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A CONVENIENT ONE-STEP GINGEROL SYNTHESIS

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Abstract: Racemic 6-gingerol can be obtained in a one-pot reaction by hexanal addition to the dianion of zingerone at low temperature. Similarly, addition of octanal or decanal to the dianion provides 8-gingerol or 10-gingerol, respectively. Acid treatment of the gingerols allows for formation of the corresponding shogaols.

Gingerol is one of the medicinally active components of the ginger root (*Zingiber officinale* Roscoe).[1] Both 6-gingerol (**1**) and 6-shogaol (**2**) are from the class of compounds called vanilloids. Other important therapeutic vanilloids include the analgesics capsaicin (see Figure 1) and resinferatoxin.[2] A number of exciting advances in the understanding of pain relief have recently been published that relate to this class of compounds.[3] Yet, there is still much to learn from the interactions of vanilloids with pain-blocking receptors.

We have been interested in the synthesis of 6-gingerol in order to test for its presence in commercial ginger root preparations. Although there are several syntheses of this active ingredient reported recently in the literature,[4] none take advantage of a one-step procedure. In fact, one of the earlier reports[5] described an attempted one-step aldol condensation, but found it to be unsuccessful.

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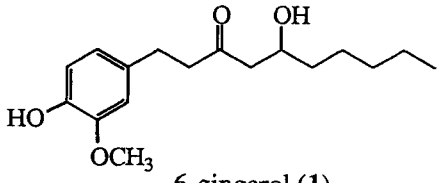
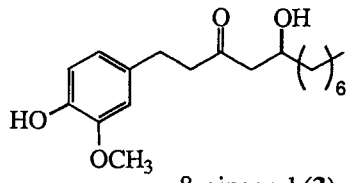
In addition to 6-gingerol, the dehydrated 6-shogaol is also a component of the ginger rhizome, particularly dried preparations. A standard for its analysis was needed as well. A general synthetic scheme that would also allow a practical approach to 8- and 10-gingerol (see Figure 1) was the ultimate goal. These compounds and their dehydrated analogues (8-shogaol and 10-shogaol) have not received much attention in the literature. Their potential for medicinal use warrants this report on their synthesis and characterization.

A logical approach to a β-hydroxy ketone makes use of the aldol reaction. Ideally, the kinetic enolate of the commercially available 4-aryl-2-butanone (zingerone, **5**) would react with hexanal, octanal, or decanal to provide the corresponding gingerols (**1**, **3**, or **4** respectively) following a mild acidic work-up.

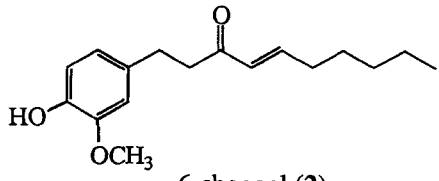
FIG. 1.



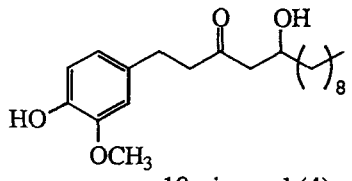
6-gingerol (**1**)



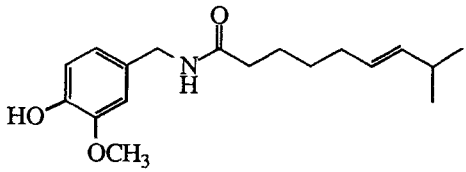
8-gingerol (**3**)



6-shogaol (**2**)

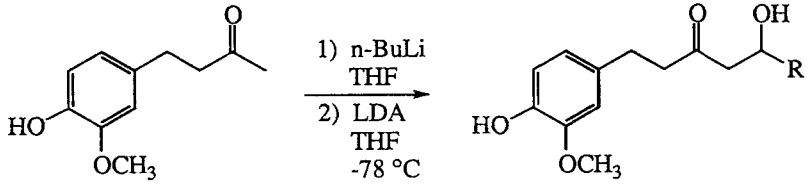


10-gingerol (**4**)



capsaicin

FIG. 2.



zingerone (**5**)

1 R = $(CH_2)_4CH_3$
3 R = $(CH_2)_6CH_3$
4 R = $(CH_2)_8CH_3$

Our initial attempt at producing the desired enolate of zingerone involved deprotonation of the phenolic proton with NaH followed by low temperature enolate formation with LDA. This procedure was not successful. However, treatment of butanone **5** with 1.0 equivalent of butyllithium at -78 °C followed by addition to one equivalent of LDA gave the dianion to which the appropriate aldehyde was added at -78 °C. This gave excellent yields of the desired gingerols.

Using this procedure we have been able to obtain 6-, 8-, and 10-gingerol. Each of these β-hydroxy ketones upon treatment with 10% aq. HCl gives rise to the corresponding 6-, 8-, and 10-shogaols in good to excellent yield. It was interesting to find that the proton signals for the $ArCH_2CH_2COR$ portion of the shogaols appear as a singlet at 2.8 ppm on a 200 MHz NMR. A HETCOR experiment and 500 MHz NMR proton spectrum allowed for differentiation and confirmation that the two methylene groups were indeed present.

Experimental Section: Gingerol. To a flame-dried flask were added 1.0 equivalent of zingerone and dry THF (0.7 M). The solution was cooled to -78 °C and 1.0 equivalent of n-BuLi in hexane was added. The resulting mixture was stirred for 30 min at -78 °C then added dropwise to LDA which was prepared from

one equivalent of diisopropyl amine and one equivalent of n-BuLi in 0.7 M THF at -78 °C. The reaction was stirred at low temperature for 3 h, then 1.0 equivalent of the appropriate aldehyde (hexanal, octanal, or decanal) in THF (0.7 M) at -78 °C was added. After stirring for 3 h at -78 °C, the reaction was warmed to 0 °C for one hour then quenched with 10% HCl and ether extracted. The crude oil was chromatographed (4 x 30 cm SiO_2, $CHCl_3$:EtOAc gravity column) to yield pure gingerol. The yield of gingerol was 75-95%. The major impurity is the result of butyllithium addition to the zingerone.

The spectral data for 6-gingerol[6] were: 200 MHz ^{1}H NMR δ ($CDCl_3$) 6.82 (d, 1 H, J = 7.6 Hz, ArH), 6.67 (m, 2 H, ArH), 5.52 (s, 1 H, ArOH), 4.02 (m, 1 H, $R_2C\underline{H}OH$), 3.86 (s, 3 H, $ArOCH_3$), 2.94 (s, 1 H, OH), 2.77 (m, 4 H, $ArCH_2CH_2COR$), 2.52 (m, 2 H, $RCOC\underline{H}_2CHOHR$), 1.27 (bs, 8 H, $(-CH_2-)_4$), 0.87 (t, 3 H, $-CH_2C\underline{H}_3$). 50 MHz ^{13}C NMR δ ($CDCl_3$) 209.90, 144.89, 142.36, 131.01, 120.95, 114.62, 111.12, 67.82, 56.00, 49.47, 45.57, 36.53, 31.84, 29.39, 25.24, 22.69, 14.12.

The spectral data for 8-gingerol[4f] were: 200 MHz ^{1}H NMR δ ($CDCl_3$) 6.82 (d, 1 H, J = 7.6 Hz, ArH), 6.65 (m, 2 H, ArH), 5.60 (s, 1 H, ArOH), 4.02 (m, 1 H, $R_2C\underline{H}OH$), 3.86 (s, 3 H, $ArOCH_3$), 2.99 (bs, 1 H, OH), 2.77 (m, 4 H, $ArCH_2CH_2COR$), 2.52 (m, 2 H, $RCOC\underline{H}_2CHOHR$), 1.26 (bs, 12 H, $(-CH_2-)_6$), 0.87 (t, 3 H, $-CH_2C\underline{H}_3$). 50 MHz ^{13}C NMR δ ($CDCl_3$) 209.95, 144.85, 142.36, 131.01, 119.08, 112.76, 109.34, 65.97, 54.15, 47.62, 43.70, 34.72, 30.05, 27.75, 27.52, 27.49, 23.71, 20.89, 12.33; HRMS m/z calc. 322.2144, obs. 322.2128.

The spectral data for 10-gingerol[4f] were: 200 MHz ^{1}H NMR δ ($CDCl_3$) 6.82 (d, 1 H, J = 7.4 Hz, ArH), 6.65 (m, 2 H, ArH), 5.54 (bs, 1 H, ArOH), 4.02 (m, 1 H, $R_2C\underline{H}OH$), 3.86 (s, 3 H, $ArOCH_3$), 2.77 (m, 4 H, $ArCH_2CH_2COR$),

2.52 (m, 2 H, RCOC$\underline{H}_2$CHOHR), 1.45 (bs, 1 H, OH), 1.25 (bs, 16 H, (-CH_2-)$_8$), 0.87 (t, 3 H, -$CH_2C\underline{H}_3$). 50 MHz ^{13}C NMR δ ($CDCl_3$) 209.98, 144.83, 142.36, 131.01, 119.08, 112.73, 109.32, 65.97, 54.15, 47.60, 43.71, 34.71, 30.15, 27.87, 27.80 (x 2), 27.56, 27.52, 23.71, 20.92, 12.36; HRMS m/z calc. 350.2457, obs. 350.2447. Mp 40 °C (from pet. ether).

Shogaol. A THF solution (.05 M) of gingerol was combined with an equal volume of 10% HCl and the mixture was heated for 4 h. The cooled solution was ether extracted and water washed. Concentration gave a crude oil with quantitative recovery. Purification with chromatography gave 85-95% of the desired enone.

The spectral data for 6-shogaol[7] were: 200 MHz ^{1}H NMR δ ($CDCl_3$) 6.81 (dt, 1 H, J = 15.6 Hz, J = 7.0 Hz, RCOCH=C$\underline{H}$$CH_2$-), 6.86-6.62 (m, 3 H, ArH), 6.10 (dt, 1 H, J = 15.6 Hz, J = 2 Hz, RCOC$\underline{H}$=$CHCH_2$-), 5.47 (s, 1 H, ArOH), 3.87 (s, 3 H, $ArOCH_3$), 2.85 (m, 4 H, $ArCH_2CH_2COR$), 2.18 (m, 2 H, RCOCH=CHC$\underline{H}_2$-), 1.45 (m, 2 H, CH_2), 1.27 (bs, 4 H, $(CH_2)_2$), 0.89 (t, 3 H, -$CH_2C\underline{H}_3$). 125 MHz ^{13}C NMR δ ($CDCl_3$) 199.77, 147.84, 146.36, 143.86, 133.24, 130.30, 120.79, 114.27, 111.08, 55.86, 41.98, 32.43, 31.32, 29.87, 27.76, 22.41, 13.93.

The spectral data for 8-shogaol were: 200 MHz ^{1}H NMR δ ($CDCl_3$) 6.81 (dt, 1 H, J = 16 Hz, J = 7.0 Hz, RCOCH=C$\underline{H}$$CH_2$-), 6.85-6.65 (m, 3 H, ArH), 6.10 (dt, 1 H, J = 15.8 Hz, J = 1.6 Hz, RCOC$\underline{H}$=$CHCH_2$-), 5.50 (s, 1 H, ArOH), 3.86 (s, 3 H, $ArOCH_3$), 2.84 (m, 4 H, $ArCH_2CH_2COR$), 2.18 (m, 2 H, RCOCH=CHC$\underline{H}_2$-), 1.43 (m, 2 H, CH_2), 1.26 (bs, 8 H, $(CH_2)_4$), 0.87 (t, 3 H, -$CH_2C\underline{H}_3$). 50 MHz ^{13}C NMR δ ($CDCl_3$) 198.27, 146.30, 144.76, 142.25, 131.63, 128.67, 119.15, 112.64, 109.43, 54.14, 40.25, 30.75, 29.97, 28.11, 27.39, 27.29, 26.34, 20.86, 12.31; HRMS (CI) m/z calc. 305.2117, obs. 305.2124.

The spectral data for 10-shogaol were: 300 MHz ^{1}H NMR δ ($CDCl_3$) 6.82 (dt, 1 H, J = 15.9 Hz, J = 6.6 Hz, RCOCH=C<u>H</u>CH_2-), 6.84-6.65 (m, 3 H, ArH), 6.10 (dt, 1 H, J = 15.9 Hz, J = 1.2 Hz, RCOC<u>H</u>=CHCH_2-), 5.54 (s, 1 H, ArOH), 3.87 (s, 3 H, $ArOCH_3$), 2.84 (m, 4 H, $ArCH_2CH_2COR$), 2.19 (m, 2 H, RCOCH=CHC<u>H</u>$_2$-), 1.43 (m, 2 H, CH_2), 1.26 (bs, 12 H, $(CH_2)_6$), 0.88 (t, 3 H, -CH_2C<u>H</u>$_3$). 75 MHz ^{13}C NMR δ ($CDCl_3$) 200.00, 148.09, 146.58, 144.06, 133.44, 130.49, 120.98, 114.48, 111.28, 56.05, 42.18, 32.69, 32.06, 30.06, 29.67, 29.58, 29.48, 29.38, 28.29, 22.86, 14.31; HRMS (CI) m/z calc. 333.2430, obs. 333.2426.

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