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A Chemoenzymatic Approach to the Stereocontrolled Synthesis of the C1–C11 fragment of (+)-Peloruside A

Heike Schönherr,[a] Jan Mollitor,[a] and Christoph Schneider*[a]

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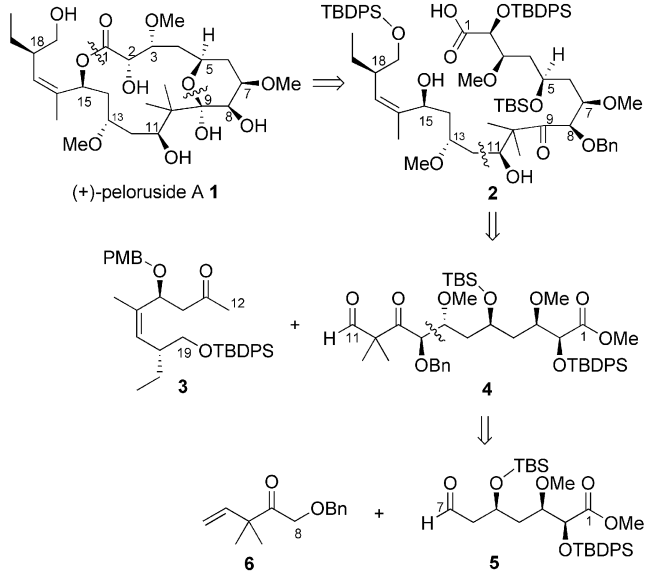
A highly efficient and diastereoselective synthesis of the C1–C11 fragment of the marine natural product (+)-peloruside A has been developed. Through enzymatic desymmetrization of diethyl 3-hydroxyglutarate with lipase B from *Candida antarctica* a large-scale access to enantiomerically highly enriched starting material was achieved. Subsequent stereogenerating key steps utilized in the synthesis were a Sharpless asymmetric dihydroxylation and a doubly diastereoselective Mukaiyama aldol reaction to set up the stereogenic centers at C2, C3, C5, C7 and C8 with correct absolute configuration.

Introduction

The macrolide (+)-peloruside A (**1**) was isolated from the New Zealand marine sponge *Mycale hentscheli* in 2000 by Northcote and co-workers.[1] It features a 16-membered macrocyclic lactone with an embedded lactol ring, 10 chiral centers, multiple hydroxy and methoxy groups in either 1,2- or 1,3-arrangements, and a side chain with a *Z*-configured trisubstituted alkene moiety. It was shown to display potent antitumor activity against P388 murine leukemia cells with an IC_{50} value of 10 ng/mL.[2] Studies have demonstrated that peloruside A like paclitaxel (Taxol®) exhibits microtubule-stabilizing activity and arrests cells in the G2-M phase of the cell cycle. It was also reported that peloruside A is less susceptible than paclitaxel to MDR-cell lines and is also potent in Taxol® resistant cells on the basis of a different, non-taxoid binding site of tubulin.[3–5] These aspects underline the impact of peloruside A as a new antitumor agent with significant clinical potential. Given the significant biological activity, the low natural abundance and the synthetically challenging structure of the natural product peloruside A has attracted large attention among synthetic research groups worldwide.[6–16]

The first total synthesis of peloruside A (**1**) by de Brabander et al. established the absolute stereochemistry of (+)-peloruside A.[17] Thus far, three more total syntheses have been published by Taylor, Ghosh, and Evans and their respective co-workers.[18–20] Whereas in the Brabander and Taylor syntheses the pyran was assembled in the form of a dihydropyranone ring ahead of the macrolactonization, the Ghosh and Evans syntheses featured a macrolactonization of the seco acid of the natural product followed by an acid-catalyzed lactol formation in the final step. Our retrosynthetic analysis of peloruside A is based upon an aldol coupling of methyl ketone **3** (C12–C19 fragment) and aldehyde **4** (C1–C11 fragment) similar to what Evans reported in his synthesis.[10] For the synthesis of aldehyde **4** we anticipated that a Mukaiyama aldol reaction of the trimethylsilyl enol ether of α-benzyloxy ketone **6** with aldehyde **5** should give rise to the required 7,8-*anti*-stereochemistry with the terminal alkene easily being converted into the aldehyde moiety (Scheme 1).



Scheme 1. Retrosynthetic analysis of (+)-peloruside A **1**.

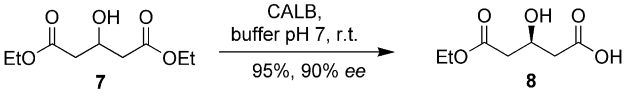
[a] Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Germany
Fax: +49-341-9736599
E-mail: schneider@chemie.uni-leipzig.de

For a large-scale synthesis of aldehyde **5** we envisioned as the first step a chemoenzymatic desymmetrization reaction of diethyl 3-hydroxyglutarate (**7**) to furnish mono acid **8** with the first chiral center established in high optical purity. Desymmetrization reactions of prochiral molecules are particularly attractive for the synthesis of small chiral compounds especially when conducted in a catalytic manner. The enzyme lipase B from the yeast *Candida antarctica* is known to catalyze esterifications, ester hydrolyses and acyltransfer reactions. Immobilized on an acrylate resin it tolerates temperatures of up to 70 °C[21,22] and a variety of organic solvents[23] and reactions can easily be run on large scales. Furthermore dialkyl 3-hydroxyglutarates are excellent substrates for such hydrolytic desymmetrization reactions with lipases. This might be due to additional hydrogen bonding between the hydroxy group and an acceptor in the binding pocket of the enzyme. Jacobsen et al. previously determined the enantioselectivity of similar enzymatic hydrolyses and was also able to establish the absolute configuration of the newly formed chiral center by co-crystallization of the acid with (*R*)-phenylethylamine.[24]

Results and Discussion

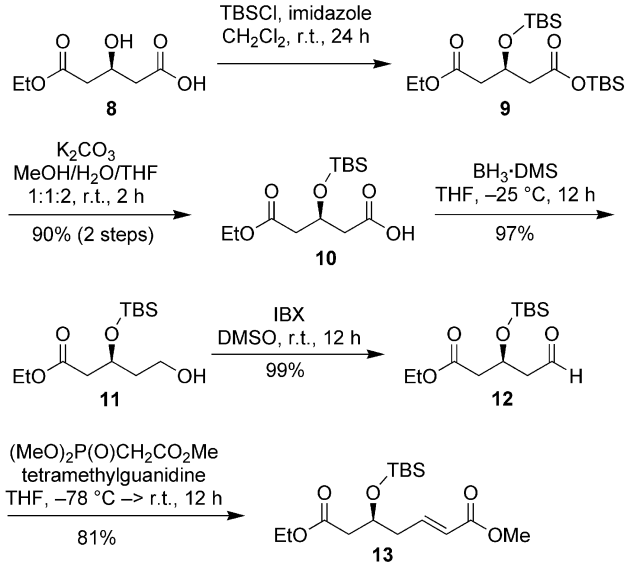
Synthesis of the C1–C7 Aldehyde 5

In the first step of the synthesis diethyl 3-hydroxyglutarate (**7**) was treated with immobilized lipase B from *Candida antarctica* (Novozym 435, enzyme loading 10 000 U/g). The reaction was completed within 45 min in a buffer solution with pH = 7 at room temperature. The enzyme was removed by filtration and could be used several times after storage in dichloromethane. The highly pure mono acid **8** was isolated in 30–50 g batches with yields of typically 95% after a simple acid-base wash (Scheme 2). No further purification was necessary. In order to determine the enantioselectivity of the hydrolysis mono acid **8** was converted into the corresponding benzyl ester the enantiomeric excess of which was measured through HPLC-analysis on a chiral stationary phase.



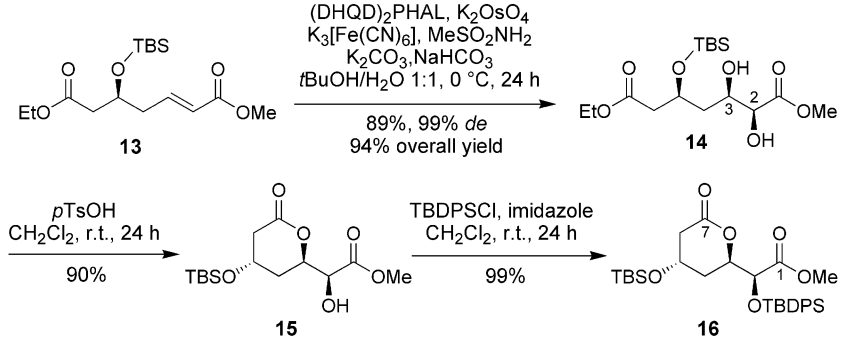
Scheme 2. Enzymatic hydrolysis of diethyl 3-hydroxyglutarate **7**.

The free hydroxy group of **8** was subsequently protected as a TBS ether. Because the competing formation of the silyl ester could not be avoided, two equivalents of TBSCl and imidazole as base were employed to furnish the bissilylated compound **9**. Crude **9** was then treated with K_2CO_3 in a 1:1:2 mixture of MeOH/H_2O/THF to hydrolyze the silyl ester and yield acid **10** in 90% yield over two steps. Large-scale purification of **10** proved to be very simple as the potassium carboxylate of **10** separated as an ionic liquid between the organic und aqueous phase during the extraction which was easily isolated and furnished very clean product upon acidification without any chromatographic purification necessary (Scheme 3). Chemoselective reduction of the acid in the presence of the ester was accomplished using borane dimethylsulfide complex.[25] After 12 h alcohol **11** was obtained in excellent yield without further purification. Mild IBX-oxidation proved to be the method of choice for oxidizing **11** to the corresponding aldehyde **12** which was isolated in quantitative yield after aqueous extraction of DMSO used as solvent.[26] Again no chromatographic purification was necessary at this stage. Horner–Wadsworth–Emmons reaction of aldehyde **12** with trimethyl phosphonoacetate and tetramethylguanidine as base furnished α,β-unsaturated methyl ester **13** in good yield and as pure *E*-isomer after 12 h at –78 °C → r.t. (Scheme 3).

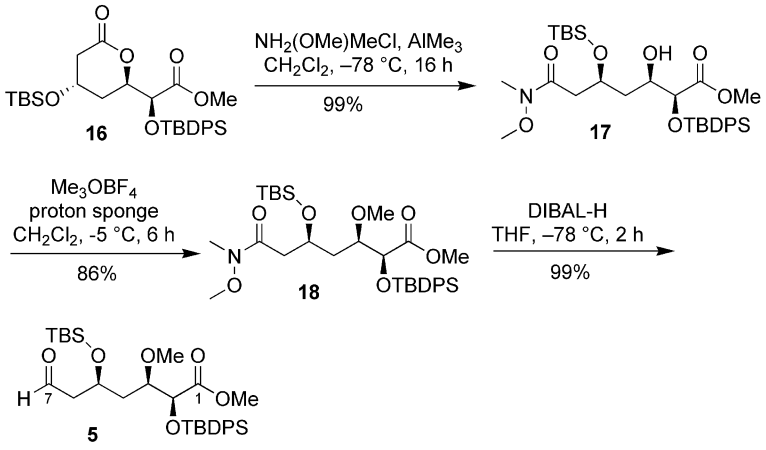


Scheme 3. Synthesis of α,β-unsaturated methyl ester **13**.

(*E*)-Enoate **13** was now ideally suited to install the required 2,3-*syn*-dioxygenation of the natural product via a Sharpless asymmetric dihydroxylation. High yields and enantioselectivities were achieved with a fortified AD-mix comprising 1 mol-% $K_2OsO_2(OH)_4$ as osmium source, 5 mol-% $(DHQD)_2PHAL$ as chiral ligand, $K_3[Fe(CN)_6]$ as co-oxidant, and methanesulfonamide as additive to facilitate osmate ester hydrolysis in a two-phase system of *tert*-butanol and water.[27] A buffered system with K_2CO_3 and $NaHCO_3$ proved advantageous to avoid strong basic conditions and retroaldol reaction of the product. After chromatographic purification *syn*-diol **14** was isolated as a single diastereomer in 89% yield. The minor enantiomer from the enzymatic hydrolysis was at this stage easily separated as a diastereomer by chromatography. The additional ester group in **14** was used advantageously to distinguish between the 2- and 3-hydroxy groups as the 3-hydroxy group had to be chemoselectively converted into a methyl ether. For this purpose *syn*-diol **14** was treated with *para*-toluenesulfonic acid to effect a size-selective lactonization and formation of lactone **15** in good yield. The 2-hydroxy group was now easily protected as a TBDPS ether using TBDPSCl and



Scheme 4. Synthesis of lactone **16**.



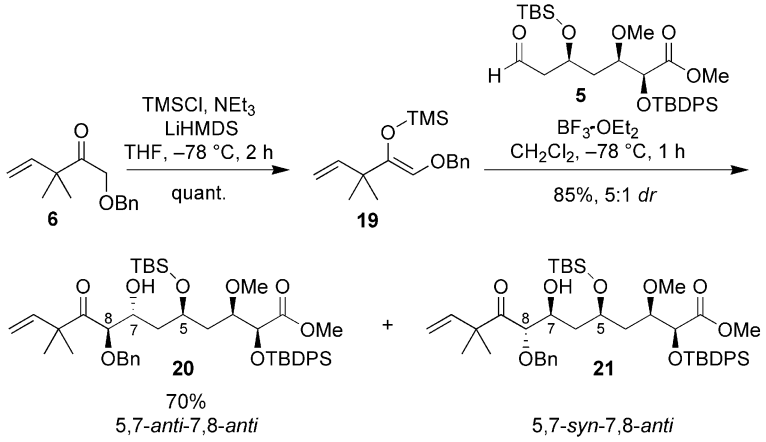
Scheme 5. Synthesis of aldehyde **5**.

imidazole (Scheme 4). For the subsequent steps this very bulky protecting group provided significant steric shielding of the adjacent ester and helped to differentiate between the ester and lactone moiety.

To access the C1–C7 aldehyde **5** for the doubly diastereoselective Mukaiyama aldol reaction lactone **16** was transferred into Weinreb amide **17** in quantitative yield. This amidation proceeded chemoselectively under lactone ring-opening without attack at the methyl ester. The 3-hydroxy group was methylated using Meerwein salt and proton sponge.[28] Weinreb amide **18** was again chemoselectively reduced to furnish aldehyde **5** in excellent yields (Scheme 5).[29]

Doubly Diastereoselective Mukaiyama Aldol Reaction

In order to install the C7- and C8-stereogenic centers of peloruside A with the desired *anti* configuration we envisioned a substrate-controlled Mukaiyama aldol reaction of

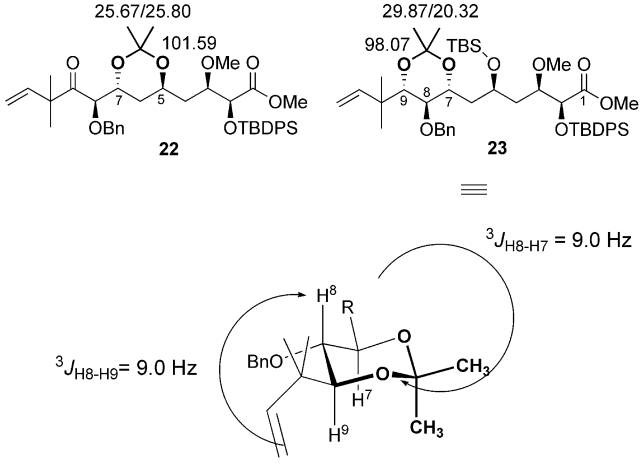


Scheme 6. Mukaiyama aldol reaction of silyl enol ether **19** and aldehyde **5**.

the silyl enol ether of α-benzyloxy ketone **6** with the C1–C7-aldehyde **5**. Pagenkopf and co-workers had reported quite a similar carbon–carbon formation in their synthesis of a fragment of peloruside A.[30] In addition, various Lewis acid-catalyzed additions of silyl nucleophiles towards β-silyloxy aldehydes have been shown to proceed with remarkably high 1,3-*anti*-diastereoselectivities.[31–33] Based upon this precedence we investigated a number of Lewis acids (e.g. $MeAlCl_2$, $TiCl_4$, $SnCl_4$, $MgBr_2{\cdot}OEt_2$) as mediators for the reaction of silyl enol ether **19** and aldehyde **5** and eventually found $BF_3{\cdot}OEt_2$ optimal. When silyl enol ether **19** and aldehyde **5** were treated with 1.3 equiv. of $BF_3{\cdot}OEt_2$ in dichloromethane at –78 °C, complete conversion was observed within 1 h and two diastereomers were isolated through column chromatography in a combined yield of 85% and a ratio of 5:1. Fortunately, pure diastereomer **20** with the correct 5,7-*anti*-7,8-*anti* configuration was easily separated from the minor diastereomer **21** in 70% yield by chromatography (Scheme 6).

Stereochemical Proof

To verify the 5,7-*anti* configuration of major diastereomer **20** it was converted into 5,7-*anti*-diol acetonide **22** through selective 5-OH-desilylation and acetonide formation. ^{13}C NMR spectroscopic analysis of the acetonide methyl signals and the quaternary carbon according to the method developed by Rychnovsky[34] clearly revealed the 5,7-*anti* configuration (Scheme 7).Likewise, the 7,8-*anti* configuration was secured through *syn*-diastereoselective reduction of the 9-keto group with $Zn(BH_4)_2$ and subsequent formation of the corresponding 7,9-*syn*-diol acetonide **23** which can be deduced from the characteristic ^{13}C chemical shifts. The 7,8-relative configuration was now easily assigned based upon the characteristic trans-diaxial coupling constants $^3J_{H7\text{-}H8}$ = 9.0 Hz and $^3J_{H8\text{-}H9}$ = 9.0 Hz placing the 7,8,9-substituents in this chair in equatorial positions (Scheme 7). The configuration of the minor diastereomer **21** has not been so rigorously assigned, but on the basis of almost identical coupling constants $^3J_{H7\text{-}H8}$ = 4.4 Hz for **20** and 4.7 Hz for **21** we assume a 7,8-*anti* configuration in both stereoisomers.



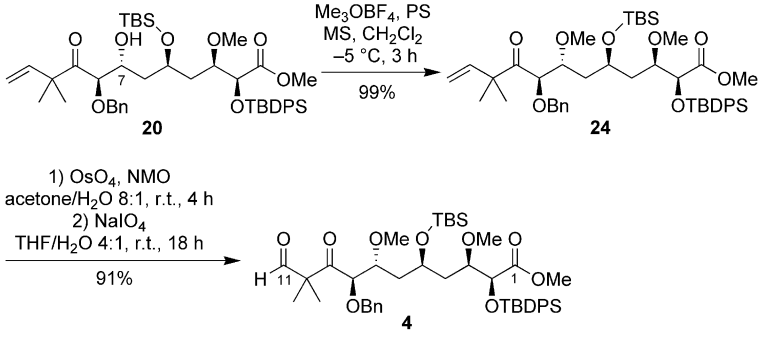
Scheme 7. Stereochemical proof of the 5,7-*anti*-7,8-*anti* configuration of aldol product **20**.

Synthesis of Aldehyde 4

The final steps of the synthesis of the C1–C11 aldehyde **4** commenced with the methylation of the 7-OH group with Meerwein salt in the presence of proton sponge which proceeded in almost quantitative yield. The terminal double bond was then converted into the aldehyde moiety in high yield by a sequential dihydroxylation and oxidative cleavage of the resulting diol (Scheme 8).

Conclusions

An efficient and convergent synthesis of the C1–C11 fragment of (+)-peloruside A has been developed. Aldehyde **4** containing the stereocenters at C2, C3, C5, C7, and C8 with the correct absolute configuration was synthesized in an overall yield of 28% in 15 steps (longest linear sequence). The enzymatic desymmetrization of diethyl 3-hydroxyglutarate in the first step of the sequence allowed the preparation of large amounts of highly enantiomerically enriched starting material in up to 50 g scale. A Sharpless dihydroxylation and a substrate-controlled aldol coupling introduced the chiral centers at C2 and C3 and C7 and C8, respectively. The C1–C11 fragment **4** of (+)-peloruside A



Scheme 8. Synthesis of aldehyde **4**.

prepared as described above closely resembles a building block which Evans successfully converted into the natural product in his synthesis of (+)-peloruside A.[20]

Experimental Section

General: All reactions were carried out with magnetic stirring under argon. Dry solvents were distilled from the indicated drying agents: dichloromethane (CaH_2), tetrahydrofuran (K), *N*,*N*-dimethylformamide (CaH_2). Acetonitrile and chloroform were obtained from VWR in HPLC quality (HiPerSolvCHROMANORM). Diethyl ether (E), hexane (Hex) and petroleum ether (PE) for chromatography were technical grade and distilled from KOH. Ethyl acetate (EE) was distilled from $CaCl_2$. All reactions were monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F_{254} plates (Merck KGaA); spots were visualized by treatment with a solution of vanillin (0.5 g), conc. acetic acid (10 mL), and conc. H_2SO_4 (5 mL) in methanol (90 mL), or with a solution of $KMnO_4$ (3.0 g), K_2CO_3 (20 g), and acetic acid (0.25 mL) in water (300 mL), or a solution of phosphomolybdic acid hydrate (1.0 g) in ethanol (50 mL). Flash column chromatography was performed using Merck silica gel 60 230–400 mesh (0.040–0.063 mm). Triethylamine and diisopropylethylamine were distilled from CaH_2. All other chemicals were used as received from commercial suppliers. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 and 2000 (200 MHz), Varian Gemini 300 BB (300 MHz) and with Bruker Avance DRX 400 (400 MHz) spectrometers. Chemical shifts are reported relative to tetramethylsilane as internal standard or the residual solvent signals [chloroform: δ (^{13}C) = 77.16 ppm]. Melting points were determined on a Boetius heating table. Elemental analyses were obtained from the microanalytical laboratory of the Dept. of Chemistry at the University of Leipzig. IR spectra were obtained with a FTIR spectrometer (Genesis ATI, Mattson/Unicam). ESI mass spectra were recorded on a Bruker APEX II FT-ICR (high resolution) and on a Bruker ESQUIRE. Optical rotations were measured using a Schmidt & Haensch Polartronic D polarimeter. HPLC analyses were performed on a JASCO MD-2010 plus instrument with a chiral stationary phase column (Chiralcel OD purchased from Daicel Chemical Industries, Ltd.).

(*S*)-5-Ethoxy-3-hydroxy-5-oxopentanoic Acid (8): Lipase B from *Candida antarctica* (7.07 g, enzyme loading 10000 U/g) was added to a solution of diethyl 3-hydroxyglutarate (40.2 g, 0.20 mol) in phosphate buffer (280 mL, pH 7). The solution was stirred for 1 h at room temp. After completion of the reaction the immobilized enzyme was filtered off and washed with dichloromethane (200 mL). The filtrate was acidified to pH 2 by adding 1 M HCl. The aqueous phase was saturated with NaCl and extracted with ethyl acetate (5 × 150 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The title compound **7** was obtained as a colorless oil without further purification (33.3 g, 96%). R_f = 0.17 (PE/EtOAc, 1:1). $[\alpha]_D^{22}$ = +1.7 (*c* = 11.5, acetone); ref.[24] +1.8 (*c* = 11.5, acetone). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.51–2.67 (m, 4 H, 2-CH_2, 4-CH_2), 4.16 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2CH_3), 4.42–4.52 (m, 1 H, 3-C*H*), 7.60 (s, 1 H, COO*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.23 (CH_2CH_3), 40.57 (2-CH_2), 40.65 (4-CH_2), 61.14 (CH_2CH_3), 64.72 (3-*C*H), 172.1 (1-*C*OOEt), 177.7 (5-*C*OOH) ppm. IR (film): $\tilde{\nu}$ = 2985, 1728, 1405, 1377, 1275, 1196, 1094, 1038, 876, 607 cm^{-1}. MS (ESI): *m*/*z* (%) = 199 [M + Na]$^+$. $C_7H_{12}O_5$ (17) [176].

(*R*)-1-Benzyl 5-Ethyl 3-Hydroxypentanedioate: Carbonyldiimidazole (115 mg, 0.710 mmol, 1.05 equiv.) was added to a solution of hydroxy acid **8** (120 mg, 0.680 mmol, 1 equiv.) in dichloromethane (15 mL). After the CO_2 evolution was finished a solution of imidazole (4 mg, 0.03 mmol, 4 mol-%) and sodium (1 mg, 0.04 mmol, 6 mol-%) in THF (1 mL) was added. The blue solution was stirred at room temp. for 1 h. 1 M HCl (10 mL) was added and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:80 w/w) using a mixture of petroleum ether and ethyl acetate [3:2 (v/v)] as an eluent. The title compound was obtained as a colorless oil (125 mg, 69%). R_f = 0.61 (PE/EtOAc, 1:1). *ee* = 90%. Enantiomeric assay: Chiralcel OD, isocratic (*n*-hexane/*i*PrOH, 95:5, flow 0.5 mL/min) λ_{max} = 204 nm, t_1 = 21.1 min, t_2 = 28.8 min. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.65–2.79 (m, 4 H, 2-CH_2, 4-CH_2), 4.18 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2CH_3), 4.46–4.56 (m, 1 H, 3-C*H*), 5.16 (s, 2 H, CH_2Ph), 7.30–7.42 (m, 5 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.13 (CH_2CH_3), 41.45 (4-CH_2), 41.83 (2-CH_2), 61.56 (CH_2CH_3), 64.88 (3-*C*H), 66.43 (OCH_2Ph), 127.0, 127.6, 128.4, 135.9 (Ph-C), 173.3 (1-*C*OOEt), 174.7 (5-*C*OOBn) ppm. MS (ESI): *m*/*z* (%) = 289 [M + Na]$^+$. $C_{14}H_{18}O_5$ (29) [266].

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-ethoxy-5-oxopentanoic Acid (10): Imidazole (12.6 g, 185 mmol, 2.0 equiv.) was added to a solution of hydroxy acid **8** (16.3 g, 92.8 mmol, 1 equiv.) in dichloromethane (150 mL). At room temp. *tert*-butyldimethylsilyl chloride (TBSCl) (32.0 g, 212 mmol, 2.3 equiv.) and a small amount of 4-(dimethylamino)pyridine (DMAP) were added. A white precipitation was observed. The solution was stirred for 24 h at room temp. Water (100 mL) was added and the mixture was acidified with 0.5 M HCl (20 mL). The aqueous phase was saturated with NaCl and extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The crude product **9** was used directly in the next reaction. It was dissolved in a mixture of MeOH/H_2O/THF, 1:1:2 (140 mL). K_2CO_3 (64.0 g, 463 mmol, 5 equiv.) was added and the suspension was stirred for 2 h at room temp. The mixture was diluted with water until the solution was clear and PE (150 mL) was added. Three phases were formed and the middle phase was separated from the organic and the aqueous phase. It was acidified with 0.5 M HCl (pH 2). The aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The title compound **10** was obtained as a colorless oil without further purification (24.5 g, 90%). R_f = 0.60 (EtOAc). $[\alpha]_D^{22}$ = 2.8 (*c* = 3.96, acetone). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.85 [s, 9 H, $C(CH_3)_3$], 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.58 (dd, $^3J_{H,H}$ = 12.0, $^3J_{H,H}$ = 6.0 Hz, 2 H, 4-CH_aH_b), 2.63 (dd, $^2J_{H,H}$ = 7.5, $^3J_{H,H}$ = 6.0 Hz, 2 H, 2-$CH_{a'}H_{b'}$), 4.13 (q, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2CH_3), 4.48–4.59 (m, 1 H, 3-C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.85 ($SiCH_3$), –4.81 ($SiCH_3$), 14.27 (CH_2CH_3),17.99 [$C(CH_3)_3$], 25.74 [$C(CH_3)_3$], 42.39 (2-CH_2), 42.56 (4-CH_2), 60.70 (3-*C*H), 66.22 (CH_2CH_3), 171.1 (1-*C*OOEt), 177.3 (5-*C*OOH) ppm. IR (film): $\tilde{\nu}$ = 2957, 2931, 2858, 1737, 1714, 1473, 1464, 1378, 1257, 1202, 1157, 1095, 1051, 1028, 971, 940, 916, 838, 812, 779, 735 cm^{-1}. MS (ESI): *m*/*z* = 313 [M + Na]$^+$. $C_{13}H_{26}O_5Si$ (290.43): calcd. C 53.76, H 9.02, O 27.54; found C 53.40, H 8.89, O 27.50.

Ethyl (*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-hydroxypentanoate (11): A solution of carboxylic acid **10** (20.0 g, 69.0 mmol, 1 equiv.) in

THF (200 mL) was cooled to –25 °C. BH_3·SMe_2 (7.80 g, 100 mmol, 1.5 equiv.) was added slowly at this temperature via syringe. The solution was stirred at room temp. for 12 h. A mixture of H_2O and AcOH (1:1, 30 mL) was added and the solvent was evaporated in vacuo. The residue was given in a saturated solution of $NaHCO_3$ (150 mL). The aqueous phase was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The title compound **11** was obtained as a pale yellow oil without further purification (18.5 g, 97%). R_f = 0.25 (PE/Et_2O, 1:1). $[\alpha]_D^{22}$ = +11.7 (*c* = 9.99, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = = 0.09 (s, 6 H, SiCH_3), 0.88 [s, 9 H, C(CH_3)$_3$], 1.26 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 1.69–1.93 (m, 2 H, 4-CH_2), 2.16 (, 1 H, O*H*), 2.47–2.62 (m, 2 H, 2-CH_2), 4.12 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2CH$_3$), 4.32–4.40 (m, 1 H, 3-C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.81 (SiCH_3), 14.26 (CH_2CH_3),17.98 [*C*(CH$_3$)$_3$], 25.72 [C(*C*H$_3$)$_3$], 38.99 (4-*C*H$_2$), 42.48 (2-*C*H$_2$), 60.58 (*C*H$_2$CH$_3$), 68.25 (3-*C*H), 171.6 (1-*C*OOEt) ppm. IR (film): $\tilde{\nu}$ = 3457, 2956, 2930, 2896, 2857, 1337, 1473, 1464, 1377, 1311, 1256, 1165, 1092, 1028, 940, 837, 812, 777, 708, 663 cm^{-1}. MS (ESI): *m*/*z* = 299 [M + Na]$^+$. $C_{13}H_{28}O_4Si$ (276.18): calcd. C 56.48, H 10.21, O 23.15; found C 56.66, H 10.48, O 23.38.

Ethyl (*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-oxopentanoate (12): A solution of IBX (28.0 mg, 100 mmol, 1.55 equiv.) in DMSO (200 mL) was prepared. A solution of alcolhol **11** (17.8 g, 64.6 mmol, 1 equiv.) in DMSO (50 mL) was added and the resulting solution was stirred at room temp. for 12 h. Water was added (300 mL) and the white precipitate was filtered off. The filtrate was extracted with diethyl ether (5 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The title compound **12** was obtained as a colorless oil without further purification (17.5 g, 99%). R_f = 0.57 (PE/Et_2O, 1:1). $[\alpha]_D^{22}$ = +8.2 (*c* = 10.10, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, SiCH_3), 0.83 [s, 9 H, C(CH_3)$_3$], 1.24 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.52 (dd, $^3J_{H,H}$ = 6.0, $^3J_{H,H}$ = 1.5 Hz, 2 H, 2-CH_2), 2.61–2.66 (m, 2 H, 4-CH_2), 4.11 (q, $^3J_{H,H}$ = 7.5 Hz, 2 H, CH_2CH$_3$), 4.58–4.64 (m, 1 H, 3-C*H*), 9.78 (t, $^3J_{H,H}$ = 2.0 Hz, 1 H, C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.73 (SiCH_3), –4.69 (SiCH_3), 14.26 (CH_2CH_3),17.99 [*C*(CH$_3$)$_3$], 25.74 [C(*C*H$_3$)$_3$], 42.74 (2-*C*H$_2$), 50.96 (4-*C*H$_2$), 60.70 (3-*C*H), 65.11 (*C*H$_2$CH$_3$), 170.9 (1-*C*OOEt), 207.0 (5-*C*HO) ppm. IR (film): $\tilde{\nu}$ = 3344, 2956, 2930, 2897, 2858, 1737, 1473, 1464, 1378, 1312, 1257, 1174, 1096, 1028, 940, 838, 812, 778 cm^{-1}. MS (ESI): *m*/*z* = 297 [M + Na]$^+$. $C_{13}H_{28}O_4Si$ (274.16): calcd. C 56.90, H 9.55, O 23.32; found C 56.55, H 9.50, O 23.00.

7-Ethyl 1-Methyl (*S*,*E*)-5-(*tert*-Butyldimethylsilyloxy)hept-2-enedioate (13): A solution of aldehyde **12** (13.0 g, 47.4 mmol, 1 equiv.) and trimethyl phosphonoacetate (10.4 g, 57.0 mmol, 1.2 equiv.) in THF (200 mL) was cooled to –78 °C. Tetramethylguanidine (6.55 g, 57.0 mmol, 1.2 equiv.) was added and the solution was stirred 30 min at this temperature. The yellow reaction mixture was warmed to room temp. overnight whilst stirring. It was diluted with water (200 mL) and 1 M HCl was added until a clear solution resulted. The aqueous phase was extracted with diethyl ether (5 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:80 w/w) using a mixture of petroleum ether and diethyl ether [4:1 (v/v)] as an eluent. The title compound **13** was obtained as a colorless oil (15.6 g, 81%). R_f = 0.74 (PE/Et_2O, 1:1). $[\alpha]_D^{22}$ = +23.6 (*c* = 10.05, acetone). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 6 H, SiCH_3), 0.86 [s, 9 H, C(CH_3)$_3$], 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 2.35–2.52 (m, 4 H, 6-CH_2, 4-CH_2), 3.72 (s, 3 H, OCH_3), 4.11 (q, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2CH$_3$), 4.22–4.35 (m, 1 H, 5-C*H*), 5.86 (d, $^3J_{H,H}$ = 15.5 Hz, 1 H, 2-C*H*=CH), 6.94 (dt, $^3J_{H,H}$ = 15.5, $^3J_{H,H}$ = 7.5 Hz, 1 H, 3-C*H*=CH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.77 (SiCH_3), –4.51 (SiCH_3), 14.30 (CH_2CH_3),18.09 [*C*(CH$_3$)$_3$], 25.82 [C(*C*H$_3$)$_3$], 40.38 (4-*C*H$_2$), 42.54 (6-*C*H$_2$), 51.59 (O*C*H$_3$), 60.61 (*C*H$_2$CH$_3$), 68.39 (5-*C*H), 123.85 (2-*C*H=CH), 144.9 (3-*C*H=CH), 166.8 (1-*C*OOMe), 171.3 (7-*C*OOEt) ppm. IR (film): $\tilde{\nu}$ = 3434, 2954, 2930, 2897, 2857, 2256, 1731, 1659, 1473, 1463, 1437, 1377, 1327, 1257, 1177, 1087, 1036, 991, 917, 838, 811, 778, 734 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 213 nm (3.73). HRMS-ESI: *m*/*z* = [M + Na]$^+$ calcd. for $C_{16}H_{30}O_5Si$: 353.17602; found 353.17521. $C_{16}H_{30}O_5Si$ (330.19): calcd. C 58.15, H 9.15, O 24.21; found C 53.12, H 9.20, O 23.80.

7-Ethyl 1-Methyl (2*S*,3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxyheptanedioate (14): A solution of $K_3[Fe(CN)_6]$ (28.0 g, 85.1 mmol, 3.5 equiv.), K_2CO_3 (11.8 g, 85.1 mmol, 3.5 equiv.) and $NaHCO_3$ (9.20 g, 110 mmol, 4.4 equiv.) in 150 mL water was prepared. $(DHQD)_2PHAL$ (940 mg, 1.22 mmol, 0.05 equiv.) dissolved in *t*BuOH (150 mL) was added. K_2OsO_4·$2H_2O$ (90 mg, 0.24 mmol, 0.01 equiv.) was added to the two-phase system and it was stirred at room temp. for 1 h. The mixture was cooled to 0 °C and compound **13** (8.00 g, 24.3 mmol, 1 equiv.) and methanesulfonamide (3.00 g, 31.6 mmol, 1.3 equiv.) were added. The solution was stirred at 0 °C for 21 h. The reaction was stopped by the addition of Na_2SO_3 (20.4 g, 162 mmol, 6.5 equiv.) and water (400 mL). After stirring for 30 min the mixture was diluted with ethyl acetate (400 mL). The aqueous phase was extracted with ethyl acetate (5 × 75 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:100 w/w) using a mixture of petroleum ether and ethyl acetate [2:1 (v/v)] as an eluent. The title compound **14** was obtained as a colorless viscous oil (8.31 g, 94%). R_f = 0.51 (PE/EtOAc, 1:1). $[\alpha]_D^{22}$ = +10.5 (*c* = 2.85, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, SiCH_3), 0.09 (s, 3 H, SiCH_3), 0.88 [s, 9 H, C(CH_3)$_3$], 1.25 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, CH_2CH_3), 1.84–1.89 (m, 2 H, 4-CH_2), 2.55 (dd, $^3J_{H,H}$ = 6.5, $^3J_{H,H}$ = 3.0 Hz, 2 H, 6-CH_aH_b), 3.81 (s, 3 H, OCH_3), 4.11 (q, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2CH$_3$), 4.07–4.15 (m, 4 H, CH_2-CH$_3$, 2-C*H*, 3-C*H*), 4.31–4.40 (m, 1 H, 5-C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.62 (SiCH_3), –4.48 (SiCH_3), 14.29 (CH_2CH_3),18.01 [*C*(CH$_3$)$_3$], 25.82 [C(*C*H$_3$)$_3$], 40.56 (4-*C*H$_2$), 42.83 (6-*C*H$_2$), 52.87 (O*C*H$_3$), 60.69 (*C*H$_2$CH$_3$), 68.15 (5-*C*H), 70.32 (2-*C*H), 73.84 (3-*C*H), 171.5 (7-*C*OOEt), 173.7 (1-*C*OOMe) ppm. IR (film): $\tilde{\nu}$ = 3466, 2955, 2930, 2897, 2857, 1739, 1473, 1463, 1439, 1385, 1256, 1163, 1088, 1032, 969, 837, 811, 778 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 206 nm (2.91). HRMS-ESI: *m*/*z* = [M + Na]$^+$ calcd. for $C_{16}H_{32}O_7Si$: 387.18150; found 387.18080, [2M + Na]$^+$ calcd. 751.37323; found 751.37295. $C_{16}H_{32}O_7Si$ (364.19): calcd. C 52.72, H 8.85, O 30.73; found C 52.60, H 9.22, O 30.26.

Methyl (*S*)-2-[(2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-2-yl]-2-hydroxyacetate (15): To a solution of diol **14** (8.31 g, 22.9 mmol, 1 equiv.) in dichloromethane (200 mL) was added *p*-toluenesulfonic acid (50 mg, 0.23 mmol, 0.01 equiv.). The solution was stirred 24 h at room temp. The solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using a mixture of petroleum ether and ethyl acetate [1:1 (v/v)] as an eluent. The title compound **15** was obtained as a colorless waxy solid (7.53 g, 90%). R_f = 0.50 (PE/EtOAc, 2:1); m.p. 54–56 °C. $[\alpha]_D^{22}$ = +13.5 (*c* = 9.95, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 6 H, SiCH_3), 0.89 [s, 9 H, C(CH_3)$_3$], 1.78–1.86 (m, 1 H, 4-CH_aH_b), 2.10–2.20 (m, 1 H, 4-CH_aH_b), 2.57 (d, $^3J_{H,H}$ = 3.5 Hz, 2 H, 6-CH_2), 3.09 (s, 1 H, O*H*),

3.87 (s, 3 H, OCH_3), 4.13 (d, $^3J_{H,H}$ = 3.5 Hz, 1 H, C*H*OH), 4.38–4.43 (m, 1 H, 5-C*H*), 4.99–5.06 (m, 1 H, 3-C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.77 (Si*C*H$_3$), –4.73 (Si*C*H$_3$), 18.13 [*C*(CH$_3$)$_3$], 25.83 [C(*C*H$_3$)$_3$], 32.35 (4-*C*H$_2$), 39.27 (6-*C*H$_2$), 53.42 (O*C*H$_3$), 63.61 (5-*C*H), 72.22 (3-*C*H), 76.36 (2-*C*H), 169.3 (7-*C*OOR), 172.1 (1-*C*OOMe) ppm. IR (film): $\tilde{\nu}$ = 3447, 2956, 28.57, 1736, 1473, 1444, 1389, 1360, 1252, 1163, 1133, 1112, 1083, 1061, 1032, 1006, 993, 958, 926, 886, 838, 811, 776, 743, 710, 685, 656, 537 cm^{-1}. UV/Vis (CH$_3$CN): λ_{max} [lg(ε)] = 272 nm (3.66). HRMS-ESI: *m*/*z* = [M + Na]$^+$ calcd. for $C_{14}H_{26}O_6Si$: 341.13963; found 341.13904. $C_{14}H_{26}O_6Si$ (318.15): calcd. C 52.80, H 8.23, O 30.15; found C 53.02, H 8.66, O 29.70.

Methyl (*S*)-2-[(2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-2-yl]-2-(*tert*-butyldiphenylsilyloxy)acetate (16): To a solution of lactone **15** (7.00 g, 22.0 mmol, 1 equiv.) and imidazole (2.50 g, 33.0 mmol, 1.5 equiv.) in dichloromethane (150 mL) was added *tert*-butyldiphenylsilyl chloride (TBDPSCl) (10.0 g, 33.0 mmol, 1.5 equiv.) and a small amount of 4-(dimethylamino)-pyridine (DMAP). After stirring for 24 h at room temp. water (100 mL) and 1 M HCl (20 mL) were added. The aqueous phase was extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using a mixture of petroleum ether and ethyl acetate [5:1 (v/v)] as an eluent. The title compound **16** was obtained as a colorless oil (12.1 g, 99%). R_f = 0.42 (PE/EtOAc, 5:1). $[\alpha]_D^{22}$ = +4.6 (*c* = 1.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3), 0.86 [s, 9 H, C(CH_3)$_3$], 1.09 [2, 9 H, C(CH_3)$_3$], 1.74–1.81 (m, 1 H, 4-CH_aH$_b$), 1.88–1.97 (m, 1 H, 4-CH$_a$*H*$_b$), 2.54 (d, $^3J_{H,H}$ = 3.5 Hz, 2 H, 6-CH_2), 3.47 (s, 3 H, OCH_3), 4.30 (d, $^3J_{H,H}$ = 3.0 Hz, 1 H, C*H*OTBS), 4.36 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, C*H*OTBDPS), 4.94 (dt, $^3J_{H,H}$ = 11.5, $^3J_{H,H}$ = 3.5 Hz, 1 H, 3-C*H*), 7.36–7.46 (m, 6 H, Ph-*H*), 7.62–7.70 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.86 (Si*C*H$_3$), –4.84 (Si*C*H$_3$), 18.02 [*C*(CH$_3$)$_3$], 19.66 [*C*(CH$_3$)$_3$], 25.75 [C(*C*H$_3$)$_3$], 26.95 [C(*C*H$_3$)$_3$], 31.60 (4-*C*H$_2$), 39.38 (6-*C*H$_2$), 51.86 (OCH$_3$), 63.44 (5-*C*H), 73.87 (2-*C*H), 76.65 (3-*C*H), 127.8, 127.9, 130.2, 130.3, 132.8, 133.1, 135.9, 136.1 (Ph-*C*)169.0 (7-*C*OOR), 170.6 (1-*C*OOMe) ppm. IR (film): $\tilde{\nu}$ = 3072, 3001, 2932, 2855, 1744, 1611, 1589, 1517, 1428, 1388, 1303, 1251, 1152, 1113, 1069, 1029, 934, 822, 746, 701, 602, 506, 489 cm^{-1}. UV/Vis (CH$_3$CN): λ_{max} [lg(ε)] = 222 nm (3.76), 227 nm (3.75), 271 nm (3.22). MS (ESI): *m*/*z* = 579 [M + Na]$^+$. $C_{30}H_{44}O_6Si_2$ (556.27): calcd. C 64.71, H 7.96, O 17.24; found C 64.60, H 8.35, O 17.53.

Methyl (2*S*,3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-(*tert* butyldiphenylsilyloxy)-3-hydroxy-7-[methoxy(methyl)amino]-7-oxoheptanoate (17): A solution of *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 g, 10.8 mmol, 3 equiv.) in dichloromethane (15 mL) was cooled to –78 °C. A solution of trimethylaluminium (5.40 mL, 10.8 mmol, 3 equiv.) in hexane (2 M) was added slowly. After stirring at room temp. for 12 h the mixture was cooled to –78 °C and a solution of lactone **16** (2.00 g, 3.60 mmol, 1 equiv.) in dichloromethane (10 mL) was added dropwise. The solution was warmed to room temp. and stirred for 4 h. At 0 °C a saturated aqueous solution of sodium potassium tartrate (50 mL) was added. The suspension was stirred until a clear solution was formed. The aqueous phase was extracted with dichloromethane (3 × 70 mL). The combined organic layers were washed with 1 M HCl, dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The title compound **17** was obtained as a colorless oil in quantitative yield without further purification (2.20 g, 100%). R_f = 0.33 (PE/EtOAc, 1:1). $[\alpha]_D^{22}$ = –17.4 (*c* = 1.32, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.85 [s, 9 H, C(CH_3)$_3$], 1.11 [s, 9 H, C(CH_3)$_3$], 1.66–1.76 (m, 2 H, 4-CH_2), 2.57 (dd, $^3J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.5 Hz, 1 H, 6-CH$_a$H$_b$), 2.75 (dd, $^3J_{H,H}$ = 15.0, $^3J_{H,H}$ = 6.5 Hz, 1 H, 6-CH$_a$H$_b$), 2.91 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, O*H*), 3.16 (s, 3 H, NCH_3), 3.41 (s, 3 H, OCH_3), 3.68 (s, 3 H, NOCH_3), 3.98–4.02 (m, 1 H, 3-C*H*), 4.17 (d, $^3J_{H,H}$ = 4.0 Hz, 1 H, 2-C*H*), 4.42 (p, $^3J_{H,H}$ = 6.0 Hz, 1 H, 5-C*H*), 7.33–7.42 (m, 6 H, Ph-*H*), 7.61–7.68 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.71 (Si*C*H$_3$), –4.62 (Si*C*H$_3$), 18.07 [*C*(CH$_3$)$_3$], 19.67 [*C*(CH$_3$)$_3$], 25.95 [C(*C*H$_3$)$_3$], 27.12 [C(*C*H$_3$)$_3$], 32.05 (N*C*H$_3$), 39.64 (6-*C*H$_2$), 40.60 (4-*C*H$_2$), 51.63 (O*C*H$_3$), 61.48 (NO*C*H$_3$), 67.73 (5-*C*H), 70.65 (3-*C*H), 76.20 (2-*C*H), 127.6, 127.8, 130.0, 130.1, 132.9, 136.0, 136.2 (Ph-*C*), 171.9 (1-*C*OOMe), 172.4 (7-*C*ONR$_2$), 173.7 ppm. IR (film): $\tilde{\nu}$ = 3469, 3071, 3047, 2999, 2931, 2858, 1747, 1613, 1588, 1514, 1428, 1390, 1362, 1336, 1302, 1249, 1109, 937, 822, 743, 704, 614, 508, 487 cm^{-1}. UV/Vis (CH$_3$CN): λ_{max} [lg(ε)] = 223 nm (3.65). MS (ESI): *m*/*z* = 618 [M + H]$^+$, 640 [M + Na]$^+$, 656 [M + K]$^+$. $C_{32}H_{51}NO_7Si_2$ (617.32): calcd. C 62.20, H 8.32, O 18.12; found C 61.76, H 8.56, O 17.88.

Methyl (2*S*,3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-3-methoxy-7-[methoxy(methyl)amino]-7-oxoheptanoate (18): To a solution of Weinreb amide **17** (5.00 g, 8.18 mmol, 1 equiv.) in dichloromethane (300 mL) was added molecular sieves and the solution was cooled to –5 °C. Proton sponge (5.25 g, 24.5 mmol, 3 equiv.) was added and the mixture was stirred until the solid was dissolved. Meerwein salt (3.63 g, 24.5 mmol, 3 equiv.) was added and the solution was stirred for 6 h at –5 °C. The reaction mixture was diluted with ethyl acetate (100 mL) and the white precipitation was filtered of through Celite 545. The residue was washed with ethyl acetate (50 mL). The filtrate was washed with a saturated solution of $CuSO_4$ (4× 50 mL) and water (50 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using a mixture of petroleum ether and ethyl acetate [2:1 (v/v)] as an eluent. The title compound **18** was obtained as a colorless oil, which crystallized on storage at –10 °C (4.41 g, 85%). R_f = 0.51 (PE/EtOAc, 2:1). $[\alpha]_D^{22}$ = 19.7 (*c* = 0.71, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H, SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.85 [s, 9 H, C(CH_3)$_3$], 1.10 [s, 9 H, C(CH_3)$_3$], 1.66–1.72 (m, 1 H, 4-CH$_a$H$_b$), 1.79–1.85 (m, 1 H, 4-CH$_a$H$_b$), 2.38 (dd, $^3J_{H,H}$ = 15.0, $^3J_{H,H}$ = 4.0 Hz, 1 H, 6-CH$_a$H$_b$), 2.74–2.82 (m, 1 H, 6-CH$_a$H$_b$), 3.16 (s, 3 H, NCH_3), 3.30 (s, 3 H, OCH_3), 3.41 (s, 3 H, COOCH_3), 3.49–3.55 (m, 1 H, 3-C*H*), 3.67 (s, 3 H, NOCH_3), 4.31 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 4.31–4.41 (m, 1 H, 5-C*H*), 7.35–7.43 (m, 6 H, Ph-*H*), 7.63–7.67 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.77 (Si*C*H$_3$), –4.57 (Si*C*H$_3$), 18.07 [*C*(CH$_3$)$_3$], 19.47 [*C*(CH$_3$)$_3$], 25.97 [C(*C*H$_3$)$_3$], 27.17 [C(*C*H$_3$)$_3$], 32.15 (N*C*H$_3$), 38.39 (4-*C*H$_2$), 40.60 (6-*C*H$_2$), 51.63 (COO*C*H$_3$), 58.10 (O*C*H$_3$), 61.35 (NO*C*H$_3$), 67.08 (5-*C*H), 73.83 (2-*C*H), 79.82 (3-*C*H), 127.6, 127.8, 130.0, 130.1, 132.9, 136.0, 136.2 (Ph-*C*), 171.9 (1-*C*OOMe), 172.4 (7-*C*ONR$_2$), 173.7 ppm. IR (film): $\tilde{\nu}$ = 3429, 3075, 2978, 2933, 2836, 1728, 1641, 1613, 1587, 1514, 1464, 1441, 1392, 1367, 1302, 1249, 1158, 1087, 1036, 997, 955, 917, 822, 760 cm^{-1}. UV/Vis (CH$_3$CN): λ_{max} [lg(ε)] = 215 nm (2.69). MS (ESI): *m*/*z* = 654 [M + Na]$^+$. $C_{33}H_{53}NO_7Si_2$ (631.34): calcd. C 62.72, H 8.45, O 17.72; found C 63.09, H 8.68, O 17.29.

Methyl (2*S*,3*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-3-methoxy-7-oxoheptanoate (5): A solution of Weinreb amide **18** (1.00 g, 1.58 mmol, 1 equiv.) in THF (70 mL) was cooled to –78 °C. A solution of *i*Bu$_2$AlH (3.16 mL, 3.16 mmol, 2 equiv.) in hexane (1 M) was added dropwise. The reaction mixture was stirred for 2 h at –78 °C. A mixture of MeOH/H$_2$O, 1:10

(50 mL) was added and the solution was warmed to room temp. 1 M HCl was added until the solution was clear. The aqueous phase was saturated with NaCl and extracted with diethyl ether (4 × 50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:30 w/w) using a mixture of petroleum ether and ethyl acetate [5:1 (v/v)] as an eluent. The title compound **5** was obtained as a colorless oil (0.90 g, 99%). R_f = 0.71 (PE/EtOAc, 1:1). $[\alpha]_D^{22}$ = 14.4 (*c* = 1.67, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.02 (s, 6 H, SiCH_3), 0.85 [s, 9 H, C(CH_3)$_3$], 1.10 [s, 9 H, C(CH_3)$_3$], 1.70–1.79 (m, 2 H, 4-CH_2), 2.45–2.50 (m, 2 H, 6-CH_2), 3.25 (s, 3 H, OCH_3), 3.46 (s, 3 H, COOCH_3), 3.42–3.48 (m, 1 H, 3-C*H*), 4.24 (m, 1 H, 5-C*H*), 4.33 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 7.26–7.42 (m, 6 H, Ph-*H*), 7.63–7.67 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.69 (Si*C*H$_3$), –4.11 (Si*C*H$_3$), 18.07 [*C*(CH$_3$)$_3$], 19.51 [*C*(CH$_3$)$_3$], 25.90 [C(*C*H$_3$)$_3$], 27.08 [C(*C*H$_3$)$_3$], 37.73 (4-*C*H$_2$), 50.56 (6-*C*H$_2$), 51.62 (COO*C*H$_3$), 57.85 (O*C*H$_3$), 65.61 (5-*C*H), 73.17 (2-*C*H), 79.48 (3-*C*H), 127.8, 127.9, 130.1, 130.2, 132.8, 133.0, 135.9, 136.2 (Ph-*C*), 171.6 (1-*C*OOMe), 202.3 (7-*C*HO), 173.7 ppm. IR (film): $\tilde{\nu}$ = 3465, 3072, 3000, 2932, 2858, 1743, 1613, 1588, 1514, 1428, 1384, 1301, 1248, 1150, 1113, 1068, 1033, 936, 822, 744, 703, 604, 508, 488 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 218 nm (3.97). MS (ESI): *m*/*z* = 595 [M + Na]$^+$. $C_{31}H_{48}O_6Si_2$ (572.30): calcd. C 64.99, H 8.45, O 16.67; found C 65.27, H 8.76, O 16.39.

1-(Benzyloxy)-3,3-dimethylpent-4-en-2-ol: To a solution of α-benzyloxy acetaldehyde (1.00 g, 6.66 mmol, 1 equiv.) and prenyl bromide (1.04 g, 6.99 mmol, 1.05 equiv.) in DMF (15 mL) were added $SnCl_2 \cdot 2H_2O$ (2.25 g, 9.99 mmol, 1.5 equiv.) and NaI (1.50 g, 9.99 mmol, 1.5 equiv.). The suspension was stirred at room temp. for 5 h. An exothermic reaction and a yellow color of the solution could be observed. A solution of NH_4Cl in water (8 mL, 30%) and a solution of KF in water (8 mL, 30%) were added. The aqueous phase was extracted with diethyl ether (4 × 15 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using a mixture of *n*-pentane and diethyl ether [3:1 (v/v)] as an eluent. The title compound **20** was obtained as a colorless liquid (1.32 g, 90%). R_f = 0.62 (PE/E, 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.04 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 2.42 (s, 1 H, O*H*), 3.36 (t, $^3J_{H,H}$ = 10.0 Hz, 1 H, C*H*OH), 3.58 (m, 2 H, CH_2OBn), 4.54 (s, 2 H, OCH_2Ph), 5.00 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H, CH_2=CH), 5.02 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH_2=CH), 5.88 (dd, $^3J_{H,H}$ = 10.0, $^3J_{H,H}$ = 17.5 Hz, 1 H, CH$_2$=C*H*), 7.29–7.38 (m, 5 H, Ph-*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.94 (*C*H$_3$), 23.56 (*C*H$_3$), 39.91 [*C*(CH$_3$)$_2$], 71.67 (O*C*H$_2$-Ph), 73.48 (*C*H$_2$OBn), 76.64 (*C*HOH), 112.7 (*C*H$_2$=CH), 127.8, 127.9, 128.6, 138.2 (Ph-*C*), 144.9 (*C*H=CH$_2$) ppm. IR (film): $\tilde{\nu}$ = 3463, 2964, 2929, 2869, 1497, 1453, 1383, 1204, 1114, 1087, 1006, 912, 698, 613 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 206 nm (4.03), 252 nm (2.65). MS (ESI): *m*/*z* = 243 [M + Na]$^+$, 463 [2M + Na]$^+$. $C_{14}H_{20}O_2$ (220.15).

1-(Benzyloxy)-3,3-dimethylpent-4-en-2-one (6): To a solution of pyridinium chlorochromate (PCC) (147 mg, 0.680 mmol, 1.5 equiv.) in dichloromethane (10 mL) was added a solution of 1-(benzyloxy)-3,3-dimethylpent-4-en-2-ol (110 mg, 0.450 mmol, 1 equiv.) in dichloromethane (2 mL). The orange color of the solution turned to dark brown. After 12 h stirring at room temp. another equivalent of PCC (100 mg) was added. The solution was stirred for 2 h, diluted with diethyl ether and separated from the black precipitation by decantation. The residue was washed with diethyl ether (2 × 10 mL). The combined organic layers were filtered over silica gel and the solvent was evaporated in vacuo. The title compound **6** was obtained as a colorless oil in quantitative yield without further purification (110 mg, 99%). R_f = 0.42 (PE/E 5:1). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 6 H, CH_3), 4.28 (m, 2 H, CH_2OBn), 4.56 (s, 2 H, OCH_2Ph), 5.14 (d, $^3J_{H,H}$ = 17.0 Hz, 1 H, CH_2=CH), 5.15 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, CH_2=CH), 5.89 (dd, $^3J_{H,H}$ = 11.0, $^3J_{H,H}$ = 17.0 Hz, 1 H, CH$_2$=C*H*), 7.28–7.35 (m, 5 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.55 (*C*H$_3$), 49.40 [*C*(CH$_3$)$_2$], 71.10 (OCH$_2$-Ph), 73.17 (*C*H$_2$OBn), 115.0 (*C*H$_2$=CH), 127.9, 128.0, 128.5, 137.5 (Ph-*C*), 141.7 (*C*H=CH$_2$), 209.1 (*C*=O) ppm. IR (film): $\tilde{\nu}$ = 3433, 2976, 1723, 1453, 1383, 1275, 1121, 1027, 924, 746, 714, 699, 651 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 206 nm (4.57), 264 nm (4.28). MS (ESI): *m*/*z* = 241 [M + Na]$^+$, 459 [2M + Na]$^+$, 463 [2M + Na]$^+$. $C_{14}H_{18}O_2$ (218.13).

Methyl (2*S*,3*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-7-hydroxy-3-methoxy-10,10-dimethyl-9-oxododec-11-enoate (20): To a solution of ketone **6** (267 mg, 1.22 mmol, 1.1 equiv.) in THF (5 mL) at –78 °C trimethylsilyl chloride (1.56 mL, 12.0 mmol, 10 equiv.), trimethylamine (1.71 mL, 12.0 mmol, 10 equiv.) and a solution of LiHMDS (1 M in THF) (2.44 mL, 2.44 mmol, 2 equiv.) were added. The solution was stirred for 20 min at –78 °C. Trimethylsilyl chloride (780 µL, 6.00 mmol, 5 equiv.), trimethylamine (860 µL, 6.00 mmol, 5 equiv.) and a solution of LiHMDS (1 M in THF) (4.16 mL, 4.16 mmol, 3.4 equiv.) were added. The solution was stirred for 1 h at –78 °C. After complete conversion of **6** (TLC monitoring PE/E, 4:1, 5% NEt_3) pH 7 buffer (2 mL) and water (2 mL) were added. The mixture was warmed to room temp. The aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:30 w/w) using a mixture of petroleum ether and diethyl ether [6:1 (v/v), 5% NEt_3] as an eluent. The silyl enol ether **19** was obtained as colorless oil in quantitative yield. Compound **19** was dissolved in dichloromethane (2 mL) and added to a solution of aldehyde **5** (631 mg, 1.10 mmol, 1 equiv.) in dichloromethane (5 mL) at –78 °C. $BF_3 \cdot OEt_2$ (0.420 mL, 1.59 mmol, 1.4 equiv.) was added dropwise at this temperature. The solution was stirred for 1 h. After adding pH 7 buffer (10 mL) the mixture was warmed to room temp. The aqueous phase was extracted with diethyl ether (4 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:100 w/w) using mixtures of petroleum ether and diethyl ether [first 6:1, then 4:1 (v/v)] as an eluent. The title compound **20** was obtained as a colorless oil (618 mg, 70%). R_f = 0.11 (PE/E 5:1). $[\alpha]_D^{22}$ = 26.1 (*c* = 0.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 3 H, SiCH_3), 0.05 (s, 3 H, SiCH_3), 0.87 [s, 9 H, C(CH_3)$_3$], 1.10 [s, 9 H, C(CH_3)$_3$], 1.23 [s, 3 H, C(CH_3)$_2$], 1.24 [s, 3 H, C(CH_3)$_2$], 1.50–1.79 (m, 4 H, 4-CH_2, 6-CH_2), 3.23 (s, 3 H, OCH_3), 3.41 (s, 3 H, COOCH_3), 3.46 (m$_c$, 1 H, 3-C*H*), 4.02 (m$_c$, 1 H, 5-C*H*), 4.16 (m$_c$, 1 H, 7-C*H*), 4.27 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 4.38 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 8-C*H*), 4.43 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, OCH_2Ph), 4.55 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, OCH_2Ph), 5.16 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H, CH_2=CH), 5.17 (d, $^3J_{H,H}$ = 10.5 Hz, 1 H, CH_2=CH), 5.96 (dd, $^3J_{H,H}$ = 17.5, $^3J_{H,H}$ = 10.5 Hz, 1 H, C*H*=CH$_2$), 7.37 (m, 11 H, Ph-*H*), 7.64 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.72 (Si*C*H$_3$), –4.48 (Si*C*H$_3$), 18.05 [*C*(CH$_3$)$_3$], 19.51 [*C*(CH$_3$)$_3$], 23.52 [C(*C*H$_3$)$_2$], 23.93 [C(*C*H$_3$)$_2$], 25.98 [C(*C*H$_3$)$_3$], 27.09 [C(*C*H$_3$)$_3$], 37.07 (4-*C*H$_2$), 37.18 (6-CH_2), 50.58 [*C*(CH$_3$)$_2$], 51.51 (COO*C*H$_3$), 58.15 (3-O*C*H$_3$), 67.97 (5-*C*H), 68.83 (7-*C*H), 72.45 (O*C*H$_2$Ph), 73.97 (2-*C*H), 79.57 (3-*C*H), 83.08 (8-*C*H), 114.9 (12-*C*H$_2$=CH), 127.6, 127.8, 127.9, 128.0, 130.0, 132.9, 133.0, 135.9, 136.2, 137.9 (Ph-*C*), 141.9 (11-*C*H=CH$_2$), 171.6

(1-*C*OOMe), 211.1 (9-*C*=O) ppm. IR (film): $\tilde{\nu}$ = 3479, 2928, 2857, 1752, 1714, 1463, 1428, 1257, 1113, 837, 739, 702, 507 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 202 nm (4.60), 271 nm (4.68), 336 nm (2.48). MS (ESI): *m*/*z* = 813 $[M + Na]^+$, 829 $[M + K]^+$. HRMS-ESI: *m*/*z* = $[M + Na]^+$ calcd. for $C_{45}H_{66}O_8Si_2$ (790.43): 813.41884; found 813.41860, $[2M + Na]^+$ calcd. 1603.84847; found 1603.84724.

Isopropylidene Acetal (22): To a solution of aldol product **20** (62 mg, 78 μmol, 1 equiv.) in ACN (5 mL) in a Teflon® vessel was added a aqueous solution of HF (48%, 33 μL, 780 μmol, 10 equiv.) at –5 °C. The solution was stirred for 10 h at –5 °C. HF (10 equiv.) was added after every two hours. The reaction was stopped by adding a saturated solution of $NaHCO_3$ in water (5 mL). The aqueous phase was extracted with dichloromethane (4 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The crude diol was dissolved in acetone (2 mL) and 2,2-dimethoxypropane (114 μL, 900 μmol, 11.5 equiv.) and catalytic amounts of camphorsulfonic acid (2.1 mg, 9.0 μmol, 10 mol-%) were added at room temp. The solution was stirred for 6 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) and ethyl ether (4 mL) were added. The aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:80 w/w) using a mixture of hexane and diethyl ether [1:1 (v/v), 2% NEt_3] as an eluent. The title compound **22** was obtained as a colorless oil (16 mg, 29%). R_f = 0.58 (Hex/E, 1:1, 5% NEt_3). $[\alpha]_D^{22}$ = 21.3 (*c* = 1.59, $CHCl_3$). ^1H NMR (400 MHz, [D$_8$]toluene): δ = 1.19 [s, 18 H, SiC(CH_3)$_3$, 10-C(CH_3)$_2$, OOC(CH_3)$_a$], 1.25 [s, 3 H, OOC(CH_3)$_b$], 1.66–1.73 (m, 1 H, 6-CH$_a$CH_b), 1.88–1.95 (m, 1 H, 4-CH$_a$CH_b), 2.00–2.21 (m, 2 H, 4-CH_aCH$_b$, 6-CH_aCH$_b$), 3.14 (s, 3 H, OCH_3), 3.17 (s, 3 H, COOCH_3), 3.68 (m$_c$, 1 H, 3-C*H*), 3.97 (m$_c$, 1 H, 5-C*H*), 4.32–4.37 (m, 2 H, 7/8-C*H*), 4.34 (s, 2 H, OCH_2Ph), 4.50 (d, $^3J_{H,H}$ = 5.0 Hz, 1 H, 2-C*H*), 4.98 (d, $^3J_{H,H}$ = 17.0 Hz, 1 H, 12-CH_2=CH), 4.99 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, 12-CH_2=CH), 5.93 (dd, $^3J_{H,H}$ = 17.5, $^3J_{H,H}$ = 10.5 Hz, 1 H, 11-C*H*=CH$_2$), 7.28 (m, 10 H, Ph-H), 7.80 (m, 5 H, Ph-H) ppm. ^{13}C NMR (100 MHz, [D$_8$]toluene): δ = 19.51 [Si*C*(CH$_3$)$_3$], 24.90 [10-C(*C*H$_3$)$_2$], 25.67 [OOC(*C*H$_3$)$_a$], 25.80 [OOC(*C*H$_3$)$_b$], 28.25 [SiC(*C*H$_3$)$_3$], 35.21 (4-*C*H$_2$), 37.14 (6-CH_2), 51.56 [10-*C*(CH$_3$)$_2$], 51.85 (COO*C*H$_3$), 58.52 (O*C*H$_3$), 65.13 (7-*C*H), 69.26 (5-*C*H), 73.57 (O*C*H$_2$Ph), 75.18 (2-*C*H), 79.21 (3-*C*H), 82.91 (8-*C*H), 101.6 [OO*C*(CH$_3$)$_2$], 115.1 (12-*C*H$_2$=CH), 128.9, 129.0, 131.0, 131.1, 134.7, 137.5, 138.5 (Ph-*C*), 143.8 (11-*C*H=CH$_2$), 172.2 (1-*C*OOMe), 210.5 (9-*C*=O) ppm. IR (film): $\tilde{\nu}$ = 2932, 1751, 1715, 1428, 1382, 1224, 1113, 1027, 788, 702, 506 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 209 nm (4.28), 261 nm (2.38). MS (ESI): *m*/*z* = 739 $[M + Na]^+$. HRMS-ESI: *m*/*z* = $[M + Na]^+$ calcd. for $C_{42}H_{56}O_8Si$ (716.37): 739.36367; found 739.36293.

Isopropylidene Acetal (23): To a solution of aldol product **20** (50 mg, 63 μmol, 1 equiv.) in dichloromethane (2 mL) was added a solution of freshly prepaired $Zn(BH_4)_2$[35] in ethyl ether (0.4 M) (290 μL, 95.0 μmol, 1.5 equiv.) at –78 °C. The solution was stirred for 3 h at –78 °C. A saturated aqueous solution of NH_4Cl (1 mL) was added and the mixture was warmed to room temp. The aqueous phase was extracted with dichloromethane (4 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (5 mL) and water (5 mL), dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:80 w/w) using a mixture of hexane and diethyl ether [3:1 (v/v)] as an eluent. The diol was obtained as colorless oil, 23 mg (46%). It was dissolved in acetone (2 mL) and 2,2-dimethoxypropane (36.0 μL, 290 μmol, 10 equiv.) and catalytic amounts of camphorsulfonic acid (0.5 mg, 3.0 μmol, 10 mol-%) were added at room temp. The solution was stirred for 6 h. A saturated aqueous solution of $NaHCO_3$ (2 mL) and ethyl ether (4 mL) were added. The aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:80 w/w) using a mixture of hexane and diethyl ether [2:1 (v/v), 2% NEt_3] as an eluent. The title compound **23** was obtained as a colorless oil (16 mg, 30%). R_f = 0.71 (Hex/E, 1:3, 5% NEt_3). $[\alpha]_D^{22}$ = 19.9 (*c* = 1.60, $CHCl_3$). ^1H NMR (400 MHz, [D$_8$]toluene): δ = 0.16 (s, 3 H, SiCH_3), 0.17 (s, 3 H, SiCH_3), 1.01 [s, 9 H, C(CH_3)$_3$], 1.15 [s, 3 H, 10-C(CH_3)$_2$], 1.17 [s, 3 H, 10-C(CH_3)$_2$], 1.21 [s, 9 H, C(CH_3)$_3$], 1.43 [s, 3 H, OOC-(CH_3)$_a$], 1.48 [s, 3 H, OOC(CH_3)$_b$], 1.76–1.80 (m, 1 H, 6-CH$_a$CH_b), 1.94–1.99 (m, 2 H, 6-CH_aCH$_b$, 4-CH$_a$CH_b), 2.10–2.20 (m, 1 H, 4-CH_aCH$_b$), 2.99–3.10 (t, $^3J_{H,H}$ = 9.0 Hz, 1 H, 8-C*H*), 3.14 (s, 3 H, OCH_3), 3.27 (s, 3 H, COOCH_3), 3.61 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, 9-C*H*), 3.67 (m$_c$, 1 H, 3-C*H*), 4.11 (m$_c$, 1 H, 7-C*H*), 4.30 (m$_c$, 1 H, 5-C*H*), 4.41 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, OCH_2Ph), 4.48 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 4.55 (d, $^3J_{H,H}$ = 11.5 Hz, 1 H, OCH_2Ph), 4.89 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, 12-CH_2=CH), 5.01 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H, 12-CH_2=CH), 6.11 (dd, $^3J_{H,H}$ = 17.5, $^3J_{H,H}$ = 11.0 Hz, 1 H, 11-C*H*=CH$_2$), 7.19 (m, 11 H, Ph-*H*), 7.77 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, [D$_8$]toluene): δ = –4.26 (Si*C*H$_3$), –3.51 (Si*C*H$_3$), 19.63 [OOC(*C*H$_3$)$_a$], 20.14 [*C*(CH$_3$)$_3$], 20.32 [10-C(*C*H$_3$)$_2$], 22.18 [*C*(CH$_3$)$_3$], 25.74 [10-C(*C*H$_3$)$_2$], 26.20 [C(*C*H$_3$)$_3$], 27.22 [C(*C*H$_3$)$_3$], 29.87 [OOC(*C*H$_3$)$_b$], 40.11 (6-*C*H$_2$), 40.48 [10-*C*(CH$_3$)$_2$], 42.12 (4-*C*H$_2$), 50.80 (COO*C*H$_3$), 58.39 (O*C*H$_3$), 66.31 (5-*C*H), 70.87 (7-*C*H), 72.55 (O*C*H$_2$Ph), 74.69 (2-*C*H), 77.37 (9-*C*H), 79.10 (3-*C*H), 80.41 (8-*C*H), 98.07 [OO*C*(CH$_3$)$_2$], 110.1 (12-*C*H$_2$=CH), 127.4, 127.8, 128.0, 128.4, 130.1, 136.2, 136.5 (Ph-*C*), 146.1 (11-*C*H=CH$_2$), 171.3 (1-*C*OOMe) ppm. IR (film): $\tilde{\nu}$ = 2931, 2858, 1753, 1472, 1462, 1428, 1381, 1252, 1204, 1169, 1111, 1029, 836, 787, 701, 613, 507 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 209 nm (4.49), 264 nm (3.00). MS (ESI): *m*/*z* = 855 $[M + Na]^+$. HRMS-ESI: *m*/*z* = $[M + Na]^+$ calcd. for $C_{48}H_{72}O_8Si_2$ (832.48): 855.46612; found 855.46581.

Methyl (2*S*,3*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-10,10-dimethyl-9-oxododec-11-enoate (24): To a solution of aldol product **20** (191 mg, 0.240 mmol, 1 equiv.) in dichloromethane (8 mL) was added molecular sieves at –5 °C. Proton sponge (155 mg, 0.720 mmol, 3 equiv.) was added and the mixture was stirred until the solid was dissolved. Meerwein salt (107 mg, 0.720 mmol, 3 equiv.) was added and the solution was stirred for 3 h at –5 °C. The reaction mixture was diluted with ethyl acetate (10 mL) and the white precipitation was filtered of through Celite 545. The residue was washed with ethyl acetate (5 mL). The filtrate was washed with a saturated solution of $CuSO_4$ (4× 10 mL) and water (5 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using a mixture of petroleum ether and diethyl ether [5:1 (v/v)] as an eluent. The title compound **24** was obtained as a colorless oil (192 mg, 99%). R_f = 0.23 (PE/E, 4:1). $[\alpha]_D^{22}$ = 17.6 (*c* = 1.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 3 H, SiCH_3), 0.04 (s, 3 H, SiCH_3), 0.87 [s, 9 H, C(CH_3)$_3$], 1.10 [s, 9 H, C(CH_3)$_3$], 1.21 [s, 3 H, C(CH_3)$_2$], 1.23 [s, 3 H, C(CH_3)$_2$], 1.38–1.91 (m, 4 H, 4-CH_2, 6-CH_2), 3.24 (s, 3 H, 3-OCH_3), 3.27 (s, 3 H, 7-OCH_3), 3.40 (s, 3 H, COOCH_3), 3.39–3.48 (m, 1 H, 3-C*H*), 3.72–3.83 (m, 1 H, 7-C*H*), 4.01 (m$_c$, 1 H, 5-C*H*), 4.25 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 4.39 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, OCH_2Ph), 4.58 (d, $^3J_{H,H}$ = 12.0 Hz, 1 H, OCH_2Ph), 4.61 (d, $^3J_{H,H}$

= 3.0 Hz, 1 H, 8-C*H*), 5.15 (d, $^3J_{H,H}$ = 17.5 Hz, 1 H, CH_2=CH), 5.16 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, CH_2=CH), 5.96 (dd, $^3J_{H,H}$ = 17.5, $^3J_{H,H}$ = 11.0 Hz, 1 H, C*H*=CH$_2$), 7.37 (m, 11 H, Ph-*H*), 7.64 (m, 4 H, Ph-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.42 (Si*C*H$_3$), –3.77 (Si*C*H$_3$), 18.11 [*C*(CH$_3$)$_3$], 19.49 [*C*(CH$_3$)$_3$], 23.51 [C(*C*H$_3$)$_2$], 24.33 [C(*C*H$_3$)$_2$], 26.14 [C(*C*H$_3$)$_3$], 27.12 [C(*C*H$_3$)$_3$], 37.07 (4-*C*H$_2$), 39.45 (6-*C*H$_2$), 50.50 [*C*(CH$_3$)$_2$], 51.43 (COO*C*H$_3$), 57.02 (7-O*C*H$_3$), 58.52 (3-O*C*H$_3$), 66.30 (5-*C*H), 71.89 (O*C*H$_2$Ph), 74.35 (2-*C*H), 77.20 (7-*C*H), 79.28 (3-*C*H), 79.89 (8-*C*H), 115.1 (12-*C*H$_2$=CH), 127.6, 127.8, 127.8, 128.0, 128.4, 129.9, 130.0, 133.1, 133.1, 136.0, 136.2, 138.0 (Ph-*C*), 142.0 (11-*C*H=CH$_2$), 171.7 (1-*C*OOMe), 210.6 (9-*C*=O) ppm. IR (film): $\tilde{\nu}$ = 2931, 2857, 1753, 1715, 1471, 1428, 1113, 1055, 836, 740, 702, 506 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 205 nm (4.51), 210 nm (4.47), 259 nm (3.13). MS (ESI): *m*/*z* = 827 [M + Na]$^+$. HRMS-ESI: *m*/*z* = [M + Na]$^+$ calcd. for $C_{46}H_{68}O_8Si_2$ (804.45): 827.43449; found 827.43495.

Methyl (2*S*,3*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-3,7-dimethoxy-10,10-dimethyl-9,11-dioxoundecanoate (4): To a solution of olefin **24** (560 mg, 0.690 mmol, 1 equiv.) in acetone (8 mL), water (1 mL) and *tert*-butanol (0.1 mL) were added an aqueous solution (4%) of OsO_4 (1.1 mL, 0.170 mmol, 0.25 equiv.) and *N*-methylmorpholine *N*-oxide (98.0 mg, 0.830 mmol, 1.2 equiv.) at room temp. The solution was stirred at room temp. for 4 h. An aqueous solution (0.5 M) of $Na_2S_2O_3$ (5 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The crude diol was dissolved in a mixture of THF and water (10 mL, 4:1). Sodium periodate (298 mg, 1.39 mmol, 2 equiv.) was added at room temp. and the solution was stirred for 18 h. Water (10 mL) and ethyl acetate (5 mL) were added. The aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (1:50 w/w) using mixtures of petroleum ether and diethyl ether [5:1 (v/v)] as an eluent. The title compound **4** was obtained as a colorless oil (512 mg, 91%). R_f = 0.41 (PE/E, 3:1). $[\alpha]_D^{22}$ = 34.9 (*c* = 0.86, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, Si*C*H$_3$), 0.08 (s, 3 H, Si*C*H$_3$), 0.91 [s, 9 H, C(*C*H$_3$)$_3$], 1.09 [s, 9 H, C(*C*H$_3$)$_3$], 1.20 [s, 3 H, C(*C*H$_3$)$_2$], 1.29 [s, 3 H, C(*C*H$_3$)$_2$], 1.27–1.30 (m, 1 H, 6-C*H*$_a$CH$_b$), 1.66–1.71 (m, 2 H, 4-C*H*$_2$), 1.90 (ddd, $^3J_{H,H}$ = 14.0, $^3J_{H,H}$ = 10.5, $^4J_{H,H}$ = 2.0 Hz, 1 H, 6-CH$_a$C*H*$_b$), 3.24 (s, 3 H, 3-OC*H*$_3$), 3.39 (s, 3 H, 7-OC*H*$_3$), 3.40 (s, 3 H, COOC*H*$_3$), 3.45–3.49 (m, 1 H, 3-C*H*), 3.93–3.96 (m, 1 H, 7-C*H*), 4.03 (m$_c$, 1 H, 5-C*H*), 4.25 (d, $^3J_{H,H}$ = 2.5 Hz, 1 H, 8-C*H*), 4.28 (d, $^3J_{H,H}$ = 4.5 Hz, 1 H, 2-C*H*), 4.41 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, OC*H*$_2$Ph), 4.78 (d, $^3J_{H,H}$ = 11.0 Hz, 1 H, OC*H*$_2$Ph), 7.34 (m, 11 H, Ph-*H*), 7.65 (m, 4 H, Ph-*H*), 9.45 (s, 1 H, 11-C*H*O) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.53 (Si*C*H$_3$), –3.58 (Si*C*H$_3$), 18.17 [*C*(CH$_3$)$_3$], 19.49 [*C*(CH$_3$)$_3$], 19.88 [C(*C*H$_3$)$_2$], 20.31 [C(*C*H$_3$)$_2$], 26.13 [C(*C*H$_3$)$_3$], 27.10 [C(*C*H$_3$)$_3$], 38.66 (4-*C*H$_2$), 39.04 (6-*C*H$_2$), 51.45 (COO*C*H$_3$), 57.57 (7-O*C*H$_3$), 57.81 [*C*(CH$_3$)$_2$], 58.40 (3-O*C*H$_3$), 66.33 (5-*C*H), 73.57 (O*C*H$_2$Ph), 74.16 (2-*C*H), 79.98 (7-*C*H), 80.00 (3-*C*H), 81.89 (8-*C*H), 127.6, 127.8, 128.1, 128.3, 128.6, 129.9, 130.0, 133.0, 133.1, 135.9, 136.2, 137.2 (Ph-*C*), 171.7 (1-*C*OOMe), 199.9 (11-*C*HO), 208.9 (9-*C*=O) ppm. IR (film): $\tilde{\nu}$ = 2931, 2857, 1727, 1706, 1509, 1462, 1428, 1249, 1114, 1008, 837, 788, 703, 507 cm^{-1}. UV/Vis (CH_3CN): λ_{max} [lg(ε)] = 206 nm (4.44), 264 nm (3.15). MS (ESI): *m*/*z* = 829 [M + Na]$^+$. HRMS-ESI: *m*/*z* = [M + Na]$^+$ calcd. for $C_{45}H_{66}O_9Si_2$ (806.42): 829.41376; found 829.41305.

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