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Bioorganic & Medicinal Chemistry 12 (2004) 3203–3214
Bioorganic & Medicinal Chemistry

Structural requirements of dictyopyrones isolated from *Dictyostelium* spp. in the regulation of *Dictyostelium* development and in anti-leukemic activity

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Received 24 February 2004; revised 31 March 2004; accepted 1 April 2004
Available online 8 May 2004

Abstract—Cellular slime molds are fascinating to the field of developmental biology, and have long been used as excellent model organisms for the study of various aspects of multicellular development. We have recently isolated α-pyronoids, named dictyopyrones A–D (**1**–**4**), from various species of *Dictyostelium* cellular slime molds, and it was shown that compound **3** may regulate *Dictyostelium* development. In this study, we synthesized dictyopyrones A–D (**1**–**4**) and their analogues, investigated the physiological role of the molecules in cell growth and morphogenesis in *D. discoideum*, and further verified their effects on human leukemia K562 cells. Nitrogen-containing compounds **22** and **37** strongly inhibited cell growth in K562 leukemia cells, indicating that these compounds may be utilized as novel lead compounds for anti-leukemic agents.

1. Introduction

During certain periods of their life cycles, cellular slime molds such as *Dictyostelium* spp. form an animal-like feeding stage that later undergoes transition into a plant-like fruiting body stage. Such organisms are fascinating to the field of developmental biology, and have long been used as excellent model organisms for the study of various aspects of multicellular development, including signal transduction, cell motility, and cell differentiation.[1] Several chemical stimuli, such as DIF-1,[2] discadenine,[3] and cAMP,[4] have been identified as physiologically active substances, which act during the life cycle *of Dictyostelium discoideum*.

DIF-1 was originally identified as a factor that induces stalk cell differentiation in *D. discoideum*.[2] On the other hand, differanisole A, which has structural similarity to DIF-1, was isolated from the fungus *Chaetomium* sp. as a factor that induces erythroid differentiation in murine erythroleukemia B8 cells in vitro.[5] Furthermore, this factor was then found to induce the differentiation of some human tumor cells.[6] Interestingly, it has been shown that differanisole A induces stalk cell differentiation in vitro in *D. discoideum*[10] and also that DIF-1 induces growth arrest and erythroid differentiation in murine and human leukemia cells.[7] It has also been demonstrated that DIF-1 suppresses cell growth in rat pancreatic tumor AR42J cells[8] and human myeloid leukemia HL-60 cells.[9] These findings suggest that the chemical structure shared by DIF-1 and differanisole A may play an important role in cell growth and differentiation in multiple species and also that there might be some other substances having such a role in lower eukaryotic organisms.

We have recently isolated α-pyronoids, named dictyopyrones A–D (**1**–**4**), from various species of *Dictyostelium* cellular slime molds.[11] As only very small amounts of compounds **1**–**4** were isolated as minor constituents *of Dictyostelium* in our previous study,[11] syntheses of these compounds were required for further biological

Keywords: Cellular slime molds; *Dictyostelium discoideum*; α-pyrone; Anti-leukemic activity.
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doi:10.1016/j.bmc.2004.04.001

evaluation. Therefore, dictyopyrone C (**3**), which bears a saturated hydrocarbon side chain, was synthesized and its activity on *Dictyostelium* development was assessed. It was demonstrated that compound **3** inhibit cell growth and enhance morphogenesis in *D. discoideum*.[12] However, there are many aspects of the putative physiological and pharmacological roles of dictyopyrone-like molecules that are currently unknown.

In this study, we were prompted to synthesize dictyopyrones A–D (**1**–**4**) and their analogues. We then investigated the physiological roles of these molecules in cell growth and morphogenesis in *D. discoideum* and further verified their effects on human leukemia K562 cells. We show here that some dictyopyrone analogues regulated cell growth and morphogenesis in *D. discoideum* and also that some molecules suppressed cell growth in K562 cells in vitro.

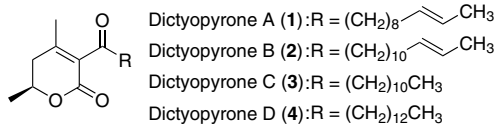
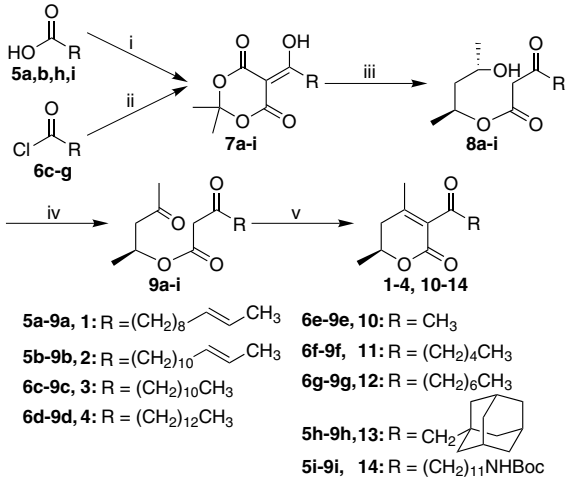


Chart 1. The structures of dictyopyrones A–D (**1**–**4**).

2. Results and discussion

2.1. Syntheses of dictyopyrones and their analogues

Syntheses of dictyopyrones A–D (**1**–**4**) and their analogues (**10**–**14**), which have modified side chains, are based on our previous work[11] (Scheme 1). Carboxylic acids **5** or acid chlorides **6** were condensed with Meldrum's acid to yield 5-acyl compounds **7**.[13] Alcoholysis of **7** with (2*S*,4*S*)-2,4-pentanediol gave β-ketoesters **8**. Oxidation of **8** and subsequent intramolecular aldol condensation allowed us to generate dictyopyrones A–D (**1**–**4**) and their analogues (**10**–**14**).



Scheme 1. The general procedure for the synthesis of dictyopyrones (**1**–**4**) and their analogues (**10**–**14**). Reagents and conditions: (i) Meldrum's acid, EDCI·HCl, DMAP, CH_2Cl_2, rt; (ii) Meldrum's acid, DMAP, CH_2Cl_2, rt; (iii) (2*S*,4*S*)-2,4-pentanediol, toluene, 80 °C; (iv) PCC, CH_2Cl_2, rt; (v) EtONa, EtOH, 0 °C.

In our previous report,[11] the *E*-double bond in the side chain of **1** was prepared by isomerization of the terminal olefin with a cobalt-containing complex; however, the isomerization gave rise to a configurational mixture ($E/Z = 12/1$). Although it was possible to separate the *E*- and *Z*-isomers using HPLC, this was tedious to carry out on a preparative scale. Therefore, a modified method for preparation of the *E*-olefin using the Horner–Emmons reaction was developed (Scheme 2). One of the hydroxyl groups in 1,10-decanediol (**15a**) was protected with a methoxymethyl group to produce **16a**. Oxidation of **16a** by PCC gave an aldehyde that was then reacted with ethyl diethylphosphonoacetate to yield, as a sole product, the α,β-unsaturated ester **17a**, which bears the *E*-olefin. Compound **17a** was reduced with DIBAL-H to yield the allyl alcohol **18a**. Reaction of **18a** with sulfur trioxide–pyridine complex, and reduction of the resulting reaction product with LAH gave the dehydrated product **19a**.[14] Deprotection of **19a** afforded **20a**, which was oxidized with PDC in DMF to afford carboxylic acid **5a**. Carboxylic acid **5a** was used as a starting material in Scheme 1. In a similar manner, carboxylic acid **5b**, which has the same side chain as compound **2**, was prepared from 1,12-dodecanediol (**15b**).

In Scheme 1, commercially available lauroyl chloride (**6c**) and myristoyl chloride (**6d**) were used as starting materials to generate **3** and **4**, respectively. Analogues **10**–**12**, which bear shorter side chains, were synthesized from their corresponding acid chlorides **6e**–**g** to find how many carbons in C-3 side chain are crucial for biological activities. Adamantaneacetic acid (**5h**) was converted into analogue **13**, in which bulkiness was added to the side chain.

ω-Amino substituted derivative **22** was synthesized for additional water solubility as described in Scheme 3.

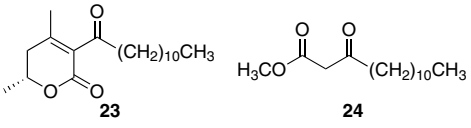
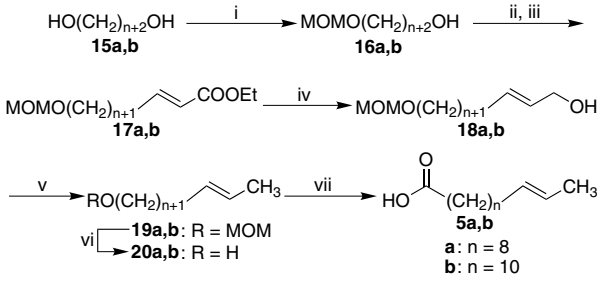
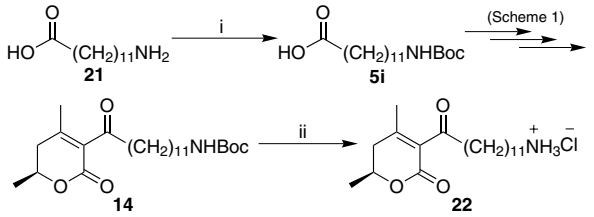


Chart 2. The structures of **23** and **24**.



Scheme 2. Synthesis of **5a** and **5b**. Reagents and conditions: (i) MOMCl, DIPEA, CH_2Cl_2, rt; (ii) PCC, CH_2Cl_2, rt; (iii) ethyl diethylphosphonoacetate, NaH, benzene, 0 °C; (iv) DIBAL-H, CH_2Cl_2, −20 °C; (v) SO_3 · pyridine, THF, then LAH, rt; (vi) 2M HCl, THF, reflux; (vii) PDC, DMF, rt.

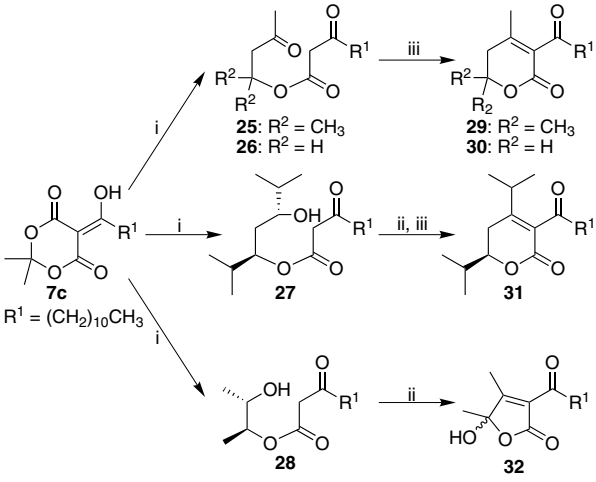


Scheme 3. Synthesis of ω-amino analogue **22**. Reagents and conditions: (i) $(Boc)_2O$, NaOH, dioxane–H_2O (1:1), rt; (ii) 10% HCl–MeOH, rt.

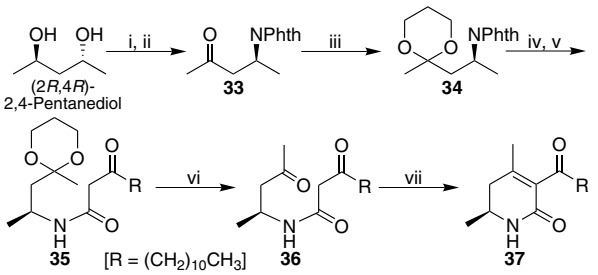
Protection of 12-aminolauric acid (**21**) gave the *N*-Boc derivative **5i**, which was converted into compound **14** via Scheme 1. The subsequent deprotection of **14** under acidic conditions afforded **22** as a hydrochloride salt. The use of (*2R*,*4R*)-2,4-pentanediol instead of (*2S*,*4S*)-2,4-pentanediol in the same method used to synthesize **3** led to analogue **23**, which is an enantiomer of **3**. Methanolysis of **7c** gave acyclic β-ketoester **24**, which is equivalent to a compound lacking C-4–C-8 in the α-pyrone moiety of **3**.

To elucidate effects of substituents on α-pyrone ring and its ring size, syntheses of **29**–**32**, in which the carbon length of the side chain was fixed at 12 as in compound **3**, were also carried out (Scheme 4). Reaction of 5-lauroyl Meldrum's acid (**7c**) with four commercially available alcohols gave the β-ketoesters **25**–**28**. Compounds **25**–**27** were converted into α-pyrones **29**–**31**, in which the 4,6-dimethyl substituents in **3** were modified to 4,6,6-trimethyl, 4-methyl, or 4,6-diisopropyl substituents, respectively. Oxidation of **28** by PCC resulted in the unexpected generation of γ-hydroxy-γ-lactone **32**.

Compound **37**, the 1-aza derivative of **3**, was synthesized using Scheme 5. Mitsunobu reaction of (2*R*,4*R*)-2,4-pentanediol with phthalimide, and subsequent oxidation by PCC afforded compound **33**, which was converted



Scheme 4. Synthesis of **29**–**32**. Reagents and conditions: (i) 4-hydroxy-4-methylpentan-2-one (for **25**), 4-hydroxybutan-2-one (for **26**), (*3S*,*5S*)-2,6-dimethylheptane-3,5-diol (for **27**) or (25,35)-2,3-butanediol (for **28**), toluene, 80 °C; (ii) PCC, CH_2Cl_2, rt; (iii) EtONa, EtOH, 0 °C.



Scheme 5. Synthesis of 1-aza derivative **37**. Reagents and conditions: (i) phthalimide, Ph_3P, DEAD, THF, 0 °C; (ii) PCC, CH_2Cl_2, rt; (iii) 1,3-propanediol, *p*TsOH, benzene, reflux; (iv) H_2NNH_2·HCl, MeOH, reflux; (v) **7c**, toluene, 80 °C; (vi) 80% AcOH, rt; (vii) EtONa, EtOH, 0 °C.

into acetal **34**. Aminolysis of **6c** by primary amine, which was afforded by treatment of **34** with hydrazine, produced β-ketoamide **35**.[15] After deprotection of **35**, intramolecular cyclization in the presence of sodium ethoxide yielded **37**.

2.2. Effects of dictyopyrones and their analogues on *Dictyostelium* cellular slime mold

The effects of dictyopyrones (**1**–**4**) and their analogues on cell growth and morphogenesis in *D. discoideum* were evaluated at concentrations of 30 and 10 μM, respec-

Table 1. The effects of dictyopyrones and their analogues on growth and morphogenesis of *D. discoideum* Ax-2 cells

Compounds	Inhibitory effect on growth[a]	Effect on morphogenesis[b]
Dictyopyrone A (**1**)	+	↑
Dictyopyrone B (**2**)	–	↑
Dictyopyrone C (**3**)	+	↑
Dictyopyrone D (**4**)	–	↑
10	–	–
11	–	–
12	+	↑
13	+	–
22	–	↑
23	+	↑
24	++	–[c]
29	+	–
30	++	↓
31	–	↑
32	++	↓
37	++	↓

[a] Ax-2 (MS) cells at the mid-late exponential growth phase (5×10^6 cells/mL) were placed at 2.5×10^5 cells/mL in fresh PS medium containing 30 μM of each compound. This was followed by incubation for 1 h at 22 °C. –, no effects (cells were morphologically normal.); +, moderate inhibition (almost all of the cells were round in shape.); ++, strong inhibition (almost all of the cells were lysed).

[b] Ax-2 (MS) cells at the mid-late exponential growth phase (5×10^6 cells/mL) were settled at 1.1×10^5 cells/cm^2 in BSS containing 10 μM of each compound. This was followed by incubation at 22 °C. ↓, inhibition (almost all of the cells were rounded and then lysed); –, no effects (the aggregation time of the cells was the same as for control cells incubated in BSS with 0.05% DMSO); ↑, enhancement (cells aggregated earlier than control cells).

[c] Inhibitory effects on differentiation were noted when cells were treated with 18 μM or higher concentrations of **24**.

tively (Table 1). Dictyopyrones A and C (**1** and **3**), which have 12 carbon side chains at C-3 with or without an *E*-double bond, inhibited cell growth and enhanced cell aggregation. Dictyopyrones B and D (**2** and **4**), which bear 14 carbon side chains with or without an *E*-double bond, only enhanced aggregation. These findings demonstrate that the presence of an *E*-olefin in the C-3 side chain should not be important for the biological activity of dictyopyrones in *Dictyostelium*. Evaluation of the shorter C-3 hydrocarbon side chain analogues indicated that the activity of analogue **12**, which contains an eight carbon side chain, was equivalent to the activity of **3**, while compounds **10** and **11**, which have two and six carbon side chains, respectively, had no activity on either cell growth or morphogenesis. Furthermore, we found that a hydrocarbon side chain containing eight or more carbon atoms was critical for enhancement of cell aggregation, while a side chain containing between 8 and 12 carbon atoms was required for the inhibition of cell growth. Analogue **13**, which contains a bulky adamantyl group in place of a 12 carbon linear chain, retained an inhibitory effect on cell growth, but showed no effect on morphogenesis. In contrast, compound **22** only enhanced morphogenesis. β-Ketoester **24** was a potent inhibitor of cell growth but had no effect on morphogenesis. This suggests that the α-pyrone ring is critical for the effects of these compounds on morphogenesis.

The activity of analogue **23** was identical to the activity of **3**, suggesting that the stereochemistry at the C-6 position is not important for activity. However, the requirements of the C-4 and C-6 methyl groups for biological activity were not distinctly accounted for in the comparative studies of **3** and its analogues **29**, **30**, and **31**.

Aza-analogue **37** and hydroxylactone **32** strongly inhibited both cell growth and morphogenesis of *D. discoideum* cells.

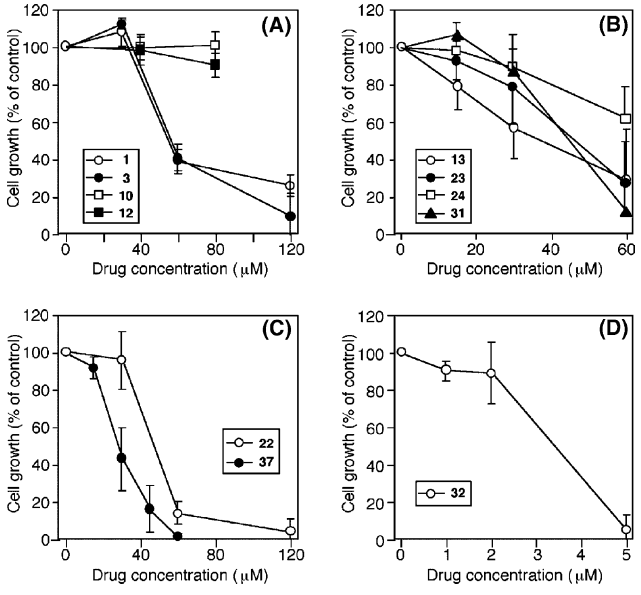


Figure 1. The effects of dictyopyrones and their analogues on the growth of human leukemia K562 cells.

2.3. Effects of dictyopyrone analogues on cell growth in human leukemia K562 cells

In order to assess whether dictyopyrones A–D (**1**–**4**) and their analogues have therapeutic potential in the treatment of leukemia, we examined and compared the effects of structurally related analogues on cell growth in human leukemia K562 cells. As shown in Figure 1A, dictyopyrones A and C (**1** and **3**) suppressed cell growth in a similar manner; at 60 μM these compounds suppressed cell growth by about 60%. At concentrations of up to 80 μM, compounds **10** and **12** did not affect cell growth, suggesting that a 12 carbon side chain is required for inhibition of growth in these cells, even though eight carbon or longer side chains were sufficient for inhibition of *Dictyostelium* cell growth.

Compounds **13**, **23**, and **31** suppressed cell growth in a dose dependent manner, as shown in Figure 1B. The effect of **24** was weaker than the effects of **1** and **3**, indicating that the structures of both the α-pyrone ring and the hydrocarbon side chain are important for the inhibition of cell growth.

The nitrogen-containing compounds **22** and **37** were more potent inhibitors of cell growth (Fig. 1C), while compound **32** was very toxic; most cells died in the presence of greater than 2 μM **32** (Fig. 1D).

3. Conclusion

In this study, we synthesized dictyopyrones A–D (**1**–**4**) and their analogues, and assessed their physiological and pharmacological activities. Since dictyopyrone A (**1**), C (**3**), and the synthesized analogues (**13**, **23**, **32**, and **37**) inhibited cell growth in both *D. discoideum* and K562 cells, there may be similar mechanisms of cell growth in *Dictyostelium* and tumor cells, although several compounds acted differently on the two types of cell.

In addition, nitrogen-containing compounds 22 and 37 strongly inhibited cell growth in K562 leukemia cells, indicating that these compounds may be utilized as novel lead compounds for anti-leukemic agents. It will be necessary to examine the in vitro and in vivo effects of dictyopyrone analogues on many other tumor cell types in order to develop more potent anti-tumor agents in the near future.

4. Experimental section

4.1. General methods

Analytical TLC was performed on silica gel 60 F254 (Merck) and RP-18 F254s (Merck). Column chromatography was carried out on silica gel 60 (70–230 mesh, Merck), and Cosmosil 140C18-OPN (Nacalai Tesque, Kyoto, Japan). NMR spectra were recorded on JEOL

JNM GX-500, AL-400, and Varian Gemini 2000. Mass spectra were measured on JEOL JMS DX-303, AX-500, and AX-700.

4.1.1. (1*S*,3*S*)-3-Hydroxy-1-methylbutyl (*E*)-3-oxotetradec-12-enoate (8a). To a solution of **5a** (286 mg, 1.44 mmol) in CH_2Cl_2 (8 mL) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (459 mg, 2.39 mmol), Meldrum's acid (396 mg, 2.75 mmol), and DMAP (35.6 mg, 0.29 mmol) at 0 °C. After being stirred for 2 h, the mixture was poured into 1 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give crude 5-acyl Meldrum's acid **7a**. This crude and (2*S*,4*S*)-2,4-pentanediol (249 mg, 2.39 mmol) were dissolved in toluene (5 mL). After being heated at 80 °C for 3 h, this mixture was evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **8a** (195 mg, 42% from **5a**). **8a**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, $J = 6.3$ Hz), 1.24–1.30 (10H, m), 1.28 (3H, d, $J = 6.3$ Hz), 1.53–1.72 (4H, m), 1.64 (3H, dq, $J = 3.3$, 1.4 Hz), 1.96 (2H, m), 2.52 (2H, t, $J = 7.4$ Hz), 3.46 (2H, s), 3.83 (1H, m), 5.22 (1H, dqd, $J = 9.6$, 6.3, 3.3 Hz), 5.35–5.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 20.7, 23.3, 23.5, 29.0, 29.1, 29.3, 29.3, 29.6, 32.6, 43.2, 45.7, 49.5, 63.5, 69.6, 124.5, 131.5, 167.6, 203.0; HREIMS m/z 326.2422 $[M]^+$ (326.2455 calcd for $C_{19}H_{34}O_4$).

In the similar procedure, compounds **8b** (yield 50%), **8h** (14%), and **8i** (35%) were prepared from the corresponding carboxylic acid (**5b**, **5h**, and **5i**), respectively. (*1S*,*3S*)-3-Hydroxy-1-methylbutyl (*E*)-3-oxohexadec-14-enoate (**8b**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, $J = 6.3$ Hz), 1.24–1.30 (14H, m), 1.28 (3H, d, $J = 6.3$ Hz), 1.53–1.72 (4H, m), 1.64 (3H, dq $J = 3.3$, 1.4 Hz), 1.95 (2H, m), 2.52 (2H, t, $J = 7.4$ Hz), 3.46 (2H, s), 3.83 (1H, m), 5.23 (1H, dqd, $J = 9.6$, 6.3, 3.3 Hz), 5.39–5.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.6, 23.2, 23.5, 29.0, 29.2, 29.3, 29.4, 29.5, 29.5, 29.6, 32.6, 43.2, 45.7, 49.5, 63.4, 69.5, 124.4, 131.5, 167.6, 203.0; HREIMS m/z 354.2798 $[M]^+$ (354.2770 calcd for $C_{21}H_{38}O_4$). (*1S*,*3S*)-3-Hydroxy-1-methylbutyl 4-(l-adamantyl)-3-oxobutanoate (**8h**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, $J = 6.0$ Hz), 1.24–1.30 (14H, m), 1.29 (3H, d, $J = 6.3$ Hz), 1.97 (3H, m), 2.26 (2H, s), 3.45 (2H, s), 3.85 (1H, dqd, $J = 9.1$, 6.0, 3.0 Hz), 5.22 (1H, dqd, $J = 9.9$, 6.3, 3.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 23.0,28.4 (3C), 33.6, 36.5 (3C), 42.2 (3C), 45.6, 49.9, 56.1, 63.4, 69.5, 167.8, 202.9; HREIMS m/z 322.2127 $[M]^+$ (322.2142 calcd for $C_{19}H_{30}O_4$). (*1S*,*3S*)-3-Hydroxy-1-methylbutyl 14-*tert*-butoxycarbonylamino-3-oxotetradecanoate (**8i**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, $J = 6.0$ Hz), 1.24–1.26 (14H, m), 1.29 (3H, d, $J = 6.3$ Hz), 1.39–1.51 (2H, m), 1.44 (9H, s), 1.52–1.65 (2H, m), 1.58 (1H, ddd, $J = 14.4$, 9.6, 3.0 Hz), 1.68 (1H, ddd, $J = 14.4$, 9.8, 3.0 Hz, H-2′b), 2.52 (2H, t, $J = 7.4$ Hz, H-4), 3.08 (2H, q, $J = 6.6$ Hz, H-14), 3.46 (2H, s), 3.84 (1H, dqd, $J = 9.8$, 6.0, 3.0 Hz), 5.23 (1H, dqd, $J = 9.6$, 6.3, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 23.0, 23.3, 26.6 (3C), 28.2, 28.3, 28.8, 29.2, 29.3, 29.3, 29.9, 35.0, 40.5, 43.1, 45.6, 49.4, 63.5, 69.5, 78.9, 156.1, 167.9, 203.4; HREIMS m/z 370.2651 $[M\text{-}t\text{BuO}]^+$ (370.2672 calcd for $C_{20}H_{36}NO_5$).

4.1.2. (1*S*,3*S*)-3-Hydroxy-1-methylbutyl 12-oxotetradecanoate (8c). To a solution of lauroyl chloride (219 mg, 1.00 mmol) in CH_2Cl_2 (3 mL) was added Meldrum's acid (159 mg, 1.10 mmol) and pyridine (162 μL, 2.00 mmol) at 0 °C. After being stirred for 3 h, the mixture was poured into 1 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated to give crude 5-acyl Meldrum's acid **7c**. This crude and (*2S*,*4S*)-2,4-pentanediol (156 mg, 1.10 mmol) were dissolved in toluene (3 mL). After being heated at 80 °C for 3 h, this mixture was evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **8c** (226 mg, 69% from **5c**). **8c**: Colorless powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.18 (3H, d, $J = 7.6$ Hz), 1.26–1.29 (16H, m), 1.28 (3H, d, $J = 3.1$ Hz), 1.55–1.63 (2H, m), 1.58 (1H, ddd, $J = 14.5$, 9.8, 3.1 Hz), 1.67 (1H, ddd, $J = 14.5$, 9.9, 2.9 Hz), 2.51 (2H, t, $J = 7.5$ Hz), 3.39 (2H, s), 3.83 (1H, m), 5.21 (1H, dqd, $J = 9.9$, 6.3, 3.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.5, 22.6, 23.1, 23.4, 28.9, 29.2, 29.3, 29.3, 29.4, 29.4, 31.8, 43.1, 45.6, 49.4, 63.4, 69.5, 167.6, 203.1; HREIMS m/z 329.2686 $[M+H]^+$ (329.2690 calcd for $C_{19}H_{37}O_4$).

In the similar procedure, compounds **8d** (yield 63%), **8e** (42%), **8f** (59%), and **8g** (49%) were prepared from the corresponding carboxylic acid (**5d**, **5e**, **5f**, and **5g**), respectively. (*1S*,*3S*)-3-Hydroxy-1-methylbutyl-3-oxohexadecanoate (**8d**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.7$ Hz), 1.19 (3H, d, $J = 6.3$ Hz), 1.24–1.28 (20H, m), 1.29 (3H, d, $J = 6.6$ Hz), 1.55–1.63 (2H, m), 1.58 (1H, ddd, $J = 14.6$, 9.6, 3.0 Hz), 1.68 (1H, ddd, $J = 14.6$, 9.6, 3.0 Hz), 2.53 (2H, t, $J = 7.3$ Hz), 3.47 (2H, s), 3.84 (1H, dqd, $J = 9.8$, 6.3, 3.0 Hz), 5.22 (1H, dqd, $J = 9.6$, 6.6, 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.4, 22.5, 23.0, 23.3, 26.1, 28.9, 29.2, 29.3, 29.5, 31.8, 43.1, 45.6, 49.4, 63.4, 69.5, 167.9, 203.4; HREIMS m/z 356.2925 $[M]^+$ (356.2924 calcd for $C_{21}H_{40}O_4$). (*1S*,*3S*)-3-Hydroxy-1-methylbutyl 3-oxobutanoate (**8e**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (3H, t, $J = 6.3$ Hz), 1.29 (3H, d, $J = 6.3$ Hz), 1.58 (1H, ddd, $J = 14.5$, 9.8, 3.1 Hz), 1.68 (1H, ddd, $J = 14.5$, 9.7, 3.0 Hz), 2.27 (3H, s), 3.48 (2H, s), 3.83 (1H, dqd, $J = 9.7$, 6.3, 3.0 Hz), 5.21 (1H, dqd, $J = 9.8$, 6.3, 3.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 23.2, 30.1, 45.5, 50.2, 63.4, 69.6, 167.4, 200.8; HREIMS m/z 188.1059 $[M]^+$ (188.1048 calcd for $C_9H_{16}O_4$). (*1S*,*3S*)-3-Hydroxy-1-methylbutyl 3-oxooctanoate (**8f**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.19 (3H, d, $J = 6.3$ Hz), 1.24–1.37 (4H, m), 1.28 (3H, d, $J = 6.3$ Hz), 1.54–1.72 (4H, m), 2.53 (2H, t, $J = 7.4$ Hz), 3.47 (2H, s), 3.84 (1H, dqd, $J = 9.5$, 6.3, 3.3 Hz), 5.23 (1H, dqd, $J = 9.6$, 6.3, 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 20.5, 20.5,

23.1, 23.2, 31.0, 43.0, 45.5, 49.4, 63.3, 69.5, 167.4, 203.0; HREIMS m/z 245.1760 $[M+H]^+$ (245.1751 calcd for $C_{13}H_{25}O_4$). (*1S*,*3S*)-3-Hydroxy-1-methylbutyl 3-oxodecanoate (**8g**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.0$ Hz), 1.16 (3H, d, $J = 6.3$ Hz), 1.21–1.28 (8H, m), 1.28 (3H, d, $J = 6.3$ Hz), 1.52–1.71 (4H, m), 2.53 (2H, t, $J = 7.3$ Hz), 3.46 (2H, s), 3.84 (1H, dqd, $J = 9.5, 6.3, 3.2$ Hz), 5.22 (1H, dqd, $J = 9.7$, 6.3, 3.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.5, 22.4, 23.1, 23.3, 26.1, 28.8, 31.5, 43.1, 45.6, 49.4, 63.4, 69.6, 167.9, 203.4; HREIMS m/z 272.1998 $[M]^+$ (272.1986 calcd for $C_{15}H_{28}O_4$).

4.1.3. (*S*)-1-Methyl-3-oxobutyl (*E*)-3-oxotetradec-12-enoate (9a). PCC (647 mg, 1.70 mmol) was added to a solution of **8a** (165 mg, 0.51 mmol) in CH_2Cl_2 (3 mL) at room temperature. After being stirred for 12 h, the mixture was filtered through a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **9a** (137 mg, 83%). **9a**: Colorless amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.27 (10H, m), 1.30 (3H, d, $J = 6.4$ Hz), 1.58 (2H, quint, $J = 7.3$ Hz), 1.64 (3H, dq, $J = 3.0$, 1.4 Hz), 1.96 (2H, m), 2.16 (3H, s), 2.51 (2H, t, $J = 7.3$ Hz), 2.59 (1H, dd, $J = 16.8$, 5.8 Hz), 2.83 (1H, dd, $J = 16.8$, 6.9 Hz), 3.39 (2H, s), 5.34 (1H, m), 5.39–5.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 19.9, 23.5, 29.0, 29.1, 29.3, 29.3, 29.6, 30.4, 32.6, 43.0, 49.2, 49.4, 68.1, 124.5, 131.5, 166.3, 202.7, 205.0; HREIMS m/z 324.2289 $[M]^+$ (324.2300 calcd for $C_{19}H_{32}O_4$).

In the similar procedure, compounds **9b–i** (yield: 75% (**9b**), 80% (**9c**), 82% (**9d**), 52% (**9e**), 77% (**9f**), 79% (**9g**), 70% (**9h**), and 54% (**9i**)) were prepared from **8b–i**, respectively. (*S*)-1-Methyl-3-oxobutyl (*E*)-3-oxohexadec-14-enoate (**9b**): Colorless amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.28 (14H, m), 1.30 (3H, d, $J = 6.6$ Hz), 1.58 (2H, quint, $J = 7.1$ Hz), 1.64 (3H, dq, $J = 3.3$, 1.4 Hz), 1.95 (2H, m), 2.16 (3H, s), 2.51 (2H, t, $J = 7.1$ Hz), 2.59 (1H, dd, $J = 16.8$, 5.8 Hz), 2.84 (1H, dd, $J = 16.8$, 7.1 Hz), 3.39 (2H, s), 5.36 (1H, m), 5.39–5.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.0, 23.4, 29.0, 29.1, 29.3, 29.4, 29.4, 29.5, 29.6, 30.4, 32.6, 43.0, 49.1, 49.4, 68.0, 124.4, 131.5, 166.3, 202.7, 205.0; HREIMS m/z 352.2623 $[M]^+$ (352.2612 calcd for $C_{21}H_{36}O_4$). (*S*)-1-Methyl-3-oxobutyl 3-oxotetradecanoate (**9c**): Colorless powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.25–1.30 (16H, m), 1.30 (3H, d, $J = 6.3$ Hz), 1.58 (2H, quint, $J = 7.2$ Hz), 2.16 (3H, s), 2.51 (2H, t, $J = 7.2$ Hz), 2.59 (1H, dd, $J = 16.9$, 5.8 Hz), 2.83 (1H, dd, $J = 16.9$, 7.1 Hz), 3.39 (2H, s), 5.34 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 19.8, 22.6, 23.4, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 30.3, 31.8, 42.9, 49.0, 49.3, 68.0, 166.4, 202.8, 205.0; HREIMS m/z 326.2502 $[M]^+$ (326.2455 calcd for $C_{19}H_{34}O_4$). (*S*)-1-Methyl-3-oxobutyl 3-oxohexadecanoate (**9d**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.6$ Hz), 1.24–1.26 (20H, m), 1.30 (3H, d, $J = 6.3$ Hz), 1.58 (2H, quint, $J = 7.4$ Hz), 2.16 (3H, s), 2.51 (2H, t, $J = 7.4$ Hz), 2.59 (1H, dd, $J = 17.1$, 5.8 Hz), 2.84 (1H, dd, $J = 17.1$, 6.3 Hz), 3.39 (2H, s), 5.35 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 19.7, 22.5, 23.3, 28.9, 29.2, 29.2, 29.3, 29.3 (2C), 29.4, 29.5, 30.3, 31.8, 43.4, 49.1, 49.3, 68.0, 166.6, 203.2, 205.4; HREIMS m/z 354.2733 $[M]^+$ (354.2768 calcd for $C_{21}H_{38}O_4$). (*S*)-1-Methyl-3-oxobutyl 3-oxobutanoate (**9e**): Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (3H, t, $J = 6.3$ Hz), 2.16 (3H, s), 2.25 (3H, s), 2.60 (1H, dd, $J = 16.8$, 5.6 Hz), 2.83 (1H, dd, $J = 16.8$, 7.2 Hz), 3.40 (2H, s), 5.35 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.8, 30.0, 30.3, 49.1, 50.2, 69.6, 166.3, 200.4, 205.1; HREIMS m/z 186.0891 $[M]^+$ (186.0891 calcd for $C_9H_{14}O_4$). (*S*)-1-Methyl-3-oxobutyl 3-oxooctanoate (**9f**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.22–1.36 (4H, m), 1.30 (3H, d, $J = 6.3$ Hz), 1.59 (2H, quint, $J = 7.4$ Hz), 2.16 (3H, s), 2.52 (2H, t, $J = 7.4$ Hz), 2.59 (1H, dd, $J = 16.8$, 5.8 Hz), 2.84 (1H, dd, $J = 16.8$, 7.1 Hz), 3.40 (2H, s), 5.36 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.8, 19.9, 23.1, 30.4, 31.1, 42.9, 49.1, 49.4, 68.0, 166.3, 202.7, 204.9; HREIMS m/z 242.1490 $[M]^+$ (242.1517 calcd for $C_{13}H_{22}O_4$). (*S*)-1-Methyl-3-oxobutyl 3-oxodecanoate (**9g**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.22–1.36 (8H, m), 1.31 (3H, d, $J = 6.2$ Hz), 1.59 (2H, quint, $J = 7.4$ Hz), 2.17 (3H, s), 2.52 (2H, t, $J = 7.4$ Hz), 2.60 (1H, dd, $J = 16.8$, 5.9 Hz), 2.84 (1H, dd, $J = 16.8$, 7.1 Hz), 3.40 (2H, s), 5.36 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 19.8, 19.9, 23.1, 26.1, 28.8, 30.4, 31.1, 42.9, 49.1, 49.4, 68.0, 166.3, 202.7, 204.9; HREIMS m/z 270.1852 $[M]^+$ (270.1831 calcd for $C_{15}H_{26}O_4$). (*S*)-1-Methyl-3-oxobutyl 4-(l-adamantyl)-3-oxobutanoate (**9h**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, d, $J = 3.3$ Hz), 1.64 (12H, m), 1.96 (3H, m), 2.17 (3H, s), 2.25 (2H, s), 2.59 (1H, dd, $J = 16.7$, 6.0 Hz), 2.85 (1H, dd, $J = 16.7$, 6.9 Hz), 3.37 (2H, s), 5.35 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 28.4 (3C), 30.3, 33.6, 36.6 (3C), 42.2 (3C), 49.2, 52.0, 55.9, 68.0, 166.6, 202.5, 205.5; HREIMS m/z 320.1994 $[M]^+$ (320.1986 calcd for $C_{19}H_{28}O_4$). (*S*)-1-Methyl-3-oxobutyl 14-*tert*-butoxycarbonylamino-3-oxotetradecanoate (**9i**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.34 (14H, m), 1.30 (3H, d, $J = 6.3$ Hz), 1.40–1.50 (2H, m), 1.44 (9H, s), 1.55–1.61 (2H, m), 2.16 (3H, s), 2.51 (2H, t, $J = 7.1$ Hz), 2.59 (1H, dd, $J = 16.8$, 5.8 Hz), 2.84 (1H, dd, $J = 16.8$, 7.1 Hz), 3.10 (2H, q, $J = 6.9$ Hz), 3.39 (2H, s), 5.35 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 23.3, 26.7 (3C), 28.3, 28.4, 28.9, 29.3, 29.3, 29.4, 29.9, 30.0, 36.6, 40.5, 42.9, 49.3, 49.4, 68.0, 78.6, 156.1, 166.7, 203.2, 205.4; HREIMS m/z 341.2264 $[M-t\text{BuO}+H]^+$ (341.2202 calcd for $C_{18}H_{31}NO_5$).

4.1.4. (*S*)-3-[(*E*)-Dodec-12-enoyl]-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (dictyopyrone A) (1). Compound **9a** (115 mg, 0.36 mmol) dissolved in ethanol (2 mL) was treated with sodium ethoxide (27.2 mg, 0.40 mmol) at room temperature for 8 h. The mixture was poured into 0.5 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **1** (68.0 mg, 62%). **1**: Colorless amorphous solid; $[\alpha]_D^{28}$ + 54.1 (*c* 1.23, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.35

(10H, m), 1.43 (3H, d, $J = 6.3$ Hz), 1.61 (2H, quint, $J = 7.3$ Hz), 1.65 (3H, dq, $J = 3.5$, 1.2 Hz), 1.95 (2H, m), 2.01 (3H, d, $J = 0.8$ Hz), 2.31 (1H, dd, $J = 18.0$, 3.7 Hz), 2.44 (1H, ddd, $J = 18.0$, 11.6, 0.8 Hz), 2.71 (1H, dt, $J = 17.2$, 7.3 Hz), 2.75 (1H, dt, $J = 17.2$, 7.3 Hz), 4.54 (1H, dqd, $J = 11.6$, 6.3,3.7 Hz), 5.35–5.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 20.4, 20.8, 23.7, 29.0, 29.1, 29.3, 29.3, 29.5, 32.5, 37.7, 43.4, 73.0, 124.5, 130.0, 131.6, 156.0, 163.1, 203.4; HREIMS m/z 306.2175 $[M]^+$ (306.2193 calcd for $C_{19}H_{30}O_3$).

In the similar procedure, compounds **2**–**4** and **10**–**14** (yield: 58% (**2**), 48% (**3**), 72% (**4**), 60% (**10**), 41% (**11**), 40% (**12**), 16% (**13**) and 68% (**14**)) were prepared from **9b**–**i**, respectively. (*S*)-3-[(*E*)-Tetradec-14-enoyl]-5,6-dihydro-4,6-dimethyl-2*H*]-pyran-2-one (dictyopyrone B) (**2**): Colorless amorphous solid; $[\alpha]_D^{28}$ + 74.5 (*c* 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20–1.35 (14H, m), 1.44 (3H, d, $J = 6.3$ Hz), 1.61 (2H, quint, $J = 7.4$ Hz), 1.64 (3H, dq, $J = 3.7$, 1.2 Hz), 1.95 (2H, m), 2.01 (3H, d, $J = 0.8$ Hz), 2.31 (1H, dd, $J = 18.0$, 3.7 Hz), 2.44 (1H, ddd, $J = 18.0$, 11.6, 0.8 Hz), 2.71 (1H, dt, $J = 17.2$, 7.4 Hz), 2.75 (1H, dt, $J = 17.2$, 7.4 Hz), 4.55 (1H, dqd, $J = 11.6$, 6.3,3.7 Hz), 5.36–5.45 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.8, 20.4, 20.8, 23.7, 29.1, 29.3, 29.4, 29.4, 29.4, 29.5, 29.6, 32.5, 37.7, 43.4, 73.0, 124.4, 130.0, 131.6, 156.0, 163.1, 203.4; HREIMS m/z 334.2494 $[M]^+$ (334.2506 calcd for $C_{21}H_{34}O_3$). (*S*)-3-Dodecanoyl-5,6-dihydro-4,6-dimethyl-2-pyran-2-one (dictyopyrone C) (**3**): Colorless amorphous solid; $[\alpha]_D^{25}$ +76.8 (*c* 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.20–1.35 (16H, m), 1.43 (3H, d, $J = 6.3$ Hz), 1.61 (2H, quint, $J = 7.3$ Hz), 2.01 (3H, d, $J = 1.0$), 2.33 (1H, dd, $J = 18.0$, 3.7 Hz), 2.44 (1H, ddd, $J = 18.0$, 11.6, 1.0 Hz), 2.70 (1H, dt, $J = 17.1$, 7.3 Hz), 2.74 (1H, dt, $J = 17.1$, 7.3 Hz), 4.55 (1H, dqd, $J = 11.5$, 6.3, 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.3, 20.6, 22.5, 23.6, 29.0, 29.2, 29.3, 29.3, 29.4, 29.4, 31.7, 37.5, 43.3, 73.0, 130.0, 156.0, 163.1, 203.3; HREIMS m/z 308.2313 $[M]^+$ (308.2350 calcd for $C_{19}H_{32}O_3$). (*S*)-3-Tetradecanoyl-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2- one (dictyopyrone D) (**4**): Colorless powder; $[\alpha]_D^{28}$ +84.7 (*c* 0.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.20–1.36 (20H, m), 1.44 (3H, d, $J = 6.3$ Hz), 1.61 (2H, quint, $J = 7.4$ Hz), 2.01 (3H, s), 2.31 (1H, dd, $J = 18.0$, 3.7 Hz), 2.44 (1H, dd, $J = 18.0$, 11.8 Hz), 2.70 (1H, dt, $J = 17.3$, 7.4 Hz), 2.74 (1H, dt, $J = 17.3$, 7.4 Hz), 4.54 (1H, dqd, $J = 11.8$, 6.3, 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.4, 20.8, 22.6, 23.8, 29.2, 29.2, 29.3, 29.3, 29.4, 29.4, 29.6, 31.9, 37.7, 43.4, 73.0, 130.0, 156.0, 163.2, 203.4; HREIMS m/z 336.2638 $[M]^+$ (336.2664 calcd for $C_{21}H_{36}O_3$). (*S*)-3-Acetyl-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (**10**): Colorless oil; $[\alpha]_D^{25}$ + 183.3 (*c* 0.418, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (3H, d, $J = 6.3$ Hz), 2.08 (3H, s), 2.34 (1H, dd, $J = 18.0$, 3.7 Hz), 2.43 (3H, s), 2.46 (1H, dd, $J = 18.0$, 11.6 Hz), 4.55 (1H, dqd, $J = 11.6$, 6.3, 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 20.8, 31.1, 37.9, 72.9, 130.0, 157.3, 163.1, 200.2; HREIMS m/z 168.0792 $[M]^+$ (168.0786 calcd for $C_9H_{12}O_3$). (*S*)-3-Hexanoyl-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (**11**): Colorless oil; $[\alpha]_D^{25}$ +112.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.25–1.38 (4H, m), 1.43 (3H, d, $J = 6.3$ Hz), 1.62 (2H, quint, $J = 7.4$ Hz), 2.01 (3H, d, $J = 0.8$ Hz), 2.34 (1H, dd, $J = 18.0$, 3.8 Hz), 2.45 (1H, ddd, $J = 18.0$, 11.6, 0.8 Hz), 2.71 (1H, dt, $J = 17.2$, 7.4 Hz), 2.75 (1H, dt, $J = 17.2$, 7.4 Hz), 4.55 (1H, dqd, $J = 11.6$, 6.3, 3.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 20.5, 20.9, 22.5, 23.4, 31.3, 37.7, 43.4, 73.1, 129.9, 156.0, 163.0, 203.2; HREIMS m/z 224.1412 $[M]^+$ (224.1411 calcd for $C_{13}H_{20}O_3$). (*S*)-3-Octanoyl-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (**12**): Colorless oil; $[\alpha]_D^{28}$ + 98.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.84 (3H, t, $J = 6.7$ Hz), 1.18–1.35 (8H, m), 1.39 (2H, d, $J = 6.3$ Hz), 1.58 (2H, quint, $J = 7.4$ Hz), 2.02 (3H, s), 2.28 (1H, dd, $J = 18.0$, 4.0 Hz), 2.42 (1H, ddd, $J = 18.1$, 11.4 Hz), 2.71 (1H, dt, $J = 17.1$, 7.4 Hz), 2.74 (1H, dt, $J = 17.1$, 7.4 Hz), 4.55 (1H, dqd, $J = 11.4$, 6.3, 4.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9, 20.3, 20.7, 22.4, 23.6, 28.9, 29.0, 31.5, 37.6, 43.3, 73.0, 130.1, 156.2, 163.3, 203.6; HREIMS m/z 252.1706 $[M]^+$ (252.1724 calcd for $C_{15}H_{24}O_3$). (*S*)-3-Adamantaneacetyl-5,6-dihydro-4,6-dirnethyl-2*H*f-pyran-2-one (**13**): Colorless powder; $[\alpha]_D^{28}$ + 60.0 (*c* 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (3H, d, $J = 6.3$ Hz), 1.62–1.71 (12H, m), 1.95 (3H, m), 2.06 (3H, s), 2.29 (1H, dd, $J = 17.9$, 3.6 Hz), 2.43 (1H, dd, $J = 17.9$, 15.1 Hz), 2.45 (1H, d, $J = 15.1$ Hz), 2.65 (1H, d, $J = 15.1$ Hz), 4.53 (1H, dqd, $J = 15.1$, 6.3, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.9, 28.6 (3C), 34.0, 36.8 (3C), 38.0, 42.5 (3C), 56.7, 73.0, 131.4, 155.7, 163.4, 202.4; HREIMS m/z 302.1888 $[M]^+$ (302.0179 calcd for $C_{19}H_{26}O_3$). (*S*)-3-(12-*tert*-Butoxycarbonylaminododecanoyl)-5,6-dihydro-4,6-dimethyl-2*H*f-pyran-2-one (**14**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (14H, m), 1.40–1.50 (2H, m), 1.44 (9H, s), 1.44 (3H, d, $J = 6.3$ Hz), 1.61 (2H, quint, $J = 7.1$ Hz), 2.01 (3H, d, $J = 0.8$ Hz), 2.31 (1H, dd, $J = 17.9$, 3.8 Hz), 2.45 (1H, ddd, $J = 17.9$, 11.4, 0.8 Hz), 2.73 (1H, dt, $J = 17.2$, 7.1 Hz), 2.76 (1H, dt, $J = 17.2$, 7.4 Hz), 3.10 (2H, q, $J = 6.5$ Hz), 4.55 (1H, dqd, $J = 11.4$, 6.3, 3.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.8, 23.6, 26.7 (3C), 28.3, 29.0, 29.1, 29.3, 29.3 (3C), 29.9, 36.6, 37.6, 40.5, 43.4, 73.0, 78.3, 130.1, 156.1, 156.3, 163.4, 203.7; HREIMS m/z 424.3028 $[M]^+$ (424.3063 calcd for $C_{24}H_{42}NO_5$).

4.1.5. 10-Methoxymethoxydecanol (16a). To a solution of 1,10-decanediol (**15a**) (3.00 g, 17.2 mmol) in CH_2Cl_2 (50 mL) was added *N*-ethyldiisopropylamine (9.00 mL, 51.6 mmol) and chloromethyl methyl ether (1.30 mL, 17.2 mmol) at 0 °C. After being stirred at room temperature for 14 h, the mixture was poured into 0.5 M hydrochloric acid and extracted with ethyl acetate three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **16a** (1.64 g, 43%). **16a**: Colorless amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24–1.31 (12H, m), 1.55 (2H, quint, $J = 6.7$ Hz), 1.59 (2H, quint, $J = 6.4$ Hz), 3.36 (3H, s), 3.51 (2H, t, $J = 6.4$ Hz), 3.61 (2H, t, $J = 6.7$ Hz), 4.61 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 26.2, 29.4, 29.4, 29.5, 29.5, 29.7, 32.7, 55.0, 62.8, 67.8, 96.2; HREIMS m/z 217.1803 $[M-H]^+$ (217.1802 calcd for $C_{12}H_{25}O_3$).

In the similar procedure, compound **16b** was prepared from 1,12-dodecanediol (**15b**) (yield 40%). 12-Methoxymethoxydodecanol (**16b**): Colorless amorphous solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.31 (16H, m), 1.57 (2H, quint, $J = 6.6$ Hz), 1.59 (2H, quint, $J = 6.6$ Hz), 3.36 (3H, s), 3.52 (2H, t, $J = 6.6$ Hz), 3.63 (2H, t, $J = 6.6$ Hz), 4.62 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 26.2, 29.4, 29.4, 29.4, 29.5, 29.5, 29.6, 29.7, 32.7, 55.0, 62.8, 67.8, 96.2; HREIMS m/z 245.2118 $[M-H]^+$ (245.2115 calcd for $C_{14}H_{29}O_3$).

4.1.6. Ethyl (*E*)-12-methoxymethoxydodec-2-enoate (17a). PCC (2.65 g, 12.3 mmol) was added to a solution of **16a** (1.78 g, 8.14 mmol) in CH_2Cl_2 (25 mL) at room temperature. After being stirred for 3 h, the mixture was filtered through a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated to give the crude aldehyde. This crude was added to a solution of ethyl diethylphosphonoacetate (1.58 g, 7.07 mmol) and sodium hydride (60% in mineral oil) (283 mg, 7.08 mmol) in benzene (10 mL) at room temperature. After being stirred for 4 h, the mixture was poured into 0.5 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (39:1) to give **17a** (1.29 g, 55% from **16a**). **17a**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.30 (10H, m), 1.29 (3H, t, $J = 7.1$ Hz), 1.45 (2H, quint, $J = 7.1$ Hz), 1.59 (2H, quint, $J = 6.7$ Hz), 2.19 (2H, qd, $J = 7.1$, 1.5 Hz), 3.36 (3H, s), 3.52 (2H, t, $J = 6.7$ Hz), 4.19 (2H, q, $J = 7.1$ Hz), 4.62 (2H, s), 5.89 (1H, dt, $J = 15.9$, 1.5 Hz), 6.91 (1H, dt, $J = 15.9$, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.2, 28.0, 29.1, 29.3, 29.4, 29.5, 29.7, 32.2, 55.1, 60.1, 67.8, 96.3, 121.1, 149.3, 166.6; HREIMS m/z 271.1927 $[M-CH_3]^+$ (271.1908 calcd for $C_{15}H_{27}O_4$).

In the similar procedure, compound **17b** was prepared from **16b** (yield 67%). Ethyl (*E*)-14-methoxymethoxytetradec-2-enoate (**17b**): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26–1.38 (14H, m), 1. 29 (3H, t, $J = 7.1$ Hz), 1.45 (2H, quint, $J = 7.1$ Hz), 1.59 (2H, quint, $J = 6.9$ Hz), 2.19 (2H, qd, $J = 7.1$, 1.4 Hz), 3.36 (3H, s), 3.52 (2H, t, $J = 6.9$ Hz), 4.18 (2H, q, $J = 7.1$ Hz), 4.62 (2H, s), 5.81 (1H, dt, $J = 15.7$, 1.4 Hz), 6.96 (1H, dt, $J = 15.7$, 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 26.2, 28.1, 29.2, 29.4, 29.5, 29.5, 29.6, 29.6, 29.8, 32.2, 55.1, 60.1, 67.9, 96.3, 121.1, 149.3, 166.6; HREIMS m/z 313.2414 $[M-H]^+$ (313.2377 calcd for $C_{18}H_{33}O_4$).

4.1.7. (*E*)-12-Methoxymethoxydodec-2-en-1-ol (18a). To a solution of **17a** (1.26 g, 4.38 mmol) in CH_2Cl_2 (19 mL) was added diisobutylaluminum hydride (1 M solution in toluene, 13.0 mL, 13.0 mmol) at −20 °C. After being stirred for 1 h, the solution was poured into saturated Rochelle salt solution and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **18a** (887 mg, 83%). **18a**: Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20–1.37 (12H, m), 1.59 (2H, quint, $J = 6.7$ Hz), 2.03 (2H, td, $J = 6.9$, 6.3 Hz), 3.36 (3H, s), 3.51 (2H, t, $J = 6.7$ Hz), 4.07 (2H, d, $J = 5.3$ Hz), 4.61 (2H, s), 5.62 (1H, dt, $J = 15.3$, 5.3 Hz), 5.66 (1H, dt, $J = 15.3$, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 29.1, 29.1, 29.4, 29.5, 29.7, 32.2, 55.1, 63.8, 67.8, 96.3, 128.8, 133.3; HREIMS m/z 212.1740 $[M-CH_3OH]^+$ (212.1775 calcd for $C_{13}H_{24}O_2$).

In the similar procedure, compound **18b** was prepared from **17b** (yield 90%). (*E*)-14-Methoxymethoxytetradec-2-en-1-ol (**18b**): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26–1.39 (16H, m), 1.59 (2H, quint, $J = 6.6$ Hz), 2.03 (2H, td, $J = 6.9$, 6.3 Hz), 3.36 (3H, s), 3.51 (2H, t, $J = 6.6$ Hz), 4.07 (2H, d, $J = 5.3$ Hz), 4.61 (2H, s), 5.62 (1H, dt, $J = 15.4$, 5.3 Hz), 5.69 (1H, dt, $J = 15.4$, 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 29.2, 29.2, 29.5, 29.5, 29.6, 29.6, 29.6, 29.8, 32.2, 55.1, 63.8, 67.9, 96.2, 128.7, 133.3; HREIMS m/z 240.2053 $[M-CH_3OH]^+$ (240.2088 calcd for $C_{15}H_{28}O_2$).

4.1.8. (*E*)-12-Methoxymethoxydodec-2-ene (19a). To a solution of **18a** (673 mg, 2.75 mmol) in THF (14 mL) was added sulfur pyridine complex (1.09 g, 6.82 mmol) at 0 °C. After being stirred for 1 h at room temperature, the mixture was treated with lithium aluminum hydride (626 mg, 16.5 mmol), and further stirred for 7 h. The reaction was quenched by methanol (10 mL), and the mixture was filtered by a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (49:1) to give **19a** (332 mg, 53%). **19a**: Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.37 (12H, m), 1.57 (2H, quint, $J = 6.6$ Hz), 1.57 (3H, dq, $J = 3.3$, 1.1 Hz), 1.94–1.96 (2H, m), 3.36 (3H, s), 3.56 (2H, t, $J = 6.6$ Hz), 4.62 (2H, s), 5.35–5.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.7, 26.1, 29.0, 29.3, 29.4, 29.4, 29.5, 29.6, 32.5, 55.0, 67.8, 96.4, 124.6, 131.7; HREIMS m/z 228.2058 $[M]^+$ (228.2088 calcd for $C_{14}H_{28}O_2$).

In the similar procedure, compound **19b** was prepared from **18b** (yield 67%). (*E*)-14-Methoxymethoxytetradec-2-ene (**19b**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20–1.32 (16H, m), 1.59 (2H, quint, $J = 6.6$ Hz), 1.64 (3H, dq, $J = 3.6$, 1.2 Hz), 1.94–1.96 (2H, m), 3.36 (3H, s), 3.52 (2H, t, $J = 6.6$ Hz), 4.62 (2H, s), 5.39–5.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 26.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 32.7, 55.1, 67.9, 96.3, 124.4, 131.6; HREIMS m/z 256.2404 $[M]^+$ (256.2401 calcd for $C_{16}H_{32}O_2$).

4.1.9. (*E*)-10-Dodecen-l-ol (20a). A solution of **19a** (56.9 mg, 0.25 mmol) in THF (1 mL) and 2 M hydrochloric acid (1 mL) was refluxed for 4 h. The mixture was poured into 0.5 M sodium hydroxide solution, and extracted with ethyl acetate three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was

chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **20a** (38.9 mg, 85%). **20a**: Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24–1.31 (12H, m), 1.56 (2H, quint, $J = 6.6$ Hz), 1.64 (3H, dq, $J = 3.3$, 1.4 Hz), 1.92–1.96 (2H, m), 3.63 (2H, t, $J = 6.6$ Hz), 5.34–5.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.3, 29.2, 29.4, 29.5, 29.5, 29.6, 29.6, 32.8, 63.1, 124.5, 131.6; HREIMS m/z 166.1709 $[M-H_2O]^+$ (166.1720 calcd for $C_{12}H_{22}$).

In the similar procedure, compound **20b** was prepared from **19b** (yield 92%). (*E*)-12-Tetradecen-1-ol (**20b**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23–1.31 (16H, m), 1.56 (2H, quint, $J = 6.7$ Hz), 1.64 (3H, dq, $J = 3.4$, 1.4 Hz), 1.92–1.99 (2H, m), 3.62 (2H, t, $J = 6.7$ Hz), 5.39–5.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.8, 29.2, 29.3, 29.4, 29.5, 29.6, 29.6, 29.6, 29.7, 32.8, 63.1, 124.4, 131.6; HREIMS m/z 212.2118 $[M]^+$ (212.2139 calcd for $C_{14}H_{28}O$).

4.1.10. (*E*)-10-Dodecenoic acid (5a). To a solution of **20a** (475 mg, 2.58 mmol) in DMF (10 mL) was added PDC (3.82 g, 10.1 mmol) at room temperature. After being stirred for 12 h, the mixture was filtered by a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **5a** (280 mg, 55%). **5a**: Colorless powder; ^{1}H NMR (300 MHz $CDCl_3$) δ 1.24–1.31 (10H, m) 1.58–1.65 (2H, m) 1.63 (3H, dq, $J = 3.4$, 1.4 Hz) 1.93–1.96 (2H, m) 2.35 (2H, t, $J = 7.4$ Hz) 5.39–5.43 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 24.5, 28.9, 29.0, 29.1, 29.2, 29.5, 32.5, 33.9, 124.7, 131.7, 180.0; HREIMS m/z 198.1612 $[M]^+$ (198.1619 calcd for $C_{12}H_{22}O_2$).

In the similar procedure, compound **5b** was prepared from **20b** (yield 59%). (*E*)-12-Tetradecenoic acid (**5b**): Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27–1.30 (14H, m) 1.58–1.65 (2H, m) 1.64 (3H, dq, $J = 3.3$, 1.4 Hz) 1.93–1.96 (2H, m) 2.35 (2H, t, $J = 7.4$ Hz) 5.35–5.48 (2H, m, H-12); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 24.7, 29.1, 29.2, 29.3, 29.5, 29.5, 29.6, 29.7, 32.7, 34.2, 124.4, 131.6, 180.3; HREIMS m/z 226.1920 $[M]^+$ (226.1931 calcd for $C_{14}H_{26}O_2$).

4.1.11. (*S*)-3-(12-Aminododecanoyl)-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one hydrochloride (22). Compound **14** (32.9 mg, 0.078 mmol) was treated with 10% hydrogen chloride containing methanol (2 mL) at room temperature for 3 h. The mixture was concentrated, and the residue was chromatographed over silica gel eluted by chloroform–methanol (19:1) to give **22** (23.9 mg, 89%). **22**: Colorless powder; $[\alpha]_D^{28}$ + 69.1 (*c* 0.74, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25–1.38 (14H, m) 1.44 (3H, d, $J = 6.3$ Hz) 1.60 (2H, quint, $J = 7.4$ Hz) 1.77 (2H, quint, $J = 7.6$ Hz) 2.01 (2H, s) 2.32 (2H, dd, $J = 18.0$, 3.7 Hz), 2.45 (1H, dd, $J = 18.0$, 11.6 Hz) 2.71 (1H, dt, $J = 17.3$, 7.4 Hz) 2.73 (1H, dt, $J = 17.3$, 7.4 Hz), 2.99 (2H, t, $J = 7.6$ Hz) 4.56 (1H, dqd, $J = 11.6$, 6.3, 3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.8, 23.7, 26.5, 27.6, 29.0, 29.1, 29.3, 29.3, 29.4, 29.4, 37.7, 40.0, 43.4, 73.1, 130.0, 156.1, 163.2, 203.4; HREIMS m/z 323.2465 $[M]^+$ (323.2460 calcd for $C_{19}H_{33}NO_3$).

4.1.12. (*R*)-3-Dodecanoyl-5,6-dihydro-4,6-dimethyl-2*H*-pyran-2-one (23). In the similar way from **7c** to **3** compound **23** was synthesized by the use of (*2R*,*4R*)-2,4-pentanediol instead of (*2S*,*4S*)-2,4-pentanediol. **23**: Colorless amorphous solid; $[\alpha]_D^{28}$ − 69.2 (*c* 1.00, $CHCl_3$). Other spectral data were identical with those of dictyopyrone C (**3**).

4.1.13. Methyl 3-oxotetradecanoate (24). A solution of **7c** (362 mg, 1.110 mmol) in methanol (4 mL) was refluxed for 2 h. The mixture was concentrated, and the residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (19:1) to give **24** (255 mg, 90%). **24**: Colorless amorphous solid; ^{1}H NMR (600 MHz, $CDCl_{33}$) δ 0.88 (3H, t, $J = 6.8$ Hz), 1.25–1.35 (16H, m), 1.59 (2H, quint, $J = 7.3$ Hz), 2.53 (2H, t, $J = 7.3$ Hz), 3.45 (2H, s), 3.74 (3H s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 22.7, 23.5, 29.0, 29.3, 29.4, 29.4, 29.5, 29.6, 31.9, 43.1, 49.0, 52.3, 167.6, 202.7; HREIMS m/z 256.2003 $[M]^+$ (256.2037 calcd for $C_{15}H_{28}O_3$).

4.1.14. 1,1-Dimethyl-3-oxobutyl 3-oxotetradecaoate (25). A solution of **7c** (278 mg, 0.85 mmol) and 4-hydroxy-4-methyl-2-pentanone (370 μL 2.99 mmol) in toluene (4.5 mL) was refluxed for 2 h. The mixture was concentrated, and the residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **25** (251 mg, 87%). **25**: Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.8$ Hz), 1.20–1.35 (16H, m), 1.58 (2H, quint, $J = 7.4$ Hz), 1.54 (6H, s), 2.15 (3H, s), 2.51 (2H, t $J = 7.4$ Hz), 3.04 (2H, s), 3.36 (2H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 22.7, 23.5, 26.4 (2C), 29.1, 29.3, 29.3, 29.4, 29.5, 29.6, 31.8, 31.9, 43.1, 50.4, 52.0, 81.6, 166.5, 203.1, 205.4; HREIMS m/z 340.2663 $[M]^+$ (340.2612 calcd for $C_{20}H_{36}O_4$).

In the similar procedure, compound **26**–**28** was prepared (yield 73% (**26**), 51% (**27**), 67% (**28**)) by the reaction of **7c** with 4-hydroxy-2-butanone, (*3S*,*5S*)-2,6-dimethyl-3,5-heptanediol and (*2S*,*3S*)-2,3-butanediol, respectively. 3-Oxobutyl 3-oxotetradecanoate (**26**): Colorless needle; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.20–1.35 (16H, m), 1.57 (3H, quint, $J = 7.3$ Hz), 2.19 (3H, s), 2.50 (2H, t, $J = 7.3$ Hz), 2.79 (2H, t, $J = 6.3$ Hz), 3.42 (2H, s), 4.40 (2H, t, $J = 6.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.6, 23.4, 29.0, 29.3, 29.3, 29.4, 29.4, 29.5, 30.2, 31.8, 42.0, 43.1, 49.0, 60.0, 167.1, 202.8, 205.3; HREIMS m/z 312.2296 $[M]^+$ (312.2301 calcd for $C_{18}H_{32}O_4$). (1*S*,3*S*)-3-Hydroxy-4-methyl-1-isopropylpentyl 3-oxotetradecanoate (**27**): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 0.93 (3H, d, $J = 6.8$ Hz), 0.93 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 0.94 (3H, d, $J = 6.8$ Hz), 1.26–1.35 (16H, m), 1.50–1.68 (5H, m), 1.85 (1H, m), 2.53 (2H, t, $J = 7.4$ Hz), 3.29 (1H, ddd, $J = 10.3$, 5.5, 2.0 Hz), 3.49 (2H, s), 5.02 (1H, ddd, $J = 10.4$, 5.3, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

14.2, 17.8, 17.9, 18.6, 18.8, 22.7, 23.6, 29.0, 29.3, 29.4, 29.5, 29.6, 29.6, 31.9, 32.1, 33.7, 35.9, 43.3, 49.4, 71.7, 77.3, 168.1, 202.8; HREIMS m/z 384.3266 $[M]^+$ (384.3237 calcd for $C_{23}H_{44}O_4$). (1*S*,2*S*)-2-Hydroxy-1-methylpropyl 3-oxotetradecanoate (**28**): Colorless powder; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.8$ Hz), 1.20 (3H, d, $J = 6.6$ Hz), 1.21 (3H, d, $J = 6.6$ Hz), 1.24–1.30 (16H, m), 1.59 (2H, quint, $J = 7.3$ Hz), 2.52 (2H, t, $J = 7.3$ Hz), 3.50 (2H, s), 3.73 (1H, quint, $J = 6.6$ Hz), 4.85 (1H, quint, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 16.4, 18.7, 22.7, 23.5, 29.0, 29.3, 29.4, 29.4, 29.5, 29.6, 31.9, 43.3, 49.5, 70.7, 76.4, 166.5, 203.8. HREIMS m/z 314.2488 $[M]^+$ (314.2455 calcd for $C_{18}H_{34}O_4$).

4.1.15. 3-Dodecanoyl-5,6-dihydro-4,6,6-trimethyl-2*H*-pyran-2-one (29). Compound **25** (207 mg, 0.61 mmol) dissolved in ethanol (5 mL) was treated with sodium ethoxide (45.6 mg, 0.67 mmol) at room temperature for 8 h. The mixture was poured into 0.5 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **29** (198 mg, 81%). **29**: Colorless amorphous solid; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.7$ Hz), 1.20–1.35 (16H, m), 1.46 (6H, s), 1.61 (2H, quint, $J = 7.4$ Hz), 1.99 (3H, s), 2.45 (2H, s), 2.73 (2H, t, $J = 7.4$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 21.1, 22.6, 23.8, 27.4 (2C), 29.1, 29.3, 29.4, 29.4, 29.5, 29.5, 31.9, 42.2, 43.5, 78.9, 129.7, 154.2, 162.5, 203.4; HREIMS m/z 322.2523 $[M]^+$ (322.2506 calcd for $C_{20}H_{34}O_3$).

In the similar procedure, compound **30** was prepared from **26** (yield 27%). 3-Dodecanoyl-5,6-dihydro-4-methyl-2*H*-pyran-2-one (**30**). Colorless amorphous solid; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.20–1.35 (16H, m), 1.62 (2H, quint, $J = 7.3$ Hz), 2.04 (3H, s), 2.49 (2H, t, $J = 6.2$ Hz), 2.73 (2H, t, $J = 7.3$ Hz), 4.38 (2H, t, $J = 6.2$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.9, 22.6, 23.8, 29.1, 29.3, 29.3, 29.4, 29.6, 29.6, 30.6, 31.9, 43.4, 65.2, 130.4, 156.7, 162.5, 203.3; HREIMS m/z 294.2221 $[M]^+$ (294.2193 calcd for $C_{18}H_{30}O_3$).

4.1.16. (*S*)-3-Dodecanoyl-5,6-dihydro-4,6-diisopropyl-2*H*-pyran-2-one (31). PCC (938 mg, 4.35 mmol) was added to a solution of **27** (557 mg, 1.45 mmol) in CH_2Cl_2 (8 mL) at room temperature. After being stirred for 8 h, the mixture was filtered through a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give (*S*)-4-methyl-1-isopropyl-3-oxopentyl 3-oxotetradecanoate (424 mg, 76%).

This compound (251 mg, 0.66 mmol) dissolved in ethanol (5 mL) was treated with sodium ethoxide (47.6 mg, 0.70 mmol) at room temperature for 8 h. The mixture was poured into 0.5 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (4:1) to give **31** (30.3 mg, 13%). **31**: Colorless amorphous solid; $[\alpha]_D^{28}$ −52.2 (*c* 1.12, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.02 (3H, d, $J = 6.5$ Hz), 1.05 (3H, d, $J = 6.5$ Hz), 1.05 (3H, d, $J = 6.5$ Hz), 1.06 (3H, d, $J = 6.5$ Hz), 1.20–1.35 (16H, m), 1.62 (2H, quint, $J = 7.5$ Hz), 1.98 (1H, m), 2.25 (1H, dd, $J = 17.6$, 11.9 Hz), 2.33 (1H, dd, $J = 17.6$, 3.8 Hz), 2.67 (1H, dt, $J = 17.4$, 7.5 Hz), 2.73 (1H, dt, $J = 17.4$, 7.5 Hz), 2.84 (1H, sept, $J = 6.5$ Hz), 4.07 (1H, ddd, $J = 11.9$, 6.5, 3.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 17.8, 18.1, 19.4 (2C), 21.0 (2C), 22.7, 23.7, 25.1, 29.2, 29.4, 29.5, 29.5, 29.7, 29.7, 31.4, 31.9 (2C), 44.0, 81.9, 128.9, 163.0, 163.5, 203.9; HREIMS m/z 364.2965 $[M]^+$ (364.2975 calcd for $C_{23}H_{40}O_3$).

4.1.17. 3-Dodecanoyl-5-hydroxy-4,5-dimethyl-5*H*-furan-2-one (32). PCC (778 mg, 3.61 mmol) was added to a solution of **28** (379 mg, 1.20 mmol) in CH_2Cl_2 (6 mL) at room temperature. After being stirred for 5 h, the mixture was filtered through a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **32** (103 mg, 28%). **32**: Colorless powder; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.9$ Hz), 1.24–1.30 (16H, m), 1.59 (2H, quint, $J = 7.3$ Hz), 1.67 (3H, s), 2.34 (3H, s), 2.87 (1H, dt, $J = 17.9$, 7.3 Hz), 2.92 (1H, dt, $J = 17.9$, 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 22.7, 23.2, 23.3, 29.1, 29.3, 29.4, 29.5, 29.6 (2C), 31.9, 42.6, 104.8, 125.2, 168.0, 173.9, 198.2; HREIMS m/z 310.2128 $[M]^+$ (310.2142 calcd for $C_{18}H_{30}O_4$).

4.1.18. (*S*)-2-(1-Methyl-3-oxobutyl)isoindole-1,3-dione (33). To a solution of (*2R*,*4R*)-2,4,-pentanediol (146 mg, 1.41 mmol) in THF (5 mL) was added triphenyl phosphine (369 mg, 1.41 mmol), phthalimide (207 mg, 1.41 mmol), and diethyl azodicarboxylate (245 mg, 1.41 mmol) at 0 °C. After being stirred for 15 h at room temperature, the mixture was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give (*1S*,*3R*)-2-(3-hydroxy-1-methylbutyl)isoindole-1,3-dione (88.4 mg, 38%).

This compound (67.4 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (2 mL), and PCC (101 mg, 0.46 mmol) was added to the solution at room temperature. After being stirred for 3 h, the mixture was filtered through a Celite pad. The filter cake was washed with diethyl ether, and the filtrate was concentrated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (9:1) to give **33** (42.8 mg, 65%). **33**: Colorless powder; $[\alpha]_D^{27}$ + 2.0 (*c* 4.99, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (3H, d, $J = 6.9$ Hz), 2.14 (3H, s), 3.01 (1H, dd, $J = 17.7$, 6.4 Hz), 3.30 (1H, dd, $J = 17.7$, 7.9 Hz), 4.84 (1H, m), 7.70 (2H, dd, $J = 5.5$, 3.1 Hz), 7.81 (2H, dd, $J = 5.5$, 3.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 30.0, 42.4, 46.7, 123.1 (2C), 131.9 (2C),

133.8 (2C), 168.1 (2C), 205.7; HREIMS m/z 231.0897 $[M]^+$ (231.0895 calcd for $C_{13}H_{13}NO_3$).

4.1.19. (*S*)-2-[1-Methyl-2-(2-methyl-1,3-dioxan-2-yl)ethyl]isoindole-1,3-dione (34). To a solution of **33** (196 mg, 0.85 mmol) in benzene (5 mL) was added 1,3-propanediol (310 μL, 4.23 mmol) and *p*-toluenesulfonic acid (9.6 mg, 0.05 mmol). After being refluxed for 4 h, the mixture was poured into saturated sodium bicarbonate solution, and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (7:3) to give **34** (212 mg, 86%). **34**: Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (1H, m), 1.40 (3H, s), 1.48 (3H, d, $J = 7.1$ Hz), 1.76 (1H, dt, $J = 13.5$, 6.0 Hz), 1.81 (1H, dd, $J = 14.8$, 3.3 Hz), 2.84 (1H, dd, $J = 14.8$, 9.9 Hz), 3.49 (1H, dd, $J = 6.0$, 3.3 Hz), 3.69–3.86 (4H, m), 4.84 (1H, dqd, $J = 9.9$, 7.1, 3.3 Hz), 7.70 (2H, dd, $J = 5.5$, 3.1 Hz), 7.81 (2H, dd, $J = 5.5$, 3.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.0, 25.0, 42.2, 42.5, 59.7, 59.8, 98.3, 122.7 (2C), 132.3 (2C), 133.4 (2C), 168.5 (2C); HREIMS m/z 289.1292 $[M]^+$ (289.1313 calcd for $C_{16}H_{19}NO_4$).

4.1.20. (*S*)-*N*-[l-Methyl-2-(2-methyl-1,3-dioxan-2-yl)ethyl]-3-oxotetradecanamide (35). To a solution of **34** (85.0 mg, 0.29 mmol) in methanol (2 mL) was added hydrazine monohydrate (300 mL, 6.21 mmol). After being refluxed for 1 h, the mixture was poured into 1 M sodium hydroxide solution, and extracted with CH_2Cl_2 three times. The organic layer was concentrated to give crude amine. This crude was dissolved in toluene (2 mL), and **7c** (145 mg, 0.44 mmol) was added to the solution. After being refluxed for 2 h, the mixture was evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–diethyl ether (4:1) to give **35** (67.9 mg, 60%). **35**: Colorless powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (3H, t, $J = 6.7$ Hz), 1.22 (3H, d, $J = 6.6$ Hz), 1.23–1.32 (16H, m), 1.43 (3H, s), 1.57 (2H, quint, $J = 7.2$ Hz), 1.77 (1H, dd, $J = 14.6$, 4.9 Hz), 1.86 (1H, dd, $J = 14.6$, 8.7 Hz), 1.85–1.95 (2H, m), 2.53 (2H, t, $J = 7.2$ Hz), 3.32 (2H, s), 3.80–3.90 (2H, m), 3.90–4.04 (2H, m), 4.15 (1H, dqd, $J = 8.7$, 6.6, 4.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 19.1, 21.5, 22.5, 23.3, 25.2, 28.9, 29.2, 29.2, 29.3, 29.4, 29.5, 31.7, 42.6, 43.5, 45.6, 50.1, 59.6, 59.6, 98.7, 164.8, 206.7; HREIMS m/z 383.3019 $[M]^+$ (383.3033 calcd for $C_{22}H_{41}NO_4$).

4.1.21. (*S*)-*N*-(1-Methyl-3-oxobutyl)-3-oxotetradecanamide (36). A solution of **35** (449 mg, 1.17 mmol) in 80% acetic acid (10 mL) was stirred for 2 h at room temperature. The mixture was concentrated, and the residue was chromatographed over silica gel eluted by *n*-hexane–diethyl ether (4:1) to give **36** (342 mg, 90%). **36**: Colorless powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (2H, t, $J = 6.7$ Hz), 1.23 (3H, d, $J = 6.9$ Hz), 1.24–1.32 (16H, m), 1.57 (2H, quint, $J = 7.0$ Hz), 2.16 (3H, s), 2.52 (2H, t, $J = 7.3$ Hz), 2.60 (1H, dd, $J = 16.7$, 6.3 Hz), 2.73 (1H, dd, $J = 16.7$, 5.4 Hz), 3.31 (2H, s), 4.34 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 20.0, 22.5, 23.2, 28.9, 29.2, 29.3, 29.4, 29.5, 29.6, 30.3, 31.7, 41.9, 43.7, 48.8, 49.1, 165.1, 206.9, 207.4; HREIMS m/z 325.2583 $[M]^+$ (325.2615 calcd for $C_{19}H_{35}NO_3$).

4.1.22. (*S*)-3-Dodecanoyl-5,6-dihydro-4,6-dimethyl-1*H*-pyridin-2-one (37). Compound **36** (302 mg, 0.93 mmol) dissolved in ethanol (7 mL) was treated with sodium ethoxide (69.4 mg, 1.02 mmol) at room temperature for 6 h. The mixture was poured into 0.5 M hydrochloric acid and extracted with diethyl ether three times. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was chromatographed over silica gel eluted by *n*-hexane–ethyl acetate (2:1) to give **37** (103 mg, 36%). **37**: Colorless powder; $[\alpha]_D^{29} + 80.0$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t, $J = 6.9$ Hz), 1.23–1.33 (16H, m), 1.61 (2H, quint, $J = 7.4$ Hz), 1.92 (3H, s), 2.22 (1H, dd, $J = 17.2$, 11.1 Hz), 2.29 (1H, dd, $J = 17.2$, 5.2 Hz), 2.71 (2H, t, $J = 7.4$ Hz), 3.70 (1H, m), 6.39 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.7, 20.9, 22.6, 23.8, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 31.8, 38.5, 43.9, 45.6, 132.7, 150.2, 165.2, 205.3; HREIMS m/z 307.2512 $[M]^+$ (307.2510 calcd for $C_{19}H_{33}NO_2$).

4.1.23. Cell culture of *D. discoideum* and developmental conditions. Vegetative cells of *D. discoideum* Ax-2 (clone MS) were axenically grown in modified HL-5 medium (PS medium).[12] Growth kinetics of Ax-2 cells with or without dictyopyrone derivatives was monitored by cell counts under a hematocytometer. Ax-2 cells were grown up to a cell density of 5×10^6 cells/mL, then cells were diluted into a cell density of 5×10^5 cells/mL in fresh growth medium with or without tested compounds. In another experiment, cells were grown into a low cell density of 5×10^5 cells/mL, followed by addition of tested compounds. These cultures were shaken at 22 °C for subsequent cell counts. To allow cells to differentiate under submerged conditions, exponentially growing cells were harvested, washed twice in BSS (Bonner's salt solution),[16] and settled down in a 24-well titer plate containing various concentrations of dictyopyrones or their analogues and were incubated at 22 °C (Charts 1 and 2).

4.1.24. Assay for cell growth in K562 cells . Human leukemia K562 cells were maintained at 37 °C (5% CO_2) in tissue culture dishes filled with a growth medium (an RPMI1640 medium with 10% fetal bovine serum, 25 μg/mL penicillin, and 50 μg/mL streptomycin; designated RPMI). For the assay for cell growth, K562 cells were incubated in a 12-well plate, each well containing 1 mL of RPMI ($3–5 \times 10^4$ cells/mL) in the presence or absence of drugs. After 3 days, 50 μL of Alamar Blue was added to each well, and after 1–2 h incubation at 37 °C (5–8% CO_2), 150 μL of each of the sample solutions was transferred into a 96-well plate, and absorbance at 570 nm (reference at 595 nm) was measured with a microplate reader (Bio-Rad, Model 550). A cell number was given as a ratio of the absorbance (% of control).

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 15710153) from the Ministry of Education, Science, Sports and Culture of Japan, and a scholarship from Mitsubishi Trust Yamamuro memorial scholarship foundation.

References and notes

1. *Dictyostelium*. A Model System for Cell and Developmental Biology, Frontiers Science Series No. 21; Maeda, Y; Inoue, K.; Takeuchi, I., Eds.; Universal Academy: Tokyo, 1997.
2. Morris, H. R.; Taylor, G. W.; Masento, M. S.; Jermyn, K. A.; Kay, R. R. *Nature* **1987**, *328*, 811–814.
3. Abe, H.; Uchiyama, M.; Tanaka, Y.; Saito, H. *Tetrahedron Lett.* **1976**, *42*, 3807–3810.
4. Konijn, T. M.; van de Meene, J. G.; Bonner, J. T.; Barkley, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *58*, 1152–1154.
5. Oka, H.; Asahi, K.; Morishima, H.; Sanada, M.; Shiratori, K.; limura, Y.; Sakurai, T.; Uzawa, J.; Iwadare, S.; Takahashi, N. *J. Antibiot.* **1985**, *38*, 1100–1102.
6. Suzuki, T.; Oka, H.; Okura, A.; Asahi, K.; Takahashi, N. *J. Antibiot.* **1986**, *39*, 869–871.
7. Asahi, K.; Sakurai, A.; Takahashi, N.; Kubohara, Y.; Okamoto, K.; Tanaka, Y. *Biochem. Biophys. Res. Commun.* **1995**, *208*, 1036–1039.
8. Kubohara, Y. *Biochem. Biophys. Res. Commun.* **1997**, *236*, 418–422.
9. (a) Kubohara, Y.; Kimura, C.; Tatemoto, K. *Dev. Growth Differ.* **1995**, *37*, 711–716; (b) Kubohara, Y.; Saito, Y.; Tatemoto, K. *FEBS Lett.* **1995**, *359*, 119–122.
10. Kubohara, Y.; Okamoto, K.; Tanaka, Y.; Asahi, K.; Sakurai, A.; Takahashi, N. *FEBS Lett.* **1993**, *322*, 73–75.
11. Takaya, Y.; Kikuchi, H.; Terui, Y.; Komiya, J.; Furukawa, K.; Seya, K.; Motomura, S.; Ito, A.; Oshima, Y. *J. Org. Chem.* **2000**, *65*, 985–989.
12. Maeda, Y.; Kikuchi, H.; Sasaki, K.; Amagai, A.; Sekiya, J.; Takaya, Y.; Oshima, Y. *Protoplasma* **2003**, *221*, 185–192.
13. Oikawa, Y.; Sugamo, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087–2088.
14. Corey, E. J.; Achiwa, K. *J. Org. Chem.* **1969**, *34*, 3667–3668.
15. Pak, C. S.; Yang, H. C.; Choi, E. B. *Synthesis* **1992**, 1213–1214.
16. Bonner, J. T. *J. Exp. Zool.* **1947**, *106*, 1–26.