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Synthesis of novel chiral dopants based on optically active *p*-substituted mandelic acids

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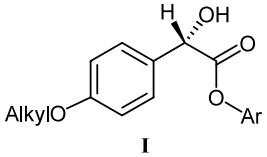
Abstract—Novel esters of optically active *p*-substituted mandelic acids (+)-**1** and (+)-**2** were prepared by a convergent synthetic strategy in high enantiomeric excess (99% ee). The esters (+)-**1** and (+)-**2** induce helical macrostructures in the mesophases of achiral liquid-crystal materials, although neither exhibits mesorphism on its own.

1. Introduction

Chirality is one of the most interesting and challenging subjects in liquid crystals.[1] Chiral phases can serve for technical applications such as displays[2] and pigments,[3] as well as for scientific objectives, for example determination of absolute configuration[4] or detection of chirality.[5] The induction of chirality in mesophases of non-chiral mesogens can be achieved by adding a small quantity of chiral dopant (up to 10%) to non-chiral liquid-crystalline hosts,[6] and molecular chirality is transferred to macroscopic chirality resulting in the formation of new phases with helical ordering. The diversity of chiral dopants reported to date has allowed certain empirical rules to be postulated for efficient chirality transfer; for example restricted conformational mobility in the chiral region of a dopant and its mesogenic-like structure can be important factors.[7] Interestingly, however, spontaneous formation of helical macrostructures has been observed in certain mesophases of bent-core mesogens,[8–10] the chirality being a consequence of the polar order and the special molecular packing of bent molecules within smectic layers.[11]

In the course of our project involving the synthesis of novel chiral liquid crystals, we have sought enantiomerically pure esters of *p*-substituted mandelic acid as potential chiral dopants. The key building block, enantiomerically pure *p*-hydroxymandelic acid, offers several interesting features. Thus, it possesses a polar group at the stereogenic carbon atom, a feature which is known to have a profound effect on the physical properties.[12] In addition, there is restricted conformational mobility of the stereogenic centre due to the steric constraint of an adjacent phenyl ring on one side and intramolecular hydrogen bonding between the oxygen atom of the α-hydroxyl and the carboxyl group[13] on the other. Consequently, the eclipsed conformation of α-hydroxyl and carboxyl group gives the molecule an overall bent shape. The presence of a 4-hydroxy and a carboxylate function offer possibilities for the elongation of the aromatic core and/or the introduction of long hydrocarbon chains, leading to molecules in which the position of the stereogenic centre may be varied. Since helical macrostructures can be observed in the absence of chirality in bent-core systems,[8–10] it is of great interest to study what effect chirality will have in conjunction with the position of the stereogenic centre, on the mesogenic properties of the system itself, as well as on the mesomorphism of the host while being used as a dopant.

Herein we describe the synthesis of two representative esters of enantiomerically pure *p*-substituted (+)-mandelic acid as potential chiral dopants. The first is representative of group **I**, bearing a polar stereogenic centre inside the rigid core at the centre of the molecule, while the second is representative of group **II**, having a stereogenic centre at the peripheral position of the rigid core. Both groups are characterised by an overall bent shape.



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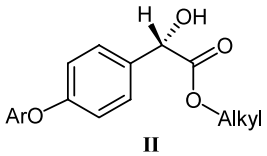

II

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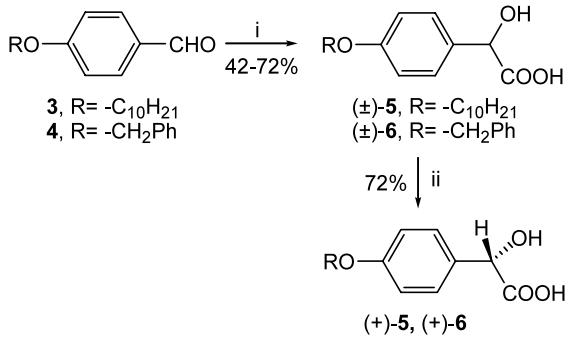
2. Results and discussion

2.1. Synthesis and characterisation

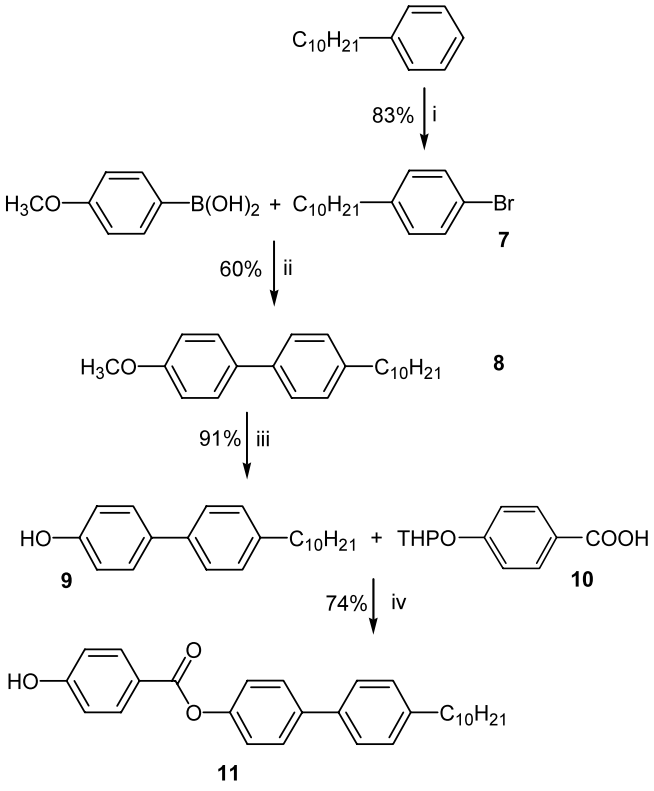
The key precursors, racemic 4-decyloxymandelic acid **5** and 4-benzyloxymandelic acid **6**, were prepared by the addition of chlorocarbene to the corresponding *p*-substituted benzaldehyde in 40–70% yield (Scheme 1). Dichlorocarbene was generated in situ from chloroform under strongly basic conditions in the presence of benzyltriethylammonium chloride (BTEAC) as a phase-transfer catalyst. The isolation procedure published for methoxymandelic acid[14] was modified because of the different solubilities of sodium decyloxy- and benzyloxy-mandelate in water and organic solvents.



Scheme 1. *Reagents and conditions*: (i) $CHCl_3$, NaOH (50%), BTAC; (ii) (a) (*R*)-(+)-PEA, $CHCl_3$, (b) HCl (2 M), Et_2O.

We have recently reported a specific protocol for efficient resolution of (±)-1-(9-anthryl)ethylamine with (*S*)-(+)-mandelic acid in chloroform.[15] Employing this protocol, we completed the resolution of racemic mandelic acids (±)-**5** and (±)-**6** with (*R*)-(+)-1-phenylethylamine in chloroform by adding equimolar quantity of the enantiomerically pure amine to hot, saturated solution of acids (±)-**5** or (±)-**6**. Slow cooling to room temperature led to the crystallisation of the diastereomeric salt of (−)-mandelic acid. The enantiomeric excesses of the (−)-enantiomers isolated from the precipitated salt were routinely low, while those from the (+)-enantiomers obtained from the soluble diastereomeric salt were exceptionally high. Therefore (+)-**5** and (+)-**6** were used in subsequent reactions.[16] The enantiomeric excesses of the acids (+)-**5** and (+)-**6** were determined after esterification with diazomethane by the Mosher ester method,[17] using a chiral HPLC column. The results revealed that resolution afforded >99% ee of (+)-**5** after a single crystallisation. All attempts to separate methyl esters of (+)-**6** and (−)-**6** either on commercial or on our own, originally developed chiral HPLC columns failed.[18,19] High enantiomeric purity of (+)-**6** (99% ee) was deduced from the chiral HPLC analysis of the ester (+)-**2** on a Chiralpak AD column.

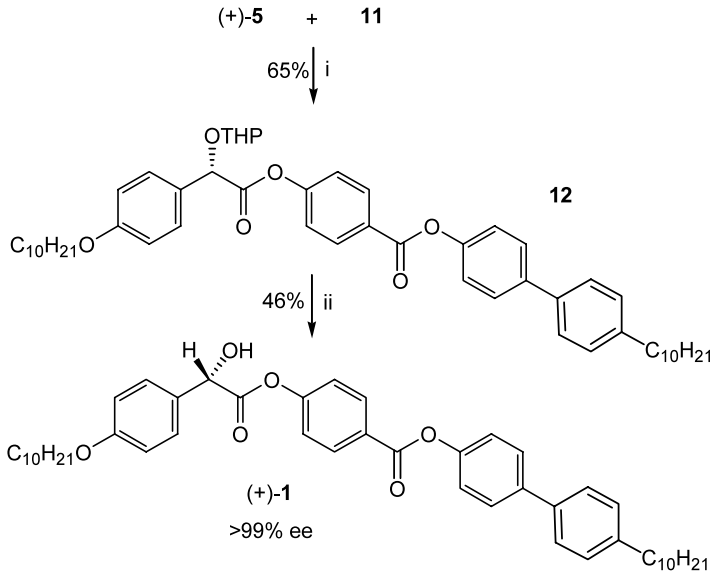
The convergent synthesis of mandelate (+)-**1**, representative of group **I**, required separate preparation of the phenol derivative, **11**, required for esterification of mandelic acid (+)-**5** (Scheme 2). Thus, bromination[20] of decylbenzene gave a mixture containing 20% of the *o*- and 80% of the *p*-bromoisomer as confirmed by GC analysis. Nevertheless, this mixture was used in the Suzuki coupling[21] with methoxyphenylboronic acid to give **8** in 60% yield. The ^{1}H NMR spectrum of the coupled product revealed the presence of the *p*-isomer only, coupling of the *o*-isomer presumably being hindered sterically. Removal of the methyl group with BBr_3 in dichloromethane at −80°C[22] gave phenol **9** in 91% yield. Esterification of 4-OTHP-protected benzoic acid with phenol **9** using dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) in tetrahydrofuran,[23] followed by removal of the protecting group using catalytic pyridinium *p*-toluenesulphonate (PPTS) in wet acetone,[24] afforded **11** in 74% yield.



Scheme 2. *Reagents and conditions*: (i) Br_2, CH_2Cl_2; (ii) $[Pd(PPh_3)_4]$, Na_2CO_3 (2 M); (iii) BBr_3, CH_2Cl_2; (iv) (a) DCC, DMAP, THF, (b) PPTS, wet acetone.

Finally, ester (+)-**1**, bearing a polar stereogenic centre inside the rigid core, was obtained by esterification of OTHP-mandelic acids (+)-**5** with alcohol **11**, followed by deprotection using PPTS in wet acetone to give ester (+)-**1** (99% ee) in ca. 25% overall yield. The enantiomeric purity of (+)-**1** remained the same as determined for the starting decyloxymandelic acids (Scheme 3).

To incorporate the stereogenic centre at the peripheral position relative to the rigid core in (+)-**2**, a long alkyl chain was introduced on the carboxylic terminus of



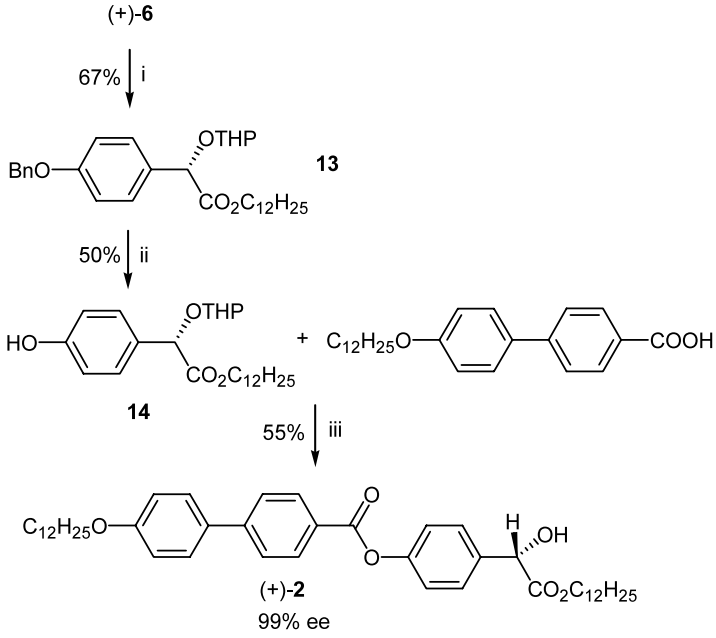
Scheme 3. *Reagents and conditions*: (i) (a) DHP, *p*-TsOH; then NaOH (1 M), (b) DCC, DMAP, THF; (ii) PPTS, wet acetone.

(+)-**6** by DCC-promoted esterification of OTHP-protected chiral benzyloxymandelic acid with 1-dodecanol[23] (Scheme 4). Hydrogenolysis[25] of the benzyl group afforded **14** which, on acylation with 4-dodecyloxybiphenyl carboxylic acid, followed by hydrolysis under mild acidic conditions, gave (+)-**2** (99% ee), in ca. 20% overall yield.

2.2. Liquid crystal properties

Investigations by polarised optical microscopy showed that both mandelates (+)-**1** and (+)-**2** melted directly into isotropic liquid phases at 123 and 108°C, respectively, and crystallised on cooling with no sign of a monotropic liquid crystal phase. Investigations of the liquid-crystalline properties by polarising optical microscopy of binary mixtures containing 4 mol% of mandelic esters (+)-**1** and (+)-**2** with the mesomorphic *p*-decyloxybenzoic acid as an achiral liquid crystalline host, showed a helical macrostructure in the mesophase. Thus, according to the textures, a N* (chiral nematic) and a SmC* (chiral smectic C) mesophase were observed instead of their achiral versions (Fig. 1).

Examination of the line periodicity of the fingerprint texture of the chiral nematic phases (which is related to the pitch[26,27]) indicated that chiral induction with (+)-**2** possessing peripheral stereogenic centre, is stronger



Scheme 4. *Reagents and conditions*: (i) (a) DHP, *p*-TsOH; then NaOH (1 M), (b) $C_{12}H_{25}OH$, DCC, DMAP, THF; (ii) Pd/C (10%), cyclohexene; (iii) (a) DCC, DMAP, THF, (b) PPTS, wet acetone.

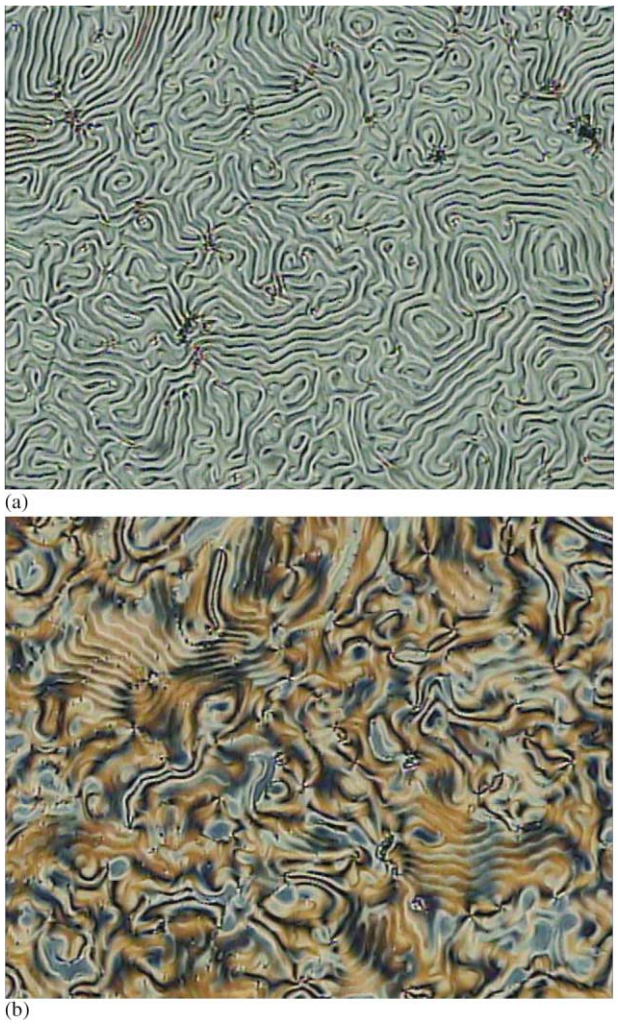


Figure 1. Textures of the chiral phases of binary mixture containing 4 mol% of (+)-**2** with the mesomorphic *p*-decyloxybenzoic acid (a) chiral nematic phase obtained at 135°C on cooling; (b) chiral smectic phase obtained at 112°C on cooling.

than that with (+)-**1** bearing stereogenic centre in the rigid core. Molecular modelling[28] revealed that, in both esters (+)-**1** and (+)-**2** conformational mobility of the chiral region of the molecule is reduced to the same extent. However they differ in the position of the stereogenic centre and in the degree of bending. Thus, while the more pronounced bending observed for the molecular structure of (+)-**1** is expected to hinder rotation around its molecular long axis and increase chirality transfer,[29] preliminary results indicate that steric shielding of the stereogenic centre is the prevailing factor, causing higher chiral induction in the mixture containing (+)-**2** as dopant.

3. Conclusion

In summary, two representative optically active, *p*-substituted mandelic acid derivatives were prepared as chiral dopants. Efficient resolution of racemic acids (±)-**5** and (±)-**6** with (*R*)-(+)-1-phenylethylamine was performed in chloroform affording, after a single crystallisation, (+)-**5** and (+)-**6** with 99% ee. Esters (+)-**1** and (+)-**2** were prepared by convergent syntheses without lost of enantiomeric purity. Investigations of the liquid crystal properties showed that while neither compound was liquid-crystalline on its own, mixing these esters with an achiral mesogenic material induced chiral mesophases. As chirality transfer is affected also by the nature of the host,[30,31] binary mixtures containing optically active mandelic esters in different hosts are under further investigation.

4. Experimental

All the solvents were either *puriss p.a.* quality or distilled over appropriate drying reagents. All the other reagents were used as purchased from *Aldrich*. ^{1}H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra: *Varian XL-Gemini 300* instrument with $SiMe_4$ as internal standard, in $CDCl_3$ unless otherwise stated; δ in ppm, J in Hz. IR spectra: *Bomem MB 102* spectrophotometer; absorption bands in cm^{-1}. Optical rotations: *Automatic Polarimeter AA-10* using Na_D wavelength; c in g sample/100 ml solvent. Mp: *Electrothermal 9100* instrument. Bp: *Büchi GKR-51* instrument for distillation under reduced pressure. TLC: *DC-Alufolien Kieselgel 60 F_{254}*, *Merck* plates; substances detected with UV lamp ($\lambda = 254$ nm). HPLC: *Hewlett Packard 1050* instrument equipped with UV detector; reverse phase column Nucleosil C-187 μm (250×4.6 mm); flow 1 ml min^{-1}, γ (sample) $\sim$0.5 g dm^{-3}; mobile phases and gradient: from 70% to pure MeOH in 20 min. Chiral HPLC analysis: *Hewlett Packard 1050* instrument equipped with UV detector using Chiralcel ODH (hexane/*i*-PrOH, 19:1, 0.8 mL/min) or Chiralpak AD (hexane–*t*-BuOH, 9:1, 1 mL/min). GC: *Hewlett Packard 5890 Series II* equipped with FI detector; column HP-17, initial temperature 70°C, final 250°C, heating rate 10°C min^{-1}. Phase temperatures and textures: *Leitz Wetzlar* polarizing microscope equipped with *Linkam TH600* hot stage and *PR600* temperature controller.

4.1. *p*-Substituted mandelic acid (±)-5,6—general procedure

To a solution of aldehyde **3** or **4** prepared as reported[32] (10 mmol), BTAC (0.5 mmol) in $CHCl_3$ (4 mL), aq. NaOH solution (4 mL, 50%) was added dropwise at 56°C. The mixture was heated at the same temperature overnight. After being allowed to cool to rt, the mixture was poured into H_2O (100 mL) and extracted with ether (3×10 mL). The aqueous layer was acidified with H_2SO_4 (50%) to pH 1 and extracted with Et_2O (5×20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum to give *p*-substituted mandelic acids (±)-**5** and (±)-**6** and in 42, and 72% yield, respectively.

4.2. (+)-4-Decyloxymandelic acid, (+)-5

To the hot, saturated solution of (±)-**5** (2.20 g, 7.15 mmol) in $CHCl_3$ (25 mL), (*R*)-(+)-PEA (0.91 mL, 7.15

mmol) was added in one shot. The solution was allowed to cool to rt over 2 h. The precipitate was separated by filtration and washed with cold $CHCl_3$ (2×10 mL). Evaporation of the mother liquor gave the diastereomeric salt of (+)-**5**, which was then suspended in ether (20 mL) and HCl (2 M) was added until the organic layer became clear. The organic layer was then separated and the aqueous solution was extracted with ether (2×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to give (+)-**5** (0.8 g, >99% ee, 72%) as a colourless solid, mp 118–119°C; $[\alpha]_D^{25}=+87$ (*c* 1.0, EtOH). IR (KBr): 3530, 2900, 1700, 1615, 1590, 1520, 1180 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta=0.85$ (t, $J=6.5$ Hz, 3H), 1.24–1.37 (m, 14H), 1.65–1.69 (m, 2H), 3.90 (t, $J=6.3$ Hz, 2H), 4.62 (s, 1H), 6.81 (d, $J=8.4$ Hz, 2H), 7.25 (d, $J=8.4$ Hz, 2H). ^{13}C NMR (DMSO-d_6): $\delta=16.69$, 25.25, 28.59, 31.78, 31.89, 31.96, 32.15, 34.47, 70.68, 74.88, 117.32, 130.48, 131.90, 162.20, 180.26. Anal. calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.23.

4.3. (+)-4-Benzyloxymandelic acid, (+)-6

To the hot, saturated solution of (±)-**6** (5.0 g, 19.4 mmol) in $CHCl_3$ (500 mL), (*R*)-(+)-PEA (2.5 mL, 19.4 mmol) was added in one portion. The solution was allowed to cool to rt over 3 h. The precipitate was separated by filtration and washed with cold $CHCl_3$ (2×15 mL). Evaporation of the mother liquor gave the diastereomeric salt of (+)-**6**, which was then suspended in ether (30 mL) and HCl (2 M) was added until the organic layer became clear. The organic layer was then separated and the aqueous solution was extracted with ether (2×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under vacuum to give (+)-**6** (1.8 g, 99% ee, 72%) as a colourless solid, mp 153–154°C; $[\alpha]_D^{25}=+103$ (*c* 1.0, EtOH). IR (KBr): 3425, 3357, 2915, 1708, 1250, 1179, 1056, 829 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta=4.92$ (s, 1H), 5.06 (s, 2H), 5.73 (s, 1H), 6.94 (d, $J=8.6$ Hz, 2H), 7.27–7.59 (m, 7H), 12.51 (s, 1H). ^{13}C NMR (DMSO-d_6): $\delta=$ 69.26, 71.97, 114.52, 127.74, 127.91, 127.99, 128.54, 132.64, 137.19, 157.96, 174.44. Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.90; H, 5.35.

4.4. 1-Bromo-4-decylbenzene, 7

Bromine (1.5 mL, 29.2 mmol) was added dropwise to a stirred and ice-cooled solution of decylbenzene (3.0 g, 13.7 mmol) and I_2 (35 mg, 0.14 mmol) in CH_2Cl_2 (5 mL), with the rigorous exclusion of light. After stirring for 1 day at rt, aq KOH (10 mL, 20%) was added. The mixture was shaken until the colour disappears and was then extracted with CH_2Cl_2 (3×20 mL). Combined extracts were dried (Na_2SO_4), filtered and the solvent was evaporated under vacuum. The crude product was purified by distillation under reduced pressure affording the compound **7** (3.37 g, 83%; bp 143–146°C at 0.2 mbar; 80% purity by GC) as a colourless oil which was used in the next step. Around 20% of 1-bromo-2-decylbenzene was identified. ^1H NMR ($CDCl_3$): $\delta=0.91$ (t, $J=6.3$ Hz, 3H), 1.25 (m, 14H), 1.54–1.59 (m, 2H), 2.54 (t, $J=7.4$ Hz, 2H), 7.03 (d, $J=8.2$ Hz, 2H), 7.37 (d, $J=8.2$ Hz, 2H).

4.5. 4′-Decyl-4-methoxybiphenyl, 8

To a vigorously stirred mixture of **7** (3.37 g, 11.34 mmol), $[Pd(PPh_3)_4]$ (0.26 g, 2.22 mmol), aq Na_2CO_3 (2 M, 11.3 mL) in toluene (25 mL), was added (4-methoxyphenyl)boronic acid (1.90 g, 12.50 mmol) dissolved in a minimum amount of EtOH (95%). The reaction mixture was heated to 90–95°C overnight, after which it was allowed to cool to room temperature and was extracted with Et_2O. The combined ether extracts were washed with brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The crude product was purified by crystallisation from EtOH to give the pure product, **8** (2.20 g, 60%); mp 83–84°C. IR (KBr): 2920, 2840, 1610, 1500, 810 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.87$ (t, $J=5.7$ Hz, 3H), 1.26–1.31 (m, 14H), 1.58–1.65 (m, 2H), 2.62 (t, $J=7.7$ Hz, 2H), 3.82 (s, 3H), 6.95 (d, $J=8.24$ Hz, 2H), 7.21 (d, $J=7.9$ Hz, 2H), 7.46 (d, $J=7.7$ Hz, 2H), 7.51 (d, $J=8.24$ Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta=13.66$, 22.21, 28.91, 29.06, 29.15, 31.08, 31.44, 35.09, 55.81, 113.60, 126.04, 127.45, 128.27, 133.23, 137.61, 140.95, 158.36. Anal. calcd for $C_{23}H_{32}O$: C, 85.13; H, 9.94. Found: C, 85.25; H, 9.90.

4.6. 4′-Decyl-4-hydroxybiphenyl, 9

A solution of BBr_3 (6 mL, 6 mmol, 1 M in CH_2Cl_2) was added carefully, through the condenser, to a stirred solution of **8** (1.8 g, 5.5 mmol) in CH_2Cl_2 (12 mL) at −80°C. The reaction mixture was allowed to attain room temperature overnight with stirring. The mixture was then hydrolysed by the careful addition of H_2O (20 mL), thus precipitating a colourless solid, which was dissolved by addition of Et_2O (40 mL). The organic layer was separated and the aqueous solution was extracted with Et_2O (2×15 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4) filtered and concentrated under reduced pressure. The crude product was purified by crystallisation from EtOH affording compound **9** (1.54 g, 91%); mp 137–138°C IR (KBr): 3500–3300, 2920, 2840, 1610, 1600, 1260, 810 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.88$ (t, $J=5.7$ Hz, 3H), 1.27–1.31 (m, 14H), 1.59–1.66 (m, 2H), 2.62 (t, $J=7.6$ Hz, 2H), 4.80 (s, 1H), 6.88 (d, $J=8.5$ Hz, 2H), 7.24 (d, $J=6.3$ Hz, 2H), 7.43–7.48 (m, 4H). ^{13}C NMR ($CDCl_3$): $\delta=14.00$, 22.57, 29.17, 29.29, 29.39, 31.43, 31.80, 35.47, 115.46, 126.42, 128.08, 128.66, 133.87, 137.96, 141.42, 154.68. Anal. calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 85.35; H, 9.69.

4.7. 4-(Tetrahydro-2*H*-pyran-2′-yloxy)benzoic acid, 10

A solution of *p*-hydroxybenzoic acid (2.0 g, 14.5 mmol), DHP (6.6 mL, 72.4 mmol) and catalytic amount of *p*-TsOH in anhydrous THF (10 mL) was stirred under Ar for 5 h at rt. Triethylamine (2 mL) was added and the solvent was evaporated. The oily residue was dissolved in acetone (20 mL) and NaOH (1 M, 20 mL) was added. After stirring overnight, acetone was evaporated, H_2O (10 mL) was added and the alkaline

solution was extracted with CH_2Cl_2 (3×15 mL). To the remaining aqueous solution CH_2Cl_2 (20 mL) followed by $NaHSO_4$ (1 M, 10 mL) were added with vigorous stirring. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated under vacuum affording compound **10** (2.79 g, 87%; 99% purity by HPLC). The product was used in the subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 1.60$–2.06 (m, 6H), 3.62–3.66 (m, 1H), 3.83–3.91 (m, 1H), 5.55 (t, $J = 2.74$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 2H), 8.07 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 18.36$, 24.91, 29.96, 61.94, 95.91, 115.81, 132.09, 132.52, 161.42, 171.79.

4.8. (4′-Decylbiphenyl-4-yl)-4-hydroxybenzoate, 11

A solution of **9** (380 mg, 1.22 mmol), **10** (544 mg, 2.45 mmol), DCC (530 mg, 2.57 mmol) and a catalytic amount of DMAP in anhydrous THF (20 mL) was stirred under Ar for 48 h at rt. The reaction mixture was filtered and the solvent removed under reduced pressure. The remaining solid was dissolved in wet acetone (10 mL) and a catalytic amount of PPTS was added. The reaction mixture was heated under reflux for 5 h. After cooling, the precipitate was collected by filtration and washed with cold acetone (5 mL). Crystallisation from EtOH gave the pure phenol **11** (390 mg, 74%), mp 200–201°C. IR (KBr): 3480–3300, 2954, 1726, 1610, 1265, 1248, 960 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 0.91$ (t, $J = 6.0$ Hz, 3H), 1.11–1.36 (m, 14H), 1.68 (m, 2H), 2.67 (t, $J = 7.1$ Hz, 2H), 5.8 (s, 1H), 6.91 (d, $J = 8.52$ Hz, 2H), 7.26–7.28 (m, 4H), 7.51 (d, $J = 7.9$ Hz, 2H), 7.63 (d, $J = 8.5$ Hz, 2H), 8.13 (d, $J = 8.5$ Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 13.94$, 22.57, 29.30, 29.44, 29.54, 31.31, 31.83, 35.55, 67.16, 115.39, 121.83, 122.34, 126.88, 127.88, 128.76, 132.53, 137.73, 138.91, 142.14, 150.26, 160.35, 164.84. Anal. calcd for $C_{29}H_{34}O_3$: C, 80.89; H, 7.96. Found: C, 81.12; H, 8.06.

4.9. [(4′-Decylbiphenoxycarbonyl)phenyl-4-yl]-2-(4-decyloxyphenyl)-2-(tetrahydro-2*H*-pyran-2-yloxy)acetate, 12

A solution of (+)-**5** (80 mg, 1.26 mmol), DHP (0.5 mL, 5.7 mmol) and a catalytic amount of *p*-TsOH in anhydrous THF (6 mL) was stirred under Ar for 2 h at rt. Triethylamine (0.3 mL) was added and the solvent was evaporated. The oily residue was dissolved in acetone (6 mL) and NaOH (1 M, 2.2 mL) was added. After stirring for 3 h, the acetone was evaporated, H_2O (6 mL) was added and the alkaline solution was extracted with CH_2Cl_2 (3×10 mL). To the remaining aqueous solution CH_2Cl_2 (10 mL) followed by $NaHSO_4$ (1 M, 5 mL) were added with vigorous stirring. The organic layer was separated and the aqueous solution extracted with CH_2Cl_2 (3×10 mL). The combined extracts were dried over Na_2SO_4, filtered and the solvent evaporated under vacuum. The oily residue so obtained was dissolved in anhydrous THF (10 mL) and DCC (0.5 g, 2.43 mmol), a catalytic amount of DMAP and phenol **11** (50 mg, 0.11 mmol) were added. The reaction mixture was stirred overnight under argon at rt. Filtration and removal of the solvent gave a mixture of diastereomers (58 mg, 65%) as a viscous oil, which was used in the subsequent reactions without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 0.80$–1.95 (m, 88H), 2.65 (t, $J = 7.6$ Hz, 4H), 3.56–3.59 (m, 2H), 3.75–3.80 (m, 2H), 3.95–4.05 (m, 4H), 4.69–4.70 (m, 1H), 5.02 (m, 1H), 5.40 (s, 1H), 5.53 (s, 1H), 6.94–6.98 (m, 4H), 7.15–7.20 (m, 4H), 7.23–7.29 (m, 8H), 7.48–7.55 (m, 8H), 7.61–7.65 (m, 4H), 8.20–8.24 (m, 4H).

4.10. (+)-[(4′-Decylbiphenoxycarbonyl)phenil-4-yl]-2-(4-decyloxyphenyl)-2-hydroxyacetate (+)-1

A solution of **12** (58 mg, 0.07 mmol) and a catalytic amount of PPTS in wet acetone (10 mL) was heated under reflux for 2 h. After cooling, the solvent was removed and the residue purified by column chromatography (silica gel; hexane–MTBE–CH_2Cl_2, 5:1:1) followed by crystallisation from hexane affording (+)-**1** (30 mg, >99% ee, 46%) as a colourless solid mp 123–124°C; $[\alpha]_D^{25} = +65$ (*c* 0.67, $CHCl_3$). IR (KBr): 3500–3350, 2962, 1731, 1289, 1250, 1083, 804 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta = 0.88$ (t, $J = 6.9$ Hz, 6H), 1.26–1.84 (m, 32H), 2.64 (t, $J = 7.6$ Hz, 2H), 3.97 (t, $J = 6.5$ Hz, 2H), 5.41 (d, $J = 5.6$ Hz, 1H), 6.96 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.8$ Hz, 2H), 7.15–7.32 (m, 4H), 7.44 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 8.2$ Hz, 2H), 7.62 (d, $J = 8.6$ Hz, 2H), 8.23 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta = 14.02$, 22.58, 25.95, 29.14, 29.24, 29.29, 29.48, 31.39, 31.80, 35.51, 68.04, 72.78, 114.81, 121.33, 121.71, 126.86, 127.50, 127.94, 128.78, 129.26, 131.79, 137.53, 142.21, 149.85, 154.28, 171.88. Anal. calcd for $C_{47}H_{60}O_6$: C, 78.30; H, 8.39. Found: C, 78.40; H, 8.41.

4.11. Dodecyl-2-(4-benzyloxyphenyl)-2-(tetrahydro-2*H*-pyran-2-yloxy)acetate, 13

The title compound was obtained from (+)-**6** (1.00 g, 3.87 mmol) and 1-dodecanol (0.66 g, 3.57 mmol) according to the procedure described for the preparation of **12**. the crude product was separated by flash column chromatography (silica gel; hexane–MTBE–CH_2Cl_2, 5:1:1). The mixture of diastereomers obtained (1.23 g, 67%) was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 0.82$–0.95 (m, 6H), 1.20–1.98 (m, 52H), 3.46–3.56 (m, 2H), 3.68–3.80 (m, 2H), 4.09–4.15 (m, 4H), 4.57–4.62 (m, 1H), 4.86–4.90 (m, 1H), 5.07 (s, 4H), 5.18 (s, 1H), 5.28 (s, 1H), 6.97 (d, $J = 8.8$ Hz, 4H), 7.34–7.43 (m, 14H).

4.12. Dodecyl-2-(4-hydroxyphenyl)-2-(tetrahydro-2*H*-pyran-2-yloxy)acetate, 14

A suspension containing **13** (1.22 g, 2.38 mmol), Pd/C (0.2 g, 10%) and cyclohexene (8 mL) in EtOH (15 mL) was heated under reflux for 4 h. Filtration and removal of the solvent gave the crude product which was purified by flash column chromatography (silica gel; hexane–MTBE–CH_2Cl_2, 5:1:1). The mixture of diastereomers obtained (0.5 g, 50%) was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): $\delta = 0.87$–0.92 (m, 6H), 1.24–1.93 (m, 52H), 3.46–3.65 (m, 2H), 3.71–3.82 (m, 2H), 4.05–4.22 (m, 4H), 4.57–4.62 (m, 1H), 4.83–4.89 (m, 1H), 5.11 (s, 1H), 5.26 (s, 1H), 6.80–6.84 (m, 4H), 7.31–7.38 (m, 4H).

4.13. (+)-Dodecyl-2-(4′-dodecyloxybiphenyl-4-carboxy)-phenyl-2-hydroxyacetate, (+)-2

The title compound was obtained from 4-dodecyloxybiphenyl carboxylic acid (91 mg, 0.24 mmol) and **14** (100 mg, 0.24 mmol) according to the procedure described for the preparation of **11**. The crude product was purified by column chromatography (silica gel; CH_2Cl_2) affording (+)-**2** (92 mg, 99% ee, 55%) as white solid, mp 108–109°C; $[\alpha]_D^{25}=+31$ (c 1.0, CH_2Cl_2). IR (KBr): 2956, 2919, 1733, 1601, 1273, 1193, 828 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.88$ (t, $J=6.4$ Hz, 6H), 1.24–1.27 (m, 38H), 1.77–1.86 (m, 2H), 4.01 (t, $J=6.5$ Hz, 2H), 4.06–4.19 (m, 2H), 5.21 (s, 1H), 6.99 (d, $J=8.6$ Hz, 2H), 7.25 (m, 2H), 7.57–7.60 (m, 4H), 7.69 (d, $J=8.3$ Hz, 2H), 8.23 (d, $J=8.3$ Hz, 2H). ^{13}C NMR ($CDCl_3$): $\delta=14.01$, 22.58, 25.54, 25.93, 28.29, 28.99, 29.13, 29.24, 29.53, 31.80, 66.43, 68.05, 72.20, 114.87, 121.72, 126.48, 127.22, 127.55, 128.26, 129.97, 130.60, 131.80, 135.80, 135.83, 145.95, 150.90, 159.50, 173.48. Anal. calcd for $C_{45}H_{64}O_6$: C, 77.10; H, 9.20. Found: C, 76.89; H, 9.08.

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