Novel Acyl α-Pyronoids, Dictyopyrone A, B, and C, from *Dictyostelium* Cellular Slime Molds

Yoshiaki Takaya,[†] Haruhisa Kikuchi,[†] Yuichi Terui,[†] Jun Komiya,[†] Ken-Ichi Furukawa,[‡] Kazuhiko Seya,[‡] Shigeru Motomura,[‡] Akira Ito,[§] and Yoshiteru Oshima*[,†]

Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba-yama, Sendai 980-8578, Hirosaki University School of Medicine, Zaifu-cho, Hirosaki 036-8562, and Kyorin Pharmaceutical Co., Ltd., 2-5 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

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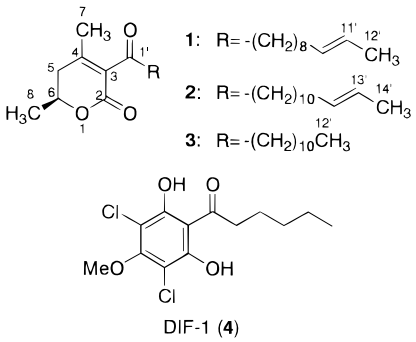
For the elucidation of the diversity of secondary metabolites of *Dictyostelium* cellular slime molds, we investigate the constituent of three species of slime molds. From the methanol extract of their fruit bodies, we obtained three novel compounds, dictyopyrone A (**1**) and B (**2**) from *D. discoideum* and *D. rhizoposium* and dictyopyrone C (**3**) from *D. longosporum*. They possess a unique α-pyrone moiety with a side chain at the C-3 position. Their relative structures were elucidated by spectral means, and the absolute configuration was confirmed by asymmetric synthesis of **1**. Since these compounds were obtained from different species of *Dictyostelium* slime molds, they may be a type of compound common to this genus.

Introduction

The cellular slime molds, Myxomycota, which is known as the most primitive fungus, have long been established as an excellent model organism for the study of various aspects of multicellular development, because of their short and very simple life cycle. The amoebas, germinated from spores, feed on bacteria by phagocytosis, and starving makes them aggregate to form a mount. The mount differentiates into either stoke cells or spores. Several chemical stimuli, such as DIF-1 (**4**),[1] discadenine,[2] and cAMP,[3] are identified as physiologically active substances which act during their life cycle, but few other secondary metabolites have been reported. Many bioactive compounds have been obtained from various kinds of microorganisms; however, the frequency of encountering novel skeletal compounds is decreasing. On the other hand, the chemistry of the slime molds is one of terrae incognitae. Among the compounds isolated from cellular slime molds, DIF-1 (**4**), a differentiation-inducing factor of *Dictyostelium* slime molds, shows a unique structure bearing a hexasubstituted benzene ring with two chlorine atoms, and other compounds such as discadenine[2] or dictyosterol[4] are also structurally characteristic. From these facts, it is believed that slime molds have the ability to produce novel metabolites. Accordingly, we set about exploring the diversity of the secondary metabolites of cellular slime molds and their utility as a resource to develop drugs of the future. In the first step of this project, we decided to examine the constituent of the slime molds exhaustively to classify the compounds produced by the microorganism. In this paper, the structure elucidation and an asymmetric total synthesis of three novel α-pyrone compounds, dictyopyrone A (**1**), B (**2**), and C (**3**), and the potency of inhibition against smooth muscle contraction of **1** are described.



Results and Discussion

Isolation and Structure Elucidation. Ethyl acetate-soluble oil (1.2 g), obtained from methanol extracts (5.6 g) of the cultured fruit body of *D. discoideum* (wet 109 g), was fractionated over silica gel. The fraction eluted with *n*-hexane−ethyl acetate (4:1) afforded **1** (2.1 mg) and **2** (0.4 mg). In the same manner, **1** (3.3 mg) and **2** (2.7 mg) were obtained from *D. rhizoposium*, and **3** (0.5 mg) was obtained from *D. longosporum*.

The molecular formula $C_{19}H_{30}O_3$ indicated for **1**, $[\alpha]^{25}_D$ +33.8 (*c* 0.071, $CHCl_3$), a colorless needle, was established by a molecular ion peak at *m*/*z* 306.2260 $[M]^+$ in its HREI-MS and analyses of its ^1H and ^{13}C NMR spectra (Table 1). The ^{13}C NMR spectrum displayed the presence of a keto carbonyl, an ester carbonyl, four olefinic, an oxymethine, nine methylene, and three methyl carbons. $^1H-^1H$ COSY and HMBC experiments showed three partial structures, **I**, **II**, and **III** (Figure 1). The tetrasubstituted olefin of unit **I** was established by long-range correlation peaks from C-3 and C-4 to both H-5 and H-7, and from the methyl carbon (C-7) to H-5 in the HMBC

* To whom correspondence should be addressed. Phone: +81-22-217-6822. Fax: +81-22-217-6821. E-mail: oshima@mail.pharm.tohoku.ac.jp.
† Tohoku University.
‡ Hirosaki University.
§ Kyorin Pharmaceutical Co., Ltd.

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Table 1. NMR Data of 1, 2, and 3[a]

position	1		2	3
	^{1}H[b]	^{13}C[c]	^{1}H[b]	^{1}H[d]
2		163.4 (s)		
3		130.3 (s)		
4		156.4 (s)		
5	2.45 (1H, dd, 18.5, 11.6) 2.31 (1H, dd, 18.5, 3.7)	38.0 (t)	2.44 (1H, dd, 18.3, 11.6) 2.30 (1H, dd, 18.3, 3.7)	2.43 (1H, dd, 18.1, 10.7) 2.23 (1H, dd, 18.1, 4.1)
6	4.55 (1H, ddq, 11.6, 3.7, 6.1)	73.3 (d)	4.54 (1H, ddq, 11.6, 3.7, 6.1)	4.53 (1H, ddq, 10.7, 6.3, 4.1)
7	2.01 (3H, s)	21.1 (q)	2.01 (3H, s)	2.00 (3H, d, 0.8)
8	1.44 (3H, d, 6.1)	20.7 (q)	1.44 (3H, d, 6.1)	1.42 (3H, d, 6.3)
1′		203.7 (s)		
2′	2.73 (2H, td, 7.3, 2.4)	43.7 (t)	2.73 (2H, td, 7.3, 2.4)	2.71 (2H, td, J = 7.7, 1.4)
3′	1.61 (2H, m)	24.0 (t)	1.61 (2H, m)	1.5−1.7 (2H, m)
4′−8′	1.2−1.4 (10H, m)	29.4 (t) 29.4 (t) 29.6 (t) 29.6 (t) 29.8 (t)	1.2−1.4 (14H, m)	1.2−1.4 (16H, m, H-4′−11′)
9′	1.94 (2H, m)	32.8 (t)		
10′	5.39−5.42 (2H, m, H-10′−11′)	131.9 (d)		
11′		124.8 (d)	1.95 (2H, m)	
12′	1.64 (3H, dt, 3.7, 1.4)	18.2 (q)	5.39−5.42 (2H, m, H-12′−13′)	0.86 (3H, t, 7.1)
14′			1.64 (3H, dd, 3.7, 1.2)	

[a] The number of protons, splitting patterns, and coupling constants (Hz) of ^{1}H NMR are indicated in parentheses. [b] Measured at 500 MHz. [c] Measured at 125 MHz. [d] Measured at 300 MHz.

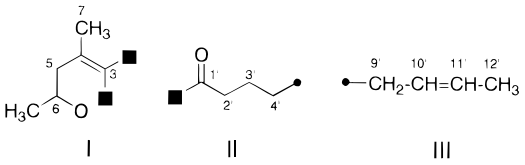

Figure 1. Partial structures of dictyopyrone A (**1**).

spectrum. However, it was observed that there remained an ester group and four methylene carbons which were not included in these partial structures. The ester group was attached to C-6 of unit **I**, since C-6 was assumed to be an oxymethine carbon as judged from the chemical shift of the ^{13}C NMR signal (δ_C 73.3). Moreover, all signals of the four methylene chains in the NMR spectra were observed obviously in the aliphatic region, δ_H 1.2−1.4 and δ_C 29.4−29.8, indicating that the methylene chain must be connected between the methylene of unit **II** and unit **III**. On the basis of consideration of these partial structures mentioned above and the molecular formula, the unique planar structure of compound **1**, bearing an α-pyrone moiety, was given. The base ion (*m*/*z* 153), which was formed by the bond cleavage between C-1′ and C-2′, also agreed with the proposed structure. The *E* configuration was assigned to the C-10′−C-11′ double bond by comparison of the chemical shifts of C-9′ (δ_C 32.8) and C-12′ (δ_C 18.2) with the calculated values (δ_C (*E*) 33.0, (*Z*) 27.0 for C-9′; δ_C (*E*) 17.0, (*Z*) 11.0 for C-12′).

The HREI-MS of **2**, $[\alpha]^{25}_D$ +36.6 (*c* 0.160, $CHCl_3$), a colorless needle, gave a molecular formula, $C_{21}H_{34}O_3$, which differs from that of **1** by two methylene units. The ^{1}H and ^{13}C NMR spectra of **2** were almost the same as those of **1**, except the appearance of signals assigned to additional methylene moieties. These findings revealed that **2** had an elongated side chain by two methylenes compared with **1**.

Dictyopyrone C (**3**), a colorless amorphous solid, $[\alpha]^{25}_D$ +71.0 (*c* 0.031, $CHCl_3$), showed a molecular ion peak at *m*/*z* 308 in its EI-MS, which differs from that of **1** by 2 mass units. The ^{1}H NMR spectra of **1** and **3** were very similar, but the signals of two olefinic protons (δ_H 5.39−5.42) and an allyl methyl proton (δ_H 1.64) of **1** disappeared in the case of **3**, and a triplet methyl signal (δ_H 0.86) was observed instead. As a result, the structure of compound **3** with a saturated side chain was suggested.

Synthesis and Absolute Configuration. The wavelength and intensity of the Cotton effect in the CD spectra of **1**, **2**, and **3** are almost the same, suggesting that they have the same absolute stereochemistry at C-6. The structures of these compounds, including the absolute configuration, were established by an asymmetric total synthesis of compound **1** and its stereoisomer using commercially available (2*R*,4*R*)- or (2*S*,4*S*)-2,4-pentanediol (**5**) as a chiral source. Our synthetic strategy is to couple a β-keto acid moiety, corresponding to C-2−C-3 and a side chain, with the 2,4-pentanediol (C-4−C-8).

Tridecanedioic acid monopotassium salt prepared from tridecanedioic acid (**6**) with an equimolar amount of potassium hydroxide was transformed to its monobenzyl ester (**7**) in 68% yield (Scheme 1).[5] The monoester **7** was converted into terminal olefinic ester **8** by oxidative decarboxylation using lead tetraacetate and a catalytic amount of cupric acetate.[6] The terminal double bond was isomerized predominantly to the desired *E* configuration at the $\Delta^{10'}$ position with $CoCl_2/Ph_3P/NaBH_4$ at −18 °C for 6 h in 84% (*Z*: 7%).[7] Hydrolysis of the benzyl ester gave (*E*)-10-dodecenoic acid (**10**), which corresponds to the side chain moiety of dictyopyrone A (**1**).

Elongation of a two-carbon unit (C-2−C-3) to the acid **10** was achieved by treatment of thionyl chloride followed by the malonic ester synthesis using Meldrum's acid.[8] Transesterification and decarboxylation of acylated Meldrum's acid (**11**) occurred in succession with (2*S*,4*S*)-2,4-pentanediol (**5*S***) in benzene by refluxing, and a β-ketoester (**12**) was obtained. Oxidation of the secondary alcohol using PDC and subsequent intramolecular aldol

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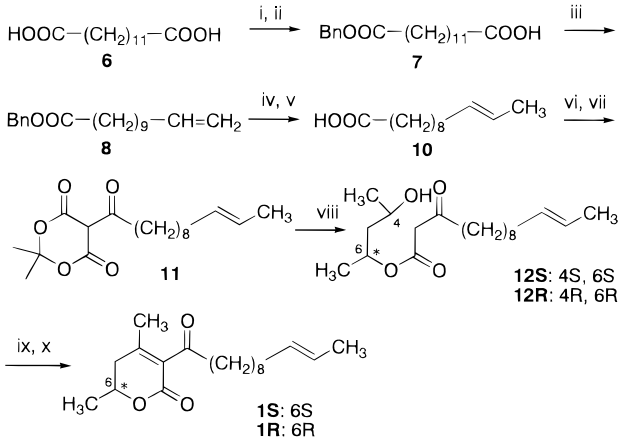
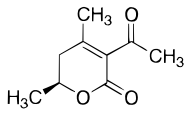
Scheme 1[a]



[a] Reagents and conditions (corrected yields): (i) KOH, methanol; (ii) $PhCH_2Br$, *n*-Bu_4NBr, toluene, reflux, 6 h (68% from **6**); (iii) $Pb(OAc)_4$, $Cu(OAc)_2$, pyridine, benzene, reflux, 4 h (76%); (iv) Ph_3P, $CoCl_2$, $NaBH_4$, THF, −18 °C (91%); (v) NaOH, CH_3CN-H_2O (99%); (vi) $SOCl_2$, benzene, reflux, 2 h; (vii) Meldrum's acid, DMAP, CH_2Cl_2, 0 °C → rt; (viii) **5*S*** or **5*R***, benzene, reflux (65% from **10**); (ix) PDC, DMF (90%); (x) K_2CO_3, CH_3CN, 50 °C (67% from **12**).

condensation allowed us to complete the synthesis of (*S*)-dictyopyrone A (**1*S***). In the same manner, (*R*)-dictyopyrone A (**1*R***) was produced by using (2*R*,4*R*)-2,4-pentanediol (**5*R***). Specific rotation of the synthetic (*S*)-dictyopyrone (**1*S***) was identical with that of the natural compound (**1**). From this result, the absolute configuration of compound **1** was determined as *S*, and consequently, compounds **2** and **3** were clarified to be of *S* configuration.

Biological Evaluation. Though very small amounts of compounds **1**−**3** were isolated in this study to submit to a bioassay, we investigated, as one of the pharmacological evaluations, the potency of inhibition against smooth muscle contraction of synthesized **1** and a model compound (**14**) of the transformation from **9** into **1** in the



14

synthetic scheme. As a result, compound **14** inhibited the contraction of rat aorta evoked by 30 mM KCl, 10^{-6} M phenylephrine, and 10^{-6} M serotonin with IC_{50} values of 0.35, 1.4, and 0.14 μM, respectively, whereas **1** was inactive. The inhibitory activities of **14** were not so strong compared to those of verapamil (IC_{50} for KCl-induced contraction, 0.1 μM), prazosin (IC_{50} for phenylephrine-induced contraction, 1.4 nM), and methysergide (IC_{50} for serotonin-induced contraction, 0.1 μM), but from the results mentioned above, it is deduced that inhibitory activity may be affected by the chain length of these compounds, and structure−activity relationship studies are hoped to give more effective compounds.

Conclusion

Three novel α-pyronoids, dictyopyrones A (**1**), B (**2**), and C (**3**), were isolated from the fruit body of *Dictyostelium* silme molds, and their structures, including the absolute configuration, were elucidated by spectroscopic analysis and chiral total synthesis. Though some α-pyronoids with a hydroxyl group at the C-4 position are known,[9] dictyopyrones bear a unique 3-acyl-4,6-dialkyl-α-pyrone ring, which has not hitherto been reported, to the best of our knowledge. Moreover, in this study, **1** and **2** were obtained from two species, *D. discoideum* and *D. rhizoposium*, and **3** was obtained from *D. longosporum*, as the comparatively major secondary metabolites except dictyosterol. These facts suggest that the compounds have an important role in the life cycle of cellular slime molds. It is interesting that compounds **1** and **14** possessing varying lengths of the side chain differ in inhibitory activity against smooth muscle contraction. Further investigations on the structure−activity relationships are now in progress using compounds synthesized by the methods shown in Scheme 1.

Experimental Section

General Methods. Melting points were uncorrected. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Column chromatography was carried out on silica gel 60 (70−230 mesh, Merck). All NMR spectra were recorded in $CDCl_3$. Chemical shifts for ^1H and ^{13}C NMR are given in parts per million (δ) relative to tetramethylsilane (δ_H 0.00) and $CDCl_3$ (δ_C 77.1) as internal standards, respectively.

Organism and Culture Conditions. The cellular slime molds used in this study were (i) *D. discoideum* (NC-4), *D. longosporum* (C-193), and *D. rhizoposium* (C-224). *D. discoideum* and the other two species were kindly supplied by Professor Y. Maeda, Tohoku University, and Dr. H. Hagiwara, National Science Museum, Ibaraki, Japan, respectively. Spores of theses species were cultured at 22 °C with *E. coli* Br on A-medium consisting of 0.5% glucose, 0.5% polypeptone, 0.05% yeast extract, 0.225% KH_2PO_4, 0.137% $Na_2HPO_4 \cdot 12H_2O$, 0.05% $MgSO_4 \cdot 7H_2O$, and 1.5% agar. When the fruit body had been formed in several days, they were harvested for extraction.

Measurement of Isometric Contraction. The thoracic aorta was prepared from male wister rats. The endothelium was removed by gently rubbing the endothelial surface with cotton pellets. The deendothelialization was checked by the abolition of acetylcholine-induced relaxation. The aorta was cut into helical strips approximately 1.5−2 mm in width and 20 mm in length. One end of the strip was secured to the glass tissue holder by a silk ligature, and the other end was connected to a force-displacement transducer. The strip was suspended in a 20 mL organ bath containing HEPES-buffered Krebs solution of the following composition (mM): NaCl (120), KCl, (4.8), $MgSO_4$, (1.3), glucose, (5.8), $CaCl_2$, (1.2), KH_2PO_4, (1.2), $NaHCO_3$, (12.6), HEPES, (10). The solution was gassed with 95% O_2−5% CO_2. The tissues were equilibrated for 1 h under a resting tension of 1 g. Isometric contraction was then measured by the transducer. The strip was precontracted three times by adding KCl (final concentration 60 mM).

Isolation of Dictyopyrone A (1) and B (2). The cultured fruit body (wet 109 g) of *D. discoideum* was extracted twice with methanol at room temperature to give the extract (5.6 g). The methanol extract (5.6 g) was partitioned with ethyl acetate and water to yield ethyl acetate solubles (1.1 g). The ethyl acetate solubles were chromatographed over SiO_2, and the column was eluted with *n*-hexane−ethyl acetate mixtures with increasing polarity. *n*-Hexane−ethyl acetate (4:1) eluent was further chromatographed over SiO_2 using an *n*-hexane−diethyl ether mixture, followed by SiO_2 column chromatography using *n*-hexane−chloroform to give crude dictyopyrones. The crude sample was purified with ODS column, and then **1** (2.1 mg) and **2** (0.4 mg) were obtained. In the same manner, the cultured fruit body (wet 202 g) of *D. rhizoposium* gave **1** (3.3 mg) and **2** (2.7 mg). A colorless needle crystal was

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generated in a very concentrated solution of **1** or **2** in an *n*-hexane−ethyl acetate mixture. Data for **1**: $[\alpha]^{25}_{D}$ +33.8 (*c* 0.071, $CHCl_3$); a colorless needle; mp 31−32 °C; UV λ_{max} (hexane) (nm (log ϵ)) 216 (sh, 3.72); CD λ (dioxane) (nm ($\Delta\epsilon$)) 269.6 (1.67), 234.0 (3.92); IR ν_{max} ($CHCl_3$) 1707 cm^{-1}; ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) data are shown in Table 1; HREI-MS *m*/*z* 306.2200 $[M]^+$ (306.2193 calcd for $C_{19}H_{30}O_3$). Data for **2**: $[\alpha]^{25}_{D}$ +36.6 (*c* 0.160, $CHCl_3$); a colorless needle; UV λ_{max} (hexane) (nm (log ϵ)) 215 (sh, 3.84); CD λ (dioxane) (nm ($\Delta\epsilon$)) 261.6 (sh, 1.80), 236.2 (3.75), 207.8 (−0.58); ^1H NMR (500 MHz) data are shown in Table 1; HREI-MS *m*/*z* 334.2467 $[M]^+$ (334.2508 calcd for $C_{21}H_{34}O_3$).

Isolation of Dictyopyrone C (3). **3** (0.5 mg) was obtained in the same manner described in the case of **1** from the methanol extract of the cultured fruit body of *D. longosporum* (wet 11 g). Data for **3**: $[\alpha]^{25}_{D}$ +71.0 (*c* 0.031, $CHCl_3$); an amorphous solid; UV λ_{max} (hexane) (nm (log ϵ)) 214 (sh, 3.80); CD λ (dioxane) (nm ($\Delta\epsilon$)) 261.4 (sh, 2.26), 238.2 (4.67), 207.6 (−1.15); ^1H NMR (300 MHz) data are shown in Table 1; EI-MS *m*/*z* 308 $[M]^+$.

Benzyl Hydrogen Tridecanedioate (7). Potassium hydroxide solution (10%) in methanol (11.0 mL, 19.7 mmol) was added dropwise to a stirred solution of tridecanedioic acid (**6**) (4.8 g, 19.7 mmol, Wako Pure Chemicals, Osaka) in methanol (150 mL) at room temperature, and then a colorless salt precipitated. After being stirred for 20 min, the mixture was evaporated to give the monopotassium salt of tridecanedioic acid. This salt was suspended in dry toluene (50 mL), and the reaction mixture was mixed with tetra-*n*-butylammonium bromide (546 mg, 1.97 mmol) and benzyl bromide (2.57 mL, 21.6 mmol). The mixture was refluxed for 6 h. After being cooled to room temperature, the mixture was poured into 0.5 M hydrochloric acid (100 mL) and extracted with diethyl ether three times. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by SiO_2 column chromatography (*n*-hexane:EtOAc = 19:1, 4:1, and 2:1) to give dibenzyl ester (1.83 g, 22%), monobenzyl ester (**7**) (3.42 g, 52%), and recovered tridecanedioic acid (1.15 g, 24%). Data for **7**: a colorless needle; ^1H NMR (300 MHz) δ 7.3−7.4 (5H, m), 5.12 (2H, s), 2.35 (2H, t, *J* = 7.4 Hz), 2.34 (2H, t, *J* = 7.4 Hz), 1.55−1.70 (4H, m), 1.2−1.4 (14H, m); ^{13}C NMR (75 MHz) δ 180.3, 174.0, 136.3, 128.7 (2C), 128.3 (3C), 66.1, 34.3, 34.0, 29.4, 29.3 (2C), 29.2 (2C), 29.0, 29.0, 24.9, 24.6; EI-MS *m*/*z* 334 $[M]^+$, 316, 306, 288, 227, 107, 91; HREI-MS *m*/*z* 334.2133 (334.2144 calcd for $C_{20}H_{30}O_4$).

Benzyl 11-Dodecenoate (8). Monobenzyl tridecanedioate (**7**) (5.64 g, 16.9 mmol), lead(IV) tetraacetate (15.0 g, 33.8 mmol), copper(II) acetate monohydrate (674 mg, 3.38 mmol), and pyridine (682 mL, 8.44 mmol) were dissolved in benzene (60 mL), stirred for 30 min at room temperature, and refluxed for 4 h. After cooling, the mixture was filtrated through Celite with diethyl ether. The filtrate was washed with 0.5 M hydrochloric acid, water, and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by SiO_2 column chromatography (*n*-hexane:EtOAc = 19:1 and 4:1) to give **8** (2.13 g, 44%) and recovered **7** (2.35 g, 42%). Data for **8**: a colorless oil; ^1H NMR (300 MHz) δ 7.3−7.4 (5H, m), 5.80 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz), 5.11 (2H, s), 4.99 (1H, ddt, *J* = 17.0, 2.2, 1.1 Hz), 4.92 (1H, ddt, *J* = 10.2, 2.2, 1.1 Hz), 2.35 (2H, t, *J* = 7.5 Hz), 2.03 (2H, q, *J* = 7.2 Hz), 1.64 (2H, quint, *J* = 7.5 Hz), 1.2−1.4 (12H, m); ^{13}C NMR (75 MHz) δ 173.9, 139.4, 136.3, 128.7 (2C), 128.3 (3C), 114.3, 66.1, 34.3, 33.8, 29.4 (2C), 29.2, 29.1 (2C), 28.9, 24.9; EI-MS *m*/*z* 288 $[M]^+$, 197, 182, 108, 91 (base); HREI-MS *m*/*z* 288.2087 (288.2088 calcd for $C_{19}H_{28}O_2$).

Benzyl (*E*)-10-Dodecenoate (9). Cobalt(II) chloride (230 mg, 1.77 mmol) and triphenylphosphine (1.39 g, 5.30 mmol) were dissolved in dry THF (12 mL) under argon at −18 °C. After being stirred for 15 min, this suspension was treated with sodium borohydride (66.9 mg, 1.77 mmol) and stirred for 30 min. Solution of **8** (255 mg, 0.88 mmol) in dry THF (6 mL) was added, and the mixture was kept for 24 h. The mixture was poured into 1 M hydrochloric acid (10 mL) and extracted with diethyl ether three times. The organic layer was combined, evaporated, suspended with methanol (15 mL), and extracted with *n*-hexane twice. The *n*-hexane layer was combined and evaporated. The residue was separated by SiO_2 column chromatography (*n*-hexane:benzene = 3:1) to give a mixture of **9** and benzyl (*Z*)-10-dodecenoate (232 mg, 0.806 mmol, 91%). HPLC analysis showed that the ratio of *E*-isomer to *Z*-isomer was 12:1. The *E*/*Z* mixture was used as **9** without further purification throughout the following synthetic scheme. Data for **9**: a colorless oil; ^1H NMR (300 MHz) δ 7.3−7.4 (5H, m), 5.39−5.42 (2H, m), 5.11 (2H, s), 2.35 (2H, t, *J* = 7.6 Hz), 1.9−2.0 (2H, m), 1.65 (2H, dt, *J* = 4.7, 1.4 Hz), 1.6−1.7 (2H, m), 1.2−1.4 (10H, m); ^{13}C NMR (75 MHz) δ 173.9, 136.3, 131.8, 128.7 (2C), 128.3 (3C), 124.7, 66.1, 34.3, 32.6, 29.6, 29.5, 29.3, 29.2, 29.1, 24.9, 17.9; EI-MS *m*/*z* 288 $[M]^+$, 197, 179, 161, 137, 91 (base); HREI-MS *m*/*z* 288.2079 (288.2088 calcd for $C_{19}H_{28}O_2$).

(*E*)-10-Dodecenoic Acid (10). **9** (841 mg, 2.92 mmol) was dissolved in acetonitrile (50 mL), and 1 M sodium hydroxide (10 mL) was added to this solution. The reaction was carried out at 60 °C for 24 h. The mixture was poured into 1 M hydrochloric acid (30 mL) and extracted with diethyl ether three times. The organic layer was extracted with 1 M sodium hydroxide three times to remove benzyl alcohol. The aqueous layer was collected, acidified with 1 M hydrochloric acid again, and extracted with diethyl ether three times. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by SiO_2 column chromatography (*n*-hexane:EtOAc = 4:1) to give **10** (contained *Z*-isomer) (571 mg, 99%). Data for **10**: a colorless oil; ^1H NMR (300 MHz) δ 11.5−11.6 (1H, br.s), 5.39−5.42 (2H, m), 2.32 (2H, t, *J* = 7.5 Hz), 1.9−2.0 (2H, m), 1.65 (2H, dt, *J* = 4.7, 1.4 Hz), 1.6−1.7 (2H, m), 1.2−1.4 (10H, m); ^{13}C NMR (75 MHz) δ 180.8, 131.7, 124.7, 34.1, 32.5, 29.6, 29.5, 29.3, 29.2, 29.1, 24.6, 17.8; EI-MS *m*/*z* 198 $[M]^+$, 180, 138, 55 (base); HREI-MS *m*/*z* 198.1593 (198.1620 calcd for $C_{12}H_{22}O_2$).

(1*S*,3*S*)-3-Hydroxy-1-methylbutyl (*E*)-3-Oxotetradec-12-enoate (12). Thionyl chloride (0.5 mL) and *N*,*N*-dimethylformamide (50 mg) were added to a solution of **10** (268 mg, 1.35 mmol) in benzene (2 mL). After the mixture was refluxed for 2 h, the solvent was evaporated. The residue was dissolved in dichloromethane (2 mL) at 0 °C. Meldrum's acid (214 mg, 1.49 mmol; Nacalai Tesque, Kyoto) and 4-(dimethylamino)-pyridine (330 mg, 2.70 mmol) in dichloromethane (2 mL) were added to this solution. After being stirred for 1.5 h at 0 °C and 1 h at room temperature, the mixture was evaporated and dissolved in diethyl ether. This solution was poured into 1 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was combined, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was mainly composed of 5-[(*E*)-10-dodecenoyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**11**), but purification was not carried out because of its unstableness. (2*S*,4*S*)-2,4-Pentanediol (422 mg, 4.06 mmol; Wako Pure Chemicals, Osaka) and **11** in benzene were refluxed for 3 h, cooled to room temperature, and evaporated. The residue in diethyl ether was washed with 0.5 M sodium hydroxide, water, and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by SiO_2 column chromatography (*n*-hexane:ethyl acetate = 4:1) to give **12** (contained *Z*-isomer) (287 mg, 65%). Data for **12**: a colorless oil; ^1H NMR (300 MHz) δ 5.39−5.42 (2H, m), 5.21 (1H, tq, *J* = 3.3, 6.3 Hz), 3.75−3.9 (1H, m), 3.46 (2H, s), 2.85−2.9 (1H, br s), 2.52 (2H, t, *J* = 7.4 Hz), 1.9−2.0 (2H, m), 1.5−1.7 (6H, m), 1.2−1.4 (10H, m), 1.28 (3H, d, *J* = 6.3 Hz), 1.19 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (75 MHz) δ 203.5, 167.9, 131.6, 124.7, 69.6, 63.4, 49.4, 45.6, 43.1, 32.5, 29.4, 29.2, 29.1, 29.0, 28.9, 23.3, 23.1, 20.5, 17.8; EI-MS *m*/*z* 327 $[M]^+$, 309, 241, 222, 69, 55, 45 (base); HREI-MS *m*/*z* 327.2515 (327.2533 calcd for $C_{19}H_{35}O_4$).

(*S*)-3-Oxo-1-methylbutyl (*E*)-3-Oxotetradec-12-enoate (13). **12** (261 mg, 0.80 mmol) in DMF (5 mL) was treated with PDC (904 mg, 2.40 mmol) at room temperature for 12 h. The mixture was filtrated through Celite with diethyl ether. The filtrate was washed with 0.5 M hydrochloric acid, water, and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by SiO_2 column chromatography (*n*-hexane:ethyl acetate = 4:1) to give **13** (contained *Z*-isomer)

(234 mg, 90%). Data for **13**: a colorless oil; ^{1}H NMR (300 MHz) δ 5.35−5.45 (4H, m), 3.39 (2H, s), 2.84 (1H, dd, J = 16.8, 6.9 Hz), 2.59 (1H, dd, J = 16.8, 6.8 Hz), 2.51 (2H, t, J = 7.4 Hz), 2.16 (3H, s), 1.9−2.0 (2H, m), 1.64 (3H, dd, J = 3.2, 1.2 Hz), 1.55−1.65 (2H, m), 1.30 (3H, d, J = 8.3 Hz), 1.2−1.4 (10H, m); ^{13}C NMR (75 MHz) δ 205.4, 203.2, 166.7, 131.7, 124.7, 68.0, 49.3, 49.1, 42.9, 32.5, 30.3, 29.5, 29.2, 29.1, 29.0, 28.9, 23.3, 19.7, 17.8; EI-MS m/z 325 $[M + H]^+$, 222, 85, 43 (base); HREI-MS m/z 325.2406 (325.2377 calcd for $C_{19}H_{33}O_4$).

(*S*)-3-[(*E*)-Dodec-12-enoyl]-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (Dictyopyrone A) (1). An acetonitrile solution (4 mL) of **13** (47.3 mg, 0.15 mmol) was treated with potassium carbonate (300 mg) at 55 °C for 24 h. The reaction mixture was filtered, and the filtrate was poured into 1 M hydrochloric acid (15 mL) and extracted with diethyl ether three times. The organic layer was combined, washed with water and brine, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by SiO_2 column chromatography (*n*-hexane:ethyl acetate = 4:1) to give **1** (contained *Z*-isomer) (17 mg, 37%) and **13** (21 mg, 45%). **1** and its *Z*-isomer were separated by preparative HPLC using TSKgel ODS 120A (25 i.d. × 250 mm, TOSOH, Tokyo) by a linear gradient of water−acetonitrile (4:6−0:10). Data for synthetic **1**: $[\alpha]^{25}_D$ +33.9 (*c* 1.234, $CHCl_3$); other spectral data were identical with those of the natural product. Data for the *Z*-isomer of **1**: ^{1}H NMR (300 MHz) δ 5.35−5.47 (2H, m), 4.55 (1H, ddq, J = 3.8, 6.3, 11.7 Hz), 2.74 (2H, dt, J = 1.4, 7.4 Hz), 2.45 (1H, dd, J = 18.1, 11.7 Hz), 2.33 (1H, dd, J = 18.1, 3.8 Hz), 2.01 (3H, s), 1.95−2.10 (2H, m), 1.60 (3H, d, J = 5.5 Hz), 1.55−1.65 (2H, m), 1.44 (3H, d, J = 6.3 Hz), 1.2−1.4 (10H, m).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for natural and synthetic compound **1**, and ^{1}H NMR spectra for **2**, **3**, and **1*Z***. This material is available free of charge via the Internet at http://pubs.acs.org.

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