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Dibromomethane as one-carbon source in organic synthesis: total synthesis of (±)- and (−)-methylenolactocin

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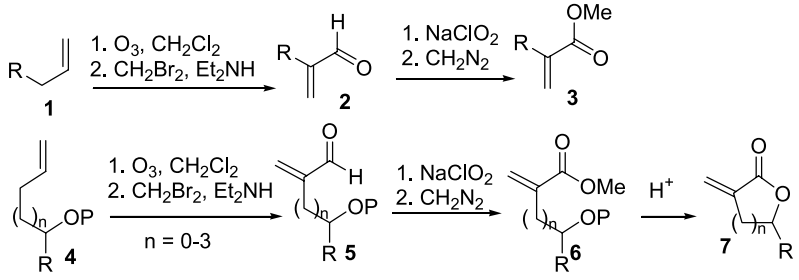
Abstract—A general method was developed to construct monocyclic α-methylene-γ-butyrolactone moiety. The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH. Application of this key step in the total synthesis of the (±)- and (−)-methylenolactocin was described.

1. Introduction

We have reported that the ozonolysis of mono-substituted alkenes **1** followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins **2** in good yields.[1] The α-substituted acroleins **2** were easily oxidized by $NaClO_2$ and then treated with CH_2N_2 to give α-substituted acrylate **3** in excellent yields. Each step in Scheme 1 is mild so that it is suitable to prepare the α-substituted acrylates with labile groups.[2] This methodology was also applied to prepare the α-methylene lactones **7** with different ring size (n=0–3) from the corresponding alkenol **4** (Scheme 1).[3]

The α-methylene-γ-butyrolactone moiety is a core skeleton in many structurally complex natural products.[4] The monocyclic, disubstituted α-methylene-γ-butyrolactones such as (−)-methylenolactocin **8a**,[5] *trans*-nephrosterinic acid **8b**,[6] and (−)-protolichesterinic acid **8c**[7] are noted for their biological activities, being antibacterial,[8a–h] antifungal,[8b] antitumor,[8h] and, in certain cases, growth regulating agents.[8i] The characteristic features of these natural products are described as follows. These structures contain α-methylene, β-carboxylic acid and γ-alkyl groups in different chain length. Both the β- and γ-substituents are *trans* to each other for compounds **8a**, **8b**, and **8c**, while they are *cis* to each other for *cis*-nephrosterinic acid (**8b′**) and alloprotolichesterolic acid (**8c′**) (Fig. 1). All these natural products have been synthesized by different methodologies.[9–12] In order to extend the synthetic applications of our α-methylenation methodology, our effort to the total synthesis of (−)-methylenolactocin is described in this article.



Scheme 1.

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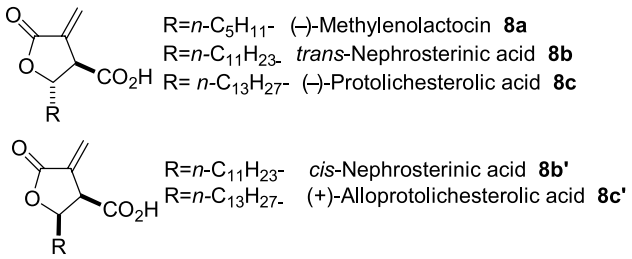


Figure 1. Monocyclic α-methylene-γ-butyrolactone natural products.

2. Results and discussions

2.1. Retrosynthetic analysis of our design in the total synthesis of α-methylene-β-carboxyl-γ-butyrolactone natural products

The retrosynthetic analysis of α-methylene-β-carboxyl-γ-butyrolactone **A** is shown in Figure 2. Several groups reported that structure **A** could be derived from the corresponding *cis*-isomer **B** via epimerization and hydrolysis in the same flask.[9l] The γ-butyrolactone **B** should be easily prepared from alkenol **C** by our methodology as shown in Scheme 1.[1] The stereoselective introduction of the β-stereogenic center of compound **C** from the allylation of the dianion of β-hydroxy ester **D** is a well known procedure in the literature.[13] The β-hydroxy ester **D** should be easily prepared by Reformatsky reaction[14a] from the methyl bromoacetate (**9**) and aldehyde (Fig. 2).

2.2. The total synthesis of the (±)-methylenolactocin (method I)

The known β-hydroxy ester **11** was prepared from methyl bromoacetate (**9**) and *n*-hexanal (**10**) in the presence of activated zinc in 78% yield.[14b] The allylation of β-hydroxy ester **11** following the procedure of Frater[13] gave the *anti*-β-hydroxy ester **12** in 85% yield (Scheme 2). The acetylation of the secondary alcohol **12** gave the corresponding acetate **13** in 96% yield. The ozonolysis of terminal olefin **13** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH[1] afforded acrolein **14** in 78% yield. The acrolein **14** was oxidized by sodium chlorite in the presence of a chlorine scavenger (i.e., 2-methyl-2-butene) to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give methyl acrylate **15** in 79% yield.[2] Acid-catalyzed cyclization of methyl acrylate **15** in methanol gave *cis*-β,γ-disubstituted lactone **16** in 82% yield. Following the literature procedure,[9l] compound **16** was treated with 6 N HCl in butanone under refluxing for 2 h to give an inseparable mixture of methylenolactocin (**8a**) and butenolide **8a′** in a ratio of 4: 1 in 77% yield. The mole ratio was determined by the ^{1}H NMR integrations of the α-methylene protons (δ 6.47 and 6.02 ppm) of compound **8a** and the γ-methine proton (δ 5.11 ppm) of compound **8a′**. After treatment with CH_2N_2, their methyl esters **17** and **18** are separable and are spectroscopically identical with previously reported samples (Scheme 2).[9j,u]

We failed to avoid the formation of side product **8a′** derived from the double bond isomerization by employing the milder reaction conditions, such as using 4 N HCl or running the reaction at 40 °C. Therefore, if the hydrolysis and epimerization of compound **16** were arranged at the last two steps of the synthetic pathway, we have to face two problems. One is the formation of the minor product **8a′** and the other is the difficulty of separating **8a′** from the methylenolactocin (**8a**). The approach of Method I led us to accomplish the total synthesis of (±)-methylenolactocin in six operation steps in 31% overall yield from β-hydroxy ester **11**. In addition, we learned from this approach that the epimerization should be carried out at the earlier stage of the synthetic pathway in order to improve the efficiency of the synthesis.

2.3. The total synthesis of the (±)-methylenolactocin (method II)

In order to inverse the configuration of the secondary alcohol at the early stage, *anti*-β-hydroxy ester **12** was subjected to the standard Mitsunobu condition.[15] Unfortunately, the desired *p*-nitrobenzoate **19** was formed in poor

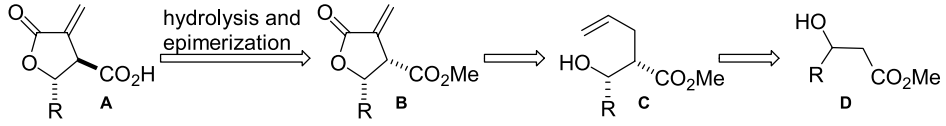
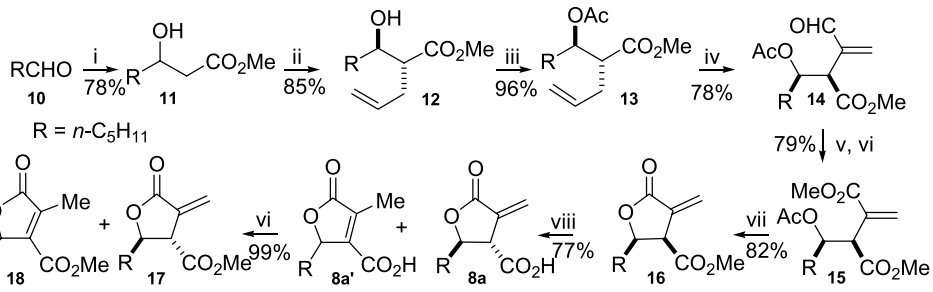


Figure 2. Retrosynthetic analysis of the methylenolactocin and its analogues.



Scheme 2. Reagents and conditions: (i) Zn, $BrCH_2CO_2Me$ (**9**), PhH, reflux, 4 h; (ii) 2.2 equiv LDA; $H_2C{=}CHCH_2Br$, −78 °C, 5 h; (iii) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 2 h; (iv) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv = 5:15), 2 h; (v) $NaClO_2$, *t*-BuOH, $NaH_2PO_4{\cdot}2H_2O$, $MeCH{=}CMe_2$, 8 h; (vi) CH_2N_2; (vi) cat. MeCOCl, MeOH, 24 h; (viii) 6 N HCl, butanone, 2 h.

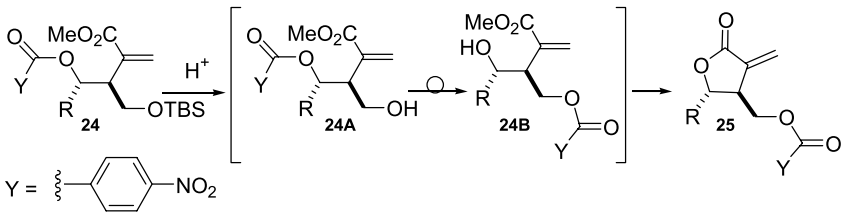
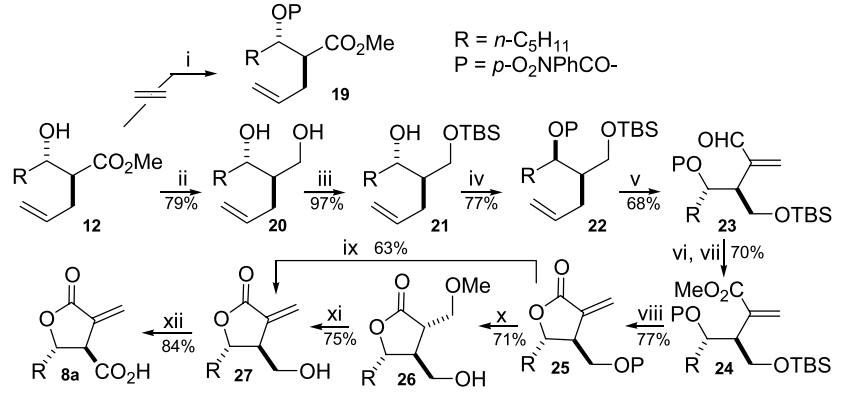


Figure 3. Proposed mechanism for the γ-lactone **25** formation via *p*-nitrobenzoyl group migration intermediate **24B**.

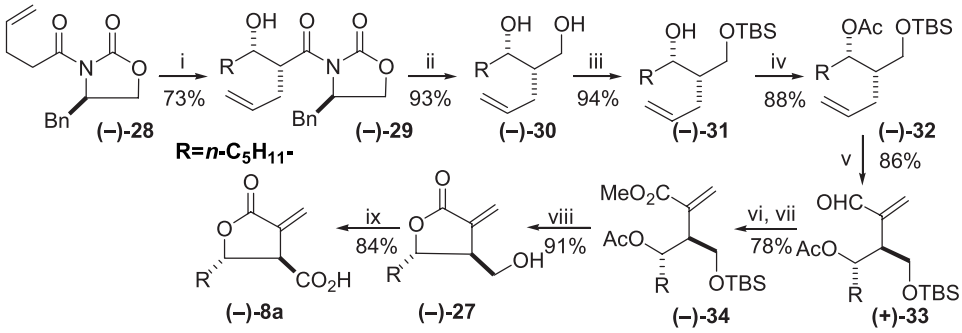
yield and most of the starting material **12** was recovered. The β-hydroxy ester **12** was reduced with Dibal-H to give the corresponding 1,3-diol **20** in 79% yield. The primary alcohol of 1,3-diol **20** was electively protected as *tert*-butyldimethylsilyl ether **21** in 97% yield. The configuration of the secondary alcohol **21** was inversed successfully by Mitsunobu reaction to give the corresponding *p*-nitrobenzoate **22** in 77% yield. The ozonolysis of terminal olefin **22** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein **23** in 68% yield. The acrolein **23** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give the methyl acrylate **24** in 70% yield. In the presence of a catalytic amount of HCl in methanol, the methyl acrylate **24** was cyclized to *trans*-β,γ-disubstituted lactone **25** in 77% yield. The possible mechanism for the formation of the lactone **25** from compound **24** was proposed as follows (Fig. 3). The *tert*-butyldimethylsilyl ether of compound **21** was selectively deprotected under acidic condition to give the primary alcohol **24A**. The 1,5-*p*-nitrobenzoyl group migration of the intermediate **24A** before the cyclization gave the lactone **25**. When the *p*-nitrobenzoate **25** was hydrolyzed by ammonium hydroxide in methanol, the corresponding primary alcohol **27** was obtained in 62% yield. Alternatively, when the *p*-nitrobenzoate **25** was treated with K_2CO_3 in methanol, not only the methanolysis, but also the 1,4-addition of methanol occurred to give the α-methoxymethyl lactone **26** in 71% yield. The β-elimination of compound **26** with DBU (i.e. 1,8-diazabicyclo[5.40]undec-7-ene) in refluxing benzene afforded the α-methylene lactone **27** in 75% yield. The primary alcohol on compound **27** was oxidized to the corresponding carboxylic acid by Jones reagent to give the (±)-methylenolactocin **8a** in 84% yield (Scheme 3). The exocyclic double bond of product **8a** was found to be intact during the oxidation process. The approach of Method II led us to accomplish the total synthesis of (±)-methylenolactocin in nine operation steps in 9.6% overall yield from β-hydroxy ester **11**.

2.4. The total synthesis of the optical active (−)-methylenolactocin

In order to prepare the methylenolactocin in optically active form, the optical active 1,3-diol **20** was needed. We began with the Bu_2BOTf-mediated asymmetric aldol reaction between *N*-acyl oxazolidinone (−)-**28**[16] and *n*-hexanal to give *syn*-aldol (−)-**29** in 73% yield (>95:5 diastereoselectivity).[17] *N*-Acyl oxazolidinone (−)-**29** was reduced with $NaBH_4$ to give the corresponding 1,3-diol (−)-**30**. Selective silylation at the primary alcohol of compound (−)-**30** followed by acetylation gave the acetate (−)-**32** in excellent yield. The ozonolysis of terminal olefin (−)-**32** followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein (+)-**33** in 86% yield. The acrolein (+)-**33** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give the methyl acrylate (−)-**34** in 78% yield. Acid-catalyzed ring closure of acrylate (−)-**34** in methanol gave the corresponding α-methylene-γ-butyrolactone (−)-**27** in 91% yield. We believe that the formation of the lactone (−)-**27** from acrylate (−)-**34** follows the similar mechanism as described in Figure 3. However, under the acidic condition, the corresponding α-methylenelactone-acetate (Y=Me, Fig. 3) intermediate undergoes the transesterification to give the desired (−)-**27** in excellent yield. Finally, compound (−)-**27** was treated with Jones reagent to give the optical active (−)-methylenolactocin ((−)-**8a**) in 84%



Scheme 3. Reagents and conditions: (i) *p*-O_2N–$PhCO_2H$, DEAD, Ph_3P; (ii) Dibal-H, 0 °C to rt, CH_2Cl_2, 2 h; (iii) TBSCl, cat. DMAP, imidazole, CH_2Cl_2, 3 h; (iv) DEAD, Ph_3P, *p*-O_2N–$PhCO_2H$, CH_2Cl_2, 8 h; (v) (a) O_3, CH_2Cl_2, −78 °C, (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv=5:15), 2 h; (vi) $NaClO_2$, *t*-BuOH, $NaH_2PO_4\cdot 2H_2O$, MeOH=CMe_2, 8 h; (vii) CH_2N_2; (viii) cat. MeCOCl, MeOH, 30 min; (ix) NH_4OH (28–30%), MeOH, 0 °C, 2 h; (x) K_2CO_3, MeOH/H_2O (2:1), rt, 20 min; (xi) DBU, PhH, reflux, 5 h; (xii) Jones reagents, 40 °C, acetone, 5 min.



Scheme 4. Reagents and conditions: (i) Bu_2BOTf, Et_3N, n-$C_5H_{11}CHO$ (**10**), −78 to 0 °C, CH_2Cl_2, 2 h; (ii) $NaBH_4$, THF/H_2O (4:1), 2 h; (iii) TBSCl, cat. DMAP, imidazole, CH_2Cl_2, 3 h; (iv) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 1.5 h; (v) (a) O_3, CH_2Cl_2, −78 °C, (b) preheated miture of Et_2NH and CH_2Br_2 (mol equiv=5:15), 2 h; (vi) $NaClO_2$, t-BuOH, $NaH_2PO_4\cdot 2H_2O$, MeCH=CMe_2, 8 h; (vii) CH_2N_2; (viii) cat. MeCOCl, MeOH, 30 min; (ix) Jones reagent, 40 °C, acetone, 5 min.

yield (Scheme 4). We have accomplished the total synthesis of (−)-methylenolactocin in eight operation steps in 29% overall yield from *N*-acyl oxazolidinone (−)-**28**.

3. Conclusions

We have developed an efficient methodology for the synthesis of methylenolactocin in racemic and optically active forms. The characteristics of this synthetic design are to introduce the α-methylene group at the early stage of the synthesis by the ozonolysis of mono-substituted alkene followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH. For the racemic synthesis, the relative stereochemistry of β- and γ-substituents was established by the stereoselective allylation of the dianion of β-hydroxy ester **11**. As for the overall yield and the number of the transformations are concerned, method I should be the most efficient design. However, we cannot solve the problem of the side product **8a′** formation during the hydrolysis. Therefore, the epimerization needed to be operated at the early stage of the synthesis. Guided by this concept, we finished the total synthesis of (±)-methylenolactocin in nine operation steps in 9.6% overall yield from β-hydroxy ester **11**. Based on the success of this approach, we tried to complete the total synthesis of (−)-methylenolactocin ((−)-**8a**). *N*-Acyl oxazolidinone (−)-**28** was used as chiral auxiliary to induce the asymmetric aldol reaction to give *syn*-aldol (−)-**29** in excellent diastereoselectivity. Starting with this chiral alcohol, we have accomplished the total synthesis of (−)-methylenolactocin in eight operation steps in 29% overall yield from (−)-**28**.

4. Experimental

4.1. General

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorption was listed. Mass spectra were measured on a VG-Trio-2000GC/MS spectrometer (National Chiao-Tung University) by electronic impact at 70 eV (unless otherwise indicated). High-resolution mass spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT 95XL (National Chung Hsing University) and FAB mass spectra were recorded with 3-nitrobenzyl alcohol matrix using argon or xenon as the target gas.

4.1.1. 3-Hydroxyoctanoic acid methyl ester (11).[14b] A suspension of the activated zinc dust[18] (392 mg, 6 mmol) in 2 mL of anhydrous benzene was heated up to reflux for 10 min. To the refluxing suspension solution was slowly added a mixture of the *n*-hexanal (**10**) (0.55 g, 5.5 mmol) and methyl bromoacetate (**9**) (0.57 mL, 6 mmol) in 10 mL of benzene in a period of 1 h. After 2 h, the reaction mixture was cooled to 0 °C and then added 1 N HCl to work up the reaction and extracted with ether (20 mL×3). The combined organic extract was dried ($MgSO_4$), concentrated, and chromatographed on silica gel column to give the desired β-hydroxy ester **11** (746 mg, 4.3 mmol) in 78% yield as a colorless oil. TLC R_f=0.48 (hexane/EtOAc=3:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.94–3.98 (m, 1H, C*H*OH), 3.66 (s, 3H, OMe), 2.95 (br, 1H, OH), 2.36–2.49 (m, 2H, CH_2CO), 1.21–1.42 (m, 8H), 0.85 (t, J=6.7 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.1 (4°), 67.8 (3°), 51.4 (1°), 41.1 (2°), 36.4 (2°), 31.5 (2°), 24.9 (2°), 22.3 (2°), 13.7 (1°); IR (CH_2Cl_2): 2931, 2859, 1738, 1438, 1168 cm^{-1}; EI mass (*m*/*z*): 173 (M^+−1, 10), 157 (100), 125 (70), 55 (48), 43 (35); HRMS *m*/*z* calcd for $C_9H_{18}O_3$ 174.1256, found: 174.1259.

4.1.2. (2*R,3*R**)-2-Allyl-3-hydroxyoctanoic acid methyl ester (12).** *n*-Butyllithium (3.95 mL, 6.33 mmol, 1.6 M in hexane) was added to a stirring solution of diisopropylamine (0.89 mL, 6.33 mmol) in THF (10 mL) at −78 °C. To the LDA solution, β-hydroxy ester **11** (0.50 g, 2.87 mmol) in 5 mL of THF was added at −78 °C and stirred at this temperature for 1 h. At −78 °C, a mixture of allyl bromide (0.30 mL, 3.44 mmol) and HMPA (1 mL) in THF (4 mL) was added to the reaction mixture. After stirring at −78 °C for 1 h, the reaction mixture was partitioned between 40% ethyl acetate/petroleum ether and saturated aqueous NH_4Cl. The combined organic phase was dried ($MgSO_4$), concentrated, and chromatographed on silica gel column to afford

product **12** (522 mg, 2.44 mmol) in 85% yield as a colorless oil. TLC R_f=0.55 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66–5.73 (m, 1H, C*H*=CH_2), 4.97–5.06 (m, 2H, CH=CH_2), 3.65 (s, 3H, OMe), 3.64–3.67 (m, 1H, C*H*OH), 2.68–2.75 (br, 1H, OH), 2.47–2.50 (m, C*H*CO), 2.36–2.39 (m, 2H, CH_2CH=CH_2), 1.23–1.42 (m, 8H), 0.84 (t, J=6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1 (4°), 134.8 (4°), 116.9 (2°), 71.6 (3°), 51.4 (1°), 50.5 (3°), 35.3 (2°), 33.6 (2°), 31.5 (2°), 25.2 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 3374, 2932, 2859, 1735, 1643, 1438, 1169, 1047 cm^{-1}; EI mass (*m*/*z*): 125 (M^+-89, 100), 113 (21), 55 (82), 43 (70), 41 (91); HRMS *m*/*z* calcd for $C_{12}H_{22}O_3$–OCH_3 183.1385, found: 183.1384.

4.1.3. (2*R,3*R**)-3-Acetoxy-2-allyloctanoic acid methyl ester (13).** To a solution of β-hydroxy ester **12** (500 mg, 2.34 mmol), DMAP (57 mg, 0.47 mmol) and Et_3N (0.49 mL, 3.5 mmol) in CH_2Cl_2 (4.7 mL) was added acetic anhydride (0.33 mL, 3.5 mmol) at rt and stirred it for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate **13** (574 mg, 2.24 mmol) in 96% yield as a pale yellow oil. TLC R_f=0.75 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70–5.77 (m, 1H, –C*H*=CH_2), 5.01–5.12 (m, 3H, –CH=CH_2 and C*H*OAc), 3.68 (s, 3H, –OCH_3), 2.70–2.75 (m, 1H, C*H*CO), 2.42–2.24 (m, 2H, –CH_2-CH=CH_2), 2.04 (s, 3H, COCH_3), 1.55–1.60 (m, 2H), 1.26–1.30 (m, 6H), 0.88 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7 (4°), 170.2 (4°), 134.8 (3°), 117.0 (2°), 73.5 (3°), 51.5 (1°), 49.1 (3°), 32.3 (2°), 31.6 (2°), 31.5 (2°), 24.7 (2°), 22.4 (2°), 20.9 (1°), 13.9 (1°); IR (CH_2Cl_2): 2955, 2933, 2861, 1743, 1437, 1238 cm^{-1}; EI mass (*m*/*z*): 241 (M^+-15, 35), 227 (32), 181 (100), 149 (47), 55 (48); HRMS *m*/*z* calcd for $C_{13}H_{21}O_4$ 241.1440 (M^+-15), found: 241.1442.

4.2. General procedure to prepare the α-substituted acrolein from terminal alkene

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar was charged with terminal alkene **13** (650 mg, 2.54 mmol) in CH_2Cl_2 (50 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged. A mixture of Et_2NH (1.4 mL, 12.7 mmol) and CH_2Br_2 (2.7 mL, 38.0 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to rt. To a solution of ozonide in CH_2Cl_2 generated above was added a preheated mixture of Et_2NH and CH_2Br_2 at −78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt. The reaction was complete in 1.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired acrolein **14** (510 mg, 1.97 mmol) in 78% yield.

4.2.1. (1′*R,2*R**)-2-(1′-Acetoxyhexyl)-3-formylbut-3-enoic acid methyl ester (14).** TLC R_f=0.38 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H, C*H*O), 6.69 (s, 1H, C=CH_2), 6.29 (s, 1H, C=CH_2), 5.27 (ddd, J=3.8, 7.6, 8.4 Hz, 1H, C*H*OAc), 4.04 (d, J=7.5 Hz, ^{1}H C*H*CO_2CH_3), 3.68 (s, 3H, CO_2CH_3), 2.02 (s, 3H, COCH_3), 1.40–1.55 (m, 2H), 1.17–1.30 (m, 6H), 0.86 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2 (4°), 170.7 (4°), 170.1 (4°), 144.2 (4°), 137.6 (2°), 73.2 (3°), 52.0 (1°), 45.4 (3°), 31.4 (2×2°), 24.6 (2°), 22.3 (2°), 20.8 (2°), 13.8 (1°); IR (CH_2Cl_2): 2955, 2860, 1744, 1696, 1435, 1236, 1024, 734 cm^{-1}; EI mass (*m*/*z*): 271 (M^++1, 1), 211 (40), 170 (42), 128 (100), 96 (52), 86 (38), 55 (13); HRMS *m*/*z* calcd for $C_{14}H_{22}O_5$ 270.1467, found: 270.1468.

4.3. General procedure to prepare the methyl acrylate from the corresponding acrolein

To a solution of acrolein **14** (700 mg, 2.71 mmol), *t*-butyl alcohol (14 mL) and 2-methyl-2-butene (0.9 mL, 570 mg, 8.13 mmol) was added dropwise a solution of sodium chlorite (565 mg, 6.23 mmol) and sodium dihydrogenphosphate dihydrate (835 mg, 5.42 mmol) in 4 mL of water. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 8 mL of water and this extracted with 30 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 25 mL portions of ether. The combined ether layers were washed with 30 mL of water, dried with Na_2SO_4, concentrated to give the crude carboxylic acid. To a solution of α-substituted acrylic acid was dissolved in 9.5 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at rt. The progress of the reaction should be monitored carefully by TLC. Excess of the CH_2N_2 will cause the further 1,3-dipolar cycloaddition on the double bond. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **15** (642 mg, 2.14 mmol) as a colorless oil in 79% yield.

4.3.1. (1′*R,2*R**)-2-(1′-Acetoxyhexyl)-3-methylenesuccinic acid dimethyl ester (15).** TLC R_f=0.68 (hexane/EtOAc=2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 1H, C=CH_2), 5.96 (s, 1H, C=CH_2), 5.32 (ddd, J=3.7, 8.1, 8.1 Hz, 1H, C*H*OAc), 3.99 (d, J=7.9 Hz, 1H, C*H*CO_2Me) 3.79 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.02 (s, 3H, COCH_3), 1.41–1.57 (m, 2H), 1.23–1.30 (m, 6H), 0.86 (t, J=6.8 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (4°), 170.1 (4°), 166.2 (4°), 135.0 (4°), 129.0 (2°), 73.4 (3°), 52.2 (1°), 52.0 (1°), 49.1 (3°), 31.5 (2°), 31.4 (2°), 24.6 (2°), 22.3 (2°), 20.8 (1°), 13.8 (1°); IR (CH_2Cl_2): 2955, 2860, 1746, 1437, 1237, 1023, 733 cm^{-1}; EI mass (*m*/*z*): 269 (M^+-31, 1), 227 (12), 158 (100), 126 (60), 55 (6); HRMS *m*/*z* calcd for $C_{14}H_{21}O_6$ 285.1338 (M^+-15), found: 285.1344.

4.4. General procedure to prepare the γ-butyrolactone from the corresponding acyloxy-acrylate under acidic condition

To a mixture of acetoxy-acrylate **15** (100 mg, 0.29 mmol) in 6 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the α-methylenelactone **16** (62 mg, 0.24 mmol) in 82% yield as a pale yellow oil.

4.4.1. (2*R,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid methyl ester (16).**[9u] TLC R_f= 0.57 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, J=2.4 Hz, 1H, C=CH_2), 5.82 (d, J=2.4 Hz, 1H, C=CH_2), 4.59–4.64 (m, 1H, C*H*OCO), 4.00 (dt, J=2.2, 7.6 Hz, 1H, C*H*C=CH_2), 3.75 (s, 3H, OMe), 1.29–1.64 (m, 8H), 0.88–0.90 (t, J=6.9 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3 (4°), 168.8 (4°), 133.7 (4°), 124.8 (2°), 78.2 (3°), 52.3 (1°), 49.1 (3°), 31.4 (2°), 31.3 (2°), 25.1 (2°), 22.3 (2°), 13.8 (1°); IR (CH_2Cl_2): 2931, 2861, 1768, 1666, 1437, 1170, 714 cm^{-1}; EI mass (*m*/*z*): 166 (M^+-60, 29), 155 (78), 127 (38), 126 (100), 67 (42); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1213.

4.4.2. (2*S,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid methyl ester (17)**[9u] **and 4-methyl-5-oxo-2-pentyl-2,5-dihydrofuran-3-carboxylic acid methyl ester (18)**[9j] A solution of methyl ester **16** (113 mg, 0.5 mmol) in butanone (3 mL) containing HCl (6 N, 3 drops) was heated under reflux for 2 h. H_2O (5 mL) was added and the organic solvent was removed. The aqueous layer was extracted with CH_2Cl_2 (3×15 mL) and solvents were evaporated to give an inseparable mixture of methylenolactocin (**8a**) and butenolide **8a**′ (mol ratio is about 4:1). To the crude mixtures in 5 mL of CH_2Cl_2 were added a solution of CH_2N_2 in ether. After stirring at rt for 20 min, the reaction mixture was concentrated, chromatographed on silica gel column to give the methyl ester of the methylenolactocin **17** (72 mg, 0.32 mmol, 64% yield) and its isomer **18** (18 mg, 0.08 mmol, 16%).

Compound **17**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, J=2.4 Hz, 1H, C=CH_2), 5.91 (d, J=2.4 Hz, 1H, C=CH_2), 4.79 (q, J=6.0 Hz, 1H, C*H*OCO), 3.80 (s, 3H, OMe), 3.56–3.59 (m, 1H, C*H*C=CH_2), 1.25–1.73 (m, 8H), 0.88–0.91 (m, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7 (4°), 168.2 (4°), 133.2 (4°), 125.0 (2°), 79.0 (3°), 52.8 (1°), 49.9 (3°), 35.7 (2°), 29.6 (2°), 24.4 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 2927, 2857, 1770, 1740, 1437, 1115, 738 cm^{-1}; EI mass (*m*/*z*): 226 (M^+, 6), 156 (68), 155 (100), 127 (90), 99 (62); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1207.

Compound **18**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (m, 1H, C*H*OCO), 3.88 (s, 3H, OMe), 2.18 (d, J=2.0 Hz, 3H, CH_3C=C), 2.04–2.07 (m, 2H), 1.25–1.58 (m, 6H), 0.88 (t, J=6.8 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8 (4°), 162.6 (4°), 147.6 (4°), 137.4 (4°), 81.3 (3°), 52.2 (1°), 32.7 (2°), 31.6 (2°), 24.4 (2°), 22.3 (2°), 13.8 (1°), 10.8 (1°); IR (CH_2Cl_2): 2928, 2859, 1768, 1728, 1438, 1152, 759 cm^{-1}; EI mass (*m*/*z*): 226 (M^+, 4), 197 (48), 156 (100), 99 (28), 67 (30); HRMS *m*/*z* calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1206.

4.4.3. (2*S,3*R**)-2-Allyloctane-1,3-diol (20).** To a solution of β-hydroxy ester **12** (1.8 g, 8.40 mmol) in 42 mL of CH_2Cl_2 was added diisobutylaluminium hydride (Dibal-H, 1 M in hexane, 21 mL, 21.0 mmol) at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. To the reaction mixture was added 10 mL of ethyl acetate in order to quench the excess of Dibal-H at 0 °C. The reaction mixture was then washed with 30 mL of water. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give diol **20** (1.23 g, 6.61 mmol) in 79% yield as a colorless oil. TLC R_f=0.29 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.87 (m, 1H, –C*H*=CH_2), 5.03–5.12 (m, 2H, –CH=CH_2), 3.91–3.94 (m, 1H, C*H*OH), 3.66–3.70 (m, 2H, –CH_2OH), 2.45 (br s, 1H, OH), 2.20–2.28 (m, 3H, –CH_2CH=CH_2 and C*H*CH$_2$OH), 1.31–1.61 (m, 8H), 0.90 (t, J=6.6 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.6 (3°), 116.4 (2°), 75.0 (3°), 63.6 (2°), 44.0 (3°), 35.4 (2°), 33.3 (2°), 31.8 (2°), 25.3 (2°), 22.6 (2°), 13.9 (1°); IR (CH_2Cl_2): 3349, 2955, 2859, 1443, 1128, 1026, 733 cm^{-1}; FAB mass (*m*/*z*): 187 (M^++1, 27), 178 (34), 169 (49), 151 (62), 136 (58), 109 (56), 95 (93), 81 (88), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{22}O_2$ 186.1620, found: 186.1624.

4.4.4. (4*R,5*S**)-4-(*tert*-Butyldimethylsilyloxymethyl)-dec-1-en-5-ol (21).** To a solution of the diol **20** (1.9 g, 10.21 mmol), DMAP (250 mg, 2.04 mmol) and imidazole (765 mg, 11.23 mmol) in 21 mL of CH_2Cl_2 was added *t*-butyldimethylsilyl chloride (1.7 g, 11.2 mmol) at rt and stirred it for 3 h. The reaction is quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give the secondary alcohol **21** (2.81 g, 9.87 mmol) in 97% yield as a pale yellow oil. TLC R_f=0.60 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73–5.84 (m, 1H, –C*H*=CH_2), 5.02–5.09 (m, 2H, –CH=CH_2), 3.91 (dd, J=3.5, 10.2 Hz, 1H, –CH_2OTBS), 3.66 (dd, J=5.0, 10.2 Hz, 1H, –CH_2OTBS), 3.59–3.64 (m, 1H, –C*H*OH), 3.29 (d, J=6.2 Hz, 1H, OH), 2.14–2.30 (m, 2H, –CH_2CH=CH_2), 1.38–1.51 (m, 3H, C*H*CH$_2$OTBS), 1.20–1.35 (m, 6H), 0.88–0.91 (m, 12H, CH$_2$CH_3 and (CH_3)$_3$CSiMe$_2$), 0.08 (s, 3H, *t*-BuSi(CH_3)$_2$), 0.07 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9 (3°), 116.3 (2°), 74.6 (3°), 64.1 (2°), 43.8 (3°), 35.7 (2°), 33.3 (2°), 32.0 (2°), 25.8 (3×1°), 25.6 (2°), 22.7 (2°), 18.1 (4°), 14.0 (1°), −5.7 (2×1°); IR (CH_2Cl_2): 3464, 2955, 2857, 1470, 1255, 1087, 777 cm^{-1}; FAB mass (*m*/*z*): 301 (M^++1, 61), 283 (23), 154 (100), 136 (99), 95 (62), 81 (58), 73 (90), 55 (65); HRMS *m*/*z* calcd for $C_{17}H_{36}O_2Si$ 300.2485, found: 300.2481.

4.4.5. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-1-pentylpent-4-enyl ester (22).** To a mixture of the secondary alcohol **21** (1.2 g, 5.90 mmol) in 18 mL of THF was added a solution of Ph_3P (2.21 g, 8.43 mmol) and 4-nitrobenzoic acid (1.41 g, 8.43 mmol) in 20 mL of THF at rt under nitrogen. To the resulted solution was added DEAD (40% in toluene, 3.83 mL, 8.43 mmol) by syringe pump dropwise in 1 h at 0 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt for 8 h. The reaction mixture was concentrated and chromatographed on silica gel column to give 4-nitrobenzoate **22** (1.46 g, 3.25 mmol) in 77% yield as a pale yellow solid. TLC R_f=0.82 (hexane/EtOAc=10:1); mp 47.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.27–8.30 (m, 2H, O_2NPh–*H*), 8.18–8.20 (m, 2H, O_2NPh–*H*), 5.77–5.87 (m, 1H, –C*H*=CH_2), 5.36 (dt, J=5.0, 7.7 Hz, 1H, C*H*OCOAr), 5.02–5.08 (m, 2H, –CH=CH_2), 3.65 (dd, J=4.8, 10.1 Hz, 1H, –CH_2OTBS), 3.57 (dd, J=6.0, 10.1 Hz, 1H, –CH_2OTBS), 2.20–2.27 (m, 2H, –CH_2-CH=CH_2), 1.91–1.95 (m, 1H, –C*H*CH$_2$OTBS), 1.71–1.78

(m, 2H), 1.26–1.30 (m, 6H), 0.85–0.90 (m, 12H, $-CH_2CH_3$ and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.01 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.2 (4°), 150.5 (4°), 136.7 (3°), 136.2 (4°), 130.6 (2×3°), 123.5 (2×3°), 116.3 (2°), 76.4 (3°), 62.1 (2°), 43.8 (3°), 31.6 (2°), 31.5 (2°), 31.3 (2°), 25.8 (3×1°), 25.3 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (2×1°); IR (CH_2Cl_2): 2955, 2857, 1725, 1530, 1274, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 173 (M^++1, 1), 224 (100), 150 (21), 109 (16), 95 (27), 55 (7); HRMS *m*/*z* calcd for $C_{24}H_{39}SiNO_5$ 449.2598, found: 449.2598.

4.4.6. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-3-formyl-1-pentylbut-3-enyl ester (23).** Following the general procedure to prepare the α-substituted acrolein from terminal alkene, compound **23** (873 mg, 1.88 mmol) was prepared from alkene **22** (1.25 g, 2.78 mmol) in 68% yield as a white solid. TLC R_f=0.85 (hexane/EtOAc=3:1); mp 77.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, CHO), 8.26–8.29 (m, 2H, O_2NPh–*H*), 8.10–8.13 (m, 2H, O_2NPh–*H*), 6.59 (s, 1H, C=CH_2), 6.17 (s, 1H, C=CH_2), 5.60 (dt, *J*=4.7, 7.3 Hz, 1H, C*H*OCO), 3.74 (dd, *J*=5.1, 10.2 Hz, 1H, CH_2OTBS), 3.63 (dd, *J*=5.5, 10.2 Hz, 1H, CH_2OTBS), 3.26–3.31 (m, 1H, C*H*C=CH_2), 1.62–1.76 (m, 2H), 1.26–1.36 (m, 6H), 0.84–0.87 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.02 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.0 (4°), 164.0 (4°), 150.5 (4°), 147.9 (4°), 137.0 (2°), 135.8 (4°), 130.6 (2×3°), 123.5 (2×3°), 75.0 (3°), 62.5 (2°), 41.8 (3°), 32.5 (2°), 31.5 (2°), 25.7 (3×1°), 24.8 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); IR (CH_2Cl_2): 2955, 2857, 1725, 1696, 1273, 1101, 719 cm^{-1}; IR (CH_2Cl_2): 2955, 2857, 1725, 1696, 1273, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 433 (M^+−30, 1), 239 (100), 224 (66), 169 (14), 150 (61), 95 (10), 75 (31), 55 (4); HRMS *m*/*z* calcd for $C_{24}H_{37}SiNO_6$ 463.2390, found: 463.2393.

4.4.7. 4-Nitrobenzoic acid (1*S,2*S**)-2-(*tert*-butyldimethylsilyloxymethyl)-3-methoxycarbonyl-1-pentylbut-3-enyl ester (24).** Following the general procedure to prepare the methyl acrylate from α-substituted acrolein, methyl acrylate **24** (650 mg, 2.14 mmol) was prepared from acrolein **23** (873 mg, 1.88 mmol) in 70% yield as a pale yellow oil. TLC R_f=0.70 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26–8.29 (m, 2H, O_2NPh–*H*), 8.12–8.15 (m, 2H, O_2NPh–*H*), 6.34 (s, 1H, C=CH_2), 5.84 (s, 1H, C=CH_2), 5.56 (dt, *J*=4.2, 7.3 Hz, 1H, C*H*OCOAr), 3.77 (dd, *J*=5.4, 10.2 Hz, 1H, CH_2OTBS), 3.72 (s, 3H, OCH_3), 3.71 (dd, *J*=6.1, 10.2 Hz, 1H, CH_2OTBS), 3.25 (q, *J*=6.0 Hz, 1H, C*H*C=CH_2), 1.66–1.80 (m, 2H), 1.24–1.37 (m, 6H), 0.84–0.90 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.01 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.01 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6 (4°), 164.1 (4°), 150.5 (4°), 138.2 (4°), 136.0 (4°), 130.6 (2×3°), 127.4 (2°), 123.5 (2×3°), 75.4 (3°), 63.0 (2°), 52.0 (1°), 45.9 (3°), 32.5 (2°), 31.6 (2°), 25.8 (3×1°), 24.9 (2°), 22.4 (2°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); IR (CH_2Cl_2): 2954, 2857, 1725, 1530, 1273, 1101, 719 cm^{-1}; EI mass (*m*/*z*): 478 (M^+−15, 1), 269 (100), 224 (48), 150 (35), 89 (19), 55 (2); HRMS *m*/*z* calcd for $C_{25}H_{39}SiNO_7$ 478.2261 (M−CH_3), found: 478.2252.

4.4.8. 4-Nitrobenzoic acid (2*S,3*S**)-4-methylene-5-oxo-2-pentyltetrahydrofuran-3-ylmethyl ester (25).** Following the general procedure to prepare the γ-butyrolactone from the corresponding acyloxy-acrylate under acidic condition, γ-butyrolactone **25** (351 mg, 1.01 mmol) was prepared from acetoxy-acrylate **24** (650 mg, 1.32 mmol) in 77% yield as a pale yellow oil. TLC R_f=0.33 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.29–8.31 (m, 2H, O_2NPh–*H*), 8.14–8.16 (m, 2H, O_2NPh–*H*), 6.45 (d, *J*=2.0 Hz, 1H, C=CH_2), 5.78 (d, *J*=2.0 Hz, 1H, C=CH_2), 5.35 (quint, *J*=4.4 Hz, 1H, C*H*OCO), 4.41 (dd, *J*=7.7, 9.6 Hz, 1H, CH_2OCOAr), 4.35 (dd, *J*=2.9, 9.6 Hz, 1H, CH_2OCOAr), 3.46–3.49 (m, 1H, C*H*C=CH_2), 1.66–1.82 (m, 2H), 1.26–1.39 (m, 6H), 0.87 (t, *J*=7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 (4°), 164.2 (4°), 150.8 (4°), 134.9 (4°), 134.1 (4°), 130.7 (2×3°), 124.9 (2°), 123.7 (2×3°), 76.7 (3°), 67.6 (2°), 42.1 (3°), 31.3 (2°), 30.1 (2°), 25.1 (2°), 22.4 (2°), 13.8 (1°); IR (CH_2Cl_2): 2961, 2859, 1766, 1723, 1527, 1269, 1102, 719 cm^{-1}; EI mass (*m*/*z*): 347 (M^+, 1), 150 (100), 104 (22), 92 (8); HRMS *m*/*z* calcd for $C_{18}H_{21}NO_6$ 347.1369, found: 347.1379.

4.4.9. (3*S,4*S**,5*S**)-4-Hydroxymethyl-3-methoxymethyl-5-pentyldihydrofuran-2-one (26).** To a mixture of 4-nitrobenzoate **25** (120 mg, 0.34 mmol) in 1.2 mL of MeOH was added a solution of K_2CO_3 (53 mg, 0.38 mmol) in 0.6 mL of water and stirred at rt for 20 min. The reaction mixture was added 1 mL of water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give hydroxy-lactone **26** (56 mg, 0.24 mmol) in 71% yield as a pale yellow oil. TLC R_f=0.35 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.10 (ddd, *J*=3.5, 8.8, 8.8 Hz, 1H, C*H*OCO), 3.86 (dd, *J*=3.7, 9.5 Hz, 1H), 3.69–3.76 (br m, 1H), 3.60 (dd, *J*=7.6, 11.0 Hz, 1H), .3.51 (dd, *J*=9.0, 9.0 Hz, 1H,), 3.43 (s, 3H, OCH_3), 2.79 (ddd, *J*=3.7, 8.6, 10.4 Hz, 1H, C*H*CO), 2.23–2.30 (m, 1H, C*H*CH_2OH), 1.64–1.73 (m, 2H), 1.26–1.33 (m, 6H), 0.90 (t, *J*=6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3 (4°), 80.4 (3°), 71.3 (2°), 62.7 (2°), 59.2 (1°), 49.4 (3°), 46.4 (3°), 34.6 (2°), 31.5 (2°), 25.3 (2°), 22.4 (2°), 13.9 (1°); IR (CH_2Cl_2): 3462, 2931, 2872, 1757, 1459, 1185, 733 cm^{-1}; EI mass (*m*/*z*): 230 (M^+, 1), 126 (29), 103 (52), 85 (35), 55 (28), 45 (100); HRMS *m*/*z* calcd for $C_{12}H_{22}O_4$ 230.1518, found: 230.1523.

4.4.10. (4*S,5*S**)-4-Hydroxymethyl-3-methylene-5-pentyldihydrofuran-2-one (27).** *Method A* (*from compound* **25**). To a mixture of 4-nitrobenzoate **25** (50 mg, 0.14 mmol) in 0.7 mL of MeOH was added a solution of ammonium water (28–30% in water, 20 μL, 0.16 mmol) at 0 °C and stirred at this temperature for 2 h. The reaction mixture was added 0.3 mL of water and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give α-methylenelactone **27** (18 mg, 0.09 mmol) in 63% yield as a pale yellow oil.

Method B (*from compound* **26**). To a solution of compound **26** (13 mg, 56.4 μmol) and DBU (9.5 mg, 62.1 μmol) in 0.7 mL of benzene. The resulting solution was heated to reflux for 5 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the

α-methylenelactone **27** (8.4 mg, 42.3 μmol) in 75% yield as a pale yellow oil. TLC R_f=0.55 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d, J=2.8 Hz, 1H, C=CH_2), 5.72 (d, J=2.4 Hz, 1H, C=CH_2), 4.40 (ddd, J=4.4, 6.4, 6.4 Hz, 1H, CHOCO), 3.74–3.79 (m, 2H, CH_2OH), 2.85–2.90 (m, 1H, CHCH$_2$OH), 1.65–1.71 (m, 3H), 1.31–1.51 (m, 6H), 0.89 (t, J=7.2 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 136.2 (4°), 123.4 (2°), 80.9 (3°), 63.8 (2°), 46.8 (3°) 36.0 (2°), 31.4 (2°), 24.6 (2°), 22.4 (2°), 13.9 (1°); IR (CH_2Cl_2): 3459, 2932, 2860, 1748, 1465, 1151, 733 cm^{-1}; FAB mass (*m*/*z*): 199 (M^++1, 16), 181 (10), 154 (23), 136 (27), 91 (40), 81 (39), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{18}O_3$ 198.1256, found: 198.1248.

4.5. General procedure to prepare the carboxylic acid from the corresponding primary alcohol by Jones reagent

To a solution of primary alcohol **27** (50 mg, 0.25 mmol) in acetone (1 mL) at 40 °C was added Jones reagent dropwise until the orange color persisted and the resulting solution was stirred at this temperature for 5 min. After cooling to 0 °C, the reaction mixture was added isopropanol to quench the excess of Jones reagent. The mixture was partitioned between CH_2Cl_2 and water. The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The residual oil was chromatographed on silica gel column to give a white solid **8a** (45 mg, 0.21 mmol) in 84% yield.

4.5.1. (2*S,3*R**)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid (8a).** TLC R_f=0.20 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, J=3.1 Hz, 1H, C=CH_2), 6.02 (d, J=2.2 Hz, 1H, C=CH_2), 4.78–4.83 (m, 1H, CHOCO), 3.62–3.64 (m, 1H, CHC=CH$_2$), 1.71–1.78 (m, 2H), 1.26–1.51 (m, 6H), 0.90 (t, J=7.0 Hz, 3H, CH_3CH$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (4°), 168.6 (4°), 132.5 (4°), 125.8 (2°), 79.2 (3°), 49.4 (3°), 35.4 (2°), 31.1 (2°), 24.2 (2°), 22.2 (2°), 13.7 (1°); IR (CH_2Cl_2): 3462, 2954, 2861, 1743, 1660, 1465, 1257, 1186, 737 cm^{-1}; EI mass (*m*/*z*): 212 (M^+, 2), 183 (24), 141 (100), 123 (21), 113 (61), 81 (9), 55 (24); HRMS *m*/*z* calcd for $C_{11}H_{16}O_4$ 212.1049, found: 212.1053.

4.5.2. (−)-(4*R*)-4-Benzyl-3-pent-4-enoyloxazolidin-2-one ((−)-28).[16] To a stirred solution of 4-pentenoic acid (1.65 g, 16.52 mmol) and Et_3N (2.8 mL, 19.98 mmol) in 48 mL of dry THF, cooled to −78 °C under nitrogen, was added pivaloyl chloride (2.08 g, 17.27 mmol). The mixture was warmed to 0 °C for 60 min, and then recooled to −78 °C. A solution of (4*S*)-(phenylmethyl)-2-oxazolidone (2.66 g, 15.0 mmol) in 42 mL of THF, stirred at −30 °C to −45 °C under nitrogen, was treated dropwise with *n*-BuLi (2.50 M in hexane, 6.6 mL, 16.52 mmol). The resulting solution was cooled to −78 °C and then added, via rapid cannulation, to the above stirred mixture containing the mixed anhydride. The resulting mixture was stirred at −78 °C for 30 min. After warming to 0 °C, the mixture was partitioned between CH_2Cl_2 and pH 7 phosphate buffer. The CH_2Cl_2 phase washed with 5% aqueous $NaHCO_3$ followed by saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residual oil was chromatographed on silica gel column to give a colorless, viscous oil (−)-**28** (3.45 g, 13.31 mmol) in 88% yield. TLC R_f=0.44 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.35 (m, 5H, Ph–*H*), 5.84–5.94 (m, 1H, CH=CH$_2$), 5.02–5.14 (m, 2H, CH=CH_2), 4.68–4.71 (m, 1H, CHNCO), 4.15–4.22 (m, 2H, CH_2OCO), 3.30 (dd, J=13.4, 3.3 Hz, 1H, PhCH_2), 2.76 (dd, J=13.4, 9.6 Hz, 1H, PhCH_2), 2.98–3.14 (m, 2H, CH_2CH=CH$_2$), 2.49–2.43 (m, 2H, CH_2CO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4 (4°), 153.4 (4°), 136.6 (4°), 135.2 (3°), 129.3 (3°), 128.9 (3°), 127.3 (3°), 115.6 (2°), 66.1 (2°), 55.0 (3°), 37.8 (2°), 34.7 (2°), 28.1 (2°); IR (CH_2Cl_2): 2980, 2872, 1782, 1703, 1389, 1210, 1101, 703 cm^{-1}.

4.5.3. (−)-(2*R*,3*S*,4*R*)-4-Benzyl-3-(3-hydroxy-2-allyloctanoyl)oxazolidin-2-one ((−)-29).[17] To a solution of oxazolidinone (−)-**28** (2.5 g, 9.65 mmol) in 17 mL of CH_2Cl_2 in an ice bath was added Bu_2OTf (1 M in CH_2Cl_2, 11.6 mL, 11.6 mmol) over a 10 min period and then addition of Et_3N (1.75 mL, 12.5 mmol) over a 10 min period. The resulting light yellow solution was stirred at 0 °C for 10 min. The ice bath was replaced with a dry ice/acetone bath (78 °C) and freshly distilled *n*-hexanal (1.4 mL, 11.6 mmol) was added by syringe over a 5 min period. The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C for 2 h, and quenched by addition of 2 mL of pH 7 buffer and 2 mL of MeOH. A solution of 1.2 mL of MeOH/30% aqueous H_2O_2 (2:1 by volume) was added dropwise and the biphasic mixture was stirred vigorously at rt for 1 h. The mixture was diluted with 100 mL of water and the layers were separated. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The crude product was chromatographed on silica gel column to give compound (−)-**29** (2.52 g, 7.0 mmol) in 73% yield as a pale yellow oil. TLC R_f=0.38 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.35 (m, 5H, Ph–*H*), 5.83–5.93 (m, 1H, CH=CH$_2$), 5.04–5.15 (m, 2H, CH=CH_2), 4.68–4.74 (m, 1H, CHNCO), 4.13–4.20 (m, 3H, CH_2OCO and O*H*), 3.91–3.94 (m, 1H, CHOH), 3.33 (dd, J=3.2, 13.3 Hz, 1H, PhCH_2), 2.64 (dd, J=10.1, 13.3 Hz, 1H, PhCH_2), 2.57–2.65 (m, 1H, CHCO), 2.46–2.51 (m, 2H, CH_2CH=CH$_2$), 1.49–1.58 (m, 2H), 1.31–1.36 (m, 6H), 0.89 (t, J=6.3 Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.3 (4°), 153.4 (4°), 135.4 (4°), 135.3 (3°), 129.3 (3°), 128.9 (3°), 127.2 (3°), 117.1 (2°), 72.0 (3°), 65.9 (2°), 55.5 (3°), 47.1 (3°), 37.9 (2°), 34.0 (2°), 31.6 (2°), 31.5 (2°), 25.6 (2°), 22.5 (2°), 13.9 (1°); $[\alpha]_D^{30}$=−7.0 (c=0.55, $CHCl_3$); IR (CH_2Cl_2): 3524, 2954, 2859, 1779, 1696, 1385, 1208, 1104, 702 cm^{-1}; EI mass (*m*/*z*): 359 (M^+, 4), 341 (24), 270 (46), 259 (77), 178 (100), 117 (66), 91 (48), 83 (40), 55 (48); HRMS *m*/*z* calcd for $C_{21}H_{29}NO_4$ 359.2097, found: 359.2093.

4.5.4. (−)-(2*S*,3*S*)-2-Allyloctane-1,3-diol ((−)-30). To a 0 °C solution of aldol (−)-**29** (100 mg, 0.28 mmol) in 2.4 mL of THF was added dropwise a solution of $NaBH_4$ (43 mg, 1.11 mmol) in 0.6 mL of deionized H_2O. Once addition was complete, the ice bath was removed and the biphasic mixture was stirred vigorously at rt for 2 h. The mixture was then recooled in an ice bath and 5 mL of 1 N HCl was added carefully to quench the excess hydride reagent. The aqueous layer was extracted with 15 mL of CH_2Cl_2. The organic layers was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude

product by silica gel column chromatography gave the diol (−)-**30** (48 mg, 0.26 mmol) in 93% yield as a colorless oil. TLC R_f=0.25 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.81 (m, 1H, C*H*=CH_2), 5.02–5.10 (m, 2H, CH=CH_2), 3.86–3.90 (m, 1H, C*H*OH), 3.80 (dd, J=6.4, 10.8 Hz, 1H, CH_2OH), 3.74 (dd, J=3.8, 10.8 Hz, 1H, CH_2OH), 2.13 (dd, J=7.2, 7.2 Hz, 2H, CH_2CH=CH_2), 1.73–1.78 (m, 1H,), 1.44–1.55 (m, 2H), 1.31–1.32 (br m, 6H), 0.89 (t, J=6.2 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.1 (3°), 116.2 (2°), 74.6 (3°), 64.4 (2°), 44.0 (3°), 33.4 (2°), 31.8 (2°), 29.9 (2°), 25.9 (2°), 22.6 (2°), 14.0 (1°); $[\alpha]_D^{28}=-7.1$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 3419, 2931, 2859, 1416, 1160, 1026, cm^{-1}; FAB mass (*m*/*z*): 187 (M^++1, 27), 178 (45), 169 (53), 151 (68), 136 (57), 109 (65), 95 (97), 81 (94), 55 (100); HRMS *m*/*z* calcd for $C_{11}H_{22}O_2$ 186.1620, found: 186.1613.

4.5.5. (−)-(4*S*,5*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-dec-1-en-5-ol ((−)-31). To a solution of the diol (−)-**30** (160 mg, 0.86 mmol), DMAP (21 mg, 0.17 mmol) and imidazole (64.4 mg, 0.94 mmol) in 1.8 mL of CH_2Cl_2 was added *t*-butyldimethylsilyl chloride (142.5 mg, 0.94 mmol) at rt and stirred it for 3 h. The reaction is quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give the silyl ether (−)-**31** (231 mg, 0.81 mmol) in 94% yield as a pale yellow oil. TLC R_f=0.38 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72–5.83 (m, 1H, C*H*=CH_2), 5.01–5.08 (m, 2H, CH=CH_2), 3.81–3.85 (m, 1H, C*H*OH), 3.78 (dd, J=5.2, 9.8 Hz, 1H, CH_2OTBS), 3.73 (dd, J=3.5, 9.8 Hz, 1H, CH_2OTBS), 3.27 (br d, J=3.7 Hz, 1H, O*H*), 2.14–2.17 (m, 2H, CH_2CH=CH_2), 1.61–1.68 (m, 1H, C*H*CH_2OTBS), 1.47–1.55 (m, 2H), 1.30–1.43 (m, 6H), 0.88–0.91 (m, 12H, CH_2CH_3 and $(CH_3)_3CSiMe_2$), 0.08 (s, 3H, *t*-BuSi(CH_3)$_2$), 0.07 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.3 (3°), 116.1 (2°), 74.9 (3°), 65.4 (2°), 43.8 (3°), 33.8 (2°), 31.9 (2°), 29.3 (2°), 25.9 (2°), 25.8 (3×1°), 22.6 (2°), 18.0 (4°), 14.0 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{31}=-8.6$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 3447, 2955, 2857, 1471, 1255, 1091, 777 cm^{-1}; FAB mass (*m*/*z*): 301 (M^++1, 7), 283 (7), 154 (27), 136 (40), 95 (21), 91 (23), 81 (24), 73 (100), 55 (42); HRMS *m*/*z* calcd for $C_{17}H_{36}O_2Si$ 300.2485, found: 300.2483.

4.5.6. (−)-Acetic acid (1*S*,2*S*)-2-(*tert*-butyldimethylsilyloxymethyl)-1-pentylpent-4-enyl ester ((−)-32). To a solution of the alcohol (−)-**31** (231 mg, 0.86 mmol), DMAP (21 mg, 0.86 mmol) and Et_3N (0.18 mL, 1.29 mmol) in 1.8 mL of CH_2Cl_2 was added acetic anhydride (0.12 mL, 1.29 mmol) at rt and stirred it for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate (−)-**32** (260 mg, 0.76 mmol) in 88% yield as a pale yellow oil. TLC R_f=0.50 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73–5.84 (m, 1H, C*H*=CH_2), 4.99–5.06 (m, 3H, CH=CH_2 and C*H*OCO), 3.56 (dd, J=5.1, 10.1 Hz, 1H, CH_2OTBS), 3.52 (dd, J=5.6, 10.1 Hz, 1H, CH_2OTBS), 2.12–2.15 (m, 2H, CH_2CH=CH_2), 2.03 (s, 3H, COCH_3), 1.72–1.79 (m, 1H, C*H*CH_2OTBS), 1.55–1.57 (m, 2H), 1.25–1.35 (br m, 6H), 0.86–0.92 (m, 12H, CH_2CH_3 and $(CH_3)_3$-$CSiMe_2$), 0.02 (s, 6H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6 (4°), 137.1 (3°), 116.0 (2°), 74.4 (3°), 61.9 (2°), 43.7 (3°), 31.7 (2°), 31.5 (2°), 31.3 (2°), 25.8 (3×1°), 25.2 (2°), 22.5 (2°), 21.2 (1°), 18.2 (4°), 14.0 (1°), −5.6 (2×1°); $[\alpha]_D^{34}=-2.9$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2857, 1740, 1471, 1242, 1098, 776 cm^{-1}; FAB mass (*m*/*z*): 343 (M^++1, 9), 307 (52), 154 (99), 136 (100), 107 (65), 91 (55), 81 (29), 73 (83), 55 (43); HRMS *m*/*z* calcd for $C_{19}H_{38}O_3Si$ 342.2590, found: 342.2580.

4.5.7. (+)-(1*S*,2*S*)-2-[2-Acetoxy-1-(*tert*-butyldimethylsilyloxymethyl)heptyl]acrolein ((+)-33). Following the general procedure to prepare the α-substituted acrolein from terminal alkene, compound (+)-**33** (1.07 g, 3.0 mmol) was prepared from alkene (−)-**32** (1.2 g, 3.50 mmol) in 86% yield as a colorless oil. TLC R_f=0.25 (hexane/EtOAc=20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, C*H*O), 6.53 (s, 1H, C=CH_2), 6.15 (s, 1H, C=CH_2), 5.27–5.31 (m, 1H, C*H*OCO), 3.63 (dd, J=5.5, 10.1 Hz, 1H, CH_2OTBS), 3.56 (dd, J=5.9, 10.1 Hz, 1H, CH_2OTBS), 3.09–3.13 (m, 1H, C*H*–C=CH_2), 1.99 (s, 3H, COCH_3), 1.48–1.51 (m, 2H), 1.25–1.27 (m, 6H), 0.84–0.90 (m, 12H), 0.02 (s, 3H, *t*-BuSi(CH_3)$_2$), −0.02 (s, 3H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.1 (4°), 170.2 (4°), 147.8 (4°), 137.0 (2°), 72.7 (3°), 62.6 (2°), 41.7 (3°), 32.4 (2°), 31.6 (2°), 25.7 (3×1°), 24.8 (2°), 22.4 (2°), 21.0 (1°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{32}=+1.4$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2858, 1741, 1697, 1471, 1239, 1104, 1022, 777 cm^{-1}; FAB mass (*m*/*z*): 357 (M^++1, 16), 297 (42), 239 (71), 117 (84), 91 (22), 81 (31), 73 (100), 55 (44); HRMS *m*/*z* calcd for $C_{19}H_{36}O_4Si$ 356.2383, found: 356.2391.

4.5.8. (−)-(1*S*,2*S*)-2-[2-Acetoxy-1-(*tert*-butyldimethylsilyloxymethyl)heptyl]acrylic acid methyl ester ((−)-34). Following the general procedure to prepare the methyl acrylate from α-substituted acrolein, methyl acrylate (−)-**34** (910 mg, 2.35 mmol) was prepared from acrolein (+)-**33** (1.07 g, 3.00 mmol) in 78% yield as a colorless oil. TLC R_f=0.70 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (s, 1H, C=CH_2), 5.77 (s, 1H, C=CH_2), 5.24 (ddd, J=5.0, 7.2, 7.2 Hz, 1H, C*H*OCO), 3.76 (s, 3H, OCH_3), 3.68 (dd, J=5.7, 10.1 Hz, 1H, CH_2OTBS), 3.63 (dd, J=6.2, 10.1 Hz, 1H, CH_2OTBS), 3.05–3.09 (m, 1H, C*H*C=CH_2), 1.98 (s, 3H, COCH_3), 1.51–1.62 (m, 2H), 1.22–1.33 (m, 6H), 0.83–0.91 (m, 12H), 0.01 (s, 6H, *t*-BuSi(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 167.7 (4°), 138.1 (4°), 127.3 (2°), 73.1 (3°), 63.0 (2°), 51.9 (1°), 45.7 (3°), 32.4 (2°), 31.6 (2°), 25.8 (3×1°), 24.9 (2°), 22.5 (2°), 21.0 (1°), 18.1 (4°), 13.9 (1°), −5.6 (1°), −5.7 (1°); $[\alpha]_D^{32}=-2.4$ (c=0.52, $CHCl_3$); IR (CH_2Cl_2): 2955, 2858, 1739, 1438, 1242, 1104, 777 cm^{-1}; FAB mass (*m*/*z*): 387 (M^++1, 15), 329 (34), 269 (52), 154 (12), 117 (40), 91 (11), 73 (100), 55 (9); HRMS *m*/*z* calcd for $C_{20}H_{38}O_5Si$ 386.2489, found: 386.2493.

4.5.9. (−)-(4*R*,5*S*)-4-Hydroxymethyl-3-methylene-5-pentyldihydrofuran-2-one ((−)-27). To a mixture of acetoxy-acrylate (−)-**34** (50 mg, 0.13 mmol) in 0.3 mL of MeOH was added catalytic amount of acetyl chloride (1 μL, 13 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the α-methylenelactone (−)-**27** (23.4 mg, 0.12 mmol) in 91% yield as a pale yellow oil. TLC R_f=0.55 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (d,

$J=2.8$ Hz, 1H, C=CH_2), 5.72 (d, $J=2.8$ Hz, 1H, C=CH_2), 4.40 (ddd, $J=4.4$, 6.4, 6.4 Hz, 1H, CHOCO), 3.74–3.79 (m, 2H, CH_2–OH), 2.85–2.90 (m, 1H, CHCH$_2$OH), 1.65–1.71 (m, 3H), 1.31–1.51 (m, 6H), 0.89 (t, $J=7.2$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (4°), 136.2 (4°), 123.4 (2°), 80.9 (3°), 63.8 (2°), 46.8 (3°) 36.0 (2°), 31.4 (2°), 24.6 (2°), 22.4 (2°), 13.9 (1°); $[\alpha]_D^{30}=-16.2$ ($c=0.52$, $CHCl_3$); IR (CH_2Cl_2): 3459, 2932, 2860, 1748, 1465, 1151, 733 cm^{-1}; FAB mass (*m/z*): 199 ($M^+ +1$, 16), 181 (10), 154 (23), 136 (27), 91 (40), 81 (39), 55 (100); HRMS *m/z* calcd for $C_{11}H_{18}O_3$ 198.1256, found: 198.1248.

4.5.10. (−)-(4*R*,5*S*)-4-Methylene-5-oxo-2-pentyltetrahydrofuran-3-carboxylic acid ((−)-8a). Following the general procedure to prepare the carboxylic acid from the corresponding primary alcohol by Jones reagent, (−)-methylenolactocin ((−)-**8a**) (492 mg, 0.21 mmol) was prepared from primary alcohol (−)-**27** (550 mg, 2.52 mmol) in 84% yield as a white solid. TLC $R_f=0.20$ (hexane/EtOAc=1:1); mp 82.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, $J=3.1$ Hz, 1H, C=CH_2), 6.02 (d, $J=2.2$ Hz, 1H, C=CH_2), 4.78–4.83 (m, 1H, CHOCO), 3.63 (ddd, $J=2.8$, 2.8, 5.6 Hz, 1H, CHC=CH$_2$), 1.71–1.78 (m, 2H), 1.26–1.51 (m, 6H), 0.90 (t, $J=7.0$ Hz, 3H, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (4°), 168.8 (4°), 132.5 (4°), 125.8 (2°), 79.2 (3°), 49.4 (3°), 35.4 (2°), 31.1 (2°), 24.2 (2°), 22.2 (2°), 13.7 (1°); $[\alpha]_D^{32}=-18.8$ ($c=0.31$, $CHCl_3$); IR (CH_2Cl_2): 3462, 2954, 2861, 1743, 1257, 1186, 737 cm^{-1}; EI mass (*m/z*): 212 (M^+, 2), 183 (24), 141 (100), 123 (21), 113 (61), 81 (9), 55 (24); HRMS *m/z* calcd for $C_{11}H_{16}O_4$ 212.1049, found: 212.1053.

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