Enantiospecific Synthesis of (+)-Nemorensic Acid, a Necic Acid Component of the Macropyrrolizidine Alkaloid, Nemorensine

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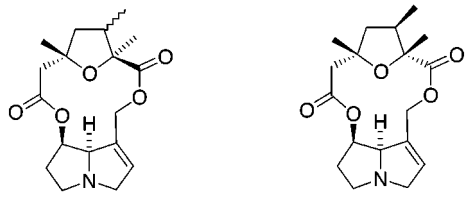
A concise enantiospecific synthesis of nemorensic acid **3**, a necic acid component of the macropyrrolizidine alkaloid nemorensine **2**, isolated from *Senecio nemorensis* L., is described. Reaction of an ϵ-halo-α,β-unsaturated ester (**8**), readily accessible from a monoterpene (−)-carvone, with samarium iodide gave a fragmentation product (**9**), where a carbon−carbon bond cleavage reaction occurred between the γ and δ positions of the carbonyl group, regioselectively. Deprotection of the silyl group of **9** brought about an intramolecular cyclization to provide tetrahydrofuran derivatives (**10**), which, upon chemical modification of the side chain, gave nemorensic acid.

Introduction

Samarium iodide has been recognized as a powerful one-electron reducing agent. Since Kagan and co-workers first introduced samarium iodide as a useful synthetic tool in organic synthesis,[1] this reagent has rapidly become an established reagent in a variety of unique and useful transformations.[2]

Recently, we developed a novel samarium iodide-promoted carbon−carbon bond cleavage reaction of γ-halo carbonyl compounds,[3] where fragmentation occurs between the α and β positions of the carbonyl group regioselectively. This fragmentation reaction has been successfully used in the syntheses of natural products including alkaloids, terpenes, and antibiotics.[4] Therefore, it would be interesting to investigate the further application of this fragmentation to an ϵ-halo-α,β-unsaturated ester, where carbon−carbon bond cleavage would be expected to take place between the γ and δ positions of the carbonyl group, regioselectively.

In this paper, we would like to report an enantiospecific synthesis of (+)-nemorensic acid **3**,[5] a necic acid component of a macropyrrolizidine alkaloid nemorensine **2**, isolated from *Senecio nemorensis* L.,[6] in which the regioselective fragmentation reaction of an ϵ-halo-α,β-unsaturated ester with samarium iodide plays as a key role. Since many macropyrrolizidine alkaloids are known to exhibit interesting biological activities,[7] such as hepatotoxic activity, and also since necic acid components contain a wide range of structural and stereochemical features, considerable effort has been devoted toward stereoselective syntheses of these alkaloids,[8] especially for the synthesis of necic acids, in optically pure forms.



1 **2**

Figure 1.

Results and Discussion

The structure of nemorensic acid was initially assigned to be **1**.[9] However, its structure, including its absolute configuration, was recently revised to be **2** based on its chiral synthesis starting from (*R*)-(+)-β-citronellol,[10] and also by X-ray analysis of nemorensine (Figure 1).[10]

As depicted for the retrosynthetic route in Scheme 1, the basic feature of our strategy for developing (+)-

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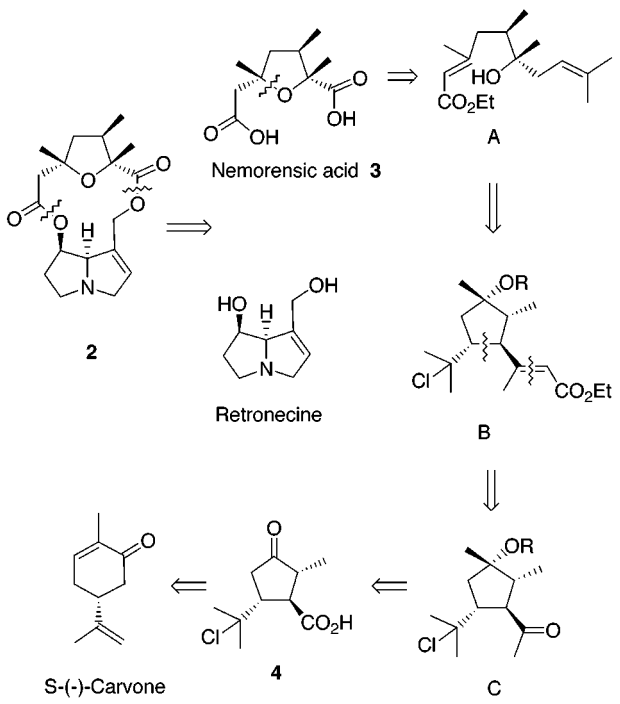
Scheme 1. Retrosynthetic Route for (+)-Nemorensic Acid



nemorensic acid involved an intramolecular Michael addition[11] of the hydroxy function to α,β-unsaturated ester (A), which could be derived from ϵ-halo-α,β-unsaturated ester (B) by a regioselective fragmentation reaction, to construct a tetrahydrofuran ring. The desired ester (B) would be prepared by Wittig olefination of ketone (C), easily accessible from the known cyclopentanone **4**.[3]

The requisite starting material was prepared as follows. An optically active cyclopentanone derivative,[3] readily derived from (−)-carvone, was treated with methyllithium to give acetyl compounds (**5** and **6**), in a ratio of ca. 2:1, in 91% yield (Scheme 2). The minor product was assumed to be **6** based on an NMR study, in which NOE was observed between two methyl groups at the 1 and 2 positions. After the major compound was converted to the corresponding triethylsilyl ether with triethylsilyl triflate, ketone **7** was subjected to a Horner−Emmons reaction to give the α,β-unsaturated esters **8**, as an inseparable mixture of stereoisomers (E/Z = >95 based on NMR analysis), in 96% yield. Since the desired ester was thus prepared, we applied samarium iodide-promoted fragmentation to **8**, and found that the reaction proceeded cleanly at room temperature and carbon−carbon bond cleavage occurred between the γ and δ positions of the carbonyl group, regioselectively, to provide olefin-esters **9**, as a mixture of stereoisomers (*E:Z* = 2:1 based on NMR analysis), in 91% yield. Treatment of acyclic α,β-unsaturated esters **9** with TBAF brought about desilylation and subsequent cyclization to give tetrahydrofuran derivatives **10** as a mixture of *cis*- and *trans*-isomers in quantitative yield. Ozonolysis of the mixture, followed by reductive treatment with sodium borohydride gave alcohols **11a** and **11b**, which could be separated by HPLC column chromatography on silica gel to give 2,5-*cis*-alcohol **11a** and 2,5-*trans*-alcohol **11b** in yields of 17% and 59%, respectively. The stereoselectivity observed in the formation of **11** can be rationalized by assuming that the cyclization proceeds via the sterically favorable transition state TS-1 to predominantly give the 2,5-*trans*-isomer, whereas, in transition state TS-2, which leads to the 2,5-*cis*-isomer, steric repulsion is present between the methyl groups at the 3 and 6 positions (Figure 2). A similar cyclization has been previously reported by White and co-workers, who observed a similar stereoselectivity.[10]

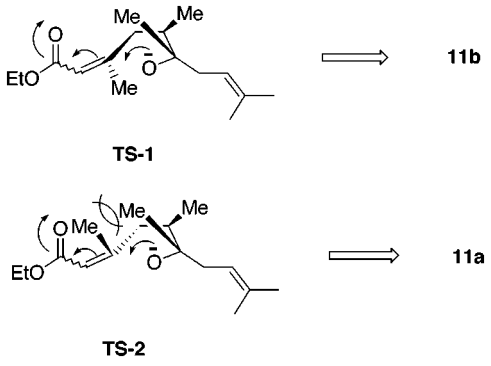
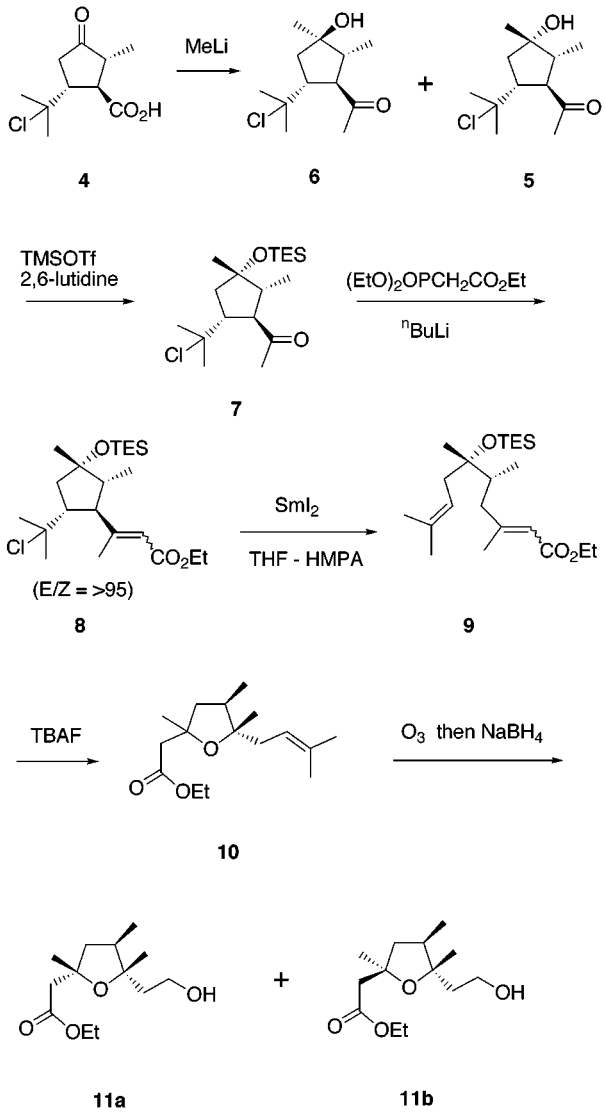


Figure 2.

Scheme 2



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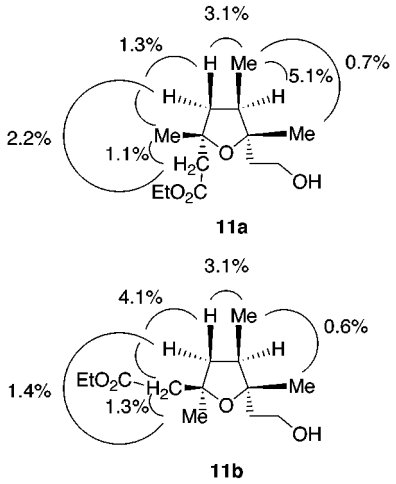

Figure 3.

The stereochemical assignment of these alcohols was made based on the analysis of their NMR spectra. In the NMR spectrum of **11a**, NOE of 1.3% between the methyl group at the 5-position and the 4-β-proton was observed in addition to that between the 4-α-proton and the methylene protons of the acetate unit. On the other hand, the 4-β-proton and 4-α-proton were correlated to the methylene protons of the acetate and methyl group at the 5-position, respectively, in the NMR spectrum of **11b**, as depicted in Figure 3.

Although the desired tetrahydrofuran derivative having the same stereochemistry as the natural compound was isolated as a minor stereoisomer, we focused our attention on conversion of the hydroxyethyl moiety to the one-carbon-reduced carboxylic acid. To determine the stereochemistry unambiguously, both alcohols **11a** and **11b** were transformed into olefins **13** and **15** using Grieco's procedure[12] via 2-nitrophenylselenides (**12** and **14**), respectively. Ozonolysis of olefin **13**, followed by reductive workup with triphenylphosphine gave an aldehyde, which without purification was subjected to further oxidation with sodium chlorite[13] and subsequent hydrolysis of the ester group to give acid **3** in 72% yield from olefin **13** (Scheme 3). The spectral properties including the specific optical rotation of **3** were identical to those reported in the literature.[10] The major isomer was also converted into the known acid **16**,[9] via aldehyde, by using the same procedure that was used to prepare **3** in 80% yield from **15**. Acid **16** was further esterified with methyl iodide to give ester **17**, in 71% yield, whose spectroscopic data were also identical to those reported in the literature.[10]

In summary, we have developed a novel stereospecific synthetic route for (+)-nemorensic acid by means of samarium iodide-promoted regioselective carbon−carbon bond cleavage reaction of an ϵ-halo-α,β-unsaturated ester. This type of fragmentation with samarium iodide is unprecedented, and the strategy developed here should also be applicable to the synthesis of other types of necic acid components of macropyrrolizidine alkaloids.

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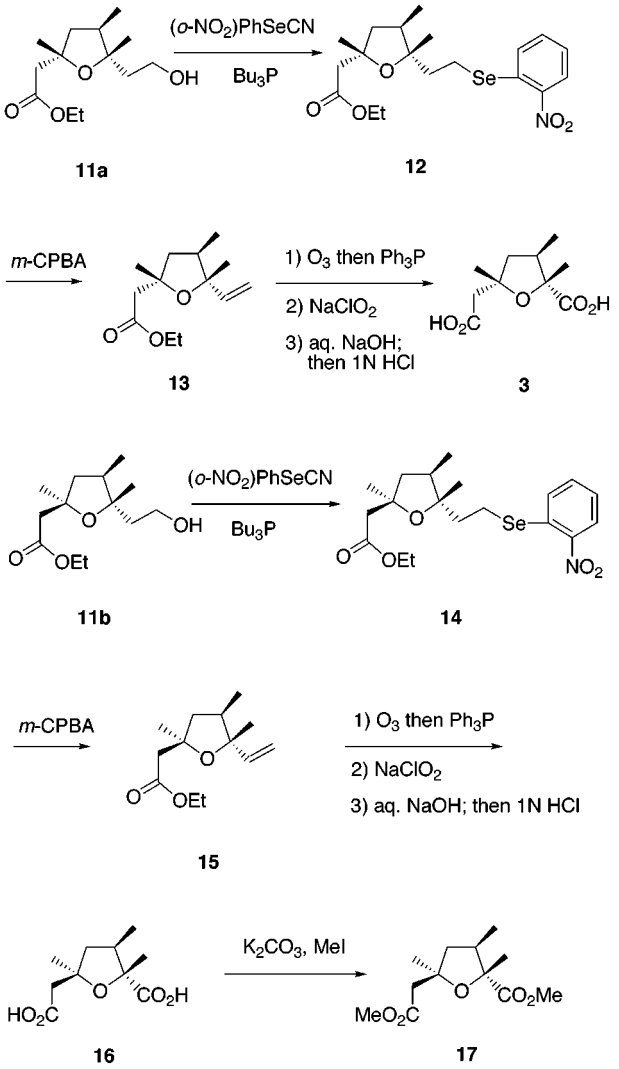
Scheme 3



Experimental Section

General Experimental Procedures. All melting points are uncorrected. IR spectra were measured for solutions in $CHCl_3$. ^1H NMR and ^{13}C NMR spectra were obtained for a solution in $CDCl_3$ unless otherwise stated, and chemical shifts are reported on the δ scale from TMS as an internal standard.

(1*S*,2*R*,3*R*,4*R*)- and (1*R*,2*R*,3*R*,4*R*)-3-Acetyl-4-(2-chloro-2-methylethyl)-1,2-dimethyl-1-cyclopentanol (5 and 6). To a stirred solution of acid (**4**) (1.0 g, 4.58 mmol) in THF (20 mL) was added dropwise methyllithium (21.6 mL, 1.06M Et_2O solution, low halide) at −78 °C, and the resulting mixture was stirred for 1 h at the same temperature and then for 12 h at room temperature. The reaction was quenched by adding aqueous NH_4Cl solution, and the mixture was extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexanes−ethyl acetate (4:1) gave alcohol (**5**) (0.55 g, 61%) as a colorless oil; $[\alpha]^{25}_D$ +20.7 (*c* 0.9, $CHCl_3$); IR 3420, 2970, 1750 cm^{-1}; ^1H NMR δ 1.10 (d, 3H, J = 7.4 Hz, 2-Me), 1.22 (s, 3H, 1-Me), 1.46 (s, 3H, 4-Me), 1.55 (s, 3H, 4-Me), 1.67−1.75 (m, 1H, 4-H), 1.87−1.93 (m, 1H, 2-H), 2.30 (s, 3H, Ac), 2.75−2.83 (m, 1H, 3-H), 2.90−3.00 (m, 2H, 5-H_2); ^{13}C NMR δ 18.43, 19.96, 20.40, 29.93, 33.17, 43.67, 44.90, 49.34, 63.24, 64.03, 111.06; HRMS calcd for $C_{12}H_{20}O_2$ (M^+ − HCl) 196.1462, found (M^+ − HCl) 196.1462. Anal. Calcd for $C_{12}H_{21}O_2Cl$: C, 61.91; H, 9.09. Found: C, 62.13; H, 9.02. Further elution with the same solvent system gave 1*R*-isomer (**6**) (0.27 mg, 30%) as a colorless oil: $[\alpha]^{25}_D$ −16.3 (*c* 0.05, $CHCl_3$); IR 3450, 1710

cm^{-1}; ^{1}H NMR δ 0.95 (d, 3H, J = 6.7 Hz, 2-Me), 1.24 (s, 3H, 1-Me), 1.44 (s, 3H, 4-Me), 1.53 (s, 3H, 4-Me), 1.85−1.95 (m, 2H, 3-H and 5-H), 2.11−2.20 (m, 1H, 2-H), 2.19 (s, 3H, Ac), 2.69−2.76 (m, 2H, 4-H and 5-H); HRMS calcd for $C_{12}H_{20}O_2$ (M^+ − HCl) 196.1462, found (M^+ − HCl) 196.1458.

(1*S*,2*R*,3*R*,4*R*)-3-Acetyl-4-(2-chloro-2-methylethyl)-1-(triethylsiloxy)-1,2-dimethylcyclopentane (7). A solution of alcohol (**5**) (10.8 g, 55.1 mmol), 2,6-lutidine (23.6 g, 220.2 mmol), and triethylsilyl trifluoromethanesulfonate (26.0 g, 110.2 mmol) in CH_2Cl_2 (200 mL) was stirred at −30 °C for 2 h under argon. After adding aqueous NH_4Cl solution, the mixture was treated with CH_2Cl_2, and the organic layer that separated was washed with brine and dried over Na_2SO_4. Removal of the solvent left a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (9:1) as an eluent to give triethylsilyl ether (**7**) (16.7 g, 88%) as a colorless oil: $[\alpha]^{25}_D$ −54.4 (*c* 0.01, $CHCl_3$); IR 2960, 1715 cm^{-1}; ^{1}H NMR δ 0.55 (q, 6H, J = 7.6 Hz, TES), 0.93 (t, 9H, J = 7.9 Hz, TES), 1.06 (d, 3H, J = 7.3 Hz, 2-Me), 1.23 (s, 3H, 1-Me), 1.41 (s, 3H, 4-Me), 1.53 (s, 3H, 4-Me), 1.75−2.18 (m, 3H, 2-H and 5-H_2), 2.20 (s, 3H, Ac), 2.53 (dd, 1H, J = 7.3 and 7.6 Hz, 3-H), 3.01 (dt, 1H, J = 7.6 and 9.8 Hz, 4-H); ^{13}C NMR δ 3.92, 4.39, 12.73, 18.63, 21.97, 30.32, 41.85, 43.09, 44.03, 48.38, 61.52, 107.75, 143.52; HRMS calcd for $C_{18}H_{35}O_2$-SiCl (M^+) 346.2095, found (M^+) 346.2088.

(*E*)-Ethyl 3-[1′-(1′*R*,2′*R*,3′*S*,5′*R*)-5′-(2″-Chloro-2″-methylethyl)-3′-(triethylsiloxy)-2′,3′-dimethylcyclopentyl]-2-butenoate (8). To a stirred solution of triethyl phosphonoacetate (2.76 g, 13.0 mmol) in THF (20 mL) was added *n*-butyllithium (8.76 mL, 1.0M THF solution) at −15 °C under argon, and the resulting mixture was stirred for an additional 30 min at the same temperature. A solution of ketone (**7**) (1.5 g, 4.33 mmol) in THF (10 mL) was added to the above solution, and the mixture was heated at reflux for 12 h. After cooling to 0 °C, the reaction was quenched by adding aqueous NH_4Cl solution, and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (9:1) as an eluent to give (*E*)-α,*β*-unsaturated ester (**8**) (1.72 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ −16.0 (*c* 0.2, $CHCl_3$); IR 2960, 1730 cm^{-1}; ^{1}H NMR δ 0.65 (q, 6H, J = 7.9 Hz, TES), 0.83 (d, 3H, J = 6.3 Hz, 2′-Me), 0.95 (t, 9H, J = 7.9 Hz, TES), 0.86−0.95 (m, 1H, 2′−H), 1.26 (t, 3H, J = 7.3 Hz, CO_2CH_2*Me*), 1.19 (s, 3H, 5′-Me), 1.28 (s, 3H, 5′-Me), 1.64 (s, 3H, 3′-Me), 1.95−2.09 (m, 3H, 5′−H and 4′−H_2), 2.13 (s, 3H, 3-Me), 4.13 (q, 2H, J = 7.3 Hz, CO_2CH_2Me), 4.68 (br s, 1H, olefinic proton); ^{13}C NMR δ 6.65, 7.10, 14.30, 14.66, 19.93, 25.52, 29.69, 46.77, 47.29, 50.58, 59.47, 61.28, 81.26, 110.68, 117.24, 145.83, 166.63; HRMS calcd for $C_{22}H_{41}O_3SiCl$ (M^+) 416.2513, found (M^+) 416.2493. Anal. Calcd for $C_{22}H_{41}O_3SiCl$: C, 63.35; H, 9.91. Found: C, 63.73; H, 10.04.

Ethyl (5*R*,6*S*)-6-(Triethylsiloxy)-3,5,6,9-tetramethyldeca-2,8-dienoate (9). To a stirred suspension of samarium metal (6.91 g, 45 mmol) in THF (50 mL) was added a solution of 1,2-diiodoethane (11.8 g, 41.8 mmol) in THF (30 mL) under argon at ambient temperature, and the solution was stirred for 30 min. After adding HMPA (6.0 mL), the resulting solution was stirred for 10 min at the same temperature. To this mixture was added a solution of ester (**8**) (5.8 g, 13.9 mmol) in THF (30 mL). After stirring for 15 min, the mixture was treated with saturated sodium hydrogen carbonate solution, an excess of ether (400 mL), and Celite (100 g). Insoluble materials were filtered off, and the filtrate was treated with water (100 mL). The organic layer was separated, and the aqueous layer was extracted with ether. The combined ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (15:1) as an eluent to give a mixture of (*E*)- and (*Z*)-α,*β*-unsaturated esters (**9**) (4.48 g, 91%) as a colorless oil: IR 2960, 1720 cm^{-1}; ^{1}H NMR δ 0.59 (q, 6H, J = 7.9 Hz, TES), 0.78 (d, 3H, J = 6.3 Hz, 5-Me), 0.96 (t, 9H, J = 7.9 Hz, TES), 0.82−0.89 (m, 2H, 7-H_2), 1.18 (s, 3H, 6-Me), 1.28 (t, 3H, J = 7.3 Hz, CO_2CH_2*Me*), 1.61 (s, 3H, 9-Me), 1.72 (s, 3H, 9-Me), 1.73−1.84 (m, 1H, 5-H), 2.11 (s, 3H, 3-Me), 2.18 (d, 1H, J = 7.4 Hz, 4-H), 2.42 (d, 1H, J = 7.4 Hz, 4-H), 4.09−4.18 (m, 2H, CO_2CH_2Me), 5.16−5.22 (m, 1H, 8-H), 5.64 (s, 0.7 H, 2-H), 5.73 (s, 0.3 H, 2-H); ^{13}C NMR δ 6.99, 7.25, 7.26, 14.13, 14.35, 18.09, 18.47, 22.71, 29.38, 29.68, 29.72, 31.95, 40.26, 59.43, 77.96, 116.87, 117.69, 120.41; HRMS calcd for $C_{22}H_{42}O_3Si$ (M^+) 353.2511, found (M^+) 353.2508. Anal. Calcd for $C_{22}H_{42}O_3Si$: C, 69.05; H, 11.06. Found: C, 69.18; H, 10.65.

A Mixture of (2*S*,3*R*,5*R*)- and (2*S*,3*R*,5*S*)-5-(Ethoxycarbonylmethyl)-2,3,5-trimethyl-2-(3′-methyl-2-butenyl)-tetrahydrofurans (10). To a stirred solution of triethylsilyl ether (**9**) (0.86 g, 2.44 mmol) in THF (30 mL) was added TBAF (1.0 M THF solution, 4.87 mL, 4.87 mmol) at ambient temperature, and the resulting solution was heated at reflux for 2 h. The mixture was treated with water (30 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (12:1) as an eluent to give an inseparable diastereomeric mixture of tetrahydrofuran derivatives (**10**) (5*S*:5*R* = 3:1) (0.65 g, 100%) as a colorless oil: IR 2970, 1735 cm^{-1}; ^{1}H NMR δ 0.97 (d, 0.75 H, J = 6.8 Hz, 3-Me), 0.99 (d, 2.25 H, J = 6.8 Hz, 3-Me), 1.14 (s, 0.75H, 2-Me), 1.16 (s, 2.25H, 2-Me), 1.25 (s, 0.75H, 5-Me), 1.31 (s, 2.25H, 5-Me), 1.26 (t, 3H, J = 7.3 Hz, CO_2CH_2*Me*), 1.59 (s, 3H, 3′-Me), 1.73 (s, 3H, 3′-Me), 1.93−2.50 (m, 5H, 3-H, CH_2CO_2, and 1′−H_2), 2.61 (t, 2H, J = 14.2 Hz, 4-H_2), 4.06−4.20 (m, 2H, CO_2CH_2Me), 5.24−5.35 (m, 1H, 2′−H); ^{13}C NMR for 5S-isomer δ 5.74, 13.39, 14.12, 17.93, 25.82, 25.96, 28.28, 33.90, 43.28, 44.55, 47.88, 60.14, 78.97, 84.97, 120.33, 171.19; ^{13}C NMR for 5R-isomer δ 6.52, 13.44, 14.15, 17.93, 25.43, 25.98, 28.80, 34.18, 43.48, 44.16, 47.06, 60.14, 79.32, 85.04, 120.33. 171.19; HRMS calcd for $C_{16}H_{28}O_3$ (M^+) 268.2038, found (M^+) 268.2048.

(2*S*,3*R*,5*S*)- and (2*S*,3*R*,5*R*)-5-(Ethoxycarbonylmethyl)-2-(2-hydroxyethyl)-2,3,5-trimethyltetrahydrofurans (11). A solution of olefin (**10**) (3.2 g, 11.9 mmol) in EtOH (60 mL) was saturated with ozone at −78 °C. The solution was stirred for 15 min at the same temperature, and the ozone was removed by exchange with argon. Sodium borohydride (0.45 g, 12.0 mmol) was added portionwise to the solution, and the mixture was then warmed to 0 °C. After the mixture was stirred for an additional 1 h at the same temperature, the reaction was quenched by adding acetone (2 mL). The solvent was removed by evaporation, and the residue was dissolved in Et_2O. The insoluble material was filtered off through a pad of Celite, and the filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexanes−ethyl acetate (4:1) gave a mixture of alcohols (**11**) (2.18 g, 75%) as a colorless oil. This mixture was separated by HPLC using a silica gel column (Waters 5SL: 250 mm × 4.6 mm i.d.; flow rate: 3.0 mL/min; column temp. 25 °C; UV detection at 210 nm) with hexanes−Et_2O (16:1) to give a 5*S*-compound (0.48 g, 17%) and 5*R*-compound (1.70 g, 59%), respectively. (2*S*,3*R*,5*S*)-Compound (**11a**): $[\alpha]^{25}_D$ +65.2 (*c* 0.1, $CHCl_3$); IR 3430, 2980, 1725 cm^{-1}; ^{1}H NMR δ 0.94 (d, H, J = 6.9 Hz, 3-Me), 1.28 (t, 3H, J = 7.2 Hz, CO_2CH_2*Me*), 1.29 (s, 3H, 2-Me), 1.31 (s, 3H, 5-Me), 1.62 (t, 1H, J = 12.5 Hz, 4-H), 1.72−1.82 (m, 2H, 1′−H_2), 2.25 (dd, 1H, J = 6.9 and 12.5 Hz, 4-H), 2.28−2.35 (m, 1H, 3-H), 2.47 (br s, 2H, CH_2-COO), 4.01 (t, 2H, J = 11.4 Hz, 2′−H_2), 4.13 (q, 2H, J = 7.2 Hz, OCH_2Me); ^{13}C NMR δ 13.18, 14.08, 24.74, 28.30, 35.98, 43.88, 44.45, 46.83, 59.57, 60.18, 80.13, 86.08, 170.75; HRMS calcd for $C_{13}H_{24}O_4$ (M^+) 244.3263, found (M^+) 244.3259. (2*S*,3*R*,5*R*)-Compound (**11b**): $[\alpha]^{25}_D$ +49.1 (*c* 0.1, $CHCl_3$); IR 3430, 2980, 1730 cm^{-1}; ^{1}H NMR δ 0.96 (d, H, J = 6.9 Hz, 3-Me), 1.26 (t, 3H, J = 7.1 Hz, CO_2CH_2*Me*), 1.28 (s, 3H, 2-Me), 1.31 (s, 3H, 5-Me), 1.73−1.90 (m, 2H, 1′−H_2), 1.83 (t, 1H, J = 12.5 Hz, 4-H), 2.01 (dd, 1H, J = 6.6 and 12.5 Hz, 4-H), 2.17−2.36 (m, 1H, 3-H), 2.57 and 2.64 (each d, each 1H, J = 13.7 Hz, CH_2COO), 4.03 (t, 2H, J = 10.6 Hz, 2′−H_2), 4.14 (q, 2H, J = 7.1 Hz, OCH_2Me); ^{13}C NMR δ 13.18, 14.04, 25.31, 27.54, 36.19, 43.62, 45.37, 47.78, 59.30, 60.33, 79.55, 85.91, 170.84; HRMS calcd for $C_{13}H_{24}O_4$ (M^+) 244.3263, found (M^+) 244.3266.

(2*S*,3*R*,5*S*)-2-Ethenyl-5-(ethoxycarbonylmethyl)-2,3,5-trimethyltetrahydrofuran (13). To a stirred solution of

alcohol (**11a**) (1.7 g, 6.96 mmol) and *o*-nitrophenyl selenenyl cyanide (2.4 g, 10.4 mmol) in THF (35 mL) was added portionwise tributylphosphine (2.1 g, 10.4 mmol) at 0 °C, and the resulting mixture was allowed to warm to room temperature and then stirred for an additional 5 h. After evaporation of the solvent, the residue was taken up with CH_2Cl_2 (50 mL). To this solution was added *m*-CPBA (7.7 g, 45.0 mmol) portionwise at 0 °C, and the mixture was again allowed to warm to room temperature and then stirred for 30 min at the same temperature. The mixture was diluted with CH_2Cl_2, washed successively with 10% sodium thiosulfate solution, saturated sodium hydrogen carbonate solution, and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (6:1) as an eluent to give olefin (**13**) (1.42 g, 91%) as a colorless oil: $[\alpha]^{25}_D$ +60.1 (*c* 0.01, $CHCl_3$); IR 2900, 1750 cm^{-1}; ^1H NMR δ 0.95 (d, H, J = 6.9 Hz, 3-Me), 1.26 (t, 3H, J = 7.3 Hz, CO_2CH_2*Me*), 1.31 (s, 3H, 2-Me), 1.35 (s, 3H, 5-Me), 1.71 (t, 1H, J = 12.4 Hz, 4-H), 1.99 (dd, 1H, J = 6.3 and 12.4 Hz, 4-H), 2.20−2.33 (m, 1H, 3H), 2.61 and 2.72 (each d, each 1H, J = 14.0 Hz, CH_2COO), 4.14 (q, 2H, J = 7.3 Hz, OC*H*$_2$Me), 5.08 (d, 1H, J = 10.7 Hz, olefinic proton), 5.27 (d, 1H, J = 17.2 Hz, olefinic proton), 5.78 (dd, 1H, J = 10.7 and 17.2 Hz, olefinic proton); ^{13}C NMR δ 14.10, 14.13, 26.38, 27.76, 33.30, 44.38, 46.71, 60.06, 79.86, 85.27, 113.29, 140.75, 170.91; HRMS calcd for $C_{13}H_{22}O_3$ (M^+) 226.1596, found (M^+) 226.1578. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.70; H, 9.85.

(2*S*,3*R*,5*R*)-2-Ethenyl-5-(ethoxycarbonylmethyl)-2,3,5-trimethyltetrahydrofuran (15). Alcohol **11b** (3.0 g, 12.3 mmol) was dehydrated by essentially the same procedure that was used to prepare its stereoisomer using Grieco's procedure to give olefin (**15**) (2.38 g, 86%) as a colorless oil: $[\alpha]^{25}_D$ +55.3 (*c* 0.02, $CHCl_3$); IR 2980, 1745 cm^{-1}; ^1H NMR δ 0.96 (d, H, J = 6.9 Hz, 3-Me), 1.26 (t, 3H, J = 7.3 Hz, CO_2CH_2*Me*), 1.32 (s, 3H, 2-Me), 1.36 (s, 3H, 5-Me), 1.71 (t, 1H, J = 12.5 Hz, 4-H), 1.99 (dd, 1H, J = 6.3 and 12.5 Hz, 4-H), 2.20−2.33 (m, 1H, 3-H), 2.58−2.75 (m, 2H, CH_2COO), 4.12 (q, 2H, J = 7.3 Hz, OC*H*$_2$Me), 5.07 (d, 1H, J = 10.7 Hz, olefinic proton), 5.26 (d, 1H, J = 17.2 Hz, olefinic proton), 5.79 (dd, 1H, J = 10.7 and 17.2 Hz, olefinic proton); ^{13}C NMR δ 14.06, 14.10, 26.84, 27.57, 43.35, 44.97, 47.79, 60.06, 79.42, 85.10, 113.19, 140.64, 170.98. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.69; H, 9.96.

***cis*-Nemorensic Acid (3).** A solution of olefin (**13**) (42 mg, 0.19 mmol) in dichloromethane (15 mL) was saturated with ozone at −78 °C. The solution was stirred for 30 min at the same temperature, and ozone was removed by exchange with argon. To this solution was added triphenylphosphine (75 mg, 29 mmol), and the resulting mixture was allowed to warm to room temperature. After evaporation of the solvent, the residue was taken up with Et_2O, and the ethereal layer was filtered through a pad of Celite to remove insoluble materials. The filtrate was concentrated to leave a residue, which, without further purification, was used in the next step. To a stirred solution of the aldehyde obtained above, 2-methyl-2-butene (53 mg, 0.76 mmol), and NaH_2PO_4 (23 mg, 0.19 mmol) in water (0.4 mL) and *tert*-butyl alcohol (1.5 mL) was added portionwise sodium chlorite (51 mg, 0.57 mmol) at room temperature, and the resulting mixture was stirred for an additional 1 h at the same temperature. The solution was acidified with 1 N hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was dissolved in methanol (2 mL). After adding 2 N NaOH solution (1 mL), the mixture was heated at reflux for 5 h and then cooled to 0 °C. The aqueous layer was washed with CH_2Cl_2 and then treated with 1 N hydrochloric acid to adjust the pH to 1−2. Removal of the solvent gave a residue, which was taken up with methanol. The insoluble material was filtered off, and the filtrate was concentrated to leave a residue, which was purified by reversed-phase column chromatography using Sep pak C18 with water to give acid (**3**) (29.6 mg, 72%) as a colorless powder: mp 174−176.5 °C [lit.,[9] 174−178 °C; lit.,[10] 174−175 °C]; $[\alpha]^{25}_D$ +88.1 (*c* 0.06, EtOH) [lit.,[9] $[\alpha]^{24}_D$ +87 (*c* 0.84, EtOH); lit.,[10] $[\alpha]^{23}_D$ +87.2 (*c* 0.24, EtOH)]; IR 2970, 1705 cm^{-1}; ^1H NMR (D_2O) δ 1.00 (d, 3H, J = 6.9 Hz, 3-Me), 1.34 (s, 3H, 2-Me), 1.42 (s, 3H, 5-Me), 1.83 (t, 1H, J = 12.5 Hz, 4-H), 2.09 (dd, 1H, J = 6.8 and 12.5 Hz, 4-H), 2.30−2.44 (m, 1H, 3-H), 2.64 (dd, 2H, J = 14.5 and 14.5 Hz, CH_2COO); HRMS calcd for $C_{10}H_{16}O_5$ (M^+) 216.0998, found (M^+) 216.0998. The spectroscopic data were identical to those reported in the literature.[9,10]

***trans*-Nemorensic Acid (16).** Ozonolysis of olefin (**15**) (50 mg, 0.22 mmol), followed by oxidation of the aldehyde with sodium chlorite and hydrolysis of the ester group was carried out using essentially the same procedure that was used to prepare *cis*-nemorensic acid to give *trans*-nemorensic acid (**16**) (38 mg, 80%) as a colorless oil: $[\alpha]^{25}_D$ +48.8 (*c* 0.1, $CHCl_3$) [lit.,[10] $[\alpha]^{23}_D$ +55.4 (*c* 0.99, $CHCl_3$)]; IR 2990, 1710 cm^{-1}; ^1H NMR (D_2O) δ 0.95 (d, H, J = 6.9 Hz, 3-Me), 1.29 (s, 3H, 2-Me), 1.36 (s, 3H, 5-Me), 1.76 (t, 1H, J = 12.5 Hz, 4-H), 2.03 (dd, 1H, J = 6.6 and 12.5 Hz, 4-H), 2.24−2.38 (m, 1H, 3-H), 2.53 and 2.54 (each d, each 1H, J = 13.8 Hz, CH_2COO); HRMS calcd for $C_{10}H_{16}O_5$ (M^+) 216.0998, found (M^+) 216.0977.

***trans*-Nemorensic Acid Dimethyl Ester (17).** A solution of acid (**16**) (24 mg, 0.11 mmol), K_2CO_3 (62 mg, 0.44 mmol), and iodomethane (40 mg, 0.28 mmol) in DMF (4 mL) was stirred at room temperature for 3 h under argon. The mixture was treated with saturated NH_4Cl solution and extracted with ethyl acetate. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel using hexanes−ethyl acetate (4:1) as an eluent to give ester (**17**) (19.2 mg, 71%) as a colorless oil: $[\alpha]^{25}_D$ +60.8 (*c* 0.01, $CHCl_3$); IR 2920, 1735 cm^{-1}; ^1H NMR δ 1.08 (d, H, J = 6.9 Hz, 3-Me), 1.25 (s, 3H, 2-Me), 1.34 (s, 3H, 5-Me), 1.92 (dd, 1H, J = 12.3 and 12.5 Hz, 4-H), 2.04 (dd, 1H, J = 6.8 and 12.5 Hz, 4-H), 2.59−2.79 (m, 3H, 3-H and 1′-H_2), 3.66 (s, 3H, Me), 3.74 (s, 3H, Me); HRMS calcd for $C_{12}H_{20}O_5$ (M^+) 244.2834, found (M^+) 244.2844.

The spectroscopic data of the synthetic compound were identical to those reported in the literature.[10]

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Supporting Information Available: IR, ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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