solution of diphenyltetramethyldisilazane (3.86 mmol, 2 equiv) in THF (7.7 mL) under argon at 0 °C. After 10 min of stirring, the solution was cooled to −78 °C and a solution of the ketone **2** (270 mg, 1.93 mmol, 1 equiv) in THF (1 mL) was added. After stirring for 1 h at −78 °C, a solution of TMSCl (7.72 mmol, 4.0 equiv) and Et_3N (1.93 mmol, 1 equiv) in THF (1 mL) was added. The reaction was stirred for 15 min at −78 °C, and then for 5 h at room temperature. The mixture was partitioned between pentane (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The pentane layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was directly used in the next step without purification.

$BF_3{\cdot}OEt_2$ (7.72 mmol, 4.0 equiv) was added to a stirred solution of enolsilane **16** (1.93 mmol, 1 equiv) and aldehyde **15** (1.93 mmol, 1.0 equiv) in anhydrous dichloromethane(15 mL) under argon at −78 °C. The reaction was stirred at −78 °C for 3 h and then partitioned between dichloromethane (100 mL) and saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with dichloromethane (3×30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. A short purification by flash chromatography (pentane/Et_2O 95:5, 90:10) afforded a mixture of diastereoisomers (700 mg, 92% over two steps) as a clear oil, which contained 57% of the desired diastereoisomer **14** (399 mg).

The mixture of β-hydroxyketone (1.77 mmol, 1.0 equiv) was dissolved in anhydrous THF (7.1 mL) under argon. To this was added freshly distilled acetaldehyde (7.08 mmol, 4.0 equiv). The solution was cooled to −15 °C (methanol/ice bath) and a freshly prepared 0.1 M solution of SmI_2 in THF (4 mL, 0.4 equiv) was added dropwise (30 min). The initial blue color disappears within 15 s. After stirring for 1 h at −15 °C, the reaction mixture was quenched by the addition of Et_2O (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with Et_2O (3× 10 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica-gel flash chromatography (pentane/Et_2O 95:5, 90:10) gave the desired product **17** (398 mg, 90%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.72$ (ddd, $^3J(H,H) = 17.3$, 10.4, 8.0 Hz, 1H), 5.48–5.33 (m, 3H), 5.10 (dd, $^3J(H,H) = 10.4$, 1.9 Hz, 1H), 5.02 (ddd, $^3J(H,H) = 17.3$, 1.9, 1.1 Hz, 1H), 3.64 (ddd, $^3J(H,H) = 8.8$, 3.8, 2.5 Hz, 1H), 3.25 (d, $^3J(H,H) = 4.4$ Hz, 1H(OH)), 3.05 (ddd, $^3J(H,H) = 10.2$, 4.4, 2.2 Hz, 1H), 2.07 (s, 3H), 2.13–1.97 (m, 3H), 1.84 (ddd, $^3J(H,H) = 14.6$, 9.9, 2.5 Hz, 1H), 1.65 (d, $^3J(H,H) = 5.8$ Hz, 3H), 1.67–1.58 (m, 2H), 1.45–1.30 (m, 3H), 0.89 (s, 9H), 0.88 (t, $^3J(H,H) =$ 7.4 Hz, 3H), 0.80 (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.77 (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.05 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.1$, 138.2, 130.1, 126.0, 116.0, 73.1, 72.2, 72.0, 51.1, 41.5, 38.0, 36.3, 34.3, 25.9, 22.5, 21.0, 18.1, 17.9, 12.1, 11.4, 9.7, −4.7, −4.0 ppm; IR (film, $CHCl_3$): $\tilde{\nu} =$ 3529, 2960, 2932, 2858, 1720, 1463, 1374, 1255, 1134, 1071, 966, 948, 914, 837, 776, 667 cm^{-1}; MS (CI): *m/z* (%): 441 $[M+1]^+$, 381, 363, 323, 309, 250, 249, 231, 213, 199, 179, 137, 113, 83.

Acetic acid (*E*)-(1*R*,2*R*,3*S*,4*S*)-1-[(2*R*,3*R*)-2-(*tert*-butyl-dimethylsilanyloxy)-3-ethyl-pent-4-enyl]-3-hydroxy-2,4-dimethyl-oct-6-enyl ester (18): Proton sponge (0.74 mmol, 5 equiv) and Me_3OBF_4 (0.74 mmol, 5 equiv) were added to a solution of alcohol **17** (65 mg, 0.148 mmol, 1 equiv) in dichloromethane (2 mL) under argon at room temperature. The heterogeneous mixture was stirred for 6 h at 40 °C and then overnight at room temperature in the dark. The brownish mixture was poured into dichloromethane (10 mL) and washed with aqueous HCl (1 M, 3×5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (pentane/Et_2O 90:10) afforded **18** (35.6 mg, 53%, 69% based on the recovered start material) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.74$ (ddd, $^3J(H,H) = 17.3$, 10.4, 8.0 Hz, 1H), 5.48–5.34 (m, 2H), 5.25 (ddd, $^3J(H,H) = 6.6$, 4.7, 1.9 Hz, 1H), 5.07 (dd, $^3J(H,H) = 10.4$, 1.9 Hz, 1H), 5.00 (ddd, $^3J(H,H) = 17.3$, 1.9, 0.8 Hz, 1H), 3.74 (dt, $^3J(H,H) = 7.7$, 3.8 Hz, 1H), 3.39 (s, 3H), 2.87 (dd, $^3J(H,H) = 9.3$, 2.2 Hz, 1H), 2.04 (s, 3H), 2.16–1.94 (m, 3H), 1.75 (ddd, $^3J(H,H) = 14.3$, 7.7, 3.8 Hz, 1H), 1.67 (d, $^3J(H,H) = 4.9$ Hz, 3H), 1.72–1.60 (m, 2H), 1.51 (ddd, $^3J(H,H) = 14.3$, 8.0, 4.7 Hz, 1H), 1.47–1.37 (m, 1H), 1.37–1.27 (m, 1H), 0.89 (s, 9H), 0.88 (t, $^3J(H,H) = 8.2$ Hz, 3H), 0.82 (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.80 (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.10 (s, 3H), 0.06 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.5$, 139.0, 130.1, 126.1, 115.6, 85.0, 72.4, 72.2, 60.9, 50.9, 40.3, 38.3, 37.2, 35.7, 25.9, 21.9, 21.3, 18.1, 18.0, 12.3, 12.1, 10.5, −4.5, −4.3 ppm; IR (film, $CHCl_3$): $\tilde{\nu} =$ 3850, 3745, 3673, 3478, 2939, 2354, 1737, 1643, 1553, 1459, 1374, 1249, 1089, 960, 813, 671 cm^{-1}; MS (CI): *m/z* (%): 455 $[M+1]^+$, 395, 363, 325, 323, 263, 231, 213, 161, 127, 95.

Acetic acid (*E*)-(1*R*,2*S*,3*S*,4*S*)-1-[(2*R*,3*R*)-3-ethyl-2-hydroxy-pent-4-enyl]-3-methoxy-2,4-dimethyl-oct-6-enyl ester (20): A solution of HCl (6 N, 600 μL) was added to a stirred solution of **18** (240 mg, 0.528 mmol, 1.0 equiv) in acetone (6 mL) at 0 °C, and the mixture was stirred for 80 min at room temperature. The reaction was diluted with Et_2O

(10 mL), washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 95:5, 80:20) afforded **20** (108 mg, 60%, 79% based on the recovered start material) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 5.55$ (ddd, $^3J(H,H) = 17.3$, 10.4, 9.3 Hz, 1H), 5.48–5.34 (m, 3H), 5.08 (dd, $^3J(H,H) = 10.4$, 2.2 Hz, 1H), 5.03 (ddd, $^3J(H,H) = 17.3$, 2.2, 0.8 Hz, 1H), 3.37 (s, 3H), 3.30 (ddd, $^3J(H,H) = 11.0$, 4.4, 1.9 Hz, 1H), 3.27 (s, 1H; OH), 2.82 (dd, $^3J(H,H) = 9.3$, 2.2 Hz, 1H), 2.11 (s, 3H), 2.13–2.08 (m, 1H), 2.04–1.91 (m, 2H), 1.87–1.79 (m, 1H), 1.79–1.69 (m, 1H), 1.69–1.60 (m, 1H), 1.66 (d, $^3J(H,H) = 5.8$ Hz, 3H), 1.34 (ddd, $^3J(H,H) = 13.5$, 10.7, 2.7 Hz, 1H), 1.28–1.18 (m, 1H), 1.37–1.27 (m, 1H), 0.86 (d, $^3J(H,H) = 7.4$ Hz, 3H), 0.85 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.81 ppm (d, $^3J(H,H) = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.4$, 139.0, 129.9, 126.3, 116.5, 85.2, 71.2, 69.5, 61.2, 52.2, 40.5, 38.8, 38.3, 35.7, 23.1, 21.1, 18.0, 12.4, 11.7, 10.6 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 2957$, 1727, 1461, 1375, 1252, 1083, 960, 839, 761, 669 cm^{-1}; MS (EI): *m/z* (%): 325 $[M-CH_3]^+$, 311, 293, 231, 213, 199, 161, 153, 128, 127, 117, 109, 95, 75, 73, 59, 55.

Acrylic acid (*E*)-(1*R*,3*R*,4*S*,5*S*,6*S*)-3-acetoxy-1-[(*R*)-1-ethylallyl]-5-methoxy-4,6-dimethyldec-8-enyl ester (13): Et_3N (0.53 mmol, 5 equiv) was added to a solution of the alcohol **20** (36 mg, 0.106 mmol, 1 equiv) in dry THF (1.0 mL) under argon at 0°C. A solution of acryloyl acid chloride (0.53 mmol, 5 equiv) in dry CH_2Cl_2 (1.0 mL) was added dropwise to the mixture and stirring was continued for a further 30 min at 0°C. Brine was added and the aqueous phase was quickly extracted with Et_2O (3× 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 90:10) afforded **13** (20 mg, 48% not optimized) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.39$ (dd, $^3J(H,H) = 17.3$, 1.4 Hz, 1H), 6.11 (dd, $^3J(H,H) = 17.3$, 10.4 Hz, 1H), 5.80 (dd, $^3J(H,H) = 10.4$, 1.4 Hz, 1H), 5.56 (ddd, $^3J(H,H) = 17.3$, 10.4, 9.1 Hz, 1H), 5.50–5.32 (m, 2H), 5.25 (ddd, $^3J(H,H) = 9.3$, 4.1, 2.2 Hz, 1H), 5.12 (dd, $^3J(H,H) = 10.4$, 2.0 Hz, 1H), 5.04 (dd, $^3J(H,H) = 17.3$, 2.0 Hz, 1H), 4.91 (ddd, $^3J(H,H) = 9.3$, 6.3, 3.0 Hz, 1H), 3.41 (s, 3H), 2.86 (dd, $^3J(H,H) = 9.3$, 2.2 Hz, 1H), 2.03 (s, 3H), 2.30–2.19 (m, 1H), 2.15–2.06 (m, 1H), 2.01–1.92 (m, 2H), 1.71 (ddd, $^3J(H,H) = 14.6$, 10.4, 4.1 Hz, 1H), 1.68–1.58 (m, 2H), 1.66 (dd, $^3J(H,H) = 5.8$, 0.8 Hz, 3H), 1.55–1.44 (m, 1H), 1.32–1.20 (m, 1H), 0.87 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.81 (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.79 ppm (d, $^3J(H,H) = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$, 165.5, 137.3, 130.2, 129.9, 128.5, 126.2, 117.5, 85.2, 72.9, 70.1, 61.1, 49.5, 40.5, 38.3, 35.7,34.5, 23.0, 21.1, 17.9, 12.3, 11.7, 10.7 ppm; IR (film, $CHCl_3$): $\tilde{\nu} = 2960$, 2929, 2875, 1724, 1636, 1620, 1492, 1370, 1261, 1198, 970, 855, 754, 670 cm^{-1}; MS (CI): *m/z* (%): 395 $[M+1]^+$, 363, 336, 335, 323, 311, 303, 192, 263, 232, 231, 229, 192, 178, 161, 149, 136, 127, 123, 95; HRMS: *m/z*: calcd for $C_{23}H_{38}O_5$ $[M-CH_2{=}CH_2, COCH_2{=}CH_2]^+$: 311.1858; found: 311.1858.

Acetic acid (*E*)-(1*R*,2*S*,3*S*,4*S*)-1-[(2*R*,3*R*)-3-ethyl-6-oxo-3,6-dihydro-2*H*-pyran-2-ylmethyl]-3-methoxy-2,4-dimethyloct-6-enyl ester (22): A solution of $Ti(OiPr)_4$ in dichloromethane (0.1 M, 0.0153 mmol, 153 μL) was added to a stirred solution of diene **13** (20 mg, 0.051 mmol, 1.0 equiv) in dichloromethane (17 mL, 0.003 M) under argon at room temperature. The resulting solution was refluxed at 40°C for 30 min and then Grubbs first-generation catalyst (0.01 mmol, 0.2 equiv) in dichloromethane (1 mL) was added. The reaction mixture was stirred at reflux for another 20 h. The mixture was cooled to room temperature and the solvent was partially evaporated. The residue was purified by flash chromatography on silica gel (pentane/Et_2O 50:50) to provide the lactone **22** (6.0 mg, 32% not optimized, 39% based on the recovered start material) as a brown oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.03$ (dd, $^3J(H,H) = 9.6$, 6.0 Hz, 1H), 6.12 (d, $^3J(H,H) = 9.6$ Hz, 1H), 5.51–5.34 (m, 2H), 5.30–5.24 (m, 1H), 4.50–4.43 (m, 1H), 3.39 (s, 3H), 2.88 (dd, $^3J(H,H) = 9.3$, 1.6 Hz, 1H), 2.07 (s, 3H), 2.30–2.22 (m, 1H), 2.17–1.90 (m, 3H), 1.82–1.70 (m, 2H), 1.67 (d, $^3J(H,H) = 5.5$ Hz, 3H), 1.64–1.47 (m, 2H), 0.97 (t, $^3J(H,H) = 7.4$ Hz, 3H), 0.89 (d, $^3J(H,H) = 6.9$ Hz, 3H), 0.82 ppm (d, $^3J(H,H) = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.6$, 164.0, 150.3, 129.9, 126.4, 120.7, 85.0, 77.4, 70.8, 61.2, 39.0, 38.1, 38.0, 35.6, 33.9, 21.1, 20.3, 17.8, 12.2, 10.8, 10.1 ppm. The data are in accordance with those described in the literature.[4g]

(5*R*,6*R*)-5-Ethyl-6-[(*E*)-(2*R*,3*S*,4*S*,5*S*)-2-hydroxy-4-methoxy-3,5-dimethyl-non-7-enyl]-5,6-dihydropyran-2-one (1): HCl (3 M, 32 μL) was added to a solution of **22** (7.5 mg, 0.02 mmol) in MeOH (160 μL) at room temperature. The reaction mixture was then heated to 60°C and stirred overnight at this temperature. The solution was cooled to room temperature and quenched by addition of saturated aqueous $NaHCO_3$ solution (200 μL) and Et_2O (5 mL). The mixture was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O 90:10) afforded pironetin (**1**) (5.4 mg, 80%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.01$ (dd, $^3J(H,H) = 9.6$, 6.2 Hz, 1H), 6.02 (d, $^3J(H,H) = 9.6$ Hz, 1H), 5.50–5.30 (m, 2H), 4.74 (dt, $^3J(H,H) = 7.9$, 4.0 Hz, 1H), 4.24–4.19 (m, 1H), 3.47 (s, 3H), 2.98 (dd, $^3J(H,H) = 6.2$, 4.4 Hz, 1H), 2.34–2.23 (m, 1H), 2.14–2.05 (m,1H), 1.97–1.59 (m, 6H), 1.67 (d, $^3J(H,H) = 5.2$ Hz, 3H), 1.57–1.45 (m, 1H), 1.01 (t, $^3J(H,H) = 7.1$ Hz, 3H), 0.97 (d, $^3J(H,H) = 7.1$ Hz, 3H), 0.96 ppm (d, $^3J(H,H) = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.8$, 150.6, 128.6, 126.8, 120.7, 91.0, 77.6, 67.2, 61.5, 39.0, 38.7, 37.1, 36.6, 36.0, 20.6, 17.8, 15.1, 12.1, 10.8 ppm; HRMS: *m/z*: $C_{19}H_{32}O_4$: calcd (%) for 292.2038 $[M-MeOH]^+$; found: 292.2037.

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