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Stereospecific synthesis of mexiletine and related compounds: Mitsunobu versus Williamson reaction

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Abstract

Mexiletine [1-(2,6-dimethylphenoxy)-2-propanamine], a chiral, orally effective antiarrhythmic agent, and several analogues substituted on either the stereogenic centre or the xylyloxy moiety, were prepared in both, highly enriched, optically active forms. According to the 'chiral pool' approach, the appropriate amino alcohols, protected as the corresponding phthalimide derivatives, were condensed with the desired phenols under either Mitsunobu (method A) or Williamson (method B) conditions. Generally, method A provided the most efficient route, both in terms of yields and number of steps necessary. Only when an isopropyl group was present on the stereogenic centre, i.e. when 2-amino-3-methylbutanol was used as the starting alcohol, method B proved to be the only available route, method A giving no product other than the starting phthalimide derivative. Regardless of the method used, enantiomeric excesses ranged from 91 to 99%. Given the availability of both variously substituted phenols and optically active amino alcohols, the two methods described herein, taken together, may serve as a versatile approach, useful to meet the needs of new chiral, optically active mexiletine analogues, possibly endowed with higher potency in exerting a use-dependent block on sodium channels and/or more resistant to biotransformations.

1. Introduction

Mexiletine **1a** (Fig. 1) is a chiral therapeutically relevant compound, clinically used as an antiarrhythmic,[1] antimyotonic,[2] and analgesic[3] agent, in its racemic form. However, several lines of evidence have shown that mexiletine enantiomers differ in both pharmacodynamics[4] and pharmacokinetics.[5] In the last decade, starting a program aimed at the discovery of sodium channel blockers effective as antimyotonic agents,[4d,6] we needed a convenient and facile stereospecific route to mexiletine and analogues of general formula **1** (Fig. 1).

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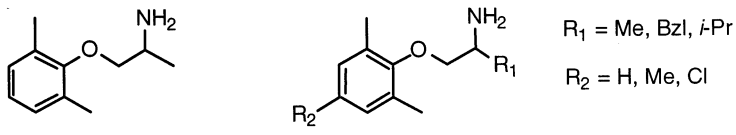
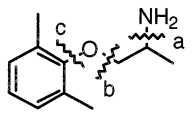


1a **1**

Figure 1. Chemical structure of mexiletine **1a** and general formula of **1a** analogues **1**

Since the resolution methods are in our opinion solvent-wasting, time-consuming, and tedious,[4a,7] we reviewed the 'chiral pool' approach syntheses reported for **1a** (illustrated by disconnections in Fig. 2). In the early 1990's, a method based on the relatively expensive chiral starting material, (+)-(*S*)-3-bromo-2-methyl-1-propanol, was reported to allow the synthesis of (−)-(*R*)-**1a**.[7a] The key step was the stereospecific Hoffmann degradation (disconnection a) of 2-methyl-3-(2,6-xylyloxy)propanamide ultimately obtained by Williamson reaction on the starting bromo alcohol (disconnection b). This four-step route does not give the target molecule in satisfactory overall yield (7%) and can not be extended to mexiletine analogues bearing substituents other than methyl on the stereogenic centre since the corresponding chiral starting alcohols are not commercially available.



1a

Figure 2. Retrosynthetic analysis on mexiletine **1a**

Recently, a concise procedure has been proposed: starting from 2 equiv. of both commercially available enantiomers of 2-amino-1-propanol and 1 equiv. of 1,3-dimethyl-2-fluorobenzenetricarbonylchromium, Loughhead et al.[8] obtained enantiomerically pure **1a** enantiomers in 32–41% yields referred to the above aryl chromium tricarbonyl complex (disconnection c).

Several related 2,6-xylyl aminoalkyl ethers were also prepared in optically active form, but the enantiomeric excess (ee) values for these analogues were not given. This elegant two-step route was not suitable for our goal, being tainted with a few drawbacks. It starts with the preparation of 1,3-dimethyl-2-fluorobenzenetricarbonylchromium from the relatively expensive 2-fluoro-*m*-xylene. Loughhead et al. did not report the yield relative to this step but referred to Mahaffy and Hamilton,[9] who prepared the above aryl chromium tricarbonyl complex in 28% yield. Thus, overall yields are not supposed to be higher than 15% and are expected to be even lower when passing to further substituted 2-fluoro-1,3-dimethylbenzenes, due to steric hindrance and/or electron-withdrawing effects.[10] Furthermore, 4-substituted 2-fluoro-1,3-dimethylbenzenes are not commercially available. Very recently, a facile synthesis of both **1a** enantiomers in moderate overall yields (24–34%) and acceptable ee (93–96%) has been proposed.[11] The key step was the stereospecific OH/NH_2 exchange by Mitsunobu's Gabriel-type synthesis-reaction of phthalimide with 1-(2,6-xylyloxy)-2-propanol (disconnection a), in turn obtained by regiospecific S_N2 propylene oxide ring opening by 2,6-xylenol (disconnection b). This route suffers from the limited

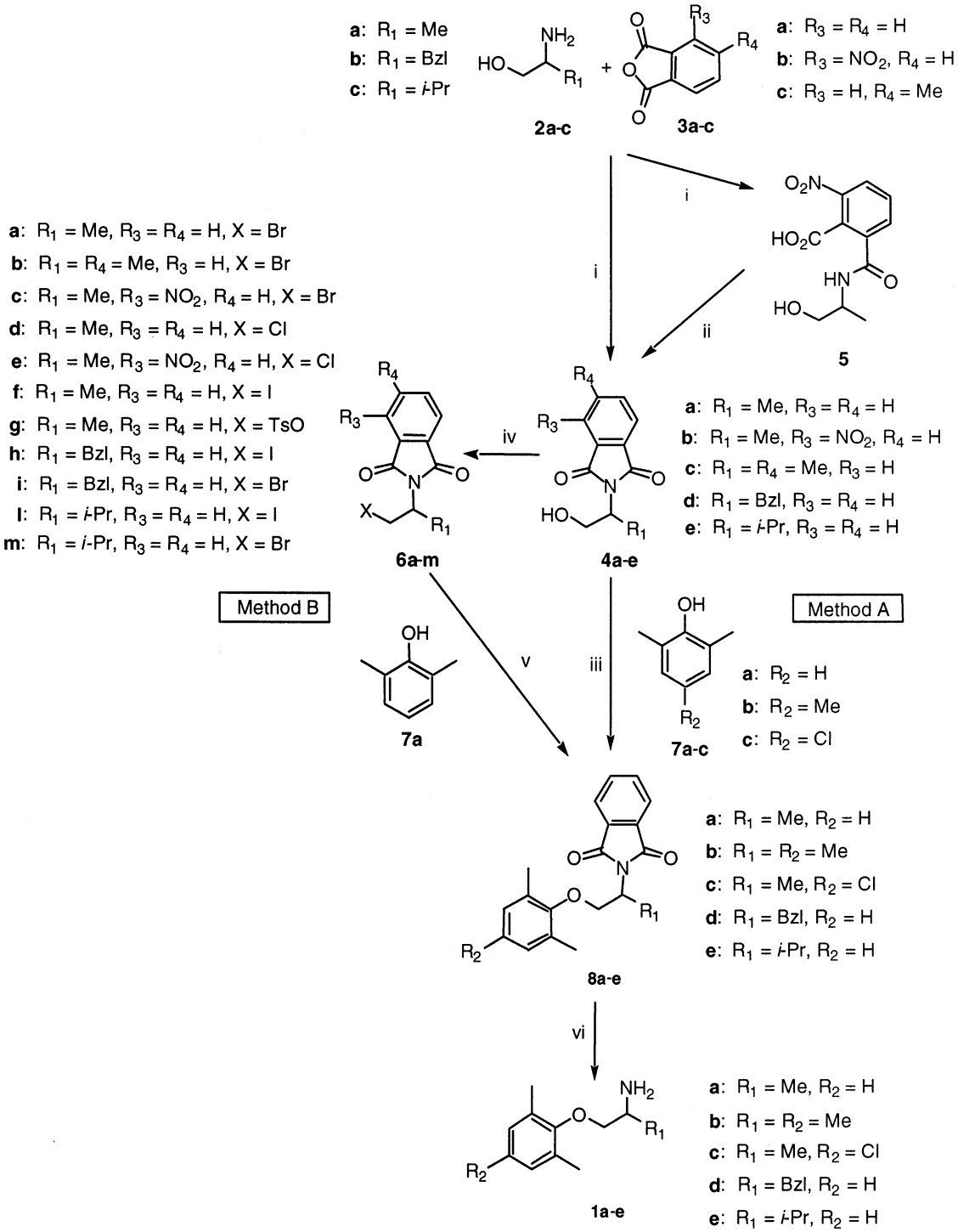
number of commercially available chiral epoxides, actually being only applicable to **1a** analogues bearing a phenyl group on the stereogenic centre.[12]

Considering the above routes as not completely satisfactory, we tried to distil the best from each of them, i.e. the use of widely available phenols to be coupled to relatively inexpensive optically active α-amino alcohols, in order to develop a new versatile route to **1**. Thus, we got inspiration from a patent by Synthelabo scientists[13] who condensed (*S*)-*N*-*tert*-butyloxycarbonyl(Boc)-2-aminopropanol with 2-bromo-5-fluorophenol under Mitsunobu conditions (disconnection b) to obtain intermediates in the synthesis of polycyclic 5-HT_3 and 5-HT_4 antagonists. The same reaction has been recently reported to allow the synthesis of (*R*)- and (*S*)-1-phenoxy-2-propanamine as intermediates to *N*-substituted adenosines.[14]

Herein we propose the modification of this route, and its application to the preparation of our target molecules **1**. The key step is an etherification reaction, which was performed under both Mitsunobu (method A) and Williamson (method B) conditions. The relative merits are discussed.

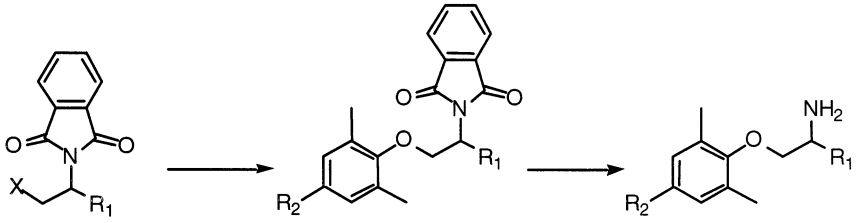
2. Results and discussion

The synthetic route adopted is shown in Scheme 1. It starts from commercially available homochiral α-amino alcohols **2a–c** which were to be submitted to a condensation step with the suitable phenols **7a–c**. We did not succeed in directly condensing **2a** with 2,6-dimethylphenol **7a** under Mitsunobu conditions, this reaction affording a complex mixture in which the desired product was absent, as stated by gas chromatograph/mass (GMS) analysis. Nor can the conversion of **2a–c** into the corresponding halides, to be submitted to Williamson reaction, be run on the amino alcohols in their free base form. Thus, a protection for the amino group of **2a–c** was needed. Instead of Boc-protection,[13,14] phthalic anhydride **3a**, a low cost solid, was chosen as the *N*-protecting agent, in our opinion being more convenient than normally used *N*-*tert*-butyloxycarbonylating agents which are liquid or relatively expensive solid reagents. Indeed, condensation of primary amines with **3a** generally gives the corresponding phthalimide derivatives in high yields,[15] and the same is true for the relative standard deprotection reaction.[16] Furthermore, phthalimide derivatives of amino alcohols have no acidic hydrogen but the alcoholic one, and this was supposed to enhance yields in the successive Mitsunobu step, where a possible competition between the *N*-Boc-amino alcohol carbamic NH and the hindered xylenolic OH might be feared. In our hands, phthalimido alcohols **4a–c** were obtained in high yields (78–94%, 72–87% after recrystallization). Two **3a** analogues, i.e. 3-nitro- and 4-methylphthalic anhydrides (**3b** and **3c**, respectively) may also be used in this step. When **3b** was used, about 40% of the starting **2a** was recovered as the corresponding 2-carboxy-3-nitrobenzoyl derivative **5**,[17] which may be converted into the desired phthalimide adduct **4b** by refluxing **5** in acidic milieu. Considering **4b** coming from the last step together with the first amount directly obtained from the condensation of **2a** with **3b**, yields were in the same range observed with **3a**, and the same is true for the condensation of **2c** with **3a** to give **4e**. However, considering the lower cost of **3a**, the latter was taken as the protecting reagent of choice. The phthalimide derivative **4a** was submitted to condensation with the desired phenols **7a–c** under Mitsunobu conditions[18] (method A) to obtain the corresponding aryl ethers **8a–c**. Yields were generally moderate (23–65%, see Table 1) and, in this respect, diisopropyl azodicarboxylate (DIAD) seems



Scheme 1. Stereospecific synthesis of mexiletine **1a** and analogues **1b–e**. Reagents and conditions: (i) toluene/Et_3N/reflux/3 h; (ii) toluene/*p*-TsOH/reflux/6 h or EtOH/HCl/reflux/24 h; (iii) THF/PPh_3/DEAD or DIAD (see text)/rt/24 h; (iv) toluene/HBr(g) or HI (g)/−5°C→rt, 18 h→80°C, 2 h (when X=Br or I); THF/$SOCl_2$/pyridine/60°C/6 h (when X=Cl); pyridine/*p*-TsCl/rt/18 h (when X=TsO); (v) DMF/Na_2CO_3/130°C/24 h; (vi) N_2H_4/AcOH/EtOH/reflux/2 h

Table 1
Aryloxy alkylamines **1** and phthalimidoalkyl aryl ether intermediates **8** from either phthalimido alcohols **4** or phthalimido alkyl halogenides **6**



4 or **6** **8** **1**

Entry	Substrate	Substitution		Method[a]	Phthalimido ether		Substitution	Amine	
		R_1	X		% Yield		R_2	% Overall yield (% ee)	
1	(−)-(*R*)-**4a**	Me	OH	A[b]	(*R*)-**8a**	29	H	(−)-(*R*)-**1a**	22 (98)[e]
2	(−)-(*R*)-**4a**	Me	OH	A[c]	(*R*)-**8a**	65	H	(−)-(*R*)-**1a**	48 (98)[e]
3	(+)-(*S*)-**4a**	Me	OH	A[b]	(*S*)-**8a**	28	H	(+)-(*S*)-**1a**	17 (99)[e]
4	(+)-(*S*)-**4a**	Me	OH	A[c]	(*S*)-**8a**	55	H	(+)-(*S*)-**1a**	40 (91)[e]
5	(−)-(*R*)-**4a**	Me	OH	A[b]	(*R*)-**8b**	22	Me	(−)-(*R*)-**1b**	17 (97)[e]
6	(+)-(*S*)-**4a**	Me	OH	A[b]	(*S*)-**8b**	31	Me	(+)-(*S*)-**1b**	25 (95)[e]
7	(−)-(*R*)-**4a**	Me	OH	A[b]	(*R*)-**8c**	52	Cl	(−)-(*R*)-**1c**	25 (98)[e]
8	(+)-(*S*)-**4a**	Me	OH	A[b]	(*S*)-**8c**	41	Cl	(+)-(*S*)-**1c**	26 (97)[e]
9	(+)-(*R*)-**4d**	Bzl	OH	A[c]	(*R*)-**8d**	43	H	(−)-(*R*)-**1d**	13 (93)[f]
10	(−)-(*S*)-**4d**	Bzl	OH	A[c]	(*S*)-**8d**	54	H	(+)-(*S*)-**1d**	14 (99)[g]
11	(+)-(*R*)-**6h**	Bzl	I	B	(*R*)-**8d**	57	H	(−)-(*R*)-**1d**·HCl	7[h] (n.d.)[d]
12	(−)-(*S*)-**6i**	Bzl	Br	B	(*S*)-**8d**	60	H	(+)-(*S*)-**1d**·HCl	8[h] (n.d.)[d]
13	(−)-(*R*)-**6l**	*i*-Pr	I	B	(*R*)-**8e**	n.d.[d]	H	(−)-(*R*)-**1e**·HI	8[h] (99)[g]
14	(+)-(*S*)-**6m**	*i*-Pr	Br	B	(*S*)-**8e**	n.d.[d]	H	(+)-(*S*)-**1e**·HI	9[h] (99)[g]

[a] Method A: Mitsunobu dehydration in THF at room temperature, in the presence of PPh_3 and either DEAD or DIAD, as specified by notes b and c; method B: Williamson etherification.
[b] Azodicarboxylate: DEAD.
[c] Azodicarboxylate: DIAD.
[d] N.d. = not determined.
[e] Ee evaluated by ^{1}H NMR, c.s.a. = *O*-*p*-chlorophenylmandelic acid, proton observed $CHCH_3$.
[f] Ee evaluated by HPLC on the corresponding *N*-acetyl derivative, c.s.p. = CHIRALCEL OD-R.
[g] Ee evaluated by HPLC, c.s.p. = CHIRALCEL OD.
[h] On the corresponding recrystallized hydrohalides.

to afford higher yields than diethyl azodicarboxylate (DEAD) (cf entries 1 and 2; 3 and 4). Considering also its lower cost and ease of handling, DIAD should be the preferred reagent. However, regardless from the azodicarboxylate used, the Mitsunobu dehydration run on *N*-phthalylvalinol **4e** failed to give the corresponding 2,6-xylyl ether **8e**, leaving **4e** unreacted. Fortunately, **8e** could be obtained in a sufficiently chemically pure form, as stated by GMS analysis, by a Williamson reaction[19] (method B, entries 13 and 14) of **7a** with **4e** iodo or bromo derivative (**6l** and **6m**, respectively), obtained in high yield from **4e** by using a procedure

previously reported for benzyl alcohols,[20] and recently applied to phthalimido alcohols.[19b] Method B, in turn, was not satisfactory in giving **8a**, regardless of the leaving group used (Br, Cl, I, TsO). The reaction, indeed, is tainted by competing elimination, which lowers yields and gives, after work up, an unresolved mixture presenting the desired product together with 2-phthalimidopropene. Neither the yields nor the work up benefited from the use of **3b** or **3c** as the protecting agent. However, **1a** enantiomers may be obtained directly submitting to hydrazinolysis the mixture resulting from the previous step. Thus method B provided **1a** enantiomers in overall yields lower (<5%) than those observed running method A (40–48%). Method B was successful also in affording **8d** enantiomers, and overall yields were about as moderate as those observed with method A (7–8%, based on the corresponding recrystallized hydrochlorides, entries 11 and 12, and 13–14%, entries 9 and 10, respectively), no significant difference being observed when reacting iodides in lieu of bromides. The final products **1a–e**, obtained by hydrazinolysis[16b] of the corresponding phthaloylated intermediates **8a–e**, were purified and stored as the corresponding hydrohalides (see Section 4). Free amine samples obtained by extraction from each of these salts underwent enantiomeric excess (ee) evaluation, which was performed by either chiral ^{1}H NMR **1a–c** or HPLC analysis on chiral stationary phase (c.s.p.) **1d–e** under the conditions described in the experimental section. For ^{1}H NMR enantiomeric excess (ee) evaluation, *O*-*p*-chlorophenylmandelic acid was used as the chiral solvating agent (c.s.a.).[21] HPLC analyses were performed on the free base forms of (+)-(*S*)-**1d**, (−)-(*R*)-**1e**, and (+)-(*S*)-**1e** (c.s.p.: CHIRALCEL OD) and on the *N*-acetyl derivative of (−)-(*R*)-**1d** (c.s.p.: CHIRALCEL OD-R). Regardless of the method used to obtain **1a–e**, ee values ranged from 91 to 99%.

3. Conclusion

In summary, the utilization of Mitsunobu (method A) and Williamson (method B) reactions for the aryl ether bond formation has allowed the synthesis of mexiletine analogues in highly enriched optically active forms. Generally, method A provided the most efficient route, both in terms of yields and number of steps necessary. However, method A failed when applied to the preparation of **1e**, i.e. when 2-amino-3-methylbutanol **2c** was used as the starting alcohol; in this case, method B proved to be the only available route. Regardless of the method used, ee values found for both enantiomers of **1a–e** were acceptable (91–99%). Some of the mexiletine analogues here reported **1d**,**e** have already shown interesting features in exerting a potent and use-dependent block on skeletal muscle sodium channels[6b,c] and may be considered as possible candidate antimyotonic agents. Being the 4-position of mexiletine metabolically hydroxylated, 4-substituted mexiletine analogues **1b**,**c** might show higher resistance to biotransformation, thus being potentially preferable to mexiletine for the therapy of myotonic disorders, which are chronic diseases.

The most enticing aspect of the synthesis reported herein seems to be the possibility to generate a variety of mexiletine analogues, given the plethora of available phenols and the availability of relatively not expensive optically active α-amino alcohols. The adaptability of the Mitsunobu reaction to solid phase synthesis[22] provides the potential for vast chemical diversity when preparing aryloxy alkylamines.

The extension of the route here presented to the preparation of mexiletine major metabolites in their optically active forms is currently under study.

4. Experimental

4.1. General

The structures of the compounds were confirmed by routine spectrometric analyses. Only spectra for compounds to our knowledge never previously described are given. Compounds used as starting materials were purchased from either Aldrich or Lancaster in the highest commercially available quality. *O*-*p*-Chlorophenylmandelic acid used as the c.s.a. was prepared in our laboratories.[21b,c] Solvents were RP grade, unless otherwise indicated. Melting points were determined on a Gallenkamp melting point apparatus in open glass capillary tubes and are uncorrected. The infrared spectra were recorded on a Perkin–Elmer 283 spectrophotometer and band positions are given in reciprocal centimetres (cm^{-1}). ^1H NMR spectra were recorded on either an FT Bruker Aspect 3000 (300 MHz) spectrometer or a Varian XL 200 spectrometer (90 MHz) using $CDCl_3$ as solvent, unless otherwise indicated. Chemical shifts are in parts per million (ppm) relative to either the solvent or tetramethylsilane as internal references, respectively. When determining ee values, **1a**–**c** free base forms were recovered by extraction of a sample of the corresponding hydrochlorides and dissolved with 2 equiv. of c.s.a. in benzene-d_6. Spectra were registered at 20°C and the splitting of a-methyl groups was observed ($\Delta\delta = 0.080$ ca). MS spectra were recorded with a Hewlett-Packard 5995c gas chromatograph/mass spectrometer at low resolution. Elemental analyses were performed on a Carlo Erba mod. 1106. Optical rotations were measured on a Perkin–Elmer 241 MC spectropolarimeter; concentrations are expressed in g/100 mL and the cell length is 1 dm. HPLC was performed on a Waters chromatograph (Waters Assoc., Milford, MA) model 600 equipped with a U6K model injector and a 481 model variable wavelength detector. When CHIRALCEL OD (DAICEL Co.) was used as the c.s.p., the mobile phase was *n*-hexane/*i*-PrOH = 99/1 (flow rate: 1.0 mL/min). When CHIRALCEL OD-R (DAICEL Co.) was used as the c.s.p., the mobile phase was MeOH/H_2O = 99/1 (flow rate: 0.4 mL/min). Chromatographic separations were performed on silica gel columns by flash chromatography (Kieselgel 60, 0.040–0.063 mm, Merck) using the technique described by Still et al.[23] TLC analyses were performed on precoated silica gel on glass or aluminium sheets (Kieselgel 60 F_{254}, Merck).

4.2. General procedure for the preparation of phthalimido alcohols *4a–e*[15]

A mixture of 2-amino-1-alcanol **2a**–**c** (13.4 mmol), anhydride **3a**–**c** (13.4 mmol), triethylamine (1.34 mmol), and 20 mL of toluene is heated under reflux in a flask fitted with a Dean–Stark tube for 3 h. During this period, the temperature of the oil bath is maintained at about 130°C and water separates. All volatile matter are then evaporated under vacuum and the solid residue is taken up with EtOAc and washed with 2N HCl, $NaHCO_3$, and H_2O. The organic phase is dried (Na_2SO_4) and concentrated under vacuum. The crude solid is recrystallized to give **4a**–**e**. When 3-nitrophthalic anhydride **3b** was used to protect **2a**, about 40% of the starting amino alcohol was recovered as the corresponding 2-carboxy-3-nitrobenzoyl derivative **5**. The latter was converted into the desired phthalimide adduct **4b** by refluxing a suspension of **5** in either toluene, separating water for 6 h in the presence of a catalytic amount of *p*-toluensulphonic acid (yield from **5** to **4b**: 49%), or EtOH/HCl 4% (24 h, yield from **5** to **4b**: 78%).

*4.2.1. (−)-(*R*)-2-(2-Hydroxy-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (−)-(*R*)-**4a***

Yield: 90% (86% after recrystallization); mp 84–85°C (EtOAc–petroleum ether), lit.:[24] 80°C (toluene); $[\alpha]_D^{20}=-14.6$ (*c* 3.2, $CHCl_3$), lit.:[24] −12.2 (*c* 1.13, $CHCl_3$); MS: *m*/*z* 205 (M^+, <1), 174 (100). Spectroscopic data were according to those reported for the enantiomer (+)-(*S*).[25]

*4.2.2. (+)-(*S*)-2-(2-Hydroxy-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**4a***

Yield: 94% (87% after recrystallization); mp 84–85°C (EtOAc–petroleum ether), lit.:[24] 86–87°C (acetone–hexane); $[\alpha]_D^{20}=+16.5$ (*c* 2, $CHCl_3$), lit.:[25] +13.7 (*c* 4.2, $CHCl_3$); MS: *m*/*z* 205 (M^+, <1), 174 (100). Spectroscopic data were according to those reported in the literature.[25]

*4.2.3. (±)-(*RS*)-2-(2-Hydroxy-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (±)-(*RS*)-**4a***

Yield: 95% (88% after recrystallization); mp 97–98°C (EtOAc–petroleum ether). Spectroscopy data were identical to those found for (+)-(*S*)-**4a**.

*4.2.4. (+)-(*S*)-2-(2-Hydroxy-1-methylethyl)-4-nitro-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**4b***

Yield: 49%; mp 113–114°C (EtOAc–hexane); $[\alpha]_D^{20}=+21.4$ (*c* 2, $CHCl_3$); IR (KBr pellet): 3520 (OH), 1770, 1720 (C=O), 1540 (NO_2); ^{1}H NMR (90 MHz): δ 1.5 (d, 3H, $J=7.5$ Hz, C*H*$_3$CH), 2.6 (br s, 1H, O*H*), 3.7–4.3 (m, 2H, C*H*$_2$CH), 4.4–4.7 (m, 1H, C*H*), 7.8–8.3 (m, 3H, Ar); MS: *m*/*z* 219 ([M−31]$^+$, 100).

*4.2.5. (±)-(*RS*)-2-(2-Hydroxy-1-methylethyl)-4-nitro-1*H*-isoindole-1,3(2*H*)-dione (±)-(*RS*)-**4b***

Yield: 58%; mp 112–114°C (EtOAc–hexane). All other nonchiroptical physical characteristics were identical to those found for (+)-(*S*)-**4b**.

*4.2.6. (+)-(*S*)-2-(2-Hydroxy-1-methylethyl)-5-methyl-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**4c***

Yield: 69%; mp 105–107°C (EtOAc–petroleum ether); $[\alpha]_D^{20}=+17.8$ (*c* 2, $CHCl_3$); IR (KBr pellet): 3502 (OH), 1766, 1693 (C=O); ^{1}H NMR (90 MHz): δ 1.4 (d, 3H, $J=7.5$ Hz, C*H*$_3$CH), 2.5 (s, 3H, C*H*$_3$Ar), 3.7–4.2 (m, 2H, C*H*$_2$CH), 4.2–4.7 (m, 1H, C*H*), 7.5 (d, 1H, $J=9$ Hz, Ar *H*C-7), 7.6 (s, 1H, Ar *H*C-4), 7.7 (d, 1H, $J=9$ Hz, Ar *H*C-6); MS: *m*/*z* 219 (M^+, <1), 188 (100).

*4.2.7. (+)-(*R*)-2-(1-Benzyl-2-hydroxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (+)-(*R*)-**4d***

Yield: 93% (77% after recrystallization); mp 110–112°C (EtOAc–petroleum ether), lit.:[26] 95–97°C (Et_2O); $[\alpha]_D^{20}=+132$ (*c* 2, $CHCl_3$), lit.:[26] +145 (*c* 2, EtOH). Spectrometry data were according to those reported in the literature.[26] Anal. calcd for ($C_{17}H_{15}NO_3$): C, 72.58; H, 5.37; N, 4.98. Found: C, 72.68; H, 5.44; N, 4.89.

*4.2.8. (−)-(*S*)-2-(1-Benzyl-2-hydroxyethyl)-1*H*-isoindole-1,3(2*H*)-dione (−)-(*S*)-**4d***

Yield: 96% (82% after recrystallization); mp 111–112°C (EtOAc–petroleum ether), lit.:[26] 96–98°C (Et_2O); $[\alpha]_D^{20}=-119$ (*c* 2, $CHCl_3$), lit.:[26] −136 (*c* 2, EtOH). Spectrometry data were according to those reported in the literature.[26] Anal. calcd for ($C_{17}H_{15}NO_3$): C, 72.58; H, 5.37; N, 4.98. Found: C, 73.00; H, 5.60; N, 4.95.

*4.2.9. (*R*)-2-[1-(Hydroxymethyl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (*R*)-**4e***

Yield: 81%; mp 36–38°C; $[\alpha]_D^{20}=-11.5$ (*c* 3.1, EtOH); $[\alpha]_D^{20}=+2.8$ (*c* 2, $CHCl_3$). ^{1}H NMR and MS spectra were according to those reported in the literature for the enantiomer (*S*).[25]

*4.2.10. (S)-2-[1-(Hydroxymethyl)-2-methylpropyl]-1H-isoindole-1,3(2H)-dione (S)-**4e***

Yield: 78% (72% after recrystallization); mp 36–37°C (EtOAc–petroleum ether); $[\alpha]_D^{20}=+11.7$ (*c* 3.2, EtOH), lit.:[25] +8.33 (*c* 2.924, EtOH); $[\alpha]_D^{20}=-2.9$ (*c* 2, $CHCl_3$); ^1H NMR and MS spectra were according to those reported in the literature.[25]

*4.2.11. (±)-(RS)-2-(2-Hydroxy-1-methylethylaminocarbonyl)-6-nitrobenzoic acid (±)-(RS)-**5***

Yield: 39%; mp 148–149°C (EtOAc–petroleum ether); IR (KBr pellet): 1720 (C=O); ^1H NMR (90 MHz, $CDCl_3$/DMSO-d_6): δ 1.2 (d, 3H, $J=7.5$ Hz, CH_3CH), 3.5 (d, 2H, $J=6.0$ Hz, CH_2CH), 3.9–4.3 (m, 1H, C*H*), 7.4–8.1 (m, 5H, Ar+O*H*+N*H*).

*4.3. General procedure for the preparation of phthalimidoalkyl aryl ethers (**8a–e**) through Mitsunobu coupling[18] (method A)*

To a stirred solution of the suitable phthalimidoalcohol (**4a–d**, 12.5 mmol), phenol (**7a–c**, 18.7 mmol), and triphenylphosphine (18.7 mmol), in dry THF (120 mL) under N_2 atmosphere, a solution containing 18.7 mmol of DEAD or DIAD, as indicated below for each product, in dry THF (120 mL) is added dropwise. The mixture is stirred at room temperature for 24 h. The solvent is then evaporated under vacuum, ether is added and the precipitate formed is filtered off. The filtrate is evaporated and the residue is purified by silica gel column chromatography (EtOAc/petroleum ether 2:8).

*4.3.1. (–)-(R)-2-[2-(2,6-Dimethylphenoxy)-1-methylethyl]-1H-isoindole-1,3(2H)-dione (–)-(R)-**8a***

Azodicarboxylate used: DIAD. Yield: 65%; $[\alpha]_D^{20}=-50$ (*c* 2.5, $CHCl_3$), lit.:[11] −55 (*c* 2.2, $CHCl_3$). Spectrometry data were in agreement with the literature.[11]

*4.3.2. (+)-(S)-2-[2-(2,6-Dimethylphenoxy)-1-methylethyl]-1H-isoindole-1,3(2H)-dione (+)-(S)-**8a***

Azodicarboxylate used: DIAD. Yield: 55%; $[\alpha]_D^{20}=+55$ (*c* 3.1, $CHCl_3$), lit.:[11] +55 (*c* 2.5, $CHCl_3$). Spectrometry data were in agreement with the literature.[11]

*4.3.3. (–)-(R)-2-[1-Methyl-2-(2,4,6-trimethylphenoxy)ethyl]-1H-isoindole-1,3(2H)-dione (–)-(R)-**8b***

Azodicarboxylate used: DEAD. Yield: 22%; $[\alpha]_D^{20}=-42$ (*c* 2.0, $CHCl_3$); IR (film): 1774, 1711 (C=O); ^1H NMR (90 MHz): δ 1.5 (d, 3H, $J=7.5$ Hz, CH_3CH), 2.2 (s overlap s at 2.25, 6H, CH_3C-2,6), 2.25 (s, 3H, CH_3C-4), 3.9 (dd, 1H, $J=9$ and $J=6$, C*H*HCH), 4.3 (apparent t, 1H, $J=9$, CH*H*CH), 4.7–5.1 (m, 1H, C*H*), 6.8 (br s, 2H, ArO *H*C), 7.8–8.0 (m, 4H, Ar C*H*); MS: m/z 323 (M^+, 11), 188 (100).

*4.3.4. (+)-(S)-2-[1-Methyl-2-(2,4,6-trimethylphenoxy)ethyl]-1H-isoindole-1,3(2H)-dione (+)-(S)-**8b***

Azodicarboxylate used: DEAD. Yield: 31%; $[\alpha]_D^{20}=+40$ (*c* 2.6, $CHCl_3$). Spectrometry data were identical to those found for (–)-(*R*)-**8b**.

*4.3.5. (–)-(R)-2-[2-(4-Chloro-2,6-dimethylphenoxy)-1-methylethyl]-1H-isoindole-1,3(2H)-dione (–)-(R)-**8c***

Azodicarboxylate used: DEAD. Yield: 52%; $[\alpha]_D^{20}=-38$ (*c* 3.0, $CHCl_3$); IR (film): 1772, 1709

(C=O); ^{1}H NMR (90 MHz): δ 1.6 (d, 3H, $J=7.5$ Hz, CH_3CH), 2.2 (s, 6H, 2CH_3Ar), 3.9 (dd, 1H, $J=9$ and 6, CHHCH), 4.4 (apparent t, 1H, $J=9$, CHHCH), 4.7–5.1 (m, 1H, CH), 7.0 (s, 2H, ArO HC), 7.7–8.0 (m, 4H, Ar CH); MS: m/z 343 (M^+, 8), 188 (100).

*4.3.6. (+)-(S)-2-[2-(4-Chloro-2,6-dimethylphenoxy)-1-methylethyl]-1*H*-isoindole-1,3(2*H*)-dione (+)-(S)-**8c***

Azodicarboxylate used: DEAD. Yield: 41%; $[\alpha]_D^{20}=+35$ (c 3.3, $CHCl_3$). Spectrometry data were identical to those found for (−)-(*R*)-**8c**.

*4.3.7. (+)-(R)-2-[1-Benzyl-2-(2,6-dimethylphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (+)-(R)-**8d***

Azodicarboxylate used: DIAD. Yield: 43% (33% after recrystallization); mp 115–116°C (EtOAc–petroleum ether); $[\alpha]_D^{20}=+33.7$ (c 2.0, $CHCl_3$); IR (KBr pellet): 1768, 1700 (C=O); ^{1}H NMR (300 MHz): δ 2.2 (s, 6H, CH_3Ar), 3.2–3.4 (m, 2H, ArCH_2CH), 3.8–4.1 (m, 1H, CHCHHO), 4.4–4.6 (m, 1H, CHCHHO), 4.8–5.3 (m, 1H, CH), 7.0 (s, 3H ArO HC), 7.3 (s, 5H, Ph HC), 7.6–7.9 (m, 4H, Ar HC); MS: m/z 385 (M^+, 9), 264 (100).

*4.3.8. (−)-(S)-2-[1-Benzyl-2-(2,6-dimethylphenoxy)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (−)-(S)-**8d***

Azodicarboxylate used: DIAD. Yield: 54% (46% after recrystallization); mp 114–115°C (EtOAc–petroleum ether); $[\alpha]_D^{20}=-36.4$ (c 2, $CHCl_3$). Spectrometry data were identical to those found for (+)-(*R*)-**8d**.

*4.4. General procedure for the preparation of bromo- or iodoalkyl phthalimides **6a–c,f,h–m***[19b,20]

Into a stirred ice-cooled solution of the suitable phthalimido alcohol **4a–e** (6 mmol) in dry toluene (30 mL) under N_2 atmosphere, HBr or HI is bubbled until saturation occurred. The mixture is stirred at −5°C for 1 h, at room temperature for 18 h, and at 80°C for 2 h. The solvent is then evaporated under vacuum and the residue, taken up with EtOAc, is washed with 6N NaOH, 2N HCl, and H_2O. The organic layer is dried (Na_2SO_4) and concentrated under vacuum to give a solid which may be purified by silica gel column chromatography (EtOAc/petroleum ether 2:8) and/or by recrystallization.

*4.4.1. (−)-(R)-2-(2-Bromo-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (−)-(R)-**(6a)***

Yield: 92% (78% after recrystallization); mp 70–71°C (benzene–hexane); $[\alpha]_D^{20}=-20.6$ (c 2, $CHCl_3$); IR (KBr pellet): 1769, 1699 (C=O); ^{1}H NMR (90 MHz): δ 1.6 (d, 3H, $J=7.5$ Hz, CH_3CH), 3.5–4.2 (m, 2H, CH_2CH), 4.4–4.9 (m, 1H, CH), 7.8–8.3 (m, 4H, Ar). MS: m/z 267 (M^+, 1), 174 (100).

*4.4.2. (+)-(S)-2-(2-Bromo-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (+)-(S)-**(6a)***

Yield: 95% (90% after recrystallization); mp 71–72°C (benzene–hexane); $[\alpha]_D^{20}=+22.4$ (c 2, $CHCl_3$). All other nonchiroptical physical characteristics were identical to those found for (−)-(*R*)-**6a**.

*4.4.3. (±)-(RS)-2-(2-Bromo-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (±)-(RS)-**(6a)***

Yield: 98% (92% after recrystallization); mp 61–62°C (benzene–hexane). All other nonchiroptical physical characteristics were identical to those found for both enantiomers.

*4.4.4. (+)-(S)-2-(2-Bromo-1-methylethyl)-5-methyl-1H-isoindole-1,3(2H)-dione (+)-(S)-(**6b**)*

Yield: 77% (68% after recrystallization); mp 84–85°C (benzene–hexane); $[\alpha]_D^{20}=+25.8$ (*c* 2, $CHCl_3$); IR (KBr pellet): 1770, 1699 (C=O); ^{1}H NMR (90 MHz): δ 1.6 (d, 3H, $J=7.5$ Hz, CH_3CH), 2.5 (s, 3H, CH_3Ar), 3.6 (dd, 1H, $J=9$ Hz and $J=6$ Hz, $CHHCH$), 4.1 (apparent t, 1H, $J=9$ Hz, $CHHCH$), 4.5–4.9 (m, 1H, CH), 7.5 (d, 1H, $J=9$ Hz, Ar *H*C-7), 7.6 (s, 1H, Ar *H*C-4), 7.7 (d, 1H, $J=9$ Hz, Ar *H*C-6); MS: *m*/*z* 281 (M^+, 1), 188 (100).

*4.4.5. (+)-(S)-2-(2-Bromo-1-methylethyl)-4-nitro-1H-isoindole-1,3(2H)-dione (+)-(S)-(**6c**)*

Yield: 70% (46% after recrystallization); mp 91–92°C (AcOEt-*i*-Pr_2O); $[\alpha]_D^{20}=+22.9$ (*c* 2.3, $CHCl_3$); IR (KBr pellet): 1801, 1732 (C=O), 1537 (NO_2); ^{1}H NMR (90 MHz): δ 1.5 (d, 3H, $J=7.5$ Hz, CH_3CH), 3.5 (dd, 1H, $J=9$ Hz and $J=6$ Hz, $CHHCH$), 4.0 (apparent t, 1H, $J=9$ Hz, $CHHCH$), 4.4–4.7 (m, 1H, CH), 7.8–8.3 (m, 3H, Ar); MS: *m*/*z* 312 (M^+, 3), 219 (100).

*4.4.6. (−)-(R)-2-(2-Iodo-1-methylethyl)-1H-isoindole-1,3(2H)-dione (−)-(R)-(**6f**)*

Yield: 80% (67% after recrystallization); mp 57–58°C (MeOH); $[\alpha]_D^{20}=-23.6$ (*c* 2, $CHCl_3$); IR (KBr pellet): 1766, 1697 (C=O); ^{1}H NMR (90 MHz): δ 1.7 (d, 3H, $J=7.5$ Hz, CH_3CH), 3.5 (dd, 1H, $J=9$ Hz and $J=6$ Hz, $CHHCH$), 3.9 (apparent t, 1H, $J=9$ Hz, $CHHCH$), 4.3–4.8 (m, 1H, CH), 7.7–8.0 (m, 3H, Ar); MS: *m*/*z* 315 ($M^{+\cdot}$, 6), 188 (100).

*4.4.7. (+)-(S)-2-(2-Iodo-1-methylethyl)-1H-isoindole-1,3(2H)-dione (+)-(S)-(**6f**)*

Yield: 95% (77% after recrystallization); mp 58–59°C (MeOH); $[\alpha]_D^{20}=+21.3$ (*c* 2, $CHCl_3$). All other nonchiroptical physical characteristics were identical to those found for (−)-(*R*)-**6f**.

*4.4.8. (±)-(RS)-2-(2-Iodo-1-methylethyl)-1H-isoindole-1,3(2H)-dione (±)-(RS)-(**6f**)*

Yield: 72% (68% after recrystallization); mp 64–65°C (MeOH). All other nonchiroptical physical characteristics were identical to those found for both enantiomers.

*4.4.9. (+)-(R)-2-(1-Benzyl-2-iodoethyl)-1H-isoindole-1,3(2H)-dione (+)-(R)-(**6h**)*

Yield: 89% (79% after recrystallization); mp 140–141°C (MeOH), lit.:[27] 141–142°C (MeOH); $[\alpha]_D^{20}=+96.0$ (*c* 2, $CHCl_3$), lit.:[27] +99.1 (*c* 1, acetone); MS: *m*/*z* 391 (M^+, 1), 300 (100). Spectroscopy data were corresponding to the literature.[27]

*4.4.10. (−)-(S)-2-(1-Benzyl-2-iodoethyl)-1H-isoindole-1,3(2H)-dione (−)-(S)-(**6h**)*

Yield: 65% (54% after recrystallization); mp 140–141°C (MeOH), lit.:[28] 138–140°C; $[\alpha]_D^{20}=-97.8$ (*c* 2, $CHCl_3$); MS: *m*/*z* 391 (M^+, 1), 300 (100). Spectroscopy data were corresponding to the literature.[28]

*4.4.11. (+)-(R)-2-(1-Benzyl-2-bromoethyl)-1H-isoindole-1,3(2H)-dione (+)-(R)-(**6i**)*

Yield: 83% (77% after recrystallization); mp 119–120°C (MeOH), lit.:[29] 119–121°C; $[\alpha]_D^{20}=+105$ (*c* 2, $CHCl_3$), lit.:[29] +120.2 (*c* 1.896, CH_2Cl_2); MS: *m*/*z* 343 (M^+, 1), 264 (100). Spectroscopy data were in agreement with those reported in the literature.[29]

*4.4.12. (−)-(S)-2-(1-Benzyl-2-bromoethyl)-1H-isoindole-1,3(2H)-dione (−)-(S)-(**6i**)*

Yield: 70% (62% after recrystallization); mp 118–119°C (MeOH), lit.:[28] 118–119°C (MeOH); $[\alpha]_D^{20}=-107$ (*c* 2, $CHCl_3$), lit.:[29] −112.2 (*c* 1.274, CH_2Cl_2); MS: *m*/*z* 343 (M^+, 1), 264 (100). Spectroscopy data were in agreement with the literature.[29]

*4.4.13. (–)-(*R*)-2-[1-(Iodomethyl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (–)-(*R*)-**6l***

Yield: 95% (80% after recrystallization); mp 107–108°C (MeOH); $[\alpha]_D^{20} = -11.0$ (*c* 2, $CHCl_3$); ^{1}H NMR (300 MHz): δ 0.91 (d, 3H, $J = 6.7$ Hz, CH_3CHCH_3), 1.07 (d, 3H, $J = 6.8$ Hz, CH_3CHCH_3), 2.33–2.46 (m, 1H, CH_3CHCH_3), 3.66 (dd, 1H, $J = 10$ Hz and $J = 3.6$ Hz, CH–CHHI), 3.97 (dd, 1H, $J = 12$ Hz and $J = 9.9$ Hz, CH–CHHI), 4.06–4.14 (m, 1H, $NCHCH_2$), 7.69–7.75 (m, 2H, Ar HC-5,6), 7.82–7.88 (m, 2H, Ar HC-4,7); MS: *m*/*z* 343 (M^+, 6), 300 (100).

*4.4.14. (+)-(*S*)-2-[1-(Iodomethyl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**6l***

Yield: 91% (68% after recrystallization); $[\alpha]_D^{20} = +10.8$ (*c* 2, $CHCl_3$). Nonchiroptical physical characteristics are identical to those found for (–)-(*R*)-6l.

*4.4.15. (–)-(*R*)-2-[1-(Bromomethyl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (–)-(*R*)-**6m***

Yield: 84% (62% after recrystallization); mp 70–71°C (MeOH), lit.:[29] 61–63°C; $[\alpha]_D^{20} = -19.4$ (*c* 2, $CHCl_3$), lit.:[29] –11.3 (*c* 1.380, CH_2Cl_2);[29] MS: *m*/*z* 295 (M^+, 9), 252 (100). Spectroscopy data were in agreement with those reported in the literature.[29]

*4.4.16. (+)-(*S*)-2-[1-(Bromomethyl)-2-methylpropyl]-1*H*-isoindole-1,3(2*H*)-dione (+)-(*S*)-**6m***

Yield: 95% (81% after recrystallization); mp 70–71°C (MeOH), lit.:[29] 61–64°C; $[\alpha]_D^{20} = +18.2$ (*c* 2, $CHCl_3$), lit.:[29] +10.0 (*c* 3.218, CH_2Cl_2);[29] MS: *m*/*z* 295 (M^+, 8), 252 (100). Spectroscopy data were in agreement with those reported in the literature.[29]

*4.5. General procedure for the preparation of cloroalkyl phthalimides **6d**,**e***

A solution of the suitable phthalimido alcohol (1.20 mmol, 1 equiv.), pyridine (0.1 mL, 1.32 mmol, 1.1 equiv.), and thionyl chloride (0.1 mL, 1.26 mmol, 1.05 equiv.) in anhydrous THF (2 mL) is stirred under nitrogen at 60°C for 6 h. Volatile components are removed under vacuum and the crude residue is taken up with Et_2O. The solution is washed with water, dried (Na_2SO_4) and concentrated under vacuum to give an oil which is purified by silica gel column chromatography (EtOAc/petroleum ether 2:8).

*4.5.1. (±)-(RS)-2-(2-Chloro-1-methylethyl)-1*H*-isoindole-1,3(2*H*)-dione (±)-(RS)-**6d***

Yield: 50%; ^{1}H NMR (90 MHz): δ 1.6 (d, 3H, $J = 7.5$ Hz, CH_3CH), 3.7 (dd, 1H, $J = 9$ Hz and $J = 6$ Hz, CHHCH), 4.2 (apparent t, 1H, $J = 9$ Hz, CHHCH), 4.4–4.8 (m, 1H, CH), 7.7–8.0 (m, 4H, Ar); MS: *m*/*z* 223 (M^+, 1), 174 (100).

*4.5.2. (±)-(RS)-2-(2-Chloro-1-methylethyl)-4-nitro-1*H*-isoindole-1,3(2*H*)-dione (±)-(RS)-**6e***

Yield: 56%; ^{1}H NMR (90 MHz): δ 1.7 (d, 3H, $J = 7.5$ Hz, CH_3CH), 3.7 (dd, 1H, $J = 9$ Hz and $J = 6$ Hz, CHHCH), 4.2 (apparent t, 1H, $J = 9$ Hz, CHHCH), 4.4–4.8 (m, 1H, CH), 7.8–8.2 (m, 3H, Ar); MS: *m*/*z* 268 (M^+, 2), 219 (100).

*4.6. Preparation of (+)-(S)-2-phthalimidopropyl toluene-*p*-sulphonate (+)-(S)-**6g***

The procedure proposed by Casara et al. was followed.[30] Yield: 82% (65% after recrystallization); mp 144–145°C (CH_2Cl_2–petroleum ether), lit:[30] 135°C (ether–CH_2Cl_2); $[\alpha]_D^{20} = +22.0$ (*c* 2, $CHCl_3$), lit.:[30] +20.0 (*c* 0.504, $CHCl_3$);[30] MS: *m*/*z* 359 (M^+, 2), 174 (100). Spectroscopy data were in agreement with those reported in the literature.[30]

4.7. General procedure for the preparation of phthalimidoalkyl aryl ethers **8a–e** through Williamson coupling[19] (method B)

A stirred mixture of 2,6-dimethylphenol (4.0 mmol) and Na_2CO_3 (4.4 mmol) in dry DMF (70 mL), is heated under N_2 atmosphere until the temperature of 130°C is reached. Then the suitable haloalkyl phthalimide **6a–c,f,h–m** is added and heating is maintained for 24 h. The solvent is then evaporated under vacuum, taken up with EtOAc, and washed with 0.5N NaOH, and H_2O. The organic layer is dried (Na_2SO_4) and concentrated under vacuum. Purification of the crude oil residue by column chromatography (EtOAc/petroleum ether 2:8) gives a crude solid which is checked for purity by GMS analysis and judged suitable for the next step. MS data for **8e** enantiomers: m/z 337 (M^+, 13), 216 (100).

4.8. General procedure for the removal of the phthalimido protecting group[16b]

To a stirred solution of the phthalimidoalkyl aryl ether **8a–e** (1 mmol) in absolute EtOH (10 mL), glacial AcOH (3 mmol), and $N_2H_4H_2O$ (3 mmol) is added. The mixture is heated under reflux for 1.5 h and then is filtered on a Celite pad; the solvent is evaporated under vacuum. The residue is taken up with EtOAc and extracted with 2N HCl, then the aqueous phase is made alkaline with 2N NaOH and extracted twice with EtOAc. The combined organic layers are dried (Na_2SO_4) and concentrated under vacuum. The final product is an uncoloured oil which is purified by crystallization of the corresponding hydrohalide, obtained treating with a few drops of the suitable hydrohalide aqueous solution and azeotropically removing water.

4.8.1. (−)-(R)-1-(2,6-Dimethylphenoxy)-2-propanamine (−)-(R)-**1a**

Yield: 78%; $[\alpha]_D^{20} = -2.1$ (c 3.0, $CHCl_3$), lit.:[11] −2.7 (c 4.7, $CHCl_3$); spectrometry data were in agreement with the literature.[11,7a] (−)-(*R*)-**1a**·HCl, yield: 28%; mp 203–204°C (EtOH–Et_2O), lit.:[11] 204–205°C (EtOH–Et_2O); $[\alpha]_D^{20} = -2.4$ (c 2.0, MeOH), 98% ee (^{1}H NMR), lit.:[8] −2.9 (c 1.00, MeOH, >99% ee). Anal. calcd for ($C_{11}H_{18}ClNO$): C, 61.85; H, 8.41; N, 6.49. Found: C, 60.93; H, 8.56; N, 6.39.

4.8.2. (+)-(S)-1-(2,6-Dimethylphenoxy)-2-propanamine (+)-(S)-**1a**

Yield: 76%; $[\alpha]_D^{20} = +2.6$ (c 3.0, MeOH), lit.:[11] +2.5 (c 4.9, $CHCl_3$); spectrometry data were in agreement with the literature.[11,7a] (+)-(*S*)-**1a**·HCl, yield: 25%; mp 196–198°C (EtOH–Et_2O), lit.:[11] 193–194°C (EtOH–Et_2O); $[\alpha]_D^{20} = +2.2$ (c 2.0, MeOH), 91% ee (^{1}H NMR), lit.:[8] +2.6 (c 1.00, MeOH, 99% ee). Anal. calcd for ($C_{11}H_{18}ClNO$): C, 61.25; H, 8.41; N, 6.49. Found: C, 61.52; H, 8.66; N, 6.46.

4.8.3. (−)-(R)-1-(2,4,6-Trimethylphenoxy)-2-propanamine (−)-(R)-**1b**

Yield: 80%; $[\alpha]_D^{20} = -1.6$ (c 3.0, $CHCl_3$); ^{1}H NMR (300 MHz): δ 1.57 (d, 3H, $J = 7.5$ Hz, CH_3CH), 1.73 (br s, 2H, NH_2), 2.22 (s, 6H, CH_3C-2,6), 2.23 (s, 3H, CH_3C-4), 3.67–3.80 (m, 1H, CH), 3.81–3.98 (m, 2H, CH_2), 6.63 (s, 2H, Ar); MS: m/z 193 (M^+, 6), 58 (100). (−)-(*R*)-**1b**·HCl, yield: 34%; mp 184–185°C (EtOH–Et_2O); $[\alpha]_D^{20} = -2.0$ (c 2.6, MeOH), 97% ee (^{1}H NMR). Anal. calcd for ($C_{12}H_{20}ClNO$): C, 62.73; H, 8.77; N, 6.10. Found: C, 62.82; H, 8.93; N, 6.16.

4.8.4. (+)-(S)-1-(2,4,6-Trimethylphenoxy)-2-propanamine (+)-(S)-**1b**

Yield: 87%; $[\alpha]_D^{20} = +1.8$ (c 2.6, $CHCl_3$). All spectrometry data were identical to those obtained from (−)-(*R*)-**1b** analyses. (+)-(*S*)-**1b**·HCl, yield: 27%; mp 187–188°C (EtOH–Et_2O); $[\alpha]_D^{20} = +1.8$

(*c* 2.4, MeOH), 95% ee (^{1}H NMR). Anal. calcd for ($C_{12}H_{20}ClNO$): C, 62.73; H, 8.77; N, 6.10. Found: C, 62.37; H, 9.13; N, 6.01.

*4.8.5. (–)-(*R*)-1-(4-chloro-2,6-dimethylphenoxy)-2-propanamine (–)-(*R*)-**1c***

Yield: 51%; $[\alpha]_D^{20}=-1.2$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz): δ 1.38 (d, 3H, $J=6.0$ Hz, CH_3CH), 1.6 (bs, 2H, NH_2) 2.25 (s, 6H, CH_3Ar), 3.61–3.72 (m, 2H, CH_2), 3.88–3.99 (m, 1H, C*H*), 7.8–8.2 (m, 3H, Ar); MS: *m*/*z* 213 (M^+, 3), 58 (100). (–)-(*R*)-**1c**·HCl, yield: 16%; mp 256–257°C (EtOH–Et_2O); $[\alpha]_D^{20}=-2.1$ (*c* 2.0, MeOH), 98% ee (^{1}H NMR). Anal. calcd for ($C_{11}H_{17}Cl_2NO$): C, 52.81; H, 6.85; N, 5.60. Found: C, 53.02; H, 7.01; N, 5.68.

*4.8.6. (+)-(S)-1-(4-chloro-2,6-dimethylphenoxy)-2-propanamine (+)-(S)-**1c***

Yield: 67%; $[\alpha]_D^{20}=+0.9$ (*c* 2.8, $CHCl_3$). All spectrometry data were identical to those obtained from (–)-(*R*)-**1c** analyses. (+)-(*S*)-**1c**·HCl, yield: 35%; mp 257–258°C (EtOH–Et_2O); $[\alpha]_D^{20}=+2.2$ (*c* 2.0, MeOH), 97% ee (^{1}H NMR). Anal. calcd for ($C_{11}H_{17}Cl_2NO$): C, 52.81; H, 6.85; N, 5.60. Found: C, 52.68; H, 7.26; N, 5.77.

*4.8.7. (–)-(R)-α-[(2,6-dimethylphenoxy)methyl]benzeneethanamine (–)-(R)-**1d***

Yield: 33%; $[\alpha]_D^{20}=-3.3$ (*c* 2.0, $CHCl_3$); MS: *m*/*z* 255 (M^+, 2), 120 (100). (–)-(*R*)-**1d**·HCl, yield: 20%; mp 195–197°C (EtOH–Et_2O), lit.:[8] 186–187°C (EtOH–Et_2O); $[\alpha]_D^{20}=-23$ (*c* 2.0, MeOH), 93% ee (HPLC analysis on the corresponding *N*-Ac-derivative, obtained by standard acetylation reaction[19b] of the free base, CHIRALCEL OD-R, t_R 14.8 min), lit.:[8] $[\alpha]_D^{20}=-20.1$ (*c* 0.40, MeOH, enantiomeric purity not given). Spectroscopy data were in agreement with the literature.[8] Anal. calcd for ($C_{17}H_{22}ClNO$): C, 68.56; H, 7.67; N, 4.70. Found: C, 58.76; H, 7.58; N, 4.77.

*4.8.8. (+)-(S)-α-[(2,6-dimethylphenoxy)methyl]benzeneethanamine (+)-(S)-**1d***

Yield: 28%; $[\alpha]_D^{20}=+4.7$ (*c* 2.0, $CHCl_3$); MS data identical to those obtained from (–)-(*R*)-**1d**. (+)-(*S*)-**1d**·HCl, yield: 18%; mp 194–196°C (EtOH–Et_2O), lit.:[8] 185–186°C (EtOH–Et_2O); $[\alpha]_D^{20}=+20$ (*c* 2.0, MeOH), 99% (HPLC, CHIRALCEL OD, t_R 19.1 min), lit.:[8] +24.5 (*c* 0.07, MeOH, enantiomeric purity not given). Spectroscopy data were in agreement with the literature.[8] Anal. calcd for ($C_{17}H_{22}ClNO$): C, 68.56; H, 7.67; N, 4.70. Found: C, 68.65; H, 7.32; N, 4.67.

*4.8.9. (–)-(R)-1-(2,6-dimethylphenoxy)-3-methyl-2-butanamine (–)-(R)-**1e***

$[\alpha]_D^{20}=-1.4$ (*c* 2.5, $CHCl_3$); MS: *m*/*z* 207 (M^+, 1), 72 (100). (–)-(*R*)-**1e**·HI, yield: 10%; mp 196–198°C ($CHCl_3$-*i*-Pr_2O); $[\alpha]_D^{20}=-3.0$ (*c* 2.0, MeOH), 99% ee (HPLC, CHIRALCEL OD, t_R 12.7 min); ^{1}H NMR (300 MHz): δ 1.12 (d, 3H, $J=6.9$ Hz, CH_3CHCH_3), 1.21 (d, 3H, $J=7.0$ Hz, CH$_3$CHCH_3), 2.29 (s, 6H, CH_3Ar), 2.45–2.52 (m, 1H, CH$_3$C*H*CH$_3$), 3.62–3.68 (m, 1H, CHC*H*CH$_2$), 3.96 (dd, 1H, $J=10.3$ Hz and $J=4.5$ Hz, CHC*H*HO), 4.13 (dd, 1H, $J=10.3$ Hz and $J=7.6$ Hz, CHCH*H*O), 6.88–6.97 (m, 3H, Ar). Anal. calcd for ($C_{13}H_{22}INO\cdot 0.5H_2O$): C, 45.36; H, 6.73; N, 4.07. Found: C, 45.76; H, 6.58; N, 4.16.

*4.8.10. (+)-(S)-1-(2,6-dimethylphenoxy)-3-methyl-2-butanamine (+)-(S)-**1e***

$[\alpha]_D^{20}=+1.9$ (*c* 2.6, $CHCl_3$); MS data identical to those obtained from (–)-(*R*)-**1e**. (+)-(*S*)-**1e**·HI, yield: 11%; mp 198–200°C ($CHCl_3$–hexane); $[\alpha]_D^{20}=+2.4$ (*c* 1.0, MeOH), 99% ee (HPLC, CHIRALCEL OD, t_R 15.1 min); ^{1}H NMR data were identical to those obtained from (–)-(*R*)-**1e**·HI. Anal. calcd for ($C_{13}H_{22}INO\cdot 0.5H_2O$): C, 45.36; H, 6.73; N, 4.07. Found: C, 45.78; H, 6.50; N, 4.20.

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