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Synthesis of long-chain fatty acid derivatives as a novel anti-Alzheimer's agent

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ABSTRACT

In order to develop new drugs for Alzheimer's disease, we prepared 17 fatty acid derivatives with different chain lengths and different numbers and positions of double bonds by using Wittig reaction and stereospecific hydrogenation of triple bonds as key reactions. Among them, (4*Z*,15*Z*)-octadecadienoic acid (**10**) and (23*Z*,34*Z*)-heptatriacontadienoic acid (**16**) showed the most potent neurite outgrowth activities on Aβ(25–35)-treated rat cortical neurons, which activities were comparable to that of a positive control, NGF. Both fatty acids **10** and **16** possess two (*Z*)-double bonds at the *n*-3 and *n*-14 positions, which might be important for the neurite outgrowth activity.

Fatty acids play a very important role in human health, growth, and development as an energy source, signaling molecules, and a structural component of membranes. In particular, long-chain polyunsaturated fatty acids (LCPUFA) including the *n*-6 fatty acids (e.g., arachidonic acid, AA) and the *n*-3 fatty acids (e.g., docosahexaenoic acid, DHA; eicosapentaenoic acid, EPA) are known to be nutritionally important fatty acids; they are essential for neurocognitive development and normal brain functions.[1] In addition, supplementation of LCPUFA are important for the development of childhood intelligence,[2] cognitive function,[3] prevention of dementia in later life.[4] Whereas several studies reported that LCPUFA such as AA, DHA, and EPA are of significant benefit in the prevention and treatment of Alzheimer's disease and other dementias by promoting neurite outgrowth.[5]

Alzheimer's disease, the most common form of dementia, is a progressive and fatal neurodegenerative disease affecting the elderly population with a prevalence rising from 1% at the age of 60 to at least 35% at the age of 90 years.[6] The growing number of elderly and the continuing expansion of life expectancy lead to a fast increase in the number of patients suffering from Alzheimer's disease. It was reported that the numbers of people with dementia were about 36.5 million worldwide in 2010.[7] Despite the great number of ongoing investigations, effective treatment is lacking. Donepezil hydrochloride, a cholinesterase inhibitor, is clinically used in the treatment of Alzheimer's disease,[8] but it plays a role just slowing the progression of the disease, rather than to cure it.[9] Therefore, the development of alternative approaches and novel agents are urgently needed for the treatment of Alzheimer's disease. Alzheimer's disease is caused by the irreversible neuronal degeneration and atrophy in the central nervous system, involving neuronal death, neuritic atrophy, and synaptic loss.[10] Actually, reinforce the neuronal networks in the damage brain might be possible by reformation of synapses and regeneration of neurite through the activation of remaining healthy neurons.[11]

In a course of our study on anti-Alzheimer's desease, we found that a $CHCl_3$ extract of *Rosa damasene* (Rosaceae) from Iran and its active constituent displayed pronounced neurite outgrowth activity under neuritic atrophy condition and the active constituent (**A**) displayed potent neurite outgrowth activity comparable to a positive control, nerve growth factor (NGF) (Fig. 1). Chemical analysis of the active constituent suggested it to be a very long-chain

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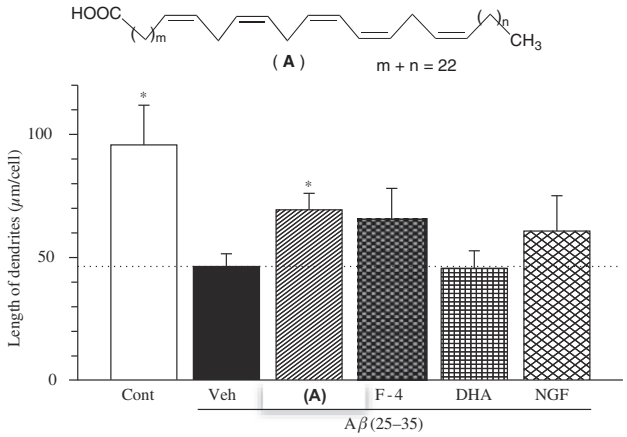


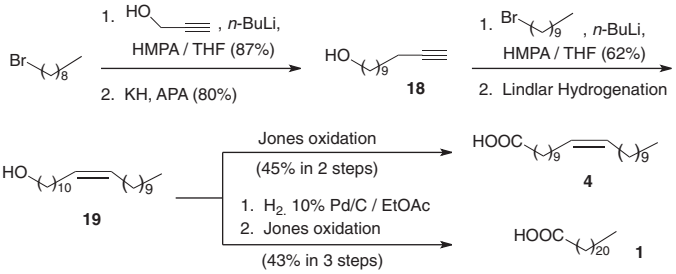
Figure 1. Dendrite extension activities of compound (A) in Aβ(25–35)-treated rat cortical neurons. Aβ(25–35), 10 μM; compound (A), 1 μM; subfraction F-4, from which compound (A) was isolated, 5 μg/mL; DHA, 1 μM; NGF, 100 ng/mL; Veh, 0.1% DMSO.

(C_{37}) polyunsaturated fatty acid although its total structure could not be determined due to a minor amount obtained. Thus, we presumed the active constituent to be a *n*-3 fatty acid by the analogy with EPA and DHA, and started to synthesize a series of fatty acids to find out anti-Alzheimer's reagent. In this letter, we would like to report the results on fatty acids with one and two double bonds (**1**–**17**, Fig. 2).

First, we synthesized four mono-unsaturated fatty acids with C_{22}, C_{28}, C_{37}, and C_{41} chain length (**4**, **6**, **8**, and **9**, respectively) and three saturated fatty acids with C_{22}, C_{28}, and C_{37} chain length (**1**, **2**, and **3**, respectively).

As shown in Scheme 1, (*Z*)-docos-11-enoic acid (**4**) and its saturated fatty acid, docosanoic acid (**1**), were synthesized by using 1-bromononane as a starting material, which was reacted with propargylic alcohol in the presence of *n*-BuLi and HMPA to afford a homologated alcohol. This alcohol was subjected to prototropic migration of triple bond with KH and 1,3-diaminopropane (APA) to form the desired terminal acetylenic alcohol **18**.[12] Alcohol **19** was obtained by the alkylation of **18**, followed by the Lindlar hydrogenation.[13,14] Finally, Jones oxidation of **19** gave fatty acid **4** with C_{22} chain length and one double bond of *cis*-configuration at the position Δ2. The corresponding saturated C_{22} fatty acid **1** was also prepared by catalytic hydrogenation of **19** over 10% Pd/C and subsequent Jones oxidation of the resulting saturated alcohol.

The synthesis of (*Z*)-octacos-14-enoic acid (**6**) and octacosanoic acid (**2**) was started with the preparation of aldehyde **20** as shown in Scheme 2. Thus, *Z*-selective Wittig reaction between aldehyde **20** and the ylide of C_{14}-phosphonium salt **21** in the presence of



Scheme 1. Synthesis of fatty acids **1** and **4**.

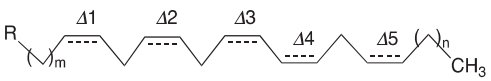
$NaN(SiMe_3)_2$ under the salt-free conditions[14] furnished a TBDPS-protected alcohol which has a desired double bond of *cis*-configuration at the position Δ1. The TBDPS protecting group was removed with TBAF to form the corresponding alcohol **5**. Finally, the same reactions were effected as the preparation of **4** and **1**, mono-unsaturated C_{28} fatty acid **6** and corresponding saturated fatty acid **2** were obtained.

According to the procedure of Weber et al.,[15] 1,18-octadecanedicarboxylic acid was converted to its methyl ester and subsequent reduction by LAH reagent to afford the diol, which was mono-protected by TBDPS.[16] A key common aldehyde **22** was synthesized from the TBDPS mono-protected alcohol in 4 steps: (1) iodination,[17] (2) reaction with propargylic alcohol,[18] (3) catalytic hydrogenation, and (4) PCC oxidation.

Wittig reaction between the aldehyde **22** and the ylide of C_{18}-phosphonium salt **23** was effected as described in Scheme 3. After deprotection and oxidation of the product, (*Z*)-hentetracont-23-enoic acid (**9**) having one double bond of *cis*-configuration at the position Δ1 and C_{41} chain length was obtained. In a similar way, (*Z*)-heptatriacont-23-enoic acid (**8**) and heptatriacontanoic acid (**3**) were synthesized by using the ylide of C_{14}-phosphonium salt **24** in place of the ylide of C_{18}-phosphonium salt in Wittig reaction (Scheme 3).

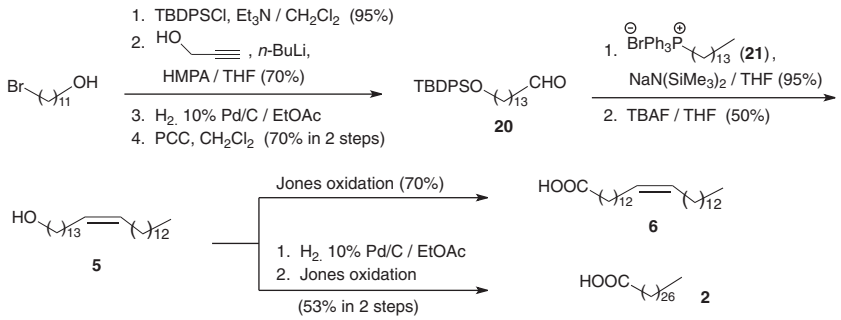
As depicted in Scheme 4, C_{37} fatty acids **13**–**16** with two *cis*-double bonds were prepared by Wittig reactions of the key aldehyde **22** with C_{14}-phosphonium salts **25**–**28**, respectively, and subsequent deprotection and oxidation.

Phosphonium salt **25** required for the synthesis of fatty acid **13** was obtained from 3-butyn-1-ol after protection of the hydroxy group as its THP ether, alkylation by 1-bromodecane, hydrogenation over Lindlar's catalyst, deprotection by PPTS, iodination, and heating with PPh_3.[19] Whereas preparation of phosphonium salt **26** was started by heating 6-bromo-1-hexanol with PPh_3 to furnish a phosphonium salt. Wittig reaction of the phosphonium salt with octanal and subsequent iodination afforded an iodide. Finally, the iodide was heated with PPh_3 to give the phosphonium salt **26**. On the other hand, oxidation of 8-bromo-1-octanol with PCC to an aldehyde, which was subjected to Wittig reaction with

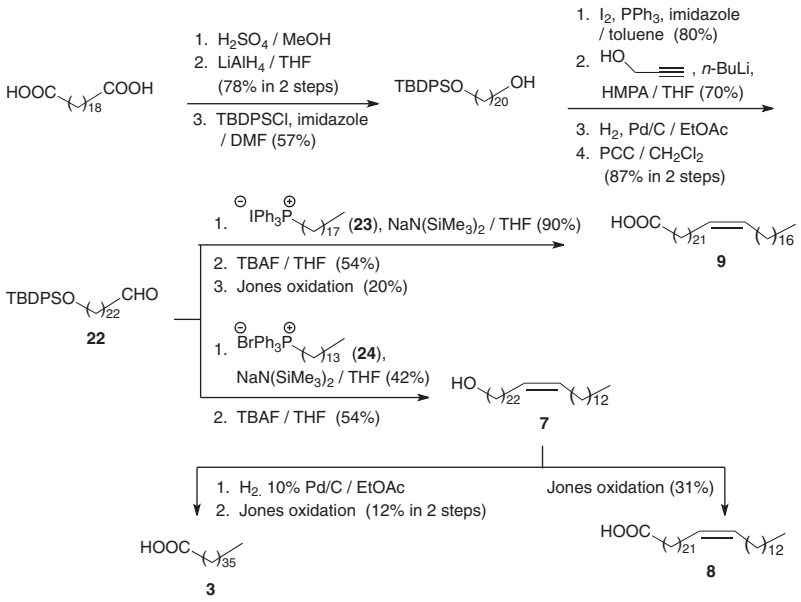


Comp.	R	m	n	Δ1	Δ2	Δ3	Δ4	Δ5	Comp.	R	m	n	Δ1	Δ2	Δ3	Δ4	Δ5
1	COOH	6	1	×	×	×	×	×	**10**	COOH	2	1	O	×	×	×	O
2	COOH	12	1	×	×	×	×	×	**11**	COOH	7	1	O	×	×	×	O
3	COOH	21	1	×	×	×	×	×	**12**	COOH	10	1	O	×	×	×	O
4	COOH	6	1	×	O	×	×	×	**13**	COOH	21	1	O	O	×	×	×
5	CH_2OH	12	1	O	×	×	×	×	**14**	COOH	21	1	O	×	O	×	×
6	COOH	12	1	O	×	×	×	×	**15**	COOH	21	1	O	×	×	O	×
7	CH_2OH	21	1	O	×	×	×	×	**16**	COOH	21	1	O	×	×	×	O
8	COOH	21	1	O	×	×	×	×	**17**	COOH	29	1	O	×	×	×	O
9	COOH	21	5	O	×	×	×	×									

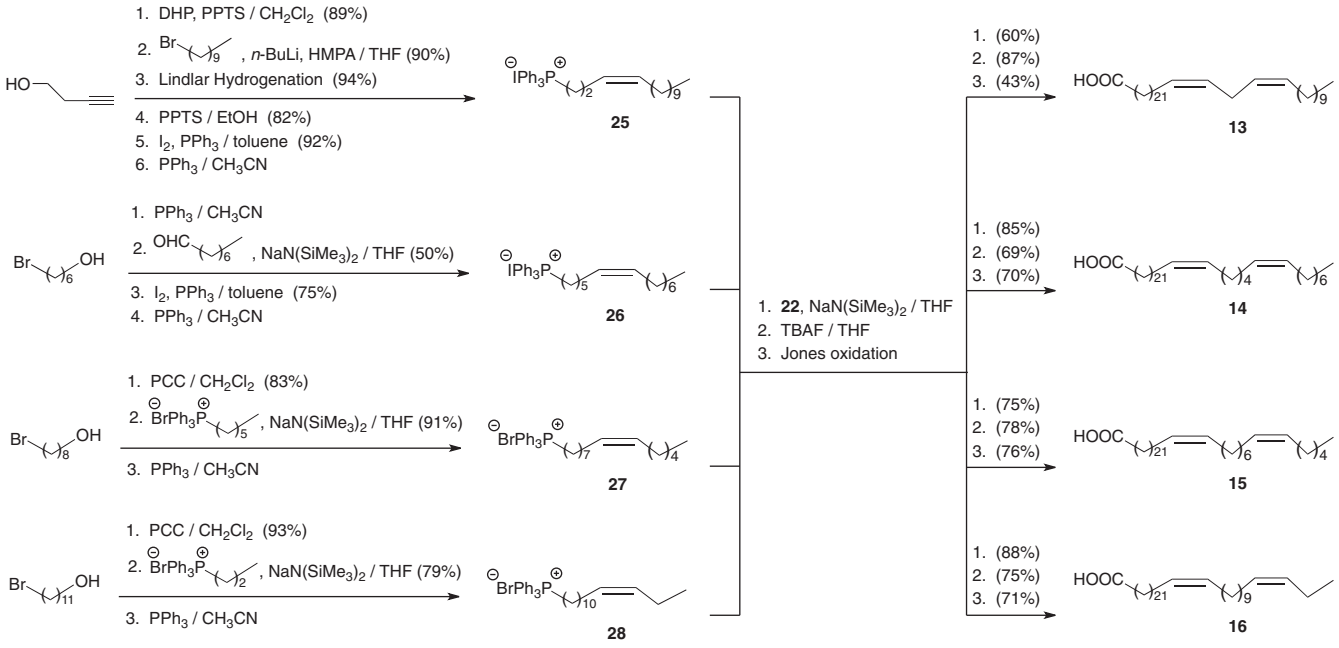
Figure 2. List of synthesized fatty acids. O: double bond; ×: single bond.



Scheme 2. Synthesis of fatty acids **2** and **6**.



Scheme 3. Synthesis of fatty acids **3**, **8**, and **9**.



Scheme 4. Synthesis of fatty acids **13**–**16**.

C_6-phoshonium salt, subsequently heated with PPh_3, to furnish the phosphonium salt **27**. Finally, the same reactions were effected as the preparation of the phosphonium salt **27**; 11-bromo-1-undecanol and C_3-phosphonium salt were used to generate the phosphonium salt **28**. These four phosphonium salts are all having C_{14} chain and one double bond of *cis*-configuration. Among them, the phosphonium salt **28** was considered as a key Wittig reagent in our experiment.

Among the four fatty acids **13**–**16**, fatty acid **16** showed the most potent neurite outgrowth activity (Fig. 2). Therefore, in the subsequent synthesis, we focused on a series of fatty acids (**10**–**12** and **17**) with two double bonds of *cis*-configuration at the positions Δ1 and Δ5 and different carbon chain length.

The synthesis of fatty acids **10**–**12** and **17** was carried out following the sequence shown in Scheme 5. These fatty acids were synthesized by means of the Wittig reactions of the key Wittig reagent **28** with the corresponding aldehydes and subsequent deprotection and oxidation. Monoprotection of commercial 1,4-butanediol, 1,9-nonanediol, and 1,12-dodecanediol with TBDPSCl and oxidation with PCC gave the corresponding aldehydes with 4-, 9-, and 12-carbon atoms, respectively, required for the synthesis of **10**–**12**. Whereas the TBDPS-mono-protected alcohol used for the key common aldehyde **22** was subjected to PCC oxidation, Wittig reaction with $BrPh_3P(CH_2)_{11}OH$, hydrogenation over 10% Pd/C, and PCC oxidation to produce the aldehyde with 31-carbon atoms required for the synthesis of **17**.

All the 17 fatty acid derivatives with different chain lengths and different numbers and positions of double bonds were tested for their neurite outgrowth activity.

Amyloid β (Aβ), a proteolytic product of amyloid-β precursor protein (APP), is the major amyloid component of amyloid deposits known as extracellular senile plaques and is thought to induce slow neuronal degeneration in the brains of Alzheimer's disease patients.[20] Though Aβ in extracellular senile plaques is Aβ(1–40) and Aβ(1–42), Aβ(25–35) is usualy used as a model of the naturally occurring Aβ.[21] This fragment similarly forms a β-sheet structure[22] and induces neuronal cell death, neuritic atrophy, and synaptic loss.[23] Moreover, a single intracerebroventricular (i.c.v.) injection of Aβ(25–35) could induce major neuropathological signs related to early stages of Alzheimer's disease in rats.[24] Thus, we used Aβ(25–35) to induce neuritic atrophy for preparing in vitro models of Alzheimer's disease.[25,26] Results are shown in Fig. 3.

NGF, which is important for the growth, maintenance, and survival of certain target neurons, was used as the positive control. Among the synthetic compounds **1**–**17**, (4*Z*,15*Z*)-octadecadienoic

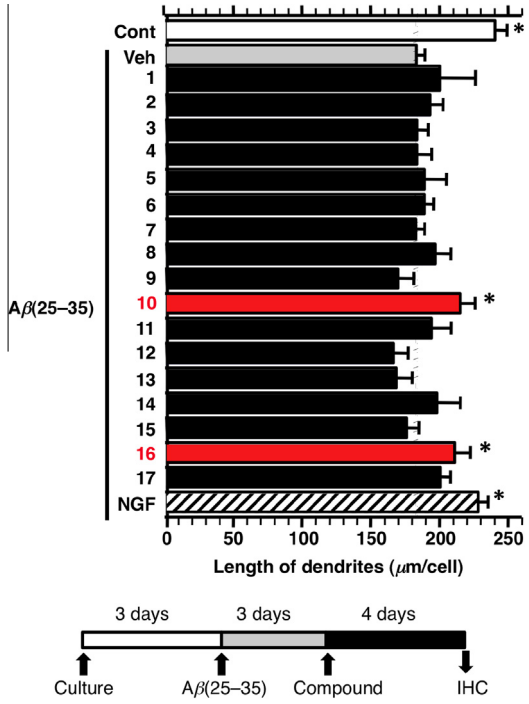
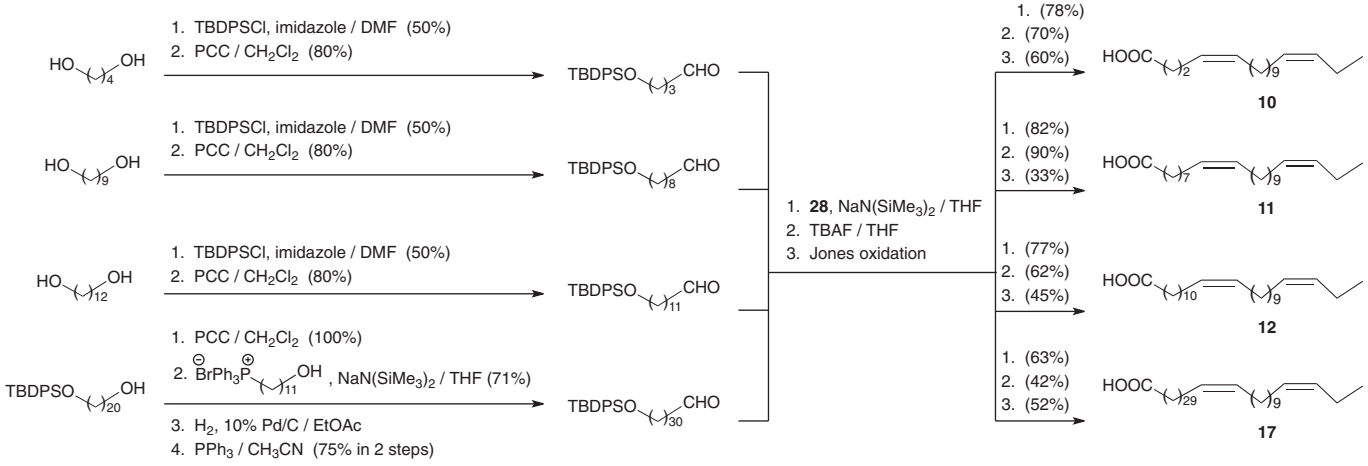


Figure 3. Dendrite extension activities of synthetic fatty acids 1–17 in Aβ(25–35)-treated rat cortical neurons. Aβ(25–35), 10 μM; 1–17, 1 μM (black columns); NGF, 100 ng/mL (hashed column). n = 8–18.

acid[27] (**10**) and (23*Z*,34*Z*)-heptatriacontadienoic acid[27] (**16**) showed the most potent neurite outgrowth activities, which is comparable to that of a positive control, NGF. Activities of the other synthetic compounds were observed in the following order: **1**, **8**, **14**, **17** > **2**, **11** > **5**, **6** > **3**, **4**, **7** > **9**, **12**, **13**, **15**. Structurally, compounds **10** and **16** both have two *Z*-double bonds at the positions Δ1 and Δ5 in C_{18} and C_{37} chain, respectively.[27] Thus, the possession of two (*Z*)-double bonds at the positions Δ1 and Δ5 may relate to their activity.

In conclusion, we prepared 17 fatty acid derivatives **1**–**17** with different chain lengths and different numbers and positions of double bonds by using Wittig reaction and stereospecific hydrogenation of triple bonds as key reactions. They were tested for their dendrite extension activities in Aβ(25–35)-treated rat cortical neurons. Among them, fatty acids **10** and **16** showed the most potent



Scheme 5. Synthesis of fatty acids **10**–**12** and **17**.

activities, which were comparable to the positive control, NGF. Compound **10** possesses two (*Z*)-double bonds at the n-3 and n-14 positions in the C_{18} chain and **16** possesses them in the C_{37} chain. These might be important for the neurite outgrowth activity. This result should suggest that these might be good candidates to develop drugs for Alzheimer's disease.

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26. Experiments were performed by the procedures described in Ref. 24a in accordance with the Guidelines for the Care and Use of Laboratory Animals of Sugitani Campus of the University of Toyama and NIH Guidelines on the Care and Use of Laboratory Animals. All protocols were approved by the Committee for Animal Care and Use of Sugitani Campus of the University of Toyama. Rat cortical neurons were cultured in 8-well chamber slides at a density of 1.45–2.6 $\times$ 10^5 cells/cm^2. The cells were treated with 10 μM Aβ(25–35) for 3 days, followed by the addition of compounds (1 μM), mouse β-NGF (100 μg/mL), or vehicle (0.1% DMSO). 4 days later, the cells were fixed with 4% paraformaldehyde and then immunostained with a monoclonal antibody against MAP2 (1:1000) as a dendritic marker. Alexa Fluor 488-conjugated goat anti-mouse IgG (1:200) was used as a second antibody. Eight to eighteen fluorescent images per treatment were captured by a fluorescent microscope AX-80 with DP70 digital camera system (Olympus, Tokyo, Japan) at 320 μm $\times$ 425 μm. The total length of dendrites was divided by neuron numbers to be calculated the average length. Statistical comparisons were perfomed with One-way analysis of variance (ANOVA), followed by the Holm-Sidak post hoc test using SigmaStat 3.5 (SYSTAT, CA, USA). Values of p <0.05 were considered significant. The data are presented as means ± SE.
27. *The spectral data of **10** and **16** are as follows:* **10**: IR (neat) 3006, 2925, 2854, 1712, 1458 (br s), 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.95 (3H, t, J = 7.4 Hz), 1.27 (14H, br s), 2.02 (8H, br s), 2.39 (2H, br s), 5.35 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 4.1, 20.5, 24.7, 27.2, 29.1–29.8, 32.6, 34.1, 126.9, 129.4, 131.5, 131.9, 179.1; MS (EI) m/z: 280 (M^+); HRMS calcd for $C_{18}H_{32}O_2$ 280.2402, found 280.2409; **16**: mp: 61–62 °C; IR (KBr) 3004, 2917, 2850, 1695, 1472 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.96 (3H, t, J = 7.4 Hz), 1.25 (50H, br s), 1.63 (2H, quint, J = 7.4 Hz), 2.02 (8H, m), 2.35 (2H, t, J = 7.4 Hz), 5.35 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.1, 20.5, 24.7, 27.2, 29.1–29.8, 32.6, 34.0, 129.3, 129.8, 130.4, 179.8; MS (EI) m/z: 546 (M^+); HRMS calcd for $C_{37}H_{70}O_2$ 546.5376, found 546.5378.