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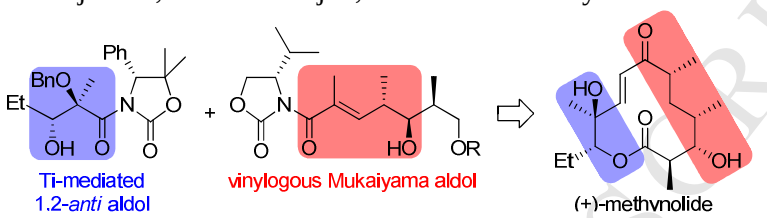

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Total synthesis of (+)-methynolide using a Ti-mediated aldol reaction of a lactyl-bearing oxazolidin-2-one, and a vinylogous Mukaiyama aldol reaction

Takahiro Suzuki[a,b,*], Masataka Fujimura[b], Kazuhiro Fujita[b], and Susumu Kobayashi[b,*]

[a] *Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan*
[b] *Faculty of Pharmaceutical Sciences, Tokyo University of Science, 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan*

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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.

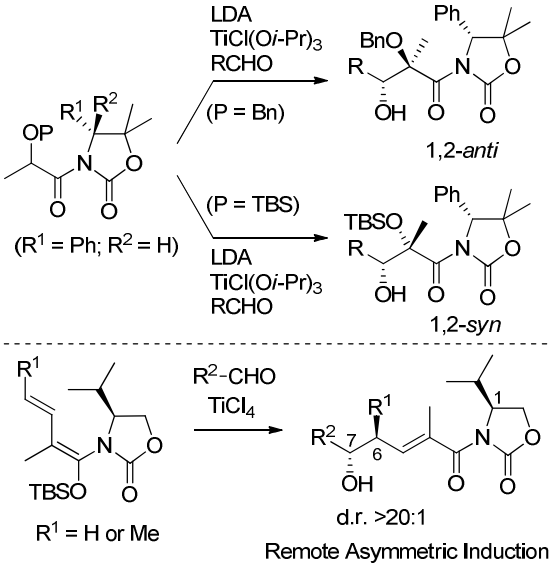
1. Introduction

Asymmetric aldol reactions using chiral oxazolidin-2-one auxiliaries are efficient and robust methods for natural product syntheses.[1] 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,[2] and a vinylogous Mukaiyama aldol reaction (VMAR)[3] 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*-δ-hydroxy-α,γ-dimethyl α,β-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.[4-6]

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[6] and has

* Corresponding authors. Tel.: +81-11-706-2703; fax: +81-11-706-4920 (T. S.); *e-mail*: takahiro-suzuki@sci.hokudai.ac.jp (T. Suzuki), kobayash@rs.noda.tus.ac.jp (S. Kobayashi)

been a key target molecule over the past four decades (Figure 1). Since the first total synthesis of (±)-**1** by Masamune and colleagues,[7] seven total syntheses[8-14] and two formal total syntheses[15,16] have been reported. Structurally, an *anti*-vicinal, secondary-tertiary diol and a δ-hydroxy-α,γ-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.



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

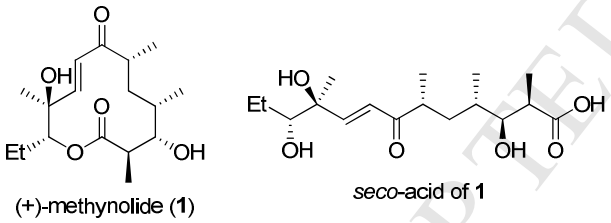
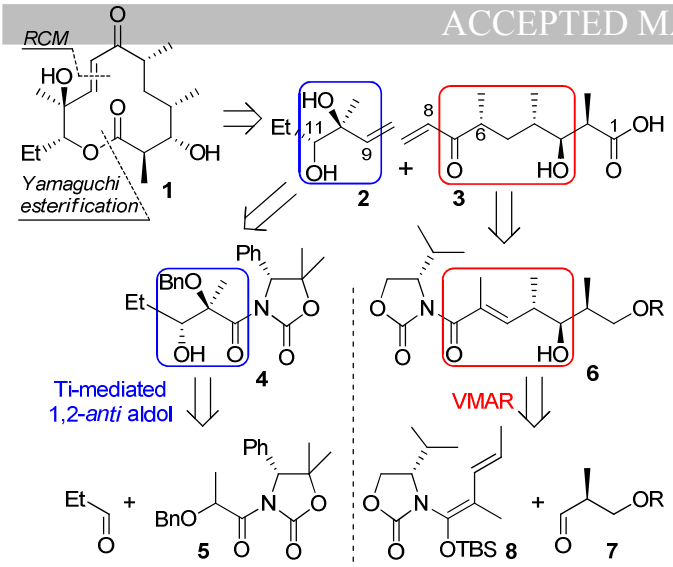


Figure 1. (+)-Methynolide and its *seco*-acid.

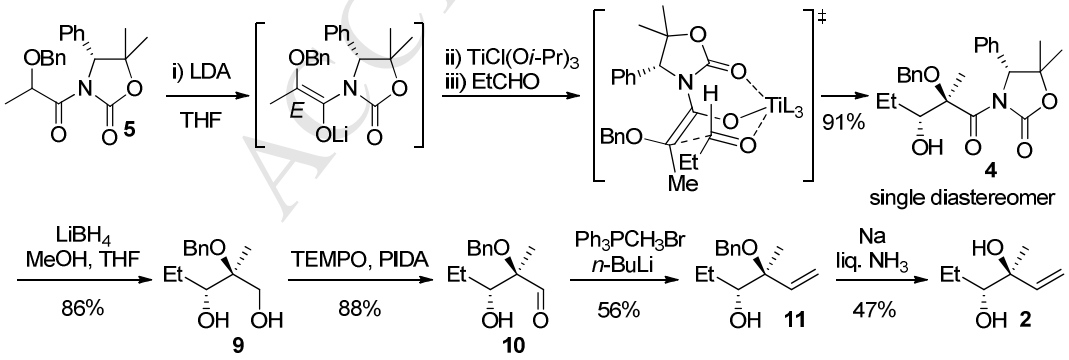
2. Results and Discussion

Our strategy involved the construction of the macrocyclic ring in **1** using a Yamaguchi esterification[17] and a ring-closing metathesis[18] (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-2-one **5**, which possesses a benzyl-protected lactyl group. C1-C8 fragment **3** could be derived from chiral aldehyde **7**[15b] by the *anti*-selective VMAR of *N,O*-acetal **8**, followed by the stereoselective 1,4-reduction of the resulting imide **6**.



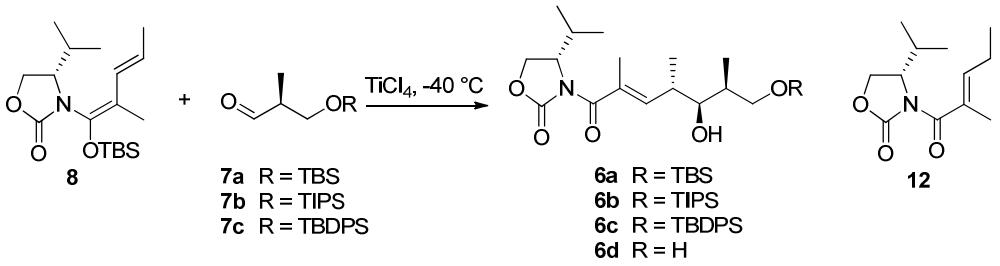
Scheme 2. Retrosynthetic analysis of (+)-**1**.

Preparation of the C9-C11 fragment was commenced with the Ti-mediated aldol reaction of the lactyl-bearing chiral oxazolidin-2-one **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 $TiCl(O\textit{i}\text{-}Pr)_3$ at −40 °C. Next, the stereoselective aldol reaction with propanal proceeded through a chelation-controlled Zimmerman-Traxler type transition state,[19] to give the aldol product **4** as a single isomer (>20:1) in 91% yield. Reductive cleavage of the oxazolidin-2-one moiety with $LiBH_4$ 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_3PCH_3Br 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*.[14]



Scheme 3. Preparation of the C9-C11 fragment.

Table 1. Vinylogous Mukaiyama aldol reactions.



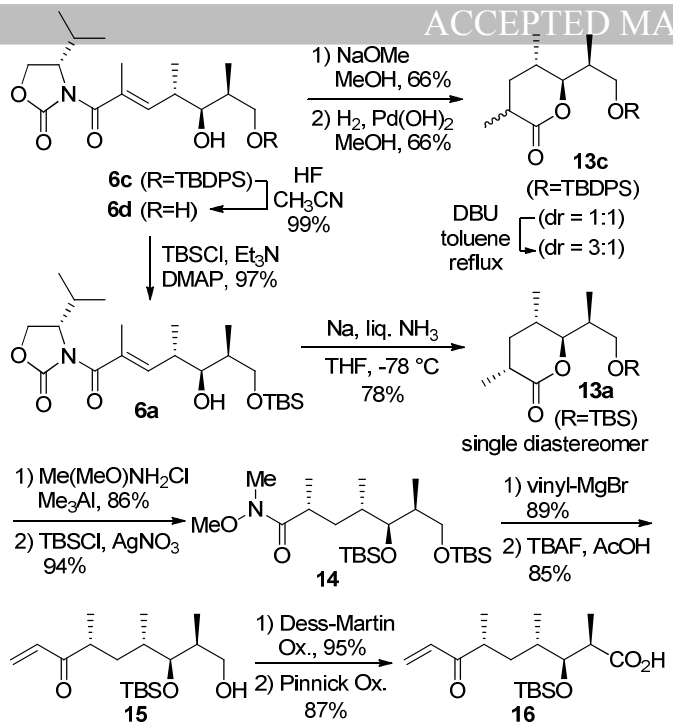
7a R = TBS
7b R = TIPS
7c R = TBDPS

6a R = TBS
6b R = TIPS
6c R = TBDPS
6d R = H

entry	aldehyde	equiv.	solvent	time (h)	yield of **6** (%)	dr[a]	recovered **8** (%)	imide **12** (%)
1	**7a**	1.5	CH_2Cl_2	36	-	-	77	16
2	**7a**	1.5	toluene	36	21 (for **6d**)	>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[b]	**7c**	1.5	toluene	36	77	>20:1	4	19
10[b]	**7c**	2.0	toluene	108	90	>20:1	3	6

[a] Diastereomeric ratio (dr) was determined by ^{1}H-NMR analysis. [b] H_2O (0.1 equiv) was added.

Synthesis of the C1-C8 fragment began with an *anti*-selective VMAR between chiral aldehydes **7a-c** and the vinyl ketene silyl *N,O*-acetal **8** (Table 1). Recent examples[5e,5f] reveal the difficulty of using VMARs with β-oxyaldehydes, probably due to the β-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 2 and 3), 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% yield on a gram scale using 2.0 equiv of aldehyde **7c** in the presence of catalytic amounts of H_2O (entry 10). The rate enhancement effect of H_2O in the VMAR was demonstrated in our previous studies.[3c]

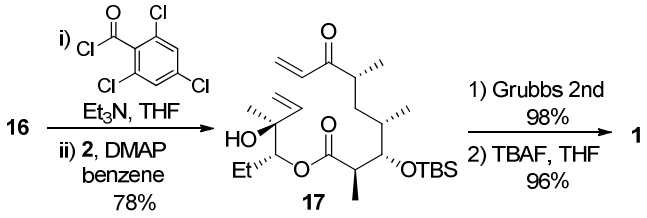


Scheme 4. Preparation of the C1-C8 fragment.

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[15] 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*-δ-hydroxy-α,γ-dimethyl α,β-unsaturated imide, and accomplished the total synthesis of septoriamycin A.[5d] When alcohol **6a**, prepared from **6c** by protecting group exchange, was subjected to Birch reaction according to Hosokawa's protocol (Na, liq. NH_3/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.*[15] It is noteworthy that this methodology provides an efficient route to the Prelog-Djerassi lactone.[20] Weinreb amide formation using Me_3Al and protection of the resulting secondary alcohol with a TBS group using TBSCl and $AgNO_3$ 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,O*-acetal **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.*[14]



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

In conclusion, we have accomplished the highly convergent total synthesis of (+)-methynolide based on two types of stereoselective 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_2Cl_2, DMF, DMSO, Et_3N, *i*-Pr_2NH, toluene were distilled from CaH_2. EtOH was distilled from $Mg(OEt)_2$. MeOH was distilled from $Mg(OMe)_2$. $TiCl_4$ was distilled from granular copper and stored in ampoules. Dry THF (209-13967) and Et_2O (047-25497) were purchased from Kanto Pure 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_{254}). ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LD400 (400MHz) and ECA-500 (400MHz) spectrometer in $CDCl_3$ as a solvent. Tetramethylsilane (TMS) served as internal standard (δ 0.0) for ^1H NMR. $CDCl_3$ (δ 77.0) were used as internal references for ^{13}C NMR. Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J_H) are reported in Hertz (Hz). Diastereomeric ratio was determined by ^1H 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^{-1}). 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)$_3$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. 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_4Cl solution and a saturated aqueous potassium sodium tartrate solution. After vigorous stirring for 3 h at room temperature, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$; 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_2), 28.5 (CH_3), 24.9 (CH_2), 23.5 (CH_3), 17.0 (CH_3), 10.7 (CH_3); IR (ATR) ν_{max} 3529, 2976, 1780, 1698, 1366, 1320, 1269, 1150, 1104 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{29}NO_5Na$ $[M+Na]^+$ 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 μmol) and MeOH (0.055 mL, 1.35 mmol) in THF (6.8 mL), was added a solution of $LiBH_4$ in THF (2.0 M 0.68 mL, 1.35 mmol) dropwise at 0°C. After stirring for 1.5 h, the reaction was quenched with saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was dissolved in EtOAc, diluted with hexane, and filtered to remove recrystallized SuperQuats. 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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, *J* = 7.3, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 138.7 (C), 128.4 (CH, 2C), 127.62 (CH, 2 C), 127.59 (CH), 79.1 (C), 77.8 (CH), 64.9 (CH_2), 63.9 (CH_2), 24.2 (CH_2), 16.6 (CH_3), 11.5 (CH_3); IR (ATR) ν_{max} 3412, 2967, 2933, 2876, 1454, 1106, 1049, 1027, 975, 732, 695 cm^{-1}; 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_2Cl_2 (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_2Cl_2 and quenched with a saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$; 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_2), 24.0 (CH_2), 14.2 (CH_3), 10.9 (CH_3); IR (ATR) ν_{max} 3455, 2968, 2936, 2877, 1730, 1454, 1385, 1134, 1111, 1052, 1026, 976, 736, 697 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$ 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 μmol) in THF (0.8 ml) was added and the resulting mixture was stirred for 3 h at 0°C, the reaction mixture was quenched with ice-cold H_2O. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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) δ 139.2 (C), 138.9 (CH), 128.3 (CH), 127.28 (CH, 2C), 127.24 (CH, 2C), 117.8 (CH_2), 80.9 (C), 79.2 (CH), 64.6 (CH_2), 24.0 (CH_2), 17.4 (CH_3), 11.2 (CH_3); IR (ATR) ν_{max} 3571, 2978, 2932, 2975, 1454, 1414, 1114, 1089, 1047, 1027, 977, 926, 733, 696 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}O_2Na$ $[M+Na]^+$ 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_3/THF (1/3, 4.4 mL) at −78 °C was added Na (7.51 mg, 327 μmol). After stirring for 13 h at −78 °C, the reaction was quenched with solid NH_4Cl. The mixture was stirred for 6 h at room temperature, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, *J* = 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 140.6 (CH), 114.5 (CH_2), 79.9 (CH), 75.5 (C), 24.9 (CH_2), 24.4 (CH_3), 11.1 (CH_3); IR (ATR) ν_{max} 3401, 2931, 1458, 1413, 1096, 976, 922, 689 cm^{-1}; HRMS (ESI) calcd for $C_7H_{14}O_2Na$ $[M+Na]^+$ 153.0891; found 153.0886.

*3.1.6. (S)-3-((4S,5S,6S,E)-7-((tert-butyldiphenylsilyl)oxy)-5-hydroxy-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_2O (10.4 mg, 0.58 mmol) in toluene (20 mL) were slowly added a solution of $TiCl_4$ 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 $NaHCO_3$ solution and saturated aqueous Rochelle's salt solution. The mixture was diluted with Et_2O and stirred vigorously at room temperature until the white slurry was completely dissolved. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 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_2), 63.4 (CH_2), 58.0 (CH), 37.0 (CH, 2C), 28.4 (CH), 26.9 (CH_3, 3C), 19.2 (C), 17.8 (CH_3), 15.6 (CH_3), 15.1 (CH_3), 13.9 (CH_3), 9.1 (CH_3);IR (ATR) ν_{max} 3525, 2963, 2931, 2858, 1770, 1687, 1210, 1111, 702 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{45}NO_5SiNa$ $[M+Na]^+$ 574.2959; found 574.2974.

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

To a solution of **6c** (480 mg, 0.87 mmol) in CH_3CN (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_2O: 10 ml). The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, 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_f 0.10 (Hexane/EtOAc = 2/1); $[\alpha]_D^{25}$ +13.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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), 3.58 (dd, *J* = 9.4, 2.3 Hz, 1H), 2.81-2.70 (m, 1H), 2.39-2.30 (m, 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 171.4 (C), 154.7 (C), 141.4 (CH), 131,7 (C), 77.5 (CH), 67.9 (CH_2), 63.5 (CH_2), 58.0 (CH), 37.3 (CH), 35.2 (CH), 28.4 (CH), 17.8 (CH_3), 15.3 (CH_3), 15.1 (CH_3), 13.9 (CH_3), 8.7 (CH_3); IR (ATR) ν_{max} 3516, 2964, 2932, 1765, 1683, 1389, 1365, 1300, 1280, 1205, 1019, 983 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$ 336.1781; found 336.1774.

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

To a solution of **6d** (128 mg, 400 μmol) in CH_2Cl_2 (6.8 ml) were added Et_3N (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 $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 171.6 (C), 154.3 (C), 142.3 (CH), 131.2 (C), 74.7 (CH), 67.0 (CH_2), 63.0 (CH_2), 58.1 (CH), 37.1 (CH), 37.0 (CH), 28.4 (CH), 26.0 (CH_3, 3C), 18.3 (C), 17.8 (CH_3), 15.6 (CH_3), 15.1 (CH_3), 14.0 (CH_3), 9.0 (CH_3), −5.4 (CH_3, 2C); IR (ATR) ν_{max} 3528, 2959, 2929, 1770, 1686, 1207, 1090, 1057, 834, 774 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{41}NO_5SiNa$ $[M+Na]^+$ 450.2646; found 450.2633.

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

To a solution of **6a** (550 mg, 1.29 mmol) in liquid NH_3/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_4Cl. The mixture was stirred for 6 h at room temperature, and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, 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_2O = 7/3); $[\alpha]_D^{25}$ +48.3 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 10.5, 1.2 Hz, 1H), 3.67 (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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 174.6 (C), 85.5 (CH), 64.7 (CH_2), 37.7 (CH_2), 37.5 (CH), 36.3 (CH), 30.6 (CH), 25.9 (CH_3, 3C), 18.3 (C), 17.4 (CH_3), 17.1 (CH_3), 8.9 (CH_3), −5.4 (CH_3, 2C); IR (ATR) ν_{max} 2956, 2930, 1731, 1087, 833, 774 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{32}O_3SiNa$ $[M+Na]^+$ 323.2012; found 323.2021.

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

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (127 mg, 1.30 mmol) in CH_2Cl_2 (2.3 mL) was added a solution of Me_3Al in hexane (1.05M, 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_2Cl_2 (2.0 mL) was added via cannula. The reaction mixture was stirred for 12 h at room temperature. The mixture was diluted with CH_2Cl_2 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_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/Et_2O = 2/1) to afford the Weinreb amide (134 mg, 86%) as a colorless oil. R_f 0.14 (Hexane/Et_2O = 1/1); $[\alpha]_D^{25}$ −12.7 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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) ν_{max} 3465, 2957, 2928, 2857, 1646, 1462, 1089, 835, 775 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{39}NO_4SiNa$ $[M+Na]^+$ 384.2540; found 384.2549.

To a solution of the Weinreb amide (62 mg, 172 μmol) and $AgNO_3$ (58 mg, 344 μmol) in DMF (2.0 mL) was added *tert*-butyldimethylsilyl chloride (52 mg, 344μmol) at 0 °C, then a white precipitate appeared immediately. After stirring for 1 h at 0 °C, the reaction mixture was diluted with Et_2O and quenched with an ice-cold aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/Et_2O = 8/1) to afford Weinreb amide **14** (77 mg, 94%) as a colorless oil. R_f 0.60 (Hexane/Et_2O = 1/1); $[\alpha]_D^{25}$ −2.3 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 3.58 (dd, *J* = 4.4, 3.0 Hz, 1H), 3.43 (dd, *J* = 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, *J* = 6.8 Hz, 3H), 0.03 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ177.9, 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) ν_{max} 2956, 2929, 2857, 1669, 1462, 1251, 1093, 833, 772 cm^{-1}; 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 (0.37M, 4.6 ml, 1.70 mmol) at 0 °C. After stirring for 1.5 h the reaction mixture was diluted with Et_2O and quenched with a saturated aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, 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_2O = 2/1); $[\alpha]_D^{25}$ +4.3 (c 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 204.0 (C), 134.9 (CH), 127.9 (CH_2), 74.3 (CH), 66.4 (CH_2), 41.4 (CH), 37.7 (CH), 36.7 (CH_2), 36.3 (CH), 26.1 (CH_3, 3C), 26.0 (CH_3, 3C), 18.3 (C), 18.2 (C), 17.5 (CH_3), 16.1 (CH_3), 11.8 (CH_3), -3.9 (CH_3), -4.4 (CH_3), -5.4 (CH_3, 2C); IR (ATR) ν_{max} 2956, 2929, 2885, 2857, 1700, 1681, 1472, 1251, 1092, 1047, 834, 772 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{50}O_3Si_2Na$ $[M+Na]^+$ 465.3190; found 465.3200.

To a solution of the enone (203 mg, 460 μmol) 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 $NaHCO_3$ solution was added and the organic layer was separated. The aqueous layer extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/Et_2O = 8/1) to afford alcohol **15** (127 mg, 85%) as a colorless oil. R_f 0.16 (Hexane/EtOAc = 5/1); $[\alpha]_D^{27}$ +3.2 (c 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.29 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.78 (dd, *J* = 10.5, 1.4 Hz, 1H), 3.62-3.55 (m, 2H), 3.47 (dd, *J* = 10.5, 5.9 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, *J* = 6.8 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 204.2 (C), 135.1 (CH), 128.1 (CH_2), 76.4 (CH), 66.5 (CH_2), 41.3 (CH), 38.4 (CH), 36.2 (CH_2), 35.5 (CH), 26.0 (CH_3, 3C), 18.2 (C), 18.1 (CH_3), 16.8 (CH_3), 12.4 (CH_3), −4.0 (CH_3), −4.4 (CH_3). IR (ATR) ν_{max} 3448, 2957, 2928, 2883, 2856, 1697, 1677, 1460, 1403, 1251, 1096, 1042, 835, 771 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{36}O_3SiNa$ $[M+Na]^+$ 351.2326; found 351.2325.

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

To a solution of **15** (7 mg, 0.021 mmol) in CH_2Cl_2 (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 $Na_2S_2O_3$ solution and a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with hexane. The combined organic layers were washed with brine, dried over Na_2SO_4, 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); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* = 0.8 Hz, 1H), 6.43 (dd, *J* = 17.4, 10.5 Hz, 1H), 6.28 (dd, *J* = 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 205.0 (CH), 203.7 (C), 135.0 (CH), 128.3 (CH_2), 74.9 (CH), 49.8 (CH), 41.3 (CH), 36.2 (CH_2), 25.7 (CH), 25.9 (CH_3, 3C), 18.3 (C), 18.2 (CH_3), 16.2 (CH_3), 9.4 (CH_3), −4.2 (CH_3), −4.3 (CH_3).

To a solution of the aldehyde (6.0 mg, 18μmol) and 2-methyl-2-butene (9.7μl, 92μmol) in *t*-BuOH (1.7 ml) were added $NaH_2PO_4 \cdot 2H_2O$ (22 mg, 144 μmol) and a solution of $NaClO_2$ (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_2SO_4, 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. R_f 0.10 (Hexane/EtOAc = 5/1); $[\alpha]_D^{22}$ +1.8 (c 0.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.45 (dd, *J* = 17.3, 10.3 Hz, 1H), 6.28 (dd, *J* = 17.3, 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); ^{13}C NMR (100 MHz, $CDCl_3$; DEPT) δ 203.8 (C), 179.3 (C), 134.8 (CH), 128.3 (CH_2), 76.9 (CH), 42.3 (CH), 41.4 (CH), 36.1 (CH_2), 35.3 (CH), 25.9 (CH_3, 3C), 18.2 (C), 18.0 (CH_3), 16.1 (CH_3), 12.6 (CH_3), −4.3 (CH_3), −4.4 (CH_3); IR (ATR) ν_{max} 2956, 2929, 2857, 1715, 1461, 1383, 1254, 1058, 836, cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{33}O_4Si$ $[M-H]^-$ 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 (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_2O, and washed with the saturated $NaHCO_3$ and brine, dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max} 3500, 2960, 2933, 2882, 2858, 1729, 1613, 1460, 1407, 1375, 1255, 1175, 1091, 1051, 836, 773 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{46}O_5SiNa$ $[M+Na]^+$ 477.3007; found 477.3001.

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

To a solution of ester **17** (12 mg, 26.4 μmol) in CH_2Cl_2 (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, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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) ν_{max} 3462, 2959, 2927, 2856, 1731, 1691, 1629, 1460,

1373, 1256, 1168, 1138, 1089, 1056, 1024, 977, 836, 755 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{42}O_5SiNa$ $[M+Na]^+$ 449.2694; found 449.2688.

To a solution of the macrolactone (7.2 mg, 17 μmol) 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_4Cl solution and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, 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, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (1H, d, *J* = 16.0 Hz), 6.34 (1H, d, *J* = 16.0 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, 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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) ν_{max} 3432, 2970, 2936, 2878, 1723, 1688, 1628, 1457, 1374, 1279, 1169, 1152, 1081, 992, 951 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{28}O_5Na$ $[M+Na]^+$ 335.1829; found 335.1828.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://

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