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An efficient synthesis of the C27–C45 fragment of lagunamide A, a cyclodepsipeptide with potent cytotoxic and antimalarial properties

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ABSTRACT

An efficient and stereoselective synthesis of the entire C27–C45 moiety of lagunamide A has been achieved from 1-[(4*S*)-4-benzyl-2-thioxothiazolidin-3-yl]propan-1-one in six steps with 22% overall yield. The key step in the synthesis is an asymmetric acetal aldol reaction featuring the enantioselective addition of a chiral thiazolidinethione-derived titanium enolate to an acetal to establish the stereochemistry at C39.

1. Introduction

Cyclodepsipeptide natural products often display remarkable biological activities along with their complex molecular scaffolds, making them interesting targets for chemical synthesis.[1] Lagunamides A and B were first isolated from the marine cyanobacterium *Lyngbya majuscule*, collected from Pulau Hantu Besar (Singapore).[2] These cyclodepsipeptides showed highly potent inhibitory activity against P383 murine leukemia cell lines with IC_{50} values of 6.4 and 20.5 nM, respectively. Furthermore, lagunamides A and B exhibited significant antimalarial properties with IC_{50} values of 0.19 and 0.91 μM, respectively, when tested against *Plasmodium falciparum*. Tan et al. have reported that lagunamide A possesses a 26-membered macrocycle and eleven stereogenic centers, which consists of a novel polyketide moiety, an α-hydroxy acid unit, two L-amino acids, and three *N*-methyl amino acid residues. In 2012, the first successful synthesis of lagunamide A was achieved by Dai et al.[3] Six diastereomers of lagunamide A were synthesized, and analysis of their NMR spectra led to a correction of the stereochemistry at C7 and C39 to the (*S*)- and (*R*)-configurations, respectively (Fig. 1). More recently, Wei et al. have prepared lagunamide A (3.0%, 20 steps) and its analogues from commercially available

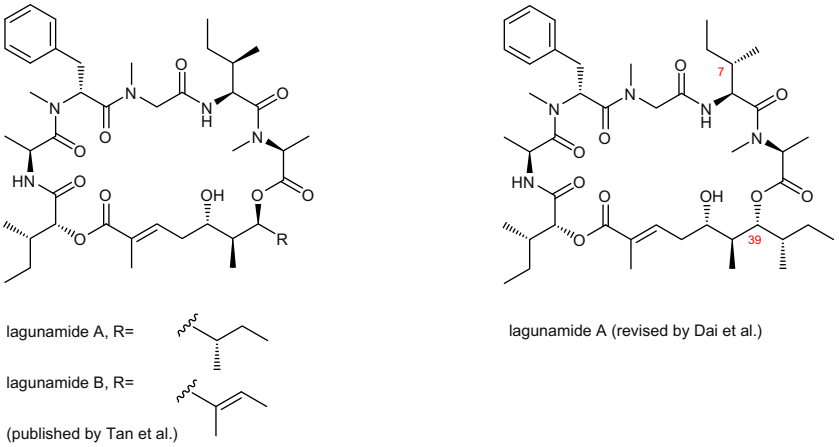

Figure 1. The structures of lagunamides A and B.

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(*S*)-2-methylbutanol.[4] Our retrosynthetic approach to lagunamide A, as shown in Scheme 1, features a disconnection of the macrocycle to polypeptide moiety **1** and unsaturated carboxyl derivative **2**. We focused on the generation of the *syn*-1,3-diol portion of **2** and built the stereogenic centers of this subunit from readily available thiazolidinethione **5** and (*S*)-1,1-dimethoxy-2-methylbutane **6**.

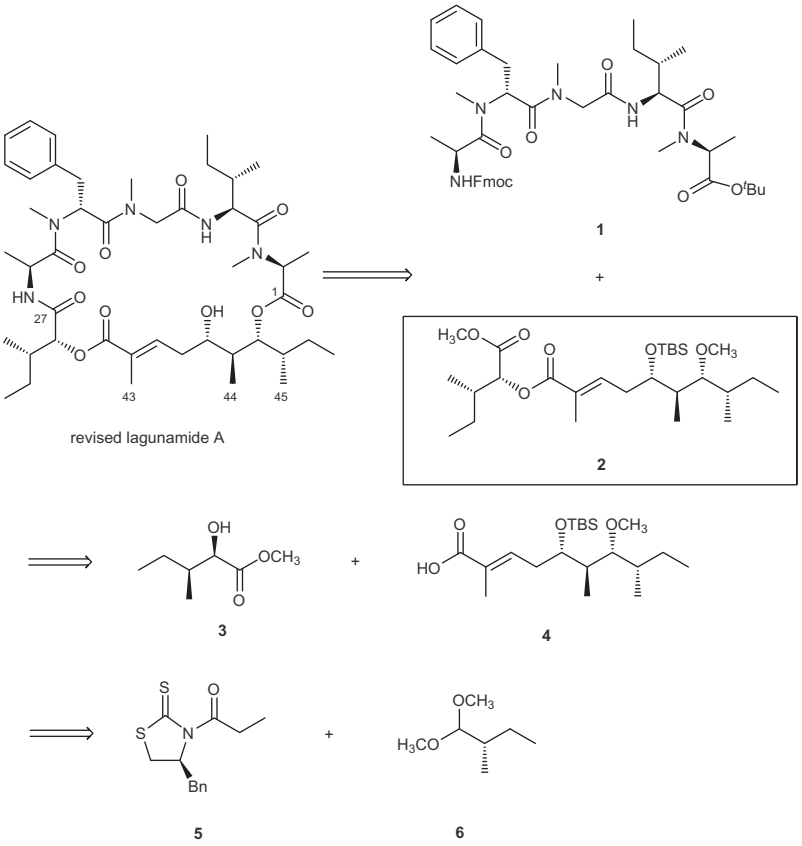
2. Results and discussion

The reaction of (*S*)-2-methylbutanal **7**[4,5] with methanol and catalytic *p*-toluenesulfonic acid (*p*-TsOH) gave chiral acetal **6** as a colorless liquid in 78% yield.[6] Following the conditions described by Crimmins[6] and Urpí,[7] the acetal aldol reaction of dimethyl acetal **6** with thiazolidinethione **5** provided the methylated aldol adduct **8** in an 82:18 diastereomeric ratio and 62% yield after purification. Reductive cleavage of the chiral auxiliary with diisobutylaluminium hydride (DIBAL-H) afforded the corresponding aldehyde,[8] which decomposed during chromatographic purification. A two-step sequence involving reduction (DIBAL-H, CH_2Cl_2, −84 °C) and Grignard addition (allylmagnesium chloride, THF, 0 °C) produced the desired adduct **9a** and its diastereomer **9b** in 99% yield in a 2:3 ratio. This stereoselectivity can be explained using the transition state model proposed by Felkin et al.[9] The inversion of configuration at the C37 hydroxy group in **9b** was performed through Dess–Martin periodinane (DMP) oxidation of **9b** to yield ketone **10** (74%), followed by stereoselective reduction to afford alcohols **9a** and **9b** (α/β = 8/1) in 95% yield (Scheme 2).

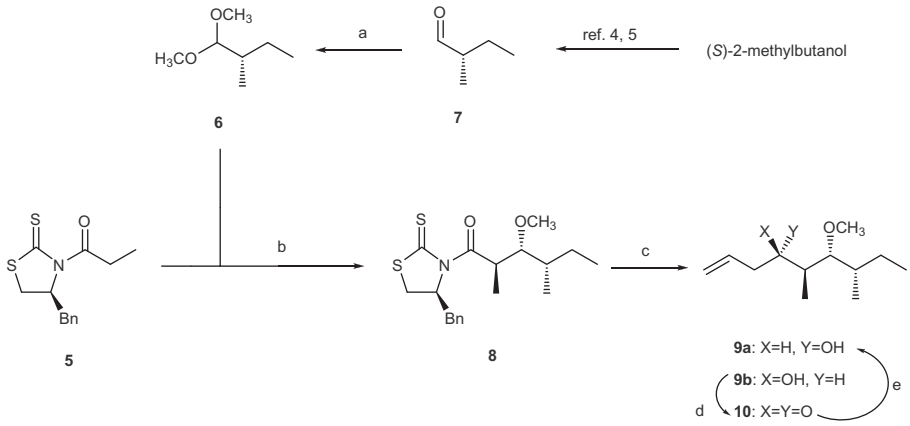
The stereochemistry of **9a** was confirmed by examining the spectra of the corresponding acetonide **12**, which was synthesized in 85% yield over two steps. The methyl ether was deprotected with iodotrimethylsilane (TMSI) generated in situ,[10] and the resulting diol **11** was re-protected by treatment with 2,2-dimethoxypropane (Scheme 3). The ^{13}C NMR chemical shifts of the acetonide methyl groups and the ketal carbon were 19.5, 30.1, and 97.6 ppm, respectively. These values are characteristics of *syn*-1,3-diol acetonides (19.4 ± 0.21, 30.0 ± 0.15, and 98.1 ± 0.83) and are clearly distinguishable from those observed for *anti*-1,3-diol acetonides (24.6 ± 0.76, 24.6 ± 0.76, and 100.6 ± 0.25).[11]

The next step in our route was the olefin cross-metathesis of **9a** with methyl methacrylate catalyzed by a Grubbs catalyst (1st or 2nd generation).[5,12] However, the reaction in CH_2Cl_2 at ambient temperature or at reflux resulted in the formation of a complex mixture of products. Fortunately, protection of the free hydroxyl group of **9a** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) afforded olefin **13** in excellent yield (94%),[13] and olefin **13** underwent cross-metathesis with methyl methacrylate in CH_2Cl_2 at 50 °C over 16 h to produce the desired alkene **14** in 59% yield.[14] The ^1H NMR singlets for the methyl groups were observed at δ 3.32 and 3.74 ppm, and suggested the presence of a methoxy group and a methyl ester group, respectively. NOESY analysis was used to determine the stereochemistry of alkene **14**. An NOE was observed between H-35/CH_2-36, but no NOE was observed between H-35/CH_3-43, thus establishing the *E*-geometry of the double bond. The methyl ester of **14** was converted into a carboxyl group by saponification in an alkaline/THF solution for 3 days and then the unsaturated carboxylic acid **15** was obtained in 97% yield.

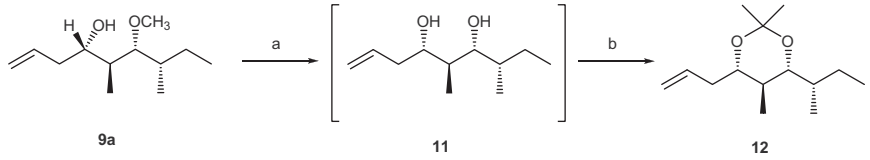
The amino group of D-allo-isoleucine was then diazotized to a hydroxyl group with retention of configuration,[15] and esterification of the resulting α-hydroxy carboxylic acid **16** gave methyl α-hydroxy ester **17**, obtained in 70% yield over two steps. The final assembly of the C27–C45 fragment of lagunamide A was accomplished by condensation of alcohol **17** with unsaturated carboxylic



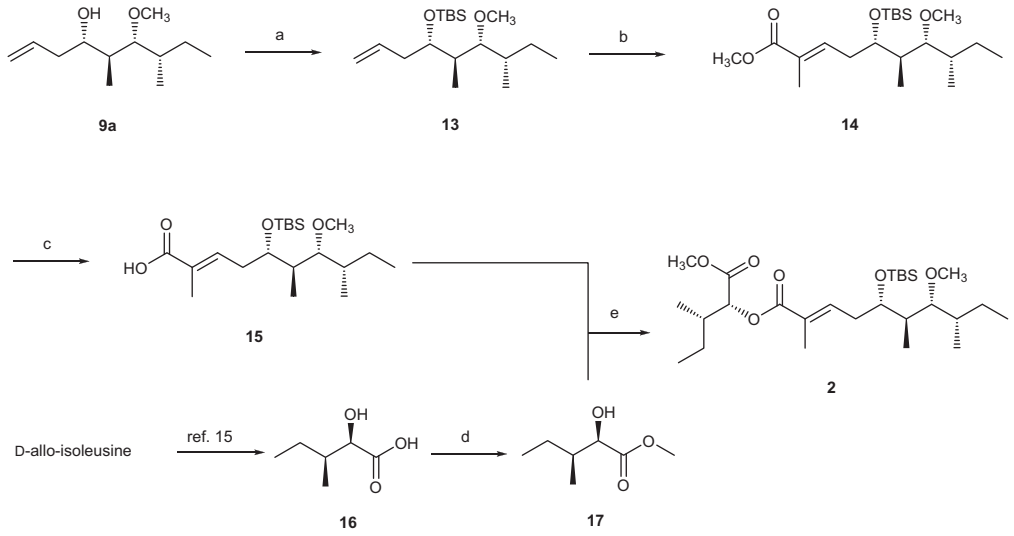
Scheme 1. Retrosynthesis of the C27–C45 fragment of lagunamide A.



Scheme 2. Reagents and conditions: (a) CH_3OH, *p*-TsOH, rt, 24 h, 78%; (b) $TiCl_4$, DIPEA, CH_2Cl_2, 0 °C, 1 h, then $SnCl_4$, **6**, −84 °C to 0 °C, 62%; (c) (i) DIBAL-H, CH_2Cl_2, −84 °C, 10 min, (ii) allylmagnesium chloride, THF, 0 °C, 1 h, 99% (**9a**/**9b** = 2/3) over two steps; (d) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 30 min, 74%; (e) $NaBH_4$, CH_3OH, 0 °C, 15 min, 95% (**9a**/**9b** = 8/1).



Scheme 3. Reagents and conditions: (a) TMSCl, NaI, CH_3CN, rt; (b) 2,2-dimethoxypropane, *p*-TsOH, rt, 4 h, 85% over two steps.



Scheme 4. Reagents and conditions: (a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 1 h, 94%; (b) methyl methacrylate, Grubbs catalyst 2nd generation, CH_2Cl_2, reflux, 16 h. 59%; (c) $KOH_{(aq)}$, THF, rt, 3 d, 97%; (d) CH_3OH, *p*-TsOH, reflux, 16 h, 70% (from D-allo-isoleucine); (e) **17**, DCC, DMAP, CH_2Cl_2, rt, 22 h, 87%.

acid **15** using 1,3-dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 to provide the desired fragment **2** in 87% purified yield (Scheme 4).

3. Conclusion

In conclusion, we have reported a convenient and efficient route for the stereoselective synthesis of the C27–C45 fragment of lagunamide A, which shows potent cytotoxic and antimalarial properties in vitro. The synthetic sequence is based on an enantioselective acetal aldol reaction to construct the C39 stereocenter and olefin cross-metathesis to build the *E* alkene skeleton. We are actively pursuing the synthesis of other members of the lagunamide family and their analogues. The results of this study will be reported in due course.

4. Experimental

4.1. General

Starting materials were obtained from commercial suppliers and were used without further purification unless otherwise stated. All reactions were performed in flame-dried apparatus under an atmosphere of nitrogen at room temperature unless otherwise stated.

CH_2Cl_2 and THF were distilled under nitrogen. Flash chromatography was carried out using Merck silica gel 60, 70–230 mesh ASTM. Optical rotations were measured on a Rudolph research analytical Autopol IV polarimeter. NMR spectra were recorded on a Varian Mercury 400 or Varian INOVA 600 spectrometer. Chemical shifts are reported as the δ value in ppm relative to TMS ($\delta = 0$), which was used as the internal standard in $CDCl_3$ for ^1H NMR spectra and the center peak of $CDCl_3$ ($\delta = 77.0$ ppm) was used as an internal standard in ^{13}C NMR spectra. Mass spectra were collected on a Finnigan/Thermo Quest MAT 95XL, Finnigan LCQ ion-trap or Thermo Scientific LTQ Orbitrap hybrid FTMS mass spectrometer.

4.2. (*S*)-1,1-Dimethoxy-2-methylbutane 6

To a solution of aldehyde **7** (7.74 g, 90 mmol) in methanol (20 mL) was added *p*-TsOH (20 mg). After 24 h, the reaction was quenched by the addition of saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure in an ice bath. The product was isolated by Kugelrohr distillation (60 mmHg, 90 °C) to give **6** (9.27 g, 78%) as a colorless liquid. $[\alpha]_D^{25} = -0.55$ (*c* 1.28, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (d, $J = 6.8$ Hz, 1H), 3.35 (s, 6H), 1.70–1.51 (m, 2H), 1.18–1.07 (m, 1H), 0.92–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.8, 53.5, 37.3, 24.6, 13.9, 11.3; MS (ESI): *m*/*z* 133 $[M+H]^+$; HRMS (ESI): *m*/*z* calcd for $[C_7H_{16}O_2+H]^+$ 133.1223, found 133.0678.

4.3. (2*R*,3*R*,4*S*)-1-[(4′*S*)-4-Benzyl-2-thioxothiazolidin-3-yl]-3-methoxy-2,4-dimethylhexan-1-one 8

A solution of thiazolidinethione **5** (3.98 g, 15 mmol) in anhydrous CH_2Cl_2 (100 mL) was cooled to 0 °C, and neat $TiCl_4$ (2.1 mL, 19.5 mmol, 1.3 equiv) then added dropwise, resulting in the formation of an orange slurry. After stirring for 5 min, DIEA (3.4 mL, 19.5 mmol, 1.3 equiv) was added dropwise. The resulting dark solution was stirred at 0 °C for 1 h, and then cooled to −84 °C for another 15 min. Neat $SnCl_4$ (3.5 mL, 30 mmol, 2 equiv) and acetal **6** (3.96 g, 30 mmol, 2 equiv) were added dropwise. After the addition was completed, the solution was stirred at −84 °C for an additional 30 min, and then slowly warmed to 0 °C over 4 h. The reaction was quenched by the addition of saturated ammonium chloride solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a yellow mixture (6.92 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (30:1) to give **8** (3.39 g, 62%) as a yellow liquid. $[\alpha]_D^{25} = -27.8$ (*c* 1.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 5.52–5.47 (m, 1H), 5.13–5.05 (m, 1H), 3.65–3.45 (m, 1H), 3.42 (s, 3H), 3.37–3.31 (m, 1H), 3.19–3.14 (m, 1H), 3.09–3.03 (m, 1H), 2.85–2.82 (m,1H), 1.61–1.51 (m, 2H), 1.42–1.26 (m,1H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.00 (t, $J = 7.2$ Hz, 3H), 0.90 (d, $J = 6.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 177.7, 137.0, 129.6, 129.1, 127.4, 87.0, 68.9, 61.3, 42.1, 37.7, 37.1, 31.4, 27.8, 15.3, 13.3, 12.7; MS (EI): *m*/*z* 365 $[M]^+$; HRMS (EI): *m*/*z* calcd for $[C_{19}H_{27}NO_2S_2]^+$ 365.1484, found 365.1479.

4.4. (4*S*,5*S*,6*R*,7*S*)-6-Methoxy-5,7-dimethylnon-1-en-4-ol 9a and diastereomer 9b

A solution of thiazolidinethione **8** (2.67 g, 7.4 mmol) in anhydrous CH_2Cl_2 (75 mL) was cooled to −84 °C, and DIBAL-H (20%, 11.3 mL, 1.5 equiv) then slowly added dropwise. The resulting solution was stirred for 10 min, quenched by the addition of saturated ammonium chloride solution and extracted with CH_2Cl_2 (2×50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a mixture containing the crude aldehyde (2.95 g). The crude aldehyde mixture was dissolved in THF (50 mL), and allylmagnesium chloride (2 M, 11 mL, 3 equiv) was added dropwise at 0 °C. After 1 h, the reaction was quenched by the addition of saturated ammonium chloride solution and extracted with EtOAc (2×50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give a crude product mixture (3.45 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (10:1) to give a diastereomeric mixture (1.47 g, 99%, **9a**/**9b** = 2/3). The diastereomers were separated by flash column chromatography eluting with hexane/EtOAc (20:1) to give **9a** (0.58 g, 39%) as a colorless liquid and diastereomer **9b** (0.88 g, 59%) as a colorless liquid. Compound **9a**: $[\alpha]_D^{25} = -16.0$ (*c* 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01–5.93 (m, 1H). 5.16–5.09 (m, 2H), 3.74–3.70 (m, 1H), 3.48 (s, 3H), 3.02 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 2.41–2.37 (m, 1H), 2.17–2.10, (m, 1H), 1.83–1.74 (m, 1H), 1.55–1.42 (m, 2H), 1.35–1.26 (m, 1H), 0.94 (t, $J = 7.4$ Hz, 3H), 0.89 (d, $J = 6.8$ Hz, 3H), 0.82 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 117.0, 90.4, 73.5, 61.1, 41.4, 38.5, 38.3, 27.8, 14.0, 13.3, 12.4; MS (APCI): *m*/*z* 201 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{12}H_{25}O_2+H]^+$ 201.1849, found 201.1854. Compound **9b**: $[\alpha]_D^{25} = +0.4$ (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–5.79 (m, 1H), 5.14–5.06 (m, 2H), 4.00–3.97 (m, 1H), 3.50 (s, 3H), 3.02 (t, $J = 5.6$ Hz, 1H), 2.35–2.28 (m, 1H), 2.18–2.11 (m, 1H), 1.77–1.66 (m, 2H), 1.48–1.40 (m, 1H), 1.20–1.13 (m, 1H), 0.97 (d, $J = 7.2$ Hz 3H), 0.94 (d, $J = 6.8$ Hz 3H), 0.91 (t, $J = 7.6$ Hz 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 117.0, 90.5, 70.6, 61.8, 39.6, 38.1, 37.6, 26.8, 14.4, 11.7, 11.3; MS (APCI): *m*/*z* 201 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{12}H_{25}O_2+H]^+$ 201.1849, found 201.1854.

4.5. (5*R*,6*R*,7*S*)-6-Methoxy-5,7-dimethylnon-1-en-4-one 10

To a solution of alcohol **9b** (1.94 g, 9.7 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C, and DMP (6.20 g, 1.5 equiv) was added portionwise. After 5 min at 0 °C, the reaction solution was stirred at ambient temperature for another 30 min. The reaction was quenched with saturated sodium sulfite solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a colorless mixture (4.02 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (20:1) to give ketone **10** (1.42 g, 74%) as a colorless liquid. $[\alpha]_D^{25} = -68.65$ (*c* 0.96, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.00–5.91 (m, 1H), 5.19–5.11 (m, 2H), 3.29 (s, 3H), 3.35–3.28 (m, 3H), 2.90–2.83 (m, 1H), 1.50–1.45 (m, 2H), 1.36–1.28 (m, 1H), 0.96–0.93 (m, 6H), 0.87 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.7, 130.7, 118.5, 86.7, 60.9, 49.0, 48.0, 36.9, 27.2, 13.8, 12.5, 12.3; MS (EI): *m*/*z* 198 $[M]^+$; HRMS (EI): *m*/*z* calcd for $[C_{12}H_{22}O_2]^+$ 198.1620, found 198.1630.

4.6. Synthesis of 9a and 9b from ketone 10

A solution of ketone **10** (1.42 g, 7.2 mmol) in methanol (50 mL) was cooled to 0 °C, and $NaBH_4$ (0.38 g, 10 mmol, 5.5 equiv) was added portionwise. After 15 min, the reaction was quenched by the addition of NaOH solution (2 M, 20 mL), concentrated in vacuo to remove the methanol, and extracted with EtOAc (3×50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield a colorless mixture (1.47 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (10:1) to give a diastereomeric mixture (1.37 g, 95%, **9a**/**9b** = 8/1).

4.7. (4*S*,5*S*,6*R*)-4-Allyl-2,2,5-trimethyl-6-[(1′*S*)-1-methylpropyl]-1,3-dioxane 12

To a solution of alcohol **9a** (0.075 g, 0.38 mmol) and NaI (0.17 g, 1.14 mmol, 3 equiv) in anhydrous CH_3CN (5 mL) was added TMSCl (0.15 mL, 1.18 mmol, 3.1 equiv) dropwise, and the solution was stirred at room temperature for 30 min, and monitored by thin-layer chromatography (TLC). The reaction was quenched with H_2O and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with saturated sodium sulfite solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford crude diol **11** (0.081 g). Crude diol **11** and *p*-TsOH (3 mg) were dissolved in 2,2-dimethoxypropane (2 mL), and then stirred at ambient temperature for 4 h. The reaction mixture was diluted with EtOAc (20 mL), and washed with saturated aqueous solution of $NaHCO_3$ (10 mL), and then brine (5 mL). After drying over anhydrous magnesium sulfate, it was filtered and concentrated in vacuo to afford a colorless mixture (0.103 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (100:1) to afford acetal **12** (0.072 g, 85%) as a colorless liquid $[\alpha]_D^{25} = +8.0$ (*c* 0.81, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96–5.87 (m, 1H), 5.09–5.02 (m, 2H), 3.54–3.43 (m, 2H), 2.42–2.37 (m, 1H), 2.22–2.15 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.55–1.26 (m, 4H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.3, 116.1, 97.6, 75.2, 74.3, 37.6, 35.0, 34.8, 30.1, 26.7, 19.5, 12.3, 12.0, 11.6; MS (APCI): *m*/*z* 227 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{14}H_{27}O_2+H]^+$ 227.2006, found 227.2001.

4.8. (1*S*,2*R*,3*R*,4*S*)-1-Allyl-3-methoxy-2,4-dimethylhexoxy]-*tert*-butyldimethylsilane 13

To a solution of alcohol **9a** (0.68 g, 3.4 mmol) in anhydrous CH_2Cl_2 (35 mL) was added triethylamine (1.4 mL, 10.3 mmol, 3 equiv) at 0 °C followed by the slow addition of TBSOTf (1.2 mL, 5.2 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 10 min, and then stirred at room temperature for another 30 min. The reaction was quenched by the addition of saturated ammonium chloride solution and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a crude mixture (2.42 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (150:1) to give **13** (1.01 g, 94%) as a colorless liquid. $[\alpha]_D^{25} = -28.9$ (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92–5.84 (m, 1H), 5.07–5.00 (m, 2H), 3.95–3.92 (m, 1H), 3.40 (s, 3H), 2.92 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 2.24–2.08 (m, 2H), 1.90–1.82 (m, 1H), 1.50–1.42 (m, 2H), 1.40–1.30 (m, 1H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 116.0, 86.6, 73.2, 60.9, 42.5, 37.7, 37.1, 27.9, 26.1, 18.3, 12.7, 12.5, 11.0, −4.2, −4.3; MS (APCI): *m*/*z* 315 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{18}H_{39}O_2Si+H]^+$ 315.2714, found 315.2720.

4.9. Methyl (*E*)-(5*S*,6*R*,7*R*,8*S*)-5-[*tert*-butyl(dimethyl)silyl]oxy-7-methoxy-2,6,8-trimethyldec-2-enoate 14

To a solution of olefin **13** (0.63 g, 2 mmol) and methyl methacrylate (4.2 mL, 40 mmol, 20 equiv) in anhydrous CH_2Cl_2 (30 mL) was added Grubbs catalyst 2nd generation (0.075 g, 5 mol %) while flushing with N_2 for 5 min. The mixture was then heated to 50 °C for 16 h. After cooling to room temperature, the solvent was removed in vacuo to obtain a yellow liquid (0.74 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (100:1) to afford **14** (0.45 g, 59%) as a colorless liquid. $[\alpha]_D^{25} = -30.2$ (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89–6.85 (m, 1H), 4.05–4.01 (m, 1H), 3.74 (s, 3H), 3.39 (s, 3H), 2.91 (dd, *J* = 9.6 Hz, 2.0 Hz, 1H), 2.31–2.27 (m, 2H), 1.85 (s, 3H), 1.90–1.84 (m, 1H), 1.55–1.42 (m, 2H), 1.38–1.31 (m, 1H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9 H), 0.87–0.83 (m, 6H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 141.4, 128.3, 86.8, 72.4, 60.9, 51.7, 42.6, 37.8, 31.9, 27.9, 26.0, 18.2, 12.9, 12.8, 12.5, 11.2, −4.3, −4.5; MS (APCI): *m*/*z* 387 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{21}H_{43}O_4Si+H]^+$ 387.2925, found 387.2931.

4.10. (*E*)-(5*S*,6*R*,7*R*,8*S*)-5-[*tert*-Butyl(dimethyl)silyl]oxy-7-methoxy-2,6,8-trimethyl-dec-2-enoic acid 15

To a solution of ester **14** (0.25 g, 0.65 mmol) in THF (5 mL) and water (2 mL) was added KOH (0.5 g) at 0 °C. The resulting solution was stirred magnetically at room temperature for 3 d, and the reaction was monitored by thin-layer chromatography (TLC). The reaction solution was acidified with dilute hydrochloric acid to pH 2, and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield a crude mixture (2.84 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (5:1) to afford carboxylic acid **15** (0.23 g, 97%) as a colorless liquid. $[\alpha]_D^{25} = -26.7$ (*c* 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04–6.99 (m, 1H), 4.08–4.03 (m, 1H), 3.40 (s, 3H), 2.91 (d, *J* = 9.2 Hz, 1H), 2.35–2.31 (m, 2H), 1.87 (s, 3H), 1.91–1.84 (m, 1H), 1.53–1.45 (m, 2H), 1.36–1.31 (m, 1H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9 H), 0.87–0.84 (m, 6H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 143.7, 128.0, 86.8, 72.2, 60.9, 42.6, 37.8, 32.2, 27.9, 26.0, 18.2, 12.9, 12.5, 12.4, 11.2, −4.4, −4.5; MS (ESI): *m*/*z* 371 $[M-H]^-$; HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{40}O_4Si-H]^-$ 371.2612, found 371.2619.

4.11. Methyl (2*R*,3*S*)-2-hydroxy-3-methylpentanoate 17

To a solution of (2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid **16** (0.53 g, 4.0 mmol) and *p*-TsOH (10 mg) in methanol (15 mL) was heated at reflux for 16 h. After cooling, the solution was concentrated in vacuo at 0 °C to afford a yellow mixture (0.64 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (10:1) to give **17** (0.41 g, 70%) as a colorless liquid $[\alpha]_D^{25} = -16.2$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, *J* = 3.2 Hz, 1H), 3.80 (s, 1H), 1.84–1.78 (m, 1H), 1.57–1.50 (m, 1H), 1.35–1.26 (m, 1H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 73.2, 52.3, 38.6, 26.0, 13.3, 11.8; MS (APCI): *m*/*z* 147 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_7H_{15}O_3+H]^+$ 147.1016, found 147.1009.

4.12. Synthesis of the C27–C45 fragment 2

To a cooled (ice bath) solution of carboxylic acid **15** (0.049 g, 0.13 mmol) and alcohol **17** (0.025 g, 0.17 mmol, 1.3 equiv) in anhydrous CH_2Cl_2 (10 mL) were added DCC (0.045 g, 0.22 mmol, 1.6 equiv) and DMAP (0.025 g, 0.2 mmol, 1.6 equiv). The mixture was stirred at 0 °C for 5 min and then stirred at room temperature for another 22 h. The reaction was quenched with saturated ammonium chloride solution and was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a crude mixture (0.156 g). The crude product was purified by flash column chromatography eluting with hexane/EtOAc (30:1) to afford **2** (0.058 g, 87%) as a colorless liquid. $[\alpha]_D^{25} = -19.1$ (*c* 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97–6.93 (m, 1H), 5.07 (d, *J* = 3.6 Hz, 1H), 4.08–4.03 (m, 1H), 3.74 (s, 3H), 3.40 (s, 3H), 2.91 (d, *J* = 9.2 Hz, 1H), 2.34–2.31 (m, 2H), 2.05–2.00 (m, 1H), 1.88 (s, 3H), 1.92–1.84 (m, 1H), 1.54–1.25 (m, 5H), 0.87 (s, 9H), 0.99–0.83 (m, 15H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 167.8, 142.2, 128.1, 86.9, 75.1, 72.1, 61.0, 52.2, 42.7,

37.8, 37.0, 32.1, 27.9, 26.2, 26.1, 18.2, 14.8, 13.0, 12.8, 12.6, 11.8, 11.1, −4.3, −4.4; MS (APCI): *m*/*z* 501 $[M+H]^+$; HRMS (APCI): *m*/*z* calcd for $[C_{27}H_{53}O_6Si+H]^+$ 501.3606, found 501.3614.

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