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Graphical Abstract

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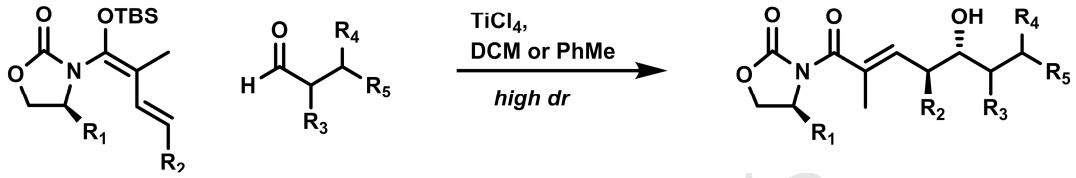

Further Insight into the Asymmetric Vinylogous Mukaiyama Aldol Reaction (VMAR); Application to the Synthesis of the C27–C45 Segment of Lagunamide A

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ABSTRACT:

Two iterative Vinylogous Mukaiyama Aldol Reactions (VMAR) have been applied in order to selectively install three contiguous stereocenters at C37, C38 and C39, of the southern hemisphere of lagunamide A. The VMAR methodology allows straightforward access of enantiomerically pure material of the essential segment via seven steps, and in an overall yield of 34 %. The synthesis has an orthogonal protecting group strategy, essential for upcoming synthesis for completion of lagunamide A. We also demonstrate that steric bulk of the chiral oxazolidinone pose certain challenges when employing stereochemically crowded α-substituted aldehydes in various VMAR's. A simple synthesis of the essential (2R,3S)-2-hydroxy-3-methylpentanoic acid fragment via Mitsunobu chemistry was also accomplished and incorporated into the C27–C45 fragment of lagunamide A.

1. Introduction

The structural combination of cyclodepsipeptides and polyketide moieties represent an interesting class of natural products with a broad range of potential therapeutics, sometimes with exceptional biological activities. In 2010, Tan reported[1a] the isolation of the complex macrocycle lagunamide A (**1**) (Figure 1) isolated from the cyanobacterium *Lyngbya majuscula*, found in Singapore.

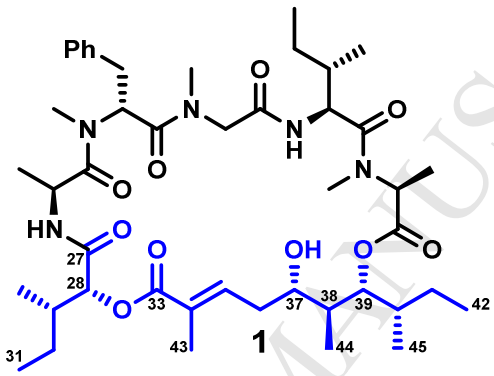
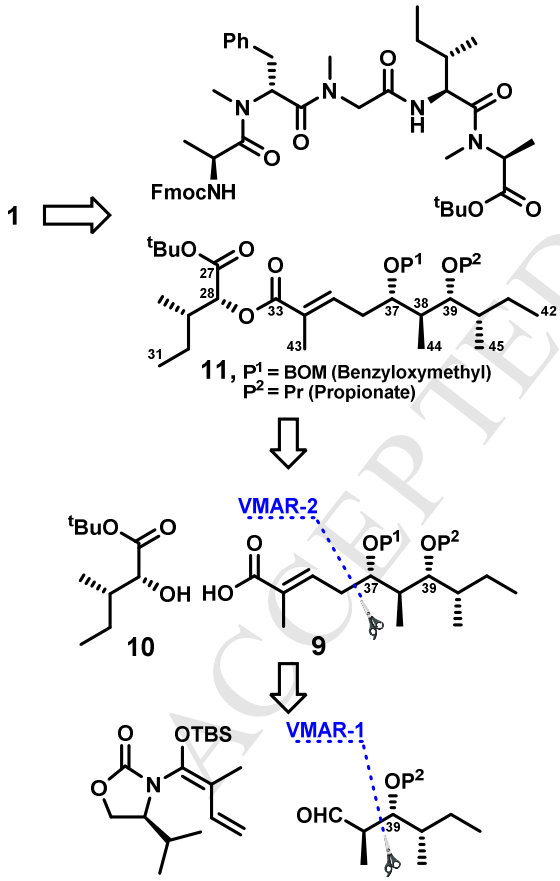


Figure 1. Lagunamide A (**1**).

Lagunamide A (**1**) not only possesses excellent anti-malarial properties (IC_{50}: 0.19–0.91 mM), but it also has unique, highly cytotoxic properties against leukemia cell lines (IC_{50}: 6.4–20.5 nM) and against colon cancer (IC_{50}: 1.6 nM).[1b] The therapeutic potential of lagunamide A coupled with its relative scarceness in nature has garnered significant interest from a number of research laboratories. Specifically, two completed total syntheses[2] and one formal synthesis[3a] of lagunamide A have been reported. Lagunamide A is structurally composed of a 26-member macrocycle with natural, unnatural, and *N*-methylated amino acids. The C27–C45 fragment is a quite unusual polyketide moiety with four contiguous stereocenters, extended by vinylogy to an α,β-unsaturated ester fragment and flanked by the (2*R*,3*S*)-2-hydroxy-3-methyl-pentanoic acid.

2. Results & discussion

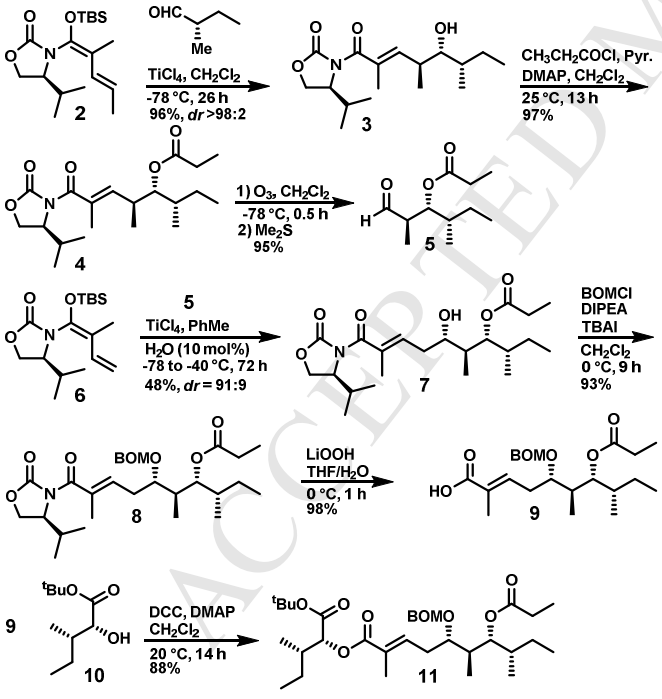
Our retrosynthetic strategy of lagunamide A (**1**) is based on the combination of the main pentapeptide and fragment **11** via either macro-lactonization or macro-lactamization methodology (Scheme 1). Structure **11** can be assembled from esterification of carboxylic acid **9** with alcohol **10**. Asymmetric vinylogous aldol reactions (VMAR's) can then be applied to establish the *anti*-aldol motif at C38–C39 (VMAR-1) and the stereocenter at C37 (VMAR-2). Thus, this strategy also allows for efficient discrimination of the protecting groups (P^1 and P^2) needed for the planned ring closure. The precise stereochemistry of **10** can be obtained from *L*-isoleucine via inversion of α-stereochemistry employing Mitsunobu technology.



Scheme 1. Strategy towards Lagunamide A (1)

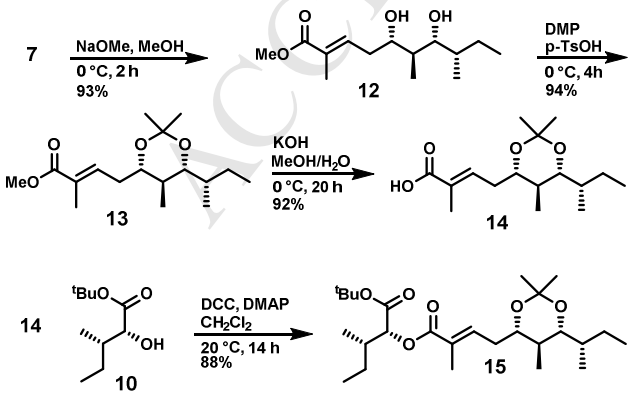
2.1 Synthesis of the C27-C45 fragment

This paper describes a short, direct, and highly asymmetric route with excellent overall yield of the C27–C45 fragment (**11**). This crucial intermediate was achieved mainly via two iterative asymmetric vinylogous aldol reactions, a powerful technique that has attracted widespread attention in the synthetic organic community,[4] where this manipulation was also instrumental in innovative natural product syntheses.[5] The version of a vinylogous Mukaiyama aldol reaction (VMAR) utilizing chiral oxazolidinones was first introduced by Kobayashi[6] in 2004. Herein, we report two such "remote" asymmetric induction reactions as general means to establish the required stereochemistry at the C37, C38 and C39 positions; by adopting the VMAR technique it greatly improved the overall yield (34%)[3b] of and decreased the number of steps[3c] to afford the southern hemisphere (**11**) of lagunamide A starting from 2(*S*)-methyl-1-butanal (Scheme 2).



Scheme 2. Synthesis of C27-C45 segment 11 applying VMAR methodologies

Thus, stereocenters C38 and C39 were installed via the first VMAR between titanium (IV) chloride pre-coordinated 2(*S*)-methyl-1-butanal and chiral vinylketene silyl *N*,*O*-acetal (**2**) in CH_2Cl_2 at -78 °C to give 96% of *anti*-alcohol **3** in excellent diastereomeric ratio (d.r.) (>98:2).[6,7] Protection of alcohol **3** as the propionate (**4**) followed by ozonolysis afforded aldehyde **5** in 95% yield. The second VMAR employing aldehyde **5** and chiral vinylketene silyl *N*,*O*-acetal **6** was more challenging however. Initially the VMAR provided a low 30% yield of alcohol product **7** (d.r. 91:9) when the reaction was conducted in the conventional CH_2Cl_2 medium, but the yield increased modestly to 48% with a d.r. (91:9) when instead toluene containing 10 mol% of water was applied as a medium and conducted for 72 h. The exact role of the presence of water during the VMAR is unknown, but water proved to reduce the reaction time and might also aid in the dissociation of titanium chelates.[8] Subsequent protection of alcohol **7** as the BOM ether provided **8** in 93% yield thus differentiating the protecting group functionalities at C37 and C39 for continued synthesis. Selective auxiliary cleavage over the ester functionality of **8** was accomplished utilizing LiOOH[9] in THF/H_2O to yield carboxylic acid **9** in 98% yield. Esterification coupling of acid **9** with α-hydroxy ester **10** was next achieved using DCC and DMAP and provided the southern portion of lagunamide A (**11**) in 88% yield. Thus, fragment **11** was obtained in a 34% overall yield in seven linear steps.



Scheme 3. Synthesis of Acetonide 15

With the intention of creating protecting group flexibility at C37 and C39 as well as verifying the generated absolute stereochemistry at C37–C39 from the VMAR's, synthesis of acetonide fragment **15** was also accomplished (Scheme 3).[2a] Removal of the chiral auxiliary and the propionate ester with methanolic sodium methoxide provided methyl ester diol **12** in 93% yield. Subsequent acetonide formation was then generated using DMP, catalytic *p*-TsOH and gave **13** in 94% yield. In order to establish the absolute stereochemistry, specific NMR data on its rigidified acetonide derivative **13** was determined (Figure 2).[10] The ^{13}C-NMR chemical shifts of the acetonide **13** methyl groups and the acetal carbon were 19.6, 30.2, and 98.0 ppm respectively, which is characteristic of a *syn*-1,3-diol acetonide configuration.[11] Moreover, not only did the observed NOE interactions reinforce the *syn*-stereochemistry but it also established the desired *E*-geometry of the alkene moiety of **13**.

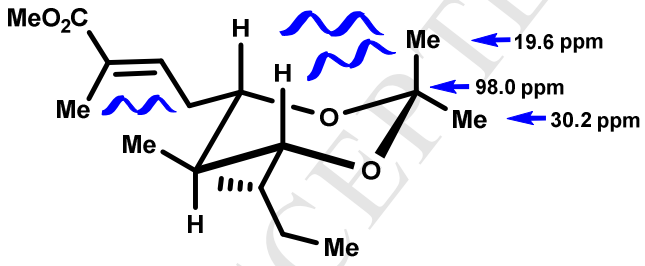


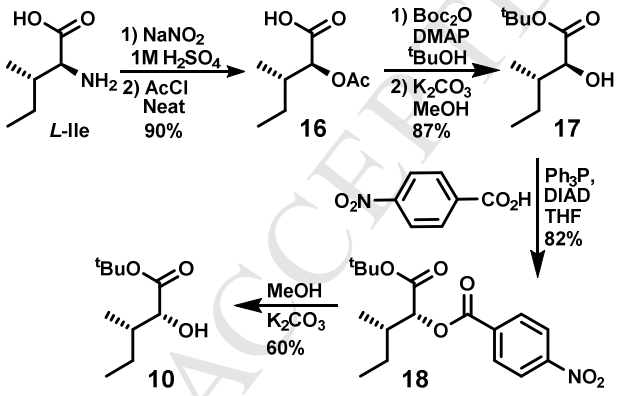
Figure 2. Major NOE observations and ^{13}C-NMR chemical shifts of *syn*-acetonide **13**.

Carboxylic acid **14** was then obtained in 92% yield by the basic hydrolysis of methyl ester **13** using aqueous potassium hydroxide in methanol. Intermediate **15** was subsequently obtained in 88% yield via the esterification of **14** with α-hydroxy ester **10** employing DCC and DMAP.

Thus, the essential southern portion of lagunamide A (**15**) was obtained in a 30% overall yield in eight linear steps. The C27–C45 intermediate was synthesized previously by Ye[2a] in an entirely different route that utilized Horner-Wadsworth-Emmons methodology to install the alkene with correct *E*-geometry. Our efforts towards fragment **15** unequivocally show an identical spectroscopic correlation to the work published by Ye, who also reported that removal of the acetonide group and selective mono-TES-silylation of the corresponding 1,3-diol at the C37-OH position was a reliable route towards synthetic lagunamide A.

2.2 Synthesis of (2*R*,3*S*)-2-hydroxy-3-methylpentanoic acid (10)

Synthesis of α-hydroxy *tert*-butyl ester **10** was accomplished in 33% overall yield on a gram scale utilizing inexpensive *L*-isoleucine (*L*-Ile) as starting material. Thus, it was more advantageous to adopt the Mitsunobu inversion of stereochemistry at the α-hydroxy stereocenter (Scheme 4) of the *L*-Ile derivative instead of manipulating the more costly *D-allo*-Ile as starting material.[12]

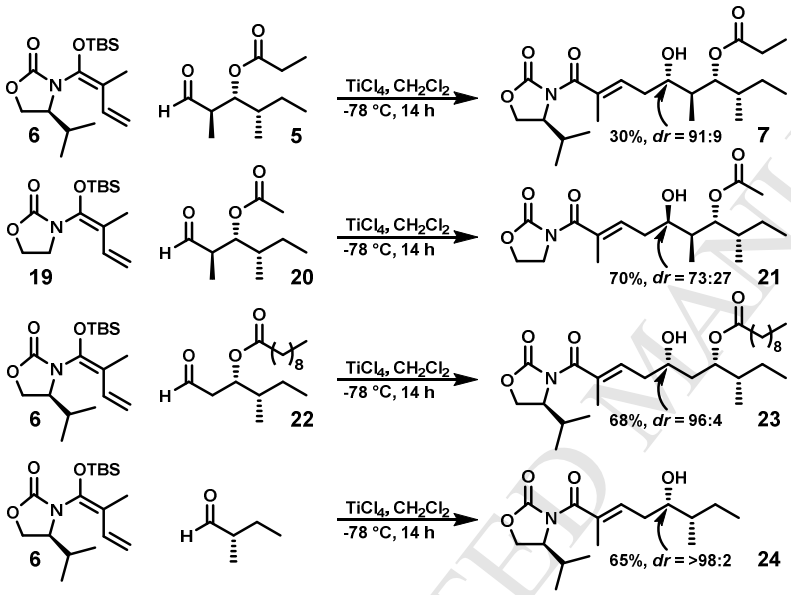


Scheme 4. Preparation of 10 from *L*-Ile

Diazotization of *L*-Ile afforded the α-hydroxy carboxylic acid,[12a] which was subsequently acetylated with neat acetyl chloride to afford **16** in 90% yield over two steps. Synthesis of the *tert*-butyl ester using Boc_2O and DMAP followed by basic hydrolysis in MeOH gave

intermediate **17** in 87% yield over two steps. Inversion of the α-hydroxy stereocenter of **17** was then completed via a straightforward Mitsunobu procedure[13] with *p*-nitrobenzoic acid, DIAD, and PPh_3 that afforded **18** in 82% yield. Mild subsequent saponification of the benzoate was then conducted using K_2CO_3 in MeOH to afford compound **10** in 60% yield.

2.3 Influence of substituted aldehydes on asymmetric VMAR



Scheme 5. Influence of Substituted Aldehydes on the Asymmetric VMAR

The VMAR demonstrated impressive versatility and stereocontrol through remote induction of an electrophilic addition as shown by the high diastereomeric ratio of the product. Even though the asymmetric VMAR was a very powerful tool, it had limitations as illustrated for the conversion of aldehyde **5** to vinylogous aldol product **7** in 48% yield when toluene was used as a medium (Scheme 2). When the VMAR was conducted in the conventional CH_2Cl_2 solvent, the yield dropped significantly to 30% of product **7**, but the lack of change in d.r. suggested a slow reaction with the aldehyde at low temperature. The amount of hydrolyzed vinylketene silyl *N,O*-acetal **6** formed over an extended amount of time also implied that the VMAR with aldehyde **5**

was rate determining. The VMAR was considerably faster when 2(*S*)-methyl-1-butanal was employed in contrast to aldehyde **5** with absolute 2(*R*)-methyl stereochemistry. Thus, it appeared as if the actual (*S*)-valine based chiral auxiliary (**6**) was detrimental to the overall yield of the VMAR using α-(*R*)-methyl substituted aldehydes. To confirm this suspicion of stereochemical crowding during the reaction, the VMAR was first conducted in the absence of the 2(*R*)-methyl stereocenter using aldehyde **22** (Scheme 5).[14] Vinylogous aldol product **23** was formed more rapidly at -78 °C, than in comparison to aldol product **7**, as the expected main diastereomer (96:4 d.r.) in 68% yield. We turned next to the influence of the (*S*)-valine based auxiliary and the bulk of the *iso*-propyl group in the VMAR. Thus, vinylketene silyl *N*,*O*-acetal **19**, lacking the chiral recognition within the 2-oxazolidone moiety, reacted readily with the stereochemically congested aldehyde **20** at -78 °C to give a 70% yield, but with the opposite major diastereomer of product **21** compared to the formed VMAR products **7** and **23**. Consequently, formation of the major diastereomer **21** was facilitated by the influence of specific α-methyl chirality of the aldehyde, but the rate of the VMAR was impeded particularly with α-(*R*)-methyl substituted aldehydes and the (*S*)-valine based auxiliary.

2.4 Proposed transition state

Based on our results from the VMAR's, we proposed the following transition state models for vinylketene silyl *N*,*O*-acetal **6**, and its nucleophilic approach to 2(*S*)- and 2(*R*)-methyl-substituted aldehydes, respectively (Figure 3).[15] As seen in both proposed transition state models the larger substituent faced away from the chiral auxiliary while the methyl group of larger 2(*R*)-methyl-substituted aldehyde **5** is pointing towards the auxiliary creating an unfavorable clash.

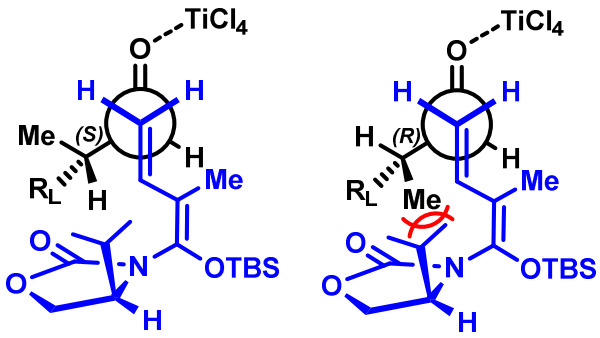


Figure 3. Proposed transition states for the nucleophilic attack of vinylketene *N*,*O*-acetal (**6**) ("blue") to *(S)*- and *(R)*-2-methyl substituted aldehydes, respectively.

3. Conclusion

This paper describes a direct vinylogous asymmetric approach to the C27–C45 southern fragment (**11**) of lagunamide A, mainly through iterations of Kobayashi's VMAR protocol.[6] The key fragment **11** was synthesized in seven steps, in an overall yield of 34%. The outcome of stereoselectivity and yield employing the VMAR using aldehydes with favorable as well as detrimental chirality at α-methyl stereocenters were also included.

4. Experimental section

4.1 General information

Melting points were recorded on Thomas Hoover Uni-Melt capillary melting point apparatus. Optical rotations were recorded on Perkin Elmer Model 343 polarimeter. IR spectra were recorded on Perkin Elmer FT-IR spectrum RXI. ^{1}H NMR spectra were recorded on a Varian 400, 500, and 600-MHz instrument using $CDCl_3$ or DMSO-d_6 with TMS as internal standard (δ = 0 ppm). $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.52 ppm) were used as internal references for ^{13}C (101, 126 and 151 MHz) NMR. All new compounds were characterized using ^{1}H- and ^{13}C

NMR, IR and MS. Chemical yields are based on purified material (>98% by ^{1}H-NMR spectroscopy). Coupling patterns are abbreviated as: s (singlet) d, (doublet), t (triplet), q (quartet) m, (multiplet), b, (broad), *J* (coupling constant). Preparative HPLC was carried out using Shimadzu SCL-10A/SPD-10A with Varian pursuit 10 C8 50-G 50mm column. Mass spectra were recorded using a Thermo Finnigan LCQ Deca or an Agilent 6330 ion trap. High-resolution mass spectra were recorded using the Agilent 6230 ESI-TOFMS. Analytical thin-layer chromatography was performed on Silicycle glass backed 60Å ultrapure silica gel. Flash chromatography was conducted using a Biotage Isolera one instrument with pre-packed silica gel columns (AnaLogix, Sepra Si 50) or self-packed Luknova and Biotage snap columns filled with silica gel (Sorbent Technologies, 60Å, 230–400 mesh). All moisture sensitive reactions were conducted under an argon atmosphere and in septum-capped oven-dried glassware unless otherwise specified. All solvents and reagents were purchased from Aldrich or Fisher Scientific unless otherwise specified. Ether and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl and were collected when the indicator became deep blue or purple. Dichloromethane was distilled from calcium hydride.

For preparation of compounds **A**, **C**, **D**, **E**, **F**, **G**, **16**, **17**; see Supplementary Data.

4.2 Experimental details

4.2.1 *N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-penta-1'*E*,3'*E*-dienyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (2).[6]

A premade solution of potassium hexamethyldisilylamide (KHMDS) (4.00 g, 20.1 mmol) in anhydrous THF (50 mL) was added dropwise to a solution of imide **A**[16] (3.00 g, 13.3 mmol) in THF (130 mL) at –78 ºC. The resulting reaction mixture was stirred for 90 min at –78 ºC

followed by the dropwise addition of a premade solution of TBSCl (3.41 g, 22.6 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred an additional 45 min at –78 ºC and then quenched with saturated ammonium chloride (50 mL). After transferring the reaction mixture to a separation funnel the mixture was extracted with ethyl acetate (3 × 25 mL). The combined organic extract was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The residual crude product was then purified with flash chromatography using hexanes/ethyl acetate 0–20% as a gradient to give 96% (4.34 g) of **2** as a white solid, mp 39–43 ºC, $[\alpha]^{20}_{D}$ -53.8º (c=0.84, $CHCl_3$) {lit.[6] oil, $[\alpha]^{25}_{D}$ -50.4º (c=0.84, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (d, C*H*CHCH$_3$, *J* = 15.5 Hz, 1H), 5.63 (dq, CH=C*H*CH$_3$, *J* = 15.5, 6.5 Hz, 1H), 4.34–4.29 (m, OC*H*$_2$, 1H), 4.15–4.09 (m, OC*H*$_2$, 1H), 4.03–3.97 (m, NC*H*, 1H), 1.98–1.90 (m, C*H*(CH$_3$)$_2$, 1H), 1.80–1.77 (dd, CHCHC*H*$_3$, *"partly hidden"*, *J* = 6.5, 1.6 Hz, 3H), 1.78 (s, C=CC*H*$_3$, 3H), 0.98 (s, ^{t}Bu, 9H), 0.94–0.91 (d, CH(C*H*$_3$)$_2$, *J* = 6.9 Hz, 6H), 0.19, 0.14 (2s, Si(C*H*$_3$)$_2$, 3H each); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.0, 134.8, 128.3, 124.5, 115.1, 64.5, 59.5, 29.5, 25.8, 18.9, 18.5, 18.2, 16.4, 12.4, -4.2, -4.7.

4.2.2 *N*-(5'*R*-Hydroxy-2',4'*S*,6'*S*-trimethyl-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (3).[17]

A solution of $TiCl_4$ (6.63 mmol, 1.50 equiv) in CH_2Cl_2 (20 mL) was added dropwise to a solution of (*S*)-2-methylbutanal (**B**)[18] (13.25 mmol, 3.00 equiv) in CH_2Cl_2 (30 mL) at –78 ºC. The resulting reaction mixture was stirred for 30 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal (**2**) (1.50 g, 4.42 mmol, 1.00 equiv) dissolved in CH_2Cl_2 (100 mL) was added dropwise over 30 min. The reaction mixture was stirred for 22 hours at –78 ºC and then

quenched with a mixture of saturated aqueous Rochelle Salt and saturated aqueous $NaHCO_3$ (50 mL, 1:1) at −78 ºC. The reaction mixture was warmed to room temperature while stirring, transferred to a separation funnel and extracted with ethyl acetate (4 × 20 mL). The combined organic extracts were washed with water (50 × mL) and brine (60 × mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified using a silica gel column (hexanes/ethyl acetate 0–25% as a gradient) to give the aldol product in an 96% (1.38 g) as colorless oil, $[\alpha]^{20}_D$ +21.6º (c=0.97, MeOH). {lit.[17] oil, $[\alpha]^{20}_D$ +24.2º (c=0.91, MeOH)} ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (dq, CHC*H*=CCH_3, *J* = 10.4, 1.5 Hz, 1H), 4.57 (ddd, NC*H*, *J* = 8.9, 5.8, 4.5 Hz, 1H), 4.34 (dd, OCH_2, *J* = 9.0, 8.9 Hz, 1H), 4.18 (dd, OCH_2, *J* = 9.0, 5.8 Hz, 1H), 3.30 (dd, C*H*OH, *J* = 8.9, 2.4 Hz, 1H), 3.00 (bs, CHO*H*, 1H), 2.78–2.69 (ddq, CHC*H*(Me)CHOH, *J* = 10.4, 9.1, 6.7 Hz, 1H), 2.38–2.31 (m, C*H*$(CH_3)_2$, 1H), 1.95 (d, CH_3C=CH, *J* = 1.5 Hz, 3H), 1.60–1.53 (m, C*H*(Me)CH_2, "*partly hidden*", 1H), 1.53–1.47 (m, CH(Me)CH_2, "*partly hidden*", 1H), 1.43–1.37 (m, CH(Me)CH_2, "*partly hidden*", 1H), 0.95–0.90 (m, 4×CH_3, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 154.5, 142.6, 131.1, 76.8, 63.4, 58.1, 37.3, 35.8, 28.4, 27.3, 17.8, 15.7, 15.2, 13.9, 12.1, 12.0; FTIR (neat, cm^{-1}) 3526, 2964, 1772, 1686, 1464, 1369, 1301, 1209, 996, 776, 688.

4.2.3 *N*-(2',4'*S*,6'*S*-Trimethyl-5'*R*-propionyloxy-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (4).

Alcohol **3** (1.93 g, 6.20 mmol, 1.00 equiv) was charged in a dry 100 mL round bottom flask under argon. The substrate was dissolved in freshly distilled CH_2Cl_2 (18 mL) and then the solution was cooled to +3 ºC using an ice/water bath. Anhydrous pyridine (2.00 mL, 24.79 mmol, 4.00 equiv) was added followed by drop-wise addition of freshly distilled propionyl

chloride (2.17 mL, 24.79 mmol, 4.00 equiv) over 5 min. After the addition of DMAP (350 mg, 3.10 mmol) the pale yellow heterogeneous reaction mixture was stirred towards ambient temperature over 13 hours. Saturated ammonium chloride (20 mL) was then added to the resulting homogeneous solution at room temperature. The reaction mixture was then transferred to a separation funnel and phases separated. The aqueous phase was then extracted with CH_2Cl_2 (3 × 20 mL), the combined organics were washed with 1M NaOH (20 mL), Brine (40 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was the purified using a silica gel column (hexanes/ethyl acetate 0–25% as a gradient) to give the aldol product in 97% (2.21 g) as colorless oil, $[\alpha]^{20}_D$ +62.5º (c=1.55, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dq, CHC*H*=CCH_3, *J* = 9.8, 1.5 Hz, 1H), 4.87 (dd, CHC*H*(OR)CH, *J* = 6.8, 5.3 Hz, 1H), 4.45 (ddd, NC*H*, *J* = 8.7, 4.7, 4.4 Hz, 1H), 4.29 (dd, OCH_2, *J* = 8.8, 8.7 Hz, 1H), 4.18 (dd, OCH_2, *J* = 8.8, 4.7 Hz, 1H), 2.91–2.83 (ddq, C*H*(Me)CH(OR), *J* = 9.8, 6.8, 6.8 Hz, 1H), 2.42–2.36 (m, C*H*(CH_3)$_2$, "*partly hidden*", 1H), 2.36–2.30 (dq, C(O)CH_2CH_3, *J* = 7.6, 3.4 Hz, 2H), 1.91 (d, CH_3C=CH, *J* = 1.5 Hz, 3H), 1.72–1.63 (m, C*H*(Me)CH_2, 1H), 1.41–1.32 (m, CH(Me)CH_2CH_3, 1H), 1.20–1.09 (m, CH(Me)CH_2CH_3, "*partly hidden*", 1H), 1.13 (t, CH_2CH_3, *J* = 7.6 Hz, 3H), 0.98 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.92 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.92–0.89 (t, CH_2CH_3, "*partly hidden*", *J* = 6.8 Hz, 3H), 0.90 (d, CH(CH_3)$_2$, "*partly hidden*", *J* = 6.8 Hz, 3H), 0.89 (d, CH(CH_3)$_2$, "*partly hidden*", *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 171.6, 153.3, 138.6, 131.4, 78.8, 63.4, 58.4, 36.1, 34.7, 28.3, 27.7, 26.3, 17.9, 16.4, 14.9, 13.7, 13.6, 11.4, 9.3; FTIR (neat, cm^{-1}) 2965, 1787, 1736, 1684; HRMS (ESI) m/z calcd for $C_{20}H_{33}NO_5Na$ $[M+Na]^+$ 390.2251, found 390.2248.

4.2.4 2*R*,4*S*-Dimethyl-3*R*-propionyloxy-1-hexanal (5).

A solution of compound **4** (1.01 g, 2.73 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled to –78 ºC. A slow stream of ozone gas was then bubbled through the solution for roughly 30 min until the solution turned light blue. The blue solution was flushed by bubbling oxygen for 15 min at –78 ºC followed by bubbling argon for 15 min until the blue color faded. Excess dimethyl sulfide (1.25 ml, 17.02 mmol) was then added drop-wise over 5 min at –78 ºC. The temperature was then raised to ambient temperature and the mixture stirred an additional 12 hours. The solvent was removed under reduced pressure and the remaining crude product was purified on a silica gel plug (hexanes in ethyl acetate, 0–15% as a gradient) to afford **5** as a clear oil in 95% (0.519 g), $[\alpha]^{20}_{D}$ –0.85º (c=3.75, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, C*H*O, *J* = 3.2 Hz, 1H), 5.13 (dd, CHC*H*(OR)CH, *J* = 7.5, 4.6 Hz, 1H), 2.69–2.60 (ddq, *H*CCHO, *J* = 7.5, 7.0, 3.2 Hz, 1H), 2.36–2.29 (q, C(O)CH_2CH$_3$, *J* = 4.8 Hz, 2H), 1.75–1.66 (m, C*H*(Me)CH$_2$,1H), 1.45–1.32 (m, CH(Me)CH_2, 1H), 1.25–1.12 (m, CH(Me)CH_2, "*partly hidden*", 1H), 1.14 (t, CH$_2$CH_3, *J* = 7.6 Hz, 3H), 1.09 (d, CHCH_3, *J* = 7.1 Hz, 3H), 0.93 (t, "*partly hidden*", CH$_2$CH_3, *J* = 7.5 Hz, 3H), 0.92 (d, CHCH_3, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.8, 174.1, 75.8, 48.6, 36.2, 27.7, 26.3, 13.5, 11.6, 11.2, 9.3; FTIR (neat, cm^{-1}) 2974, 1736, 1706; HRMS (ESI) m/z calcd for $C_{11}H_{20}O_3$ $[M+H]^+$ 201.1485, found 201.1488.

4.2.5 *N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-buta-1'*E*,3'dienyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (6).[6]

A solution of solid KHMDS (3.20 g, 16.02 mmol) in anhydrous THF (230 mL) was added dropwise to a solution of imide **C**[19] (1.81 g, 10.68 mmol) in THF (110 mL) at –78 ºC. After the reaction mixture was stirred for 90 min at –78 ºC a solution of TBSCl (4.83 g, 18.16 mmol) in

THF (25 mL) was added dropwise over 20 min at –78 ºC. The reaction mixture was stirred at –78 ºC until completion was verified via TLC analysis (~45 min). The reaction was then quenched with saturated aqueous NH_4Cl (50 mL) at –78 ºC. The temperature of the resulting mixture was allowed to reach ambient temperature and stirred for an additional 30 min. The two phase mixture was then transferred to a separation funnel, the phases separated and the aqueous phase extracted with ethyl acetate (4 × 20 mL). The combined organic phases were washed with water (50 mL), brine (50 mL) and dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the crude product was then purified with flash chromatography using hexanes/ethyl acetate 0–40% as a gradient to give 86% (2.99 g) of vinylketene silyl *N*,*O*-acetal **6** as a white solid, mp 44–49 ºC, $[\alpha]^{20}_D$ -71.0º (c=0.87, $CHCl_3$). {lit.[6] mp 48.7 ºC, $[\alpha]^{25}_D$ -65.7º (c=0.87, $CHCl_3$)}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (dd, *H*C=CH_2, *J* = 17.1, 10.0 Hz, 1H), 5.05 (d, HC=C*H*$_2$, *J* = 17.1 Hz, 1H), 4.94 (d, HC=C*H*$_2$, *J* = 10.9, 1H), 4.27–4.20 (m, OC*H*$_2$, 1H), 4.07–4.00 (m, OC*H*$_2$, 1H), 3.97–3.89 (m, NC*H*, 1H), 1.91–1.82 (m, C*H*$(CH_3)_2$, 1H), 1.71 (s, C=C(C*H*$_3$), 3H), 0.90 (s, ^{t}Bu, 9H), 0.84, 0.83 (2d, CH(C*H*$_3$)$_2$, "partly overlap", *J* = 7.0 Hz, 3H each), 0.12, 0.10 (2s, Si(C*H*$_3$)$_2$, 3H each); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 136.8, 133.9, 115.2, 112.4, 64.5, 59.5, 29.5, 25.7, 18.3, 18.1, 16.4, 11.6, -4.2, -4.7.

4.2.6 *N*-(5'*S*-Hydroxy-2',6'*S*,8'*S*-trimethyl-7'*R*-propionyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (7).

To a stirred solution of aldehyde **5** (0.350 g, 1.75 mmol) in toluene (2.0 mL) at –78 ºC under argon was slowly added $TiCl_4$ (2.65 mL, 1.0 M solution in toluene, 2.65 mmol). The reaction mixture was stirred for 20 min at –78 ºC and a solution of vinylketene silyl *N*,*O*-acetal **6** (1.30 g, 4.00 mmol) in toluene (2.5 mL) at –78 ºC was added dropwise over 10 min and stirred. The

reaction mixture was stirred for one hour at –78 ºC and 10 mol% deionized water was added. The resulting reaction mixture was then stirred at oscillating temperatures of –78 ºC and –40 ºC, switching every 12 hours for a total of 72 hours providing a dark violet to heterogeneous, dark orange reaction mixture. After the 72 hour reaction time a mixture of saturated aqueous Rochelle salt and saturated aqueous $NaHCO_3$ was added (1:1, 25 mL) at –40 ºC. The mixture was then stirred vigorously at ambient temperature until the resulting slurry became homogeneous and then transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4 × 20 mL) and the combined organic phases were washed with water (30 mL) followed by brine (40 mL). The organic phase was then dried over anhydrous sodium sulfate. After filtration the solvent was removed under reduced pressure and the remaining crude product was purified with flash chromatography using hexanes/ethyl acetate 0–35% as a gradient to give 48% (344 mg) of aldol product **7** (*dr* = 91:9) as a clear oil, $[\alpha]^{20}_{D}$ +47.2º (c=1.06, MeOH, *dr* = 91:9). ^{1}H NMR (500 MHz, $CDCl_3$) "*Major diasteromer*" δ 6.09 (dd, C=C*H*CH_2, *J* = 7.3 Hz, 1H), 4.90 (dd, CHC*H*(OR)CH, *J* = 10.0, 2.8 Hz, 1H), 4.50 (ddd, NC*H*, *J* = 9.0, 5.0, 4.8 Hz, 1H), 4.30 (dd, OC*H*$_2$CH, *J* = 9.0, 9.0 Hz, 1H), 4.17 (dd, OC*H*$_2$CH, *J* = 9.0, 5.0 Hz, 1H), 3.64–3.58 (m, CH_2C*H*(OH)CH, 1H), 2.87 (s, CHO*H*, 1H), 2.50–2.41 (m, CHC*H*$_2$CH(OH), "*partly hidden*", 1H), 2.39 (q, C(OR)C*H*$_2$$CH_3$, "*partly hidden*", *J* = 7.6 Hz, 2H), 2.37–2.31 (m, CHC*H*$(CH_3)_2$, "*partly hidden*", 1H), 2.28 (m, CHC*H*$_2$CH(OH), 1H), 1.92 (s, HC=CC*H*$_3$, 3H), 1.80–1.71 (m, CH(OH)C*H*CH_3, 1H), 1.71–1.63 (m, CH(OR)C*H*CH_3, 1H), 1.35–1.24 (m, CHC*H*$_2$$CH_3$, 1H), 1.22–1.12 (m, CHC*H*$_2$$CH_3$, "*partly hidden*" 1H), 1.17 (t, CH_2C*H*$_3$, *J* = 7.6 Hz, 3H), 0.94–0.88 (m, 4 × CHC*H*$_3$ + CH_2C*H*$_3$, 15H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 171.8, 153.7, 136.0, 132.3, 77.6, 69.0, 63.5, 58.4, 39.2, 35.8, 33.4, 28.5, 27.9, 27.2, 18.0, 15.2, 14.0, 12.7, 12.0, 9.5,

9.0; FTIR (neat, cm^{-1}) 3527, 2966, 1782, 1733, 1683, 1203; HRMS (ESI) m/z calcd for $C_{22}H_{37}NO_6Na$ $[M+Na]^+$ 434.2513, found 434.2515.

4.2.7 *N*-(5'*S*-Benzyloxymethoxy-2',6'*S*,8'*S*-trimethyl-7'*R*-propionyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (8).

To a stirred solution of **7** (*dr* = 91:9) (300 mg, 0.729 mmol) in anhydrous CH_2Cl_2 (6.0 mL), diisopropylethylamine (0.240 mL, 1.312 mmol) and tetrabutylammonium iodide (0.068 g, 0.182 mmol) under argon was added benzyloxymethylchloride (0.220 mL, 1.093 mmol, 1.50 equiv). The resulting reaction mixture was stirred for 9 h at room temperature. The mixture was then quenched with MeOH (5 mL), stirred for 10 min and the solvents evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10.0 mL), water (8 mL) was added and the mixture transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (3 × 8 mL) and combined organics were dried over anhydrous Na_2SO_4. The solvent was filtered, concentrated under reduced pressure and the residual yellow oil was purified with flash chromatography using hexanes/ethyl acetate 0–20% as a gradient to give 93% (360 mg) of **8** (*dr* = 91:9) as a colorless oil, $[\alpha]^{20}_D$ +56.7º (c=3.50, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (400 MHz, $CDCl_3$) "*Major diasteromer*" δ 7.33–7.31 (m, Ar*H*, 5H), 6.03 (ddq, MeC=C*H*CH_2, *J* = 8.1, 6.6, 1.5 Hz, 1H), 5.03 (dd, CHC*H*(OR)CH, *J* = 9.7, 2.5 Hz, 1H), 4.80 (d, OCH_2O, *J* = 7.1 Hz, 1H), 4.72 (d, OCH_2O, *J* = 7.1 Hz, 1H), 4.69 (d, OCH_2Ar, *J* = 12.0 Hz, 1H), 4.54 (d, OCH_2Ar, *J* = 12.0 Hz, 1H), 4.46 (ddd, NC*H*, *J* = 8.9, 5.3, 4.3 Hz, 1H), 4.27 (dd, OCH_2CH, *J* = 8.9, 8.9 Hz, 1H), 4.13 (dd, OCH_2CH, *J* = 8.9, 5.3 Hz, 1H), 3.60 (ddd, CH_2C*H*(OR)CH, *J* = 7.8, 5.9, 1.7 Hz, 1H), 2.71–2.62 (m, CHCH_2CH, 1H), 2.51–2.40 (m, CHCH_2CH, 1H), 2.32 (q, C(CO)C$H_2$$CH_3$, *J* = 7.6 Hz, 2H), 2.35–2.27 (m, CHC*H*$(CH_3)_2$, "*partly hidden*", 1H),1.90 (d, (CH_3)C=CH, *J* = 1.5 Hz, 3H),

1.91–1.86 (m, CHC*H*CH, "*partly hidden*", 1H), 1.66–1.57 (m, CHC*H*CH_2, 1H), 1.35–1,27 (m, CHC*H*$_2$$CH_3$, 1H), 1.13 (t, C(CO)$CH_2$C*H*$_3$, *J* = 7.6 Hz, 3H), 1.12–1.02 (m, CHC*H*$_2$$CH_3$, 1H), 0.90 (t, CH_2C*H*$_3$, *J* = 7.0 Hz, 3H), 0.90 (d, CHC*H*$_3$, "*partly hidden*", *J* = 6.9 Hz, 3H), 0.89 (d, CHC*H*$_3$, "*partly hidden*", *J* = 6.9 Hz, 3H), 0.87 (d, CHC*H*$_3$, *J* = 6.9 Hz, 3H), 0.85 (d, CHC*H*$_3$, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 171.8, 153.6, 138.3, 135.3, 132.6, 128.5, 127.9, 127.6, 96.0, 78.2, 76.4, 69.9, 63.5, 58.3, 38.2, 36.5, 32.56, 28.5, 28.0, 27.3, 18.0, 15.1, 14.0, 12.5, 12.1, 10.2, 9.6; FTIR (neat, cm^{-1}) 2966, 1786, 1733, 1683, 1456, 1212, 1038, 739; HRMS (ESI) m/z calcd for $C_{30}H_{45}NO_7Na$ $[M+Na]^+$ 554.3088, found 554.3086.

4.2.8 5*S*-Benzyloxymethoxy-2,6*S*,8*S*-trimethyl-7*R*-propionyl-oxy-2*E*-decenoic acid (9).

To a 0.05 M ice-cold solution of substrate **8** (160 mg, 0.301 mmol) in THF:H_2O (8.0 mL, 3:1) was added 30% H_2O_2 (0.267 mL, 1.48 mmol) followed by the addition of LiOH (17 mg, 0.62 mmol). The reaction mixture was stirred for 30 min at 0 ºC. Excess of peroxide was then quenched with 10% excess aqueous Na_2SO_3 (1.5 M, 1.82 mL) at 0 ºC and resulting reaction mixture was stirred an additional 15 min. Resultant mixture was buffered to pH ~9 with saturated aqueous $NaHCO_3$ and the organic solvent removed under reduced pressure. The residue was transferred to a separation funnel the aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL) and the combined organic phases were dried over anhydrous Na_2SO_4. The solvent was filtered, concentrated under reduced pressure and the crude product purified with flash chromatography using ethyl acetate/hexanes 25–75% as a gradient to give 98% (124 mg) of **9** as a clear oil, $[\alpha]^{20}_D$ +49.8º (c=1.33, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (m, Ar*H*, 1H), 7.35–7.30 (m, Ar*H*, 4H), 6.87 (ddq, MeC=C*H*CH_2, *J* = 8.3, 6.8, 1.4 Hz, 1H), 5.04 (dd, CHC*H*(OR)CH, *J* = 9.6, 2.5 Hz, 1H), 4.79 (d, OC*H*$_2$O, *J* = 7.1 Hz, 1H), 4.73 (d, OC*H*$_2$O, *J* = 7.1

Hz, 1H), 4.69 (d, ArC*H*$_2$O, *J* = 11.9 Hz, 1H), 4.54 (d, ArC*H*$_2$O, *J* = 11.9 Hz, 1H), 3.62 (ddd, CH$_2$C*H*(OR)CH, *J* = 7.8, 6.0, 1.7 Hz, 1H), 2.75–2.64 (m, C=CHC*H*$_2$CH, 1H), 2.50–2.40 (m, C=CHC*H*$_2$CH, 1H), 2.32 (q, C(CO)C*H*$_2$CH$_3$, *J* = 7.5 Hz, 2H), 1.85 (d, (C*H*$_3$)C=CH, *J* = 1.4 Hz, 3H), 1.87–1.76 (m, CHC*H*(Me)CH, "*partly hidden*", 1H), 1.66–1.54 (m, CHC*H*(Me)CH$_2$, 1H), 1.37–1.23 (m, CHC*H*$_2$CH$_3$, 1H), 1.13 (t, C(CO)CH$_2$C*H*$_3$, *J* = 7.6 Hz, 3H), 1.15–1.03 (m, CHC*H*$_2$CH$_3$, "*partly hidden*", 1H), 0.91 (t, CH$_2$C*H*$_3$, *J* = 7.2 Hz, 3H), 0.90 (d, CHC*H*$_3$, *J* = 6.8 Hz, "*partly hidden*", 3H), 0.84 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, CDCl$_3$) δ 174.1, 172.4, 140.9, 137.9, 128.4, 128.3, 127.5, 127.0, 95.7, 77.9, 76.1, 69.8, 38.1, 36.3, 32.8, 27.8, 27.0, 12.4, 12.3, 11.9, 10.2, 9.4; FTIR (neat, cm-1) 2969, 1730, 1686, 1648, 1456, 1276, 1193, 911, 735; HRMS (ESI) m/z calcd for $C_{24}H_{35}O_6$ $[M-H]^-$ 419.2439, found 419.2438.

4.2.9 2*R*-Hydroxy-3*S*-methylpentanoic acid *tert*-butyl ester (10).[2a]

Ester **18** (3.05 g, 9.04 mmol) was dissolved in anhydrous methanol (25 mL) and cooled to ~0 ºC with an ice-water bath. Solid anhydrous K_2CO_3 (1.88 g, 13.6 mmol) was added in one portion and the resulting mixture stirred vigorously for 1 h. Water (25 mL) was added and the reaction mixture was rapidly stirred until the solids dissolved. Methanol was then removed under reduced pressure and the residue was transferred to a separation funnel and extracted with EtOAc (4 × 15 mL). The combined organic phases were washed with brine (50 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified on a silica gel column (0–10% gradient of CH_2Cl_2 in toluene) to give the product in 60% (1.03 g) as colorless oil, $[\alpha]^{20}_D$ -6.36º (c=1.14, CH_2Cl_2). lit.[2a] oil, $[\alpha]^{20}_D$ -3.1º (c=0.7, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.04 (dd, CHC*H*OH, *J* = 5.6, 2.8 Hz, 1H), 2.74 (d, CHCHO*H*, *J* = 5.6 Hz, 1H), 1.77 (dtq, CH$_2$C*H*(Me)CH, *J* = 6.9, 6.9, 2.8 Hz, 1H), 1.58–1.46 (m, C*H*$_2$CH$_3$, "*partly*

hidden", 1H), 1.49 (s, ^{t}Bu, 9H), 1.37–1.25 (m, C*H*$_2$CH$_3$, 1H), 0.95 (t, C*H*$_3$CH$_2$, *J* = 7.4 Hz, 3H), 0.81 (d, C*H*$_3$CH, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 82.4, 73.2, 38.7, 28.2, 26.2, 13.1, 12.0; FTIR (neat, cm^{-1}) 3502, 2968, 1724, 1459, 1369, 1256, 1130, 849; MS (ESI) m/z calcd for $C_{10}H_{21}O_3$ $[M+H]^+$ 189.14, found 188.85.

4.2.10 1-*tert*-Butoxy-1-oxo-3*S*-methyl-2*R*-pentanyl 5'*S*-(benzyloxymethoxy)-2',6'*S*,8'*S*-trimethyl-7'*R*-(propionyloxy)dec-2'-*E*-enoate (11).

Carboxylic acid **9** (50.0 mg, 0.119 mmol) and alcohol **10** (30.0 mg, 0.159 mmol) were dissolved in distilled CH_2Cl_2 (2.0 mL) under argon atmosphere and the mixture cooled in a **3*S*** ice-water bath. DCC (40.0 mg, 0.190 mmol) and DMAP (24.0 mg, 0.190 mmol) were added at ~0 ºC, the mixture stirred for 1 h and an additional 14 hours at ambient temperature. Saturated aqueous NH_4Cl (10 mL) was added to the grey turbid reaction and the mixture transferred to a separation funnel. The aqueous phase was extracted with CH_2Cl_2 (4 × 12 mL), the combined organics dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was then purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–15%) to afford product **11** (62.0 mg, 88%) as a clear oil, $[\alpha]^{20}_D$ +24.8º (c=1.50, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, Ar*H*, 5H), 6.76 (ddq, MeC=C*H*CH$_2$, *J* = 8.2, 6.4, 1.6 Hz, 1H), 5.04 (dd, CHC*H*(OR)CH, *J* = 9.7, 2.4 Hz, 1H), 4.93 (d, *J* = 3.3 Hz, (CO)C*H*(OR)CH, 1H), 4.80 (d, OC*H*$_2$O, *J* = 7.0 Hz, 1H), 4.72 (d, OC*H*$_2$O, *J* = 7.0 Hz, 1H), 4.69 (d, ArC*H*$_2$O, *J* = 12.0 Hz, 1H), 4.55 (d, ArC*H*$_2$O, *J* = 12.0 Hz, 1H), 3.61 (ddd, CH$_2$C*H*(OR)CH, *J* = 8.8, 5.5, 1.6 Hz, 1H), 2.72–2.64 (m, C=CHC*H*$_2$CH, 1H), 2.52–2.44 (m, C=CHC*H*$_2$CH, 1H), 2.34–2.26 (m, HC(OR)C*H*(Me)CH$_2$, "*partly hidden*", 1H), 2.31 (q, C(CO)C*H*$_2$CH$_3$, *J* = 7.6 Hz, 2H), 2.02–1.94 (m, CHC*H*(Me)CH, 1H), 1.87 (bs, C*H*$_3$C=C, 3H), 1.84–1.76 (m,

CHC*H*(Me)CH_2, 1H), 1.65–1.55 (m, CH(Me)C$H_2$$CH_3$, "*partly hidden*", 1H), 1.45 (s, ^{t}Bu, 9H), 1.46–1.44 (m, CH(Me)C$H_2$$CH_3$, "*partly hidden*", 1H), 1.34–1.27 (m, CH(Me)C$H_2$$CH_3$, 1H), 1.13 (t, *J* = 7.6 Hz, CH_2CH_3, 3H), 1.10–1.04 (m, CH(Me)C$H_2$$CH_3$, 1H), 0.97 (d, *J* = 6.9 Hz, CHCH_3, 3H), 0.93 (d, *J* = 6.8 Hz, "*partly hidden*", CHCH_3, 3H), 0.90 (t, *J* = 6.8 Hz, "*partly hidden*", CH_2CH_3, 3H), 0.89 (t, *J* = 6.8 Hz, "*partly hidden*", CH_2CH_3, 3H), 0.83 (d, *J* = 6.7 Hz, CHCH_3, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 169.2, 167.4, 138.9, 138.2, 129.1, 128.5, 127.9, 127.7, 95.8, 81.9, 77.9, 76.3, 75.3, 69.9, 37.9, 36.9, 36.4, 32.6, 28.2, 28.09, 27.2, 26.4, 14.4, 12.8, 12.4, 12.1, 11.8, 10.0, 9.6; FTIR (neat, cm^{-1}) 3450, 2967, 2935, 2879, 1725, 1719, 1649, 1461, 1368, 1247, 1108, 1041, 912, 733; MS (ESI) m/z calcd for $C_{34}H_{54}O_8Na$ $[M+Na]^+$ 613.37, found 613.40.

4.2.11 Methyl 5*S*,7*R*-Dihydroxy-2,6*S*,8*S*-trimethyldec-2*E*-enoate (12).

Vinylogous alcohol **7** (250 mg, 0.608 mmol) was dissolved in anhydrous MeOH (10 mL) and stirred at 0 ºC under argon. A methanolic sodium methoxide solution, prepared at 0 ºC by adding sodium metal (0.055 g, 1.822 mmol) to anhydrous MeOH (5.0 mL) under argon, was added dropwise to the substrate over 10 min. The reaction mixture was stirred for 2 h at 0 ºC and the reaction was quenched with saturated ammonium chloride (20 mL). The volatiles were removed *in vacuo* and the resulting heterogeneous slurry was diluted with minimal water (1–2 mL) and then transferred to a separation funnel. The aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL), the combined organics dried over anhydrous sodium sulfate and filtered. The organic solvent was added silica gel (~2.5 g), the solvent removed under reduced pressure and the residual material dry loaded onto a silica gel column. The crude product was then purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–50%) to afford product

12 (145 mg, 93%) as a clear oil, $[\alpha]^{20}_{D}$ +24.8º (c=0.52, $CDCl_3$, *dr* = 91:9). ^{1}H NMR (500 MHz, $CDCl_3$) (*Major diastereomer*, ***5S***) δ 6.86 (ddq, MeC=C*H*CH_2, *J* = 7.3, 7.3, 1.5 Hz, 1H), 4.07–4.01 (m, CH_2C*H*(OH), 1H), 3.74 (s, ROC*H*$_3$, 3H), 3.57–3.52 (m, CHC*H*(OH)CH, 1H), 2.86 (bs, RO*H*, 1H), 2.52–2.43 (m, C=CHC*H*$_2$CH, 1H), 2.34–2.25 (m, C=CHC*H*$_2$CH, 1H), 2.20 (bs, RO*H*, 1H), 1.88 (d, *H*$_3$CC=CH, *J* = 1.5 Hz, 3H), 1.87–1.81 (m, CHC*H*CH, "*partly hidden*", 1H), 1.61–1.51 (m, CHC*H*CH_2, 1H), 1.44–1.36 (m, C*H*$_2$$CH_3$, 1H), 1.28–1.20 (m, C*H*$_2$$CH_3$, 1H), 0.93 (t, CH_2C*H*$_3$, "*partly hidden*", *J* = 7.5 Hz, 3H), 0.91 (d, CHC*H*$_3$, "*partly hidden*", *J* = 6.3 Hz, 3H), 0.90 (d, CHC*H*$_3$, "*partly hidden*", *J* = 6.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 139.3, 129.5, 78.0, 72.8, 51.9, 39.1, 37.2, 33.2, 26.7, 12.9, 12.8, 11.9, 11.8; FTIR (neat, cm^{-1}) 3437, 2961, 1698, 1458; MS (ESI) m/z calcd for $C_{14}H_{26}O_4$ $[M+H]^+$ 259.18, found 259.05. ^{1}H NMR (500 MHz, $CDCl_3$) (*Minor diastereomer*, ***5R***) δ 6.93 (ddq, MeC=C*H*CH_2, *J* = 8.0, 6.4, 1.5 Hz, 1H), 3.83 (ddd, CH_2C*H*(OH)CH, *J* = 7.8, 7.8, 3.6 Hz, 1H), 3.74 (s, ROC*H*$_3$, 3H), 3.57 (dd, CHC*H*(OH)CH, *J* = 9.3, 2.2 Hz, 1H), 2.53–2.44 (m, C=CHC*H*$_2$CH, 1H), 2.43–2.33 (m, C=CHC*H*$_2$CH, 1H), 1.87 (d, *H*$_3$CC=CH, *J* = 1.5 Hz, 3H), 1.77–1.66 (m, CHC*H*CH, 1H), 1.60–1.52 (m, CHC*H*CH_2, "*partly hidden*", 1H), 1.45–1.25 (m, C*H*$_2$$CH_3$, "*partly hidden*", 2H), 0.94 (t, CH_2C*H*$_3$, *J* = 7.4 Hz, 3H), 0.86 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H), 0.79 (d, CHC*H*$_3$, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 138.8, 129.6, 79.5, 76.1, 51.9, 41.0, 37.0, 34.4, 27.1, 13.2, 12.9, 12.2, 11.7.

4.2.12 Methyl (6*R*-[1'*S*-methylpropyl]-2,2,5*S*-trimethyl-1,3-dioxane-4*S*-yl)-2''-methylbut-2''*E*-enoate (13).

Diol **12** (60.0 mg, 0.232 mmol) was dissolved in 2,2-dimethoxypropane (3.0 mL) at room temperature. The reaction mixture was charged with catalytic amount of *p*-TsOH (12 mg, 70 mmol), sealed under an argon atmosphere and the reaction mixture stirred for 4 h. Saturated $NaHCO_3$ (1.0 mL) was carefully added and excess of organic solvent was removed under reduced pressure. Water (5.0 mL) and ethyl acetate (5.0 mL) was added and the mixture was transferred to a separation funnel. The aqueous phase was extracted with ethyl acetate (4 × 15 ml) the combined organic phases were dried over anhydrous sodium sulfate and then filtered. After removal of the solvent under reduced pressure the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–5%) to afford product **13** (64.0 mg, 94%) as a clear oil, $[\alpha]^{20}_D$ +4.89º (c=0.47, CH_2Cl_2, dr = 91:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (ddq, MeC=C*H*CH_2, *J* = 6.9, 6.9, 1.5 Hz, 1H), 3.74 (s, OCH_3, 3H), 3.57 (ddd, CH_2C*H*(OR)CH, *J* = 10.4, 7.5, 3.2 Hz, 1H), 3.45 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.52–2.43 (m, C=CHCH_2CH, 1H), 2.33–2.24 (m, C=CHCH_2CH, 1H), 1.84 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.57–1.51 (m, CHC*H*CH, "*partly hidden*", 1H), 1.52–1.44 (m, CHC*H*CH_2, "*partly hidden*", 1H), 1.42–1.22 (m, CHC$H_2$$CH_3$, 2H), 1.39 (s, CC$H_3$, 3H), 1.33 (s, CC$H_3$, 3H), 0.88 (t, CH_2CH_3, *J* = 7.4 Hz, 3H), 0.84 (d, CHCH_3, *J* = 6.8 Hz, 3H), 0.75 (d, CHCH_3, *J* = 6.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) (*Major diast*ereomer, **5*S***, "*syn*") δ 168.7, 139.4, 128.8, 98.0, 77.4, 74.2, 51.8, 35.6, 35.2, 33.1, 30.2, 26.9, 19.6, 12.8, 12.5, 12.2, 12.1; ^{13}C NMR (126 MHz, $CDCl_3$) (*Minor diast*ereomer, **5*R*** "*anti*") δ 168.6, 139.0, 129.0, 100.5, 77.2, 68.8, 51.8, 38.2, 36.6, 30.6, 26.4, 25.4, 23.7, 14.0, 12.9, 12.5, 12.1; FTIR (neat, cm^{-1}) 2970, 2336, 1716, 1380, 1259; HRMS (ESI) m/z calcd for $C_{17}H_{30}O_4Na$ $[M+Na]^+$ 321.2036, found 321.2034.

4.2.13 (6*R*-[1'*S*-methylpropyl]-2,2,5*S*-trimethyl-1,3-dioxane-4*S*-yl)-2"-methylbut-2"*E*-enoic acid (14).

To a stirred solution of methyl ester **13** (50.0 mg, 168 μmol) in methanol (4.0 mL) at 0 ºC was added a solution of KOH (94.0 mg, 1.68 mmol) in water (1.0 mL). The resulting mixture was then stirred for 20 h at room temperature and the reaction was quenched with saturated ammonium chloride (5 mL) and acidified with 10% HCl (2 mL). The volatiles were removed under reduced pressure, the mixture was transferred to a separation funnel and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried over anhydrous sodium sulfate and filtered. After removal of the solvent under reduced pressure the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–60%) to afford carboxylic acid **14** (45.0 mg, 94%) as a clear oil, $[\alpha]^{20}_{D}$ +5.33º (c=0.45, DMSO, dr = 91:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (bs, COO*H*, 1H), 6.70 (ddd, MeC=C*H*CH$_2$, *J* = 7.8, 6.4, 1.5 Hz, 1H), 3.61 (ddd, CH$_2$C*H*(OR)CH, *J* = 10.3, 7.6, 3.1 Hz, 1H), 3.48 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.49–2.40 (m, C=CHC*H*$_2$CH, "*partly hidden*", 1H), 2.26–2.17 (m, C=CHC*H*$_2$CH, 1H), 1.72 (d, *H*$_3$CC=CH, *J* = 1.5 Hz, 3H), 1.57–1.50 (m, CHC*H*(Me)CH, 1H), 1.44–1.36 (m, CHC*H*(Me)CH$_2$, "*partly hidden*", 1H), 1.36 (s, CC*H*$_3$, 3H), 1.34–1.17 (m, RCHC*H*$_2$CH$_3$, "*partly hidden*", 2H), 1.22 (s, CC*H*$_3$, 3H), 0.83 (t, CH$_2$C*H*$_3$, *J* = 7.5 Hz, 3H), 0.75 (d, CHC*H*$_3$, *J* = 6.8 Hz, 3H), 0.71 (d, CHC*H*$_3$, *J* = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.7, 138.2, 128.7, 97.3, 74.4, 73.3, 34.9, 34.2, 32.2, 30.0, 26.3, 19.5, 12.4, 12.4, 11.7, 11.3; FTIR (neat, cm^{-1}) 3101, 2644, 1686, 1642, 1422, 1380, 1266, 952, 908, 886, 740; MS (ESI) m/z calcd for $C_{16}H_{27}O_4$ [M-H]$^-$ 283.20, found 283.13.

4.2.14 *tert*-Butyl {6'*R*(1'''*S*-methylpropyl)-2',2',5'*S*-trimethyl-1',3'-dioxane-4'*S*-yl}-(2''-methylbute-2''*E*-enoyl)-2*R*-oxo-3*S*-methylpentanoate (15).[2a]

An oven dried round bottomed flask (5 mL) was charged with acid **14** (40.0 mg, 141 μmol) and alcohol **10** (34.0 mg, 181 μmol) and dissolved in freshly distilled CH_2Cl_2 (1.5 mL). The reaction mixture was placed under an argon atmosphere and cooled to ~0 ºC using an ice-water bath. DCC (46.0 mg, 225 μmol) and DMAP (27.0 mg, 225 μmol) were then added, the flask was sealed and the reaction mixture was stirred for 14 h at ambient temperature. The reaction was quenched by adding saturated ammonium chloride (6.0 mL). The resulting mixture was transferred to a separation funnel and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 ml). The combined organics were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and the crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–10%) to afford product **15** (56.0 mg, 88%) as a pale yellow clear oil, $[\alpha]^{20}_D$ +14.0º (c=0.45, CH_2Cl_2, dr = 91:1). lit.[2a] oil, $[\alpha]^{20}_D$ +5.2º (c=0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (ddq, MeC=C*H*CH$_2$, *J* = 7.7, 6.4, 1.4 Hz, 1H), 4.93 (d, (CO)C*H*(OR)CH, *J* = 3.3 Hz, 1H), 3.59 (ddd, CH$_2$C*H*(OR)CH, *J* = 10.3, 7.3, 3.3 Hz, 1H), 3.44 (dd, CHC*H*(OR)CH, *J* = 10.2, 2.2 Hz, 1H), 2.52–2.44 (m, C=CHC*H*$_2$CH, 1H), 2.37–2.27 (m, C=CHC*H*$_2$CH, 1H), 2.03–1.97 (m, CHC*H*(Me)CH, 1H), 1.86 (d, *H*$_3$CC=CH, *J* = 1.4 Hz, 3H), 1.62–1.49 (m, CHC*H*$_2$CH$_3$, 2H), 1.46 (s, OC(C*H*$_3$)$_3$, 9H), 1.46–1.40 (m, CH(OR)C*H*CH(OR), "*partly hidden*", 1H), 1.38 (s, CC*H*$_3$, 3H), 1.37–1.33 (m, CH(OR)C*H*CH$_2$, "*partly hidden*", 1H), 1.32 (s, CC*H*$_3$, 3H), 1.30–1.25 (m, CHC*H*$_2$CH$_3$, "*partly hidden*", 2H), 0.98 (d, *J* = 6.9 Hz, CHC*H*$_3$, 3H), 0.93 (t, *J* = 7.5 Hz, CH$_2$C*H*$_3$, 3H), 0.87 (t, *J* = 7.4 Hz, CH$_2$C*H*$_3$, 3H), 0.82 (d, *J* = 6.8 Hz, CHC*H*$_3$, 3H), 0.74 (d, *J* = 6.6 Hz, CHC*H*$_3$, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.6, 140.2, 128.4, 97.9, 81.8, 75.4, 75.1, 74.0, 36.9, 35.3, 35.1, 32.9, 30.2, 28.2, 26.8, 26.4, 19.6, 14.4, 12.7, 12.4,

12.2, 11.9, 11.8; FTIR (neat, cm^{-1}) 3386, 2965, 2930, 2878, 1749, 1716, 1461, 1380, 1229, 1130, 740; MS (ESI) *m/z* calcd for $C_{26}H_{46}O_6Na$ $[M+Na]^+$ 477.32, found 477.29.

4.2.15 1-(*tert*-Butoxy)-3*S*-methyl-1-oxopentan-2*R*-yl-4-nitrobenzoate (18).

An oven-dried two-necked round-bottom flask (250 mL) was charged under an argon atmosphere with alcohol **17**[20] (1.50 g, 7.97 mmol), 4-nitrobenzoic acid (2.24 g, 13.5 mmol), and triphenylphosphine (3.55 g, 13.5 mmol) in freshly distilled THF (50 mL). The homogenous reaction mixture was stirred and cooled to ~0 ºC using an ice-water bath. Diisopropyl azodicarboxylate, "DIAD", (13.5 mmol) was added dropwise by syringe, maintaining the reaction temperature below 10 ºC. The reaction was allowed to warm to ambient temperature and stirred for an additional 18 h. The reaction was quenched with saturated sodium bicarbonate (20 mL). The THF was removed under reduced pressure and the residue was transferred to a separation funnel and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with water (3 × 50 mL), brine (50 mL), and dried over anhydrous sodium sulfate. After filtration of the organic solvent, the solution was concentrated under reduced pressure and the crude product purified by flash chromatography. The crude was diluted with 5 mL diethyl ether, injected into a 100g silica column and ran with diethyl ether-hexanes as a gradient (0% 2 CV, 0–20% 10 CV, 20% 2 CV) to afford product **18** in 82% yield (2.20 g) as a bright yellow oil, $[\alpha]^{20}_D$ -29.1º (c=2.3, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, Ar*H*, *J* = 8.8 Hz, 2H), 8.24 (d, Ar*H*, *J* = 8.8 Hz, 2H), 5.19 (d, C*H*CO, *J* = 3.2 Hz, 1H), 2.16–2.12 (m, CH_3CH, 1H), 1.57–1.49 (m, CH_3CH_2, "*partly hidden*", 1H), 1.48 (s, *t*Bu, 9H), 1.46–1.33 (m, CH_3CH_2, 1H), 1.09 (d, CH_3CH, *J* = 6.9 Hz, 3H), 0.99 (t, CH_3CH_2, *J* = 7.4 Hz, 3H); ^{13}C NMR

(126 MHz, $CDCl_3$) δ 168.4, 164.3, 150.6, 135.4, 130.8, 123.6, 82.4, 76.3, 36.7, 28.0, 26.2, 14.3, 11.7.

4.2.16 *N*-(1'-*tert*-Butyldimethylsilyloxy-2'-methyl-buta-1'*E*,3'-dienyl)-4*S*-1,3-oxazolidin-2-one (19).

A solution of solid KHMDS (3.20 g, 16.02 mmol) in anhydrous THF (230 mL) was added drop wise over 30 min to a solution of the corresponding imide[21] (1.81 g, 10.7 mmol) in anhydrous THF (110 mL) under an argon atmosphere at -78 ºC. The mixture was stirred for an additional 90 min at -78 ºC, followed by the drop wise addition of a solution of TBSCl (4.83 g, 18.16 mmol) in THF (25 mL) over 30 min at -78 ºC. The reaction was stirred and maintained at -78 ºC for 45 min The reaction was then quenched with a saturated aqueous NH_4Cl (75 mL) and the temperature of the reaction mixture was increased to ambient temperature and the mixture stirred for an additional 30 min. The two phase mixture was then transferred to a separation funnel, the phases separated and the aqueous phase extracted with ethyl acetate (4 × 30 mL). The combined organic phases were washed with water (100 mL), brine (100 mL) and dried over anhydrous sodium sulfate. The solvent was filtered, concentrated under reduced pressure and the crude product purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) to afford the vinylketene silyl *N*,*O*-acetal **19** as a white solid in 86% yield (2.61 g), mp 44–48 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (dd, C*H*=CH_2, *J* = 17.2, 10.9 Hz, 1H), 5.16 (dd, CH=C*H*$_2$, *J* = 17.2, 1.2 Hz, 1H), 5.03 (dd, CH=C*H*$_2$, *J* = 10.9, 1.2 Hz, 1H), 4.41 (dd, OC*H*$_2$CH$_2$, *J* = 8.1, 8.1 Hz, 2H), 3.76 (dd, CH_2C*H*$_2$N, *J* = 8.1, 8.1 Hz, 2H), 1.80 (s, CC*H*$_3$, 3H), 0.98 (s, OSiC(C*H*$_3$)$_3$, 9H), 0.20 (s, OSi(C*H*$_3$)$_2$, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.7, 137.6, 133.3,

114.8, 113.1, 62.3, 45.0, 25.8, 18.2, 11.5, -4.4; FTIR (neat, cm^{-1}) 2931, 2860, 1760, 1650, 1472, 1260; MS (ESI) m/z calcd for $C_{14}H_{26}NO_3Si$ $[M+H]^+$ 284.16, found 284.12.

4.2.17 2*R*,4*S*-Dimethyl-3*R*-acetyloxy-1-hexanal (20).

Synthesis of aldehyde **20** follows the same protocol as the preparation of aldehyde **5**. Thus, substrate **F** (450 mg, 1.27 mmol) was treated ozone at -78 ºC and subsequently Me_2S. After work-up and purification with flash chromatography using EtOAc and hexanes as a gradient (0–10%) provided aldehyde **20** in 90% yield (213 mg) as a clear oil. Aldehyde **20** was used immediately in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, CHO, *J* = 3.2 Hz, 1H), 5.12 (dd, CHC*H*(OR)CH, *J* = 7.6, 4.6 Hz, 1H), 2.70–2.60 (m, CHOC*H*(Me), 1H), 2.05 (s, COCH_3, 3H), 1.76–1.65 (m, C*H*CH_2, 1H), 1.45–1.34 (m, CH_2CH_3, 1H), 1.25–1.13 (m, CH_2CH_3, 1H), 1.09 (d, CH_3CH, *J* = 7.1 Hz, 3H), 0.93 (t, CH_3CH_2, *J* = 7.1 Hz, "*partly hidden*", 3H), 0.92 (d, CH_3CH, *J* = 7.1 Hz, "*partly hidden*", 3H).

4.2.18 *N*-(5'*S*-Hydroxy-2',6'*S*,8'*S*-trimethyl-7'*R*-acetyloxy-2'*E*-decenoyl)-1,3-oxazolidin-2-one (21), *major diastereomer* (**5*S***).

To a stirred solution of aldehyde **20** (50.0 mg, 0.269 mmol) in distilled CH_2Cl_2 (3.0 mL) under argon at -78 °C was added neat $TiCl_4$ (0.050 ml, 0.402 mmol). After the reaction mixture was stirred for an additional 20 min a solution of vinylketene silyl *N*,*O*-acetal **19** (228 mg, 0.804 mmol) in CH_2Cl_2 (6.0 mL) was slowly added over 20 min at -78 °C under an argon atmosphere. After allowing the reaction mixture to stir for 14 h at -78 °C the resulting orange solution was quenched with saturated aqueous mixture of Rochelle Salt and saturated $NaHCO_3$ (50:50, 20 mL). The temperature was then increased to ambient temperature and the mixture stirred an

additional 30 min. The mixture was transferred to a separation funnel and the aqueous phase was extracted with ethyl acetate (4 × 15 ml). The combined organic phases were washed with water (30 mL), brine (40 mL) and dried over anhydrous sodium sulfate. The solvent was filtered, concentrated under reduced pressure and the crude product purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) spiked with 2.5% methylene chloride to give a 73:27 distereomeric mixture of aldol products **21** in 70% yield (67.5 mg) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ *(Major diastereomer*) 6.03 (ddq, MeC=C*H*CH, *J* = 7.9, 6.5, 1.5 Hz, 1H), 4.89 (dd, CHC*H*(OR)CH, *J* = 10.0, 2.6 Hz, 1H), 4.42 (dd, OCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 4.01 (dd, NCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 3.67–3.59 (m, C*H*OH, 1H), 2.91–2.77 (bs, CHO*H*, 1H), 2.51–2.40 (m, C=CHCH_2CH, 1H), 2.40–2.31 (m, C=CHCH_2CH, 1H), 2.27–2.18 (m, CH$_3$C*H*, 1H), 2.11 (s, COCH_3, 3H), 1.96–1.89 (m, CH$_3$C*H*, "*partly hidden*", 1H), 1.92 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.79–1.64 (m, CH_2CH$_3$, 2H), 0.90 (t, CH_3CH$_2$, *J* = 7.2 Hz, "*partly hidden*", 3H), 0.89 (d, CH_3CH, *J* = 6.8 Hz, "*partly hidden*", 3H), 0.89 (d, CH_3CH, *J* = 6.8 Hz, "*partly hidden*", 3H); δ (*Minor diastereomer*) 5.97 (ddq, MeC=C*H*CH, *J* = 7.9, 6.5, 1.5 Hz, 1H), 4.87 (dd, CHC*H*(OR)CH, *J* = 10.0, 3.2 Hz, 1H), 4.41 (dd, OCH_2CH$_2$, *J* = 8.2, 8.2 Hz, 2H), 4.02 (dd, NCH_2CH$_2$, *J* = 8.2, 8.2 Hz, "*partly hidden*", 2H), 3.78–3.69 (m, C*H*OH, 1H), 2.91–2.77 (bs, CHO*H*, 1H), 2.52–2.42 (m, C=CHCH_2CH, "*partly hidden*", 1H), 2.36–2.29 (m, C=CHCH_2CH, "*partly hidden*", 1H), 2.22–2.14 (m, CH$_3$C*H*, "*partly hidden*", 1H), 2.11 (s, COCH_3, 3H), 1.96–1.89 (m, CH$_3$C*H*, "*partly hidden*", 1H), 1.93 (d, H_3CC=CH, *J* = 1.5 Hz, 3H), 1.82–1.66 (m, CH_2CH$_3$, "*partly hidden*", 2H), 0.94 (d, CH_3CH, *J* = 6.8 Hz, 3H), 0.93–0.87 (m, CH_3CH$_2$ and CH_3CH, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (*Major diastereomer*) 172.8, 171.8, 153.2, 136.0, 131.6, 77.9, 69.1, 62.3, 43.4, 39.2, 35.7, 33.4, 27.2, 21.1, 14.0, 12.6, 12.0, 9.0;

FTIR (neat, cm^{-1}) 3524, 2929, 1784, 1727, 1680, 1384, 1243, 1038, 762; HRMS (ESI) m/z calcd for $C_{18}H_{29}NO_6Na$ $[M+Na]^+$ 378.1887, found 378.1886.

4.2.19 3*S*-Decanoyloxy-4*S*-methyl-1-hexanal (22).

Synthesis of aldehyde **22** follows the same protocol as the preparation of aldehyde **5**. Thus, substrate **G** (200 mg, 0.443 mmol) was treated ozone at -78 ºC and subsequently Me_2S. After work-up and purification with flash chromatography using EtOAc and hexanes as a gradient (0–15%) provided aldehyde **22** in 90% yield (113 mg) as a clear oil. Aldehyde **22** was used immediately in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73–9.71 (m, CHO, 1H), 5.32 (ddd, CH_2CH(OR)CH, *J* = 8.5, 5.6, 3.2 Hz, 1H), 2.68–2.60 (m, CH_2CHO, 1H), 2.60–2.54 (m, CH_2CHO, 1H), 2.34 (dd, $COCH_2CH_2$, *J* = 7.5, 7.5 Hz, 2H), 2.28 (m, $COCH_2CH_2$, 2H), 1.67–1.55 (m, $CHCH_3$ and CH_2, 3H), 1.50–1.40 (m, $CHCH_2CH_3$, 1H),1.35–1.20 (m, 5 × CH_2, 10H), 1.20–1.10 (m, $CHCH_2CH_3$, 1H), 0.95 – 0.85 (m, 3 × CH_3, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 173.6, 71.6, 46.2, 38.6, 34.6, 34.0, 32.0, 29.5, 29.3, 25.5, 25.2, 24.9, 22.8, 14.4, 14.2, 11.8.

4.2.20 *N*-(5'*S*-Hydroxy-2',8'*S*-dimethyl-7'*S*-decanoyloxy-2'*E*-decenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (23).

To a solution of aldehyde **22** (60.0 mg, 0.211 mmol) in CH_2Cl_2 (3.0 mL) at -78 ºC was added neat $TiCl_4$ (25 μL, 0.232 mmol) under argon and reaction mixture stirred for 20 min. Then a solution of **6** (69 mg, 0.212 mmol) in distilled CH_2Cl_2 (3.0 mL) was added dropwise over 20 min at -78 ºC under an argon atmosphere. The reaction mixture was stirred for 14 h at -78 ºC the resulting orange solution was quenched with a mixture of saturated aqueous Rochelle Salt and saturated $NaHCO_3$ (50:50, 10 mL) at -78 ºC. The reaction mixture was warmed to room

temperature, stirred for an additional 30 min, then transferred to a separation funnel and the aqueous phase extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with water (20 mL), brine (30 mL) and dried over anhydrous Na_2SO_4, filtered and the organic solvent removed under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–40%) spiked with 2.5% methylene chloride to give aldol product **23** (96:4 dr) as a colorless oil in 68% yield (72 mg), $[\alpha]^{20}_D$ +56.8º (c=0.82, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddq, C=C*H*CH_2, *J* = 9.4, 6.3, 1.5 Hz, 1H), 5.02 (ddd, CH_2C*H*(OR)CH, *J* = 8.8, 4.0, 4.0 Hz, 1H), 4.54 (ddd, NC*H*, *J* = 8.9, 5.4, 4.4 Hz, 1H), 4.32 (dd, OC*H*$_2$CHN, *J* = 8.9, 8.9 Hz, 1H), 4.17 (dd, OC*H*$_2$CHN, *J* = 8.9, 5.4 Hz, 1H), 3.79–3.71 (m, C*H*OH, 1H), 3.00 (bs, O*H*, 1H), 2.43–2.30 (m, C=CHC*H*$_2$, "*partly hidden*", 2H), 2.29 (dd, COC*H*$_2$CH$_2$, *J* = 8.1, 7.0 Hz, 2H), 1.95–1.86 (m, C*H*CH_3, "*partly hidden*", 1H), 1.92 (bs, C=CC*H*$_3$, 3H), 1.79–1.65 (m, C*H*(Me)CH_2, "*partly hidden*", 1H), 1.65–1.55 (m, CHC*H*$_2$CH, 2H), 1.50–1.37 (m, CH(Me)C*H*$_2$$CH_3$, 1H), 1.34 – 1.23 (m, 7 × C*H*$_2$, 14H), 1.20 – 1.09 (m, CH(Me)C*H*$_2$$CH_3$, 1H), 0.96 – 0.84 (m, 5 × C*H*$_3$, 15H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 171.4, 154.2, 134.6, 133.3, 74.2, 68.4, 63.5, 58.2, 38.8, 38.6, 36.3, 34.7, 31.8, 29.4, 29.23, 29.21, 29.15, 28.4, 25.7, 25.0, 22.6, 17.8, 15.1, 14.0, 13.9, 13.7, 11.7; FTIR (neat, cm^{-1}) 2961, 2928, 2858, 1783, 1730, 1684, 1464, 1366, 1298, 1206, 773; HRMS (ESI) m/z calcd for $C_{28}H_{49}NO_6Na$ $[M+Na]^+$ 518.3452, found 518.3448.

4.2.21 *N*-(5'*S*-Hydroxy-2',6'*S*,-dimethyl-2'*E*-octenoyl)-4*S*-isopropyl-1,3-oxazolidin-2-one (24).

To a solution of (*S*)-methylbutanal (**B**)[18] (87.0 mg, 1.01 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added neat $TiCl_4$ (101 μL, 0.922 mmol) under argon and reaction mixture stirred for 20 min. Then a solution of **6** (300 mg, 0.922 mmol) in distilled CH_2Cl_2 (3.0 mL) was added dropwise over 20 min at -78 ºC under an argon atmosphere. The reaction mixture was stirred for 14 h at -78 ºC the resulting orange solution was quenched with a mixture of saturated aqueous Rochelle Salt and saturated $NaHCO_3$ (50:50, 20 mL) at -78 ºC. The reaction mixture was warmed to room temperature, stirred for an additional 30 min, then transferred to a separation funnel and the aqueous phase extracted with ethyl acetate (4 × 15 mL). The combined organic extracts were washed with water (30 mL), brine (40 mL) and dried over anhydrous Na_2SO_4, filtered and the organic solvent removed under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate in hexanes as a gradient (0–30%) spiked with 2.5% methylene chloride to give aldol product **24** (>98:2 dr) as a colorless oil in 65% yield (178 mg), $[\alpha]^{20}_D$ +21.8º (c=1.5, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (ddq, MeC=C*H*CH_2, *J* = 9.8, 5.9, 1.6 Hz, 1H), 4.55 (ddd, NC*H*, *J* = 9.0, 5.4, 4.5 Hz, 1H), 4.32 (dd, OCH_2CH, *J* = 9.0, 9.0 Hz, 1H), 4.18 (dd, OCH_2CH, *J* = 9.0, 5.4 Hz, 1H), 3.64–3.57 (m, C*H*OH, 1H), 2.69 (bs, RO*H*, 1H), 2.43 (ddd, C=CCH_2, *J* = 13.7, 9.8 Hz, 1H), 2.39–2.31 (m, C*H*$(CH_3)_2$, *J* = 7.0, 4.5 Hz, 1H), 2.28–2.20 (m, C=CCH_2, 1H), 1.94 (bt, C=CCH_3, *J* = 1.6 Hz, 3H), 1.60–1.50 (m, C*H*CH_2CH_3, 1H), 1.52–1.44 (m, CHCH_2CH_3, 1H), 1.25–1.15 (m, CHCH_2CH_3, 1H), 0.95 (d, CHCH_3, *J* = 7.0 Hz, 3H), 0.93 (d, CHCH_3, *J* = 7.0 Hz, "*partly hidden*", 3H), 0.92 (t, CH_2CH_3, *J* = 7.5 Hz, "*partly hidden*", 3H), 0.91 (d, CHCH_3, *J* = 7.0 Hz, "*partly hidden*", 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 154.2, 135.9, 132.8, 73.6, 63.5, 58.2, 40.0, 33.9, 28.4, 25.8, 17.8, 15.1, 14.1, 13.7, 11.7; FTIR (neat, cm^{-1}) 3529, 2968, 2928, 1772, 1686, 1389, 1366, 1297, 1211, 1054, 1015, 913, 737; MS (ESI) m/z calcd for $C_{16}H_{27}NO_4$ $[M+H]^+$ 298.19, found 298.00.

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at

References and notes

1. (a) Tripathi, A.; Puddick, J.; Prinsep, M. R.; Rottmann, M.; Tan, L. T. *J Nat Prod*. **2010**, *73*, 1810–1814; (b) Tripathi, A.; Fang, W.; Leong, D. T.; Tan, L. T. *Mar. Drugs* **2012**, *10*, 1126–1137.
2. (a) Dai, L.; Chen, B.; Lei, H.; Wang, Z.; Liu, Y.; Xu, Z.; Ye, T. *Chem Commun*. **2012**, *48*, 8697–8699; (b) Huang, W.; Ren, R. G.; Dong, H. Q.; Wei, B. G.; Lin, G.Q. *J. Org Chem*. **2013**, 78, 21, 10747–10762.
3. (a) Liu, H.-M.; Chang, C.-Y.; Lai, Y.-C.; Yang, M.-D.; Chang, C.-Y. *Tetrahedron: Asymmetry*. **2014**, *25*, 187–192; (b) 22% yield over 6 steps from (*S*)-2-methylbutanal, see: ref 3a. (c) 37% yield over 10 steps from 3-(benzyloxy)propanal, see: ref 2a.
4. Hassan, A,; Zbieg, J. R.; Krische, M. J. *Angew. Chem. Int. Ed*., **2011**, *50*, 3493–3496.

5. (a) Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H.-H. *Nat. Prod. Rep*. **2014**, *31*, 563–594; (b) Suenaga, K.; Mutou, T.; Shibata, T.; Itoh, T.; Fujita, T.; Takada, N.; Hayamizu, K.; Takagi, M.; Irifuni, T.; Kigoshi, H.; Yamada, K. *Tetrahedron*, **2004**, *60*, 8509–8527.
6. Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc*. **2004**, *126*, 13604–13605.
7. (a) Shirokawa, S.-I.; Shinoyama, M.; Ooi, I.; Hosokawa, S.; Nakazaki, A.; Kobayashi S. *Org Lett*. **2007**, *9*, 849–852. See also: (b) Mukaeda, Y.; Kato, T.; Hosokawa, S. *Org. Lett*. **2012**, *14*, 5298–5301; (c) Tsukada, H.; Mukaeda, Y.; Hosokawa, S. *Org. Lett*. **2013**, *15*, 678–681; (d) Takahashi, Y.; Otsuka, M.; Harichi, M.; Mukaeda, Y.; Hosokawa, S. *Org. Lett*. **2014**, *16*, 4106–4109.
8. Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Lett*. **2010**, 51, 2, 287–289.
9. Evans, D. A.; Wu, L. D.; Wiener, J. J. M.; Johnson, J. S.; Ripen, D. H. B.; Tedrow, J. S. *J. Org. Chem*. **1999**, 64, 6411–6417.
10. The absolute *syn*-stereochemistry of acetonide **13** was determined with ^{13}C-NMR. The absolute stereochemistry of fragment **15** was determined via NMR and was identical with previous report, see: Ref 2a. See also Supplementary Data for additional information.
11. The characteristic ^{13}C-NMR chemical shifts for the methyl groups and the acetal carbon of the *syn*-1,3-diol: 19.4 ± 0.21, 30.0 ± 0.15 and 98.1 ± 0.83 ppm, and for the corresponding *anti*-diol: 24.6 ± 0.76, and 100.6 ± 0.25 ppm, see: (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett*. **1990**, 31, 7099–7100; (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, 31, 945–948.

12. (a) Pettit, G. R.; Hu, S.; Knight, J. C.; Chapuis, J. C. *J. Nat. Prod*. **2009**, *72*, 372–379; (b) Yajima, T.; Horikawa, T.; Takeda, N.; Takemura, E.; Hattori, H.; Shimazaki, Y.; Shiraiwa, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1285–1287.
13. Martin, S. F.; Dodge, J. A. *Tetrahedron Lett*. **1991**, *32*, 3017–3020.
14. For reaction details and equivalents using substrates **6** and **19** (Scheme 5). Ratio of aldehyde vs. substrate was purposely set to 1:1, except for formation of product **21**, 3:1 ratio, see: Experimental.
15. Based on Spartan calculations and NOE experiments the auxiliary can adopt a nearly perpendicular direction against the diene segment, see: ref 6.
16. Jahns, C.; Hoffman, T.; Mueller, T.; Gerth, K.; Washausen, P.; Hoefle, G.; Reichenbach, H.; Kalesse, M.; Mueller, R. *Angew. Chem., Int. Ed. Engl*. **2012**, *51*, 5239–5243.
17. Hosokawa, S.; Matsushita, K.; Tokimatsu, S.; Toriumi, T.; Suzuki, Y.; Tatsuta, K. *Tetrahedron Lett.* **2010**, *51*, 5532–5536.
18. 2(*S*)-Methylbutanal was obtained from 2(*S*)-methylbutanol using TEMPO and sodium hypochlorite as the oxidizer, see: Anelli, P.; Montanari, F.; Quici, S. *Org. Synth. Coll. Vol. 8*, **1993**, 367–372.
19. Haesler, J.; Schindelholz, I.; Riguet, E.; Bochet, C. G.; Hug, W. *Nature* **2007**, *446*, 526–529.
20. Beveridge, R. E.; Batey, R. *Org. Lett.* **2014**, *16*, 2322–2325.
21. Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556–6564.