Enantioselective Synthesis of (−)-(*R*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone [(−)-(*R*)-[6]-Gingerol]

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(+)-(*S*)-[6]-Gingerol [(*S*)-**1**], which is well known in the manufacture of food products[1], has recently been found to be a cardiotonic agent[2]. Despite the easy availability[1] of (*S*)-**1** from the dried rhizomes of *Zingiber officinale* Roscoe, only one synthesis affording (−)-(*R*)-[6]-gingerol in 36% enantiomeric excess is known[3]. Thus, the latter enantiomer is a rather inaccessible compound.

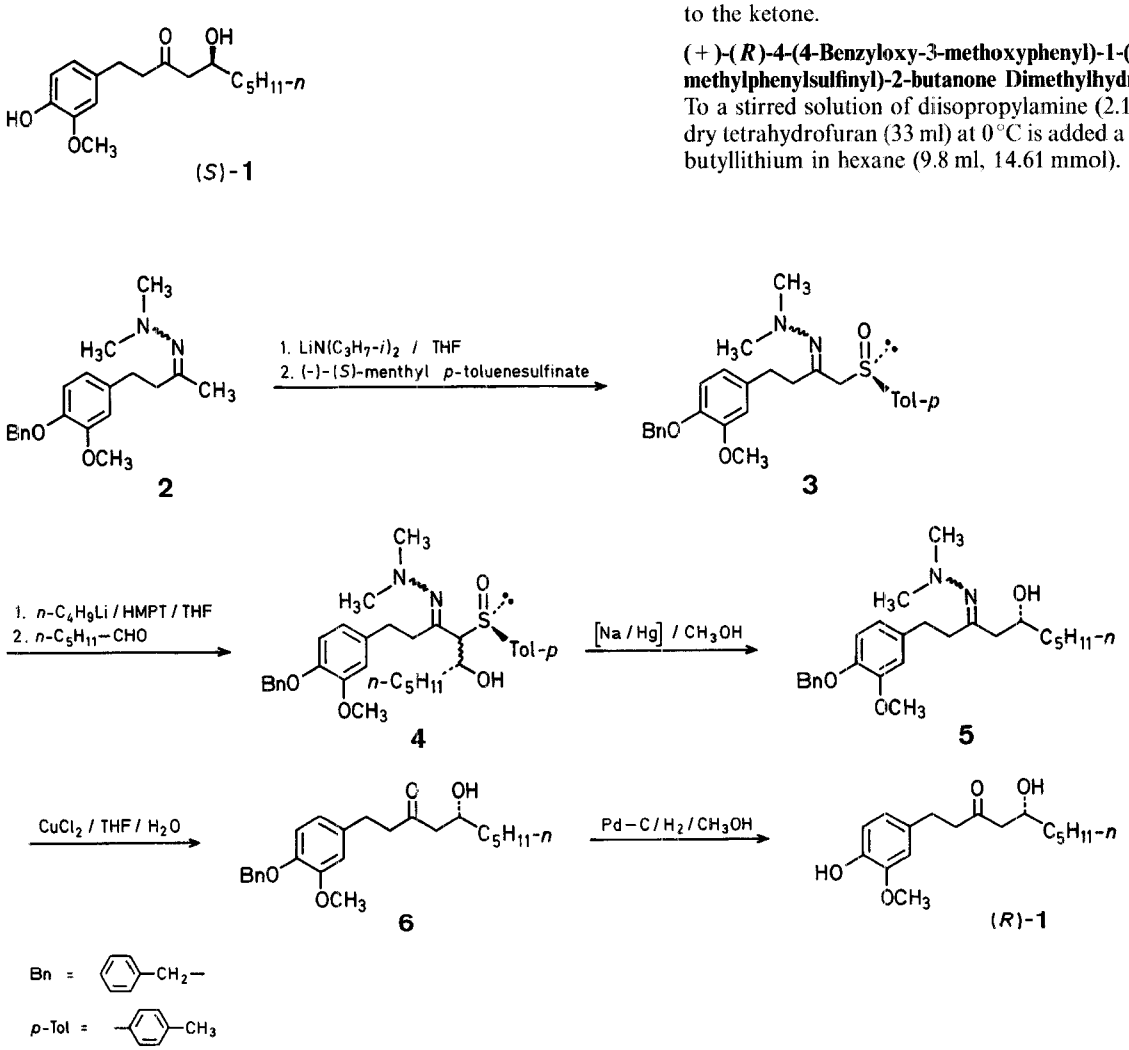
We have now developed a synthesis of (−)-(*R*)-[6]-gingerol [(*R*)-**1**] in fair enantiomeric excess by exploiting asymmetric induction mediated by optically pure α-sulfinylhydrazones[4,5]. 4-(4-Benzyloxy-3-methoxyphenyl)-2-butanone dimethylhydrazone[3] (**2**) was metallated with lithium diisopropylamide and reacted with (−)-(*S*)-menthyl *p*-toluenesulfinate. (+)-(*R*)-4-(4-Benzyloxy-3-methoxyphenyl)-1-(*p*-toluene-sulfinyl)-2-butanone dimethylhydrazone (**3**) thus obtained in a 1 : 1 *E*/*Z* (C=N) ratio is converted into hydroxyketone **6** by the following three-step, one-pot procedure (i.e., without isolation of the intermediates). Metallation of **3** with butyllithium in the presence of hexamethylphosphoric triamide (HMPT) and subsequent addition of hexanal at −10 °C gave the aldol derivatives **4** as a mixture of diastereoisomers. The β-hydroxyhydrazone **5** obtained from the reductive desulfurization[6] of crude **4** was hydrolyzed using copper(II) chloride[7] in aqueous tetrahydrofuran to give, after chromatographic purification, crystalline (−)-(*R*)-1-(4-benzyloxy-3-methoxyphenyl)-5-hydroxydecan-3-one (**6**) with (60 ± 1.0)% enantiomeric excess [optical rotation comparison[3,8] and ^{1}H-N.M.R. in $CDCl_3$, $Eu(hfc)_3$ as chiral shift reagent]. Debenzylation of compound **6** according to Ref.[3] gave (*R*)-**1** with unchanged optical purity.

The stereochemistry of the aldol-type addition to hexanal was found to be strongly dependent on temperature; indeed, a reaction temperature lower than −10 °C causes a notable decrease in stereoselectivity.

Kieselgel 60 F_{254} (Merck) was used for T.L.C. Silica gel 270–400 mesh was used for flash chromatography[9]. Optical rotations were measured with a Perkin Elmer 141 polarimeter. Microanalyses were performed with a Perkin-Elmer 240 instrument. I.R. spectra were recorded with a Perkin-Elmer 681 spectrophotometer. ^{1}H-N.M.R. and ^{13}C-N.M.R. spectra were recorded with Varian XL-100 and Varian XL-200 or Bruker WP-80 instruments, respectively.

4-(4-Benzyloxy-3-methoxyphenyl)-2-butanone Dimethylhydrazone (2):
Prepared according to Ref.[3]. The product is purified by flash chromatography (ether/hexane 9/1 containing 4% triethylamine). In the absence of triethylamine, compound **2** is quantiatively cleaved to the ketone.

(+)-(*R*)-4-(4-Benzyloxy-3-methoxyphenyl)-1-(4-methylphenylsulfinyl)-2-butanone Dimethylhydrazone (3):
To a stirred solution of diisopropylamine (2.14 ml, 15.33 mmol) in dry tetrahydrofuran (33 ml) at 0 °C is added a 1.5 molar solution of butyllithium in hexane (9.8 ml, 14.61 mmol). After 15 min, the so-



lution is cooled to −78 °C and a solution of compound **2** (5 g, 15.33 mmol) in dry tetrahydrofuran (16.5 ml) is added dropwise. The yellow mixture is then allowed to warm to 0 °C during 2 h and cooled again to −78 °C giving a clear suspension. To this stirred suspension, a solution of (−)-(*S*)-menthyl *p*-toluenesulfinate (2.15 g, 7.3 mmol) in dry tetrahydrofuran (25 ml) is added during 20 min. After a further 20 min at −78 °C, the solution is quenched with saturated ammonium chloride solution (35 ml) and extracted with ether (3 × 20 ml). The organic layers are combined, dried with sodium sulfate, and evaporated in vacuo. The residual product is purified by flash chromatography (ether/methanol 99/1 containing 4% triethylamine); yield: 3.2 g (94% based on sulfinate); $[\alpha]_D^{20}$: +71.5° (*c* 1.2, acetone)

$C_{27}H_{32}N_2O_3S$	calc.	C 69.80	H 6.94
(464.6)	found	69.74	6.90

I.R. ($CHCl_3$) ν = 1590 cm^{-1} (C=N), 1100–1000 cm^{-1} (S=O).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.32 [s, 6H, $N(CH_3)_2$]; 2.40 (s, 3H, C—CH_3); 2.48–2.98 (m, 4H, CH_2—CH_2); 3.64 [AB system, 1H, CH_2—SO (*E*)]; 3.84 [br. s, 4H, AB system, CH_2—SO (*Z*) + OCH_3]; 5.10 (s, 2H, CH_2—C_6H_5); 6.52–6.83 (m, 3H, C_6H_3); 7.19–7.62 ppm (m, 9H, C_6H_5 + C_6H_4).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}) (selected data): δ = 21.29 (H_3C—C); 31.50, 32.10, 32.60, 38.97 (CH_2—CH_2); 47.21, 47.29 (N—CH_3); 55.84 (OCH_3); 58.18 [CH_2—SO (*Z*)]; 62.69 [CH_2—SO (*E*)]; 71.08 (CH_2—C_6H_5); 112.13 [C=N (*E*)]; 163.22 ppm [C=N (*Z*)].

(−)-(*R*)-1-(4-Benzyloxy-3-methoxyphenyl)-5-hydroxydecan-3-one (6):

(5R)-1-(4-Benzyloxy-3-methoxyphenyl)-5-hydroxy-4-(4-methylphenylsulfinyl)-3-decanone Dimethylhydrazone (**4**): To a stirred solution of compound **3** (318 mg, 0.685 mmol) in dry tetrahydrofuran (13.7 ml) at −85 °C in a dry oxygen-free nitrogen atmosphere is added dropwise, a 1.4 molar solution of butyllithium (734 µl, 1.028 mmol) in hexane. The mixture is stirred at −85 °C for 30 min. Then, *HMPT (360 µl, 2.06 mmol)* is added and the red solution is allowed to warm to −10 °C over 45 min. Hexanal (246 µl, 2.06 mmol) is now added in one portion. The resultant clear solution is stirred for 1 h at −10 °C and then quenched with saturated aqueous ammonium chloride. The organic layer is separated and the aqueous layer extracted with ether (3 × 4 ml). The organic layers are combined, dried with sodium sulfate, and evaporated in vacuo; yield of crude **4**: 350 mg.

A pure sample of the major diastereoisomer of the alcohols **4** can be obtained by flash chromatography (ethyl ether / triethylamine 4%) of small amount of the crude product **4**.

$C_{33}H_{44}N_2O_4S$	calc.	C 70.18	H 7.85
(564.8)	found	70.25	7.87

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 0.8–1.1 (t, 3H, CH_3—10); 1.1–1.7 (m, 8H, CH_2 6–9); 2.26–2.53 (m, 4H, CH_2 1–2); 2.29 [s, 6H, $N(CH_3)_2$]; 2.40 (s, 3H, C_6H_4—CH_3); 3.58 (d, 1H, CH—SO, *J* = 4.8 Hz); 3.88 (s, 3H, OCH_3); 4.13 (m, 1H, CH—OH); 5.13 (s, 2H, CH_2—C_6H_5); 6.40–6.83 (m, 3H, C_6H_3); 7.26–7.73 ppm (m, 9H, C_6H_4 + C_6H_5).

Hydroxyketone **6**: The crude product **4** (350 mg; containing some unreacted **3**) is dissolved in anhydrous methanol (27 ml) and this solution is cooled to −20 °C under a nitrogen atmosphere. Anhydrous sodium dihydrogen phosphate (NaH_2PO_4; 490 mg, 4.08 mmol) and freshly ground 10% sodium amalgam (938 mg, 4.08 mg-atom of sodium) are added with vigorous stirring. The reaction is monitored by T.L.C. (silica gel, ether/hexane 9/1, triethylamine 4%) and is continued until compound **4** has disappeared. Additional equimolecular amounts of phosphate and amalgam can be added to complete the reaction if the amalgam is not ground very finely. After 2–4 h, saturated aqueous ammonium chloride solution (20 ml) is added and the suspension is allowed to warm to room temperature with vigorous stirring during 15 min. The suspension is decanted into a separatory funnel, extracted with ether (5 × 10 ml) and evaporated in vacuo. The crude product **5** thus obtained (containing some **2** and 4-methylbenzenethiol) is dissolved in tetrahydrofuran (3 ml) and this solution is added dropwise to a stirred solution of copper(II) chloride dihydrate (233.6 mg, 1.37 mmol) in tetrahydrofuran/water (2.2/1; 11.2 ml) containing pH 7 phosphate buffer (3.8 ml). After 15 h, the mixture is treated with ammonium chloride/ammonium hydroxide solution (pH 8; 7 ml), extracted with dichloromethane (3 × 4 ml), dried with sodium sulfate, and concentrated in vacuo. The residual product is purified by flash chromatography (ether/hexane 75/25) to give pure **6** as a colorless solid; yield: 80 mg (30% based on **3**); m.p. 65–66 °C (Ref.[3], m.p. 67 °C); $[\alpha]_D^{20}$: −12.4° (*c* 1.1, chloroform); e.e. 60 (± 1.0)% according to ^{1}H-N.M.R. spectrometry using $Eu(hfc)_3$. The values obtained represent the average of three preparations. All other spectroscopic properties are in agreement with literature values[3,8].

(−)-(*R*)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone [(*R*)-1; (−)-(*R*)-[6]-Gingerol][3]:

yield: 60 mg (98%); $[\alpha]_D^{20}$: −15.1° (*c* 0.84, chloroform); optical purity: 60%, by comparison with the value of the natural compound[3] which is $[\alpha]_D^{24}$: 25.1° (*c* 1, chloroform).

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