Supporting Information for

Application of the Lithiation-Borylation Reaction to the Rapid and Enantioselective Synthesis of the Bisabolane Family of Sesquiterpenes

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1. General Information

$^1$H NMR spectra were recorded at indicated field strengths using CDCl$_3$ (7.27 ppm) as the internal standard. $^1$H NMR coupling constants are reported in Hz and refer to apparent multiplicities and not true coupling constants. Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, sp = septet, m = multiplet, dd = doublet of doublet, etc.), integration and assignment. $^{13}$C NMR spectra were recorded at indicated field strengths with complete proton decoupling using CDCl$_3$ as an internal standard (77.0 ppm), Carbon nuclei attached to boron are not observed in $^{13}$C NMR due to quadrupolar relaxation. $^{11}$B NMR spectra were recorded at indicated field strengths with complete proton decoupling and using BF$_3$·Et$_2$O (0.0 ppm) as an external standard. All IR data was obtained on a Perkin-Elmer Spectrum One FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer 241MC polarimeter. High resolution mass spectra were recorded using Electronic Ionization (EI), Electron Spray Ionization (ESI) or Chemical Ionization (CI).

Analytical TLC was carried out using aluminium backed plates pre-coated (0.25 mm) with Merck Silica Gel 60 F$^{254}$. Compounds were visualized by exposure to UV-light or by dipping the plates in PMA or KMnO$_4$ followed by heating. Flash chromatography was carried out using Merck Silica Gel 60, 230-400 mesh. Chiral HPLC was performed on Agilent 1100 equipped with HP Chemstation software using Daicel Chiralpak IA, IB or IC columns (4.6 × 250 mm × 5 μm) fitted with guards (4 × 10 mm), and monitored by DAD (Diode Array Detector).

All air- and water-sensitive reactions were carried out in oven-dried glassware under an Ar atmosphere using standard Schlenk manifold technique. Anhydrous solvents were purified by means of a Grubbs-type solvent system and stored over 4 Å molecular sieves under Ar.$^1$ TMEDA was distilled over CaH$_2$ and stored under Ar.
2. Abbreviations

Et$_2$O  diethyl ether  
THF  tetrahydrofuran  
EtOAc  ethyl acetate  
TMEDA  tetramethylethlenediamine  
MeOH  methanol  
NMR  nuclear magnetic resonance  
PE  petroleum ether  
s-BuLi  sec-butyl lithium  
tBu  tert-butyl  
d.r./dr  diastereomeric ratio  
e.r./er  enantiomeric ratio  
DCM  dichloromethane  
IPA  isopropanol  
TBAF  tetra-$n$-butyl ammonium fluoride  
CbCl  $N,N'$-diisopropylcarbamoyl chloride  
BHT  butylated hydroxy toluene (2,6-di-tert-butyl-4-methylphenol)  
PhMe  Toluene  
AcCl  Acetyl chloride  
DMF  dimethylformamide  
CAN  Ceric ammonium nitrate
3. Experimental details

4,4,5,5-tetramethyl-2-(4-methylpent-3-enyl)-1,3,2-dioxaborolane 8

To a suspension of magnesium filings (0.88 mg, 37 mmol) in THF (10 mL) activated with dibromoethane, was added 5-bromo-2-methyl-2-pentene (2.0 g, 12 mmol) dropwise. After the initial exotherm had subsided the solution was refluxed for 4 h. The reaction mixture was added dropwise to a solution of iPrOBpin (3.1 mL, 15 mmol) in THF (10 mL) at −78 °C and stirred for 20 min. The reaction was allowed to warm to rt at which point the grey precipitate formed was observed to dissolve. The reaction mixture was cooled to 0 °C and NH4Cl(aq) (20 mL) was added before warming to rt. The layers were separated and the aqueous layer extracted with Et2O (3 × 10 mL). The combined organic extracts were dried over MgSO4, filtered and concentrated in vacuo. Purification by flash column chromatography (3% EtOAc/PE, SiO2) gave 8 (1.6 g, 60%) as an oil.

*R* (10% EtOAc/PE) 0.75;

1H NMR (400 MHz; CDCl3) δ 5.12 (t sept, J = 7.2, 1.5 Hz, 1H, 3-H), 2.09 (apparent q, J = 7.7 Hz, 2H, 2-H2), 1.67 (d, J = 1.5 Hz, 3H, CH3), 1.61 (apparent s, 3H, CH3), 1.24 (s, 12H, 2 × OC(CH3)2), 0.82 (t, J = 7.7 Hz, 2H, 1-H2);

13C NMR (100 MHz, CDCl3) δ 130.5 (C-4), 126.9 (C-3), 83.0 (2 ×OC(CH3)2), 25.81 (CH3), 24.9 (2 ×OC(CH3)2), 22.6 (CH3), 17.8 (C-2);

11B NMR (96 MHz, Et2O) δ 33;

IR(CDCl3) v_{max}/cm^{-1} 2981 (C-H), 1380 (B-O), 1144 (B-C);

(S)-1-tolylethyl diisopropylcarbamate 7a

Prepared according to the procedure of T.G. Elford et al.2 (93%, 99:1 e.r.)
**HPLC** (Chiralpak® IA, 210 nm, 10% isopropanol/\(n\)-hexane, 0.7 mL min\(^{-1}\)), \(t_r:\) minor (\(R\)) 5.6 min, major (\(S\)) 11.8 min.

\[(S)\text{-}(+)-\alpha\text{-Curcumene 1}\]

\(s\)-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.38 mL, 0.49 mmol) was added dropwise to a solution of 7a (0.10 g, 0.38 mmol, e.r. >99:1) in Et\(_2\)O (1.5 mL) at \(-78^\circ\text{C}\), such that the temperature of the reaction did not rise above \(-70^\circ\text{C}\). After stirring for 15 minutes, 8 (1.0 M in Et\(_2\)O; 0.57 mL, 0.57 mmol) was added dropwise, such that the temperature of the reaction did not rise above \(-70^\circ\text{C}\). The solution was allowed to stir at \(-78^\circ\text{C}\) for a further 1 hour, before MgBr\(_2\)·OEt\(_2\) (1.0 M in MeOH; 0.57 mL, 0.57 mmol) was added dropwise. The reaction was allowed to stir at room temperature for 2 h before NaH\(_2\)PO\(_4\) (1.0 M aq.; 5.0 mL, 5.0 mmol) was added to the reaction mixture. The layers were separated and the aqueous phase extracted with Et\(_2\)O (3 \(\times\) 10 mL). The combined organic phases were dried over MgSO\(_4\), filtered and concentrated \(\text{in vacuo}\). The resulting oil was dissolved in pentane (2 mL), TBAF·3H\(_2\)O (0.17 g, 0.57 mmol) was added, and the mixture heated at 50 °C (sealed tube) for 12 h. After cooling to room temperature, the reaction mixture was filtered through silica and concentrated \(\text{in vacuo}\). Purification by flash column chromatography (0→2% Et\(_2\)O/PE; SiO\(_2\)) gave (\(S\))-\(\text{(+)}\)-\(\alpha\)-curcumene 1 (0.065 g, 85%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature\(^3\)

\(R_f\) (100% PE) 0.7;

\(\text{\textsuperscript{1}H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.15-7.10 (m, 4H, ArH), 5.13 (tsept., \(J = 7.1, 1.4\) Hz, 1H, 5-H), 2.69 (apparent sext, \(J = 7.1\) Hz, 1H, 2-H), 2.35 (s, 3H, ArCH\(_3\)), 1.97-1.86 (m, 2H, 4-H\(_2\)), 1.82-1.74 (m, 2H, 6-H\(_2\)).
1.71 (br. s, 3H, 7-H3), 1.68-1.56 (m, 2H, 3-H2), 1.56 (br. s, 3H, 8-H3), 1.25 (d, J = 7.1 Hz, 3H, 1-H3);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 144.6 (C-1’), 135.1 (C-4’), 131.4 (C-6), 128.9 (2 × C-3’), 126.9 (2 × C-2’), 124.6 (C-5), 39.0 (C-2), 38.5 (C-3), 26.2 (C-7), 25.7 (C-4), 22.5 (C-1), 21.0 (ArCH$_3$), 17.7 (C-8);

IR(neat)$\nu_{\text{max}}$/cm$^{-1}$: 2920 (C-H), 1514, 1452 (CH$_3$), 1375 (CH$_3$), 1020, 814 (Ar C-H).

$\text{[\alpha]}_{D}^{23} +34.2$ (c. 0.76, CHCl$_3$) (Lit.: $\text{[\alpha]}_{D}^{25} +42.7$ (c. 1.0, CHCl$_3$)).

e.r. inferred from that of S1 (vide infra).

(S)-(+)4-p-Tolylpentan-1-ol S1

![Chemical structure of S1]

A stream of O$_3$/O$_2$ was passed through a solution of (S)-(+)α-curcumene 1 (36 mg, 0.18 mmol) in CH$_2$Cl$_2$/MeOH (1:1 v/v; 8.5 mL) at –78 °C until a blue tinge persisted (ca 15 min). A stream of N$_2$ was then passed through the solution until loss of colouration (ca 15 min). NaBH$_4$ (48 mg, 1.3 mmol) was added, and the solution allowed to warm to room temperature. After stirring at room temperature for 2 h the solvent was removed in vacuo, and the residue dissolved in Et$_2$O (10 mL) and H$_2$O (10 mL) was added. The layers were separated and the aqueous phase extracted with Et$_2$O (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to give alcohol (S)-S1 (0.030 g, 98%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature.$^3$

$R_f$: (30% EtOAc/PE). 0.21;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.13-7.08 (m, 4H, ArH), 3.60 (t, J = 6.5 Hz, 2H, 1-H$_2$), 2.68 (apparent sext, J = 7.0 Hz, 1H, 4-H), 2.33 (s, 3H, ArCH$_3$), 1.67-1.61 (m, 2H, 2-H$_2$), 1.57-1.40 (m, 2H, 3-H$_2$), 1.26 (d, J = 7.0 Hz, 3H, 7-H$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.3 (C-1’), 135.4 (C-4’), 129.0 (2 × C-Ar), 126.8 (2 × C-Ar), 63.1 (C-1), 39.3 (C-4), 34.4 (C-2), 31.0 (C-3), 22.5 (C-5), 21.0 (ArCH$_3$).
IR (neat) $v_{\text{max}}/\text{cm}^{-1}$: 3327 (br., O-H), 2924 (C-H), 1514, 1455 (CH$_3$), 1375 (CH$_3$), 1057 (C-O), 815 (Ar C-H).

$[\alpha]_{D}^{22.5}$ +6.6 (c. 0.60, CHCl$_3$) (Lit.:$^{58}$ $[\alpha]_{D}^{25}$ +30.1 (c. 1.0, CHCl$_3$)).

**HPLC** (Chiralpak® IB, 210 nm, 5% isopropanol/n-hexane, 0.7 mL min$^{-1}$), $t_r$: minor ($R$) 10.2 min, major ($S$) 11.8 min.

**(R)-(+-) Gossonorol 2**

$s$-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.76 mL, 0.98 mmol) was added to a solution of carbamate 7a (0.20 g, 0.76 mmol) in Et$_2$O (3 mL) at $-78$ °C, such that the temperature of the reaction did not rise above $-70$ °C. After stirring for 15 minutes, pinacol boronic ester 8 (1.0 M in Et$_2$O; 1.14 mL, 1.14 mmol) was added slowly, such that the temperature of the reaction did not rise above $-70$ °C. The solution was allowed to stir at $-78$ °C for a further 1 h, before MgBr$_2$·OEt$_2$ (1.0 M in MeOH; 1.14 mL, 1.14 mmol) was added dropwise. The reaction was warmed to r.t and stirred for 2 h before THF containing BHT (~6 mg in 5 mL) was added to the reaction mixture. The reaction was cooled to 0 °C and a solution of NaOH$_{(aq)}$ (2.0 M, 2.4 mL, 4.8 mmol) and H$_2$O$_2(aq)$ (30% w/v, 0.92 mL, 9.0 mmol) was added. The resulting biphasic mixture was warmed to r.t and stirred for 12 h. The reaction was diluted with H$_2$O (10 mL), the layers separated and the aqueous phase extracted with Et$_2$O (3 × 10 mL). The combined organic phases washed with brine (15 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (10%
EtOAc/PE, SiO\textsubscript{2}) gave (R)-(+)gossonorol 2 (0.141 g, 85\%, e.r. 98:2) as a colourless oil. Characterization data were consistent with literature.\textsuperscript{4}

\(R_f: 0.28\) (10\% EtOAc/PE).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta 7.34\) (d, \(J = 7.8\) Hz, 2H, 2 \(\times 2^\prime\)-H), 7.17 (d, \(J = 7.8\) Hz, 2H, 2 \(\times 3^\prime\)-H), 5.12 (tsept., \(J = 7.0, 1.3\) Hz, 1H, 5-H), 2.36 (s, 3H, Ar-CH\textsubscript{3}), 2.02-1.81 (m, 5H, 3-H\(_2\), 4-H\(_2\) and OH), 1.67 (br. s, 3H, 7-H\(_3\)), 1.55 (s, 3H, 1-H\(_3\)), 1.52 (br. s, 3H, 8-H\(_3\));

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta 144.9\) (C-1\textprimed), 135.9 (C-4\textprimed), 132.1 (C-6), 128.8 (2 \(\times\) C-Ar), 124.7 (2 \(\times\) C-Ar), 124.2 (C-5), 74.8 (C-2), 43.7 (C-3), 30.5 (C-1), 25.7 (C-7), 22.9 (C-4), 20.9 (ArCH\textsubscript{3}), 17.6 (C-8).

\textbf{IR} (neat): \(\nu_{\text{max}}/\text{cm}^{-1}: 3430\) (br., O-H), 2968 (C-H), 2922 (C-H), 1513 (CH\(_3\)), 1374 (CH\(_3\)), 1019 (C-O), 817 (Ar C-H).

\(\left[\alpha\right]_D^{23.2} +6.0\) (c. 1.0, CHCl\textsubscript{3}).

\textbf{HPLC} (Chiralpak\textsuperscript{\textregistered} IA, 210 nm, 3\% isopropanol/\textit{n}-hexane, 0.7 mL min\textsuperscript{-1}), \(t_r: \) major (R) 12.9 min, minor (S) 14.7 min.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{synthesis_diagram.png}
\end{figure}

Synthesis of (R)-(−)-Curcuphenol 3
2-Methoxy-4-methylacetophenone S2

K₂CO₃ (9.4 g, 68 mmol) and dimethyl sulfate (2.7 mL, 29 mmol) were added to a solution of 2'-hydroxy-4'-methylacetophenone S2 (3.8 mL, 27 mmol) in anhydrous acetone (50 mL), and the mixture was heated at reflux for 36 h. After cooling to room temperature the suspension was filtered through Celite. The reaction was diluted with H₂O (100 mL) and the aqueous phase extracted with EtOAc (3 × 75 mL). The combined organic phases were washed sequentially with H₂O (100 mL) and brine (75 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (15% EtOAc/PE, SiO₂) gave methyl ether 9b (4.14 g, 93%) as white needles, mp 36-38 °C (Lit. 55 35-37 °C). All analytic data corresponded to that reported in the literature.⁵

Rf (25% EtOAc/PE) 0.5;

¹H NMR (400 MHz, CDCl₃): δ 7.68 (d, J = 7.9 Hz, 1H, 6-ArH), 6.82 (d, J = 7.9 Hz, 1H, 5-ArH), 6.77 (s, 1H, 3-ArH), 3.90 (s, 3H, OMe), 2.59 (s, 3H, 8-H₃), 2.38 (s, 3H, ArCH₃).

¹³C NMR (100 MHz, CDCl₃): δ 199.1 (C=O), 159.1 (C-6), 144.8 (C-4), 130.5 (C-6), 125.4 (C-1), 121.3 (C-5), 112.2 (C-3), 55.3 (OMe), 31.8 (C-8), 21.8 (ArCH₃).

IR (CHCl₃) νmax/cm⁻¹ 1668 (C=O), 1607 (Ar-H), 1359 (OMe);
m/z (%) (EI) 164 (25, M⁺), 149 (100), 91 (30);

Anal Calc’d for C₁₀H₁₂O₂: C, 73.15; H, 7.37; Found: C, 73.39; H, 7.43.

(R)-(+-)-1-(2'-Methoxy-4'-methylphenyl)ethanol S3

HCO₂H (0.6 mL, 15 mmol) was added slowly to triethylamine (0.9 mL, 6 mmol) at 0 °C. The mixture was allowed to warm to room temperature before addition of 9b (0.46 g, 2.81 mmol) and (R)-RuCl[(1R,2R)-p-TsNCH(C₆H₅)CH(C₆H₅)NH₂]η⁶-p-cymene) (19 mg, 0.03 mmol).
After stirring for 96 h, H$_2$O (15 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed sequentially with saturated aqueous NaHCO$_3$ solution (20 mL) and brine (20 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to give a black oil. Purification by flash column chromatography (25% EtOAc/PE, SiO$_2$) gave alcohol S$_3$ (296 mg, 63%, e.r. 98:2 inferred from 7b, vide infra) as a colourless oil; unreacted ketone S$_1$ (0.074 g, 16%) was recovered as colourless needles.

**R$_f$:** (25% EtOAc/PE) 0.33;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.22 (d, $J = 7.7$ Hz, 1H, 6'-Ar), 6.79 (d, $J = 7.7$ Hz, 1H, 5'-ArH), 6.72 (s, 1H, 3'-ArH), 5.07 (app. quin., $J = 6.6$ Hz, 1H, 1-H), 3.86 (s, 3H, OMe), 2.64 (br. d, $J = 5.4$ Hz, 1H, OH), 2.36 (s, 3H, Ar-CH$_3$), 1.51 (d, $J = 6.6$ Hz, 3H, 2-H$_3$);

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.5 (C-2'), 138.3 (C-4'), 130.4 (C-6'), 125.9 (C-1'), 121.2 (C-5'), 111.4 (C-3'), 66.4 (C-2), 55.2 (OMe), 22.8 (C-1), 21.5 (ArCH$_3$).

IR (neat) $\nu_{\text{max}}$/cm$^{-1}$: 3374 (O-H), 2969 (C-H), 1613 (Ar-H);

$m/z$ (%): (EI) 166 (20, M$^+$), 151 (80), 133 (80), 121 (40), 105 (100), 91 (25), 77 (35);

Anal Calc’d for C$_{10}$H$_{14}$O$_2$: C, 72.26; H, 8.49; Found: C, 71.48; H, 8.42;

$[\alpha]_D^2$: +21.4 (c, 0.98, CHCl$_3$);

(R)-1-(2'-Methoxy-4'-methylphenyl)ethyl diisopropylcarbamate 7b

Et$_3$N (0.29 mL, 2.1 mmol) was added dropwise to a solution of S$_3$ (0.28 g, 1.7 mmol) and CbCl (0.33 g, 2.0 mmol) in CH$_2$Cl$_2$ (8 mL) at rt, the reaction mixture was then heated to reflux and stirred for 96 h. The reaction was cooled to rt and quenched by addition of H$_2$O (10 mL), the layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo, purification by flash column chromatography (10% EtOAc/PE, SiO$_2$) gave carbamate 7b (0.37 g, 75%, e.r. 98:2) as a colourless oil.

**R$_f$:** (10% EtOAc/PE) 0.31;
**1H NMR** (400 MHz, CDCl₃): δ 7.24 (d, J = 7.6 Hz, 1H, 6’-ArH), 6.77 (d, J = 7.6 Hz, 1H, 5’-ArH), 6.69 (s, 1H, 3’-ArH), 6.15 (q, J = 6.4 Hz, 1H, 1-H), 4.09-3.78 (br. m, 2H, 2 × NCH(CH₃)₂), 3.82 (s, 3H, OMe), 2.34 (s, 3H, Ar-CH₃), 1.49 (d, J = 6.4 Hz, 3H, 2-H), 1.30- 1.20 (br. m, 12H, 2 × NCH(CH₃)₂);

**13C NMR** (100 MHz, CDCl₃): δ 155.8 (2’-C), 155.1 (C=O), 138.1 (4’-C), 128.7 (6’-C), 125.9 (1’-C), 121.0 (5’-C), 111.4 (3’-C), 67.8 (1-C), 55.3 (OMe), 45.7 (br., 2 × NCH(CH₃)₂), 21.9 (2-C), 21.5 (ArCH₃), 21.1 (br., 2 × NCH(CH₃)₂);

**IR (neat)** ν max/cm⁻¹: 2969 (C-H), 2923 (C-H), 1685 (C=O);

**HRMS (ESI)** Calc’d for C₁₇H₂₈NO₃ 294.2064 ([M+H]⁺); Found 294.2063

[α]D₂₂: −12.2 (c. 0.98, CHCl₃).

**HPLC** (Chiralpak® IA, 210 nm, 3% isopropanol/n-hexane, 0.7 mL min⁻¹), tR: major (R) 7.0 min, minor (S) 7.8 min.

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**10b**

s-BuLi (1.3 M in cyclohexane/hexane (92:8); 0.11 mL, 0.14 mmol) was added to a solution of 7b (32 mg, 0.11 mmol) and TMEDA (26 μL, 0.17 mmol) in Et₂O (1.0 mL) at −78 °C, such that the temperature of the reaction did not rise above −70 °C. After stirring for 1 h, 8 (1.0 M in Et₂O; 0.17 mL, 0.17 mmol) was added slowly, such that the temperature of the reaction did not rise above −70 °C. The solution was allowed to stir at −78 °C for a further 1 h, before MgBr₂ OEt₂ (1.0 M in MeOH; 0.18 mL, 0.18 mmol) was added dropwise. The cooling bath was removed, and the reaction allowed to stir at room temperature for 4 h before addition of NaH₂PO₄ (1.0 M aq.; 1.5 mL). The layers were separated, the aqueous phase extracted with
Et₂O (3 × 10 mL), and the combined organic phases dried over MgSO₄, filtered and concentrated in vacuo. The resulting oil was dissolved in PhMe (1.0 mL), TBAF·3H₂O (52 mg, 0.17 mmol) was added, and the mixture heated at 50 °C for 12 h. After cooling to room temperature, filtration through SiO₂ and concentration in vacuo, purification by flash column chromatography (5% EtOAc/PE, SiO₂) gave (R)-(−)-curcuphenol methyl ether 10b (17 mg, 58%) as a colourless oil. Characterisation data were consistent with those reported in the literature.³

**Rf:** (5% EtOAc/PE) 0.47;

**¹H NMR** (400 MHz, CDCl₃) δ 7.06 (d, J = 7.7 Hz, 1H, 6’-ArH), 6.76 (d, J = 7.7 Hz, 1H, 5’-ArH), 6.69 (s, 1H, 3’-ArH), 5.13 (tsept., J = 7.1, 1.4Hz, 1H, 5-H), 3.82 (s, 3H, OMe), 3.15 (apparent sext, J = 7.1 Hz, 1H, 2-H), 2.35 (s, 3H, ArCH₃), 2.03-1.85 (m, 2H, 4-H₂), 1.71-1.62 (m, 1H, 3-HH), 1.69 (br. s, 3H, 7-H₃), 1.58-1.49 (m, 1H, 3-HH) 1.56 (br. s, 3H, 8-H₃), 1.19 (d, J = 7.1 Hz, 3H, 1-H₃);

**¹³C NMR** (100 MHz, CDCl₃) δ 156.9 (C-2’), 136.2 (C-4’), 132.8 (C-1’), 131.1 (C-6), 126.5 (C-6’), 124.9 (C-5), 121.1 (C-5’), 111.5 (C-3’), 55.3 (OMe), 37.2 (C-3), 31.4 (C-2), 26.3 (C-4), 25.7 (C-7), 21.4 (ArCH₃), 21.1 (C-1), 17.6 (C-8).

**IR** (neat)νmax/cm⁻¹: 2917 (C-H), 1612 (Ar-H), 1506,1452 (CH₃), 1258 (C-O-C (Ar C-H).

\[\alpha\]D²⁵ −3.9 (c. 0.26, CHCl₃) (Lit.:⁸⁸ [α]D²⁵ −5.8 (c. 1.0, CHCl₃)).

(R)-(−)-Curcuphenol 3

A solution of EtSH (28 µL, 0.38 mmol) in DMF (1 mL) was added dropwise to NaH (60% dispersion in mineral oil, 15 mg, 0.38 mmol), previously washed with anhydrous hexane (3 × 1mL), in DMF (1 mL) at rt. A solution of 10b (18 mg, 0.08 mmol) in DMF (0.5mL) was added and the reaction was heated to 120 °C and stirred for 24 h. The reaction was cooled to rt and 1M HCl(aq) (0.5 mL) and H₂O (2 mL) were added to the reaction mixture. The aqueous phase was extracted with Et₂O (3 × 5 mL) and the combined organic phases were washed
with brine (10 mL), dried over MgSO$_4$, filtered and concentrated \textit{in vacuo}. Purification by flash column chromatography (5\% Et$_2$O/PE, SiO$_2$) gave (R)-(-)-curcuphenol 3 (14 mg, 81\%, e.r. 96:4) as a colourless oil. Characterisation data were consistent with those reported in the literature.$^3$

$R$: (5\% EtOAc/PE) 0.18;

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.05 (d, $J$ = 7.8 Hz, 1H, 6'-ArH), 6.73 (d, $J$ = 7.8 Hz, 1H, 5'-ArH), 6.60 (s, 1H, 3'-ArH), 5.14 (tsept, $J$ = 7.0, 1.4 Hz, 1H, 5-H), 4.63 (s, 1H, OH), 2.97 (apparent sext, $J$ = 7.0 Hz, 1H, 2-H), 2.28 (s, 3H, ArCH$_3$), 2.03-1.92 (m, 2H, 4-H$_2$), 1.72-1.56 (m, 2H, 3-H$_2$), 1.70 (br. s, 3H, 7-H$_3$), 1.55 (br. s, 3H, 8-CH$_3$), 1.24 (d, $J$ = 7.0 Hz, 3H, 1-H$_3$);

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ = 152.8 (C-2'), 136.5 (C-4'), 132.0 (C-1'), 129.9 (C-6), 126.8 (C-6'), 124.6 (C-5), 121.7 (C-5'), 116.2 (C-3'), 37.3 (C-3), 31.4 (C-2), 26.1 (C-4), 25.7 (C-7), 21.1 (ArCH$_3$), 20.9 (C-1), 17.7 (C-8).

IR (neat) $\nu_{\text{max}}$/cm$^{-1}$: 3340 (br., OH), 2925 (C-H), 1507,1446 (CH$_3$), 1120 (C-OH), 806 (Ar C-H);

[\alpha]_D^{213} = -18.4$^\circ$ (c. 0.40, CHCl$_3$) (Lit.:$^{10}$ [\alpha]_D^{25} = -20.9$^\circ$ (c. 1.0, CHCl$_3$))

HPLC (Chiralpak® IA, 210 nm, 1\% isopropanol/n-hexane, 0.7 mL min$^{-1}$), $t_r$: minor (S) 39.9 min, major (R) 44.8 min.
Synthesis of (R)-(−)-curcuquinone 5 and (R)-(−)-curcuhydroquinone 4

1,4-dimethoxy-2-methylbenzene S4 (2.0 mL, 17.4 mmol) was added to a solution of AcCl (3.1 mL, 43.5 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was cooled to -30 °C and AlCl₃ (2.78 g, 20.9 mmol) was added in portions to the reacting mixture at -30 °C. The reaction mixture was stirred for 2 h at -30 °C, before pouring onto H₂O and ice (200 mL). The slurry was diluted with CH₂Cl₂ (100 mL), the layers separated and the aqueous layer extracted with CH₂Cl₂ (3 × 100 mL). The combined organic phases were washed with H₂O (100 mL), dried over MgSO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/PE, SiO₂) gave ketone 9c (2.76 g, 82%) as colourless needles (mp 74-76 °C (CH₃Cl), (lit.: S₈ 76 °C (hexane))); Characterisation data were consistent with those reported in the literature.⁵

Rᶠ = 0.40 (10% EtOAc/PE);
$^1$H NMR (400 MHz, CDCl$_3$) 7.29 (s, 1H, 3-ArH), 6.79 (s, 1H, 6-ArH), 3.88 (s, 3H, OMe), 3.82 (s, 3H, OMe), 2.62 (s, 3H, 8-H$_3$), 2.26 (s, 3H, ArCH$_3$);

$^{13}$C NMR (101 MHz, CDCl$_3$) 198.7 (C=O), 153.6 (C-5), 151.6 (C-2), 133.7 (C-1), 125.3 (C-4), 114.8 (C-3), 110.9 (C-6), 56.0 (OMe), 55.8 (OMe), 32.0 (C-8), 16.7 (ArCH$_3$);

IR (neat) $\nu_{\max}$/cm$^{-1}$: 1661 (C=O), 1610 (ArH), 1398 (CH$_3$), 1214 (C-O-C), 1042 (C-O-C), 886, 802 (Ar C-H);

$m/z$ (EI) 195 (M$^+$ + 1.6%), 194 (M$^+$, 51), 179 (M$^+$ -H$_2$O 100), 164 (M -CH$_3$ -H$_2$O, 9),

(+)-(R)-1-(2,5-Dimethoxy-4-methylphenyl)ethanol S5

HCO$_2$H (6 mL, 140 mmol) was added slowly to Et$_3$N (9 mL, 60 mmol) at 0 °C. The mixture was stirred for 10 minutes at 0 °C and was allowed to warm to room temperature. Acetophenone 9c (5.00 g, 25 mmol) and RuCl[(1R, 2R)-p-TsNCH(CH$_3$)$_2$NH$_2$](η$^6$-p-cymene) (163 mg, 0.25 mmol, 0.01 eq) were added and the reaction was stirred at rt for 10 days. H$_2$O (100 mL) was added and the reaction was extracted with Et$_2$O (3 × 100 mL). The combined organic phases were washed sequentially with saturated NaHCO$_3$(aq) (100 mL) and brine (100 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (10→15% EtOAc/PE, SiO$_2$) gave alcohol S5 (2.63 g, 52%, 92% bsrn, e.r. 96:4 inferred from 7c) as colourless needles (mp= 46-48 °C (PE));

$R_f$ (15% EtOAc:PE) 0.25;

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.87 (s, 1H, 6-ArH), 6.71 (s, 1H, 3-ArH), 5.08 (q, $J = 6.7$ Hz, 1H, 7-H), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 2.68 (br. s., 1H, OH), 2.23 (s, 3H, ArCH$_3$), 1.50 (d, $J = 6.7$ Hz, 3H, 8-H$_3$);

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.7 (C-5), 150.0 (C-2), 131.4 (C-1), 125.9 (C-4), 113.8 (C-3), 108.8 (C-6), 66.5 (C-7), 56.0 (OMe), 55.9 (OMe), 23.2 (C-8), 16.2 (ArCH$_3$).
IR (neat) $\nu_{\text{max}}$/cm$^{-1}$: 3489 (br. O-H), 2932 (C-H), 1453 (C=O), 1202 (C-O-C), 1080, 1040 (C-O-C), 824 (Ar C-H).

$m/z$ (EI) 207.1 (11), 197.1 (M+2%, 16), 196.1 (M, 30), 179.1 (M –OH, 100), 178.1 (M –H2O, 34), 164.1 (M – 2 × CH3 –H2O, 8).

HRMS (CI): calculated for C$_{11}$H$_{17}$O$_3$: 197.1178 found 197.1171.

$[\alpha]_p^{20.1}$: +6.81 (c. 0.29, CHCl$_3$)

(R)-1-(2,5-Dimethoxy-4-methylphenyl)ethyl diisopropylcarbamate 7c

Alcohol S5 (100 mg, 0.51 mmol) was added to a solution of NaH (60% dispersion in mineral oil, 31 mg, 0.76 mmol), previously washed with hexane (3 × 0.5 mL), in THF (3 mL) at rt and the reaction was stirred for 1 h. CbCl (102 mg, 0.62 mmol) was added and the reaction was then stirred at reflux for 16 h. The reaction was cooled to rt and H$_2$O (5 mL) was added dropwise. The layers were separated and the aqueous phase was extracted with Et$_2$O (3 × 10 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/PE, SiO$_2$) gave carbamate 7c (157 mg, 92%, e.r. 96:4) as colourless needles (mp 77-79 °C (PE)) after crystallisation.

$^1$H NMR (400MHz, CDCl$_3$) $\delta$ 6.87 (s, 1H, 6-ArH), 6.69 (s, 1H, 3-ArH), 6.14 (q, J = 6.5 Hz, 1H, 7-H), 4.28-3.68 (br. m., 2H, 2 × NCH(CH$_3$)$_2$), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 2.21 (s, 3H, ArCH$_3$), 1.50 (d, J = 6.5 Hz, 3H, 8-H$_3$), 1.27 (br. m., 12H, 2 × NCH(CH$_3$)$_2$).

$^{13}$C NMR (101MHz, CDCl$_3$) $\delta$ 155.0 (C=O), 151.7 (C-5), 149.5 (C-2), 129.6 (C-1), 125.9 (C-4), 114.2 (C-3), 108.6 (C-6), 68.1 (C-7), 56.2 (OMe), 55.9 (OMe), 46.0 (br. 2 × NCH(CH$_3$)$_2$), 22.1 (C-8), 21.0 (br. 2 × NCH(CH$_3$)$_2$), 16.2 (ArCH$_3$).

IR (neat) $\nu_{\text{max}}$/cm$^{-1}$: 2968 (C-H), 1683 (C=O), 1428 (CH$_3$), 1287 (C-O-C), 1044 (C-O-C), 794 (Ar C-H);

$m/z$ (Cl) 385.2 (3), 324.2 (M + 1%, 2), 323.2 (M, 16), 180.1 (13), 179.1 (M –HO-Cb, 100), 178.1 (M – Cb –H$_2$O, 35);
HRMS (CI): calculated for C_{18}H_{29}NO_{4}: 323.2097 found 323.2091.  
[\alpha]_D^{21.4}: +7.14 (c. 1.4, CHCl_3).

HPLC (Chiralpak® IB, 210 nm, 2% isopropanol/hexane, 0.8 ml/min), \( t_r = 9.3 \) min major (\( R \)), 11.4 min minor (\( S \)).

\((R)-(\rightarrow)-\text{Curcuhydroquinone dimethyl ether 10c}\)

\( s\)-BuLi (1.37 M in cyclohexane/hexane (92:8), 0.43 mL, 0.59 mmol) was added dropwise to a solution of carbamate 7c (146 mg, 0.45 mmol) and TMEDA (0.09 mL, 0.59 mmol) in Et_2O (1.5 mL) at -78 °C such that the temperature of the reaction did not rise above -70 °C. After stirring for 15 minutes, a solution of pinacol boronic ester 8 (142 mg, 0.68 mmol) in Et_2O (0.4 mL) was then added dropwise over 10 min. The reaction was stirred at -78 °C for 2 h and a solution of MgBr_2 (1M in MeOH, 0.68 mL, 0.68 mmol) was then added and the reaction was warmed to rt and stirred overnight. The reaction was quenched with an aqueous solution of NaH_2PO_4 (1M, 8 mL), the layers were separated and the aqueous layer extracted into Et_2O (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO_4, filtered and concentrated \textit{in vacuo}. TBAF·3H_2O (213 mg, 0.68 mmol) was added to a solution of the crude material in PhMe (3 mL) and the reaction heated to 50 °C and stirred for 20 h. The reaction was cooled to room temperature and filtered through SiO_2, eluting with pentane, the crude material was concentrated \textit{in vacuo} and purified by flash column chromatography (5% EtOAc:PE, SiO_2) to give the Curcuhydroquinone dimethyl
ether 10c as a clear, colourless oil (79 mg, 67%, 94:6 e.r.). All characterisation data matched that reported in the literature.  

**Rf** (5% EtOAc:PE) = 0.60

**1H NMR** (400 MHz, CDCl₃) δ 6.69 (s, 1H, 6’-ArH), 6.68 (s, 1H, 3’-ArH), 5.13 (br. t, J = 7.2 Hz, 1H, 5-H), 3.80 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.15 (apparent sext, J = 7.0 Hz, 1H, 2-H), 2.22 (s, 3H, ArCH₃), 2.01-1.85 (m, 2H, 4-H₂), 1.68 (s, 3H, 7-H₃), 1.67-1.56 (m, 2H, 3-H₂), 1.55 (s, 3H, 8-H₃), 1.20 (d, J = 7.0 Hz, 3H, 1-H₃);

**13C NMR** (101 MHz, CDCl₃) δ 151.8 (C-5’), 150.8 (C-2’), 134.0 (C-1’), 131.1 (C-6) , 124.8 (C-5), 124.2 (C-4’), 114.3 (C-3’), 109.8 (C-6’), 56.4 (OMe), 56.1 (OMe), 37.3 (C-3), 31.8 (C-2), 26.3 (C-4), 25.7 (C-7) , 21.3 (C-1), 17.6 (C-8), 16.1 (ArCH₃).

**IR**(neat)νₓmax/cm⁻¹: 2961 (C-H), 1464 (CH₃), 1398, 1206 (C-O-C), 1048 (C-O-C), 825, 798 (Ar C-H).

m/z (EI) 262 (M⁺, 56), 179 (M –methylpentene, 100), 165 (M –methylpentene -CH₃, 20), 152 (M –methylpentene -2 × CH₃, 27), 91 (tropylium,15).

[α]D²¹ -32.0 (c 1.0, CH₃Cl) Lit. (S)-enantiomer [α]D²⁰ + 40.9, (c 2.0, CH₂Cl)

**HPLC** (Chiralpak® IA, 210 nm, 2% isopropyl alcohol/hexane, 0.5 mL/min, rt) tᵣ = 12.3 min minor (S), 13.8 min major(R) 94:6
(R)-(−)-curcuquinone 5

A solution of CAN (227 mg, 0.41 mmol) in H₂O (1 mL) was added dropwise to a solution of Curcuhydroquinone dimethyl ether 10c (35 mg, 0.13 mmol) in MeCN (2 mL) and one drop of PE at rt. The reaction was stirred for 30 min before being extracted into CH₂Cl₂ (2 × 10 mL), concentrated in vacuo and purified by flash column chromatography (5% EtOAc:PE, SiO₂) to yield the product (R)-(−)-curcuquinone 5 as a bright yellow oil (12 mg, 41%). All characterisation data matched that reported in the literature.⁷

Rf (5% EtOAc:PE) = 0.37

¹H NMR (CDCl₃, 500 MHz) δ 6.59 (q, J = 1.6 Hz, 1H, 6'-H), 6.51 (d, J = 1.0 Hz, 1H, 3’-H), 5.06 (apparent tsept, J = 7.1, 1.4 Hz, 1H, 5-H), 2.92 (1H, apparent sextd, J = 6.9, 1.0 Hz, 2-H), 2.04 (d, J = 1.6 Hz, 3H, ArCH₃), 2.01-1.91 (m, 2H, 4-H), 1.67 (apparent q, 3H, J = 1.4 Hz, 7-H), 1.61-1.53 (m, 1H, 3-H), 1.56 (br. s, 3H, 8-H), 1.48-1.41 (m, 1H, 3-H), 1.12 (d, J = 6.9, 3H, 1-H);

¹³C NMR (CDCl₃, 126 MHz) δ 188.5 (C=O), 187.4 (C=O), 154.2 (C-2’), 145.1 (C-5’), 133.8 (C-6’), 132.1 (C-6), 131.1 (C-3’), 123.8 (C-5), 35.8 (C-2), 31.3 (C-3), 25.8 (C-7), 25.7 (C-4), 19.5 (CH₃), 17.7(CH₃), 15.4(C-8)

[α]ᵢ²⁰ = 0.0 (c 0.4, CH₂Cl₂) Lit. (S)-enantiomer [α]ᵢ²⁰ + 0.9 (c 1.0, CH₂Cl₂)
(R)-(-)-curcuhydroquinone 4

NaBH₄ (5.7 mg, 0.15 mmol) was slowly added to a solution of curcuquinone 5 (12 mg, 0.05 mmol) in MeOH (0.5 mL) at 0 °C. The reaction was warmed to rt and stirred for 15 min. NH₄Cl(aq) (1 mL) and H₂O (1 mL) were added and the reaction was extracted with EtOAc (3 × 4mL). The combined organic phases were washed with brine (2 mL), dried over MgSO₄, filtered and concentrated in vacuo to give (R)-(-)-curcuhydroquinone 4 as a clear, colourless oil (11 mg, 92%). All characterisation data matched that reported in the literature.⁷

¹H NMR(CDCl₃, 500 MHz) 6.59 (s, 1H, 6’-H), 6.57 (q, J = 0.6 Hz, 1H, 3’-H), 5.13 (tsept, J = 7.0, 1.4 Hz, 1H, 5-H), 4.32 (br. s, 1H, OH), 4.28 (br. s, 1H, OH), 2.94 (apparent sext., J = 7.0 Hz, 1H, 2-H), 2.18 (s, 3H, ArCH₃), 2.00-1.89 (m, 2H, 4-H₂), 1.69 (apparent q, J = 1.4 Hz, 3H, 7-H₃), 1.67-1.54 (m, 2H, 3-H₂), 1.55 (d, J = 1.2 Hz, 3H, 8-H₃), 1.21 (d, J = 7.0 Hz, 3H, 1-H₃)

¹³C NMR (CDCl₃, 126 MHz) 147.8 (C-5’), 146.6 (C-2’), 132.2 (C-1’), 131.7 (C-6), 124.5 (C-4’), 121.7 (C-6’), 117.9 (C-5), 113.4 (C-3’), 37.4 (C-3), 31.4 (C-2), 26.0 (C-4), 25.7 (C-7), 21.1 (C-1), 15.4 (C-8) 12.7 (ArCH₃)

[α]²⁰_D -40.0 (c 0.2, CH₃Cl) Lit. (S)-enantiomer [α]²⁰_D + 47.1 (c 1.0, CH₃Cl)
4. Copies of $^1$H NMR and $^{13}$C NMR spectra

B(pin)

[Diagram of NMR spectrum with labeled peaks]
5. References