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Enantioselective Total Synthesis of Multifidene, a Sex Pheromone of Brown Algae

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Abstract: The total synthesis of multifidene, a sex pheromone found in brown algae, is described. The synthesis features the highly enantioselective and diastereoselective addition reaction of an aldehyde to a nitroolefin in the presence of a Hayashi–Jørgensen catalyst and a Nef reaction initiated by visible light irradiation. These key reactions enabled the 11-step synthesis from commercially available compounds. The synthetic pheromones are examined with gametes.

Keywords: total synthesis; sex pheromone; multifidene; conjugate addition; Hayashi–Jørgensen catalyst; Nef reaction

Citation: Umezawa, T.; Hara, M.; Kinoshita-Terauchi, N.; Matsuda, F. Enantioselective Total Synthesis of Multifidene, a Sex Pheromone of Brown Algae. *Organics* **2022**, *3*, 187–195. https://doi.org/10.3390/org3030015

Academic Editor: George Kokotos

Received: 20 April 2022
Accepted: 30 June 2022
Published: 8 July 2022

1. Introduction

The chemical structure of multifidene (**1**), obtained from marine brown algae *Cutleria multifida* as one of its sex pheromones, was first determined by Jaenicke, Müller and Moore in 1974 (Figure 1) [1] as a C_{11} hydrocarbon. Other C_{11} hydrocarbon pheromones, such as ectocarpene (**2**), hormosirene (**3**) and finavarrene (**4**), from brown algae have been previously reported [2–5]. To date, 11 parent pheromones and more than 50 of their stereoisomers [6–10] have been identified in brown algae and several microalgae [11–13]. In the brown algae, the C_{11} hydrocarbons are presumed to have the following functions. In sexual reproduction, C_{11} hydrocarbons from female gametes contribute to their efficient mating by inducing the release of male gametes and by attracting male gametes [10]. In vegetative thalli, C_{11} hydrocarbons prevent feeding as a chemical defense [14,15].

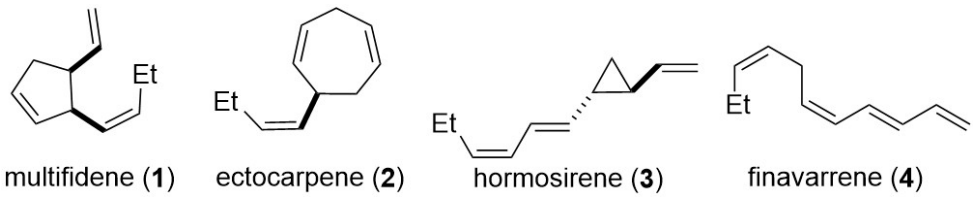


Figure 1. Chemical structures of C_{11} pheromones.

In the 1980s, extensive chemical and biological studies of the brown algae through biosynthesis, pheromone-mediated spermatozoid release, chemotaxis and synthesis of the pheromones were reported [7]. Concerning the synthesis of **1**, several reports have been published [16–23]. Some of them are shown in Figure 2. In the synthesis of Hemamalini and co-workers, starting from optically active carboxylic acid, a cobalt-mediated radical cyclization reaction was employed to obtain lactone. This lactone was successfully derived to **1** in four steps. Furstoss and co-workers utilized a kinetic resolution of racemic cyclobutanone with the fungus *Cnninghamella echinulata* to obtain optically active lactone in >98% ee, which

was converted to **1**. In 2019, our research group revealed the novel function (i.e., control of the phototactic sign) of sex pheromones in the phototaxis of male gametes in the brown alga *Mutimo cylindricus* with synthetic ectocarpene (**2**) [23]. Furthermore, we revealed that this conversion of the phototactic sign coincided with the dynamics of the intracellular cyclic nucleotide and Ca^{2+} concentration. The C_{11} sex pheromones are biologically synthesized from unsaturated fatty acid **5** [24], as shown in Figure 3. Hydrogen abstraction from an active methylene followed by single-electron oxidation generates a carbocation, which is further subjected to a decarboxylation reaction, giving various intermediates and/or final compounds. As a result, the C_{11} pheromones are released from female gametes as a mixture. It is possible that each pheromone may show different functions against gametes. In this paper, we describe the enantioselective total synthesis of multifidene (**1**) through a conjugate addition reaction by a Hayashi–Jørgensen catalyst and the Nef reaction under visible right irradiation as key steps in order to study the function of each C_{11} pheromone and develop molecular probes to identify the mechanisms of action.

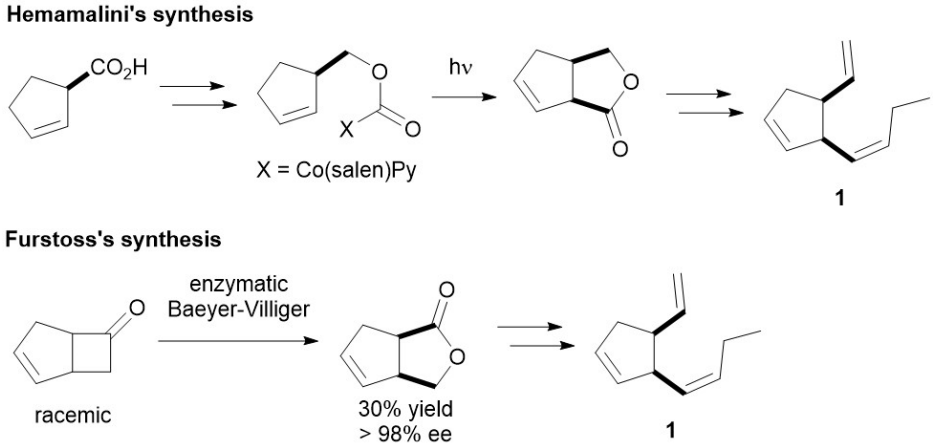


Figure 2. Previous syntheses of optically active multifidene.

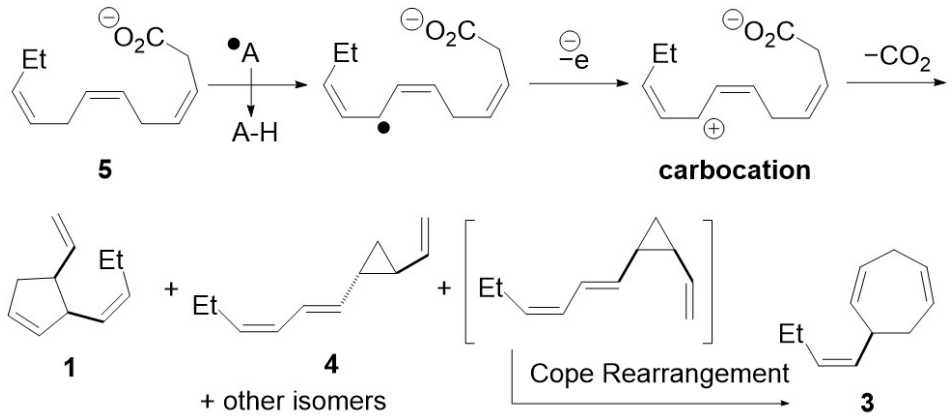


Figure 3. Proposed biosynthesis of C_{11} pheromones.

2. Materials and Methods

2.1. General Methods

The IR spectra were recorded on a JASCO FTIR-4100 Type A spectrometer (JASCO corporation, Tokyo, Japan) using a NaCl cell. The ^{1}H NMR and ^{13}C NMR spectra were recorded using a JNM-EX 400 (400 MHz and 100 MHz) spectrometer (JEOL Ltd., Tokyo, Japan). Chemical shifts were reported in ppm relative to $CHCl_3$ in $CDCl_3$ for ^{1}H NMR (δ = 7.26) and ^{13}C NMR (δ = 77.0). Splitting patterns for ^{1}H NMR were designated as "s, d, t, q, m, dt, dd, and td". These symbols indicate "singlet, doublet, triplet, quartet, multiplet, doublettriplet, doubletdoublet, and tripletdoublet", respectively. All commercially obtained

reagents were employed as received. Analytical TLC was carried out using pre-coated silica gel plates (Wako TLC Silicagel 70F_{254}, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). Wakogel 60N 63–212 μm was used for column chromatography.

*2.2. Total Synthesis of Multifidene (**1**)*

2.2.1. Alcohol **S1**

To a solution of cis-2-butane-1, 4-diol (1.85 g, 21.0 mmol) in DMF (30 mL) were added imidazole (4.28 g, 63.0 mmol) and TESCl (7.60 mL, 50.4 mmol) at 0 °C under an Ar atmosphere. The mixture was stirred at room temperature for 16 h, quenched with EtOH and saturated $NaHCO_3$, extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, filtered through short silica gel pad and concentrated in vacuo. The crude TES ether was employed directly in the next reaction.

Ozone was bubbled through a solution of the crude TES ether in MeOH-CH_2Cl_2 (40 mL, 19:1 v/v) at −78 °C for 4 h. To the mixture was added PPh_3 (5.50 g, 21.0 mmol). The mixture was warmed to room temperature, stirred for 1 h, dried over Na_2SO_4 and concentrated in vacuo. The crude aldehyde **12** was employed directly in the next reaction.

To a solution of the crude aldehyde **12** in THF-*t*BuOH (80 mL, 1:1 v/v) were added $MeNO_2$ (2.56 mL, 46.2 mmol) and KO*t*Bu (471 mg, 8.40 mmol) at room temperature. The mixture was stirred for 1 h, quenched with saturated $NaHCO_3$, extracted with AcOEt, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: EtOAc = 99:1, 98:2, 96:4 then 94:6) to obtain the alcohol **S1** (6.40 g, 27.2 mmol, 65% over 3 steps) as a colorless oil: IR (neat) 3446, 2956, 2913, 2878, 1556, 1458, 1416, 1379, 1240, 1206, 1122, 1006, 963, 943, 886, 804, 744, 674, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.62 (6H, q, J = 7.8 Hz), 0.96 (9H, t, J = 7.8 Hz), 2.76 (1H, d, J = 6.8 Hz), 3.70 (2H, d, J = 4.9 Hz), 4.34–4.41 (1H, m), 4.45–4.56 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.1, 6.6, 63.3, 68.9, 77.9; HRMS (ESI-orbitrap) m/z: $[M+Na]^+$; Calcd for $C_9H_{21}NO_4NaSi$ 258.1132; Found 258.1136.

2.2.2. Adduct **7**

To a solution of **S1** (1.14 g, 4.84 mmol) in CH_2Cl_2 (16 mL) were added NEt_3 (1.68 mL, 12.1 mmol) and MsCl (525 μL, 6.77 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 5 min, quenched with saturated NH_4Cl, extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered through short silica gel pad and concentrated in vacuo. The crude olefin **7** was employed directly in the next reaction.

To a solution of the crude olefin **7** in PhMe (10 mL) were added 4-pentenal (**9**) (573 μL, 5.81 mmol), *p*-nitrophenol (134 mg, 0.968 mmol) and catalyst *S*-**8** (157 mg, 0.484 mmol) in PhMe (3.0 mL) at −15 °C to room temperature under Ar atmosphere. The mixture was stirred for 22 h and purified by silica gel column chromatography (hexane: EtOAc = 99.5:0.5, 99:1 then 98:2) to obtain the adduct **7** (1.25 g, 4.15 mmol, 85% over 2 steps) as a colorless oil: $[\alpha]_D^{26}$ + 32.9 (c 1.84, $CHCl_3$); IR (neat) 2956, 2912, 2877, 2735, 1725, 1642, 1556, 1457, 1416, 1378, 1240, 1104, 1005, 920, 797, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.59 (6H, q, J = 7.8 Hz), 0.94 (9H, t, J = 7.8 Hz), 2.30–2.37 (1H, m), 2.50–2.57 (1H, m), 2.67 (1H, q, J = 6.8 Hz), 2.81–2.86 (1H, m), 3.70 (2H, d, J = 5.4 Hz), 4.46 (1H, dd, J = 12.7, 4.9 Hz), 4.57 (1H, dd, J = 12.7, 8.3 Hz), 5.13 (1H, d, J = 9.8 Hz), 5.14 (1H, d, J = 17.1 Hz), 5.71–5.79 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.1, 6.6, 30.4, 39.6, 50.1, 60.8, 74.1, 76.6, 77.0, 77.3, 118.3, 134.1, 202.1; HRMS (ESI-orbitrap) m/z: $[M+Na]^+$; Calcd for $C_{14}H_{27}NO_4NaSi$ 324.1612; Found 324.1608.

2.2.3. Diolefin **13**

To a solution of $MePh_3PBr$ (3.53 g, 9.90 mmol) in THF (10 mL) was added NaHMDS (1.0 M in THF, 9.00 mL, 9.00 mmol) at 0 °C under Ar. After 10 min, **7** (1.25 g, 4.15 mmol) in THF (10 mL) was added to the mixture at −40 °C. The mixture was stirred for 10 min, warmed to 0 °C, quenched with saturated NH_4Cl, extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by

silica gel column chromatography (hexane: EtOAc = 99:1 then 98:2) to obtain the diolefin **13** (1.10 g, 3.67 mmol, 88%) as a colorless oil: $[\alpha]_D^{26}$ −12.9 (*c* 1.51, $CHCl_3$); IR (neat) 3078, 2956, 2912, 2877, 1640, 1554, 1457, 1418, 1377, 1239, 1109, 1002, 918, 797, 744, 677 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.55 (6H, q, *J* = 7.8 Hz), 0.91 (9H, t, *J* = 7.8 Hz), 2.05–2.13 (1H, m), 2.21–2.28 (2H, m), 2.32–2.37 (1H, m), 3.64 (2H, d, *J* = 5.4 Hz), 4.34–4.43 (2H, m), 4.99–5.11 (4H, m), 5.50–5.59 (1H, m), 5.63–5.73 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.2, 6.6, 35.9, 42.3, 42.4, 60.6, 75.2, 76.6, 77.0, 77.3, 116.8, 117.7, 135.6, 138.3; HRMS (ESI-orbitrap) *m*/*z*: $[M+Na]^+$; Calcd for $C_{15}H_{29}NO_3NaSi$ 322.1813; Found 322.1809.

2.2.4. Triolefin **6**

To a solution of **13** (164 mg, 0.548 mmol) in TFE-DCE (3.0 mL, 9:1 *v*/*v*) were added fluorescein (18.2 mg, 0.0548 mmol) and Cs_2CO_3 (357 mg, 1.09 mmol) at −20 °C under O_2 atmosphere. The mixture was stirred for 46 h under visible light irradiation (ν max = 470 nm, 610 mW), filtered through short path silica gel pad and concentrated in vacuo to obtain the crude aldehyde **14**, which was employed directly in the next reaction.

To a solution of $MePh_3PBr$ (360 mg, 1.03 mmol) in THF (5.0 mL) was added NaHMDS (1.0 M in THF, 1.00 mL, 1.00 mmol) at 0 °C under Ar. After 5 min, the crude aldehyde **14** in THF (2.5 mL) was added to the mixture at −40 °C. The mixture was stirred for 10 min at −40 °C and 20 min at 0 °C, quenched with saturated NH_4Cl, extracted with AcOEt, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: EtOAc = 99.8:0.2 then 99.5:0.5) to obtain the triolefin **6** (70.8 mg, 0.266 mmol, 48% over 2 steps) with recovery of **13** (15.2 mg, 9%): a colorless oil; $[\alpha]_D^{26}$ −35.6 (*c* 0.59, $CHCl_3$); IR (neat) 3076, 2955, 2911, 2877, 1640, 1457, 1416, 1380, 1239, 1097, 994, 913, 803, 742, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.58 (6H, q, *J* = 7.8 Hz), 0.95 (9H, t, *J* = 7.8 Hz), 2.10–2.16 (2H, m), 2.29–2.35 (1H, m), 2.40–2.47 (1H, m), 3.49–3.58 (2H, m), 4.97–5.10 (6H, m), 5.53–5.64 (2H, m), 5.69–5.77 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.4, 6.8, 37.1, 43.2, 49.6, 64.2, 115.6, 116.2, 117.4, 136.4, 137.3, 138.7; HRMS (ESI-orbitrap) *m*/*z*: $[M+Na]^+$; Calcd for $C_{16}H_{30}ONaSi$ 289.1964; Found 289.1956.

2.2.5. Cyclopentene **15**

To a solution of **6** (22.3 mg, 0.0837 mmol) in CH_2Cl_2 (3.0 mL) was added Grubbs 1st generation catalyst (3.4 mg, 0.00413 mmol) at room temperature under Ar atmosphere. After 15 h, MeOH (33.4 μL, 0.837 mmol) and CSA (3.80 mg, 0.0165 mmol) were added. The mixture was further stirred for 90 min, quenched with Et_3N (2.30 μL, 0.0165 mmol) and concentrated in vacuo. The crude product was purified by silica gel column chromatography (pentane: Et_2O = 95:5 then 90:10) to obtain the cyclopentene **15** (9.90 mg, 0.0797 mmol, 95%) as a colorless oil: $[\alpha]_D^{23}$ + 180 (*c* 0.20, $CHCl_3$); IR (neat) 3361, 2923, 2853, 1540, 1507, 1024, 910, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.24–2.31 (1H, m), 2.48 (1H, dd, *J* = 16.6, 8.3 Hz), 2.87–2.94 (1H, m), 3.03 (1H, quin, *J* = 8.3 Hz), 3.60 (2H, d, *J* = 5.4 Hz), 5.07 (1H, dd, *J* = 10.2, 1.9 Hz), 5.14 (1H, d, *J* = 17.1 Hz), 5.64–5.65 (1H, m), 5.88–5.91 (1H, m), 6.03 (1H, dt, *J* = 17.1, 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.2, 44.6, 51.4, 62.8, 115.5, 130.8, 132.5, 139.6; HRMS (ESI-orbitrap) *m*/*z*: $[M+Na]^+$; Calcd for $C_8H_{12}ONa$ 147.0786; Found 147.0782.

2.2.6. Multifidene (**1**)

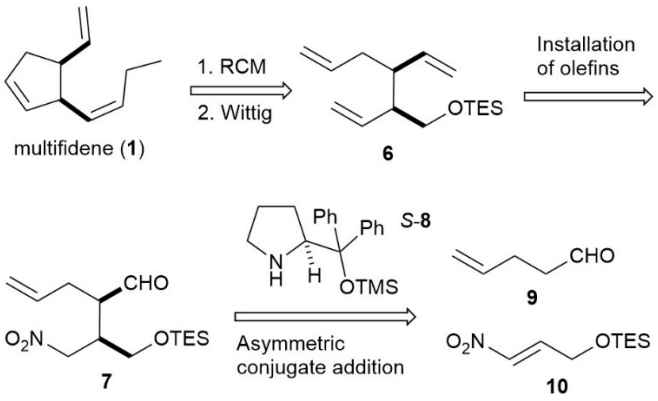
To a solution of **15** (46.7 mg, 0.376 mmol) in CH_2Cl_2 (1.8 mL) was added DMP (191 mg, 0.450 mmol) at 0 °C. The reaction mixture was stirred for 25 min, quenched with saturated $NaHCO_3$: 20% $Na_2S_2O_3$ (1:1, *v*/*v*) and extracted with Et_2O. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to obtain the crude aldehyde, which was employed directly in the next reaction.

To a solution of *n*$PrPh_3PBr$ (385 mg, 1.00 mmol) in Et_2O (3.0 mL) was added NaHMDS (1.0 M in THF, 0.900 mL, 0.900 mmol) at 0 °C under Ar. After 10 min, the crude aldehyde in Et_2O (2.0 mL) was added to the mixture at −78 °C. The mixture was stirred for 10 min at −78 °C and 20 min at 0 °C, quenched with saturated NH_4Cl, extracted with Et_2O, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue

was purified by silica gel column chromatography (pentane only) to obtain multifidene **1** (15.9 mg, 0.106 mmol, 28% over 2 steps) as a colorless oil: $[\alpha]_D^{23}$ + 162.5 (*c* 0.20, pentane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, t, *J* = 7.8 Hz), 2.03–2.10 (2H, m), 2.24–2.31 (1H, m), 2.41–2.51 (1H, m), 2.97 (1H, quint., *J* = 7.8 Hz), 3.59–3.64 (1H, m), 4.91–5.02 (2H, m), 5.13 (1H, tt, *J* = 11.0, 1.5 Hz), 5.39 (1H, dt, *J* = 11.0, 7.3 Hz), 5.58–5.61 (1H, m), 5.76–5.78 (1H, m), 5.87 (1H, ddd, *J* = 17.3, 10.3, 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 20.8, 37.1, 46.7, 46.8, 114.0, 128.3, 129.4, 131.9, 134.3, 140.2.

3. Results and Discussion

Our synthetic aim is to develop a flexible synthetic route to multifidene (**1**) in order to access derivatives such as the enantiomer of **1** or a molecular probe to investigate the molecular mechanism of the pheromone functionality. The retrosynthetic analysis toward **1** is shown in Scheme 1. It was envisioned that asymmetric conjugate addition between aldehyde **6** and nitroolefin **7** by the Hayashi–Jørgensen catalyst *S*-**8** [25] would construct adduct **9** with the contiguous stereoconfiguration of **1**. After the conversion of the aldehyde and nitro groups into the corresponding double bonds in triolefin **10**, a ring-closing metathesis reaction (RCM) and subsequent Wittig reaction provides **1**.

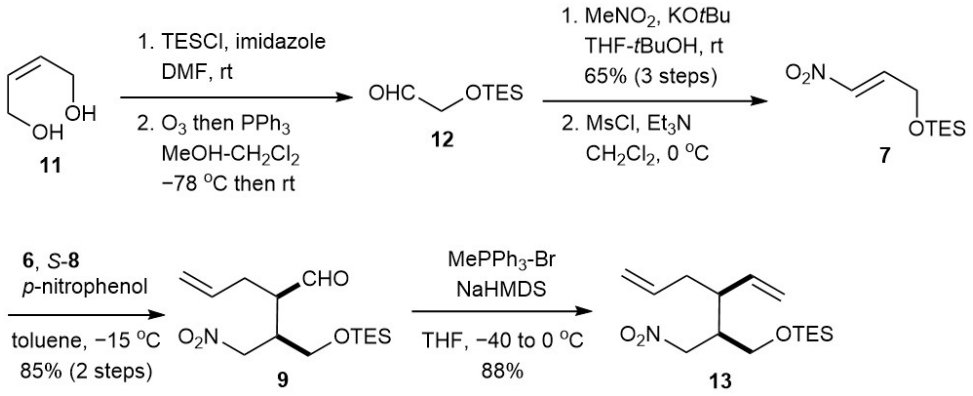


Scheme 1. Retrosynthetic analysis.

The synthesis started with the commercially available *cis*-2-butene-1, 4-diol (**11**) (Scheme 2). The protection of the two hydroxy groups of **11** with TES groups and ozonolysis of the double bond afforded aldehyde **12**. The treatment of **12** with $MeNO_2$ and KO*t*Bu furnished an alcohol, which was dehydrated to provide nitroolefin **10**. The subsequent addition reaction with commercially available 4-pentenal (**6**) in the presence of the Hayashi–Jørgensen catalyst *S*-**8** at −15 °C produced adduct **7** with high stereoselectivity (>95% ee and 7:1 dr) and high yield (85% over 2 steps) [25,26] (see Supplementary Materials for the enantiopurity of **7**). The newly formed absolute configurations were determined by final conversion to **1**, and diastereoselectivity was estimated by ^{1}H NMR analysis. In this reaction, the lower temperature was important because lower diastereoselectivity was observed in the ^{1}H NMR spectrum at room temperature or 0 °C. The aldehyde in **7** was transformed into a vinyl group through a Wittig reaction.

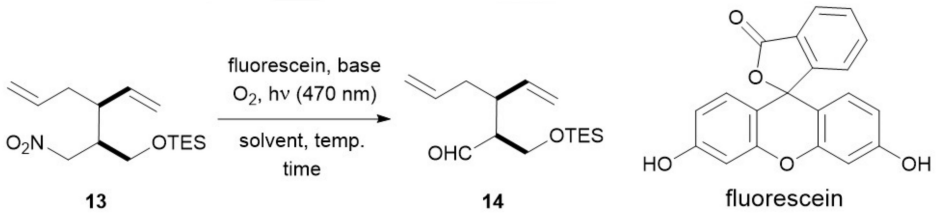
With the diolefin **13** in hand, the Nef reaction, i.e., conversion of the nitro group to an aldehyde, was investigated next. The previously reported conditions, such as NaOMe-H_2SO_4 [27], DABCO-O_2 [28], $KMnO_4$-Base (K_2CO_3 [29] or KOH [30]), $TiCl_3$ [31] or Cu (0)-TMEDA-O_2 [32], resulted in undesired products or low yields. In the pioneering publication on the Nef reaction in 1986 to form aldehydes, rose bengal enabled the conversion of a nitro group to an aldehyde in the presence of molecular oxygen and irradiation with a tungsten lamp [33]. Based on the recent progress on photoreactions in this decade, we attempted to optimize this reaction. The results of the investigation are summarized in Table 1. First, bases (NaOMe, KO*t*Bu, and Cs_2CO_3) were investigated (entries 1–6). The reactions were carried out with 1.5 equivalents of base (NaOMe, KO*t*Bu, or Cs_2CO_3) in MeOH-DCE (1,2-

dichloroethane) or TFE (2,2,2-trifluoroethanol)-DCE solvent in the presence of a catalytic amount of fluorescein under visible light irradiation (470 nm, 620 mW) for 8 h at 0 °C. The addition of the less polar solvent, DCE, was essential to dissolve **13** in an alcoholic solvent. The Nef reactions with NaOMe were less effective than other bases, producing the desired aldehyde **14** as a minor component (entries 1, 2). When KO*t*Bu was used in MeOH-DCE, starting material **13** was completely consumed, although a considerable amount of side products was observed in the ^{1}H NMR spectrum of the crude product (entry 3). The structures of the side products could not be determined due to the complexity of the mixture. The reaction in TFE-DCE produced a mixture of **13** and **14** in a ratio of 45:55 along with trace amounts of side products (entry 4). Cs_2CO_3 showed a similar tendency as KO*t*Bu, but the ratio was improved to 33:67 in TFE-DCE solvent (entries 5, 6). The reaction in EtOH with Cs_2CO_3 (entry 7) was similar to that in MeOH. Other solvents, *i*PrOH or MeCN, resulted in a lower conversion of **13** (entries 8, 9).



Scheme 2. Synthesis of the optically active olefin **13**.

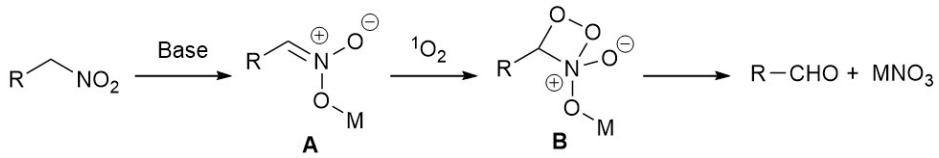
Table 1. Optimization of the Nef reaction [1].



Entry	Base (Equiv.)	Solvent	Time	Temp.	Ratio (13:14) [2]
1	NaOMe (1.5)	MeOH-DCE (9:1)	8 h	0 °C	76:24
2	NaOMe (1.5)	TFE-DCE (9:1)	8 h	0 °C	91:9
3	KO*t*Bu (1.5)	MeOH-DCE (9:1)	8 h	0 °C	0:100 [3]
4	KO*t*Bu (1.5)	TFE-DCE (9:1)	8 h	0 °C	45:55
5	Cs_2CO_3 (1.5)	MeOH-DCE (9:1)	8 h	0 °C	0:100 [3]
6	Cs_2CO_3 (1.5)	TFE-DCE (9:1)	8 h	0 °C	33:67
7	Cs_2CO_3 (1.5)	EtOH-DCE (9:1)	8 h	0 °C	0:100 [3]
8	Cs_2CO_3 (1.5)	*i*PrOH-DCE (9:1)	8 h	0 °C	86:14
9	Cs_2CO_3 (1.5)	MeCN-DCE (9:1)	8 h	0 °C	96:4
10	Cs_2CO_3 (2.0)	TFE-DCE (9:1)	8 h	0 °C	0:100 [4]
11	Cs_2CO_3 (2.0)	TFE-DCE (9:1)	16 h	−10 °C	0:100 [4]
12	Cs_2CO_3 (2.0)	TFE-DCE (9:1)	16 h	−20 °C	44:56
13	Cs_2CO_3 (2.0)	TFE-DCE (9:1)	48 h	−20 °C	13:87 [5]

[1] 40–50 mg (ca 0.14 mmol) of **13** was used for the optimization, otherwise mentioned; [2] The ratio of **13** and **14** was estimated with crude ^{1}H NMR; [3] Considerable amount of side products were observed; [4] Partial epimerization was observed; [5] 164 mg of **13** was used.

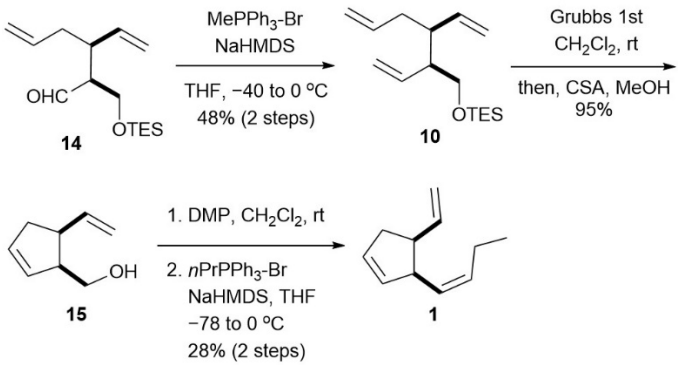
A possible reaction pathway based on the previous work is described in Scheme 3 [33]. The abstraction of an α-hydrogen of the nitro group produces nitronate **A**. The subsequent reaction of **A** with singlet molecular oxygen generated from O_2 and fluorescein under light irradiation produces adduct **B** through [2+2] cycloaddition. Adduct **B** dissociates to furnish an aldehyde. The above results indicated that effects of the solvent were crucial for the conversion of **13**. A primary alcohol efficiently promoted the Nef reaction when Cs_2CO_3 was employed as a base. It is assumed that a less bulky base generated from the alcohol and Cs_2CO_3 can readily abstract an α-hydrogen. Among the reactions with Cs_2CO_3, those in EtOH and TFE were noteworthy. As shown in entries 6 and 7, EtOH completely consumed **13** within 8 h, although side products were formed, whereas TFE exhibited a slower reaction rate than EtOH. We believe this slower reaction inhibits the formation of side products, and generates a less basic and/or less nucleophilic profile [34] of 2, 2, 2-trifluoroethoxide, which affects the reaction rate.



Scheme 3. Possible reaction mechanism.

The reaction was further examined for the efficient formation of **14** by screening equivalents of Cs_2CO_3 and reaction temperatures with the TFE-DCE solvent system. Two equivalents of Cs_2CO_3 consumed the starting material; however, the partial epimerization of the product at the α-position was observed (entry 10). Although a longer reaction time (16 h) was required, a lower temperature (−10 °C) produced a similar result as that at 0 °C (entry 11). The Nef reaction at −20 °C for 16 h provided a 44:56 mixture of **13** and **14** (entry 12), and the ratio of **14** at −20 °C was improved through a much longer reaction time (48 h) (entry 13). The efficiency of this Nef reaction was affected by reaction scale; however, for this entry, more than 100 mg of **13** was used for the effective total synthesis of **1**.

With the optimized conditions for the Nef reaction in hand, we completed the total synthesis of multifidene (**1**), as shown in Scheme 4. The resultant labile aldehyde **14** was transformed into triolefin **6** in 48% yield over two steps from **13**. The ring-closing metathesis reaction with the Grubbs 1st generation catalyst [35] proceeded regioselectively to produce the desired cyclopentene **15** after the removal of the TES group under mild acidic conditions [36]. We rationalized this regioselectivity by kinetic control. The desired product is the favored five-membered ring, but other possible products are much less favored, such as a four-membered ring. Cyclopentene **15** was successfully transformed into multifidene (**1**) in 28% yield over two steps: Dess–Martin oxidation and *Z*-selective Wittig reaction. In the final steps, we assumed that a low yield is due to a partial isomerization reaction of the labile β,γ-unsaturated aldehyde to the α,β-unsaturated aldehyde under the strong basic conditions of the Wittig reaction because a spot having UV absorption was observed in TLC analysis in the Wittig reaction. This spot was not found in the oxidation reaction. Although a one-pot operation of Swern oxidation and Wittig reaction as non-isomerization conditions have been reported [16], this operation in our study resulted in the recovery of the aldehyde. Some bases were also screened to result in a lower yield or complex mixture. ^1H and ^{13}C NMR spectra of synthetic **1** were identical with those of the previously prepared compound [17].



Scheme 4. Total synthesis of multifidene.

4. Conclusions

In summary, the enantioselective total synthesis of multifidene was described. The conjugate addition of an aldehyde to a nitroolefin in the presence of a Hayashi–Jørgensen catalyst and the newly developed Nef reaction producing a labile aldehyde with fluorescein under visible light irradiation enabled the efficient synthesis. The developed synthetic route opens up an opportunity to prepare the enantiomer or diastereomers of multifidene, or other derivatives with a cyclohexene core or a molecular probe. We are currently investigating a bioassay to determine the relationship between chemotaxis and phototaxis of this pheromone with brown algae.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/org3030015/s1: determination of enantiopurity of adduct **9**, and the NMR spectra of the synthetic samples.

Author Contributions: T.U. and N.K.-T. designed the study; T.U. and M.H. synthesized the compounds; T.U. acquired the funds; T.U., N.K.-T. and F.M. analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by The Akiyama Life Science Foundation (2019-5).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article or Supplementary Materials.

Conflicts of Interest: The authors declare no conflict of interest.

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