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Stereoselective synthesis of malyngic acid and fulgidic acid

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ABSTRACT

A new stereoselective total synthesis of malyngic acid has been achieved from a known oxazolidinone derivative via eight steps involving the Evans asymmetric alkylation as the chirality-inducing step and chelation-controlled $Zn(BH_4)_2$ reduction of an α-hydroxy ketone intermediate for the installation of the 12,13-*anti* stereochemistry. Fulgidic acid, the C12-epimer of malyngic acid, has also been synthesized in eight steps from the same starting material by using *syn*-selective K-Selectride reduction of an α-alkoxy ketone intermediate.

1. Introduction

Malyngic acid (**1**), which belongs to the oxylipin family of natural products, was isolated by Cardellina and Moore from the marine blue-green alga *Lyngbya majuscula*, and characterized as a trihydroxy unsaturated fatty acid on the basis of spectroscopic analyses coupled with chemical degradation to known compounds (Fig. 1).[1] Fulgidic acid (**2**), on the other hand, was first isolated by Herz and Kulanthaivel from the terrestrial higher plant *Rudbeckia fulgida*, and identified as the C12-epimer of **1** from the comparison of its NMR data with those of malyngic acid (**1**).[2] Soon after the isolation from *R. fulgida*, the fatty acid **2** was also isolated by Kato and co-workers from the rice plant *Oryza sativa* along with its 15,16-dihydro analog **3**. Both **2** and **3** were found to play an essential role in the self defense of the rice plant by exhibiting antifungal activity against the rice blast fungus *Pyricularia oryzae*.[3] Compound **3** was later reisolated by Nagai and co-workers from the medicinal plant *Pinelliae tuber* as an effective oral adjuvant for nasal influenza vaccine, and named pinellic acid.[4] The interesting arrangement of hydroxyls on the unsaturated fatty acid chains of **1**–**3** as well as the agriculturally and medicinally important bioactivities of **2** and **3**, respectively, prompted a considerable number of synthetic studies on these natural products.[5–7] From the viewpoint of methodology to install the C12,13-stereochemistry, those syntheses could be classified into four groups: (1) ring opening of a *cis*-substituted epoxide with oxygen nucleophiles;[3] (2) the Sharpless asymmetric oxidations;[4b,5a,6e,7d,e,g,h] (3) derivation from natural products with an appropriate vicinal diol unit;[5b,6b,c,7b,i,j,l] and (4) diastereoselective addition of organometallics to α-oxygenated aldehydes.[7f,k] We describe herein a new stereodivergent approach to **1** and **2** using two types of diastereoselective reductions of chiral α-oxygenated ketone intermediates for the establishment of the C12,13-*anti* and cis stereochemistries embedded in **1** and **2**, respectively.

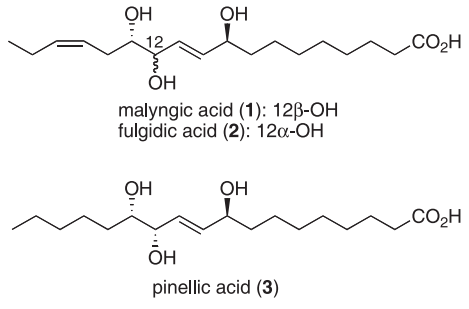

Fig. 1. Structures of malyngic acid (**1**), fulgidic acid (**2**), and pinellic acid (**3**).

2. Results and discussion

Our retrosynthetic analysis of **1** and **2** is shown in Scheme 1. We envisaged that malyngic acid **1** with C12,13-*anti* stereochemistry would be obtainable from **4** via a diastereoselective reduction under chelation-controlled conditions, while fulgidic acid **2**, the

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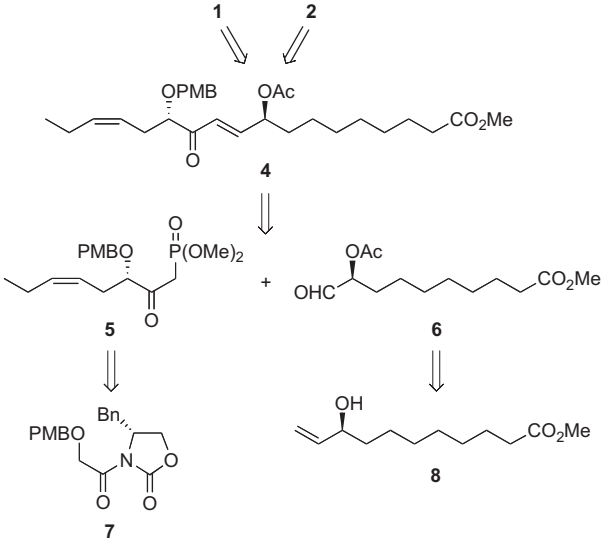
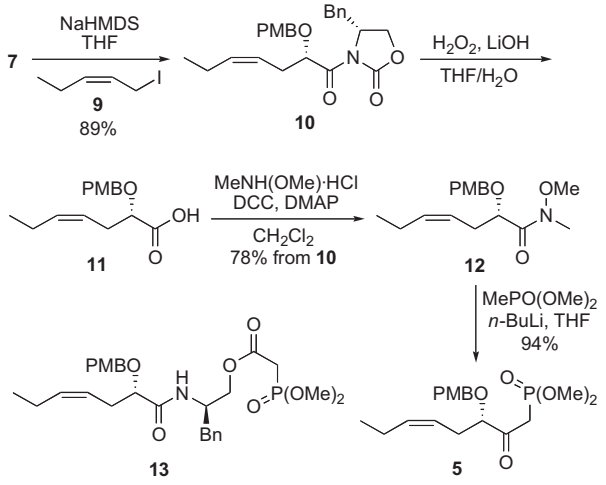
C12,13-*syn* epimer of **1**, could be synthesized from the common intermediate **4** by means of a *syn*-selective reduction according to the Felkin–Anh transition state model. The α-alkoxy ketone intermediate **4** would be traced back to phosphonate **5** and aldehyde **6** by dissecting the double bond conjugated to the ketone function. The PMBO-bearing chiral center of **5** was considered to be installed by the Evans asymmetric alkylation of known oxazolidinone derivative **7**, and the α-acetoxy aldehyde **6** would be prepared by the oxidative cleavage of the double bond of known allylic alcohol **8**.



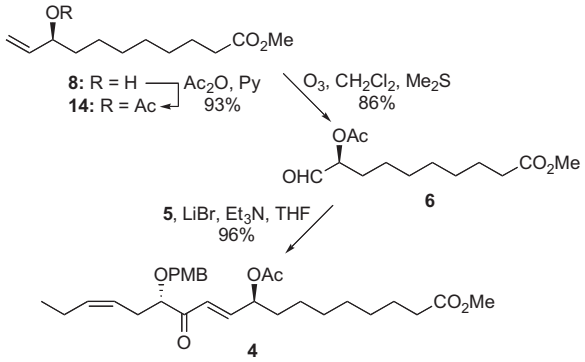
Scheme 1. Retrosynthetic analysis of **1** and **2**.

According to our synthetic plan, the starting material **7**[8] was subjected to the Evans asymmetric alkylation with (*Z*)-1-iodo-2-pentene **9**[9] to give **10** in 89% yield (Scheme 2).[10] Hydrolytic removal of the oxazolidinone moiety of **10** with alkaline hydrogen peroxide afforded carboxyallic acid **11**, which was then converted into the corresponding Weinreb amide **12** in 78% overall yield from **10**. Treatment of **12** with the carbanion prepared from dimethyl methylphosphonate and *n*-BuLi gave keto phosphonate **5** in 94% yield.[11] In order to transform **10** into **5** in a single step, we also attempted the direct treatment of **10** with the phosphonate carbanion in THF. This reaction, however, resulted in the formation of a mixture containing the desired product **5** (35% isolated yield) and amide **13** (24% isolated yield) stemming from the undesired nucleophilic attack of the carbanion at the ring carbonyl.[12]



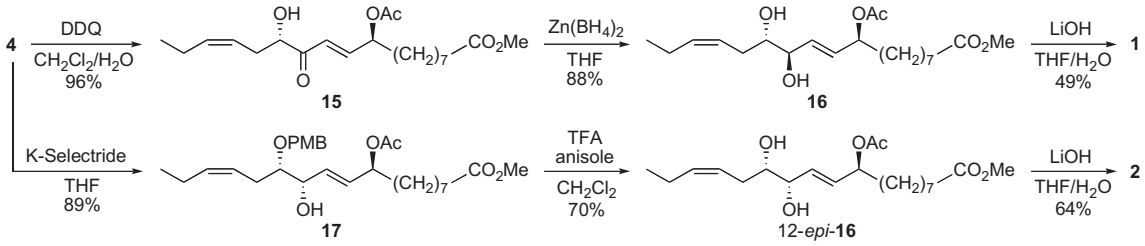
Scheme 2. Preparation of phosphonate intermediate **5**.

The preparation of the other building block **6** was achieved in two steps consisting of the acetylation of the known chiral allylic alcohol **8** and ozonolysis of the resulting acetate **14** (Scheme 3); compound **8** in turn was obtained in 80% yield with >98% enantiomeric excess by the Sharpless kinetic resolution of the corresponding racemate according to our previous procedure.[7j] The Horner–Wadsworth–Emmons (HWE) olefination between **5** and **6** proceeded smoothly to give **4** in 96% yield after chromatographic removal of a minute amount of its *Z*-siomer contained in the crude reaction product.



Scheme 3. Preparation of key intermediate **4**.

With the key intermediate **4** in hand, we went on to the final stage of the synthesis of **1** and **2** (Scheme 4). Oxidative removal of the PMB group of **4** with DDQ gave hydroxy ketone **15**, which was then subjected to reduction with $Zn(BH_4)_2$.[13] As was predicted from many precedents, this chelation-controlled reduction proceeded highly diastereoselectively to afford 12,13-*anti* diol **16** in 88% yield after chromatographic purification. Finally, hydrolysis of the two ester groups with aq LiOH furnished malyngic acid **1** as a white solid, the spectral and physical properties of which showed good agreement with those of the natural product.[1] To synthesize the other target molecule, fulgidic acid (**2**), the PMB-protected ketone **4** was reduced with K-Selectride in THF to give a 16:1 diastereomeric mixture of 12,13-*syn* diol **17** and its C12-epimer.[14] Reduction of **4** with L-Selectride/THF,[15] $NaBH_4/CeCl_3$/MeOH,[16] and $NaBH_4$/MeOH also gave the Felkin–Anh product **17** preferentially in yields of 75%, 94%, and 98%, respectively, but the diastereoselectivities of these conditions were lower (9:1, 5.7:1, 2.3:1, respectively) than that of



Scheme 4. Stereodivergent conversion of **4** into **1** and **2**.

the K-Selectride conditions. Deprotection of the PMB group of **17** with TFA in CH_2Cl_2 in the presence of anisole followed by chromatographic removal of a small amount of **16** originating from 12-*epi*-**17** afforded 12-*epi*-**16**,[17] which was then hydrolyzed to give fulgidic acid **2** as a white solid. The ^1H and ^{13}C NMR data of **2** were identical with those of natural fulgidic acid.[18]

3. Conclusion

An enantioselective total synthesis of malygic acid (**1**) was achieved in 26% overall yield from known oxazolidinone derivative **7** via eight steps. The new synthetic route utilized the Evans asymmetric alkylation as the chirality-inducing step and established the 12,13-*anti* stereochemistry of **1** by chelation-controlled $Zn(BH_4)_2$ reduction of α-hydroxy ketone intermediate **15** prepared from its PMB-protected form **4**. Fulgidic acid (**2**), the C12-epimer of **1**, was also synthesized from **7** in 25% overall yield via eight steps involving *syn*-selective K-Selectride reduction of the common intermediate **4** as the pivotal transformation.

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 MR-400 spectrometer (400 MHz for ^1H and 100 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. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Column chromatography was conducted with Merck silica gel 60 (7–230 mesh) or Kanto Kagaku silica gel 60 N (spherical neutral, particle size 100–210 μm). Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and CH_3CN from CaH_2.

*4.1.1. (Z)-1-Iodo-2-pentene (**9**).* To a stirred solution of (*Z*)-2-penten-1-ol (0.500 mL, 4.95 mmol) and NaI (1.50 g, 10.0 mmol) in CH_3CN (15 mL) was added $BF_3{\cdot}OEt_2$ (1.30 mL, 10.3 mmol) at 0 °C under N_2. The mixture was stirred at room temperature for 1.25 h and quenched with satd aq $NaHCO_3$ and $Na_2S_2O_3$. The mixture was extracted with pentane and the extract was successively washed with water (×2) and brine, dried ($MgSO_4$), and concentrated in vacuo to give **9** (694 mg, 71%). IR: ν_{max} 3016 (m), 1640 (w), 1146 (s), 742 (m); ^1H NMR: δ 1.03 (3H, t, *J*=7.6 Hz), 2.07–2.16 (2H, m), 3.92 (2H, d, *J*=8.8 Hz), 5.48 (1H, dt, *J*=10.6, 7.4 Hz), 5.68–5.77 (1H, m); ^{13}C NMR: δ 0.5, 13.0, 20.1, 126.0, 136.4; HRMS (EI): *m*/*z* calcd for C_5H_9I, 195.9749; found, 195.9751 (M^+). This compound was chemically and isomerically pure enough to enable its direct use in the next step without chromatographic purification.

*4.1.2. (R)-4-Benzyl-3-[(S)-2-(4-methoxybenzyloxy)-4-heptenoyl]-2-oxazolidinone (**10**).* To a stirred solution of NaHMDS (1.07 M in THF, 1.65 mL, 1.77 mmol) in THF (10 mL) was added dropwise a solution of **7** (420 mg, 1.18 mmol) in THF (5 mL) at −78 °C under N_2. After 1 h, a solution of **9** (688 mg, 3.51 mmol) in THF (5 mL) was added, and the resulting mixture was stirred at the same temperature for 3 h. The mixture was quenched with satd aq NH_4Cl and extracted with hexane/EtOAc (1:1). The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **10** (447 mg, 89%). $[\alpha]_D^{25}$ −80.5 (*c* 1.10, $CHCl_3$); IR: ν_{max} 1775 (vs), 1705 (s), 1612 (w), 1513 (m), 1245 (s); ^1H NMR: δ 0.95 (3H, t, *J*=7.6 Hz), 2.03–2.11 (2H, m), 2.50–2.64 (2H, m), 2.70 (1H, dd, *J*=13.3, 9.7 Hz), 3.23 (1H, dd, *J*=13.3, 3.3 Hz), 3.79 (3H, s), 4.12–4.17 (2H, m), 4.48 (1H, d, *J*=11.2 Hz), 4.53 (1H, d, *J*=11.2 Hz), 4.56–4.62 (1H, m), 5.12 (1H, dd, *J*=7.1, 5.0 Hz), 5.43–5.56 (2H, m), 6.84–6.88 (2H, m), 7.18–7.21 (2H, m), 7.27–7.35 (5H, m); ^{13}C NMR: δ 14.1, 20.7, 30.8, 37.9, 55.0, 55.3, 66.7, 72.4, 76.5, 113.6 (2C), 122.8, 127.4, 128.9 (2C), 129.4 (2C), 129.7, 130.0 (2C), 134.8, 135.0, 153.0, 159.3, 172.7; HRMS (FAB): *m*/*z* calcd for $C_{25}H_{29}NO_5Na$, 446.1944; found, 446.1944 ($[M+Na]^+$).

*4.1.3. (2S,4Z)-N-Methoxy-2-(4-methoxybenzyloxy)-N-methyl-4-heptenamide (**12**).* To a stirred solution of **10** (1.02 g, 2.41 mmol) in THF/H_2O (3:1, 48 mL) were added dropwise 30% aq H_2O_2 (930 mg, 8.20 mmol) and $LiOH{\cdot}H_2O$ (200 mg, 4.77 mmol) at 0 °C. After 1.5 h, the mixture was quenched with 1.5 M aq Na_2SO_3 and gradually warmed to room temperature over 1.5 h. The mixture was concentrated in vacuo, and the residue was diluted with EtOAc and extracted with satd aq $NaHCO_3$. The aqueous solution was acidified with 2 M aq HCl to pH ca. 2, and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give **11** (548 mg). To a stirred solution of **11** (539 mg, 2.04 mmol) in CH_2Cl_2 (10 mL) were added MeNH(OMe)·HCl (300 mg, 3.08 mmol), DMAP (429 mg, 3.51 mmol), and DCC (724 mg, 3.51 mmol) at 0 °C under N_2. The mixture was gradually warmed to room temperature over 3 h and filtered through a pad of Celite. The filtrate was successively washed with satd aq NH_4Cl, satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **12** (570 mg, 78% from **10**). $[\alpha]_D^{27}$ +46.8 (*c* 1.10, $CHCl_3$); IR: ν_{max} 1670 (s), 1612 (m), 1513 (s), 1246 (s); ^1H NMR: δ 0.93 (3H, t, *J*=7.6 Hz), 1.99–2.08 (2H, m), 2.43–2.55 (2H, m), 3.20 (3H, s), 3.58 (3H, s), 3.80 (3H, s), 4.28 (1H, br t, *J*=5.7 Hz), 4.35 (1H, d, *J*=11.5 Hz), 4.62 (1H, d, *J*=11.5 Hz), 5.37–5.53 (2H, m), 6.84–6.88 (2H, m), 7.26–7.30 (2H, m); ^{13}C NMR: δ 14.1, 20.5, 30.1, 32.3, 55.2, 61.3, 71.0, 75.0, 113.6 (2C), 123.6, 129.5 (2C), 129.9, 134.2, 159.2, 172.9; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{26}NO_4$, 308.1862; found, 308.1865 ($[M+H]^+$).

*4.1.4. Dimethy [(S)-3-(4-methoxybenzyloxy)-2-oxo-5-octenyl]phosphonate (**5**).* To a stirred solution of $MeP(O)(OMe)_2$ (0.903 mL, 8.33 mmol) in THF (50 mL) was added dropwise a solution of *n*-BuLi (1.59 M in hexane, 5.00 mL, 7.59 mmol) at −78 °C under N_2. After 1 h, a solution of **12** (513 mg, 1.67 mmol) in THF (10 mL) was added, and the resulting mixture was stirred for 5 h. The mixture was quenched with satd aq NH_4Cl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **5** (580 mg, 94%). $[\alpha]_D^{25}$ −17.3 (*c* 1.13, $CHCl_3$); IR: ν_{max} 1718 (w), 1612 (w), 1514 (m), 1247 (s), 1025 (vs); ^1H NMR: δ 0.95 (3H, t, *J*=7.6 Hz), 1.99–2.08 (2H, m), 2.40–2.53 (2H, m), 3.16 (1H, dd, *J*=21.9, 14.6 Hz), 3.32 (1H, dd, *J*=21.7, 14.6 Hz), 3.76 (3H, d, *J*=5.7 Hz), 3.79 (3H, d, *J*=5.5 Hz), 3.81 (3H, s), 4.46 (1H, d, *J*=11.2 Hz), 4.57 (1H, d, *J*=11.2 Hz), 5.29–5.37 (1H, m), 5.47–5.54 (1H, m), 6.86–6.90 (2H, m), 7.26–7.30 (2H, m); ^{13}C NMR: δ 14.0, 20.6, 29.3, 36.2 (d, *J*=133.1 Hz), 52.9 (d, *J*=5.3 Hz), 53.0 (d, *J*=5.3 Hz), 55.2, 72.2, 84.0 (d, *J*=2.9 Hz), 113.8 (2C), 122.6, 129.4, 129.6 (2C), 134.9, 159.4, 203.9 (d, *J*=6.9 Hz); HRMS (FAB): *m*/*z* calcd for $C_{18}H_{28}O_6P$, 371.1623; found, 371.1625 ($[M+H]^+$).

*4.1.5. Methyl (S)-9-acetoxy-10-undecenoate (**14**).* To a stirred solution of **8** (112 mg, 0.523 mmol) in pyridine (0.26 mL) was added Ac_2O (0.15 mL, 1.59 mmol) at room temperature. After 6.5 h, the mixture was quenched with satd aq $NaHCO_3$, stirred for 35 min, and then extracted with ether. The extract was successively washed with cold 1 M HCl (×2), satd aq $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **14** (124 mg, 93%). $[\alpha]_D^{25}$ −7.25 (*c* 1.02, $CHCl_3$); IR: ν_{max} 1736 (vs), 1650 (w), 1235 (s); ^1H NMR: δ 1.25–1.34 (8H, m), 1.56–1.66 (4H, m), 2.06 (3H, s),

2.30 (2H, t, J=7.7 Hz), 3.67 (3H, s), 5.13–5.25 (3H, m), 5.77 (1H, ddd, J=17.3, 10.5, 6.3 Hz); ^{13}C NMR: δ 21.2, 24.8, 24.9, 28.97, 29.04, 29.1, 34.0, 34.1, 51.4, 74.8, 116.5, 136.6, 170.3, 174.2; HRMS (FAB): m/z calcd for $C_{14}H_{25}O_4$, 257.1753; found, 257.1758 ([M+H]$^+$).

*4.1.6. Methyl (S)-9-acetoxy-10-oxodecanoate (**6**).* Ozone was bubbled into a stirred solution of **14** (124 mg, 0.484 mmol) in CH_2Cl_2 (6 mL) at −78 °C until the disappearance of **14** was observed by TLC monitoring. Me_2S (excess) was then added, and the mixture was gradually warmed to room temperature. The mixture was concentrated in vacuo, and the residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **6** (107 mg, 86%). $[\alpha]_D^{25}$ −23.5 (c 1.15, $CHCl_3$); IR: ν_{max} 2725 (w), 1734 (s), 1230 (m); ^{1}H NMR: δ 1.28–1.36 (6H, m), 1.36–1.45 (2H, m), 1.57–1.66 (2H, m), 1.67–1.87 (2H, m), 2.18 (3H, s), 2.30 (2H, t, J=7.5 Hz), 3.67 (3H, s), 4.98 (1H, br dd, J=8.3, 4.8H), 9.51 (1H, d, J=0.8 Hz); ^{13}C NMR: δ 20.6, 24.8, 28.5 (2C), 28.9 (2C), 29.0, 34.0, 51.4, 78.2, 170.6, 174.2, 198.3; HRMS (FAB): m/z calcd for $C_{13}H_{23}O_5$, 259.1545; found, 259.1550 ([M+H]$^+$).

*4.1.7. Methyl (9S,13S)-9-acetoxy-13-(4-methoxybenzyloxy)-12-oxo-10,15-octadecadienoate (**4**).* A mixture of **5** (821 mg, 2.22 mmol) and $LiBr\cdot H_2O$ (465 mg, 4.43 mmol) in THF (27 mL) was stirred at room temperature for 30 min under N_2. To the mixture was added dropwise Et_3N (0.37 mL, 2.65 mmol) and the mixture was stirred for 1 h. A solution of **6** (601 mg, 2.33 mmol) in THF (22 mL) was then added, and the resulting mixture was stirred overnight at room temperature. The mixture was quenched with satd aq NH_4Cl, concentrated in vacuo, diluted with water, and then extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **4** (1.07 g, 96%) as a single geometrical isomer. $[\alpha]_D^{25}$ −33.2 (c 1.16, $CHCl_3$); IR: ν_{max} 1737 (s), 1698 (m), 1514 (m), 1232 (s); ^{1}H NMR: δ 0.92 (3H, t, J=7.5 Hz), 1.26–1.36 (8H, m), 1.56–1.69 (4H, m), 1.93–2.05 (2H, m), 2.10 (3H, s), 2.30 (2H, t, J=7.6 Hz), 2.44 (2H, t, J=6.9 Hz), 3.66 (3H, s), 3.81 (3H, s), 3.92 (1H, t, J=6.6 Hz), 4.36 (1H, d, J=11.2 Hz), 4.49 (1H, d, J=11.2 Hz), 5.28–5.36 (1H, m), 5.38–5.44 (1H, m), 5.44–5.52 (1H, m), 6.61 (1H, dd, J=15.7, 1.5 Hz), 6.84–6.91 (3H, m), 7.22–7.27 (2H, m); ^{13}C NMR: δ 14.0, 20.6, 21.0, 24.8, 24.9, 28.96, 29.01, 29.1, 30.2, 33.8, 34.0, 51.4, 55.2, 72.0, 72.8, 83.8, 113.8 (2C), 122.6, 124.0, 129.4, 129.7 (2C), 134.7, 144.9, 159.4, 170.0, 174.2, 200.7; HRMS (EI): m/z calcd for $C_{29}H_{42}O_7Na$, 525.2829; found, 525.2830 ([M+Na]$^+$).

*4.1.8. Methyl (9S,10E,13S,15Z)-9-acetoxy-13-hydroxy-12-oxo-10,15-octadecadienoate (**15**).* To a stirred mixture of **4** (206 mg, 0.410 mmol) and water (0.4 mL) in CH_2Cl_2 (4.1 mL) was added DDQ (280 mg, 1.23 mmol) at 0 °C. The mixture was warmed to room temperature and stirred overnight. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **15** (151 mg, 96%). $[\alpha]_D^{25}$ +4.5 (c 1.02, $CHCl_3$); IR: ν_{max} 3481 (w), 1737 (s), 1697 (m), 1635 (m), 1231 (s); ^{1}H NMR: δ 0.95 (3H, t, J=7.5 Hz), 1.26–1.37 (8H, m), 1.57–1.70 (4H, m), 1.98–2.07 (2H, m), 2.11 (3H, s), 2.30 (2H, t, J=7.6 Hz), 2.37–2.45 (1H, m), 2.54–2.62 (1H, m), 3.48 (1H, br s, OH), 3.67 (3H, s), 4.43 (1H, t, J=5.5 Hz), 5.28–5.36 (1H, m), 5.39–5.45 (1H, m), 5.50–5.58 (1H, m), 6.36 (1H, dd, J=15.6, 1.4 Hz), 6.90 (1H, dd, J=15.6, 5.3 Hz); ^{13}C NMR: δ 14.1, 20.7, 20.9, 24.77, 24.84, 28.9, 28.95, 29.01, 31.8, 33.7, 33.9, 51.4, 72.5, 75.3, 122.0, 123.9, 135.4, 145.7, 170.0, 174.2, 199.9; HRMS (FAB): m/z calcd for $C_{21}H_{35}O_6$, 383.2433; found, 383.2435 ([M+H]$^+$).

*4.1.9. Methyl (9S,10E,12R,13S,15Z)-9-acetoxy-12,13-dihydroxy-10,15-octadecadienoate (**16**).* To a stirred solution of $ZnCl_2$ (71.2 mg, 0.522 mmol) in THF (1 mL) was added $NaBH_4$ (40.0 mg, 1.06 mmol) at 0 °C under Ar. The mixture was stirred overnight at room temperature, and then re-cooled to 0 °C. To the mixture was added dropwise a solution of **15** (50.0 mg, 0.131 mmol) in THF (5 mL). After 30 min, the mixture was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **16** (44.1 mg, 88%). $[\alpha]_D^{25}$ −20.1 (c 1.17, $CHCl_3$); IR: ν_{max} 3468 (m), 1736 (s), 1237 (s), 1020 (m); ^{1}H NMR: δ 0.97 (3H, t, J=7.6 Hz), 1.24–1.34 (8H, m), 1.52–1.69 (4H, m), 2.01–2.10 (2H, m), 2.05 (3H, s), 2.11–2.19 (1H, m), 2.21–2.29 (1H, m), 2.30 (2H, t, J=7.5 Hz), 2.48 (1H, br s, OH), 3.67 (3H, s), 3.66–3.72 (1H, m), 4.16 (1H, dd, J=5.5, 3.9 Hz), 5.22 (1H, q, J=6.5 Hz), 5.33–5.41 (1H, m), 5.52–5.59 (1H, m), 5.70 (1H, dd, J=15.8, 6.5 Hz), 5.78 (1H, dd, J=15.8, 6.0 Hz); ^{13}C NMR: δ 14.2, 20.7, 21.3, 24.8, 25.0, 28.9, 29.00, 29.04, 29.8, 34.0, 34.3, 51.4, 73.8, 74.3 (2C), 124.1, 130.5, 131.5, 135.1, 170.5, 174.3; HRMS (FAB): m/z calcd for $C_{21}H_{37}O_6$, 385.2590; found, 385.2595 ([M+H]$^+$).

*4.1.10. (9S,10E,12R,13S,15Z)-9,12,13-Trihydroxy-10,15-octadecadienoate (**1**).* A mixture of **16** (36.0 mg, 0.0936 mmol), water (0.05 mL), and $LiOH\cdot H_2O$ (43.6 mg, 1.04 mmol) in THF (0.15 mL) was stirred for 3 h at room temperature and for an additional 1 h at 40 °C. The mixture was concentrated in vacuo, diluted with water, and then extracted with ether. The aq solution was acidified with 0.9 M citric acid to pH 3 and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH) to give **1** (15.2 mg, 49%) as a white solid. Mp: 48.7–49.8 °C (lit.[1] mp 48.5–51 °C); $[\alpha]_D^{22}$ +7.4 (c 0.730, MeOH) [lit.[1] $[\alpha]_D^{24.5}$ +7.5 (c 1.2, MeOH), lit.[5a] $[\alpha]_D$ +7.7 (MeOH)]; IR: ν_{max} 3316 (m), 1696 (s), 1434 (m), 1073 (s); ^{1}H NMR (CD_3CN): δ 0.94 (3H, t, J=7.5 Hz), 1.24–1.34 (8H, m), 1.39–1.48 (2H, m), 1.50–1.59 (2H, m), 2.03 (2H, quint, J=7.3 Hz), 2.03–2.12 (1H, m), 2.14–2.22 (1H, m), 2.25 (2H, t, J=7.5 Hz), 3.50 (1H, dt, J=8.4, 4.3 Hz), 3.91–3.95 (1H, m), 3.98–4.03 (1H, m), 5.39 (1H, dtt, J=10.8, 6.8, 1.4 Hz), 5.46 (1H, dtt, J=10.8, 6.8, 1.4 Hz), 5.59–5.68 (2H, m); ^{13}C NMR (CD_3OD): δ 14.6, 21.7, 26.1, 26.5, 30.2, 30.4, 30.5, 31.7, 35.0, 38.3, 73.3, 75.96, 76.02, 126.35, 130.6, 134.4, 136.8, 177.8; HRMS (FAB): m/z calcd for $C_{18}H_{32}O_5Na$, 351.2148; found, 351.2151 ([M+Na]$^+$).

*4.1.11. (9S,10E,12S,13S,15Z)-9-Acetoxy-12-hydroxy-13-(4-methoxybenzyloxy)-10,15-octadecadienoate (**17**).* To a stirred solution of **4** (106 mg, 0.211 mmol) in THF (2.1 mL) was added K-Selectride (1 M in THF, 0.220 mL, 0.220 mmol) at −78 °C under N_2. After 80 min, the mixture was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give **17** (94.2 mg, 89%) as a 16:1 diastereomeric mixture. $[\alpha]_D^{20}$ −3.4 (c 2.57, $CHCl_3$); IR: ν_{max} 3508 (w), 1735 (s), 1613 (w), 1514 (m), 1240 (s); ^{1}H NMR: δ 0.97 (3H, t, J=7.6 Hz), 1.24–1.33 (8H, m), 1.55–1.65 (4H, m), 2.00–2.08 (2H, m), 2.04 (3H, s), 2.24–2.32 (1H, m), 2.29 (2H, t, J=7.5 Hz), 2.36–2.44 (1H, m), 2.54 (1H, d, J=4.5 Hz, OH), 3.32–3.37 (1H, m), 3.66 (3H, s), 3.81 (3H, s), 4.01–4.07 (1H, m), 4.42 (1H, d, J=11.0 Hz), 4.62 (1H, d, J=11.0 Hz), 5.21–5.27 (1H, m), 5.36–5.52 (2H, m), 5.66–5.75 (2H, m), 6.86–6.90 (2H, m), 7.23–7.27 (2H, m); ^{13}C NMR: δ 14.1, 20.7, 21.2, 24.8, 25.0, 28.0, 28.99, 29.04, 29.1, 34.0, 34.3, 51.4, 55.2, 72.1, 72.9, 74.1, 81.5, 113.8 (2C), 123.7, 129.5 (2C), 130.1, 130.9, 132.3, 134.1, 159.3, 170.3, 174.2; HRMS (FAB): m/z calcd for $C_{29}H_{44}O_7Na$, 527.2985; found, 527.2985 ([M+Na]$^+$).

*4.1.12. Methyl (9S,10E,12S,13S,15Z)-9-acetoxy-12,13-dihydroxy-10,15-octadecadienoate (12-epi-**16**).* To a stirred solution of **17** (25.8 mg, 0.0511 mmol) and anisole (54 μL, 0.50 mmol) in CH_2Cl_2 (4.7 mL) was added a solution of TFA (36 μL, 0.47 mmol) in CH_2Cl_2 (0.4 mL) at 0 °C. After being stirred at room temperature for 30 h, the mixture was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The

extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc) to give 12-*epi*-**16** (13.7 mg, 70%) as a 16:1 diastereomeric mixture. This could be further purified by SiO_2 column chromatography to afford diastereomerically pure 12-*epi*-**16**. $[\alpha]_D^{25}$ −36 (*c* 0.48, $CHCl_3$); IR: ν_{max} 3444 (w), 1736 (s), 1237 (s), 1019 (m); ^{1}H NMR: δ 0.97 (3H, t, *J*=7.5 Hz), 1.24–1.34 (8H, m), 1.55–1.66 (4H, m), 1.69 (1H, s, OH), 2.01–2.11 (2H, m), 2.05 (3H, s), 2.20–2.32 (2H, m), 2.30 (3H, t, *J*=7.6 Hz), 2.45 (1H, s, OH), 3.47–3.54 (1H, m), 3.67 (3H, s), 3.95–4.02 (1H, m), 5.20–5.26 (1H, m), 5.35–5.44 (1H, m), 5.53–5.61 (1H, m), 5.68–5.77 (2H, m); ^{13}C NMR: δ 14.2, 20.7, 21.3, 24.8, 24.9, 28.9, 28.99, 29.03, 30.8, 34.0, 34.2, 51.5, 73.97, 74.04, 74.5, 123.7, 131,4, 131.9, 135.2, 170.4, 174.3; HRMS (FAB): *m*/*z* calcd for $C_{21}H_{37}O_6$, 385.2590; found, 385.2591 ($[M+H]^+$).

*4.1.13. (9S,10E,12S,13S,15Z)-9,12,13-Trihydroxy-10,15-octadecadienoate (**2**).* A mixture of 12-*epi*-**16** (53.5 mg, 0.139 mmol), water (0.07 mL), and LiOH·H_2O (35.0 mg, 0.834 mmol) in THF (0.21 mL) was stirred for 2.5 h at room temperature and for an additional 1.5 h at 40 °C. The mixture was acidified with 1 M aq citric acid and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (CH_2Cl_2/MeOH) to give **2** (29.3 mg, 64%) as a white solid. Mp 71.5–72.3 °C; $[\alpha]_D^{23}$ −12 (*c* 0.705, $CHCl_3$) [lit.[18] $[\alpha]_D^{25}$ −7.1 (*c* 1.0, $CHCl_3$)]; IR: ν_{max} 3536 (w), 3322 (m), 3013 (w), 1694 (s); ^{1}H NMR (CD_3OD): δ 0.97 (3H, t, *J*=7.6 Hz), 1.29–1.38 (8H, m), 1.46–1.55 (2H, m), 1.55–1.64 (2H, m), 2.02–2.16 (3H, m), 2.28 (3H, t, *J*=7.5 Hz), 2.35 (1H, dt, *J*=14.6, 4.9 Hz), 3.43–3.48 (1H, m), 3.96 (1H, t, *J*=4.9 Hz), 4.05 (1H, q, *J*=5.1 Hz), 5.41–5.50 (2H, m), 5.67–5.77 (2H, m); ^{13}C NMR (CD_3OD): δ 14.6, 21.7, 26.1, 26.5, 30.2, 30.4, 30.6, 31.5, 35.1, 38.3, 73.0, 75.8, 75.9, 126.4, 131.1, 134.3, 136.5, 177.9; HRMS (FAB): *m*/*z* calcd for $C_{18}H_{31}O_5$, 327.2172; found, 327.2169 ($[M-H]^-$).

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Supplementary data

^{1}H and ^{13}C NMR spectra of compounds **9**, **10**, **12**, **5**, **14**, **6**, **4**, **15**, **16**, **1**, **17**, 12-*epi*-**16**, and **2** can be found. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.005. These data include MOL files and InChiKeys of the most important compounds described in this article.

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