

TOTAL SYNTHESIS OF (RS)- AND (R)-3-ALKANOYL-5-HYDROXYMETHYLTETRONIC ACID HOMOLOGUES, HIV-1 PROTEASE INHIBITORY NATURAL PRODUCTS¹

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Abstract- 5-Acetoxymethyl- γ -butyrolactone-3-carboxylic acids [(*RS*)-**4a** and (*S*)-**4a**] were prepared as racemic form starting from dibenzyl allylmalonate (**5b**) and optically active *S* form starting from (4*S*)-4-[2,2-bis(benzyloxycarbonyl)ethyl]-2,2-dimethyl-1,3-dioxolane [(*S*)-**6b**], and the 3-position of (*RS*)-**4a** and (*S*)-**4a** was acylated to afford (*RS*)-**3a**, (*S*)-**3a**, and (*S*)-**3b**. Phenylselenenylation of (*RS*)-**3a**, (*S*)-**3a**, and (*S*)-**3b** followed by H₂O₂-oxidation and subsequent acidic hydrolysis afforded the HIV-1 protease inhibitory 3-alkanoyl-5-hydroxymethyltetronic acids [(*RS*)-**1a**, (*R*)-**1a**, and (*R*)-**1d**, respectively].

In 1994, Roggo and his co-workers isolated several natural products having HIV-1 protease inhibitory activity from the cultures of *Actinomycete* strain (DSM 7357) and determined their plane structures as sodium salt of 3-alkanoyl-5-hydroxymethyltetronic acids (**1**) (Figure 1).² Osada and his co-workers isolated **1d** from the cultures of *Streptomyces* sp. 88-682 and found its tyrosine phosphatase inhibitory activity.³ The absolute configuration of **1d** was determined to be *R* by an asymmetric synthesis.⁴ On the other hand, Hida and his co-workers also isolated two analogues of **1** as a phospholipase A₂ inhibitor from the cultures of *Streptomyces* sp. AL-462 and synthesized their derivatives having *R* configuration from *D*-ribose.⁵

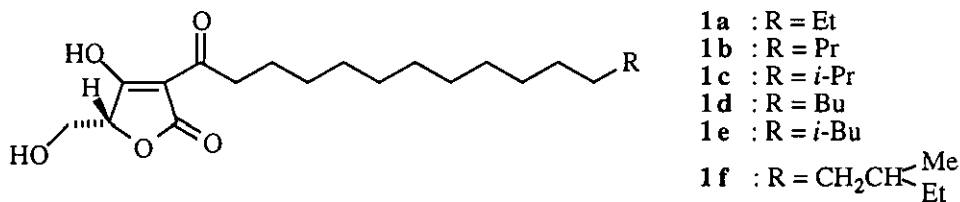
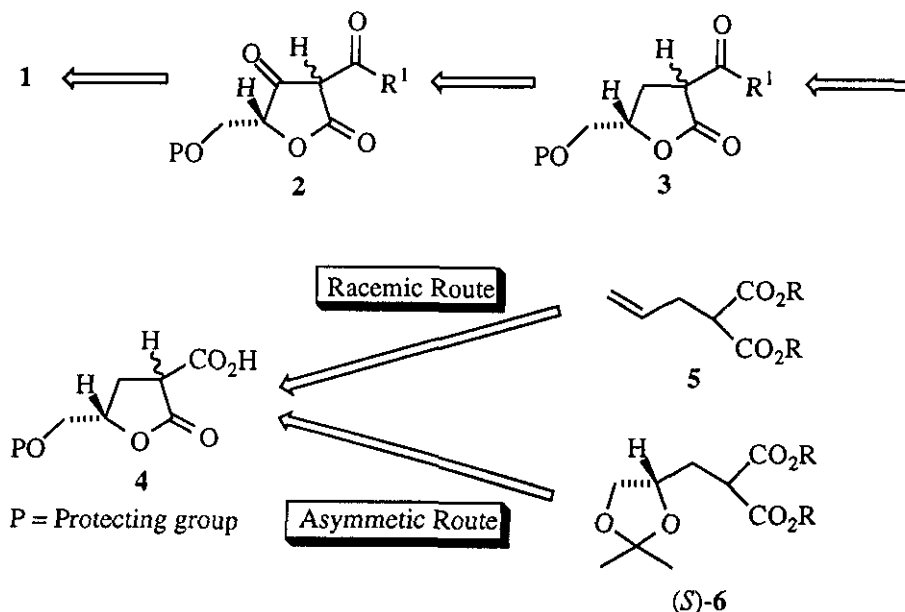


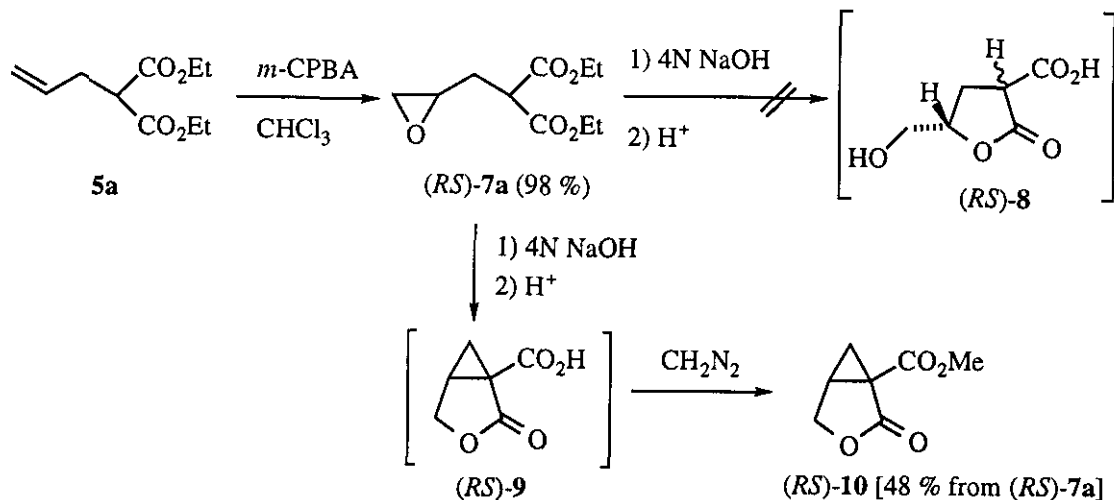
Figure 1

Because of the important biological activities, we were interested in the synthesis of the natural and non-natural **1** derivatives and planned development of its efficient synthetic route. To prepare various **1**

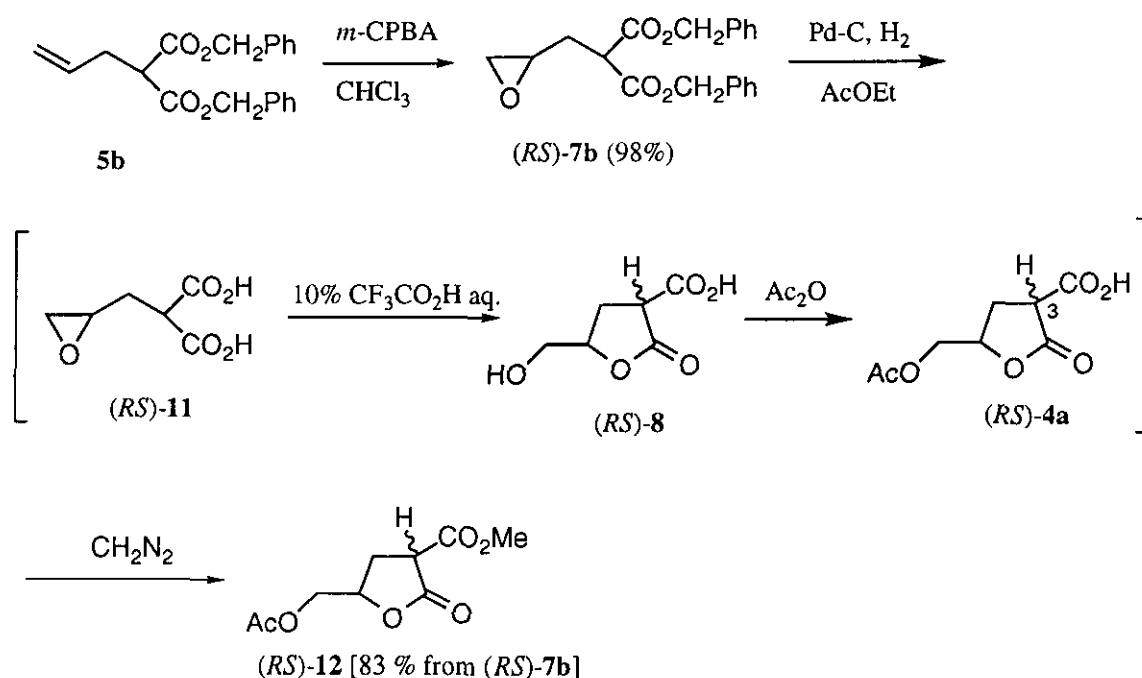
analogues from a common intermediate (4), we thought that introduction of the 3-alkanoyl side chains should be performed at the latter stage of the synthetic route as shown in Scheme 1. In this paper, we describe the total synthesis of racemic **1a**, optically active (*R*)-**1a** and (*R*)-**1d** according to this plan.



First, we examined synthesis of racemic **1** in order to establish a general synthetic route. Diethyl allylmalonate (**5a**) was oxidized to give the epoxide [(*RS*)-**7a**] in 98 % yield. The epoxide [(*RS*)-**7a**] was subjected to simultaneous hydrolysis of the epoxy and ester groups with 4N NaOH in order to get the γ -lactonic acid [(*RS*)-**8**], but the obtained product was the unexpected bicyclic compound [(*RS*)-**9**], structure of which was confirmed by means of spectral and analytical data of its methyl ester [(*RS*)-**10**] (Scheme 2).⁶



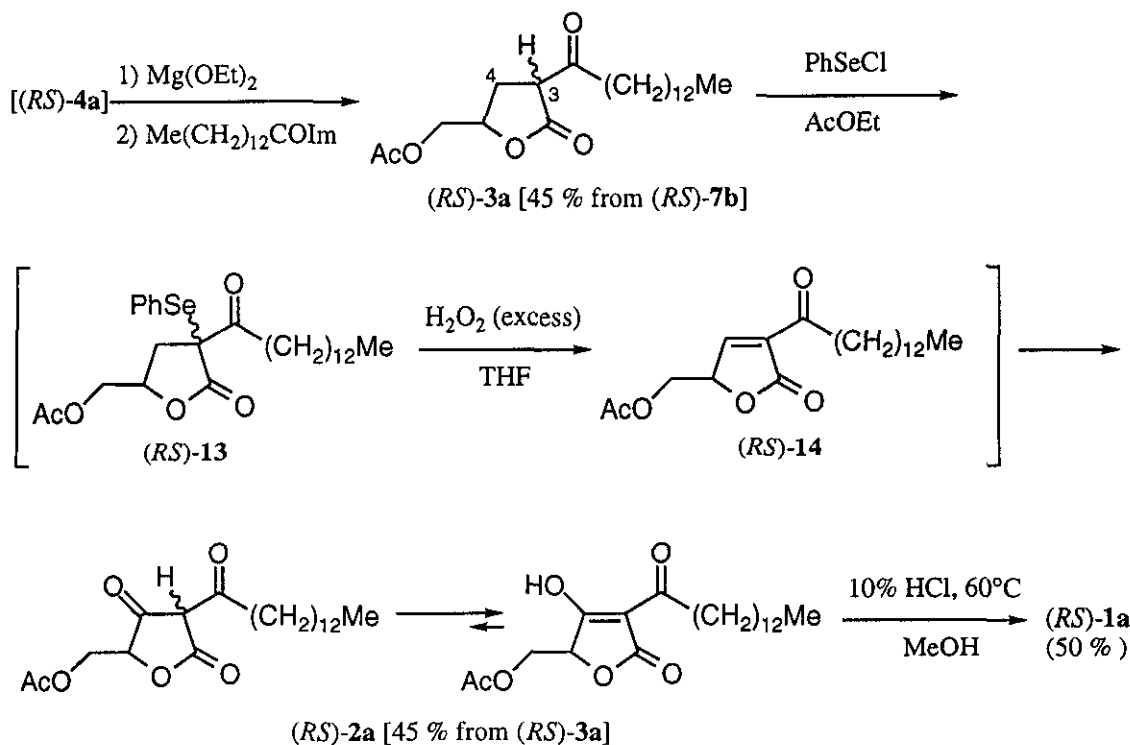
Next, we planned a route without alkaline hydrolysis. The dibenzyl allylmalonate (**5b**) was oxidized with *m*-CPBA to give (*RS*)-**7b** in high yield. The benzyl groups of (*RS*)-**7b** were removed by catalytic hydrogenation to afford the diacid [(*RS*)-**11**], which was treated with aqueous 10 % trifluoroacetic acid followed by acetylation to give the lactone [(*RS*)-**4a**]. To confirm the structure of the lactonecarboxylic acid [(*RS*)-**4a**], (*RS*)-**4a** was methylated with diazomethane to give the lactone [(*RS*)-**12**] as a mixture of *cis* and *trans* isomers (Scheme 3). Spectral data of (*RS*)-**12** supported the structure. Namely, the MS of (*RS*)-**12** showed the molecular ion peak at 216 *m/z* (C₉H₁₂O₆). In its IR spectrum, the carbonyl groups were observed at 1750 and 1733 cm⁻¹, and ¹H-NMR spectrum showed the methyl protons of the acetyl group at 2.11 ppm (3H), and methyl protons of the ester group at 3.82 and 3.83 ppm (total 3H).



Scheme 3

Introduction of the alkanoyl group to the 3-position of (*RS*)-**4a** was performed according to the modified Masamune reaction.⁷ That is, treatment of the lactonecarboxylic acid [(*RS*)-**4a**] with magnesium diethoxide followed by addition of *N*-tetradecanoylimidazole gave the 3-tetradecanoyl- γ -lactone [(*RS*)-**3a**] as a mixture of *cis* and *trans* isomers in 45% yield from (*RS*)-**7b**. The carbonyl group at the 4-position in (*RS*)-**3a** would be introduced *via* formation of a double bond at the C3-C4 position. Introduction of the double bond was attempted according to the phenylselenenylation strategy.⁸ Phenylselenenylation of the 3-position of (*RS*)-**3a** and subsequent treatment with a large excess of H₂O₂ did not give the expected product [(*RS*)-**14**], but surprisingly (*RS*)-**2a** [45 % yield from (*RS*)-**3a**].⁹ The structure of (*RS*)-**2a** was determined on the basis of its spectral data and positive FeCl₃ color reaction. The molecular formula of (*RS*)-**2a** was determined as C₂₁H₃₄O₆ on the basis of HR-MS and elemental analysis. The ¹H-NMR spectrum showed no olefinic proton. In IR spectrum, the carbonyl absorption bands were observed at

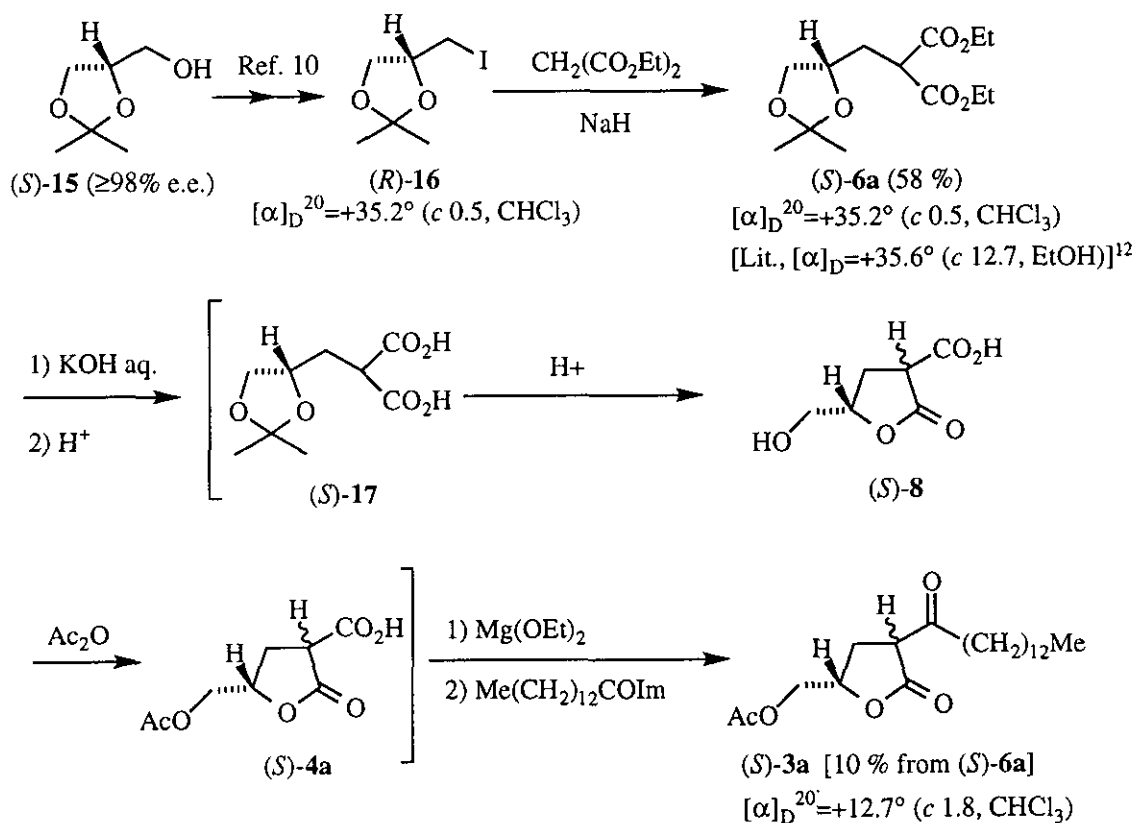
1792, 1741, and 1706 cm^{-1} . These data all support the structure of (*RS*)-**2a**. Finally, the acetyl group of (*RS*)-**2a** was hydrolyzed in an acidic aqueous medium to give (*RS*)-**1a** in 50% yield (Scheme 4).



Scheme 4

We next tried synthesis of the optically active natural products. Commercially available (*S*)-glycerol acetonide [(*S*)-**15**]¹⁰ was transformed to the iodide [(*S*)-**16**] according to the Fischer's methods.¹¹ Diethyl malonate was alkylated with (*S*)-**16** by the Mori's method to give (*S*)-**6a** in 58% yield.¹² Alkaline hydrolysis of (*S*)-**6a** followed by treatment with 10% trifluoroacetic acid gave the γ -lactone [(*S*)-**8**] and then the hydroxyl group of (*S*)-**8** was acetylated to give the γ -lactonecarboxylic acid [(*S*)-**4a**]. Introduction of the tetradecanoyl group to the 3-position of (*S*)-**4a** was carried out according to the above-mentioned manner to give (*S*)-**3a**, but the overall yield of (*S*)-**3a** was very low [10 % yield from (*S*)-**6a**]. This low yield would be attributable to loss of (*S*)-**17** upon extraction because of its high water solubility (Scheme 5).

We thought the low yield would be overcome by using a route starting with dibenzyl malonate, namely, the benzyl group can be removed by catalytic hydrogenation to result in easy isolation of (*S*)-**17** without aqueous work-up. Thus, dibenzyl malonate was alkylated with (*R*)-**16** to give (*S*)-**6b** in 64% yield.¹¹ Hydrogenolysis of the benzyl group in (*S*)-**6b** gave the diacid [(*S*)-**17**], which was subjected to the same treatment as mentioned above. Tetradecanoyl and hexadecanoyl groups were introduced into the 3-position of (*S*)-**4a** to give the γ -lactone [(*S*)-**3a** and (*S*)-**3b**] in 58% and 54% yields from (*S*)-**6b**, respectively.



Scheme 5

Finally, each γ -lactone [$(S)\text{-3a}$ and $(S)\text{-3b}$] was converted to $(R)\text{-1a}$ and $(R)\text{-1d}$, respectively, by the above-mentioned procedure (Scheme 6).

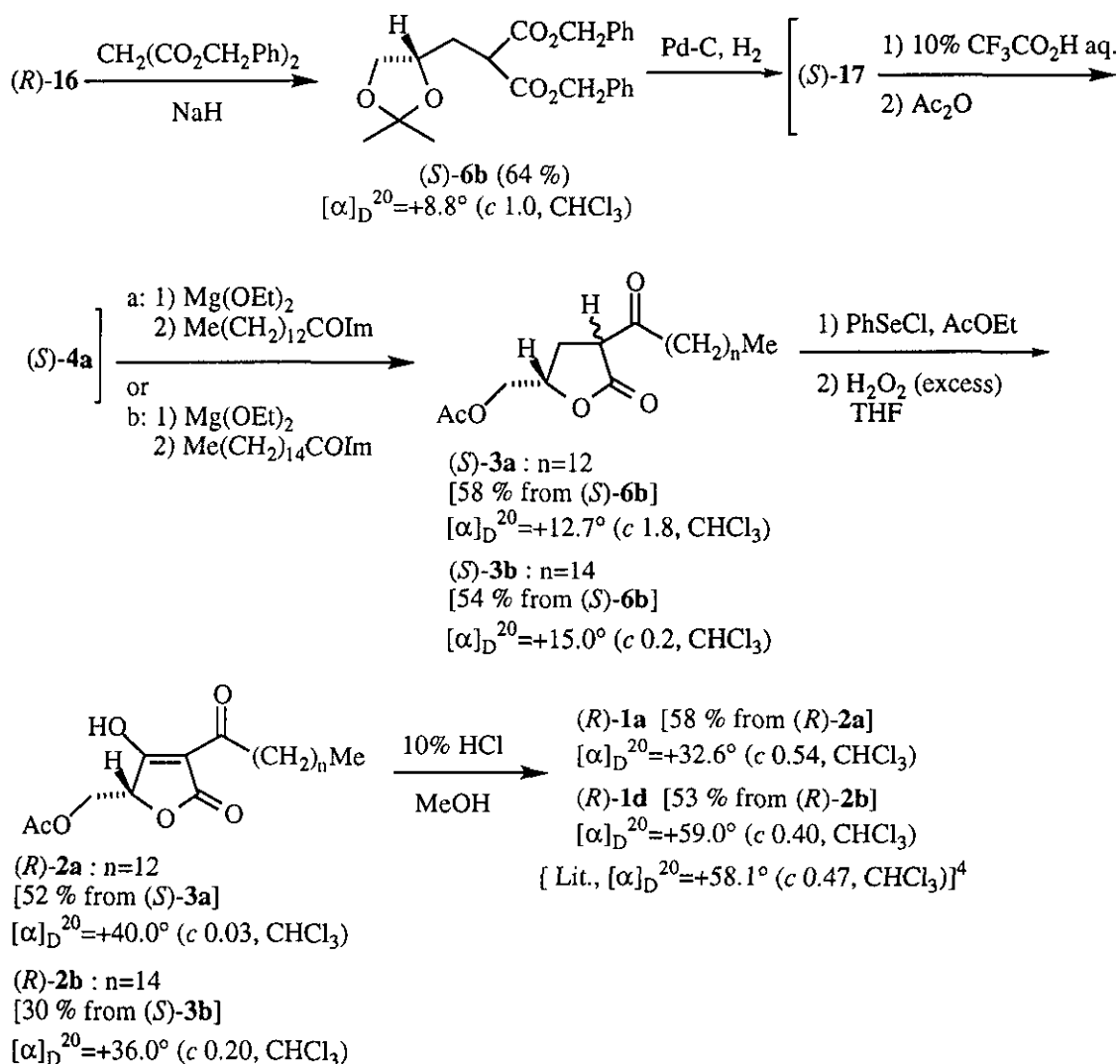
In conclusion, we developed a new route to the total synthesis of **1** using the novel oxidation reaction. Now, we are applying the present method to the synthesis of several artificial analogues of **1**.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. M. Sodeoka (Sagami Chemical Research Center) for kindly supplying the spectral data of $(R)\text{-1d}$, and Dr. T. Hida (Takeda Chemical Industries, LTD) for valuable advice and supplying the spectral data of $(R)\text{-1a}$ and $(R)\text{-1d}$.

EXPERIMENTAL

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. IR spectra were taken with a Shimadzu IR-435 spectrophotometer. NMR spectra were measured on a Varian XL-300 (^1H : 300 MHz, ^{13}C : 75 MHz) with tetramethylsilane as an internal standard and chemical shifts are reported in ppm. MS were recorded with a JEOL JMS-SX 102A QQ spectrometer. Silica gel 60 (Merck) for column chromatography and Silica gel 60 PF₂₅₄ (Nacalai Tesque Inc.) for preparative TLC (PTLC) were used. All extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure.



Scheme 6

Diethyl (2,3-Epoxypropyl)malonate [(*RS*)-7a]: To a solution of diethyl allylmalonate (**5a** : 5.01 g, 25.0 mmol) in CHCl_3 (35 mL) was added portionwise *m*-CPBA (5.18 g, 30.0 mmol) at 0°C under an N_2 atmosphere and the whole was stirred for 12 h at rt. After addition of H_2O , the mixture was extracted with CHCl_3 . The combined organic extracts were washed with 10 % NaOH solution and H_2O , dried, and evaporated. The residue was purified by column chromatography (ethyl acetate / *n*-hexane = 1 / 7) to give (*RS*)-**7a** (5.29 g, 98 %) as colorless oil. IR (CHCl_3) : 1738, 1725 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.28 (t, 3H, $J = 7.1$ Hz), 1.29 (t, 3H, $J = 7.1$ Hz), 2.01 (dt, 1H, $J = 14.4, 6.1$ Hz), 2.27 (ddd, 1H, $J = 4.6, 8.7, 14.4$ Hz), 2.53 (dd, 1H, $J = 2.6, 4.9$ Hz), 2.78 (t, 1H, $J = 4.9$ Hz), 3.00 - 3.10 (m, 1H), 3.54 (dd, 1H, $J = 6.1, 8.7$ Hz), 4.10 - 4.30 (m, 4H). HR-FABMS (m/z) : Calcd for $\text{C}_{10}\text{H}_{17}\text{O}_5 = 217.1076$. Found = 217.1062 ($\text{M}+\text{H}$)⁺.

Methyl 3,3a,4,4a-Tetrahydro-3-oxo-1H-cyclopropa[c]furan-3a-carboxylate [(RS)-10]: To a solution of (RS)-7a (2.16 g, 10.0 mmol) in EtOH (10 mL) was added dropwise 4N NaOH solution (10 mL) and the whole was heated at 50°C for 2 h with stirring. After neutralization with concentrated HCl under ice-cooling, the mixture was extracted with CHCl₃. The combined extracts were washed with H₂O, dried, and evaporated to give crude (RS)-9. To the solution of (RS)-9 in MeOH (10 mL) added dropwise a large excess of diazomethane in ether [prepared from nitrosomethylurea (5.1 g), ether (50 mL), and 50% KOH (15 mL)] and the whole was stirred for 2 h at rt. After evaporation of the solvent, the residue was purified by column chromatography (ethyl acetate / *n*-hexane = 3 / 2) to give (RS)-10 [749 mg, 48 % from (RS)-7a] as colorless oil. IR (CHCl₃) : 1776, 1724 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.42 (dd, 1H, *J* = 4.8, 5.3 Hz), 2.10 (dd, 1H, *J* = 4.8, 8.9 Hz), 2.74 - 2.81 (m, 1H), 3.82 (s, 3H), 4.21 (d, 1H, *J* = 9.5 Hz), 4.38 (dd, 1H, *J* = 4.9, 9.5 Hz). ¹³C-NMR (CDCl₃) δ: 20.9, 28.0, 29.2, 52.8, 67.0, 167.2, 170.4. HR-EIMS (*m/z*) : Calcd for C₇H₈O₄ = 156.0423. Found = 156.0439 (M⁺).

Dibenzyl (2,3-Epoxypropyl)malonate [(RS)-7b]: Using the procedure described above for the synthesis of (RS)-7a with 5b (3.24 g, 10.0 mmol), the title compound [(RS)-7b; 3.32 g, 98 %] was obtained as colorless oil. IR (CHCl₃) : 1745, 1727 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.05 (dt, 1H, *J* = 14.4, 6.1 Hz), 2.29 (ddd, 1H, *J* = 4.7, 8.7, 14.4 Hz), 2.46 (dd, 1H, *J* = 2.6, 4.9 Hz), 2.70 (t, 1H, *J* = 4.9 Hz), 2.96 - 3.02 (m, 1H), 3.65 (dd, 1H, *J* = 6.1, 8.7 Hz), 5.15 (s, 2H), 5.17 (ABq, 2H, *J* = 12.3 Hz), 7.20 - 7.40 (m, 10H). ¹³C-NMR (CDCl₃) δ: 31.6, 47.2, 48.9, 49.7, 67.4, 128.2, 128.4, 128.5, 135.1, 168.5, 168.5. HR-FABMS (*m/z*) : Calcd for C₂₀H₂₁O₅ = 341.1389. Found = 341.1401 (M+H)⁺.

5-Acetoxymethyl-3-methoxycarbonyl- γ-butyrolactone [(RS)-12]: A suspension of (RS)-7b (1.66 g, 4.88 mmol), 5% Pd-C (120 mg) in ethyl acetate (12 mL) was hydrogenolyzed under a hydrogen atmosphere at atmospheric pressure for 2 h at rt. After removal of the catalyst by filtration, the filtrate was evaporated off to give 2,3-epoxypropylmalonic acid [(RS)-11, 759 mg] as colorless oil. IR (CHCl₃) : 3359, 1761, 1739 cm⁻¹. ¹H-NMR (CDCl₃) : no signals for the benzyl group. HR-FABMS (*m/z*) : Calcd for C₆H₈O₅Na = 183.0269. Found = 183.0262 (M+Na)⁺. The mixture of (RS)-11, acetone (3 mL) and 10% CF₃COOH aqueous solution (6 mL) was stirred for 2 h at rt. The solvents were concentrated and a small amount of water was evaporated together with benzene azeotropically. Acetic anhydride (5 mL) was added to the residue [(RS)-8] and the whole was stirred for 12 h at rt. After addition of 10% HCl, the mixture was stirred for 10 min and extracted with ether. The combined extracts were dried, concentrated, and evaporated together with toluene to remove the remained acetic anhydride and acetic acid completely. To a solution of (RS)-4a in ether (5 mL) was added dropwise a large excess of diazomethane in ether [prepared from nitrosomethylurea (2.5 g), ether (25 mL), and 50% KOH solution (7 mL)] under ice-cooling and the whole was stirred for 2 h at rt. After evaporation of the solvent, the residue was purified by column chromatography (ethyl acetate / *n*-hexane = 1 / 3) to give (RS)-12 [875 mg, 83 % from (RS)-7b] as colorless oil. IR (CHCl₃) : 1750, 1733 cm⁻¹. ¹H-NMR (CDCl₃) δ: 2.11 (s, 3H), 2.33 (ddd, 0.5H, *J* = 5.9, 9.9, 13.4 Hz), 2.24 (ddd, 0.5H, *J* = 8.7, 9.9, 13.2 Hz), 2.60 (ddd, 0.5H, *J* = 7.0, 9.9, 13.2 Hz), 2.79 (ddd, 0.5H, *J* = 6.5, 8.0, 13.4 Hz), 3.71 (dd, 0.5H, *J* = 6.5, 9.9 Hz), 3.71 (t, 0.5H, *J* = 9.9 Hz),

3.82 and 3.83 (each s, total 3H), 4.18 (dd, 0.5H, $J = 4.8$, 12.4 Hz), 4.21 (dd, 0.5H, $J = 6.1$, 12.4 Hz), 4.35 (dd, 0.5H, $J = 3.0$, 12.4 Hz), 4.37 (dd, 0.5H, $J = 3.2$, 12.4 Hz), 4.68 - 4.78 and 4.86 - 4.95 (each m, total 1H). HR-FABMS (m/z): Calcd for $C_9H_{13}O_6 = 217.0712$. Found = 217.0732 ($M+H$)⁺.

5-Acetoxymethyl-3-tetradecanoyl- γ -butyrolactone [(*RS*)-3a]: To a solution of the crude lactonecarboxylic acid [(*RS*)-4a: prepared from (*RS*)-7b (1.66 g, 4.88 mmol) by the same procedure described above] in THF (3 mL) was added in one portion magnesium diethoxide (286 mg, 2.5 mmol) under an N_2 atmosphere and the whole was stirred for 2 h at rt. After evaporation of the solvent, the magnesium salt of (*RS*)-4a was used without further purification. To a solution of CDI (810 mg, 5.00 mmol) in DMF (5 mL) was added in one portion myristic acid (1.14 g, 5.00 mmol) under an N_2 atmosphere at 0°C and the whole was stirred for 2 h at rt. To the mixture was added in one portion the crude magnesium salt obtained above and the whole was stirred for 24 h at rt. After addition of 5% HCl solution, the mixture was extracted with ether. The combined organic layers were washed with sat. $NaHCO_3$ solution, dried, and evaporated. The residue was purified by column chromatography (ethyl acetate / *n*-hexane = 1 / 3) to give (*RS*)-3a [807 mg, 45 % from (*RS*)-7b] as colorless crystals. mp 47.0 - 48.0°C (from *n*-hexane). IR ($CHCl_3$): 1770, 1740, 1707 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 0.88 (t, 3H, $J = 6.7$ Hz), 1.20 - 1.40 (m, 20H), 1.63 (quint, 2H, $J = 7.4$ Hz), 2.09 and 2.11 (each s, total 3H), 2.35 (t, 2H, $J = 7.4$ Hz), 2.54 - 2.68 (m, 1H), 2.82 - 3.07 (m, 1H), 3.77 (t, 0.5H, $J = 9.3$ Hz), 3.79 (dd, 0.5H, $J = 6.4$, 10.6 Hz), 4.10 - 4.36 (m, 2H), 4.66 - 4.84 (m, 1H). HR-EIMS (m/z): Calcd for $C_{21}H_{36}O_5 = 368.2563$. Found = 368.2563 (M^+).

5-Acetoxymethyl-3-tetradecanoyltetronic Acid [(*RS*)-2a]: To a solution of (*RS*)-3a (1.21 g, 3.30 mmol) in ethyl acetate (6 mL) was added portionwise phenylselenenyl chloride (670 mg, 3.50 mmol) at rt and the whole was stirred for 12 h. After addition of H_2O , the mixture was extracted with ethyl acetate. The combined organic layers were washed with H_2O , dried, and evaporated. The unreacted phenylselenenyl chloride was removed by short column chromatography (ethyl acetate / *n*-hexane = 1 / 3) to give (*RS*)-13 as colorless oil. IR ($CHCl_3$): 1780, 1740, 1705 cm^{-1} . To the solution of (*RS*)-13 in THF (5 mL) added dropwise 30% H_2O_2 solution (3.5 mL, ca. 31 mmol) at 0°C and the whole was stirred for 2 h. Saturated $NaHSO_3$ solution was added to decompose the unreacted H_2O_2 and the mixture was extracted with ethyl acetate. The combined organic layers were washed with H_2O , dried, and evaporated. The residue was purified by column chromatography (ethyl acetate / *n*-hexane = 1 / 2) to give (*RS*)-2a [567 mg, 45 % from (*RS*)-3a] as colorless crystals. mp 78.0 - 79.0°C (from ethyl acetate - *n*-hexane). IR ($CHCl_3$): 1792, 1741, 1706 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 0.88 (t, 3H, $J = 6.7$ Hz), 1.20 - 1.40 (m, 20H), 1.55-1.65 (m, 2H), 2.10 (s, 3H), 2.60 (t, 2H, $J = 7.3$ Hz), 4.29 (s, 1H), 4.40 (d, 2H, $J = 2.8$ Hz), 4.78 (t, 1H, $J = 2.8$ Hz). Anal. Calcd for $C_{21}H_{34}O_6$: C, 65.94; H, 8.96. Found: C, 66.13; H, 9.12.

5-Hydroxymethyl-3-tetradecanoyltetronic Acid [(*RS*)-1a]: A mixture of (*RS*)-3a (200 mg, 0.52 mmol), MeOH (5 mL), and 10% HCl solution (1 mL) was heated at 40°C for 5 h with stirring. After evaporation of the MeOH, the mixture was extracted with ethyl acetate. The combined organic layers were washed with H_2O , dried, and evaporated. The residue was purified by PTLC (ethyl acetate / *n*-hexane = 1

/ 1) to give (*RS*)-**1a** (88 mg, 50 %) as colorless crystals. mp 59.0 - 61.0°C (from ethyl acetate - *n*-hexane). IR (KBr) : 3380, 1771, 1712 cm⁻¹. ¹H-NMR (CDCl₃) : 0.88 (t, 3H, *J* = 6.8 Hz), 1.20 - 1.40 (m, 20H), 1.52 - 1.66 (m, 2H), 2.80 (dt, 1H, *J* = 18.8, 7.2 Hz), 2.93 (dt, 1H, *J* = 18.8, 7.3 Hz), 3.84 (dd, 1H, *J* = 2.7, 13.2 Hz), 4.07 (dd, 1H, *J* = 2.7, 13.0 Hz), 4.41 (dt, 1H, *J* = 8.3, 2.7 Hz), 4.78 (d, 1H, *J* = 8.3 Hz). FAB-HRMS (*m/z*) : Calcd for C₁₉H₃₃O₅ = 341.2328. Found = 341.2354 (M+H)⁺.

(5S)-5-Acetoxymethyl-3-tetradecanoyl-γ-butyrolactone [(S)-3a]: A mixture of (*S*)-**6a** (1.37 g, 5.00 mmol: prepared according to the Mori's method¹²) in MeOH (5 mL) and 2.4 N KOH (5 mL) was refluxed for 4 h. After cooling, the mixture was washed with ether. The combined organic layers were extracted with water. The combined aqueous layers were acidified with 2N H₂SO₄ and concentrated *in vacuo* to give the semisolid residue, which was stirred with the mixture of acetone-EtOH (4 : 1, 50 mL) for 10 min, filtered, and washed with the same solvent (*ca.* 25 mL). The combined filtrates and washings were concentrated to give a crude lactonic acid [(*S*)-**8**]. This (*S*)-**8** was converted to the title compound [(*S*)-**3a**; 183 mg, 10 % from (*S*)-**6a**] using the procedure described above for the synthesis of (*RS*)-**3a**. mp 41.0 - 43.0 °C (from *n*-hexane). [α]_D²⁰ = +12.66° (*c* 1.8, CHCl₃).

(4S)-4-[2,2-Bis(benzoxycarbonyl)ethyl]-2,2-dimethyl-1,3-dioxolane [(S)-6b]: To a suspension of sodium hydride (480 mg, 12.0 mmol, 60 % dispersion in mineral oil) in THF (5 mL) was added dropwise a solution of dibenzyl malonate (2.84 g, 10.0 mmol) in THF (5 mL) under an N₂ atmosphere at 0°C and the whole was stirred for 20 min. A solution of (*R*)-**16** (2.42 g, 10.0 mmol) in THF (5 mL) was added dropwise to the mixture and the whole was refluxed for 5 h. After addition of H₂O, the mixture was extracted with ether. The combined organic layers were washed with H₂O, dried, and evaporated. The residue was purified by column chromatography (ethyl acetate / *n*-hexane = 1 / 10) to give (*S*)-**6b** (2.55 g, 64 %) as colorless needles. mp 50.0 - 51.0°C (from ethyl acetate - *n*-hexane). IR (CHCl₃) : 1740, 1727 cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.29 (s, 3H), 1.36 (s, 3H), 2.12 (ddd, 1H, *J* = 5.6, 8.6, 14.1 Hz), 2.24 (ddd, 1H, *J* = 3.9, 9.0, 14.1 Hz), 3.54 (dd, 1H, *J* = 6.4, 8.0 Hz), 3.70 (dd, 1H, *J* = 5.6, 9.0 Hz), 4.01 (dd, 1H, *J* = 6.1, 8.0 Hz), 4.05 - 4.15 (m, 1H), 5.14 (s, 2H), 5.16 (ABq, 2H, *J* = 12.2 Hz), 7.25 - 7.40 (m, 10H). HR-FABMS (*m/z*) : Calcd for C₂₃H₂₇O₆ = 399.1807. Found = 399.1819 (M+H)⁺. [α]_D²⁰ = +8.80° (*c* 1.0, CHCl₃).

(5S)-5-Acetoxymethyl-3-tetradecanoyl-γ-butyrolactone [(S)-3a]: Using the procedure described above for the synthesis of (*RS*)-**3a** from (*RS*)-**7b** with (*S*)-**6b** (1.99 g, 5.00 mmol), the title compound [(*S*)-**3a**; 1.07 g, 58 %] was obtained as colorless crystals. mp 47.0 - 48.0°C (from *n*-hexane). [α]_D²⁰ = +12.7° (*c* 1.8, CHCl₃).

(5R)-5-Acetoxymethyl-3-tetradecanoyltetronic Acid [(R)-2a]: Using the procedure described above for the synthesis of (*RS*)-**2a** with (*S*)-**3a** (1.20 g, 3.30 mmol), the title compound [(*R*)-**2a**; 588 mg, 45 %] was obtained as colorless crystals. mp 78.0 - 79.0°C (from ethyl acetate / *n*-hexane). [α]_D²⁰ = +40.0° (*c* 0.03, CHCl₃).

(5R)-5-Hydroxymethyl-3-tetradecanoyltetronic Acid [(R)-1a]: Using the procedure described above for the synthesis of (RS)-1a with (R)-2a (200 mg, 0.52 mmol), the title compound [(R)-1a; 102 mg, 58 %] was obtained as colorless crystals. mp 57.0 - 59.0°C (from ethyl acetate / *n*-hexane). $[\alpha]_{D_{20}}^{20} = +32.6^\circ$ (c 0.54, CHCl₃).

(5S)-5-Acetoxymethyl-3-hexadecanoyl- γ -butyrolactone [(S)-3b]: Using the procedure described above for the synthesis of (RS)-3a from (RS)-7b with (S)-6b (1.19 g, 3.00 mmol) and palmitic acid, the title compound [(S)-3b; 642 mg, 54 %] was obtained as colorless crystals. mp 50.0 - 51.0°C (from *n*-hexane). IR (CHCl₃) : 1770, 1740, 1720 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (t, 3H, *J* = 6.7 Hz), 1.20 - 1.40 (m, 24H), 1.50 - 1.70 (m, 2H), 2.09 and 2.11 (each s, total 3H), 2.35 (t, 2H, *J* = 7.6 Hz), 2.54 - 2.70 (m, 1H), 2.82 - 3.08 (m, 1H), 3.48 (dd, 0.5H, *J* = 7.1, 14.0 Hz), 3.72 - 3.82 (m, 0.5H), 4.08 - 4.38 (m, 2H), 4.66 - 4.84 (m, 1H). HR-EIMS (*m/z*) : Calcd for C₂₃H₄₀O₅ = 396.2876. Found = 396.2867 (M⁺). $[\alpha]_{D_{20}}^{20} = +15.0^\circ$ (c 0.2, CHCl₃).

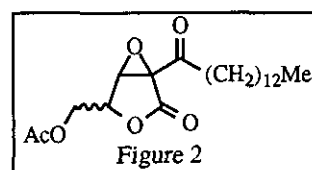
(5R)-5-Acetoxymethyl-3-hexadecanoyltetronic Acid [(R)-2b]: Using the procedure described above for the synthesis of (RS)-2a with (S)-3b (594 mg, 1.50 mmol), the title compound [(R)-2b; 184 mg, 30 %] was obtained as colorless crystals. mp 71.0 - 73.0°C (from ethyl acetate - *n*-hexane). IR (CHCl₃) : 1768, 1740, 1720 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (t, 3H, *J* = 6.6 Hz), 1.20 - 1.40 (m, 24H), 1.63 (quint, 2H, *J* = 7.1 Hz), 2.10 (s, 3H), 2.35 and 2.60 (each t, total 2H, *J* = 7.4 Hz), 4.31 (s, 1H), 4.40 (d, 2H, *J* = 2.7 Hz), 4.78 (t, 1H, *J* = 2.7 Hz). HR-FABMS (*m/z*) : Calcd for C₂₃H₃₉O₆ = 411.2746. Found = 411.2757 (M+H)⁺. $[\alpha]_{D_{20}}^{20} = +36.0^\circ$ (c 0.2, CHCl₃).

(5R)-3-Hexadecanoyl-5-hydroxymethyltetronic Acid [(R)-1d]: Using the procedure described above for the synthesis of (RS)-1a with (R)-2b (100 mg, 0.24 mmol), the title compound [(R)-1d; 47 mg, 53 %] was obtained as colorless crystals. mp 101.0 - 104°C (from ethyl acetate - *n*-hexane). IR (CHCl₃) : 3375, 1785, 1709 cm⁻¹. ¹H-NMR (CDCl₃) δ : 0.88 (t, 3H, *J* = 6.7 Hz), 1.20 - 1.40 (m, 24H), 1.55 - 1.65 (m, 2H), 2.79 (dt, 1H, *J* = 18.8, 7.3 Hz), 2.94 (dt, 1H, *J* = 18.8, 7.3 Hz), 3.89 (dd, 1H, *J* = 2.1, 12.8 Hz), 4.04 (dd, 1H, *J* = 2.8, 12.8 Hz), 4.36 (br d, 1H, *J* = 8.4 Hz), 4.76 (d, 1H, *J* = 8.4 Hz). HR-FABMS (*m/z*) : Calcd for C₂₁H₃₇O₅ = 369.2641. Found = 369.2650 (M+H)⁺. $[\alpha]_{D_{20}}^{20} = +58.1^\circ$ (c 0.47, CHCl₃).

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 9. This novel oxidation might proceed *via* the epoxide shown in Figure 2 as an important intermediate. The epoxide might be derived from (RS)-14 by the further oxidation with excess of H_2O_2 , or $PhSeO_nH$ ($n = 1 - 3$) generated *in situ*.
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