Since procyanidins (oligomeric catechin or epicatechin) were reported to exhibit health benefits, much attention has been paid to the synthesis of these compounds, especially those that are longer than trimers. In the present study, syntheses of cinnamtannin A3 (epicatechin pentamer), A4 (epicatechin hexamer), catechin tetramer, pentamer, arecatannin A2 (epicatechin-epicatechin-epicatechin-catechin) and A3 (epicatechin-epicatechin-epicatechin-epicatechin-catechin) were achieved. The key reaction was a Lewis acid mediated equimolar condensation. The antitumor effects of these synthesized compounds against a human prostate cancer cell line (PC-3) were investigated. Among the tested compounds, cinnamtannin A3, A4 and arecatannin A3, which possess epicatechin oligomers longer than tetramers as the basic scaffold, showed significant activities for suppression of cell growth, invasion and FABP5 (fatty acid-binding protein 5) gene expression. Effects on cell cycle distribution showed that cell cycle arrest in the G2 phase was induced. Furthermore, these epicatechin oligomers suppressed significantly the expression of the cancer-promoting gene, FABPS, which is related to cell proliferation and metastasis in various cancer cells. Interestingly, the suppressive activities were associated with the degree of oligomerization of epicatechin. Thus, synthetic studies clearly demonstrate that epicatechin oligomers longer than trimers have significant anti-tumorigenic activities, but not the catechin counterparts.
of a nucleophilic partner (ca. 4.0 eq.) for condensation to prevent further oligomerization. The disadvantage of this procedure is that the excess nucleophilic partner must be removed after condensation. The other method reported used a C-8 bromide derivative to prevent the formation of further oligomerization.

Various types of proanthocyanidins have been synthesized to evaluate their biological activities. The synthesis of procyanidin dimers such as procyanidin B1, B2, B3 and B4 using Yb(OTf)$_3$ mediated equimolar condensation$^{14}$ and their content in apple juice$^{15}$ has been reported by us. The anti-inflammatory activity of these compounds has also been reported$^{16,17}$. Recently, the synthesis of procyanidin trimers such as procyanidin C1 and C2 using Yb(OTf)$_3$ or silver Lewis acid mediated equimolar condensation was presented$^{18,19}$. Currently, minimal effort has been made to the screening of Lewis acids for equimolar condensation to construct the skeleton of proanthocyanidin oligomers. Synthesis of catechin and epicatechin oligomers using an equimolar condensation approach has not been reported. In this article, the total syntheses of an epicatechin pentamer, named cinnamattannin A3 (1, Epi-5), a catechin tetramer (3, Cat-4), pentamer (4, Cat-5), arecatannin A2 (epicatechin-epicatechin-epicatechin-catechin, ATA2) and A3 (epicatechin-epicatechin-epicatechin-epicatechin-catechin, ATA3) were achieved.

Figure 1. The structures of synthesized catechin and epicatechin oligomers. Syntheses of cinnamattannin A3 (epicatechin pentamer, Epi-5), A4 (epicatechin hexamer, Epi-6), catechin tetramer (Cat-4), pentamer (Cat-5), arecatannin A2 (epicatechin-epicatechin-epicatechin-catechin, ATA2) and A3 (epicatechin-epicatechin-epicatechin-epicatechin-catechin, ATA3) were achieved.
satisfied yield. The present study also reveals that epicatechin oligomers longer than trimers, but not the catechin counterparts, have significant anti-tumorigenic activities against human prostate cancer cells.

Results
Synthesis of cinnamtannin A3 (1, epicatechin pentamer, Epi-5) and A4 (2, epicatechin hexamer, Epi-6). For the synthesis of cinnamtannin A3 (1, Epi-5), equimolar condensation of trimeric nucleophile 7 with dimeric electrophile 9, which was prepared previously, was examined using Zn(OTf)₂ in CH₂Cl₂. We found that 3.0 eq. of Zn(OTf)₂ for 21 h gave the condensed product in 61% yield (see, Supplementary Table 1). Hydrolysis of the diacetate of 10 using n-Bu₄NOH afforded 12 in 90% yield. The benzyl groups of 12 were deprotected by hydrogenolysis over Pearlman’s catalyst followed by lyophilization to afford cinnamtannin A3 (1, Epi-5) in good yield. The optical rotation value, ¹H and ¹³C NMR spectral data of synthetic 1 were in good agreement with reported values. For the synthesis of cinnamtannin A4 (2, Epi-6), equimolar condensation of tetrameric nucleophile 8 with dimeric electrophile 9 using a Lewis acid in CH₂Cl₂ was performed. It was found that 5.0 eq. of Zn(OTf)₂ afforded condensed product 12 in 27% yield along with 70% recovery of the starting material 8. Thus, 1.7 eq. of nucleophile 8 was used to afford condensed product 11 in 64% yield. Other Lewis acids such as Yb(OTf)₃ and AgOTf gave 11 in very low yield. Deprotection of the acetyl groups of 11 with n-Bu₄NOH afforded 13. The ¹H
and $^{13}$C NMR spectral data of 13 were in good agreement with reported values. Subsequent hydrogenolysis of the benzyl groups afforded cinnamtannin A4 (2, Epi-6) in 21% yield. The reason for the low yield at the deprotection steps is the cleavage of inter-flavan bonds during Pd(OH)$_2$ catalyzed hydrogenolysis of the benzyl groups. We found that the reactivity of the hydrogenolysis of the benzyl group of 13 was quite low probably because of steric hindrance caused by highly oligomerization. As a result, the cleavage of inter-flavan bonds took place at the same time. The specific rotation value of synthetic 2 was in good accordance with that of the reported value. Although the $^1$H NMR data of 2 showed broad peaks, the ESI-TOFMS spectra of 2 supports the structure (Fig. 2).

Synthesis of the catechin tetramer (3, Cat-4) and pentamer (4, Cat-5). Equimolar condensation of trimeric nucleophile 14, which was prepared previously, with 16 was examined using silver Lewis acids and Yb(OTf)$_3$ in CH$_2$Cl$_2$. AgBF$_4$ gave the condensed product 17 in low yield. Next, 1.5 eq. of AgOTf was used and a longer reaction time to give the condensed product in a moderate yield. Using 3.0 eq. of Lewis acid gave sluggish results (see, Supplementary Table 2). The condensed product 17 was transformed into tetraol 19 using 10% KOH. The $^1$H and $^{13}$C NMR spectral data of 19 were in good agreement with reported values. The $^1$H NMR data of 2 showed broad peaks, the ESI-TOFMS spectra of 2 supports the structure (Fig. 2).

**Figure 3.** Synthesis of catechin tetramer (3, Cat-4) and pentamer (4, Cat-5). Catechin tetramer (3, Cat-4) and pentamer (4, Cat-5) were synthesized using AgOTf mediated equimolar condensation. AgOTf, silver trifluoromethanesulfonate, DIBALH, diisobutylaluminium hydride, DMAP, N, N, dimethyl-4-aminopyridine.
oligomer. On the other hand, silver Lewis acids were suitable for catechin oligomer probably because of three dimensional structural difference to activate elimination groups. Acetylation of 18 using Ac₂O in the presence of catalytic amounts of DMAP in pyridine to afford pentaacetate was followed by reduction of all acetyl groups to give 20 in 77% yield for 2 steps. The benzyl groups of 20 were deprotected by hydrogenolysis over Pearlman’s catalyst followed by lyophilization to afford catechin pentamer (⁴, Cat-5) in good yield (Fig. 3).

Synthesis of arecatannin A2 (⁵, ATA2) and A3 (⁶, ATA3). As for arecatannin A2 (⁵, ATA2), we have investigated Zn and Yb Lewis acids for equimolar condensation between an epicatechin-catechin nucleophile 21, which was prepared previously ¹⁴, and a dimeric epicatechin electrophile ⁹. Among the Lewis acids tested, it was found that 5.0 eq. of Zn(OTf)₂ gave condensed product 23 in 64% yield (see, Supplementary Table 4). Hydrolysis of the diacetate of 23 using n-Bu₄NOH afforded 25 in 89% yield ⁵. The benzyl groups of 25 were deprotected by hydrogenolysis over Pearlman’s catalyst followed by lyophilization to afford arecatannin A2 (⁵, ATA2) in good yield. The optical rotation value, ¹H and ¹³C NMR spectral data and mass spectrum data of synthetic ⁵ were in good accordance with the reported values ¹².

As for arecatannin A3 (⁶, ATA3), we have investigated Zn and Yb Lewis acids for equimolar condensation between an epicatechin-epicatechin-catechin nucleophile 22, which was synthesized previously ²¹, with the dimeric epicatechin electrophile ⁹. Among the Lewis acids tested, it was found that 5.0 eq. of Yb(OTf)₃ gave condensed product 24 in 59% yield (see, Supplementary Table 5). Hydrolysis of the diacetate of 24 using n-Bu₄NOH afforded 26 in 90% yield ⁵. The benzyl ether of 26 was deprotected by hydrolysis over Pearlman’s catalyst followed by lyophilization to afford arecatannin A3 (⁶, ATA3) in good yield. The optical rotation value, ¹H and ¹³C NMR spectral data of synthetic ⁶ were in good agreement with previously reported values (Fig. 4) ¹².
against PC-3 prostate cancer cell lines together with arecatannin A1 (ATA1) \(^21\) and cinnamtannin A2 (Epi-4) \(^23\), notype and utilizes fatty acid oxidation as a dominant bioenergetics pathway to support proliferation\(^{31–33}\).

FABP5.

More recently, the FABP5 gene has been shown to be epigenetically regulated during human prostate carcinogenesis\(^{39}\) and that high-expression of FABP5 is responsible for the promotion of cell growth and invasion in various cancer cells\(^{38,39}\), suggesting that it plays a critical role in tumorigenesis of various cancer cells. Altered fatty acid metabolism is thought to be a hallmark of cancer\(^{30}\). Especially, prostate cancer represents lipogenic phenotype and utilizes fatty acid oxidation as a dominant bioenergetics pathway to support proliferation\(^{31–33}\). FABP5 might be responsible for fatty acid metabolism as a lipid transporter and/or an important regulatory factor.

Figure 5. Effects of various concentrations of test compounds on PC-3 prostate cancer cell proliferation. Effects of various concentrations of test compounds on PC-3 cancer cell proliferation using a cell count method. The experimental procedure for preparation of test compounds was described in Biochemical methods of Supplementary Information. After treatment of cells with either the catechin tetramer (Cat-4), catechin pentamer (Cat-5), cinnamtannin A2 (Epi-4), cinnamtannin A3 (Epi-5), cinnamtannin A4 (Epi-6), arecatannin A1 (ATA1), arecatannin A2 (ATA2) or arecatannin A3 (ATA3) for 48 h, cell proliferation was determined by cell counting as shown in the experimental section. The values are presented as the rate of inhibition of cell proliferation by the treated sample when compared with that of the untreated control (vehicle). Values are means ± S.Ds. for three independent experiments. Two-way ANOVA followed by Dunnett’s multiple comparison test was used to compare means. \(*P < 0.05\) or \(**P < 0.01\).

Epicatechin oligomers longer than trimers suppress cell proliferation of PC-3 prostate cancer cells. Our interest was focused on examining the antitumor activities of the newly synthesized procyanidins. Procyanidins with basic scaffolds less than trimers have not been shown to have any activities for suppression of cell growth and apoptosis induction\(^{22}\). Thus, tetramer and pentamer species were tested for anti-cancer activity. The synthesis of compounds 1–6 allowed us to obtain sufficient quantities of purified compounds to screen against PC-3 prostate cancer cell lines together with arecatannin A1 (ATA1) \(^{31}\) and cinnamtannin A2 (Epi-4) \(^{23}\), which were prepared previously (Fig. 5). Results were obtained by cell count measurement. (−)–Epigallocatechin-3-gallate (EGCG) was used as a positive control. As shown in Fig. 5, epigallocatechin gallate (EGCG), cinnamtannin A3 (Epi-5, 1), cinnamtannin A4 (Epi-6, 2) and arecatannin A3 (ATA3, 6) exhibited significant cell growth inhibitory activity. Inhibitory effects on cell growth were clearly associated with the degree of oligomerization of epicatechin (tetramer, pentamer and hexamer) (Fig. 5). Although cell growth inhibitory activity of the epicatechin oligomers longer than trimers might be partially attributed to cell cycle arrest (Fig. 6), further mechanistic study should be needed. Interestingly, no activity was observed for the catechin tetramer (Cat-4) and pentamer (Cat-5), probably because of differences in the three-dimensional structures (Fig. 9). Dimeric and trimeric procyanidins, which others have reported to show activity on small cell lung, colorectal cancer cell lines and skin tumor promotion in mouse epidermis in vivo\(^{24,25}\), showed no activity in prostate cancer cell lines.

Pentameric procyanidins induce cell cycle arrest in PC-3 prostate cancer cells. Cell growth and proliferation are related to the cell cycle progression. In this study with FACS analysis, treatment of PC-3 prostate cancer cells with cinnamtannin A3 (Epi-5, 1) for 48 h induced an increase in the G2 phase population from 24.59% to 41.30% and an S phase fraction decrease from 16.67% to 10.69%. Epi-5 blocked the PC-3 prostate cancer cell cycle at the G2 phase within 48 h (Supplementary Figure 1). A similar tendency was observed in ATA3 (data not shown). A lower S phase population is indicative of a slower cell division rate and slower tumor growth. We also investigated whether the epicatechin oligomers (Epi-5 and Epi-6) induce G2/M phase arrest by changing the mRNA and protein levels of G2/M phase cell cycle regulators (Cdc2, Cdc25C and Cyclin B1). The results showed that treatment of PC-3 cells with Epi-5 or Epi-6 for 48 h at a dose of 50 μmol/L significantly decreased these mRNA and protein levels in comparison with the control (Fig. 6), suggesting that the G2/M cell cycle arrest might be induced in PC-3 cells. Interestingly, these results are different from those of Kozikowski and co-workers who reported that treatment of human breast cancer cells (MDA MB 231) with Epi-5 induced G1/G0 arrest\(^5\). However, additional efforts are required to elucidate the mechanisms of action (Fig. 6).

Epicatechin oligomers longer than trimers suppress expression of the cancer-promoting gene, FABP5.

Previous work by Fujii and co-workers reported that the FABP5 gene is highly expressed and involved in metastasis in prostate cancer cells\(^{26,27}\).

More recently, the FABP5 gene has been shown to be epigenetically regulated during human prostate carcinogenesis\(^{39}\) and that high-expression of FABP5 is responsible for the promotion of cell growth and invasion in various cancer cells\(^{38,39}\), suggesting that it plays a critical role in tumorigenesis of various cancer cells. Altered fatty acid metabolism is thought to be a hallmark of cancer\(^{30}\). Especially, prostate cancer represents lipogenic phenotype and utilizes fatty acid oxidation as a dominant bioenergetics pathway to support proliferation\(^{31–33}\). FABP5 might be responsible for fatty acid metabolism as a lipid transporter and/or an important regulatory factor,
suggesting that its critical role in metabolic alterations of fatty acid metabolism in prostate cancer. Indeed, we have found that siRNA-mediated knockdown of FABP5 expression significantly decreased fatty acid-metabolizing enzymes and metastasis. Therefore, we have been screening potential anti-cancer agents by assessing inhibitory activity for the gene expression of FABP5. Thus, the compounds which suppress the expression of FABP5 might be promising chemopreventive agents against prostate cancer metastasis. As shown in Fig. 7, Epi-5 significantly suppressed the expression of FABP5 at mRNA and protein levels. ATA2 and ATA3, which possess the catechin unit at the end of oligomers, showed weaker activities than Epi-5. Interestingly, no suppressive activity was observed for the Cat-4 and Cat-5 probably because of differences in the three-dimensional structures, as mentioned in Fig. 9. It would be interesting to examine whether a putative target molecule interacting with the epicatechin oligomer (e.g. Epi-5), but not with the catechin counterparts, showed negligible suppressive activities of FABP5 gene expression. Further studies are required to investigate how to suppress expression of this gene by these compounds. In addition, as the epicatechin oligomer (e.g. Epi-5) has been shown to strongly suppress the expression oncogenic genes other than FABP5, it would be interesting to investigate the regulatory mechanisms underlying suppression of these gene expressions by Epi-5.

Epicatechin oligomers longer than trimers suppress invasive activity of PC-3 prostate cancer cells. As shown in Fig. 8, cinnamtannin A3 (Epi-5, 1) and A4 (Epi-6, 2) significantly decreased the number of cells invading through the Matrigel-coated membrane. This finding strongly suggests that epicatechin oligomers (Epi-5 or Epi-6) might suppress the invasiveness of PC-3 prostate cancer cells during metastasis. Suppression of invasion was clearly associated with the degree of oligomerization of epicatechin (pentamer and hexamer) at the 30 μmol/L dose level (Fig. 8). As FABP5 is responsible for invasiveness of cancer cells during metastasis, suppression of the invasive activity by these epicatechin oligomers is, in part, attributable to down-regulation...
of FABP5 gene expression by them (Fig. 7). We have tried to examine whether the epicatechin oligomer (Epi-5) suppresses key proteins for invasion such as MMPs (matrix metalloproteases). No significant suppression of these proteins was observed.

**Structural analyses of epicatechin or catechin oligomers.** To investigate the anti-cancer activities of procyanidins based on the degree of oligomerization of epicatechin or catechin, three dimensional structures of the pentamers: epicatechin pentamer (Epi-5), arecatannin A3 (ATA3) and catechin pentamer (Cat-5) were calculated. The internal coordinates of the pentamers have rotational freedom. The conformation of the procyanidin dimer can rotate around the internal flavan bond between C-4 and adjacent C-8 atoms (C-4:C-8), which...
Figure 8. Effects of test compounds on the invasive activity of PC-3 prostate cancer cells. Test compounds (30 μmol/L) with the degree of oligomerization of epicatechin [pentamer (Epi-5), hexamer (Epi-6), ATA2 and ATA3] decreased invasive activities of PC-3 prostate cancer cells. The experimental procedure for preparation of test compounds was described in Biochemical methods of Supplementary Information. The invasive cells were fixed, stained and counted. Representative images of three independent experiments are shown in (a) and (c). Scale bar, 400 μm. The relative activities of cell invasion are shown in (b) and (d). The data are the means ± S.D. of three independent experiments. One-way ANOVA followed by Tukey’s multiple comparison test was used to compare means. *P < 0.05 or **P < 0.01.
prescribes the relative direction of the first and second flavan units. It was reported that the catechin dimer may form two stable rotamers around the C-4:C-8 bond named as the compact (Co) and extended (Ex) rotamers. The Co and Ex rotamer exhibits negative (~−120°) and positive (~+60°) torsion angle around the C-4:C-8 bond, respectively. Herein, each pentamer of Epi-5, ATA3 and Cat-5 contains the four C-4:C-8 bonds and can adopt a total of 16 possible conformations. The stable conformation among them was then determined computationally. Sixteen initial structures were prepared with different rotamer states for Epi-5, ATA3 and Cat-5. These initial structures were optimized without restraint by density functional theory at the B3LYP level with the 6–31(d) basis set in the gas phase, which was conducted with Gaussian09 package. Energies of the optimized structures were compared and the lowest-energy structure (LES) determined. The LESs of the pentamers and the energy-minimized structure of EGCG are shown in Fig. 9. Interestingly, the rotamer patterns of Epi-5 and ATA3 LESs are the same as Co-Co-Ex-Ex from the top of the C-4:C-8 bonds, whereas that of Cat-5 LES is Ex-Ex-Co-Ex. Furthermore, the three-dimensional distribution of the hydroxy groups is similar between Epi-5 and ATA3 LESs but not EGCG. This result suggests that Epi-5 and ATA3 might interact with a putative target molecule (receptor) via position-specific hydrogen bonds for regulating anti-cancer activities, as different mechanism from EGCG such as suppressing cell proliferation and cell invasion of PC-3 prostate cancer cells, while Cat-5 is not capable of such activity.

Discussion
Although reports of the synthesis of catechin and/or epicatechin oligomers, especially those longer than a trimer are rather limited, in the present study syntheses of cinnamtannin A3 (epicatechin pentamer, 1), catechin tetramer (3), pentamer (4), arecatannin A2 (5) and A3 (6) were achieved via Lewis acid mediated equimolar condensation. As to the synthesis of 2, 1.7 eq. of nucleophile was necessary to obtain condensed product in good yield. Due to the establishment of synthetic method of various degrees of procyanidin oligomers, studies on their structural activity relationship and chemical probe syntheses would be possible. This synthetic study enabled us to evaluate the biological activities of procyanidins based on the degree of oligomerization of epicatechin or catechin. We investigated the anti-cancer activity of these compounds against human PC-3 prostate cancer cell lines. Among these compounds, cinnamtannin A4 (2), the pentamer of epicatechin derivatives, cinnamtannin A3 (1) and arecatannin A3 (3) showed significant activities for suppression of cell growth, invasion and FABP5 gene expression. On the other hand, compounds with oligomeric states less than tetramers and the catechin pentamer did not show any activities for suppression of cell growth, invasion and FABP5 gene expression. We found that the cytotoxic effects were clearly associated with the degree of oligomerization of epicatechin. As shown in Fig. 6, the
levels of Cdc2, Cdc25C and Cyclin B1, critical regulators in the transition from G2 to S phase\textsuperscript{39}, were significantly reduced in PC-3 cells treated with epicatechin oligomers, suggesting that the G2/M cell cycle arrest might be induced in PC-3 cells. Thus, the cell growth inhibitory activities of cinnamtyannin A3 (Epi-5, 1) and A4 (Epi-6, 2) might be partly ascribed to their tendency to block the cell cycle partly at the G2 phase, but further mechanistic study should be needed to clarify suppression of cell proliferation by them. These compounds also suppressed the expression of cancer-promoting genes such as FABP5 and invasion of cancer cells, suggesting that they represent promising anti-metastatic agents. Analyses of three-dimensional structures of epicatechin or catechin oligomers by theoretical calculations strongly suggested structural characteristic required for their anti-cancer activities. It would be interesting to examine whether Epi-5 and ATA3 would interact with a putative target molecule for regulating anti-cancer activities, while Cat-5 is not capable of such activity. Further mechanistic studies of their anti-cancer activities are now in progress.

Among green tea catechin, EGCG is the most abundant and anti-cancer constituent\textsuperscript{37}. EGCG has been demonstrated to have cancer preventive activities in various cancer cells mediated by its antioxidant activity and its specific receptors to regulate gene expression and cellular signaling\textsuperscript{38,39}. However, we have preliminarily found that EGCG has less inhibitory activity for the cancer-promoting gene (FABP5) expression and less invasive activity compared with these epicatechin oligomers (unpublished results). As shown in Fig. 9, the structural comparison between EGCG and Epi-5 or ATA3 suggests that the pentamers might interact with a potent receptor other than that EGCG binds to.

Recently, it has been reported that procyanidins regulate vascular endothelial functions, suggesting implication for cardiovascular health\textsuperscript{40–43}. Although the regulatory mechanisms of vascular endothelial functions by the oligomeric procyanidins in red wine remains unclear, they are hypothesized to bind to a potent specific cell surface protein involved in mechanosensing or to act as receptor agonists, initiating mechanotransduction signaling in the vascular endothelial cells. It would be interesting to examine functional and structural differences of potential target protein/receptor for epicatechin oligomers between cancer cells and endothelial cells.

In conclusion, we demonstrated that epicatechin oligomers longer than trimers have significant anti-cancer activities, but not the catechin counterparts. Furthermore, the present study suggests that cinnamtyannin A3 and A4 might be potential chemo-preventive agents for various cancers including prostate cancer. Further \textit{in vivo} and mechanistic studies are needed to confirm these anti-cancer activities.

Methods

General. All melting points reported were uncorrected. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were measured with a Bruker DRX 500 FT-NMR spectrometer in CDCl\textsubscript{3} or CD\textsubscript{3}OD at 500 and 125 MHz, respectively. Chemical shifts were relative to tetramethylsilane as an internal standard. The coupling constants are given in Hz. Mass spectra were obtained on Waters Xevo QTOF (MS-A) and Shimadzu LCMS-IT-TOF (MS-B) mass spectrometers. IR spectra were recorded with a JASCO FT-IR 480 Plus infrared spectrometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter. HPLC data were recorded with GL Science GL-7400 (HPLC-A), Shimadzu HPLC LC-VP series (HPLC-B) and Waters ACQUITY UPLC (HPLC-C).

Statistical analysis. GraphPad Prism 7.03 was used for statistical analyses. Data were expressed as the mean ± S.D. For multiple comparisons were calculated using one-way analysis of variance (ANOVA) with Tukey’s post-hoc test or two-way ANOVA with Dunnett’s post-hoc test. Statistical significance were indicated by the following indications: *P < 0.05, **P < 0.01.

Experimental data. For supplementary Tables 1–5, see Supplementary Information pages 3–7. For the synthesis procedures of compounds 1–25, see Supplementary Information pages 8–18. For biochemical methods, see Supplementary Information pages 19–21. For supplementary Figures 1 and 2, see Supplementary Information pages 23–24. For \textsuperscript{1}H and \textsuperscript{13}C NMR of synthesized compounds, HPLC data and MS spectra of compounds 1–6, see Supplementary Information pages 26–69.

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Author Contributions

H.F. and H.M. conceived and supervised the study; H.M. and H. F. designed experiments; K.T., M.S., K.M., C.I., K.T., K.K., S.S., N.K., M.I., M.K., Y.H., S.K. and K.U. performed experiments; K.T., M.S., K.M., C.I., M.I., K.U., H.F. and H.M. analyzed data; H.M. and H.F. wrote the paper.

Additional Information

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