dure of Saunders and Edison,[19] bp 120 °C (75 mm) (lit.[19] 121 °C (75 mm)).

(2-Phenylethyl-2-*t*)dimethylsulfonium bromide was obtained in 75% yield by the reaction of 0.07 mol methyl 2-phenylethyl-2-*t* sulfide with 0.14 mol of methyl bromide in 100 mL of nitromethane for 12 h. The product was precipitated by the addition of ether and recrystallized from ethanol-ether, mp 136-137 °C (lit.[19] 136.5-137 °C).

Determination of Isotope Effects. Separate solutions of the substrate and the freshly prepared base were equilibrated for 1 h in a bath maintained within ±0.05 °C of the stated temperature. Sufficient base solution was added to the substrate solution to give final concentrations of 0.1-0.3 M and a reaction half life of 1-10 h. Aliquots of the reaction mixture were withdrawn periodically and diluted with ethanol for measuring the styrene absorbance. The molar absorbances of Saunders and Williams[34] were used in calculating the fraction of reaction. At the desired extent of reaction the reaction mixture was quenched by acidification with hydrochloric acid. The quenched reaction mixture was added to 25 mL of pentane, 100 mL of water was added, and the pentane layer separated. The aqueous layer was extracted five times with 10-mL portions of pentane, and the combined extracts washed with water and dried over anhydrous potassium carbonate. The pentane solution was treated with bromine until the color persisted, the pentane removed, water added to the residue, and the precipitated styrene dibromide recrystallized from methanol-water, mp 74 °C (lit.[35] 73 °C).

Counting of substrate and styrene dibromide was done on 10-50 mg samples in 15 mL of scintillation cocktail to ±0.2% precision using a Beckman LS-100C liquid scintillation counter. The cocktail consisted of 26.6 g of BuPBD and 0.4 g of Me_2POPOP in 4 L of toluene. For the sulfonium and ammonium salts, 20 mg of the salt sample was dissolved in 1 mL of distilled water and 15 mL of Beckman Ready-Solv HP added to give a clear solution. Quench corrections were determined by the external standard channels ratio method. Counting efficiencies were in the 35-45% range. Each vial was counted twice, and the activities used in calculating the isotope effects were based on 2-4 separate weighings of each sample.

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(35) Shriner, R. L.; Fuson, R. C.; Curtin, D. Y.; Morrill, T. C. "The Systematic Identification of Organic Compounds", 6th ed.; Wiley: New York, 1980; p 557.

Reaction of α-(Phenylsulfinyl)acetonitrile with Aldehydes and Ketones to γ-Hydroxyalkenenitriles and Syntheses of Terpenoids

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Abstract: Reaction of α-(phenylsulfinyl)acetonitrile (**1**) with aldehydes or ketones in the presence of base directly affords γ-hydroxyalkenenitriles. Some terpenoids, such as dendrolasin (**9**), sirenin (**17**), and conjugated trienoic acid (3,7,11,15-tetramethylhexadeca-2,4,6,10,14-pentenoic acid (**24**)), were synthesized by employing the new C^2 unit homologation method.

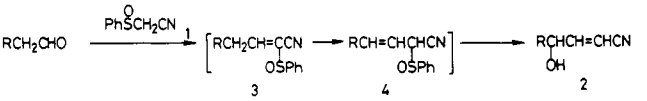
As part of our continuing interest in the reaction of organosulfur compounds, the reaction of the carbanion, derived from a sulfinyl-activated methylene compound, with electrophile became a matter of prime interest because of the versatility in functionalization of the products by the sulfinyl group.[1] Here, we describe one of our current developments on organosulfur-mediated synthetic method; the reaction of α-(phenylsulfinyl)acetonitrile (**1**) with aldehydes or ketones in the presence of base to give γ-hydroxyalkenenitriles.[2] We also report the syntheses of several terpenoids by use of the methodology.

Results and Discussion

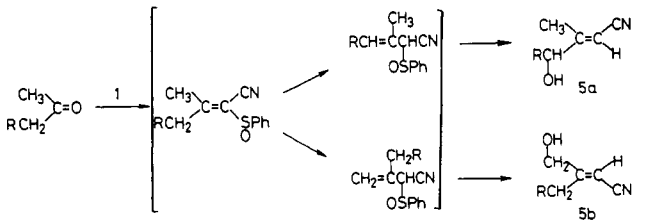
Reaction of α-(Phenylsulfinyl)acetonitrile (1) with Aldehydes or Ketones. α-(Phenylsulfinyl)acetonitrile (**1**) was readily obtained by treatment of α-chloroacetonitrile with thiophenol and sodium carbonate, followed by oxidation of the resulting α-(phenylthio)acetonitrile with sodium periodate or hydrogen peroxide.

As an interesting fact, we have found out that the room-temperature reaction of **1** with aldehydes and piperidine in methanol directly affords γ-hydroxyalkenenitriles **2** in quantitative yield without contamination of α-(phenylsulfinyl)alkenenitriles **3** or **4**. As a working hypothesis, it was assumed that **2** should be derived from **3**, which in turn is converted to **4** by double bond migration.

Scheme I



Scheme II



Sigmatropic rearrangement of the sulfinyl group of **4** would give **2**[3] (Scheme I). Furthermore, it should be noted that the geometry of **2** is specifically *E*. The similar reaction of **1** with ketones gave the corresponding γ-hydroxyalkenenitrile. In particular, room-temperature treatment of **1** with methyl ketone such as octan-2-one and piperidine in methanol selectively gave 3-methyl-4-hydroxynon-2-enenitrile (**5a**) in 84% yield. In contrast, the re-

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(2) Nokami, J.; Mandai, T.; Imakura, Y.; Nishiuchi, K.; Kawada, M.; Wakabayashi, S. *Tetrahedron Lett.* **1981**, *22*, 4489.

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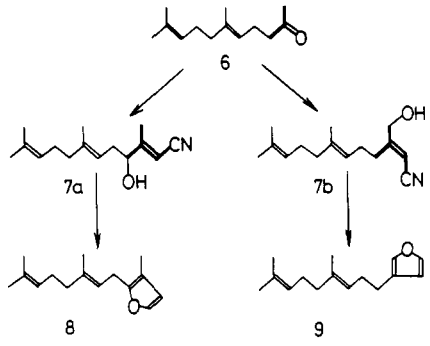
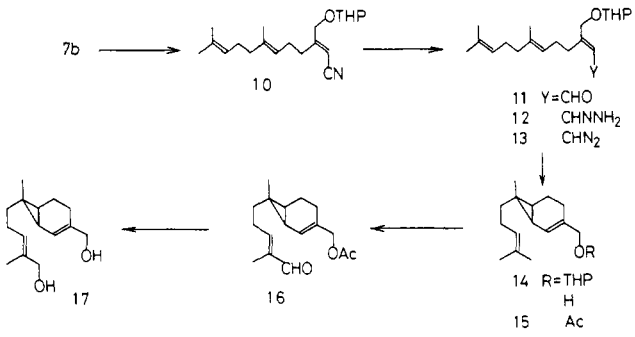
Scheme III



Scheme IV



action of **1** with octan-2-one in refluxing benzene containing a catalytic amount of piperidine and acetic acid afforded a mixture of **5a** and 3-(hydroxymethyl)non-2-enenitrile (**5b**) in the ratio of 1:7 (**5a**:**5b**) in 76% yield (Scheme II). This fact is interesting in the following points: (1) the two carbon homologation proceeds in ketones as well as aldehydes; (2) the α carbon atom attaching to the carbonyl group is oxidatively functionalized; and (3) it is possible to oxidize selectively either the methylene or the methyl group adjacent to the carbonyl carbon of methyl ketones. Then this reaction is quite different from the usual two-carbon homologation of the carbonyl carbon atom, e.g., the Wittig reaction by the corresponding ylide[4] and the Knoevenagel reaction by α-cyanoacetic acid.[5] This new methodology played an important role in our design of terpenoid syntheses.

Synthesis of Sesquiterpene Furan 8 and Its Homologue 9 (Dendrolasin).[6] Our synthetic strategy for some terpenoids was to build a functionalized isoprene unit by the reaction of **1** with methyl ketone as shown in Scheme III. Reaction of 6,10-dimethylundeca-5,9-dien-2-one (geranylacetone) (**6**) with **1** in refluxing benzene in the presence of a catalytic amount of piperidine and acetic acid afforded **7a** and **7b** in 10% and 63% isolated yields, respectively. On the other hand, the reaction of **6** with **1** and piperidine in methanol at room temperature gave specifically **7a** in 85% yield. The γ-hydroxyalkenenitriles **7a** and **7b** were separately converted to the corresponding furans **8** and **9** in yields of 66% and 75%, respectively, by the reduction with diisobutylaluminum hydride (DIBAH) and followed by acid-catalyzed dehydration.

Synthesis of Sirenin (17). The synthesis of sirenin[7] was carried out according to Scheme IV. The γ-hydroxyalkenenitrile **7b** was converted to tetrahydropyranyl ether **10** to give aldehyde **11** by reduction of the cyano group with DIBAH without the formation of **9**. The enal **11** was reacted with anhydrous hydrazine and followed with active manganese dioxide to give diazo compound **13** via hydrazone **12**. The diazo compound **13** was treated with

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(6) Reference 2. Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5225 and references contained therein.
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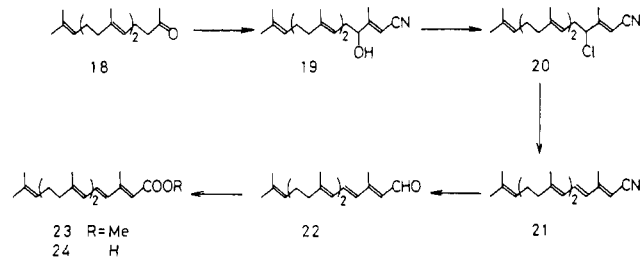
Scheme V



excess copper(I) iodide in dry tetrahydrofuran (THF) at room temperature for 25 h under nitrogen to yield the sirenin skeletal compound **14** in 34% yield based on aldehyde **11**. The geometry of the $\alpha\beta$ double bond of **7b** was shown to be *Z* by the satisfactory yield of the cyclization reaction. Oxidation of the methyl group by selenium dioxide[8] was carried out in refluxing aqueous dioxane after conversion of the tetrahydropyranyloxy compound **14** to acetoxy compound **15**. Sirenin (**17**) was obtained by treatment of **16** with DIBAH at −5 °C in dry ether for 15 min.

Synthesis of 3,7,11,15-Tetramethylhexadeca-2,4,6,10,14-pentenoic Acid (23). Finally, we employed our reaction for the synthesis of the conjugated trienoic acid **23** which is called to exhibit more anticancerous activity than letinoid compound such as vitamin A.[9] Commercially available 6,10,14-trimethylpentadeca-5,9,13-trien-2-one (**18**) was treated with **1** and piperidine (excess) in acetonitrile in the presence of a catalytic amount of acetic acid at room temperature for 24 h to give the corresponding γ-hydroxyalkenenitrile **19** (Scheme V). Conversion of **19** to the conjugated trienenitrile **21** was carried out via dehydrochlorination of **20**. The conjugated trienenitrile **21** was reduced to the corresponding aldehyde by DIBAH reduction at −5 °C in ether. There was a mixture of *E* and *Z* isomer to the carbonyl group in the ratio of ca. 3/1 (*E*/*Z*). The *E*-aldehyde **22** was easily isolated by column chromatography on silica gel. Oxidation of **22** to methyl ester **23** was accomplished by treating **22** with sodium cyanide, acetic acid, and active manganese dioxide in methanol for 12 h (Corey's method)[10] in good yield. The conjugated trienoic acid **24**, which had all *E* geometry, was obtained as a pale yellowish crystal by alkaline hydrolysis of **23**.

Experimental Section

General. All the melting points are uncorrected. The infrared (IR) spectra were recorded on a Hitachi 260-30 spectrometer. The ^1H and ^{13}C NMR spectra were obtained on a Jeol FX-100 spectrometer using tetramethylsilane (δ 0) as internal standard in $CDCl_3$.

Preparation of α-(Phenylsulfinyl)acetonitrile (1). α-Chloroacetonitrile (13 mL), thiophenol (42 mL), and sodium carbonate (65 g) were mixed in 200 mL of acetone, and the mixture was stirred continuously at 50 °C for 5 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was extracted with ether, and the extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo and distillation of the product gave α-(phenylthio)acetonitrile (58 g, 95% yield, bp 145 °C (12 mmHg)). To a methanol (500 mL) solution of α-(phenylthio)acetonitrile (15 g), sodium periodate (27 g, solved in 150 mL of water) was added at 0 °C. After stirring at 0 °C for 10 h, white precipitate was removed by filtration from the reaction mixture. The filtrate was concentrated in vacuo, and the residue was extracted with dichloromethane. The extract was washed with brine, dried, and evaporated in vacuo to give white crystal **1** (recrystallized from ether, mp 59 °C, 85% yield).

γ-Hydroxyalkenenitrile (2, 5a, and 5b). To a solution of sulfoxide **1** (234 mg, 1.43 mmol) in benzene (5 mL), hexanal (172 mg, 1.71 mmol) and piperidine (122 mg, 1.43 mmol) were added with stirring. After the stirring was continued for 1.5 h at room temperature, hydrochloric acid (1 N, 3 mL) was added to the reaction mixture, and the organic layer was separated, washed with brine, dried, and concentrated in vacuo. The

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(9) Eisai, Co. Ltd., Belg. Patent BE 888290. *Chem. Abstr.* **1982**, *96*, 35600e.
(10) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.

residue was column chromatographed on silica gel (ether/hexane = 1/4) to give 4-hydroxyoct-2-enenitrile (**2**) (162 mg, 81%): IR (neat) 3450, 2940, 2860, 2220, 1715, 1670, 1630, 1460, 1130, 1080, 960 cm^{-1}; ^1H NMR δ 0.89 (3 H, br t), 1.0–1.8 (8 H, br), 4.25 (1 H, m), 5.66 (1 H, dd, J = 2 and 16 Hz), 6.79 (1 H, dd, J = 4 and 16 Hz); ^{13}C NMR δ 14.0 (q), 22.5 (t), 24.8 (t), 31.6 (t), 36.2 (t), 70.7 (t), 98.1 (d), 117.5 (s), 157.7 (d). To a methanol (3 mL) solution of **1** (330 mg, 2.0 mmol), octan-2-one (308 mg, 2.4 mmol) and piperidine (170 mg, 2.0 mmol) were added. The mixture was stirred for 18 h at room temperature and then was concentrated in vacuo. After addition of hydrochloric acid (1 N, 3 mL), the residue was extracted with dichloromethane. The extract was washed with brine, dried, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel (ether/hexane = 1/4) to give **5a** in 84% yield: IR (neat) 3450, 2950, 2880, 2230, 1670, 1635, 1450, 1130, 1020, 830 cm^{-1}; ^1H NMR δ 0.89 (3 H, br t), 1.1–1.8 (8 H, br), 2.00 (3 H, s), 4.10 (1 H, br t, J = 6 Hz), 5.48 (1 H, s); ^{13}C NMR δ 13.7 (q), 17.1 (q), 22.2 (t), 24.5 (t), 31.3 (t), 34.5 (t), 74.0 (d), 93.9 (d), 116.9 (s), 167.0 (s). A solution of sulfoxide **1** (216 mg, 1.3 mmol), octan-2-one (168 mg, 1.3 mmol), piperidine (22 mg, 0.26 mmol), and acetic acid (16 mg, 0.26 mmol) in benzene (5 mL) was heated at 80 °C for 30 h with stirring. The reaction mixture was washed with brine, dried, and concentrated in vacuo. The residue was column chromatographed on silica gel (ether/hexane = 1/4) to give a mixture of **5a** and **5b** (**5a**/**5b** = 1/7) in 76% yield. Further purification by column chromatography on silica gel (ether/hexane = 1/6) gave **5b** in 50% yield: IR (neat) 3450, 2930, 2850, 2210, 1630, 1465, 1100, 1050, 800 cm^{-1}; ^1H NMR δ 0.89 (3 H, br t), 1.1–1.7 (8 H, br), 2.33 (2 H, t, J = 7 Hz), 4.15 (2 H, d, J = 2 Hz), 5.52 (1 H, t, J = 2 Hz); ^{13}C NMR δ 13.9 (q), 22.3 (t), 28.1 (t), 28.9 (t), 31.2 (t), 32.0 (t), 63.4 (t), 92.5 (d), 116.9 (s), 168.1 (s).

Reaction of Sulfoxide 1 with 6,10-Dimethylundeca-5,9-dien-2-one (Geranylacetone) (6). A solution of **1** (1.65 g, 10 mmol), geranylacetone **6** (2.91 g, 15 mmol), and piperidine (0.85 g, 10 mmol) in methanol (30 mL) was stirred for 17 h at room temperature. After workup as described above, 3,7,11-trimethyl-4-hydroxy-2,6,10-trienenitrile (**7a**) (2.0 g) was selectively obtained in 85% yield: IR (neat) 3450, 2980, 2940, 2870, 2230, 1660, 1635, 1445, 1380, 1090, 1020, 790, 740 cm^{-1}; ^1H NMR δ 1.61 (6 H, s), 1.68 (3 H, s), 2.02 (3 H, s), 2.0–2.5 (6 H, m), 4.14 (1 H, t, J = 6 Hz), 5.07 (2 H, m), 5.50 (1 H, br); ^{13}C NMR δ 16.2 (q), 17.6 (2 × q), 25.7 (q), 26.4 (t), 33.8 (t), 39.7 (t), 73.7 (d), 94.5 (d), 116.9 (s), 117.9 (d), 123.7 (d), 131.4 (s), 139.7 (s), 165.6 (s). To a dry benzene (13 mL) solution of **1** (213 mg, 1.29 mmol) was added **6** (126 mg, 0.65 mmol), piperidine (41 mg, 0.48 mmol), and acetic anhydride (13 mg, 0.13 mmol). The mixture was stirred at 80 °C for 3 days. After workup as described above, **7b** and **7a** were obtained (96 mg (63%) and 15 mg (10%), respectively). **7b**: IR (neat) 3500, 2980, 2940, 2875, 2240, 2875, 2240, 1635, 1450, 1380, 1070, 820 cm^{-1}; ^1H NMR δ 1.52 (6 H, s), 1.61 (3 H, s), 1.9–2.4 (8 H, m), 4.12 (2 H, d, J = 2 Hz), 5.00 (2 H, m), 5.46 (1 H, t, J = 2 Hz); ^{13}C NMR δ 16.1 (q), 17.7 (q), 25.7 (q), 26.6 (2 × t), 32.2 (t), 39.6 (t), 64.0 (t), 93.3 (d), 116.9 (s), 121.7 (d), 122.5 (s), 123.9 (d), 1379.1 (s), 167.1 (s).

Synthesis of Furan 8 and Its Homologue 9 (Dendrolasin). To a solution of the γ-hydroxyalkenenitrile **7a** or **7b** (2 mmol) in dry ether (15 mL), diisobutylaluminum hydride (DIBAH) (2.0 mL of a 2.2 M hexane solution, 4.4 mmol) was added at −5 °C with stirring. After stirring for 1 h at 0 °C, hydrochloric acid (2 N, 3 mL) was added to the reaction mixture. The stirring was continued for several hours at 10 °C to complete the conversion of γ-hydroxyalkenal to the corresponding furan **8** or **9**. **8** (66% yield based on **7a**): IR (neat) 2970, 2930, 1500, 1440, 1370, 1145, 1080, 885, 720 cm^{-1}; ^1H NMR δ 1.59, 1.67, 1.71, and 1.96 (12 H, each s), 2.03 (4 H, br), 3.28 (2 H, d, J = 7 Hz), 5.08 (1 H, m), 5.26 (1 H, t, J = 7 Hz), 6.14 (1 H, d, J = 2 Hz), 7.20 (1 H, d, J = 2 Hz); ^{13}C NMR δ 9.7 (q), 16.1 (q), 17.6 (q), 25.1 (t), 25.6 (q), 26.5 (t), 39.6 (t), 112.6 (d), 113.2 (s), 119.7 (d), 123.9 (d), 131.1 (s), 136.2 (s), 139.5 (d), 149.8 (s). **9** (Dendrolasin) (75% yield based on **7b**): IR (neat) 2970, 2920, 2850, 1495, 1440, 1370, 1155, 1060, 1020, 865, 770 cm^{-1}; ^1H NMR δ 1.59 (6 H, s), 1.68 (3 H, s), 2.01 (4 H, br), 2.0–2.6 (4 H, m), 5.1 (2 H, m), 6.26 (1 H, br), 7.19 (1 H, br), 7.31 (1 H, t, J = 2 Hz); ^{13}C NMR δ 16.0 (q), 17.6 (q), 25.0 (t), 25.6 (q), 26.7 (t), 28.5 (t), 39.7 (t), 110.9 (d), 123.5 (d), 124.1 (d), 124.7 (s), 130.9 (s), 135.4 (s), 138.5 (d), 142.1 (d).

Synthesis of Sirenin (17). Conversion of 7b to 10. To a stirred solution of **7b** (1.5 g, 6.4 mmol) in CH_2Cl_2 (20 mL) were added *p*-toluenesulfonic acid (ca. 30 mg) and 3,4-dihydro-α-pyrane (1.8 mL, 20 mmol). The mixture was stirred for 1 h at 0 °C. The reaction mixture was washed with aqueous $NaHCO_3$ and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ether/hexane = 1/4) to give tetrahydropyranyl ether **10** (2.0 g, 99%): IR (neat) 2940, 2860, 2220, 1635, 1445, 1380, 1200, 1130, 1070, 1035, 965, 900, 865, 810 cm^{-1}; ^1H NMR δ 1.53 (6 H, s), 1.60 (3 H, s), 1.3–1.8 (6 H, m), 1.94 (4 H, br), 2.0–2.4 (4 H, m), 3.6 (2 H, m), 4.08 (2 H, dd, J = 2 and 17 Hz), 4.54 (1 H, br), 5.04 (2 H, m), 5.43 (1 H, t, J = 2 Hz); ^{13}C NMR δ 15.5 (q), 17.1 (q), 18.7 (t), 24.8 (q), 25.1 (t), 26.1 (2 × t), 29.8 (t), 31.9 (t), 39.1 (t), 61.4 (t), 67.1 (t), 93.7 (d), 97.5 (d), 116.0 (s), 121.3 (d), 123.5 (d), 130.4 (s), 136.3 (s), 163.2 (s).

Reduction of Nitrile 10 to Aldehyde 11. To a stirred solution of nitrile **10** (753 mg, 2.37 mmol) in dry ether (5 mL) was added DIBAH (1.2 mL of a 2.2 M hexane solution, 2.64 mmol) at −5 °C. After stirring for 1 h at between −5 and 0 °C, the reaction mixture was poured into ice water and neutralized with diluted hydrochloric acid. The product was extracted with ether. The extract was washed with brine, dried, and concentrated to a residue, which was column chromatographed on silica gel (ether/hexane = 1/3) to give aldehyde **11** (700 mg, 92%): IR (neat) 2950, 2870, 1680, 1450, 1125, 1040 cm^{-1}; ^1H NMR δ 1.54 (6 H, s), 1.61 (3 H, s), 1.3–2.6 (10 H, m), 3.3–3.9 (2 H, m), 4.15 (2 H, dq, J = 2 and 17 Hz), 4.60 (1 H, br), 5.04 (2 H, m), 6.11 (1 H, d, J = 8 Hz), 9.75 (1 H, d, J = 8 Hz); ^{13}C NMR δ 16.1 (q), 17.6 (q), 19.1 (t), 25.4 (t), 25.6 (q), 26.5 (t), 28.0 (t), 28.8 (t), 30.3 (t), 39.6 (t), 61.9 (t), 68.6 (t), 97.9 (d), 121.8 (d), 123.9 (d), 125.3 (d), 131.1 (s), 137.2 (s), 161.9 (s), 190.3 (d).

Conversion of Aldehyde 11 to Diazo Compound 13 via Hydrazone 12, and Synthesis of 14. To a solution of aldehyde **11** (1.0 g, 3.1 mmol) in ethanol (10 mL) were added anhydrous hydrazine (0.12 g, 3.76 mmol) and triethylamine (380 mg, 3.76 mmol) under nitrogen at room temperature. After stirring for 1.5 h, the reaction mixture was concentrated under reduced pressure to afford crude hydrazone **12**. The crude hydrazone **12** (ca. 1 g) was added to a stirred suspension of finely powdered active manganese dioxide (6.8 g, 78.2 mmol) in CH_2Cl_2 at −5 °C. The stirring was continued for 1 h. The reaction mixture was filtered to remove MnO_2 and the filtrate was concentrated in vacuo to crude diazo compound **13**: IR (neat) 2950, 2880, 2070 (very strong), 1640, 1450, 1200, 1120, 1080, 1035, 1010 cm^{-1}. To a suspension of CuI (1.13 g, 6.3 mmol) in dry THF (35 mL), a dry THF (10 mL) solution of the crude **13** (ca. 1 g) was added with stirring for a period of 6 h at room temperature under nitrogen. The mixture was stirred at this temperature for 18 h before the starting diazo compound disappeared upon checking the TLC. The reaction mixture was filtered and concentrated in vacuo to residue, which was chromatographed on silica gel (ether/hexane = 1/20), to give bicyclic compound **14** in 35% yield (0.33 g) based on aldehyde **11**. **14**: IR (neat) 2950, 2870, 1450, 1200, 1120, 1015 cm^{-1}; ^1H NMR δ 0.87 (3 H, s), 1.61 and 1.67 (6 H, each s), 0.8–2.2 (16 H, m), 3.3–4.0 (2 H, m), 3.98 (2 H, q, J = 12 Hz), 4.58 (1 H, br), 5.09 (1 H, t, J = 7 Hz), 5.81 (1 H, d, J = 4 Hz); ^{13}C NMR δ 12.7 (q), 17.5 (q), 17.5 (t), 19.5 (t), 21.5 (d), 21.8 (d), 23.7 (t), 25.5 (2 × t), 25.5 (g), 28.9 (s), 30.6 (t), 42.9 (t), 61.9 (t), 71.2 (t), 97.1 (d), 122.8 (d), 124.5 (d), 130.5 (s), 133.8 (s).

Conversion of 14 to 15. The tetrahydropyranyl ether **14** (43 mg, 0.141 mmol) was stirred with 0.5 N sulfuric acid (0.7 mL) in acetonitrile (1.3 mL) at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate, washed with brine, and concentrated in vacuo to give an alcohol in 85% yield: IR (neat) 3350, 2980, 2930, 2860, 1450, 1380, 1015, 830 cm^{-1}; ^1H NMR δ 0.87 (3 H, s), 1.61 and 1.68 (6 H, each s), 0.7–2.2 (10 H, m), 4.01 (2 H, s), 5.10 (1 H, t, J = 7 Hz), 5.82 (1 H, br); ^{13}C NMR δ 12.7 (q), 17.5 (q), 17.5 (t), 21.6 (2 × d), 23.4 (t), 25.5 (t), 25.7 (q), 28.9 (s), 42.8 (t), 67.5 (t), 121.4 (d), 124.4 (d), 130.7 (s), 136.7 (s). The alcohol (103 mg, 0.46 mmol) was treated with acetic anhydride (1 mL) and pyridine (0.04 mL, 0.46 mmol) at 0 °C for 1 h. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ and with brine and dried. Evaporation of the solvent in vacuo and purification of the product by column chromatography on silica gel (ether/hexane = 1/5) gave acetate **15** (116 mg, 95%): IR (neat) 2980, 2930, 2860, 1740, 1450, 1380, 1230, 1100, 960 cm^{-1}; ^1H NMR δ 0.79 (3 H, s), 1.53 and 1.60 (6 H, each s), 1.96 (3 H, s), 0.7–2.1 (10 H, m), 4.38 (2 H, s), 5.01 (1 H, t, J = 7 Hz), 5.82 (1 H, d, J = 4 Hz); ^{13}C NMR δ 11.5 (q), 16.2 (t), 16.5 (q), 19.8 (q), 20.7 (2 × d), 22.6 (t), 24.4 (t), 24.6 (q), 28.2 (s), 41.8 (t), 67.7 (t), 123.3 (d), 123.6 (d), 129.6 (s), 130.6 (s), 169.4 (s). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.83; H, 10.10.

Oxidation of 15 to 16. The acetate **15** (109 mg, 0.41 mmol) was heated with SeO_2 (44 mg, 0.50 mmol) in aqueous dioxane (95 v/v, 2 mL) with stirring for 1 h. The reaction mixture was concentrated in vacuo and then diluted with ether. The solution was washed with brine, dried, and concentrated in vacuo. The residue was column chromatographed on silica gel (ether/hexane = 1/8) to yield an aldehyde **16** (54 mg, 47%): ^1H NMR δ 0.91 (3 H, s), 1.76 (3 H, d, J = 1 Hz), 2.06 (3 H, s), 0.8–2.1 (8 H, m), 2.45 (2 H, q, J = 8 Hz), 4.47 (2 H, s), 5.90 (1 H, d, J = 4 Hz), 6.50 (1 H, dt, J = 1 and 8 Hz), 9.39 (1 H, s).

Sirenin (17). To a solution of the aldehyde **16** (24 mg, 0.087 mmol) in dry ether (3 mL) was added DIBAH (0.15 mL of a 2.2 M hexane solution, 0.33 mmol) at −5 °C, and the mixture was stirred for 15 min.

The reaction mixture was poured into diluted hydrochloric acid, and extracted with ether. The extract was washed with brine, dried, and concentrated in vacuo. The residue was column chromatographed on silica gel (ether/hexane = 1/2) to give sirenin (**17**) in 95% yield: IR (neat) 3350, 2925, 2860, 1450, 1380, 1060, 1010 cm^{-1}; ^1H NMR δ 0.87 (3 H, s), 1.67 (3 H, s), 0.8–2.0 (8 H, m), 2.12 (2 H, q, J = 8 Hz), 4.00 (4 H, s), 5.39 (1 H, br t, J = 7 Hz), 5.85 (1 H, m); ^{13}C NMR δ 12.7 (q), 13.6 (q), 17.5 (t), 21.6 (2 × d), 23.4 (t), 25.1 (t), 28.8 (s), 42.4 (t), 67.4 (t), 68.8 (t), 121.2 (d), 126.0 (d), 134.1 (s), 136.9 (s).

Synthesis of 3,7,11,15-Tetramethylhexadeca-2,4,6,10,14-pentenoic Acid (24). Reaction of 1 with 6,10,14-Trimethylpentadeca-5,9,13-trien-2-one (18). To a solution of **1** (3.2 g, 19.4 mmol) in acetonitrile (15 mL) were added commercial ketone **18** (3.5 g, 13.3 mmol), piperidine (2.5 mL), and acetic acid (0.05 mL), and then the mixture was stirred for 24 h at room temperature. After workup as described above, the crude product was column chromatographed on silica gel (ether/hexane = 1/5) to give γ-hydroxyalkenenitrile **19** (2.7 g, 67%): IR (neat) 3500, 2960, 2920, 2850, 2220, 1630, 1435, 1380, 1080, 1010, 820 cm^{-1}; ^1H NMR δ 1.60 (6 H, s), 1.62 (3 H, s), 1.67 (3 H, s), 2.00, 2.01, and 2.05 (11 H, each s), 2.26 (2 H, m), 4.09 (1 H, m), 5.08 (2 H, m), 5.49 (1 H, t, J = 1 Hz); ^{13}C NMR δ 16.0 (q), 16.2 (q), 17.5 (q), 17.6 (q), 25.6 (q), 26.4 (t), 26.7 (t), 33.9 (t), 39.6 (2 × t), 73.8 (d), 94.4 (d), 116.8 (s), 118.0 (d), 123.5 (d), 124.1 (d), 130.8 (s), 135.0 (s), 139.6 (s), 165.6 (s).

Conversion of 19 to 20. A solution of **19** (2.5 g, 8.3 mmol) and triphenylphosphine (3.5 g, 13.3 mmol) in carbon tetrachloride (5 mL) was stirred for 24 h at 15 °C. The reaction mixture was filtered through ca. 10 g of silica gel with hexane to remove an insolved material. The filtrate was concentrated in vacuo, and the residue was column chromatographed on silica gel with benzene to give γ-chloroalkenenitrile **20** (1.6 g, 60%): IR (neat) 2970, 2930, 2860, 2220, 1435, 1380, 820, 715 cm^{-1}; ^1H NMR δ 1.60, 1.62, and 1.67 (12 h, each s), 2.00 and 2.03 (8 H, br), 2.11 (3 H, d, J = 1 Hz), 2.56 (2 H, t, J = 7 Hz), 4.33 (1 H, t, J = 7 Hz), 5.08 (2 H, m), 5.40 (1 H, t, J = 1 Hz); ^{13}C NMR δ 16.0 (q), 16.4 (q), 16.8 (q), 17.7 (q), 25.7 (q), 26.4 (t), 26.7 (t), 34.9 (t), 39.7 (2 × t), 63.5 (d), 98.5 (d), 115.9 (s), 117.9 (d), 123.6 (d), 124.3 (d), 131.0 (s), 135.3 (s), 139.8 (s), 161.2 (s).

Dehydrochlorination of 20 to 21. A solution of **20** (1.2 g, 3.75 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.3 mL, 9.22 mmol) in dry benzene (5 mL) was stirred for 24 h at room temperature. The reaction mixture was washed successively with aqueous tartaric acid and brine, dried, and concentrated in vacuo. The residue was column chromatographed on silica gel (benzene/hexane = 1/1) to yield conjugated trienenitrile **21** (0.75 g, 75%): IR (neat) 3050, 2960, 2920, 2850, 2200, 1630, 1603, 1565, 1440, 1375, 1340, 1215, 950, 750 cm^{-1}; ^1H NMR δ 1.59 (6 H, s), 1.67 (3 H, s), 1.85 (3 H, d, J = 1 Hz), 2.0–2.2 (8 H, m), 2.18 (3 H, d, J = 1 Hz), 5.09 (2 H, m), 5.14 (1 H, s), 5.92 (1 H, d, J = 11 Hz), 6.17 (1 H, d, J = 15 Hz), 6.80 (1 H, dd, J = 11 and 15 Hz); ^{13}C NMR δ 16.0 (q), 16.6 (q), 17.2 (q), 17.6 (q), 25.6 (q), 26.3 (t), 26.7 (t), 39.6 (t), 40.2 (t), 95.8 (d), 117.9 (s), 123.0 (d), 124.0 (d), 124.2 (d), 129.4 (d), 131.0 (s), 132.3 (d), 135.5 (s), 145.8 (s), 156.9 (s).

Reduction of Nitrile 21 to Aldehyde 22. To a stirred solution of **21** (0.5 g, 1.76 mmol) in dry ether (5 mL) was added dropwise DIBAH (1.0 mL of a 2.2 M hexane solution, 2.2 mmol) at −5 °C. After stirring at this temperature for 1.5 h, the reaction mixture was diluted with ethyl acetate (5 mL) and poured into aqueous tartaric acid. The organic layer was extracted with ether, and the extract was washed with brine and dried. Removal of the solvent in vacuo gave a crude aldehyde. The crude product was purified by column chromatography on silica gel (ether/hexane = 1/10) to give aldehyde **22** (*E* isomer) in 64% yield: IR (neat) 2960, 2930, 2850, 1660, 1630, 1600, 1440, 1380, 1210, 1110, 950 cm^{-1}; ^1H NMR δ 1.60 (6 H, s), 1.67 (3 H, s), 1.88 (3 H, d, J = 1 Hz), 2.00, 2.14, and 2.18 (8 H, each br), 2.30 (3 H, d, J = 1 Hz), 5.08 (2 H, m), 5.93 (1 H, d, J = 8 Hz), 6.01 (1 H, d, J = 11 Hz), 6.25 (1 H, d, J = 15 Hz), 7.00 (1 H, dd, J = 11 and 15 Hz), 10.05 (1 H, d, J = 8 Hz); ^{13}C NMR δ 13.0 (q), 16.0 (q), 17.3 (q), 17.7 (q), 25.7 (q), 26.4 (t), 26.6 (t), 39.7 (t), 40.3 (t), 123.3 (d), 124.2 (d), 125.0 (d), 128.6 (d), 131.2 (s), 132.6 (d), 132.9 (d), 135.7 (s), 146.0 (s), 155.1 (s), 190.9 (d).

Oxidation of Aldehyde 22 to Methyl Ester 23. To a stirred mixture of sodium cyanide (0.2 g, 4.1 mmol) and active manganese dioxide (2.0 g, 23.0 mmol) in methanol (5 mL), a solution of aldehyde **22** (0.2 g, 0.7 mmol) in methanol (2 mL) and acetic acid (0.13 mL) was added. After stirring for 20 h at room temperature, the reaction mixture was filtered to remove an insoluble material, and the filtrate was concentrated in vacuo. The residue was extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and brine, dried, and evaporated in vacuo. The residual oil was column chromatographed on silica gel (ether/hexane = 1/10) to give methyl ester **23** (75%): IR (neat) 2930, 2860, 1715, 1605, 1430, 1235, 1150, 950 cm^{-1}; ^1H NMR δ 1.59 (6 H, s), 1.67 (3 H, s), 1.84 (3 H, s), 1.99, 2.12, and 2.15 (8 H, each br), 2.32 (3 H, d, J = 1 Hz, 3.67 (3 H, s), 5.10 (2 H, m), 5.72 (1 H, s), 5.94 (1 H, d, J = 11 Hz), 6.14 (1 H, d, J = 15 Hz), 6.83 (1 H, dd, J = 11 and 15 Hz); ^{13}C NMR δ 13.0 (q), 15.3 (q), 16.4 (q), 16.9 (q), 25.0 (q), 25.8 (t), 26.1 (t), 39.0 (t), 39.6 (t), 50.0 (q), 116.9 (d), 122.9 (d), 123.6 (d), 124.3 (d), 130.3 (d), 130.3 (s), 132.7 (d), 134.7 (s), 143.0 (s), 152.4 (s), 166.7 (s).

Hydrolysis of Methyl Ester 23 to Carboxylic Acid 24. A solution of **23** (30 mg, 0.09 mmol) and potassium hydroxide (11 mg, 0.2 mmol) in 2-propanol (1 mL) was stirred at 55–60 °C for 1 h. The reaction mixture was concentrated in vacuo and washed with hexane. The residue was acidified with diluted hydrochloric acid and extracted with ether. The extract was washed with brine, dried, and evaporated in vacuo. The residue (27 mg) was crystallized in hexane at −20 °C. Recrystallization of the product from ligroin gave **24** (mp 78 °C, 21 mg) in 75% yield.

Registry No. 1, 17665-58-6; **2**, 93040-85-8; **5a**, 81156-41-4; **5b**, 81156-42-5; **6**, 61692-34-0; **7a**, 93040-86-9; **7b**, 93040-87-0; **8**, 39007-93-7; **10**, 93040-88-1; **11**, 93040-89-2; **12**, 93040-90-5; **13**, 93040-91-6; **14** (R = H), 28624-05-7; **14** (R = THP), 93040-92-7; **15**, 93040-93-8; **16**, 93040-94-9; **17**, 23623-26-9; **18**, 1117-52-8; **19**, 93040-95-0; **20**, 93040-96-1; **21**, 93040-97-2; **22**, 93040-98-3; **23**, 93040-99-4; **24**, 81485-25-8; α-chloroacetonitrile, 107-14-2; α-(phenylthio)acetonitrile, 5219-61-4; hexanal, 66-25-1; octan-2-one, 111-13-7; 3,4-dihydro-α-pyran, 110-87-2; thiophenol, 108-98-5; hydrazine, 302-01-2; **9**, 23262-34-2.