Synthesis of elenic acid, an inhibitor of topoisomerase II from the sponge *Plakinastrella* sp.

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(*R*)-(−)-Elenic acid 1, an inhibitor of topoisomerase II isolated from the marine sponge *Plakinastrella* sp., has been synthesized starting from hexadecane-1,16-diol 2 and methyl (*S*)-3-hydroxy-2-methylpropanoate 6.

Elenic acid **1**, an inhibitor of topoisomerase II, was isolated from the Indonesian sponge *Plakinastrella* sp. and characterized by Scheuer and co-workers in 1995.[1] Elenic acid has a rather unusual structure, in which its phenol portion and β,γ-unsaturated carboxylic acid moiety are linked with a long hydrocarbon chain. Scheuer and co-workers also determined the absolute configuration at C-2 to be *R* by employing Kusumi's method.[2] According to them, its inhibitory activity for topoisomerase II is very strong with an IC_{50} value of 0.1 μg ml^{-1}.[1] Since topoisomerase II is considered to be an indicator enzyme in the treatment of lung cancer,[3] elenic acid offers much promise for clinical use. We became interested in the unique structure and strong activity of elenic acid, and undertook a project to synthesize it stereoselectively.

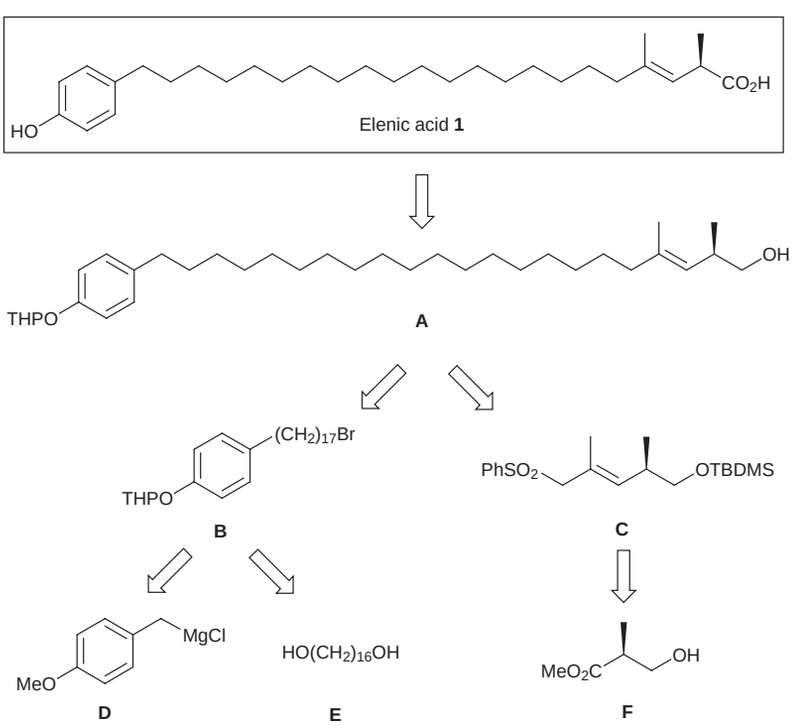
Results and discussion

Synthetic plan

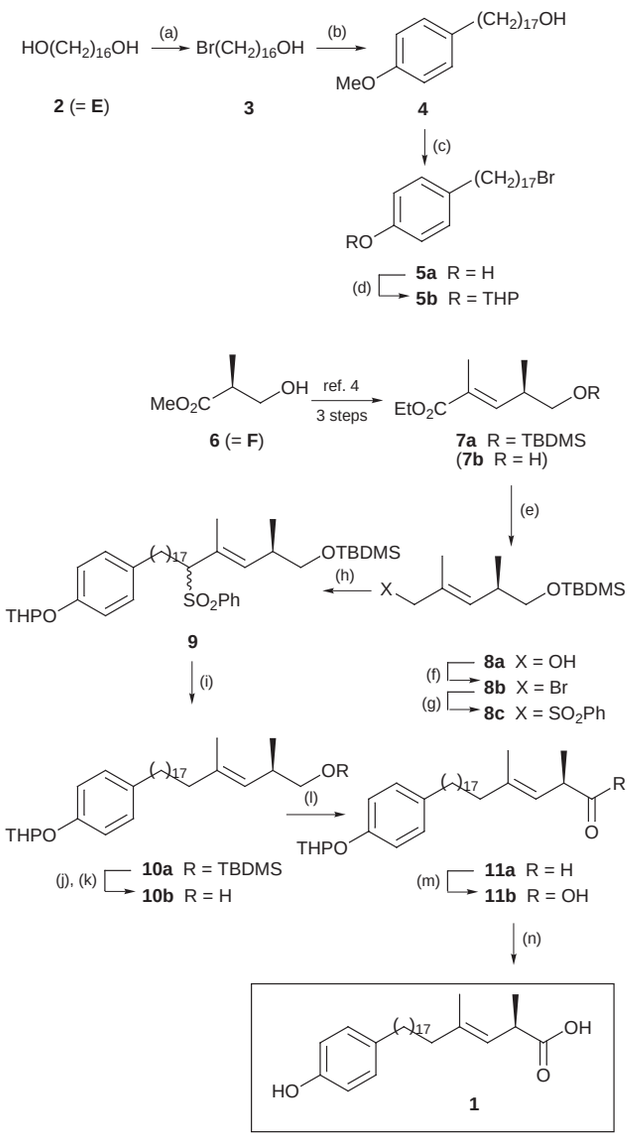
Elenic acid **1** is composed of a phenol, a long chain and a β,γ-unsaturated carboxylic acid portion. Our synthetic plan is shown in Scheme 1. The target compound **1** is easily obtained from **A**, which can be prepared by the coupling of **B** and **C**. The intermediate **B** is obtainable from **D** and **E**, while **C** can be prepared from **F** (>99.8% ee).

The above synthetic plan was realized as follows (Scheme 2). First, hexadecane-1,16-diol (**2**, = **E**) was converted into the corresponding bromohydrin **3** in 57% yield. This was treated with an excess of *p*-methoxybenzylmagnesium chloride (**D**) in the presence of dilithium tetrachlorocuprate (Li_2CuCl_4) to give alcohol **4** in 77% yield. Treatment of **4** with hydrobromic acid afforded 17-*p*-hydroxyphenyl-1-bromoheptadecane **5a** in 76% yield. Tetrahydropyranyl (THP) protection of the phenolic hydroxy group of **5a** gave THP ether **5b** (= **B**) in 97% yield. The overall yield of **5b** was 32% based on **2** in four steps.

Methyl (*S*)-3-hydroxy-2-methylpropanoate **6** (= **F**, >99.8% ee) was converted to the ester **7a** by the known procedure (81%, three steps).[4] The ^1H NMR spectrum of **7a** suggested the *E*:*Z* ratio of **7a** to be 19:1. For determination of the enantiomeric purity of **7a**, it was deprotected to the corresponding alcohol **7b** in the conventional manner. GLC Analysis of **7b** employing a chiral stationary phase allowed the enantiomeric purity of **7b** to be estimated as 94.0% ee (see Experimental). The regioisomeric and enantiomeric purities of **7a** were in accord with those reported[4] and judged as sufficient for the purpose of our



Scheme 1 Structure and retrosynthetic analysis of elenic acid



Scheme 2 Synthesis of elenic acid. *Reagents*, *conditions and yields:* (a) aq. HBr, C_6H_6 (57%); (b) *p*-$MeOC_6H_4CH_2MgCl$, Li_2CuCl_4, THF (77%); (c) aq. HBr, AcOH (76%); (d) DHP, TsOH (97%); (e) DIBAL, hexane, CH_2Cl_2 (quant.); (f) Bu″Li, TsCl, LiBr, Et_2O, HMPA (quant.); (g) $PhSO_2Na{\cdot}2\,H_2O$, DMF (84% yield based on **8a**); (h) Bu″Li, THF, HMPA, **5b** (78%); (i) $PdCl_2$(dppp), $LiEt_3BH$, THF (93%); (j) TBAF, THF (94%); (k) Recrystallization from MeOH (70%); (l) Dess–Martin periodinane, C_5H_5N, CH_2Cl_2 (quant.); (m) $NaClO_2$, NaH_2PO_4, DMSO, MeCN, H_2O (67% based on **10b**); (n) aq. HCl, THF (74%).

synthesis. Reduction of the ester **7a** with diisobutylaluminium hydride (DIBAL) gave the known alcohol **8a**[4] (quant.), which was converted to the corresponding bromide **8b** under Stork's conditions.[5] It was then treated with sodium benzenesulfinate to afford the phenyl sulfone **8c** (= **C**) in 84% yield based on **8a**. The overall yield was 68% based on **6** in six steps.

The resulting sulfone **8c** was treated with Bu″Li and bromide **5b** successively to furnish the coupled product **9** in 78% yield. Reductive cleavage of the phenylsulfonyl group was carried out by employing $LiEt_3BH$ and $PdCl_2(dppp)_2$ in THF according to Inomata and co-workers to give **10a** in 93% yield.[6] However, the ^{1}H NMR spectrum of the resulting compound **10a** suggested it to be contaminated with inseparable by-product(s) (<20%). The most probable structure of the by-product(s) was the double bond isomer(s) with unsaturation at C-4. Compound **10a** could not be purified further. The TBDMS protecting group of **10a** was then removed by treatment with tetrabutylammonium fluoride (TBAF) to give alcohol **10b** (= **A**) in 94% yield. Fortunately, **10b** was a solid and could be purified by recrystallization. After several recrystallizations from methanol, the unwanted (*Z*)-isomer and the double bond positional isomer(s) could be removed completely, and pure **10b** was obtained in 70% yield. Purified **10b** was then oxidized with Dess–Martin periodinane[7] followed by sodium chlorite[8] to afford carboxylic acid **11b** (67%, two steps). Finally, removal of the THP group was achieved by treatment with hydrochloric acid to give (*R*)-elenic acid **1** as a white amorphous powder, $[a]_D^{25}$ −30 (*c* 0.38, $CHCl_3$) {lit.,[1] −27.2 (*c* 2.2, $CHCl_3$)}, in 74% yield. The overall yield of **1** was 7.6% based on **2** in 10 steps or 16% based on **6** in 12 steps. The enantiomeric purity of synthetic **1** was estimated to be 87.3% ee by means of HPLC analysis (see Experimental). The reason for the partial loss of enantiomeric purity (94.0% ee at the stage of **7a** to 87.3% ee at **1**) might be due to partial racemization in the course of the final three steps. Unfortunately, all attempts to enrich the enantiomeric purity of synthetic **1** by recrystallization were unsuccessful. The ^{1}H and ^{13}C NMR spectra of synthetic **1** were in good accord with those of the natural product.

Experimental

All bps and mps were uncorrected. IR Spectra were measured as films for oils and as KBr disks or Nujol suspensions for solids on a JASCO A-102 spectrometer or a Perkin-Elmer 1640 spectrometer. ^{1}H NMR spectra were recorded at 90 MHz on a JEOL EX-90A spectrometer, at 270 MHz on a JEOL JNM EX 270L spectrometer, or at 300 MHz on a Bruker DPX 300 spectrometer. The peak for $SiMe_4$ or solvent ($CHCl_3$: δ 7.26) was used as the internal standard. *J* Values are given in Hz. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL JNM EX 270L spectrometer or at 75.5 MHz on a Bruker DPX 300 spectrometer with the solvent peak ($CDCl_3$: δ 77.0) used as an internal standard. Optical rotations were measured on a JASCO DIP-1000 polarimeter. Mass spectra were recorded on a JEOL JMS-SX102A mass spectrometer. Refractive indexes were measured on an ATAGO Abbe refractometer 1T.

16-Bromohexadecan-1-ol 3

To a solution of hexadecane-1,16-diol **2** (1.00 g, 3.87 mmol) in benzene (30 cm^3), hydrobromic acid (48%; 0.78 cm^3, 6.9 mmol) was added and the mixture was stirred for 5 h under reflux. This mixture was poured into water and extracted with $CHCl_3$. The extract was washed successively with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *bromo alcohol* **3** (713 mg, 57%) as a white solid, mp 48–50 °C; ν_{max}(Nujol)/cm^{-1} 3300m (OH); δ_H(90 MHz; $CDCl_3$) 1.20–1.90 (29 H, m, 2–15-H, OH), 3.41 (2 H, t, *J* 7, 16-H), 3.64 (2 H, t, *J* 6, 1-H). This was employed in the next step without further purification.

17-(*p*-Methoxyphenyl)heptadecan-1-ol 4

A THF solution of *p*-methoxybenzylmagnesium chloride was prepared from *p*-methoxybenzyl chloride (0.58 g, 3.7 mmol) and magnesium (90 mg, 3.7 mmol) in THF (3 cm^3) in the usual manner. The resulting Grignard reagent and an Li_2CuCl_4 solution (0.10 mol dm^{-3} in THF; 0.3 cm^3, 0.03 mmol) was added successively to a suspension of bromo alcohol **3** (296 mg, 921 μmol) in THF (3 cm^3) at −78 °C under Ar. This mixture was allowed to warm to room temperature with stirring overnight. After quenching with saturated aq. NH_4Cl, it was extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 and then recrystallized from hexane to give the *alcohol* **4** (257 mg, 77%) as colorless plates, mp 77–78 °C (Found: C, 79.10; H, 11.49. $C_{24}H_{42}O_2$ requires C, 79.50; H, 11.67%); ν_{max}(Nujol)/cm^{-1} 3250m (OH), 1610w (Ar), 1580w (Ar), 1515m

(Ar), 1115m, 1070m, 1025m, 815m; δ_H(90 MHz; $CDCl_3$) 1.25 (30 H, br s, 2–16-H), 2.17 (1 H, s, OH), 2.54 (2 H, t, *J* 7, 17-H), 3.64 (2 H, q-like, *J* 6, 1-H), 3.79 (3 H, s, OMe), 6.81 (2 H, d, *J* 9, 3′- and 5′-H), 7.10 (2 H, d, *J* 9, 2′- and 6′-H).

17-(*p*-Hydroxyphenyl)-1-bromoheptadecane 5a

To a solution of **4** (2.28 g, 6.29 mmol) in acetic acid (60 cm^3), hydrobromic acid (48%; 75 cm^3) was added and the stirring was continued for 8 h under reflux. This mixture was then concentrated under reduced pressure. The residue was diluted with water and extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *bromide* **5a** (1.97 g, 76%) as a white crystalline solid, mp 87 °C; ν_{max}(KBr)/cm^{-1} 3400m, (OH), 1620m (Ar), 1600w (Ar), 1520s (Ar), 820m (Ar); δ_H(90 MHz; $CDCl_3$) 1.10–2.00 (30 H, m, 2–16-H), 2.53 (2 H, t, *J* 7, 17-H), 3.41 (2 H, t, *J* 7, 1-H), 4.67 (1 H, br s, OH), 6.74 (2 H, d, *J* 8, 3′- and 5′-H), 7.04 (2 H, d, *J* 8, 2′- and 6′-H). This was employed in the next step without further purification.

17-(*p*-Tetrahydropyranyloxy)phenyl-1-bromoheptadecane 5b

A mixture of **5a** (85.5 mg, 0.208 mmol), 2,3-dihydro-2*H*-pyran (0.10 ml, 1.1 mmol) and $TsOH{\cdot}H_2O$ (~3 mg, catalytic amount) in dry diethyl ether was stirred for 19 h at room temperature. This mixture was poured into water and extracted with diethyl ether. The extract was washed with saturated aq. $NaHCO_3$, water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *THP ether* **5b** (99.7 mg, 97%). This was employed in the next step without further purification. A small amount of **5b** was further purified by recrystallization from hexane to give colorless plates, mp 59–60 °C (Found: C, 67.93; H, 9.81. $C_{28}H_{47}O_2Br$ requires C, 67.86; H, 9.56%); ν_{max}(KBr)/cm^{-1} 1610w (Ar), 1515s (Ar), 1230s, 990s; δ_H(90 MHz; $CDCl_3$) 1.10–2.00 (36 H, br s, 2–16-H, 3″-, 4″- and 5″-H), 2.55 (2 H, t, *J* 7, 17-H), 3.41 (2 H, t, *J* 7, 1-H), 3.55–4.10 (2 H, m, 6″-H), 5.38 (1 H, br s, 2″-H), 6.95 (2 H, d, *J* 9, 3′- and 5′-H), 7.10 (2 H, d, *J* 9, 2′- and 6′-H).

Enantiomeric purity of 7a

A small amount of the TBDMS ether **7a** was converted to the corresponding alcohol **7b** by treatment with TBAF in THF. The resulting compound **7b** was analyzed by GLC to determine its enantiomeric purity. GLC analysis [column: Chirasil DEX-CB (0.25 mm × 25 m, 120 °C, +1 °C min^{-1}; carrier gas: He, pressure 110 kPa)]: t_R/min 15.0 [97.0%, (*R*)-**7b**], 16.5 [3.0%, (*S*)-**7b**]. The anantiomeric purity of **7b** was estimated to be 94.0% ee. The enantiomeric purity of **7a** should be equal to that of **7b**.

(*R*)-1-Bromo-5-*tert*-butyldimethylsilyloxy-2,4-dimethylpent-2-ene 8b

Bu″Li (1.59 mol dm^{-3} in *n*-hexane; 2.4 cm^3, 3.8 mmol) was added dropwise to a solution of **8a** (922.5 mg, 3.77 mmol) in dry diethyl ether (10 cm^3) and dry HMPA (10 cm^3) at 0 °C under Ar, and the mixture was stirred for 10 min at 0 °C. To this solution, TsCl (934 mg, 4.90 mmol) was added portionwise. After stirring for 1 h at 0 °C, LiBr (1.64 g, 8.78 mmol) was added to this mixture portionwise. The reaction mixture was allowed to warm to room temperature with stirring during 2 h and poured into saturated aq. $NaHCO_3$. It was then extracted with pentane–diethyl ether (1 : 2). The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give the *bromide* **8b** (1.24 g, quant.) as a colorless oil. δ_H(90 MHz; $CDCl_3$) 0.03 (6 H, s, SiMe), 0.80–0.95 (12 H, m, 4-Me, Bu′), 1.77 (3 H, br s, 2-Me), 2.43 (1 H, m, 4-H), 3.42 (2 H, d, *J* 7, 5-H), 3.98 (2 H, d, *J* 4, 1-H), 5.20–5.45 (1 H, m, 3-H). This was employed in the next step without purification.

(*R*)-5-*tert*-Butyldimethylsilyloxy-2,4-dimethylpent-2-enyl phenyl sulfone 8c

A mixture of **8b** (1.24 g, ~3.77 mmol), $NaHCO_3$ (50 mg, 0.60 mmol) and $NaSO_2Ph{\cdot}2\ H_2O$ (1.56 g, 7.79 mmol) in dry DMF (12 cm^3) was stirred for 3 d at room temperature. It was then poured into water and extracted with diethyl ether. The extract was washed with water, saturated aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *sulfone* **8c** (1.17 g, 84% based on **8a**) as a colorless oil; n_D^{25} 1.5001 (Found: C, 61.71; H, 9.09. $C_{22}H_{44}OSi$ requires C, 61.91; H, 8.75%); $[\alpha]_D^{27}$ +6.9 (*c* 0.21 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1585w (Ar), 1445m (Ar), 1320s (SO_2), 1310s, 1250m (Si–Me), 1150s (SO_2), 1085s (SO_2), 835m, 690m (C–S); δ_H(90 MHz; $CDCl_3$) 0.00 (6 H, s, SiMe), 0.75 (3 H, d, *J* 7, 4-Me), 0.85 (9 H, s, Bu′), 1.79 (3 H, br d, *J* 1.5, 2-Me), 2.41 (1 H, m, 4-H), 3.20 (2 H, m, 5-H), 3.73 (2 H, s, 1-H), 4.76 (1 H, br d, *J* 8, 3-H), 7.45–7.90 (5 H, m, Ar-H).

(2*R*,5*RS*)-1-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-5-phenylsulfonyl-22-(*p*-tetrahydropyranyloxyphenyl)docos-3-ene 9

To a stirred solution of **8c** (223 mg, 605 μmol) in dry THF (3 cm^3) and HMPA (0.5 cm^3), Bu″Li (1.54 mol dm^{-3} in *n*-hexane; 0.394 cm^3, 608 μmol) was added dropwise at −78 °C under Ar. After stirring for 30 min at −78 °C, a solution of **5b** (250 mg, 504 μmol) in dry THF (3 cm^3) was added dropwise to this solution. It was stirred for 2 h at −78 °C and 15 h at 4 °C, diluted with water, and extracted with diethyl ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *sulfone* **9** (308 mg, 78%) as a colorless oil; n_D^{25} 1.5070; $[\alpha]_D^{25}$ +3.3 (*c* 0.29 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1610w (Ar), 1510s (Ar), 1305s (SO_2), 1250w (Si–Me), 1145s (SO_2), 1085s (SO_2), 835s, 690m (C–S); δ_H(90 MHz; $CDCl_3$) −0.02 and 0.00 (total 6 H, each s, SiMe), 0.53 (3 H, d, *J* 7, 2-Me), 0.84 and 0.86 (total 9 H, each s, Bu′), 1.10–2.00 (38 H, br s 6–21-H, 3″-, 4″- and 5″-H), 1.68 (3 H, br s, 4-Me), 2.40–2.70 (3 H, m, 2- and 22-H), 2.90–4.10 (5 H, m, 1-, 5- and 6″-H), 4.66–4.90 (1 H, m, 3-H), 5.38 (1 H, br s, 2″-H), 6.95 (2 H, d, *J* 9, 3′- and 5′-H), 7.10 (2 H, d, *J* 9, 2′- and 6′-H), 7.45–7.90 (5 H, m, SO_2-ArH). This was employed in the next step without purification.

(*R*)-1-*tert*-Butyldimethylsilyloxy-2,4-dimethyl-22-(*p*-tetrahydropyranyloxyphenyl)docos-3-ene 10a

To a mixture of **9** (200 mg, 255 μmol) and $PdCl_2$(dppp) (15.1 mg, 25.6 μmol) in dry THF (3 cm^3), $LiEt_3BH$ (1.0 mol dm^{-3} in THF; 0.384 cm^3, 384 μmol) was added at 0 °C. The mixture was stirred for 15 h at 4 °C, diluted with water and extracted with diethyl ether. The extract was washed with water, aq. NaCN (10%) and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *title compound* **10a** (153 mg, 93%) as a colorless oil; n_D^{23} 1.4855 (Found: C, 76.33; H, 11.91. $C_{22}H_{44}OSi$ requires C, 76.57; H, 11.60%); $[\alpha]_D^{25}$ −2.2 (*c* 0.22 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1610w (Ar), 1510s (Ar), 1250w (Si–Me), 970s, 835s, 775s; δ_H(300 MHz, $CDCl_3$) 0.04 (6 H, s, SiMe), 0.82 (~0.6 H, d, *J* 6.4, 2-Me of 4-ene isomer), 0.89 (9 H, s, Bu′), 0.91 (3 H, d, *J* 5.7, 2-Me), 1.25 (32 H, br s, 6–21-H), 1.55–2.15 (8 H, m, 5-, 3″-, 4″- and 5″-H), 1.61 (3 H, d, *J* 1.2, 4-Me), 2.54 (2 H, t, *J* 7.6, 22-H), 2.61 (1 H, m, 2-H), 3.31 (1 H, dd, *J* 9.7 and 7.7, 1-Ha), 3.44 (1 H, dd, *J* 9.7 and 5.9, 1-Hb), 3.60 and 3.93 (total 2 H, each m, 6″-H), 4.87 (1 H, dd, *J* 9.2 and 1.1, 3-H), 5.10 (~0.2 H, t, *J* 7.7, 5-H of 4-ene isomer), 5.38 (1 H, t, *J* 3.2, 2″-H), 6.96 (2 H, d, *J* 8.6, 3′- and 5′-H), 7.08 (2 H, d, *J* 8.6, 2′- and 6′-H).

(*R*)-2,4-Dimethyl-22-(*p*-tetrahydropyranyloxyphenyl)docos-3-en-1-ol 10b

TBAF (1.0 mol dm^{-3} in THF; 0.3 cm^3, 0.3 mmol) was added to a solution of **10a** (320 mg, 519 μmol) in dry THF (1.3 cm^3) at room temperature, and the stirring was continued for 5 h. It was

then poured into water and extracted with diethyl ether. The extract was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *alcohol* **10b** (247 mg, 94%) as a white solid. For the removal of the minor isomers, (*Z*)-**10b** and the 4-ene-isomer, the crude product **10b** was purified by recrystallization from methanol to give pure (*E*)-**10b** (70%) as colorless leaflets, mp 48.5–49.5 °C (Found: C, 79.06; H, 11.42. $C_{35}H_{60}O_3$ requires C, 79.49; H, 11.44%); $[\alpha]_D^{26}$ +11.9 (*c* 0.52 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3380s (O–H), 1610w (Ar), 1230m, 980m; δ_H(300 MHz; $CDCl_3$) 0.93 (3 H, d, *J* 6.7, 2-Me), 1.26 (32 H, br s, 6–21-H), 1.45–2.03 (9 H, m, 5-, 3″-, 4″-, 5″-H and OH), 1.65 (3 H, d, *J* 1.1, 4-Me), 2.54 (2 H, br t, *J* 7.6, 22-H), 2.62 (1 H, m, 2-H), 3.33 (1 H, m, 1-Ha), 3.46 (1 H, m, 1-Hb), 3.60 and 3.93 (total 2 H, each m, 6″-H), 4.88 (1 H, dd, *J* 9.4 and 0.9, 3-H), 5.38 (1 H, t, *J* 3.2, 2″-H), 6.96 (2 H, d, *J* 8.6, 3′- and 5′-H), 7.08 (2 H, d, *J* 8.6, 2′- and 6′-H).

(*R*)-2,4-Dimethyl-22-(*p*-tetrahydropyranyloxyphenyl)docos-3-enal 11a

Dess–Martin periodinane (517 mg, 1.22 mmol) and pyridine (0.4 cm^3) were dissolved in CH_2Cl_2 (8 cm^3) under Ar. To this solution, a solution of **10b** (130 mg, 246 μmol) in CH_2Cl_2 (1.5 cm^3) was added slowly at room temperature. This mixture was stirred for 2 h, diluted with saturated aq. $NaHSO_3$–saturated aq. $Na_2S_2O_3$ (1 : 1) and extracted with diethyl ether. The extract was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure to give the crude *aldehyde* **11a** (130 mg, quant.); ν_{max}(Nujol)/cm^{-1} 1725m (C=O). This was employed in the next step without further purification.

(*R*)-2,4-Dimethyl-22-(*p*-tetrahydropyranyloxyphenyl)docos-3-enoic acid 11b

A mixture of **11a** (97.5 mg, ~185 μmol), NaH_2PO_4 (114 mg, 1.54 mmol), $NaClO_2$ (80%; 53 mg, 0.47 mmol), DMSO (1.9 cm^3), CH_3CN (0.9 cm^3) and water (2.4 cm^3) was stirred for 2 d at room temperature. It was then diluted with brine and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give the *carboxylic acid* **11b** (67 mg, 67% based on **10b**) as a colorless amorphous solid, mp 46–48 °C; $[\alpha]_D^{24}$ −28 (*c* 0.35, in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1700s (C=O), 1510s (Ar), 1235m, 1110m; δ_H(300 MHz; $CDCl_3$) 1.18–1.45 (33 H, m, 2-Me and 6–21-H), 1.50–1.87 (8 H, m, 5-, 3″-, 4″- and 5″-H), 1.66 (3 H, d, *J* 1.1, 4-Me), 1.99 (2 H, t, *J* 7.5, 5-H), 2.53 (2 H, t, *J* 7.6, 22-H), 3.36 (1 H, dq, *J* 9.2 and 7.0, 2-H), 3.60 and 3.93 (total 2 H, each m, 6″-H), 5.14 (1 H, br d, *J* 9.2, 3-H), 5.38 (1 H, t, *J* 3.2, 2″-H), 6.96 (2 H, d, *J* 8.6, 3′- and 5′-H), 7.08 (2 H, d, *J* 8.6, 2′- and 6′-H); *m*/*z* 542 (M$^+$). This was employed in the next step without purification.

(*R*)-2,4-Dimethyl-22-(*p*-hydroxyphenyl)docos-3-enoic acid (elenic acid) 1

To a solution of **11b** (62 mg, 0.11 mmol) in THF (1 cm^3), hydrochloric acid (4.0 mol dm^{-3}; 1 cm^3, 4 mmol) was added. After stirring for 30 min at room temperature, this mixture was diluted with brine and extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed over SiO_2 to give *elenic acid* **1** (39 mg, 74%) as a white amorphous solid. An analytical sample was obtained by recrystallization from $CHCl_3$ to give a white amorphous powder, mp 90.5–92.5 °C [Found: (HREI-MS) M$^+$, 458.3760. $C_{30}H_{50}O_3$ requires *M*, 458.3752]; $[\alpha]_D^{25}$ −30 (*c* 0.38, in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3600m (OH), 3015w (CH), 2925s (CH), 2850s (CH), 1740m (C=O), 1705s (C=O), 1650w, 1510s (Ar), 1460m (CH), 1170w; δ_H(300 MHz; $CDCl_3$) 1.22 (3 H, d, *J* 7.0, 2-Me), 1.25 (28 H, br s, 7–20-H), 1.36 (2 H, quintet-like, *J* 7.5, 6-H), 1.56 (8 H, br quintet, *J* 7.2, 21-H), 1.66 (3 H, d, *J* 0.8, 4-Me), 1.98 (2 H, t, *J* 7.5, 5-H), 2.52 (2 H, t, *J* 7.5, 22-H), 3.36 (1 H, dq, *J* 9.2 and 7.0, 2-H), 5.14 (1 H, br d, *J* 9.2, 3-H), 6.74 (2 H, d, *J* 8.4, 3′- and 5′-H), 7.03 (2 H, d, *J* 8.4, 2′- and 6′-H); δ_C(75.5 MHz; $CDCl_3$) 16.3, 17.9, 27.7, 29.2, 29.5, 29.6, 29.7, 31.7, 35.0, 38.5, 39.5, 115.0, 122.7, 129.4, 135.2, 138.8, 153.3, 180.4; *m*/*z* 458 (M$^+$, 47.6%), 440 (M$^+$ − H_2O, 29.9), 412 (M$^+$ − CO, 27.9), 330 (7.0), 107 (100).

Enantiomeric purity of elenic acid 1

The synthetic (*R*)-elenic acid **1** was converted to the corresponding (*R*)-naphthylethylamide by the conventional manner using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. For comparison, the (*S*)-naphthylethylamide was also prepared. These amides were analyzed by HPLC analysis [column, Pegasil Silica 60-5 (4.6 mm φ × 250 mm); solvent, *n*-hexane–THF (150 : 1); flow, 0.5 cm^3 min^{-1}; detection at 254 nm]: t_R/min 14.5 [6.35%, (*R*)-naphthylethylamide of (*S*)-**1**], 16.7 [93.65%, (*R*)-naphthylethylamide of (*R*)-**1**]. The enantiomeric purity of synthesized **1** was determined to be 87.3% ee.

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