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Registry No. **1a**, 78804-17-8; **1b**, 78804-18-9; **3a**, 78804-19-0; **3b**, 78804-20-3; **3c**, 78804-21-4; **3d**, 78804-22-5; **3e**, 78804-23-6.

Supplementary Material Available: Tables IV–VIII containing exact mass measurements, fractional coordinates, temperature factors, bond distances, and bond angles and Figure 2, a packing diagram (7 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Multifidene, the Gamete Attractant of the Phaeophyte *Cutleria multifida*

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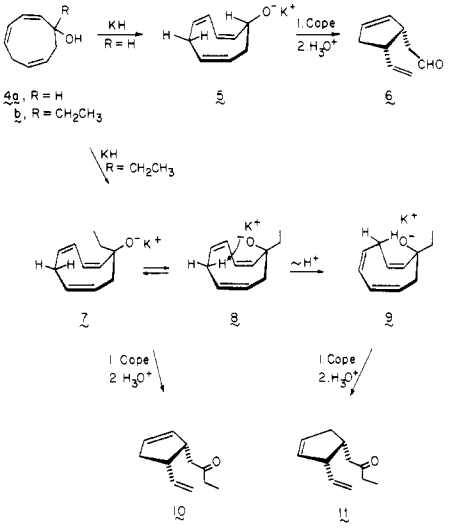
A short, stereoselective total synthesis of racemic multifidene has been achieved. The key elements of the synthetic scheme are (i) oxyanionic Cope rearrangement of *cis*[3]-2,4,7-cyclononatrienol and in situ trapping of the resulting enolate with chlorotrimethylsilane, (ii) stereocontrolled introduction of a phenylseleno group α to the aldehyde functionality, (iii) addition of an ethyl fragment under conditions where the polar PhSe substituent can induce high levels of stereoselection, and (iv) a double inversion sequence to introduce a cis double bond cleanly.

The anisogamous marine brown alga *Cutleria multifida* (Smith) Grev., which can be found in the springtime at various locales along the Mediterranean coast, achieves reproduction by sexual chemotaxis.[1] The vital need for successful fertilization begins when a larger female gynogamete of the Phyophyte releases a small quantity[2] of a volatile three-component hydrocarbon mixture in order to attract to itself tiny androgametes (sperm). After these have accumulated (sometimes violently and always in large numbers), mating occurs between a single pair and the resulting cell fusion leads to zygote formation. At this point, the supernumerary male cells lose interest and depart.[2-4] This dramatic long-range attraction of the sperm through the water has been shown to be triggered by multifidene (**1**), the male-attracting agent and major constituent of the hydrocarbon essential oil.[5,6] Subsequent synthetic studies by Jaenicke and Boland have led to the development of two viable routes to this biologically active substance.[7] Heating must be avoided during the final step which liberates **1** to avert contamination with the isomeric inactive hydrocarbons **2** and **3** to which multifidene is related by Cope rearrangement. We now describe a most direct and highly stereoselective total synthesis of multifidene (**1**) which takes advantage of the stereocontrolled anionic oxy-Cope ring contraction of *cis*[3]-2,4,7-cyclononatrienol[8] as well as the steric and chemical properties of a phenylselenyl substituent.

Scheme I



Our strategy centered around medium-ring alcohol **4a**, which was previously shown to undergo rapid isomerization at room temperature when in the form of its potassium alkoxide.[8] Mechanistically implicated in the efficient conversion to aldehyde **6** is the tublike conformer **5** wherein the alkoxide substitutent is oriented exo on the alicyclic framework, (Scheme I). When the ethyl homologue **4b** was similarly treated with potassium hydride in dry tetrahydrofuran, conversion to a mixture of the isom-

(1) Jaenicke, L.; Müller, D. G. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 61.

(2) A half-year of mass culture of the algae and extraction of the female gametes served to yield only 3.7 mg of the mixture: Müller, D. G. In "Marine Natural Products Chemistry"; Faulkner, D. J., Fenical, D. J., Eds.; Plenum Press: New York, 1977; pp 351–360.

(3) Müller, D. J. *Z. Pflanzenphysiol.* **1976**, *80*, 120.

(4) Jaenicke, L. In "Biochemistry of Sensory Functions"; Jaenicke, L., Ed.; Springer-Verlag: New York, 1974; pp 307–309.

(5) Jaenicke, L.; Muller, D. G.; Moore, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 3324.

(6) Jaenicke, L.; Boland, W. *Justus Liebigs Ann. Chem.* **1976**, 1135.

(7) Boland, W.; Jaenicke, L. *Chem. Ber.* **1978**, *111*, 3262. These authors have also give attention to the synthesis of closely related molecules: *J. Org. Chem.* **1979**, *44*, 4819.

(8) (a) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972, (a) Paquette, L. A.; Crouse, G. D. *Tetrahedron*, in press.

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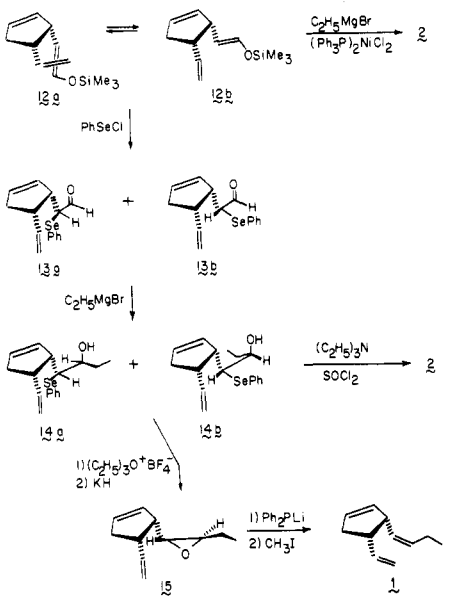
Scheme II

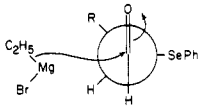


eric dienones **10** and **11** was observed.[9] This undesirable loss of regioselectivity appears general for tertiary alcohols of this type[9] and presumably stems from the well-established dynamic behavior of *cis*[3]-1,3,6-cyclononatrienes[10] which allows for rapid interconversion of **7** and **8** (note similar bulk of substituents at C-1). Once **8** is produced, intramolecular abstraction of the proximal doubly allylic ring proton becomes kinetically feasible and [1,3] hydrogen sigmatropy is induced.[11] Ultimately, **7**/**8** and **9** experience the [3,3] carbon sigmatropy which delivers **10** and **11**, respectively. Because this projected scheme proved not to be rewarding, a more broadly serviceable, regiocontrolled route was devised.

Following isomerization of the potassium salt of **4a** as before, the reaction mixture was treated with chlorotrimethylsilane and the silyl enol ether **12** was isolated. Because the various vinyl proton absorptions in **12** overlap significantly, it did not prove possible to confirm the trans stereochemical assignment by ^{1}H NMR. To establish this important point, **12** was coupled in stereocontrolled fashion (retention) with ethylmagnesium bromide through use of dichlorobis(triphenylphosphine)nickel according to Kumada's prescription[12] (Scheme II). Informatively, **2** was formed as a single stereoisomer. The exclusive proximal relationship of the cyclopentene double bond with the more substituted olefinic substitutent is particularly noteworthy.

In order to achieve proper installation of the butenyl side-chain stereochemistry, recourse was made to the introduction of a control element. For this purpose, the phenylseleno group was chosen because of its superior directing ability[13] and overall ease of manipulation.[14] An examination of molecular models showed that **12** could exist in two low-energy conformations (**12a** and **12b**) in which either face of the silyl enol ether double bond could become exposed to attack by an electrophile. Nonetheless, the addition of phenylselenyl chloride was expected, as a consequence of persistant steric screening by the neighboring vinyl substitutent, to deliver predominantly **13a**. In actuality, two α-seleno aldehydes assigned structures **13a** and **13b** were produced in a 9:1 ratio and 64% combined overall yield from **4a**.[15]

Stereoselective induction during the 1,2-addition of organometallics to α-heterosubstituted aldehydes has been extensively described in the literature,[16] and α-seleno aldehydes are no exception.[13] The particularly relevant fact in the latter case is the finding that the rather polar PhSe moiety leads to improved stereochemical control by fostering approach predominantly in line with the transition state model shown below:



In the present context, such events would transform **13a** into **14a** and **13b** into **14b**. To gain support for these formulations, the oily α-hydroxy selenide mixture obtained above was treated with thionyl chloride/triethylamine in dichloromethane, a reagent combination known to induce trans elimination of the hydroxyl and selenyl functionalities.[17] This chemical transformation afforded isomerically pure **2**, a result which nicely accommodates the theoretical expectations just presented.

To arrive at **1**, it remained only to reverse the stereochemical course of this elimination. As selenyl groups are not known to undergo cis elimination, replacement with a different substituent was mandated. This need was conveniently met by a double S_N2 displacement scheme, first by oxygen of selenium, followed by phosphorus of oxygen. When exposed to triethyloxonium fluoroborate, the **14a**/**14b** mixture was converted to the corresponding selenonium salts, which were then cyclized in the presence of potassium hydride.[18] Some partitioning of the diastereomers occurs during this process, perhaps as a result of different ring closure rates, to give essentially pure **15** (^{13}C NMR analysis). For our purposes, however, the presence of the second trans epoxide would not prove to be a complication, since it likewise would ultimately deliver **1**. When **15** was treated with lithium diphenylphosphide and methyl iodide according to Vedejs and Fuchs,[19] isomerically pure multifidene was produced.

In summary, the conversion of **4a** to **1** was easily achieved in relatively few steps. It is expected that this approach will prove generally serviceable for the appendage of side chains which feature either cis or trans olefin geometry.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer. The ^{1}H NMR spectra were determined with

(9) Crouse, G. D.; Paquette, L. A. *Tetrahedron Lett.* **1981**, 3167.
(10) Paquette, L. A.; Ley, S. V.; Traynor, S. G.; Martin, J. T.; Geckle, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 8162.
(11) The rearranged alcohol corresponding to **9** can, in fact, be isolated at shorter reaction times. The driving force underlying this reaction is the greater degree of conjugative overlap available in the diene component of **9**. These points will be elaborated upon later in a separate paper.
(12) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, 3915.
(13) Léonard-Coppens, A. M.; Krief, A. *Tetrahedron Lett.* **1976**, 3227.
(14) Rémion, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, 1385.
(15) Attempts to effect the direct condensation of the rearranged potassium enolate with phenylselenyl chloride resulted in the formation of mixtures of unselenated, monoselenated, and diselenated aldehydes.
(16) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112, (b) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1263, (c) Karabatsos, G. J. *Ibid.* **1967**, *89*, 1367, (d) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199, (e) Maurette, M. T.; Gaset, A.; Mathis, R.; Lattes, A. *Bull. Soc. Chim. Fr.* **1975**, 398, (f) Handel, H.; Pierre, J. L. *Tetrahedron Lett.* **1976**, 741.
(17) Rémion, J.; Krief, A. *Tetrahedron Lett.* **1976**, 3743.
(18) This reagent combination has proved technically simpler to utilize than the $CH_3I/AgBF_4$ and KO-*t*-Bu pair described earlier: (a) Dumont, W.; Krief, A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 350. (b) Van Ende, D.; Dumont, W.; Krief, A. *Ibid.* **1975**, *14*, 700.
(19) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.

Varian T-60 and EM-390 instruments, and apparent splittings are given in all cases. The ^{13}C NMR spectra were recorded on Bruker HX-90 and WP-80 instruments. Mass spectra were measured on an AEI-MS9 spectrometer at an ionizing energy of 70 eV. Microanalytical determinations were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

***cis*-3-[(*E*)-2-((Trimethylsilyl)oxy)ethenyl]-4-vinylcyclopent-1-ene (12).** A 1.0-g sample of potassium hydride dispersion in mineral oil (23.6%, 5.9 mmol) was washed twice under nitrogen with 20-mL portions of dry ether. A solution of **4a** (0.50 g, 3.7 mmol)[8] in anhydrous ether (20 mL) was added and the mixture was stirred at room temperature for 6 h, cooled to −78 °C, and treated simultaneously with triethylamine (2 mL) and chlorotrimethylsilane (1.5 mL, 13 mmol). After 1 h at −78 °C, the reaction mixture was allowed to warm to 0 °C and poured into 50 mL of cold water. The layers were separated and the aqueous phase was extracted with ether (50 mL). The combined organic layers were washed quickly with cold brine (50 mL), dried, and concentrated. Several hours at 50–60 mm served to remove volatile impurities. The residual yellow oil showed no trace of aldehyde (^1H NMR) or other impurities and was used without further purification in subsequent reactions: ^1H NMR ($CDCl_3$) δ 6.3–5.6 (m, 5 H), 5.1 (q, J = 2 Hz, 1 H), 4.95 (t, J = 2 Hz, 1 H), 3.5–2.7 (m, 2 H), 2.6–2.3 (m, 2 H), and 0.2 (s, 9 H).

***cis*-3-((E)-1-Butenyl)-4-vinylcyclopent-1-ene (2).** Ethyl bromide (0.54 g, 5 mmol) was slowly added to magnesium (0.15 g, 6.1 mmol) in ether (25 mL) and the mixture was magnetically stirred for 1 h during which time reflux was seen. The supernatant solution was transferred via syringe to a nitrogen-blanketed flask charged with 100 mg of dichlorobis(triphenylphosphine)nickel. The ether was removed in vacuo and replaced with 20 mL of benzene. Unpurified **12** (0.35 g, 1.6 mmol) was added via syringe and the solution was heated at the reflux temperature for 4 h, cooled, dissolved in ether, filtered, and evaporated. VPC purification (12 ft × 0.25 in. 15% SE-30, 130 °C) of the resulting oil showed it to be a single product (98 mg, 42% isolated) identified as "isomultifidene" (**2**) by comparison with spectra (90-MHz ^1H NMR and IR) of the authentic material:[7] m/e calcd 148.1252 (M^+), obsd 148.1257.

Phenylselenation of 12. Unpurified **12** (780 mg, 3.7 mmol) dissolved in 20 mL of anhydrous ether was stirred magnetically at −78 °C while a solution of phenylselenyl chloride (750 mg, 3.9 mmol) in 10 mL of ether was slowly introduced via syringe during 10 min. Upon completion of the addition, the reaction mixture was allowed to warm to 0 °C when it was poured into a mixture of brine (25 mL) and ether (25 mL). The organic layer was separated, washed with brine, dried, and concentrated to leave a reddish oil. Chromatography on silica gel (elution with 8% ethyl acetate in petroleum ether) furnished pure **13** (700 mg, 64% overall from **4a**); IR (neat) 3070, 2940, 2850, 2720, 1710, 1640, 1000, 915, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.4 (d, J = 3 Hz, 1 H), 7.6–7.2 (m, 5 H), 6.1–5.6 (m, 3 H), 5.05 (m, 1 H), 4.9 (m, 1 H), 3.6 (dd, J = 9 and 3 Hz, 1 H), 3.4–2.9 (m, 2 H), 2.9–2.4 (m, 2 H); ^{13}C NMR ($CDCl_3$ ppm) provided indication that the ratio of **13a**/**13b** was approximately 9:1. For **13a**: 191.10, 138.78, 135.99, 131.68, 131.56, 129.26, 128.89; 126.10, 116.57, 54.92, 46.97, 45.39, and 38.83 ppm. For **13b**: 192.55, 137.75, 135.63, 132.59, 131.62, 130.23, 129.26, 128.89, 116.82, 53.88, 47.88, 46.00, and 37.98 ppm; m/e calcd 292.0366 (M^+) obsd 292.0357.

Grignard Addition to 13. Ethylmagnesium bromide was prepated in the usual manner from 430 mg (4 mmol) of ethyl bromide and 97 mg (4 mmol) of magnesium turnings in 20 mL of anhydrous ether. The reaction mixture was cooled to −116 °C and a solution of **13** (600 mg, 2 mmol) in ether (5 mL) was slowly added. After 30 min, the solution was allowed to warm to −78 °C where it was stirred for 1 h. Acetic acid was added and the mixture was warmed to 0 °C. Brine (20 mL) and ether (30 mL) were added, the layers were separated, and the aqueous phase was extracted with ether. The combined organic phases were washed with saturated sodium bicarbonate solution (30 mL) and brine (30 mL) prior to drying and solvent evaporation. Medium-pressure liquid chromatographic purification of the residue on silica gel (elution with 10% ethyl acetate in petroleum ether) returned 50 mg of unreacted **13** and gave 462 mg (76% based on recovered starting material) of **14** as a clear oil: IR (neat) 3450, 3060, 3040, 2920, 2860, 2840, 1635, 1575, 1020, 995, 910, 730, 685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 5 H), 6.4–6.0 (m, 1 H), 6.0–5.7 (m, 2 H), 5.3–5.0 (m, 2 H), 3.7–2.9 (series of m, 4 H), 2.7–2.35 (m, 2 H), 1.5 (q, J = 7 Hz, 2 H), 0.9 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 139.23, 133.99, 133.36, 131.95, 129.62, 129.14, 127.39, 116.51, 74.47, 56.07, 48.01, 46.36, 38.49, 26.75, 10.68 ppm; m/e calcd 322.0835 (M^+), obsd 322.0827.

Anal. Calcd for $C_{11}H_{22}OSe$: C, 63.55; H, 6.90. Found: C, 63.64; H, 6.69.

Conversion of 14 to 2. To a solution of **14** (180 mg, 0.56 mmol) and triethylamine (0.5 g, 5 mmol) in 10 mL of dichloromethane was added a solution of thionyl chloride (0.15 g; 1.3 mmol) in the same solvent (2 mL) over 5 min. After 30 min, the reaction mixture was poured into water and extracted with ether. The combined organic layers were washed with 5% hydrochloric acid (10 mL) and brine (10 mL) prior to drying and solvent evaporation. The reddish oily residue was taken up in pentane and eluted through a silica gel column to furnish 53 mg (64%) of **2** as a colorless oil. The spectra of this material were identical with those of the sample obtained earlier.

Epoxide 15. A solution of **14** (390 mg, 1.2 mmol) in 10 mL of dry 1,2-dimethoxyethane was stirred magnetically under nitrogen while triethyloxonium tetrafluoroborate (275 mg, 1.4 mmol) was added at room temperature over several minutes. After 2 h, the reaction mixture was taken up in a syringe and added to a stirred slurry of oil-free potassium hydride (300 mg of 23% oil suspension, 1.8 mmol) in 5 mL of dimethoxyethane. After 30 min at room temperature, the mixture was poured into brine (40 mL) and ether (40 mL) and the aqueous layer was extracted with ether. The combined organic phases were washed with brine (40 mL), dried, and concentrated to leave a reddish oil. This material was purified by medium-pressure liquid chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether). There was isolated 140 mg (71%) of **15** as a colorless oil: IR (neat) 3050, 2965, 2920, 2840, 1640, 1610, 1455, 990, 905, 890, 810, 720, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.2–5.7 (m, 2 H), 5.5 (m, 1 H), 5.2–4.95 (m, 2 H), 3.2–2.9 (distorted q, J = 7 Hz, 1 H), 2.9–2.3 (m, 5 H), 2.65–2.3 (m, 2 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 139.09, 132.54, 129.67, 114.91, 57.97 (2 C), 51.07, 45.20, 37.53, 25.05, 9.95 ppm; m/e calcd 164.1201 (M^+), obsd 164.1197.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.33; H, 9.75.

Multifidene (1). Lithium diphenylphosphide was prepared according to the method of Vedejs and Fuchs[19] and standardized by titration with diphenylacetic acid. A 1.5-mL aliquot of 1.0 M solution (1.5 mmol) was introduced via syringe to a stirred solution of **15** (175 mg, 1.06 mmol) in 5 mL of dry tetrahydrofuran. After 48 h, methyl iodide (250 mg, 1.7 mmol) was added via syringe and the reaction mixture was stirred for an additional 2 h before being poured into brine (50 mL) and extracted with ether (2 × 50 ml). The combined organic layers were washed with brine (30 mL), dried, filtered, evaporated, taken up in pentane, refiltered, and carefully evaporated to leave pure multifidene (~100%). VPC and TLC analyses indicated the material to be homogeneous. Preparative VPC isolations gave 80 mg (51%) of **1** as a clear, colorless oil, whose IR and ^1H NMR spectra are idential with those of the natural product:[7] ^{13}C NMR ($CDCl_3$) 140.25, 134.38, 132.00, 129.96, 128.41, 114.04, 46.84 (2 C), 37.18, 20.77, 14.41 ppm.

Acknowledgment. This research was made possible by the generous financial assistance of the National Institutes of Health (Grant GM-28468). We thank Professor Jaenicke and Dr. Boland for making available to us the spectra of **1**, **2**, and **3**.

Registry No. (±)-**1**, 60933-34-8; (±)-**2**, 68366-04-1; (±)-*cis*-**4a**, 78790-51-9; (±)-**12**, 78739-41-0; (±)-**13a**, 78739-42-1; (±)-**13b**, 78780-95-7; (±)-**14a**, 78739-43-2; (±)-**14b**, 78780-96-8; (±)-**15**, 78739-44-3; phenylselenyl chloride, 5707-04-0.