

New Synthesis of the Pungent Principles of Ginger—Zingerone and Shogaol

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A high-yield, multigram synthesis of zingerone (4) and shogaol (6), two of the pungent principles of ginger (*Zingiber officinale* Roscoe), is described. Both 4 and 6 were prepared by addition of organolithium reagents to 3-(4-hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylpropanamide (3), which was in turn prepared from ferulic acid (1) in 79% yield. The addition of methyllithium to 3 gave 4 in 63% (unoptimized) yield from 1. Similarly, the addition of heptynyllithium to amide 3, followed by Cr(II) reduction of the resulting alkyne, gave 6 in 69% overall yield from 1.

Zingerone (4) [4-(4-hydroxy-3-methoxyphenyl)-2-butanone] and shogaol (6) [1-(4-hydroxy-3-methoxyphenyl)-dec-4-en-3-one] are two of the pungent principles found in ginger root oleoresin (*Zingiber officinale* Roscoe) (Connell and Sutherland, 1969; Banno and Mukaiyama, 1976). Both 4 and 6 have been synthesized using a variety of strategies (Connell and Sutherland, 1969; Banno and Mukaiyama, 1976; Enders et al., 1979; Denniff et al., 1981; Bunce and Reeves, 1989; Vig et al., 1990). However, we desired to develop a new procedure that would allow us to prepare both compounds in gram quantities by the addition of appropriate organometallic reagents to a common intermediate. To accomplish this objective, our strategy (Figure 1) was to prepare and use 3-(4-hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylpropanamide (3) as a common intermediate to which the appropriate organometallic reagents could be added to yield 4 or the precursor to 6, alkyne 5.

RESULTS AND DISCUSSION

To prepare the desired amide 3, it was first necessary to prepare 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (2). Compound 2 was in turn obtained by catalytic hydrogenation (Pd/C) of commercially available 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (1). The desired reduction (1 → 2) was accomplished in quantitative yield on a 30-g scale. With 2 on hand, we proceeded to test whether methyllithium could be added to obtain 4 in high yield, thereby eliminating the need to prepare 3. While not unexpected (Jorgenson, 1971; Seidel et al., 1990), the addition of methyllithium to 2 was sluggish at 25 °C, with 26%, 29%, and 31% isolated yields of 4 being obtained after 24, 48, and 72 h, respectively. Given these results, the addition of an alkynyllithium reagent to 2 (i.e., 2 → 5) was not expected to be productive, and this expectation was confirmed experimentally. Therefore, to facilitate the addition of the necessary organolithium reagents, 2 was converted to the *N*-methoxy-*N*-methylamide 3 (Nahm and Wienreb, 1981). A one-pot procedure for 3 was developed in which 2 was treated with SOCl₂ in CH₂Cl₂, followed by addition of *N,O*-dimethylhydroxylamine hydrochloride and finally pyridine. Good yields of 3 (79%) were obtained on reaction scales as large as 5.0 g. Methyllithium added smoothly to amide 3, giving 4 in 80%

yield (not optimized) on a 1.0-g scale. Amide 3 also allowed the addition of heptynyllithium to proceed readily at -78 °C, giving 5 in 99% yield on reaction scales as large as 2.5 g. Alkyne 5 was reduced to 6 in 88% yield on a 2.5-g reaction scale using aqueous CrSO₄ (Castro and Stephens, 1964).

In conclusion, the approach to 4 and 6 presented here allows for their preparation in good overall yield (63% and 69%, respectively) and on a moderate scale from readily available starting materials. The preparations outlined should be of general utility to those seeking to prepare 4 and 6 or other compounds available from these compounds or amide 3.

EXPERIMENTAL PROCEDURES

General Procedures. All reactions were carried out under an atmosphere of nitrogen, except where noted. THF was distilled from sodium benzophenone ketal, CH₂Cl₂ was distilled from CaH₂, and ethyl acetate (EtOAc) and hexanes were distilled through a Vigreux column. All other reagents and solvents were used as purchased. Yields were calculated for materials judged to be homogeneous by TLC and NMR. TLC was performed on aluminum-backed Kieselgel 60 F₂₅₄ plates having a 0.2-mm coating thickness, visualizing with a 254-nm UV lamp, and staining with an ethanol solution of 12-molybdophosphoric acid. Medium-pressure column chromatography (MPLC) was accomplished using silica gel having an average pore diameter of 60 Å and particle size of 50 μm. Melting points were obtained in open-end capillary tubes and are uncorrected. ¹H NMR spectra were acquired at 60 MHz using TMS as internal standard. IR spectra are approximately ±4 cm⁻¹. All MS spectra were obtained under EI conditions at 70 eV. Combustion analysis was carried out by Desert Analytics of Tucson, AZ.

3-(4-Hydroxy-3-methoxyphenyl)propanoic Acid (2). A solution of 30 g (103 mmol) of 3-(4-hydroxy-3-methoxyphenyl)-2-propenoic acid (1) in 600 mL of anhydrous ethanol was magnetically stirred under a H₂ atmosphere for 5 days in the presence of a catalytic amount of 10% Pd/C. The reaction mixture was filtered through Celite and concentrated in vacuo to give 30.2 g (100%) of 2 as an off-white, amorphous solid: mp 90.0–91.0 °C [lit. 90–91 °C (Pearl, 1959)]; ¹H NMR (CDCl₃) δ 8.85–7.75 (br s, 2H), 6.96–6.57 (m, 3H), 3.82 (s, 3H), 3.10–2.45 (m, 4H); IR (mull) 3500–2500 (m), 1699 (s); MS *m/z* (relative intensity) 196 (M⁺, 28), 150 (5), 137 (100), 122 (8), 107 (8), 91 (6), 77 (8). Anal. Calcd for C₁₀H₁₂O₄: C, 61.22; H, 6.16. Found: C, 61.23; H, 6.15.

3-(4-Hydroxy-3-methoxyphenyl)-*N*-methoxy-*N*-methylpropanamide (3). A solution of 5.00 g of 2 (25.5 mmol), 100 mL of CH₂Cl₂, and 2.23 mL (3.64 g, 30.6 mmol) of SOCl₂ was refluxed for 8 h. The progress of the reaction was followed by TLC using aliquots quenched with anhydrous MeOH [*R_f* of ester, 0.56 (EtOAc)]. The reaction mixture was cooled to room tempera-

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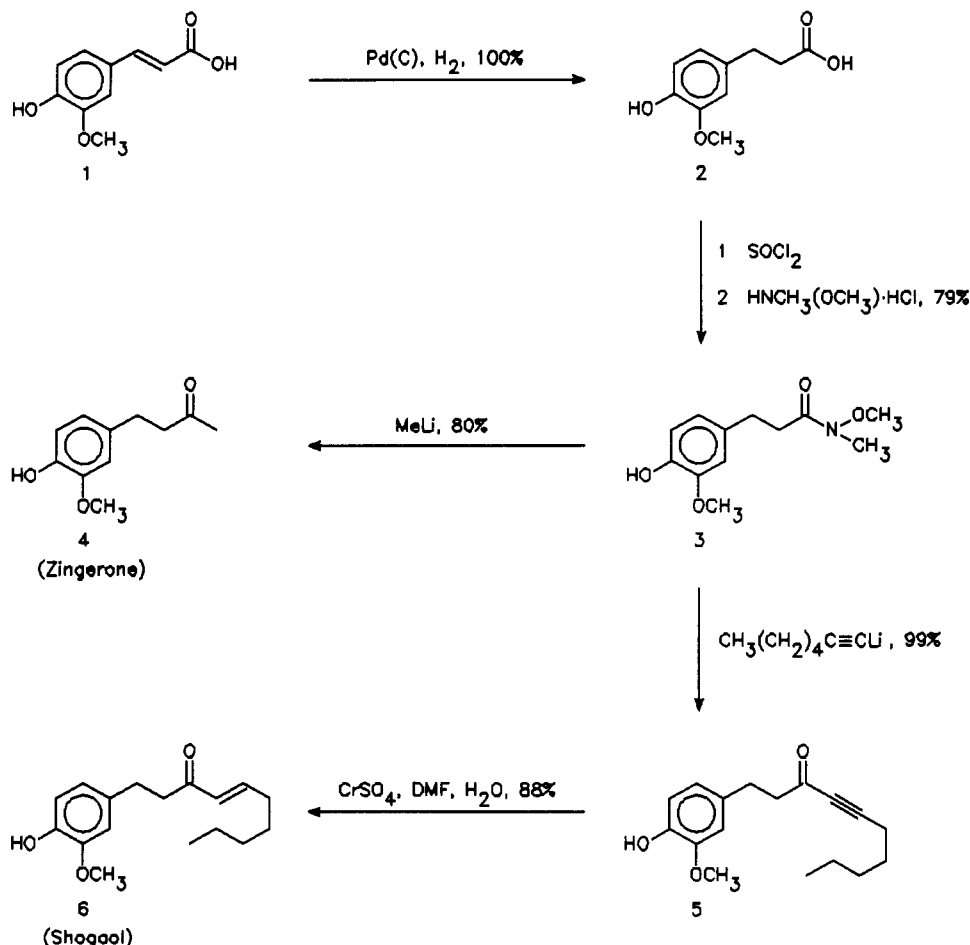


Figure 1. Synthetic procedures for the preparation of compounds 2-6.

ture, and 3.00 g (30.6 mmol) of *N,O*-dimethylhydroxylamine hydrochloride was added, followed by slow addition of 4.53 mL (4.43 g, 56.1 mmol) of pyridine. After 24 h, the reaction was judged complete by TLC and concentrated in vacuo. Suction filtration through a 3-cm pad of 60-mesh silica gel using EtOAc as eluant, followed by in vacuo concentration, gave a viscous yellow oil. Purification by MPLC on a 2.5 × 60 cm column using EtOAc gave 4.83 g (79%) of 3 as a light-yellow oil: R_f 0.30 (EtOAc); $^1\text{H NMR}$ (CDCl_3) δ 7.02-6.60 (m, 3 H), 6.33 (s, 1 H), 3.82 (s, 3 H), 3.58 (s, 3 H), 3.17 (s, 3 H), 2.98-2.47 (m, 4 H); IR (neat) 3550-3100 (s), 1653 (s); MS m/z (relative intensity) 239 (M^+ , 18), 179 (6), 150 (7), 137 (100), 122 (6), 107 (6), 91 (9), 77 (8). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.96; H, 6.90; N, 5.59.

4-(4-Hydroxy-3-methoxyphenyl)-2-butanone (4). To a stirring solution of 1.00 g of 3 (4.18 mmol) in 25 mL of THF at -78°C was added dropwise, over 5 min, 7.0 mL (10.45 mmol) of MeLi (1.5 M in Et_2O). The reaction was allowed to stir for 30 min, then warmed to room temperature over 2 h before it was quenched by pouring into a solution of 15 mL of 10% HCl and 15 g of crushed ice. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined ethereal extracts were washed with saturated NaHCO_3 (1 × 10 mL) and brine (1 × 10 mL), dried over MgSO_4 , and concentrated in vacuo. Purification by MPLC on a 1.5 × 60 cm column using 30% (v/v) EtOAc/hexane gave 0.65 g (80%) of 4 as a clear oil, which solidified to give a white solid upon refrigeration: mp 40.5-41.0 $^\circ\text{C}$ [lit. 41-42 $^\circ\text{C}$ (Connell and Sutherland, 1969)]; R_f 0.33 [40% (v/v) EtOAc/hexane]; $^1\text{H NMR}$, IR, and MS data were in agreement with those previously published (Banno and Makaiyama, 1976; Bunce and Reeves, 1989). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$: C, 68.02; H, 7.27. Found: C, 68.00; H, 7.26.

1-(4-Hydroxy-3-methoxyphenyl)dec-4-yn-3-one (5). To a stirring solution of 4.80 mL (3.52 g, 36.57 mmol) of 1-heptyne in 25 mL of THF at -78°C was slowly added, over 10 min, 22.9 mL

(36.57 mmol) of *n*-BuLi (1.6 M in hexane). The lithium reagent was allowed to continue stirring for 30 min before adding it dropwise, via cannula and over a 20-min period, to a stirring solution of 2.50 g (10.45 mmol) of 3 in 50 mL of THF at -78°C . After 15 min, the reaction was allowed to warm to room temperature over a 4-h period. The reaction mixture was then quenched by slowly pouring it into a stirring solution of 75 mL of 10% HCl and 75 g of crushed ice. Fifty milliliters of Et_2O was added, the layers were separated, and the aqueous layer was extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with saturated NaHCO_3 (1 × 15 mL) and brine (1 × 15 mL), dried over MgSO_4 , and concentrated in vacuo. Purification by MPLC on a 2.5 × 60-cm column using 20% (v/v) EtOAc/hexane gave 2.86 g (99%) of 5 as a light-yellow oil: R_f 0.46 [40% (v/v) EtOAc/hexane]; $^1\text{H NMR}$ δ 6.95-6.53 (m, 3 H), 5.57 (s, 1 H) 3.80 (s, 3 H), 2.85 (m, 4 H), 2.48-2.04 (m, 2 H), 1.55-1.07 (m, 6 H), 1.07-0.78 (m, 3 H); IR (neat) 3600-3200 (s), 2211 (s), 1735 (m), 1671 (s); MS m/z (relative intensity) 274 (M^+ , 36), 203 (49), 150 (62), 137 (100), 119 (18), 107 (13), 91 (21), 77 (15). Anal. Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_3$: C, 74.42; H, 8.08. Found: C, 74.41; H, 8.35.

1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one (6). To a stirring solution of 2.50 g (9.11 mmol) of 5 in 50 mL of DMF and 18 mL of H_2O was added 36.5 mL of a 0.5 N CrSO_4 solution, which was prepared according to a literature procedure (Castro and Kray, 1961). After 24 h, TLC analysis indicated the reaction was complete, so the reaction was saturated with $(\text{NH}_4)_2\text{SO}_4$ and allowed to stir for 15 min. The reaction mixture was diluted with 250 mL of H_2O and then extracted with Et_2O (5 × 30 mL). The combined ethereal extracts were washed with brine (1 × 30 mL), dried over MgSO_4 , and concentrated in vacuo. Purification by MPLC on a 2.5 × 60-cm column using 20% (v/v) EtOAc/hexane gave 2.21 g (88%) of 6 as a light-yellow oil: R_f 0.13 [15% (v/v) EtOAc/hexane]; $^1\text{H NMR}$, IR, and MS data were in agreement with those previously published (Banno and Mukaiyama, 1976; Vig et al., 1990). Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{O}_3$: C, 73.88; H, 8.75. Found: C, 74.39; H, 8.75.

ACKNOWLEDGMENT

Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research and the NSF College Science Instrumentation Program (Grant CSI-8750071) for partial support to purchase an FT-IR instrument.

LITERATURE CITED

- Banno, K.; Mukaiyama, T. A New Synthesis of the Pungent Principles of Ginger—Zingerone, Gingerol and Shogaol. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1453-1454.
- Bunce, R. A.; Reeves, H. D. Amberlyst-15 Catalyzed Addition of Phenols to α,β -Unsaturated Ketones. *Synth. Commun.* **1989**, *19*, 1109-1117.
- Castro, C. E.; Kray, W. C., Jr. The Cleavage of Bonds of Low Valent Transition Metal Ions. The Homogeneous Reduction of Alkyl Halides by Chromous Sulfate. *J. Am. Chem. Soc.* **1961**, *83*, 2768-2773.
- Castro, C. E.; Stephens, R. D. The Reduction of Multiple Bonds by Low-Valent Transition Metal Ions. The Homogeneous Reduction of Acetylenes by Chromous Sulfate. *J. Am. Chem. Soc.* **1964**, *86*, 4358-4362.
- Connell, D. W.; Sutherland, M. D. A Re-Examination of Gingerol, Shogaol, and Zingerone, The Pungent Principles of Ginger (*Zingiber Officinale* Roscoe). *Aust. J. Chem.* **1969**, *22*, 1033-1043, and references cited therein.
- Denniff, P.; Macleod, I.; Whiting, D. A. Synthesis of the (\pm)-[n]-Gingerols (Pungent Principles of Ginger) and Related Compounds through Regioselective Aldol Condensations: Relative Pungency Assays. *J. Chem. Soc., Perkins Trans. 1* **1981**, 82-87.
- Enders, D.; Eichenauer, H.; Pieter, R. *Chem. Ber.* **1979**, *112*, 3703-3714.
- Jorgenson, M. J. Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1971; Vol. 18; pp 1-97.
- Nahm, S.; Weinreb, S. M. N-Methoxy-N-Methylamides as Effective Acylating Agents. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.
- Pearl, I. A. Studies on Lignin and Related Products. XIV. Spectral and Chromatographic Data on Lignin Model Compounds in the Phenylpropane Series. *J. Org. Chem.* **1959**, *24*, 736-740.
- Seidel, J. L.; Epstein, W. W.; Davidson, D. W. Neotropical Ant Gardens I. Chemical Constituents. *J. Chem. Ecol.* **1990**, *16*, 1791-1816.
- Vig, O. P.; Bari, S. S.; Sharma, A.; Sattar, M. A. A New Synthesis of Shogaol. *Indian J. Chem.* **1990**, *29B*, 284-286.

Received for review July 26, 1991. Accepted November 21, 1991.

Registry No. 1, 1135-24-6; 2, 1135-23-5; 3, 138152-12-2; 4, 122-48-5; 5, 138152-13-3; 6, 555-66-8; HNCH₃(OCH₃)·HCl, 6638-79-5; CH₃(CH₂)₄C≡CLi, 42017-07-2.