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A concise synthesis of pinellic acid using a cross-metathesis approach

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ABSTRACT

A new enantioselective synthesis of pinellic acid, a trihydroxy unsaturated fatty acid exhibiting oral adjuvant activity for nasally administered influenza vaccine, has been accomplished using a cross-metathesis reaction between two terminal olefin intermediates as the key step. This synthesis is the shortest to date, furnishing pinellic acid in 17% overall yield via only seven steps from a readily available known dihydroxy ester.

1. Introduction

(9*S*,10*E*,12*S*,13*S*)-(−)-9,12,13-Trihydroxy-10-octadecenoic acid (**1**) was first isolated by Kato and co-workers from a rice cultivar (Sasanishiki) suffering from the rice blast disease, and shown to exhibit clear inhibitory activity against the rice blast fungus (Fig. 1).[1] The gross structure of **1** was assigned spectroscopically, and the stereochemistry was determined through its synthetic studies coupled with CD spectral analysis of a *p*-bromobenzoate derivative prepared from a natural sample of **1**.[1,2] The agriculturally important biological activity of **1** prompted its total synthesis, and one synthesis of the methyl ester of **1** using (+)-dimethyl tartrate as the starting material as well as a synthesis of stereoisomers of **1** from a sugar derivative was reported.[3,4] The trihydroxy fatty acid (**1**) was later reisolated by Yamada and co-workers from the tuber of the medicinal plant *Pinellia ternata* as an effective oral adjuvant for nasally administered influenza HA vaccine and given the trivial name pinellic acid.[5] Soon after the rediscovery, Omura and co-workers reported a series of synthetic works on **1** and its stereoisomers, in which they confirmed the stereochemistry of **1** and elucidated the stereochemistry–activity relationship including the findings that the natural stereoisomer **1** exhibited the most potent adjuvant activity and, interestingly, the activity of its *C*12-epimer was comparable to that of **1**.[6–8] Inspired by the medicinally intriguing biological activity of **1**, four additional syntheses of **1** or its stereoisomers have recently been reported.[9–12] The previous syntheses employed dithiane chemistry,[6–8] acetylenic coupling methodology including the Sonogashira reaction,[9–11] or the Wittig olefination[12] to construct the carbon skeleton of the target molecules. In this paper, we describe a new concise approach to **1** via a cross-metathesis reaction, which has led to the shortest synthesis of **1** among those reported so far.

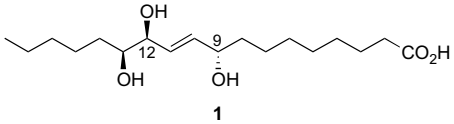

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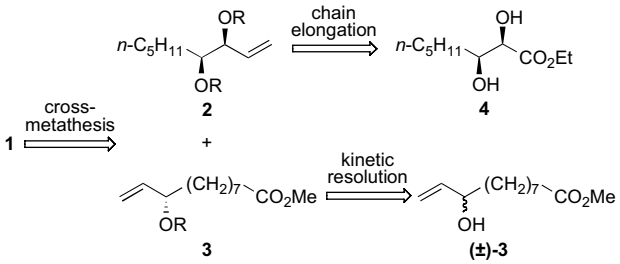
Figure 1. Structure of pinellic acid (**1**).



Scheme 1. Synthetic plan for pinellic acid (**1**).

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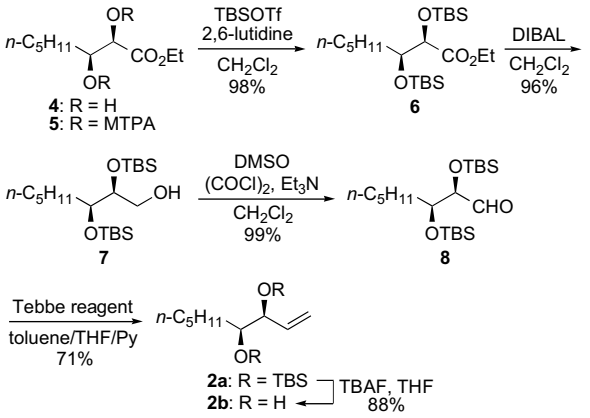


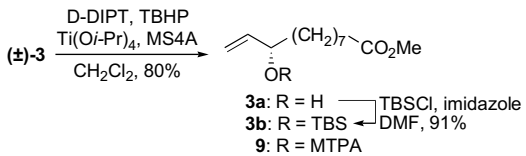
Scheme 2. Preparation of **2a** and **2b**.

2. Results and discussion

Our retrosynthetic analysis of **1** is shown in Scheme 1. We planned to construct the C10–C11 double bond of **1** by the cross-metathesis reaction between oxygen-containing terminal olefins **2** and **3**. Compound **2** would be obtainable via one-carbon elongation of known dihydroxy ester **4**, while the other component of the cross-metathesis reaction (**3**) should readily be prepared by the Sharpless kinetic resolution of racemic alcohol (±)-**3**, which is also a known compound.

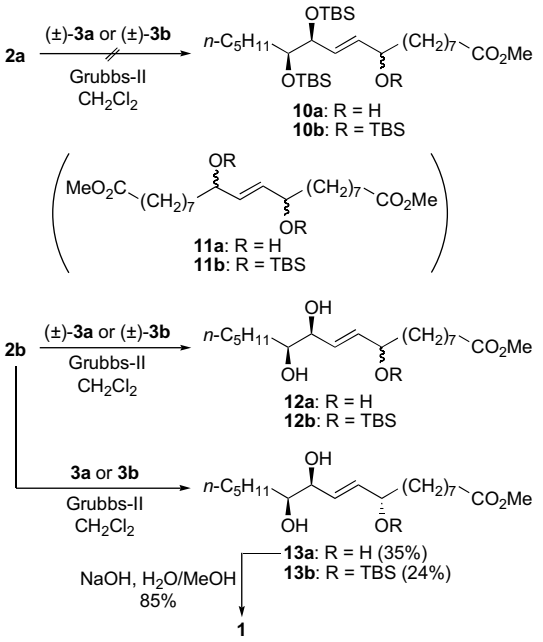
The preparation of the TBS-protected and unprotected forms of **2** (i.e., **2a** and **2b**) is shown in Scheme 2. The known dihydroxy ester **4**,[13] which was obtained from commercially available ethyl (*E*)-2-octenoate in 98% yield by the Sharpless asymmetric dihydroxylation using AD-mix-α and estimated to be >98% ee by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters **5**, was protected as its bis-TBS ether **6** by treatment with TBSOTf and 2,6-lutidine in dichloromethane. The product **6**, obtained in 98% yield, was reduced with DIBAL to give alcohol **7** in 96% yield, which was then oxidized under the Swern oxidation conditions to afford aldehyde **8** in almost quantitative yield. Installation of a terminal double bond in **8** leading to **2a** proved to be more problematic than expected. When **8** was subjected to two kinds of Wittig reaction conditions, Ph_3PCH_3Br/*n*-BuLi/ether and Ph_3PCH_3Br/NaHMDS/THF, the desired product **2a** was obtained in only 23% yield in the former case, and none of the desired olefin was produced in the latter case, affording merely a complex mixture. Exposure of **8** to CH_2I_2/Zn/Al$(CH_3)_3$/THF was also unsuccessful, resulting only in the recovery of the starting aldehyde.[14] Fortunately, this olefination was finally found to be achievable by treating **8** with the Tebbe reagent [$Cp_2TiCH_2AlCl(CH_3)_2$] in toluene/THF/Py, giving **2a** in a good yield of 71%.[15,16] Deprotection of **2a** with TBAF in THF afforded the olefinic diol **2b** in 88% yield.

The preparation of the unprotected form of **3** (i.e., **3a** in Scheme 3) was performed in 80% yield by simply subjecting the racemic alcohol (±)-**3** to the Sharpless kinetic resolution conditions;[17] the starting material (±)-**3** in turn was obtained in ca. 60% yield by allylic oxidation of commercially available methyl 10-undecenoate with SeO_2/TBHP according to a literature procedure.[18] The enantiomeric excess of **3a** was determined to be >98% by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters **9**. The allylic alcohol **3a** was converted into the corresponding TBS-protected form (**3b**) in 91% yield.



Scheme 3. Preparation of **3a** and **3b**.

With terminal olefins **2** and **3** in hand, we moved on to the final stage of the synthesis (Scheme 4). Since preliminary experiments using the first generation Grubbs catalyst revealed that the cross-



Scheme 4. Completion of the synthesis of pinellic acid (**1**).

metathesis reactions between **2a** and (±)-**3a**, and between **2a** and (±)-**3b** as well, gave neither the desired cross-metathesis products (**10a** and **10b**, respectively) nor the undesired self-metathesis (homodimerization) products of (±)-**3a** and **3b** (**11a** and **11b**, respectively) in detectable amounts, all of subsequent metathesis experiments were conducted using the second generation Grubbs catalyst (5 mol% Grubbs-II, 3 equiv of (±)-**3a** or (±)-**3b**, CH_2Cl_2, 40 °C, 5 h).[19,20] As shown in Scheme 4, even the use of Grubbs-II did not lead to the successful formation of the desired cross-coupling products **10a** and **10b** (resulting only in the recovery of **2a**), but we could observe the formation of a large amount of **11a** in the reaction of **2a** and (±)-**3a** by changing the metathesis catalysts from the first generation to the second generation; a small amount of **11b** was also generated when the reaction between **2a** and (±)-**3b** was continued overnight. To overcome the inertness of **2a** to the metathesis reaction, we also tried the reaction with use of its unprotected form (**2b**), since it had sometimes been documented that the protection of allylic alcohols exerted an adverse effect on cross-metathesis reaction.[21] To our delight, exposure of **2b** to (±)-**3a** and also to (±)-**3b** under the above-mentioned metathesis conditions furnished the desired cross-metathesis products **12a** (ca. 40% yield) and **12b** (ca. 25% yield),[22] respectively. From the product yields obtained, we could also find that the unprotected olefin (±)-**3a** was better than the protected olefin (±)-**3b** as the coupling partner of **2b** in the present case.[23,24] Indeed, the cross-metathesis reaction of **2b** with optically active olefin **3a** afforded, after complete consumption of **2b**, the desired cross-metathesis product **13a** in 35% isolated yield along with the homodimers of **2b** and **3a** as well as the starting material **3a** employed in excess (see the Experimental section for each yield), while the metathesis with the other optically active olefin (**3b**) bearing the TBS protecting group gave **13b** in a lower yield of 24% together with the homodimer of **2b** and a trace amount of the homodimer of **3b** in addition to the starting material **3b** (see the Experimental section for each yield). The ^{1}H and ^{13}C NMR spectra of **13a** and **13b** indicated that both of the compounds were produced with complete *E*-geometrical selectivity. Finally,

saponification of **13a** afforded in 85% yield the target molecule **1**, the ^{1}H and ^{13}C NMR spectral data of which were identical with those previously reported.[2,5–8,11] The specific rotation ($[\alpha]_D^{25}$ −9.5 (*c* 0.30, MeOH)) and melting point (mp 103.5–104.0 °C) of **1** also showed good agreement with those reported in the literature.[5–8,11]

3. Conclusion

The enantioselective synthesis of pinellic acid **1** was accomplished in 17% overall yield from known dihydroxy ester **4** via only seven steps involving the cross-metathesis reaction between terminal olefins **2b** and **3a** as the key step. Although we needed to use a threefold excess of the hydroxy olefin **3a** in the cross-metathesis step to increase the yield of the desired product **13a**, the ready availability of **3a** in only two steps from the cheap commercially available ester, methyl 10-dodecenoate, is considered to alleviate the problem. Efforts to improve the efficiency of the cross-metathesis step as well as synthetic studies on structurally related polyhydroxy fatty acids with various biological activities are now underway and will be reported in due course.

4. Experimental

4.1. General

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian UNITY plus-500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) unless otherwise stated. Optical rotation values were measured with a Jasco DIP-371 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the EI or FAB mode. Merck silica gel 60 (7–230 mesh) was used for column chromatography. Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 from CaH_2; toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

4.1.1. *Determination of the enantiomeric excess of **4***

Compound **4** ($[\alpha]_D^{25}$ −14.4 (*c* 1.00, EtOH)) was converted into the corresponding (*R*)- and (*S*)-MTPA esters (**5**) by treating with (*S*)- and (*R*)-MTPACl, respectively, in pyridine. The ^{1}H NMR signal for the methine proton at the C3 position of the (*R*)-MTPA ester was observed at 5.55 ppm (dt, *J*=2.0, 7.1 Hz), while that of the (*S*)-MTPA ester appeared at 5.61 ppm (dt, *J*=2.0, 7.3 Hz). In each spectrum of the diastereomeric MTPA esters, no signal due to the corresponding diastereomer was observed. Therefore, compound **4** was estimated to be optically pure within the limit of NMR detection.

4.1.2. *Ethyl (2R,3S)-2,3-bis(tert-butyldimethylsilyloxy)octanoate (**6**)*

To a stirred solution of **4** (388 mg, 1.90 mmol) and 2,6-lutidine (1.32 ml, 11.4 mmol) in CH_2Cl_2 (40 ml) was added TBSOTf (1.30 ml, 5.68 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, quenched with brine, and then extracted with water. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=100:1 to 20:1) to give **6** (804 mg, 98%) as a pale yellow oil. $[\alpha]_D^{25}$ −2.86 (*c* 1.10, $CHCl_3$); IR *ν* 1755 (m), 1252 (s), 1106 (s), 835 (vs), 774 (vs); ^{1}H NMR *δ* 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.88 (t, *J*=6.8 Hz, 3H), 0.91 (s, 9H), 1.22–1.40 (m, 7H), 1.27 (t, *J*=7.3 Hz, 3H), 1.68–1.75 (m, 1H), 3.81–3.84 (m, 1H), 4.11–4.21 (m, 3H); ^{13}C NMR *δ* −5.1, −4.8, −4.4, −4.36, 14.0, 14.2, 18.0, 18.3, 22.6, 25.4, 25.7, 25.7 (3C), 25.8 (3C), 31.9, 32.5, 60.5, 74.6, 74.8, 172.3; HRMS (FAB) *m*/*z* calcd for $C_{22}H_{49}O_4Si_2$ ($[M+H]^+$) 433.3169, found 433.3170.

4.1.3. *(2S,3S)-2,3-Bis(tert-butyldimethylsilyloxy)-1-octanol (**7**)*

To a stirred solution of **6** (308 mg, 0.711 mmol) in CH_2Cl_2 (6 ml) was added dropwise a solution of DIBAL (1.02 M in hexane, 1.53 ml, 1.56 mmol) at −70 °C. After 1.5 h, the mixture was quenched with satd Rochelle's salt aq and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=30:1) to give **7** (266 mg, 96%) as a colorless oil. $[\alpha]_D^{25}$ −28.0 (*c* 1.05, $CHCl_3$); IR *ν* 3476 (br w), 1254 (m), 1097 (m), 833 (s), 808 (m), 773 (s); ^{1}H NMR *δ* 0.07 (s, 3H), 0.08 (s, 3H), 0.09 (s, 6H), 0.87–0.91 (m, 21H), 1.18–1.38 (m, 6H), 1.43–1.50 (m, 1H), 1.65–1.71 (m, 1H), 2.34 (t, *J*=5.4 Hz, 1H, OH), 3.55–3.60 (m, 1H), 3.64–3.67 (m, 1H), 3.72–3.79 (m, 2H); ^{13}C NMR *δ* −4.7 (2C), −4.6, −4.3, 14.0, 17.9, 18.0, 22.5, 25.7 (3C), 25.8 (3C), 26.2, 30.4, 31.8, 63.2, 73.7, 75.4; HRMS (FAB) *m*/*z* calcd for $C_{20}H_{47}O_3Si_2$ ($[M+H]^+$) 391.3064, found 391.3068.

4.1.4. *(2R,3S)-2,3-Bis(tert-butyldimethylsilyloxy)octanal (**8**)*

To a stirred solution of $(COCl)_2$ (0.11 ml, 1.28 mmol) in CH_2Cl_2 (8 ml) was added dropwise DMSO (0.18 ml, 2.56 mmol) at −70 °C. After 20 min, a solution of **7** (333 mg, 0.85 mmol) in CH_2Cl_2 (9 ml) was added, and the mixture was stirred for 1 h. The mixture was gradually warmed to −60 °C, quenched with water, and then extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=50:1) to give **8** (328 mg, 99%) as a pale yellow oil. $[\alpha]_D^{23}$ −39.8 (*c* 0.500, $CHCl_3$); IR *ν* 1738 (m), 1254 (m), 1106 (m), 835 (s), 774 (s); ^{1}H NMR *δ* 0.04 (s, 3H), 0.07 (s, 6H), 0.08 (s, 3H), 0.88 (t, *J*=6.8 Hz, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 1.20–1.34 (m, 6H), 1.36–1.42 (m, 1H), 1.69–1.75 (m), 3.86 (dt, *J*=7.8, 4.4 Hz, 1H), 4.02 (d, *J*=4.4 Hz, 1H), 9.76 (d, *J*=1.0 Hz, 1H); ^{13}C NMR *δ* −5.2, −4.57, −4.55, −4.51, 14.0, 18.0, 18.2, 22.5, 25.5, 25.70 (3C), 25.72 (3C), 31.7, 32.6, 74.6, 80.0, 203.9; HRMS (EI) *m*/*z* calcd for $C_{20}H_{44}O_3Si_2$ (M^+) 388.2829, found 388.2832.

4.1.5. *(3S,4S)-Bis(tert-butyldimethylsilyloxy)-1-nonene (**2a**)*

To a stirred solution of **8** (76.8 mg, 0.197 mmol) in toluene/THF/pyridine (3:1:0.03, 4.03 ml) was added dropwise the Tebbe reagent (0.5 M in toluene, 0.47 ml, 0.237 mmol) at −70 °C. The mixture was gradually warmed to −10 °C over 3 h, and quenched with successive addition of Et_3N (0.4 ml) and satd $NaHCO_3$ aq. The mixture was extracted with ether, and the extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=50:1) to give **2a** (54.5 mg, 71%) as a pale yellow oil. $[\alpha]_D^{24}$ −67.9 (*c* 0.45, $CHCl_3$); IR *ν* 3095 (w), 3025 (w), 1254 (m), 832 (s), 772 (s); ^{1}H NMR *δ* 0.04 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (t, *J*=7.3 Hz, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 1.14–1.31 (m, 6H), 1.37–1.43 (m, 1H), 1.52–1.57 (m, 1H), 3.55–3.58 (m, 1H), 4.12–4.15 (m, 1H), 5.13 (dt, *J*=10.3, 2.0 Hz, 1H), 5.25 (dt, *J*=17.1, 2.0 Hz, 1H), 5.98 (ddd, *J*=3.9, 10.3, 17.1 Hz, 1H); ^{13}C NMR *δ* −4.9, −4.7, −4.6, −4.2, 14.0, 18.0, 18.2, 22.6, 25.8, 25.8 (3C), 25.9 (3C), 30.7, 31.9, 75.31, 75.34, 114.5, 137.1; HRMS (EI) *m*/*z* calcd for $C_{21}H_{46}O_2Si_2$ (M^+) 386.3036, found 386.3040.

4.1.6. *(3S,4S)-1-Nonene-3,4-diol (**2b**)*

To **2a** (neat, 47.1 mg, 0.121 mmol) was added a solution of TBAF (1.0 M in THF, 0.27 ml, 0.27 mmol) at 0 °C with stirring, and the mixture was gradually warmed to 10 °C over 3 h. The mixture was diluted with satd NH_4Cl aq, and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=3:1) to give **2b** (17.0 mg, 88%) as a pale yellow oil. $[\alpha]_D^{23}$ −25.5 (*c* 1.02, $CHCl_3$); IR *ν* 3374 (br s), 3082 (w), 1650 (w), 1049 (m), 991 (m), 923 (m); ^{1}H NMR *δ* 0.89 (t, *J*=6.8 Hz, 3H), 1.25–1.56 (m, 8H), 2.23 (br s, 2H, OH), 3.46–3.52 (m, 1H), 3.92–3.96 (m, 1H), 5.25 (d, *J*=10.7 Hz, 1H), 5.36 (d, *J*=17.1 Hz, 1H), 5.87 (ddd, *J*=6.3, 10.7, 17.1 Hz); ^{13}C NMR

δ 14.0, 22.6, 25.3, 31.8, 32.8, 74.3, 76.2, 117.4, 137.7; HRMS (FAB) *m*/*z* calcd for $C_9H_{18}NaO_2Na$ ($[M+Na]^+$) 181.1204, found 181.1212.

4.1.7. Methyl (S)-9-hydroxy-10-undecenoate (**3a**)

To a stirred mixture of powdered 4 Å molecular sieves (10 g) in CH_2Cl_2 (40 ml) was successively added diisopropyl D-tartrate (1.60 ml, 7.56 mmol), Ti(O*i*-Pr)$_4$ (1.86 ml, 6.30 mmol), and a solution of TBHP (ca. 5 M in toluene, 2.52 ml, 12.6 mmol) at −20 °C. After 30 min, a solution of (±)-**3** (1.35 g, 6.30 mmol) in CH_2Cl_2 (30 ml) was added, and the resulting mixture was stirred at −20 °C for 3 days. The mixture was quenched with an ice-cooled solution of $FeSO_4$ (4.4 g) in 10% aq tartaric acid (15 ml), stirred for an additional 30 min, and then gradually warmed to room temperature. After being stirred for 1 h, the mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=6:1 to 2:1) to give **3a** (541 mg, 80% of the theoretical amount) as a pale yellow oil together with an epoxidized product (660 mg, 92% of the theoretical amount) as a colorless oil. $[\alpha]_D^{25}$ +5.75 (*c* 1.00, $CHCl_3$); IR ν 3449 (br m), 3080 (w), 1738 (s), 1199 (m), 1172 (m); ^{1}H NMR δ 1.28–1.43 (m, 7H), 1.47–1.57 (m, 3H), 1.57–1.65 (m, 3H), 2.30 (t, *J*=7.3 Hz, 2H), 3.67 (s, 3H), 4.09 (q, *J*=6.3 Hz, 1H), 5.10 (d, *J*=10.7 Hz, 1H), 5.22 (d, *J*=17.1 Hz, 1H), 5.87 (ddd, *J*=6.3, 10.7, 17.1 Hz, 1H); ^{13}C NMR δ 24.9, 25.2, 29.0, 29.1, 29.3, 34.1, 37.0, 51.5, 73.2, 114.6, 141.3, 174.3; HRMS (FAB) *m*/*z* calcd for $C_{12}H_{23}O_3$ ($[M+H]^+$) 215.1647, found 215.1644.

4.1.8. Determination of the enantiomeric excess of **3a**

Compound **3a** was converted into the corresponding (*R*)- and (*S*)-MTPA esters (**9**) by treating with (*S*)- and (*R*)-MTPACl, respectively, in pyridine. The ^{1}H NMR signal for the olefinic proton at the C10 position of the (*R*)-MTPA ester was observed at 5.72 ppm (ddd, *J*=6.8, 10.7, 17.6 Hz), while that of the (*S*)-MTPA ester appeared at 5.82 ppm (ddd, *J*=7.3, 10.3, 17.6 Hz). In each spectrum of the diastereomeric MTPA esters, no signal due to the corresponding diastereomer was observed. Therefore, compound **3a** was estimated to be optically pure within the limit of NMR detection.

4.1.9. Methyl (S)-9-(tert-butyldimethylsilyl)oxy-10-undecenoate (**3b**)

To a stirred solution of **3a** (63.1 mg, 0.294 mmol) in DMF (0.5 ml) were added imidazole (60.1 mg, 0.883 mmol) and TBSCl (66.5 mg, 0.442 mmol) at 0 °C. The mixture was gradually warmed to room temperature over 4 h, quenched with brine, and then extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=100:1) to give **3b** (82.8 mg, 86%) as a pale yellow oil. $[\alpha]_D^{23}$ −6.00 (*c* 1.00, $CHCl_3$); IR ν 1742 (s), 1252 (m), 1199 (w), 1171 (w), 836 (m), 775 (m); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 1.29 (m, 8H), 1.40–1.50 (m, 2H), 1.62 (m, 2H), 2.30 (t, *J*=7.3 Hz, 2H), 3.67 (s, 3H), 4.09 (dt, *J*=5.9, 6.3 Hz, 1H), 5.01 (d, *J*=10.3 Hz, 1H), 5.12 (d, *J*=17.1 Hz, 1H), 5.79 (ddd, *J*=6.3, 10.3, 17.1 Hz, 1H); ^{13}C NMR δ −4.8, −4.4, 18.3, 24.9, 25.1, 25.9 (3C), 29.1, 29.2, 29.4, 34.1, 38.0, 51.4, 73.8, 113.4, 141.9, 174.3; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{36}O_3SiNa$ ($[M+Na]^+$) 351.2331, found 351.2334.

4.1.10. Methyl (9S,10E,12S,13S)-9,12,13-trihydroxy-10-octadecenoate (**13a**)

To a stirred solution of **2b** (20.0 mg, 0.126 mmol) and **3a** (81.2 mg, 0.379 mmol) in CH_2Cl_2 (2.5 ml) was added the second generation Grubbs catalyst (5.4 mg, 6.3 μmol) at room temperature, and the mixture was stirred at 40 °C for 5 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=1:1) to give **13a** (14.8 mg, 35%) as a white solid together with the homodimer of **2b** (9.6 mg), the homodimer of **3a** (32.3 mg), and the starting material **3a** (26.0 mg). Mp 92.5–93.0 °C; $[\alpha]_D^{26}$ −9.00 (*c* 0.60, $CHCl_3$) (lit.[3] $[\alpha]_D^{25}$ −7.03 (*c* 1.28, $CHCl_3$)); IR ν 3542 (m), 3314 (br m), 1729 (s), 1250 (m), 1175 (m), 975 (m); ^{1}H NMR ($CDCl_3/D_2O$) δ 0.89 (t, *J*=6.8 Hz, 3H), 1.26–1.56 (m, 18H), 1.58–1.64 (m, 2H), 2.30 (t, *J*=7.3 Hz, 2H), 3.45–3.49 (m, 1H), 3.67 (s, 3H), 3.94 (t, *J*=6.3 Hz, 1H), 4.14 (q, *J*=5.9 Hz, 1H), 5.71 (dd, *J*=6.3, 15.6 Hz, 1H), 5.82 (dd, *J*=5.9, 15.6 Hz, 1H); ^{13}C NMR δ 14.0, 22.6, 24.8, 25.2, 25.3, 28.9, 29.1, 29.2, 31.8, 32.9, 34.0, 37.1, 51.5, 72.0, 74.6, 75.3, 129.7, 136.2, 174.4; HRMS (FAB) *m*/*z* calcd for $C_{19}H_{37}O_5$ ($[M+H]^+$) 345.2641, found 345.2641.

4.1.11. Methyl (9S,10E,12S,13S)-9-(tert-butyldimethylsilyl)oxy-12,13-dihydroxy-10-octadecenoate (**13b**)

To a stirred solution of **2b** (13.0 mg, 82.2 μmol) and **3b** (81.1 mg, 0.246 mmol) in CH_2Cl_2 (6.5 ml) was added the second generation Grubbs catalyst (1.7 mg, 2.0 μmol) at room temperature, and the mixture was stirred at 40 °C. After 2.5 h, additional catalyst (1.7 mg, 2.0 μmol) was added, and resulting mixture was stirred at 40 °C for another 2.5 h. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (hexane/EtOAc=10:1 to 3:1) to give **13b** (9.1 mg, 24%) as a yellow oil together with the homodimer of **2b** (6.7 mg), and the starting material **3b** (72.7 mg). $[\alpha]_D^{22}$ −11.9 (*c* 0.13, $CHCl_3$); IR ν 3410 (br m), 1742 (s), 1251 (m), 1198 (w), 1172 (w), 971 (w), 835 (m), 775 (m); ^{1}H NMR ($CDCl_3/D_2O$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.89 (t, *J*=6.6 Hz, 3H), 1.25–1.53 (m, 20H), 1.60–1.62 (m, 2H), 2.30 (t, *J*=7.3 Hz, 2H), 3.43 (dt, *J*=2.4, 6.8 Hz, 1H), 3.67 (s, 3H), 3.90 (t, *J*=6.8 Hz, 1H), 4.12 (dt, *J*=5.9, 6.3 Hz, 1H), 5.59 (dd, *J*=6.8, 15.6 Hz, 1H), 5.75 (dd, *J*=5.9, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.8, −4.4, 14.0, 18.2, 22.6, 24.8, 25.0, 25.2, 25.9, 29.0, 29.1, 29.3, 31.9, 32.9, 34.1, 38.1, 51.5, 72.6, 74.7, 75.7, 128.4, 137.2, 174.4; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{50}O_5SiNa$ ($[M+Na]^+$) 481.3325, found 481.3324.

4.1.12. (9S,10E,12S,13S)-9,12,13-Trihydroxy-10-octadecenoic acid (**1**)

To a stirred solution of **13a** (10.5 mg, 30 μmol) in MeOH (0.140 ml) was added 1 M NaOH aq (35 μl, 35 μmol) and the mixture was stirred at 40 °C for 5 h. The mixture was quenched with 1 M HCl aq (35 μl) at 0 °C and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 ($CHCl_3$/MeOH=10:1) to give **1** (8.5 mg, 85%) as a white solid. Mp 103.5–104.0 °C (lit.[8] mp 104–106 °C, lit.[11] mp 104–106 °C); $[\alpha]_D^{25}$ −9.8 (*c* 0.30, MeOH) (lit.[5] $[\alpha]_D^{28}$ −8.1 (*c* 0.32, MeOH), lit.[8] $[\alpha]_D^{25}$ −8.0 (*c* 0.30, MeOH), lit.[11] $[\alpha]_D^{25}$ −7.9 (*c* 0.30, MeOH)); IR ν 3543 (m), 3317 (br m), 2954 (w), 2921 (s), 2846 (s), 1693 (s), 1461 (w), 1070 (w), 974 (w); ^{1}H NMR (CD_3OD) δ 0.91 (t, *J*=6.8 Hz, 3H), 1.25–1.43 (m, 14H), 1.44–1.63 (m, 6H), 2.26 (t, *J*=7.3 Hz), 3.38–3.43 (m, 1H), 3.90 (t, *J*=5.4 Hz, 1H), 4.04 (q, *J*=5.4 Hz, 1H), 5.67 (dd, *J*=5.4, 15.6 Hz, 1H), 5.71 (dd, *J*=5.4, 15.6 Hz, 1H); ^{13}C NMR (CD_3OD) δ 14.5, 23.8, 26.3, 26.5, 26.7, 30.3, 30.5, 30.6, 33.2, 33.6, 35.5, 38.4, 73.1, 75.8, 76.6, 131.1, 136.6, 178.4; HRMS (FAB) *m*/*z* calcd for $C_{18}H_{35}O_5Na$ ($[M+Na]^+$) 353.2304, found 353.2307.

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **4**–**8**, **2a**, **2b**, **3a**, **3b**, **9**, **13a**, **13b**, and **1**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.063.

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