Synthesis of Anacardic Acids, 6-[8(*Z*),11(*Z*)-Pentadecadienyl]salicylic Acid and 6-[8(*Z*),11(*Z*),14-Pentadecatrienyl]salicylic Acid

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11-Chloro-3-methoxy-2-undecenal was synthesized from 8-bromooctanol, and an annelation reaction with this aldehyde and ethyl acetoacetate proceeded to give the ethyl 6-(8-chlorooctyl)salicylate. Ethyl 6-(8-chlorooctyl)salicylate was converted to ethyl 6-(7-formylheptyl)-2-methoxybenzoate through the iodide after protection of the phenolic hydroxyl group. Finally, the Wittig reaction with the aldehyde and triphenylphosphonium iodides in the presence of BuLi gave the methoxybenzoates, and then treatments of these methoxybenzoates with BBr_3 in CH_2Cl_2 and 10% NaOH in ethanol gave 6-[8(*Z*),11(*Z*)-pentadecadienyl]salicylic acid (anacardic acid 3) and 6-[8(*Z*),11(*Z*),14-pentadecatrienyl]salicylic acid (anacardic acid 4) which were isolated from plants of the anacardiaceae.

Key words anacardic acid; synthesis; annelation reaction; aldehyde

It is known that constituents of cashew-nut shells (*Anacardium occidentate*, anacardiaceae), anacardic acids are a mixture of four 6-alkylsalicylic acids, 6-pentadecylsalicylic acid (**1**), 6-[8(*Z*)-pentadecenyl]salicylic acid (**2**), 6-[8(*Z*),-11(*Z*)-pentadecadienyl]salicylic acid (**3**), and 6-[8(*Z*),11(*Z*),-14-pentadecatrienyl]salicylic acid (**4**) (Chart 1).[1] These compounds have shown various physiological activities, inhibition of prostaglandin synthesis, antifeedant activities and antitumor activities such as those described in refs. 2—4.

On the other hand, many methods for synthesizing anacardic acids **1** and **2** from a benzene skeletal structure have been reported,[5—8] and we have reported methods for synthesizing anacardic acids **1** and **2** utilizing an annelation reaction by means of the combination of two synthons, that is to say, *via* isoxazole derivertives[9] and 3-methoxyaclolein derivatives.[10]

However, no detailed studies on the synthesis of anacardic acids **3** and **4** which have two or three double bonds in the sidechain have been reported. Therefore, we have studied methods for the synthetic preparation of **3** and **4** according to our previous report.[10] First, we planned to synthesize anacardic acid **3** by performing a condensation and an annelation reaction with the 3-methoxyaclolein derivative (**6**) and dianion of ethyl acetoacetate after we composed the sidechain function (**5**) of anacardic acid **3**, and after the part of the alcohol was changed into 3-methoxyaclolein derivative (**6**) (Chart 2). We tried various methods for the synthesis of **5** as shown in Chart 3, but it was difficult to prepare the desired compound.

Thus we attempted to induce an annelation reaction in advance of the synthesis of the sidechain function. Several 3-methoxyacrolein derivatives were synthesized and investigated regarding the condensation and an annelation reaction to yield salicylate. In consequence, only 11-chloro-3-methoxyaclorein was condensed with ethyl acetoacetate to give the condensed product, 6-(8-chlorooctyl)salicylate. As shown in Chart 4, 11-chloro-3-methoxyaclorein (**11**) was synthesized from 8-bromooctanol (**7**), that is to say, bromoalcohol was converted into 1-bromo-8-chlorooctane (**8**), and then the coupling reaction of the chloride with 3,3-diethoxy-1-propyne in the presence of butyllithium (BuLi) and hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF) gave the coupling product (**9**), in a 89.4% yield as a colorless oil, which was treated with H_3PO_4 and hydroquinone in dioxane to give the aldehyde (**10**) followed by MeONa in methanol to yield the 11-chloro-3-methoxy-2-undecenal (**11**). An annelation reaction with this aldehyde and ethyl acetoacetate proceeded to give the salycilate (**12**) in a 43.6% yield (Chart 4).

Next, we tried to synthesize anacardic acid **2** from **12** as the preliminary experiment in order to establish the synthetic method for preparation of anacardic acids **3** and **4**. 6-(8-Chlorooctyl)salicylate (**12**) was converted to aldehyde (**15**) through the iodide (**14**) after a protection of phenolic hydroxyl group (**13**). Kamikawa and co-workers synthesized ethyl 2-methoxy-6-[8(*Z*)-pentadecenyl]benzoate (**17**) which was derivative of anacardic acid **2** utilizing the Wittig reaction employing this aldehyde (**15**) and heptyltriphenylphosphonium iodide (**16**).[5] According to the above method after it proceeded through the Witting reaction with **15** and **16**, we obtained the product (**17**) in a 76.4% yield. The protecting groups were removed by successive treatments with BBr_3 in CH_2Cl_2 and 10% NaOH in ethanol to give the anacardic acid

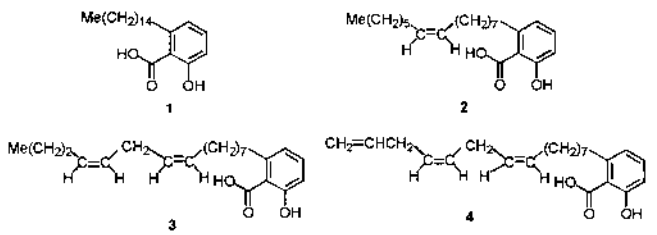

Chart 1

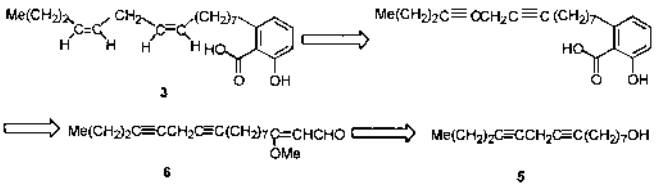

Chart 2

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2 in a 62.2% yield from **17** (Chart 5).

Consequently, it was anticipated that anacardic acids **3** and **4** were synthesized from aldehyde (**15**). Therefore, we tried to synthesize the sidechain functions of anacardic acid **3** and **4** from 3-butynol. The coupling reaction of 3-butynol (**19**) with alkyl iodide in the presence of BuLi and HMPA in THF gave the coupling products (**20**: 70.6%, **24**: 90.4%), which were reduced with Lindlar catalyst in quinoline and hexane to yield the *cis*-alkenyl alcohols (**21**: 65.1%, **25**: 75.3%) as colorless oils. These *cis*-alkenyl alcohols were treated with iodine in the presence of PPh_3 and imidazole to give the iodides (**22**: 65.5%, **26**: 71.9%) as colorless oils, which were converted to derivatives of triphenylphosphonium iodides (**23**: 95.5%, **27**: 99.3%) with PPh_3 in acetonitrile. Finally, The Wittig reaction with these triphenylphosphonium iodides (**23**, **27**) and aldehyde (**15**) in the presence of BuLi gave the

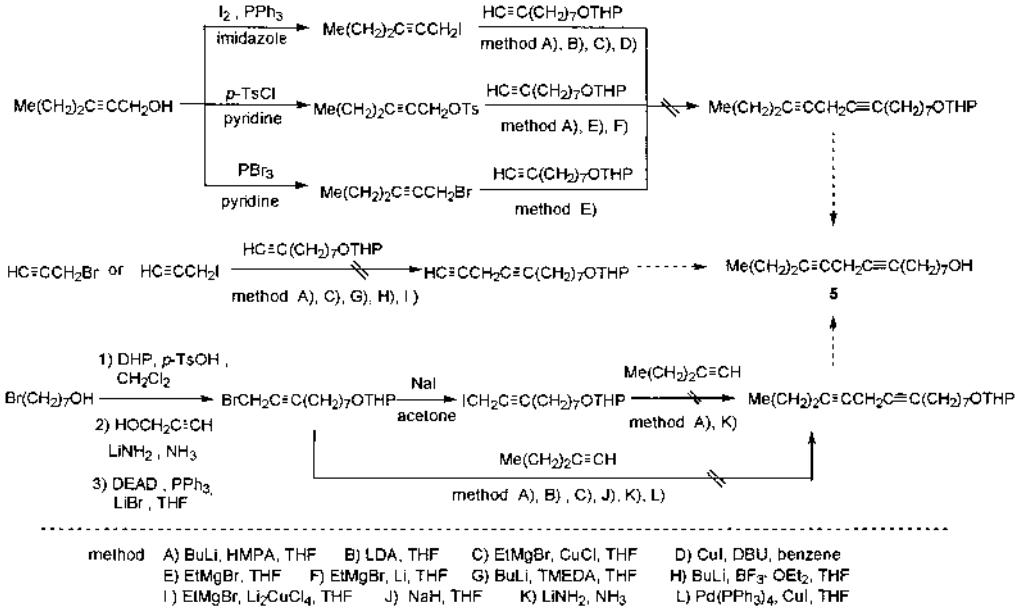

Chart 3

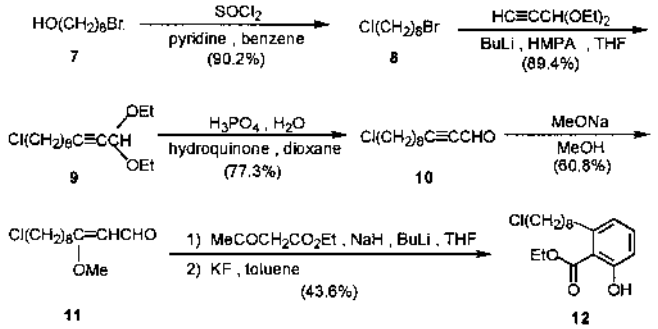

Chart 4

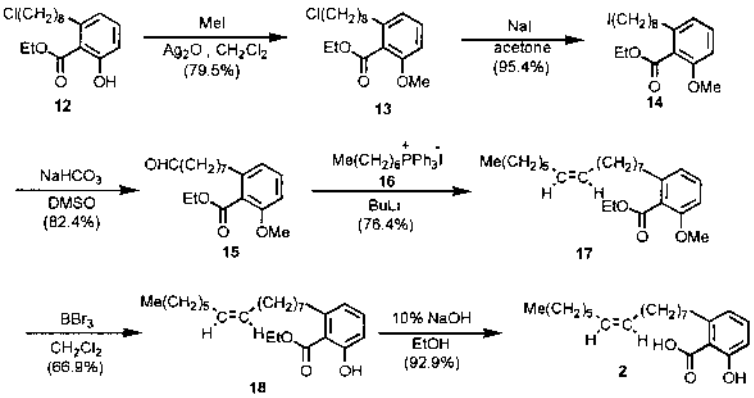

Chart 5

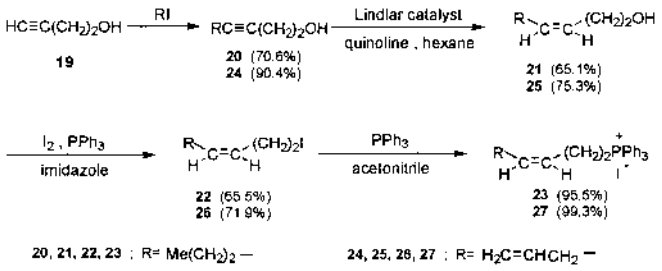

Chart 6

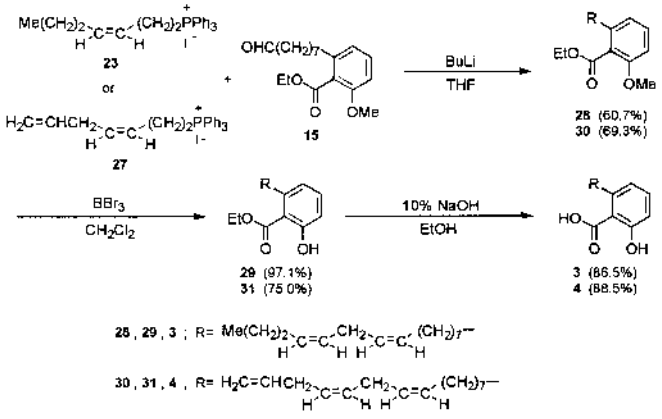

Chart 7

methoxybenzoates (**28**: 60.7%, **30**: 69.3%), and then treatments of these methoxybenzoates (**28**, **30**) with BBr_3 in CH_2Cl_2 and 10% NaOH in ethanol gave anacardic acids **3** and **4** in 84.0% (**28**→**3**) and 66.4% (**30**→**4**) yields (Charts 6, 7). All physical data for synthetic products **3** and **4** showed structures for **3** and **4**.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus. IR spectra were recorded with Hitachi 260-10 spectrometer and JEOL A-202 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-EX90 and JEOL JNM-α500 spectrometer in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a JEOL JMS-D 300. Waco-gel was used for column chromatography.

1-Bromo-8-chlorooctane (8) A solution of 8-bromooctanol (198.6 mg) in benzene (2 ml) and pyridine (126.6 mg) was heated to 60 °C under a nitrogen atmosphere. After thionyl chloride (116 μl) was added dropwise with stirring, the mixture was stirred at 75 °C for 7 h. The reaction mixture was treated with cold water and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=4 : 1) to yield 195.3 mg (90.2%) of **8** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.34—1.48 (8H, m), 1.70—1.86 (4H, m), 3.42 (2H, t, J=6.7 Hz), 3.54 (2H, t, J=6.6 Hz).

11-Chloro-1,1-Diethoxy-2-undecyne (9) BuLi in hexane (1.66 M, 18.6 ml) and HMPA (2.44 ml) were successively added dropwise to a stirred solution of propiolaldehyde diethylacetal (1.79 g) in THF (30 ml) at 0 °C under a nitrogen atmosphere. After 30 min, a solution of **8** (1.57 g) in THF (5 ml) was added to the reaction mixture and the whole was stirred at 0 °C for 1 h under a nitrogen. And then the reaction mixture was quenched with saturated NH_4Cl solution, extracted with AcOEt, washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=3 : 2) to yield 1.72 g (89.4%) of **9** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2242. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (6H, t, J=7.0 Hz), 1.28—1.56 (10H, m), 1.77 (2H, m), 2.24 (2H, dt, J=7.1, 1.7 Hz), 3.57 (4H, m), 3.74 (2H, m), 5.26 (1H, t, J=1.7 Hz). Chemical ionization (CI)-MS m/z: 273, 275 (M^++1).

11-Chloro-2-undecynal (10) H_2O (48 ml), 85% H_3PO_4 (26 ml) and hydroquinone (910 mg) was added to a solutoin of **9** (2.29 g) in dioxane (150 ml) and the mixture was refluxed at 100 °C for 4.5 h. The reaction mixture was concentrated under vacuum. An aqueous solution of the residue was then extracted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=1 : 1) to yield 1.29 g (77.3%) of **10** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2238, 2202, 1710, 1673. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.80 (12H, m), 2.39 (2H, t, J=7.0 Hz), 3.54 (2H, t, J=6.7 Hz), 9.18 (1H, s). CI-MS m/z: 201, 203 (M^++1).

11-Chloro-3-methoxy-2-undecenal (11) Sodium methoxide (1.0 M, 1.8 ml) was added to a solutoin of **10** (301.5 mg) in anhydrous methanol (10 ml) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was treated with water, and acidified with 10% HCl and then extracted with diethyl ether. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 212.6 mg (60.8%) of **11** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1660, 1607. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.80 (12H, m), 2.60 (2H, t, J=7.4 Hz), 3.53 (2H, t, J=6.5 Hz), 3.68 (3H, s), 5.38 (1H, d, J=7.8 Hz), 9.80 (1H, d, J=7.8 Hz). CI-MS m/z: 233, 235 (M^++1).

Ethyl 6-(8-Chlorooctyl)salicylate (12) A solution of ethyl acetoacetate (1.67 g) in THF (20 ml) was treated with NaH (362 mg) and stirred at 0 °C for 10 min under nitrogen, BuLi (1.65 M, 9.15 ml) in hexane was then added dropwise with stirring. After the reaction mixture was cooled to −30 °C, **11** (167.1 mg) in THF (1 ml) was added to the reaction mixture, and the whole was stirred at −30 °C for 3.5 h under a nitrogen. The reaction mixture was quenched with saturated NH_4Cl, and acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. A solution of the residue in toluene (30 ml) and KF (836.6 mg) was refluxed for 15 h. The reaction mixture was concentrated under a vacuum. A solution of the residue in H_2O was extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 98.2 mg (43.6%) of **12** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1659, 1609, 1576. ^{1}H-NMR ($CDCl_3$) δ: 1.25—1.80 (12H, m), 1.44 (3H, t, J=7.1 Hz), 2.90 (2H, dd, J=7.6, 6.1 Hz), 3.54 (2H, t, J=6.7 Hz), 4.44 (2H, q, J=7.1 Hz), 6.71 (1H, dd, J=7.3, 1.2 Hz), 6.84 (1H, dd, J=8.2, 1.2 Hz), 7.29 (1H, dd, J=8.2, 7.3 Hz), 11.23 (1H, s). High-MS m/z: 312.1551, 314.1505 (Calcd for $C_{17}H_{25}ClO_3$: 312.1546, 314.1463).

Ethyl 6-(8-Chlorooctyl)-2-methoxybenzoate (13) Ag_2O (46.4 mg) and MeI (249 μl) was added to a solution of **12** (15.9 mg) in CH_2Cl_2 (2 ml) and the mixture was stirred at room temperature for 24 h. After filtration, the reaction mixture was concentrated under a vacuum. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 13.0 mg (79.5%) of **13** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1730, 1584. ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.70 (12H, m), 1.37 (3H, t, J=7.2 Hz), 2.55 (2H, t, J=7.4 Hz), 3.52 (2H, t, J=6.5 Hz), 3.81 (3H, s), 4.39 (2H, q, J=7.2 Hz), 6.75 (1H, d, J=8.1 Hz), 6.80 (1H, d, J=7.2 Hz), 7.26 (1H, dd, J=7.2, 8.1 Hz). High-MS m/z: 326.1647, 328.1688 (Calcd for $C_{18}H_{27}ClO_3$: 326.1547, 328.1620).

Ethyl 6-(8-Iodooctyl)-2-methoxybenzoate (14) A solution of **13** (9.5 mg) and NaI (45 mg) in acetone was refluxed for 24 h. The reaction mixture was quenched with cold water, extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 11.6 mg (95.4%) of **14** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1732, 1585. ^{1}H-NMR ($CDCl_3$) δ: 1.29—1.38 (8H, m), 1.38 (3H, t, J=7.1 Hz), 1.59 (2H, m), 1.81 (2H, quin, J=7.0 Hz), 2.55 (2H, t, J=7.9 Hz), 3.18 (2H, t, J=7.0 Hz), 3.81 (3H, s), 4.39 (2H, q, J=7.1 Hz), 6.76 (1H, d, J=7.8 Hz), 6.81 (1H, d, J=7.8 Hz), 7.26 (1H, t, J=7.8 Hz). High-MS m/z: 418.1032 (Calcd for $C_{18}H_{27}IO_3$: 418.1008).

Ethyl 6-(7-Formylheptyl)-2-methoxybenzoate (15) **14** and $NaHCO_3$ (8.4 mg) were dissolved with dimethyl sulfoxide (DMSO) (2 ml), and the whole was stirred at 90 °C for 11 h under nitrogen. The reaction mixture was treated with cold water and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 12.3 mg (82.4%) of **15** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1730, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.26—1.64 (10H, m), 1.37 (3H, t, J=7.0 Hz), 2.41 (2H, dt, J=7.3, 1.8 Hz), 2.55 (2H, t, J=7.8 Hz), 3.81 (3H, s), 4.39 (2H, q, J=7.1 Hz), 6.76 (1H, d, J=7.8 Hz), 6.80 (1H, d, J=7.8 Hz), 7.26 (1H, t, J=7.8 Hz), 9.75 (1H, t, J=1.8 Hz). High-MS m/z: 306.1865 (Calcd for

$C_{18}H_{26}O_4$: 306.1830).

Hepthyltriphenylphosphonium Iodide (16) PPh_3 (1.73 g) was added to a solution of 1-iodoheptane (995 mg) in acetonitrile (30 ml), and the whole was stirred at 90 °C for 24 h under nitrogen. The mixture was allowed to stand at room temperature for 18 h with stirring. After filtration, the solid obtained was washed with THF to yield 1.92 g (97.1%) of **16** as a colorless solid. This compound was employed for next reaction without purification. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t, J=5.6 Hz), 1.10—1.80 (10H, m), 3.45—3.85 (2H, m), 7.66—7.96 (15H, m).

Ethyl 2-Methoxy-6-[8(*Z*)-pentadecenyl]benzoate (17) BuLi (1.58 M, 159 μl) was successively added to a stirred solution of **16** (115 mg) in THF (2 ml) at room temperature under a nitrogen. After 1 h, a solution of **15** (14.4 mg) in THF was added to the reaction mixture and the whole was stirred at 0 °C for 30 min under a nitrogen. And then the reaction mixture was quenched with saturated NH_4Cl, extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 13.9 mg (76.4%) of **17** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1730, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.7 Hz), 1.20—1.40 (18H, m), 1.37 (3H, t, J=7.2 Hz), 1.99 (4H, t, J=6.0 Hz), 2.55 (2H, t, J=7.9 Hz), 3.81 (3H, s), 4.39(2H, q, J=7.2 Hz), 5.35 (2H,t, J=5.5 Hz), 6.75 (1H, d, J=7.8 Hz), 6.81 (1H, t, J=7.8 Hz), 7.25 (1H, t, J=7.8 Hz). High-MS m/z: 388.1865 (Calcd for $C_{25}H_{40}O_3$: 388.1830).

Ethyl 6-[8(*Z*)-Pentadecenyl]salycylate (18) A solution of **17** (13.2 mg) in absolute CH_2Cl_2 was added to a solution of BBr_3 (6.4 μl) in anhydrous CH_2Cl_2 at 0 °C under a nitrogen, and the whole was stirred at room temperature for 15 min under a nitrogen. And then the reaction mixture was quenched with cold water and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 8.5 mg (66.9%) of **18** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3100, 1660, 1608. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=5.7 Hz), 1.25—1.60 (21H, m), 1.98 (4H, m), 2.91 (2H, t, J=7.4 Hz), 4.43 (2H, q, J=7.1 Hz), 5.34 (2H, m), 6.71 (1H, dd, J=8.3, 1.3 Hz), 6.81 (1H, dd, J=7.4, 1.3 Hz), 7.28 (1H, dd, J=8.3, 7.4 Hz), 11.20 (1H, s). Low MS m/z: 374 (M^+), High MS m/z Calcd for $C_{24}H_{38}O_3$ (M^+): 374.2821. Found: 374.2827.

6-(8-Pentadecenyl)salicylic Acid (2) A solution of **18** (10.2 mg) in EtOH and 10% NaOH (1 ml) were refluxd for 2 h. A solution of the reaction mixture was acidified with 10% HCl and then extracted with hexane. The organic layer was washed with saturated NaCl solution., dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=1 : 2). The eluate fraction was recrystalized from hexane to yield 9.2 mg (92.9%) of **2** as colorless crystals, mp 45—48 °C. IR ν_{max}^{KBr} cm^{-1}: 2930, 2850, 1650, 1600. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.7 Hz), 1.25—1.60 (18H, m), 1.97 (4H, m), 2.93 (2H, t, J=7.4 Hz), 5.35 (2H, m), 6.71 (1H, dd, J=8.3, 1.3 Hz), 6.81 (1H, dd, J=7.4, 1.3 Hz), 7.28 (1H, dd, J=8.3, 7.4 Hz). Low MS m/z: 346 (M^+). *Anal.* Calcd for $C_{22}H_{34}O_3$: C, 76.25; H, 9.90. Found: C, 76.08; H, 10.06.

3-Heptynol (20) Dihydropyrane (DHP) (4.88 ml) and *p*-toluenesulfonic acid (TsOH) (120 mg) were added to a solution of **19** (3.6 g) in CH_2Cl_2 and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with cold water and saturated $NaHCO_3$ solution, and extructed with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 9.63 g (95.2%) of 1-[2-(tetrahydropyranyl)oxy]-3-butyne as a colorless oil. [IR ν_{max}^{KBr} cm^{-1}: 3270. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.81 (6H, m), 1.97 (1H, t, J=2.6 Hz), 2.49 (2H, dd, J=7.0, 2.6 Hz), 3.44—4.00 (4H, m), 4.64 (1H, br s). CI-MS m/z: 155 (M^++1).] BuLi (1.58 M, 9.45 ml) and HMPA (2.7 ml) were successively added to a solution of 1-[2-(tetrahydropyranyl)oxy]-3-butyne (2.0 g) in THF (10 ml) at 0 °C with stirring. After a solution of propyl iodide (3.79 g) in THF was added to this solution, the whole was stirred at 0 °C for 1 h. The mixture was then allowed to stand at room temperature for 1 h. The reaction mixture was treated with saturated NH_4Cl solution and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 2.07 g (81.4%) of 1-[2-(tetrahydropyranyl)-oxy]-3-heptyne as a colorless oil. [IR ν_{max}^{KBr} cm^{-1}: 2250. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 1.43—1.86 (6H, m), 2.12 (2H, dd, J=7.0, 2.4 Hz), 2.46 (2H, dd, J=7.0, 2.4 Hz), 3.47—3.57 (2H, m), 3.75—3.93 (2H, m), 4.65 (1H, t, J=3.6 Hz). CI-MS m/z: 197 (M^++1). A solution of 1-[2-(tetrahydropyranyl)oxy]-3-heptyne (597 mg) in anhydrous EeOH (20 ml) and pyridinium paratoluenesulfonic acid (PPTS) (153.3 mg) was stirred at 55 °C for 3 h. The reaction mixture was concentrated under vacuum. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 311.2 mg (91.1%) of **20** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3362, 2230. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.45—1.59 (2H, m), 1.87 (1H, br s), 2.15 (2H, dd, J=7.0, 2.4 Hz), 2.44 (2H, dd, J=6.3, 2.4 Hz), 3.68 (2H, br s).

3(*Z*)-Heptenol (21) A mixture of Lindlar's catalyst (Pd $CaCO_3$, 40 mg), quinoline (10 μl) and **20** (193.5 mg) in hexane (4.0 ml) was stirred at room temperature for 16 h under H_2. After the mixture was filtered, 10% HCl was added to the filter liquid and extracted with ether. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=2 : 1) to yield 128.3 mg (65.1%) of **21** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3350, 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.1 Hz), 1.19—1.52 (2H, m), 1.56 (1H, br s), 2.05 (2H, q, J=6.5 Hz), 2.33 (2H, q, J=6.5 Hz), 3.64 (2H, t, J=7.2 Hz), 5.34—5.64 (2H, m).

1-Iodo-3(Z)-heptene (22) A solution of PPh_3 (378 mg) and imidazole (98 mg) in mixture of diethyl ether and acetonitrile (3 : 1, 35 ml) was stirred at 0 °C for 10 min and then iodine (366 mg) was added to this solution. The whole was stirred at 0 °C for 15 min. A solution of **21** (54.4 mg) in mixture of diethyl ether and acetonitrile (3 : 1, 1 ml) was added to this solution with stirring at 0 °C. The mixture was then allowed to stand at room temperature for 1 h. The reaction mixture was treated with saturated $NaHCO_3$ solution and extracted with ether. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 70.4 mg (65.5%) of **22** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1660. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7.1 Hz), 1.20—1.53 (2H, m), 2.01 (2H, q, J=6.7 Hz), 2.63 (2H, q, J=6.7 Hz), 3.13 (2H, t, J=7.2 Hz), 5.29 (1H, m), 5.38 (1H, m).

3(*Z*)-Heptenyltriphenylphosphonyl Iodide (23) PPh_3 (123.5 mg) was added to a solution of **22** (70.4 mg) in acetonitrile (5 ml) and the whole was stirred at 90 °C for 24 h. After the mixture was then allowed to stand at room temperature for 24 h, the reaction mixture was concentrated under vacuum. The residue was washed with diethyl ether. A colorless solid was obtained almost quantitatively, and this compound was employed in the next reaction without purification. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, m), 1.15—1.40 (2H, m), 1.50—1.90 (2H, m), 2.30—2.60 (2H, m), 3.52—3.83 (2H, m), 5.46 (1H, m), 5.54 (1H, m), 7.75—7.97 (15H, m).

6-Hepten-3-ynol (24) A solution of **19** (490.6 mg) in THF (3 ml) was successively added dropwise to a solution of EtMgBr in THF (0.9 M, 23.3 ml) with stirring, and the mixture was stirred at 40 °C for 1 h under a nitrogen atmosphere. After a solution of allyl iodide (3.5 g) in THF (5 ml) was added to this solution, the whole was stirred for 20 min. And then CuCl (21 mg) was added to the reaction mixture, the whole was refluxed for 1 h. The reaction mixture was quenched with cold water and upper solution was removed by decantation. The precipitate was dissolved in THF, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=4 : 1) to yield 695.7 mg (90.4%) of **24** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3352, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (1H, br s), 2.48 (2H, m), 2.97 (2H, m), 3.71 (2H, q, J=5.4 Hz), 5.11 (1H, dt, J=10.0, 1.7 Hz), 5.31 (1H, dt, J=16.9, 1.7 Hz), 5.84 (1H, m).

3(*Z*),6-Heptadienol (25) A mixture of Lindlar's catalyst (Pd $CaCO_3$, 100 mg), quinoline (50 μl) and **24** (550 mg) in hexane (20 ml) was stirred at room temperature for 16 h under H_2. After the mixture was filtered, 10% HCl was added to the filter liquid and extracted with diethyl ether. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=2 : 1) to yield 421.6 mg (75.3%) of **25** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3350, 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (2H, q, J=6.3 Hz), 2.84 (2H, q, J=6.4 Hz), 3.66 (2H, q, J=6.0 Hz), 4.95 (1H, m), 5.15 (1H, m), 5.41 (1H, m), 5.53 (1H, m), 5.68 (1H, m).

1-Iodo-3(*Z*),6-heptadiene (26) A solution of PPh_3 (952 mg) and imidazole (247 mg) in a mixture of diethyl ether and acetonitrile (3 : 1, 60 ml) was stirred at 0 °C for 10 min and then iodine (922 mg) was added to this solution, the whole was stirred at 0 °C for 15 min. A solution of **25** (135.3 mg) in mixture of diethyl ether and acetonitrile (3 : 1, 1 ml) was added to this solution with stirring at 0 °C. The mixture was then allowed to stand at room temperature for 1 h. The reaction mixture was treated with saturated $NaHCO_3$ solution and extracted with diethyl ether. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 70.4 mg (65.5%) of **26** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1640. ^{1}H-NMR ($CDCl_3$) δ: 2.55—2.95 (4H, m), 3.15 (2H, t, J=7.3 Hz), 4.95—5.30 (2H, m), 5.35—6.05 (3H, m).

3(*Z*),6-Heptadienyltriphenylphosphonium Iodide (27) PPh_3 (105.0 mg) was added to a solution of **26** (68.3 mg) in acetonitrile (5 ml), the whole was

stirred at 90 °C for 24 h. After the mixture was then allowed to stand at room temperature for 24 h, the reaction mixture was concentrated under vacuum. The residue was washed with diethyl ether. A colorless solid was obtained almost quantitatively, and this compound was employed in the next reaction without purification. ^{1}H-NMR ($CDCl_3$) δ: 2.32—2.70 (4H, m), 3.67—3.95 (2H, m), 4.75—4.15 (2H, m), 5.30—5.85 (3H, m), 7.20—8.07 (15H, m).

Ethyl 2-Methoxy-6-[8(*Z*),11(*Z*)-pentadecadienyl]benzoate (28) BuLi in hexane (1.58 M, 89 ml) was successively added dropwise to a stirred solution of **23** (68.4 mg) in THF (2 ml) at room temperature under a nitrogen atmosphere. After 1 h, a solution of **15** (10.9 mg) in THF (1 ml) was added to the reaction mixture and the whole was stirred at room temperature for 30 min under a nitrogen atmosphere. And then the reaction mixture was quenched with cold water, extracted with AcOEt, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 9.0 mg (66.7%) of **28** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1730, 1600, 1580, 1480. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, *J*=7.3 Hz), 1.26—1.42 (12H, m), 1.36 (3H, t, *J*=7.2 Hz), 2.04 (4H, m), 2.55 (2H, t, *J*=7.9 Hz), 2.77 (2H, t, *J*=5.6 Hz), 3.81 (3H, s), 4.39 (2H, q, *J*=7.1 Hz), 5.32—5.40 (4H, m), 6.75 (1H, d, *J*=7.9 Hz), 6.81 (1H, d, *J*=7.9 Hz), 7.26 (1H, t, *J*=7.9 Hz). High-MS *m*/*z*: 386.2833 (Calcd for $C_{24}H_{38}O_3$: 386.2821).

Ethyl [8(*Z*),11(*Z*)-Pentadecadienyl]salicylate (29) A solution of **28** (10.9 mg) in absolute CH_2Cl_2 was added to a solution of BBr_3 (5.4 μl) in anhydrous CH_2Cl_2 at 0 °C under a nitrogen, and the whole was stirred at room temperature for 1 h under a nitrogen. And then the reaction mixture was quenched with cold water and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 10.2 mg (97.1%) of **29** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1660, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, *J*=7.3 Hz), 1.22—1.60 (12H, m), 1.43 (3H, t, *J*=7.2 Hz), 1.94—2.07 (4H, m), 2.75 (2H, m), 2.95 (2H, t, *J*=7.8 Hz), 4.44 (2H, q, *J*=7.3 Hz), 5.32—5.43 (4H, m), 6.71 (1H, dd, *J*=7.9, 1.2 Hz), 6.83 (1H, dd, *J*=7.9, 1.2 Hz), 7.28 (1H, t, *J*=7.9 Hz) 11.24 (1H, s). High-MS *m*/*z*: 372.2664 (Calcd for $C_{24}H_{36}O_3$: 372.2664).

6-[8(*Z*),11(*Z*)-Pentadecadienyl]salicylic Acid (3) A solution of **29** (4.0 mg) in EtOH (1 ml) and 10% NaOH (1 ml) was refluxed for 6 h. The reaction mixture was then acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (AcOEt) to yield 3.2 mg (86.5%) of **3** as a brown oil. IR ν_{max}^{KBr} cm^{-1}: 1700, 1680, 1660, 1650, 1640, 1605, 1580, 1450. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, *J*=6.9 Hz), 1.05—1.70 (12H, m), 1.89—2.27 (4H, m), 2.77 (2H, t, *J*=5.7 Hz), 2.95 (2H, t, *J*=6.4 Hz), 5.27—5.45 (4H, m), 6.75 (1H, d, *J*=8.4 Hz), 7.34 (1H, d, *J*=8.4 Hz) 7.85 (1H, d, *J*=8.4 Hz). High-MS *m*/*z*: 344.2345 (Calcd for $C_{22}H_{32}O_3$: 344.2350).

Ethyl 2-Methoxy-6-[8(*Z*),11(*Z*),14-pentadecatrienyl]benzoate (30) BuLi in hexane (1.58 M, 190 μl) was successively added dropwise to a stirred solution of **27** (138 mg) in THF (2 ml) at room temperature under a nitrogen atmosphere. After 1 h, a solution of **15** (21.8 mg) in THF (1 ml) was added to the reaction mixture and the whole was stirred at room temperature for 30 min under nitrogen. And then the reaction mixture was quenched with cold water, extracted with AcOEt, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 18.9 mg (69.3%) of **30** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 1730, 1600, 1580, 1480. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.75 (10H, m), 1.37 (3H, t, *J*=7.1 Hz), 1.90—2.18 (2H, m), 2.55 (2H, t, *J*=7.7 Hz), 2.65—2.98 (4H, m) 3.81 (3H, s), 4.39 (2H, q, *J*=7.1 Hz), 5.05 (2H, m), 5.29—5.50 (4H, m), 5.78 (1H, m), 6.75 (1H, d, *J*=7.7 Hz), 6.80 (1H, d, *J*=7.7 Hz), 7.26 (1H, t, *J*=7.7 Hz). High-MS *m*/*z*: 384.2665 (Calcd for $C_{25}H_{36}O_3$: 384.2664).

Ethyl [8(*Z*),11(*Z*),14-Pentadecatrienyl]salicylate (31) A solution of **30** (10.9 mg) in anhydrous CH_2Cl_2 was added to a solution of BBr_3 (3.8 μl) in anhydrous CH_2Cl_2 at 0 °C under nitrogen, and the whole was stirred at room temperature for 1 h under nitrogen. And then the reaction mixture was quenched with cold water, extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=9 : 1) to yield 4.5 mg (75.0%) of 31 as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3400, 1740, 1660, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.70 (10H, m), 1.43 (3H, t, *J*=7.2 Hz), 1.90—2.10 (2H, m), 2.70—2.98 (6H, m), 4.44 (2H, q, *J*=7.2 Hz), 5.04 (2H, m), 5.29—5.52 (4H, m), 5.80 (1H, m), 6.72 (1H, d, *J*=8.7 Hz), 6.81 (1H, d, *J*=.7 Hz), 7.29 (1H, d, *J*=8.7 Hz), 11.21 (1H, s). High-MS *m*/*z*: 370.2540 (Calcd for $C_{24}H_{34}O_3$: 370.2508).

6-[8(*Z*),11(*Z*),14-Pentadecatrienyl]salicylic Acid (4) A solution of **31** (4.5 mg) in EtOH and 10% NaOH (1 ml) was refluxed for 6 h. The reaction mixture was then acidified with 10% HCl and extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (AcOEt) to yield 3.7 mg (88.5%) of **4** as a brown oil. IR ν_{max}^{KBr} cm^{-1}: 1700, 1660, 1650, 1605, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.10—1.70 (10H, m), 1.90—2.13 (2H, m), 2.70—3.05 (6H, m), 4.90—5.20 (2H, m), 5.20—5.50 (4H, m), 5.55—6.00 (1H, m), 6.76 (1H, d, *J*=7.9 Hz), 6.85 (1H, d, *J*=7.9 Hz), 7.35 (1H, d, *J*=7.9 Hz). High-MS *m*/*z*: 342.2225 (Calcd for $C_{22}H_{30}O_3$: 342.2195).

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