Synthesis of Anacardic Acids Utilizing an Annelation Reaction of Isoxazoles with Ethyl Acetoacetate

Mitsuru SATOH,* Naoki TAKEUCHI, Takeshi FUJITA, Katsuya YAMAZAKI, and Seisho TOBINAGA

Showa College of Pharmaceutical Sciences, 3-3165 Higashitamagawagakuen,Machida-shi, Tokyo 194-8543, Japan.
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Anacardic acids, 6-pentadecylsalicylic acid (1) and 6-[8(*Z*)-pentadecenyl]salicylic acid (2) were synthesized from isoxazoles by annelation reactions with ethyl acetoacetate.

Key words anacardic acid; synthesis; annelation reaction

Anacardic acid was isolated in 1847 from cashew-nut shells (*Anacardium occidentate*, anacardiaceae) by Staedeler.[1] It was subsequently found that anacardic acid was 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**).[2] Anacardic acids **1** and **5** have also been described as constituents of *Ozoroa mucronate* (anacardiaceae). These results suggested that the term anacardic acid was a suitable general name for 6-alkylsalicylic acids.[3]

On the other hand, ginkgoic acid (**2**) and bilobol (**6**) were isolated from *Ginkgo biloba* by Kawamura *et al.* in 1928, and they also reported that ginkgoic acid (**2**) and 6-(8-pentadecenyl)salicylic acid, one of the anacardic acids, have the same structure. (Chart 1)[4]

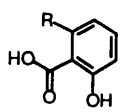
It is known that anacardic acids show various physiological activities.[5—8] For thermore, many synthetic methods for anacardic acids have been reported, as outlined in Chart 2. However, the starting materials for all these syntheses have a benzene skeletal structure.[9—12]

In our laboratory, we have developed a novel annelation reaction by combination of two synthons which are an enaminone, 1-dimethylamino-5-phenyl-1,4-pentadien-3-one and the dianion of acetoacetate, and have succeeded in the synthesis of 3,4-dihydro-8-hydroxy-3-phenylisocoumarin.[13] It is by now well established that isoxazole reacts with $Fe_2(CO)_9$ in the presence of water followed by acetoacetate, to afford an annelation reaction to give (+)- and (−)-mellein which are fungal metabolites, derived from *Cercospora* sp. and *Aspergillus* sp.[14] This result suggested that a variety of compounds may be synthesized from isoxazole with suitable protection of the enaminones. Therefore, we have studied a new synthetic method for preparation **1** and **2** according to our previous report,[14] by the annelation reaction of enaminone derived from suitable isoxazoles, with ethyl acetoacetate. As shown in Chart 3, coupling reaction of 1-bromopentadecane (**8**) with 3,3-diethoxy-1-propyne (**7**) in the presence of butyllithium (BuLi) and hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF) gave the product (**9**), in 91.9% yield as a colorless oil, which was treated with NH_2OH HCl in ethanol and water to yield the 5-pentadecylisoxazole (**10**), mp 36—38 °C, in 94.7% yield. This isoxazole (**10**) was converted to the oily enaminone (**11**), by reaction with $Fe_2(CO)_9$ in the presence of water, and the enaminone was then condensed with $MeCOCH_2CO_2Et$ to give the ester (**12**) as a colorless oil. Compound (**12**) was hydrolyzed with 10% NaOH to yield 6-pentadecylsalicylic acid (**1**), mp 84—86 °C, in 81.1% yield as colorless crystals. All physical data for synthetic **1** were identical with those of the natural product.[7,9]

7-Bromo-1-heptanol (**13**) was treated with dihydropyran (DHP) in the presence of 1-(*S*)-(+)-camphorsulfonic acid (CSA) to yield the ether (**14**) as an oil in 72.3% yield. Coupling reaction of ether (**14**) with 1-octyne in the presence of BuLi and HMPA gave alkyne (**15**), which was hydrolyzed with 10% HCl in ethanol to give alcohol (**16**) as an oil in 90.3% yield. Alcohol (**16**) was then converted to chloride (**17**), followed by conversion to iodide (**18**). Compound (**17**) did not undergo coupling reaction with 3,3-diethoxy-1-propyne. In a similar manner as before, anacardic acid (**2**), mp 45—48 °C, was derived from iodide (**18**) *via* 5-(8-pentadecynyl)isoxazole (**20**). All physical data for synthetic **2** were identical with those of the natural product (Chart 4).[7,9]

Experimental

All melting points were determined on a Yanagimoto melting point appa-



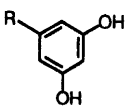
1: R = -$(CH_2)_{14}CH_3$

2: R = -$(CH_2)_7CH{=}CH(CH_2)_5CH_3$

3: R = -$(CH_2)_7CH{=}CHCH_2CH{=}CH(CH_2)_2CH_3$

4: R = -$(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$

5: R = -$(CH_2)_9CH{=}CH(CH_2)_3CH_3$



6: R = -$(CH_2)_7CH{=}CH(CH_2)_5CH_3$

bilobol

Chart 1

* To whom correspondence should be addressed.

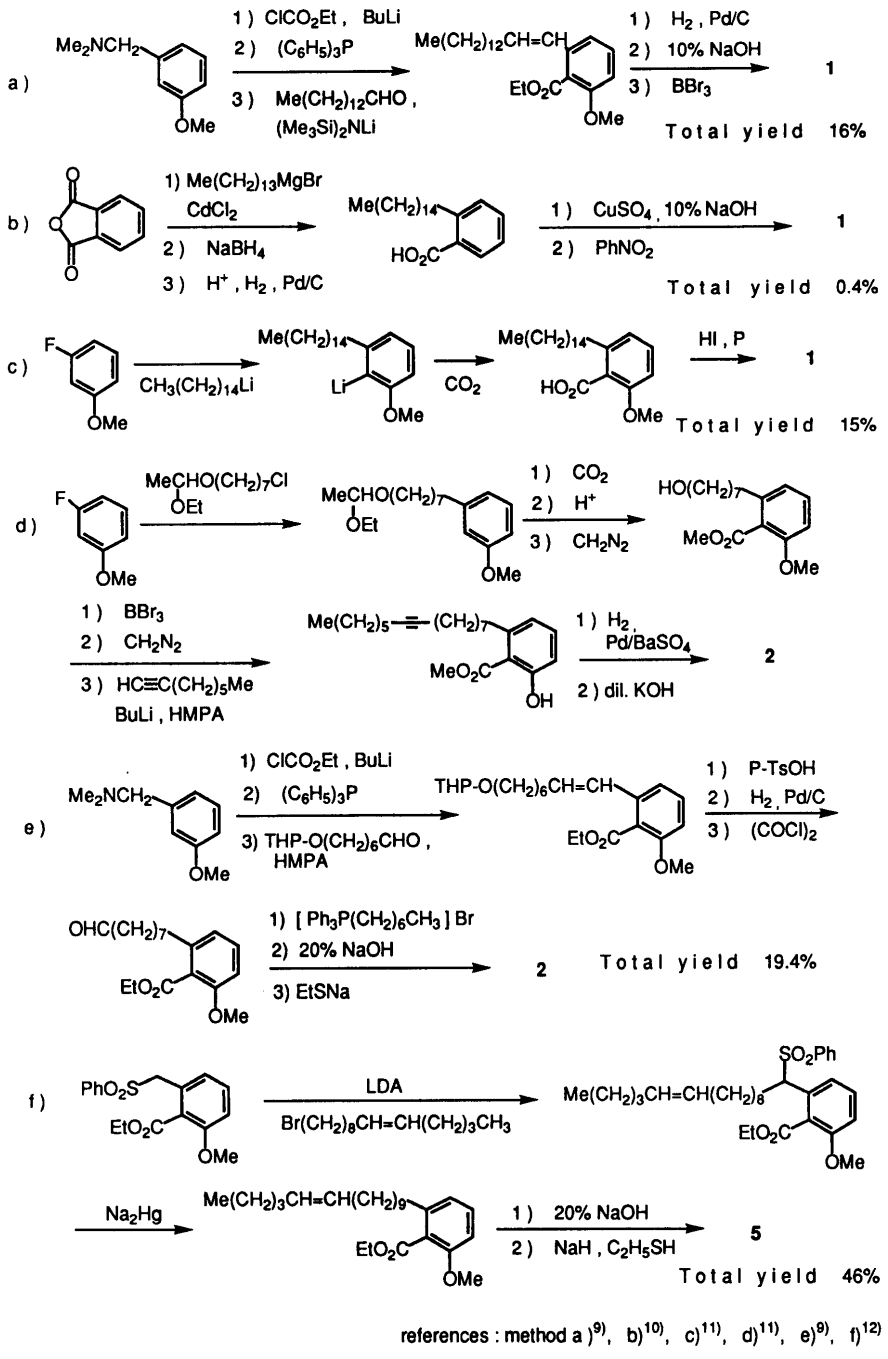


Chart 2. Reported Synthetic Methods for Anacardic Acids

ratus. IR spectra were recorded with a Hitachi 260-10 spectrometer and a JEOL A-202 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured on a JEOL JNM-EX90 spectrometer in $CDCl_3$ containing tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL JMS-D 300 instrument. Wacogel was used for column chromatography.

1,1-Diethoxy-2-octadecyne (9) BuLi in hexane (6.41 ml) and HMPA (1.82 ml) were successively added dropwise to a stirred solution of **7** (1.28 g) in THF at 0 °C under a nitrogen atmosphere. After 10 min, a solution of **8** (5.82 g) in THF was added to the reaction mixture and the whole was stirred at 0 °C for 1 h under nitrogen. The reaction mixture was quenched with saturated NH_4Cl, extracted with AcOEt, washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$ = 1 : 1) to yield 3.08 g (91.9%) of **9** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2210. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=4.7 Hz), 1.05—1.57 (32H, m), 2.23 (2H, dd, J=1.5, 5.3 Hz), 3.46—3.84 (4H, m), 5.25 (1H, s).

5-Peptadecylisoxazole (10) Hydroxylamine hydrochloride (75 mg) was added to a solution of **9** (2.77 g) in EtOH (30 ml) and H_2O (6 ml) and the mixture was refluxed for 1 h. The reaction mixture was concentrated under vacuum. An aqueous solution of the residue was then extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$ = 1 : 1). The eluate fraction was recrystallized from EtOH H_2O to yield 1.65 g (94.7%) of **10** as colorless crystals, mp 36—38 °C. IR ν_{max}^{KBr} cm^{-1}: 1595. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=5.3 Hz), 1.25—1.50 (26H, m), 2.76 (2H, t, J=7.2 Hz), 5.95 (1H, d, J=1.7 Hz), 8.13 (1H, d, J=1.7 Hz). Low MS *m/z*: 279 (M^+). *Anal.* Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.96; N, 5.01; O, 5.67. Found: C, 77.28; H, 11.81; N, 5.05; O, 5.86.

1-Amino-1-octadecen-3-one (11) Diiron nonacarbonyl (259.2 mg) and H_2O (6.5 ml) were added to a stirred solution of **10** (100 mg) in benzene (7 ml) at 45 °C under nitrogen. After 30 min, the reaction mixture was poured into water and extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4) and concentrated. A brown oil was obtained almost quantitatively, and this compound was employed in the next reaction without purification.

Ethyl 6-Pentadecylsalicylate (12) A solution of ethyl acetoacetate (370

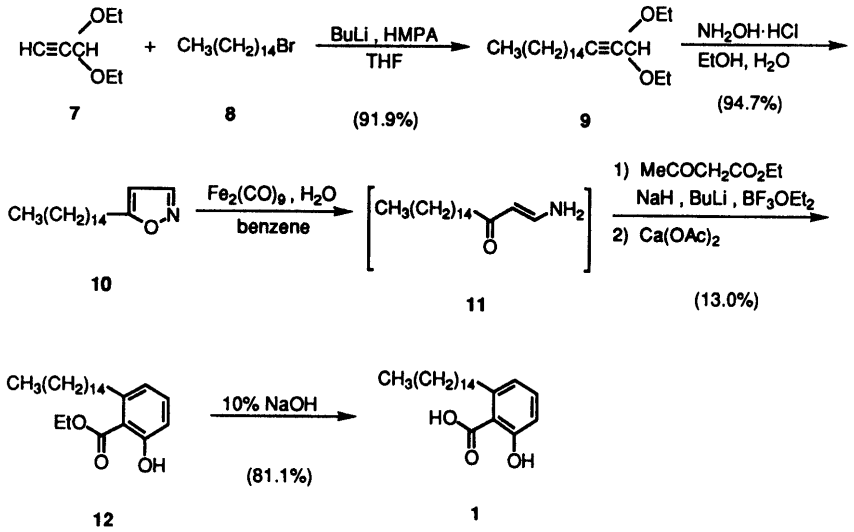


Chart 3

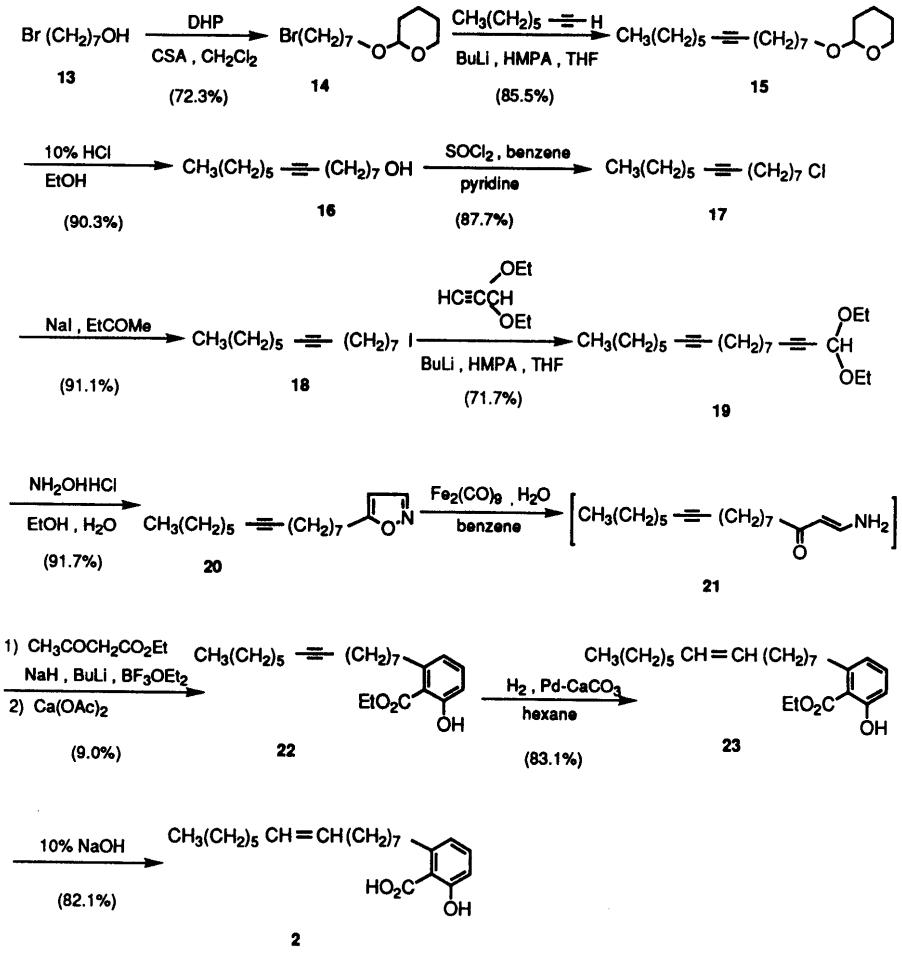


Chart 4

mg) in THF (5 ml) was treated with NaH (75 mg) and stirred at 0 °C for 10 min under nitrogen. BuLi (2.2 ml) was then added with stirring. After the reaction mixture was cooled to −30 °C, **11** and BF_3OEt_2 (0.35 ml) in THF (2 ml) were added to the reaction mixture, and after 10 min the mixture was stirred at 0 °C for 2 h. The reaction mixture was then acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was dissolved in ethanol (15 ml), treated with $Ca(OAc)_2$ (634 mg), and refluxed for 15 h. The reaction mixture was then concentrated under vacuum. A solution of the residue in H_2O was extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=2 : 1) to yield 17.6 mg (13.0%) of **12** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3100, 1665, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=5.7 Hz), 1.25—1.55 (29H, m), 2.90 (2H, m), 4.43 (2H, q, J=7.1 Hz), 6.70 (1H, dd, J=8.3, 1.3 Hz), 6.82 (1H, dd, J=7.4, 1.3 Hz), 7.28 (1H, dd, J=8.3, 7.4 Hz), 11.21 (1H, s). Low MS m/z: 376 (M^+). High MS Calcd for $C_{24}H_{40}O_3$ m/z: 376.2975 (M^+). Found: 376.2965.

6-Pentadecylsalicylic Acid (1) A solution of **12** (29 mg) in EtOH and 10% NaOH (1 ml) was refluxed for 2 h. The reaction mixture was then acidified with 10% HCl 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 : $CHCl_3$=1 : 1). The eluate fraction was recrystallized from hexane to yield 15 mg (81.1%) of **1** as colorless crystals, mp 84—86 °C. IR ν_{max}^{KBr} cm^{-1}: 3053, 2920, 2850, 1655, 1604. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.4 Hz), 1.24—1.56 (26H, m), 2.96 (2H, m), 6.76 (1H, dd, J=8.3, 1.3 Hz), 6.85 (1H, dd, J=7.4, 1.3 Hz), 7.34 (1H, dd, J=8.3, 7.4 Hz). Low MS m/z: 348 (M^+). *Anal.* Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41; O, 13.78. Found: C, 75.61; H, 10.36; O, 14.03.

7-Bromo-1-(2-tetrahydropyranyloxy)heptane (14) DHP (2.7 g) and CSA as catalyst were added to a solution of **13** (5.1 g) in CH_2Cl_2 and the mixture stirred at room temperature for 4 h. The reaction mixture was then extracted with $CHCl_3$ and the organic layer was washed with saturated $NaHCO_3$ and saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=8 : 1) to yield 5.01 g (72.3%) of **14** as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.40—1.86 (16H, m), 3.25—4.00 (6H, m), 4.59 (1H, m). CI-MS m/z: 281 (M^++1), 279 (M^++1).

1-(2-Tetrahydropyranyloxy)-8-pentadecyne (15) BuLi (34.8 ml) and HMPA (9.7 ml) were added to a solution of 1-octyne (5.94 g) in THF at −30 °C with stirring. After a solution of **14** (5.02 g) in THF was added to this solution, the whole was stirred at −30 °C for 1 h. The mixture was then allowed to stand at room temperature. 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=15 : 1) to yield 4.7 g (85.5%) of **15** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2250. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.7 Hz), 1.38—1.81 (24H, m), 2.13 (4H, m), 3.25—3.94 (4H, m), 4.56 (1H, m). CI-MS m/z: 309 (M^++1).

8-Pentadecyn-1-ol (16) A solution of **15** (585 mg) in MeOH (15 ml) and 10% HCl (15 ml) was refluxed for 2 h. The reaction mixture was then treated with water 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=3 : 1) to yield 384 mg (90.3%) of **16** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3300, 2300. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.7 Hz), 1.14—1.63 (18H, m), 2.13 (4H, m), 3.64 (2H, t, J=6.2 Hz) . CI-MS m/z: 225(M^++1).

1-Chloro-8-pentadecyne (17) A solution of **16** (2.2 g) in benzene (13 ml) was treated with $SOCl_2$ (13.2 g) and pyridine (670 mg) and the whole was stirred at 50 °C. To the reaction mixture was added water, followed by extraction with hexane. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=3 : 1) to yield 2.89 g (87.7%) of **17** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2300. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.9 Hz), 1.38—1.77 (18H, m), 2.14 (4H, m), 3.53 (2H, t, J=6.4 Hz) . CI-MS m/z: 245 (M^++1).

1-Iodo-8-pentadecyne (18) A solution of **17** (50 mg) and NaI (160 mg) in methyl ethyl ketone was refluxed for 14 h. The reaction mixture was then treated with water and extracted with hexane. The organic layer was washed with saturated NaCl, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=3 : 1) to yield 63 mg (91.6%) of **18** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2300. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.7 Hz), 1.27—1.56 (18H, m), 2.14 (4H, m), 3.18 (2H, t, J=6.9 Hz). Low MS m/z: 334 (M^+), High MS Calcd for $C_{15}H_{27}I$ m/z: 334.1154 (M^+). Found: 334.1154.

1,1-Diethoxy-2,11-octadecadiyne (19) BuLi (5.1 ml) and HMPA (1.39 ml) were added to a solution of propiolaldehyde diethyl acetal (1.0 g) in THF at 0 °C with stirring. After a solution of **18** (2.48 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. The reaction mixture was quenched 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=1 : 1) to yield 1.8 g (71.7%) of **19** as a colorless oil. This compound was employed in the next reaction without purification. IR ν_{max}^{KBr} cm^{-1}: 2300. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.8 Hz), 1.15—1.56 (24H, m), 2.07—2.24 (6H, m), 3.49—3.76 (4H, m), 5.25 (1H, s).

5-(8-Pentadecynyl)isoxazole (20) Compound **19** (155 mg) was dissolved in EtOH (2 ml) and water (0.4 ml) and treated with hydroxylamine hydrochloride (63 mg), and refluxed for 1 h. The solution was then concentrated under vacuum. A solution of the residue in H_2O was extracted with hexane. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=1 : 1) to yield 117 mg (91.7%) of **20** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2350, 1590. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=5.8 Hz), 1.37—1.78 (18H, m), 2.10 (4H, m), 2.77 (2H, t, J=7.4 Hz), 5.93 (1H, d, J=1.7 Hz), 8.13 (1H, d, J=1.7 Hz). Low MS m/z: 275 (M^+). High MS Calcd for $C_{18}H_{29}NO$ m/z: 275.224 (M^+) . Found: 275.2239.

1-Amino-1(*E*)-octadecen-11-yn-3-one (21) Diiron nonacarbonyl (130.0 mg) and H_2O (6.0 mg) were added to a solution of **20** (100 mg) in benzene (6 ml) and stirred at 45 °C for 30 min under nitrogen. The reaction mixture was poured into water and then extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried and concentrated. The brown oil, **21** was obtained almost quantitatively. This compound was employed in the next reaction without purification.

Ethyl 6-(8-Pentadecynyl)salicylate (22) A solution of ethyl acetoacetate (390 mg) in THF (5 ml) was treated with NaH (81 mg) and stirred at 0 °C for 10 min under nitrogen. BuLi (2.5 ml) was then added dropwise with stirring. After the reaction mixture was cooled at −30 °C, **21** (108 mg) and BF_3OEt_2 (0.38 ml) in THF (3 ml) were added to the reaction mixture, followed by stirring for 10 min, and then at 0 °C for 2 h. The reaction mixture was then acidified with HCl and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was dissolved in ethanol (15 ml), treated with $Ca(OAc)_2$ (694 mg), and refluxed for 15 h. The reaction mixture was then concentrated under vacuum, and a solution of the residue in H_2O extracted with $CHCl_3$. The organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=1 : 1) to yield 12.0 mg (9.0%) of **22** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 3200, 1658, 1608. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=5.7 Hz), 1.25—1.62 (21H, m), 1.98 (4H, m), 2.10 (4H, m), 2.91 (2H, t, J=8.1 Hz), 4.43 (2H, q, J=7.1 Hz), 6.72 (1H, dd, J=8.3, 1.3 Hz), 6.81 (1H, dd, J=7.2, 1.3 Hz), 7.24 (1H, dd, J=8.3, 7.2 Hz), 11.20 (1H, s). Low MS m/z: 372 (M^+). High MS Calcd for $C_{24}H_{36}O_3$ m/z: 372.2665 (M^+). Found: 372.2673.

Ethyl 6-[8(*Z*)-Pentadecenyl]salicylate (23) A mixture of Lindlar's catalyst (Pd $CaCO_3$, 20 mg) and **22** (18.4 mg) in hexane (3.0 ml) was stirred at room temperature for 16 h under H_2. The mixture was filtered and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$=2 : 1) to yield 15.0 mg (83.1%) of **23** 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 Calcd for $C_{24}H_{38}O_3$ m/z: 374.2821 (M^+). Found: 374.2827.

6-[8(*Z*)-Pentadecenyl]salicylic Acid (2) A solution of **23** (12.2 mg) in EtOH and 10% NaOH (1 ml) were refluxed for 2 h. The reaction mixture was then acidified with 10% HCl and 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 recrystallized from hexane to yield 9.2 mg (82.0%) 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 ; O, 13.85. Found: C, 76.08; H, 10.06; O, 13.86.

References

1) Staedeler, *Annalen der Chemie und Pharmacie*, **63**, 137—164 (1847).

2) Paul V. J. , Yeddanapalli, *Nature* (London), **174**, 604 (1954).
3) Kubo I., "Science year," World-Book-Childcraft, Chicago, p. 126 (1981).
4) Tyman J. H. P., *Chem. Soc. Rev.*, **8**, 499—536 (1979); Kawamura J., *Jpn. J. Chem.*, **3**, 89—92 (1928); Furukawa S., *Sci. Papers Inst. Phys. Chem. Res.*, **24**, 304—313, 314—319, 320—324 (1934); *Idem*, *ibid.*, **26**, 178—185 (1935).
5) Kubo I., Himejima M., *J. Agric. Food Chem.*, **39**, 418—421 (1991).
6) Mumma R. O., *Biochem. Biophys. Res. Commun.*, **176**, 775—780 (1991).
7) Nishino C., Kobayashi K., Tamao Y. , Ohya J., Jpn. Kokai Tokkyo Koho, 67—72 (1989).
8) Okamoto H. and Takashina S., Jpn. Kokai Tokkyo Koho, 325—328 (1990).
9) Kubo I., Yamagiwa Y., Ohashi K., Sakamoto Y., Hirakawa S. and Kamikawa T., *Tetrahedron*, **43**, 3387—3394 (1987).
10) Durrani A. A. , Tyman, J. H. P., *J. Chem. Soc., Perkin Trans.* **1**, 2069—2078 (1979).
11) Durrani A. A. , Tyman, J. H. P., *J. Chem. Soc., Perkin Trans.* **1**, 2079—2087 (1979).
12) Tyman J. H. P., *J. Org. Chem.*, **41**, 894 (1976).
13) Takeuchi N., Handa S., Koyama K., Kamata K., Goto K., Tobinaga S., *Chem. Pharm. Bull.*, **39**, 1655—1658 (1991).
14) Takeuchi N., Goto K., Sasaki Y., Fujita T., Okazaki K., Kamata K., Tobinaga S., *Heterocycles*, **33**, 357—374(1992).