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An Efficient Synthesis of (R)-(+)-Recifeiolide and Related Macrolides by Using Enantiomerically Pure (R)-(–)-5-Methyl-2,2,2-triphenyl-1,2λ^5-oxaphospholane

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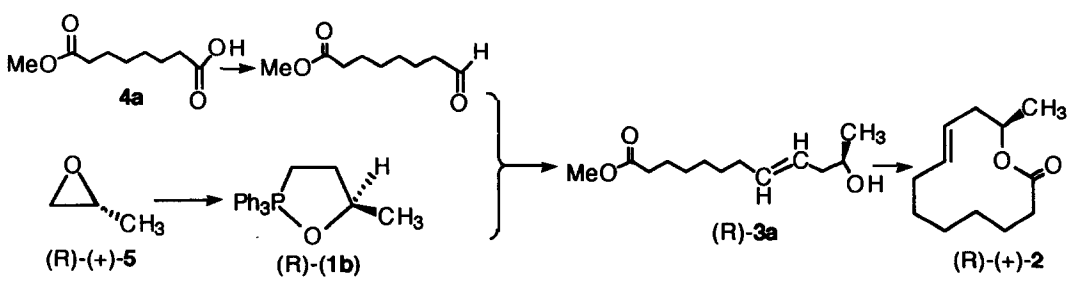
Abstract: *E*-(R)-(+)-8-Dodece-11-olide, which is known as recifeiolide, was synthesized by a six-step reaction starting from (R)-(+)-propene oxide in a total yield of 53 %. The key step of this synthesis is the preparation of (R)-(–)-methyl 11-hydroxy-8-dodecenate using (R)-(–)-5-methyl-2,2,2-triphenyl-1,2λ^5-oxaphospholane. By using this method, enantiomerically pure 13- and 14-membered macrolides were also synthesized.

Studies of the reaction of Wittig reagents with epoxides have been carried out for more than thirty years.[1] In 1967, Hands and Mercer reported the first isolation of a 2,2,2-triphenyl-1,2λ^5-oxaphospholane (**1a**).[2] *E*-8-Dodece-11-olide (**2**), which is known as recifeiolide, was independently synthesized by several groups.[3] The synthesis of enantiomerically pure *E*-(R)-(+)-**2**, first reported by Gerlach *et al.*, includes the optical resolution of 1,3-butanediol and macrocyclization of methyl *E*-11-hydroxy-8-dodecenoic acid (**3a**) using sodium hydroxide, 2,2'-dipyridyl disulfide, triphenylphosphine, and silver perchlorate.[4] Other methods include the yeast reduction of *E*-11-oxo-8-dodecenoic acid,[5] the intramolecular cyclization of vinyl ether,[6] and the partial stereoselective reduction of 1-none-8-yne.[7] The synthesis of *E*-(R)-(+)-**2** from commercially available methyl suberate (**4a**) and enantiomerically pure (R)-(+)-propene oxide (**5**) seems to be the most straightforward and efficient method as shown in Scheme 1. However, to our knowledge, there is no report about the synthesis of (R)-(+)-**2** using this procedure.



Scheme 1.

We have recently prepared optically pure 2,2,2-triphenyl-5-alkyl-1,2λ^5-oxaphospholanes (**1**) and reacted **1** with aldehydes to afford the corresponding enantiomerically pure homoallylic alcohols in nearly

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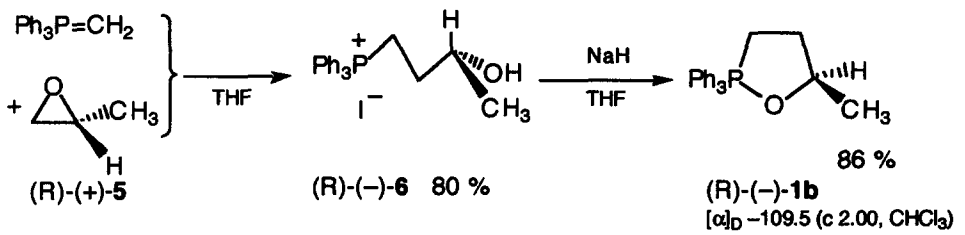
quantitative yields.[8] To show the potential of **1** in the synthesis of natural products, we herein report an efficient short-step synthesis of (R)-(+)-**2** and related macrolides.

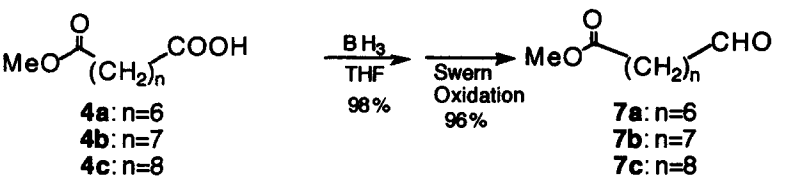
Results and Discussion

(R)-(–)-5-methyl-2,2,2-triphenyl-1,2λ^5-oxaphospholane (**1b**) was prepared by the reaction of (R)-(–)-3-hydroxybutyltriphenylphosphonium iodide (**6**), which was prepared from methylenetriphenylphosphorane and (R)-(+)-**5**, with sodium hydride (Scheme 2).[8]



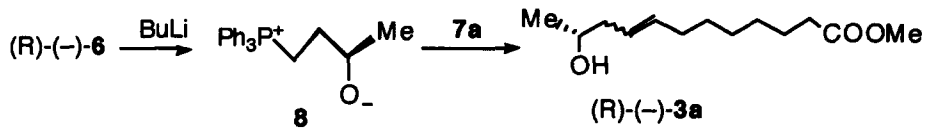
Scheme 2.

Methyl 8-oxooctanoate (**7a**) was prepared by the following two-step reaction starting from methyl suberate (**4a**) in 94 % total yield. Starting with methyl azelate (**4b**) and methyl sebacate (**4c**), methyl 9-oxononanate (**7b**) and methyl 10-oxodecanoate (**7c**) were prepared in a similar manner (Scheme 3).



Scheme 3.

The synthesis of (R)-(–)-methyl 11-hydroxy-8-dodecenate (**3a**), which is a key intermediate in the synthesis of (R)-(+)-**2**, was then tried. Gerlach and co-workers reported the synthesis of (R)-(–)-**6** starting from racemic 1,3-butandiol and 1-methoxycyclooctene by a ten-step reaction in only 20 % total yield. They synthesized (R)-(–)-**3a** by the Wittig olefination using γ-oxide ylide (**8**) and **7a** in 37 % yield (Scheme 4).[4] Wasserman *et al.* also reported that the reaction of racemic **8** with oxazolaldehyde affords the corresponding homoallylic alcohol in 52 % yield.[3g] Thus, another method for the synthesis of (R)-(–)-**3a** is desirable.

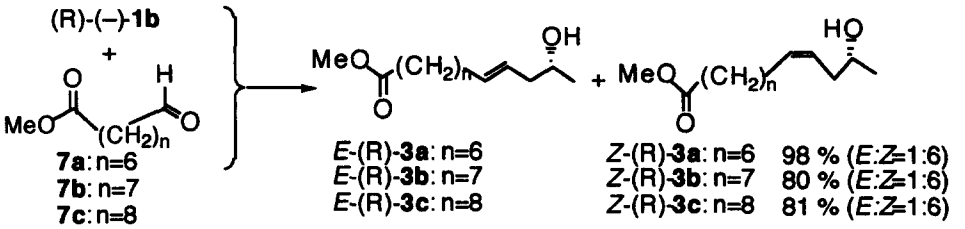


Scheme 4.

Since homoallylic alcohols are prepared by the reaction of 1,2λ^5-oxaphospholanes with aldehydes in nearly quantitative yields,[8] the reaction of (R)-(–)-**1b** with **7a** was carried out. When (R)-(–)-**1b** was treated with **7a** in refluxing toluene, (R)-(–)-**3a** was obtained in nearly quantitative yield (98 %; *E*:*Z*=1:6). Analogously, (R)-(–)-methyl 12-hydroxytridec-9-enate (**3b**, 80 %; *E*:*Z*=1:6) and (R)-(–)-methyl 13-hydroxytetradec-10-enate (**3c**, 81 %; *E*:*Z*=1:6) were also prepared (Scheme 5).

Recently, Tatsuta and Yasuda reported the synthesis of deacetyl-caloporoside, an inhibitor of the $GABA_A$ receptor ion channel.[9] They prepared (R)-15-bromo-pentadec-4-en-2-ol (66 %) by the reaction of

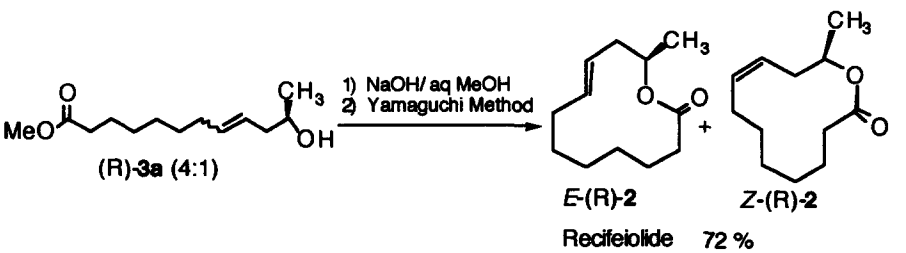
11-bromoundecanal with **6**. Salt **6** was prepared by a five-step reaction starting from methyl 4,6-dideoxy-α-D-xylo-hexopyranoside.[10] The present method has advantages over their synthetic methods, since the salt **6** was prepared through a one- or two-step operation from commercially available enantiomerically pure



Scheme 5.

propene oxide. Other enantiomerically pure salts **6** were prepared through a one- or two-step operation from enantiomerically pure epoxides.[8] The yields of **3a-c** are much higher than those achieved by the above three methods.[3g,4,10] Thus, the present method provides a practical synthesis of optically pure, long-chain homoallylic alcohols.

The *E:Z* ratio of ester **3a** was easily changed by diphenyl disulfide sensitized photoisomerization (4:1 for 12 h irradiation). Gerlach and coworkers separated the *E*-form of methyl 11-hydroxydodec-8-enate (**3a**) using Ag impregnated silica gel.[4] However, this method is not effective due to a slight difference between the R_f values of *E*- and *Z*-**3a**. We have carried out this separation according to Gerlach's procedure. When this process was repeated three times, only 15 % of *E*-**3a** was isolated. Thus, this method was not practical. Without any separation, the following macrocyclization was carried out. Hydrolysis of **3a** followed by macrocyclization using Yamaguchi method[11] afforded an *E*- and *Z*-mixture of (R)-(+)-8-docece-11-olide (**2**) in 72 % yield (Scheme 6).

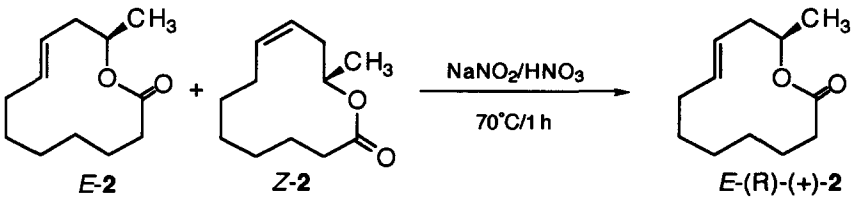


Scheme 6.

The separation of this mixture was successfully completed using silica gel HPLC (Merck Si 60) without any difficulty. The enantiomeric excess of (R)-(+)-**2** was determined using an optically active lanthanide shift reagent [Eu(tfc)$_3$] and GPC analysis.[7] Thus, this method provides a practical synthesis of the *E*- and *Z*-macrolides.

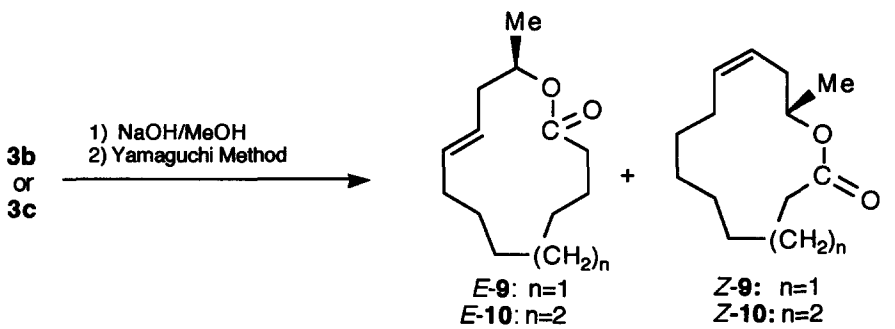
Recently, Mahajan and Resck reported the synthesis of racemic **2** via acetylenic lactones.[12] They have found that the *Z* to *E* isomerization of **2** was accomplished using sodium nitrite and nitric acid. Thus, macrolactonization can be carried out without any separation of the *E*- and *Z*- mixture of methyl 11-hydroxy-8-dodecenate (**3a**). Transformation of *E*-**2** from *Z*-**2** was successfully accomplished using sodium nitrite and nitric acid according to the method reported by Mahajan and Resck (Scheme 7). Thus, the total synthesis of (R)-(+)-**2** in 53 % yield starting from oxaphospholane (R)-**1b** was accomplished.

There are numerous methods for the synthesis of **2**.[3-7, 12] The present method provides a simple and efficient synthesis of **2**. Since the reaction of **1b** with aliphatic aldehydes preferentially gave Z-rich homoallylic alcohols, this method also provides a practical synthesis of macrolides containing a Z-double bond moiety. Actually, without photoisomerization, Z-(R)-(+)-8-dodecen-11-olide (**2**) was obtained in 40



Scheme 7.

% total yield starting from enantiomerically pure (R)-(+)-**5**. (R)-(+)-9-Tridece-12-olide (**9**) and (R)-(+)-10-tetradece-13-olide (**10**) were also obtained in a similar manner (Scheme 8). The enantiomeric excess of the products was determined by GPC analysis.



Scheme 8.

In summary, enantiomerically pure (R)-(+)-recifeiolide was successfully synthesized by six-step reactions from commercially available propene oxide and methyl suberate. We are continuing our effort to explore the synthetic application of the present method to natural products.

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Experimental

General: Melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained with a JEOL FX-90Q or a JEOL GSX-400 spectrometer. Chemical shifts are given in ppm units downfield from tetramethylsilane. Optical rotations were recorded on a JASCO Dip-140 polarimeter. The enantiomeric excess of (R)-(+)-**2** was determined by using an optically active lanthanide shift reagent [Eu(tfc)$_3$]. The enantiomeric excess of the products (R)-**2**, *E*-**9**, *Z*-**9**, *E*-**10**, and *Z*-**10** was determined by GPC analysis using 0.25 mm x 25 m Chiral GPC column (Cyclodextrine-β-236M, Chrompack) equipped with a GC-353B GPC system (GL Sciences). TLC analyses were performed using Merck Silica gel 60 F254 aluminum plates.

Material: Optically active (R)-(–)-**5** was purchased from Merck (ee >97 %). Monomethyl ester **4a**, **4b**, and **4c** were purchased from Aldrich. (R)-(–)-**1b** was prepared by a method in our previous paper.[8]

Reaction of Methyl Suberate (4a) with Borane-THF Complex.

To a solution of **4a** (1.88 g, 10 mmol) in THF (15 mL) was added a solution of BH_3/THF (10 mL, 1 M, 10 mmol) at -20°C. The reaction mixture was stirred for 12 h at room temperature, then added saturated

aqueous sodium carbonate (15 mL), and extracted with ether (10 mL x 3). The combined extracts were dried over magnesium sulfate, filtered, and concentrated to afford a colorless oil of methyl 8-hydroxyoctanoate (1.70 g, 9.8 mmol, 98 %). bp 95-100°C/0.3 mmHg. ^{1}H NMR ($CDCl_3$) δ 1.26 (br , 6 H, 3 CH_2), 1.46-1.75 (m, 5 H, OH, 2 x CH_2), 2.23 (t, 2 H, $COCH_2$), 3.55 (t, 2 H, CH_2OH), 3.59 (s, 3 H, CH_3CO). ^{13}C NMR ($CDCl_3$) δ=24.7 (CH_3), 24.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 32.7 (CH_2), 34.0 (CH_2), 51.4 (CH_3O), 62.9 (CH_2OH), 174.3 (C=O). HRMS: Calcd for $C_9H_{18}O_3$ (M^+) 174.1255. Found: 174.1226.

Methyl 9-hydroxynonanate was prepared in a similar manner. The reagents used in the preparation were: **4b** (6.71 g, 33 mmol), BH_3/THF (37 mL, 1 Mol, 37 mmol), and THF (70 mL). Distillation of the extract gave methyl 9-hydroxynonanate (5.63 g, 30 mmol, 90 %). ^{1}H NMR ($CDCl_3$) δ 1.25-1.35 (br, 8 H, 4 x CH_2), 1.49-1.75 (m, 2 x CH_2), 2.31 (t, *J*= 7.5 Hz, 2 H, $COCH_2$), 3.63 (t, *J*= 6.8 Hz, 2 H, CH_2OH), 3.67 (s, 3 H, OMe). ^{13}C NMR ($CDCl_3$) δ=24.9 (Me), 25.7 (CH_2), 29.1 (CH_2), 29.2 (2 x CH_2), 32.8 (CH_2), 34.8 (CH_2), 51.5 (OMe), 63.0 (CH_2OH), 174.2 (C=O). HRMS: Calcd for $C_{10}H_{20}O_3$ (M^+) 188.1411. Found: 188.1441.

Methyl 10-hydroxydecanoate was prepared in a similar manner. The reagents used in the preparation were: **4c** (2.04 g, 10 mmol), BH_3/THF (11 mL, 1 Mol, 11 mmol), and THF (25 mL). Flash chromatography using a 3:1 dichloromethane:ethyl acetate mixture gave methyl 10-hydroxydecanoate (1.71g, 90 %). ^{1}H NMR ($CDCl_3$) δ 1.26-1.40 (br, 10 H, 5 x CH_2), 1.50-1.69 (m, 4 H, 2 x CH_2), 2.30 (t, *J*= 7.5 Hz, 2 H, $COCH_2$), 3.64 (dt, 2 H, *J*= 4.6 Hz, CH_2OH), 3.67 (s, 3 H, OMe). The ^{1}H NMR spectrum is identical with that of the authentic sample from Aldrich.

Swern Oxidation of Methyl 8-Hydroxyoctanoate.

To a solution of oxalyl chloride (1.74 mL, 20 mmol) and dimethyl sulfoxide (1.89 mL, 26.6 mmol) in dichloromethane (35 mL) was added methyl 8-hydroxyoctanoate (1.74 g, 10 mmol) in dichloromethane (5 mL) at –78°C. After stirring for 2 h, triethyl amine (10.1 g, 100 mmol) was added to this solution and the reaction mixture was warmed up to room temperature. The reaction mixture was poured into sat. NH_4Cl solution and washed with water (30 mL x 3). The organic layer was separated, dried over $MgSO_4$, and concentrated to afford a pale yellow oil, which was chromatographed over silica gel by elution with dichloromethane-hexane to give methyl 8-oxooctanoate (**7a**, 1.48 g, 8.6 mmol, 86 %). ^{1}H NMR ($CDCl_3$) δ 1.30-1.42 (br, 4 H, 2 x CH_2), 1.58-1.69 (br, 4 H, 2 x CH_2), 2.31 (t, *J*= 7.3 Hz, 2 H, $CHOCOCH_2$), 2.40-2.46 (dt, *J*= 7.3 Hz, 2 H, CH_2CHO), 3.67 (s, 3 H, MeOCO), 9.76 (t, *J*= 10.8 Hz, 1 H, CHO). ^{13}C NMR ($CDCl_3$) δ 21.9 (CH_2), 24.7 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 43.8 ($\underline{C}H_2CHO$), 51.5 (MeO), 174.1 (C=O), 202.6 (CHO). ^{1}H NMR spectrum of this ester is identical with the reported one.[4]

Methyl 9-oxononanate (**7b**) was prepared in a similar manner. The reagents used in the preparation were: oxalyl chloride (3.20 g, 25 mmol), dimethyl sulfoxide (4.0 mL, 56 mmol), methyl 9-hydroxynonanate (3.73 g, 20 mmol), dichloromethane (80 mL), and triethylamine (10.2 g, 100 mmol). Flash chromatography using dichloromethane gave **6b** (2.95 g, 79 %). ^{1}H NMR ($CDCl_3$) δ 1.26-1.41 (m, 6 H, 3 CH_2), 1.51-1.70 (m, 4 H, 2 x CH), 2.31 (t, *J*=7.3 Hz, 2 H, CH_2COOCH_3), 2.39 (dt, *J*=1.5 and 7.3 Hz, 2 H, CH_2CHO) 3.67 (s, 3 H, CH_3), 9.77 (t, *J=1.5 Hz*, 1 H, CHO) ^{13}C NMR ($CDCl_3$) δ 21.8 (CH_2), 24.7 (CH_2), 28.8 (CH_2), 28.8 (CH_2), 33.9 (CH_2), 43.8 (CH_2CHO), 51.5 (Me), 174.1 (C=O), 202.7 (CHO). HRMS: Calcd for $C_{10}H_{18}O_3$ (M^+) 186.1255. Found: 186.1222.

Methyl 10-oxodecanoate (**7c**) was prepared in a similar manner. The reagents used in the preparation were: oxalyl chloride (1.60 g, 12.6 mmol), DMSO (2.0 mL, 28.2 mmol), methyl 10-hydroxydecanoate (2.15 g, 10.6 mmol), dichloromethane (35 mL) and triethylamine (7 mL, 95.3 mmol) to give **7c** (1.91 g, 9.52 mmol, 90 %). ^{1}H NMR ($CDCl_3$) δ 1.21-1.41 (br m, 8 H, CH_2), 1.53-1.71 (br m, 4 H, CH_2), 2.30 (t, *J*= 7.2 Hz, 2 H, $C\underline{H}_2COOMe$), 2.42 (dt, *J*= 1.8 and 7.3 Hz, 2H, $C\underline{H}_2CHO$), 3.67 (s, 3H, Me), 9.83 (t, *J*= 1.8 Hz, 1 H, CHO). ^{13}C NMR ($CDCl_3$) δ 22.0 (CH_2), 25.0 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 34.1 (CH_2), 43.9 (CH_2CHO), 51.5 (Me), 174.3 (C=O), 202.9 (CHO). HRMS: Calcd for $C_{11}H_{20}O_3$ (M^+) 200.1411. Found: 200.1378.

Reaction of (R)-(–)-Oxaphospholane 1b with 7a

To a refluxing solution of (R)-(–)-**1b** (1.74 g, 5.1 mmol) in toluene (45 mL) was added a solution of **7a** (0.88 g, 5.1 mmol) in toluene (10 mL). After refluxing for 6 h, the reaction mixture was concentrated to give nearly colorless solid which was extracted with pentane (15 mL x 3). The combined extracts were concentrated to afford a pale yellow oil of **3a** (1.11 g, 5.0 mmol, 98 %). The *E:Z* ratio of **3a** was 1:6.

To a solution of **3a** (0.33 g, 1.55 mmol) in benzene (5 mL) was added diphenyl disulfide (0.010 g, 0.031 mmol) and UV light was irradiated for 12 h with a medium pressure mercury lamp. The *E:Z* ratio was changed into 4:1. The reaction mixture was evaporated and chromatographed over silica gel by elution with dichloromethane to afford a colorless oil, which contains a mixture of methyl *E*- and *Z*-11-hydroxy-8-dodecenate (**3a**). Pure *E*-**3a** was obtained by chromatography of the mixture on $AgNO_3$-impregnated silica gel using 1:1 dichloromethane-hexane mixture as eluant. *E*-(R)-(–)-**3a** (0.050 g, 0.23 mmol, 15 %). ^1H NMR ($CDCl_3$) δ 1.18 (d, *J*= 6.1 Hz, 3 H, CHOHMe), 1.26-1.41 (br, 5 H, 2 CH_2, OH), 1.55-1.68 (m, 4 H, 2 x CH_2), 2.00-2.10 (m, 2 H, CH_2), 2.15-2.27 (m, 2 H, CH_2), 2.31 (t, *J*= 7.9 Hz, 2 H, $COCH_2$), 3.67 (s, 3 H, MeCO), 3.78-3.86 (m, 1 H, CHOH), 5.35-5.45 (m, 1 H, CH=CH), 5.52-5.57 (m, 1 H, CH=CH).

Methyl 12-hydroxy-9-tridecenoate (**3b**) was prepared in a similar manner. The reagents used in the preparation were: The reagent used in the preparation were: oxaphospholane R-(–)-**1b** (2.80 g, 8.4 mmol), **7b** (1.59 g, 8.5 mmol), and toluene (9 mL) to give a mixture of *E* and *Z*-**3b** (1.64 g, 6.8 mmol, 80 %). ^1H NMR ($CDCl_3$) δ 1.18 (d, *J*= 6.3 Hz, 3 H, *E*-Me), 1.21 (d, *J*= 6.3 Hz, 3 H, *Z*-Me), 1.25-1.35 (br, CH_2), 1.65-1.70 (br m, CH_2), 2.00-2.30 (br m, CH_2), 3.67 (s, 3 H, *E*- and *Z*-OMe), 3.75-3.86 (m, 1 H, *E*- and *Z*-CHOH), 5.39 (m, 1 H, *E*- and *Z*-olefinic CH), 5.55 (m, 1 H, *E*- and Z-olefinic CH). ^{13}C NMR ($CDCl_3$) δ 22.9 (*Z*-Me), 25.0 (*Z*-CH_2), 27.5 (*Z*-CH_2), 29.2 (*Z*-CH_2), 29.3 (*Z*-CH_2), 29.7 (*Z*-CH_2), 34.2 (*Z*-CH_2), 37.2 (*Z*-CH_2), 51.5 (*Z*-OMe), 67.7 (*Z*-CH), 124.9 (*Z*-CH=), 133.2 (*Z*-CH=), 174.1 (*Z*-C=O). HRMS: Calcd for $C_{14}H_{26}O_3$ (M^+) 242.1880. Found: 242.1896.

Methyl 13-Hydroxy-10-tetradecenoate (**3c**) was prepared in a similar manner. The reagents used in the preparation were: oxaphospholane R-(–)-**1b** (1.10 g, 3.2 mmol), **7c** (0.638 g, 3.4 mmol), and toluene (5 mL) to give a mixture of *E* and *Z*-**3c** (0.66 g, 2.6 mmol, 81 %). (R)-(–)-**3c**: ^1H NMR ($CDCl_3$) δ 1.18 (d, *J*= 6.3 Hz, 3 H, *E*-Me), 1.21 (d, *J*= 5.9 Hz, 3 H, Z-Me), 1.25-1.35 (br, CH_2), 1.65-1.70 (br m, CH_2), 2.00-2.30 (br m, CH_2), 3.67 (s, 3 H, *E*- and Z-OMe), 3.75-3.86 (m, 1 H, *E*- and *Z*-CHOH), 5.39 (m, 1 H, *E*- and Z-olefinic CH), 5.55 (m, 1 H, *E*- and Z-olefinic CH). ^{13}C NMR ($CDCl_3$) δ 22.9 (*Z*-Me), 25.0 (*Z*-CH_2), 27.5 (*Z*-CH_2), 29.2 (*Z*-CH_2), 29.3 (*Z*-CH_2), 29.7 (*Z*-CH_2), 34.2 (*Z*-CH_2), 37.2 (*Z*-CH_2), 51.5 (*Z*-OMe), 67.7 (*Z*-CH), 124.9 (*Z*-CH=), 133.2 (*Z*-CH=), 174.1 (*Z*-C=O). The peaks of *E*-form (**3c**) are too small. HRMS; Calcd for $C_{15}H_{28}O_3$ (M^+): 256.2039. Found: 256.2127.

Hydrolysis of 3a: To a stirred solution of a *E* and *Z* mixture of (R)-(–)-**3a** (0.23 g, 1.0 mmol) in methanol (5 mL) was added a solution of aq. NaOH (4 N, 3 mL). After refluxing for 3 h, the reaction mixture was neutralized by 1 N HCl and extracted with ether (10 mL x 3). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated to give crude 11-hydroxy-8-dodecenoic acid (0.21 g, 1.0 mmol). The product was used for next step without further purification.

Hydrolysis of **3b** was prepared in a similar manner. The reagents used in the preparation were: E and Z mixture of **3b** (0.48 g, 2.0 mmol), aq NaOH (3 N, 8 mL). Crude 12-hydroxy-9-tridecenoic acid was obtained in nearly quantitative yield (0.46 g, 2.0 mmol).

Hydrolysis of **3c** was prepared in a similar manner. The reagents used in the preparation were: E and Z mixture of **3c** (0.51 g, 2.0 mmol), aq NaOH (3 N, 10 mL). Crude 13-hydroxy-10-tetradecenoic acid was obtained in nearly quantitative yield (0.48 g, 2.0 mmol).

Preparation of *E*-R-(+)-2 (Recifeiolide) by Yamaguchi Method

To a solution of a *E*- and *Z*-mixture of (R)-(–)-11-hydroxy-8-dodecenoic acid (0.11 g, 0.5 mmol) and triethylamine (0.50 g, 5 mmol) in benzene (4 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (0.12 g, 0.5 mmol) in benzene (5 mL). After being stirred for 6 h, the reaction mixture was filtered and the

filtrate was diluted with benzene (150 mL). This solution was added dropwise to a solution of 4-(N,N-dimethylamino)pyridine (0.25 g, 2.0 mmol) in toluene (50 mL) over a period of 2 h. After being stirred for 8 h, the reaction mixture was washed with water (30 mL x 3), dried over $MgSO_4$, and concentrated to give a pale brown oil, which was chromatographed over silica gel by elution with hexane/ethyl acetate (5:1) to afford a *E:Z* mixture of (R)-(+)-**2** (0.068 g, 0.35 mmol, 70 %). The mixture was subjected to HPLC separation (Merck silica gel) by elution using a 98:2 hexane:ethyl acetate mixture to afford pure (R)-(+)-recifeiolide (0.049 g, 0.25 mmol, 50 %) and *Z*-(R)-(+)-8-dodecen-11-olide (**2**) (0.0078 g, 0.04 mmol, 8 %).

E-(R)-(+)-**2**: ee >97 %; $[\alpha]_D$ +68.9 (c 0.76, $CHCl_3$) {lit.[4] $[\alpha]_D$ +70 (c 1.0, $CHCl_3$)} ^1H NMR ($CDCl_3$) δ 1.15 (m, 2 H, CH_2), 1.24 (d, *J*= 6.4 Hz, 3 H, Me), 1.35-1.58 (m, 5 H, CH_2), 1.82 (m, 1 H, CHH), 1.96 (m, 1 H, CHH), 2.07-2.42 (m, 5 H, CH_2), 5.15 (m, 1 H, CH), 5.30 (m, 2 H, CH=CH). ^{13}C NMR ($CDCl_3$) δ 20.5 (Me), 23.2 (CH_2), 24.2 (CH_2), 24.6 (CH_2), 24.9 (CH_2), 30.2 (CH_2), 32.9 (CH_2), 40.9 (CH_2), 68.5 (CH_2), 127.0 (=CH), 133.4 (=CH), 173.4 (COO).

Z-(R)-(+)-**2**: ee >97 %; $[\alpha]_D$ +41.1 (c 1.66, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.29 (d, *J*=6.4 Hz, 3 H, Me), 1.15-1.62 (m, 6 H, CH_2), 1.84 (m, 1 H, CHH), 2.05 (m, 1 H, CHH), 2.15 (m, 1 H, CHH), 2.23 (m, 1 H, CHH), 2.36 (m, 1 H, CHH), 2.50 (m, 1 H, CHH), 5.22 (m, 1 H, CH), 5.42 (m, 1 H, =CH), 5.55 (m, 1 H, =CH). ^{13}C NMR ($CDCl_3$) δ 19.1 (Me), 24.1 (CH_2), 25.2 (CH_2), 27.1 (CH_2), 32.3 (CH_2), 32.8 (CH_2), 68.5 (CH_2), 123.6 (=CH), 133.4 (=CH), 173.0 (COO).

Z- to *E*-Isomerization of (R)-(+)-2.

To a suspension of *Z*-(R)-(+)-8-dodecen-11-olide (**2**; 98 mg, 0.5 mmol) in water (0.5 mL) was added aq. $NaNO_2$ (2M, 0.1 mL) and dil. HNO_3 (2M, 0.1 mL). After stirring for 1 h at 75°C, the reaction mixture was cooled to room temperature and extracted three times with hexane (5 mL). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated to afford a yellow oil, which was chromatographed over silica gel (short path) using a 3:1 hexane:ethyl acetate mixture to afford pure *E*-(R)-(+)-**2** (recifeiolide) in 91 % yield (91 mg). Spectral data of *E*-(R)-(+)-**2** was identical with that of the authentic sample.

Synthesis of 9 and 10 by Yamaguchi Method.

(R)-(+)-9-Tridece-12-olide (**9**) was prepared in a similar manner. The reagents used in the preparation were: 12-hydroxy-9-tridecenoic acid (0.62 g, 2.7 mmol), triethylamine (1.99 g, 8.0 mmol), 2,4,6-trichlorobenzoyl chloride (1.10 g, 11 mmol), THF (15 mL),.4-dimethylaminopyridine (0.98 g, 8.0 mmol), and toluene (500 mL). Flash chromatography of the extract gave a *E* and *Z* mixture (5:1) of (R)-(+)-10-Tridece-12-olide **9** (0.52 g, 2.5 mmol, 93 %). The mixture was subjected to HPLC separation (Merck silica gel) by elution using a 98:2 hexane:ethyl acetate mixture to afford pure *E*-(R)-(+)-**9** (0.34 g, 1.6 mmol, 59 %) and *Z*-(R)-(+)-**9** (0.057 g, 0.27 mmol, 10 %).

E-(R)-(+)-**9**: ee >97 %, $[\alpha]_D$ +64.4 (c=0.164, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=1.23 (d, *J*= 5.9 Hz, 3 H, Me), 1.20-1.45 (m, 10 H, CH_2), 1.62-1.70 (m, 2 H, CH_2), 2.01 (m, 1 H, CHH), 2.14-2.39 (m, 3 H, CH_2), 4.98 (m, 1 H, CHMe), 5.37 (m, 1 H, =CH), 5.53 (m, 1 H, =CH). ^{13}C NMR ($CDCl_3$) δ=20.7 (Me), 24.0 (CH_2), 26.9 (CH_2), 27.1 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 32.4 (CH_2), 34.2 (CH_2), 39.4 (CH_2), 69.8 (CH), 126.3 (=CH), 134.4 (=CH), 173.7 (COO). HRMS; Calcd for $C_{13}H_{22}O_2$ (M^+): 210.1620. Found: 210.1611.

Z-(R)-(+)-**9**: ee >97 %, $[\alpha]_D$ +58.8 (c=0.223, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.29 (d, *J*= 6.3 Hz, 3 H, Me), 1.15-1.70 (m, 9 H, CH_2), 2.08 (br m, 2 H, CH_2), 2.20-2.34 (m, 4 H, CH_2), 2.43 (m, 1H, CHH), 5.06 (m, 1 H, CHMe), 5.40 (m, 1 H, =CH), 5.47 (m, 1 H, =CH). ^{13}C NMR ($CDCl_3$) δ 19.9 (Me), 23.4 (CH_2), 24.5 (CH_2), 25.5 (CH_2), 25.9 (CH_2), 27.3 (CH_2), 29.3 (CH_2), 33.4 (CH_2), 35.1 (CH_2), 70.0 (CH), 124.5 (=CH), 132.4 (=CH), 174.06 (COO). HRMS; Calcd for $C_{13}H_{22}O_2$ (M^+): 210.1620. Found: 210.1618.

(R)-(+)-10-Tetradece-13-olide (**10**) was prepared in a similar manner. The reagents used in the preparation were: 13-hydroxy-10-tetradecenoic acid (0.30 g, 1.21 mmol), triethylamine (0.45 g, 4.2 mmol),

2,4,6-trichlorobenzoyl chloride (0.75 g, 3.08 mmol), THF (25 mL), 4-dimethylaminopyridine (1.17 g, 9.58 mmol), and toluene (500 mL). Flash chromatography of the extract gave a E and Z mixture (5:1) of (R)-(+)-10-Tetradece-13-olide (**10**) (0.27 g, 1.20 mmol, 99 %). The mixture was subjected to HPLC separation (Merck silica gel) by elution using a 98:2 hexane:ethyl acetate mixture to afford pure *E*-(R)-(+)-**10** (0.017 g, 0.073 mmol, 6 %) and *Z*-(R)-(+)-**10** (0.083 g, 0.38 mmol, 31 %).

E-(R)-(+)-**10**: ee >97 %, $[\alpha]_D$ +14.2 (c 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.25 (d, *J*= 6.4 Hz, 3 H, Me), 1.20-1.66 (m, 12 H, CH_2), 1.94 (br m, 1 H, CHH), 2.06 (br m, 1 H, CHH), 2.20-2.42 (m, 4 H, CH_2), 4.90 (m, 1 H, CH), 5.40 (m, 2 H, =CH). ^{13}C NMR ($CDCl_3$) δ 20.4 (Me), 23.9 (CH_2), 24.1 (CH_2), 25.5 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.4 (CH_2), 30.9 (CH_2), 35.3 (CH_2), 39.1 (CH_2),71.0 (CH), 126.6 (=CH), 132.6 (=CH), 173.5 (COO). HRMS; Calcd for $C_{14}H_{24}O_2$ (M^+): 224.1776. Found: 224.1834.

Z-(R)-(+)-**10**: ee >97 %, $[\alpha]_D$ +21.7 (c 1.51, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.27 (d, *J*= 6.4 Hz, 3 H, Me), 1.20-1.43 (m, 10 H, CH_2), 1.62-1.73 (m, 2 H, CH_2), 1.95 (m, 1 H, CHH), 2.13 (m, 1 H, CHH), 2.20-2.46 (m, 4 H, CH_2), 5.13 (m, 1 H, CH), 5.44 (m, 1 H, =CH), 5.61 (m, 1 H, =CH). ^{13}C NMR ($CDCl_3$) δ 20.3 (Me), 23.7 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 25.8 (CH_2 x 2), 27.4 (CH_2), 33.8 (CH_2), 34.0 (CH_2), 70.1 (CH), 125.6 (=CH), 132.2 (=CH), 173.6 (COO). HRMS; Calcd for $C_{14}H_{24}O_2$ (M^+): 224.1776. Found: 224.1777.

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