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Short Note

5-(6-Hydroxy-6-methyl-5-oxoheptan-2-yl)-2-methyl Phenyl Acetate

Maya Damayanti Rahayu [1,2], Susi Kusumaningrum [1] and Hayun Hayun [2,*]

[1] Center of Technology For Pharmaceutical and Medical, Agency for the Assessment and Application of Technology (BPPT), Jl. M.H Thamrin 8, Jakarta 10340, Indonesia; maya.damayanti@bppt.go.id (M.D.R.); susi.kusumaningrum@bppt.go.id (S.K.)

[2] Faculty of Pharmacy, Universitas Indonesia, Depok 1424, Indonesia

* Correspondence: hayun.ms@ui.ac.id; Tel.: +62-21-874-4738

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Abstract: We synthesized a novel compound, 5-(6-hydroxy-6-methyl-5-oxoheptan-2-yl)-2-methylphenyl acetate, in a good yield by oxidation of 1-*O*-acetyl-xanthorrizol using potassium permanganate in acidic condition. The structure was elucidated by Fourier Transform Infrared (FTIR), ^{1}H-Nuclear Magnetic Resonance (NMR) and ^{13}C-NMR, two-dimensional (2D)-HSQC, Distortionless Enhancement by Polarization Transfer (DEPT), 2D-Heteronuclear Multiple Bond Correlation (HMBC), and High-Resolution Mass Spectra (HRMS) spectral data.

Keywords: 1-*O*-acetyl-xanthorrhizol; xanthorrizol; oxidation; potassium permanganate

1. Introduction

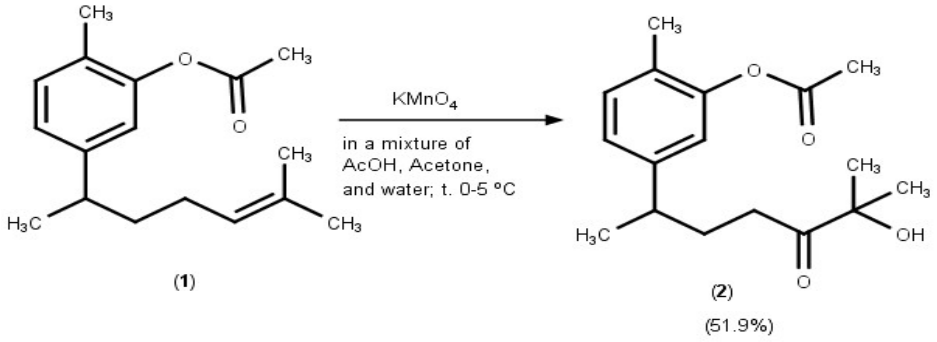
Xanthorrhizol, 2-methyl-5-[(2*R*)-6-methylhept-5-en-2-yl]phenol, is a major component extracted from *Curcuma xanthorrhiza* Roxb (Java turmeric) rhizomes. It has been established to have a variety of biological activities such as anticancer, anti-inflammatory, anticandidal, anti-hyperglycaemic, antibacterial, antioxidant, and anti-hypertensive [1–9]. Several xanthorrizol derivatives have been synthesized such as by esterification of the hydroxyl group, bromination of the phenyl ring, and epoxidation, asymmetric dihydroxylation, or hydrogenation of the carbon-carbon double bond of the compound [10,11]. Permanganate is a well-known and versatile oxidizing agent used to oxidize the carbon-carbon double bonds in organic chemistry [12]. However, there is no report of the use of this reagent for oxidation of xanthorrizol or its derivatives. Herein, we reported the oxidation of 1-*O*-acetyl-xanthorrizol using permanganate to acquire a new xanthorrizol derivative, 5-(6-hydroxy-6-methyl-5-oxoheptan-2-yl)-2-methylphenyl acetate.

2. Results and Discussion

The title compound, 5-(6-hydroxy-6-methyl-5-oxoheptan-2-yl)-2-methylphenyl acetate, was synthesized via a method summarize in Scheme 1. The starting material, 1-*O*-acetyl-xanthorrhizol (**1**), was a known compound prepared by acetylation of xanthorrizol according to phenol acetylation method reported earlier [10,11,13]. Compound **1** was oxidized by potassium permanganate at 0–5 °C in a mixture of glacial acetic acid, acetone, and distilled water and produced a moderate yield (51.9%) of the title compound (**2**).

The Fourier Transform Infrared (FTIR) spectrum of the compound **2** exhibited the appearance of hydroxyl, carbonyl ester, and carbonyl ketone bands at 3482, 1762, and 1710 cm^{-1}. In the ^{1}H-NMR spectrum, the appearance of a singlet peak at δ 3.71 ppm confirmed the formation of the hydroxyl group, while the presence of two singlet peaks at δ 1.26 and 1.27 ppm indicated that the two methyl group bound to quaternary carbon. In the ^{13}C-NMR spectrum, the appearance of peaks at δ 214.6 and

76.3 ppm confirmed the formation of ketone (C=O) and C-O aliphatic groups [14,15]. Furthermore, in Distortionless Enhancement by Polarization Transfer (DEPT) spectrum showed that carbon peak at δ 76.3 ppm was a quaternary carbon. The structure was supported by a two-dimensional (2D) Heteronuclear Multiple Bond Correlation (HMBC) spectrum displaying correlations between proton on a hydroxyl group at δ 3.71 ppm with thecarbon at δ 76.3, 26.6, and 26.5 ppm; protons on two methyl groups at δ 1.26 and 1.27 ppm with the carbon at δ 76.3 ppm; and other proton-carbon correlations due to two-bonds—four-bond couplings [14] (Figure 1 and Table 1), and a High-Resolution Electrospray Ionization Mass Spectometry (HRESIMS), which showed a molecular ion peak at m/z 315.1563 ([M + Na]$^+$). All data obtained are in entire agreement with the structure of the title compound.



Scheme 1. Synthesis of the title compound **2** from 1-*O*-Acetyl-xanthorrizol (**1**).

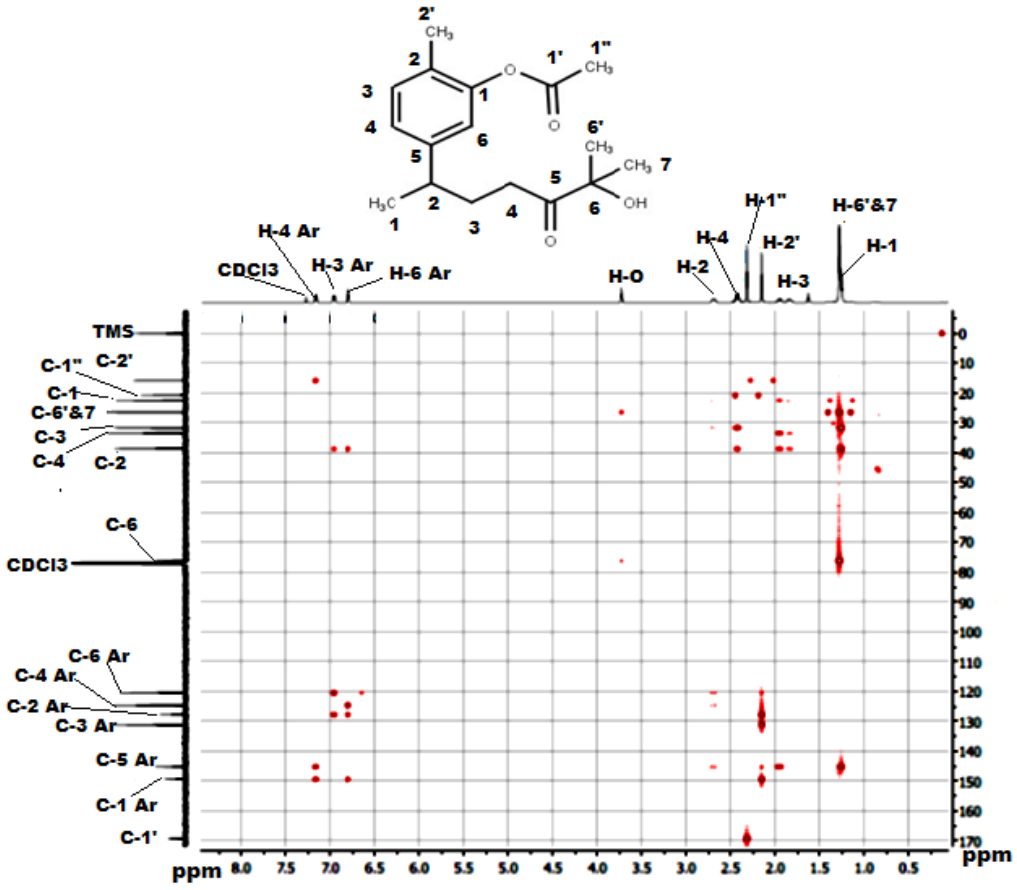


Figure 1. Two-dimensional (2D)-Heteronuclear Multiple Bond Correlation (HMBC) spectrum of the title compound **2**.

Table 1. HMBC Correlations for the title compound **2**.

	Proton	H-1	H-2	H-3	H-4	H-6′	H-7	H-1″	H-2′	H-3 Ar	H-4 Ar	H-6 Ar	H-O
Carbon	**ppm**	**1.25**	**2.67**	**1.82 & 1.91**	**2.41**	**1.26**	**1.27**	**2.31**	**2.14**	**6.95**	**7.14**	**6.79**	**3.71**
C-1	22.7	DB *	α	β	γ								
C-2	38.9	α	DB *	α	β					γ		β	
C-3	31.8	β	α	DB *	α								
C-4	33.6			α	DB *								
C-5	214.6												
C-6	76.3					α	α						α
C-6′	26.6					DB *							β
C-7	26.5						DB *						β
C-1′	169.4							α					
C-1″	21.0							DB *					
C-2′	15.9								DB *		γ		
C-1 Ar	149.5								β		γ	α	
C-2 Ar	127.9								α	α		β	
C-3 Ar	131.3								β	DB *			
C-4 Ar	124.7		β								DB *	β	
C-5 Ar	145.4	β	α	β							α	α	
C-6 Ar	120.6		β							γ		DB *	

* DB = Directly bonded proton-carbon, which are not seen in HMBC; α = due to a two-bond coupling ($^2J_{CH}$); β = due to a three-bond coupling ($^3J_{CH}$); γ = due to a four-bond coupling ($^4J_{CH}$).

Based on the above result, the oxidation of the carbon-carbon double bond of the side chain of xanthorrizol by permanganate ion (one equimolar) in acidic condition produced an α-hydroxy ketone compound as the main product (51.9% yield). However, the side products of the reaction have not been identified yet. The result reported earlier showed that the oxidation of carbon-carbon double bond in acidic condition afforded the cleavage products as the main product [12], for example, the oxidation of carbon-carbon double bond of the side chain of eugenol by permanganate ion (five equimolar) in acidic condition produced 3,4-dimethoxybenzyl carboxylic acid [16]. The difference of the amount of permanganate ion used may cause different results in the oxidation reaction.

3. Materials and Methods

3.1. General

Xanthorrhizol was supplied by Java Plant, Karanganyar, Indonesia. Potassium permanganate, hydrogen peroxide (Merck, Darmstadt, Germany), and solvents used were obtained commercially. A purity test was performed using thin layer chromatographic (TLC) method on silica gel 60 F254 plates (Merck). The infrared (IR) spectrum was recorded on a FTIR Spectrophotometer (Nicolet iS10, Thermo Fisher Scientific, Waltham, MA, USA); Nuclear Magnetic Resonance (NMR) spectra were measured on an NMR spectrometer (Agilent, Santa Clara, CA, USA) at 500 MHz for proton and 125 MHz for carbon using in $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. High-resolution Mass spectra (HRMS) was recorded on an LCT Premier XE-TOF Mass Spectrometer (Waters Corp., Milford, MA, USA) in positive electrospray ionization (ESI) mode.

3.2. Synthesis of the Title Compound **2**

1-*O*-Acetyl-xanthorrhizol (**1**) was prepared by acetylation of xanthorrizol using phenol acetylation method reported earlier [10,11,13] with little modification. Furthermore, to a solution of the compound **1** (2.44 mmol, 635.3 mg) in a mixture of glacial acetic acid (5.45 mL), acetone (11 mL), and distilled water (4.3 mL), potassium permanganate crystal (2.7 mmol, 428 mg) was added slowly for 6 h while stirring in an ice bath (0–5 °C), then followed by additional stirring for 1 h. The reaction was monitored using TLC. Upon completion, the reaction solution was poured onto 12 mL of distilled water, and then, 2–3 drops of hydrogen peroxide solution were added to decolorize the reaction. The main product was extracted with dichloromethane and purified by column chromatography using a mixture of hexane

and ethyl acetate (5:2) as the mobile phase to provide **2** as a yellow liquid in 51.9% yield and Rf = 0.5 (hexane-ethyl acetate = 5:2).

FTIR (KBr) υmax cm^{-1}: 3482 (O-H), 2932, 2971 (CH aliphatic), 1762 (C=O ester), 1710 (C=O ketone), 1217 (C-O ester) [14]. ^{1}H-NMR and 2D-HSQC (500 Hz, $CDCl_3$), δ, ppm: 7.14 (1H, d, *J* = 8, H-4_{Ar}), 6.95 (1H, d, *J* = 8, H-3_{Ar}), 6.79 (1H, s, H-6_{Ar}), 3.71 (1H, s, HO), 2.67 (1H, m, H-2, C-HC-Ar), 2.41 (2H, m, H-4, C-H_2C-C=O), 2.31 (3H, s, H-1″, H_3C-$_{acetate}$), 2.14 (3H, s, H2′, H_3C-Ar), 1.82 and 1.91 (2 peak: 1H, m and 1H, m, H-3, C-CH_2-C), 1.26 and 1.27 (6H, 2 s, H-6′ and 7, 2 CH_3-C), 1.25 (3H, d, *J* = 7, H-1, CH_3-CH). ^{13}C-NMR and HSQC (500 MHz, $CDCl_3$), δ, ppm: 214.6 (1C, C-5, C=O_{ketone}), 169.4 (1C, C-1′, C=$O_{acetate}$), 149.5 (1C, C-1_{Ar}), 145.4 (1C, C-5_{Ar}), 131.3 (1C, C-3_{Ar}), 127.9 (1C, C-2_{Ar}), 124.7 (1C, C-4_{Ar}), 120.6 (1C, C-6_{Ar}), 76.3 (1C, C-6, C-O), 38.9 (1C, C-2), 33.6 (1C, C-4), 31.8 (1C, C-3), 26.6 and 26.5 (2 peak 1C and 1C, C-6′ and 7), 22.7 (1C, C-1), 21.0 (1C, C-1″, CH_3-$_{acetate}$), 15.9 (1C, C-2′, CH_3-Ar). DEPT: Quaternary carbon, δ (ppm): 214.6 (C-5, C=O_{ketone}), 169.4 (C-1′, C=$O_{acetate}$), 149.5 (C-1_{Ar}), 145.4 (C-5_{Ar}), 127.9 (C-2_{Ar}), and 76.3 (C-6, C-OH). Secondary carbons, δ, ppm: 33.6 (C-4) and 31.8 (C-3). HRESIMS (*m*/*z*) found 315.1563 ([M + Na]$^+$), calculated masses for $C_{17}H_{24}O_4Na$: 315.1572 (error −2.9 ppm).

Supplementary Materials: The following are available online, Figure S1: FTIR of the title compound **2**, Figure S2: ^{1}H-NMR of the title compound **2**, Figure S3: ^{13}C-NMR of the title compound **2**, Figure S4: 2D-HSQC of the title compound **2**, Figure S5: DEPT of the title compound **2**, Figure S6: HRESI-MS of the title compound **2**.

Author Contributions: H.H. and S.K. conceived and designed the experiments; M.D.R. performed the experiments; H.H. and M.D.R. analyzed the data; S.K. and H.H. contributed reagents/materials; H.H. and M.D.R. wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Nurcholis, W.; Munshif, A.A.; Ambarsari, L. Xanthorrhizol contents, α-glucosidase inhibition, and cytotoxic activities in ethyl acetate fraction of Curcuma zanthorrhiza accessions from Indonesia. *Rev. Bras. Farmacogn.* **2018**, *28*, 44–49. [CrossRef]
2. Chung, W.Y.; Park, J.H.; Kim, M.J.; Kim, H.O.; Hwang, J.K.; Lee, S.K.; Park, K.K. Xanthorrhizol inhibits 12-O-tetradecanoylphorbol-13-acetate-induced acute inflammation and two-stage mouse skin carcinogenesis by blocking the expression of ornithine decarboxylase, cyclooxygenase-2 and inducible nitric oxide synthase through mitogen-activated protein kinases and/or the nuclear factor-κB. *Carcinogenesis* **2007**, *28*, 1224–1231. [PubMed]
3. Kang, Y.J.; Park, K.K.; Chung, W.Y.; Hwang, J.K.; Lee, S.K. Xanthorrhizol, a natural sesquiterpenoid, induces apoptosis and growth arrest in HCT116 human colon cancer cells. *J. Pharmacol. Sci.* **2009**, *111*, 276–284. [CrossRef] [PubMed]
4. Kim, M.; Kim, C.; Song, Y.; Hwang, J.K. Antihyperglycemic and Anti-Inflammatory Effects of Standardized Curcuma xanthorrhiza Roxb. Extract and Its Active Compound Xanthorrhizol in High-Fat Diet-Induced Obese Mice. *Evid. Based Complement. Alternat. Med.* **2014**. [CrossRef]
5. Choi, M.; Kim, S.H.; Chung, W.Y.; Hwang, J.K.; Park, K.K. Xanthorrhizol, a natural sesquiterpenoid from Curcuma xanthorrhiza, has an anti-metastatic potential in experimental mouse lung metastasis model. *Biochem. Biophys. Res. Commun.* **2004**, *326*, 210–217. [CrossRef] [PubMed]

6. Cheah, Y.H.; Azimahtol, H.L.P.; Abdullah, N.R. Xanthorrhizol Exhibits Antiproliferative Activity on MCF-7 Breast Cancer Cells via Apoptosis Induction. *Anticancer Res.* **2006**, *26*, 4527–4534. [PubMed]
7. Rukayadi, Y.; Yong, D.; Hwang, J.K. In vitro anticandidal activity of xanthorrhizol isolated from Curcuma xanthorrhiza Roxb. *J. Antimicrob. Chemother.* **2006**, *57*, 1231–1234. [CrossRef] [PubMed]
8. Lee, L.Y.; Shim, J.S.; Rukayadi, Y.; Hwang, J.K. Antibacterial Activity of Xanthorrhizol Isolated from Curcuma xanthorrhiza Roxb. against Foodborne Pathogens. *J. Food Prot.* **2008**, *71*, 1926–1930. [CrossRef] [PubMed]
9. Oon, S.F.; Nallappan, M.; Tee, T.T.; Shohaimi, S.; Kassim, N.K.; Sa'ariwijaya, M.S.F.; Cheah, Y.H. Xanthorrhizol: A review of its pharmacological activities and anticancer properties. *Cancer Cell Int.* **2015**. [CrossRef] [PubMed]
10. Aguilar, M.I.; Delgado, G.; Villarreal, M.L. New bioactive derivatives of xanthorrhizol. *Rev. Soc. Quím. Mex.* **2001**, *45*, 56–59.
11. Sirat, H.M.; Hong, N.M.; Jauri, M.H. Chemistry of xanthorrhizol: Synthesis of several bisabolane sesquiterpenoids from xanthorrhizol. *Tetrahedron Lett.* **2007**, *48*, 457–460. [CrossRef]
12. Dash, S.; Patel, S.; Mishra, B.K. Oxidation by permanganate: Synthetic and mechanistic aspects. *Tetrahedron* **2009**, *65*, 707–739. [CrossRef]
13. Lugemwa, F.N.; Shaikh, K.; Hochstedt, E. Facile and Efficient Acetylation of Primary Alcohols and Phenols with Acetic Anhydride Catalyzed by Dried Sodium Bicarbonate. *Catalysts* **2013**, *3*, 954–965. [CrossRef]
14. Silverstein, R.M.; Webster, F.X.; Kiemle, D.J. *Spectrometric Identification of Organic Compounds*, 7th ed.; John Wiley & Sons, Inc.: New York, NY, USA, 2005.
15. MarvinSketch 17.17.0. Chemaxon Ltd. 1998–2017. Available online: http://www.chemaxon.com (accessed on 20 November 2018).
16. Alimuddin, A.H.; Mardjan, M.I.D.; Chairil, S.M.; Anwar4, A.; Sholikhah, E.N. Synthesis 7-Hydroxy-3',4'-dimethoxyisoflavon from Eugenol. *Indones. J. Chem.* **2011**, *11*, 163–168.