Table 2
Family-Reported Practice in Prognosis Disclosure

No.	Item	*n*	%
1	The physician assured sufficient symptom control	315	77.0
2	The physician assured sufficient care at the patient's last hour	303	74.1
3	The physician said, "We will respect the patient's wishes"	276	67.5
4	The physician explained mainly in words	275	67.2
5	The physician made maximum efforts to understand my distress	262	64.1
6	The physician paced his/her explanation with the state of my/patient's preparation	243	59.4
7	The physician gave concrete advice for my actual concern	242	59.2
8	The physician was knowledgeable about the most advanced treatments	236	57.7
9	The physician respected my values	229	56.0
10	The physician assured the continuing responsibility of physician for medical care	226	55.3
11	The physician suggested what we should do because the patient's condition was relatively good	213	52.1
12	The prognosis is an "average," and it does not have to be suitable for the patient	199	48.7
13	The physician discussed how to achieve my wishes, such as home care	190	46.5
14	The physician clearly told me the disease is incurable	172	42.1
15	The physician showed the thought, "I don't want to give up"	147	35.9
16	The physician explained in terms of daily life perspectives	131	32.0
17	The physician said, "I can do nothing for the patient any longer"	117	28.6
18	The physician told the longest predicted prognosis	94	23.0
19	The physician told the shortest predicted prognosis	93	22.7
20	The physician said, "Treatment might be possible at some time in the future"	73	17.8
21	The physician told the average prognosis	65	15.9
22	The physician used graphs and tables	40	9.8
23	The physician told the one-year survival rate	24	5.9
24	The physician told the five-year survival rate	16	3.9

less specific than family (11.7%, $n=48$), and more specific than family (4.6%, $n=19$).

Table 2 shows the percentages of family members who agreed (agree or strongly agree/yes) with each statement. Over 70% of the respondents reported that the physician assured sufficient symptom control at the patient's last hour.

Family Perception of Prognostic Disclosure

In the overall evaluation of prognosis communication, more than half of the family members felt that the method of prognostic disclosure should be improved: no improvement (39.9%, $n=163$), some improvement (40.8%, $n=167$), considerable improvement (11.5%, $n=47$), and much improvement (7.8%, $n=32$).

About half of the bereaved family members stated that the amount of prognostic information provided by the physician was more or less than they expected: much less than expected (13.7%, $n=56$), less than expected (19.8%, $n=81$), more than expected (11.7%, $n=48$), and much more than expected (3.2%, $n=13$). The responses to "Did you lose hope after the prognosis communication?" were strongly agree 24.7% ($n=101$), agree 25.9% ($n=106$), and agree a little 25.7% ($n=105$), and the responses to "Was the prognosis communication useful in preparing for the patient's death?" were strongly agree 13.9% ($n=57$), agree 43.3% ($n=177$), and agree a little 26.4% ($n=108$).

Factors Associated with the Family-Perceived Necessity for Improvement

Table 3 shows the results of the univariate analyses of the family perception on amount of information, loss of hope, and usefulness of prognostic disclosure in preparation for patient death, types of prognostic disclosure, and communication strategies obtained from family members at each level of necessity of improvement. There were significant differences across family perception on amount of information, loss of hope, and usefulness of prognostic disclosure in preparation for patient death and 12 communication strategies between families who rated a high necessity for improvement and families who rated a low necessity.

Path Analysis for Familial Evaluation

We carried out a path analysis by first selecting 12 communication strategies, family perception on amount of information, loss of hope, and usefulness of prognostic disclosure in preparation for patient death, and type of

Table 3
Determinants of Family-Reported Necessity for Improvement in the Prognostic Disclosure

	Total	No Improvement		Some or More Improvement		
Item	*n*	*n*	%	*n*	%	*P*
The physician assured sufficient symptom control	315	146	89.6	169	68.7	0.000
The physician explained mainly in words	275	109	66.9	166	67.5	0.324
The physician assured sufficient care at the patient's last hour	303	139	85.3	164	66.7	0.000
The physician said, "We will respect the patient's wishes"	276	127	77.9	149	60.6	0.000
I lost my hope after the prognostic disclosure	216	70	42.9	146	59.3	0.000
The physician made maximum efforts to understand my distress	262	129	79.1	133	54.1	0.000
The prognostic disclosure was useful in preparing for patient's death	243	114	69.9	129	52.4	0.000
The physician was knowledgeable about the most advanced treatments	236	111	68.1	125	50.8	0.000
The physician gave concrete advice for my actual concern	242	121	74.2	121	49.2	0.000
The prognosis is an "average," and it does not have to be suitable for the patient	199	80	49.1	119	48.4	0.484
The physician paced his/her explanation with the state of my/patient's preparation	243	126	77.3	117	47.6	0.000
The physician assured the continuing responsibility of the physician for medical care	226	111	68.1	115	46.7	0.000
The physician respected my values	229	115	70.6	114	46.3	0.000
The physician suggested what we should do because the patient's condition was relatively good	213	103	63.2	110	44.7	0.000
The physician told me clearly the disease is incurable	172	63	38.7	109	44.3	0.151
The physician discussed how to achieve my wishes, such as home care	190	93	57.1	97	39.4	0.000
The physician said, "I can do nothing for the patient any longer"	117	32	19.6	85	34.6	0.001
The physician explained in terms of daily life perspectives	131	54	33.1	77	31.3	0.389
I felt that the amount of information was insufficient	205	130	79.8	75	30.5	0.000
The physician showed the thought, "I don't want to give up"	147	73	44.8	74	30.1	0.002
The physician told the shortest predicted prognosis	93	38	23.3	55	22.4	0.526
The physician told the longest predicted prognosis	94	40	24.5	54	22.0	0.366
The physician said, "Treatment might be possible at some time in the future"	73	30	18.4	43	17.5	0.455
The physician told the average prognosis	65	26	16.0	39	15.9	0.520
The physician used graphs and tables	40	14	8.6	26	10.6	0.287
The physician told the five-year survival rate	24	12	7.4	12	4.9	0.222
The physician told the one-year survival rate	16	8	4.9	8	3.3	0.295

prognostic disclosure received as independent variables in the initial model, because they were observed to be significant predictors of necessity for improvement in the univariate analysis. Next, we drew all paths according to the results of the correlation analysis. We repeated the analysis and sequentially dropped paths that were not significant until all of the paths in the model became significant ($P < 0.05$). The variables "The prognosis represents an average, and it doesn't have to turn out that way for the patient," "The physician told me the disease is definitively incurable," "The physician said, 'Treatment may be possible at some time in the future,'" and "The physician explained daily life perspectives" were dropped from the model, because all of the paths from these variables did not reach significance. Fig. 1 represents the final model. The fit indices for this model were Chi-square (40) = 177.4, $P = 0.000$; goodness-of-fit index = 0.94; adjusted goodness-of-fit index = 0.86; comparative fit index = 0.91; and root mean-square error of approximation = 0.10. Correlations between independent variables were omitted to simplify the model. Overall, the final model accounted for 41% of the variance in the necessity for improvement.

The parameter with the highest value explaining the necessity for improvement was the family perceived evaluation that the amount of prognosis information was insufficient (beta = 0.39, $P < 0.001$). Furthermore, family perception of loss of hope and usefulness of the prognosis in the preparation for patient death had significant direct effects on the necessity for improvement (beta = 0.21, $P < 0.001$ and beta = −0.18, $P < 0.001$, respectively). There were also three communication strategies that explained the necessity for improvement, as follows: "The physician said, 'I can do nothing for the patient any longer'" (beta = 0.11, $P = 0.005$), "The physician paced his/her explanation with the state of my/patient's preparation" (beta = −0.21, $P < 0.001$), and "The physician said, 'We will respect the patient's wishes'" (beta = −0.10, $P = 0.013$).

Discussion

In Japan, family members have a special role in communicating bad news, including predicted prognosis.[19] However, only a few empirical studies have specifically addressed the preferences and experiences of family members in receiving information about the patient's prognosis,[18] and familial views on optimal ways of presenting the prognosis have not been explored. This is, to our knowledge, the first large, multicenter survey to investigate family reported experiences in receiving prognostic disclosure.

Our survey revealed the experience of families of patients with cancer in Japan in receiving prognostic disclosure. Over 80% of the families received prognostic disclosure. This agrees closely with results of a previous Japanese study.[19] The proportions of subjects who received each type of disclosure were told specific periods with some ranges or probability (40% in the previous survey vs. 52% in our survey) and told definite periods without ranges or probability (38% vs. 34%, respectively). In contrast, over 45% of the subjects answered that the patients were not told specific periods about their prognosis. These data support the view that Japanese family members have a special role in communicating prognosis, and it seems to be important for physicians to consider methods of communicating a patient's prognosis to family members. This study also demonstrated that 60% of family members reported that some, considerable, or much improvement was necessary in the methods of prognostic disclosure. This result suggests that methods in prognosis disclosure would need more improvement in general.

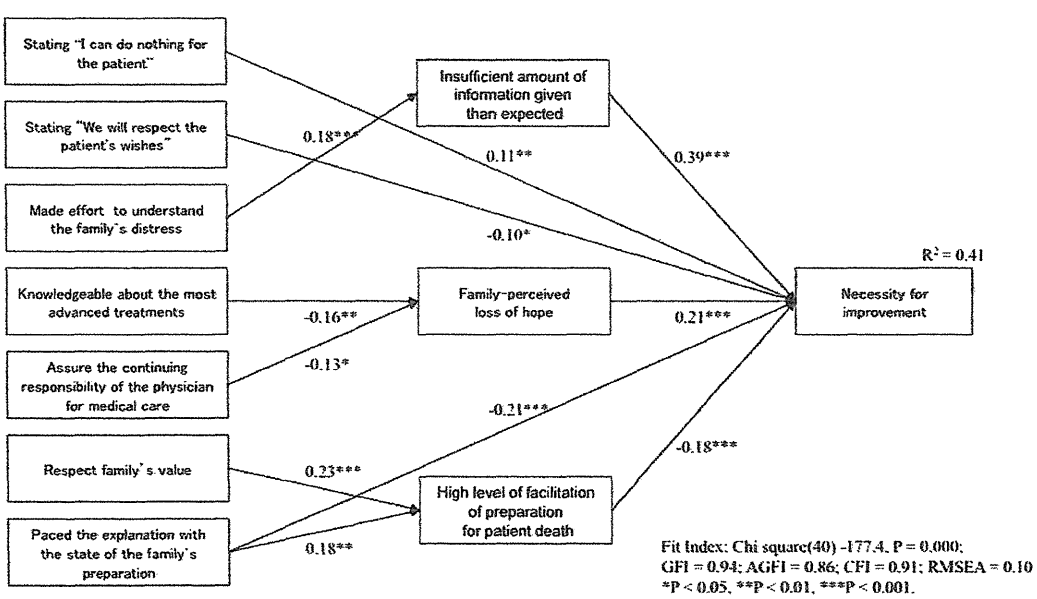

Fig. 1. Model for the relevant factors for family-perceived need for improvement.

The most important finding in the present study was the clarification of the determinants of the necessity for improvement in prognostic disclosure. Using path analysis, we determined that 41% of the variance for increased perceptions for the necessity for improvement was related mainly to the five variables: 1) insufficient amount of information given than expected; 2) loss of hope and failure in facilitation of preparation for patient death; 3) not providing information carefully in consideration of the family's preparation; 4) stating "Nothing can be done;" and 5) not stating "We will respect the patient's wishes."

First, the disclosure of an insufficient amount of information than expected had the largest effect on the necessity for improvement. In a previous study of parents of pediatric patients with cancer, almost all participants wanted as much information as possible about the prognosis, although they found the prognostic information very upsetting.[8] It also is said that 69.6% of caregivers of Korean cancer patients want to know their own terminal condition.[29] The results of the present study show that this may be similar in the case of Japanese adult patients. Physicians, therefore, should comprehend family members' needs and communicate as much information as the family members want.

Second, the results of this study suggested that maintaining the family's hope and facilitating their preparation for a patient's death have a significant and moderate effect on the family member's evaluation of the prognosis communication. In previous studies of patients with cancer, both maintaining patients' hope and helping them prepare for death were of great importance for patients.[5] The present study confirmed that these two factors are equally important in terms of the patient's family also. Maintaining hope while simultaneously preparing for a patient's death seems contradictory, and thus, it may represent a difficult issue for physicians. For patients, a useful way of accomplishing this task is to acknowledge all of the possible outcomes and to expand their planning goals to include both recovery and death.[5,20] In this study, loss of hope was significantly accounted for by the two descriptions: "The physician was knowledgeable about the most advanced treatments" and "The physician assured continuing responsibility as the physician for medical care." One possible interpretation of this result is that hope for family members means receiving assurance of continuing responsibility for medical care by a physician who is knowledgeable about up-to-date treatments. In addition, the type of disclosure they received affected the facilitation of preparation for patient death: "The physician paced his/her explanation with the state of my/patient's preparation" and "The physician respected my values." This finding means that although detailed prognostic information helps families in preparing for a patient's death, it is important to provide information with careful consideration for families' preferences and values. These results confirm that maintaining hope and preparing for death need not be mutually exclusive.[5]

Third, about 30% of the family members reported that the physician said she/he could do nothing for the patient, and this experience had a strong influence on the family-perceived necessity for improvement. This result was consistent with a finding from a previous study that indicated that both patients and families received the phrase from physician "I can do nothing for the patient any longer" with serious negative emotions when they were informed of the ending of cancer treatment.[19,30] From this finding, physicians are advised to emphasize what they can do, such as providing symptom control, instead of stating "nothing can be done" in the prognostic disclosure.

It is notable that family members who were told the physician will respect the patient's wishes reported a lower level of necessity for improvement. It is also noted that the disclosure of prognostic information as it corresponds to patient's values is essential for patients to make decisions about the terminal phase.[31] At the same time, over 70% of physicians in Japan have experience of not telling patients their prognosis according to the request of family members.[22] The results of the present study indicate the possibility that many family members have a conflict between their wish to respect the patient's wishes and their hesitancy about communicating the prognosis to the patient. Thus, in prognosis disclosure, physicians should assure the family of the intent to respect the patient's wishes while also conferring with the family on how to achieve this.

This study had several limitations. First, as the response rate was not very high (64%), the study subjects might not be representative of the population. Second, the study subjects were limited to the families of patients who had been admitted to PCUs, and the findings might not be applicable to families in other settings. Moreover, prognostic disclosure is sometimes required for admission to a PCU; thus, the amount of disclosure might be higher than in a general ward. The future survey of families of patients who had not been admitted to PCUs will be expected as the next step. Third, due to a lack of validated instruments, primary endpoints were measured without formal reliability and validity testing. Fourth, some factors that might be relevant, such as symptom distress and experience of anticancer therapy, were not analyzed as to whether they might influence the perception of prognostic communication. Fifth, this study depended on the retrospective evaluation of bereaved family members, and recall bias could exist. Confirmation of the findings will require prospective observational or interventional studies. Finally, due to the lack of comparable studies, we compared our results mainly with those of patient surveys, but preferences might be different between patients and families.

Conclusion

When receiving communication about a patient's prognosis, 60% of bereaved family members reported that some, considerable, or much improvement in the communication methods was necessary. Strategies for care providers to improve family perception include 1) providing as much prognostic information as families want; 2) supporting families' hopes by keeping up with up-to-date treatments and by assuring continuing responsibility as the physician for medical care; 3) facilitating the preparation for death by providing information in consideration of the family's preparations and values; 4) stressing what they can do instead of saying that nothing can be done for the patient; and 5) assuring the family that they will respect the patient's wishes. These suggested communication strategies should be tested in future prospective observational or interventional studies.

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Synthesis and antitumor evaluation of arctigenin derivatives based on antiausterity strategy

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ABSTRACT

A series of new (−)-arctigenin derivatives with variably modified *O*-alkyl groups were synthesized and their preferential cytotoxicity was evaluated against human pancreatic cancer cell line PANC-1 under nutrient-deprived conditions. The results showed that monoethoxy derivative **4i** (PC_{50}, 0.49 μM), diethoxy derivative **4h** (PC_{50}, 0.66 μM), and triethoxy derivative **4m** (PC_{50}, 0.78 μM) showed the preferential cytotoxicities under nutrient-deprived conditions, which were identical to or more potent than (−)-arctigenin (**1**) (PC_{50}, 0.80 μM). Among them, we selected the triethoxy derivative **4m** and examined its *in vivo* antitumor activity using a mouse xenograft model. Triethoxy derivative **4m** exhibited also *in vivo* antitumor activity with the potency identical to or slightly more than (−)-arctigenin (**1**). These results would suggest that a modification of (−)-arctigenin structure could lead to a new drug based on the antiausterity strategy.

1. Introduction

Pancreatic cancer is the most aggressive cancer of all and has an exceptionally high global mortality rate, with an estimated 267,000 deaths worldwide in 2008. It ranks 8th or 9th as the most frequent cause of cancer death worldwide and is the 4th or 5th most frequent cause of cancer death in most developed countries, including the United States, Europe, and Japan [1]. Moreover, it has been estimated that the number of deaths from pancreatic cancer will reach 484,000 by 2030 [1]. Pancreatic cancer rapidly metastases and lead the patients to die in a short period of the diagnosis. Thus, the 5-year survival rate of the patients with the pancreatic cancer is the lowest among several cancers [2,3]. Though surgery is the only treatment method that offers any prospect of potential cure, chemotherapy with 5-fluorouracil and gemcitabine is also used for palliative therapy of advanced pancreatic cancer. However pancreatic cancer is largely resistant to most known chemotherapeutic agents including 5-fluorouracil and gemcitabine [4]. Therefore effective chemotherapeutic agents that target pancreatic cancer are urgently needed.

Tumor cells, in general, proliferate very fast, and the demand for essential nutrients, oxygen, *etc.* is always high. The immediate environment of cancers increasing in size, however, often becomes heterogeneous and some regions of large cancers often possess microenvironmental niches, which exhibit a significant gradient of critical metabolites including oxygen, glucose, other nutrients, and growth factors [5]. Thus, many cancer cells get the critical metabolites by randomly recruiting new blood vessels, a phenomenon commonly known as angiogenesis, to survive under such severe conditions. However, human pancreatic cancer survives with an extremely poor blood supply and becomes more malignant [6]. The method by which pancreatic cancer survives is by getting a remarkable tolerance to extreme nutrient starvation [7]. Therefore, it has been hypothesized that eliminating the tolerance of cancer cells to nutrition starvation

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may allow a novel biochemical approach known as "anti-austerity" for cancer therapy [8].

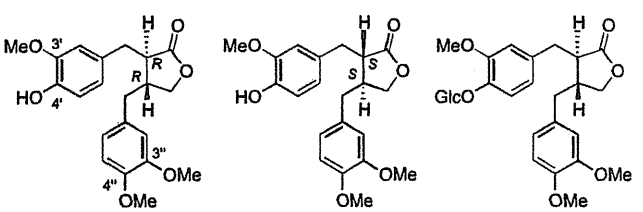
In this regard, we screened 500 medicinal plants used in Kampo medicine to identify agents that preferentially reduce the survival of nutrient-deprived human pancreatic cancer PANC-1 cells. The screen led to the isolation of (−)-arctigenin (**1**) as the active principle of *Arctium lappa* [9]. In addition to pancreatic cancer, arctigenin has been reported to inhibit lung, skin, and stomach cancers [10]. Thus, we started the synthetic work of arctigenin derivatives to obtain more effective drugs against pancreatic cancer. In *A. lappa*, (−)-arctigenin is mainly contained as its glucoside, arctiin, and after consumption arctiin was reported to be deglucosidated to (−)-arctigenin (**1**), followed by demethylation and dehydroxylation by intestinal bacteria to metabolites **I**–**V** [11]. As reported previously, (−)-arctigenin showed potent preferential cytotoxicity, whereas its glucoside, arctiin, showed no cytotoxicity [9]. In our preliminary examination, moreover, metabolites **I** and **V** (Fig. 1) showed weaker activity. These facts should suggest that the 4′-hydroxyl group should be important for the preferential cytotoxicity and that (−)-arctigenin is deactivated through the demethylation/demethoxylation. In addition, the enantiomer of (−)-arctigenin (**1**), (+)-arctigenin (Fig. 1), showed very weak preferential cytotoxicity, indicating the importance of the 2*R*,3*R* absolute stereochemistry of (−)-form. Thus, with an intention to improve the metabolism stability, we have synthesized 15 arctigenin derivatives **4a**–**o** with different alkoxy substituent and the 2*R*,3*R*-configuration, and the *in vitro* preferential cytotoxicity of them was characterized under nutrient-deprived conditions. Then, the triethoxy derivative **4m**, exhibiting the *in vitro* activity identical to **1** and having no methoxy group which may be metabolized, was selected and further evaluated the effect against tumor cell growth *in vivo* in a cancer xenograft mouse model.

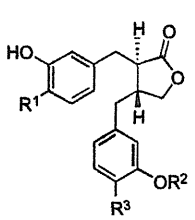
2. Results and discussion

2.1. Chemistry

First we planned the synthesis of derivatives on the 3′ position of (−)-arctigenin. For this purpose, (−)-arctigenin (**1**) was converted to the diol **2** [12], which was transformed into 6 derivatives **4a**–**f** via selective protection of **2**, alkylation of **3**, followed by deprotection of the benzyl group (Scheme 1).

Next we planned the efficient and flexible synthesis of a variety of derivatives on the 3′, 3″, and 4″ positions of (−)-arctigenin.





	R^1	R^2	R^3
I	OH	Me	OMe
II	H	Me	OMe
III	H	H	OMe
IV	H	H	OH
V	H	H	H

Fig. 1. Structures of (−)-arctigenin (**1**) and its analogs.

3,4-Dihydroxybenzaldehyde was converted to the alcohol **7** via known benzyl ether **5** [13] and aldehyde **6** [14]. Mono-alkylation of diethyl malonate with the mesylate of **7** afforded the ester **8**. Reduction of **8** and lipase-mediated transesterification of the resulting diol provided the mono-acetate (+)-**9**. The enantiomeric excess of (+)-**9** was determined to be 98% ee by the HPLC analysis using the chiral column (Chiralcel OJ). The absolute stereochemistry of (+)-**9** was determined by the comparison of the optical rotation with known lactone **13a**, prepared from (+)-**9** via mesylate **10**, benzyl ether **11**, and lactone **12a** as shown in Scheme 2. Other lactones **13b**–**f** were also prepared from (+)-**9**, and these lactones **13b**–**f** were alkylated on the α-position with several alkyl halides to afford the di-substituted lactones **14a**–**i**. Finally deprotection of the benzyl group furnished the desired derivatives **4g**–**o**.

From the comparison of the *in vitro* activity of the synthesized derivatives **4a**–**o** against the human pancreatic cancer cell line PANC-1, the triethoxy derivative **4m** was chosen as the potent candidate for the *in vivo* experiment. As the more effective synthesis of **4m**, we investigated the modified synthesis of the lactone **13d**. 3,4-Dihydroxybenzaldehyde was converted to the ester **17** via known aldehyde **15** [15] and alcohol **16** [16] as the same procedure for the synthesis of **8**. After reduction of **17**, lipase-mediated transesterification of the resulting diol afforded the mono-acetate **18**, whose enantiomeric excess was determined to be 98% ee again by the Mosher method. The mono-acetate **18** was then transformed into the lactone **13d** via mesylate **19** (Scheme 3).

2.2. In vitro preferential cytotoxicity of arctigenin derivatives

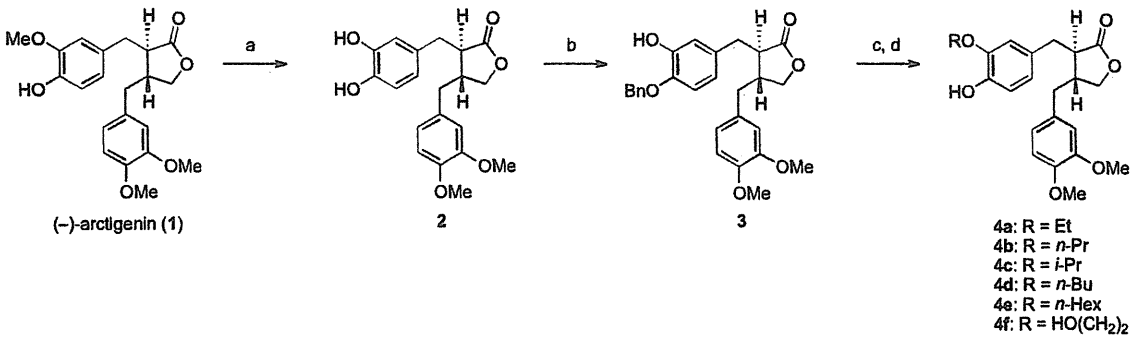
All of the (−)-arctigenin derivatives **4a**–**o** were evaluated for their *in vitro* preferential cytotoxic activity against human pancreatic cancer PANC-1 cells in nutrient-deprived medium (NDM). The PANC-1 cell line is highly resistant to nutrient starvation, and can survive in NDM even after 48 h of starvation [6,7,8]. However, this tolerance to nutrient starvation was remarkably eliminated by the tested compounds in a concentration-dependent manner. The tested compounds exhibited different potency of toxicity (Fig. 2) and their preferential cytotoxicities are obtained as the 50% cytotoxic concentration in NDM (PC_{50} value) (Table 1). Among the (−)-arctigenin derivatives **4a**–**o**, monoethoxy derivative **4i** showed the most potent preferential cytotoxicity (PC_{50}, 0.49 μM), followed by diethoxy derivative **4h** (PC_{50}, 0.66 μM) and triethoxy derivative **4m** (PC_{50}, 0.78 μM), which were identical to or more potent than (−)-arctigenin (**1**) (PC_{50}, 0.80 μM).

On the relationship between the substituents and the preferential activity, the 3′ position seems to favor smaller substituent since the PC_{50} values of **1** and **4a**–**d** increase in the order: **1** (MeO) < **4a** (EtO) = **4b** (*n*-PrO) < **4c** (*i*-PrO) < **4d** (*n*-BuO). This would suggest the importance of the 4′-hydroxy group for the preferential activity. On the other hand, there is not clear relationship on the substituents at the 3″ and 4″ positions, although smaller substituents seems to be favor.

The order of *in vitro* preferential cytotoxicity (PC_{50}) was **4i** > **4h** > **4m**. Whereas **4h** and **4i** have the methoxy groups which was reported to be demethylated and then deoxygenated by intestinal bacteria and/or hepatic enzyme [11]. Thus, we selected the triethoxy derivative **4m** to pursue a further examination, from a viewpoint of metabolism stability.

2.3. In vivo antitumor activity of triethoxy derivative 4m

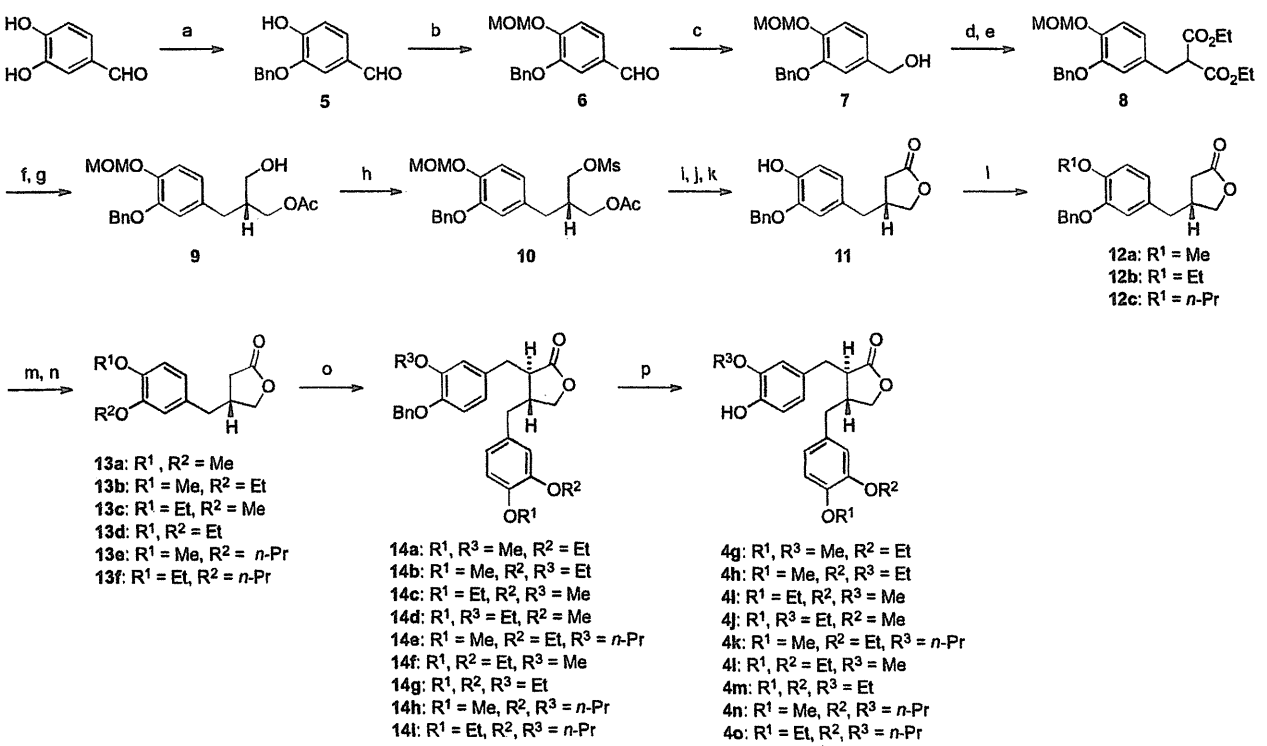
The triethoxy derivative **4m** showed the *in vitro* preferential cytotoxicity also against human pancreatic cancer cell line CAPAN-1 under glucose deficient conditions with a intensity similar to (−)-arctigenin (**1**) (Fig. 3). We used PANC-1 cell line for *in vitro*



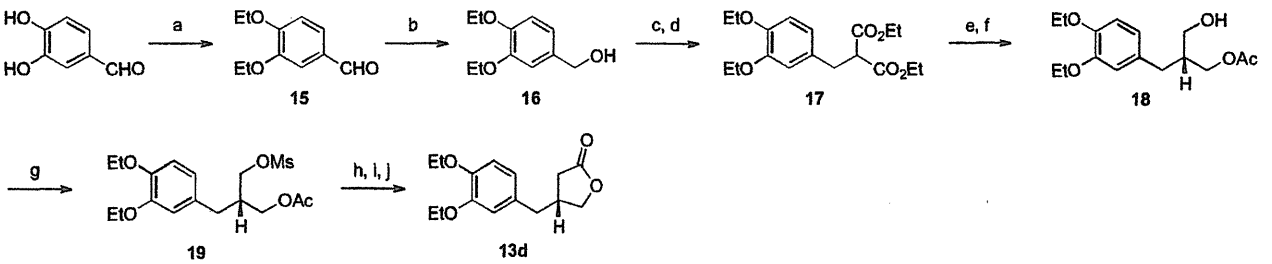
Scheme 1. Reagents and conditions: a: $AlCl_3$, pyridine, CH_2Cl_2, reflux (quant.); b: BnBr, K_2CO_3, KI, acetone, reflux (63%); c: RI or RBr, K_2CO_3, acetone, reflux for **4a–e** or 2-benzyloxyethanol, Ph_3P, DEAD, CH_2Cl_2, rt for **4f**; d: H_2, $Pd(OH)_2$, MeOH, rt.

study because of its ready growth [17], while mouse xenograft model can be prepared with CAPAN-1 cell line more easily than with PANC-1 cell line [18]. Thus, we used mouse xenograft model with CAPAN-1 cell line for comparing the *in vivo* effect of triethoxy derivative **4m** with (−)-arctigenin (**1**).

Mice were inoculated with 5×10^6 CAPAN-1 cells s.c. on the back and then administered triethoxy derivative **4m**, (−)-arctigenin (**1**), or vehicle, as described in Experimental. The body weight of the animals was monitored weekly (Fig. 4A) and no significant body weight loss was recognized in the treated group versus the vehicle control group at any time during the experimental period. This fact, together with the behavior of the treated animals, indicated that the tested compounds might have no toxicity at the dose used. The treatment was initiated from the 15th day by i.p. injection of the drug at the dose of 50 μg/mouse/d on 6 days of the week (or vehicle in the control group) until the 28th day. The tumor size was measured weekly. As is evident from the tumor growth curve shown in Fig. 4B, the tumor volume increased steadily in the control group, whereas the increase was significantly less prominent in the groups treated by triethoxy derivative **4m** or (−)-arctigenin (**1**). There was a significant difference in the tumor size at the day 21 between the groups treated by triethoxy derivative **4m** or (−)-arctigenin (**1**) and the control group ($P < 0.05$). Similarly, the mean wet weight and the size of the tumor were higher in the



Scheme 2. Reagents and conditions: a: BnBr, K_2CO_3, KI, acetone, reflux (64%); b: MOMCl, DIPEA, CH_2Cl_2, rt (quant.); c: $NaBH_4$, MeOH, rt (95%); d: MsCl, Et_3N, CH_2Cl_2, rt; e: diethyl malonate NaH, DMF, rt (72% in 2 steps); f: $LiAlH_4$, THF, reflux; g: lipase-PS (Amano), vinyl acetate, i-Pr_2O–THF rt (80% in 2 steps, 98% ee); h: MsCl, Et_3N, CH_2Cl_2, rt; i: KCN, DMSO, 90 °C; j: LiOH, THF–H_2O, rt; k: 10% NaOH (aq), reflux, then 10% HCl (aq)–THF, rt (73% in 4 steps); l: MeI or EtI or n-PrBr, K_2CO_3, acetone, reflux (88% for **12a**, 86% for **12b**, 87% for **12c**); m: H_2, $Pd(OH)_2$, MeOH; n: MeI or EtI, K_2CO_3, acetone, reflux (55% in 2 steps for **13a**, 55% in 2 steps for **13b**, 55% in 2 steps for **13c**, 47% in 2 steps for **13d**, 80% in 2 steps for **13e**, 77% in 2 steps for **13f**); o: LiHMDS, substituted BnBr, HMPA, THF, −78 °C to rt (44% for **14a**, 59% for **14b**, 43% for **14c**, 53% for **14d**, 40% for **14e**; 48% for **14f**; 56% for **14g**, 49% for **14h**; 33% for **14l**); p: H_2, $Pd(OH)_2$, MeOH (89% for **4g**, 63% for **4h**, 57% for **4i**, 63% for **4j**, 56% for **4k**, 81% for **4l**, 66% for **4m**, 46% for **4n**, 63% for **4o**).



Scheme 3. Reagents and conditions: a: EtI, K_2CO_3, acetone, reflux (92%); b: $NaBH_4$, MeOH, rt (74%); c: MsCl, Et_3N, CH_2Cl_2, rt; d: diethyl malonate NaH, DMF, rt (87% in 2 steps); e: $LiAlH_4$, THF, reflux; f: lipase-PS (Amano), vinyl acetate, *i*-Pr_2O–THF rt (53% in 2 steps, 98% ee); g: MsCl, Et_3N, CH_2Cl_2, rt (79%); h: KCN, DMSO, 90 °C; i: LiOH, THF–H_2O, rt; j: 10% NaOH (aq), reflux, then 10% HCl (aq)-THF, rt (60% in 3 steps).

control group than the groups treated by triethoxy derivative **4m** or (−)-arctigenin (**1**) (Fig. 4C–F). These data indicate that triethoxy derivative **4m** also exerted antitumor activity *in vivo* with the potency identical to or slightly more than (−)-arctigenin (**1**).

3. Conclusion

In summary, a series of new (−)-arctigenin derivatives modified on *O*-alkyl groups were synthesized and their preferential cytotoxicity was evaluated against human pancreatic cancer cell line PANC-1 under nutrient-deprived conditions. The results showed that monoethoxy derivative **4i** (PC_{50}, 0.49 μM), diethoxy derivative **4h** (PC_{50}, 0.66 μM), and triethoxy derivative **4m** (PC_{50}, 0.78 μM) showed the preferential cytotoxicities under nutrient-deprived conditions, which were identical to or more potent than (−)-arctigenin (**1**) (PC_{50}, 0.80 μM). Among them, we selected the triethoxy derivative **4m** and examined *in vivo* antitumor activity with mouse xenograft model. Triethoxy derivative **4m** exhibited also *in vivo* antitumor activity with the potency identical to (−)-arctigenin (**1**). These results would suggest that a modification of (−)-arctigenin structure could lead to a new drug based on the antiausterity strategy.

4. Experimental

4.1. Chemistry

4.1.1. General conditions

Chemicals were purchased from Sigma–Aldrich, Merck, Nakalai Tesque, Wako Pure Chemicals, and Kanto Chemicals, and used without further purification. Column chromatography was done on Cica silica gel 60N (spherical, neutral; particle size, 40–50 μm, Kanto Chemical Co., Inc., Tokyo, Japan), while thin-layer chromatography (TLC) was performed on Merck silica gel $60F_{254}$ plates (Merck KGaA, Darmstadt, Germany). Melting points were taken on a Yanaco micromelting point apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were acquired in the specified solvent, in a Varian Gemini 300 spectrometer (300 and 75 MHz for ^1H and ^{13}C, respectively) or Varian UNITY plus 500 spectrometer (500 and 125 MHz for ^1H and ^{13}C, respectively) (Varian Inc., Palo Alto, CA, USA), with tetramethylsilane (TMS) as internal standard. The chemical shifts (δ) are reported in ppm downfield from TMS and coupling constants (J) are expressed in Hertz. Optical rotations were obtained in the specified solvent on a JASCO DIP-1000 digital polarimeter (JASCO Corp., Tokyo, Japan). IR spectra were measured with a JASCO FT/IR-460 Plus spectrophotometer (JASCO Corp.). The low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a Shimadzu GCMS-QP 500 mass spectrometer (Shimadzu Corp., Kyoto, Japan), JEOL D-200, or JEOL AX505 mass spectrometer (JEOL Ltd., Tokyo, Japan) in the electron impact mode at the ionization potential of 70 eV.

4.1.2. Synthesis of (−)-arctigenin derivatives 4a–4f

4.1.2.1. (3R,4R)-3-(4-Benzyloxy-3-hydroxybenzyl)-4-(3,4-dimethoxybenzyl)dihydrofuran-2-one (3). To a stirred solution of (3R,4R)-3-(3,4-dihydroxybenzyl)-4-(3,4-dimethoxybenzyl)dihydrofuran-2-one (**2**) [12] (65.4 mg, 0.18 mmol) in acetone (2 mL) were added K_2CO_3 (37.3 mg, 0.27 mmol), KI (5.97 mg, 0.036 mmol), and BnBr (21.4 μL, 0.18 mmol), and the resulting mixture was refluex for 5 h. After cooling, the reaction mixture was filtered, and the filtrate was evaporated. The residue was chromatographed on silica gel (10 g, hexane:acetone = 4:1) to give **3** (51.2 mg, 63%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.60 (1H, br), 2.47–2.63 (4H, m), 2.86–2.98 (2H, m), 3.80 (3H, s), 3.85 (3H, s), 3.80–3.89 (1H, m), 4.09–4.14 (1H, m), 5.13 (2H, s), 6.47–6.80 (6H, m), 7.28–7.44 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.59, 38.19, 41.15, 46.53, 55.82, 55.98, 71.08, 71.21, 111.22, 111.72, 112.79, 113.95, 120.43, 121.20, 127.12, 127.69, 128.39, 130.30, 130.73, 136.98, 146.91, 147.67, 148.84, 149.63, 178.46; IR (neat): 1514 (C=C), 1769 (C=O) cm^{-1}; MS (EI) m/z 449 (M^+); HRMS (EI): calcd for $C_{27}H_{28}O_6$: 448.1886 (M^+), found: 448.2743; $[\alpha]_D^{26}$ −20.7 (*c* 0.85, $CHCl_3$).

4.1.2.2. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-(3-ethoxy-4-hydroxybenzyl)dihydrofuran-2-one (4a). To a stirred solution of **3** (44.7 mg, 0.10 mmol) in acetone (5 mL) were added K_2CO_3 (82.6 mg, 0.60 mmol), EtI (26.5 μL, 0.33 mmol), and the reaction mixture was refluxed for 48 h. After cooling, the reaction mixture was filtered, and the filtrate was evaporated. The residue was dissolved in MeOH (6 mL). To the solution was added 20% $Pd(OH)_2$ (10 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 16 h. The catalyst was removed by filtration and the filtrate was evaporated. The residue was chromatographed on silica gel (7 g, hexane : acetone = 3:1) to give **4a** (13.4 mg, 35% in 2 steps) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41 (3H, t, J = 7.1 Hz), 2.42–2.64 (4H, m), 2.90 (2H, d, J = 5.2 Hz), 3.80 (3H, s), 3.84 (3H, s), 3.80–3.88 (1H, m), 4.02 (2H, q, J = 7.1 Hz), 4.08–4.13 (1H, m), 5.66 (1H, br), 6.46–6.75 (4H, m), 6.81 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.85, 30.94, 34.48, 38.15, 40.90, 46.58, 55.85, 64.38, 71.24, 111.11, 111.61, 112.29, 113.94, 120.43, 121.83, 129.20, 130.30, 144.47, 145.80, 147.62, 148.81, 178.51; IR (neat): 1516 (C=C), 1766 (C=O), 3446 (OH) cm^{-1}; MS (EI) m/z 386 (M^+); HRMS (EI): calcd for $C_{22}H_{26}O_6$: 386.1729 (M^+), found: 386.1724; $[\alpha]_D^{26}$ −20.5 (*c* 0.98, $CHCl_3$).

4.1.2.3. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-(4-hydroxy-3-propoxybenzyl)dihydrofuran-2-one (4b). By the procedure similar to synthesis of **4a**, (−)-arctigenin derivative **4b** was prepared from **3** and *n*-PrBr (18% in 2 steps) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.04 (3H, t, J = 1.9 Hz), 1.77–1.87 (2H, m), 2.42–2.67 (4H, m), 2.81–3.01 (2H, m), 3.78–3.86 (7H, m), 3.90–4.00 (2H, m), 4.09–4.14 (1H, m), 5.59–5.63 (1H, br), 6.47–6.85 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.60, 22.60, 29.34, 31.81, 34.55, 38.22, 41.49, 46.65, 53.80, 55.82, 70.35, 71.29, 111.71, 113.94, 115.27, 120.47, 121.85, 112.34, 129.28,

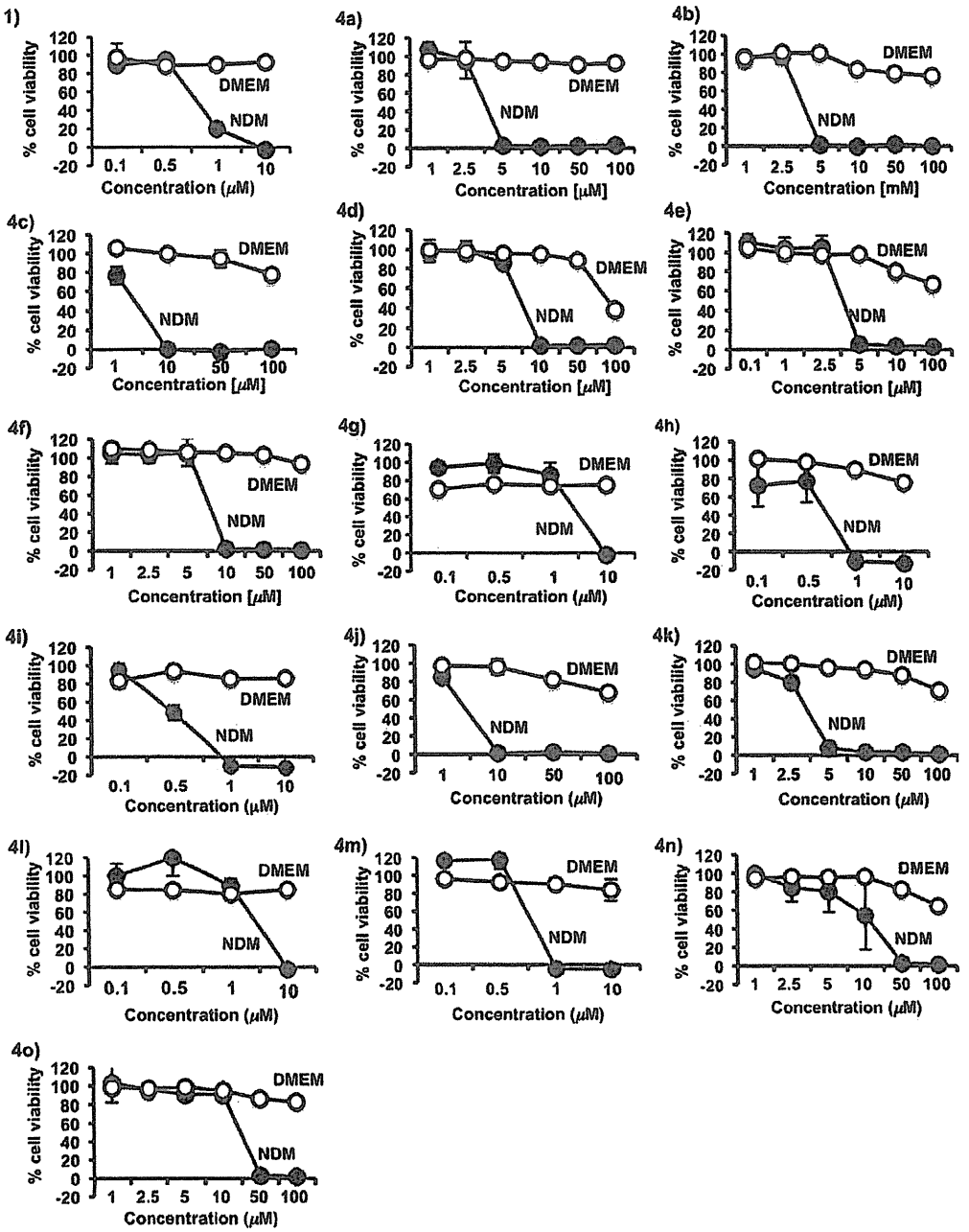


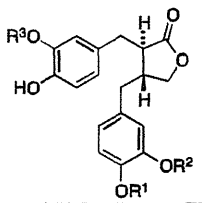
Fig. 2. Effects of (−)-arctigenin derivatives on cell survival in the PANC-1 cell line under nutrient-deprived conditions. Cells were seeded at a density of 2×10^4 per well in 96-well plates and incubated in fresh complete medium for 24 h. The cells were then washed with PBS and the medium was changed to nutrient-deprived medium (NDM, ●) or normal DMEM (○) together containing graded concentrations of (−)-arctigenin derivatives. Points, mean from triplicate experiments. The cell number at the start of the starvation was considered to be 100%. The cell count was measured by the WST-8 cell counting kit method, as described in experimental. The numbers **1** and **4a–o** mean the data of (−)-arctigenin (**1**) and (−)-arctigenin derivatives **4a–o**, respectively.

130.59, 144.52, 147.69, 178.54; IR (neat): 1456 (C=C), 1769 (C=O) cm^{-1}; MS (EI) *m/z* 400 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 400.1886 (M^+), found: 400.1893; $[\alpha]_D^{26}$ −15.7 (*c* 1.45, $CHCl_3$).

4.1.2.4. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-(4-hydroxy-3-i-propoxybenzyl)dihydrofuran-2-one (4c). By the procedure similar to synthesis of **4a**, (−)-arctigenin derivative **4c** was prepared from **3** and *i*-PrI (18% in 2 steps) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.31–1.35 (6H, m), 1.59 (1H, br), 2.41–2.68 (4H, m), 2.80–3.00 (2H, m), 3.80–3.88 (7H, m), 4.07–4.12 (1H, m), 4.49–4.57 (1H, m), 6.48–6.84 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.02, 34.39, 3.12, 41.45, 46.65, 55.81, 71.19, 111.25, 111.68, 113.41, 114.18, 115.49, 120.61, 122.09, 129.26, 130.43, 144.70, 145.48, 146.59, 147.84, 149.02, 178.72; IR (neat): 1716 (C=O), 3629 (OH) cm^{-1}; MS (EI) *m/z* 400 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 400.1886 (M^+), found: 400.1926; $[\alpha]_D^{24}$ −37.7 (*c* 0.41, $CHCl_3$).

4.1.2.5. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-(4-hydroxy-3-butyloxybenzyl)dihydrofuran-2-one (4d). By the procedure similar to synthesis of **4a**, (−)-arctigenin derivative **4d** was prepared from **3**

Table 1
Preferential cytotoxicity of (−)-arctigenin (1) and series of new (−)-arctigenin derivatives **4a–4o** against human pancreatic cancer PANC-1 cells in nutrient-deprived medium (NDM).



Compound	R^1	R^2	R^3	PC_{50} (μM)	Compound	R^1	R^2	R^3	PC_{50} (μM)
1 (arctigenin)	Me	Me	Me	0.80	**4h**	Me	Et	Et	0.66
4a	Me	Me	Et	3.74	**4i**	Et	Me	Me	0.49
4b	Me	Me	*n*-Pr	3.74	**4j**	Et	Me	Et	4.77
4c	Me	Me	*i*-Pr	4.16	**4k**	Me	Et	*n*-Pr	3.54
4d	Me	Me	*n*-Bu	7.14	**4l**	Et	Et	Me	4.85
4e	Me	Me	*n*-Hex	3.89	**4m**	Et	Et	Et	0.78
4f	Me	Me	$HO(CH_2)_2$	7.70	**4n**	Me	*n*-Pr	*n*-Pr	13.6
4g	Me	Et	Me	4.71	**4o**	Et	*n*-Pr	*n*-Pr	28.6

and *n*-BuBr (25% in 2 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (3H, t, J = 7.1 Hz), 1.48 (2H, dd, J = 15.1, 7.1 Hz), 1.74–1.83 (2H, m), 2.41–2.66 (4H, m), 2.80–3.02 (2H, m), 3.82 (3H, s), 3.83 (3H, s), 3.85 (1H, m), 3.94–4.03 (2H, m), 4.08–4.14 (1H, m), 5.59 (1H, m), 6.50–6.84 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.97, 19.32, 31.31, 55.82, 55.92, 68.60, 68.65, 71.21, 71.27, 111.19, 111.67, 112.32, 113.92, 120.46, 129.29, 130.34, 130.46, 144.52, 144.71, 145.59, 145.96, 147.69, 148.92, 178.53; IR (neat): 1515 (C=C), 1769 (C=O), 3446 (OH) cm^{-1}; MS (EI) *m/z* 414 (M^+); HRMS (EI): calcd for $C_{24}H_{30}O_6$: 414.2042 (M^+), found: 414.2000; $[\alpha]_D^{26}$ −20.2 (*c* 1.15, $CHCl_3$).

4.1.2.6. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-(3-hexyloxy-4-hydroxybenzyl)dihydrofuran-2-one (4e). By the procedure similar to synthesis of **4a**, (−)-arctigenin derivative **4e** was prepared from **3** and 1-bromohexane (35% in 2 steps) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.90 (3H, t, J = 6.4 Hz), 1.25–1.27 (2H, m), 1.33–1.35 (4H, m), 1.45 (2H, m), 1.75–2.66 (4H, m), 2.81–3.01 (2H, m), 3.82 (3H, s), 3.85 (3H, s), 3.84–3.89 (1H, m), 3.94–4.02 (2H, m), 4.09–4.14 (1H, m), 5.56–5.61 (1H, m), 6.47–6.84 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.11, 22.67, 25.78, 29.25, 31.62, 34.56, 38.22, 40.02, 46.65, 55.82, 68.92, 71.21, 111.19, 111.67, 112.32, 113.92, 115.25, 120.56, 121.83, 129.29, 130.43, 130.34, 144.52, 147.67, 148.92, 178.53; IR (neat): 1457 (C=C), 1764 (C=O), 3689 (OH) cm^{-1}; MS (EI) *m/z* 442 (M^+); HRMS (EI): calcd for $C_{26}H_{34}O_6$: 442.2355 (M^+), found: 442.2336; $[\alpha]_D^{26}$ −10.1 (*c* 0.65, $CHCl_3$).

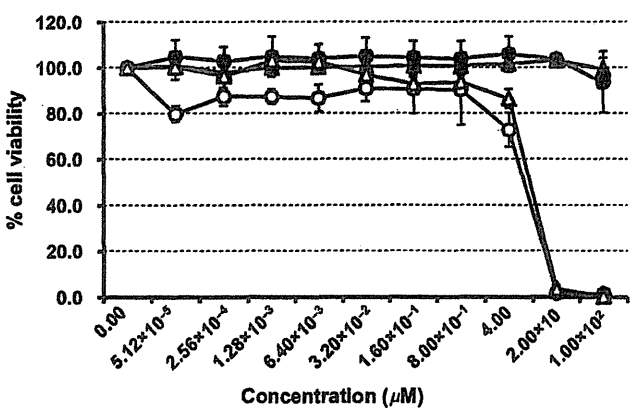


Fig. 3. Effect of triethoxy derivative **4m** and (−)-arctigenin (1) on cell survival in the CAPAN-1 cell line under glucose-deprived conditions. ●, (−)-arctigenin (1) in normal DMEM; ▲, triethoxy derivative **4m** in normal DMEM; ○, (−)-arctigenin (1) in glucose-deprived medium; △, triethoxy derivative **4m** in glucose-deprived medium.

4.1.2.7. (3R,4R)-4-(3,4-Dimethoxybenzyl)-3-[4-hydroxy-3-(2-hydroxyethoxy)benzyl]dihydrofuran-2-one (4f). By the procedure similar to synthesis of **4a**, (−)-arctigenin derivative **4f** was prepared from **3** and 2-benzyloxyethanol (20% in 2 steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42–2.59 (4H, m), 2.78–2.94 (2H, m), 3.76 (3H, s), 3.83 (3H, s), 3.73–3.80 (1H, m), 3.86–4.07 (6H, m), 4.13–4.16 (1H, m), 6.40–6.75 (4H, m), 6.81 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.24, 38.22, 40.69, 46.53, 55.72, 55.97, 61.08, 69.82, 71.45, 111.30, 111.56, 113.00, 115.02, 120.67, 122.55, 129.00, 130.44, 145.02, 146.10, 147.38, 148.72, 178.83; IR (neat): 1517 (C=C), 1765 (C=O), 3420 (OH) cm^{-1}; MS (EI) *m/z* 402 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 402.1679 (M^+), found: 402.1671; $[\alpha]_D^{26}$ −19.7 (*c* 1.10, $CHCl_3$).

4.1.3. Synthesis of (−)-arctigenin derivatives 4g–4o

4.1.3.1. (4-Benzyloxy-3-methoxymethoxyphenyl)methanol (7). To a stirred solution of 4-benzyloxy-3-methoxymethoxybenzaldehyde (**6**) [14] (7.03 g, 25.8 mmol) in MeOH (50 mL) was added $NaBH_4$ (3.88 g, 103 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O (50 mL), and the aqueous mixture was extracted with CH_2Cl_2 (50 mL × 3). The organic extracts were combined, dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (40 g, hexane:acetone = 3:1) to give **7** (6.66 g, 95%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (1H, br), 3.53 (3H, s), 5.01 (2H, s), 5.16 (2H, s), 5.24 (2H, s), 6.88–6.96 (2H, m), 7.16 (1H, d, J = 1.9 Hz), 7.30–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.13, 64.64, 70.88, 95.40, 114.25, 116.22, 121.06, 126.98, 127.61, 128.27, 134.16, 136.82, 146.60, 148.19; IR (neat): 1511 (C=C), 3419 (OH) cm^{-1}; MS (EI) *m/z* 274 (M^+); HRMS (EI): calcd for $C_{16}H_{18}O_4$: 274.1205 (M^+), found: 274.1188.

4.1.3.2. 2-(4-Benzyloxy-3-methoxymethoxybenzyl)malonic acid diethyl ester (8). To a stirred solution of **7** (711 mg, 2.59 mmol) in CH_2Cl_2 (26 mL) were added NEt_3 (0.43 mL, 3.11 mmol) and MsCl (0.22 mL, 2.85 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (20 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 3), and the organic layer and extracts were combined, dried over $MgSO_4$. The

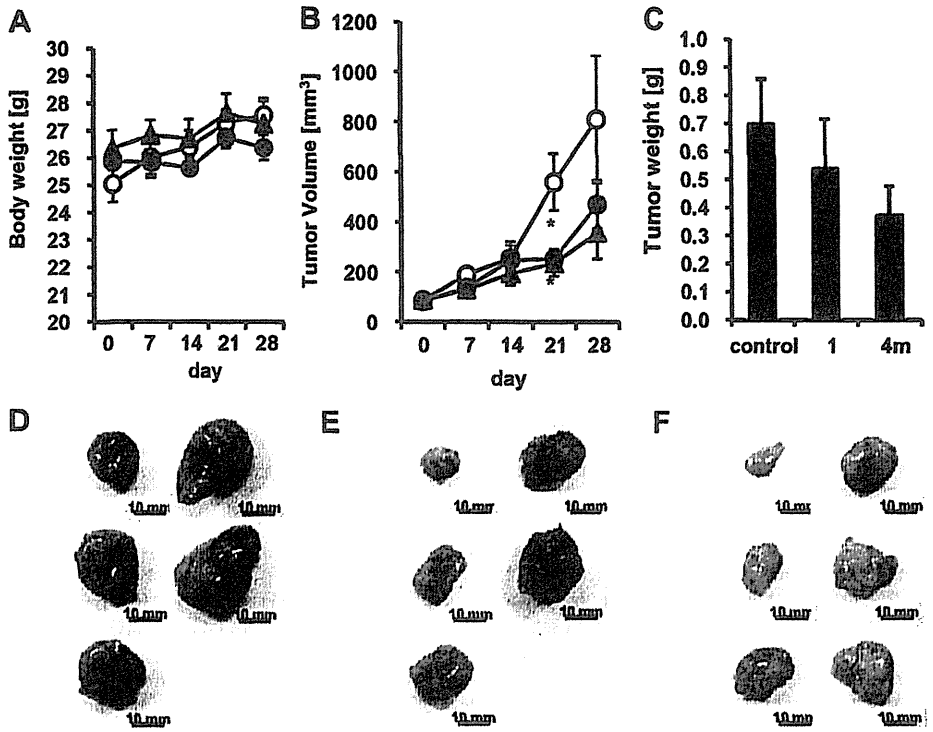


Fig. 4. Effect of triethoxy derivative **4m** and (−)-arctigenin (**1**) on the growth of CAPAN-1 cells in nude mice. A, body weight of mice. ○, control group (n = 5); ●, group treated with triethoxy derivative **4m** (n = 6); △, group treated with (−)-arctigenin (**1**) (n = 5). B, the tumor volume in the mice. ○, control group; ●, group treated with triethoxy derivative **4m**; △, group treated with (−)-arctigenin (**1**). C, wet weight of the tumor in the mice on the last day of the experiment. D–F, photographs of the tumor after sacrifice on the last day of control group, of group treated with (−)-arctigenin (**1**), and of group treated with triethoxy derivative **4m**, respectively.

solvent was removed under reduced pressure to give a pale yellow oil, which was used directly in the next step. To a stirred solution of diethyl malonate (0.79 mL, 5.18 mmol) in DMF (10 mL) was added NaH (60%, 207 mg, 5.18 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. To the solution was added a solution of the oil obtained above in DMF (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 20 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (10 mL), and the aqueous mixture was extracted with Et_2O (20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, evaporated to give a pale yellow oil which was chromatographed on silica gel (20 g, hexane:acetone = 15:1) to give **8** (776 mg, 72% in 2 steps) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (6H, t, J = 7.1 Hz), 3.13 (2H, d, J = 7.6 Hz), 3.50 (3H, s), 3.60 (1H, t, J = 7.6 Hz), 4.16 (4H, q, J = 7.1 Hz), 5.11 (2H, s), 5.19 (2H, s), 6.74–6.83 (2H, m), 7.00 (1H, d, J = 1.7 Hz), 7.28–7.42 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.05, 34.09, 53.93, 56.16, 61.35, 70.92, 95.64, 114.31, 117.98, 122.74, 127.01, 127.63, 128.31, 130.09, 136.95, 146.64, 147.71, 168.56; IR (neat): 1510 (C=C), 1732 (C=O) cm^{-1}; MS (EI) m/z 416 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_7$: 416.1835 (M^+), found: 416.1832.

4.1.3.3. (R)-Acetic acid 3-(4-benzyloxy-3-methoxymethoxyphenyl)-2-hydroxymethylpropyl ester ((+)-9). To a stirred solution of **8** (1.66 g, 3.98 mmol) in THF (40 mL) was added $LiAlH_4$ (378 mg, 9.96 mmol) at 0 °C, and the resulting suspension was refluxed for 12 h. The reaction was quenched with 10% NaOH (aq) (20 mL), and the mixture was extracted with AcOEt (20 mL × 5). The organic extracts were combined dried over $MgSO_4$, and the solvent was evaporated to give diol, which was used directly in the next step. To a stirred solution of the diol obtained above in i-Pr_2O–THF (20 mL, 4:1) were added lipase-PS (397 mg) and vinyl acetate (0.52 mL, 5.67 mmol), and the reaction mixture was stirred at room temperature for 2 h. The catalyst was filtered and the filtrate was evaporated to give residue, which was chromatographed on silica gel (30 g, hexane:acetone = 15:1) to give (+)-**9** (1.20 g, 80% in 2 steps) as a pale yellow oil. The enantiomeric excess of (+)-**9** was determined to be a 98% ee by the following HPLC analysis; chiralcel OJ (0.46 cm × 25 cm), hexane/2-propanol = 1/1, flow rate = 0.5 mL/min, λ = 254 nm, (+)-**9**; t_R = 29.7 min, (−)-**9**; 25.5 min ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.70 (1H, br), 2.09 (3H, s), 2.17 (1H, s), 2.55–2.62 (2H, m), 3.47–3.62 (2H, m), 3.52 (3H, s), 4.03–4.20 (2H, m), 5.13 (2H, s), 5.21 (2H, s), 6.72–6.98 (3H, m), 7.30–7.44 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.99, 33.75, 42.47, 56.27, 62.08, 63.94, 71.14, 95.72, 114.534, 118.21, 122.92, 127.11, 127.71, 128.40, 132.46, 137.11, 146.82, 147.48, 171.47; IR (neat): 1739 (C=O), 3165 (OH) cm^{-1}; MS (EI) m/z 374 (M^+); HRMS (EI): calcd for $C_{21}H_{26}O_6$: 374.1729 (M^+), found: 374.1723; $[\alpha]_D^{26}$ +13.5 (c 1.14, $CHCl_3$).

4.1.3.4. (R)-Acetic acid 3-(4-benzyloxy-3-methoxymethoxyphenyl)-2-methanesulfonyloxymethylpropyl ester (10). To a stirred solution of (+)-**9** (666 mg, 1.78 mmol) in CH_2Cl_2 (8 mL) were added MsCl (0.15 mL, 1.95 mmol) and NEt_3 (0.32 mL, 2.31 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with H_2O (8 mL), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were combined dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (30 g, hexane:acetone = 15:1) to give **10** (775 mg, 96%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.03 (3H, s), 2.27–2.34 (1H, m), 2.61 (2H, d, J = 7.42 Hz), 2.93 (3H, s), 3.47 (3H, s), 3.96–4.19 (4H, m), 5.08 (2H, s), 5.18 (2H, s), 6.69–6.95 (3H, m), 7.24–7.41 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.91, 33.41, 37.26, 39.61, 56.29, 62.94, 68.34, 71.13, 95.67, 114.65, 118.05,

122.84, 127.12, 127.76, 128.42, 130.88, 136.98, 146.98, 147.72, 170.56; IR (KBr): 1242 (S=O), 1736 (C=O) cm^{-1}; MS (EI) *m/z* 452 (M^+); HRMS (EI): calcd for $C_{22}H_{28}O_8S$: 452.1505 (M^+), found: 452.1512; $[\alpha]_D^{25}$ +2.76 (*c* 1.40, $CHCl_3$).

*4.1.3.5. (R)-4-(4-Benzyloxy-3-hydeorxybenzyl)dihydrofuran-2-one (**11**).* To a stirred solution of **10** (993 mg, 2.19 mmol) in DMSO (20 mL) was added KCN (150 mg, 2.19 mmol), and the resulting mixture was heated at 90 °C for 3 h. After cooling, the reaction was quenched with H_2O (20 mL), and the aqueous mixture was extracted with Et_2O/AcOEt (1:1, 20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give cyanide, which was used directly in the next step. To a stirred solution of cyanide obtained above in THF–H_2O (3:1, 8 mL) was added $LiOH \cdot H_2O$ (91.9 mg, 2.19 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with H_2O (10 mL), and the aqueous mixture was extracted with Et_2O (20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give alcohol, which was used directly in the next step. The alcohol obtained above was dissolved in 10% NaOH (aq) (10 mL), and the mixture was refluxed for 5 h. After cooling, 10% HCl (aq) (20 mL) and THF (20 mL) were added to the reaction mixture, and the resulting solution was stirred at room temperature for 50 h. The aqueous reaction mixture was extracted with Et_2O (30 mL × 3), and the organic extracts were combined, dried over $MgSO_4$, and evaporated to give a residue, which was chromatographed on silica gel (20 g, hexane:acetone = 3:1) to give **11** (479 mg, 73% in 4 steps) as a colorless solid: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.17–2.32 (1H, m), 2.52–2.69 (3H, m), 2.74–2.86 (1H, m), 3.91–4.05 (1H, m), 4.30–4.36 (1H, m), 5.09 (2H, s), 5.67 (1H, br), 6.59–6.89 (3H, m), 7.36–7.85 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.25, 37.22, 38.41, 71.22, 72.63, 112.26, 114.78, 120.04, 127.69, 128.32, 128.61, 131.72, 136.09, 144.50, 145.89, 176.68; IR (KBr): 1647 (C=O), 3445 (OH) cm^{-1}; MS (EI) *m/z* 298 (M^+); HRMS (EI): calcd for $C_{18}H_{18}O_4$: 298.1205 (M^+), found: 298.1204; $[\alpha]_D^{26}$ +5.6 (*c* 0.13, $CHCl_3$); mp: 137–139 °C.

*4.1.3.6. (R)-4-(4-Benzyloxy-3-methoxybenzyl)dihydrofuran-2-one (**12a**).* To a stirred solution of **11** (330 mg, 1.1 mmol) in acetone (15 mL) were added K_2CO_3 (168 mg, 1.2 mmol) and MeI (0.41 mL, 6.6 mmol), and the reaction mixture was refluxed for 24 h. After cooling, the insoluble materials were filtered, and the filtrate was evaporated to give a residue, which was chromatographed on silica gel (15 g, hexane:acetone = 4:1) to give **12a** (304 mg, 88%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.17 (2H, s), 2.24–2.30 (1H, m), 3.88 (3H, s), 4.03–4.05 (1H, m), 4.30–4.35 (1H, m), 5.13 (2H, s), 6.61–6.64 (2H, m), 6.81–6.83 (1H, m), 7.27–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 34.29, 37.30, 38.64, 56.06, 71.11, 72.60, 112.32, 114.23, 120.52, 127.12, 127.72, 128.40, 131.25, 136.96, 146.91, 149.66, 176.65; IR (neat): 1654 (C=C), 1774 (C=O) cm^{-1}; MS (EI) *m/z* 312 (M^+); HRMS (EI): calcd for $C_{19}H_{20}O_4$: 312.1362 (M^+), found: 312.1380; $[\alpha]_D^{25}$ +4.9 (*c* 0.95, $CHCl_3$).

*4.1.3.7. (R)-4-(4-Benzyloxy-3-ethoxybenzyl)dihydrofuran-2-one (**12b**).* By the procedure similar to preparation of **12a**, **12b** was prepared from **11** and EtI (84%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (3H, t, J = 4.4 Hz), 2.28 (1H, dd, J = 17.3, 6.9 Hz), 2.60 (1H, dd, J = 17.3, 8.0 Hz), 2.67–2.84 (3H, m), 4.02–4.13 (3H, m), 4.32 (1H, dd, J = 9.1, 6.9 Hz), 5.12 (2H, s), 6.60–6.69 (2H, m), 6.84 (1H, d, J = 8.2 Hz), 7.30–7.77 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.03, 34.29, 37.31, 38.61, 64.74, 71.37, 72.62, 114.29, 115.22, 120.73, 127.08, 127.63, 128.34, 131.46, 137.20, 147.33, 149.18, 176.67; IR (neat): 1507 (C=C), 1772 cm^{-1} (C=O); MS (EI) *m/z* 326 (M^+); HRMS (EI): calcd for $C_{20}H_{22}O_4$: 326.1518 (M^+), found: 326.1523; $[\alpha]_D^{26}$ +3.4 (*c* 1.78, $CHCl_3$).

*4.1.3.8. (R)-4-(4-Benzyloxy-3-propoxybenzyl)dihydrofuran-2-one (**12c**).* By the procedure similar to preparation of **12a**, **12c** was prepared from **11** and *n*-PrBr (87%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ: 1.04 (3H, t, J = 7.0 Hz), 1.84 (2H, sextet, J = 7.0 Hz), 2.26 (1H, dd, J = 17.5, 7.0 Hz), 2.57 (1H, dd, J = 17.5, 8.1 Hz), 2.64–2.71 (2H, m), 2.74–2.83 (1H, m), 3.96 (2H, t, J = 7.0 Hz), 4.00 (1H, dd, J = 9.2, 5.9 Hz), 4.30 (1H, dd, J = 9.2, 7.0 Hz), 5.09 (2H, s), 6.60 (1H, d, J = 8.1 Hz), 6.67 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 7.27–7.42 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.46, 22.55, 34.07, 37.15, 38.43, 70.65, 71.32, 72.55, 114.28, 115.38, 120.69, 127.10, 127.63, 128.34, 131.61, 137.31, 147.37, 149.52, 176.84; IR (neat): 1508 (C=C), 1773 (C=O) cm^{-1}; MS (EI) *m/z* 340 (M^+); HRMS (EI): calcd for 340.1675 (M^+), found: 340.1667; $[\alpha]_D^{26}$ −1.0 (*c* 1.05, $CHCl_3$).

*4.1.3.9. (R)-4-(3,4-Dimethoxybenzyl)dihydrofuran-2-one (**13a**).* To a stirred solution of **12a** (302 mg, 0.97 mmol) in MeOH (5 mL) was added 20% $Pd(OH)_2$ (20 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 15 h. The catalyst was removed by filtration and the filtrate was evaporated to give phenol, which was used directly in the next step. To a stirred solution of the phenol obtained above in acetone (10 mL) were added K_2CO_3 (201.1 mg, 1.46 mmol) and MeI (0.18 mL, 2.92 mmol), and the resulting mixture was refluxed for 19 h. After cooling, the insoluble materials were filtered, and the filtrate was evaporated to give a residue, which was chromatographed on silica gel (10 g, hexane:acetone = 4:1) to give **13a** (130 mg, 55% in 2 steps) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 2.33 (1H, dd, J = 18.0, 9.3 Hz), 2.61 (1H, dd, J = 17.4, 8.1 Hz), 2.70–2.87 (3H, m), 3.87 (3H, s), 3.88 (3H, s), 4.05 (1H, dd, J = 9.3, 6.3 Hz), 4.33 (1H, dd, J = 9.3, 6.6 Hz), 6.66–6.72 (2H, m), 6.82 (1H, d, J = 8.1 Hz); $[\alpha]_D^{24}$ +22.2 (*c* 0.87, $CHCl_3$) (ref. [19], $[\alpha]_D^{25}$ +23.8).

*4.1.3.10. (R)-4-(4-Ethoxy-3-methoxybenzyl)dihydrofuran-2-one (**13b**).* By the procedure similar to preparation of **13a**, **13b** was prepared from **12a** and EtI (55% in 2 steps) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.46 (3H, t, J = 7.1 Hz), 2.29 (1H, dd, J = 17.6, 6.9 Hz), 2.63 (1H, dd, J = 17.6, 8.0 Hz), 2.71–2.88 (3H, m), 3.86 (3H, s), 4.03 (1H, dd, J = 9.1, 6.9 Hz), 4.06 (2H, q, J = 7.1 Hz), 4.34 (1H, dd, J = 9.1, 6.9 Hz), 6.65–6.68 (2H, m), 6.81 (1H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.92, 34.32, 37.36, 38.65, 55.98, 64.38, 72.63, 112.01, 112.84, 120.56, 130.59, 147.06, 149.26, 176.68; IR (neat): 1514 (C=C), 1778 (C=O) cm^{-1}; MS (EI) *m/z* 250 (M^+); HRMS (EI): calcd for $C_{14}H_{18}O_4$: 250.1205 (M^+), found: 250.1192; $[\alpha]_D^{24}$ +4.4 (*c* 1.66, $CHCl_3$).

*4.1.3.11. (R)-4-(3-Ethoxy-4-methoxybenzyl)dihydrofuran-2-one (**13c**).* By the procedure similar to preparation of **13a**, **13c** was prepared from **12b** and MeI (55% in 2 steps) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (3H, t, J = 6.9 Hz), 2.29 (1H, dd J = 17.3, 6.6 Hz), 2.61 (1H, dd, J = 17.3, 8.0 Hz), 2.67–2.87 (3H, m), 3.86(3H, s), 4.01–4.12 (3H, m), 4.34 (1H, dd, J = 9.1, 6.6 Hz), 6.62–6.69 (2H, m), 6.81 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.87, 34.24, 37.31, 38.54, 55.95, 64.35, 72.58, 111.61, 113.24, 120.54, 130.52, 148.01, 148.22, 176.63; IR (neat): 1541 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 250 (M^+); HRMS (EI): calcd for $C_{14}H_{18}O_4$: 250.1205 (M^+), found: 250.1207; $[\alpha]_D^{27}$ +4.4 (*c* 1.94, $CHCl_3$).

*4.1.3.12. (R)-4-(3,4-Diethoxybenzyl)dihydrofuran-2-one (**13d**).* By the procedure similar to preparation of **13a**, **13d** was prepared from **12b** and EtI (47% in 2 steps) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41–1.47 (6H, m), 2.28 (1H, dd, J = 17.3, 6.6 Hz), 2.59 (1H, dd, J = 17.3, 8.0 Hz), 2.67–2.86 (3H, m), 4.00–4.11 (5H, m), 4.32 (1H, dd, J = 9.3, 6.6 Hz), 6.64–6.67 (2H, m), 6.81 (1H, d, J = 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.97, 34.30, 37.36, 38.61, 64.64, 64.69, 72.65,

113.70, 114.12, 120.78, 130.70, 147.53, 148.72, 176.68; IR (neat): 1507 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 264 (M^+); HRMS (EI): calcd for $C_{15}H_{20}O_4$: 264.1362 (M^+), found: 264.1369; $[\alpha]_D^{26}$ +5.4 (*c* 1.29, $CHCl_3$).

*4.1.3.13. (R)-4-(4-Methoxy-3-propoxybenzyl)dihydrofuran-2-one (**13e**).* By the procedure similar to preparation of **13a**, **13e** was prepared from **12c** and MeI (80% in 2 steps) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t, J = 7.1 Hz), 1.87 (2H, sextet, J = 7.1 Hz), 2.29 (1H, dd, J = 17.5, 6.8 Hz), 2.60 (1H, dd, J = 17.5, 8.1 Hz), 2.65–2.73 (2H, m), 2.77–2.84 (1H, m), 3.85 (1H, s), 3.96 (2H, t, J = 7.1 Hz), 4.03 (1H, dd, J = 9.3, 6.1 Hz), 4.33 (1H, dd, J = 9.3, 7.0 Hz), 6.67 (1H, s), 6.68 (1H, d, J = 7.8 Hz), 6.81 (1H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.37, 22.44, 34.15, 37.23, 38.45, 56.00, 70.51, 72,57, 111.89, 113.52, 120.60, 130.67, 148.25, 148.62, 176.86; IR (neat): 1516 (C=C), 1778 (C=O) cm^{-1}; MS (EI) *m/z* 264 (M^+); HRMS(EI): calcd for $C_{15}H_{20}O_4$: 264.1362 (M^+), found: 264.1345; $[\alpha]_D^{26}$ +3.2 (*c* 1.05, $CHCl_3$).

*4.1.3.14. (R)-4-(4-Ethoxy-3-propoxybenzyl)dihydrofuran-2-one (**13f**).* By the procedure similar to preparation of **13a**, **13f** was prepared from **12c** and EtI (77% in 2 steps) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t, J = 7.0 Hz), 1,42 (3H, t, J = 6.8 Hz), 1.87 (2H, sextet, J = 7.0 Hz), 2.28 (1H, dd, J = 17.5, 7.0 Hz), 2.60 (1H, dd, J = 17.5, 8.0 Hz), 2.64–2.72 (2H, m), 2.74–2.85 (1H, m), 3.94 (2H, t, J = 7.0 Hz), 4.01–4.09 (3H, m), 4.32 (1H, dd, J = 9.1, 6.9 Hz), 6.64 (1H, s), 6.65 (1H, d, J = 8.0 Hz), 6.81 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.35, 14.79, 22.50, 34.10, 37.16, 38.38, 64.67, 70.72, 72.56, 114.05, 114.31, 120.78, 130.88, 147.64, 149.09, 176.85; IR (neat): 1510 (C=C), 1774 (C=O) cm^{-1}; MS (EI) *m/z* 278 (M^+); HRMS (EI): calcd for $C_{16}H_{22}O_4$: 278.1518 (M^+), found: 278.1512; $[\alpha]_D^{26}$ +1.2 (*c* 1.05, $CHCl_3$).

*4.1.3.15. (3R,4R)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(3-ethoxy-4-methoxybenzyl)dihydrofuran-2-one (**14a**).* To a stirred solution of **13b** (29.6 mg, 0.12 mmol) in THF (2 mL) were added LiHMDS (1.6 M in THF, 0.12 mL, 0.18 mmol), HMPA (31 μL, 0.18 mmol) at −78 °C, and the resulting solution was stirred at the same temperature for 0.5 h. To the reaction mixture was added a solution of 4-benzyloxy-3-methoxybenzyl bromide [20] (52.3 mg, 0.19 mmol) in THF (2 mL), and allowed to warm to room temperature over 1 h, and then stirred at the same temperature for 20 h. The reaction was quenched with H_2O (4 mL), and the aqueous mixture was extracted with Et_2O (10 mL × 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give residue, which was chromatographed on silica gel (10 g, hexane:acetone = 4:1) to give **14a** (25 mg, 44%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.44 (3H, t, J = 6.9 Hz), 2.46–2.65 (4H, m), 2.91–2.95 (2H, m), 3.79–3.90 (1H, m), 3.84 (6H, s), 4.01 (2H, q, J = 6.9 Hz), 4.08–4.20 (1H, m), 5.12 (2H, s), 6.50–6.80 (6H, m), 7.28–7.43 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.77, 34.48, 38.02, 41.09, 46.42, 55.90, 64.28, 65.18, 71.03, 71.16, 111.57, 112.85, 113.35, 113.92, 114.02, 120.54, 121.28, 127.17, 127.20, 127.76, 128.46, 130.32, 130.82, 137.06, 147.01, 148.09, 148.26, 149.73, 178.65; IR (neat): 1515 (C=C), 1770 (C=O) cm^{-1}; MS (EI) *m/z* 476 (M^+); HRMS (EI): calcd for $C_{29}H_{32}O_6$: 476.2199 (M^+), found: 476.2197; $[\alpha]_D^{25}$ −16.4 (*c* 0.77, $CHCl_3$).

*4.1.3.16. (3R,4R)-3-(4-Benzyloxy-3-ethoxybenzyl)-4-(3-ethoxy-4-methoxybenzyl)dihydrofuran-2-one (**14b**).* By the procedure similar to preparation of **14a**, **14b** was prepared from **13b** and 4-benzyloxy-3-ethoxybenzyl bromide [21] (59%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.40 (6H, m), 2.36–2.51 (4H, m), 2.81–2.85 (2H, m), 3.71–3.78 (1H, m), 3.75 (3H, s), 3.90–4.05 (5H, m), 5.02 (2H, s), 6.40–6.80 (6H, m), 7.14–7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.75, 14.82, 34.43, 37.99, 41.05, 46.39, 55.86, 64.22, 64.47, 71.14, 71.26, 111.51, 113.24, 114.59, 114.97, 120.51, 121.39, 127.11, 127.64, 128.35, 130.31, 130.99, 137.27, 147.33, 148.03, 148.23, 149.24, 178.65; IR (neat): 1507 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 490 (M^+); HRMS (EI): calcd for $C_{30}H_{34}O_6$: 490.2355 (M^+), found: 490.2383; $[\alpha]_D^{26}$ −14.8 (*c* 1.46, $CHCl_3$).

*4.1.3.17. (3R,4R)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(4-ethoxy-3-methoxybenzyl)dihydrofuran-2-one (**14c**).* By the procedure similar to preparation of **14a**, **14c** was prepared from **13c** and 4-benzyloxy-3-methoxybenzyl bromide [20] (43%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, t, J = 6.9 Hz), 2.47–2.63 (4H, m), 2.91–2.95 (2H, m), 3.84 (3H, s), 3.91 (3H, s), 3.91–3.95 (1H, m), 4.09 (2H, q, J = 6.9 Hz), 4.03–4.14 (1H, m), 5.16 (2H, s), 6.48–6.96 (6H, m), 7.28–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.90, 34.58, 38.19, 41.13, 46.55, 55.98, 64.35, 65.29, 71.06, 110.88, 112.03, 112.82, 113.89, 113.97, 119.21, 120.44, 121.22, 127.69, 128.40, 130.26, 130.73, 134.03, 136.98, 146.91, 149.61, 178.49; IR (neat): 1261 (C=C), 1770 (C=O) cm^{-1}; MS (EI) *m/z* 476 (M^+); HRMS (EI): calcd for $C_{29}H_{32}O_6$: 476.2199 (M^+), found: 476.2209; $[\alpha]_D^{26}$ −9.0 (*c* 1.75, $CHCl_3$).

*4.1.3.18. (3R,4R)-3-(4-Benzyloxy-3-ethoxybenzyl)-4-(4-ethoxy-3-methoxybenzyl)dihydrofuran-2-one (**14d**).* By the procedure similar to preparation of **14a**, **14d** was prepared from **13c** and 4-benzyloxy-3-ethoxybenzyl bromide [21] (53%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41–1.48 (6H, m), 2.44–2.67 (4H, m), 2.88–2.93 (2H, m), 3.79 (3H, s), 3.80–3.87 (1H, m), 4.02–4.14 (5H, m), 5.11 (2H, s), 6.45–6.96 (6H, m), 7.27–7.45 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.62, 14.69, 30.69, 34.27 37.89, 40.87, 46.28, 55.66, 64.12, 64.35, 71.04, 71.12, 111.92, 112.61, 114.52, 114.84, 120.38, 121.31, 127.02, 127.52, 128.23, 130.29, 130.91, 137.17, 146.91, 147.20, 149.10, 178.55; IR (neat): 1515 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 490 (M^+); HRMS (EI): calcd for $C_{30}H_{34}O_6$: 490.2355 (M^+), found: 490.2383; $[\alpha]_D^{24}$ −17.9 (*c* 1.14, $CHCl_3$).

*4.1.3.19. (3R,4R)-3-(4-Benzyloxy-3-propoxybenzyl)-4-(3-ethoxy-4-methoxybenzyl)dihydrofuran-2-one (**14e**).* By the procedure similar to preparation of **14a**, **14e** was prepared from **13b** and 4-benzyloxy-3-propoxybenzyl bromide, prepared from 4-benzyl-3-propoxybenzaldehyde [22], (40%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t, J = 7.1 Hz), 1.45 (3H, t, J = 7.8 Hz), 1.84 (2H, sextet, J = 7.1 Hz), 2.46–2.64 (4H, m), 2.86–2.99 (2H, m), 3.80–3.87 (4H, m), 3.94 (2H, t, J = 7.1 Hz), 4.00 (2H, q, J = 7.8 Hz), 4.06–4.11 (1H, m), 5.10 (2H, s), 6.48–6.82 (6H, m), 7.28–7.44 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.47, 14.75, 22.56, 34.47, 38.00, 41.10, 46.40, 55.87, 64.25, 70.53, 71.35, 111.55, 113.29, 114.71, 115.25, 120.52, 121.37, 127.18, 127.57, 127.63, 128.33, 130.35, 131.126, 137.34, 147.40, 148.07, 148.26, 149.57, 178.64; IR (neat): 1514 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 504 (M^+); HRMS(EI): calcd for $C_{31}H_{36}O_6$: 504.2512 (M^+), found: 504.2538; $[\alpha]_D^{24}$ −10.7 (*c* 0.75, $CHCl_3$).

*4.1.3.20. (3R,4R)-3-(4-Benzyloxy-3-methoxybenzyl)-4-(3,4-diethoxybenzyl)dihydrofuran-2-one (**14f**).* By the procedure similar to preparation of **14a**, **14f** was prepared from **13d** and 4-benzyloxy-3-methoxybenzyl bromide [20] (48%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.41–1.59 (6H, m), 2.43–2.63 (4H, m), 2.91–2.95 (2H, m), 3.82–3.90 (1H, m), 3.85 (3H, s), 3.82–3.89 (1H, m), 3.97–4.12 (5H, m), 5.12 (2H, s), 6.49–6.80 (6H, m), 7.26–7.44 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.85, 34.50, 38.07, 41.12, 46.50, 55.96, 64.59, 71.09, 71.21, 112.90, 113.63, 114.06, 114.20, 120.78, 121.33, 127.26, 127.81, 128.51, 130.50, 130.86, 137.12, 147.06, 147.60, 148.77, 149.76, 178.70; IR (neat): 1509 (C=C), 1772 (C=O) cm^{-1}; MS (EI) *m/z* 490 (M^+); HRMS (EI): calcd for $C_{30}H_{34}O_6$: 490.2355 (M^+), found: 490.2388; $[\alpha]_D^{25}$ −13.5 (*c* 0.98, $CHCl_3$).

*4.1.3.21. (3R,4R)-3-(4-Benzyloxy-3-ethoxybenzyl)-4-(3,4-diethoxybenzyl)dihydrofuran-2-one (**14g**).* By the procedure similar to preparation of **14a**, **14g** was prepared from **13d** and 4-benzyloxy-3-ethoxybenzyl bromide [21] (56%) as a pale yellow oil: ^1H NMR

(300 MHz, $CDCl_3$) δ: 1.41–1.44 (9H, m), 2.42–2.60 (4H, m), 3.82–3.86 (1H, m), 4.02–4.13 (7H, m), 5.11 (2H, s), 6.47–6.81 (6H, m), 7.27–7.44 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.87, 34.50, 38.09, 41.11, 46.50, 64.60, 71.22, 71.37, 113.63, 114.17, 114.69, 115.08, 120.79, 121.48, 127.21, 127.71, 128.42, 130.53, 131.07, 137.35, 147.41, 147.95, 148.78, 149.32, 178.73; IR (neat): 1514 (C=C), 1770 (C=O) cm^{-1}; MS (EI) *m/z* 504 (M^+); HRMS (EI): calcd for $C_{31}H_{36}O_6$: 504.2512 (M^+), found: 504.6139; $[\alpha]_D^{25}$ −12.0 (*c* 0.58, $CHCl_3$).

4.1.3.22. (3R,4R)-3-(4-Benzyloxy-3-propoxybenzyl)-4-(4-methoxy-3-propoxybenzyl)dihydrofuran-2-one (14h). By the procedure similar to preparation of **14a**, **14h** was prepared from **13e** and 4-benzyloxy-3-propoxybenzyl bromide (49%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02–1.08 (6H, m), 1.82–1.88 (4H, m), 2.45–2.63 (4H, m), 2.85–2.97 (2H, m), 3.83 (3H, s), 3.83–4.60 (6H, m), 5.10 (2H, s), 6.51–6.96 (6H, m), 7.28–7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.48, 14.84, 22.56, 34.46, 38.00, 41.07, 46.45, 64.71, 65.15, 70.55, 70.74, 71.18, 71.35, 71.37, 112.76, 114.42, 115.12, 119.34, 120.77, 121.40, 127.13, 127.15, 127.64, 128.34, 128.36, 130.63, 131.13, 137.36, 147.98, 149.58, 178.73; IR (neat): 1514 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 518 (M^+); HRMS(EI): calcd for $C_{32}H_{38}O_6$: 518.2668 (M^+), found: 518.2669; $[\alpha]_D^{25}$ −12.2 (*c* 0.75, $CHCl_3$).

4.1.3.23. (3R,4R)-3-(4-Benzyloxy-3-propoxybenzyl)-4-(4-ethoxy-3-propoxybenzyl)dihydrofuran-2-one (14i). By the procedure similar to preparation of **14a**, **14i** was prepared from **13f** and 4-benzyloxy-3-propoxybenzyl bromide (33%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02–1.08 (6H, m), 1.41 (3H, t, J = 7.1 Hz), 1.80–1.91 (4H, m), 2.41–2.63 (4H, m), 2.87–2.94 (2H, m), 3.82–3.96 (5H, m), 4.01 (2H, q, J = 7.1 Hz), 4.05–4.10 (1H, m), 5.10 (2H, s), 6.49–6.96 (6H, m), 7.28–7.45 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.50, 22.59, 34.51, 38.05, 41.12, 46.48, 56.00, 65.22, 70.57, 71.40, 111.86, 112.79, 113.63, 114.72, 115.30, 119.36, 120.55, 121.40, 127.16, 127.28, 127.65, 128.36, 130.41, 131.16, 137.37, 147.43, 148.25, 148.58, 149.62, 178.70; IR (neat): 1508 (C=C), 1767 (C=O) cm^{-1}; MS (EI) *m/z* 532 (M^+); HRMS (EI): calcd for $C_{33}H_{40}O_6$: 532.2825 (M^+), found: 518.2817; $[\alpha]_D^{25}$ −6.3 (*c* 0.80, $CHCl_3$).

4.1.3.24. (3R,4R)-4-(3-Ethoxy-4-methoxybenzyl)-3-(4-hydroxy-3-methoxybenzyl)dihydrofuran-2-one (4g). To a stirred solution of **14a** (47.5 mg, 0.10 mmol) in MeOH (5 mL) was added 20% $Pd(OH)_2$ (20 mg), and the resulting suspension was stirred under a hydrogen atmosphere at 1 atm for 20 h. The catalyst was removed by filtration and the filtrate was evaporated to give a residue, which was chromatographed on silica gel (10 g, hexane:acetone = 3:1) to give **4g** (34.1 mg, 89%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, t, J = 7.1 Hz), 2.43–2.65 (4H, m), 2.91–2.94 (2H, m), 3.81–3.89 (1H, m), 3.83 (3H, s), 3.84 (3H, s), 4.01 (2H, q, J = 7.1 Hz), 4.12 (1H, dd, J = 9.1, 6.9 Hz), 5.53 (1H, s), 6.47–6.65 (4H, m), 6.69 (1H, d, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.80, 30.91, 34.46, 38.09, 40.95, 46.55, 55.83, 55.94, 64.30, 71.27, 99.88, 111.54, 113.26, 114.10, 120.58, 122.08, 129.47, 130.35, 144.52, 146.67, 148.11, 148.33; IR (neat): 1513 (C=C), 1771 (C=O) cm^{-1}; MS (EI) *m/z* 386 (M^+); HRMS (EI): calcd for $C_{22}H_{26}O_6$: 386.1729 (M^+), found: 386.1693; $[\alpha]_D^{25}$ −17.2 (*c* 1.44, $CHCl_3$).

4.1.3.25. (3R,4R)-4-(3-Ethoxy-4-hydroxybenzyl)-3-(3-ethoxy-4-methoxybenzyl)dihydrofuran-2-one (4h). By the procedure similar to preparation of **4g**, **4h** was prepared from **14b** (63%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.42–1.47 (6H, m), 2.46–2.63 (4H, m), 2.92 (2H, d, J = 5.8 Hz), 3.81–3.89 (1H, m), 3.84 (3H, s), 3.97–4.12 (5H, m), 5.60 (1H, br), 6.48–6.84 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.78, 30.88, 34.39, 38.04, 40.90, 46.53, 55.90, 64.26, 64.39, 71.24, 111.51, 112.37, 113.21, 114.01, 120.55, 121.95, 129.34, 130.35, 144.59, 145.93, 148.08, 148.03, 178.74; IR (neat): 1516 (C=C), 1768 (C=O) cm^{-1}; MS (EI) *m/z* 400 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 400.1886 (M^+), found: 400.1868; $[\alpha]_D^{27}$ −16.9 (*c* 1.13, $CHCl_3$).

4.1.3.26. (3R,4R)-4-(4-Ethoxy-3-methoxybenzyl)-3-(4-hydroxy-3-methoxybenzyl)dihydrofuran-2-one (4i). By the procedure similar to preparation of **4g**, **4i** was prepared from **14c** (57%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, t, J = 7.1 Hz), 2.44–2.67 (4H, m), 2.93 (2H, d, J = 5.8 Hz), 3.81 (3H, s), 3.82 (3H, s), 3.84–3.99 (1H, m), 4.03–4.15 (1H, m), 4.08 (2H, q, J = 7.1 Hz), 5.30 (1H, br), 6.47–6.66 (4H, m), 6.75 (1H, d, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.90, 30.99, 34.53, 38.22, 40.97, 46.63, 55.89, 64.35, 71.31, 111.48, 112.00, 112.71, 114.04, 120.47, 122.01, 129.37, 130.30, 144.39, 146.54, 146.99, 149.18, 178.56; IR (neat): 1749 (C=O), 3648 (OH) cm^{-1}; MS (EI) *m/z* 386 (M^+); HRMS (EI): calcd for $C_{22}H_{26}O_6$: 386.1729 (M^+), found: 386.1693; $[\alpha]_D^{26}$ −9.5 (*c* 0.71, $CHCl_3$).

4.1.3.27. (3R,4R)-4-(3-Ethoxy-4-hydroxybenzyl)-3-(4-ethoxy-3-methoxybenzyl)dihydrofuran-2-one (4j). By the procedure similar to preparation of **4g**, **4j** was prepared from **14d** (63%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.46 (6H, m), 2.41–2.66 (4H, m), 2.91 (2H, d, J = 6.0 Hz), 3.80 (3H, s), 3.81–3.87 (1H, m), 4.00–4.10 (5H, m), 5.64 (1H, br), 6.47–6.65 (4H, m), 6.74 (1H, d, J = 8.2 Hz), 6.82 (1H, d, J = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.75, 30.86, 34.35, 38.06, 40.84, 46.54, 55.78, 64.26, 64.37, 71.24, 111.98, 112.38, 112.69, 114.00, 120.52, 121.95, 129.32, 130.38, 144.58, 145.91, 147.07, 149.25; IR (neat): 1771 (C=O), 3548 (OH) cm^{-1}; MS (EI) *m/z* 400 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 400.1886 (M^+), found: 400.1897; $[\alpha]_D^{26}$ −12.4 (*c* 1.04, $CHCl_3$).

4.1.3.28. (3R,4R)-4-(3-Ethoxy-4-methoxybenzyl)-3-(4-hydroxy-3-propoxybenzyl)dihydrofuran-2-one (4k). By the procedure similar to preparation of **4g**, **4k** was prepared from **14e** (56%) as a pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (3H, t, J = 7.4 Hz), 1.45 (3H, t, J = 7.1 Hz), 1.82 (2H, sextet, J = 7.4 Hz), 2.48–2.63 (4H, m), 2.91 (2H, d, J = 5.9 Hz), 3.81–3.88 (4H, m), 3.93 (2H, t, J = 7.4 Hz), 4.02 (2H, q, J = 7.1 Hz), 4.06–4.12 (1H, m), 5.57 (1H, s), 6.48 (1H, s), 6.54 (1H, d, J = 10.2 Hz), 6.60 (1H, d, J = 10.2 Hz), 6.66 (1H,s), 6.75 (1H, d, J = 8.2 Hz), 6.82 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.43, 14.79, 22.49, 34.41, 38.05, 40.95, 46.54, 55.92, 64.29, 70.32, 71.24, 111.55, 112.43, 113.26, 114.01, 120.57, 121.93, 129.37, 130.37, 144.64, 146.05, 148.12, 148.33, 178.75; IR (neat): 1516 (C=C), 1769 (C=O), 3589 (OH) cm^{-1}; MS (EI) *m/z* 414 (M^+); HRMS (EI): calcd for $C_{24}H_{30}O_6$: 414.2042 (M^+), found: 414.2046; $[\alpha]_D^{26}$ −10.6 (*c* 1.10, $CHCl_3$).

4.1.3.29. (3R,4R)-4-(3,4-Diethoxybenzyl)-3-(4-hydroxy-3-methoxybenzyl)dihydrofuran-2-one (4l). By the procedure similar to preparation of **4g**, **4l** was prepared from **14f** (81%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25–1.45 (6H, m), 2.44–2.66 (4H, m), 2.92 (2H, d, J = 6.0 Hz), 3.83 (3H, s), 3.85–3.89 (1H, m), 3.98–4.13 (5H, m), 5.55 (1H, br), 6.49–6.67 (4H, m), 6.76 (1H, d, J = 7.8 Hz), 6.82 (1H, d, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.84, 30.91, 34.40, 38.04, 40.94, 46.56, 55.84, 64.58, 71.25, 111.56, 113.60, 114.11, 120.77, 122.10, 129.47, 130.51, 144.51, 146.65, 147.57, 148.78, 178.75; IR (neat): 1766 (C=O), 2978 (OH) cm^{-1}; MS (EI) *m/z* 400 (M^+); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 400.1886 (M^+), found: 400.1858; $[\alpha]_D^{27}$ −16.0 (*c* 1.33, $CHCl_3$).

4.1.3.30. (3R,4R)-4-(3,4-Diethoxybenzyl)-3-(4-hydroxy-3-ethoxybenzyl)dihydrofuran-2-one (4m). By the procedure similar to preparation of **4g**, **4m** was prepared from **14g** (66%) as a pale yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ: 1.40–1.46 (9H, m), 2.42–2.67 (4H, m), 2.91 (2H, d, J = 5.7 Hz), 3.85 (1H, dd, J = 9.1, 7.4 Hz), 3.97–4.12

(7H, m), 5.59 (1H, br), 6.49–6.66 (4H, m), 6.75 (1H, d, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.81, 14.85, 34.39, 38.06, 40.92, 46.58, 64.42, 64.59, 71.27, 112.43, 113.62, 114.05, 114.10, 120.80, 122.00, 129.37, 130.53, 144.61, 145.94, 147.58, 148.80, 178.79; IR (neat): 1516 (C=C), 1761 (C=O) cm^{-1}; MS (EI) m/z 414 (M$^+$); HRMS (EI): calcd for $C_{24}H_{30}O_6$: 414.2042 (M$^+$), found: 414.2024; $[\alpha]_D^{25}$ −14.0 (c 0.70, $CHCl_3$).

*4.1.3.31. (3R,4R)-4-(4-Methoxy-3-propoxybenzyl)-3-(4-hydroxy-3-propoxybenzyl)dihydrofuran-2-one (**4n**).* By the procedure similar to preparation of **4g**, **4n** was prepared from **14h** (46%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02–1.07 (6H, m), 1.78–1.90 (4H, m), 2.47–2.65 (4H, m), 2.92 (2H, d, J = 5.9 Hz), 3.81 (3H, s), 3.81–3.95 (5H, m), 4.08–4.12 (1H, m), 5.56 (1H, br), 6.50 (1H, s), 6.53 (1H, d, J = 7.9 Hz), 6.60 (1H, d, J = 7.9 Hz), 6.66 (1H, s), 6.75 (1H, d, J = 8.2 Hz), 6.82 (1H, d, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ:10.39, 22.45, 22.47, 34.37, 38.01, 40.91, 46.54, 56.00, 70.29, 70.48, 71.23, 77.21, 111.81, 112.43, 113.53, 114.00, 120.55, 121.90, 129.34, 130.41, 144.61, 146.03, 148.22, 148.58, 178.74; IR (neat): 1516 (C=C), 1767 (C=O), 3422 (OH) cm^{-1}; MS (EI) m/z 428 (M$^+$); HRMS (EI): calcd for $C_{25}H_{32}O_6$: 428.2199 (M$^+$), found: 428.2216; $[\alpha]_D^{25}$ −13.7 (c 0.70, $CHCl_3$).

*4.1.3.32. (3R,4R)-4-(4-Ethoxy-3-propoxybenzyl)-3-(4-hydroxy-3-propoxybenzyl)dihydrofuran-2-one(**4o**).* By the procedure similar to preparation of **4g**, **4o** was prepared from **14i** (63%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02–1.07 (6H, m), 1.42 (3H, t, J = 7.1 Hz), 1.80–1.86 (4H, m), 2.41–2.63 (4H, m), 2.92 (2H, d, J = 5.9 Hz), 3.83–3.96 (5H, m), 4.01 (2H, q, J = 7.1 Hz), 4.07–4.11 (1H, m), 5.57 (1H, s), 6.51–6.84 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.50, 22.59, 34.51, 38.05, 41.12, 46.48, 56.00, 65.22, 70.57, 71.40, 111.86, 112.79, 113.63, 114.72, 115.30, 119.36, 120.55, 121.40, 127.16, 127.28, 127.65, 128.36, 130.41, 131.16, 137.37, 147.43, 148.25, 148.58, 149.62, 178.7010.45, 14.87, 22.50, 22.60, 34.37, 38.04, 40.92, 46.58, 64,76, 70.33, 70.76, 71.26, 100.36, 112.48, 114.02, 114.06, 114.38, 129.37, 130.67, 144.63, 146.04, 147.70, 149.14; IR (neat): 1508 (C=C), 1770 (C=O) cm^{-1}; MS (EI) m/z 442 (M$^+$); HRMS (EI): calcd for $C_{26}H_{34}O_6$: 442.2355 (M$^+$), found: 442.2350; $[\alpha]_D^{25}$ −12.9 (c 0.50, $CHCl_3$).

*4.1.4. Effective synthesis of (3R,4R)-4-(3,4-diethoxybenzyl)-3-(4-hydroxy-3-ethoxybenzyl)dihydrofuran-2-one (**4m**)*

*4.1.4.1. 2-(3,4-Diehtoxybenzyl)malonic acid diethyl ester (**17**).* To a stirred solution of (3,4-diehtoxyphenyl)methanol (**16**) [16,23] (733 mg, 3.74 mmol) in CH_2Cl_2 (20 mL) were added NEt_3 (0.67 mL, 4.86 mmol) and MsCl (0.32 mL, 4.11 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (10 mL), and the organic layer were separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL × 3), and the organic layer and extracts were combined, dried over $MgSO_4$. The solvent was removed under reduced pressure to give a pale yellow oil, which was used directly in the next step. To a stirred solution of diethyl malonate (1.14 ml, 7.48 mmol) in DMF (20 mL) was added NaH (60%, 299 mg, 7.48 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. To the solution was added a solution of the oil obtained above in DMF (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 25 h. The reaction was quenched with sat. $NaHCO_3$ (aq) (10 mL), and the aqueous mixture was extracted with Et_2O (20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, evaporated to give a pale yellow oil which was chromatographed on silica gel (20 g, hexane:acetone = 15:1) to give **17** (1.10 g, 87% in 2 steps) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.15–1.30 (6H, m), 1.39–1.46 (6H, m), 3.13 (2H, d, J = 8.0 Hz), 3.59 (1H, t, J = 8.0 Hz), 4.01–4.24 (8H, m), 6.68–6.78 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.77, 13.83, 14.57, 14.60, 34.06, 41.37, 53.82, 61.11, 64.19, 113.33, 114.09, 120.83, 130.28, 147.28, 148.33, 166.34, 168.64; IR (neat): 1516 (C=C), 1731 (C=O) cm^{-1}; MS (EI) m/z 338 (M$^+$); HRMS (EI): calcd for $C_{23}H_{28}O_6$: 338.1729 (M$^+$), found: 338.1766.

*4.1.4.2. (R)-Acetic acid 3-(3,4-diethoxyphenyl-2-hydroxymethylpropyl ester (**18**).* To a stirred solution of **17** (1.43 g, 4.23 mmol) in THF (40 mL) was added $LiAlH_4$ (401 mg, 10.6 mmol) at 0 °C, and the resulting suspension was refluxed for 12 h. The reaction was quenched with 10% NaOH (aq) (20 mL), and the mixture was extracted with AcOEt (20 mL × 5). The organic extracts were combined dried over $MgSO_4$, and the solvent was evaporated to give diol, which was used directly in the next step. To a stirred solution of the diol obtained above in i-Pr_2O–THF (15 mL, 4:1) were added Lipase-PS (323 mg) and vinyl acetate (0.45 ml, 4.85 mmol), and the reaction mixture was stirred at room temperature for 2 h. The catalyst was filtered and the filtrate was evaporated to give residue, which was chromatographed on silica gel (30 g, hexane:acetone = 4:1) to give **18** (669 mg, 53% in 2 steps) as a pale yellow oil. The enantiomeric excess of **18** was determined to be a 98% ee by the Moscher's method [24]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.39–1.44 (6H, m), 2.06 (3H, s), 2.23 (1H, br), 2.49–2.64 (2H, m), 3.45–3.59 (2H, m), 4.01–4.08 (6H, m), 4.15 (1H, dd, J = 11.3, 4.7 Hz), 6.66–6.70 (2H, m), 6.78 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.88, 20.91, 33.86, 42.53, 62.07, 64.03, 64.55, 64.63, 113.69, 114.52, 121.22, 131.91, 147.23, 148.70, 171.68; IR (neat): 1513 (C=C), 1721 (C=O) cm^{-1}; MS (EI) m/z 296 (M$^+$); HRMS (EI): calcd for $C_{16}H_{24}O_5$: 296.1624 (M$^+$), found: 296.1594; $[\alpha]_D^{28}$ +18.8 (c 1.47, $CHCl_3$); 98% ee.

*4.1.4.3. (R)-Acetic acid 3-(3,4-Diethoxyphenyl-2-methanesulfonyloxymethylpropyl ester (**19**).* To a stirred solution of **18** (1.45 g, 4.96 mmol) in CH_2Cl_2 (25 mL) were added MsCl (0.42 ml, 5.45 mmol) and NEt_3 (0.89 ml, 6.45 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction was quenched with H_2O (20 mL), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL × 3). The organic extracts were combined dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (40 g, hexane:acetone = 4:1) to give **19** (1.48 g, 79%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41–1.46 (6H, m), 2.08 (3H, s), 2.32–2.36 (1H, m), 2.65 (2H, d, J = 7.4 Hz), 2.99 (3H, s), 4.00–4.23 (8H, m), 6.65–6.70 (2H, m), 6.80 (1H, d, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.85, 20.81, 30.90, 33.49, 37.21, 39.71, 63.02, 64.60, 68.48, 113.70, 114.40, 121.22, 130.36, 147.53, 148.82, 170.78; IR (neat): 1512 (C=C), 1735 (C=O) cm^{-1}; MS (EI) m/z 374 (M$^+$); HRMS (EI): calcd for $C_{17}H_{26}O_7S$: 374.1399 (M$^+$), found: 374.1362; $[\alpha]_D^{25}$ +2.1 (c 0.68, $CHCl_3$).

*4.1.4.4. (R)-4-(3,4-Diethoxybenzyl)dihydrofuran-2-one (**13d**) from **19**.* To a stirred solution of **19** (1.12 g, 3.00 mmol) in DMSO (25 mL) was added KCN (205 mg, 3.00 mmol), and the resulting mixture was heated at 90 °C for 3 h. After cooling, the reaction was quenched with H_2O (25 mL), and the aqueous mixture was extracted with Et_2O/AcOEt (1:1, 20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give cyanide, which was used directly in the next step. To a stirred solution of cyanide obtained above in THF–H_2O (3:1, 12 mL) was added $LiOH{\cdot}H_2O$ (126 mg, 3.00 mmol), and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with H_2O (10 mL), and the aqueous mixture was extracted with Et_2O (20 mL × 3). The organic extracts were combined, dried over $MgSO_4$, and evaporated to give alcohol, which was used directly in the next step. The alcohol obtained above was dissolved in 10% NaOH (aq) (15 mL), and the mixture was refluxed for 5 h. After cooling, 10% HCl (aq) (30 mL) and THF (30 mL) were added to