Bull, Inst. Chem. Res., Kyoto Univ., Vol. 61, No. 2, 1983

REVIEW

Male Gamete-Attracting Substances of Marine Algae

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Received May 6, 1983

KEY WORDS: Marine Algae/ Gamete-Attracting Substance/

I. INTRODUCTION

Plants physiologists have observed for a long time that male-reproductive cells are attracted by female cells. In 1845, Thuret[1] reported that eggs of *Fucus* attract the spermatozoids. Cook *et al.*[2,3] demonstrated that motile spermatozoids are lured to a volatile substance secreted by mature eggs of brown marine algae, *Fucus serratus* L. and *F. vesiculosus* L. . However, an attempted search for isolation and identification of this principle from eggs gave inconclusive results. Hlubucek *et al*[4] explored extracts from macerated female and male ripe tips of *Fucus* with helium-gas stream and identified *n*-hexane specifically in the female plants. In 1973, Müller in co-operation with chemists[5] succeeded in isolation of the volatile attractant of spermatozoids, an isomer of 1,3,5-octatrienes, fucoserratene from eggs and oogonia of *F. serratus* a dioecious brown alga. This attractant was later identified with (3*E*, 5*Z*)-octa-1,3,5-triene (**1**) by synthesis and biological activities[6].

Earlier, Müller *et al.*[7] isolated for the first time male-attracting substance from cultures of a brown marine alga *Ectocarpus siliculosus* and its structure was determined as (*S*)-(+)-6-(1*E*-but-1-enyl)-cycloheptа-1,4-diene (**2**). Since discover of ectocarpene in 1971, five more male gamete-attracting-substances have been identified: multifidene[8] [*cis**-1-vinyl-2-(1*E*-but-1-enyl)-cyclopent-3-ene] (**4**), fucoserratene[5] [(3*E*,5*Z*)-octa-1,3,5-triene] (**1**), dictyopterene C′[9] [(−)-(*R*)-6-butyl-cyclohepta-1,4-diene] (**3**), desmarestene[10] [6-(1*Z*-buta-1,3-dienyl)-cyclohepta-1,4-diene] (**5**) and viridiene[11] [*cis*-1-vinyl-2-(1*Z*-buta-1,3-dienyl)-cyclopent-3-ene] (**6**), in the marine Phaeophyta, *Cutleria, Fucus, Dictyopteris, Desmarestia* and *Syringoderma,* respectively.

II. SYNTHESIS OF MALE GAMETE-ATTRACTING SUBSTANCES

Dictyopterenes C′[(−)-**3**] and D′ [ectocarpene: (+)-**2**] have been isolated as "Ocean smell" from the essential oils of brown algae, *Dictopteris plagiogramma* (Montagne) *Vickers; D. australis* Sonder,[12-14] *D. prolifera* and *D. undulata*[15,16] together with dictyopterenes A [(+)-**7**] and B [(−)-**8**]. The thermal rearrangement of the con-

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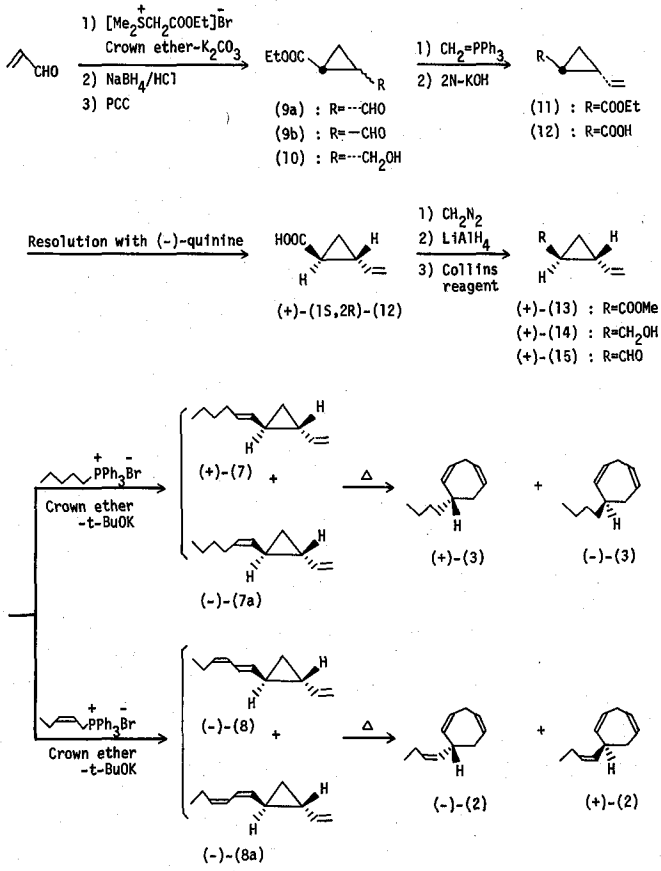
* *cis, trans*-notation for stereochemical structure of the cyclopropane ring.

stituents of "Ocean smell" [(+)-**7** and (−)-**8**] to male-gamete attractants [(+)-**3** and (−)-**2**], respectively, stimulated syntheses of **7**[17-22] and **8**[23] in racemic forms. However, optically active dictyopterenes have not been synthesized so far. Thus, the authors studied on stereoselective syntheses of (+)-dictyopterene A [(+)-**7**], (−)-dictyopterene B[(−)-**8**], and the related compounds as shown in Scheme 1.[32]



Scheme 1. Synthetic Route of Dictyopterenes A and B, and Their Geometrical Isomers.

In the first stage of the synthetic route, the key synthon, ethyl *trans*-2-formylcyclopropanecarboxylate (**9a**) was prepared by condensation of acrolein with the ylid of carboethoxymethyl dimethylsulfonium bromide (the method of Payne)[24] or the sulfonium salt (a modified method)[25] in liquid-solid two-phase systems using crown ethers. With the modified method, to a mixture of the sulfonium halide, bases and crown ether in THF and/or dichloromethane, was added the unsaturated aldehyde at room temperature and **9a** was obtained in 60–70% yields after stirring for a while (Table I). From the data in Table I, it was found that the *trans*-isomer (**9a**) is selectively produced in THF using 18-crown-6-potassium carbonate and in the absence of crown ethers, little or no cyclopropane is formed. A major advantage of this procedure is the simplicity of the one step reaction to afford selectively the *trans*-isomer in

Table I. Crown Ether and Solvent Effects in the Formation of **9a** and **7a** in Liquid-solid Two-phase Systems.

Solvent	Base and Catalyst	trans/cis[a] (*E*)/(*Z*)	Yield (%)
formation of cyclopropanes		(*trans*/*cis*)	
THF	K_2CO_3 18-crown-6	95/ 5	58[b]
THF+CH_2Cl_2[f]	K_2CO_3 18-crown-6	88/12	62[c]
CH_2Cl_2	K_2CO_3 18-crown-6	87/13	67[c]
CH_2Cl_2	NaOH 18-crown-6	81/19	71[c]
formation of alkenes		(*E*/*Z*)	
THF	t-BuOK 18-crown-6	5/95	77[d]
$C_2H_5OC_2H_5$	t-BuOK 18-crown-6	7/93	70[e]
CH_2Cl_2	t-BuOK 18-crown-6	10/90	80[e]
THF	t-BuOK Dibenzo-18-crown-6	6/94	60[e]
CH_2Cl_2	t-BuOK Dibenzo-18-crown-6	9/91	65[e]

a Determined by GLC. b Distilled yield of **9a**+**9b**.
c GLC yield of **9a**+**9b**. d Distilled yield of **7**+**7a**.
e GLC yield of **7**+**7a** f THF: CH_2Cl_2/50: 50

satisfactory yields. This procedure promises to be a general method for syntheses of functionalized cyclopropanes from S-ylids and α, β-unsaturated aldehydes.

In the next step the Wittig reaction between the *trans*-aldehyde (**9a**) and methylidenetriphenylphosphorane afforded ethyl 2-vinylcyclopropanecarboxylate (**11**) (90%). The ethyl ester (**11**) was hydrolyzed to 2-vinylcyclopropanecarboxylic acid (**12**). Chemical resolution of the carboxylic acid (**12**) with (−)-quinine gave (+)-**12**; $[\alpha]_D^{26}+178°$. The absolute configuration of (+)-**12** was determined to be 1*S*: 2*R* since the Lemieux oxidation of this (+)-acid, gave (+)-(*R*, *R*)-*trans*-1,2-cyclopropanedicarboxylic acid which after Sephadex LH-20 column chromatography and recrystallization from acetonitrile had mp 175–177° and $[\alpha]_D^{26}+201°$.[26] The optical purity of (+)-**12**, $[\alpha]_D^{26}+178°$, was evaluated to be 85% from both the rotation value of the derived dicarboxylic acid and the enantiomeric composition on glc analysis of the diastereomeric esters of (+)-**12** with (−)-(*R*)-2-octanol. Thus, the maximum rotation of (+)-(1*S*, 2*R*)-**12** should be $[\alpha]_D^{26}+210°$ in ethanol.

Esterification of (+)-**12** with diazomethane and the subsequent reduction with $LiAlH_4$, gave a hydroxy-cyclopropane, [(+)-**14**] (92%); $[\alpha]_D^{26}+54°$.

This alcohol [(+)-**14**] was oxidized with Collins reagent[27] to an aldehyde [(+)-**15**] (88%), $[\alpha]_D^{26}+161°$.

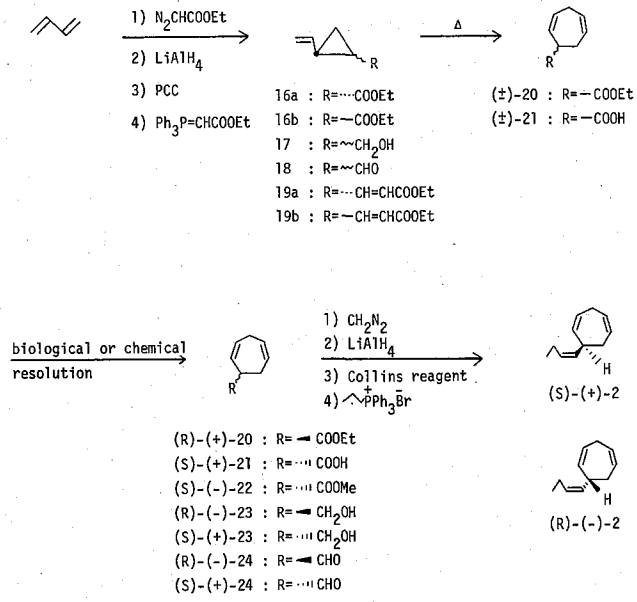
In the final stage of the synthetic route, the Wittig reaction of (+)-**15** with a pentylidenetriphenylphosphorane afforded a geometrical mixture of dictyopterene

A [(+)-**7**] and the (*Z*)-isomer [(−)-**7a**] (65%, *E*/*Z*=40/60) according to the method of Schlosser.[28] The glc separation of the mixture [(+)-**7** and (−)-**7a**] allowed the isolation of (+)-**7**, $[\alpha]_D^{26}$ +65°, which was found to be identical with the natural (+)-dictyopterene A in *D. prolifera*[15,16] and *D. undulata*[16] in all respects except the magnitude of optical rotation. The synthetic compound (+)-**7** had 87% optical purity on the basis of the reported $[\alpha]_D^{25}$ +72° (*c*=6.74, $CHCl_3$), 96.3% optical purity of naturally occurring dictyopterene A.[14]

On the other hands, the geometrical isomer [(−)-**7a**] is stereoselectively prepared according to the method of Boden[25] as indicated in Table I. The Wittig reaction between the aldehyde [(+)-**15**], $[\alpha]_D^{26}$ +161°, and amyltriphenylphosphonium bromide in THF using crown ether-*t*-BuOK at −10°C, gave exclusively the geometrical (*Z*)-isomer [(−)-**7a**] of dictyopterene A, (77%), $[\alpha]_D^{26}$-123°. The geometrical purity of (−)-**7a** was found to be 95% by glc analysis.

According to the method of Schlosser,[28] a mixture of (−)-**8** and (−)-**8a** was obtained by the Wittig reaction of the aldehyde [(+)-**15**], $[\alpha]_D^{26}$ +161°, with (*Z*)-2-pentenylidenetriphenylphosphorane in a mixed solvent of diethyl ether and THF. The mixture of **8** and **8a** was partially rearranged to an enantiomer [(−)-**2**] of the naturally occurring ectocarpene [(+)-**2**] during glc analysis. The retention times of the rearranged isomer (−)-**2** and the synthetic (−)-**8** were identical with those of natural dictyopterene B and ectocarpene, respectively, in the essential oils of *D. prolifera*[15,16] and *D. undulata*.[16] To discuss the relationship between biological activity and absolute configuration of ectocarpene, highly optical-active ectocarpene [(+)-**2**] and its antipode [(−)-**2**] were stereoselectively synthesized *via* biological and chemical resolution using microorganism and (−)-quinine.[33]

As shown in Scheme 2, the copper-catalyzed reaction of ethyl diazoacetate and



Scheme 2. Synthetic Route of Ectocarpene and Its Antipode.

1, 3-butadiene gave a mixture of ethyl *trans*- and *cis*-2-vinylcyclopropanecarboxylate[29] (**16a**: **16b**=55: 45) (24%), which were reduced to the alcohols **17** with $LiAlH_4$. Oxidation of **17** with PPC[30] gave the aldehydes (**18**) (57%), which were converted into a mixture of cyclopropane ester **19a** and cycloheptadiene ester (±)-**20** (55: 45) (97%)[31] by the Wittig reaction between **18** and ethoxycarbonylmethylenetriphenylphosphorane in CH_2Cl_2. The *cis*-cyclopropane ester **19b** produced during the Wittig reaction, rearranged to (±)-**20** spontaneously and the *trans*-isomer **19a** was then quantitatively converted into the cycloheptadiene ester (±)-**20** by refluxing in xylene or non-sensitized photochemical reaction in benzene. This racemic cycloheptadiene ester (±)-**20** was resolved by microbiological asymmetric hydrolysis with *Rhodotorula* and the corresponding carboxylic acid (±)-**21** was resolved with (−)-quinine.

From the result of screening of our stocked fourty microorganisms, eight microorganisms in Table II were selected for asymmetric hydrolysis of (±)-**20**. *Rhodotorula minuta* var. *texensis* IFO 1102, *Rhodotorula minuta* var. *texensis* IFO 0412, *Rhodotorula glutinis* var. *rebescens* IFO 0413 and *Rhodotorula glutinis* IFO 0711 were found to have the enzyme activity to hydrolyze enantioselectively the cycloheptadiene ester (±)-**20** to the corresponding carboxylic acid. The enantioselectivity on the hydrolysis of (±)-**20** was different by used microorganisms.

Table II. Enatioselective Hydrolysis of the Ethyl Ester (±)-**20** to the Corresponding Carboxylic Acid with Microorganisms.

Microorganism[a]	Shaking time (hr)	Hydrolytic ratio (%)	$[\alpha]_D^{27}$	*e.e.* (%)
Rhodotorula				
minuta var. *texensis* IFO 1102	72	15	+8.9°	89
minuta var. *texensis* IFO 0412	72	18	+6.6°	66
glutinis var. *rebescens* IFO 0413	72	22	+1.5°	15
glutinis IFO 0711	72	29	+1.4°	14
rubra IFO 0714	72	24	0°	0
Enterobacter				
aerogenes IFO 3317	72	3	0°	0
Bacillus				
subtilis IFO 3026	18	100	0°	0
Baker's yeast	9	28	0°	0

a: Dried cell (0.5 g)/substrate (1.0 g)/potassium phosphate buffer, pH 7.0 (100 ml).

The preparative scale hydrolysis was carried out using *Rhodotorula minuta* var. *texensis* IFO 1102 with substrate concentration of 1% as shown in Table III. When hydrolytic ratio was attained to 14%, the optically active carboxylic acid (*S*)-(+)-**21**, $[\alpha]_D^{30}$ +8.9° (*c*=1.74, EtOH, 89% optical purity) and the ester (+)-**20**, $[\alpha]_D^{30}$ +0.3° (*c*=10.1, EtOH) were isolated. This carboxylic acid [(+)-**21**] was converted to an antipode [(−)-**2**] of ectocarpene [(+)-**2**] as shown in Fig. 2. Thus, the absolute configuration of (+)-**21** was determined as (*S*) and the optical purity of (+)-**21**, $[\alpha]_D^{28}$ +8.9°, was evaluated to be 89% from the reported maximum rotation value of

Table III. Preparative Asymmetric Hydrolysis by *Rhodotrula minuta* var. *texensis* IFO 1102

Substrate (**20**)[a]		Hydrolytic ratio (%)	Carboxylic Acid [(+)-**21**]		Ethyl Ester [(+)-**20**]	
$[\alpha]_D$, (g)	*Rhodotorula* dried cells (g)		Yield (g)[b]	$[\alpha]_D$ (% *e.e.*)	Yield (g)[b],	$[\alpha]_D$ (% *e.e.*)
0°	14.0/7.0	14	1.3	+8.9° (89)	6.5	+0.3° (14)
+0.3°	6.5/3.5	15	0.6	+5.6° (56)	2.7	+0.8° (36)
+0.8°	2.7/1.4	55	0.7	+1.1° (11)	0.7	+1.7° (78)

a: Substrate concentration of 1% (potassium phosphate buffer, pH 7.0).
b: Isolated yield. The total recovery of the carboxylic acid and the ester was generally low (~50%).

ectocarpene [$[\alpha]_D^{23}$ +75°][14] and the enantiomeric composition on GLC analysis of the diastereomeric esters of (+)-**21** with (−)-(*R*)-2-octanol.

To obtain (*R*)-(+)-**20** with high optical purity, the recovered ester (+)-**20**, $[\alpha]_D^{30}$ +0.3°, was again treated with the same microorganism to give a mixture of the carboxylic acid (+)-**21**, $[\alpha]_D^{30}$ +5.6° (*c*=1.39, EtOH, 56% *e.e.*), and the ester (+)-**20**, $[\alpha]_D^{30}$ +0.8° (*c*=1.06, EtOH, 36% *e.e.*). The further enantioselective hydrolysis of the isolated ester (36% *e.e.*) gave (*R*)-(+)-**20** with highest optical purity, $[\alpha]_D^{30}$ +1.7° (*c*=1.04, EtOH, 78% *e.e.*) at 55% hydrolytic ratio.

On the other hand, resolution of (±)-**21** with (−)-quinine gave (*S*)-(+)-**21** (95% *e.e.*) and (*R*)-(−)-**21** (*e.e.*~38%).

(*S*)-(+)-2,5-Cycloheptadienecarboxylic acid [(+)-**21**, 95% *e.e.*] and (*R*)-(+)-ethyl 2, 5-cycloheptadienecarboxylate [(+)-**20**, 78% *e.e.*] thus obtained, were reduced to the corresponding alcohols [(*S*)-(+)-**23**: $[\alpha]_D^{32}$ +8.5° and (*R*)-(−)-**23**: $[\alpha]_D^{32}$ −7.0°], respectively. Pilot experiments for oxidation of the alcohol (±)-**23** to the aldehyde (±)-**24** indicates that Collins reagent[27] is best for oxidation of the 2, 5-cycloheptadiene alcohol because isomerization of the double bond at C-2 of (±)-**23** to the conjugated system (1, 5-heptadienylcarbaldehyde) was not observed. Thus, both enantiomers of the alcohol [(+)-**23** and (−)-**23**] were oxidized to the aldehydes [(*S*)-(+)-**24** and (*R*)-(−)-**24**] with Collins reagent, respectively.

The Wittig reaction of the aldehydes [(*S*-(+)-**24** and (*R*)-(−)-**24**] with propyltriphenylphosphonium bromide in THF in solid-liquid two phase using 18-crown ether-*t*-BuOK afforded practically pure (*Z*)-olefins, (*R*)-(−)-**2**; $[\alpha]_D^{34}$ −68.4° (*e.e.* 95%) and (*S*)-(+)-**2**; $[\alpha]_D^{34}$ +56.2°, ectocarpene (*e.e.* 78%), respectively.

The synthetic ectocarpene and its enantiomer were identical except the magnitude of optical rotation, with the thermally rearranged isomers [(+)-**2** ($[\alpha]_D^{26}$ +11.3°) and (−)-**2** ($[\alpha]_D^{26}$-11.0°)], respectively, from (*S*, *S*)-(+)-1-[(*E*, *Z*)-hexa-1′, 3′-dienyl]-2-vinylcyclopropane (containing geometrical isomer, $[\alpha]_D^{26}$ +77°) and dictyopterene B (partially optical active, $[\alpha]_D^{26}$ −37°).[14,32] The retention times of the synthesized ectocarpene and its antipode were identical with those of natural ectocarpene in the essential oils of *D. prolifera* and *D. undulata*.[16]

More recently, the syntheses of other chiral attractants[34,35]-multifidene* (**4**),

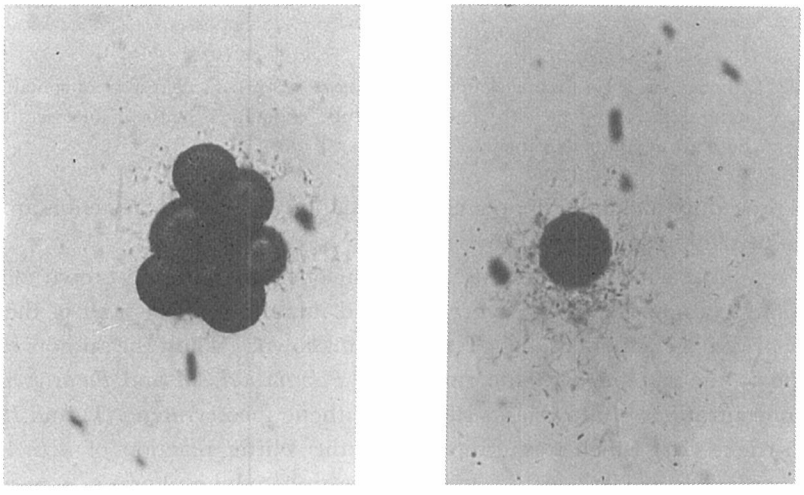
desmarestene* (**5**) and viridiene* (**6**)- have aroused keen interest from receptor specificity and threshold concentration in the Phaeophyte.

III. MALE GAMETE-ATTRACTING SUBSTANCE IN HERMAPHRODITE BROWN ALGAE, *PELVETIA WRIGHTII* AND *FUCUS EVANESCENS*.

Müller and Jaenicke[5,6], in 1973, isolated the volatile attractant of spermatozoids, (3*E*, 5*Z*)-octa-1,3,5-triene (fucoserratene, **1**) from the eggs and oogonia of a dioecious brown alga, *Fucus serratus*. However, male gamete-attracting substances of hermaphrodite brown algae have not been explored so far.

Hermaphrodite brown algae, *Pelvetia wrightii* and *F. evanescens* were collected in the tidal flat along the Charatsunai coast of Muroran, Hokkaido, October and June respectively. The mature receptacles which were detached from the plants, were wiped with gauze and rinsed in filtered sea water to remove diatoms and microorganisms.[36] The cleaned receptacles were kept at 18°C in a growth chamber illuminated with white fluorescent lamps at about 2500 lux for 8 hr and then transferred to Yamaguchi University, in a container at 5°C with dry ice.

When the receptacles cold-treated were soaked in sea water, the ripe female gametes of *Fucus* attracted male gametes released from antherida as shown in Fig. 1. Thus, the attractant was extracted as follows. The treated receptacles (22.4 kg) emerged the contents of the conceptacles were soaked in MeOH saturated with pentane for 3 days and pentane-soluble portion was chromatographed on an alumina gel and florisil gel with pentane. Early fractions were further separated by $AgNO_3$-silica gel column chromatography followed by preparative glc. The structure of the attractant

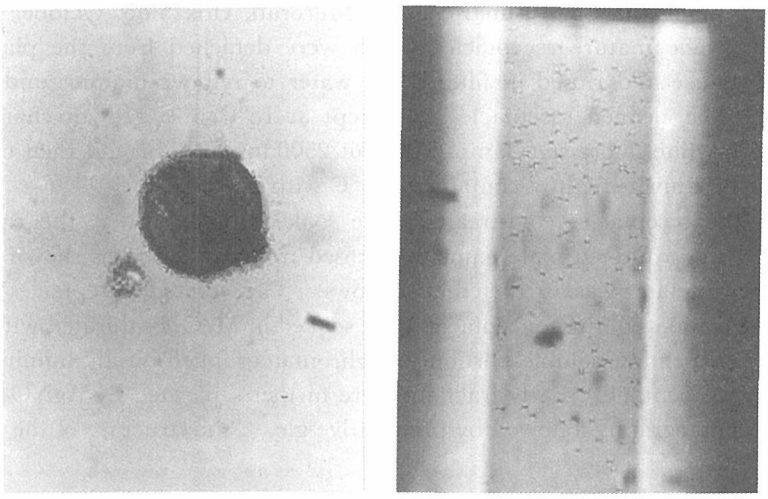


(a) (b)

Fig. 1. Chemotaxis of a hermaphrodite brown alga, *F. evanescens*.
(a) an oogonium containing eight female gametes attracts male gametes. (b) a female gamete attracting male gametes.

* The configurations are still unknown.

was fully substantiated by comparison of UV, MS, ^{1}H–NMR and ^{13}C–NMR data[5,37] with those of authentic **1** which was prepared by a Wittig reaction between **1**, *trans*-3-pentadienal and propyltriphenyl phosphonium bromide in THF in solid-liquid two phase using 18-crown ether-*t*-BuOK.[38] The separated attractant was found to show spermatozoid-attracting activity of spermatozoids like synthetic (3*E*, 5*Z*)-octa-1,3,5-triene as shown in Fig. 2. The natural **1** from *P. wrightii* was shown to contain a small amount (~5%) of (3*E*, 5*E*)-octa-1,3,5-triene (**1a**)[39-40] by ^{13}C–NMR. From a hermaphrodite alga, *F. evanescens*, the male-gamete attractant, **1** (4×10^{-5}% based on the weight of fresh receptacles), was separated according to the procedure described above.



(a) (b)

Fig. 2. Chemotaxis assay for male gametes of *F. evanescens*. (a) a spherosil bead containing natural fucoserratene, (b) a capillary tube containing synthetic fucoserratene, both attracting male gametes.

This procedure including fluorescent illumination and cold treatment is an effective method of attractants extraction.[41]

The roles of **1a** in the seriated sex behavior of hermaphrodite brown algae, particularly and examination of the synergistic and inhibitory effects and of the species-specificity of sexual chemotaxis, have remained unknown. Thus, the authors examined quantitatively the response of male gametes of *Pelvetia wrightii* and *Fucus evanescens* to various concentrations of attractants such as synthetic fucoserratene (**1**) and (3*E*, 5*E*)-octa-1,3,5-triene (**1a**) which were prepared by the Wittig reaction of (2*E*, 4*Z*)- and (2*E*, 4*E*)-hepta-2,4-dienals with methylidenetriphenylphosphorane, respectively. The (*E*)-isomer (**1a**) of fucoserratene (**1**) was found to have attractive properties. However, the threshold concentration is ca. 10 times higher than that of synthetic fucoserratene according to the method of Müller.[42] The addition of (*E*)-isomer to fucoserratene did not substantially affect to attraction of male-gametes. From these facts and findings, fucoserratene may be considered to be the only intrinsic attractant.[43]

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