Total Synthesis of Natural Gingerols, the Three Active Principles of Ginger

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Natural gingerols, (+)(*S*)[6]-, (+)(*S*)[8]-, and (+)(*S*)[10]-gingerols, the three active principles of ginger, have been prepared from a common optically active intermediate **9** which was readily made by asymmetric synthesis from a chiral β-keto sulfoxide **5**.

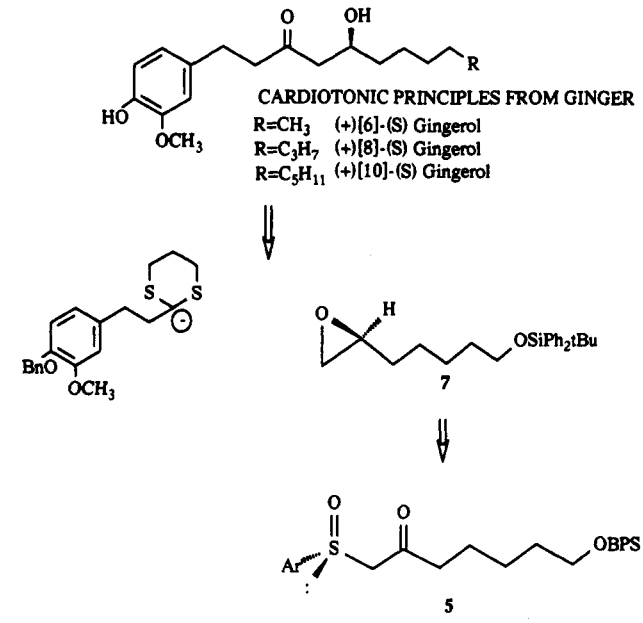
The rhizome of ginger (*Zingiber officinale* Roscoe) has been used not only as a seasoning spice but also as an important medicine in Japan and China. Three compounds, (+)(*S*)[6]-, (+)(*S*)[8]-, and (+)(*S*)-[10] gingerols, have been shown to be the active principles of ginger.[1] Several syntheses have been already reported in literature: two for the racemic compounds,[2a,b] two asymmetric syntheses of [6]-gingerol[2c,d] with enantiomeric excesses ranging from 40–60%, and two stereoselective syntheses of [6]-gingerol from an optically pure Δ^2-isoxazoline obtained by resolution[2e] or by asymmetric synthesis.[2f]

We report in this paper the asymmetric synthesis of the three gingerols in optically pure form from a common intermediate readily made from the optically active epoxide **7** obtained from the β-keto sulfoxide **5** (Scheme I).

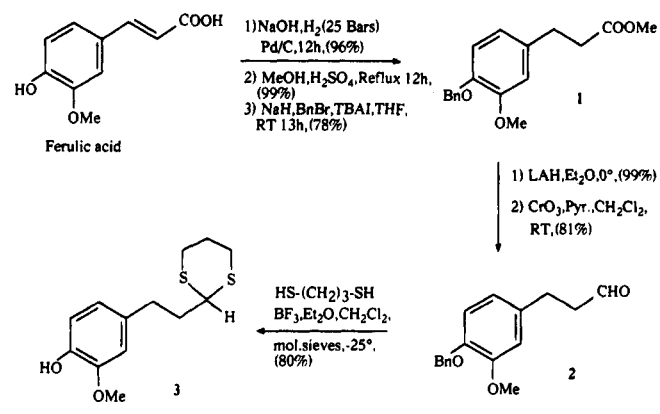
Ferulic acid sodium salt was hydrogenated over Pd/C before esterification with methanol and benzylation of the phenol group (Scheme II). The aldehyde **2** was then prepared in two high-yield steps: reduction to the alcohol with lithium aluminum hydride followed by chromic oxidation to the aldehyde. Finally thioacetalization was carried out with propanedithiol in presence of boron trifluoride etherate which also removed the benzyl protecting group.

The synthesis of the epoxide **7** started from ϵ-caprolactone (Scheme III) which was used as a precursor of the hydroxy ester **4**. After protecting the primary hydroxyl group with a diphenyl-*tert*-butylsilyl group, the ester reacted with (+)(*R*)-methyl *p*-tolyl sulfoxide carbanion to give in 88% yield the β-keto sulfoxide **5**. Reduction with DIBAL gave as expected[3] the (*S*)-alcohol in a de > 95% determined by the ^{1}H NMR of the crude product from the signal of the methylene group α to sulfur. Finally the sulfoxide was reduced to the sulfide with trimethylsilyl chloride and zinc. The corresponding methylsulfonium

Scheme I



Scheme II



salt was made with trimethyloxonium tetrafluoroborate and the epoxide **7** was obtained by adding potassium carbonate.

The key intermediate **9** for gingerol synthesis was prepared from the epoxide **7** and the thioacetal **3** (Scheme IV). The dithiane carbanion was made with butyllithium and TMEDA and its reaction with **7** was carried out in presence of *N,N'*-dimethyl-*N,N'*-(1,3-propanediyl)urea[4] (DMPU) as a cosolvent. The adduct **8** was obtained in

(1) Shoji, N.; Iwasa, A.; Takemoto, T.; Ishida, Y.; Ohizumi, Y. *J. Pharm. Sci.* **1982**, *71*, 1174 and cited references.

(2) (a) Denniff, P.; Whiting, D. A. *J. Chem. Soc. Chem. Commun.* **1976**, 712–713. (b) Denniff, P.; Macleod, I.; Whiting, D. A. *J. Chem. Soc. Perkin Trans. I*, **1981**, 82–87. (c) Enders, D.; Eichenauer, H.; Pieter, R. *Chem. Ber.* **1979**, *112*, 3703–3714. (d) Annunziata, R. *Synthesis* **1984**, 702–703. (e) Cinquini, M.; Cozzi, F.; Gilardi, A. J. *Chem. Soc. Comm.* **1984**, 551–552. (f) Legall, T.; Lellouche, J. P.; Beaucourt, J. P. *Tetrahedron Lett.* **1989**, *30*, 6521–24.

(3) (a) Solladié, G.; Demailly, G.; Greck, C. *Tetrahedron Lett.* **1985**, *26*, 435. (b) Solladié, G.; Demailly, G.; Greck, C. *J. Org. Chem.* **1985**, *50*, 1552. (c) Solladié, G.; Frechou, C.; Demailly, G.; Greck, C. *J. Org. Chem.* **1986**, *51*, 1912. (d) Solladié-Cavallo, A.; Suffert, J.; Adib, A.; Solladié, G. *Tetrahedron Lett.* **1990**, *31*, 6649. (e) Solladié, G.; Ziani-Chérif, C.; Jesser, F. *Tetrahedron Lett.* **1992**, *33*, 931–34.

(4) Mukhopadhyay, T.; Seebach, D. T. *Helv. Chim. Acta* **1982**, *65*, 385–391.

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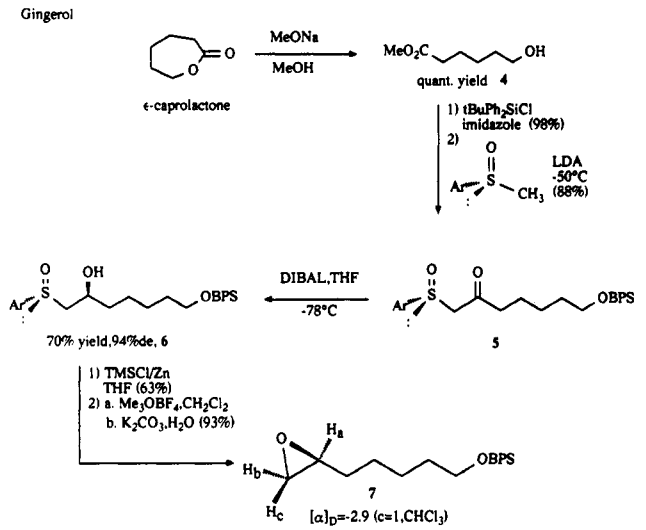
Scheme III



92% yield. The two hydroxyl groups were then protected as THP ethers, the *tert*-butyldiphenylsilyl group was removed, and the primary hydroxyl was transformed into tosylate **9** in an overall 83% yield.

(+)(*S*)[6]-Gingerol was easily obtained (Scheme V) from **9** by reduction of the tosylate group with lithium aluminum hydride, hydrolysis of thioacetal with methyl iodide, and calcium carbonate and acid hydrolysis of the THP group. (+)(*S*)-[8] and -[10]-gingerols were obtained from **9** by tosylate displacement with lithium ethylcyanocuprate and lithium butylcyanocuprate, respectively, followed by thioacetal and THP hydrolysis. The synthetic (+)(*S*)-[6]-, -[8]-, and -[10]-gingerols showed spectral characteristics that were identical to those of the natural products.

Experimental Section

2-[2-(4-Hydroxy-3-methoxyphenyl)ethyl]-1,3-dithiane (3). (1) Reduction of Ferulic Acid. A solution of ferulic acid (15 g, 77.2 mmol) in aqueous sodium hydroxide (6.16 g, 154.4 mmol, 130 mL of water) containing 10% Pd/C (100 mg) was hydrogenated under 30 bars of H_2 for 12 h. After filtration of the catalyst, the solution was acidified (pH = 2) with concd H_2SO_4, extracted with CH_2Cl_2 (4 × 120 mL), dried over Na_2SO_4, and the solvent was evaporated: yield 14.85 g (75.74 mmol, 98%); mp 96.7 °C; R_f 0.1 (ether/hexane: 1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.66 (t, 2 H, J = 7 Hz, CH_2), 2.9 (t, 2 H, J = 7 Hz, CH_2), 3.87 (s, 3 H, OCH_3, 6.69–6.87 (m, 3 arom H). Anal. calcd for $C_{10}H_{12}O_4$: C, 61.25; H, 6.12. Found: C, 61.16; H, 6.13.

(2) Esterification of Dihydroferulic Acid. A solution of dihydroferulic acid (14.85 g, 75.74 mmol) in methanol (150 mL) containing concd H_2SO_4 (10 drops) was refluxed overnight. Then water (150 mL) was added, the organic phases were washed with saturated NaCl (100 mL) and dried over Na_2SO_4, and the solvent was evaporated: yield 15.66 g (74.5 mmol, 98%); R_f 0.33 (ether/hexane: 1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.6 (t, 2 H, J = 7 Hz, CH_2), 2.89 (t, 2 H, J = 7 Hz, CH_2), 3.68 (s, 3 H, CO_2CH_3), 3.87 (s, 3 H, OMe), 5.53 (bs, 1 H, OH), 6.66–6.86 (m, 3 arom H).

(3) Protection of the Phenol Group in Compound 1. The ester 1 (15.66 g, 74.5 mmol) in THF (150 mL) was added to sodium hydride (2.14 g, 89.4 mmol) in THF (300 mL) at 0 °C and stirred 0.5 h before adding at 0 °C benzyl bromide (15.29 g, 89.4 mmol) and tetrabutylammonium iodide (2.76 g, 7.45 mmol). At the end of the reaction (TLC), the reaction mixture was hydrolyzed with saturated NH_4Cl (250 mL), acidified with 5% H_2SO_4 (pH = 3–4) and extracted with ether (2 × 150 mL). The organic phases were dried (Na_2SO_4) and evaporated: yield 17.98 g (80%); mp 51–2 °C (ether); R_f 0.17 (ether/hexane: 1/4); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.61 (t, 2 H, J = 8 Hz, CH_2), 2.9 (t, J = 8 Hz, CH_2), 3.68 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, OMe), 5.13 (s, 2 H, CH_2O), 6.74 (m, 3 arom H), 7.38 (m, 5 arom H). Anal. calcd for $C_{18}H_{20}O_4$: C, 72.02; H, 6.66. Found: C, 71.87; H, 6.63.

(4) Reduction of the Ester Group. The preceding ester (7.33 g, 24.4 mmol) in ether (200 mL) was added at 0 °C to $LiAlH_4$ (1.45 g, 38 mmol) in ether (30 mL). At the end of the reaction (TLC), the reaction mixture was hydrolyzed with water (30 mL) and 5% H_2SO_4 (10 mL), extracted with ether (3 × 50 mL), dried (Na_2SO_4), and evaporated: yield 6.35 g (95%); mp 67–8 °C (ether–hexane); R_f 0.35 (ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (bs, 1 H, OH), 1.88 (q, 2 H, CH_2), 2.66 (t, 2 H, J = 7 Hz, CH_2), 3.68 (t, 2 H, J = 7 Hz, CH_2OH), 3.85 (s, 3 H, OMe), 5.13 (s, 2 H, CH_2O), 6.65–6.83 (m, 3 arom H), 7.29–7.47 (m, 5 arom H). Anal. calcd for $C_{17}H_{20}O_3$: C, 75.02; H, 7.35. Found: C, 75.08; H, 7.37.

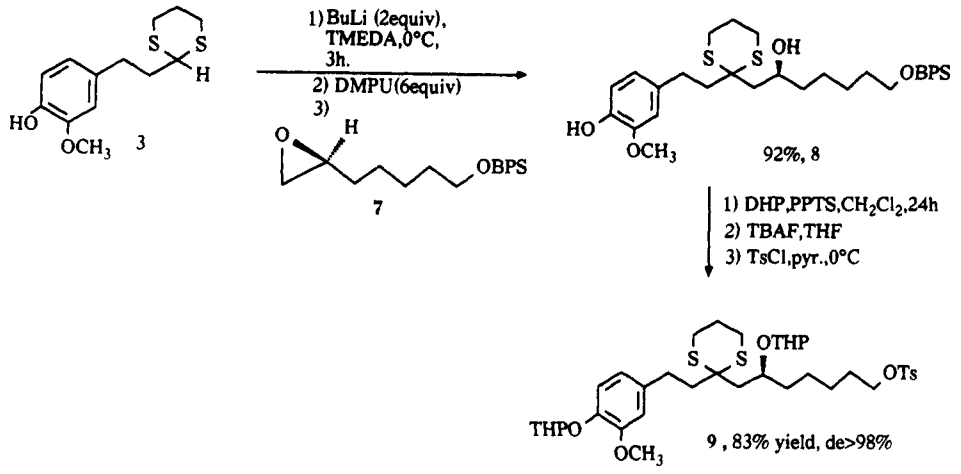
(5) Oxidation of the Hydroxyl Group. Chromium trioxide (24.6 g, 0.268 mol) was added in small portions to pyridine (43 mL, 0.533 mol) in CH_2Cl_2 (200 mL) at 0 °C and then the preceding alcohol (8 g, 29.4 mmol) in CH_2Cl_2 (200 mL) was added to the solution. The reaction mixture was stirred at room temperature overnight, and then ether (100 mL) and silica gel (30 g) were added to the solution. After stirring vigorously for 2 h, the solvent was evaporated. The resulting dried powder was then poured on silica gel column (h = 10 cm, d = 4 cm) impregnated with ether and washed with ether (3 × 100 mL). The ether solution was washed with 10% HCl (3 × 150 mL, and with unsaturated $KHCO_3$ (100 mL), dried ($MgSO_4$), and evaporated to give aldehyde **2**: yield 6.6 g (81%); mp 64–5 °C (ether–hexane); R_f 0.29 (ether/hexane: 2/3); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.76 (td, 2 H, CH_2), 2.9 (t, 2 H, J = 7 Hz, CH_2), 3.88 (s, 3 H, OMe), 5.13 (s, 2 H, CH_2O), 6.63–6.82 (m, 3 arom H), 7.29–7.46 (m, 5 arom H), 9.82 (t, 1 H, J = 1 Hz, CHO). Anal. calcd for $C_{17}H_{18}O_3$: C, 75.58; H, 6.66. Found: C, 75.60; H, 6.44.

(6) Protection of the Aldehyde Group and Deprotection of the Phenol. 1,3-Propanedithiol (1.8 g, 16.67 mmol) and boron trifluoride etherate (3.22 mL, 25.68 mmol) were dropwise added at 0 °C to a solution of aldehyde **2** (3.47 g, 12.84 mmol) in CH_2Cl_2 (100 mL). After stirring 1.5 h at 0 °C, saturated $NaHCO_3$ (30 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl, dried (Na_2SO_4), and evaporated. The product **3** was purified by silica gel column chromatography (ether/CH_2Cl_2/hexane: 1/2/7) to separate the product **3** from a small amount (15%) of the thioacetal still having a benzyloxy group (R_f 0.20): yield 2.9 g (80%); mp 54–6 °C; R_f 0.35; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.79–2.17 (m, 4 H, CH_2 β to S), 2.72–2.87 (m, 6 H, CH_2 α to S and benzylic CH_2), 3.87 (s, 3 H, OMe), 3.97 (t, 1 H, J = 7 Hz, CH α to S), 5.51 (bs, 1 H, OH), 6.67–6.85 (m, 3 arom H). Anal. calcd for $C_{13}H_{18}O_2S_2$: C, 57.77; H, 6.66. Found: C, 58.18; H, 7.06.

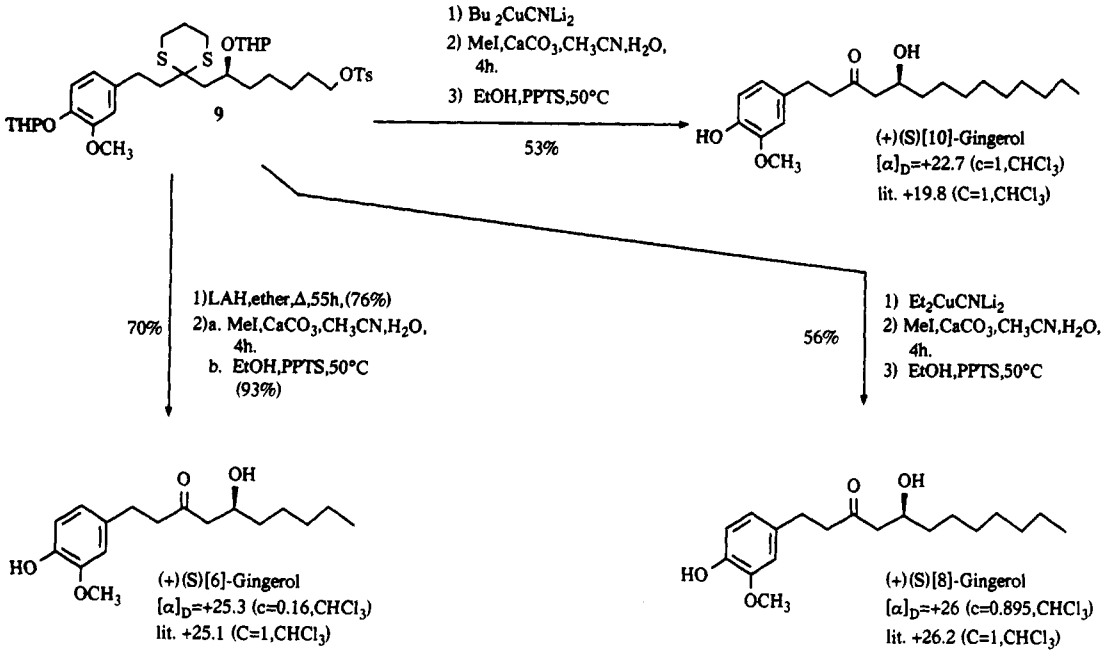
(+)(*R*)-1-(*p*-Tolylsulfinyl)-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanone (5). (1) Methyl 6-Hydroxyhexanoate (4) from ε-Caprolactone. Sodium methoxide (0.5 g, 9.26 mmol) was added to a solution of ε-caprolactone (40 g, 350 mmol) in MeOH (200 mL) and the mixture refluxed overnight. After evaporating the excess of methanol, ether (150 mL) was added and the solution washed with 5% AcOH (30 mL), H_2O (70 mL), and saturated NaCl (100 mL), and dried (Na_2SO_4). After evaporating the solvent, the product **4** was distilled (bp_{18} = 91 °C): yield 50.47 g (99%); R_f 0.44 (ether/hexane: 4/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37–1.44 (m, 2 H, CH_2-4), 1.54–1.68 (m, 4 H, CH_2-5, CH_2-3), 1.89 (bs, 1 H, OH), 2.32 (t, 2 H, J = 7 Hz, CH_2-2), 3.63 (t, 2 H, J = 6 Hz, CH_2-6), 3.65 (s, 3 H, OMe).

(2) Protection of the Hydroxyl Group. The hydroxy ester 4 (6.64 g, 45.47 mmol) was added to a solution of imidazole (7.74 g, 113.67 mmol, 2.5 equiv) in DMF (50 mL). Then *tert*-butyldiphenylsilyl chloride (15 g, 54.57 mmol, 1.2 equiv) was added and the reaction stirred at room temperature for 24 h. After adding saturated NH_4Cl (60 mL), the aqueous phase was extracted with ethyl acetate (3 × 120 mL). The organic phases were washed with water (100 mL), dried (Na_2SO_4), and evaporated. The product was purified by silica gel column chromatography (EtOAc/hexane: 8/92): yield 17.49 g (quantitative); R_f 0.34; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9 H, *t*-Bu), 1.36–1.47 (m, 2 H, CH_2), 2.31 (t, 2 H, J = 7 Hz, CH_2CO_2Me), 3.67 (t, 2 H, J = 6 Hz, CH_2OSi, and S, 3 H, CO_2CH_3), 7.34–7.7 (m, 10 arom H). Anal. calcd for $C_{23}H_{32}O_3Si$: C, 71.88; H, 8.32. Found: C, 71.87; H, 8.33.

Scheme IV



Scheme V



(3) β-Keto Sulfoxide 5. n-Butyl lithium (71.72 mL, 0.109 mol, 2.4 equiv) was added a −15 °C to diisopropylamine (11.03 g, 0.109 mol, 2.4 equiv) in THF (100 mL) and stirred for 0.5 h. Then a solution of (+)(*R*)-methyl *p*-tolyl sulfoxide (14 g, 90.8 mmol, 2 equiv) in THF (50 mL) was added at −78 °C and stirred for 1 h. The preceding ester (17.44 g, 45.4 mmol) in THF (50 mL) was slowly added and the reaction mixture were stirred at −50 °C till all the ester was consumed (TLC). Hydrolysis was carried out with saturated NH_4Cl (150 mL) and the pH adjusted to 3–4 with 5% H_2SO_4. After extraction with ethyl acetate (3 × 150 mL), the organic phases were washed with NaCl (75 mL), dried (Na_2SO_4), and evaporated. Crude **5** was purified by silica gel column chromatography (ether/hexane: 3/1): yield: 20.16 g (88%); R_f 0.42; $[\alpha]_D$ +97° ($CHCl_3$, *c* 0.63); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 9 H, *t*-Bu), 1.27–1.37 (m, 2 H, CH_2), 1.51–1.59 (m, 4 H, $2CH_2$), 2.41–2.48 (s + m, 5 H, CH_3Ar, CH_2CO), 3.63 (t, 2 H, J = 6 Hz, CH_2OSi), 3.79 (AB, 2 H, J_{AB} = 13.4 Hz, $\Delta\nu$ = 24.98 Hz, CH_2SO), 7.33 and 7.54 [$(AB)_2$, 4 H, J_{AB} = 8.12 Hz, 4 tolyl H], 7.44–7.66 (m, 10 arom H). Anal. calcd for $C_{30}H_{38}O_3SSi$: C, 71.14; H, 7.50. Found: C, 70.89; H, 7.72.

(+)[(*S*)*R*,2*S*]-1-(*p*-Tolylsulfinyl)-7-[(*tert*-butyldiphenylsilyl)oxy]-2-heptanol (6). A 1 M DIBAL solution in toluene (33 mL) was dropwise added at −78 °C to a solution of β-keto sulfoxide **5** (16.36 g, 32.3 mmol) in THF (300 mL). After stirring for 2 h, methanol (300 mL) was added at −78 °C and the mixture allowed to reach room temperature and concentrated. The residue was diluted with water (150 mL) and 5% H_2SO_4 (70 mL) and extracted with CH_2Cl_2 (4 × 200 mL). The organic phases were washed with saturated NaCl (150 mL), dried (Na_2SO_4), and evaporated. The β-hydroxy sulfoxide **6** was purified by silica gel column chromatography (ether/CH_2Cl_2:1/9): yield 13.72 g (84%); R_f 0.2; $[\alpha]_D$ +119.8° ($CHCl_3$, *c* = 0.403), de 95%, determined by ^1H NMR from the signal of the methylene group α to sulfur; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.04 (s, 9 H, tBu), 1.22–1.53 (m, 8 H, $4CH_2$), 2.42 (s, 3 H, $ArCH_3$), 2.62–3.07 (AB of ABX, 2 H, J_{AB} = 13.5 Hz, J_{AX} = 9.8 Hz, J_{BX} = 1.6 Hz, $\Delta\nu$ = 74.6 Hz, $CH_2S(O)$), 3.62 (t, 2 H, J = 6 Hz, CH_2OSi), 3.99 (bs, 1 H, OH), 4.14 (m, X from ABX, 1 H, CHOH), 7.27–7.69 (m, 14 arom H). Anal. calcd for $C_{30}H_{40}O_3SSi$: C, 70.86; H, 7.86. Found: C, 70.66; H, 7.88.

(−)(2*S*)-1,2-Epoxy-7-[(*tert*-butyldiphenylsilyl)oxy]heptane (7). (1) Sulfoxide Reduction to Sulfide in Compound 6. Zinc powder (1.11 g, 17 mmol) was added to a solution of β-hydroxy sulfoxide **6** (8.02 g, 15.7 mmol) in THF (40 mL). After stirring at room temperature for 15 min, the reaction mixture was cooled at 0 °C and trimethylsilyl chloride (3.49 g, 32.18 mmol, 2.05 equiv) was dropwise added. Stirring was continued at room temperature for 45 min and pentane (150 mL) was added. After filtration on silica gel, the solvent was evaporated and the product purified by silica gel column chromatography (ether/hexane: 1/4): yield 4.89 g (63%); R_f 0.27; $[\alpha]_D$ +15.8° ($CHCl_3$, *c* = 0.99); ^1H NMR/$CDCl_3$, 200 MHz) δ 1.09 (s, 9 H, *t*-Bu), 1.31–1.63 (m, 8 H, $4CH_2$), 2.35 (s, 3 H, CH_3Ar), 2.45 (bs, 1 H, OH), 2.75–3.16 (AB of ABX, 2 H, J_{AB} = 13.6 Hz, J_{AX} = 3.36 Hz, J_{BX} = 8.8 Hz, $\Delta\nu$ = 67.4 Hz, CH_2S), 3.62–3.68 (t, 2 H, J = 6 Hz, CH_2OSi and X of ABX, 1 H, CHOH), 7.11 and 7.34 [$(AB)_2$, J_{AB} = 8 Hz, 4 tolyl H], 7.34–7.69 (m, 10 arom H). Anal. calcd for $C_{30}H_{40}O_2SSi$: C, 73.16; H, 8.12. Found: C, 73.18; H, 7.99.

(2) Preparation of the Epoxide 7. Trimethyloxonium tetrafluoroborate (1.61 g, 10.89 mmol) was added to the β-hydroxy sulfide (4.47 g, 9.08 mmol) solution in CH_2Cl_2 (30 mL) and the mixture was stirred for 2 h at room temperature. Then an aqueous solution (30 mL) of Na_2CO_3 (2.51 g, 18.16 mmol, 2 equiv) was added and stirring was continued for 6 h. The aqueous phase was extracted with ether (3 × 15 mL), and the organic extracts were washed with saturated NaCl (30 mL), dried, and evaporated. The crude epoxide 7 was purified by silica gel column chromatography (ether/hexane: 1/9): yield 3.18 g (95%); R_f 0.35; $[\alpha]_D$ −2.8° ($CHCl_3$, c = 1.018); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9 H, tBu), 1.43–1.62 (m, 8 H, $4CH_2$), 2.46 (A of ABX, 1 H, J_{AB} = 5 Hz, J_{AX} = 2.74 Hz, Hc), 2.75 (B of ABX, 1 H, J_{AB} = 5 Hz, J_{BX} = 4 Hz, $\Delta\nu$ = 60.52 Hz, Hb), 2.9 (X of ABX, 1 H, Ha) 3.67 (t, 2 H, J = 6 Hz, CH_2OSi), 7.34–7.7 (m, 10 arom H). Anal. calcd for $C_{23}H_{32}O_2Si$: C, 75.00; H, 8.68. Found: C, 75.20; H, 8.48.

(+)(6*S*)-10-(4-Hydroxy-3-methoxyphenyl)-8,8-(1,3-propanediyldithio)-6-hydroxy-1-[(*tert*-butyldiphenylsilyl)oxy]decane (8). *n*-BuLi (1.31 mL, 1.9 mmol) was dropwise added at −20 °C to a solution of thioacetal 3 (245.1 mg, 0.9 mmol) in THF (5 mL), followed by the addition of TMEDA (0.815 mL, 5.4 mmol, 6 equiv). The reaction mixture was stirred for 2.5 h at 0 °C and *N*,*N*′-dimethyl-*N*,*N*′-(1,3-propanediyl)urea (DMPU, 0.65 mL, 5.4 mmol, 6 equiv) was added at 0 °C. Ten minutes later, the solution was cooled at −20 °C and a solution of epoxide 7 (0.4 g, 1.08 mmol) in THF (5 mL) was added. Stirring was continued at −20 °C for 3 h, at 0 °C for 2 h, and overnight at room temperature. Saturated NH_4Cl (15 mL) was then added, followed by 5% H_2SO_4 to adjust the pH at 3–4. Extraction was carried out with ether (3 × 20 mL). Crude 8 was purified by silica gel column chromatography (ether/CH_2Cl_2/hexane: 15/20/65: yield 354 mg (92%); R_f 0.17; $[\alpha]_D$ +4.6° (c = 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (s, 9 H, *t*-Bu), 1.26–1.62 (m, 8 H, $4CH_2$), 1.93–2.41 (m, 7 H, $3CH_2$ β to S and OH), 2.62–3.02 (m, 6 H, CH_2 α to S and benzylic CH_2), 3.66 (t, 2 H, J = 6 Hz, CH_2OSi), 3.88 (s, 3 H, OMe), 4.01 (m, 1 H, CHOH), 5.52 (bs, 1 H, phenol), 6.68–6.86 (m, 3 arom H), 7.28–7.70 (m, 10 arom H). Anal. calcd for $C_{36}H_{50}O_4S_2Si$: C, 67.71; H, 7.83. Found: C, 67.51; H, 7.60.

(6*S*)-9-[4-(Tetrahydropyranyloxy)-3-methoxyphenyl]-8,8-(1,3-propanediyldithio)-6-(tetrahydropyranyloxy)-1-[(*p*-tolylsulfonyl)oxy]decane (9).

(1) Protection of the Two Hydroxyl Groups in Compound 8. A mixture of compound 8 (2.764 g, 4.32 mmol), dihydropyran (1.18 mL, 13 mmol), and *p*-toluenesulfonic acid (2.16 mg, 0.2 equiv) in CH_2Cl_2 (40 mL) was stirred overnight at room temperature. After adding saturated $NaHCO_3$ (20 mL), the solution was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were washed with saturated NaCl (20 mL), dried (Na_2SO_4), and evaporated. Crude product was purified by silica gel column chromatography (ether/CH_2Cl_2/hexane: 1/1/3): yield 3.12 g (88.5%); R_f 0.56; ^{1}H NMR ($CDCl_3$ 200 MHz) δ 1.05 (s, 9 H, *t*-Bu), 1.18–2.28 (m, 26 H, 13 CH_2), 2.75–2.83 (m, 6 H, 3 CH_2), 3.56–3.69 (m, 2 H, CH_2CH_2OCH and t, 2 H, J = 6 Hz, CH_2OSi), 3.86 (s, 3 H, OCH_3), 3.86–4.08 (m, 3 H, CH_2CH_2OCH and CHOCH), 4.65 and 4.75 (2 t, 1 H, CHOCH in the two diastereomers made during the reaction and due to the new asymmetric carbon on the tetrahydropyran ring), 5.34 (t, 1 H, J = 3 Hz, OCHO), 6.7–7.05 (m, 3 arom H), 7.35–7.69 (m, 10 arom H).

(2) Deprotection of the Primary Hydroxyl Group. A solution of the preceding compound (2.79 g, 3.46 mmol) in THF (20 mL) and tetrabutylammonium fluoride (TBAF, 6.92 mL of a 1 M solution in THF) was stirred at room temperature for 1 h. After evaporating the solvent, ether (10 mL) and water (1 mL) were added and the mixture was stirred for 20 min and the solution was dried (Na_2SO_4). The product was finally purified by chromatography (ether/CH_2Cl_2/hexane: 1/1/3): yield 1.96 g (quantitative); R_f 0.71 (AcOEt); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.3–2.5 (m, 26 H, 13 CH_2), 2.65–2.9 (m, 6 H, 3 CH_2), 3.55–3.66 (t, 2 H, J = 6 Hz CH_2OH and m, 2 H, (CH_2OCH), 3.84 (s, 3 H, OCH_3), 3.95–4.12 (m, 3 H, CH_2OCH and CHOCH), 4.65 and 4.73 (2 m, 1 H, $OCHCH_2$ in the two diastereomers), 5.33 (t, 1 H J = 3 Hz, OCHO), 6.68–7.04 (m, 3 arom H).

(3) Preparation of the Tosylate 9. To a solution of the preceding alcohol (1.96 g, 3.34 mmol) in chloroform (50 mL) and cooled at 0 °C, pyridine (1 mL, 12.34 mmol) and tosyl chloride (1.5 g, 7.89 mmol) were added. The reaction mixture was stirred at 0 °C for 6 h and overnight at room temperature. After adding ether (30 mL) the solution was filtrated over silica gel and evaporated and product 9 was purified by chromatography (ether/hexane: 4/1): yield 2.32 g (94%); R_f 0.64; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23–2.29 (m, 26 H, 13 CH_2), 2.42 (s, 3 H, CH_3Ar), 2.69–2.82 (m, 6 H, CH_2), 3.4–3.65 (m, 2 H, CH_2OCH), 3.82 (s, 3 H, OCH_3), 3.84–4.1 (m, 3 H, CHOCH and CH_2OCH and t, 2 H, J = 6 Hz, CH_2OS), 4.59 and 4.69 (2 m, 1 H, $OCHOCH_2$ in the 2 diastereomers), 5.32 (t, 1 H, J = 3 Hz, OCHOC), 6.65–7.03 (m, 3 arom H), 7.3–7.78 [$(AB)_2$, J = 8 Hz, 4 tolyl H)].

(+)(*S*)[6]-Gingerol. (1) Reduction of the Tosylate 9. $LiAlH_4$ (45 mg, 1.18 mmol.) was added to solution of tosylate 9 (110 mg, 0.14 mmol) in ether (10 mL). The solution was refluxed for 48 h and hydrolyzed with water (1 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the product was purified by chromatography (ether/hexane: 65/35): yield 51 mg (76%); R_f 0.56; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (t, 3 H, CH_3), 1.11–2.49 (m, 26 H, 13 CH_2, 2.69–2.91 (m, 6 H, 3 CH_2), 3.63 (t, 2 H, 26 H, CH_2OCH), 3.87 (s, 3 H, OMe), 3.87–4.2 (m, 3 H, CHOCH and OCH_2CH_2), 4.65 and 4.75 (2 m, 1 H, $OCHOCH_2$ of the diastereomers), 5.36 (m, 1 H, OCHO), 6.69–7.03 (m, 3 arom H).

(2) Deprotection of the OH Groups and of the Ketone Group. Methyl iodide (0.2 mL, 0.456 g, 3.2 mmol) and calcium carbonate (0.135 g, 1.35 mmol) were added to a solution of the preceding alcohol (37 mg, 0.067 mmol) in a 4/1 acetonitrile/water mixture (5 mL)). The reaction mixture was stirred at 35 °C for 24 h. Then ether (10 mL) and water (3 mL) were added and stirring was continued at room temperature for 1 h. After drying (Na_2SO_4), the solution was filtered over silica gel and the solvent was evaporated. Then the residue was diluted with ethanol (2 mL), PPTS (3 mg) was added, and the mixture was heated at 55 °C for 2 h. After evaporating the solvent, the product, (*S*)[6]-gingerol, was purified by preparative TLC: yield 18.3 mg (93%); R_f 0.27 (ether/hexane: 65/35); $[\alpha]_D$ +25.3° (c = 0.16, $CHCl_3$) [lit.[2c] +25.1° (c = 1, $CHCl_3$), lit.[1] +27.8° (c = 1, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3 H, J = 6.8 Hz, CH_3), 1.21–1.50 (m, 4 H, CH_2-2, CH_2-3), 1.5–1.82 (m, 4 H, CH_2-4, CH_2-5), 2.41 (t, 2 H, J = 7 Hz, CH_2-10), 2.57 (t, 2 H, CH_2-9), 2.61–2.86 (m, 2 H, CH_2-7), 3.88 (s, 3 H, OCH_3), 4.05 (m, 1 H, CHOH), 5.48 (bs, 1 H, phenol H), 6.65–6.85 (m, 3 arom H); ^{13}C NMR ($CDCl_3$) δ 13.87 (C-1), 22.39 (C-3), 23.26 (C-4), 31.27 and 31.41 (C-5 and C-2), 36.33 (C-9), 43.59 (C-10), 48.86 (C-7), 55.83 (OCH_3), 66.84 (CHOH), 111.03–120.88 (3 arom CH), 133.74 (arom CCH_2), 143.66 (arom COH), 146.34 (arom $COCH_3$), 212.61 (C-8).

(+)(*S*)[10]-Gingerol. (1) Displacement of the Tosyl Group in Compound 9 by Lithium *n*-Butylcyanocuprate. To a suspension of cuprous cyanide (732.6 mg, 8.18 mmol) in ether (30 mL) was slowly added at −78 °C and under argon *n*-BuLi (11.24 mL, 16.36 mmol). Then the temperature was allowed to reach −40 °C in order to obtain a yellow solution. A solution of tosylate 9 (60.4 mg, 0.818 mmol) in ether (5 mL) was then added at −78 °C. Reaction temperature was allowed to reach −20 °C and stirring was continued for 2 h. Finally a 10% ammonium hydroxyde solution in saturated ammonium chloride (30 mL) was added and it was extracted with ether (2 × 40 mL). After evaporating the solvent the product was purified by column chromatography (ether/hexane: 1/3): yield 0.488 g (99%); R_f = 0.3; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.33 Hz, CH_3), 1.27–2.43 (m, 34 H, 17 CH_2), 2.71–2.87 (m, 6 H, $2CH_2$ α to S, benzylic CH_2), 3.48–3.62 (m, 2 H, CH_2O), 3.84 (s, 3 H, OCH_3), 3.84–4.1 (m, 3 H, CHOTHP and CH_2O), 4.66 and 4.75 (2 m, 1 H, OCHO in the 2 diastereomers), 5.34 (t, 1 H, J = 3 Hz, OCHOA), 6.68–7.05 (m, 3 arom H).

(2) Deprotection of the OH Groups and of the Ketone Group. (*S*)[10]-gingerol was obtained from the preceding compound (387.8 mg, 0.637 mmol). The dithioacetal was hydrolyzed with methyl iodide/calcium carbonate (58% yield) and the THP group with PPTS/ETOH (90% yield) according to the procedure described for [6]-gingerol: yield 118.3 mg (53%); R_f = 0.21 (ether/hexane: 1/1); mp 45–6 (lit.[1] 42–3 °C), $[\alpha]_D$ +22.7° ($CHCl_3$, c = 1.02) (lit.[1] +19.8° (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3 H, J = 6 Hz, CH_3), 1.26 (m, 16 H, 8 CH_2), 2.53 (t, 2 H, CH_2-11), 2.79 (m, 4 H, CH_2-13, CH_2-14), 3.87 (s, 3 H, OCH_3), 4.02 (m, 1 H, CHOH), 5.49 (s, 1 H, phenolic H), 6.63–6.85 (m, 3 arom H); ^{13}C NMR ($CDCl_3$) δ 14.02 (C-1), 22.57–49.28 (11 CH_2), 55.73 (OCH_3), 67.59 (CHOH), 110.96–120.6 (3 arom

CH), 132.51 (arom CCH_2), 143.9 (arom COH), 146.42 (arom $COCH_3$), 211.35 (C-12). Anal. calcd for $C_{21}H_{34}O_4$: C, 72.02; H, 9.7. Found: C, 71.80; H, 9.5.

(+)(*S*)[8]-Gingerol. (1) Displacement of the Tosyl Group in Compound 9 by Lithium Ethylcyanocuprate. The procedure described before the synthesis of [10]-gingerol was applied to compound **9** (1.29 g, 1.75 mmol) and lithium ethylcyanocuprate [prepared from ethyllithium (27.5 mL, 27.49 mmol)]: yield 1.014 g (quantitative yield); R_f = 0.41 (ether/hexane 28/72); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 1.27–2.5 (m, 30 H, 15 CH_2), 2.65–2.87 (m, 6 H, benzylic CH_2, 2 CH_2 α to S), 3.48–3.62 (m, 2 H, CH_2O), 3.84 (s, 3 H, OMe), 3.84–4.15 (m, 3 H, CHOTHP, CH_2OCH), 4.66–4.75 (2 m, 1 H, $CHOCH_2$ in the 2 diastereomers), 5.34 (t, 1 H, J = 3 Hz, OCHOAr), 6.68–7.05 (m, 3 arom H).

(2) Deprotection of the OH Groups and of the Ketone Group. (*S*)[8]-Gingerol was obtained from the preceding compound (0.892 g, 1.53 mmol). The dithioacetal was hydrolyzed with methyl iodide/calcium carbonate (64% yield) and the THP group with PPTS/EtOH (88% yield) according to the procedure described for [6]-gingerol: yield 0.196 g (88%); R_f 0.18 (ether/hexane: 1/1); mp 29–30 °C (lit. 28–30 °C); $[\alpha]_D$ +26° ($CHCl_3$, c = 0.895), lit.[1] +26.2° ($CHCl_3$, c = 1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, 3 H, J = 6 Hz, CH_3), 1.32 (m, 12 H, 6 H_2), 2.01–2.26 (m, 2 H, CH_2-9), 2.33 (t, 2 H, J = 7.5 Hz, CH_2-11), 2.78 (t, 2 H, J = 7.5 Hz, benzylic CH_2), 3.01 (bs, 1 H, OH), 3.30 (s, 3 H, OCH_3), 4.01 (m, 1 H, CHOH), 5.65 (bs, 1 H, phenolic H); ^{13}C NMR ($CDCl_3$) δ 14.1 (C-1), 22.65–49.34 (9 C, CH_2), 55.82 (OCH_3), 67.7 (C-8), 111.07–120.68 (3 C, aromatic CH), 132.59–146.54 (3 C, arom C), 211.5 (C-10). Anal. calcd for $C_{19}H_{30}O_4$: C, 70.83; H, 9.31. Found: C, 70.96; H, 9.51.