Baker's yeast mediated enantioselective synthesis of the bisabolane sesquiterpenes curcumene, turmerone, dehydrocurcumene and nuciferal

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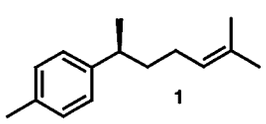
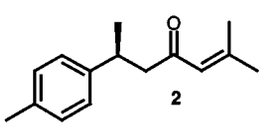
Fermenting baker's yeast converts the allylic alcohol **6** into enantiomerically pure (*S*)-(+)-3-(*p*-tolyl)butan-1-ol **7** which is a useful chiral building block for the synthesis of bisabolane sesquiterpenes. The versatility of this approach is shown in the preparation of (*S*)-(+)-curcumene, (*S*)-(+)-turmerone, (*S*)-(+)-dehydrocurcumene and (*E*,*S*)-(+)-nuciferal.

Introduction

The monocyclic aromatic sesquiterpenes of the bisabolane family are constituents of a large number of essential oils. Most of these compounds possess a benzylic asymmetric centre, *e.g.* compounds **1**–**4**, and have been isolated from natural



(*S*)-(+)-Curcumene



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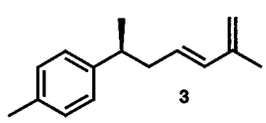

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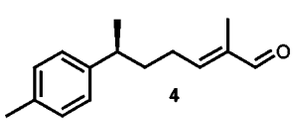


(*E*)-(*S*)-(+)-Nuciferal

sources in enantiomerically pure form. Although several basic[1] approaches have been reported for the construction of the bisabolane skeleton, few of them are enantioselective syntheses. This paucity of methods is due to the difficulty associated with the introduction of the stereocentre in the benzylic position and, in most cases, the methodologies applied to this end require the extensive use of chiral auxiliaries or enantiopure intermediates.

Since it is widely known that fermenting baker's yeast is of great utility preparing chiral intermediates for the synthesis of natural products,[2] we decided to study a baker's yeast mediated approach to enantiopure bisabolane sesquiterpenes. Herein, we report the enantioselective preparation of (*S*)-(+)-3-(*p*-tolyl)butan-1-ol **7** by the yeast reduction of the easily available allylic alcohol **6**. The compound **7** is an useful chiral building block for the synthesis of the most common bisabolane sesquiterpenes which show the same (*S*) absolute configuration.

Results and discussion

The bisabolane sesquiterpenes (*S*)-(+)-α-curcumene **1** and (*S*)-(+)-*ar*-turmerone **2** are constituents of many essential oils and have been recognized as flavour components of the *Zingiber*[3] and *Curcuma*[4] species. The structurally related compounds (*S*)-dehydrocurcumene **3** and (*S*,*E*)-nuciferal **4** show the same absolute configuration and were isolated from vetiver oil[5] and from the wood oil of *Torreya nucifera*[6] respectively.

It is well-known that a single enantiomer can show different odor qualities from its racemate. Therefore, in order to study the aromatic properties of this kind of compound, we decided to synthesize these bisabolane sesquiterpenes in enantiopure (*S*) form. To this end we needed an easily available chiral intermediate which could act as a common building block for the synthesis of the above mentioned natural products.

The preparations described in the literature are based essentially on the enantioselective synthesis of (*R*)-(+)-2-(*p*-tolyl)propanol,[7] (*S*)-(+)-3-(*p*-tolyl)butanol[8] and (*S*)-(+)-4-(*p*-tolyl)pentanol.[9] The latter alcohol was the direct precursor of curcumene and nuciferal and can be prepared by C-2 homologation of (*R*)-(+)-2-(*p*-tolyl)propanol. Although this alcohol is available by enzymic resolution of the racemic acetate[10] and from 4-methylcinnamic alcohol through asymmetric Sharpless epoxidation,[7] a direct approach to turmerone and dehydrocurcumene has not been described.

Until now the best starting building block seems to be (*S*)-(+)-3-(*p*-tolyl)butanol (or the butanoate) which was used (in enantiopure or racemic form) in the preparation of curcumene,[8] turmerone,[11] nuciferal[12] and dehydrocurcumene.[13] Meyers obtained this alcohol in enantiopure form by addition of *p*-tolyllithium to α,β-unsaturated oxazolines,[8] while Fujisawa prepared (*S*)-(+)-3-(*p*-tolyl)butyric acid by ring opening of (*R*)-(+)-β-methyl-β-propiolactone with di-*p*-tolylcuprate.[14] In these latter preparations a stoichiometric amount of chiral auxiliary or the use of an enantiopure lactone is necessary.

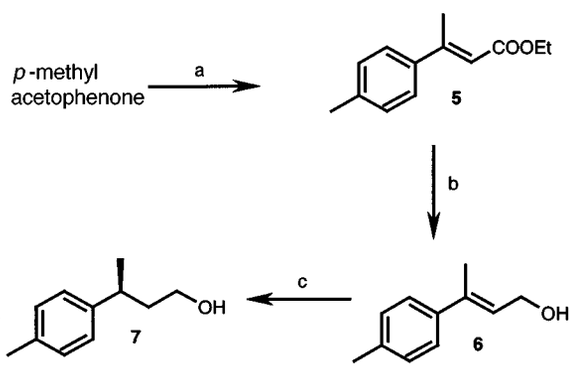
We investigated a baker's yeast mediated preparation of (*S*)-(+)-3-(*p*-tolyl)butanol in order to obtain this compound on a multigram scale starting from inexpensive precursors. The enantioselective microbial saturation of the double bond in β-methyl-α,β-unsaturated alcohols has been explored[15] and it is known to be highly stereospecific. Since the allylic alcohol **6** is easily available by Horner–Wadsworth–Emmons reaction of *p*-methylacetophenone with triethyl phosphonoacetate and sodium hydride[16] followed by reduction of the resulting ester with DIBAH, we selected this compound as the starting material for baker's yeast reduction (Scheme 1).

Although β-aryl-β-methyl-α,β-unsaturated alcohols are not described in the literature as substrates for this kind of reaction, we found that baker's yeast is able to reduce the latter compounds with high enantioselectivity to give the saturated alcohol bearing the benzylic asymmetric centre. (*S*)-(+)-3-(*p*-

Tolyl)butanol **7** was obtained in about 20% isolated yield with excellent optical purity (ee >95%) after reaction of **6** with fermenting baker's yeast for 3–5 days at room temperature. These results are similar to those reported for the reduction of the non-aromatic β-methyl-β-alkyl-α,β-unsaturated alcohol geraniol which was reduced to (*R*)-(+)-citronellol in 25% yield (3 days, ee >98%).[17]

In addition, the reduction of **6** was performed in the presence of a non-polar resin in order to establish optimal conditions for the large-scale preparation of **7**.[18] Although we found the same results in terms of yields and optical purity (21%, ee >95%) this experimental procedure enables us to perform the reduction at a high concentration of substrate (5 g l^{-1}) and by a very simple work-up procedure (see Experimental section).

The transformation of **7** in the title compounds was achieved by a divergent pathway (Scheme 2). Oxidation of enantiopure alcohol **7** with pyridinium chlorochromate furnished the aldehyde **8** which on treatment with the Grignard **10** gave a mixture of diastereoisomeric alcohols. These latter products were not isolated but oxidated directly with MnO_2 in refluxing $CHCl_3$ to give (*S*)-(+)-turmerone **2** (71% overall yield), possessing optical properties identical to those reported {$[\alpha]_D^{20}$ = +62.7 (*c* 1.25, hexane), lit.,[11] $[\alpha]_D^{22}$ = +64 (*c* 4.5, hexane), lit.,[4] $[\alpha]_D$ 68 (neat)}.

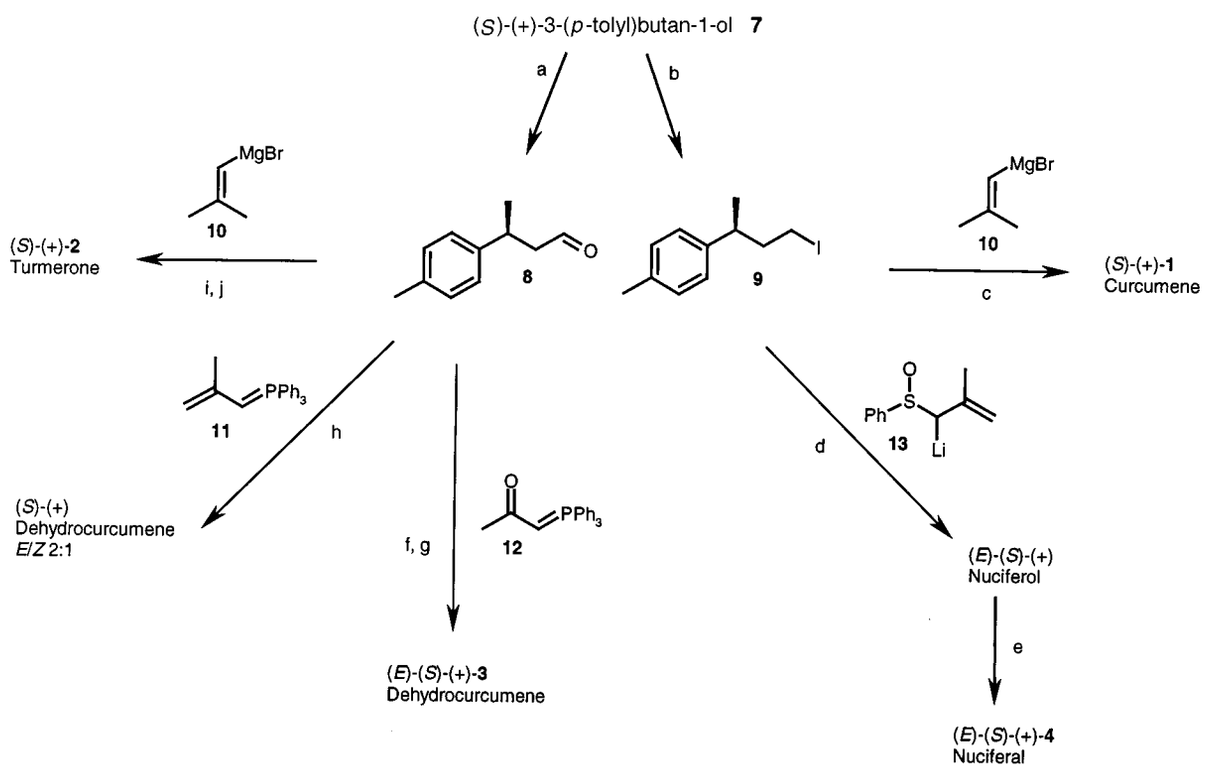


Scheme 1 *Reagents and conditions*: a, $(EtO)_2POCH_2COOEt$, NaH, THF, 86%; b, DIBAH, THF, 90%; c, baker's yeast, 5 d, 21%.

Following Vig's method,[13] the above mentioned aldehyde was treated with the ylide **11**. Unfortunately, Wittig reaction gives invariably a mixture of *cis–trans* dehydrocurcumene isomers (*E*:*Z* 2:1 based on NMR analysis). In order to develop a regiospecific path to **3**, we used the more stabilized ylide **12** instead of **11**. The unsaturated methyl ketone obtained was then treated with (triphenylphosphonio)methanide to give **3** in satisfactory chemical yield (64% overall) and complete regiochemical control (only the *E* isomer was detected by NMR analysis).

Through routine steps, the alcohol **7** was converted into iodide **9** which gives access to sesquiterpene **1** and **4** after further elaborations. In effect, copper catalysed[19] coupling of **9** with Grignard **10** afforded enantiopure curcumene **1** in 77% yield {$[\alpha]_D^{20}$ = +43 (*c* 2, $CHCl_3$), lit.,[3] $[\alpha]_D$ = +45.1 (*c* 0.75, $CHCl_3$)}. Moreover, alkylation of the latter iodide with the lithium salt of sulfoxide **13** was performed according to the procedure described by Evans.[12] The resulting mixture of alkylated sulfoxides was cleaved by triethyl phosphite–methanol to afford, after purification, the (*S*)-(+)-*trans*-nuciferol. Manganese dioxide oxidation of the latter gave enantiopure (*S*)-(+)-nuciferal **4** whose analytical data are identical to those published for the natural product {$[\alpha]_D^{20}$ = +59 (*c* 1, $CHCl_3$), lit.,[6] $[\alpha]_D$ = + 62.07 (*c* 16.55, $CHCl_3$)}.

Thus, these experimental results demonstrate the utility of the enantiopure alcohol **7** as the building block for the preparation of bisabolane sesquiterpenes bearing a benzylic asymmetric centre of (*S*) configuration. Moreover, baker's yeast confirms its versatility in the reduction of triply substituted olefins by stereoselective hydrogenation of β-aryl-β-methyl-α,β-unsaturated alcohols. Further studies on the reduction of β-cyclohexenyl-β-methyl-α,β-unsaturated alcohols, with the aim of finding a stereoselective path to bisabolene sesquiterpenes, are now in progress and will be presented in due course.



Scheme 2 *Reagents and conditions*: a, PCC, CH_2Cl_2, 93%; b, TsCl, Py, NaI, acetone, 65% overall; c, **10**, THF, CuI cat. 77%; d, **13**, THF, $(EtO)_3P$, 49%; e, MnO_2, $CHCl_3$, 90%; f, **12**, $CHCl_3$; g, Ph_3PCH_2, Et_2O, 64% overall; h, **11**, benzene 78%; i, **10**, THF; j, MnO_2, $CHCl_3$, 71% overall.

Experimental

Optical rotations were measured on a Propol automatic digital polarimeter, and are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^{1}H). 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 spectrometer. TLC analyses were performed on Merck Kieselgel 60 F_{254} plates. All the chromatographic separations were carried out on silica gel columns. GC analysis was performed on a DANI 86.10 HT with a FID detector, fitted with a CHROMPACK CHIRASIL DEX CB column, 25 m × 0.25 mm i.d.

Baker's yeast reduction of alcohol 6

A 10 l open cylindrical glass vessel equipped with a mechanical stirrer was charged with tap water (4 l) and glucose (250 g). Fresh baker's yeast (1 kg) was added in small pieces to the stirred mixture and the fermentation allowed to proceed for 2 h. Resin XAD 1180 (100 g) was added in one portion and the substrate (20 g, 123 mmol) dissolved in the minimum amount of ethanol (50 ml) was added dropwise. The vigorous stirring was continued for 5 days at room temperature, while a slow stream of air was passed through the mixture. During this time additional baker's yeast (250 g) and glucose (100 g) were added each time after 48, 72 and 96 h since the fermentation started. The resin was then separated by filtration on a sintered glass funnel (porosity 0, >160 μm) and the water phase 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 (22 g). The latter was dissolved in $CHCl_3$ and treated with MnO_2 (60 g) stirring the mixture at reflux for 5 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 3-(*p*-tolyl)but-2-en-1-al (12 g, 75 mmol) and pure (*S*)-(+)-3-(*p*-tolyl)butan-1-ol **7** (4.3 g, 26 mmol) as a pale yellow oil, 21% yield, ee 95% (the optical purity was determined as described below). A further purification by bulb to bulb distillation (oven temperature 110 °C/0.5 Torr) afforded **7** as a colourless oil without significant loss of weight. $[\alpha]_D^{20} = +31.6$ (*c* 1, $CHCl_3$), lit.,[4] $[\alpha]_D = +33$ (*c* 1.89, $CHCl_3$) (Found: C, 80.35; H, 9.77; $C_{11}H_{16}O$ requires C, 80.44; H, 9.74%); ν_{max} (film)/cm^{-1} 3336 (OH), 2959, 1515, 1455, 1045, 816; δ_H 1.25 (3H, d, *J* 7, ArCH*Me*), 1.75–1.88 (2H, m, CH*CH*$_2$CH$_2$OH), 2.10 (1H, s, CH$_2$*OH*), 2.31 (3H, s, Ar*Me*), 2.73–2.92 (1H, m, Ar*CH*Me), 3.42–3.63 (2H, m, CH$_2$*CH*$_2$OH), 7.09 (4H, s, Ar*H*); *m*/*z* (EI) 164 (M$^+$, 47%), 146 (M$^+$ − H_2O, 6), 131 (38), 119 (M$^+$ − CH$_2$CH$_2$OH, 100), 105 (12), 91 (7).

Determination of the optical purity of 7

(*S*)-(+)-3-(*p*-Tolyl)butan-1-ol **7** (100 mg, 0.6 mmol), in CCl_4 (0.5 ml) was treated with (*R*)-(+)-MTPACl[20] [(*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride] (280 mg, 1.2 mmol) and pyridine (0.5 ml) at room temperature for 24 h. The mixture was diluted with diethyl ether (80 ml) and washed in turn with 5% HCl aq. (100 ml) and $NaHCO_3$ sat. (50 ml). The organic phase was dried, concentrated under reduced pressure and purified by column chromatography to give the pure (*S*,*R*) ester (205 mg, 95%); δ_H 1.24 (3H, d, *J* 6.8, ArCH*Me*), 1.85–2.04 (2H, m, CH*CH*$_2$CH$_2$OH), 2.32 (3H, s, Ar*Me*), 2.65–2.83 (1H, m, Ar*CH*Me), 3.55 (3H, s, O*Me*), 4.05–4.30 (2H, m, CH$_2$*CH*$_2$OMTPA), 6.95–7.14 (4H, m, Ar*H*), 7.35–7.55 (5H, m, Ar*H*). A sample of racemic **7** was prepared from **5** by hydrogenation (H_2, Pd/C) and $LiAlH_4$ reduction. The (*R*)-(+)-MTPA ester of the latter compound had an identical spectrum except that the methyl doublet at 1.24 ppm became a double doublet (*J* 6.8, 1.5). The optical purity of the first sample was determined by comparison of the area of two peaks of a doublet and was ee >95%. A further confirmation of this analytical data was obtained by GC analysis of the two above mentioned samples which showed 95.5% ee. Program temperature for the GC chiral analysis: 70 °C 3 min, 3.5 °C min^{-1}, 140 °C 1 min, 8 °C min^{-1}, 180 °C 20 min; injector 60 °C, detector 180 °C. Retention times: (*R*,*R*)-MTPA ester 43.4 min, (*S*,*R*)-MTPA ester 43.75 min; carrier N_2 (0.8 bar).

(*S*)-(+)-3-(*p*-Tolyl)butanal 8

(*S*)-(+)-3-(*p*-Tolyl)butan-1-ol **7**, 800 mg (4.9 mmol) in CH_2Cl_2 (5 mL) was added in one portion to a solution of pyridinium chlorochromate (1.57 g, 7.3 mmol) in CH_2Cl_2 (30 ml) and stirred at room temperature until no more starting alcohol was detected by TLC analysis (2 h). The mixture was then diluted with diethyl ether (80 ml) and filtred on a layer of Celite. The organic phase was washed with water, dried on Na_2SO_4 and concentrated under reduced pressure. Bulb to bulb distillation of the residue (oven temperature 80 °C/0.2 Torr) give **8** as a colourless oil, in 93% yield (0.75 g, 4.6 mmol); $[\alpha]_D^{20} = +39.6$ (*c* 1, $CHCl_3$) (Found: C, 81.51; H, 8.66; $C_{11}H_{14}O$ requires C, 81.43; H, 8.63%); ν_{max} (film)/cm^{-1} 2964, 1723 (CO), 1516, 1454, 817; δ_H 1.30 (3H, d, *J* 7, ArCH*Me*), 2.32 (3H, s, Ar*Me*), 2.55–2.75 (2H, m, CH*CH*$_2$CHO), 3.17–3.42 (1H, m, Ar*CH*Me), 7.11 (4H, s, Ar*H*), 9.70 (1H, t, *J* 2, CHCH$_2$-*CHO*); *m*/*z* (EI) 162 (M$^+$, 23%), 147 (27), 119 (M$^+$ − CH$_2$CH$_2$-CHO, 100), 91 (16).

(*S*)-(+)-3-(*p*-Tolyl)butyl iodide 9

(*S*)-(+)-3-(*p*-Tolyl)butan-1-ol **7** (1 g, 6.1 mmol) in CH_2Cl_2 (5 mL) was treated with tosyl chloride (1.5 g, 7.9 mmol) and pyridine (0.65 ml, 8 mmol) and stirred at room temperature for 5 h. The mixture was then diluted with diethyl ether (100 ml), washed with HCl 5% aq. (50 ml) and dried over Na_2SO_4. The solvent was eliminated under reduced pressure and the residue was treated with NaI (3 g, 20 mmol) in dry acetone (30 ml) at reflux for 2 h. The reaction mixture was diluted with water (100 ml), extracted with diethyl ether and the organic phase was washed with a solution (1%, 80 ml) of $Na_2S_2O_3$. The crude iodide was purified by chromatography and bulb to bulb distillation (oven temperature 95 °C/0.2 Torr) to give **9** as a colourless oil (1.1 g, 4 mmol, 65% yield); $[\alpha]_D^{20} = +54$ (*c* 2, $CHCl_3$) (Found: C, 48.30; H, 5.37; I, 46.33; $C_{11}H_{15}I$ requires C, 48.19; H, 5.47; I, 46.29%); ν_{max} (film)/cm^{-1} 2960, 2925, 1514, 1454, 1236, 1171, 816, 699; δ_H 1.24 (3H, d, *J* 7, ArCH*Me*), 2.0–2.15 (2H, m, CH*CH*$_2$CH$_2$I), 2.32 (3H, s, Ar*Me*), 2.70–3.25 (3H, m, Ar*CH*Me + CH$_2$*CH*$_2$I), 7.10 (4H, s, Ar*H*); *m*/*z* (EI) 274 (M$^+$, 24%), 127 (9), 119 (100), 91 (17), 77 (5).

(*S*)-(+)-Curcumene 1

The iodide **9** (600 mg, 2.2 mmol) in dry THF (10 ml) was cooled to −40 °C and treated under nitrogen with CuI (80 mg, 0.4 mmol) and Grignard **10** (3.5 mmol, 1 M solution in THF). The reaction was allowed to warm to 0 °C and stirred at this temperature for 5 h. Work-up with NH_4Cl aq., extraction with diethyl ether and concentration of the dried (Na_2SO_4) organic phase gave crude **1**. Purification of the latter by chromatography and bulb to bulb distillation (oven temperature 90 °C/0.3 Torr) afforded pure (*S*)-(+)-curcumene as a colourless oil (340 mg, 1.7 mmol, 77% yield); $[\alpha]_D^{20} = +43$ (*c* 2, $CHCl_3$) (Found: C, 88.97; H, 10.85; $C_{15}H_{22}$ requires C, 89.04; H, 10.87%); ν_{max} (film)/cm^{-1} 2962, 2923, 2857, 1515, 1516, 1453, 1376, 816; δ_H 1.21 (3H, d, *J* 7, ArCH*Me*), 1.53 (3H, s, CHC*Me*-Me), 1.50–1.68 (2H, m, *CH*$_2$CHC), 1.67 (3H, s, CHCMe*Me*), 1.80–1.95 (2H, m, CH*CH*$_2$CH$_2$), 2.32 (3H, s, Ar*Me*), 2.55–2.65 (1H, m, Ar*CH*Me), 5.07 (1H, br t, *J* 6, CH$_2$*CH*C), 7.07 (4H, s,

Ar*H*); *m*/*z* (EI) 202 (M^+, 64%), 171 (8), 157 (10), 145 (18), 132 (79), 119 (100), 105 (56), 91 (24).

(*S*)-(+)-Turmerone 2

The aldehyde **8** (350 mg, 2.1 mmol) in dry THF (10 ml) was cooled to 0 °C and treated under nitrogen with Grignard **10** in THF (2.5 mmol, 1 M solution). The reaction mixture was stirred at this temperature for 1 h, then quenched with saturated NH_4Cl aq. (50 ml) and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude alcohol was treated with MnO_2 (1.8 g, 21 mmol) in $CHCl_3$ at reflux for 3 h and the residue obtained upon filtration and evaporation of the solvent was purified by column chromatography using hexane–ethyl acetate (9:1—4:1) as eluent to give pure (*S*)-(+)-turmerone as a pale yellow oil (320 mg, 1.5 mmol, 71% yield); $[a]_D^{20} = +62.7$ (*c* 1.25, hexane) (Found: C, 83.35; H, 9.23; $C_{15}H_{20}O$ requires C, 83.28; H, 9.25); ν_{max} (film)/ cm^{-1} 2963, 1687 (CO), 1620, 1515, 1446, 1377, 1119, 1012, 817; δ_H 1.23 (3H, d, *J* 7.5, ArCH*Me*), 1.86 (3H, s, CHC*Me*Me), 2.10 (3H, s, CHCMe*Me*), 2.30 (3H, s, Ar*Me*), 2.53–2.80 (2H, m, CH*CH*$_2$CO), 3.10–3.39 (1H, m, Ar*CH*Me), 6.02 (1H, s, CO*CH*CMeMe), 7.09 (4H, s, Ar*H*); *m*/*z* (EI) 216 (M^+, 85%), 201 (M^+ − Me, 32), 173 (7), 132 (37), 119 (89), 91 (10), 83 (100).

(*S*)-(+)-Dehydrocurcumene 3

The aldehyde **8** (360 mg, 2.2 mmol) in $CHCl_3$ (10 ml) was treated at reflux with the ylide **12** (1.4 g, 4.4 mmol) for 12 h. The mixture was then concentrated under reduced pressure and the residue purified by column chromatography to give the unsaturated methyl ketone which was used without further purification. This latter was dissolved in dry diethyl ether (5 ml) and added under nitrogen to a stirred solution of (triphenylphosphonio)methanide (3 mmol) in the same solvent (30 ml). The obtained mixture was heated at reflux for 2 h and then quenched with saturated NH_4Cl aq. (50 ml), extracted twice with ether, washed with water, dried over Na_2SO_4 and evaporated. The residue was dissolved in hexane (30 ml) and the triphenylphosphine oxide eliminated by crystallization (ice bath cooling). The liquid phase was concentrated under reduced pressure and the remaining oil purified by bulb to bulb distillation (oven temperature 80–90 °C/0.2 Torr) to give pure **3** as a colourless oil (280 mg, 1.4 mmol, 64% yield); $[a]_D^{20} = +20.2$ (*c* 2, $CHCl_3$) (Found: C, 90.10; H, 9.80; $C_{15}H_{20}$ requires C, 89.92; H, 9.98%); ν_{max} (film)/ cm^{-1} 2960, 2925, 1609, 1514, 1454, 1376, 967, 883, 815; δ_H1.23 (3H, d, *J* 7, ArCH*Me*), 1.78 (3H, s, *Me*C=CH$_2$), 2.20–2.50 (2H, m, ArCH*CH*$_2$), 2.32 (3H, s, Ar*Me*), 2.67–2.84 (1H, m, Ar*CH*Me), 4.84 (2H, s, MeC=*CH*$_2$), 5.48–5.64 (1H, m, CH$_2$*CH*CH), 6.13 (1H, d, *J* 16, CH$_2$CH*CH*), 7.10 (4H, s, Ar*H*); *m*/*z* (EI) 200 (M^+, 10%), 145 (5), 143 (12), 119 (100), 91 (24), 71 (20), 57 (23).

(*E*,*S*)-(+)-Nuciferal 4

To a cooled (−78 °C) solution of lithium diisopropylamide (2.2 mmol) in 30 ml of dry THF under nitrogen was added the allylic sulfoxide **13** (380 mg, 2.1 mmol) and the resulting mixture stirred for 30 min. The iodide **9** (410 mg, 1.5 mmol) in dry THF (5 ml) was then added in one portion and the temperature was raised to −20 °C. After 4 h the reaction was quenched with saturated NH_4Cl (50 ml) and extracted twice with CH_2Cl_2. The dried (Na_2SO_4) organic phase was concentrated under reduced pressure to give a mixture of α and γ alkylated sulfoxides and unreacted **13**. The latter oil was dissolved in methanol (20 ml) and treated with triethyl phosphite (10 ml) at room temperature for 24 h. The methanol–$(EtO)_3P$ mixture was eliminated by evaporation under reduced pressure and the residue purified by column chromatography to give (*E*)-nuciferol (160 mg). Oxidation with MnO_2 (1 g, 11 mmol) in $CHCl_3$ (40 ml) at room temperature (2 h) gave the crude aldehyde (150 mg). Purification by bulb to bulb distillation (oven temperature 125 °C/0.3 Torr) afforded pure nuciferal (130 mg, 0.6 mmol, 40% yield overall) as a colourless oil; $[a]_D^{20} = +59$ (*c* 1, $CHCl_3$) (Found: C, 83.45; H, 9.33; $C_{15}H_{20}O$ requires C, 83.28; H, 9.25%); ν_{max} (film)/cm^{-1} 2958, 1689 (CO), 1515, 1454, 1285, 818; δ_H1.26 (3H, d, *J* 7, ArCH*Me*), 1.65 (3H, s, *Me*CCHO), 1.60–1.85 (2H, m, CHCH$_2$*CH*$_2$), 2.10–2.40 (2H, m, CH*CH*$_2$CH$_2$), 2.41 (3H, s, Ar*Me*), 2.50–2.80 (1H, m, Ar*CH*Me), 6.43 (1H, t, *J* 7, CH$_2$-*CH*C), 7.07 (4H, s, Ar*H*), 9.33 (1H, s, MeC*CHO*); *m*/*z* (EI) 216 (M^+, 3%), 183 (2), 174 (5), 158 (27), 145 (25), 133 (25), 119 (100), 105 (28), 91 (27), 77 (11).

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