Synthesis of Elenic Acid, an Inhibitor of Topoisomerase II

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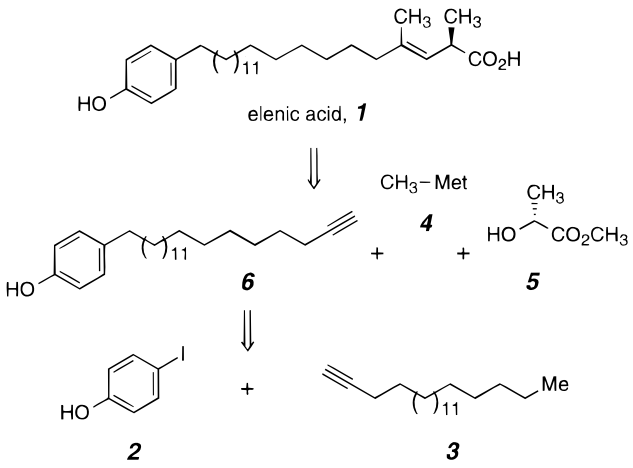
A short, efficient synthesis of elenic acid, a marine natural product with interesting biological activity, has been completed. Critical features of the synthesis are the development of methodology for the one-pot elaboration of an alkyne to an (*E*)-β,γ-unsaturated ester with a stereocenter at the α-position and the use of the zipper reaction of a 1-arylalkyne. This reaction has not been previously reported with aromatic substrates. The synthesis strategy provides considerable flexibility for the preparation of structural analogues.

Elenic acid (**1**) is an attractive synthetic target due to its unusual structure among marine natural products and its potent biological activity. Elenic acid was isolated from the Indonesian sponge *Plakinastrella* sp. (0.012 wt %) and characterized by Scheuer and co-workers in 1995.[1] Elenic acid has been shown to display impressive cytotoxicity with an IC_{50} of 5 μg/mL in P-388, A-549, and MEL-28 bioassays. In addition it inhibits topoisomerase II, an indicator enzyme in the treatment of lung cancer,[2] at 0.1 μg/mL. Such activity compares favorably with the currently used clinical agents doxorubicin and etoposide.[3]

The first synthesis of elenic acid was reported recently by Mori and co-workers.[4] We have chosen a different route for the enantiospecific construction of elenic acid as shown in Scheme 1. Our synthesis is short and offers potential for the preparation of analogues by varying any of the four readily available building blocks used in the preparation of the natural product itself, namely 4-iodophenol (**2**), 1-eicosyne (**3**), a metalated methane reagent **4**, and methyl (*R*)-(+)-lactate (**5**). The synthesis is designed to construct the alkynylphenol (**6**) and to elaborate the β,γ-unsaturated acid moiety directly from this substrate. The terminal three-carbon unit of elenic acid thus originates from methyl (*R*)-(+)-lactate, available commercially with 96% enantiomeric excess.

A model study was initially undertaken to assess the feasibility and enantioselectivity of the proposed alkyne elaboration sequence. (2*S*,3*E*)-Methyl 2,4-dimethyltetradec-3-enoate (**10**) was prepared as shown in Scheme 2. Negishi's zirconium-catalyzed carboalumination of 1-dodecyne, **7**, followed by treatment of the resulting vinylalane with methyllithium generated the vinylalanate **8** *in situ*.[5] Reaction with triflate (***S***)-**9**,[6] derived from methyl (*S*)-(−)-lactate (97% ee), afforded the desired

Scheme 1



adduct **10** in 96% yield. Whitesell[7] has shown that a vinylalanate can displace a primary alkyl triflate for effective carbon−carbon bond formation. Vinylalanates have also been used as nucleophiles in carbon−carbon bond formation with epoxides,[8] enones,[9] and carbonyl-containing substrates.[5] We have demonstrated for the first time that this reaction can be used for the construction of a β,γ-unsaturated ester containing a stereocenter at the α- and allylic position. Only the desired (*E*)-β,γ-unsaturated ester was observed by ^{1}H NMR and GC/MS analyses. Isomerization of the double bond and/or epimerization of the stereocenter was not observed (*vide infra*).

Hydrolysis of the ester **10** to the carboxylic acid **11** and coupling of this acid with (*S*)- or (*R*)-α-methylbenzylamine in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine gave the two expected amide diastereomers, (***S,S***)-**12** and (***S,R***)-**12**. ^{1}H NMR analysis of the crude reaction products did not reveal the presence of a minor diastereomer. GC/MS analysis definitively

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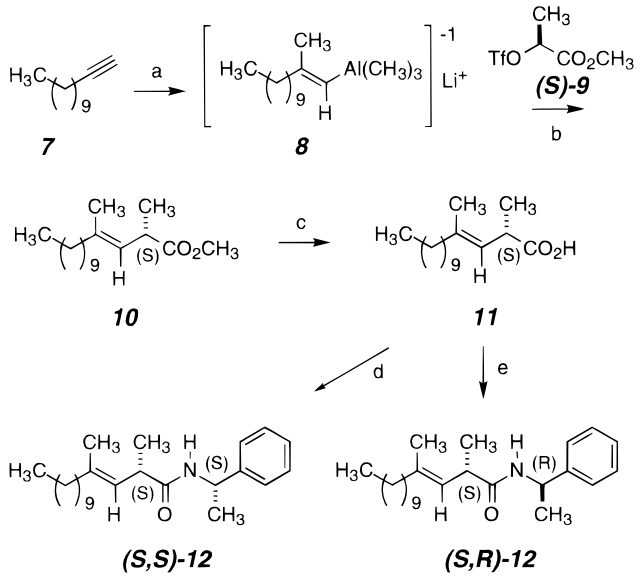
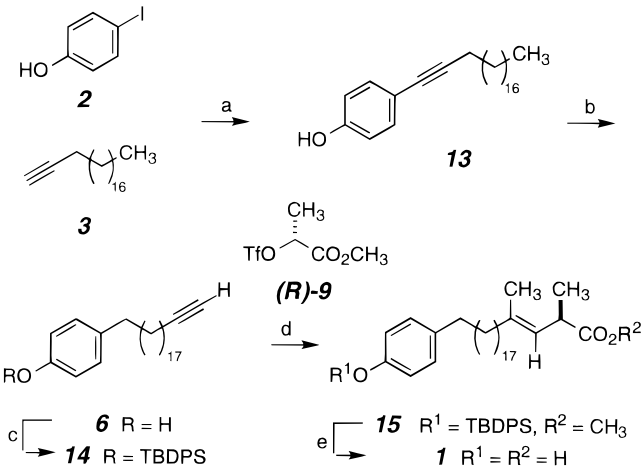
Scheme 2[a]



[a] Reagents, conditions, and yields: (a) (i) $(CH_3)_3Al$, Cp_2ZrCl_2, (ii) CH_3Li; (b) (i) (***S***)**-9**, (ii) saturated $NaHCO_3$ (96%); (c) (i) LiOH, THF, H_2O, (ii) H_3O^+ (73%); (d) (i) DCC, DMAP, (ii) (*S*)-α-methylbenzylamine (99% ee) (61%); (e) (i) DCC, DMAP, (ii) (*R*)-α-methylbenzylamine (96% ee) (75%).

Scheme 3[a]



[a] Reagents, conditions, and yields: (a) $(Ph_3P)_4Pd$,CuI, *i*-Pr_2NH, RT, 15 h (88%); (b) KAPA, $H_2N(CH_2)_3NH_2$, 65 °C, 20 h (41%); (c) TBDPSCl, DMAP, imidazole, RT, 15 h (93%); (d) (i) $(CH_3)_3Al$, Cp_2ZrCl_2, 12 h; (ii) CH_3Li, −40 °C; (iii) (***R***)**-9**, RT, 48 h; (iv) $NaHCO_3$ (95%); (f) LiOH, THF, H_2O, 16 h (79%).

confirmed the enantiospecificity of the displacement reaction.[10]

The success of the model study encouraged its application to the synthesis of elenic acid (Scheme 3). 1-Eicosyne (**3**) was prepared in 71% overall yield from 1-eicosene. Bromination and dehydrobromination of the crude 1,2-dibromoeicosane with LDA yielded 1-eicosyne (**3**). Palladium-catalyzed coupling of **3** with 4-iodophenol (**2**) in the presence of $Cu^{I}I$ and diisopropylamine proceeded smoothly to give the internal alkyne **13** in 88% yield. Isomerization to the terminal alkyne **6** was effected in 41% yield with KAPA in 1,3-diaminopropane.[11] Alkyne "zipper" reactions of an alkyne that is conjugated to an aromatic ring are previously unreported.

Protection of the phenol **6** as the TBDPS ether afforded the key intermediate **14** in 93% yield for elaboration of the remaining functionality of elenic acid. Zirconium-catalyzed carboalumination of **14**, addition of methyllithium, and alkylation with triflate (***R***)**-9** afforded the desired adduct **15** in 95% yield. Treatment of ester **15** with lithium hydroxide in aqueous tetrahydrofuran afforded elenic acid (**1**) directly. The synthetic elenic acid was identical by comparison of ^1H and ^{13}C NMR, IR, melting point, and optical rotation data to that reported by Scheuer[1] and by Mori.[4] The (*S*)-(−)-enantiomer of elenic acid ((***S***)**-1**) was also prepared by the reaction of alkyne **14** with the triflate derived from methyl (*S*)-(−)-lactate ((***S***)**-9**). It exhibited identical spectral properties and the expected opposite sign of rotation.

A stereospecific synthesis of elenic acid has been accomplished in five steps with an overall yield of 26% from 1-eicosyne (**3**) and 4-iodophenol (**2**). The synthesis involves a novel zipper reaction of a 1-arylalkyne and a one-pot elaboration of a terminal alkyne to an (*E*)-β,γ-unsaturated ester containing an α-stereocenter. This is an attractive route for the preparation of structural analogues.

Experimental Section

General Experimental Details. Flash chromatography was performed using the indicated solvent system on EM reagent silica gel 60 (230−400 mesh).[12] THF was distilled from sodium/benzophenone ketyl. Hexanes, DMF, CH_2Cl_2, and 1,2-dichloroethane were distilled from CaH_2. Diethylamine, diisopropylamine, 1,3-diaminopropane, and pyridine were distilled from KOH and stored over 4 Å molecular sieves. Air- and/or moisture-sensitive reactions were carried out under N_2 or Ar using oven-dried glassware and standard syringe/septa techniques.

Methyl (*S*)-2-[[(Trifluoromethyl)sulfonyl]oxy]propanoate ((S)-9). Pyridine (1.42 mL, 17.6 mmol, 1.1 equiv) in 30 mL of CH_2Cl_2 was cooled to 0 °C, trifluoromethanesulfonic anhydride (2.8 mL, 16.2 mmol, 1.05 equiv) was added, and the resulting mixture was stirred 10 min. Methyl (*S*)-(−)-lactate (1.53 mL, 16.0 mmol, 1 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then warmed to room temperature. The mixture was filtered, and the filter cake was washed with ether. The filtrate was evaporated *in vacuo* (<25 °C), and the residue was triturated with ether and filtered. The solvent was evaporated, and the residue was passed through a short flash column (~4 cm) with ether. Evaporation of the solvent gave a colorless oil (2.68 g, 11.4 mmol, 71%).[6] Molecular sieves were added to the product, and it was stored at −10 °C.

(2*S*,3*E*)-Methyl 2,4-Dimethyltetradec-3-enoate (10). Trimethylaluminum (2 M in hexanes, 1.2 mL, 2.4 mmol, 2.4 equiv) and zirconocene dichloride (292 mg, 1 mmol, 1 equiv) were combined in 3 mL of 1,2-dichloroethane in a 25 mL modified Schlenk flask, and the pale yellow solution was stirred for 15 min. Dodecyne (**7**) (166 mg, 213 μL, 1 mmol, 1 equiv) was added, and the reaction mixture was stirred overnight. Volatile material was removed *in vacuo* (0.5 mmHg), and the residue was heated *in vacuo* at 50 °C for 30 min. The yellow residue was washed twice with hexanes (2 and 1 mL portions), and the hexane-soluble vinylalane was cannulated

(10) The two diastereomeric amides have the following GC retention times: (*S*,*S*), 20.17 min; (*S*,*R*), 20.39 min. Examination of the TIC (total ion chromatogram) of the crude amide (***S,S*)-12** showed the presence of 1.2% of the (*R*,*S*) diastereomer. Examination of the TIC of the crude amide (***S,R*)-12** showed the presence of 3.8% of the (*S*,*S*) diastereomer. Considering the advertised enantiomeric purity of the starting materials, this diastereomeric ratio confirms the absence of product racemization under the reaction conditions.

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into a 15 mL pear-shaped flask. The hexane solution was then cooled to −40 °C, and methyllithium (1.4 M in ether, 0.75 mL, 1 equiv) was added. After stirring for 5 min, (***S***)-**9** (510 mg, 2.5 mmol, 2.5 equiv) was added dropwise, and the solution was allowed to warm gradually to room temperature. The reaction mixture was stirred at room temperature for 48 h, then quenched by the careful addition of 5 mL of saturated sodium bicarbonate solution. The precipitated aluminum salts were removed by vacuum filtration, and the filtrate was diluted with 10 mL of water and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2% ethyl acetate/hexanes) to yield the product (258 mg, 0.96 mmol, 96%) as a colorless oil: $[\alpha]_D^{RT} = +76.4$ (*c* = 11.67, $CHCl_3$); IR (neat) 1742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14 (d, *J* = 8.5 Hz, 1H), 3.67 (s, 3H), 3.34 (dq, *J* = 7.1, 9.1 Hz, 1H), 1.98 (t, *J* = 7.8 Hz, 2H), 1.64 (s, 3H), 1.38 (quintet, *J* = 7.0 Hz, 2H), 1.26 (s, 14H), 1.20 (d, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR (57 MHz, $CDCl_3$) 176.4, 138.1, 123.6, 51.5, 39.3, 38.6, 31.7, 29.4, 29.3, 29.1, 28.9, 27.5, 22.4, 17.8, 15.9, 13.8; GC/MS (*m*/*z*) 268 (M^+), 236, 209, 181, 124, 88, 69 (base). Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.37; H, 12.11.

(2*R*,3*E*)-Methyl 2,4-Dimethyltetradec-3-enoate. By a similar procedure, trimethyl aluminum (2 M in hexanes, 3.6 mL, 7.2 mmol, 2.4 equiv) and zirconocene dichloride (876 mg, 3 mmol, 1 equiv) were combined in 5 mL of 1,2-dichloroethane. Dodecyne (834 mg, 3 mmol, 1 equiv) was added. The resulting vinylalane was transferred from the solid residue using hexanes (2 × 2 mL). The hexane extracts were cooled to −40 °C and treated with methyllithium (1.4 M in diethylether, 2.14 mL, 3 mmol, 1 equiv), and (***R***)-**9** (800 mg, 3.9 mmol, 1.3 equiv). Workup and chromatography gave the desired product as a colorless oil (767 mg, 2.2 mmol, 73%), $[\alpha]_D^{25} = -74.23$ (*c* = 9.38, $CHCl_3$).

(2*S*,3*E*)-2,4-Dimethyltetradec-3-enoic Acid (11). A solution of the ester **10** (181.0 mg, 0.67 mmol, 1 equiv) and LiOH (274 mg, 6.70 mmol, 10 equiv) in aqueous THF (2 mL THF, 1 mL H_2O) was stirred overnight at room temperature. After removal of the THF on the rotovap, the reaction mixture was diluted with 10 mL of water and acidified with 10% HCl. The aqueous solution was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by MPLC (SiO_2, 10% ethyl acetate/hexanes) to afford **11** as a colorless oil (123.8 mg, 0.48 mmol, 73%): $[\alpha]_D^{RT} = +70.81$ (*c* = 9.71, $CHCl_3$); IR (neat) 3500−2500 (br), 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 (d, *J* = 9.1 Hz, 1H), 3.36 (dq, *J* = 7.1, 9.1 Hz, 1H), 1.99 (t, *J* = 7.1 Hz, 2H), 1.66 (s, 3H), 1.39 (quintet, *J* = 6.2 Hz, 2H), 1.26 (br s, 14H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.4, 138.9, 123.0, 39.4, 38.6, 31.8, 29.5, 29.3, 29.2, 29.0, 27.5, 22.5, 17.6, 16.1, 13.9; GC/MS (*m*/*z*) 254 (M^+), 181, 128, 97, 83 (base). Anal. Calcd for $C_{16}H_{30}O_2$: C, 75.54; H, 11.89. Found: C, 75.76; H, 11.95.

(*S*)-*N*-(α-Methylbenzyl)-(2*S*,3*E*)-2,4-dimethyltetradec-3-enamide [(*S*,*S*)-12]. Acid **11** (47 mg, 0.18 mmol, 1 equiv), dimethylaminopyridine (44 mg, 0.36 mmol, 2 equiv), and dicyclohexylcarbodiimide (74 mg, 0.36 mmol, 2 equiv) were dissolved in 1.0 mL of CH_2Cl_2 and treated with (*S*)-α-methylbenzylamine (50 μL, 0.36 mmol, 2 equiv). The reaction mixture was stirred overnight at room temperature, then eluted through a plug of SiO_2 with additional CH_2Cl_2. Evaporation of the solvent and purification of the residue by flash chromatography (SiO_2, 10% ethyl acetate/hexanes) gave the amide (40 mg, 0.11 mmol, 61%) as a colorless oil that solidified on standing (mp 43.5−44.0 °C): IR (neat) 3286, 1636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.95 (d, *J* = 7.4 Hz, 1H), 5.15 (d, *J* = 8.1 Hz, 1H), 5.09 (quintet, *J* = 7.4 Hz, 1H), 3.18 (dq, *J* = 7.1, 8.7 Hz, 1H), 2.02 (t, *J* = 7.4 Hz, 2H), 1.65 (s, 3H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.38 (m, 2H), 1.25 (br s, 14H), 1.20 (d, *J* = 8.1 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.0, 143.6, 139.9, 128.8, 127.3, 126.1, 124.9, 48.3, 40.0, 39.4, 31.7, 31.4, 29.4, 29.3, 20.2, 20.1, 29.0, 27.7, 22.4, 21.7, 17.7, 16.1, 13.8; GC/MS (*m*/*z*) 357 (M^+), 177, 105 (base), 69.

(*R*)-*N*-(α-Methylbenzyl)-(2*S*,3*E*)-2,4-dimethyltetradec-3-enamide [(*S*,*R*)-12]. By a similar procedure, the acid **11** (25 mg, 0.10 mmol, 1 equiv), dimethylaminopyridine (25 mg, 0.20 mmol, 2 equiv), dicyclohexylcarbodiimide (41 mg, 0.20 mmol, 2 equiv), and (*R*)-α-methylbenzylamine (30 μL, 0.20 mmol, 2 equiv) afforded after purification the corresponding amide (***S*,*R***)-**12** (27 mg, 0.075 mmol, 75%) as a colorless oil that solidified on standing (mp 40.5−42.0 °C): IR (neat) 3286, 1641 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.95 (d, *J* = 7.3 Hz, 1H), 5.17 (d, *J* = 8.8 Hz, 1H), 5.09 (quintet, *J* = 7.4 Hz, 1H), 3.14 (dq, *J* = 7.1, 8.7 Hz, 1H), 2.02 (t, *J* = 7.7 Hz, 2H), 1.59 (s, 3H), 1.45 (d, *J* = 6.8 Hz, 3H), 1.38 (m, 2H), 1.26 (br s, 14H), 1.14 (d, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 6.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.1, 143.7, 140.0, 128.8, 127.3, 126.2, 124.9, 48.4, 40.0, 39.4, 31.7, 31.3, 29.43, 29.40, 20.3, 29.1, 29.0, 27.7, 22.5, 21.6, 17.6, 16.1, 13.8; GC/MS (*m*/*z*) 357 (M^+) 177, 105 (base), 69.

1-Eicosyne (3). A solution of 1-eicosene (10.0 g, 0.036 mol, 1 equiv) in 150 mL of anhydrous ether was cooled to 0 °C. Bromine (6.9 g, 2.2 mL, 0.043 mol, 1.2 equiv) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min. It was then allowed to warm to room temperature and was quenched by the addition of saturated aqueous sodium bisulfite solution. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), and concentrated to afford 1,2-dibromoeicosane (15.82 g, 0.035 mol, 99%) as a white solid that was subsequently used without purification. 1,2-Dibromoeicosane (15.80 g, 0.035 mol, 1 equiv) in 100 mL of THF at 0 °C was treated with a solution of lithium diisopropylamide [prepared from diisopropylamine (40.2 mL, 0.288 mol, 8 equiv) and *n*-BuLi (2.5 M in THF, 57.6 mL, 0.144 mol, 4 equiv) in 50 mL of THF]. The reaction mixture was stirred at 0 °C for 3 h and then gradually warmed to room temperature and stirred overnight. The reaction was then quenched with water (100 mL) and extracted with ether. The combined ether extracts were washed with 1 M HCl, water, and brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography in three batches (SiO_2, hexanes) gave the product (7.11 g, 0.025 mol, 71%) as a colorless oil.[13]

1-(4-Hydroxyphenyl)-1-eicosyne (13). Tetrakis(triphenylphosphine)palladium(0) (500 mg, 0.43 mmol, 0.02 equiv) and copper(I) iodide (250 mg, 1.3 mmol, 0.07 equiv) were added to 25 mL of diisopropylamine in a 100 mL round-bottomed flask. The solution was stirred for 5 min, then 4-iodophenol, **2** (4.75 g, 21.6 mmol, 1.2 equiv), was added in one portion. After stirring for an additional 15 min, a solution of eicosyne (**3**) (5.00 g, 18 mmol, 1 equiv) in 25 mL of diisopropylamine was added dropwise. The reaction mixture was stirred overnight at room temperature, quenched by the addition of 10 mL of saturated aqueous potassium carbonate and 10 mL of saturated aqueous ammonium chloride, and diluted with 50 mL of water. The resulting solution was extracted with ether. The combined organic extracts were washed with 10% HCl, water, and brine, dried ($MgSO_4$), filtered, and concentrated. Chromatography (SiO_2, 10% ethyl acetate/hexanes) in three batches gave the internal alkyne **13** (5.86 g, 15.8 mmol, 88%) as a white solid: mp 71−72 °C; IR (KBr) 3418, 1607 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 2.38 (t, *J* = 7, 2H), 1.59 (quintet, *J* = 7, 2H), 1.26 (br s, 30H), 0.88 (t, *J* = 7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 155.9, 139.2, 133.2, 115.5, 88.6, 80.3, 31.9, 29.5, 29.4, 29.1, 29.0, 28.7, 22.5, 19.9, 19.2 , 13.9; GC/MS (*m*/*z*) 370 (M^+), 187, 174, 133 (base), 131, 107, 77, 55. Anal. Calcd for $C_{26}H_{42}O$: C, 84.26; H, 11.42. Found: C, 84.17; H, 11.77.

20-(4-Hydroxyphenyl)-1-eicosyne (6). Lithium wire (567 mg, 81 mmol, 30 equiv) was added to 40 mL of 1,3-diaminopropane in a 100 mL two-necked pear flask. The solution was heated at 80 °C for 2 h until the blue color had discharged

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and the white lithium salt was evident. The reaction mixture was cooled to room temperature, and potassium *tert*-butoxide (7.90 g, 64.8 mmol, 24 equiv) was added in one portion. The resulting yellow solution was stirred for 15 min. A solution of the internal alkyne (1.00 g, 2.7 mmol, 1 equiv) in 5 mL of 1,3-diaminopropane was added dropwise, and the blood-red solution was heated at 65 °C overnight. The resulting brown solution was cooled to room temperature and then in an ice bath and quenched with saturated aqueous ammonium chloride. The resulting mixture was poured into 100 mL of water and acidified with 105 mL of concentrated HCl. This mixture was then extracted with chloroform. Evaporation of the chloroform, addition of 100 mL of benzene, and subsequent evaporation afforded a tan solid that was adsorbed onto SiO_2 and added to the top of a chromatography column. Flash chromatography (10% ethyl acetate/hexanes) gave the product (408 mg, 1.10 mmol, 41%) as a white solid: mp 70.3−70.6 °C; IR (KBr) 3414, 3300 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 7.17 (d, $J = 8.5$ Hz, 2H), 6.76 (d, $J = 8.5$ Hz, 2H), 4.66 (br s, 1H), 2.54 (t, $J = 7.0$ Hz, 2H), 2.19 (dt, $J = 2.5$, 7.0 Hz, 2H), 1.95 (t, $J = 2.5$ Hz, 1H), 1.57 (m, 4H), 1.26 (br s, 28H); ^{13}C NMR (75 MHz, $CDCl_3$) 130.8, 129.6, 127.6, 115.7, 115.2, 67.9, 34.9, 31.6, 29.5, 28.93, 28.59, 28.3, 18.2; GC/MS (*m*/*z*) 370 (M^+), 354, 281, 207, 133, 120, 107 (base). Anal. Calcd for $C_{26}H_{42}O$: C, 84.26; H, 11.42. Found: C, 84.29; H, 11.79.

20-(4-*tert*-Butyldiphenylsiloxyphenyl)-1-eicosyne (14). The phenol **6** (426 mg, 1.15 mmol, 1 equiv), imidazole (156 mg, 2.3 mmol, 2 equiv), and 4-dimethylaminopyridine (140 mg, 1.15 mmol, 1 equiv) were combined in 5 mL of DMF. *tert*-Butylchlorodiphenylsilane (397 μL, 1.72 mmol, 1.5 equiv) was added dropwise. The reaction mixture was stirred overnight and then quenched by the addition of 5 mL of saturated aqueous sodium bicarbonate. The reaction mixture was diluted with 30 mL of water and extracted with ether. The combined ether extracts were washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Purification of the residue by MPLC (hexanes) afforded the product as a colorless oil (682 mg, 1.11 mmol, 97%) that crystallized on standing: mp 52−53 °C; IR (neat) 3311, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, $J = 6.4$ Hz, 4H), 7.45 (m, 6H), 6.88 (d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 2.45 (t, $J = 7.6$ Hz, 2H), 2.18 (dt, $J = 2.5$, 7.0 Hz), 1.94 (t, $J = 2.5$ Hz), 1.54−1.33 (m, 4H), 1.24 (br s, 24H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.72, 135.79, 135.57, 133.47, 129.96, 129.15, 127.88, 119.49, 84.84, 67.98, 34.94, 31.41, 29.51, 29.34, 29.10, 28.95, 28.61, 28.35, 26.39, 18.20. Anal. Calcd for $C_{42}H_{60}OSi$: C, 82.83; H, 9.93. Found: C, 83.12; H, 10.03.

(2*R*,3*E*)-Methyl 22-(4-*tert*-Butyldiphenylsiloxyphenyl)-2,4-dimethyldocos-3-enoate (15). Trimethylaluminum (2 M in hexanes, 0.72 mL, 1.44 mmol, 2.4 equiv) and zirconocene dichloride (175.2 mg, 0.60 mmol, 1 equiv) were combined in 2 mL of 1,2-dichloroethane in a 25 mL modified Schlenk flask, and the pale yellow solution was stirred for 15 min. Alkyne **15** (370 mg, 0.60 mmol, 1 equiv) dissolved in 1 mL of 1,2-dichloroethane was added via cannula, and the reaction mixture was stirred overnight. Volatile material was removed *in vacuo* (0.5 mmHg), and the residue was heated *in vacuo* at 50 °C for 30 min. The yellow residue was washed twice with hexanes (2 and 1 mL portions). The hexane-soluble vinylalane was cannulated into a 15 mL pear-shaped flask. The hexane solution was then cooled to −40 °C, and methyllithium (1.4 M in ether, 0.43 mL, 0.60 mmol) was added. After stirring for 5 min, (***R***)-**9** (388 mg, 1.9 mmol, 3.1 equiv) was added dropwise, and the solution was allowed to warm gradually to room temperature. The reaction mixture was stirred at room temperature for 20 h, then quenched by the careful addition of saturated sodium bicarbonate solution. The precipitated aluminum salts were removed by vacuum filtration, and the filtrate was diluted with 10 mL of water and extracted with ether. The combined ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography (SiO_2, 2% ethyl acetate/hexanes) to yield the product (407 mg, 0.57 mmol, 95%) as a colorless oil: $[\alpha]_D^{RT} = -27.7$ ($c = 10.48$, $CHCl_3$); IR (neat) 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, $J = 6.5$ Hz, 4H), 7.36 (m, 6H), 6.86 (d, $J = 8.3$ Hz, 2H), 6.64 (d, $J = 8.3$ Hz, 2H), 5.12 (d, $J = 9.1$ Hz, 1H), 3.64 (s, 3H), 3.31 (dq, $J = 7.1$, 9.1 Hz, 1H), 2.43 (t, $J = 7.5$ Hz, 2H), 1.95 (t, $J = 7.1$ Hz, 2H), 1.58 (s, 3H), 1.48 (quintet, $J = 6.0$ Hz, 2H), 1.35 (quintet, $J = 6.1$ Hz, 2H), 1.22 (br s, 28H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.7, 138.0, 135.5, 133.4, 129.9, 129.1, 128.1, 127.8, 123,7, 119.5, 51.5, 39.3, 38.6, 34.9, 31.4, 29.5, 29.3, 29.1, 28.9, 27.5, 26.4, 19.2, 17.8, 15.9. Anal. Calcd for $C_{47}H_{70}O_3Si$: C, 79.38; H, 9.92. Found: C, 79.59; H, 10.10.

(*R*)-(−)-Elenic Acid (1). Ester **16** (210 mg, 0.29 mmol, 1 equiv) was dissolved in 2 mL of THF under argon. Lithium hydroxide, monohydrate (237 mg, 5.8 mmol, 20 equiv), and 2 mL of water were added, and the reaction mixture was stirred overnight at room temperature. THF was removed *in vacuo*, and the remaining solution was diluted with 5 mL of water, acidified with 10% HCl, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated to yield a crude product that was purified by flash chromatography (SiO_2, 30% ethyl acetate/hexanes). Elenic acid was obtained as a white amorphous solid (105 mg, 0.22 mmol, 79%), $[\alpha]_D^{25} = -31$ ($c = 0.31$, $CHCl_3$), whose mp, IR, ^1H NMR, and ^{13}C NMR data duplicate that reported by Mori[4] and by Scheuer.[1]

(*S*)-(+)-Elenic Acid. Alkyne **15** (320 mg, 0.53 mmol, 1 equiv) was treated in a manner analogous to the preparation of ester **17**, with trimethylaluminum (2 M in hexanes, 0.53 mL, 2 equiv), zirconocene dichloride (154.7 mg, 0.53 mmol, 1 equiv), methyllithium (1.4 M in ether, 0.38 mL, 0.53 mmol, 1 equiv), and (***S***)-**9** (270 mg, 1.32 mmol, 2.5 equiv). The crude product was purified by chromatography (SiO_2, 2% ethyl acetate/hexanes) to yield the desired ester (233 mg, 0.33 mmol, 61%) as a colorless oil, $[\alpha]_D^{25} = +28.7$ ($c = 8.73$, $CHCl_3$), which was identical to **16** by ^1H and ^{13}C NMR and IR spectroscopy. The (*S*)-ester (121 mg, 0.17 mmol, 1 equiv) was treated with lithium hydroxide monohydrate (139 mg, 3.4 mmol, 20 equiv) in 2 mL of 1:1 aqueous tetrahydrofuran to afford (*S*)-(+)-elenic acid (59.5 mg, 0.13 mmol, 76%) as a white amorphous solid, $[\alpha]_D^{25} = +32$ ($c = 0.36$, $CHCl_3$), otherwise spectroscopically identical to (*R*)-(−)-elenic acid.

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