Experimental Section

The IR spectra were recorded on a Perkin-Elmer 710B spectrometer. ^{1}H NMR spectra were recorded at 500 or 60 MHz on a Bruker AM-500 or a Varian T-60 spectrometer, respectively, using tetramethylsilane as an internal standard. GLC analyses were carried out on a Varian 3700 gas chromatograph on a 30-m JE&W DB-5 (0.25-μm phase thickness) fused capillary column with the column temperature at 200 °C for 1 min, followed by a rise of 12 °C/min to 310 °C, at which the temperature was held for 30 min. The mass spectra were taken on a Finnigan 4000 mass spectrometer. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from sodium benzophenone ketyl immediately prior to use.

3,7,11,15-Tetramethylhexadecane-1,2-diol (6). Commercially available phytol (**5**; Aldrich) was purified by column chromatography on silica gel to give the pure mixture of *E* and *Z* isomers that were used in the hydroboration step.[12]

To a solution of disiamylborane (15 mL, 10.5 mmol) in tetrahydrofuran was added phytol (**5**; 3.0 g, 10.1 mmol). After the evolution of hydrogen stopped, a solution of borane (10.5 mL, 10.5 mmol) in tetrahydrofuran was added. After the mixture was stirred at 0 °C for 1.5 h, the excess hydride was decomposed by the cautious addition of water. The oxidation was carried out by adding 4 mL of 3 N sodium hydroxide, followed by dropwise addition of 1.5 mL of 30% hydrogen peroxide. The solution was then saturated with potassium carbonate, and the layers separated. The organic layer was dried over magnesium sulfate and evaporated. Column chromatography on silica gel using 1:1 ethyl acetate–*n*-hexane as eluent gave 510 mg (18%) of the primary alcohol **7** followed by 2.13 g (70%) of **6**.

6: IR (neat film) 3300, 2930, 2900, 2840, 1452, 1368, 1352, 991 cm^{-1}; 500-MHz ^{1}H NMR ($CDCl_3$) δ 3.70–3.64 (m, 1 H, CHO), 3.58–3.48 (m, 2 H, CH_2O), 3.12 (br s, 2 H, OH), 1.59–1.06 (m, 22 H, CH and CH_2), 0.92–0.84 (overlapping d, 15 H, CH_3); MS, *m/e* 314 (M^+), 296 ($M^+ - H_2O$).

7: IR (neat film) 3300, 2930, 2900, 2850; 500-MHz ^{1}H NMR ($CDCl_3$) δ 3.71–3.63 (m, 2 H, CH_2O), 1.61–1.06 (m, 23 H, CH, CH_2, and OH), 0.894 (d, 3 H, J = 6.5 Hz, CH_3), 0.867 (d, 6 H, J = 6.6 Hz, 2 CH_3), 0.845 (d, 6 H, J = 6.6 Hz, 2 CH_3); MS, *m/e* 298 (M^+), 280 ($M^+ - H_2O$).

2,6,10,14-Tetramethylpentadecanal (8). To a solution of the diol **6** (510 mg, 1.62 mmol) in 20 mL of methylene chloride was added an excess of yellow mercuric oxide–iodine reagent (prepared by the method of Goosen[10]) and the mixture stirred under a nitrogen atmosphere in the dark overnight. The mixture was extracted with ether, washed with 10% aqueous sodium thiosulfate and water, dried over magnesium sulfate, and concentrated to give 390 mg (85%) of **8** as a colorless oil. This crude aldehyde was unstable to silica gel chromatography and thus was used immediately for the next step.

8: IR (neat film) 2935, 2900, 2840, 2700, 1720, 1460, 1370 cm^{-1}; 60-MHz ^{1}H NMR ($CDCl_3$) δ 9.53 (d, 1 H, J = 2 Hz, CHO), 2.2–2.0 (m, 1 H, CHCO), 1.6–0.75 (m, 36 H).

(*E*)-2,6,10,14,17,21,25,29-Octamethyltriacont-15-ene (9). Lithium wire (134 mg, 19.3 mmol) and titanium trichloride (850 mg, 5.50 mmol) was slurried in 15 mL of dry dimethoxyethane (DME) under an argon atmosphere, and the mixture was refluxed for 1 h. After cooling to 25 °C, a solution of the crude aldehyde **8** (390 mg, 1.38 mmol) in 4 mL of DME was added. After a further 20 h at reflux, the reaction mixture was cooled to 25 °C, diluted with hexane, filtered through a small pad of Florisil on a sintered-glass filter, and evaporated to leave as a residue a black oil. Column chromatography on silica gel using *n*-hexane as eluent achieved only a partial separation, still leaving a mixture of components shown by GC to contain several monomeric (i.e., C_{19}) components. Therefore, the mixture was heated in a flask at a temperature of 100 °C (0.5 mmHg) for 1 h. The residue in the flask was then rechromatographed as before on silica gel using *n*-hexane as eluent to give 215 mg (59%) of **9** as a colorless oil.

9: 500-MHz ^{1}H NMR ($CDCl_3$) δ 5.18 (m, 2 H, CH), 2.04 (m, 2 H, =CCH), 1.54–0.83 (m, 72 H, includes four distinct peaks at 0.873, 0.860, 0.850, and 0.837 for the methyl groups); MS, *m/e* 532 (M^+), 517 ($M^+ - 15$).

2,6,10,14,17,21,25,29-Octamethyltriacontane (1). A mixture of the alkene **9** (210 mg, 0.395 mmol), 10% platinum on carbon (600 mg), and 50 mL of freshly distilled acetic acid was stirred under a hydrogen atmosphere for 30 min at 25 °C. The reaction mixture was then filtered and concentrated to give a yellowish oil. Column chromatography on silica gel using *n*-hexane as eluent gave 178 mg (85%) of **1** as a colorless oil. **1**: 500-MHz ^{1}H NMR ($CDCl_3$) δ 1.54–1.51 (m, 44 H), 0.873, 0.860, 0.852, 0.833 (4 s, 30 H); MS, *m/e* 534 (M^+), 519 ($M^+ - 15$), 505, 463, 449, 448, 429, 421, 420, 407, 393, 380, 379, 378 (lower peaks match published spectrum[8]).

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Registry No. **1**, 70967-41-8; (*E*)-**5**, 150-86-7; (*Z*)-**5**, 5492-30-8; **6**, 30220-53-2; **7**, 645-72-7; **8**, 105373-75-9; **9**, 105373-76-0.

(12) By careful column chromatography, samples of the *E* and *Z* isomers could be isolated, with the *Z* isomer eluting from the column first. The stereochemical assignment was made by the position of the methyl resonance in the 500-MHz ^{1}H NMR spectrum of each isomer, appearing at δ 1.669 for the *E* isomer and at δ 1.736 for the *Z* isomer.[13]

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Synthesis of Radioiodinated Juvenile Hormone Analogues

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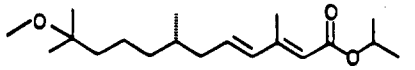
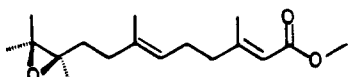
Methoprene (**1**) is a metabolically and environmentally stable analogue of the insect juvenile hormone JH III (**2**).



1



2

It was developed by Zoecon for fly and mosquito control, and it was the first insect growth regulator (IGR) to be registered for use in pest control.[1] Recently, it has become an important ingredient in home-use flea control products. Tritium-[2] and carbon-14-labeled[2] isotopomers of methoprene have been prepared in order to study the degradation products[3] in target organisms, nontarget organisms, and the ecosystem. Despite the economic importance of this IGR, little is known of its mode of action on a molecular level. In order to determine the macromolecular binding sites for such a potent hormone analogue, high specific activity juvenoids are required. We recently described the preparation of enantiomerically enriched JH I and JH II labeled with tritium at high specific activity (58 Ci/mmol).[4] These and other radiolabeled juvenoids[5,6]

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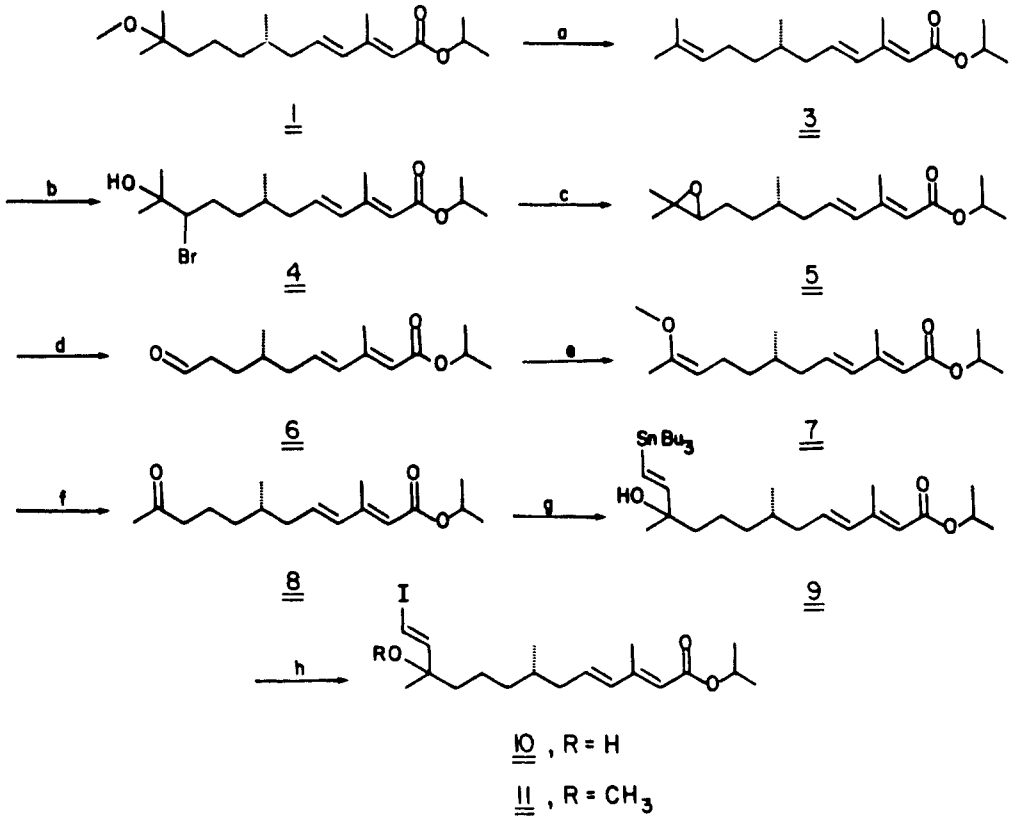
0022-3263/86/1951-5447$01.50/0

Scheme I. Synthesis of [[^{125}I]- and [[^{127}I]Iodovinyl]methoprenol (IVMA, 10) and (Iodovinyl)methoprene (IVM, 11)[a]



[a] Reagents: (a) concentrated H_2SO_4, hexane, 20 °C, 14 days (94%); (b) NBS, THF, H_2O, 0 °C, 1 h, and then cyclohexene to quench; (c) K_2CO_3, CH_3OH, 20 °C, 1 h (60%); (d) H_5IO_6, THF, 20 °C, 0.5 h (62%); (e) $CH_3CH(OCH)_3PPh_3$, *n*-BuLi, THF, 43 °C, 1 h; (f) H_3^+O, CH_3OH, 20 °C, 20 min (54%); (g) (*E*)-$Bu_3SnCH{=}CHSnBu_3$, *n*-BuLi, THF, 0 °C, 2 h, and then NH_4Cl, H_2O (44%); (h) for ^{127}I compound, titrate with I_2 in $CHCl_3$, and then add KF, CH_3OH followed by 5% $NaHSO_3$ (95%); (i) for ^{125}I compound, $Na^{125}I$, H_2O_2/CH_3CO_2H, pH 4.5 buffer, 20 °C, 12 h, and then $NaHSO_3$.

enable the detection of proteins that bind juvenile hormones or IGRs with subnanomolar dissociation constants. In this paper, we describe the first synthesis of a radioiodinated juvenoid, an iodovinyl analogue of methoprene with both high biological activity and high specific activity (>2000 Ci/mmol). The iodovinyl group is metabolically stable[7] and can be introduced into a methoprene-like molecule in a position where increased steric size and hydrophobicity are both well tolerated.[1]

The biologically active (7*S*) enantiomer of methoprene (1) was converted to the dodecatrienoate **3** (94%) by sulfuric acid mediated elimination of methanol in a biphasic hexane mixture (Scheme I). Selective oxidation of the terminal alkene with NBS–THF–water gave the bromohydrin **4** (65%), which was closed to the epoxide **5** with methanolic base (90%). Oxidative cleavage of the epoxide with periodic acid in aqueous THF produced the aldehyde **6** (62%). Reaction of the aldehyde **6** with 1-methoxyethyl triphenylphosphorylide followed by acidic hydrolysis of the enol ether **7** gave the methyl ketone **8** (54%).[8] The lithio reagent derived from (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene[7,9] was added to the ketone at room temperature to give the vinylstannane **9** in 44% yield. Control of the chemoselectivity of this process was unexpectedly difficult and was solved by adding the cold lithio reagent (0 °C) to the ketone at room temperature. Finally, titration of **9** with iodine in chloroform gave a quantitative yield of the (iodovinyl)methoprenol (IVMA, **10**). The radioiodination was conducted by addition of hydrogen peroxide to a pH 4.5 buffered acetic acid solution of the vinylstannane and no-carrier added sodium [^{125}I]iodide.[7]

Addition of 100-fold excess of 10% ferric chloride on methanol-doped silica gel to **10** resulted in 63% yield of the methoxy analogue **11** (IVM). All the compounds in the series **1–11** showed λ_{max} 259 nm (ϵ 19 500–22 000) characteristic of the dienoate system. Both IVMA and IVM showed a distinctive pair of doublets at 6.20–6.60 ppm ($^3J_{trans}$ = 14.5–14.8 Hz) corresponding to H-12 and H-13. Mass spectral data for both IVMA and IVM showed >75% relative abundance peaks (196.9446 and 210.9614, respectively) that correspond to α cleavage between C-10 and C-11.

Unlabeled IVMA (**10**) and IVM (**11**) both show potent juvenoid activity by in vitro and in vivo assays using *Manduca sexta* larvae. Indeed, IVMA is 4 times more active than methoprene, and this observation justified the examination of the radioiodinated material.[10] Furthermore, [^{125}I]-labeled IVMA showed saturable, specific binding to isolated nuclei of epidermal cells with K_D 3 nM.[11]

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Experimental Section

(7*S*)-Methoprene (90% pure, GC) was obtained from Zoecon Corp. Sodium [^{125}I]iodide (5 mCi, 17.4 Ci/mg) was purchased from Du Pont (NEN). Solvents were distilled before use. Anhydrous THF and ether were distilled from benzophenone ketyl. Flash chromatographic purifications were carried out on Woelm silica (32–63 μm) and Woelm alumina. TLC was performed using MN Polygram Sil G/UV 254 (4 × 8 cm) TLC plates. All products were homogeneous by TLC (R_f's are reported for 20% EtOAc/hexane). ^{1}H NMR spectra were determined on an NT-300 spectrometer. Mass spectra (HR-MS) were carried out at 70-eV ionization potential on a Spectros MS 30 spectrometer with a DS 50 data system; UV spectra were measured in hexane on an LKB Ultraspec II. Gas chromatography was carried out on a Varian 3700 equipped with a fused silica capillary column (DB-5, 30m × 0.263 mm). Radioactive samples were counted in an LKB 1218 Rackbeta liquid scintillation counter using a PPO/POPOP/toluene scintillation cocktail. Autoradiography was performed on Kodak XAR-5 film.

Isopropyl (2*E*,4*E*)-3,7,11-Trimethyl-2,4,10-dodecatrienoate (3). To 5 g (16 mmol) of methoprene (1) in 200 mL of hexane was added 15 drops of concentrated sulfuric acid, and the mixture was stirred at ambient temperature for 14 days (complete as monitored by TLC). The dark brown solution was decanted through a 2-cm pad of Florisil, dried in vacuo, and chromatographed (SiO_2, 5% EtOAc/hexane) to give 4.2 g (15 mmol) of triene **3**: 94% yield; TLC, R_f 0.65; ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J = 6.6 Hz, C-7 CH_3), 1.26 [d, J = 6.2 Hz, OCH(CH_3)$_2$], 1.68 (s, C-11 CH_3), 1.76 (s, H-12), 2.28 (d, J = 1 Hz, C-3 CH_3), 5.04 [m, J = 5 Hz, H-10 + OCH(CH_3)$_2$], 5.71 (d, J = 1 Hz, H-2), 6.06 (m, H-4 + H-5).

Isopropyl (2*E*,4*E*)-10,11-Epoxy-3,7,11-trimethyl-2,4-dodecadienoate (5). To a solution of 2.5 g (9 mmol) of triene **3** in 150 mL of THF at 0 °C was added enough water to give a cloudy mixture. The reaction flask was shielded from light, and 1.6 g (9 mmol) of *N*-bromosuccinimide (NBS) was added portionwise. The mixture was stirred (0 °C, 1 h) after which any unreacted NBS was quenched by the addition of 3 mL of cyclohexene. THF was removed under reduced pressure, and the aqueous layer was extracted 3× with 100 mL of ether. The extract was washed (brine), dried ($MgSO_4$), and concentrated to give a yellow oil that was used directly in the next step.

To a solution of crude bromohydrin **4** in 100 mL of methanol was added 1.86 g (13 mmol) of dry K_2CO_3. After stirring (1 h, 20 °C), the solvent was removed and 100 mL of ether added. The organic layer was washed (H_2O, brine), dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 5% EtOAc/hexane), yielding 1.6 g (5.4 mmol) of the epoxide **5**: 60% yield; TLC, R_f 0.55; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 6.6 Hz, C-7 CH_3), 1.26 [d, J = 6.2 Hz, OCH(CH_3)$_2$], 1.27 (s, C-11 CH_3), 1.31 (s, H-12), 2.29 (d, J = 2 Hz, C-3 CH_3), 2.72 (t, J = 6 Hz, H-10), 5.07 [septet, J = 6 Hz, OCH(CH_3)$_2$], 5.69 (d, J = 1 Hz, H-2), 6.12 (m, H-4 + H-5).

Isopropyl (2*E*,4*E*)-10-Oxo-3,7-dimethyl-2,4-decadienoate (6). To 1.6 g (5.4 mmol) of epoxide **5** in 60 mL of dry THF was added 1.23 g (5.4 mmol) of periodic acid. The reaction was stirred for 0.5 h and then quenched with 50 mL of water. The THF was removed in vacuo, and the aqueous layer was extracted 3× with 60 mL of ether. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 10% EtOAc/hexane) to give 900 mg (36 mmol) of aldehyde **6**, 62% yield. To prevent decomposition during chromatography, the silica gel was pretreated with a 10% triethylamine/hexane solution: TLC, R_f 0.37; ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 6.6 Hz, C-7 CH_3), 1.25 [d, J = 6.2 Hz, OCH(CH_3)$_2$], 2.23 (d, J = 1 Hz, C-3 CH_3), 5.04 [septet, J = 6.2 Hz, OCH(CH_3)$_2$], 5.64 (d, J = 1 Hz, H-2), 6.05 (m, H-4 + H-5), 9.72 (t, J = 2 Hz, H-10).

Isopropyl (2*E*,4*E*)-11-Keto-3,7-dimethyl-2,4-dodecadienoate (8). A suspension of 200 mg (0.62 mmol) of (α-methoxyethyl)-triphenylphosphonium chloride[8] in 2 mL of dry THF was cooled to −43 °C under N_2 (CH_3CN–dry ice bath), and (0.42 mmol) of *n*-BuLi was added dropwise, giving a characteristic red color. Stirring was continued for 1 h, then 105 mg (0.42 mmol) of aldehyde **6** in 1 mL of dry THF was added rapidly, and the mixture was stirred at −43 °C for 20 min. It was then warmed to room temperature for an additional 40 min, quenched with 1 mL of H_2O, and extracted (3 × 5 mL of ether). The combined organics were concentrated to give the crude enol ether **7**.

Methanol (5 mL) and 2–3 drops of 5 N HCl were added to the crude enol ether **7**, and the mixture was stirred (20 min). The methanol was removed in vacuo and 20 mL of 1:1 ether–H_2O added. The organic layer was washed (brine), dried ($MgSO_4$), and chromatographed (SiO_2, 10% EtOAc/hexane) to give 120 mg (0.43 mmol) of the pure ketone **8**: 54% yield; TLC, R_f 0.42; ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J = 6.6 Hz, C-7 CH_3), 1.26 [d, J = 6.2 Hz, OCH(CH_3)$_2$], 2.18 (s, H-12), 2.26 (d, J = 1 Hz, C-3 CH_3), 2.41 (t, J = 7.7 Hz, H-10), 5.04 [septet, J = 6.2 Hz, OCH(CH_3)$_2$], 5.67 (d, J = 1 Hz, H-2), 6.08 (m, J = 1 Hz, H-4 + H-5).

Isopropyl (2*E*,4*E*)-13-(Tri-*n*-butylstannyl)-11-hydroxy-3,7,11-trimethyl-2,4,12-tridecatrienoate (9). A hexane solution of *n*-BuLi (0.47 mmol) was added to 350 mg (0.58 mmol) of (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene[12,13] in 2 mL of dry THF at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C and then transferred by double-ended needle to 120 mg (0.43 mmol) ketone **8** in 1 mL of dry THF, which was at ambient temperature. The reaction was allowed to stir for an additional 2 h at ambient temperature under N_2 and was then quenched with 2 mL of 5% NH_4Cl. The reaction was extracted (3 × 10 mL of ether), dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 5% EtOAc/hexane) to give 113 mg (0.19 mmol) of the vinylstannane **9**: 44% yield; TLC, R_f 0.63; ^{1}H NMR ($CDCl_3$) δ 0.85–0.95 (m, 18 H), 1.24–1.37 (m, 17 H), 1.45–1.57 (m, 11 H), 2.26 (d, J = 1 Hz, C-3 CH_3), 5.04 [septet, J = 6.2 Hz, OCH(CH_3)$_2$], 5.67 (d, J = 1 Hz, H-2), 6.06 (m, H-4 + H-5 + H-12 + H-13).

Isopropyl (2*E*,4*E*)-13-Iodo-11-hydroxy-3,7,11-trimethyl-2,4,12-tridecatrienoate (IVMA, 10). A 0.1 M solution of iodine in chloroform was added at room temperature to 113 mg (0.19 mmol) of vinylstannane **9** in 2 mL of chloroform until the pink color remained. Then, 0.5 mL of 1 M potassium fluoride in methanol was added followed by 0.5 mL of 5% aqueous sodium bisulfite. The mixture was extracted (1:9 EtOAc/$CHCl_3$), dried ($MgSO_4$), concentrated, and chromatographed (SiO_2, 5% EtOAc/hexane) to give 78 mg (0.18 mmol) of the iodovinyl alcohol **10**: 95% yield; purity >90% by GC; TLC, R_f 0.44; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.6 Hz, C-7 CH_3), 1.26 [d, J = 6.3 Hz, OCH(CH_3)$_2$], 1.27 (s, C-11 CH_3), 2.26 (d, J = 1 Hz, C-3 CH_3), 5.04 [septet, J = 6.3 Hz, OCH(CH_3)$_2$], 5.67 (d, J = 1 Hz, H-2), 6.07 (m, H-4 + H-5), 6.31 (d, J = 14.5 Hz, H-12), 6.59 (d, J = 14.5 Hz, H-13); UV, λ_{max} 259 nm (ε 20400); HRMS (70 eV) m/e (rel intens) 434.1316 (1) $C_{19}H_{31}O_3I$, 247.1678 (25), 201.1603 (21), 196.9446 (75) C_4H_6OI, 111.0446 (100) $C_6H_7O_2$, 107.0807 (54), 93.0664 (63), 81.0642 (86), 79.0483 (61); MW for $C_{19}H_{31}O_3I$, calcd 434.1317, found 434,1316.

10% Ferric Chloride on Silica Gel. 10% ferric chloride on silica gel was prepared according to the literature.[14] We discovered that incomplete removal of methanol from the ferric chloride/silica gel slurry (rotary evaporation followed by evaporation for 2 h, 40 °C, 1 torr) resulted in a useful reagent for converting a tertiary allylic alcohol to a tertiary allylic methyl ether.

Isopropyl (2*E*,4*E*)-13-Iodo-11-methoxy-3,7,11-trimethyl-2,4,12-tridecatrienoate (IVM, 11). A 15-mg (0.035-mmol) portion of IVMA (**10**) was suspended in 3 mL of 1:9 EtOAc/hexane, 1 g of 10% $FeCl_3/SiO_2$ (prepared in methanol) was added, and the resultant mixture was stirred vigorously for 5 min. The mixture was filtered through glass wool and the $FeCl_3/SiO_2$ was washed with 1:9 EtOAc/hexane until all the organics were extracted. Purification by silica gel column chromatography (5% EtOAc/hexane) gave 10 mg (0.022 mmol) of the desired iodovinyl methyl ether **11**: 63% yield; TLC, R_f 0.60; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 6.7 Hz, C-7 CH_3), 1.20 (s, C-11 CH_3), 1.23 [d, J = 6.3 Hz, OCH(CH_3)$_2$], 2.26 (d, J = 1 Hz, C-3 CH_3), 3.16 (s, C-11 OCH_3), 5.04 [septet, J = 6.3 Hz, OCH(CH_3)$_2$], 5.67 (d, J = 1 Hz, H-2), 6.07 (m, J = 1 Hz, H-4 + H-5), 6.2 (d, J = 14.8 Hz, H-12), 6.51 (d, J = 14.8 Hz, H-13); UV, λ_{max} 259 nm (ε 21300); HRMS (70 eV) m/e (rel intens) 416.1221 (1) $C_{19}H_{29}O_2I$, 247.1699 (16), 210.9614

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(100) C_5H_8OI, 201,1633 (12), 111.0478 (19) $C_6H_7O_2$, 107.0828 (16), 93.0700 (17), 81.0693 (21), 79.0538 (20).

Isopropyl (2*E*,4*E*)-13-[^{125}I]Iodo-11-hydroxy-3,7,11-trimethyl-2,4,12-tridecatrienoate (10a). In a 5-mL test tube was added 0.5 mL of a 5% sodium acetate/acetic acid buffer solution (pH 4.54) containing sodium [^{125}I]iodide (5.0 mCi). To this was added 3 mg (0.005 mmol) of stannane **9** in 0.5 mL of THF, followed by 0.5 mL of a 2:1 hydrogen peroxide/acetic acid solution. The reaction was stirred for 24 h at room temperature and extracted with four 1.5-mL portions of EtOAc. The organics were washed (5 mL of 5% aqueous $NaHSO_3$) and chromatographed on activity III neutral alumina in a disposable pipet column to give 2.2 mCi of the [^{125}I]IVMA (**10a**; 44% radiochemical yield). Use of silica gel for this purification resulted in decomposition of IVMA to a less polar byproduct. Autoradiography of TLC plates indicated that the radioactivity comigrated with radioinert IVMA (**10**).

Isopropyl (2*E*,4*E*)-13-[^{125}I]Iodo-11-methoxy-3,7,11-trimethyl-2,4,12-tridecatrienoate (11a). To 0.5 g of 10% ferric chloride on silica gel (prepared in methanol) was added 0.6 mCi of **10a** in 1.5 mL of 1:9 EtOAc/hexane. The slurry was stirred vigorously for 5 min, filtered through glass wool, and purified with activity III alumina to give 0.4 mCi of the [^{125}I]IVM (**11a**; 66% radiochemical yield). Autoradiography of TLC plates indicated that the radioactivity comigrated with radioinert IVM (**11**).

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Dilithiated Vicinal Diester Route to Sesquiterpenes. Total Synthesis of (±)-Vetiselinene and the Formal Synthesis of Other Eudesmane Sesquiterpenes

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Since our original disclosures that the dianions of vicinal diesters can be readily prepared[1] and that these dianions undergo classical alkylation and acylation reactions[2] and can be annelated,[2-4] we[2-7] and others[8-12] explored the application of these reactions in the synthesis of natural and nonnatural products.[13] We have investigated the annelation of the dilithiated dimethyl cyclohex-4-ene-1,2-dioate to produce intermediates for the preparation of the eudesmane sesquiterpenes[5] and now report the total synthesis of (±)-vetiselinene (**19**)[14] and the formal syntheses of a number of other sesquiterpenes by this route. Treatment of dimethyl cyclohex-4-enedioate (**1a**) with LDA in THF gave a solution of the dianion **2a**, which on addition of ethyl 4-bromobutanoate (**3**) gave, over 5 days at −78 °C, the desired bicyclo[4.4.0]decanone diester derivative **4a** in 40% yield.[5] The corresponding diethyl **1b** and di-*tert*-butyl **1c** diesters gave higher yields of annelated product, but purification and saponification of the diethyl derivative proved more difficult. Treatment of **4a** with NaCl in Me_2SO at 160 °C[15] gave the keto ester **5** as a mixture of cis and trans isomers. Ketalization of **5** with 1,2-ethanediol gave **6** in poorer yield than expected but exclusively as the trans isomer. Reduction of **6** with $LiAlH_4$ gave the desired alcohol **7** in 81% yield, the spectral properties again only indicating the presence of the trans isomer. Selenation of **7** with *N*-(phenylseleno)phthalimide[16] gave the seleno ether **8**, the spectral properties again indicating only the presence of the trans isomer. Reduction of **8** with Raney nickel gave the desired alkene **9** in 76% yield, contaminated by 8% of a compound tentatively identified as the corresponding alkane **10**. The spectral properties of **9** were in accord with those of Torii and co-workers,[17] and the chemical shift of the angular methyl group substantiates the trans ring junction.[18] Treatment of **9** with *m*-chloroperoxybenzoic acid gave the desired epoxide **11** of the stereochemistry shown. Reduction of **11** with lithium in a mixture of liquid NH_3 and dimethoxyethane at low temperature gave the alcohol **12**, which was not purified but was oxidized directly to the ketone **13** with pyridinium chlorochromate in 61% overall yield from **11**. The spectral properties of compounds **11**–**13** were in accord with those reported by Torii and co-workers.[17] The ketone **13** was then treated with isopropylmagnesium chloride in THF at −50 °C, and the resulting alcohol **14** was not purified but was dehydrated with H_2SO_4 to give a mixture of ketones in 42% yield. This mixture was separated by HPLC to give **15**, **16**, **17**, and **18** in the approximate proportions 6:2:1:1. The ^{1}H NMR spectrum of **15** shows signals at δ 5.39 (br s, 1 H), 2.4–1.6 (m, 12 H), 0.94 (d, 6 H, J = 6.8 Hz), and 0.71 (s, 3 H), and the decoupled ^{13}C NMR spectrum had 14 signals. Ketone **16** has signals in the ^{1}H NMR spectrum at δ 5.34 (br s, 1 H), 2.60–1.38 (m, 12 H), 1.05 (s, 3 H), and 0.95 (d, 6 H, J = 6.8 Hz). The chemical shifts of the angular methyl groups are consistent with the assigned stereochemistries. Treatment of **15** with $Ph_3P{=}CH_2$ in Me_2SO gave (±)-vetiselinene (**19**) in 75% yield. The ^{1}H NMR spectrum shows signals at δ 5.39 (br s, 1 H), 4.75 (br s, 1 H), 4.52 (br s, 1 H), 1.20–2.40 (m, 12 H), 0.96 (d, 6 H, J = 6.6 Hz), and 0.65 (s, 3 H), and the decoupled ^{13}C NMR spectrum showed 15 signals. The carbonyl absorption present in the

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