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# Total synthesis of (+)-methynolide using a Ti-mediated aldol reaction of a lactyl-bearing oxazolidin-2-one, and a vinylogous Mukaiyama aldol reaction

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# 1. Introduction

Asymmetric aldol reactions using chiral oxazolidin-2-one auxiliaries are efficient and robust methods for natural product syntheses.<sup>1</sup> In this context, we have developed two highly stereoselective aldol reactions (Scheme 1): a Ti-mediated aldol reaction of a lactyl-bearing chiral oxazolidin-2-one,<sup>2</sup> and a vinylogous Mukaiyama aldol reaction (VMAR)<sup>3</sup> that enabled 1,7-remote asymmetric induction through the use of a vinyl ketene silyl *N*,*O*acetal. In the former reaction, the protecting group of the secondary alcohol in the lactyl moiety controls the stereochemistry of lithium enolate, resulting in the stereoselective formation of an *anti*- or *syn*-1,2-diol derivative through chelation-controlled Zimmerman-Traxler type transition states. The latter reaction directly affords the *anti*- $\delta$ -hydroxy- $\alpha$ , $\gamma$ -dimethyl  $\alpha$ , $\beta$ -unsaturated carbonyl unit, which is present in many naturally occurring compounds. Both types of aldol reaction have been successfully used in natural product syntheses by many research groups, including our own.<sup>4–6</sup>

To further demonstrate the synthetic utility of these methods, we chose (+)-methynolide (**1**) as a target molecule. (+)-Methynolide is an aglycon of the 12-membered macrolidic antibiotic methymycin<sup>6</sup> and has been a key target molecule over the past four decades (Fig. 1). Since the first total synthesis of (±)-**1** by Masamune and colleagues,<sup>7</sup> seven total syntheses<sup>8–14</sup> and two formal total syntheses<sup>15,16</sup> have been reported. Structurally, an *anti*-vicinal, secondary-tertiary diol and a  $\delta$ -hydroxy- $\alpha$ , $\gamma$ -dimethyl ketone constitute the *seco*-acid of **1**. Herein, we report a highly convergent total synthesis of (+)-methynolide that demonstrate the utility of our synthetic methodologies.

# 2. Results and discussion

Our strategy involved the construction of the macrocyclic ring in **1** using a Yamaguchi esterification<sup>17</sup> and a ring-closing metathesis<sup>18</sup> (RCM) between the C9-C11 fragment **2**, and the C1-C8 fragment **3** (Scheme 2). The stereochemistry of *anti*-1,2-diol **2** could be constructed by the Ti-mediated aldol reaction of chiral oxazolidin-2one **5**, which possesses a benzyl-protected lactyl group. C1-C8 fragment **3** could be derived from chiral aldehyde **7**<sup>15b</sup> by the *anti*-selective VMAR of *N*,O-acetal **8**, followed by the stereoselective 1,4-

ABSTRACT

A highly convergent total synthesis of (+)-methynolide, based on two types of stereoselective aldol reaction, was achieved. The C1-C8 and C9-C11 fragments of (+)-methynolide were prepared by a vinylogous Mukaiyama aldol reaction using a vinyl ketene silyl *N,O*-acetal, and a Ti-mediated aldol reaction of a lactyl-bearing chiral oxazolidin-2-one, respectively. Yamaguchi esterification of both fragments and ring-closing metathesis afforded (+)-methynolide.

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Scheme 1. Two types of aldol reaction developed by us.



Fig. 1. (+)-Methynolide and its seco-acid.



Scheme 2. Retrosynthetic analysis of (+)-1.

reduction of the resulting imide **6**.

Preparation of the C9-C11 fragment was commenced with the Ti-mediated aldol reaction of the lactyl-bearing chiral oxazolidin-2one **5** (Scheme 3). Deprotonation of imide **5** with LDA at -78 °C afforded the lithium (*E*)-enolate, which underwent a Li/Ti exchange by exposure to excess TiCl(Oi-Pr)<sub>3</sub> at -40 °C. Next, the stereoselective aldol reaction with propanal proceeded through a chelation-controlled Zimmerman-Traxler type transition state,<sup>19</sup> to give the aldol product **4** as a single isomer (>20:1) in 91% yield. Reductive cleavage of the oxazolidin-2-one moiety with LiBH<sub>4</sub> in the presence of MeOH and the TEMPO-mediated selective oxidation of the resulting primary alcohol gave aldehyde **10**. Wittig olefination of aldehyde **10** with Ph<sub>3</sub>PCH<sub>3</sub>Br and BuLi provided terminal olefin **11** in moderate yield. Deprotection of the tertiary alcohol was best carried out under Birch condition to accomplish the synthesis of the C9-C11 fragment **2** in five steps. The spectral data of **2** are identical to those reported by Kang et al.<sup>14</sup>

Synthesis of the C1-C8 fragment began with an anti-selective VMAR between chiral aldehydes 7a-c and the vinyl ketene silyl N,Oacetal 8 (Table 1). Recent examples<sup>5e,5f</sup> reveal the difficulty of using VMARs with  $\beta$ -oxyaldehydes, probably due to the  $\beta$ -elimination of an oxygen functional group, and/or chelation that results in the deactivation of the Lewis acid. Indeed, our VMAR using aldehydes **7a** (R = TBS) or **7b** (R = TIPS) failed (entries 1–4). In entry 2, aldol product 6d was obtained in 21% yield probably due to desilylation of 6a or 7a. When using aldehyde 7b (entries 3 and 4), the desired aldol 6b was obtained in low yield, along with recovered 8 and imide **12**, derived by hydrolysis of **8**. The VMAR with aldehyde **7c** (R = TBDPS, entry 5) gave a mixture of aldol products (dr 1.3:1) in moderate yield, under standard conditions. In contrast, the use of toluene as the solvent (entry 6) resulted in increased yield and selectivity (dr > 20:1), although measurable amounts of **8** and **12** remained. After extensive experiments, we found that the desired anti-aldol product 6c could be obtained in 90% vield on a gram scale using 2.0 equiv of aldehvde **7c** in the presence of catalytic amounts of H<sub>2</sub>O (entry 10). The rate enhancement effect of H<sub>2</sub>O in the VMAR was demonstrated in our previous studies.<sup>3c</sup>

Next, we investigated the construction of the remaining, C6, stereocenter (Scheme 4). At first, we attempted the epimerization of lactone 13c, which was prepared by the alkaline methanolysis of 6c using NaOMe, followed by Pd-catalyzed hydrogenation involving concomitant lactonization. Although the treatment of the diastereomeric mixture of **13c** (dr 1:1) with DBU<sup>15</sup> increased the dr to 3:1, this route proved to be ineffective for the concise total synthesis. Recently, Hosokawa and colleagues reported the stereoselective 1,4-reduction of an *anti*- $\delta$ -hydroxy- $\alpha$ , $\gamma$ -dimethyl  $\alpha$ , $\beta$ unsaturated imide, and accomplished the total synthesis of septoriamycin A.<sup>5d</sup> When alcohol **6a**, prepared from **6c** by protecting group exchange, was subjected to Birch reaction according to Hosokawa's protocol (Na, liq. NH<sub>3</sub>/THF, -78 °C), the desired lactone 13a was obtained in 78% yield as a single diastereomer. The stereochemistry of 13a was confirmed by comparison of its spectra with the spectral data reported by Cossy et al.<sup>15</sup> It is noteworthy that this methodology provides an efficient route to the Prelog-Djerassi lactone.<sup>20</sup> Weinreb amide formation using Me<sub>3</sub>Al and protection of the resulting secondary alcohol with a TBS group using TBSCl and AgNO<sub>3</sub> provided amide 14. Addition of vinyl magnesium bromide and selective deprotection of the primary alcohol using TBAF in the presence of AcOH afforded alcohol 15. Two-step oxidation (Dess-Martin oxidation and Pinnick oxidation) of alcohol 15 afforded the C1-C8 fragment 16 in 10 steps from N,Oacetal 8.

With both fragments **2** and **16** in hand, we proceeded to the final stage of the total synthesis of methynolide (Scheme 5). Yamaguchi esterification of **16** and **2** afforded ester **17** in 78% yield. Macrocyclization of **17** by RCM, using Grubbs 2nd generation catalyst, gave the corresponding macrolactone in 98% yield. Finally, desilylation with TBAF completed the total synthesis of (+)-**1** in 25% overall yield and in 13 steps from the *N*,*O*-acetal **8** (total of 18 steps). The spectroscopic data of our synthetic (+)-**1** are identical to those reported by Kang et al.<sup>14</sup>



Scheme 3. Preparation of the C9-C11 fragment.

 Table 1

 Vinylogous Mukaiyama aldol reactions.



Entry	Aldehyde	Equiv.	Solvent	Time (h)	Yield of <b>6</b> (%)	dr <sup>a</sup>	Recovered <b>8</b> (%)	Imide <b>12</b> (%)
1	7a	1.5	CH <sub>2</sub> Cl <sub>2</sub>	36	-	_	77	16
2	7a	1.5	toluene	36	21 (for <b>6d</b> )	>20:1	65	11
3	7b	1.5	$CH_2Cl_2$	36	10	2:1	20	40
4	7b	1.5	toluene	36	14	4:1	43	29
5	7c	1.5	$CH_2Cl_2$	36	48	1.3:1	ND	25
6	7c	1.5	toluene	36	64	>20:1	15	18
7	7c	1.5	toluene	120	77	>20:1	4	16
8	7c	2.0	toluene	36	70	>20:1	8	20
9 <sup>b</sup>	7c	1.5	toluene	36	77	>20:1	4	19
10 <sup>b</sup>	7c	2.0	toluene	108	90	>20:1	3	6

<sup>a</sup> Diastereomeric ratio (dr) was determined by <sup>1</sup>H NMR analysis.

<sup>b</sup> H<sub>2</sub>O (0.1 equiv) was added.

In conclusion, we have accomplished the highly convergent total synthesis of (+)-methynolide based on two types of stereo-selective aldol reactions: a Ti-mediated aldol reaction of the lactyl-bearing chiral oxazolidin-2-one **5**, and a vinylogous Mukaiyama aldol reaction of the vinyl ketene silyl *N*,*O*-acetal **8**, developed in our laboratory.

# 3. Experimental section

#### 3.1. General methods

All non-aqueous reactions were performed under an atmosphere of dry argon in flame-dried glassware unless otherwise indicated. Solvents were distilled under an atmosphere of argon before use and transferred via an oven-dried syringe or cannula. CH<sub>2</sub>Cl<sub>2</sub>, DMF, DMSO, Et<sub>3</sub>N, *i*-Pr<sub>2</sub>NH, toluene were distilled from CaH<sub>2</sub>. EtOH was distilled from Mg(OEt)<sub>2</sub>. MeOH was distilled from Mg(OMe)<sub>2</sub>. TiCl<sub>4</sub> was distilled from granular copper and stored in ampoules. Dry THF (209-13967) and Et<sub>2</sub>O (047-25497) were purchased from Kanto Chemical Industries Ltd, in anhydrous Grade. Flash chromatography was performed with PSQ-100B (Fuji Silysia Co. Ltd. Japan). Solvents for chromatography are listed as volume/ volume ratios. Analytical thin layer chromatography was performed using commercial silica gel plates (E. Merck, Silica Gel 60 F<sub>254</sub>). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a JEOL JNM-LD400

(400 MHz) and ECA-500 (500 MHz) spectrometer in CDCl<sub>3</sub> as a solvent. Tetramethylsilane (TMS) served as internal standard ( $\delta$  0.0) for <sup>1</sup>H NMR. CDCl<sub>3</sub> ( $\delta$  77.0) were used as internal references for <sup>13</sup>C NMR. Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J<sub>H</sub>) are reported in Hertz (Hz). Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis. Infrared spectra (FT-IR) were recorded on a PerkinElmer Spectrum spectrometer and a JASCO FT-IR-4100. Absorbance frequencies are recorded in reciprocal centimeters (cm<sup>-1</sup>). High resolution mass spectra (HRMS) were obtained from Applied Biosystems mass spectrometer (API QSTAR pulsar i) and Thermo Scientific Exactive for electrospray ionization (ESI). Optical rotations were determined using a JASCO P-1030 and P-2200 digital polarimeter in 100-mm cells and the sodium D line (589 nm) at room temperature in the solvent and concentration indicated.

#### 3.1.1. (R)-3-((2R,3R)-2-(benzyloxy)-3-hydroxy-2-

#### methylpentanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (4)

To a solution of LDA (prepared from DIPA (1.3 ml, 9.05 mmol) and *n*-BuLi (2.66 M in hexane, 3.2 ml, 8.49 mmol) at -78 °C for 30 min) in THF (24.0 ml), was added a solution of **5** (2.0 g, 5.66 mmol) in THF (16.0 ml) at -78 °C. After stirring for 30 min at -78 °C, Ti(O-*i*Pr)<sub>3</sub>Cl (1.0 M in THF, 22.6 ml, 22.6 mmol) was added to the resulting mixture and stirred for 90 min at -40 °C.



Scheme 4. Preparation of the C1-C8 fragment.



Scheme 5. Completion of the total synthesis of (+)-1.

After cooling to -78 °C, a solution of propanal (493 mg, 8.49 mmol) in THF (16.0 ml) was added via cannula and stirred for 3 h at -40 °C. The reaction mixture was quenched with a saturated aqueous NH<sub>4</sub>Cl solution and a saturated aqueous potassium sodium tartrate solution. After vigorous stirring for 3 h at room temperature, the aqueous laver was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford **4** (2.1 g, 91%, dr > 20:1) as a colorless oil.  $R_f$  0.48 (Hexane/EtOAc = 2/1);  $[\alpha]_{D}^{25}$  –33.8 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.40–7.20 (m, 8H), 7.19–7.16 (m, 2H), 5.16 (s, 1H), 4.48 (s, 2H), 4.33–4.20 (m, 1H), 2.95 (d, J = 6.8 Hz, 1H), 1.74 (s, 3H), 1.48–1.34 (m, 2H), 0.99 (dd, J = 7.3, 7.3 Hz, 3H), 0.97 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 174.2 (C), 151.8 (C), 138.1 (C), 136.2 (C), 128.7 (CH, 2C), 128.5 (CH, 2C), 128.2 (CH, 2C), 127.3 (CH, 2C), 127.2 (CH, 2C), 86.0 (C), 82.1 (C), 75.4 (CH), 69.0 (CH), 66.4 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 24.9 (CH<sub>2</sub>), 23.5 (CH<sub>3</sub>), 17.0 (CH<sub>3</sub>), 10.7 (CH<sub>3</sub>); IR (ATR) v<sub>max</sub> 3529, 2976, 1780, 1698, 1366, 1320, 1269, 1150, 1104 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>24</sub>H<sub>29</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup> 434.1937; found 434.1947.

#### 3.1.2. (2S,3R)-2-(benzyloxy)-2-methylpentane-1,3-diol (9)

To a solution of **4** (278 mg, 676  $\mu$ mol) and MeOH (0.055 ml, 1.35 mmol) in THF (6.8 mL), was added a solution of LiBH<sub>4</sub> in THF

(2.0 M 0.68 mL, 1.35 mmol) dropwise at 0 °C. After stirring for 1.5 h, the reaction was guenched with saturated agueous NH<sub>4</sub>Cl solution. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The crude product was dissolved in EtOAc, diluted with hexane, and filtered to remove recrystallized Super-Ouats. The residue was purified by flash column chromatography (hexane/EtOAc = 4/1) to afford **9** (130 mg, 86%) as a colorless oil.  $R_f$ 0.13 (Hexane/EtOAc = 2/1);  $[\alpha]_D^{25}$  +14.0 (c 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.38–7.27 (m, 5H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 3.80 (dd, *J* = 12.0, 5.7 Hz, 1H), 3.71 (dd, *J* = 12.0, 5.1 Hz, 1H), 3.69–3.64 (m, 1H), 2.77 (brs, 1H), 2.72 (dd, J = 5.7, 5.1 Hz, 1H), 1.68-1.58 (m, 1H), 1.52-1.41 (m, 1H), 1.16 (s, 3H), 1.08 (dd, I = 7.3, 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT)  $\delta$  138.7 (C), 128.4 (CH, 2C), 127.62 (CH, 2 C), 127.59 (CH), 79.1 (C), 77.8 (CH), 64.9 (CH<sub>2</sub>), 63.9 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 16.6 (CH<sub>3</sub>), 11.5 (CH<sub>3</sub>); IR (ATR) v<sub>max</sub> 3412, 2967, 2933, 2876, 1454, 1106, 1049, 1027, 975, 732, 695 cm<sup>-1</sup>; HRMS (ESI) calcd for  $C_{13}H_{20}O_3Na [M+Na]^+$  247.1304; found 247.1306.

#### 3.1.3. (2R,3R)-2-(benzyloxy)-3-hydroxy-2-methylpentanal (10)

To a solution of 9 (25.5 mg, 110 µmol) and TEMPO (1.7 mg, 11 µmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.1 ml), PIDA (40.3 mg, 125 µmol) was added at room temperature After stirring for 18 h at room temperature, the reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> and quenched with a saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 8/1) to afford **10** (20.4 mg, 88%) as colorless oil.  $R_f$  0.60 (Hexane/EtOAc = 2/ 1);  $[\alpha]_{D}^{25}$  +49.5 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.79 (s, 1H), 7.40–7.29 (m, 5H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 3.71–3.67 (m, 1H), 2.51 (d, J = 3.2 Hz, 1H), 1.64–1.55 (m, 1H), 1.48–1.38 (m, 1H), 1.36 (s, 3H), 1.03 (dd, *J* = 7.4, 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 205.1 (CH), 137.9 (C), 128.5 (CH, 2C), 128.0 (CH), 127.5 (CH, 2C), 84.8 (C), 77.2 (CH), 66.7 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 10.9 (CH<sub>3</sub>); IR (ATR) v<sub>max</sub> 3455, 2968, 2936, 2877, 1730, 1454, 1385, 1134, 1111, 1052, 1026, 976, 736, 697 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>13</sub>H<sub>18</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup> 245.1148; found 245.1153.

#### 3.1.4. (3R,4S)-4-(benzyloxy)-4-methylhex-5-en-3-ol (11)

To a solution of methyltriphenylphosphonium bromide (136 mg, 380 µmol) in THF (1.1 ml), a solution of *n*-BuLi in hexane (1.62 M, 0.205 mL, 332 µmol) was slowly added at 0 °C. After stirring for 1 h at 0 °C, a solution of 10 (21.1 mg, 95  $\mu$ mol) in THF (0.8 ml) was added and the resulting mixture was stirred for 3 h at 0 °C, the reaction mixture was guenched with ice-cold H<sub>2</sub>O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine. dried over Na<sub>2</sub>SO<sub>4</sub>. filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to afford **11** (11.7 mg, 56%) as a colorless oil.  $R_f 0.76$  (Hexane/EtOAc = 2/1);  $[\alpha]_D^{25}$  -3.6 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.37–7.20 (m, 5 H), 5.97 (dd, J = 17.7, 11.0 Hz, 1H), 5.98 (dd, J = 11.0, 1.2 Hz, 1H), 5.28 (dd, J = 17.7, 1.2 Hz, 1H), 4.41 (s, 2H), 3.45 (ddd, *J* = 10.5, 5.3, 3.1 Hz, 1H), 2.61 (d, *J* = 3.1 Hz, 1H), 1.56–1.49 (m, 1H), 1.37–1.20 (m, 1H), 1.34 (s, 3H), 1.02 (dd, J = 7.6, 7.3 Hz, 3H);  $^{13}C$  NMR (100 MHz, CDCl\_3; DEPT)  $\delta$  139.2 (C), 138.9 (CH), 128.3 (CH), 127.28 (CH, 2C), 127.24 (CH, 2C), 117.8 (CH<sub>2</sub>), 80.9 (C), 79.2 (CH), 64.6 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 17.4 (CH<sub>3</sub>), 11.2 (CH<sub>3</sub>); IR (ATR) v<sub>max</sub> 3571, 2978, 2932, 2975, 1454, 1414, 1114, 1089, 1047, 1027, 977, 926, 733, 696 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>14</sub>H<sub>20</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 243.1355; found 243.1357.

## 3.1.5. (3S,4R)-3-methylhex-1-ene-3,4-diol (2)

To a solution of **11** (14.4 mg, 65 µmol) and *t*-BuOH (1.6 mL) in

liquid NH<sub>3</sub>/THF (1/3, 4.4 mL) at -78 °C was added Na (7.51 mg, 327  $\mu mol).$  After stirring for 13 h at -78 °C, the reaction was quenched with solid NH<sub>4</sub>Cl. The mixture was stirred for 6 h at room temperature, and then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/ $Et_2O = 3/2$  to 1/1) to afford **2** (4.0 mg, 47%) as a colorless oil.  $R_f$  0.47 (Hexane/EtOAc = 2/1);  $[\alpha]_{D}^{25}$  +16.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.93 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.33 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.21 (dd, *J* = 10.7, 1.2 Hz, 1H), 3.33 (d, I = 10.2 Hz, 1H), 2.29 (s, 1H), 1.87 (br, 1H), 1.65-1.56 (m, 2H), 1.30 (s, 3H), 1.02 (dd, J = 7.3, 7.3 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 140.6 (CH), 114.5 (CH<sub>2</sub>), 79.9 (CH), 75.5 (C), 24.9 (CH<sub>2</sub>), 24.4 (CH<sub>3</sub>), 11.1 (CH<sub>3</sub>); IR (ATR) *v*<sub>max</sub> 3401, 2931, 1458, 1413, 1096, 976, 922, 689 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>7</sub>H<sub>14</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup> 153.0891; found 153.0886.

## 3.1.6. (*S*)-3-((4*S*,5*S*,6*S*,*E*)-7-((tert-butyldiphenylsilyl)oxy)-5hydroxy-2,4,6-trimethylhept-2-enoyl)-4-isopropyloxazolidin-2-one (**6c**)

To a solution of aldehyde 7c (3.8 g, 11.6 mmol) and H<sub>2</sub>O (10.4 mg, 0.58 mmol) in toluene (20 mL) were slowly added a solution of TiCl<sub>4</sub> in toluene (1.0 M, 5.8 mL, 5.8 mmol), followed by N,O-acetal 8 (2.0 g, 5.8 mmol) for one portion at -78 °C. After stirring for 108 h at -40 °C, the reaction was poured into a 1:1 mixture of saturated aqueous NaHCO<sub>3</sub> solution and saturated aqueous Rochelle's salt solution. The mixture was diluted with Et<sub>2</sub>O and stirred vigorously at room temperature until the white slurry was completely dissolved. The aqueous layer was extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to afford **6c** (2.9 g, 90%, dr > 50:1) as a colorless oil.  $R_f$  0.57 (Hexane/ EtOAc = 2/1;  $[\alpha]_{D}^{25}$  +11.9 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.68–7.66 (m, 4H), 7.43–7.35 (m, 6H), 5.78 (dq, J = 10.2, 1.5 Hz, 1H), 4.56 (ddd, *J* = 9.0, 5.6, 4.5 Hz, 1H), 4.33 (dd, *J* = 9.0, 8.8 Hz, 1H), 4.18 (dd, J = 9.0, 5.6 Hz, 1H), 3.76 (dd, J = 9.8, 6.8 Hz, 1H), 3.64 (dd, J = 9.9, 6.5 Hz, 1H), 3.54 (d, J = 9.0 Hz, 1H), 3.11 (s, 1H), 2.75–2.60 (m, 1H), 2.39-2.31 (m, 1H), 1.96-1.84 (m, 1H), 1.96 (d, J = 1.5 Hz, 3H), 1.06 (s, 9H), 0.99–0.86 (m, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) & 171.6 (C), 154.3 (C), 142.2 (CH), 135.58 (CH, 2C), 135.56 (CH, 2C), 133.99 (C), 133.97 (C), 131.2 (C), 129.46 (CH), 129.44 (CH), 127.56 (CH, 2C), 127.53 (CH, 2C), 74.4 (CH), 67.3 (CH<sub>2</sub>), 63.4 (CH<sub>2</sub>), 58.0 (CH), 37.0 (CH, 2C), 28.4 (CH), 26.9 (CH<sub>3</sub>, 3C), 19.2 (C), 17.8 (CH<sub>3</sub>), 15.6 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 9.1 (CH<sub>3</sub>); IR (ATR) *v*<sub>max</sub> 3525, 2963, 2931, 2858, 1770, 1687, 1210, 1111, 702 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>32</sub>H<sub>45</sub>NO<sub>5</sub>SiNa [M+Na]<sup>+</sup> 574.2959; found 574.2974.

## 3.1.7. (*S*)-3-((*4S*,5*S*,6*S*,*E*)-5,7-*d*ihydroxy-2,4,6-trimethylhept-2enoyl)-4-isopropyloxazolidin-2-one (*6d*)

To a solution of **6c** (480 mg, 0.87 mmol) in CH<sub>3</sub>CN (8.7 mL), 46% HF aqueous solution (1.2 mL) was slowly added at 0 °C. After stirring for 12 h at 0 °C, the reaction mixture was quenched with an aqueous 20% KOH solution (KOH: 2.8 g, H<sub>2</sub>O: 10 ml). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc = 1/1) to afford **6d** (269 mg, 99%) as a colorless oil. *R*<sub>f</sub> 0.10 (Hexane/EtOAc = 2/1);  $[\alpha]_{15}^{25}$  +13.5 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.73 (dq, *J* = 10.3, 1.3 Hz, 1H), 4.59 (ddd, *J* = 8.9, 5.7, 4.4 Hz, 1H), 4.36 (dd, *J* = 9.1, 8.9 Hz, 1H), 4.21 (dd, *J* = 9.1, 5.7 Hz, 1H), 3.80 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.70 (dd, *J* = 10.6, 5.4 Hz, 1H), 1.96–1.80 (m, 3H), 1.95 (d, *J* = 1.3 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.92–0.90 (m, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT)  $\delta$  171.4 (C),

154.7 (C), 141.4 (CH), 131,7 (C), 77.5 (CH), 67.9 (CH<sub>2</sub>), 63.5 (CH<sub>2</sub>), 58.0 (CH), 37.3 (CH), 35.2 (CH), 28.4 (CH), 17.8 (CH<sub>3</sub>), 15.3 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 8.7 (CH<sub>3</sub>); IR (ATR)  $\nu_{max}$  3516, 2964, 2932, 1765, 1683, 1389, 1365, 1300, 1280, 1205, 1019, 983 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>16</sub>H<sub>27</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup> 336.1781; found 336.1774.

## 3.1.8. (*S*)-3-((*4S*,5*S*,6*S*,*E*)-7-((*tert-butyldimethylsilyl*)*oxy*)-5hydroxy-2,4,6-trimethylhept-2-enoyl)-4-isopropyloxazolidin-2-one (*6a*)

To a solution of **6d** (128 mg, 400  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (6.8 ml) were added Et<sub>3</sub>N (0.23 ml, 1.63 mmol), tert-butyldimethylsilyl chloride (246 mg, 1.63 mmol), followed by DMAP (9.9 mg, 82.0 µmol) at room temperature. After stirring for 12 h at room temperature, the reaction mixture was quenched with a saturated aqueous NaHCO<sub>3</sub> solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 5/1) to afford **6a** (169 mg, 97%) as a colorless oil.  $R_f$  0.69 (Hexane/EtOAc = 2/1);  $[\alpha]_D^{25}$  +16.0 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.80 (dq, J = 10.2, 1.4 Hz, 1H), 4.57 (ddd, J = 8.9, 6.2, 5.1 Hz, 1H), 4.34 (dd, J = 9.0, 8.9 Hz, 1H), 4.19 (dd, J = 9.0, 6.2 Hz, 1H), 3.69 (dd, J = 9.8, 6.7 Hz, 1H), 3.58 (dd, J = 9.8, 6.6 Hz, 1H), 3.48 (ddd, J = 9.3, 4.6, 2.2 Hz, 1H), 3.19 (d, J = 2.2 Hz, 1H), 2.78–2.60 (m, 1H), 2.40–2.33 (m, 1H), 1.95 (d, J = 1.4 Hz, 3H), 1.93–1.85 (m, 1H), 0.94–0.80 (m, 21H), 0.06 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 171.6 (C), 154.3 (C), 142.3 (CH), 131.2 (C), 74.7 (CH), 67.0 (CH<sub>2</sub>), 63.0 (CH<sub>2</sub>), 58.1 (CH), 37.1 (CH), 37.0 (CH), 28.4 (CH), 26.0 (CH<sub>3</sub>, 3C), 18.3 (C), 17.8 (CH<sub>3</sub>), 15.6 (CH<sub>3</sub>), 15.1 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), 9.0 (CH<sub>3</sub>), -5.4 (CH<sub>3</sub>, 2C); IR (ATR) v<sub>max</sub> 3528, 2959, 2929, 1770, 1686, 1207, 1090, 1057, 834. 774 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>22</sub>H<sub>41</sub>NO<sub>5</sub>SiNa [M+Na]<sup>+</sup> 450.2646; found 450.2633.

## 3.1.9. (3R,55,65)-6-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2yl)-3,5-dimethyltetrahydro-2H-pyran-2-one (**13a**)

To a solution of **6a** (550 mg, 1.29 mmol) in liquid NH<sub>3</sub>/THF (5/1, 77 mL) was added Na (88.8 mg, 3.86 mmol) at -78 °C. After stirring for 5 min at -78 °C, the reaction was quenched with solid NH<sub>4</sub>Cl. The mixture was stirred for 6 h at room temperature, and then extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/  $Et_2O = 8/1$ ) to afford lactone **13a** (293 mg, 78%) as a colorless oil.  $R_f$ 0.33 (Hexane/Et<sub>2</sub>O = 7/3);  $[\alpha]_D^{25}$  +48.3 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $(400 \text{ MHz}, \text{CDCl}_3) \delta 4.19 \text{ (dd}, J = 10.5, 1.2 \text{ Hz}, 1\text{H}), 3.67 \text{ (dd}, J = 9.7,$ 8.8 Hz, 1H), 3.49 (dd, J = 9.7, 6.1 Hz, 1H), 2.53-2.40 (m, 1H), 1.96–1.80 (m, 3H), 1.38 (ddd, J = 12.3, 12.3, 12.3 Hz, 1H), 1.28 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 0.89 (s, 9H), 0.84 (d, J = 7.1 Hz, 3H), 0.05 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT)  $\delta$  174.6 (C), 85.5 (CH), 64.7 (CH<sub>2</sub>), 37.7 (CH<sub>2</sub>), 37.5 (CH), 36.3 (CH), 30.6 (CH), 25.9 (CH<sub>3</sub>, 3C), 18.3 (C), 17.4 (CH<sub>3</sub>), 17.1 (CH<sub>3</sub>), 8.9 (CH<sub>3</sub>), -5.4 (CH<sub>3</sub>, 2C); IR (ATR) v<sub>max</sub> 2956, 2930, 1731, 1087, 833, 774 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>16</sub>H<sub>32</sub>O<sub>3</sub>SiNa [M+Na]<sup>+</sup> 323.2012; found 323.2021.

## 3.1.10. (2R,4S,5S,6S)-5,7-bis((tert-butyldimethylsilyl)oxy)-Nmethoxy-N,2,4,6-tetramethylheptanamide (**14**)

To a suspension of *N*,O-dimethylhydroxylamine hydrochloride (127 mg, 1.30 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.3 mL) was added a solution of Me<sub>3</sub>Al in hexane (1.05 M, 1.24 ml, 1.30 mmol) very slowly at -78 °C. The mixture was allowed to warm up to room temperature and the clear colorless resulting solution was stirred for 2 h. After cooling the solution to 0 °C, a solution of **13** (130 mg, 0.43 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added via cannula. The reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and cooled to 0 °C. To the mixture, a saturated aqueous Rochelle's

salt solution was added very slowly and stirred for 1.5 h at room temperature. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/Et<sub>2</sub>O = 2/1) to afford the Weinreb amide (134 mg, 86%) as a colorless oil. *R*<sub>f</sub> 0.14 (Hexane/Et<sub>2</sub>O = 1/1); [ $\alpha$ ]<sub>D</sub><sup>25</sup> –12.7 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.71 (s, 3H), 3.71–3.65 (m, 2H), 3.44 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.19 (s, 3H), 3.08 (brs, 1H), 2.85 (brs, 1 H), 2.21–2.15 (m, 1H), 1.78–1.73 (m, 1H), 1.43–1.40 (m, 1H), 1.15–1.08 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 3.2 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.06 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  178.2, 78.1, 68.4, 61.5, 37.7, 36.6, 34.8, 33.3, 25.9, 18.8, 18.3, 16.8, 9.5, –5.51; IR (ATR) *v*<sub>max</sub> 3465, 2957, 2928, 2857, 1646, 1462, 1089, 835, 775 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>18</sub>H<sub>39</sub>NO<sub>4</sub>SiNa [M+Na]<sup>+</sup> 384.2540; found 384.2549.

To a solution of the Weinreb amide (62 mg, 172 µmol) and AgNO<sub>3</sub> (58 mg, 344 µmol) in DMF (2.0 mL) was added tert-butyldimethylsilyl chloride (52 mg, 344 µmol) at 0 °C, then a white precipitate appeared immediately. After stirring for 1 h at 0 °C, the reaction mixture was diluted with Et<sub>2</sub>O and quenched with an icecold aqueous NaHCO<sub>3</sub> solution. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et<sub>2</sub>O = 8/1) to afford Weinreb amide 14 (77 mg, 94%) as a colorless oil. Rf 0.60 (Hexane/Et<sub>2</sub>O = 1/1);  $[\alpha]_{D}^{25}$  –2.3 (c 1.0, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.69 (s, 3H), 3.58 (dd, I = 4.4, 3.0 Hz, 1H), 3.43 (dd, I = 9.8, 6.8 Hz, 1H), 3.36 (dd, *J* = 9.8, 6.8 Hz, 1H), 3.17 (s, 3H), 2.99 (brs, 1H), 1.89–1.82 (m, 1H), 1.78–1.72 (m, 1H), 1.58–1.51 (m, 1H), 1.13–1.04 (m, 1H), 1.12 (d, J = 7.1 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.90 (s. 9H). 0.89 (s, 9H), 0.85 (d, I = 6.8 Hz, 3H), 0.03 (s, 12H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) &177.9, 75.3, 66.7, 61.4, 38.0, 37.3, 36.6, 32.9, 32.2, 26.1, 25.9, 18.7, 18.4, 18.3, 16.1, 12.2, -3.9, -4.4, -5.4; IR (ATR) v<sub>max</sub> 2956, 2929, 2857, 1669, 1462, 1251, 1093, 833, 772 cm<sup>-1</sup>; HRMS (ESI) calcd for  $C_{24}H_{53}NO_4Si_2Na [M+Na]^+ 498.3405$ ; found 498.3411.

### 3.1.11. (4R,6S,7S,8S)-7-((tert-butyldimethylsilyl)oxy)-9-hydroxy-4,6,8-trimethylnon-1-en-3-one (**15**)

To a solution of 14 (270 mg, 568 µmol) in THF (12.8 mL) was added a solution of vinylmagnesium bromide in THF (0.37 M, 4.6 ml, 1.70 mmol) at 0 °C. After stirring for 1.5 h the reaction mixture was diluted with Et<sub>2</sub>O and quenched with a saturated aqueous NH<sub>4</sub>Cl solution. The organic layer was separated, and the aqueous layer was extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/ $Et_2O = 25/1$ ) to afford the enone (223 mg, 89%) as a colorless oil.  $R_f 0.83$  (Hexane/Et<sub>2</sub>O = 2/1);  $[\alpha]_D^{25}$  +4.3 (c 0.9, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.45 (dd, J = 17.4, 10.5 Hz, 1H), 6.28 (dd, J = 17.4, 1.3 Hz, 1H), 5.75 (dd, J = 10.5, 1.3 Hz, 1H), 3.67 (dd, *J* = 4.6, 2.4 Hz, 1H), 3.41 (dd, *J* = 9.5, 7.8 Hz, 1H), 3.34 (dd, *J* = 9.5, 6.1 Hz, 1H), 2.98–2.89 (m, 1H), 1.88–1.81 (m, 1H), 1.77–1.71 (m, 1H), 1.60-1.53 (m, 1H), 1.16-1.08 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.90-0.88 (m, 21H), 0.82 (d, J = 6.8 Hz, 3H), 0.03 (s, 6H), 0.02 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 204.0 (C), 134.9 (CH), 127.9 (CH<sub>2</sub>), 74.3 (CH), 66.4 (CH<sub>2</sub>), 41.4 (CH), 37.7 (CH), 36.7 (CH<sub>2</sub>), 36.3 (CH), 26.1 (CH<sub>3</sub>, 3C), 26.0 (CH<sub>3</sub>, 3C), 18.3 (C), 18.2 (C), 17.5 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 11.8 (CH<sub>3</sub>), -3.9 (CH<sub>3</sub>), -4.4 (CH<sub>3</sub>), -5.4 (CH<sub>3</sub>, 2C); IR (ATR) v<sub>max</sub> 2956, 2929, 2885, 2857, 1700, 1681, 1472, 1251, 1092, 1047, 834, 772 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>24</sub>H<sub>50</sub>O<sub>3</sub>Si<sub>2</sub>Na [M+Na]<sup>+</sup> 465.3190; found 465.3200.

To a solution of the enone (203 mg, 460  $\mu$ mol) in THF (5.6 mL) was added an equimolar mixture of AcOH/TBAF in THF (ca 1.0 M, 15 eq., 6.9 mL) portionwise over 1.5 days at room temperature. A saturated aqueous NaHCO<sub>3</sub> solution was added and the organic

layer was separated. The aqueous layer extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et<sub>2</sub>O = 8/1) to afford alcohol 15 (127 mg, 85%) as a colorless oil. R<sub>f</sub> 0.16 (Hexane/ EtOAc = 5/1);  $[\alpha]_{D}^{27}$  +3.2 (c 0.45, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.45 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.29 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.78 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, I = 10.5, 1.4 Hz), 3.47 (dd, I5.9 Hz, 1H), 2.99-2.90 (m, 1H), 1.95-1.83 (m, 2H), 1.77 (brs, 1H), 1.62–1.56 (m, 1H), 1.18–1.06 (m, 1H), 1.12 (d, J = 6.8 Hz, 3H), 0.93-0.90 (m, 12H), 0.86 (d, I = 6.8 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 204.2 (C), 135.1 (CH), 128.1 (CH<sub>2</sub>), 76.4 (CH), 66.5 (CH<sub>2</sub>), 41.3 (CH), 38.4 (CH), 36.2 (CH<sub>2</sub>), 35.5 (CH), 26.0 (CH<sub>3</sub>, 3C), 18.2 (C), 18.1 (CH<sub>3</sub>), 16.8 (CH<sub>3</sub>), 12.4 (CH<sub>3</sub>), -4.0 (CH<sub>3</sub>), -4.4 (CH<sub>3</sub>). IR (ATR) *v*<sub>max</sub> 3448, 2957, 2928, 2883, 2856, 1697, 1677, 1460, 1403, 1251, 1096, 1042, 835, 771 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>18</sub>H<sub>36</sub>O<sub>3</sub>SiNa [M+Na]<sup>+</sup> 351.2326; found 351.2325.

## 3.1.12. (2R,3S,4S,6R)-3-((tert-butyldimethylsilyl)oxy)-2,4,6trimethyl-7-oxonon-8-enoic acid (**16**)

To a solution of 15 (7 mg, 0.021 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.0 ml), Dess-Martin periodinane (22.6 mg, 53 µmol) was added at room temperature After stirring for 2 h at room temperature, the reaction mixture was quenched with a saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and a saturated aqueous NaHCO3 solution. The aqueous layer was extracted with hexane. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/ EtOAc = 12/1) to afford the aldehyde (6.6 mg, 95%) as a colorless oil.  $R_f 0.50$  (Hexane/EtOAc = 5/1); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.74 (d, I = 0.8 Hz, 1H), 6.43 (dd, I = 17.4, 10.5 Hz, 1H), 6.28 (dd, I = 17.4, 1.5 Hz, 1H), 5.79 (dd, J = 10.5, 1.5 Hz, 1H), 3.96 (dd, J = 8.5, 4.2 Hz, 1H), 2.95-2.88 (m, 1H), 2.53-2.47 (m, 1H), 1.89-1.82 (m, 1H), 1.61–1.55 (m, 1H), 1.21–1.07 (m, 1H), 1.12 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.3 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) δ 205.0 (CH), 203.7 (C), 135.0 (CH), 128.3 (CH<sub>2</sub>), 74.9 (CH), 49.8 (CH), 41.3 (CH), 36.2 (CH<sub>2</sub>), 25.7 (CH), 25.9 (CH<sub>3</sub>, 3C), 18.3 (C), 18.2 (CH<sub>3</sub>), 16.2 (CH<sub>3</sub>), 9.4 (CH<sub>3</sub>), -4.2 (CH<sub>3</sub>), -4.3 (CH<sub>3</sub>).

To a solution of the aldehyde (6.0 mg, 18 µmol) and 2-methyl-2butene (9.7 µl, 92 µmol) in t-BuOH (1.7 ml) were added NaH2- $PO_4 \cdot 2H_2O$  (22 mg, 144 µmol) and a solution of NaClO<sub>2</sub> (13 mg, 140 µmol) in water (1.0 ml) at room temperature. The mixture was allowed to stir for 3 h at room temperature, and then extracted with AcOEt. The combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 12/1) to afford carboxylic acid 16 (5.0 mg, 87%) as a colorless oil. Rf 0.10 (Hexane/EtOAc = 5/1);  $[\alpha]_D^{22}$  +1.8 (c 0.23, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $(400 \text{ MHz}, \text{CDCl}_3) \delta 6.45 \text{ (dd, } I = 17.3, 10.3 \text{ Hz}, 1\text{H}), 6.28 \text{ (dd, } I = 17.3, 10.3 \text{ Hz}, 10.3 \text{ Hz})$ 1.3 Hz, 1H), 5.77 (dd, *J* = 10.3, 1.3 Hz, 1H), 3.88 (dd, *J* = 9.3, 4.1 Hz, 1H), 2.95-2.86 (m, 1H), 2.67-2.61 (m, 1H), 1.95-1.88 (m, 1H), 1.61-1.55 (m, 1H), 1.34-1.25 (m, 1H), 1.18-1.11 (m, 1H), 1.17 (d, J = 7.1 Hz, 3H), 1.12 (d, J = 7.1 Hz, 3H), 0.93–0.88 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>; DEPT) & 203.8 (C), 179.3 (C), 134.8 (CH), 128.3 (CH<sub>2</sub>), 76.9 (CH), 42.3 (CH), 41.4 (CH), 36.1 (CH<sub>2</sub>), 35.3 (CH), 25.9 (CH<sub>3</sub>, 3C), 18.2 (C), 18.0 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 12.6 (CH<sub>3</sub>), -4.3 (CH<sub>3</sub>), -4.4 (CH<sub>3</sub>); IR (ATR)  $\nu_{max}$  2956, 2929, 2857, 1715, 1461, 1383, 1254, 1058, 836, cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>18</sub>H<sub>33</sub>O<sub>4</sub>Si [M–H]<sup>–</sup> 341.2154; found 341.2153.

# 3.1.13. (3R,4S)-4-hydroxy-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3-((tert-butyldimethylsilyl)oxy)-2,4,6-trimethyl-7-oxonon-8-enoate (**17**)

To a solution of carboxylic acid 16 (41 mg, 120 µmol) in THF

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(1.8 mL) at room temperature were added triethylamine (22 µl, 156 µmol) and 2,4,6-trichlorobenzoyl chloride (35 mg, 144 µmol). The mixture was stirred for 3 h at room temperature and the solids were filtered off and washed with hexane (3.6 ml). The combined solution was concentrated under reduced pressure. The residue was dissolved in benzene (1.2 ml). To the resulting solution, a solution of diol 2 (25 mg, 192 µmol) and DMAP (21 mg, 168 µmol) in benzene (2.4 ml) was added. After stirring for 3 h, the reaction mixture was diluted with Et<sub>2</sub>O, and washed with the saturated NaHCO<sub>3</sub> and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc = 12/1) to afford ester **17** (42 mg, 78%) as a colorless oil.  $R_f 0.74$  (Hexane/EtOAc = 2/1);  $[\alpha]_D^{23}$  +18.1 (c 0.21, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.41 (dd, J = 17.5, 10.2 Hz, 1H), 6.29 (dd, J = 17.5, 1.4 Hz, 1H), 5.97 (dd, J = 17.3, 10.8 Hz, 1H), 5.82 (dd, J = 10.2, 10.2 Hz) 1.4 Hz, 1H), 5.37 (dd, J = 17.3, 1.2 Hz, 1H), 5.17 (dd, J = 10.8, 1.2 Hz, 1H), 4.79 (dd, J = 9.8, 3.2 Hz, 1H), 3.83 (dd, J = 8.6, 1.7 Hz, 1H), 3.40 (s, 1H), 2.97-2.84 (m, 2H), 2.01-1.94 (m, 1H), 1.71-1.55 (m, 3H), 1.40–1.34 (m, 1H), 1.21 (d, J = 7.5 Hz, 3H), 1.13 (d, J = 7.5 Hz, 3H), 0.97–0.85 (m, 9H), 0.91 (s, 9H), 0.07 (s, 6 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) § 205.2, 176.4, 140.8, 135.5, 129.0, 113.9, 80.9, 76.8, 74.5, 43.4, 40.7, 36.5, 33.9, 26.1, 25.2 (3C), 23.1, 18.9, 18.5, 17.9, 16.1, 10.7, -3.71, -3.74; IR (ATR) v<sub>max</sub> 3500, 2960, 2933, 2882, 2858, 1729, 1613, 1460, 1407, 1375, 1255, 1175, 1091, 1051, 836, 773 cm<sup>-1</sup>; HRMS (ESI) calcd for  $C_{25}H_{46}O_5SiNa$  [M+Na]<sup>+</sup> 477.3007; found 477.3001.

#### 3.1.14. *Methynolide* (1)

To a solution of ester **17** (12 mg, 26.4  $\mu$ mol) in CH<sub>2</sub>Cl<sub>2</sub> (5.3 mL) was added Grubbs catalyst 2nd Generation (3.4 mg, 4.0 µmol) at room temperature. The mixture was stirred for 3 h at room temperature and then concentrated in vacuo to give dark brown oil. The residue was purified by flash column chromatography (hexane/ EtOAc = 6/1) to afford the macrolactone (11 mg, 98%) as a colorless oil.  $R_f 0.62$  (Hexane/EtOAc = 2/1);  $[\alpha]_D^{23}$  +68.6 (c 0.12, CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.59 (d, J = 16.0 Hz, 1H), 6.35 (d, J = 16.0 Hz, 1H), 4.76 (dd, J = 11.0, 2.2 Hz, 1H), 3.64 (d, J = 10.2 Hz, 1H), 2.68–2.51 (m, 2H), 1.96–1.89 (m, 1H), 1.68–1.48 (m, 2H), 1.37 (s, 3H), 1.30-1.20 (m, 9H), 0.95-0.88 (m, 15H), 0.08 (s, 3H), 0.07 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  204.2, 175.4, 148.7, 125.7, 79.1, 76.2, 74.5, 45.1, 44.4, 34.5, 33.5, 26.2 (3 C), 21.3, 19.5, 18.6, 18.5, 17.7, 17.4, 10.7, -3.1, -3.3; IR (ATR) v<sub>max</sub> 3462, 2959, 2927, 2856, 1731, 1691, 1629, 1460, 1373, 1256, 1168, 1138, 1089, 1056, 1024, 977, 836, 755 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>23</sub>H<sub>42</sub>O<sub>5</sub>SiNa [M+Na]<sup>+</sup> 449.2694; found 449.2688.

To a solution of the macrolactone (7.2 mg, 17  $\mu mol)$  in THF (3.2 mL) at room temperature was added a solution of TBAF in THF (1.0 M, 0.169 ml, 0.169 mmol) and stirred for 14 h. The reaction mixture was quenched with the saturated NH<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc = 3/1) to afford methynolide 1 (5.1 mg, 96%) as a white amorphous solid.  $R_f$ 0.45 (Hexane/EtOAc = 1/1);  $[\alpha]_D^{22}$  +72.8 (c 0.11, CHCl<sub>3</sub>); <sup>1</sup>H NMR  $(500 \text{ MHz}, \text{CDCl}_3) \delta 6.59 (1\text{H}, \text{d}, J = 16.0 \text{ Hz}), 6.34 (1\text{H}, \text{d}, J = 16.0 \text{ Hz}),$ 4.78 (1H, dd, J = 10.9, 2.3 Hz), 3.58 (1H, d, J = 10.3 Hz), 2.64–2.53 (2H, m), 1.97-1.90 (2H, m), 1.63 (1H, t, J = 12.3 Hz), 1.53-1.51 (3H, t)m), 1.38 (3H, s), 1.34 (3H, d, J = 7.4 Hz), 1.33–1.27 (1H, m), 1.21 (3H, d, J = 7.4 Hz), 1.02 (3H, d, J = 5.7 Hz), 0.91 (3H, t, J = 7.2 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  204.1, 174.8, 148.8, 125.5, 77.9, 76.4, 74.5, 45.2, 43.5, 33.4, 33.1, 21.2, 19.4, 17.6, 17.4, 16.6, 10.7; IR (ATR)  $\nu_{\rm max}$  3432, 2970, 2936, 2878, 1723, 1688, 1628, 1457, 1374, 1279, 1169, 1152, 1081, 992, 951 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>17</sub>H<sub>28</sub>O<sub>5</sub>Na [M+Na]<sup>+</sup> 335.1829; found 335.1828.

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#### Appendix A. Supplementary data

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