# A Practical and Efficient Synthetic Route to Dihydropipercide and Pipercide[1]

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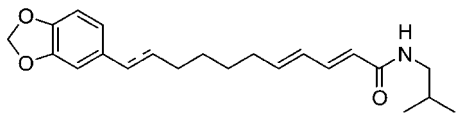
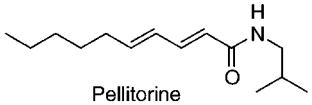
Dihydropipercide **1** and Pipercide **2** are examples of hydrophobic insecticidal isobutylamide derivatives isolated from *Piper Nigrum L.* which have received synthetic attention over the past decade. Novel structural features combining the *N*-isobutyldieneamide array, found in related natural products such as Pellitorine, with the 3,4-methylenedioxyphenyl moiety, found in insecticide synergists including Piperonyl Butoxide and Sesamex, render these as attractive targets for synthesis. Although a variety of synthetic routes to related natural products have appeared in the literature, practical methods for the preparation of the title compounds were lacking. Convenient and convergent 10−11-step protocols were developed which provided access to gram quantities of the targets. Methyl 6-oxohexanoate **4** was prepared from cyclohexanone enol acetate **3** via a tandem ozonolysis, methanolysis, hydrolysis process. Subsequent olefination and olefin isomerization steps followed by further elaboration provided the targets **1** and **2**. Noteworthy features of this methodology include the convenient synthesis of oxoester intermediate **4** and the phenythio radical-induced olefin isomerization of intermediate **6** which afforded high yields of >99.5% *E*-olefin **13**. These are both somewhat uncommon but potentially useful processes which may find further application in organic synthesis.

A rich variety of unsaturated fatty acid amides have been isolated from the Compositae, Piperaceae, and Rutaceae plant families.[2] Especially well-explored over the years have been extracts from the *Piper nigrum L* (black pepper) and *Anacyclus pyrethrum DC* plants, which have yielded several biologically interesting compounds.[2c,3,4] The novel hydrophobic insecticidal amides dihydropipercide **1**[5] and pipercide **2**[6] were isolated from the fruit of *Piper nigrum L* by Miyakado et al. They have received considerable synthetic attention over the past decade (Scheme 1). Although several diverse synthetic routes to these substances have appeared in the literature,[7] practical, scaleable protocols for the preparation of the title compounds were lacking. Pellitorine, isolated from the same plant species, is regarded as the prototypical dieneamide insecticide, and has been the subject of numerous synthetic investigations.[8] Pellitorine and related dieneamides were found to express interesting, albeit modest levels of insecticidal activity. Similar to pyrethroid insecticides, the reported mode of action of the lipophilic dieneamide class is inhibition of transport of sodium or potassium cations across the membranes of insect nerve cells.[2c,4b,9]

**Scheme 1. Naturally Occurring Hydrophobic Unsaturated (2*E*,4*E*)-Dienamide Insecticides**



**1**, Dihydropipercide, 10-11 single bond
**2**, Pipercide, 10-11 (E)-olefin



Pellitorine

Structurally, Pellitorine, Dihydropipercide, and Pipercide share a common C10−11 hydrophobic *N*-isobutyl dieneamide backbone. Interestingly, the latter members also feature the 3,4-methylenedioxyphenyl moiety, a motif found in commercial insecticide synergists. Pip-

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(1) Dedicated with genuine respect and admiration to Professor Victor A. Snieckus, Department of Chemistry, Guelph-Waterloo Centre for Graduate Work in Chemistry, Ontario, Canada, on the occasion of his 60th birthday.

(2) Crombie, L.; Fisher, D. *Tetrahedron Lett.* **1985**, *26*, (a) 2477, (b) 2481. (c) Miyakado, M.; Nakayama, I.; Ohno, N. In *Insecticides of Plant Origin*, Arnason, J. T., Philogene, B. J. R., Morand, P., Eds.; ACS Symposium Series 387; American Chemical Society: Washington, DC, 1989.

(3) Seminal contributions: Crombie, L. *J. Chem. Soc.* **1955**, (a) 1007, (b) 999. (c) Jacobson, M. *J. Am. Chem. Soc.* **1949**, *71*, 366.

(4) (a) Authoritative reviews: Jacobson, M. In *Naturally Occurring Insecticides*, Ch. 4; Jacobson, M., Crosby, D. G., Eds.; John Wiley: New York, 1971. (b) Hsu, H. C. F. In *Comprehensive Insect Physiology, Biochemistry, and Pharmacology*, Vol. 12, Ch. 9; Kerkut, G. A., Gilbert, L. I., Eds.; Pergamon Press: New York, 1985.

(5) Miyakado, M.; Nakayama, I.; Yoshioka, H. *Agric. Biol. Chem.* **1980**, *44*, 1701.

(6) Miyakado, M.; Nakayama, I.; Yoshioka, H.; Nakatani, N. *Agric. Biol. Chem.* **1979**, *43*, 1609.

(7) Dihydropipercide and Pipercide total synthesis: (a) Strunz, G. M.; Finlay, H. *Tetrahedron* **1994**, *50*, 11113. (b) Sabharwal, A.; Dogra, V.; Sharma, S.; Kaira, R.; Vig, O. P.; Kad, G. L. *J. Indian Chem. Soc.* **1990**, *67*, 318. (c) Bloch, R.; Hassan-Gonzales, D. *Tetrahedron* **1986**, *42*, 4975. (d) Crombie, L. Denman, R. *Tetrahedron Lett.* **1984**, *25*, 4267. (e) Miyakado, M.; Yoshioka, H. *Agric. Biol. Chem.* **1979**, *43*, 2413.

(8) Pellitorine synthesis: (a) Jacobson, M. *J. Am. Chem. Soc.* **1953**, *75*, 2584. Most recent approaches: (b) Abarbri, M.; Parrain, J. L.; Duchene, A. *Synth. Commun.* **1998**, *28*, 239. (c) Semple, J. E. *Org. Prep. Proc. Intl.* **1995**, *27*, 582.

(9) The reported neurological, synergism, and mode of action results were confirmed by independent studies at Shell. Personal communication from Dr. M. E. Schroeder, Shell Development BSRC.

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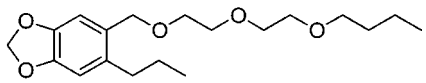
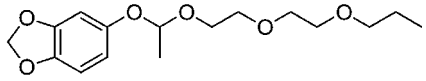
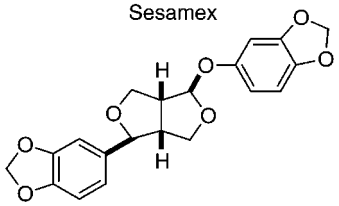
**Scheme 2. Insecticide Synergists Featuring the 3,4-Methylenedioxyphenyl Motif**



Piperonyl Butoxide

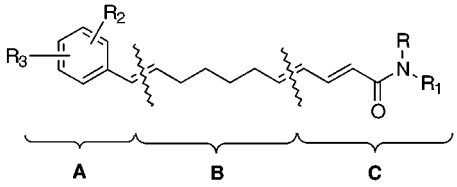


Sesamex



Sesamolin

**Scheme 3. Retrosynthetic Disconnections for Targets and New Analogs**




eronyl Butoxide, Sesamex, and Sesamolin (Scheme 2) are representative examples of synergists incorporating methylenedioxyphenyl groups and are known to inhibit cytochrome P-450 MFO enzymes.[10] On the basis of their interesting structural features and in order to develop leads for future classes of potentially safe, environmentally friendly insecticides, a synthesis program was initiated in our laboratories. Herein, we disclose efficient and practical synthetic routes to **1** and **2** which allowed for the preparation of multigram quantities of these interesting targets.

Retrosynthetic analysis of the subject molecules and our proposed analogues revealed they could be conveniently divided into three generic segments A−B−C as depicted in Scheme 3.

We were interested in constructing the AB section at the indicated olefinic site which would feature either Johnson orthoacetate Claisen rearrangement[11] or Wittig-type olefination[12] steps early in the synthesis. A priori, the orthoacetate Claisen approach was very attractive since it would provide controlled (*E*)-olefin geometry, while the Wittig route employing a semistabilized benzylic ylide would be less stereoselective. However, we ultimately found the latter approach to be more convenient, delivering a key intermediate in high overall yield which possessed the desired chain length. Mild methods for efficient isomerization were then sought which would correct the olefin geometry problem at a subsequent stage. After perusal of literature conditions,[13] we were delighted to unearth the isomerization protocol of Henrick[14] which utilizes phenylthio radicals generated from a thiophenol−oxygen mixture. After appropriate functional group modifications, we envisioned construction of the BC fragment at the indicated olefinic site via application of a Horner−Emmons−Wadsworth[15] olefination reaction. Subsequent amidation protocols would then complete the construction of the delicate (2*E*,4*E*)-dieneamide moiety.

Utilizing a modification of Bedoukian's procedure,[16] cyclohexanone was treated with a mixture of acetic anhydride and *p*-toluenesulfonic acid to produce the corresponding enol acetate **3** in 79−89% yield (Scheme 4). This reaction was readily scaled-up to 2 mol with satisfactory results. Ozonolysis of **3** in methanol at −78 °C, reductive ozonide fragmentation with dimethyl sulfide, and direct hydrolysis of the crude product in 2/1/1 THF/acetic acid/water afforded methyl 6-oxohexanoate **4** of high purity in 65−70% distilled yield. Although a number of routes to this valuable intermediate have been published,[17] the process described herein was very dependable and reproducible in our hands. We routinely processed 25−50 g batches of **3** and obtained **4** in comparable overall yields.

For the construction of the aromatic portion of Dihydropipercide and Pipercide, piperonyl alcohol was treated with dry hydrogen bromide to produce piperonyl bromide in 93% yield. The crude bromide was treated with triphenylphosphine and afforded the phosphonium salt **5**[7] in 95% yield. Although only modest stereoselectivity is realized in Wittig reactions with semistabilized benzylic ylides,[12g,k,18] we were interested in developing a practical, efficient, and high-yielding olefination procedure. Prior conversion of salt **5** to the corresponding ylide with *n*-butyllithium and subsequent coupling with **4** was optimal for the Wittig process and delivered product **6**

(10) (a) Mukerjee, S. K.; Walia, S.; Saxena, V. S.; Tomar, S. S. *Agric. Biol. Chem.* **1982**, *46*, 1277. (b) Tomar, S. S.; Dutta, S. *Indian J. Ent.* **1980**, *42*, 802. (c) Tomar, S. S.; Saxena, V. S., ref 10b, 713. (d) Su, H. C. F. *J. Econ. Entomol.* **1977**, *70*, 18. (e) Gordon, H. T.; Jao, L. T. *J. Econ. Entomol.* **1971**, *64*, 546.

(11) Johnson orthoacetate Claisen rearrangement: (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741. (b) Brenna, E.; Caraccia, N.; Fuganti, C.; Fuganti, D.; Grasselli, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3801. (c) Basavaiah, D.; Pandiaraju, S.; Krishnamacharyulu, M. *Synlett* **1996**, 747. (d) Guthrie, A. E.; Semple, J. E.; Joullie, M. M. *J. Org. Chem.* **1982**, *47*, 2369.

(12) Wittig olefination reaction: (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44. (b) Wittig, G. *Science* **1980**, *210*, 600. (c) Vedejs, E.; Peterson, M. J. *Adv. Carbanion Chem.* **1996**, *2*, 1. (d) Walker, B. J. *Organophosphorus Chem.* **1996**, *27*, 264. (e) Ager, D. J. *Org. React.* **1990**, *38*, 1. (f) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 3. (g) Maercker, A. *Org. React.* **1965**, *14*, 270.

(13) For a useful compilation of olefin isomerization protocols, see: Larock, R. C. *Comprehensive Organic Transformations*, 109; VCH Publishers: New York, 1989.

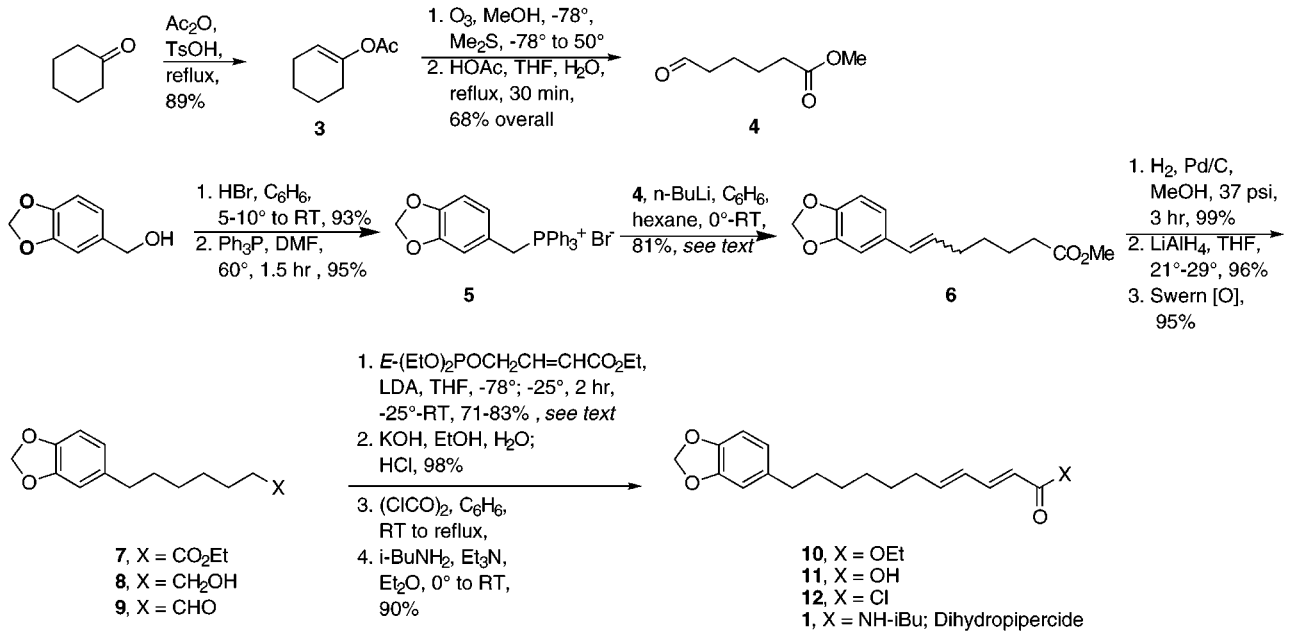
(14) Thiophenyl radical olefin isomerization: (a) Henrick, C. A.; Willy, W. E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1. (b) We wish to thank our colleague Mr. Thomas L. Brown of Shell BSRC for bringing this excellent procedure to our attention.

(15) Horner−Wadsworth−Emmons reaction: (a) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803. (b) Coleman, R. S.; Carpenter, A. J. *Tetrahedron* **1997**, *53*, 16313. (c) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recl.* **1997**, Issue 7, 1283. (d) Lawrence, N. J. *Prep. Alkenes*; Williams, J. M. J., Ed.; Oxford University Press: Oxford, U.K., 1996; p 19. (e) Kelly, S. E. *Compr. Org. Synth.* **1991**, *1*, 755. (f) Wadsworth, W. S. *Org. React.* **1977**, *25*, 73. (g) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

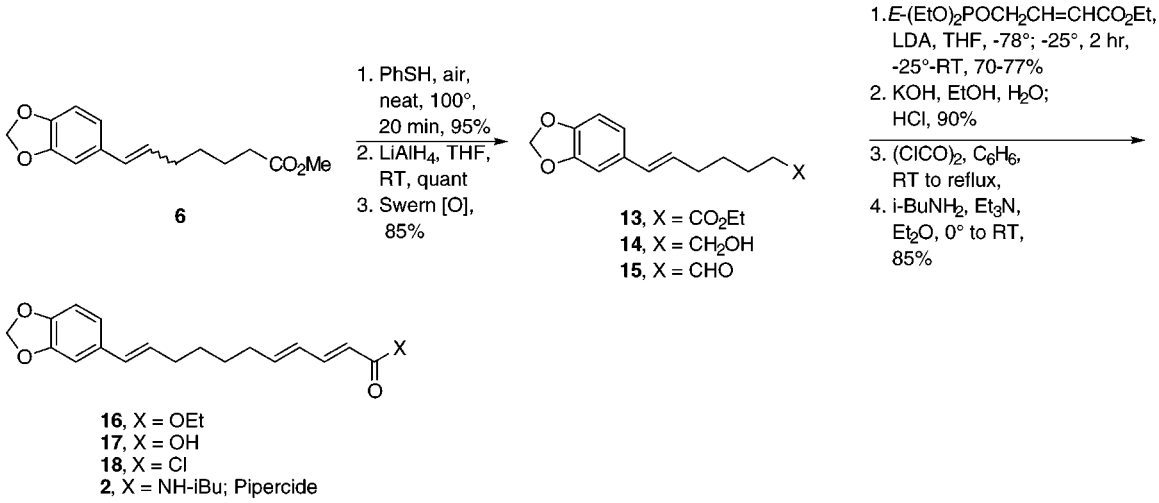
(16) Bedoukian, P. Z. *J. Am. Chem. Soc.* **1945**, *67*, 1430.

(17) Interestingly, a CAS Sci-Finder search (May, 1998) on the synthesis of Me 6-oxohexanoate **9** revealed many (ca. 77 hits) literature and patent citations. We believe the method disclosed herein is very practical and in our hands has consistently provided good yields of pure material. Following is a listing of protocols which are complimentary to ours and would appear most suitable for laboratory scale preparation of this useful intermediate: (a) Hon, Y. S.; Yan, J. L. *Tetrahedron* **1997**, *53*, 5217. (b) Floresca, R.; Kurihara, M.; Watt, D. S.; Demir, A. *J. Org. Chem.* **1993**, *58*, 2196. (d) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150. (e) Bosone, E.; Farina, P.; Guazzi, G.; Innocenti, S.; Marotta, V. *Synthesis* **1983**, 942. (f) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (g) Buchi, G.; Wuest, H. *Helv. Chim. Acta* **1979**, *62*, 2661.

**Scheme 4. Synthesis of Dihydropipercide 1**




**Scheme 5. Synthesis of Pipercide 2**




in 81% yield. The latter reaction conditions proved reliable and allowed for the facile synthesis of 30−40 g of pure product. GC analysis revealed that **6** was a 7/3 *E*/*Z*-olefinic mixture, a result which was consistent with related Wittig reaction products obtained from semistabilized benzylic ylides.[12,18]

Hydrogenation of **6** with 10% palladium on carbon in methanol afforded saturated ester **7** in quantitative yield. Reduction with lithium aluminum hydride provided the corresponding alcohol **8** in 96% yield, which in turn was oxidized with the Swern reagent[19] to the aldehyde **9** in 95% yield.

For assembly of the BC portion of our targets, Horner−Emmons−Wadsworth olefination conditions[15] were examined including temperatures ranging from −78 to 0 °C. We determined experimentally that a temperature range of −30 to −25 °C was most desirable for the condensation and betaine elimination steps of the reaction, providing the geometrically pure (2*E*,4*E*)-dienoate **10** in 71−83% yield.

Hydrolysis of ester **10** with potassium hydroxide afforded the carboxylic acid **11** in nearly quantitative yield. Conversion of **11** to the corresponding acid chloride **12** by treatment with oxalyl chloride, followed by reaction with isobutylamine produced the target Dihydropipercide **1** in 90% yield. The physical and spectroscopic properties of material produced in this fashion were in good agreement with the literature values.[5,7b,d,20]

The synthesis of Pipercide **2** commenced with isomerization of olefin mixture **6** to the pure (*E*)-olefin **13** as depicted in Scheme 5. Although isomerization under classical conditions with iodine[13] led to further enrichment of the desired (*E*)-isomer, we found that application of the thermal thiophenol−air system[14] was most useful in terms of reaction rate, efficiency, and yield of product **13**. Presumably, a phenylthio radical is generated in situ under these conditions which initially adds to the distal *β*-olefinic carbon to generate a new secondary benzylic radical. Under such thermodynamic conditions, this intermediate would then rotate to the lowest energy form

(18) House, H. O.; Jones, V. K.; Frank, J. *J. Org. Chem.* **1964**, *29*, 3327.

(19) (a) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297. (c) Tidwell, T. T. *Synthesis* **1990**, 857.

and collapse to deliver the (*E*)-isomer. In practice, treatment of the olefin mixture **6** with thiophenol under neat conditions at 95−100 °C with occasional injection of air aliquots gave pure (*E*)-olefin ester **13** in 95% isolated yield. $^1$H NMR and GC analysis revealed **13** to be essentially (≥99.5%) isomerically pure. A temperature range of 90−100 °C appeared optimal for our substrate. The isomerization reaction will also proceed at lower temperatures. We realized comparable yields of **13** by isomerization of **6** at 80−95 °C, although the reaction rate drops proportionately at these lower temperatures.

Reduction of ester **13** with lithium aluminum hydride produced the alcohol **14** in quantitative yield, which was oxidized under Swern conditions[19] to the corresponding aldehyde **15** in 85% yield. In analogy to the chemistry described above, aldehyde **15** was converted to the sensitive (2*E*,4*E*,10*E*)-trienoate **16** in 70−77% yield after silica flash chromatography. The intermediates **10** and **16** appeared to be sensitive to silica gel chromatography, so in order to obtain these products in the specified yields, it was very important to minimize the residency time of these compounds on the chromatography column.

Hydrolysis of ester **16** with potassium hydroxide afforded the carboxylic acid **17** in 90% yield. Conversion to the corresponding acid chloride **18** by treatment with oxalyl chloride followed by reaction with isobutylamine produced the second target Pipercide **2** in 85% yield. The physical and spectroscopic properties of material produced in this fashion were in good agreement with the literature values.[7,20]

In conclusion, we have developed an efficient and practical 10−11-step protocol to Dihydropipercide **1** and Pipercide **2**. The methodology developed herein has allowed for the preparation of gram quantities of these insecticidal natural products. The readily scaleable and practical synthesis of the versatile intermediate methyl 6-oxohexanoate **4** from cyclohexanone enol acetate **3** via a tandem ozonolysis, reductive decomposition, hydrolysis protocol is noteworthy. Also of interest is the thermal thiophenol−air free radical-induced olefin isomerization process which smoothly and rapidly converted intermediate **6** to the all-(*E*)-olefinic ester **13** in excellent yields. These are somewhat uncommon yet potentially useful processes which may find further application in organic synthesis.

## Experimental Section

All melting points are uncorrected and are reported in degrees Centigrade (°C). All reactions were run under a positive pressure of nitrogen. All solvents were anhydrous and were used as purchased from Aldrich. Thin-layer chromatography was performed using Merck silica gel 60 F-254 plates. Visualization was effected with UV and/or 7% phosphomolybdic acid solution in ethanol. Elution solvents were as stated in the following text or one of the following solvent systems: SS-1, tetrahydrofuran/hexane 2/48; SS-2, tetrahydrofuran/ethyl acetate/hexane 2/8/40; SS-3, tetrahydrofuran/ethyl acetate/hexane 2/15/33; SS-9, tetrahydrofuran/ethyl acetate/hexane 12.5/12.5/25. Gas−liquid chromatography (GLC) was performed on a Hewlett-Packard 5710A gas chromatograph equipped with a 3390A integrator, a thermal conductivity detector, and 5% 0V-101 ($^1/_8$ in. × 4 ft) columns. Analyses were performed under the following conditions: detector temperature 300 °C; injection port 250 °C; oven starting temperature 80 °C; rate of increase in oven temperature 32 °C/min.

**1-Acetoxycyclohexene 3.** The following is a modified literature procedure.[16] A mixture of freshly distilled cyclohexanone (196.3 g, 2.00 mol, 207 mL), acetic anhydride (408.4 g, 4.00 mol, 377 mL), and *p*-toluenesulfonic acid monohydrate (2 g) was stirred and refluxed while distilling off acetic acid through a 12 in. Vigreux column. After 4 h, the pot temperature rose from 138 to 156 °C. The mixture was cooled, dissolved in 1500 mL of ether, and extracted with 4 × 200 mL of saturated $NaHCO_3$, 2 × 200 mL of $H_2O$, and 1 × 200 mL of brine. After drying ($MgS0_4$), removal of solvent gave a dark liquid that was distilled in vacuo through a 3 ft Vigreux column. After a small forerun of liquid with bp 35 °C/0.75 mm, the product **3** was collected at 27 °C/0.60 mm, (lit.[16] bp 74−76 °C/17 mm), yield = 249.5 g, 89% of theory as a colorless liquid: TLC (ethyl acetate/hexane 1/5) $R_f = 0.5$; IR (NaCl, 10% in $CH_2Cl_2$) 2930 (vs), 2845 (m), 1740 (vs), 1680 (m); NMR (60 MHz, $CDCl_3$) $\delta$ 1.4−2.4 (m, 8H), 2.1 (s, 3H), 5.33 (m, 1H). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.82; H, 8.70.

**Methyl 6-Oxohexanoate 4.** A solution of **3** (28.0 g, 0.20 mol) in 250 mL of dry methanol was ozonized (Welsbach style T-709, 7−9 psi so as to produce ca. 2% ozone) at −78 °C for about 3 h until a faint blue color persisted. Dry air was blown through the solution to remove the excess ozone, and then dimethyl sulfide (30 mL) was added. The dry ice bath was removed, and upon warming, the reaction mixture was smoothly exothermed to 50 °C. It was then stirred at ambient temperature overnight (predominant formation of methyl acetal intermediate). The solvent was evaporated, and the residue was diluted with 200 mL of THF, 200 mL of acetic acid, and 100 mL of water. The solution was refluxed for 30 min, cooled, and poured into ether. The organic phase was extracted with a 20% NaOH solution, a 10% NaOH solution, and brine and dried ($MgSO_4$). Removal of solvent gave 28.7 g of oil that was distilled in vacuo through a short path still to afford 19.58 g (68% yield) of **4** as a colorless liquid, bp 97−98 °C/8 mm (lit.[17d] bp 83−86 °C/1.5 mm): TLC (hexanes/ethyl acetate 3/1) $R_f = 0.25$; IR (NaCl, 10% in $CH_2Cl_2$) 1720 (vs); NMR (60 MHz, $CDCl_3$) $\delta$ 1.67 (m, 4H), 2.37 (m, 4H), 3.62 (s, 3H), 9.67 (t, 1H); MS No $M^+$, fragment ions support structure. Intermediate **4** was stored in the freezer at −25 °C under a nitrogen atmosphere and was stable for several months under these conditions.

**3,4-Methylenedioxybenzyltriphenylphosphonium Bromide 5.** A solution of piperonyl alcohol (15.22 g, 0.10 mol) in 75 mL of benzene was treated with a stream of hydrogen bromide gas for 30 min at 5−10 °C, and the solution was stirred at ambient temperature overnight. The mixture was poured into ice−water and extracted with $CH_2Cl_2$. The organic phase was extracted with saturated $NaHCO_3$ solution, $H_2O$, and brine and dried ($MgSO_4$). Removal of solvent gave 20.0 g (93.0% yield) of piperonyl bromide as a solidifying oil. A mixture of piperonyl bromide (18.0 g, 0.0837 mol) and triphenylphosphine (21.95 g, 0.0837 mol) in 100 mL of dry DMF was heated to 60 °C under nitrogen for 1.5 h, cooled, and refrigerated for 2 days. The first crop of product was collected by suction filtration, washed with toluene, air-dried, and vacuum-dried at 100 °C overnight to afford 28.53 g of **5** as tiny, colorless needles, mp 236.5−238.5 °C. Dilution of the filtrate with toluene and processing as described above gave a second crop of 9.21 g, mp 233−236 °C. The combined yield of **5** was 37.74 g, 94.5% of theory: IR (KBr) 1580 (m), 1480 (s), 1435 (s), 1245 (vs), 1100 (s), 1025 (s); NMR (60 MHz, $CDCl_3$) $\delta$ 5.27 (d, 2H), 5.83 (s, 2H), 6.53 (brs, 3H), 7.4−8.0 (m, 15H). Anal. Calcd for $C_{26}H_{22}BrO_2P$: C, 65.42; H, 4.65. Found: C, 65.80; H, 4.75.

**Methyl 7-(3,4-Methylenedioxyphenyl)-6-(*E*,*Z*)-heptenoate 6.** To a suspension of vacuum oven-dried **5** (83.70 g, 0.175 mol) in 300 mL of dry benzene at ambient temperature under nitrogen was added *n*-butyllithium (125.0 mL of 1.4 M in hexane, 0.175 mol) dropwise via syringe so as to maintain 16−19 °C (water bath cooling). The deep red solution was stirred at ambient temperature for 30 min, and a solution of **4** (25.2 g, 0.175 mol) in 35 mL of dry benzene was added with external cooling over 45 min so as to maintain 15 ± 2 °C. The mixture was stirred at ambient temperature for 2 h and diluted with 1 L of hexane. The organic phase was extracted

(20) Miyakado, M.; Nakayama, I.; Inoue, A.; Hatakoshi, M.; Ohno, N. J. *Pesticide Sci. Jpn.* **1983**, *10*, (a) 11, (b) 25.

with water and brine and dried ($MgSO_4$). Removal of solvent gave 42 g of amber oil that was purified by flash column chromatography on silica gel using ether as eluent and afforded 37.02 g of **6** (80.5% yield) as a light amber oil; TLC (SS-3) $R_f = 0.55$; GLC: $t_R$ 6.07 and 6.49 min, ratio ca. 3:7. A portion distilled through a short path still had bp 169 °C/0.04 mm; IR (NaCl, 10% in $CH_2Cl_2$) 1735 (vs), 1600 (m); NMR (60 MHz, $CDCl_3$) $\delta$ 1.55 (m, 4H), 2.25 (m, 4H), 3.63 (s, 3H), 5.87 (s, 2H), 5.5−7.3 (m, 5H); MS *m/e* 262 ($M^+$). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.62; H, 7.20.

**Methyl 7-(3,4-Methylenedioxyphenyl)heptanoate 7.** A mixture of **6** (6.55 g, 0.025 mol) and palladium on charcoal (0.5 g, 10%) in 75 mL of methanol was hydrogenated on a Parr Shaker for 3 h at 37 psi. After suction filtration through Celite, the filtrate was concentrated in vacuo to give 6.36 g (96% yield) of **7** as a light amber oil; GLC $t_R$ 6.32 min; IR (NaCl, 10% $CH_2Cl_2$) 1720 (vs); NMR (60 MHz, $CDCl_3$) $\delta$ 1.47 (m, 8H), 2.40 (m, 4H), 3.62 (s, 3H), 5.85 (s, 2H), 6.63 (m, 3H); MS 264 *m/e* ($M^+$). Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.43; H, 7.83.

**7-(3,4-Methylenedioxyphenyl)heptanol 8.** To a magnetically stirred solution of **7** (5.72 g, 0.022 mol) in 100 mL of anhydrous THF was added portionwise at 21 °C lithium aluminum hydride (0.84 g, 0.022 mol), raising the temperature to 29 °C and providing vigorous gas evolution. After stirring 1 h and diluting with 300 mL of ether, about 5 mL of water was added dropwise until no further reaction was apparent. Anhydrous $MgSO_4$ (15 g) was added, the mixture was stirred for 3 h and filtered, and the filtrate was concentrated in vacuo to give 5.65 g of crude product. Recrystallization from ether/hexane afforded 5.19 g (96% yield) of **8** as a colorless solid, mp 20.0−22.0 °C: TLC (SS-2) $R_f = 0.13$; IR (KBr) 3300 (s, br); NMR (60 MHz, $CDCl_3$) $\delta$ 1.35 (m, 10H), 1.97 (s, 1H), 2.47 (m, 2H), 3.53 (m, 2H), 5.78 (s, 2H), 6.53 (m, 3H); MS 236 *m/e* ($M^+$). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.51; H, 8.80.

**7-(3,4-Methylenedioxyphenyl)heptanal 9.** To a magnetically stirred solution of oxalyl chloride (2.79 g, 0.022 mol) in 80 mL of dry $CH_2Cl_2$ at −65 °C under nitrogen was added dropwise anhydrous DMSO (3.78 g, 0.048 mol). After stirring at this temperature for 30 min, a solution of **8** (4.76 g, 0.020 mol) in 20 mL of anhydrous $CH_2Cl_2$ was added dropwise. Four hours later, the reaction was quenched with $Et_3N$ (10.3 g, 0.10 mol) and warmed to −10 °C overnight. The mixture was stirred for 2 h at room temperature, diluted with $CH_2Cl_2$, and extracted with water. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford 5.17 g of yellow oil. Flash chromatography on silica using a gradient of SS-1 to SS-2 afforded 4.46 g (95% yield) of **9** as a light amber oil: TLC (SS-2) $R_f = 0.39$; GLC $t_R$ 5.82 min; IR (NaCl, 10% $CH_2Cl_2$) 1723 (vs); NMR (60 MHz, $CDCl_3$) $\delta$ 1.37 (m, 8H), 2.41 (m, 4H), 5.80 (s, 2H), 6.57 (m, 3H), 9.73 (t, 1H, $J = 1.5$ Hz); MS 234 *m/e* ($M^+$). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.57; H, 7.65.

**Ethyl 11-(3,4-Methylenedioxyphenyl)-(2*E*,4*E*)-undecadienoate 10.** To a magnetically stirred solution of anhydrous diisopropylamine (7.86 g, 0.078 mol, distilled from $CaH_2$) in 10 mL of anhydrous THF was added dropwise under $N_2$ at −74 °C *n*-butyllithium (5.0 g, 0.078 mol, 52.0 mL of 1.5 M in hexane). After stirring 30 min, triethyl-4-phosphonocrotonate (18.5 g, 0.074 mol) in 20 mL of anhydrous THF was added dropwise at −23 °C over 45 min. After 5 min, aldehyde **9** (8.64 g, 0.037 mol) in 10 mL of anhydrous THF was added dropwise at −23 °C. After stirring for 2 h, the mixture was warmed to ambient temperature, poured into 300 mL of a saturated aqueous $NaHCO_3$ solution, and extracted with ether (4×). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to provide 23.42 g of dark amber oil. Flash chromatography with 5% $Et_2O$/hexane afforded 10.15 g (83% yield) of **10** as an amber oil: TLC (SS-2) $R_f = 0.42$; IR (NaCl, 10% in $CH_2Cl_2$) 1695 (vs), 1625 (s), 1600 (m); NMR (360 MHz, $CDCl_3$) $\delta$ 1.27 (t, 3H, $J = 7.1$ Hz), 1.29 (m, 4H), 1.43 (m, 2H), 1.57 (m, 2H), 2.15 (dt or q, 2H, $J = 6.5$ Hz), 2.51 (t, 2H, $J = 7.6$ Hz), 4.19 (q, 2H, $J = 7.1$ Hz), 5.77 (d, 1H, $J = 15.3$ Hz), 5.90 (s, 2H), 6.05−6.19 (m, 2H), 6.60 (d, 1H, $J = 7.9$ Hz), 6.65 (s, 1H), 6.70 (dd, 1H, $J = 7.8$, 1.5 Hz), 7.24 (dd, 1H, $J = 15.5$, 9.5 Hz); MS 330 *m/e* ($M^+$). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.95; H, 8.13.

**11-(3,4-Methylenedioxyphenyl)-(2*E*,4*E*)-undecadienoic Acid 11.** To a magnetically stirred solution of **10** (3.30 g, 0.010 mol) in 100 mL of ethanol was added a solution of KOH (2.24 g, 0.04 mol) in 100 mL of ethanol/water 3:1. The reaction was stirred overnight at ambient temperature, diluted with ethanol, and evaporated to dryness in vacuo. The residue was dissolved in water, extracted with ether, acidified to pH 2 with concentrated HCl, and re-extracted with ether. The combined extracts were washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo to afford 5.90 g of crude product as a colorless solid. This material was recrystallized from $Et_2O$/hexane to provide 2.96 g (98% yield) of **11** as a colorless solid, mp 94.5−96.0 °C (lit.[5] mp 103−104 °C): IR (NaCl, 2% KBr) 3200−2800 (m, br), 1684 (vs), 1630 (s), 1613 (s); NMR (60 MHz, $CDCl_3$) $\delta$ 1.4 (m, 8H), 2.15 (m, 2H), 2.50 (m, 2H), 5.73 (d, 1H, $J = 15$ Hz), 5.87 (s, 2H), 6.13 (m, 2H), 6.63 (m, 3H), 6.9−8.0 (m, 2H); MS 302 *m/e* ($M^+$) Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.60; H, 7.25.

**(2*E*,4*E*)-*N*-Isobutyl-11-(3,4-methylenedioxyphenyl)-2,4-undecadienamide, Dihydropipercide 1.** To a magnetically stirred solution of **11** (3.62 g, 0.012 mol) in 100 mL of benzene at ambient temperature was added dropwise oxalyl chloride (3.81 g, 0.030 mol) with moisture exclusion ($CaCl_2$ drying tube). After stirring for 1 h at ambient temperature and 2 h at reflux, the solution was cooled. Excess oxalyl chloride and benzene were removed in vacuo and the crude acid chloride **12** was redissolved twice in fresh portions of benzene and reevaporated. The resultant material was held under high vacuum until a constant theoretical yield of 3.85 g of product **12** was obtained. The residue was dissolved in 25 mL of anhydrous diethyl ether and added dropwise to a solution of isobutylamine (1.32 g; 0.018 mol) and triethylamine (2.43 g; 0.024 mol) in 50 mL of ether at 0 °C. After warming to room temperature overnight, the reaction was diluted with ether and washed with portions of water, 3 N HCl, a saturated $NaHCO_3$ solution, water, and brine. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford 4.9 g of colorless solid. Recrystallization from ether/ethyl acetate/hexane 4/1/5 provided 3.86 g (90% yield) of Dihydropipercide **1** as colorless needles, mp 89.5−91.5 °C (lit.[7d] mp 94−95 °C): TLC (SS-3) $R_f = 0.25$; IR (NaCl, 10% $CH_2Cl_2$) 3400 (m), 3270 (m), 1650 (s), 1615 (s), 1600 (s); NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (d, 6H, $J = 6.7$ Hz), 1.32 (m, 4H), 1.41 (m, 2H), 1.56 (m, 2H), 1.80 (septet, 1H, $J = 6.7$ Hz), 2.13 (dt or q, 2H, $J = 6.6$ Hz), 2.51 (t, 2H, $J = 7.6$ Hz), 3.16 (t, 2H, $J = 6.7$ Hz), 5.52 (brs, 1H), 5.75 (d, 1H, $J = 15.1$ Hz), 5.90 (s, 2H), 6.04−6.11 (m, 2H), 6.67 (m, 3H), 7.18 (dd, 1H, $J = 15.1$, 9.8 Hz); MS 357 *m/e* ($M^+$). Anal. Calcd for $C_{22}H_{31}NO_3$: C, 73.92; H, 8.74; N, 3.92. Found: C, 74.20; H, 8.84; N, 3.83.

**Methyl 7-(3,4-Methylenedioxyphenyl)-6-(*E*)-heptenoate 13.** To a magnetically stirred solution of **6** (44.59 g, 0.17 mol) and thiophenol (4.46 g, 10 wt %) under $N_2$ at 95−100 °C was injected a 10 mL aliquot of air by syringe. Heating was continued for 20 min, during which time an additional 10 mL aliquot of air was injected by syringe. Flash silica gel chromatography of the reaction mixture with 1% THF in hexane as eluent afforded 42.36 g (95.0% yield) of **13** as a colorless liquid: TLC (hexane/ether 9/1) $R_f = 0.18$; GLC $t_R$ 6.50 min; IR (NaCl, 10% in $CH_2Cl_2$) 1735 (vs); NMR (360 MHz, $CDCl_3$) $\delta$ 1.49 (m, 2H), 1.66 (m, 2H), 2.19 (m, 2H), 2.33 (t, 2H, $J = 7.5$ Hz), 3.67 (s, 3H), 5.92 (s, 2H), 6.02 (dt, 1H, $J = 15.7$, 7.0 Hz), 6.29 (d, 1H, $J = 15.7$ Hz), 6.73 (m, 2H), 6.88 (s, 1H); MS 262 *m/e* ($M^+$). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.86; H, 7.10.

**7-(3,4-Methylenedioxyphenyl)-6-(*E*)-heptenol 14.** To a magnetically stirred solution of **13** (5.79 g, 0.022 mol) in 100 mL of anhydrous THF under $N_2$ at room temperature was added portionwise lithium aluminum hydride (0.84 g, 0.022 mol). After 3 h, 4 mL of water was added dropwise followed by anhydrous $MgSO_4$ (20 g). After stirring for 3 h, the solids were removed by suction filtration. The filtrate was evaporated in vacuo to afford 5.87 g of crude alcohol product as an

amber oil. Crystallization from ether/hexane provided 5.11 g (99% yield) of **14** as colorless needles, mp 40.0−41.5 °C: GLC $t_R$ 6.50 min; IR (NaCl, 10% in $CH_2Cl_2$) 3580 (m), 3450 (w), 2900 (8), 1220 (m); NMR (60 MHz, $CDCl_3$) $\delta$ 1.58 (m, 6H), 2.05 (s, 1H, $D_2O$ exchangeable), 2.20 (m, 2H), 3.73 (m, 2H), 5.98 (s, 2H), 6.00−6.37 (m, 2H), 6.80−7.03 (m, 3H); MS 234 *m/e* ($M^+$). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.46; H, 7.92.

**7-(3,4-Methylenedioxyphenyl)-6-(*E*)-heptenal 15.** Anhydrous DMSO (1.89 g, 0.024 mol) was added dropwise to a magnetically stirred solution of oxalyl chloride (1.40 g, 0.011 mol) in 40 mL of anhydrous $CH_2Cl_2$ under $N_2$ at −60 °C. After stirring at −65 °C for 30 min, a solution of **14** (2.34 g, 0.010 mol) in 10 mL of anhydrous $CH_2Cl_2$ was added dropwise. The reaction was stirred for 1 h, and then $Et_3N$ (5.14 g, 0.051 mol) was added dropwise. The mixture was stirred at −60 °C for 30 min, warmed to room temperature, and stirred for 1 h. The mixture was diluted with $CH_2Cl_2$, washed with water and brine, dried ($MgSO_4$), and evaporated in vacuo to afford the crude product which was purified by flash chromatography on silica gel, eluting with 10% EtOAc in hexane and provided 1.97 g (85% yield) of **15** as an amber oil: TLC (SS-2) $R_f$ = 0.31; GLC $t_R$ 6.44 min; IR (NaCl, 10% in $CH_2Cl_2$) 1723 (s); NMR (60 MHz, $CDCl_3$) $\delta$ 1.57 (m, 4H), 2.30 (m, 4H), 5.83 (s, 2H), 5.93 (m, 2H), 6.60−6.90 (m, 3H), 9.67 (t, 1H, $J$ = 2 Hz); MS 232 *m/e* ($M^+$). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.50; H, 6.99.

**Ethyl 11-(3,4-Methylenedioxyphenyl)-(2*E*,4*E*,l0*E*)-undecatrienoate 16.** To a magnetically stirred solution of diisopropylamine (2.12 g, 0.021 mol, distilled from $CaH_2$) in 3 mL of anhydrous THF under $N_2$ at −78 °C was added *n*-butyllithium (1.32 g, 0.021 mol; 15.0 mL of 1.4 M in hexane) dropwise. After stirring for 30 min, a solution of triethyl-4-phosphonocrotonate (5.00 g, 0.020 mol) in 5 mL of anhydrous THF was added dropwise over a period of 20 min. After stirring for 10 min further, a solution of aldehyde **15** (2.32 g, 0.010 mol) in 3 mL of anhydrous THF was added dropwise. The mixture was warmed to −20 °C so as to maintain a homogeneous solution, and after 4 h the mixture was warmed to ambient temperature, poured into 100 mL of saturated aqueous $NaHCO_3$ solution, and extracted with three portions of ether. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to afford the crude product. Purification by flash chromatography on silica gel using a gradient system of 5% $Et_2O$/hexane to 35% $Et_2O$/hexane provided 2.53 g (77% yield) of trienoate **16** as an amber oil: TLC (SS-2) $R_f$ = 0.37; IR 1711 (vs), 1641 (m), 1618 (w); NMR (360 MHz, $CDCl_3$) $\delta$ 1.28 (t, 3H, $J$ = 7.1 Hz), 1.46 (m, 4H), 2.17 (m, 4H), 4.19 (q, 2H, $J$ = 7.1 Hz), 5.78 (d, 1H, $J$ = 15.4 Hz), 5.92 (s, 2H), 6.02 (dt, 1H, $J$ = 15.6, 7.0 Hz), 6.06−6.16 (m, 2H), 6.28 (d, 1H, $J$ = 15.6 Hz), 6.73 (m, 2H), 6.88 (s, 1H), 7.24 (dd, 1H, $J$ = 15.2, 10.0 Hz); MS 328 *m/e* ($M^+$). Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.95; H, 7.32.

**11-(3,4-Methylenedioxyphenyl)-(2*E*,4*E*,10*E*)-undecatrienoic Acid 17.** To a magnetically stirred solution of potassium hydroxide (4.26 g, 0.076 mol) in 50 mL of water and 100 mL of ethanol was added a solution of **16** (6.31 g, 0.019 mole) in 35 mL of ethanol. The mixture was stirred overnight at ambient temperature and evaporated in vacuo to dryness. The residue was diluted with water and was extracted with three portions of ether, which was discarded. The aqueous phase was then acidified to pH 1 with concentrated HCl and re-extracted with five portions of ether. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to provide the crude product which was recrystallized from ether/hexane and then $CHCl_3$ to afford 5.14 g (90% yield) of acid **17** as colorless needles, mp 128.0−130.0 °C (lit[7e] mp 136−137 °C, from benzene): TLC (SS-9) $R_f$ = 0.37; IR (KBr, 2%) 3400 (m, br), 1670 (s), 1655 (s), 1620 (m), 1595 (m); NMR (360 MHz, $CDCl_3$) $\delta$ 1.49 (m, 4H), 2.18 (m, 4H), 5.77 (d, 1H, $J$ = 15.4 Hz), 5.91 (s, 2H), 6.04 (dt, 1H, $J$ = 15.5, 7.1 Hz), 6.08−6.19 (m, 2H), 6.30 (d, 1H, $J$ = 15.5 Hz), 6.75 (m, 2H), 6.88 (s, 1H), 7.26 (dd, 1H, $J$ = 15.4, 10.0 Hz); MS 300 *m/e* ($M^+$). Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.83; H, 6.52.

**(2*E*,4*E*,l0*E*)-*N*-Isobutyl-11-(3,4-methylenedioxyphenyl)-2,4,10-undecatrienamide, Pipercide 2.** To a magnetically stirred suspension of acid **17** (1.50 g, 5.00 mmol) in 50 mL of benzene at room temperature was added dropwise by syringe oxalyl chloride (1.05 g, 8.30 mmol) with moisture exclusion ($CaCl_2$ drying tube). The resultant bright yellow solution was stirred for 30 min and then heated to reflux for 1 h. After cooling, excess oxalyl chloride and benzene were removed in vacuo, and the crude acid chloride **18** was redissolved twice in fresh portions of benzene and re-evaporated. The residue was dissolved in 20 mL of anhydrous ether and added rapidly dropwise to a solution of isobutylamine (0.731 g, 10.0 mmol) and triethylamine (1.01 g, 10.0 mmol) in 50 mL of anhydrous ether at −5 to 0 °C. After 1 h, the solution was warmed to ambient temperature and stirred overnight. The mixture was diluted with $CH_2Cl_2$ and washed with water, 3 N HCl, saturated $NaHCO_3$ solution, water, and brine. Drying ($MgSO_4$) and concentration in vacuo afforded the crude product which was recrystallized from a mixture of $CH_2Cl_2$, $Et_2O$, and hexane to afforded 1.31 g of Pipercide **2** as colorless needles, mp 121.5−123.0 °C, and a second crop of 0.20 g, mp 117.0−118.5 °C (lit.[7a] mp 112−118 °C; lit.[7d] mp 120 °C after prior softening, from cyclohexane; lit.[7e] mp 114−115 °C); combined yield, 1.51 g (85%): TLC (SS-3) $R_f$ = 0.21; IR (KBr, 2% in KBr) 3304 (vs br), 1657 (s), 1630 (s), 1615 (s), 1256 (vs), 999 (s), 924 (m); NMR (360 MHz, $CDCl_3$) $\delta$ 0.92 (d, 6H, $J$ = 6.6 Hz), 1.47 (m, 4H), 1.80 (septet, 1H, $J$ = 6.6 Hz), 2.17 (m, 4H), 3.16 (t, 2H, $J$ = 6.6 Hz), 5.49 (brs, 1H), 5.75 (d, 1H, $J$ = 15.1 Hz), 5.92 (s, 2H), 6.02 (dt, 1H, $J$ = 15.6, 7.2 Hz), 6.03−6.17 (m, 2H), 6.28 (d, 1H, $J$ = 15.6 Hz), 6.74 (m, 2H), 6.88 (s, 1H), 7.18 (dd, 1H, $J$ = 15.1, 10.0 Hz); MS 355 *m/e* ($M^+$). Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22, N, 3.94. Found: C, 74.23; H, 8.40; N, 3.84.

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