Enantiocontrolled synthesis of (+)-curcuquinone and (-)-curcuhydroquinone

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Dedicated to Professor Keiichiro Fukumoto on his 70th birthday
(received 30 Jun 03; accepted 30 Sept 03; published on the web 16 Oct 03)

Abstract
An enantiocontrolled synthesis of the monocyclic bisabolene-type sesquiterpenoids (+)-curcuquinone **1** and (-)-curcuhydroquinone **2** has been accomplished using a porcine pancreatic lipase (PPL)-mediated desymmetrization of the prochiral σ-symmetrical 2-aryl-1,3-propanediol **6** as the key reaction step.

Keywords: Sesquiterpene, curcuquinone, curcuhydroquinone, lipase, enantioselective synthesis

Introduction

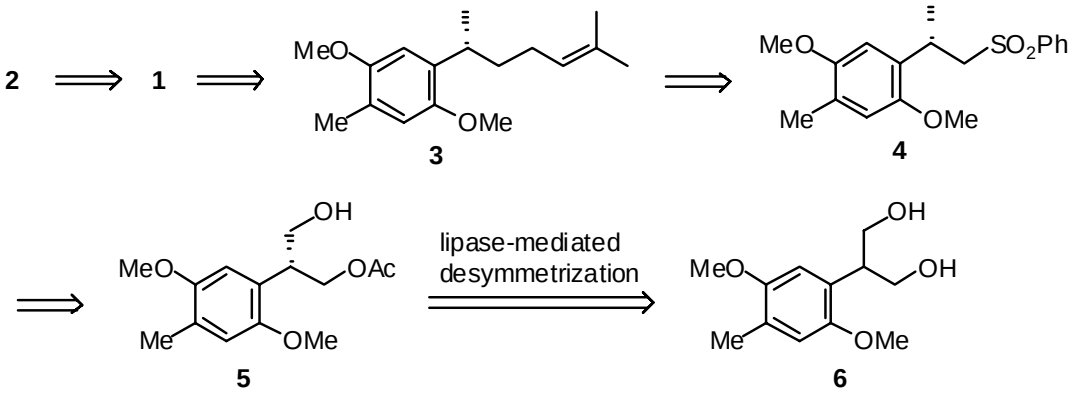
Curcuquinone (**1**) and curcuhydroquinone (**2**) are two aromatic bisabolene sesquiterpenoids isolated from the Caribbean gorgonian *Pseudopterogorgia rigida* by Fenical *et al.*[1] and are responsible for its antibiotic properties. Although several syntheses of these terpenoids as the racemic forms[2] have been published, very few synthetic reports on the optically active forms[3] are available. In particular, the enantioselective synthesis of the natural enantiomer has never been reported. Given the biological profile of these terpenoids and also their versatility as chiral building blocks for constructing biologically important natural products, *e.g.*, heliannuol A and D,[3a] the development of an efficient and enantioselective synthetic route is of significant value. In this paper, we report an enantiocontrolled synthesis of the natural enantiomers of **1** and **2** (Figure 1).

Our basic strategy is shown in Scheme 1. We envisaged preparing the target molecules from the curcuhydroquinone dimethyl ether (**3**), which would be derived from the sulfone (**4**) *via* a sequential prenylation and desulfonylation. The pivotal construction of the benzylic tertiary stereogenic center with the *R* configuration in **5** would be realized by employing the lipase-

mediated desymmetrization[3a,4] of the prochiral σ-symmetrical 2-aryl-1,3-propanediol (**6**) (Scheme 1).

curcuquinone **1** curcuhydroquinone **2**

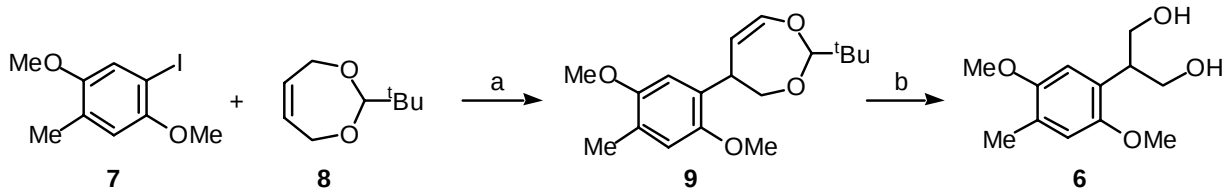
Figure 1



Scheme 1. Retrosynthetic analysis.

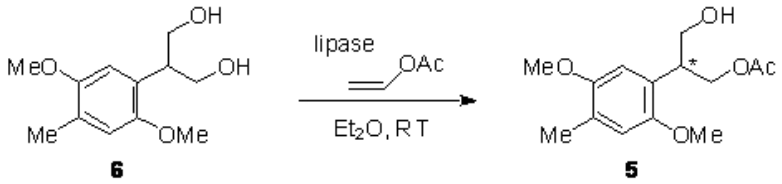
Results and Discussion

Preparation of a σ-symmetrical 2-aryl-1,3-propanediol (**6**) as the substrate of chemo-enzymatic desymmetrization began with the Heck reaction[5] of the iodide (**7**)[6] with the cyclic acetal (**8**)[5a] to give the coupled product (**9**) in 90% yield. Ozonolytic cleavage of the double bond, followed by reductive workup with $NaBH_4$, provided the desired diol (**6**) in 87% yield (Scheme 2).



Scheme 2. *Reagents and Conditions:* (a) $Pd(OAc)_2$, Ph_3P, i-Pr_2NEt, DMF, 80°C, 90%; (b) O_3, MeOH, -78°C then $NaBH_4$, RT, 87%.

With the requisite diol in hand, we examined optimum conditions for its conversion into the optically active monoacetate (**5**) using a wide variety of lipases. Of these, porcine pancreatic lipase (PPL)-mediated transesterification of the prochiral diol (**6**) in diethyl ether, using vinyl acetate as an acetyl donor, provided **5** in 41% yield (94% yield based on the consumed **6** with 78% *ee* (HPLC on a Chiralcel OJ column). Although the absolute configuration of the stereogenic center could not be determined at this stage, it was established to be *R*- by the eventual conversion to the natural curcuhydroquinone (**2**). Alternatively, the (*S*)-monoacetate (**5**) was obtained by transesterification using CAL or lipase PS-C in diethyl ether as shown in Scheme 3.



run	lipase	reaction time, h	yield, %[a]	ee, %[b]	abs. config.
1	PPL	36	41 (94)	78	*R*
2	CAL	3.5	8 (81)	>99	*S*
3	PS-C	4	56 (100)	93	*S*

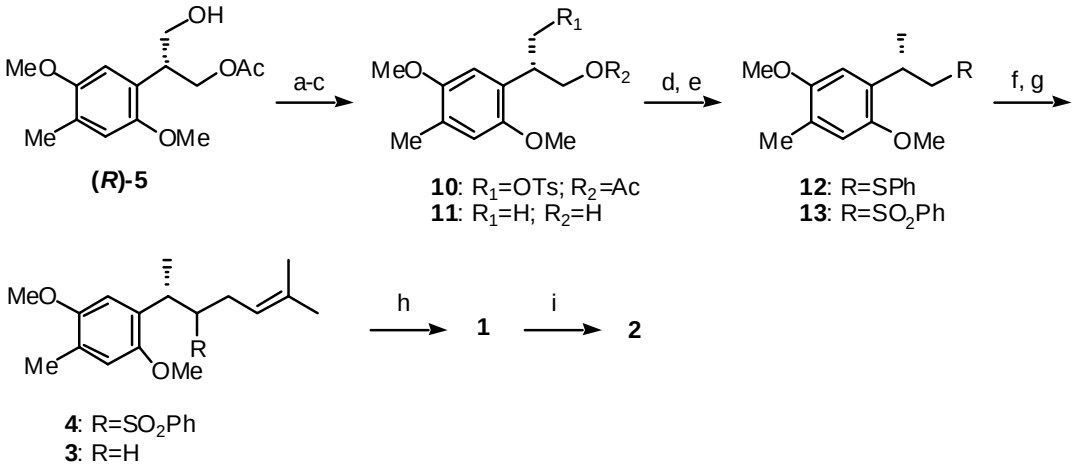
[a]Yields in parentheses indicated those based on the consumed diol (**6**).
[b] Determined by HPLC analysis using Chiralcel OJ column.

Scheme 3. Lipase-mediated desymmetrization of the diol **6**.

The (*R*)-monoacetate thus obtained was then tosylated and reductively deoxygenated with $NaBH_4$ in hot DMSO to give the alcohol (**11**) after reductive treatment with $LiAlH_4$. Fortunately, it was obtained as a crystalline solid and recrystallization from hexane gave the optically pure **11** in 71% overall yield for the three steps. Sequential Hata reaction[7] and *m*-CPBA oxidation of the resulting sulfide (**12**) gave the sulfone (**13**) in 82% yield. Treatment of **13** with *n*-BuLi-HMPA and prenyl bromide yielded the carbon-elongated sulfone (**4**), which was reduced with 5% Na–Hg under sonication to provide **3** in 83% yield for the two steps. Oxidation of **3** with ceric ammonium nitrate in aqueous acetonitrile furnished curcuquinone (**1**) in 56% yield, $[\alpha]_D$ +1.47° (*c* 2.8, $CHCl_3$); $[\alpha]_{577}$ +4.32° (*c* 2.8, $CHCl_3$) {lit.[1a] $[\alpha]_D$ -1.3° (*c* 9.1, $CHCl_3$); for the enantiomer,[3b] $[\alpha]_D$ -0.9° (*c* 1.0, $CHCl_3$)}, which was reduced with sodium dithionite in aqueous THF to cleanly provide curcuhydroquinone (**2**), $[\alpha]_D$ -48° (*c* 2.8, $CHCl_3$) {lit.[1a] $[\alpha]_D$ -21° (*c* 0.9, $CHCl_3$); lit.[1b] $[\alpha]_D$ -34° (*c* 0.93, $CHCl_3$)} in 98% yield. The spectroscopic properties of synthetic **1** and **2** were identical with those of the natural products (Scheme 4).

Conclusions

We have accomplished the first enantioselective synthesis of (+)-curcuquinone (**1**) and (-)-curcuhydroquinone (**2**) employing a PPL-mediated transesterification of a prochiral σ-symmetrical 2-aryl-1,3-propanediol as the key reaction step. We also demonstrated that enantiomeric analogs can be prepared by the chemo-enzymatic desymmetrization protocol. The synthetic route shown here is general and efficient, and can also be applied to the synthesis of other related terpenoids.



(a) TsCl, Et_3N, 4-DMAP, CH_2Cl_2, RT, 96%; (b) $NaBH_4$, DMSO, 60°C; (c) $LiAlH_4$, THF, 0°C, 74% (2 steps); (d) PhSSPh, n-Bu_3P, pyridine, RT, 99%; (e) *m*-CPBA, $KHCO_3$, CH_2Cl_2, RT, 83%; (f) n-BuLi, HMPA, prenyl bromide, THF, -78°C, 98%; (g) 5% Na-Hg, Na_2HPO_4, MeOH, RT, 85%; (h) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, RT, 56%; (i) $Na_2S_2O_4$, THF, H_2O, RT, 98%.

Scheme 4

Experimental Section

General Procedures. ^1H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL JMS FX-200 (200 MHz), JEOL GSX-400 (400 MHz), Bruker ARX 400 (400 MHz) and JEOL AL 400 (400 MHz) spectrometers, unless otherwise noted. ^{13}C NMR were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) or TMS (0.00 ppm) using JEOL AL 300 (75 MHz), JEOL GSX-400 (100 MHz), Bruker ARX 400 (100 MHz) and JEOL AL 400 (100 MHz) spectrometers. Chemical shifts are reported in ppm (from TMS). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. IR spectra were recorded on Perkin Elmer 1720 FT-IR,

Hitachi 215 and JASCO FT/IR-410 spectrophotometers. MS spectra were obtained on JEOL JMS-DX303, JMS-AX500 and JMS-SX102A. Elemental analyses were performed with a Yanaco MT-3 CHN-Corder. Optical rotations were determined on JASCO P-1010. Analytical thin layer chromatography (TLC) was performed on precoated plates (0.25 mm, silica gel Merck $60F_{245}$), and compounds were visualized with UV light and *p*-anisaldehyde stain. Column chromatography was performed on a silica gel, KANTO Silica Gel 60 N (63-210 mesh). Melting points were measured with a Yanaco MP-500D melting point apparatus and are uncorrected. All reactions were performed in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise noted. "RT" denotes room temperature.

2-*tert*-Butyl-6-(2,5-dimethoxy-4-methylphenyl)-4,5-dehydro-1,3-dioxepane (9). A mixture of **7** (20 g, 72 mmol), **8** (12.8 mL, 86 mmol), *i*-Pr_2NEt (38 mL, 216 mmol), $Pd(OAc)_2$ (0.48 g, 2.2 mmol) and Ph_3P (1.2 g, 4.3 mmol) in DMF (60 mL) was stirred at 80 ^oC for 13 h. After removal of the solvent, the residue was extracted with benzene and the extracts were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent, followed by chromatography on silica gel (hexane–ethyl acetate, 95:5, v/v) gave **9** (19.8 g, 90%) as a yellow oil. ^1H NMR ($CDCl_3$) δ: 0.98 (9H, s), 2.21 (3H, s), 3.08 (1H, t, *J*=11.1 Hz), 3.76 (3H, s), 3.78 (3H, s), 4.13 (1H, q, *J*=5.5 Hz), 4.20 (1H, s), 4.29 (1H, m), 4.75 (1H, d, *J*= 7.7 Hz), 6.42 (1H, dd, *J*=3.2, 7.7 Hz), 6.68 (1H, s), 6.70 (1H, s). ^{13}C NMR ($CDCl_3$) δ 16.2 (q), 24.9 (q), 35.9 (s), 41.2 (d), 56.1 (q), 56.2 (q), 74.5 (t), 111.3 (d), 113.4 (d), 114.1 (d), 125.8 (s), 126.8 (s), 145,1 (d), 150.7 (s). IR (neat) /cm^{-1} 1048, 1211, 1650, 2954. MS (EI) *m/z* 306 (M^+). HRMS (EI) Calcd for $C_{18}H_{26}O_4$: 306.1831. Found: 306.1838.

2-(2,5-Dimethoxy-4-methylphenyl)propane-1,3-diol (6). Ozone was bubbled through a stirred solution of **9** (2.0 g, 6.5 mmol) in MeOH at -78 ^oC for 90 min. After release of excess ozone, $NaBH_4$ (0.37 g, 9.8 mmol) was added to the solution at 0 ^oC and the mixture was stirred at RT for 8 h. Evaporation of the solvent left a residue which was extracted with AcOEt, and the extracts were dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 1:1, v/v) to give the diol **6** (1.3 g, 87%) as colorless prisms, mp 70.3 ^oC (hexane). ^1H NMR ($CDCl_3$) δ: 1.83 (2H, br s, D_2O exchangeable), 2.21 (3H, s), 3.45 (1H, quint., *J*=6.4 Hz), 3.78 (6H, s), 3.93 (2H, dd, *J*=5.5, 10.9 Hz), 4.00 (2H, m), 6.69 (1H, s), 6.72 (1H, s). ^{13}C NMR ($CDCl_3$) δ 16.2 (q), 43.8 (d), 56.1 (q), 56.2 (q), 65.2 (t), 111.4 (d), 114.4 (d), 125.4 (s), 126.0 (s), 151.2 (s), 151.9 (s). IR ($CHCl_3$) /cm^{-1} 1048, 1207, 3275. MS (EI) *m/z* 226 (M^+). HRMS (EI) Calcd for $C_{12}H_{18}O_4$: 226.1205. Found: 226.1208. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.49; H, 7.93%.

General procedure for the lipase-mediated desymmetrization of the diol (6)

A mixture of **6** (1 eq), vinyl acetate (2 eq), and lipase (substrate:lipase=1:2, w/w) in Et_2O was stirred at RT. After the mixture was filtered, the filtrate was concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 3:2, v/v) to give the optically active acetate **5**. The enantiomeric excess (*ee*) was determined by HPLC [Chiralcel OJ column, flow rate 1.

(2*S*)-3-Acetoxy-2-(2,5-dimethoxy-4-methylphenyl)propan-1-ol ((*S*)-5). A colorless oil. $[\alpha]_D$ -17.3° (c 1.04, $CHCl_3$, >99% *ee*). ^{1}H NMR ($CDCl_3$) δ: 1.89 (1H, s, D_2O exchangeable), 2.05 (3H, s), 2.21 (3H, s) 3.53 (1H, quint., *J*=5.9 Hz), 3.78 (6H, s), 3.85 (2H, d, *J*=6.0 Hz), 4.42 (1H, dd, *J*=7.7, 10.9 Hz), 4.36 (1H, dd, *J*=5.9, 10.9 Hz), 6.72 (2H, s). ^{13}C NMR ($CDCl_3$) δ 16.2 (q), 21.0 (q), 41.1 (d), 56.1 (q), 56.2 (q), 63.2 (t), 64.5 (t), 111.4 (d), 114.3 (d), 124.8 (s), 126.2 (s), 151.2 (s), 151.8 (s), 171.4 (s). IR (neat) /cm^{-1} 1045, 1211, 1738, 3457. MS (EI) *m/z* 268 (M^+). HRMS (EI) Calcd for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1317.

(2*R*)-3-Acetoxy-2-(2,5-dimethoxy-4-methylphenyl)propan-1-ol ((*R*)-5). A colorless oil. $[\alpha]_D$ +11.8° (c 0.34, $CHCl_3$, 75% *ee*). ^{1}H NMR ($CDCl_3$) δ: 1.89 (1H, s, D_2O exchangeable), 2.05 (3H, s), 2.21 (3H, s) 3.53 (1H, quint., *J*=5.9 Hz), 3.78 (6H, s), 3.85 (2H, d, *J*=6.0 Hz), 4.42 (1H, dd, *J*=7.7, 10.9 Hz), 4.36 (1H, dd, *J*=5.9, 10.9 Hz), 6.72 (2H, s). ^{13}C NMR ($CDCl_3$) δ 16.2 (q), 21.0 (q), 41.1 (d), 56.1 (q), 56.2 (q), 63.2 (t), 64.5 (t), 111.4 (d), 114.3 (d), 124.8 (s), 126.2 (s), 151.2 (s), 151.8 (s), 171.4 (s). IR (neat) /cm^{-1} 1045, 1211, 1738, 3457. MS (EI) *m/z* 268 (M^+). HRMS (EI) Calcd for $C_{14}H_{20}O_5$: 268.1311. Found: 268.1317.

(2*S*)-1-Acetoxy-2-(2,5-dimethoxy-4-methylphenyl)-3-(4-methylphenyl-sulfonyloxy)propane (10). To a solution of **(*R*)-5** (369.5 mg, 1.38 mmol), NEt_3 (0.58 mL, 4.14 mmol) and 4-dimethylaminopyridine (16.8 mg, 0.14 mmol) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonyl chloride (526.2 mg, 2.76 mmol) at 0 ˚C and the mixture was stirred at RT for 8.5 h. Sat. NH_4Cl aq. was added to the mixture and extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a residue, which was chromatographed on silica gel (hexane–ethyl acetate, 4:1, v/v) to give the tosylate **10** (559.1 mg, 96%) as a pale yellow oil; $[\alpha]_D$ +4.92° (c 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s), 2.19 (3H, s), 2.43 (3H, s), 3.62 (1H, m), 3.67 (3H, s), 3.72 (3H, s), 4.28 (4H, m), 6.53 (1H, s), 6.60 (1H, s), 7.60 (2H, d, *J*=8.2 Hz), 7.65 (2H, d, *J*=8.2 Hz). ^{13}C NMR ($CDCl_3$) δ: 16.2 (q), 20.8 (q), 21.6 (q), 38.3 (d), 55.9 (q), 56.0 (q), 63.4 (t), 69.7 (t), 111.4 (d), 114.0 (d), 122.5 (s), 126.6 (s), 127.9 (d), 129.6 (d), 132.9 (s), 144.6 (s), 150.8 (d), 151.6 (d), 170.7 (d). IR (neat) /cm^{-1} 2955, 1741, 1508, 1365, 1177, 1045. MS (EI) *m/z* 422 (M^+). HRMS (EI) Calcd for $C_{21}H_{26}O_7S$: 422.1399. Found: 422.1410.

(2*S*)-2-(2,5-Dimethoxy-4-methylphenyl)-1-propanol (11). A mixture of **10** (2.37 g, 6 mmol) and $NaBH_4$ (1.2 g, 30 mmol) was stirred in DMSO (50 mL) at 60 ^{o}C for 9 h. The mixture was extracted with benzene, and the extracts washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in THF (10 mL) and the solution was added dropwise to a suspension of $LiAlH_4$ (0.57 g, 15 mmol) in THF (15 mL) at 0 ˚C. After being stirred for 30 min, the mixture had Et_2O/water (9:1, v/v, 15 mL) added and was then stirred at RT for 1 h. The mixture was filtered through Celite, and the filtrate dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 19:1, v/v) to give the alcohol **11** (850 mg, 74% for the two steps) as colorless needles. Recrystallization from hot hexane gave the optically pure alcohol **11** [Chiralcel OD, flow rate 0.5 mL/min, hexane–isopropanol, 99:1, v/v, (*R*)-**11**: *t*= 41 min, (*S*)-**11**: *t*=44 min] as colorless needles. Mp 97.1–97.9 ˚C; $[\alpha]_D$ -15^o (c 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.26 (3H, d, *J*=6.8 Hz), 1.54 (1H, s, D_2O exchangeable), 2.21 (3H, s), 3.42 (1H, m), 3.69 (2H, d, *J*=6.8 Hz), 3.78

(3H, s), 3.80 (3H, s), 6.70 (1H, s), 6.71 (1H, s). ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 16.7 (q), 35.5 (d), 56.1 (q), 56.3 (q), 68.0 (t), 110.3 (d), 114.4 (d), 125.3 (s), 129.8 (s), 151.1 (s). 152.0 (s). IR ($CHCl_3$) /cm^{-1} 3383, 2934, 1207. MS (EI) *m/z* 210 (M^+). HRMS (EI) Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1245. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.27; H, 8.49%.

(2*S*)-2-(2,5-Dimethoxy-4-methylphenyl)-1-phenylthiopropane (12). To a solution of **11** (400 mg, 1.44 mmol) and PhSSPh (943 mg, 4.3 mmol) in pyridine (10 mL) was added n-Bu_3P (1.07 mL, 4.3 mmol) at RT. After being stirred for 8 h, the mixture was diluted with Et_2O (15 mL), treated with 15% aq. NaOH and then washed successively with 10% aq. HCl and sat. $NaHCO_3$ aq. The residue was extracted with Et_2O and the extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give the sulfide **12** (570 mg, 99%) as a colorless oil. $[\alpha]_D$ -57.9° (c 1.58, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ, 1.37 (3H, d, *J*=6.5 Hz), 2.20 (3H, s), 2.96 (1H, dd, *J*=8.8, 12.8 Hz), 3.31 (1H, dd, *J*=5.5, 12.8 Hz), 3.38 (1H, m), 3.74 (3H, s), 3.78 (3H, s), 6.669 (1H, s), 6.673 (1H, s), 7.25 (5H, m). ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 19.1 (q), 33.0 (d), 40.6 (t), 56.1 (q), 56.2 (q), 110.1 (d), 114.2 (d), 125.2 (s), 125.4 (d), 128.7 (d), 128.8 (d), 131.4 (s), 137.3 (s), 150.8 (s), 151.8 (s). IR (neat) /cm^{-1} 1048, 1210, 2959. MS (EI) *m/z* 302 (M^+). HRMS (EI) Calcd for $C_{18}H_{22}O_2S$: 302.1341. Found: 302.1368.

(2*S*)-2-(2,5-Dimethoxy-4-methylphenyl)-1-phenylsulfonylpropane (13). To a solution of **12** (540 mg, 1.8 mmol) in CH_2Cl_2 (12 mL) was added *m*-CPBA (822 mg, 4.0 mmol) and $KHCO_3$ (107 mg, 0.6 mmol) at 0 °C. After being stirred for 2 h at RT, sat. $NaHCO_3$ aq. was added, and extracted with CH_2Cl_2. The extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give the sulfone **13** (498 mg, 83%) as colorless needles, mp 57.4–58.9 °C (benzene/hexane). $[\alpha]_D$ -7.97° (c 2.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, d, *J*=7.3 Hz), 2.13 (3H, s), 3.31 (1H, dd, *J*=7.6, 14.0 Hz), 3.51 (1H, m), 3.58 (3H, s), 3.64 (1H, dd, *J*=5.6, 14.0 Hz), 3.74 (3H, s), 6.45 (1H, s), 6.53 (1H, s). 7.44 (2H, m), 7.75 (1H, m), 7.77 (2H, d, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 16.0 (q), 19.9 (q), 31.2 (d), 55.5 (q), 56.1 (q), 61.6 (t), 111.1 (d), 113.9 (d), 125.8 (s), 127.9 (d), 128.7 (d), 128.9 (s), 133.0 (d), 139.9 (s), 150.3 (s), 151.6 (s). IR ($CHCl_3$) /cm^{-1} 3019, 1504, 1304, 1142. MS (EI) *m/z* 334 (M^+). HRMS (EI) Calcd for $C_{18}H_{22}O_4S$: 334.1239. Found: 334.1259. Anal. Calcd for $C_{18}H_{22}O_4S$: C, 64.63; H, 6.63. Found: C, 64.30; H, 6.55%.

(6*S*)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-5-phenylsulfonyl-2-heptene (4). To a solution of **13** (1.2 g, 3.6 mmol) and HMPA (4.8 mL) in THF (15 mL) was added dropwise n-BuLi (1.61 *M* in hexane solution, 3.4 mL, 5.4 mmol) at -78 °C and stirred for 30 min. The mixture was further stirred at 0 °C for 30 min and cooled to -78 °C. A solution of 4-bromo-2-methyl-2-butene (1.2 mL, 10.8 mmol) in THF (10 mL) was added and stirred for 30 min at the same temperature. The reaction mixture was quenched by the addition of sat. aq. NH_4Cl and extracted with CH_2Cl_2. The extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give the olefin **4** (1.4 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.38 (3H, s), 1.41 (3H, s),

1.43 (3H, d, *J*=7.3 Hz), 2.16 (3H, s), 2.67 (1H, m), 3.61 (9/4H, s), 3.69 (3/4H, s), 3.75 (3/4H, s), 3.77 (9/4H, s), 4.71 (3/4H, m), 4.90 (1/4H, s), 6.52 (3/4H, s), 6.54 (1/4H, s), 6.63 (1/4H, s), 6.66 (3/4H, s), 7.58 (3H, m), 7.81 (1/2H, d, *J*=7.3 Hz), 7.85 (3/2H, d, *J*=7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 13.1 (q), 16.0 (q), 17.4 (q), 22.5 (t), 25.5 (q), 31.9 (d), 55.6 (q), 56.3 (q), 67.0 (d), 111.4 (d), 113.6 (d), 121.3 (d), 125.7 (s), 128.3 (d), 128.6 (d), 128.7 (s), 132.9 (d), 140.5 (s), 150.4 (s), 151.5 (s), 151.6 (s). IR (neat) /cm^{-1} 1049, 1211. MS (EI) *m/z* 402 (M^+). HRMS (EI) Calcd for $C_{23}H_{30}O_4S$: 402.1865. Found: 402.1888.

(6*R*)-6-(2,5-Dimethoxy-4-methylphenyl)-2-methyl-2-heptene (3). A mixture of **4** (350 mg, 0.87 mmol), Na_2HPO_4 (494 mg, 3.48 mmol) and 5% Na–Hg (1.4 g) in MeOH (7 mL) was sonicated at RT for 6 h. After filtration through a pad of Celite, the mixture was extracted with AcOEt and the extracts washed with water and brine, then dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give the olefin **3** (193 mg, 85%) as a colorless oil. $[\alpha]_D$ -34.3^o (c 1.57, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, d, *J*=6.8 Hz), 1.48–1.67 (5H, m), 1.67 (3H, s), 2.20 (3H, s), 3.14 (1H, sextet, *J*=7.3 Hz), 3.76 (3H, s), 3.78 (3H, s), 5.12 (1H, m), 6.666 (1H, s), 6.6674 (1 H, s). ^{13}C NMR ($CDCl_3$) δ 16.1 (q), 17.6 (q), 21.3 (q), 25.7 (q), 26.4 (t), 31.9 (d), 37.3 (t), 56.1 (q), 56.4 (q), 109.8 (d), 114.4 (d), 124.2 (s), 124.9 (d), 131.1 (s), 134.0 (s), 150.9 (s), 151.9 (s). IR (neat) /cm^{-1} 1050, 1209. MS (EI) *m/z* 262 (M^+). HRMS (EI) Calcd for $C_{17}H_{26}O_2$: 262.1933. Found: 262.1933.

(*R*)-(+)-Curcuquinone (1). To a solution of **3** (40 mg, 0.15 mmol) in CH_3CN/H_2O (7:3, v/v, 0.8 mL) was added $(NH_4)_2Ce(NO_3)_6$ (307 mg, 0.56 mmol) at 0 ^{o}C, and the mixture stirred at RT for 10 min. The mixture was extracted with Et_2O and the extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give (*R*)-(+)-curcuquinone **1** (20 mg, 56%) as a yellow oil, $[\alpha]_D$ +1.47° (c 2.82, $CHCl_3$), $[\alpha]_{577}$ +4.32° (c 2.82, $CHCl_3$) {lit.[1a] $[\alpha]_D$ -1.3° (c 9.1, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, d, *J*=7.3 Hz), 1.39–1.60 (5H, m), 1.66 (3H, d, *J*=0.8 Hz), 1.96 (2H, m), 2.03 (3H, d, *J*=1.2 Hz), 2.91 (1H, sextet, *J*=6.8 Hz), 5.04 (1H, t, *J*=7.0 Hz), 6.50 (1H, d, *J*=0.8 Hz), 6.58 (1H, d, *J*=1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 15.4 (q), 17.7 (q), 19.5 (q), 25.7 (q), 25.8 (t), 31.3 (d), 35.8 (t), 123.8 (d), 131.1 (d), 132.1 (s), 133.8 (d), 145.1 (s), 154.2 (s), 187.4 (s), 188.5 (s). IR (neat) /cm^{-1} 1653. MS (EI) *m/z* 232 (M^+). HRMS (EI) Calcd for $C_{15}H_{20}O_2$: 232.1463. Found: 232.1481.

(*R*)-(–)-Curcuhydroquinone (2). A solution of **1** (28.2 mg, 0.12 mmol) in THF (0.6 mL) had added a solution of $Na_2S_2O_4$ (211 mg, 1.20 mmol) in H_2O (0.4 mL) at 0 ^{o}C, and was stirred at RT for 5 min. The mixture was extracted with Et_2O and the extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel (hexane–ethyl acetate, 9:1, v/v) to give (*R*)-(-)-curcuhydroquinone **2** (27.8 mg, 98%) as a colorless oil. $[\alpha]_D$ -48.0° (c 2.78, $CHCl_3$) {lit.[1a] $[\alpha]_D$ -21° (c 0.9, $CHCl_3$)}. ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, d, *J*=7.3 Hz), 1.54 (3H, s), 1.68 (3H, s), 2.17 (3H, s), 2.93 (1H, sextet, *J*=6.8 Hz), 4.30 (2H, br s, D_2O exchangeable), 5.11 (1H, m), 6.55 (1H, s), 6.58 (1H, s). ^{13}C NMR ($CDCl_3$) δ 15.5 (q), 17.7 (q), 21.1 (q), 25.7 (q), 26.0 (t), 31.4 (d), 37.3 (t), 113.5 (d), 118.0 (d), 121.9 (s), 124.6 (d), 131.9 (s), 132.1 (s), 146.6 (s), 147.8 (s). IR (neat) /cm^{-1} 3250. MS (EI) *m/z* 234 (M^+). HRMS (EI) Calcd for $C_{15}H_{22}O_2$: 234.1620. Found: 234.1629.

References

1. (a) McEnroe, F. J.; Fenical, W. *Tetrahedron* **1978**, *34*, 1661. (b) Bohlmann, F.; Zdero, C.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 2245.
2. (a) Sanchez, I. H.; Lemini, C.; Joseph-Natahn, P. *J. Org. Chem.* **1981**, *46*, 4666. (b) Ono, M.; Yamamoto, Y.; Todoroki, R.; Akita, H. *Heterocycles* **1994**, *37*, 181. (c) Ono, M.; Yamamoto, Y.; Akita, H. *Chem. Pharm. Bull.* **1995**, *43*, 553.
3. (a) Takabatake, K.; Nishi, I.; Shindo, M.; Shishido, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1807. (b) Fuganti, C.; Serra, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3758.
4. (a) Guanti, G.; Narisano, E.; Podgorski, S.; Thea, S.; Williams, A. *Tetrahedron* **1990**, *46*, 7081. (b) Bando, T.; Shishido, K. *Heterocycles* **1997**, *46*, 111. (c) Bando, T.; Shishido, K. *Synlett* **1997**, 665. (d) Bando, T.; Namba, Y.; Shishido, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2159. (d) Shishido, K.; Bando, T. *J. Mol. Cat. B: Enzymatic* **1998**, *5*, 183. (e) Sato, K.; Bando, T.; Shindo, M.; Shishido, K.; *Heterocycles* **1999**, *50*, 11. (f) Sato, K.; Yoshimura, T.; Shindo, M.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 309. (g) Kisyuku, H.; Shindo, M.; Shishido, K. *Chem. Commun*. **2003**, 350.
5. (a) Takano, S.; Samizu, K.; Ogasawara, K. *Synlett* **1993**, 393. (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2437. (c) Koga, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett*. **1994**, *35*, 1227.
6. Hubig, S. M.; Jung, W.; Kochi, J. K. *J. Org. Chem.* **1994**, *59*, 8261.
7. (a) Nakagawa, I.; Hata, T. *Tetrahedron Lett*. **1975**, 1409. (b) Nakagawa, I.; Aki, K.; Hata, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1315.