Improved Synthesis of Anacardic Acids, 6-Pentadecylsalicylic Acid and 6-[8(*Z*)-Pentadecenyl]salicylic Acid, from Aldehyde and Acetoacetate

Mitsuru SATOH,* Naoki TAKEUCHI, Takashi FUJITA, Katsuya YAMAZAKI, Tsuyoshi NISHIMURA, and Seisho TOBINAGA

Showa College of Pharmaceutical Sciences, 3–3165 Higashitamagawagakuen, Machida, Tokyo 194–8543, Japan.
Received March 2,1999; accepted May 25,1999

Anacardic acids, 6-pentadecadienylsalicylic acid and 6-[8(*Z*)-pentadecatrienyl]salicylic acid were synthesized from aldehyde and acetoacetate with 1,2-addition.

Key words anacardic acid; synthesis; aldehyde

In nature, there are many kinds of phenol derivatives, phenolic lipid, or long chain phenol, which are essentially divided into two types. One of them consists of the compounds, in which the side-chain is isoprenoid, as in α-tocopherol, having been derived biogenetically from "mevalonate," and the other consists of the compounds which are nonisoprenoid and of "polyketide" origin, having no branched chain, as in the saturated compound, anacardic acid, 6-pentadecyl salicylic acid (Chart 1).[1)]

Considerable interest has focused on the second group, anacardic acids because these compounds showed various physiological activities, inhibition of prostaglandin synthesis, antifeedant activities and antitumor activities.[2—4)] Therefore, we studied the synthesis of anacardic acids. In the previous paper, we reported a new synthesis of anacardic acids **1**, **2** utilizing an annelation reaction of isoxazoles with ethyl acetoacetate (Chart 2).[5)]

However, the results of the annelation reaction *via* isoxazoles did not give us satisfactory yield. Accordingly, pursuing higher yield we investigated the reaction with α, β unsaturated aldehyde and acetoacetate. First, coupling reaction of alkylhalide with 3,3-diethoxy-1-propyne in the presence of butyllithium (BuLi) and hexamethylphosphoric triamide (HMPA) in tetrahydrofuran (THF) gave the coupling products (**5**, **10**) as colorless oil, which were treated with H_3PO_4 and hydroquinone in dioxane to yield the aldehydes (**6**, **11**). These aldehydes, upon treatment with sodium methoxide (NaOMe) and methanol (MeOH), were converted to 3-methoxyacroleins (**7**, **12**). These 3-methoxyacroleins were then condensed with ethyl acetoacetate ($MeCOCH_2CO_2Et$) to give the condenced compounds (**8**, **13**) as colorless oil; without purification, these were treated with KF in toluene to give the esters (**9**, **14**) as colorless oil in 72.4% (**7**→**9**) and 41.0% (**12**→**14**) yield, and have already been converted to anacardic acids (**1**, **2**) in the manner described previously (Chart 3).[5)]

α-tocopherol

anacardic acids

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 = -$(CH_2)_7CH{=}CHCH_2CH{=}CHCH_2CH{=}CH_2$

Chart 1

Experimental

All melting points were determined on a Yanagimoto melting point apparatus. 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 JEOL JNM-EX90 and JEOL JNM-α500 spectrometers 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.

2-Octadecynal (6) H_2O (10.8 ml), 85% H_3PO_4 (6.0 ml) and hydroquinone (200 mg) was added to a solution of **5**[5)] (1.0 g) in dioxane (35 ml) and the mixture was refluxed at 100 °C for 16 h. The reaction mixture was concentrated under vacuum. An aqueous solution of the residue was then ex-

B: 12.0% & 8.2% from **A**

1: R = -$(CH_2)_{14}CH_3$
2: R = -$(CH_2)_7CH{=}CH(CH_2)_5CH_3$

Chart 2

5, 10

6, 11 (89.0 %)

7, 12

8, 13

9, 14 (**7** → **9** 72.4 %) (**12** → **14** 41.0 %)

5, 6, 7, 8, 9: R = -$(CH_2)_{14}CH_3$
10, 11, 12, 13, 14: R = -$(CH_2)_7C{\equiv}C(CH_2)_5CH_3$

Chart 3

* To whom correspondence should be addressed.

tracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : $CHCl_3$ = 1 : 1) to yield 695 mg (89.0%) of **6** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2940, 2875, 2300, 2220, 1670. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.6 Hz), 1.26—1.65 (26H, m), 2.40 (2H, td, J=7.0, 1.0 Hz), 9.18 (1H, t, J=1.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.08, 19.09, 22.67, 27.52, 28.82, 29.34, 29.40, 29.55, 29.60 (2C), 29.63 (2C), 29.66 (2C), 31.90, 81.67, 99.36, 177.20. Low MS *m/z*: 264 (M^+). High-MS *m/z*: 264.2447 (Calcd for $C_{18}H_{32}O$: 264.2452).

3-Methoxy-2-octadecenal (7) NaOMe (79 mg) was added to a solution of **6** (300 mg) in absolute methanol (30 ml) and the mixture was stirred at room temperature for 2 h under nitrogen. The reaction mixture was treated with water, acidified with 10% HCl and then 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=4 : 1). The eluate fraction was recrystallized from hexane to yield 278 mg (82.6%) of **7** as colorless crystals, mp 42—48 °C. IR ν_{max}^{KBr} cm^{-1}: 1691, 1674, 1601. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.2 Hz), 1.25 (26H, br s), 2.60 (2H, t, J=7.1 Hz), 3.68 (3H, s), 5.38 (1H, d, J=7.8 Hz), 9.81 (1H, d, J=7.8 Hz). Low MS m/z : 296 (M^+). High-MS *m/z*: 296.2736 (Calcd for $C_{19}H_{36}O_2$: 296.2715).

Ethyl 6-Pentadecylsalicylate (9) A solution of ethyl acetoacetate (397 mg) in THF (20 ml) was treated with NaH (90 mg) and stirred at 0 °C for 10 min under nitrogen. BuLi in hexane (1.54 M, 2.6 ml) was then added with stirring. After the reaction mixture was cooled to −30 °C, **7** (50 mg) in THF (5 ml) was added, and the mixture was stirred at −30 °C for 3.5 h under nitrogen. The reaction mixture was quenched with saturated NH_4Cl, then acidified with 10% HCl and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried and concentrated. A solution of the residue and KF (110 mg) in toluene (10 ml) was refluxed for 15 h. The reaction mixture was then concentrated under vacuum. A solution of the residue in H_2O was extracted with $CHCl_3$, and the organic layer was washed with saturated NaCl solution, dried and concentrated. The residue was subjected to silica gel chromatography (hexane : AcOEt=10 : 1) to yield 64 mg (72.4%) of **9** as a colorless oil, whose spectroscopic data were identical with those of an authentic sample.[5]

2,11-Octadecadiynal (11) The reaction was carried out using H_2O (8.2 ml), 85% H_3PO_4 (4.6 ml), hydroquinone (153 mg) and **10**[5] (673 mg) in a manner similar to the preparation of **6** to yield 482 mg (92.0%) of **11** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2930, 2237, 1716, 1672. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz), 1.26—1.50 (18H, m), 1.60 (2H, q, J=7.3 Hz), 2.15 (4H, m), 2.41 (2H, t, J=7.3 Hz), 9.18 (1H, t, J=1.0 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.08, 18.72, 18.77, 19.13, 22.60 (2C), 27.49, 28.56 (2C), 28.74, 29.02, 29.14, 31.39, 80.02, 80.43, 81.71, 99.33, 177.28. CI-MS *m/z*: 261 (M^++1).

3-Methoxy-2-octadecen-11-ynal (12) The reaction was carried out using NaOMe (79 ml) and **11** (100 mg) in a manner similar to the preparation of **7** to yield 81 mg (72.3%) of **12** as a colorless oil. IR ν_{max}^{KBr} cm^{-1}: 2932, 2856, 1662, 1608. ^{1}H-NMR (C_6D_6) δ: 0.86 (3H, t, J=5.5 Hz), 1.14—1.41 (18H, m), 2.14 (6H, m), 2.87 (3H, s), 5.24 (1H, d, J=7.5 Hz), 9.87 (1H, d, J=7.5 Hz). CI-MS *m/z*: 293 (M^++1).

Ethyl 6-(8-Pentadecynyl)salicylate (14) The reaction was carried out using acetoacetate (433 mg), NaH (100 mg), BuLi (1.54 M, 2.8 ml) **12** (54 mg) and KF (280 mg) in a manner similar to the preparation of **9** to yield 28 mg (41.0%) of **14** as a colorless oil. This compound was identical with the authentic sample obtained previously.[5]

References

1) Tyman John H. P., *Chem. Soc. Rev*., **8**, 499—536 (1979).
2) Kubo I., Kim M., Naya K., Komatsu S., Yamagiwa Y., Ohashi K., Sakamoto Y., Hirakawa S., Kamikawa T., *Chem. Lett*., **1987** 1101—1104.
3) Matsumoto T., Sei T., *Agric. Biol. Chem*., **51**, 249—250 (1987).
4) Itokawa H., Totsuka N., Nakahara K., Maezuru N., Takaya K., Kondo M., Inamatsu M., Morita H., *Chem. Pharm. Bull*., **37**, 1619—1621 (1989).
5) Satoh M., Takeuchi N., Fujita T., Yamazaki K., Tobinaga S., *Chem. Pharm. Bull*., **46**, 1501—1505 (1998).