Enantioselective synthesis of (+)-nuciferal, (+)-(*E*)-nuciferol and (+)-α-curcumene by chiral hydrogenesterification reaction

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Using chiral hydrogenesterification reaction as the key step, the stereoselective synthesis of (+)-nuciferal **1**, (+)-(E)-nuciferol 2 and (+)-a-curcumene 3 has been achieved.

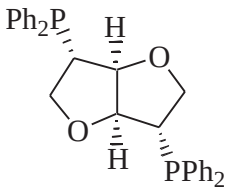
Keywords: phenolic sequiterpenes, *Torreya nucifera*

A variety of phenolic sesquiterpenes of the bisabolane family have been isolated from many different natural sources.[1] They are the olfactorally active components of a large number of essential oils and show a wide range of biological activities. These compounds are attractive synthetic targets to verify the use of new synthetic methodology.

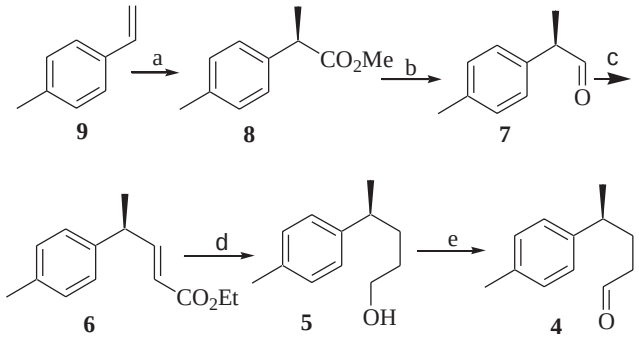
The monocyclic aromatic bisabolane type sesquiterpene (+)-nuciferal **1** was isolated from the wood oil of *Torreya nucifera* by Sakai, Nishimura and Hirose in 1965.[1a] The structures of (+)-nuciferal **1** and (+)-(*E*)-nuciferol **2** resemble the two sinensals which promise to become important materials for the creation of orange flavours.[2] Consequently it would be of interest to compare the organoleptic properties of (+)-nuciferal **1** with those of the sinensals. (+)-α-Curcumene **3** has been recognised as odour components of the distantly related gorgonians *Plexaurella dichotoma, P. grisea and P. fusifera*.[3] Although a number of syntheses of their tacemates have been descripted,[4] their stereospecific synthesis has only been described by Seiichi Takano.[5] Herein, we reported a facile and convenient route to (+)-nuciferal **1**, (+)–(*E*)-nuciferol **2** and (+)-α-curcumene **3** through asymmetric reductive sterification to construct the benzyl chiral carbon with high stereoselectivity.

Results and discussion

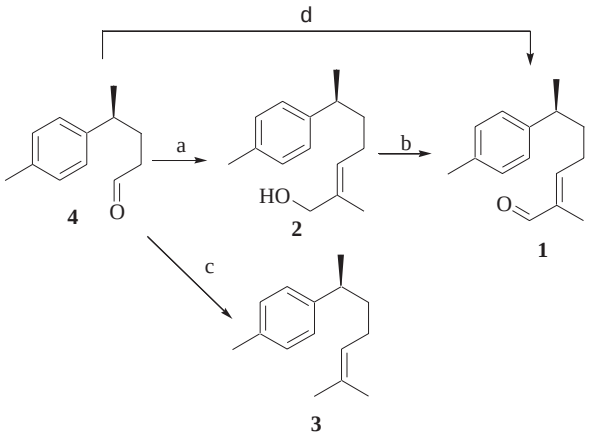
The hydrogenation and esterification reaction has been examined by several groups.[6] Lu and coworkers reported that the complex of DPPFF [(1,4: 3,6-dihydro-2, 5-dideoxy-2, 5-bis (diphenylphosphino)-L-iditol[7a]) (Fig. 1)] with Pd is a very effectively asymmetric homogeneous catalyst in hydrogenation and esterification of styrene derivatives. The best condition was that the temperature was 80 °C, the pressure of CO was 6 MPa, the solvent was 1,4-dioxane, and the ratio of DPPFF (mol) and $PdCl_2$ (mol) was 3:1.[7b] As far as styrene was concerned, when the hydrogenation-esterification reaction was performed, (*R*)-2-phenyl-propionate was obtained. Under these conditions, DPPFF showed very high enatioselectivity (ee>90%) and regioselectivity.



Enlightened by this useful reaction, our strategy is outlined in Scheme 1. The commercially available *p*-methyl styrene **9** was used as starting material. Compound **8** was obtained in 77% yield and in 90% e.e after carrying out of a hydrogenation-esterification using the optimised condition mentioned above. Compound **8** was reduced by LAH and then subjected to Swern oxidation to afford an aldehyde **7**. The carbon chain was extended by Wittig olefination to give **6**. Compound **6** was be reduced by LAH in THF to give the saturated alcohol derivative **5**. The key intermediate **4** was then obtained through Swern oxidation. Takano had synthesised this key intermediate **4** by eight steps in a relative laborious manner.[5a]



Scheme 1 Reagents and conditions: (a) DPPFF (Fig. 1), $PdCl_2$, $CuCl_2{\cdot}2H_2O$, 6 M Pa CO, MeOH, 1,4 dioxane, 77%, 90% ee; (b) (i), LAH, 97%; (ii), $(COCl)_2$, DMSO, then Et_3N, 98%; (c) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 97%; (d) LAH, THF, reflux, 98%; (e) $(COCl)_2$, DMSO, then Et_3N, 98%.



Scheme 2 Reagents and conditions: (a) (i), NaH, DME, triethyl phosphonopropionate, 24 h, 90%; (ii), LAH/$AlCl_3$ (1:3), 98%; (b) MnO_2, CCl_4, reflux, 99%; (c) isopropyl triphenylphosphonium iodide, BuLi, THF, 80%; (d) $Ph_3P{=}C(CH_3)CHO$, toluene, reflux for 2 days, 90%.

The key intermediate **4** was treated with $Ph_3P{=}C(CH_3)CHO$ to give (+)-nuciferal **1** (Scheme 2), or treated with triethyl 2-phosphonopropionate and then reduced by LAH/$AlCl_3$ to give (+)-(*E*)-nuciferol **2**. Further oxidation with MnO_2 in CCl_4 afforded (+)-nuciferal **1**. Compound **4** reacted with isopropylidenetriphenyl- phosphorane in THF to afford (+)-α-curcumene **3**.

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In summary, we have developed a synthetic route to this class of sesquiterpene from cheap starting materials. The present route may be applicable to other members of the bisabolane family.

Experimental

The ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$ solution with Varian 300 MHz or Bruker AC 200 spectrometers if not noted otherwise. The chemical shifts are referenced to TMS in ppm on the 'δ' scale. Mass spectra were recorded on a HP-5988 mass spectrometer (EI). Optical rotations were determined on a JASCO J-20C polarimeter with 0.2 dm tube. HRMS(EI) were performed on a Bruker FT-MS analyser. Chiral analysis was performed on Varian Dynamax SD-300 using a Chiralcel column CDMPC (150×4.6mm D).

(R)-Methyl 2-p-tolylpropanoate **8**: $PdCl_2$ (0.08 mmol), $CuCl_2{\cdot}2H_2O$ (0.185 mmol), MeOH (0.5 ml), *p*-methylstyrene (0.5 g, 4.2 mmol) was dissolved in 1,4-dioxane (5 ml) in an autoclave under argon. The atmosphere was exchanged by CO gas, then the pressure of CO was increased to 6 MPa, and the autoclave was sealed. The mixture was stirred at 80 ^{0}C for 24 hours. The mixture was transferred to an flask to evaporate the solvent and the residue was chromatographied to give (*R*)-methyl 2-*p*-tolylpropanoate (580 mg, 77%) as an oil. ^{1}H NMR: 1.48 (d, *J* = 7.2 Hz, 3H), 2.32, (s, 3H), 3.68 (s, 3H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), MS: 178 (M^+, 9), 119 (100), 91 (22). $[\alpha]_D^{20}$= +10 (c =0.8, $CHCl_3$). HRMS: Found 178.0992, Required $C_{11}H_{14}O_2$ 178.0994.

(R)-2-p-Tolylpropanal **7**: To a suspension of LAH (266 mg, 7 mmol) in absolute ether was added 2-*p*-tolylpropionate (890 mg, 5 mmol) in absolute ether (10 ml) at 0 ^{0}C. The reaction was quenched with several drops of saturated sodium sulfate after completion. Ethyl acetate (50 ml) was added to above mixture then dried over Na_2SO_4. The solvent was evaporated and (*R*)-2-*p*-tolylpropanol was obtained as a colourless oil (735 mg, 98%). ^{1}H NMR: 1.24 (d, *J* = 6.9 Hz, 3H), 1.58 (br s, 1H), 2.32 (s, 3H), 2.85–2.93 (m, 1H), 3.64 (d, *J* = 6.9 Hz, 2H), 7.12 (s, 4H), $[\alpha]_D$=+14.6 (c=5.0,$CHCl_3$), e.e.>90%, MS (EI): *m*/*z* 150 (22), 119 (100), 91 (39).

At–70°C, to a mixture of DMSO (780 mg, 10 mmol) and oxalyl chloride (635 mg, 5 mmol) in anhydrous methylene chloride was added (*R*)-2-*p*-tolylpropanol (900 mg, 4.1 mmol) in anhydrous methylene chloride (10 ml). When the mixture was warmed to room temperature, triethylamine (5 ml) was added. The reaction mixture was quenched with water (20 ml) and extracted with ether (3×30 ml). The combined layer was washed by diluted HCl and brine and dried with Na_2SO_4. The solvent was evaporated and the residue was purified by column chromatography to afford the (*R*)-2-*p*-tolylpropanal (696 mg, 98%). ^{1}H NMR: 1.44 (d, *J* = 6.9 Hz, 3H), 2.34 (s, 3H), 3.60 (t, *J* = 6.9 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 9.67 (s, 4H), MS (EI): *m*/*z* 148 (M^+, 8), 132 (2), 119 (100), 91 (40). $[\alpha]_D$=+14.7, (c= 1.6, $CHCl_3$). Found 148.0886, Required $C_{11}H_{12}O$ 148.0888.

(4S, 2E) Ethyl 4-p-tolylpent-2-enoate **6**: To a solution of **7** (690 mg, 4.6 mmol) in dry benzene (20 ml) was added ethyl triphenylphosphonoacetate (1.6g, 4.6mmol), and then the mixture was refluxed for 4 hours. The reaction mixture was diluted with ethyl acetate (80 ml) and the combined solution was washed with dilute HCl, water and brine and then dried over Na_2SO_4. The solvent was evaporated in *vacuo* and the residue was purified by column chromatography to give (4S, 2*E*) Ethyl 4-*p*-tolylpent-2-enoate (909 mg, 96%) as a colourless oil. $[\alpha]_D$=–15.3, (c= 1, $CHCl_3$). lit.[8] $[\alpha]_D$= –13.6, (c=1.3, $CHCl_3$). ^{1}H NMR: 1.24 (t, *J* = 7.2, Hz, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 2.31 (s, 2H), 3.54–3.61 (m, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 5.80 (d, *J* = 15.6 Hz, 1H), 7.06–7.15 (m, 5H). ^{13}C NMR: 14.04, 20.00, 20.78, 41.45, 60.04, 119.74, 127.02, 129.15, 136.10, 140.10, 152.66, 166.61. MS (EI) *m*/*z* 218 (M^+, 43), 189 (18), 173 (32), 145 (100), 129 (98), 115 (41), 91 (40). HRMS: Found 218.1308, Required, $C_{14}H_{18}O_2$ 218.1307.

(S)-4-p-tolylpentan-1-ol **5**: To a suspension of LAH (380 mg, 10 mmol) in anhydrous THF was slowly added compound **6** (800 mg, 3.66 mmol) in THF (10 ml) at room temperature, and then the mixture was refluxed for 5 hours. The reaction was monitored by TLC until completion. Then the reaction was quenched by slow addition of 0.35 ml water, and 0.7 ml 10% NaOH and then 2.1 ml water. Then voluminous white aluminum salts precipitated. Ethyl acetate (50 ml) was added to the above mixture and the combined mixture was dried with $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography to give (*S*)-4-*p*-tolylpentan-1-ol **5** (304 mg, 98%) as a colourless oil. $[\alpha]_D$=+13.2, (c=0.7, $CHCl_3$). lit.[8] $[\alpha]_D$= 14.6, (c=0.74, $CHCl_3$).^{1}H NMR: 1.23 (d, *J* = 6.9 Hz, 3H), 1.43–1.57 (m, 2H), 1.58–1.60 (m, 2H), 2.34 (s, 3H), 2.36–2.69 (m, 1H), 3.61 (br s, 2H), 7.16 (s, 4H). ^{13}C NMR: 20.91, 22.45, 30.90, 34.37, 39.30, 62.94, 126.77, 128.98, 135.29, 144.24. MS (EI): *m*/*z* 178 (M^+, 3), 132 (100), 119 (82), 105 (21), 91 (45). HRMS: Found 178.1356, Required, $C_{12}H_{18}O$ 178.1358.

(S)-4-p-tolylpentanal **4**: Compound **5** (900 mg, 4.1 mmol) in anhydrous methylene chloride (10 ml) was added to a cold solution (-65 $^\circ$C) DMSO (780 mg, 10 mmol) and oxalyl chloride (635 mg, 5 mmol) in anhydrous methylene chloride. The mixture was warmed to room temperature and triethylamine (2 ml). Then the mixture was extracted with ether and the combined layers were washed with dilute HCl and brine and then dried with Na_2SO_4. The solvent was evaporated and the residue was purified through column chromatography to afford the (*S*)-4-*p*-tolylpentanal (696 mg, 98%). $[\alpha]_D$= +33.0, (c= 0.7, $CHCl_3$) ^{1}H NMR: 1.25 (d, *J* = 6.9 Hz, 3H), 1.80–2.01 (m, 2H), 2.11–2.27 (m, 2H), 2.32 (s, 3H), 2.65–2.71 (m, 1H), 7.13 (s, 4H), 9.85 (s, 1H), ^{13}C NMR: 20.91, 22.31, 31.04, 38.82, 42.14, 126.79, 128.97, 135.70, 142.91, 202.40. MS (EI): *m*/*z* 176 (M^+, 10), 145 (3), 132 (2), 119 (100), 91 (21). HRMS: Found 176.1200, Required, $C_{12}H_{16}O$ 176.1201.

(S)-Nuciferal **1**: To a solution of (*S*)-4-*p*-tolylpentanal **4** (50 mg, 0.28 mmol) in dry toluene (5 ml) was added (triphenylphosphoranylidene)propionaldehyde (200 mg, 0.6 mmol) and the mixture was refluxed for 3 days. Then the toluene was evaporated and the residue was chromatographied to give (*S*)-nuciferal (48 mg, 80%) as a colourless oil. $[\alpha]_D^{20}$= +51 (c 1.0, $CHCl_3$) (Natural[1a], $[\alpha]_D^{20}$= +60.07 (c 16.55, $CHCl_3$)] $\tilde{\nu}$ film/cm^{-1}: 2958, 1689, 1515, 1454, 1285, 818; ^{1}H NMR: 1.27 (d, *J* = 7 Hz, 3H), 1.65 (s, 3H), 1.70–1.81 (m, 2H), 2.16–2.28 (m, 2H), 2.64 (s, 3H), 2.64–2.74 (m, 1H), 6.42 (t, *J* = 7.2 Hz, 3H) 7.06 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 9.35 (s, 1H). ^{13}C NMR: 9.14, 20.98, 22.52, 27.26, 36.86, 39.30, 126.84, 129.17, 135.73, 139.34, 143.36, 154.74, 195.30. MS: 216 (M^+, 3), 173 (2), 158 (20), 145 (19) 133 (17), 119 (100). HRMS: Found 216.1517, Required, $C_{12}H_{16}O$ 216.1514.

(S, E)-Nuciferol **2**: was added to a suspension of NaH (17 mg, 60% in mineral oil) in DME (10 ml), triethyl phosphonopropionate (100 mg, 0.42 mmol) was added. The mixture was stirred for 30 min and then a solution of (*S*)-4-*p*-tolylpentanal **4** (50 mg, 0.28 mmol) in dry DME (5 ml) was added and the mixture was stirred for 24 hours at room temperature. Then dilute HCl was added to quench the reaction. The organic phase was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with water and brine and then dried with Na_2SO_4. The solvent was evaporated in *vacuo* and the residue was purified by column chromatography to give (*S, E*)-ethyl 2-methyl-6-*p*-tolylhept-2-enoate (50 mg, 90%) as a colourless oil.

To a solution of this ester in anhydrous THF (5 ml) was added excess LAH/$AlCl_3$ over 10 min., then the mixture stirred for 20 hours. And the reaction was quenched with several drops saturated sodium and then ethyl acetate (20 ml) was added to the mixture. The combined solution was dried over Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on silica gel to give (*S, E*)-nuciferol (41 mg, 98%) as a colourless oil. $[\alpha]_D^{20}$= +35.1 (c 0.9, $CHCl_3$) $\tilde{\nu}$ film/cm^{-1}: 3380. ^{1}H NMR: 1.18 (d, *J* = 7 Hz, 3H), 1.53–1.59 (m, 2H), 1.70 (s, 3H), 1.85–1.92 (m, 3H), 2.29 (s, 3H), 2.59–2.61 (m, 1H), 3.85 (s, 2H), 5.14 (t, *J* = 7 Hz, 1H), 6.94 (s, 4H). MS: 218 (M^+, 10), 157 (13), 145 (11), 132 (30), 119 (100). HRMS: Found 218.1670, Required, $C_{15}H_{22}O$ 218.1671.

(S)-Curcumene **3**: Buli (1.4 mmol) was added over 10 min. To a suspension of isopropyl triphenylphosphonium iodide (600 mg, 1.4 mmol) in anhydrous THF. The mixture became brown and the precipitate disappeared. A solution of (*S*)-4-*p*-tolylpentanal **4** (50 mg, 0.28 mmol) in dry THF was added to the above solution through a syringe. The mixture was stirred for 24 hours, and quenched with dilute HCl, and extracted with ether. The combined organic solutions were dried and evaporated. Chromatography of the residual oil on silica gel gave (+)-curcumene (45 mg, 79%) as a colourless oil. $[\alpha]_D^{20}$=+45.3 (c 1.15, $CHCl_3$), (Natural[1d], $[\alpha]_D^{20}$= +45.10 (c 0.75, $CHCl_3$)] IR: $\tilde{\nu}$ film/cm^{-1}: 2962, 2923, 2857, 1516, 1453, 1376, 816; ^{1}H NMR: 1.21 (d, *J* = 7 Hz, 3H), 1.53 (s, 3H), 1.60–1.67 (m, 2H), 1.68 (s, 3H) 1.80–1.95 (m, 2H), 2.32 (s, 3H), 2.55–2.65 (m, 1H), 5.10 (t, *J* = 6.9 Hz, 1H), 7.09 (s, 4H). MS: 202 (M^+, 27), 187 (4), 159 (22), 145 (27), 132 (76), 119 (100). HRMS: Found 202.1725, Required, $C_{15}H_{22}$ 202.1722.

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