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Synthesis and CD spectroscopy of polyethers with homochiral and heterochiral layers of stereocentres

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ABSTRACT

Eight polyethers with three to nine stereocentres have been synthesised using chiral base methodology. Examination of the polyethers by CD spectroscopy revealed clear differences between homochiral isomers and isomers with a heterochiral relationship between an 'inner' layer of stereocentres and an 'outer' layer of stereocentres. A hypothesis to account for these differences has been advanced.

1. Introduction

A good understanding of how individual components of a large molecular structure can be used to create and control its properties is desirable, because it would facilitate more informed manipulation and exploitation of macromolecules and supramolecular structures in applications such as catalysis, drug delivery, molecular recognition and light emitting and light harvesting processes.[1–5] Dendritic-type molecules have for some time been considered good models for disordered and semi-ordered structures such as polymers, aggregates, clusters and liquid crystals, and they are now starting to find applications of their own. For example, Dendritic nanotechnologies have recently encapsulated both cisplatin and carboplatin anticancer drugs in the voids of polyamidoamine dendrimers.[6] The dendrimer-drug conjugates are active against aggressive tumour models, are water-soluble and have lower toxicity and greater stability on storage than the unbound drugs.

Introduction of chirality into dendrimers increases their potential structural diversity and future applications still further. A wide range of dendritic structures has been explored in order to probe the relationship between the chirality of the individual elements and the properties of the global structure of the macromolecule.[7,8] These include dendrimers with a chiral core and achiral branches, dendrimers with chiral peripheral surface groups and dendrimers with chiral branching units.

Comparisons of dendritic molecules with a homochiral and heterochiral relationship between layers, however, are rare. In one example, Chow prepared a series of homochiral and heterochiral layered tartrate-derived dendrimers including isomers **1** and **2** (Fig. 1), and compared them using CD spectroscopy.[9,10] It was found that the chiroptical effect of an L-chiral unit in the outer shell did not exactly eliminate the effect of a D-chiral unit in the inner shell, and it was concluded that the outer chiral layer was chiroptically slightly different from the inner layer.

Later, Lellek examined the structural features of homochiral dendrimer **3** and a heterochiral isomer **4** (Fig. 2), based on (*R*)- and (*S*)-2,2′-dimethoxy-1,1′-binaphthalene building blocks.[11] Differences between the homochiral and heterochiral isomers observed in CD and NMR studies were explained by suggesting that the N–H groups of the amides in the homochiral isomer form hydrogen bonds that change the position of its conformational equilibria relative to that of the heterochiral isomer.

We describe herein the synthesis of eight novel polyethers with different relationships between the chirality at the centre of the molecule (inner chirality) and at the edge (outer chirality). An investigation of the eight molecules by CD spectroscopy has revealed that the homochiral and heterochiral isomers have significantly different spectroscopic properties, and a hypothesis to account for these differences is advanced. The synthesis of the four isomers of **16** (Schemes 2 and 4) and a brief discussion of their CD spectra have been reported in a preliminary communication.[12]

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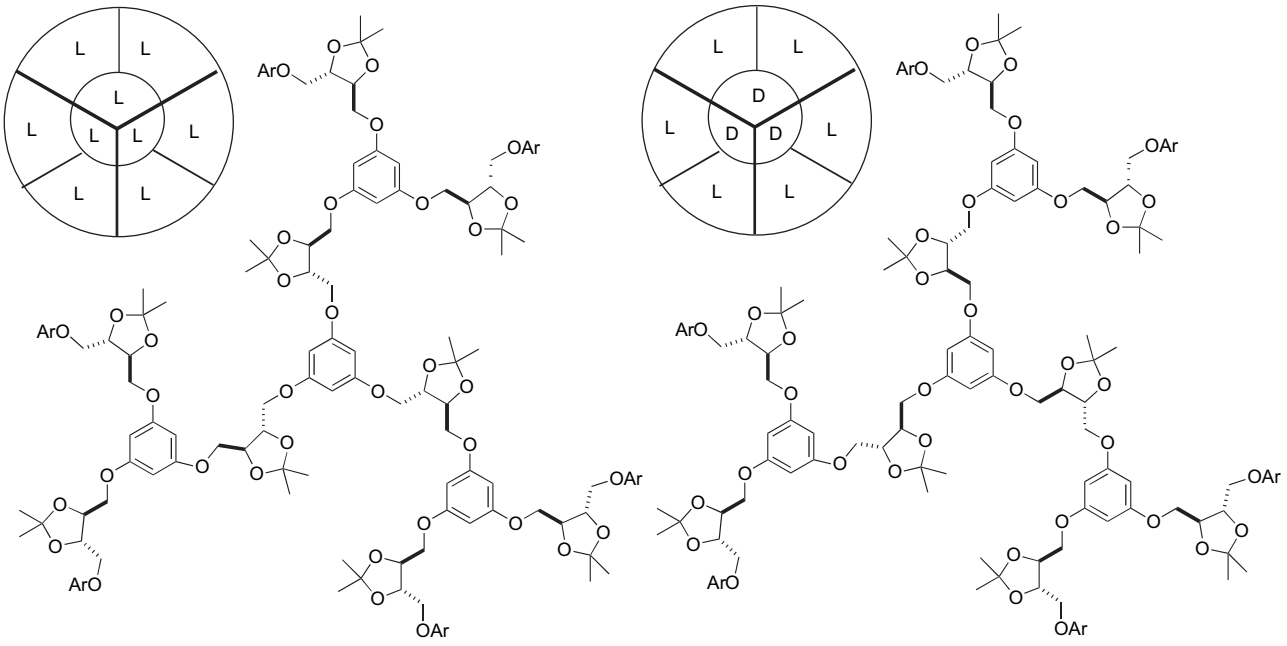


Figure 1. Homo- and heterochiral dendrimers derived from tartaric acid.

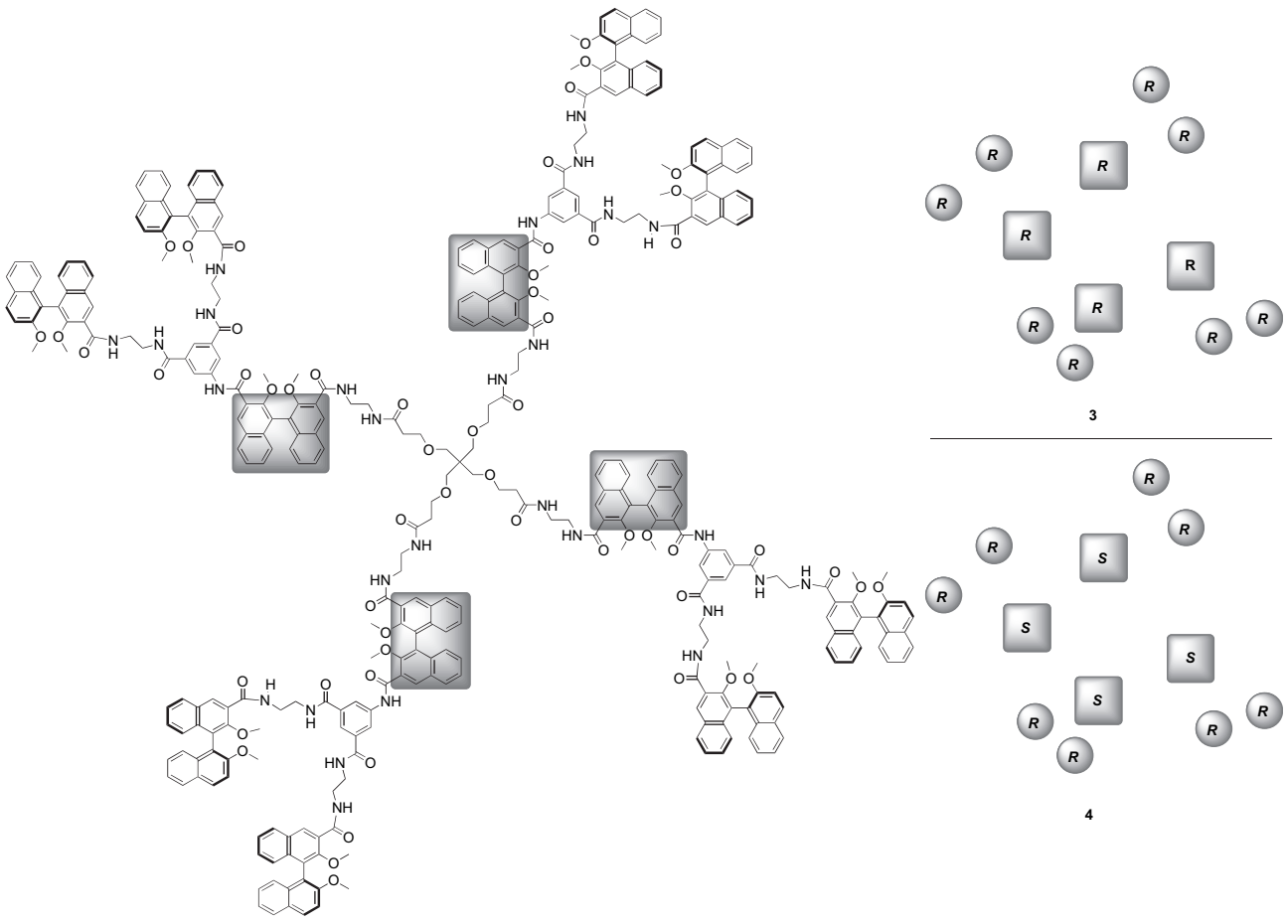
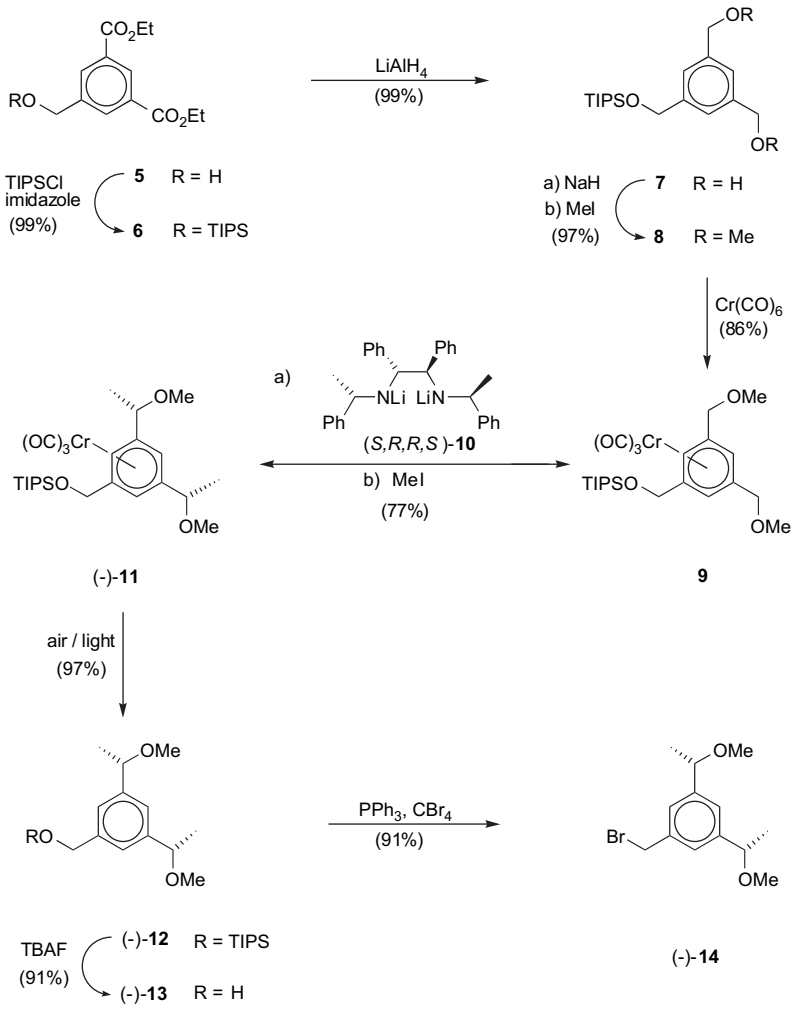


Figure 2. Homo- and heterochiral dendrimers with axially chiral units.



Scheme 1. Synthesis of the electrophile (−)-**14**.

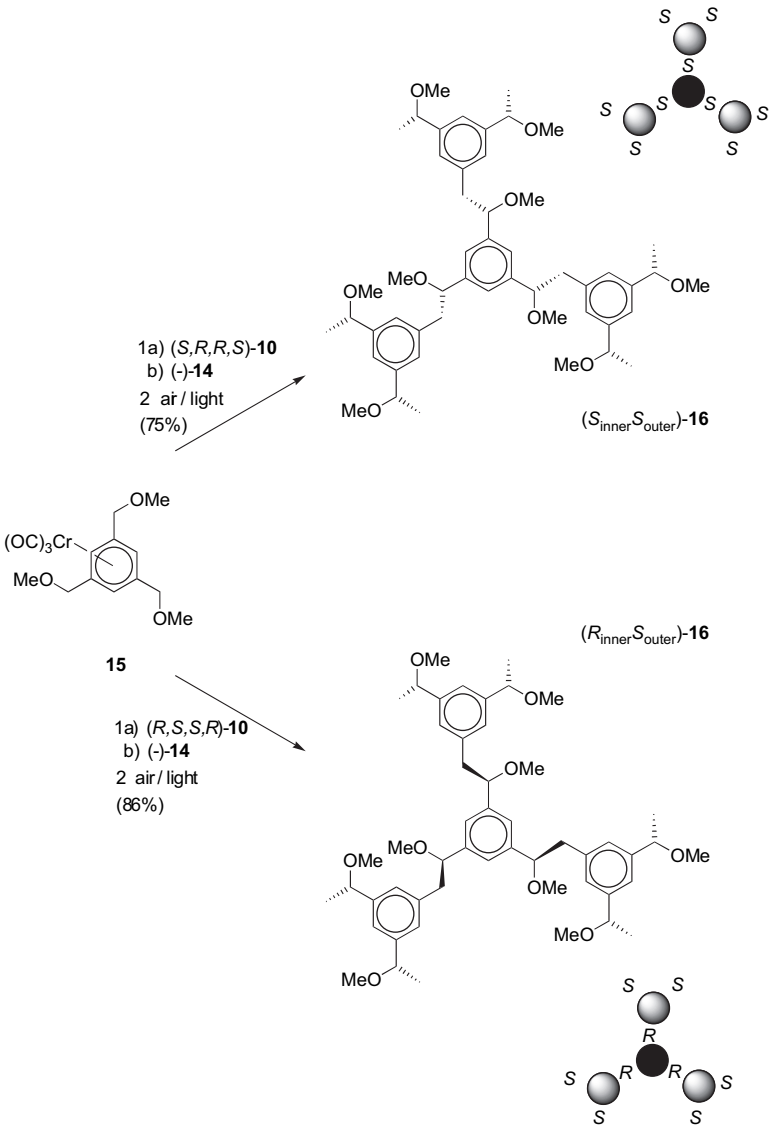
2. Results and discussion

2.1. Synthesis

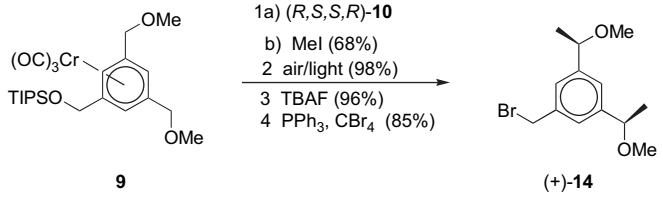
Our previous work on the use of chiral base chemistry to create multiple stereocentres around an aromatic core with high levels of stereochemical control,[13,14] led us to predict that asymmetric functionalisation of tris ether **15** (Scheme 2) with bromide (−)-**14** (Scheme 1) would lead to the homochiral polyether ($S_{inner}S_{outer}$)-**16** using chiral base (*S*,*R*,*R*,*S*)-**10**, and the heterochiral polyether ($R_{inner}S_{outer}$)-**16** using chiral base (*R*,*S*,*S*,*R*)-**10** (Scheme 2). The synthesis of the required bromide (−)-**14** is depicted in Scheme 1. Initially, the hydroxyl group of commercially available diethyl 5-(hydroxymethyl)isophthalate **5** was protected as the corresponding triisopropylsilyl ether **6** in quantitative yield. This protecting group was chosen due to its reported stability to a range of reducing agents, as well as sodium hydride.[15] The two ethyl ester groups were subsequently reduced in the presence of the protected alcohol with lithium aluminium hydride to give diol **7** as a white solid, which was then converted into the diether **8**. As chromium(0) is known to insert into benzylic halide bonds even under mild conditions,[16] it was decided to form the chromium complex **9** prior to converting the silyl ether into a bromide. The complexation proceeded smoothly to give **9**, after which the two stereogenic centres required at the periphery of target molecules **16** were installed in 100% de and 90% ee by deprotonation of **9** with 1.5 equiv of the chiral base (*S*,*R*,*R*,*S*)-**10** followed by an iodomethane quench. Air and light promoted oxidative removal of the tricarbonylchromium(0) unit from (−)-**11** gave (−)-**12** in excellent yield, leaving only the conversion of the triisopropyl ether into a bromide necessary to access the desired electrophile (−)-**14**. Initially the conversion from (−)-**12** to (−)-**14** was attempted using a one-pot deprotection/bromination procedure employing triphenylphosphine dibromide,[17] but this proved unsuccessful and a two step protocol was adopted. Conversion of functionalised benzyl alcohols to bromides is frequently achieved using triphenylphosphine and bromide. In particular, Seebach reported this reaction in the presence of benzyl ether groups and several other sensitive functionalities.[18] Thus the TIPS ether (−)-**12** was deprotected to reveal the benzyl alcohol (−)-**13** by treatment with tetrabutylammonium fluoride. Bromination of the benzylic alcohol proceeded smoothly using the Seebach procedure to give the desired electrophile (−)-**14**.

The readily available tricarbonylchromium(0) complex **15**[13,14] was deprotonated with 3 equiv of chiral base (*S*,*R*,*R*,*S*)- or (*R*,*S*,*S*,*R*)-**10**, and bromide (−)-**14** was added. After purification by column chromatography, removal of the chromium(0) moiety by decomplexation in the presence of air and sunlight afforded the desired homochiral and heterochiral isomers ($S_{inner}S_{outer}$)-**16** and ($R_{inner}S_{outer}$)-**16** (Scheme 2).

It was considered prudent at this stage of the project to synthesise the enantiomers of ($S_{inner}S_{outer}$)- and ($R_{inner}S_{outer}$)-**16** in order to ascertain that these did indeed give the expected equal and opposite CD traces. Accordingly, the bromide electrophile (+)-**14** was synthesised from chromium complex **9** (Scheme 3) and this

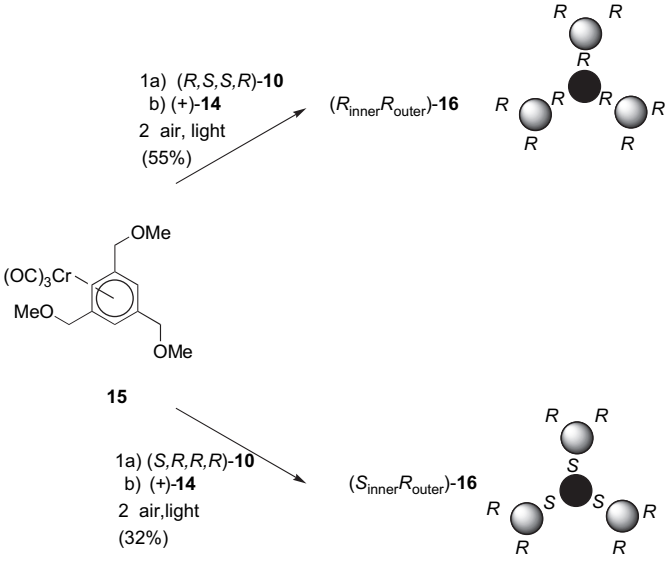


Scheme 2. Synthesis of ($S_{inner}S_{outer}$)- and ($R_{inner}S_{outer}$)-**16**.



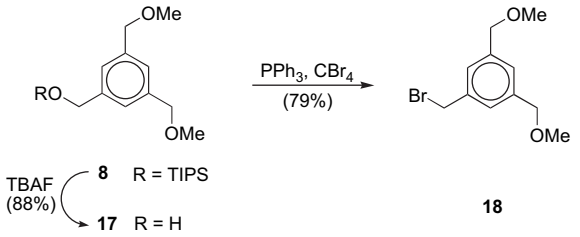
Scheme 3. Synthesis of the electrophile (+)-**14**.

was used with the two enantiomers of the chiral base to produce polyethers ($R_{inner}R_{outer}$)- and ($S_{inner}R_{outer}$)-**16** (Scheme 4) [the difference in yields probably reflects the smaller scale used for the reaction that gives ($S_{inner}R_{outer}$)-**16**]. The four stereoisomers of **16** were characterised by mp, IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis. It is worthy of note at this point that the ^{13}C NMR spectra of the diastereoisomers of **16** were very similar in $CDCl_3$, and that the ^{1}H NMR spectra of the two diastereoisomers were very similar to each other in $CDCl_3$, benzene and acetonitrile at room temperature, and in methanol over the range 183–333 K.



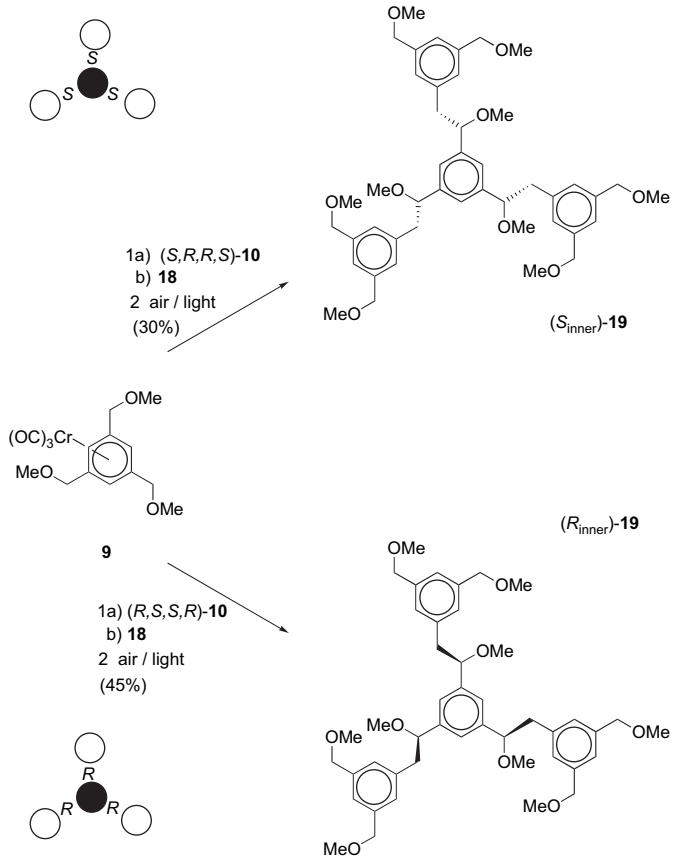
Scheme 4. Synthesis of ($R_{inner}R_{outer}$)- and ($S_{inner}R_{outer}$)-**16**.

In order to investigate the effect of removing the peripheral chiral centres from polyethers **16**, as monitored by CD spectroscopy, molecules (S_{inner})-**19** and (R_{inner})-**19** (Scheme 6) were synthesised next. Their synthesis required an achiral electrophile, which was readily obtained by removal of the silyl protecting group from **8** to give monoalcohol **17**, followed by bromination to give benzyl bromide **18** (Scheme 5).



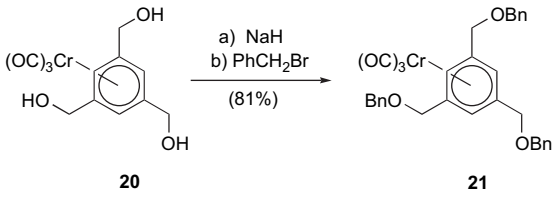
Scheme 5. Synthesis of achiral electrophile **18**.

Reaction of core molecule **9** with each enantiomer of the chiral base **10** followed by quenching with electrophile **18** gave (S_{inner})-**19** and (R_{inner})-**19** as required (Scheme 6).



Scheme 6. Synthesis of (S_{inner})-**19** and (R_{inner})-**19**.

In order to probe the effect of introducing greater steric bulk into what appeared to be cavities in molecules **16**, and at the same time enhance the opportunities for aromatic–aromatic interactions, it was decided to study molecules ($S_{inner}R_{outer}$)- and ($R_{inner}R_{outer}$)-**22** (Scheme 8) in which the core methyl ethers have been replaced with benzyl ethers. Their synthesis required the tris benzyl ether **21**, which was duly synthesised from the readily available tricarbonyl[1,3,5-tris(hydroxymethyl)benzene]chromium(0) **20**[19] by a multiple deprotonation using sodium hydride followed by quenching with benzyl bromide (Scheme 7).



Scheme 7. Synthesis of the benzyl ether core **21**.

Reaction of the new core with each of the enantiomers of the chiral base **10** followed by quenching with the chiral electrophile (+)-**14** gave the target molecules ($S_{inner}R_{outer}$)- and ($R_{inner}R_{outer}$)-**22** (Scheme 8).

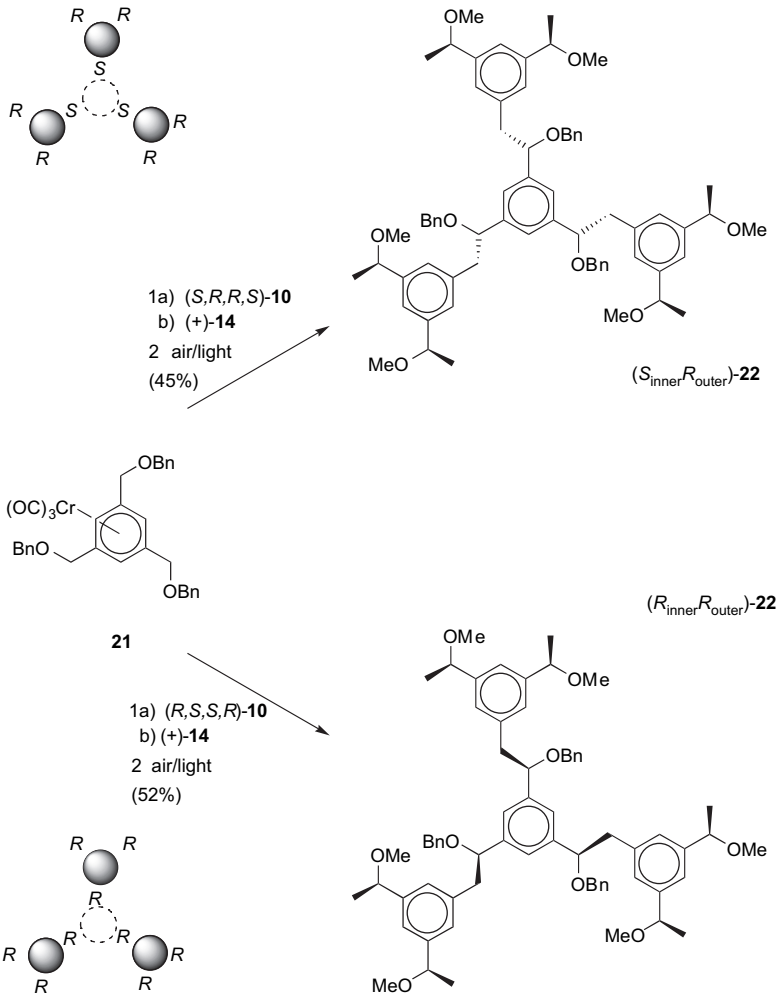
2.2. CD spectroscopy

As the isomers of **16** had given very similar NMR spectra in a range of solvents, it was decided to examine them using the relatively fast CD timescale to see if differences between the isomers emerged. The UV and CD spectra of the four stereoisomers ($R_{inner}R_{outer}$)-**16**, ($S_{inner}S_{outer}$)-**16**, ($R_{inner}S_{outer}$)-**16** and ($S_{inner}R_{outer}$)-**16** are illustrated in Figure 3.

All four isomers gave rise to identical UV spectra in which the classical aryl chromophore was observed with the ^1L_b transition at 260 nm, the ^1L_a at 215 nm, and the degenerate ^1E_a and ^1E_b transitions around 200 nm (Fig. 3, upper chart). The CD spectra differed, however, particularly in the ^1L_b region (Fig. 3, lower chart, 230–280 nm). The CD in the ^1L_b region is sensitive to the freedom of rotation around the long axis of the aryl ring as this transition is polarised across the short axis (see Fig. 4 for the definitions of short and long axes). Thus the modest magnitude of the CD at 260–275 nm observed for the heterochiral isomers ($R_{inner}S_{outer}$)-**16** and ($S_{inner}R_{outer}$)-**16** is typical of an aryl group free to rotate or rock about its long axis. The magnitude of the CD observed for the homochiral isomers ($R_{inner}R_{outer}$)-**16** and ($S_{inner}S_{outer}$)-**16** in this region, however, is exceptionally large (>10 times the magnitude generally observed for aryl groups in chiral environments[20]), suggesting that rotation about the long axis is severely restricted in these isomers.

Figure 4 defines the electronic transition dipole moments of the peripheral aryl groups in ($S_{inner}S_{outer}$)-**16**. The solid arrow indicates the dipole moment associated with the ^1L_a and ^1E_b bands, which are found at lower wavelength (180–230 nm) in the chart in Figure 3. A basic premise of exciton coupling theory is that two electronic transition dipoles, which ideally are degenerate, couple to produce a bisignate feature with a longer wavelength (lower energy) CD sign that effectively defines the chirality of the two interacting moments. Accordingly the bisignate couplet, which changes sign at 198 nm for the heterochiral isomers and 203 nm for the homochiral isomers (Fig. 3) is interpreted as a signature of a 'helical' arrangement of the three pendant aryl groups in all four isomers. Inspection of the four spectra illustrated in Figure 3 reveals that the helices formed by the pendant chromophores are dependent on the chirality of the core template (the inner chirality) and not the chirality of the peripheral groupings (the outer chirality).

The UV and CD spectra of the enantiomeric pair of molecules lacking chirality at their periphery [(R_{inner})-**19**] and (S_{inner})-**19**] are illustrated in Figure 5. The presence of the bisignate feature of the CD spectra at lower wavelength is indicative of helical structure once again, and comparison with the spectra of the isomers of **19** in Figure 3 reveals that in **16** and **19** the *S* core leads to the same handedness manifested by signals that go from negative to positive with increasing wavelength. Interestingly the higher wavelength bands of **19** are intermediate in intensity between those observed for the isomers of **16**.



Scheme 8. Synthesis of ($S_{inner}R_{outer}$)- and ($R_{inner}R_{outer}$)-**22**.

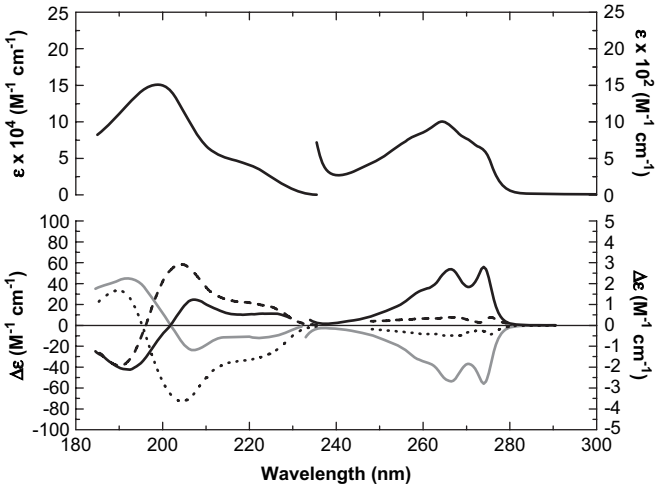


Figure 3. The UV spectra of **16** (upper chart) and the CD spectra of ($R_{inner}R_{outer}$)-**16** (—), ($S_{inner}S_{outer}$)-**16** (▬), ($R_{inner}S_{outer}$)-**16** (···) and ($S_{inner}R_{outer}$)-**16** (--) (lower chart). (NB: The LH *y* axes correspond to the *x* axis range 180–230 nm and the RH *y* axes correspond to the *x* axis range 230–300 nm.)

The UV and CD spectra of the diastereoisomeric pair of molecules **22**, which have benzyl ethers rather than methyl ethers associated with their inner chiral centres are shown in Figure 6. Once again the bisignate feature is observed at lower wavelength in the CD spectra, and once again the handedness of the helix is governed by the inner chiral centres. The higher wavelength features of the CD spectra are remarkably similar to those observed for the methyl ether diastereoisomers (Fig. 3), suggesting that the secondary structures defined by the CD spectra are very similar despite the significant difference between their inner ether groups.

Although it is clear from the above discussion that the homochiral and heterochiral isomers of **16** and **22** present significantly different CD spectra, a closer examination of the spectra of **16** revealed a further difference. Inspection of the spectra depicted in Figure 4 revealed that although the UV absorption spectra of the homo- and heterochiral compounds are virtually superimposable, the vibronic structures in the CD spectra are notably different. The first CD component in the heterochiral stereoisomers is at 275.5 nm (36,297 cm^{-1}), whilst the first feature in the homochiral stereoisomer is at 273.8 nm (36,521 cm^{-1}) (Fig. 7). This difference (224 cm^{-1}) implies that the homochiral stereoisomer CD is based upon a false vibronic origin and confirms that the origin of the optical activity is different for the homo- and heterochiral isomers.

Finally, a variable temperature study of the homochiral isomer ($S_{inner}S_{outer}$)-**16** and heterochiral isomer ($R_{inner}S_{outer}$)-**16** was performed using a 5:2:5 (v/v/v) mixture of ether, ethanol and isopentane as the solvent. The spectrum of the homochiral isomer ($S_{inner}S_{outer}$)-**16** remained essentially unchanged throughout (Fig. 8, charts A and B). In contrast the heterochiral isomer ($R_{inner}S_{outer}$)-**16** showed dramatic changes at around −130 °C, associated with aggregation (Fig. 8, charts C and D). The UV became severely distorted

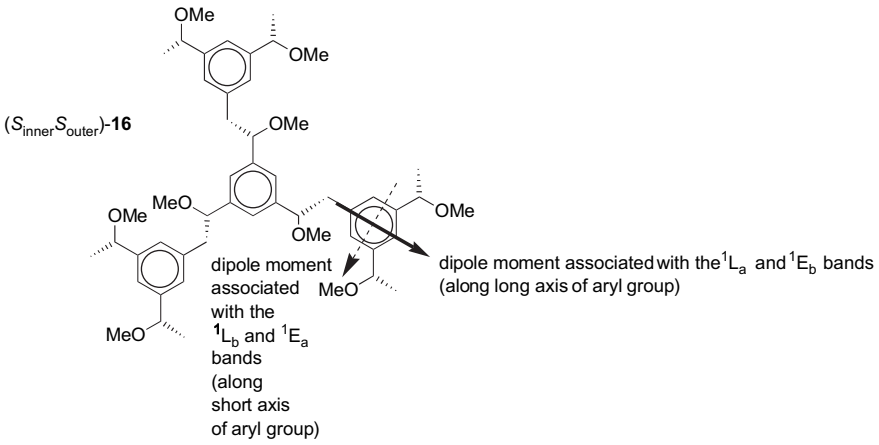


Figure 4. Relationship between UV and CD bands and dipole moments of ($S_{inner}S_{outer}$)-**16**.

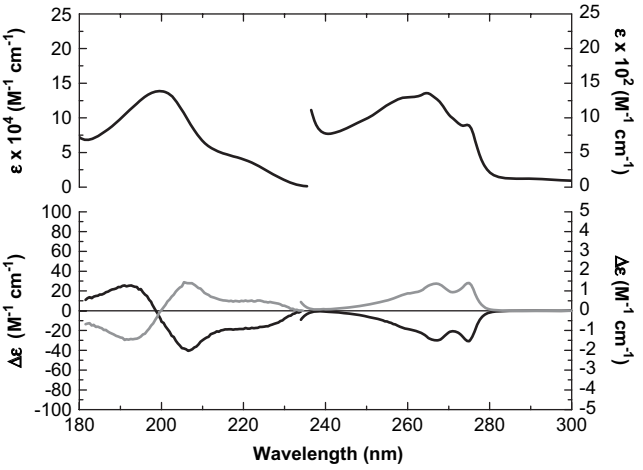


Figure 5. The UV spectra of **19** (upper chart) and the CD spectra of (R_{inner})-**19** (—), (S_{inner})-**19** (—) (lower chart).

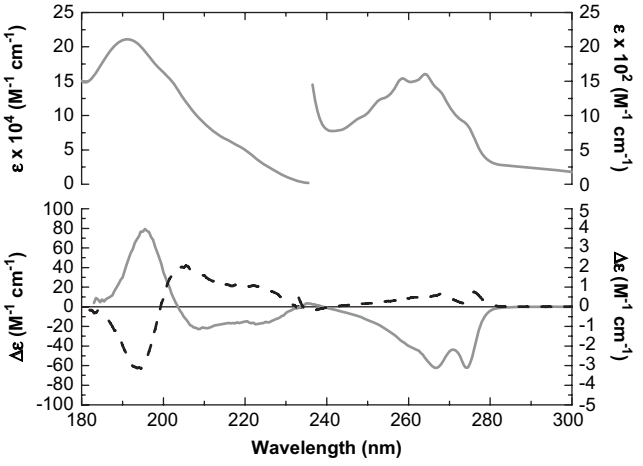


Figure 6. The UV spectra of **22** (upper chart) and the CD spectra of ($R_{inner}R_{outer}$)-**22** (—) and ($S_{inner}R_{outer}$)-**22** (--) (lower chart).

and the CD spectrum showed an enhanced signal at 240–275 nm and a significant negative feature at 325 nm. The latter is typical of a chiral supramolecular structure of the sort normally associated with condensed nucleic acids.[21]

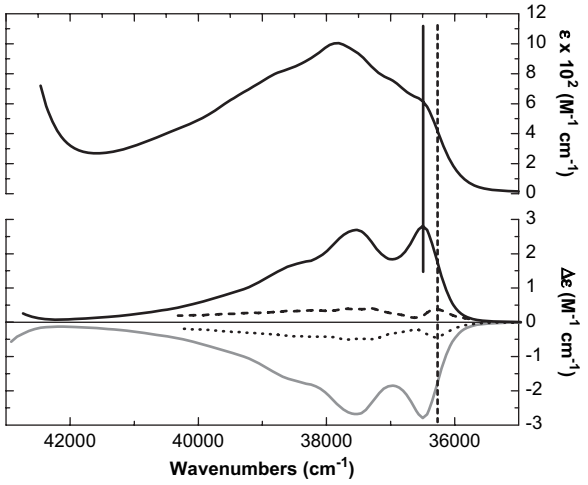


Figure 7. UV spectra of **16** (upper chart) and the CD spectra of ($R_{inner}R_{outer}$)-**16** (—), ($S_{inner}S_{outer}$)-**16** (—), ($R_{inner}S_{outer}$)-**16** (···) and ($S_{inner}R_{outer}$)-**16** (--) (lower chart) with the *x* axis in cm^{-1}.

3. Conclusion

Chiral base chemistry has been used to construct dendritic-type molecules with control over two layers of stereocentres. Although the NMR spectra of molecules with homochiral layers and heterochiral layers were very similar, their CD spectra revealed several significant differences. For example the CD spectra in the range 240–280 nm gave much higher $\Delta\varepsilon$ values for the homochiral isomers than the heterochiral isomers (Figs. 3 and 6) suggesting that the aryl rings of the homochiral isomers are more restricted than the aryl rings of the heterochiral isomers in their movement about their long axis. Closer examination of this area of the spectrum revealed that the vibronic structures in the CD spectra were notably different (Fig. 7). Moreover, the behaviour of homochiral and heterochiral isomers on cooling was significantly different (Fig. 8) with the heterochiral isomer displaying behaviour typical of a chiral supramolecular structure at temperatures around −130 °C.

The CD spectra of all the isomers of **16**, **19** and **22** also presented clear evidence for a helical arrangement of aryls, the handedness of which was controlled by the inner layer of stereocentres. Moreover, a comparison of Figures 3 and 6 depicting the spectra of isomers of **16** and **22** suggested that the substitution of the inner methyl ethers with benzyl ethers had essentially no effect on the CD behaviour of the molecules.

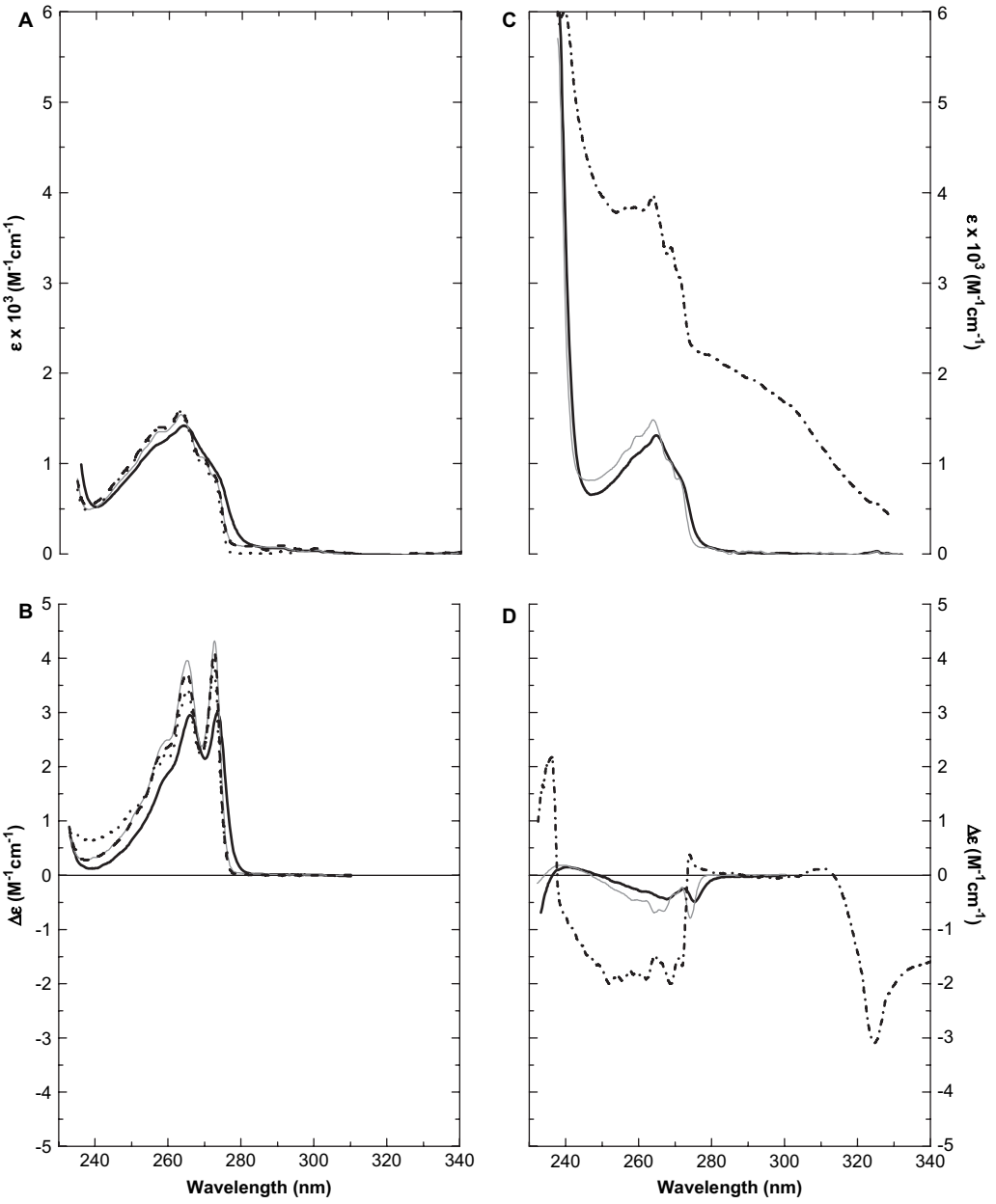


Figure 8. The UV spectra of ($S_{inner}S_{outer}$)-**16** (chart A) and the CD spectra of ($S_{inner}S_{outer}$)-**16** (chart B) at 20 °C (–), −100 °C (–), −120 °C (– –), and −137 °C (· · ·), and the UV spectra of ($R_{inner}S_{outer}$)-**16** (chart C) and the CD spectra of ($R_{inner}S_{outer}$)-**16** (chart D) at 20 °C (–), −100 °C (–), and −130 °C (· —· —).

A working hypothesis for the observations described above is proposed as follows. In order for the relationship of the two layers of stereocentres to have a significant effect on the conformational equilibria of the molecules, it is most likely that the molecules adopt condensed rather than extended conformations. It is postulated that the molecule is drawn into condensed conformations such as the one shown in Figure 9 by favourable aromatic–aromatic interactions.[22] It is postulated that in the homochiral isomer the balance between energy lowering aromatic–aromatic interactions and energy raising steric interactions between the atoms around the outer chiral centres favours tighter conformations, whilst in the heterochiral molecules the steric interactions become more dominant and favour a more relaxed set of conformations that allow more freedom of movement around the long axes of the aromatic rings that make up the helix. It is of note that this picture of the molecules is consistent with the almost identical behaviour of the isomers of the methyl and benzyl ethers **16** and **22** in their CD spectra, as it places these ethers towards the periphery of the molecule rather than within the interior of the structure as suggested by the extended representations used in the description of their synthesis. This working hypothesis will be tested and refined

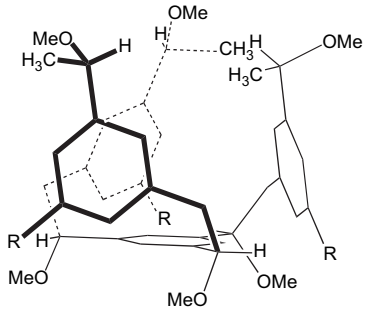


Figure 9. A representation of ($R_{inner}R_{outer}$)-**16**, which would lead to interplay between inner and outer chirality (for clarity one of the $CH(CH_3)OMe$ groups on each of the outer aryl rings has been replaced by R).

in the future by the construction and analysis of molecules bearing functional groups that can be used to rigidify it through, for example, hydrogen bonding.

4. Experimental

4.1. General

All reactions and manipulations involving organometallic compounds were performed under an inert atmosphere of dry nitrogen, using standard vacuum line Schlenk techniques.[23] Flasks were saturated with nitrogen using at least three evacuate/fill cycles. Reactions and operations involving the use of (arene)-tricarbonylchromium(0) complexes were protected from light. THF was distilled over sodium benzophenone and used immediately. DCM was distilled from calcium hydride. Tricarbonyl(1,3,5-trimethoxymethylbenzene)chromium(0) **15**[14] and tricarbonyl(1,3,5-trihydroxymethylbenzene)chromium(0) **20**[19] were prepared according to literature procedures. The concentration of *n*-butyllithium was determined by titration against diphenylacetic acid in THF.[24] All other chemicals were used as purchased from commercial sources. Thin layer chromatography (TLC) was performed on Merck silica gel glass plates 60 (F_{254}), using UV light (254 nm) as visualising agent and/or vanillin or potassium permanganate as developing agents. Flash column chromatography was performed using BDH silica gel (particle size 33–70 μm).

Melting points were recorded on a Sanyo Gallenkamp melting point apparatus in open capillaries and are uncorrected. Optical rotations were recorded on an AA 10 polarimeter from Index Instruments, using a 1 dm path length and concentrations are given as g dL^{-1}. IR spectra were recorded on a Perkin Elmer Spectrum RX FT-IR spectrometer. NMR spectra were recorded at room temperature on Bruker AC 300F, DRX 400, AV 400 or AV 500 instruments in $CDCl_3$, unless otherwise stated. *J* values are reported in hertz and chemical shifts in parts per million. Mass spectra were recorded on Micromass Platform II and Micromass AutoSpec-Q instruments by the mass spectrometry service at Imperial College London. Elemental analyses were performed by the London Metropolitan University microanalytical service.

4.1.1. Diethyl 5-(triisopropylsilyloxymethyl)isophthalate **6**

A solution of diethyl 5-(hydroxymethyl)isophthalate **5** (1.010 g, 4.0 mmol), imidazole (0.545 g, 8.0 mmol, 2.0 equiv) and triisopropylsilyl chloride (0.94 mL, 4.4 mmol, 1.1 equiv) in dry DCM (12 mL) was stirred at rt under an inert atmosphere for 16 h. The reaction mixture was diluted with DCM (20 mL), washed with water (2×15 mL), then brine (20 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The resulting opaque oil was purified by flash column chromatography on silica gel (hexane/EtOAc 99:1 → 95:5) to afford the title compound **6** (1.620 g, 99%) as a colourless oil. R_f=0.42 (SiO_2; hexane/EtOAc 9:1); IR (ν_{max}, DCM): 1724 (C=O), 1237, 1116 (C–O–C ester), 1029 (Si–O–C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.13 (d, *J*=6.6 Hz, 18H; $CH(CH_3)_2$), 1.18–1.25 (m, 3H; $CH(CH_3)_2$), 1.43 (t, *J*=7.2 Hz, 6H; $CO_2CH_2CH_3$), 4.42 (q, *J*=7.2 Hz, 4H; $CO_2CH_2CH_3$), 4.95 (s, 2H; CH_2OSi), 8.26 (s, 2H; $C_{Ar}H$), 8.59 (s, 1H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.0 ($CH(CH_3)_2$), 14.3 (OCH_2CH_3), 18.0 ($CH(CH_3)_2$), 61.3 (OCH_2CH_3), 64.2 (CH_2OSi), 125.4 ($C_{Ar}CO_2Et$), 129.1, 130.9 ($C_{Ar}H$), 142.7 ($C_{Ar}CH_2OSi$), 166.0 (C=O) ppm; MS (FAB$^+$): *m*/*z* (%): 409 (71) [M^++H], 363 (76) [M^+−EtO], 321 (50) [M^+−2EtO], 235 (100) [M^+−2EtO−^{i}Pr]; elemental analysis (%) calcd for $C_{22}H_{36}O_5Si$ (408.60): C 64.67, H 8.88; found: C 64.60, H 8.69.

4.1.2. 1-(Triisopropylsilyloxymethyl)-3,5-dihydroxymethylbenzene **7**

A 50 mL RB flask was charged with lithium aluminium hydride (0.873 g, 23.0 mmol, 2.2 equiv) and placed under vacuum for 20 min. The flask was saturated with nitrogen and dry THF (75 mL) was added. The resulting slurry was cooled to 0 °C and a solution of diethyl 5-(triisopropylsilyloxymethyl)isophthalate **6** (4.27 g, 10.5 mmol) in THF (75 mL) was added via a cannula. Subsequently, the reaction mixture was allowed to reach rt and then stirred at 70 °C for 15 h. After cooling to rt, the suspension was carefully quenched with water (10 mL) and filtered through a pad of Celite®, which was washed with $CHCl_3$ (300 mL). Solvents were removed under reduced pressure to afford the title compound **7** (3.440 g, 99%) as a clear oil, which solidified into a white wax on standing. R_f=0.24 (SiO_2; $CHCl_3$/MeOH 9.5:0.5); mp 53–55 °C; IR (ν_{max}, DCM): 3603 (O–H), 1107 (C–O), 1067 (Si–O–C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.12 (d, *J*=6.6 Hz, 18H; $CH(CH_3)_2$), 1.18–1.23 (m, 3H; $CH(CH_3)_2$), 1.90 (br t, *J*=5.7 Hz, 2H; CH_2OH), 4.71 (br d, *J*=5.7 Hz, 4H; CH_2OH), 4.86 (s, 2H; CH_2OSi), 7.29 (s, 2H; $C_{Ar}H$), 7.30 (s, 1H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.0 (CH), 18.1 (CH_3), 64.8, 65.3 (CH_2), 123.7, 124.0 ($C_{Ar}H$), 141.2, 142.5 (C_{Ar}) ppm; MS (CI): *m*/*z* (%): 342 (100) [M+NH_4^+]; elemental analysis (%) calcd for $C_{18}H_{32}O_3Si$ (324.53): C 66.62, H 9.94; found: C 66.53, H 9.78.

4.1.3. 1-(Triisopropylsilyloxymethyl)-3,5-dimethoxymethylbenzene **8**

To a stirred and cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil) (0.604 g, 15.1 mmol, 2.6 equiv), previously washed with hexane (5 mL), in THF (30 mL), was added a solution of 1-(triisopropylsilyloxymethyl)-3,5-dihydroxymethylbenzene **7** (1.890 g, 5.8 mmol) in THF (10 mL) via a cannula. The reaction mixture was allowed to warm to rt and was then stirred at 70 °C for 75 min. After cooling to rt, iodomethane (1.44 mL, 23.2 mmol, 4.0 equiv) was added in one portion via a syringe. Stirring was continued for 16 h. A saturated aqueous solution of NH_4Cl (10 mL) was added, the organic phase was separated and the aqueous phase extracted with DCM (3×40 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude oil was filtered through a pad of silica gel to afford the title compound **8** (1.990 g, 97%) as a pale yellow oil. R_f=0.48 (SiO_2; hexane/EtOAc 9:1); IR (ν_{max}, DCM): 1105 (C–O–C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.09 (d, *J*=6.6 Hz, 18H; $CH(CH_3)_2$), 1.13–1.22 (br m, 3H; $CH(CH_3)_2$), 3.38 (s, 6H; OCH_3), 4.46 (s, 4H; CH_2OCH_3), 4.84 (s, 2H; CH_2OSi), 7.19 (s, 1H; $C_{Ar}H$), 7.26 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.0 (CH), 18.0, 58.1 (CH_3), 64.8, 74.6 (CH_2), 124.4, 125.5 ($C_{Ar}H$), 138.3, 142.1 (C_{Ar}) ppm; MS (CI): *m*/*z* (%): 370 (100) [M+NH_4^+], 196 (51) [M^+−(^{i}Pr)$_3$Si+H]; elemental analysis (%) calcd for $C_{20}H_{36}O_3Si$ (352.58): C 68.13, H 10.29; found: C 68.03, H 10.19.

4.1.4. Tricarbonyl[1-(triisopropylsilyloxymethyl)-3,5-dimethoxymethylbenzene]chromium(0) **9**

A dry 250 mL RB flask fitted with a water condenser was charged with 1-(triisopropylsilyloxymethyl)-3,5-dimethoxymethylbenzene **8** (2.120 g, 6.0 mmol), hexacarbonylchromium(0) (1.320 g, 6.0 mmol), dry di-*n*-butyl ether (91 mL) and dry THF (9 mL). The stirred suspension was protected from light and thoroughly saturated with nitrogen, before heating it to 135 °C. After 42 h, the resulting yellow reaction mixture was allowed to cool to rt and filtered through a pad of Celite® to remove any oxidised chromium. The filtrate was concentrated and the crude product purified by flash column chromatography on silica gel (hexane/EtOAc, 98:2 → 95:5) to afford the desired complex **9** as a yellow oil (2.530 g, 86%). R_f=0.48 (SiO_2; hexane/EtOAc 8:2); IR (ν_{max}, DCM): 1966, 1888 (2×C≡O), 1110 (C–O–C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.12 (d, *J*=6.2, 18H; $CH(CH_3)_2$), 1.16–1.22 (m, 3H; $CH(CH_3)_2$), 3.49 (s, 6H; OCH_3), 4.26 (s, 4H; CH_2OCH_3), 4.66 (s, 2H; CH_2OSi), 5.33 (s, 1H; $C_{Ar}H$), 5.40 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.9 (CH), 18.0 (CH_3), 59.0 (OCH_3), 63.4, 73.0 (CH_2), 88.8, 90.1 ($C_{Ar}H$), 107.5, 112.3 (C_{Ar}), 232.6 (CO) ppm; MS (EI): *m*/*z* (%): 488 (45) [M^+],

404 (87) [M^+-3CO], 361 (100) [$M^+-3CO-{}^iPr$]; elemental analysis (%) calcd for $C_{23}H_{36}CrO_6Si$ (488.61): C 56.54, H 7.43; found: C 56.35, H 7.40.

4.1.5. (−)- and (+)-Tricarbonyl[1,3-bis(1-methoxyethyl)-5-(triisopropylsilyloxymethyl)benzene]-chromium(0) (−)- and (+)-**11**

n-Butyllithium (4.15 mL, 2.24 M, 9.30 mmol, solution in hexanes, 3.0 equiv) was added dropwise to a stirred solution of the diamine corresponding to diamide (*S*,*R*,*R*,*S*)-**10** (1.95 g, 4.65 mmol, 1.5 equiv) in THF (32 mL) at −78 °C. The solution was allowed to warm to rt over a period of 30 min to aid the formation of a bislithium amide. The resulting deep purple solution was then re-cooled to −78 °C before a solution of heat gun dried lithium chloride (0.197 g, 4.65 mmol, 1.5 equiv) in THF (10 mL) was added via a cannula. The reaction mixture was stirred for a further 10 min before a pre-cooled (−78 °C) solution of complex **9** (1.52 g, 3.10 mmol, 1.0 equiv) in THF (20 mL) was introduced dropwise via a short cannula. Stirring was continued at −78 °C for 60 min before iodomethane (1.16 mL, 18.6 mmol, 6.0 equiv) was added in one portion via a syringe. The resulting yellow solution was then stirred until the reaction was judged complete by TLC (75 min). The reaction was quenched with MeOH (3 mL) and the solvent was removed in vacuo. The resulting yellow residue was then dissolved in DCM, the diamine was removed from the product mixture by an HCl (12 mL, 1.0 M) wash, and the aqueous phase extracted with DCM (24 mL). The extract was dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/Et_2O, 96:4) afforded (−)-**11** as a yellow oil. The enantiomeric purity was determined by HPLC analysis (Chiralcel OD; *n*-hexane/^{i}PrOH 99.5:0.5, 0.2 mL min^{-1}, 330 nm); (−)-enantiomer: t_R=26.4 min; (+)-enantiomer: t_R=28.3 min.

The procedure for (−)-**11** was repeated using the diamine corresponding to diamide (*R*,*S*,*S*,*R*)-**10** and 1.47 mmol (0.720 g) of complex **9** to provide (+)-**11**.

(−)-**11**: Yield=1.230 g, 77%. $[\alpha]_D^{24}$ −41 (*c* 1.16, DCM); HPLC analysis: 90% ee. R_f=0.37 (SiO_2; hexane/EtOAc 9:1); IR (ν_{max}, DCM): 1963, 1885 (2×C≡O), 1116 (C–O–C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11–1.18 (d+m, *J*=6.2 Hz, 21H; ^{i}Pr), 1.45 (d, *J*=3.1 Hz, 3H; CHC*H*$_3$), 1.46 (d, *J*=3.1 Hz, 3H; CHC*H*$_3$), 3.49 (s, 6H; OCH_3), 4.10–4.13 (m, 2H; C*H*CH$_3$), 4.61 (s, 2H; CH_2OSi), 5.41 (s, 2H; $C_{Ar}H$), 5.58 (s, 1H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.9 (*C*H(CH$_3$)$_2$), 18.0 (CH(*C*H$_3$)$_2$), 22.5 (CHCH$_3$), 57.5 (OCH_3), 63.5 (CH_2), 76.9 (*C*HCH$_3$), 88.2, 88.6, 89.3 ($C_{Ar}H$), 110.6, 112.4 (C_{Ar}), 233.1 (CO) ppm; MS (EI): *m*/*z* (%): 516 (11) [M^+], 432 (19) [M^+-3CO], 349 (27) [$M^+-3CO-OCH_3-Cr$], 145 (100) [$M^+-3CO-2OCH_3-Cr-OSi(^iPr)_3$]; elemental analysis (%) calcd for $C_{25}H_{40}CrO_6Si$ (516.66): C 58.12, H 7.80; found: C 58.30, H 7.70.

(+)-**11**: Yield=0.520 g, 68%. $[\alpha]_D^{24}$ +41 (*c* 1.15, DCM); HPLC analysis: 88% ee; elemental analysis (%) calcd for $C_{25}H_{40}CrO_6Si$ (516.66): C 58.12, H 7.80; found: C 58.20, H 7.76; all other data were identical to that obtained for (−)-**11**.

4.1.6. (−)- and (+)-1,3-Bis(1-methoxyethyl)-5-(triisopropylsilyloxymethyl)benzene (−)- and (+)-**12**

The dialkylated complex (−)-**11** (0.325 g, 0.63 mmol) was dissolved in dry DCM (30 mL) and the solution was thoroughly saturated with air. The reaction mixture was stirred in an open vessel at rt in direct sunlight until the reaction was complete by TLC (22 h). The crude green product mixture was filtered through a pad of Celite® and neutral alumina, the pad was thoroughly washed with dry Et_2O and the filtrate was concentrated under reduced pressure to afford the product as a colourless oil.

The procedure for (−)-**12** was repeated using 2.50 mmol (1.290 g) of complex (+)-**11** to provide (+)-**12**.

(−)-**12**: Yield=0.233 g, 97%. $[\alpha]_D^{24}$ −82 (*c* 1.58, DCM); R_f=0.32 (SiO_2; hexane/EtOAc 9:1); IR (ν_{max}, neat film): 1115 (C–O–C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (d, *J*=6.6 Hz, 18H; SiCH(C*H*$_3$)$_2$), 1.18–1.23 (m, 3H; SiC*H*(CH$_3$)$_2$), 1.46 (d, *J*=6.5 Hz, 6H; CHC*H*$_3$), 3.25 (s, 6H; OCH_3), 4.33 (q, *J*=6.5, 2H; C*H*CH$_3$), 4.88 (s, 2H; CH_2OSi), 7.14 (s, 1H; $C_{Ar}H$), 7.22 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=12.0 (SiCH(CH$_3$)$_2$), 18.0 (SiCH(*C*H$_3$)$_2$), 23.7 (CHCH$_3$), 56.4 (OCH_3), 65.0 (CH_2), 79.6 (*C*HCH$_3$), 122.5 ($C_{Ar}H$), 122.8 ($C_{Ar}H$), 142.1, 143.6 (C_{Ar}) ppm; MS (CI): *m*/*z* (%): 398 (100) [$M+NH_4^+$], 366 (28) [M^+-CH_3+H], 224 (81) [$M^+-Si(^iPr)_3$]; elemental analysis (%) calcd for $C_{22}H_{40}O_3Si$ (380.64): C 69.42, H 10.59; found: C 69.52, H 10.53.

(+)-**12**: Yield=0.932 g, 98%. $[\alpha]_D^{24}$ +84 (*c* 1.64, DCM); elemental analysis (%) calcd for $C_{22}H_{40}O_3Si$ (380.64): C 69.42, H 10.59; found: C 69.63, H 10.55; all other data were identical to that obtained for (−)-**12**.

4.1.7. (−)- and (+)-1,3-Bis(1-methoxyethyl)-5-(hydroxymethyl)benzene (−)-**13** and (+)-**13**

To a solution of (−)-1,3-bis(1-methoxyethyl)-5-(triisopropylsilyloxymethyl)benzene (−)-**12** (0.188 g, 0.49 mmol, 1.0 equiv) in dry THF (3.3 mL) was added tetrabutylammonium fluoride (0.98 mL, 1 M in THF, 2 equiv) dropwise via a syringe. The resulting pale yellow mixture was stirred under an inert atmosphere for 3.5 h before any remaining unreacted tetrabutylammonium fluoride was quenched by addition of a saturated aqueous solution of NH_4Cl (3.3 mL). The layers were separated and the aqueous phase was washed with DCM (3×3.3 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/EtOAc 80:20→70:30) afforded the title compound (−)-**13** as a colourless oil, which solidified to form a white solid on standing.

The procedure for (−)-**13** was repeated using 2.40 mmol (0.920 g) of complex (+)-**12** to provide (+)-**13**.

(−)-**13**: Yield=0.100 g, 91%. R_f=0.33 (SiO_2; hexane/EtOAc 1:1); mp 66–67 °C; $[\alpha]_D^{24}$ −142 (*c* 0.118, DCM); IR (ν_{max}, DCM): 3603 (O–H), 1114, 1064 (C–O–C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.46 (d, *J*=6.5 Hz, 6H; CHC*H*$_3$), 1.74 (s, 1H; OH), 3.26 (s, 6H; OCH_3), 4.34 (q, *J*=6.5, 2H; C*H*CH$_3$), 4.74 (s, 2H; C*H*$_2$OH), 7.21 (s, 1H; $C_{Ar}H$), 7.29 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=23.7 (CHCH$_3$), 56.5 (OCH_3), 65.3 (CH_2), 79.6 (*C*HCH$_3$), 123.3 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 141.4, 144.2 (C_{Ar}) ppm; MS (EI): *m*/*z* (%): 224 (6) [M^+], 209 (100) [M^+-CH_3]; elemental analysis (%) calcd for $C_{13}H_{20}O_3$ (224.3): C 69.61, H 8.99; found: C 69.56, H 9.03.

(+)-**13**: Yield=0.519 g, 96%. $[\alpha]_D^{24}$ +141 (*c* 1.24, DCM); elemental analysis (%) calcd for $C_{13}H_{20}O_3$ (224.3): C 69.61, H 8.99; found: C 69.54, H 9.09; all other data were identical to that obtained for (−)-**13**.

4.1.8. (−)- and (+)-1,3-Bis(1-methoxyethyl)-5-(bromomethyl)benzene (−)- and (+)-**14**

To a solution of (−)-1,3-bis(1-methoxyethyl)-5-(hydroxymethyl)benzene (−)-**13** (0.535 g, 2.4 mmol, 1.0 equiv) in dry THF (48 mL) was added triphenylphosphine (0.944 g, 3.6 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min and then carbon tetrabromide (1.19 g 3.6 mmol, 1.5 equiv) was added, which eventually resulted in the formation of a white precipitate. The reaction mixture was saturated with nitrogen and the reaction was stirred at rt under an inert atmosphere in the dark until it was deemed complete by TLC (1.5 h). The mixture was then filtered and the precipitate was washed with dry THF. Evaporation of the filtrate and purification by flash column chromatography on silica gel (hexane/EtOAc 95:5→90:10) afforded the desired bromide (−)-**14** as a colourless oil.

The procedure for (−)-**14** was repeated using 2.3 mmol (0.514 g) of complex (−)-**13** to provide (+)-**14**.

(−)-**14**: Yield=0.630 g, 91%. $[\alpha]_D^{24}$ −109 (*c* 1.55, DCM); IR (ν_{max}, DCM): 1115, 1097 (C–O–C), 568 (C–Br) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.43 (d, *J*=6.5 Hz, 6H; CHC*H*$_3$), 3.24 (s, 6H; OCH_3), 4.30 (q,

J=6.5, 2H; C*H*CH_3), 4.50 (s, 2H; CH_2Br), 7.17 (t, J=1.5 Hz, 1H; $C_{Ar}H$), 7.25 (d, J=1.5 Hz, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=23.7 (CH*C*H_3), 33.5 (CH_2), 56.6 (OCH_3), 79.3 (*C*HCH_3), 124.0, 125.9 ($C_{Ar}H$), 138.2, 144.6 (C_{Ar}) ppm; MS (EI): m/z (%): 288 (10) [M^+], 286 (10) [M^+], 273 (98) [M^+-CH_3], 271 (100) [M^+-CH_3], 207 (42) [M^+−Br]. HRMS (EI): m/z(%) calcd for $C_{13}H_{19}BrO_2$: 288.0548, 286.0568, found: 288.0545 [M^+], 286.0569 [M^+].

(+)-**14**: Yield=0.561 g, 85%. $[\alpha]_D^{24}$ +110 (*c* 1.07, DCM); all other data collected was identical to that obtained for (−)-**14**.

4.1.9. ($S_{inner}S_{outer}$)-**16**, ($R_{inner}R_{outer}$)-**16**, ($R_{inner}S_{outer}$)-**16** and ($S_{inner}R_{outer}$)-**16**

n-Butyllithium (0.72 mL, 1.80 mmol, 2.50 M in hexanes, 6.0 equiv) was added dropwise to a stirred solution of the diamine corresponding to diamide (*S*,*R*,*R*,*S*)-**10** (0.378 g, 0.90 mmol, 3.0 equiv) in THF (18 mL) at −78 °C. The solution was allowed to warm to rt over a period of 30 min. The resulting deep purple solution was then re-cooled to −78 °C before a solution of heat gun dried lithium chloride (0.038 g, 0.90 mmol, 3.0 equiv) in THF (2 mL) was added via a cannula. The reaction mixture was stirred for a further 10 min before a pre-cooled (−78 °C) solution of complex **15** (0.104 g, 0.30 mmol, 1.0 equiv) in THF (3 mL) was introduced dropwise via a short cannula. Stirring of the resulting orange mixture was continued at −78 °C for 1 h before a solution of bromide electrophile (−)-**14** (0.327 g, 1.10 mmol, 3.8 equiv) in THF (7 mL) was added via a short cannula. The resulting yellow solution was then stirred until the reaction was judged complete by TLC (5 h). The reaction was quenched with MeOH (2 mL) and the solvent was removed in vacuo. Purification of the yellow residue by flash column chromatography on silica gel (hexane/Et_2O, 100:0–60:40) afforded the desired chromium complex. This was then dissolved in dry DCM (15 mL) and the yellow solution was saturated with air. The reaction mixture was stirred in an open vessel at rt in direct sunlight until the reaction was complete (20 h). The crude green product mixture was filtered through a Pasteur pipette containing a plug of Celite® and neutral alumina, the filter plug was rinsed with dry Et_2O and the filtrate was evaporated to afford the product ($S_{inner}S_{outer}$)-**16** as a white solid.

The procedure for ($S_{inner}S_{outer}$)-**16** was repeated using (a) the diamine corresponding to diamide (*R*,*S*,*S*,*R*)-**10** and the electrophile (+)-**14** on 0.27 mmol (0.094 g) of complex **15** to provide ($R_{inner}R_{outer}$)-**16**; (b) the diamine corresponding to diamide (*R*,*S*,*S*,*R*)-**10** and the electrophile (−)-**14** on 0.27 mmol (0.096 g) of complex **15** to provide ($R_{inner}S_{outer}$)-**16** and (c) the diamine corresponding to diamide (*S*,*R*,*R*,*S*)-**10** and the electrophile (+)-**14** on 0.20 mmol (0.068 g) of complex **15** to provide ($S_{inner}R_{outer}$)-**16**.

($S_{inner}S_{outer}$)-**16**: Yield=0.185 g, 75%. Mp 84–85 °C; IR (ν_{max}, DCM): 1114, 1099 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.39 (d, J=6.5 Hz, 18H; CH_3), 2.82 (dd, J=14.0, 5.0 Hz, 3H; CHCH*H*), 3.04 (dd, J=14.0, 8.5 Hz, 3H; CH*CH*H), 3.13 (s, 9H; inner OCH_3), 3.20 (s, 18H; outer OCH_3), 4.24 (q, J=6.5 Hz, 6H; *C*HCH_3), 4.31 (dd, J=8.5, 5.0 Hz, 3H; *CH*CHH), 7.01 (s, 6H; $C_{Ar}H$), 7.04 (s, 3H; $C_{Ar}H$), 7.08 (s, 3H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=23.7 (CH_3), 44.7 (CH_2), 56.4, 56.8 (OCH_3), 79.5, 84.8 (CH), 122.0, 124.2, 126.2 ($C_{Ar}H$), 139.0, 142.2, 143.5 (C_{Ar}) ppm; MS (ESI): m/z (%): 852 (100) [M^++Na]; elemental analysis (%) calcd for $C_{51}H_{72}O_9$ (829.11): C 73.88, H 8.75; found: C 73.72, H 8.71.

($R_{inner}R_{outer}$)-**16**: Yield=0.123 g, 55%. Mp 87–88 °C; elemental analysis (%) calcd for $C_{51}H_{72}O_9$ (829.11): C 73.88, H 8.75; found: C 73.93, H 8.89; all other analytical data were identical to that of ($S_{inner}S_{outer}$)-**16**.

($R_{inner}S_{outer}$)-**16**: Yield=0.179 g, 86%. Mp 86.5–87.5 °C; IR (ν_{max}, DCM): 1114, 1099 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=1.39 (d, J=6.5 Hz, 18H; CH_3), 2.82 (dd, J=14.0, 5.1 Hz, 3H; CHCH*H*), 3.04 (dd, J=14.0, 8.0 Hz, 3H; CH*CH*H), 3.12 (s, 9H; inner OCH_3), 3.19 (s, 18H; outer OCH_3), 4.24 (q, J=6.5 Hz, 6H; *C*HCH_3), 4.31 (dd, J=8.0, 5.1 Hz, 3H; *CH*CHH), 7.00 (s, 6H; $C_{Ar}H$), 7.04 (s, 3H; $C_{Ar}H$), 7.08 (s, 3H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=23.7 (CH_3), 44.6 (CH_2), 56.4, 56.8 (OCH_3), 79.5, 84.7 (CH), 121.8, 124.2, 126.2 ($C_{Ar}H$), 138.9, 142.1, 143.5 (C_{Ar}) ppm; MS (ESI): m/z (%): 852 (100) [M^++Na]; elemental analysis (%) calcd for $C_{51}H_{72}O_9$ (829.11): C 73.88, H 8.75; found: C 73.87, H 8.68.

($S_{inner}R_{outer}$)-**16**: Yield=0.056 g, 32%. Mp 84–86 °C; elemental analysis (%) calcd for $C_{51}H_{72}O_9$ (829.11): C 73.88, H 8.75; found: C 73.89, H 8.96; all other analytical data were identical to that of ($R_{inner}S_{outer}$)-**16**.

4.1.10. 1,3-Bis(methoxymethyl)-5-(hydroxymethyl)benzene **17**

To a solution of 1-(triisopropylsilyloxymethyl)-3,5-dimethoxymethylbenzene **8** (1.560 g, 4.4 mmol) in dry THF (29 mL) was added tetrabutylammonium fluoride (8.85 mL, 8.8 mmol, 1.0 M, 2.0 equiv) dropwise via a syringe. The resulting pale yellow mixture was stirred under an inert atmosphere for 3 h before any remaining unreacted tetrabutylammonium fluoride was quenched by addition of a saturated aqueous solution of NH_4Cl (10 mL). The layers were separated and the aqueous phase was washed with DCM (3×20 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (hexane/EtOAc 70:20→50:50) afforded the desired product as a pale yellow oil (0.758 g, 88%). R_f=0.22 (SiO_2; hexane/EtOAc 1:1); IR (ν_{max}, neat film): 3417 (O–H), 1098 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.92 (br s, 1H; OH), 3.42 (s, 6H; O*C*H_3), 4.48 (s, 4H; *C*H_2OCH_3), 4.71 (s, 2H; *C*H_2OH), 7.29 (s, 1H; $C_{Ar}H$), 7.30 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=58.3 (CH_3), 65.1, 74.5 (CH_2), 125.5, 126.2 ($C_{Ar}H$), 138.8, 141.4 (C_{Ar}) ppm; MS (EI): m/z (%): 196 (78) [M^+], 165 (100) [M^+-OCH_3]; elemental analysis (%) calcd for $C_{11}H_{16}O_3$ (196.24): C 67.32, H 8.22; found: C 67.26, H 8.27.

4.1.11. 1,3-Bis(methoxymethyl)-5-(bromomethyl)benzene **18**

To a solution of 1,3-bis(methoxymethyl)-5-(hydroxymethyl)benzene **17** (0.741 g, 3.8 mmol) in dry THF (76 mL) was added triphenylphosphine (1.490 g, 5.7 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min and then carbon tetrabromide (1.880 g, 5.7 mmol, 1.5 equiv) was added, which eventually resulted in the formation of a white precipitate. The reaction mixture was saturated with nitrogen and the reaction was stirred at rt under an inert atmosphere in the dark until judged complete by TLC (90 min). The mixture was filtered and the precipitate was washed with dry THF. Evaporation of the filtrate and purification by flash column chromatography on silica gel (hexane/EtOAc 95:5→90:10) afforded the desired bromide as a colourless oil (0.780 g, 79%). R_f=0.80 (SiO_2; hexane/EtOAc 1:1); IR (ν_{max}, DCM): 1101 (C–O–C), 563 (C–Br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=3.43 (s, 6H; O*C*H_3), 4.48 (s, 4H; *C*H_2OCH_3), 4.52 (s, 2H; CH_2Br), 7.29 (s, 1H; $C_{Ar}H$), 7.33 (s, 2H; $C_{Ar}H$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=33.3 (CH_2), 58.4 (CH_3), 74.2 (CH_2), 126.8, 127.5 ($C_{Ar}H$), 138.1, 139.2 (C_{Ar}) ppm; MS (EI): m/z (%): 260 (43) [M^+], 258 (49) [M^+], 229 (60) [M^+-OCH_3], 227 (66) [M^+-OCH_3], 179 (100) [M^+−Br]; elemental analysis (%) calcd for $C_{11}H_{15}BrO_4$ (259.14): C 50.98, H 5.83; found: C 51.06, H 5.90.

4.1.12. (S_{inner})-**19**, (R_{inner})-**19**

n-Butyllithium (1.28 mL, 1.80 mmol, 1.41 M in hexanes, 6.0 equiv) was added dropwise to a stirred solution of the diamine corresponding to diamide (*S*,*R*,*R*,*S*)-**10** (0.378 g, 0.90 mmol, 3.0 equiv) in THF (14 mL) at −78 °C. The solution was allowed to warm to rt over a period of 30 min to aid the formation of a bislithium amide. The resulting deep purple solution was then re-cooled to −78 °C before a solution of heat gun dried lithium chloride (0.038 g, 0.90 mmol, 3.0 equiv) in THF (2 mL) was added via a cannula. The reaction mixture was stirred for a further 15 min

before a pre-cooled (−78 °C) solution of complex **15** (0.104 g, 0.30 mmol, 1.0 equiv) in THF (5 mL) was introduced dropwise via a short cannula. Stirring of the resulting orange mixture was continued at −78 °C for 60 min before a solution of 1,3-bis(methoxymethyl)-5-(bromomethyl)benzene **18** (0.360 g, 1.39 mmol, 4.6 equiv) in THF (6 mL) was added via a short cannula. The resulting yellow solution was then stirred until the reaction was complete by TLC (2.5 h). The reaction was quenched with MeOH (2 mL) and the solvent was removed in vacuo. Purification of the yellow residue by flash column chromatography on silica gel (hexane/Et_2O, 100:0→0:100) afforded the desired trisfunctionalised chromium complex. The complex (0.078 g, 0.09 mmol, 1.0 equiv) was dissolved in dry DCM (15 mL) and the yellow solution was saturated with air. The reaction mixture was stirred in an open vessel at rt in direct sunlight until the reaction was complete by TLC (48 h). The crude green product mixture was filtered through a Pasteur pipette containing a plug of Celite® and neutral alumina, the filter plug was thoroughly rinsed with dry Et_2O and the filtrate was evaporated to dryness to afford the product (S_{inner})-**19** as a colourless film.

The procedure for (S_{inner})-**19** was repeated using the amine corresponding to (*R*,*S*,*S*,*R*)-**10** on 0.31 mmol (0.108 g) of complex **15** to give (R_{inner})-**19**.

(S_{inner})-**19**: Yield (chiral base reaction)=0.078 g, 30%; amount used for decomplexation step=0.078 g, 0.09 mmol; yield (decomplexation)=0.076 g, 99%; 30% yield over 2 steps. IR (ν_{max}, neat film): 1100 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=2.80 (dd, *J*=13.8, 5.3 Hz, 3H; CHCH*H*), 3.02 (dd, *J*=13.8, 8.0 Hz, 3H; CHC*H*H), 3.13 (s, 9H; inner OCH_3), 3.36 (s, 18H; outer OCH_3), 4.29 (dd, *J*=8.0, 5.3 Hz, 3H; C*H*CHH), 4.39 (s, 12H; CH_2O), 7.01 (s, 6H; $C_{Ar}H$), 7.03 (s, 3H; $C_{Ar}H$), 7.12 (s, 3H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=44.6 ($CHCH_2$), 56.7 (inner OCH_3), 58.1 (outer OCH_3), 74.5 (CH_2O), 84.8 (*C*HCH$_2$), 124.3, 124.9, 128.0 ($C_{Ar}H$), 138.1, 138.9, 142.0 (C_{Ar}) ppm; MS (ESI): *m*/*z* (%): 767 (100) [M^++Na]; elemental analysis (%) calcd for $C_{45}H_{60}O_9$ (744.95): C 72.55, H 8.12; found: C 72.44, H 7.94.

(R_{inner})-**19**: Yield (chiral base reaction)=0.172 g, 63%; amount used for decomplexation step=0.143 g, 0.16 mmol; yield (decomplexation)=0.086 g, 72%; 45% yield over 2 steps. Elemental analysis (%) calcd for $C_{45}H_{60}O_9$ (744.95): C 72.55, H 8.12; found: C, 72.61, H 8.13; all other data obtained were identical to that of (S_{inner})-**19**.

4.1.13. Tricarbonyl[1,3,5-tris(benzyloxymethyl)-benzene]chromium(0) *21*

To a stirred and cooled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 0.480 g, 12.0 mmol, 4.0 equiv), previously washed with hexane (5 mL), in THF (40 mL), was added a solution of tricarbonyl[1,3,5-tris(hydroxymethyl)benzene]chromium(0) **20** (0.913 g, 3.0 mmol) in THF (20 mL) via a cannula. The reaction mixture was allowed to warm to rt, a condenser was fitted to the reaction vessel and the system was thoroughly saturated with nitrogen and stirred at 70 °C for 2 h. After cooling to rt, the condenser was replaced with a septum-containing adapter. The flask was saturated with nitrogen and benzyl bromide (2.14 mL, 18.0 mmol, 6.0 equiv) was added in one portion via a syringe. The resulting yellow/white mixture was protected from light and stirred overnight at rt. A saturated aqueous solution of NH_4Cl (20 mL) was added, the organic phase was separated and the aqueous phase extracted with DCM (3×60 mL). The combined organic layers were washed with brine (120 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc 100:0→65:35) to afford the desired product (1.400 g, 81%) as a yellow solid. R_f=0.51 (SiO_2; hexane/EtOAc 8:2); mp 78–80 °C; IR (ν_{max}, DCM): 1961, 1881 (2×C≡O), 1100 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ=4.31 (s, 6H; $C_{Ar}CH_2O$), 4.65 (s, 6H; OCH_2C_{Ar}), 5.36 (s, 3H; $C_{Ar}H$), 7.30–7.35 (m, 3H; $C_{Ar}H$), 7.37 (d, *J*=4.4 Hz, 12H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=70.3, 73.3 (CH_2), 90.0 ($C_{Cr}H$), 108.0 (C_{Cr}), 127.9, 128.0, 128.5 ($C_{Ar}H$), 137.4 (C_{Ar}), 232.5 (CO) ppm; MS (EI): *m*/*z* (%): 574 (14) [M^+], 490 (100) [M^+−3CO], 399 (6) [M^+−3CO−$PhCH_2$]; elemental analysis (%) calcd for $C_{33}H_{30}CrO_6$ (574.58): C 68.98, H 5.26; found: C 68.84, H 5.22.

4.1.14. ($S_{inner}R_{outer}$)-*22*, ($R_{inner}R_{outer}$)-*22*

n-Butyllithium (0.62 mL, 1.56 mmol, 2.50 M in hexanes, 6.0 equiv) was added dropwise to a stirred solution of the diamine corresponding to diamide (*S*,*R*,*R*,*S*)-**10** (0.328 g, 0.78 mmol, 3.0 equiv) in THF (12 mL) at −78 °C. The solution was allowed to warm to rt over a period of 30 min to aid the formation of a bislithium amide. The resulting deep purple solution was then recooled to −78 °C before a solution of heat gun dried lithium chloride (0.033 g, 0.78 mmol, 3.0 equiv) in THF (3 mL) was added through a cannula. The reaction mixture was stirred for a further 10 min before a pre-cooled (−78 °C) solution of tricarbonyl[1,3,5-tris(benzyloxymethyl)benzene]chromium(0) **21** (0.148 g, 0.26 mmol, 1.0 equiv) in THF (4 mL) was introduced dropwise via a short cannula. Stirring of the resulting orange mixture was continued at −78 °C for 60 min before a solution of (+)-**14** (0.309 g, 1.08 mmol) in THF (5 mL) was added via a short cannula. The resulting yellow solution was then stirred until the reaction was complete (4 h). The reaction was quenched with MeOH (2 mL) and the solvent was removed in vacuo. Purification of the yellow residue by flash column chromatography on silica gel (hexane/EtOAc 97:3→80:20) afforded the desired trisfunctionalised chromium complex. This was dissolved in dry DCM (5 mL) and the yellow solution was saturated with air. The reaction mixture was stirred in an open vessel at rt in direct sunlight until the reaction was complete (48 h). The crude green product mixture was filtered through a Pasteur pipette containing a plug of Celite® and neutral alumina, the filter plug was thoroughly rinsed with dry Et_2O and the filtrate was evaporated to dryness to afford the desired product ($S_{inner}R_{outer}$)-**22** as a colourless film.

The procedure for ($S_{inner}R_{outer}$)-**22** was repeated using the amine corresponding to (*R*,*S*,*S*,*R*)-**10** on 0.30 mmol (0.172 g) of complex **21** to give ($R_{inner}R_{outer}$)-**22**. The column chromatography was performed using (hexane/EtOAc 97:3→50:50).

($S_{inner}R_{outer}$)-**22**: Yield=0.125 g, 45%. IR (ν_{max}, DCM): 1114, 1097 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ=1.45 (d, *J*=6.4 Hz, 18H; CHC*H*$_3$), 3.01 (dd, *J*=13.8, 4.6 Hz, 3H; CHCH*H*), 3.11 (s, 18H; OCH_3), 3.24 (dd, *J*=13.8, 8.7 Hz, 3H; CHC*H*H), 4.15 (q, *J*=6.4 Hz, 6H; C*H*CH$_3$), 4.22 (d, *J*=12.4 Hz, 3H; OCH*H*Ph), 4.52 (d, *J*=12.4 Hz, 3H; OC*H*HPh), 4.60 (dd, *J*=8.7, 4.6 Hz, 3H; C*H*CHH), 7.04 (m, 3H; $C_{Ar}H$), 7.12 (t, *J*=7.5 Hz, 6H; $C_{Ar}H$). 7.20 (d, *J*=7.5 Hz, 6H; $C_{Ar}H$), 7.23 (br s, 3H; $C_{Ar}H$), 7.26 (br s, 6H; $C_{Ar}H$), 7.37 (s, 3H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, C_6D_6): δ=24.4 (*C*HCH$_3$), 45.5 (CH_2), 56.3 (OCH_3), 70.7 (CH_2Ph), 79.9 (*C*HCH$_3$), 82.8 (*C*HCH$_2$), 122.4, 125.0, 126.9, 127.6, 128.3, 128.5 ($C_{Ar}H$), 139.1, 139.5, 143.3, 144.5 (C_{Ar}) ppm; MS (ESI): *m*/*z* (%): 1080 (100) [M^++Na]; elemental analysis (%) calcd for $C_{69}H_{84}O_9$ (1057.4): C 78.38, H 8.01; found: C 78.51, H 7.92.

($R_{inner}R_{outer}$)-**22**: Yield=0.162 g, 52%. IR (ν_{max}, DCM): 1114, 1097 (C–O–C) cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ=1.45 (d, *J*=6.4 Hz, 18H; $CHCH_3$), 3.02 (dd, *J*=13.8, 4.6 Hz, 3H; CHCH*H*), 3.13 (s, 18H; OCH_3), 3.25 (dd, *J*=13.8, 8.8 Hz, 3H; CHC*H*H), 4.15 (q, *J*=6.4 Hz, 6H; C*H*CH$_3$), 4.21 (d, *J*=12.3 Hz, 3H; OCH*H*Ph), 4.53 (d, *J*=12.3 Hz, 3H; OC*H*HPh), 4.61 (dd, *J*=8.8, 4.6 Hz, 3H; C*H*CHH), 7.05 (m, 3H; $C_{Ar}H$), 7.13 (t, *J*=7.5 Hz, 6H; $C_{Ar}H$). 7.19 (d, *J*=7.5 Hz, 6H; $C_{Ar}H$), 7.24 (br s, 3H; $C_{Ar}H$), 7.27 (br s, 6H; $C_{Ar}H$), 7.39 (s, 3H; $C_{Ar}H$) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ=24.4 (*C*HCH$_3$), 45.6 (CH_2), 56.3 (OCH_3), 70.8 (CH_2Ph), 79.9 (*C*HCH$_3$), 82.8 (*C*HCH$_2$), 122.4, 125.0, 126.8, 127.6, 128.5 ($C_{Ar}H$), 139.1, 139.5, 143.4, 144.5 (C_{Ar}) ppm. MS (ESI): *m*/*z* (%): 1080 (100) [M^++Na]; elemental analysis (%) calcd for $C_{69}H_{84}O_9$ (1057.4): C 78.38, H 8.01; found: C 78.29, H 7.90.

4.2. CD experimental

Simultaneous UV and CD spectra were measured with a nitrogen-flushed Chirascan spectrometer.[25] The solvent used for the room temperature studies was CH_3CN, and the path length was 1 cm in the near UV region (400–230 nm), and 0.5 mm in the far UV region (230–180 nm). Sample concentrations were in the order of 0.5 mg/mL in the near UV region and 0.1 mg/mL in the far UV. Spectra were accumulated with a 0.5 nm collection every 2 s.

For the variable temperature study, a Jasco J720 spectrometer was used, and the instrument was equipped with a Jobin–Yvon low temperature unit. A 1 cm path length was employed. CD spectra of the samples (0.5 mg/mL in ether/EtOH/isopentane 5:2:5 v/v/v) were recorded in the 350–230 nm wavelength region at room temperature (20 °C) then cooled to −100 °C and −130 °C [−137 °C for ($R_{inner}S_{outer}$)-**16**] using liquid nitrogen. The temperature was measured directly with a thermocouple probe in the sample solution. Spectra were accumulated with a 0.2 nm collection every 4 s. UV and CD spectra of ether/EtOH/isopentane (5:2:5 v/v/v) were also measured at 20 °C and −100 °C to confirm that there was no abnormality in the solvent behaviour at low temperature.

All UV and CD spectra were solvent baseline corrected and normalised for concentration and path length to give ε and $\Delta\varepsilon$.

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