Baker's yeast-mediated enantioselective synthesis of the bisabolane sesquiterpenes (+)-curcuphenol, (+)-xanthorrhizol, (−)-curcuquinone and (+)-curcuhydroquinone

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Fermenting baker's yeast converts the unsaturated aldehydes **5a–c** into the saturated alcohols **6a–c**, respectively. The microbial saturation of substrates adsorbed on a nonpolar resin proceeds in high chemical yields and shows complete enantioselectivity in the formation of the (*S*)-(+) isomers. Enantiopure **6a–c** are versatile chiral building blocks for the synthesis of bisabolane sesquiterpenes. Their usefulness is shown in the preparation of (*S*)-(+)-curcuphenol, (*S*)-(+)-xanthorrhizol, (*S*)-(−)-curcuquinone and (*S*)-(+)-curcuhydroquinone.

Introduction

The phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[1] Differently from the non-phenolic bisabolane compounds, which are the olfactorally active components of a large number of essential oils, they show a wide range of biological activities. Curcuphenol **1** (Fig. 1), curcuquinone **3** and curcuhydroquinone **4** were isolated from the Caribbean gorgonian *Pseudopterogorgia rigida*[2] and show antibacterial properties against *Staphylococcus aureus* and *Vibrio anguillarum*. The closely related xanthorrhizol **2** was extracted from *Curcuma xanthorrhixa*[3] and *Iostephane heterophylla*[4] which are plants of different geographic origins, used in traditional medicine. Moreover, the recent isolation of the heliannuols,[5] which are a group of allelochemical phenolic sesquiterpenes structurally related to **4**, spreads the known biological activities of this kind of compound. In addition, opposite enantiomers show different properties, as in the case of curcuphenol where the (*S*)-(+)-enantiomer **1** shows antitumoral activity[6] whilst the (*R*)-(−)-enantiomer shows the antibacterial features described above. Though several approaches have been reported for the construction of the bisabolane skeleton,[7] only a few enantioselective syntheses of these sesquiterpene phenols have been reported in the literature[8–10] due to the difficulty of introducing a stereogenic center in the benzylic position. We have previously[11] shown that the baker's yeast reduction of (*E*)-3-(*p*-tolyl)but-2-en-1-ol affords enantiopure (*S*)-(+)-3-(*p*-tolyl)butan-1-ol, which is a chiral buiding block for the synthesis of the most common bisabolane sesquiterpenes. Further studies on the microbial reduction of (*R*)- and (*S*)-3-(4-methylcyclohex-3-enyl)but-2-enal[12] allow us to prepare enantioselectively the well known bisabolene sesquiterpenes (+)-epijuvabione and (−)-juvabione.

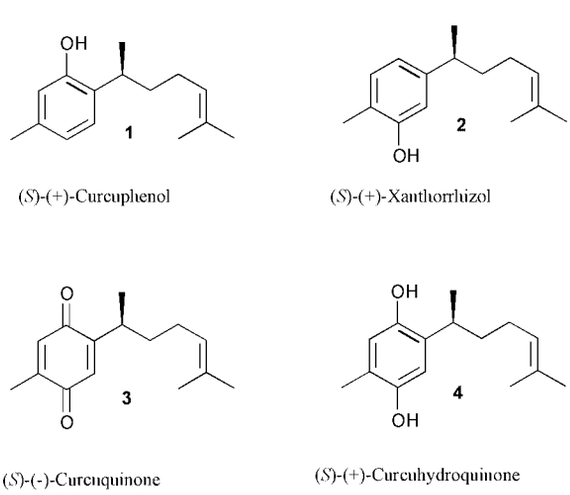
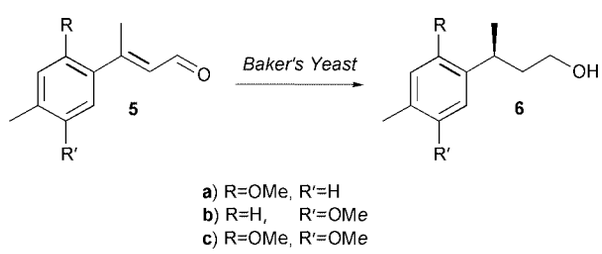


Fig. 1

Now, as part of a programme of synthesis of phenolic sesquiterpenes,[8c,13] we report on the enantioselective synthesis of the title compounds **1–4**. Their preparation was based on the baker's yeast reduction (Scheme 1) of aldehydes **5a–c**, to afford enantiopure alcohols **6a–c**, respectively. These latter are useful building blocks for the synthesis of phenolic sesquiterpenes of (*S*) absolute configuration.



Scheme 1

Results and discussion

Following our previous findings, we were looking for a synthetic method for the preparation of aldehydes **5a–c** which are the substrates of choice for the microbial reduction. As shown in Scheme 2, they were prepared following a common pathway from the related esters **9**, **15** and **18** by reduction to the allylic alcohol followed by oxidation. The esters were themselves synthesized from the substituted acetophenones **8**, **14** and **17** by Horner–Wadsworth–Emmons reaction with triethyl phosphonoacetate (ethyl diethoxyphosphorylacetate) and sodium hydride.[14] Since this latter reaction afforded a mixture of *E*/*Z* isomers in ≈5:1 ratio and the enantioselectivity in the yeast reduction is lowered by the presence of the *Z* isomer,[12] we purified the mixture by chromatography in order to submit the pure (*E*)-aldehydes **5a–c** to the reduction. The synthesis of the acetophenones **8**, **14** and **17** differed depending on the

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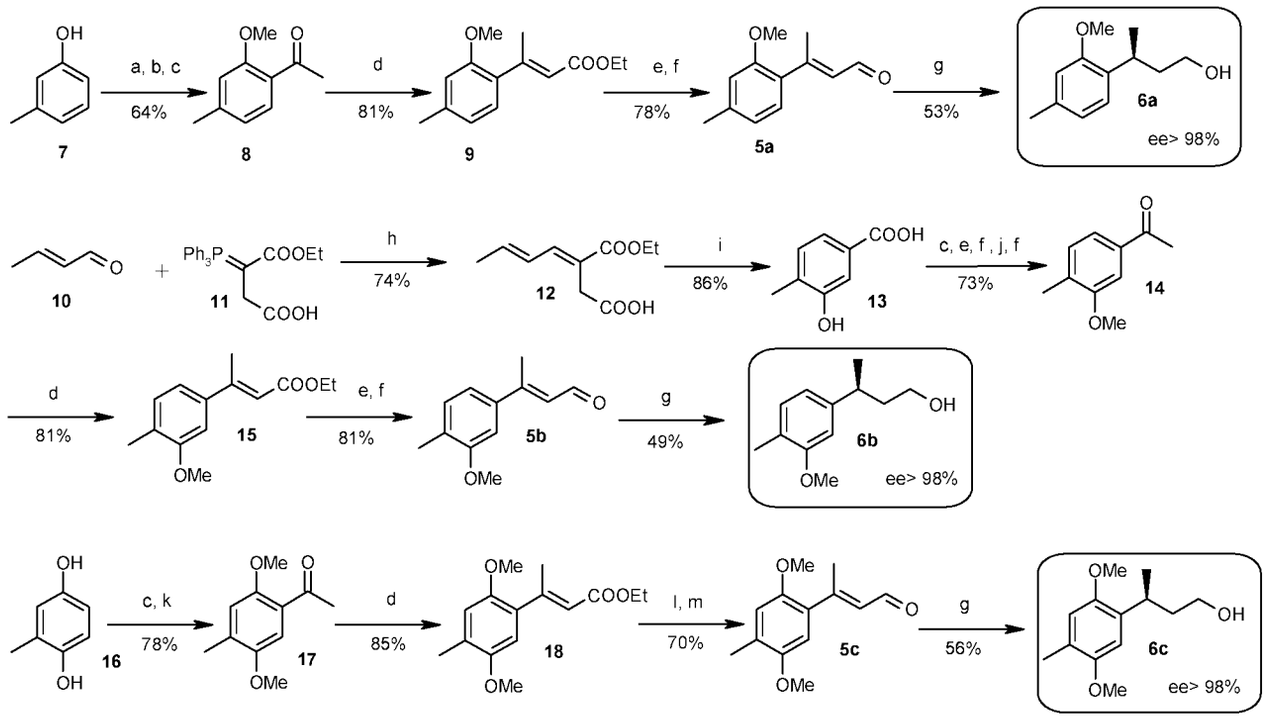


Scheme 2 *Reagents and conditions*: a) Ac_2O Py; b) $AlCl_3$; c) Me_2SO_4 K_2CO_3, acetone; d) $(EtO)_2POCH_2CO_2Et$, NaH; e) $LiAlH_4$, THF; f) MnO_2, $CHCl_3$, reflux; g) baker's yeast, 4–6 d; h) benzene reflux; i) $ClCO_2Et$, Et_3N, THF; then aq. KOH, reflux; j) MeMgCl, THF, 0 °C; k) AcCl, CH_2Cl_2, $SnCl_4$; l) DIBALH, THF; m) ClCOCOCl, DMSO, CH_2Cl_2, Et_3N.

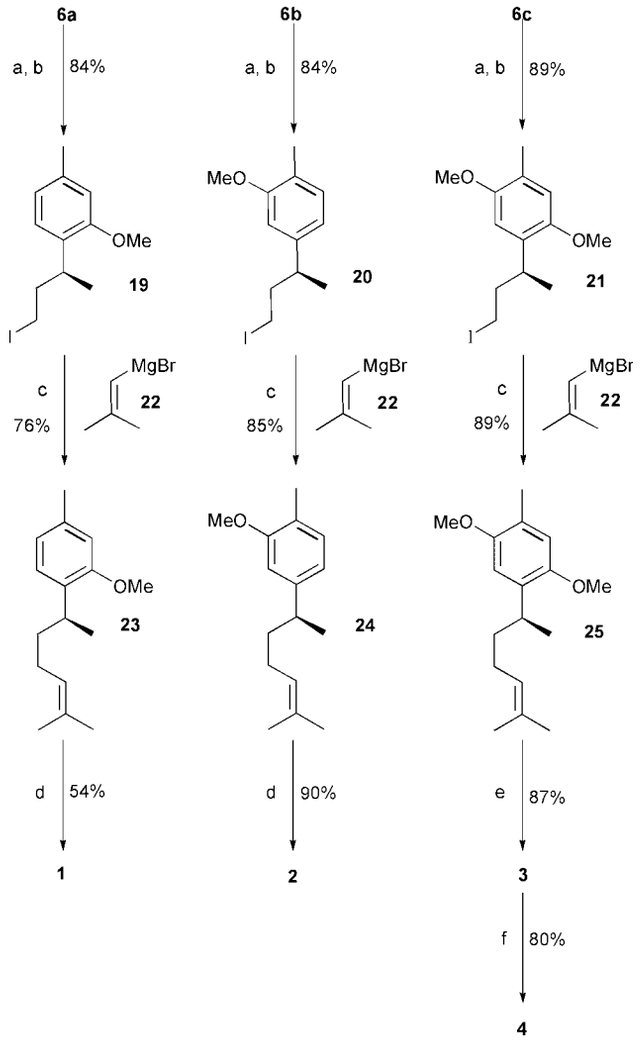
substitution of the aromatic moiety. 2-Methoxy-4-methylacetophenone **8** was prepared according to the literature[15] starting from *m*-cresol **7** by acetylation, Fries transposition and methylation. A similar pathway was used to synthesize 2,5-dimethoxy-4-methylacetophenone **17**. Commercially available 2-methylhydroquinone **16** was methylated with Me_2SO_4 and then converted into **17** by treatment with AcCl and $SnCl_4$.[16] However, 3-methoxy-4-methylacetophenone **14** was prepared using a completely different approach. Since the reported procedure based on a functionalization of *p*-methylacetophenone[17] afforded **14** in only low yield, we decided to construct the aromatic ring by benzanullation[18] of the hexadienoic acid derivative **12**. This latter was prepared from crotonaldehyde **10** by Wittig reaction with ylide **11**,[19] and then was submitted to cyclization using ethyl chloroformate and triethylamine as base. After KOH treatment, we obtained the acid **13**, which was converted into the suitable benzophenone **14** in good yield by a number of straightforward synthetic steps.

Following the methodology described above, the three (*E*) aldehydes **5a**–**c** were obtained on a multigram scale. In order to achieve a large-scale preparation of the enantiopure alcohols **6a**–**c**, we performed the microbial reduction by adsorbing the substrates on a nonpolar resin (XAD 1180). This procedure allowed us to use a high concentration of substrate (5–10 g L^{-1}) and the product was recovered by simple filtration of the resin. Extraction of the latter with a suitable solvent afforded the crude saturated alcohols **6a**–**c**, which were purified as described in the Experimental section. The results of the biotransformation showed a high conversion of the aldehydes into the saturated alcohols (49–56% yield as isolated products) in only 4–6 days of incubation. The determination of the optical purity of alcohols **6a**–**c** was performed by comparing the NMR spectra of the (−)-MPTA esters[20] of the latter alcohols with those obtained from racemic **6a**–**c** (see Experimental section). Since the alcohols **6a**–**c**, obtained from yeast reduction, appeared as single isomers, we can establish an enantiomeric excess >98%.

The transformation of the C_{11} (*S*)-(+)-alcohols **6a**–**c** into the C_{15} sesquiterpene skeleton was achieved by an effective procedure we have previously[8c,11] used for this kind of compound (Scheme 3). To this end, the alcohols were converted into the related iodides **19**–**21**, respectively, *via* the tosyl ester derivatives and substitution with NaI in acetone. The coupling of the iodides with the Grignard reagent **22** catalyzed by copper(I) iodide[21] afforded enantiopure **23**–**25** which show the whole C_{15} bisabolane framework. The methyl ether functionality of compounds **23** and **24** was cleaved using sodium ethanethiolate in DMF[22] to give (*S*)-(+)-curcuphenol **1** and (*S*)-(+)-xanthorrhizol **2**, respectively, showing the same analytical data as those reported in the literature for the natural products[2–4,6] except for **2**, whose sign of rotation was reversed and with similar amplitude of that of the natural (*R*)-(−)-xanthorrhizol. The same procedure performed on a sample of **25** gave unsatisfactory results since an inseparable mixture with the monomethylated hydroquinone was obtained. Instead, oxidation of **25** with cerium(IV) ammonium nitrate (CAN) in aq. MeCN[23] smoothly afforded the (*S*)-(−)-curcuquinone **3** which could be easily reduced with $NaBH_4$ to (*S*)-(+)-curcuhydroquinone **4**. The spectroscopical data of these two compounds were in good agreement with those of synthetic[10,24] and natural[2,25] products, except for **3** whose sign of rotation was reported[2] as (−) for the (*R*) isomer. Since we had synthesized **3** and **4** starting from the (*S*) alcohol **6c** and we obtained the known (*S*)-(+)-curcuhydroquinone, the absolute configuration of **3** was unambiguously (*S*).

Experimental

Mps were measured on a Reichert melting-point apparatus, equipped with a Reichert microscope, and are uncorrected. Optical rotations were measured on a Propol automatic digital polarimeter, and $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}. Microanalyses were determined on a Carlo Erba 1106 analyzer. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. ^1H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^1H). The chemical-shift scale is based on internal tetramethylsilane. *J*-Values are given in Hz. Mass spectra were measured on a Finnigan-MAT TSQ 70 spec-



Scheme 3 *Reagents and conditions*: a) TsCl, Py, CH_2Cl_2; b) NaI, acetone, reflux; c) CuI cat., THF; d) NaSEt, DMF, reflux; e) CAN, aq. MeCN; f) $NaBH_4$, MeOH.

trometer. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns. Baker's yeast was obtained from Gist-brocades (DSM Bakery Ingredients Italy s.p.a.).

Preparation of acetophenones 8, 14 and 17

2-Methoxy-4-methylacetophenone 8. Prepared from **7** according to the reported procedure[15] and further purified by crystallization from hexane; yield 64%, mp 35–37 °C (from hexane) (Found: C, 73.25; H, 7.39. Calc. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37%); ν_{max}(film)/cm^{-1} 1656, 1605, 1418, 1292, 1259, 1172, 1033, 812, 604; δ_H 2.36 (3H, s, Ar*Me*), 2.57 (3H, s, ArCO*Me*), 3.87 (3H, s, OMe), 6.72–6.82 (2H, m, ArH), 7.66 (1H, d, *J* 8.1, ArH); *m*/*z* (EI) 165 (M^+ + 1, 2%), 164 (M^+, 19), 149 (100), 134 (4), 119 (3), 106 (8), 91 (20), 77 (7), 65 (5), 51 (3), 43 (3).

(*E*,*E*)-3-(Ethoxycarbonyl)hepta-3,5-dienoic acid 12. Crotonaldehyde **10** (18 g, 257 mmol) as a solution in benzene (150 mL) was treated with 1-ethyl hydrogen 2-(triphenylphosphanylidene)butane-1,4-dioate **11** (100 g, 246 mmol) at reflux for 4 h. The solvent was removed under reduced pressure, the residue was dissolved in hexane–diethyl ether (2:1), and the triphenylphosphine oxide eliminated by crystallization. The liquid phase was concentrated and the remaining oil was purified by chromatography using hexane–ethyl acetate (95:5→8:2) as eluent to afford exclusively the *acid* **12** (36 g, 74%) as a single (*E*,*E*) isomer, mp 72–73 °C (from hexane) (Found: C, 60.56; H, 7.14. $C_{10}H_{14}O_4$ requires C, 60.59; H, 7.12%); ν_{max}(film)/cm^{-1} 1704, 1647, 1426, 1305, 1233, 1092, 971, 767; δ_H 1.29 (3H, t, *J* 7, OCH_2*Me*), 1.89 (3H, d, *J* 5.4, *Me*CHCH), 3.47 (2H, s, CH_2CO_2H), 4.22 (2H, q, *J* 7, OCH_2Me), 6.14–6.38 (2H, m, MeC*HCH*), 7.34 (1H, d, *J* 10, C*H*CCO$_2$Et); *m*/*z* (EI) 198 (M^+, 3%), 183 (3), 154 (63), 139 (29), 125 (29), 111 (66), 97 (19), 79 (100), 67 (11), 53 (16), 39 (15).

3-Hydroxy-4-methylbenzoic acid 13. $ClCO_2Et$ (21 mL, 220 mmol) was added in one portion to a solution of acid **12** (35 g, 177 mmol) in dry THF (200 mL), and then Et_3N (75 mL, 538 mmol) was added dropwise, keeping the temperature under 20 °C. The mixture was stirred for 15 min and then acidified with an excess of 5% aq. HCl and extracted with ethyl acetate (3 × 150 mL). The organic phase was concentrated and the residue was dissolved in ethanol (80 mL). The resulting solution was treated with aq. KOH (25 g, 445 mmol in 100 mL) and heated at reflux for 2 h. After cooling, the mixture was acidified with conc. HCl and extracted with ethyl acetate (3 × 150 mL). The combined organic portions were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography using hexane–ethyl acetate (8:2→1:2) as eluent followed by crystallization to give pure *acid* **13**[26] (23.2 g, 86%), mp 220–221 °C (from hexane–ethyl acetate) (Found: C, 63.06; H, 5.33. $C_8H_8O_3$ requires C, 63.15; H, 5.30%); ν_{max}(film)/cm^{-1} 3377, 1663, 1611, 1586, 1428, 1302, 1232, 1182, 880, 762, 640; δ_H 2.18 (3H, s, Ar*Me*), 7.17 (1H, d, *J* 8, Ar*H*), 7.32 (1H, d, *J* 8, ArH), 7.40 (1H, s, ArH), 9.7 (1H, br s, ArOH), 12.6 (1H, br s, CO_2H); *m*/*z* (EI) 152 (100), 135 (38), 123 (3), 107 (82), 77 (32), 67 (3), 63 (4), 51 (9), 45 (3), 39 (6).

3-Methoxy-4-methylacetophenone 14. Acid **13** (20 g, 132 mmol) as a solution in dry acetone (200 mL) was refluxed for 10 h with Me_2SO_4 (38 mL, 402 mmol) and dry K_2CO_3 (65 g, 470 mmol). The resulting mixture was concentrated under reduced pressure, diluted with water (300 mL) and extracted with diethyl ether (3 × 150 mL). The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and the residue was reduced at rt with $LiAlH_4$ (6 g, 158 mmol) in dry THF (150 mL). The reaction was quenched by dropwise addition of ethyl acetate (200 mL) followed by addition of 5% aq. HCl (200 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic phases were washed with brine (200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The obtained benzylic alcohol was dissolved in $CHCl_3$ (200 mL) and treated with MnO_2 (50 g, 575 mmol) at reflux for 3 h. The reaction mixture was filtered and the liquid phase was concentrated under reduced pressure. The residue was dissolved in dry THF (150 mL) and treated with MeMgCl (55 mL of a 3 M solution in THF, 165 mmol) while being stirred under nitrogen at 0 °C for 1 h. Acidic work-up with 5% aq. HCl (200 mL), extraction with ethyl acetate (3 × 100 mL), and concentration of the organic phase gave the crude carbinol, which was oxidized directly with MnO_2 (50 g, 575 mmol) in $CHCl_3$ (200 mL) at reflux for 4 h. Filtration and concentration of the organic phase gave crude **14**. Purification of the latter by chromatography with hexane→hexane–ethyl acetate 9:1 as eluent, afforded pure *3-methoxy-4-methylacetophenone* **14**[17] (15.9 g, 73%) (Found: C, 73.30; H, 7.35. $C_{10}H_{12}O_2$ requires C, 73.15; H, 7.37%); ν_{max}(film)/cm^{-1} 1682, 1606, 1579, 1501, 1408, 1271, 1227, 1038, 877; δ_H 2.26 (3H, s, Ar*Me*), 2.58 (3H, s, ArCO*Me*), 3.88 (3H, s, OMe), 7.19 (1H, d, *J* 7.5, ArH), 7.41–7.48 (2H, m, ArH); *m*/*z* (EI) 165 (M^+ + 1, 6%), 164 (M^+, 54), 149 (100), 121 (21), 106 (7), 91 (29), 77 (13), 65 (3), 51 (4), 43 (6).

2,5-Dimethoxy-4-methylacetophenone 17. Methylhydroquinone **16** (40 g, 322 mmol) as a solution in dry acetone (400 mL) was refluxed for 12 h with Me_2SO_4 (90 mL, 950 mmol) and K_2CO_3 (150 g, 1085 mmol). The resulting mixture was

concentrated under reduced pressure, diluted with water (500 mL), and extracted with diethyl ether (3 × 250 mL). The organic phase was washed with brine (300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (150 mL) and was treated with AcCl (28 mL, 394 mmol) followed by the dropwise addition of $SnCl_4$ (38 mL, 325 mmol). The resulting solution was stirred at rt for 2 h and then was poured in ice–water. The mixture was extracted with diethyl ether (2 × 300 mL) and the organic phase was washed successively with 5% aq. $NaHCO_3$ (2 × 200 mL) and brine (200 mL). Evaporation of the solvent, distillation of the residue, and crystallization of the latter from hexane afforded pure *ketone* **17**[16] (49 g, 78%), mp 76 °C (from hexane) (Found: C, 67.95; H, 7.28. $C_{11}H_{14}O_3$ requires C, 68.02; H, 7.27%); ν_{max}(film)/cm^{-1} 1661, 1610, 1501, 1398, 1214, 1042, 886, 802, 638, 574; δ_H 2.26 (3H, s, Ar*Me*), 2.61 (3H, s, ArCO*Me*), 3.82 (3H, s, OMe), 3.87 (3H, s, OMe), 6.79 (1H, s, ArH), 7.29 (1H, s, ArH); *m*/*z* (EI) 195 (M^+ + 1, 6%), 194 (M^+, 51), 179 (100), 164 (9), 151 (7), 136 (10), 121 (8), 91 (11), 77 (6), 65 (4), 53 (3), 43 (6).

Preparation of esters 9, 15 and 18

Ethyl (2*E*)-3-(2-methoxy-4-methylphenyl)but-2-enoate 9*E*. Triethyl phosphonoacetate (72 g, 321 mmol) was added dropwise under nitrogen over a period of 2 h to a stirred suspension of NaH (60% in mineral oil; 13 g, 325 mmol) in dry THF (250 mL) at rt. To the resulting mixture was slowly added a solution of ketone **8** (45 g, 274 mmol) in dry THF (100 mL) and the reaction mixture was heated at reflux for 2 h. After cooling, the mixture was poured onto ice–water and extracted with diethyl ether (3 × 200 mL). The organic phase was washed with brine (2 × 100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was chromatographed using hexane–ethyl acetate 95 : 5 as eluent (R_f **9*E***: 0.22; R_f **9*Z***: 0.11) to afford pure *ester* **9*E*** (41 g, 64%) (Found: C, 71.88; H, 7.75. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74%); ν_{max}(film)/cm^{-1} 2934, 1715, 1630, 1571, 1504, 1465, 1409, 1366, 1340, 1274, 1175, 1041, 875, 812; δ_H 1.29 (3H, t, *J* 7.3, OCH$_2$*Me*), 2.35 (3H, s, Ar*Me*), 2.48 (3H, d, *J* 1.4, ArC*Me*), 3.80 (3H, s, OMe), 4.19 (2H, q, *J* 7.3, OC*H*$_2$Me), 5.89 (1H, d, *J* 1.4, C*H*CO$_2$Et), 6.67–6.79 (2H, m, ArH), 7.03 (1H, d, *J* 7.9, ArH); *m*/*z* (EI) 235 (M^+ + 1, 5%), 234 (M^+, 33), 219 (1), 203 (96), 189 (38), 175 (100), 159 (12), 145 (55), 131 (12), 115 (20), 105 (13), 91 (17), 77 (8), 65 (4), 51 (3), 39 (3). The last eluted fractions gave **ethyl (2*Z*)-3-(2-methoxy-4-methylphenyl)but-2-enoate 9Z** (11 g, 17%) (Found: C, 71.85; H, 7.70%); ν_{max}(film)/cm^{-1} 2978, 1728, 1610, 1507, 1466, 1372, 1260, 1174, 1151, 1041, 812; δ_H 1.09 (3H, t, *J* 7.3, OCH$_2$*Me*), 2.13 (3H, d, *J* 1.4, ArC*Me*), 2.35 (3H, s, Ar*Me*), 3.78 (3H, s, OMe), 3.98 (2H, q, *J* 7.3, OC*H*$_2$Me), 5.94 (1H, d, *J* 1.4, C*H*CO$_2$Et), 6.70–6.80 (2H, m, ArH), 6.91 (1H, d, *J* 7.9, ArH); *m*/*z* (EI) identical to **9*E***.

Ethyl (2*E*)-3-(3-methoxy-4-methylphenyl)but-2-enoate 15.[17] Obtained exclusively as the *E-isomer*; colorless oil (81%) (Found: C, 71.60; H, 7.75%); ν_{max}(film)/cm^{-1} 1713, 1626, 1572, 1509, 1465, 1411, 1343, 1293, 1231, 1159, 1042, 851, 814; δ_H 1.32 (3H, t, *J* 6.9, OCH$_2$*Me*), 2.22 (3H, s, Ar*Me*), 2.57 (3H, d, *J* 1.1, ArC*Me*), 3.86 (3H, s, O*Me*), 4.22 (2H, q, *J* 6.9, OC*H*$_2$Me), 6.13 (1H, d, *J* 1.1, C*H*CO$_2$Et), 6.91 (1H, d, *J* 1.5, ArH), 6.99 (1H, dd, *J* 7.8 and 1.5, ArH), 7.12 (1H, d, *J* 7.8, ArH); *m*/*z* (EI) 235 (M^+ + 1, 14%), 234 (M^+, 87), 219 (2), 205 (11), 189 (76), 188 (100), 175 (11), 160 (29), 145 (20), 131 (16), 115 (23), 103 (9), 91 (16), 77 (10), 65 (4), 51 (4), 39 (3).

Ethyl (2*E*)-3-(2,5-dimethoxy-4-methylphenyl)but-2-enoate 18*E*. Purified by chromatography using hexane–ethyl acetate 9 : 1 as eluent (R_f **18*E***: 0.29; R_f **18*Z***: 0.19) to give *colorless crystals* (71%), mp 61–62 °C (from hexane) (Found: C, 67.98; H, 7.65. $C_{15}H_{20}O_4$ requires C, 68.16; H, 7.63%); ν_{max}(film)/cm^{-1} 1710, 1630, 1508, 1468, 1400, 1342, 1213, 1174, 1041, 877, 807; δ_H 1.31 (3H, t, *J* 7.3, OCH$_2$*Me*), 2.23 (3H, s, Ar*Me*), 2.50 (3H, d, *J* 1.3, ArC*Me*), 3.77 (3H, s, O*Me*), 3.79 (3H, s, O*Me*), 4.20 (2H, q, *J* 7.3, OC*H*$_2$Me), 5.91 (1H, d, *J* 1.3, C*H*CO$_2$Et), 6.64 (1H, s, Ar*H*), 6.72 (1H, s, Ar*H*); *m*/*z* (EI) 265 (M^+ + 1, 7), 264 (M^+, 45), 249 (1), 233 (48), 219 (17), 205 (100), 189 (18), 176 (20), 161 (37), 149 (6), 133 (5), 115 (8), 105 (7), 91 (8), 77 (10), 65 (6), 51 (4), 39 (7).

Ethyl (2*Z*)-3-(2,5-dimethoxy-4-methylphenyl)but-2-enoate 18*Z*. *Colorless crystals* (14%), mp 49–50 °C (from hexane) (Found: C, 67.95; H, 7.60%); ν_{max}(film)/cm^{-1} 1720, 1646, 1513, 1468, 1402, 1214, 1167, 1042, 868, 811; δ_H 1.09 (3H, t, *J* 7.1, OCH$_2$*Me*), 2.15 (3H, d, *J* 1.5, ArC*Me*), 2.22 (3H, s, Ar*Me*), 3.74 (3H, s, OMe), 3.76 (3H, s, OMe), 3.99 (2H, q, *J* 7.1, OC*H*$_2$Me), 5.95 (1H, m, C*H*CO$_2$Et), 6.52 (1H, s, ArH), 6.72 (1H, s, ArH); *m*/*z* (EI) identical to **18*E***.

Preparation of aldehydes 5a–c

(2*E*)-3-(2-Methoxy-4-methylphenyl)but-2-enal 5a. The ester **9*E*** (50 g, 215 mmol) as a solution in dry THF (300 mL) was reduced with $LiAlH_4$ (8.2 g, 216 mmol) at 0 °C. The reaction was quenched by dropwise addition of ethyl acetate (300 mL) followed by addition of 5% aq. HCl (650 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic phases were washed with brine (2 × 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude allylic alcohol was dissolved in $CHCl_3$ (250 mL) and treated at reflux with MnO_2 (80 g, 920 mmol) for 6 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ was purified by distillation (bp 125 °C/0.1 mmHg) to afford pure *aldehyde* **5a** (32 g, 78%) as a colorless oil (Found: C, 75.95; H, 7.40. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%); ν_{max}(film)/cm^{-1} 2939, 1670, 1610, 1501, 1465, 1411, 1282, 1259, 1169, 1133, 1037, 812; δ_H 2.37 (3H, s, Ar*Me*), 2.52 (3H, d, *J* 1.4, ArC*Me*), 3.82 (3H, s, OMe), 6.14 (1H, dq, *J* 8.1 and 1.4, C*H*COH), 6.72–6.82 (2H, m, ArH), 7.07 (1H, d, *J* 7.8, ArH), 10.14 (1H, d, *J* 8.1, CHCO*H*); *m*/*z* (EI) 190 (M^+, 4%), 175 (19), 159 (100), 147 (10), 131 (8), 115 (14), 91 (15), 77 (7), 65 (3), 51 (3), 39 (3).

(2*E*)-3-(3-Methoxy-4-methylphenyl)but-2-enal 5b. *Colorless oil* (81%), bp 130 °C/0.3 mmHg (Found: C, 75.92; H, 7.40%); ν_{max}(film)/cm^{-1} 1655, 1509, 1418, 1267, 1238, 1135, 1038, 844, 815; δ_H 2.25 (3H, s, Ar*Me*), 2.56 (3H, d, *J* 1.1, ArC*Me*), 3.86 (3H, s, OMe), 6.41 (1H, dq, *J* 8 and 1.1, C*H*COH), 6.98 (1H, d, *J* 1.6, ArH), 7.08 (1H, dd, *J* 7.9 and 1.6, ArH), 7.17 (1H, d, *J* 7.9, ArH), 10.18 (1H, d, *J* 8, CHCO*H*); *m*/*z* (EI) 190 (M^+, 26%), 175 (100), 159 (29), 147 (17), 131 (11), 115 (19), 91 (21), 77 (11), 63 (3), 51 (4), 39 (3).

(2*E*)-3-(2,5-Dimethoxy-4-methylphenyl)but-2-enal 5c. The ester **18*E*** (30 g, 114 mmol) as a solution in dry THF (150 mL) was reduced with DIBALH (170 mL of 1.5 M solution in toluene) at 0 °C. The reaction was quenched by dropwise addition of ethyl acetate (200 mL) followed by addition of 5% aq. HCl (400 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic phases were washed with brine (2 × 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and dropped into a Swern oxidant mixture which had been previously prepared by addition of DMSO (20 g, 256 mmol) to a cooled solution (−78 °C) of ClCOCOCl (16 g, 126 mmol) in CH_2Cl_2 (150 mL). The resulting suspension was treated with Et_3N (60 g, 593 mmol) and the reaction mixture was allowed to warm to rt. After 2 h the mixture was diluted with CH_2Cl_2 (250 mL), washed with water (4 × 100 mL), and the organic phase was concentrated under reduced pressure. The residue was purified by chromatography, using hexane–ethyl acetate (95 : 5→8 : 2) as

eluent, to give pure *aldehyde* **5c** (17.6 g, 70%) as a yellow oil (Found: C, 70.75; H, 7.35. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%); ν_{max}(film)/cm^{-1} 2936, 2850, 1667, 1501, 1466, 1398, 1213, 1043, 861, 811, 693; δ_H 2.24 (3H, s, Ar*Me*), 2.54 (3H, d, *J* 1.2, ArC*Me*), 3.79 (6H, s, OMe), 6.15 (1H, dd, *J* 8.1 and 1.2, C*H*COH), 6.66 (1H, s, ArH), 6.76 (1H, s, ArH), 10.16 (1H, d, *J* 8.1, CHCO*H*); *m*/*z* (EI) 220 (M$^+$, 10%), 205 (2), 189 (100), 174 (8), 161 (6), 145 (5), 137 (3), 115 (6), 105 (3), 91 (7), 77 (4), 65 (2), 51 (1), 39 (2).

Baker's yeast reduction of aldehydes 5a–c to alcohols 6a–c

A 10 L open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (5 L) and glucose (350 g). Fresh baker's yeast (1.5 kg) was added in small pieces to the stirred mixture and fermentation was allowed to proceed for 2 h. The aldehyde **5a** (30 g, 158 mmol), adsorbed on the resin XAD 1180 (150 g), was added in one portion. Vigorous stirring was continued for 4 days at room temperature. During this time more baker's yeast (250 g) and glucose (100 g) were added after both 24 and 48 h since commencement of fermentation. The resin was then separated by filtration on a sintered glass funnel (porosity 0, >160 μm) and the water phase was extracted again with further resin (50 g). The combined resin crops were extracted with ethyl acetate (4 × 150 mL) and the acetate solution was washed with brine. The dried organic phase (Na_2SO_4) was concentrated under reduced pressure to give an oil (34 g). This latter was composed mainly of saturated alcohol **6a** and the related unsaturated allylic alcohol, also produced by microbiological reduction. These two compounds showed identical R_f-values and were not separable by chromatography. In order to obtain pure **6a** we converted selectively the allylic alcohol in the starting aldehydes **5a** by MnO_2 oxidation. The crude mixture was dissolved in $CHCl_3$ and treated with MnO_2 (70 g), with stirring of the mixture at reflux for 6 h. The residue obtained upon filtration and evaporation of the $CHCl_3$ phase was purified by column chromatography, using hexane–ethyl acetate (9 : 1→3 : 1) as eluent, to give pure *(3S)-3-(2-methoxy-4-methylphenyl)butan-1-ol* **6a**[8c] (16.4 g, 53%) as a pale yellow oil; $[\alpha]_D^{20}$ +22.8 (*c* 4, $CHCl_3$) (Found: C, 74.05; H, 9.35. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%); ν_{max}(film)/cm^{-1} 3368, 2959, 1612, 1579, 1506, 1465, 1412, 1258, 1042, 812; δ_H 1.26 (3H, d, *J* 6.9, ArCH*Me*), 1.60–1.76 (1H, m, *H*CHCH$_2$OH), 1.82–1.98 (1H, m, HC*H*CH$_2$OH), 2.35 (3H, s, Ar*Me*), 2.42 (1H, br s, OH), 3.27–3.46 (2H, m, ArC*H*Me + CH$_2$*H*CHOH), 3.49–3.59 (1H, m, CH$_2$HC*H*OH), 3.83 (3H, s, OMe), 6.69 (1H, s, ArH), 6.77 (1H, d, *J* 7.7, ArH), 7.07 (1H, d, *J* 7.7, ArH); *m*/*z* (EI) 195 (M$^+$ + 1, 3%), 194 (M$^+$, 25), 179 (1), 161 (6), 149 (100), 135 (7), 119 (11), 105 (8), 91 (13), 77 (5), 65 (2), 51 (1), 39 (1).

(3*S*)-3-(3-Methoxy-4-methylphenyl)butan-1-ol 6b.[9] *Colorless oil* (49%); $[\alpha]_D^{20}$ +26.9 (*c* 2, $CHCl_3$), $[\alpha]_D^{20}$ +32.8 (*c* 6, acetone) (Found: C, 74.02; H, 9.37%); ν_{max}(film)/cm^{-1} 3348, 2958, 1612, 1583, 1514, 1465, 1416, 1257, 1136, 1043, 995, 856, 817; δ_H 1.26 (3H, d, *J* 6.9, ArCH*Me*), 1.75–1.89 (3H, m, C*H*$_2$CH$_2$OH + OH), 2.18 (3H, s, Ar*Me*), 2.74–2.92 (1H, m, ArC*H*Me), 3.45–3.63 (2H, m, CH$_2$C*H*$_2$OH), 3.81 (3H, s, OMe), 6.62–6.73 (2H, m, ArH), 7.04 (1H, d, *J* 7.5, ArH); *m*/*z* (EI) 195 (M$^+$ + 1, 7%), 194 (M$^+$, 55), 163 (10), 150 (100), 149 (92), 135 (56), 123 (8), 119 (14), 117 (15), 105 (9), 91 (26), 77 (11), 65 (4), 51 (3), 41 (3).

(3*S*)-3-(2,5-Dimethoxy-4-methylphenyl)butan-1-ol 6c. This compound was obtained by yeast reduction of aldehyde **5c** under the same conditions as described above but prolonging the fermentation for an additional 36 h. Moreover the saturated alcohol **6c** showed a different R_f-value to that of the unsaturated alcohol, so it was separated from the reaction mixture directly by chromatography without MnO_2 treatment as a *pale yellow oil* (56%); $[\alpha]_D^{20}$ +40.7 (*c* 4, $CHCl_3$) (Found: C, 69.73; H, 8.95. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%); ν_{max}(film)/cm^{-1} 3369, 2958, 1505, 1466, 1399, 1209, 1047, 863; δ_H 1.27 (3H, d, *J* 7, ArCH*Me*), 1.52–1.70 (1H, m, *H*CHCH$_2$OH), 1.82–1.99 (1H, m, HC*H*CH$_2$OH), 2.20 (3H, s, Ar*Me*), 2.48 (1H, s, OH), 3.28–3.44 (2H, m, CH$_2$*H*CHOH + ArC*H*Me), 3.47–3.59 (1H, m, CH$_2$HC*H*OH), 3.79 (6H, s, OMe), 6.67 (1H, s, ArH), 6.70 (1H, s, ArH); *m*/*z* (EI) 225 (M$^+$ + 1, 8%), 224 (M$^+$, 42), 209 (2), 191 (4), 179 (100), 164 (25), 149 (9), 135 (4), 119 (3), 105 (3), 91 (12), 77 (8), 65 (3), 53 (3), 39 (4).

Determination of the optical purity of alcohols 6a–c

The three alcohols (*S*)-(+)-**6a**–**c** were converted into their (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl esters [(*S*)-MTPA esters]. In a typical preparation, a solution of (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (0.2 mmol) in CCl_4 (0.5 mL) was added to a solution of the substrate alcohol (0.15 mmol) in CCl_4 (0.5 mL) containing dry pyridine (0.5 ml). The mixture was stirred at rt for 24 h and then was diluted with diethyl ether (60 mL). The solution was washed successively with 5% aq. HCl (30 mL), saturated aq. Na_2CO_3 (30 mL) and brine (30 mL). The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford the (*S*)-MTPA esters of alcohols (*S*)-**6a**–**c**, which were utilized for NMR spectral measurement.

The samples of racemic alcohols **6a**–**c** were synthesized from esters **9**, **15** and **18** by hydrogenation (H_2, Pd/C) and $LiAlH_4$ reduction. The (*S*)-MTPA esters of the latter were prepared as described above.

The NMR (400 MHz; $CDCl_3$) spectra of the esters derived from the racemic alcohols **6a**–**c** were very different to those obtained from the optically active ones. We used the signals due to the benzylic methyl group for determination of the enantiomerical purity. The relevant signals are listed below:

(±)-**6a**-(*S*)-MTPA ester: two doublets, δ_H 1.208 and 1.214, *J* 6.9 each.

(±)-**6b**-(*S*)-MTPA ester: two doublets, δ_H 1.247 and 1.255, *J* 6.9 each.

(±)-**6c**-(*S*)-MTPA ester: two doublets, δ_H 1.228 and 1.235, *J* 6.9 each.

(*S*)-(+)-**6a**-(*S*)-MTPA ester: doublet, δ_H 1.208, *J* 6.9.

(*S*)-(+)-**6b**-(*S*)-MTPA ester: doublet, δ_H 1.247, *J* 6.9.

(*S*)-(+)-**6c**-(*S*)-MTPA ester: doublet, δ_H 1.228, *J* 6.9.

Since the latter three samples of **6a**–**c** MTPA esters showed exclusively the three doublets at δ 1.208, 1.247 and 1.228, respectively, their ees were >98% (1% of analytical sensitivity).

Preparation of iodides 19, 20 and 21

(3*S*)-3-(2-Methoxy-4-methylphenyl)butyl iodide 19. A solution of alcohol **6a** (2 g, 10.3 mmol) in CH_2Cl_2 (10 mL) was treated with tosyl chloride (2.5 g, 13.1 mmol) and pyridine (1.1 mL, 13.6 mmol) and stirred at room temperature for 5 h. The mixture was then diluted with diethyl ether (150 mL), washed with 5% aq. HCl (70 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was treated with NaI (7 g, 46.7 mmol) in dry acetone (80 mL) at reflux for 2 h. The reaction mixture was diluted with water (200 mL), extracted with diethyl ether, and the organic phase was washed with a solution (2%; 100 mL) of $Na_2S_2O_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The crude iodide was purified by chromatography, using hexane→hexane–ethyl acetate 95 : 5 as eluent, to give pure *iodide* **19**[8c] as a colorless oil (2.65 g, 84%); $[\alpha]_D^{20}$ +13.7 (*c* 2, $CHCl_3$) (Found: C, 47.50; H, 5.60; I, 41.63. $C_{12}H_{17}IO$ requires C, 47.39; H, 5.63; I, 41.72%); ν_{max}(film)/cm^{-1} 2959, 1611, 1579, 1507, 1460, 1259, 1043, 812; δ_H 1.21 (3H, d, *J* 6.9, ArCH*Me*), 1.97–2.28 (2H, m, C*H*$_2$CH$_2$I), 2.32 (3H, s, Ar*Me*), 3.01–3.11 (2H, m, CH$_2$C*H*$_2$I), 3.15–3.31 (1H, m, ArC*H*Me), 3.80 (3H, s, OMe), 6.67 (1H, s, ArH), 6.73 (1H, d, *J* 7.7, ArH), 7.02 (1H, d, *J* 7.7, ArH); *m*/*z* (EI) 305

(M^+ + 1, 3%), 304 (M^+, 21), 161 (3), 149 (100), 134 (4), 119 (13), 105 (9), 91 (19), 77 (8), 65 (4), 51 (3), 39 (6).

(3*S*)-3-(3-Methoxy-4-methylphenyl)butyl iodide 20. *Colorless oil* (84%); $[\alpha]_D^{20}$ +61.3 (*c* 2, $CHCl_3$) (Found: C, 47.47; H, 5.61; I, 41.65%); ν_{max}(film)/cm^{-1} 2958, 1612, 1583, 1513, 1464, 1415, 1257, 1135, 1043, 851, 815; δ_H 1.27 (3H, d, *J* 6.9, ArC*H*Me), 2.01–2.12 (2H, m, CH_2CH_2I), 2.18 (3H, s, Ar*Me*), 2.74–2.90 (1H, m, ArC*H*Me), 2.90–3.01 (1H, m, CH_2HCHI), 3.05–3.17 (1H, m, CH_2HCHI), 3.83 (3H, s, OMe), 6.64–6.74 (2H, m, ArH), 7.05 (1H, d, *J* 7.3, ArH); *m*/*z* (EI) 305 (M^+ + 1, 6%), 304 (M^+, 41), 177 (1), 161 (2), 149 (100), 135 (15), 117 (12), 105 (6), 91 (25), 77 (10), 65 (5), 51 (6), 39 (8).

(3*S*)-3-(2,5-Dimethoxy-4-methylphenyl)butyl iodide 21. *Colorless oil* (89%); $[\alpha]_D^{20}$ +44.8 (*c* 2, $CHCl_3$) (Found: C, 46.89; H, 5.75; I, 37.90. $C_{13}H_{19}IO_2$ requires C, 46.72; H, 5.73; I, 37.97); ν_{max}(film)/cm^{-1} 2958, 1505, 1465, 1399, 1209, 1048, 861; δ_H 1.24 (3H, d, *J* 6.9, ArCH*Me*), 2.03–2.13 (1H, m, *H*CHCH$_2$I), 2.14–2.25 (1H, m, HC*H*CH$_2$I), 2.20 (3H, s, Ar*Me*), 3.02–3.12 (2H, m, CH_2CH_2I), 3.18–3.28 (1H, m, Ar*CH*Me), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 6.65 (1H, s, ArH), 6.68 (1H, s, ArH); *m*/*z* (EI) 335 (M^+ + 1, 7%), 334 (M^+, 54), 319 (1), 206 (1), 192 (3), 179 (100), 164 (24), 149 (11), 135 (5), 115 (6), 105 (6), 91 (17), 77 (13), 65 (5), 53 (6), 39 (8).

Preparation of compounds 23–25

(*S*)-(+)-Curcuphenol methyl ether 23. The iodide **19** (2 g, 6.6 mmol) as a solution in dry THF (40 mL) was cooled to −60 °C and treated under nitrogen with CuI (140 mg, 0.7 mmol) and Grignard **22** (10 mmol; 2 M solution in THF). The reaction mixture was allowed to warm to 0 °C and was stirred at this temperature for 8 h. Work-up with aq. NH_4Cl, extraction with diethyl ether, and concentration of the dried (Na_2SO_4) organic phase gave the crude product. The latter was purified by chromatography with hexane→hexane–ethyl acetate 95:5 as eluent. Bulb-to-bulb distillation (oven temperature 115 °C/0.2 mmHg) afforded pure *(S)-(+)-curcuphenol methyl ether* **23**[8c] as a colorless oil (1.15 g, 76%); $[\alpha]_D^{20}$ +7.8 (*c* 1, $CHCl_3$) (Found: C, 82.75; H, 10.38. $C_{16}H_{24}O$ requires C, 82.70; H, 10.41%); ν_{max}(film)/cm^{-1} 2960, 2925, 1612, 1579, 1506, 1459, 1260, 1044, 810; δ_H 1.17 (3H, d, *J* 6.9, ArCH*Me*), 1.40–1.75 (2H, m, ArCHC*H*$_2$CH$_2$), 1.53 (3H, s, CHC*Me*Me), 1.67 (3H, s, CHCMe*Me*), 1.82–2.05 (2H, m, ArCHCH$_2$C*H*$_2$), 2.32 (3H, s, Ar*Me*), 3.04–3.21 (1H, m, ArC*H*Me), 3.79 (3H, s, OMe), 5.11 (1H, br t, *J* 7, C*H*CMeMe), 6.66 (1H, s, ArH), 6.74 (1H, d, *J* 7.7, Ar*Me*), 7.04 (1H, d, *J* 7.7, ArH); *m*/*z* (EI) 233 (M^+ + 1, 6%), 232 (M^+, 36), 217 (4), 189 (2), 175 (8), 162 (13), 149 (100), 135 (15), 119 (9), 110 (10), 91 (15), 77 (4), 69 (5), 55 (3), 41 (8).

(*S*)-(+)-Xanthorrhizol methyl ether 24.[9,22] Yield 85%; *colorless oil* (oven temperature 120 °C/0.2 mmHg); $[\alpha]_D^{20}$ +42.5 (*c* 2, $CHCl_3$), $[\alpha]_D^{20}$ +45.4 (*c* 5, acetone) (Found: C, 82.62; H, 10.38%); ν_{max}(film)/cm^{-1} 2960, 2925, 1613, 1583, 1513, 1465, 1415, 1257, 1134, 1044, 852, 815; δ_H 1.23 (3H, d, *J* 6.9, ArCH*Me*), 1.50–1.65 (2H, m, ArCHC*H*$_2$CH$_2$), 1.53 (3H, s, CHC*Me*Me), 1.67 (3H, s, CHCMe*Me*), 1.82–1.96 (2H, m, ArCHCH$_2$C*H*$_2$), 2.18 (3H, s, Ar*Me*), 2.57–2.73 (1H, m, ArC*H*Me), 3.82 (3H, s, OMe), 5.09 (1H, t with further unresolved couplings, *J* 7.1, C*H*CMeMe), 6.65 (1H, s, ArH), 6.68 (1H, dd, *J* 7.3 and 1.6, ArH), 7.03 (1H, d, *J* 7.3, ArH); *m*/*z* (EI) 233 (M^+ + 1, 8%), 232 (M^+, 44), 217 (1), 189 (3), 175 (7), 162 (19), 150 (100), 135 (63), 119 (9), 105 (6), 91 (17), 77 (5), 69 (4), 55 (5), 41 (10).

(*S*)-(+)-Curcuhydroquinone dimethyl ether 25.[24] Yield 89%; *colorless oil* (oven temperature 140 °C/0.2 mmHg); $[\alpha]_D^{20}$ +40.9 (*c* 2, $CHCl_3$) (Found: C, 77.70; H, 9.97. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99%); ν_{max}(film)/cm^{-1} 2960, 2929, 1505, 1466, 1399, 1208, 1049, 861; δ_H 1.18 (3H, d, *J* 7, ArCH*Me*), 1.45–1.75 (2H, m, ArCHC*H*$_2$CH$_2$), 1.54 (3H, s, CHC*Me*Me), 1.67 (3H, s, CHCMe*Me*), 1.82–2.00 (2H, m, ArCHCH$_2$C*H*$_2$), 2.20 (3H, s, Ar*Me*), 3.00–3.23 (1H, m, ArC*H*Me), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 5.12 (1H, br t, *J* 7.1, C*H*CMeMe), 6.67 (2H, s, ArH); *m*/*z* (EI) 263 (M^+ + 1, 10%), 262 (M^+, 56), 247 (1), 231 (1), 219 (1), 205 (4), 192 (8), 179 (100), 165 (20), 152 (27), 135 (4), 115 (5), 105 (4), 91 (15), 77 (8), 69 (9), 55 (7), 41 (23).

Demethylation of methyl ethers 23 and 24

(*S*)-(+)-Curcuphenol 1. Ethanethiol (1.5 mL, 20.3 mmol) was added dropwise to a suspension of NaH (60% in mineral oil; 880 mg, 22 mmol) in dry DMF (40 mL) under nitrogen. The reaction temperature was kept below 20 °C by external cooling, and after the addition was complete the mixture was stirred for 30 min at rt. The methyl ether **23** (900 mg, 3.9 mmol) was then added and the mixture was heated to reflux for 5 h. After cooling, the mixture was diluted with water (100 mL), neutralized with conc. HCl, and extracted with diethyl ether (2 × 100 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by chromatography using hexane–ethyl acetate (95:5→8:2) as eluent. Bulb-to-bulb distillation (oven temperature 120 °C/0.1 mmHg) afforded pure (*S*)-(+)-curcuphenol **1**[2,6,8] as a pale yellow oil (450 mg, 54%); $[\alpha]_D^{20}$ +24.8 (*c* 1, $CHCl_3$) (Found: C, 82.74; H, 10.20. Calc. for $C_{15}H_{22}O$: C, 82.52; H, 10.16%); ν_{max}(film)/cm^{-1} 3450, 2962, 2925, 1620, 1581, 1510, 1453, 1377, 1288, 944, 810; δ_H 1.23 (3H, d, *J* 6.9, ArCH*Me*), 1.44–1.78 (2H, m, ArCHC*H*$_2$CH$_2$), 1.54 (3H, s, CHC*Me*Me), 1.68 (3H, s, CHCMe*Me*), 1.85–2.05 (2H, m, ArCHCH$_2$C*H*$_2$), 2.27 (3H, s, Ar*Me*), 2.86–3.06 (1H, m, ArC*H*Me), 4.70 (1H, s, OH), 5.12 (1H, t with further unresolved couplings, *J* 7, C*H*CMeMe), 6.58 (1H, s, ArH), 6.72 (1H, d, *J* 7.8, ArH), 7.03 (1H, d, *J* 7.8, ArH); *m*/*z* (EI) 219 (M^+ + 1, 5%), 218 (M^+, 32), 203 (3), 175 (1), 161 (10), 148 (34), 135 (100), 121 (23), 115 (14), 105 (5), 91 (19), 83 (4), 77 (6), 69 (6), 55 (6), 41 (9).

(*S*)-(+)-Xanthorrhizol 2.[9,22] Yield 90%; pale yellow oil (oven temperature 125 °C/0.1 mmHg); $[\alpha]_D^{20}$ +47.6 (*c* 2, acetone) (Found: C, 82.65; H, 10.15%); ν_{max}(film)/cm^{-1} 3387, 2961, 2925, 1590, 1450, 1421, 1376, 1251, 1122, 813; δ_H 1.19 (3H, d, *J* 6.9, ArCH*Me*), 1.50–1.63 (2H, m, ArCHC*H*$_2$CH$_2$), 1.53 (3H, s, CHC*Me*Me), 1.67 (3H, s, CHCMe*Me*), 1.81–1.96 (2H, m, ArCHCH$_2$C*H*$_2$), 2.19 (3H, s, Ar*Me*), 2.48–2.68 (1H, m, ArC*H*Me), 4.70 (1H, br s, OH), 5.08 (1H, t with further unresolved couplings, *J* 7.2, C*H*CMeMe), 6.60 (1H, d, *J* 1.5, ArH), 6.67 (1H, dd, *J* 7.7 and 1.5, ArH), 7.02 (1H, d, *J* 7.7, ArH); *m*/*z* (EI) 219 (M^+ + 1, 7%), 218 (M^+, 48), 203 (1), 175 (4), 161 (11), 148 (32), 136 (100), 121 (67), 107 (7), 91 (20), 77 (9), 69 (6), 55 (8), 41 (13).

Preparation of curcuquinone 3 and curcuhydroquinone 4

(*S*)-(−)-Curcuquinone 3. To a solution of curcuhydroquinone dimethyl ether **25** (400 mg, 1.5 mmol) in acetonitrile (20 mL) was added dropwise aq. CAN (2.5 g, 4.6 mmol in 15 mL). After being stirred for 30 min at rt, the reaction mixture was extracted with chloroform (2 × 80 mL) and the organic phase was concentrated under reduced pressure. The residue was purified by chromatography using hexane–ethyl acetate (95:5→8:2) as eluent. Bulb-to-bulb distillation (oven temperature 115 °C/0.1 mmHg) afforded pure (*S*)-(−)-curcuquinone **3**[2,24] (310 mg, 87%); $[\alpha]_D^{20}$ −0.9 (*c* 1, $CHCl_3$), $[\alpha]_{546}^{20}$ −15.6 (*c* 1, $CHCl_3$) (Found: C, 77.73; H, 8.65. Calc. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%); ν_{max}(film)/cm^{-1} 2967, 1656, 1611, 1450, 1377, 1242, 913; δ_H 1.10 (3H, d, *J* 6.9, quinoneCH*Me*), 1.33–1.60 (2H, m, ArCHC*H*$_2$CH$_2$), 1.53 (3H, s, CHC*Me*Me), 1.64 (3H, s, CHCMe*Me*), 1.85–2.00 (2H, m, ArCHCH$_2$C*H*$_2$), 2.02 (3H, d, *J* 1.6, quinone*Me*), 2.77–2.98 (1H, m, quinoneC*H*Me), 5.03 (1H, br t, *J* 7, C*H*CMeMe), 6.49 (1H, m, COCHC), 6.57 (1H, q, *J* 1.6, MeCC*H*CO); *m*/*z* (EI) 234 (M^+ + 2, 6%), 232 (M^+, 3), 217 (1),

189 (2), 175 (3), 164 (5), 151 (100), 137 (4), 122 (32), 107 (5), 91 (6), 79 (6), 69 (7), 55 (6), 41 (13).

(*S*)-(+)-Curcuhydroquinone 4. A cooled (0 °C) solution of (*S*)-(−)-curcuquinone **3** (350 mg, 1.5 mmol) in MeOH (20 mL) was stirred with $NaBH_4$ (100 mg, 2.6 mmol). After 15 min, 5% aq. HCl (40 mL) was added and the mixture was extracted with ethyl acetate (2 × 70 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography using hexane–ethyl acetate (9:1→7:3) as eluent to afford pure curcuhydroquinone **4**[2,10,24] (280 mg, 80%); $[a]_D^{20}$ +47.1 (*c* 1, $CHCl_3$) (Found: C, 76.73; H, 9.48. Calc. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%); ν_{max}(film)/cm^{-1} 3342, 2963, 2927, 1516, 1456, 1418, 1377, 1306, 1188, 1002, 874, 832; δ_H 1.19 (3H, d, *J* 6.9, ArCH*Me*), 1.49–1.65 (2H, m, ArCHCH_2CH$_2$), 1.53 (3H, s, CHC*Me*Me), 1.68 (3H, s, CHCMe*Me*), 1.86–2.01 (2H, m, ArCHCH$_2$CH_2), 2.16 (3H, s, Ar*Me*), 2.80–3.02 (1H, m, ArC*H*Me), 4.48 (2H, br s, OH), 5.12 (1H, br t, *J* 7.1, C*H*-CMeMe), 6.55 (1H, s, ArH), 6.58 (1H, s, ArH); *m*/*z* (EI) 235 (M^+ + 1, 7%), 234 (M^+, 51), 191 (2), 177 (6), 164 (16), 151 (100), 137 (21), 124 (8), 107 (3), 95 (8), 77 (5), 69 (6), 55 (6), 41 (8).

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