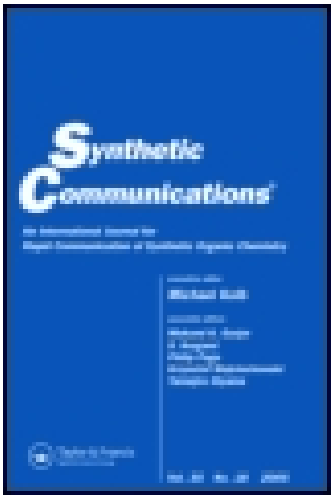

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Dibromomethane as One-Carbon Source in Organic Synthesis: Formal Total Synthesis of (±)-Nephrosteranic Acid

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Dibromomethane as One-Carbon Source in Organic Synthesis: Formal Total Synthesis of (±)-Nephrosteranic Acid

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Abstract: A diastereoselective formal total synthesis of (±)-nephrosteranic acid (**10**) is described. The key step is to introduce the α-methylene group by the ozonolysis of monosubstituted alkenes followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH. The α-methyl group of compound **10** was formed from the reduction of the corresponding α-methylene precursor.

Keywords: *cis*-nephrosterinic acid, nephrosteranic acid, α-methylenation, α-methylene-γ-butyrolactones, paraconic acids, α-substituted acrolein

INTRODUCTION

We have reported that the ozonolysis of monosubstituted 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 (Scheme 1).[2] This methodology was also

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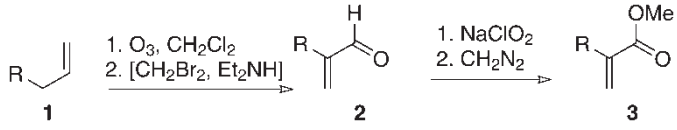


Scheme 1.

applied to prepare the α-methylene lactones with different ring size from the corresponding alkenol.[3]

Various bioactive α-methylene-γ-butyrolactones have been isolated from microorganisms, and some specific examples are shown in Fig. 1. The structures **4**–**9** contain α-methylene, β-carboxylate, and γ-alkyl groups in different chain lengths. Both the β- and γ-substituents are *trans* to each other for compounds **4**–**6** and *cis* to each other for compounds **7**–**9**. We have successfully applied the methodology described in Scheme 1 to the total synthesis of the ($\pm$)- and ($-$)-methylenolactocin (**4**) and ($\pm$)-canadensolide (**9**).[4]

Paraconic acids are a family of chiral trisubstituted γ-butyrolactones with a methyl group at the α position and a carboxylic acid at the β position, isolated from various species of moss, lichens, and fungus. They possess important biological activities, such as antitumor, antibiotic, antifungal, and antibacterial properties. Because of their important potential pharmacological applications, several total and formal total syntheses of members of this class of compounds **10**–**14** (Fig. 1) have been described in both racemic and optically active forms.[5–9]

There are two major strategies for the total synthesis of the paraconic acid natural products **A** as shown in Fig. 2. First, the diastereoselective

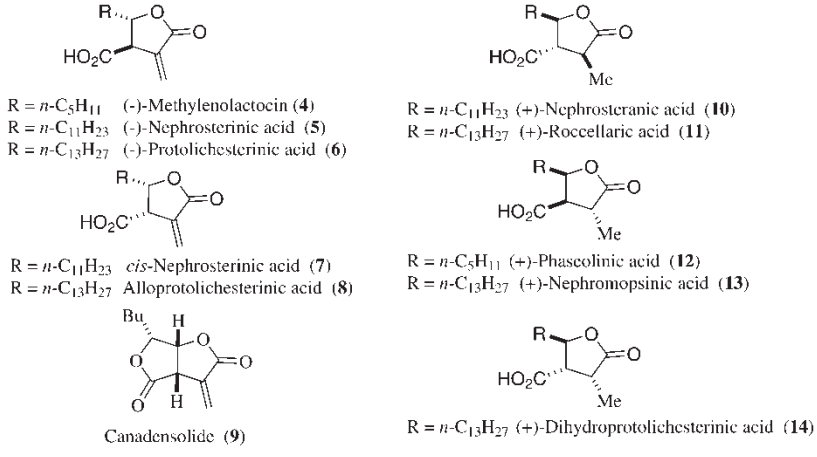


Figure 1. Natural products with β,γ-disubstituted-α-methylene-γ-butyrolactone moiety (**4**–**9**) and some typical paraconic acid natural products (**10**–**14**).

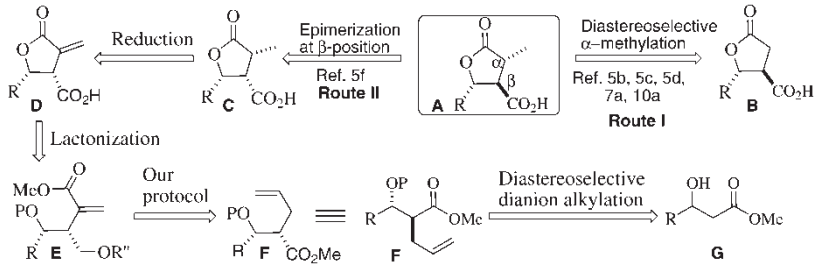


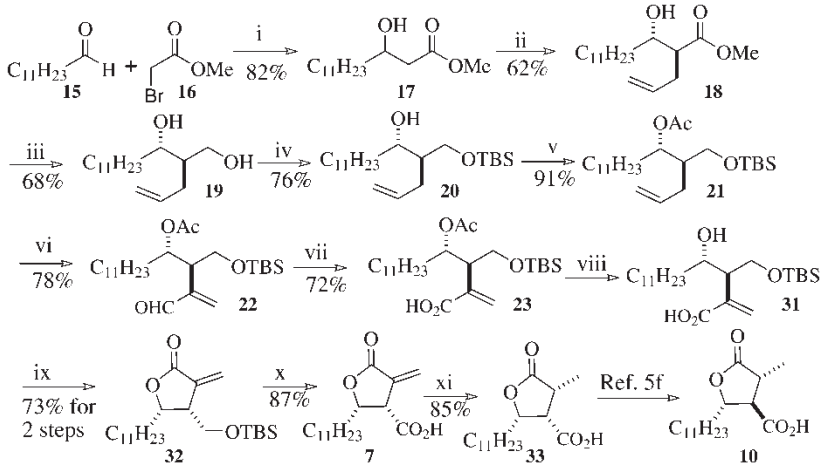
Figure 2. Two major strategies to prepare the paraconic acid natural products **A** via routes I and II and the retrosynthetic analysis of our total synthesis of natural product **A** via route II.

α-methylation of the β-substituted-γ-butyrolactone precursors **B** gives compound **A** (route I).[5b,5c,5d,7a,10a] Second, the α-methyl group is introduced by the hydrogenation of the α-methylene-γ-butyrolactone precursors **D**.[9b,11] The further epimerization at β-position of compound **C** is required to synthesize the target molecule **A** (i.e., route II).[5f,7b,9a] In continuation of our interest in using the α-methylenation methodology in natural product synthesis,[4] we want to develop a general synthetic pathway that is applicable to prepare paraconic acids. In this article, we describe our effort in the stereoselective synthesis of epinephrosteranic acid (**33**), which is a useful precursor in the total synthesis of nephrosteranic acid (**10**).

RESULTS AND DISCUSSION

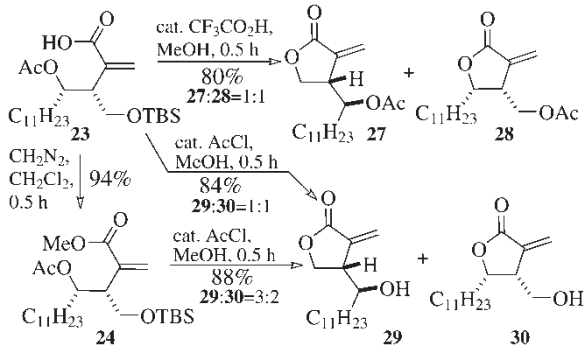
The retrosynthetic analysis of α-methyl-β-carboxyl-γ-butyrolactone **A** is shown in Fig. 2. Structure **A** could be derived from the corresponding *cis*, *cis*-isomer **C** via stereoselective epimerization.[5f] The α-methyl group of *cis*,*cis*-isomer **C** should be prepared from the stereoselective reduction of the corresponding α-methylene lactone **D**. The γ-butyrolactone **D** should be easily prepared from alkenol **F** by our methodology as shown in Scheme 1. The stereoselective introduction of the β- and γ-stereogenic centers of compound **F** from the allylation of the dianion of β-hydroxy ester **G** is a well-known procedure in the literature.[12]

The β-hydroxy ester **17** was prepared from *n*-decanal (**15**) and methyl bromoacetate (**16**) in the presence of activated zinc in 82% yield. The allylation of β-hydroxy ester **17** following the procedure of Frater[12b] gave the *anti*-β-hydroxy ester **18** in 62% yield (Scheme 2). The hydroxy ester **18** was reduced by diisobutylaluminum hydride to give the corresponding diol **19** in 68% yield. Selective silylation at the primary alcohol of compound **19** followed by acetylation gave the acetate **21** in excellent yield. The ozonolysis of terminal olefin **21** followed by addition of a preheated mixture of CH_2Br_2



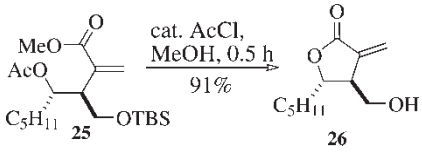
Scheme 2. Reagents and conditions: (i) Zn, PhH, reflux, 3 h; (ii) 2.2 equiv. LDA, THF, −78°C, 1 h; $H_2C{=}CHCH_2Br$, −78°C to rt, 1 h; (iii) Dibal-H, CH_2Cl_2, 0°C to rt, 2 h; (iv) TBSCl, imidazole, cat. DMAP, CH_2Cl_2, 3 h; (v) Ac_2O, cat. DMAP, Et_3N, CH_2Cl_2, 2 h; (vi) O_3, CH_2Cl_2, −78°C; preheated mixture of Et_2NH and CH_2Br_2, 1.5 h; (vii) $NaClO_2$, *t*-BuOH, $NaH_2PO_4 \cdot 2H_2O$, $MeCH{=}CMe_2$, 2.5 h; (viii) KOH, 0°C to rt, MeOH, 1.5 h; (ix) *o*-nitrophenylsulfonyl chloride, Na_2CO_3, CH_2Cl_2, 0.5 h; (x) Jones, reagent, acetone, 40°C, 5 min; (xi) H_2, 10% Pd/C, EtOAc, 4 h.

and Et_2NH afforded acrolein **22** in 78% yield. The acrolein **22** was oxidized by sodium chlorite in the presence of a chlorine scavenger (i.e., 2-methyl-2-butene) to give the corresponding acrylic acid **23** in 72% yield (Scheme 2). Acrylic acid **23** was subsequently treated with CH_2N_2 to give the methyl acrylate **24** in 94% yield (Scheme 3).



Scheme 3.

We reported that the *erythro*-acrylate **25** gave the cyclized product **26** in excellent yield under acidic conditions as shown in Eq. (1).[4a]



However, when the *threo*-acrylate **24** was treated with a catalytic amount of AcCl in MeOH, a mixture of the α-methylene-γ-butyrolactone **29** and **30** was obtained in a ratio of 3:2 in 88% yield (Scheme 3). Under similar condition, acrylic acid **23** also affords a mixture of the γ-butyrolactone **29** and **30** in a ratio of 1:1 in 84% yield. On the other hand, when acrylic acid **23** was treated with a catalytic amount of trifluoroacetic acid in MeOH at 0°C, a mixture of the γ-butyrolactone **27** and **28** was obtained in a ratio of 1:1 in 80% yield (Scheme 3). Apparently, the less acidic condition will retain the acetate functionality to get products **27** and **28**.

The possible mechanism for the formation of the lactones **29** and **30** from acrylate **24** was proposed as follows (Fig. 3). The *tert*-butyldimethylsilyl ether of compound **24** was selectively deprotected under acidic conditions to give the primary alcohol **24a**. The equilibrium occurs between compounds **24a** and **24b** via 1,5-acetyl group migration. These two intermediates undergo cyclization to give the acetoxy-lactones **27** and **28**, respectively. The cyclization is disfavored from intermediate **24b** because of the nonbonding

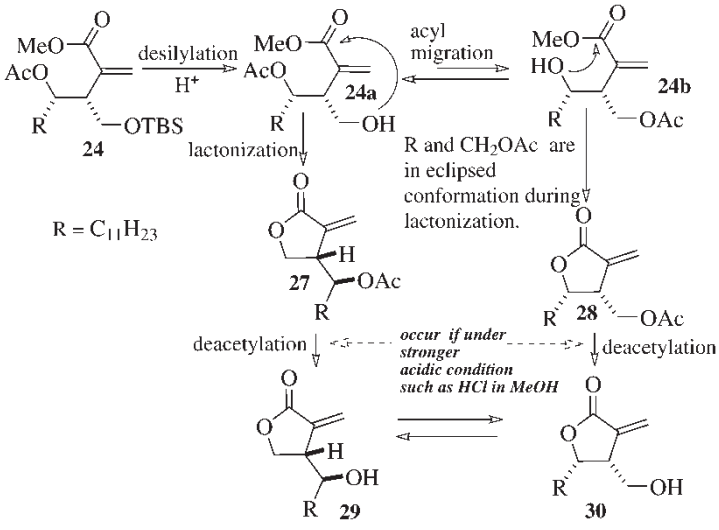


Figure 3. Proposed mechanism for the γ-butyrolactone **27**–**30** formation via intermediates **24a** and **24b**.

interaction of two substituents in its eclipsed conformation. If under stronger acidic condition, further transesterification of lactones **27** and **28** occurred to give the corresponding hydroxyl-lactones **29** and **30**, respectively. In addition, when pure compound **29** was stirring in a catalytic amount of AcCl in MeOH, an equilibrated mixture of **29** and **30** was formed, which indicates that compounds **29** and **30** will equilibrate with each other under acidic conditions.

To solve the problem of the lactonization, acrylic acid **23** was treated with KOH in methanol to give the deacetylation product **31**, which was treated with *o*-nitrophenylsulfonyl chloride[13] in the presence of Na_2CO_3 to give α-methylene-γ-butyrolactone **32** in 72% yield over two steps (Scheme 2). Finally, compound **32** was treated with Jones reagent to give *cis*-nephrosteranic acid (**7**) in 87% yield. Catalytic hydrogenation of compound **7** gave the all-*cis* isomer **33** as a sole product in 85% yield. The β-chiral center of the epinephrostereanic acid (**33**) was reported previously to give the desired natural product (**10**).[5f] Thus, this work constitutes a formal total synthesis of ($\pm$)-nephrosteranic acid (**10**). Both (*R*)-**17** and (*S*)-**17** were prepared in excellent enantioselectivity by enzymztic methodology.[14] Therefore, it is feasible to prepare the optical active nephrosteranic acid (**10**) by our synthetic design.

CONCLUSIONS

The special features of our synthetic design are as follows. The relative stereochemistry of β- and γ-substitutents was established by the stereoselective allylation of the dianion of β-hydroxy ester **17**. The α-methylene-γ-butyrolactone moiety was derived from the corresponding terminal alkene of compound **18** by the methodology developed in our laboratory. The stereoselectivity in the reduction of the α-methylene-γ-butyrolactone **7** was controlled by its β- and γ-substitutents. In conclusion, we completed the formal total synthesis of ($\pm$)-nephrostereanic acid (**10**) in 11 operation steps in 7.2% overall yield to give epinephrosteranic acid (**33**) starting from *n*-decanal (**15**).

EXPERIMENTAL

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 are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX400 spectrometer, and chemical shifts were given in parts per million (ppm) downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin-Elmer 682 spectrophotometer, and only noteworthy absorptions were listed. Mass

spectra were measured on a Micromass Trio-2000 GC/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 mass spectrometer (National Chung Hsing University). 3-Nitrobenzyl alcohol (NBA) was used as FAB mass matrix.

3-Hydroxytetradecanoic Acid Methyl Ester (17)

A suspension of the activated zinc dust (3.92 g, 60 mmol) in 20 mL of anhydrous benzene was heated up to reflux for 10 min. To the refluxing suspension solution, a mixture of the *n*-decanal (**15**) (10 g, 54.25 mmol) and methyl bromoacetate (**16**) (5.62 mL, 59.13 mmol) in 100 mL of benzene was slowly added during a period of 1 h. After 2 h, the reaction mixture was cooled to 0°C, and then 1*N* HCl was added to work up the reaction and extracted with ether (150 mL × 3). The combined organic extract was dried ($MgSO_4$), concentrated, and chromatographed on silica-gel column to give the desired β-hydroxy ester **17** (11.5 g, 44.49 mmol) in 82% yield as a colorless oil. TLC $R_f = 0.51$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97–4.04 (m, 1H, -C<u>H</u>OH), 3.71 (s, 3H), 2.83 (brd, $J = 4.0$ Hz, 1H), 2.52 (dd, $J = 16.4$ and 3.1 Hz, 1H, -C<u>H</u>$_2$CO), 2.41 (dd, $J = 16.4$ and 9.0 Hz, 1H, -C<u>H</u>$_2$CO), 1.21–1.55 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 (s), 68.0 (d), 51.6 (q), 41.1, 36.5, 31.9, 29.6, 29.57, 29.53, 29.51, 29.48, 29.3, 25.4, 22.6, 14.0 (q); IR (thin film, NaCl plates): 3455, 2927, 2854, 1731, 1442, 1288, 1172, 914, 732 cm^{-1}; EI mass (*m*/*z*): 258 (M^+, 1), 103 (100), 74 (20), 71 (17), 55 (12); HRMS calcd. for $C_{15}H_{30}O_3$ 258.2195; found: 258.2205.

(2*R**,3*S**)-2-Allyl-3-hydroxytetradecanoic Acid Methyl Ester (18)

n-Butyllithium (26.6 mL, 42.57 mmol, 1.6 M in hexane) was added to a stirring solution of diisopropylamine (6.00 mL, 42.57 mmol) in THF (70 mL) at −78°C. To the lithium diisopropylamide (LDA) solution, β-hydroxy ester **17** (5.0 g, 19.35 mmol) in 35 mL of THF was added at −78°C and stirred at this temperature for 1 h. At −78°C, a mixture of allyl bromide (2.02 mL, 23.18 mmol) and hexamethylphosphoramide (HMPA) (6.7 mL) in THF (25 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 **18** (3.6 g, 12.06 mmol) in 62% yield as a pale yellow oil. TLC $R_f = 0.62$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70–5.80 (m, 1H, -C<u>H</u>=CH$_2$), 5.03–5.12 (m, 2H, -CH=C<u>H</u>$_2$), 3.70 (s, 3H), 3.68–3.69 (m, 1H, -C<u>H</u>OH),

2.52–2.56 (m, 1H, -CHCO$_2$Me), 2.40–2.46 (m, 2H), 1.24–1.49 (m, 20H), 0.88 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1 (s), 134.8 (d), 116.9, 71.6 (d), 51.3 (q), 50.5 (d), 35.4, 33.6, 31.8, 29.48, 29.47, 29.42, 29.40, 29.36, 29.2, 25.6, 22.5, 13.9 (q); IR (thin film, NaCl plates): 3482, 2927, 2854, 1727, 1446, 1168, 914, 732 cm^{-1}; EI mass (m/z): 298 (M^+, 1), 143 (86), 114 (100), 95 (14), 83 (41), 61 (41), 55 (46); HRMS calcd. for $C_{18}H_{34}O_3$ 298.2508, found: 298.2507.

(2*R**,3*S**)-2-Allyltetradecane-1,3-diol (19)

To a solution of β-hydroxy ester **18** (1.8 g, 6.02 mmol) in 30 mL of CH_2Cl_2, diisobutylaluminum hydride (Dibal-H, 1 M in hexane, 15.1 mL, 15.1 mmol) was added 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, 8 mL of ethyl acetate was added to quench the excess of Dibal-H at 0°C. The reaction mixture was then washed with 20 mL of water. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on a silica-gel column to give diol **19** (1.11 g, 4.09 mmol) in 68% yield as a pale yellow oil. TLC $R_f = 0.22$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.86 (m, 1H, -CH=CH$_2$), 5.03–5.12 (m, 2H, -CH=CH$_2$), 3.91–3.94 (m, 1H, -CHOH), 3.66–3.71 (m, 2H, -CH$_2$OH), 2.46 (br s, 1H), 2.22–2.26 (m, 3H, -CH$_2$CH=CH$_2$ and -CHCH$_2$OH), 1.22–1.60 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.7 (d), 116.4, 75.1 (d), 63.7, 44.0 (d), 35.5, 33.4, 31.9, 29.62, 29.60, 29.57, 29.3, 25.7, 22.6, 14.0 (q); IR (thin film, NaCl plates): 3370, 2927, 2857, 1457, 1257, 1029, 910, 732 cm^{-1}; FAB mass (m/z): 271 ($M^+ + 1$, 8), 253 (36), 235 (24), 154 (60), 136 (61), 123 (24), 95 (64), 81 (68), 69 (76), 55 (100); HRMS calcd. for $C_{17}H_{35}O_2$ ($M^+ + H$) 271.2637, found: 271.2635.

(4*R**,5*S**)-4-[(*tert*-Butyldimethylsilyloxy)methyl]hexadec-1-en-5-ol (20)

To a solution of the diol **19** (800 mg, 2.96 mmol), DMAP (*N*,*N*-dimethylaminopyridine, 72.5 mg, 0.59 mmol) and imidazole (222 mg, 3.26 mmol) in 6 mL of CH_2Cl_2, *t*-butyldimethylsilyl chloride (0.49 g, 3.26 mmol) was added at rt and stirred 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 a silica-gel column to give the secondary alcohol **20** (864 mg, 2.25 mmol) in 76% yield as a colorless oil. TLC $R_f = 0.84$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.73–5.83 (m, 1H, -CH=CH$_2$), 5.02–5.09 (m, 2H, -CH=CH$_2$), 3.91 (dd, $J = 10.1$ and 3.5 Hz, 1H, -CH$_2$OTBS), 3.66 (dd, $J = 10.2$ and 5.0 Hz, 1H, -CH$_2$OTBS),

3.60–3.63 (m, 1H, -CHOH), 3.31 (d, $J = 6.2$ Hz, 1H, OH), 2.14–2.30 (m, 3H, -CH_2CH=CH_2 and CHCH$_2$OTBS), 1.21–1.56 (m, 20H), 0.83–0.95 (m, 12H), 0.073 [s, 3H, *t*-BuSi(CH_3)$_2$], 0.069 [s, 3H, *t*-BuSi(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9 (d), 116.3, 74.7 (d), 64.1, 43.7, 35.7, 33.3, 31.9, 29.8, 29.7, 29.6, 29.3, 25.9 (q), 25.8, 22.7, 18.1 (s), 14.1 (q), −5.7 (q); IR (thin film, NaCl plates): 3505, 2927, 2857, 1465, 1253, 1087, 914, 840, 732 cm^{-1}; FAB mass (*m*/*z*): 385 ($M^+ + 1$, 4), 367 (4), 281 (12), 221 (20), 207 (16), 221 (16), 147 (42), 73 (100); HRMS calcd. for $C_{23}H_{49}O_2Si$ ($M^+ + H$) 385.3502, found: 385.3497.

(4*R**,5*S**)-4-[(*tert*-Butyldimethylsilyloxy)methyl]hexadec-1-en-5-yl Acetate (21)

To a solution of alcohol **20** (600 mg, 1.56 mmol), DMAP (38 mg, 0.31 mmol), and Et_3N (0.33 mL, 2.3 mmol) in CH_2Cl_2 (3.1 mL), acetic anhydride (0.22 mL, 2.3 mmol) was added at rt and stirred for 2 h. The reaction mixture was concentrated and chromatographed on a silica-gel column to afford the acetate **21** (605.8 mg, 1.42 mmol) in 91% yield as a pale yellow oil. TLC $R_f = 0.70$ (hexane/EtOAc = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.71–5.82 (m, 1H, -CH=CH_2), 4.99–5.05 (m, 3H, -CH=CH_2 and -CHOAc), 3.62 (dd, $J = 10.2$ and 5.5 Hz, 1H, -CH_2OTBS), 3.54 (dd, $J = 10.2$ and 5.6 Hz, 1H, -CH_2OTBS), 2.08–2.13 (m, 2H, -CH_2CH=CH_2), 2.03 (s, 3H, -COCH_3), 1.77–1.85 (m, 1H, -CHCH$_2$OTBS), 1.25–1.30 (m, 20H), 0.85–0.91 (m, 12H), 0.03 [s, 6H, *t*-BuSi(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5(s)136.7 (d), 116.3, 74.6 (d), 61.8, 43.8 (d), 31.9, 31.8, 31.2, 29.64, 29.62, 29.58, 29.56, 29.53, 29.3, 26.0, 25.9 (q × 3), 25.6, 22.7, 21.2 (q), 18.2 (s), 14.1 (q), −5.5 (q), −5.6 (q); IR (thin film, NaCl plates): 2927, 2857, 1739, 1465, 1245, 1099, 914, 840, 732 cm^{-1}; EI mass (*m*/*z*): 427 ($M^+ + 1$, 4), 307 (18), 289 (16), 154 (100), 136 (81), 107 (32), 77 (36); HRMS calcd. for $C_{25}H_{51}O_3Si$ ($M^+ + H$) 427.3607, found: 427.3611.

(3*R**,4*S**)-3-[(*tert*-Butyldimethylsilyloxy)methyl]-2-formylpentadec-1-en-4-yl Acetate (22)

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 **21** (700 mg, 1.64 mmol) in CH_2Cl_2 (30 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 (0.90 mL, 8.20 mmol) and CH_2Br_2 (1.7 mL, 24.5 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 previously, a preheated mixture of Et_2NH and CH_2Br_2 was added

at −78°C. After the addition, the cooling bath was removed, and the reaction mixture was stirred at rt. The reaction was completed 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 and chromatographed on the silica-gel column to give the desired acrolein **22** (564 mg, 1.28 mmol) as a colorless oil in 78% yield. TLC $R_f = 0.43$ (hexane/EtOAc = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, CHO), 6.40 (s, 1H, -C=C$\underline{H}_2$), 6.16 (s, 1H, -C=C$\underline{H}_2$), 5.15 (td, $J = 8.1$ and 3.7 Hz, 1H, -C$\underline{H}$OAc), 3.74 (dd, $J = 10.0$ and 6.3 Hz, 1H, -C$\underline{H}_2$OTBS), 3.61 (dd, $J = 10.0$ and 4.4 Hz, 1H, -C$\underline{H}_2$OTBS), 3.10–3.15 (m, 1H), 2.03 (s, 3H, -COC$\underline{H}_3$), 1.22–1.56 (m, 20H), 0.80–0.90 (m, 12H), −0.01 [s, 3H, *t*-BuSi(C$\underline{H}_3$)$_2$], −0.02 [s, 3H, *t*-BuSi(C$\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz)δ 193.9 (s), 170.3 (s), 148.5 (s), 136.4, 72.8 (d), 61.5, 41.9 (d), 31.9, 31.8, 29.6, 29.5, 29.4, 29.3, 25.8 (q × 3), 25.0, 22.6, 21.0 (q), 18.1 (s), 14.1 (q), −5.6 (q), −5.7 (q); IR (thin film, NaCl plates): 2927, 2857, 1739, 1697, 1465, 1369, 1241, 1106, 948, 840, 779 cm^{-1}; FAB Mass (m/z): 441 ($M^+ + 1$, 4), 307 (28), 289 (16), 154 (100), 136 (81), 107 (32), 89 (32); HRMS calcd. for $C_{25}H_{49}O_4Si$ ($M^+ + H$) 441.7395, found: 441.7397.

(3*R**,4*S**)-4-Acetoxy-3-[(*tert*-butyldimethylsilyloxy)methyl]-2-methylenepentadecanoic Acid (23)

To a solution of acrolein **22** (200 mg, 0.45 mmol), *t*-butyl alcohol (2.3 mL), and 2-methyl-2-butene (0.15 mL, 95.2 mg, 1.36 mmol), a solution of sodium chlorite (94.4 mg, 1.04 mmol) and sodium dihydrogenphosphate dihydrate (139.4 mg, 0.91 mmol) in 0.7 mL of water was added dropwise. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue was dissolved in 1.3 mL of water, and this was extracted with 5 mL of hexane. The aqueous layer was acidified to pH 3 with 2*N* HCl and extracted with two 4.2-mL portions of ether. The combined ether layers were washed with 5 mL of water, dried with Na_2SO_4, and concentrated to give the crude carboxylic acid. The residue was chromatographed on a silica-gel column to give acrylic acid **23** (149.1 mg, 0.33 mmol) as a colorless oil in 72% yield. TLC $R_f = 0.18$ (hexane/EtOAc = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.39 (s), 1H, -C=C$\underline{H}_2$), 5.66 (s, 1H, -C=C$\underline{H}_2$), 5.20 (td, $J = 8.0$ and 3.6 Hz, 1H, -C$\underline{H}$OAc), 3.76 (dd, $J = 10.0$ and 6.5 Hz, 1H, -C$\underline{H}_2$OTBS), 3.71 (dd, $J = 10.0$ and 4.8 Hz, 1H, -C$\underline{H}_2$OTBS), 3.02–3.07 (m, 1H), 2.03 (s, 3H, -OCOC$\underline{H}_3$), 1.16–1.29 (m, 20H), 0.85–0.91 (m, 12H), 0.01 [s, 6H, *t*-BuSi(C$\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5 (s), 170.8 (s), 139.5 (s), 127.8, 73.5 (d), 62.1, 46.0 (d), 31.9, 29.62, 29.61, 29.57, 29.51, 29.3, 25.8 (q × 3), 22.7, 21.1 (q), 18.1 (s), 14.1 (q), −5.57 (q), −5.61 (q); IR (thin film, NaCl plates): 3455, 2927, 2857, 1735, 1461, 1249, 1164, 1103, 840, 732 cm^{-1}; FAB mass (m/z): 439 (M^+-17, 2), 397 (M^+-59, 2), 365 (4), 117 (24), 73 (100); HRMS calcd. for $C_{25}H_{47}O_4Si$ (M^+-OH) 439.3244, found: 439.3241.

(3*R**,4*S**)-4-Acetoxy-3-[(*tert*-butyldimethylsilyloxy)methyl]-2-methylenepentadecanoic Acid Methyl Ester (24)

To a solution of α-substituted acrylic acid **23** (149.1 mg, 0.33 mmol) in 1 mL of CH_2Cl_2, a solution of CH_2N_2 in ethyl ether was added at rt. The progress of the reaction should be monitored carefully by thin-layer chromatography (TLC). Excess of the CH_2N_2 will cause further 1,3-dipolar cycloaddition on the double bond. The reaction mixture was concentrated, and the residue was chromatographed on a silica-gel column to give methyl acrylate **24** (144.5 mg, 0.31 mmol) as a pale yellow oil in 94% yield. TLC $R_f = 0.43$ (hexane/EtOAc = 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.34 (s, 1H, -C=C$\underline{H}_2$), 5.65 (s, 1H, -C=C$\underline{H}_2$), 5.16 (td, $J = 8.0$ and 3.7 Hz, 1H, -C$\underline{H}$OAc), 3.76 (s, 3H, OCH_3), 3.73 (dd, $J = 9.9$ and 6.7 Hz, 1H, -C$\underline{H}_2$OTBS), 3.68 (dd, $J = 9.9$ and 4.9 Hz, 1H, -C$\underline{H}_2$OTBS), 3.06–3.11 (m, 1H), 2.03 (s, 3H, -OCOC$\underline{H}_3$), 1.23–1.29 (m, 20H), 0.85–0.89 (m, 12H), −0.008 [s, 3H, *t*-BuSi(C$\underline{H}_3$)$_2$], −0.01 [s, 3H, *t*-BuSi(C$\underline{H}_3$)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (s), 167.3 (s), 138.8 (s), 127.1, 73.3 (d), 62.1, 51.9 (q), 46.0 (d), 31.9, 29.6, 29.5, 29.43, 29.39, 29.28, 25.7 (q × 3), 25.0, 22.6, 21.0 (q), 18.1 (s), 14.0 (q), −5.6 (q), −5.7 (q); IR (thin film, NaCl plates): 2927, 2857, 1735, 1461, 1373, 1241, 1106, 948, 840, 779 cm^{-1}; EI Mass (*m*/*z*): 439 (M^+-31, 2), 413 (11), 353 (100), 327 (20), 117 (79), 89 (47), 75 (31), 57 (12), 55 (10); HRMS calcd. for $C_{26}H_{51}O_5Si$ ($M^+ + H$) 471.3506, found: 471.3518.

(*S**)-1-[(*R**)-4-Methylene-5-oxotetrahydrofuran-3-yl]dodecyl Acetate (27) and [(2*S**,3*R**)-4-Methylene-5-oxo-2-undecyltetrahydrofuran-3-yl] Methyl Acetate (28)

To a mixture of acetoxy–acrylic acid **23** (20.2 mg, 0.044 mmol) in 1 mL of MeOH, a catalytic amount of trifluoroacetic acid was added and stirred at rt for 0.5 h. The reaction mixture was concentrated and chromatographed on a silica-gel column to give the α-methylenelactone **27** (5 mg, 0.015 mmol) in 40% yield and α-methylenelactone **28** (5 mg, 0.015 mmol) in 40% yield. Compound **27**, pale yellow oil; TLC $R_f = 0.36$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.36 (d, $J = 2.6$ Hz, 1H, -C=C$\underline{H}_2$), 5.72 (d, $J = 2.6$ Hz, 1H, -C=C$\underline{H}_2$), 5.17–5.21 (m, 1H, -C$\underline{H}$OAc), 4.41 (dd, $J = 9.0$ and 9.0 Hz, 1H, -C$\underline{H}_2$OCO), 4.30 (dd, $J = 9.0$ and 5.4 Hz, 1H, -C$\underline{H}_2$OCO), 3.29–3.34 (m, 1H), 2.03 (s, 3H, -OCOC$\underline{H}_3$), 1.21–1.60 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (s), 170.1 (s), 134.5 (s), 124.0, 73.3, 66.3 (d), 42.0 (d), 31.9, 31.4, 29.6, 29.5, 29.4, 29.3, 25.5, 22.6, 20.8 (q), 14.1 (q); IR (thin film, NaCl plates): 2927, 2854, 1762, 1461, 1373, 1234, 1118, 1041, 817, 728 cm^{-1}; EI mass (*m*/*z*): 325 ($M^+ + 1$, 1), 252 (39), 140 (25), 127 (33), 109 (42), 98 (100), 81 (28), 69 (28), 55 (48); HRMS calcd. for $C_{19}H_{32}O_4$ 324.2301, found: 324.2294. Compound **28**, pale yellow oil; TLC $R_f = 0.45$

(hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.32 (d, $J = 2.4$ Hz, 1H, -C=C$\underline{H}_2$), 5.69 (d, $J = 2.4$ Hz, 1H, -C=C$\underline{H}_2$), 4.55–4.61 (m, 1H, -C$\underline{H}$OCO), 4.17–4.27 (m, 2H, -C$\underline{H}_2$OAc), 3.36–3.38 (m, 1H), 2.08 (s, 3H, -OCOC$\underline{H}_3$), 1.21–1.62 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4 (s), 169.3 (s), 136.3 (s), 123.1, 79.3 (d), 62.2, 41.5 (d), 31.8, 30.4, 29.5, 29.4, 29.3, 29.2, 25.7, 22.5, 20.6 (q), 14.0 (q); IR (thin film, NaCl plates): 2927, 2857, 1766, 1747, 1461, 1373, 1234, 1114, 1022, 914, 813, 732 cm^{-1}; EI mass (m/z): 325 ($M^+ + 1$, 3), 264 (12), 140 (97), 125 (16), 98 (100), 81 (25), 69 (35), 55 (72); HRMS calcd. for $C_{19}H_{32}O_4$ 324.2301, found: 324.2309.

(*S**)-4-[(*R**)-1-Hydroxydodecyl]-3-methylenedihydrofuran-2(3*H*)-one (29) and (4*R**,5*S**)-4-(Hydroxymethyl)-3-methylene-5-undecyldihydrofuran-2(3*H*)-one (30)

Method One (in CF_3CO_2H in MeOH)

To a mixture of acetoxy–acrylate **24** (130 mg, 0.28 mmol) in 2 mL of MeOH, a catalytic amount of acetyl chloride (2 μL, 29 μmol) was added and stirred at rt for 0.5 h. The reaction mixture was concentrated and chromatographed on a silica-gel column to give α-methylenelactone **29** (41 mg, 0.14 mmol) in 52% yield and **30** (28 mg, 0.10 mmol) in 36% yield.

Method Two (in CH_3COCl in MeOH)

To a mixture of acetoxy–acrylate **23** (137 mg, 0.30 mmol) in 2 mL of MeOH, a catalytic amount of acetyl chloride (2.1 μL, 30 μmol) was added and stirred at rt for 0.5 h. The reaction mixture was concentrated and chromatographed on a silica-gel column to give the α-methylenelactone **29** (35.6 mg, 0.13 mmol) in 42% yield and **30** (35.7 mg, 0.13 mmol) in 42% yield.

Compound **29**, pale yellow solid; mp 67.4–68.8°C; TLC $R_f = 0.20$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.40 (d, $J = 2.6$ Hz, 1H, -C=C$\underline{H}_2$), 5.71 (d, $J = 2.6$ Hz, 1H, -C=C$\underline{H}_2$), 4.44 (dd, $J = 9.2$ and 4.9 Hz, 1H, -C$\underline{H}_2$OCO), 4.36 (dd, $J = 9.2$ and 9.2 Hz, 1H, -C$\underline{H}_2$OCO), 3.82–3.85 (m, 1H, -C$\underline{H}$OH), 3.11–3.16 (m, 1H), 1.66 (brd, $J = 4.2$ Hz, 1H), 1.26–1.52 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9 (s), 136.0 (s), 123.4, 72.4, 66.6 (d), 44.4 (d), 34.0, 31.9, 29.6, 29.50, 29.49, 29.42, 29.3, 25.7, 22.6, 14.1 (q); IR (thin film, NaCl plates): 3444, 2919, 2854, 1747, 1465, 1268, 1064, 817, 736 cm^{-1}; FAB mass (m/z): (283, $M^+ + 1$, 1), 98 (100), 83 (22), 69 (48), 55 (48); HRMS calcd. for $C_{17}H_{31}O_3$ ($M^+ + 1$) 283.2273, found: 283.2270. Compound **30**, white solid; mp 67.1–69.3°C; TLC $R_f = 0.11$ (hexane/EtOAc = 5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (d, $J = 2.2$ Hz, 1H, -C=C$\underline{H}_2$), 5.69 (d, $J = 2.2$ Hz, 1H, -C=C$\underline{H}_2$), 4.55–4.60 (m, 1H,

-CHOCO), 3.83–3.89 (m, 1H, -CH$_2$OH), 3.74–3.80 (m, 1H, -CH$_2$OH), 3.22–3.28 (m, 1H), 1.54–1.68 (m, 4H), 1.26–1.34 (m, 16H), 0.89 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (s), 137.1 (q), 122.9 (t), 80.3 (d), 60.9 (t), 44.6 (d), 31.9 (t), 30.2 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.33 (t), 29.29 (t), 26.0 (t), 22.6 (t), 14.1 (q); IR (thin film, NaCl plates): 3413, 2923, 2857, 1751, 1461, 1346, 1272, 1052, 817, 736 cm^{-1}; EI mass (m/z): 282 (M^+, 1), 252 (23), 127 (27), 109 (11), 98 (100), 81 (20), 69 (36), 55 (39); HRMS calcd. for $C_{17}H_{30}O_3$ 282.2195, found: 282.2196.

(4*R**,5*S**)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-3-methylene-5-undecyldihydrofuran-2(3*H*)-one (32)

To mixture of acetoxy–acrylic acid **23** (40 mg, 0.087 mmol) in MeOH (0.5 mL), a solution of KOH (4.9 mg, 0.087 mmol) in MeOH (0.5 mL) was added and stirred at 0°C for 1.5 h. The reaction mixture was concentrated, diluted with water, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to give a crude product of compound **31**, which can be used directly for the further reaction. To a solution of compound **31** in CH_2Cl_2 (1 mL), Na_2CO_3 (93.1 mg, 0.88 mmol) was added. After 15 min, *o*-nitrobenzenesulfonyl chloride (29 mg, 0.131 mmol) was added, and the mixture was left to stir at room temperature for 15 min water was added to the mixture and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by silica-gel column chromatography (hexane/EtOAc = 98:2) provided **32** as a colorless oil (25.3 mg, 73%). TLC $R_f = 0.82$ (hexane/EtOAc = 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.24 (d, $J = 2.2$ Hz, 1H, -C=CH$_2$), 5.61 (d, $J = 2.2$ Hz, 1H, -C=CH$_2$), 4.50–4.56 (m, 1H, -CHOCO), 3.70–3.78 (m, 2H, -CH$_2$OTBS), 3.13–3.18 (m, 1H, -CHCO$_2$H), 1.25–1.67 (m, 20H), 0.83–0.88 [m, 12H, -CH$_2$CH$_3$ and -(CH$_3$)$_3$CSiMe$_2$], 0.05 [s, 3H, *t*-BuSi(CH$_3$)$_2$], 0.04 [s, 3H, *t*-BuSi(CH$_3$)$_2$]; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2 (s), 137.6 (s), 122.2, 80.3 (d), 61.8, 44.9 (d), 31.9, 30.2, 29.6, 29.5, 29.41, 29.36, 29.30, 26.0, 25.7 (q × 3), 22.7, 18.1 (s), 14.1 (q), −5.6 (q), −5.7 (q); IR (thin film, NaCl plates): 2954, 2926, 2855, 1769, 1464, 1256, 1113, 940, 814, 723 cm^{-1}; EI mass (m/z): 397 ($M^+ + 1$, 1), 339 (100), 309 (37), 73 (26), 55 (27); HRMS calcd. for $C_{23}H_{44}O_3Si$ 396.3060, found: 396.3068.

(2*S**,3*S**)-4-Methylene-5-oxo-2-undecyltetrahydrofuran-3-carboxylic Acid (7)

To a solution of silyl ether **32** (50 mg, 0.13 mmol) in acetone (1 mL) at 40°C, Jones reagent was added dropwise until the orange color persisted, and the

resulting solution was stirred at this temperature for 5 min. After cooling to 0°C, isopropanol was added 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 a silica-gel column to give a white solid **7** (32.5 mg, 0.11 mmol) in 87% yield. Mp 65.4–66.7°C; TLC $R_f = 0.34$ (hexane/EtOAc = 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.45 (d, $J = 2.2$ Hz, 1H, -C=C$\underline{H}_2$), 5.89 (d, $J = 2.2$ Hz, 1H, -C=C$\underline{H}_2$), 4.67 (td, $J = 8.0$ and 5.4 Hz, 1H, -C$\underline{H}$OCO), 4.01–4.04 (m, 1H), 1.25–1.76 (m, 20H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9 (s), 168.8 (s), 133.2 (s), 125.6, 78.0 (d), 48.8 (d), 31.9, 31.4, 29.6, 29.5, 29.4, 29.3, 29.2, 25.5, 22.7, 14.1 (q); IR (thin film, NaCl plates): 3309, 2923, 2854, 1756, 1465, 1268, 1168, 819, 721 cm^{-1}; EI Mass (m/z): 296 (M^+, 17), 251 (100), 155 (44), 141 (28), 123 (26), 95 (25), 81 (23), 69 (37), 57 (74), 55 (58); HRMS calcd. for $C_{17}H_{28}O_4$ 296.1988, found: 296.1992.

(2*S**,3*S**,4*R**)-4-Methyl-5-oxo-2-undecyltetrahydrofuran-3-carboxylic Acid (33)

Under a hydrogen atomosphere in a ballon, a mixture of compound **10** (20 mg, 0.067 mmol) and 10% Pd/C (7.3 mg, 0.007 mmol) in 2 mL of EtOAc was stirred at room temperature for 4 h. The reaction mixture was filtered through Celite®, and the filtrate was concentrated. The crude mixture was chromatographed on a silica-gel column to give a white solid **33** (17.2 mg, 0.057 mmol) in 85% yield. Mp 101.3–102.9°C, (100–102°C[5f]); TLC $R_f = 0.44$ (hexane/EtOAc = 3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.43 (td, $J = 8.7$ and 5.2 Hz, 1H, -C$\underline{H}$OCO), 3.34 (dd, $J = 7.4$ and 5.2 Hz, 1H, -C$\underline{H}$CO$_2$H), 2.94 (quint. $J = 7.4$ Hz, 1H, -C$\underline{H}$CH$_3$), 1.81–1.90 (m, 1H), 1.63–1.71 (m, 1H), 1.32 (d, $J = 7.1$ Hz, 3H), 1.26–1.59 (m, 18H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8 (s), 174.1 (s), 78.8 (d), 50.3 (d), 39.1 (d), 31.9, 30.9, 29.6, 29.5, 29.4, 29.3, 29.2, 25.9, 22.7, 14.1 (q), 10.3 (q); IR (thin film, NaCl plates): 3496, 3054, 2923, 2854, 1781, 1716, 1463, 1265, 1186, 1002, 966, 738 cm^{-1}; EI Mass (m/z): 298 (M^+, 4), 253 (42), 225 (37), 114 (59), 97 (71), 87 (59), 81 (51), 69 (94), 55 (100); HRMS calcd. for $C_{17}H_{30}O_4$ 298.2144, found: 298.2145.

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