(*S*)-(-)-Fluorenylethylchloroformate (FLEC); preparation using asymmetric transfer hydrogenation and application to the analysis and resolution of amines

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Dedicated to Professor Steve Davies.

Abstract:

Fluorenylethylchoroformate (FLEC) is a valuable chiral derivatisation reagent that is used for the resolution of a wide variety of chiral amines. Herein we describe an improved preparation of (*S*)-(-)-FLEC using an efficient asymmetric catalytic transfer hydrogenation as the key step. We also demonstrate the application of FLEC as a chiral Fmoc equivalent for chiral resolution, with facile deprotection, of tetrahydroquinaldines, and its capacity for inducing regioselective outcomes in nitration reactions.

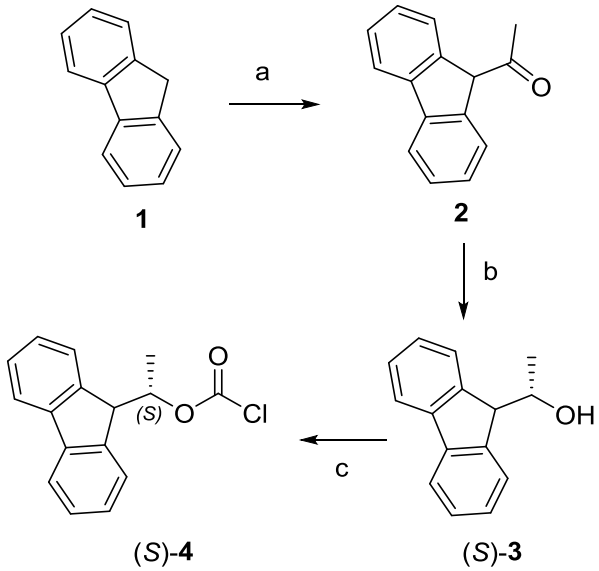
Introduction:

Fluorenylethylchloroformate (FLEC) is a useful and versatile reagent for the diastereomeric resolution of amino acids and amines.[1,2] Since its introduction, FLEC has been applied to the analysis of many natural and synthetic products and these have been the subject of a comprehensive recent review.[3] It is however very expensive to purchase which has limited its application in synthesis.

We have previously described an improved route to (*R*)-(+)-FLEC, (*R*)-**4** from flourene (**1**), *via* ketone **2** and alcohol **3** (Scheme 1) using the Corey-Bakshi-Shibata (CBS) reaction and its application to the synthesis of unusual chiral amino acids in peptide research.[4] Fluorenylethyloxycarbonyl (Feoc) derivatives could act both as an amino acid resolving agent and protecting group for peptide synthesis. Borowiecki and co workers recently reported an alternate method to prepare the alcohol (***S***)-**3** based on enzymatic kinetic resolution.[5] In their method, 9-acetylfluorene (**2**) was prepared by refluxing *9H*-fluorene (**1**) with EtOAc in ether and under strongly basic conditions (a mixture of *t*-BuOK and *t*-BuONa) for 3 h in a high isolated yield (97%). This ketone was then reduced to the racemic alcohol by sodium borohydride ($NaBH_4$). Lipase-catalysed kinetic resolution yielded the the enantiopure *S*-alcohol and the *R*-acetate.

Results and Discussion.

The success of the asymmetric CBS reduction was still short of our hopes so we continued our studies of catalysts for chiral reduction of acetylfluorene. Among ruthenium catalysts, those containing the combination of an η^6-arene and a chiral sulfonated diphenylethanediamine ligand (TsDPEN), first introduced by Noyori and co-workers have been widely applied to synthetic applications in recent years.[6,7] In 2005, Wills and co-workers introduced the tethered ruthenium catalyst, (*R,R*)-teth-TsDpen-RuCl **5** (Fig. 1a), reporting that the introduction of the tether greatly increases the reaction rate and improves the stability of the catalyst.[8] Recent research on this and other classes of tethered catalysts has accelerated in recent years with several new catalysts and applications reported.[9] Moreover such catalysts are compatible with the use of formic acid/triethylamine mixtures as hydrogen source and solvent, which renders them capable of asymmetric reductions of a wide range of substrates under convenient conditions.



Scheme 1. Reagents and conditions: a) EtOAc/*t*-BuOK, Et_2O, reflux, 5 h, 48%; b) 0.3 mol% (*R*,*R*)-teth-TsDpen-RuCl **5**, 2:5 HCO_2H,Et_3N (FA/TEA), 45 min, 91%, 83% ee, 72%, > 97% ee after recrystallisation; c) triphosgene, TEA, CH_2Cl_2, 25°C, 2 h, 90%.

We investigated the reduction of ketone **2** to alcohol **3** using (*R*,*R*)-teth-TsDpen-RuCl **5** in a 5:2 mixture of formic acid/triethylamine and were pleased to obtain the alcohol in 64% yield after column chromatography, but were surprised to identify the (*S*)-(-) enantiomer as the major product in 76% *ee*. Based on the report of Zhou and co-workers[10] we changed the ratio to a 2:5 mixture of formic acid/triethylamine. Under these conditions, the yield was improved to 91% and the (*S*)-(-) enantiomer was obtained in 83% ee. Recrystalization yielded (*S*)-(-)-1-(9-fluorenyl)ethanol (**3**) in 72% yield and > 97% *ee* (Scheme 1). The absolute stereochemistry was verified by comparison to the commercially sourced (*S*)-isomer and previously prepared (*R*)-isomer (further details are given in the Supporting Information) In this synthesis of (*S*)-**3**, just 45 mg of catalyst was required to generate 3.80 g of product in >97% ee. The observed stereochemical outcome, i.e. formation of the *S*-configuration product, was somewhat surprising due to the anticipated *R*-alcohol outcome for reduction of acetophenone derivatives (Fig. 1b),[8,9,11] but this can be attributed to the additional steric hindrance that the fluorenyl group lends to the ketone forcing the larger group into the less sterically-congested region of the catalyst (Fig. 1c) in analogy with what has been observed with dialkyl ketones.[12]

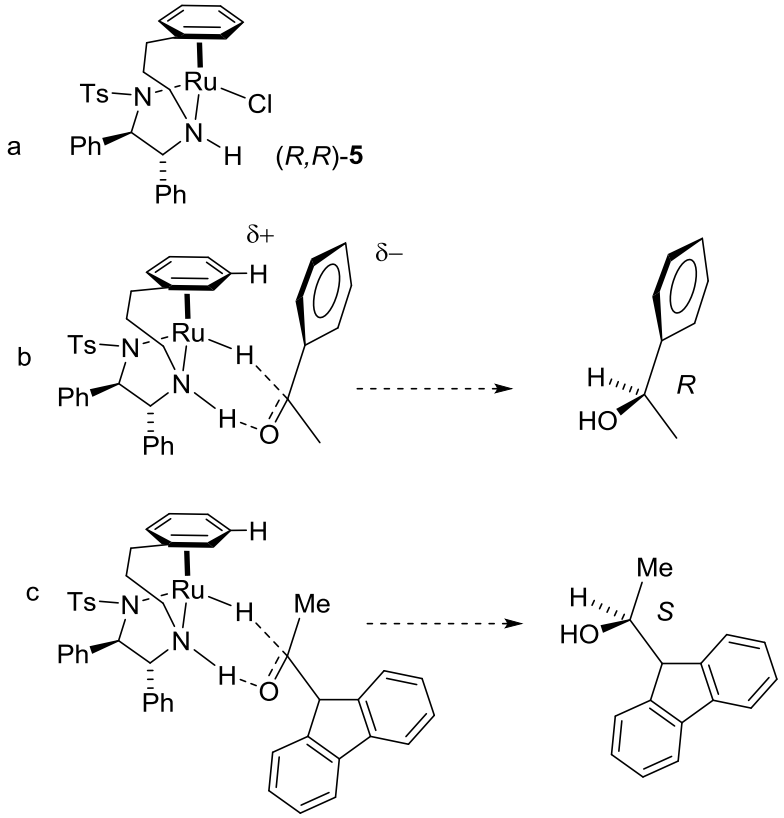
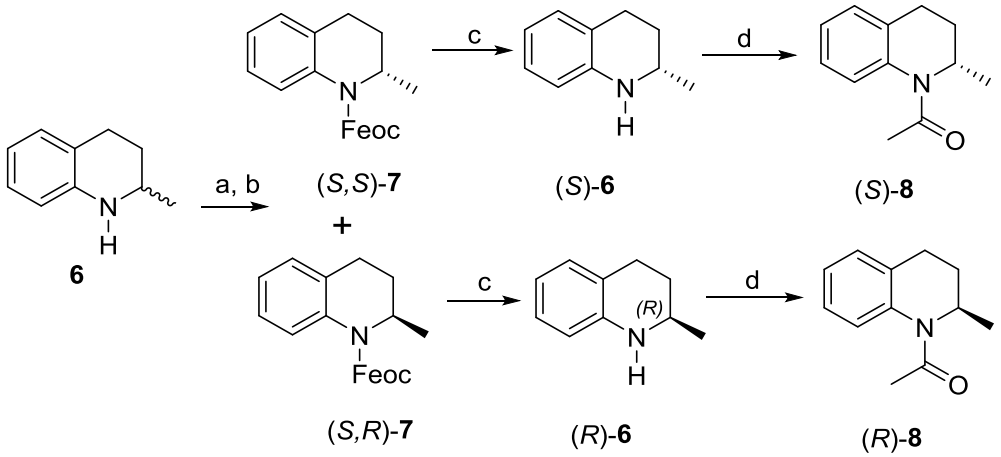


Figure 1. a) Catalyst (*R,R*)-**5**. B) Approach of acetophenone to (*R,R)*-**5**. c) Proposed approach of ketone **2** to (*R,R)*-**5**.

As well as the success of the reaction, another virtue was the operational simplicity with no special preparation of the solvents required other than degassing by a stream of nitrogen, which allows direct addition to the ketone which is not stable for extended periods. The corresponding chloroformate reagent (**4**) was then obtained by treatment of the alcohol with triphosgene, as previously described.[4]

While we previously investigated the use of FLEC to derivatise a series of racemic amino acids, we turned our attention now to the derivatisation of tetrahydroquinaldines. These heterocycles have been identified as lead compounds in fragment based drug design of bromodomain inhibitors and elaborated in the Bromodomain and Extra-Terminal Domain (BET) inhibitor, I-BET-726 which contains the *S*-tetrahydroquinaldine scaffold.[13,14] Again we had in mind the utility of FLEC not just as an analytical reagent, but as a combined resolving and protecting group.



Scheme 2. Reagents and conditions: a) (*S*)-**4**, TEA, CH_2Cl_2, RT, overnight 81% mixture, isolated (*S,S*)-**7** 11%, (*S,R*)-**7** 21%. b) column chromatography, RP-HPLC. c) piperidine, DBU, MeOH, 85% (*S*)-**6,** 81% (*R*)-**6**. d) CH_2Cl_2, Ac_2O, RT, 16h, 90% (*S*)-**8,** 93% (*R*)-**8**.

Treatment of tetrahydroquinaldine **6** with FLEC under basic conditions led to complete conversion to the carbamate **7** (Scheme 2). The diastereomers were isolated from the crude reaction by normal phase silica chromatography and were resolved by semi-preparative RP-HPLC (see Supporting Information) to give the desired (*S,S*)-**7** and (*S,R*)-**7** in 99% and 94% de respectively. The resultant product (*S,S*)-**7** was deprotected to give the (*S*)-**6** enantiomer, as confirmed by independent synthesis using phthaloyl-L-leucine as the resolving agent.[15] Acetylation yielded the BET inhibitor scaffold (*S*)-**8** (Scheme 2), which was shown to be >97% ee by chiral chromatography. The absolute stereochemistry was verified by comparison to the (*S*)-isomers and (*R*)-isomers prepared by resolution with phthaloyl-leucine (further details are given in the Supporting Information), confirming the successful FLEC-based diastereomeric resolution.

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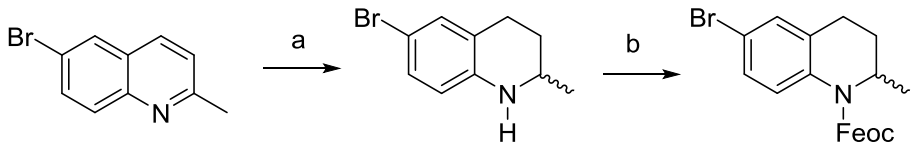
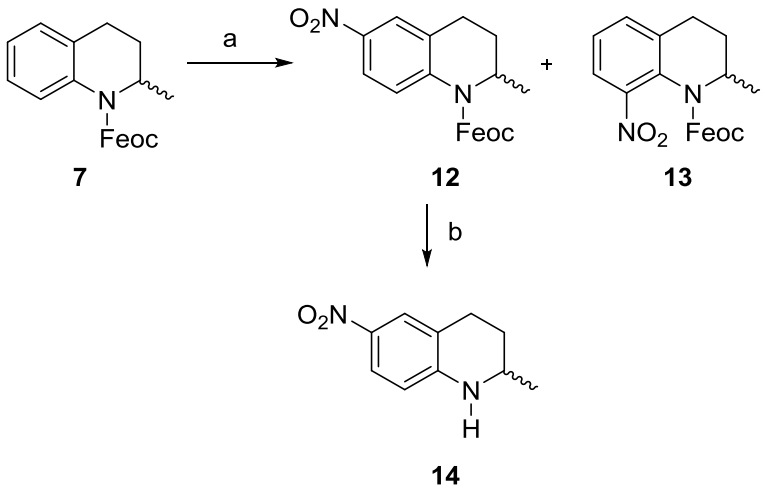


9 **10** **11**

Scheme 3. Reagents and conditions: a) $NaCNBH_3$, AcOH, RT, 5 h, 62%; b) (*S*)-**4**, CH_2Cl_2, RT, overnight, 20%.

As an analytical reagent, we could evaluate the different enantiomers of **10** formed either by the aromatic bromination of **6** or by the reduction of 6-bromoquinaldine **9** (Scheme 3)**.** FLEC derivatisation yielded the diastereomers of **11** which were resolved by RP-HPLC (Supporting Information). This provides a means of analysing the outcome of attempts at asymmetric quinoline reductions which are also desirable transformations (for example, using **5** or other chiral catalysts[16]).



7 **12** **13** **14**

Scheme 4. Reagents and conditions: a) KNO_3/H_2SO_4 in CH_2Cl_2, RT, 2.5 h, 79% (64% **12** and 15% **13**), b) pyrrolidine, CH_2Cl_2, 10 min, 60%.

Finally, we examined the potential for the FLEC-group to add regioselection to its list of valuable properties, by attempting nitration of Feoc-protected tetrahydroquinaldine (Scheme 4). This was inspired by recent comparable descriptions of regioselective nitration of Fmoc-protected tetrahydroquinoline and phthaloyl-leucinyltetrahydroquinaldine, where the appended group potentially hinders access to the C8 position allowing regioselective C6 nitration.[17,18] The reaction was attempted on the mixture of diastereomers (**7**), in order to observe any

difference that may be due to the diastereomeric form. While the reaction was successful and notably no nitration of the Feoc-group was seen, we did observe nitration at both C6 (**12**) and C8 (**13**) in a 4:1 ratio (further details of the HPLC resolution are given in the Supporting Information). Moreover, the ratio of regioisomers was the same irrespective of the diastereomeric form. The regioisomer, **12** was readily isolated by column chromatography and then successfully deprotected, to yield the racemic nitroquinaldine **14**. While not providing regiospecificity, the combination of regioselection, diastereomeric resolution and ease of deprotection supports this approach for the elaboration of other chiral amine substrates.

Conclusion.

In summary, we have developed a practical synthesis of the chiral derivatising reagent, (*S*)-fluorenylethylchloroformate (FLEC) **4**, and shown the utility of the reagent in the separation of enantiomers of unusual amines such as tetrahydroquinaldine derivatives. The FLEC enantiomers could be utilized as a combined resolving and protecting group with potential also for regioselection in synthetic medicinal chemistry applications.

Experimental Section.

General methods and instrumentation.

Fluorene and (*S*)-fluorenylalcohol were supplied by Fluka. Quinaldine was supplied by Tokyo Chemical Industry Co. Ltd. (TCI), Japan. (*R,R*)-teth-TsDpen-RuCl **5** was supplied by Johnson Matthey, UK. 6-Bromoquinaldine was supplied by Sigma-Aldrich. DIPEA, piperidine, triethylamine, EDC, DMAP and pyridine were purchased from Sigma-Aldrich. All other materials were reagent grade and purchased from either Sigma-Aldrich, Alfa-Aesar, Merck, Boron Molecular, GL Biochem, Matrix Scientific, Indofine Chemicals, Fluorochem or Apollo Scientific. All anhydrous solvents used were obtained from an MB SPS-800 Solvent Purification System. 1-(*9H*-Fluoren-9-yl)ethan-1-one **2** was prepared following a published procedure.[5,19]

The ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance III Nanobay 400 MHz spectrometer coupled to the BACS 60 automatic sample changer and obtained at 400.13 MHz and 100.62 MHz respectively, with experiments conducted at 298 K. All

spectra were processed using MestReNova 6.0 software. Chemical shifts (δ) for all the ^{1}H NMR spectra were reported in parts per million (ppm) referenced to an internal standard of residual proteo-solvent: δ 2.50 ppm for d_6-dimethylsulfoxide (d_6-DMSO), δ 3.31 ppm d_4–methanol (d_4-CD_3OD), and δ 7.26 ppm for d_1-chloroform ($CDCl_3$). The ^{1}H NMR spectra were reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz (Hz), peak integration and assignment. In reporting the spectral data, the following abbreviations have been used: Ar = aromatic, s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, hept = heptet, m = multiplet, br = broad. Chemical shifts (δ) for all the ^{13}C NMR were also reported in parts per million (ppm) referenced to an internal standard of residual proteo-solvent: δ 39.52 ppm for d_6-dimethylsulfoxide (d_6-DMSO), δ 49.00 ppm for d_4-methanol (CD_3OD), δ 77.16 ppm for d_1-chloroform ($CDCl_3$). The ^{13}C NMR spectra were reported as chemical shifts: (δ) and signals assigned as: (CO) = carbonyl carbon, (C) = quaternary carbon, (CH) = methine carbon, (CH_2) = methylene carbon and (CH_3) = methyl carbon.

Analytical Thin Layer Chromatography (TLC) was performed on silica gel 60 F_{254} pre-coated plates (0.25 mm, Merck ART 5554) and visualised by ultraviolet light, iodine or phosphomolybdic acid stain as was necessary. silica gel P60 (Velocity Scientific Solution) was used for silica gel flash chromatography.

Analytical Reverse-Phase High Performance Liquid Chromatography (RP-HPLC) was conducted on an Agilent Infinity 1260 system fitted with Zorbax Eclipse Plus C-8 Rapid Resolution 4.6 × 100 mm, 3.5 μm column (Agilent Technologies, Palo Alto, CA) using a binary solvent system (solvent A: 0.1% TFA, 99.9% H_2O; solvent B: 0.1% TFA, 99.9% acetonitrile (ACN), with ultraviolet (UV) detection at 254 nm. Except where otherwise indicated, the method used a linear gradient elution profile of 5-80% solvent B over 10 min at a flow rate of 1 mL/min.

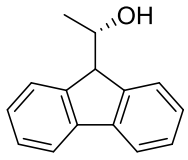
Preparative RP-HPLC was conducted on Agilent Infinity 1260 system fitted with Alltima C-8, 22 × 250 mm, 5 μm column. This system used 0.1% TFA in Milli-Q water as the aqueous buffer and 0.1% TFA in ACN as the organic buffer. The eluting profile was a linear gradient of 0 - 80% ACN in water over 40 min at 10 - 20 mL/min.

Analytical and semi-preparative chiral-HPLC were conducted on an Agilent Infinity 1260 system fitted with either of Lux 5μ Cellulose-1 or Amylose-2 columns 150 × 4.60 mm, as indicated. Isocratic elution of 10% ethanol and 90% petroleum spirits at a flow rate of 1 mL/min was used with UV detection at 254 nm.

All high resolution mass spectrometry (HRMS) analyses were performed on an Agilent 6224 time-of-flight (TOF) Mass spectrometer coupled to an Agilent 1290 Infinity liquid chromatography (LC/MS) (Agilent, Palo Alto, CA). All data were acquired and reference mass corrected *via* a dual-spray electrospray ionisation (ESI) source. Each scan or data point on the Total Ion Chromatogram (TIC) is an average of 13,700 transients, producing one spectrum every second. Mass spectra were created by averaging the scans across each peak and background subtracting against the first 10 seconds of the TIC. The acquisition was performed using the Agilent Mass Hunter Data Acquisition software version B.05.00 Build 5.0.5042.2 and analysis were performed using Mass Hunter Qualitative Analysis version B.05.00 Build 5.0.519.13. MS conditions were: Drying gas flow: 11 L/min; Nebuliser: 45 psi; Drying gas temperature: 325 °C; Capillary voltage (Vcap): 4000 V; Fragmentor: 160 V; Skimmer: 65 V; OCT RFV: 750 V; Scan range acquired: 100–1500 *m/z*; Internal reference ions: Positive Ion Mode *m/z* = 121.050873 and 922.009798. Chromatographic separation was performed using an Agilent Zorbax SB-C18 Rapid Resolution HT 2.1 × 50 mm, 1.8 μm column (Agilent Technologies, Palo Alto, CA) using an acetonitrile gradient (5% to 100%) over 3.5 min at 0.5 mL/min. Solvent A = aqueous 0.1% formic acid, Solvent B = ACN /0.1% formic acid.

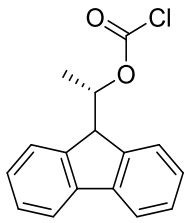
All low resolution mass spectrometry (LRMS) analyses were performed on an Agilent ultra-HPLC/MS (1260/6120) mass spectrometer coupled to an Agilent 1290 Infinity system. LC/MSD Chemstation Rev.B.04.03 coupled with Masshunter Easy Access Software was used. MS conditions are: Drying gas temperature: 325°C; Capillary voltage (Vcap): 3000 V; Scan range acquired: 100–1000 *m/z*; Ion mode: API-ES; Chromatographic separation was performed using an Agilent Poroshell 120 EC-C18 3 × 50 mm, 2.7 μm. Solvent A = aqueous 0.1% formic acid, Solvent B = ACN /0.1% formic acid. A gradient mixture of B (5% to 100%) was used over 2.5 min at 0.5 mL/min. Melting points were determined on a Mettler Toledo MP50 melting point system and are presented uncorrected.

(S)-1-(9H-Fluoren-9-yl)ethan-1-ol (*S*)-**3**.[5]



A 5:2 (molar) azeotrope of formic acid and TEA (30 mL) and (*R*,*R*)-teth-TsDpen-RuCl **5** (45 mg, 0.080 mmol, 0.3% molar ratio) was degassed under N_2 for 30 min. To the degassed mixture was added ketone **2** (5.25 g, 25.2 mmol) and the reaction mixture was stirred at 40°C for 14 h. The reaction mixture was cooled to RT and poured into water (150 mL) then acidified with 1 M aqueous HCl to pH ~ 3. The aqueous layer was extracted with diethyl ether (3 × 100 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give the crude product (4.80g, 91%, 83% ee) The residue was purified by column chromatography (2 - 60% EtOAc in petroleum benzine) then recrystallised (3% EtOAc in petroleum benzene) to provide the title compound (*S*)-**3** as white needles (3.80 g, 72%, > 97% *ee*). Mp: 101 – 102°C (lit.[5] mp: 100 – 102 °C). TLC: R_f (15% EtOAc in petroleum benzine) = 0.2. Analytical RP-HPLC: t_R = 2.62 min, purity >99%. ESI-HRMS (*m/z*): calcd for $C_{15}H_{15}O^+$ $[M+H]^+$, 211.1045; found, 211.1043. Analytical CHPLC (Lux Cellulose-1): t_R = 5.63 min (*S*) and 6.44 min (*R*), > 97% (*ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.5 Hz, 2H, Ar<u>H</u>), 7.76 – 7.72 (m, 1H, Ar<u>H</u>), 7.58 – 7.54 (m, 1H, Ar<u>H</u>), 7.45 – 7.38 (m, 2H, Ar<u>H</u>), 7.37 – 7.30 (m, 2H, Ar<u>H</u>), 4.59 (qd, *J* = 6.3, 4.4 Hz, 1H, C<u>H</u>(OH)), 4.19 (d, *J* = 4.4 Hz, 1H, C<u>H</u>CH(OH), 1.65 (s, 1H, O<u>H</u>) and 0.96 (d, *J* = 6.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (C), 143.9 (C), 142.0 (C), 141.8 (C), 127.5 (2 × CH), 127.0 (CH), 126.9 (CH), 125.7 (CH), 124.8 (CH), 120.0 (CH), 119.9 (CH), 70.5 (CH), 54.6 (CH) and 18.7 (CH_3) ppm.

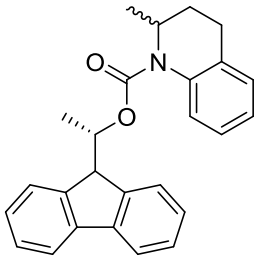
(S)-1-(9H-Fluoren-9-yl)ethyl carbonochloridate [*(S)-FLEC*] (*S*)-**4.**[1,4,5,19]



To a stirred solution of triphosgene (128 mg, 0.431 mmol) in dry CH_2Cl_2 (4 mL) at 0°C was added (*S*)-**3** (208 mg, 0.991 mmol) in one portion followed by a solution of pyridine (110 mg, 1.39 mmol) in CH_2Cl_2 (5 mL) over 30 minutes at 0 – 5 °C. The mixture was allowed to warm slowly to RT and stirring was continued for a further 2.5 h. The resulting mixture was washed with ice-cold water (3 × 25 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (*S*)-1-(9*H*-fluoren-9-yl)ethyl carbonochloridate (**4**) as a clear oil (243 mg, 90%). The ^{1}H NMR of the isolated product

showed 95% purity, with the remaining 5% being identified as the starting alcohol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.5, 3.9 Hz, 2H, ArH), 7.68 (dd, *J* = 7.5, 0.9 Hz, 1H, ArH), 7.53 – 7.50 (m, 1H, ArH), 7.46 – 7.39 (m, 2H, ArH), 7.38 – 7.30 (m, 2H, ArH), 5.67 (qd, *J* = 6.4, 4.4 Hz, 1H, CHCH$_3$), 4.40 (d, *J* = 4.4 Hz, 1H, CHCHCH$_3$), 0.83 (d, *J* = 6.4 Hz, 3H, CH$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (CO), 142.2 (C), 142.1 (C), 141.9 (C), 141.7 (C), 128.23 (CH), 128.17 (CH), 127.50 (CH), 127.45 (CH), 126.3 (CH), 124.5 (CH), 120.3 (CH), 120.2 (CH), 81.9 (CH), 51.1 (CH) and 13.9 (CH$_3$) ppm.

(*S,S*) *and* (*S,R*)*-1-(9H-Fluoren-9-yl)ethyl-2-methyl-3,4-dihydroquinoline-1(2H)-carboxylate* **7.**



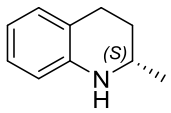
To a solution of racemic tetrahydroquinaldine (THQ) (6) (352 mg, 2.4 mmol) in CH_2Cl_2 (12 mL) at 0°C was added (*S*)-**4** (980 mg, 3.6 mmol) and TEA (290 mg, 2.80 mmol). The mixture was stirred overnight at RT, the solvent was evaporated in vacuo and the residue was taken up in EtOAc and washed with 1 M aqueous HCl (3 × 40 mL) and brine (1 × 40 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was purified by silica gel column chromatography (3 - 60% EtOAc in petroleum benzine) to afford 7 (750 mg, 81%, <1% de) as a white solid. The diastereomers were resolved by RP-HPLC (35 - 80% ACN in 0.1% aq. TFA) to give (*S,S*)-**7** (80 mg, 11%, 99% de) and (*S,R*)-7 (150 mg, 21%, 94% de).

(*S,S*)-**7**: Mp 57 – 59 °C. TLC: R_f (10% EtOAc in petroleum benzine) = 0.34. Analytical RP-HPLC: 20-80% solvent B, 5 minutes, t_R = 3.83 min (*S*/*S*), purity >99% (de). ESI-HRMS (*m/z*): calcd for $C_{26}H_{26}NO_2^+$ $[M+H]^+$, 384.1958; found, 384.1966. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.6 Hz, 2H, ArH), 7.59 (t, *J* = 8.7 Hz, 2H, ArH), 7.50 (d, *J* = 7.5 Hz, 1H, ArH), 7.43 – 7.29 (m, 3H, ArH), 7.26 – 7.02 (m, 4H, ArH), 5.81 – 5.66 (m, 1H, CHCHCO), 4.72 – 4.54 (m, 1H, NCH), 4.38 (d, *J* = 3.1 Hz, 1H, CHCHCO), 2.78 – 2.59 (m, 2H, CCH$_2$), 2.27 (td, *J* = 12.9, 6.6 Hz, 1H, CCH$_2$CH$_2$), 1.55 (td, *J* = 13.3, 6.9 Hz, 1H, CCH$_2$CH$_2$), 1.20 (d, *J* = 6.5 Hz, 3H, OCHCH$_3$) and 0.83 (d, *J* = 6.3 Hz, 3H, NCHCH$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (CO), 143.6 (C), 143.5

(C), 142.2(C), 141.7 (C), 136.7 (C), 132.3 (C), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 126.0 (CH), 125.7 (CH), 124.8 (CH), 124.3 (CH), 120.0 (CH), 119.9 (CH), 74.3 (CH), 52.2 (CH), 49.9 (CH), 31.5 (CH_2), 25.5 (CH_2), 19.8 (CH_3) and 14.9 (CH_3) ppm.

(*S,R*)-**7**: Mp: 103 – 105°C. TLC: R_f (10% EtOAc in petroleum benzine) = 0.28. . Analytical RP-HPLC: 20-80% solvent B, 5 minutes, t_R = 3.95 min (*S*/*R*) >99% purity, 94% (de). ESI-HRMS (*m/z*): calcd for $C_{26}H_{26}NO_2^+$ $[M+H]^+$, 384.1958; found, 384.1965. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.5, 2.9 Hz, 2H, ArH), 7.53 (dd, *J* = 12.4, 7.8 Hz, 2H, ArH), 7.41 – 7.27 (m, 3H, ArH), 7.25 – 7.06 (m, 5H, ArH), 5.80 – 5.71 (m, 1H, CHCHCO), 4.77 – 4.65 (m, 1H, NCH), 4.29 (d, *J* = 3.8 Hz, 1H, CHCHCO), 2.79 – 2.64 (m, 2H, CCH_2), 2.36 – 2.24 (m, 1H, CCH_2CH_2), 1.56 (td, *J* = 13.4, 6.8, Hz, 1H, CCH_2CH_2), 1.24 (d, *J* = 6.5 Hz, 3H, $OCHCH_3$) and 0.78 (d, *J* = 6.4 Hz, 3H, $NCHCH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (CO), 143.5 (C), 143.4 (C), 142.2 (C), 141.7 (C), 136.7 (C), 132.7 (C), 127.8 (CH), 127.7 (CH), 127.5 (CH), 127.2 (CH), 126.9 (CH), 126.4 (CH), 126.19 (CH), 126.17 (CH), 124.7 (CH), 124.4 (CH), 120.0 (CH), 119.8 (CH), 74.0 (CH), 51.9 (CH), 49.9 (CH), 31.5 (CH_2), 25.5 (CH_2), 19.8 (CH_3) and 14.9 (CH_3) ppm.

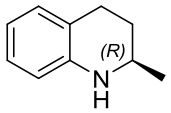
(S)-2-Methyl-1,2,3,4-tetrahydroquinoline, (*S*)-**6.** [15]



To a solution of carbamate (*S,S*)-**7** (40 mg, 0.10 mmol) in MeOH (1.0 M) was added piperidine (0.05 mL) and DBU (0.05 mL). The mixture was stirred at RT for 2 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (0 - 15% EtOAc in petroleum benzine) to give the title compound (*S*)-**6** as a pale yellow oil (13 mg, 85%). TLC: R_f (10% EtOAc in petroleum benzine) = 0.80. Analytical RP-HPLC: t_R = 3.80 min, >99% purity. ESI-HRMS (*m/z*): calcd for $C_{10}H_{14}N^+$ $[M+H]^+$, 148.1121; found, 148.1122. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 – 6.92 (m, 2H, ArH), 6.63 – 6.58 (m, 1H, ArH), 6.50 – 6.44 (m, 1H, ArH), 3.88 – 3.48 (br, 1H, NH), 3.49 – 3.29 (m, 1H, CH), 2.91 – 2.65 (m, 2H, CH_2), 2.00 – 1.85 (m, 1H, CH_2), 1.65 – 1.59 (m, 1H, CH_2) and 1.23 – 1.18 (d, *J* = 6.3 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$)

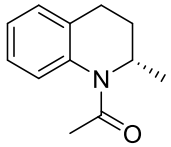
δ 144.9 (C), 129.4 (CH), 126.8 (CH), 121.2 (C), 117.1 (CH), 114.1 (CH), 47.3 (CH), 30.3 (CH_2), 26.7 (CH_2) and 22.8 (CH_3) ppm.

(R)-2-Methyl-1,2,3,4-tetrahydroquinoline (*R*)-**6.**[21]



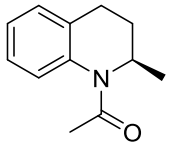
To a solution of carbamate (*S,R*)-**7** (40 mg, 0.10 mmol) in MeOH (1.0 M) was treated as for (*S,S*)-**7a** above to give (*R*)-**6** as an oil (12 mg, 81%). TLC: R_f (10% EtOAc in petroleum benzine) = 0.8. Analytical RP-HPLC: t_R = 3.81 min, purity >99%. The data matched that previously reported for (*S*)-**6** above.

(S)-1-(2-Methyl-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (*S*)-**8.**



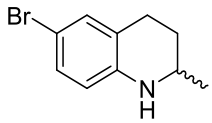
To a solution of (*S*)-1-(2-Methyl-3,4-dihydroquinolin-1(2*H*)-yl)ethan-1-one (*S*)-**6** (30 mg, 0.20 mmol) (1.0 equiv.) in dichloromethane (CH_2Cl_2) (0.1 M) at 0°C was added acetic anhydride (4.0 equiv.) and the mixture was allowed to stir at room temperature (RT) for 16 h. The mixture was poured into ice-water and acidified with 1 M aqueous HCl to pH~ 4. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried (Na_2SO_4), and concentrated *in vacuo* to give (*S*)-**8** (35 mg, 90%) as a colourless crystalline solid. Mp: 50 – 51°C. TLC: R_f (15% EtOAc in petroleum benzine) = 0.3. Analytical RP-HPLC: 6.62 min, >99% purity. ESI-HRMS (*m/z*): calcd for $C_{12}H_{16}NO^+$ $[M+H]^+$, 190.1226; found, 190.1227. Analytical CHPLC: Lux Amylose-2, t_R = 5.07 min (*S*) 97% (*ee*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.03 (m, 4H, Ar<u>H</u>), 4.78 (br.s, 1H, C<u>H</u>CH_3), 2.67 – 2.44 (m, 2H, CC<u>H</u>$_2$), 2.41 – 2.28 (m, 1H, CH_3CHC<u>H</u>$_2$), 2.14 (s, 3H, C(O)C<u>H</u>$_3$), 1.41 – 1.23 (m, 1H, CH_3CHC<u>H</u>$_2$) and 1.12 (d, *J* = 6.5 Hz, 3H, C<u>H</u>$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7 (CO), 166.3 (C), 137.7 (C), 127.4 (CH), 126.2 (CH), 125.9 (CH), 125.6 (CH), 48.4 (CH), 32.7 (CH_2), 26.2 (CH_2), 23.0 (CH_3) and 20.3 (CH_3) ppm. The product was identical to a sample obtained by acetylation of (*S*)-**6** from diastereomeric resolution.[15]

(R)-1-(2-Methyl-3,4-dihydroquinolin-1(2H)-yl)ethan-1-one (*R*)-**8**.



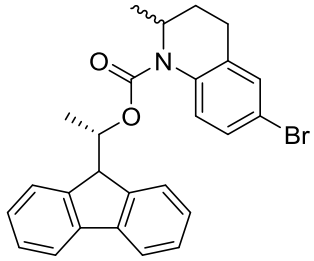
(*R*)-1-(2-Methyl-3,4-dihydroquinolin-1(2*H*)-yl)ethan-1-one (*2R*)-**6** (25 mg, 0.18 mmol) was treated as for (*2S*)-**6** above to give the desired compound (*R*)-1-(2-methyl-3,4-dihydroquinolin-1(2*H*)-yl)ethan-1-one (*R*)-**8** (30 mg, 93%) as a clear oil. TLC: R_f (15% EtOAc in petroleum benzine) = 0.3. Analytical RP-HPLC t_R = 6.62 min, >99% purity. ESI-HRMS (*m/z*): calcd for $C_{12}H_{16}NO^+$ $[M+H]^+$, 190.1226; found, 190.1227. Analytical CHPLC (Lux Amylose-2: t_R = 6.08 min (*R*) 94% (*ee*). The data matched that previously reported for (*S*)-**8** above.

6-Bromo-2-methyl-1,2,3,4-tetrahydroquinoline **10.**[16b,20]



To a solution of 6-bromo-2-methylquinoline (6-bromoquinaldine, **9**) (2.00 g, 9.01 mmol) in glacial AcOH (5.0 mL) kept below 30°C was added $NaCNBH_4$ (1.13 g, 18.1 mmol) portionwise. The mixture was stirred at RT for 5 h. The reaction mixture was then neutralised by saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography to provide the title compound **10** as a brown solid (1.26 g, 62%). Mp: 43-45°C. TLC: R_f (10% EtOAc in petroleum benzine) = 0.5. ESI-HRMS (*m/z*): calcd for $C_{10}H_{13}BrN^+$ $[M(^{79}Br)+H]^+$, 227.0258; found, 227.0252. Analytical CHPLC: t_R = 3.25 min and 3.75 min (racemic). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.1 Hz, 1H, Ar<u>H</u>), 7.04 (d, *J* = 8.4 Hz, 1H, Ar<u>H</u>), 6.35 (d, *J* = 8.4 Hz, 1H, Ar<u>H</u>), 3.59 (br.s, 1H, N<u>H</u>), 3.45 – 3.29 (m, 1H, NHC<u>H</u>), 2.89 – 2.56 (m, 2H, C<u>H</u>$_2$), 2.02 – 1.82 (m, 1H, C<u>H</u>$_2$), 1.62 – 1.44 (m, 1H, C<u>H</u>$_2$) and 1.21 (d, *J* = 6.3 Hz, 3H, C<u>H</u>$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3(CH), 132.9 (C), 131.0 (CH), 129.0 (C), 125.9 (CH), 123.3 (C), 51.8 (CH), 26.6 (CH_2), 24.5 (CH_2) and 18.0 (CH_3) ppm.

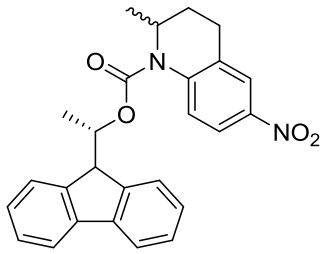
(*S,S*)- and (*S,R)-1-(9H-Fluoren-9-yl)ethyl-2-methyl-3,4-dihydroquinoline-1(2H)-carboxylate* **11.**



Compound **11** was prepared as for **7**, above using **10** (24mg, 0.15mmol) and (*S*)-**4** (42 mg, 0.16 mmol). The products were purified by column chromatography (10% Et_2O in petroleum benzine) to yield a mixture of diastereoisomers **11** as a colourless oil (10 mg, 20%).

R_f (10% Et_2O in petroleum benzine) = 0.3. Analytical RP-HPLC: 80-100% B, 9 minutes, t_R = 3.38, 3.55 min (*S*/*R*) >99% purity. ESI-HRMS (*m/z*): calcd for $C_{26}H_{25}NO_2{}^{81}Br^+$ $[M+H]^+$, 464.1048; found, 464.1053. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.5 Hz, 2H, ArH) 7.72 (dd, *J* = 7.5, 2.9 Hz, 2H, ArH), 7.59 (dd, *J* = 7.8, 1 Hz, 1H, ArH) 7.54 (d, *J* = 7.8 Hz, 1H, ArH), 7.50 (d, *J* = 7.8 Hz, 1H, ArH) 7.42 – 7.17 (m, 15H, ArH), 5.76 – 5.71 (m, 2H, CHCHCO), 4.67 (q, 1H, NCH), 4.61 (q, 1H, NCH), 4.36 (d, *J* = 3.8 Hz, 1H, CHCHCO) 4.29 (d, *J* = 3.8 Hz, 1H, CHCHCO), 2.73 – 2.58 (m, 4H, CCH_2), 2.27 – 2.17 (m, 2H, CCH_2CH_2), 1.56 (m, 5H, CCH_2CH_2), 1.19 (d, *J* = 6.5 Hz, 3H, $OCHCH_3$) 1.15 (d, *J* = 6.5 Hz, 3H, $OCHCH_3$) and 0.89 (d, *J* = 6.4 Hz, 3H, $NCHCH_3$) 0.8 (d, *J* = 6.4 Hz, 3H, $NCHCH_3$) ppm.

(S)-1-(9H-Fluoren-9-yl)ethyl-2-methyl-6-nitro-3,4-dihydroquinoline-1(2H)-carboxylate **12**.



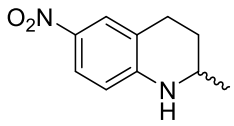
To a solution of **7** (58 mg, 0.15 mmol) in CH_2Cl_2 (2.0 mL) at RT was added concentrated sulphuric acid (15 mg, 0.15 mmol) and potassium nitrate (15 mg, 0.15 mmol). The mixture was stirred for 2.5 h The mixture was poured over ice and then extracted with CH_2Cl_2 (3 × 20 mL) and washed successively with 5% aqueous $NaHCO_3$ (20 mL), water (20 mL) and brine (20 mL). The solution was dried (Na_2SO_4) and

concentrated *in vacuo.* The residue was purified by column chromatography (15% EtOAc in petroleum spirit) to afford **12** (diastereomeric mixture of (*S*,*S*) and (*S*,*R*)) (41 mg, 64%).

12: TLC: R_f (15% EtOAc in petrol) = 0.4. ESI-HRMS (*m/z*): calcd for $C_{26}H_{24}N_2O_4^+$ $[M]^+$, 428.1736; found, 428.1736. Analytical RP-HPLC: 20-100% CH_3CN in 0.05% TFA at a flow rate of 0.2 mL/min over 10 min on a C8, 100 Å, 5 µm, (150 × 4.6 mm I.D.) column (Phenomenex), t_R = 15.01 min and 15.12 min (equal diastereomeric mixture of (*S*,*S*) and (*S*,*R*)), purity >99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.87 (m, 2H, ArH), 7.70 (s, 1H), 7.59 (dd, *J* = 4.7, 4.1 Hz, 2H, ArH), 7.52 – 7.47 (m, 1H, ArH), 7.35 – 7.26 (m, 4H, ArH), 7.13 – 7.01 (m, 1H, ArH), 5.68 (qd, *J* = 6.5, 3.7 Hz, 1H, COCH), 4.65 – 4.55 (m, 1H, NCH), 4.24 (d, *J* = 3.3 Hz, 1H, COCHCH), 2.75 (ddd, *J* = 13.4, 9.2, 5.1 Hz, 2H, CH_2), 2.14 – 2.00 (m, 1H, CH_2), 1.60 – 1.53 (m, 1H, CH_2), 1.12 – 1.08 (m, 3H, CH_3) and 0.94 (d, *J* = 6.4 Hz, 3H, NCHCH_3) ppm.

Further elution yielded the 8-nitro substituted regioisomer **13** as mixture of (*S*,*S*) and (*S*,*R*) diastereomers. Analytical RP-HPLC: t_R = 15.25 min and 15.35 min (equal diastereomeric mixture of (*S*,*S*) and (*S*,*R*)), purity 70%. (10 mg, 15%): TLC: R_f (40% EtOAc in petrol) = 0.30. ESI-LRMS (*m/z*): $C_{26}H_{25}N_2O_4^+$ $[M+H]^+$, 429.18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.95 (m, 2H, ArH), 7.65 – 7.59 (m, 3H, ArH), 7.52 – 7.47 (m, 1H, ArH), 7.35 – 7.26 (m, 4H, ArH), 7.13 – 7.01 (m, 1H, ArH), 5.81 – 5.75 (m 1H, COCH), 4.65 – 4.55 (m, 1H, NCH), 1.39 – 1.25 (m, 1H, COCHCH), 2.85 – 2.74 (m, 2H, CH_2), 2.20 – 2.11 (m, 1H, CH_2), 1.75 – 1.60 (m, 1H, CH_2), 1.21 – 1.19 (m, 3H, CH_3) and 0.80 (d, *J* = 6.4 Hz, 3H, NCHCH_3) ppm.

2-Methyl-6-nitro-1,2,3,4-tetrahydroquinoline **14.**[13]



To a solution of carbamate, **12** (37 mg, 0.091 mmol) in CH_2Cl_2 (0.01 M) was added pyrrolidine (1.0 mL). The mixture was stirred at RT for 10 - 15 min. The solvent was removed *in vacuo* to give the crude product as a yellow liquid. The crude liquid was purified by RP-HPLC (60 - 100% ACN in water and 0.1% TFA) to give **14** as a yellow solid (10 mg, 60%).

Mp: 132.0 - 133.4 °C (lit.[13] mp: 140 – 142 °C). TLC: R_f (15% EtOAc in petroleum benzine) = 0.4. Analytical RP-HPLC: t_R = 3.20 min, purity >99%. ESI-HRMS (*m/z*):

calcd for $C_{10}H_{13}N_2O_2^+$ $[M+H]^+$, 193.0972; found, 193.0970. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H, ArH), 6.39 – 6.33 (m, 1H, ArH), 4.55 (br.s, 1H, NH), 3.59 – 3.49 (m, 1H, CHCH$_3$), 2.83 – 2.78 (m, 2H, CH$_2$), 2.04 – 1.96 (m, 1H, CH$_2$), 1.61 – 1.51 (m, 1H, CH$_2$) and 1.27 (d, *J* = 6.4 Hz, 3H, CH$_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (C), 125.9 (CH), 124.4 (CH), 121.2 (C), 119.8 (C), 112.2 (CH), 47.3 (CH), 28.9 (CH_2), 26.3 (CH_2) and 22.3 (CH_3) ppm.

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Conflict of interest

The authors declare no conflicts of interest.

Data sharing statement

The research data (and/or materials) supporting this publication can be accessed at http://wrap.warwick.ac.uk/ and https://monash.figshare.com/.

Supporting Information.

†Electronic Supporting Information (ESI) available: NMR spectra and HPLC spectra relating to ee and dr determination are available as Supporting Information. See DOI: 10.1039/b000000x.

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