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# Total synthesis of 12,13-desoxyepothilone B (Epothilone D)

Robert L. Broadrup[a,b,*], Hema M. Sundar[a,b], Charles S. Swindell[a,b]

[a] *Protarga, Inc., 2200 Renaissance Blvd., Suite 450, King of Prussia, PA 19406, USA*
[b] *Department of Chemistry, Bryn Mawr College, Bryn Mawr, PA 19010, USA*

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**Abstract**

A highly convergent total synthesis of 12,13-desoxyepothilone B (**4**, Epothilone D) is described involving the coupling of vinyl iodide (**5**) and olefin (**6**). Key steps in the synthesis are the introduction of chirality at C15 via highly enantioselective lipase-mediated enzymatic resolution, diastereoselective alkylation at C8, highly diastereoselective Evans aldol reaction to establish C6–C7, and Mukaiyama aldol reaction to introduce chiral center C3. Palladium catalyzed Suzuki coupling of (**5**) and (**6**) provided the methyl ester (**27**), which was converted to 12,13-desoxyepothilone B (**4**).


*Keywords:* Epothilone D; 12,13-desoxyepothilone B; Lipase resolution; Diastereoselective alkylation; aldol reaction; Suzuki coupling

## 1. Introduction

Epothilones are macrolide natural products exhibiting potent antitumor activity against a wide spectrum of human tumor cell lines including multi-drug resistant cell

* Corresponding author. Fax: +1 801 757 9514.
*E-mail address:* organicrob@comcast.net (R.L. Broadrup).

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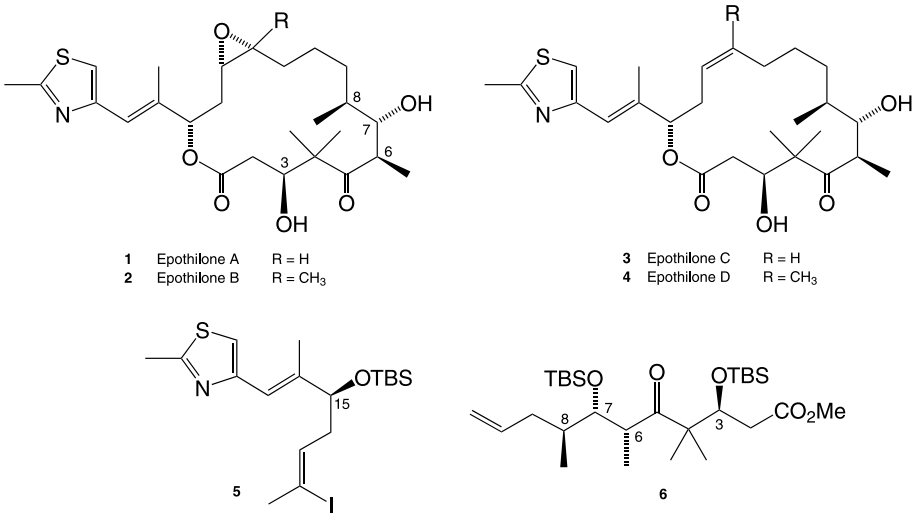


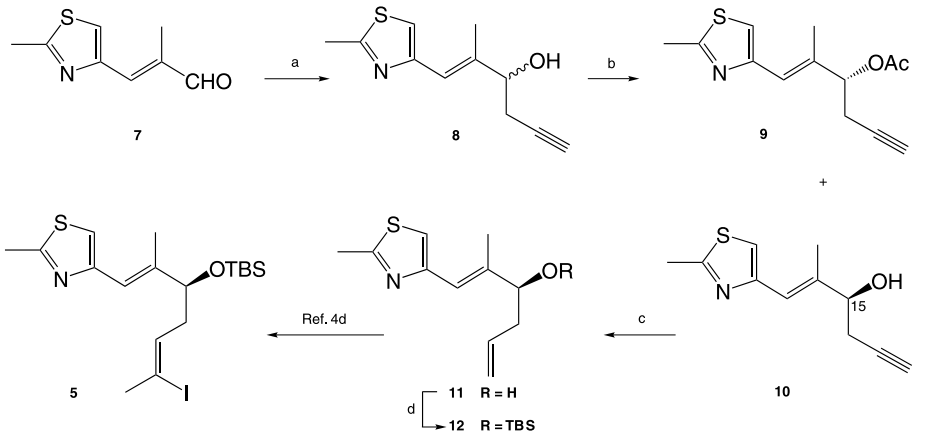

Fig. 1. Structures of Epothilones A and B, Epothilones C and D, vinyl iodide **5**, and olefin **6**.

lines (Fig. 1) [1]. Hofle et al. [2] isolated epothilones from the myxobacterium *Sorangium cellulosum*. Bollag et al. [3] established that epothilones are microtubule stabilizing agents, similar to the anticancer drug taxol. Since these findings numerous syntheses have been reported on epothilones [4]. Danishefsky and co-workers [5] demonstrated that 12,13-desoxyepothilone B (**4**, Epothilone D) has a more promising in vivo profile than Epothilone B. Epothilone D is currently undergoing clinical trials [6] and is isolated only as a very minor constituent from bacterial fermentation compared to the two major constituents, Epothilones A and B. In this paper, we describe an efficient synthesis of Epothilone D.

## 2. Results and discussion

Our approach to the synthesis of 12,13-desoxyepothilone B (Epothilone D) involves palladium catalyzed Suzuki coupling of vinyl iodide (**5**) and olefin (**6**) followed by macrolactonization. Synthesis of vinyl iodide (**5**) commenced from the known thiazole aldehyde (**7**) [7], utilizing a lipase-mediated enzymatic resolution (Scheme 1). Aldehyde (**7**) was treated with propargyl bromide in the presence of activated zinc dust in THF at room temperature to afford the racemic homopropargyl alcohol (**8**). Enzymatic resolution of the racemic alcohol with *Pseudomonas* AK lipase at 40 °C for 18 h in the presence of vinyl acetate/3 Å molecular sieves [8] provided the *S*-homopropargyl alcohol (**10**) in >99% e.e. and in 80% yield along with the *R*-acetate (**9**).

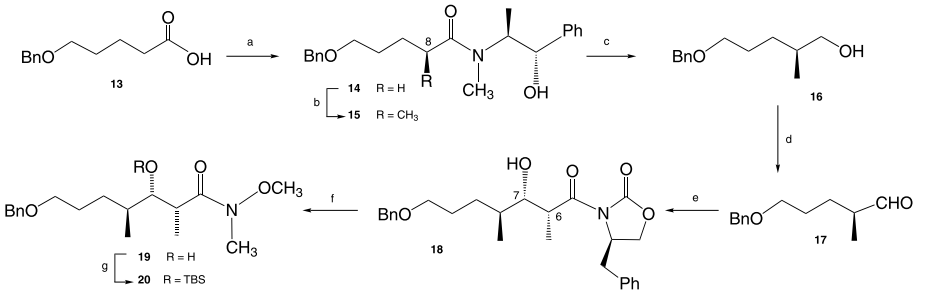
The absolute configuration at C15 in (**10**) was confirmed by its conversion to the known *S*-homoallylic alcohol (**11**) via Lindlar reduction. Independently, Zhu and




Scheme 1. Synthesis of vinyl iodide (**5**). Reagents and conditions. (a) Propargyl bromide, activated Zn dust, THF, room temperature, 18 h, 80%; (b) *Pseudomonas* AK lipase, vinyl acetate, 3 Å molecular sieves, anhydrous hexanes, 40 °C, 18 h, 80% yield, >99% e.e.; (c) $H_2$/Lindlar catalyst, THF, room temperature, 1 h, 94%; and (d) TBDMS-OTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C.

Panek [9] reported the synthesis of (**10**) by a modified procedure. Silylation of (**11**) using TBDMS-OTf and 2,6-lutidine provided (**12**), which was converted to the vinyl iodide following the sequence of reactions reported in the literature [4d].

Synthesis of olefin (**6**) started from 5-benzyloxypentanoic acid (**13**), which was prepared from the commercially available δ-valerolactone as described in the literature [10]. Myers's pseudoephedrine chiral auxiliary approach [11] was utilized to introduce the chiral center at C8 (Scheme 2). Treatment of 5-benzyloxypentanoic acid (**13**) with 1*S*,2*S*-pseudoephedrine in the presence of pivaloyl chloride and

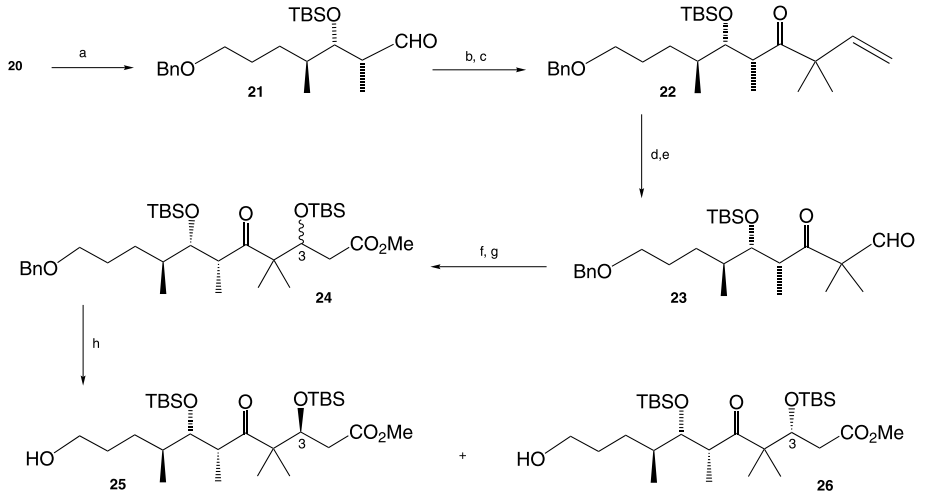



Scheme 2. Synthesis of Weinreb amide (**20**). Reagents and conditions. (a) 1*S*,2*S*-pseudoephedrine, pivaloyl chloride, $Et_3N$, THF/$CH_3CN$, 0 °C to room temperature, 87%; (b) LDA, LiCl, $CH_3I$, THF, −78 °C to 0 °C, 94%, >99% d.e.; (c) $BH_3 \cdot NH_3$ complex, LDA, THF, 0 °C to room temperature, 75%; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C to −30 °C, 84%; (e) $Bu_2B$-OTf, $Et_3N$, $CH_2Cl_2$, (*S*)-4-benzyl-3-propionyloxazolidinone, −78 °C to 0 °C, 95%, 96:4 mixture of diastereomers; (f) $CH_3ONHCH_3 \cdot HCl$, $Me_3Al$, THF, −5 °C to room temperature, 80%; and (g) TBDMS-OTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 30 min, 96%.

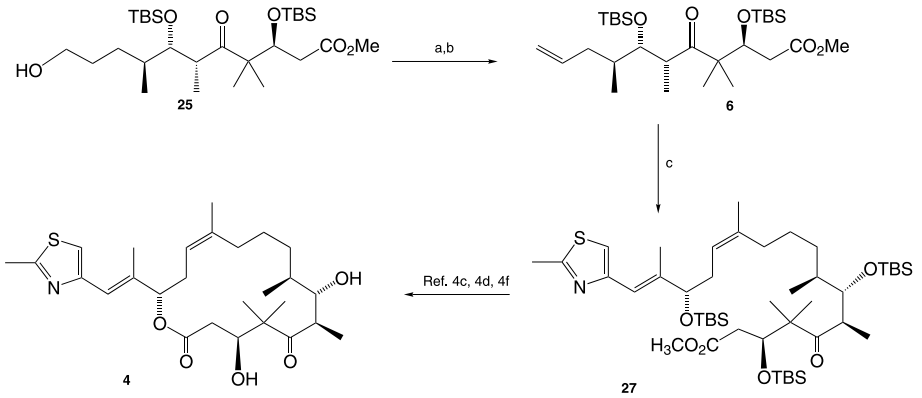
triethylamine afforded the pseudoephedrine amide (**14**) in 87% yield. Alkylation of (**14**) with methyl iodide in the presence of LDA and LiCl at −78 °C furnished (**15**) in 94% yield with >99% d.e. Alcohol (**16**) was obtained in 75% yield by the reduction of the amide (**15**) with borane-ammonia complex and LDA at 0 °C. After completion of our synthesis, Altmann et al. [12] reported the synthesis of alcohol (**16**) utilizing (*S*)-4-benzyloxazolidinone as a chiral auxiliary.

The aldol condensation approach has been used by several groups to establish the C6–C7 bond, although only a few have described high diastereoselectivity for this process [13]. Our strategy involved the application of Evans' aldol methodology to introduce C6–C7 with high diastereoselectivity in a highly convergent route. Thus, Swern oxidation of (**16**) afforded the aldehyde (**17**), which was subsequently used in an Evans aldol reaction [14] with (*S*)-4-benzyl-3-propionyloxazolidinone in the presence of dibutylboron trifluoromethanesulfonate to generate C6–C7 carbon–carbon bond. The aldol product was isolated in 95% yield as an inseparable mixture of diastereomers by TLC [96:4, in favor of the desired isomer (**18**)]. Separation of the diastereomers was achieved by converting (**18**) to the corresponding Weinreb amide via transamidation ($AlMe_3$, MeO(Me)NH · HCl) [15]. The major diastereomer (**19**) was isolated in 80% yield after purification by flash chromatography on silica gel (Scheme 2).

Introduction of the chiral center at C3 was achieved by Lewis acid-mediated Mukaiyama aldol reaction of the aldehyde (**23**), which was prepared from (**19**) through a six-step sequence (Scheme 3). Silylation of (**19**) provided (**20**), followed




Scheme 3. Synthesis of primary alcohol (**25**). Reagents and conditions. (a) DIBAL-H, THF, −78 °C to −50 °C, 91%; (b) Prenylmagnesium chloride, THF, room temperature, 1 h, 94%; (c) TPAP, NMO, $CH_3CN$:$CH_2Cl_2$ (4:1), room temperature, 2 h, 76%; (d) $OsO_4$, NMO, THF:*t*-butanol:$H_2O$ (4:2:1), room temperature, 16 h; (e) $NaIO_4$, THF:$H_2O$ (1:1), room temperature, 6 h, 92% for 2 steps; (f) 1-*t*-butyldimethylsilyloxy-1-methoxyethene, $BF_3 \cdot Et_2O$, $CH_2Cl_2$, −78 °C, 5 h, 97%; (g) TBDMS-OTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 30 min, 97%; and (h) $H_2$, $Pd(OH)_2$ on carbon, room temperature, atm. pressure, $CH_3OH$, 7 h, 68%.




Scheme 4. Synthesis of olefin (**6**) and epothilone D (**4**). Reagents and conditions. (a) 2-$NO_2$-PhSeCN, $Bu_3P$, pyridine, THF, room temperature, 16 h, 96%; (b) MCPBA, $CH_2Cl_2$, −15 °C (30 min), then $(iPr)_2NH$, room temperature, 30 min, 67%; and (c) 9-BBN, THF, room temperature, 6 h, then vinyl iodide (**5**), $PdCl_2$(dppf), $Cs_2CO_3$, $Ph_3As$, DMF, $H_2O$, room temperature, 15 h, 84%.

by reduction with DIBAL-H in THF provided aldehyde (**21**). Reaction of (**21**) with prenyl magnesium chloride followed by oxidation with catalytic tetra-*n*-propylammonium perruthenate (TPAP) in the presence of *N*-methyl morpholine oxide [16] afforded ketone (**22**) in 76% yield. Transformation to aldehyde (**23**) was achieved by sequential $OsO_4$ dihydroxylation and oxidative cleavage with $NaIO_4$.

Condensation of the aldehyde (**23**) with 1-*tert*-butyldimethylsilyloxy-1-methoxyethene in the presence of boron trifluoride etherate [17] followed by silylation of the resulting aldol product with TBDMS-OTf and 2,6-lutidine provided the silyl ether (**24**) as an inseparable 2.6:1 mixture of diastereomers at C3 (diastereomeric ratio was determined by $^1H$ NMR based on the chemical shift of the methine proton at C3). Debenzylation of (**24**) afforded a mixture of primary alcohols (**25**) and (**26**), which were easily separated by flash chromatography to furnish the desired diastereomer in 68% yield (Scheme 3). Alcohol (**25**) was transformed into olefin (**6**) via selenoxide elimination [18].

Hydroboration of (**6**) with 9-BBN and subsequent coupling of the resulting trialkylborane adduct with vinyl iodide (**5**) [19] catalyzed by $PdCl_2$(dppf) provided the methyl ester (**27**) in 84% yield. Finally, the methyl ester (**27**) was converted to 12,13-desoxyepothilone B (**4**) by a four-step sequence via Yamaguchi's macrolactonization as reported in the literature [4d–4f] (Scheme 4).

## 3. Materials and methods

### *3.1. General methods*

All glassware was dried in the oven prior to use. All reactions were carried out under an argon atmosphere. Precoated soft layer silica gel GF uniplates (Analtech)

were used for TLC, and the plates were visualized with UV light or potassium permanganate and ammonium molybdate sprays. Silica gel, Merck, (230–400 mesh, 60 Å, VWR Scientific) was used for flash chromatography. $^{1}H$ (300 MHz) and $^{13}C$ NMR (75 MHz) spectra were recorded in $CDCl_3$ using a Bruker FT-NMR spectrometer. Chemical shifts and coupling constants are reported in ppm and Hz, respectively.

### 3.2. 4-[(1E,3S)-3-Hydroxy-2-methylhex-1-en-5-ynyl]-2-methylthiazole (**10**)

Activated zinc dust (4.69 g, 72 mmol) was added to a solution of the aldehyde (4.0 g, 24 mmol) in dry tetrahydrofuran (50 mL) at room temperature. Propargyl bromide (7.1 mL, 80 wt % solution in toluene) was then added dropwise over a period of 10 min, and the resulting suspension was stirred at room temperature for 15 h. The reaction was quenched by the addition of 10% aq. $NH_4Cl$ solution (25 mL) and stirred for 1 h. The reaction mixture was then filtered through a celite pad, which was rinsed with dichloromethane (50 mL). The combined filtrate was concentrated at reduced pressure. The resulting crude product was purified by flash chromatography, eluting with 1:1 ethyl acetate: hexane, to furnish 3.97 g of racemic homopropargyl alcohol **8** (80%).

To a dilute solution of the racemic homopropargyl alcohol **8** (1.42 g, 6.85 mmol) in dry hexanes (213 mL) at room temperature was added lipase powder (*Pseudomonas* species, Amano AK, 2.84 g), followed by powdered dry molecular sieves (3 Å, 1.18 g) and vinyl acetate (3.2 mL). The resulting suspension was stirred at 40 °C under argon overnight. The reaction mixture was diluted with dichloromethane (100 mL) and filtered through Whatman No. 3 filter paper to remove the molecular sieves and lipase. The filtrate was concentrated under reduced pressure to give a yellow oil which was purified immediately by flash chromatography, eluting with 3:7 ethyl acetate: hexane followed by 1:1 ethyl acetate: hexane, to furnish the *R*-acetate **9** followed by the 570 mg of *S*-alcohol **10** (80%, yield, >99% e.e.).

$[\alpha]_D$: $-2.8°$ ($c = 1.41$, chloroform); (literature [9b]: $-2.6$, $c = 0.58$, dichloromethane).

IR (of racemate **8**) (Film, $cm^{-1}$): 3281, 2916, 2112, 1508, 1430, 1193, 1154, 1034, 972, 875, 793.

$^{1}H$ NMR: $\delta$ 2.07(s, 3 H), 2.21(t, $J = 3$ Hz, 1 H), 2.48–2.64 (m, 2 H), 2.71 (s, 3 H), 4.33–4.39 (m, 1 H), 6.61 (s, 1 H), 6.97 (s, 1 H).

$^{13}C$ NMR: $\delta$ 164.99, 152.60, 140.32, 119.85, 116.08, 81.0, 75.50, 70.86, 26.18, 19.28, 14.35.

HRMS (of racemate **8**) (FAB) *m/z* calculated for $C_{11}H_{13}NOS$ $(M + H)^+$ 208.0796. Found 208.0802.

### 3.3. 4-[(1E,3S)-3-Hydroxy-2-methylhex-1,5-dienyl]-2-methylthiazole (**11**)

To a solution of the *S*-homopropargyl alcohol **10** (2.56 g, 12.3 mmol) in dry tetrahydrofuran (100 mL) was added Lindlar catalyst (20 wt % Pd on C, 200 mg, purchased from Aldrich) and the reaction mixture was stirred under a hydrogen

atmosphere at room temperature for about 1 h. The reaction mixture was filtered through a pad of celite, which was rinsed with dichloromethane (50 mL). The combined filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography, eluting with 3:7 ethyl acetate: hexane, to afford 2.4 g of homoallylic alcohol **11** as a yellow oil (94%).

$[\alpha]_D$: −19.5° ($c = 1.43$, chloroform); (literature [4d]: −15.9, $c = 4.9$, chloroform).

$^1$H NMR: $\delta$ 2.05 (s, 3 H), 2.32–2.69 (m, 2 H), 2.71 (s, 3 H), 4.19–4.28 (m, 1 H), 5.11–5.19 (m, 2 H), 5.74–5.89 (m, 1 H), 6.56 (s, 1H), 6.95 (s, 1 H).

### *3.4. (1S, 2S)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N-methyl-5-benzyloxypentamide (**14**)*

To a solution of 5-benzyloxypentanoic acid (8.6 g, 41.35 mmol) in dry acetonitrile (170 mL) at 0 °C was added triethylamine (5.76 mL, 41.35 mmol) followed by pivaloyl chloride (5.1 mL, 41.35 mmol). Dry tetrahydrofuran (35 mL) was added to enable stirring of the thick white suspension. After being stirred at 0 °C for 30 min, a solution of 1*S*,2*S*-pseudoephedrine (7.5 g, 45.5 mmol) and triethylamine (6.34 mL, 45.5 mmol) in dry tetrahydrofuran (120 mL) was added rapidly via cannula. The reaction mixture was stirred between 0 and 5 °C for about 1 h, warmed to room temperature over a period of 2 h, and then quenched by the addition of water (50 mL). After removal of solvents under reduced pressure, the aqueous phase was extracted with dichloromethane ($3 \times 150$ mL). The combined organic phase was washed with 1 N aq. HCl (150 mL), saturated aq. $NaHCO_3$ (150 mL), brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography, eluting with a gradient of 3:7 ethyl acetate: hexane to 8:2 ethyl acetate: hexane, to furnish 12.74 g of **14** as a thick viscous liquid (87%).

$[\alpha]_D$: 78.98 ($c = 2.15$, chloroform).

IR (Film, cm$^{-1}$): 3392, 2936, 2863, 1622, 1455, 1405, 1104, 1051, 737, 700.

$^1$H NMR (mixture of rotamers): $\delta$ 0.97 and 1.1 (d, $J = 7$ Hz, 3 H, N—CH—$CH_3$, rotamers) 1.63–1.76 (m, 4 H), 2.23–2.48 (m, 2 H), 2.78 and 2.91 (s, 3 H, N—Me rotamers), 3.47–3.53 (m, 2 H), 4.40–4.48 (m, 1 H) 4.5 (s, 2 H), 4.53–4.59 (m, 1 H), 7.26–7.35 (m, 10 H).

$^{13}$C NMR (mixture of rotamers): 174.4 and 173.7 (C=O), 142.05, 141.68, 138.14, 138.10, 128.06, 127.93, 127.91, 127.85, 127.53, 127.25, 127.19, 127.11, 127.05, 126.51, 126.16, 75.49, 74.72, 72.42, 69.73, 69.64, 57.86, 56.72, 33.39, 32.79, 31.64, 28.95, 28.80, 26.56, 21.67, 21.36, 15.06, 13.94.

MS: $C_{22}H_{29}NO_3$, 356.3 ($MH^+$).

### *3.5. (1S,2S)-N-(2-Hydroxy-1-methyl-2-phenylethyl)-N,2-dimethyl-5-benzyloxypentamide (**15**)*

To a suspension of anhydrous LiCl (9 g, 211.2 mmol) in tetrahydrofuran (45 mL) was added diisopropylamine (11.1 mL, 79.2 mmol), and the resulting suspension was cooled to −78 °C in a dry ice-acetone bath. A solution of *n*-BuLi (1.6 M in hexanes,

45.8 mL, 73.22 mmol) was added dropwise via cannula. The resulting yellow suspension was stirred at 0 °C for 10 min and then cooled to −78 °C. An ice-cold solution of amide **14** (12.5 g, 35.2 mmol) in dry tetrahydrofuran (45 mL followed by 20 mL rinse) was added via cannula over a period of 10 min. The reaction mixture was stirred at −78 °C for 1 h, then stirred at 0 °C for 15 min, and finally stirred at room temperature for 5 min before being recooled to 0 °C. Methyl iodide was added, and the reaction mixture was stirred at 0 °C for 45 min. The reaction was quenched by the addition of saturated aq. $NH_4Cl$ solution (5 mL). The reaction mixture was partitioned between saturated aq. $NH_4Cl$ solution (300 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted with ethyl acetate ($2 \times 100$ mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude product was purified by flash chromatography, eluting with 3:7 ethyl acetate:hexane followed by 1:1 ethyl acetate: hexane to furnish 12.25 g of **15** as a thick viscous liquid (94%).

$[\alpha]_D$: 92.22 ($c = 2.4$, chloroform).

IR (Film, $cm^{-1}$): 3391, 2936, 2864, 1615, 1455, 1409, 1103, 1050, 738, 700.

$^1H$ NMR (mixture of rotamers): $\delta$ 0.96 and 1.01 (d, $J = 7$ Hz, 3 H, N—CH—$CH_3$, rotamers), 1.16 (d, $J = 7$ Hz, 3 H), 1.39–1.79 (m, 4 H), 2.59–2.68 (m, 1 H), 2.73 and 2.91 (s, 3 H, N—Me rotamers), 3.39–3.51 (m, 2 H), 4.29–4.45 (m, 1 H), 4.45 and 4.48 (s, 2 H, $C_6H_5CH_2$, rotamers), 4.54–4.61 (m, 1 H), 4.8–5.29 (brs, 1 H, OH), 7.24–7.37 (m, 10 H).

$^{13}C$ NMR (mixture of rotamers): 177.88 and 177.14 (C=O), 142.18, 141.79, 138.07, 128.06, 127.93, 127.91, 127.75, 127.53, 127.33, 127.24, 127.17, 127.14, 127.08, 126.94, 126.49, 125.97, 125.88, 75.54, 74.72, 72.48, 72.41, 69.88, 69.73, 58.20, 57.53, 35.67, 34.88, 32.75, 30.66, 30.28, 30.11, 27.09, 26.94, 26.85, 17.22, 17.05, 15.29, 13.95.

MS: $C_{23}H_{31}NO_3$, 370.3 ($MH^+$).

### *3.6. 2-Methyl-5-benzyloxypentanol (**16**)*

To a solution of lithium diisopropylamide in tetrahydrofuran (140 mL) [prepared from diisopropylamine (19.1 mL, 136.5 mmol) and *n*-BuLi (1.6 M solution in hexanes, 79.2 mL, 126.75 mmol)] at 0 °C was added $BH_3{\cdot}NH_3$ complex (4.5 g, 130 mmol) in one portion. The resulting suspension was stirred at 0 °C for 15 min, warmed to room temperature, and stirred for 15 min. The reaction mixture was then recooled to 0 °C, and amide **15** (12 g, 32.5 mmol) in tetrahydrofuran (85 mL followed by 20 mL rinse) was added via cannula. The reaction mixture was warmed to room temperature, stirred for 16 h, cooled to 0 °C and quenched by the addition of 3 N aq. HCl (330 mL) and then stirred at 0 °C for 30 min. The reaction mixture was extracted with diethyl ether ($3 \times 160$ mL), and the combined organic extracts were washed with 3 N aq. HCl (60 mL), 2 N aq. NaOH (60 mL), followed by brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was stirred with 1 N aq. NaOH (65 mL) for 1 h and extracted with diethyl ether ($3 \times 150$ mL). The combined organic phase was washed with water, brine, and dried ($Na_2SO_4$). After evaporation of the solvent, the crude alcohol was purified by flash chromatog-

raphy, eluting with 2:8 ethyl acetate: hexane, to afford 5.1 g of the alcohol **16** as a colorless liquid (75%).

IR (Film, $cm^{-1}$): 3391, 2936, 2870, 1496, 1455, 1361, 1205, 1099, 1029, 737, 698.

$^1H$ NMR: $\delta$ 0.93 (d, $J = 6.7$ Hz, 3 H), 1.1–1.3 (m, 1 H), 1.45–1.78 (m, 4 H), 3.41–3.51 (m, 4 H), 4.51 (s, 2 H), 7.26–7.35 (m, 5 H).

$^{13}C$ NMR: $\delta$ 138.09, 128.01 (2 C), 127.33 (2 C), 127.20, 72.54, 70.39, 67.21, 35.16, 29.25, 26.74, 16.3.

MS: $C_{13}H_{20}O_2$, 209.2 ($MH^+$).

### *3.7. 2-Methyl-5-benzyloxypentanal (**17**)*

To a cold (−78 °C) solution of oxalyl chloride (2.44 mL, 28 mmol) in dry dichloromethane (60 mL) was added dry dimethylsulfoxide (3.98 mL, 56 mmol). After 5 min, a solution of the alcohol **16** (4.2 g, 20 mmol) in dichloromethane (10 mL) was added via cannula, and the resulting white suspension was stirred at −78 °C for 30 min. Triethylamine (12.28 mL, 88 mmol) was then added, followed by 20 mL of dichloromethane to enable stirring of the thick suspension. After stirring at −30 °C for 40 min, the reaction mixture was diluted with pentane (300 mL). The organic phase was washed with 1 M aq. $NaHSO_3$ solution ($2 \times 100$ mL) followed by water ($2 \times 100$ mL). The combined organic layer was dried ($Na_2SO_4$), and the solvent was removed at reduced pressure (bath temperature 30–35 °C). Purification by flash chromatography, eluting with 2:8 ethyl acetate:hexane, afforded 3.44 g of the pure aldehyde **17** (84%).

$^1H$ NMR: $\delta$ 1.10 (d, $J = 6.7$ Hz, 3 H), 1.41–1.52 (m, 1 H), 1.61–1.71 (m, 2 H), 1.73–1.88 (m, 1 H), 2.04–2.39 (m, 1 H), 3.48 (t, $J = 6$ Hz, 2 H), 4.52 (s, 2 H), 7.26–7.38 (m, 5 H), 9.61 (d, $J = 4$ Hz, 1 H, CHO).

$^{13}C$ NMR: $\delta$ 204.83, 138.09, 128.27 (2 C), 127.50 (2 C), 127.46, 72.82, 69.82, 45.93, 27.04 (2 C), 13.24.

### *3.8. 3-(2R,3S,4S)-(2,4-Dimethyl-3-hydroxy-7-benzyloxyheptanoyl)-(4S)-4-benzyl-2-oxazolidinone (**18**)*

To a solution of (*S*)-4-benzyl-3-propionyloxazolidinone (7.78 g, 33.4 mmol) in dichloromethane (48 mL) at −78 °C was added di-*n*-butylboron triflate (1.0 M solution in dichloromethane, 36.74 mL, 36.74 mmol) over a period of 50 min. The solution turned orange during the addition. After completion of the addition, triethylamine (5.6 mL, 40.08 mmol) was added over a period of 10 min. The resulting pale yellow reaction mixture was stirred at 0 °C for 45 min, recooled to −78 °C, and then aldehyde **17** (3.44 g, 16.7 mmol) was added in one portion (neat, followed by 2 mL rinse with dichloromethane). The reaction mixture was stirred at −78 °C for 30 min and then at 0 °C for 2 h. The reaction was quenched by the addition of aq. phosphate buffer (pH 7, 72 mL) followed by slow addition of 30% aq. $H_2O_2$ (7.2 mL), and the reaction mixture was stirred at 5 °C for 30 min. The aqueous phase was separated and extracted with dichloromethane ($2 \times 100$ mL). The combined organic phase was washed once with water (100 mL), brine, dried ($Na_2SO_4$), and concentrated under reduced

pressure. The crude reaction mixture was purified by flash chromatography, eluting with 2:8 ethyl acetate:hexane followed by 3:7 ethyl acetate: hexane, to afford 14 g of the aldol product **18** as a 96:4 mixture of diastereomers (95%).

$^1$H NMR (major diastereomer): $\delta$ 0.89 (d, $J = 6.8$ Hz, 3 H), 1.23 (d, $J = 7$ Hz, 3 H), 1.49–1.86 (m, 5 H), 2.77 (dd, $J = 13.4$, 9.5 Hz, 1 H), 2.99 (brs, 1 H), 3.25 (dd, $J = 13.3$, 3.2 Hz, 1 H), 3.43–3.54 (m, 2 H), 3.62 (dd, $J = 9$, 2 Hz, 1 H), 3.95 (dd, $J = 9$, 3.2 Hz, 1 H), 4.15–4.27 (m, 2 H), 4.5 (s, 2 H), 4.64–4.74 (m, 1 H), 7.21–7.53 (m, 10 H).

$^{13}$C NMR (major diastereomer): $\delta$ 177.83, 152.82, 138.55, 135.00, 129.37 (2 C), 128.90 (2 C), 128.28 (2 C), 127.59 (2 C), 127.42, 127.36, 75.03, 72.81, 70.78, 66.08, 55.10, 39.46, 37.69, 35.46, 29.11, 26. 80, 15.36, 9.63.

### *3.9. (2R,3S,4S)-N-Methoxy-N-2,4-trimethyl-3-hydroxy-7-benzyloxyheptanamide (**19**)*

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (9.15 g, 93.8 mmol) in dry tetrahydrofuran (55 mL) at −5 °C was added trimethylaluminum (2.0 M solution in hexanes, 48 mL, 96 mmol) via cannula (with gas evolution during initial addition), and the resulting clear solution was stirred at room temperature for 45 min. It was recooled to −5 °C, and a solution of the aldol product **18** (13.73 g, 31.24 mmol) in tetrahydrofuran (55 mL) was added via cannula. The reaction mixture turned cloudy but became clear after 15–20 min. The reaction mixture was gradually warmed to room temperature over 16 h, cannulated into saturated aq. Rochelle salt solution (150 mL), and stirred for 1 h. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic phases were washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography, eluting with 1:1 *t*-butyl methyl ether:hexane to afford 8.00 g of the pure diastereomer **19** as a viscous oil (80%).

$[\alpha]_D$: −11.97 (c = 1.57, chloroform).

IR (Film, $cm^{-1}$): 3460, 2937, 2872, 1651, 1456, 1386, 1101, 993, 739, 699.

$^1$H NMR: $\delta$ 0.86 (d, J = 6.8 Hz, 3 H), 1.14 (d, $J = 6.3$ Hz, 3 H), 1.19–1.28 (m, 1 H), 1.49–1.64 (m, 2 H), 1.72–1.87 (m, 2 H), 3.08–3.10 (m, 1 H), 3.19 (s, 3 H), 3.43–3.53 (m, 3 H), 3.69 (s, 3 H), 3.99 (s, 1 H), 4.50 (s, 2 H), 7.24–7.34 (m, 5 H).

$^{13}$C NMR: $\delta$ 178.44, 138.56, 128.17 (2 C), 127.49 (2 C), 127.28, 75.21, 72.22, 70.85, 61.37, 35.45, 35.06, 31.80, 28.79, 26.84, 15.32, 9.61.

MS: $C_{18}H_{29}NO_4$, 324.2 ($MH^+$).

### *3.10. (2R,3S,4S)-N-Methoxy-N,2,4-trimethyl-3-(t-butyldimethylsilyoxy)-7-benzyloxyheptanamide (**20**)*

To a solution of Weinreb amide **19** (8.00 g, 25 mmol) in dichloromethane (60 mL) at 0 °C was added 2,6-lutidine (10.2 mL, 87.5 mmol) followed by *t*-butyldimethylsilyl triflate (12 mL, 52.25 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with

dichloromethane (2 × 100 mL). The combined organic layers were washed with water, brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography, eluting with 2:8 ethyl acetate:hexane. The product obtained after the evaporation of solvent was taken up in dichloromethane (45 mL) and hexane (150 mL), concentrated under reduced pressure, and dried at high vacuum for 16 h to afford 10.5 g of the silyl ether **20** as a colorless liquid (96%).

IR (Film, $cm^{-1}$): 2935, 2857, 1652, 1463, 1385, 1257, 1053, 997, 837, 775, 698.

$^1H$ NMR: $\delta$ −0.06 (s, 3 H), −0.58 (s, 3 H), 0.85 (s, 9 H), 0.88 (d, $J = 6.8$ Hz, 3 H), 1.07 (d, $J = 6.9$ Hz, 3 H), 0.91–1.08 (m, 1 H), 1.35–1.67 (m, 4 H), 3.06 (s, 3 H), 3.02–3.06 (m, 1 H), 3.37 (5, $J = 6.5$ Hz, 2 H), 3.57 (s, 3 H), 3.81 (dd, $J = 8.2$, 2 Hz, 1 H), 4.42 (s, 2 H), 7.19–7.28 (m, 5 H).

$^{13}C$ NMR: 176.81, 138.35, 127.92 (2 C), 127.19 (2 C), 127.05, 76.33, 72.45, 70.47, 60.97, 38.43, 37.76, 31.90, 27.77, 27.59, 25.79 (3 C), 18.02, 16.00, 15.26, −4.21, −4.28.

MS: $C_{24}H_{43}NO_4Si$, 438.4 ($MH^+$).

### *3.11. (2R,3S,4S)]-2,4-Dimethyl-3-(t-butyldimethylsilyoxy)-7- benzyloxyheptanal (**21**)*

To a cold solution (−78 °C) of the silylated Weinreb amide **20** (10.4 g, 24 mmol) in tetrahydrofuran (90 mL) was added di-iso-butylaluminumhydride (1.0 M solution in toluene, 50 mL, 50 mmol) over a period of 30 min. The reaction mixture was stirred for 30 min at −78 °C after the completion of addition and then warmed to −50 °C over a period of 30 min. Excess di-iso-butylaluminumhydride was quenched by the addition of methanol (1.5 mL, 37 mmol) at −78 °C, and the reaction mixture was then stirred for 30 min. The reaction mixture was cannulated into a saturated aq. Rochelle salt solution (250 mL). Dichloromethane (100 mL) was added and the mixture was stirred at room temperature for 30 min. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic phase was washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure (bath temperature 30–35 °C). The crude aldehyde was purified on a short silica gel column, eluting with 2:8 ethyl acetate:hexane, to provide 8.1 g of aldehyde **21** (91%).

$^1H$ NMR: $\delta$ 0.0 (s, 3 H), 0.06 (s, 3 H), 0.87 (s, 9 H), 0.92 (d, $J = 7$ Hz, 3 H), 1.1 (d, $J = 7$ Hz, 3 H), 1.09–1.16 (m, 1 H), 1.46–1.78 (m, 4 H), 2.36–2.52 (m, 1 H), 3.45 (t, $J = 6.5$ Hz, 2 H), 4.00 (dd, $J = 5.5$, 3.6 Hz, 1 H), 4.5 (s, 2 H), 7.26 - 7.38 (m, 5 H), 9.72 (d, $J = 1$ Hz, 1 H).

$^{13}C$ NMR: 205.06, 138.47, 128.26 (2 C), 127.55 (2 C), 127.42, 74.80, 72.87, 70.46, 49.80, 37.94, 29.02, 27.66, 25.85 (3 C), 18.16, 15.79, 8.59, −4.25 (2 C).

### *3.12. (5R,6S,7S-)-3,3,5,7-Tetramethyl-6-(t-butyl)dimethylsilyloxy-10-benzyloxy-dec-1-ene-4-one (**22**)*

To a cold solution (0 °C) of aldehyde **21** (8 g, 21.34 mmol) in THF (40 mL) was added dropwise a solution (0.78 M, 45 mL, 35 mmol) of prenylmagnesium chloride

[prepared from prenyl chloride (5.65 mL, 50 mmol) and Mg turnings (3.65 g, 150 mmol mmol) in tetrahydrofuran (64 mL)], and the reaction mixture was stirred at room temperature for 1 h and quenched by the addition of saturated aq. $NH_4Cl$ solution (40 mL). The residue obtained after evaporation of the solvent under reduced pressure was extracted with dichloromethane ($2 \times 100$ mL). The combined organic phase was washed with brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. Purification by flash chromatography, eluting with 2:98 ethyl acetate:hexane followed by 5:95 ethyl acetate:hexane, afforded 9.00 g of the alcohol as a mixture of diastereomers (94%).

To a solution of the diastereomeric mixture of alcohols (9.00 g, 20 mmol) in dichloromethane:acetonitrile (4:1, 45 mL) were added powdered 4 Å molecular sieves (10 g) and anhydrous *N*-methylmorpholine-*N*-oxide (4.7 g, 40 mmol), followed by tetra-*n*-propylammonium perruthenate (705 mg, 2 mmol). The resulting dark colored suspension was stirred at room temperature for 2 h, followed by solvent removal under reduced pressure. The residue was purified by flash chromatography, using a column with a small quantity of celite on top, eluting with 2:98 *t*-butyl methyl ether:hexane followed by 5:95 ethyl acetate:hexane, to afford 6.8 g of ketone **22** (76%) as a pale yellow liquid.

IR (Film, $cm^{-1}$): 2932, 2857, 1703, 1634, 1463, 1362, 1256, 1114, 987, 877, 837, 775, 735, 697.

$^1H$ NMR: $\delta$ 0.0 (s, 6 H), 0.84 (s, 9 H), 0.85 (d, $J = 5.6$ Hz, 3 H), 0.97 (d, $J = 7$ Hz, 3 H), 1.01–1.11 (m, 1 H), 1.14 (s, 3 H), 1.17 (s, 3 H), 1.2–1.43 (m, 3 H), 1.58–1.68 (m, 1 H), 3.08 (quintet, $J = 7$ Hz, 1 H), 3.38 (t, $J = 6.4$ Hz, 2 H), 3.75 (dd, $J = 8$, 2 Hz, 1 H), 4.44 (s, 2 H), 5.07 (dd, 2 H), 5.87 (dd, $J = 17$, 11 Hz, 1 H), 7.19–7.29 (m, 5 H).

$^{13}C$ NMR: $\delta$ 216.15, 142.31, 138.56, 128.21 (2 C), 127.44 (2 C), 127.35, 114.21, 76.99, 72.75, 70.76, 51.35, 44.36, 38.63, 27.95, 27.26, 26.13 (3 C), 23.95, 23.72, 18.39, 17.26, 16.67, −3.79, −3.82.

### *3.13. (5R,6S,7S-)-2,2,4,6-tetramethyl-5-(t-butyl)dimethylsilyloxy-9-benzyloxynonanal (**23**)*

To a solution of ketone **22** (6.8 g, 15.22 mmol) in a mixture of tetrahydrofuran (24 mL) and *t*-butanol (12 mL) was added water (6 mL), followed by *N*-methylmorpholine-*N*-oxide (2.2 g, 18.78 mmol) and osmium tetroxide (2.5 wt % solution in *t*-butanol, 8 mL, 0.787 mmol). The resulting yellow solution was stirred at room temperature for 16 h. The reaction was quenched by the addition of $Na_2SO_3$ (8.35 g) followed by water (150 mL), and the resulting dark reaction mixture was stirred at room temperature for 45 min. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate ($2 \times 100$ mL). The combined organic phase was washed once with water followed by brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 2:8 ethyl acetate:hexane followed by 1:1 ethyl acetate:hexane. The diol was isolated as a thick viscous liquid slightly contaminated with *t*-butanol and was used for the next reaction without further purification.

To a solution of the diol in tetrahydrofuran (75 mL), $NaIO_4$ (5 g, 23.38 mmol) was added in one portion followed by water (75 mL), and the resulting colorless slurry was stirred at room temperature for 6 h. The reaction mixture was diluted with dichloromethane (100 mL). The organic layer was separated, and the aqueous phase was extracted with dichloromethane ($2 \times 100$ mL). The combined organic layer was washed with water, brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 2:8 ethyl acetate:hexane, to afford 6.29 g of the aldehyde **23** (92% for 2 steps).

$^1$H NMR: $\delta$ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.89 (s, 9 H), 0.91 (d, $J = 7$ Hz, 3 H), 1.02 (d, $J = 7.3$ Hz, 3 H), 1.01–1.25 (m, 1 H), 1.32 (s, 3 H), 1.33 (s, 3 H), 1.25–1.53 (m, 2 H), 1.65–1.74 (m, 2 H), 3.05 (quintet, $J = 7$ Hz, 1 H), 3.45 (t, $J = 7.6$ Hz, 2 H), 3.86 (dd, $J = 7.6$, 2.6 Hz, 1 H), 4.49 (s, 2 H), 7.22–7.35 (m, 5 H), 9.59 (s, 1 H).

$^{13}$C NMR: $\delta$ 212.29, 200.54, 138.53, 128.19 (2 C), 127.46 (2 C), 127.34, 76.35, 72.76, 70.49, 60.97, 45.31, 38.96, 27.88 (2 C), 26.03 (3 C), 19.83, 19.72, 18.31, 16.61, 15.38, −3.97 (2 C).

### *3.14. Methyl(3R,6R,7S,8S)-3,7-di-(t-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-11-benzyloxyundecanoate and methyl (3S,6R,7S,8S)-3,7-di-(t-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo- 11-benzyloxyundecanoate (**24**)*

To a solution of aldehyde **23** (6.3 g, 14.1 mmol) in dry dichloromethane at −78 °C was added $BF_3 \cdot Et_2O$ (1.8 mL, 14.2 mmol), and the reaction mixture was stirred for 5 min. The silyl ketene acetal, 1-*t*-butyldimethylsilyloxy-1-methoxyethene (3.2 g, 16.9 mmol), was added, and the reaction mixture was stirred at −78 °C for 5 h. The reaction was quenched by the addition of aq. phosphate buffer (pH 7) and extracted with dichloromethane ($3 \times 100$ mL). The combined organic phase was washed once with water, brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 95:5 ethyl acetate:hexane followed by 2:8 ethyl acetate:hexane to afford 7.1 g of the aldol product (97%) as a mixture of diastereomers (2.6:1) epimeric at C-3.

To a solution of the above aldol product (7.1 g, 13.62 mmol) in dichloromethane (55 mL) at 0 °C was added 2,6-lutidine (6 mL, 51.5 mmol) followed by *t*-butyldimethylsilyl triflate (6.5 mL, 28.3 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction was quenched by the addition of saturated aq. $NaHCO_3$ solution (50 mL), and the reaction mixture was then filtered through celite to clarify the thick emulsion. The organic layer was separated, and the aqueous layer was extracted with dichloromethane ($2 \times 100$ mL). The combined organic phase was washed with water, brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was taken up in dichloromethane (15 mL) and hexane (50 mL), and concentrated under reduced pressure to remove 2,6-lutidine. This residue was purified by flash chromatography, eluting with 5:95 ethyl acetate:hexane, and the resulting purified material was dried under high vacuum for 16 h to afford 8.4 g of silyl ether **24** (mixture of diastereomers epimeric at C-3, 2.6:1) as a colorless liquid (97%).

IR (Film, $cm^{-1}$): 2931, 2857, 1744, 1695, 1472, 1361, 1256, 1097, 988, 837, 776, 734, 698.

$^1$H NMR (major diastereomer): $\delta$ 0.01 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.87 (s, 9 H), 0.91 (s, 9H). 0.90 (d, $J = 6.8$ Hz, 3 H), 1.05 (d, $J = 6.8$ Hz, 3 H), 1.08 (s, 3 H), 1.23 (s, 3 H), 1.26–1.45 (m, 4 H), 1.58–1.78 ( m, 1 H), 2.22 (dd, $J = 16$, 7.1 Hz, 1 H), 2.36 (dd, $J = 16$, 3 Hz, 1 H), 3.09 (quintet, $J = 7$ Hz, 1 H), 3.42 ( t, 2 H), 3.61 (s, 3 H), 3.74 (dd, $J = 7.5$, 1.8 Hz, 1 H), 4.35 (dd, $J = 7$, 3 Hz, 1 H), 4.44 (s, 2 H), 7.22–7.5 (m, 5 H).

### *3.15. Methyl(3S,6R,7S,8S)-3,7-di-(t-butyldimethylsilyloxy)-4,4,6,8-tetramethyl-5-oxo-11-hydroxyundecanoate (**25**)*

To a solution of silyl ether **24** (3 g, 4.7 mmol) in methanol (15 mL) was added Pearlman's catalyst (10% $Pd(OH)_2$ on carbon, 500 mg, purchased from Aldrich), and the reaction mixture was stirred at room temperature under a hydrogen atmosphere maintained with a balloon for 7 h. The reaction mixture was filtered through celite, and the celite pad was washed with ethyl acetate ($3 \times 60$ mL). The combined ethyl acetate filtrate was concentrated under reduced pressure. The crude reaction mixture was purified by flash chromatography, eluting first with 5:95 ethyl acetate:hexane followed by 1:9 ethyl acetate:hexane, to afford 1.75 g of the major diastereomer **25** (68%).

IR (Film, cm$^{-1}$): 3445, 2955, 2858, 1745, 1695, 1473, 1373, 1257, 1090, 989, 837, 776, 670.

$^1$H NMR: $\delta$ −0.05 (s, 3 H), 0.00 (s, 6 H), 0.04 (s, 3 H), 0.81 (s, 9 H), 0.84 (s, 9 H), 0.87 (d, $J = 6.8$ Hz, 3 H), 0.99 (d, $J = 6.9$ Hz, 3 H), 1.03 (s, 3 H), 1.16 (s, 3 H), 1.19–1.66 (m, 6 H), 2.22 (dd, $J = 16$, 7.1 Hz, 1 H), 2.36 (dd, $J = 16$, 3 Hz, 1 H), 3.09 (quintet, $J = 7$ Hz, 1 H), 3.57 (t, $J = 6.6$ Hz, 2 H), 3.61 (s, 2 H), 3.73 (dd, $J = 7.3$, 2 Hz, 1 H), 4.34 (dd, $J = 7$, 3 Hz, 1 H).

$^{13}$C NMR: $\delta$ 218.53, 172.91, 77.95, 73.94, 63.61, 53.89, 52.03, 45.51, 40.51, 38.87, 31.35, 27.19, 26.58 (3 C), 26.34 (3 C), 24.08, 19.38, 18.86, 18.56, 18.04, 16.10, −3.29, −3.39, −4.12, −4.24.

HRMS (FAB) *m/z* calculated for $C_{28}H_{58}O_6Si_2$ $(M + H)^+$ 547.3850. Found 547.3849.

Elution of the column with 1:1 ethyl acetate:hexane afforded 670 mg of the minor diastereomer **26** (26%).

$^1$H NMR: $\delta$ −0.04 (s, 3 H), −0.01 (s, 3 H), 0.00 (s, 6 H), 0.78 (s, 9 H), 0.83 (s, 9 H), 0.87 (d, $J = 6.8$ Hz, 3 H), 0.98 (d, $J = 7$ Hz, 3 H), 1.01–1.1 (m, 4 H), 1.14 (s, 3 H), 1.17–1.65 (m, 5 H), 2.24 (dd, $J = 16$, 6.7 Hz, 1 H), 2.33 (dd, $J = 16$, 3.8 Hz, 1 H), 3.07 (quintet, $J = 7$ Hz, 1 H), 3.55 (t, $J = 6.6$ Hz, 2 H), 3.61 (s, 2 H), 3.75 (dd, $J = 7.3$ Hz, 1.8 Hz, 1 H), 4.48 (dd, $J = 6.7$ Hz, 3.8 Hz, 1 H).

### *3.16. Methyl (3S,6R,7S,8S)-3,7-bis [(t-butyl) dimethylsilyloxy]-4,4,6,8-tetramethyl-5-oxoundec-11-enoate (**6**)*

To a solution of alcohol **25** (4.2 g, 7.68 mmol) in dry tetrahydrofuran (12 mL) and pyridine (4 mL) was added *o*-nitrophenyl selenocyanate (4.36 g, 19.2 mmol), followed by tri-*n*-butylphosphine (4.8 mL, 19.3 mmol), and the resulting dark red suspension was stirred under argon at room temperature in the dark for 16 h. Solvent

was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 5:95 ethyl acetate:hexane followed by 1:9 ethyl acetate:hexane, to afford 5.4 g of the selenide as a yellow viscous liquid (96%).

To a solution of the selenide (5.4 g, 7.4 mmol) in dichloromethane (15 mL) at −15 °C was added *m*-chlorobenzoic acid (57–86%, 2.7 g) in one portion. The reaction mixture became a red suspension, which was stirred at −15 °C for 30 min. Diisopropylamine (2.2 mL, 15.7 mmol) was added, and the resulting dark red solution was warmed to room temperature and stirred for 30 min. Water was added followed by saturated aq. $NaHCO_3$, and the reaction mixture was extracted with ethyl acetate ($3 \times 100$ mL). The combined organic phase was washed with saturated aq. $NaHCO_3$, followed by brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 2:98 ethyl acetate:hexane followed by 5:95 ethyl acetate:hexane, to afford 2.6 g of olefin **6** as a yellow oil (67%).

IR (Film, $cm^{-1}$): 2956, 2858, 1747, 1695, 1641, 1472, 1297, 1256, 1091, 989, 837, 776, 668.

$^1H$ NMR: $\delta$ 0.01 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.87 (s, 9 H), 0.89 (d, $J = 6$ Hz, 3 H), 0.91 (s, 9 H), 1.05 (d, $J = 7$ Hz, 3 H), 1.08 (s, 3 H), 1.23 (s, 3 H), 1.35 - 1.45 (m, 1 H), 1.79–1.90 (m, 1 H), 2.27 (dd overlapped with a multiplet, $J = 16$, 7 Hz, 2 H), 2.42 (dd, $J = 16$, 3 Hz, 1 H), 3.16 (quintet, $J = 7$ Hz, 1 H), 3.67 (s, 3 H), 3.82 (dd, $J = 8$, 1.8 Hz, 1 H), 4.41 (dd, $J = 7$, 3.2 Hz, 1 H), 4.97–5.03 (m, 2 H), 5.66–5.79 (m, 1 H).

$^{13}C$ NMR: $\delta$ 217.98, 172.37, 137.76, 115.68, 77.65, 73.66, 53.50, 51.59, 45.62, 40.19, 38.00, 35.16, 26.24 (6 C), 25.96 (3 C), 23.68, 19.11, 18.54, 18.18, 18.00, 15.72, −3.53, −3.66, −4.51, −4.63.

### *3.17. Methyl (3S,6R,7S,8S,12Z,15S,16E)-3,7,15-Tri-(t-butyldimethylsilyloxy)-4,4,6,8,12,16-hexamethyl-17-(2-methylthiazol-5-yl)-5-oxoheptadeca-12,16 dienoate (**27**)*

To a solution of olefin **6** (2.5 g, 4.73 mmol) in dry tetrahydrofuran under argon was added a solution of 9-borabicyclo[3.3.1]nonane (0.4 M solution in tetrahydrofuran, 24 mL, 9.6 mmol), and the reaction mixture was stirred at room temperature for 6 h. In a separate flask, cesium carbonate (3.1 g, 9.5 mmol) was added to a solution of the vinyl iodide (**5**, 2.85 g, 6.15 mmol) in dry dimethylformamide under vigorous stirring, followed by triphenylarsine (156 mg, 0.51 mmol), $PdCl_2$(dppf) (416 mg, 0.51 mmol), and water. To this flask was added the borane solution via cannula. The orange reaction mixture turned dark brown for a brief period and then to pale yellow over several hours. The reaction mixture was stirred at room temperature for 14 h, poured into water, and the aqueous phase was extracted with diethyl ether. The combined ether layer was washed with water followed by brine, dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 5:95 ethyl acetate:hexane, to afford 4.25 g of the ester **27** as yellow oil (84%).

IR (Film, $cm^{-1}$): 2931, 2858, 1744, 1695, 1472, 1361, 1256, 1084, 989, 837, 776, 669.

$^1$H NMR: $\delta$ −0.05 (s, 6H), −0.04 (s, 3 H), −0.01 (s, 3H), 0.00 (s, 3H), 0.04 (s, 3 H), 0.84 (d, $J = 6$ Hz, 3 H), 0.84 (s, 9 H), 0.83 (s, 9 H), 0.81 (s, 9 H), 0.98 (d, $J = 6.8$ Hz, 3 H), 1.01 (s, 3 H), 1.04–1.39 (m, 6 H), 1.17 (s, 3 H), 1.57 (s, 3 H), 1.94 (singlet overlapped with a multiplet, 4 H), 2.21 (dd, $J = 16$, 7 Hz, overlapped with a multiplet, 3 H), 2.37 (dd, $J = 16$, 3 Hz, 1 H), 2.66 (s, 3 H), 3.08 (quintet, $J = 7$ Hz, 1 H), 3.62 (s, 3 H), 3.71 (dd, $J = 7$, 1.7 Hz, 1 H), 4.03 (t, $J = 6.6$ Hz, 1 H), 4.34 (dd, $J = 7$, 3 Hz, 1 H), 5.08 (t, $J = 6$ Hz, 1 H), 6.40 (s, 1 H), 6.86 (s, 1 H).

$^{13}$C NMR: $\delta$ 217.9, 173.5, 164.0, 153.5, 142.8, 136.8, 121.1, 118.6, 114.9, 78.6, 76.8, 73.5, 53.5, 51.2, 45.1, 40.1, 38.9, 35.5, 32.4, 30.9, 26.1 (3 C), 25.9 (3 C), 25.2 (3 C), 23.2, 19.1, 19.2, 18.2, 18.3, 18.0, 16.1, 14.5, −3.2, −4.1, −4.5.

HRMS (FAB) *m/z* calculated for $C_{46}H_{87}NO_6SSi_3$ $(M + H)^+$ 866.5640. Found 866.5628.

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