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

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 C11 hydrocarbon. Other C11 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 C11 hydrocarbons are presumed to have the following functions. In sexual reproduction, C11 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, C11 hydrocarbons prevent feeding as a chemical defense [14,15].

![Chemical structures of C11 pheromones.](image)

Figure 1. Chemical structures of C11 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 Cunninghamella 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 Ca²⁺ concentration. The C₁₁ 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 C₁₁ 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 C₁₁ pheromone and develop molecular probes to identify the mechanisms of action.

**Hemamalini's synthesis**

![Hemamalini's synthesis](image)

**Furstoss's synthesis**

![Furstoss's synthesis](image)

**Figure 2.** Previous syntheses of optically active multifidene.

**Figure 3.** Proposed biosynthesis of C₁₁ 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 ¹H NMR and ¹³C 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 CHCl₃ in CDCl₃ for ¹H NMR (δ = 7.26) and ¹³C NMR (δ = 77.0). Splitting patterns for ¹H NMR were designated as “s, d, t, q, m, dt, dd, and td”. These symbols indicate “singlet, doublet, triplet, quartet, multiplet, doublettriplet, doubleldoublet, 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 70F254, 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 1 h, quenched with EtOH and saturated NaHCO3, extracted with AcOEt, washed with water and brine, dried over Na2SO4, 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-CH2Cl2 (40 mL, 19:1 v/v) at −78 °C for 4 h. To the mixture was added PPh3 (5.50 g, 21.0 mmol). The mixture was warmed to room temperature, stirred for 1 h, dried over Na2SO4 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-tBuOH (80 mL, 1:1 v/v) were added MeNO2 (2.56 mL, 46.2 mmol) and KOtBu (471 mg, 8.40 mmol) at room temperature. The mixture was stirred for 1 h, quenched with saturated NaHCO3, extracted with AcOEt, dried over Na2SO4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: EtOAc = 99:1, 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, 1725, 1642, 1556, 1457, 1379, 1240, 1206, 1122, 1063, 943, 886, 804, 744, 674, 635 cm−1; 1H NMR (CDCl3, 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); 13C NMR (CDCl3, 100 MHz) δ 4.1, 6.6, 63.3, 68.9, 77.9; HRMS (ESI-orbitrap) m/z: [M+Na]+; Calcd for C9H21NO4NaSi 258.1132; Found 258.1136.

2.2.2. Adduct 7

To a solution of S1 (1.14 g, 4.84 mmol) in CH2Cl2 (16 mL) were added NEt3 (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 NH4Cl, extracted with AcOEt, washed with brine, dried over Na2SO4, 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 (1.25 g, 4.15 mmol, 85% over 2 steps) as a colorless oil: [α]D30 + 32.9 (c 1.84, CHCl3); IR (neat) 2956, 2912, 2877, 2735, 1725, 1642, 1556, 1457, 1416, 1378, 1240, 1104, 1005, 920, 797, 745 cm−1; 1H NMR (CDCl3, 400 MHz) δ 0.59 (6H, q, J = 7.8 Hz), 0.94 (9H, t), 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); 13C NMR (CDCl3, 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 C14H21NO4NaSi 324.1612; Found 324.1608.

2.2.3. Diolefin 13

To a solution of MePPh2PBr (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 NH4Cl, extracted with AcOEt, washed with brine, dried over Na2SO4, 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, 1317, 1239, 1109, 1002, 978, 797, 744, 677 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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) $\delta$ 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$_3$NaSi 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$_2$CO$_3$ (357 mg, 1.09 mmol) at $-20^\circ$C under O$_2$ atmosphere. The mixture was stirred for 46 h under visible light irradiation ($v$ 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$_3$PBr (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 $0^\circ$C under Ar. After 5 min, the crude aldehyde 14 in THF (2.5 mL) was added to the mixture at $-40^\circ$C. The mixture was stirred for 10 min at $-40^\circ$C and 20 min at $0^\circ$C, quenched with saturated NH$_4$Cl, extracted with AcOEt, washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane: EtOAc = 99:1 then 98:2) to obtain the triolefin 6 (70.8 mg, 0.266 mmol, 48% over 2 steps) with recovery of 13 (15.2 mg, 9%); a colorless oil; $[\alpha]_D^{23}$ − 35.6 ($c$ 0.59, CHCl$_3$); IR (neat) 3076, 2955, 2912, 2877, 1640, 1457, 1416, 1380, 1239, 1097, 994, 913, 803, 742, 669 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 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) $\delta$ 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$_2$Cl$_2$ (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$_3$N (2.30 µL, 0.0165 mmol) and concentrated in vacuo. The crude product was purified by silica gel column chromatography (pentane: Et$_2$O = 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$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.24–2.31 (1H, $m$), 2.48 (1H, $d$, $J$ = 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, $d$, $J$ = 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) $\delta$ 38.2, 44.6, 51.4, 62.8, 115.6, 116.2, 117.4, 136.4, 137.3, 138.7; HRMS (ESI-orbitrap) $m/z$: [M+Na]$^+$; Calcd for C$_8$H$_{12}$ONa 147.0786; Found: 147.0782.

2.2.6. Multifidene (1)

To a solution of 15 (46.7 mg, 0.376 mmol) in CH$_2$Cl$_2$ (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$_2$S$_2$O$_3$ (1:1, $v/v$) and extracted with Et$_2$O. The combined extracts were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to obtain the crude aldehyde, which was employed directly in the next reaction.

To a solution of nPr$_3$PBr (385 mg, 1.00 mmol) in Et$_2$O (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$_2$O (2.0 mL) was added to the mixture at $-78^\circ$C. The mixture was stirred for 10 min at $-78^\circ$C and 20 min at 0°C, quenched with saturated NH$_4$Cl, extracted with Et$_2$O, washed with brine, dried over Na$_2$SO$_4$, 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) $\delta$ 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) $\delta$ 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 nitroene 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.](image)

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 KOtBu 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$_2$SO$_4$ [27], DABCO-O$_2$ [28], KMnO$_4$-Base (K$_2$CO$_3$ [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, KOtBu, and Cs$_2$CO$_3$) were investigated (entries 1–6). The reactions were carried out with 1.5 equivalents of base (NaOMe, KOtBu, or Cs$_2$CO$_3$) 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 KOtBu was used in MeOH-DCE, starting material 13 was completely consumed, although a considerable amount of side products was observed in the 1H 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). Cs2CO3 showed a similar tendency as KOtBu, but the ratio was improved to 33:67 in TFE-DCE solvent (entries 5, 6). The reaction in EtOH with Cs2CO3 (entry 7) was similar to that in MeOH. Other solvents, iPrOH 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) |
|-------|---------------|-----------------------|------|-------|---------------|
| 1     | NaOMe (1.5)   | MeOH-DCE (9:1)        | 8 h  | 0 °C  | 76:24         |
| 2     | NaOMe (1.5)   | MeOH-DCE (9:1)        | 8 h  | 0 °C  | 91:9          |
| 3     | KOtBu (1.5)   | MeOH-DCE (9:1)        | 8 h  | 0 °C  | 0.100 3       |
| 4     | KOtBu (1.5)   | MeOH-DCE (9:1)        | 8 h  | 0 °C  | 0.100 3       |
| 5     | Cs2CO3 (1.5)  | MeOH-DCE (9:1)        | 8 h  | 0 °C  | 33:67         |
| 6     | Cs2CO3 (1.5)  | TFE-DCE (9:1)         | 8 h  | 0 °C  | 100 3         |
| 7     | Cs2CO3 (1.5)  | EtOH-DCE (9:1)        | 8 h  | 0 °C  | 100 3         |
| 8     | Cs2CO3 (1.5)  | TFE-DCE (9:1)         | 8 h  | 0 °C  | 96:4          |
| 9     | Cs2CO3 (1.5)  | MeCN-DCE (9:1)        | 8 h  | 0 °C  | 0.100 4       |
| 10    | Cs2CO3 (2.0)  | TFE-DCE (9:1)         | 8 h  | 0 °C  | 100 4         |
| 11    | Cs2CO3 (2.0)  | TFE-DCE (9:1)         | 16 h | -10 °C| 0.100 4       |
| 12    | Cs2CO3 (2.0)  | TFE-DCE (9:1)         | 16 h | -20 °C| 44:56         |
| 13    | Cs2CO3 (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 1H 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$_2$CO$_3$ was employed as a base. It is assumed that a less bulky base generated from the alcohol and Cs$_2$CO$_3$ can readily abstract an α-hydrogen. Among the reactions with Cs$_2$CO$_3$, 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.](image)

The reaction was further examined for the efficient formation of 14 by screening equivalents of Cs$_2$CO$_3$ and reaction temperatures with the TFE-DCE solvent system. Two equivalents of Cs$_2$CO$_3$ 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. $^1$H 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.

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