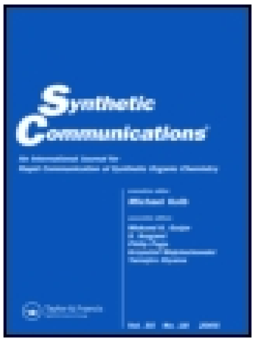

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Synthesis of chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl or 2-hydroxy-3-methyl-3-butenyl group from prenylated chalcones

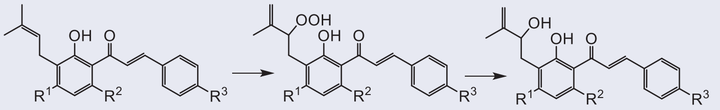
Kazuhiro Sugamoto, Toru Yoshifuji, Shuhei Soejima, and Yoshihiro Honda

Faculty of Engineering, University of Miyazaki, Miyazaki, Japan

ABSTRACT

Chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl or 2-hydroxy-3-methyl-3-butenyl groups, such as xanthoangelol E (1a), xanthoangelol D (**2a**), psorachalcone A (**2 b**), xanthohumol D (**2c**), and related derivatives were first synthesized by using the ene reaction of prenylated chalcones with singlet oxygen.

GRAPHICAL ABSTRACT



3a: R^1=OMe, R^2=H, R^3=OH
3b: R^1=R^3=OH, R^2=H
3c: R^1=R^3=OH, R^2=OMe
3d: R^1=OMe, R^2=R^3=H

1a: R^1=OMe, R^2=H, R^3=OH
1b: R^1=R^3=OH, R^2=H
1c: R^1=R^3=OH, R^2=OMe
1d: R^1=OMe, R^2=R^3=H

2a: R^1=OMe, R^2=H, R^3=OH
2b: R^1=R^3=OH, R^2=H
2c: R^1=R^3=OH, R^2=OMe
2d: R^1=OMe, R^2=R^3=H

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KEYWORDS
word; xanthoangelol E; xanthoangelol D; psorachalcone A; xanthohumol D; singlet oxygen

Chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl or 2-hydroxy-3-methyl-3-butenyl groups, such as xanthoangelol E (**1a**), xanthoangelol D (**2a**), psorachalcone A (**2 b**), and xanthohumol D (**2c**) were isolated from extracts of plants as biologically active compounds (Supplementary Figure 1). Compounds **1a** and **2a** were isolated from *Angelica keiskei.*[1] The hydroperoxide **1a** showed to inhibit the production of thromboxane B_2 and 12-hydroxy-5,8,10-heptadecatrienoic acid from exogenous arachidonic acid in platelets[2] and to inhibit phenylephrine-induced vasoconstriction through endothelium-dependent production of EDRF/NO and/or thorough the reduction of the $[Ca^{2+}]i$ induced by phenylephrine.[3] The alcohol **2a** was reported to inhibit endothelin-1 production through the suppression of nuclear factor-κB,[4] to inhibit inflammatory-induced plasminogen activator inhibitor production,[5] and to inhibit influenza virus neuraminidase.[6] The alcohol **2 b** was reported to be isolated from *Maclura tinctoria*[7] and *Psoralea corylifolia.*[8] The alcohol **2c** was isolated from *Humulus lupulus,*[9] exhibited potent inhibitory activity of nitric oxide production.[10] Recently, F. Sang et al. reported the synthesis of chalcones bearing 2-hydroxy-3-methyl-3-butenyl groups, such as xanthoangelol D (**2a**), angusticornin A, and paratocarpin E with ene reaction using

CONTACT Kazuhiro Sugamoto sugamoto@cc.miyazaki-u.ac.jp Faculty of Engineering, University of Miyazaki, Miyazaki, Japan

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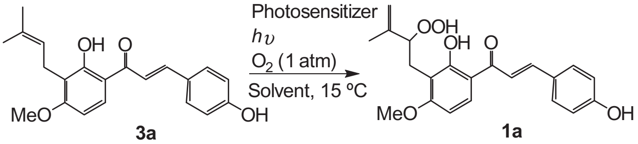
Table 1. Photooxygenation of **3a** under various conditions and lifetime of $^1\Delta g$ in solvent.



Entry	Conditions Photosensitizer	Solvent	Time (h)	Yield (%)[a]	Lifetime of $^1\Delta g$ (μs)[b]
1	TPP	CH_2Cl_2	0.5	40	82.9
2	Rose bengal	MeOH	10	38	10.4
3	Methylene blue	MeOH	10	32	10.4
4	Methylene blue	2-PrOH	10	44	22.1
5	Methylene blue	Acetone	1	49	50.5
6	Methylene blue	CH_3CN	1	57	58.3

[a] Isolated yield.
[b] These data are taken from reference 14.

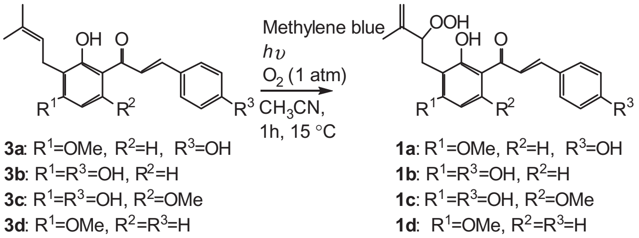
tetraphenylporphin (TPP) as the photosensitizer followed by reduction with triphenylphosphine.[11] However , no work has been done on the synthesis of chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl groups. In this paper, we report the synthesis of these chalcone **1a**, **2a-c** and their related derivatives from prenylated chalcones.

Prenylated chalcones, such as 4-hydroxyderricin (**3a**), isobavachalcone (**3b**), derricin (**3d**), were prepared according to our previous report.[12] Xanthohumol (**3c**) was synthesized according to the literature.[13] Helesbeux et al. reported the ene reaction of ortho-prenylphenol derivatives with singlet oxygen ($^1\Delta g$) using tetraphenylporphin (TPP) as the photosensitizer followed by a reduction with PPh_3 to give *ortho*-(2-hydroxy-3-methyl-3-butenyl)phenol derivatives.[14] Although the intermediately produced unstable hydroperoxide was detected by ^1H-NMR, it was not isolated. The ene reaction of $^1\Delta g$ with 4-hydroxyderricin (**3a**) was first attempted in the presence of TPP as the photosensitizer (Table 1, entry 1). Xanthoangelol E (**1a**) with unstable hydroperoxy moiety was first synthesized by this method in 40% yield, along with inseparable by-products. However, compound **1a** was difficult to separate from tpp by SiO_2 column chromatography. Rodgers was reported the natural lifetime of $^1\Delta g$ in many solvent systems.[15] Table 1 shows the photooxygenation of **3a** under various conditions and lifetime of $^1\Delta g$ in each solvents. Although the reaction of **3a** in MeOH using rose bengal (RB) or methylene blue (MB) as photosensitizer were slow, the yield of **1a** was moderate. MB was the easiest to separate from **1a** by SiO_2 column chromatography. Entries 4–6 shows the effect of solvent on the photooxygenation using MB. In the case of using MB as photosensitizer, the reaction time on the photooxygenation of **3a** is dependent on lifetime of $^1\Delta g$ in each solvent. The yield of **1a** increase with an increase in the lifetime of $^1\Delta g$. The reaction conditions in entry 6 gave the best result.

The conditions of the photooxygenation using MB in CH_3CN was applied to several prenylated chalcones (Table 2). The photooxygenatio of **1b–1d** gave the corresponding chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl group in moderate yields (entries 2–4).

Next, we tried the one-pot synthesis of chalcones bearing 2-hydroxy-3-methyl-3-butenyl groups from the prenyled chalcones. Table 3 shows the photooxygenation of prenylated chalcones in the presence of MB in CH_3CN followed by reduction with

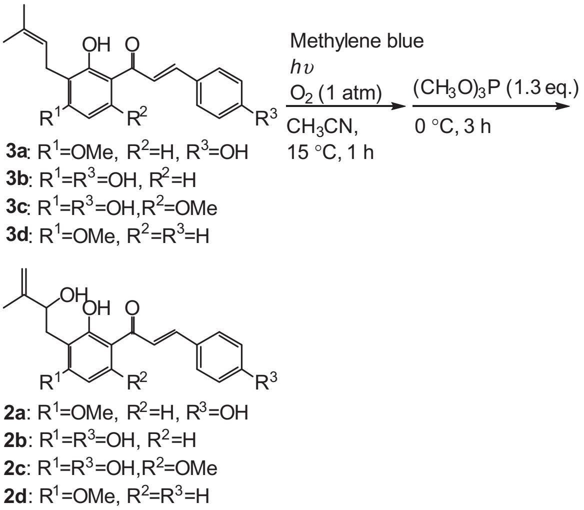
Table 2. Photooxygenation of prenylated chalcones (**3a-d**) in the presence of methylene blue as photosensitizer.



Entry	Substrate	Product	Yield (%)
1	**3a**	**1a**	57
2	**3b**	**1b**	42
3	**3c**	**1c**	12
4	**3d**	**1d**	37

Bold values represent compound numbers.

Table 3. Synthesis chlcones bearing 2-hydroxy-3-methyl-3-butenyl group (**2a–d**) from prenylated chalcones (**3a–d**).



Entry	Substrate	Product	Yield (%)
1	**3a**	**2a**	56
2	**3b**	**2b**	47
3	**3c**	**2c**	39
4	**3d**	**2d**	52

Bold values represent compound numbers.

trimethylphosphite. Thus chalcones bearing 2-hydroxy-3-methyl-3-butenyl group such as xanthoangelol D (**2a**), psorachalcone A (**2b**), and xanthohumol D (**2c**) could be synthesized from corresponding prenylated chalcones in 56, 47, and 39% yield, respectively (entries 1–3).

In summary, the present method allowed for the synthesis of chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl or 2-hydroxy-3-methyl-3-butenyl groups, such as xanthoangelol E (**1a**), xanthoangelol D (**2a**), psorachalcone A (**2b**), xanthohumol D (**2c**), and related derivatives from prenylated chalcones.

General procedure for the synthesis of chalcones bearing 2-hydroperoxy-3-methyl-3-butenyl (1a–d)

Oxygen was bubbled trough a CH_3CN solution (30 cm^3) of prenylated chalcone (30 mg) and methylene blue (3 mg) as photosensitizer. The reaction mixture was water-cooled at 15 °C and irradiated with a halogen lamp (500 W) for 1 h. The reaction was terminated when the substrate was completely consumed by checking on TLC. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography with hexane-ethyl acetate.

General procedure for the synthesis of chalcones bearing 2-hydroxy-3-methyl-3-butenyl (2a–d)

Oxygen was bubbled trough a CH_3CN solution (30 cm^3) of prenylated chalcone (30 mg) and methylene blue (3 mg) as photosensitizer. The reaction mixture was water-cooled at 15 °C and irradiated with a halogen lamp (500 W) for 1 h. The reaction was terminated when the substrate was completely consumed by checking on TLC. To this reaction solution was added 1.3 equiv. of trimethylphosphite at 0 °C, and the mixture was stirred for 3 h. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography with hexane-ethyl acetate.

References

[1] Baba, K.; Nakata, K.; Taniguchi, M.; Kido, T.; Kozawa, M. Chalcones from *Angelica keiskei*. *Phytochemistry* **1990**, *29*, 3907–3910. DOI: 10.1016/0031-9422(90)85357-L.

[2] Fujita, T.; Sakuma, S.; Sumiya, T.; Nishida, H.; Fujimoto, Y.; Baba, K.; Kozawa, M. The Effects of Xanthoangelol E on Arachidonic Acid Metabolism in the Gastric Antral Mucosa and Platelet of the Rabbit. *Res. Commun. Chem. Pathol. Pharmacol* **1992**, *77*, 227–240.

[3] Matsuura, M.; Kimura, Y.; Nakata, K.; Baba, K.; Okuda, H. Artery Relaxation by Chalcones Isolated from the Roots of *Angelica keiskei*. *Planta Med.* **2001**, *67*, 230–235. DOI: 10.1055/s-2001-12011.

[4] Sugii, M.; Ohkita, M.; Taniguchi, M.; Baba, K.; Kawai, Y.; Tahara, C.; Takaoka, M.; Matsumura, Y. Xanthoangelol D Isolated from the Roots of *Angelica keiskei* Inhibits Endothelin-1 Production through the Suppression of Nuclear Factor-κB. *Biol. Pharm. Bull.* **2005**, *28*, 607–610. DOI: 10.1248/bpb.28.607.

[5] Ohkura, N.; Nakakuki, Y.; Taniguchi, M.; Kanai, S.; Nakayama, A.; Ohnishi, K.; Sakata, T.; Nohira, T.; Matsuda, J.; Baba, K.; et al. Xanthoangelols Isolated from *Angelica keiskei* Inhibit Inflammatory-Induced Plasminogen Activator Inhibitor 1 (PAI-1) Production. *BioFactors* **2011**, *37*, 455–461. DOI: 10.1002/biof.187.

[6] Park, J. Y.; Jeong, H. J.; Kim, Y. M.; Park, S.-J.; Rho, M.-C.; Park, K. H.; Ryu, Y. B.; Lee, W. S. Characteristic of Alkylated Chalcones from *Angelica keiskei* on Influenza Virus Neuraminidase Inhibition. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5602–5604. DOI: 10.1016/j.bmcl.2011.06.130.

[7] ElSohly, H. N.; Joshi, A. S.; Nimrod, A. C.; Walker, L. A.; Clark, A. M. Antifungal Chalcones from *Maclura tinctoria*. *Planta Med.* **2001**, *67*, 87–89. DOI: 10.1055/s-2001-10621.

[8] Yu, L.-L.; Chen, Y.-G.; Liu, J.-C.; Lu, Y.-O.; Gui, S.-H. *Polish J. Chem.* **2005**, *79*, 1173–1177.

[9] Tevens, J. F.; Taylor, A. W.; Nickerson, G. B.; Ivancic, M.; Henning, J.; Haunold, A.; Deinzer, M. L. Prenylflavonoid Variation in *Humulus lupulus*: Distribution and

Taxonomic Significance of Xanthogalenol and 4′-O-Methylxanthohumol. *Phytochemistry* **2000**, *53*, 759–775. DOI: 10.1016/s0031-9422(00)00005-4.

[10] Zhao, F.; Watanabe, Y.; Nozawa, H.; Daikonnya, A.; Kondo, K.; Kitanaka, S. Prenylflavonoids and Phloroglucinol Derivatives from Hops (*Humulus lupulus*). *J. Nat. Prod.* **2005**, *68*, 43–49. DOI: 10.1021/np0499113.

[11] Li, Y.; Sun, B.; Zhai, J.; Fu, L.; Zhang, S.; Zhang, J.; Liu, H.; Xie, W.; Deng, H.; Chen, Z.; Sang, F. *Tetrahedron Lett.* **2019**, *60*, 1511156.

[12] Sugamoto, K.; Matsusita, Y-i.; Matsui, K.; Kurogi, C.; Matsui, T. Synthesis and Antibacterial Activity of Chalcones Bearing Prenyl or Geranyl Groups from *Angelica keiskei*. *Tetrahedron* **2011**, *67*, 5346–5359. DOI: 10.1016/j.tet.2011.04.104.

[13] Khupse, R. S.; Erhardt, P. W. Total Synthesis of Xanthohumol. *J. Nat. Prod.* **2007**, *70*, 1507–1509. DOI: 10.1021/np070158y.

[14] Helesbeux, J.-J.; Duval, O.; Guilet, D.; Seraphin, D.; Rondeau, D.; Richomme, P. Regioselectivity in the Ene Reaction of Singlet Oxygen with Ortho-Prenylphenol Derivatives. *Tetrahedron* **2003**, *59*, 5091–5104. DOI: 10.1016/S0040-4020(03)00733-6.

[15] Rodgers, M. A. J. *J. Am. Chem. Soc.* **1983**, *105*, 6210–6205.