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Studies on the Syntheses of Sesquiterpene Lactones. III. Improved Synthesis of Vulgarin

Masayoshi ANDO,* Kiyoshi TAJIMA, and Kahei TAKASE

Department of Chemistry, Faculty of Science, Tohoku University, Aramaki-aza-Aoba, Sendai 980

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Synopsis. An improved synthesis of vulgarin is described. Epoxidation of 1-oxo-5α*H*,6β,11β*H*-eudesm-3-en-6,13-olide and successive treatment of the resulting epoxide with silica gel gave vulgarin. Oxidation of 1-oxo-5α*H*,6β,11β*H*-eudesm-3-en-6,13-olide with air or oxygen gas gave 4α-hydroperoxy-1-oxo-5α*H*,6β,11β*H*-eudesm-2-en-6,13-olide and 4β-hydroperoxy-1-oxo-5α*H*,6β,11β*H*-eudesm-2-en-6,13-olide, which were transformed into vulgarin and C_4-epivulgarin, respectively.

Many compounds with a γ-hydroxy α,β-unsaturated carbonyl moiety fused on various skeletons have been found in natural products. Since some of them have considerable biological activities as shown in abscisic acid and ecdysone, the synthesis of γ-hydroxy α,β-unsaturated carbonyl moiety has drawn much attention, several efficient methods for preparing this functional group being reported.[1] Vulgarin (**5**) is a typical example of the sesquiterpenes possessing a γ-hydroxy α,β-unsaturated carbonyl group.[2] Reports have been given on the synthesis of vulgarin[3,5] and its α-methylene γ-lactone derivative, arglanine.[4,5] In connection with the general synthesis of γ-hydroxy α,β-unsaturated carbonyl moiety we have examined a more efficient synthesis of vulgarin.

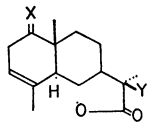
The starting material is a β,γ-unsaturated acetal (**1**) prepared from the corresponding α,β-unsaturated ketone.[5] Treatment of **1** with boiling 50% aqueous acetic acid gave the desired β,γ-unsaturated ketone (**2**)[2,4] in a quantitative yield. Methods for the preparation of γ-hydroxy α,β-unsaturated ketones *via* the corresponding β,γ-unsaturated ketones are limited[1] probably because of difficulty in the preparation of the intermediates.[6] Since the β,γ-unsaturated ketone (**2**) was obtained in an excellent yield, the synthesis of vulgarin *via* intermediate (**2**) was examined in two procedures.

Epoxidation of **2** with *m*-chloroperbenzoic acid gave an epoxy ketone (**4**) in a quantitative yield. The stereochemical assignment of the epoxide ring of **4** is based on the consideration that the epoxidation proceeds from the less hindered α-side. **4** was transformed into vulgarin in 90% yield by treatment with silica gel TLC for 1 h.

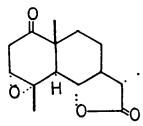
During the course of attempted purification of **2** by TLC of silica gel we observed that this compound gradually turned into two kinds of more polar substances at the surface of silica gel. In order to examine the transformation, **2** was allowed to stand on the surface of silica gel in TLC on exposure to air for 12 days to give 4α-hydroperoxide (**7**) in a 46% yield and 4β-hydroperoxide (**8**) in a 13% yield accompanied by vulgarin in a 9% yield. The structure of **7** and **8** were deduced from the analyses of their NMR spectra. The assigned stereochemistry at C_4 in **7** and **8** was unambiguously demonstrated by their conversion into vulgarin and C_4-epivulgarin (**6**) in quantitative yields by treatment with KI in aqueous acetic acid.

The oxidation reaction of **2** by molecular oxygen in solution was also investigated. Since the γ-lactone moiety was considered to be sensitive in autoxidation in strong basic conditions, we chose neutral or slightly acidic[7] conditions. The β,γ-unsaturated ketone (**2**) gave vulgarin by bubbling oxygen gas into 50% aqueous acetic acid solution at refluxing temperature. This reaction was very slow at room temperature but proceeded in a moderate rate by addition of active charcoal[8] into the reaction mixture. In this case the major product was not vulgarin but the corresponding hydroperoxide (**7**). In MeOH and DMF solutions, the oxidation reaction of **2** by molecular oxygen in the presence of active charcoal proceeded in the same manner as in 50% aqueous acetic acid solution. The results are summarized in Table 1. The resulting hydroperoxides (**7**) and (**8**) were transformed into vulgarin and C_4-epivulgarin, respectively, in quantitative yields.

The acetal (**1**) also gave vulgarin (**5**) in a 50% yield by bubbling oxygen gas in boiling 50% aqueous acetic acid solution. Yamakawa *et al.* reported a similar reaction in an acetal (**3**), but did not mention the reaction path.[4] These reactions probably proceeded through autoxidation of the corresponding β,γ-unsaturated ketones formed under the reaction conditions and successive decomposition of the resulting hydroperoxides to the corresponding alcohols.



(**1**) X=⟨O O⟩, Y=H
(**2**) X=O, Y=H
(**3**) X=⟨O O⟩, Y=SeC_6H_5



(**4**)

(**5**) X=OH, Y=CH_3
(**6**) X=CH_3, Y=OH
(**7**) X=O_2H, Y=CH_3
(**8**) X=CH_3, Y=O_2H

Experimental

All the melting points were uncorrected. IR spectra were determined on Shimadzu IRG-1 and Nihonbunko IRA-2 spectrometers. NMR spectra were recorded on a Hitachi R-24 spectrometer in $CDCl_3$ containing TMS as an internal standard.

1-Oxo-5αH,6β,11βH-eudesm-3-en-6,13-olide (2) from 1,1-Ethylenedioxy-5αH,6β,11βH-eudesm-3-en-6,13-olide (1). A solution of **1** (800 mg, 2.74 mmol) in 50% AcOH aq (76 ml) was refluxed for 1 h and 15 min under N_2, cooled and poured into satd. NaCl aq soln. The mixture was worked up as usual to give 677 mg (100%) of **2**, (mp 139 °C).

Table 1. Oxidation of 2 with molecular oxygen

Run	Reaction conditions				Isolated yield/%			
	Solvent	Catalyst	Temperature	Time/h[a]	7	8	5	6
i	50% AcOH aq	None	Room temp	24	(Recovered starting material)			
ii	50% AcOH aq	None	Reflux	2.5	0	0	24	0
iii	50% AcOH aq	C[b]	Reflux	1	0	0	38	9
iv	50% AcOH aq	C[b]	Room temp	70	49	13	19	0
v	MeOH	C[b]	Room temp	87	71	16	12	0
vi	DMF	C[b]	Room temp	76	62	9	12	0

a) The reactions were stopped at the time when **2** disappeared in the reaction mixture by TLC analysis except in the case of run i. b) Active charcoal (powder).

3α,4α-Epoxy-1-oxo-5αH,6β,11βH-eudesman-6,13-olide (4). A mixture of **2** (47 mg, 0.19 mmol) and *m*-chloroperbenzoic acid (33 mg, 0.19 mmol) in CH_2Cl_2 (3 ml) was allowed to stand at room temperature for 75 h. The mixture was worked up as usual to give 50 mg (100%) of spectroscopically pure **4** as a crystalline material, which was recrystallized from ether to give prisms, mp 151 °C. IR (KBr): 1770 and 1712 cm^{-1}. NMR: δ 1.24 (3H, d, J=6.4 Hz, C_{11}–Me), 1.27 (3H, s, C_{10}–Me), 1.59 (3H, s, C_4–Me), 2.05 (1H, d, J=11.5 Hz, C_5–H), 2.79 (1H, d, J=1.6 Hz, C_2–H), 2.83 (1H, d, J=4.0 Hz, C_2–H), 3.25 (1H, dd, J=1.6 and 4.0 Hz, C_3–H), 4.06 (1H, broad t, J=11.5 Hz, C_6–H). Found: C, 67.82; H, 7.71%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

Vulgarin from 4. The $CHCl_3$ solution of **4** (50 mg, 0.19 mmol) was impregnated into TLC of silica gel (Merck GF_{254}, thickness 0.25 mm, 20 cm×20 cm sheet), which was developed by dipping in AcOEt–$CHCl_3$ (1:1) for 1 h. The most polar band was collected and extracted with acetone to give 45 mg (90%) of vulgarin.

Air Oxidation of 2 at the Surfaces of Silica Gel TLC. The $CHCl_3$ solution of **2** (21 mg, 0.08 mmol) was impregnated into TLC of silica gel (Merck GF_{254}, thickness 0.25 mm, 20 cm×10 cm sheet), which was developed by dipping in AcOEt–$CHCl_3$ (1:1). The TLC plate was dried and allowed to stand at room temperature exposed to air for 12 days. The black band monitored by an UV lamp was collected from TLC and extracted with acetone to give 22 mg of oil, which was shown to be a 10:3 mixture of **7** and **8** from the analysis of the NMR spectrum. This was purified by preparative TLC [Merck silica gel GF_{254}, thickness 0.25 mm, EtOAc:$CHCl_3$ (1:1)]. The first band (R_f 0.50) gave 3 mg (13%) of **8**, which was recrystallized from ether to give colorless prisms; mp 178 °C. IR (KBr): 3360, 3300, 1765, 1745, and 1682 cm^{-1}. NMR: δ 1.21 (3H, d, J=6.8 Hz, C_{11}–Me), 1.32 (3H, s, C_{10}–Me), 1.67 (3H, s, C_4–Me), 2.14 (1H, d, J=11.6 Hz, C_5–H), 4.24 (1H, m, C_6–H), 5.98 (1H, d, J=10.2 Hz, C_2–H), and 6.76 (1H, d, J=10.2 Hz, C_3–H). The second band (R_f 0.40) gave 11 mg (46%) of **7**, which was recrystallized from ether to give colorless prisms; mp 175 °C. IR (KBr): 3320, 1770, 1748, 1677, and 1660 cm^{-1}. NMR: δ 1.22 (3H, d, J=6.4 Hz, C_{11}–Me), 1.25 (3H, s, C_{10}–Me), 1.48 (3H, s, C_4–Me) 2.85 (1H, d, J=11.6 Hz, C_5–H), 4.13 (1H, dd, J=8.0 and 11.6 Hz, C_6–H), 6.02 (1H, d, J=10.6 Hz, C_2–H), 6.72 (1H, d, J=10.6 Hz, C_3–H). Found: C, 63.86; H, 7.41%. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19%.

Oxidation of 2 by Molecular Oxygen in MeOH in the Presence of Active Charcoal. Oxygen gas was bubbled into a solution of **2** (20 mg, 0.08 mmol) in MeOH (3 ml) in the presence of active charcoal (20 mg) at room temperature for 87 h. The mixture was worked up as usual to give 22 mg of oil, which was separated by TLC (Merck silica gel GF_{254}, thickness 0.25 mm, EtOAc:$CHCl_3$=1:1) to give 16 mg (71%) of **7**, 3.5 mg (16%) of **8**, and 2.5 mg (12%) of vulgarin.

Vulgarin from 7. A mixture of **7** (9 mg, 0.032 mmol), KI aq soln (KI 30 mg, H_2O 1.5 ml), AcOH (0.1 ml), and $CHCl_3$ (0.5 ml) was stirred for 2 h at room temperature. The mixture was worked up as usual to give 8.5 mg (100%) of vulgarin.

C_4-Epivulgarin from 8. **8** (9 mg, 0.032 mmol) was treated as mentioned above to give 8.5 mg (100%) of C_4-epivulgarin.

Oxidation of 1 by Molecular Oxygen in Boiling 50% AcOH Aq Soln. Oxygen gas was bubbled into a solution of **1** (30 mg, 0.10 mmol) in 50% AcOH aq soln (3 ml) under refluxing for 3 h, cooled and poured into satd. NaCl aq soln. The mixture was worked up as usual to give an oily crude product, which was chromatographed over silica gel (Merck, <230 mesh, 1.5 g) and eluted with $CHCl_3$ to give 13.5 mg (50%) of vulgarin.

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