Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9483–9496

Total synthesis, elucidation of absolute stereochemistry, and adjuvant activity of trihydroxy fatty acids

Tatsuya Shirahata,[a,b] Toshiaki Sunazuka,[a,c] Kiminari Yoshida,[a,b] Daisuke Yamamoto,[a,b] Yoshihiro Harigaya,[b] Isao Kuwajima,[c] Takayuki Nagai,[a,c] Hiroaki Kiyohara,[a,c] Haruki Yamada[a,c] and Satoshi Ōmura[a,c,*]

[a]*Kitasato Institute for Life Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[b]*School of Pharmaceutical Science, Kitasato University, Shirokane, Minato-ku, Tokyo 108-8641, Japan*
[c]*The Kitasato Institute, Shirokane, Minato-ku, Tokyo 108-8642, Japan*

Received 10 April 2006; accepted 16 June 2006

Abstract—Pinellic acid from the tuber of *Pinellia ternate*, an active herbal component of the traditional Japanese herbal (Kampo) medicine Sho-seiryu-to, is a C18 trihydroxy fatty acid whose absolute stereochemistry has now been determined. All stereoisomers of pinellic acid were synthesized via regioselective asymmetric dihydroxylation, regioselective inversion, and stereoselective reduction in order to determine their absolute stereochemistries and adjuvant activities. Among this series of isomers, the (9*S*,12*S*,13*S*)-compound, which is a natural product, exhibited the most potent adjuvant activity. Spectral data for all of the stereoisomers of the 1,2-allylic diols were compared and related to their stereochemistries.

1. Introduction

Infection with the influenza virus is epidemic and can be lethal for patients with respiratory diseases and those who are elderly.[1] The primary method for the treatment of influenza is to use the influenza vaccine as a prophylaxis. Subcutaneous injection of this vaccine is known to induce production of serum antiviral IgG antibodies (Abs) that give a protective effect against proliferation of the virus in lung tissue. Because the influenza virus infects the nasal cavity first, intranasal inoculation of the influenza vaccine has been attempted in order to increase its safety and prevent antigenic variation. However, it has been shown that vaccinations in the nasal cavity are less effective than subcutaneous ones and may not provide sufficient immunostimulation. In order to overcome these problems, using adjuvants for enhancement of the local mucosal immune response has been reported.

Several traditional Japanese herbal (Kampo) medicines have been used for the treatment of cold-like symptoms in which the influenza virus is known to be the causative agent. Oral administration of the Kampo medicine, Sho-seiryu-to (SST), has been used clinically for the treatment of cold symptoms. In preliminary studies SST exhibited potent antiviral activity against influenza due to an immunostimulating activity against nasally inoculated influenza antigen. Our research indicated that SST had oral adjuvant activity for nasally administered influenza vaccine.[2–4] It was clear that the activity of SST was due to ingredients from *Pinellia ternate*, one of the component herbs of SST. Further investigation determined that pinellic acid **1** isolated from *P. ternate* was the compound responsible for the adjuvant activity (Fig. 1). Pinellic acid **1** is an effective oral adjuvant candidate for nasal influenza vaccine; however, *P. ternate* contains only a small amount of **1** and their stereochemistry was unknown.[5] Although information about the stereochemistry of these types of fatty acids has been reported,[6] there were not absolute to overcome our problems. Herein, not only the enantioselective total synthesis and assignment of the stereochemistry of **1**, but also the synthesis of stereoisomers and their adjuvant activities, are reported.

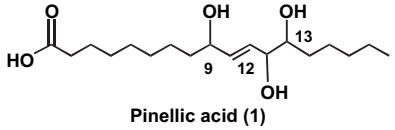
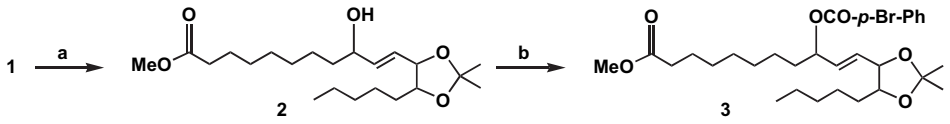


Figure 1. Structure of pinellic acid **1**.

Keywords: Total synthesis; Adjuvant; Determination of stereochemistry.
* Corresponding author. Tel.: +81 3 3444 6101; fax: +81 3 3444 6380; e-mail: omura-s@kitasato.or.jp

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.06.088



Scheme 1. Derivatization of **1**. Reagents and conditions: (a) (1) $TMSCHN_2$, benzene/MeOH (10:1), rt, 2.5 h; (2) 2,2-dimethoxypropane, PPTS, CH_2Cl_2, 60 °C, 48 h (100% from **1**); (b) *p*-Br-BzCl, DMAP, pyridine, rt, 10 h (68%).

2. Estimation of absolute stereochemistry of 1

To determine the absolute stereochemistry of pinellic acid, spectral analysis of its derivatives provided insightful information. The CD exciton method[7] was used for the estimation of C9 stereochemistry at the allylic alcohol. The esterification of **1** followed by dimethylacetalization gave acetonide **2** with free alcohol at C9 (Scheme 1). Both coupling constant ($J_{12,13}$=8.0 Hz) in the ^{1}H NMR spectrum of **2** and NOE analysis indicate a *syn* configuration at the C12–C13 diol (Fig. 2).

The corresponding *p*-bromobenzoate **3** was prepared with *p*-bromobenzoyl chloride from **2**. The coupling constant between H9 and H10 in the ^{1}H NMR spectrum of **3** was 7.0 Hz, indicating an antiperiplanar conformation of these two protons. Moreover, a positive Cotton effect [λ_{max} ($\Delta\varepsilon$): 244.8 (+6.97), 220.8 (+2.13), 209.1 (+5.97) (MeOH)] of **3** in the CD spectrum suggested a 9*S* configuration[8] (Fig. 3).

Based on these results, the absolute configuration of **1** was determined to be either **4** (9*S*,12*S*,13*S*) or **5** (9*S*,12*R*,13*R*) (Fig. 4). We then attempted to establish a convergent synthetic route to **4** and **5** in order to synthesize all of the possible stereoisomers.

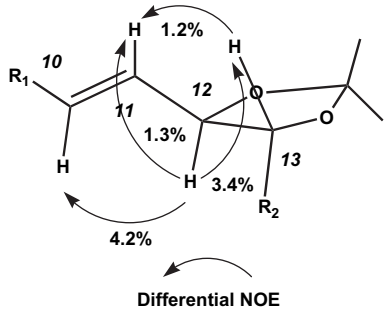


Figure 2. NOE analysis of **2**.

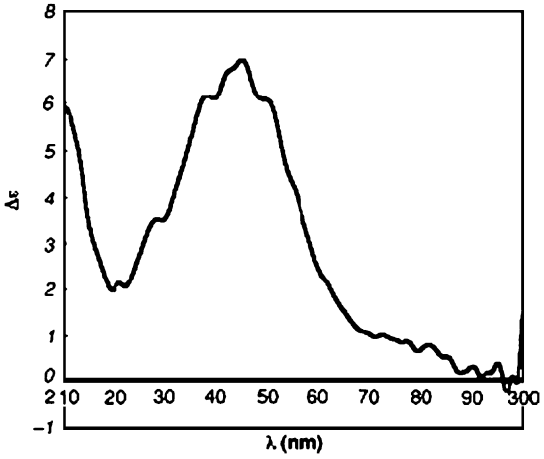


Figure 3. CD spectrum of **3**.

3. Total synthesis

3.1. Synthetic strategy

The strategic disconnection is outlined in Figure 5. The most important challenge in this synthesis is to construct the stereochemistry of the three hydroxy groups. The *syn*-diol at C12–C13 would be prepared from a diene by regioselective asymmetric dihydroxylation,[9] and the C12–C13 *anti*-diol would be constructed via regioselective protection of the C12 hydroxy group followed by inversion of the C13 hydroxy group. Stereoselective reduction from the corresponding enone would give the allylic alcohol at C9.

3.2. Synthesis of the C18 skeleton

The synthesis of C18 skeleton **11** utilizing dithiane coupling[10] is shown in Scheme 2. *tert*-Butyl ester **7** was converted from the carboxylic acid moiety in suberic acid monomethyl ester **6** with $(Boc)_2O$ and DMAP in *t*-BuOH. The diester **7** was transformed to iodide **8** in good yield by hydrolysis of the methyl ester, followed by reduction of the carboxylic acid,[11] and iodination of the resultant primary alcohol. The C9–C18 skeleton **10** was derived from commercially available 2,4-decadienal **9**. Lithiation of **10** with *n*-BuLi and subsequent addition of **8** gave diene **11** in high yield (Scheme 2).

3.3. Synthesis of 4

The regioselective asymmetric dihydroxylation of **11** using AD-mix containing $(DHQ)_2PHAL$ gave C12–C13 *syn*-diol (−)-**12**[12] in disappointing yield and enantiomeric excess (55%, 80% ee). However, the use of modified Sharpless ligand [(DHQ)PHAL(DHQ)$Me^+ \cdot I^-$][9] for the hydroxylation resulted in 64% yield with 95% ee. The protection of the diol (−)-**12** with excess TBSOTf followed by the deprotection of dithioacetal (−)-**13** provided enone (−)-**14**.

The stereoselective reduction of enone (−)-**14** to provide the (9*S*)-alcohol was attempted. Diastereoselectivity was not achieved with $NaBH_4$ or (*R*)-CBS[13] (diastereoselectivity 5:1). (*S*)-BINAL-H[12,14] noticeably improved the diastereoselectivity due to the π-electron at C10–C11 and the bulky *O*-TBS group (diastereoselectivity >20:1). The desilylation with TBAF gave triol (−)-**15** as a single isomer. Since deprotection of *tert*-butyl ester with TFA caused elimination of the hydroxy groups at the C9 and C12 allylic positions, the hydrolysis of the *tert*-butyl ester was achieved by a highly concentrated alkaline solution to afford (−)-**4**, which has the 9*S*,12*S*,13*S* configuration (Scheme 3). Compound (−)-**4** was

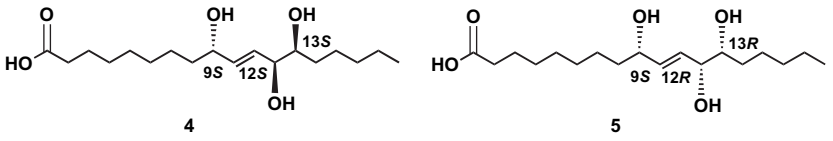


Figure 4. Possible structures for **1**.

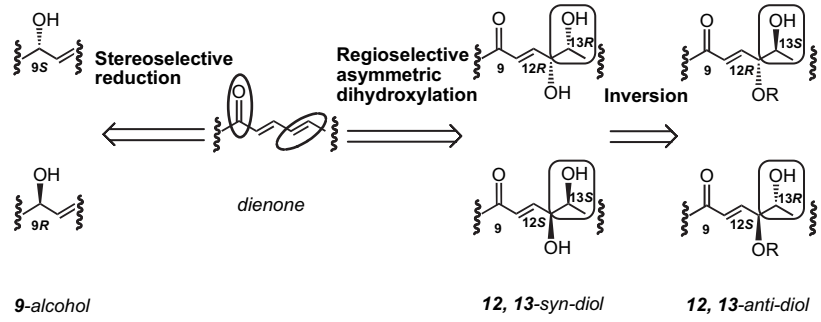
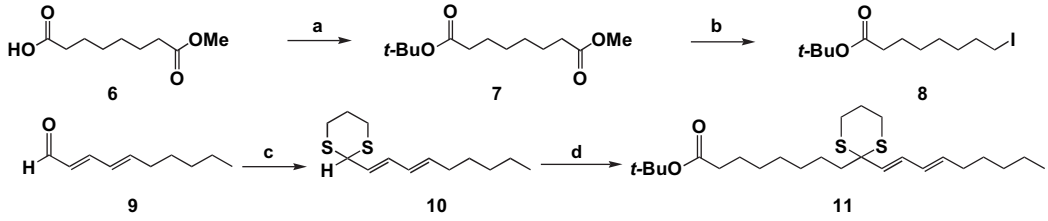
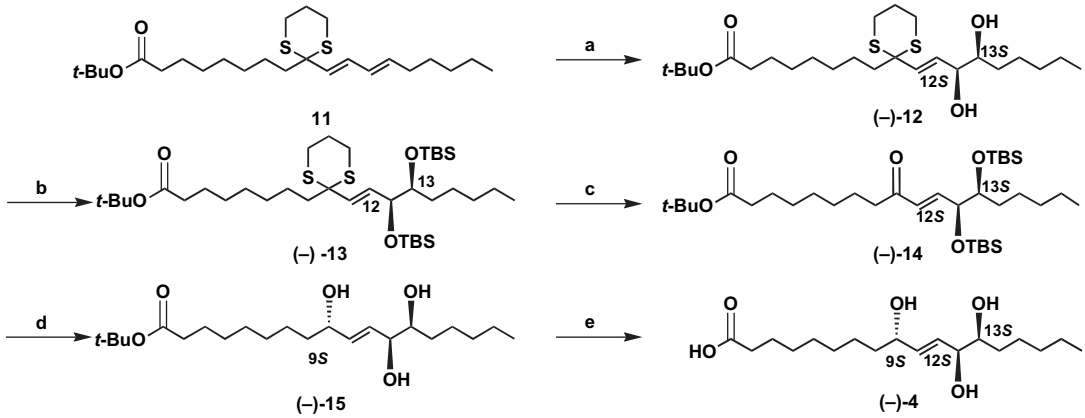


Figure 5. Synthetic strategy for all stereoisomers of **1**.



Scheme 2. Synthesis of the C18 skeleton **11**. Reagents and conditions: (a) $(Boc)_2O$, DMAP, *t*-BuOH, rt, 1 h (82%); (b) (1) 0.1 N NaOH in THF/MeOH/H_2O (3:1:1), rt, 28 h; (2) $BH_3\cdot$THF, THF, 0 °C to rt, 24 h; (3) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 2 h (77% from **7**); (c) 1,3-propanedithiol, $BF_3\cdot OEt_2$, CH_2Cl_2, 0 °C to rt, 10 h (96%); (d) *n*-BuLi, THF, −78 °C, 1 h, then **8**, −78 °C, 1 h (85%).



Scheme 3. Synthesis of **4**. Reagents and conditions: (a) (DHQ)PHAL(DHQ)$Me^+\cdot I^-$, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4\cdot 2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 °C, 41 h (64%, 95% ee); (b) TBSOTf, 2,6-lutidine, −78 °C, 30 min (89%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min (83%); (d) (1) (*S*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [76% from (−)-**14**]; (e) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (82%).

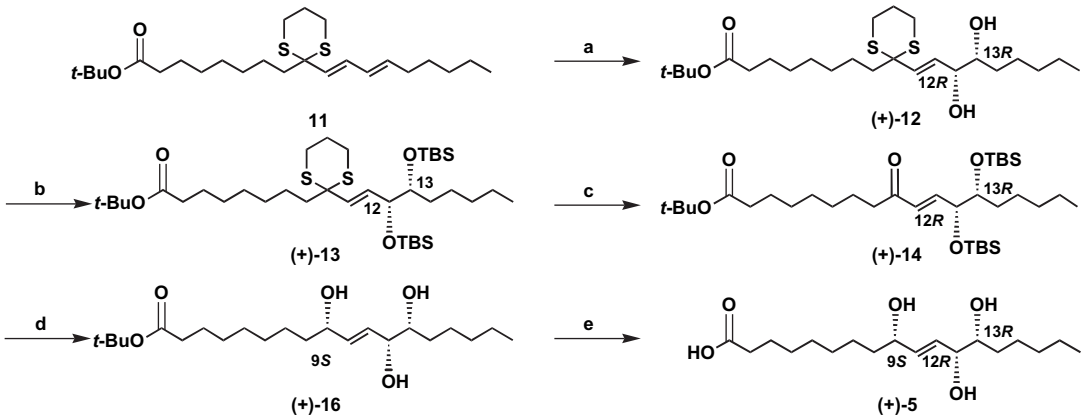
identical in all respects with natural product **1** [400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, IR, HRMS, optical rotation {$[\alpha]_D^{25}$ −8.0 (*c* 0.30, MeOH); natural:[4] $[\alpha]_D^{28}$ −8.1 (*c* 0.32, MeOH)}, and oral adjuvant activity] (Scheme 4).[15]

3.4. Synthesis of 5

For the synthesis of (+)-**5**, (+)-**12** with absolute configuration 12*R*,13*R* was required. Following the synthetic route for (−)-**4**, asymmetric dihydroxylation using AD-mix-β containing $(DHQD)_2PHAL$ of **11** gave diol (+)-**12** in 75% yield with 92% ee (Scheme 4). After the installation of the diol, the sequence of five reactions was the same, yielding (+)-**5**. The trihydroxy fatty acid (+)-**5** was not identical to natural product **1** [400 MHz ^{1}H NMR, 100 MHz ^{13}C NMR, and optical rotation {$[\alpha]_D^{23}$ +29.8 (*c* 0.45, MeOH)}].

3.5. Synthesis of (+)-4 and (−)-5

In order to investigate the oral administration of pinellic acid analogs as adjuvants for the intranasal inoculation of influenza HA vaccine, the synthesis of enantiomers of (−)-**4**

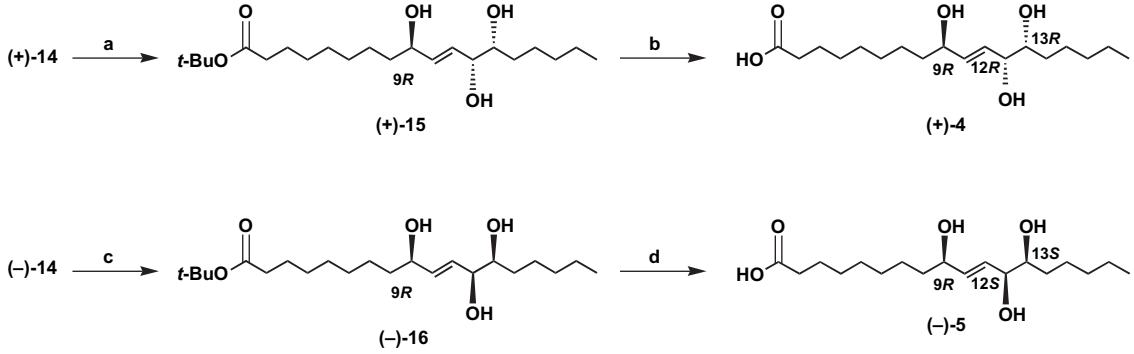


Scheme 4. Synthesis of **5**. Reagents and conditions: (a) $(DHQD)_2PHAL$, $K_3[Fe(CN)_6]$, K_2CO_3, $K_2OsO_4 \cdot 2H_2O$, methanesulfonamide, *t*-BuOH/H_2O (1:1), 0 °C, 73 h (75%, 92% ee); (b) TBSOTf, 2,6-lutidine, −78 °C, 30 min (87%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 30 min (83%); (d) (1) (*S*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [76% from (−)-**14**]; (e) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (76%).

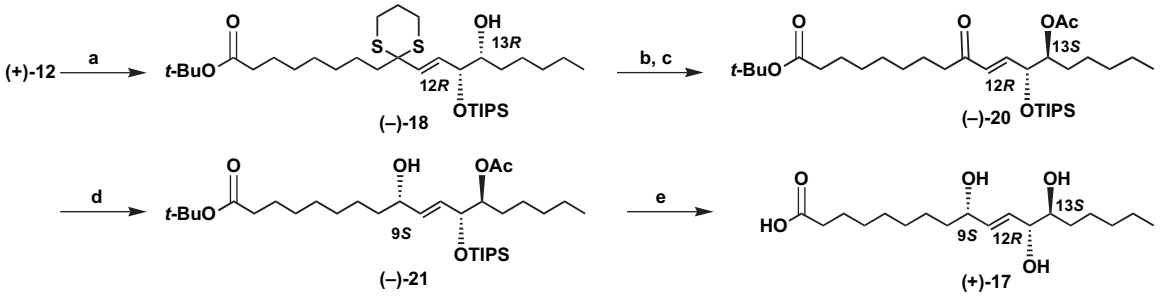
and (+)-**5** containing the *syn* configuration at C12–C13 is required. To construct the C9 hydroxy group, (*R*)-BINAL-H would be applied to the corresponding intermediates (+)-**14** and (−)-**14**.[12] As expected, stereoselective reduction (diastereoselectivity >20:1) followed by deprotection of the TBS group gave the (9*R*)-alcohol. Finally, hydrolysis according to the above procedure furnished (+)-**4** and (−)-**5** successfully (Scheme 5).

3.6. Synthesis of 17

The C12–C13 *anti*-isomers were also constructed in order to investigate structure–activity relationships. The key step is regioselective protection of the C12 hydroxy group in the C12–C13 *syn*-diol followed by inversion of the C13 hydroxy group. The preparation of **17** (9*S*,12*R*,13*S*) is shown in Scheme 6. The protecting groups were selected carefully because only one hydroxy group (C12 or C13) should be protected. The C12 hydroxy group is more reactive than C13 due to its allylic position, therefore, the chemoselective protection of the C12 hydroxy group in (+)-**12** was attempted. Installation of a TBS group only on the C12 hydroxy group was problematic even at low temperature with slow addition of reagent (C12 *O*-TBS: 75%, C13 *O*-TBS: 18%). The use of the more bulky TIPS group successfully provided C12 *O*-TIPS (−)-**18**[12] in good yield (90%), with no formation of the C13 *O*-TIPS compound.



Scheme 5. Synthesis of (+)-**4** and (−)-**5**. Reagents and conditions: (a) (1) (*R*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1); (2) TBAF, THF, 70 °C, 3 h [63% from (+)-**14**]; (b) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (67%); (c) (1) (*R*)-BINAL-H, THF, −78 °C, 1 h (diastereoselectivity >20:1), (2) TBAF, THF, 70 °C, 3 h [57% from (−)-**14**]; (d) 2.0 N KOH in EtOH/H_2O (5:1), rt, 46 h (51%).



Scheme 6. Synthesis of (+)-**17**. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 8 h (90%); (b) (1) $ClCH_2SO_2Cl$, pyridine, 0 °C, 2 h; (2) CsOAc, 18-crown-6, benzene, 80 °C, 20 h (83%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 5 min (97%); (d) (*S*)-BINAL-H, THF, −78 °C, 90 min (99%, dr >20:1); (e) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, rt, 45 h (94%).

Next, we attempted inversion of the hydroxy group at C13. Failure of the normal conditions for Mitsunobu inversion[16] (DEAD, benzoic acid, PPh_3) necessitated the use of the new Mitsunobu conditions[17] (TMAD, *p*-nitrobenzoic acid, PBu_3), which gave the (13*S*)-compound in 55% yield. Unfortunately, this method presents difficulties for large-scale synthesis. We next attempted a stepwise reaction to construct a leaving group before inversion by nucleophilic attack. While a methanesulfonyl group would be ideal as a leaving group, Corey's conditions[18] using K_2O are too strong to get an inversion product. Fortunately, a small conversion with CsOAc provided an insight in the search for another leaving group. On the basis of this information, Nakata's method,[19] using a monochloromethanesulfonyl group ($ClSO_2CH_2Cl$, pyridine) followed by treatment with CsOAc, gave the protected C12–C13 *anti*-diol (−)-**19** in good yield.

In order to derive the alcohol group from the ketone, deprotection of the dithioacetal furnished enone (−)-**20**. The stereoselective reduction of the ketone at C9 in (−)-**20** required the reoptimization of reaction conditions due to the presence of the bulky *O*-TIPS group. While (*R*)-CBS reduction furnished (−)-**21**[12] in good selectivity (diastereoselectivity 16:1), (*S*)-BINAL-H was found to be more efficient[12] (diastereoselectivity >20:1). Finally deprotection of the acetyl and *tert*-butyl groups by hydrolysis and desilylation with TBAF gave (+)-**17** (Scheme 6).

3.7. Synthesis of the remaining stereoisomers

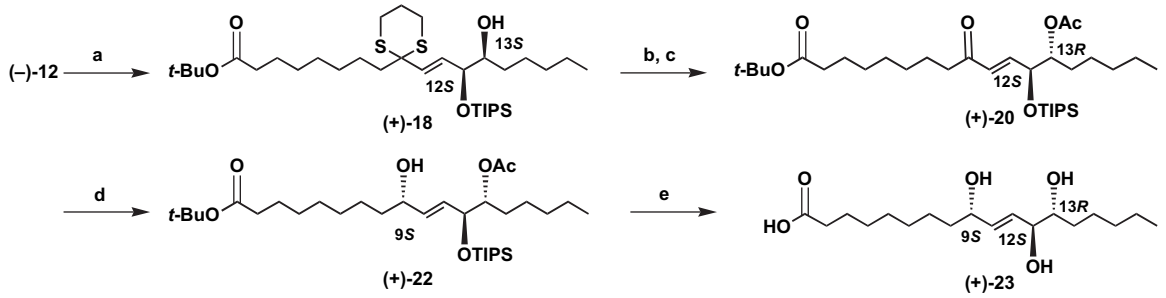
Synthesis of (+)-**23** with 9*S*,12*S*,13*R* stereocenters was accomplished according to the following synthetic route, utilizing (−)-**12** as the starting material (Scheme 7). It should be noted that the stereoselectivity of the (*S*)-BINAL reduction of (+)-**20** was lower than that of (−)-**20** (diastereoselectivity 13:1). The reason for this phenomenon is explained by the steric hindrance of the C12 *O*-TIPS group. With the completion of the syntheses for the C12–C13 *anti*-diols as shown in Schemes 7 and 8, all the stereoisomers of pinellic acid have now been prepared from their corresponding intermediates.[12]

4. Stereochemistry of the allylic 1,2-diol

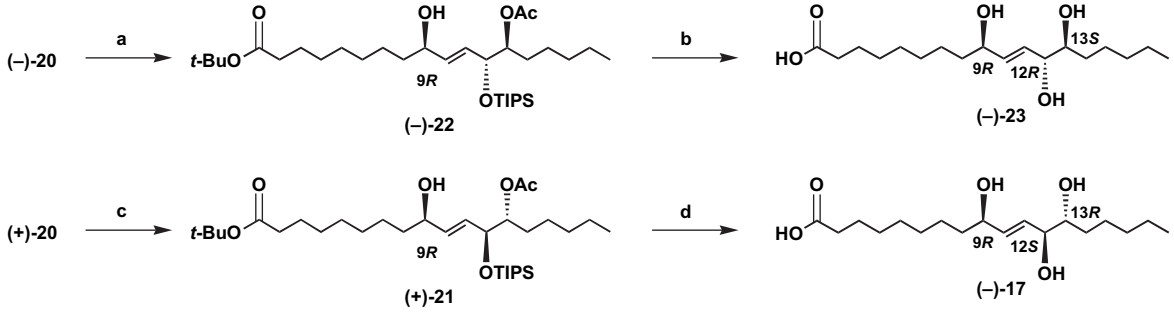
The syntheses of both allylic *syn*- and *anti*-1,2-diols of pinellic acid have been established and it is critical for the stereochemistries of the C12–C13 diols to be confirmed. The protection of the C12–C13 diol of (+)-**12** with 2-methoxypropene and CSA afforded (+)-**24**. In the ^1H NMR spectrum, an NOE between H11 and H13 resonances is observed, suggesting that H12 and H13 of (+)-**24** are antiperiplanar (Scheme 9, Fig. 6).

Deprotection of the OAc and *O*-TIPS groups in (−)-**19** afforded (+)-**26**. This was followed by acetalization of the C12–C13 diol to give (+)-**27**. In the ^1H NMR spectrum, while there is an NOE between protons H11 and H12, there is no NOE between protons H11 and H13, indicating that H12 and H13 of (+)-**27** are synperiplanar (Scheme 10, Fig. 7).

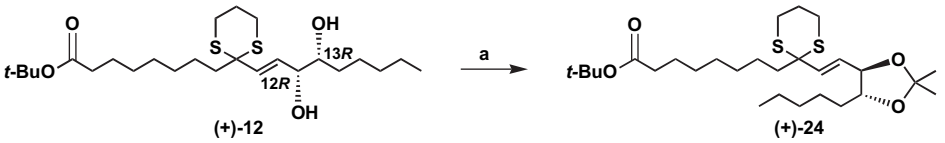
These studies have established a new method to determine the configuration of allylic 1,2-diols.



Scheme 7. Synthesis of (+)-**23**. Reagents and conditions: (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 8 h (79%); (b) (1) $ClCH_2SO_2Cl$, pyridine, 0 °C, 1 h; (2) CsOAc, 18-crown-6, benzene, 80 °C, 20 h (75%); (c) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (5:1), rt, 5 min (89%); (d) (*S*)-BINAL-H, THF, −78 °C, 1 h (99%, dr 13:1); (e) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (98%).



Scheme 8. Synthesis of (−)-**23** and (−)-**17**. Reagents and conditions: (a) (*R*)-BINAL-H, THF, −78 °C, 1 h (82%, dr 13:1); (b) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (94%); (c) (*R*)-BINAL-H, THF, −78 °C, 1 h (98%, dr >20:1); (d) (1) 1.0 N KOH in EtOH/H_2O (4:1), rt, 5 days; (2) TBAF, THF, 45 h (18%).



Scheme 9. Synthesis of (+)-**24**. Reagents and conditions: (a) 2-methoxypropene, CSA, CH_2Cl_2, 0 °C, 5 min (96%).

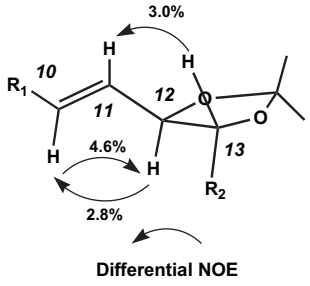


Figure 6. NOE analysis of (+)-**24**.

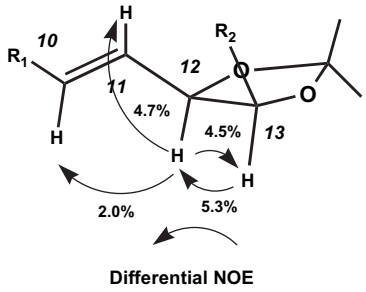


Figure 7. NOE analysis of (+)-**27**.

5. Comparison of spectral data of all the stereoisomers of pinellic acid

Comparison of the ^{1}H NMR spectra of all synthetic stereoisomers of pinellic acid (Fig. 8) shows a relationship between the stereochemistry and the pattern of the ^{1}H NMR resonances. Focusing on the peaks of C12–C13 diol, the H13 proton in the *syn*-diol is at higher field than in the *anti*-diol. Moreover, the peak patterns of H10 and H11 are opposite in the *anti*- and *syn*-diols. The relationship between the stereochemistry of C9 and C12 and the coupling pattern of H10 and H11 is also interesting. When the configuration of C9 and C12 is the same (*S*,*S* or *R*,*R*), the chemical shifts of H10 and H11 (two doublet of doublets) are very close. When the configuration is different, the chemical shifts of H10 and H11 are further apart.

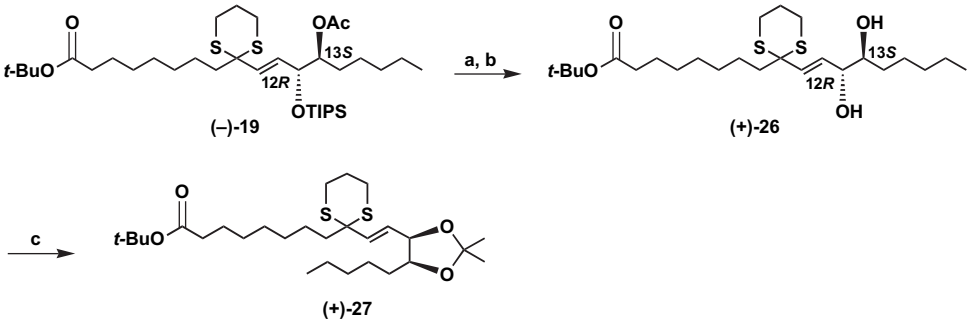
This type of information could never have been discovered until all the stereoisomers had been synthesized. Syntheses of fatty acids like pinellic acid could contribute to the determination of stereochemistry of molecules of the same type as **1**.[6]

6. Adjuvant activity of all the stereoisomers of pinellic acid

The oral administration of pinellic acid analogs as an adjuvant for the intranasal inoculation of influenza HA vaccine was investigated. Mice were orally administered with pinellic acid analogs (1 g/mouse) using intragastric gavage followed by the intranasal inoculation of HA vaccine (1 g/mouse). Three weeks later, the same procedure was repeated. The IgA and IgG antibody responses against anti-influenza virus in the nasal cavity and serum in the vaccinated mice were examined one week after vaccination. The results of the adjuvant activity of all stereoisomers are shown in Figure 9.[20]

The antiviral IgA and IgG antibody responses, induced in the nasal cavities of mice given pinellic acid (−)-**1** with vaccine, were enhanced 5.2- and 2-folds, respectively, compared with control mice given the vaccine and solvent alone. Among the C9 isomers of pinellic acid, the (9*S*)-compounds showed much stronger activity compared with the (9*R*)-compounds. Thus, stereochemistry at the C9 hydroxyl group is critical for adjuvant activity. Among the (9*S*)-derivatives, the adjuvant activities of the C13 (*S*)-compounds were stronger than that of the C13 (*R*)-compounds, while the stereochemistry of the C12 hydroxyl group was not important for adjuvant activity. It is interesting that the adjuvant activity of the enantiomer of natural pinellic acid is weaker than that of the natural one.

Also, in the data shown in Figure 9, the adjuvant activity of pinellic acid (−)-**1** from a natural source was lower than that of the synthetic one. This result is presumably due to the chemical purity of the available sample.



Scheme 10. Synthesis of (+)-**27**. Reagents and conditions: (a) KO*t*-Bu, *t*-BuOH, rt, 16 h (47%); (b) TBAF, THF, rt, 16 h (97%); (c) 2-methoxypropene, CSA, CH_2Cl_2, 0 °C, 20 min (98%).

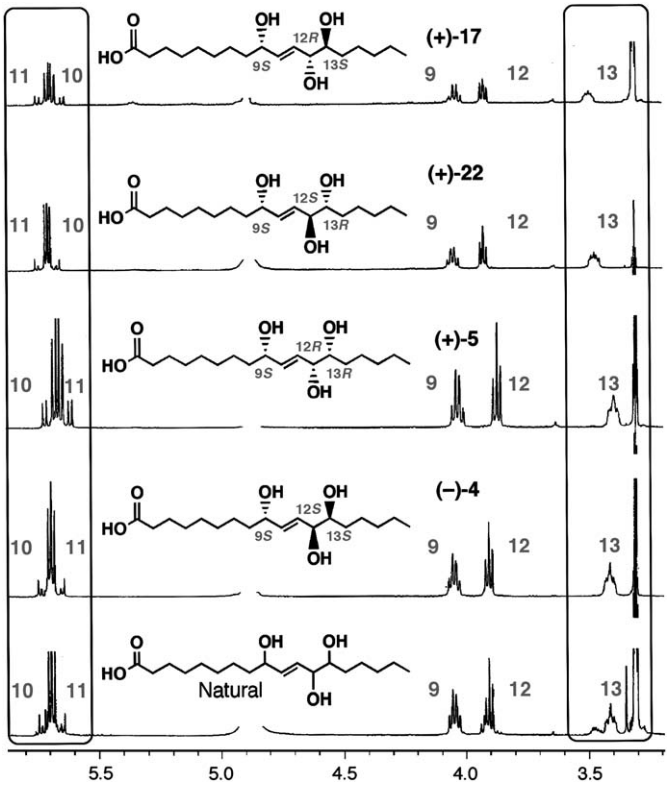


Figure 8. ^{1}H NMR spectra of all stereoisomers of pinellic acid.

In conclusion, we have established synthetic routes to prepare all the stereoisomers of **1** via regioselective asymmetric dihydroxylation, stereoselective inversion, and stereoselective reduction. In this series, the (9*S*,12*S*,13*S*)-compound has the most potent adjuvant activity. Studies on the mechanism of adjuvant and protective effects of

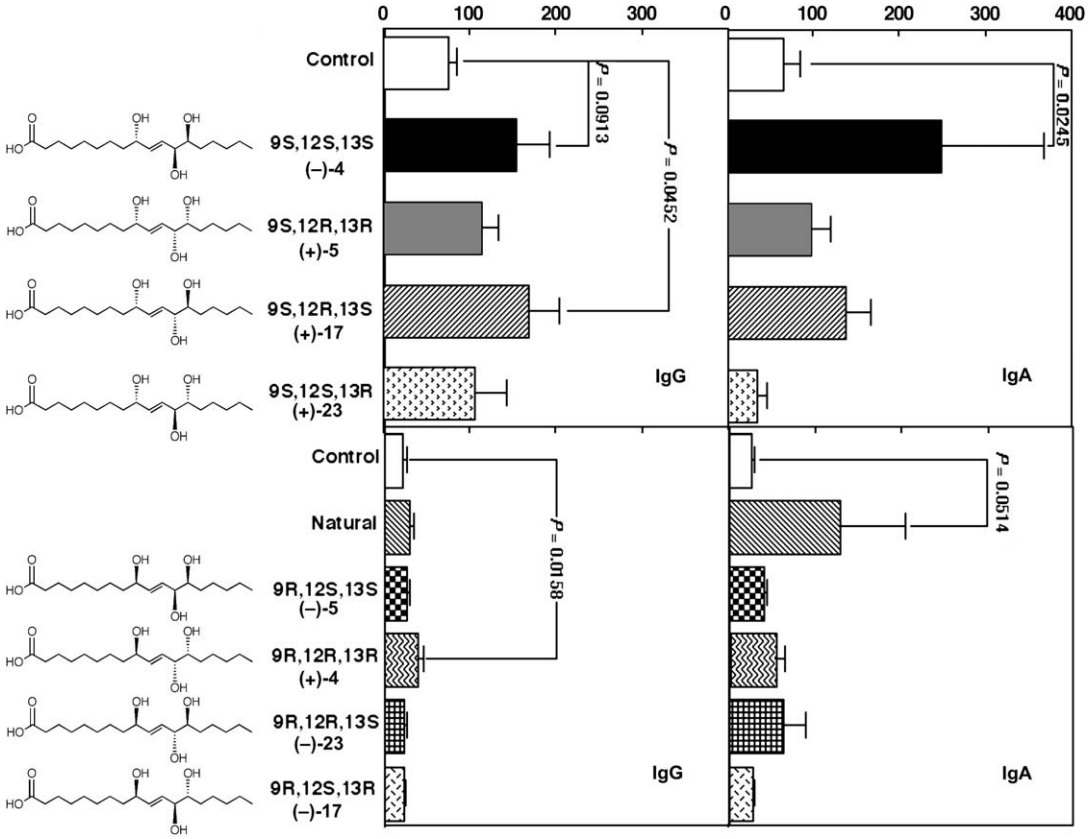


Figure 9. Anti-influenza virus antibody titer (fluorescence intensity).

pinellic acid with nasal influenza HA vaccine against influenza virus infection are currently under way.

7. Experimental

7.1. General

Dry THF, toluene, ethyl ether, and CH_2Cl_2 were purchased from Kanto Chemical Co. Precoated silica gel plates with a fluorescent indicator (Merck 60 F_{254}) were used for analytical and preparative thin-layer chromatography. Flash column chromatography was carried out with Merck silica gel 60 (Art. 1.09385). ^1H and ^{13}C NMR spectra were measured on JEOL JNM-EX270 (270 MHz) or Varian VXR-300 (300 MHz) or Varian XL-400 (400 MHz) or Varian UNITY-400 (400 MHz). All infrared spectra were measured on a Horiba FT-210 spectrometer. Melting points were measured on a Yanagimoto Micro Melting Apparatus. High- and low-resolution mass spectra were measured on a JEOL JMS-DX300 and JEOL JMS-AX505 HA spectrometer. Elemental analysis data were measured on a Yanaco CHN CORDER MT-5.

7.2. Estimation of absolute stereochemistry of 1

7.2.1. 12,13-*O*-Isopropylidene-9,12,13-trihydroxyoctadecaenoic acid methyl ester (2). To a solution of pinellic acid (**1**, 9.6 mg, 29 μmol) in benzene/MeOH (10:1) (2.2 mL) was added $TMSCHN_2$ (2.0 M solution in hexane, 29 μL, 58 μmol) and stirred at rt for 2.5 h, after that time the solution was concentrated. To the solution of residue in CH_2Cl_2 (0.6 mL) were added 2,2-dimethoxypropane (14 μL, 0.12 mmol) and PPTS (7.3 mg, 29 μmol), and then stirred at 60 °C for 48 h. The solution was cooled to rt and treated with H_2O (500 μL) followed by extraction with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (3 mL), dried, and evaporated, and the residue was purified by column chromatography (hexane/AcOEt=7:1) to give **2** (11 mg, 100%) as a colorless oil. R_f=0.48 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{28}$ 0.00 (*c* 0.15, MeOH); IR (KBr) ν cm^{-1}: 3452, 1741; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.84 (dd, *J*=15.5, 5.6 Hz, 1H), 5.65 (dd, *J*=15.5, 7.1 Hz, 1H), 4.16 (m, 1H), 4.00 (dd, *J*=8.0, 7.1 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 2.30 (t, *J*=7.6 Hz, 2H), 1.63–1.24 (m, 20H), 1.412, 1.405 (s, 3H each), 0.89 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.4, 137.9, 127.4, 108.4, 81.8, 80.9, 71.8, 51.4, 37.1, 34.1, 31.9, 31.9, 29.3, 29.14, 29.05, 27.3, 27.0, 25.8, 25.2, 24.9, 22.5, 14.0; HRMS (FAB, NBA matrix) *m/z*: 407.2742 $[M+Na]^+$, Calcd for $C_{22}H_{40}O_5Na$: 407.2773 [M+Na].

7.2.2. 9-(4-Bromobenzoyloxy)-12,13-*o*-isopropylidene-12,13-dihydroxyoctadecaenoic acid methyl ester (3). To a solution of **2** (1.0 mg, 2.6 μmol) in pyridine were added *p*-bromobenzoyl chloride (5.5 mg, 26 μmol) and DMAP (0.3 mg, 26 μmol), and then stirred at rt for 10 h. The resulting mixture was treated with H_2O (0.5 mL) and extracted with $CHCl_3$ (3 mL×3). The organic layer was washed with satd aq NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=5:1) to give **3** (1.0 mg, 68%) as a colorless oil. R_f=0.60 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{22}$ −10.0 (*c* 0.06, $CHCl_3$); CD (*c* 5.3×10^{-5}, MeOH) λ_{max} ($\Delta\varepsilon$): 244.8 (+6.97), 220.8 (+2.13), 209.1 (+5.97); IR (KBr) ν cm^{-1}: 1724, 1633; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, *J*=8.9 Hz, 2H), 7.58 (d, *J*=8.9 Hz, 2H), 5.84 (dd, *J*=15.2 Hz, 1H), 5.76 (dd, *J*=15.2, 6.8 Hz, 1H), 5.50 (dt, *J*=7.0, 6.0 Hz, 1H), 3.99 (dd, *J*=8.5, 6.8 Hz, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 2.29 (t, *J*=7.9 Hz, 2H), 1.21–1.79 (m, 20H), 1.41, 1.40 (s, 3H each), 0.88 (t, *J*=6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.9, 131.7 (2C), 131.1 (2C), 130.7, 81.6, 80.8, 74.7, 51.4, 34.3, 34.0, 31.9, 31.9, 29.3, 29.2 (2C), 27.3, 27.0, 25.6, 25.0, 24.9, 22.5, 14.0; HRMS (FAB, NBA matrix), *m/z*: 589.2149 $[M+Na]^+$, Calcd for $C_{29}H_{43}O_6BrNa$: 589.2141 [M+Na].

7.3. Total synthesis

7.3.1. Synthesis of C18 skeleton.

7.3.1.1. *tert*-Butyl-7-methoxycarbonylheptanoate (7). To a solution of suberic acid monomethyl ester (**6**, 5.00 mL, 5.24 g, 27.8 mmol) in *t*-BuOH (56 mL) were added $(Boc)_2O$ (9.58 mL, 41.7 mmol) and DMAP (1.02 g, 0.34 mmol). The mixture was stirred at rt for 1 h. The resulting mixture was treated with 0.2 N HCl (20 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give **7** (5.58 g, 82%) as a colorless oil. R_f=0.41(silica gel, hexane/AcOEt=5:1); IR (KBr) ν cm^{-1}: 1734; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.62 (s, 3H), 2.26 (t, *J*=7.3 Hz, 2H), 2.16 (t, *J*=7.3 Hz, 2H), 1.51–1.61 (complex m, 4H), 1.40 (s, 9H), 1.31–1.21 (complex m, 4H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 174.1, 173.0, 79.8, 51.3, 35.4, 33.9, 28.7, 28.6, 28.0 (3C), 24.8, 24.7; HRMS (FAB NBA matrix) *m/z*: 245.1750 $[M+H]^+$, Calcd for $C_{13}H_{25}O_4$: 245.1753 [M+H].

7.3.1.2. *tert*-Butyl-8-iodooctanoate (8). To a solution of 1.5 N NaOH in MeOH/H_2O/THF (3:1:1) (113 mL) was added **7** (5.51 g, 22.6 mmol) and stirred at rt for 28 h. The mixture was treated with 1.0 N HCl (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated.

The residue was dissolved in THF (41.6 mL) at 0 °C. To the mixture was added BH_3·THF (1.0 M solution in THF, 20.8 mL), after that time, the solution was warmed up to rt and stirred at rt for 12 h. The resulting mixture was treated with satd aq $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated.

The residue was dissolved in CH_2Cl_2 (100 mL) at 0 °C. To the mixture were added imidazole (2.10 g, 30.9 mmol), PPh_3 (8.10 g, 30.9 mmol), and I_2 (6.27 g, 24.7 mmol), after that time, the solution was warmed up to rt and stirred at rt for 2 h. The resulting mixture was treated with satd aq $NaHCO_3$ (50 mL) and extracted with $CHCl_3$ (50 mL×3). The organic layer was washed with H_2O (50 mL), 0.1 N Na_2SO_3 soln (50 mL), 30% aq H_2O_2 (50 mL), satd aq NaCl (50 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give **8** (5.53 g, 77% from **7**) as

a colorless oil. R_f=0.47 (silica gel, hexane/AcOEt=4:1); IR (KBr) ν cm^{-1}: 1730; ^1H NMR (270 MHz, $CDCl_3$) δ: 3.18 (t, J=7.3 Hz, 2H), 2.20 (t, J=7.6 Hz, 2H), 1.76–1.87 (complex m, 2H), 1.53–1.60 (complex m, 2H), 1.44 (s, 9H), 1.26–1.41 (complex m, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.0, 79.8, 35.4, 33.3, 30.2, 29.0, 28.7, 28.1, 28.0 (3C), 24.9; HRMS (EI) m/z: 326.0763 $[M]^+$, Calcd for $C_{12}H_{23}O_2I$: 326.0743 [M].

7.3.1.3. (*E*,*E*)-1-(1,3-Dithian)-2,4-decadiene (10). To a solution of (*E*,*E*)-2,4-decadienal (**9**, 21.4 g, 25.0 mL, 141 mmol) in CH_2Cl_2 (140 mL) at 0 °C were added 1,3-propanedithiol (18.3 g, 17.0 mL, 169 mmol) and $BF_3\cdot Et_2O$ (3.92 g, 3.40 mL, 27.6 mmol), and then the reaction mixture was warmed up to rt, stirred for 12 h. The resulting mixture was treated with satd aq $NaHCO_3$ (200 mL) and extracted with $CHCl_3$ (100 mL×3). The organic layer was washed with satd aq NaCl (100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give **10** (32.7 g, 96%) as a colorless oil. R_f=0.52 (silica gel, hexane/AcOEt=5:1); IR (KBr) ν cm^{-1}: 1653; ^1H NMR (270 MHz, $CDCl_3$) δ: 6.34 (dd, J=15.2, 10.6 Hz, 1H), 5.99 (dd, J=15.2, 10.6 Hz, 1H), 5.73 (dt, J=15.2, 7.2 Hz, 1H), 5.59 (dd, J=15.2, 7.9 Hz, 1H), 4.66 (d, J=7.9 Hz, 1H), 2.96–2.79 (complex m, 4H), 2.23–2.02 (complex m, 3H), 1.91–1.77 (m, 1H), 1.39–1.19 (complex m, 6H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 137.3, 133.9, 128.8, 126.8, 47.6, 32.8, 31.3, 30.2 (2C), 29.0, 25.1, 22.5, 14.0; HRMS (EI) m/z: 242.1169 $[M]^+$, Calcd for $C_{13}H_{22}O_2$: 242.1163 [M].

7.3.1.4. (*E*,*E*)-9-(1,3-Dithian)-10,12-octadecadienoic acid-*tert*-butyl ester (11). To a solution of **10** (200 μL, 206 mg, 0.851 mmol) in THF (8.5 mL) was added *n*-BuLi (1.53 M solution in hexane, 612 μL, 0.936 mmol) at −78 °C dropwise (ca. 15 min). The resulting mixture was stirred at −78 °C for 1 h followed by the addition of **8** (327 μL, 416 mg, 1.28 mmol) in one portion. The reaction mixture was stirred at −78 °C for 1 h, after that time, the solution was treated with satd aq NH_4Cl (10 mL) and extracted with AcOEt (10 mL×3). The organic layer was washed with satd aq NaCl (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give **11** (318 mg, 85%) as a colorless oil. R_f=0.36 (silica gel, hexane/AcOEt=20:1, twice); IR (KBr) ν cm^{-1}: 1730, 1695; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.39 (dd, J=15.2, 10.4 Hz, 1H), 6.12 (dd, J=14.9, 10.4 Hz, 1H), 5.76 (dt, J=14.9, 7.2 Hz, 1H), 5.54 (d, J=15.2 Hz, 1H), 2.88 (ddd, J=14.0, 11.2, 2.5 Hz, 2H), 2.64 (ddd, J=14.0, 5.2, 3.0 Hz, 2H), 2.18 (t, J=7.2 Hz, 2H), 2.12–2.06 (m, 2H), 2.05–1.98, 1.93–1.91 (m, 1H each), 1.82–1.78 (m, 2H), 1.59–1.52 (m, 2H), 1.47–1.36 (complex m, 4H), 1.44 (s, 9H), 1.34–1.19 (complex m, 10H), 0.89 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 173.2, 135.5, 133.8, 133.6, 129.0, 79.8, 54.9, 42.3, 35.5, 32.6, 31.4, 29.5, 29.0 (2C), 28.9, 28.1 (3C), 27.2 (2C), 25.5, 25.0, 23.7, 22.5, 14.0; HRMS (EI) m/z: 440.2779 $[M]^+$, Calcd for $C_{25}H_{44}O_2S_2$: 440.2783 [M].

7.3.2. Synthesis of (9*S*,12*S*,13*S*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((−)-4).

7.3.2.1. (12*S*,13*S*)-(*E*)-12,13-Dihydroxy-9-(1,3-dithian)-10-octadecaenoic acid-*tert*-butyl ester ((−)-12). A well-stirred solution of (DHQ)PHAL(DHQ)$Me^+\cdot I^-$ (10.0 mg, 11.0 μmol), $K_3[Fe(CN)_6]$ (264.4 mg, 0.803 mmol), K_2CO_3 (110.8 mg, 0.803 mmol), and $K_2OsO_4\cdot 2H_2O$ (4.0 mg, 0.011 mmol) in *t*-BuOH/H_2O (1:1) (2.6 mL) was treated with methanesulfonamide (25.5 mg, 0.268 mmol) at ambient temperature. The clear yellow solution was cooled to 0 °C and **11** (117.8 mg, 0.268 mmol) was added. The solution was stirred vigorously at 0 °C for 40 h 50 min and then quenched with solid Na_2SO_3 (50 mg), warmed to ambient temperature, and stirred for further 30 min. The resultant mixture was extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (−)-**12** (81.2 mg, 64%, 95% ee) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ −4.5 (*c* 1.08, $CHCl_3$); IR (KBr) ν cm^{-1}: 3421, 1730, 1628; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.91 (dd, J=15.5, 6.6 Hz, 1H), 5.75 (d, J=15.5 Hz, 1H), 4.04 (dd, J=6.6, 5.3 Hz, 1H), 4.01–3.00 (m, 1H), 2.87 (ddd, J=14.2, 11.5, 2.6 Hz, 2H), 2.68–2.63 (m, 2H), 2.35 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, J=7.3 Hz, 2H), 2.06–2.01 (m, 2H), 1.93–1.88 (m, 2H), 1.67–1.28 (complex m, 18H), 1.44 (s, 9H), 0.89 (t, J=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.8, 136.5, 133.6, 80.4, 75.9, 75.1, 54.7, 42.4, 35.9, 33.5, 32.3, 29.8, 29.4, 29.3, 28.5 (3C), 27.5 (2C), 25.8, 25.6, 25.4, 24.0, 22.9, 14.4; HRMS (FAB, NaI matrix), m/z: 497.2743 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

7.3.2.2. (12*S*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-13). To a solution of (−)-**12** (372 mg, 0.787 mmol) in CH_2Cl_2 (7.9 mL) were added 2,6-lutidine (916 μL, 7.87 mmol) and TBSOTf (900 μL, 3.93 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min. The resultant mixture was treated with H_2O (1 mL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=100:1) to give (−)-**13** (489 mg, 89%) as a colorless oil. R_f=0.60 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ −24.1 (*c* 1.01, $CHCl_3$); IR (KBr) ν cm^{-1}: 3442, 1731, 1630; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.98 (dd, J=15.2, 6.6 Hz, 1H), 5.59 (d, J=15.8 Hz, 1H), 4.24 (m, 1H), 3.59 (m, 1H), 2.98–2.87 (complex m, 1H), 2.86–2.64 (complex m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.00–1.87 (complex m, 2H), 1.80 (m, 2H), 1.44 (s, 9H), 1.67–1.14 (complex m, 18H), 0.91–0.86 (complex m, 21H), 0.11–0.03 (m, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 133.4, 133.0, 79.9, 75.5, 75.0, 55.0, 42.3, 35.6, 31.9, 31.1, 29.6, 29.1 (2C), 28.1 (3C), 27.1, 27.0, 26.0, 25.8 (3C), 25.7, 25.1, 23.7, 22.5, 18.2, 18.0, 14.0, −4.1, −4.6 (2C), −4.8; HRMS (FAB, NBA matrix), m/z: 701.4539 $[M]^+$, Calcd for $C_{37}H_{74}O_4Si_2S_2$: 702.4534 [M].

7.3.2.3. (12*S*,13*S*)-(*E*)-9-Oxo-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-14). To a mixture of (−)-**13** (494 mg, 0.704 mmol) and $CaCO_3$ (141 mg, 1.41 mmol) in THF (14 mL) was added a solution of $Hg(ClO_4)_3$ (638 mg, 1.41 mmol) in H_2O (2.8 mL) dropwise. The resultant mixture was stirred at rt for 30 min, and then diluted with ether (5 mL). This mixture was filtered through Celite. The residue was concentrated and dissolved in $CHCl_3$ (5 mL). This solution was washed with satd aq

NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**14** (357 mg, 83%) as a colorless oil. R_f=0.55 (silica gel, hexane/AcOEt=6:1); $[\alpha]_D^{27}$ −49.7 (*c* 0.99, $CHCl_3$); IR (KBr) ν cm^{-1}: 1733, 1677, 1633; ^1H NMR (270 MHz, $CDCl_3$) δ: 6.97 (dd, *J*=16.2, 3.6 Hz, 1H), 6.29 (d, *J*=16.2 Hz, 1H), 4.31 (m, 1H), 3.61 (m, 1H), 2.55 (t, *J*=7.3 Hz, 2H), 2.19 (t, *J*=7.6 Hz, 2H), 1.44 (s, 9H), 1.67–1.18 (complex m, 18H), 0.92–0.89 (complex m, 18-H_3), 0.09–0.03 (m, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 201.2, 173.7, 146.4, 129.8, 80.3, 76.2, 75.0, 40.7, 36.0, 32.2, 31.6, 29.6 (2C), 29.4, 28.6 (3C), 26.4, 26.3 (3C), 26.2 (3C), 25.5, 24.9, 23.0, 18.6, 18.4, 14.4, −3.8, −4.0, −4.3 (2C), −4.4.

7.3.2.4. (9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-15). To a solution of (−)-**14** (349.0 mg, 0.570 mmol) in THF (11 mL) was added (*S*)-BINAL-H (0.5 M solution in THF, 7.52 mL, 3.76 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 2 h 30 min. The resultant mixture was treated with 1.0 N HCl (10 mL) and extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with 1.0 N NaOH (20 mL), satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in THF (5.8 mL) at rt. To the mixture was added TBAF (1.0 M solution in THF, 1.25 mL, 1.25 mmol) and stirred at 70 °C for 3 h. This resultant mixture was treated with H_2O (1.0 mL) and extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (toluene/AcOEt=2:1) to give (−)-**15** (168.1 mg, 76%) as a colorless oil. R_f=0.29 (silica gel, toluene/AcOEt=1:2); $[\alpha]_D^{27}$ −8.8 (*c* 0.16, $CHCl_3$); IR (KBr) ν cm^{-1}: 3305, 1727; ^1H NMR (270 MHz, $CDCl_3$) δ: 5.83 (dd, *J*=15.5, 5.6 Hz, 1H), 5.67 (dd, *J*=15.5, 5.9 Hz, 1H), 4.15 (dd, *J*=12.2, 5.9 Hz, 1H), 3.94 (t, *J*=5.93 Hz, 1H), 3.47 (m, 1H), 2.34 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, *J*=7.6 Hz, 2H), 1.63 (m, 2H), 1.44 (s, 9H), 1.52–1.30 (complex m, 18H), 0.98 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.2, 129.7, 79.9, 75.3, 74.6, 72.0, 37.1, 35.6, 32.9, 31.8, 29.2, 29.1, 28.9, 28.1, 25.3, 25.2, 25.0, 22.6, 14.0; HRMS (FAB, NBA matrix), *m/z*: 409.2913 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.2.5. (9*S*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-4). To a solution of 2.0 N KOH in EtOH/H_2O (4:1) (500 μL) was added (−)-**15** (6.5 mg, 16.8 μmol) and stirred at rt for 46 h. The mixture was cooled to 0 °C, treated with 1.0 N HCl (500 μL), and extracted with $CHCl_3$ (2 mL×3). The organic layer was washed with satd aq $NaHCO_3$ (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography ($CHCl_3$/MeOH=10:1) to give (−)-**4** (4.5 mg, 82%) as a white solid. R_f=0.24 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 104–106 °C (MeOH); $[\alpha]_D^{25}$ −8.0 (*c* 0.30, MeOH), {natural; $[\alpha]_D^{28}$ −8.1 (*c* 0.32, MeOH)}; IR (KBr) ν cm^{-1}: 3372 (s), 1695 (m), 1637 (m); ^1H NMR (400 MHz, CD_3OD) δ: 5.72 (dd, *J*=15.5, 5.0 Hz, 1H), 5.67 (dd, *J*=15.5, 5.0 Hz, 1H), 4.05 (ddd, *J*=6.5, 6.0, 5.0 Hz, 1H), 3.91 (dd, *J*=5.5, 5.0 Hz, 1H), 3.41 (ddd, *J*=8.5, 5.5, 2.5 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 4H), 1.45–1.25 (m, 14H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.8, 136.6, 131.1, 76.5, 75.8, 73.0, 38.3, 35.0, 33.6, 33.1, 30.5, 30.4, 30.2, 26.6, 26.5, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2305 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na]; Anal. Calcd for $C_{18}H_{34}O_5 \cdot 1/2H_2O$: C, 63.69; H, 10.39. Found: C, 63.77; H, 10.03.

7.3.3. Synthesis of (9*S*,12*R*,13*R*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-5).

7.3.3.1. (12*R*,13*R*)-(*E*)-12,13-Dihydroxy-9-(1,3-dithian)-10-octadecaenoic acid-*tert*-butyl ester ((+)-12). A well-stirred solution of AD-mix-β (1.68 g) in *t*-BuOH/H_2O (1:1) (1.2 mL) was treated with methanesulfonamide (25.5 mg, 0.268 mmol) at ambient temperature. The clear yellow solution was cooled to 0 °C and **11** (528 mg, 1.20 mmol) was added. The solution was stirred vigorously at 0 °C for 73 h and then quenched with solid Na_2SO_3 (500 mg), warmed to ambient temperature, and stirred for further 30 min. The resultant mixture was extracted with $CHCl_3$ (20 mL×3). The organic layer was washed with satd aq NaCl (20 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (+)-**12** (424 mg, 75%) as a colorless oil. $[\alpha]_D^{24}$ +5.2 (*c* 1.08, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 497.2740 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

7.3.3.2. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-13). According to the synthesis of (−)-**13**, (+)-**12** (77.9 mg) gave (+)-**13** (115 mg, 87%) as a colorless oil. $[\alpha]_D^{27}$ +22.4 (*c* 0.41, $CHCl_3$); HRMS (FAB, NBA matrix), *m/z*: 701.4534 $[M]^+$, Calcd for $C_{37}H_{74}O_4Si_2S_2$: 704.4534 [M].

7.3.3.3. (12*R*,13*R*)-(*E*)-9-Oxo-12,13-di-*tert*-butyldimethylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-14). According to the synthesis of (−)-**14**, (+)-**13** (93.8 mg) gave (+)-**14** (67.4 mg, 83%) as a colorless oil. $[\alpha]_D^{27}$ +22.4 (*c* 0.41, $CHCl_3$).

7.3.3.4. (9*S*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-16). According to the synthesis of (−)-**15**, (+)-**14** (26.1 mg) gave (+)-**16** (12.4 mg, 76%) as a colorless oil. R_f=0.20 (silica gel, toluene/AcOEt=1:2), $[\alpha]_D^{28}$ +7.4 (*c* 0.19, $CHCl_3$); IR (KBr) ν cm^{-1}: 3392 (s), 1732 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.83 (dd, *J*=15.5, 5.6 Hz, 1H), 5.67 (dd, *J*=15.5, 5.9 Hz, 1H), 4.15 (dd, *J*=12.2, 5.9 Hz, 1H), 3.94 (1H, t, *J*=5.93 Hz, 1H), 3.47 (m, 1H), 2.34 (br s, 1H), 2.26 (br s, 1H), 2.19 (t, *J*=7.6 Hz, 2H), 1.63 (m, 2H), 1.44 (s, 9H), 1.52–1.30 (complex m, 18H), 0.98 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.2, 129.7, 79.9, 75.3, 74.6, 72.0, 37.1, 35.6, 32.9, 31.8, 29.2, 29.1, 28.9 (2C), 28.1 (3C), 25.3, 25.2, 25.0, 22.6, 14.0; HRMS (FAB, NBA matrix), *m/z*: 409.2913 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.3.5. (9*S*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-5). According to the synthesis of (−)-**4**, (+)-**16** (12.4 mg) gave (+)-**5** (8.1 mg, 76%) as a white solid. R_f=0.23 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 68–71 °C (MeOH); $[\alpha]_D^{23}$ +29.8 (*c* 0.45, MeOH); IR (KBr) ν cm^{-1}: 3430 (s), 1697 (m), 1632 (m); ^1H NMR (400 MHz, CD_3OD) δ: 5.70 (dd, *J*=15.5, 5.5 Hz, 1H), 5.64 (dd,

J=15.5, 6.0 Hz, 1H), 4.03 (ddd, J=6.5, 6.0, 5.5 Hz, 1H), 3.87 (dd, J=6.0, 5.5 Hz, 1H), 3.40 (ddd, J=7.0, 5.5, 2.0 Hz, 1H), 2.27 (t, J=7.5 Hz, 2H), 1.60 (dt, J=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 4H), 1.44–1.25 (m, 14H), 0.91 (t, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 178.2, 136.7, 131.3, 76.7, 75.7, 73.2, 38.3, 36.0, 33.8, 33.1, 30.5, 30.4, 30.2, 26.5, 26.5, 26.2, 23.7, 14.4; HR-FABMS m/z: 353.2309 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.4. Syntheses of (9*R*,12*R*,13*R*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-4) and (9*R*,12*S*,13*S*)-trihydroxy-10-octadienoic acid ((−)-5).

7.3.4.1. (9*R*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-15). According to the synthesis of (−)-**15**, the reduction of (+)-**14** (26.1 mg) using (*R*)-BINAL-H gave (+)-**15** (10.8 mg, 63%) as a colorless oil. $[\alpha]_D^{27}$ +6.6 (c 0.21, $CHCl_3$); HRMS (FAB, NBA matrix), m/z: 409.2908 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.4.2. (9*R*,12*R*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-4). According to the synthesis of (−)-**4**, the deprotection of (+)-**15** (10.8 mg) gave (+)-**4** (4.8 mg, 67%) as a white solid. Mp 98–104 °C (MeOH); $[\alpha]_D^{28}$ +12.9 (c 0.48, MeOH); HR-FABMS m/z: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.4.3. (9*R*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-16). According to the synthesis of (−)-**15**, the reduction of (−)-**14** (10.8 mg) using (*R*)-BINAL-H gave (−)-**16** (8.9 mg, 57%) as a colorless oil. $[\alpha]_D^{27}$ −9.9 (c 0.99, $CHCl_3$); HRMS (FAB, NBA matrix), m/z: 409.2910 $[M]^+$, Calcd for $C_{22}H_{42}O_5Na$: 409.2930 [M].

7.3.4.4. (9*R*,12*S*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-5). According to the synthesis of (+)-**5**, the deprotection of (−)-**16** (8.9 mg) gave (−)-**5** (3.7 mg, 51%) as a white solid. Mp 69–74 °C (MeOH); $[\alpha]_D^{22}$ −24.0 (c 0.30, MeOH); HR-FABMS m/z: 353.2307 [M+Na], Calcd for $C_{18}H_{34}O_5Na$: 353.2304.

7.3.5. Synthesis of (9*S*,12*R*,13*S*)-(*E*)-9,12,13-trihydroxy-10-octadienoic acid ((+)-17).

7.3.5.1. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid *tert*-butyl ester ((−)-18). To a mixture of (+)-**12** (326 mg, 0.689 mmol) and 2,6-lutidine (160 μL, 7.87 mmol) in CH_2Cl_2 (14 mL) was added TIPSOTf (194 μL, 0.723 mmol) dropwise over 20 min at −78 °C. The reaction mixture was stirred at −78 °C for 8 h. The resultant mixture was treated with H_2O (1 mL) and extracted with $CHCl_3$ (10 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**18** (391 mg, 90%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=5:1); $[\alpha]_D^{24}$ −4.8 (c 1.01, $CHCl_3$); IR (KBr) ν cm^{-1}: 3442 (s), 1731 (m), 1630 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.91 (dd, J=15.5, 7.6 Hz, 1H), 5.68 (d, J=15.5 Hz, 1H), 4.16 (dd, J=7.6, 6.9 Hz, 1H), 4.01–3.00 (m, 1H), 2.92–2.77 (m, 2H), 2.69–2.63 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.11–1.87 (m, 2H), 1.83–1.67 (m, 2H), 1.67–1.58 (complex m, 18H), 1.42 (s, 9H), 1.15–1.02 (m, 21H), 0.89 (t, J=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 135.7, 133.7, 79.9, 77.3, 75.5, 54.2, 42.2, 35.5, 32.6, 31.9, 29.7, 29.6, 29.1, 29.0, 28.0 (3C), 27.0, 26.9, 25.7, 25.5, 23.9, 22.6, 18.1 (6C), 14.0, 12.5 (3C); HRMS (FAB, NaI matrix) m/z: 653.4061 $[M+Na]^+$, Calcd for $C_{34}H_{66}O_4SiS_2Na$: 653.4070 [M+Na].

7.3.5.2. (12*R*,13*S*)-(*E*)-13-Acetoxy-9-(1,3-dithian)-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-19). To a solution of (−)-**18** (13.0 mg, 0.021 mmol) in pyridine (0.5 mL) was added $ClCH_2SO_2Cl$ (3.9 μL, 0.030 mmol) at 0 °C. The resultant mixture was stirred at 0 °C for 2 h, treated with H_2O (0.5 mL), and successfully extracted with $CHCl_3$ (5 mL×3). The combined organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, and concentrated.

To a solution of the residue of previous reaction in benzene was added CsOAc (19.8 mg, 0.10 mmol) and 18-crown-6 (4.1 mg, 0.021 mmol) at rt. The resultant mixture was warmed, refluxed for 20 h, and then cooled to rt again to treat with H_2O (500 μL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=50:1) to give (−)-**19** (11.5 mg, 83% from (−)-**18**) as a colorless oil. R_f=0.50 (silica gel, hexane/AcOEt=8:1); $[\alpha]_D^{24}$ −21.8 (c 0.87, $CHCl_3$); IR (KBr) ν cm^{-1}: 1734 (s), 1635 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.89 (dd, J=15.5, 6.3 Hz, 1H), 5.69 (d, J=15.5 Hz, 1H), 4.95–4.89 (m, 1H), 4.47 (dd, J=6.3, 2.6 Hz, 1H), 2.93–2.79 (m, 2H), 2.69–2.61 (m, 2H), 2.18 (t, J=7.3 Hz, 2H), 2.05 (s, 3H), 2.02–1.87 (m, 2H), 1.83–1.66 (m, 2H), 1.47–1.15 (complex m, 18H), 1.43 (s, 9H), 1.10–0.95 (m, 21H), 0.87 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 170.8, 135.0, 133.1, 79.9, 77.4, 77.2, 54.3, 42.2, 35.5, 31.7, 29.6, 29.1, 29.0 (2C), 28.1 (3C), 27.0, 26.9, 25.5, 25.3, 25.0, 23.8, 22.4, 21.2, 18.0 (6C), 14.0, 12.5 (3C); HRMS (FAB, NaI matrix), m/z: 695.4162 $[M+Na]^+$, Calcd for $C_{36}H_{68}O_5SiS_2Na$: 695.4175 [M+Na].

7.3.5.3. (12*R*,13*S*)-(*E*)-13-Acetoxy-9-oxo-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-20). To a mixture of (−)-**19** (304 mg, 0.452 mmol) and $CaCO_3$ (90.4 mg, 0.904 mmol) in THF (4.5 mL) was added a solution of $Hg(ClO_4)_3$ (410 mg, 0.904 mmol) in H_2O (900 μL) dropwise. The resultant mixture was stirred at rt for 5 min, and then diluted with ether (2 mL). This mixture was filtered through Celite. The residue was concentrated and dissolved in $CHCl_3$ (15 mL). This solution was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give (−)-**20** (250 mg, 97%) as a colorless oil. R_f=0.55 (silica gel, hexane/AcOEt=6:1); $[\alpha]_D^{24}$ −22.0 (c 0.98, $CHCl_3$); IR (KBr) ν cm^{-1}: 1735 (m), 1680 (m), 1633 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 6.71 (dd, J=15.8, 5.9 Hz, 1H), 6.24 (d, J=15.8 Hz, 1H), 4.93 (m, 1H), 4.48 (dd, J=5.9, 3.6 Hz, 1H), 2.55 (t, J=7.6 Hz, 2H), 2.19 (t, J=7.3 Hz, 2H), 2.04 (s, 3H), 1.73–1.17 (complex m, 18H), 1.44 (s, 9H), 1.12–0.98 (m, 21H), 0.87 (t, J=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 200.3, 173.2, 170.6, 144.6, 130.5, 79.8, 76.4, 74.2, 40.2, 35.5, 31.5, 31.4, 29.0 (2C), 28.9, 28.9, 28.0 (3C), 25.2, 24.9, 24.1, 22.4, 21.0, 17.9 (6C), 13.9, 12.3 (3C); HRMS

(FAB, NaI matrix); *m/z*: 605.4202 [M+Na]$^+$, Calcd for $C_{33}H_{62}O_6SiS_2Na$: 605.4213 [M+Na].

7.3.5.4. (9*S*,12*R*,13*S*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-21). To a solution of (−)-**20** (18.7 mg, 0.033 mmol) in THF (300 μL) was added (*S*)-BINAL-H (0.5 M solution in THF, 215 μL, 0.107 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h 30 min. The resultant mixture was treated with 1.0 N HCl (1 mL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with 1.0 N NaOH (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=10:1) to give (−)-**21** (18.6 mg, 99%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=4:1); $[\alpha]_D^{25}$ −18.9 (*c* 1.40, $CHCl_3$); IR (KBr) ν cm^{-1}: 1733 (m), 1630 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.69 (dd, *J*=15.8, 5.6 Hz, 1H), 5.62 (dd, *J*=15.8, 5.9 Hz, 1H), 4.93 (m, 1H), 4.29 (dd, *J*=5.9, 3.0 Hz, 1H), 4.11–4.07 (m, 1H), 2.19 (t, *J*=7.3 Hz, 2H), 2.03 (s, 3H), 1.79–1.20 (complex m, 20H), 1.44 (s, 9H), 1.10–0.98 (m, 21H), 0.87 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.2, 170.8, 135.2, 130.2, 79.9, 77.1, 74.8, 72.2, 37.1, 35.5, 31.5, 29.3, 29.2, 29.0, 28.9, 28.1 (3C), 25.3, 25.2, 25.0, 22.5, 21.2, 18.0 (6C), 14.0, 12.4 (3C); HRMS (FAB, NaI matrix), *m/z*: 607.4372 [M+Na]$^+$, Calcd for $C_{33}H_{64}O_6SiNa$: 607.4370 [M+Na].

7.3.5.5. (9*S*,12*R*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-17). To a solution of 1.0 N KOH in EtOH/H_2O (4:1) (500 μL) was added (−)-**20** (17.2 mg, 29.8 μmol) and stirred at rt for 120 h. The mixture was cooled to 0 °C and treated with 1.0 N HCl (500 μL) and extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq $NaHCO_3$ (5 mL), satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated.

To a solution of the residue of previous reaction in THF (10 mL) at 0 °C was added TBAF (1.0 M solution in THF, 30 μL, 29.8 μmol). The resultant mixture was warmed to rt and stirred for 45 h before being treated with satd aq NH_4Cl (500 μL) and extracted with AcOEt (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (AcOEt) to give (+)-**17** (9.3 mg, 94%) as a white solid. R_f=0.23 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 67–70 °C (MeOH); $[\alpha]_D^{25}$ +7.8 (*c* 0.18, MeOH); IR (KBr) ν cm^{-1}: 3421 (s), 1699 (m), 1637 (m); ^{1}H NMR (400 MHz, CD_3OD) δ: 5.72 (dd, *J*=15.8, 5.5 Hz, 1H), 5.66 (dd, *J*=15.8, 6.0 Hz, 1H), 4.04 (ddd, *J*=6.5, 6.0, 5.0 Hz, 1H), 3.91 (dd, *J*=5.5, 4.5 Hz, 1H), 3.49 (ddd, *J*=7.5, 4.5, 2.0 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.6, 6.9 Hz, 2H), 1.55–1.50 (m, 4H), 1.45–1.25 (m, 14H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.8, 136.7, 130.9, 76.6, 75.7, 73.3, 38.4, 35.1, 33.7, 33.1, 30.6, 30.4, 30.2, 26.7, 26.5, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2307 [M+Na], Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6. Syntheses of all the stereoisomers of pinellic acid.

7.3.6.1. (12*S*,13*S*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-18). According to the synthesis of (−)-**18**, (−)-**12** (166 mg) gave (+)-**18** (154 mg, 79% based on recovered (−)-**12**) as a colorless oil. $[\alpha]_D^{29}$ +5.9 (*c* 0.37, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 653.4053 [M+Na]$^+$, Calcd for $C_{34}H_{66}O_4SiS_2Na$: 653.4070 [M+Na].

7.3.6.2. (12*S*,13*R*)-(*E*)-13-Acetoxy-9-(1′,3-dithian)-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-19). According to the synthesis of (−)-**19**, (+)-**18** (154 mg) gave (+)-**19** (124 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ +23.6 (*c* 1.10, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 695.4148 [M+Na]$^+$, Calcd for $C_{36}H_{68}O_5SiS_2Na$: 695.4175 [M+Na].

7.3.6.3. (12*S*,13*R*)-(*E*)-13-Acetoxy-9-oxo-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-20). According to the synthesis of (−)-**20**, (+)-**19** (114 mg) gave (+)-**20** (89 mg, 89%) as a colorless oil. $[\alpha]_D^{25}$ +22.6 (*c* 0.83, $CHCl_3$); HRMS (FAB, NaI matrix), *m/z*: 605.4201 [M+Na]$^+$, Calcd for $C_{33}H_{62}O_6SiS_2Na$: 605.4213 [M+Na].

7.3.6.4. (9*S*,12*S*,13*R*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-22). According to the synthesis of (−)-**21**, the reduction of (+)-**20** (78.0 mg) using (*S*)-BINAL-H gave (+)-**22** (70.3 mg, 99% based on recovered (+)-**20**) as a colorless oil. R_f=0.43 (silica gel, hexane/AcOEt=4:1); $[\alpha]_D^{25}$ +25.8 (*c*, $CHCl_3$); IR (KBr) ν cm^{-1}: 3439 (s), 1734 (m), 1640 (m); ^{1}H NMR (270 MHz, $CDCl_3$) δ: 5.71 (m, 2H), 4.86 (m, 1H), 4.28 (dd, *J*=5.3, 4.0 Hz, 1H), 4.13–4.07 (m, 1H), 2.19 (t, *J*=7.3 Hz, 2H), 2.04 (s, 3H), 1.79–1.20 (complex m, 18H), 1.44 (s, 9H), 1.10–0.98 (m, 21H), 0.87 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 170.9, 135.2, 130.5, 79.9, 77.2, 74.8, 72.2, 37.1, 35.5, 31.7, 29.4, 29.3, 29.0 (2C), 28.0 (3C), 25.3, 25.0, 21.2, 21.2, 18.0 (6C), 14.0, 12.4 (3C); HRMS (FAB, NBA matrix), *m/z*: 607.4364 [M+Na]$^+$, Calcd for $C_{33}H_{64}O_6SiNa$: 607.4370 [M+Na].

7.3.6.5. (9*S*,12*S*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((+)-23). According to the synthesis of (+)-**17**, the deprotection of (+)-**22** (45.9 mg) gave (+)-**23** (25.7 mg, 98%) as a white solid. R_f=0.24 (silica gel, $CHCl_3$/MeOH/AcOH=10:1:0.1); mp 91–94 °C (MeOH); $[\alpha]_D^{25}$ +6.7 (*c* 0.14, MeOH); IR (KBr) ν cm^{-1}: 3420 (s), 1701 (m), 1637 (m); ^{1}H NMR (400 MHz, CD_3OD) δ: 5.73 (dd, *J*=15.9, 5.0 Hz, 1H), 5.68 (dd, *J*=15.9, 5.5 Hz, 1H), 4.05 (ddd, *J*=6.0, 5.5, 5.0 Hz, 1H), 3.93 (dd, *J*=5.0, 4.5 Hz, 1H), 3.47 (ddd, *J*=8.5, 4.5, 2.1 Hz, 1H), 2.27 (t, *J*=7.5 Hz, 2H), 1.60 (dt, *J*=7.5, 7.0 Hz, 2H), 1.55–1.50 (m, 2H), 1.45–1.25 (m, 16H), 0.91 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ: 177.7, 136.5, 130.9, 76.5, 75.7, 73.0, 38.3, 34.9, 33.5, 33.1, 30.5, 30.3, 30.2, 26.7, 26.4, 26.1, 23.7, 14.4; HR-FABMS *m/z*: 353.2336 [M+Na]$^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6.6. (9*R*,12*R*,13*S*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-22). According to the synthesis of (+)-**22**, the reduction of (−)-**20** (67.8 mg) using (*R*)-BINAL-H gave (−)-**22** (55.4 mg, 82%) as a colorless oil.

7.3.6.7. (9*R*,12*R*,13*S*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-23). According to the synthesis of (+)-**17**, the deprotection of (−)-**22** (26.5 mg) gave (−)-**23**

(14.0 mg, 94%) as a white solid. Mp 88–93 °C (MeOH); $[\alpha]_D^{30}$ −5.3 (*c* 0.15, MeOH); HR-FABMS *m/z*: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.3.6.8. (9*R*,12*S*,13*R*)-(*E*)-13-Acetoxy-9-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-21). According to the synthesis of (−)-**21**, the reduction of (+)-**20** (32.9 mg) using (*R*)-BINAL-H gave (+)-**21** (79.4 mg, 98%) as a colorless oil.

7.3.6.9. (9*R*,12*S*,13*R*)-(*E*)-9,12,13-Trihydroxy-10-octadecaenoic acid ((−)-17). According to the synthesis of (+)-**17**, the deprotection of (+)-**21** (32.9 mg) gave (−)-**17** (7.5 mg, 18%) as a white solid. Mp 65–74 °C (MeOH); $[\alpha]_D^{30}$ −7.1 (*c* 0.14, MeOH); HR-FABMS *m/z*: 353.2307 $[M+Na]^+$, Calcd for $C_{18}H_{34}O_5Na$: 353.2304 [M+Na].

7.4. Stereochemistry on allylic 1,2-diol

7.4.1. (12*R*,13*R*)-(*E*)-9-(1,3-Dithian)-12,13-isopropylidenedioxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-24). To a solution of (+)-**12** (47.3 mg, 99.7 μmol) in CH_2Cl_2 (1.0 mL) were added CSA (2.3 mg, 9.97 μmol) and 2-methoxypropene (147 μL, 150 μmol) at 0 °C. The resultant mixture was stirred at 0 °C for 5 min, treated with H_2O (1 mL), and then extracted with $CHCl_3$ (5 mL×3). The organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=20:1) to give (+)-**24** (49.0 mg, 96%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{22}$ +27.2 (*c* 1.50, $CHCl_3$); IR (KBr) ν cm^{-1}: 3461 (s), 1730 (m), 1630 (m); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.86 (dd, *J*=15.0, 7.2 Hz, 1H), 5.74 (d, *J*=15.0 Hz, 1H), 4.11 (dd, *J*=8.0, 7.2 Hz, 1H), 3.69 (ddd, *J*=8.0, 6.5, 5.0 Hz, 1H), 2.91–2.84 (m, 2H), 2.67–2.61 (m, 2H), 2.18 (t, *J*=7.2 Hz, 2H), 2.06–2.00 (m, 1H), 1.88–1.82 (m, 1H), 1.79 (ddd, *J*=11.0, 6.0, 3.5 Hz, 2H), 1.59–1.21 (complex m, 18H), 1.44 (s, 9H), 1.41 (s, 6H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 137.2, 131.3, 108.6, 81.8, 80.9, 79.9, 54.7, 42.4, 35.6, 32.0, 31.9, 29.6, 29.1, 29.0, 28.1 (3C), 27.3, 27.2 (2C), 27.0, 25.8, 25.5, 25.0, 23.6, 22.5, 14.0; HRMS (FAB, NAI matrix), *m/z*: 514.3145 $[M]^+$, Calcd for $C_{28}H_{50}O_2$: 514.3151 [M].

7.4.2. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-13-hydroxy-12-triisopropylsiloxy-10-octadecaenoic acid-*tert*-butyl ester ((−)-25). To a solution of (−)-**19** (26.3 mg, 39.1 μmol) in *t*-BuOH (800 μL) was added KO*t*-Bu (17.5 mg, 157 μmol) at rt. The resultant mixture was stirred at rt for 16 h, treated with 1.0 N HCl (1 mL), and then extracted with $CHCl_3$ (3 mL×5). The combined organic layer was washed with satd aq NaCl (5 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=40:1) to give (−)-**25** (11.5 mg, 47%) as a colorless oil. R_f=0.44 (silica gel, hexane/AcOEt=5:1); $[\alpha]_D^{23}$ −12.5 (*c* 0.72, $CHCl_3$); IR (KBr) ν cm^{-1}: 3434 (s), 1724 (m), 1625 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.93 (dd, *J*=15.5, 7.3 Hz, 1H), 5.64 (d, *J*=15.5 Hz, 1H), 4.29 (dd, *J*=7.3, 3.3 Hz, 1H), 3.77–3.67 (m, 1H), 2.97–2.84 (m, 2H), 2.66–2.57 (m, 2H), 2.18 (t, *J*=7.6 Hz, 2H), 2.01 (br s, 1H), 1.82–1.76 (m, 2H), 1.67–1.58 (complex m, 20H), 1.44 (s, 9H), 1.14–1.07 (m, 21H), 0.87 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 135.7, 133.6, 79.9, 76.2, 75.2, 54.6, 42.4, 35.6, 32.6, 32.0, 29.7, 29.1, 29.0, 28.1 (3C), 27.1, 27.0, 25.6, 25.5, 25.1, 23.7, 22.5, 18.1 (6C), 14.1, 12.4 (3C); HRMS (FAB, NBA matrix), *m/z*: 630.4178 $[M]^+$, Calcd for $C_{34}H_{66}O_4S_2Si$: 630.4172 [M].

7.4.3. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-dihydroxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-26). To a solution of (−)-**25** (4.3 mg, 6.8 μmol) in THF (500 μL) was added TBAF (1.0 M solution in THF, 6.8 μL, 6.8 μmol) at rt. The resultant mixture was stirred at rt for 16 h, treated with H_2O (500 μL), and then extracted with $CHCl_3$ (3 mL×3). The combined organic layer was washed with satd aq NaCl (3 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=1:1) to give (+)-**26** (3.1 mg, 97%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{24}$ +0.4 (*c* 0.52, $CHCl_3$); IR (KBr) ν cm^{-1}: 3428 (s), 1731 (m), 1630 (m); ^1H NMR (270 MHz, $CDCl_3$) δ: 5.98 (dd, *J*=15.2, 6.9 Hz, 1H), 5.72 (d, *J*=15.2 Hz, 1H), 4.23 (d, *J*=6.9, 3.6 Hz, 1H), 3.77–3.71 (m, 1H), 2.94–2.81 (m, 2H), 2.68–2.32 (m, 2H), 2.19 (t, *J*=7.3 Hz, 2H), 1.84–1.78 (m, 2H), 1.67–1.28 (complex m, 20H), 1.44 (s, 9H), 0.89 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 173.3, 136.4, 131.3, 80.0, 75.1, 74.2, 54.7, 42.0, 35.5, 32.4, 31.8, 29.4, 29.0, 28.9, 28.1 (3C), 27.2 (2C), 25.5 (2C), 24.9, 23.7, 22.5, 14.0; HRMS (FAB, NBA matrix), *m/z*: 497.2744 $[M+Na]^+$, Calcd for $C_{25}H_{46}O_4S_2Na$: 497.2735 [M+Na].

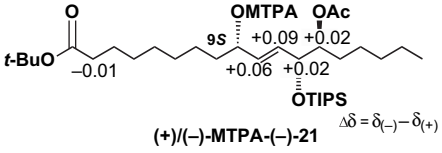
7.4.4. (12*R*,13*S*)-(*E*)-9-(1,3-Dithian)-12,13-isopropylenedioxy-10-octadecaenoic acid-*tert*-butyl ester ((+)-27). To a solution of (+)-**26** (17.1 mg, 37.3 μmol) in CH_2Cl_2 (0.7 mL) were added CSA (0.9 mg, 3.73 μmol) and 2-methoxypropene (5.3 μL, 56.0 μmol) at 0 °C. The resultant mixture was stirred at 0 °C for 20 min, treated with H_2O (1 mL), and then extracted with $CHCl_3$ (2 mL×3). The organic layer was washed with satd aq NaCl (2 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/AcOEt=20:1) to give (+)-**27** (18.2 mg, 98%) as a colorless oil. R_f=0.38 (silica gel, hexane/AcOEt=1:1); $[\alpha]_D^{25}$ 0.0 (*c* 0.87, $CHCl_3$); IR (KBr) ν cm^{-1}: 3446 (s), 1730 (m), 1628 (m); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.88 (dd, *J*=15.0, 8.0 Hz, 1H), 5.67 (d, *J*=15.0 Hz, 1H), 4.60 (dd, *J*=8.0, 6.0 Hz, 1H), 4.15 (ddd, *J*=8.0, 6.0, 5.0 Hz, 1H), 2.94–2.84 (m, 2H), 2.67–2.60 (m, 2H), 2.18 (t, *J*=7.2 Hz, 2H), 2.06–2.00, 1.88–1.82 (m, 1H each), 1.80–1.75 (m, 2H), 1.58–1.23 (m, 18H), 1.49 (s, 3H), 1.43 (s, 9H), 1.37 (s, 3H), 0.88 (t, *J*=6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 136.7, 130.5, 108.1, 79.9, 78.9, 78.4, 54.5, 42.3, 35.6, 31.9, 30.7, 29.6, 29.1, 29.0, 28.4, 28.1 (3C), 27.1, 27.1, 25.9, 25.7, 25.5, 25.0, 23.7, 22.6, 14.0.

Acknowledgements

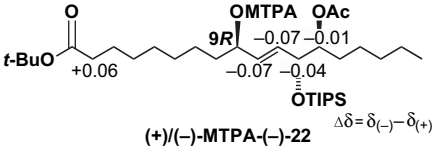
This work was supported by the Ministry of Education, Science, Sports, and Culture, Japan and the Japan Keirin Association, a Grant of the 21st Century COE Program. We acknowledge and thank Ms. Noriko Sato for NMR measurements and Ms. Chikako Sakabe and Ms. Akiko Nakagawa for mass spectrometric analysis.

References and notes

1. Murphy, B. R.; Webster, R. G. Orthomyxoviruses. In *Virology*, 2nd ed.; Fields, B. N., Knipe, D. M., Eds.; Raven: New York, NY, 1990; pp 1091–1152.
2. Nagai, T.; Yamada, H. *Immunopharmacol. Immunotoxicol.* **1998**, *20*, 267–281.
3. Nagai, T.; Yamada, H. *Int. J. Immunopharmacol.* **1994**, *16*, 605–613.
4. Nagai, T.; Urata, M.; Yamada, H. *Immunopharmacol. Immunotoxicol.* **1996**, *18*, 193–208.
5. Nagai, T.; Kiyohara, H.; Munakata, K.; Shirahata, T.; Sunazuka, T.; Harigaya, Y.; Yamada, H. *Int. Immunopharmacol.* **2002**, *2*, 1183–1193.

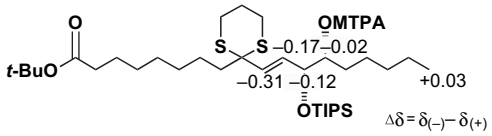


(+)/(–)-MTPA-(–)-21



(+)/(–)-MTPA-(–)-22

6. (a) Kato, T.; Yamaguchi, Y.; Ohnuma, S.; Uehara, T.; Namai, T.; Kodama, M.; Shiobara, Y. *Chem. Lett.* **1986**, 577–580; (b) Colin, D. F.; William, S. P. *Biochim. Biophys. Acta* **1983**, *754*, 57–71; (c) Hanberg, M. *Lipids* **1991**, *26*, 407–415.
7. Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590–5591.
8. (a) Kouda, K.; Ooi, T.; Kaya, K.; Kusumi, T. *Tetrahedron Lett.* **1996**, *37*, 6347–6350; (b) Uehara, H.; Oishi, T.; Yoshikawa, K.; Mochida, K.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 8641–8645.
9. For review, see: Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
10. Grobel, B. T.; Seebach, D. *Synthesis* **1977**, 357–402.
11. Okuma, K.; Hashimoto, S.; Ono, M.; Shioji, K.; Matsuyama, H.; Bestmann, H. J. *Tetrahedron* **1998**, *54*, 4243–4250.
12. Stereochemistry of all hydroxy groups was determined by Mosher's method. We prepared the corresponding (+/−)-MTPA esters of (−)-**18** (for C12–C13) and (−)-**21** and (−)-**22** (for C9). These results confirmed that the dihydroxylation with DHQ_2(PHAL) afforded 12*R*,13*R* and the stereoselective reduction with (*S*)-BINAL-H gave 9*S*, while the same reduction with (*R*)-BINAL-H gave 9*R*, as shown in the following figure: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.



(+)/(–)-MTPA-(–)-18

13. For review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
14. Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709–6716.
15. Sunazuka, T.; Shirahata, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Nagai, T.; Kiyohara, H.; Yamada, H.; Ōmura, S. *Tetrahedron Lett.* **2002**, *43*, 1265–1268.
16. For review, see: Mitsunobu, O. *Synthesis* **1981**, 1–28.
17. For review, see: Tsunoda, T.; Ito, S. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 631–641.
18. Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, *37*, 3183–3186.
19. Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6145–6148.
20. Shirahata, T.; Sunazuka, T.; Yoshida, K.; Yamamoto, D.; Harigaya, Y.; Nagai, T.; Kiyohara, H.; Yamada, H.; Ōmura, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 937–941.