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STRUCTURE AND SYNTHESIS OF [*n*]-DEHYDROSHOGAOLS FROM *ZINGIBER OFFICINALE*

TIAN-SHUNG WU,* YOU-CHENG WU, PEI-LIN WU, CHING-YUH CHERN, YANN-LII LEU and YU-YI CHAN

Department of Chemistry, National Cheng Kung University, Tainan, Taiwan, R.O.C.

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Key Word Index—*Zingiber officinale*; Zingiberaceae; rhizomes; ginger; [6]-dehydroshogaol; [8]-dehydroshogaol; [10]-dehydroshogaol.

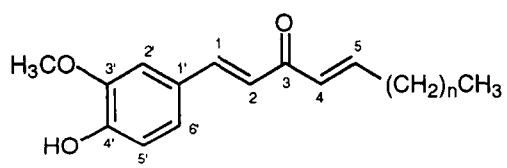
Abstract—Three new dehydroshogaols have been isolated from the rhizomes of *Zingiber officinale*. Their structures were established by spectroscopic analysis and synthesis.

INTRODUCTION

Ginger (Chinese name: shengjiang), the rhizomes of *Zingiber officinale*, is a well-known spice and frequently prescribed in traditional Chinese medicine as a stomachic, antiemetic, antidiarrheal, expectorant, antiasthmatic, haemostatic and cardiotonic, for the treatment of gastrointestinal and respiratory diseases [1]. Numerous chemical investigations of the pungent and bioactive principles of ginger have been carried out [2–14]. In the course of our continuing research for novel biologically active compounds from natural sources, bioassay-directed fractionation led to the isolation and characterization of three new dehydroshogaols, [6]-dehydroshogaol (**1**), [8]-dehydroshogaol (**2**) and [10]-dehydroshogaol (**3**), from a diethyl ether extract of the rhizomes of *Z. officinale*. We describe herein the structural elucidation and the synthesis of these compounds.

RESULTS AND DISCUSSION

[6]-Dehydroshogaol (**1**) was isolated as a yellow syrup which showed the molecular formula, $C_{17}H_{22}O_3$, as determined by HR mass spectrometry. The IR spectrum showed hydroxyl absorption at 3400 cm^{-1} and carbonyl absorption at 1654 cm^{-1}. The ^1H NMR spectrum apparently exhibited an ABC-pattern signal at δ 6.93 (*d*, J = 8.4 Hz), 7.04 (*d*, J = 1.6 Hz) and 7.04 (*dd*, J = 8.4, 1.6 Hz), indicating the presence of a 1′,3′,4′-trisubstituted benzene nucleus (Table 1). Two of the substituents were suggested to be a phenolic group (δ 5.87, D_2O-exchangeable) at C-4′ and a methoxyl group (δ 3.95) at C-3′, whose regiochemistry was confirmed by a clear NOE between OMe (δ 3.95) and H-2′ (δ 7.07) in a NOESY experiment. The latter substituent was identified as a *trans*-α,β-unsaturated carbonyl group at δ 6.82 and 7.58 (*d*, J = 16.2 Hz) from the downfield signals and its large coupling constant. The other set of deshielded vinyl proton signals at δ 6.84 (*dt*, J = 15.6, 1.6 Hz) and 7.0 (*dt*, J = 15.6, 7.6 Hz), as well as unresolvable multiplets between δ 0.8–1.8, suggested the existence of an alkenyl group bearing a five-carbon long-chain residue attached to the open end of the carbony group. A NOESY experiment, H-2 showing NOE to H-4, supported this connectivity. Based on the above analyses, the structure of [6]-dehydroshogaol was established as **1**.



1: n = 4
2: n = 6
3: n = 8

[8]-Dehydroshogaol (**2**) and [10]-dehydroshogaol (**3**) exhibited similar spectroscopic properties to that of **1** (Table 1). The major difference was in their mass spectra which showed a $[M]^+$ at m/z 302 and 330, respectively, corresponding to the addition of 28 and 56 amu to that of **1** ($[M]^+$ m/z 274). Consequently, these data led us to deduce the structure of [8]-dehydroshogaol as **2** and [10]-dehydroshogaol as **3**.

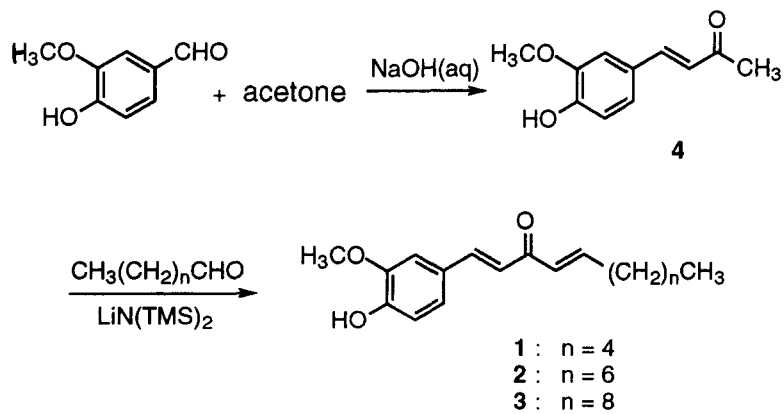
In order to confirm these structures, synthesis of [*n*]-dehydroshogaols was carried out, as summarized in Scheme 1. Aldol condensation between vanillin and acetone in sodium hydroxide gave dehydrogingerone (**4**), and further condensation of **4** with alkanal in the

* Author to whom correspondence should be addressed.

Table 1. ^{1}H NMR spectral data of compounds **1–3** (400 MHz in $CDCl_3$, *J* in Hz)

	1	**2**	**3**
H-2′	7.07 (*d*, 1.6)	7.07 (*d*, 2.4)	7.08 (*d*, 2.0)
H-5′	6.93 (*d*, 8.4)	6.93 (*d*, 8.0)	6.93 (*d*, 8.0)
H-6′	7.14 (*dd*, 8.4, 1.6)	7.13 (*dd*, 8.0, 2.4)	7.14 (*dd*, 8.0, 2.0)
3′-OMe	3.95 *s*	3.94 *s*	3.94 *s*
4′-OH†	5.87 *br*	5.89 *br*	5.90 *br*
H-1	7.58 (*d*, 16.2)	7.57 (*d*, 16.0)	7.58 (*d*, 15.6)
H-2	6.82 (*d*, 16.2)	6.84 (*d*, 16.0)	6.44 (*d*, 15.6)
H-4	6.48 (*dt*, 15.6, 1.6)	6.43 (*dt*, 16.0, 2.4)	6.82 (*d*, 16.0)
H-5	7.00 (*dt*, 15.6, 7.6)	6.99 (*dt*, 16.0, 7.2)	7.00 (*dt*, 16.0, 6.8)
H-6	2.27 (*qd*, 7.6, 1.6)	2.26 (*qd*, 7.2, 2.8)	2.27 (*q*, 6.8)
H-7	1.51 *m*	1.50 *m*	1.50 *m*
H-8-H-n	1.33 *m* (4H)	1.32 *m* (8H)	1.28 *m* (12H)
Me (terminal)	0.90 (*t*, 6.8)	9.90 (*t*, 7.2)	0.88 (*t*, 6.8)

† ??



Scheme 1. Synthesis of [*n*]-dehoydroshogaols.

presence of lithium *bis*(trimethylsilyl)amide ($LiN(TMS)_2$) afforded dehydroshogaols **1–3** in moderate yields [15]. The spectral data (UV, IR, EI, ^{1}H and ^{13}C NMR) and TLC of the synthetic compounds **1–3** were consistent with the naturally occurring dehydroshogaols.

EXPERIMENTAL

Mps: uncorr. UV: MeOH IR: KBr. MS: direct inlet system. NMR: TMS as int. standard.

Plant material

Fresh ginger, rhizomes of *Z. officinale* Roscoe, were purchases from a market in Tainan, Taiwan.

Extraction and separation

The ginger (64.4 kg) was chopped and then filtered. The filtrate was partitioned between Et_2O and H_2O. The acetone extracts were combined, concentrated, and partitioned between Et_2O and H_2O. The ethereal solution was subjected to silica gel CC using a gradient of C_6H_6 and Me_2CO as eluent to yield twenty-four frs. The combination of frs 5–8 was repeated rechromatographed to afford **1** (2 mg), **2** (3 mg) and **3** (2 mg), successively.

[6]-*Dehydroshogaol* (**1**)

Yellow syrup. HRMS: calcd for $C_{17}H_{22}O_3$, *m/z* 274.1568 $[M]^+$, found 274.1571. UV λ_{max} nm (log ε): 258 (3.93), 355 (4.02). IR ν_{max} cm^{-1}: 3354, 2956, 1654, 1625. EIMS *m/z* (rel. int.): 274 ($[M]^+$, 56), 217 (50), 177 (100), 145 (29), 137 (91), 117 (13), 89 (16), 77 (15), 55 (33). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.4, 27.9, 31.4, 32.7, 56.0, 109.7, 114.8, 122.8, 123.3, 127.4, 129.0, 143.3, 147.2, 148.0, 148.1, 189.3.

[8]-*Dehydroshogaol* (**2**)

Yellow syrup. HRMS: calcd for $C_{19}H_{26}O_3$, *m/z* 302.1882 $[M]^+$, found 302.1881. UV λ_{max} nm (log ε): 258 (3.96), 357 (4.10). IR ν_{max} cm^{-1}: 3395, 2925, 1660, 1614. EIMS *m/z* (rel. int.): 302 ($[M]^+$, 26), 217 (67),

204 (25), 177 (100), 150 (25), 145 (32), 137 (83). ^{13}C NMR ($CDCl_3$): δ 14.0, 22.6, 28.1, 29.0, 29.1, 31.7, 32.7, 55.9, 109.7, 114.8, 122.7, 123.2, 127.3, 129.0, 143.3, 146.8, 148.0, 148.2, 189.3.

[10]-*Dehydroshogaol* (**3**)

Yellow syrup. HRMS: calcd for $C_{21}H_{30}O_3$, *m/z* 330.2195 $[M]^+$, found 330.2193. UV λ_{max} nm (log ε): 257 (4.04), 355 (4.18). IR ν_{max} cm^{-1}: 3533, 2925, 1660, 1614. EIMS *m/z* (rel. int.): 330 ($[M]^+$, 26), 217 (82), 204 (29), 177 (100), 150 (32), 145 (34), 137 (98), 117 (21), 69 (20), 57 (30), 55 (46). ^{13}C NMR ($CDCl_3$): δ 14.1, 22.7, 28.2, 29.2, 29.3, 29.4, 29.5, 31.8, 32.7, 55.9, 109.7, 114.8, 122.7, 123.3, 127.3, 129.0, 143.4, 146.8, 148.0, 148.2, 189.3.

General procedure for synthesis of [n]-*dehydroshogaols*

Dehydrogingerone (**4**) was obtained by the aldol condensation of vanillin (2.5 g, 16.4 mmol) with Me_2CO (100 ml) in 10% aq. NaOH [15]. Then, **4** (2 g, 10.4 mmol) in 10 ml of THF was added dropwise, over 10 min, to a THF soln (75 ml) of $LiN(TMS)_2$ (20.8 mmol) at 0° under Ar. After a further 1 h, alkanal (10.4 mmol) was added and the mixt. stirred at 0° for 3 h. EtOAc was then added and the resulting mixt. washed with 5% aq. HCl and satd aq. NaCl. The organic layer was dried (Na_2SO_4) and concd *in vacuo*. The residue was purified by CC to afford dehydroshogaols **1** (1 g, 35% yield), **2** (1.2 g, 38% yield) and **3** (1.1 g, 32% yield) and identified by comparison with the corresponding naturally occurring compounds.

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