HETEROCYCLES, Vol. 77, No. 2, 2009, pp. 759 - 765. © The Japan Institute of Heterocyclic Chemistry
Received, 28th July, 2008, Accepted, 5th September, 2008, Published online, 8th September, 2008
DOI: 10.3987/COM-08-S(F)65

SYNTHETIC STUDIES OF MANGOSTIN DERIVATIVES WITH AN INHIBITORY ACTIVITY ON PDGF-INDUCED HUMAN AORTIC SMOOTH CELLS PROLIFERATION

Yuko Nishihama,[1] Takahisa Ogamino,[1] Wen Lei Shi,[2] Byung-Yoon Cha,[2] Takayuki Yonezawa,[2] Toshiaki Teruya,[1, 2] Kazuo Nagai,[2] Kiyotake Suenaga,[1] Je-Tae Woo,[2] and Shigeru Nishiyama[1*]

[1]Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

[2]Department of Biological Chemistry, Chubu University, 1200 Matsumoto-cho, Kasugai 487-8501, Japan

Abstract — The mangostin derivatives **3**—**10**, were synthesized by halogenation, electrochemical oxidation, and *m*CPBA oxidation of α- and γ-mangostins (**1**, **2**). Among them, the hydroxyl **9** and the benzopyran **10** derivatives produced by *m*CPBA, showed remarkable antiproliferative activities against human aortic smooth muscle cells (HASMC) induced by platelet-derived growth factor (PDGF).

INTRODUCTION

Natural products possessing the xanthone-skeleton are found in a wide range of plants, and exhibit a variety of biological activities. We have performed synthetic and biological studies of α-mangostin (**1**),[1] a representative naturally occurring xanthone.[2] Although xanthones are generally obtained in large quantities, there have been no previous reports of chemical modification studies with the aim of production of new bioactive substance, with the exception of our previous report.[3] Given such chemical transformation, it is expected that to be possible to construct of novel bioactive substances starting from naturally abundant sources. Indeed, we proposed such a possibility by acquiring mangostin congeners with remarkable inhibitory activity against acidic sphingomyelinase.[3]

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto in celebration of his 75th birthday.

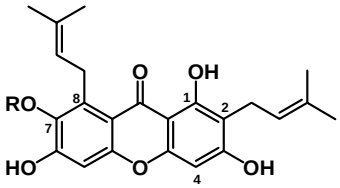


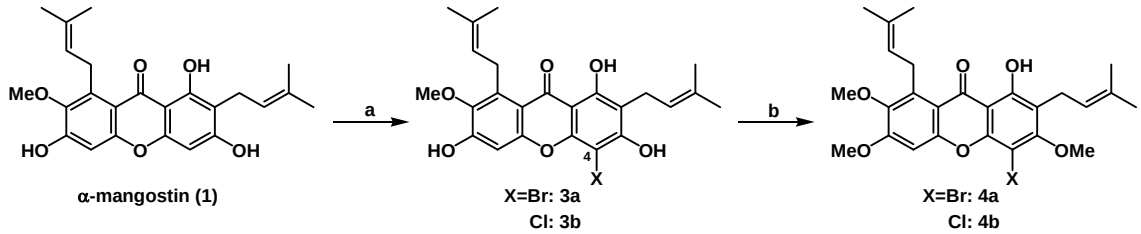
Figure 1

As part of our ongoing synthetic project mentioned above, we have carried out chemical modification of α- and γ-mangostins (**1**, **2**) by halogenation, phenolic oxidation, and *m*CPBA oxidation to examine the antiproliferative activity against HASMC, which is accumulated in the endothelium with foam cells derived from LDL cholesterol comprising arteriosclerotic plaques. The grown and hypertrophic plaque will reduce and block blood flow leading to atherosclerosis, which will cause brain infarction and cardiac infarction. HASMC growth is promoted by growth factors, such as PDGF.[4] Accordingly, suppression of HASMC-growth caused by PDGF may be useful to prevent atherosclerosis. Here, we report chemical modification of the mangostin derivatives from **1** and **2** and their antiproliferative activity against HASMC.

RESULTS AND DISCUSSION

Synthesis of halogenated mangostin derivatives

In addition to a scaffold leading to diverse functionalities, we are interested in the biological effects of halogens. Halogenated mangostin derivatives were synthesized as shown in Scheme 1. Treatment of **1** with NBS or NCS effected selective halogenation at the C-4 position to give **3a** and **3b**, respectively, in moderate yields, along with the O-methylated derivatives **4a** and **4b** prepared from **3** by the standard procedure.

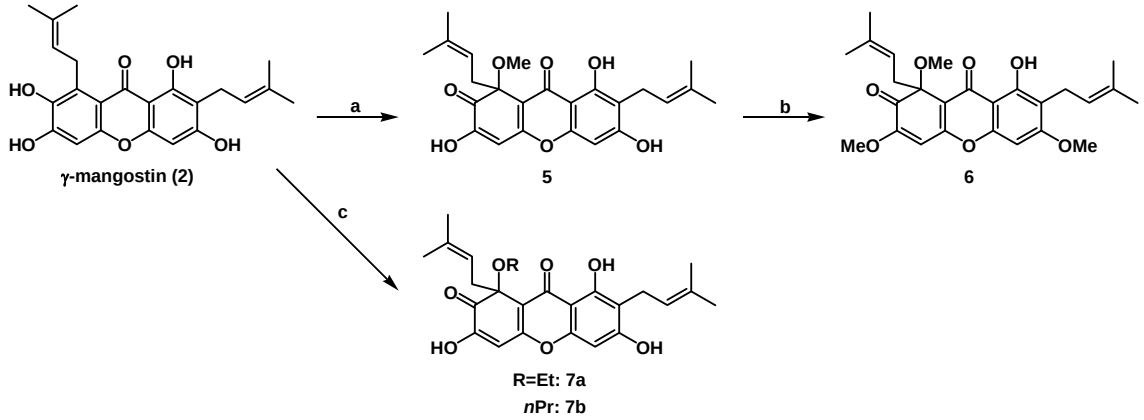


Scheme 1. *Reagents and conditions*: (a) NBS or NCS, THF, **3a**; 51%, **3b**; 46% (b) MeI, K_2CO_3, DMF, **4a**; 67%, **4b**; 77%

Phenolic oxidation of γ-mangostin[5]

As part of our synthetic investigation employing electroorganic chemistry toward biologically active

substances, **2**[6] was oxidized to understand the chemical features of the phenol functionalities (Scheme 2). Direct anodic oxidation [constant current electrolysis (C.C.E.); glassy carbon beaker as an anode; platinum wire as a cathode; $LiClO_4$ as a supporting salt] of **2** in MeOH gave the corresponding methoxydienone **5**[7] in 51% yield, which on reaction with MeI-K_2CO_3 gave **6**. Direct anodic oxidation in an EtOH solution yielded no reaction due to preferential oxidation of the solvent. The unsuccessful anodic oxidation prompted us to examine the electrochemically generated hypervalent iodobenzene species, which is produced from PhI under the anodic oxidation conditions using CF_3CH_2OH as a solvent. Although the generated oxidant was used without isolation, the active species may be bis(2,2,2-trifluoroethoxy)phenyliodine(III).[8] Reaction of **2** with the oxidant in the presence of EtOH or *n*PrOH effected nucleophilic attack of the solvent to produce the expected dienones **7a** and **7b**.[9]



Scheme 2. *Reagents and conditions*: (a) C.C.E. (0.3 mA/cm^2), 2 F/mol, MeOH, 51%. (b) MeI, K_2CO_3, DMF, 66%. (c) Oxidized iodobenzene, EtOH or *n*PrOH, **7a**; 36%, **7b**; 41%.

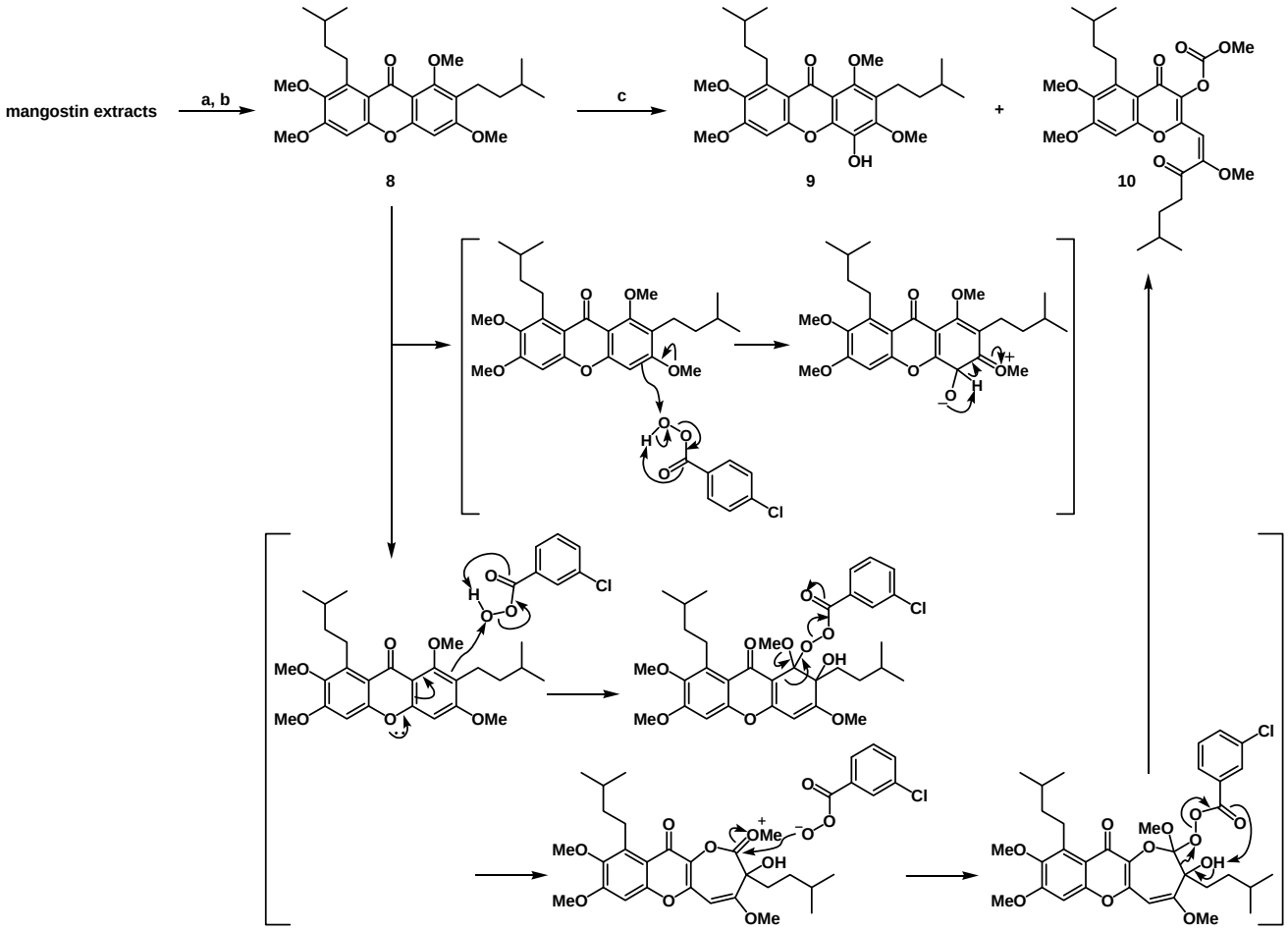
*Oxidation of the mangostin derivative **8***

Among the reaction conditions examined for structural conversion of the stable xanthone skeleton, we observed that *m*CPBA oxidation of **8** produced by two-step procedure from a mixture of mangostins with *m*CPBA, gave **9** and **10**[7], along with a complex mixture (Scheme 3). While **9** underwent hydroxylation at the C-4 position similar to halogenation, the right aromatic ring of **8** was opened oxidatively to give the benzopyran **10**, through a plausible mechanism depicted in Scheme 3.

Biological Activity

The inhibitory activities of natural **1** and **2**, along with **3**—**7**, **9**, and **10** against PDGF-induced HASMC proliferation were examined by the [^{3}H] thymidine incorporation procedure.[9] In contrast to **3**—**7**, which showed weak to moderate activities, compounds **9** and **10** produced by *m*CPBA-mediated oxidation exhibited remarkable inhibitory activities at a concentration of 1 μM (Figure 2(a)). Their

concentration-dependent inhibitory effects were confirmed at 0.1, 1, and 10 μM, and **9** with the most effective activity showed an IC_{50} 0.1 μM (Figure 2 (b)). Unfortunately, the reason why the hydroxyl function of **9** contributed higher inhibitory activity than the Br-function of **3a** remains unclear.



Scheme 3. *Reagents and conditions*: (a) MeI, K_2CO_3, DMF, 40 ℃. (b) H_2, Pd-C, MeOH, 98%. (c) *m*CPBA, CH_2Cl_2, **9**; 12%, **10**; 19%.

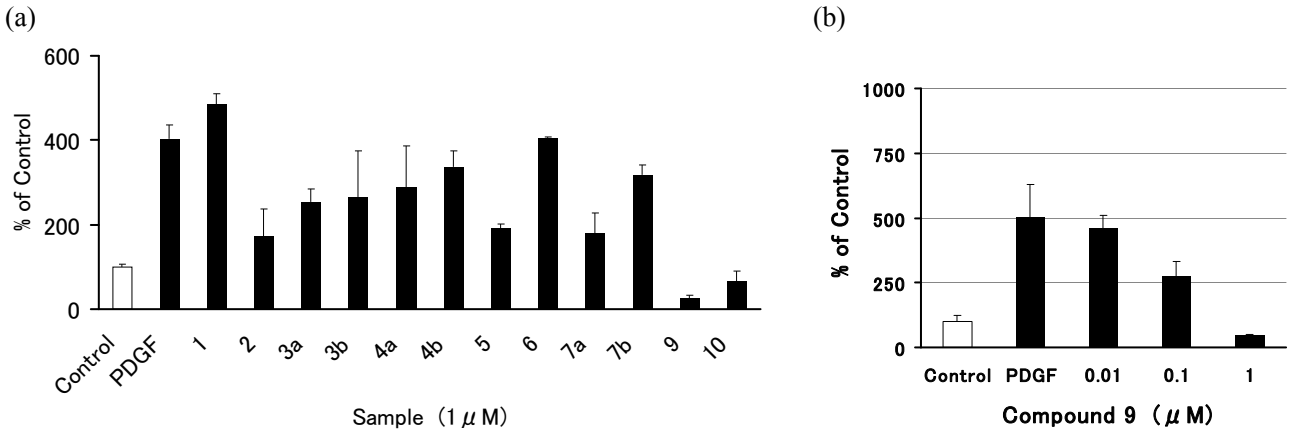


Figure 2. Inhibitory activity on PDGF-stimulated HASMC proliferation

CONCLUSIONS

Chemical modification of natural **1** and **2** was carried out to provide halogenated, oxidized compounds **3**—**10**. Compounds **9** and **10** exhibited potent inhibitory activities on PDGF-mediated HASMC proliferation. Further investigations to determine the structure-activity relationship of the inhibitory activities of the xanthone derivatives against HASMC are currently in progress in our laboratory.

ACKNOWLEDGMENTS

The authors are grateful to Professor Shigeru Ohba, Keio University, for single X-ray crystallographic analysis of the mangostin derivatives and fruitful discussion. This work was supported by High-Tech Research Center Project for Private Universities matching fund subsidy from MEXT, 2006-2011.

REFERENCES (AND NOTES)

1. Isolation: W. Schmid, *Liebigs Ann. Chem.*, 1855, **93**, 83; O. Dragendorff, *Liebigs Ann. Chem.*, 1930, **482**, 280. Structural determination: P. Yates and G. H. Stout, *J. Am. Chem. Soc.*, 1958, **80**, 1691; F. Scheinmann, *Chem. Commun.*, 1967, 1015; G. H. Stout, M. M. Krahn, P. Yates, and H. B. Bhat, *Chem. Commun.*, 1968, 211.
2. K. Iikubo, Y. Ishikawa, N. Ando, K. Umezawa, and S. Nishiyama, *Tetrahedron Lett.*, 2002, **43**, 291.
3. M. Hamada, K. Iikubo, Y. Ishikawa, A. Ikeda, K. Umezawa, and S. Nishiyama, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3151.
4. R. Ross, *Nature*, 1993, **362**, 801.
5. K. Kobayashi, S. Nishiyama, K. Sato, and T. Shibata, Jpn. Kokai Tokkyo Koho, 2007, 21pp.
6. A preliminary work was reported: see, Y. Nishihama, Y. Amano, T. Ogamino, and S. Nishiyama, *Electrochem.*, 2006, **74**, 609.
7. Structures of **5** and **10** were determinate by single X-ray crystallographic analysis. The detailed results will be reported elsewhere, owing to their inadequate R factors.
8. Y. Amano and S. Nishiyama, *Tetrahedron Lett.*, 2006, **47**, 6505.
9. The yields were not optimized.
10. [^{3}H]-Thymidine Incorporation Assay: Cell proliferation was determined by [^{3}H]-thymidine incorporation. HASMC were incubated for 20 hours with or without PDGF-BB (20 ng/mL) and indicated concentrations of mangostins and its derivatives and then pulse-labeled with 1 μCi/mL of [^{3}H]-thymidine for 4 hours. Cells were harvested using a Universal Harvester (Perkin Elmer), and then transferred to a GF/C filter (Perkin Elmer). The filter was dried and counted in scintillation fluid using a Microplate Scintillation and Luminescence Counter-Topcount NXT (Perkin Elmer).
11. Compounds details: compound **3a**; IR (film) 3486, 2919 and 1602 cm^{-1}; δ_H (ACETN), 1.63 (6H, s),

1.77 (3H, s), 1.82 (3H, s), 3.40 (2H, d, *J* =7.2 Hz), 4.14 (2H, d, *J* =6.8 Hz), 5.22 (1H, t, *J* =7.2 Hz), 5.28 (1H, t, *J* =6.8 Hz), 6.89 (1H, s), 13.95 (1H, s); δ_C (ACETN), 17.9, 18.3, 22.7, 25.8, 26.0, 26.3, 86.7, 101.1, 104.5, 111.5, 111.6, 122.7, 124.1, 129.0, 131.3, 131.9, 141.9, 151.5, 152.4, 153.1, 158.4, 160.4, 182.7 **3b**; δ_H ($CDCl_3$), 1.67 (3H, s), 1.69 (3H, s), 1.80 (3H, s), 1.81 (3H, s), 3.42 (2H, d, *J* = 7.3 Hz), 3.80 (3H, s), 4.06 (2H, d, *J* =5.9 Hz), 5.22 (1H, t, *J* =5.9 Hz), 5.25 (1H, t, *J* =7.3 Hz), 6.34 (1H, br), 6.38 (1H, br), 6.93 (1H, s), 13.60 (1H, s); **4a**; δ_H ($CDCl_3$), 1.68 (3H, s), 1.69 (3H, s), 1.81 (3H, s), 1.85 (3H, s), 3.44 (2H, d, *J* =7.3 Hz), 3.81 (3H, s), 3.92 (3H, s), 4.01 (3H, s), 4.11 (2H, d, *J* =6.8 Hz), 5.21 (1H, t, *J* =6.8 Hz), 5.24 (1H, t, *J* =7.3 Hz), 6.89 (1H, s), 13.68 (1H, s); **4b**; δ_H ($CDCl_3$), 1.66 (3H, s), 1.67 (3H, s), 1.79 (3H, s), 1.83 (3H, s), 3.40 (2H, d, *J* =7.2 Hz), 3.79 (3H, s), 3.92 (3H, s), 3.98 (3H, s), 4.09 (2H, d, *J* =6.0 Hz), 5.20 (2H, m), 6.87 (1H, s), 13.58 (1H, s); **5**; IR (KBr disk) 3369, 2915 and 1644 cm^{-1}; δ_H (ACETN), 1.45 (3H, s), 1.55 (3H, s), 1.78 (3H, s), 1.85 (3H, s), 2.89 (1H, dd, *J* =7.8, 12.7 Hz), 3.13 (3H, s), 3.37 (1H, dd, *J* =7.8, 12.7 Hz), 3.47 (2H, d, *J* =6.8 Hz), 4.75 (1H, t, *J* =7.8 Hz), 5.28 (1H, t, *J* =6.8 Hz), 6.41 (1H, s), 6.49 (1H, s), 13.4 (1H, s); δ_C (ACETN), 17.9, 18.0, 21.6, 25.8, 25.9, 38.5, 53.8, 83.0, 93.8, 104.6, 108.9, 110.6, 113.2, 114.3, 120.8, 136.1, 137.7, 151.8, 154.8, 159.5, 160.0, 161.3, 178.4, 199.1; **6**; δ_H ($CDCl_3$), 1.43 (3H, s), 1.52 (3H, s), 1.66 (3H, s), 1.77 (3H, s), 2.84 (1H, dd, *J* =8.6, 13.2 Hz), 3.10 (3H, s), 3.25 (1H, dd, *J* =7.3, 13.2 Hz), 3.34 (2H, d, *J* =6.8 Hz), 3.85 (3H, s), 3.89 (3H, s), 4.77 (1H, t, *J* =8.0 Hz), 5.20 (1H, t, *J* =6.8 Hz), 6.17 (1H, s), 6.37 (1H, s), 13.05 (1H, s); **7a**; δ_H ($CDCl_3$), 1.11 (3H, t, *J* =6.9 Hz), 1.37 (3H, s), 1.47 (3H, s), 1.70 (3H, s), 1.77 (3H, s), 2.80 (1H, dd, *J* =7.9 Hz, 13.5 Hz), 3.04-3.10 (1H, m), 3.20-3.34 (2H, m), 3.38 (2H, d, *J* =6.6 Hz), 4.65 (1H, t, *J* =7.9 Hz), 5.21 (1H, t, *J* =6.9 Hz), 6.34 (1H, br), 6.37 (1H, s), 13.38 (1H, s); δ_C ($CDCl_3$), 15.7, 18.0, 21.6, 25.8, 25.9, 38.8, 61.9, 82.2, 90.1, 93.8, 108.7, 110.5, 113.7, 114.4, 121.0, 135.8, 137.4, 152.2, 154.7, 159.6, 159.9, 161.2, 171.5, 178.3, 199.7; **7b**; δ_H ($CDCl_3$), 0.34 (3H, t, *J* =7.3 Hz), 1.45 (3H, s), 1.54 (3H, s), 1.58 (2H, m), 1.77 (3H, s), 1.85 (3H, s), 2.88 (1H, dd, *J* =7.3 Hz, 12.7 Hz), 2.96 (1H, m), 3.22 (1H, m), 3.44 (1H, dd, *J* =7.3 Hz, 12.7 Hz), 3.46 (2H, d, *J* =6.3 Hz), 4.71 (1H, t, *J* =7.3 Hz), 5.28 (1H, t, *J* =6.3 Hz), 6.42 (1H, s), 6.47 (1H, s), 6.50 (1H, br), 6.88 (1H, br), 13.45 (1H, s); δ_C ($CDCl_3$), 10.5, 18.0, 21.6, 23.2, 25.8, 25.9, 38.6, 68.2, 82.0, 93.8, 104.7, 108.8, 110.5, 114.0, 114.4, 120.9, 135.9, 137.5, 151.7, 154.8, 159.6, 159.6, 161.2, 178.4, 199.5; **8**; IR (film) 2954, 1650 and 1614 cm^{-1}; δ_H ($CDCl_3$), 0.92 (6H, d, *J* =6.8 Hz), 0.98 (6H, d, *J* =6.8 Hz), 1.35 (2H, m), 1.46 (2H, m), 1.59 (1H, m), 1.76 (1H, m), 2.62 (2H, t, *J* =8.0 Hz), 3.35 (2H, t, *J* =7.8 Hz), 3.78 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 6.49 (1H, s), 6.63 (1H, s); δ_C ($CDCl_3$), 21.1, 22.5, 22.6, 24.8, 28.4, 28.7, 39.1, 40.4, 55.7, 55.8, 61.0, 61.9, 93.9, 97.4, 110.6, 114.6, 121.7, 138.1, 143.5, 154.1, 156.1, 156.6, 158.3, 162.0, 175.9; HRMS (EI) calcd for $C_{27}H_{36}O_6$ (M^+) 456.2512, found: *m/z* 456.2512; **9**; mp 156-157℃ (hexane-EtOAc); IR (disk):

3311, 2954, 1592 and 1454 cm^{-1}; δ_H ($CDCl_3$), 0.94 (6H, d, *J* =6.4 Hz), 0.96 (6H, d, *J* =6.4 Hz), 1.43 (4H, m), 1.62 (2H, m), 1.75 (1H, m), 2.63 (2H, t, *J* =8.0 Hz), 3.32 (2H, t, *J* =8.0 Hz), 3.79 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 3.95 (3H, s), 5.65 (1H, br), 6.73 (1H, s); δ_C ($CDCl_3$), 22.0, 22.5, 22.6, 25.0, 28.6, 28.8, 39.9, 40.4, 55.9, 61.1, 61.2, 62.2, 97.5, 113.3, 114.4, 125.9, 132.9, 139.4, 143.3, 143.8, 148.9, 150.6, 153.9, 157.0, 176.2; HRMS; *m*/*z* 472.2445 (calcd for $C_{27}H_{36}O_7$ M^+, 472.2461); **10**; IR (film) 2954, 1776 and 1635 cm^{-1}; δ_H ($CDCl_3$), 0.88 (6H, d, *J* =6.4 Hz), 0.93 (6H, d, *J* =6.4 Hz), 1.37 (2H, m), 1.66 (4H, m), 2.73 (2H, t, *J* =7.3 Hz), 3.27 (2H, t, *J* =7.8 Hz), 3.77 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 3.91 (3H, s), 5.57 (1H, s), 6.47 (1H, s); δ_C ($CDCl_3$), 22.4, 22.6, 24.7, 27.6, 28.6, 32.0, 55.8, 55.9, 56.6, 61.1, 89.1, 97.5, 115.4, 132.4, 139.0, 144.6, 151.1, 152.9, 154.0, 156.9, 161.6, 171.3, 199.4.