Chlorogenic Acid Derivatives with Alkyl Chains of Different Lengths and Orientations: Potent α-Glucosidase Inhibitors

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α-Glucosidases play important roles in the digestion of carbohydrates and biosynthesis of viral envelope glycoproteins. Inhibitors of α-glucosidase are promising candidates for the development of antitype II diabetics and anti-AIDS drugs. Here, we report the synthesis and α-glucosidase inhibitory activity of mono- and diketal/acetal derivatives of chlorogenic acid. The diketal derivatives showed more potent inhibitory activity than the monoketals. The 1,7-(5-nonanone) 3,4-(5-nonanone)-chlorogenic acid diketal showed remarkable inhibitory activity against α-glucosidases with potency better than that of 1-deoxynojirimycin hydrochloride. Four diasteremers of pelargonaldehyde diacetal and two of monoacetal derivatives of chlorogenic acid were synthesized in this study. They showed significant potent inhibition similar to or more potent than the ketal counterparts. Acetals with the alkyl chain oriented toward position 2 of chlorogenic acid showed more potent activity than those oriented toward position 6.

Introduction

Glycosidases are hydrolytic enzymes that play a vital role in digestion of carbohydrates and biosynthesis of glycoproteins. Inhibitors of α-glucosidase may potentially reduce the progression of diabetes by decreasing the digestion and absorption of carbohydrates. In addition, α-glucosidase inhibition is a promising strategy for the development of novel anti-HIV agents, as glycosylation of the viral envelope glycoproteins is essential for the virus infectivity.[1,2] Recently, catechin derivatives of less hydrophilicity, due to the introduction of alkyl side chains, were reported to exhibit potent α-glucosidase inhibitory activity.[3,4] Considering that chlorogenic acid is an abundant and highly hydrophilic natural product carrying a catechol group like catechin, we attempted the present investigation in order to obtain novel α-glucosidase inhibitors by optimizing the hydrophilicity of chlorogenic acid via addition of alkyl chains of various lengths. Ketal and acetal groups are frequently used to protect hydroxyl or carbonyl groups during chemical synthesis. These groups are also found in the structures of drug candidates or drugs themselves such as ketoconazole,[5] and 3β-acetoxyandrost-1,5-diene-17-ethylene ketal.[6] As the substrates of α-glucosidase are polysaccharides (carbohydrates), which are virtually monosacharides connected to each other through acetal (glycosyl) bonds, it is speculated that the addition of ketal or acetal bonds to chlorogenic acid derivatives may increase the inhibitory activity on α-glucosidases. The constrained structures of acetal derivatives of chlorogenic acid make it possible to prepare compounds with alkyl chains of different orientations and thus provide the opportunity to investigate also the effect of the chain orientations on bioactivity. In this paper, we would like to describe the synthetic methods and the α-glucosidase inhibitory activity of chlorogenic acid derivatives with alkyl chains of different lengths and orientations.

Chemistry. The diketal or diacetal derivatives (compounds **21**−**28** and **35**−**38**) were prepared according to the method described for catechin derivatives with modification.[3,4] The synthetic route is illustrated in Scheme 1. Chlorogenic acid was allowed to react with the corresponding ketones or aldehyde to form the desired diketal or diacetal derivatives. The diasteremers, **35**−**38**, were separated by preparative HPLC. Interestingly, when treating the diketal/diacetal compounds with 0.4N HCl in MeOH−H_2O, the 3,4-ketal/acetal groups were selectively hydrolyzed (Scheme 2). The C4−O bond of the 3,4-ketal/acetal groups was equatorial to the quinic acid ring and thus was less sterically hindranced and could be attacked by a proton cation during the hydrolysis process more easily than did the axial orientated C1−O. As a result, the 1,7-ketal/acetal groups were more stable than the 3,4-ketal/acetal groups. The 1,7-monoketal compounds **1**−**8** or 1,7-monoacetal compounds **33** and **34** were obtained after purifying the hydrolyzed products using octadecylsilanized silica (ODS[a]) column chromatography.

The structures of the synthesized compounds were confirmed by NMR and MS spectra. The orientations of the alkyl chains in the structures of **33**−**38** were determined by 2D NMRs, including NOE experiments. The ^{1}H NMR signals were assigned to each proton by H−H correlation spectroscopy (COSY) and heteronuclear multiple bond correlation (HMBC) experiments. Nuclear overhauser effect (NOE) was observed between H-1″ (δ 5.69) and H-2a (δ 2.30) in the spectrum of **33** and between H-1″ (δ 5.71) and H-6a (δ 2.43) in the spectrum of **34**, indicating that the alkyl chain was orientated toward position 6 (α-orientation) in the structure of **33** and toward position 2 (β-orientation) in the structure of **34**. Similarly, the orientations of the alkyl chains in the structures of **35**−**38** were determined by the following key NOE correlations: **35**, NOE correlations between H-1″ (δ 5.65) and H-2a (δ 2.43) indicated that the first alkyl chain was α-orientated. Another NOE correlation between H-1‴ (δ 5.02) and H-3 (δ 4.38) indicated that H-1‴ oriented upward and thus the second alkyl chain oriented downward (α-orientation); **36**, NOE correlation between H-1″

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[a] Abbreviations: ODS, octadecylsilanized silica; COSY, H−H correlation spectroscopy; HMBC, heteronuclear multiple bond correlation; NOE, Nuclear overhauser effect; ESI-MS, electrospray ionization mass; APCI-MS, atmospheric pressure chemical ionization mass.

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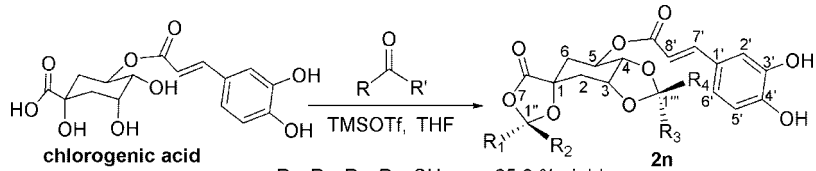
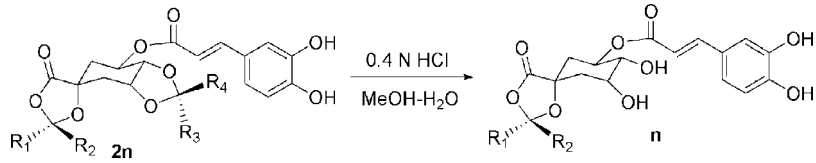
Scheme 1. Chemical Structures and Synthesis of the Diketal or Diacetal Derivatives



21	$R_1=R_2=R_3=R_4=CH_3$	65.9 % yield
22	$R_1=R_2=R_3=R_4=CH_2CH_3$	48.6 % yield
23	$R_1=R_2=R_3=R_4=(CH_2)_2CH_3$	45.3 % yield
24	$R_1=R_2=R_3=R_4=(CH_2)_3CH_3$	43.1 % yield
25	$R_1=R_2=R_3=R_4=(CH_2)_4CH_3$	43.0 % yield
26	$R_1=R_2=R_3=R_4=(CH_2)_5CH_3$	27.5 % yield
27	$R_1=R_2=R_3=R_4=(CH_2)_6CH_3$	15.3 % yield
28	$R_1=R_2=R_3=R_4=(CH_2)_7CH_3$	10.7 % yield
35	$R_1=(CH_2)_7CH_3$, R_2=H, $R_3=(CH_2)_7CH_3$, R_4=H	9.2 % yield
36	$R_1=(CH_2)_7CH_3$, R_2=H, R_3=H, $R_4=(CH_2)_7CH_3$	9.2 % yield
37	R_1=H, $R_2=(CH_2)_7CH_3$, $R_3=(CH_2)_7CH_3$, R_4=H	18.8 % yield
38	R_1=H, $R_2=(CH_2)_7CH_3$, R_3=H, $R_4=(CH_2)_7CH_3$	33.2 % yield

Scheme 2. Chemical Structures and Synthesis of 1,7-Monoketal or 1,7-Monoacetal Compounds



1	$R_1=R_2=CH_3$	79.6% yield
2	$R_1=R_2=CH_2CH_3$	71.5% yield
3	$R_1=R_2=(CH_2)_2CH_3$	81.0% yield
4	$R_1=R_2=(CH_2)_3CH_3$	81.2% yield
5	$R_1=R_2=(CH_2)_4CH_3$	76.3% yield
6	$R_1=R_2=(CH_2)_5CH_3$	72.9% yield
7	$R_1=R_2=(CH_2)_6CH_3$	40.1% yield
8	$R_1=R_2=(CH_2)_7CH_3$	80.3% yield
33	$R_1=(CH_2)_7CH_3$, R_2=H	78.7% yield
34	R_1=H, $R_2=(CH_2)_7CH_3$	78.7% yield

(δ 5.65) and H-2a (δ 2.43) indicated the first chain was α-orientated. Because signals for H-1‴ and H-5 in the spectra of **36** were completely overlapped, we irradiated the H-2‴ signal instead of the H-1‴ signal to determine the orientation of the second chain. NOE was observed for H-3 at δ 4.41 upon irradiation of the signal for H-2‴ at δ 1.61 and thus indicated that the second chain was β-orientated; **37**, NOE correlations between H-1″ (δ 5.62) and H-6a (δ 2.36) indicated the β-orientated nature of the first chain; NOE correlations between H-1‴ (δ 5.04) and H-3 (δ 4.39) as well as between H-1‴ (δ5.62) and H-4 (δ 4.21) indicated the α-orientated nature of the second chain; **38**, NOE correlations between H-1″ (δ 5.62) and H-6 (δ 2.39) as well as between H-3 (δ 4.41) and H-2‴ (δ 1.61) indicated that both of the alkyl chains were β-orientated. Molecular modeling study using an Insight II (2000) performed on an Octane SiliconGraphics confirmed that in the conformations with minimized energy, protons experienced NOE were spatially closer than those that did not have NOE. For example, the distances between H-1″ and H-2a (3.29 Å) was shorter than those between H-1″ and H-6 (4.44 Å and 5.14Å) in **33**, while in **34**, the distances between H-1″ and H-6a (3.48 Å) were shorter than those between H-1″ and H-2 (4.43 and 5.20 Å). The 3D structures of these compounds with the distances indicated (in white) for the protons having NOE effects are shown in the Supporting Information (Figures S65−S67).

The catechin derivative **PC1** (Figure 1) was synthesized and purified according to the method described in the literature, and its structure was confirmed by comparing its spectral data with those of reported.[3,4]

Results and Discussion

α-Glucosidase Inhibitory Activity and Structure−Activity Relationships of the Chlorogenic Acid Derivatives. α-Glucosidase inhibitory activity was determined using the procedure reported by Hakamata et al.[3] with modifications. The assays were carried out in 96-well plates with 4-nitrophenyl α-D-glucopyranoside as substrate and two α-glucosidases from *Bacillus stearothermophilus* and from *Saccharomyces cerevisiae*, respectively. The results of the biological assay of two series of chlorogenic acid derivatives, diketals/diacetals and 1,7-monoketals/1,7-monoacetals, against the two α-glucosidases are shown in Table 1. It was observed that with the length of the

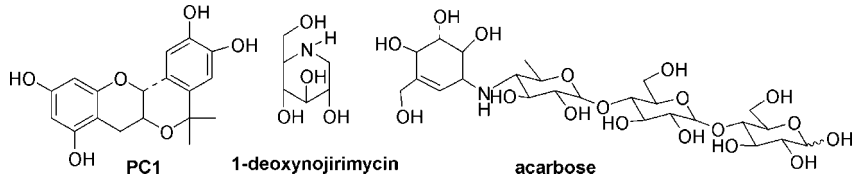


Figure 1. Structures of the catechin analogue PC1, 1-deoxynojirimycin, and acarbose.

Table 1. Inhibition of α-Glucosidase by Chlorogenic Acid Derivatives

	IC$_{50}$ ± RSD (n = 3)	
compound	IC$_{50}$a[a] (μM)	IC$_{50}$b[b] (μM)
chlorogenic acid	2822.5 ± 2.1%	>2822.5 ± 11.7%
1	2536.1 ± 8.9%	114.2 ± 12.2%
2	127.8 ± 3.6%	71.1 ± 8.1%
3	62.2 ± 4.7%	19.4 ± 0.4%
4	14.4 ± 0.2%	3.4 ± 5.3%
5	14.2 ± 2.5%	3.6 ± 4.2%
6	3.9 ± 6.6%	3.4 ±1.2%
7	3.6 ± 5.0%	4.3 ± 7.2%
8	5.1 ± 4.1%	3.0 ± 2.9%
21	154.2 ± 2.2%	391.3 ± 4.2%
22	44.9 ± 1.1%	26.5 ± 11.2%
23	5.5 ± 3.5%	3.3 ± 3.6%
24	0.8 ± 1.4%	0.3 ± 2.0%
25	1.1 ± 9.2%	0.8 ± 1.4%
26	0.8 ± 1.8%	0.5 ± 7.6%
27	0.9 ± 7.1%	0.4 ± 4.4%
28	0.9 ± 9.0%	0.5 ± 4.1%
33	10.9 ± 6.4%	3.3 ± 5.7%
34	12.5 ± 2.0%	3.6 ± 7.9%
35	2.0 ± 2.8%	1.0 ± 8.4%
36	1.8 ± 5.9%	0.8 ± 8.6%
37	0.8 ± 4.1%	0.3 ± 2.0%
38	0.7 ± 3.2%	0.3 ± 3.8%
acarbose	0.1 ± 2.7%	0.1 ± 4.0%
PC[c]	2.4 ± 3.6%	1.8 ± 4.5%
PC1[d]	29.6 ± 4.7%	18.5 ± 4.9%

[a] IC$_{50}$a: concentration at which 50% activity of α-glucosidase from *B. stearothermophilus* (Sigma, G-3651) was inhibited. [b] IC$_{50}$b: concentration at which 50% activity of α-glucosidase from *S. cerevisiae* (Toyobo, AGH-211) was inhibited. [c] **PC**: 1-deoxynojirimycin hydrochloride as a positive control. [d] **PC1**: a catechin derivative reported to have potent α-glucosidase inhibitory activity.[3]

alkyl chain increased, inhibition on both enzymes increased significantly up to the 5-nonanone derivatives in the ketals (**1**−**8** and **21**−**28**) of both series. As the length of the alkyl chain further increased, the activity had little change in the diketals (**24**−**28**). Over 176- and 33-fold increase in the inhibitory activity on the two enzymes was found with **4** (n = 4) compared to **1** (n = 1) in the monoketal series, suggesting the existence of important hydrophobic interactions between these type of compounds and the enzymes. More potent inhibitory activity was observed in the diketal series **21**−**28**. Compound **24** (n = 4) was found to be 185 and 1300 times more potent than **21** (n = 1) and 17 and 11 times more potent than **4** (monoketal) on the two α-glucosidases, suggesting that there were at least two sites of hydrophobic interactions between the enzymes and these compounds.

Of the acetal derivatives, the diacetals (**35**−**38**) showed more potent inhibitory activity than the corresponding monoacetals (**33**−**34**), a phenomenon similar to that observed in ketal derivatives. Interestingly, in the four diacetal isomers (**35**−**38**), the orientations of the lipophilic chains at position 1″ appreciably affected their activity, with the β-oriented ones showing 2-fold increased activity than the α-oriented counterparts (**38**: IC$_{50}$ = 0.7 and 0.3 μM vs **36**: IC$_{50}$ = 1.8 and 0.8 μM; **37** 0.8 and 0.3 μM vs **35**: 2.0 and 1.0 μM). The orientation of the lipophilic chain at positions 1‴ had little effect on the activity.

Looking at the 3D structures (see Supporting Information, Figure S68), it was found out that the configuration difference at the C-1‴ has less influence on the spatial arrangement (relative orientations) of the two lipophilic chains and the catechol group, which resulted in the similar 3D images for **37** (1″-β-chain, 1‴-α-chain) and **38** (1″-β-chain, 1‴-β-chain). On the other hand, configuration at C-1″ affected the 3D images more obviously as those for compounds **36** (1″-α-chain, 1‴-β-chain) and **38** (1″-β-chain, 1‴-β-chain). Generally, the 1″-α-chains were spatially more close to the catechol group than the 1″-β-chain.

Of all these chlorogenic acid derivatives synthesized, 17 showed more potent activity than the catechin derivative **PC1**. Significantly improved inhibitory activities were observed with compounds **24**, **37**, and **38**, all of which contained two sets of nine carbon-chains in their structures. The activities of these compounds were less potent than acarbose but were better than another well-known glucosidase inhibitor, 1-deoxynojirimycin hydrochloride, and were more than 37 times more potent than the catechin derivative **PC1**.

Stability of the Acetal Bonds in Artificial Gastric Juice and Artificial Intestinal Juice. Compound **38**, which showed the most potent α-glucosidase inhibitory activity, was incubated with artificial gastric juice and artificial intestinal juice. It was found that this compound remained intact in artificial gastric juice for 48 h and intact in artificial intestinal juice for 12 h. In artificial intestinal juice, 3.4% and 4.5% of **38** was decomposed to **34** after incubation for 24 and 48 h, respectively. The results demonstrated again that the 1,7-monoketal/acetal bonds were more stable than the 3,4-ketal/acetal bonds due to the reason stated in the chemistry part above.

Conclusions

The present study provided a practical method for the preparation of diketal/diacetal and 1,7-monoketal/monoacetal derivatives of chlorogenic acid. Lipophilic chlorogenic acid derivatives with different chain lengths and chain orientations were synthesized. Some of these compounds showed remarkable α-glucosidase inhibitory activity.

Penta-*O*-galloyl-D-glucopyranose and its analogues have been reported to have antidiabetic activities by stimulating the glucose transport activities.[7] Chlorogenic acid and its derivatives with a lipophilic chain at position 1 were reported to have antidiabetic activities through the inhibition of hepatic glucose-6-phosphate translocase.[8] Considering that the chlorogenic acid derivatives synthesized in this paper possess both the galloyl-like phenolic groups and lipophilic chains, it is expected that these compounds may be used for molecular modeling to design and develop novel antidiabetic compounds that target at various points, including α-glucosidase to attenuate the progress of the disease. Further in vivo study of these compounds on diabetic mice is planned to be carried out in our laboratory. The results will be reported in a separate paper. The strong inhibitory effects of these compounds on α-glucosidase also suggest that these alkyl

chlorogenic acid derivatives may be used as lead compounds for the development of new type of anti-AIDS agents.

Experimental Section

Chemistry. Pelargonaldehyde was purchased from Tokyo Kasei Kogyo Co. Ltd. Dehydrated tetrahydrofuran, HPLC-grade methanol, and acetonitrile were purchased from Wako Pure Chemical Industries, Ltd. Other chemical reagents were purchased from Sigma-Aldrich, Inc. unless otherwise indicated. Column chromatography was carried out on Wakogel 50C18 (38−63 μm, Wako Pure Chemical Industries, Ltd.). Preparative HPLC was performed on a Tosoh CCPM- II system (Tosoh Co., Tokyo) equipped with a UV 8020 detector and a 5C18-AR-II waters HPLC column (20 mm × 200 mm). NMR spectra were measured with a Varian Unity 500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) or a Varian Gemini 300 (^{13}C, 75 MHz) NMR spectrometer. TMS was used as an internal standard and *J* values were reported in hertz. Analytic HPLC was carried out on an Agilent 1100 system (Agilent Technologies, Waldbronn, Germany) equipped with degasser, binary pump, and photodiode array detector. Electrospray ionization mass (ESI-MS) and atmospheric pressure chemical ionization mass (APCI-MS) spectra were obtained on an Esquire 3000^{plus} spectrometer (Bruker Daltonik GmbH, Bremen, Germany). The purities of synthesized compounds were verified with ^{1}H NMR, ^{13}C NMR, and HPLC (see Supporting Information).

Synthesis of the Catechin Derivative PC1. PC1 was synthesized and its structure was confirmed by spectroscopic method according to the literature.[3,4]

General Method for the Synthesis of 1,7,3,4-Chlorogenic Acid Diketals and 1,7,3,4-Chlorogenic Acid Diacetals. To the solution of chlorogenic acid (1 mmol) and ketone (3 mmol) in 7 mL of dehydrated tetrahydrofuran in an ice bath, trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1 mmol) was slowly added. The mixture was stirred at room temperature overnight. The reaction was stopped by addition of ice−water and 1N NaOH of the same volume of TMSOTf. The product was purified using an ODS or silica gel column eluted with gradient MeOH-H_2O.

1,7-(Acetone) 3,4-(Acetone)-chlorogenic Acid Diketal (21). After synthesis using acetone as a ketone and purification on ODS, the product was obtained from the 65% MeOH eluted part (yield: 65.9%). **21**: crystalline powder; $[\alpha]_D$ −33.7 (*c* 0.3, MeOH); mp 201−203 °C. ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H) and 1.58 (s, 3H) and 1.63 (s, 3H) and 1.64 (s, 3H) (−C$\underline{H}_3$), 1.93 (dd, 1H, *J* = 11.0, 13.5 Hz, H-6a), 2.26 (dd, 1H, *J* = 3.0, 13.5 Hz, H-6b), 2.33 (m, 2H, H-2a,2b), 4.25 (t, *J* = 7.0 Hz, 1H, H-4), 4.55 (m, 1H, H-3), 5.28 (m, 1H, H-5), 6.12 (d, *J* = 15.5 Hz, 1H, H-8′), 6.81 (d, *J* = 8.0 Hz, 1H, H-5′), 6.88 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6′), 6.99 (br s, 1H, H-2′), 7.52 (d, *J* = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 25.4 and 27.7 and 28.1 and 28.4 (−$\underline{C}H_3$), 34.5 (C-2), 35.8 (C-6), 69.9 (C-5), 72.4 (C-3), 75.9 (C-4), 78.2 (C-1), 109.7 and 111.3 (C-1″ and C-1‴) 114.2 and 114.3 (C-2′ and C-8′), 115.3 (C-5′), 122.5 (C-6′), 126.9 (C-1′), 144.2 (C-4′), 145.9 (C-7′), 146.9 (C-3′), 167.1 (C-9′), 174.4(C-7). ESI-MS (negative): 433.5 ([M − H]$^-$, 100%).

1,7-(3-Pentanone) 3,4-(3-Pentanone)-chlorogenic Acid Diketal (22). After synthesis using 3-pentanone as a ketone and purification on ODS, the product was obtained from the 80% MeOH eluted part (yield: 48.6%). **22**: crystalline powder; $[\alpha]_D$ −32.6 (*c* 0.08, MeOH); mp 63−65 °C. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7.5 Hz, 3H, −$CH_2C\underline{H}_3$), 0.97 (m, 9H, −$CH_2C\underline{H}_3$), 1.84 (m, 2H, −$C\underline{H}_2CH_3$), 1.68 (m, 7H, −$C\underline{H}_2CH_3$ and H-6a), 2.28 (m, 3H, H-2a,2b,6b), 4.29 (t, *J* = 7.0 Hz, 1H, H-4), 4.58 (m, 1H, H-3), 5.35 (m, 1H, H-5), 6.05 (d, *J* = 15.5 Hz, 1H, H-8′), 6.78 (d, *J* = 8.0 Hz, 1H, H-5′), 6.83 (d, *J* = 8.0 Hz, 1H, H-6′), 6.94 (s, 1H, H-2′), 7.46 (d, *J* = 15.5 Hz, 1H, H-7′).^{13}C NMR ($CDCl_3$) δ 7.5 and 7.8 and 8.6 (−$CH_2\underline{C}H_3$), 29.0 and 29.4 and 31.2 (−$\underline{C}H_2CH_3$), 34.6 (C-2), 35.8 (C-6), 70.6 (C-5), 72.3 (C-3), 75.9 (C-4), 77.8 (C-1), 113.8 (C-2′), 114.1 (C-1‴), 114.5 (C-8′), 115.1 (C-5′), 115.2 (C-1″), 122.5 (C-6′), 127.1 (C-1′), 144.1 (C-4′), 145.6 (C-7′), 146.6 (C-3′), 167.0 (C-9′), 174.7 (C-7). ESI-MS (negative): 489.3 ([M− H]$^-$, 100%).

1,7-(4-Heptanone) 3,4-(4-Heptanone)-chlorogenic Acid Diketal (23). After synthesis using 4-heptanone as a ketone and purification on ODS, the product was obtained from the 80−90% MeOH eluted part (yield: 45.3%). **23**: wax; $[\alpha]_D$ −23.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 12H, −$CH_2CH_2C\underline{H}_3$), 1.41 (m, 8H) and1.62 (m, 2H) and 1.73 (m, 6H) and1.92 (t, *J* = 12.0 Hz, 1H) (−$C\underline{H}_2C\underline{H}_2CH_3$ and H-6a), 2.25 (m, 3H, H-2a,2b,6b), 4.27 (t, *J* = 7.0 Hz, 1H, H-4), 4.56 (m, 1H, H-3), 5.35 (m, 1H, H-5), 6.11 (d, *J* = 15.5 Hz, 1H, H-8′), 6.78 (d, *J* = 8.0 Hz, 1H, H-5′), 6.84 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6′), 6.98 (d, *J* = 1.5 Hz, 1H, H-2′), 7.49 (d, *J* = 15.5 Hz, 1H, H-7′).^{13}C NMR ($CDCl_3$) δ 13.9 and 14.2 and 14.3 (−$CH_2CH_2\underline{C}H_3$), 16.4 and 16.6 and 16.8 and 17.5 (−$CH_2\underline{C}H_2CH_3$), 34.5 (C-2), 35.7 (C-6), 38.8 and 39.5 and 40.6 and 40.9 (−$\underline{C}H_2CH_2CH_3$), 70.6 (C-5), 72.0 (C-3), 75.9 (C-4), 77.6 (C-1), 113.0 (C-2′), 114.0 and 114.4 (C-8′, C-1″, and C-1‴), 115.1 (C-6′), 122.4 (C-5′), 126.9 (C-1′), 144.3 (C-4′), 145.7 (C-7′), 146.8 (C-3′), 167.0 (C-9′), 174.9 (C-7). ESI-MS (negative): 545.5 ([M − H]$^-$, 100%).

1,7-(5-Nonanone) 3,4-(5-Nonanone)-chlorogenic Acid Diketal (24). After synthesis using 5-nonanone as a ketone and purification on ODS, the product was obtained from the 90% MeOH eluted part (yield: 43.1%). **24**: white wax-like powder; $[\alpha]_D$ −21.9 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.92 (m, 12H, −$CH_2CH_2CH_2C\underline{H}_3$), 1.38 (m, 16H) and 1.62 (m, 2H) and 1.76 (m, 6H) and 1.92 (t, *J* = 12.0 Hz, 1H) (−$C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$ and H-6a), 2.25 (m, 3H, H-2a,2b,6b), 4.27 (t, *J* = 7.0 Hz, 1H, H-4), 4.56 (m, 1H, H-3), 5.30 (m, 1H, H-5), 6.13 (d, *J* = 15.5 Hz, 1H, H-8′), 6.79 (d, *J* = 8.0 Hz, 1H, H-5′), 6.86 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6′), 6.99 (d, *J* = 1.5 Hz, 1H, H-2′), 7.51 (d, *J* = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 13.9 and 14.0 (−$CH_2CH_2CH_2\underline{C}H_3$), 22.5 and 22.6 and 22.8 and 23.0 and 25.2 and 25.4 and 25.7 and 26.4 and 35.3 and 37.0 and 38.3 and 38.5 (−$\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$), 34.6 (C-2), 35.7 (C-6), 70.4 (C-5), 72.0 (C-3), 75.6 (C-4), 77.6 (C-1), 113.1 (C-2′), 114.0 and 114.5 and 114.6 (C-8′, C-1″ and C-1‴), 115.1 (C-6′), 122.4 (C-5′), 127.1 (C-1′), 144.3 (C-4′), 145.6 (C-7′), 146.8 (C-3′), 166.8 (C-9′), 174.9 (C-7). ESI-MS (negative): 601.4 ([M − H]$^-$, 100%).

1,7-(6-Undecanone) 3,4-(6-Undecanone)-chlorogenic Acid Diketal (25). After synthesis using 6-undecanone as a ketone and purification on ODS, the product was obtained from the 95% MeOH eluted part (yield: 43.0%). **25**: wax; $[\alpha]_D$ −19.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 12H, −$CH_2CH_2CH_2CH_2C\underline{H}_3$), 1.27 (m, 18H) and1.43 (m, 6H) and 1.62 (m, 2H) and 1.80 (m, 6H) and1.91 (t, *J* = 12.0 Hz, 1H) (−$C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$ and H-6a), 2.25 (m, 3H, H-2a,2b,6b), 4.29 (t, *J* = 7.0 Hz, 1H, H-4), 4.57 (m, 1H, H-3), 5.31 (m, 1H, H-5), 6.08 (d, *J* = 15.5 Hz, 1H, H-8′), 6.78 (d, *J* = 8.0 Hz, 1H, H-5′), 6.84 (dd, *J* = 1.5, 8.0 Hz, 1H, H-6′), 6.95 (d, *J* = 1.5 Hz, 1H, H-2′), 7.47 (d, *J* = 15.5 Hz, 1H, H-7′).^{13}C NMR ($CDCl_3$) δ 14.2 and 14.3 (−$CH_2CH_2CH_2CH_2\underline{C}H_3$), 22.7 and 22.8 and 23.0 and 23.2 and 23.5 and 24.2 and 31.9 and 32.2 and 32.3 and 36.8 and 37.4 and 38.9 and 39.0 (−$\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$), 34.9 (C-2), 36.0 (C-6), 70.7 (C-5), 72.3 (C-3), 75.9 (C-4), 77.9 (C-1), 113.6 (C-2′), 114.4 and 114.9 (C-8′, C-1″, and C-1‴), 115.4 (C-6′), 122.8 (C-5′), 127.4 (C-1′), 144.5 (C-4′), 145.9 (C-7′), 146.9 (C-3′), 167.0 (C-9′), 175.2 (C-7). ESI-MS (negative): 693.5 ([M + Cl]$^-$, 70%), 657.5 ([M − H]$^-$, 70%).

1,7-(Dihexyl ketone) 3,4-(Dihexyl ketone)-chlorogenic Acid Diketal (26). After synthesis using dihexyl ketone as a ketone and purification on a silica gel column, the product was obtained from the $CHCl_3$−MeOH 98:2 eluted part (yield: 27.5%). **Cr26**: wax; $[\alpha]_D$ −17.1 (*c* 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 12H, −$CH_2CH_2CH_2CH_2CH_2C\underline{H}_3$), 1.28 (m, 26H) and 1.40 (m, 6H) and 1.62 (m, 2H) and 1.80 (m, 6H) and 1.91 (t, *J* = 12.5 Hz, 1H) (−$(C\underline{H}_2)_5CH_3$ and H-6a), 2.25 (m, 3H, H-2a,2b,6b), 4.27 (t, *J* = 7.0 Hz, 1H, H-4), 4.56 (m, 1H, H-3), 5.28 (m, 1H, H-5), 6.07 (d, *J* = 15.5 Hz, 1H, H-8′), 6.77 (d, *J* = 8.0 Hz, 1H, H-5′), 6.82 (d, *J* = 8.0 Hz, 1H, H-6′), 6.98 (br s, 1H, H-2′), 7.46 (d, *J* = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.0 and 14.1 (−$(CH_2)_5\underline{C}H_3$), 22.5 and 22.6 and 23.0 and 23.3 and 23.5 and 24.2 and 29.1 and 29.5 and 29.6 and 31.6 and 31.7 and 31.8 and 36.6 and 37.2 and 38.6 and 38.8 (−$(\underline{C}H_2)_5CH_3$), 34.6 (C-2), 35.7 (C-6),

70.2 (C-5), 71.8 (C-3), 75.5 (C-4), 77.4 (C-1), 113.0 (C-2′), 114.0 and 114.3 and 114.6 (C-8′, C-1″, and C-1‴), 115.2 (C-6′), 122.3 (C-5′), 126.9 (C-1′), 144.0 (C-4′), 145.2 (C-7′), 146.5 (C-3′), 166.3 (C-9′), 174.6 (C-7). APCI-MS (negative): 713.9 ([M − H]$^-$, 100%).

1,7-(Diheptyl Ketone) 3,4-(Diheptyl Ketone)-chlorogenic Acid Diketal (27). After synthesis using diheptyl ketone as a ketone and purification on silica gel column, the product was obtained from the $CHCl_3$−MeOH 98:2 eluted part (yield: 15.3%). **Cr27**: wax; $[\alpha]_D$ −19.1 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 12H, $-(CH_2)_2\underline{C}H_3$), 1.25 (m, overlapped with H_2O signal) and 1.39 (m, 6H) and 1.60 (m, 2H) and 1.76 (m, 6H) and 1.91 (t, J = 12.0 Hz, 1H) ($-(C\underline{H}_2)_6CH_3$ and H-6a), 2.22 (m, 3H, H-2a,2b,6b), 4.25 (t, J = 5.5 Hz, 1H, H-4), 4.52 (br s, 1H, H-3), 5.24 (br s, 1H, H-5), 6.05 (d, J = 15.5 Hz, 1H, H-8′), 6.74 (br s, 1H, H-5′), 6.79 (br s, 1H, H-6′), 6.97 (br s, 1H, H-2′), 7.45 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.2 ($-(CH_2)_6\underline{C}H_3$), 22.7 and 23.2 and 23.4 and 23.7 and 24.4 and 29.2 and 29.3 and 29.4 and 29.5 and 30.0 and 31.8 and 31.9 and 36.7 and 37.4 and 38.8 and 39.0 ($-(\underline{C}H_2)_6CH_3$), 34.7 (C-2), 35.8 (C-6), 70.3 (C-5), 72.0 (C-3), 75.6 (C-4), 77.5 (C-1), 113.0 (C-2′), 114.3 and 114.6 (C-8′, C-1″, and C-1‴), 115.5 (C-6′), 122.5 (C-5′), 126.9 (C-1′), 144.3 (C-4′), 145.3 (C-7′), 147.1 (C-3′), 166.4 (C-9′), 174.7 (C-7). APCI-MS (negative): 769.8 ([M − H]$^-$, 100%).

1,7-(9-Heptadecanone) 3,4-(9-Heptadecanone)-chlorogenic Acid Diketal (28). After synthesis using 9-heptadecanone as a ketone and purification on silica gel column, the product was obtained from the $CHCl_3$−MeOH 98:2 eluted part (yield: 10.7%), wax; $[\alpha]_D$ −17.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 12H, $-(CH_2)_7\underline{C}H_3$), 1.26 (m, overlapped with H_2O signal) and 1.41 (m, 6H) and 1.60 (m, 2H) and 1.76 (m, 6H) and 1.90 (t, J = 12.0 Hz, 1H) ($-(C\underline{H}_2)_7CH_3$ and H-6a), 2.27 (m, 3H, H-2a,2b,6b), 4.27 (t, J = 5.5 Hz, 1H, H-4), 4.56 (br s, 1H, H-3), 5.29 (br s, 1H, H-5), 6.14 (d, J = 15.5 Hz, 1H, H-8′), 6.80 (br s, 1H, H-5′), 6.88 (br s, 1H, H-6′), 7.00 (br s, 1H, H-2′), 7.51 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 14.1 ($-(C\underline{H}_2)_7CH_3$), 22.6 and 22.7 and 23.1 and 23.3 and 23.6 and 24.3 and 26.2 and 29.2 and 29.4 and 29.5 and 29.6 and 29.9 and 31.8 and 31.9 and 36.6 and 37.3 and 38.7 and 38.9 ($-(CH_2)_7CH_3$), 34.7 (C-2), 35.8 (C-6), 70.3 (C-5), 72.0 (C-3), 75.6 (C-4), 77.5 (C-1), 113.1 (C-2′), 114.4 and 115.0 (C-8′, C-1″, and C-1‴), 115.1 (C-6′), 122.5 (C-5′), 127.3 (C-1′), 144.1 (C-4′), 145.3 (C-7′), 146.5 (C-3′), 166.4 (C-9′), 174.9(C-7). APCI-MS (negative): 825.8 ([M − H]$^-$, 100%).

1,7-Pelargonaldehyde 3,4-Pelargonaldehyde-chlorogenic Acid Diacetal (35−38). After synthesis using pelargonaldehyde and purification on ODS, an isomeric mixture was obtained from 90% MeOH eluted part (yield: 70.5%). This mixture was purified using preparative HPLC eluted with 90−100% MeOH in 60 min at a flow rate of 5 mL/min to obtain **37** at 43 min, **38** at 46 min, and a mixture of **35** and **36** at 38 min, in a ratio of 2.0:3.6:2.0. The mixture of **35** and **36** was further applied to the same preparative HPLC eluted with 90−96% MeOH in 60 min at a flow rate of 5 mL/min to obtain **35** at 44 min and **36** at 45 min in a ratio of about 1:1. **35**, crystalline powder; $[\alpha]_D$ −25.8 (c 0.3, $CHCl_3$) mp 62−63 °C. ^{1}H NMR ($CDCl_3$) δ 0.88 [m, 6H, $-(CH_2)_7C\underline{H}_3$], 1.26 (m, 20H) and 1.44 (m, 4H) and 1.75 (m, 2H) and 1.84 [$-(C\underline{H}_2)_7CH_3$], 2.02 (dd, J = 10.0, 14.0 Hz, 1H, H-6a), 2.14 (dd, J = 5.0, 16.0 Hz, 1H, H-2a), 2.24 (m, 1H, H-6b), 2.43 (d, J = 15.0 Hz, 1H, H-2b), 4.22 (t, J = 6.5 Hz, 1H, H-4), 4.38 (m, H-3), 5.02 (t, J = 4.5 Hz, 1H, H-1‴), 5.21 (m, 1H, H-5), 5.65 (t, J = 4.5 Hz, 1H, H-1″), 6.15 (d, J = 15.5 Hz, 1H, H-8′), 6.82 (d, J = 8.5 Hz, 1H, H-5′), 6.90 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.00 (d, J = 2.0 Hz, 1H, H-2′), 7.55 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 14.1 [$-(CH_2)_7\underline{C}H_3$], 22.6 and 22.8 and 23.6 and 29.1 and 29.2 and 29.4 and 29.5 and 29.8 and 31.8 and 34.0 and 34.3 and 34.5 [$-(\underline{C}H_2)_7CH_3$ and C-6 and C-2], 70.1 (C-5), 73.7 (C-3), 75.1 (C-4), 77.4 (C-1), 104.1 (C-1‴), 105.2 (C-1‴), 114.3 (C-2′), 114.8 (C-8′), 115.3 (C-5′), 122.5 (C-6′), 127.2 (C-1′), 144.0 (C-3′), 145.7 (C-7′), 146.5 (C-4′), 166.7 (C-9′), 174.7 (C-7). Important NOE correlations: H-1″ and H-2, H-1‴ and H-3. ESI-MS (negative): 601.4 ([M − H]$^-$, 100%). **36**, white wax-like powder; $[\alpha]_D$ −40.9 (c 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 0.87 [m, 6H, $-(CH_2)_7C\underline{H}_3$], 1.30 [m, 24H, $-CH_2(C\underline{H}_2)_6CH_3$], 1.61 [m, 2H, 1‴-$C\underline{H}_2(CH_2)_6CH_3$], 1.83 (m, 2H, 1″-$CH_2(C\underline{H}_2)_6CH_3$], 1.95 (dd, J = 12.5, 13.5 Hz, 1H, H-6a), 2.02 (dd, J = 4.5, 15.5 Hz, 1H, H-2a), 2.24 (m, 1H, H-6b), 2.43 (d, J = 15.5 Hz, 1H, H-2b), 4.31 (dd, J = 5.0, 8.0 Hz, 1H, H-4), 4.41 (m, H-3), 5.34 (m, 2H, H-5 and H-1‴), 5.65 (dd, J = 4.0, 5.5 Hz, 1H, H-1″), 6.19 (d, J = 15.5 Hz, 1H, H-8′), 6.84 (d, J = 8.5 Hz, 1H, H-5′), 6.94 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.01 (d, J = 2.0 Hz, 1H, H-2′), 7.55 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR (CD_3OD) δ 14.1 [$-(CH_2)_7\underline{C}H_3$], 22.6 and 22.7 and 23.6 and 29.1 and 29.3 and 29.4 and 30.2 and 31.8 and 34.4 and 34.8 and 35.4 [$-(\underline{C}H_2)_7CH_3$ and C-6 and C-2], 67.5 (C-5), 72.5 (C-3), 77.0 (C-4), 77.8 (C-1), 104.1 (C-1″), 104.3 (C-1‴), 114.4 (C-2′), 114.7 (C-8′), 115.4 (C-5′), 122.5 (C-6′), 127.2 (C-1′), 144.0 (C-3′), 145.8 (C-7′), 146.6 (C-4′), 166.9 (C-9′), 174.2 (C-7). Important NOE correlations: H-1″ and H-2, 1‴-$C\underline{H}_2$ and H-3. ESI-MS (negative): 601.4 ([M − H]$^-$, 100%). **37**: crystalline powder; $[\alpha]_D$ −36.7 (*c* 1.34, $CHCl_3$); mp 138−140 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 [m, 6H, $-(CH_2)_7C\underline{H}_3$], 1.27 (m, 20H) and 1.43 (m, 4H)[$-CH_2(C\underline{H}_2)_6CH_3$], 1.80 [m, 5H, $C\underline{H}_2(CH_2)_6CH_3$ and H-6a], 2.36 (m, 3H, H-2a, 2b and 6b), 4.21 (t, J = 6.5 Hz, 1H, H-4), 4.39 (m, H-3), 5.04 (t, J = 4.5 Hz, 1H, H-1‴), 5.17 (m, 1H, H-5), 5.62 (t, J = 4.5 Hz, 1H, H-1″), 6.10 (d, J = 15.5 Hz, 1H, H-8′), 6.80 (d, J = 8.5 Hz, 1H, H-5′), 6.86 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 6.98 (d, J = 2.0 Hz, 1H, H-2′), 7.50 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 14.1 [$-(CH_2)_7\underline{C}H_3$], 22.6 and 22.8 and 23.6 and 29.1 and 29.2 and 29.3 and 29.4 and 30.5 and 31.8 and 32.9 and 34.1 [$-(\underline{C}H_2)_7CH_3$ and C-6 and C-2], 70.4 (C-5), 74.1 (C-3), 75.2 (C-4), 77.6 (C-1), 103.7 (C-1″), 105.2 (C-1‴), 114.3 (C-2′), 114.4 (C-8′), 115.3 (C-5′), 122.6 (C-6′), 127.1 (C-1′), 144.1 (C-3′), 145.9 (C-7′), 146.7 (C-4′), 167.0 (C-9′), 174.4 (C-7). Important NOE correlations: H-1″ and H-6, 1‴ and H-3. ESI-MS (negative): 601.4 ([M − H]$^-$, 100%). **38**: crystalline powder; $[\alpha]_D$ −55.9 (c 0.3, $CHCl_3$); mp 101−103 °C. ^{1}H NMR ($CDCl_3$) δ 0.87 [m, 6H, $-(CH_2)_7C\underline{H}_3$], 1.25 (m, 20H) and 1.40 (m, 4H)[$-CH_2(C\underline{H}_2)_6CH_3$], 1.61 (m, 2H, 1‴-$C\underline{H}_2(CH_2)_6CH_3$], 1.67 (t, J = 12.5 Hz, 1H, H-6a), 1.84 [m, 2H, 1‴-$C\underline{H}_2(CH_2)_6CH_3$], 2.32 (partly overlapped, H-2a and 2b), 2.39 (partly overlapped, H-6b), 4.30 (dd, J = 5.0, 8.0 Hz, 1H, H-4), 4.44 (m, H-3), 5.29 (m, 1H, H-5), 5.36 (t, J = 5.0 Hz, 1H, H-1‴), 5.62 (t, J = 4.5 Hz, 1H, H-1″), 6.15 (d, J = 15.5 Hz, 1H, H-8′), 6.83 (d, J = 8.5 Hz, 1H, H-5′), 6.93 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 9.01 (br s, 1H, H-2′), 7.53 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 14.1 [$-(CH_2)_7\underline{C}H_3$], 22.6 and 22.6 and 23.7 and 29.1 and 29.2 and 29.3 and 29.4 and 31.1 and 31.8 and 33.3 and 34.0 and 34.9 [$-(\underline{C}H_2)_7CH_3$ and C-6 and C-2], 67.7 (C-5), 72.5 (C-3), 76.8 (C-4), 70.0 (C-1), 103.8 (C-1‴), 104.2 (C-1″), 114.4 (C-2′), 114.6 (C-8′), 115.5 (C-5′), 122.6 (C-6′), 127.2 (C-1′), 144.0 (C-3′), 145.9 (C-7′), 146.6 (C-4′), 167.1 (C-9′), 174.1 (C-7). Important NOE correlations: H-1″ and H-5, 1‴-$C\underline{H}_2$ and H-3. ESI-MS (negative): 601.5 ([M − H]$^-$, 100%).

General Method for the Synthesis of 1,7-Chlorogenic Acid Ketals and 1,7-Chlorogenic Acid Acetals. The diketal or diacetal (**22**−**25**, **35**−**38**) was stirred at room temperature for 1 h in a MeOH−H_2O (8:2) solution containing 0.4 N HCl. The mixture was neutralized with 1N NaOH to pH 6 and was subjected to evaporation to remove MeOH. The residue was purified using an ODS column eluted with MeOH−H_2O to yield the 1,7-chlorogenic acid ketals or 1,7-chlorogenic acid acetals.

1,7-(Acetone)-chlorogenic Acid Ketal (1,7-Chlorogenic Acid Acetonide (1). The title compound was obtained from 60% MeOH eluted part of an ODS column after acid hydrolysis of **21** (yield: 79.6%). **1**: crystalline powder; $[\alpha]_D$ −7.6 (*c* 0.7, MeOH); mp 88−90 °C. ^{1}H NMR (CD_3OD, 500 MHz) δ 1.61 (s, 3H) and 1.62 (s, 3H) ($-CH_3$), 1.91 (dd, J = 10.5, 13.5 Hz, 1H, H6a), 2.06 (dd, J = 14.5, 3.5 Hz, 1H, H-2a), 2.13 (m, 1H, H-2b), 2.30 (m, 1H, H-6b), 3.72 (dd, J = 3.5, 9.5 Hz, 1H, H-4), 4.23 (m, 1H, H-3), 5.35 (m, 1H, H-5), 6.28 (d, J = 15.5 Hz, 1H, H-8′), 6.78 (d, J = 8.0 Hz, 1H, H-5′), 6.94 (dd, J = 2.0, 8.0 Hz, 1H, H-6′), 7.05 (d, J = 2.0 Hz, 1H, H-2′), 7.59 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR (CD_3OD) δ 28.5 and 28.6 ($\underline{C}H_3$), 39.2 (C-2 and C-6), 70.4 (C-3), 70.8 (C-5), 73.4 (C-4), 81.0 (C-1), 112.1 (C-1″), 115.2 (C-2′ and 8′), 116.5 (C-5′), 123.0 (C-6′), 127.7 (C-1′), 146.7 (C-4′), 147.2

(C-7′), 149.5 (C-3′), 168.8 (C-9′), 175.4 (C-7). ESI-MS (negative): 393.3 ([M − H]$^-$, 100%).

1,7-(3-Pentanone) Ketal (2). The title compound was obtained from 70% MeOH eluted part of an ODS column after acid hydrolysis of **22** (yield: 71.5%). **2**: crystalline powder; $[\alpha]_D$ +4.4 (*c* 0.5, MeOH); mp 103−105 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 0.97 (m, 6H, $-CH_2C\underline{H}_3$), 1.84 (m, 5H, $-C\underline{H}_2CH_3$ and H-6a), 2.08 (br d, J = 14.0 Hz, 1H, H-2a), 2.20 (br d, J = 14.0 Hz, 1H, H-2b), 2.34 (br d, J = 12.0 Hz, 1H, H-6b), 3.73 (br d, J = 6.5 Hz, 1H, H-4), 4.26 (br s, 1H, H-3), 5.35 (m, 1H, H-5), 6.17 (d, J = 15.5 Hz, 1H, H-8′), 6.80 (br s, 1H, H-5′), 6.84 (d, J = 7.5 Hz, 1H, H-6′), 7.01 (br s, 1H, H-2′), 7.53 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$−CD_3OD) δ 7.3 ($-CH_2\underline{C}H_3$), 31.0 ($-\underline{C}H_2CH_3$), 31.1 ($-\underline{C}H_2CH_3$), 37.2 (C-2), 37.7 (C-6), 69.4 (C-4), 69.6 (C-3), 72.7 (C-5), 79.5 (C-1), 113.7 (C-2′), 114.0 (C-8′) 115.2 (C-5′), 115.3 (C-1″), 122.2 (C-6′), 126.4 (C-1′), 144.6 (C-4′), 146.2 (C-7′), 147.5 (C-3′), 167.7 (C-9′), 173.4 (C-7). ESI-MS (negative): 421.3 ([M − H]$^-$, 100%).

1,7-(4-Heptanone) Ketal (3). After acid hydrolysis of **23** and purification on ODS, **Cr3** was obtained from 50−60% MeOH eluted part (yield: 81.0%). **3**: crystalline powder: $[\alpha]_D$ +9.9 (*c* 0.06, MeOH); mp 180−182 °C. ^{1}H NMR (CD_3OD) δ 0.98 (m, 6H, $-CH_2CH_2C\underline{H}_3$), 1.46 (m, 4H) and 1.79 (m, 5H) ($-C\underline{H}_2C\underline{H}_2CH_3$), 1.86 (dd, J = 11.0, 13.5 Hz, 1H, H-6a), 2.05 (dd, J = 3.0, 15.0 Hz, 1H, H-2a), 2.14 (m, 1H, H-2b), 2.29 (m, 1H, H-6b), 3.73 (dd, J = 3.5, 9.0 Hz, 1H, H-4), 4.22 (dd, J = 3.5, 6.5 Hz, 1H, H-3), 5.31 (m, 1H, H-5), 6.28 (d, J = 15.5 Hz, 1H, H- H-8′), 6.78 (d, J = 8.5 Hz, 1H, H-5′), 6.92 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.05 (d, J = 2.0 Hz, 1H, H-2′), 7.59 (d, J = 15.5 Hz, 1H, H-7′).^{13}C NMR (CD_3OD) δ 14.3 and 14.4($-CH_2CH_2C\underline{H}_3$), 17.7 and 17.8 ($-CH_2C\underline{H}_2CH_3$), 39.0 ($-\underline{C}$-2 and C-6), 41.9 and 42.2 ($-\underline{C}H_2CH_2CH_3$), 70.4 (C-3), 71.0 (C-5), 73.4 (C-4), 80.7 (C-1), 115.0 and 115.2 (C-2′, 8′, 1″), 116.5 (C-5′), 123.0 (C-6′), 127.8 (C-1′), 146.8 (C-4′), 147.2 (C-7′), 149.6 (C-3′), 168.8 (C-9′), 175.6 (C-7). ESI-MS (negative): 449.2 ([M − H]$^-$, 100%).

1,7-(5-Nonanone) Chlorogenic Acid Ketal (4). After acid hydrolysis of **24 a**nd purification on ODS, **4** was obtained from 60% MeOH eluted part (yield: 81.2%) as a crystalline powder, $[\alpha]_D$ +17.8 (*c* 0.4, MeOH); mp 194−195 °C. ^{1}H NMR (CD_3OD) δ 0.97 (m, 6H, $-CH_2CH_2CH_2C\underline{H}_3$), 1.41 (m, 8H) and 1.87 (m, 5H) ($-C\underline{H}_2C\underline{H}_2$-$C\underline{H}_2CH_3$, and H-6a), 2.08 (dd, J = 3.0, 15.0 Hz, 1H, H-2a), 2.16 (m, 1H, H-2b), 2.32 (m, 1H, H-6b), 2.29 (m, 1H, H-2b), 3.73 (dd, J = 3.5, 9.0 Hz, 1H, H-4), 4.23 (dd, J = 3.5, 6.5 Hz, 1H, H-3), 5.34 (m, 1H, H-5), 6.30 (d, J = 15.5 Hz, 1H, H-8′), 6.80 (d, J = 8.5 Hz, 1H, H-5′), 6.97 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.07 (d, J = 2.0 Hz, 1H, H-2′), 7.62 (d, J = 15.5 Hz, 1H, H-7′).^{13}C NMR (CD_3OD) δ 14.3 ($-CH_2CH_2CH_2\underline{C}H_3$), 23.6 ($-CH_2CH_2\underline{C}H_2CH_3$), 26.5 and 26.6 ($-CH_2\underline{C}H_2CH_2CH_3$), 39.1 (C-2, 6), 39.5 and 39.7 ($-\underline{C}H_2CH_2$-CH_2CH_3), 70.4 (C-3), 70.9 (C-5), 73.4 (C-4), 80.7 (C-1), 115.0 (C-2′), 115.2 (C-1″ and C-8′), 116.5 (C-5′), 123.0 (C-6′), 127.8 (C-1′), 146.8 (C-3′), 147.2 (C-7′), 149.6 (C-4′), 168.7 (C-9′), 175.6 (C-7). ESI-MS (negative): 477.3 ([M − H]$^-$, 100%).

1,7-(6-Undecanone) Chlorogenic Acid Ketal (5). After acid hydrolysis of **25** and purification on ODS, **5** was obtained from 80% MeOH eluted part (yield: 76.3%) of an ODS column as a crystalline powder, $[\alpha]_D$ +22.2 (*c* 0.6, MeOH); mp 171−172 °C. ^{1}H NMR ($CDCl_3$ + CD_3OD 1:1) δ 0.91 (m, 6H, $-CH_2CH_2$-$CH_2CH_2C\underline{H}_3$), 1.32 (m, 8H, $-CH_2CH_2C\underline{H}_2C\underline{H}_2CH_3$), 1.42 (m, 4H, $-CH_2C\underline{H}_2CH_2CH_2CH_3$), 1.83 (m, 4H, $-C\underline{H}_2CH_2CH_2CH_2CH_3$), 1.93 (dd, J = 11.0, 13.0 Hz, 1H, H-6a), 2.09 (dd, J = 3.0, 15.0 Hz, 1H, H-2a), 2.20 (m, 1H, H-2b), 2.34 (m, 1H, H-6b), 3.72 (dd, J = 3.5, 9.5 Hz, 1H, H-4), 4.24 (m, H-3), 5.34 (m, 1H, H-5), 6.26 (d, J = 15.5 Hz, 1H, H-8′), 6.82 (d, J = 8.5 Hz, 1H, H-5′), 6.93 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.06 (d, J = 2.0 Hz, 1H, H-2′), 7.62 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$ + CD_3OD 1:1) δ 13.4 ($-CH_2CH_2CH_2CH_2\underline{C}H_3$), 22.0 and 22.5 and 22.6 and 31.2 and 37.2 and 37.6 and 38.4 and 38.5 ($-\underline{C}H_2\underline{C}H_2\underline{C}H_2\underline{C}H_2CH_3$ and C-2, C-6), 69.1 (C-3), 69.2 (C-5), 72.3 (C-4), 79.2 (C-1), 113.6 and 114.4 and 115.0 (C-2′,1″, C-8′, and C-5′), 121.8 (C-6′), 126.2 (C-1′), 144.7 (C-3′), 145.9 (C-7′), 147.5 (C-4′), 167.3 (C-9′), 173.7 (C-7). ESI-MS (negative): 505.4 ([M − H]$^-$, 100%).

1,7-(6-Undecanone) Chlorogenic Acid Ketal (6). After acid hydrolysis of **26** and purification on ODS, **6** was obtained from 90% MeOH eluted part (yield: 72.6%) of an ODS column as an amorphous powder, $[\alpha]_D$ +20.9 (*c* 0.2, MeOH). ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 6H, $-(CH_2)_5C\underline{H}_3$), 1.28 (m, 16H, $-CH_2(C\underline{H}_2)_4CH_3$), 1.80 (m, 4H, $-C\underline{H}_2(CH_2)_4CH_3$), 1.93 (t, J = 12.5 Hz, 1H, H-6a), 2.10 (dd, J = 3.0, 15.0 Hz, 1H, H-2a), 2.25 (br d, J = 15.0, 1H, H-2b), 2.34 (br dd, J = 2.5, 12.5 Hz, 1H, H-6b), 3.74 (dd, J = 3.5, 9.5 Hz, 1H, H-4), 4.27 (br s, H-3), 5.37 (m, 1H, H-5), 6.11 (d, J = 15.5 Hz, 1H, H-8′), 6.80 (d, J = 8.5 Hz, 1H, H-5′), 6.83 (br d, J = 8.5 Hz, 1H, H-6′), 6.98 (br s, J = 2.0 Hz, 1H, H-2′), 7.48 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.1 ($-(CH_2)_5\underline{C}H_3$), 22.6 and 23.4 and 29.2 and 31.6 and 37.4 and 38.1 and 38.9 ($-(\underline{C}H_2)_5CH_3$ and C-2, C-6), 69.6 (C-3), 70.1 (C-5), 73.5 (C-4), 79.6 (C-1), 114.2 and 114.5 and 114.9 and 115.5 (C-2′, C-1″, C-8′, and C-5′), 122.4 (C-6′), 126.9 (C-1′), 143.9 (C-3′), 146.0 (C-7′), 146.7 (C-4′), 167.4 (C-9′), 172.7 (C-7). ESI-MS (negative): 533.4 ([M − H]$^-$, 100%)

1,7-(8-Pentadecanone) Chlorogenic Acid Ketal (7). After acid hydrolysis of **27** and purification on a silica gel column, **7** was obtained from $CHCl_3$−MeOH 9:1 eluted part (yield: 40.1%, and 41.0% of **27** was recovered) as a wax; $[\alpha]_D$ +20.8 (*c* 0.3, MeOH). ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.5 Hz, 3H) and 0.89 (t, J = 7.0 Hz, 3H) ($-(CH_2)_6C\underline{H}_3$), 1.26 (m, 16H, $-(CH_2)_2(C\underline{H}_2)_4CH_3$), 1.37 (m, 4H, $-CH_2C\underline{H}_2(CH_2)_4CH_3$), 1.78 (m, 4H, $-C\underline{H}_2(CH_2)_5CH_3$), 1.93 (br t, J = 12.5 Hz, 1H, H-6a), 2.10 (br d, J = 14.5 Hz, 1H, H-2a), 2.23 (br d, J = 14.5 Hz, 1H, H-2b), 2.30 (br d, 1H, J = 12.5 Hz, H-6b), 3.75 (br d, J = 14.0 Hz, 1H, H-4), 4.28 (br s, H-3), 5.38 (m, 1H, H-5), 6.06 (d, J = 15.5 Hz, 1H, H-8′), 6.78 (br s, 2H, H-2′,6′), 6.95 (br s, 1H, H-5′), 7.44 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$) δ 14.0 ($-(CH_2)_6\underline{C}H_3$), 22.6 and 23.3 and 29.0 and 29.4 and 31.6 and 38.8 ($-(\underline{C}H_2)_6CH_3$), 37.3 (C-2), 38.0 (C-6), 69.3 (C-5), 70.1 (C-3), 73.4 (C-4), 79.4 (C-1), 113.8 (C-8′), 114.5 (C-5′), 114.7 (C-1″), 115.4 (C-2′), 122.3 (C-6′), 126.6 (C-1′), 144.0 (C-3′), 146.0 (C-7′), 146.9 (C-4′), 167.4 (C-9′), 172.5 (C-7). APCI-MS (negative): 561.5.4 ([M − H]$^-$, 100%).

1,7-(9-Heptadecanone) Chlorogenic Acid Ketal (8). After acid hydrolysis of **28** in 95% MeOH and purification on a silica gel column, **8** was obtained from $CHCl_3$−MeOH 9:1 eluted part (yield: 80.3%) as a wax; $[\alpha]_D$ +24.1 (*c* 0.3, MeOH). ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 6.5 Hz, 3H) and 0.89 (t, J = 7.0 Hz, 3H) ($-(CH_2)_7C\underline{H}_3$), 1.26 (m, 20H, $-(CH_2)_2(C\underline{H}_2)_5CH_3$), 1.36 (m, 4H, $-CH_2C\underline{H}_2(CH_2)_5CH_3$), 1.78 (m, 4H, $-C\underline{H}_2(CH_2)_6CH_3$), 1.94 (br t, J = 12.5 Hz, 1H, H-6a), 2.11 (dd, J = 2.5, 14.5 Hz, 1H, H-2a), 2.25 (br d, J = 14.5 Hz, 1H, H-2b), 2.31 (br d, 1H, J = 12.5 Hz, H-6b), 3.75 (dd, J = 3.0, 10.5 Hz, 1H, H-4), 4.29 (br s, H-3), 5.38 (m, 1H, H-5), 6.06 (d, J = 16.0 Hz, 1H, H-8′), 6.78 (br s, 2H, H-2′,6′), 6.95 (br s, 1H, H-5′), 7.45 (d, J = 16.0 Hz, 1H, H-7′). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 14.2 ($-(CH_2)_7\underline{C}H_3$), 22.7 and 23.4 and 29.2 and 29.4 and 29.5 and 31.9 and 38.9 ($-(\underline{C}H_2)_7CH_3$), 37.4 (C-2), 38.1 (C-6), 69.5 (C-5), 70.2 (C-3), 73.5 (C-4), 79.5 (C-1), 114.0 (C-8′), 114.6 (C-5′), 114.9 (C-1″), 115.5 (C-2′), 122.4 (C-6′), 126.8 (C-1′), 144.0 (C-3′), 146.1 (C-7′), 146.8 (C-4′), 167.5 (C-9′), 172.7 (C-7). APCI-MS (negative): 589.5 ([M − H]$^-$, 100%).

1,7-Pelargonaldehyde-chlorogenic Acid Acetal (33−34). A mixture of the isomers **33** and **34** (78.7%) was obtained from 70% MeOH eluted part of an ODS column after acid treatment of **35**−**38**. This mixture was purified using preparative HPLC eluted with 70−80% MeOH in 60 min to obtain **33** at 27 min and **34** at 29 min, respectively. **33**, crystalline powder; $[\alpha]_D$ −14.3 (*c* 0.1, CH_3OH); mp 115−117 °C. ^{1}H NMR (CD_3OD) δ 0.90 [t, J = 6.5 Hz, 3H, $-(CH_2)_7C\underline{H}_3$], 1.38 (m, 10H) and 1.47 (m, 2H) and 1.80 [m, 2H, $-(C\underline{H}_2)_7CH_3$], 1.85 (overlapped, H-2a), 1.96 (dd, J = 13.0, 11.0 Hz, 1H, H-6a), 2.20 (m, 1H, H-6b), 2.30 (m, 1H, H-2b), 3.72 (dd, J = 3.5, 9.5 Hz, 1H, H-4), 4.21 (m, H-3), 5.36 (m, 1H, H-5), 5.69 (t, J = 4.5 Hz, 1H, H-1″), 6.29 (d, J = 15.5 Hz, 1H, H-8′), 6.78 (d, J = 8.5 Hz, 1H, H-5′), 6.95 (dd, J = 2.0, 8.5 Hz, 1H, H-6′), 7.05 (d, J = 2.0 Hz, 1H, H-2′), 7.60 (d, J = 15.5 Hz, 1H, H-7′). ^{13}C NMR (CD_3OD) δ 14.4 [$-(CH_2)_7CH_3$], 23.7 and 30.3 and 30.4 and 30.6 and 33.0 and 34.0 and 35.2 and 38.3 [$-(CH_2)_7CH_3$ and C-2, C-6], 70.6 (C-3), 70.7 (C-5), 73.8 (C-4),

80.6 (C-1), 104.7 (C-1″), 115.1 (C-8′), 115.2 (C-2′), 115.2 (C-5′), 123.0 (C-6′), 127.8 (C-1′), 145.3 (C-3′), 146.8 (C-4′), 147.1 (C-7′), 168.8 (C-9′), 175.7 (C-7). Important NOE correlation: H-1′ and H-2. ESI-MS (negative): 477.3 ($[M - H]^-$, 100%). **34**, crystalline powder; $[\alpha]_D$ −9.8 (*c* 0.5, CH_3OH); mp 106−108 °C. ^1H NMR (CD_3OD) δ 0.92 [t, $J = 6.5$ Hz, 3H, $-(CH_2)_7\underline{CH_3}$], 1.38 (m, 10H) and 1.48 (m, 2H) and 1.84 [m, 2H, $-(\underline{CH_2})_7CH_3$], 1.79 (overlapped, H-6a), 2.11 (m, 2H, H-2a, 2b), 2.43 (m, 1H, H-6b), 3.76 (dd, $J =$ 3.5, 9.5 Hz, 1H, H-4), 4.27 (m, H-3), 5.34 (m, 1H, H-5), 5.71 (t, $J = 4.5$ Hz, 1H, H-1″), 6.29 (d, $J = 15.5$ Hz, 1H, H-8′), 6.79 (d, $J = 8.5$ Hz, 1H, H-5′), 6.96 (dd, $J = 2.0$, 8.5 Hz, 1H, H-6′), 7.06 (d, $J = 2.0$ Hz, 1H, H-2′), 7.60 (d, $J = 15.5$ Hz, 1H, H-7′). ^{13}C NMR (CD_3OD) δ 14.4 [$-(CH_2)_7\underline{C}H_3$], 23.7 and 23.8 and 30.3 and 30.4 and 30.6 and 33.0 and 35.1 [$-(\underline{C}H_2)_7CH_3$], 33.5 (C-6), 38.3 (C-2), 69.8 (C-3), 70.9 (C-5), 73.3 (C-4), 80.6 (C-1), 104.5 (C-1″), 115.1 (C-8′ and C-2′), 116.5 (C-5′), 123.0 (C-6′), 127.8 (C-1′), 146.8 (C-3′), 147.3 (C-4′), 149.6 (C-7′), 168.7 (C-9′), 175.7 (C-7). Important NOE correlation: H-1′ and H-6. ESI-MS (negative): 477.3 ($[M - H]^-$, 100%).

Biological Methods

α-Glucosidase Inhibitory Assay. The α-glucosidase inhibitory activity was determined using the procedure reported by Hakamata et al.[3] with modifications for carrying out in 96-well plates. Briefly, each well of the plates contained 40 μL of 2 mM 4-nitrophenyl α-D-glucopyranoside (purchased from TCI) in 100 mM potassium phosphate buffer (pH 7.0) and 5 μL of sample in DMSO. The reaction was initiated by the addition of 5 μL of the enzyme solution (0.30 μu/ml from *Bacillus stearothermophilus*, or 0.667 μu /ml from *Saccharomyces cerevisiae*). The plates were incubated at 37 °C for 20 min. The absorbance at 405 nm before and after incubation was measured with an InterMed ImmunoReader (Nippon InterMed K.K. Tokyo, Japan). The increased absorbance (ΔA) was compared with that of the control (DMSO in place of sample solution) to calculate the inhibition.

$$\% \text{ inhibition} = (\Delta A_{\text{control}} - \Delta A_{\text{sample}})/\Delta A_{\text{control}}$$

Stability Test. The artificial gastric juice was prepared by mixing 1.64 mL of 1N HCl and 1 g of pepsin (Sigma P7000) in 80 mL of distilled H_2O and diluting to 100 mL. Artificial intestine juice was prepared by mixing 0.68 g of KH_2PO_4 and 1 g of pancreatin (sigma p7545) in 30 mL of H_2O, adjusting by 0.5N NaOH to pH 6.8 and diluting to 100 mL. For the stability test, 5 μL of 10 mM **38** was added to vials containing 45 μL of the artificial gastric juice or intestine juice and the mixture was incubated at 37 °C. The reaction was stopped by adding 0.5 mL of MeOH to the vials. The vials were centrifuged and the supernatants were analyzed by LC-PAD-MS on a COSMOSIL 5C18-MS-II Waters column (150 mm × 4.6 mm i.d.; Nacalai Tesque, Inc. Kyoto, Japan) with a flow rate of 1 mL/min. The mobile phase contained solvents A and B, where A was 0.1% formic acid in water and B was 0.1% formic acid in acetonitrile. The linear gradient profile was from 20 to 100% B in 10 min and maintained at 100% B for 5 min. Peak areas detected at 320 nm were used to quantify **38** and its hydrolyzed produced **34**.

Supporting Information Available: HPLC charts, NMR spectra, and 3D models of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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