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A New Synthesis of the Pungent Principles of Ginger — Zingerone, Gingerol and Shogaol —

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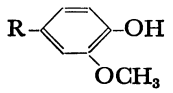
Synopsis. The pungent principles of ginger —zingerone, gingerol and shogaol— are synthesized starting with vanillin in good yields by utilizing the Lewis acid-promoted cross aldol reaction in each key step.

In recent publications we reported a potential synthetic method[2] for the preparation of various cross aldols by the $TiCl_4$-promoted reactions of silyl enol ethers with carbonyl compounds. In the present paper, a successful application of the above mentioned method to the syntheses of the pungent principles of ginger[3] —zingerone, gingerol and shogaol— is described. Of these compounds, zingerone and shogaol were synthesized by Nomura *et al.*[3] according to the conventional base catalyzed aldol reaction, however, there is no report concerning the synthesis of gingerol.

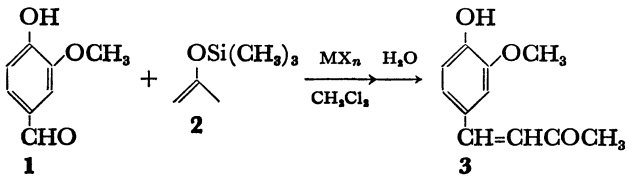


Zingerone R = $CH_2CH_2COCH_3$

Gingerol R = $CH_2CH_2COCH_2CH(CH_2)_4CH_3$ (OH)

Shogaol R = $CH_2CH_2COCH{=}CH(CH_2)_4CH_3$

Zingerone: When vanillin was treated with 2-trimethylsiloxy-1-propene (**2**) in the presence of $TiCl_4$, 2-methoxy-4-(3-oxo-1-butenyl)phenol(**3**) was obtained only in 7% yield and 90% of vanillin was recovered. Then, the reaction of **2** with vanillin was investigated in detail using various Lewis acids, and it was found that **3** was obtained in the optimum yield when $BF_3 \cdot OEt_2$ was employed (see the Table 1).

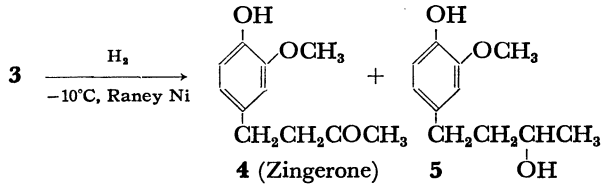


1 + **2** → (MX_n, CH_2Cl_2; H_2O) → **3**

TABLE 1. REACTION OF THE SILYL ENOL ETHER **2** WITH VANILLIN IN THE PRESENCE OF LEWIS ACID

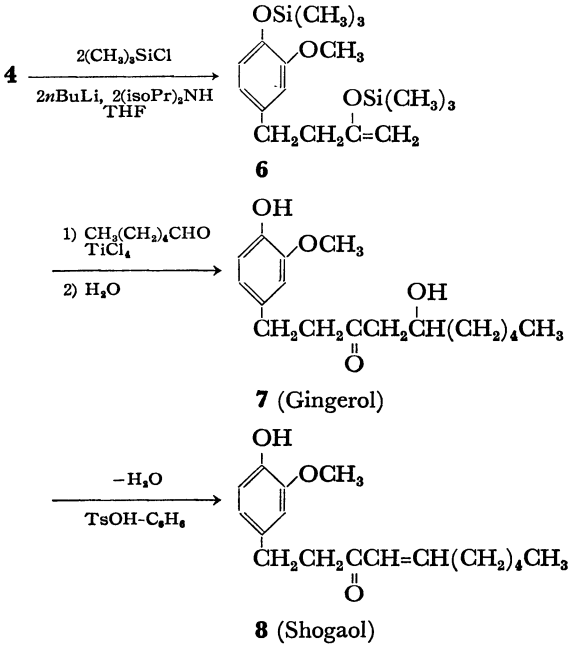
Lewis acid	Temp (°C)	Time (h)	Yield of **3** (%)
$TiCl_4$	0	2	7
$SnCl_4$	0	2	4
$AlCl_3$	0	2	5
$BF_3 \cdot OEt_2$	0	2	68
	r.t.	3	89

The catalytic hydrogenation of **3** over Raney nickel afforded 2-methoxy-4-(3-oxobutyl)phenol (**4**) (zingerone: colorless needles, mp 36—37 °C) and 2-methoxy-4-(3-hydroxybutyl)phenol(**5**) in 75% and 16% yields, respectively.



3 → (H_2, −10°C, Raney Ni) → **4** (Zingerone) + **5**

Gingerol and Shogaol: The silylation of **4** was carried out by a modification of House's method.[4] The treatment of a tetrahydrofuran solution of **4** with lithiodiisopropylamine, followed by addition of chlorotrimethylsilane, resulted in the formation of 2-methoxy-4-(3-trimethylsiloxy-3-butenyl)phenoxytrimethylsilane (**6**) in 69% yield. The reaction of **6** with hexanal in the presence of $TiCl_4$ gave *dl*-4-(5-hydroxy-3-oxodecyl)-2-methoxyphenol (**7**) (gingerol)[5] in 92% yield. 2-Methoxy-4-(3-oxo-4-decenyl)phenol (**8**) (shogaol) was obtained in 95% yield by the dehydration of **7** with TsOH–benzene. The structure of **8** was confirmed by comparison with the authentic sample (IR and NMR spectra).



4 → ($2(CH_3)_3SiCl$, $2nBuLi$, $2(isoPr)_2NH$, THF) → **6**

6 → (1) $CH_3(CH_2)_4CHO$, $TiCl_4$; (2) H_2O) → **7** (Gingerol)

7 → ($-H_2O$, TsOH-C_6H_6) → **8** (Shogaol)

Experimental

Preparation of Zingerone (**4**). A dichloromethane (10 ml) solution of 1.30 g (10 mmol) of **2** was added dropwise into a mixture of 0.76 g (5 mmol) of **1** and 0.705 g (5 mmol) of $BF_3 \cdot OEt_2$ in dichloromethane (40 ml) under an argon atmosphere at room temperature, and the reaction mixture was stirred for 3 h. After hydrolysis with water (50 ml) at the temperature, the resulting organic layer was extracted with ether (100 ml), and the extract was washed with saturated NaCl solution (80 ml × 3) and dried over anhydrous Na_2SO_4.

The ethereal solution was condensed and then petroleum ether (30 ml) was added into the residue. The yellow precipitate was filtered and recrystallized from ligroin to yield 0.768 g (80%) of **3**. After evaporation of the filtrate, the residue was purified by preparative TLC (silica gel) using dichloromethane as a developer to give 0.086 g (9%) of **3** (total yield 89%) [IR (KBr disk): 3400, 1640, 1620 cm^{-1}; NMR ($CDCl_3$): δ 2.39 (s, 3H), 3.93 (s, 3H), 6.12 (b, 1H), 6.60 (d, J=16 Hz, 1H), 6.9—7.1 (m, 3H), 7.53 (d, J=16 Hz, 1H)]. A methanol (50 ml) solution of 3.92 g (20 mmol) of **3** was treated with hydrogen for 2 h at −10 °C in the presence of 0.3 g of Raney nickel (commercially produced Raney nickel was thoroughly washed with methanol). About 480 ml of hydrogen was absorbed. After filtration, the filtrate was evaporated, and the residual oil was purified by column chromatography (silica gel) using dichloromethane as a developer to give 2.91 g (75%) of **4** (zingerone)[IR(KBr disk): 3420, 1715 cm^{-1}; NMR (CCl_4): δ 2.04 (s, 3H), 2.69 (quasi s, 4H), 5.90 (b, 1H), 6.4—6.8 (m, 3H)] and 0.630 g (16%) of **5** [IR (neat): 3390 cm^{-1}; NMR (CCl_4): δ 1.21 (d, J=6 Hz, 3H), 1.3—4.0 (m, 5H), 3.81 (s, 3H), 6.18 (b, 1H), 6.9—7.1 (m, 3H)].

Trimethylsilylation of Zingerone (**6**). A hexane solution of 110 mmol of *n*-BuLi was added in 200 ml of THF. The resulting solution was treated with 11 g (110 mmol) of diisopropylamine at −10 °C. To this solution, 9.7 g (50 mmol) of **4** was added dropwise over a 20 min period with stirring at −10 °C. After stirring for an additional 30 min at the temperature, 1.19 g (110 mmol) of chlorotrimethylsilane was added into the mixture. The resulting mixture was stirred for 30 min, diluted with 300 ml of ether, and washed rapidly with two 200 ml portions of cold aq. 10% $KHSO_4$ and cold aq. $NaHCO_3$. The resulting organic layer was dried and concentrated Fractional distillation of the residue with a spinning Teflon-band column gave fraction 1; bp 172—173 °C/5.5 Torr, consisting of the pure **6** (11.6 g, 69%) [IR (neat): 1620 cm^{-1}; NMR (CCl_4): δ 0.18 (s, 9H), 0.20 (s, 9H), 2.0—3.0 (m, 4H), 3.76 (s, 3H), 3.97 (s, 2H), 6.63 (s, 3H)] and fraction 2; bp 173—179 °C/5.5 Torr, containing **6** and unknown compounds (4.5 g).

Preparation of Gingerol (**7**). To a dichloromethane (40 ml) solution of hexanal (0.347 g, 3.3 mmol) and $TiCl_4$ (0.567 g, 3 mmol) was added a dichloromethane (10 ml) solution of **6** (1.017 g, 3 mmol) at −78 °C, and the reaction mixture was stirred for 1 h at the temperature. After usual work-up, the resulting mixture was chromatographed on silica gel. Elution with dichloromethane afforded 0.828 g (92%) of **7** (gingerol) [IR (neat): 3450, 1710 cm^{-1}; NMR (CCl_4): δ 0.86 (t, J=5 Hz, 3H), 1.0—1.8 (m, 8H), 2.44 (d, J=5.5 Hz, 2H), 2.67 (s, 4H), 3.73 (s, 3H), 3.8—4.0 (m, 1H), 6.3—7.0 (m, 3H)].

Preparation of Shogaol (**8**). A solution of **7** (0.60 g, 2 mmol) in dry benzene (50 ml) was refluxed with *p*-toluenesulfonic acid (0.2 g). The resulting crude product was chromatographed on silica gel. Elution with benzene gave 0.534 g (75%) of **8** (shogaol) [IR (neat): 3430, 1665, 1630 cm^{-1}; NMR (CCl_4): δ 0.88 (t, J=5 Hz, 3H), 1.0—2.3 (m, 8H), 2.76 (s, 4H), 3.78 (s, 3H), 5.71 (d, J=18 Hz, 1H), 6.0—6.8 (m, 4H)].

References

1) Present address; The First Institute, Tokushima Faculty, Otsuka Pharmaceutical Company, Ltd., 463-10 Kagasuno, Kawauchi-cho Tokushima-Shi 771-01.

2) a) T. Mukaiyama, K. Narasaka, and K. Banno, *Chem. Lett.*, **1973**, 1011. b) T. Mukaiyama, K. Banno, and K. Narasaka, *J. Am. Chem. Soc.*, **96**, 7503 (1974). c) K. Banno and T. Mukaiyama, *Chem. Lett.*, **1975**, 741.

3) The pungent principles of ginger consist of zingerone, gingerol, and shogaol, which were isolated and assinged by Lapworth *et al.* and by Nomura *et al*: H. Nomura, *J. Chem. Soc.*, **111**, 769 (1917); A. Lapworth, L. K. Peason, and F. A. Royle, *ibid.*, **111**, 777 (1917); H. Nomura and S. Hotta, *Sci. Rep. Tohoku Imp. Univ.*, **7**, 67, 79 (1918); *ibid.*, **14**, 119, 131, 144 (1925); H. Nomura and S. Tsurumi, *ibid.*, **16**, 589 (1927); *ibid.*, **17**, 973 (1928).

4) H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **34**, 2324 (1969).

5) This product was led to the diacetate on treatment with acetic anhydride in pyridine and was confirmed by NMR and mass spectra [NMR (CCl_4): δ 0.89 (t, J=5 Hz, 3H), 1.0—1.8 (m, 8H), 1.91 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$), 2.50 (d, J=5 Hz, 2H), 2.71 (t, J=3 Hz, 4H), 3.74 (s, 3H), 5.10 (m, 1H), 6.5—6.9 (m, 3H); mass: *m/e* 378 (M^+)].